Risks and harms of binge drinking in young people: Bridging neurobiological, cognitive, and psychological perspectives

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Abstract

Binge drinking is highly prevalent among young people and can lead to health harms and engagement with other high-risk behaviors. While neurobiology, cognition, and psychopathology are central pathways to binge drinking, limited research bridges these perspectives, examines the developmental dynamics between them, or applies a multigenerational approach. To address these knowledge gaps, this thesis aims to examine the inter-related precursory risks of binge drinking, explore the added impact of multigenerational alcohol use, and determine the severity and recoverability of alcohol-related harms in young people.

Study 1 is the first rigorous review of the neurobiological and cognitive precursory risks and harms of binge drinking. Findings show that aberrant neurodevelopment increases risk, with aberrations further exacerbated by binge drinking. **Study 2** explores the dynamics between cognitive and psychological risk factors for binge drinking. The world-first study indicates that psychopathology in combination with poor executive functioning is associated with greater consumption. **Studies 3–5** investigate the impact of multigenerational alcohol use. The mega-analyses show that preadolescents with familial alcohol use problems or low- to moderate-level prenatal alcohol exposure exhibit established risk markers of binge drinking. **Study 6** examines cognitive harms following binge drinking in young people. Outcomes show that binge drinking is associated with inhibitory control deficits and demonstrate, for the first time, that these deficits do not recover over the short term.

The research in this thesis is the first to robustly show that 1) precursory neurobiological features predate binge drinking and co-occurring psychopathology plays a key role; 2) these precursors are particularly prevalent among young people with added familial risk; and 3) neurobiological and cognitive harms follow binge drinking and do not recede in the short term. The findings provide critical evidence from a multidisciplinary and developmental perspective for global prevention and intervention efforts as well as positive alcohol use policies. Greater prioritization of targeting the whole family will significantly reduce the prevalence of binge drinking and related disabling consequences across the lifespan.

Thesis statement of originality

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

This thesis has not been submitted for any other degree or purposes.

Briana Lees
1 February 2021

Author attribution statement

The work contained in the body of this thesis, except otherwise acknowledged, is the result of my own investigations. I am the first and corresponding author of each publication. Citations are provided on page xi.

Study 1 / **Chapter 2** is published in *Neuropsychology Review*. The authors are Briana Lees (BL), Louise Mewton (LM), Lexine A. Stapinski (LAS), Lindsay M. Squeglia (LMS), Caroline D. Rae, and Maree Teesson (MT). BL conceptualized the study with assistance from LM, LAS, and MT. BL and LM completed the screening process. BL conducted the narrative synthesis, meta-analysis, and quality assessment and wrote the manuscript draft. All authors critically revised the manuscript and approved the final version.

Study 2 / **Chapter 3** is published in *Addictive Behaviors.* The authors are BL, LAS, Katrina Prior (KP), Matthew Sunderland, Nicola Newton (NN), Andrew Baillie (AB), MT, and LM. BL, LAS, MT, and LM conceptualized the study. BL and KP acquired the data. BL conducted the analysis and wrote the manuscript draft. All authors critically revised the manuscript and approved the final version.

Study 3 / **Chapter 4** is published in *Drug & Alcohol Dependence*. The authors are BL, LAS, MT, LMS, Joanna Jacobus (JJ), and LM. BL and LM conceptualized the study. BL acquired the data, conducted the analysis, interpreted the results, and wrote the manuscript draft. All authors critically revised the manuscript and approved the final version.

Study 4 / **Chapter 5** is published in the *American Journal of Psychiatry*. The authors are BL, LM, JJ, Emilio A. Valadez, LAS, MT, Susan F. Tapert, and LMS. BL conceptualized the study with assistance from LMS, LM, LAS, and MT. BL acquired the data, conducted the analysis, interpreted the results, and wrote the manuscript draft. All authors critically revised the manuscript and approved the final version.

Study 5 / **Chapter 6** is published in *Drug & Alcohol Dependence.* The authors are BL, LM, LAS, MT, and LMS. BL and LMS conceptualized the study. BL acquired the data, conducted the analysis, interpreted the results, and wrote the manuscript draft. All authors critically revised the manuscript and approved the final version.

Study 6 / **Chapter 7** is being prepared for submission to *Addiction*. The authors are BL, LM, KP, NN, AB, MT, and LAS. BL and LAS conceptualized the study. BL and KP acquired the data. BL conducted the analysis and wrote the manuscript draft. All co-authors have critically revised the manuscript draft in preparation for submission.

Author attribution statement (cont.)

In addition to the work contained in the body of this thesis, relevant publications from during my candidature have been included as appendices. I am the first author on four of the five publications and the corresponding author on three. Where I am not the corresponding author, permission to include these items in the appendices has been granted by the corresponding authors.

Briana Lees
1 February 2021

As supervisors for the candidate upon which this thesis is based, we can confirm that the author attribution statement above is correct.

Louise Mewton **Maree Teesson** **Lexine A. Stapinski**
1 February 2021

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List of abbreviations

ABCD	Adolescent Brain Cognitive Development (Study)
ACC	Anterior cingulate cortex
ADHD	Attention deficit hyperactivity disorder
aOR	Adjusted odds ratio
AUD	Alcohol use disorder
AUDIT	Alcohol Use Disorders Identification Test
BAC	Blood alcohol concentration
BAS	Behavioral Avoidance Scale
BF	Bayes factor
BIS	Behavioral Inhibition Scale
BOLD	Blood-oxygen-level-dependent
CBCL	Child Behavior Checklist
CFA	Confirmatory factor analysis
CFI	Comparative Fit Index
CI	Confidence interval
DASS	Depression and Anxiety Stress Scale
DMQ-R	Drinking Motives Questionnaire-Revised
DSM-5	Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
DTI	Diffusion tensor imaging
DUI	Driving under the influence
EEG	Electroencephalography
EF	Executive functioning
ERP	Event-related potentials
FASD	Fetal alcohol spectrum disorder
FDR	False discovery rate
FHD	Family history density
FHN	Family history negative
FHP	Family history positive
FIML	Full information maximum likelihood
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GAD	Generalized Anxiety Disorder (Questionnaire)
GRADE	Grades of Recommendation, Assessment, Development, and Evaluation
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th revision
K-SADS	Schedule for Affective Disorders and Schizophrenia for School-Age Children

List of abbreviations (cont.)

LMS	Latent moderated structural equation model
LMMS	Latent mediated moderation structural equation model
MAR	Missing at random
MEG	Magnetoencephalography
Mini-SPIN	Mini-Social Phobia Inventory
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NCANDA	National Consortium on Alcohol and Neurodevelopment in Adolescence
NHMRC	National Health and Medical Research Council
NIH	National Institutes of Health
PAE	Prenatal alcohol exposure
PFC	Prefrontal cortex
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PTSD	Post-traumatic stress disorder
RMSEA	Root mean square error of approximation
RT	Reaction time
SPS-6	Social Phobia Scale-Short Form
SIAS-6	Social Interaction Anxiety Scale-Short Form
SRMR	Standardized root mean square residual
SUD	Substance use disorder
TLFB	Timeline follow-back
TLI	Tucker–Lewis Index
UK	United Kingdom
UPPS-P	Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form
US	United States
WCST	Wisconsin Card Sorting Test

Publications associated with this thesis

Lees, B., Mewton, L., Stapinski, L., Squeglia, L. M., Rae, C., & Teesson, M. (2018). Binge drinking in young people: Protocol for a systematic review of neuropsychological, neurophysiological and neuroimaging studies. *BMJ Open, 8*, e023629.

Lees, B., Mewton, L., Stapinski, L., Squeglia, L. M., Rae, C.D., & Teesson, M. (2019). Neurobiological and cognitive profile of young binge drinkers: A systematic review and meta-analysis. *Neuropsychology Review, 29*(3), 357–385.

Lees, B., Stapinski, L. A., Prior, K., Sunderland, M., Newton, N., Baillie, A., Teesson, M., & Mewton, L. (2020). Exploring the complex inter-relations between internalizing symptoms, executive functioning and alcohol use in young adults. *Addictive Behaviors, 106*, 106351.

Lees, B., Stapinski, L. A., Teesson, M., Squeglia, L. M., Jacobus, J., & Mewton, L. (2021). Problems experienced by children from families with histories of substance misuse: An ABCD Study. *Drug & Alcohol Dependence, 218*, 108403.

Lees, B., Mewton, L., Jacobus, J., Valadez, E. A, Stapinski, L. A., Teesson, M., Tapert, S. F., & Squeglia, L.M. (2020). Association of prenatal alcohol exposure with psychological, behavioral, and neurodevelopmental outcomes in children from the Adolescent Brain Cognitive Development Study. *American Journal of Psychiatry, 177*(11), 1060–1072.

Lees, B., Mewton, L., Stapinski, L. A., Teesson, M., & Squeglia, L. M. (2020). Association of prenatal alcohol exposure with preadolescent alcohol sipping in the ABCD Study. *Drug & Alcohol Dependence, 214*, 108187.

Lees, B., Mewton L., Prior, K., Newton, N. C., Baillie, A. J., Teesson, M., & Stapinski, L. A. (in preparation). Binge drinking trajectories and executive functioning performance among young adults: A longitudinal investigation.

Additional publications during candidature

Snijder, M., Stapinski, L., **Lees, B**., Newton, N., Champion, K., Chapman, C., Ward, J., & Teesson, M. (2018). Substance use prevention programs for Indigenous adolescents in the United States of America, Canada, Australia and New Zealand: Protocol for a systematic review. *JMIR Research Protocols*, *7*(2), e38.

Snijder, M., **Lees, B**., Stearne, A., Ward, J., Newton, N., & Stapinski, L. (2019). Risk and protective factors of substance use and related harms among Aboriginal and Torres Strait Islander people: Protocol for a systematic review. *BMJ Open*, *9*, e024418.

Stapinski, L. A., Prior, K., Newton, N. C., Deady, M., Kelly, E., **Lees, B**., Teesson, M., & Baillie, A. J. (2019). Protocol for the *Inroads* study: A randomised controlled trial of an online, cognitive behavioural therapy-based early intervention to reduce anxiety and hazardous alcohol use among young people. *JMIR Research Protocols*, *8*(4), e12370.

Aguinaldo, L., Squeglia, L. M., Gray, K., Coronado, C., **Lees, B**., Tomko, R. L., & Jacobus, J. (2019). Behavioral treatments for adolescent cannabis use disorder: A rationale for cognitive retraining. *Current Addiction Reports, 6*(4), 437–442.

Lees, B., Mewton, L., Stapinski, L. A., & Teesson, M. (2020). Binging, boozing, and the teenage brain. *Frontiers for Young Minds, 8*, 1–8.

Lees, B., Meredith, L. R., Kirkland, A. E., Bryant, B. E., & Squeglia, L. M. (2020). Effect of alcohol use on the adolescent brain and behavior. *Pharmacology, Biochemistry & Behavior*, *192*, 172906. Invited review.

Lees, B., Aguinaldo, L., Squeglia, L. M., Infante, M. A., Wade, N. E., Hernandez Meija, M., & Jacobus, J. (2020). Parental family history of alcohol use disorder and neural correlates of response inhibition in children from the Adolescent Brain Cognitive Development (ABCD) Study. *Alcoholism: Clinical & Experimental Research, 44*(6), 1234–1244.

Lees, B., Squeglia, L. M., McTeague, L. M., Forbes, M. K., Krueger, R. F., Sunderland, M., Baillie, A. J., Koch, F., Teesson, M., & Mewton, L. (2020). Altered neurocognitive functional connectivity and activation patterns underlie psychopathology in preadolescence. *Biological Psychiatry: Cognitive Neuroscience & Neuroimaging*. Advance online publication.

Additional publications during candidature (cont.)

Lees, B., Squeglia, L. M., Breslin, F. J., Thompson, W. K., & Paulus, M. P. (2020). Screen media activity does not displace other recreational activities among 9–10 year-old youth: A cross-sectional ABCD Study. *BMC Public Health, 20*, 1783.

Mewton, L., **Lees, B**., & Rao, R. T. (2020). Lifetime perspective on alcohol and brain health. *BMJ, 371*, m4691.

Snijder, M., Stapinski, L., **Lees, B**., Ward, J., Conrod, P., Mushquash, C., Belone, L., Champion, K., Chapman, C., Teesson, M., & Newton, N. (2020). Preventing substance use among Indigenous adolescents in the United States of America, Canada, Australia and New Zealand: A systematic review of the literature. *Prevention Science*, *21*(1), 65–85.

Mewton, L., Hodge, A., Gates, N., Visontay, R., **Lees, B**., & Teesson, M. (2020). A randomized double-blind trial of cognitive training for the prevention of psychopathology in at-risk youth. *Behaviour Research & Therapy*, *132*, 103672.

Debenham, J., Newton, N., Birrell, L., Yücel, M., **Lees, B**., & Champion, K. (2020). Cannabis and illicit drug use during neurodevelopment and the associated structural, functional and cognitive outcomes: Protocol for a systematic review. *JMIR Research Protocols, 9*(7), e18349.

Snijder, M., **Lees, B**., Stearne, A., Ward, J., Garlick Bock, S., Newton, N., & Stapinski, L. A. (2021). An ecological model of drug and alcohol use and related harms among Aboriginal and Torres Strait Islander Australians: A systematic review of the literature. *Preventative Medicine Reports, 21*, 101277.

Lees, B., Garcia, A., Debenham, J., Kirkland, A. E., Bryant, B. E., Mewton, L., & Squeglia, L. M. (under review; 6 July 2020). Promising vulnerability markers of substance use and misuse: A review of neurobehavioral studies. *Neuropharmacology*. Invited review.

Lees, B., Elliott, E. J., Allsop, S., Thomas, S., Riches, J., Nepal, S., Rice, L., Newton, N. C., Mewton, L., Teesson, M., & Stapinski, L. A. (under review; 2 October 2020). Fetal alcohol spectrum disorder resources for educators working within primary school settings: A scoping review protocol. *BMJ Open*.

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Mewton, L., **Lees, B**., Squeglia, L. M., Forbes, M. K., Sunderland, M., Krueger, R., Koch, F., Baillie, A., Slade, T., Hoy, N., & Teesson, M. (under review; 20 November 2020). The relationship between brain structure and general psychopathology in preadolescents. *Journal of Child Psychology & Psychiatry*.

Debenham, J., Birrell, L., Champion, K., **Lees, B**., Yücel, M., & Newton, N. C. (under review; 25 November 2020). Examining neuropsychological and neurophysiological predictors and consequences of cannabis and illicit drug use during neurodevelopment: A systematic review of longitudinal studies in young people. *The Lancet Child & Adolescent Health.*

Snijder, M., Stapinski, L., Ward, J., **Lees, B**., Chapman, C., Champion, K., Doyle, M., Watson, I., Sarra, R., Lear, A., Garlick Bock, S., Teesson, M., & Newton, N. (under review; 19 January 2021). Strong and Deadly Futures: Co-development of a web-based wellbeing and substance use prevention program for Aboriginal and Torres Strait Islander and non-Aboriginal adolescents. *International Journal of Environmental Research & Public Health.*

Presentations arising from this thesis

Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2018, November). Binge drinking is associated with cognitive and neural differences in youth: Evidence from a systematic review and meta-analysis. Oral presentation. Presented at the *Australasian Professional Society on Alcohol and Other Drugs Conference*, Auckland.

Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2018, November). Binge drinking and the developing brain. Oral presentation. Presented at the *Society for Mental Health Research*, Noosa.

Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2018, November). Binge drinking and the teenage brain: Evidence from a systematic review and meta-analysis of neural and cognitive dysfunction. Poster presented at the *Australasian Cognitive Neuroscience Society Conference*, Melbourne.

Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2019, February). The cause–effect relationship of binge drinking and neural and cognitive dysfunction. Poster presented at the *International Neuropsychological Society Conference*, New York.

Lees, B., Squeglia, L. M., Mewton, L., Jacobus, J., Stapinski, L. A., Valadez, E., Tapert, S. F., & Teesson, M. (2019, November). The risk of prenatal alcohol use on the developing brain. Oral presentation. Presented at the *Society for Mental Health Research Conference*, Melbourne.

Lees, B. (2020, May). The Adolescent Brain Cognitive Development (ABCD) Study: Results from an international collaboration. Presented at *The Matilda Centre for Research in Mental Health and Substance Use*. Sydney.

Lees, B., Mewton, L., Stapinski, L. A., Teesson, M., & Squeglia, L.M. (2020, November). Prenatal alcohol exposure and early alcohol use experimentation. Presented at the *Australasian Professional Society on Alcohol and Other Drugs Early Career Researchers Conference*. Sydney.

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Lees, B., Snijder, M., Bradd, D., Stapinski, L. A., Ward, J., Newton, N., Champion, K., Chapman, C., & Teesson, M. (2018, October). Combining evidence, photos and stories to inform culturally appropriate drug prevention for Indigenous youth. Oral presentation. Presented at the *Global Evidence and Implementation Summit*, Melbourne.

Lees, B., Snijder, M., Stapinski, L. A., Ward, J., Newton, N., Champion, K., Chapman, C., & Teesson, M. (2018, October). Do alcohol and other drug prevention programs work for Indigenous youth? A systematic review. Poster presented at the *Global Evidence and Implementation Summit*, Melbourne.

Lees, B., Snijder, M., Bradd, D., Stapinski, L. A, Ward, J., Newton, N., Champion, K., Chapman, C., & Teesson, M. (2018, October). Promoting Positive Choices for Aboriginal and Torres Strait Islander youth. Poster presented at the *Society for Mental Health Research*, Noosa.

Lees, B., Snijder, M., Bradd, D., Stapinski, L. A, Ward, J., Newton, N., Champion, K., Chapman, C., & Teesson, M. (2018, November). Combining evidence, photos and stories to inform culturally appropriate drug prevention for Indigenous youth. Invited presentation at the *Alliance for the Prevention of Mental Disorders Conference*, Noosa.

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Lees, B., Lawler, S., Debenham, J., & McFadden, D. (2019). Write-well bootcamp. *University of Sydney*. $1,200.

Stapinski, L. A., Newton, N., Snijder, M., Doyle, M., Champion, K., & Chapman, C. (*Chief Investigators*). Conigrave, K., Wilson, S., Lee, K., **Lees, B**., Ward, J., Slade, T., & Teesson, M. (*Associate Investigators*). (2019–2023). Strong and Deadly Futures: A cluster randomised controlled trial of a computerised school-based alcohol and drug prevention program for Aboriginal and Torres Strait Islander students. *NHMRC*. $1,900,000.

Newton, N., Debenham, J., Lawler, S., **Lees, B**., Stapinski, L. A., Birrell, L., & Teesson, M. (2019). Neuroscience animations: Drug information from inside the brain. *NSW Health*. $55,949.

Prior, K., Stapinski, L., Wiers, R., Mahoney, A., Curtis, J., Salemink, E., Teachman, B., Newton, N., Teesson, M., Baillie, A., Deady, M., McLellan, L., Mewton, L., & **Lees, B**. (2019). Anxiety and alcohol use during the transition to young adulthood: Can we re-train the brain? *University of Sydney*. $10,000.

Stapinski, L. A, **Lees, B**., Nepal, N., Newton, N., Mewton, L., Elliot, E., Allsop, S., Thomas, S., Rice, L., & Teesson, M. (2020–2022). Understanding FASD in schools: Capacity building for educators. *Australian Government Department of Health*. $600,000.

Awards arising from this thesis

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Lees, B. (2018). Early and Mid-Career Travel Award (First Place). *Society for Mental Health Research*.

Lees, B. (2019). Three Minute Thesis Competition (First Place). *Sydney Medical School at The University of Sydney*.

Lees, B. (2019). Three Minute Thesis Competition (Finalist). *Faculty of Medicine and Health at The University of Sydney*.

Lees, B. (2020). Best Research Paper in Basic Science by a PhD Student (First Place). *Society for Mental Health Research*.

Media coverage arising from this thesis

Study 4 reported in **Chapter 5** (Lees et al., 2020; *American Journal of Psychiatry*) received print and online media coverage, with an estimated total reach of over 20 million people worldwide. Internationally, news articles reporting on this publication appeared in 55 outlets in the following countries: Australia, Brazil, Canada, China, Ghana, India, Indonesia, Nigeria, Pakistan, Portugal, Spain, Uganda, United Kingdom (UK), United States (US), and Venezuela. Highlights include *Forbes* (US), *Sydney Morning Herald* (Australia), *Daily Mail* (UK), and *MSN* (UK).

The implications of **Study 1** (**Chapter 2**) and **Study 4** (**Chapter 5**) were considered in an editorial on alcohol use and brain health (Mewton, Lees, & Rao, 2020; *BMJ,* available in **Appendix E**). The editorial received print, online, radio, and television coverage, with an estimated total reach of over 20 million people worldwide. Internationally, news articles reporting on this publication appeared in 115 outlets in the following countries: Argentina, Australia, South Korea, UK, and US. Highlights include *Channel Nine News* (Australia), *ABC Health Report* (Australia), *Daily Mail* (UK), and *Huffington Post* (UK).

Public impact of this thesis

Study 4 reported in **Chapter 5** (Lees et al., 2020; *American Journal of Psychiatry*) provides clear, robust evidence for the first time that there is no completely safe level of alcohol consumption during pregnancy to avoid risk of harm to offspring. These findings have resulted in real-world public impact.

Policy-based impact. The findings were supported by experts involved in the drafting of the NHMRC *Australian Guidelines to Reduce Health Risks from Drinking Alcohol* (Professor K. Conigrave, personal communication, 22 September 2020). Guideline three, updated in late 2020, now states "to reduce the risk of harm to their unborn child, women who are pregnant or planning a pregnancy should not drink alcohol." The guidelines inform the public about health risks and provide recommendations to reduce risks to a low level.

Education-based impact. The findings have also informed a statewide alcohol and pregnancy campaign by the Government of Western Australia. The *One Drink* campaign aims to increase the proportion of the Western Australian community who are aware that there is no safe amount or stage during pregnancy to consume alcohol. The campaign involves statewide television commercials supported by cinema, radio, out-of-home advertising, digital, and social advertising. The campaign will run from January 2021 to May 2022.

Following the study findings, a $600,000 federal funding grant was secured to develop an information portal on the effects of alcohol use in pregnancy. This portal aims to disseminate the study findings to >80% of parents and educators across Australia. The portal will be live in late 2021/early 2022.

Service-based impact. The Royal Australian College of General Practitioners (>40,000 members) provided a statement on the findings: "[this is] a reminder for practitioners to be proactive in starting the conversation about alcohol in pregnancy, even before a woman is expecting" (Lewin, 2020). This has large potential to influence practitioners' advice for pregnant clients across Australia.

Chapter 1

General introduction

Preface

The transition between childhood and adulthood involves major biological, psychological, and social role changes that allow a young person to develop the capabilities for realizing their full potential and achieving healthy and fulfilling lives (Sawyer et al., 2018). This transitional age period can be a vulnerable time, often marked by increased risk-taking and the initiation of health risk behaviors. For instance, alcohol use initiation commonly occurs during this transitional period. Binge drinking (i.e., ≥4 [females] or ≥5 [males] standard drinks in a sitting; Substance Abuse and Mental Health Services Administration, 2016) is highly prevalent among young people and can lead to acute health harms, engagement with other high-risk behaviors, and heightened probability of developing an alcohol use disorder (AUD) (Addolorato et al., 2018; Chung et al., 2018; Heron et al., 2012). Explicating the precursory risks and consequential harms associated with binge drinking in young people can ultimately inform prevention and early intervention initiatives, as well as policies aimed at reducing the prevalence of alcohol-related harms.

The life course approach recognizes the central biological and psychological pathways that influence behavioral choices, such as binge drinking (Jacob et al., 2017). Rapid neural developments occur between the ages of 10 and 24 years, which means young people are particularly receptive to experimenting with alcohol and are more sensitive to alcohol-related neurotoxic harms (Spear, 2018). The risk of binge drinking is also greater in the presence of symptoms of psychopathology, which often first manifest during this period and may be related to, or exacerbated by, neurobiological and cognitive aberrations

(Castillo-Carniglia et al., 2019; Grant et al., 2015; Ning et al., 2020). Additionally, the life course approach appreciates the multigenerational risks associated with familial influence and the shaping of the wider social, economic, and cultural environment (Jacob et al., 2017). Importantly, complex and dynamic interactions exist between neurobiology, cognition, psychopathology, and broader familial and environmental influences. However, most research examining the precursory risks and consequential harms of binge drinking does not consider this constellation of factors together, resulting in significant knowledge gaps.

Four major gaps in the evidence base have been identified. First, the neurobiological and cognitive precursory risk and consequential harm profiles associated with binge drinking in young people remain poorly described. Second, the interactions in young people between psychopathology, cognition, and alcohol use—especially for internalizing psychopathology and higher-order executive functions—remain unclear. Third, the added impact of familial alcohol use behaviors on the likelihood of young people presenting with established precursory risk factors for binge drinking has been insufficiently researched. Specifically, studies of young people with familial alcohol use problems and low- to moderate-level prenatal alcohol exposure (PAE) are scarce and riddled with methodological concerns. Fourth, the recoverability from neurobiological and cognitive harms following binge drinking in young people is virtually unknown. Methodological limitations exist in the small literature on these research topics, and include inadequate consideration and adjustment for broader familial and environmental confounding factors, small sample sizes that are underpowered to detect small-to-moderate effects, and questions about causality and directionality in cross-sectional studies.

To address these gaps and methodological limitations in the evidence base, multifaceted and developmentally sensitive approaches are required. This thesis was designed to address these limitations and capture the inter-relations between individual-level risks and harms of binge drinking in young people, as well as broader multigenerational and environmental impacts. Here, neurobiological, cognitive, and psychological precursory risks and consequential harms associated with binge drinking in young people are investigated, with broader familial, social, and societal factors considered in the study designs.

Four research questions were formulated that address the gaps identified above and provide an innovative and critical contribution to the area of study in young people:

1. **What are the individual-level precursory risks associated with binge drinking and how do they interact?**

   Chapter 2 reports on the first rigorous systematic review and meta-analysis to explicate the neurobiological and cognitive risks associated with binge drinking. **Chapter 3** reports on the first structural equation modelling study to investigate interactions between internalizing psychopathology, executive functioning (EF) deficits, and alcohol use behaviors.

2. **Does familial alcohol use, including familial alcohol use problems and alcohol use during pregnancy, heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?**

   Chapters 4–6 report on the largest studies to investigate neurobiological, cognitive, psychological, and early alcohol use risk profiles of young people with familial alcohol use problems (**Chapter 4**) and PAE (**Chapter 5**: neurobiological, cognitive, psychological; **Chapter 6**: alcohol use).

3. **What are the neurobiological and cognitive consequential harms associated with binge drinking?**

   Chapter 2 (systematic review and meta-analysis) delineates neurobiological and cognitive harms of binge drinking identified in previous studies. **Chapter 7** reports on the first Australian longitudinal study to examine cognitive harms following binge drinking in young people.

4. **Do neurobiological and cognitive harms recede following reductions in binge drinking frequency?**

   Chapter 2 reviews the evidence base of neurobiological and cognitive recovery and **Chapter 7** presents the first study to examine whether reductions in binge drinking lead to improved higher-order cognitive functioning over the short term.

In the following sections of this first chapter, a literature review is provided on alcohol use patterns among young people and individual-level risks and harms associated with binge drinking; noting gaps in the evidence base. Six novel empirical studies are reported in the subsequent chapters. **Chapters 2–6** have undergone extensive peer review and have been published in high-impact journals. The studies they report involved multidisciplinary, cross-national teams of collaborators from Australia and the United States (US).

1.1 Alcohol use: Prevalence, harms, and burden of disease

1.1.1 Prevalence and hazardous patterns of alcohol use

Alcohol use in the general population is heterogeneous, ranging from low, normative use to heavy, pathological use. Globally, alcohol is the most frequently used substance; 43% of the population aged 15 years or older are current drinkers, defined as those who report any alcohol consumption in the previous year (World Health Organization, 2018). In high-income nations such as Australia, the US, and throughout Europe, higher rates of current drinkers are observed than the global average. In 2019, 77% of individuals in Australia aged ≥14 years and 65% of individuals in the US aged ≥12 years were current drinkers (Australian Institute of Health and Welfare, 2020b; Substance Abuse and Mental Health Services Administration, 2020). Meanwhile, approximately 72% of individuals aged ≥15 years across 30 European countries were current drinkers in 2016 (World Health Organization, 2019).

Alcohol use initiation commonly occurs during adolescence, defined by the World Health Organization as 10–19 years of age (World Health Organization, 2020). The prevalence rates of alcohol use among adolescents in Australia, the US, and across Europe are reported in Table 1.1. These statistics were derived from large observational population studies, including the Australian Secondary Students' Alcohol and Drug Survey in 2017 ($n \approx$ 20,000) (Guerin & White, 2020), the US Monitoring the Future Study in 2019 ($n \approx$ 42,500) (Johnston et al., 2020), and the European School Survey Project on Alcohol and Other Drugs, which collected data from 35 countries in 2019 ($n \approx$ 100,000) (ESPAD Group, 2020). Compared with Australian adolescents, a higher proportion of adolescents in Europe and a lower proportion of adolescents in the US consume any alcohol (Table 1.1). The survey data suggest that 19% (US) to 27% (Australia) of young people aged 13 years were current drinkers and 25% (US) to 47% (Europe) had consumed alcohol in their lifetime. By age 17, approximately 52% (US) to 76% (Australia) of individuals were current drinkers.

While some young people may occasionally experiment with small amounts of alcohol, others drink at levels that are hazardous to their health and to the community. Hazardous adolescent drinking often involves binge episodes that cluster around social events and are separated by periods of abstinence (Chung et al., 2018). Binge drinking is defined as ≥4 or

≥5 standard drinks on a single occasion, for females and males, respectively (Substance Abuse and Mental Health Services Administration, 2016), and is more common among individuals aged 10–24 years (i.e., 'young people' as defined by the World Health Organization, 2020) than any other age group (Australian Institute of Health and Welfare, 2020b; Substance Abuse and Mental Health Services Administration, 2020; World Health Organization, 2019). At age 15, binge drinking was reported by 5% of Australian adolescents in the previous week, 9% of adolescents in the US in the previous fortnight, and 13% of European adolescents in the previous month (Table 1.1). Notably, over the previous 15–20 years there has been a steady decline in the number of adolescents who report any alcohol consumption (ESPAD Group, 2020; Guerin & White, 2020; Johnston et al., 2020). Nonetheless, early alcohol use experimentation and binge drinking are still highly prevalent and remain a major public health concern.

Table 1.1. Prevalence rates of alcohol use among adolescents in Australia, the US, and Europe.

Alcohol use	**Age (years)**	**Australia in 2017 (%)**	**US in 2019 (%)**	**Europe in 2019 (%)**
1 full drink in past month	13	11	8	-
	15	31	18	47
	17	54	29	-
1 full drink in past year	13	27	19	-
	15	55	38	-
	17	76	52	-
1 full drink in lifetime	13	-	25	33
	15	-	43	79
	17	-	59	-
Recent binge drinking[a]	13	1	4	7
	15	5	9	13
	17	13	14	-

[a] Recent binge drinking defined as previous 7 days (Australia), 2 weeks (US), or 4 weeks (Europe). Australian data were derived from Guerin and White (2020); US data from Johnston et al. (2020); and European data from ESPAD Group (2020).

1.1.2 Harms and burden of disease associated with alcohol use

Among young people, early alcohol use experimentation and binge drinking can lead to acute health harms and engagement with other high-risk behaviors (Chung et al., 2018). The risk for many adverse consequences increases with greater quantity of alcohol

consumed and greater frequency of binge drinking episodes (Jackson, 2008). Acute health-related consequences can include alcohol poisoning, alcohol-related black-outs, car fatalities, alcohol-related injuries and assault, and increased risk for sexually transmitted infection (Chung et al., 2018). Of concern, alcohol use (particularly when consumed in binge episodes) has been identified as the leading risk factor for death and disability among young people (Mokdad et al., 2016). Risk behaviors associated with binge drinking include simultaneous use of other licit and illicit substances, driving under the influence (DUI), and unprotected sexual intercourse (Chung et al., 2018). While these acute adverse consequences are not unique to adolescents, young people are at higher risk of certain harms because of their relative inexperience with the effects of alcohol, such as alcohol poisoning, and because they are more likely to consume alcohol in unsupervised environments, frequently fueled by peer influence (Chung et al., 2018).

Adolescent alcohol use is also predictive of future consumption levels and the likelihood of being diagnosed with an AUD, defined as impaired control over alcohol use despite adverse social, occupational, or health consequences (American Psychiatric Association, 2013). For instance, early alcohol use experimentation in a non-religious setting by age 12–13 has been associated with binge drinking two to six years later (Aiken et al., 2018; Donovan & Molina, 2011; Jackson et al., 2015). Approximately 70–90% of individuals who binge drink in adolescence continue to do so into their late 20s (Degenhardt et al., 2013), with adolescent drinking patterns explaining up to 43% of consumption levels more than 30 years later (Pitkänen et al., 2008). Moreover, adolescents aged 13–15 who report any previous year binge drinking are 8.6 times (95% confidence interval [CI] 5.3–14.0) more likely to experience AUD-related symptoms by age 16 (Heron et al., 2012) and 7.7 times (95% CI 2.4–24.5) more likely to experience an AUD by age 19, than non-binge drinking peers (Yuen et al., 2020). Further, individuals who experience an AUD in their lifetime are 7.1 times (95% CI 6.1–8.2) more likely to experience a comorbid substance use disorder (SUD) than individuals without an AUD (Compton et al., 2007). Therefore, early alcohol use experimentation is a risk factor for adolescent binge drinking, which in turn, is strongly predictive of a future AUD diagnosis and related to other SUDs.

It is concerning that adolescent alcohol use patterns foretell future consumption given that alcohol use across the lifespan is one of the 10 leading risk factors for burden of disease in all global comparative risk assessments to date (Shield et al., 2020). Over 40 disease and

injury categories in the World Health Organization's International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), including AUD, alcohol poisoning, and fetal alcohol spectrum disorders (FASD), are fully attributable to alcohol use (World Health Organization, 2016). Additionally, more than 200 ICD-10 codes are partially attributable to alcohol. Disease categories include infectious disease, cardiovascular disease, gastrointestinal disease, cancer, diabetes, dementia, mental disorders, and chronic and acute injuries (Rehm et al., 2017). For all categories, the relationship between alcohol and health outcomes is mostly linear, where increased doses of alcohol are associated with increased harm (Rehm et al., 2017). Notably, the frequency of binge drinking occasions primarily determines the adverse risk and subsequent harm associated with alcohol (Rehm et al., 2017). Together, these data indicate that the specific pattern of binge drinking carries amplified risk of negative health outcomes across the lifespan.

Given that binge drinking can have significant repercussions in terms of acute and chronic health outcomes, engagement with other risk behaviors, and the probability of developing an AUD across the lifespan, it is critical that precursory risk factors for the initial uptake of binge drinking in young people are identified to inform prevention and early intervention efforts.

1.2 Precursory risk factors of binge drinking

Young people are in a sensitive transitional period characterized by major biological developments, which occur alongside psychological and social role changes (Sawyer et al., 2018). From a life course perspective, normative and maladaptive patterns of neurobiological, cognitive, and psychological development are considered key precursory risk factors influencing early binge drinking, further shaped by broader familial alcohol use behaviors and environmental influences (Jacob et al., 2017). All of these factors are dynamic and interactive, yet these complex precursory risk profiles have not been widely examined in empirical studies. This is a critical gap in the evidence base. The following subsections synthesize research on central precursory risk factors of binge drinking in young people (Subsection 1.2.1: neurobiological and cognitive; Subsection 1.2.2: psychological;

Subsection 1.2.3: interactions between these factors), highlighting knowledge gaps and methodological limitations that are later addressed in the empirical chapters of this thesis.

1.2.1 Neurobiological and cognitive precursory risk factors

Rapid neural developments and related cognitive changes occur from around the age of 10 until the early 30s, with adolescence (ages 10–19) and young adulthood (ages 20–24) representing especially sensitive developmental stages (Spear, 2013). The nature of these developments means young people are particularly susceptible to binge drinking and are more sensitive to alcohol-related neurotoxic harms (Spear, 2018). The major neural and cognitive developments that occur in young people, and the dominant neurodevelopmental theories of early alcohol use are described below prior to synthesizing and appraising the current evidence base for neural and cognitive precursory risk factors for binge drinking.

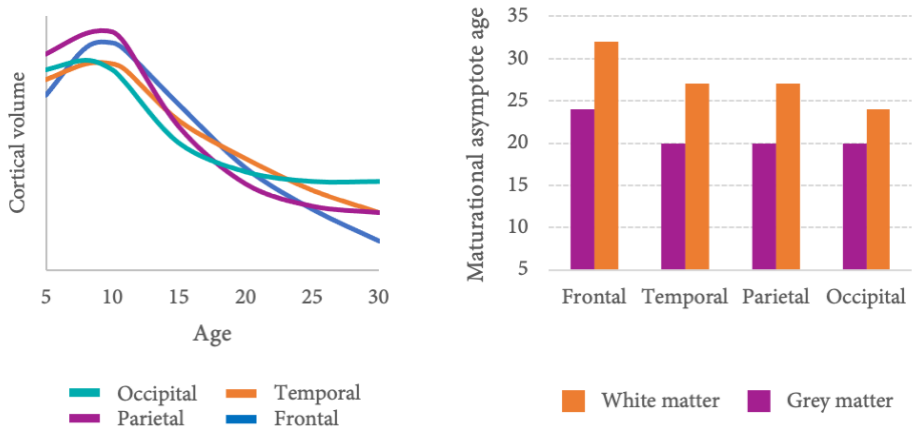
1.2.1.1 Neurodevelopment in young people

Evidence suggests that the brain undergoes three sensitive development periods throughout early life, including during gestation (from conception to birth), early childhood (birth to age 6), and during adolescence and young adulthood (Fuhrmann et al., 2015; Glynn & Sandman, 2011). The brain is already 90% of its total size by the age of 6; however, important developments continue to occur throughout adolescence and into adulthood, reaching a maturational asymptote by the early 30s (Lebel & Beaulieu, 2011; Tamnes et al., 2017). Structural developments include changes in the ratio of gray and white matter volume, which each mature in a time-varying developmental trajectory. Gray matter consists predominantly of neuronal cell bodies, dendrites, synapses, glial cells, and unmyelinated axons (Purves et al., 2017). After structures reach their peak size in preadolescence (8–12 years), marked cortical thinning begins around puberty, reflected by reductions in gray matter volume (Figure 1.1) (Shaw et al., 2008). This process has been described as gray matter undergoing synaptic pruning of superfluous neuronal connections and reductions in glial cells (Shaw et al., 2008; Tamnes et al., 2017). Synaptic pruning is proposed to result in more specialized functional networks and more efficient processing of information (Blakemore, 2008; Giorgio et al., 2010). Cortical thinning reaches a

maturational asymptote in the occipital and parietal lobes by the early 20s, and in the temporal and executive frontal regions by the late 20s (Østby et al., 2009).

Simultaneously, white matter volume and integrity increase over this period in a mostly linear pattern (Lebel & Beaulieu, 2011; Østby et al., 2009). White matter consists of myelin-coated axons and is primarily concentrated in the inner brain (Purves et al., 2017). Myelin increases distributed brain connectivity between distant brain regions, such as cortico–subcortical regions, relative to more local connectivity, like cortico–cortical regions (Baker et al., 2015; Dennis et al., 2013; Fair et al., 2009). These shifts in brain connectivity result in more efficient within-network communication and more integrated between-network communication (Fair et al., 2009). White matter maturation stabilizes later than gray matter maturation; the parietal and occipital lobes reach an asymptote in the mid–late 20s, while white matter in the frontal lobe does not reach maturity until the early 30s (Figure 1.1) (Østby et al., 2009). Further, ontogenic changes in neurotransmitter systems occur, including peaks in dopamine receptors throughout the mesocortical (includes projections from the ventral tegmental area in the midbrain to the dorsal striatum, prefrontal cortex [PFC], thalamus, and parietal regions) and mesolimbic dopamine reward systems (includes projections from the ventral tegmental area to the amygdala, anterior cingulate cortex [ACC], orbitofrontal cortex, and nucleus accumbens), which are fundamental in the neural processing of motivation and rewards (Ernst & Luciana, 2015).

Figure 1.1. Schema illustrating the trajectories of regional cortical volume development and ages of maturational asymptote.



Note. Data from Østby et al. (2009) were used for trajectories of regional cortical volume and data from Tamnes et al. (2010) were used for maturational asymptote age.

Typically, basic sensorimotor and brainstem systems associated with primary functions reach a maturational asymptote first. This is followed by limbic regions important for processing rewards, then frontal regions supporting higher-order cognitive functions (Giedd & Rapoport, 2010; Shaw et al., 2008). Refinements in brain structure and function occur in parallel with the complex integration of cognitive processing and socioemotional regulation. Maturation of affect regulation and higher-order executive functions (i.e., inhibitory control, working memory, mental flexibility; Miyake & Friedman, 2012) continues into the mid-20s and strongly influences risk-taking behaviors such as binge drinking as well as peer affiliation, decision-making, and wellbeing (Crone & Dahl, 2012). Given that young people undergo sensitive neurobiological and cognitive developments, it is important to consider early alcohol use behaviors in the context of ongoing brain maturation.

1.2.1.2 Neurodevelopmental theories of binge drinking

The described sequencing of neural and cognitive developments that occur in young people underpins neurodevelopmental risk-taking theories. These theories suggest that young people, compared with adults, are particularly sensitive to rewarding stimuli and engaging in risk-taking behaviors, such as binge drinking. According to dominant dual systems models that describe the 'imbalance hypothesis', salience of rewarding stimuli results from a developmental imbalance of two neural systems: a rapidly developing dopaminergic mesolimbic system that increases salience and motivation to pursue rewards (i.e., 'socioemotional neural system', including limbic and ventral striatal structures); and a gradually developing self-regulating frontal system that restrains impulses (i.e., 'cognitive control system', including the PFC, lateral parietal regions, and ACC) (Casey et al., 2008; Luna et al., 2015; Steinberg, 2010). During adolescence and young adulthood, the reactivity of the socioemotional neural system is thought to be particularly sensitive and may prevail over controlled responses in emotionally salient environments, such as those where peer influence may have an impact and when there is potential to obtain an immediate reward. While a dominant socioemotional neural system has traditionally been considered a liability for young people, more recently, theorists have proposed that the tendency to approach, explore, and take risks while young may serve an adaptive purpose (Romer et al., 2017; Telzer, 2016). A moderate level of risk-taking may motivate young people to engage

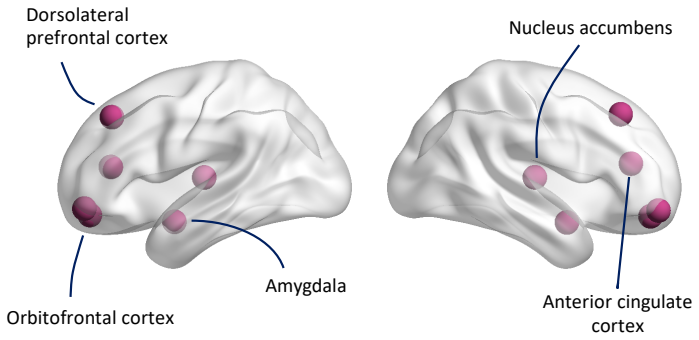
in new experiences and facilitate improved drive, cognition, and resilience toward gaining positive rewards. However, a highly developed and governing socioemotional neural system alongside an especially underdeveloped cognitive control system is thought to contribute to high levels of risk-taking that may have detrimental health consequences (Spear, 2018). In relation to alcohol use behaviors among young people, dual systems models posit that the magnitude of the imbalance between the developing socioemotional and cognitive control systems should predict propensity for engaging in binge drinking (Meisel et al., 2019). Notably, the development of these systems is not biologically deterministic. More recent variants of these models increasingly acknowledge the complexity of neurobiological changes that occur in young people and emphasize the interacting roles of neurobiology and the environmental context in which risk-taking takes place (Shulman et al., 2016). Overall, these theoretical models provide neurobiological and cognitive targets for empirical research to examine whether developmental deviations or delays in socioemotional and cognitive control systems are precursory risk factors of binge drinking in young people.

1.2.1.3 Reviews of neurobiological and cognitive risk factors for binge drinking

Over the previous two decades, a rapidly growing evidence base has emerged on neurobiological and cognitive precursory risk factors for binge drinking in adolescence and young adulthood. Several narrative reviews (e.g., Cservenka & Brumback, 2017; Hermens & Lagopoulos, 2018; Spear, 2018) and two systematic reviews (Carbia et al., 2018; Ewing et al., 2014) synthesize the evidence base. In summary, these reviews concluded that there are several structural (smaller cortical gray and white matter volume, lower white matter integrity), functional (aberrant neural response during EF tasks), and cognitive differences (impairments in attention, EF, memory) associated with binge drinking in adolescence and young adulthood. Aberrant regions are generally consistent with the main predictions of dual systems models, marked in Figure 1.2. However, efforts to synthesize, review, and critically appraise the findings of these often underpowered studies have been inadequate. First, narrative reviews often have low methodological rigor. While this type of review can provide an overview of the evidence base, it frequently lacks explicit criteria for article selection, evades rigorous and diverse search strategies, and provides no critical appraisal of study quality (Pae, 2015). This results in serious methodological shortcomings, such as

subjective selection bias of included studies, which can lead to preferential and sometimes invalid conclusions. Second, previous systematic reviews on neurodevelopment and binge drinking also have methodological limitations. The most significant concern is that they do not aim to disentangle neurobiological and cognitive precursory risk factors of binge drinking (i.e., those present prior to uptake) from the consequential harms following binge drinking. Additional methodological limitations of these systematic reviews include: 1) absence of exclusion criteria for concurrent substance use, such as cannabis and tobacco use, which confounds the specific risks (and harms) associated with binge drinking; 2) inclusion of young people with AUDs who drink despite clinically significant social and physiological consequences and thus likely differ in magnitude of harms from socially functioning binge drinking populations (i.e., Ewing et al., 2014); 3) inclusion of only adolescents aged 10–19 years despite continued brain development into the third decade (i.e., Ewing et al., 2014); and 4) lack of quantitative synthesis of the literature despite this method being the most rigorous form of assessing the magnitude of outcomes across studies with small samples that might otherwise appear to have conflicting findings (Gurevitch et al., 2018). To date, there has also been limited systematic and quantitative synthesis of findings across neuroimaging and cognitive studies. Integration of these data is crucial because the refinement of cognitive processes is interleaved with the maturation of brain structure and function, and together these processes may make an important contribution to binge drinking behaviors in young people (Spear, 2018).

Figure 1.2. Prefrontal, limbic, and ventral striatal structures associated with binge drinking in young people.



To address the identified methodological shortcomings of previous reviews and improve understanding of the neurobiological and cognitive precursory risk factors of binge drinking, **Chapter 2** reports on a rigorous systematic review and meta-analysis of the binge drinking, neurobiology, and cognitive literature. The eligibility criteria and approach used for the review address each of the methodological concerns outlined above. This review has been published in a peer-reviewed journal, *Neuropsychology Review*, and answers the first research question of this thesis: *'What are the individual-level precursory risks associated with binge drinking and how do they interact?'*

1.2.2 Psychological precursory risk factors

In addition to the central role of ongoing brain maturation in early alcohol use behaviors, the risk of binge drinking is also greater in the presence of symptoms of psychopathology and mental disorders, which typically emerge during preadolescence, adolescence, or young adulthood (Castillo-Carniglia et al., 2019; Grant et al., 2015; Ning et al., 2020). Empirically derived developmental frameworks indicate that symptoms of psychopathology and mental disorders can be grouped within two fundamental dimensions, including externalizing and internalizing spectra (as well as somatoform, psychotic, and thought disorder dimensions) (Kotov et al., 2017). Externalizing symptoms include oppositionality, aggression, overactivity, and poor impulse control, with related mental disorders including conduct disorder, oppositional defiant disorder, and attention deficit hyperactivity disorder (ADHD) (Achenbach, 1991; Kotov et al., 2017). Meanwhile, internalizing symptoms include low mood, anxiety, social withdrawal, and fearfulness, with associated mental disorders including anxiety disorders, mood disorders, post-traumatic stress disorder (PTSD), phobias, and eating pathology (Achenbach, 1991; Kotov et al., 2017). These clinical dimensions are thought to map onto personality traits; externalizing with behavioral disinhibition and antagonism, and internalizing with negative affectivity and neuroticism (Kotov et al., 2017).

Adolescents with early externalizing symptoms are thought to have an underlying tendency toward behavioral disinhibition, and as a result, are more likely to perform impulsive and risk-taking activities, such as binge drinking (Kotov et al., 2017). Indeed, an extensive literature demonstrates that early externalizing symptoms and disorders, such as childhood

and adolescent conduct disorder and ADHD, are robust precursory risk factors of binge drinking in adolescence and young adulthood (Bevilacqua et al., 2018; Elkins et al., 2018; Erskine et al., 2016; Howard et al., 2015). In relation to internalizing psychopathology and binge drinking, the 'self-medication hypothesis' posits that individuals use alcohol as a form of tension reduction for internalizing symptoms and disorders (Khantzian, 2003). However, there is inconsistent evidence on whether internalizing disorders in young people increase risk for subsequent binge drinking. A recent systematic review of longitudinal studies focusing on anxiety disorders between the ages of 3 and 24 years, and future alcohol use, binge drinking, and AUD at ages 11–42 provides mixed evidence regarding the relationships between internalizing symptoms and alcohol outcomes (Dyer et al., 2019). In that review, 32 studies reported a positive association (i.e., anxiety disorders were a risk factor), 25 reported null effects, and 17 reported a negative association (i.e., anxiety disorders were a protective factor). Dyer and colleagues, along with authors of a meta-analysis examining prospective AUD risk (Groenman et al., 2017), highlight the need to examine potential moderating and mediating variables to better understand the relationship between internalizing symptoms and alcohol use behaviors, including the role of drinking motives. Inconsistent findings are thought to reflect the fact that some young people use alcohol to cope with internalizing symptoms (i.e., self-medicate) while others have different, and potentially more adaptive, coping strategies (Castillo-Carniglia et al., 2019; Turner et al., 2018). Explanations for which young people will use alcohol as a form of self-medication remain speculative and further research is needed. This thesis explores this research gap in **Chapter 3**, described further in the next subsection.

As previously noted, evidence from the broader field emphasizes the dynamic and interacting nature of neurobiology, cognition, and psychopathology. However, these inter-relations have not been widely studied in regard to the 'self-medication hypothesis' or the risk of binge drinking. To improve understanding of which young people will use alcohol to cope with negative affect, the inter-relations between individual-level factors are considered in the following subsection.

1.2.3 Interactions between precursory risk factors

The 'triple network of psychopathology' model theorizes that aberrant brain function of neurocognitive networks underlie a wide range of psychopathologies, including internalizing and externalizing symptoms and disorders (Menon, 2011). Indeed, this model is supported by recent meta-analyses (McTeague et al., 2017; Sha et al., 2019; Sprooten et al., 2017) and mega-analyses (Lees, Squeglia et al., 2020; Shanmugan et al., 2016; Xia et al., 2018)[1] that have demonstrated underlying functional disorganization of neurocognitive networks among young people with psychopathology. Moreover, neurobiological aberrations have been linked to co-occurring adolescent externalizing psychopathology and alcohol use behaviors in a large-scale study (Castellanos-Ryan et al., 2014). Interestingly, patterns of dysconnectivity associated with externalizing psychopathology tend to manifest earlier in preadolescence and have a more stable time-course (Xia et al., 2018). Meanwhile, the magnitude of functional aberrations associated with internalizing psychopathology shows greater variation in young people and intensifies throughout adolescence and into young adulthood (Xia et al., 2018). Given the relationship between neurobiology and cognition, it can therefore be hypothesized that young people with psychopathology will also exhibit overt cognitive deficits in related domains (i.e., EF), with greater performance variation anticipated among individuals with internalizing compared with externalizing symptoms.

A narrative review of 35 meta-analyses conducted between 2005 and 2015 demonstrates that EF deficits are pervasive across all dimensions of psychopathology (Snyder et al., 2015). Pooled effect sizes across meta-analyses have shown that individuals with externalizing disorders exhibit moderate to large deficits in working memory, inhibition, and mental flexibility, while individuals with internalizing disorders exhibit moderate deficits in these domains (Snyder et al., 2015). Deficits in EF have previously been linked to binge drinking in young people (Carbia et al., 2018). Further, research reveals reasonable heterogeneity in EF ability among young people with internalizing symptoms (Mullin et al., 2020; Sommerfeldt et al., 2016). Individual variability in EF performance among young people

[1] As an aside to this thesis, Lees, Squeglia et al. (2020) examined the relationship between broad dimensions of psychopathology and neural function in 9,074 young people. This peer-reviewed and published paper is provided in Appendix A.

with internalizing psychopathology could provide greater insight into which individuals may turn to alcohol to cope with negative affect.

Theoretical frameworks hypothesize that individuals with high internalizing symptoms and low EF ability are more likely to engage in binge drinking as a result of using alcohol to cope with, and offset, negative affect (Martins et al., 2018; Wiers et al., 2007). This is because individuals with poor EF do not have sufficient cognitive resources to effectively cope with internalizing symptoms in a more adaptive manner. This hypothesis has not been empirically tested despite calls for research into the underlying role of cognition in the relationship between internalizing psychopathology and alcohol use (Sher & Vergés, 2016). To address this gap in the evidence base, **Chapter 3** explores for the first time the inter-relating risks of EF ability and internalizing psychopathology on maladaptive coping mechanisms and binge drinking among young people. This peer-reviewed study, published in *Addictive Behaviors*, improves understanding of the interacting nature of individual-level risk factors associated with binge drinking, thereby addressing the first research question of this thesis.

Overall, Section 1.2 has described the central, individual-level precursory risk factors of binge drinking in young people and outlined how two peer-reviewed and published empirical chapters in this thesis address gaps and methodological limitations in the evidence base. As noted at the beginning of this section, such precursory risk factors of binge drinking are shaped by broader familial alcohol use behaviors. Familial influences that may heighten the probability of a young person presenting with established individual-level risk factors for binge drinking are considered in the next section.

1.3 Influence of familial alcohol use on precursory risk factors

The life course approach acknowledges that the biological and psychological pathways that influence the development of behaviors such as alcohol use can occur across generations (Jacob et al., 2017). Familial alcohol use behaviors can impact a young person through varying mechanisms, including genetic risk, neurobiology, and shared environment (Young-Wolff et al., 2011). Two populations with heightened familial risk of binge drinking include young people with familial history of alcohol use problems (i.e., genetic and

environmental risk) and young people with PAE (i.e., neurobiological, genetic, and environmental risk) (Dodge et al., 2019; Young-Wolff et al., 2011). The neurobiological, cognitive, and psychological risk profiles of these young people remain unclear because of methodological limitations (i.e., evidence base for familial alcohol use problems; Subsection 1.3.1) or a scarcity of empirical studies (i.e., evidence base for low- to moderate-level PAE; Subsection 1.3.2), which are further described below. Determining the risk profile of these populations can assist in prevention and intervention efforts as well as improving understanding of the contributing mechanisms that heighten risk of binge drinking. A broad multigenerational and developmental perspective of adolescent binge drinking has not often been considered in the literature and represents one of the key strengths of this thesis.

1.3.1 Familial alcohol use problems

Familial alcohol use problems are wide ranging and can lead to employment or educational problems, marital troubles, arrests, acute and chronic health harms, and AUD, among other outcomes (American Psychiatric Association, 2013). Twin studies have demonstrated that alcohol use behaviors are strongly influenced by genetic factors, with the heritability of early alcohol use experimentation and initiation estimated as 20–50%, binge drinking as approximately 40%, and AUD as 50–60% (de Moor et al., 2011; Verhulst et al., 2015; Ystrom et al., 2014). A shared environment with a family member with alcohol use problems explains an additional 10% of the risk (Verhulst et al., 2015). Of concern, more than 1 in 10 adults experiences an alcohol or substance use problem in their lifetime (Jones et al., 2020). Equally, 1 in 10 children live with a parent with alcohol use problems (Lipari & Van Horn, 2017) and up to one in four children grow up with a family member with alcohol use problems, including AUD (Grant, 2000). Compared with young people from families with no alcohol use problems, individuals with familial problems are 2.9 times (95% CI 1.7–4.9) more likely to transition into regular alcohol use (Lieb et al., 2002), they report more frequent binge drinking ($d = 0.2$; small effect size) (Elliott et al., 2012), and are 4.4 times (95% CI 3.9–5.0) more likely to develop an AUD themselves (Yoon et al., 2013). For these reasons, substance-naïve young people with familial alcohol use problems have been identified as a vulnerable population for the uptake of binge drinking and prospective AUD (Babor et al., 2017).

Research has examined the neurobiological, cognitive, and psychological risk profiles of young people with familial alcohol use problems to improve understanding of potential mechanisms increasing risk of prospective binge drinking. However, there are several methodological concerns with the evidence base, which are addressed in **Chapter 4** of this thesis. The current state of the literature is described below.

1.3.1.1 Neurobiological aberrations

A relatively large body of evidence has examined the functional neurobiological mechanisms that may be associated with increased risk of binge drinking among young people with familial alcohol use problems.[2] A recent meta-analysis of 22 functional neuroimaging studies, involving 1,092 participants, identified that young people with familial alcohol use problems exhibit greater striatal activation in the putamen during tasks with a motivational or reward component (e.g., monetary incentive) while no differences were observed in the PFC compared with controls (Tervo-Clemmens et al., 2020). The authors concluded that young people with familial alcohol use problems exhibit an exaggerated socioemotional-cognitive control imbalance, which could increase risk of future binge drinking and other risk-taking behaviors.

The evidence regarding structural brain aberrations among young people with familial alcohol use problems is less clear. A narrative review of 12 structural neuroimaging studies identified that this population of young people exhibit lower frontal and amygdala volume and greater cerebellar volume than peers with no familial history of problems (Comstock et al., 2019). However, a critical assessment of these studies exposes a number of methodological concerns. First, 75% of the studies recruited substance-using participants, which does not allow for investigation of pre-existing neurobiological aberrations. Second, several of these structural neuroimaging studies utilized small samples ($n < 50$) that were underpowered to detect small-to-moderate effects (Benegal et al., 2007; Hanson et al., 2010; Hill et al., 2001, 2007). Finally, none of the studies examined cortical area or thickness

[2] As an aside to this thesis, Lees, Aguinaldo, Squeglia et al. (2020) examined neural response to an EF task among 6,898 preadolescents with and without familial alcohol use problems. This peer-reviewed and published paper is provided in Appendix B.

differences among young people with familial alcohol use problems, despite the genetic influence on cortical thickness and area indices being estimated as 81% and 89%, respectively (Panizzon et al., 2009). **Chapter 4** addresses these methodological limitations by examining multiple morphometric indicators (i.e., volume, cortical thickness, area) in over 11,000 substance-naïve preadolescents from the Adolescent Brain Cognitive Development (ABCD) Study, the largest long-term study of brain development and child health in the US, where one in four have grown up with a family member with alcohol use problems.

1.3.1.2 Cognitive aberrations

In terms of cognitive risk indicators, a PubMed literature search identified 15 studies examining individuals with familial alcohol use problems and 10 studies focused on young people (see Appendix **1** Table 1). Studies have reported cognitive deficits in young people with familial alcohol use problems in various neuropsychological domains, including memory (Ozkaragoz et al., 1997), planning (Tarter et al., 1989), problem solving (Hill et al., 2001), verbal and language abilities (Sher et al., 1991; Tapert & Brown, 2000), visuospatial functioning (Hill et al., 2001; Ozkaragoz et al., 1997; Tarter et al., 1989), impulsivity (Henderson et al., 2018; Tarter et al., 1989), attention (Harden & Pihl, 1995; Ozkaragoz et al., 1997; Tapert & Brown, 2000; Tarter et al., 1989), delay discounting/delayed reward gratification (Corral et al., 2003; Herting et al., 2010), and EF (Corral et al., 2003; Harden & Pihl, 1995; Nigg et al., 2004). On the face of it, young people with familial alcohol use problems experience a variety of cognitive deficits not seen in their peers. However, methodological concerns limit the interpretability of these findings. While individuals recruited into these studies did not present with alcohol-related problems or an AUD themselves, many were drinking alcohol and using substances (see **Appendix 1** Table 1). This was not accounted for in statistical analyses and is likely confounding results. Further, studies rarely controlled for, or examined the influence of psychopathology, prenatal alcohol or other substance exposure; or familial history of psychopathology, which may further confound the findings. **Chapter 4** addresses these limitations when examining seven cognitive functioning domains by accounting for relevant confounding factors in the study design.

1.3.1.3 Psychopathology

Several studies have shown that young people with familial alcohol use problems experience greater odds of being diagnosed with externalizing disorders, including conduct disorder, oppositional defiant disorder, and ADHD (Hill et al., 2011; Vidal et al., 2012). Increased odds of anxiety and affective disorders were also reported in two studies (Hill et al., 2008; Hill & Muka, 1996). Again, there are limitations in these studies; primarily, most have not adjusted for confounding factors that could influence the risk of psychopathology in this population, such as comorbid psychopathology in family members, parenting style, environmental stressors, familial relationships, or prenatal exposures. Additionally, potential neurobiological or cognitive mechanisms underlying, or contributing to, these symptoms and disorders are understudied in this population. Interestingly, the meta-analysis by Tervo-Clemmens and colleagues (2020) reveals that functional neural differences in young people with familial alcohol use problems are significantly more common among those with co-occurring externalizing psychopathology, yet links between structural aberrations and psychopathology in young people with familial problems have not been identified. To address limitations in the evidence base, **Chapter 4** explores the impact of numerous variables that may be confounding associations between familial alcohol use problems with psychopathology symptoms and mental disorders. Further, the relationship between psychopathology and neurobiology in young people with familial alcohol use problems is examined.

In summary, there are significant methodological concerns regarding previous studies examining neurobiological, cognitive, and psychological vulnerabilities that may act as precursory risk factors for binge drinking in this population. Addressing all of the limitations outlined above, **Chapter 4** provides a comprehensive risk profile assessment of over 11,000 substance-naïve preadolescents with and without familial alcohol use problems. The analysis explores neurobiological, cognitive, psychological, and early alcohol use risk factors. This empirical study has been published in a peer-reviewed journal, *Drug & Alcohol Dependence*, and answers the second research question of this thesis: *'Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?'*

1.3.2 Prenatal alcohol exposure

The second population of young people with heightened risk of binge drinking are those with PAE. Transfer of familial risk among this cohort is thought to occur via genetic and environmental pathways, as well as from direct neural insults (Reynolds et al., 2011). Internationally, alcohol use during pregnancy is relatively common. A meta-analysis of 328 studies, representing 50 countries, estimates a global prevalence rate of alcohol use during pregnancy of 10% (95% CI 9–11%), with higher rates observed in the United Kingdom (UK) (41%), Australia (36%), and throughout Europe (25%) (Popova et al., 2017). Ethanol, the type of alcohol found in beverages, is a teratogen that crosses the placenta and can cause harm to a developing fetus. Ethanol concentrations are higher and longer lasting in the fetal environment because the enzymes responsible for metabolizing ethanol (i.e., alcohol dehydrogenase, cytochrome P450 2E1, catalase) are not yet active in the fetus during the first 16 weeks following conception, with only low levels of activity observable during the remaining gestational period (Ehrhart et al., 2019; Gupta et al., 2016). The resulting high concentrations of ethanol can cause harm to any organ or system in the developing fetus, with the brain being most vulnerable to sustained damage (Ehrhart et al., 2019; Goodlett et al., 2005).

Depending on the nature and severity of alcohol-related harm to the fetus, various diagnoses under the umbrella term 'FASD' can be given, including fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, fetal alcohol effects, and alcohol-related birth defects (Cook et al., 2016). Recent global estimates suggest 1 of every 13 women who consume alcohol during pregnancy will deliver a child with FASD, equivalent to 7.7 per 1,000 children from the general population (prevalence rates range from 0.0 [Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates] to 111.1 [South Africa] per 1,000 children); Lange, Probst et al., 2017).

The risk profiles of individuals diagnosed with FASD have been extensively explored. In contrast, less is known about the risk profiles of offspring with PAE who do not meet criteria for a FASD diagnosis. The relevant research literature is synthesized below and the knowledge gaps that inform **Chapters 5–6** are outlined.

1.3.2.1 Risk profiles of individuals with fetal alcohol spectrum disorder

A large body of research has examined the risk profiles of individuals with FASD. Critically, the prevalence of binge drinking and alcohol-related problems among individuals with FASD is higher than in the general population (Dodge et al., 2019; McLachlan et al., 2020). Higher rates are observed even when accounting for genetic risk (Yates et al., 1998), which suggests that disparate etiologic mechanisms may be contributing to alcohol use choices among offspring with familial alcohol use problems and FASD. Additionally, a FASD diagnosis is associated with varied deficits, including permanent brain damage, as well as widespread cognitive deficits and externalizing and internalizing psychopathology (Cook et al., 2016; Khoury & Milligan, 2019; Lange, Rovet et al., 2017; Popova et al., 2016; Tsang et al., 2016; Weyrauch et al., 2017). These neural aberrations and associated deficits can increase risk of binge drinking and alcohol-related problems observed among individuals with FASD.

1.3.2.2 Risk profiles of individuals with low- to moderate-level prenatal alcohol exposure

The majority of women who consume alcohol during pregnancy do so at low levels (see Table 1.2 for prenatal alcohol use classification). For example, of the ~40% of Australian women who drink alcohol during pregnancy, 97% consume one or two standard drinks/occasion (Australian Institute of Health and Welfare, 2020a). The risk of delivering a child with FASD is reduced with low or moderate levels, compared with heavy-level consumption or binge drinking (May & Gossage, 2011). However, offspring with low- to moderate-level PAE also appear to have heightened risk of binge drinking and experiencing AUD-related symptoms, when accounting for other substance use, familial alcohol use problems, and life stressors (Alati et al., 2006; Goldschmidt et al., 2019). Given the high prevalence of women consuming low levels of alcohol while pregnant, the elevated risk of offspring binge drinking is of considerable concern at a population level.

Table 1.2. Prenatal alcohol use classification (O'Leary et al., 2010).

		Standard drinks per week	
		<7	**≥7**
Standard drinks per occasion	**1–2**	Low	Heavy
	3–4	Moderate	Heavy
	≥5	Binge	Binge + Heavy

The neurobiological, cognitive, and psychological risk profiles that may be contributing to drinking choices among young offspring with low- to moderate-level PAE is relatively unknown. One narrative review notes a complete absence of structural neuroimaging studies of young people with low- or moderate-level PAE (Donald et al., 2015), while meta-analyses identify six cognitive studies (Flak et al., 2014) and three studies of psychopathology (Tsang et al., 2016). A more recent systematic review of PAE and offspring psychopathology identifies just one additional study reporting on low-level PAE (Easey et al., 2019). Overall, preliminary evidence indicates that low- to moderate-level PAE may be associated with poorer psychological outcomes but not cognitive deficits. These conclusions should be interpreted with caution given the very small evidence base.

Considering the high prevalence of low-level alcohol use during pregnancy in the general population, a better understanding of the risk profiles of young people exposed to this pattern of drinking and the precursory risk factors that may be increasing the likelihood of binge drinking engagement is critical. **Chapter 5** investigates associations between low- to moderate-level alcohol use during pregnancy, and neurobiological (i.e., brain structure and function), cognitive, and psychological outcomes in over 9,700 preadolescents enrolled in the ABCD Study. Utilizing the same cohort, **Chapter 6** examines associations between maternal alcohol use patterns during pregnancy and early alcohol use experimentation in offspring—a known precursory risk factor for adolescent binge drinking. **Chapter 5** has been published in *The American Journal of Psychiatry* and **Chapter 6** has been published in *Drug & Alcohol Dependence*. Both chapters address the second research question of this thesis: *'Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?'*

In summary, Section 1.3 has described two populations where familial alcohol use behaviors heighten a young person's likelihood of engaging in binge drinking. The

individual-level precursory risk profiles that may contribute to alcohol use behaviors among these young populations were unclear (due to methodological limitations and a scarcity of empirical studies) and three published empirical chapters in this thesis were designed to address these knowledge gaps. The following section moves beyond the precursory risk factors of binge drinking described in Sections 1.2 and 1.3 to alcohol-related consequential harms. Given that young people are within a sensitive neurodevelopmental stage, focus has been placed on the neurobiological and cognitive consequential harms of binge drinking.

1.4 Neurobiological and cognitive harms from binge drinking

Normative neurobiological developments in young people increase the likelihood of experiencing neural and cognitive harms from binge drinking (Spear, 2018). Alcohol-induced harms are arguably even more impactful for young people than adults, given that educational and employment attainment, learning, and ongoing neurodevelopment are some of the most important tasks of adolescence. Additionally, neurocircuitry frameworks of addiction posit that alcohol-induced neurobiological and cognitive harms are integral to the transition from occasional binge drinking to AUDs and escalating psychopathology (Koob & Volkow, 2010, 2016). To inform intervention efforts aimed at interrupting the trajectory toward AUD, it is important to identify the specific neurobiological and cognitive consequential harms that can result from binge drinking in young people (Subsection 1.4.1) and the degree of recovery observed following reductions in use (Subsection 1.4.2).

1.4.1 Reviews of neurobiological and cognitive harms from binge drinking

A rapidly growing evidence base has emerged over the past two decades investigating the neurobiological and cognitive harms following alcohol use initiation and binge drinking in young people, as recently synthesized in narrative reviews (Lees, Meredith, Kirkland et al., 2020; Spear, 2018; Squeglia & Gray, 2016). The most recent narrative review includes 28

longitudinal studies (Lees, Meredith, Kirkland et al., 2020).[3] These reviews concluded that a linear relationship exists between the quantity and frequency of alcohol consumed over the follow-up period and the extent of neurobiological and cognitive harms. While differences have been observed between young people who remain abstinent and those who engage in moderate drinking, greater disparities are often observed following binge drinking (Lees, Meredith, Kirkland et al., 2020; Spear, 2018). Studies frequently report accelerated gray matter volume declines and attenuated white matter development of frontal and limbic regions following binge drinking (Lees, Meredith, Kirkland et al., 2020; Spear, 2018; Squeglia & Gray, 2016). These narrative reviews also report developmental declines in gray matter volume throughout the temporal lobes, which are thought to play an important role in learning and memory (Squire et al., 2004; Wixted & Squire, 2011). Related cognitive deficits have been observed, where binge drinking during adolescence has been linked to poorer EF, learning, and memory across follow-up assessments (Lees, Meredith, Kirkland et al., 2020).

Methodological concerns around previous narrative reviews limit the ability to conclude that binge drinking, specifically, can result in neurobiological and cognitive harms among young people. Those reviews had broader primary aims, such as determining the harms associated with any substance use, and thus include studies where participants frequently reported co-occurring cannabis, tobacco, or other substance use. While some studies in these reviews include other substance use as a covariate in statistical models, this approach can only reduce variance related to other substance use, not eliminate the effects. Further, as described in Subsection 1.2.3 '*Interactions between precursory risk factors,*' neurobiological and cognitive differences can underlie psychopathology symptoms and disorders. The eligibility criteria in previous narrative reviews allowed for inclusion of studies where participants had psychopathology symptoms and mental disorders. Therefore, neurobiological and cognitive aberrations related to psychopathology may have been misattributed to alcohol use effects in some of these studies.

To improve understanding of the specific neurobiological and cognitive consequential harms of binge drinking, **Chapter 2** reports on a robust systematic review and meta-

[3] Lees, Meredith, Kirkland et al. (2020) was an invited narrative review by *Pharmacology, Biochemistry & Behavior*. This peer-reviewed and published review is provided in Appendix C.

analysis. To remove the possibility of misattributing other substance use harms or psychopathology-related neural and cognitive aberrations to alcohol, the review excludes studies where participants reported co-occurring substance use or mental disorders. As noted above, this published review also synthesizes the precursory risk factors of binge drinking. Further, it identifies an important research gap, since addressed by the empirical study described in **Chapter 7**. Specifically, there was a dearth of longitudinal studies examining the impact of various binge drinking trajectories (i.e., increased, sustained, or reduced) on EF performance. Therefore, **Chapter 7** reports on the first Australian longitudinal study to examine binge drinking trajectories and EF harms in young adults. Together, these chapters answer the third research question of this thesis: *'What are the neurobiological and cognitive consequential harms associated with binge drinking?'*

1.4.2 Reversal of alcohol-related neurobiological and cognitive harms

Very limited research has examined whether alcohol-related neurobiological and cognitive harms persist or recede following reductions in binge drinking among young people. A recent narrative review identifies just one neuroimaging study examining neural response to alcohol cues following one month of monitored abstinence (Lees, Meredith, Kirkland et al., 2020). Further, a 2018 systematic review identifies four studies assessing cognitive outcomes following total abandonment of binge drinking for one month to two years (Carbia et al., 2018). Overall, preliminary evidence indicates that young people who stop drinking for one month no longer exhibit altered neural response to alcohol cues; however, they show sustained overt deficits in mental flexibility, working memory, and verbal memory that may only begin to resolve over longer periods of abstinence (i.e., two years). In light of the methodological limitations of these reviews that have been previously outlined (i.e., low methodological rigor of narrative reviews, inclusion of studies with concurrent substance use and psychopathology), the systematic review presented in **Chapter 2** also synthesizes studies examining neural and cognitive outcomes following reductions in alcohol use or abstinence.

While early evidence of neural recovery is promising, sustained overt cognitive deficits are a considerable concern given the critical focus on continued educational attainment, learning, pursuit of employment, and broader personal and social role transitions during

this developmental period. Crucial gaps in knowledge remain and must be further examined. Of primary importance is that the impact of reduced binge drinking rather than total abstinence on cognitive outcomes has not yet been explored. From a harm reduction perspective, it is critical that research examines cognitive functioning trajectories associated with positive behavior change (Marlatt et al., 2011). It is particularly important to examine reductions in alcohol use, as only around 8% of young people stop drinking completely, while one in three (35%) current drinkers will reduce their frequency of binge drinking and quantity of alcohol consumed (Australian Institute of Health and Welfare, 2020b). Thus, the abstinence-related cognitive outcomes reported in the literature are less relevant for the majority of the population who will continue to binge drink or consume alcohol at some level. A further gap in the evidence base to date is the focus on very short (i.e., one month) or long term (i.e., two years) abandonment of alcohol use. The cognitive functioning outcomes between these two time-points have not yet been examined. It is crucial that research examines whether cognitive deficits begin to recover prior to the two-year follow-up assessment, given the critical focus on education and learning outcomes in adolescence and young adulthood.

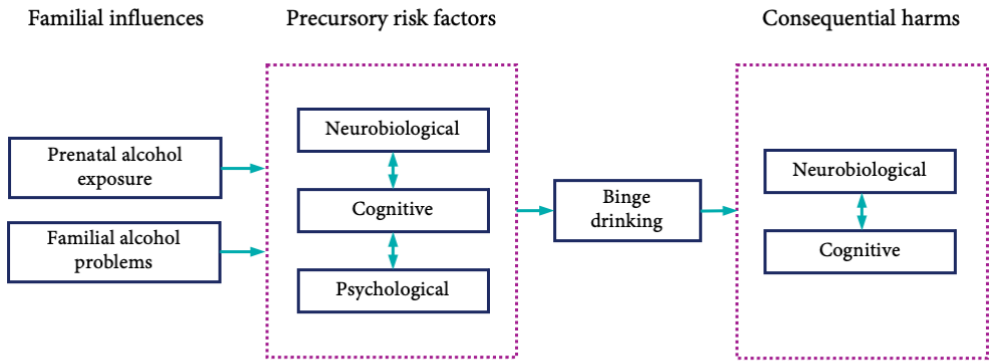
Chapter 7 addresses these gaps in the evidence base by investigating trajectories in binge drinking patterns (i.e., increased/sustained, reduced, no binge drinking) and cognitive task performance over six months following early intervention for alcohol use problems. Along the continuum from prevention through treatment, early intervention initiatives focus on enhancing resilience and interrupting maladaptive trajectories before such behaviors become established and dysfunctional (Guralnick, 2011). Based on the meta-analysis results in **Chapter 2**, focus was placed on EF performance among young people. **Chapters 2** and **7** address the final research question of this thesis: *'Do neurobiological and cognitive harms recede following reductions in binge drinking frequency?'*

1.5 Thesis aims and outline

The overall aim of this thesis is to explicate the precursory risks and consequential harms associated with binge drinking in young people. A developmentally sensitive approach has been undertaken, which considers the inter-relations between individual-level risks and harms of binge drinking, as well as broader multigenerational and environmental impacts.

To achieve this aim, four research questions were formulated to improve understanding of: 1) the neurobiological, cognitive, and psychological precursory risk factors associated with binge drinking in young people; 2) the added risk linked to familial alcohol use behaviors; 3) the neurobiological and cognitive harms following binge drinking; and 4) the impact of early intervention on reducing these harms. Explicating these precursory risks and consequential harms of binge drinking in young people can ultimately inform prevention and early intervention initiatives and policies aimed at reducing the prevalence of alcohol-related harms. Figure 1.3 provides an outline of the research areas covered in this thesis.

Figure 1.3. Logic model of thesis.



The subsequent chapters of this thesis are as follows. **Chapter 2** is the first rigorous systematic review and meta-analysis investigating the neurobiological and cognitive risks and harms associated with binge drinking in young people aged 10–24 years. A total of 58 studies are reviewed.

Chapter 3 explores for the first time the complex inter-relations between EF, internalizing psychopathology, and escalating alcohol use trajectories among 155 young people aged 17–24 years. Cross-sectional data from the Australian *Inroads* randomized control trial (Stapinski et al., 2019) are analyzed using confirmatory factor analysis (CFA) and structural equation models. The *Inroads* trial is the first trial internationally to investigate the impact of an online intervention for alcohol and internalizing psychopathology problems in young people.

Chapters 4–6 present the largest studies internationally to investigate the neurobiological, cognitive, psychological, and early alcohol use risk profiles of preadolescents aged 9–10 years with familial alcohol use problems and low- to moderate-level PAE (n > 9,700). These chapters utilize data from the ABCD Study. Linear mixed models and multilevel cross-sectional and longitudinal mediation models are applied.

Chapter 7 is the first Australian study to examine cognitive harms following binge drinking in young people. It is also the first study internationally to examine whether EF deficits recede following early intervention and reductions in binge drinking frequency over a six-month period. Data from the *Inroads* trial are analyzed using repeated measures mixed model analyses and Bayesian hypothesis testing.

Chapter 8 is the final chapter of this thesis. It synthesizes and interprets the findings of the empirical chapters and collates the evidence pertaining to the four overarching research questions of this thesis. The implications of the thesis findings for practice and policy are then considered from a life course and multigenerational prevention perspective before outlining challenges and suggested future directions for research.

Chapters 2–6 have undergone peer review and have been published in high-impact journals. These chapters are direct replicates of the published journal versions, excluding the chapter prefaces composed specifically for this thesis. Additionally, the referencing style, abbreviations, and language in published chapters have been altered for consistency throughout the thesis (abbreviations are defined the first time a term is used in the thesis and employed thereafter, and UK spelling has been updated to US spelling). The numbering of the appendices has also been modified.

Chapter 2

Neurobiological and cognitive profile of young binge drinkers: A systematic review and meta-analysis

Preface

Previous reviews have concluded that adolescents and young adults who report binge drinking exhibit neurobiological and cognitive differences from non- or low-drinking peers. However, it remains unclear whether such differences are present prior to binge drinking or if they are a consequence of binge drinking. Additionally, the confounding effects of concurrent substance use and mental disorders have not been adequately considered. This chapter reports on a rigorous systematic review and meta-analysis of 58 studies that aimed to differentiate the neurobiological and cognitive precursory risks from the consequential harms of binge drinking during a sensitive neurodevelopmental period. Methodological limitations of previous reviews are addressed.

This chapter addresses the first, third, and fourth research questions of this thesis: '*What are the individual-level precursory risks associated with binge drinking and how do they interact?*'; '*What are the neurobiological and cognitive consequential harms associated with binge drinking?*'; and '*Do neurobiological and cognitive harms recede following reductions in binge drinking frequency?*' This study involved a multidisciplinary international team of collaborators and has been published as Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C. D., & Teesson, M. (2019). *Neuropsychology Review*, *29*(3), 357–385. Supplementary materials are available in **Appendix 2**. The accompanying published protocol paper for the systematic review and meta-analysis is available in **Appendix D**.

2.1 Abstract

This review provides the first systematic and quantitative synthesis of the literature examining the relationship between binge drinking, cognition, brain structure, and function in youth aged 10 to 24 years. PubMed, EMBASE, Medline, PsychINFO, and ProQuest were searched for neuroimaging, neurophysiological, and neuropsychological studies. A total of 58 studies (21 neuroimaging, 16 neurophysiological, 21 neuropsychological) met the eligibility criteria and were included in the review. Overall, abnormal or delayed development of key frontal executive control regions may predispose youth to binge drink. These abnormalities appear to be further exacerbated by the uptake of binge drinking, in addition to alcohol-related neural aberrations in reward-seeking and incentive salience regions, indexed by cognitive deficits and maladaptive alcohol associations. A meta-analysis of neuropsychological correlates identified that binge drinking in youth was associated with a small overall neurocognitive deficit ($g = -0.26$) and specific deficits in decision-making ($g = -1.70$) and inhibition ($g = -0.39$). Using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) evidence profile, the certainty in outcomes ranged from very low to low. Future prospective longitudinal studies should address concomitant factors, exposure thresholds, and age-related vulnerabilities of binge drinking, as well as the degree of recovery following discontinuation of use.

2.2 Introduction

Adolescence (10 to 19 years) and young adulthood (20 to 24 years) are unique transitional periods associated with age-related neural and cognitive changes (Crews et al., 2007; Spear, 2013). Behaviorally, this period is characterized by heightened exploration, risk-taking, sensation seeking, and socialization (Steinberg, 2010). Together, this contributes to a young person's increased propensity to experiment and engage in risk-taking behaviors, including alcohol and other drug use, and consume elevated levels of alcohol relative to that of adults (MacPherson et al., 2010).

Adolescent drinking frequently consists of heavy binges separated by periods of abstinence, as it often clusters around social events (Bräker et al., 2015). Binge drinking is defined as a pattern of alcohol use that brings blood alcohol concentration (BAC) levels to 0.08 g/dL which typically occurs after the consumption of four or more standard alcoholic drinks for females and five or more drinks for males, over a two-hour period (National Institute on Alcohol Abuse and Alcoholism, 2018; Substance Abuse and Mental Health Services Administration, 2016). This episodic pattern of drinking is most common among adolescents in Western countries. For instance, in the US, 4%, 9%, and 14% of 14, 16, and 18 year olds, respectively, reported binge drinking in the previous two weeks (Johnston et al., 2019). Similarly, in Australia, 2%, 9%, and 17% of 14, 16, and 17 year olds reported binge drinking in the previous week (White & Williams, 2016). Across 35 European countries, an average of 35% of secondary school students reported binge drinking in the previous month, with the highest prevalence in Austria, Cyprus, and Denmark, where more than 50% of students reported this drinking pattern (Kraus et al., 2016). The prevalence of binge drinking sharply increases from adolescence to young adulthood, with 38% of 18 to 25 year olds in the US (Substance Abuse and Mental Health Services Administration, 2017), 42% of 18 to 24 year olds in Australia (Australian Institute of Health and Welfare, 2017), and 42% of 16 to 24 year olds in the UK (Office for National Statistics, 2018) reporting binge drinking at least monthly. These statistics are concerning because early alcohol use and binge drinking are associated with a myriad of short- and long-term negative consequences including black-outs, hangovers, and alcohol poisoning (Hermens & Lagopoulos, 2018; Labhart et al., 2018), alcohol and drug use disorders (Dwyer-Lindgren et al., 2018), other mental health problems (Teesson et al., 2010; Welsh et al., 2017), risky sexual behaviors

(Townshend et al., 2014), injuries (Rehm & Shield, 2014), increased risk of violence exposure (Oosterhoff et al., 2016), and suicide (Pompili et al., 2010).

A variety of factors undoubtedly contribute to the elevated levels of alcohol consumption in adolescence and young adulthood, and maturational changes in the brain are likely to play a central role. Subcortical limbic regions that modulate reward, emotion, and impulsive motivations mature during mid-adolescence (14 to 17 years), prior to the development of prefrontal top-down executive control circuits in early adulthood (21 to 24 years) (Shulman et al., 2016). This imbalance in brain region development is thought to create a reward bias which enhances a young person's affinity toward novel and risky activities, including alcohol use (Casey et al., 2008; Steinberg, 2010). There is growing evidence that aberrant neural and cognitive developmental trajectories may cause some adolescents to be at an even greater risk of alcohol initiation (Squeglia & Cservenka, 2017). Furthermore, alcohol use during adolescence and young adulthood also appears to cause gradual attrition of cognitive functions and aberrant neural development trajectories (Spear, 2018). Since binge drinking is the dominant pattern of use among young people, it is critical that we investigate how this pattern of drinking is related to abnormalities in the developing brain and explore the associated negative consequences of binge drinking during a vulnerable developmental period.

The current evidence on the association between binge drinking and neurodevelopment during adolescence and young adulthood has been previously summarized in several narrative reviews (Cservenka & Brumback, 2017; Hermens & Lagopoulos, 2018; Petit, Maurage et al., 2014; Spear, 2018) and two systematic reviews (see Carbia et al., 2018 for neuropsychological studies; see Ewing et al., 2014 for neuroimaging studies). Overall, these reviews have concluded that there were a number of structural (smaller gray and white matter volume, and lower white matter integrity), functional (abnormal activation during EF and verbal encoding tasks, and latency differences during cognitive tasks in P1, N1, P3, P3b, and P450), and cognitive (impairments in attention, EF, and verbal, non-verbal, and spatial working memory) differences associated with binge drinking in youth. However, previous systematic reviews are limited by: 1) the inclusion of concurrent substance use which may confound the specific effects of binge drinking; 2) providing no quantitative synthesis of the literature; 3) not disentangling the antecedents and consequences of binge drinking by synthesizing prospective longitudinal studies; and 4) only including

adolescents aged 10 to 19 years despite continued brain development until the mid-20s (i.e., Ewing et al., 2014). To date, there has also been limited systematic and quantitative synthesis of results across the cognitive and neuroscience fields. We are not aware of any systematic review which has integrated neuroimaging, neurophysiological, and neuropsychological data. Integrating this data is crucial because the refinement of cognitive processes is interleaved with the maturation of neural structure and function, and together these processes make an important contribution to excessive alcohol consumption (Spear, 2018).

The aim of this systematic review is to provide an update on the rapidly expanding neuroimaging, neurophysiological, and neuropsychological literature on binge drinking and neurodevelopment; understand the causal relationship between neural structure and function, cognition, and binge drinking; address limitations of previous systematic reviews; and conduct the first meta-analysis of these studies. By assessing this literature collectively, we will be able to provide a broader understanding of the impact binge drinking has on brain development and behavior. Identifying antecedents of drinking will inform early detection and the development of prevention and early intervention initiatives. While understanding the consequences of binge drinking is crucial for targeted cognitive and physiological treatment efforts.

2.3 Methods

2.3.1 Search strategy and study eligibility

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) and Meta-Analysis of Observational Studies in Epidemiology guidelines. The protocol was registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (registration number: CRD42018086856) and has been previously published (**Appendix D**) (Lees et al., 2018). Search terms were combinations of medical subject headings describing the participants (adolescent, teenager, youth, emerging adult, young adult), the exposure variable (alcohol, binge drinking, ethanol), and the assessment methods measuring the outcomes of interest (neuroimaging, brain imaging, magnetic

resonance imaging [MRI], functional MRI [fMRI], diffusion tensor imaging [DTI], magnetic resonance spectroscopy [MRS], neurophysiological, electroencephalography [EEG], event-related potentials [ERP], neuropsychological, cognitive, verbal working memory tests, episodic memory tests, visuospatial working memory tests, verbal fluency tests, EF tests, digit symbol substitution tests, reaction time, attention). See **Appendix 2** for the search strategy.

Relevant literature from PubMed, EMBASE, Medline, PsychINFO, and ProQuest was systematically searched to identify neuroimaging, neurophysiological, and neuropsychological studies that assessed the impact of binge drinking on neurodevelopment and neuropsychological task performance in adolescents and young adults, where the majority of participants were aged 10 to 24 years at first assessment. Studies were excluded if the majority of participants were significantly involved in substances other than alcohol (i.e., >5 cannabis use per month, >25 lifetime other drug use occasions), or if any participants had been clinically diagnosed with an AUD, or any psychiatric, neurological, or pharmacological condition to ensure that outcomes were specific to binge drinking. Studies were included if participants also met criteria for moderate (for females: 1–3 drinks on any single day and ≤7 drinks per week; for males: 1–4 drinks on any single day and ≤14 drinks per week) or heavy drinking (for females: >3 drinks on any single day and/or >7 drinks per week; for males: >4 drinks on any single day and/or >14 drinks per week) with binges (National Institute on Alcohol Abuse and Alcoholism, 2018). Peer-reviewed cross-sectional and longitudinal neuroimaging, neurophysiological, and neuropsychological studies that provided original data were included. Reviews, reports, and information in books or letters were not included. Further details of the search strategy and selection criteria are available in **Appendix 2** and the published protocol, see **Appendix D** (Lees et al., 2018).

Systematic literature searches were conducted by reviewer one (BL) in April 2018 to assess publications from database inception to April 1, 2018. A snowballing technique was applied where the reference list of identified articles was screened for suitable studies. Reviewer one screened all titles and abstracts from the peer-reviewed databases to determine eligibility for inclusion in the review. Reviewer two (LM) independently screened a random selection of 25% of abstracts to ensure accuracy in the study selection. Inter-rater reliability for abstracts of potentially eligible studies was high (96% agreement), Cohen's kappa

(k = 0.803). Full-text versions of the potentially eligible studies were independently assessed by both reviewers to further determine eligibility for inclusion. Again, there was high inter-rater reliability of studies to be included in the review (87% agreement), k = 0.743. Consultation was held between the reviewers at the time of abstract screening and full-text assessment to reconcile the differences of opinion, and consensus in study selection was reached.

Meta-analyses were only conducted if the available data met established criteria (Muller et al., 2018) that requires all included experiments use the same search coverage (i.e., the same brain coverage, EEG and ERP components, neurocognitive domains) and that there were a sufficient number of studies included in the analysis (i.e., >17–20 experiments) (Eickhoff et al., 2016). There was large heterogeneity in the EEG and ERP components measured for varying neurocognitive domains in neurophysiological studies, and there was insufficient data in neuroimaging structural (9 MRI, 1 DTI, 1 MRS studies) and functional experiments (10 fMRI studies). Therefore, a narrative synthesis was conducted. There was sufficient homogenous data to conduct a meta-analysis for neuropsychological studies (n = 42). Only observational, cross-sectional studies were included in the meta-analysis. Longitudinal studies were not included in the meta-analysis because reliable estimates were indeterminable; there were only six longitudinal studies reporting neuropsychological data, and there was large heterogeneity in length of follow-up (i.e., 1–60 months) and methods of reporting data (i.e., baseline drinking criteria differed; where some studies reported no alcohol use at baseline and binge at follow-up, others reported on continued binge behaviors). However, cross-sectional data (binge drinking *vs.* non-binge drinking participants) from longitudinal studies formed part of the meta-analysis of neuropsychological studies where available. Further details of the meta-analysis methods are provided in **Appendix 2**.

2.3.2 Data extraction

Following the PRISMA guidelines, data on study information, participant characteristics, alcohol characteristics, and study characteristics were extracted into a table (see Table 2.1). The amount of alcohol in standard drinks differed across regions (i.e., US *vs.* Europe) and this was noted during extraction. Standard drinks were converted to US criteria (14 g of

pure alcohol per standard drink) to ensure consistency in reported results. The significant results for all neuroimaging, neurophysiological, and longitudinal neuropsychological studies were extracted into tables and classified according to the study type (see **Appendix 2** Tables 4–6). All data was presented in terms of differences identified in the binge drinking sample compared to the non-binge drinking sample. Meta-analysis data presented in this review and a corresponding data dictionary is available on the Open Science Foundation website (https://osf.io/nx9cv/). To examine the effect of binge drinking on cognitive domains, reviewer one (BL) classified neuropsychological tasks into domains based on established theoretical principles of cognitive function (American Psychiatric Association, 2013; Schneider & McGrew, 2018), following widely known sources (Lezak et al., 2012; Strauss et al., 2006) and previous reviews (Carbia et al., 2018; Scott et al., 2018). These domains were behavioral inhibition in impulsivity tasks, decision-making, delay discounting, expressive language, immediate memory, inhibition, long-term memory, mental flexibility, planning, processing speed, recent memory, receptive language, recognition of emotions, sustained attention, visual perceptual, visuoconstructional, and working memory. Various frameworks exist that categorize these domains into overarching cognitive constructs, such as EF or fluid reasoning (e.g., the Diagnostic and Statistical Manual of Mental Disorders cognitive domains [American Psychiatric Association, 2013], the Cattell–Horn–Carroll taxonomy [Schneider & McGrew, 2018], and the Research Domain Criteria constructs [Cuthbert & Kozak, 2013]). Due to inconsistencies across these frameworks, analyses were only conducted at the domain level. See Table 3 in **Appendix 2** for tests in each cognitive domain.

2.3.3 Statistical analyses

Comprehensive Meta-Analysis Version 3.0 (Borenstein et al., 2014) was used to compute effect sizes for individual studies, domains, and an overall effect for neurocognition, as well as determine the sampling variance of each effect size and the risk of bias. Random-effects models were adopted to account for wide variations in participant characteristics and methodological factors. The standardized mean difference was used as the measure of effect size and the Hedges correction for small sample bias (Hedges' *g*: 0.2 = small, 0.5 = medium, 0.8 = large) was applied (Hedges & Olkin, 1985). Measures where low scores indicated better performance were adjusted so that a negative *g* statistic indicated worse performance

in the binge drinking group. Most studies with neurocognitive behavioral measures reported on multiple cognitive tasks with multiple outcomes, indexing multiple cognitive domains. In cases where a study reported on more than one outcome for a single task indexing a single domain, the summary score was used (e.g., the Iowa Gambling Task net score) or a composite score was calculated (e.g., the 2-dot and 6-dot accuracy scores for the Visual Working Memory Task were averaged to calculate a composite score). In cases where a study used two cognitive tasks for one domain (e.g., the Digit Span Backward and N-Back Tasks, indexing working memory), the tasks were grouped together, and the average effect size was calculated. Finally, for the overall analysis of neurocognition, which included all domains, studies that reported on multiple domains were grouped together, and the average effect size was calculated.

To test for small study effects and the potential of publication bias, a funnel plot and trim and fill analysis were conducted. The funnel plot provided a visual sense of the relationship between effect size and precision (see **Appendix 2** Figure 1). To quantify the amount of bias captured by the funnel plot, Egger's linear regression method was used for each domain (Egger et al., 1997; Sterne et al., 2001). The Duval and Tweedie trim and fill method (Duval & Tweedie, 2000) for random-effects analyses provided an estimate of potential missing effects and yielded an effect size estimate after the bias had been taken into account.

2.3.4 Methodological quality

The methodological quality of the studies was assessed using the GRADE approach (Brozek et al., 2009). In this rating system, observational studies receive a very low quality score and are upgraded only when there are no important threats to validity, there are large magnitudes of effects, a dose response is present, or when all plausible confounding factors are working against the direction of the observed effect (Ryan & Hill, 2016). Factors that reduce the quality of evidence include study limitations (risk of bias), inconsistency of results, indirectness of evidence, and imprecision. Risk of bias for neuroimaging and neurophysiological studies was considered against critical study limitations, including 1) failure to apply appropriate eligibility criteria; 2) utilization of flawed measurement of outcomes; 3) failure to adequately control for confounding variables; and 4) for longitudinal studies, inadequate procedures to follow-up participants (Schünemann et al.,

2013). Risk of bias for neuropsychological studies was measured in the meta-analysis through Egger's linear regression method (Egger et al., 1997; Sterne et al., 2001). Unexplained heterogeneity of results was assessed through examination of variance in point estimates across studies and the *Q*, I^2, *tau*, and tau^2 statistics in the meta-analysis (Schünemann et al., 2013). Directness of evidence is a measure ensuring research directly compares the study populations of interest (i.e., participants aged 10 to 24 years) with the correct dose (i.e., binge drinking) and outcomes of interest (i.e., cognitive, functional or structural measures), and compares these findings to a suitable control (i.e., non-binge drinking participants). Imprecision of results occurs when studies have included relatively few participants, and this leads to wide CIs. Imprecision was assessed using the Optimal Information Size approach, where the total number of participants included in each outcome measure must be larger than the number of participants generated by a conventional sample size calculation for a single adequately powered trial, using G*Power (Faul et al., 2007).

2.4 Results

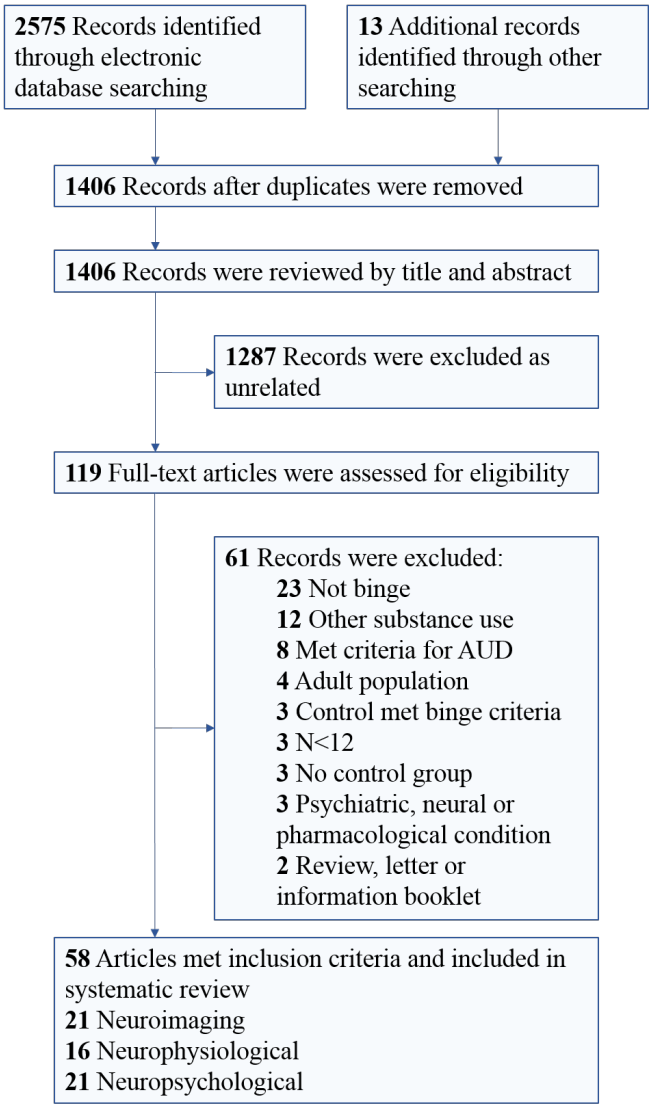
2.4.1 Characteristics of studies

There were 58 eligible studies (Figure 2.1, Table 2.1); 21 neuroimaging studies (12 of which reported neuropsychological data), 16 neurophysiological studies (10 of which reported neuropsychological data), and 21 neuropsychological-only studies. There were seven neuroimaging, six neurophysiological, and six neuropsychological-only longitudinal studies. Of these longitudinal studies, six neuroimaging, one neurophysiological, and three neuropsychological-only studies conducted baseline assessments prior the onset of regular alcohol use or binge drinking.

Studies were published between 2004 and 2018. There was considerable growth in the number of published studies, particularly for neuroimaging and neuropsychological-only studies. For neuroimaging studies, 81% were published after 2012, and 57% have been published since the last systematic review (between 2014 and 2018). Seventy-six per cent of these studies were conducted in the US, 14% were conducted in the UK, 5% were conducted in Belgium, and 5% were conducted in China. For neurophysiological studies, there has

been a steady number of published papers with 50% published between 2009 and 2012, and 50% published between 2013 and 2017. Sixty-three per cent were conducted in Spain, 31% were conducted in Belgium, and 6% were conducted in the US. For neuropsychological-only studies, there was a recent spike in publications with 35% of studies being published in 2016 and 2017. Forty-three per cent were conducted in Spain, 24% were conducted in the UK, 14% were conducted in the US, 5% were conducted in Canada, and 5% were conducted in Korea.

Figure 2.1. PRISMA diagram: Flowchart of searches for studies included in systematic review.



2.4.2 Methodological considerations

Using the GRADE evidence profile, the certainty in outcomes ranged from very low to low (Table 2.2). The majority of studies were observational (98%; 39 cross-sectional studies, 19 prospective cohort longitudinal studies) and one fMRI study was an interventional pre-post design (2%). Twelve outcomes (60%), including behavioral inhibition only, decision-making, delay discounting, expressive language, inhibition, planning, processing speed, recent memory, receptive language, visual perceptual, visuoconstructional, and recognition of emotions received a very low certainty score. There was serious concern of risk of bias for decision-making ($t = 2.57$, $p < .05$), inhibition ($t = 2.50$, $p < .05$), and processing speed ($t = 2.27$, $p < .05$), as measured by Egger's test. There was serious concern of inconsistency of results for decision-making, inhibition, processing speed, and recent memory, where I^2 was between 75 and 100%. Finally, there was serious concern of imprecision in results for behavioral inhibition only, delay discounting, expressive language, planning, receptive language, visual perceptual, visuoconstructional, and recognition of emotions, where the number of participants included in the review was smaller than the required number of participants generated from a sample size calculator for a single adequately powered trial. Eight outcomes (40%), including brain electrical activity, functional neural activity, immediate memory, long-term memory, mental flexibility, neural structure and connectivity, sustained attention, and working memory were upgraded from very low to low because there were no important threats to validity (i.e., risk of bias, inconsistency in results, indirectness of evidence, imprecision of results, publication bias). The indirectness of evidence was not serious for any outcome.

