CHARACTERIZING NEURAL AND PSYCHOSOCIAL PREDICTORS OF INTERNALIZING PSYCHOPATHOLOGY IN EARLY ADOLESCENCE

By

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A DISSERTATION

2023-12-04

Presented to the Department of Behavioral Neuroscience and the Oregon Health and Science University School of Medicine

In partial fulfilment of the requirements of the degree of Doctor of Philosophy

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Acknowledgements

No words that I write here could ever truly do justice to the unwavering support, unconditional love, and unending encouragement that I have received from my mentors, colleagues, friends, and family over these past six years. It really is true that no one does this alone.

First and foremost, to my phenomenal mentor, Dr. Bonnie Nagel - you are the reason that I came to OHSU to begin with. I have always admired your commitment to the pursuit of research that will have a tangible, real-world impact on people's lives. Your passion and enthusiasm are truly infectious, and I feel so lucky to be part of lab that is dedicated to transforming adolescent mental health. Some of my favorite memories of graduate school involve sitting in your office, dreaming up new project ideas, asking challenging questions, and imagining how we can push the boundaries of what's been done so far. Thank you for taking a chance on me as your graduate student, and for believing that I could really make it as a scientist. Thank you for your patience, but also for pushing me to let go of my perfectionism when it was holding me back. But most of all, thank you for your unparalleled kindness and understanding. You have been so much more than just an academic mentor to me, and for that I will always be profoundly grateful.

To the incredibly bright, talented, compassionate, and wonderful humans who I am fortunate enough to call lab-mates and friends, Angelica Morales, Scott Jones, Gareth Harman, Amanda Del

Giacco, and Mizan Gaillard - you all have made my graduate school experience unforgettable. Thank you for commiserating with me through all of the late nights, failed analyses, buggy code, and manuscript/grant rejections, and thank you for celebrating with me through all of the successful projects, passed exams, and publications. Regardless of the outcome (because science is science), it has been such a joy to share in this journey with you.

To all of the members of the Developmental Brain Imaging Lab, past and present - thank you for being the most supportive, thoughtful, and kindhearted colleagues that a person could wish for. You all have taught me so much, and none of this would be possible without you.

To my dissertation advisory committee, Joel Nigg, Alice Graham, and Kristen Mackiewicz Seghete - your constructive feedback and insightful contributions to this work and to my development as a scientist are immeasurable. You are all exemplary scientists, and I am continually in awe of the fact that I am surrounded by such brilliant humans. Thank you for working with me through all of the different iterations of this project and for helping me to navigate every stumbling block along the way.

To Oscar Miranda-Dominguez and Nora Byington - thank you for your unfathomable patience in teaching me everything I needed to know about polyneuro risk scores, and for volunteering your time to answer my never-ending list of questions.

To the Department of Behavioral Neuroscience and all its students, past and present - thank you for creating such a welcoming and supportive environment for me to learn and grow. The friends that I have made here over the past six years have left an indelible mark on my life and for that I am so deeply appreciative.

To all of the participants of the Adolescent Brain and Cognitive Development Study[SM] and their families - thank you for graciously offering up your time year after year to take part in this monumental feat of a project.

To Bettsy and Wally Preble - your generosity is truly immeasurable. Thank you for inviting me over for dinners at your home, welcoming me to Easter with your family, and checking up on me all throughout graduate school. I have so enjoyed getting to know the both of you, and it's because of you that I felt like I had a home and a family in Portland the moment I arrived.

To the strong, brilliant, inspiring women who have always been my most ardent champions, Cassidy Johnston, Jacqueline Reid, and Lauren Wells - your ambition, courage, and tenacity are unlike that of anyone else I know. You have always challenged me to dream bigger, to work harder, and to go after the life that I want. Your friendship means the world to me, and I hope you know that I wouldn't have been able to get here without you.

To my dearest friend, Mollie Marr - thank you for all of the coffee breaks at Dornbecher, the venting sessions in your office, the road trip sing-alongs, and the late nights spent pouring over more than a few take-out boxes from Apizza Scholl's while watching Ru Paul's Drag Race on repeat. You are so genuinely kind, so fiercely intelligent, and when I think of my role model in life, I think of you. I can't wait for all of our future adventures.

To Derrick Dewindt - while it may seem that hammer throwing and a Ph.D. in neuroscience have very little to do with one another, the grit and determination that you instilled in me is something that I will always be grateful for. You showed me that I was capable of defying expectations.

To Dr. Noel Wescombe - I know that you will never see this, but I hope you rest in peace knowing that you continue to make a difference in this world through your legacy and your students. Your

welcoming and gentle presence made me feel at home during a time when I was struggling to get through the day. Thank you for giving me the confidence to pursue my own path in research, to explore, to make mistakes, and to figure it out along the way.

To Dr. Alisha Epps Smith - I am eternally grateful that you ended up at Whitworth, and that I had the privilege of learning from you during my time there. I have always looked up to you as a mentor, as a scientist, and as a friend. Thank you for your endless support and encouragement.

To Dr. Mike Sardinia - I could fill an entire book with all the reasons why I am so thankful to have you in my life. I wouldn't be here without you, it's as simple as that. You have shown me time and time again what it means to be an inquisitive and thoughtful scientist, as well as a generous and kind human. I aspire to be even just a fraction of the extraordinary person that you are. Thank you for believing in me when I didn't believe in myself, and for reminding me that I am enough, exactly as I am.

To my new-found family, Kyle, Iva-Marie, and Maddie Connall - You welcomed me into your home and into your lives with open arms. Thank you for loving me like one of your own. I count myself among the luckiest people in the world to have you all as my family.

To my parents, Allen and Renea Kliamovich, and my sister, Krissy - thank you for your unconditional love, support and encouragement. Thank you for always reminding me of what really matters, and for giving me perspective when I needed it most. You have always been my safe haven, and I can't even begin to tell you how grateful I am for that.

To my sweetest cat, Fred - you have put up with more of my shenanigans than anyone should ever have to. I love you dearly.

And last, but certainly not least, to my partner, my husband, my best friend, Elliot Connall - you have stood by my side through every twist and turn of the last six years, and I know that it has not always been easy. I don't think either of us fully understood what we were signing up for back in January of 2018, but no matter what, we always make it through. Thank you for pulling me away from my computer when I desperately needed to take a break, for making sure that I slept and ate and continued to be a (somewhat functional) human being, and for making me laugh and smile when everything seemed to be going wrong. You are my everything.

Abbreviations, Symbols, and Units

ABCC – ABCD-BIDS Community Collection

ABCD – Adolescent Brain and Cognitive Development

ADHD – attention-deficit hyperactivity disorder

ARMS – ABCD Reproducible Matched Samples

ATT – attention

BICEPS – Brain Imaging Connectivity Extraction Program Solution

BIDS – Brain Imaging Data Structure

BPM-Y – Brief Problem Monitor - Youth Report

BWAS – brain-wide association study

CBCL – Child Behavior Checklist

CIFTI – Connectivity Informatics Technology Initiative

CiO – cingulo-opercular network

CiP – cingulo-parietal network

CV – cross-validation

DAN – dorsal attention network

DMN – default mode network

DSM – Diagnostic and Statistical Manual

EXT – externalizing

FA – flip angle

FD – framewise displacement

FOV – field of view

FPN – fronto-parietal network

GAD – Generalized Anxiety Disorder

HCP – Human Connectome Project

HiTOP – Hierarchical Taxonomy of Psychopathology

ICD – International Classification of Diseases

INT – internalizing

LASSO – least absolute shrinkage and selection operator

MAE – mean absolute error

MDD – Major Depressive Disorder

MNI – Montreal Neurological Institute

NDA – NIMH Data Archive

NIH - National Institutes of Health

NIMH – National Institute of Mental Health

PLSR – partial least squares regression

PNRS – polyneuro risk score

RDoC – Research Domain Criteria

ReT – retrosplenial temporal network

RMSE – root mean squared error

ROI – region of interest

RSFC – resting-state functional connectivity

rs-fMRI – resting-state functional magnetic resonance imaging

RSN – resting-state network

SAL – salience network

TE – echo time

TR – repetition time

YSR – Youth Self-Report

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Abstract

It is difficult to overstate the gravity of the current mental health crisis in the United States. In the past several years alone, rates of clinically elevated internalizing symptoms (i.e., anxiety and depression) have nearly doubled, with 1 in 4 adolescents under the age of 18 experiencing significant depressive symptoms, and 1 in 5 experiencing significant anxiety. Importantly, both the acute and long-term ramifications of adolescent-emergent internalizing psychopathology can be profoundly detrimental. Not only are individuals who develop symptoms of anxiety or depression during this sensitive developmental timeframe more likely to struggle with interpersonal relationships and substance use, but they are also at increased risk for chronic and recurrent depression later in life, as well as higher rates of suicidality. Even at sub-clinical levels, internalizing symptoms during adolescence can be precursors to lasting psychosocial impairment. It is for these reasons that a multitude of studies have aimed to disentangle the neural and psychosocial correlates of internalizing psychopathology in adolescent populations. Ideally, a comprehensive understanding of the factors associated with anxiety and depression in youth would lend insight to inform targeted intervention strategies aimed at staving off deleterious health outcomes. However, it is well documented that psychotherapy and antidepressant medications, while effective, typically offer only modest improvement in symptoms, particularly in younger children and adolescents.

It's possible that one of the major barriers to identifying at-risk youth early on, as well as to developing more effective treatment strategies, is the lack of consensus regarding the neurobiological and psychosocial factors that precipitate anxiety and depression. During adolescence, the converging influences of hormonal, cognitive, and psychosocial maturation interact reciprocally with brain development to confer an increased susceptibility to internalizing psychopathology. At the same time, this dynamic developmental state obscures the neurobiology associated with the core symptoms of anxiety and depression. To further complicate matters, any single neurobiological, psychosocial, environmental, or behavioral predictor typically only explains a small amount of phenotypic variance in internalizing psychopathology. This means that multivariate techniques integrating a combination of predictive factors *simultaneously* will likely be necessary to robustly and accurately characterize risk phenotypes associated with complex mental health conditions. Fortunately, advancements in analytic strategies, coupled with rich datasets from several large longitudinal consortium studies, are laying the groundwork for researchers to examine potential biomarkers for a variety of psychiatric and health outcomes in new and innovative ways.

The overarching goal of the present work is to characterize the most robust predictors of internalizing psychopathology in early adolescence by taking advantage of multivariate analytic techniques that maximize predictive power. Chapter 1 sets the stage for this work by summarizing the extant literature on internalizing psychopathology during childhood and into the early adolescent period. By exploring the clinical presentation, epidemiology, and known risk factors for anxiety and depression in youth, this section will frame the subsequent dissertation studies. Chapter 2 introduces the Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®), which is a landmark consortium project aimed at examining trajectories of brain development and child health across adolescence. The ABCD Study® is the source of the data analyzed in subsequent chapters of this dissertation, and so Chapter 2 will highlight key aspects of participant

recruitment, study protocol, and eligibility criteria. Chapter 3 details the first aim of this dissertation research, which focuses on using resting-state fMRI (rs-fMRI) to identify a profile of brain function that is predictive of internalizing symptoms. Taking a cue from the field of genetics and genome-wide association studies, this chapter employs a novel, multivariate analytic framework to generate a 'polyneuro risk score' (PNRS) that is associated with internalizing symptoms in early adolescence. Chapter 4 details the second aim of this dissertation research, which identifies psychosocial, environmental, and behavioral predictors of internalizing symptoms. This chapter leverages a variety of multivariate modeling techniques, including penalized regression methods and ensemble machine learning, to forecast internalizing psychopathology and identify 'non-brain' risk factors. The findings from these two analyses are discussed in depth in Chapter 5, with a particular emphasis on what can be gleaned from neuroimaging vs. more straightforward and simple questionnaires. Together, the results from this project demonstrate the utility of multivariate modeling approaches for robustly characterizing predictors of internalizing psychopathology in adolescence. This work also helps to reconcile prior literature by identifying both neural and psychosocial risk factors in a large and demographically diverse sample and paves the way for future longitudinal analyses in this cohort across the next decade of life.

Chapter 1

Introduction

1.1 Internalizing Psychopathology During Development

Internalizing psychopathology can be broadly defined as the spectrum of mental health conditions characterized by negative, inwardly focused emotions and behaviors (e.g., depressed mood, anxiety, social withdrawal). Psychiatric disorders of this particular category, some of the most notable of which are major depressive disorder (MDD) and generalized anxiety disorder (GAD), display a dramatic rise in prevalence during adolescence. Recent estimates suggest that, between 2005 and 2017, past-year rates of major depressive episodes among adolescents aged 12-17 have increased as much as 52% (from 8.7% to 13.2%) (Substance Abuse and Mental Health Services Administration, 2022; Twenge et al., 2019; Wilson & Dumornay, 2022). Studies conducted since the COVID-19 pandemic have shown that, globally, 1 in 4 adolescents have experienced clinically elevated levels of depression symptoms, while 1 in 5 have experienced clinically elevated levels of anxiety (Lebrun-Harris et al., 2022; Racine et al., 2021). Comparatively, only 1% to 2% of youth under the age of 13 experience significant impairment due to internalizing disorders (Spoelma et al., 2023).

Although this is likely an underestimate, given that anxiety- and depression-related symptoms may manifest differently in young children (i.e., as abrupt mood changes, anger, or irritability) (Thapar et al., 2012), it is clear that the prevalence of internalizing conditions increases substantially between childhood and adolescence. Many researchers have postulated that puberty-related changes in both neurodevelopment (e.g., neuroplasticity due to dendritic spine turnover, rebalancing of inhibition vs. excitation in the frontal cortex) and psychosocial processes (e.g., relationships with peers, social cognition, sense of identity) likely coalesce to create a unique window of vulnerability for internalizing psychopathology (Casey et al., 2019; Pfeifer & Allen, 2021), though the exact mechanism remains unclear.

Unfortunately, the experience of anxiety- and depression-related problems during this critical developmental timeframe has been shown to be associated with a myriad of adverse outcomes both within the adolescent period and beyond. The continuity and duration of depressive symptoms during adolescence have both been shown, independently, to be associated with significantly higher odds for self-harm, suicidal ideation, and suicide attempt (Zubrick et al., 2017). This is particularly striking given that suicide is one of the leading causes of death for individuals between the ages of 10 and 24 years, second only to accidents/unintentional injuries (Heron, 2021). Rates of suicide attempts and deaths by suicide among youth have also increased exponentially in the past decade (Center for Disease Control (CDC), 2019). Such staggering numbers of preventable deaths underscore the gravity of the current mental health crisis in the United States, but it isn't just the presence of a clinical disorder that confers risk for potentially catastrophic outcomes. Even moderate internalizing symptoms that do not constitute a full-syndrome diagnosis appear to be a gateway to lasting psychosocial impairment among other problems (Clayborne et al., 2019; Noyes et al., 2022). The extent to which adolescents report depressive symptoms is positively correlated with difficulties in school, interpersonal relationship problems, including intimate partner violence

victimization, a greater likelihood of substance use, a greater likelihood of chronic/recurring depression, and heightened suicidality (Allen et al., 2014; Clayborne et al., 2019; Jonsson et al., 2010; McLeod et al., 2016; Zisook et al., 2007). It is for this reason that a primary aim of developmental research for the past several decades has been to identify the neurobiological and psychosocial underpinnings that give rise to internalizing psychopathology. Ultimately, the hope is to develop targeted intervention strategies that will reliably halt symptom escalation and prevent adverse health outcomes. Subsequent sections of this chapter will describe the clinical presentation of internalizing psychopathology in youth, contextualize the research that has been done thus far to investigate risk factors and possible mechanisms, and outline current challenges and opportunities in the field.

1.1.1 Clinical Presentation and Epidemiology

Internalizing psychopathology is often conceptualized in contrast to another broad dimension of emotional and behavioral problems - externalizing psychopathology (Achenbach, 1966). Whereas internalizing conditions are typically defined by self-directed negative emotionality, externalizing conditions often manifest as outwardly directed problem behaviors occurring in relation to the environment (e.g., aggression, hyperactivity, impulsivity). Within this framework, internalizing *symptoms*, such as rumination (i.e., repetitive negative thought patterns), feelings of loneliness, social isolation, or withdrawal, sadness, and worry are features that are common to multiple categories of internalizing *disorders*, such as generalized anxiety disorder (GAD), major depressive disorder (MDD), and obsessive-compulsive disorder (OCD) to name a few. These kinds of symptoms are often referred to as 'transdiagnostic' in the literature, as they cut across the artificial lines that distinguish diagnostic categories. Although this dissertation will focus on internalizing

symptoms broadly, it is important to note that much of the foundational work in the field of developmental psychopathology has operated within the framework of diagnostic classification, whether that be in the form of the American Psychiatric Association's Diagnostic and Statistical Manual (DSM) (Robins et al., 1981) or the World Health Organization's International Classification of Diseases (ICD) (World Health Organization, 1996). Under these more traditional nosologies, clinical subtypes are defined by phenotypic data (i.e., commonly occurring groups of symptoms), so the distinction of anxiety vs. depressive disorders as separate categories means that early lines of research into these conditions proceeded mostly independently from one another (Zahn-Waxler et al., 2000). Not only that, but much of that seminal work took a case-control approach by comparing individuals with a diagnosis of either anxiety or depression to 'healthy controls' without such a diagnosis. A thorough review of the epidemiology and clinical presentation of internalizing psychopathology necessitates synthesizing findings from studies that define internalizing problems according to diagnostic classifications with those that take a more dimensional approach to examining internalizing symptoms across a continuum of severity, irrespective of diagnosis. For a more in-depth discussion of the limitations of diagnostic classification structures as they relate to neuroscience research aimed at predicting future risk, see Section 1.3.1.

1.1.1.1 Anxiety-Related Symptoms and Disorders

In its most basic form, anxiety is the brain's response to perceived danger. While it is adaptive in scenarios where an individual is under threat and needs to avoid a particular situation or stimulus, anxiety can become pathological when it occurs outside of this context and in an excessive or persistent manner (Pine et al., 2009). There is some evidence to suggest that a temperament of behavioral inhibition, characterized by a negative reaction to novelty, during infancy and early childhood may contribute to the emergence of anxiety disorders in later childhood and adolescence

(N. A. Fox et al., 2023; Muris et al., 2011). In fact, anxiety disorders are the most commonly occurring type of mental health condition among children in the United States (Beesdo et al., 2007). The age of onset for separation anxiety disorder (i.e., fear of separation from caregivers) and specific phobia (i.e., fear of identifiable objects or situations) tend to be around early to middle childhood, while generalized anxiety disorder (i.e., pervasive worry with no specific focus) and social phobia (i.e., fear of social or performance situations) become more common during the transition from late childhood into adolescence (Kessler et al., 2005; Lijster et al., 2017). Each of these diagnostic classifications share common features, including extreme fear/worry, physiological symptoms of anxious arousal (e.g., restlessness, stomachaches, fatigue), avoidance/withdrawal, and subjective distress (Beesdo et al., 2009). There is substantial evidence to suggest that youth who experience excessive anxiety in childhood and adolescence are at increased risk for maintaining this phenotype into adulthood (termed 'homotypic' continuity). By the same token, epidemiological studies have demonstrated that anxiety often precedes depression ('heterotypic' continuity) (Beesdo et al., 2007; Beesdo-Baum & Knappe, 2012; Williamson et al., 2005). Regardless, the two conditions are known to be highly comorbid (Beesdo et al., 2010; Garber & Weersing, 2010; Kessler et al., 2005; Konac et al., 2021), and the comorbidity rates are likely underestimated (e.g., a formal diagnosis of an anxiety disorder may be accompanied by depressive symptoms that do not meet the clinical threshold). It may be the case that for some individuals there is a developmental progression from anxiety to depression (Ranøyen et al., 2018).

1.1.1.2 Depression-Related Symptoms and Disorders

In contrast to anxiety, depression is most often characterized by feelings of sadness or hopelessness, coupled with a loss of interest in activities that were once enjoyable (anhedonia). In children and adolescents especially, depressed mood may take the form of irritability. The prevalence of

depressive disorders rises substantially into adolescence, with a sharp uptick between the ages of 15 and 18 years (Hankin et al., 1998; Salk et al., 2016; Thapar et al., 2012). It is also at this time that stark sex differences become apparent. The nearly two-to-one preponderance of depressive disorders among female adolescents as compared to male adolescents have been well documented for decades, despite many societal changes that have occurred (Breslau et al., 2017; Cyranowski et al., 2000; Hankin et al., 1998; Salk et al., 2016), and may be linked to hormonal changes during puberty that increase stress sensitivity in young girls (Andersen & Teicher, 2008; Kundakovic & Rocks, 2022; McGuire et al., 2019). Adolescent depression typically follows a recurrent, episodic course (Birmaher et al., 2004; Emslie et al., 2005) and presents with considerable homotypic continuity (Mulraney et al., 2021). The temporal pattern of early anxiety predicting later depression (of which the reverse has not emerged as a robust developmental phenomenon) likely implies some overlapping biological processes. Clark and Watson postulated the existence of a tripartite model in which anxiety and depression share a general distress factor ('negative affectivity'), but that physiological hyperarousal is specific to anxiety, and anhedonia is specific to depression (Clark & Watson, 1991). Though other models have been proposed (Burns & Eidelson, 1998; Cole et al., 1997; Phillips et al., 2002; Watson, 2009), the idea these two distinct clinical disorders may share some of the same underlying features remains important for developmental research aimed at both prediction and treatment.

1.1.2 Treatments and Outcomes

So far, even combinations of psychotherapy and pharmacologic intervention have been unable to completely stem the tide of escalating internalizing symptoms during adolescence. Cognitive behavioral therapy (CBT) (J. B. Klein et al., 2007; March et al., 2004; Weisz et al., 2006) and interpersonal psychotherapy (IPT) (Mufson et al., 2004) have received the most evidential support

for mild to moderate depression in adolescents, but appear less effective in severe cases. CBT remains the gold standard of psychotherapy for anxiety in children and adolescents (Higa-McMillan et al., 2016; Silverman et al., 2008). The most prevalent and effective pharmacologic intervention for adolescent depression is treatment with selective serotonin reuptake inhibitors (SSRIs), specifically fluoxetine (Goodyer et al., 2007; Hetrick et al., 2007; March et al., 2004) and escitalopram (Emslie et al., 2009). In combination with CBT, these medications offer significant clinical benefit to more than half of patients, although their positive effects can take several months to become apparent (Cipriani et al., 2016; Dwyer & Bloch, 2019; Kennard et al., 2009; Walkup, 2017). Fluoxetine (Birmaher et al., 2003), paroxetine (Wagner et al., 2004), and sertraline (Walkup et al., 2008) are more commonly recommended treatments for anxiety in youth. Selective norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine, have empirical support as a complementary treatment option for anxiety (Rynn et al., 2007). That said, SSRIs and SNRIs both come with a multitude of potential side effects, including drowsiness, fatigue, headaches, stomach pain, nausea, and even increased suicidality (Bridge et al., 2007; Hetrick et al., 2007). In October of 2004, the Food and Drug Administration (FDA) issued a somewhat controversial "black box" label warning for antidepressant medications (of any class), as they may amplify suicide risk in children and adolescents up to the age of 25 years. Ultimately, treatment response has been shown to vary substantially on a case-by-case basis, suggesting that individual differences are a primary driver of treatment efficacy and may provide key insights into the biological and psychosocial mechanisms that contribute to internalizing psychopathology (Dwyer & Bloch, 2019; Karyotaki et al., 2021; Kraemer et al., 2002).

1.2 Adolescent Development and Emerging Risk

1.2.1 Defining the Adolescent Period

Often signified by the onset of puberty, adolescence is typically conceptualized as the transitional developmental stage between childhood and adulthood (Casey et al., 2008; Ernst et al., 2006). During this time, youth experience remarkable physical, cognitive, behavioral, and social maturation, as they become increasingly independent from their primary caregivers. Some of the hallmarks of this transition that may be particularly relevant for the emergence of internalizing psychopathology include greater emotional reactivity (especially coupled with a developing understanding of emotions and how to manage emotional responses) (Hofmann et al., 2012; Mennin et al., 2007) and increased sensitivity to social context (i.e., more time spent with peers rather than primary caregivers necessitates developing skills for navigating social pressures) (Crone & Dahl, 2012). It's likely that neurodevelopmental changes associated with these emblematic features of adolescence coalesce to create a window of vulnerability that is unique to this period of life (Pine et al., 2001; Steinberg, 2005). Most definitions for the end of adolescence are culturally and socially defined by milestones, such as graduating from high school, moving out of the childhood home, attaining legal voting or drinking age, or working for a living (Blakemore & Mills, 2014; Sawyer et al., 2018). However, from a neurobiological standpoint, critical brain regions are still undergoing protracted development clear through the third decade of life (Sawyer et al., 2018). Indeed, the adolescent brain's impressive capacity for experience-dependent neuroplasticity opens the door to perturbations that may lead to psychopathology, while at the same time maintaining the malleability necessary for intervention to be particularly effective.

1.2.2 Neurodevelopment

1.2.2.1 Neurodevelopment: Normative Trajectories

Neuroimaging has emerged as a powerful tool in advancing our understanding of normative neurodevelopmental trajectories from childhood though adolescence. By allowing researchers to non-invasively visualize and study the structural and functional changes in the developing brain, neuroimaging has shed light on critical aspects of cognitive, emotional, and social development that provide a backdrop against which to compare deviations that may be associated with psychopathology (Galván, 2021).

Structural MRI (sMRI) leverages the differential magnetic properties of hydrogen atoms in various tissue types to measure the size (area/volume), thickness, or physical architecture of particular brain regions. Initial investigation by Giedd and colleagues demonstrated non-linear decreases in cortical gray matter volume (largely made up of neuronal cell bodies), coupled with relatively linear increases in white matter volume (largely made up of axonal myelin), throughout the adolescent period (Giedd et al., 1999) - findings which have since been replicated several times (Gogtay et al., 2004; Mills et al., 2016; Sowell et al., 2004). It has been hypothesized that cortical thinning, which occurs in a regionally specific manner beginning in the primary somatosensory cortex and ending with the prefrontal and temporal cortices, reflects a process of synaptic refinement, where unnecessary synapses are pruned away so that more metabolic resources can be allocated to strengthening important connections. Subcortical structures display non-linear developmental trajectories that vary both by region and by sex (Herting et al., 2018; Jones et al., 2023; Mills et al., 2021; Wierenga et al., 2018). Studies that have used diffusion-weighted imaging (DWI) to examine the development of white matter tracts during adolescence have noted a general pattern of increasing anisotropy (i.e., the degree to which water preferentially diffuses along one axis; possibly related to fiber density, axonal diameter, and/or myelination) and decreasing diffusivity (i.e., the

directionally invariant magnitude of water diffusion), continuing into early adulthood (Beaulieu, 2002; Lebel et al., 2012). In a trend that mirrors cortical development, short range commissural and projection tracts appear to reach maturity earlier than the long-range association tracts (e.g., the inferior and superior longitudinal fasciculi and fronto-occipital fasciculus) that are associated with complex higher-order cognition (Lebel et al., 2012).

Functional magnetic resonance imaging (fMRI), which may be performed while a participant is engaged in a cognitive task (i.e., task-based fMRI) or under no particular stimulus/condition at all (i.e., resting-state fMRI; rs-fMRI), utilizes an indirect measure of neuronal activity to interrogate the functional organization of the brain. By examining low frequency fluctuations in the blood-oxygen level dependent (BOLD) signal across different brain regions, researchers are able to make inferences about how their coordinated activity supports different cognitive functions (Biswal et al., 1995; M. D. Fox & Raichle, 2007; Logothetis & Wandell, 2004). Distinct groups of brain regions that exhibit highly correlated fluctuations in BOLD signaling at rest are often referred to as 'resting-state networks' or RSNs. Many studies have demonstrated the reproducibility of these networks across development (Betzel et al., 2014; Gordon et al., 2016; Power et al., 2011) and have shown that their coordinated activity can be reliably elicited by various cognitive tasks (S. M. Smith et al., 2009; Yeo et al., 2011). Importantly, there is not a perfect one-to-one correspondence between *structural* architecture (i.e., white matter tracts) and *functional* connectivity (Suárez et al., 2020), suggesting instead that the organized co-activation of brain regions belonging to an RSN arise from a complex interplay of indirect, polysynaptic connections (Messé et al., 2014; Suárez et al., 2020), shared inputs (Bettinardi et al., 2017), complementary chemoarchitecture (Heuvel et al., 2016), and correlations in gene expression (Richiardi et al., 2015). This framework provides a stage for neuromodulation (e.g., synaptic plasticity in the form of long-term potentiation and long-term depression) to sculpt and refine the signaling pathways between different brain regions. Across

development, there appear to be simultaneous progressions toward increased segregation (i.e., regions *close in anatomical proximity* becoming more functionally *differentiated* from one another), as well as increased integration (regions that are *anatomically distant* forming *strongly correlated* functional networks to support different cognitive processes), though more nuanced, network-specific developmental changes have also been detected (Fair et al., 2009; Gu et al., 2015; Marek et al., 2016).