Table 2.1. Overview of study characteristics (n = 58). [1]

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
Neuroimaging: MRI										
Brumback et al., 2016 [L2] (USA)	SU, prenatal SU, premature birth, NI, DSM4 A1, MI, LD, psychotropic medication	-	-	127	13.6	138	13.6	T1: <10 days in life or ≤2 days in week T2: 1+ BD occasion, past yr	24:0 BD occasions, past yr	N/R
Kvamme et al., 2016 (UK)	SU, PD, NI, HI	-	-	18:12	21.3	23:23	21.3	BD occasion weekly for >6 mths	N/R	24 hrs
Lisdahl et al., 2013 (USA)	DSM4 A1, NI, HI, prenatal SU, NC sensory, premature birth, psychotropic medication, MI, SU, LH	-	-	31:15	18.0	35:25	17.7	1+ BD occasion, past 3 mths	2.5:0 PDr	26.7:211.7
Mashhoon et al., 2014 (USA)	DSM4 A1, NI, PD, SU, HI, MI, SU dependence, psychotropic medication, pregnancy	-	-	12:11	22.0	16:15	21.5	3+ BD occasions per mth	11.2:1.7 UPW	6.1:12.1
Pfefferbaum et al., 2016 (USA)	BA	-	-	113	12.0–21.9	674	12.0–21.9	1+ BD occasion, past yr	1-137:0 BD occasions, past yr	N/R
Pfefferbaum et al., 2018 [L1] (USA)	SU	-	-	61:66	15.5	180:176	15.5	T1: ≤3 drinks per occasion (F, M 12–13.9yrs), ≤4 drinks per occasion (M 14–19.9yrs), ≤5 drinks per occasion (M 20yrs+) T2: 1+ BD occasion	9.6:0 BD occasions	N/R

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
Squeglia et al., 2012a (USA)	DSM4 A1, NI, MI, LH, SU, prenatal PD, prenatal SU, premature birth, psychotropic medication	Complex figure, Digits (forward, backward), Color word interference, Towers, Reading score	Immediate memory, inhibition, LT memory, mental flexibility, receptive language, visuoconstructional, WM	15:14	18.2	15:15	18.0	2+ BD occasions, past 3mths	9.3:0.4 PDr	21.0:N/A
Squeglia et al., 2014 [L3] (USA)	T1: SU, DSM4 A1, prenatal SU, NI, MI, psychotropic medication	Letter-number switch, Color word interference, Towers	Inhibition, mental flexibility	12:8	18.0	13:7	17.2	T1: <10 days in life or ≤2 days in week T2: 1+ BD occasion	4.7:0.3	37.1:119.3
Squeglia et al., 2015 [L8] (USA)	DSM4 A1, NI, MI, psychotropic medication, premature birth, prenatal SU, illicit SU, NC sensory, BA, poor English	-	-	45:30	19.6	31:28	17.3	T1: 0 T2: 1+ BD occasion	9.8:0.2 PDr	N/R
Neuroimaging: DTI										
McQueeny et al., 2009 (USA)	NI, PD, AUD, SUD, prenatal SU, psychotropic medication	-	-	12:2	18.1	12:2	18.0	1+ BD occasion, past 3 mths	8.2:0.1 PDr	20.3:513.3
Neuroimaging: MRS										
Silveri et al., 2014 (USA)	HI, BA, psychotropic medication, SU	Trail making, Go/No-Go, Block design, Mental rotation	Inhibition, mental flexibility, processing speed, sustained attention, visual perception, visuoconstructional	10:11	21.9	14:13	21.6	1+ BD occasion	5.0:1.7	5.9:13.1
Neuroimaging: fMRI										
Ames et al., 2014a (USA)	PD, NI, psychotropic medication	Operation span	WM	9:8	20.2	5:14	20.8	8+ (F), 15+ (M) drinks per week,	6.2:3.0	Test day

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
								with 2+ BD occasions per week		
Ames et al., 2014b (USA)	PD, NI, psychotropic medication	Alcohol Go/No-Go	Inhibition, processing speed, sustained attention	10:11	20.2	7:13	20.8	8+ (F), 15+ (M) drinks per week, with 2+ BD occasions per week	6.1:3.0	N/R
Banca et al., 2016 (UK)	PD, NI, HI, SUD, MI	Beads task, Delay discounting	Delay discounting, DM	17:13	22.2	17:13	21.9	1+ BD occasion, past 3mths	13.2:4.8 UPW	24 hrs
Brumback et al.,2015[L4weeks] (USA)	PD, SU, HI, DSM4 A1, NI, MI, prenatal SU, NC sensory, psychoactive medication	-	-	10:12	17.9	9:7	17.4	3+ BD occasions past mth, >100 lifetime drinking occasions	5.7:2.5	N/R
Campanella et al., 2013 (Belgium)	MI, CNS condition, NC sensory, SU, alcohol abstinence	Digits (forward, backward), N-back	Immediate memory, processing speed, sustained attention, WM	7:9	20.9	7:9	21.6	2+ BD occasions per week	6.6:2.6	24 hrs
Maurage et al., 2013 (UK)	AUD history, SU, psychoactive medication, nicotine dependence, MI, CNS condition, NC sensory, high depression-anxiety score	2-alternative forced choice	Recognition of emotion	7:5	24.2	7:5	23.4	3 BD occasions per week, with >2 drinks per hr	7.5:1.4	3 days
Squeglia et al., 2011 (USA)	DSM A1 history, prenatal SU, premature birth, NI, MI, psychotropic medication, DSM4 A1, NC sensory, SU	Complex figure, Block design, Digits (forward, backward), Digit vigilance, Digit symbol, Reading score	Immediate memory, LT memory, processing speed, receptive language, sustained attention, visuoconstructional, WM	27:13	18.0	31:24	17.9	1+ BD occasion, past 3 mths	2.7:0	27.6:226.1
Squeglia et al., 2012b E1 (USA)	Prenatal SU, MI, NI, DSM4 A1, PD history, psychotropic	Visual WM	WM	20	17.6	20	17.6	1+ BD occasion	N/R	N/R

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
	medication, poor English, NC sensory, LH									
Squeglia et al., 2012b E2 [L3] (USA)	T1: SU, prenatal SU, MI, NI, DSM4 A1, PD history, psychotropic medication, poor English, NC sensory, LH	Visual WM	WM	14:7	18.5	14:7	17.7	T1: 0 T2: 1+ BD occasion	6.1:0.3	N/R
Wetherill et al., 2013 [L3] (USA)	PD history, prenatal SU, premature birth, LH, MI, NI, DSM4 A1, psychotropic medication, SU, NC sensory, poor English	Go/No-Go	Inhibition	11:9	18.5	11:9	17.6	1+ BD occasion	4.2:0.2	N/R
Xiao et al., 2013 (China)	NC sensory, NI, PD	Iowa Gambling	DM	8:6	17.3	5:11	17.1	1+ BD occasion, past mth	N/R	N/R
Neurophysiological: MEG										
Correas et al., 2015 (Spain)	MI, NI history, DSM4 A1, DSM A1 history, SUD history, SU, NC sensory, AUDIT >20	-	-	17:18	18.0	21:17	18.0	1+ 0.8%+ BAC occasion, past mth	N/R	24 hrs
Neurophysiological: EEG										
Courtney et al., 2010 (USA)	AUD history, NI, PD, SU, alcohol abstinence, psychotropic medication, MI	-	-	32:32	20.4	16:16	21.1	Low BD: 1+ BD occasion, past 6 mths High BD: 1+ occasion of ≥10 drinks within 2 hrs, past 6 mths	5.7:3.0	N/R

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
López-Caneda et al., 2017a (Spain)	NC sensory, HI, NI, DSM4 AI, SUD history, psychotropic medication, AUDIT >20, SU	-	-	20:20	18.1	21:19	18.1	1+ 0.8%+ BAC occasion, past mth	4.9:0.7	24 hrs
Neurophysiological: ERP										
Crego et al., 2009, 2010 (Spain)[5]	AUDIT >20, SU, NC sensory, NI, DSM A1 history, >90 GSI, 2+ symptoms on SCL-90-R, AUD, alcohol abstinence	Continuous performance	Behavioral inhibition, processing speed, sustained attention	21:21	18.9	27:26	18.7	1+ BD occasion per mth, with >3 drinks per hr	3.6:0.7	12 hrs
Crego et al., 2012 (Spain)	NC sensory, NI, DSM A1 A2, DSM A1 history, SUD history, SU, AUD, LH, AUDIT >20	Visual oddball	Processing speed, sustained attention	17:15	18.8	28:25	18.5	1+ BD occasion per mth, with >3 drinks per hr	3.6:0.7	12 hrs
Folgueira-Ares et al., 2017 [L2] (Spain)	NC sensory, NI, DSM4 A1 A2, DSM4 A1 history, SU besides cannabis, AUDIT >20	Visual face-name association	Recent memory	14:11	20.8	13:12	20.5	1+ BD occasion per mth, with >3 drinks per hr	3.6:1.4	12 hrs
Lannoy et al., 2017 (Belgium)	AUD, AUD history, NI, PD, medication, MI, NC sensory, SU	Speeded Go/No-Go, Balloon analogue risk	DM, inhibition, processing speed, sustained attention	8:12	20.3	7:13	21.2	16+ BD score (drinks per hr; times drunk last 6mths; % of being drunk when drinking)	5.1:3.2	3 days
López-Caneda et al., 2012 [L2] (Spain)	AUD history, SUD, PD history, SU except cannabis, NI, NC sensory, AUDIT >20	Go/No-Go	Inhibition, processing speed, sustained attention	13:10	18.8	11:14	18.6	1+ BD occasion per mth, with >3 drinks per hr, maintain 2 yrs	9.4:1.7 UPW	24 hrs

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
López-Caneda et al., 2013 [L2] (Spain)	NC sensory, NI, DSM4 A1 A2, SU except cannabis, PD history, SUD history, AUDIT >20	Visual oddball	Processing speed, sustained attention	15:11	18.8	15:16	18.5	1+ BD occasion per mth, with >3 drinks per hr, maintain 2 yrs	4.0:1.2	24 hrs
López-Caneda et al., 2014 [L2] (Spain)	NC sensory, NI, DSM4 A1 A2, SU except cannabis, PD history, SU, AUDIT >20	Go/No-Go	Inhibition, processing speed, sustained attention	11:11	18-19	11:14	18-19	1+ BD occasion per mth, with >3 drinks per hr, maintain 2 yrs	14.0:1.0 UPW	24 hrs
López-Caneda et al., 2017b (Spain)	NC sensory, NI, DSM4 A1 A2 history, PD history, SUD history, psychotropic medication, >20 AUDIT, SU except cannabis	Go/No-Go	Inhibition, processing speed, sustained attention	17:19	18.1	20:16	18.1	1+ 0.8%+ BAC occasion, past mth	0.17:0.01 BAC	24 hrs
Maurage et al., 2009 [L9mth] (Belgium)	AUD history, SU, psychotropic medication, high alcohol consumption, BD prior to university, MI, NI, NC sensory, high depression-anxiety score, PD	-	-	7:11	18.2	7:11	18.2	T1: No BD T2: 20 units per week	8.9:0	3 days
Maurage et al., 2012 (Belgium)	AUD history, SU, psychotropic medication, high alcohol consumption, BD prior to university, MI, NI, NC sensory, high depression-anxiety score	Visual oddball	Visual perception	22:18	21.1	11:9	21.6	Low BD: 2+ BD occasions per week, 15–29 units per week High BD: 3+ occasions of ≥10 drinks	8.2:0.79	5 days

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
Petit et al., 2012 (Belgium)	MI, NI, NC sensory, SU, AUD history, high alcohol consumption, BD prior to university, drinking pattern shift during university, psychotropic medication	-	-	12:6	21.3	8:10	21.9	1+ BD occasion	21.7:1.1 UPW	N/R
Petit et al., 2014 [L1] (Belgium)	MI, NI, SU (other than cannabis, tobacco, alcohol), alcohol abstinence	-	-	11:4	22.0	4:11	22.0	Maximum of 3–4 BD occasions per week	7.6:2.4	24 hrs
Neuropsychological										
Carbia et al., 2017a, 2017b[L6] (Spain)	SU except cannabis, tobacco, AUD, NC sensory, NC motor, MI history, AUD history, DSM4 history, >90/2+ symptoms GSI SCL-90-R	Logical memory, self-ordered pointing, RAVLT	Immediate memory, long-term memory, mental flexibility, recent memory, WM	40:39	18.9	36:40	18.6	1+ 0.8%+ BAC occasion, per mth	3.4:1.0	N/R
Gil-Hernandez et al., 2017 (Spain)[3]	SU, NI, AUD, AUD history, PD	Digits (forward, backward), Spatial span (forward, backward), Letter-number, Verbal fluency (phonemic, semantic), Trail making, Stroop	Expressive language, immediate memory, inhibition, mental flexibility, processing speed, WM	78:80	13.8 17.1 19.8	89:75	13.7 16.8 19.7	1+ BD occasion per mth for 6 mths	N/R	24 hrs
Goldstein et al., 2016 E1 (Canada)	NC sensory, PD	Concentration memory	WM	12:19	18.5	9:11	18.5	1+ BD occasion	N/R	N/R
Hartley et al., 2004 (UK)	N/R	Delayed word recall, Delayed line drawing recall, CANTAB	LT memory, mental flexibility, planning, visual perception, WM	9:5	21.5	6:7	20.9	24+ BD score (drinks per hr; times drunk last 6mths; %	18.8:0 UPW	During study

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
		(Delayed match to sample, Spatial WM, IDED, Stockings of Cambridge)						of being drunk when drinking)		
Heffernan et al., 2010 (UK)	SU	Prospective remembering video procedure	LT memory	7:14	18.7	5:24	18.6	2+ BD occasions per week	26.4:4.1 UPW	3.7:6.6
Henges et al., 2012 (USA)	NI, NC sensory	Stop signal reaction	Inhibition, sustained attention	20:20	19.5	26:4	19.6	1+ 0.8%+ BAC occasion	10.3:4.5 PDr	N/R
Johnson et al., 2008 (China)	N/R	Iowa Gambling, Self-ordered pointing	DM, WM	13:9	16.0	90:95	16.2	1+ BD occasion	3-5:0 drinking days	N/R
Jones et al., 2017[L1] (USA)	PD, no family history information, MI, PD history, prenatal SU, SU	Delay discounting	Delay discounting	19:14	14.5	43:40	14.0	3+ BD occasions, past 3 mths	N/R	N/R
Moreno et al., 2012 (Spain)	NC sensory, PD, NI, SU	2-choice, Iowa Gambling, Go/No-Go, Stop	DM, inhibition	10:12	19.5	11:15	20.1	1+ BD occasion per mth	4.4:0	3 days
Morris et al., 2016 (UK)	PD, SUD, MI, psychotropic medication	4-choice serial reaction time, Stop signal	Behavioral inhibition, inhibition	18:14	22.1	36:28	23.1	1+ BD occasion per week, past 3 mths	15.8:4.1 UPW	N/R
Mota et al., 2013[L2] (Spain)	NI, PD, SU except cannabis, tobacco, AUD, NC sensory, NC motor, PD history, AUD history, AUDIT >20	RAVLT, Logical memory, Family pictures, Digits backward, Spatial location backward, Self-ordered pointing, Zoo map, Key search	Immediate memory, LTM memory, recent memory, WM	22:27	18.8	19:21	18.5	1+ BD occasion per week	N/R	Test day
Parada et al., 2011 (Spain)[4]	>90/2+ symptoms GSI SCL-90-R, NI, SU, PD, PD history, AUD, AUD history	RAVLT, Logical memory, Family pictures	Immediate memory, LTM memory, mental flexibility, recent memory, WM	32:30	18.9	31:29	18.7	1+ BD occasion per mth	N/R	24 hrs

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
Parada et al., 2012 (Spain)[4]	>90/2+ symptoms GSI SCL-90-R, NI, SU, PD, PD history, AUD, AUD history	Digits backward, Spatial span backward, Self-ordered pointing, Phonetic fluency, Zoo map, Key search, WCST	Expressive language, mental flexibility, WM	32:30	18.9	31:29	18.7	1+ BD occasion per mth	N/R	24 hrs
Sanhueza et al., 2011 (Spain)	SU, PD, NI	TAVEC, Digits forward, Corsi blocks, Stroop, Tower of Hanoi, BVRT	Immediate memory, inhibition, LT memory, mental flexibility, processing speed, recent memory, WM	8:13	19.0	17:25	18.9	6+ (F) or 8+ (M) drinks per occasion	6.9:0.9	N/R
Scaife et al., 2009 (UK)	MI, NI, AUD, SUD	Paired associates learning, CANTAB (Spatial WM, Simple reaction time, IDED)	Mental flexibility, processing speed, recent memory, WM	18:12	20.7	13:17	22.3	24+ BD score (drinks per hr; times drunk last 6 mths; % of being drunk when drinking)	N/R	12 hrs
Squeglia et al., 2009[L1-5] (USA)	Prenatal SU, MI, DSM4 A1, PD history, NC sensory, LH, SU	CVLT, Color word interference, Towers, Letter-number, Complex figure copy, Digit vigilance, Block design, Digits (forward, backward), Digit symbol coding	Immediate memory, inhibition, LT memory, mental flexibility, processing speed, sustained attention, visuoconstructional, WM	36:13	13.8	24:16	13.5	T1: 0 T2: 1+ BD occasion	8.0:0.3 UPM	N/R
Townshend et al., 2005 (UK)	MI, NI, AUD, SUD	CANTAB (Matching to sample, Spatial WM), Vigilance	Inhibition, selective attention, WM	23:15	20.9	13:21	20.9	24+ BD score (drinks per hr; times drunk last 6 mths; % of being drunk when drinking)	33.3:20.5 UPW	12 hrs
Vinader-Caerols et al., 2017 (Spain)	Medication, PD, irregular sleep, SU, SUD, AUD history	Immediate visual memory, WM	Recent memory, WM	18:24	18-19	18:24	18-19	3+ BD occasions per mth, past yr	4.6:0	Test day
Xiao et al., 2009[L1] (China)	N/R	Iowa Gambling, Self-ordered pointing	DM, WM	10:2	16.4	71:78	16.2	1+ BD occasion, past mth	1.4:0.6	N/R

Source (country of origin)	Exclusion criteria	Cognitive paradigm	Cognitive subdomain	Binge		Comparison		Alcohol use criteria for BD group	Use BD:C UPO	Abstinent BD:C[2]
				n M:F	Age	*n* M:F	Age			
									2.7:0.7	
Yoo et al., 2016 (Korea)	PD, MI, NI, AUD, AUD history	Iowa Gambling, Reversal learning	DM, mental flexibility	12:18	21.8	12:19	21.7	1+ BD occasion, past 2 weeks, 12–26 AUDIT score	N/R	24 hrs

AUD: alcohol use disorder; AUDIT: Alcohol Use Disorders Identification Test; BA: brain abnormalities; BAC: blood alcohol concentration; BD: binge drink; BVRT: Benton Visual Retention Test; C: control participants; CNS: central nervous system; DM: decision-making; DSM4 A1/A2: clinically diagnosed with any DSM4 Axis 1/Axis 2 condition; E1: experiment 1; E2: experiment 2; F: female; GSI SCL-90-R: Global Severity Index Symptom Check List-90-Revised; HI: head injury; IDED: CANTAB Intradimensional Extradimensional Shift Task; L: longitudinal (years); LD: learning disability; LH: left-handed; M: male; MI: chronic medical illness; mth: month; N/A: not applicable NC: non-corrected; NI: neurological illness; N/R: not reported; PD: psychiatric disorder; PDr: peak drinks; RAVLT: Rey Auditory Verbal Learning Task; SU: substance use; SUD: substance use disorder; T1: baseline assessment; T2: follow-up assessment; UPM: units per month; UPO: units per occasion; UPW: units per week; WCST: Wisconsin Card Sorting Test; WM: working memory. TAVEC = Spanish version of California Verbal Learning Test.

[1] Study characteristics presented for first time point where binge drinkers are compared to control (i.e., in longitudinal studies this may be at baseline or follow-up).

[2] Where alcohol abstinence is reported as X:X, this refers to the number of days for binge drinkers: controls.

3 Gil-Hernandez et al. (2017) reported on neurocognitive performance in three age groups (13–15 yrs, 18 yrs, 22 yrs). This study was classified as three studies in the meta-analysis.

[4] Parada et al 2011, 2012 report on the same participant sample, and is therefore classified as one study in the meta-analysis.

[5] Crego et al 2009, 2010 report the same cognitive data, the duplicate data was removed from the meta-analysis.

Table 2.2. GRADE evidence profile for neuroimaging, neurophysiological and neuropsychological studies.

Outcome	Certainty assessment							Certainty
	№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	
Behavioral inhibition only	2	observational	unclear [b]	not serious	not serious	serious[d]	none	very low
Brain electrical activity[3]	13	observational	not serious	not serious	not serious	not serious	none	low
Decision-making	7	observational	serious [a]	serious[c]	not serious	not serious	none	very low
Delay discounting	2	observational	unclear [b]	not serious	not serious	serious[d]	none	very low
Expressive language	4	observational	not serious	not serious	not serious	serious[d]	none	very low
Functional neural activity[1]	10	observational	not serious	not serious	not serious	not serious	none	low
Immediate memory	11	observational	not serious	not serious	not serious	not serious	none	low
Inhibition	18	observational	serious[a]	serious[c]	not serious	not serious	none	very low
Long-term memory	9	observational	not serious	not serious	not serious	not serious	none	low
Mental flexibility	12	observational	not serious	not serious	not serious	not serious	none	low
Neural structure, connectivity[2]	13	observational	not serious	not serious	not serious	not serious	none	low
Planning	1	observational	unclear [b]	not serious	not serious	serious[d]	none	very low
Processing speed	18	observational	serious [a]	serious[c]	not serious	not serious	none	very low
Recent memory	7	observational	not serious	serious[c]	not serious	not serious	none	very low
Receptive language	2	observational	unclear [b]	not serious	not serious	serious[d]	none	very low
Recognition of emotions	1	observational	unclear [b]	not serious	not serious	serious[d]	strong association	very low
Sustained attention	13	observational	not serious	not serious	not serious	not serious	none	low
Visual perceptual	3	observational	not serious	not serious	not serious	serious[d]	none	very low
Visuoconstructional	4	observational	not serious	not serious	not serious	serious[d]	none	very low
Working memory	20	observational	not serious	not serious	not serious	not serious	none	low

[1] BOLD; fMRI; [2] Structural MRI studies (volume, surface area, cortical thickness), structural DTI studies (FA), structural MRS; [3] EEG, MEG, ERP.

[a] Egger's test $p < .05$; [b] A minimum of three studies are needed to calculate risk of publication bias using Egger's linear regression method; [c] Unexplained heterogeneity of results was assessed through examination of variance in point estimates across studies, and the Q, I^2, tau and tau^2 statistics in the meta-analysis, in addition to examination of large differences in effect size; [d] The number of participants included in the review was smaller than the required number of participants generated from a sample size calculator for a single adequately powered trial.

2.4.3 Longitudinal studies

Longitudinal studies provided insight into the cause-effect relationship of structural and functional brain differences, neurocognitive deficits, and binge drinking in adolescents and young adults. The following section reports on observed group differences between future binge drinking and non-binge drinking participants that predated heavy episodic use and perhaps represent vulnerability factors that promote greater consumption of alcohol following initiation of use. This is followed by a synthesis of studies that reported neural and cognitive consequences of binge drinking and the results following abstinence from binge patterns of drinking.

2.4.3.1 Pre-existing aberrations

Six of ten longitudinal neuroimaging, neurophysiological, and neuropsychological studies that examined youth prior to binge drinking have provided evidence of neural and cognitive differences in adolescents and young adults that later predict the uptake of binge drinking over a 9-month to 13-year period. A structural neuroimaging study, which captures static images of the brain in an MRI scanner, observed 40 adolescents for three years, where the mean age was 15 years at baseline and 17.6 years at follow-up (Squeglia, Rinker et al., 2014). The researchers found that individuals who later transitioned to heavy drinking with regular binges (n = 20) recorded smaller baseline brain volume in regions important for EF and reward processing (ACC, inferior frontal gyrus, cingulate gyrus), and less right cerebellar white matter at baseline, when compared to participants who did not engage in binge drinking. A second structural imaging study examined 265 substance-naïve adolescents aged 12 to 14 at baseline and followed them annually for up to 13 years (maximum age 27) (Brumback et al., 2016). They found that the surface area of the right dorsolateral PFC at baseline predicted the number of subsequent binge drinking occasions, with smaller surface area indicating more binges.

Functional neuroimaging studies, which measure neural activity in response to a task, also provided insight into the vulnerability markers of youth at heightened risk of binge drinking. The standard variable of interest used in fMRI studies is blood-oxygen-level-dependent (BOLD) signal which measures the regional differences in cerebral blood flow

and volume to delineate regional neural activity. A three-year functional neuroimaging study of 40 participants aged 15 years at baseline measured changes in BOLD signal response to a visual working memory task (Squeglia, Pulido et al., 2012). During the three-year follow-up period (mean age at follow-up = 18.1 years), 20 participants initiated regular heavy alcohol use and met criteria for binge drinking. At baseline, these participants exhibited less BOLD signal to cognitive challenges than continuous non-drinkers in regions associated with working memory and other executive functions, including the right inferior parietal lobule and the left medial frontal gyrus. In this study, lower baseline BOLD signal in these regions predicted a higher number of subsequent peak drinks during binge sessions and a higher number of drinking days. A second functional neuroimaging study assessed response inhibition, using an event-related Go/No-Go Task, in 28 participants who were aged 11.7–16.7 years at baseline (Wetherill et al., 2013). At the three-year follow-up, 14 participants had initiated heavy drinking with binges (mean = 18.5 years) and these participants exhibited less BOLD response at baseline during the Go/No-Go Task in cortical (frontal, parietal) and subcortical regions (putamen, cerebellum) implicated in processes of working memory and response inhibition, when compared to individuals who did not initiate binge drinking.

Neurophysiological measures have also been used to investigate the relationship between neural activity and binge drinking. An EEG measures the electrical brain wave patterns by using electrodes attached to the scalp, and an ERP is the measured electrical response to a specific task or event. One nine-month longitudinal study measured the ERP components of 36 first-year university students aged 18 years in an auditory task based on emotional valence detection (Maurage et al., 2009). This study found that individuals who initiated binge drinking by age 19 exhibited delayed P1, N2, and P3b latencies indexing deficits in perceptive and decisional processes at baseline, when compared to those who did not initiate binge drinking. Importantly, the extent of these latency delays was proportional to the severity of binge drinking behavior. Finally, one neuropsychological study observed 181 adolescents over a one-year period and participants who transitioned to binge drinking by age 17 exhibited poorer performance on the Iowa Gambling Task at baseline compared to non-bingeing participants (Xiao et al., 2009). Poorer task performance, reflecting poorer decision-making ability, predicted consumption of a greater number of drinks over the following year.

In summary, longitudinal studies provided evidence that smaller brain volume in frontal regions, less cerebellar white matter, smaller prefrontal surface area, less brain activation in frontoparietal regions during inhibition and working memory tasks, slowed cerebral activity, and poorer decision-making ability were associated with a greater likelihood of initiating binge drinking during adolescence or young adulthood.

2.4.3.2 Consequences of binge drinking

Twelve neuroimaging, neurophysiological, and neuropsychological studies provide evidence that binge drinking during adolescence and young adulthood has structural and functional neural consequences. A structural neuroimaging study observed 135 adolescents aged 15 years at baseline over a 3.5-year period (Squeglia et al., 2015). Over the follow-up period, 75 participants (mean age at follow-up = 19.6 years) initiated heavy drinking and met binge drinking criteria. Disrupted brain volume maturation was observed for these participants with greater neocortical, frontal, and temporal gray matter volume reductions, and attenuated white matter growth of the pons and corpus callosum at follow-up, when compared to low-drinkers who had consumed a maximum of four drinks in the previous year. In this study, male and female drinkers exhibited similar deviations in neural developmental trajectories. As part of the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) Study, Pfefferbaum et al. (2018) examined 483 participants aged 12 to 21 years over a two-year period. Of the adolescents and young adults who initiated alcohol use, 65 met criteria for moderate drinking with a mean age of 16.7 years and an average of 3.7 lifetime binges, and 62 met criteria for heavy drinking with a mean age of 17.1 years and an average of 15.8 lifetime binges. Following relatively low levels of binge drinking, the participants exhibited accelerated reductions in gray matter volume in frontal regions important for executive control, including the caudal middle and superior frontal gyrus, and the posterior cingulate cortex. Furthermore, the neuroimaging study by Squeglia et al. (2014), which followed 40 adolescents aged 15 for three years, reported accelerated gray matter volume reductions in cortical (left inferior and middle temporal gyrus; important in visual object recognition and language comprehension) and subcortical (left ventral diencephalon, left caudate, brainstem; important for sensory integration, motor control, feedback processing, reward and habit learning) regions in adolescents who initiated heavy drinking with binges (mean = 18 years) compared to

adolescents who remained non- or low-drinkers over the follow-up period (mean = 17.2 years).

The functional neuroimaging study by Wetherill, Squeglia et al. (2013) also identified neural consequences of binge drinking. From baseline to follow-up, participants aged 18.5 years who initiated heavy drinking exhibited increases in response inhibition BOLD contrast, while non- or low-drinkers aged 17.6 years showed attenuated responses. At follow-up, heavy drinkers reported greater response inhibition activity than non- or low-drinkers in cortical (middle frontal, right inferior parietal) and subcortical (left cerebellar tonsil) structures in order to successfully inhibit prepotent responses. As previously noted, the functional neuroimaging study by Squeglia, Pulido et al. (2012) reported less brain activation during a working memory task among binge drinkers prior to the onset of alcohol use. Following alcohol uptake, binge drinking adolescents aged 18.5 years showed increased BOLD response, whereas non-drinkers aged 17.7 years exhibited attenuated activation when compared to baseline in frontoparietal executive control regions. Therefore, the group differences in BOLD response identified at baseline were no longer present at follow-up.

Five neurophysiological longitudinal studies have followed continuous binge drinking participants over a period of one to six years. These studies did not assess participants prior to binge drinking uptake, and therefore, conclusions can only be drawn about the consequences of chronic binge drinking patterns rather than the effect of the uptake of binge drinking. López-Caneda and colleagues conducted two-year studies and assessed the transitional period from adolescence (18 to 19 years) to young adulthood (20 to 21 years) in three separate neurophysiological publications (López-Caneda et al., 2012, 2013, 2014). The 2012 and 2014 studies utilized the Go/No-Go Task to measure response inhibition and the 2013 study utilized a Visual Oddball Task to measure complex attention. López-Caneda et al. (2012) followed 48 participants while López-Caneda et al. (2014) followed 57 participants. Both studies reported increased P3 amplitude, related to working memory and inhibitory control, in the central, parietal, and frontal regions, as well as increased activation in the PFC and insula during inhibiting responses at follow-up in continuous binge drinkers compared to non- or low-drinkers. López-Caneda et al. (2013) followed 57 continuous binge drinkers and reported increased P3b amplitude in the central and parietal regions during attentional control at both evaluation times, with a more pronounced

difference after two years of consistent binge drinking. A larger P3b amplitude was associated with an earlier onset of regular drinking, and greater frequency and quantity of binge drinking. These findings from López-Caneda and colleagues suggest that continuous binge drinking may have a cumulative effect on brain activity and the anomalous activity may reflect degradation of underlying attentional and EF mechanisms. A one-year study by Petit, Kornreich et al. (2014) observed 30 young adults, aged 22 at baseline, during a Visual Oddball Task with alcohol-related cues. Continuous binge drinking over the follow-up period was associated with the emergence of electrophysiological abnormalities affecting visual (decreased P1 amplitude) and decisional processing (decreased P3 amplitude) for non-alcohol-related stimuli, compared to non-binge drinkers. At follow-up, binge drinkers showed enhanced P3 amplitude to alcohol-related stimuli, suggesting the emergence of a bias toward alcohol with continuous binge drinking behavior. Finally, Folgueira-Ares et al. (2017) assessed 50 young adults (mean = 20.6 years) during an associative memory task, measuring recent memory, and reported that consistent binge drinking over a two-year period was associated with increased vertex positive potential amplitude in the central region and increased difference due to memory effect amplitude in the centro-parietal and parieto-occipital regions for incorrect delayed memories, when compared with controls. Despite the absence of behavioral differences, these results indicate that consistent binge drinking is associated with anomalous processing during the encoding memory phase.

In terms of neurocognitive functioning, two longitudinal studies assessed youth before and after binge drinking initiation, and three longitudinal studies followed continuous binge drinking participants. A one-year study observed 116 young adolescents with a mean age of 14.5 years at baseline (Jones et al., 2017). A subsample began binge drinking during the follow-up period and the authors observed that higher total lifetime drinks predicted escalated impulsive choice in a delay discounting task, when compared with adolescents who did not initiate binge drinking during the same period. A second neuropsychological study followed 89 young adolescents, with a mean age of 13.7 years at baseline, for one to five years (Squeglia et al., 2009). For females who transitioned into moderate to heavy drinking with binges, more past year drinking days predicted a greater reduction in visuoconstructional functioning as measured by the Complex Figure Test, and for males who transitioned into binge drinking, more past year hangover symptoms predicted worsened sustained attention as measured by the Digit Vigilance Test, when compared to

females and males who remained non- or low-drinkers. A study by Mota et al. (2013) observed 89 young people with a mean age of 18.7 years at baseline over a two-year period and found consistent binge drinking was associated with poorer immediate and delayed recall, retention, and working memory at age 20.5 years. Finally, two papers reported on a sample who were followed up for a six-year period during the ages of 18 to 23 years (Carbia, Cadaveira, Caamano-Isorna et al., 2017; Carbia, Cadaveira, López-Caneda et al., 2017). Consistent binge drinking over a six-year period was associated with poorer immediate and delayed recall compared to stable non-binge drinkers, and this deficit remained stable over the follow-up period (Carbia, Cadaveira, Caamano-Isorna et al., 2017). In this study, male and female drinkers exhibited similar deficits in episodic memory. Meanwhile, the second publication by Carbia, Cadaveira, López-Caneda et al. (2017) investigating working memory reported deficits in working memory span among binge drinkers compared to non-binge drinkers at baseline, however these participants (n = 76) showed some improvement over the following four years.

Together, these findings indicate that following the uptake of binge drinking, adolescents and young adults report accelerated gray matter volume reductions in cortical (neocortical, frontal, temporal, cingulate) and subcortical regions (ventral diencephalon, caudate, brainstem), attenuated growth in white matter structures, aberrations in frontoparietal brain activity during EF tasks, and deficits in delay discounting, visuoconstructional functioning, and sustained attention. Consistent binge drinking over a period of one to two years had a cumulative impact on brain wave activity during tasks of inhibition, complex attention, and recent associative memory, as well as when exposed to alcohol-related cues. Consistent binge drinking over a period of two to six years was associated with poorer learning and long-term, episodic, and working memory.

2.4.3.3 Discontinuation of binge drinking

Five studies reported on young people who discontinued binge drinking over a follow-up period of one month to six years. A functional neuroimaging study observed 38 adolescents, aged 16 to 19 years (Brumback et al., 2015). At baseline, binge drinkers exhibited greater BOLD response than controls when observing alcoholic vs. non-alcoholic beverage images, and following one month of monitored alcohol abstinence, BOLD

response was similar between bingers and controls. A neurophysiological study evaluated ERP components in 57 university students at ages 18 to 19 and 20 to 21 during an inhibition task (López-Caneda et al., 2014). Participants who had stopped binge drinking during the follow-up period displayed an intermediate position where their P3 amplitude, reflecting cognitive processing demand, was larger than control but smaller than continuous binge drinkers. Three neuropsychological studies have reported on the discontinuation of binge drinking. The first study followed youth, with a mean age of 18.8 years at baseline, over a two-year period and found that youth who stopped binge drinking by approximately age 21 improved their long-term memory performance; while their performance was superior to youth who continued to binge drink over the follow-up, they continued to perform worse than the non-drinkers (Mota et al., 2013). On the other hand, a second sample reported in two papers (Carbia, Cadaveira, Caamano-Isorna et al., 2017; Carbia, Cadaveira, López-Caneda et al., 2017), found no improvement in immediate recall or long-term memory performance in the short term (approximately two years). However, long-term abandonment of binge drinking (two to four years) led to improvements in immediate recall which matched performance in continuous non-binge drinking youth, and improvements in long-term memory which reflected an intermediate position between binge and non-drinkers (Carbia, Cadaveira, Caamano-Isorna et al., 2017). Furthermore, the participants who discontinued binge drinking reported an intermediate position between continuous binge drinking and non-binge drinking participants in working memory performance (Carbia, Cadaveira, López-Caneda et al., 2017). Overall, this suggests that some neural and cognitive effects of binge drinking appear to reduce after discontinuation; however, performance does not match those who have never engaged in binge drinking. Further details of all prospective longitudinal studies are provided in **Appendix 2**.

2.4.4 Cross-sectional studies

The following section reports on neural and cognitive group differences observed between binge drinkers and non- or low-drinkers in cross-sectional studies, where causality cannot be determined. The neuroimaging and neurophysiological evidence is presented first in a narrative synthesis, followed by a meta-analysis of neuropsychological findings.

2.4.4.1 Structural differences

A total of eight structural neuroimaging studies reported on aberrations associated with binge drinking in adolescence or young adulthood. Lisdahl et al. (2013) examined 106 adolescents aged 16 to 19 years, of which 46 had engaged in binge drinking in the month prior to testing. They found that higher peak drinks (i.e., where participants met binge drinking criteria) predicted lower global white matter volume in the left hemisphere and lower gray and white matter volume in the right hemisphere. Another study examined 76 young adults (mean = 21.3 years) and identified sex differences; compared to non- or low-drinkers, male bingers reported lower cortical volume and female bingers showed higher volume in cortical (prefrontal, inferior- and mid-temporal, motor, somatosensory) and subcortical (striatal) regions, which are important for EF, reinforcement of behavior and reward, and movement (Kvamme et al., 2016). In terms of cortical thickness, a study by Squeglia, Sorg et al. (2012) examined 59 adolescents aged 16 to 19 years and reported sex differences where male binge drinkers exhibited decreased cortical thickness while female binge drinkers exhibited increased cortical thickness in regions of the cognitive control frontal cortex when compared to non-binge drinking participants. Furthermore, a study of 54 young people aged 18 to 24 reported decreased cortical thickness in the mid-ACC and posterior cingulate cortex among binge drinkers (Mashhoon et al., 2014). Cross-sectional baseline data from the NCANDA consortium showed that the number of binges in the previous year predicted decreased frontal and parietal cortical thickness (regions implicated in EF) in binge drinking youth with an average age of 18.6 years (Pfefferbaum et al., 2016). One cross-sectional MRS study, examining neurochemical changes, examined 54 young adults with a mean age of 21.7 years, and found greater binge drinking was associated with decreased gray matter voxel content, decreased gamma-aminobutyric acid (GABA; an inhibitory neurotransmitter), and N-acetyl aspartate/creatine (NAA/Cr; a marker of neuronal integrity) in the ACC, which is relevant to EF, and increased white matter voxel content in the ACC (Silveri et al., 2014). This study further stratified the 23 binge drinkers into subgroups based on whether they had experienced alcohol-induced black-outs (n = 14) or no black-outs (n = 9) and concluded that the observed group differences were driven by binge drinking individuals who had experienced black-outs. Finally, one cross-sectional DTI study of 28 adolescents was included in this review (McQueeny et al., 2009). DTI is an MRI technique sensitive to the movement of water, and a common outcome variable of this technique is fractional anisotropy which is sometimes

reported as a measure of white matter integrity. This study reported lower fractional anisotropy in binge drinkers aged 18 years, reflecting poorer integrity in major white matter pathways throughout widespread regions of the brain, including the corpus callosum, internal and external capsules, coronal radiata, longitudinal fasciculus, and the cerebellar white matter tracts.

Overall, structural neuroimaging studies have found that binge drinking is associated with lower global gray and white matter volume, lower gray matter voxel content, decreased cortical thickness in frontal regions, decreased GABA and NAA/cr in the ACC, and poorer white matter integrity throughout the brain. Sex differences have been identified, where male binge drinkers have shown decreased volume and cortical thickness, while female binge drinkers have displayed the inverse.

2.4.4.2 Functional differences

Five fMRI studies measured brain activity during EF tasks, including working memory, inhibition, and decision-making. One study examined 32 young adults (mean = 21.3 years) and measured working memory with a Two-Back Task in binge and non-binge drinkers (Campanella et al., 2013). Analyses revealed higher bilateral activity in the pre-supplementary motor area in binge drinkers than matched controls. In this study, the number of drinks per occasion was positively correlated with higher BOLD response in the dorsomedial PFC, which is important for stimulus perception and inceptive salience, and the number of drinking occasions per week was predictive of higher BOLD activity in subcortical regions important for mental flexibility, including the cerebellum, thalamus, and insula. A second fMRI study also reported greater BOLD activity in the supplementary motor area, as well as regions of the frontal gyrus and inferior parietal gyrus in heavy and binge drinkers aged 15 to 19 years (n = 20) compared to non-drinkers (n = 20) during a visual working memory task (Squeglia, Pulido et al., 2012). A third fMRI study measured brain functioning during a spatial working memory task in 95 adolescents aged 16 to 19 years and those who met criteria for binge drinking reported decreased BOLD response in frontal regions important for working memory, compared to non-binge drinking participants (Squeglia et al., 2011). Sex differences were reported, where female binge drinkers exhibited lower BOLD responses and male binge drinkers exhibited greater BOLD

responses to the spatial working memory task in the frontal, ACC, temporal and cerebellar cortices, when compared with non-drinking controls. A fourth study measured inhibition in 41 participants aged 18 to 22 years and found that heavy and binge drinking participants exhibited greater BOLD activation in the frontal cortex and ACC (implicated in inhibitory control and decision-making), and insula (implicated in incentive salience, reward and habit circuitry) during the no-go responses in the alcohol-related Go/No-Go Task, when compared to non-binge drinking participants (Ames et al., 2014). Finally, Xiao et al. (2013) assessed 28 adolescents (mean = 17.1 years) using the Iowa Gambling Task. Binge drinking was associated with abnormal decision-making, reflected by greater BOLD activity in subcortical regions underpinning emotion and reward processing, including the left amygdala and bilaterally in the insula.

One fMRI study measured brain activity during affective processing, and a second study measured activity during presentation of alcohol cues. Maurage et al. (2013) observed 24 young adults (mean = 23.8 years) during a Two-Alternative Choice Task that aimed to capture affective processing and recognition of emotions. They found that binge drinkers showed greater BOLD response in the right middle frontal gyrus and lower BOLD activity bilaterally in the superior temporal gyrus, which is important for processing of affective changes, when compared to low-drinkers. Finally, Brumback et al. (2015) examined 38 adolescents aged 16 to 18.9 years during an Alcohol Cue Reactivity Task and found greater BOLD activity in cortical (ACC) and subcortical regions implicated in reward, decision-making, and movement, including the dorsal striatum, globus pallidus, cerebellum, and parahippocampal gyrus, in binge drinkers when compared to controls.

Two EEG and one magnetoencephalography (MEG) study have examined differences between binge and non-binge drinking young people. The MEG is a non-invasive technique which measures the magnetic fields of neural activity. A study of 96 participants with a mean age of 20.6 years reported an association between binge drinking and increased mean spectral power reflecting a hyperactive central nervous system when compared to non-binge drinkers (Courtney & Polich, 2010). Additionally, they observed an association between extreme binge drinking (i.e., 10+ drinks on a single occasion; Johnston et al., 2017) and greater delta power when compared to regular-binge drinking. López-Caneda et al. (2017) assessed 80 adolescents with a mean age of 18.1 years and reported greater beta density (parahippocampus, fusiform gyrus; eyes open) and theta density (cuneus, lingual

gyrus; eyes closed) in binge drinking participants when compared to non-binge drinkers, reflecting neurofunctional deficits in inhibitory control processes. Finally, Correas et al. (2015) examined 73 adolescents aged 18 and reported higher theta power (occipital) and functional connectivity (frontal-parietal), beta connectivity (frontal-temporal), and delta connectivity (frontal-temporal) among binge drinkers. In this study, binge drinking compared to non-binge drinking participants also exhibited lower alpha power (temporal, occipital) and connectivity (frontal-temporal), which has an important functional role in the inhibitory process.

Four neurophysiological studies have measured ERP components during tasks of complex attention. One study, reported in two papers, assessed 95 young people aged 18 to 20 years and showed lower overall activation in the PFC (indicative of neurofunctional deficits in EF), a smaller late positive component in the frontal and central regions (Crego et al., 2010), and greater N2 amplitude, reflecting higher levels of attentional effort, in the central and parietal cortex in binge drinkers compared to controls (Crego et al., 2009). Lannoy et al. (2017) assessed 40 young adults (mean = 20.7 years) and reported slower error processing (delayed error positivity component latency) in the central region among binge drinkers when compared to control. Finally, Maurage et al. (2012) examined 60 young adults aged 19 to 24 years and reported ERP deficits affecting both basic and cognitive control processes, including delayed P100, N100, N2b, P3a, and P3b latency and decreased N100, N170, P100, P2, and N2b amplitude among binge drinkers when compared with controls. This study also examined extreme- compared to regular-binge drinking participants and found delayed P100, N100, N2b, and P3a latency and decreased N170 and P2 amplitude among extreme binge drinkers.

Neurophysiological studies have also measured ERP amplitude in tasks of inhibition and alcohol cues. Lannoy et al. (2017) reported deficits in electrophysiological correlates of inhibitory control (greater error-related negativity amplitude) in the frontal region during a speeded Go/No-Go Task. Lastly, Petit et al. (2012) reported evidence of early processing enhancement to alcohol cues in binge drinkers aged 19 to 26, indexed by higher P100 amplitudes in the central region and right hemisphere. In this study, longer duration of binge habits and increased number of alcohol doses per week were positively associated with higher P100 amplitude.

Overall, findings from fMRI and neurophysiological studies have provided insight into the functional aberrations associated with binge drinking. In adolescents and young adults, binge drinking was correlated with greater brain activity during working memory, inhibition, and attentional tasks, higher brain wave activity during resting state, and aberrations in sensory and cognitive ERP components during attentional control and inhibition.

2.4.5 Meta-analysis of neurocognitive measures

The following section reports on the results of a meta-analysis of neurocognitive deficits associated with binge drinking, utilizing cross-sectional data. Of the 58 studies included in this review, 43 reported on neuropsychological data. One study had overlapping samples and data was removed (Crego et al., 2010). Four studies which reported on different tasks using overlapping samples were classified as two studies (Carbia, Cadaveira, Caamano-Isorna et al., 2017; Carbia, Cadaveira, López-Caneda et al., 2017; Parada et al., 2011, 2012), and one study which reported on three separate samples, grouped by age, were classified as three studies (Gil-Hernandez et al., 2017). Therefore, 42 studies were found to be eligible for the meta-analysis, with 3,065 participants, including 1,313 binge drinkers and 1,752 comparison participants who did not meet criteria for binge drinking. A total of 186 effect sizes from 42 studies were coded (mean = −0.21 [*S.E.* = 0.25]; range = −4.34 to 3.25). Binge drinkers in the studies had a mean age of 18.88 (*SD* = 1.30) years and were 53% male. Comparison participants had a mean age of 18.83 (*SD* = 1.43) and 48% were male. The studies in this analysis were sampled from schools, universities, and the general population. Figure 1 in **Appendix 2** displays a funnel plot of neuropsychological effect size estimates against their standard error. Visual inspection of this funnel plot revealed slight asymmetry, and the test of Egger et al. (1997) for small study effects revealed significant bias (t = 3.04; p = .002; see Table 2.3 for Egger's test of each domain). The Duval and Tweedie trim and fill method filled an additional five effect sizes and increased the effect size by approximately 23.1% in random-effects analyses (from g = −0.26; 95% CI −0.42, −0.10 to g = −0.32; 95% CI −0.47, −0.17).

Table 2.3 displays effect sizes by neurocognitive domain, which ranged from g = −1.70 to 0.34. The overall mean neurocognitive effect size was g = −0.26, and on average the

between-study variance estimate was 0.01 ($p < .001$), indicating that variance between studies was significantly more than that explained by sampling error alone. Binge drinking was associated with significant deficits in decision-making ($g = -1.70$) and inhibition ($g = -0.39$), and enhanced processing speed ($g = 0.34$). Deficits in social cognition were observed in one study of emotion recognition and this was significantly associated with binge drinking ($g = -1.05$). Effect sizes were non-significant in the domains of mental flexibility ($g = -0.13$), planning ($g = -0.67$), behavioral inhibition ($g = -0.27$), delay discounting ($g = -0.12$), expressive ($g = -0.10$) and receptive language ($g = 0.17$), immediate memory ($g = 0.03$), long-term memory ($g = -0.04$), recent memory ($g = -0.53$), sustained attention ($g = -0.15$), visual perceptual ($g = 0.05$), visuoconstructional ($g = 0.05$), and working memory ($g = -0.15$). Significant heterogeneity was observed for decision-making, inhibition, recent memory, processing speed, and overall neurocognition, while no significant heterogeneity was reported for all other domains. Meta-analysis results based on a small number of studies (i.e., planning, delay discounting, behavioral inhibition, receptive language, recognition of emotions, visual perceptual) should be interpreted with caution due to the small sample size and lack of power. For a summary of the neural and cognitive aberrations that were pre-existing, consequential, and correlational with binge drinking, see Table 2.4.

Table 2.3. Meta-analysis findings.

Domain	Meta-analysis					Heterogeneity						Publication bias (Egger's)	
	k	*n* (BD:C)	Hedges' *g*	*p*	95% CI	*Q*	*df*	*p*	*T*	T^2	I^2	*t*	*p*
Behavioral inhibition only	2	74:117	−0.27	0.08	−0.58, 0.03	1.09	1	0.300	0.06	0.00	8%	-	-
Decision-making	7	149:453	−1.70	0.002	−2.77, −0.63	115.64	6	<0.001	1.39	1.94	95%	2.57	0.025
Delay discounting	2	62:102	−0.12	0.475	−0.44, 0.20	0.35	1	0.553	0.00	0.00	0%	-	-
Expressive language	4	220:224	−0.10	0.313	−0.30, 0.10	3.37	3	0.338	0.07	0.01	11%	0.21	0.426
Immediate memory	11	490:523	0.03	0.731	−0.13, 0.19	16.62	10	0.083	0.17	0.03	40%	0.10	0.461
Inhibition	18	569:660	−0.39	0.026	−0.74, −0.05	144.94	17	<0.001	0.70	0.49	83%	2.50	0.012
Long-term memory	9	344:384	−0.04	0.702	−0.27, 0.18	17.67	8	0.024	0.25	0.06	55%	1.58	0.079
Mental flexibility	12	421:455	−0.13	0.289	−0.37, 0.11	33.27	11	<0.001	0.34	0.12	67%	1.17	0.135
Planning	1	14:13	−0.67	0.100	−1.47, 0.13	0.00	0	1.000	0.00	0.00	0%	-	-
Processing speed	18	592:671	0.34	0.040	0.02, 0.67	135.93	17	<0.001	0.66	0.44	87%	2.27	0.019
Recent memory	7	316:317	−0.53	0.076	−1.11, 0.06	74.12	6	<0.001	0.75	0.56	92%	2.19	0.040
Receptive language	2	69:85	0.17	0.296	−0.15, 0.48	0.03	1	0.852	0.00	0.00	0%	-	-
Recognition of emotions	1	12:12	−1.05	0.013	−1.88, −0.22	0.00	0	1.000	0.00	0.00	0%	-	-
Sustained attention	13	385:467	−0.15	0.237	−0.41, 0.10	40.01	12	<0.001	0.38	0.15	70%	1.18	0.131
Visual perceptual	3	78:50	0.05	0.778	−0.30, 0.40	1.79	2	0.409	0.00	0.00	0%	0.67	0.312
Visuoconstructional	4	119:139	0.05	0.753	−0.24, 0.33	4.05	3	0.256	0.15	0.02	26%	0.78	0.258
Working memory	20	724:1035	−0.15	0.082	−0.32, 0.02	48.50	19	<0.001	0.29	0.09	61%	0.72	0.241
Neurocognition	42	1313:1752	−0.26	0.001	−0.42, −0.10	163.72	41	0.00	0.44	0.19	75%	3.04	0.002

k: number of studies; *n:* pooled sample size; CI: confidence interval; heterogeneity (*Q* value, degrees of freedom [df], significance test [*p* value], standard deviation of true effects [tau; T], variance of true effects [tau^2; T^2], true/total variance [I^2]); BD: binge drinkers; C: comparators.

Note. Where there were ≤2 studies, Egger's test of publication bias could not be calculated.

Table 2.4. Overview of findings: Structural and functional correlates of binge drinking in young people.

	Brain structure	Brain function	Neurophysiological	Cognitive
Pre-existing features	↓ Cortical volume (ACC, frontal, cingulate) ↓ Surface area (DLPFC) ↓ White matter volume (cerebellar)	↓ Brain activation during tasks of working memory (parietal, frontal), inhibition (frontal, parietal, putamen, cerebellar)	Delayed P1, N2, P3b latencies during emotional valence task	↓ Decision-making
Consequences of binge drinking	↓ Gray matter volume (neocortex, frontal, temporal, diencephalon, caudate, brainstem, PCC) ↓ White matter growth (pons, corpus callosum)	↑ Brain activation during tasks of inhibition (frontal, parietal, cerebellar) Aberrant brain activation during tasks of working memory (frontal, parietal)	↑ Amplitude during tasks of inhibition (P3), attention (P3b), associative memory (VPP, DM), alcohol related cues (P3) ↑ PFC, insula activation during task of inhibition ↓ Amplitude during non-alcohol related cues (P1, P3)	↓ Recent memory ↓ Long-term memory ↓ Sustained attention (males) ↓ Visuoconstructional function (females) ↓ Working memory (improvement with time) ↑ Impulsivity (delay discounting)
Cross-sectional correlates with binge drinking	↓ Cortical thickness (frontal, parietal, ACC, PCC) ↓ GABA (ACC) ↓ Gray matter volume (L hemisphere) ↓ Gray matter voxel content (ACC) ↓ NAA/cr (ACC) ↓ White matter integrity (corona radiata, corpus callosum, longitudinal fasciculus, internal & external capsule, fornix, cerebellar peduncle) ↓ White matter volume (L,R hemisphere) ↑ White matter voxel content (ACC) Abnormal cortical volume (↓ males, ↑ females; PFC, temporal, motor, somatosensory, striatal) Abnormal cortical thickness (↓ males, ↑ females; frontal)	↓ Brain activation during tasks of emotion recognition (temporal) ↑ Brain activation during tasks of decision-making (amygdala, insula), inhibition (frontal, ACC, insula), working memory (frontal, parietal, supplementary motor, PFC, cerebellar, thalamus, insula), alcohol cue reactivity (ACC, dorsal striatum, globus pallidus, cerebellar, parahippocampal), emotion recognition (frontal) Aberrant brain activation during spatial working memory (↓ females, ↑ males; frontal, ACC, temporal, cerebellar)	↓ Alpha connectivity (frontal-temporal) ↓ Alpha power (temporal, occipital) ↓ Amplitude during tasks of attention (N100, N170, P100, P2, N2b, LPC) ↓ PFC activation ↑ Amplitude during tasks of attention (N2), inhibition (ERN), alcohol cue reactivity (P100) ↑ Beta (frontal-temporal), delta (frontal-temporal), theta (frontal-parietal) connectivity ↑ Beta (parahippocampal, fusiform), theta (cuneus, lingual) density ↑ Delta, theta, mean spectral power Delayed P100, N100, N2b, P3a, P3b, Pe latency during tasks of attention	↓ Decision-making ↓ Inhibition ↓ EF ↓ Emotion recognition ↑ Processing speed
Effect of discontinuation of binge drinking	-	Normalized brain activation during alcohol related cues	↓ P3 amplitude during task of inhibition*	↑ Long-term memory* ↑ Recent memory ↑ Working memory*

* Results of ex-binge drinkers reflect an intermediate position between continuous binge and non-binge drinking participants.

ACC: anterior cingulate cortex; DLPFC: dorsolateral prefrontal cortex; DM: difference due to memory effect; ERN: error-related negativity; L: left; LPC: late potential component; Pe: error positivity component; PCC: posterior cingulate cortex; PFC: prefrontal cortex; R: right; VPP: vertex positive potential.

2.5 Discussion

The purpose of this systematic review was to provide a synthesis of the neuroimaging, neurophysiological, and neuropsychological literature investigating binge drinking in young people aged 10 to 24 years. A total of 58 studies met the eligibility criteria for the systematic review (see Figure 2.1), including 21 neuroimaging, 16 neurophysiological, and 21 neuropsychological studies. Correlates of binge drinking were summarized from 39 cross-sectional studies and eight longitudinal studies, while the antecedents and consequences of binge drinking were drawn from one interventional pre-post study and 18 prospective longitudinal studies. A meta-analysis was only appropriate for the neuropsychological correlates of binge drinking and 42 studies were included in the analysis. The certainty in outcomes ranged from very low to low (see Table 2.2), and while methodological issues merit serious consideration, the following tentative conclusions have been drawn about the relationship between binge drinking, brain development, and cognition.

2.5.1 Vulnerability markers of binge drinking

Developmental deviations in the frontal region, which plays a critical role in EF, appeared to be a key risk factor for the onset of binge drinking in adolescents and young adults. Specifically, young people who displayed structural (i.e., reduced brain volume and surface area in key frontal regions), functional (i.e., reduced neural activity in the frontoparietal region during EF tasks, delayed ERP latencies indexing decisional processes), and cognitive (i.e., poorer decision-making ability) deviations from the expected developmental trajectory were more likely to initiate binge drinking. These deviations may reflect an underdeveloped or abnormal frontal region where impulse control is still relatively immature, allowing for unmediated reward-seeking behaviors like binge drinking (Casey et al., 2008). These findings are consistent with the broader work in this field examining vulnerability markers of alcohol initiation in adolescence through to AUD in adulthood (Bernardin et al., 2014; Silveri et al., 2016; Squeglia & Cservenka, 2017). This review provides support for the continuum hypothesis; where binge drinkers display analogous deficits that are quantitatively less marked than alcohol-dependent individuals (Enoch, 2006). This may suggest that the deficits linked with binge drinking are likely to contribute

to the maintenance of problematic patterns of alcohol use, including alcohol addiction through the inability to suppress maladaptive behavior despite the adverse consequences (Volkow et al., 2013).

Targeting these shared vulnerability mechanisms by strengthening EF in childhood and adolescence may be a promising prevention avenue to combat the shared risk for some youth of alcohol initiation and binge drinking in adolescence, and binge drinking and AUD in adulthood. Cognitive training treatment strategies have demonstrated success in reducing alcohol use (Bowley et al., 2013), and in a range of clinical populations including SUDs (Keshavan et al., 2014). However, the effectiveness of cognitive training as a prevention initiative has not been thoroughly investigated. There is evidence to suggest that greater inhibitory control skills and greater integration of emotion regulation and impulse control in childhood are associated with reductions in alcohol use by early adolescence (Pentz et al., 2016), providing possible targets for future prevention initiatives, with trials currently underway (Bourque et al., 2016; Mewton et al., 2017; O'Leary-Barrett et al., 2017).

2.5.2 Consequences of binge drinking

Pre-existing deficits in key frontoparietal regions were further exacerbated as a consequence of binge drinking in adolescence and young adulthood; young people exhibited accelerated gray matter volume reductions and recruited greater cerebral activity during EF tasks following the uptake of binge drinking. These findings support a frontal dysfunction hypothesis in binge drinking youth, which is similar to conclusions drawn for individuals with AUD (Moselhy et al., 2001; Zorko et al., 2004). Youth also exhibited attenuated white matter development, and accelerated gray matter volume reductions in the neocortex, caudate, and across the limbic reward system following binge drinking, which is also consistent with the broader research field on alcohol use and neurofunction (Bernardin et al., 2014; Silveri et al., 2016; Squeglia & Gray, 2016; Zilverstand et al., 2018). Accelerated gray matter reductions may reflect non-beneficial pruning or premature cortical gray matter decline which is similar to patterns observed in adults with AUD (Pfefferbaum et al., 1992) and 'normal' aging (Pfefferbaum et al., 2013). Furthermore, alterations in white matter development and cortical thinning disrupts efficient information processing required for cognitive and motor abilities (Squeglia et al., 2013),

and likely contributes to the alcohol-related cognitive dysfunctions identified in this review, including deficits in attention, learning, long-term and working memory, and visuoconstructional function. Impairment to the caudate nucleus, limbic, and frontal regions may be integral to the continuation of binge drinking, caused by a disruption in the mediation between reward hypersensitivity, goal selection, and impulse control in the decision-making process around whether to drink and to what extent (Grahn et al., 2008; Spear, 2014). Cognitive substrates of these brain regions also appear to be impacted in binge drinking youth. Deficits in delay discounting were reported following the uptake of binge drinking and this relates to an increased motivation and impulsiveness toward reward and instant gratification in the decision-making process (da Matta et al., 2012). Additionally, cross-sectional neuropsychological evidence obtained from the meta-analysis reported an overall neurocognitive deficit in binge drinking youth, with specific deficits in decision-making and inhibition, and enhanced processing speed which may be indicative of increased impulsivity (Scaife & Duka, 2009). Overall, this review provides evidence of unbalanced interactions between reward-seeking, impulsive, and higher-order EF brain regions and the cognitive substrates in binge drinking youth.

Components of the Positive Valence System which are related to the early stages of addictive disorders (Koob & Le Moal, 2005)—namely, approach motivations, reward learning, and maladaptive habits (Morris & Cuthbert, 2012)—were implicated in binge drinking youth. Cognitive and neurobiological models of addiction propose that maladaptive reinforcement learning occurs following alcohol use, increasing the salience toward substances (Berridge, 2007). This implicit motivation toward alcohol use is linked to poorer EF processes, including decision-making (Day et al., 2015). Increased approach motivations compounded with poorer EF ability leads to maladaptive habit formation and impaired response inhibition (Everitt & Robbins, 2016; Hogarth et al., 2013; Wiers & Gladwin, 2017; Zilverstand et al., 2018). Support for this progression toward addiction was found in this review, where consistent binge drinking over one to two years was associated with aberrant brain wave activity when exposed to alcohol-related cues, and consistent binge drinking over two to six years was associated with maladaptive learning and memory, and poorer EF ability. Furthermore, cross-sectional evidence reported higher neural activity in binge drinkers during decision-making and alcohol cue reactivity tasks in regions including, but not limited to, the amygdala, insula, and hippocampus, which are implicated in incentive salience, habit circuitry, emotion regulation, and reward valuation

(Öner, 2018). Overall, these findings suggest that there is a bias in approach motivations and reward appraisal following consistent binge drinking in youth and this may be a gateway for the development of addiction in these youth.

2.5.3 Discontinuation of binge drinking

This review also found preliminary, yet promising, evidence that discontinuation of binge drinking may lead to partial neural and cognitive recovery. Alcohol abstinence resulted in normalized BOLD response to alcohol cues and improved some neural (P3 amplitude during inhibition) and cognitive (recent, long-term, and working memory) deficits associated with binge drinking, however performance did not match those who had never engaged in binge drinking. The mechanisms by which recovery may occur are not well understood. One suggestion is the young brain is more plastic and may be better at recovering from alcohol-related insults following abstinence (Berlucchi, 2011). On the other hand, improved cognitive performance following discontinuation of use may reflect enhanced neuroadaptation mechanisms (Bernardin et al., 2014). The duration of use may equally influence the rate of recovery, with young people experiencing a greater likelihood or recovery than individuals dependent on alcohol for a longer duration (Pitel et al., 2009; Schottenbauer et al., 2007). Critically, further evidence is required to determine whether recovery of other neural and cognitive domains—particularly substrates of EF—is possible, and whether habits and cognitive motivations can be updated to reorient the relationship between alcohol-related cues and incentives, executive control, and reward in binge drinking youth. There is growing evidence to suggest that re-training approach biases to alcohol cues is effective in both undergraduate and clinical samples (Kakoschke et al., 2017; Wiers et al., 2013). Interventions that target this relationship may be beneficial in improving decision-making processes and updating cognitive motivations in favor of reducing a young binge drinking person's alcohol use which will hopefully serve to lessen the likelihood of progression from binge drinking in youth to AUD.

2.5.4 Sex differences

Consistent with existing reviews (Carbia et al., 2018; Ewing et al., 2014; Silveri et al., 2016), sex differences were imbedded within a small number of neuroimaging and

neuropsychological studies where binge drinking females exhibited increased cortical thickness in the frontal lobe, less brain activation during a spatial working memory task in frontal, temporal, and cerebellar regions, and displayed poorer visuoconstructional function, when compared to non-binge drinking females. Alternatively, binge drinking males exhibited less intracranial volume in the striatum, more brain activation during a spatial working memory task, and poorer sustained attention when compared to non-binge drinking males. These results parallel findings among adolescents with AUD (Caldwell et al., 2005; Medina et al., 2008). The different manifestations of cognitive and neural decrements could relate to divergent neurodevelopmental trajectories, physiological responses to alcohol, and social factors influencing drinking onset (Squeglia et al., 2011). Neural activation differences across fronto-cortical regions could have a greater influence on cognitive performance. In the study by Squeglia et al. (2011), hypoactivation in the frontal region of female binge drinkers correlated with poorer attention and working memory performance, and in contrast, male binge drinkers exhibited equal or greater activation in frontal areas which was associated with better cognitive performance on spatial tasks. The reduced activation among young female binge drinkers during EF processes could have important implications, as diminished working memory may contribute to further substance use involvement (Casey et al., 2008). Further research which is sufficiently powered to examine sex differences is required to provide insight into the nuanced effects on cognition, brain structure, and function in males and females, however at this time, it appears that males may be less adversely influenced by binge drinking; a similar conclusion to that drawn by Ewing et al. (2014) and Silveri et al. (2016).

2.5.5 Methodological considerations

Although there have been considerable advancements in this field of research, definitive conclusions about the relationship between binge drinking, cognition, brain structure, and function cannot be drawn at this time. Clear comparisons of findings are a challenge as many studies in this field lack statistical power from limited sample sizes with wide age ranges which reduces precision of results (Button et al., 2013). There was serious concern of imprecision for the cognitive domains of behavioral inhibition, delay discounting, expressive language, planning, receptive language, visual perceptual, visuoconstructional, and recognition of emotions due to the small number of studies ($n \leq 4$) with small sample

sizes, where the number of participants included in the review was smaller than the required number generated from a sample size calculator for a single adequately powered trial. The preliminary DTI, MRS, resting-state EEG, and MEG findings should also be interpreted with caution due to small sample sizes and lack of power.

We found that there were inconsistencies in the measures used to assess neural and cognitive outcomes, and in the measures used to quantify alcohol use. These factors likely contributed to the considerable heterogeneity in results for the cognitive domains of decision-making, inhibition, processing speed, and recent memory. While we used standardized criteria to assess binge drinking status, there was large variation in the frequency and quantity of alcohol being consumed by the participants. In the majority of studies, binge drinking samples were fairly modest (e.g., 1–2 binges in the past 3 months as inclusion criteria), while others captured young people drinking at levels largely above these lower-cut offs (i.e., extreme binge drinking). Importantly, the tentative findings identified in the review reflect patterns of drinking behavior that are consonant with a large proportion of adolescents and young people (Australian Institute of Health and Welfare, 2017; Johnston et al., 2017; Kraus et al., 2016; Office for National Statistics, 2018; Substance Abuse and Mental Health Services Administration, 2017; White & Williams, 2016). However, caution should be taken when extrapolating results found in this review to youth with much heavier binge patterns, such as weekly binges, as there is not enough data available to delineate the effects of infrequent from frequent binges, and binge from extreme binges at this time. Further to this point, included studies mostly relied on self-reports of binge drinking. Incorporation of real-time measures, such as smart phone technology and biological markers of alcohol use (e.g., phosphatidylethanol, ethyl glucuronide, carbohydrate-deficient transferrin), would greatly improve the accuracy of reporting and would elucidate the more nuanced effects of drinking on neurofunction and cognition.

While it was beyond the scope of this review to examine comorbidities, we found throughout the screening process that in the broader field, there was a lack of explicit consideration of psychiatric comorbidities and other substance use. Other mental health conditions are known to affect neurofunction, for example, depression has been shown to have a negative impact on neural (Bora et al., 2012) and cognitive function (Lee et al., 2012). Further, the exclusion of papers exploring co-occurring substance use may have minimized

the effects observed in this review, as those engaging in extreme binge drinking are likely to be misusing other substances. Understanding the relationships between co-occurring mental disorders and the differential effects of other substances on the developing brain is an important next step, however much larger sample sizes are needed to parse these factors. Of note, studies in this review were not excluded if participants were tobacco users. A long history of smoking is associated with neural atrophy and accelerated cognitive decline in adults (Swan & Lessov-Schlaggar, 2007). For the majority of cases, the number of participants using tobacco were low and the patterns of use were infrequent. Again, much larger studies are needed to determine the differential effects of tobacco from alcohol on neural and cognitive development in youth.

A limitation of the meta-analysis was overarching cognitive constructs, such as EF or fluid reasoning, were not calculated due to inconsistencies in categorization of cognitive domains across theoretical frameworks. A further limitation was the exclusion of longitudinal studies from the meta-analysis because reliable estimates were indeterminable from the small number of published studies. More prospective longitudinal data that begins examining youth prior to alcohol uptake is critically needed to address concomitant factors of alcohol use and determine whether: 1) neural and cognitive vulnerabilities to alcohol vary at different points of neurodevelopment during adolescence and young adulthood (Sullivan et al., 2011); 2) what the exposure thresholds are for negative impacts on neural and cognitive development; 3) how alcohol-related harms such as alcohol-induced black-outs impact neurodevelopment; 4) whether extended alcohol use during youth differentially impacts neurodevelopment;, and 5) the degree to which neural and cognitive recovery can occur. Large multi-site studies such as the ABCD Study (Volkow et al., 2018), NCANDA project (Sullivan et al., 2016), and IMAGEN Study (Schumann et al., 2010) are underway and will help answer the existing gaps in the literature. Finally, the majority of published studies have originated from a small number of research teams and have included predominantly Caucasian youth from upper middle-class families. Thus, replication of design and findings across more diverse samples in research laboratories from other countries is encouraged in order to improve both the comparability and robustness of these findings (Munafò et al., 2017; Open Science Collaboration, 2015). Together, this will allow for future quantitative analyses of neuroimaging and neurophysiological studies to draw more conclusive evidence on the relationship between binge drinking and neurodevelopment.

2.5.6 Conclusion

Overall, recent research has substantially advanced our understanding of the complicated relationship between adolescent brain development and binge drinking, with prospective, longitudinal designs parsing pre-existing vulnerabilities from alcohol-related consequences. Although studies in young binge drinkers have identified deficits, the existing research on the impact of binge drinking on brain and cognitive development has yet to yield consistent, replicated findings. Tentatively, abnormal or delayed development of key frontal executive control regions may predispose youth to binge drink. Following the uptake of binge drinking, there is some evidence that neurotoxic effects are apparent in the reward-seeking, incentive salience, and executive control regions, indexed by cognitive deficits and maladaptive alcohol associations. These deficits may further increase the propensity for young people to engage in risky and sensation-seeking activities, including alcohol and drug use, abuse, and addiction. Further research in this area has the potential to significantly impact global health by informing the development of targeted prevention and intervention strategies to address the vulnerabilities and consequences of binge drinking in youth.

Chapter 3

Interaction of internalizing symptoms and executive functioning on alcohol use outcomes

Preface

As outlined in **Chapter 1**, research has provided strong support for the hypothesis that externalizing symptoms are precursory risk factors of binge drinking in adolescence and young adulthood. In contrast, the evidence base for associations between internalizing symptoms and alcohol use is mixed. Exploring the dynamics between psychopathology and neurocognition may help clarify this relationship. Largely untested theoretical frameworks postulate that high internalizing symptoms in interaction with low EF is associated with escalating alcohol consumption, as a result of turning to alcohol to cope with, and offset, negative affect. To address this gap in the evidence base, **Chapter 3** explores for the first time the inter-relating risks of EF processes and internalizing psychopathology on maladaptive coping mechanisms and alcohol use among older adolescents and young adults.

This chapter addresses the first research question of this thesis: *'What are the individual-level precursory risks associated with binge drinking and how do they interact?'* This chapter has been published as Lees, B., Stapinski, L. A., Prior, K., Sunderland, M., Newton, N., Baillie, A., Teesson, M., & Mewton, L. (2020). *Addictive Behaviors, 106*, 106351. Supplementary materials are available in **Appendix 3**.

3.1 Abstract

Objective: Globally, the prevalence of hazardous drinking[4] peaks in young adulthood, and there is mixed evidence on whether internalizing symptoms and EF deficits are associated with this increased risk. This study tested whether internalizing symptoms in interaction with EF deficits are associated with high AUD symptoms in emerging adulthood, via drinking motives to cope with negative affect and alcohol consumption.

Method: An Australian sample of 155 young adults aged 17 to 24 years (M = 20.97, SD = 2.40) provided self-report data on internalizing symptom severity and alcohol-related outcomes (n = 155), and neuropsychological data measuring EF (n = 104). CFAs were conducted to identify two latent variables representing internalizing symptoms and EF. A series of latent moderated structural equation models (LMS) and a latent mediated moderation structural equation model (LMMS) examined the inter-relations between internalizing symptoms, EF, and alcohol measures.

Results: High levels of internalizing symptoms in interaction with EF deficits were associated with strong drinking motives to cope with negative affect, high past month alcohol consumption, and greater AUD symptoms. Drinking motives to cope with negative affect and alcohol consumption mediated the relationship between the internalizing symptoms and EF latent interaction term with AUD symptoms.

Conclusions: This research highlights greater EF resources are associated with low desires to drink hazardous amounts of alcohol as a maladaptive way to cope with negative feelings among young people. It therefore may be useful to target EF ability alongside internalizing symptomology in alcohol prevention and intervention initiatives.

[4] In this chapter, hazardous drinking refers to binge drinking.

3.2 Introduction

Alcohol use is a global public health concern, with rates of hazardous drinking rising throughout adolescence and peaking in young adulthood at a time when the brain is still under development (World Health Organization, 2018). In Western countries, nearly one in two young adults aged 18 to 24 years engage in high-risk, hazardous drinking at least once per month (i.e., five or more standard drinks on a single occasion), and approximately one in six engage in very high-risk levels of drinking at least once per year (i.e., 10 or more standard drinks on a single occasion; Australian Institute of Health and Welfare, 2017; Office for National Statistics, 2018; Substance Abuse and Mental Health Services Administration, 2017). Models of brain development have proposed that maturational changes occurring in brain systems underlying reward and emotion regulation (subcortical limbic circuitry; maturing earlier) and higher-level executive functions critical for self-regulation (prefrontal circuitry; maturing later) contribute to normative increases in alcohol use by amplifying reactivity to novel and rewarding stimuli (Casey et al., 2008; Shulman et al., 2016; Steinberg, 2010). However, these models are not sufficient for understanding the complex nature of individual differences in hazardous drinking levels observable among some emerging adults. Further examination of the factors associated with this peak in hazardous drinking is therefore of critical importance to inform prevention and early intervention initiatives.

A large literature considers hazardous drinking from a developmental framework and posits two constructs associated with problematic drinking: 1) motivations to use alcohol through externalizing (i.e., delinquency, impulsivity) and internalizing pathways (i.e., negative emotionality related to depression, anxiety and psychological distress; Cooper et al., 2016; Hussong et al., 2018); and 2) deficits in EF (Day et al., 2015; Gierski et al., 2013). Extensive evidence is available on the associations between externalizing symptoms and hazardous drinking, however less evidence is available for internalizing symptoms (i.e., 'the self-medication hypothesis'; Blume et al., 2000; Khantzian, 1997), despite high levels of comorbidity with hazardous alcohol use (see review in Hardee et al., 2018). The limited number of studies examining depression (Pedrelli et al., 2016), general anxiety (Dyer et al., 2019), social anxiety (E. P. Morris et al., 2005), and psychological distress (Keyes et al., 2012) with alcohol use and symptoms of AUD among young people have reported mixed findings. There is also conflicting evidence for the relationship between EF deficits and

hazardous drinking in young people. In some cases, research supported the EF deficit hypothesis of alcohol misuse (Gierski et al., 2013), whereby EF deficits have predicted individual variability in alcohol initiation age (Khurana et al., 2012; Peeters et al., 2015), the quantity and frequency of alcohol use during adolescence and young adulthood (see review in Lees et al., 2019; Spear, 2018), and experiences of alcohol-related harms (Finn et al., 2009). Yet other studies have failed to show an association between EF and alcohol-related outcomes (e.g., Pieters et al., 2012, 2014; van Deursen et al., 2015). The current evidence for associations between internalizing symptoms and EF with hazardous alcohol use therefore presents a complex picture in young people, and exploration of potential moderating and mediating influences may help explain these discrepant findings.

To date, very little research has examined the inter-relations between internalizing symptoms and EF (Duijkers et al., 2016; Hunt et al., 2015), and consequently, potential interactions and the associations with hazardous drinking and AUD symptoms remains unexplored in young people. It is particularly important to examine this cohort given the relatively early stages of their engagement with hazardous drinking, which may cause further neurobiological harms on the vulnerable young adult brain (Lees et al., 2019). There are three major theoretical frameworks (i.e., attentional control, drinking motives, dual process modelling) that may help explain how these constructs interact to influence alcohol use in emerging adulthood. First, the attention control theory proposes that negative affect symptoms are associated with EF deficits (Eysenck et al., 2007). This occurs because individuals with high internalizing symptoms have dominant emotion-based subcortical limbic circuitry and subordinate prefrontal circuitry critical for EF, resulting in impaired EF efficiency (Eysenck & Derakshan, 2011). Empirical studies have provided support for this theory in young people, where poor EF performance has been associated with anxiety (Castaneda et al., 2008; Visu-Petra et al., 2012) and depression (Castaneda et al., 2008; Hermens et al., 2011; Matthews et al., 2008), although a broader examination of clustered internalizing symptoms has yet to be explored. Second, the drinking motives model posits that internalizing symptomology and hazardous alcohol use are related, in part, by motivations to offset negative affect, using alcohol as a coping mechanism (Cooper, 1994; Cooper et al., 1995). This proposal was supported in a self-report study of young people (Stapinski et al., 2016). Coping motives in particular have been associated with heavier drinking patterns and alcohol-related problems (Cooper, 1994; Cooper et al., 1992), and are considered to be a common pathway to alcohol use through which the influence of

other, more distal, factors are mediated, such as internalizing symptoms (Cooper et al., 2016). Third, dual process models posit that EF deficits in combination with affect-driven motives, induced by internalizing symptoms, should be more strongly associated with hazardous drinking (Wiers et al., 2007). However, little research has directly examined this proposal (Martins et al., 2018).

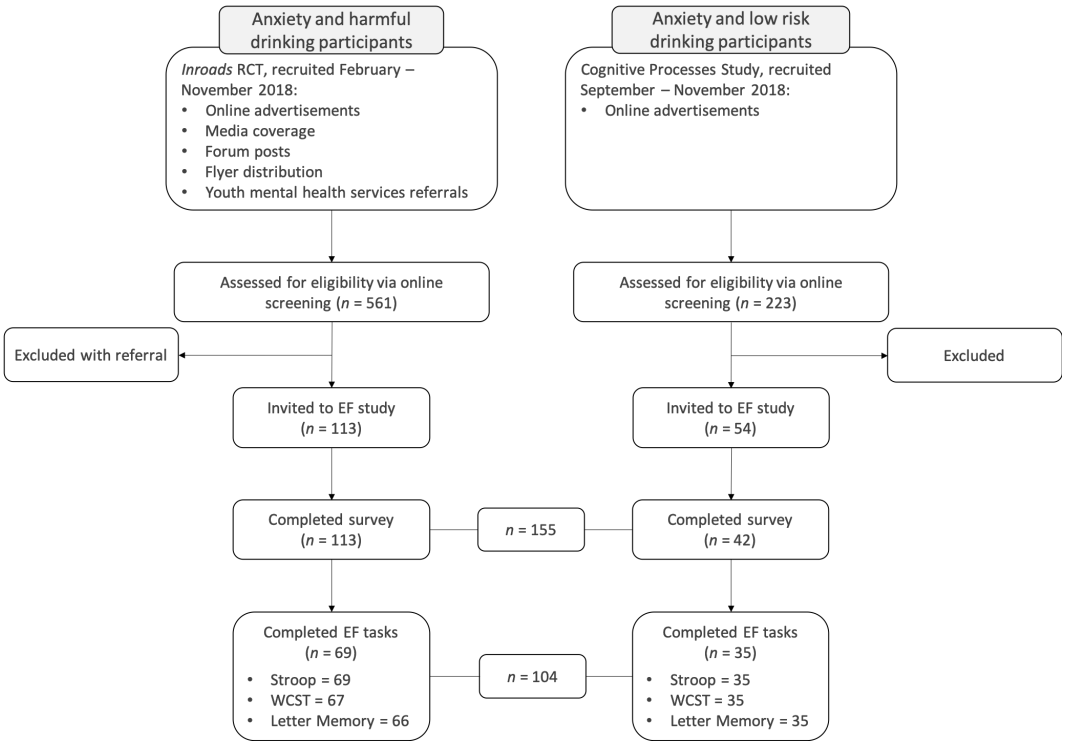
Based on these frameworks, we conceptualized and tested three hypotheses: 1) the association between internalizing symptoms and drinking motives to cope with negative affect would be stronger for young adults with lower compared to higher EF; 2) for young adults with higher internalizing symptoms and lower EF performance, high drinking motives to cope with negative affect would be associated with high alcohol use; and 3) high drinking motives to cope with negative affect and alcohol consumption would mediate the association with AUD symptoms among these individuals.

3.3 Methods

3.3.1 Participants

A sample of 155 Australians (68% female), aged 17 to 24 years (M = 20.97, SD = 2.40) participated in this study. Two groups of participants were recruited: 1) young adults who reported anxiety symptoms and hazardous levels of alcohol use (as indicated by ≥8 on the Alcohol Use Disorders Identification Test [AUDIT]; Babor et al., 2001); and 2) young adults who reported anxiety symptoms and low risk alcohol use (<8 on the AUDIT). Group one participants were collected as part of a baseline assessment for a randomized controlled trial examining the efficacy of *Inroads;* an internet-delivered early intervention for anxiety and hazardous alcohol use among young adults (Stapinski et al., 2019). To ensure coverage of the full spectrum of alcohol use severity, the *Inroads* sample was supplemented with group two, who reported anxiety symptoms and low risk alcohol use. The recruitment strategy is summarized in Figure 3.1.

Figure 3.1. Flow diagram of the recruitment strategy for this study.



Note. EF = executive functioning; RCT = randomized controlled trial.

Eligibility criteria for both samples were: 1) aged between 17 and 24 years; 2) living in Australia; 3) experiencing at least mild symptoms of anxiety (ranging from mild to severe), as indicated by a score ≥5 on the Generalized Anxiety Disorder Questionnaire-7 (GAD-7; Spitzer et al., 2006) or a score ≥6 on the Mini-Social Phobia Inventory (Mini-SPIN; Seeley-Wait et al., 2009); and 4) had access to the internet and a computer with a mouse. By requiring participants to meet only one of two relatively low anxiety-related thresholds, we were able to capture a full spectrum of internalizing symptoms (see Table 3.1 and **Appendix 3** for further details). Participants were excluded if they: 1) were unable to provide contact information; 2) had insufficient English literacy to engage with study materials; 3) reported daily use of cannabis or benzodiazepines, or weekly use of psychostimulants (assessed by the National Institute on Drug Abuse Quick Screen Questions; Zgierska et al., 2014); 4) had significant risk of complicated alcohol withdrawal; 5) had active suicidal ideation (indicated by a single item assessing experience of suicidal thoughts and intent in the past two weeks); 6) had active symptoms of psychosis (score ≥3 on the Psychosis Screening Questionnaire;

Bebbington & Nayani, 1995); or 7) were currently accessing ongoing psychological treatment for mental health or drug or alcohol problems.

3.3.2 Procedure

The study received ethical approval from the University of New South Wales Human Research Ethics Committee (HC17185) and the University of Sydney Human Research Ethics Committee (2018/877). Participants who responded to the study advertisements gave written informed consent and were directed to complete a 15-minute online eligibility assessment. Those who were eligible and consented to participate completed an evaluation which consisted of two phases, undertaken on separate days: 1) a 30–45-minute online survey, hosted securely on the inroads.org.au site; and 2) approximately 30 minutes of online neuropsychological testing via Inquisit Web 5.0.10 (Inquisit 5, 2016), which was conducted within two weeks of completing the survey. At each phase, participants were provided with detailed instructions via phone, text, and email to ensure rigorous task completion. Participants were required to complete the online survey before being given access to the online neuropsychological tasks. Participants enrolled in the active *Inroads* intervention group were required to complete neuropsychological tasks prior to entering the active treatment phase. Participants were instructed to complete the neuropsychological battery in a quiet environment with no distractions and were advised not to use pen and paper as an aid to completing the tasks. Neuropsychological tasks were counterbalanced across participants. All data were stored on encrypted servers, protected by high-end firewall systems. Participants received a $30 gift voucher as reimbursement for their time.

3.3.3 Measures

3.3.3.1 Internalizing symptoms

An internalizing latent variable was derived using the following measures: 1) the GAD-7 (Spitzer et al., 2006); 2) the 21-item Depression and Anxiety Stress Scale (DASS; Lovibond & Lovibond, 1995); and 3) the composite score of the 12-item Social Phobia Scale and Social Interaction Anxiety Scale short forms (SIAS-6/SPS-6; Peters et al., 2012). The GAD-7

assessed symptoms across a range of anxiety disorders, including GAD, panic, and social anxiety. The DASS assessed symptoms of anxious arousal, stress, and depression. While the SIAS-6/SPS-6 assessed symptoms specific to social interaction and performance anxiety.

3.3.3.2 Executive functioning

An EF latent variable was derived from three subdomains based on an established empirical model of EF (inhibition, set shifting, information updating; Miyake et al., 2000)[5], and were assessed using Inquisit Web (Inquisit 5, 2016). The tasks described below have been shown to be psychometrically robust in assessing EF performance (Kopp et al., 2019; Martinez-Loredo et al., 2017; Miyake et al., 2000; Nyongesa et al., 2019).

Inhibition of prepotent responses. The Stroop Color-Word Test (Stroop, 1935): Over 84 trials, participants were shown color words and asked to indicate the color of the font by key press. There were three trial types, with reaction time recorded: 1) congruent trials: color word and color font were consistent; 2) incongruent trials: color word and color font were not consistent; and 3) control trials: colored rectangles were presented.

Mental set shifting. The Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948): Participants sorted cards into categories and no instructions were given in regard to the categorization rule. After each categorization, feedback was provided on whether their response was correct. There were three categorization principles (color, shape, number) that changed, without prior warning, each time the participant made 10 consecutive correct responses for a category. The task ended when the participant completed two sequences of the three categorization principles, or when the participant reached 128 cards.

Information updating and monitoring. The Letter Memory Task (Friedman et al., 2008): Participants viewed a series of letters one at a time on the computer screen and were asked to rehearse out loud the previous three letters in the series. Without prior warning, the last letter disappeared (after 5, 7, or 9 letters) and the participants were required to enter the

[5] In this chapter, set shifting refers to mental flexibility and information updating refers to working memory.

previous three letters from a letter matrix on the screen. Participants completed 12 trials (four per set of 5, 7, and 9 letters), where the order was randomly determined.

3.3.3.3 Alcohol measures

The 28-item Drinking Motives Questionnaire-Revised (DMQ-R; Grant et al., 2009) assessed alcohol use motives in the past six months across five subscales; coping-anxiety and coping-depression (internally generated, negative reinforcement), enhancement (internally generated, positive reinforcement), conformity (externally generated, negative reinforcement), or social (externally generated, positive reinforcement). A composite score of the coping-anxiety and coping-depression subscales was created to measure generic internalizing coping motives, shown to be psychometrically sound in adolescents (Cooper, 1994) and young adults (MacLean & Lecci, 2000). The timeline follow-back (TLFB; Sobell et al., 1979; Sobell & Sobell, 1995) procedure obtained participants' retrospective estimates of daily drinking over the previous 30 days to calculate total past month alcohol consumption. The AUDIT (Babor et al., 2001) obtained participants' alcohol use consumption and related harms, with higher scores indicative of more severe Diagnostic and Statistical Manual Mental Disorders Fifth Edition (DSM-5) AUD symptomology (Hagman, 2016).

3.3.4 Data analyses

CFAs were conducted using continuous indicator measures to identify two latent variables, representing internalizing symptoms and EF. The internalizing latent variable included five indicators: GAD-7, DASS-Anxiety, DASS-Depression, DASS-Stress, and composite SIAS-6/SPS-6. The EF latent variable also included five indicators: the Stroop incongruent trials reaction time, WCST categories completed, WCST trials to complete the first category, WCST perseverative errors, and the Letter Memory Task proportion correct score. Possible EF indicators were selected based on previous studies (Curtin & Fairchild, 2003; Kopp et al., 2019; Miyake et al., 2000), with the five included indicators providing the best model fit to the data. The CFAs used robust maximum likelihood estimation to account for the moderate violation in normality. Model fit for the CFAs were determined using the root mean square error of approximation (RMSEA), Comparative Fit Index (CFI), the Tucker–

Lewis Index (TLI), the standardized root mean square residual (SRMR), and the chi-square goodness of fit statistic (χ^2). Acceptable model fit was indicated by < .08 RMSEA and SRMR values, and ≥ .90 CFI and TLI values (Brown, 2006). Non-significant χ^2 values indicated there was no significant difference between the sample covariance matrix, representing good model fit (Byrne, 1998).

To examine the associations between the internalizing and EF latent variables on observed alcohol-related outcomes, and associations between alcohol measures, we first estimated main effects using regressions. Second, we estimated three random-effects LMS' to examine the interaction between internalizing symptoms and EF on drinking motives to cope with negative affect, alcohol consumption, and AUD symptoms. Third, we evaluated a LMMS to investigate the indirect effects of coping-motivated drinking and consumption on the association between the interaction term and AUD symptoms. As being a lifetime non-drinker precludes the use of alcohol as a coping motive, sensitivity analyses for all models including the coping variable were re-estimated with lifetime non-drinkers excluded (n = 5). Missing neuropsychological data for the Stroop (n = 51), WCST (n = 53), and Letter Memory Task (n = 54) was accounted for in the LMS and LMMS using full information maximum likelihood estimation (FIML), which handles incomplete indicator observations by using all available information in the models to estimate parameters rather than deleting cases with missing data. FIML produces unbiased estimates under the assumption that data are missing at random (MAR). To ensure the current analyses were robust under the assumptions of MAR, variables associated with non-response were identified and included in the models. All analyses included age, sex, and education level as covariates. In order to isolate effects of drinking motives to cope, which are internally generated and negatively reinforced, the opposing internally generated drinking motive—enhancement motives—which are positively reinforced, was added as a covariate during sensitivity analyses. Conventional fit indices are not available for LMS, therefore three models (null, main effects, interaction) were compared for each alcohol measure, using the difference in scaled log likelihood multiplied by two (scaled $\Delta\chi^2$). Significance indicated improvement in model fit from entering additional parameters into the model (see **Appendix 3** for details). Previous Monte Carlo data simulation techniques of structural equation models demonstrate that the current sample size is adequate for the analyses (Wolf et al., 2013). All analyses were conducted in Mplus, version 8.4 (Muthén & Muthén, 2017).

3.4 Results

Table 3.1 provides the participant descriptive statistics. Participants who declined to participate in neuropsychological testing (n = 51) were more likely to report significantly higher AUD symptoms (**Appendix 3** Table 1).

Table 3.1. Descriptive statistics.

	n	**Mean**	***SD***	**Minimum**	**Maximum**	**Possible scale range**
Sex (F:M)	106:49					
Highest education (%)						
Primary school	13 (8.4)					
Secondary school	69 (44.5)					
Trade/apprenticeship	7 (4.5)					
Other tertiary diploma	21 (13.5)					
Bachelor degree or higher	45 (29)					
Age	155	20.97	2.40	17	24	
Internalizing symptoms						
GAD-7	155	12.50	4.34	2	21	0–21
DASS-Anxiety	155	15.99	8.61	0	38	0–42
DASS-Depression	155	19.95	9.90	2	42	0–42
DASS-Stress	155	22.01	8.17	6	42	0–42
SIAS-6/SPS-6	155	18.97	10.22	0	45	0–48
Alcohol measures						
Age of first drink[1]	155	15.21	1.99	6	21	
DMQ-R internalizing coping	155	3.27	2.29	0	8	0–10
DMQ-R enhancement	155	1.84	1.18	0	4	0–5
TLFB past month consumption	155	75.96	88.09	0	527	
AUDIT total score	155	16.40	9.90	0	35	0–40
Executive functioning measures						
Stroop incongruent RT (ms)	103	1153.45	325.96	645.14	2400.50	
WCST categories completed	102	4.98	1.62	1	6	
WCST perseverative errors	102	37.27	22.10	1.06	100	
WCST trials to complete 1st category	102	13.28	5.07	10	47	
Letter Memory Task accuracy (%)	101	85.64	14.91	42.00	100.00	

Note. AUDIT = Alcohol Use Disorders Identification Test; DASS = Depression and Anxiety Stress Scale; DMQ-R = Drinking Motives Questionnaire-Revised; F = female; GAD-7 = Generalized Anxiety Disorder Questionnaire; M = male; ms = milliseconds; RT = reaction time; SIAS-6/SPS-6 = Social Phobia Scale and Social Interaction Anxiety Scale; TLFB = timeline follow-back; WCST = Wisconsin Card Sorting Test.
[1] Five participants (from the low risk alcohol group) reported they have never tried alcohol.

Adequate internal consistency was observed for internalizing (GAD-7: α = .824; DASS: α = .895; SIAS-6/SPS-6: α = .887) and alcohol-related scales (DMQ-R internalizing: α = .955; DMQ-R enhancement: α = .891; TLFB: α = .945; AUDIT: α = .911). Participants in the hazardous alcohol group had consumed an average of 102 drinks over the previous month (*SD* = 89.91, range = 0–527), while participants in the low risk alcohol group had consumed an average of 5 drinks (*SD* = 7.46, range = 0–29). Five participants (3.2%) in this study had never consumed alcohol.

3.4.1 Model fit

The CFA measurement models for the internalizing (CFI = .988, TLI = .976, RMSEA = .045, SRMR = .031, χ^2 = 6.563, *ns*) and EF latent variables (CFI = .978, TLI = .956, RMSEA = .059, SRMR = .056, χ^2 = 6.837, *ns*) were acceptable. The two LMS' estimating the interaction of internalizing symptoms and EF on drinking motives to cope with negative affect ($\Delta\chi^2$ = −8.128, Δdf = 1, p < .001) and total past month alcohol consumption ($\Delta\chi^2$ = 81.907, Δdf = 1, p < .001) were the most parsimonious models. No improvement in model fit resulted from adding parameters to the AUD symptoms models (Table 3.2).

Table 3.2. Latent moderated structural equation model fit comparison.

Model	Null (∅) / main (γ) / interaction (ω)	Log likelihood	Parameters	Scaled correction	$\Delta\chi^2$	Δ *df*	Residual variance	Unique variance (%)
INTxEF → drink to cope	∅	−2827.377	41	1.515		-	0.988	-
	γ	−2815.668	43	1.465	53.000***	2	0.818	17.0
	ω	−2809.837	44	1.399	−8.128***	1	0.700	11.8
INTxEF → alcohol consumption	∅	−3480.417	41	1.491		-	0.873	-
	γ	−3474.872	43	1.467	11.403***	2	0.772	10.1
	ω	−3462.201	44	1.440	81.907***	1	0.553	21.9
INTxEF → AUD symptoms	∅	−3144.405	41	1.360		-	0.874	-
	γ	−3141.923	43	1.337	−0.749	2	0.838	3.6
	ω	−3139.973	44	1.317	−0.187	1	0.786	5.2

Note. Standardized residual variance values are reported. In the null models (∅), effects of internalizing symptoms, executive functioning and the interaction term on the dependent variable were constrained to zero. In the main effect models (γ), the internalizing symptoms and executive functioning latent variables were freely estimated, with a fixed interaction term of zero. In the interaction effect models (ω), the effects of internalizing symptoms, executive functioning and the interaction term were freely estimated. INT = internalizing symptoms; EF = executive functioning; AUD: alcohol use disorder.
*** p < .001.

3.4.2 Main effects

Table 3.3 presents the main effect outcomes. High internalizing symptoms were only significantly associated with strong drinking motives to cope with negative affect ($\beta = 0.358$, *S.E.* = 0.096, $p < .001$). Deficits in EF were significantly associated with strong drinking motives to cope with negative affect ($\beta = 0.319$, *S.E.* = 0.122, $p = .009$) and high alcohol consumption ($\beta = 0.333$, *S.E.* = 0.107, $p = .002$). Strong drinking motives to cope with negative affect were associated with high alcohol consumption ($\beta = 0.450$, *S.E.* = 0.061, $p < .001$) and AUD symptoms ($\beta = 0.621$, *S.E.* = 0.052, $p < .001$). High alcohol consumption was also associated with high AUD symptoms ($\beta = 0.599$, *S.E.* = 0.047, $p < .001$). Results related to coping motives remained consistent when lifetime non-drinkers were excluded (**Appendix 3** Table 2) and when enhancement motives were added as a covariate during sensitivity analyses (**Appendix 3** Table 3).

Table 3.3. Outcomes of main effects using regressions and results of the latent moderation models of internalizing symptoms and executive dysfunction on alcohol-related outcomes.

	Coping motive			Alcohol use			AUD symptoms		
	β	***S.E.***	***p***	***β***	***S.E.***	***p***	***β***	***S.E.***	***p***
Main effects									
Internalizing	0.358	0.096	< .001	−0.073	0.112	.512	0.117	0.093	.207
EF deficit	0.319	0.122	.009	0.333	0.107	.002	0.189	0.100	.060
Coping		–		0.450	0.061	< .001	0.621	0.052	< .001
Alcohol use		–			–		0.599	0.047	< .001
Age	0.140	0.238	.557	0.425	0.092	< .001	0.429	0.073	< .001
Sex	0.088	0.074	.229	−0.155	0.067	.021	−0.036	0.074	.628
Education	−0.029	0.145	.843	−0.139	0.097	.150	−0.177	0.102	.082
Latent moderation models									
INT x EF	−0.305	0.093	.001	−0.465	0.128	< .001	−0.191	0.085	.025

All parameters are standardized. INT = internalizing symptoms; EF = executive functioning; coping = DMQ-R composite score for coping with internalizing symptoms; alcohol use = timeline follow-back total alcohol consumption; AUD symptoms = AUDIT total score.

3.4.3 Latent moderation structural equation models

The interaction term accounted for 11.8%, 21.9%, and 5.2% of unique variance in drinking motives to cope with negative affect, alcohol consumption, and AUD symptoms, respectively (Table 3.2). A significant interaction between internalizing symptoms and EF

on drinking motives to cope with negative affect (β = −0.305, *S.E.* = 0.093, p = .001), alcohol consumption (β = −0.465, *S.E.* = 0.128, p < .001), and AUD symptoms (β = −0.191, *S.E.* = 0.085, p = .025) was observed (Table 3.3). The relationship between the interaction term and drinking motives to cope with negative affect remained significant when lifetime non-drinkers were excluded (**Appendix 3** Table 2) and when enhancement motives were added as a covariate during sensitivity analyses (**Appendix 3** Table 3). An examination of simple slopes confirmed that high internalizing symptomology and EF deficits were associated with strong drinking motives to cope with negative affect, high alcohol consumption, and greater AUD symptoms (Figure 3.2).

3.4.4 Latent mediated moderation structural equation model

The findings are reported in Table 3.4 and illustrated in Figure 3.3. Of importance to our hypotheses, the indirect effect of drinking motives to cope with negative affect and alcohol consumption on the association between the internalizing symptoms and EF interaction term with AUD symptoms was significant (β = −5.566, *S.E.* = 2.600, p = .032). Full mediation was implied by the combination of a significant indirect effect and a non-significant direct effect (β = −8.440, *S.E.* = 5.333, p = .144) of the interaction term on AUD symptoms. Results were robust to the exclusion of lifetime non-drinkers (**Appendix 3** Table 4) and when enhancement motives were added as a covariate during sensitivity analyses (**Appendix 3** Table 5).

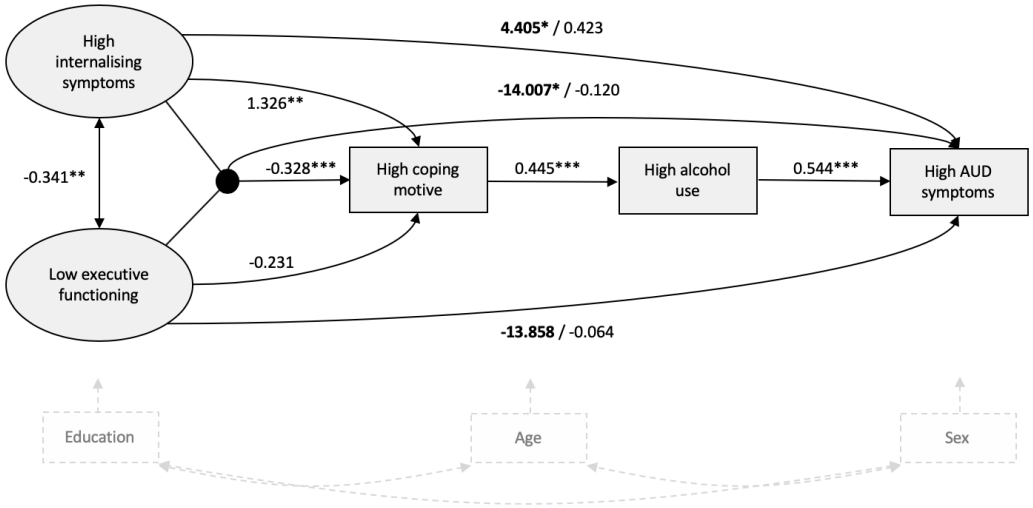
Figure 3.2. Association between internalizing symptoms and alcohol outcomes at lower (–1 *SD*) and higher (+1 *SD*) levels of executive functioning. This figure demonstrates higher internalizing symptoms are associated with stronger drinking motives to cope with internalizing symptoms, higher alcohol consumption and greater AUD symptoms for participants with lower levels of executive functioning.

Table 3.4. Total, direct and indirect effects of internalizing symptoms, executive dysfunction and the interacting term in a LMMS.

Paths	Total effect			Direct effect			Indirect effect		
	β	***S.E.***	***p***	***β***	***S.E.***	***p***	***β***	***S.E.***	***p***
INT → drink to cope → alcohol → AUD symptoms	4.405	1.813	.015	2.507	1.474	.089	1.899	0.640	.003
EF → drink to cope → alcohol → AUD symptoms	−13.858	32.620	.671	−7.377	21.587	.733	−6.482	11.812	.583
INTxEF → drink to cope → alcohol → AUD symptoms	−14.007	6.893	.042	−8.440	5.333	.114	−5.566	2.600	.032

All parameters are unstandardized. INT = internalizing symptoms; EF = executive functioning; drink to cope = DMQ-R composite score for coping with internalizing symptoms; alcohol = timeline follow-back total alcohol consumption; AUD symptoms = AUDIT total score.

Figure 3.3. Results of the latent mediated moderation model.



Note. The black circle represents the latent internalizing symptoms and executive functioning interaction term. Parameters in bold are unstandardized total effects. Other parameters are standardized direct effects. Covariates are illustrated in gray.

3.5 Discussion

To our knowledge, this is the first study to model the complex inter-relations between internalizing symptoms, EF, and alcohol-related outcomes in young adults. We found that internalizing symptoms in conjunction with EF deficits were associated with strong drinking motives to cope with negative affect, high alcohol consumption, and greater AUD

symptoms. The interaction between internalizing symptoms and EF deficits on AUD symptoms was mediated via associations with drinking motives to cope with negative affect and alcohol consumption.

The results are consistent with the three theoretical frameworks which we drew upon. The LMS and LMMS results align with the attention control theory, which posits that internalizing symptoms interact with cognitive capacity in young adults (Eysenck et al., 2007; Eysenck & Derakshan, 2011). The finding that internalizing symptoms severity was independently, and in interaction with EF, related to coping-motivated drinking is in line with the premises of the drinking motives and dual process models (Cooper, 1994; Cooper et al., 1995; Wiers et al., 2007). Furthermore, the indirect relationship between the internalizing and EF interaction on AUD symptoms observed in the LMMS was fully mediated by drinking motives to cope with negative affect and alcohol consumption, which aligns with Cooper and colleagues' hypothesis (Cooper et al., 2016) that drinking motives are a key mechanism by which more distal variables influence alcohol outcomes. This critical finding may help explain previous discrepant results on the relationship between internalizing symptomology and problematic drinking in young adults (Dyer et al., 2019; Keyes et al., 2012; Morris et al., 2005; Pedrelli et al., 2016).

These findings are particularly important given the young age of these participants and the relatively early stages of their engagement with hazardous drinking patterns, during a critical neurodevelopmental period. These drinking behaviors may cause further neurobiological harms on the developing brain (Lees et al., 2019), particularly in regard to the neurobiological substrate of EF, the PFC, which continues maturing into the mid-twenties (Gogtay et al., 2004). Hazardous drinking during brain maturation may result in a feed-forward cycle of further EF deficits, via neural harm to the developing PFC. Greater EF deficits in these youth could contribute to the maintenance of hazardous patterns of alcohol use and increased risk of progression to AUD, through the inability to suppress maladaptive coping behavior despite the adverse consequences, although this needs to be verified in longitudinal studies (Volkow et al., 2013).

Despite finding that greater EF resources are associated with low desires to drink hazardous amounts of alcohol as a maladaptive way to cope with negative feelings, EF ability has been somewhat overlooked as a protective resource of this kind among those presenting with

internalizing symptoms (Wiers et al., 2007). Greater availability of resources for cognitive operations may allow young adults to more effectively manage anxious and depressive symptoms (Riglin et al., 2016). Incorporating strategies to strengthen EF in addition to targeting internalizing symptoms in prevention and intervention initiatives may be beneficial. Cognitive training strategies have demonstrated success in reducing alcohol use (Bowley et al., 2013) and in a range of clinical populations, including mental and SUDs (Keshavan et al., 2014). However, the effectiveness of cognitive training as a prevention initiative has not been thoroughly investigated, with trials currently underway (Bourque et al., 2016; Mewton et al., 2017; O'Leary-Barrett et al., 2017).

3.5.1 Strengths and limitations

A strength of this study is the broad range of symptoms represented in the sample, from mild to severe treatment-seeking levels of internalizing behaviors and alcohol consumption. This enabled us to employ robust CFA, LMS, and LMMS analyses which are seldom used in substance-use-based neuropsychological research. Although this study provides important insights, further examination into the robustness of the LMMS is required. Replication is necessary in other, larger and more diverse samples, such as the ABCD Study (Volkow et al., 2018), to determine whether the model can be extended to help explain the uptake, frequency, and quantity of other substance use from early adolescence through to adulthood. A limitation of this study is the cross-sectional nature which highlights a critical issue from a broader perspective of the difficulty in disentangling the temporal ordering of the associations among brain maturation, behavioral risk factors, and alcohol use. The current sample consisted predominantly of females, which also limits generalizability. Participants who declined to participate in the neuropsychological testing component of this study were more likely to report significantly greater AUD symptoms. Considering the associations between EF deficits and alcohol-related outcomes, the effects of this missing data may have attenuated the observed associations toward the null. This potentially means the reported associations are smaller in magnitude than the true effects. Externalizing symptoms were not assessed in this sample and we were therefore unable to control for this in analyses. Lastly, participants were not asked to provide confirmation of compliance with instructions for the online neuropsychological testing. Despite evidence to suggest that online neuropsychological testing is reliable and valid (Raz et al., 2012),

future studies using online neuropsychological assessments could incorporate real-time measures of compliance, such as visual and audio recordings of completion.

3.5.2 Conclusions

This study was the first to find that greater internalizing symptoms in conjunction with EF deficits were related to AUD symptoms in Australian young adults via associations with drinking motives to cope with negative affect and alcohol consumption. Novel targets of EF training may be an appropriate adjunct alongside targeting internalizing symptoms in prevention and intervention initiatives. Further research is required to test the robustness of this model in other samples at different stages of use and within a longitudinal framework.