The default mode network (DMN) is perhaps the most well-studied RSN in the adolescent literature. Primarily comprised of the medial prefrontal cortex (mPFC), posterior cingulate cortex (PCC), inferior parietal cortex, and precuneus, the DMN is often referred to as a 'task-negative' network because it is deactivated when the brain is engaged in effortful cognitive processing of an external stimulus (Buckner et al., 2008; Raichle, 2015). However, the DMN's role in cognition has since been shown to be much more expansive, serving a critical role in a multitude of internally-focused mental processes, such as autobiographical recall (Benoit & Schacter, 2015; Kim, 2012; Ritchey & Cooper, 2020), self-referential thought (Gusnard et al., 2001), rumination (Hamilton et al., 2015), interoception (Craig, 2009), mind wandering (Christoff et al., 2009), and future imagining (Bellana et al., 2017). Though it has been well-documented that within-network connectivity of the DMN increases from childhood through adolescence (Gu et al., 2015; Supekar et al., 2010), with the overall architecture of the network roughly resembling that of the adult DMN by age 10, a recent large, longitudinal study of children utilizing a graph theoretical approach showed that this does not occur uniformly across the network (F. Fan et al., 2021). Fan and colleagues were able to identify distinct sub-clusters within the DMN, each with slightly different developmental trajectories, that appear to mirror the three sub-clusters exhibited in adults: a midline core sub-system, a dorsomedial prefrontal cortex (dmPFC) sub-system, and a medial temporal (MT) sub-system (Andrews-Hanna et al., 2010; Braga et al., 2019; Buckner & DiNicola,

2019). It's possible that the differential maturation of these functional systems underlies the evolution of self-related and social-cognitive processes during adolescence. The DMN also displays a significant increase in integration (between-network connectivity) during adolescent development that supports its role as a connecting system.

One key network that the DMN interacts with is fronto-parietal network (FPN), which can be thought of as opposing the function of the DMN. This 'task-positive' network has components in the dorsolateral prefrontal cortices (dlPFC) and intraparietal sulci, and it is thought to mediate top-down, goal-directed activities such as planning, reasoning, problem solving, and inhibitory control (Dosenbach et al., 2007; Marek & Dosenbach, 2018). The FPN is often conceptualized as a 'flexible hub' for cognitive control because its connectivity with the DMN and the dorsal attention network (DAN) varies in response to task demands (Zabelina & Andrews-Hanna, 2016). This kind of dynamic, adaptive coupling that enables efficient task switching is thought to result from increased functional segregation of the FPN during adolescent development (Gu et al., 2015). The salience network (SAL) is anchored in the anterior insula and dorsal anterior cingulate cortex (dACC), but also includes several subcortical structures, namely the amygdala and the ventral striatum (VS). The SAL is largely responsible for detecting novel, salient stimuli (Seeley et al., 2007), and by doing so helps to guide the balance between the FPN and DMN in response to cognitive demands (Uddin et al., 2011). With central hubs situated at the interface between the limbic system and higher-order cortical processing areas, the SAL is particularly relevant for processing reward, motivation, emotion, and pain, and then allocating the appropriate attentional resources toward the most important information. Like the FPN, the SAL displays a normative increase in segregation during adolescent development which is thought to support improved sensitivity to socio-affective information (e.g., emotions of peers, social status) (Gu et al., 2015; Rosen et al., 2018).

1.2.2.2 Neurodevelopment: Potential Risk Factors

Although numerous studies have demonstrated structural alterations in both cortical (e.g., frontal and parietal cortices) (Hao et al., 2017; Modabbernia et al., 2022; Peterson et al., 2009; Schmaal et al., 2017) and limbic regions (e.g., amygdala and hippocampus) (Little et al., 2014; MacMaster et al., 2008; Pagliaccio et al., 2014; Picci et al., 2022; Rosso et al., 2005; Smolker et al., 2022) in association with internalizing psychopathology in youth, the functional neuroimaging literature is somewhat less congruent. Most of this work has focused, perhaps unsurprisingly, on the neural circuitry that is associated with motivation, reward processing, and emotionality. A number of task-based fMRI studies have supported a pattern of blunted reward response in the VS among adolescents with depression - a mechanism which is thought to contribute to anhedonia, specifically (Forbes et al., 2009; Keren et al., 2018; Luking et al., 2016; Morgan et al., 2013). There is some evidence to suggest that altered functional connectivity between the prefrontal (e.g., medial prefrontal cortex - mPFC; anterior cingulate cortex - ACC) and limbic (e.g., amygdala, hippocampus) regions that mediate emotion regulation is associated with current (C. G. Connolly et al., 2013; Cyr et al., 2021; Jin et al., 2011; Pannekoek et al., 2014; Porta-Casteràs et al., 2020) and future (C. G. Connolly et al., 2017; Fischer et al., 2018; Scheuer et al., 2017) depression and anxiety in adolescents. However, the directionality of this relationship remains unclear (Toenders et al., 2019).

Several fMRI studies in both adults (Kaiser et al., 2015) and adolescents (Kaiser et al., 2019) with depression have provided evidence for weaker within-network connectivity of the FPN and stronger between-network connectivity of the FPN with the DMN. This work seems to implicate either a diminished capacity for emotion regulation in general, or difficulties disengaging from ruminative thought patterns. Yet perhaps one of the more robust findings to emerge from the adult rs-fMRI literature in recent years is the identification of hyperconnectivity within the DMN individuals with

depression (Kaiser et al., 2015). Some have postulated that because of its involvement in self-reflective thought and internally focused attention, altered functioning of the DMN could be partly responsible for the perseverative negative thought patterns (rumination) that are such a prominent characteristic of both depression and anxiety (Hamilton et al., 2015; McLaughlin & Nolen-Hoeksema, 2011). Indeed, there is evidence to suggest that *greater* within-network connectivity of the DMN predicts internalizing symptoms (Chahal et al., 2021; Y. Lee et al., 2023), and that this may vary by sex (Dorfschmidt et al., 2022; Ernst et al., 2019; Y. Lee et al., 2023). However, there are also studies which implicate *lower* within-network functional connectivity of the DMN as a common neural substrate across multiple forms of psychopathology (Albertina et al., 2022; Karcher et al., 2021). A recent longitudinal rs-fMRI study by Son and colleagues demonstrated that greater depressive symptomatology was associated with a trajectory of *decreasing* within-network DMN connectivity during adolescence (Son et al., 2023). They further showed that this effect was driven by changes within the more anterior, dmPFC sub-system. Still other studies have not found any evidence of alterations to the DMN in youth with internalizing psychopathology (Burkhouse et al., 2019; Pannekoek et al., 2014; Qu et al., 2021).

It is likely that small sample sizes, disparate methodologies, and the dynamic backdrop of adolescent neurodevelopment contribute to these incongruent findings. For a more in-depth discussion of the current challenges to identifying robust neural correlates of psychiatric conditions, particularly in adolescence, see Section 1.3.1. Regardless, this lack of consensus surrounding the associated neurobiology of internalizing psychopathology in adolescence has stalled progress toward the development of more effective early intervention strategies.

1.2.3 Psychosocial Development

1.2.3.1 Psychosocial Development: Normative Trajectories

Adolescence is also a time of profound change when it comes to psychosocial development. This period of life, and early adolescence in particular (i.e., approximately 10-14 years of age), is characterized by exploration, experimentation, and growth, especially around identity and self-concept. As young adolescents spend less time around their primary caregivers, they take on greater autonomy and independence that allows them to develop a sense of self apart from the familial environment (Guyer et al., 2016; Nelson et al., 2016). There are additional layers to this task, including grappling with ethnic/racial identity, sexual orientation and gender identity, and spirituality/faith. Adolescents' relationship with their caregivers gradually become more equal and reciprocal as compared to childhood, which also has the potential to lead to conflict (Branje, 2018).

Although family support remains an important buffer against external stressors, adolescents spend an increasing amount of time around their peers and rely more on their close friend group for support (Letkiewicz et al., 2023). Additional time spent around peers necessitates that adolescents learn how to adapt to the affective cues of others in order to navigate complex social situations (Crone & Dahl, 2012). In the early stages of this process, youth may notice that they emphasize or de-emphasize certain aspects of their personality or behavior in different company to facilitate social acceptance. This context-dependent switching is reflective of a greater focus on the perception of their peers, which also influences identity development (Brechwald & Prinstein, 2011). In fact, there is substantial research to suggest that young adolescents are particularly susceptible to peer influence, both toward prosocial behavior (Allen & Antonishak, 2008; Choukas-Bradley et al., 2015; Guroglu et al., 2014; Romer et al., 2017) and toward risk-taking behavior (Baumgartner et al., 2011; Chein et al., 2011; Nesi et al., 2017; A. R. Smith et al., 2014).

An increased propensity for risk-taking behavior is one of the hallmarks of adolescent development (Steinberg, 2008) and is thought to be evolutionarily adaptive (Duell & Steinberg, 2019; Ellis et al., 2012), but it can also act as a catalyst for adverse health outcomes related to alcohol and substance use, reckless driving, and risky sexual behavior (Baumgartner et al., 2011; Chein et al., 2011; Dishion et al., 2004; Nesi et al., 2017). During the later adolescent period (i.e., approximately 15-18 years of age), youth begin to spend more time around mixed-sex peer groups, whereas friend groups during childhood are predominately same-sex (J. Connolly et al., 2000). This transition can amplify adolescents' struggles with identity and peer influence as they become more interested in romantic relationships (Molloy et al., 2014). To manage the demands of a complex and ever-changing social environment, adolescent development is associated with corresponding improvements in cognitive flexibility (Hauser et al., 2015).

1.2.3.2 Psychosocial Development: Potential Risk Factors

The considerable sex difference in prevalence of internalizing psychopathology that emerges around puberty has been well-documented for decades (Cyranowski et al., 2000; Hankin et al., 1998; Salk et al., 2017), though the mechanism for this disparity remains unsettled. It's possible that the precipitous rise in depression among young girls is related to changes in circulating gonadal hormones (Angold, Costello, Erkanli, & Worthman, 1999; W. E. Copeland et al., 2019), though some have also suggested that negative experiences surrounding the physical changes associated with puberty (e.g., breast development, menstruation) are to blame (Ke et al., 2018). Importantly for this dissertation, recent work from the IMAGEN consortium points to sex-specific maturation of the DMN as a contributing factor (Ernst et al., 2019). Using resting-state fMRI, Ernst and colleagues found a puberty-by-sex interaction, where female adolescents of a more advanced pubertal stage displayed weaker within- and between-network functional connectivity of the DMN,

whereas the opposite pattern (more advanced pubertal stage associated with stronger connectivity) was seen in male adolescents. Lower functional connectivity of the ACC was then found to be predictive of higher internalizing symptoms two years later.

In addition to female sex-assigned-at-birth, a family history of psychopathology is an established risk factor for adolescent-emergent depression and anxiety, and again, there may be several possible mechanisms that mediate this association. First, family and twin studies have provided strong evidence that depression, in particular, has a genetic component. Heritability estimates from those studies are around 35% (Sullivan et al., 2000), and more recent genome-wide association studies (GWAS) have identified several important genetic loci that contribute to the condition (Howard et al., 2018; Wray et al., 2018). However, psychopathology also influences parenting behavior, thus increasing risk for the emergence of depression and anxiety in youth (Griffith et al., 2023; Hammen et al., 2004; A. E. Pine & Garber, 2023). The caregiver-child relationship can have dramatic consequences that echo throughout adolescence and into adulthood. Not only is a positive relationship with open communication important for social support (Lewinsohn et al., 1998), but it also provides the adolescent with a safe environment in which to develop a healthy relationship with their emotions and learn effective emotion regulation strategies (Morris et al., 2017; Zimmer-Gembeck et al., 2021). Both of these characteristics can help to buffer the effects of stressful or traumatic life events, which are also associated with elevated risk of internalizing psychopathology (Jenness et al., 2019; Kendler et al., 1999).

1.3 Goals of Prediction in Developmental Psychopathology

1.3.1 Challenges

There are already several thoughtful commentaries on the current challenges facing neuroimaging research in the realm of developmental psychiatry (Feczko et al., 2019; Nees et al., 2021), but the main take-aways are worth reiterating here.

As previously alluded to, the traditional diagnostic classifications of psychiatric conditions (e.g., the DSM and ICD frameworks) simultaneously include substantial heterogeneity within individual disorders and significant overlap between them (Achenbach, 2020; Feczko et al., 2019). With regard to this first problem, much of the extant literature has treated disorders like MDD and GAD as unitary entities, when in reality, that is far from the case. For example, according to the DSM-V criteria for MDD, an individual must present with five or more symptoms during the same two-week period, with at least one of those symptoms being depressed mood or loss of pleasure. Among the other possible symptoms are significant weight loss or gain, increase or decrease in appetite, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, difficulty concentrating, and recurrent thoughts of death or suicide (*Diagnostic and Statistical Manual of Mental Disorders*, 2013). All told, there are 256 different symptom combinations that could meet the threshold for diagnosis (Buch & Liston, 2021). Such heterogeneity in the clinical manifestation of a single disorder not only makes it difficult to identify robust, reproducible neural and psychosocial correlates, but it may also suggest that such diagnostic categories simply don't have the same biological validity as the underlying transdiagnostic symptoms of which they are comprised (e.g., rumination, lethargy/fatigue, anhedonia). This leads to the second issue of shared symptoms that are present across diagnostic boundaries. These common, or 'transdiagnostic' features, which often exist on a continuum of severity themselves,

make the case-control approach to biomarker identification problematic. Not only are there shared symptoms across different diagnoses (e.g., difficulty concentrating is a common symptom across MDD, GAD, and attention-deficit hyperactivity disorder - ADHD, among others), but those symptoms are often present to a lesser degree in 'normative' or 'healthy control' samples.

Another major barrier that has stalled progress is the downward translation of findings from the adult literature to youth samples, assuming that the neural underpinnings of internalizing psychopathology would be the same or similar. While it is understandable that the implication of fronto-limbic circuitry or the DMN in adult depression may be relevant for similar psychiatric conditions in youth, the dynamic neurodevelopmental and psychosocial processes that take place during adolescence are unique. Taking a constrained perspective that hinges on findings in fully mature adults and applying that to an entirely different age demographic may inadvertently ignore unique contributors to psychopathology that are only relevant for adolescence. This idea is underscored by accumulating evidence showing that youth depression is phenotypically distinct from adult depression (Rice et al., 2019).

And finally, for the last several decades, neuroimaging research has relied heavily on mass univariate approaches for identifying neural correlates of psychiatric disorders. While this approach can be useful for testing hypotheses about specific group differences (with the caveats listed above regarding group heterogeneity) at the level of one or several brain regions, it usually only explains a small amount of phenotypic variance (Marek et al., 2022; Poldrack et al., 2017). Even network-based analyses that aim to examine within- and between-network dynamics on a larger scale using graph theory have been limited in their ability to capture robust brain-behavior associations. Such studies have also been difficult to replicate, contributing to the 'reproducibility crisis' that was catapulted to the front pages of scientific journals in 2016 (Eklund et al., 2016). As

with the heterogeneity problem, this is another situation where the analytic approach doesn't necessarily align with what is known about associated biology. It has become increasingly apparent that complex, multifaceted behavioral phenotypes, such as mental health disorders, likely arise from patterns of brain activity that integrate multiple different networks and are distributed across the cortex and subcortical structures - not just one or two connections. Yet, a majority of the extant neuroimaging literature has taken a 'seed-based' approach where researchers only analyze the connections between a handful of regions. Additionally, these studies have often been performed in small samples, and the implementation of more complex, multivariate methods that integrate patterns of activity across the brain would require sample sizes on the order of thousands of individuals (Marek et al., 2022).

1.3.2 Opportunities

Though the combination of these challenges may seem insurmountable, there have been several major developments in the field that have put scientists in a position to overcome them. Firstly, there has been an increased focus in recent years on measuring psychiatric symptoms in a dimensional manner. The movement toward frameworks such as the Research Domain Criteria (RDoC) and Hierarchical Taxonomy of Psychopathology (HiTOP) models, which build upon the idea that transdiagnostic symptoms exist along a continuum of severity, reflect a growing recognition of the limitations of the conventional diagnostic categories when it comes to identifying pathophysiological mechanisms. Secondly, the past decade has seen the commencement of several large, longitudinal consortium studies aimed at characterizing trajectories of adolescent health and development. One such project, the Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®), includes a sample of nearly 12,000 youth, between the ages of 9 and 10 years at baseline,

with follow-up assessments projected to continue through early adulthood. The existence of such large and demographically diverse datasets, coupled with complementary advancements in sophisticated, multivariate analytic techniques, means that researchers are now poised to examine potential biomarkers for a myriad of psychiatric outcomes (Gratton et al., 2022). And finally, the field of developmental neuroimaging is beginning to draw inspiration from the success of multivariate techniques used in genomics (i.e., polygenic risk scores) (Visscher et al., 2017) to improve prediction. Given the small individual effect sizes of brain-behavior relationships (Marek et al., 2022), approaches that aggregate these estimates from across the cortex and subcortical structures to produce a summary score may offer better predictions of psychopathology (Byington et al., 2023; Mooney et al., 2021; Zhao et al., 2020).

1.4 Study Objectives

This dissertation aims to leverage each of these opportunities (1. a dimensional approach to studying transdiagnostic symptoms, 2. a large, longitudinal dataset with multiple waves of assessments, and 3. a novel, multivariate prediction method derived from genomics literature) to advance our understanding of adolescent internalizing psychopathology. The overarching goals of this work are two-fold. First, a multivariate approach that takes into account the non-sparse nature of the explanatory signal in the brain is used to characterize a phenotype of resting-state functional connectivity that is associated with internalizing symptomatology (i.e., a polyneuro risk score; PNRS). Second, using a competitive modeling approach with several different regression and ensemble learning techniques, this project will identify key behavioral, psychosocial, and environmental predictors of internalizing symptomatology in the same sample. By comparing the relative predictive power of the 'brain vs. behavior', this work will endeavor to shed light on the

utility of neuroimaging for prediction in psychiatry and inform future research into early intervention and treatment strategies.

Chapter 2

Methods and Materials

2.1 The Adolescent Brain and Cognitive Development[SM] Study (ABCD Study®)

2.1.1 Consortium Goals and Overall Design

The Adolescent Brain and Cognitive Development[SM] Study (ABCD Study®) is a large, multi-site consortium initiative funded by the National Institutes of Health that aims to comprehensively examine relationships between adolescent neurodevelopment and a multitude of behavioral, environmental, social, and biological influences (Volkow et al., 2018). The baseline cohort consisted of 11,877 youth, who were between the ages of 9 and 10 years at the time of study enrollment, recruited from 21 research sites distributed across the United States.

2.1.2 Participants

2.1.2.1 Sampling and Recruitment

The ABCD Study® used a probability sampling of elementary schools within defined catchment areas for each of 21 research sites in order to identify and contact eligible participants and their families while minimizing the risk of bias due to self-selection (Feldstein Ewing, Chang, et al., 2018; Garavan et al., 2018). This recruitment strategy was devised to reflect national sociodemographic proportions on sex-assigned-at-birth, racial identity, ethnicity, and socioeconomic status, thus facilitating epidemiologically informed research. However, it is important to note that designing the study in this way does not guarantee that the sample is representative of the broader U.S. population across other dimensions related to adolescent development (Garavan et al., 2018; Saragosa-Harris et al., 2022). Once a list of elementary schools was identified, ABCD Study® research sites contacted school district superintendents and principals for approval to distribute recruitment materials and host researcher-led presentations (Garavan et al., 2018). Interested families completed a brief phone screening and were enrolled if they met the inclusion criteria for the study (see Section 2.1.2.2). A subset of research sites (University of Colorado - Boulder, University of Minnesota, Virginia Commonwealth University, and Washington University St. Louis) also recruited twins by contacting families through birth registries (Iacono et al., 2018). This sub-study was intended to facilitate analyses that would examine the dissociable environmental and genetic components of a variety of health outcomes. Participant recruitment took place between September of 2016 and August of 2018.

2.1.2.2 Inclusion and Exclusion Criteria

Exclusionary criteria for initial enrollment in the ABCD Study® were as follows: MRI contraindications, major neurological disorders, lack of English fluency, premature birth (gestational

age less than 28 weeks or birthweight less than 1,200 grams), history of traumatic brain injury, or current diagnosis of schizophrenia, mild or severe autism spectrum disorder, intellectual disability, or substance use disorder. These criteria were intentionally broad so as to Parents/guardians provided voluntary informed consent to participate, and children provided assent. Study protocols were approved by each research site's respective Institutional Review Board.

2.1.3 Study Protocol

Participants in the ABCD® Study are followed prospectively for a decade of life with annual assessments of physical and mental health (Barch et al., 2018; Uban et al., 2018), neurocognitive functioning (Luciana et al., 2018), substance use (Lisdahl et al., 2018), and cultural and environmental factors (C. C. Fan et al., 2021; Zucker et al., 2018). Every other year, study visits incorporate a comprehensive neuroimaging protocol with both structural and functional acquisitions (Casey et al., 2018). Periodic follow-up assessments every six months consist of a much shorter battery that is administered virtually to capture interim data on mental health and substance use.

2.1.3.1 Assessments and Interviews

CULTURE AND ENVIRONMENT

Regarding cultural and environmental factors, the ABCD Study® baseline protocol aimed to assess three broad domains: 1) cultural/ethnic group identity, experiences and values, 2) proximal social environment (e.g., home, neighborhood, school) and 3) social interaction. Ethnic identity was assessed via the Multigroup Ethnic Identity Measure - Revised (MEIM-R) (Phinney & Ong, 2007). Several different measures of acculturation (i.e., how cultural practices change as a result of contact

between different cultures) were administered, including the Vancouver Index of Acculturation (VIA), which measures the degree of attachment to a heritage culture vs. the mainstream culture (Ryder et al., 2000), the PhenX Acculturation Questionnaire (https://www.phenxtoolkit.org), which assess proficiency and preference for speaking a language other than English, and the Native American Cultural Acculturation Scale (Garrett & Pichette, 2000), which evaluates the degree of identification with indigenous cultural values. The Mexican American Cultural Values Scale (MACVS) (Knight et al., 2010) was used to assesses various components of traditional Latino/a/x values, including familism, religion, respect, and gender roles. Caregivers completed 3 items from the PhenX Neighborhood Safety assessment (https://www.phenxtoolkit.org) and youth only answered 1 question about whether they felt their neighborhood was safe (Mujahid et al., 2007). The 12-item Inventory for School Risk and Protective Factors (SRPF) derived from the School Social Environment subdomain in the Phenx Toolkit (https://www.phenxtoolkit.org) was administered to evaluate aspects of the school environment and the youth's experience at school (e.g., involvement, support). Youth completed the Acceptance subscale from the Child Report of Behavior Inventory (CRPBI) which is designed to gauge their perception of their caregiver's warmth, acceptance, and responsiveness (Schaefer, 1965). They also completed the Family Conflict subscale from the Family Environment Scale (Moos & Moos, 1994). Derived from a wealth of prior literature, the Parental Monitoring Scale was also included in the baseline study protocol to assess parents' active efforts to keep track of a child's whereabouts Karoly et al. (2016). Finally, youth also completed the Prosocial Behavior subscale from the Strengths and Difficulties Questionnaire (R. Goodman et al., 1998; R. Goodman & Scott, 1999) which measured their tendency to engage in behaviors that help others. Further details regarding each of these assessments and the rationale for their inclusion have been published previously (Zucker et al., 2018).

PHYSICAL HEALTH

Participants completed an extensive demographic questionnaire, mostly comprised of items from the PhenX Toolkit (https://www.phenxtoolkit.org). The General Social Survey was used to inquire about family income and members of the household (T. W. Smith, 2015), and additional questions were administered to assess youth friendships and bullying, school performance, gender identity, and sexual orientation. The Developmental History Questionnaire (DHQ), originally developed by the Adolescent Component of the National Comorbidity Survey (Kessler et al., 2009), was used to measure a variety of early developmental milestones and prenatal exposures. Caregivers were asked whether the youth was born premature, and if so by how many weeks. Their birthweight was also recorded. Several items of this questionnaire inquired about the age at which the youth began to roll over, sit without assistance, walk without assistance, ands say their first words. There were also questions about medical problems that may have occurred during pregnancy (e.g., severe nausea, heavy bleeding, preeclampsia/toxemia, pregnancy-related diabetes or high blood pressure, etc.) or during birth (e.g., blue at birth, slow heartbeat, convulsions, requiring oxygen or blood transfusion, etc.). Additionally, caregivers were asked about the biological mother's substance use during pregnancy. Caregivers and youth were both asked to complete the Pubertal Development Scale as a measure of perceived physical maturation associated with puberty (Petersen et al., 1988)

The Sleep Disturbances Scale for Children (SDSC) (Bruni et al., 1996) was administered to evaluate sleep disturbances among youth participants (e.g., difficulties initiating or maintaining sleep, sleep breathing disorders, issues with arousal, sleep-wake transition, etc.). Youth were also asked about their level of physical activity with questions about how many days in the past week they exercised for at least 60 minutes per day, engaged in exercise to strengthen/tone their muscles, or had physical education (PE) class in school (Eaton et al., 2012). To measure lifetime and past year

involvement in various sports and activities, youth completed the Sports and Activities Involvement Questionnaire (SAI-Q) (Huppertz et al., 2016). Their body mass index (BMI) and weight status were also recorded. Measurements of height and weight were taken as the average of up to 3 separate measurements and BMI (kg/m^2) was calculated and converted to sex- and age-specific percentiles using the CDC 2000 Growth Chart (Kuczmarski et al., 2002). Caregivers answered a series of medical history questions derived from the Missouri Assessment of Genetics Interview for Children (MAGIC) Health Services Utilization Questionnaire (Todd et al., 2003) as well as the Modified Ohio State University TBI Screen - Short Version (Bogner et al., 2017; Corrigan & Bogner, 2007). A Screen Time Questionnaire was also given to both caregivers and youth (Hull et al., 2014; Sharif et al., 2010). Further details regarding each of these measures and the rationale for their inclusion have been published previously (Barch et al., 2018; Palmer et al., 2021).

MENTAL HEALTH

The crux of the mental health assessment in the ABCD Study® is the Kiddie Schedule for Affective Disorders and Schizophrenia for DSM-5 (KSADS-5) (Kaufman et al., 1997, 2020; Kaufman et al., 2013; Kaufman & Schweder, 2004; Kobak et al., 2013). The KSADS-5 is a semi-structured interview designed to measure current and past symptoms of psychopathology in children and adolescents, including mood disorders, anxiety disorders, psychosis, substance use, disruptive behavioral disorders, and sleep problems and it is currently one of the most widely used diagnostic tools across both research and clinical settings. Caregivers completed all of the diagnostic modules at baseline, whereas youth only completed the Mood, Social Anxiety, Generalized Anxiety Disorder, Suicide, and Sleep modules. In terms of dimensional assessments, caregivers also completed the Child Behavior Checklist (CBCL), which is designed to measure behavioral and emotional problems in youth (Achenbach, 2009). They were also asked to complete the Mania Scale derived from the

Parent General Behavior Inventory (PGBI) in order to assess hypomanic symptoms associated with bipolar disorder (Youngstrom et al., 2001, 2008). The Family History Assessment Module Screener (FHAM-S) was administered to gauge family history of psychopathology (J. P. Rice et al., 1995), and the Adult Self Report used to assess behavioral dimensions relevant to caregiver's own mental health (Achenbach, 2009)

At the baseline visit, youth completed the Prodromal Questionnaire Brief Version (PQ-B) to assess risk for psychosis (Ising et al., 2012; Loewy et al., 2005, 2011, 2012; Therman et al., 2014). An abbreviated version of the UPPS-P (for urgency, perseverance, premeditation, and sensation seeking) was used to measure different aspects of impulsivity that may contribute to risk-taking behavior during adolescence (Cyders et al., 2007; Cyders & Smith, 2008; Lynam, 2013; Whiteside et al., 2005). Behavioral inhibition (i.e., avoidance behavior stimulated by punishment or non-reward) vs. activation (i.e., approach behavior stimulated by positive reinforcement) was assessed using the BIS-BAS (behavioral inhibition system, behavioral activation system) (Carver & White, 1994; Pagliaccio et al., 2016). The ABCD Study's Mental Health Workgroup has published a thorough description of each of these measures and provided justification for their inclusion in the protocol (Barch et al., 2018).