Chapter 4

Risk profiles of preadolescents with familial alcohol use problems

Preface

Chapters 2 and **3** sought to improve understanding of the precursory risk factors of binge drinking among young people. As described in **Chapter 1**, familial alcohol use behaviors may increase the likelihood of young people presenting with such risk factors. Research has examined the risk profiles of young people with familial alcohol use problems; however, the evidence base contains significant methodological limitations. The primary concerns include analysis of underpowered samples and limited adjustment of potentially confounding factors. Addressing these limitations, this chapter reports on the largest published study to examine the neurobiological, cognitive, psychological, and early alcohol use risk profiles of preadolescents with familial alcohol and/or other substance use problems. Both alcohol and other substance use was considered given the substantial overlap in familial problems reported in the current sample (alcohol and substance use problems = 49%, alcohol only = 41%, other substances only = 10%).

This chapter addresses the second research question of this thesis: '*Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?*' This study involved a multidisciplinary international team of collaborators and has been published as Lees, B., Stapinski, L. A., Teesson, M., Squeglia, L. M., Jacobus, J., & Mewton, L. (2021). *Drug & Alcohol Dependence, 218*, 108403. Supplementary materials are available in **Appendix 4**.

4.1 Abstract

Background: There are significant knowledge gaps of the vulnerabilities faced by youth from families with histories of alcohol or substance misuse. This study aimed to provide a comprehensive assessment of the problems experienced by substance-naïve children with positive family histories of substance misuse (FHP).

Methods: Baseline data from up to 11,873 children (52.1% male), aged 9.0–10.9 years (M = 9.9±0.6), enrolled in the US-based ABCD Study were utilized. Mixed models tested cross-sectional associations between family history of substance misuse, assessed categorically and continuously, with neurobiological, cognitive, behavioral, and psychological outcomes, when controlling for confounding factors, including family history of psychopathology, and correcting for multiple comparisons.

Results: One in four (26.3%) youth were categorized as FHP (defined as ≥one parent or ≥two grandparents with misuse history). Controlling for confounding, FHP youth exhibited thinner whole cortices and greater surface area in frontal and occipital regions than youth with no such history ($|ds| \geq 0.04$, $ps < .001$). FHP youth experienced greater psychopathology and sleep disturbance ($|ds| \geq 0.36$, $ps < .001$) and were more likely to be diagnosed with multiple mental disorders (*adjusted odds ratio* [*aOR*] ≥ 1.22, $ps < .001$), with severity of effects dependent on family history density (FHD) of substance misuse. Differences in cognition, impulsivity, and motivation were non-significant. Psychopathology, mental disorders, and sleep disturbance were negatively correlated with various neural indices ($|rs| = 0.01–0.05$, $ps < .05$).

Conclusions: At age 9–10 years, FHP youth can experience numerous problems, with psychopathology and mental disorders being some of the most significant. Therefore, prevention efforts should target psychopathology vulnerabilities in FHP children.

4.2 Introduction

AUD and other SUDs are widespread disorders that are increasing in occurrence, with a recent 12-month prevalence rate of 7.8% to 12.7% among US adults (Grant et al., 2017; Substance Abuse and Mental Health Services Administration, 2019). SUDs are associated with negative outcomes such as work absence, homelessness, mental disorders, suicide, accidents, and violence (Schifano et al., 2020; Teesson et al., 2010). Additionally, SUDs are related to a number of cognitive impairments and changes in brain structure and connectivity (Lees, Meredith, Kirkland et al., 2020; Ramey & Regier, 2018). Several factors lead to the development of SUDs, including genetics as demonstrated through twin and adoption studies, as well as environmental and psychological influences (Enoch, 2006; Enoch & Goldman, 2001). Heritability estimates of SUDs range from 30% to 60% (Knopik et al., 2004; Verhulst et al., 2015), and a shared environment with an individual with SUD explains an additional 10% of the risk (Verhulst et al., 2015). Approximately one in four children in the US grow up with an individual with SUD in their immediate family (Grant, 2000). Individuals with a first-degree relative who has a history of SUD (i.e., family history positive [FHP]) are approximately four to nine times more likely to develop a SUD in their lifetimes, compared to individuals with no such history (family history negative [FHN]) (Merikangas et al., 1998). In addition, the likelihood of developing a SUD is correlated with the number of affected first- and second-degree relatives (i.e., FHD) (Dawson et al., 1992). For these reasons, FHP substance-naïve youth with affected first- and second-degree relatives have been identified as 'at-risk' individuals for onset of SUD within the research community (Cservenka, 2016).

A large body of literature has examined the neurobiological mechanisms by which heritable risk for SUD may be partly transmitted. Functional neuroimaging studies suggest that FHP youth exhibit altered neural activation during EF, reward responsiveness, and emotional processing tasks (Cservenka, 2016; Lees, Aguinaldo, Squeglia et al., 2020; Tervo-Clemmens et al., 2020). Likewise, cognitive studies have identified poorer behavioral performance on measures of inhibition, working memory, and impulsivity for FHP compared to FHN youth (for review, see Squeglia & Cservenka, 2017). Relatively few studies, however, have focused on structural brain differences in FHP youth. A 2019 review identified that FHP youth have altered brain volume in several frontal and subcortical regions compared to FHN, with little to no information available on cortical thickness and area differences

(Comstock et al., 2019). When compared to FHN peers, FHP youth had lower frontal (Benegal et al., 2007) and amygdala volumes (Benegal et al., 2007; Dager et al., 2015; Hill et al., 2001, 2013) and greater cerebellar volumes (Benegal et al., 2007; Hill et al., 2007, 2011, 2016). Some studies reported no group differences in hippocampal (Dager et al., 2015; Hill et al., 2001) or nucleus accumbens volume (Squeglia, Jacobus et al., 2014), while others had reported greater hippocampal volume among FHP males (Hanson et al., 2010) and greater nucleus accumbens volumes among FHP females (Cservenka et al., 2015). Several studies identified have utilized small samples that are underpowered to detect small-to-moderate effects and have often used a selective regions-of-interest approach. Furthermore, a number of studies have examined offspring who use alcohol or other substances themselves, which likely confounds family history results (Comstock et al., 2019). A comprehensive evaluation of multiple morphometric indicators (i.e., volume, cortical thickness, surface area) examining widespread brain regions in a large sample of substance-naïve youth may resolve previous conflicting findings and provide more reliable biomarkers in 'at-risk' youth of later substance use problems.

In addition to neurobiological and cognitive risk indicators in FHP youth, heightened psychopathology may also increase vulnerability to onset of SUDs. Multiple studies show that FHP children have an increased risk for developing externalizing disorders, including conduct disorder, oppositional defiant disorder, and ADHD (Hill et al., 2011; Vidal et al., 2012). Increased odds of anxiety and affective disorders have also been observed in some studies (Hill et al., 2008; Hill & Muka, 1996). Limitations of these studies exist. First, the large majority of studies have not adjusted for factors other than family history of SUD that may influence the risk of psychopathology in FHP youth, such as comorbid psychopathology in family members, parenting style, or prenatal exposures (Lees, Mewton, Jacobus et al., 2020). Second, only a small number of studies have assessed elevations in risk with the number of affected first- and second-degree FHP relatives (i.e., FHD). Third, potential mechanisms underlying, or contributing to, these disorders are understudied in this population. For example, psychopathology may be a function of altered neurobiological mechanisms in FHP youth (Benegal et al., 2007) as well as environmental stressors and familial relationships (Barnow et al., 2002; Ryan et al., 2016). In summary, there are significant gaps in knowledge of the specific vulnerabilities that may antedate the development of SUDs in this 'at-risk' population. A better understanding of the problems FHP youth experience is essential in order to improve targeted prevention initiatives.

The aim of the current study was to provide a comprehensive assessment of the neurobiological, cognitive, behavioral, and psychological factors related to FHP and FHD. Data from youth aged 9 to 10 years enrolled in the ABCD Study were utilized. Based on the current evidence base, it was hypothesized that FHP youth, with at least one parent or two grandparents with a history of substance use problems, would exhibit altered brain morphometry, greater impulsivity, and poorer EF compared to FHN youth, with no first- or second-degree relatives with a history of SUD. It was also hypothesized that FHP youth would experience greater psychopathology and would be more likely to endorse low-level alcohol use experimentation (e.g., sipping) than FHN peers. Finally, it was predicted that greater FHD would be associated with poorer outcomes in youth.

4.3 Methods

4.3.1 Participants

This study examined baseline cross-sectional data from 11,873 children (52.1% male), aged 9.0–10.9 years (M = 9.9±0.6), included in the ABCD Study annual release 2.0.1. A detailed account of the recruitment strategy has been previously published (Garavan et al., 2018). A probability sample was recruited through schools, selected based on sex, race/ethnicity, socioeconomic status, and urbanicity. All parents/caregivers provided written informed consent and all children provided assent to the research protocol approved by the institutional review board at each of the 21 data collection sites.

4.3.2 Explanatory measures

The presence of lifetime symptoms associated with SUDs in biological parents and grandparents were assessed in the modified, parent-reported Family History Assessment Module Screener (Rice et al., 1995). Other second-degree relatives (i.e., aunts, uncles, half siblings) were not considered in the primary analyses due to >20% missing data and because parents' account of more distal relatives are likely to be less accurate (Andreasen et al., 1977, 1986; Thompson et al., 1982). Based on previous definitions (Cservenka, 2016), a three-level categorical variable was derived where youth were categorized as: 1) 'FHP' if they had ≥one biological parent or ≥two biological grandparents with histories of alcohol

and/or other substance use problems; 2) 'FHN' if they had no parent or grandparent with histories of problems; or 3) 'N/A' if they had just one grandparent with histories of problems (data available for n = 11,873). To evaluate the extent to which the presence of substance-related problems may contribute to childhood outcomes, FHD scores were calculated based on the sum of positive reports of problems from biological parents (+0.5) and biological grandparents (+0.25). The FHD scores could range from 0 to 4, with a score of 0 indicating absence of problems (data available for n = 11,298). Participants categorized as 'N/A' were excluded from FHP categorical analyses but were included in the FHD analyses. See **Appendix 4** for relevant questionnaire items and further details on derived variables.

4.3.3 Outcome measures

4.3.3.1 Structural brain indices (youth)

Indices of cortical thickness, surface area, and volume were examined from 34 cortical parcellations and 8 subcortical (volume only) segmentations per hemisphere based on the Desikan–Killiany brain registration atlas (Desikan et al., 2006). Volumetric and area, but not thickness, measures were corrected for intracranial volume (Schmansky, 2020). Details on MRI data acquisition are described in detail elsewhere (Casey et al., 2018) and briefly in **Appendix 4**.

4.3.3.2 Cognition (youth performance)

The cognitive assessment included seven National Institutes of Health (NIH) Toolbox tasks and composite scores for total cognition (based on all tasks), fluid cognition (Pattern Comparison, Working Memory, Sequential Memory, Flanker, Card Sort), and crystallized cognition (Vocabulary, Reading Recognition) (Luciana et al., 2018). All scores were age-corrected standard scores, where higher scores indicate greater cognitive performance. Both composite scores and individual task scores were examined as outcomes of interest.

4.3.3.3 Impulsivity and motivation (youth report)

Impulsivity was assessed using the Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form (UPPS-P) (Whiteside et al., 2005). Motivation was examined using the four subscales of the Behavioral Avoidance/Inhibition Scales (BIS/BAS) (Pagliaccio et al., 2016).

4.3.3.4 Psychopathology and lifetime mental disorder diagnoses (parent report)

Psychopathology was examined in children using the eight empirically based syndrome scales and higher-order factors of the Child Behavior Checklist (CBCL) (Achenbach, 2009). The internalizing factor was calculated from three scales (anxious depressed, withdrawal, somatic complaints), the externalizing factor from two scales (rule breaking, aggressive), and the total problems factor from all syndrome scales (previous scales in addition to social problems, thought problems, attention deficits). Here, higher scores indicate greater psychopathology. Both syndrome scales and higher-order factors were examined as outcomes of interest. Lifetime mental disorder diagnoses (i.e., past and/or present) were determined from the Schedule for Affective Disorders and Schizophrenia for School-Age Children (K-SADS), based on DSM-5 criteria (Kobak et al., 2013). The low prevalence of panic disorder (n = 27), hallucinations (n = 45), and agoraphobia (n = 55) precluded the examination of these disorders in the current study.

4.3.3.5 Sleep disturbance (parent report)

The Sleep Disturbance Scale for Children total score was utilized, where higher scores reflect greater sleep disturbance (Bruni et al., 1996).

4.3.3.6 Youth alcohol experimentation (youth report)

Lifetime endorsement of non-religious low-level alcohol use (i.e., sip of alcohol) was assessed via the youth-reported iSay Sip Inventory (Jackson et al., 2015).

4.3.4 Covariates

The following 12 fixed covariates were included in all statistical models and were dummy coded (see **Appendix 4** for details): 1) sex; 2) race/ethnicity; 3) parent education; 4) household income; 5) marital status; 6) PAE; 7) prenatal substance use exposure; and family history of psychopathology in first and/or second-degree relatives related to 8) psychosis; 9) depression; 10) anxiety; 11) antisocial behavior; and 12) mania (Table 4.1). Youth age was included as a continuous fixed effect. During sensitivity analysis, youth-reported parental monitoring and parental warmth/acceptance and parent-reported family conflict were included as three additional continuous fixed effects.

4.3.5 Statistical analysis

All continuous outcome variables were winsorized to ±3 *SD* to minimize the influence of extreme values. A series of linear mixed models were performed using R version 4.0.0 ('glmmTMB' package; Wood, 2017). Model parameters were estimated by the restricted maximum likelihood. Random intercept parameters accounted for family membership (i.e., siblings, twins, triplets) and research site or MRI scanner (i.e., for analyses with brain indices only), where family membership was nested within 22 research sites or 29 scanner sites (as some research sites have multiple scanners). Participants with missing data were excluded from analyses.

First, associations between the categorical family history variable (FHP/FHN) and outcomes of interest were examined when accounting for fixed effects (see Subsection 4.3.4). Youth categorized as 'N/A' (i.e., with just one grandparent with a history of alcohol or substance-use-related problems) were excluded from this analysis (n = 1,792). Second, additive effects of family problems were explored by entering FHD continuous scores as predictors alongside the fixed covariates. Spline regression models were estimated for continuous outcome variables to model smooth functions, including linear and nonlinear associations ('mgcv' package). Third, in order to explore whether aberrant structural brain indices were related to other problems observed in FHP youth, follow-up bivariate Pearson correlations were conducted between all outcome variables significantly associated with FHP. Finally, two sensitivity analyses were conducted where: 1) significant behavioral

analyses were re-run after entering parental monitoring, parental warmth/acceptance, and family conflict as additional fixed covariates to adjust for possible confounding effects of parenting; and 2) categorical family history analyses were re-run after excluding other relatives (i.e., aunts, uncles, siblings) from the FHN group with known parent-reported histories of alcohol or other substance use problems.

The false discovery rate (FDR) was utilized to correct for multiple comparisons in primary and sensitivity analyses, run across all behavioral models (38 FDR-corrected comparisons) and run separately across each series of morphometric indices (34 FDR-corrected comparisons for cortical thickness and area parcellations, 42 FDR-corrected comparisons for cortical volume parcellations and subcortical volume segmentations), where pFDR < .05 was equivalent to $p < .001$ (Benjamini & Hochberg, 1995). A post hoc analysis confirmed there were no matrilineal- or patrilineal-specific associations with child outcomes.

4.4 Results

4.4.1 Family history positive child outcomes

Of the 11,873 youth (52.1% male, 9.9±0.6 years) with data available on family history of SUD, 4,918 (41.4%) had at least one biological parent or grandparent with a history of alcohol or substance-use-related problems. For the categorical analysis, 3,126 (26.3%) were classified as FHP (i.e., ≥one parent or ≥two grandparents with a history of problems), 6,955 (58.6%) were classified as FHN (i.e., no first-degree family history of problems), and 1,792 (15.1%) were excluded because they had just one grandparent with a history of problems. A summary of all covariate associations is provided in **Appendix 4**.

4.4.1.1 Brain structure, cognition, impulsivity, and motivation

FHP youth exhibited lower whole brain cortical thickness than FHN youth ($d = -0.1$, pFDR < .05), when adjusting for covariates, including age, sex, race/ethnicity, parent education, household income, marital status, PAE, prenatal substance use exposure, and family histories of five types of psychopathology (Figure 4.1). In adjusted models, FHP youth also

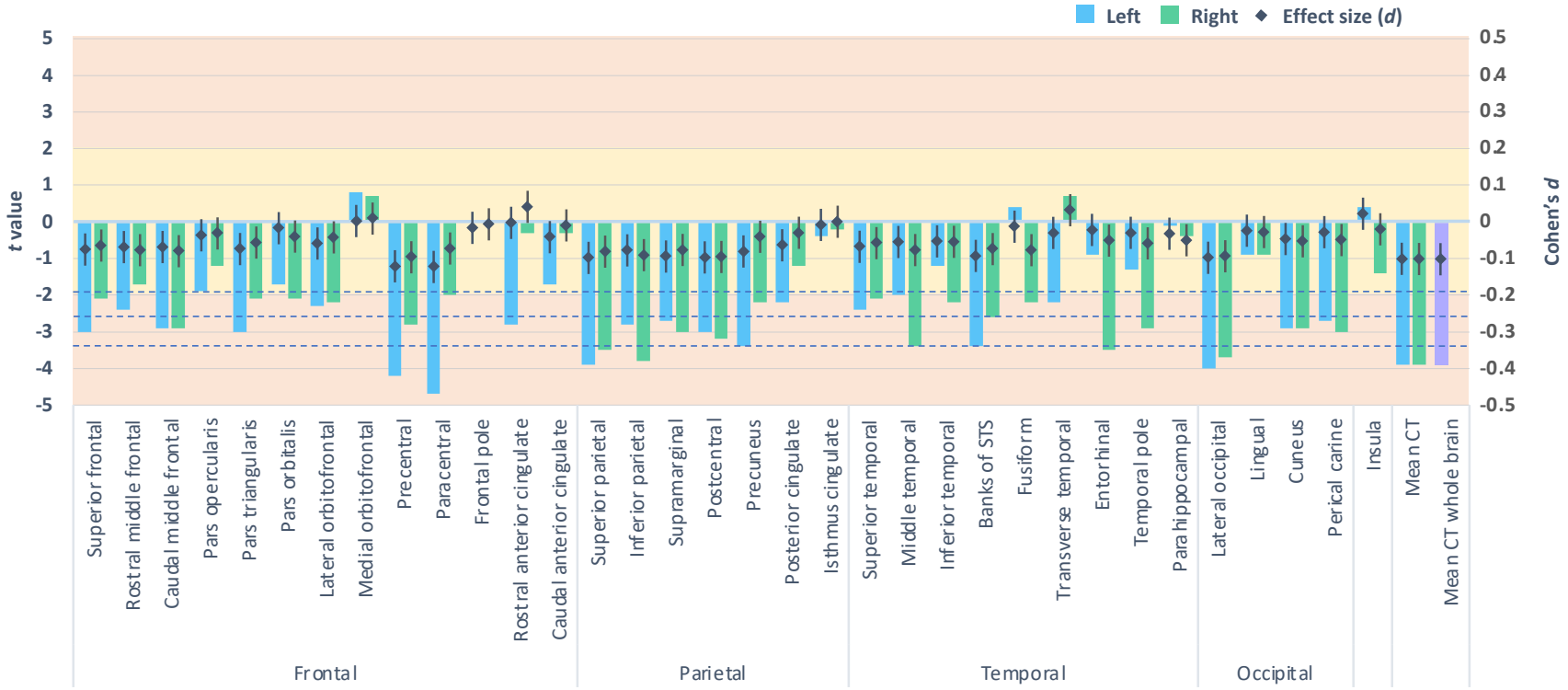
exhibited thinner cortices in nine specific regions, including the left precentral and paracentral lobules, bilateral superior and right inferior parietal lobules, left precuneus, right middle temporal gyrus, left banks of the superior temporal sulcus, right entorhinal cortex, and bilateral lateral occipital sulcus ($ds \leq -0.05$, pFDRs $< .05$) (Figure 4.1). FHP youth also exhibited greater cortical area in the right precentral lobule and right lateral occipital sulcus than FHN peers ($ds = 0.04$, pFDRs $< .05$) (Figure 4.2). No group differences for brain volume passed FDR correction (**Appendix 4** Figure 1). Furthermore, no group differences for cognitive performance or for measures of impulsivity or motivation passed FDR correction (Figure 4.3).

Table 4.1. Sociodemographic characteristics of FHN and FHP youth (n = 10,081[1]).

	FHN		FHP		*p*
	n	**%**	***n***	**%**	
Total participants	6,955	69.0	3,126	31.0	
Male	3,631	52.2	1,597	51.1	.292
Age (*M* [*SD*])	9.9	0.6	9.9	0.6	.943
Race/Ethnicity [a]					< .001
White	3,632	52.2	1,534	49.1	
Black	1,064	15.3	479	15.3	
Hispanic	1,371	19.7	694	22.2	
Asian	219	3.1	12	0.4	
Other	659	9.5	402	12.9	
Household income [a]					< .001
$25,000–50,000	1,669	24.0	1,192	38.1	
$50,000–100,000	1,688	24.3	869	27.8	
>$100,000	2,972	42.7	818	26.2	
Don't know/refuse to answer	626	9.0	247	7.9	
Parent Education [a]					< .001
<High school	468	6.7	233	7.5	
High school/GED equivalent	705	10.1	402	12.9	
College	1,726	24.8	1,250	40.0	
Bachelor degree	2,080	29.9	711	22.7	
Postgraduate degree	1,963	28.2	527	16.9	
Married	5,466	78.6	1,822	58.3	< .001
In utero alcohol exposure	1,401	20.1	1,004	32.1	< .001
In utero drug exposure	248	3.6	506	16.2	< .001
Family history of depression [b]	2,986	42.9	2,151	68.8	< .001
Family history of anxiety	1,368	19.7	1,197	38.3	< .001
Family history of antisocial behavior	1,199	17.2	1,756	56.2	< .001
Family history of mania	619	8.9	702	22.5	< .001
Family history of psychosis	464	6.7	548	17.5	< .001

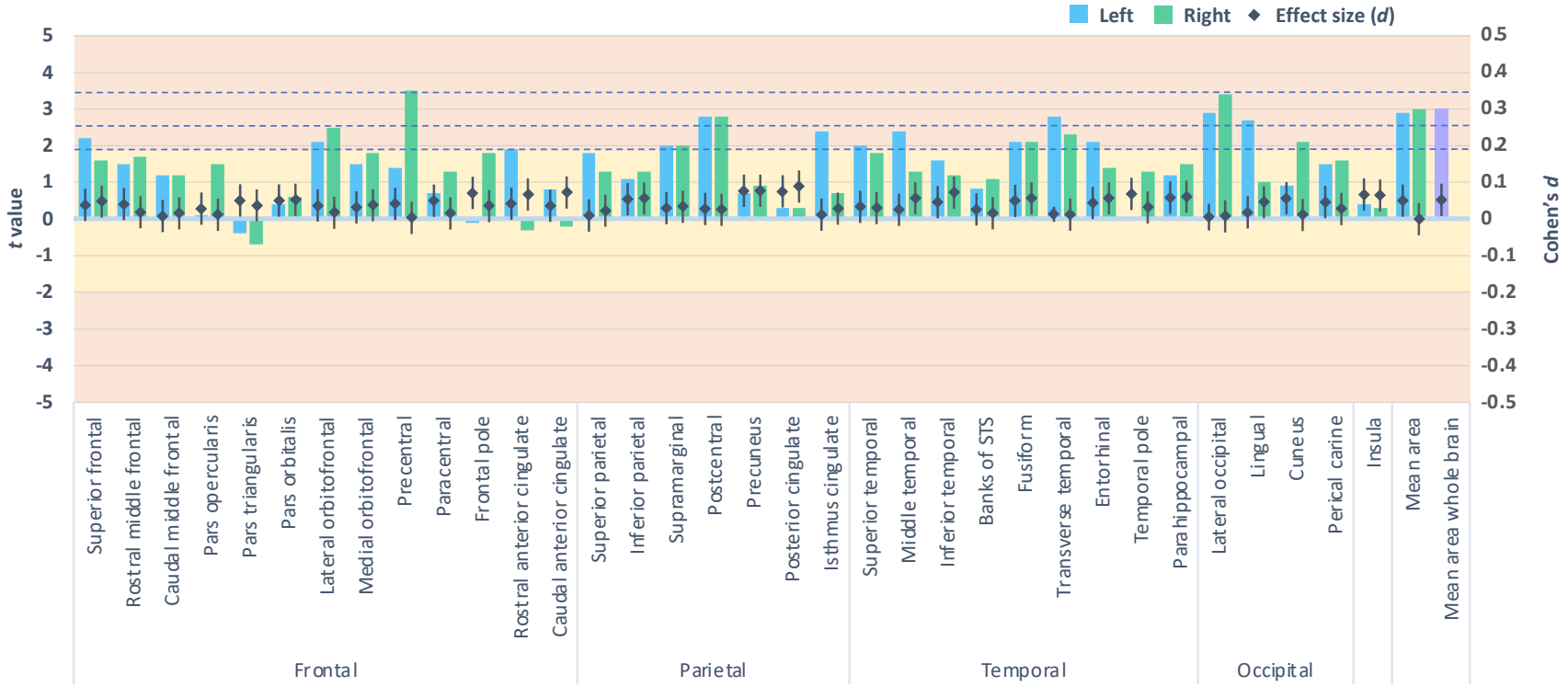
[1] Of 11,873 participants with available data on family history of substance use-related problems, 1,792 participants had just one grandparent (and no parent) with a history of problems and therefore did not meet criteria for FHP or FHN. [a] There were missing data for the following variables: Race/ethnicity (FHN = 10, FHP = 5), Parent education (FHN = 13, FHP = 3). [b] Family history of psychopathology variables includes any first or second-degree relative with past or present problems.

Figure 4.1. Cortical thickness among FHP compared to negative youth, when adjusting for fixed and random effects.



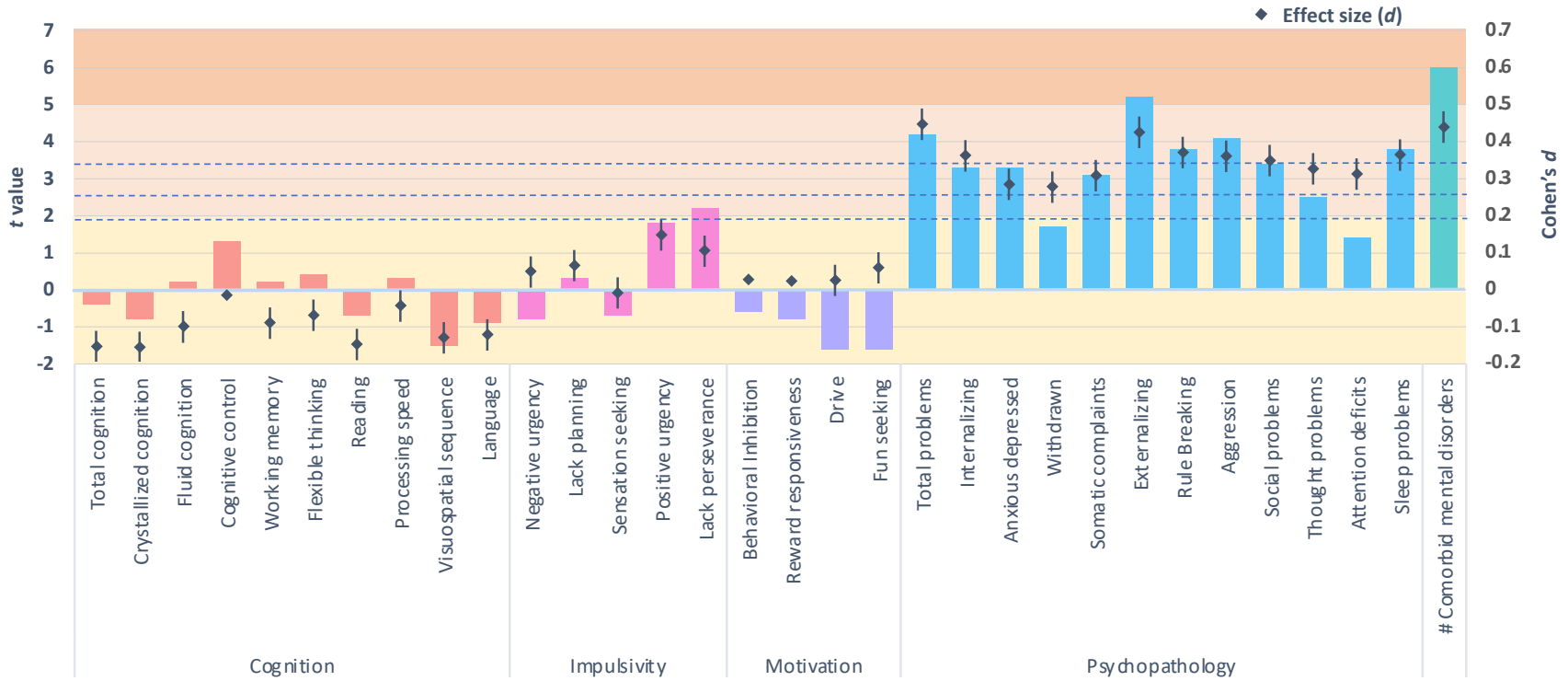
Columns represent the *t* values derived from mixed models (left axis) and the dot plot illustrates the accompanying effect sizes (Cohens *d* with 95% CIs; right axis). Dotted horizontal lines reflect *p* values .05, .01, and .001 (*p*FDR = .05). Yellow shading indicates the very small effect size range and orange indicates the small range.

Figure 4.2. Cortical area among FHP compared to negative youth, when adjusting for fixed and random effects.



Columns represent the t values derived from mixed models (left axis) and the dot plot illustrates the accompanying effect sizes (Cohen's *d* with 95% CIs; right axis). Dotted horizontal lines reflect *p* values .05, .01, and .001 (*p*FDR = .05). Yellow shading indicates the very small effect size range and orange indicates the small range.

Figure 4.3. Associations between FHP youth and behavioral outcomes, when adjusting for fixed and random effects.



Columns represent the *t* values derived from mixed models (left axis) and the dot plot illustrates the accompanying effect sizes (Cohen's *d* with 95% CIs; right axis). Dotted horizontal lines reflect *p* values .05, .01, and .001 (*p*FDR = .05). Yellow shading indicates the very small effect size range, light orange indicates small, and dark orange indicates the medium range.

4.4.1.2 Psychopathology and lifetime mental disorders

Compared to FHN peers, FHP youth exhibited significantly greater total psychopathological problems, driven by externalizing syndrome scales, in addition to greater sleep disturbance, when adjusting for covariates (*ds* ≥ 0.36, *p*FDRs < .05) (Figure 4.3). In adjusted models, FHP youth were significantly more likely to have a lifetime mental disorder diagnosis than FHN youth and were at increased odds of presenting with multiple mental disorders, when examined both categorically (Table 4.2) and continuously (Figure 4.3) (*p*FDRs < .001). Compared to FHN, FHP youth were more likely to have a lifetime diagnosis of separation anxiety, PTSD, and specific phobias in adjusted models (all *aOR*s > 1.22, *p*FDRs < .001) (Table 4.2). Prevalence rates of all mental disorders examined are available in Table 4.2 and severity of psychopathology for all CBCL measures are available in **Appendix 4** Figure 2.

Table 4.2. Summary of the odds of youth from families with substance use problems (FHP) experiencing mental disorders compared to youth from families with no problems (FHN).

Lifetime mental disorder diagnoses	**FHN (%)**	**FHP (%)**	***aOR*[a]**	**95% CI**	***t***	***p*FDR**
Number of disorders						
1+ Disorder(s)	45.1	60.0	1.22	1.09–1.36	3.39	< .001
2+ Disorders	20.3	36.5	1.37	1.20–1.58	4.49	< .001
3+ Disorders	9.9	22.4	1.55	1.30–1.84	5.00	< .001
4+ Disorders	4.4	13.5	1.83	1.47–2.28	5.44	< .001
Specific diagnoses						
Depression	1.7	4.7	1.46	1.07–1.99	2.38	.578
Generalized Anxiety	3.1	7.3	1.46	0.49–4.29	0.68	.496
Separation Anxiety	6.5	14.1	1.54	1.29–1.84	4.70	< .001
Social Anxiety	3.8	6.4	1.15	0.90–1.46	1.12	.261
Delusions	1.4	2.9	1.29	0.90–1.086	1.37	.171
ADHD	17.1	28.5	1.18	1.03–1.34	2.38	.578
Oppositional Defiant	11.3	20.0	1.25	1.07–1.46	2.85	.136
Conduct Disorder	2.1	5.7	1.43	1.06–1.92	2.34	.646
OCD	7.9	12.9	1.17	0.98–1.40	1.72	.085
Bipolar/Related Disorder	3.2	4.9	1.09	0.83–1.43	0.65	.517
PTSD	0.9	4.9	2.68	1.82–3.96	4.96	< .001
Specific Phobia	23.6	32.7	1.22	1.08–1.38	3.25	.034

aOR = adjusted odds ratio, ADHD = attention deficit hyperactivity disorder, CI = confidence interval, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder.
[a] Reference group = FHN youth.

4.4.1.3 Youth alcohol experimentation

No significant group difference was observed for youth lifetime endorsement of sipping alcohol by ages 9 to 10 years, when adjusting for covariates (*aOR* = 0.98, 95% CI 0.85–1.14, *p* = .80).

4.4.2 Family history density child outcomes

Of the 11,298 youth with available FHD data, 4,478 (39.6%) had at least one parent or grandparent with a history of alcohol or other substance use-related problems. Among those with a parent and/or grandparent with SUD-related problems, the mean density score was 0.8 ± 0.8 and the maximum was 4 (see **Appendix 4** Figure 3 for histogram of FHD scores).

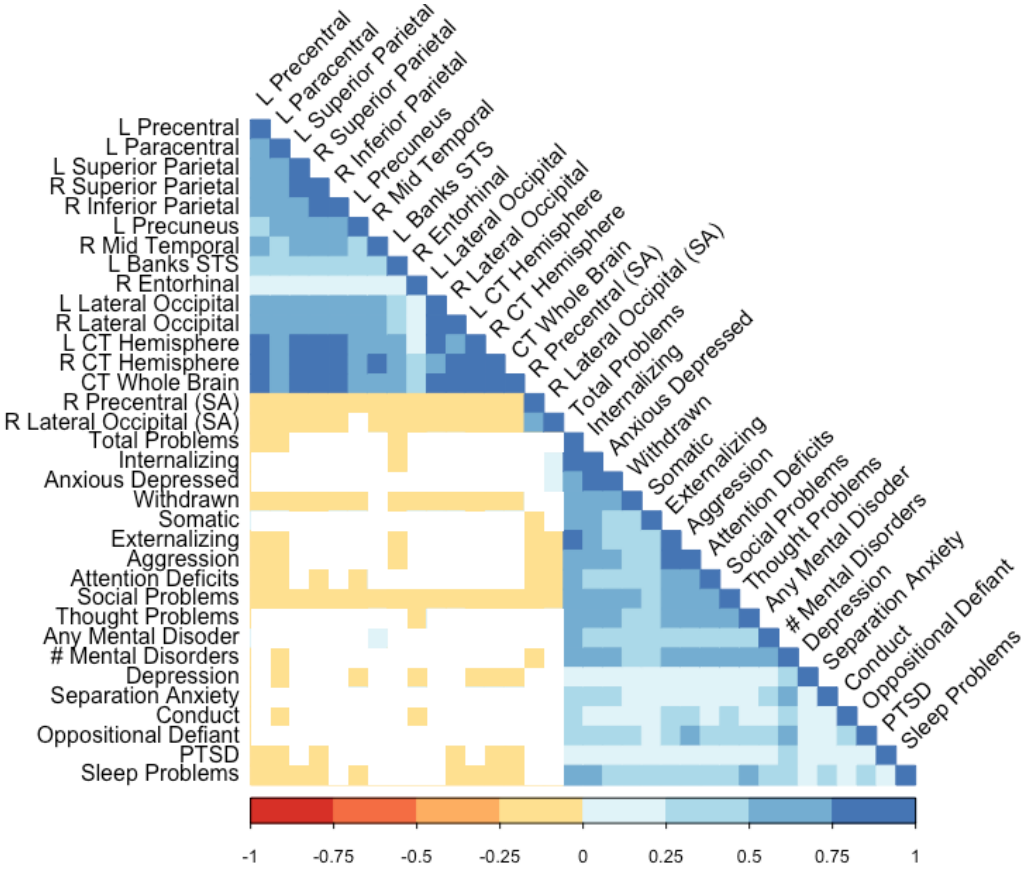
Negative associations were observed between FHD and regional cortical thickness in the left paracentral and right inferior parietal lobules and in the left banks of superior temporal sulcus (*p*FDRs < .05; **Appendix 4** Table 1). All behavioral associations observed for FHP youth were replicated in FHD analyses, excluding phobia disorders. Additionally, greater FHD was also associated with greater internalizing psychopathology, social and thought problems, as well as greater odds of a lifetime diagnosis of depression, oppositional defiant disorder, and conduct disorder (*p*FDRs < .05; **Appendix 4** Table 2). Spline models demonstrated linear associations between FHD and all significant outcomes.

Based on the finding that there were significant group and FHD differences for neural indices, additional analyses were conducted to determine whether structural differences were related to variability in psychopathology and mental disorders. Figure 4.4 illustrates follow-up bivariate correlational analyses which indicated that various cortical thickness and surface area measures were significantly and negatively related to psychopathology symptoms, sleep disturbance, as well as lifetime PTSD diagnoses (*r*s = −0.01 to −0.05, *p* < .05). Correlations by FHP and FHN groups are reported in **Appendix 4** Figures 4-5.

4.4.3 Sensitivity analyses

When parental monitoring, parental warmth/acceptance, and family conflict were included as additional fixed covariates, the majority of significant findings remained consistent with the exceptions of greater total and internalizing psychopathology and greater odds of meeting criteria for oppositional defiant disorder and conduct disorder (**Appendix 4** Table 3-4). Findings were consistent when excluding youth with known positive histories of SUD-related problems among aunts, uncles, or siblings (**Appendix 4** Table 5).

Figure 4.4. Significant correlations (colored squares) are illustrated for childhood outcomes found to be associated with family history of substance use problems (n = 10,299). White squares indicate non-significant correlations.



4.5 Discussion

The present study provided a comprehensive assessment of the neurobiological, cognitive, behavioral, and psychological problems experienced by substance-naïve youth aged 9–10

years with a family history of alcohol or other substance use problems. Consistent with hypotheses, the findings indicate that, even after controlling for sociodemographic factors, prenatal substance exposure, and family history of psychopathology, FHP youth exhibit altered brain structure (very small effect), greater psychopathology (small effect), and sleep disturbance (small effect), with the severity of most problems dependent upon FHD. Compared to FHN, FHP youth were 22% (95% CI 9–36%) more likely to have at least one mental disorder, with greater FHD linked to increased odds of both externalizing (conduct, oppositional defiant) and internalizing (depression, separation anxiety, PTSD) diagnoses. FHP youth also experienced clinical comorbidity. FHP youth, compared to FHN, were 37% (20–58%) more likely to have ≥two mental disorders, 55% (30–84%) more likely to have ≥three disorders, and 83% (47–128%) more likely to have ≥four mental disorders. In contrast to hypotheses, FHP youth did not perform significantly worse on cognitive tasks, were not more impulsive, and did not endorse alcohol sips more than FHN youth. These findings were in a largely substance-naïve cohort of youth who had not consumed a full drink of alcohol or tried other substances (99.999%), negating potential confounding effects of offspring substance use.

4.5.1 Comparison of identified family history positive vulnerabilities with previous studies

The current neurobehavioral findings replicate a study by Henderson et al. 2018 who reported lower cortical thickness in FHP compared to FHN substance-naïve adolescents and a study by Ryan et al. 2016 who reported null findings for cognition and impulsivity in a similarly aged substance-naïve cohort (M = 10.97±0.84). However, in contrast to the present results, previous studies have also reported volumetric differences between FHP and FHN youth, and related cognitive and impulsivity deficits (for review, see Comstock et al., 2019; Cservenka, 2016; McPhee et al., 2018; Squeglia & Cservenka, 2017). While conflicting findings have been reported for hippocampal and nucleus accumbens volume (as summarized in the introduction), previous studies have consistently reported greater cerebellar and lower amygdala volume among FHP individuals (Comstock et al., 2019). Disparities in results are partly due to rigorous multiple comparisons correction in the current study ($p < .001$ / pFDR $< .05$), where nominally significant group differences were observed for several morphometric indices (including cerebellar volume; see **Appendix 4**

Figure 1) and a measure of impulsivity ($p < .05$). Additionally, post hoc analysis of the psychometric properties of the impulsivity (UPPS-P) and motivation (BIS/BAS) scales indicated poor internal consistency for ~50% of the subscales which may explain the null findings in the current study (see **Appendix 4** Table 6). Conflicting findings with prior studies may also relate to the earlier neurodevelopment stage under investigation (i.e., preadolescence), possible sampling biases in previously underpowered studies, and disparities in covariate adjustments, such as PAE and other prenatal substance exposures, family history of psychopathology, race/ethnicity, and socioeconomic factors, which accounted for much of the variance in brain volume and area, cognition, and impulsivity in the current study. Furthermore, much of the previous work on FHP and FHD have recruited older samples who already engage in substance use which is known to affect neurodevelopment (Lees et al., 2019). It has been suggested that reciprocal relations exist between impulsiveness, reward responsiveness, and substance use (Ryan et al., 2016), where past substance use is linked to increased sensation seeking and greater subsequent use, which in turn may negatively affect cognition (e.g., MacPherson et al., 2010). Considering the current cohort are largely substance-naïve, it will be important to examine growth trajectories of neurodevelopment, cognition, and impulsiveness as youth enter adolescence and some begin to experiment further with substance use.

Unique regional variations between cortical thickness and area measures were observed among FHP youth. While cortical thickness and surface area are both highly heritable, these measurements are found to be genetically and phenotypically independent, with unique regional variations particularly among youth undergoing critical neurodevelopmental changes (Panizzon et al., 2009). Additionally, small negative correlations between some cortical thickness and area measures were found, perhaps as a result of 'cortical stretching' (lower thickness with greater surface area); a normal neurodevelopmental process occurring throughout childhood involving early growth of white matter which stretches the adjacent gray matter tissue (Hogstrom et al., 2013). FHP youth may exhibit an exaggerated stretching pattern, although longitudinal examination of gray and white matter trajectories is required.

FHP youth were more likely to experience mental illness than FHN peers and an additive effect of FHD was found for the prevalence of mental disorders and severity of psychopathology. These findings are consistent with other studies that have compared

psychopathology symptoms and disorders between FHP and FHN youth (e.g., El-Sheikh & Buckhalt, 2003; Hill & Muka, 1996; Ryan et al., 2016; Vidal et al., 2012). Of note, the severity of psychopathology symptoms did not reach clinically significant levels in the current study (CBCL *T*-Scores ≤ 60, *p*FDR < .05), which is also consistent with previous work in FHP preadolescents (Ryan et al., 2016). Importantly, this study adds to the existing literature by demonstrating that the effect of FHP and FHD on psychopathology and mental disorders were above and beyond that of sociodemographic characteristics, prenatal exposures, family history of psychopathology, and parenting factors.

Finally, despite FHP youth experiencing greater externalizing symptoms, these youth did not report significantly higher levels of impulsivity. Post hoc correlation analyses indicated these variables were only weakly correlated (**Appendix 4** Figure 6), which could reflect the poor internal consistency of impulsivity subscales in the ABCD Study.

4.5.2 Potential mechanisms underlying psychopathology and pathways to future SUDs

The follow-up correlational analyses demonstrated that psychopathology and mental disorders were related to thinner cortices and greater regional cortical area, which adds to a growing body of literature proposing that neurobiological mechanisms may underlie or contribute to psychopathology in childhood and adolescence (Benegal et al., 2007; Lees, Squeglia et al., 2020; Parker et al., 2020). Additionally, psychopathology was related to family functioning (see 'Covariate Associations' in **Appendix 4**), albeit, independently of family history of substance use problems. Nevertheless, indications of adverse childhood experiences were observed in FHP youth, including youth experiencing the greatest odds of PTSD (*aOR* = 3.3, 95% CI = 2.3–4.8) compared to any other mental disorder, high sleep disturbance, and reports of high family conflict. This is in accord with previous research which suggests FHP youth experience greater family disharmony and childhood psychopathology which increases vulnerability to later SUD (Barnow et al., 2002; El-Sheikh & Buckhalt, 2003). Future longitudinal analysis is required to delineate causal pathways between neurobiology, adverse childhood experiences, and psychopathology.

Unexpectedly, no group differences were observed for alcohol experimentation in the current cohort despite previous research demonstrating that FHP offspring are at much higher odds of having early-onset SUD themselves (Merikangas et al., 1998). This may suggest that a family history of SUD does not directly lead to curiosity about substance use, or substance use initiation and escalation in offspring. Instead, it may be the case that a number of mediating and moderating factors in FHP youth lead to later substance use problems. Previous studies have found that childhood externalizing disorders including conduct disorder and oppositional defiant disorder often precede SUDs in FHP young adults (Hill et al., 2011) and general samples (Nock et al., 2006, 2007). In contrast, the presence of anxiety disorders alone in FHP children do not appear to predict later development of SUDs (Hill et al., 2011), although, internalizing symptoms coupled with poor EF may do so (Lees, Stapinski, Prior et al., 2020). FHP youth in the current study with greater FHD were at greater odds of meeting criteria for these disorders and this may increase their risk for future SUDs as they enter adolescence. Furthermore, our recent study showed that youth were more likely to endorse sipping alcohol by ages 9–10 if they had been exposed to alcohol while in utero (Lees, Mewton, Stapinski et al., 2020). There is relatively high overlap among FHP and prenatally exposed individuals (here, 32%), thus, in utero exposures may account for some of the variance in substance use initiation previously not accounted for in FHP studies.

Based on the current evidence, prevention efforts designed to interrupt the intergenerational transmission of SUDs should consider targeting psychopathology and mental disorders in FHP substance-naïve children before they enter adolescence and begin experimenting with alcohol and other substances. Intervention initiatives should continue to treat and aim to reduce the prevalence of SUDs in parents.

4.5.3 Strengths and limitations

A key strength of this study was the utilization of a mixed model analytic approach which allowed for appropriate adjustment of the complexity of factors that may influence youth neurobiology, cognition, psychopathology, and behavior. Using this approach showed for the first time in a large-scale study that FHP youth experience greater psychopathology and mental disorders which are related to aberrant brain structure. This study also has several

limitations. First, this is a cross-sectional assessment, which enabled establishment of associations but does not address causation. The longitudinal component of ABCD will be essential to begin to delineate causal pathways. Second, FHP classification in the current study was based on histories of any alcohol or other substance use problems (e.g., marital separation, DUI, alcohol treatment program), rather than a positive SUD diagnosis. A threshold of just one problem was required, as sensitivity of symptoms was prioritized over specificity. It is likely that a SUD threshold for FHP classification would have resulted in stronger rather than weaker associations. Third, unmeasured confounding factors may be contributing to the observed associations. Fourth, data were not available on the percentage of family members with past versus current SUD-related symptoms, precluding examination of the impact of current problems on child outcomes. Fifth, cortical surface reconstruction and subcortical segmentation were performed using FreeSurfer version 5.3. Versions 6.0 and 7.0 have since been released and appear to have improved volumetric segmentation (as determined by dice scores) and perhaps the utilization of v5.3 contributed to the null findings of volumetric measures. Lastly, genetic influences of FHP were not examined and are likely to have an important underlying role in the observed associations.

4.5.4 Conclusions

Overall, FHP youth exhibit aberrant brain structure, greater psychopathology symptoms, and increased odds of mental disorders, with severity of problems related to FHD of substance misuse. At ages 9–10, FHP youth do not appear to present with problems related to impulsiveness, reward responsiveness, or cognitive deficits. Associations preceded offspring alcohol or other substance use and were robust to the inclusion of potential confounding factors, such as sociodemographic characteristics, prenatal exposures, family history of psychopathology, and parenting factors. The results indicate that psychopathology and mental disorders could be partially underpinned by neurobiological differences, although longitudinal analysis is required to determine causal mechanisms. Based on the current findings and wider evidence base, psychopathology in FHP children may increase risk of chronic problems with mental and SUDs, resulting in reduced quality of life, and should therefore be targeted in prevention efforts.

Chapter 5

Risk profiles of preadolescents with prenatal alcohol exposure

Preface

In addition to individuals with familial alcohol use problems, a second population with heightened familial risk of binge drinking are those with PAE. The risk profiles of individuals diagnosed with FASD and heavy-level PAE have been extensively explored. In contrast, very little is known about the risk profiles of offspring with low- to moderate-level PAE, despite this pattern of consumption being the most prevalent among pregnant women. Capitalizing on the cohort utilized in **Chapter 4**, this chapter investigates associations between low- to moderate-level alcohol use during pregnancy and neurobiological (i.e., brain structure and function), cognitive, and psychological outcomes in over 9,700 preadolescents. Notably, this study is 100 times larger than the previous largest neuroimaging study and 10 times larger than the previous largest behavioral study, providing concrete evidence of the effects of low- to moderate-level PAE on offspring for the first time.

This chapter addresses the second research question of this thesis: '*Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?*' This study involved a multidisciplinary international team of collaborators and has been published as Lees, B., Mewton, L., Jacobus, J., Valadez, E. A, Stapinski, L. A., Teesson, M., Tapert, S. F., & Squeglia, L. M. (2020). *American Journal of Psychiatry, 177*(11), 1060–1072. Supplementary materials are available in **Appendix 5**.

5.1 Abstract

Objective: Data on the neurodevelopmental and associated behavioral effects of light to moderate in utero alcohol exposure are limited. This retrospective investigation tested for associations between reported maternal prenatal alcohol use and psychological, behavioral, and neurodevelopmental outcomes in substance-naïve youths.

Methods: Participants were 9,719 youths (ages 9.0 to 10.9 years) from the ABCD Study. Based on parental reports, 2,518 (25.9%) had been exposed to alcohol in utero. Generalized additive mixed models and multilevel cross-sectional and longitudinal mediation models were used to test whether PAE was associated with psychological, behavioral, and cognitive outcomes, and whether differences in brain structure and resting-state functional connectivity partially explained these associations at baseline and one-year follow-up, after controlling for possible confounding factors.

Results: PAE of any severity was associated with greater psychopathology, attention deficits, and impulsiveness, with some effects showing a dose-dependent response. Children with PAE, compared with those without, displayed greater cerebral and regional volume and greater regional surface area. Resting-state functional connectivity was largely unaltered in children with in utero exposure. Some of the psychological and behavioral outcomes at baseline and at the one-year follow-up were partially explained by differences in brain structure among youths who had been exposed to alcohol in utero.

Conclusions: Any alcohol use during pregnancy is associated with subtle yet significant psychological and behavioral effects in children. Women should continue to be advised to abstain from alcohol consumption from conception throughout pregnancy.

5.2 Introduction

Alcohol use during pregnancy has been related to poorer offspring postnatal health and cognitive and behavioral outcomes from birth through adulthood (Caputo et al., 2016). The global prevalence rate of any alcohol use in pregnancy is approximately 10% (Popova et al., 2017). Factors such as dose and exposure patterns, as well as accompanying environmental factors, likely contribute to the significant variability in the range and magnitude of adverse pregnancy outcomes associated with PAE.

One of the most disabling potential outcomes of drinking during pregnancy is fetal alcohol syndrome, which has an estimated global prevalence in the general population of 14.6 per 10,000 people (Popova et al., 2017). Fetal alcohol syndrome is associated with brain anomalies, postnatal growth restriction, and facial dysmorphology, as well as psychological, behavioral, and cognitive deficits (Cook et al., 2016). FASD is a more inclusive umbrella term used to describe individuals within the overarching category of PAE, including fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, fetal alcohol effects, and alcohol-related birth defects. Estimates suggest that one of every 13 women who consumed alcohol during pregnancy delivered a child with FASD, equivalent to 76.9 per 10,000 children in the general population (Lange, Probst et al., 2017). Children with FASD exhibit poorer behavior and emotions, lower intelligence, cognitive deficits, and neurodevelopmental delays (Lange, Rehm et al., 2017; Mattson et al., 2019). Neuroimaging studies show that youths with FASD, who were exposed to heavy alcohol use in utero (i.e., >7 drinks/week), exhibit smaller cerebral surface area and aberrant cortical thickness (both thinner and thicker cortices have been reported) and generally show widespread reductions in brain volume throughout cortical and subcortical regions when compared with unexposed youths (Donald et al., 2015; Hendrickson et al., 2018; Robertson et al., 2015; Treit & Beaulieu, 2018; Zhou et al., 2018), although other studies have reported increased gray matter in the parietal and temporal lobes (Sowell et al., 2001). Youths with FASD also exhibit reduced resting-state functional connectivity in the default, salience, dorsal and ventral-attention, and executive control networks (Fan et al., 2017).

Although there is an established literature on the adverse outcomes associated with heavy alcohol use in pregnancy, evidence of the effects of lighter alcohol use (i.e., <7 drinks/week) on offspring psychological, behavioral, and neurodevelopmental outcomes is sparse and

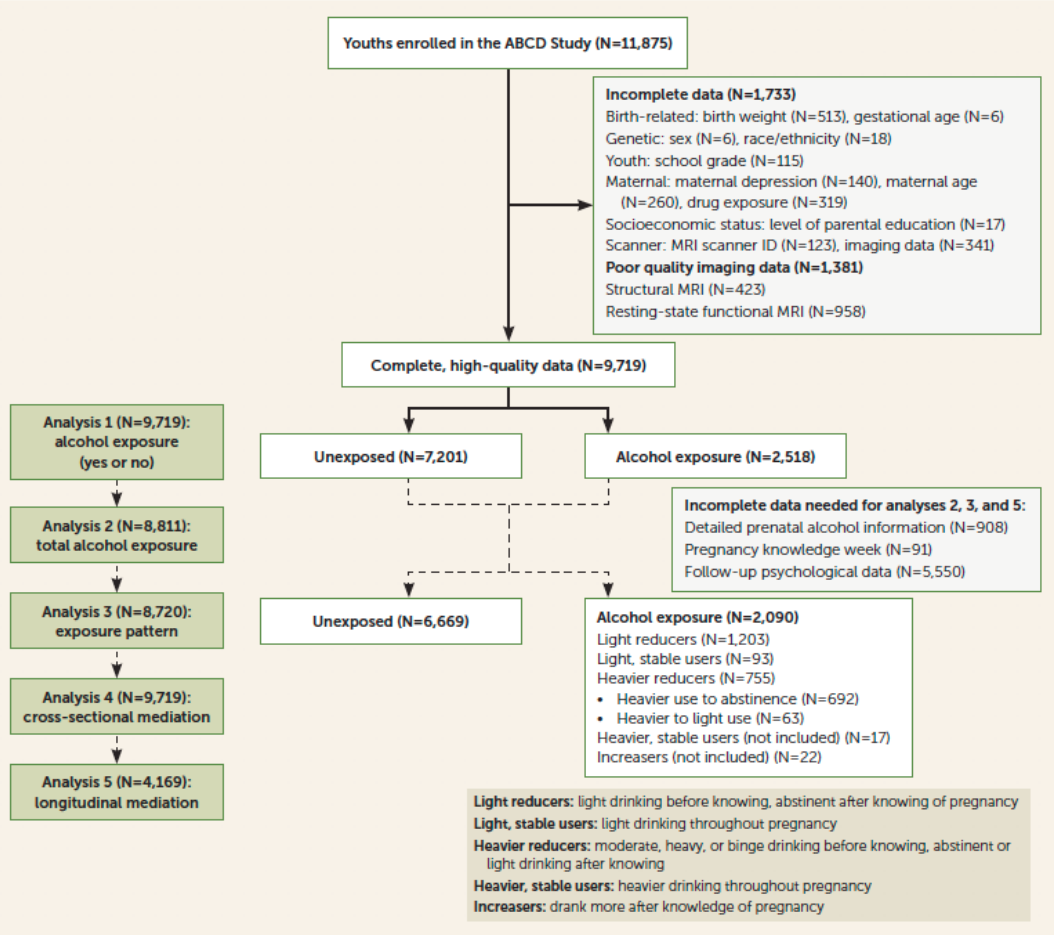
inconsistent, perhaps because of sample size and inadequate adjustment for potential confounding factors in some studies (Comasco et al., 2018). To fill these knowledge gaps, the present study utilized clinical interview, youth and parent self-report, cognitive tasks, and structural and resting-state functional MRI data from 9,719 community-based children ages 9–10 years in the ABCD Study. We aimed to address four research questions critical for families, clinicians, and policy makers. First, do psychological, behavioral, and neurodevelopmental (i.e., brain structure, brain function, and cognition) outcomes differ between youths prenatally exposed to alcohol and unexposed youths during preadolescence, before youths have initiated alcohol and other substance use? Second, is there a dose-dependent relationship between levels of alcohol exposure and outcomes of interest? Third, what are the common alcohol exposure patterns in the ABCD community sample, and are these patterns associated with adverse outcomes? And fourth, do structural and functional brain differences mediate the association between PAE and neurobehavioral outcomes? An examination of this large, diverse community sample of children in the US, where patterns of exposure are more typical of the general population, is urgently needed.

5.3 Methods

5.3.1 Study population

This study used data from the ABCD Study annual release 2.0.1, which consists of 11,875 participants born between 2005 and 2008. A detailed account of the recruitment strategy has been previously published (Garavan et al., 2018). A probability sample was recruited through schools and selected based on sex, race/ethnicity, socioeconomic status, and urbanicity. Children with FASD were not explicitly excluded from study participation. All parents provided written informed consent, and all children provided assent to the research protocol approved by a central institutional review board. Of the 11,875 participants enrolled, 2,156 were removed from the present analyses because of incomplete data (n = 1,733) and/or because brain scans did not pass the ABCD Study's quality control (n = 1,381) (Casey et al., 2018). Therefore, up to 9,719 participants were included in the analyses (Figure 5.1).

Figure 5.1. Selection of the ABCD cohort for each series of analyses in a study of the association of PAE with psychological, behavioral, and neurodevelopmental outcomes in children.



5.3.2 Prenatal alcohol exposure

PAE was measured using the modified Developmental History Questionnaire (Kessler et al., 2009; Merikangas et al., 2009) through parents' retrospective report of maternal alcohol use before and after knowledge of pregnancy (no or yes), the maximum number of drinks consumed on a single occasion, and the average number of drinks consumed per week during pregnancy. From this information, a dichotomous PAE variable was derived (exposure indicates any use at any time during pregnancy), an estimate of the total number of drinks consumed during pregnancy was calculated, and youths were categorized into common alcohol exposure patterns based on established prenatal alcohol use classification (O'Leary et al., 2010). Further details and relevant questions from the ABCD protocol are provided in **Appendix 5**.

5.3.3 Psychological and behavioral variables

Psychopathology was examined in children using the eight empirically based syndrome scales and higher-order factors of the parent-reported CBCL (Achenbach, 2009). Lifetime mental disorder diagnoses (i.e., past and/or present) were determined using parent-reported responses on the K-SADS, based on DSM-5 criteria (Kobak et al., 2013). Impulsivity was assessed using the 20-item UPPS-P (Whiteside et al., 2005). Motivation was examined using the four subscales of the BIS/BAS (Pagliaccio et al., 2016). The single-item Cash Choice Task was utilized as a measure of delayed gratification, motivation, and impulsivity (Wulfert et al., 2002). All data were available for baseline assessment (n = 9,719), and one-year follow-up data were available for all psychopathology syndrome scales and higher-order factors as measured by the CBCL and for the externalizing disorders as measured by the K-SADS (n = 4,169).

5.3.4 Cognitive variables

The NIH Toolbox (Gershon et al., 2013) fluid intelligence battery was utilized, and this includes the Picture Sequence Memory, Dimensional Change Card Sort, Flanker Inhibitory Control and Attention, List Sorting Working Memory, and Pattern Comparison Processing Speed Tasks. All scores were age-corrected standard scores. The Rey Auditory Verbal Learning Test was utilized to measure verbal learning (trials I–V) and immediate (trial VI) and delayed (trial VII) memory (Strauss et al., 2006).

5.3.5 Covariates

We adjusted for fixed and random effects. Fixed covariates were chosen based on prior evidence of an association with the outcomes or because of statistically significant group differences in the present sample (Table 5.1). Birth-related covariates included weight and whether the child was born prematurely (yes, no, unknown). Genetic covariates included sex at birth (female, male) and race/ethnicity (White, Black, Hispanic, Asian, other). Youth age at time of assessment and school grade performance (grades A to F) were also included. Maternal covariates included maternal age at birth, a history of maternal depression (yes, no, unknown), and other substance use during pregnancy, with tobacco, cannabis, cocaine,

and heroin use (yes, no, unknown) each included as separate variables. The highest level of parental education was used as an indicator of socioeconomic status (less than high school diploma, high school diploma or General Equivalency Diploma, some college, bachelor degree, postgraduate degree). Random effects included nesting youths within families to account for sibling effects and nesting youths within MRI scanner site.

5.3.6 Imaging procedure

Imaging acquisition and scanning parameters are described elsewhere (Casey et al., 2018). Briefly, all scans were uploaded to a shared server that is maintained by the Data Analysis, Informatics, and Resource Center of the ABCD Study. Brain data were collected on 3-T scanners, including the Siemens MAGNETOM PRISMA, the GE Discovery MR750, and the Philips Achieva. The T_1 images were corrected for gradient nonlinearity distortions using scanner-specific, nonlinear transformations. Cortical reconstruction and volumetric segmentation were performed by the Data Analysis, Informatics, and Resource Center using FreeSurfer, version 5.3.0. The Desikan–Killiany brain registration atlas was used in the present analyses to examine cortical thickness, surface area, and volume of 68 cortical regions, as well as volume in 40 subcortical segmentations. Participants also completed four 5-minute resting-state BOLD scans, with their eyes open and fixated on a crosshair. Resting-state images were acquired in the axial plane using an echo-planar imaging sequence. Using a functional atlas, cortical surface regions were grouped into 12 predefined large-scale networks (Gordon et al., 2016): auditory, cingulo-opercular, cingulo-parietal, default-mode, dorsal-attention, fronto-parietal, retrosplenial-temporal, salience, sensorimotor-hand, sensorimotor-mouth, ventral-attention, and visual networks. Resting-state functional connectivity strength indices were then calculated using the Fisher r-to-z transformation of the average correlation values between pairs of regions within each large-scale network (n = 12), between these 12 networks (n = 66), and between the networks and 19 subcortical regions (n = 228). The Data Analysis, Informatics, and Resource Center used a combination of automated and manual methods to review the data sets for quality control before sharing data via the National Institute of Mental Health Data Archive.

Table 5.1. Youth and parental characteristics in a study of PAE and mental health outcomes in children (n = 9,719).

Characteristic	**Unexposed youths (*n* = 7,201)**		**Youths with PAE (*n* = 2,518)**		***p***
Youth variables	***n***	**%**	***n***	**%**	
Sex					.32
Male	3,776	52.4	1,291	51.3	
Female	3,425	47.6	1,227	48.7	
Race					< .001
White	3,631	50.4	1,630	64.7	
Black	1,126	15.6	216	8.6	
Hispanic	1,574	21.9	407	16.2	
Asian	139	1.9	27	1.1	
Other	731	10.2	238	9.5	
Born premature					.07
Yes	1,417	19.7	443	17.6	
No	5,757	79.9	2,065	82.0	
Unknown	27	0.4	10	0.4	
Prenatal tobacco exposure					< .001
Yes	637	8.8	628	24.9	
No	6,551	91.0	1,865	74.1	
Unknown	13	0.2	25	1.0	
Prenatal cannabis exposure					< .001
Yes	204	2.8	325	12.9	
No	6,987	97.0	2,150	85.4	
Unknown	10	0.1	43	1.7	
Prenatal cocaine exposure					< .001
Yes	9	0.1	44	1.7	
No	7,187	99.8	2,446	97.1	
Unknown	5	0.1	28	1.1	
Prenatal heroin exposure					< .001
Yes	7	0.1	8	0.3	
No	7,190	99.8	2,482	98.6	
Unknown	4	0.1	28	1.1	
School grade					< .001
A	3,233	44.9	1,190	47.3	
B	2,408	33.4	788	31.3	
C	776	10.8	226	9.0	
D	130	1.8	43	1.7	
F	28	0.4	7	0.3	
Ungraded	626	8.7	264	10.5	
Consumed full drink of alcohol	10	0.1	6	0.2	.44
	Mean	***SD***	**Mean**	***SD***	
Age (years)	9.9	0.6	9.9	0.6	.89
Birthweight (lb)	6.6	1.5	6.7	1.4	< .001
Parent variables	***n***	**%**	***n***	**%**	
Highest parent education					< .001
<High school diploma	547	7.6	59	2.3	
High school diploma/General Equivalency Diploma	838	11.6	155	6.2	
Some college	2,191	30.4	687	27.3	
Bachelor	1,999	27.8	809	32.1	
Postgrad	1,626	22.6	808	32.1	
Maternal depression					< .001
Yes	1,530	21.2	656	26.1	
No	5,495	76.3	1,763	70.0	
Unknown	176	2.4	99	3.9	
	Mean	***SD***	**Mean**	***SD***	
Maternal age at delivery (years)	29.2	6.3	30.1	5.9	< .001
Week of pregnancy knowledge	6.9	7.0	6.9	5.7	.93

5.3.7 Statistical analysis

A series of generalized additive mixed models and multilevel mediation analyses were performed using R, version 3.5.3 (the "mgcv" package), and Mplus, version 8.4, respectively. Participants with missing or inadequate imaging quality data were excluded from analyses. In all analyses with imaging measures, the FDR was used to correct for multiple comparisons, and the adjusted *p* values are reported (Benjamini & Hochberg, 1995).

5.3.7.1 Associations with prenatal alcohol exposure

First, PAE was examined as a dichotomous variable (unexposed or exposed). Generalized additive mixed models exploring associations with psychological, behavioral, neural, and cognitive outcomes were run adjusting only for random effects and then were repeated after entering all covariates as fixed effects (see Subsection 5.3.5). Structural and functional neural indices found to be significantly associated with PAE when adjusting for fixed and random effects were identified as regions of interest for the remaining analyses. Follow-up analyses included intracranial volume as an additional covariate in statistically significant volumetric models. Considering the large number of functional indices explored and the strict multiple comparisons adjustment applied, uncorrected results were also reported for connectivity within and between a narrower selection of major networks previously associated with FASD (Fan et al., 2017). To examine dose-dependent relationships, spline models with 1.5% winsorization to convert outliers were conducted to flexibly fit associations between the estimated total number of drinks consumed during pregnancy and outcomes of interest, adjusting for fixed and random effects. Next, the prevalence of alcohol exposure patterns was estimated, and the effect of these patterns of drinking in pregnancy on the outcomes of interest was examined using generalized additive mixed models. The week of maternal pregnancy awareness was added as an additional covariate. Follow-up analyses examined whether there were differential effects associated with varying gradations of alcohol use throughout pregnancy.

Sensitivity analyses were conducted, where the dichotomous PAE groups were demographically matched on all covariates after excluding rarer cases on which groups were mismatched, including youths with other in utero substance use exposure and positive

reports of maternal depression (using the R package "MatchIt"). The aforementioned association analyses were then repeated with this more homogeneous subsample (n = 2,542; see **Appendix 5** Tables 10–12).

5.3.7.2 Mediation analysis

Cross-sectional multilevel mediation analyses were conducted to determine whether significant associations between PAE and psychological, behavioral, and cognitive outcomes were partially explained by differences in brain structure or function, when adjusting for fixed and random effects. Here, significant mediation effects are strictly a measure of association, which does not prove causality.

For psychological measures where one-year follow-up data were available, longitudinal multilevel mediation analyses were conducted (n = 4,169). The follow-up psychological data were entered into models alongside baseline parental reports of PAE and imaging measures to explore prospective associations between PAE, brain structure and function, and psychological outcomes, when accounting for fixed and random effects.

5.4 Results

5.4.1 Study sample

Of the 9,719 youths included in these analyses (52.1% male), 2,518 (25.9%) had parent-reported in utero alcohol exposure. Demographic characteristics are provided in Table 5.1, and psychological, behavioral, and cognitive characteristics of youths are provided in Table 1 in **Appendix 5**. The winsorized estimated total number of drinks consumed during pregnancy ranged from 0 to 90, and among those who consumed alcohol, the mean number of drinks was 26.9 (SD = 24.5). A significantly larger proportion of youths prenatally exposed to alcohol, compared with unexposed youths, were exposed to tobacco (n = 628; 24.9%), cannabis (n = 325; 12.9%), cocaine (n = 44; 1.7%), and heroin (n = 8; 0.3%).

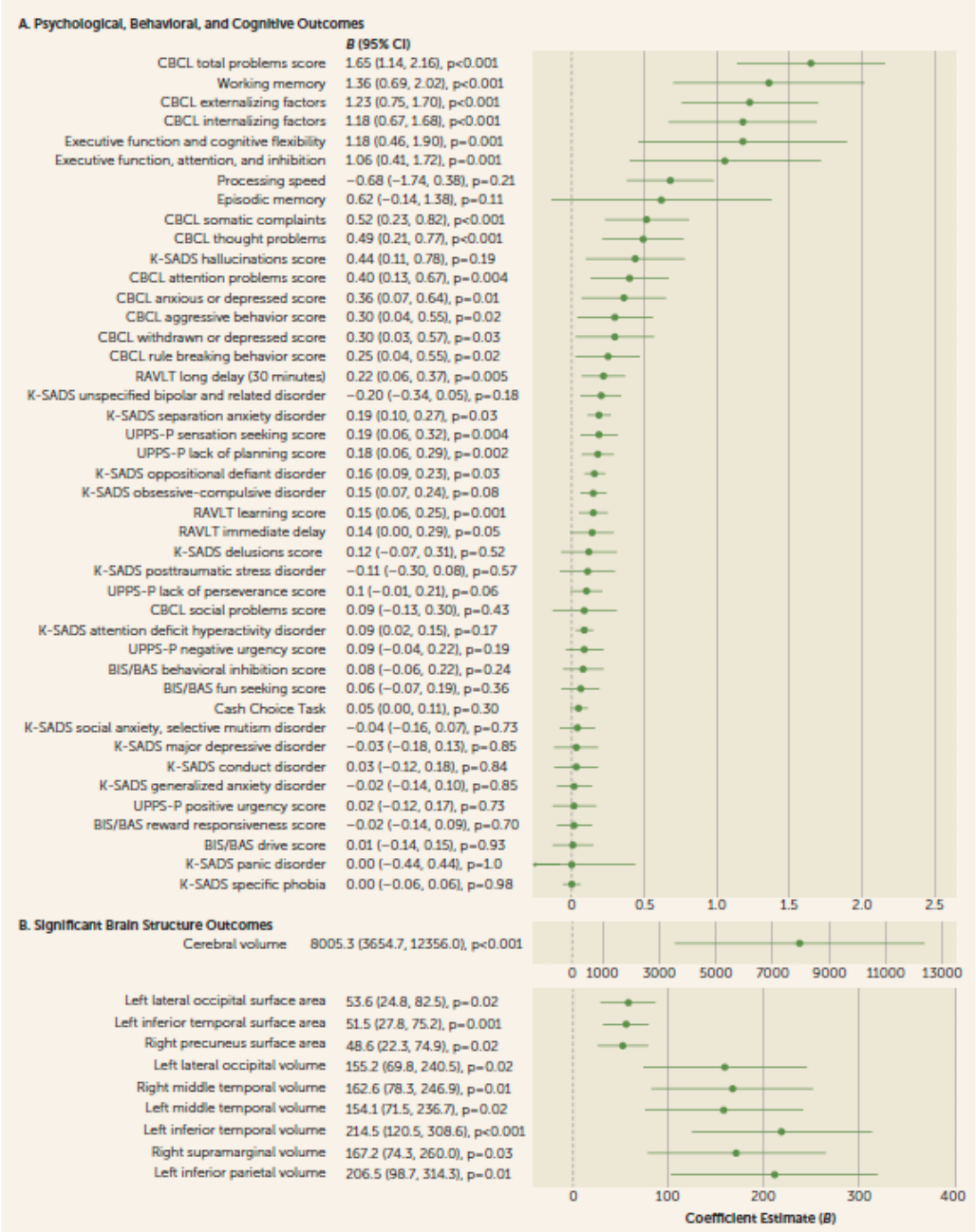
5.4.2 Associations with prenatal alcohol exposure

5.4.2.1 Dichotomous prenatal alcohol exposure associations

Results of unadjusted models and effect sizes are provided in Tables 2–5 in **Appendix 5**. In covariate-adjusted models, youths prenatally exposed to alcohol exhibited significantly greater psychopathology, impulsivity, and cognitive functioning compared with unexposed youths (Figure 5.2). Exposed youths were more likely to have a lifetime diagnosis of separation anxiety disorder (*aOR* = 1.21, 95% CI = 1.11–1.31) and oppositional defiant disorder (*aOR* = 1.17, 95% CI = 1.09–1.26) relative to unexposed youths.

Exposed youths also exhibited greater total cerebral volume and greater regional cortical volume and surface area throughout the temporal, occipital, and parietal lobes, relative to unexposed youths. Regional cortical volume differences in the left inferior temporal lobe passed FDR correction when intracranial volume was included as an additional covariate (**Appendix 5** Table 6). No significant differences between exposed and unexposed youths were observed for cortical thickness. Compared with unexposed youths, exposed youths exhibited hypoconnectivity between the auditory network and the right ventral diencephalon, and hyperconnectivity between the sensorimotor-hand and salience networks (**Appendix 5** Table 4). Connectivity within and between the other networks and subcortical indices was not significantly associated with PAE (see **Appendix 5** Table 5 for uncorrected results of networks previously associated with FASD). Considering that no significant associations were observed within or between established networks previously associated with FASD, no further results of functional analyses are presented here (additional results are provided in **Appendix 5**, including a summary of significant associations between covariates and outcomes in Table 7).

Figure 5.2. Association of PAE of any severity, compared with no exposure, with psychological and behavioral problems, cognitive functioning, and cortical volume and surface area in preadolescent children.[a]



[a] Unstandardized regression coefficients and associated 95% CIs, as well as *p* values or FDR-adjusted *p* values for neural outcomes, are presented for the effects of PAE compared with no exposure. Only brain regions where the model passed the FDR correction for volume or surface area are presented. These generalized additive mixed models controlled for fixed and random effects. Fixed effects included race/ethnicity, sex, age, whether the child was born premature, child birth weight, school grade, prenatal tobacco exposure, prenatal cannabis exposure, prenatal heroin exposure, prenatal cocaine exposure, maternal age at birth, level of parental education, and maternal depression. Random effects included family and MRI scanner site. Working memory was measured by the Toolbox List Sorting Working Memory Test. Executive function and cognitive flexibility were measured by the Toolbox Dimensional Change Card Sort Task. Executive function, attention, and inhibition were measured by the Toolbox Flanker Task. Processing speed was measured by the Toolbox Pattern Comparison Processing Speed Test. Episodic memory was measured by the Toolbox Picture Sequence Memory Test. BIS/BAS = behavioral avoidance and behavioral inhibition scales; CBCL = Child Behavior Checklist; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; RAVLT = Rey Auditory Verbal Learning Test; UPPS-P = Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form.

5.4.2.2 Dose-dependent associations

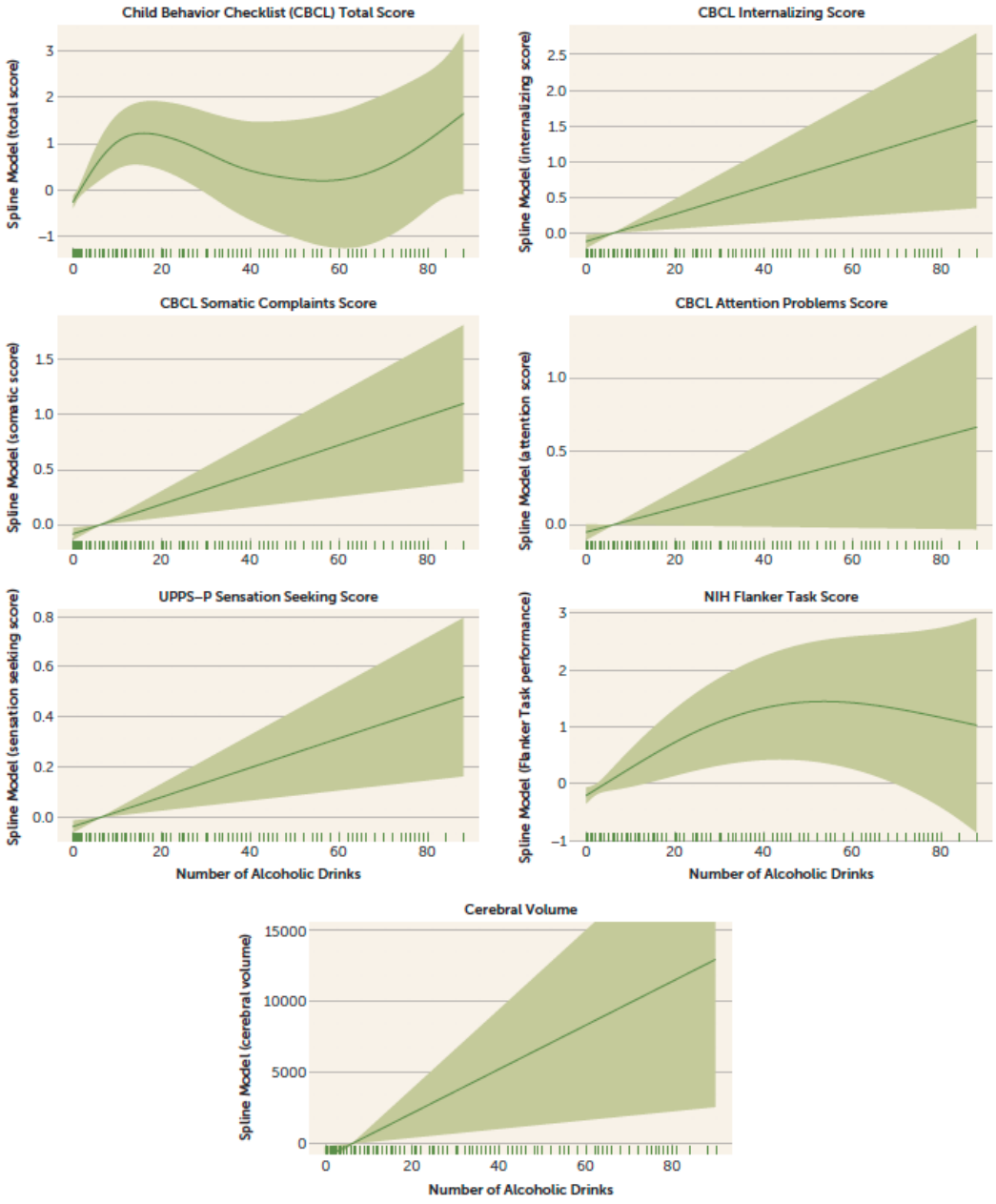
In covariate-adjusted models, linear and nonlinear associations were observed between the estimated total number of drinks consumed during pregnancy and total psychological problems, internalizing psychopathology and somatic complaints, attention deficits, sensation-seeking behavior, and performance on the Flanker Task, which measured attention and inhibitory control (Figure 5.3; see also **Appendix 5** Table 8). The total number of drinks was linearly associated with greater cerebral volume (Figure 5.3). Both linear and nonlinear associations were observed between the total number of drinks and regional volume throughout the temporal, occipital, and parietal lobes (**Appendix 5** Figure 1). Dose-dependent responses were not observed for any other outcome of interest.

5.4.2.3 Exposure pattern associations

Six patterns of parent-reported alcohol use in pregnancy were identified (Figure 5.1). Because of sample size, exposure pattern analyses were limited to abstinent mothers, light reducers, light, stable users, and heavier reducers, accounting for 98.1% of the sample. On average, light reducer mothers consumed 2.3 drinks/week for the first seven weeks (*SD* = 5.6) of pregnancy (mean total drinks = 15.8, *SD* = 14.7). Light stable-drinking mothers consumed approximately 1.1 drinks/week throughout pregnancy (mean total drinks = 44.0, *SD* = 25.8), while heavier reducer mothers consumed approximately 5.3 drinks/week for the first seven weeks (*SD* = 5.1) of pregnancy (mean total drinks = 36.2, *SD* = 25.5). Participant characteristics for each group are provided in **Appendix 5** Table 9.

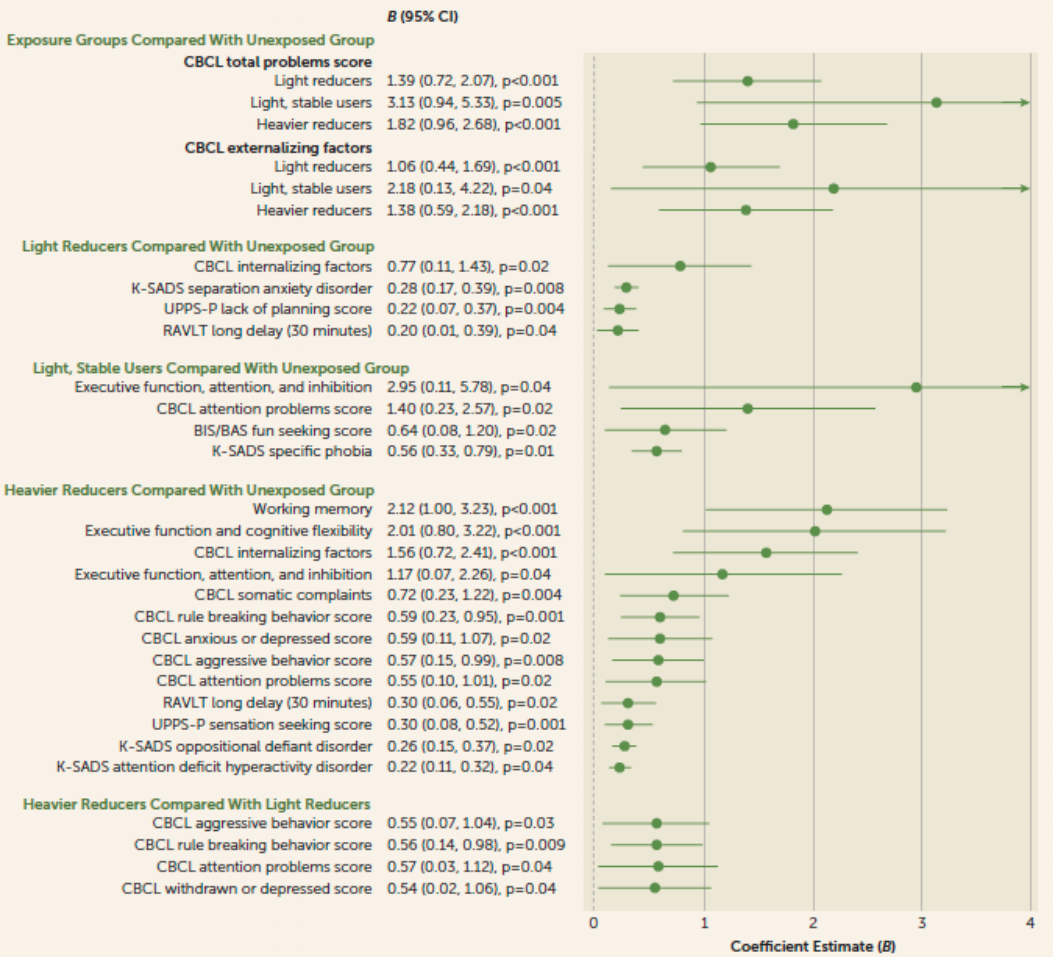
Covariate-adjusted models showed that, compared with unexposed youths, all exposure groups exhibited greater psychopathology and behavioral problems, varying mental disorders (i.e., separation anxiety disorder, oppositional defiant disorder, specific phobia, and/or ADHD), and greater cognitive functioning. Children of heavier reducers also reported greater withdrawn or depressed behavior, attention deficits, rule breaking behavior, and aggression compared with children of light reducers. Significant associations are presented in Figure 5.4.

Figure 5.3. Spline models demonstrating a significant dose-dependent relationship between the estimated total number of alcoholic drinks consumed during pregnancy and offspring psychopathology, cognitive functioning, and brain volume, adjusted for fixed and random effects.[a]



[a] NIH = National Institutes of Health; UPPS-P = Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form.

Figure 5.4. Association of PAE patterns with varying psychological and behavioral problems among children.[a]



[a] Results of all psychological, behavioral, cognitive, and neural indices analyses are provided in Table 10 in Appendix 5. Unstandardized regression coefficients, associated 95% CIs, and *p* values are presented for significant associations. These generalized additive mixed models controlled for fixed and random effects. Fixed effects included race/ethnicity, sex, age, whether the child was born premature, child birth weight, school grade, prenatal tobacco exposure, prenatal cannabis exposure, prenatal heroin exposure, prenatal cocaine exposure, maternal age at birth, level of parental education, maternal depression, and the week the mother became aware of pregnancy. Random effects included family and MRI scanner site. Executive function, attention, and inhibition were measured by the Toolbox Flanker Task. Executive function and cognitive flexibility were measured by the Toolbox Dimensional Change Card Sort Task. Working memory was measured by the Toolbox List Sorting Working Memory Test. BIS/BAS = behavioral avoidance and behavioral inhibition scales; CBCL = Child Behavior Checklist; K-SADS = Schedule for Affective Disorders and Schizophrenia for School-Age Children; RAVLT = Rey Auditory Verbal Learning Test; UPPS-P = Urgency, Premeditation, Perseverance, Sensation Seeking, Positive Urgency, Impulsive Behavior Scale for Children-Short Form.

Youths with exposure to any pattern of drinking exhibited greater total cerebral volume relative to unexposed youths in covariate-adjusted models. Regional brain volume and surface area disparities were also observed for all PAE groups compared with unexposed youths, although no significant differences were observed between PAE groups. When gradations of use were explored separately for heavier reducers (i.e., heavier to light

compared with heavier to abstinence), similar results were found for both groups. Results of all psychological, behavioral, cognitive, and neural indices analyses are provided in **Appendix 5** Table 10.

5.4.2.4 Sensitivity analysis

When youths were demographically matched, results remained generally consistent (**Appendix 5** Tables 11–16). Of note, the majority of previously observed cognitive benefits for youths prenatally exposed to alcohol were no longer found. When examined dichotomously, no cognitive domains were significantly different between groups. A nonlinear association remained for total drinks and Flanker Task performance. Some structural brain indices were no longer significantly different between groups or were no longer dose dependent.

5.4.3 Mediation analysis

Structural brain indices were negatively associated with psychological and behavioral outcomes and partially mediated all significant associations between PAE and neurobehavioral outcomes in covariate-adjusted cross-sectional models (**Appendix 5** Tables 17–31). Inconsistent mediation was observed, where at least one of the mediated effects occurred in a different direction to the direct effect (MacKinnon et al., 2006); for example, PAE was significantly associated with greater brain volume and surface area and with greater psychopathology and behavioral problems, while greater brain volume and surface area were negatively associated with psychopathology and behavioral problems. Conversely, for Flanker Task attention and inhibitory control performance, consistent positive associations were observed. Longitudinal mediation models replicated associations between PAE, varying baseline structural brain indices, and follow-up psychopathology and externalizing disorders (**Appendix 5** Tables 32–42).

5.5 Discussion

5.5.1 Alcohol exposure findings

To our knowledge, this is the largest examination of PAE and psychological, behavioral, and neurodevelopmental outcomes in preadolescence. The estimated total number of drinks consumed during pregnancy ranged from 0 to 90 following outlier conversion. This alcohol dose is relatively low, and the parent-reported exposure patterns prevalent in the ABCD cohort are more typical and reflective of the general population than those investigated in previous studies of FASD (Popova et al., 2017).

PAE of any severity was associated with greater psychopathology, impulsivity, and likelihood of being diagnosed with separation anxiety and oppositional defiant disorder, with some observed dose-related associations. Heavier exposure was also associated with greater withdrawn or depressed behavior, attention deficits, rule breaking, aggression, and a greater likelihood of being diagnosed with ADHD. Early, light exposure, compared with no exposure, was associated with better attention and inhibitory skills. Exposed youths also exhibited greater cerebral volume, in a dose-dependent manner, and greater volume and surface area, but not cortical thickness, throughout regions of the parietal, temporal, and occipital lobes, after accounting for potentially confounding factors. Resting-state functional connectivity was largely unaltered in these youths. Aberrant brain structure partially mediated associations between PAE and psychological, behavioral, and cognitive outcomes at baseline and at the one-year follow-up. These reported associations passed a stringent demographic matching protocol. Unmodifiable factors greatly contributed to the large effect sizes in the adjusted models. Of the modifiable factors, PAE was a critical determinant of brain structure, and some neurobehavioral outcomes, accounting for >50% of the explained variance by modifiable factors. The findings were in a largely substance-naïve cohort of youths (99.999%), allowing for investigation of the effects of PAE on the developing brain and behavior in the absence of youths' own substance use, which is known to affect neurodevelopment (Lees et al., 2019).

5.5.2 Comparison with other studies

Our findings replicate previous clinical studies indicating that children exposed to alcohol in utero have higher rates of mental disorders and present with behavioral anomalies, including impulsiveness and attention deficits (Comasco et al., 2018). Results from our dose-dependent and exposure pattern analyses support the notion that the severity of psychopathology and behavioral problems depends on alcohol dose and timing of exposure. The present results are also consistent with previous reports using the ABCD cohort of associations between psychopathology, brain structure, and resting-state functional connectivity (Cheng et al., 2020; Pornpattananangkul et al., 2019). Consistent with previous meta-analyses, a small, beneficial association between PAE and cognitive ability was observed (Flak et al., 2014; Testa et al., 2003). However, when participants were demographically matched, the vast majority of associations were no longer significant. This association may be the result of residual confounding from socioeconomic status and other demographic variables, as previously hypothesized (Flak et al., 2014; Testa et al., 2003). Other confounding variables not captured in this analysis may be contributing to the positive association between early, light exposure and attention and inhibition.

The long-term neurostructural and functional effects of light maternal drinking, where offspring who do not necessarily present with FASD, have not been well studied. Consistent with our findings, one study has reported larger regional volume among youths prenatally exposed to alcohol relative to unexposed youths (Sowell et al., 2002). However, in contrast to our results, a common finding, when investigated both categorically and continuously, has been less volume and surface area among youths with FASD and those with heavier PAE compared with unexposed youths (Donald et al., 2015; Lebel et al., 2011). Furthermore, a previous study of youths with FASD reported hypoconnectivity between numerous large-scale neurocognitive networks (Fan et al., 2017), yet in the present study, no significant alterations in resting-state functional connectivity were observed within or between these networks (**Appendix 5** Table 5).

The disparate findings may be explained by the large discrepancies in clinical severity of PAE between the ABCD sample and previous cohorts. The impact of heavier PAE may have a differential effect on preadolescent brain structure and function. Interestingly, some regions of the occipital, temporal, and parietal lobes exhibited an inverted-U association

between alcohol dose and volume or surface area (**Appendix 5** Figure 1). It is possible, therefore, that we would have observed reduced volume and surface area among youths exposed to heavier doses (i.e., >90 drinks consumed during pregnancy). Furthermore, potentially confounding factors in previous studies of children with heavier PAE or FASD may contribute to the discrepant findings, such as greater co-occurring substance exposure, early-life stress, and quality of parental care. Importantly, our findings suggest that youths exposed to even light alcohol doses in utero exhibit widespread differences in brain structure, when compared with unexposed youths.

Finally, our results are consistent with previous studies of children with FASD that have linked behavioral, psychological, and cognitive outcomes to changes in brain structure (Treit & Beaulieu, 2018). However, our study is the first to test and identify inconsistent mediation between these variables (MacKinnon et al., 2006). Similar to previous conclusions drawn on the effects of PAE (Feldman et al., 2012), our results suggest that there is no safe threshold for alcohol consumption during pregnancy.

5.5.3 Interpretation and potential biological mechanisms underlying neurobehavioral outcomes

Alcohol is a known teratogen in utero, and it is thought to affect regions of the developing fetal brain via neural proliferation and migration errors, hypoxia, and cell death (Goodlett et al., 2005). The teratogenic effects likely differ as a result of dose, frequency, and timing of exposure and may vary across brain regions. Our findings demonstrate that there are complex effects of PAE on offspring development. Here, we provide four potential interpretations of mechanisms underlying associations between PAE, differences in brain structure, and neurobehavioral consequences.

First, our results may reflect a compensatory response of some brain regions attempting to counter the effects of other, poorer functioning regions affected by low alcohol doses (Nuñez et al., 2011). Our inconsistent mediation findings provide some support for this interpretation, where greater brain volume and surface area were associated with better neurobehavioral outcomes, yet youths who were exposed to alcohol in utero exhibited greater volume and surface area but more neurobehavioral problems at baseline and

follow-up. Despite a potential compensatory response of the brain to counter the effects of relatively low doses of alcohol, these youths continue to show subtle, yet poorer, psychological and behavioral outcomes through early life.

Second, our findings may also suggest that relatively light PAE may result in slightly atypical neurodevelopment. Such exposure may slow or alter the overall process of gray matter maturation, where greater absolute volume and surface area in exposed youths represent delayed or incomplete cortical pruning compared with this process in unexposed, prepubertal youths (Eckstrand et al., 2012). Consistent with this hypothesis, we observed this trend largely in regions where gray matter loss in unexposed children progresses linearly from childhood through adolescence (Gogtay et al., 2004). Typically among this age group, the left hemisphere matures earlier than the right (i.e., left hemisphere gray matter loss prior to right hemisphere gray matter loss; Giedd et al., 1996; Gogtay et al., 2004). Greater volume and surface area among exposed youths in left posterior cortices, known to develop most rapidly between childhood and adolescence, provide further support of delayed development. Examining the developmental trajectories of this cohort when multiple waves of imaging data are available will provide further insight into whether atypical development is occurring among exposed youths.

Third, the inconsistent mediation findings may also be partly capturing the effects of the inverted-U associations between total alcohol dose and regional brain volume and surface area. Youths exposed to greater alcohol doses (i.e., approximately 90 drinks consumed during pregnancy) exhibited greater psychopathology and behavioral problems between ages 9 and 10 than youths exposed to lighter doses (i.e., approximately 40 drinks), and these more heavily exposed youths exhibited lower volume and surface area in regions of the parietal and temporal lobes than youths exposed to lighter doses.

Lastly, there may be other critical changes resulting from PAE that mediate associations with brain structure differences and psychological and behavioral outcomes. For example, ethanol provokes a wide range of epigenetic modifications, including altered DNA and histone methylation, which persist from birth through childhood (Ungerer et al., 2013). Animal studies suggest that PAE affects DNA methylation through antagonistic effects on methyl donors, such as folate, and via long-lasting changes in gene expression (Ungerer et al., 2013). Preliminary evidence from studies of children with FASD show genome-wide

differences in DNA methylation (Portales-Casamar et al., 2016). Further research is required to examine epigenetic markers and their role in adverse outcomes among exposed youths; DNA methylation or other epigenetic markers could potentially provide objective indicators of PAE.

Limitations of our study include potential maternal underreporting of alcohol use during pregnancy, imprecise retrospective data on the timing, amount, and frequency of alcohol exposure, and absence of data on trimester-specific alcohol exposure. The effects of underreporting by mothers who indicated alcohol use during pregnancy may have inflated the observed associations, while underreporting by mothers who indicated no alcohol use when they did in fact consume alcohol would have attenuated the associations toward the null. Future studies may benefit from interviewing an independent reporter of prenatal maternal alcohol use. Furthermore, data were not available on mothers who regularly consumed less than a full unit of alcohol. Therefore, youths exposed to this pattern of drinking would have been included in the unexposed group, potentially diluting outcome effects. Despite the large sample size, there were relatively few cases of youths exposed to stable light drinking throughout pregnancy, and too few cases of stable heavier drinking or increased consumption throughout pregnancy, to examine the impact on offspring. There is a larger body of existing evidence based on the consequences of heavier alcohol exposure (Donald et al., 2015). The small sample size of youths exposed to light, stable drinking throughout pregnancy resulted in wider variance in outcome measures and may underestimate the true impact. Other notable explanatory variables of early life that may influence the observed associations between PAE and neurobehavioral outcomes include childhood adversity and quality of parental care. These variables may contribute to mediating effects of neurodevelopment and possible epigenetic modifications (Dunn et al., 2019). The baseline ABCD Study protocol did not capture these variables, although future waves will. Longitudinal analyses of this cohort should consider these variables as possible confounding factors. In addition, we did not examine the effect of preconception paternal alcohol exposure on preadolescent brain structure, and this should be explored in future studies.

In conclusion, relatively light levels of PAE were associated with small yet significantly greater psychological and behavioral problems, including internalizing and externalizing psychopathology, attention deficits, and impulsiveness. These outcomes were linked to

differences in cerebral and regional brain volume and regional surface area among exposed youths aged 9 to 10 years. Examination of dose-dependent relationships and light alcohol exposure patterns during pregnancy shows that children with even the lowest levels of exposure demonstrate poorer psychological and behavioral outcomes as they enter adolescence. Associations preceded offspring alcohol use and were robust to the inclusion of potential confounding factors and during stringent demographic matching procedures, increasing the plausibility of the findings. Women should continue to be advised to abstain from alcohol consumption from conception throughout pregnancy.

Chapter 6

Prenatal alcohol exposure and early alcohol use experimentation

Preface

Chapter 5 has shown that preadolescents with low- to moderate-level PAE present with established precursory risk factors of adolescent binge drinking, including psychopathology, behavioral problems, and aberrant brain structure. Another robust predictor of adolescent binge drinking is early alcohol use experimentation. It remains unknown whether young people with low- to moderate-level PAE experience greater odds of early experimentation than unexposed peers. Utilizing the same large and diverse cohort as **Chapters 4** and **5**, this chapter reports on the first study internationally to examine alcohol use patterns in preadolescents exposed to low or moderate levels of alcohol while in utero.

This chapter addresses the second research question of this thesis: *'Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?'* The study involved a multidisciplinary international team of collaborators chapter and has been published as a short communication: Lees, B., Mewton, L., Stapinski, L. A., Teesson, M., & Squeglia, L. M. (2020). *Drug & Alcohol Dependence, 214*, 108187.

6.1 Abstract

Background: Early alcohol use initiation is one of the strongest predictors of AUDs. Identifying modifiable risk factors for problematic alcohol use can guide prevention initiatives. Globally, approximately 10% of women consume alcohol during pregnancy, however the impact of PAE on offspring alcohol use patterns has been understudied. The aim of this study was to examine associations between PAE and preadolescent alcohol use behaviors.

Methods: Cross-sectional data were utilized from 10,119 children aged 9.0 to 10.9 years (M = 9.9, SD = 0.6) enrolled in the ABCD Study, based in the US. Linear mixed models tested associations between PAE and endorsement of non-religious alcohol sipping in offspring, when adjusting for confounding factors.

Results: In total, 2,675 (26.4%) youth were prenatally exposed to alcohol. Among PAE youth, total standard drinks consumed during pregnancy ranged from 0.4–90.0 drinks (M = 26.8, SD = 24.5). Compared to unexposed youth, those with any alcohol exposure during early pregnancy (∼0–7 weeks) were 1.7 times (95 % CI 1.4–2.0, $p < .0001$) more likely to endorse sipping alcohol by ages 9–10, while youth with low-level doses of alcohol throughout the entire pregnancy were 2.9 times (95 % CI 1.9–4.6, $p < .0001$) more likely to endorse sipping, when adjusting for confounding factors. A dose-dependent association between total standard drinks consumed during pregnancy and youth sipping endorsement was observed ($\beta = 0.2$, 95 % CI 0.1–0.2, $p < .0001$).

Conclusions: This study shows that any alcohol use during pregnancy may play an important role in very early alcohol use experimentation among offspring by ages 9–10.

6.2 Introduction

Globally, one in 10 women consume alcohol during pregnancy, and of these women, ~90% consume low levels where offspring do not meet criteria for FASD (Popova et al., 2017). Recently, we showed that relatively low-level PAE (i.e., 1–90 standard drinks consumed during pregnancy) was associated with early childhood externalizing problems, impulsiveness, attention deficits, aggression, and neurobehavioral aberrations (Lees, Mewton, Jacobus et al., 2020). Despite these behaviors being established correlates of early alcohol initiation and escalation (Erskine et al., 2016; Groenman et al., 2017; Lees et al., 2019; Meque et al., 2019), the impact of PAE on offspring alcohol use patterns are relatively understudied.

Previous research has focused on the effects of frequent, heavy alcohol use during pregnancy. Baer et al. (2003) reported that exposure to five or more drinks per occasion was associated with alcohol problems in offspring at age 21. Alati et al. (2006) found that exposure to three or more drinks per occasion increased the odds of AUDs at age 21, compared to no or low levels of PAE. Likewise, Goldschmidt et al. (2019) reported that prenatal exposure to one or more drinks per day was linearly associated with increased odds of reporting symptoms of AUDs at age 22. Two studies drawing on the adolescent cohort (10-16 years) from the Maternal Health Practices and Child Development Project examined youth exposed to daily alcohol use, either in the first trimester only or throughout the entire pregnancy (Cornelius, De Genna et al., 2016; Cornelius, Goldschmidt et al., 2016). First trimester PAE was associated with higher levels of drinking in adolescence (Cornelius, De Genna et al., 2016), and exposure to more than one drink per day throughout pregnancy was associated with persistent adolescent drinking (Cornelius, Goldschmidt et al., 2016). In summary, heavy and frequent exposure to alcohol in utero has been associated with increased odds of offspring alcohol use and related problems in adolescence and young adulthood.

To our knowledge, no studies have explored associations between offspring alcohol use and low-level PAE which is more typical of the general population (Popova et al., 2017). There has also been very little attention given to the impact of PAE on early alcohol use experimentation in preadolescents. Earlier age of alcohol use initiation is one of the strongest predictors of a lifetime diagnosis of AUD, and predicts a more severe chronic

course of use throughout adolescence and adulthood (Grant & Dawson, 1997; Guttmannova et al., 2011). Therefore, it is critical that associations between PAE and early alcohol use behaviors are explored to progress knowledge of potentially modifiable risk factors for problematic alcohol use in young people. To fill these important gaps in the literature, the current study examined associations between lower-level PAE and lifetime report of alcohol experimentation in 10,119 children aged 9 to 10 years from the ABCD Study. It was hypothesized that PAE youth would be at higher odds of endorsing alcohol experimentation by ages 9 to 10 than unexposed youth, controlling for demographic and socioenvironmental variables.

6.3 Methods

6.3.1 Participants

The ABCD Study release 2.0.1 contains cross-sectional baseline data from 11,875 children aged 9.0 to 10.9 years and their parents. A probability sample was recruited through schools proximal to the 21 research sites across the US (Hagler et al., 2019). Informed consent and assent were obtained from a parent or legal guardian and the child, respectively. Procedures were approved by a central institutional review board. Of the 11,875 participants enrolled, 1,756 were removed from the current analysis because of incomplete data (n = 10,119).

6.3.2 Outcome measure

The iSay Sip Inventory (Jackson et al., 2015) assessed youth-reported sipping endorsement via the question "*have you ever had alcohol not as part of a religious ceremony?*". While the number of sipping occasions were assessed, data were positively skewed with little gradation (M = 2.3, SD = 1.4, max = 15), therefore, the outcome was examined as a dichotomous (y/n) rather than continuous measure. The majority of youth sipped from their parent's drink (79.5%), with one in four (26.3%) doing so while their parent wasn't looking. Very few youth had consumed a full drink of alcohol (n = 21) or tried tobacco (n = 81) or cannabis (n = 12).

6.3.3 Explanatory measures

6.3.3.1 Prenatal alcohol exposure (parent report)

Retrospective report of maternal alcohol use before and after knowledge of pregnancy was assessed via the modified Developmental History Questionnaire (Kessler et al., 2009; Merikangas et al., 2009). From the available data, three PAE measures were derived (for details, see Lees, Mewton, Jacobus et al., 2020): 1) a dichotomous variable capturing any exposure (n = 10,119); 2) a categorical PAE variable of common patterns of drinking (n = 9,091); and 3) a continuous estimate of total standard drinks consumed during pregnancy, following 1.5% winsorization to convert outliers (n = 9,180). To categorize youth into common alcohol exposure patterns, maternal drinking was categorized into abstinent (<1 standard drink/occasion throughout pregnancy), light (1–2 drinks/occasion, <7 drinks/week), moderate (3–4/occasion, <7/week), heavy (<5/occasion, 7+/week), or binge drinking (5+/occasion) before and after knowing of pregnancy (O'Leary et al., 2010). Common patterns were identified: 1) abstinent throughout pregnancy; 2) low-level use during early pregnancy (light before knowing, abstinent after knowing of pregnancy); 3) heavier-level use during early pregnancy (moderate, heavy, and binge drinkers before knowing, abstinent or light drinking after knowing); and 4) low-level use throughout pregnancy. Further details and relevant questions from the ABCD protocol are described elsewhere (Lees, Mewton, Jacobus et al., 2020).

6.3.3.2 Covariates (youth and parent report)

The following fixed effects were included in all statistical models and were dummy coded: sex (M/F), race/ethnicity (White, Black, Hispanic, Asian, Other), parent education (<high school diploma, high school diploma or equivalent, college, bachelor degree, postgraduate degree), household income (<50K, 50–100K, >100K), and marital status (single-parent household, married). Youth age was included as a continuous fixed effect. Other potentially confounding parent-reported dummy-coded variables were examined: prenatal tobacco, cannabis, heroin, or cocaine exposure (y/n), maternal depression (y/n), youth alcohol access (easy, hard, unknown), and past/present parental alcohol problems (y/n; e.g., alcohol-related marital separation or family problems, fired from work, arrests or DUIs, health problems, alcohol treatment program). In addition, birthweight, gestational age,

maternal age, and youth-reported parental monitoring were explored as potentially confounding continuous covariates.