NEUROCOGNITION

The neurocognitive battery for the ABCD Study ® at baseline was designed to assess cognitive processes that were particularly salient for the early to mid-adolescent period. Special emphasis was placed on tasks that would probe either 1) cognitive processes which may be impacted by future substance use, or 2) cognitive processes which may underlie the adolescent propensity for risk-taking behavior (Luciana et al., 2018).

Participants completed both a visual acuity test (Snellen Chart) (Snellen, 1862) and an assessment of handedness (Edinburgh Handedness Inventory) (Oldfield, 1971; Veale, 2014). They then completed seven NIH Toolbox® tasks (http://www.nihtoolbox.org) on a tablet. For the Toolbox Picture Vocabulary Task®, youth listened to a series of different words and were asked to indicate which picture on screen best matched the meaning of the word that was said (Gershon et al., 2013, 2014). This task assesses language and verbal intellect. The Toolbox Oral Reading Recognition Task® measured the youth's ability to pronounce printed letters or words and is thought to be a reflection of their exposure to language and reading skills (Gershon et al., 2013, 2014). The Toolbox Pattern Comparison Processing Speed Test® was used to measure visual processing speed (Carlozzi et al., 2013, 2014, 2015). Youth were shown two pictures at a time and were asked to touch a button on the tablet screen to indicate whether they were 'the same' or 'not the same'. For the Toolbox List Sorting Working Memory Test® youth were presented with a sequence of pictures of either animals or foods of different sizes (Tulsky et al., 2013, 2014). They were then asked to repeat this list of items back to the researcher in order from smallest to largest. This task was used to measure working memory. To assess episodic memory, youth completed the Toolbox Picture Sequence Memory Test® wherein they were presented with a sequence of pictures depicting activities or events and were asked to recall that sequence (Bauer et al., 2013; Dikmen et al., 2014). The Toolbox Flanker Task® was included in the baseline neurocognitive battery to evaluate executive function, attention, and response inhibition (Zelazo et al., 2013, 2014). For this task, four flanking stimuli (two on the left side and two on the right side) are presented all facing one direction (either left or right), and the middle stimulus is facing either the same direction (congruent trial) as the flanking stimuli or the opposite direction (incongruent trial). Youth were then prompted to touch a button on the screen to indicate the direction of the middle stimulus. This task was scored according to both speed and accuracy. The final NIH Toolbox® task was the

Toolbox Dimensional Change Card Sort Task® where youth were presented with two objects at the bottom of the tablet screen. A third object then appeared on the screen, and they had to sort that object according to either color or shape to one of the objects at the bottom of the screen (Zelazo et al., 2013, 2014). This task was used to measure cognitive flexibility. For each of the NIH Toolbox® tasks, raw scores, un-corrected standard scores, and age-corrected standard scores were produced (Casaletto et al., 2015), as were a Total Score Composite, a Crystalized Intelligence Composite, and a Fluid Intelligence Composite (Akshoomoff et al., 2013).

In order to assess delay discounting (i.e., the depreciation of a reward's value relative to the delay of its receipt), participants also completed a one-item Cash Choice Task in which they were asked if they would rather receive a smaller amount of money sooner ($75 in 3 days) or a larger amount of money later ($115 in 3 months) (Wulfert et al., 2002). The Rey Auditory Verbal Learning Test (RAVLT) was administered to measure auditory learning, memory, and recognition (Strauss et al., 2006). Researchers read a list of 15 unrelated words out loud 5 times followed by a distractor list of 15 words. Youth were then asked to recall as many words as they could from the initial list. After a 30-min delay and completing other tasks, youth were asked to recall as many words as possible from the list a second time. To evaluate non-verbal reasoning, youth completed the Matrix Reasoning subtest from the Wechsler Intelligence Test for Children-V (WISC-V) (Wechsler, 2014). This task required participants to select the image that would complete a visuospatial array of several stimuli. Finally, youth completed the Little Man Task (LMT) to gauge visuospatial processing (Acker & Acker, 1982). In this task, a figure of a person holding a briefcase in one hand is presented in one of four orientations (right side up, upside down, facing the participant, or facing away from the participant), and for each trial youth must indicate in which hand the person is holding the briefcase. Further details regarding each of these tasks, the rationale for their inclusion, and baseline performance statistics have been published previously (Luciana et al., 2018).

SUBSTANCE USE

At baseline, youth were asked if they had heard of different substances and their response determined whether follow-up questions were administered. Gating details for each instrument have been presented in prior work (Lisdahl et al., 2018). Substance use categories included alcohol, cannabis and cannabinoids, nicotine, caffeine, inhalants, prescription medications and 'other'. The 'other' category included additional substances that were only endorsed if the youth mentioned them - they were not explicitly brought up by the researcher to avoid exposure to novel substances (e.g., cocaine, methamphetamine, MDMA/ecstasy, ketamine, heroin, hallucinogens, etc.). If youth endorsed prior substance use at baseline, they were asked about lifetime patterns of use (e.g., age at first use, total lifetime quantity, maximum dose consumed, date of last use). A computerized Timeline Followback (TLFB) interview was used to gauge recent low-level use (e.g., first sip of alcohol or first puff/taste of cannabis/nicotine) and more detailed 6-month use data (e.g., quantity and frequency of use) (Robinson et al., 2014; Sobell & Sobell, 1996). Youth were also asked about recent patterns of caffeine use (e.g., average number of caffeinated drinks per week and maximum dose consumed in the past 6 months). The Participant Last Use Survey (PLUS) form was administered to both the youth and their caregiver on any day that the youth completed an MRI scan or neurocognitive assessment to gauge how substance use in the past 24 hours may have impacted brain function and task performance (Brown et al., 2015).

Several additional questionnaires were used to assess factors that may impact risk for substance use. Youth completed a 9-item instrument, adapted from the Population Assessment of Tobacco and Health (PATH) Study, that was designed to measure their intention to use alcohol, nicotine, and cannabis in the future (Hyland et al., 2017). Youth were also asked about how many of their friends used different substances, modified from the PhenX Peer Substance Use Questionnaire

(https://www.phenxtoolkit.org) (Johnston, 2005). If participants endorsed regular substance use, they were asked to complete the PhenX Acute Subjective Responses to Alcohol/Marijuana/Tobacco Questionnaires as appropriate (https://www.phenxtoolkit.org). Caregivers participating in the study completed a 9-item questionnaire adapted from the PhenX Community Risk and Protective Factors Questionnaire (https://www.phenxtoolkit.org) that included questions about substance access and availability (e.g., how easy would it be for the youth to obtain alcohol, marijuana, other drugs, etc.). Caregivers were also asked about household rules regarding substance use and how they were enforced (Dishion et al., 2003). Consequences of substance use were assessed via the Hangover Symptoms Scale (HSS) (Slutske et al., 2003) and three self-report symptom measures of substance use disorders: the Rutgers Alcohol Problem Index (RAPI) [White1989], the Marijuana Problem Index (MAPI) (Johnson & White, 1989; Simons et al., 1998), the Drug Problem Index (DAPI) (Johnson & White, 1989; Kingston et al., 2011), and 10 items from the nicotine-dependence section of the PATH Study (Hyland et al., 2017)

LINKED EXTERNAL DATA

In order to assess a variety of state- and community-level environmental factors that may impact development, the ABCD Study® also includes linked external data based on participants' primary residential address (Cardenas-Iniguez, 2023; C. C. Fan et al., 2021). First, a composite was used to generate state-level measures of race, gender, and ethnicity bias. The legality of marijuana use (e.g., recreational, medicinal, no legal access) was also included as a state-level measure. Urbanization was assessed via gross residential density, population density, national walkability index, traffic counts, and proximity to roads (https://population.un.org/wpp/, https://www.federalregister.gov/documents/2011/08/24/2011-21647/urban-area-criteria-for-the-2010-census, https://www.epa.gov/smartgrowth/smart-location-mapping#walkability,

https://demographics5.arcgis.com/arcgis/rest/services/USA_Traffic_Counts/MapServer/0) (Ramsey & Bell, 2014). Several different measures were used to assess neighborhood quality. The Area deprivation index (ADI) is a composite, multivariable measure associated with neighborhood disadvantage and socioeconomic status (Singh, 2003). The Social Vulnerability Index (SVI) is published by the Center for Disease Control (CDC) and was used to assess community vulnerability to stressors such as natural disasters and disease outbreaks (https://www.atsdr.cdc.gov/placeandhealth/svi/index.html) (Flanagan et al., 2011). These census-tract level variables are grouped by several themes: socioeconomic status, household composition and disability, minority status and language, and housing type and transportation. The Opportunity Atlas provides a census-tract-level measure of economic opportunity based on the predicted average incomes for a cohort of 20,000 people (Chetty et al., 2018). The Child Opportunity Index (COI) 2.0 is a national assessment of neighborhood opportunity based on three domains: education, health and environment, and social and economic opportunities (Acevedo-Garcia et al., 2014, 2020). County-level Uniform Crime Reporting Data (https://doi.org/10.3886/ICPSR33523.v2) was also included as part of the ABCD Study's linked external data, as was risk of lead exposure (based on housing age and poverty rates; see https://github.com/voxmedia/data-projects/blob/master/vox-lead-exposure-risk/calculate-lead-risk.py). Finally, several natural environment variables were included, such as air quality (via residential exposure to fine particulate - $PM_{2.5}$, nitrous dioxide - NO_2, and ozone - O_3), elevation, and climate (via maximum daily temperature and vapor pressure deficit) (Daly et al., 2015). A particularly thoughtful discussion of recommendations for the use of these linked external data is available as a preprint (Cardenas-Iniguez, 2023).

2.1.3.2 Neuroimaging

IMAGE ACQUISITION

Participants were scanned on either a 3T Siemens Prisma, General Electric MR750, or Philips instrument, depending on the research site. Scanning parameters were harmonized across research sites and scanner platforms (Casey et al., 2018). The scan session itself consisted of a localizer, acquisition of a 3D T1-weighted image, two 5-minute runs of resting-state fMRI, a diffusion weighted imaging (DWI) sequence, acquisition of a 3D T2-weighted image, one or two more runs of resting-state fMRI (depending on the amount of motion in the previous runs), and a series of three fMRI tasks (a Monetary Incentive Delay Task, a Stop Signal Task, and an Emotional N-Back Task) (Casey et al., 2018).

For the resting-state portion of the neuroimaging session (TR = 800 ms, TE = 30 ms, FA =52°, 2.4 mm iso-voxels, 60 slices, FOV = 216 x 216 mm), participants were instructed to keep their eyes open and fixated on a crosshair (Casey et al., 2018). They received either three or four resting-state runs, each lasting five minutes, depending on the amount of motion identified in the initial runs. Head motion was monitored in real time using FIRMM (Framewise Integrated Real-time Motion Monitoring), which enabled scan operators to make adjustments during the visit in order to maximize the amount of usable data collected (Dosenbach et al., 2017).

IMAGE PROCESSING

Neuroimaging data utilized in this dissertation were released as part of the ABCD-BIDS Community Collection (ABCC; NDA Collection 3165). In an effort to improve data accessibility and reproducibility of analyses across the research community, ABCC provides both raw imaging data, as well as processed derivatives that conform to Brain Imaging Data Structure (BIDS)

formatting standards (Feczko et al., 2021; Gorgolewski et al., 2016). The processing pipeline for functional MRI data is a modified version of the Human Connectome Project (HCP) pipeline (Glasser et al., 2013) that has been optimized to accommodate the various scanner platforms of the 21 research sites. A detailed description of this pipeline, as well as the associated code, are publicly available at https://collection3165.readthedocs.io/en/stable/.

To summarize, images were examined for scanner artifacts, incomplete sequences, or incorrect scanning parameters by the ABCD® Data Analysis and Informatics Center. Subsequently, the data underwent seven preprocessing stages: 1) PreFreesurfer, 2) Freesurfer, 3) PostFreesurfer, 4) Volume, 5) Surface, 6) Functional Connectivity Processing, and 7) Executive Summary Generation. The *'PreFreesurfer'* step included brain extraction and denoising, after which the anatomical data (T1- and T2-weighted images) were normalized and rigidly aligned to a standard MNI template. *'Freesurfer'* segmented the subcortical structures and used the anatomical data from *'PreFreesurfer'* to create cortical surface meshes in native space, then registered them to the MNI template. In *'PostFreesurfer'*, the cortical surface meshes in native space were converted to CIFTI (Connectivity Informatics Technology Initiative) format, such that data from the cortical gray matter were represented as a 2D surface mesh, and data from subcortical gray matter were retained as 3D voxels, combined in a single file of "gray-ordinates" (Glasser et al., 2013). Compared to a traditional volume-based approach, surface-based processing markedly improves issues with volume-based smoothing which can obscure spatial localization of the MR signal (Anticevic et al., 2008; Tucholka et al., 2012). The *'Volume'* and *'Surface'* stages registered the functional data to the MNI template and projected the functional data to the CIFTI surfaces, respectively. Additional *'Functional Connectivity Processing'* included the following steps: demeaning and detrending the data with respect to time, denoising with regressors for signal (white matter, cerebrospinal fluid, and global signal) and movement (translational and rotational) variables, and bandpass filtering

with a 2nd order Butterworth filter. After these standard pre-processing steps, a respiratory motion filter was applied, and a motion censoring procedure was used to generate temporal masks at a range of framewise displacement (movement of one frame relative to the previous frame; FD) thresholds. Finally, both dense timeseries (.dtseries) and parcellated timeseries (.ptseries) data were produced, and a web-based executive summary was created to facilitate visual quality assurance of these outputs.