6.3.4 Analysis

Linear mixed-effects models, fitted using maximum likelihood estimation, were used with random effects for family nested within research site (R package: 'glmmTMB'). Analyses examined the association between the three PAE variables and youth sipping endorsement. For each analysis, three statistical models were compared using the ANOVA function and Bayesian Information Criterion: 1) sociodemographic variables only (i.e., sex, age, race/ethnicity, parent education, marital status, household income); 2) PAE and fixed-effect sociodemographic covariates; and 3) PAE, sociodemographic, and other potentially confounding fixed-effect covariates (i.e., prenatal tobacco, cannabis, heroin, or cocaine exposure, parental alcohol problems, birthweight, gestational age, maternal age, maternal depression, parent monitoring, youth alcohol access). For the patterns of exposure analysis, week of pregnancy knowledge (M = 6.9, SD = 6.7) was entered as an additional fixed-effect covariate in models 2 and 3. While PAE findings from models 2 and 3 were consistent, model 2 was the best fit to the data and used in the final analysis, reported herein. Of the potentially confounding fixed-effect covariates included in model 3, prenatal heroin exposure (n = 16), low parent monitoring, and easier alcohol access were significantly associated with increased odds of offspring sipping endorsement. Considering these associations, post hoc analysis examined possible interactions between PAE with parent monitoring and youth alcohol access. Sensitivity analyses examined whether associations remained when youth with prenatal tobacco or other drug exposure (n = 1,367), and/or parental history of alcohol problems (n = 1,381) were excluded, and remaining PAE and unexposed youth were demographically matched 1:1 on covariates that significantly differed between groups (i.e., race/ethnicity, parent education, household income; R package: 'MatchIt'). The more homogenous subsample included 3,122 youth (50.0% PAE).

6.4 Results

Of 10,119 youth included in the analyses, 2,675 (26.4%) were prenatally exposed to alcohol (Table 6.1). Among those with PAE, total standard drinks consumed during pregnancy

ranged from 0.4 to 90.0 drinks (M = 26.8, SD = 24.5), following outlier conversion. Compared to unexposed youth, the *aOR* of sipping endorsement was 1.7 (95% CI = 1.5 to 1.9, p < 2e-16) for those exposed to any alcohol in utero.

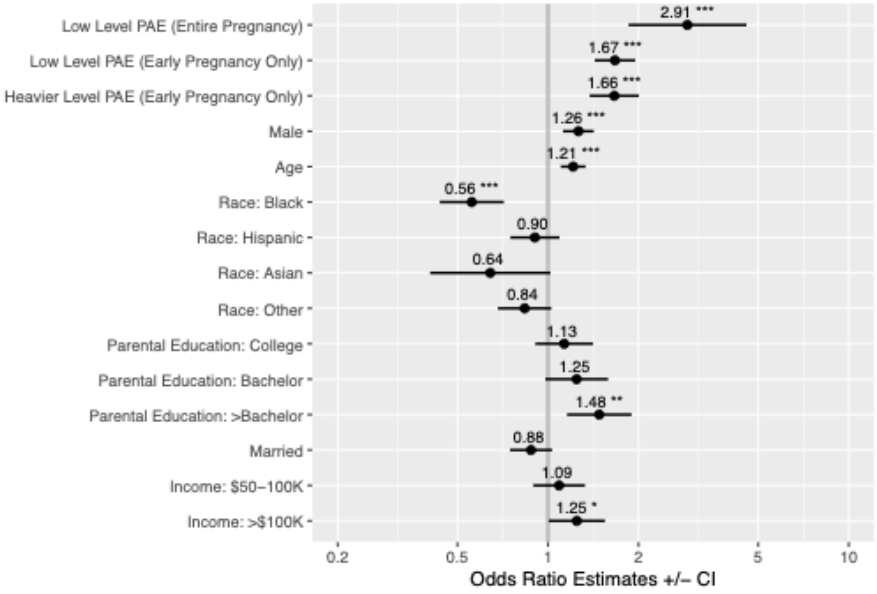
Table 6.1. Characteristics of unexposed and prenatally alcohol exposed youth (n = 10,119).

	Unexposed youth	**Prenatally exposed youth**	***p***
Overall, No. (%)	7444 (73.6)	2675 (26.4)	
Male, No. (%)	3899 (52.4)	1366 (51.1)	.25
Age, mean (*SD*)	9.9 (0.6)	9.9 (0.6)	.73
White, No. (%)	3795 (51.0)	1720 (64.3)	< .001
Parent ≥Bachelor education, No. (%)	3790 (50.9)	1723 (64.5)	< .001
Married/defacto, No. (%)	5525 (74.2)	2009 (75.1)	.38
Household income >100k, No. (%)	2774 (37.3)	1362 (50.9)	< .001
Tobacco use during pregnancy, No. (%)	677 (9.1)	667 (24.9)	< .001
Cannabis use during pregnancy, No. (%)	223 (3.0)	349 (13.1)	< .001
Cocaine use during pregnancy, No. (%)	10 (0.1)	49 (1.8)	< .001
Heroin use during pregnancy, No. (%)	8 (0.1)	8 (0.3)	< .001
Parent history of alcohol problems, No. (%)	892 (12.0)	520 (19.4)	< .001
Lifetime sipping endorsement, No. (%)	1059 (14.2)	686 (25.7)	< .001
	No. (%)	**Mean drinks (*SD*)**	
Total alcohol use, mean (*SD*)*		26.8 (24.5)	
Low-level use during early pregnancy	1285 (48.0)	16.1 (18.8)	
Heavier-level use during early pregnancy	803 (30.0)	47.8 (76.3)	
Low-level use throughout pregnancy	95 (3.6)	49.0 (35.9)	

Due to missing data for alcohol use patterns, % does not equate to 100. Mean drinks are calculated from the subsample who consumed alcohol during pregnancy.

When exploring common patterns of alcohol exposure, the *aOR* was 1.7 (95% CI = 1.4 to 2.0, p = 7.9e-11) for those exposed to low-level doses of alcohol during early pregnancy only, 1.7 (95% CI = 1.4 to 2.0, p = 1.3e-07) for those exposed to heavier-level doses of alcohol during early pregnancy only, and 2.9 (95% CI = 1.9 to 4.6, p = 3.5e-06) for those exposed to low-level doses of alcohol throughout pregnancy (Figure 6.1). A dose-dependent association between total standard drinks consumed during pregnancy and youth sipping endorsement was observed (β = 0.2, *S.E.* = 0.03, Z = 5.8, p = 7.3e-09).

Figure 6.1. Associations between PAE and endorsement of alcohol sipping by age 9 to 10 years.[a]



[a] Odds ratio estimates with 95% CIs are presented. Reference categories for each variable: PAE = unexposed youth; sex = female; race = White; parent education = high school; marital status = single-parent household; income = <$50K.

Other significant correlates of sipping endorsement by age 9 to 10 years included male sex (*aOR* = 1.3, 95% CI = 1.1 to 1.4, *p* = .0001), older age (*aOR* = 1.2, 95% CI = 1.1 to 1.3, *p* = 7.6e-05), highly educated (>bachelor) parents (*aOR* = 1.5, 95% CI = 1.2 to 1.1.9, *p* = .002), and high household income (*aOR* = 1.3, 95% CI = 1.0 to 1.6, *p* = .04), see Figure 6.1. Compared to White youth, Black youth were less likely to endorse lifetime alcohol sipping (*aOR* = 0.6, 95% CI = 0.4 to 0.7, *p* = 3.2e-06).

Interactions between PAE and parent monitoring, and youth alcohol access were not significantly associated with sipping endorsement. Sensitivity analyses confirmed that all findings were consistent when excluding those with prenatal tobacco or other drug exposure, and/or parental history of alcohol problems and demographically matching 3,122 remaining youth.

6.5 Discussion

This study is the first to show that low-level alcohol use during any stage of pregnancy is associated with increased odds of offspring's early (age 9–10) alcohol use. This association

remained significant after controlling for potentially confounding factors, and during stringent demographic matching procedures which excluded youth with prenatal tobacco or other drug exposure, or parental history of alcohol problems.

The results add to the small body of literature on the impact of PAE on offspring alcohol use behaviors in adolescence (Cornelius, De Genna et al., 2016; Cornelius, Goldschmidt et al., 2016) and young adulthood (Alati et al., 2006; Baer et al., 2003; Goldschmidt et al., 2019). Taken together, these studies demonstrate continuity of risk related to PAE from preadolescent alcohol experimentation, to adolescent high and chronic drinking, and early-onset alcohol problems and AUDs in young adulthood.

Several factors may be contributing to associations between PAE and offspring alcohol use behaviors, including sociocultural, neurobiological, and genetic influences. It is well established that factors such as parental rules, parental alcohol use, and availability of substances are risk factors of early alcohol use behaviors (Simons-Morton et al., 2001). While parental monitoring and accessibility of alcohol use were related to youth alcohol experimentation in the current study, potential moderating effects with PAE were not observed. This indicates that these relationships are not significantly inter-related and may suggest that PAE and sociocultural factors relate to alcohol use through differing mechanisms. For example, our prior research revealed dose-dependent alcohol-associated brain differences in youth with PAE, which partially explained later externalizing problems (Lees, Mewton, Jacobus et al., 2020). Future longitudinal studies should explore whether alcohol-associated changes in the fetal brain are also contributing to alcohol use behaviors. It has been suggested that PAE may selectively enhance the pleasantness and emotional reactivity of alcohol odor and taste in offspring, and this may contribute to greater escalation in drinking behaviors (Anunziata et al., 2020; Hannigan et al., 2015). Genetic associations between parental and offspring alcohol use patterns are also a possibility. The current study did not observe a significant association between parental history of alcohol problems and endorsement of alcohol sipping in offspring. However, associations with non-problematic parental alcohol use behaviors or parental alcohol use patterns during the child's lifespan were not explored and may show different results. Further research is needed to improve understanding of how maternal drinking during pregnancy confers risk to offspring alcohol use to better inform prevention and intervention strategies.

Key strengths of this study include the large, diverse sample of youth which allowed for robust estimates and detailed characterization of the relationship between PAE and offspring alcohol experimentation. Additionally, it is the first study in this field to examine the effects of PAE where levels of exposure are more reflective of the general population (Popova et al., 2017). Furthermore, using a mixed model analytic approach allowed for appropriate adjustment of the complexity of factors that influence youth behaviors. Study limitations include: 1) potential maternal underreporting of alcohol use during pregnancy; 2) imprecise retrospective data on exposure patterns; 3) absence of data on trimester-specific exposure; 4) lack of data on non-problematic parental alcohol use behaviors; 5) ~20% missing data for patterns of PAE; and 6) utilization of a probability sample which is not necessarily representative of the US population. Additionally, the influence of paternal contribution to offspring behavior was not examined and should be examined alongside PAE in future studies.

In conclusion, this study shows that any alcohol use during any stage of pregnancy may play an important role in very early alcohol use experimentation among offspring by ages 9–10.

Chapter 7

Binge drinking and executive functioning trajectories among young adults

Preface

The findings from **Chapters 2** and **3** include cross-sectional and longitudinal associations between binge drinking and cognitive functioning performance in adolescents and young adults. However, the literature examining EF deficits from binge drinking is sparse. **Chapter 2** identified a small number of longitudinal studies examining the impact of binge drinking on EF performance over time and an even smaller number of studies examining EF recovery following reductions in alcohol use. This chapter addresses these gaps in the evidence base by investigating trajectories in binge drinking patterns (i.e., increased/sustained, reduced, or no binge drinking) and EF over six months following early intervention for alcohol use problems. Notably, this is the first study internationally to examine recovery over the short term and the first to investigate the impact of reduced alcohol use rather than total abstinence. This is critical to explore given the very low prevalence of young people choosing to stop drinking completely.

This chapter addresses the third and fourth research questions of this thesis: '*What are the neurobiological and cognitive consequential harms associated with binge drinking?*' and '*Do neurobiological and cognitive harms recede following reductions in binge drinking frequency?*' This chapter is in preparation for submission to *Addiction*. Supplementary materials are available in **Appendix 6**.

7.1 Abstract

Background: Binge drinking is more prevalent among young adults than any other age group and this pattern of consumption is associated with deficits in EF. It remains relatively unknown whether such deficits can improve in the short term following reductions in alcohol use. Therefore, the primary aim of this study was to explore the relationship between reductions in binge drinking frequency and EF.

Methods: An Australian sample of 99 young adults (M_{age} = 21.0, SD = 2.4) reporting a spectrum of drinking behaviors from no use to probable AUD were followed over six months, and provided self-report survey data on alcohol use and neuropsychological data measuring EF at two time-points. Participants were grouped into one of three trajectory classifications: continuous non-binge drinking; reduced binge drinking; or sustained/increased binge drinking. Linear regressions (baseline associations) and mixed models (longitudinal associations) were applied, using frequentist and Bayesian approaches.

Results: At baseline, binge drinking was significantly associated with poorer inhibitory control but not mental flexibility or working memory. A significant group by time interaction indicated that both the reduced and sustained/increased binge drinking groups exhibited declines in inhibitory control over time compared with continuous non-binge drinking participants. Mental flexibility performance significantly improved for all participants over the course of the study, with the largest effects observed in the reduced group. No significant differences over time or between groups were observed for working memory performance.

Conclusions: Reduced binge drinking did not result in improved inhibitory control over six months. In fact, any report of binge drinking throughout the study was associated with continued declines in performance. Further research is required to determine whether inhibitory control deficits improve over a longer period of reduced or discontinued binge drinking among young people.

7.2 Introduction

Alcohol use continues to be a global public health concern. Alcohol is the most frequently used substance worldwide and one of the 10 leading risk factors for burden of disease (Shield et al., 2020). A common pattern of alcohol consumption among young people is binge drinking, defined as the consumption of four or more standard drinks for females and five or more drinks for males on a single occasion (Substance Abuse and Mental Health Services Administration, 2016). In high-income countries, including Australia, around four in five young adults aged 18–24 years report previous year alcohol consumption and nearly one in two engage in binge drinking at least monthly (Australian Institute of Health and Welfare, 2020b; Substance Abuse and Mental Health Services Administration, 2019; World Health Organization, 2019).

The high prevalence of binge drinking is concerning because young adults continue to undergo substantial neurodevelopmental changes (Somerville, 2016). Following development of lower-order sensorimotor regions and the reward-related limbic system during adolescence, frontal regions and related networks continue to mature through the mid-twenties, which leads to improved higher-order EF critical for self-regulation (Giedd & Rapoport, 2010; Shaw et al., 2008; Stiles & Jernigan, 2010). It has been proposed that the later maturation of these higher-order networks may make young adults particularly sensitive to the deleterious effects of alcohol because of ongoing neural developments (Spear, 2018).

Indeed, a review of neuroimaging studies finds that young people exhibit accelerated decreases in frontal gray matter volume and increased neural activation during EF tasks following uptake of binge drinking (Lees et al., 2019). Likewise, studies of young people with AUD report frontal aberrations at both the structural and functional level (Leiker et al., 2019; Medina et al., 2008). Such alterations are interpreted as neurodevelopmental interruptions from alcohol use or compensatory mechanisms to counter overt cognitive deficits. Further, a meta-analysis of neuropsychological studies indicates that binge drinking in adolescence and young adulthood is associated with an overall small neurocognitive deficit ($g = -0.26$) and specific impairments in EF (e.g., poorer inhibitory control; $g = -0.39$) (Lees et al., 2019). Additionally, some individual studies have observed

overt deficits in other EF domains, including working memory, following the uptake of binge drinking in young people (Mahedy et al., 2018; Mota et al., 2013).

Alcohol-induced neurocognitive deficits arguably have greater impact on adolescents and young adults than on older individuals given the critical focus on continued educational attainment, learning, and ongoing neurodevelopment during this period. Whether such overt deficits in EF among young people can improve following reductions in alcohol use remains relatively unknown. A six-year prospective study of young adults aged 18–19 years at baseline found that long-term (two–four years) cessation of binge drinking was associated with improved working memory, where performance was significantly better than those who continued to binge drink but worse than non-drinkers (Carbia, Cadaveira, López-Caneda et al., 2017). Additionally, a positive association has been reported between the number of days since last alcohol and other substance use, and composite performance on working memory and mental flexibility at a 10-year follow-up assessment of young adults who had previously met criteria for an AUD (Hanson et al., 2011).

While there is preliminary evidence of some recovery in certain EF domains following binge drinking cessation, gaps in the literature remain. First, inhibitory weakness is generally the largest EF deficit associated with binge drinking and the persistence of this deficit remains unknown. Second, the literature to date has focused on long-term cessation of binge drinking or alcohol use over multiple years, and the more immediate EF outcomes have not been examined. Shorter-term outcomes are important to consider given ongoing neurodevelopment, learning, and pursuit of employment, as well as broader personal and social role transitions that are ongoing in young adulthood. Last, the effect of reductions in binge drinking, rather than total abstinence, on EF performance has not yet been explored. From a harm reduction perspective, it is critical that research examines EF trajectories associated with positive behavior change (Marlatt et al., 2011). It is particularly important to examine reductions in alcohol use as only around 8% of the young adult population stop drinking entirely, while one in three (35%) current drinkers will reduce their frequency of binge drinking and quantity of alcohol consumed (Australian Institute of Health and Welfare, 2020b). Therefore, the EF outcomes following abstinence are less relevant for the majority of the population who will continue to binge drink and consume alcohol at some level.

To address gaps in the evidence base, the current study aimed to: 1) examine baseline associations between binge drinking and EF among young adults; and 2) explore the severity and recoverability of deficits in EF associated with different trajectories of binge drinking frequency over a six-month period. It was hypothesized that young adults who reported binge drinking in the previous month at baseline would exhibit poorer EF performance than non-binge drinking counterparts. Considering the limited evidence base for EF recovery and the differing focus of previous studies (i.e., abstinence over a long-term period), longitudinal analyses were exploratory and specific hypotheses were not established.

7.3 Methods

7.3.1 Participants

Two cohorts were utilized in the analysis. Cohort 1 (n = 69) were a subset of participants reporting both hazardous drinking and anxiety who were enrolled in a randomized controlled trial examining the efficacy of *Inroads*; an internet-delivered early intervention for hazardous alcohol use and anxiety among young adults (Stapinski et al., 2019). Participants were randomized to active intervention or control. The intervention was an online, five-module, psychologist-supported cognitive behavior therapy program designed to target hazardous drinking and anxiety symptoms. The control group received information about alcohol-related harms and current Australian NHMRC guidelines for safe drinking. Participants in Cohort 2 (n = 30) were recruited separately as low-drinking comparators for the *Inroads* participants. Cohorts were recruited in 2017 and 2018 through online advertisements, media coverage, flyer distribution, and youth mental health service referrals; see Lees, Stapinski, Prior et al. (2020) for details. Here, participants from both cohorts were pooled to increase statistical power and to examine a broader spectrum of binge drinking changes over a six-month period.

Inclusion criteria for both cohorts were: 1) aged 17–24 years; 2) living in Australia; 3) experiencing at least mild symptoms of anxiety, as indicated by a score ≥5 on the GAD-7 (Spitzer et al., 2006) or a score ≥6 on the Mini-SPIN (Seeley-Wait et al., 2009); and 4) having access to a computer with internet and a mouse. By requiring participants to meet only one

of two relatively low anxiety-related thresholds, a full spectrum of symptoms was captured at baseline (GAD-7 possible range = 0–21, observed range = 5–21; Mini-SPIN possible and observed range = 0–12) and follow-up (GAD-7 range: 0–20). For Cohort 1, eligible participants reported hazardous levels of alcohol use (AUDIT scores ≥8) and eligible Cohort 2 participants were those reporting low risk alcohol use (AUDIT <8) (Babor et al., 2001). Exclusion criteria for both cohorts were: 1) unable to provide contact information; 2) insufficient English literacy to engage with study materials; 3) reported daily use of cannabis or benzodiazepines, or weekly use of psychostimulants, as assessed by the National Institute on Drug Abuse Quick Screen Questions (Zgierska et al., 2014); 4) significant risk of complicated alcohol withdrawal; 5) active suicidal ideation (indicated by a single item assessing experience of suicidal thoughts and intent in the previous two weeks); 6) active symptoms of psychosis, as indicated by a score ≥3 on the Psychosis Screening Questionnaire (Bebbington & Nayani, 1995); or 7) currently accessing ongoing psychological treatment for mental health or drug or alcohol problems.

7.3.2 Procedure

The study received ethics approval from the University of New South Wales Human Research Ethics Committee (HC17185) and the University of Sydney Human Research Ethics Committee (2018/877). Participants who responded to the study advertisements gave written informed consent and were directed to complete a 15-minute online eligibility assessment. Those who were eligible and consented to participate completed an evaluation at baseline and at six months post-baseline, which consisted of two phases, undertaken on separate days. These phases included a 30–45-minute online survey and approximately 30 minutes of online neuropsychological testing via Inquisit Web 5.0.10 (Inquisit 5, 2016), which was conducted within two weeks of completing the survey. At each phase, participants were provided with detailed instructions via phone, text, and email to ensure rigorous task completion. For baseline assessment, participants enrolled in the active *Inroads* intervention group were required to complete neuropsychological tasks prior to entering the active treatment phase. Participants were instructed to complete the neuropsychological battery in a quiet environment with no distractions and were advised not to use pen and paper as an aid to completing the tasks. The order of neuropsychological

tasks was counterbalanced across participants. All data were stored on encrypted servers, protected by high-end firewall systems.

7.3.3 Measures

7.3.3.1 Substance use and clinical data

The TLFB (Sobell et al., 1979; Sobell & Sobell, 1995) was used to obtain participants' retrospective estimates of daily drinking over the previous 30 days to allow calculation of frequency of binge drinking episodes and total previous month alcohol consumption. The National Institute on Drug Abuse Quick Screen Questions (Zgierska et al., 2014) was used to assess other substance use over the previous 12 months at baseline and follow-up, including cannabis and other illicit substances. A single item assessed age of first full drink of alcohol ("how old were you when you first took one or more drinks or alcohol?"). The GAD-7 was employed to assess symptoms across a range of anxiety disorders at baseline and follow-up, including generalized anxiety, panic, and social anxiety (Spitzer et al., 2006). Scores from the Mini-SPIN were not included as a covariate in statistical models as the inventory was used for screening and data were only available at baseline assessment.

7.3.3.2 Executive functioning

Based on the empirical model by Miyake and colleagues, three EF subdomains were assessed: inhibitory control, mental flexibility, and working memory (Miyake et al., 2000).

The Stroop Color-Word Task (Stroop, 1935) assessed inhibitory control. Over 84 trials, participants were shown color words and indicated the font color by key press. There were three trial types, with reaction time (RT) recorded: congruent (color word and font consistent), incongruent (color word and font not consistent), and control trials (colored rectangles presented). From these trials, the following speed-based interference score was calculated (Van Der Elst et al., 2006) and utilized in analyses:

$$Interference = incongruent\ RT - ([congruent\ RT + control\ RT] / 2)$$

The WCST (Grant & Berg, 1948) was employed to assess mental flexibility. Here, participants sorted cards into categories and no instructions were given in regard to the categorization rule. Feedback was provided after each categorization on whether their response was correct. There were three categorization principles (color, shape, number) that changed—without warning—each time the participant made 10 consecutive correct responses for a category. The task ended when the participant completed two sequences of the three categorization principles, or reached 128 cards. Three test derivatives were utilized in analyses: total errors, perseveration errors (i.e., keep applying old categorization rule), and number of categories completed.

The Letter Memory Task (Friedman et al., 2008) was employed to assess working memory. Participants viewed a series of letters one at a time on a computer screen and were asked to rehearse out loud the previous three letters in the series. Without warning, the last letter disappeared (after 5, 7, or 9 letters) and participants were required to enter the previous three letters from a letter matrix. Participants completed 12 trials (four per set of 5, 7, and 9 letters), where the order was randomly determined. Trial accuracy was utilized in the analysis.

7.3.4 Statistical analysis

The primary analysis was performed using R, version 4.0.2 (R Core Team, 2020) and the secondary analysis using JASP, version 0.13.1 (JASP Team, 2020). Prior to conducting analyses, all extreme outliers were winsorized to scores three standard deviations above or below the mean. Examination of continuous data indicated non-normal distributions; thus, log transformations were applied and utilized in analyses. EF indices were converted during analyses, so higher scores indicated better performance.

7.3.4.1 Primary analysis

Baseline demographic, clinical, and substance use data were analyzed by a series of *t* tests for continuous variables and chi-square tests for categorical variables to compare binge and non-binge drinking participants as well as those who did and did not complete the follow-up assessment. Next, a series of linear regressions was conducted to examine baseline

associations, where the binge drinking group was entered as the independent variable, sex as a covariate, and EF score as the dependent variable. Finally, longitudinal data were analyzed using linear mixed models with restricted maximum likelihood approximation. To account for the impact of response attrition, the models estimated missing responses based on all available information using FIML. Consistent with previous studies examining cognitive function following abstention (Carbia, Cadaveira, Caamano-Isorna et al., 2017; Carbia, Cadaveira, López-Caneda et al., 2017), a three-level binge drinking trajectory categorical variable was generated, which reflected: 1) no binge drinking at baseline or follow-up; 2) any reduction in binge drinking frequency at follow-up; and 3) sustained or increased frequency of binge drinking at follow-up—hereafter referred to as no binge drinking, reduced binge drinking, and sustained/increased binge drinking, respectively. A series of models first investigated the main effect of time across groups and the next series modelled the time by group interaction on EF measures. Considering some participants received an intervention during the follow-up period, a three-level cohort variable (Cohort 1 intervention, Cohort 1 control, Cohort 2) was included as an additional covariate alongside sex. In follow-up analyses, potentially confounding variables were tested to determine whether they had an explanatory role, including time-varying dummy-coded variables measuring previous year cannabis and illicit substance use (never, once or twice, monthly, weekly, daily or almost daily) and continuous variables measuring anxiety symptoms (GAD-7 score) and age of drinking onset, as early onset has been associated with neurobiological differences (Lees, Meredith, Kirkland et al., 2020).

7.3.4.2 Secondary Bayesian analysis

Additional Bayesian analyses were conducted. Under a frequentist null hypothesis significance testing framework, non-significant findings are inherently ambiguous and do not indicate no effect (Wasserstein et al., 2019). In contrast, Bayesian analyses provide the ability to obtain evidence in favor of the null hypothesis and discriminate between absence of evidence (e.g., because of insufficient statistical power) and evidence of absence (i.e., no true effect). The Bayes factor (BF) compares the predictive performance of the null *vs.* alternative hypotheses and is presented alongside primary analysis results. A BF_{10} <0.33 provides sufficient evidence to accept the null and a BF_{10} >3 provides sufficient evidence to accept the alternative hypothesis (Gelman et al., 2013). A joint frequentist–Bayesian

approach has been recommended to reduce *p* value misinterpretation, particularly in regard to non-significant findings (Benjamin & Berger, 2019).

7.4 Results

7.4.1 Participants

Of 784 young adults screened (Cohort 1 n = 561, Cohort 2 n = 223), 167 were eligible to participate (Cohort 1 n = 113, Cohort 2 n = 54) and 99 completed the EF tasks and had complete survey data at baseline (Cohort 1 n = 69, Cohort 2 n = 30; 71.7% female; M_{age} = 21.0, SD = 2.4). At six-month follow-up, 68 participants had complete data (Cohort 1 n = 44, Cohort 2 n = 24; retention rate: 68.7%). Attrition group analyses indicated that participants who did and did not complete the follow-up assessment were similar on demographic and substance use variables (see **Appendix 6** Table 1). However, participants lost to follow-up reported significantly higher anxiety-related symptoms at baseline compared with those who continued to participate in the study ($t(97) = -3.6$, $p < .001$).

7.4.2 Demographic and alcohol use characteristics

For the baseline analyses, participants from the pooled sample were categorized into any previous month binge drinking (n = 75) or no previous month binge drinking groups (n = 24); see Table 7.1 for descriptive characteristics. Among binge drinking participants, total previous month alcohol consumption ranged from 5 to 336 standard drinks (median = 66.2) at baseline and they reported binge drinking on 1–29 days (median = 5.0). The AUDIT scores for approximately 70% of binge drinking participants suggested probable AUD. For non-binge drinking participants, total previous month alcohol consumption ranged from 0 to 105 standard drinks (median = 2.5) at baseline. Table 7.2 reports on changes in binge drinking patterns over six months for the three binge drinking trajectory groups.

Table 7.1. Demographic, clinical and substance use characteristics at baseline.

	Binge drinking *n* = 75		Non-binge drinking *n* = 24		*p*
	Mean	*SD* / %	Mean	*SD* / %	
Age (years)	21.2	2.3	20.4	2.7	.150
Female *n* (%)	51	68.0%	20	83.3%	.147
Anxiety symptoms[a]	12.1	4.0	14.0	4.2	.053
Previous month total drinks	89.3	76.2	9.8	22.8	< .001
Previous month # binge episodes	7.5	7.0	0.0	0.0	< .001
Possible alcohol use disorder *n* (%)[b]	40	70.2%	0	0.0%	< .001
Age at first drink (years)	14.8	1.7	16.7	2.0	< .001
≥Monthly cannabis use *n* (%)	12	16.0%	1	4.2%	.004
≥Monthly other substance use *n* (%)	12	16.0%	0	0.0%	< .001

[a] Possible scale range for Generalized Anxiety Questionnaire-7 is 0–21.
[b] The AUDIT total score was ≥20; possible range is 0–40.

Table 7.2. Changes in binge drinking frequency occasions over six months.

		Reduced *n* = 21			Sustained/increased *n* = 32			Non-binge drinking *n* = 15		
		Mean	*SD*	Range	Mean	*SD*	Range	Mean	*SD*	Range
Change in BD	*N*	−4.8	3.9	−15.0, −1.0	2.1	2.1	0.0, 7.0	0.0	0.0	0.0, 0.0
frequency	%	−97.7	62.8	−200.0, −18.2	58.1	65.1	0.0, 200.0	0.0	0.0	0.0, 0.0

Note. BD = binge drinking; *N* = change in number of previous month binge drinking occasions from baseline to follow-up; % = percentage change in frequency of previous month binge drinking occasions. Four participants from the reduced group reported no binge drinking at the follow-up assessment.

7.4.3 Executive functioning performance at baseline

At baseline and after adjusting for sex, participants who reported previous month binge drinking performed significantly worse on the inhibitory control Stroop Task than participants who did not binge drink (β = −0.79, 95% CI [−1.13, −0.45], p < .0001, d = −1.09, BF_{10} = 1899.60). No significant group differences at baseline were observed for the mental flexibility WCST (total error: β = −0.07, 95% CI [−0.43, 0.28], p = .69, d = −0.10, BF_{10} = 0.22; perservative error: β = −0.26, 95% CI [−0.62, −0.10], p = .15, d = −0.34, BF_{10} = 0.50; categories completed: β = −0.19, 95% CI [−0.55, 0.17], p = .31, d= −0.24, BF_{10} = 0.31), or the working memory Letter Memory Task (β = −0.04, 95% CI [−0.40, 0.32], p = .83, d = −0.05, BF_{10} = 0.19).

7.4.4 Binge drinking and executive functioning trajectories

Statistically significant main effects for time were observed for inhibitory control Stroop Task and mental flexibility WCST performance indices after adjusting for sex and cohort. Across groups and over time, Stroop Task performance declined (β = −1.35, 95% CI [−1.56, −1.14], p < .0001) and WCST performance improved on two of three indicators (total error: β = 0.41, 95% CI [0.23, 0.59], p < .0001; categories completed: β = 0.22, 95% CI [0.05, 0.39], p = .01; preservative error: β = −0.11, 95% CI [−0.36, 0.14], p = .40). No significant change in Letter Memory Task performance was observed over time (β = −0.08, 95% CI [−0.34, 0.19], p = .58).

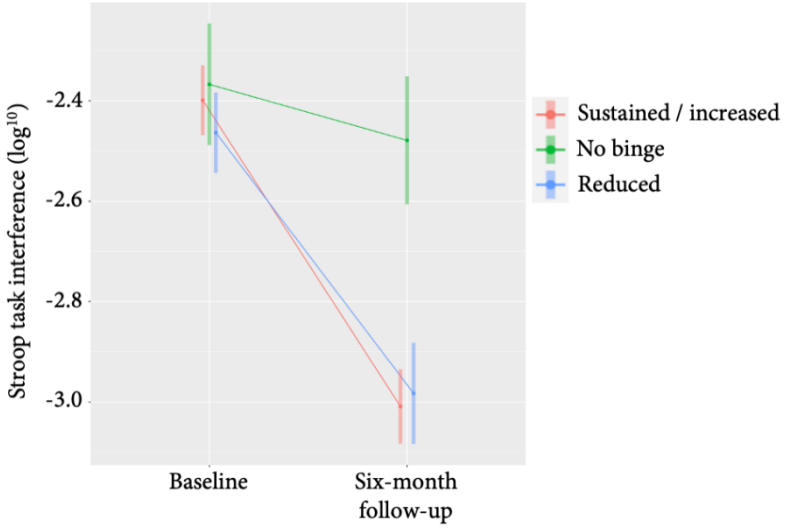
After adjusting for sex and cohort, a significant group by time interaction was observed for inhibitory control Stroop Task performance, but not for mental flexibility WCST or working memory Letter Memory Task performance (Table 7.3). Examination of simple effects indicated that participants who sustained/increased their frequency of binge drinking performed 23.8% (range −48.2 to −2.39) worse on the Stroop Task at follow-up compared with baseline performance (p < .0001; d = −1.25). Likewise, participants who reduced their frequency of binge drinking performed 21.1% (range −42.1 to −7.31) worse at follow-up compared with baseline performance (p < .0001; d = −1.21). Meanwhile, performance remained constant among participants who reported no binge drinking over the course of the study (p = 0.10; d = −0.50). At the follow-up assessment, poorer performance relative to non-binge drinking participants was observed for participants reporting sustained/increased binge drinking (p < .0001; d = −2.24) or reduced binge drinking (p < .0001; d = −2.04) and there was no significant difference in follow-up performance between those who sustained/increased or reduced their frequency of binge drinking (p = .91; d = 0.17) (Figure 7.1). The statistically significant group by time interaction for Stroop Task performance remained unchanged after adjusting for potentially confounding variables, including age, previous year cannabis use, previous year other illicit substance use, anxiety symptoms, and age of first drink. These additional variables were not significantly associated with task performance (ps ≥ .15).

Table 7.3. Group by time mixed model results for the relationship between binge drinking trajectory and executive functioning performance over six months, where positive scores indicate superior performance.

	β	95% CI	*p*	*d*	BF_{10}
		Reduced *vs.* sustained/increased binge drinking			
Stroop	0.28	−0.12, 0.68	.18	0.42	0.21
WCST total errors	0.15	−0.30, 0.60	.53	0.20	0.89
WCST perservative errors	0.21	−0.27, 0.69	.39	0.24	2.13
WCST categories completed	0.47	−0.02, 0.95	.07	0.56	11.03
Letter Memory	−0.49	−1.03, 0.06	.09	−0.49	0.21
		Reduced *vs.* non-binge drinking			
Stroop	−1.16	−1.65, −0.67	< .0001	−1.98	213.89
WCST total errors	0.01	−0.54, 0.55	.98	0.04	0.26
WCST perservative errors	−0.01	−0.59, 0.57	.98	0.00	0.46
WCST categories completed	0.29	−0.30, 0.88	.33	0.34	0.57
Letter Memory	0.11	−0.55, 0.77	.74	0.10	0.31
		Sustained/increased *vs.* non-binge drinking			
Stroop	−1.44	−1.90, −0.98	< .0001	−2.14	141.90
WCST total errors	−0.14	−0.65, 0.37	.59	−0.14	0.49
WCST perservative errors	−0.22	−0.76, 0.33	.43	−0.22	0.30
WCST categories completed	−0.17	−0.73, 0.38	.55	−0.16	0.39
Letter Memory	0.60	−0.02, 1.22	.06	0.53	0.31

Note. Outcomes are standardized. CI = confidence interval; *d* = effect size for mean group difference within repeated measures design; BF = Bayes factor. BF_{10} >3 indicates support for the alternative hypothesis (i.e., there is a difference between two groups). BF_{10} <0.33 indicates support for the null hypothesis (i.e., there is no difference between two groups).

Figure 7.1. Participants with reduced or sustained/increased binge drinking trajectories performed significantly worse over time on the inhibitory control Stroop Task.



7.4.5 Bayesian analysis of longitudinal associations

Consistent with conclusions drawn from frequentist analyses, the BF indicated there was sufficient evidence for group differences between non-binge drinking participants and both binge drinking groups for inhibitory control Stroop Task performance, and sufficient evidence to accept the null hypothesis for all working memory Letter Memory Task group comparisons (see Table 7.3). There was insufficient evidence to accept the null or alternative hypothesis for the majority of mental flexibility WCST group comparisons. However, in contrast to frequentist analyses, the BF indicated there was sufficient evidence of a difference between the reduced and increased/sustained binge drinking groups for the number of completed categories in the WCST. Post hoc comparisons indicated that the reduced binge drinking group significantly improved performance over time, by 19.0% (range −2.0 to 88.4; $p < .001$; $d = 0.82$), while the performance of the increased/sustained group remained constant (+6.5%; range −10.7 to 79.6; $p = .10$; $d = 0.37$).

7.5 Discussion

The main aim of this study was to explore whether EF deficits associated with binge drinking in young adulthood persist or recover following reduced bingeing frequency over a six-month period. At baseline, large deficits among binge drinking participants were observed for inhibitory control but not mental flexibility or working memory. Both the reduced and sustained/increased binge drinking groups exhibited large, continuing declines in inhibitory control over time compared with the non-binge drinking group. In contrast, mental flexibility performance improved for all participants over the course of the study, with some evidence of greater improvements among the reduced (large effect) versus sustained/increased binge drinking groups (small effect) on one of the indices. No significant differences over time or between groups were observed for working memory performance.

The baseline associations observed in the current study are consistent with a recent cross-sectional meta-analysis that found a significant association between binge drinking in adolescence and young adulthood and poorer inhibitory control, but not mental flexibility or working memory (Lees et al., 2019). To our knowledge, this study is the first to examine

whether such inhibitory control deficits can improve with reductions in the frequency of binge drinking during a sensitive neurodevelopmental period. Over six months, there was no evidence of improvement; instead, participants who reduced their frequency of binge drinking continued to show declining performance in a manner similar to those who sustained or increased their binge drinking. Evidence from the neuroimaging literature supports a frontal dysfunction hypothesis where any level of binge drinking during adolescence and young adulthood is associated with accelerated, ongoing gray matter volume reductions and attenuated white matter development (Lees et al., 2019; Moselhy et al., 2001; Zorko et al., 2004). Volume reductions may reflect non-beneficial pruning or premature cortical gray matter decline, which is similar to patterns observed in adults with AUD and in 'normal' aging (Pfefferbaum et al., 2013). The continued decline in inhibitory control performance may reflect the ongoing neural impact of any binge drinking during adolescence and young adulthood.

Reductions in binge drinking frequency, or discontinuation of use, for a longer period of time may be required to observe a plateauing effect, with even longer periods likely needed to observe possible improvements in inhibitory control performance. There is promising evidence to indicate that the duration of use may influence the rate of recovery, with young people experiencing a greater likelihood of recovery than older adults dependent on alcohol for a longer duration (Le Berre et al., 2017; Pitel et al., 2009; Schottenbauer et al., 2007). When examining cognitive recovery more broadly, there is preliminary evidence to indicate that two to four years of discontinued binge drinking in young adults is associated with some improvement in delayed recall (Mota et al., 2013) and working memory (Carbia, Cadaveira, López-Caneda et al., 2017), which reflects an intermediate position between binge and non-drinking individuals. A similar length of discontinued binge drinking has been associated with improvements in immediate recall to a level aligned with non-drinking control performance (Carbia, Cadaveira, Caamano-Isorna et al., 2017). Overall, the current findings add to the growing body of evidence that alcohol-related cognitive deficits in young people may begin to recover following relatively long periods of no binge drinking (i.e., >two years). Further exploration of alcohol reduction thresholds should be explored in longitudinal studies spanning multiple years.

There was no evidence in this study to indicate that binge drinking results in mental flexibility or working memory deficits, supported by both frequentist and Bayesian

analyses. Previous observations of an association between alcohol use and working memory often report deficits after chronic bingeing or heavy drinking for multiple years (Mota et al., 2013; Stavro et al., 2013) or do not control or match participants on other confounding factors (for a review of studies, see Lees et al., 2019) and this may account for the discrepant findings. Interestingly, mental flexibility performance improved over the six-month study period for binge drinking and non-binge drinking participants. Improved performance may reflect continued neuromaturation and cognitive efficiency, enhanced neuroadaptation mechanisms, or cognitive task familiarity (Bernardin et al., 2014). Of note, cross-sectional and longitudinal examination of neural activation during tasks measuring working memory have indicated that young adults who binge drink generally exhibit greater task-evoked neural response than non-binge drinking counterparts, even in the absence of overt performance deficits (Squeglia, Pulido et al., 2012; Wetherill et al., 2013). These studies have proposed that altered functional activation may reflect recruitment of additional resources to ensure adequate overt task performance. Therefore, the non-significant findings observed for mental flexibility and working memory could reflect compensatory mechanisms and may not necessarily indicate absence of underlying neural dysfunction among young adults who binge drink.

Strengths of this study include the use of frequentist (i.e., linear mixed models) and Bayesian analyses to examine the longitudinal associations between changes in binge drinking frequency and performance in three EF domains. Linear mixed models adequately deal with response correlation in repeated measures (such as correlated measurement errors and participants' heterogeneity), resulting in greater statistical power (Gibbons et al., 2010). Bayesian hypothesis testing analyses enabled explicit discrimination of evidence of absence (i.e., no true effect) from absence of evidence (e.g., because of insufficient statistical power) for associations between binge drinking and EF. Limitations of this study should also be noted. First, there was high sample attrition, which resulted in a relatively small sample at follow-up assessment—although missing data were estimated in linear mixed models with FIML, a rigorous and recommended method for mitigating bias associated with response attrition (Hox et al., 2017; West et al., 2014). Second, the sample consisted predominantly of female participants, which limits generalizability. Third, externalizing symptoms were not assessed in this sample and we were therefore unable to control for this in analyses. Fourth, participants were not asked to provide confirmation of compliance with instructions for the online neuropsychological testing. Despite evidence that online

neuropsychological testing is reliable and valid (Raz et al., 2012), future studies using online neuropsychological assessments could incorporate real-time measures of compliance, such as visual and audio recordings of completion. Finally, only a single task assessed each EF domain, making it difficult to determine whether the effects were task specific or could be generalized across measures of the same domain (Bartholow et al., 2018).

In conclusion, this study found a cross-sectional and prospective association between binge drinking and inhibitory control deficits in young adults aged 17–24 years. Any report of binge drinking throughout the study was associated with continued declines in inhibitory control over six months. In contrast, no consistent evidence was found for an association between binge drinking and mental flexibility or working memory. Further research is required to determine whether inhibitory control deficits improve over a longer period of reduced or discontinued binge drinking among young people.

Chapter 8

General discussion

8.1 Background

Alcohol is the most frequently used substance around the globe and consumption often begins during adolescence (World Health Organization, 2018). Consuming alcohol in binge episodes is particularly prevalent among young people and can lead to acute health harms, engagement with other high-risk behaviors, and heightened probability of developing an AUD (Chung et al., 2018). Explicating the precursory risks and consequential harms associated with binge drinking in young people can ultimately inform prevention and early intervention initiatives and policies aimed at reducing the prevalence of alcohol-related harms.

Neurobiology, cognition, and psychopathology are of central importance when considering the drinking choices of young people. Rapid neural developments occur over the ages of 10–24 years, which means young people are especially receptive to risk-taking behaviors, like binge drinking, and are more sensitive to alcohol-related neurotoxic harms (Spear, 2018). Additionally, the risk of binge drinking is greater in the presence of psychopathology, which often first manifests during this period and may be related to, or exacerbated by, neurobiological and cognitive aberrations (Castillo-Carniglia et al., 2019; Grant et al., 2015; Ning et al., 2020). Importantly, complex and dynamic interactions exist between these individual-level factors and broader multigenerational and environmental influences. However, limited research has examined these dynamic relationships, which has resulted in significant knowledge gaps.

Four major gaps in the evidence base were identified in **Chapter 1** of this thesis. First, the literature has poorly described the neurobiological and cognitive precursory risk and consequential harm profiles associated with binge drinking in young people. Second, limited research has examined the interactions between psychopathology, cognition, and alcohol use, especially for internalizing psychopathology and higher-order EF. Third, insufficient research has examined the added impact of familial alcohol use behaviors on the likelihood of young people presenting with established precursory risk factors for binge drinking. Fourth, there has been virtually no research on the recoverability from neurobiological and cognitive harms following binge drinking in young people. Methodological limitations were identified in the literature on these research topics, including inadequate consideration and adjustment for broader familial and environmental confounding factors, small sample sizes that are underpowered to detect small-to-moderate effects, and questions about causality and directionality in cross-sectional studies.

This thesis was designed to address these limitations and capture the inter-relations between neurobiological, cognitive, and psychological risks and harms of binge drinking in young people, as well as the broader multigenerational and environmental impacts considered in the study designs. Four research questions were formulated from a life course perspective to address the gaps identified above and provide an innovative and critical contribution to the area of study in young people:

1. What are the individual-level precursory risks associated with binge drinking and how do they interact? (**Chapters 2–3**)
2. Does familial alcohol use, including familial alcohol use problems and alcohol use during pregnancy, heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking? (**Chapters 4–6**)
3. What are the neurobiological and cognitive consequential harms associated with binge drinking? (**Chapters 2** and **7**)
4. Do neurobiological and cognitive harms recede following reductions in binge drinking frequency? (**Chapters 2** and **7**)

Overall, this thesis offers a multifaceted, multigenerational, and developmentally sensitive approach to understanding the precursory risks and consequential harms of binge drinking in young people. The preceding chapters describe world-first research (**Chapters 2–3** and

7) and the largest international empirical investigations on these research topics to date (**Chapters 4–6**), which include multidisciplinary, cross-national teams of collaborators from Australia and the US. In this concluding chapter, findings from the six empirical studies are integrated to address the four central research questions of this thesis, posed in **Chapter 1**. A discussion follows of the implications of the thesis findings for practice and policy, prior to closing with the current challenges and suggested future directions of research.

8.2 Overview of findings

A summary of the key findings from each empirical chapter is provided in Table 8.1. The thesis findings related to each of the four central research questions are summarized below before outlining the main conclusions drawn from the empirical studies.

8.2.1 What are the individual-level precursory risks associated with binge drinking and how do they interact?

Aberrant neurobiological features are present prior to the onset of binge drinking in adolescents and young adults. The findings from the systematic review in **Chapter 2** suggest that structural and functional developmental deviations in executive frontal regions are a key risk factor for the onset of binge drinking in young people. However, the review indicates that more evidence is required to determine whether overt cognitive deficits are a precursory risk factor for future binge drinking.

The empirical chapters of this thesis present several novel findings with respect to precursory risks. The findings from **Chapter 3** indicate that levels of alcohol consumption are moderated by EF for individuals with high internalizing symptoms. Further, small cross-sectional correlations are reported in **Chapter 4** between brain structure and psychopathology in preadolescents with familial alcohol use problems. Similarly, in **Chapter 5** aberrant brain structure is shown to partially mediate the association between PAE with current and future psychopathology symptoms and externalizing disorders. These findings provide further evidence that neurobiological aberrations are linked to

psychopathology in young people, and this constellation of mechanisms could act as precursory risk factors for binge drinking.

Table 8.1. Summary of the research questions and key findings from this thesis.

Research question	Chapter aim and overview	Key findings
1: What are the individual-level precursory risks associated with binge drinking and how do they interact?	**Chapter 2:** Review the neurobiological and cognitive precursory risks for binge drinking at ages 10–24 years; 58 studies were included in the review.	↓ Cortical volume and surface area in frontal (executive) regions ↓ Neural response during EF tasks
	Chapter 3: Explore interactions between internalizing symptoms and EF, and the relationship with alcohol use and AUD symptoms in adolescents and young adults (n = 155).	High internalizing symptoms in interaction with EF deficits associated with: ↑ Drinking motive to cope with negative affect ↑ Alcohol use (including binge drinking) ↑ AUD symptoms
2: Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?	**Chapter 4:** Examine the risk profiles of preadolescents with familial alcohol/substance use problems (n = 11,873). Outcomes examined: brain structure, cognition, psychopathology, and early alcohol use.	↓ Whole brain cortical thickness ↑ Surface area in frontal and occipital regions ↑ Psychopathology and mental disorders No cognitive deficits Not more likely to experiment with alcohol than peers with no familial problems
	Chapters 5–6: Examine the risk profiles of preadolescents with PAE (n = 10,119). Outcomes examined: brain structure, brain function, cognition, psychopathology (Chapter 5), and early alcohol use (Chapter 6).	↑ Cerebral volume ↑ Surface area in parietal, temporal, and occipital regions ↑ Psychopathology and mental disorders ↑ Alcohol use experimentation No cognitive deficits
3: What are the neurobiological and cognitive consequential harms associated with binge drinking?	**Chapter 2:** Review the neurobiological and cognitive consequential harms of binge drinking; 58 studies were included in the review.	↓ Cortical and subcortical volume throughout widespread regions ↑ Neural response during EF tasks ↓ EF (particularly inhibitory control) and memory
	Chapter 7: Investigate binge drinking and EF trajectories among adolescents and young adults over a six-month period (n = 99).	Binge drinking frequency associated with decreased inhibitory control. Working memory and mental flexibility not affected by binge drinking.
4: Do neuro-biological and cognitive harms recede following reductions in binge drinking?	**Chapter 2:** Review neurobiological and cognitive outcomes following reductions in binge drinking; 58 studies were included in the review.	Two–four years of alcohol abstinence: ↑ Recent and long-term memory ↑ Working memory
	Chapter 7: Investigate whether EF deficits recover following reductions in the frequency of binge drinking over a six-month period (n = 99).	Reduced binge drinking frequency associated with continued deterioration of inhibitory control over six months.

8.2.2 Does familial alcohol use heighten the probability of a young person presenting with established individual-level precursory risk factors for binge drinking?

Robust evidence is presented in **Chapter 4** that young people with familial alcohol use problems exhibit differences in neocortical brain structure. Of particular importance, these preadolescents show aberrations in frontal regions, perhaps reflecting increased risk of binge drinking in adolescence and young adulthood when alcohol is likely to become more available (despite not reporting greater odds of alcohol use experimentation in the preadolescent period when access to alcohol is more restricted). Likewise, **Chapters 5–6** demonstrate that young people with low- to moderate-level PAE also exhibit aberrant neocortical structure and are at greater odds of experimenting with alcohol by age 9–10.

Additionally, strong evidence is provided in **Chapters 4–5** that young people with familial alcohol use problems or PAE experience elevated externalizing and internalizing psychopathology symptoms and are at greater odds of being diagnosed with one or more lifetime mental disorders. Greater externalizing and internalizing symptoms may increase risk of prospective binge drinking among these young people (Bevilacqua et al., 2018; Dyer et al., 2019; Elkins et al., 2018; Erskine et al., 2016; Howard et al., 2015).

8.2.3 What are the neurobiological and cognitive consequential harms associated with binge drinking?

Significant neurobiological and cognitive consequential harms occur following binge drinking in adolescence and young adulthood. Studies synthesized in **Chapter 2** indicate that young people experience escalated neocortical gray matter volume reductions and require greater neural recruitment during EF tasks following uptake of binge drinking. Moreover, **Chapters 2** and **7** demonstrate that young people exhibit alcohol-related deficits in EF and memory. Examination of EF subdomains in **Chapter 7** reveals that young people who binge drink over a six-month period experience a deterioration of inhibitory control but not working memory or mental flexibility. This observation is consistent with the cross-sectional meta-analysis results in **Chapter 2**.

8.2.4 Do neurobiological and cognitive harms recede following reductions in binge drinking frequency?

The findings from **Chapter 2** indicate that further studies are required to determine whether the neurobiological harms outlined above recede following reductions in binge drinking. Studies synthesized in **Chapter 2** suggest that discontinuation of binge drinking for two to four years can lead to some improvement in EF and memory, with performance being intermediate between that of continuous binge drinking and non-drinking young people. However, **Chapter 7** provides no evidence that inhibitory control deficits recover following reductions in binge drinking frequency over a shorter period (i.e., six months). In fact, young adults who reduce their binge drinking show continued deterioration in a pattern similar to those who sustain or moderately increase their frequency of binge episodes.

8.2.5 Summary of main thesis findings

Three central conclusions can be drawn from the empirical chapters of this thesis:

1. **Neurobiology, psychopathology, and the interactions between these mechanisms are central precursory risk factors of binge drinking in young people.**

The systematic review highlights the underlying role of the frontal lobe in prospective binge drinking. By only including studies where young participants reported no concurrent substance use, mental disorders, or AUD diagnosis, the review circumvents confounding effects and provides more concrete evidence regarding the neurobiological pathway to binge drinking. Meanwhile, the chapter exploring data from the world-first *Inroads* trial highlights the complex inter-relations between frontal lobe-mediated EF, psychopathology, and alcohol consumption. Rigorous factor analyses and structural equation models were employed in this study which are seldom used in substance-related neuropsychological research. Additionally, the ABCD mega-analyses illustrate a relationship between brain structure and experiences of psychopathology, which may increase risk of future adolescent binge drinking.

2. Multigenerational alcohol use impacts a young person's neurodevelopment, experiences of psychopathology, and early alcohol use choices.

In the largest international studies to date, young people with familial alcohol use problems or low- to moderate-level PAE were shown to experience established risk factors for adolescent binge drinking. Data came from the ABCD Study, which is the largest long-term study of brain development and child health in the US. The large and diverse probability sample mitigates reproducibility concerns (Marek et al., 2020) and affords utilization of sophisticated analytic strategies, including linear and nonlinear mixed model analyses and cross-sectional and longitudinal multilevel mediation models. Additionally, extensive sensitivity analyses were conducted, which involved stringent matching protocols and participant exclusions to eliminate potential confounding effects. These analytic strategies ensured robust findings were drawn from the large epidemiological dataset, leading to the conclusion that multigenerational alcohol use must be considered in the context of adolescent development and behavior (including alcohol use choices).

3. Binge drinking results in widespread neurobiological and cognitive consequential harms. Overt cognitive deficits do not recede in the short term.

The systematic review illustrates that binge drinking leads to reduced cortical and subcortical brain volume, aberrant brain function, and poorer memory and EF. By examining multiple EF domains, the final empirical chapter illustrates that the deteriorating effects of binge drinking are specific to inhibitory control, rather than mental flexibility or working memory. The *Inroads* study is also the first internationally to show that reduced binge drinking frequency does not lead to cognitive recovery in the short term (six months). A joint frequentist–Bayesian mixed model analysis approach increased the robustness of these novel findings.

In sum, the present thesis makes a unique and important contribution to understanding the complex dynamics between neurobiological, cognitive, and psychological precursory risks and consequential harms of binge drinking during adolescence and young adulthood, as well as the shaping of broader multigenerational and environmental influences. This integrated and developmentally sensitive approach is a key strength of this thesis. The central conclusions of the thesis have important and wide-ranging societal implications that are discussed in the next section.

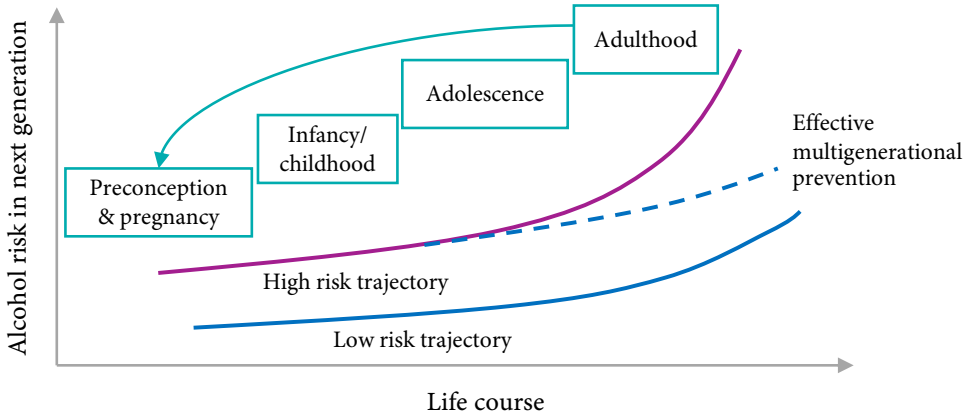
8.3 Implications of thesis findings

The research questions and overall aim of this thesis were shaped by a life course perspective. This concept acknowledges that there are key stages in a person's life that have particular relevance for their health, including gestation and early childhood, adolescence and young adulthood, and later adult life (Kuh & Shlomo, 2004). As outlined in **Chapter 1**, the life course approach recognizes that there are biological and psychological pathways that influence the development of disease and maladaptive behaviors (e.g., binge drinking) across an individual's lifespan or across generations (e.g., parental alcohol use), while appreciating that individual experiences are shaped by the wider social, economic, and cultural context (Jacob et al., 2017). In this section the implications of the thesis findings are considered through a life course and multigenerational prevention lens.[6]

The family-conscious multigenerational perspective on prevention extends beyond a singular harm reduction focus in young people and moves toward recognizing and intervening in multiple stages of the family life cycle, including alcohol use prevention and early intervention for women of reproductive age, intervention and treatment for parents and caregivers with alcohol use problems, and prevention of perpetuation to younger generations (Jackson, 2019). Figure 8.1 illustrates the life course and multigenerational prevention framework for alcohol use and related harms. At a population level, the ultimate goal of considering alcohol use prevention from a multigenerational perspective is to curb escalating alcohol use trajectories from a young age and reduce the likelihood of individuals experiencing highly disabling related harms across the lifespan and across generations. The following subsections describe the implications of the thesis findings for practice (Subsection 8.3.1) and policy (Subsection 8.3.2) from a multigenerational and life course prevention perspective. Notably, many of the strategies outlined for practice and policy are relevant to other substances, with similar approaches recommended for tobacco (Cummings et al., 2021) and opioid use (Compton & Jones, 2021) prevention and intervention.

[6] The implications of Chapters 2 and 5 are considered from a life course perspective in Mewton, L., Lees, B., & Rao, R.T. (2020). Lifetime perspective on alcohol and brain health. *BMJ, 371*, m4691. See Appendix E.

Figure 8.1. A life course and multigenerational prevention framework for alcohol use and related harms.



Note. As an example, a child born with familial alcohol use problems and/or PAE would be categorized as high risk for early alcohol use experimentation, adolescent binge drinking, and future AUD. Effective multigenerational prevention and intervention efforts can alter this trajectory and reduce the risk of a young person developing an AUD.

8.3.1 Implications for practice

The findings from this thesis suggest that the multigenerational impacts of alcohol use must be more widely acknowledged, and prevention and intervention initiatives should be implemented at several levels, including targeted initiatives for adults with alcohol use problems, and universal initiatives for women of reproductive age; health care providers; caregivers; and young people. Recommendations for practice are described below.

8.3.1.1 Women of reproductive age

The findings from this thesis along with the broader evidence base indicate that any alcohol use during any stage of pregnancy can increase risk of harm to offspring. However, approximately 38% of health care providers in the US convey to their clients that alcohol is safe to use during at least one trimester of pregnancy (Chiodo et al., 2019). More effective translation of research findings to clinicians is required to eliminate mixed messaging on safe levels of consumption during pregnancy. Broad public awareness campaigns, dissemination platforms, and greater investment in health promotion will help eliminate mixed messaging in health care systems and across society more broadly.

Educating health care providers on the impacts of PAE is critical as universal screening and brief personalized intervention are among the most effective initiatives for preventing alcohol use during pregnancy (Shogren et al., 2017). Of concern, it is currently estimated that only one-third of health care providers in the US conduct routine screening, less than one-quarter use a screening tool, and 1 in 10 use a screening tool validated with pregnant women (Chiodo et al., 2019). Validated alcohol use screening tools for use with pregnant women include the four-item T-ACE (Sokol et al., 1989) and the five-item TWEAK (Chan et al., 1993), while the three-item AUDIT–Consumption has been recommended as a universal screener for women of reproductive age (Edwards et al., 2020). Screening must then be supplemented with a personalized, stepped care response based on the individual's score. These discussions can support and empower women of reproductive age planning a pregnancy, currently pregnant, or at risk of unintended pregnancy (e.g., not using effective contraception) to make informed choices about their drinking (Schölin & Fitzgerald, 2019). For pregnant women experiencing alcohol use problems, referral to specialized holistic support is required, as is postpartum support for the mother and support for child assessment and development. Brief interventions and motivational interviews delivered by health care providers, nutritionists, researchers, or via the internet hold promise in supporting these women (Fergie et al., 2019). Additionally, consideration should be given to the context in which the woman lives: families and cultures that accept heavy drinking, having a partner who is a frequent or heavy drinker, and attending social gatherings centered around alcohol can all contribute to a woman's alcohol choices while pregnant (May & Gossage, 2011). Overall, universal screening, brief intervention, and targeted treatment (when indicated) for women of reproductive age can reduce the prevalence of alcohol use during pregnancy and mitigate risk of harm to an unborn child.

8.3.1.2 Parents and caregivers

Intervention initiatives should continue to treat and aim to reduce the prevalence of alcohol use problems, including AUDs, in parents, caregivers, and older adults. More broadly, health care providers should screen all patients for heavy drinking and AUDs and use clinical opportunities to intervene (Compton et al., 2015). Often despite their best intentions, parents and caregivers with alcohol or other substance use problems can display a wide range of parenting deficits (e.g., impaired emotional responsiveness, poor

facilitation of sleeping and eating routines) and can have difficulties in providing stable and nurturing environments (Solis et al., 2012). As a consequence, young people living in these households are at greater risk of adverse childhood experiences, which likely plays an important role in the relationship between psychopathology and binge drinking (Young et al., 2007). Intervention initiatives with dual foci on substance use treatment and parenting skills have proven effective in reducing parental substance use, improving mental health outcomes, and building parent–child attachment (Niccols et al., 2012). While family members may feel shame or embarrassment when sharing their own difficulties with young people, research indicates that knowledge of family history and awareness of hardship is linked to higher youth self-esteem and internal locus of control as well as lower incidence of behavioral problems—attributes linked to delayed alcohol use experimentation and binge drinking (Duke et al., 2008).

Moreover, there should be greater awareness and improved messaging for parents and family members about the impact their attitudes can have on a young person's behavior. For instance, approximately one in four parents do not think their attitudes toward substances affect their adolescent's substance use, yet increasingly liberal parental views toward substance misuse are associated with greater alcohol consumption in offspring (Moore et al., 2010). Likewise, adolescents who are given alcohol by their parents have greater odds of subsequent binge drinking and experiencing alcohol-related harms (Clare et al., 2019; Mattick et al., 2018). Authoritative parenting and positive parenting strategies, such as encouragement of prosocial behaviors, conflict resolution, and parental monitoring can protect children from high-risk behaviors (Shakya et al., 2012). In addition, strict rule setting and frequent, high-quality communication about alcohol use is associated with the lowest amount of adolescent drinking (Koning et al., 2012). Digital health dissemination platforms are a suitable vehicle for relaying these strategies to parents and caregivers. For example, *Positive Choices* is an Australian platform that provides free, evidence-based resources and strategies to parents and caregivers for the prevention of alcohol use in young people (Stapinski et al., 2017). These strategies have been accessed by more than one million users, demonstrating the vast reach that can be achieved via digital dissemination tools. Overall, the behaviors and attitudes of parents and family members are highly linked to adolescent alcohol use and integral to the prevention of perpetuation to younger generations.

8.3.1.3 Young people

The prevention of binge drinking among young people must remain a primary focus to reduce the global prevalence of alcohol-related harms that can have ongoing negative impacts throughout a young person's life. Compared with clinical- or community-based services, the school environment is uniquely positioned to disseminate universal and targeted initiatives at a population scale, particularly when resources are distributed via the internet. A systematic review of 90 studies finds that universal alcohol and other substance use prevention programs disseminated in elementary school can reduce intentions to use alcohol, change positive expectancies about substance use, and prevent alcohol use experimentation (Tremblay et al., 2020). Considering established comorbidity between alcohol use and psychopathology, mental health prevention programs must also be broadly disseminated at a young age. A meta-analysis of 43 studies demonstrates that elementary school-based mental health prevention and early intervention programs and services can decrease psychopathology symptoms, including externalizing (moderate decrease) and internalizing psychopathology (small decrease) as well as attention problems (small decrease) (Sanchez et al., 2018). Importantly, this meta-analysis finds mental health programs do not reduce alcohol and substance use experimentation; thus, all elementary students should receive both evidence-based substance use and mental health programs.

Evidence shows that prevention initiatives are more effective when program boosters are delivered over several years (Gearing et al., 2013). Secondary school prevention programs are therefore critical and should reaffirm knowledge about the harms of alcohol use, incorporate effective therapeutic elements (i.e., those based on cognitive behavioral therapy), and address changing social contexts that occur in adolescence. Universal secondary school prevention programs that are disseminated to the entire class via the internet have been shown to reduce growth in binge drinking over 30 months by up to 75% (Teesson et al., 2020). Moreover, secondary school-based programs targeting cognitive control and risk-taking behaviors in high-risk adolescents have been found to prevent alcohol use initiation, binge drinking, and alcohol-related harms by approximately 50% for up to three years (Edalati & Conrod, 2019; Newton et al., 2016; Teesson et al., 2017). These targeted programs have also been successful in reducing the likelihood of adolescents transitioning from internalizing and externalizing symptoms to disorders, by roughly 25%, in addition to reducing alcohol consumption among young people with pre-existing

psychopathology (Edalati & Conrod, 2019). These findings regarding the secondary benefits of targeted substance use preventions are important given the psychopathology risk profiles observed among youth experiencing the impact of multigenerational alcohol use.

To complement multigenerational prevention efforts and interrupt trajectories toward AUD, early interventions must be disseminated on a large scale for adolescents who are already binge drinking but who do not yet meet criteria for AUD (and therefore do not require specialist treatment services). A systematic review and meta-analysis of 53 trials and over 33,000 participants concludes that brief, internet-delivered early interventions for alcohol use among young people can reduce binge drinking and alcohol use problems over the long term with a small effect size (Smedslund et al., 2019). These conclusions align with those drawn by a previously published meta-analysis that also conducted subgroup analyses, revealing that interventions with multiple sessions have stronger effects than brief, single session comparators (Carney & Myers, 2012). Similarly, evidence supports internet-delivered early intervention programs for reducing symptoms of psychopathology (Das et al., 2016; Garrido et al., 2019). Therefore, early interventions such as *Inroads* (Stapinski et al., 2019) are well suited for global dissemination via the internet to young people who are struggling with their alcohol use and mental health. Overall, evidence-based prevention and early intervention initiatives targeting young people are underutilized around the globe (Compton et al., 2019). Yet, they can effectively prevent, delay, and interrupt hazardous alcohol use trajectories toward AUD and related harms across the lifespan and thus must be implemented at a population level.

In summary, a multigenerational approach to alcohol use prevention should target women of reproductive age, health care providers, parents, caregivers, and young people. While alcohol use prevention and intervention are of critical importance, other individual (i.e., psychopathology, cognition) and interpersonal factors must be considered and addressed concurrently to reduce the likelihood of young people binge drinking, developing an AUD, or experiencing alcohol-related harms.

8.3.2 Implications for policy

Prevention and intervention initiatives aimed at individuals form an important part of a comprehensive strategy for tackling problematic alcohol consumption and related harms. However, an individual's choices around alcohol use are embedded within an environment that is shaped by commercial, regulatory, legislative, and cultural influences. Public health measures that affect the whole population can have a strong effect on behavior change (e.g., smoke-free legislation) (West, 2017). Therefore, implementing population-level positive alcohol policies and guidelines alongside initiatives aimed at individuals are critical for multigenerational prevention of alcohol use and related problems.

8.3.2.1 Policies related to alcohol use during pregnancy

The findings from this thesis have important policy implications related to alcohol use during pregnancy. Of considerable concern, a recent comparison of international alcohol consumption guidelines indicates that only 49% of the 57 countries examined have national guidelines for drinking during pregnancy (Stockley et al., 2019). All countries that provide guidelines for alcohol consumption during pregnancy indicate that abstinence is the safest option to avoid risk of harm to an unborn child. Compared with nations in other continents, European and South American countries are less likely to have guidelines for drinking during pregnancy (Stockley et al., 2019) and this may contribute to higher prevalence rates of alcohol consumption observed in these regions (Popova et al., 2017). Clear recommendations that alcohol consumption is contraindicated during pregnancy and conception planning must be included in national alcohol guidelines to minimize mixed messaging around safe levels of alcohol use currently being conveyed to families by health care providers (Chiodo et al., 2019).

Another important area for policy is alcohol labelling. New evidence shows that large and clearly marked alcohol warning labels are an effective population-level strategy both for raising awareness and reducing alcohol intake in alignment with national drinking guidelines (Schoueri-Mychasiw et al., 2020; Zhao et al., 2020). The US became the first country to legislate for pregnancy warning labels on alcohol products in 1989. Since then, only 11 more countries have mandated pregnancy warning labels (Food Standards Australia New Zealand, 2020). Australia, Japan, and the UK have schemes for voluntary

pregnancy warning labels on alcohol products, although low uptake has been reported. For instance, in Australia the voluntary scheme has been in place since 2011 yet only 48% of alcohol products feature a pregnancy health warning label (Siggins Miller, 2017). Globally, policy makers need to address these major shortfalls in current legislation for pregnancy warning labels and national alcohol use guidelines. These population-level strategies can prevent alcohol use during pregnancy and will complement a comprehensive multigenerational prevention approach to alcohol use and related harms.

8.3.2.2 Policies related to alcohol use across the lifespan

Population-level strategies aimed at preventing alcohol use during pregnancy are underpinned by supportive alcohol policy more broadly. According to the World Health Organization, the most effective and cost-effective policy-based strategies are increasing the price of alcohol (via minimum alcohol pricing or taxes) and reducing and restricting the physical availability and the marketing of alcohol (World Health Organization, 2017). For example, a number of provinces in Canada have implemented a minimum price, with a concomitant reduction in alcohol consumption (Stockwell et al., 2012), alcohol-related hospital admissions (Stockwell et al., 2013), and alcohol-related deaths (Zhao et al., 2013). In the UK, it is estimated that a £0.50 minimum price per standard drink would reduce alcohol consumption by roughly 7% and prevent close to 3,000 deaths per year (Purshouse et al., 2010). Importantly, epidemiological modelling suggests that minimum price policies will particularly benefit young people and the heaviest drinkers (Purshouse et al., 2010).

Restricting physical availability of alcohol can also have a positive impact on alcohol behaviors, particularly in delaying uptake among young people. For example, young people who do not have access to alcohol within the home are less likely to experiment with alcohol at a young age and binge drink during adolescence (Lauckner et al., 2020)—a finding that complements recommendations described above that parents withhold supply of alcohol to offspring (Clare et al., 2019; Mattick et al., 2018). Further, at a population level, local licensing and zoning ordinances that limit the density of alcohol outlets within a community are associated with decreased alcohol consumption and related harms, such as injuries, crime, and violence (Campbell et al., 2009; Foster et al., 2017; Grubesic & Pridemore, 2011; Reboussin et al., 2011).

In reference to alcohol marketing, there is consistent evidence that exposure to media and commercial communications on alcohol increase the likelihood that individuals (particularly adolescents) will drink and escalate their consumption (Anderson et al., 2009; Grenard et al., 2013; Smith & Foxcroft, 2009). Consequently, the World Health Organization's (2010) *Global Strategy to Reduce Harmful Use of Alcohol* recommends establishing national regulatory or co-regulatory frameworks to monitor both content and volume of alcohol marketing. Of concern, a recent query into the progress of this strategy indicates that 80 countries had made no progress in the first five years following publication, 47 had reported some progress, while 11 countries reported decreased progress (Jernigan & Trangenstein, 2017). Further, just 19 countries had taken any new actions since 2010 in implementing statutory regulations that address new marketing techniques for alcohol, such as screen media campaigns (Jernigan & Trangenstein, 2017). Thus, it has been recommended that a framework on alcohol marketing control, like that for tobacco, should obligate countries to undertake a minimum of activities to control and address alcohol marketing and to implement global agreements regarding marketing across borders and online (Jernigan & Ross, 2019). Implementation of alcohol marketing restrictions could significantly alter the uptake of alcohol use among young people.

Finally, there is evidence to suggest that raising the legal purchase age can serve to support other effective alcohol reduction measures. A cross-national study following young people in Australia and the US from the age of 13 to 25 shows that Australian youth (legal drinking age = 18) report greater rates of alcohol use compared with youth in the US (legal drinking age = 21) (Epstein et al., 2020). Other data from the US, where the legal drinking age changed from 21 to 18 and then back to 21, show that alcohol consumption, particularly binge drinking, among young people increased when legislation allowed for drinking at a lower age, and then decreased when the legal drinking age reverted back to 21 (Plunk et al., 2013). Similarly, adults in the US who had been legally allowed to purchase alcohol before age 21 were 1.3 times (95% CI 1.2–1.5) more likely to meet criteria for an AUD during the previous year than were adults who were legally allowed to drink at age 21, and this association held even 20–30 years later (Norberg et al., 2009).

Overall, population-level alcohol policies and national guidelines are an important foundation for a cohesive multigenerational prevention strategy. Positive alcohol policies can reshape the environment that influences an individual's choices around alcohol use by

amending national drinking guidelines and mandating warning labels on alcohol products as well as determining the availability, accessibility, and promotion of alcohol products and venues on a wide scale. These evidence-based strategies can supplement distribution of prevention initiatives aimed at the individual to reduce the prevalence and global impact of alcohol use and related harms.

8.4 Future directions

The findings of this thesis not only have clear implications for practice and policy, but can also guide future research directions in the field of adolescent alcohol use (Subsection 8.4.1) and health more broadly (Subsection 8.4.2). Suggestions for future research are outlined below.

8.4.1 Alcohol use research

This thesis identifies that preadolescents with familial alcohol use problems and low- to moderate-level PAE show established precursory risk factors for adolescent binge drinking, including greater levels of psychopathology, aberrant brain structure, and—in the case of PAE—early alcohol use experimentation. The longitudinal component of the ABCD Study is currently underway and will be essential for future work to determine whether these populations do in fact experience greater odds of adolescent binge drinking. Future longitudinal work should also aim to test the relative predictive value of the risk profiles reported in this thesis for escalating alcohol and other substance use throughout adolescence. The added risk related to genetics, adverse childhood experiences, and peer groups on alcohol use choices could also be the focus of future work with these populations.

Further, the findings of this thesis highlight the neurotoxic effects of binge drinking, and many questions surrounding the recoverability of these deficits remain unanswered. The systematic review in **Chapter 2** identifies just one study examining neural recovery and **Chapter 7** adds to a small body of just four studies examining cognitive recovery from binge drinking. Considering the high prevalence of binge drinking in adolescence and young adulthood and the sustained deficits over the short term (i.e., six months), further work is desperately needed. Future work should focus on longitudinal changes in brain

structure and neural response to EF tasks following reductions in binge drinking, as well as investigating the longevity of inhibitory control and memory deficits. The effectiveness of cognitive training programs to aid recovery should also be examined, as should the role of these overt deficits in progression to AUD, treatment responsiveness, and relapse likelihood.

Future research should also aim to address methodological concerns. A key limitation to much of the work described in this thesis, and the evidence base at large, is the use of observational human data. Inherent in its observational nature are difficulties in establishing causality and directionality without randomization, with the principal concern being confounding. While many of the studies presented in this thesis were able to control for a large range of confounding factors, there are limitations to this multiple regression approach (Ohlsson & Kendler, 2020). Numerous methods, mainly from econometrics, have been developed in recent years in response to the confounding problem in observational data (Marinescu et al., 2018). These methods, rarely used in this field thus far, include complex models that aim to adjust for all confounders (e.g., Granger causal models, structural equation models, Bayesian networks, state–space models) and quasi-experimental causality models (e.g., regression discontinuity design, difference-in-differences approach, instrumental variable approaches, including Mendelian randomization). Future work should make use of these techniques to improve understanding of the causal neurobiological and psychological pathways to adolescent binge drinking. Consortium-sized longitudinal datasets, such as the ABCD Study, are suitably positioned to conduct these analyses.

In sum, future work should aim to build on the current thesis findings by utilizing consortium-sized longitudinal datasets to test the relative predictive power of precursory risk factors for binge drinking; further examine the longevity of alcohol-related neurobiological and cognitive harms; and employ statistical techniques that can examine causal pathways to binge drinking. The findings from this thesis are relevant not only to future alcohol use research but to health and risk behavior research more broadly. In the following subsection, future research directions related to this thesis are considered from a broad life course and multigenerational health perspective.

8.4.2 Life course epidemiology and health research

Life course epidemiology is not only relevant to alcohol use and the prevention of AUD; rather, this approach is applicable to all modifiable factors influencing an individual's health and wellbeing. To date, life course epidemiology has largely focused on relationships between one exposure at various life stages (e.g., here, alcohol exposure in prenatal and adolescent period) and the probability of health outcomes months, years, or decades later. However, with the increasing availability of large-scale birth cohort and prospective longitudinal datasets, research can move beyond investigation of a single exposure model such as alcohol and toward an accumulation of risk model.

An accumulation of risk model is centered on the total amount and sequencing of exposures. Such a model posits that as the number and severity of exposures increase, there is cumulative damage to biological systems. In turn, this increases risk of non-communicable diseases such as diabetes and cardiovascular disease, obesity, musculoskeletal, mental, neurological, and SUDs. By considering the dynamics between exposures, such models are viewed as more advantageous in life course epidemiology as they have stronger predictive power in providing etiological insights (Blane et al., 2007). The behavioral factors responsible for a large portion of the global burden of disease include alcohol, tobacco, excess weight (related to physical inactivity), and diet (World Health Organization, 2009). Examination of the clustering of these factors during sensitive development periods (i.e., prenatal, early childhood, adolescence and young adulthood, older adulthood) and the cumulative impacts on brain, mental, and physical health within the context of broader socioeconomic, environmental, and genetic effects will be an important next step to improve understanding of individual risk for various non-communicable diseases, including AUD, across the lifespan. Ultimately, the life course epidemiological research approach is crucial to guiding individual- and population-level multigenerational strategies that aim to prevent risk factor exposure, beginning in utero and continuing with interventions for young people and adults to reduce disease risk and burden in future generations.

8.5 Conclusions

This thesis provides comprehensive insight into the precursory risks and consequential harms of binge drinking in young people. This was achieved by examining the complex dynamics between neurobiology, cognition, and psychopathology, with broader familial and environmental factors considered in the study designs. Three central conclusions can be drawn from the studies presented in the thesis. First, they demonstrate that precursory neurobiological features predate adolescent binge drinking, with co-occurring psychopathology increasing risk of escalating consumption. Second, established precursory risk factors of binge drinking (i.e., aberrant brain structure, psychopathology, early alcohol use experimentation) appear to be particularly prevalent among young people with familial alcohol use problems or PAE, emphasizing the multigenerational impacts of alcohol use. Third, the findings indicate that following the uptake of binge drinking, young people can experience neurobiological and cognitive harms that may persist for a number of years, even following reductions in alcohol use. In sum, this thesis adds novel and critical knowledge to the evidence base in understanding the precursory risks and consequential harms associated with binge drinking in young people.

The findings from this thesis provide support for considering alcohol use behaviors from a life course and multigenerational perspective. There is a need for greater global prevention and intervention efforts, as well as positive alcohol use policies that consider all individuals within the family circle, including relatives struggling with alcohol use, women of reproductive age, and young people entering the important transitional stage from childhood to adulthood. Greater awareness of the multigenerational impacts of alcohol use and greater prioritization of treating the whole family will significantly reduce the prevalence of adolescent binge drinking and related disabling consequences across the lifespan at a population level.

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Appendix A

Functional connectivity and psychopathology in preadolescence

Preface

This study involved a multidisciplinary international team of collaborators and has been published as Lees, B., Squeglia, L. M., McTeague, L. M., Forbes, M. K., Krueger, R. F., Sunderland, M., Baillie, A. J., Koch, F., Teesson, M., & Mewton, L. (2020). *Biological Psychiatry: Cognitive Neuroscience & Neuroimaging.* Advance online publication. https://dx.doi.org/10.1016/j.bpsc.2020.09.007.

BL and LM conceptualized the study. BL conducted the analysis, interpreted the data, and wrote the manuscript. All co-authors provided feedback to manuscript drafts and approved the final manuscript. BL is the corresponding author.

Archival Report

Biological Psychiatry: CNNI

Altered Neurocognitive Functional Connectivity and Activation Patterns Underlie Psychopathology in Preadolescence

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ABSTRACT

BACKGROUND: Neurocognitive deficits are common among youth with mental disorders, and patterns of aberrant brain function generally cross diagnostic boundaries. This study investigated associations between functional neurocircuitry and broad transdiagnostic psychopathology dimensions in the critical preadolescent period when psychopathology is emerging.

METHODS: Participants were 9- to 10-year-olds from the Adolescent Brain Cognitive Development Study. Factor scores of general psychopathology, externalizing, internalizing, and thought disorder dimensions were calculated from a higher-order model of psychopathology using confirmatory factor analysis (N = 11,721) and entered as explanatory variables into linear mixed models to examine associations with resting-state functional connectivity (n = 9074) and neural activation during the emotional n-back task (n = 6146) when covarying for sex, race/ethnicity, parental education, and cognitive function.

RESULTS: All dimensions of psychopathology were commonly characterized by hypoconnectivity within the dorsal attention and retrosplenial-temporal networks, hyperconnectivity between the frontoparietal and ventral attention networks and between the dorsal attention network and amygdala, and hypoactivation of the caudal middle frontal gyrus. Externalizing pathology was uniquely associated with hyperconnectivity between the salience and ventral attention networks and hyperactivation of the cingulate and striatum. Internalizing pathology was uniquely characterized by hypoconnectivity between the default mode and cingulo-opercular networks. Connectivity between the cingulo-opercular network and putamen was uniquely higher for internalizing pathology and lower for thought disorder pathology.

CONCLUSIONS: These findings provide novel evidence that broad psychopathology dimensions are characterized by common and dissociable patterns, particularly for externalizing pathology, of functional connectivity and task-evoked activation throughout neurocognitive networks in preadolescence.

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Mental disorders often first manifest during childhood, adolescence, or young adulthood (1–3). Diagnoses based on classification systems such as DSM tend to have heterogeneous clinical presentations with high rates of comorbidity (4,5). This clinical comorbidity is mirrored by functional neurocircuit nonspecificity, where multiple disorders appear to have shared etiology (6–10). In the triple network of psychopathology model, aberrant functional organization of the salience, frontoparietal, and default mode neurocognitive networks and subnetworks (i.e., cingulo-opercular, cinguloparietal, dorsal and ventral attention, retrosplenial-temporal) are theorized to underlie a wide range of psychopathologies (11). Clinical symptoms are thought to be a function of enhanced or reduced salience detection, which has cascading consequences in terms of attentional allocation of frontoparietal systems important for higher-order cognition and the ability to balance internal mental processes with external stimulus–driven cognitive and affective processes (11).

Recent meta-analyses lend support to common underlying functional disorganization of neurocognitive networks across mental disorders. For example, Sha *et al.* (6) reported shared alterations in functional connectivity across 8 mental disorders within and between the 3 large-scale neurocognitive networks. Likewise, McTeague *et al.* (7) demonstrated a common transdiagnostic pattern of disruption in the salience and multidemand frontoparietal network during cognitive control tasks among patients with various disorders across the life span, including schizophrenia, bipolar or unipolar depression, anxiety, and substance use disorders. Furthermore, Sprooten *et al.* (9) demonstrated common task-evoked functional patterns throughout subcortical regions subserving higher-order cognitive and emotional processes (i.e., striatum, amygdala,

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hippocampus) in individuals 18 to 65 years of age. These overlapping patterns of functional connectivity and task-evoked activation resonate with prior reports of common neurostructural [e.g., (10)] and genetic underpinnings across mental disorders [e.g., (12,13)].

Despite growing interest in identifying common biomarkers of mental disorders, current limitations are notable. First, most studies contributing to these meta-analyses have focused on adult populations, and the limited existing work in youth has often used relatively small samples, resulting in underpowered meta-analyses to detect differences in youth. Second, studies have usually adopted a categorical case-control design, and while the incidence of psychiatric comorbidity is high, studies generally do not evaluate its impact. These limitations of traditional approaches using diagnostic categories have motivated a shift toward alternative research frameworks, such as the Research Domain Criteria (14) and Hierarchical Taxonomy of Psychopathology (15,16). Accordingly, an emerging body of literature has focused on identifying biomarkers associated with an overarching general psychopathology factor (or p factor) as well as shared and unique biomarkers of lower-order broad dimensional spectra that represent latent liabilities toward externalizing (e.g., antisocial behavior, hyperactivity), internalizing (e.g., depression, anxiety), and thought disorder (e.g., disorganized thoughts, delusional beliefs, hallucinations, obsessions, compulsions) pathology (17–19). Taking a dimensional approach removes arbitrary boundaries between categorical disorders by grouping related disorders together and assigning unrelated disorders to different dimensional spectra. This approach outperforms traditional diagnostic categories in prediction of onset, chronicity, and severity of mental illness as well as individuals' treatment response and functional impairment (4).

Working within this framework of latent dimensions, two studies have examined neurocognitive functional correlates of psychopathology in youth. One study examined patterns of functional connectivity associated with four dimensions of psychopathology (mood, fear, externalizing, psychosis) in 999 youths 8 to 22 years of age from the Philadelphia Neurodevelopmental Cohort (20). The investigators found that a loss of network segregation between the default mode and executive networks (salience, frontoparietal) emerged as a common feature across all dimensions. Capitalizing on data from the same cohort, Shanmugan *et al.* (21) identified that a transdiagnostic general psychopathology factor was associated with failed activation of executive regions within the cingulo-opercular network (linked to the salience network) during the n-back working memory task. They also observed dissociable patterns of task-evoked activation for anxious-misery (internalizing), behavioral (externalizing), and psychosis-spectrum (part of thought disorder) dimensions in varying executive regions. Overall, these two studies provide early support for the notion that common and dissociable alterations in functional patterns of neurocognitive networks may underlie general and lower-order dimensions of psychopathology in youth.

These previous studies span a wide age range from childhood to young adulthood (8–22 years; mean age, 15–16 years), a developmental period characterized by marked changes in both neurobiology and psychopathology. Given that psychopathology often first manifests in preadolescence, it is critical to investigate the functional neurocircuitry correlates of psychopathology in this important developmental period. Using data from the Adolescent Brain Cognitive Development (ABCD) Study, this preregistered analysis (22) aimed to investigate how transdiagnostic dimensions of psychopathology (internalizing, externalizing, thought, general psychopathology) relate to 1) alterations in intrinsic, large-scale functional connectivity (resting-state functional magnetic resonance imaging [fMRI] analysis) and 2) alterations in extrinsic, context-specific neural processes (task-evoked fMRI analysis) during a task of working memory.

METHODS AND MATERIALS

Participants

Cross-sectional baseline data were analyzed from the ABCD Study curated annual release 2.0.1, which contains post-processed, precomputed data from 11,875 children 9 to 10 years of age (mean [SD] age, 9.9 [0.6] years; 52.1% male) born between 2005 and 2008. A probability sample was recruited through schools proximal to the 21 research sites across the United States (23). Informed consent and assent were obtained from a parent or legal guardian and the child, respectively. All procedures were approved by a central institutional review board at the University of California San Diego, and in some cases by individual site institutional review boards (e.g., Washington University in St. Louis).

Indicators of Psychopathology

Past and present mental disorder diagnoses were determined using parent-reported responses to the self-administered computerized Schedule for Affective Disorders and Schizophrenia for School-Age Children for DSM-5 (K-SADS-5) (24). The computerized version of the K-SADS-5 has been shown to have good psychometric properties (25). Past and present disorders were combined to provide an index of lifetime disorder status (present/absent) for each of the 14 disorders examined (Table 1). A total of 5831 (49.7%) youths had at least one lifetime mental disorder diagnosis, marginally higher than previous U.S. community samples of youths 13 to 14 years of age (approximately 45%) (26). Comorbidity was common, with fewer youths meeting criteria for a single category (n = 2856) than for multiple categories (n = 2975). Among youths meeting criteria for more than one disorder, the mean (SD) number of mental disorders diagnosed was 3.11 (1.39) (Figures S1, S2).

Resting-State fMRI Connectivity

fMRI acquisition, scanning parameters, and the ABCD Study preprocessing pipeline are described elsewhere (27,28) and in the Supplement. Briefly, brain data were collected on 3T scanners, including MAGNETOM Prisma (Siemens Healthcare AG, Erlangen, Germany), Discovery MR750 (GE Healthcare, Waukesha, WI), and Achieva (Philips Healthcare, Cambridge, MA) scanners. Participants completed four 5-minute resting-state blood oxygen level–dependent (BOLD) scans, with their

Table 1. Summary of Demographic and Clinical Data (*N* = 11,721)[a]

	Total, *N* (%)	Male, %	Caucasian, %	Age, Years, Mean (SD)	Cognition, Mean (SD)[b]	Parent University Educated, %
Psychiatric Disorder[c]	5831 (49.7)	56.1	53.1	9.9 (0.6)	46.9 (11.2)	52.1
Typically Developing	5890 (50.3)	48.4	51.2	9.9 (0.6)	48.6 (11.2)	54.8
Externalizing Disorder Pathology						
Attention-deficit/hyperactivity disorder	2428 (20.7)	66.4	51.0	9.9 (0.6)	44.7 (11.0)	49.0
Oppositional defiant disorder	1666 (14.2)	62.4	58.0	9.9 (0.6)	46.7 (11.3)	52.8
Conduct disorder	374 (3.2)	70.6	41.4	9.9 (0.6)	44.0 (10.5)	37.2
Internalizing Disorder Pathology						
Major depressive disorder	318 (2.7)	56.9	44.0	10.0 (0.6)	45.5 (11.3)	50.6
Generalized anxiety disorder	510 (4.4)	52.0	62.7	10.0 (0.6)	46.8 (11.7)	55.3
Panic disorder	32 (0.3)	56.3	46.9	10.1 (0.7)	46.9 (13.9)	43.8
Separation anxiety disorder	1048 (8.9)	53.5	57.0	9.9 (0.6)	46.5 (11.3)	56.0
Social anxiety disorder	547 (4.7)	52.8	56.5	10.0 (0.6)	46.5 (11.0)	56.1
Posttraumatic stress disorder	231 (2.0)	56.3	41.6	10.0 (0.6)	44.4 (10.0)	37.7
Specific phobia	3130 (26.7)	51.2	51.1	9.9 (0.6)	47.5 (11.1)	49.5
Thought Disorder Pathology						
Hallucinations	55 (0.5)	60.0	54.5	9.9 (0.6)	45.9 (11.4)	43.6
Delusions	215 (1.8)	54.9	35.8	9.9 (0.6)	44.7 (10.8)	37.2
Obsessive-compulsive disorder	1096 (9.4)	59.9	49.4	9.9 (0.6)	46.1 (11.2)	46.2
Bipolar disorder	428 (3.7)	55.8	39.3	9.9 (0.6)	45.3 (10.3)	38.8

[a]Comorbidity was quite common; 2975 youths are in multiple case-control diagnostic categories.
[b]Fully corrected total cognition composite T-score from the NIH Toolbox.
[c]Any lifetime psychiatric disorder endorsement.

eyes open and fixated on a crosshair. Resting-state images were acquired in the axial plane using an echo-planar imaging sequence. Mean (SD) framewise displacement for participants with high-quality resting-state data was 0.28 (0.28) mm. Using a functional atlas, cortical-surface regions were grouped into 12 predefined large-scale networks (29), including 8 neurocognitive networks (cingulo-opercular, cinguloparietal, default mode, dorsal attention, frontoparietal, retrosplenial-temporal, salience, ventral attention) and 4 sensory networks (auditory, sensorimotor hand, sensorimotor mouth, visual). Gordon parcellation was chosen because it comprises major cortical functional networks, covers the entire cortical surface, has been shown to exceed many other network parcellations with respect to homogeneity of BOLD signal within each parcellation (29,30), and has been used previously in preadolescent populations (31). Resting-state functional connectivity strength indices were then calculated using the Fisher *r*-to-*z* transformation of the average correlation values between pairs of regions within each large-scale network (n = 12), between these 12 networks (n = 66), and between the networks and bilateral subcortical regions (n = 108). Postprocessed data were used in the current analyses.

Task-Evoked fMRI Activation

Data from the emotional n-back task were used (27). Depending on the condition, children needed to indicate whether the stimulus was the same as the one shown 2 trials earlier (2-back), or the target stimulus shown at the beginning (0-back). Stimuli included houses and emotional and neutral faces. Task-based changes in the BOLD signal were computed at the individual subject level using a general linear model implemented in Analysis of Functional NeuroImages 3dDeconvolve (32). The general linear model coefficients and *t* statistics were cortically mapped and projected 1 mm into cortical gray matter using FreeSurfer (https://surfer.nmr.mgh.harvard.edu/). Mean (SD) framewise displacement for participants with high-quality task data was 0.25 (0.25) mm. The present study used postprocessed functional task data mapped to 34 cortical parcellations (33) and 9 subcortical segmentations (34). The left and right hemisphere mean BOLD activity levels for each region were averaged to create single bilateral values. As a measure of working memory, the contrast between 2-back and 0-back conditions, regardless of stimulus type, was used in the current analyses.

Statistical Analysis

Confirmatory factor analyses of the K-SADS-5 data indicated that when compared with both a single-factor and bifactor model, a higher-order model provided the best fit to the data (root mean square error of approximation = 0.014, comparative fit index = 0.987, Tucker-Lewis index = 0.984). See Supplement for further details. In accordance with the literature more broadly [e.g., (1,15,18,35–38)], the higher-order model consisted of 3 lower-order dimensions representing externalizing (attention-deficit/hyperactivity disorder, oppositional defiant disorder, conduct disorder), internalizing (major depressive disorder, generalized anxiety disorder, posttraumatic stress disorder, panic disorder, separation anxiety

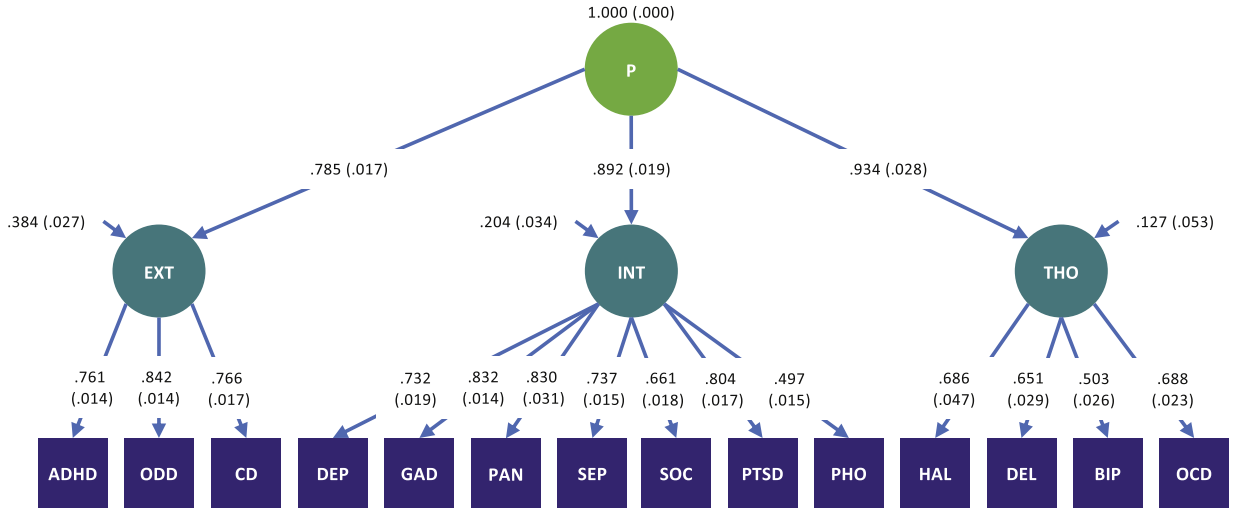

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Figure 1. Higher-order model of the structure of psychopathology in preadolescents (N = 11,721). ADHD, attention-deficit/hyperactivity disorder; BIP, bipolar disorder; CD, conduct disorder; DEL, delusions; DEP, major depressive disorder; EXT, externalizing disorder pathology; GAD, generalized anxiety disorder; HAL, hallucinations; INT, internalizing disorder pathology; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; P, general psychopathology; PAN, panic disorder; PHO, specific phobia; PTSD, posttraumatic stress disorder; SEP, separation anxiety disorder; SOC, social anxiety disorder; THO, thought disorder pathology.

disorder, social anxiety disorder), and thought (hallucinations, delusions, obsessive-compulsive disorder, bipolar disorder) disorder pathology, as well as a single higher-order dimension representing general psychopathology that accounts for the correlations among lower-order factors (Figure 1). To produce stable and reliable factor score estimates that were representative of the population-based sample, the factor analysis was based on the whole sample that provided K-SADS-5 data (N = 11,721). Measurement invariance testing was conducted within a multigroup framework to ensure that the factor structure represented in Figure 1 met criteria for scalar measurement invariance[1] in the subsamples that provided valid resting-state (n = 9074) and emotional n-back (n = 6146) data that passed the extensive quality control procedure of the ABCD Study in every fMRI run (see Supplement for details). The subsamples included and excluded in these analyses were comparable in terms of manifest clinical characteristics, although there were some differences in demographic characteristics (Tables S4 and S5). Mean factor score loadings for participants meeting criteria for each of the K-SADS-5 mental disorder diagnostic categories and for typically developing participants (i.e., participants who did not meet criteria for any lifetime mental disorder) were as expected (Figure 2). Increasing factor scores adequately captured the increasing number of mental disorder diagnoses per participant (Figure S2).

Once the preferred confirmatory factor analysis model of psychopathology was determined, a series of linear mixed models were performed in R version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) using lme4 (39), with family unit and MRI scanner site modeled as crossed random intercepts and sex (female, male) and race/ethnicity (White, Black, Hispanic, Asian, other) included as covariates. All analyses were false discovery rate (FDR) corrected for multiple comparisons (40). Preregistered analyses examined associations between factor scores of each dimension (entered in separate models without adjusting for the presence of the other, correlated dimensions) and 1) within-network connectivity for each of the 12 Gordon networks (12 FDR-corrected comparisons); 2) between-network connectivity (11 FDR-corrected comparisons per network); 3) subcortical connectivity (cerebellum, thalamus, caudate, putamen, pallidum, hippocampus, amygdala, nucleus accumbens, ventral diencephalon) to the Gordon networks (9 FDR-corrected comparisons per network); and 4) task-evoked fMRI activation (34 FDR-corrected comparisons for cortical parcellations, 9 FDR-corrected comparisons for subcortical segmentations). Post hoc analyses were conducted where lower-order dimensions (i.e., externalizing, internalizing, thought disorder) were entered into models simultaneously to explicate unique associations in a multiple regression framework. Collinearity diagnostics indicated absence of troubling collinearity at the variable-set level (i.e., overall multicollinearity between dimensions), while 2 of the 4 variable pairing indices indicated possible collinearity between the internalizing and thought disorder dimensions (see Supplement). A series of preregistered sensitivity analyses was conducted to test whether results were robust to the inclusion of additional covariates, including cognitive function (as determined by the fully corrected total cognition composite T-score from the NIH Toolbox [https://www.healthmeasures.net/explore-measurement-systems/nih-toolbox]) and parental education (a proxy for socioeconomic status). Similar to previous studies (20,21,41), results are expressed as z scores, and effect sizes are expressed as R^2 (both full and partial model with just the psychopathology dimension of interest).

[1]Factor structure, factor loadings, and item thresholds were constrained to be equal across groups.

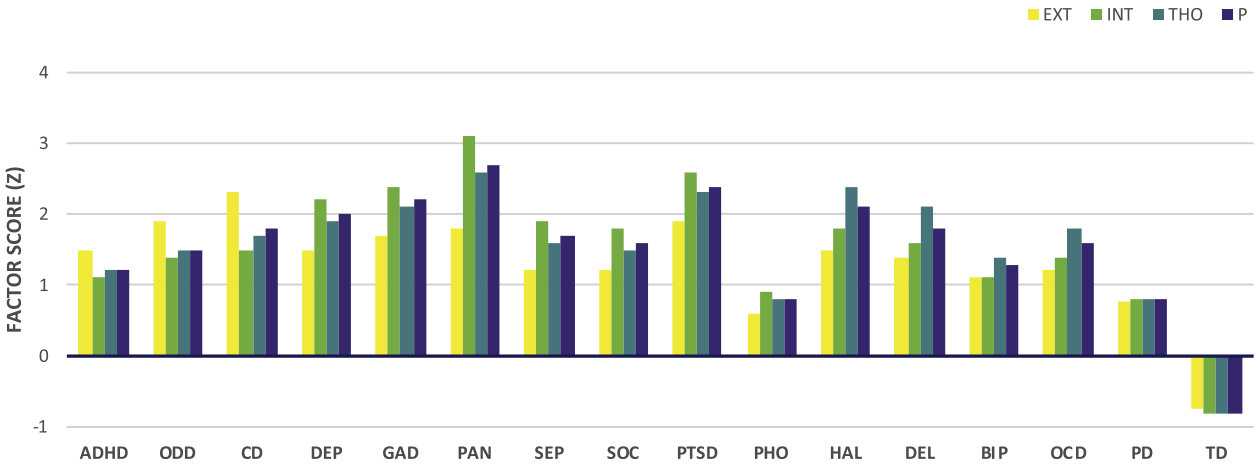

Figure 2. Mean factor scores of each psychopathology dimension for each case-control diagnostic category. ADHD, attention-deficit/hyperactivity disorder; BIP, bipolar disorder; CD, conduct disorder; DEL, delusions; DEP, major depressive disorder; EXT, externalizing disorder pathology; GAD, generalized anxiety disorder; HAL, hallucinations; INT, internalizing disorder pathology; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder; P, general psychopathology; PAN, panic disorder; PD, any psychiatric disorder; PHO, specific phobia; PTSD, posttraumatic stress disorder; SEP, separation anxiety disorder; SOC, social anxiety disorder; TD, typically developing (i.e., did not meet criteria for any lifetime mental disorder); THO, thought disorder pathology.

RESULTS

Functional Connectivity Patterns in Large-Scale Networks

Common patterns of altered network-level connectivity across higher- and lower-order dimensions of psychopathology included lower connectivity within the neurocognitive dorsal attention (full-model R^2s = .14, partial R^2s $\geq$ .001) and retrosplenial-temporal networks (full-model R^2s = .14, partial R^2s $\geq$ .002) and greater connectivity between the neurocognitive frontoparietal and ventral attention networks (full-model R^2s = .15, partial R^2s = .001) after adjusting for sex and race/ethnicity (Figure 3A–D). When examining associations between network and subcortical connectivity, all dimensions of psychopathology were associated with heightened connectivity between the dorsal attention network and the amygdala (full-model R^2s $\geq$ .05, partial R^2s = .001) (Figure 3E–H) after adjusting for sex and race/ethnicity.

When accounting for overlap among dimensions in these analyses (i.e., lower-order dimensions entered simultaneously into models), externalizing pathology was uniquely characterized by heightened connectivity between the neurocognitive salience and ventral attention networks (full-model R^2 = .12, partial R^2 = .001) and lower connectivity between the sensorimotor mouth and auditory networks (full-model R^2 = .12, partial R^2 = .001), sensorimotor hand and visual networks (full-model R^2 = .21, partial R^2 = .001), and cingulo-opercular and visual networks (full-model R^2 = .07, partial R^2 = .00002) after adjusting for sex and race/ethnicity (Figure 4A). Internalizing pathology was uniquely associated with lower connectivity between the neurocognitive default mode and cingulo-opercular networks (full-model R^2 = .18, partial R^2 = .0002) (Figure 4B). No statistically significant differences in within- or between-network connectivity were found for the thought disorder dimension after adjusting for sex and race/ethnicity and in the context of the other dimensions. When examining associations between network and subcortical connectivity, the externalizing dimension was uniquely associated with heightened connectivity between the cinguloparietal network and caudate (full-model R^2 = .10, partial R^2 = .0001), the sensorimotor hand network and caudate (full-model R^2 = .18, partial R^2 = .001), the sensorimotor hand network and pallidum (full-model R^2 = .04, partial R^2 = .001), and the ventral attention network and putamen (full-model R^2 = .03, partial R^2 = .001) (Figure 4C). The internalizing and thought disorder dimensions exhibited unique divergent patterns between the cingulo-opercular network and putamen, where the internalizing dimension was associated with higher connectivity (full-model R^2 = .12, partial R^2 = .001), and the thought disorder dimension was associated with lower connectivity (full-model R^2 = .12, partial R^2 = .0003) (Figure 4D, E).

Task-Evoked Activation During Working Memory

All psychopathology dimensions, when entered into separate models, were associated with lower activation in the caudal middle frontal gyrus during the emotional n-back task when accounting for the effects of sex and race/ethnicity (full-model R^2s $\geq$ .004, partial R^2s = .001) (Figure 5). When accounting for overlap among dimensions in multiple regression analyses, externalizing pathology was uniquely characterized by greater activation in the rostral (full-model R^2 = .02, partial R^2 = .0004) and caudal (full-model R^2 = .01, partial R^2 = .0001) anterior cingulate, insula (full-model R^2 = .02, partial R^2 = .0001), nucleus accumbens (full-model R^2 = .004, partial R^2 = .0001), putamen (full-model R^2 = .05, partial R^2 = .00005), and pallidum (full-model R^2 = .004, partial R^2 = .00004) after adjusting for sex and race/ethnicity (Figure 6). No unique associations for internalizing or thought disorder dimensions passed FDR correction.

Sensitivity Analyses

All observed associations remained after adjusting for parental education, excluding connectivity between the sensorimotor

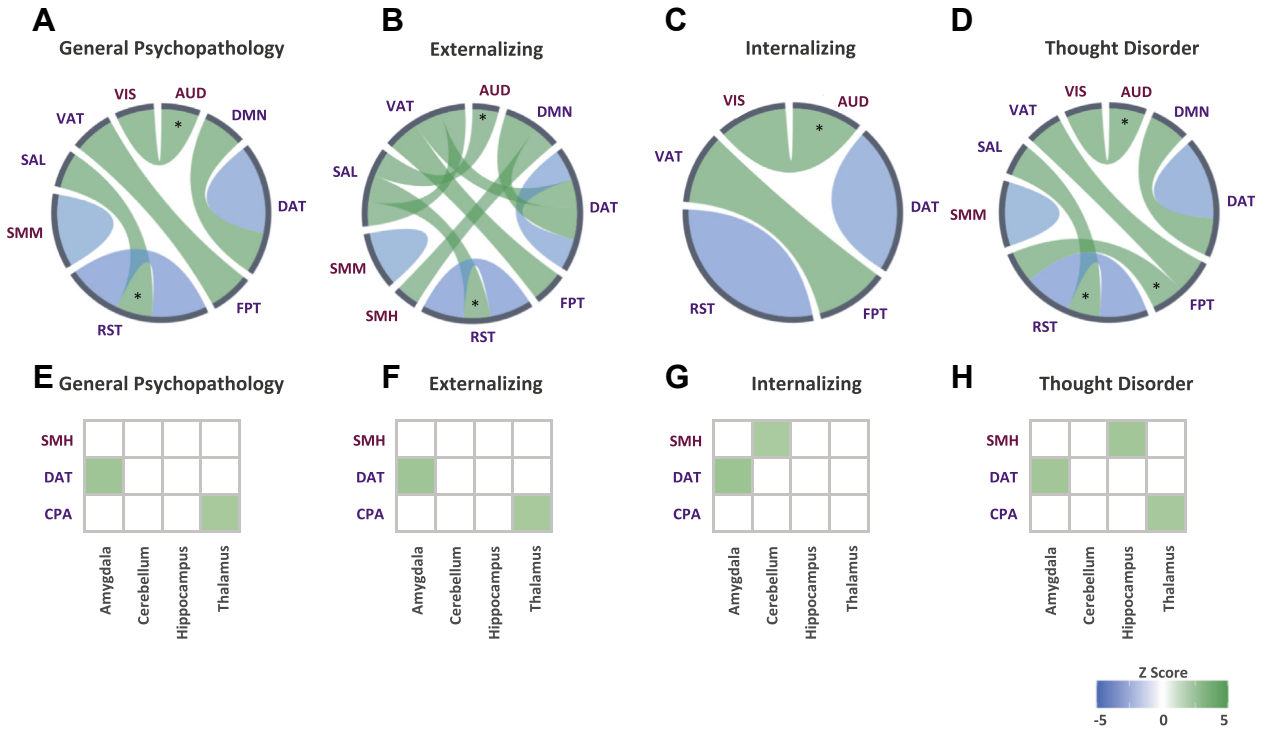

Figure 3. **(A–D)** Alterations in connectivity patterns within and between large-scale networks and **(E–H)** alterations in connectivity between networks and bilateral subcortical regions when adjusting for sex and race/ethnicity. Associations marked with an asterisk (*) were no longer significant when adjusting for cognitive function. Line thickness reflects relative strength of associations within each dimension (n = 9074). AUD, auditory; CPA, cinguloparietal; DAT, dorsal attention; DMN, default mode; FPT, frontoparietal; RST, retrosplenial-temporal; SAL, salience; SMH, sensorimotor hand; SMM, sensorimotor mouth; VAT, ventral attention; VIS, visual.

hand and visual networks and sensorimotor hand network and pallidum for externalizing pathology (Figure 4). Several associations no longer passed FDR correction after adjusting for cognitive function, indicated by an asterisk in Figures 3–6. Table 2 summarizes the common and dissociable connectivity and task-evoked activation patterns across dimensions of psychopathology, with and without adjustment for these additional covariates.

DISCUSSION

In a large sample of preadolescents, the current study examined associations between diverse psychopathology, resting-state functional connectivity, and neural activation during a task of working memory. All dimensions of psychopathology were characterized by common patterns of aberrant functional connectivity and task-evoked activation throughout neurocognitive networks. While unique associations were observed for all lower-order dimensions, a dissociable neurocircuitry pattern was most evident for externalizing pathology.

Common alterations across dimensions included hypoconnectivity within the dorsal attention and retrosplenial-temporal networks, hyperconnectivity between the frontoparietal and ventral attention networks and between the dorsal attention network and amygdala, and hypoactivation in the caudal middle frontal gyrus during the emotional n-back task. Externalizing pathology was uniquely characterized by hyperconnectivity between the salience and ventral attention networks, hypoconnectivity between the sensory networks, heightened network-subcortical connectivity, and hyperactivation of the cingulate, striatum, and insula during working memory, although alterations involving the sensory network and insula were no longer significant when accounting for variance in cognitive function. In contrast, internalizing pathology was characterized by hypoconnectivity between the default mode and cinguloparietal networks and hyperconnectivity between the cingulo-opercular network and putamen, where the reverse pattern was observed for thought disorder pathology. Taken together, the results suggest that psychopathology is associated with aberrant functional patterns throughout neurocognitive networks and regions during preadolescence.

Common Functional Connectivity Alterations Associated With Psychopathology

Findings across studies converge to suggest that altered connectivity within and between neurocognitive networks may be a common biomarker underlying vulnerability to a wide range of mental disorders (6,20). Prior studies have identified more widespread alterations across neurocognitive networks than observed in the current study, including a previous study of adolescents (20) and a meta-analysis of adults (6). These inconsistencies may be due to the relatively early developmental period under study (preadolescence), perhaps indicating that neurobiological

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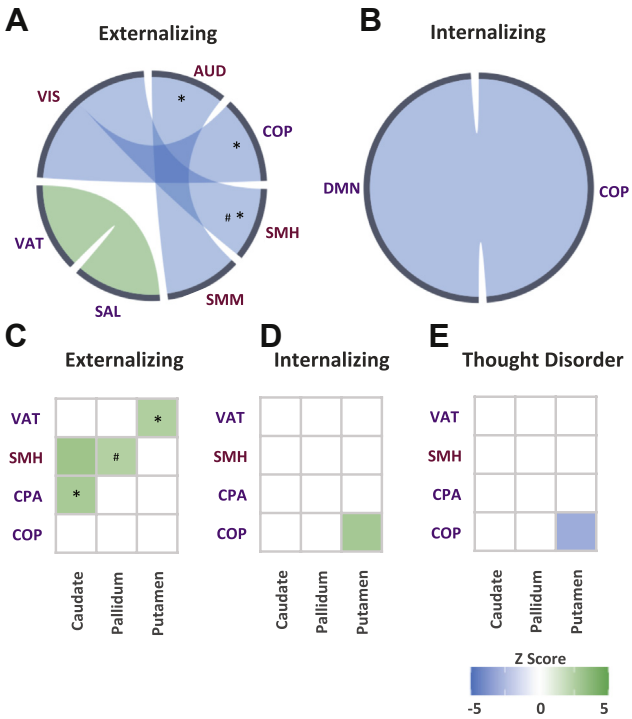

Figure 4. **(A, B)** Alterations in connectivity patterns within and between large-scale networks and **(C–E)** alterations in connectivity between networks and bilateral subcortical regions when adjusting for sex and race/ethnicity. Associations marked with an asterisk (*) or hash (#) were no longer significant when adjusting for cognitive function or parental education, respectively. Line thickness reflects relative strength of associations within each dimension (n = 9074). AUD, auditory; COP, cingulo-opercular; CPA, cinguloparietal; DMN, default mode; SAL, salience; SMH, sensorimotor hand; SMM, sensorimotor mouth; VAT, ventral attention; VIS, visual.

underpinnings of psychopathology become more pervasive throughout the life span.

This study was the first to examine associations between psychopathology and network-subcortical connectivity. Hyperconnectivity between the dorsal attention network and the amygdala received the highest loadings for all dimensions of psychopathology. The amygdala has long been the focus of disordered emotional processing (42,43) and is a prominent subcortical structure of the neurocognitive salience network (11). In accordance with the present findings, a recent meta-analysis identified a common pattern of aberrant neural activation during emotional processing in the amygdala and regions of the executive network (inclusive of the dorsal attention network) across psychiatric disorders (8).

Interestingly, these transdiagnostic functional impairments in neurocognitive networks parallel behavioral and structural evidence of common disruptions in neurocircuitry underlying cognitive control capacity and emotional processing (10,44,45). Overall, this study adds to a convergent body of literature that shows highly coordinated networks and subcortical regions that are sensitive to demands on cognitive control and emotional processing underlie complex and wide-ranging psychiatric symptoms across different age groups.

Dissociable Patterns of Connectivity Associated With Lower-Order Dimensions of Psychopathology

Lower-order dimensions of psychopathology were characterized by some unique functional connectivity patterns in networks or subcortical regions that subserve cognitive control. The direction of effects between neurocognitive networks observed in the current study for the externalizing (i.e., hyperconnectivity) and internalizing (i.e., hypoconnectivity) dimensions are consistent with a previous study of youths 8 to 22 years of age from the Philadelphia Neurodevelopmental Cohort (20). In contrast, that study also observed differentiated patterns of connectivity for the thought disorder dimension in the default mode and executive networks. Likewise, prior studies of patients with schizophrenia have identified altered connectivity within the default mode network (46–48). There is evidence to suggest that patterns of dysconnectivity linked to lower-order dimensions of psychopathology parallel clinical trajectories of these disorders. This may explain why associations for the thought disorder dimension did not pass FDR correction in the current study of preadolescents compared with prior studies in older populations [e.g., (20,46–48)]. Externalizing aggression-focused syndromes, as captured in the present study, typically manifest earlier in childhood and have a more stable trajectory (49). Internalizing syndromes often manifest next, followed by thought disorder syndromes later in adolescence, often escalating in severity throughout adolescence and adulthood (50,51). Likewise, preliminary evidence suggests that patterns of dysconnectivity associated with the externalizing dimension manifest earlier and have a more stable time course, while patterns associated with the internalizing and thought disorder dimensions strengthen throughout adolescence and into young adulthood (20). Considering that the current sample comprises preadolescents, it is expected that functional connectivity alterations associated with the internalizing and thought disorder dimensions will continue to diverge throughout adolescence and into young adulthood in parallel with symptom escalation.

Common and Dissociable Patterns of Task-Evoked Activation Across Psychopathology Dimensions

In addition to the robust finding that altered functional connectivity in neurocognitive networks (i.e., dorsal and ventral attention, retrosplenial-temporal, frontoparietal) is a transdiagnostic biomarker for psychopathology, the current study also identified that hypoactivation within the salience network (i.e., caudal middle frontal gyrus) during a working memory task is common across dimensions of psychopathology, in line with previous research (7,21). This network is thought to be essential for adaptive switching between other neurocognitive networks (11). In contrast, externalizing pathology was uniquely associated with hyperactivation in the anterior cingulate cortex and subcortical regions. The anterior regions of the cingulate cortex are key nodes of the default mode network (52). Recent neuroanatomical modeling has also revealed that the thalamus and basal forebrain (including the

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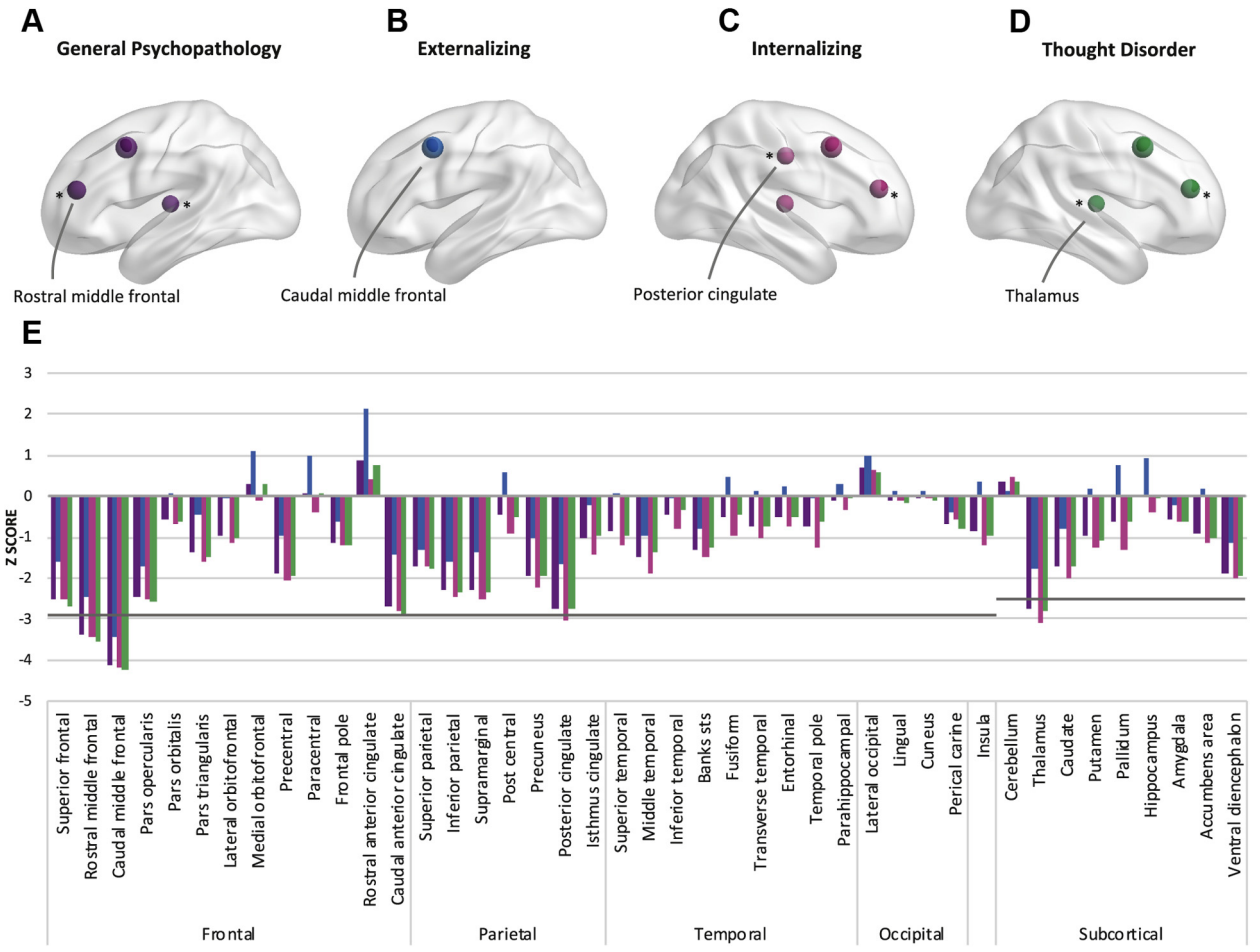

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Figure 5. Lower task-evoked activation during the emotional n-back task (2 vs. 0 contrast) was observed for dimensions of psychopathology in the middle frontal gyrus **(A–D)**, posterior cingulate **(C)**, and thalamus **(A, C, D)**. Associations in panels **(A–D)** marked with an asterisk (*) were no longer significant when adjusting for cognitive function. **(E)** *z* scores for all parcellations and segmentations examined when entered as predictors into mixed models separately (n = 6146). The nodes on the brain figures represent the location where activation differed for youths with higher psychopathology factor scores, and the size corresponds to the *z* score.

nucleus accumbens, pallidum, putamen) are of central importance for the functioning of the default mode network (53). These findings dovetail the dissociable effects observed for functional connectivity, where the externalizing dimension was characterized by hyperconnectivity between the neurocognitive salience and ventral attention networks. As noted above, dissociable patterns of neural activation for the internalizing and thought disorder dimensions may become more pronounced with age.

Toward a Neurocognitive Network Perspective of Psychopathology

The current findings align with the triple network of psychopathology model (11), which posits that aberrant functional organization of the salience (including cingulo-opercular), frontoparietal (including dorsal and ventral attention), and default mode (including retrosplenial-temporal) networks and subnetworks and their network interactions underlie a wide range of psychopathologies, as does the amygdala, which is crucial for the detection of biologically salient affective cues. While aberrant patterns were not observed throughout all neurocognitive networks, as noted above, it is anticipated that patterns will continue to diverge with age and severity of psychopathology symptoms. Longitudinal data spanning early development and adolescence are needed to establish the causal relationship between neurobiology and psychopathology. To date, evidence suggests that compromised brain health is an antecedent for psychopathology, whether that be through genetic susceptibilities (13,54,55), prenatal exposures (56), early life stressors (57), or some other mechanism. Interestingly, there is some evidence to suggest that psychopathology in children 8 years of age has downstream effects on brain development at age 10 (58). A cascading interaction between psychopathology and the brain may exist during this critical developmental period, and future work using this cohort when longitudinal data are available will help delineate these associations.

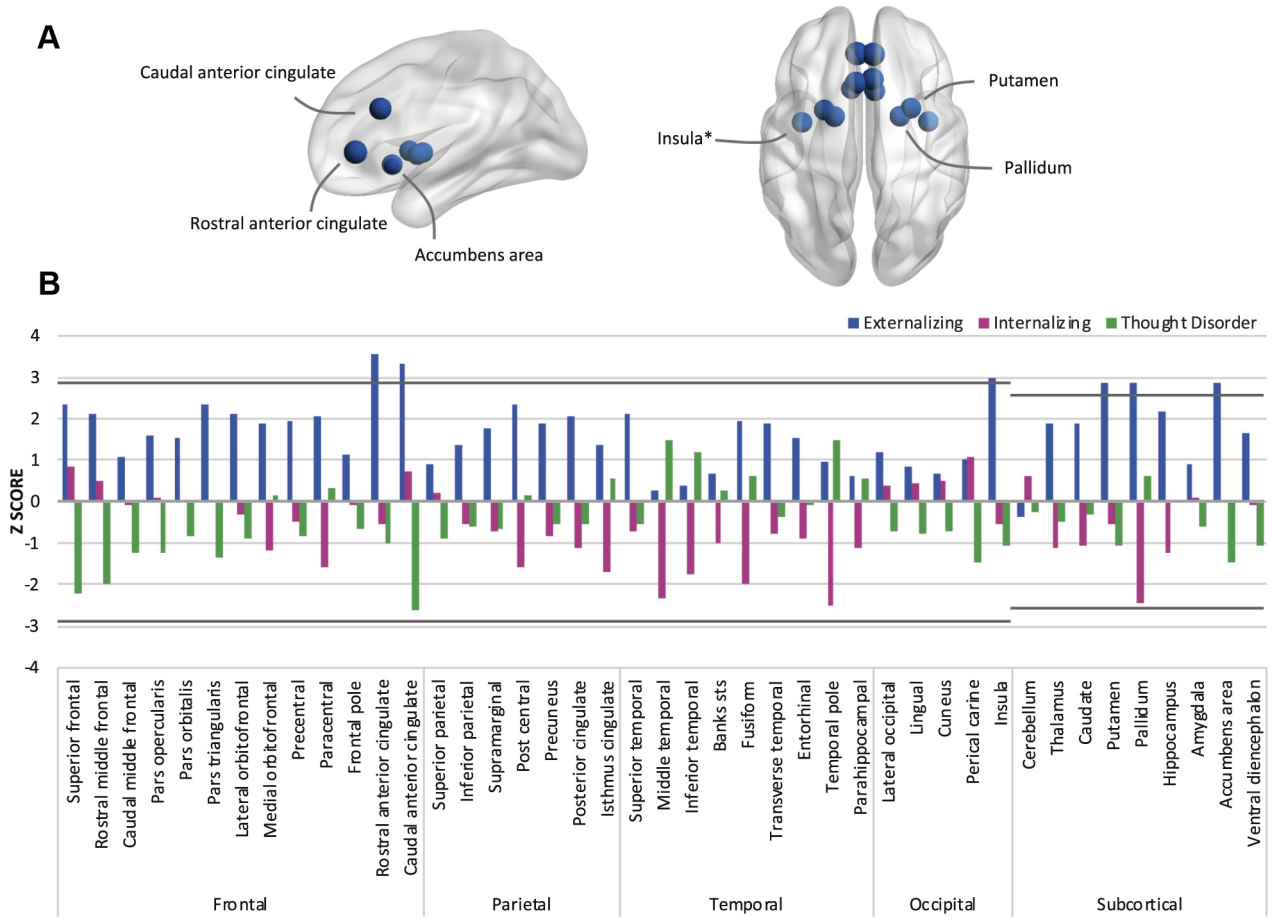

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Figure 6. **(A)** Regions exhibiting heightened connectivity, which was uniquely associated with externalizing pathology, during the emotional n-back task (2 vs. 0 contrast). Associations marked with an asterisk (*) were no longer significant when adjusting for cognitive function. **(B)** *z* scores for all parcellations and segmentations when examined in a multiple regression framework (n = 6146). The nodes on the brain figures represent the location where activation differed for youths with higher externalizing pathology factor scores, and the size corresponds to the *z* score.

Strengths and Limitations

The current study has several strengths. The ABCD Study is a multisite, demographically diverse, population-based study that is the largest of its kind to investigate child brain development. Here, lifetime mental disorders were highly prevalent, perhaps reflecting the use of parent report rather than clinician report (25) and the relative sensitivity of the K-SADS-5 to lower-level symptoms (59). This sensitivity allowed for linkage of psychopathology with functional neurocircuitry in a manner not necessarily tied to strict clinician-rated disorder thresholds. The high incidence of psychiatric comorbidity was accounted for by using factor analysis to examine general psychopathology and lower-order broad dimensional spectra representing latent liabilities toward externalizing, internalizing, and thought disorder pathology. Independent of the imaging analyses, this work demonstrates the coherence of symptoms across disorders in the preadolescent period, which are typically considered disparate. The large sample size allowed for inclusion of low base rate disorders that are rare in the preadolescent period. The narrow age range included in this study allowed for exploration of developmentally specific relationships between detailed neurobiological indices and psychopathology during a critical developmental period when the trajectories of the lower-order dimensions begin to shift, but before many mental disorders emerge.

These findings also need to be interpreted within the context of some limitations. ABCD Study data are cross-sectional at present and cannot determine causality between psychopathology and functional neurocircuitry aberrations. There were large amounts of excluded data for the fMRI analyses (n = 2647–5575). Although the clinical characteristics and structure of psychopathology were similar for data included and excluded from the analyses, the excluded data may have affected the representativeness of the sample and thus the generalizability of the results. There was evidence of possible collinearity between the internalizing and thought disorder dimensions, and some caution should be taken when interpreting the dissociable effects for

Table 2. Summary of Aberrant Functional Connectivity and Neural Activation During a Working Memory Task Associated With Latent Dimensions of Psychopathology Among 9- to 10-Year-Olds, When Adjusting for Sex and Race/Ethnicity

	Common Biomarkers	Dissociable Biomarkers
Functional Connectivity		
Within Networks	↓ Dorsal attention ↓ Retrosplenial-temporal	–
Between Networks	↑ Frontoparietal—ventral attention	Externalizing ↑ Salience—ventral attention ↓ Sensorimotor mouth—auditory[a] ↓ Sensorimotor hand—visual[a,b] ↓ Cingulo-opercular—visual[a]
		Internalizing ↓ Default mode—cingulo-opercular
Network-Subcortical	↑ Dorsal attention—amygdala	Externalizing ↑ Sensorimotor hand—caudate ↑ Cinguloparietal—caudate[a] ↑ Sensorimotor hand—pallidum[b] ↑ Ventral attention—putamen[a]
		Internalizing ↑ Cingulo-opercular—putamen
		Thought disorder ↓ Cingulo-opercular—putamen
Neural Activation During Working Memory		
Cortical	↓ Caudal middle frontal	Externalizing ↑ Caudal, rostral anterior cingulate cortex
Subcortical	–	Externalizing ↑ Nucleus accumbens ↑ Putamen ↑ Pallidum ↑ Insula[a]

[a]No longer significant when adjusting for cognitive function.
[b]No longer significant when adjusting for parental education.

these dimensions. Furthermore, the current study analyzed cortical parcellations and subcortical segmentations; however, future studies could explore voxelwise analytical approaches. Finally, replicating these findings in other large independent samples will be important to determine the robustness of the functional patterns underlying psychopathology found here and at different stages throughout the life span.

Conclusions

The current study revealed that broad dimensions of psychopathology are characterized by common and dissociable patterns, particularly for externalizing pathology, of functional connectivity and task-evoked activation throughout neurocognitive networks in preadolescence when adjusting for sex, race/ethnicity, cognitive function, and parental education. In the context of other studies, it appears that neural disruptions associated with psychopathology may become more pervasive across the life span, in parallel with clinical trajectories of each disorder. The broad dimensions examined in this study span multiple traditional disorder categories and provide further support for the consideration of mental diagnoses from a dimensional perspective, as suggested by the Research Domain Criteria and Hierarchical Taxonomy of Psychopathology. Future evaluations should examine the practical utility of identified functional biomarkers to predict clinical trajectories as well as prevention and intervention responses.

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Data used in the preparation of this article were obtained from the ABCD Study (https://abcdstudy.org), held in the National Institute of Mental Health Data Archive. This is a multisite, longitudinal study designed to recruit more than 10,000 children 9 to 10 years of age and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners (Grant Nos. U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, and U24DA041147). A full list of supporters is available at https://abcdstudy.org/nih-collaborators. A list of participating sites and a complete list of the study investigators can be found at https://abcdstudy.org/principal-investigators.html. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in analysis or writing of this article.

This article reflects the views of the authors and may not reflect the opinions or views of the National Institutes of Health or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from the curated annual release 2.0.1.

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ARTICLE INFORMATION

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Appendix B

Neural correlates of familial alcohol use problems

Preface

This study involved a multidisciplinary international team of collaborators and has been published as Lees, B., Aguinaldo, L., Squeglia, L. M., Infante, M. A., Wade, N. E., Hernandez Meija, M., & Jacobus, J. (2020). *Alcoholism: Clinical & Experimental Research,* 44(6), 1234-1244.

BL and JJ conceptualized the study. LA conducted the analysis. BL interpreted the data and wrote the manuscript. All co-authors provided feedback to manuscript drafts and approved the final manuscript. JJ is the corresponding author.

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ALCOHOLISM CLINICAL & EXPERIMENTAL RESEARCH

Parental Family History of Alcohol Use Disorder and Neural Correlates of Response Inhibition in Children From the Adolescent Brain Cognitive Development (ABCD) Study

Briana Lees, Laika Aguinaldo, Lindsay M. Squeglia, Maria Alejandra Infante, Natasha E. Wade, Margie Hernandez Mejia, and Joanna Jacobus

Background: Youth whose parents have alcohol use disorder (AUD) are at higher risk for earlier initiation and greater magnitude of alcohol use, and have a higher likelihood of developing an AUD than their peers without parental history of AUD. This increased risk may be partly attributable to altered development of inhibitory control and related neural circuitry. This study examined neural activation during a motor response inhibition Stop Signal Task (SST) in substance-naïve youth aged 9 to 10 years with and without parental family history of AUD.

Methods: Baseline cross-sectional survey and functional magnetic resonance imaging (fMRI) data were drawn from 6,898 youth in the US-based Adolescent Brain Cognitive Development Study. Generalized additive mixed models were conducted to examine the association between maternal, paternal, and parental (both mother and father) family history of AUD with neural activation during successful and failed response inhibition. Family history interactions with sex and stratification by ethnicity were explored.

Results: Of 6,898 participants, 951 (14%) were family history positive for any parental AUD. Paternal history of AUD was associated with greater activation for successful inhibition in the right medial orbital frontal gyrus, compared to youth with no family history. Maternal history of AUD was associated with greater activation for failed response inhibition among females in the cerebellum, compared to females with no such history. Parental history (both mother and father) of AUD was associated with greater activation during successful inhibition in the left paracentral gyri and left superior parietal lobule. Maternal history and parental history of AUD findings were accounted for by a family history of substance use disorder in general. All effect sizes were relatively small.

Conclusions: Substance-naïve children with a parental family history of AUD exhibit greater neural activation in some regions of the fronto-basal ganglia and cerebellar networks when they successfully or unsuccessfully inhibit a response as compared to children with no such family history. This unique neural response pattern could reflect a compensatory response and may represent an inherent neurobiological vulnerability to risk-related behaviors in these youth which will be examined in future longitudinal analyses of this cohort.

Key Words: Response Inhibition, Functional Magnetic Resonance Imaging, Alcohol Use Disorder, Family History, Stop Signal Task.

LATE CHILDHOOD IS a vulnerable developmental period characterized by significant neural and cognitive changes (Crews et al., 2007; Spear, 2013). Important morphometric restructuring and functional neuromaturation continue in parallel throughout this period (Tamnes et al., 2017). The resulting increased neural efficiency (de Graaf-Peters and Hadders-Algra, 2006) is thought to improve cognition, such as executive functions (Casey et al., 2005). Inhibitory control is one component of higher-order executive functions (Giedd et al., 1999; Gogtay et al., 2004). It is subserved by neural circuitry in the fronto-basal ganglia network (Koyama et al., 2017; Lopez-Caneda et al., 2014), which includes the prefrontal (PFC) and inferior frontal cortices (IFC), the presupplementary motor area, basal ganglia, and primary motor cortex (Aron, 2011). Typically developing children exhibit progressive reductions in neural network activation across the medial and lateral parts of the PFC and age-related increases in the IFC and insula that are associated with improved inhibitory control performance (Casey et al., 1997; Somerville et al., 2011; Tamm et al., 2002). Therefore, functional differences in fronto-basal ganglia network development may be related to an inherent

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neurobiological vulnerability in the cognitive control network and thus difficulty suppressing maladaptive behaviors. This in turn may promote risky actions, such as excessive alcohol use (Casey et al., 2008; Shulman et al., 2016; Steinberg, 2010).

The onset of alcohol use typically occurs during adolescence when the brain continues to undergo critical development. In the United States (US), 24% of high school students have consumed alcohol (more than just a few sips) by age 14, and 59% have done so by age 18 (Johnston et al., 2019). Of particular concern, approximately 4% and 14% of US high school students aged 14 and 18 years, respectively, have engaged in binge drinking (i.e., the consumption of 5+ drinks in a row) in the past 2 weeks (Johnston et al., 2019). These statistics are concerning because excessive alcohol use during adolescence is associated with a myriad of negative consequences including alcohol and substance use disorders (AUD, SUD; Dwyer-Lindgren et al., 2018), and other mental health problems (Pompili et al., 2010; Teesson et al., 2010; Welsh et al., 2017). Alcohol use during adolescence has also been associated with alterations in brain structure and function, including aberrant activation patterns during response inhibition tasks (for review, see Lees et al., 2020; Lees et al., 2019; Squeglia and Cservenka, 2017; Squeglia and Gray, 2016), as well as poorer test performance across cognitive domains, with executive functions and memory being the most vulnerable (Gould, 2010; Lees et al., 2019). Recent longitudinal neuroimaging studies have begun investigating, and have shown, that underlying neural vulnerabilities of response inhibition in substance-naïve children appear to contribute to earlier initiation and problematic progression of alcohol use during adolescence (Squeglia and Cservenka, 2017).

Vulnerability for early alcohol initiation is heightened among individuals with a positive family history (FH+) of AUD, particularly among those with a FH+ first-degree relative (Dawson et al., 1992). FH+ has been associated with earlier initiation and greater magnitude of alcohol use, a 3- to 5-fold increased likelihood of developing an AUD (Cotton, 1979; McCaul et al., 1990), and a heightened likelihood of experiencing alcohol-related problems in adolescence (Lieb et al., 2002), when compared to family history negative (FH−) youth. FH+ risk is thought to be driven at least partially by deficits in motor response inhibition (Sher et al., 2005; Tarter et al., 2003). Emerging research has aimed to uncover the neurobiological markers that may increase risk for early alcohol use and AUD in FH+ youth aged between 8 and 19 years who are largely substance-naïve (Squeglia and Cservenka, 2017). Preliminary functional magnetic resonance imaging (fMRI) research, utilizing the Go/NoGo Task, suggests that FH+ youth may have altered development of the fronto-basal ganglia network. Some studies have reported reduced activation among FH+ youth in the right ventral and lateral parts of the PFC (Koyama et al., 2017), and the fronto-parietal regions (Schweinsburg et al., 2004), while others have reported greater activation among FH+ youth in the ventral caudate (Heitzeg et al., 2010) and frontal regions (Acheson et al., 2014b), when compared to FH− youth. Furthermore, longitudinal research has suggested that alcohol-naïve FH+ youth show increasing anterior cingulate activity over time, while their FH− peers showed the expected reduction in fronto-striatal response to the Go/NoGo Task (Hardee et al., 2014). These fMRI studies highlight that FH+ youth consistently show altered brain activity during response inhibition tasks compared to their FH− peers.

To date, motor response inhibition fMRI studies examining FH+ substance-naïve youth have been restricted to small sample sizes with mostly Caucasian adolescents. This has not allowed for adequate examination of response inhibition as related to: (i) the mother and father's independent heritable influence of AUD history on their child's neurobiological development or (ii) variability as related to demographic and genetic differences, such as race/ethnicity and sex. Previous neuropsychological research has reported differential effects of paternal and maternal AUD on offspring cognition and impulsivity (Corte and Becherer, 2007; Ozkaragoz et al., 1997), yet how this translates to neural activation during response inhibition remains unknown. Furthermore, differences in alcohol use behaviors by race/ethnicity and sex have been documented (Flewelling et al., 2004; Johnston et al., 2019); however, comparisons of these groups on neurobiological predictors of alcohol use remain limited. More nuanced understanding of neural functioning in FH+ (mother, father, both parents) individuals from diverse backgrounds will advance our understanding of the underlying biological vulnerabilities to alcohol-related problems, and will inform early intervention strategies.

In the present study, we sought to examine neural activation to a motor response inhibition Stop Signal Task (SST) in parental FH+/− substance-naïve youth aged 9 to 10 years enrolled in the Adolescent Brain Cognitive Development (ABCD) Study (Auchter et al., 2018; Garavan et al., 2018; Volkow et al., 2018). The stop-signal paradigm probes neural networks reflective of motor response inhibition, similar to the Go/NoGo Task, but requires greater inhibitory control (Nee et al., 2007). We investigated maternal, paternal, and parental (both mother and father) FH of AUD. By drawing on the large ABCD dataset, we were also able to explore differential ethnicity effects and sex interactions, and adjust for in utero exposure to alcohol for the first time. It was hypothesized that FH+ youth would show altered activity in regions known to be involved in SST performance, particularly in fronto-basal ganglia network regions (Cieslik et al., 2015), when compared to FH− youth. We also anticipated that youth with 2 parents reporting a history of AUD would show greater genetic liability and thus increased vulnerability resulting in greater neural response deviation than youth with 1 FH+ parent or FH− youth (Khemiri et al., 2020).

MATERIALS AND METHODS

This study used baseline cross-sectional data from the ABCD Data Release 2.0.1. The ABCD study is a 10-year longitudinal study across 21 US-based sites, recruiting 11,878 participants, and funded by the National Institutes of Health (Volkow et al., 2018). A total of 6,898 participants had valid parental history, demographic, and fMRI SST data following quality control processing (Fig. 1). The Institutional Review Board at the University of California, San Diego, approved all aspects of this study for the ABCD consortium.

Recruitment

A detailed account of the recruitment strategy has been previously published (Garavan et al., 2018). The ABCD study primarily utilized a probability sample recruited through schools, where school selection was based on sex, race and ethnicity, socioeconomic status, and urbanicity. Interested participants and their families completed a brief eligibility interview over the phone to ensure interested youth were 9 to 10 years old and had no MRI contraindications (i.e., irremovable metal in body).

Procedure

Youth and their parent/guardian presented for study session(s) at their local research site to complete the baseline visit. Parents/guardians provided written consent while the child provided written assent. Youth and their parent/guardian were in separate, private rooms during study participation to maintain confidentiality of their survey responses. The baseline measures included questionnaires, neurocognitive testing, biological samples, and an MRI scan (Lisdahl et al., 2018; Luciana et al., 2018; Uban et al., 2018). Study assessment was completed over an 8-hour research session (or two 4-hour sessions). Parents and youth were compensated financially and with prizes for their time.

Family History of Alcohol Use Disorders

Full descriptions of ABCD environmental, health, and mental health questionnaires are described elsewhere (Barch et al., 2018; Lisdahl et al., 2018; Zucker et al., 2018). The parent/guardian completed a 15-minute modified version of the Family History Assessment Module Screener (FHAM-S; Rice et al., 1995). Parents/guardians reported on the presence or absence of a range of mental health symptoms including those associated with AUD in all first- and second-degree blood relatives of the youth, including biological siblings, parents, grandparents, aunts, and uncles. Only parental history of alcohol and drug use problems were of interest for the current study (Cservenka, 2016).

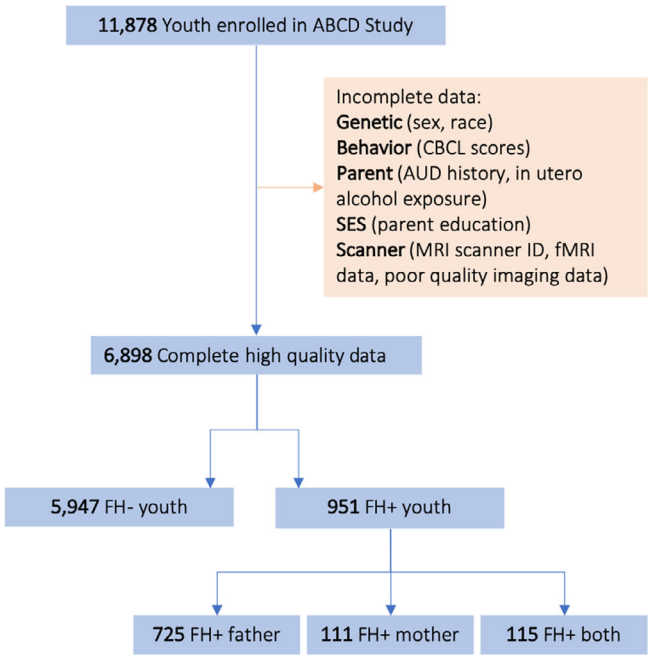

Fig. 1. Selection of the ABCD cohort for analyses.

Covariates

Covariates were chosen based on prior evidence of an association with the outcomes (Table 1). Standard ABCD demographic covariates included race, age, sex, and parental education. Substance-related covariates included parental retrospective report of maternal alcohol use during pregnancy (yes/no), as reported in the modified Developmental History Questionnaire (Kessler et al., 2009a; Kessler et al., 2009b; Merikangas et al., 2009). Youth emotional and behavioral covariates included internalizing, externalizing, and total behavioral problems from the Child Behavior Checklist (CBCL; Achenbach and Rescorla, 2013).

fMRI Stop Signal Task

Full task information has been described previously (Casey et al., 2018). The SST measures domains of motor response inhibition and impulsivity, showing child/adolescent-specific and substance use effects (Smith et al., 2014; Whelan et al., 2012). The SST requires participants to withhold or interrupt a motor response to a "Go" stimulus when it is followed unpredictably by a signal to stop. Participants completed 2 sets, each containing 180 trials. Each trial began with the presentation of a leftward or rightward pointing arrow, and participants were instructed to indicate the direction, responding quickly and accurately via a 2-button response panel. Thirty of the trials were "Stop" trials where the leftward or rightward facing arrow was followed by an up-right arrow, indicating to participants to stop their prepotent "Go" response. To ensure that there were approximately 50% successful and 50% unsuccessful inhibition trials for Stop trials, a tracking algorithm varied the interval of trials (see Casey et al., 2018 for further details). Mean beta weights for correct stop contrasts (correct stop contrasted with correct go) and failed stop contrasts (incorrect stop contrasted with correct go) were used in all analyses to compare neural response differences to both successful and unsuccessful inhibition trials.

Imaging Data Acquisition and Processing

Full MRI and fMRI acquisition and scanning parameters are described elsewhere (Casey et al., 2018). All scans were uploaded to a shared server that was processed by the Data Analytics and Information Core (DAIC) of ABCD, to maintain consistency across methodology and ensure quality. Details on data processing are described by Hagler and colleagues (2018). All parcellations based on the Desikan-Killiany Atlas were examined (68 cortical and 30 subcortical regions). Only participants whose SST task scans met all quality checks by DAIC were used in analyses. There was no significant difference in the number of FH− (81%) and FH+ youth (80%) who provided useable, high-quality SST fMRI data.

Data Analysis

Differences in demographic and behavioral variables between the FH+/− for AUD (none, father, mother, both parents) were determined using χ^2 tests for categorical data and ANOVAs for

Table 1. Demographic Characteristics of Sample at Baseline, $N = 6,898$

		FH+ n=951		
	FH− n=5947	Father n = 725	Mother n = 111	Both n = 115
Age (mean [SD])	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)
Race (%)[a,c,d]				
White	55.7	53.2	54.1	50.4
Hispanic	19.6	23.2	16.2	11.3
Black	13.3	11.2	17.1	13.0
Asian	2.0	0.4	0.0	0.9
Other	9.4	12.0	12.6	24.4
Sex (%)				
Female	48.4	50.3	50.5	45.2
Male	51.6	49.7	49.6	54.8
Highest Parent Education (%)[a,b,c,d,f]				
<HS Diploma	5.0	5.2	9.0	7.0
HS Dip/GED	10.0	11.5	9.9	18.3
Some College	27.8	40.0	40.5	43.5
Bachelor	30.8	25.0	24.3	16.5
Post Grad	26.4	17.9	16.2	14.8
In utero alcohol exposure (%)[a,b,c,d,e,f]				
Not exposed	76.0	67.6	61.3	39.1
Exposed	24.0	32.4	38.7	60.9
FH of SUD (%)[a,b,c,d,e,f]				
FH−	95.3	63.5	64.0	41.7
FH+ Father	3.5	31.7	8.1	11.3
FH+ Mother	0.7	1.2	21.6	5.2
FH+ Both	0.5	3.4	6.3	41.7
Internalizing (T-score [SD])[a,c,d,e]	47.8 (10.4)	50.7 (10.8)	48.8 (11.7)	52.6 (11.6)
Externalizing (T-score [SD])[a,b,c,d,e,f]	44.8 (9.8)	47.4 (10.4)	46.4 (10.8)	50.7 (11.4)
Total problems (T-score [SD])[a,c,d,e,f]	44.9 (10.9)	47.8 (11.4)	46.3 (11.7)	51.2 (12.8)

No significant group differences between youth of FH+ mothers vs FH+ fathers.
[a]FH− youth ≠ FH+ youth, $p < .05$
[b]FH− youth ≠ youth of FH + mothers, $p < 0.05$
[c]FH− youth ≠ youth of FH + fathers, $p < 0.05$
[d]FH− youth ≠ youth of FH + both parents, $p < 0.05$
[e]Youth of FH + mothers ≠ youth of FH + both parents, $p < 0.05$
[f]Youth of FH + fathers ≠ youth of FH + both parents, $p < 0.05$

continuous variables. First, a series of generalized additive mixed models (GAMM) were conducted to examine the association between parental FH+/− and neural activation during correct stop and failed stop contrasts in the SST task, using the *GAMM4* package in R, version 3.5.3. Covariates included race/ethnicity, age, sex, parental education, in utero alcohol exposure, total emotional/behavioral problems, externalizing symptoms, and internalizing symptoms, as well as nesting of subjects by scanner. Participants with missing data for any of these variables were excluded from analyses. This series of models were then repeated to examine family history × sex interactions. Next, a series of main effect and sex interaction GAMMs were conducted for significant regions and contrasts, with participants grouped by race/ethnicity to account for the heterogeneity of socioeconomic and social covariates (e.g., income, youth education) within ethnic groups across FH+/− (i.e., FH− vs. FH+ for Asian, Black, Hispanic, White). All covariates, besides race/ethnicity, were included in this pass. Finally, sensitivity analyses were conducted to determine whether results were specific to parental FH of AUD or whether they were influenced by other substance use problems. Analyses described above were repeated for significant brain regions with parental FH of SUD included as an additional covariate. In all analyses, the false discovery rate (FDR) was used to correct for multiple comparisons and the adjusted *p*-values are reported (Benjamini and Hochberg, 1995; Benjamini and Yekutieli, 2001).

Table 2. Behavioral Data for the Stop Signal Task, N = 6,898

		FH + n=951		
	FH− n=5947	Father n = 725	Mother n = 111	Both n = 115
Mean Go RT (ms mean [SD])	472.5 (82.2)	468.8 (78.4)	470.1 (74.7)	467.5 (88.0)
Mean Stop RT (ms mean [SD])	301.5 (79.6)	302.3 (79.3)	290.3 (73.9)	298.0 (75.5)
Correct Go (%)[a,b,c,d]	81.4	80.7	82.8	77.0
Correct Stop (%)	50.8	50.7	51.7	50.9
Failed Stop (%)	45.4	45.3	43.7	45.2

No significant group differences: FH− youth vs youth of FH + mothers, FH− youth vs youth of FH + fathers, youth of FH + mothers vs FH + fathers.
[a]FH− youth ≠ FH + youth, $p < 0.05$
[b]FH− youth ≠ youth of FH + both parents, $p < 0.05$
[c]Youth of FH + mothers ≠ youth of FH + both parents, $p < 0.05$
[d]Youth of FH + fathers ≠ youth of FH + both parents, $p < 0.05$

RESULTS

Participant Characteristics

Demographic characteristics of FH− and FH+ youth are provided in Table 1. Of 6,898 participants, 951 youth (13.8%) were FH+ for parental AUD: 725 youth had a FH+ father, 111 had a FH+ mother, and 115 had 2 FH+ parents. In terms of parent-reported in utero alcohol exposure, 24.0% of FH−, and 32.4%, 38.7%, and 60.9% of youth with a FH+ father, mother, and both parents were exposed, respectively. There were relatively high rates of cooccurring alcohol and substance use problems among parents: 31.7%, 21.6%, and 41.7% of FH+ AUD father-only, mother-only, and both parents also reported a SUD history, respectively. Youth with 2 FH+ parents had the highest internalizing, externalizing, and total problems on the CBCL, compared to youth with 1 FH+ parent or FH− youth. Participants in all groups scored similarly on SST performance, besides youth with 2 FH+ parents who had a lower correct go rate than other groups (Table 2).

Between-Group Family History Findings. Table 3 and Fig. 2 present brain regions exhibiting significantly greater activation for correct stop and failed stop contrasts among FH+ compared to FH− youth, when controlling for relevant covariates. Children with FH+ mothers had greater activation for failed stop contrasts in the right cerebellum compared to FH− youth ($R^2 = 0.003$). FH+ fathers had greater neural activation for correct stop contrasts in the right medial orbital frontal cortex compared to FH− youth ($R^2 = 0.001$). For children with 2 FH+ parents, greater neural activation for correct stop contrasts was observed in the left paracentral lobule ($R^2 = 0.002$) and left superior parietal lobule ($R^2 = 0.048$; Fig. 3). No significant between-group differences were observed for any other ROI. A family history x sex interaction was observed in the right cerebellum ($B = 0.288$, SE = 0.055, $p < 0.001$, $R^2 = 0.003$). Female youth of FH+ mothers exhibited significantly greater activation than FH− female youth for the failed stop contrast ($p < 0.001$), while no significant difference was observed between male youth of FH+ mothers compared to FH− parents in the cerebellum. No other significant interactions were observed. The results for FH+ fathers remained significant during sensitivity analyses when FH of SUD was included as an additional covariate; however, the results for FH+ mothers (main effect and family history × sex interaction) and 2 FH+ parents were no longer significant.

Ethnicity Findings. Demographic characteristics for each ethnic group are provided. Between-group analyses for all regions that showed significant group differences for correct stop and failed stop contrasts were rerun separately for each ethnic group, as summarized in Table 4. When controlling for relevant covariates, Hispanic youth with FH+ mothers exhibited significantly greater activation for failed stop contrasts in the right cerebellum compared to FH− Hispanic youth ($R^2 = 0.034$). Hispanic youth with FH+ fathers exhibited significantly greater activation for correct stop contrasts in the right medial orbital frontal lobe compared to FH− Hispanic youth ($R^2 = 0.009$). White youth with 2 FH+ parents exhibited greater activation in the left paracentral lobule ($R^2 = 0.001$) and left superior parietal lobule ($R^2 = 0.003$), when compared to White FH− youth for correct stop contrasts.

FH+ mother × sex interactions were driven by Hispanic families: Female Hispanic youth with FH+ mothers exhibited significantly greater activation than FH− female Hispanic youth in the right cerebellum ($p < 0.001$) for failed stop contrasts. No significant differences were observed among FH+ and FH− male Hispanic youth in the cerebellum, or for any other ethnicity. During sensitivity analyses when FH of SUD was included as an additional covariate, the results remained significant for Hispanic families (main effects and FH × sex interaction), while the results did not remain significant for White families. No significant between-group differences were observed for Asian or Black youth.

DISCUSSION

Leveraging a large multisite US sample, this study compared neural response in substance-naïve youth aged 9 to 10 years with and without parental FH of AUD during a response inhibition task. Overall, substance-naïve youth with a FH+ mother had significantly greater neural activation for the failed stop contrast in the right cerebellum compared to FH− youth. Exploration of sex interactions demonstrated that this effect was driven by activation differences in young females. Youth with a FH+ father had significantly greater neural response as compared to FH− youth for the

Table 3. Brain Regions Exhibiting Greater Activation in FH+ Compared to FH− Youth for the Correct Stop vs. Correct Go Contrast, After Controlling for Relevant Covariates. There Were No Significant Differences Between Groups for the Incorrect Stop vs. Correct Go Contrast. N = 6,898

FH + parent	Contrast	Region	*B (SE)*	*p*	R^2	AIC	BIC
Mother	Failed stop vs correct go	Cerebellum, R	0.288 (.055)	<0.001	0.0033	7234.6	7371.4
Father	Correct stop vs correct go	Medial orbital frontal, R	0.083 (.025)	0.034	0.0013	13007.9	13144.7
Both	Correct stop vs correct go	Paracentral, L	0.058 (.017)	0.029	0.0016	−4262.3	−4125.6
		Superior parietal, L	0.063 (.019)	0.048	0.0019	−2518.8	−2382.0

L: left; R: right. Only regions where the model passed the FDR correction are presented.

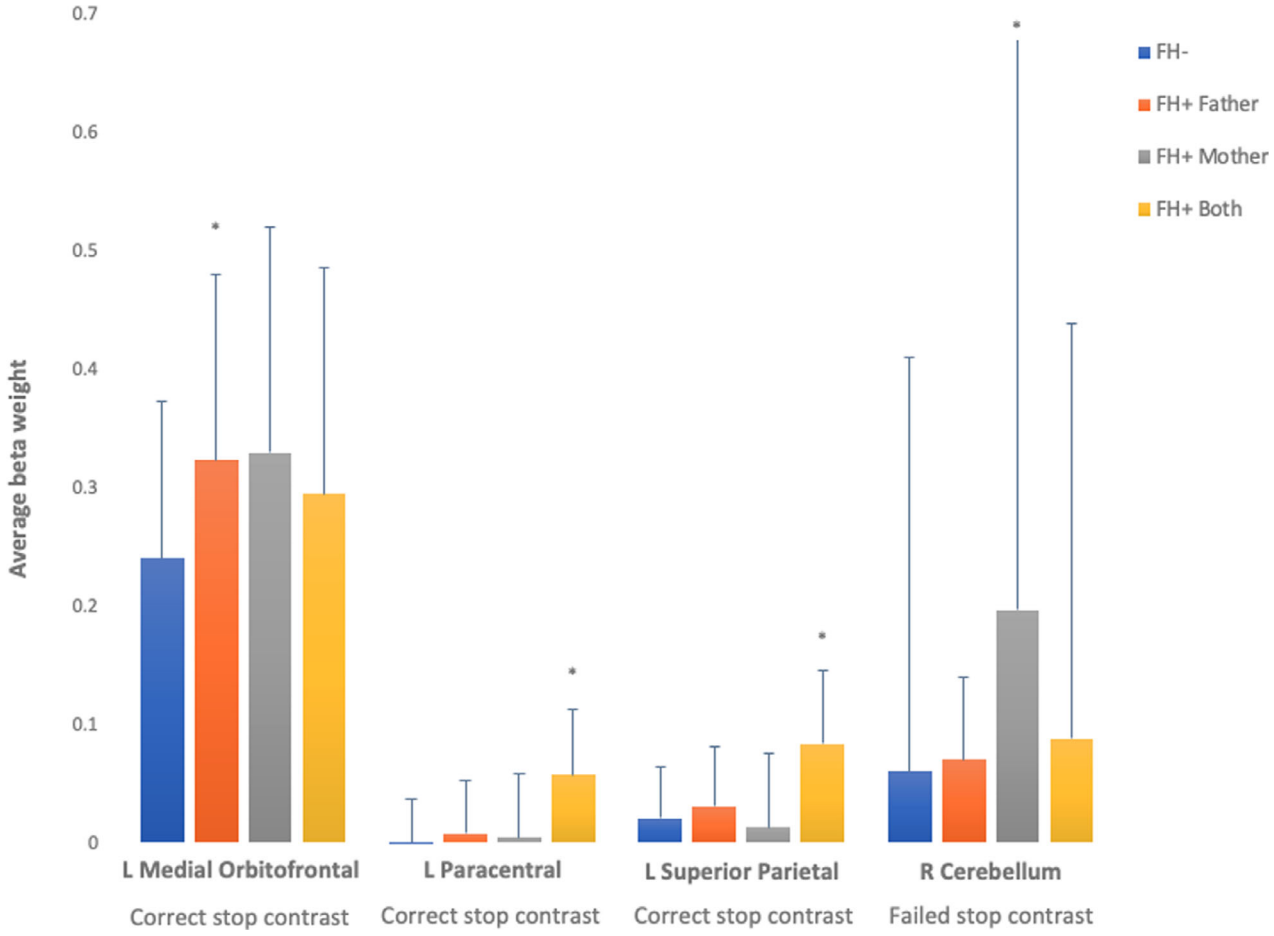

Fig. 2. Summary of brain parcellations exhibiting significantly greater activation in FH+ vs. FH− youth. Blue = greater activation among FH+ vs. FH− youth during failed stop contrast. Red = greater activation among FH+ vs. FH− youth during correct stop contrast. OFC = orbitofrontal cortex.

successful stop contrast in the right medial orbital frontal gyrus. Youth with 2 FH+ parents demonstrated greater neural response for the successful stop contrast in the left paracentral and left superior parietal lobule compared to FH− youth. Sensitivity analyses demonstrated activation differences observed among youth with FH+ mothers or 2 FH+ parents were accounted for by FH of SUD effects. Neural activation profiles differed for each ethnic group; greater response for female youth with FH+ mothers and greater response for youth with FH+ fathers were driven by Hispanic families, while greater response for youth with 2 FH+ parents was driven by White families. Only effects observed among Hispanic families were robust to inclusion of FH of SUD as an additional covariate. Between-group effect sizes were very small.

Our findings align with previous research and suggest that greater activation in FH+ youth aged 9 to 10 years occurs in some regions of the fronto-basal ganglia network (i.e., PFC, supplementary motor area) during successful response inhibition (Acheson et al., 2014a; Acheson et al., 2014b; DeVito et al., 2013; Silveri et al., 2011). Greater activation was also observed in parts of the default network (left superior parietal lobule), which is involved in diverse cognitive operations, including aspects of attention, visuospatial processing, and executive functioning (Johns, 2014; Koenigs et al., 2009). Greater neural activation in the cerebellum during failed response inhibition has been previously reported among FH+ youth (Acheson et al., 2014b). Observed effects were small which is consistent with previous research in this age group (Acheson et al., 2014b). Other studies have reported larger effect sizes (Acheson et al., 2014a) and have also reported increased fronto-basal ganglia network activation during failed response inhibition contrasts for FH+ individuals (Heitzeg et al., 2010; Jamadar et al., 2012). However, these smaller, less diverse study samples included adolescents and adults who had initiated substance use. Therefore, these findings may reflect an altered neural response pattern that is more characteristic of a later stage of neurodevelopment among FH+ individuals.

To the best of our knowledge, no previous study has investigated the association between FH of AUD and neural activation during response inhibition using a family-based design, stratified by race/ethnicity. Drawing on the large ABCD dataset meant we were uniquely positioned to explore

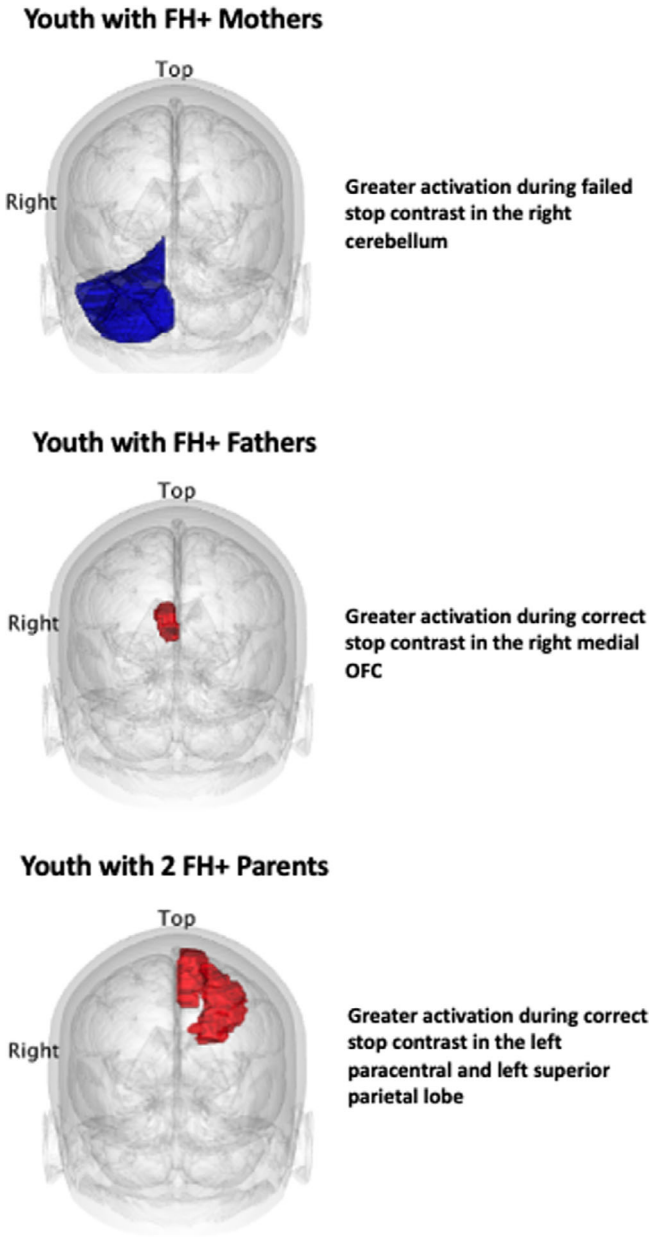

Fig. 3. Significantly greater neural activation for correct stop contrast (correct stop vs. correct go) observed in youth with fathers or both parents exhibiting a history of alcohol use problems, compared to FH− youth. Significantly greater neural activation for failed stop contrast (failed stop vs. correct go) observed in youth with mothers exhibiting a history of alcohol use problems, compared to FH− youth. $n = 6{,}898$. *p(FDR) < 0.05

these effects, allowing us to better understand phenotypic mechanisms of FH of AUD. We found that both paternal and parental AUD when compared to FH− were associated with greater activation across portions of the fronto-basal ganglia network. This was not observed in youth with a maternal FH of AUD. Interestingly, maternal FH of AUD was associated with activation differences in the cerebellum of young females. Previous studies have reported weaker fronto-cerebellar connectivity in FH+ youth (Cservenka, 2016) and in adults with AUDs (Sullivan et al., 2003). Altered cerebellar activation has been associated with reward processing and risky decision making in FH+ youth (Cservenka, 2016), although whether these neurofunctional differences increase risk for excessive alcohol use remains unknown. Future prospective investigations of this cohort should explore how connectivity within and between the fronto-basal ganglia and cerebellar networks confers risk to uptake, and escalation, of alcohol use. While we hypothesized that youth with 2 FH+ parents would show greater deviations than youth with 1 FH+ parent, our findings suggest that maternal and paternal AUD potentially confer differential risk to offspring neurofunction in the fronto-basal ganglia network. Previous research has reported that paternal AUD is associated with poorer response inhibition, impulsivity, and externalizing problems, such as alcohol use, in offspring (Corte and Becherer, 2007; Grekin et al., 2005; Ozkaragoz et al., 1997); however, the neural mechanisms of this differential risk remain unknown. The null fronto-basal ganglia network findings for maternal AUD may also be partly due to adjustment for in utero alcohol exposure (39% of FH+ mothers reported alcohol use during pregnancy), which is known to impact offspring brain development (Lees et al., Under review). It is important to note that given the lower frequency of FH+ mothers compared to FH+ fathers in the ABCD study, analyses examining a maternal effect had lower statistical power and this may have yielded less reliable estimates, as observed by similar average beta weights with larger standard errors in the medial orbital frontal gyrus (Fig. 3).

Neural activation to response inhibition in FH+ youth also appears to vary across racial/ethnic groups. Race and ethnicity variables may be a proxy for more meaningful factors, such as level of acculturation, quality of education, socioeconomic status, and racial socialization, which may be contributing to differences in neurofunction (Manly, 2006). Genetic and other biological variants associated with different racial and ethnic backgrounds (e.g., aldehyde dehydrogenase 2 deficiency) can also induce pronounced effects on alcohol consumption, which may also be contributing to the observed findings (Edenberg, 2007). Further neuroimaging research is required in a diverse ethnic population to investigate mechanisms underlying differential parental risk for altered offspring neurodevelopmental trajectories.

Patterns of greater activation in FH+ youth may reflect heightened processing effort and energy utilization throughout the fronto-basal ganglia network to successfully inhibit prepotent responses, which is more automatic and less effortful for FH− youth. Greater neural response may reflect a developmental lag in functional organization to some extent, given the lack of findings in the ventrolateral PFC, a key region for developmental changes in inhibition-related neural response (Aron et al., 2007; Braet et al., 2009). Previous research suggests that altered white matter integrity may also contribute to neural response differences via decreased neural efficiency and the need for recruitment of more neural resources (thus resulting in greater neural response;

Table 4. Brain Regions Exhibiting Greater Activation in FH+ Compared to FH− Youth for the Correct Stop vs. Correct Go Contrast When Ethnicity Groups Were Analyzed Separately, After Controlling for Relevant Covariates. *N* = 6,898

			Asian *N* = 122		Black *N* = 908		Hispanic *N* = 1363		White *N* = 3819	
FH + Parent	Contrast	Region	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*
Mother	Failed stop vs correct go	Cerebellum, R	NA		−0.108 (0.109)	1.000	0.928 (0.132)	<0.001	−0.003 (0.042)	1.000
Father	Correct stop vs correct go	Medial orbital frontal, R	−0.074 (0.232)	1.000	0.187 (0.118)	0.339	0.181 (0.048)	<0.001	0.056 (0.024)	0.083
Both	Correct stop vs correct go	Paracentral, L	−0.111 (0.142)	1.000	0.061 (0.060)	0.937	0.064 (0.057)	0.810	0.052 (0.020)	0.023
		Superior parietal, L	−0.094 (0.172)	1.000	0.086 (0.070)	0.674	0.078 (0.064)	0.665	0.063 (0.023)	0.018

L: left; R: right. Reference group for analyses was FH− youth who identified as 1 of the 4 ethnicities. Youth identifying as 'other' race/ethnicity were not included in these analyses. FDR-corrected *p*-values are presented. NA = fixed-effect model matrix is rank deficient. N = total number of participants for each racial category.

Burzynska et al., 2013; Zhu et al., 2015). Greater recruitment of inhibitory control regions in FH+ youth may therefore reflect an altered neurodevelopmental trajectory of the fronto-basal ganglia network, creating an inherent neurobiological vulnerability, which affects their ability to suppress behavior. Examining the developmental trajectories of neural responses during cognitive control in this cohort when multiple waves of data are available, and correlating these to risk-related behaviors that change between childhood and adolescence (i.e. uptake of alcohol), may help identify patterns of brain activity that predict the onset of heavy alcohol use in FH+ youth.

There are several limitations to this study. Firstly, information on FH of AUD or SUD, as well as in utero alcohol exposure, may have been underreported or imprecisely recalled. Self-report data on substance use can be influenced by social stigma, desirability bias, and fear of intervention by child protection or social services (Johnson and Fendrich, 2005; Stone, 2015). Effects of reporting influenced by social stigma can also significantly vary by race/ethnicity (Garland and Bumphus, 2012; Kulesza et al., 2016). The effects of underreporting and imprecise recollection of substance use resulting in FH of AUD misclassification would likely attenuate the observed association toward the null. Potentially, this means the reported associations are smaller in magnitude than the true effects. Secondly, despite the large sample size, there were relatively few cases of youth with FH+ mother or 2 FH+ parents. The small sample size of youth with FH+ mothers or 2 FH+ parents resulted in wider variance in neural responses and may underestimate the true impact. This was also evident when we conducted analyses for separate race/ethnicity. The ABCD cohort has a smaller proportion of Asian and Black families relative to White and Hispanic, and this resulted in very small FH+ samples of Asian and Black youth. The low statistical power may yield less reliable estimates for these cases. The current study was uniquely positioned to separately explore maternal and paternal AUD on youth neurofunction; however, the effects of second- and third-degree relatives with AUD (i.e., FH+ density) should be further explored in future studies. Finally, as this study utilized observational and cross-sectional data, it remains unclear how greater forebrain activations may relate to risk for developing substance use disorders. Altered and/or delayed development of regions of the fronto-basal ganglia and cerebellar networks could be a risk factor and potential mechanistic target for intervention. However, we observed very small effect sizes in a small portion of the fronto-basal ganglia network, and this may limit applicability of neural responses to inhibitory control in late childhood as a clinically relevant marker of later alcohol use outcomes. Larger effect sizes in more regions have been observed with older cohorts (Acheson et al., 2014a) and may reflect a more advanced stage of altered neurodevelopment in FH+ individuals. Longitudinal analyses in the ABCD cohort are necessary to address these issues.

In conclusion, substance-naïve children aged 9 to 10 years with parental FH of AUD exhibited greater neural activation in some regions of the fronto-basal ganglia and cerebellar networks when successfully or unsuccessfully inhibiting a response during the SST compared to FH− youth, although effect sizes were very small. These youth are part of the longitudinal ABCD study, and as they reach adolescence, we will investigate how elevated activation during response inhibition at baseline predicts later uptake of risk-related behaviors.

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CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix C

Effect of alcohol on the adolescent brain and behavior

Preface

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BL conceptualized the study, conducted the narrative synthesis, and wrote the manuscript draft. All authors provided input on data interpretation and read, revised, and approved the final manuscript. BL is the corresponding author.

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Review

Effect of alcohol use on the adolescent brain and behavior

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A B S T R A C T

Adolescence is a particularly vulnerable neurodevelopmental period marked by high rates of engagement with risky alcohol use. This review summarizes the cognitive and neural consequences following alcohol use during adolescence from longitudinal design studies in humans and animals. Findings from human adolescent studies suggest that binge drinking and heavy alcohol use is associated with poorer cognitive functioning on a broad range of neuropsychological assessments, including learning, memory, visuospatial functioning, psychomotor speed, attention, executive functioning, and impulsivity. Alcohol use during adolescence is associated with accelerated decreases in gray matter and attenuated increases in white matter volume, and aberrant neural activity during executive functioning, attentional control, and reward sensitivity tasks, when compared to non-drinking adolescents. Animal studies in rodents and non-human primates have replicated human findings, and suggest cognitive and neural consequences of adolescent alcohol use may persist into adulthood. Novel rodent studies demonstrate that adolescent alcohol use may increase reward responsiveness of the dopamine system to alcohol later in life, as well as disrupt adolescent neurogenesis, potentially through neuroinflammation, with long-lasting neural and behavioral effects into adulthood. Larger longitudinal human cognitive and neuroimaging studies with more diverse samples are currently underway which will improve understanding of the impact of polysubstance use, as well as the interactive effects of substance use, physical and mental health, and demographic factors on cognition and neurodevelopment.

1. Introduction

Adolescence is a critical developmental phase involving significant physical, cognitive, emotional, social, and behavioral changes. Cognitive features of adolescence include heightened reward sensitivity, sensation seeking and impulsive action, and diminished self-control to inhibit emotions and behaviors (Casey, 2015; Romer et al., 2017). This contributes to the high rates of engagement in risky behaviors, including the initiation and escalation of alcohol use. Adolescent-specific brain developments may predispose young people to be particularly vulnerable to the potentially serious and long-lasting alcohol-related consequences (Spear, 2016).

Cross-sectional design studies have established a relationship between adolescent alcohol use, brain development, and cognitive function (Lees et al., 2019). Over the past decade, researchers have attempted to understand the direction of this relationship. Considering that it would be highly unethical to randomize youth to different alcohol-using groups, human research is limited to natural observational studies. This makes it difficult to discern correlational from causal findings. Prospective, longitudinal designs have been used to help delineate between pre-existing alterations and post-alcohol effects on brain development by assessing youth before they have ever used alcohol or other drugs and continuing to assess them over time as a portion of the participant population naturally transitions into substance use. This design allows for examination of normal developmental neural trajectories in youth who have never used alcohol or drugs during adolescence, and compares their brain maturation to youth who transition into substance use.

A recent review summarized potentially pre-existing neurobiological markers of alcohol use in humans (Squeglia and Cservenka, 2017). While previous reviews have explored the neurobiological consequences of alcohol use, limitations exist. Some previous reviews have summarized studies examining the impact of one adolescent drinking pattern (Lees et al., 2019), or one study type (i.e., neuropsychological studies (Carbia et al., 2018), neuroimaging studies (Ewing et al., 2014)). Broader, more inclusive, reviews on the effects of alcohol use exist, although they require updating due to the rapidly expanding evidence base (Jacobus and Tapert, 2013; Hermens et al., 2013). The aim of this review is to therefore provide an update on the growing literature by summarizing the neural and cognitive consequences of varying patterns of alcohol use during adolescence, from prospective longitudinal studies in humans, rodents and non-human primates. In order to provide a broader context of the neural and cognitive consequences of alcohol use, this review begins with an overview of adolescent brain development and the global prevalence rates of adolescent alcohol use before summarizing the effects of adolescent alcohol use on

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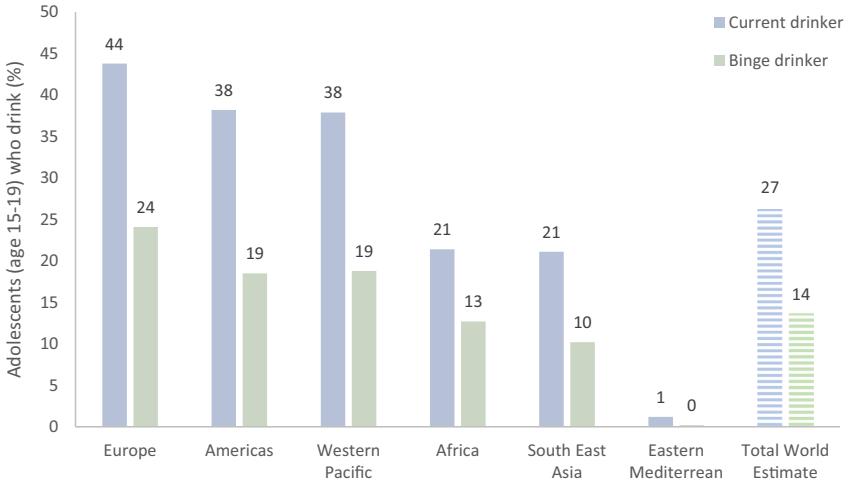

Fig. 1. Prevalence of current alcohol use and binge drinking in adolescents aged 15 to 19. In this data, binge drinking was defined as 60 + grams of pure alcohol (~4 standard US drinks) on at least one occasion per month (World Health Organization. Global Status Report on Alcohol and Health, 2018).

the brain and behavior from both human and animal studies. A focus has been placed on neuroimaging, neuropsychological, and neurophysiological studies as a means to provide a better understanding of the underlying neurobiological consequences of early alcohol use. Findings from cross-sectional studies are not included.

2. Overview of the adolescent brain

The brain undergoes significant neurodevelopment during adolescence, with maturation continuing until around age 25 (Giedd, 2008; Gogtay et al., 2004). Brain gray matter, which includes mostly nerve cell bodies and dendrites, tends to decrease during normal adolescent brain development via removal of weak synaptic connections and changes in the extracellular matrix (Gogtay et al., 2004; Paus, 2005; Petanjek et al., 2011; Raznahan et al., 2014; Sowell et al., 1999; Stiles and Jernigan, 2010). Concurrently, white matter volume and white matter integrity increase over this period with continued myelination of axons, allowing for more efficient communication between brain regions (Giedd, 2004; Lebel and Beaulieu, 2011; Lebel et al., 2012; Yap et al., 2013). Some research suggests that through this process, distributed connectivity and circuitry between distant brain regions is increased relative to more local connectivity (Baker et al., 2015; Fair et al., 2009; Dennis et al., 2013); however, this finding has been debated (Power et al., 2012).

Various regions of the brain have time-varying developmental trajectories, with lower order sensorimotor regions maturing first, followed by limbic regions important for processing rewards, and frontal regions associated with higher order cognitive functioning developing later in adolescence and young adulthood (Sowell et al., 1999; Stiles and Jernigan, 2010; Giedd and Rapoport, 2010; Shaw et al., 2008). Adolescent brain developmental trajectories tend to differ by sex, with female brains developing one to two years earlier than males. For instance, cortical gray matter reaches peak thickness in the parietal lobes at ages 10 (female) and 12 (male), and in the frontal lobes at ages 11 (female) and 12 (male). Although this pattern is reversed for the temporal lobes, which reaches maximal thickness at ages 16 (male) and 17 (female; Giedd, 2004).

Neurotransmitter systems, which transmit chemical signals across synapses, also undergo significant change in adolescence. Dopamine projections to the limbic and frontal regions often peak during adolescence (Ernst, 2014; Spear, 2011). This is associated with amplified neural sensitivity following rewards, compared to adulthood (Hoogendam et al., 2013; Simon and Moghaddam, 2015). Inhibitory control is generally lower in adolescence than adulthood, reflecting greater excitatory synapses and less GABAergic inhibitory neurotransmitters in higher-order frontal regions, with the ratio reversing in later adolescence and into adulthood (Selemon, 2013). Reward hypersensitivity in combination with low inhibition is thought to increase adolescents' drive for risky and novel experiences, such as alcohol use (Simon and Moghaddam, 2015; Doremus-Fitzwater and Spear, 2016). Neurotoxin exposure, particularly alcohol use, during adolescence can affect healthy brain development, with even minor changes in neurodevelopmental trajectories affecting a range of cognitive, emotional, and social functioning (Lees et al., 2019). Alcohol use during adolescence could therefore set the stage for cognitive problems into adulthood, conferring functional consequences throughout life.

3. Global prevalence of adolescent alcohol use

Alcohol use among adolescents is heterogeneous, ranging from low, normative use to heavy, pathological use. Alcohol is the most frequently used substance, as it is generally the easiest for adolescents to access (World Health Organization. Global Status Report on Alcohol and Health, 2018). The average age of initiation for alcohol use among US and Australian adolescents is 15 years (Aiken et al., 2018; Richmond-Rakerd et al., 2017). Across Europe, most adolescents begin drinking alcohol between ages 12 and 16, with 25% of adolescents in this region first consuming alcohol by age 13 (World Health Organization, 2018). The worldwide estimate of adolescents (age 15–19) who drank alcohol in the past month is 27%, ranging from 1 to 44% across countries (Fig. 1; World Health Organization. Global Status Report on Alcohol and Health, 2018). Higher rates of past month adolescent drinking occur in higher income countries; the highest rates are observed in the European region (44%), and the lowest rates are observed in the Eastern Mediterranean region (1.2%; World Health Organization. Global Status Report on Alcohol and Health, 2018; Inchley et al., 2018). Past month alcohol use among adolescents in other countries ranges from 38% in the Americas and Western Pacific regions, to 21% in Africa and Southeast Asia, and 14% in Japan (World Health Organization. Global Status Report on Alcohol and Health, 2018; Morioka et al., 2013).

It is also important to consider common drinking patterns among adolescents, therefore many studies use the alcohol use classification summarized in Fig. 2 (*National Institute on Alcohol Abuse and Alcoholism. Drinking Levels Defined*, 2018; Substance Abuse and Mental Health Services Administration, 2016). While rates of heavy drinking are highest among young people aged 20 to 24, heavy alcohol use among adolescents remains a concern. Binge drinking is a pattern of alcohol

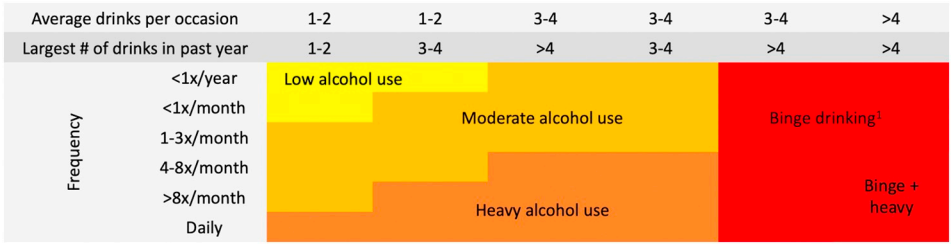

Fig. 2. Alcohol use classification chart.
[1]Binge drinking is typically ≥4 drinks within 2 h (females) and ≥5 drinks within 2 h (males), where the blood alcohol concentration (BAC) level rises to 0.08 g/dL (*National Institute on Alcohol Abuse and Alcoholism. Drinking Levels Defined*, 2018).
The chart is based on the National Institute on Alcohol Abuse and Alcoholism, and Substance Abuse and Mental Health Services Administration levels of alcohol use definitions (*National Institute on Alcohol Abuse and Alcoholism. Drinking Levels Defined*, 2018; Substance Abuse and Mental Health Services Administration, 2016).

use that raises blood alcohol concentration (BAC) levels to 0.08 g/dL, which typically occurs after the consumption of four or more standard drinks for females and five or more drinks for males within a two hour period (*National Institute on Alcohol Abuse and Alcoholism. Drinking Levels Defined*, 2018). Binge drinking in young people aged 15 to 19 is particularly prevalent (Fig. 1), with global estimates of 14% reporting this drinking pattern over the previous month (World Health Organization. Global Status Report on Alcohol and Health, 2018). The highest rates of binge drinking are in the European region (24%; World Health Organization. Global Status Report on Alcohol and Health, 2018), particularly in Austria, Cyprus, and Denmark where > 50% of students report this binge drinking pattern (ESPAD Group, 2016). In the US, 4% and 14% of adolescents aged 14 and 18, respectively, report binge drinking in the previous two weeks (Johnston et al., 2019). Similarly in Australia, 2% and 17% of 14 and 17 year olds report binge drinking in the previous week (White and Williams, 2016). Approximately 13% of adolescents in Africa and 10% of adolescents in South East Asia report past month binge drinking (World Health Organization. Global Status Report on Alcohol and Health, 2018).

As noted previously with neurodevelopment trajectories, sex differences are also reported in alcohol use estimates, which show higher rates of drinking occur among young males than females (World Health Organization. Global Status Report on Alcohol and Health, 2018). Globally, 22% of males and 5% of females binge drink during adolescence. When focusing on country-specific adolescent binge drinking, rates are reported as 36% of males and 12% of females in Europe; 30% of males and 6% of females in the Americas and Western Pacific Regions; and approximately 17–21% of adolescent males and 3–4% of adolescent females binge drink in Africa and South East Asia.

Overall, these general and sex-specific prevalence rates represent a recent decline in general alcohol use and binge drinking that parallels an increase in the number of adolescents who abstain from alcohol use altogether (Looze et al., 2015; Inchley et al., 2016; Pennay et al., 2018; Pape et al., 2018). Despite these declines, adolescent alcohol consumption remains a major public health concern. There is clear evidence that adolescent alcohol use is associated with a wide range of adverse outcomes in both the short and long term. Negative consequences of adolescent alcohol use include gradual attrition of cognitive functions and aberrant neural development trajectories (Lees et al., 2019).

4. Adolescent alcohol effects on the human brain

Prospective longitudinal neuropsychological, neuroimaging, and neurophysiological studies have identified cognitive and neural consequences directly related to initiation and escalation of adolescent alcohol use. Overall, adolescent alcohol use has been found to negatively affect cognition, brain structure, and function (Table 1); however, the level to which alcohol use and different patterns of drinking affects male and female brain functioning has been debated. Research in this field is also limited to natural observational studies, and it is common for a portion of adolescents to use multiple substances (e.g., alcohol and cannabis use). While studies may try to statistically control for other drug use to parse the relative contribution of alcohol use on brain functioning, this method is imperfect given the high collinearity between alcohol and other drug use variables as well as potential interactive effects. Longitudinal studies with very large sample sizes are currently underway and may help to answer these important issues (Volkow et al., 2018; Schumann et al., 2010; Brown et al., 2015).

4.1. Neuropsychological consequences of alcohol use

Neuropsychological test batteries enable tracking of cognitive skills over time to detect potential effects of alcohol use on cognition and intellectual development. Alcohol-induced deficits are arguably even more impactful for adolescents than adults, given that educational attainment, learning, and ongoing neural development are the most critical developmental tasks of adolescence. Notably, alcohol use behaviors at ages 12 to 14 predict lower educational achievement in later years, even after accounting for confounding factors such as sex and externalizing behavior (Latvala et al., 2014). A recent meta-analysis of cross-sectional studies reported adolescent binge drinking was associated with an overall cognitive deficit and specific impairments in decision-making and inhibition (Lees et al., 2019). Herein, we report on longitudinal studies that have identified potential negative effects of adolescent binge drinking and heavy alcohol use on memory, learning, visuospatial function, executive function, reading ability and impulsivity.

The Avon Longitudinal Study of Parents and Children is an ongoing population-based study in the UK. Utilizing data from 3141 adolescents, frequent binge drinkers exhibited poorer working memory compared to the low alcohol group. However, this association was attenuated when adjusting for sociodemographic variables, tobacco, and cannabis use (Mahedy et al., 2018). In a sample of 89 young people who did not have a history of psychiatric disorders and did not regularly consume other drugs, consistent binge drinking over two years in late adolescence was associated with poorer immediate and delayed recall, retention, and working memory, compared to non-binge drinkers (Mota et al., 2013). Conversely, a four-year study of 234 adolescents unexpectedly found that more alcohol use predicted better working memory, driven largely by a relationship between recent blackout history and auditory attention scores, when controlling for age, socioeconomic status, abstinence, gender, and baseline performance (Nguyen-Louie et al., 2015). Although, this was in contrast to other findings in this study which demonstrated that more alcohol use days predicted worse verbal memory and visuospatial ability. Approximately 40% of the cohort had tried cannabis, and 18% had tried other illicit drugs. No follow-up tests supported the unexpected working memory finding, such as removing sex and other covariates from the regression models. The authors conclude that unreliability of self-report alcohol use data may have also contributed to the unexpected result. A study using eight years of data from 2226 youth in the Tracking Adolescents' Individual Lives Survey

Table 1
Summary of consequences of adolescent alcohol use in humans and rodents.

	Humans	Rodents
Cognitive	*Binge/heavy drinking* vs *control*: ↓ Immediate recall (short-term memory) (Mota et al., 2013; Carbia et al., 2017a) ↓ Delayed retention, recall (long-term memory) (Mota et al., 2013; Hanson et al., 2011a; Hanson et al., 2011b; Carbia et al., 2017a) ↓ Learning (Hanson et al., 2011a; Hanson et al., 2011b) ↓ Visuospatial function (Hanson et al., 2011b) ↓ Working memory (Mahedy et al., 2018; Mota et al., 2013) *Dose-dependent relationships*: ↑ Alcohol use = ↓ General cognitive functioning (Hanson et al., 2011a) ↓ Verbal memory (Nguyen-Louie et al., 2015; Winward et al., 2014; Nguyen-Louie, 2016) ↓ Executive functioning (Winward et al., 2014) ↓ Semantic clustering (Winward et al., 2014) ↓ Reading skills (Winward et al., 2014) ↓ Visuospatial function (Nguyen-Louie et al., 2015) (females only (Squeglia et al., 2009)) ↑ Impulsivity (Jones et al., 2017) ↑ Withdrawal/hangovers symptoms = ↓ General cognitive functioning (Winward et al., 2014) ↓ Psychomotor speed (Nguyen-Louie et al., 2015) ↓ Attention (males) (Squeglia et al., 2009)	*Sustained effects into adulthood*: ↓ Executive functioning (Coleman et al., 2011; Coleman et al., 2014; Gass et al., 2014) ↑ Risk-taking (Gass et al., 2014; Risher et al., 2013; Torcaso et al., 2017; Desikan et al., 2014; Ehlers et al., 2011; Ehlers et al., 2013) ↑ Impulsivity (Gass et al., 2014; Risher et al., 2013; Torcaso et al., 2017; Desikan et al., 2014; Ehlers et al., 2011; Ehlers et al., 2013) *Adolescent-specific effects*: ↓ Learning (Tapia-Rojas et al., 2018; Marco et al., 2017; Montesinos, 2015) ↓ Memory (Tapia-Rojas et al., 2018; Marco et al., 2017; Montesinos, 2015)
Neural	*Binge/heavy drinking* vs *control*: ↓ Gray matter volume, particularly frontal, temporal (Pfefferbaum et al., 2018; Sullivan et al., 2020; Squeglia et al., 2015; Squeglia et al., 2014; Luciana et al., 2013) ↓ White matter growth (Sullivan et al., 2020; Squeglia et al., 2015; Squeglia et al., 2014; Luciana et al., 2013; Jones and Nagel, 2019) ↓ White matter integrity (Bava et al., 2013; Jacobus et al., 2013a; Jacobus et al., 2013b) ↑ Cerebrospinal fluid volume cerebellum (Sullivan et al., 2020) ↑ Brain activation during executive functioning (Squeglia et al., 2012; Wetherill et al., 2013) ↓ Brain activation during reward sensitivity tasks (Cservenka et al., 2015; Jones et al., 2016) ↑ P3 amplitude, particularly fronto-parietal during executive functioning and attentional control (Lopez-Caneda et al., 2013; Lopez-Caneda et al., 2012; Lopez-Caneda et al., 2014) *Dose-dependent relationships*: ↑ Alcohol use = ↓ Gray matter frontal volume (Pfefferbaum et al., 2018) ↓ Brain activation during reward sensitivity tasks (Cservenka et al., 2015)	*Sustained effects into adulthood*: ↓ Gray matter volume (Pascual et al., 2014) ↓ Cortical thickness (Vetreno et al., 2014) ↓ White matter integrity (Pascual et al., 2014; Vetreno et al., 2016; Vargas et al., 2014; Montesinos et al., 2015; Wolstenholme et al., 2017) ↓ Synaptic plasticity (Tapia-Rojas et al., 2018) ↓ Connectivity between brain regions (Broadwater et al., 2018) ↓ Neurogenesis (Broadwater et al., 2014; Liu and Crews, 2017; Morris et al., 2010; Sakharkar, 2016; Briones and Woods, 2013; Scheidt, 2015; Fernandez et al., 2016) ↑ Neuroinflammation (Alfonso-Loeches et al., 2013) *Dose-dependent relationships*: ↑ GABA inhibitory tone on dopamine system = ↑ Risky decision-making (Schindler et al., 2016) ↓ Cholinergic tone = ↑ Disinhibition (Ehlers et al., 2011) ↑ Risk-taking (Boutros et al., 2015) ↓ Executive functioning (Fernandez and Savage, 2017)

(TRAILS) found that light and heavy adolescent alcohol use was not associated with deterioration in executive functioning, compared to no alcohol use, when controlling for baseline performance, age, and tobacco use (Boelema et al., 2015). A four-year study of 92 adolescents found low alcohol consumption was associated with subtle improvements in inhibitory control (Jurk et al., 2018). No negative effect of low-level alcohol use on the development of school grades, spatial working memory or rapid visual processing was found. Therefore, binge drinking may have specific detrimental effects on executive functioning, in comparison to lighter doses. Inconsistent findings may also partly reflect psychiatric and other substance use comorbidities.

A 10-year longitudinal study followed heavy alcohol using and control youth from age 16 until early adulthood (~age 25). Youth diagnosed with a psychiatric disorder, besides conduct disorder, were excluded from the study at intake. Heavy alcohol use and withdrawal symptoms were associated with worsening verbal memory and learning over time (Hanson et al., 2011a; Hanson et al., 2011b), as well as relative declines in visuospatial function (Hanson et al., 2011b). Heavier use patterns, and greater hangover and withdrawal symptoms over time were related to worse cognitive functioning, suggesting a dose-dependent relationship between alcohol use and cognitive functioning (Hanson et al., 2011a). Dose-dependent relationships between alcohol use and cognitive impairment have been replicated in other studies. Higher total life-time drinks predicts escalated impulsive choice (Jones et al., 2017), and poorer cognitive flexibility, verbal recall, semantic clustering, and reading skills (Winward et al., 2014). Higher drinking days over a four-year period predicted worse verbal memory and visuospatial ability (Nguyen-Louie et al., 2015). Higher estimated peak BAC over six years predicted worse verbal learning, and immediate, short and long-term delayed and cued recall (Nguyen-Louie, 2016). Greater post-drinking effects predict worse psychomotor speed (Nguyen-Louie et al., 2015), and more withdrawal symptoms over the past month are associated with greater decrements in cognitive functioning (Winward et al., 2014). Overall, heavy alcohol use during adolescence has been associated with a range of cognitive deficits, with some cognitive domains showing dose-dependent relationships where greater alcohol use is associated with poorer cognitive functioning (see Table 1).

4.2. Sex-related neuropsychological consequences of alcohol use

Adolescent alcohol use may differentially impact male and female cognitive function, furthering the implications of noted sex differences within brain development and alcohol use estimates. A five-year

longitudinal study followed 89 young adolescents from ages 14 to 19, where a portion transitioned into moderate (14%) or heavy (33%) alcohol use (Squeglia et al., 2009). Conduct disorder was present in 15% (female) and 39% (male) of drinkers, and 0% of controls. Drinkers had consumed alcohol at moderate or heavy levels for an average of 2.8 years since initiation (SD = 1.3). For females, more drinking days in the past year predicted a greater reduction in visuospatial performance from baseline to follow-up. For males, a tendency was seen for more hangover symptoms in the previous year to predict relative worsening of sustained attention. While drinkers had used cannabis and other drugs, these substances did not predict any change in cognitive functioning. A six-year study followed 155 older adolescents from age 18 every 22-months. Consistent binge drinkers, who continued to engage in binge drinking behavior throughout the entirety of the study, represented 35%, 23% and 10% of the sample at first follow up one, two and three, respectively. Consistent binge drinkers presented difficulties in immediate and delayed recall, with similar deficits for males and females compared to controls (Carbia et al., 2017a), while no disadvantage for either sex was observed for decision-making ability (Carbia et al., 2017b). This suggests that some cognitive domains may be differentially impacted in adolescent males and females who drink, while other domains may be similarly affected. Further longitudinal research on sex differences in other cognitive domains known to be affected by alcohol use (i.e., learning, executive functions, impulsivity) should be conducted.

4.3. Structural brain consequences

Adolescent alcohol-induced alterations in neurodevelopmental trajectories (including accelerated decreases in gray matter volume, attenuated increases in white matter volume and density, and poorer white matter integrity) may underlie some long-term cognitive deficits. Here, longitudinal studies reporting on structural brain changes following alcohol use in adolescence are discussed. The National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA) is a nationally representative prospective longitudinal study being conducted in the US, designed to disentangle the complex relationships between onset, escalation, and desistance of alcohol use in adolescence and neuromaturation (Brown et al., 2015). At baseline all adolescents were no/low alcohol, tobacco, cannabis and other drug use consumers. Approximately 50% of the cohort endorsed ≥ 1 externalizing and ≥ 2 internalizing symptoms. By the two-year follow-up assessment, 356 participants were no/low alcohol consumers, 65 had initiated moderate drinking, and 62 had initiated heavy drinking (Pfefferbaum et al., 2018). Adolescents who remained no/low alcohol consumers served as a control group for estimating typical developmental trajectories over the same age range as the drinkers. Youth who initiated heavy drinking showed abnormal neurodevelopmental trajectories compared to continuously non-/low-drinking controls, with accelerated decreases in frontal gray matter volume. Marginal differences in frontal gray matter were also observed in moderate drinkers, and although not significant, their intermediate position between no/low and heavy drinkers suggests a dose-dependent effect (Pfefferbaum et al., 2018). By the three- to four-year follow up assessment, 328 youth were no/low drinkers, 120 were moderate drinkers and 100 were heavy drinkers (Sullivan et al., 2020). Moderate and heavy drinkers continued to exhibit altered neurodevelopmental trajectories, including accelerated cerebellar gray matter declines, white matter expansion, and cerebrospinal fluid volume expansion relative to controls. Cannabis co-use did not contribute to these effects (Pfefferbaum et al., 2018; Sullivan et al., 2020).

These findings replicate earlier longitudinal studies with smaller sample sizes showing adolescent heavy drinkers had altered neurodevelopmental trajectories, including accelerated decreases in gray matter in frontal and temporal lobes (Squeglia et al., 2015; Squeglia et al., 2014; Luciana et al., 2013), and attenuated increases in white matter growth over time in the frontal, temporal and occipital lobes, cingulate, corpus callosum, and pons, compared to non-using controls (Squeglia et al., 2015; Luciana et al., 2013). A prospective four-year study measured within-subject changes in brain volume for males and females. Heavy-drinking males and females showed similar deviations in neural developmental trajectories compared to continuously non-drinking controls, including accelerated decreases in gray matter volume (particularly in frontal and temporal regions), and attenuated increases in white matter volume over the follow-up, even after controlling for cannabis and other substance use (Squeglia et al., 2015).

In a sample of 113 alcohol-naïve adolescents aged 11 to 16 at baseline, 45 went on to binge drink before turning 21. Binge drinking throughout adolescence predicted altered frontostriatal white matter microstructural development when compared to developmental trajectories of non-using healthy adolescents (Jones and Nagel, 2019). Three studies examining adolescents who used alcohol and cannabis showed these youth had consistently poorer white matter integrity across 7 to 20 clusters compared to controls, as well as poorer cognitive functioning over an 18-month (Bava et al., 2013) to three-year period (Jacobus et al., 2013a; Jacobus et al., 2013b). Mixed findings were reported for the specific effects of alcohol, with two studies reporting that heavy drinking predicts worsening white matter integrity (Bava et al., 2013; Jacobus et al., 2013a) with either no effect (Bava et al., 2013) or added effect (Jacobus et al., 2013a) of co-occurring cannabis use. A third study reported that white matter integrity effects were driven by heavy cannabis initiation (Jacobus et al., 2013b). The right superior longitudinal fasciculus, connecting the fronto-parietal-temporal networks, was the only consistent white matter tract across studies to show poorer white matter integrity among alcohol users compared to control.

Overall, binge and heavy drinking appears to affect the normal developmental trajectories of gray and white matter maturation during adolescence, particularly in the frontal and temporal lobes, and interconnecting networks. Some studies have reported accompanying cognitive deficits alongside aberrant neurodevelopmental trajectories. Patterns observed among alcohol-using youth may represent accelerated but non-beneficial pruning of gray matter, attenuated connective efficiency of white matter tracts, or alternatively, premature cortical gray matter decline similar to volume declines related to accelerated aging in adult alcoholics (Pfefferbaum et al., 1992) or even “normal” aging (Pfefferbaum et al., 2013; Pfefferbaum et al., 1994). Adults who engage in sustained problematic drinking exhibit similar structural alterations and have speeded gray and white matter decline, which suggests alcohol use is associated with accelerated brain aging (Pfefferbaum et al., 1992; Pfefferbaum et al., 2013; Guggenmos et al., 2017). Existing studies tend to group youth by “drinkers” versus “controls”. To address this methodological limitation, the Adolescent Brain Cognitive Development (ABCD) Study is underway with a larger sample size (~12,000) which will allow more nuanced investigation of the dose-dependent effect of alcohol on neural development (Volkow et al., 2018; Luciana et al., 2018).

4.4. Functional brain consequences

Task-based functional neuroimaging studies measure brain activation by detecting changes in blood direction while participants complete tasks. These studies can help link structural brain changes with behavioral and cognitive deficits following alcohol initiation in adolescence. Functional neuroimaging studies have identified potential effects of alcohol use on adolescent brain activation during tasks of working memory, inhibitory control, and reward sensitivity. In a longitudinal study, 40 12- to 16-year-old adolescents were scanned before they ever used alcohol or drugs and then were rescanned approximately three years later (Squeglia et al., 2012; Wetherill et al., 2013). In total, 15% of participants who transitioned into heavy drinking by late adolescence presented with conduct disorder. These heavy drinking adolescents showed less baseline brain activation in

frontal and parietal regions during a visual working memory (Squeglia et al., 2012) and inhibition task (Wetherill et al., 2013) when compared to controls. Neural activation during these tasks increased from baseline to follow-up in youth who initiated drinking compared to decreased activation in those who remained abstinent over the follow-up. This suggests that youth who initiate heavy drinking may require more executive cognitive control to perform at the same level as non-users.

Heavy alcohol use may also affect reactivity and sensitivity to reward. Adolescent binge drinking was associated with less cerebellar (Cservenka et al., 2015) and dorsal striatum (Jones et al., 2016) activation during a monetary reward and decision making task, respectively. More drinks per drinking day predicted less activation within these regions among binge drinkers (Cservenka et al., 2015). This suggests binge drinking may affect the emotional component of reward processing and decision making, as damage to the posterior cerebellum has been associated with cognitive and emotional deficits (Stoodley and Schmahmann, 2010), while the dorsal striatum is integral to incorporating emotional information into reward and decision-making (Balleine et al., 2007).

Neurophysiological studies conducted in Spain over a two-year period have measured event-related potential (ERP) components among consistent binge drinking and non-binge drinking youth during inhibitory and complex attention tasks (Lopez-Caneda et al., 2013; Lopez-Caneda et al., 2012; Lopez-Caneda et al., 2014). In separate studies of 38 to 57 participants, consistent binge drinkers exhibited increased P3 amplitude (related to working memory and inhibitory control) in the central, parietal and frontal regions, as well as increased activation in the prefrontal cortex and insula during inhibitory responses, compared to non- or low-drinkers (Lopez-Caneda et al., 2012; Lopez-Caneda et al., 2014). Consistent binge drinkers also reported increased P3b amplitude in the central and parietal regions during an attentional control task compared to controls, with more pronounced differences observed after two years of consistent binge drinking (Lopez-Caneda et al., 2013).

Taken together these studies suggest that neural differences are observable as a consequence of alcohol use, mirroring the behavioral findings from neuropsychological and neurostructural studies. Functional changes were not examined in relation to neuropsychological deficits; thus, it is not possible to infer whether changes in neural response were related to poorer cognitive outcomes. Sex differences in neural activation following the uptake of alcohol use in adolescence remain unknown. Of note, these functional findings come from small samples (< 30 drinkers in each study) and include mostly Caucasian participants from high socioeconomic status groups. More longitudinal fMRI and ERP studies in larger, more diverse samples are needed to better understand the specific effect of alcohol on neural functioning in adolescence.

4.5. Neurobiological consequences: integrating findings from human studies

Determining how adolescent alcohol use may lead to overt cognitive and behavioral deficits is critical, and early structural and functional brain changes may help us understand this relationship. Following adolescent alcohol initiation, structural brain changes appear to occur. Studies have consistently reported accelerated decreases in gray matter volume and attenuated white matter growth of the frontal and temporal lobes, with poorer white matter integrity throughout related networks (Pfefferbaum et al., 2018; Sullivan et al., 2020; Squeglia et al., 2015; Squeglia et al., 2014; Luciana et al., 2013; Jones and Nagel, 2019; Bava et al., 2013; Jacobus et al., 2013a; Jacobus et al., 2013b). The frontal lobe is thought to be critical for higher-order cognitive control, and the temporal lobe plays an important role in learning and memory (Otero and Barker, 2014; Squire and Zola-Morgan, 1991). Damage to these regions may result in overt cognitive impairments. Likewise, neuropsychological studies demonstrate a possible dose-dependent response of alcohol use on executive functioning ability (Mota et al., 2013; Boelema et al., 2015) and learning and memory (Nguyen-Louie et al., 2015; Winward et al., 2014; Nguyen-Louie, 2016). Preliminary functional neuroimaging and neurophysiological research complements findings from neuropsychological and structural neuroimaging studies; transitions into heavy alcohol use and binge drinking result in increased neural activation in fronto-parietal regions during executive functioning and attentional control tasks (Squeglia et al., 2012; Wetherill et al., 2013; Lopez-Caneda et al., 2013; Lopez-Caneda et al., 2012; Lopez-Caneda et al., 2014). This suggests that heavy alcohol use initiation and continuation may have a cumulative effect on brain activity, and anomalous activity may reflect degradation of underlying attentional and executive functioning mechanisms. Heavy drinkers may therefore require more executive cognitive control to perform at the same level as non-users. Overall, integration of human neuroimaging, neuropsychological, and neurophysiological studies suggest that moderate to heavy alcohol use may initially result in structural brain changes, and with heavier binge doses, the resulting neural impairments may lead to more overt functional consequences (i.e., cognitive functioning deficits).

It is important to note that previous reviews illustrate that premorbid cognitive and neural vulnerabilities predispose some adolescents to initiate, and misuse, alcohol (Lees et al., 2019; Squeglia and Cservenka, 2017). Presently, it is not clear whether neurobiological deficits are the direct results of adolescent alcohol use, irrespective of predispositions, or whether those youth exhibiting vulnerability markers prior to alcohol initiation then experience worse neurobiological outcomes following uptake. Larger prospective longitudinal studies that are currently underway will help disentangle these complex relationships (Volkow et al., 2018; Luciana et al., 2018).

5. Cognitive and neural functioning following alcohol remittance

Studies have examined the effects of alcohol remittance (i.e., discontinuation of alcohol use) in adolescence on cognitive and neural functioning. A 10-year study found remitted youth, who had previously met criteria for an alcohol use disorder, performed similarly to youth with persistent disorders on tasks measuring visuospatial functioning and language abilities (Hanson et al., 2011b). The majority of youth in this study also met criteria for at least one other substance use disorder. Similarly, no improvements were reported for immediate or delayed recall in a sample of 20 young people who had stopped binge drinking for two years (Carbia et al., 2017a). However, another two-year study which included 16 ex-binge drinkers found some improvement in delayed recall which reflected an intermediate position between binge and non-drinkers at age 21 (Mota et al., 2013). Longer-term abandonment of binge drinking (two to four years) in healthy older adolescents who occasionally report cannabis and/or tobacco use, was associated with improvements in immediate recall which matched non-drinking control performance (Carbia et al., 2017a), and improvements in long-term memory (Carbia et al., 2017a) and working memory (Carbia et al., 2017c) which again reflected an intermediate position between binge and non-drinkers.

One functional neuroimaging study reported that, after one month of abstinence, adolescents who previously drank heavily no longer exhibited alterations in reward activation to alcohol cues, highlighting the potential for adolescents to benefit from early intervention and recover from the short-term effects of alcohol (Brumback et al., 2015). Overall, these results provide mixed evidence as to whether cognitive functioning in adolescents who drink heavily can be modified or improved after abstinence, reductions in drinking, or treatment. While there is preliminary support that abstinence may be related to recovery in brain functioning, more evidence is required. Future research is needed to clarify when cognitive and neural recovery is most likely, and if certain cognitive and neural domains are more malleable than others following changes in substance use. This knowledge will benefit practitioners working with adolescents and can ultimately inform alcohol use treatment practices.

6. Adolescent alcohol effects in animals

Human research is limited to natural observational studies which have typically assessed youth into early adulthood at the latest. Conversely, researchers have much higher levels of control over experimental conditions in animal studies, including frequency, amount and duration of alcohol exposure, and have often assessed rodents or non-human primates into late adulthood after the termination of alcohol use. Therefore, animal studies can provide helpful insight into knowledge gaps from human literature on consequences of adolescent alcohol use. Notably, much of the work using rodent models has been conducted only in males; where possible, rodent research testing both sexes is reported.