2.2 Methods Specific to This Dissertation

2.2.1 Participants

Participants included in the analyses for this dissertation were selected from the ongoing ABCD Study®, provided that their data met several additional requirements. First, participants were required to have completed at least two assessments of the Brief Problem Monitor - Youth Form (BPM-Y) between the first mid-year interview and the 2-year follow-up (detailed in Section 2.2.2). Second, participants were required to have an rs-fMRI scan at baseline that passed quality control criteria (detailed in Section 2.2.3)

2.2.2 Internalizing Symptoms

Youth completed the Brief Problem Monitor - Youth Form (BPM-Y) beginning at the first mid-year interview, with continued administration at 6-month intervals. The BPM-Y is a short self-report instrument adapted from the longer Youth Self-Report (YSR), which aims to evaluate attentional, behavioral, and internalizing problems in youth between the ages of 6 and 18 years (Achenbach et al., 2011; Achenbach & Rescorla, 2001). For this questionnaire, participants were

asked to rate the degree to which each of 19 statements have described them over the course of the past week. Items are rated on an ordinal scale, with possible response options ranging from "Not True" (0), to "Somewhat True" (1), or "Very True" (2). The statements are distributed across three subscales to assess attention and hyperactivity problems (ATT; 6 items), externalizing and behavioral problems (EXT; 7 items), and internalizing problems (INT; 6 items). The statements that comprise the internalizing subscale were designed to gauge feelings of guilt and worthlessness, fearfulness and worrying, as well as general unhappiness or depressed mood. To generate a cumulative measure of internalizing symptom burden over time, participants' scores on the BPM-Y internalizing subscale were added across follow-up timepoints, starting from the first mid-year interview (approximately 6 months after enrollment) through the 2-year follow-up visit. Missing visit data were imputed prior to summation, and further details can be found in Section 2.2.5. After imputation, each participant's cumulative BPM-Y internalizing symptom score was calculated as the sum of their scores on the internalizing subscale at each wave of data collection. To improve normality, a Box-Cox transformation was applied to the cumulative BPM-Y internalizing scores prior to analysis.

2.2.3 Resting-State fMRI

Participants identified as having an average FD $>$ 0.2mm were excluded from the present analysis in order to minimize the impact of motion artifacts (Power et al., 2014). Additionally, included participants were required to have at least eight minutes of data after motion censoring. Connectivity matrices were generated using BICEPS (https://gui-environments-documentation.readthedocs.io/en/latest/GUI_environments/) - a graphical user interface developed in Matlab that applies motion censoring and outlier detection to

the parcellated timeseries (.ptseries) data while retaining a consistent amount of data across participants (here, eight minutes).

2.2.4 Data Partitioning

2.2.4.1 ABCD Reproducible Matched Samples (ARMS)

To facilitate tests of replicability, the ABCD Study® cohort has been divided into three demographically matched groups, referred to as the ABCD Reproducible Matched Samples (ARMS) (Feczko et al., 2021). ARMS-1 and ARMS-2 are each comprised of 5,786 participants, while ARMS-3 is a smaller model testing group of only 305 participants. The ARMS were matched on nine sociodemographic variables thought to be relevant for, or potentially confound, developmental outcomes. These included research site, sex-assigned-at-birth, age, grade, race/ethnicity, highest level of parental education, handedness, combined family income, and exposure to anesthesia. Participants belonging to the same family were assigned to the same ARMS in order to maximize independence between the groups, and the number of siblings, twins, and triplets were also matched across groups.

2.2.4.2 Participant Inclusion Flowchart

After excluding participants for a missing rs-fMRI scan at the baseline visit (n = 1,194), rs-fMRI data that did not pass the quality control standards described above (n = 3,939), or more than two missing BPM-Y assessments during the specified follow-up period (n = 223), these analyses included a total sample of 6,521 youth across the three ARMS (Figure 2.1). Because recent work has demonstrated that exceedingly large sample sizes are needed to accurately estimate brain-behavior relationships (Marek et al., 2022), the analyses described in Chapter 3 and Chapter

4 make use of a large discovery dataset and a smaller validation dataset. After considering several potential data splits (first using ARMS-1 for discovery and ARMS-2 for validation, then using ARMS-2 for discovery and ARMS-1 for validation, and finally using both ARMS-1 and ARMS-2 combined for discovery and the smaller ARMS-3 for validation), we proceeded with the analytic strategy that used the largest discovery set (ARMS-1 and ARMS-2 combined) and the smaller validation set (ARMS-3).

2.2.5 Missing Data

2.2.5.1 Outcome Variable

As previously alluded to, BPM-Y internalizing symptom scores were imputed for participants with missing data for one or two follow-up visits. Although multiple imputation is a well-supported and effective approach for dealing with missing data because it reflects the uncertainty in the values that were imputed, the computational demands of this project precluded repeated analysis of multiple imputed datasets. Additionally, the ability to pool final parameter estimates with Rubin's rules has not yet been implemented in the code base. For these reasons, these analyses utilized an alternative approach in which multiple imputed datasets were combined prior to analysis (Bernanke et al., 2022). The R package *mice* (van Buuren & Groothuis-Oudshoorn, 2011) was used to impute participants' missing BPM-Y internalizing symptom scores and several sociodemographic characteristics (participant age, sex-assigned-at-birth, race, ethnicity, annual household income, highest level of parental education, and research site) were included as auxiliary variables to help inform the imputation. Observations were clustered at the level of the participant. This process was repeated for 100 iterations, after which a single, merged, imputed dataset was generated by

replacing missing BPM-Y internalizing symptom scores with the average of the 100 imputed values.

2.2.5.2 Predictor Variables

For the analyses presented in Chapter 4, item-level responses from across a variety of questionnaires and assessments were gathered as potential predictor variables. Although there is no gold standard regarding the threshold for discarding predictor variables on the basis of missing data, imputing or modeling missing data is generally preferred. That said, there were concerns, in this case, about imputing missing values due to the nature of the type of missingness observed. Initially, predictor variables with more than 15% missing data were excluded from the analysis based on support from prior work with ABCD Study® data (Harman et al., 2021; Ho et al., 2022; Xiang et al., 2022). Predictor variables with 15% missing data or less were imputed using K-nearest neighbors (k=7). Importantly, an overwhelming majority of the variables that were excluded due to excessive missingness were due to conditional/branching logic rather than from non-response/skipping. For example, one question from the KSADS-5 Background Items inquired about gender identity by asking the caregiver, "Is your child transgender?" As a follow-up, there is a subsequent question that asks, "Has this caused any problems for you/your child with your family or with kids at school?" If the youth does not identify as transgender, the response to the second question would be missing by default. Again, while it is generally recommended to impute missing data rather than to drop entire variables, this approach would not make sense for intentional missingness such as this. It is possible that an imputation strategy could provide an implausible value (e.g., an answer of "yes" to the second question above, when the answer to the first question was "no"). Likewise, it would be inadvisable to simply replace these intentionally missing values with a response of "no". In the example presented above, such an approach would be akin to saying that a majority of youth

in the sample do not experience problems due to being transgender. While this is technically true, it's not because they *wouldn't* experience problems if they were transgender, it's because they're *not transgender*, and that information is already captured by the first question.

Chapter 3

Leveraging distributed brain signal at rest to predict internalizing symptoms in youth

Deriving a polyneuro risk score from the ABCD Study® cohort

3.1 Abstract

The prevalence of internalizing psychopathology rises precipitously from early to mid-adolescence, yet the neural phenotypes associated depression and anxiety during this developmental period remain unclear. Youth from the Adolescent Brain and Cognitive Development Study^{SM} (ABCD Study®; ages 9-10 years at baseline) with a resting-state fMRI scan and mental health data were eligible for inclusion. Internalizing subscale scores from the Brief Problem Monitor - Youth Form

were combined across two years of follow-up to generate a cumulative measure of internalizing symptom burden. The total sample (n=6,521) was split into a large discovery set and a smaller validation set. Brain-behavior associations of resting-state functional connectivity with internalizing symptom scores were estimated in the discovery set. The weighted contributions of each functional connection were then aggregated using multivariate statistics to generate a polyneuro risk score (PNRS) for each participant. The predictive power of the PNRS was evaluated in the validation set. The PNRS explained 9.47% of the observed variance in internalizing symptom scores in the validation set. Model performance peaked when the top 2% of the most significant functional connections identified in the discovery set were retained. The resting-state networks that were implicated most prominently were the default mode network, dorsal attention network, and cingulo-parietal network. These findings were significant ($p<1*10^{-6}$) as accounted for by permutation testing (n=7,000). These results suggest that the neural phenotype associated with internalizing symptoms during adolescence is functionally distributed. The PNRS approach is a novel method for capturing relationships between resting-state functional connectivity and behavior.

3.2 Introduction

Internalizing problems (e.g., depressed mood, anxiety, somatic complaints, withdrawal), display a marked rise in prevalence during adolescence. Recent estimates suggest that as many as 11%-13% of adolescents between the ages of 12 and 17 have already met criteria for a mood disorder, such as major depression or dysthymia, in their lifetime (Merikangas et al., 2010; Twenge et al., 2019), while this figure is more than doubled for anxiety disorders (W. Copeland et al., 2011; Merikangas et al., 2010; and for review see Beesdo-Baum & Knappe, 2012). Some have postulated that the

dynamic shifts in hormonal, cognitive, neurobiological, and psychosocial processes that occur during puberty create a unique window of vulnerability to internalizing psychopathology. Interestingly, it is also at this point in development where sex differences in the prevalence of internalizing symptoms emerge (Hankin et al., 1998). Several meta-analyses have now demonstrated that, while rates for internalizing disorders are roughly equivalent during childhood, girls' risk for developing anxiety or depression surpasses that of boys by more than two times beginning in adolescence, and this disparity persists through the lifespan (Salk et al., 2017). These findings bolster the conceptualization of early adolescence, marked by the beginning of puberty, as a critical timeframe for the emergence of internalizing psychopathology (for review, see Zahn-Waxler et al., 2000). Importantly, there is a substantial body of literature to suggest that the experience of anxiety- and depression-related symptoms during this pivotal developmental stage is associated with a myriad of adverse health outcomes. For youth between the ages of 9 and 17 years, mood disorders, anxiety disorders, and substance use problems each independently increase the risk of suicide attempts later in life (Gould et al., 1998), which is particularly striking given that suicide is the second leading cause of death for individuals between the ages of 10 and 24 years (Heron, 2021). But it isn't just the presence of a clinical disorder that confers risk. Even moderate symptoms that do not constitute a full-syndrome disorder are associated with impairments in school performance, difficulties with interpersonal relationships, and a greater likelihood of substance use (Fergusson et al., 2005; Lewinsohn et al., 1998; Zisook et al., 2007).

One silver lining, however, is that the brain is capable of remarkable experience-dependent plasticity during adolescence (Andersen & Teicher, 2008; Casey et al., 2019). Intervention in this sensitive window could not only halt symptom escalation in its tracks, but may also stave off long-term health consequences. In fact, there is already significant evidence that cognitive behavioral therapy, psychotherapy, and community- or school-based didactic/experiential programs can substantially

reduce symptom burden among adolescent populations (for review, see Das et al., 2016). And yet, response to such treatment still varies on a case-by-case basis, suggesting that individual differences are a primary driver of treatment efficacy (Cash et al., 2019; Karyotaki et al., 2021). This has been a primary motivation for identifying reliable biomarkers in the field of psychiatry. Determining which individuals are at greatest risk for developing internalizing problems or are most likely to benefit from a specific treatment would not only provide insight into mechanistic drivers of psychopathology, but also support the targeted distribution of effective intervention and treatment strategies. Among potential biomarkers for psychiatric conditions that have been considered, resting-state functional connectivity (RSFC), which reflects coordination in spontaneous neural signals from different brain regions in the absence of any particular stimulus or task, has been identified as a promising candidate (Woodward & Cascio, 2015). Neuroimaging studies of RSFC have identified a variety of correlates for depressive disorders in youth, but unfortunately, developmental psychopathology as a field has suffered from the downward translation of findings in adult research, resulting in an overwhelming *a priori* focus on fronto-limbic connectivity. While it is indeed the case that adolescents with a current diagnosis of clinical depression display aberrant connectivity between fronto-limbic regions, including the amygdala, hippocampus, insula, dorsolateral prefrontal cortex, anterior cingulate cortex, and precuneus, the directionality of these findings vary significantly (Cullen et al., 2014; Jin et al., 2011; J. Lee et al., 2019; Pannekoek et al., 2014).Studies that have taken a network-based approach provide evidence for alterations in the default mode network (DMN) - a group of brain regions that display greater coordinated activity at rest - in association with the anhedonic features of internalizing disorders (Burkhouse et al., 2019; Davey et al., 2012). But again, the directionality of the relationship is unclear. A recent meta-analysis that examined neuroimaging predictors of depression in adolescence highlighted the large degree of variability in study samples, methods, and results (Toenders et al., 2019).