6.1. Comparable cross-species findings

Animal studies can never completely reproduce all human features, and there have been notable differences in analyses used to examine the consequences of alcohol use on the adolescent human (e.g., cognitive, neuroimaging) and rodent brain (e.g., molecular, cellular). However, rodent studies have started to use measures that are similar to those used in human studies, and have provided evidence for cross-species similarities in findings. Partly consistent with human research, cognitive studies in male rodents have shown that adolescent alcohol use predicts poorer executive functioning in adulthood, including cognitive flexibility (Coleman et al., 2011; Coleman et al., 2014), set shifting (Gass et al., 2014), and extinction of responses following termination of reinforcer cues (Gass et al., 2014; Risher et al., 2013; Miller et al., 2017). Adolescent alcohol use in male rodents has also been associated with poorer inhibition, reflecting heightened impulsivity and risk taking in adulthood (Gass et al., 2014; Risher et al., 2013; Torcaso et al., 2017; Desikan et al., 2014; Ehlers et al., 2011; Ehlers et al., 2013). Similar to human studies, moderate alcohol use and binge drinking in male and female rodents predicts alterations in learning and memory during adolescence (Tapia-Rojas et al., 2018; Marco et al., 2017; Montesinos, 2015), however this may have minimal effects on later learning and memory in adulthood (Acheson et al., 2013; Semenova, 2012). In terms of neural consequences of adolescent alcohol use, adult male and female rodents show attenuated neurodevelopment, including reduced volume in the corpus callosum (Pascual et al., 2014), attenuated thickness in frontal regions (Vetreno et al., 2014), decreased connectivity between frontal regions, the nucleus accumbens and dorsal striatum (Broadwater et al., 2018), poorer white matter integrity (Pascual et al., 2014; Vetreno et al., 2016; Vargas et al., 2014; Montesinos et al., 2015; Wolstenholme et al., 2017) and impaired synaptic plasticity (Tapia-Rojas et al., 2018), similar to human adolescent studies. Interestingly, greater volume reductions were predictive of later relapse drinking in adult rats (Pascual et al., 2014). Experimental rodent studies also support cross-sectional findings in human studies (Medina, 2008; De Bellis et al., 2005) that females may be more vulnerable than males to the neurotoxic effects of alcohol (Pascual et al., 2014).

Non-human primate findings parallel rodent and human results. In a recent study, rhesus macaques were imaged before and after one year of alcohol exposure. Findings showed that brain volume increased in controls throughout adolescence into early adulthood; however, heavy drinking macaques showed reduced rates of brain growth over the follow-up period, particularly in white matter regions and the thalamus, in a dose-dependent manner (Shnitko et al., 2019). These structural changes may be associated with cognitive aberrations continuing into adulthood.

6.2. Adolescent versus adult alcohol use in rodents

Studies that have compared equivalent exposures to alcohol in adolescent and adult animals have found that the effects of alcohol exposure during adulthood are generally less pronounced than after comparable alcohol exposure in adolescence (Crews et al., 2016). Adolescents are less sensitive than adults to many of the intoxicating alcohol effects that serve as cues to stop drinking, such as alcohol's motor-impairing, sedative, social-inhibiting, and hangover-inducing effects (Spear, 2013). Comparatively, adolescents are more sensitive than adults to desirable consequences of low levels of alcohol use, including social facilitation and rewarding effects (Spear, 2013). Rodent studies show that as adults, former adolescent alcohol-exposed animals still exhibit 'adolescent-like' insensitivities to alcohol's motor-impairing, sedative, and taste aversive effects (White et al., 2002; Toalston et al., 2014; Saalfield and Spear, 2015), while retaining adolescent-typical increased sensitivities to alcohol's rewarding effects (Toalston et al., 2014; Quoilin et al., 2012). This may contribute to consistent drinking patterns from adolescence into adulthood.

6.3. Novel rodent findings

Rodent studies provide novel insight into areas which have not yet been studied in great detail in humans, such as effects of adolescent alcohol use on neurotransmitters, neurogenesis, and neuroinflammation. There are marked developments that occur in the dopamine neurotransmitter system during adolescence, important for reward-motivated behavior. Limited human research shows dopamine system development is disrupted following alcohol use, although most studies have focused on older, alcohol-dependent adults (Meyerhoff et al., 2013). Findings from rodent studies suggest the dopamine system is particularly sensitive to the effects of alcohol use during adolescence (for review, see Spear, 2018). Following alcohol use, adolescent male rodents show increased GABA inhibitory tone on the dopamine system neurons in the nucleus accumbens (Schindler et al., 2016). This decreases tonic dopamine tone and increases phasic dopamine responses to rewarding and risky activities, and in turn, appears to increase risky decision-making following alcohol use. Preliminary evidence also suggests these dopamine system changes enhance later reactivity to the rewarding, but not harmful, effects of alcohol (Spear, 2018), although this requires further investigation in both animal and human studies.

Adolescent alcohol use also appears to disrupt other neurotransmitter systems, including the cholinergic system of the basal forebrain (Crews et al., 2016). These neurons play critical roles in cognitive functions, including learning and memory. Multiple studies show that repeated alcohol use during adolescence reduces the number of neurons showing immunoreactivity to choline *O*-acetyltransferase (ChAT) in the basal forebrain (Coleman et al., 2011; Ehlers et al., 2011; Vetreno et al., 2014; Boutros et al., 2015; Swartzwelder, 2015; Fernandez and Savage, 2017). This decline in ChAT immunoreactivity is associated with greater disinhibitory behavior (Ehlers et al., 2011), increased risky behavior (Boutros et al., 2015), and decreased performance on set-shifting tasks (Fernandez and Savage, 2017) in adulthood following alcohol remittance. This suggests adolescent alcohol use leads to loss of cholinergic tone which has lasting functional consequences.

Neurogenesis involves formation of new neurons and integration into functional neural networks, which is a critical component of nervous system development (Pino et al., 2017). Rates of neurogenesis are influenced by environmental factors. Repeated alcohol use in adolescence, but not adulthood, decreases neurogenesis (Broadwater et al., 2014), and such changes may be evident long after alcohol use has stopped (Broadwater et al., 2014; Liu and Crews, 2017; Morris et al., 2010). The mechanisms underlying neurogenesis disruptions following adolescent alcohol use remains unclear. One suggestion is the suppression of neurotrophins, such as brain-derived neurotrophic factor (BDNF), which is a regulator of the survival and differentiation of newly generated neurons. Adolescent alcohol use appears to decrease BDNF expression in the hippocampus and interrupts neurogenesis (Sakharkar, 2016; Briones and Woods, 2013; Scheidt, 2015; Fernandez et al., 2016). Further evidence of the role of BDNF in neurogenesis disruption comes

from a study where a BDNF agonist was administered to male rodents previously exposed to alcohol (Briones and Woods, 2013). Administration resulted in neurogenesis, and reversed depression-like symptoms observed during alcohol withdrawal and abstinence following repeated alcohol use in adolescence.

Repeated exposure to alcohol during adolescence also induces long-lasting neural and behavioral changes via the induction of neuroinflammation. Alcohol stimulates the release of innate pro-inflammatory cytokines that can disrupt synaptic plasticity and lead to neuropathology and cell death (Crews and Vetreno, 2011; Crews, 2017). Studies including male and female mice demonstrate that females are more vulnerable than males to the neuroinflammatory effects of alcohol (Alfonso-Loeches et al., 2013). Rodent studies have examined ways to reduce neuroinflammation caused from adolescent alcohol use. For instance, administration of a neuroimmune drug, ibudilast, reduced alcohol drinking in dependent male rodents by 50% (Bell et al., 2015), and administration of an anti-inflammatory drug, indomethacin, prevented cell death, and reduced cognitive and motor deficits that were evident after adolescent alcohol exposure (Pascual et al., 2007). Furthermore, female rodents with altered gene expression of TLR4, which reduced inflammatory activation following alcohol use, did not show behaviors consistent with adolescent alcohol use, such as anxiety and heightened reward sensitivity to alcohol (Montesinos et al., 2016). Overall, animal studies provide evidence of lasting impacts of adolescent alcohol use into adulthood, with growing evidence of retention of adolescent-like phenotypes.

7. Future directions and conclusions

Recent prospective, longitudinal designs have greatly increased our knowledge of the complex relationship between adolescent brain development and alcohol use by parsing out the pre-existing vulnerabilities from the consequential effects of use. However, with high heterogeneity in patterns of alcohol and other substance use during this critical neurodevelopmental period, more research is needed to determine what developmental processes and cognitive domains may be most responsive to prevention and treatment initiatives. The larger multi-site studies currently underway (e.g., ABCD, NCANDA) will hopefully help disentangle the complicated picture of substance co-use, the interactive effects of adolescent substance use and psychopathology, sex and other demographic factors, health habits, and genetic vulnerabilities, among other important factors related to substance use. It is necessary to understand substance-specific effects, especially given growing US legalization and rise in rates of cannabis use, the dramatic rise in adolescent e-cigarette use, and global concerns regarding opioid dependency and associated deaths. These larger studies are positioned to differentiate the specific neural developmental effects of alcohol as well as cannabis, tobacco, e-cigarettes, opioids, cocaine, hallucinogens, and amphetamines. Future studies also need to make concerted efforts to enroll more adolescents with diverse backgrounds, as substance use effects may not generalize across ethnicities and cultures (most research to date has been in Caucasian youth from upper middle class families), various family structures, or psychopathology profiles. This knowledge will benefit practitioners working with adolescents, and hopefully, inform future substance use prevention and intervention initiatives.

Better understanding the dose-dependent effects of substances will enable improved public health information to inform policies regarding limiting amounts of adolescent use and controlling potency of substance-containing products. Specifically, it will be useful to know how adolescent binge drinking compared to lower levels of drinking differentially affects cognition and behavior. Additionally, a greater understanding of short compared to longer-term neural and cognitive effects of alcohol use and remittance in adolescence through to adulthood is needed to better inform treatment. Researchers are starting to track these changes in short and longer-term effects using neural markers of substance use to better understand how an individual is responding to treatment (Cservenka and Nagel, 2016). Targeting cognitive makers of substance use through cognitive retraining treatment strategies has demonstrated some success in reducing alcohol use (Bowley et al., 2013), as well as in a range of clinical populations including various substance use disorders (Aguinaldo et al., 2019). Researchers are also beginning to investigate the effectiveness of cognitive training as a prevention initiative for adolescent substance use (Bourque et al., 2016; Mewton et al., 2017; O'Leary-Barrett et al., 2017), although early findings suggest this method may need to be supplemented with a substance use prevention program (Mewton et al., n.d.).

Of note, all of the human longitudinal studies in this review relied on youth self-report of substance use. Some of the existing studies also used ranges for self-report questionnaires, which weakens the ability to understand dose-dependent relationships. Substance use researchers are beginning to incorporate real time measures via smart phone technology, more sophisticated biological markers (i.e., blood, urine, saliva, and hair samples), as well as daily reporting or real-time tracking of drug use through youths' smart phones and wearable devices (Tomko et al., 2019). These nuanced tools will help improve the accuracy and reliability of reports to better quantify the frequency and amount of alcohol consumed. Better neuroimaging standards, such as scanning under neutral conditions to control for factors like time since last alcohol use, and more consistency in measures used to assess cognitive functioning are also suggested as an area of future research.

Cross-species findings show comparability in effects of alcohol use on the adolescent brain and behavior, and novel experimental rodent studies on the consequences of alcohol use can guide future work in human adolescents. For instance, researchers are now focused on quantification of various neurochemicals and transmitters in the brain measured through Magnetic Resonance Spectroscopy (MRS; Cohen-Gilbert et al., 2014). Understanding such neurochemical changes could help us better understand the neurobiological effects of substance use, the mechanisms of change, and alterations incurred through psychotherapy or pharmacological treatment.

Overall, it is clear that adolescent alcohol use is associated with neural and cognitive consequences (see Table 1 for summary). Drawing on the most recent longitudinal studies, this review has integrated findings from human neuropsychological, neuroimaging and neurophysiological studies, and the animal literature. Neurobiological research suggests a dose-dependent relationship may occur between alcohol use with brain differences and cognitive deficits. Structural and functional brain changes may initially occur following moderate to heavy alcohol doses, while more overt cognitive deficits may be the result of neural insults from heavy and binge doses. Future longitudinal studies should examine the mediating role of brain structure and function on associations between adolescent alcohol use and cognitive and behavioral consequences. Emerging work has begun to characterize the time-limited and potentially recoverable, versus persisting neural and cognitive effects of alcohol use. Current findings and future research has the potential to significantly improve global health by informing the development of prevention and intervention strategies to address alcohol mechanisms associated with neural and cognitive consequences in adolescence.

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Appendix D

Protocol paper for Chapter 2

Preface

This protocol paper involved a multidisciplinary international team of collaborators and has been published as Lees, B., Mewton, L., Stapinski, L. A., Squeglia, L. M., Rae, C., & Teesson, M. (2018). *BMJ Open,* 8, e023629.

BL conceptualized the study and is the guarantor of the review. BL, LM, and LAS developed the study design and protocol. LMS, CR, and MT provided feedback on the study design and protocol. BL wrote the first draft of the manuscript. All authors read, revised and approved the final manuscript. BL is the corresponding author.

BMJ Open

Binge drinking in young people: protocol for a systematic review of neuropsychological, neurophysiological and neuroimaging studies

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ABSTRACT

Introduction Binge drinking is the most common pattern of alcohol use among young people in Western countries. Adolescence and young adulthood is a vulnerable developmental period and binge drinking during this time has a higher potential for neurotoxicity and interference with ongoing neural and cognitive development. The purpose of this systematic review will be to assess and integrate evidence of the impact of binge drinking on cognition, brain structure and function in youth aged 10–24 years. Cross-sectional studies will synthesise the aberrations associated with binge drinking, while longitudinal studies will distinguish the cognitive and neural antecedents from the cognitive and neural effects that are a consequence of binge drinking.

Methods and analysis A total of five peer-reviewed databases (PubMed, EMBASE, Medline, PsychINFO, ProQuest) will be systematically searched and the search period will include all studies published prior to 1 April 2018. The search terms will be a combination of MeSH keywords that are based on previous relevant reviews. Study selection will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and study quality will be assessed using The Grades of Recommendation, Assessment, Development and Evaluation approach. All studies will be screened against eligibility criteria designed to synthesise studies that examined a young binge drinking sample and used neuropsychological, neurophysiological or neuroimaging assessment techniques. Studies will be excluded if participants were significantly involved in other substances or if they had been clinically diagnosed with an alcohol use disorder, or any psychiatric, neurological or pharmacological condition. If available data permits, a meta-analysis will be conducted.

Ethics and dissemination Formal ethics approval is not required as primary data will not be collected. The results will be disseminated through a peer-reviewed publication, conference presentations and social media.

Trial registration number International Prospective Register for Systematic Reviews (PROSPERO) number: CRD42018086856.

Strengths and limitations of this study

- This systematic review and meta-analysis will be the first to synthesise neuropsychological, neurophysiological and neuroimaging studies examining the developmental impact of binge drinking on cognition, brain structure and function in youth.
- This review will report on cross-sectional and longitudinal data to first identify the cognitive and neural aberrations associated with binge drinking and second to distinguish the antecedents of binge drinking from the effects that may be caused by binge drinking.
- Identified cognitive and neural precursors and consequences of binge drinking will be informative for prevention, early intervention and treatment efforts.
- While studies will be excluded if participants had been clinically diagnosed with an alcohol use disorder, mild alcohol dependence that has not been formally diagnosed may be more prevalent in adolescent binge drinkers, and this may increase the risk of bias in the review towards a binge population that was seeking help or treatment.

INTRODUCTION

Alcohol misuse among young people is widely recognised as a global health priority[1] and has raised concern about the neurotoxic effects of alcohol use on a large scale.[2] Binge drinking is a pattern of alcohol use that brings blood alcohol concentration levels to 0.08 g/dL which typically occurs after the consumption of four or more alcoholic drinks per drinking occasion (ie, at the same time or within a couple of hours of each other) for females and five or more drinks per occasion for males.[3 4] This episodic pattern of drinking, where an individual drinks less frequently but in larger amounts, is most common among adolescents in Western countries.[5–7] For instance, approximately 10%–16% (USA), 23% (UK) and 15% (Australia) of young adults aged 15–17 years report binge drinking in the previous month.[8–10] The prevalence of binge drinking sharply increases from adolescence to young adulthood, with

40%–50% of young adults reporting binge drinking at least monthly.[6 9 11–13] Extreme binge drinking (defined as 10 or more drinks per occasion) is also common, with 29% of young adults in Australia and 16% of US adolescents engaging in this behaviour.[9 14 15] This is concerning because early alcohol use and binge drinking is associated with a myriad of short-term and long-term negative consequences including blackouts, hangovers and alcohol poisoning,[16 17] alcohol and drug use disorders,[18–20] other mental health problems,[21] risky sexual behaviours,[22 23] injuries[24 25] and increased risk of being a victim of assault or accidental death.[26 27]

Studies consistently indicate that alcohol use and misuse during adolescence (10–19 years) and young adulthood (20–24 years) has a higher potential for neurotoxicity and interference with ongoing neural and cognitive development than during later adulthood.[16 25 28–36] This is because adolescence and young adulthood is a vulnerable developmental period characterised by significant neural changes. Although brain size is thought to stabilise around the age of 5 years,[37] important morphometric restructuring and functional neuromaturation continues to occur during adolescence and young adulthood with substantial myelinisation, synaptic refinement and changes in grey and white matter volume until the age of 25 years.[38] The reward and mesolimbic systems mature during mid-adolescence, prior to the development of prefrontal and cognitive control regions which continue to develop into late adolescence.[39–42] This has a twofold effect; first this hypersensitivity to reward during adolescence results in an increased propensity to engage in risky and sensation-seeking activities, including drug and alcohol use.[43] Second, risky drinking during prefrontal brain development may interfere with neuromaturation and translate to ongoing neural aberrations and top-down cognitive processing deficits, reducing youth's ability to enable self-control and resist temptations (inhibition); to see reason, problem solve and consider alternatives (working memory) and to plan and change perspective (cognitive flexibility).[44] Collectively, these changes in cognitive processing may lead to increased motivation to consume alcohol and a decreased ability to regulate this motivation and drinking behaviour. As many of these developmental changes occur in brain regions that appear to be particularly sensitive to alcohol,[45 46] it is critical that research examines the associated negative consequences of risky episodic drinking during a vulnerable developmental period as the neural insults may have ongoing cognitive and behavioural impacts.

The growing concern about alcohol use among young people has led to a significant increase in the number of studies using neuropsychological, neurophysiological and neuroimaging techniques to determine the effects on brain and cognitive development. Over the past decade, there has also been a rise in the number of longitudinal designs that assess young people before they initiate alcohol use and continue to assess them over time as a portion begin to initiate use. These prospective longitudinal studies have made it possible to disentangle the antecedents and consequences of alcohol use in young people. A recent review of longitudinal studies that concentrated on alcohol initiation in adolescence found that reduced grey matter volume (frontal), less white matter volume (cerebellar, nucleus accumbens, anterior cingulate), poor white matter integrity (fronto-limbic), decreased activation during inhibition and working memory tasks and increased reward response (frontal) were antecedents of alcohol use initiation in adolescence.[47] Accelerated decreases in grey matter (frontal, temporal), attenuated white matter development (pons, corpus callosum), poor white mater integrity and increased brain activation during inhibition and working memory tasks were reported consequences following alcohol use initiation. In terms of cognitive domains, poorer inhibitory functioning and working memory were antecedents of alcohol initiation in adolescence while poorer verbal learning and memory, visuospatial functioning, psychomotor speed and working memory were reported effects following alcohol use initiation in adolescence. By distinguishing the antecedents from the consequences of alcohol use initiation, this review provides researchers with specific neural and cognitive domains to target in prevention and treatment efforts.

Considering binge drinking is the dominant pattern of use among young people, it is important to understand the neural and cognitive impact this pattern of drinking has on the developing brain. Several narrative reviews (summarising neuropsychological, neurophysiological and neuroimaging studies[7 17 28 45 48 49]) and one systematic review from 2014 (including only neuroimaging studies[50]) have summarised the recent binge-drinking literature. The systematic review concluded that there were a number of structural changes associated with binge drinking, including smaller grey and white matter volume compared with non-binge drinkers[29 51] and lower white matter integrity across more than 18 white matter regions.[52 53] Functional differences reported in binge drinkers included less activation during a spatial working memory task[54] and abnormal activation during verbal encoding[55] and decision-making tasks.[56] In terms of neuropsychological studies, narrative reviews have concluded that binge drinking is associated with several cognitive deficits, including impairments in verbal, non-verbal and spatial working memory, as well as attention and executive function.[33–35 57] A review of neurophysiological studies found that young binge drinkers displayed latency differences in several event-related potential (ERP) components, including P1, N1, P3, P3b and P450, in response to a number of cognitive functioning tasks.[28] The early positive and negative voltage deflections (P1, N1) reflect initial sensory differences between binge drinkers and non-binge drinkers, while the later components (P3, P3b, P450) reflect differences in the way participants processed the cognitive tasks. Overall, there is a growing evidence base that consistently demonstrates neural and cognitive aberrations associated with binge drinking.

More recently, there has been an increase in the number of prospective longitudinal studies examining the effect of binge drinking among young people. Integrating these new findings is essential to understanding whether the neural and cognitive precursors and consequences of binge drinking are similar or divergent to the domains related to alcohol initiation in adolescence.

The aim of this systematic review is to therefore provide an update on the expanding literature and synthesise the neuropsychological, neurophysiological and neuroimaging literature on binge drinking and neurodevelopment. This review will also address limitations identified in the previous systematic review. The authors of the 2014 systematic review limited their search to one peer-reviewed database, included adolescents aged 10–19 years and included concurrent substance use. Searching a broader range of peer-reviewed databases may identify studies which were potentially missed in the previous review. Expanding the age range to include young people aged 10–24 years aligns with evidence that neuromaturation continues into the mid-20s,[38] as well as the WHO's definition of young people.[58] To examine the specific effect of binge drinking on brain development and functioning, studies should exclude individuals with concurrent regular use of drugs other than alcohol[45 47] as well as exclude samples that characterised drinking based on non-binge, heavy drinking or diagnostic criteria, including alcohol abuse, dependence and alcohol use disorder, due to the heterogeneity of drinking behaviours and related harms.[49] Alcohol use disorder is characterised by continued alcohol use despite clinically significant social and physiological consequences, including substance abuse, affective symptoms and other psychopathology.[59] Therefore, the type, extent and magnitude of the neural and cognitive aberrations associated with alcohol use disorder are likely to differ from those associated with an adolescent, socially functioning binge drinking population. Additionally, no review has systematically integrated neuropsychological, neurophysiological and neuroimaging data. Integrating neuropsychological and neurophysiological studies with neuroimaging research is crucial because cognitive processes make an important contribution to excessive alcohol consumption[57] and assessing this data conjointly will provide a broader understanding of the impact binge drinking has on brain development and behaviour. Finally, previous reviews have not critically appraised the within-study risk of bias or overall quality of the body of literature.

This review will involve conducting a systematic literature search of cross-sectional and longitudinal studies to assess and integrate the evidence regarding the impact of binge drinking on cognition, brain structure and function, utilising neuropsychological, neurophysiological (electroencephalography (EEG), ERP) and neuroimaging (MRI, functional MRI (fMRI), diffusion tensor images (DTI), magnetic resonance spectroscopy (MRS)) studies. If available data permits, a meta-analysis will be conducted to determine the overall effects of binge drinking on the outcomes of interest. By including cross-sectional studies, we aim to synthesise the cognitive and neural aberrations associated with binge drinking in young people. On the other hand, longitudinal studies that track individuals over time will distinguish cognitive and neural antecedents that predict later binge drinking from the cognitive and neural effects that are a consequence of binge drinking during adolescence and young adulthood (see figure 1 for logic model). Due to the limited number of published longitudinal studies at the time of the previous systematic review, this systematic review will be the first to infer causality. The predisposing and consequential factors may not be mutually exclusive and some of the vulnerability factors that predict binge drinking behaviour may also be further impacted by the initiation and continuation of binge drinking. Importantly, identified precursors of binge drinking will be informative for prevention and early intervention efforts. Meanwhile, by identifying consequences of binge drinking, treatment efforts will be able to pursue targeted cognitive and physiological training to determine whether these neural insults have ongoing cognitive and behavioural impacts or whether they can recover following a decrease in alcohol use.

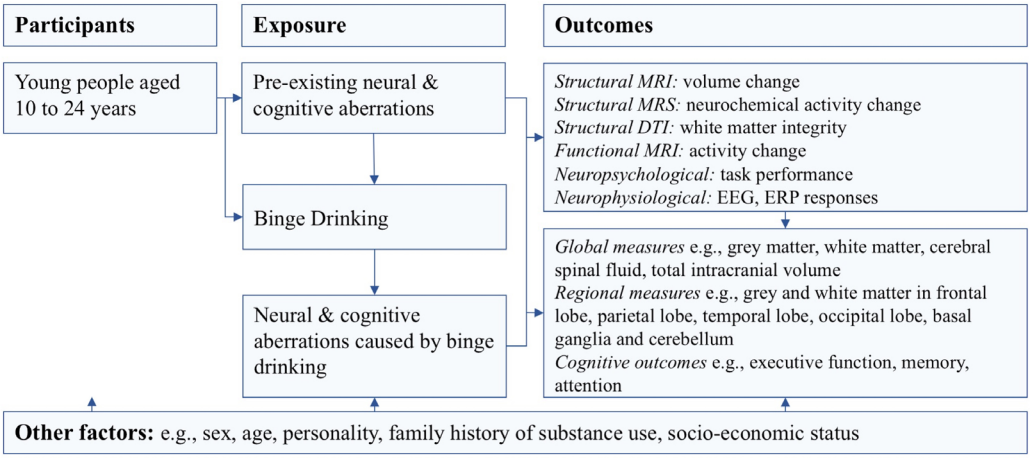

Figure 1 Logic model: antecedents and consequences of binge drinking in adolescents and young adulthood.

OBJECTIVES

1. To assess and integrate evidence of the impact of binge drinking on cognitive, structural and functional development in people aged 10–24 years, compared with healthy controls who do not meet the criteria for binge drinking.
2. To synthesise the cognitive and neural aberrations associated with binge drinking by utilising cross-sectional data.
3. To identify the cognitive, structural and functional features that predispose youth to binge drinking and separate this from the cognitive, structural and functional features that may be a consequence of binge drinking.
4. To examine the within-study risk of bias and assess the quality of the body of evidence examining the relationship between binge drinking and cognitive, structural and functional deficits in adolescents and young adults.

METHODS

This protocol follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement[60] found in the online Supplementary File. This protocol has been registered with the PROSPERO International Prospective Register of Systematic Reviews of the University of York (registration number: CRD42018086856).

Search strategy

Relevant literature from PubMed, EMBASE, Medline, PsycINFO and ProQuest will be systematically searched using a comprehensive search strategy which was developed using medical subject headings (MeSH). The Ovid Medline search strategy is provided in the online Supplementary File, which will be replicated for the other electronic databases. This strategy will search through all relevant literature published from database inception to 1 April 2018. A snowballing technique will be employed where the reference list of identified articles will also be screened for suitable studies.

Search terms will be used to identify neuropsychological, neurophysiological and neuroimaging studies assessing the impact of binge drinking on neurodevelopment and neuropsychological task performance in adolescents and young adults. The search terms will be based on previous reviews examining the association between substance use, cognition, brain structure and function.[16 50 61 62] Search terms will be combinations of MeSH keywords describing the participants (adolescent, teenager, youth, emerging adult, young adult), the exposure variable (alcohol, binge drinking, ethanol) and the assessment methods measuring the outcomes of interest (neuroimaging, brain imaging, MRI, fMRI, DTI, MRS, neurophysiological, EEG, ERP, neuropsychological, cognitive, verbal working memory tests, episodic memory tests, visuospatial working memory tests, verbal fluency tests, executive function tests, digit symbol substitution tests, reaction time, attention). Two reviewers will be involved in independently screening articles, extracting data and assessing the methodological quality.

Box 1 Selection criteria

Inclusion criteria

Population
1. Participants aged 10–24 years at first assessment.
2. Study is available in the English language.
3. n>12 participants per group.
4. Human participants (no animal studies).

Exposure
5. Inclusion of binge drinking sample.

Comparator
6. Inclusion of a control group who do not meet criteria for binge drinking.

Outcomes
7. Use of neuropsychological, neurophysiological, structural or functional imaging techniques.
8. Presentation of main effects.

Study characteristics
9. Peer-reviewed study.
10. Cross-sectional or longitudinal data.
11. Empirical data.
12. Published before 1 April 2018.

Exclusion criteria

Exposure
13. Studies that involved participants who met criteria for alcohol use disorder.
14. Studies that involved participants who were significantly involved with substances other than alcohol.
15. Studies that involved participants who had other clinically diagnosed psychiatric, neurological or pharmacological conditions.

Study characteristics
16. Reviews, information in books or letters.

Eligibility criteria

Eligibility criteria for this review are defined using population, intervention/exposure, comparator, outcome, and study characteristics. Box 1 provides an overview of the selection criteria.

Population

Study samples will be limited by age to human adolescents and young adults ranging from 10–24 years at first assessment, which is consistent with the WHO's definition of young people.[58] Studies that include both a sample of young people and an adult sample (>24 years) will be included if the majority of participants are aged 10–24 years or if a separate analysis for participants within the age range of this review was provided. A minimum of 12 participants per group (binge, comparator) must be included within the study analysis, consistent with a previous review in this area.[50] Finally, studies must be available in the English language to be included in this review.

Exposure

Studies must include a binge drinking sample, where binge drinking is defined as four or more drinks per occasion for females or five or more drinks per occasion for males.[3 4] Consistent with the previous reviews in this area, studies will not be included in this review if samples have ever met diagnostic criteria (eg, alcohol abuse or alcohol use disorder),[49] or if majority of the participants were significantly involved with substances other than alcohol (ie, >5 cannabis use per month, >25 lifetime other drug use occasions[54 63 64]). It is noted that mild alcohol dependence that has not been clinically diagnosed may be more prevalent in adolescent or young adult binge drinkers, and this may result in an increased risk of bias in the review towards a binge-drinking population that was seeking help or treatment compared with binge drinkers who were not. Studies that include participants who smoke tobacco will be included. Participant disclosure of other substance use or a urine sample identifying other substance use will be sufficient to exclude these studies. Studies that included participants who had other clinically diagnosed psychiatric, neurological or pharmacological conditions will also be excluded from this review to ensure that outcomes are specific to binge drinking.

Comparator

Inclusion of a control group is required for studies to be included in this review. Studies must compare participants who meet the criteria for binge drinking with healthy controls who have never consumed alcohol or who have consumed low levels of alcohol but have never met the criteria for binge drinking.

Outcomes

Studies must report empirical data where the primary outcomes of interest are global and regional volume (structural images), global and regional activity (functional images; cerebral blood flow or blood oxygen level dependent signal), white matter integrity (DTI), neurochemical activity (MRS; glutamate, gamma-aminobutyric acid, N-acetylaspartate), brain electrical activity (EEG, ERP responses) and cognitive task performance. Global measures include grey matter, white matter, cerebral spinal fluid and total intracranial volume differences between the active and control group. Regional measures include white matter and grey matter (frontal lobe, parietal lobe, temporal lobe, occipital lobe, basal ganglia and cerebellum) differences between the active and control group. For neuroimaging and neurophysiological studies, detailed results of significant findings will be reported. For neuropsychological studies, significant differences in cognitive task performance between the active and control group will be reported.

Study characteristics

Peer-reviewed cross-sectional and longitudinal neuropsychological, neurophysiological and neuroimaging studies that provide original data and were published before 1 April 2018 will be included. Reviews and information in books or letters will not be included. Any publication that reported data using two or more techniques from the same subject (eg, structural MRI and functional MRI) will be considered separately in the review.

Selection procedure

Two researchers will be involved in the review and selection procedure. Reviewer one (BL) will screen all titles and abstracts from the peer-reviewed databases to determine eligibility for inclusion in the review. Reviewer two (LM) will independently screen a random selection of 25% of abstracts to ensure accuracy in the study selection. Cohen's kappa will be calculated to assess the inter-rater agreement between the two reviewers. To ensure a strong level of agreement, a Cohen's kappa of at least 0.8 is required.[65] Full-text versions of the potentially eligible studies will be assessed by both reviewers to further determine eligibility for inclusion. Again, Cohen's kappa will be calculated at the full-text screening stage. Consultation between reviewers will be held at the time of abstract screening and full-text assessment to reconcile any differences of opinion. If consensus cannot be reached, a third member of the research team (LS) will review the eligibility of the study.

Data extraction

All citations will be imported into Covidence[66] and Endnote.[67] Endnote will be used to store and manage all review data. Covidence will be used to screen titles, abstracts and full texts. Reviewer one will extract data using a data extraction spreadsheet in Excel. Study characteristics will be extracted from published papers, with study authors contacted in the event of missing data. The following information will be extracted from the included studies.

1. *Study information:* names of authors, year of publication, primary outcome measurements, statistical approaches.
2. *Participant characteristics:* sample size, sex, age, handedness, other substance use (ie, tobacco use, cannabis use that is <5 occasions/month).
3. *Alcohol characteristics:* age of onset, frequency of binge drinking, mean quantity of alcohol consumed.
4. *Study characteristics:* imaging modality and analysis, binge drinking sample and control group criteria, cognitive task performed, cognitive and neural domain measured, neurophysiological activity measured, rest/active condition (for functional imaging studies) and exclusion criteria, including the absence of neurological, psychiatric or pharmacological conditions, alcohol use disorder or significant involvement with substances other than alcohol.
5. *Results:* results of outcomes of interest for this review.

Data analysis and quality assessment

A table summarising the results will be produced, including information about imaging modality and

analysis or neuropsychological tests, sample information, alcohol characteristics, and the study findings. For longitudinal studies, pre-existing cognitive, structural and functional features will be separated from cognitive, structural and functional features that are evident as a consequence of binge drinking. If available data permits, a meta-analysis will be conducted using comprehensive meta-analysis. Hedges' g will be calculated to determine the binge drinking between-group standardised mean effect size from outcomes of interest (global and regional volume, white matter integrity, neural activity and cognitive performance). A random-effects model will be adopted as wide variations in participant characteristics and methodological factors are expected between the studies.

In the case of insufficient homogenous data, a narrative synthesis of the main results extracted from the studies will be completed. The studies will be classified according to the study type (ie, neuropsychological task, neurophysiological measurement, structural imaging, functional imaging) and a summary of differences identified in the binge drinking sample compared with the control group will be reported in text.

Following data extraction, the quality of each study will be critically appraised using The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[68] The GRADE system entails an assessment of the quality of a body of evidence for each individual outcome. The GRADE approach defines the quality of the body evidence as the extent to which one can be confident that an estimate of effect or association is close to the quantity of specific interest. This involves considerations of within-study risk of bias (methodological quality of design), directness of evidence, heterogeneity of results, precision of results and the probability of publication bias. Reviewer one will critically appraise all included studies using the GRADE system. Reviewer two will assess the quality of a random selection of 25% of studies to ensure scoring accuracy. Consultation between reviewers will be held to reconcile any differences of opinion.

Patient and public involvement

Patients and the public were not involved in this systematic review protocol.

Ethics and dissemination

Ethical approval is not required for this study. The systematic review will be published in a peer-reviewed journal, presented at conferences and will be shared on social media platforms.

CONCLUSION

This paper summarises the protocol for a systematic review of neuropsychological, neurophysiological and neuroimaging studies conducted in youth who binge drink. The purpose of this review is to assess and integrate the evidence of the developmental impact of binge drinking on cognition, brain structure, and function. Cross-sectional studies will be included in order to synthesise the cognitive and neural aberrations associated with binge drinking in young people. Longitudinal data will be sought to distinguish cognitive and neural antecedents of binge drinking from the cognitive and neural effects that are a consequence of binge drinking during adolescence and young adulthood. This review will be the first to synthesise neuropsychological, neurophysiological and neuroimaging evidence in a systematic way, to include a meta-analysis of the findings, and the first to assess the quality of the body of neuropsychological, neurophysiological and neuroimaging studies. This review aims to provide researchers, policy makers and programme developers with identified antecedents and consequences of binge drinking that will be informative for prevention, early intervention and treatment efforts.

Contributors BL conceptualised the study and is the guarantor of the review. BL, LM and LS developed the study design and protocol. LMS, CR and MT provided feedback on the study design and protocol. BL wrote the first draft of the manuscript. All authors read, revised and approved the final manuscript.

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Competing interests None declared.

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Data sharing statement This paper does not include original data.

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Appendix E

Life course approach to alcohol and brain health

Preface

This study involved a multidisciplinary international team of collaborators and has been published as Mewton, L, Lees, B., & Rao, R.T. (2020). *BMJ,* 371, m4691.

LM and RTR conceptualized the study and LM wrote the manuscript. All co-authors provided feedback to manuscript drafts and approved the final manuscript. LM is the corresponding author.

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Lifetime perspective on alcohol and brain health

Harm prevention policies must take the long view

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The maintenance of brain health is central to health and wellbeing across the lifespan.[1] Evidence suggests three periods of dynamic brain changes that may be particularly sensitive to the neurotoxic effects of alcohol: gestation (from conception to birth), later adolescence (15-19 years), and older adulthood (over 65 years). Highly prevalent patterns of alcohol use may cause harm during these sensitive periods, including low level prenatal alcohol exposure, adolescent binge drinking, and low-to-moderate alcohol use in older adulthood.[2] Although these patterns of alcohol exposure may be associated with less harm to individuals than sustained heavy drinking, the overall burden of harm in populations is likely to be large.

From fetal development to later life, the human brain goes through several periods of dynamic change. The prenatal period is characterised by extensive production, migration, and differentiation of neurons, accompanied by substantial apoptosis.[3] Adolescence is characterised by synaptic pruning and increased axonal myelination.[4] Older adulthood is associated with brain atrophy, which accelerates after the age of 65 years, largely driven by decreases in neuron size and reductions in the number of dendritic spines and synapses.[5] Each of these changes in neurocircuitry could increase sensitivity to the effects of environmental exposures such as alcohol.[6]

From cradle to grave

Globally, around 10% of pregnant women consume alcohol, with the rates considerably higher in European countries than the global average.[7] Heavy alcohol use during pregnancy can cause fetal alcohol spectrum disorder, associated with widespread reductions in brain volume and cognitive impairment. But recent evidence indicates that even low or moderate alcohol consumption during pregnancy is significantlyassociated with poorer psychological and behavioural outcomes in offspring, partially mediated by aberrant brain structure.[8]

More than 20% of 15-19 year olds in European and other high income countries report at least occasional binge drinking (defined as 60 g of ethanol in a single drinking occasion).[9] Longitudinal studies indicate that the transition to binge drinking in adolescence is associated with reduced neocortical volume and functional connectivity, attenuated white matter development, and small to moderate deficits in a wide range of cognitive functions.[4 10] In older people, alcohol use disorders were recently shown to be one of the strongest modifiable risk factors for all types of dementia (particularly early onset) compared with other established risk factors such as hypertension and smoking.[11]

Although alcohol use disorders are relatively rare in older adults, many older people frequently consume low to moderate amounts of alcohol.[12] Recently, even moderate drinking was shown to be associated with small but significant loss of brain volume in midlife,[13] supporting previous research indicating an association between low risk drinking and brain damage in older adults.[2] However, it is currently unclear whether these structural changes translate into functional cognitive impairment.

The evidence for the adverse effects of alcohol on brain health is compelling, but it is limited by the observational nature of the analyses. These findings require further replication, with a focus on more rigorous causal modelling.

Demographic trends

Demographic trends may compound the effect of alcohol use on brain health. Women are now just as likely as men to drink alcohol and experience alcohol related harms.[14] In higher income countries, consumption has increased among older people[15] while in low and middle income countries, consumption and related harms have increased across the population. Global consumption is forecast to rise further in the next decade.[16] The effects of the covid-19 pandemic on alcohol use and related harms are unclear, but alcohol use increased in the long term after other major public health crises.[16]

A lifecourse perspective on brain health supports the formulation of policy and public health interventions to reduce alcohol use and misuse at all ages. This could increase longevity and quality of life by reducing the prevalence of fetal alcohol spectrum disorders, aberrant neurocognitive development in adolescence, and dementia in later life. An integrated approach to harm reduction across the lifespan is required in public health, mental health, primary care, social care, and voluntary sectors.[17]

Population based interventions such as guidelines on low risk drinking, alcohol pricing policies, and lower drink driving limits need to be accompanied by the development of training and care pathways that consider the human brain at risk throughout life. The effect of harm reduction strategies on maintaining brain health in both individuals and populations can then be more fully evaluated.

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Appendix 1

Supplementary materials for Chapter 1

Table 1. Cross-sectional and longitudinal studies examining cognitive differences between youth with and without family histories of alcohol use disorders.

						Outcomes													Covariates/Matched				
	N	Age	Study length (years)	Familial AUD/SUD	Substance-naïve?	Working memory	Set shifting	Inhibition	Impulse control	Delay discounting	Plan/problem solve	Memory	Attention	Learning	Motor function	Visuospatial	Language	Intellectual function	Sociodemographic	Emotion/behaviour	Substance use	IQ	Prenatal exposure
Lovallo et al. (2006)	350	18-30	0	A	×			↓											x				
Acheson et al. (2011b)	298	24	0	A/S	×					↑									x			x	x
Saunders et al. (2008)	230	18-30	0	A	×				↓														
Nigg et al. (2004)	198	3	11	A	×	-		↓									-						
Henderson et al. (2018)	188	13-18	0	A	✓	↓			↓														
Ozkaragoz et al. (1997)	184	10-14	0	A	✓							↓	↓			↓		↓	x			x	
Gierski et al. (2012)	155	18-59	0	A	×	↓	↓			↑			↓						x				
Tapert and Brown (2000)	151	13-18	0	A	×							-	↓			-	↓		x	x			
Squeglia et al (2014a)	94	12-14	0	A	✓			-			-	-	-	-		-			x			x	
Tarter et al. (1989)	92	8-17	0	A	×			↓	↓		↓		↓		↓	↓		-	x				
Acheson et al. (2011a)	72	21-35	0	A	×				↓				-		-				x				
Hill et al. (2001)	34	17.5	7	A/S	×						↓					↓	↓		x			x	
Herting et al. (2010)	33	11-15	0	A	✓					↑													
Harden & Pihl (1995)	28	8-15	0	A	×	↓			-			-	↓	↓				-	x			x	x
Corral et al. (2003)	22	11-17	3	A	×	↓				↑							-	↓	x				

A = alcohol use disorder history, AUD = alcohol use disorder, S = substance use disorder history, SUD = substance use disorder history, - = non-significant finding. Age = age at first assessment. Cross-sectional studies have a study length of 0. The covariates/matched section includes variables that groups were matched on or variables included as covariates in statistical models.

Appendix 2

Supplementary materials for Chapter 2

Table 5: Selection criteria

Inclusion Criteria
Population
1 Participants aged 10-24 years at first assessment
2 Study is available in the English language
3 N > 12 participants per group
4 Human participants (no animal studies)
Exposure
5 Inclusion of binge drinking sample
Comparator
6 Inclusion of a control group who do not meet criteria for binge drinking
Outcomes
7 Use of neuroimaging, neurophysiological or neuropsychological techniques
8 Presentation of main effects
Study characteristics
9 Peer-reviewed study
10 Cross-sectional or longitudinal data
11 Empirical data
12 Published before 1 April 2018
Exclusion Criteria
Exposure
13 Studies that involved participants who met criteria for alcohol use disorder
14 Studies that involved participants who were significantly involved with substances other than alcohol
15 Studies that involved participants who had other clinically diagnosed psychiatric, neurological or pharmacological conditions
Study characteristics
16 Reviews, information in books, letters

Table 6: Search strategy for Medline.

Search	**Terms**
1.	(alcohol OR binge OR binge drink* OR ethanol).mp
2.	(neuroimage* OR brain OR brain imag* OR magnetic resonance OR functional magnetic resonance OR diffusion tensor imag* OR MRI OR fMRI OR DTI OR MRS OR neuropsycholog* OR neurophysiolog* OR electrophysiolog* OR EEG OR ERP OR cogniti* OR verbal working memory OR episodic memory OR visuospatial working memory OR verbal fluency OR executive function OR digit symbol substitution OR reaction time OR attention).mp.
3.	(adol* OR youth OR emerging adult OR young adult OR teen*).mp.
5.	Limit 1-3 to human
6.	Limit 1-4 to English language
7.	Limit 1-5 to "Article" [Publication Type]
[mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms].	

This search strategy was repeated for each database.

Meta-analysis methods

Meta-analysis data presented in this study and a corresponding data dictionary are available on the Open Science Foundation website (https://osf.io/nx9cv/).

Data Extraction

The following information was extracted from the included studies:

1. *Study information:* names of authors, year of publication, primary outcome measurements, statistical approaches;
2. *Participant characteristics:* sample size, sex, age, handedness, other substance use (i.e., tobacco use, cannabis use that is <5 occasions/month);
3. *Alcohol characteristics:* age of onset, frequency of binge drinking, mean quantity of alcohol consumed;
4. *Study characteristics:* imaging modality and analysis, binge drinking sample and control group criteria, cognitive task performed, cognitive and neural domain measured, neurophysiological activity measured, rest/active condition (for functional imaging studies), and exclusion criteria, including absence of neurological, psychiatric, or pharmacological conditions, alcohol use disorder or significant involvement with substances other than alcohol; and
5. *Results:* results of outcomes of interest for this review.

Effect size calculation

The standardised mean difference statistic (d) was used as the measure of effect size, which was calculated in Comprehensive Meta-Analysis as $d = \frac{M_{BD} - M_C}{S_p}$, where M_{BD} and M_C are the mean scores on a neuropsychological test for the binge drinking and comparison groups, respectively, and S_p is the pooled within-group standard deviation, $S_p = \sqrt{\frac{(n_1-1)S_1^2 + \cdots + (n_k-1)S_k^2}{n_1 + \cdots + n_k - k}}$, where n is the sample size of each group and s is the standard deviation of each group (Cohen, 1988). The Hedges correction for small sample bias was applied (Hedges, 1985). For studies in which mean scores and standard deviations were not reported, authors were contacted and asked to provide this information. When authors could not be reached (no email reply after one-month), effect sizes were derived from figures. Numerical values were extracted from figures using WebPlotDigitizer version 4.1 (https://automeris.io/WebPlotDigitizer/), as per the protocol of a previous meta-analysis examining cannabis use and neuropsychological function (Scott et al., 2018). By convention, d values of 0.2, 0.5, and 0.8 correspond to small, medium, and large effect sizes, respectively (Cohen, 1988), although it should be noted that these categorisations are broad. In this meta-analysis, IQ was not examined as an outcome since many studies used a measurement of IQ or IQ estimate to match groups, which would bias effect sizes.

Analysis of Bias

To examine potential small study bias in the literature, funnel plot tests and exploratory analyses were conducted. These procedures include visual inspection of the funnel plot, the method of Egger and colleagues (Egger et al., 1997) to test for small study effects, and the trim-and-fill method of Duval and Tweedie (Duval and Tweedie, 2000) to fill potentially missing effect sizes. Significant funnel plot asymmetry was interpreted as potentially indicative of publication bias across the literature. This asymmetry often occurs when smaller studies with low precision and null or unexpected effects are systematically missing from the published literature. The trim-and-fill method is a sensitivity analysis that estimates the number of potentially missing effect sizes and examines the effects of imputing the missing effect sizes. The change in effect size and the number of filled effect sizes generated from this analysis provides an indication of analysis of bias across the literature. Both the funnel plot tests and the trim-and-fill method were conducted in Comprehensive Meta-Analysis.

Appendix Results

Publication bias

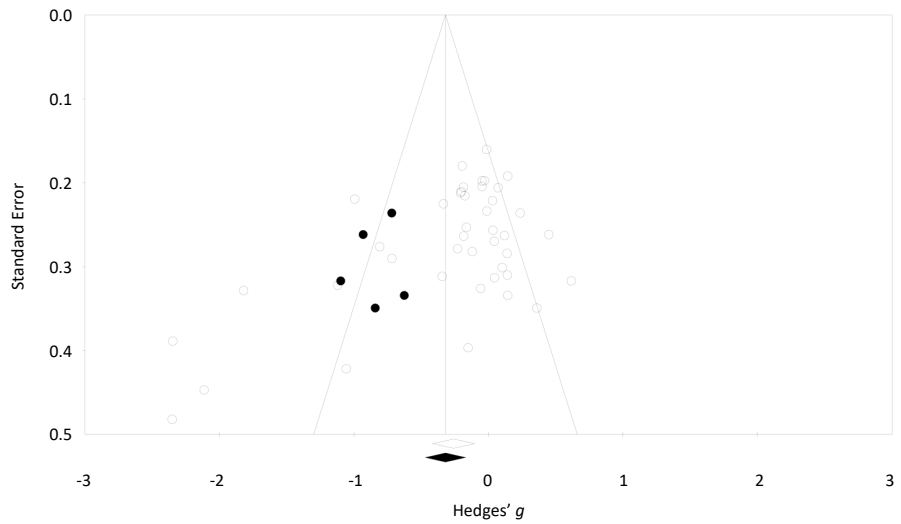


Figure 2: Funnel plot of the meta-analysis with imputed effect sizes.

The funnel plot is a measure of study size on the vertical axis as a function of effect size on the horizontal axis. There is a higher concentration of studies on the right hand-side of the mean. This reflects the fact that more studies have been published with positive effect sizes. The trim and fill method uses an interactive procedure to 'trim'/remove the most extreme small studies from the positive side of the funnel plot, recomputing the effect size at each iteration, until the funnel plot is symmetric around the new, adjusted effect size. The 'trimmed' studies are then added to the analysis and an imputed mirror effect size is computer to 'fill' and correct the adjusted variance (Duval and Tweedie, 1998, 2000a, 2000b). Five studies were imputed.

Table 7: Cognitive tasks included in meta-analysis.

Cognitive Domain		
Processing Speed		
Test	**N**	**%**
Go/No-Go: Reaction Time	5	22.7
D-KEFS Trail Making Test: Number Sequencing	4	19.4
Stroop Test: Number Of Colours Named	4	19.4
Visual Oddball Task: Reaction Time	2	9.1
WAIS-III Digit Symbol	2	9.1
Beer Go/No-Go: Go Reaction Time	1	4.5
CANTAB Matching To Sample Visual Search: Choice Time	1	4.5
CANTAB Simple Reaction Time: Movement Time	1	4.5
Continuous Performance Test: Reaction Time	1	4.5
N-Back: Control Condition Reaction Time	1	4.5
Total	**22**	**100**
Sustained Attention		
Test	**N**	**%**
Go/No-Go: Correct Responses	4	30.1
Digit Vigilance Test	2	15.4
Go/No-Go: Go Hit Rate	2	15.4
Visual Oddball Task: Correct Responses	2	15.4
Continuous Performance Test: Correct Responses	1	7.7
Beer Go/No-Go: No-Go Hit Rate	1	7.7
N-Back Control Condition Performance	1	7.7
Total	**13**	**100**
Decision-Making		
Test	**N**	**%**
Iowa Gambling Task: Net Score	5	55.6
Balloon Analogue Task: Risk Total Score	1	11.1
Beads Task: Number Of Beads Drawn	1	11.1
Information Sampling Task	1	11.1
Two-Choice Task	1	11.1
Total	**9**	**100**
Inhibition		
Test	**N**	**%**
Go/No-Go: Correct Inhibition	5	26.3
Stroop Test: Interference Index	4	21.1
D-KEFS Colour Word Interference Time	3	15.8
Go/No-Go: Commission Errors	2	10.5
Beer Go/No-Go: D’	1	5.3
Go/No-Go: D’	1	5.3
Gordon Diagnostic System Vigilance Task: Commission Errors	1	5.3
Stop Signal Task: Latency of Stop Process	1	5.3
Stop Task: Reaction Time	1	5.3
Total	**19**	**100**
Mental Flexibility		
Test	**N**	**%**
D-KEFS Trail Making Test: Number Letter Switching	5	33.3
D-KEFS Towers Total Achievement Score	3	20.0
CANTAB Intradimensional Extradimensional Shift Task: Compound Discrimination Number Of Errors	1	6.7
CANTAB Intradimensional Extradimensional Shift Task: Total Adjusted Errors	1	6.7
D-KEFS Trail Making Test: B-A Score	1	6.7
RAVLT Perseveration Errors	1	6.7
Reversal-Learning Task: Contingency Learning Stage Accuracy	1	6.7
TAVEC Perseveration Errors	1	6.7
Wisconsin Card Sorting Task-III % Perseverations	1	6.7
Total	**15**	**100**

Planning		
Test	**N**	**%**
Spatial Working Memory Strategy Task	1	50
Stockings of Cambridge	1	50
Total	**2**	**100**
Working Memory		
Test	**N**	**%**
Digits Backward (WMS-III, WMS-II, WAIS-III)	10	24.4
Self-Ordered Pointing Test	5	12.2
Spatial Span Backwards (WMS-III, WMS-II, WAIS-III)	4	9.8
CANTAB Spatial Working Memory Task: Errors	3	7.3
Spatial Span Forwards	3	7.3
BADS Key Search Task	2	4.9
Concentration Memory Task	1	2.4
Corsi Blocks	1	2.4
D-KEFS Trail Making Test: Number Letter Sequencing	3	2.4
BADS Zoo Map Task: Composite Score	1	2.4
BADS Zoo Map Task: Raw Score	1	2.4
Hanoi-T	1	2.4
N-Back N1 Performance	1	2.4
Operation Span Task	1	2.4
RAVLT Proactive Interference	1	2.4
Spatial Location Backwards Task	1	2.4
Visual Working Memory Task: Accuracy	1	2.4
Working Memory Task (WMS-III)	1	2.4
Total	**41**	**100**
Behavioural Inhibition Only		
Test	**N**	**%**
Continuous Performance Task: False Alarms	1	50.0
Four-Choice Serial Reaction Time Task	1	50.0
Total	**2**	**100**
Delay Discounting		
Test	**N**	**%**
Delay Discounting Task	2	100.0
Total	**2**	**100**
Expressive Language		
Test	**N**	**%**
Verbal Fluency: Phonetic Fluency	3	50.0
Verbal Fluency: Semantic Fluency	3	50.0
Total	**6**	**100**
Receptive Language		
Test	**N**	**%**
WRAT-3 Reading Score	2	100.0
Total	**2**	**100**
Immediate Memory		
Test	**N**	**%**
Digits Forward (WAIS-III)	8	61.5
RAVLT List 1 To 5	3	23.1
TAVEC Immediate Recall	1	7.7
CVLT List A Total 1 To 5	1	7.7
Total	**13**	**100**
Long-Term Memory		
Test	**N**	**%**
Logical Memory Retention (WMS-III)	4	21.1
Complex Figure Delay Accuracy	3	15.8
Family Pictures Retention (WMS-III)	3	15.8

RAVLT Task A VII	3	15.8
Delayed Line Recall	2	10.5
CVLT Long Delay Free Recall	1	5.3
Delayed Word Recall	1	5.3
Prospective Remembering Video Procedure	1	5.3
TAVEC Long-Term Recall	1	5.3
Total	**19**	**100**
Recent Memory		
Test	**N**	**%**
Logical Memory I (WMS-III)	3	23.1
RAVLT Task VI	3	23.1
Visual Face Name Memory Task	2	15.4
Benton Visual Retention Test: Immediate	1	7.7
Family Pictures I (WMS-III)	1	7.7
Immediate Visual Memory (WMS-III)	1	7.7
Paired Associates Learning: Number Of Errors	1	7.7
TAVEC Short-Term Recall	1	7.7
Total	**13**	**100**
Visual Perception		
Test	**N**	**%**
CANTAB Delayed Match To Sample: Pattern Recognition	1	25.0
CANTAB Delayed Match To Sample: Spatial Recognition	1	25.0
Mental Rotation	1	25.0
Visual Oddball Face Detection: Composite Score	1	25.0
Total	**4**	**100**
Visuoconstructional		
Test	**N**	**%**
Complex Figure Copy Accuracy	3	50.0
WAIS-III Block Design: T-Score	3	50.0
Total	**6**	**100**
Recognition of Emotions		
Test	**N**	**%**
Affective Two-Alternative Forced Choice Task	1	100.0
Total	**6**	**100**
Overall	**186**	**-**

% = percent of studies within each domain that included the neuropsychological test in the primary source; n = number of studies; BADS: Behavioural Assessment of the Dysexecutive Syndrome; CANTAB: Cambridge Neuropsychological Test Automated Battery; CVLT: California Verbal Learning Test; D-KEFS: Delis-Kaplan Executive Functioning System; RAVLT: Rey Auditory Verbal Learning Test; TAVEC: Spanish version of the CVLT; WAIS: Wechsler Adult Intelligence Test; WMS: Wechsler Memory Scale; WRAT: Wide Range Achievement Test.

Table 8: Summary of findings for neuroimaging studies (n=21).

Source	Binge Comparison[1]		ROI [Cognitive Domain]	Results[+]
	n M:F	Age		
MRI				
Brumback et al. 2016[LA]	127 138	13.6	FC, OFC, DLPFC, ACC, IC, PC	T1 *Corr (SA):* ↓ R DLPFC = ↑ BD*
Kvamme et al. 2016	18:12 23:23	21.3 21.3	Ventral striatum	*BD vs C* ↓ *M*, ↑ *F (vol)*: PFC, striatum, R fusiform gyrus, motor preparatory regions, somatosensory cortex, L mid-TC* *Corr (vol):* ↑ AUDIT = ↓ R superior FC**, ↓ L paracentral**
Mashhoon et al. 2014	12:11 16:15	22.0 21.5	ACC, PCC, POS	*BD vs C (CT):* ↓ R mid-ACC*, L dorsal PCC** *Corr (CT):* ↑ UPW = ↓ mid-ACC**
Lisdahl et al. 2013	31:15 35:25	18.0 17.7	Cerebellar	*Corr (vol):* ↑ peak BD = ↓ L hemisphere white*, ↓ L hemisphere grey*, ↓ R hemisphere grey**
Pfefferbaum et al. 2016	113 674	12.0- 21.9	FC, PC, OC, CC	*Corr (CT):* ↑ drinks = ↓ PC*, ↓ FC*
Pfefferbaum et al. 2018[LA]	61:66 180:176	15.5 15.5	FC, TC, PC, OC, CC, Insular, total neocortex, central white matter, pons, corpus callosum	*T2 BD vs C (grey vol):* ↓ FC**, ↓ causal middle frontal*, ↓ superior FC*, ↓ PCC*
Squeglia et al. 2012	15:14 15:15	18.2 18.0	FC	*BD vs C M (CT):* ↓ L pars orbitalis*, ↓ L medial orbital frontal gyrus*, ↓ L rostral ACC* *BD vs C F (CT):* ↑ L frontal pole** *Corr BD F (CT):* ↑ L pars orbitalis = ↓ visuospatial*; ↑ L frontal pole = ↓ inhibition*, ↓ attention* *Corr BD M (CT):* ↑ rostral ACC = ↓ attention**
Squeglia et al. 2014[LA]	12:8 13:7	15.1 14.9	Whole brain	T1 *BD vs C (vol):* ↓ R rostral ACC*, ↓ R caudal ACC*, ↓ R pars triangularis*, ↓ L isthmus cingulate*, ↓ R cerebellar white* T2 *BD vs C (vol):* ↓ L ventral diencephalon*, ↓ L inferior temporal gyrus*, ↓ L mid-temporal gyrus*, ↓ L caudate*, ↓ brain stem* T2 *Corr (vol):* ↑ lifetime alcohol use occasions = ↓ L caudate*, brain stem*
Squeglia et al. 2015[LA]	45:30 31:28	15.7 13.7	Grey: neocortex, lobar regions, allocortex. White: pons, corpus callosum, central	T2 *BD vs C (vol):* ↓ total neocortex*, ↓ FC*, ↓ lateral FC*, ↓ TC***, ↓ pons***, ↓ corpus callosum*** *BD vs C F (vol):* ↓ total neocortex*, ↓ lateral FC*, ↓ pons*, ↓ corpus callosum** *BD vs C M (vol):* ↓ TC**, ↓ pons**, ↓ corpus callosum**
DTI (FA)				
McQueeny et al. 2009	12:2 12:2	18.1 18.0	Whole brain	*BD vs C:* ↓ L R anterior coronal radiata**, ↓ corpus callosum (body, genu)**, ↓ L posterior limb of internal capsule**, ↓ L R external capsule**, ↓ L fornix/stria terminalis**, ↓ inferior & superior cerebellar peduncle**, ↓ L posterior coronal radiata**, ↓ L R superior longitudinal fasciculus**, ↓ L inferior longitudinal fasciculus** *Corr:* ↑ Lifetime hangover experiences = ↓ corpus callosum
MRS (voxel content, GABA, NAA/cr, Glu/cr)				
Silveri et al. 2014	10:11 14:13	21.9 21.6	ACC, POS	*BD vs C (voxel content):* ↓ ACC grey*, ↑ ACC white* *BD vs C (GABA):* ↓ ACC* *BD vs C (NAA/cr)* ↓ ACC* *Black out vs no black out BD (voxel content):* ↓ ACC grey*, ↑ ACC white*, ↓ POS*; *(GABA):* ↓ ACC*; *(Glu/cr):* ↓ ACC*; *(NAA/cr):* ↓ ACC* *Corr (GABA BD):* ↓ ACC = ↑ YAACQ*, ↓ abstraction***, ↓ inhibition*; ↓ POS = ↑ YAACQ*
fMRI (BOLD)				
Ames et al. 2014a	9:8 5:14	20.2 20.8	Whole brain [WM]	*BD vs C:* ns dorsal striatum, insula, OFC
Ames et al. 2014b	10:11 7:13	20.2 20.8	Whole brain [inhibition, processing speed]	*BD vs C:* ↑ R DLPFC***, ↑ ACC/ mid-ACC***; ↑ R anterior insula (exposure to beer cues during no-go)***
Banca et al. 2016	17:13 17:13	22.2 21.9	Whole brain [delay discounting, DM]	*BD vs C:* ns cerebellum, DLPFC, inferior PC, thalamus
Brumback et al. 2015[LB]	10:12 9:7	17.9 17.4	NA, ACC, DSGP, OFC, DLPFC [alcohol cue reactivity]	T1 *BD vs C:* ↑ dorsal striatum, globus pallidus bilaterally*, ↑ L ACC* (cue reactivity); ↑ L R cerebellum*, ↑ L parahippocampal gyrus* (alcohol vs non-alcohol pictures) T2 *ex-BD vs C:* ns DSGP, L ACC, R cerebellum T2 *Corr BD:* ↑ alcohol cravings = ↑ L ACC (alcohol pictures)*
Campanella et al. 2013	7:9 7:9	20.9 21.6	Whole brain	*BD vs C:* ↑ L R pre-supplementary motor area (WM)***

			[immediate memory, processing speed, sustained attention, WM]	*Corr BD:* ↑ drinks per occasion = ↑ L frontal superior medial DMPFC (WM)***; ↑ drinking occasions per week = ↑ L R cerebellum***, R thalamus***, R insula*** (WM)
Maurage et al. 2013	7:5 7:5	24.2 23.4	Whole brain [social cognition]	*BD vs C:* ↑ R mid-frontal gyrus*, ↓ bilateral superior temporal gyri (L*, R***)
Squeglia et al. 2011	27:13 31:24	18.0 17.9	ROI: Bilateral superior frontal, R inferior frontal, bilateral ACC, R superior parietal lobule, whole brain [immediate & long term memory, receptive language, visuoconstructional, WM]	ROI analysis *BD vs C:* ↓ R superior frontal gyrus*, R inferior frontal gyrus* (spatial WM vs attention) *BD vs C F:* ↓ ACC*, ↓ R inferior frontal gyrus*, ↓ R dorsal*, ↓ R anterior superior frontal gyri* (spatial WM) *BD vs C M:* ↑ ACC*, ↑ R inferior frontal gyrus*, ↑ R dorsal*, ↑ R anterior superior frontal gyri* (spatial WM) Whole brain *BD vs C F:* ↓ L medial frontal*, ↓ R mid-temporal*, ↓ L superior temporal gyri*, ↓ L cerebellar declive* (spatial WM vs attention); ↓ R dorsal superior frontal**, ↓ R anterior superior frontal**, ↓ R inferior frontal**, ↓ ACC**, ↓ L medial frontal**, ↓ R mid-temporal**, ↓ L superior temporal**, ↓ L declive** (spatial WM) *BD vs C M:* ↑ L medial frontal*, ↑ R mid-temporal*, ↑ L superior temporal gyri*, ↑ L cerebellar declive* (SWM vs vigilance); ↑ L medial frontal*, R mid-temporal*, ↑ L superior temporal*, ↑ L declive* (spatial WM) *Corr F BD:* ↓ Attention (vigilance completion) = ↓ R dorsal superior frontal gyrus (spatial WM)*; ↓ WM (digit backward performance) = ↓ L declive* *Corr M BD:* ↑ Visuospatial (complex figure copy accuracy, block design) = ↑ R inferior frontal gyrus*
Squeglia et al. 2012b E1	20 20	17.6 17.6	Whole brain [WM]	*BD vs C:* ↑ L medial frontal gyrus/supplementary motor area*, ↑ R mid- superior frontal gyrus*, ↑ R superior frontal gyrus*, ↑ R inferior parietal/supramarginal gyrus*
Squeglia et al. 2012b E2[LA]	14:7 14:7	15.1 14.8	FC, PC, OC [WM]	T1 *BD transitioner vs C:* ↓ R inferior parietal lobule**, ↓ L medial frontal gyrus** T1 *Corr:* ↓ L medial frontal = ↑ subsequent peak drinks***, ↑ drinking days**, ↑ drinks consumed in month before T2*; ↓ R inferior parietal lobule = ↑ peak drinks in year preceding T2*** T2 *BD transitioner vs C:* ns R inferior parietal lobule, L medial frontal gyrus T2 *Corr:* ↓ Past-year drinks/occasion = ↑ medial frontal gyrus (T1 → T2)*, ↑ inferior parietal lobule*; ↑ past month drinking days = ↑ medial frontal gyrus (T1 → T2)*; ↑ withdrawal/ hangover symptoms = ↑ medial frontal gyrus (T1 → T2)**
Wetherill et al. 2013[LA]	11:9 11:9	14.7 14.1	Whole brain [inhibition]	T1 *BD vs C:* ↓ bilateral mid-frontal gyri*, ↓R inferior parietal lobule*, ↓ L putamen*, ↓ L cerebellar tonsil* (inhibition) T2 *BD vs C:* ↑ bilateral mid-frontal gyri*, ↑ R inferior parietal lobule*, ↑ L cerebellar tonsil* (inhibition) *Corr:* ↑ Lifetime number of drinks = ↑ BOLD contrast R mid-frontal gyrus (attention vs inhibition, T1 → T2)***
Xiao et al. 2013	8:6 5:11	17.3 17.1	Whole brain [DM]	*BD vs C:* ↑ L amygdala*, L R insula* *Corr BD:* ↑ Drinking problems = ↓ R OFC***, ↑ R insula***

[LA] Longitudinal study, baseline = all participants are abstinent/no binge; [LB] Longitudinal study, baseline = meet binge criteria. * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

[+] The results are presented in terms of differences identified in the binge drinking sample compared to the non-binge drinking sample.

[1] For sample size and age, binge participants are presented on first line followed by non-binge participants on the following line. Data is provided for the first time point when binge drinking participants are compared to non-binge participants (i.e. for longitudinal studies, this may be at baseline or at follow up).

ACC: anterior cingulate cortex; BD: binge drink; BOLD: blood-oxygen-level dependent; C: control participants; CC: cingulate cortex; Corr: correlation; CT: cortical thickness; DGSP: dorsal striatum and globus pallidus; DLPFC: dorsolateral prefrontal cortex; DM: decision-making; F: female; FA: fractional anisotropy; FC: frontal cortex; GABA: gamma-Aminobutyric acid; Glu/Cr: glutamate/creatine; IC: insular cortex; L: left; M: male; NA: nucleus accumbens; NAA/Cr: N-acetyl aspartate/creatine; ns: non-significant; OC: occipital cortex; OFC: orbitofrontal cortex; PC: parietal cortex; PCC: posterior cingulate cortex; PFC: prefrontal cortex; POS: parieto-occipital sulcus; R: right; ROI: region of interest; SA: surface area; T1: baseline; T2: follow-up; TC: temporal cortex; UPW: units per week; vol: volume; WM: working memory; YAACQ: Young Adult Alcohol Consequences Questionnaire.

Table 9: Summary of findings for neurophysiological studies (n=16).

Source	Binge Comparison		Band/Component [Cognitive Domain]	Results[+]
	n M:F	Age[1]		
MEG				
Correas et al. 2015	17:18 21:17	18.0 18.0	Delta, theta, alpha, beta	*BD vs C:* ↑ theta power in occipital cluster*, ↓ alpha power in temporal-occipital cluster*, ↑ delta functional connectivity R frontal – R temporal**, ↑ theta functional connectivity mid frontal – mid parietal*, ↑ beta functional connectivity R frontal – R temporal***, ↓ alpha functional connectivity L frontal – L temporal** *Corr BD:* ↑ BAC value = ↓ alpha functional connectivity L frontal – L temporal***
EEG				
Courtney et al. 2010	32:32 16:16	20.4 21.1	Delta, theta, alpha, beta	↑ *BD vs* ↓ *BD:* ↑ delta** *BD vs C:* ↑ mean spectral power*
Lopez-Caneda et al. 2017a	20:20 21:19	18.1 18.1	Delta, theta, alpha, beta	*BD vs C:* ↑ beta density (eyes open, resting) in R parahippocampal gyrus, fusiform gyri; ↑ theta density (eyes closed) in cuneus, lingual gyrus
ERP				
Crego et al. 2009	21:21 27:26	18.9 18.7	Whole brain, PCA, P3, N2 [behavioural inhibition, processing speed, sustained attention]	*BD vs C:* ↑ N2 central*, PC** (attention); P3 ns
Crego et al. 2010	21:21 27:26	18.9 18.7	Whole brain, eLORETA [processing speed, sustained attention]	*BD vs C:* ↓ LPC FC*, central* (attention); ↓ activation R anterior PFC* (attention)
Crego et al. 2012	17:15 28:25	18.8 18.5	Whole brain, P3b, N2, eLORETA [processing speed, sustained attention]	*BD vs C:* ↑ P3b amplitude FC***, Cz***, PC**; N2 ns
Folgueira-Ares et al. 2017[LB]	14:11 13:12	20.8 20.5	VPP [recent memory]	*BD vs C:* 350-500ms ↓ difference due to memory (DM effect) at centroparietal, parieto-occipital (correct vs incorrect memory)*; ↑ VPP amplitude at C3*, Cz*
Lannoy et al. 2017	8:12 7:13	20.3 21.2	ERN, Pe, CRN [DM, inhibition, processing speed, sustained attention]	*Go/No-go BD vs C:* ↑ ERN amplitude Fz (inhibition vs attention)*; delayed Pe latency Cz (attention)* *Balloon analogue task BD vs C:* ns (abstraction)
Lopez-Caneda et al. 2012[LB]	13:10 11:14	18.8 18.6	P3,N2, eLORETA [complex attention, inhibition, processing speed]	*BD vs C:* ↑ P3 Cz*, PC* (attention, T1, T2); ↑ P3 FC***, Cz***, PC** (inhibition, T2); ↑ activation R inferior PFC, insula (inhibition)
Lopez-Caneda et al. 2013[LB]	15:11 15:16	18.8 18.5	P1, N1, N2, P3 [processing speed, sustained attention]	*BD vs C:* ↑ P3b amplitude PC*(T1), Cz*(T2), PC***(T2) *Corr:* ↓ age of onset = ↑ P3b amplitude PC (T1*, 2**); ↑ alcohol quantity = ↑ P3b amplitude PC**; ↑ alcohol intensity of consumption = ↑ P3b amplitude PC*
Lopez-Caneda et al. 2014[LB]	11:11 X 3:7 11:14	18-19	N2, P3 [inhibition, processing speed, sustained attention]	*BD vs C:* ↑ P3 amplitude FC*, Cz*, PC* (inhibition, T2); ↑ P3 amplitude (attention)* *Corr:* ↓ age of onset = ↑ P3 amplitude FC (inhibition, T2*); ↑ speed of consumption = ↑ P3 amplitude (inhibition, T2)*; ↑ weekly quantity of alcohol consumed = ↑ P3 amplitude (inhibition, T2)**; ↓ age of onset + ↑ speed of consumption = ↑ P3 amplitude FC (inhibition, T2)
Lopez-Caneda et al. 2017b	17:19 20:16	18.1 18.1	P3 [inhibition, processing speed, sustained attention]	*BD vs C:* ↓ delta, theta at Cz*, Pz* (overall); ↓ delta, theta at Fz**, Pz** (inhibition)
Maurage et al. 2009[LA]	7:11 7:11	18.2 18.2	P1, N2, P3 [auditory]	*BD vs C:* ↑ P1 latency***, N2 latency***, P3b latency** (T2) *Corr:* ↑ mean alcohol intake = ↑ P1 latency*; ↑ mean alcohol intake = ↑ N2 latency **; ↑ mean alcohol intake = ↑ P3b latency**
Maurage et al. 2012	22:18 11:9	21.1 21.6	P100, N100, N170, P2, N2b, P3a, P3b [visual perception]	↑ *BD vs C:* ↑ P100 latency***, ↓ P100 amplitude*, ↑ N100 latency***, ↓ N100 amplitude*, ↓ N170 amplitude***, ↓ P2 amplitude***, ↑ N2b latency**, ↓ N2b amplitude***, ↑ P3a latency***, ↑ P3b latency**, ↓ P3b amplitude** ↓ *BD vs C:* ↓ P100 amplitude*, ↓ N100 amplitude*, ↓ N170 amplitude***, ↓ P2 amplitude**, ↓ N2b amplitude***, ↑ P3b latency**, ↓ P3b amplitude** ↑ *BD vs* ↓ *BD:* ↑ P100 latency*, ↑ N100 latency**, ↓ N170 amplitude*, ↓ P2 amplitude*, ↑ N2b latency*, ↑ P3a latency**

Petit et al. 2012	12:6 8:10	21.3 21.9	P100, P3b, N2b	*BD vs C:* ↑ P100 amplitude Cz*, R hemisphere* (alcohol stimuli) *Corr:* ↑ duration of binge habit = ↑ P100 amplitude (alcohol-related cues); ↑ number of doses per week = ↑ P100 amplitude to alcohol-related cues*
Petit et al. 2014[LB]	11:4 4:11	22.0 22.0	P1, P3	*BD vs C:* ↓ P1 amplitude (T2 vs T1)**; ↓ P3 amplitude (non-alcohol stimuli, T2 vs T1)**

[LA] Longitudinal study, baseline = all participants are abstinent/no binge; [LB] Longitudinal study, baseline = meet binge criteria,
[+] The results are presented in terms of differences identified in the binge drinking sample compared to the non-binge drinking sample.
[1] For sample size and age, binge participants are presented on first line followed by non-binge participants on the following line. Data is provided for the first time point when binge drinking participants are compared to non-binge participants (i.e. for longitudinal studies, this may be at baseline or at follow up).
BD: binge drink; C: control participants; Corr: correlation; Cz: central; DM: decision-making; FC/Fz: frontal; L: left; LPC: late positive component; ns: non-significant; PC/Pz; parietal; PFC: prefrontal cortex; R: right; T1: baseline; T2: follow-up; z: electrode placed on the midline sagittal plane of the skull.

Table 10: Summary of longitudinal findings for neuropsychological studies (n=6).

Source	Study length	Baseline characteristics (i.e. are they bingers)	Binge Comparison		Significant cognitive Task [Domain]	Results[+]
			n M:F	Age[1]		
Carbia et al. 2017a	T1: baseline T2: 2yrs-post T3: 4yrs-post T4: 6yrs-post	BD: T1-T4 BD Ex-BD: T1 BD, T2, T3 or T4 non-BD C: non-BD	40:39 36:40	18.9 18.6	Logical memory, RAVLT [WM, immediate, long term & recent memory]	T1 vs T4 *BD vs C:* ↑ RAVLT intrusion errors* (↓ LTM), ↓ immediate recall*, ↓ delayed recall** T1 vs T4 *Ex-BD:* ↑ LTM*, ↑ immediate recall* T1 vs T2 *BD:* ↓ RAVLT perseverative errors (↑ mental flexibility) *Short-term Ex-BD vs C*: ↓ immediate recall*, ↓ delayed recall**
Carbia et al. 2017b	T1: baseline T2: 2yrs-post T3: 4yrs-post T4: 6yrs-post	BD: T1-T4 BD Ex-BD: T1 BD, T2, T3 or T4 non-BD C: non-BD	40:39 36:40	18.9 18.6	Self-ordered pointing [WM]	T1 vs T2 *BD:* ↑ WM span (3rd trial, 4th block)* T1 vs T3 *BD:* ↑ WM span (1st trial, 3rd block; 1st trial, 4th block)*
Jones et al. 2017	T1: baseline T2: 1yr-post	BD: T1 non-BD, T2: BD C: non-BD	19:14 43:40	14.5 14.0	[Delay discounting]	*Corr:* ↑ lifetime drinks = ↑ Discounting rates across age* (↓ WM)
Mota et al. 2013	T1: baseline T2: 2yrs-post	BD: T1-T2 BD Ex-BD: T1 BD, T2 non-BD C: non-BD	18:15 X4:12 19:21	18.8 X18.9 18.8	Logical memory, family pictures, self-ordered pointing [immediate, long term, recent, working memory]	T1 vs T2 *BD:* ↓ Recall of themes*, delayed recall of themes*, retention* (logical memory; ↓ learning, ↓ delayed memory) T1 vs T2 *Ex-BD:* ↑ retention** (family pictures; ↑ delayed memory)
Squeglia et al. 2009	T1: baseline T2: 1-5yrs-post	BD: T1 non-BD, T2: BD C: non-BD	36:13 24:16	13.8 13.5	Complex figure copy, WASI block, digit vigilance [immediate, long term & working memory, inhibition, mental flexibility, processing speed, sustained attention, visuoconstructional]	T1 vs T2 *R F BD:* ↑ drinking days past 12mths= ↓ visuospatial function***; ↑ drinking days past 3mths= ↓ complex figure delay*** (↓ delayed memory) T1 vs T2 *R M BD:* ↑ hangover symptoms = ↓ DVT competition time*** (↓ attention)
Xiao et al. 2009	T1: baseline T2: 1yr-post	BD: T1 non-BD, T2: BD C: non-BD	10:2 71:78	16.4 16.2	Iowa Gambling; [DM]	T1 vs T2 *R:* ↑ IGT performance at T1; attention) = ↓ drinks consumed at T2)**

[+] The results are presented in terms of differences identified in the binge drinking sample compared to the non-binge drinking sample.
[1] For sample size and age, binge participants are presented on first line followed by non-binge participants on the following line. Data is provided for the first time point when binge drinking participants are compared to non-binge participants (i.e. for longitudinal studies, this may be at baseline or at follow up).
BD: binge drink; C: control participants; Corr: correlation; DVT: Digit Vigilance Task; DM: decision-making; ex-BD: ex-binge drinking participants; IGT: Iowa Gambling Task; RAVLT: Rey Auditory Verbal Learning Task; T1: baseline; T2-4: follow-up; WASI: Wechsler Abbreviated Scale of Intelligence; WM: working memory; yr: year.

Meta-Analysis Forest Plots

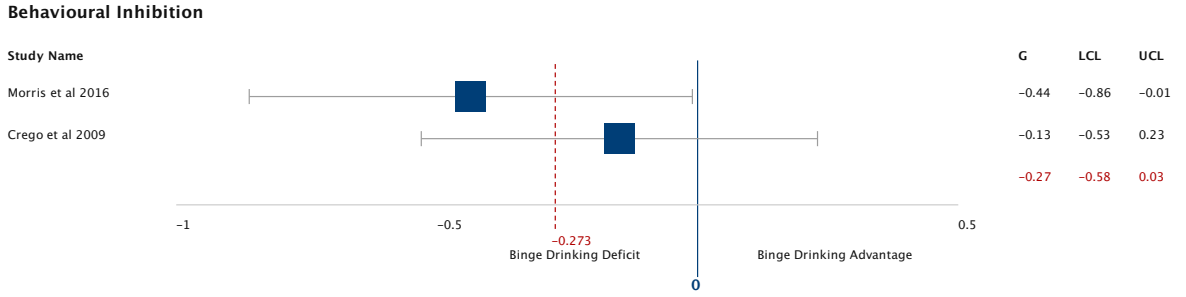


Figure 3: Forest Plot of Behavioural Inhibition.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=1.09, df=1, p=0.300. The standard deviation of true effects (T) is 0.06, and the variance of true effect sizes (T^2) is 0.00. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 8%.

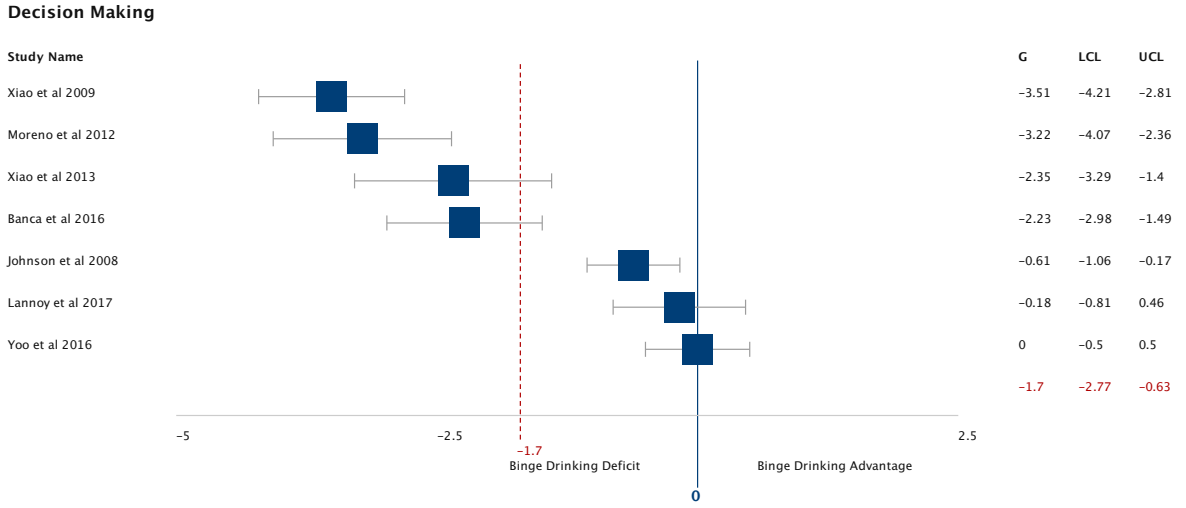


Figure 4: Forest Plot of Decision Making.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=115.64, df=6, p<0.001. The standard deviation of true effects (T) is 1.39, and the variance of true effect sizes (T^2) is 1.94. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 95%.

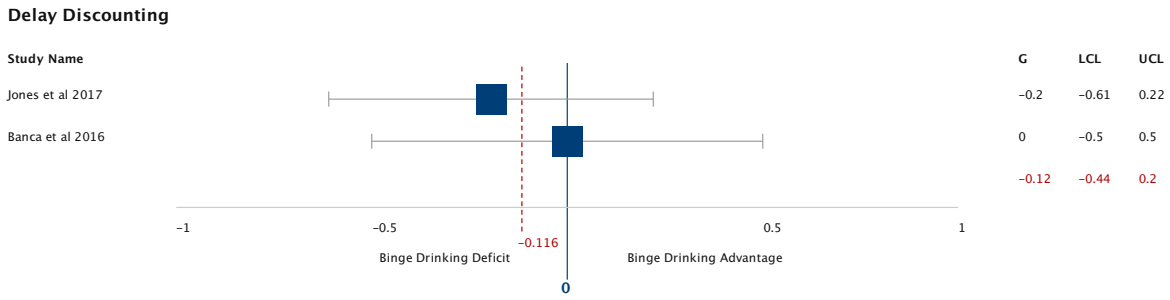


Figure 5: Forest Plot of Delay Discounting.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=0.35, df=1, p=0.553. The standard deviation of true effects (T) is 0.00, and the variance of true effect sizes (T^2) is 0.00. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 0%.

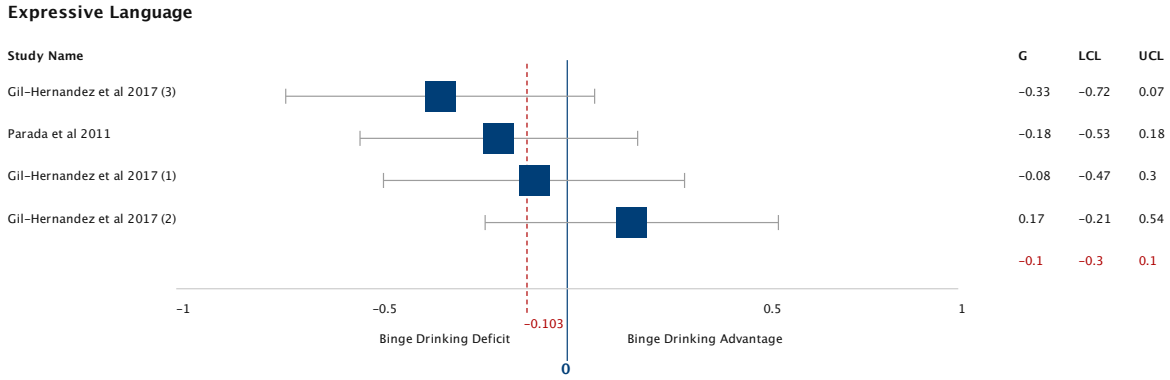


Figure 6: Forest Plot of Expressive Language.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=3.37, df=3, p=0.338. The standard deviation of true effects (T) is 0.07, and the variance of true effect sizes (T^2) is 0.01. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 11%.

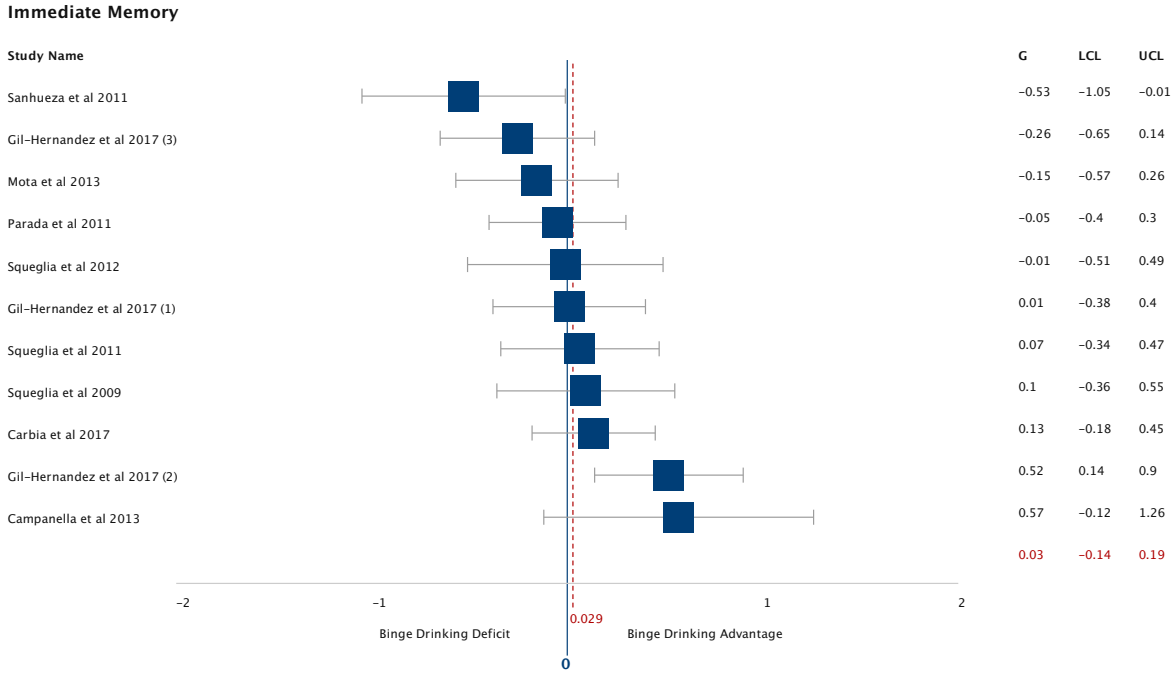


Figure 7: Forest Plot of Immediate Memory.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=16.62, df=10, p=0.083. The standard deviation of true effects (T) is 0.17, and the variance of true effect sizes (T^2) is 0.03. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 40%.

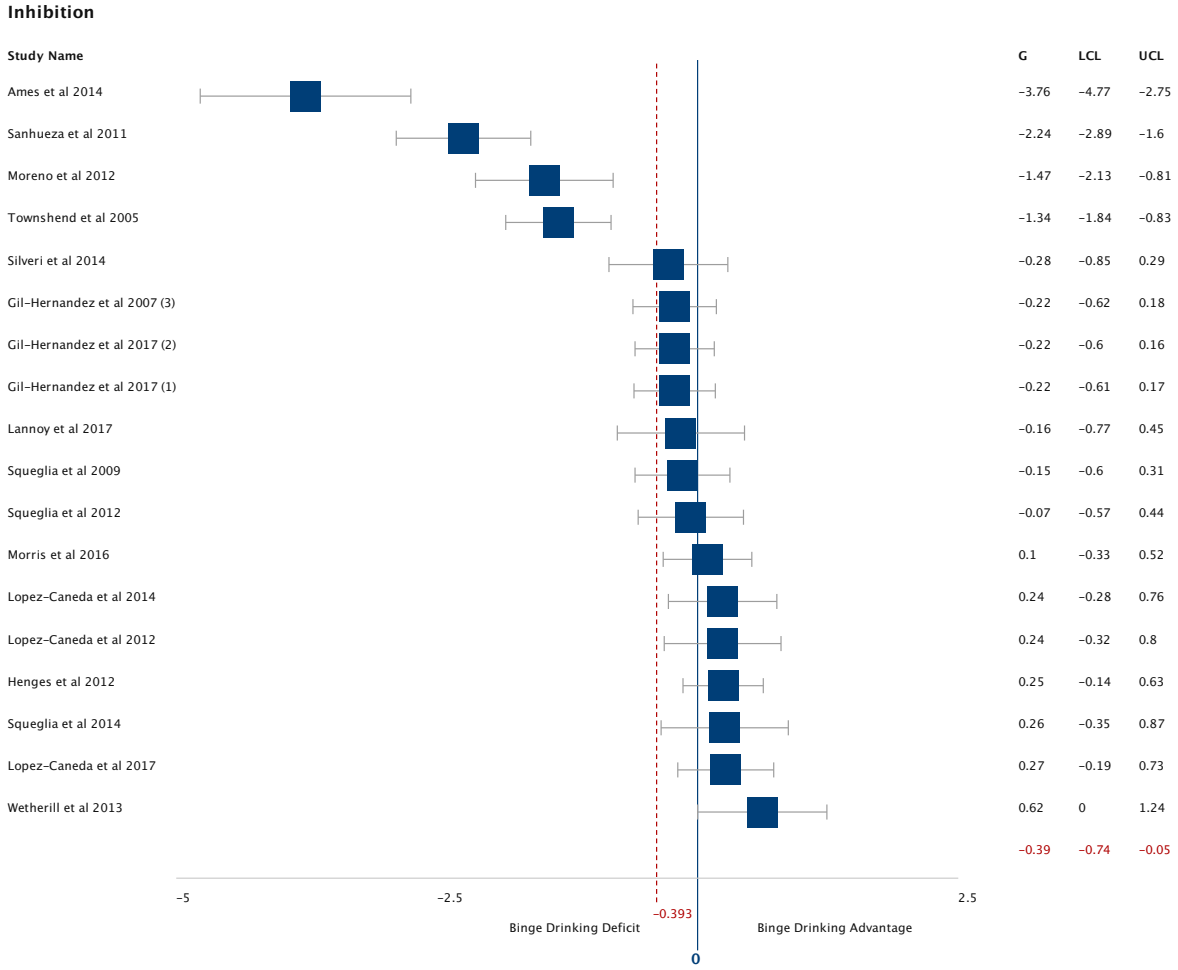


Figure 8: Forest Plot of Inhibition.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=144.94, df=17, p<0.001. The standard deviation of true effects (T) is 0.70, and the variance of true effect sizes (T^2) is 0.49. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 83%.

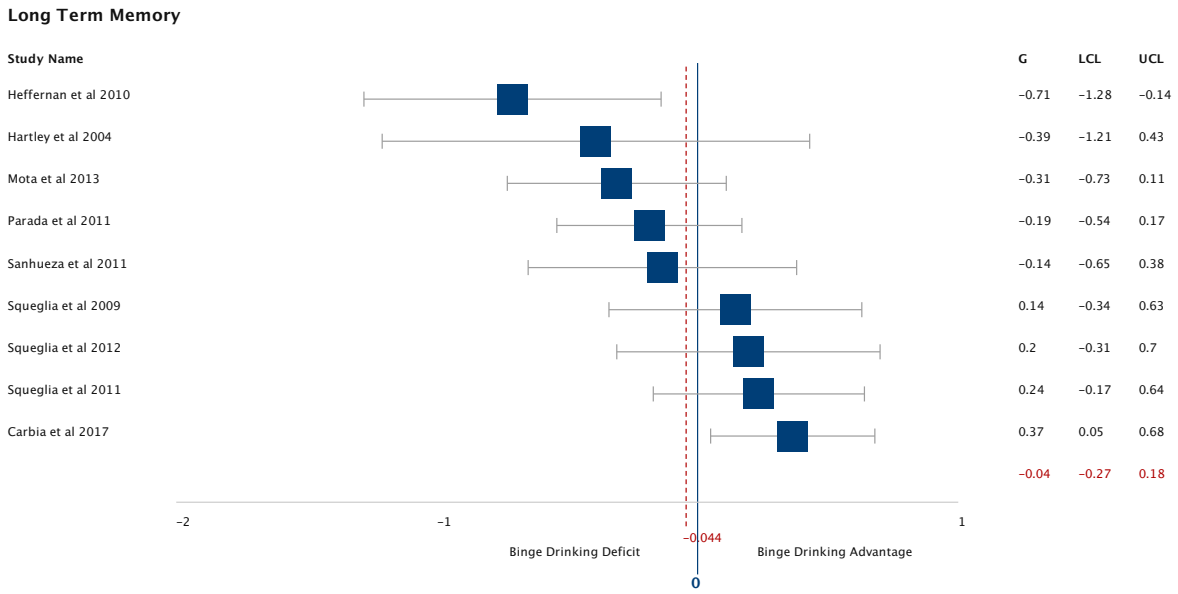


Figure 9: Forest Plot of Long Term Memory.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=17.67, df=8, p=0.024. The standard deviation of true effects (T) is 0.25, and the variance of true effect sizes (T^2) is 0.06. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 55%.

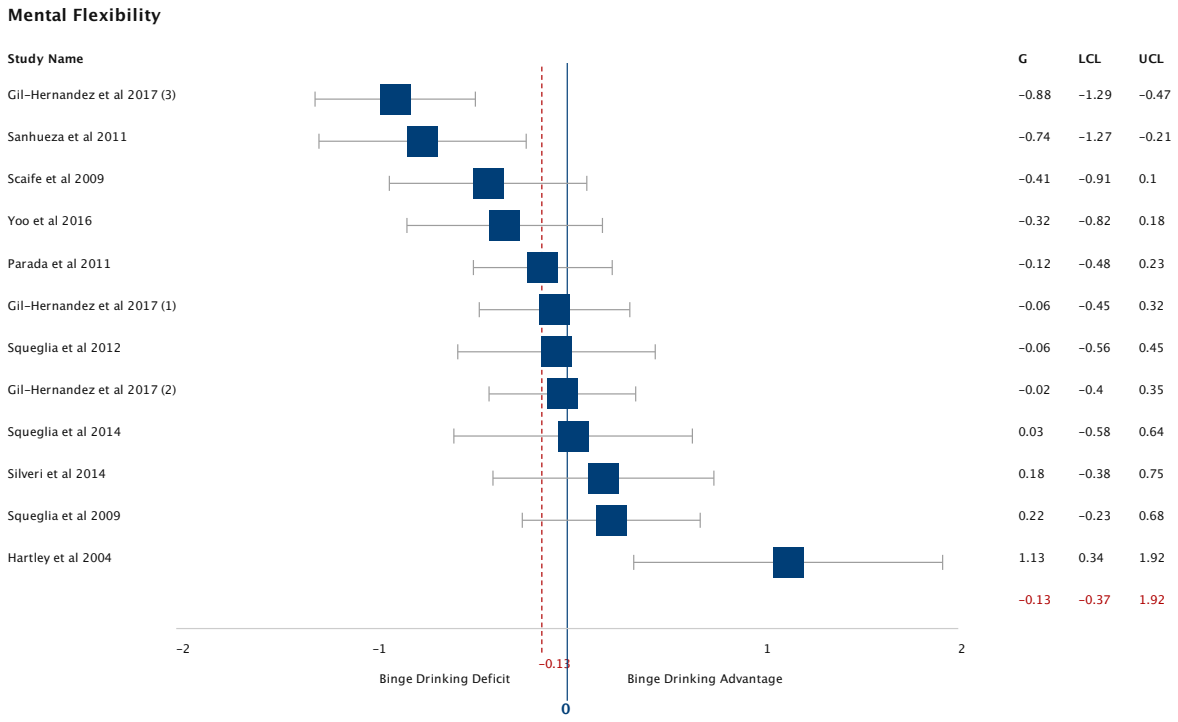


Figure 10: Forest Plot of Mental Flexibility.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=33.27, df=11, p<0.001. The standard deviation of true effects (T) is 0.34, and the variance of true effect sizes (T^2) is 0.12. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 67%.

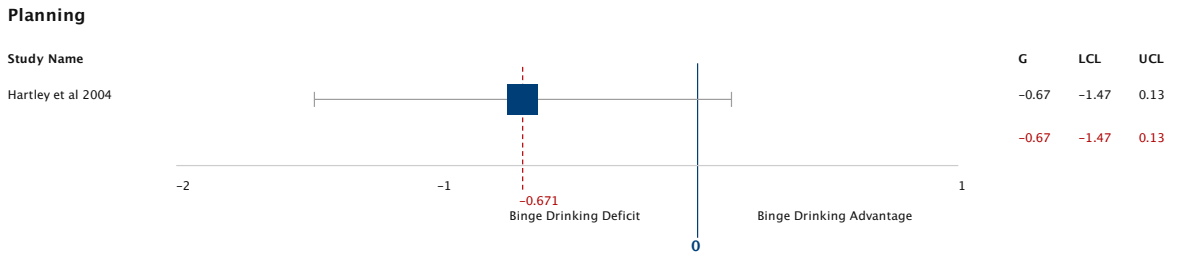


Figure 11: Forest Plot of Planning.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=0.00, df=1, p=1.000. The standard deviation of true effects (T) is 0.00, and the variance of true effect sizes (T^2) is 0.00. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 0%.

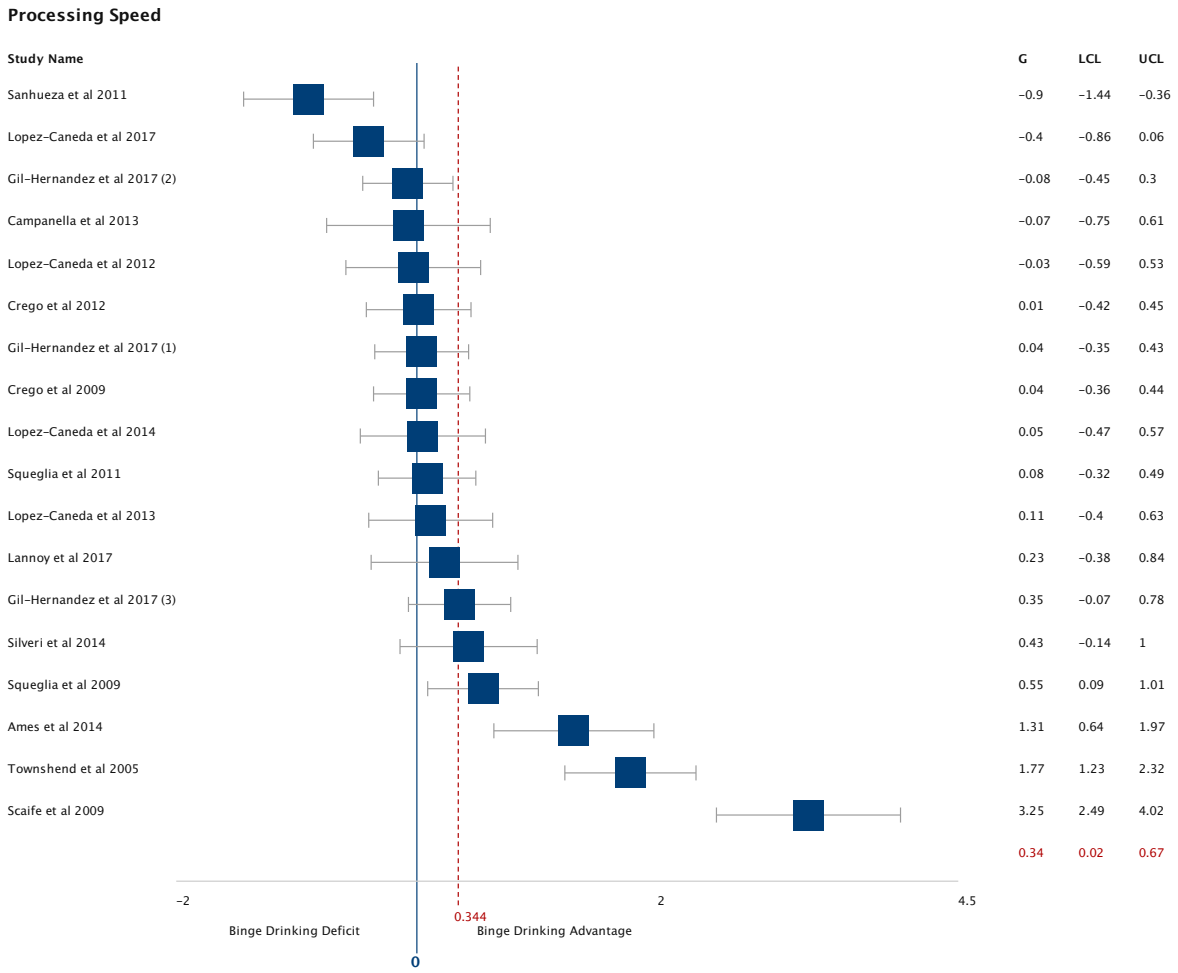


Figure 12: Forest Plot of Processing Speed.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=135.93, df=17, p<0.001. The standard deviation of true effects (T) is 0.66, and the variance of true effect sizes (T^2) is 0.44. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 87%.

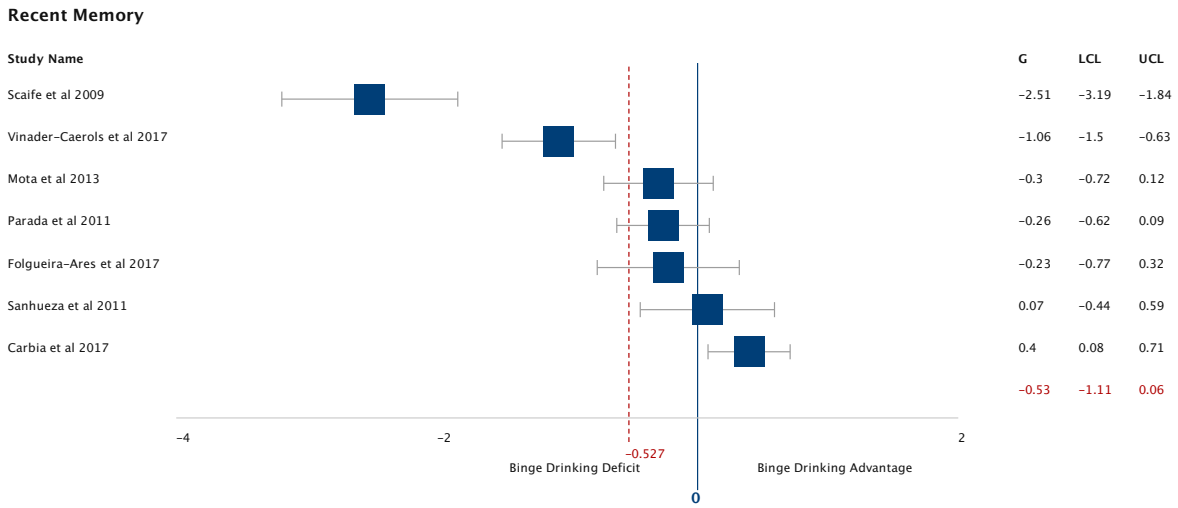


Figure 13: Forest Plot of Recent Memory.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=74.12, df=6, p<0.001. The standard deviation of true effects (T) is 0.75, and the variance of true effect sizes (T^2) is 0.56. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 92%.

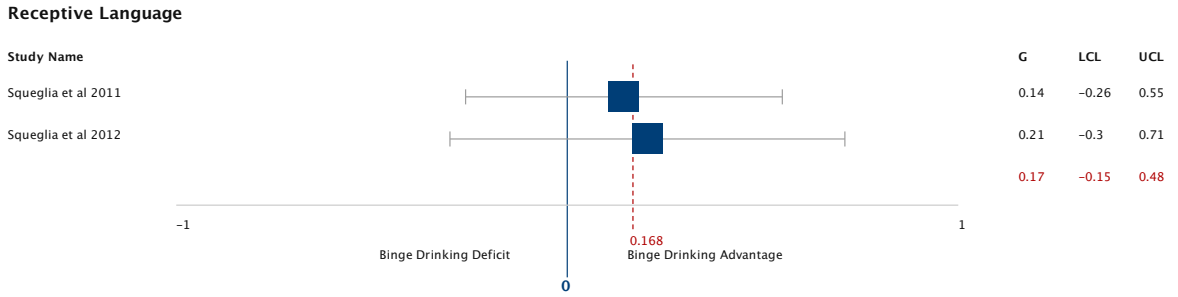


Figure 14: Forest Plot of Receptive Language.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=0.03, df=1, p=0.852. The standard deviation of true effects (T) is 0.00, and the variance of true effect sizes (T^2) is 0.00. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 0%.

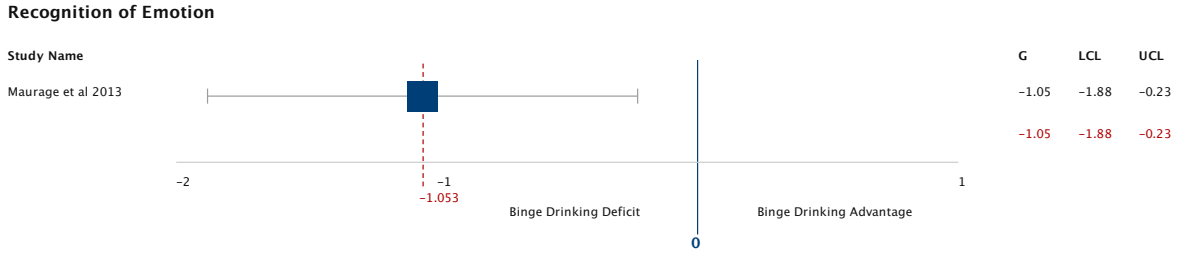


Figure 15: Forest Plot of Recognition of Emotion.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=0.00, df=0, p=1.000. The standard deviation of true effects (T) is 0.00, and the variance of true effect sizes (T^2) is 0.00. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 0%.

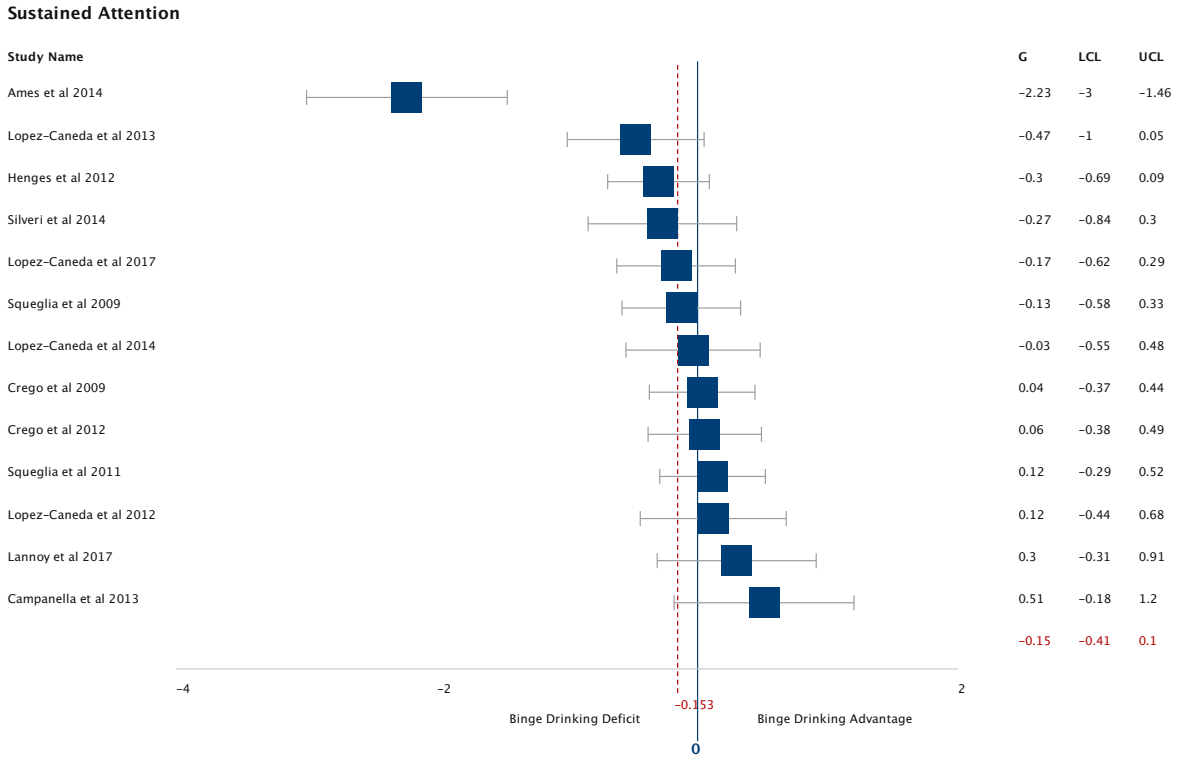


Figure 16: Forest Plot of Sustained Attention.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=40.01, df=12, p<0.001. The standard deviation of true effects (T) is 0.38, and the variance of true effect sizes (T^2) is 0.15. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 70%.

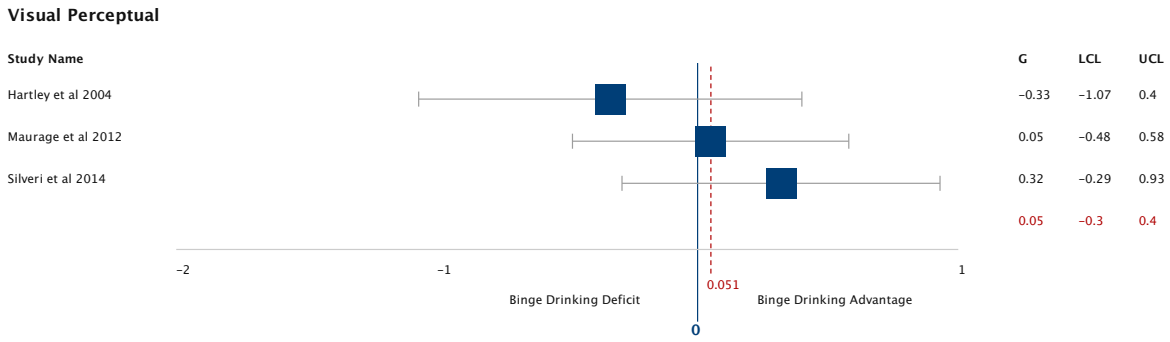


Figure 17: Forest Plot of Visual Perceptual.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=1.79, df=2, p=0.409. The standard deviation of true effects (T) is 0.00, and the variance of true effect sizes (T^2) is 0.00. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 0%.

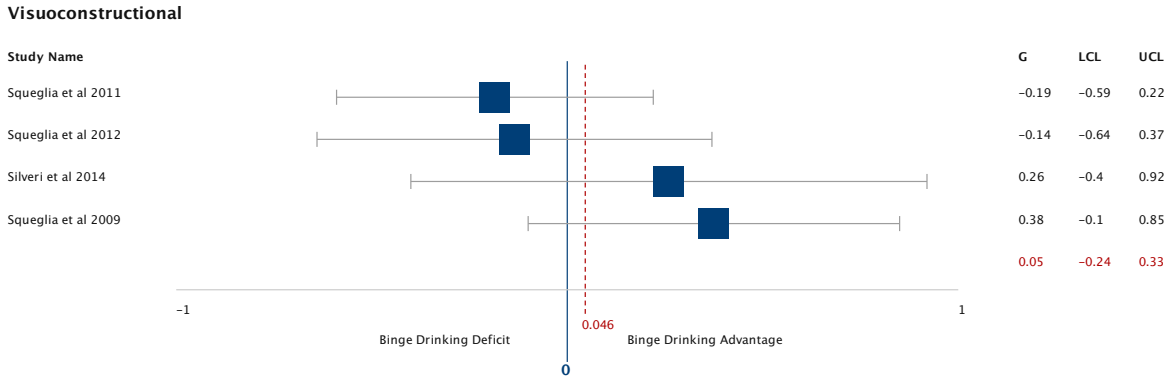


Figure 18: Forest Plot of Visuoconstructional.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=4.05, df=3, p=0.256. The standard deviation of true effects (T) is 0.15, and the variance of true effect sizes (T^2) is 0.02. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 26%.

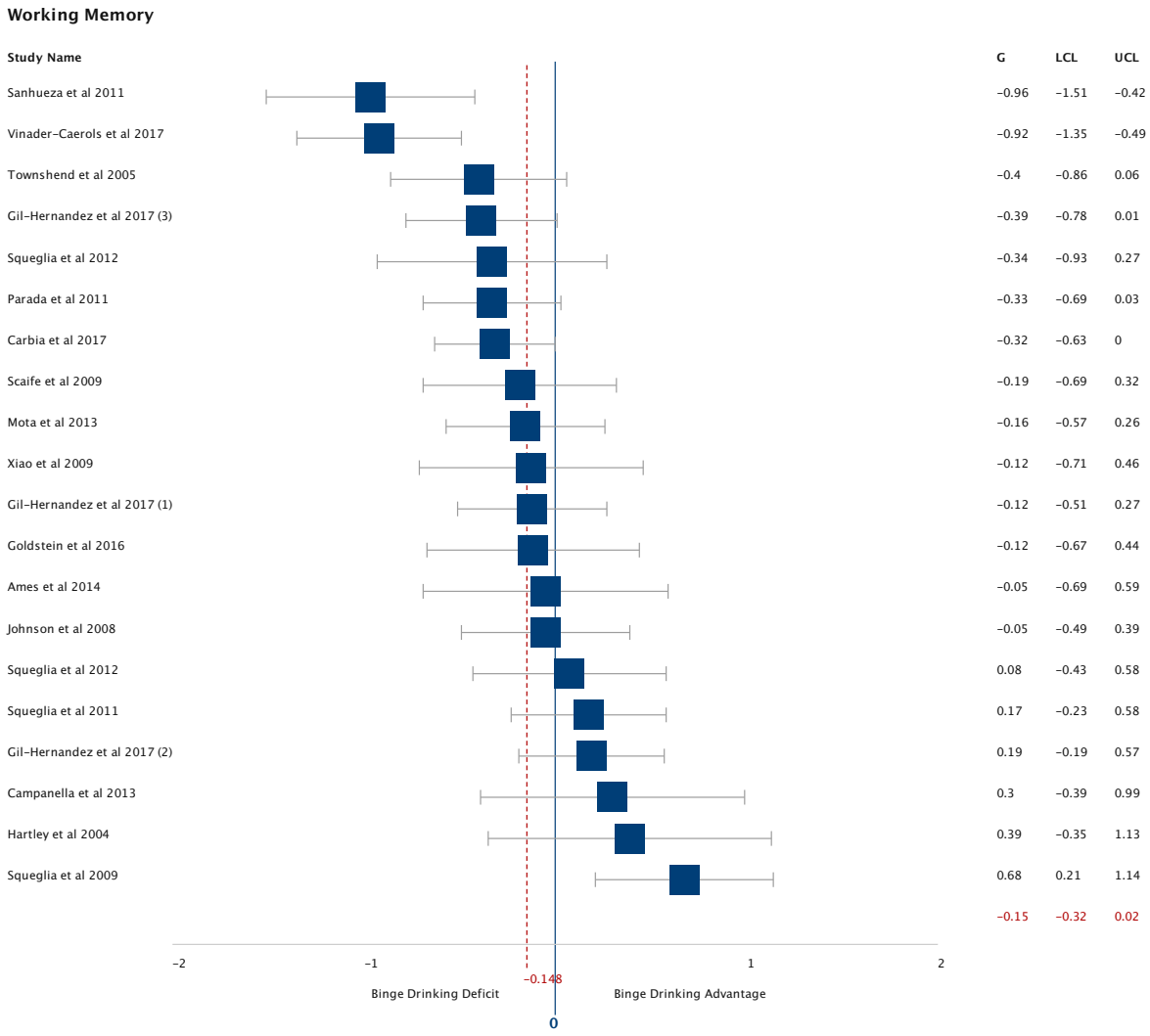


Figure 19: Forest Plot of Working Memory.

Mean weighted effect sizes for each neurocognitive test. Black-filled squares indicate the study effect sizes, white-filled squares indicate the domain effect size, the black bands indicate the errors bars, 95% CI. Q=48.50, df=19, p<0.001. The standard deviation of true effects (T) is 0.29, and the variance of true effect sizes (T^2) is 0.09. The proportion of the observed variance reflecting differences in true effect sizes (I^2) is 61%.

Table 11: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Check List.

Section/topic	#	Checklist item	Reported on page # of manuscriptf
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	1-2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	1-2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2-3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3,11
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	11
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	11
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	11
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	11

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	12
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	12-19
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	19, table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 2, 3
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	19-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	25

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Appendix 3

Supplementary materials for Chapter 3

Measuring model fit for latent moderated structural equation models.

Conventional fit indices are not available for moderation structural equation models. LMS' were therefore compared with the difference in scaled log likelihood multiped by two, resulting in a scaled $\Delta\chi^2$, performed using an online calculator: http://www.uoguelph.ca/~scolwell/lldifftest.html. Three models were compared for each of the alcohol-related outcomes: (i) A null model where the effects of internalising symptoms, EF and the interaction term were constrained to zero; (ii) a main effect model with freely estimated internalising symptoms and EF latent variables, and a fixed interaction term of zero; and (iii) an interaction effect model with freely estimated effects of internalising symptoms, EF and the interaction term. The null and main effect models were firstly compared, followed by the main effect and interaction effect models. Significance indicated improvement in model fit as a result of entering additional parameters into the model. Percentage of variance attributed to the added parameters (i.e., internalising symptoms and EF, interaction term) was calculated by subtracting the standardised residual variance of the alcohol-related outcome in the more constrained model from that in the less constrained model.

Table A.1

Descriptive characteristics comparing participants who did and not did complete the neuropsychological testing.

	Completed cognitive testing (n=104)	Declined cognitive testing (n=51)	*p*
Sex (F:M)	75:29	31:20	.156
Highest education			.183
Primary school	9	4	
Secondary school	42	27	
Trade/Apprenticeship	4	3	
Other Tertiary Diploma	16	5	
Bachelor Degree or higher	33	12	
Age	20.92 (2.44)	21.02 (2.32)	.815
Internalising symptoms			
GAD-7	12.61 (4.09)	12.16 (4.83)	.551
DASS-Anxiety	15.56 (8.30)	16.86 (9.25)	.377
DASS-Depression	19.56 (10.08)	20.75 (9.56)	.485
DASS-Stress	22.25 (7.89)	21.53 (8.79)	.608
SIAS-6/SPS-6	19.43 (10.40)	18.04 (9.87)	.427
Alcohol measures			
Age of first drink	15.23 (2.07)	15.18 (1.84)	.885
DMQ-R internalising coping	4.19 (2.37)	4.44 (2.11)	.526
DMQ-R enhancement	2.82 (1.22)	2.89 (1.09)	.733
TLFB past month consumption	68.97 (85.19)	90.22 (92.95)	.159
AUDIT total score	14.79 (10.28)	19.69 (8.22)	.003

Note. AUDIT: Alcohol Use Disorders Identification Test; DASS = Depression and Anxiety Stress Scale; DMQ-R: Drinking Motives Questionnaire-Revised; F = female; GAD-7 = Generalised Anxiety Disorder Questionnaire; M = male; SIAS-6/SPS-6 = Social Phobia Scale and Social Interaction Anxiety Scale; TLFB: Timeline Follow Back.

Figure A.1: Histograms illustrate that participants exhibited a full spectrum of internalising symptoms, from mild to severe.

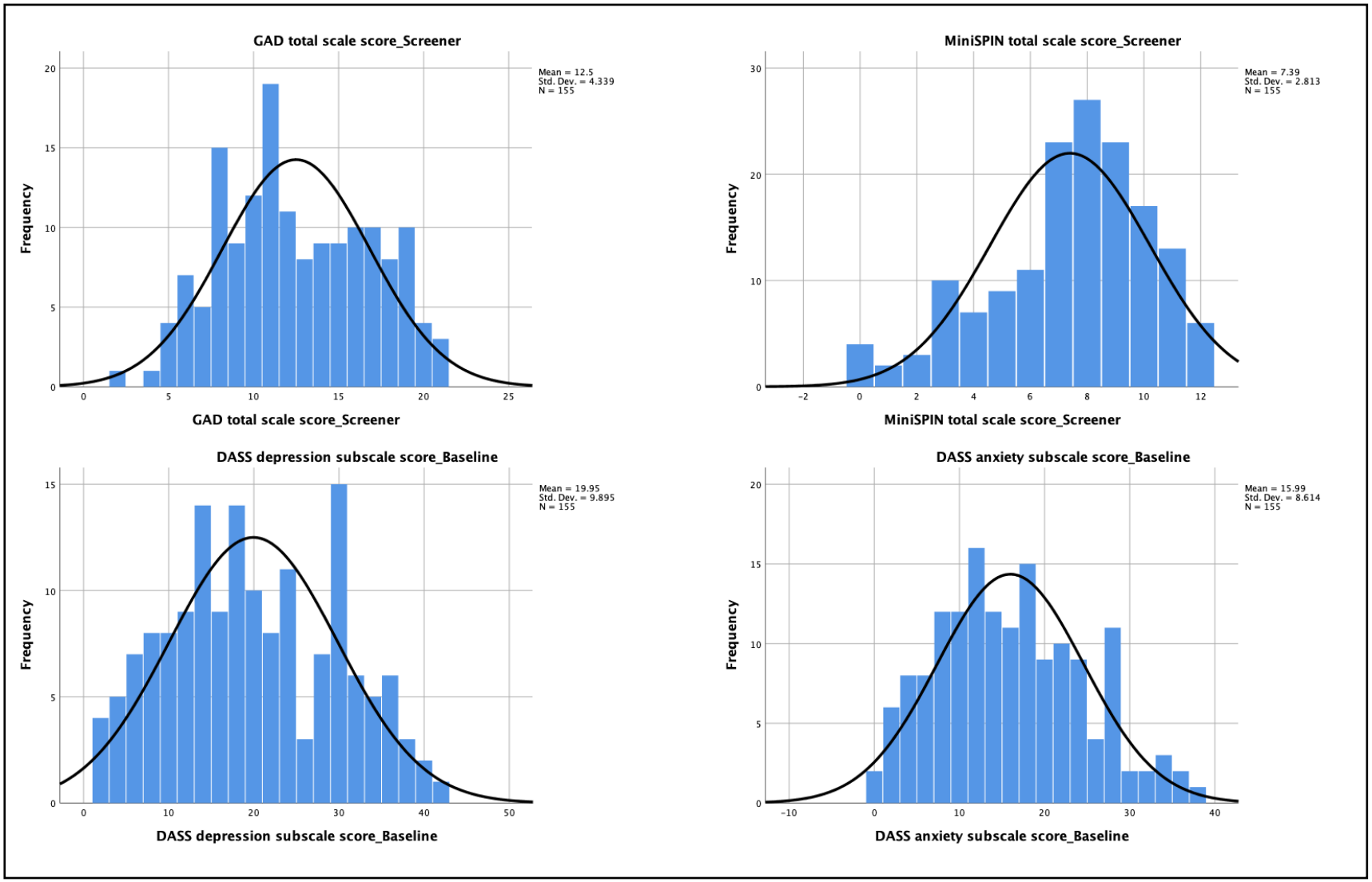


Figure A.1 continued: Histograms illustrate that participants exhibited a full spectrum of internalising symptoms, from mild to severe.

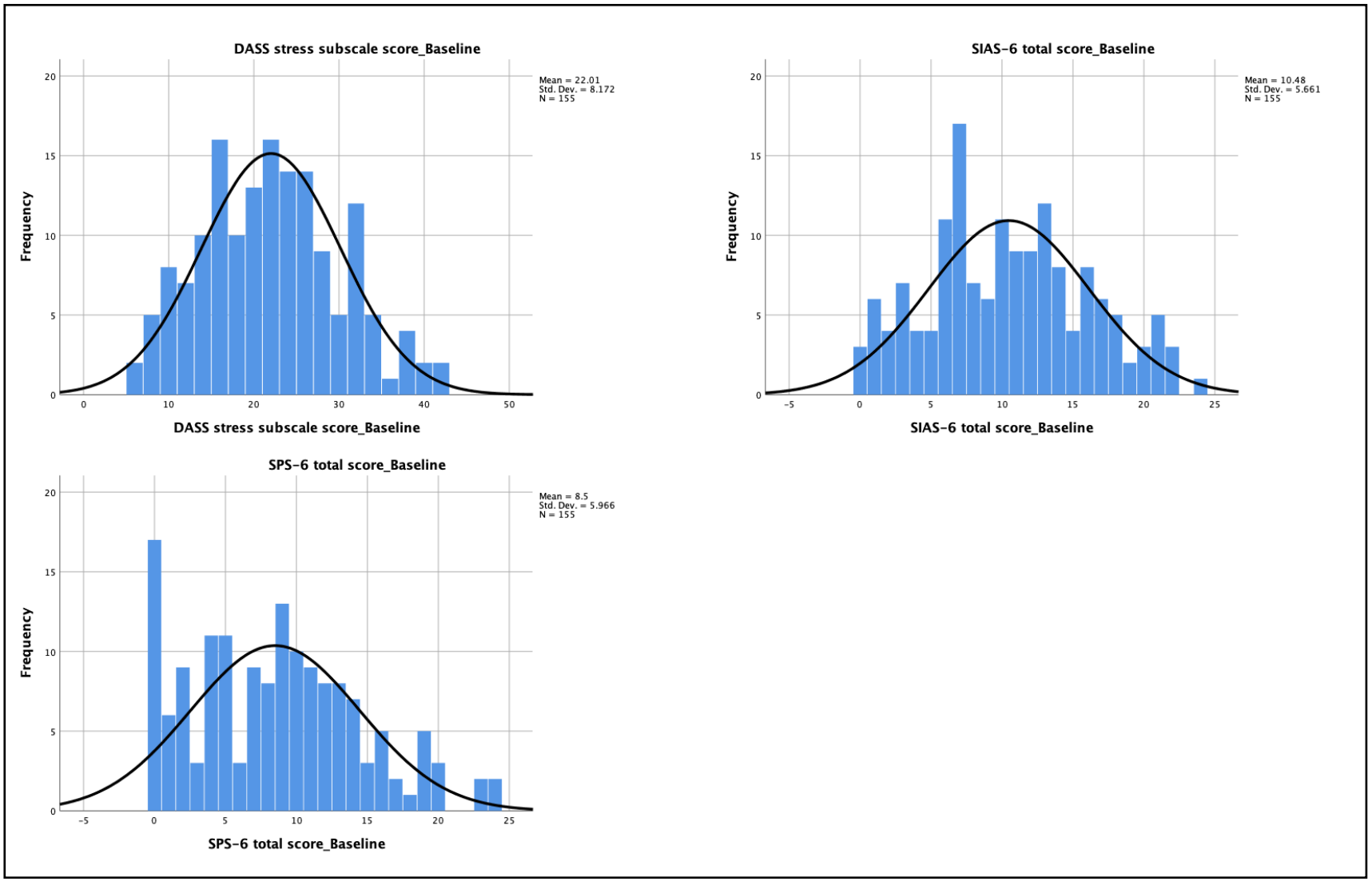


Table A.2

Results of main effects using regressions and results of the latent moderation models of internalising symptoms and executive dysfunction on the drinking to cope with internalising symptoms outcome, when lifetime non-drinkers were excluded from analyses.

	Coping motive		
	β	*S.E.*	*p*
Main Effects			
INT	0.394	0.078	<.001
EF deficit	0.292	0.100	.004
Age	0.036	0.104	.727
Sex	0.092	0.082	.257
Education	-0.015	0.104	.885
Latent Moderation Models			
INTxEF → coping	-0.296	0.082	<.001

Note. All parameters are standardised. INT = internalising symptoms; EF = executive functioning; coping = DMQ-R composite score for coping with internalising symptoms.

Table A.3

Outcomes of main effects using regressions and results of the latent moderation models of internalising symptoms and executive dysfunction on alcohol-related outcomes, when enhancement motives are added as a covariate.

	Coping motive			Alcohol use			AUD symptoms		
	β	*S.E.*	*p*	*β*	*S.E.*	*p*	*β*	*S.E.*	*p*
Main Effects									
Coping		-		0.321	0.084	<.001	0.337	0.070	<.001
Enhancement		-		0.194	0.093	.036	0.430	0.068	<.001
Latent Moderation Models									
INTxEF → coping	-0.203	0.073	.005		-			-	

Note. All parameters are standardised. coping = DMQ-R composite score for coping with internalising symptoms; enhancement = DMQ-R enhancement subscale; alcohol use = timeline follow back total alcohol consumption; AUD symptoms = AUDIT total score.

Table A.4

Total, direct and indirect effects of internalising symptoms, executive dysfunction and the interacting term in a latent mediated moderation structural equation model, when lifetime non-drinking participants were removed from analyses.

	Total effect			Direct effect			Indirect effect		
Paths	*β*	*S.E.*	*p*	*β*	*S.E.*	*p*	*β*	*S.E.*	*p*
INT → drink to cope → alcohol → AUD symptoms	3.288	1.608	.041	1.873	1.333	.160	1.414	0.484	.003
EF → drink to cope → alcohol → AUD symptoms	-28.178	23.006	.221	-17.675	18.107	.329	-10.504	6.333	.097
INTxEF → drink to cope → alcohol → AUD symptoms	-14.846	7.515	.048	-9.103	6.265	.146	-5.744	2.498	.022

Note. All parameters are unstandardised. INT = internalising symptoms; EF = executive functioning; drink to cope = DMQ-R composite score for coping with internalising symptoms; alcohol = timeline follow back total alcohol consumption; AUD symptoms = AUDIT total score.

Table A.5

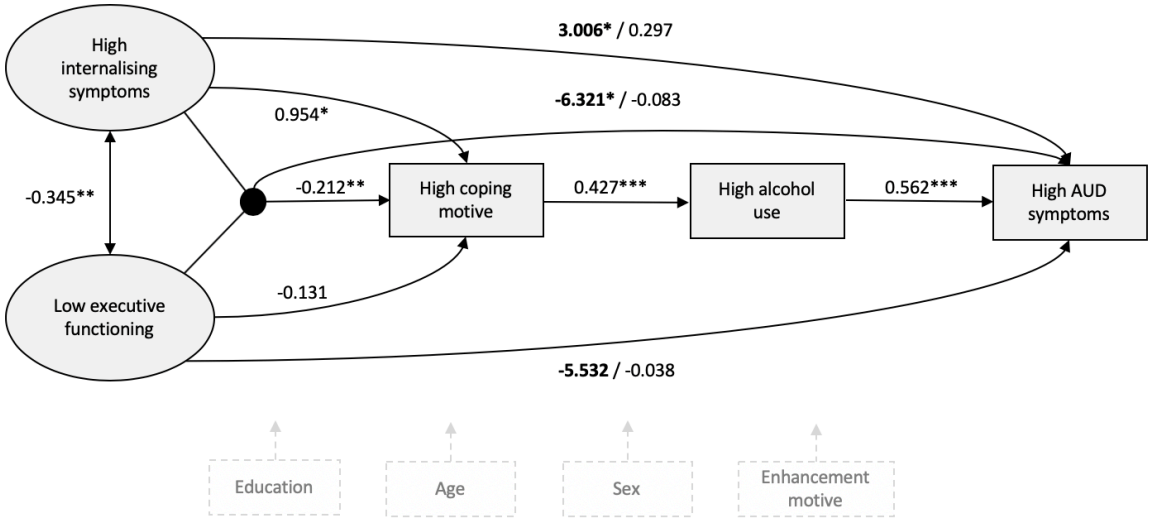
Total, direct and indirect effects of internalising symptoms, executive dysfunction and the interacting term in a latent mediated moderation structural equation model, when enhancement motives are added as a covariate.

	Total effect			Direct effect			Indirect effect		
Paths	*β*	*S.E.*	*p*	*β*	*S.E.*	*p*	*β*	*S.E.*	*p*
INT → drink to cope → alcohol → AUD symptoms	3.006	1.221	.014	1.697	1.069	.113	1.309	0.449	.004
EF → drink to cope → alcohol → AUD symptoms	-5.532	16.308	.734	-3.024	11.404	.791	-2.507	5.586	.654
INTxEF → drink to cope → alcohol → AUD symptoms	-6.321	3.149	.045	-3.922	2.831	.166	-2.399	0.993	.016

Note. All parameters are unstandardised. INT = internalising symptoms; EF = executive functioning; drink to cope = DMQ-R composite score for coping with internalising symptoms; alcohol = timeline follow back total alcohol consumption; AUD symptoms = AUDIT total score.

Figure A.2

Results of the latent mediated moderation model when enhancement motives were added as a covariate.



Note. The black circle represents the latent internalising symptoms and executive functioning interaction term. Parameters in bold are unstandardised total effects. Other parameters are standardised direct effects. Covariates are illustrated in grey.

Appendix 4

Supplementary materials for Chapter 4

Method Details

Explanatory measures

Relevant family history of substance use problems questions.

1. Has a blood relative of your child ever had any problems due to alcohol, such as: Marital separation or divorce; Laid off or fired from work; Arrests or DUIs; Alcohol harmed their health; In an alcohol treatment program; Suspended or expelled from school 2 or more times; Isolated self from family, caused arguments or were drunk a lot.
2. Has a blood relative of your child ever had any problems due to drugs, such as: Marital separation or divorce; Laid off or fired from work; Arrests or DUIs; Drugs harmed their health; In a drug treatment program; Suspended or expelled from school 2 or more times; Isolated self from family, caused arguments or were high a lot.

Calculating Family History Density.

To evaluate the extent to which the presence of substance-related problems may contribute to childhood outcomes, FHD scores of alcohol-related problems and substance use-related problems were calculated based on the sum of positive reports of problems from biological parents (+0.5) and biological grandparents (+0.25). The FHD scores were then combined across alcohol and substance use-related problems and could range from 0 to 4, with a score of 0 indicating absence of problems. Data on family history problems related to alcohol and other substances were combined due to relatively high overlap in positive samples (38.8% alcohol only, 13.2% other substances only, 48.0% alcohol and other substance use-related

problems), resulting in multicollinearity when exploring these two variables separately. While the categorical variable can be derived with some missing data (e.g., children were categorized as FHP if there was a positive parent report, but the grandparents' histories were unknown), the FHD score requires a complete history in order to accurately calculate the extent of problems. Therefore, FHD scores could only be calculated for a subsample of youth (n=11,298).

Outcome measures

Magnetic resonance imaging procedure.

All scans were uploaded to a shared server that is maintained by the Data Analytics and Information Core (DAIC) of ABCD. Brain data were collected on 3T scanners, including Siemens MAGNETOM Prisma, GE Discovery MR750, and Philips Achieva scanners. The T1 images were corrected for gradient nonlinearity distortions using scanner-specific, nonlinear transformations. Cortical reconstruction and volumetric segmentation were performed by DAIC using FreeSurfer v5.3.0. The Desikan-Killiany brain registration atlas was used in the present analyses to examine cortical thickness, surface area, and volume of 68 cortical regions, and volume in eight subcortical regions. DAIC used a combination of automated and manual methods to review the datasets for quality control prior to sharing data via the NDA database. Only participants with high quality imaging data were included in brain-related analyses (n=9,820).

Cognition (youth performance).

The cognitive assessment included seven NIH Toolbox® tasks (Luciana et al., 2018): Toolbox Pattern Comparison Processing Speed Test, List Sorting Working Memory Test, Picture Sequence Memory Test (visuospatial sequencing), Flanker Task (cognitive control),

Dimensional Change Card Sort Task (flexible thinking), Toolbox Picture Vocabulary Task (language) and Oral Reading Recognition Task. Calculated total cognition, fluid cognition and crystallized cognition composite scores were also utilized. All scores were age-corrected standard scores, where higher scores indicate greater cognitive performance.

Covariates.

The following fixed covariates were included in all statistical models and were dummy coded (Table 1): sex (M/F), race/ethnicity (White, Black, Hispanic, Asian, Other), parent education (<high school diploma, high school diploma or equivalent, college, Bachelor's degree, Postgraduate degree), household income (<50K, 50-100K, >100K, don't know/refuse to answer), marital status (single parent household, married), prenatal alcohol exposure (no/yes), prenatal substance use exposure (no/yes), past/present family history in first and/or second degree relatives (including biological parents, grandparents, uncles, aunts, and/or siblings) of psychosis (no, yes, unknown), past/present family history in first and/or second degree relatives of depression (no, yes, unknown), past/present family history in first and/or second degree relatives of anxiety (no, yes, unknown), past/present family history in first and/or second degree relatives of antisocial behavior (no, yes, unknown), and past/present family history in first and/or second degree relatives of mania (no, yes, unknown).Youth age was included as a continuous fixed effect. During sensitivity analyses, youth-reported parental monitoring and parental warmth/acceptance, and parent-reported family conflict were included as three additional continuous fixed effects.

Statistical Analyses: Equations

1. Dichotomous family history variable

Outcome variable ~ family history of substance use problems + age + sex + race/ethnicity + parent education + family income + marital status + prenatal alcohol exposure + prenatal other substance exposure + family history (anxiety) + family history (depression) + family history (anti-social) + family history (mania) + family history (psychosis) + (1 | research site: family)

Note 1. Youth categorized as 'N/A' (i.e., with just one grandparent with a history of alcohol or substance-use related problems) were excluded from this analysis (n=1,792).

Note 2. For the sensitivity analysis which excluded participants from the family history negative group with positive aunts, uncles, or siblings (n=1,024), this equation was used.

2. Family history problems density score

Outcome variable ~ s(density score) + age + sex + race/ethnicity + parent education + family income + marital status + prenatal alcohol exposure + prenatal other substance exposure + family history (anxiety) + family history (depression) + family history (anti-social) + family history (mania) + family history (psychosis) + (1 | research site: family)

3. Sensitivity analysis, including family environment covariates

Outcome variable ~ family history of substance use problems + age + sex + race/ethnicity + parent education + family income + marital status + prenatal alcohol exposure + prenatal other substance exposure + family history (anxiety) + family history (depression) + family history (anti-social) + family history (mania) + family history (psychosis) ***+ family conflict + parental monitoring + parental warmth/acceptance +*** *(1 | research site : family)*

For all analyses that included morphometric indices, 'research site' was replaced with 'MRI scanner'.

Additional Results

Figure 1: *t* values are illustrated for associations between any family history of substance use problems and cortical and subcortical volume indices, when adjusting for fixed and random effects.

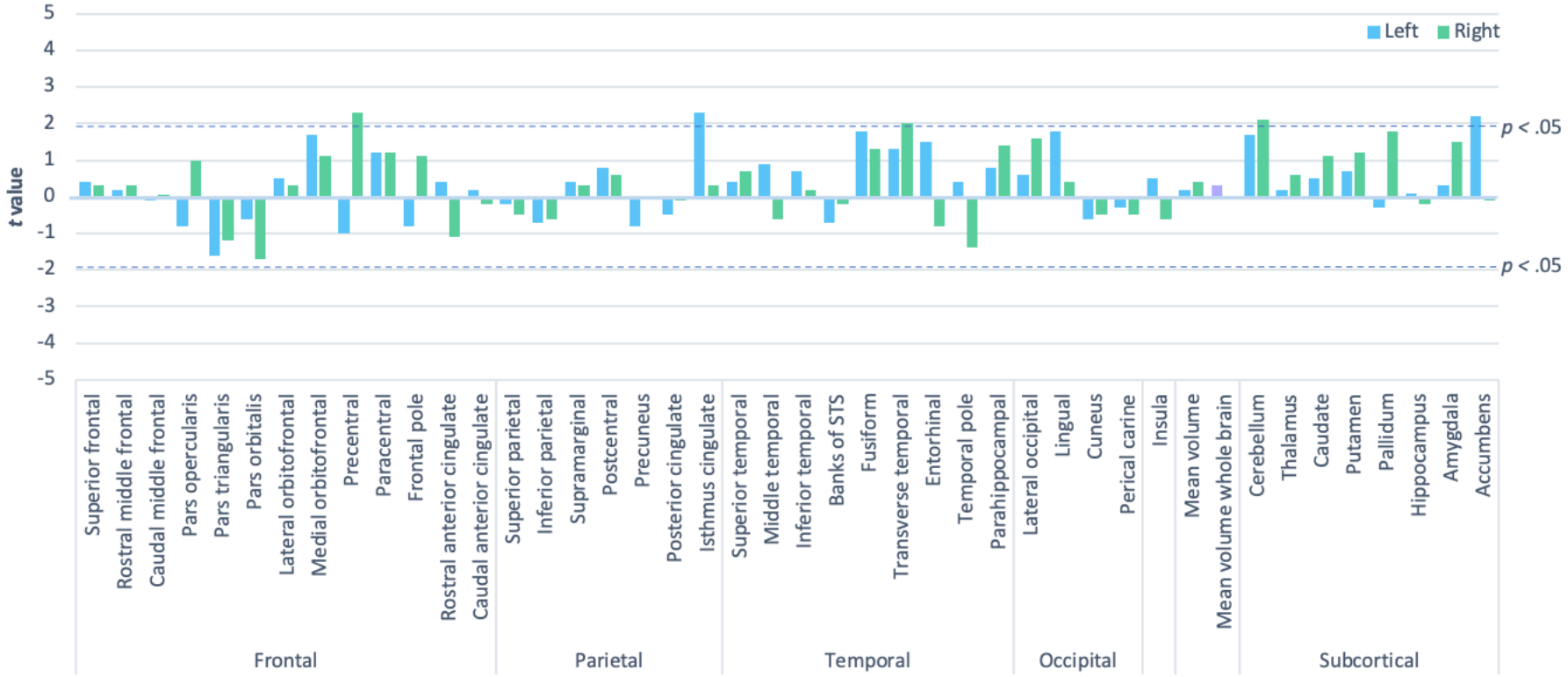


Figure 2: Mean psychopathology syndrome scale and higher order factor scores for increasing family density scores of SUD. Error bars are standard errors of the mean.

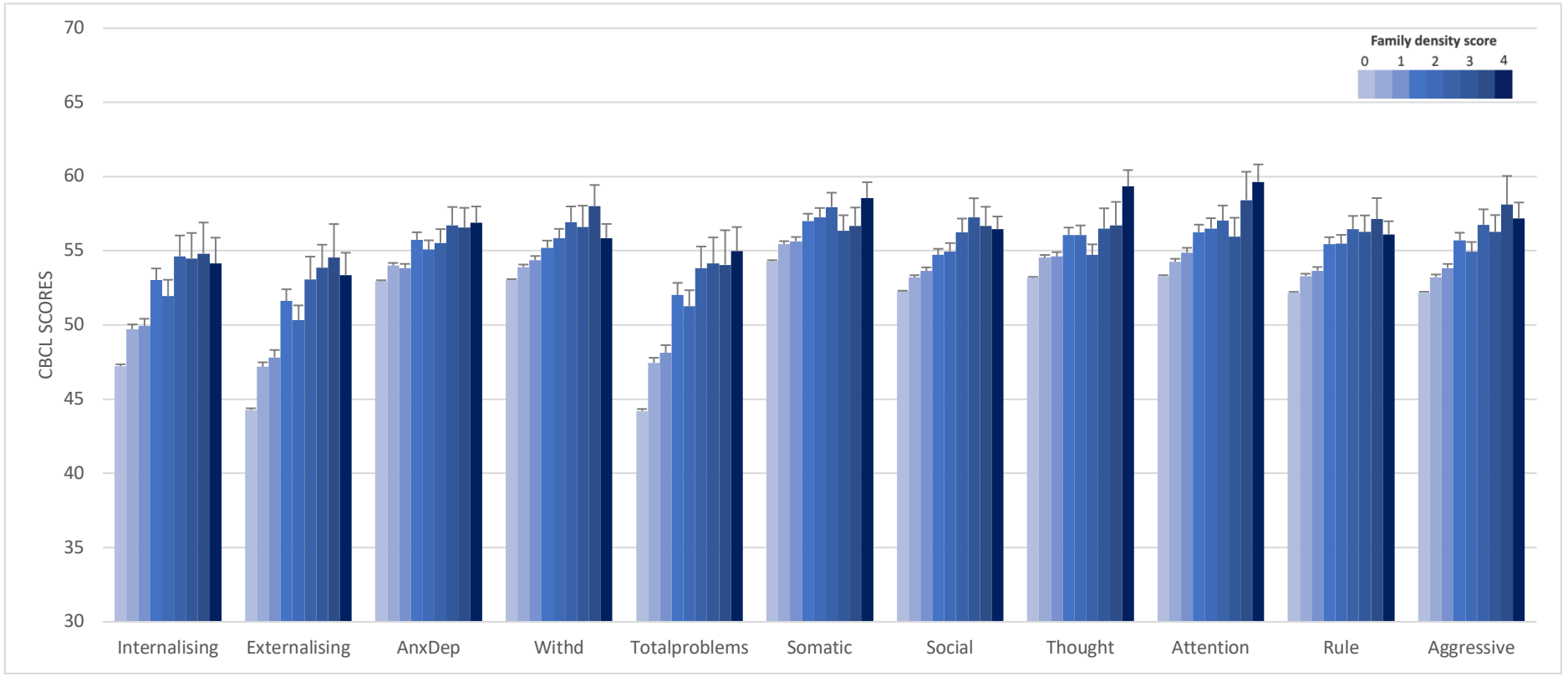
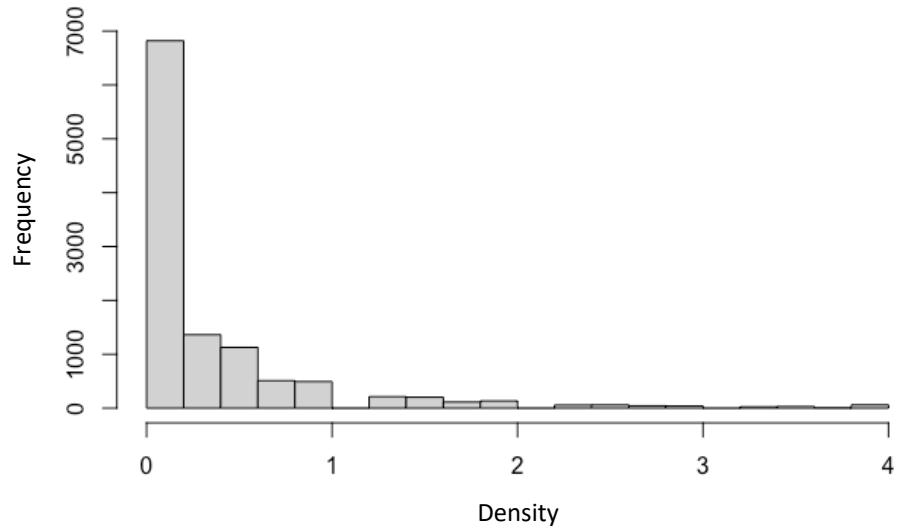
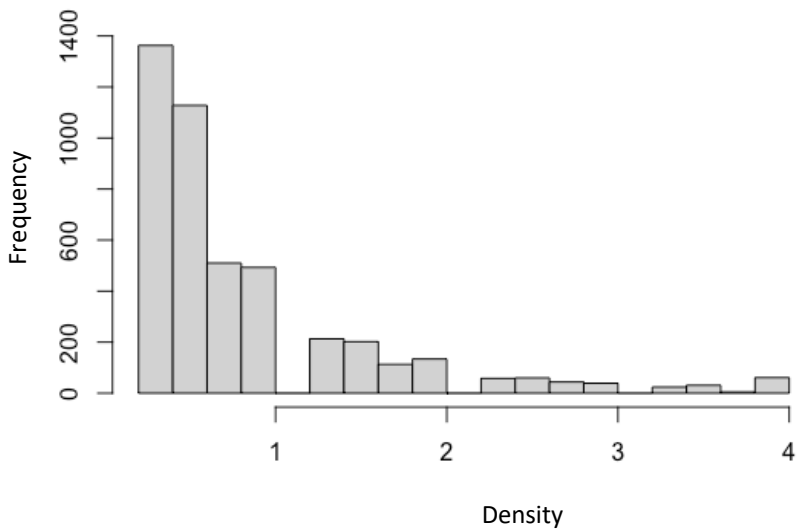


Figure 3: Histogram of family history density of alcohol and other substance use-related problems in biological parents and grandparents. A. Shows density range when including scores of 0 (i.e., absence of problems). B. Shows density range among youth with at least one parent or grandparent with a history of problems.

A.



B.



Results: Family history density of substance use problems

Table 1: Mixed model results for family history density of substance use problems and significant cortical thickness indices. N=9,820

Cortical thickness indices	***B***	***SE***	***t***	***p***	***FDR p***	R^2
Left Paracentral	-0.01	0.003	-3.33	.000878	.030	<.001
Right Inferior Parietal	-0.01	0.003	-3.31	.000943	.032	<.001
Left Banks of Superior Temporal Sulcus	-0.01	0.003	-3.57	<.001	.014	<.001

Fixed effects: age, sex, race/ethnicity, parent education, household income, marital status, prenatal alcohol exposure, prenatal drug exposure, family history of anxiety, family history of depression, family history of antisocial behavior, family history of mania, family history of psychosis.
Random effects: family nested within MRI scanner.

Table 2: Mixed model results for family history density of substance use problems.

Outcome	*B*	*SE*	*t*	*p*	*FDR p*	R^2
Neurocognition (NIH Toolbox®)						
Flanker (cognitive control)	0.76	0.26	2.94	.003	.102	<.001
List sort (working memory)	-0.17	0.27	-0.63	.53		.003
Card sort (flexible thinking)	0.27	0.28	0.97	.33		.001
Picture vocab (language)	-0.36	0.29	-1.24	.22		.004
Pattern (processing speed)	0.12	0.42	0.30	.77		<.001
Picture sequence (visuospatial)	-0.55	0.30	-1.81	.07		.005
Reading	-0.49	0.35	-1.41	.16		.006
Fluid cognition	0.19	0.32	0.59	.56		.002
Crystallized cognition	-0.46	0.32	-1.46	.15		.006
Total cognition	-0.15	0.31	-0.47	.64		.006
Impulsivity (UPPS-P)						
Negative urgency	0.02	0.05	0.34	.73		.002
Lack planning	0.06	0.05	1.27	.20		.001
Sensation seeking	0.03	0.05	0.62	.53		<.001
Positive urgency	0.07	0.06	1.31	.19		.005
Lack perseverance	0.11	0.04	2.47	.01	.340	.002
Motivation (BIS/BAS)						
Behavioral inhition	-0.01	0.05	-0.10	.92		<.001
Reward responsiveness	0.04	0.05	0.90	.37		<.001
Drive	-0.01	0.06	-0.10	.92		<.001
Fun seeking	0.06	0.05	1.29	.20		.003
Psychopathology (CBCL)						
Total problems	1.03	0.21	4.96	<.001	<.001	.04
Internalising	0.78	0.20	3.99	<.001	<.001	.03
Anxious Depressed	0.54	0.11	4.88	<.001	<.001	.02
Withdrawn	0.35	0.11	3.30	<.001	.033	.02
Somatic	0.39	0.11	3.46	<.001	.018	.02
Externalising	1.18	0.19	6.23	<.001	<.001	.04
Rule Breaking	0.48	0.09	5.53	<.001	<.001	.04
Aggressive	0.65	0.10	6.55	<.001	<.001	.04
Social	0.42	0.09	4.81	<.001	<.001	.03
Thought	0.47	0.11	4.29	<.001	<.001	.03
Attention	0.34	0.11	3.05	.002	.068	.03
Sleep disturbance	0.86	0.15	5.65	<.001	<.001	.03
Disorders (KSADS)						
Number of disorders	0.23	0.03	8.53	<.001	<.001	.05
	aOR	***95% CI***	***t***	***p***	***FDR p***	R^2
1+ Mental disorder(s)	1.19	1.10 – 1.30	4.05	<.001	<.001	.02
2+ Disorders	1.27	1.15 – 1.40	4.71	<.001	<.001	.05
3+ Disorders	1.36	1.21 – 1.53	5.25	<.001	<.001	.06
4+ Disorders	1.45	1.26 – 1.66	5.30	<.001	<.001	.07
Depression	1.39	1.18 – 1.64	3.87	<.001	.004	.03
Generalized anxiety						.05
Separation	1.26	1.13 – 1.41	4.11	<.001	<.001	.02
Social	1.06	0.91 – 1.24	0.77	.44		.01
Delusions	1.19	0.97 – 1.47	1.67	.10		.02
ADHD	1.13	1.03 – 1.23	2.60	.009	.306	.02
Oppositional defiant	1.23	1.12 – 1.36	4.15	<.001	<.001	.02

Conduct	1.31	1.12 – 1.54	3.29	<.001	.034	.04
OCD	1.08	0.96 – 1.21	1.29	.20		.01
Bipolar	1.08	0.91 – 1.29	0.92	.36		.01
PTSD	1.72	1.44 – 2.05	5.95	<.001	<.001	.07
Phobia	1.10	1.01 – 1.20	2.30	.02	.680	.01
Substance Use						
Sipped alcohol	0.95	0.85 – 1.05	-1.01	.31		<.001

aOR = adjusted odds ratio, CI = confidence interval, SE = standard error, ADHD = attention deficit hyperactivity disorder, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder.

Fixed effects: age, sex, race/ethnicity, parent education, household income, marital status, prenatal alcohol exposure, prenatal drug exposure, family history of anxiety, family history of depression, family history of antisocial behavior, family history of mania, family history of psychosis.

Random effects: family nested within research site.

Covariate associations.

Compared to females, males exhibited significantly greater cortical thickness, cognition, impulsivity, psychopathology, and family conflict and less sleep disturbance, parent monitoring, and acceptance. Older age was significantly associated with thinner cortices and higher cognition, parent monitoring, and acceptance. Compared to other race/ethnicities, White youth exhibited significantly greater cortical thickness, cognition, and psychopathology. Lower parent education and household income was significantly associated with lower cortical thickness, cognition, parent monitoring, and acceptance and greater impulsivity, psychopathology, sleep disturbance, and family conflict. Compared to unexposed peers, youth with prenatal alcohol exposure had thinner cortices, lower parent monitoring and acceptance and greater impulsivity, psychopathology, sleep disturbance, and family conflict. Finally, youth with a family history of psychopathology in first and/or second degree relatives had lower cognition, parent monitoring, and acceptance and greater impulsivity, psychopathology, sleep disturbance, and family conflict than youth with no such history.

Sensitivty Analysis Results: Family Environment Covariates

Table 3: Mixed model results for family history of alcohol/other substance use problems (dichotomous variables) when including parental monitoring, parental warmth/acceptance, and family conflict as additional fixed covariates. Outcomes previously associated with FHP were examined.

Outcome	***B***	***SE***	***t***	***p***	***FDR p***
Psychopathology (CBCL)					
Total problems	0.75	0.27	2.73	.006	.204
Externalising	0.89	0.25	3.57	<.001	.012
Rule Breaking	0.30	0.12	2.53	.012	.408
Aggressive	0.33	0.13	2.47	.013	.442
Sleep problems	0.58	0.21	2.83	.005	.170
Disorders (KSADS)					
Number of disorders	0.18	0.04	5.06	<.001	<.001
	aOR	***95% CI***	***t***	***p***	***FDR p***
1+ Mental disorder(s)	1.16	1.04 – 1.30	2.56	.011	.374
2+ Disorders	1.28	1.11 – 1.48	3.46	<.001	.019
3+ Disorders	1.46	1.22 – 1.74	4.21	<.001	<.001
4+ Disorders	1.73	1.38 – 2.16	4.76	<.001	<.001
Separation	1.50	1.25 – 1.80	4.39	<.001	<.001
PTSD	2.59	1.75 – 3.83	4.75	<.001	<.001

aOR = adjusted odds ratio, CI = confidence interval, SE = standard error, ADHD = attention deficit hyperactivity disorder, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder. Effect sizes are reported in the manuscript (*Cohen's d*).
Fixed effects: age, sex, race/ethnicity, parent education, household income, marital status, prenatal alcohol exposure, prenatal drug exposure, family history of anxiety, family history of depression, family history of antisocial behavior, family history of mania, family history of psychosis, parent monitoring, parent warmth/acceptance, family conflict.
Random effects: family nested within research site.

Table 4: Mixed model results for family history density of substance use problems when including parental monitoring, parental warmth/acceptance, and family conflict as additional fixed covariates. Outcomes previously associated with FHP were examined.

Outcome	***B***	***SE***	***t***	***p***	***FDR p***	***R^2***
Psychopathology (CBCL)						
Total problems	0.70	0.20	3.52	<.001	.014	.04
Internalising	0.56	0.19	2.90	.004	.126	.03
Anxious Depressed	0.43	0.11	3.92	<.001	<.001	.02
Withdrawn	0.24	0.10	2.31	.021	.71	.02
Somatic	0.32	0.11	2.81	.005	.170	.02
Externalising	0.84	0.18	4.65	<.001	<.001	.04
Rule Breaking	0.37	0.09	4.33	<.001	<.001	.04
Aggressive	0.49	0.10	5.12	<.001	<.001	.04
Social	0.32	0.09	3.75	<.001	.006	.03
Thought	0.36	0.11	3.33	<.001	.029	.03
Sleep disturbance	0.68	0.15	4.54	<.001	<.001	.03
Disorders (KSADS)						
Number of disorders	0.20	0.03	7.48	<.001	<.001	.05
	aOR	***95% CI***	***t***	***p***	***FDR p***	***R^2***
1+ Mental disorder(s)	1.15	1.06 – 1.26	3.21	<.001	.044	.02
2+ Disorders	1.21	1.10 – 1.34	3.73	<.001	.006	.05
3+ Disorders	1.30	1.16 – 1.47	4.36	<.001	<.001	.06
4+ Disorders	1.39	1.21 – 1.61	4.56	<.001	<.001	.07
Depression	1.36	1.15 – 1.60	3.54	<.001	.014	.03
Separation	1.23	1.10 – 1.38	3.57	<.001	.012	.02
Oppositional defiant	1.16	1.05 – 1.28	2.84	.005	.156	.02
Conduct	1.24	1.05 – 1.47	2.56	.011	.360	.04
PTSD	1.68	1.40 – 2.01	5.62	<.001	<.001	.07

aOR = adjusted odds ratio, CI = confidence interval, SE = standard error, ADHD = attention deficit hyperactivity disorder, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder.

Fixed effects: age, sex, race/ethnicity, parent education, household income, marital status, prenatal alcohol exposure, prenatal drug exposure, family history of anxiety, family history of depression, family history of antisocial behavior, family history of mania, family history of psychosis, family history of psychosis, parent monitoring, parent warmth/acceptance, family conflict.

Random effects: family nested within research site.

Sensitivty Analysis Results: Excluding Other Relatives from Family History Negative Group

Table 5: Mixed model results for family history of alcohol/other substance use problems (dichotomous variables) when excluding youth with known positive histories of substance use problems among an aunt, uncle, full sibling, and/or half sibling from the family history negative group (*n*=1,024). Outcomes previously associated with FHP were examined.

Outcome	***B***	***SE***	***t***	***p***	***FDR p***
Psychopathology (CBCL)					
Total problems	1.13	0.30	3.70	<.001	.007
Externalising	1.23	0.28	4.44	<.001	<.001
Rule Breaking	0.38	0.13	2.94	.003	.102
Aggressive	0.46	0.15	3.11	.002	.068
Sleep problems	0.76	0.22	3.39	<.001	.024
Disorders (KSADS)					
Number of disorders	0.21	0.04	5.30	<.001	<.001
	aOR	***95% CI***	***t***	***p***	***FDR p***
1+ Mental disorder(s)	1.19	1.06 – 1.34	2.90	.004	.125
2+ Disorders	1.36	1.17 – 1.58	4.06	<.001	<.001
3+ Disorders	1.54	1.28 – 1.86	4.59	<.001	<.001
4+ Disorders	1.80	1.42 – 2.28	4.83	<.001	<.001
Separation	1.50	1.24 – 1.82	4.11	<.001	<.001
PTSD	*NA*				
Cortical thickness					
Left precentral	-0.016	0.004	-3.68	<.001	.007
Left paracentral	-0.020	0.005	-4.33	<.001	<.001
Left superior parietal	-0.014	0.004	-3.58	<.001	.010
Right superior parietal	-0.014	0.004	-3.52	<.001	.014
Right inferior parietal	-0.016	0.004	-3.66	<.001	.010
Left precuneus	-0.011	0.004	-3.03	.002	.068
Right middle temporal	-0.017	0.005	-3.21	.001	.034
Left banks of STS	-0.016	0.005	-3.36	<.001	.027
Left lateral occipital	-0.017	0.004	-4.01	<.001	<.001
Right lateral occipital	-0.016	0.004	-3.67	<.001	.007
Left mean thickness	-0.011	0.003	-3.43	<.001	.020
Right mean thickness	-0.011	0.003	-3.62	<.001	.010
Mean thickness	-0.011	0.003	-3.58	<.001	.010
Surface area					
Right precentral	0.611	0.164	3.72	<.001	.007
Right lateral occipital	0.584	0.164	3.56	<.001	.014

aOR = adjusted odds ratio, CI = confidence interval, SE = standard error, ADHD = attention deficit hyperactivity disorder, OCD = obsessive compulsive disorder, PTSD = post-traumatic stress disorder.
Fixed effects: age, sex, race/ethnicity, parent education, household income, marital status, prenatal alcohol exposure, prenatal drug exposure, family history of anxiety, family history of depression, family history of antisocial behavior, family history of mania, family history of psychosis.
Random effects: family nested within research site (or scanner site for MRI measures).
NA = model would not run due to computational singularity.

Correlations

Figure 4: Correlations among family history positive youth.

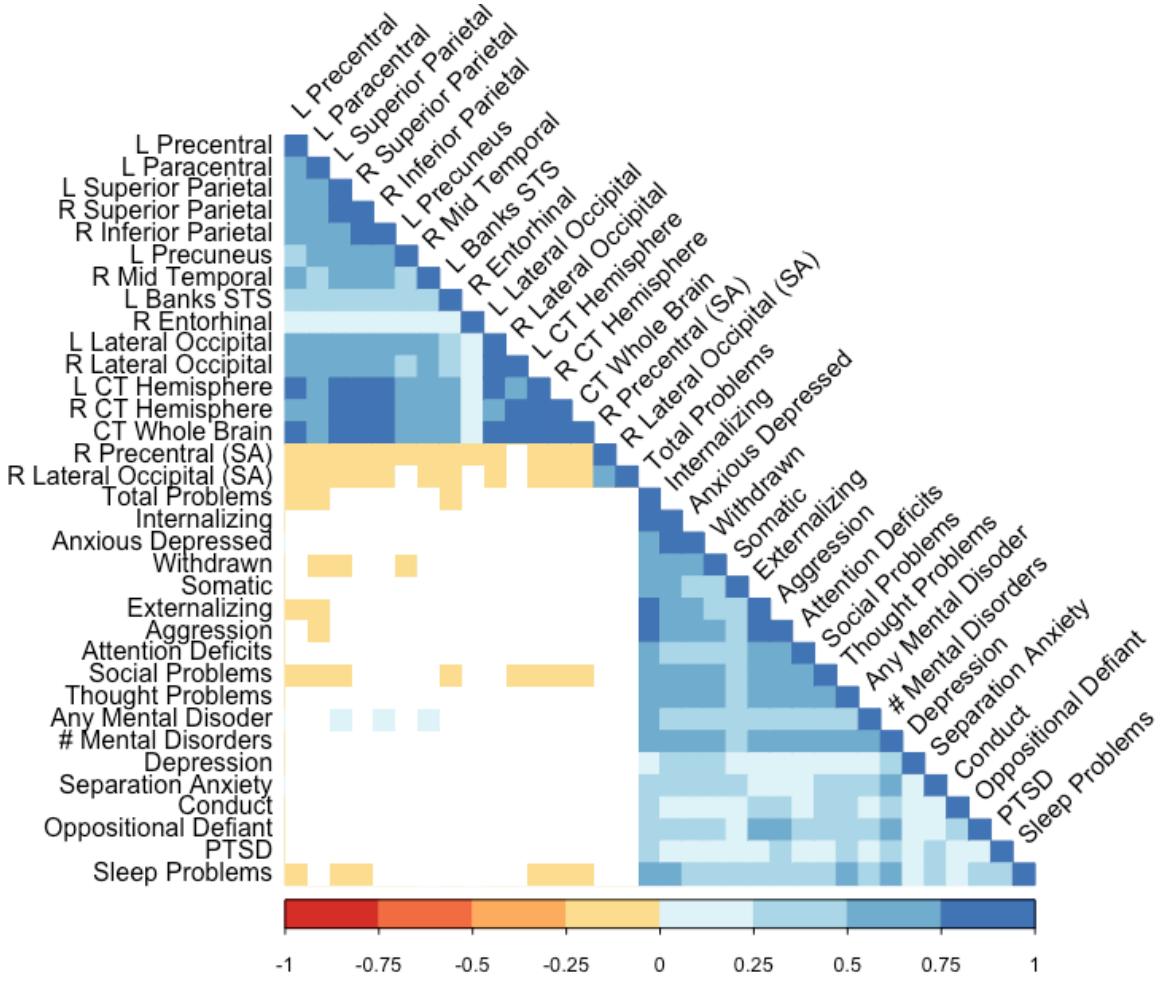
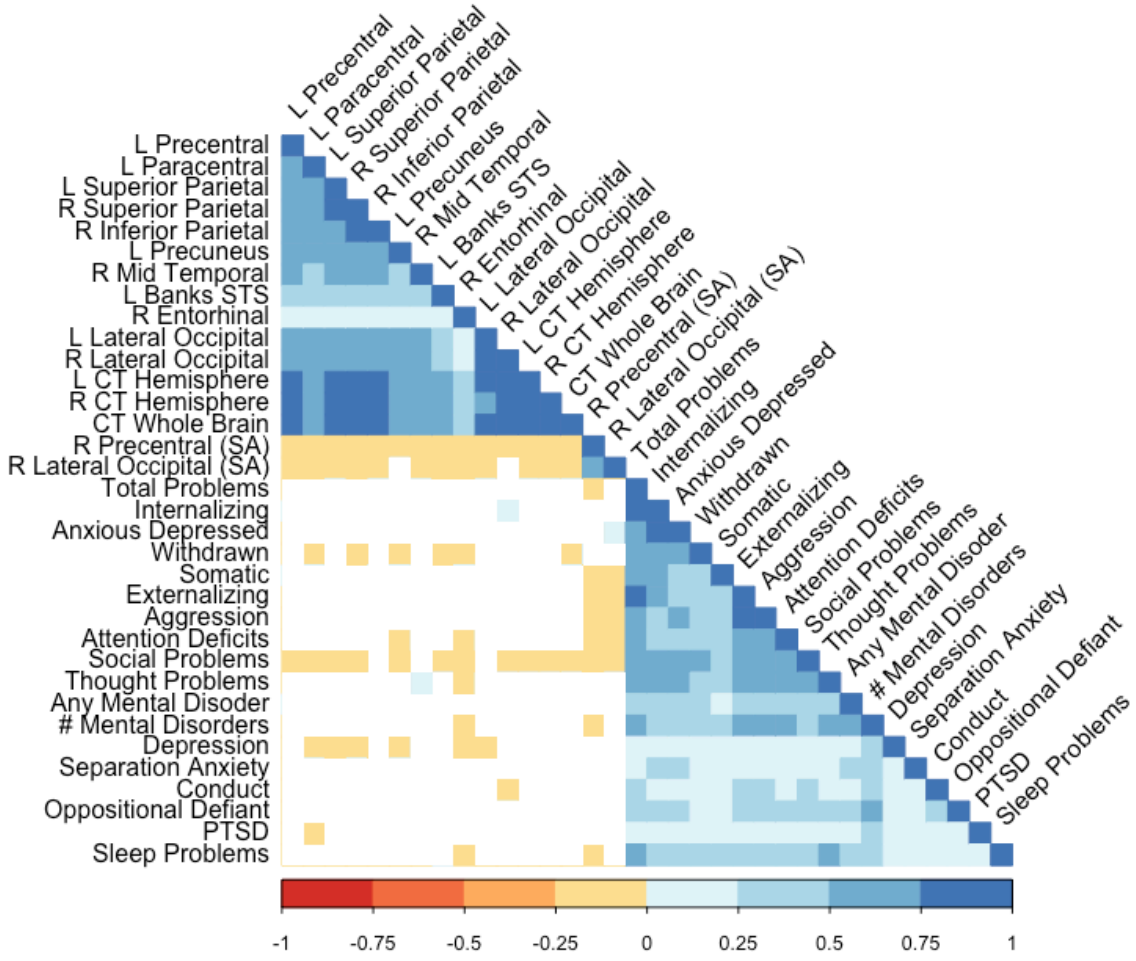


Figure 5: Correlations among family history negative youth.

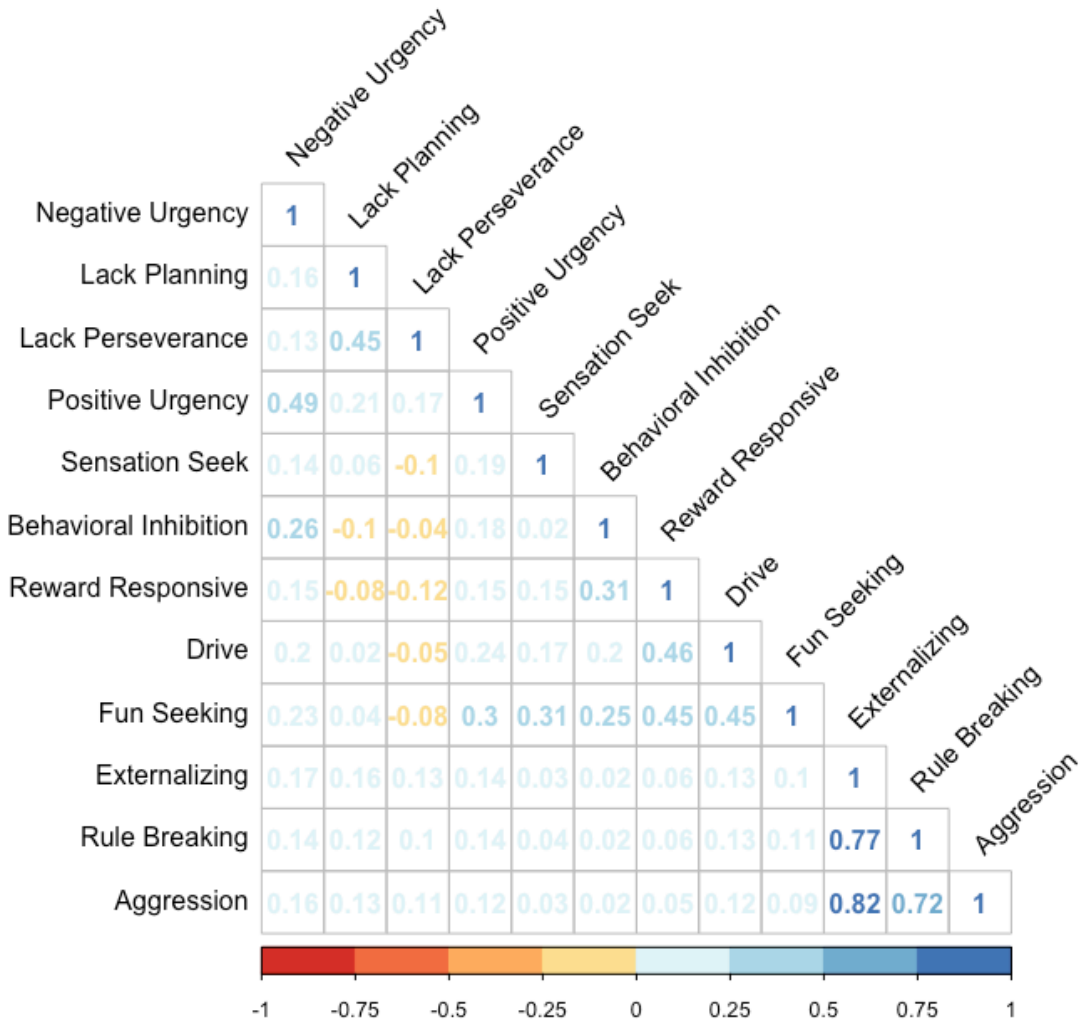


Post-Hoc Analyses

Table 6: Psychometric properties of the UPPS and BIS/BAS

Sub-scales	Cronbach's alpha	Average inter-item correlation
UPPS-P		
Negative Urgency	0.63	0.30
Lack planning	0.73	0.40
Sensation seeking	0.49	0.19
Positive urgency	0.77	0.46
Lack perseverance	0.70	0.36
BIS/BAS		
Behavioral inhibition	0.56	0.17
Reward responsiveness	0.73	0.35
Drive	0.77	0.46
Fun seeking	0.66	0.32

Figure 6: Correlations (*r*) between externalizing psychopathology, impulsivity (UPPS-P), and motivation (BIS/BAS) subscales.



Appendix 5

Supplementary materials for Chapter 5

Lees et al. Association of prenatal alcohol exposure with psychological, behavioral, and neurodevelopmental outcomes in children from the Adolescent Brain Cognitive Development Study.

Methods: Additional Details

The validated Developmental History Questionnaire, originally developed by the Adolescent Component of the National Comorbidity Survey (Merikangas et al., 2009, Kessler et al., 2009), was modified by the ABCD team to include additional questions on maternal use of substances during pregnancy.

ABCD Baseline Alcohol Use Questions During Pregnancy

- Before you/biological mom found out you/biological mom were pregnant, but while you might have been pregnant with this child, did you use any of the following? Alcohol?
- Before knowing of pregnancy, what was the maximum number of drinks consumed in one sitting?
- Before knowing of pregnancy, what was the average number of drinks consumed per week?
- Once you/biological mom knew you/she were pregnant, were you/biological mom use any of the following? Alcohol?
- After knowing of pregnancy, what was the maximum number of drinks consumed in one sitting?
- After knowing of pregnancy, what was the average number of drinks consumed per week?

Examining prenatal alcohol exposure.

The categorical PAE variable included all youth with any parent-reported prenatal alcohol exposure before or after knowledge of pregnancy. To examine the dose-dependent relationship of PAE on outcomes of interest, an estimate of the total number of drinks consumed during pregnancy was calculated. This was based on: a) average number of drinks consumed per week before pregnancy knowledge, b) the week the mother learned of pregnancy, c) average number of drinks consumed per week following pregnancy knowledge, and d) gestational week of birth. Two weeks were subtracted from reported week of pregnancy knowledge to adjust for conception date.

Estimate of total drinks = ab + c(d – b – 2)

To explore the effect of common PAE patterns, maternal drinking was categorized into abstinent (< 1 standard drink/occasion throughout pregnancy), light (1-2 drinks/occasion, <7 drinks/week), moderate (3-4/occasion, <7/week), heavy (<5/occasion, 7+/week), or binge drinking (5+/occasion) before and after knowing of pregnancy, based on established prenatal alcohol use classification (O'Leary et al., 2010). Common patterns were identified:

1) Abstinent throughout pregnancy;
2) Light reducers (light before knowing, abstinent after knowing of pregnancy);
3) Heavier reducers (moderate, heavy, and binge drinkers before knowing, abstinent or light drinking after knowing);
4) Stable light drinkers throughout pregnancy;
5) Stable heavier drinkers throughout pregnancy;
6) Increasers (drank more after knowledge of pregnancy).

Additional Results

Supplementary Table S1. Psychological, behavioral and cognitive characteristics.

	Total	No prenatal alcohol exposure		Prenatal alcohol exposure		
	N	N	%	N	%	*p*
Past/present mental disorders						
Depression	264	195	2.7	69	2.7	1.0
Generalized Anxiety Disorder	409	288	4.0	121	4.8	.10
Panic Disorder	27	18	0.2	9	0.4	.51
Separation Anxiety	834	554	7.7	280	11.1	<.001
Social Anxiety/Selective Mutism Disorder	453	326	4.5	127	5.0	.32
Hallucinations	46	28	0.4	18	0.7	.06
Delusions	163	116	1.6	47	1.9	.45
Attention Deficit Hyperactivity	1,870	1,314	18.2	556	22.1	<.001
Oppositional Defiant Disorder	1,283	868	12.1	415	16.5	<.001
Conduct Disorder	271	190	2.6	81	3.2	.15
Obsessive-Compulsive Disorder	844	597	8.3	247	9.8	.02
Unspecific Bipolar and Related Disorder	324	251	3.5	73	2.9	.18
Post Traumatic Stress Disorder	170	116	1.6	54	2.1	.10
Specific Phobia	2,511	1,826	25.4	685	27.2	.08
Cash Choice Task – delayed gratification	5,535	4,067	56.5	1,468	58.3	.29
	Mean	**Mean**	**SD**	**Mean**	**SD**	***p***
Psychological problems (CBCL)						
Total problems	45.6	45.0	11.3	47.2	10.8	<.001
Externalizing	45.4	45.0	10.1	46.6	10.3	<.001
Rule breaking behavior	52.6	52.5	4.6	52.9	4.9	<.001
Aggressive behavior	52.7	52.5	5.2	53.1	5.7	<.001
Internalizing	48.4	48.0	10.6	49.5	10.4	<.001
Anxious/Depressed	53.4	53.3	5.9	53.8	6.0	<.001
Withdrawn/Depressed	53.4	53.3	5.6	53.7	5.9	.005
Somatic complaints	54.9	54.7	6.0	55.4	6.2	<.001
Social problems	52.7	52.6	4.6	52.8	4.6	.129
Thought problems	53.7	53.5	5.7	54.3	6.1	<.001
Attention problems	53.8	53.6	5.9	54.2	6.3	<.001
Impulsivity (UPPS-P)						
Lack of planning	7.8	7.7	2.4	7.9	2.3	<.001
Sensation seeking	9.8	9.7	2.7	10.0	2.6	<.001
Negative urgency	8.5	8.4	2.6	8.6	2.6	.02
Positive urgency	8.0	8.0	3.0	7.9	2.9	.62
Lack of perseverance	7.0	7.0	2.2	7.1	2.2	.07
Motivation (BIS/BAS)						
Behavioral inhibition	5.5	5.5	2.9	5.5	2.8	.47
Reward responsiveness	8.8	8.8	2.4	8.7	2.4	.09
Drive	4.1	4.1	3.1	4.0	2.9	.04
Fun seeking	5.7	5.7	2.7	5.7	2.5	.04
NIH Toolbox fluid intelligence						
Processing Speed (Pattern Comparison)	93.8	93.7	22.0	94.2	22.2	.43
Working memory (List Sorting)	100.9	100.2	14.7	102.9	14.4	<.001
Episodic memory (Picture Sequence)	101.4	101.0	16.0	102.50	16.4	<.001
Executive function / attention / inhibition (Flanker)	95.6	95.2	13.7	96.8	13.3	<.001
Executive function / cognitive flexibility (Dimensional Change Card Sort)	96.9	96.4	15.1	98.3	15.3	<.001
RAVLT						
Learning (Trials I-V avg)	8.9	8.8	2.0	9.1	1.9	<.001
Immediate delay (Trial VI)	9.7	9.6	3.0	10.0	2.9	<.001
Long (30 min) delay (Trial VII)	9.2	9.1	3.2	9.6	3.1	<.001

PAE Dichotomous Analysis: Additional Results

Supplementary Table S2: Psychological, behavioral, and cognitive outcomes associated with any prenatal alcohol exposure, when adjusting for random effects only (family, site).

	***B* (95% CI)**	***p***	**R^2**
CBCL			
Total problems	2.61 (2.08, 3.13)	<.001	.007
Externalizing	1.95 (1.47, 2.43)	<.001	.005
Rule breaking behavior	0.56 (0.34, 0.78)	<.001	.002
Aggressive behavior	0.70 (0.45, 0.95)	<.001	.002
Internalizing	1.91 (1.42, 2.41)	<.001	.004
Anxious/depressed	0.69 (0.41, 0.97)	<.001	.001
Withdrawn/depressed	0.50 (0.23, 0.77)	<.001	.001
Somatic complaints	0.78 (0.49, 1.07)	<.001	.002
Social problems	0.28 (0.06, 0.49)	.01	.000
Thought problems	0.93 (0.66, 1.21)	<.001	.003
Attention problems	0.79 (0.50, 1.07)	<.001	.002
KSADS			
Depression	0.01 (-0.13, 0.15)	.93	.000
Generalized Anxiety Disorder	0.19 (0.08, 0.30)	.08	.000
Panic Disorder	0.35 (-0.06, 0.76)	.39	.000
Separation Anxiety	0.41 (0.33, 0.49)	<.001	.003
Social Anxiety/Selective Mutism Disorder	0.10 (0.00, 0.21)	.33	.000
Hallucinations	0.60 (0.30, 0.91)	.05	.000
Delusions	0.15 (-0.03, 0.32)	.40	.000
Attention Deficit Hyperactivity	0.25 (0.19, 0.30)	<.001	.002
Oppositional Defiant Disorder	0.38 (0.31, 0.44)	<.001	.004
Conduct Disorder	0.20 (0.06, 0.33)	.14	.000
Obsessive-Compulsive Disorder	0.20 (0.12, 0.28)	.01	.000
Unspecific Bipolar and Related Disorder	-0.19 (-0.33, -0.06)	.15	.000
Post Traumatic Stress Disorder	0.29 (0.12, 0.45)	.08	.000
Specific Phobia	0.09 (0.04, 0.14)	.09	.000
UPPS-P			
Lack of planning	0.29 (0.18, 0.40)	<.001	.003
Sensation seeking	0.26 (0.13, 0.38)	<.001	.002
Negative urgency	0.09 (-0.04, 0.21)	.17	.000
Positive urgency	-0.02 (-0.16, 0.12)	.80	.000
Lack of perseverance	0.11 (0.00, 0.21)	.05	.000
BIS/BAS			
Behavioral inhibition	0.09 (-0.04, 0.22)	.19	.000
Reward responsiveness	-0.07 (-0.18, 0.04)	.23	.000
Drive	-0.10 (-0.25, 0.04)	.15	.000
Fun seeking	0.05 (-0.08, 0.17)	.43	.000
NIH Toolbox			
Processing Speed (Pattern Comparison)	0.07 (-0.96, 1.09)	.90	.000
Working memory (List Sorting)	2.63 (1.95, 3.32)	<.001	.007
Episodic memory (Picture Sequence)	1.46 (0.71, 2.22)	<.001	.002
Executive function / attention / inhibition (Flanker)	1.55 (0.92, 2.19)	<.001	.003
Executive function / cognitive flexibility (Dimensional Change Card Sort)	1.81 (1.10, 2.52)	<.001	.003
RAVLT			
Learning	-0.23 (-0.24, -0.22)	<.001	.003
Immediate delay	0.37 (0.23, 0.51)	<.001	.003
Long (30 min) delay	0.46 (0.32, 0.61)	<.001	.004
Cash Choice Task	0.08 (0.03, 0.12)	.12	.000

Unstandardized regression coefficients and associated 95% confidence interval, p-value and R^2 value are presented for the effects of prenatal alcohol exposure compared to no exposure. GAMMs controlled for random effects (family, scanner/site).

Supplementary Table S3: Structural brain measures associated with any prenatal alcohol exposure, when adjusting for random effects only (family, site).

Region		*B* (95% CI)	*p*	R^2
Cortical volume				
Frontal				
Caudal middle frontal	L	162.2 (90.0-234.4)	<.001	.003
Lateral orbitofrontal	L	160.2 (111.2-209.2)	<.001	.005
	R	128.2 (78.7-177.7)	<.001	.005
Pars opercularis	L	100.8 (51.3-150.2)	.004	.002
Pars orbitalis	L	60.0 (42.1-77.9)	<.001	.005
	R	46.2 (24.7-67.6)	.002	.002
Precentral	L	191.5 (101.4-281.7)	.002	.002
	R	174.1 (84.4-263.8)	.01	.002
Rostral middle frontal	L	265.7 (141.2-390.2)	.002	.002
	R	289.9 (164.2-415.5)	<.001	.002
Superior frontal	L	343.2 (191.0-495.4)	<.001	.003
	R	392.4 (240.2-544.5)	<.001	.004
Frontal pole	L	16.3 (7.7-25.0)	.01	.001
	R	23.2 (12.0-34.5)	.004	.002
Caudal middle frontal	L	152.2 (79.4-224.9)	<.001	.002
Medial orbitofrontal	R	81.5 (45.7-117.3)	<.001	.003
Parietal				
Postcentral	L	210.2 (126.0-294.4)	<.001	.003
Precuneus	L	219.4 (143.1-295.7)	<.001	.003
	R	257.3 (176.2-338.5)	<.001	.004
Superior parietal	L	263.3 (158.1-368.4)	<.001	.003
	R	251.9 (146.5-357.3)	<.001	.002
Supramarginal	L	209.6 (109.2-310.1)	0.003	.002
	R	259.3 (166.1-352.5)	<.001	.003
Inferior parietal	L	266.8 (158.1-375.5)	<.001	.002
Inferior parietal	R	292.7 (166.4-418.9)	<.001	.002
Temporal				
Fusiform	L	230.0 (150.7-309.4)	<.001	.005
	R	201.6 (124.1-279.1)	<.001	.004
Parahippocampal	L	37.0 (16.2-57.7)	0.033	.002
	R	49.4 (29.1-69.6)	<.001	.003
Superior temporal	L	188.5 (102.7-274.2)	<.001	.002
	R	214.8 (137.1-292.5)	<.001	.004
Transverse temporal	L	24.6 (11.8-37.4)	0.012	.002
	R	22.9 (12.8-33.0)	<.001	.003
Banks of superior temporal sulcus	L	53.9 (29.9-78.0)	<.001	.002
Inferior temporal	L	343.0 (246.2-439.8)	<.001	.006
	R	236.3 (144.2-328.3)	<.001	.003
Middle temporal	L	303.9 (217.9-390.0)	<.001	.006
	R	339.3 (248.9-429.8)	<.001	.006
Temporal pole	R	38.2 (21.6-54.8)	<.001	.002
Occipital				
Cuneus	L	56.6 (28.5-84.6)	.005	.002
	R	76.0 (44.1-107.9)	<.001	.002
Lingual	L	124.1 (66.7-181.5)	.002	.003
	R	125.6 (70.0-181.2)	<.001	.003
Lateral occipital	L	319.0 (228.3-409.7)	<.001	.005
	R	300.9 (203.9-397.9)	<.001	.004
Cingulate				
Caudal anterior	L	53.6 (25.3-81.9)	.014	.001
Isthmus	L	58.8 (29.5-88.2)	.006	.002

Region		*B* (95% CI)	*p*	R^2
Posterior	L	66.5 (34.7-98.3)	.003	.002
Rostral anterior	L	57.2 (29.3-85.1)	.004	.002
Insula	L	72.8 (32.2-113.3)	.03	.002
Subcortical volume				
Cerebellum	L	563.3 (311.0-815.6)	<.001	.003
	R	618.3 (359.7-876.9)	<.001	.004
Thalamus	L	73.7 (40.-107.4)	<.001	.001
	R	59.8 (27.4-92.3)	.01	.001
Hippocampus	L	39.4 (19.3-59.4)	.004	.001
	R	48.2 (28.4-68.0)	<.001	.002
Amygdala	L	18.5 (8.5-28.4)	.01	.001
	R	18.7 (8.7-28.8)	.01	.001
Ventral diencephalon	L	30.5 (11.8-49.2)	.05	.001
	R	47.2 (28.4-65.9)	<.001	.003
Intracranial		17582.0 (11190.3-23972.7)	<.001	.002
Cerebrum		15586.0 (10642.9-20529.7)	<.001	.005
Total grey		532.5 (300.2-764.8)	<.001	.002
Surface area				
Frontal				
Caudal middle frontal	L	50.2 (29.0-71.3)	.002	.003
	R	49.1 (27.5-70.8)	<.001	.003
Lateral orbitofrontal	L	37.3 (23.0-51.5)	<.001	.004
	R	32.9 (18.0-47.8)	<.001	.004
Medial orbitofrontal	L	25.4 (13.5-37.2)	.002	.003
	R	26.2 (16.0-36.4)	<.001	.004
Pars opercularis	L	25.9 (11.7-40.1)	.02	.002
Pars orbitalis	L	12.0 (7.8-16.1)	<.001	.004
	R	10.5 (5.4-15.7)	.004	.002
Precentral	L	54.3 (25.3-83.3)	.02	.002
Rostral middle frontal	L	73.1 (33.8-112.4)	.02	.002
	R	91.4 (50.7-132.1)	<.001	.003
Superior frontal	L	103.5 (59.1-147.9)	<.001	.004
	R	110.0 (65.4-154.5)	<.001	.004
Frontal pole	R	5.1 (2.7-7.4)	.002	.002
Parietal				
Inferior parietal	L	69.6 (35.6-103.6)	.004	.003
	R	74.9 (35.8-114.0)	.01	.002
Postcentral	L	53.1 (26.7-79.6)	.006	.003
Precuneus	L	64.0 (39.1-88.8)	<.001	.003
	R	78.0 (50.5-105.5)	<.001	.003
Superior parietal	L	81.1 (46.2-116.0)	<.001	.003
	R	78.8 (44.5-113.2)	<.001	.003
Supramarginal	L	54.7 (23.6-85.8)	.04	.002
	R	70.0 (41.2-98.7)	<.001	.004
Temporal				
Fusiform	L	56.0 (35.2-76.9)	<.001	.004
	R	52.0 (31.2-72.8)	<.001	.004
Middle temporal	L	58.5 (37.4-79.6)	<001	.005
	R	65.2 (42.7-87.7)	<.001	.005
Banks of superior temporal sulcus	R	14.7 (7.1-22.3)	.01	.002
Inferior temporal	L	77.9 (53.4-102.4)	<.001	.006
	R	55.4 (32.7-78.0)	<.001	.004
Superior temporal	R	46.1 (25.5-66.7)	<.001	.004
Traverse temporal	R	5.7 (3.0-8.3)	.002	.002
Occipital				

Region		*B* (95% CI)	*p*	R^2
Lingual	L	35.0 (14.9-55.1)	.04	.002
	R	39.3 (19.8-58.7)	.005	.002
Lateral occipital	L	90.8 (60.4-121.2)	<.001	.006
	R	76.9 (45.7-108.2)	<.001	.004
Cingulate				
Caudal anterior	L	14.7 (7.2-22.2)	.009	.002
Isthmus	L	18.4 (8.7-28.1)	.01	.002
Posterior	L	19.3 (9.4-29.3)	.01	.002
Cortical thickness				
Parietal				
Postcentral	L	.01 (.01-.02)	.03	.000
Temporal				
Middle temporal	R	.01 (.01-.020)	.04	.000
Occipital				
Cuneus	L	.01 (.01-.02)	.01	.001
	R	.02 (.01-.03)	<.001	.002
Lateral occipital	L	.01 (.00-.02)	.04	-.001
	R	.01 (.01-.02)	.004	-.001
Lingual	L	.01 (.01-.02)	.03	.001

Unstandardized regression coefficients and associated 95% confidence interval, false discovery rate adjusted p-value and R^2 value are presented for the effects of prenatal alcohol exposure compared to no exposure. Only regions where the model passed the FDR correction for volume, surface area or cortical thickness are presented. These generalized additive mixed models controlled for random effects only (family, scanner/site).

Supplementary Table S4: Functional connectivity indicies associated with any prenatal alcohol exposure. Only the associations which passed FDR correction in unadjusted models are presented.

	***B* (95% CI)**	***p***	***R*²**
Unadjusted Models			
Between networks			
Sensorimotor hand – salience	0.007 (0.002, 0.011)	.03	.002
Network – subcortical region			
Auditory – right ventral diencephalon	-0.001 (-0.018, -0.006)	<.001	.002
Default – left amygdala	0.013 (0.005, 0.020)	.02	.001
Salience – left ventral diencephalon	-0.010 (-0.016, -0.004)	.01	.001
Adjusted Models			
Between networks			
Sensorimotor hand – salience	0.010 (0.002, 0.012)	.002	.027
Network – subcortical region			
Auditory – right ventral diencephalon	-0.010 (-0.018, -0.006)	.001	.012
Default – left amygdala	0.015 (0.004, 0.019)	.09	.003
Salience – left ventral diencephalon	-0.008 (-0.015, -0.001)	.48	.006

Unstandardized regression coefficients and associated 95% confidence interval, false discovery rate adjusted p-value and R^2 value are presented for the effects of prenatal alcohol exposure compared to no exposure. Only the network connectivity associations where the model passed the FDR correction in unadjusted models are presented. Unadjusted generalized additive mixed models controlled for random effects only (family, scanner/site). Adjusted models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use) and random (family, scanner/site) effects.

Note, hyperconnectivity between the default network and left amygdala, and hypoconnectivity between the salience network and left ventral diencephalon, among PAE compared to unexposed youth was no longer significant in the covariate-adjusted models.

Supplementary Table S5: Functional connectivity within and between major networks which have previously been associated with fetal alcohol spectrum disorder. No associations were significant in unadjusted or adjusted models.

	***B* (95% CI)**	***p***	**R^2**
Unadjusted models			
Within networks			
Default	0.002 (-0.002, 0.006)	.30	-0.0002
Salience	-0.005 (-0.014, 0.005)	.33	0.0002
Dorsal attention	0.002 (-0.002, 0.006)	.42	-0.0003
Fronto-parietal	-0.001 (-0.005, 0.003)	.56	0.0000
Between networks			
Default – salience	0.001 (-0.003, 0.005)	.64	0.0000
Default – dorsal attention	-0.001 (-0.004, 0.003)	.67	-0.0003
Default – fronto-parietal	0.000 (-0.003, 0.003)	.87	-0.0001
Salience – dorsal attention	0.000 (-0.004, 0.004)	.91	0.0000
Salience – fronto-parietal	0.000 (-0.005, 0.004)	.82	0.0000
Dorsal attention – fronto-parietal	0.000 (-0.002, 0.003)	.81	0.0000
Covariate-adjusted models			
Within networks			
Default	0.001 (-0.003, 0.004)	.79	.027
Salience	-0.008 (-0.018, 0.002)	.13	.004
Dorsal attention	0.000 (-0.004, 0.004)	.96	.012
Fronto-parietal	-0.002 (-0.006, 0.002)	.33	.012
Between networks			
Default – salience	0.000 (-0.006, 0.004)	.69	.008
Default – dorsal attention	0.000 (-0.003, 0.004)	.82	.027
Default – fronto-parietal	0.000 (-0.003, 0.003)	.77	.006
Salience – dorsal attention	0.001 (-0.003, 0.006)	.52	.006
Salience – fronto-parietal	-0.001 (-0.006, 0.003)	.61	.002
Dorsal attention – fronto-parietal	0.000 (-0.002, 0.003)	.71	.002

Unstandardized regression coefficients and associated 95% confidence interval, p-value and R^2 value are presented for the effects of prenatal alcohol exposure compared to no exposure. Unadjusted generalized additive mixed models controlled for random effects only (family, scanner/site). Adjusted models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use) and random (family, scanner/site) effects.

Supplementary Table S6: Dichotomous PAE variable follow-up analysis for regional brain ROIs when including intracranial volume as an additional covariate.

		***B* (95% CI)**	***p***	***R^2***
Volume				
Inferior parietal	L	118.1 (25.1, 211.0)	.08	.356
Supramarginal	R	89.1 (9.0, 169.1)	.18	.358
Inferior temporal	L	126.4 (46.9, 205.8)	.01	.323
Middle temporal	L	82.1 (12.9, 151.2)	.12	.439
	R	79.5 (11.6, 147.4)	.13	.498
Lateral occipital	L	89.3 (15.1, 163.5)	.11	.412

Unstandardized regression coefficients and associated 95% confidence interval, false discovery rate adjusted p-value and R^2 value are presented for generalized additive model results for the effects of prenatal alcohol exposure compared to no exposure. Only regional brain ROIs identified from first series of analyses are presented. These generalized additive mixed models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use) and random (family, scanner/site) effects.

Supplementary Table S7: Significant associations between covariates included in GAMMs and outcomes

	Structural MRI	Resting-state functional MRI	Behavioral outcomes	Cognitive outcomes
			Higher scores = Greater problems	*Higher scores = Better performance*
Youth measures				
↑ Age	-	+/-	+	+
Being female	+	-	+	-
Race (compared to white)	-	+/-	+/-	+/-
Born premature	+		+	
↑ Birthweight	+	-		+
↑ School grades	+		-	+
Tobacco exposure		-	+	
Cannabis exposure			+	
Heroin exposure				
Cocaine exposure			+	
↑ School grade		+		
Parent measures				
↑ Parent education	+		-	+
Maternal depression			+	+/-
↑ Maternal age	+		-	+

"+" = positive association, "-" = negative association, "+/-" = both positive and negative associations were observed. If there is no + or -, no significant association was observed in the GAMMs.

Dose-Dependent Relationship Analysis Results

Supplementary Table S8: Generalized additive model results for alcohol use as a continuous measure, using an estimate of total drinks throughout pregnancy, when adjusting for fixed and random effects.

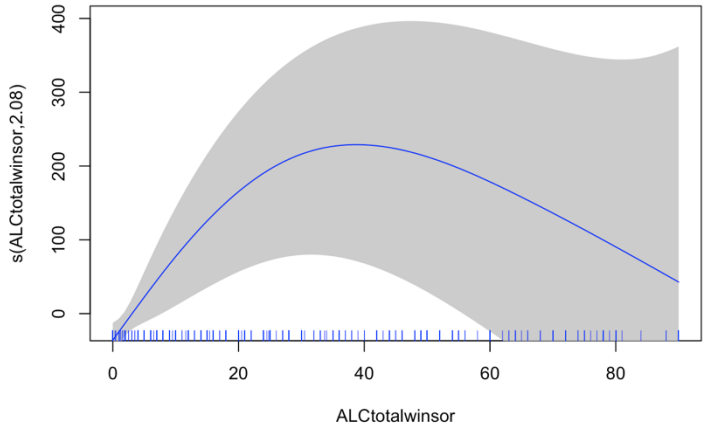
	B (95% CI)	*p*	R^2
CBCL			
Total problems	0.02 (0.00, 0.03)	.009	.137
Externalizing	0.01 (0.00, 0.03)	.07	.107
Rule breaking behavior	0.00 (0.00, 0.01)	.47	.111
Aggressive behavior	0.00 (0.00, 0.01)	.35	.089
Internalizing	0.02 (0.00, 0.32)	.02	.076
Anxious/depressed	0.01 (0.00, 0.01)	.14	.051
Withdrawn/depressed	0.01 (0.00, 0.01)	.14	.071
Somatic complaints	0.01 (0.01, 0.02)	.001	.042
Social problems	0.00 (0.00, 0.01)	.63	.102
Thought problems	0.00 (0.00, 0.01)	.22	.078
Attention problems	0.01 (0.00, 0.02)	.04	.169
KSADS			
Depression	0.00 (-0.01, 0.00)	.83	.027
Generalized Anxiety Disorder	0.00 (-0.01, 0.00)	.53	.026
Panic Disorder	0.00 (-0.01, 0.00)	.54	.003
Separation Anxiety	0.00 (-0.01, 0.00)	.31	.026
Social Anxiety/Selective Mutism Disorder	0.00 (-0.01, 0.00)	.50	.015
Hallucinations	0.00 (-0.01, 0.00)	.42	.004
Delusions	0.00 (-0.01, 0.00)	.95	.010
Attention Deficit Hyperactivity	0.00 (0.00, 0.00)	.11	.130
Oppositional Defiant Disorder	0.00 (0.00, 0.00)	.46	.049
Conduct Disorder	-0.01 (-0.01, 0.00)	.19	.040
Obsessive-Compulsive Disorder	0.00 (0.00, 0.01)	.12	.019
Unspecific Bipolar and Related Disorder	0.00 (-0.01, 0.00)	.33	.017
Post Traumatic Stress Disorder	0.00 (-0.01, 0.00)	.42	.030
Specific Phobia	0.00 (0.00, 0.00)	.25	.019
UPPS-P			
Lack of planning	0.002 (-0.002, 0.005)	.35	.030
Sensation seeking	0.006 (0.002, 0.009)	.003	.026
Negative urgency	0.002 (-0.002, 0.005)	.42	.017
Positive urgency	0.001 (-0.003, 0.006)	.47	.049
Lack of perseverance	0.001 (-0.002, 0.004)	.46	.049
BIS/BAS			
Behavioral inhibition	0.003 (-0.001, 0.007)	.12	.010
Reward responsiveness	0.001 (-0.002, 0.005)	.48	.023
Drive	0.001 (-0.004, 0.005)	.77	.060
Fun seeking	0.003 (-0.001, 0.007)	.99	.023
NIH Toolbox			
Processing Speed (Pattern Comparison)	-0.006 (-0.037, 0.024)	.67	.056
Working memory (List Sorting)	0.013 (-0.006, 0.032)	.176	.151
Episodic memory (Picture Sequence)	0.000 (-0.022, 0.021)	.97	.091
Executive function / attention / inhibition (Flanker)	0.023 (0.005, 0.042)	.01	.051
Executive function / cognitive flexibility (Dimensional Change Card Sort)	0.014 (-0.007, 0.035)	.183	.080
RAVLT			
Learning	-0.66 (-0.97, -0.35)	<.001	.130

Immediate delay		0.00 (0.00, 0.01)	.45	.130
Long (30 min) delay		0.00 (0.00, 0.01)	.10	.137
Cash Choice Task		-0.001 (-0.002, 0.000)	.55	.005
Brain structure				
Volume				
Cerebrum		8005.30 (3654.66, 12355.96)	<.001	.342
Inferior parietal	L	206.53 (98.71, 314.34)	.01	.150
Supramarginal	R	167.17 (74.34, 260.01)	.03	.135
Inferior temporal	L	214.54 (120.51, 308.57)	<.001	.194
Middle temporal	L	154.07 (71.46, 236.67)	.02	.205
	R	162.64 (78.3, 246.9)	.01	.258
Lateral occipital	L	155.15 (69.8, 240.5)	.02	.248
Surface area				
Precuneus	R	48.62 (22.3, 74.9)	.02	.215
Inferior temporal	L	51.46 (27.75, 75.17)	.001	.196
Lateral occipital	L	53.64 (24.8, 82.5)	.02	.213
Functional connectivity				
Sensorimotor hand – salience		0.00 (0.00, 0.00)	.45	.005
Auditory – right ventral diencephalon		-0.0002 (-0.0003, -0.00002)	.03	.011

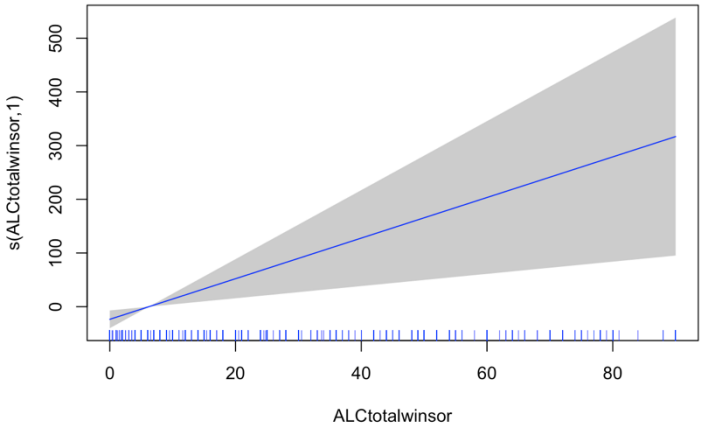
Unstandardized regression coefficients and associated 95% confidence interval, p-value/false discovery rate adjusted p-value (for brain ROIs) and R^2 value are presented for generalised additive model results for alcohol use as a continuous measure, using an estimate of total drinks throughout pregnancy. Only brain ROIs identified from first series of analyses are presented. These generalized additive mixed models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects. N=8811. Data winsorized at .015.

Supplementary Figure S1: Spline models for estimated total number of alcoholic drinks consumed during pregnancy with offspring brain volume and surface area, when adjusting for fixed and random effects.

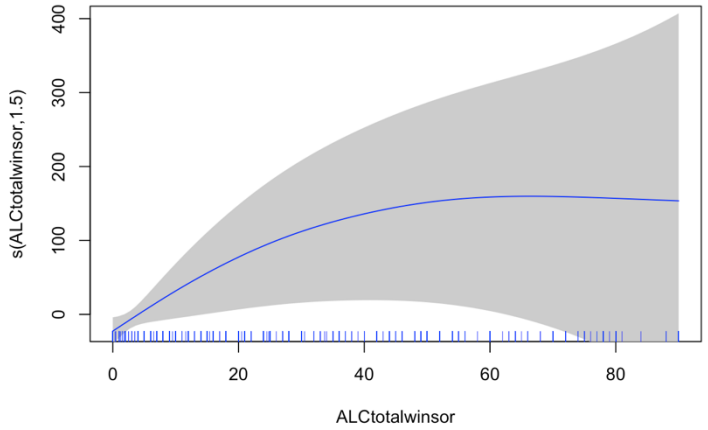
A. Left inferior parietal volume



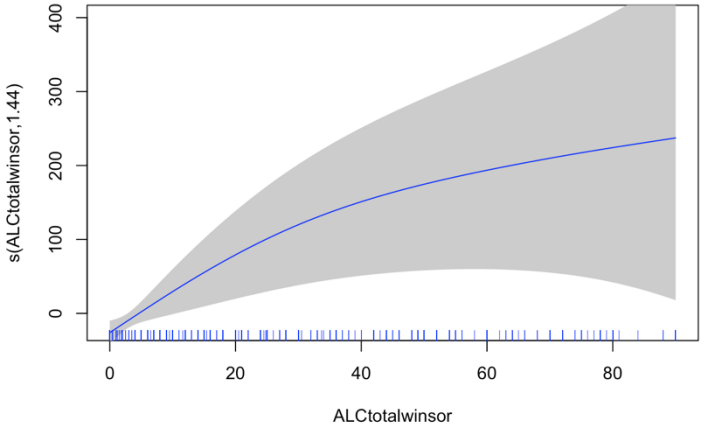
B. Right supramarginal volume



C. Left inferior temporal volume

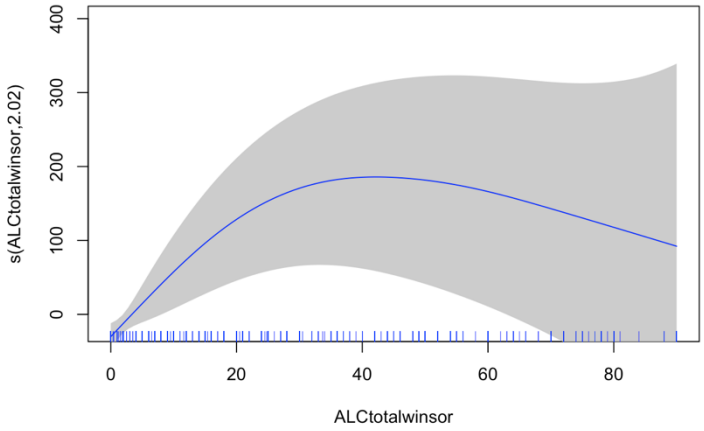


D. Left middle temporal volume

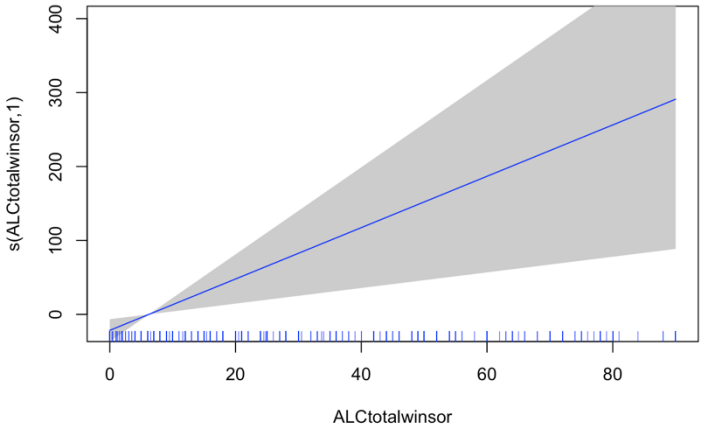


Supplementary Figure S1 continued:

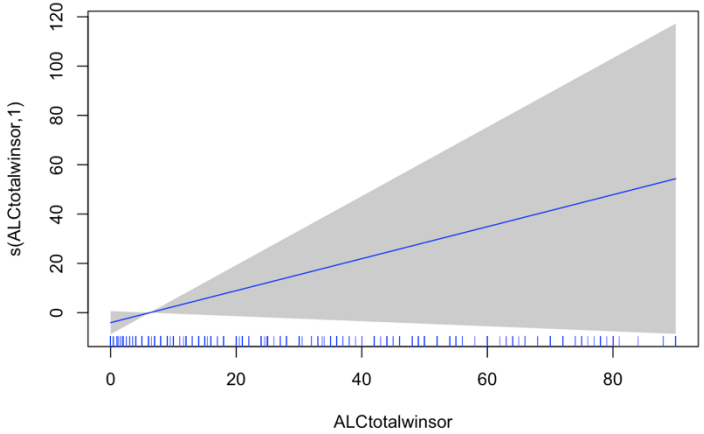
E. Right middle temporal volume



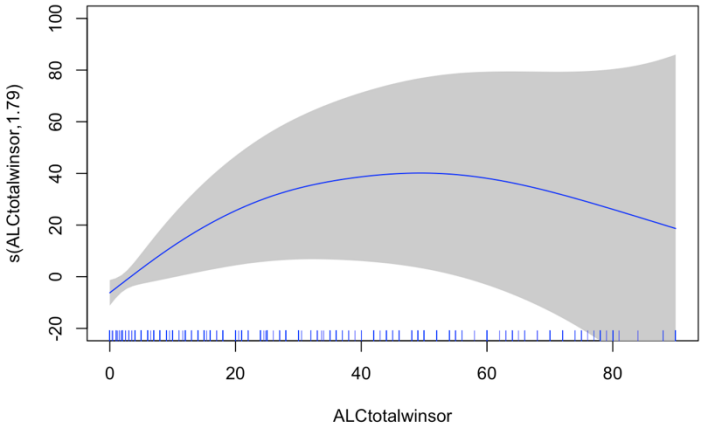
F. Left lateral occipital volume



G. Right precuneus surface area

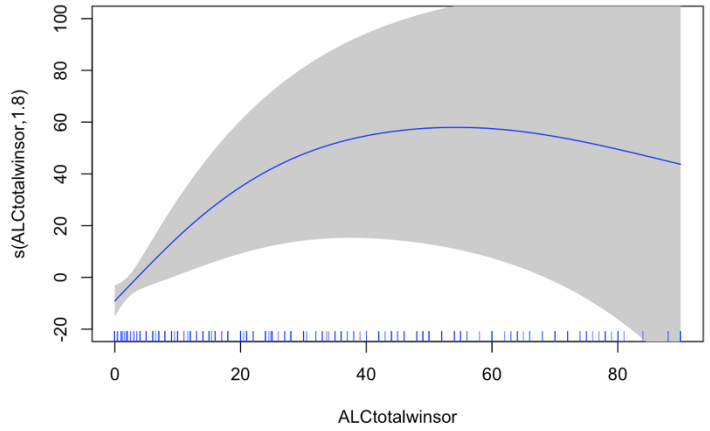


H. Left Inferior temporal surface area

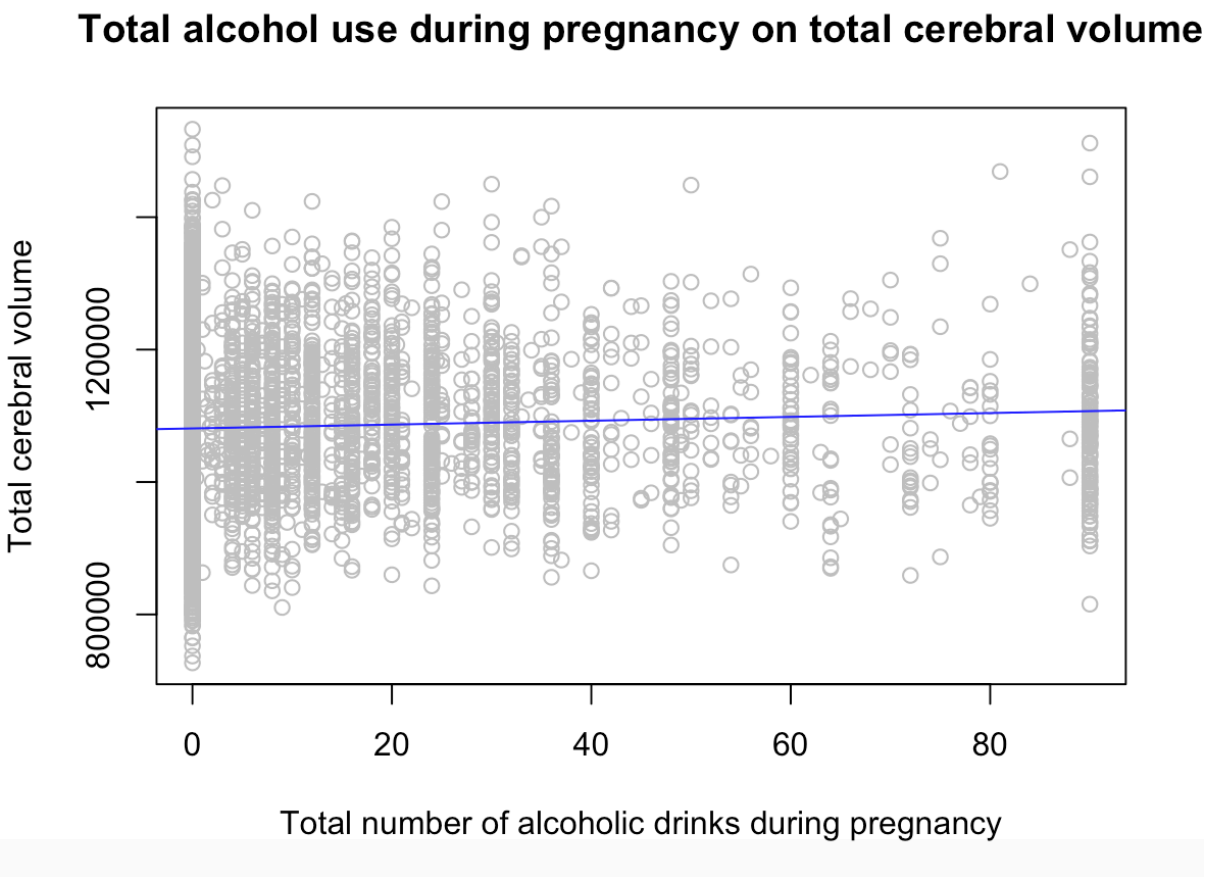


Supplementary Figure S1 continued:

I. Left lateral occipital surface area



Supplement Figure S2: Data points on plot of total drinks consumed during pregnancy and total cerebral volume



Exposure Pattern Analysis Results

Supplementary Table S9: Demographic, psychological, behavioral, and cognitive characteristics for unexposed, light reducers, stable light drinkers and heavier reducers.