Some of the above-noted issues that impede comparability across studies are already being addressed by leveraging symptom dimensionality in addition to diagnostic classification. Internalizing symptoms have long been recognized as a core component shared across several psychiatric diagnoses, including major depressive disorder, dysthymia, generalized anxiety disorder, and post-traumatic stress disorder, among others (Kotov et al., 2017; Lahey et al., 2004). Although anxiety disorders typically emerge earlier than depression (Axelson & Birmaher, 2001; Kessler et al., 2005), there is a high degree of comorbidity between the two during adolescence (Angold, Costello, & Erkanli, 1999; Costello et al., 2003). Compared to depression, relatively fewer studies have examined RSFC correlates of anxiety disorders in adolescent populations, but many of the same brain regions appear to be implicated (Cyr et al., 2021; Porta-Casteràs et al., 2020), thus highlighting the importance of examining underlying transdiagnostic features. It is also likely that a reliance on diagnostic classifications, as previously mentioned, contributes to a lack of replicability across studies. The difference between sub-clinical symptoms and a full-syndrome disorder is often subjective functional impairment and reported distress (Costello et al., 1999; Fergusson et al., 2005; Gotlib et al., 1995; D. N. Klein et al., 2009). In fact, studies that have focused on sub-clinical internalizing symptoms provide evidence for alterations in RSFC that are evident well before the onset of a clinically diagnosable disorder (Chahal et al., 2021; Kaiser et al., 2019; Padgaonkar et al., 2020). However, the bigger existential challenge that currently plagues neuroimaging research in psychiatry is that often, as a field, we only find what we look for and we only look for what we already know. That is to say, research studies have tended to examine brain networks that have already been shown to be associated with a given behavior, symptom, or disorder. A narrow focus on neural circuitry that guides emotion regulation may inadvertently overlook the dynamic interactions between many other brain regions that give rise to the complex phenomenon of internalizing psychopathology, which includes somatic complaints, social withdrawal, fatigue and

lethargy, among other features. It is well-established that both limbic and prefrontal brain regions undergo pronounced development and reorganization during the teenage years (Casey et al., 2019), and that these systems are integral for emotion processing, which is a large component of internalizing psychopathology. That said, multifaceted behavioral phenotypes likely arise from patterns of functional connectivity that integrate several networks that are distributed across the cortex and subcortical structures. The success of multivariate approaches in the field of genetics, which aggregate many small effects from individual genes to measure risk (e.g., polygenic risk scores)(Visscher et al., 2017), has inspired methods in neuroimaging which have so far yielded greater predictive power and better classification performance (Byington et al., 2023; Mooney et al., 2021; Zhao et al., 2020). However, as is the case with genome-wide association studies, extraordinarily large sample sizes are necessary to robustly estimate brain-behavior relationships (Marek et al., 2022). The present study not only leverages the large population-based sample of the Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®), but also demonstrates the utility of applying an analytic method that takes into account the non-sparse nature of the explanatory signal in the brain to better understand correlates of internalizing symptomatology. This work implements a novel, multivariate prediction method (Byington et al., 2023) similar to the one described by Zhao and colleagues (Zhao et al., 2020) to identify a phenotype of RSFC that relates to emerging internalizing symptoms in early adolescence. In the first stage of the analysis, brain-behavior associations of resting-state functional connectivity with internalizing symptom scores were estimated in a discovery set. Then, the weighted contributions of each functional connection were aggregated using multivariate statistics (partial least squares regression; PLSR) to generate a polyneuro risk score (PNRS) for each participant. The predictive power of the PNRS was then evaluated in the validation set. While we hypothesized that connectivity between fronto-limbic regions would be among some of the most important features relating to internalizing

problems, based on the extant literature to date, we also expected that components of the DMN would be strongly implicated, given this network's role in behavioral features of internalizing symptomatology, including self-referential thought and rumination (Hamilton et al., 2015).

3.3 Methods and Materials

3.3.1 Participants

As described in Section 2.2.1, participants included in the present analysis were part of the ongoing Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®). Details regarding sampling and recruitment for the ABCD Study® (Feldstein Ewing, Chang, et al., 2018; Feldstein Ewing, Bjork, et al., 2018; Garavan et al., 2018; Iacono et al., 2018; Volkow et al., 2018), components of the ABCD Study® protocol (Barch et al., 2018; Casey et al., 2018; C. C. Fan et al., 2021; Lisdahl et al., 2018; Luciana et al., 2018; Palmer et al., 2021; Uban et al., 2018; Zucker et al., 2018), and inclusion/exclusion criteria for the study have all been published previously and are discussed in Section 2.1.

3.3.2 Measures

3.3.2.1 Internalizing Symptoms

Internalizing symptoms were assessed via the Brief Problem Monitor - Youth Form (BPM-Y). A cumulative measure of internalizing symptom burden was generated by summing internalizing subscale scores collected between the first mid-year interview and the 2-year follow-up. Details regarding the calculation of this cumulative score, as well as the BPM-Y itself, can be found in Section 2.2.

3.3.2.2 Sociodemographic Characteristics

Additional sociodemographic characteristics were acquired via caregiver-report. These included youth age at each assessment, youth sex assigned at birth, youth racial identity, youth ethnicity, annual household income, and the highest level of education attained by either caregiver (Barch et al., 2018).

3.3.3 Neuroimaging

As detailed in Section 2.1.3.2 and Section 2.2.3, resting-state fMRI scans from the baseline visit were processed according to a modified version of the HCP pipeline. Parcellated connectivity matrices were generated using BICEPS (https://gui-environments-documentation.readthedocs.io/en/latest/GUI_environments/) for participants who were determined to have at least 8 minutes of data with FD < 0.2mm.

3.3.4 Statistical Analysis

3.3.4.1 Data Partitioning

Participants with a baseline resting-state fMRI scan that met the quality control standards listed above and at least two BPM-Y assessments between the first mid-year interview and the 2-year follow-up were included in this analysis. The final sample was split into a large discovery dataset (N = 6,357) and a smaller validation dataset (N = 164) as described in Section 2.2.4 (Figure 2.1).

3.3.4.2 BWAS-PNRS Framework

In keeping with the method proposed by Zhao (Zhao et al., 2020) and as implemented by Byington and colleagues (Byington et al., 2023), the BWAS-PNRS modeling approach follows a two-step

procedure. First, a large discovery set is used to estimate the individual contribution of each functional connection toward predicting an outcome of interest. The result of this step is a list of β-weights (reflecting the effect size of the relationship, one for each functional connection), sorted by their within-sample predictive power (measured by the amount of variance explained in the outcome, R^2). Once the relative rank of each connection is estimated, the second step utilizes the β-weights to predict the outcome of interest in a separate validation set. The effects of the most significant connections are combined to form a polyneuro risk score (PNRS). To minimize the risk of overfitting, regularization is performed using partial least squares regression (PLSR) when estimating the PNRS for each participant in the validation set. PLSR has a tuning parameter (the number of preserved components) which determines the balance between signal and noise, and hold-out cross-validation is used to optimize this tuning parameter. Further details for each step are described below.

BRAIN-WIDE ASSOCIATIONS

In step one, we have assumed that there is a linear relationship between the outcome variable (here, cumulative BPM-Y internalizing symptom score) and RSFC between each pair of brain regions. We have also assumed that by aggregating the predictions from the most important functional connections it is possible to calculate a predicted outcome for a given participant. In other words, for each functional connection (v), we modeled a participant's cumulative BPM-Y internalizing score ($\widehat{y}$) as follows:

$$\widehat{y} = \sum_{v=1}^{k} x_v \beta_v + covariate_1 \beta_{v,1} + covariate_2 \beta_{v,2} + ... \tag{3.1}$$

Where x_v represents the functional connectivity for a given pair of brain regions (v), β_v is the parameter estimate that describes the least squares relationship between x_v and the outcome variable, y; $covariate_i$ is a confounding variable that may impact the association between x_v and y (in the case of this analysis, the following covariates were included: participant age, sex assigned at birth, race, ethnicity, annual household income, highest level of parental education, and research site), $\beta_{v,i}$ is the parameter estimate necessary to control for this confounder, and $v = 1...k$ are the k most significant connections. For each participant in the discovery set, parameter estimates (β-weights) were calculated for functional connectivity at each pair of brain regions (Figure 3.1). These parameter estimates were then evaluated in terms of their significance (p-value) and variance explained in the outcome (R^2).

POLYNEURO RISK SCORES

The parameter estimates generated from the brain-wide association analysis were aggregated using multivariate statistics to generate a polyneuro risk score (PNRS) for each participant and applied to the validation set. Here, we used partial least squares regression (PLSR) to generate latent components from the large set of features (β-weights for each functional connection) in a manner that maximized the covariance between the outcome variable (cumulative BPM-Y internalizing scores) and the features (Rosipal, 2006). A hold-3-out cross-validation procedure with 10,000 permutations was used to identify the optimal number of latent components to retain from the PLSR. This process (PLSR and cross-validation) was repeated using various subsets of the data to determine which groups of functional connections yielded the best predictive performance in the validation set. Functional connections identified in the discovery set were sorted according to their within-sample p-value, and various thresholds of the top connections (k in Equation 3.1; e.g., the

top connection, the top 0.1% of most significant connections, the top 0.2% of most significant connections, etc.) were used to generate the PNRS.

MODEL EVALUATION

The mean absolute error (MAE) between the observed BPM-Y internalizing symptom score for each participant and their predicted score was used to assess model accuracy. The variance observed in BPM-Y internalizing symptom scores that could be explained by the PNRS (R^2) was used to evaluate explanatory power. Null data were generated by randomly permuting the assignments of BPM-Y internalizing symptom scores 7,000 times. To determine model significance, the distribution of MAE values produced from models trained on un-permuted data were compared to those from permuted data. This comparison was quantified via Cohen's d effect size.

The entirety of this analytic framework was implemented in Matlab version 2021a (containerized source code and corresponding documentation is available via ReadTheDocs at https://polyneuro-risk-score.readthedocs.io/en/latest/), although initial data cleaning and post-hoc data visualizations were generated using R version 4.2.0.

3.4 Results

3.4.1 Participant Characteristics

Sociodemographic characteristics for the final sample of 6,521 participants included in this analysis are presented in Table 3.1. The discovery set (ARMS-1 and ARMS-2 combined) differed significantly from the validation set (ARMS-3) with respect to self-reported racial identity in a few categories. There were significantly more participants who identified as White in the discovery set

as compared to the validation set. There were significantly fewer participants in discovery set who identified with another racial identity (not listed among the options) than there were in the validation set. The two groups were similar with respect to all other key variables, including cumulative BPM-Y internalizing symptom scores.

3.4.2 Brain-Wide Associations

Parameter estimates (β-weights) generated in this discovery set, with cumulative BPM-Y internalizing symptom scores as the outcome variable and controlling for covariates (participant age, sex assigned at birth, racial identity, ethnicity, annual household income, highest level of education attained by either caregiver, and research site) are displayed in the Manhattan plot in Figure 3.2. The most significant connection identified in the brain-wide association involves two regions belonging to the DMN (first row in Figure 3.3). Figure 3.3 illustrates the topographical locations of the brain regions implicated at each threshold, as well as the sum of the absolute value of the β-weights for each region and their Gordon network assignments (Figure 3.3). When examining progressively more of the most significant connections (increasing from the top connection alone to the top 2% of connections) there is greater involvement of the DMN, along with components of the dorsal attention (DAN), retrosplenial temporal (ReT), cingulo-parietal (CiP), and cingulo-opercular (CiO) networks, as well as regions that are not assigned to any network. Importantly, the spatial distribution of the regions contributing to the top 2% of functional connections is spread out across the brain, involving a multitude of functional networks. The relative proportion of functional connections with positive vs. negative β-weights are shown in Figure 3.4. On average, most within-network functional connections of the DMN are inversely associated with internalizing symptom scores (i.e., more of the β-weights are negative), as are connections between the CiP and

the DMN, between the ReT and other unassigned parcels, between the DMN and the ReT, between the DMN and other unassigned parcels, and between the CiP and other unassigned parcels. Conversely, functional connections between the DMN and the DAN, between the CiO and the DMN, between the DMN and the visual network, and between the DAN and other unassigned parcels tend to be positively associated with internalizing symptom scores (i.e., more of the β-weights are positive). However, there remains significant heterogeneity across all network pairs.

3.4.3 Polyneuro Risk Scores

Model performance peaked when the top 2% of functional connections identified in the discovery set were used to generate PNRS in the validation set (Table 3.2). The PNRS using the top 2% of functional connections was able to explain 9.47% of the variance in cumulative BPM-Y internalizing symptom scores as shown in Table 3.2 and Figure 3.5. When compared to the most significant functional connection alone, the top 2% of connections identified in the discovery set explained almost double the amount of variance (9.47% versus 5.07%).

3.5 Discussion

The present study demonstrates the utility of a multivariate analytic approach for identifying RSFC phenotypes associated with internalizing symptomatology in youth. By characterizing brain-behavior associations in a large discovery dataset, and then aggregating these distributed effect estimates with PLSR to create a polyneuro risk score (PNRS), we were able to explain 9.47% of the variance in cumulative internalizing symptom scores across two years of follow-up.

The importance of this analysis lies in its application of a novel framework (BWAS-PNRS), leveraging the globally distributed nature of explanatory brain signal, to predict such a complex behavioral phenotype. Although this method has been shown to capture brain-behavior associations for robust components of cognition (Byington et al., 2023), its performance when used to predict cumulative internalizing symptoms across a period of years is remarkable. These findings are especially striking when compared alongside recent work by Ho and colleagues which utilized a broad set of multimodal features (psychosocial, environmental, neural, etc.) to identify predictors of depressive symptoms, also in the ABCD Study® sample (Ho et al., 2022). When incorporating average RSFC within and between the canonical resting-state networks (as defined by the Gordon parcellation), they found RSFC features to be relatively weaker predictors of future depressive symptoms as compared to environmental and psychosocial variables such as family conflict, parental history of depression, and sleep duration. Not only that, but their overall estimates of explained variance ranged from 8.9% to 10.3% depending on the modelling approach (e.g., elastic net, gradient boosted trees). Here, we achieved an explained variance of 9.47% for internalizing symptoms across two years of follow-up using only RSFC features. Our findings would suggest that applying a multivariate approach to RSFC data may yield greater predictive power than traditional univariate analyses or network averaging methods. However, there are several considerations that remain. First, Ho and colleagues relied on caregiver-reported depressive symptoms (as measured by the Child Behavior Checklist; CBCL) as their outcome measure of interest, whereas we focused here on youth-report. Discordant reporting of mental health symptoms has been demonstrated in the ABCD Study® cohort (Olfson et al., 2023), and this likely contributes to inconsistent findings across studies. There is evidence to suggest that caregivers tend to underreport their children's internalizing symptoms, perhaps because features such as depressed mood, lethargy, and worry are less outwardly observable as compared to externalizing symptoms such as impulsivity, aggression,

and inattention (Herjanic & Reich, 1997). In future analyses, thoughtful integration or comparison of caregiver- and youth-report measures would offer deeper insight into how to best capture brain-behavior associations. Second, it should be noted that when we initially explored other data splits (e.g., using either ARMS-1 or ARMS-2 alone as a discovery set, rather than combined), we found that the performance of the PNRS in the validation set was substantially diminished. We attribute this to the issue of sample size, supporting the recent argument that, due to the small effect sizes of individual brain-behavior associations, many thousands of individuals are required for accurate characterization (Marek et al., 2022). By using the larger combined discovery set, we were able to leverage all of the functional connections across the brain to reveal multiple resting-state networks that contribute to internalizing symptoms in youth.