	No prenatal alcohol exposure n=6669	Light reducer n=1203	Stable light n=93	Heavier reducer n=755	*p*
Age (mean [SD])	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	9.9 (0.6)	.82
Sex (%)					.24
Female	47.7	527.7	48.0	51.3	
Male	52.3	47.3	52.0	48.7	
Race (%)					<.001
White	51.4	81.7	64.9	68.9	
Hispanic	21.6	10.8	15.5	17.1	
Black	15.1	2.2	8.4	6.0	
Asian	1.8	0.0	1.5	0.4	
Other	10.1	5.4	9.6	7.7	
Highest Parent Education (%)					<.001
<HS Diploma	7.2	0.0	1.7	1.5	
HS Dip/GED	11.2	3.2	4.2	6.1	
Some College	30.4	12.9	21.9	33.2	
Bachelor	28.0	34.4	35.3	30.6	
Post Grad	23.1	49.5	36.7	28.6	
Birth weight (lbs [SD])	6.5 (1.5)	6.7 (1.4)	6.9 (1.6)	6.6 (1.5)	<.001
Maternal age (mean [SD])	29.3 (6.2)	30.9 (5.5)	33.5 (4.6)	29.4 (5.9)	<.001
Found out pregnant (weeks [SD])	6.9 (7.0)	6.8 (5.6)	5.7 (4.4)	6.8 (5.1)	.10
Total drinks	0.0 (0.0)	15.8 (14.7)	44.0 (25.8)	36.2 (25.5)	
Maternal Depression (%)					<.001
Yes	21.2	22.6	22.4	29.1	
No	76.5	74.2	74.9	67.3	
Unknown	2.3	3.2	2.7	3.6	
Born premature (%)					.14
Yes	79.5	81.7	82.6	80.1	
No	20.2	17.2	17.2	19.7	
Unknown	0.3	1.1	0.2	0.1	
Tobacco exposure (%)					<.001
Yes	8.8	8.6	15.0	35.1	
No	91.0	91.4	84.8	63.8	
Unknown	0.2	0.0	0.2	1.1	
Cannabis exposure (%)					<.001
Yes	2.8	9.7	6.2	18.4	
No	97.1	89.2	92.7	80.1	
Unknown	0.1	1.1	1.1	1.5	
Heroin exposure (%)					.40
Yes	0.1	0.0	0.0	0.1	
No	99.9	100.0	99.9	99.6	
Unknown	0.0	0.0	0.1	0.3	
Cocaine exposure (%)					<.001
Yes	0.1	0.0	0.5	1.3	
No	99.8	100.0	99.3	97.9	
Unknown	0.0	0.0	0.2	0.8	
Impulsivity (m [SD])					
Negative urgency	8.4 (2.6)	8.6 (2.6)	8.1 (2.5)	8.6 (2.6)	.04
Positive urgency	8.0 (3.0)	7.9 (2.9)	7.4 (2.8)	8.1 (2.9)	.26
Lack of planning	7.7 (2.4)	8.0 (2.3)	8.0 (2.2)	7.8 (2.3)	<.001
Lack of perseverance	7.0 (2.3)	7.1 (2.1)	7.3 (2.3)	7.1 (2.2)	.28

	No prenatal alcohol exposure n=6669	Light reducer n=1203	Stable light n=93	Heavier reducer n=755	*p*
Sensation seeking	9.7 (2.7)	10.0 (2.5)	10.2 (2.7)	10.2 (2.7)	<.001
Emotional/behavioural problems (m [SD])					
Total problems	45.0 (11.3)	46.2 (9.9)	47.5 (9.7)	48.1 (11.4)	<.001
Externalizing	44.9 (10.1)	45.7 (9.4)	46.3 (9.1)	47.3 (11.1)	<.001
Rule breaking behavior	52.5 (4.6)	52.3 (4.0)	51.9 (4.1)	53.5 (5.6)	<.001
Aggressive behavior	52.5 (5.2)	52.5 (4.6)	52.7 (3.9)	53.7 (6.6)	<.001
Internalizing	48.0 (10.6)	48.6 (9.9)	49.1 (10.2)	50.4 (10.9)	<.001
Anxious/Depressed	53.3 (5.9)	53.4 (5.4)	53.8 (6.4)	54.4 (6.6)	.001
Withdrawn/Depressed	53.3 (5.9)	53.0 (5.2)	52.9 (5.1)	54.1 (6.2)	.001
Somatic complaints	54.7 (6.0)	55.0 (5.8)	55.6 (6.5)	55.8 (6.5)	<.001
Social problems	52.6 (4.6)	53.7 (5.3)	52.4 (4.1)	53.2 (5.1)	.009
Thought problems	53.5 (5.7)	53.6 (5.3)	54.4 (5.9)	54.6 (6.4)	<.001
Attention problems	53.6 (5.9)	52.4 (4.1)	54.7 (6.1)	54.8 (7.1)	<.001
Past/presented mental disorders (%)					
Depression	2.8	2.3	1.9	3.6	.15
Generalized Anxiety	4.3	4.7	4.4	6.6	.03
Panic	0.2	1.2	0.3	0.3	.44
Separation Anxiety	8.2	14.0	11.8	11.1	<.001
Social Anxiety/Selective Mutism	4.9	5.8	5.1	5.4	.92
Hallucinations	0.4	1.2	0.6	0.7	.55
Delusions	1.7	1.2	1.7	1.9	.95
Attention Deficit Hyperactivity	19.0	24.4	19.8	26.5	<.001
Oppositional Defiant	12.7	14.0	15.0	20.4	<.001
Conduct	2.7	2.3	2.7	2.6	.99
Obsessive-Compulsive	8.5	7.0	9.3	9.8	.52
Unspecific Bipolar and Related Disorder	3.6	2.3	3.1	2.6	.47
Post Traumatic Stress	1.7	1.2	1.5	2.8	.17
Specific Phobia	26.6	38.4	28.1	28.7	.05
Motivation (m [SD])					
Behavioral inhibition	5.5 (2.9)	5.5 (2.7)	5.9 (2.9)	5.6 (2.8)	.56
Reward responsiveness	8.8 (2.4)	8.8 (2.4)	8.5 (2.3)	8.7 (2.3)	.38
Drive	4.1 (3.1)	4.0 (3.0)	3.8 (3.1)	4.0 (3.0)	.18
Fun seeking	5.7 (2.7)	5.7 (2.5)	6.1 (2.8)	5.8 (2.5)	.33
NIH Toolbox fluid intelligence (m [SD])					
Processing Speed (Pattern Comparison)	93.8 (22.0)	94.6 (22.3)	97.5 (18.0)	94.2 (22.5)	.33
Working memory (List Sorting)	100.4 (14.5)	102.8 (14.3)	105.9 (12.7)	103.4 (14.5)	<.001
Episodic memory (Picture Sequence)	101.2 (16.0)	102.9 (16.3)	102.1 (16.1)	102.1 (16.4)	.005
Executive function / attention / inhibition (Flanker)	95.2 (13.7)	97.0 (13.0)	99.2 (13.0)	96.6 (13.1)	<.001
Executive function / cognitive flexibility (Dimensional Change Card Sort)	96.5 (15.2)	98.6 (15.1)	99.2 (14.4)	98.9 (15.7)	<.001
RAVLT (m [SD])					
Learning (Trials I-V avg)	8.8 (2.0)	9.2 (1.9)	8.9 (2.1)	9.1 (1.9)	<.001
Immediate delay (Trial VI)	9.7 (3.0)	10.1 (2.9)	9.7 (3.1)	10.0 (2.9)	<.001
Long (30 min) delay (Trial VII)	9.1 (3.2)	9.7 (3.0)	9.4 (3.4)	9.6 (3.1)	<.001
Cash Choice Task delayed gratification (%)	58.4	61.0	58.1	58.6	.70

Supplementary Table S10: GAMM results for common patterns of alcohol exposure during pregnancy, when compared to unexposed youth.

	Light reducer n=1203		*Stable light* n=93		*Heavier reducer* n=755		
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	R^2
CBCL							
Total problems	1.39 (0.72, 2.07)	<.001	3.13 (0.94, 5.33)	.005	1.82 (0.96, 2.68)	<.001	.136
Externalizing	1.06 (0.44, 1.69)	<.001	2.18 (0.13, 4.22)	.04	1.38 (0.59, 2.18)	<.001	.106
Internalizing	0.77 (0.11, 1.43)	.02	1.51 (-0.66, 3.68)	.17	1.56 (0.72, 2.41)	<.001	.076
Anxious Depressed	0.13 (-0.24, 0.51)	.49	0.60 (-0.63, 1.83)	.34	0.59 (0.11, 1.07)	.02	.050
Withdrawn	-0.07 (-0.42, 0.29)	.71	0.09 (-1.08, 1.25)	.89	0.50 (0.05, 0.95)	.03	.070
Somatic	0.35 (-0.04, 0.74)	.08	1.06 (-0.21, 2.33)	.10	0.72 (0.23, 1.22)	.004	.041
Thought	0.20 (-0.16, 0.56)	.28	0.97 (-0.21, 2.15)	.11	0.44 (-0.02, 0.89)	.06	.076
Attention	0.17 (-0.18, 0.53)	.34	1.40 (0.23, 2.57)	.02	0.55 (0.10, 1.01)	.02	.167
Rule breaking	0.01 (-0.27, 0.29)	.96	0.03 (-0.90, 0.95)	.96	0.59 (0.23, 0.95)	.001	.111
Aggressive	0.05 (-0.28, 0.38)	.75	0.47 (-0.61, 1.55)	.40	0.57 (0.15, 0.99)	.008	.087
KSADS							
Separation Anxiety	0.28 (0.17, 0.39)	.008	0.41 (-0.09,0.74)	.20	0.05 (-0.19, 0.09)	.71	.025
Attention Deficit Hyperactivity	0.03 (-0.06, 0.12)	.71	0.39 (0.01, 0.66)	.15	0.22 (0.11, 0.32)	.04	.130
Oppositional Defiant Disorder	0.11 (0.01, 0.20)	.26	-0.01 (-0.33, 0.32)	.99	0.26 (0.15, 0.37)	.02	.046
Specific Phobia	0.07 (0.00, 0.14)	.34	0.56 (0.33, 0.79)	.01	-0.05 (-0.15, 0.04)	.57	.020
UPPS-P							
Lack of planning	0.22 (0.07, 0.37)	.004	0.25 (-0.25, 0.75)	.32	0.06 (-0.13, 0.25)	.53	.029
Sensation seeking	0.13 (-0.05, 0.30)	.15	0.40 (-0.17, 0.96)	.17	0.30 (0.08, 0.52)	.007	.026
BIS/BAS							
Fun seeking	0.11 (-0.06, 0.28)	.20	0.64 (0.08, 1.20)	.02	0.05 (-0.17, 0.26)	.66	.024
NIH Toolbox							
Working memory (List Sorting)	0.50 (-0.37, 1.38)	.26	1.96 (-0.92, 4.85)	.18	2.12 (1.00, 3.23)	<.001	.152
Executive function / attention / inhibition (Flanker)	0.84 (-0.02, 1.69)	.06	2.95 (0.11, 5.78)	.04	1.17 (0.07, 2.26)	.04	.051
Executive function / cognitive flexibility (Dimensional Change Card Sort)	0.85 (-0.10, 1.79)	.08	0.57 (-2.57, 3.70)	.72	2.01 (0.80, 3.22)	.001	.082

		Light reducer n=1203		*Stable light* n=93		*Heavier reducer* n=755		
		B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	R^2
RAVLT								
Learning		-0.55 (-1.24, 1.39)	.12	-0.14 (-2.38, 2.11)	.90	-0.12 (-0.21, 0.00)	.006	.131
Immediate delay		0.11 (-0.07, 0.29)	.23	-0.52 (-1.12, 0.09)	.09	0.21 (-0.02, 0.44)	.08	.131
Long (30 min) delay		0.20 (0.01, 0.39)	.04	-0.38 (-1.01, 0.26)	.24	0.30 (0.06, 0.55)	.02	.138
Brain Structure								
Volume								
Cerebrum		7122.20 (1494.00, 12750.48)	.01	20544.50 (2551.57, 38537.43)	.03	10844.80 (3754.16, 17935.39)	.003	.338
Inferior parietal	L	263.04 (123.50, 402.57)	.001	710.07 (259.74, 1160.41)	.01	126.15 (-50.34, 302.63)	.97	.149
Supramarginal	R	156.29 (36.90, 276.68)	.07	140.00 (-249.18, 529.18)	1.000	162.21 (9.85, 314.56)	.22	.134
Inferior temporal	L	209.35 (87.89, 330.81)	.004	219.71 (-172.90, 612.32)	1.000	212.27 (58.62, 365.92)	.02	.190
Middle temporal	L	162.54 (55.47, 269.19)	.02	134.14 (-210.88, 479.16)	1.000	161.54 (26.35, 296.73)	.12	.201
	R	160.87 (52.02, 269.73)	.02	151.36 (-199.35, 502.06)	1.000	167.58 (29.96, 305.20)	.10	.251
Lateral occipital	L	159.90 (49.77, 270.03)	.03	359.49 (3.96, 715.01)	.29	128.41 (-10.88, 267.71)	.42	.245
Surface area								
Precuneus	R	37.99 (2.85, 72.13)	.09	114.06 (3.82, 224.29)	.13	57.92 (14.77, 101.08)	.03	.210
Inferior temporal	L	44.13 (13.48, 74.79)	.01	38.04 (-60.85, 136.93)	1.000	63.9 (25.08, 102.64)	.004	.192
Lateral occipital	L	47.53 (10.33, 84.73)	.04	104.57 (-15.36, 224.50)	.26	69.67 (21.62, 115.72)	.01	.212
Functional connectivity								
Sensorimotor hand – salience		0.01 (0.00, 0.01)	.008	0.00 (-0.02, 0.02)	.86	0.01 (0.00, 0.02)	.02	.006
Auditory – right ventral diencephalon		-0.01 (-0.02, 0.00)	.002	-0.01 (-0.04, 0.01)	.42	-0.01 (-0.02, 0.00)	.20	.011

Unstandardized regression coefficients and associated 95% confidence interval, p-value/false discovery rate adjusted p-value (for brain ROIs) and R^2 value are presented for generalized additive model results for common patterns of alcohol exposure during pregnancy, when compared to unexposed youth. Only brain ROIs identified from first series of analyses are presented. These generalized additive mixed models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.
N= 8720.

PAE Sensitivity Analysis: Participant between group one-to-one matching on demographic characteristics.

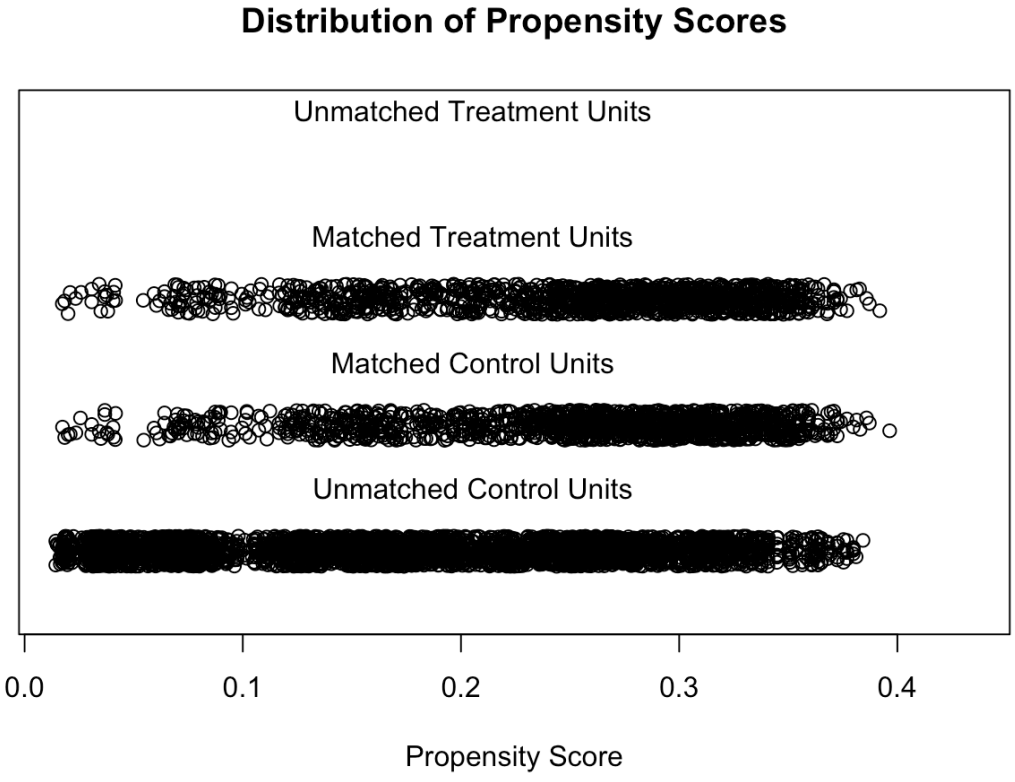
The dichotomous PAE groups were demographically matched after excluding all cases of rare phenotypes on which groups were mismatched, including other in utero substance use exposure and positive reports of maternal depression. All PAE association analyses were then repeated with this more homogenous subsample.

Supplementary Table S11: Sample Sizes

	Unexposed	Exposed
All	4,928	1,271
Matched	1,271	1,271
Unmatched	3,657	0

Supplementary Table S12: Summary of balance for matched data

	Means Exposed	Means Unexposed	Mean Diff
Distance	0.25	0.25	0.00
Race (white)	0.70	0.70	0.00
Race (black)	0.05	0.06	-0.01
Race (Hispanic)	0.15	0.15	0.00
Race (Asian)	0.02	0.01	0.00
Race (Other)	0.08	0.08	0.00
Birth weight	6.72	6.78	-0.05
Maternal age	31.59	31.49	0.10
<HS Diploma	0.03	0.02	0.00
Some College	0.17	0.18	0.00
Bachelor	0.37	0.38	-0.01
Post Grad	0.42	0.41	0.01



Supplementary Table S13: Demographic characteristics that participants were matched one-to-one on for sensitivity analyses.

	Unexposed n=1,271	**Exposed** n=1,271	*p*
Age (M [SD])	9.9 (0.6)	9.9 (0.6)	.38
Sex (F; n [%])	605 (47.6)	631 (49.6)	.32
Race (n [%])			.95
White	894 (70.3)	889 (69.9)	
Black	71 (5.6)	64 (5.0)	
Hispanic	186 (14.6)	190 (14.9)	
Asian	19 (1.5)	21 (1.7)	
Other	101 (7.9)	107 (8.4)	
Born premature (n [%])	202 (15.9)	211 (16.6)	.53
Birth weight (M [SD])	6.8 (1.3)	6.7 (1.4)	.32
Maternal age (M [SD])	31.5 (5.3)	31.6 (5.2)	.63
Highest Parent Education (n [%])			.92
<HS Diploma	13 (1.0)	13 (1.0)	
HS Dip/GED	27 (2.1)	32 (2.5)	
Some College	227 (17.9)	222 (17.5)	
Bachelor	483 (38.0)	468 (36.8)	
Post Grad	521 (41.0)	536 (42.2)	

Supplementary Table S14: Sensitivity matched-participant analysis – GAMMs for any alcohol use (dichotomous variable) in pregnancy on all outcomes of interest.

	B (95% CI)	*p*	R^2
CBCL			
Total problems	2.28 (1.48, 3.09)	<.001	.021
Externalizing	1.64 (0.90, 2.37)	<.001	.018
Rule breaking behavior	0.22 (-0.07, 0.50)	.14	.018
Aggressive behavior	0.23 (-0.11, 0.56)	.19	.007
Internalizing	1.45 (0.67, 2.33)	<.001	.007
Anxious/depressed	0.47 (0.04, 0.90)	.03	.002
Withdrawn/depressed	0.27 (-0.11, 0.64)	.16	.019
Somatic complaints	0.40 (-0.03, 0.83)	.07	.005
Social problems	0.16 (-0.13, 0.45)	.28	.012
Thought problems	0.54 (0.14, 0.93)	.01	.009
Attention problems	0.52 (0.12, 0.91)	.01	.017
KSADS			
Depression	0.08 (-0.57, 0.74)	.80	.008
Generalized Anxiety Disorder	0.10 (-0.30, 0.51)	.62	.001
Panic Disorder	0.41 (-2.54, 3.35)	.79	-.012
Separation Anxiety	0.31 (0.02, 0.60)	.03	.000
Social Anxiety/Selective Mutism Disorder	-0.05 (-0.44, 0.34)	.81	-.001
Hallucinations	0.16 (-0.86, 1.18)	.76	.004
Delusions	-0.34 (-1.09, 0.41)	.36	-.004
Attention Deficit Hyperactivity	0.16 (-0.06, 0.38)	.14	.021
Oppositional Defiant Disorder	0.25 (0.01, 0.49)	.04	.007
Conduct Disorder	-0.02 (-0.61, 0.56)	.93	.004
Obsessive-Compulsive Disorder	0.16 (-0.14, 0.45)	.30	.006
Unspecific Bipolar and Related Disorder	-0.07 (-0.58, 0.44)	.78	.008
Post Traumatic Stress Disorder	-0.71 (-1.63, 0.21)	.13	.000
Specific Phobia	0.23 (0.03, 0.43)	.02	.001
UPPS-P			
Lack of planning	0.19 (0.02, 0.36)	.03	.021
Sensation seeking	0.29 (0.09, 0.49)	.005	.029
Negative urgency	0.15 (-0.05, 0.35)	.13	.008
Positive urgency	0.15 (-0.06, 0.37)	.17	.024
Lack of perseverance	0.07 (-0.10, 0.24)	.40	.014
BIS/BAS			
Behavioral inhibition	0.13 (-0.08, 0.35)	.22	.003
Reward responsiveness	0.04 (-0.14, 0.22)	.63	.025
Drive	0.08 (-0.14, 0.31)	.46	.034
Fun seeking	0.17 (-0.02, 0.37)	.09	.011
NIH Toolbox			
Processing Speed (Pattern Comparison)	-0.15 (-1.86, 1.55)	.86	.030
Working memory (List Sorting)	0.61 (-0.48, 1.70)	.27	.052
Episodic memory (Picture Sequence)	0.61 (-0.67, 1.89)	.25	.035
Executive function / attention / inhibition (Flanker)	1.05 (-0.00, 2.10)	.05	.004
Executive function / cognitive flexibility	1.19 (-0.28, 2.41)	.06	.015

		B (95% CI)	*p*	R^2
(Dimensional Change Card Sort)				
RAVLT				
Learning		0.04 (-0.11, 0.18)	.60	.111
Immediate delay		0.02 (-0.20, 0.24)	.85	.080
Long (30 min) delay		0.01 (-0.22, 0.24)	.95	.080
Cash Choice Task		0.09 (-0.07, 0.25)	.27	.010
Brain Structure				
Volume				
Cerebrum		9907.80 (3023.09, 16792.56)	.005	.294
Inferior parietal	L	245.92 (75.87, 415.97)	.03	.119
Supramarginal	R	184.68 (36.07, 333.29)	.08	.104
Inferior temporal	L	239.59 (90.34, 388.84)	.01	.142
Middle temporal	L	140.83 (10.75, 270.90)	.20	.163
	R	58.52 (-74.76, 191.80)	1.00	.205
Lateral occipital	L	161.47 (23.59, 299.36)	.13	.177
Surface area				
Precuneus	R	82.12 (41.25, 122.98)	<.001	.167
Inferior temporal	L	71.86 (33.58, 110.15)	<.001	.151
Lateral occipital	L	52.70 (6.43, 98.97)	.08	.162
Functional connectivity				
Sensorimotor hand – salience		0.01 (0.00, 0.01)	.24	.008
Auditory – right ventral diencephalon		-0.13 (-0.02, 0.00)	.01	.006

Unstandardized regression coefficients and associated 95% confidence interval, p-value/false discovery rate adjusted p-value (for brain analyses) and R^2 value are presented for generalised additive model results for alcohol use as a categorical measure. Only brain ROIs identified from first series of analyses are presented. These generalized additive mixed models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, school grade) and random (family, scanner/site) effects.

Supplementary Table S15: Sensitivity matched-participant analysis – GAMM results for alcohol use as a continuous measure, using an estimate of total drinks throughout pregnancy, when adjusting for fixed and random effects.

	B (95% CI)	*p*	R^2
CBCL			
Total problems	0.03 (0.00, 0.05)	.02	.054
Externalizing	0.02 (0.00, 0.05)	.02	.033
Rule breaking behavior	0.00 (-0.01, 0.01))	.48	.043
Aggressive behavior	0.01 (0.00, 0.02)	.20	.023
Internalizing	0.01 (-0.01, 0.04)	.29	.012
Anxious/depressed	0.00 (-0.01, 0.02)	.71	.019
Withdrawn/depressed	0.00 (-0.01, 0.01)	.96	.023
Somatic complaints	0.00 (-0.01, 0.02)	.66	.005
Social problems	0.00 (-0.01, 0.01)	.98	.054
Thought problems	0.01 (0.00, 0.02)	.13	.022
Attention problems	0.01 (0.00, 0.02)	.04	.119
KSADS			
Depression	0.00 (-0.02, 0.02)	.91	.006
Generalized Anxiety Disorder	0.00 (-0.01, 0.01)	.67	.009
Panic Disorder	0.13 (-0.05, 0.31)	.14	.429
Separation Anxiety	0.01 (0.00, 0.01)	.13	.005
Social Anxiety/Selective Mutism	0.01 (-0.01, 0.02)	.34	-.003
Disorder			
Hallucinations	0.00 (-0.04, 0.04)	.97	.015
Delusions	0.00 (-0.02, 0.02)	.81	.018
Attention Deficit Hyperactivity	0.00 (0.00, 0.01)	.16	.114
Oppositional Defiant Disorder	0.00 (0.00, 0.01)	.34	.013
Conduct Disorder	-0.01 (-0.03, 0.01)	.44	.034
Obsessive-Compulsive Disorder	0.01 (0.00, 0.01)	.10	.007
Unspecific Bipolar and Related	0.00 (-0.02, 0.01)	.60	.004
Disorder			
Post Traumatic Stress Disorder	0.00 (-0.04, 0.03)	.63	.028
Specific Phobia	0.00 (-0.01, 0.00)	.47	.003
UPPS-P			
Lack of planning	0.00 (0.00, 0.01)	.56	.018
Sensation seeking	0.01 (0.00, 0.02)	.002	.028
Negative urgency	0.00 (0.00, 0.01)	.13	.012
Positive urgency	0.00 (0.00, 0.01)	.27	.035
Lack of perseverance	0.00 (0.00, 0.00)	.99	.039
BIS/BAS			
Behavioral inhibition	0.01 (0.00, 0.01)	.02	.006
Reward responsiveness	0.00 (0.00 0.01)	.49	.033
Drive	0.00 (-0.01, 0.01)	.78	.045
Fun seeking	0.01 (0.00, 0.01)	.09	.014
NIH Toolbox			
Processing Speed	0.03 (-0.02, 0.08)	.30	.045
(Pattern Comparison)			
Working memory (List	0.00 (-0.03, 0.04)	.80	.090
Sorting)			
Episodic memory	0.00 (-0.04, 0.04)	.94	.062
(Picture Sequence)			
Executive function /	0.05 (0.02, 0.08)	.002	.020
attention / inhibition			
(Flanker)			
Executive function /	0.03 (0.00, 0.07)	.06	.042
cognitive flexibility			

		B (95% CI)	*p*	R^2
(Dimensional Change Card Sort)				
RAVLT				
Learning		0.00 (-0.01, 0.00)	.37	.140
Immediate delay		0.00 (-0.01, 0.00)	.26	.100
Long (30 min) delay		0.00 (-0.01, 0.00)	.18	.099
Cash Choice Task		0.00 (0.00, 0.01)	.16	.005
Brain Structure				
Volume				
Cerebrum		119.10 (-87.73, 325.88)	.26	.30
Inferior parietal	L	2.71 (-2.47, 7.89)	1.00	.117
Supramarginal	R	1.76 (-2.74, 6.27)	1.00	.102
Inferior temporal	L	0.95 (-3.64, 5.55)	1.00	.144
Middle temporal	L	2.28 (-1.63, 6.19)	1.00	.156
	R	-0.99 (-5.01, 3.04)	1.00	.189
Lateral occipital	L	6.56 (2.45, 10.66)	.01	.186
Surface area				
Precuneus	R	0.20 (-1.05, 1.45)	.75	.157
Inferior temporal	L	0.24 (-0.92,1.41)	1.00	.150
Lateral occipital	L	1.55 (0.19, 2.92)	.08	.176
Functional connectivity				
Sensorimotor hand – salience		0.00 (0.00, 0.00)	.15	.006
Auditory – right ventral diencephalon		0.00 (0.00, 0.00)	.23	.006

Unstandardized regression coefficients and associated 95% confidence interval, p-value/false discovery rate adjusted p-value (for brain analyses) and R^2 value are presented for generalised additive model results for alcohol use as a continuous measure. Only brain ROIs identified from first series of analyses are presented. These generalized additive mixed models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, school grade) and random (family, scanner/site) effects.

Supplementary Table S16: Sensitivity matched-participant analysis – GAMM results for common patterns of alcohol exposure during pregnancy compared to no exposure, when adjusting for fixed and random effects.

	Light reducer n=729		*Stable light* n=53		*Heavier reducer* n=284		
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	R^2
CBCL							
Total problems	1.69 (0.73, 2.64)	<.001	5.06 (2.33, 7.78)	<.001	3.18 (1.85, 4.51)	<.001	.066
Externalizing	1.40 (0.52, 2.27)	.002	3.79 (1.28, 6.30)	.003	2.19 (0.98, 3.41)	<.001	.047
Internalizing	0.64 (-0.32, 1.59)	.19	3.17 (0.44, 5.91)	.02	1.84 (0.51, 3.16)	.007	.013
Anxious Depressed	0.06 (-0.48, 0.59)	.84	1.48 (-0.05, 3.02)	.06	0.51 (-0.23, 1.26)	.18	.017
Withdrawn	0.04 (-0.39, 0.47)	.86	0.60 (-0.66, 1.86)	.35	0.24 (-0.36, 0.84)	.44	.025
Somatic	0.14 (-0.39, 0.66)	.62	1.42 (-0.09, 2.94)	.07	0.59 (-0.14, 1.32)	.12	.006
Thought	0.23 (-0.24, 0.70)	.34	1.45 (0.08, 2.82)	.04	0.36 (-0.30, 1.01)	.29	.026
Attention	0.06 (-0.40, 0.52)	.79	2.27 (0.94, 3.61)	<.001	0.79 (0.14, 1.42)	.02	.137
Rule breaking	0.16 (-0.17, 0.49)	.35	0.10 (-0.86, 1.06)	.84	0.53 (0.07, 0.99)	.03	.043
Aggressive	0.10 (-0.29, 0.50)	.61	0.79 (-0.35, 1.94)	.18	0.64 (0.09, 1.19)	.02	.032
KSADS							
Depression	0.27 (-0.67, 1.21)	.58	1.69 (0.05, 3.35)	.04	0.70 (-0.44, 1.84)	.22	.015
Separation Anxiety	0.34 (0.01, 0.67)	.05	0.98 (0.22, 1.74)	.01	0.17 (-0.32, 0.66)	.48	.011
Attention Deficit Hyperactivity	0.07 (-0.20, 0.34)	.64	0.79 (0.21, 1.48)	.02	0.41 (0.06, 0.76)	.03	.119
Oppositional Defiant Disorder	0.37 (0.08, 0.66)	.01	0.45 (-0.35, 1.25)	.26	0.38 (-0.01, 0.77)	.06	.021
Specific Phobia	0.25 (0.01, 0.49)	.03	0.82 (0.23, 1.41)	.007	0.22 (-0.02, 0.46)	.18	.007
UPPS-P							
Lack of planning	0.27 (0.06, 0.48)	.01	0.32 (-0.30, 0.94)	.31	0.21 (-0.09, 0.50)	.17	.029
Sensation seeking	0.29 (0.04, 0.54)	.02	0.62 (-0.08, 1.33)	.08	0.40 (0.56, 0.74)	.02	.033
BIS/BAS							
Behavioral inhibition	0.00 (-0.26, 0.25)	.98	1.10 (0.35, 1.85)	.004	0.09 (-0.27, 0.45)	.64	.011
Fun seeking	0.03 (-0.20, 0.27)	.77	0.56 (-0.12, 1.25)	.11	-0.01 (-0.33, 0.32)	.97	.013
NIH Toolbox							
Working memory (List Sorting)	0.23 (-1.08, 1.54)	.73	1.76 (-2.01, 5.53)	.36	2.45 (0.63,4.28)	.008	.076
Executive function / attention / inhibition (Flanker)	1.38 (0.13, 2.63)	.03	3.24 (-0.37, 6.85)	.08	1.30 (-0.46, 3.04)	.14	.025

		Light reducer n=729		*Stable light* n=53		*Heavier reducer* n=284		
		B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	R^2
Executive function / cognitive flexibility (Dimensional Change Card Sort)		0.53 (-0.92, 1.98)	.47	0.04 (-4.13, 4.21)	.99	3.00 (0.98, 5.01)	.004	.050
RAVLT								
Learning		0.06 (-0.11, 0.23)	.47	-0.42 (-0.91, 0.07)	.09	0.14 (-0.09, 0.38)	.24	.144
Immediate delay		0.07 (-0.19, 0.33)	.59	-0.53 (-1.28, 0.22)	.17	0.20 (-0.16, 0.57)	.27	.100
Long (30 min) delay		0.19 (-0.09, 0.46)	.19	-0.67 (-1.46, 0.13)	.10	0.18 (-0.20, 0.57)	.35	.101
Brain Structure								
Volume								
Cerebrum		9352.00 (656.26, 18047.73)	.04	24635.00 (40.81, 49229.23)	.05	15876.20 (4162.20, 27590.29)	.008	.323
Inferior parietal	L	323.23 (101.08, 545.38)	.02	903.49 (271.87, 1535.10)	.03	130.89 (-169.62, 431.39)	1.0	.130
Supramarginal	R	213.99 (21.57, 406.41)	.17	286.49 (-258.33, 831.31)	1.0	325.93 (65.66, 586.18)	.08	.112
Inferior temporal	L	357.24 (165.48, 549.00)	<.001	130.87 (-414.95, 676.69)	1.0	335.42 (75.96, 594.88)	.03	.160
Middle temporal	L	124.99 (-40.11, 290.09)	.84	176.03 (-291.57, 643.64)	1.0	160.92 (-62.17, 384.02)	.96	.163
	R	125.11 (-45.34, 295.56)	.90	118.81 (-363.73, 601.35)	1.0	142.86 (-87.53, 373.25)	1.0	.200
Lateral occipital	L	213.64 (39.75, 387.53)	.10	612.93 (117.37, 1108.49)	.09	303.41 (68.06, 538.75)	.07	.209
Surface area								
Precuneus	R	72.69 (20.69, 124.70)	.02	140.18 (-8.87, 289.24)	.20	59.04 (-11.47, 129.56)	.30	.186
Inferior temporal	L	98.18 (48.91, 147.44)	<.001	47.62 (-91.45, 186.69)	.50	100.82 (34.25, 167.40)	.009	.163
Lateral occipital	L	63.51 (4.53, 122.48)	.10	213.62 (47.20, 380.05)	.04	117.85 (38.13, 197.57)	.01	.190
Functional connectivity								
Sensorimotor hand – salience		0.01 (-0.03, 0.05)	.31	-0.02 (-0.06, 0.02)	.30	0.02 (0.00, 0.04)	.02	.009
Auditory – right ventral diencephalon		-0.01 (-0.02, 0.00)	.04	0.00 (-0.04, 0.04)	.89	0.00 (-0.02, 0.01)	.42	.007

'Unstandardized regression coefficients and associated 95% confidence interval, p-value/false discovery rate adjusted p-value (for brain ROIs) and R^2 value are presented for generalized additive model results for common patterns of alcohol exposure during pregnancy, when compared to unexposed youth. Only brain ROIs identified from first series of analyses are presented. These generalized additive mixed models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, school grade) and random (family, scanner/site) effects. N= 1908.

Multilevel Mediation Analysis: Cross-sectional baseline analysis to examine associations between PAE, brain structure, and psychological, behavioral, and cognitive outcomes. (Tables S17-S31).

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade), and random (family, scanner/site) effects.

Supplementary Table S17: Mediation Analyses – CBCL Total Problems

	PAE → Brain (A)		Brain → Total Problems (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Total Problems (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.002 (-0.003, -0.001)	<.001	-0.08 (-0.12, -0.04)	<.001	1.53 (1.20, 2.12)	<.001	1.44 (1.11, 2.05)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.05 (-0.09, -0.02)	<.001	1.50 (1.18 2.09)	<.001	1.44 (1.11, 2.05)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.02 (-0.04, -0.01)	<.001	-0.05 (-0.09, -0.02)	<.001	1.50 (1.18, 2.09)	<.001	1.44 (1.11, 2.05)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.03 (-0.04, -0.01)	<.001	-0.06 (-0.09, -0.02)	<.001	1.50 (1.18, 2.10)	<.001	1.44 (1.11, 2.05)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.03 (-0.07, -0.01)	<.001	1.48 (1.16, 2.08)	<.001	1.44 (1.11, 2.05)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.02 (-0.04, -0.02)	<.001	-0.05 (-0.9, -0.02)	<.001	1.50 (1.18, 2.09)	<.001	1.44 (1.11, 2.05)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.02 (-0.04, -0.01)	<.001	-0.04 (-0.07, -0.01)	<.001	1.49 (1.17, 2.08)	<.001	1.44 (1.11, 2.05)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.06 (-0.12, -0.02)	<.001	-0.05 (-0.09, -0.02)	<.001	1.50 (1.17, 2.09)	<.001	1.44 (1.11, 2.05)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.07 (-0.12, -0.04)	<.001	-0.06 (-0.11, -0.03)	<.001	1.52 (1.19, 2.11)	<.001	1.44 (1.11, 2.05)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.07 (-0.12, -0.04)	<.001	-0.04 (-0.08, -0.01)	<.001	1.49 (1.17, 2.08)	<.001	1.44 (1.11, 2.05)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.09 (-2.27, 2.15)	.48	0.00 (-0.02, 0.02)	.48	1.35 (0.99, 2.01)	<.001	1.35 (0.98, 2.02)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	-0.50 (-2.50, 1.11)	.28	0.01 (-0.02, 0.03)	.28	1.34 (0.98, 2.00)	<.001	1.36 (1.00, 2.00)	<.001

Supplementary Table S18: CBCL Externalizing Psychopathology

	PAE → Brain (A)		Brain → Externalizing Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Externalizing Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.95 (25.39, 51.6)	<.001	-0.002 (-0.003, -0.001)	<.001	-0.08 (-0.12, -0.05)	<.001	1.13 (0.84, 1.67)	<.001	1.05 (0.74, 1.60)	<.001
Inferior temporal L	2.93 (1.99, 3.68)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.06 (-0.10, -0.03)	<.001	1.11 (0.82, 1.65)	<.001	1.05 (0.74, 1.60)	<.001
Middle temporal L	2.20 (1.37, 2.87)	<.001	-0.03 (-0.04, -0.02)	<.001	-0.06 (-0.10, -0.03)	<.001	1.12 (0.83, 1.66)	<.001	1.05 (0.74, 1.60)	<.001
Middle temporal R	2.23 (1.37, 2.91)	<.001	-0.03 (-0.05, -0.02)	<.001	-0.07 (-0.11, -0.04)	<.001	1.13 (0.83, 1.67)	<.001	1.04 (0.74, 1.60)	<.001
Lateral occipital L	2.10 (1.23, 2.79)	<.001	-0.02 (-0.04, -0.01)	<.001	-0.04 (-0.08, -0.02)	<.001	1.10 (0.81, 1.64)	<.001	1.05 (0.75, 1.60)	<.001
Inferior parietal L	2.12 (1.06, 2.97)	<.001	-0.02 (-0.03, -0.02)	<.001	-0.05 (-0.08, -0.02)	<.001	1.10 (0.81, 1.64)	<.001	1.05 (0.75, 1.60)	<.001
Supramarginal R	1.88 (0.96, 2.61)	<.001	-0.02 (-0.04, -0.02)	<.001	-0.04 (-0.8, -0.02)	<.001	1.10 (0.81, 1.64)	<.001	1.05 (0.75, 1.60)	<.001
Surface area										
Inferior temporal L	0.79 (0.55, 0.99)	<.001	-0.09 (-0.13, -0.51)	<.001	-0.07 (-0.11, -0.03)	<.001	1.12 (0.83, 1.66)	<.001	1.05 (0.74, 1.60)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.08 (-0.12, -0.52)	<.001	-0.07 (-0.12, -0.04)	<.001	1.13 (0.83, 1.67)	<.001	1.05 (0.74, 1.60)	<.001
Precuneus R	0.60 (0.34, 0.81)	<.001	-0.07 (-0.12, -0.04)	<.001	-0.05 (-0.08, -0.02)	<.001	1.10 (0.81, 1.64)	<.001	1.05 (0.75, 1.60)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	-0.85 (-2.98, 1.02)	.16	-0.01 (-0.02, 0.01)	.18	1.07 (0.74, 1.67)	<.001	1.06 (0.73, 1.67)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.43 (-1.38, 1.89)	.34	-0.01 (-0.03, 0.02)	.34	1.10 (0.74, 1.67)	<.001	1.08 (0.75, 1.65)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S19: CBCL Internalizing Psychopathology

	PAE → Brain (A)		Brain → Internalizing Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Internalizing Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.001 (-0.002, 0.000)	.010	-0.03 (-0.07, 0.00)	.010	0.99 (0.68, 1.56)	<.001	0.95 (0.64, 1.54)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.02, 0.00)	.140	-0.01 (-0.06, 0.01)	.140	0.98 (0.66-1.55)	<.001	0.95 (0.64, 1.54)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.01 (-0.02, 0.00)	.120	-0.01 (-0.5, 0.01)	.120	0.97 (0.66-1.55)	<.001	0.95 (0.64, 1.54)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.01 (-0.02, 0.00)	.060	-0.02 (-0.5, 0.01)	.060	0.98 (0.67-1.55)	<.001	0.95 (0.64, 1.54)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (-0.02, 0.01)	.280	-0.01 (-0.04, 0.01)	.280	0.97 (0.66-1.54)	<.001	0.95 (0.64, 1.54)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.03 (-0.06, -0.01)	<.001	0.99 (0.68-1.56)	<.001	0.95 (0.64, 1.54)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.01 (-0.02, 0.00)	.030	-0.02 (-0.04, 0.00)	.030	0.98 (0.67-1.55)	<.001	0.95 (0.64, 1.53)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.01 (-0.06, 0.03)	.250	-0.01 (-0.05, 0.02)	.250	0.97 (0.66-1.54)	<.001	0.95 (0.64, 1.54)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.03 (-0.07, 0.00)	.020	-0.03 (-0.07, 0.00)	.020	0.99 (0.67-1.56)	<.001	0.95 (0.64, 1.54)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.04 (-0.08, 0.00)	.020	-0.02 (-0.05, 0.00)	.020	0.98 (0.67-1.55)	<.001	0.95 (0.64, 1.54)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.12 (-2.15, 2.10)	.47	0.00 (-0.02, 0.02)	.49	0.82 (0.47, 1.45)	<.001	0.81 (0.46, 1.46)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	-0.58 (-2.51, 0.97)	.22	0.01 (-0.01, 0.04)	.22	0.81 (0.46, 1.45)	<.001	0.83 (0.48, 1.44)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S20: CBCL Anxious and Depressive Symptoms

	PAE → Brain (A)		Brain → Anxiety Depression Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Anxiety Depression Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	0.00 (-0.001, 0.000)	.010	-0.02 (-0.04, 0.00)	.010	0.23 (0.05, 0.55)	.010	0.21 (0.02, 0.54)	.010
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.012, 0.001)	.050	-0.01 (-0.04, 0.00)	.050	0.22 (0.04, 0.55)	.010	0.20 (0.02, 0.54)	.010
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.01 (-0.01, 0.00)	.060	-0.01 (-0.03, 0.00)	.060	0.22 (0.04, 0.55)	.010	0.21 (0.02, 0.54)	.010
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.01 (-0.02, 0.00)	.010	-0.02 (-0.04, 0.00)	.010	0.22 (0.05, 0.55)	.010	0.21 (0.02, 0.54)	.010
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (-0.01, 0.01)	.490	0.00 (-0.02, 0.01)	.490	0.21 (0.03, 0.54)	.010	0.20 (0.03, 0.54)	.010
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.01 (-0.02, -0.004)	<.001	-0.02 (-0.04, -0.01)	<.001	0.23 (0.05, 0.56)	.010	0.21 (0.02, 0.54)	.010
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.01 (-0.01, 0.00)	.030	-0.01 (-0.03, 0.00)	.030	0.22 (0.04, 0.55)	.010	0.21 (0.03, 0.54)	.010
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.01 (-0.04, 0.01)	.140	-0.01 (-0.03, 0.01)	.140	0.22 (0.04, 0.55)	.010	0.20 (0.02, 0.54)	.010
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.01 (-0.03, 0.01)	.110	-0.01 (-0.03, 0.01)	.110	0.22 (0.04, 0.55)	.010	0.20 (0.02, 0.54)	.010
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.01 (-0.04, 0.01)	.110	-0.01 (-0.02, 0.00)	.110	0.22 (0.04, 0.54)	.010	0.21 (0.03, 0.54)	.010
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.04 (-1.24, 1.15)	.48	0.00 (-0.01, 0.01)	.48	0.15 (-0.05, 0.51)	.06	0.15 (-0.05, 0.51)	.08
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	-0.43 (-1.52, 0.44)	.14	0.01 (-0.01, 0.02)	.14	0.15 (-0.05, 0.50)	.08	0.16 (-0.04, 0.50)	.06

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S21: CBCL Withdrawn/Depressed

	PAE → Brain (A)		Brain → Withdrawal Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Withdrawal Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.001 (-0.001, 0.000)	<.001	-0.03 (-0.05, -0.01)	<.001	0.29 (0.11, 0.60)	<.001	0.25 (0.08, 0.57)	.010
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.02, 0.00)	<.001	-0.03 (-0.05, -0.01)	<.001	0.28 (0.11, 0.59)	<.001	0.25 (0.08, 0.57)	.010
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.01 (-0.02, 0.00)	<.001	-0.02 (-0.04, -0.01)	<.001	0.28 (0.11, 0.59)	<.001	0.25 (0.08, 0.57)	.010
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.01)	<.001	0.28 (0.11, 0.60)	<.001	0.25 (0.08, 0.57)	.010
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (-0.01, 0.00)	.230	-0.01 (-0.02, 0.01)	.230	0.26 (0.09, 0.58)	<.001	0.25 (0.08, 0.57)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.28 (0.11, 0.59)	<.001	0.25 (0.08, 0.57)	.010
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.28 (0.11, 0.59)	<.001	0.25 (0.08, 0.57)	.010
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.03 (-0.05, -0.01)	.010	-0.02 (-0.04, 0.00)	.010	0.28 (0.11, 0.59)	<.001	0.25 (0.08, 0.57)	.010
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.01 (-0.03, 0.01)	.260	-0.01 (-0.03, 0.01)	.260	0.26 (0.09, 0.58)	<.001	0.25 (0.08, 0.57)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.04 (-0.06, -0.02)	<.001	-0.02 (-0.04, -0.01)	<.001	0.28 (0.11, 0.59)	<.001	0.25 (0.08, 0.57)	.010
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.36 (-0.84, 1.41)	.26	0.00 (-0.01, 0.01)	.28	0.18 (0.00, 0.52)	.03	0.18 (-0.01, 0.52)	.03
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	-0.42 (-1.44, 0.40)	.13	0.01 (-0.01, 0.02)	.13	0.18 (-0.01, 0.51)	.04	0.19 (0.00, 0.52)	.02

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S22: CBCL Somatic Complaints

	PAE → Brain (A)		Brain → Somatic Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Somatic Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	0.00 (-0.001, 0.000)	.150	-0.01 (-0.03, 0.01)	.150	0.41 (0.23, 0.75)	<.001	0.40 (0.22, 0.74)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	0.00 (-0.01, 0.01)	.500	0.00 (-0.02, 0.02)	.500	.0.41 (0.22, 0.74)	<.001	0.40 (0.22, 0.74)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.01 (-0.01, 0.00)	.060	-0.01 (-0.03, 0.00)	.060	0.42 (0.24, 0.75)	<.001	0.40 (0.22, 0.74)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.01 (-0.01, 0.00)	.060	-0.01 (-0.03, 0.00)	.060	0.42 (0.24, 0.75)	<.001	0.40 (0.22, 0.74)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (-0.01, 0.00)	.280	0.00 (-0.02, 0.01)	.280	0.41 (0.23, 0.74)	<.001	0.40 (0.22, 0.74)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	0.00 (-0.01, 0.00)	.110	-0.01 (-0.02, 0.00)	.110	0.41 (0.23, 0.75)	<.001	0.40 (0.22, 0.74)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.01 (-0.01, 0.00)	.030	-0.01 (-0.03, 0.00)	.030	0.42 (0.24, 0.75)	<.001	0.40 (0.22, 0.74)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	0.01 (-0.02, 0.03)	.280	0.01 (-0.02, 0.03)	.280	0.40 (0.22, 0.74)	<.001	0.40 (0.22, 0.74)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.01 (-0.04, 0.00)	.070	-0.01 (-0.04, 0.00)	.070	0.42 (0.24, 0.76)	<.001	0.40 (0.24, 0.76)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.02 (-0.05, 0.00)	.010	-0.01 (-0.03, 0.00)	.010	0.42 (0.24, 0.75)	<.001	0.40 (0.22, 0.74)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	-0.36 (-1.67, 0.78)	.28	0.00 (-0.01, 0.01)	.30	0.32 (0.12, 0.68)	<.001	0.31 (0.11, 0.68)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.56 (-0.55, 1.45)	.12	-0.01 (-0.02, 0.01)	.12	0.32 (0.12, 0.69)	<.001	0.32 (0.12, 0.68)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S23: CBCL Thought

	PAE → Brain (A)		Brain → Thought Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Thought Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.001 (-0.001, 0.000)	<.001	-0.02 (-0.05, -0.01)	<.001	0.39 (0.22, 0.71)	<.001	0.37 (0.19, 0.69)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.015, -0.003)	<.001	-0.02 (-0.05, -0.01)	<.001	0.39 (0.22, 0.71)	<.001	0.37 (0.19, 0.9)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.01 (-0.02, 0.00)	.010	-0.02 (-0.04, 0.00)	.010	0.39 (0.21, 0.70)	<.001	0.37 (0.19, 0.69)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.01 (-0.01, 0.00)	.020	-0.01 (-0.03, 0.00)	.020	0.38 (0.21, 0.70)	<.001	0.37 (0.19, 0.69)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (-0.01, 0.01)	.410	0.00 (-0.02, 0.01)	.410	0.37 (0.20, 0.69)	<.001	0.37 (0.19, 0.69)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.39 (0.22, 0.71)	<.001	0.37 (0.19, 0.69)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.01 (-0.01, 0.00)	.010	-0.01 (-0.03, 0.00)	.010	0.38 (0.21, 0.70)	<.001	0.37 (0.19, 0.69)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.03 (-0.06, -0.01)	.010	-0.02 (-0.04, -0.01)	.010	0.39 (0.22, 0.71)	<.001	0.37 (0.19, 0.69)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.01 (-0.04, 0.00)	.100	-0.01 (-0.03, 0.00)	.100	0.38 (0.21, 0.70)	<.001	0.37 (0.19, 0.69)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.03 (-0.06, 0.01)	<.001	-0.02 (-0.03, 0.00)	<.001	0.39 (0.22, 0.70)	<.001	0.37 (0.19, 0.69)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.49 (-0.73, 1.56)	.18	0.00 (-0.01, 0.01)	.20	0.30 (0.11, 0.64)	<.001	0.30 (0.11, 0.65)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.17 (-0.87, 1.00)	.38	0.00 (-0.02, 0.01)	.38	0.30 (0.12, 0.65)	<.001	0.31 (0.12, 0.64)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S24: CBCL Attention Problems

	PAE → Brain (A)		Brain → Attention Deficits (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Attention Deficits (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.001 (-0.002, -0.001)	<.001	-0.05 (-0.08, -0.03)	<.001	0.43 (0.25, 0.75)	<.001	0.37 (0.19, 0.71)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.01)	<.001	0.41 (0.23, 0.73)	<.001	0.37 (0.19, 0.71)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.01)	<.001	0.40 (0.23, 0.73)	<.001	0.37 (0.19, 0.71)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.04 (-0.06, -0.02)	<.001	0.41 (0.24, 0.74)	<.001	0.37 (0.19, 0.71)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.01)	<.001	0.40 (0.22, 0.73)	<.001	0.37 (0.19, 0.71)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.40 (0.22, 0.73)	<.001	0.37 (0.19, 0.71)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.02 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.02)	<.001	0.41 (0.23, 0.73)	<.001	0.37 (0.19, 0.71)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.04 (-0.07, -0.02)	<.001	-0.03 (-0.6, -0.01)	<.001	0.41 (0.23, 0.74)	<.001	0.37 (0.19, 0.71)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.04 (-0.06, -0.02)	<.001	-0.04 (-0.06, -0.02)	<.001	0.41 (0.23, 0.74)	<.001	0.37 (0.19, 0.71)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.05 (-0.08, -0.03)	<.001	-0.03 (-0.05, -0.01)	<.001	0.41 (0.23, 0.73)	<.001	0.37 (0.19, 0.71)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.58 (-0.67, 1.67)	.12	0.00 (0.00, 0.01)	.14	0.33 (0.14, 0.68)	<.001	0.33 (0.14, 0.69)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	-0.21 (-1.26, 0.64)	.29	0.00 (-0.01, 0.02)	.29	0.33 (0.14, 0.68)	<.001	0.34 (0.15, 0.68)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S25: CBCL Rule Breaking

	PAE → Brain (A)		Brain → Rule Breaking Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Rule Breaking Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.001 (-0.001, -0.001)	<.001	-0.04 (-0.06, -0.02)	<.001	0.26 (0.12, 0.51)	<.001	0.22 (0.08, 0.48)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.02)	<.001	0.25 (0.12, 0.50)	<.001	0.22 (0.08, 0.48)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.02 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.02)	<.001	0.26 (0.12, 0.51)	<.001	0.22 (0.08, 0.48)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.02 (-0.02, -0.01)	<.001	-0.04 (-0.06, -0.02)	<.001	0.26 (0.12, 0.51)	<.001	0.22 (0.08, 0.48)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.04, -0.01)	<.001	0.25 (0.11, 0.50)	<.001	0.22 (0.08, 0.48)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.24 (0.11, 0.49)	<.001	0.22 (0.08, 0.48)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.02 (0.02, -0.01)	<.001	-0.03 (-0.05, -0.01)	<.001	0.25 (0.11, 0.50)	<.001	0.22 (0.08, 0.48)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.04 (-0.06, -0.03)	<.001	-0.03 (-0.05, -0.02)	<.001	0.25 (0.12, 0.51)	<.001	0.22 (0.08, 0.48)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.03 (-0.05, -0.02)	<.001	-0.03 (-0.05, -0.01)	<.001	0.25 (0.11, 0.50)	<.001	0.22 (0.08, 0.48)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.03 (-0.05, -0.02)	<.001	-0.02 (-0.03, -0.01)	<.001	0.24 (0.10, 0.49)	<.001	0.22 (0.08, 0.48)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	-0.66 (-1.62, 0.17)	.05	0.00 (-0.01, 0.00)	.07	0.26 (0.11, 0.52)	<.001	0.25 (0.10, 0.52)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.16 (-0.65, 0.81)	.36	0.00 (-0.01, 0.01)	.36	0.25 (0.11, 0.52)	<.001	0.25 (0.11, 0.51)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S26: CBCL Aggressive Symptoms

	PAE → Brain (A)		Brain → Aggressive Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Aggressive Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	-0.001 (-0.001, -0.001)	<.001	-0.04 (-0.07, -0.02)	<.001	0.36 (0.20, 0.65)	<.001	0.31 (0.15, 0.61)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.05, -0.01)	<.001	0.35 (0.19, 0.34)	<.001	0.31 (0.15, 0.61)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	-0.02 (-0.02, -0.01)	<.001	-0.03 (-0.06, -0.02)	<.001	0.35 (0.19, 0.64)	<.001	0.31 (0.15, 0.61)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	-0.02 (-0.02, -0.01)	<.001	-0.04 (-0.06, -0.02)	<.001	0.35 (0.20, 0.64)	<.001	0.31 (0.15, 0.61)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	-0.01 (-0.02, 0.00)	<.001	-0.02 (-0.04, -0.01)	<.001	0.34 (0.18, 0.63)	<.001	0.31 (0.15, 0.61)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.34 (0.18, 0.63)	<.001	0.31 (0.15, 0.61)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, -0.01)	<.001	0.34 (0.18, 0.63)	<.001	0.31 (0.15, 0.61)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	-0.05 (-0.07, -0.03)	<.001	-0.04 (-0.06, -0.02)	<.001	0.35 (0.19, 0.64)	<.001	0.31 (0.15, 0.61)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	-0.04 (-0.06, -0.02)	<.001	-0.03 (-0.06, -0.02)	<.001	0.35 (0.19, 0.64)	<.001	0.31 (0.15, 0.61)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	-0.04 (-0.06, -0.02)	<.001	-0.02 (-0.04, -0.01)	<.001	0.34 (0.18, 0.63)	<.001	0.31 (0.15, 0.61)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	-1.03 (-2.14, -0.07)	.02	-0.01 (-0.02, 0.00)	.04	0.30 (0.13, 0.61)	<.001	0.29 (0.12, 0.60)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.36 (-0.58, 1.11)	.23	-0.01 (-0.02, 0.01)	.23	0.30 (0.13, 0.61)	<.001	0.30 (0.13, 0.60)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S27: UPPS-P Lack of Planning

	PAE → Brain (A)		Brain → Lack Planning (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Lack Planning (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	0.00 (0.00, 0.00)	.360	0.00 (-0.01, 0.01)	.360	0.19 (0.11, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	0.00 (0.00, 0.00)	.400	0.00 (-0.01, 0.01)	.400	0.18 (0.11, 0.31)	<.001	0.18 (0.11, 0.32)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	0.00 (0.00, 0.00)	.410	0.00 (-0.01, 0.01)	.410	0.19 (0.12, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	0.00 (0.00, 0.00)	.380	0.00 (-0.01, 0.00)	.380	0.19 (0.12, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (0.00, 0.00)	.410	0.00 (-0.01, 0.01)	.410	0.19 (0.11, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	0.00 (0.00, 0.00)	.400	0.00 (-0.01, 0.00)	.400	0.19 (0.12, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	0.00 (0.00, 0.00)	.290	0.00 (-0.01, 0.00)	.290	0.19 (0.12, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	0.00 (-0.01, 0.01)	.350	0.00 (-0.01, 0.01)	.350	0.19 (0.12, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	0.00 (-0.01, 0.01)	.310	0.00 (-0.01, 0.01)	.310	0.18 (0.11, 0.31)	<.001	0.18 (0.11, 0.32)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	0.00 (-0.01, 0.01)	.450	0.00 (-0.01, 0.00)	.450	0.19 (0.12, 0.32)	<.001	0.18 (0.11, 0.32)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.21 (-0.30, 0.65)	.16	0.00 (0.00, 0.01)	.18	0.20 (0.12, 0.34)	<.001	0.20 (0.12, 0.34)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.02 (-0.41, 0.36)	.48	0.00 (-0.01, 0.01)	.48	0.20 (0.12, 0.34)	<.001	0.20 (0.12, 0.34)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S28: UPPS-P Sensation Seeking

	PAE → Brain (A)		Brain → Sensation Seeking (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Sensation Seeking (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	0.00 (0.00, 0.00)	.050	0.01 (0.00, 0.02)	.050	0.22 (0.14, 0.36)	<.001	0.22 (0.14, 0.37)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	0.00 (0.00, 0.01)	.060	0.01 (0.00, 0.02)	.060	0.22 (0.14, 0.36)	<.001	0.22 (0.14, 0.37)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	0.00 (0.00, 0.01)	.050	0.01 (0.00, 0.01)	.050	0.22 (0.14, 0.36)	<.001	0.22 (0.14, 0.37)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	0.00 (0.00, 0.01)	.030	0.01 (0.00, 0.02)	.030	0.22 (0.14, 0.36)	<.001	0.22 (0.14, 0.37)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.00 (0.00, 0.01)	.040	0.01 (0.00, 0.01)	.040	0.22 (0.14, 0.36)	<.001	0.22 (0.14, 0.37)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	0.00 (0.00, 0.00)	.130	0.00 (0.00, 0.01)	.130	0.22 (0.14, 0.37)	<.001	0.22 (0.14, 0.37)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	0.00 (0.00, 0.01)	.090	0.00 (0.00, 0.01)	.090	0.22 (0.14, 0.37)	<.001	0.22 (0.14, 0.37)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	0.01 (-0.01, 0.02)	.100	0.01 (0.00, 0.01)	.100	0.22 (0.14, 0.37)	<.001	0.22 (0.14, 0.37)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	0.00 (-0.01, 0.01)	.230	0.00 (-0.01, 0.01)	.230	0.22 (0.14, 0.37)	<.001	0.22 (0.14, 0.37)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	0.01 (0.00, 0.02)	.070	0.00 (0.00, 0.01)	.070	0.22 (0.14, 0.37)	<.001	0.22 (0.14, 0.37)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	0.19 (-0.39, 0.69)	.25	0.00 (0.00, 0.01)	.27	0.19 (0.10, 0.35)	<.001	0.19 (0.10, 0.35)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.44 (-0.04, 0.83)	.03	-0.01 (-0.02, 0.00)	.03	0.20 (0.11, 0.36)	<.001	0.19 (0.10, 0.35)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S29: NIH Flanker Task

	PAE → Brain (A)		Brain → Flanker (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Flanker (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	39.43 (24.62, 51.22)	<.001	0.003 (0.002, 0.003)	<.001	0.10 (0.05, 0.16)	<.001	1.07 (0.66, 1.81)	<.001	1.15 (0.77, 1.91)	<.001
Inferior temporal L	2.87 (1.91, 3.63)	<.001	0.02 (0.004, 0.033)	.010	0.05 (0.01, 0.10)	.010	1.11 (0.70, 1.86)	<.001	1.15 (0.76, 1.92)	<.001
Middle temporal L	2.23 (1.39, 2.90)	<.001	0.03 (0.01, 0.04)	<.001	0.06 (0.02, 0.11)	<.001	1.10 (0.70, 1.85)	<.001	1.15 (0.76, 1.92)	<.001
Middle temporal R	2.30 (1.44, 2.99)	<.001	0.03 (0.01, 0.04)	<.001	0.06 (0.02, 0.11)	<.001	1.11 (0.70, 1.85)	<.001	1.15 (0.76, 1.92)	<.001
Lateral occipital L	2.18 (1.29, 2.88)	<.001	0.03 (0.01, 0.04)	<.001	0.06 (0.03, 0.12)	<.001	1.10 (0.70, 1.85)	<.001	1.15 (0.77, 1.91)	<.001
Inferior parietal L	2.22 (1.15, 3.08)	<.001	0.01 (-0.002, 0.02)	.05	0.02 (-0.01, 0.06)	.05	1.11 (0.74, 1.89)	<.001	1.15 (0.76, 1.91)	<.001
Supramarginal R	1.94 (1.01, 2.69)	<.001	0.01 (-0.004, 0.03)	.06	0.02 (-0.01, 0.05)	.06	1.14 (0.74, 1.89)	<.001	1.16 (0.76, 1.91)	<.001
Surface area										
Inferior temporal L	0.77 (0.53, 0.97)	<.001	0.11 (0.05, 0.16)	<.001	0.08 (0.04, 0.14)	<.001	1.08 (0.68, 1.83)	<.001	1.15 (0.76, 1.92)	<.001
Lateral occipital L	0.93 (0.63, 1.17)	<.001	0.10 (0.06, 0.14)	<.001	1.07 (0.67, 1.82)	<.001	1.07 (0.67, 1.82)	<.001	1.15 (0.76, 1.92)	<.001
Precuneus R	0.57 (0.31, 0.78)	<.001	0.11 (0.05, 0.15)	<.001	0.06 (0.02, 0.11)	<.001	1.11 (0.70, 1.86)	<.001	1.15 (0.77, 1.91)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.02	-0.43 (-3.36, 2.13)	.37	0.00 (-0.02, 0.02)	.37	1.18 (0.73, 2.00)	<.001	1.17 (0.71, 2.00)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, -0.01)	<.001	0.68 (-1.80, 2.68)	.31	-0.01 (-0.04, 0.02)	.31	1.19 (0.73, 2.01)	<.001	1.19 (0.74, 1.98)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S30: KSADS Oppositional Defiant Disorder

	PAE → Brain (A)		Brain → ODD (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → ODD (C)		Total Effect	
	B (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*
Brain Structure										
Volume										
Cerebrum	38.711 (20.530, 53.418)	<.001	-0.0001 (-0.0002, 0.0000)	.03	-0.004 (-0.009, 0.000)	.03	0.164 (0.078, 0.239)	<.001	0.160 (0.077, 0.234)	<.001
Inferior temporal L	2.734 (1.554, 3.689)	<.001	-0.002 (-0.004, 0.000)	<.001	-0.006 (-0.012, -0.002)	<.001	0.167 (0.081, 0.241)	<.001	0.160 (0.077, 0.234)	<.001
Middle temporal L	2.214 (1.174, 3.054)	<.001	-0.002 (-0.004, 0.000)	.04	-0.004 (-0.009, 0.000)	.04	0.164 (0.079, 0.240)	<.001	0.160 (0.077, 0.235)	<.001
Middle temporal R	2.200 (1.136, 3.061)	<.001	-0.001 (-0.003, 0.000)	.06	-0.003 (-0.009, 0.000)	.06	0.162 (0.079, 0.238)	<.001	0.159 (0.077, 0.234)	<.001
Lateral occipital L	1.949 (0.864, 2.827)	<.001	-0.001 (-0.002, 0.001)	.23	-0.001 (-0.005, 0.003)	.23	0.161 (0.076, 0.236)	<.001	0.159 (0.077, 0.234)	<.001
Inferior parietal L	2.372 (1.044, 3.446)	<.001	-0.002 (-0.004, 0.000)	.005	-0.005 (-0.001, -0.001)	.005	0.164 (0.080, 0.241)	<.001	0.160 (0.077, 0.235)	<.001
Supramarginal R	2.016 (0.853, 2.957)	<.001	-0.002 (-0.003, 0.000)	.03	-0.003 (-0.008, 0.001)	.03	0.162 (0.078, 0.238)	<.001	0.159 (0.077, 0.235)	<.001
Surface area										
Inferior temporal L	7.336 (4.291, 9.799)	<.001	-0.001 (-0.002, 0.000)	<.001	-0.007 (-0.013, -0.002)	<.001	0.167 (0.081, 0.243)	<.001	0.160 (0.077, 0.235)	<.001
Lateral occipital L	0.871 (0.500, 1.171)	<.001	-0.003 (-0.009, 0.003)	.12	-0.003 (-0.008, 0.002)	.12	0.163 (0.077, 0.239)	<.001	0.160 (0.077, 0.235)	<.001
Precuneus R	0.570 (0.215, 0.804)	<.001	-0.008 (-0.015, -0.001)	.02	-0.004 (-0.009, 0.000)	.02	0.163 (0.078, 0.238)	<.001	0.160 (0.076, 0.233)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.007 (0.000, 0.012)	.01	-0.166 (-0.538, 0.183)	.17	-0.001 (-0.005, 0.001)	.18	0.159 (0.076, 0.235)	<.001	0.159 (0.076, 0.235)	<.001
Auditory – right ventral diencephalon	-0.015 (-0.023, -0.008)	<.001	-0.123 (-0.399, 0.136)	.23	0.002 (-0.002, 0.006)	.23	0.157 (0.075, 0.233)	<.001	0.159 (0.073, 0.239)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S31: KSADS Separation Anxiety

	PAE → Brain (A)		Brain → Separation Anxiety (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Separation Anxiety (C)		Total Effect	
	B (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*
Brain Structure										
Volume										
Cerebrum	38.71 (20.53, 53.42)	<.001	0.00 (0.00, 0.00)	.12	0.00 (-0.01, 0.00)	.12	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.03
Inferior temporal L	2.73 (1.55, 3.69)	<.001	0.00 (0.00, 0.00)	.29	0.00 (-0.01, 0.01)	.29	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.02
Middle temporal L	2.21 (1.17, 3.05)	<.001	0.00 (0.00, 0.00)	.20	0.00 (-0.01, 0.00)	.20	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.02
Middle temporal R	2.20 (1.14, 3.06)	<.001	0.00 (0.00, 0.00)	.28	0.00 (-0.01, 0.00)	.28	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.03
Lateral occipital L	1.95 (0.86, 2.83)	<.001	0.00 (0.00, 0.00)	.32	0.00 (-0.01, 0.00)	.32	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.03
Inferior parietal L	2.37 (1.04, 3.45)	<.001	0.00 (0.00, 0.00)	.12	0.00 (-0.01, 0.00)	.12	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.03
Supramarginal R	2.02 (0.85, 2.96)	<.001	-0.003 (-0.005, -0.001)	<.001	-0.005 (-0.011, -0.001)	<.001	0.10 (0.00, 0.18)	.02	0.10 (0.00, 0.17)	.03
Surface area										
Inferior temporal L	7.34 (4.29, 9.80)	<.001	0.00 (0.00, 0.00)	.42	0.00 (-0.01, 0.01)	.42	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.02
Lateral occipital L	0.87 (0.50, 1.17)	<.001	0.00 (-0.01, 0.00)	.30	0.00 (-0.01, 0.00)	.30	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.03
Precuneus R	0.57 (0.22, 0.80)	<.001	-0.01 (-0.01, 0.00)	.06	0.00 (-0.01, 0.00)	.06	0.10 (0.00, 0.17)	.03	0.10 (0.00, 0.17)	.03
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.01	-0.14 (-0.55, 0.27)	.23	0.00 (0.00, 0.00)	.24	0.10 (0.00, 0.17)	.03	0.09 (0.00, 0.17)	.03
Auditory – right ventral diencephalon	-0.02 (-0.02, -0.01)	<.001	-0.10 (-0.41, 0.20)	.30	0.00 (0.00, 0.01)	.30	0.10 (0.00, 0.17)	.03	0.0 (-0.01, 0.17)	.03

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Longitudinal Multilevel Mediation Analysis: *Examining associations between PAE, baseline brain structure, and one-year follow-up psychological outcomes. (Tables S31-S41).*

Supplementary Table S32: Mediation Analyses – CBCL Total Problems At One-Year Follow-Up

	PAE → Brain (A)		Brain → Total Problems (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Total Problems (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	0.00 (0.00, 0.00)	.11	-0.03 (-0.10, 0.01)	.11	1.69 (1.21, 2.58)	<.001	1.65 (1.16, 2.56)	<.001
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.01 (-0.03, 0.00)	.06	-0.03 (-0.10, 0.01)	.06	1.70 (1.22, 2.58)	<.001	1.65 (1.16, 2.56)	<.001
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.03, 0.01)	.31	-0.01 (-0.05, 0.03)	.31	1.67 (1.19, 2.55)	<.001	1.66 (1.17, 2.55)	<.001
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.01 (-0.03, 0.01)	.19	-0.02 (-0.08, 0.02)	.19	1.68 (1.20, 2.56)	<.001	1.65 (1.16, 2.55)	<.001
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.01 (-0.03, 0.01)	.11	-0.02 (-0.06, 0.01)	.13	1.69 (1.20, 2.56)	<.001	1.66 (1.17, 2.55)	<.001
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.02 (-0.04, -0.01)	<.001	-0.03 (-0.07, 0.00)	.05	1.69 (1.21, 2.57)	<.001	1.66 (1.16, 2.55)	<.001
Supramarginal R	1.34 (-0.08, 2.44)	.05	-0.01 (-0.03, 0.01)	.15	-0.01 (-0.04, 0.01)	.20	1.68 (1.20, 2.55)	<.001	1.66 (1.17, 2.55)	<.001
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.04 (-0.11, 0.02)	.10	-0.03 (-0.10, 0.02)	.10	1.70 (1.21, 2.58)	<.001	1.65 (1.17, 2.56)	<.001
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.04 (-0.10, 0.01)	.06	-0.04 (-0.12, 0.01)	.06	1.70 (1.22, 2.59)	<.001	1.65 (1.17, 2.56)	<.001
Precuneus R	0.77 (0.37, 1.08)	<.001	-0.01 (-0.08, 0.05)	.43	0.00 (-0.06, 0.04)	.43	1.67 (1.18, 2.55)	<.001	1.65 (1.17, 2.55)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-0.27 (-3.88, 2.81)	.41	0.00 (-0.02, 0.01)	.40	1.52 (1.00, 2.46)	<.001	1.51 (0.98, 2.47)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-2.20 (-5.27, 0.28)	.04	0.02 (-0.01, 0.06)	.06	1.49 (0.97, 2.44)	<.001	1.52 (0.99, 2.45)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S33: CBCL Internalizing Psychopathology At One-Year Follow-Up

	PAE → Brain (A)		Brain → Internalizing Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Internalizing Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	0.00 (0.00, 0.00)	.32	0.01 (-0.05, 0.06)	.32	1.07 (0.60, 1.93)	<.001	1.07 (0.60, 1.94)	<.001
Inferior temporal L	2.88 (1.46, 3.97)	<.001	0.00 (-0.02, 0.01)	.29	-0.01 (-0.07, 0.03)	.29	1.10 (0.63, 1.95)	<.001	1.07 (0.60, 1.95)	<.001
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.02, 0.02)	.35	0.01 (-0.04, 0.04)	.35	1.08 (0.61, 1.93)	<.001	1.07 (0.61, 1.94)	<.001
Middle temporal R	2.48 (1.19, 3.47)	<.001	0.01 (-0.02, 0.02)	.31	0.01 (-0.04, 0.06)	.31	1.07 (0.60, 1.92)	<.001	1.07 (0.60, 1.94)	<.001
Lateral occipital L	1.78 (0.48, 2.79)	.02	0.01 (-0.02, 0.02)	.31	0.01 (-0.03, 0.04)	.33	1.08 (0.61, 1.93)	<.001	1.08 (0.61, 1.94)	<.001
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.03, 0.00)	.03	-0.02 (-0.05, 0.01)	.08	1.10 (0.64, 1.95)	<.001	1.08 (0.60, 1.94)	<.001
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.00 (-0.02, 0.02)	.44	0.00 (-0.03, 0.03)	.47	1.08 (0.62, 1.93)	<.001	1.08 (0.61, 1.94)	<.001
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	0.02 (-0.06, 0.07)	.34	0.02 (-0.05, 0.07)	.34	1.07 (0.60, 1.92)	<.001	1.07 (0.61, 1.95)	<.001
Lateral occipital L	1.15 (0.70, 1.51)	<.001	0.02 (-0.04, 0.07)	.24	0.02 (-0.05, 0.08)	.24	1.06 (0.59, 1.92)	<.001	1.07 (0.61, 1.95)	<.001
Precuneus R	0.77 (0.37, 1.08)	<.001	0.02 (-0.05, 0.07)	.34	0.01 (-0.05, 0.06)	.34	1.07 (0.60, 1.93)	<.001	1.07 (0.60, 1.94)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-0.08 (-3.59, 2.92)	.46	0.00 (-0.02, 0.02)	.43	1.03 (0.52, 1.95)	<.001	1.02 (0.51, 1.95)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-2.61 (-5.59, -0.20)	.02	0.02 (0.00, 0.07)	.04	1.00 (0.49, 1.92)	<.001	1.04 (0.52, 1.94)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S34: CBCL Externalizing Psychopathology At One-Year Follow-Up

	PAE → Brain (A)		Brain → Externalizing Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Externalizing Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	-0.001 (-0.002, -0.001)	<.001	-0.07 (-0.14, -0.02)	<.001	1.31 (0.88, 2.11)	<.001	1.24 (0.80, 2.05)	<.001
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.03 (-0.04, -0.01)	<.001	-0.07 (-0.13, -0.02)	<.001	1.32 (0.89, 2.11)	<.001	1.24 (0.79, 2.05)	<.001
Middle temporal L	1.92 (0.67, 2.88)	<.001	-0.01 (-0.03, 0.01)	.09	-0.02 (-0.06, 0.01)	.09	1.27 (0.84, 2.06)	<.001	1.24 (0.80, 2.04)	<.001
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.02 (-0.04, -0.01)	<.001	-0.05 (-0.11, -0.01)	<.001	1.30 (0.87, 2.09)	<.001	1.24 (0.79, 2.05)	<.001
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.02 (-0.04, 0.00)	.01	-0.03 (-0.08, 0.00)	.03	1.28 (0.85, 2.07)	<.001	1.24 (0.80, 2.04)	<.001
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.02 (-0.03, -0.01)	<.001	-0.02 (-0.07, 0.00)	.05	1.28 (0.85, 2.06)	<.001	1.24 (0.80, 2.04)	<.001
Supramarginal R	1.34 (-0.08, 2.44)	.05	-0.01 (-0.03, 0.00)	.02	-0.02 (-0.05, 0.00)	.07	1.27 (0.84, 2.05)	<.001	1.25 (0.80, 2.04)	<.001
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.10 (-0.17, -0.05)	<.001	-0.08 (-0.15, -0.03)	<.001	1.33 (0.90, 2.12)	<.001	1.24 (0.80, 2.05)	<.001
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.06 (-0.11, -0.02)	<.001	-0.06 (-0.13, -0.02)	<.001	1.31 (0.88, 2.10)	<.001	1.23 (0.80, 2.05)	<.001
Precuneus R	0.77 (0.37, 1.08)	<.001	-0.02 (-0.09, 0.02)	.16	-0.02 (-0.07, 0.02)	.16	1.27 (0.84, 2.06)	<.001	1.24 (0.80, 2.05)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-1.39 (-4.62, 1.36)	.13	0.00 (-0.03, 0.01)	.24	1.19 (0.72, 2.03)	<.001	1.18 (0.70, 2.03)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.88 (-3.62, 1.33)	.22	0.01 (-0.01, 0.04)	.22	1.17 (0.71, 2.02)	<.001	1.19 (0.72, 2.02)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S35: CBCL Somatic Complaints At One-Year Follow-Up

	PAE → Brain (A)		Brain → Somatic Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Somatic Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	0.00 (0.00, 0.00)	.37	0.01 (-0.03, 0.03)	.37	0.39 (0.12, 0.87)	.01	0.39 (0.12, 0.88)	<.001
Inferior temporal L	2.88 (1.46, 3.97)	<.001	0.00 (-0.01, 0.01)	.31	-0.01 (-0.04, 0.02)	.31	0.40 (0.14, 0.88)	.01	0.39 (0.12, 0.88)	.01
Middle temporal L	1.92 (0.67, 2.88)	<.001	-0.01 (-0.02, 0.00)	.14	-0.01 (-0.04, 0.01)	.14	0.41 (0.14, 0.89)	<.001	0.39 (0.12, 0.88)	.01
Middle temporal R	2.48 (1.19, 3.47)	<.001	0.00 (-0.02, 0.01)	.18	-0.01 (-0.04, 0.01)	.18	0.41 (0.14, 0.89)	<.001	0.39 (0.12, 0.88)	.01
Lateral occipital L	1.78 (0.48, 2.79)	.02	0.00 (-0.01, 0.01)	.46	0.00 (-0.02, 0.02)	.46	0.40 (0.13, 0.88)	.01	0.39 (0.13, 0.88)	<.001
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, 0.00)	.05	-0.01 (-0.03, 0.00)	.10	0.41 (0.14, 0.88)	<.001	0.39 (0.13, 0.88)	.01
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.00 (-0.02, 0.00)	.15	-0.01 (-0.02, 0.01)	.20	0.40 (0.14, 0.88)	<.001	0.39 (0.13, 0.88)	.01
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	0.01 (-0.03, 0.04)	.35	0.01 (-0.03, 0.04)	.35	0.39 (0.13, 0.87)	.01	0.39 (0.13, 0.88)	<.001
Lateral occipital L	1.15 (0.70, 1.51)	<.001	0.01 (-0.03, 0.03)	.32	0.01 (-0.03, 0.04)	.32	0.38 (0.12, 0.87)	.01	0.39 (0.13, 0.88)	<.001
Precuneus R	0.77 (0.37, 1.08)	<.001	-0.02 (-0.05, 0.01)	.15	-0.01 (-0.04, 0.01)	.15	0.41 (0.14, 0.89)	<.001	0.39 (0.12, 0.88)	.01
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	0.40 (-1.58, 2.08)	.34	0.00 (-0.01, 0.01)	.47	0.40 (0.12, 0.92)	.01	0.40 (0.11, 0.92)	.01
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.48 (-2.16, 0.87)	.24	0.01 (-0.01, 0.03)	.24	0.40 (0.11, 0.91)	.01	0.40 (0.12, 0.91)	.01

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S36: CBCL Attention Problems At One-Year Follow-Up

	PAE → Brain (A)		Brain → Attention Deficits (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Attention Deficits (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	0.00 (0.00, 0.00)	.05	-0.02 (-0.06, 0.00)	.05	0.33 (0.08, 0.79)	.01	0.30 (0.05, 0.77)	.01
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.01 (-0.02, 0.00)	.09	-0.01 (-0.05, 0.01)	.09	0.33 (0.08, 0.78)	.01	0.30 (0.05, 0.77)	.01
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.02, 0.01)	.19	-0.01 (-0.03, 0.01)	.19	0.32 (0.07, 0.77)	.01	0.31 (0.05, 0.77)	.01
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.01 (-0.02, 0.00)	.05	-0.02 (-0.05, 0.00)	.05	0.33 (0.08, 0.78)	.01	0.30 (0.05, 0.77)	.01
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.01 (-0.02, -0.001)	.01	-0.01 (-0.04, 0.00)	.03	0.33 (0.08, 0.78)	.01	0.31 (0.05, 0.77)	.01
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, 0.00)	.01	-0.01 (-0.04, 0.00)	.06	0.32 (0.08, 0.78)	.01	0.31 (0.05, 0.77)	.01
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.00 (-0.02, 0.00)	.13	-0.01 (-0.02, 0.00)	.18	0.32 (0.07, 0.77)	.01	0.31 (0.06, 0.77)	.01
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.02 (-0.06, 0.01)	.11	-0.01 (-0.05, 0.01)	.11	0.33 (0.08, 0.78)	.01	0.30 (0.05, 0.77)	.01
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.03 (-0.06, -0.01)	.01	-0.03 (-0.07, -0.01)	.01	0.34 (0.09, 0.80)	.01	0.30 (0.05, 0.77)	.01
Precuneus R	0.77 (0.37, 1.08)	<.001	-0.01 (-0.05, 0.01)	.18	-0.01 (-0.04, 0.01)	.18	0.32 (0.07, 0.77)	.01	0.30 (0.05, 0.77)	.01
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-0.62 (-2.42, 0.91)	.21	0.00 (-0.01, 0.01)	.30	0.20 (-0.06, 0.67)	.07	0.19 (-0.08, 0.67)	.09
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.74 (-2.27, 0.49)	.11	0.01 (-0.01, 0.03)	.13	0.19 (-0.07, 0.66)	.10	0.20 (-0.07, 0.66)	.10

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S37: CBCL Anxious and Depressive Symptoms At One-Year Follow-Up

	PAE → Brain (A)		Brain → Anxiety Depression Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Anxiety Depression Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	-0.01 (-0.05, 0.03)	.29	-0.01 (-0.04, 0.02)	.29	0.26 (-0.02, 0.78)	.04	0.25 (-0.04, 0.77)	.04
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.01 (-0.02, 0.00)	.12	-0.01 (-0.04, 0.01)	.12	0.27 (-0.01, 0.78)	.04	0.25 (-0.04, 0.77)	.04
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.01, 0.01)	.33	0.00 (-0.02, 0.03)	.35	0.25 (-0.03, 0.76)	.04	0.26 (-0.03, 0.77)	.04
Middle temporal R	2.48 (1.19, 3.47)	<.001	0.00 (-0.01, 0.01)	.42	0.00 (-0.03, 0.02)	.42	0.26 (-0.02, 0.77)	.04	0.25 (-0.04, 0.77)	.04
Lateral occipital L	1.78 (0.48, 2.79)	.02	0.00 (-0.01, 0.01)	.42	0.00 (-0.02, 0.01)	.43	0.26 (-0.02, 0.77)	.04	0.26 (-0.03, 0.77)	.04
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, 0.00)	.04	-0.01 (-0.03, 0.00)	.09	0.27 (-0.01, 0.78)	.04	0.25 (-0.04, 0.77)	.04
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.00 (-0.01, 0.01)	.26	0.00 (-0.01, 0.02)	.29	0.25 (-0.03, 0.76)	.04	0.26 (-0.03, 0.77)	.04
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.01 (-0.05, 0.02)	.28	-0.01 (-0.04, 0.02)	.28	0.26 (-0.02, 0.78)	.04	0.25 (-0.03, 0.77)	.04
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.01 (-0.04, 0.02)	.29	-0.01 (-0.04, 0.02)	.29	0.26 (-0.02, 0.78)	.04	0.25 (-0.03, 0.77)	.04
Precuneus R	0.77 (0.37, 1.08)	<.001	0.02 (-0.02, 0.05)	.10	0.01 (-0.01, 0.04)	.10	0.24 (-0.04, 0.75)	.04	0.25 (-0.03, 0.77)	.04
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	0.29 (-1.65, 1.94)	.37	0.00 (-0.01, 0.01)	.48	0.26 (-0.02, 0.76)	.04	0.26 (-0.03, 0.77)	.04
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-1.24 (-2.88, 0.09)	.03	0.01 (0.00, 0.04)	.05	0.24 (-0.04, 0.75)	.04	0.26 (-0.02, 0.76)	.04

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S38: CBCL Withdrawn/Depressed At One-Year Follow-Up

	PAE → Brain (A)		Brain → Withdrawal Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Withdrawal Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	0.00 (0.00, 0.00)	.48	0.00 (-0.04, 0.03)	.48	0.25 (-0.04, 0.78)	.04	0.25 (-0.05, 0.78)	.05
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.01 (-0.02, 0.00)	.11	-0.01 (-0.04, 0.01)	.11	0.26 (-0.03, 0.79)	.04	0.25 (-0.05, 0.78)	.05
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.01, 0.01)	.45	0.00 (-0.02, 0.02)	.45	0.25 (-0.04, 0.78)	.04	0.25 (-0.05, 0.78)	.05
Middle temporal R	2.48 (1.19, 3.47)	<.001	0.00 (-0.01, 0.01)	.41	0.00 (-0.03, 0.03)	.41	0.25 (-0.04, 0.78)	.04	0.25 (-0.05, 0.78)	.05
Lateral occipital L	1.78 (0.48, 2.79)	.02	0.00 (-0.01, 0.01)	.44	0.00 (-0.02, 0.01)	.45	0.25 (-0.04, 0.78)	.04	0.25 (-0.04, 0.78)	.04
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, 0.00)	.02	-0.01 (-0.04, 0.00)	.07	0.26 (-0.03, 0.79)	.04	0.25 (-0.05, 0.78)	.05
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.01 (-0.01, 0.02)	.12	0.00 (-0.01, 0.03)	.15	0.24 (-0.05, 0.77)	.05	0.25 (-0.04, 0.78)	.04
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.01 (-0.05, 0.03)	.35	-0.01 (-0.04, 0.02)	.35	0.26 (-0.04, 0.78)	.04	0.24 (-0.05, 0.78)	.05
Lateral occipital L	1.15 (0.70, 1.51)	<.001	0.01 (-0.03, 0.04)	.30	0.01 (-0.03, 0.04)	.30	0.24 (-0.05, 0.77)	.05	0.25 (-0.05, 0.78)	.05
Precuneus R	0.77 (0.37, 1.08)	<.001	0.01 (-0.03, 0.04)	.35	0.01 (-0.02, 0.03)	.35	0.24 (-0.04, 0.77)	.04	0.25 (-0.05, 0.78)	.05
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	0.11 (-1.89, 1.80)	.47	0.00 (-0.01, 0.01)	.46	0.25 (-0.04, 0.78)	.04	0.25 (-0.04, 0.78)	.04
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.03 (-1.73, 1.34)	.48	0.00 (-0.02, 0.02)	.48	0.25 (-0.04, 0.78)	.04	0.26 (-0.03, 0.77)	.04

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S39: CBCL Thought At One-Year Follow-Up

	PAE → Brain (A)		Brain → Thought Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Thought Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	0.00 (0.00, 0.00)	.08	-0.02 (-0.06, 0.01)	.08	0.58 (0.30, 0.18)	<.001	0.55 (0.27, 1.06)	<.001
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.01 (-0.02, 0.00)	.09	-0.02 (-0.04, 0.01)	.09	0.57 (0.30, 1.07)	<.001	0.56 (0.27, 1.06)	<.001
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.02, 0.01)	.24	-0.01 (-0.03, 0.01)	.24	0.56 (0.29, 1.06)	<.001	0.56 (0.28, 1.06)	<.001
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.00 (-0.02, 0.01)	.32	0.00 (-0.03, 0.02)	.32	0.56 (0.29, 1.06)	<.001	0.56 (0.28, 1.06)	<.001
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.01 (-0.02, 0.00)	.06	-0.01 (-0.03, 0.00)	.13	0.57 (0.30, 1.06)	<.001	0.56 (0.28, 1.06)	<.001
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, 0.00)	.06	-0.01 (-0.03, 0.00)	.11	0.57 (0.30, 1.06)	<.001	0.56 (0.28, 1.06)	<.001
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.00 (-0.01, 0.01)	.25	0.00 (-0.01, 0.02)	.28	0.55 (0.28, 1.05)	<.001	0.56 (0.28, 1.06)	<.001
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.03 (-0.07, 0.01)	.06	-0.02 (-0.06, 0.01)	.06	0.58 (0.30, 1.08)	<.001	0.55 (0.28, 1.06)	<.001
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.03 (-0.06, 0.00)	.01	-0.03 (-0.06, 0.00)	.01	0.58 (0.30, 1.08)	<.001	0.55 (0.27, 1.06)	<.001
Precuneus R	0.77 (0.37, 1.08)	<.001	0.00 (-0.04, 0.03)	.48	0.00 (-0.03, 0.02)	.48	0.56 (0.29, 1.06)	<.001	0.56 (0.28, 1.06)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-0.88 (-2.77, 0.72)	.12	0.00 (-0.02, 0.01)	.23	0.56 (0.29, 1.06)	<.001	0.56 (0.28, 1.06)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.52 (-2.13, 0.77)	.22	0.01 (-0.01, 0.02)	.22	0.55 (0.28, 1.05)	<.001	0.56 (0.29, 1.05)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S40: CBCL Rule Breaking At One-Year Follow-Up

	PAE → Brain (A)		Brain → Rule Breaking Symptoms (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → Rule Breaking Symptoms (C)		Total Effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	-0.001 (-0.001, -0.001)	<.001	-0.04 (-0.08, -0.02)	<.001	0.46 (0.25, 0.82)	<.001	0.41 (0.20, 0.79)	<.001
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.02 (-0.02, -0.01)	<.001	-0.04 (-0.07, -0.01)	<.001	0.45 (0.25, 0.82)	<.001	0.41 (0.20, 0.79)	<.001
Middle temporal L	1.92 (0.67, 2.88)	<.001	-0.01 (-0.02, 0.00)	.01	-0.01 (-0.04, 0.00)	.03	0.43 (0.23, 0.80)	<.001	0.41 (0.20, 0.79)	<.001
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.06, -0.01)	<.001	0.44 (0.24, 0.81)	<.001	0.41 (0.20, 0.79)	<.001
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.02 (-0.03, -0.01)	<.001	-0.02 (-0.05, 0.01)	.07	0.43 (0.23, 0.80)	<.001	0.42 (0.20, 0.78)	<.001
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, 0.00)	.05	0.43 (0.23, 0.80)	<.001	0.41 (0.20, 0.78)	<.001
Supramarginal R	1.34 (-0.08, 2.44)	.05	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, 0.00)	.03	0.43 (0.23, 0.80)	<.001	0.41 (0.20, 0.78)	<.001
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.05 (-0.08, -0.02)	<.001	-0.04 (-0.07, -0.01)	<.001	0.45 (0.25, 0.82)	<.001	0.41 (0.20, 0.79)	<.001
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.04 (-0.06, -0.02)	<.001	-0.04 (-0.07, -0.01)	<.001	0.45 (0.25, 0.82)	<.001	0.41 (0.20, 0.79)	<.001
Precuneus R	0.77 (0.37, 1.08)	<.001	-0.03 (-0.06, -0.01)	.01	-0.02 (-0.04, 0.00)	.01	0.43 (0.23, 0.80)	<.001	0.41 (0.20, 0.79)	<.001
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-0.85 (-2.23, 0.34)	.08	0.00 (-0.01, 0.00)	.21	0.42 (0.22, 0.78)	<.001	0.41 (0.21, 0.78)	<.001
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	0.07 (-1.11, 1.03)	.47	0.00 (-0.01, 0.01)	.47	0.42 (0.22, 0.78)	<.001	0.42 (0.22, 0.78)	<.001

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S41: CBCL Aggressive Symptoms At One-Year Follow-Up

	PAE → brain (a)		Brain → aggressive symptoms (b)		Overall indirect effect (a*b)		Direct effect: PAE → aggressive symptoms (c)		Total effect	
	B (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*	*B* (95% CI)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	-0.001 (-0.001, 0.000)	<.001	-0.03 (-0.07, -0.01)	<.001	0.18 (-0.05, 0.59)	.06	0.14 (-0.10, 0.56)	.14
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.06, -0.01)	<.001	0.17 (-0.06, 0.58)	.07	0.14 (-0.10, 0.56)	.14
Middle temporal L	1.92 (0.67, 2.88)	<.001	-0.01 (-0.02, 0.00)	.01	-0.02 (-0.04, 0.00)	.03	0.16 (-0.07, 0.57)	.10	0.14 (-0.10, 0.56)	.13
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.01 (-0.02, -0.01)	<.001	-0.03 (-0.06, -0.01)	<.001	0.17 (-0.06, 0.58)	.07	0.14 (-0.10, 0.56)	.14
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.04, 0.00)	.07	0.16 (-0.07, 0.57)	.10	0.14 (-0.10, 0.56)	.14
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.01 (-0.02, -0.01)	<.001	-0.02 (-0.05, 0.00)	.05	0.16 (-0.06, 0.57)	.10	0.14 (-0.10, 0.56)	.14
Supramarginal R	1.34 (-0.08, 2.44)	.05	-0.01 (-0.02, 0.00)	.04	-0.01 (-0.03, 0.00)	.07	0.15 (-0.07, 0.56)	.13	0.14 (-0.10, 0.56)	.14
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.05 (-0.08, -0.02)	<.001	-0.03 (-0.07, -0.01)	<.001	0.18 (-0.05, 0.59)	.06	0.14 (-0.09, 0.56)	.14
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.03 (-0.06, -0.01)	<.001	-0.03 (-0.06, -0.01)	<.001	0.17 (-0.06, 0.58)	.06	0.14 (-0.10, 0.56)	.14
Precuneus R	0.77 (0.37, 1.08)	<.001	-0.01 (-0.04, 0.01)	.20	-0.01 (-0.03, 0.01)	.009	0.15 (-0.05, 0.59)	.06	0.14 (-0.10, 0.56)	.14
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-1.39 (-2.95, -0.07)	.02	0.00 (-0.02, 0.01)	.19	0.15 (-0.08, 0.56)	.13	0.14 (-0.09, 0.56)	.14
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.47 (-1.80, 0.60)	.17	0.00 (-0.01, 0.02)	.17	0.14 (-0.09, 0.55)	.16	0.15 (-0.08, 0.55)	.14

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

Supplementary Table S42: KSADS Oppositional Defiant Disorder At One-Year Follow-Up

	PAE → Brain (A)		Brain → ODD (B)		Overall Indirect Effect (A*B)		Direct Effect: PAE → ODD (C)		Total Effect	
	B (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*	*B* (SE)	*p*
Brain Structure										
Volume										
Cerebrum	50.27 (28.25, 67.27)	<.001	-0.0002 (-0.0004, -0.00002)	.03	-0.01 (-0.02, 0.00)	.02	0.11 (0.00, 0.20)	.03	0.10 (-0.01, 0.19)	.05
Inferior temporal L	2.88 (1.46, 3.97)	<.001	-0.004 (-0.008, -0.001)	<.001	-0.01 (-0.02, 0.00)	<.001	0.11 (0.00, 0.20)	.03	0.10 (-0.01, 0.19)	.05
Middle temporal L	1.92 (0.67, 2.88)	<.001	0.00 (-0.01, 0.00)	.09	0.00 (-0.01, 0.00)	.10	0.11 (-0.01, 0.20)	.04	0.10 (-0.01, 0.19)	.05
Middle temporal R	2.48 (1.19, 3.47)	<.001	-0.003 (-0.006, 0.000)	.01	-0.01 (-0.02, 0.00)	.01	0.11 (-0.01, 0.20)	.05	0.10 (-0.01, 0.19)	.06
Lateral occipital L	1.78 (0.48, 2.79)	.02	-0.003 (-0.007, 0.000)	.01	0.00 (-0.01, 0.00)	.10	0.11 (-0.01, 0.20)	.04	0.10 (-0.01, 0.19)	.05
Inferior parietal L	1.51 (-0.10, 2.75)	.05	-0.004 (-0.007, -0.002)	<.001	-0.01 (-0.01, 0.00)	.07	0.11 (-0.01, 0.20)	.03	0.10 (-0.01, 0.19)	.04
Supramarginal R	1.34 (-0.08, 2.44)	.05	0.00 (0.00, 0.00)	.22	0.00 (-0.01, 0.00)	.26	0.10 (-0.01, 0.19)	.05	0.10 (-0.01, 0.19)	.05
Surface area										
Inferior temporal L	0.86 (0.50, 1.14)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.02 (-0.03, -0.01)	<.001	0.12 (0.00, 0.21)	.01	0.10 (-0.01, 0.19)	.05
Lateral occipital L	1.15 (0.70, 1.51)	<.001	-0.02 (-0.03, -0.01)	<.001	-0.02 (-0.03, -0.01)	<.001	0.12 (0.00, 0.21)	.01	0.10 (-0.01, 0.19)	.05
Precuneus R	0.77 (0.37, 1.08)	<.001	0.00 (-0.02, 0.01)	.17	0.00 (-0.01, 0.00)	.17	0.11 (-0.01, 0.20)	.04	0.10 (-0.01, 0.19)	.05
Functional connectivity										
Sensorimotor hand – salience	0.01 (0.00, 0.01)	.19	-0.04 (-0.64, 0.42)	.46	0.00 (0.00, 0.00)	.48	0.10 (-0.01, 0.19)	.05	0.10 (-0.01, 0.19)	.05
Auditory – right ventral diencephalon	-0.01 (-0.02, 0.00)	.02	-0.19 (-0.60, 0.18)	.19	0.00 (0.00, 0.01)	.19	0.10 (-0.01, 0.19)	.05	0.10 (-0.01, 1.19)	.04

All multilevel mediation models controlled for fixed (age, sex, race/ethnicity, birthweight, premature birth, maternal age at birth, highest parent education, maternal depression, other prenatal substance use, school grade) and random (family, scanner/site) effects.

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Appendix 6

Supplementary materials for Chapter 7

Additional Results

Table 1. Demographic, clinical, and substance use characteristics at baseline for participants who did and did not complete the follow-up assessment.

	Completed follow-up N=68 Mean (SD)	Did not complete follow-up N=31 Mean (SD)	p
Age (years)	20.8 (2.4)	21.3 (2.5)	.33
Female n (%)	47	24	.61
Anxiety symptoms[a]	11.5 (4.0)	14.4 (3.8)	<.001
Past month total drinks	61.0 (60.0)	86.7 (96.1)	.10
Past month # binge episodes	5.0 (5.8)	7.0 (8.4)	.18
Age at first drink (years)	15.1 (1.9)	15.5 (1.9)	.44
≥Monthly cannabis use n (%)	6 (8.8)	7 (22.6)	.15
≥Monthly other substance use n (%)	7 (10.3)	5 (16.1)	.38

[a] Measured by the Generalised Anxiety Disorder Questionnaire-7 (GAD-7).