Although the primary aim of this work has been to maximize predictive power by leveraging the globally distributed nature of brain function, it is helpful to examine the individual networks that contribute most substantially to this phenotype in order to understand what neurobiological mechanisms may be associated with internalizing psychopathology in youth. As we hypothesized, many of the most significant functional connections identified in the discovery set involved components of the DMN. The DMN is known to play a key role in self-referential processing and mind-wandering (Hamilton et al., 2015; McEvoy et al., 2013; and for review see Raichle, 2015), and for this reason, it has often been investigated in relation to the cognitive features of both depression (i.e., rumination) and anxiety (i.e., worry) (Hamilton et al., 2015; Kaiser et al., 2015, 2019; McEvoy et al., 2013; Sheline et al., 2009). Some have proposed that the function of the DMN may underlie the repetitive negative thinking and internally focused attention that is a shared feature of several emotional disorders (McEvoy et al., 2013; McLaughlin & Nolen-Hoeksema, 2011; Nolen-Hoeksema et al., 2008). One study analyzing data from the IMAGEN consortium demonstrated that intrinsic functional connectivity of the DMN was not only predictive of future internalizing symptoms

among a slightly older sample of adolescents (mean age = 14.6 years), but that this relationship differed by sex assigned at birth (Ernst et al., 2019). Coupled with our work here, these findings may point toward the DMN as a potential mechanistic driver of the increasing prevalence of internalizing psychopathology during adolescence. As participants in the ABCD Study® cohort mature into middle and late adolescence, further analyses could potentially disentangle sex-specific RSFC profiles associated with internalizing symptoms. However, it is worth noting that dividing the cohort by sex assigned at birth would result in significantly smaller discovery and validation sets, which may not be as amenable to this analytic approach (Marek et al., 2022). As noted by Byington and colleagues, further work will be necessary to determine whether the specific connections identified here are replicable across other populations (Byington et al., 2023).

Our results nicely parallel other work utilizing ABCD® Study data to examine RSFC correlates of more general psychopathology. Notably, Karcher and colleagues recently demonstrated that both within-network RSFC of the DMN and between-network RSFC of the DMN with the cingulo-opercular (CiO) network and other "unassigned" network ROIs were robustly correlated with a general psychopathology "p"-factor (Karcher et al., 2021). In our analysis, RSFC of these unassigned brain regions with both the DMN and the DAN were strongly related to internalizing symptoms. To interpret these findings, we compared the topographical locations of the unassigned parcels with other well-established functional parcellation schemes (Power et al., 2011; Yeo et al., 2011). We found that, depending on the parcellation, these brain regions were often attributed to either a general task-negative network (essentially the DMN) or to a limbic network that also included regions such as the orbitofrontal cortex and temporal pole. This provides further support for our initial hypothesis that functional connections implicated in emotion processing and internally focused attention would be particularly relevant for predicting internalizing symptoms. It is interesting to note that, although not the focus of this work, performing this same analysis using

the externalizing symptom scale of the BPM-Y did not yield the same pronounced involvement of the DMN (Figure 3.6). Additionally, predictive power reached its maximum at 5.14% explained variance using the top 0.5% of the most significant functional connections for externalizing symptoms (Table 3.4 and Figure 3.7). These findings suggest that the phenotype we identified with the BWAS-PNRS approach is specific to internalizing symptoms, despite known comorbidity between internalizing and externalizing problems (Beauchaine & Cicchetti, 2016; Schettini et al., 2021).

Among some of the other key networks revealed by this brain-wide association study were the cingulo-opercular and cingulo-parietal networks. It has been suggested that the cingulo-opercular network, which consists primarily of the dorsal anterior cingulate, anterior insula, prefrontal cortex, and thalamus, may function as a task control network by maintaining focused effort, coordinating task processes, and detecting errors in behavior (Sadaghiani & D'Esposito, 2015; Sestieri et al., 2014). The cingulo-opercular network and fronto-parietal network are often considered together to exert flexible control over goal-directed behavior (Dosenbach et al., 2006, 2007). In the context of internalizing symptoms, the involvement of these networks could relate to difficulties with cognitive control and increased error sensitivity. Indeed, altered RSFC of the cingulo-opercular network has been noted in both individuals with anxiety (Sylvester et al., 2012) and individuals with depression (Kaiser et al., 2015; Wu et al., 2016). We also identified the DAN as significantly contributing to internalizing symptoms in this sample. The dorsal attention network, which is comprised of the dorsolateral prefrontal cortex and intraparietal sulcus, is involved in orienting attention to external tasks and tuning out other irrelevant stimuli. Adolescents with anhedonia (i.e., lack of interest or pleasure - a key feature of depression) demonstrate a greater tendency toward mind-wandering with a greater focus on unpleasant content, which has been found to be associated with aberrant RSFC between the DAN and salience network (Webb et al., 2021). Lower RSFC of the DAN has also been

identified in individuals with major depressive disorder (Sacchet et al., 2016). Together with alterations to the DMN, the DAN may be associated with a bias toward internally focused, negative rumination at the expense of attending to the external world (Kaiser et al., 2015). Another very interesting network that emerged was the retrosplenial temporal network, which has been described as a type of "memory gateway" (Kaboodvand et al., 2018). The retrosplenial temporal network is thought to mediate processes such as autobiographical memory, self-imagining, and perspective-taking (Kaboodvand et al., 2018; Spreng et al., 2009). Through its interactions with the DMN, it's possible that differential functioning of the retrosplenial temporal network contributes to an attention bias toward negative information and events, which then become the focus of rumination.

Despite the utilization of a large discovery dataset and novel analytic approach, there are several limitations to this work that warrant consideration. First, there were notable differences between the discovery set and the validation set with respect to self-reported racial identity. Although these differences were not present in the original ARMS, they emerge after excluding participants due to missing data or resting-state fMRI scans that did not pass quality control. As other investigators have demonstrated, ABCD Study® participants with low-noise rs-fMRI data (as compared to high-noise) are more likely to come from socioeconomically privileged families, are less racially diverse, score higher on neurocognitive tests, and report better physical and mental health (Cosgrove et al., 2022). This is not a trivial issue, as head motion is known to confound RSFC analyses and is typically used as criteria for determining scan quality. Although we endeavored to strike a balance between data quality and generalizability when it came to selecting inclusion criteria for the present analysis (building upon prior work to optimize sample size through motion censoring parameters (Byington et al., 2023)), it is still the case youth from disadvantaged or minoritized groups were disproportionately excluded due to an insufficient amount of neuroimaging

data that passed our current procedures for quality control, as we demonstrate by comparing the sociodemographic distribution of participants included in this analysis to the rest of the ABCD Study® cohort (Table 3.3). Future efforts are needed to both increase quality data collection and identify quality control procedures that maximize participant inclusion. Another limitation of this work is our use of a cumulative measure of internalizing symptoms, reported across several years of follow-up. The BPM-Y only captures brief snapshots in time and is not a comprehensive measure of mental health. With future waves of data collection it will be possible to better characterize trajectories of internalizing symptoms across time in order to gain a more nuanced perspective on risk for psychopathology, perhaps even distinguishing between different types of symptoms (e.g., affective, cognitive, somatic). Additionally, the insights that we have drawn about the most relevant networks are influenced by the assignments of the Gordon parcellation scheme. Though the analytic strategy (the BWAS-PNRS) itself is not biased toward identifying primarily cortical-cortical circuitry in the most important functional connections, the network assignments that we have used to interpret these findings are. For example, in this parcellation scheme, all of the subcortical structures are grouped together as a single RSN, which is not reflective of known functional loops incorporating different cortical regions and subcortical nuclei (Ji et al., 2019). Finally, at the time of this analysis, diagnostic classifications from the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) were unavailable in the ABCD® Data Release 4.0 due to an error in the programming algorithm (see document 3a. NDA 4.0 Changes and Known Issues of the release notes). In the future, we hope to understand how well the brain-behavior associations identified here can predict emergence into a clinically diagnosable internalizing disorder.

In sum, we have demonstrated that RSFC between brain regions belonging to several different resting-state networks, including the default mode network (DMN), the dorsal attention network (DAN), the cingulo-opercular (CiO) network, the cingulo-parietal (CiP) network, and the

retrosplenial temporal (ReT) network, are associated with internalizing symptoms in youth. By aggregating measures of functional connectivity with multivariate statistics to create a polyneuro risk score (PNRS), we were able to explain a significant amount of variance in self-reported internalizing symptoms across several waves of follow-up. The BWAS-PNRS framework is a powerful tool for robustly characterizing brain-behavior associations, and, given the modifiability of RSFC, may be particularly useful for informing the development of targeted intervention strategies to reduce symptom burden.

3.6 Acknowledgements

3.6.1 Funding Statement

Data used in the preparation of this article were obtained from the Adolescent Brain and Cognitive Development Study^{SM} (ABCD Study®; https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multi-site, longitudinal study designed to recruit more than 10,000 children ages 9-10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, and U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and

implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or view of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from [NIMH Data Archive Digital Object Identifier (10.15154/1523041)]. Research reported in this publication was also supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award number TL1TR002371.

3.6.2 Data Availability Statement

Qualified researchers can request access to ABCD Study® data at https://nda.nih.gov/abcd/request-access. The data used in this report came from the online repository for ABCD Data Release 4.0 and can be found at [NIMH Data Archive Digital Object Identifier (10.15154/1523041)].

Chapter 4

Identifying psychosocial predictors of internalizing symptoms in youth

Findings from the ABCD Study®

4.1 Abstract

There have been a myriad of studies to examine individual psychosocial, environmental, and behavioral predictors of internalizing psychopathology in youth. However, with the advent of large consortium projects such as the Adolescent Brain and Cognitive Development Study^{SM} (ABCD Study®) and sophisticated modeling strategies designed to handle high-dimensional data, the present analysis aims to take a multi-dimensional approach that incorporates a broad array of

potential risk factors *simultaneously*. Youth from the ABCD Study®; (ages 9-10 years at baseline) with a resting-state fMRI scan and mental health data were eligible for inclusion. Internalizing subscale scores from the Brief Problem Monitor - Youth Form were combined across two years of follow-up to generate a cumulative measure of internalizing symptom burden. The total sample (n=6,521) was split into a large discovery set and a smaller validation set. Individual items from assessments of culture and environment, physical health, mental health, neurocognition, and substance use were considered as potential predictive features. Using a nested cross-fold validation scheme, a series of predictive models (linear regression, LASSO regression, ridge regression, elastic net regression, random forest, and extreme gradient boosted trees) were evaluated in the discovery dataset. The best performing model, as identified by variance explained (R^2), root mean squared error (RMSE) and mean absolute error (MAE), was subsequently applied to the holdout validation dataset. The final model (an elastic net) significantly predicted internalizing symptom scores with an R^2 of 27.22%. Among the most important features identified in this final model were features related to fearfulness and worry, self-esteem, and family relationships. These findings not only demonstrate the value of multivariate models for prediction of mental health symptoms, but they also highlight key targets for intervention and prevention strategies (e.g., improving caregiver-child communication and bolstering self-esteem).

4.2 Introduction

In light of the fact that depression and anxiety are among the most prevalent mental health problems during adolescence (Merikangas et al., 2010), a substantial amount of developmental research in recent years has been aimed at identifying psychosocial predictors of these conditions. Even at sub-clinical levels, symptoms of depression and anxiety have been shown to be associated

with a host of adverse health outcomes in adolescence and into adulthood, including difficulties with school and interpersonal relationships, a greater likelihood of substance use, and heightened suicidality (Fergusson et al., 2005; Lewinsohn et al., 1998; Zisook et al., 2007). Despite a preponderance of work showing strong correlations between individual psychosocial factors, such as maternal history of depression (S. H. Goodman & Gotlib, 1999; Weissman & Jensen, 2002), family conflict (Hammen et al., 2004), early pubertal timing (Deardorff et al., 2013), and stressful life events (Jenness et al., 2019), and internalizing psychopathology, relatively fewer studies have attempted to synthesize this work by examining multiple of these constructs together. This is, in large part, due to the need for large sample sizes to accommodate complex statistical models with many predictors.

Recent work by Ho and colleagues leveraged the abundance of data collected as part of the Adolescent Brain and Cognitive Development^{SM} Study (ABCD Study®) to examine a broad set of predictive features from across demographic, environmental, and neurobiological domains to predict internalizing symptom scores on the Child Behavior Checklist (CBCL) at baseline and at 1-year follow-up (Ho et al., 2022). They found that parental history of depression, family conflict, and sleep duration were among the most important predictors for both concurrent and future depressive symptoms in youth. Adolescents with a family history of depression, particularly on the maternal side, may be exposed to a combination of genetic (e.g., genetic variants that impact monoamine neurotransmitter systems such as serotonin and dopamine, altered development and functioning of neurocircuitry associated with mood regulation (Howard et al., 2018; Merwe et al., 2019; Wray et al., 2018; Zeng et al., 2023)) and environmental factors (e.g., parenting style and behavior, parental modeling of coping strategies (Griffith et al., 2023; Hammen et al., 2004; A. E. Pine & Garber, 2023)) that increase their susceptibility to internalizing psychopathology. Family conflict can disrupt the crucial support system that adolescents rely on during their formative years, leading to

significant psychological distress (Rice et al., 2006). Insufficient sleep has also been consistently linked to elevated risk for depression and anxiety during adolescence, as sleep deprivation is known to affect cognitive functioning, exacerbate stress responses, and contribute to difficulties with emotion regulation (Dewald-Kaufmann et al., 2014). Ho and colleagues also demonstrated that combining multi-level predictors within a machine learning framework explained between 9% and 16% of the variance in symptom scores. While these findings are not particularly surprising - parental history of depression, family conflict, and sleep disturbances have all independently been shown to relate to internalizing psychopathology during adolescence - the idea that a variety of predictive variables can be utilized together to make more accurate predictions about future mental health challenges is indicative of where the field of developmental psychology is moving. The question now is how we can best utilize this information to improve prediction.

Much of the extant literature on psychosocial and environmental predictors of depression- and anxiety-related symptoms in adolescence has relied on composite or summary scores from various assessments, which may obscure some of the more granular, nuanced risk features that are particularly important. Large consortium datasets such as the ABCD Study® cohort now provide researchers with the statistical power to interrogate item-level predictors of mental health conditions, which can then inform the implementation of focused intervention strategies. Not to mention, many of the same core constructs are assessed across different assessments, not unlike transdiagnostic symptoms that are present across multiple categories of disorders (for further discussion of symptom dimensionality vs. diagnostic classification systems, see Section 1.3.1). By identifying the individual items that are most relevant for predicting internalizing symptom, it may be possible to further streamline risk screenings. Knowing that family environment is predictive of internalizing psychopathology is useful, but perhaps not so much as understanding the *specific* aspects of that environment that matter (e.g., openness of communication with the caregiver

vs. perceived acceptance/warmth), at least from a clinical perspective. Finally, a majority of studies based on the ABCD Study® data so far have utilized caregiver-reported measures of psychopathology, both dimensional (e.g., the CBCL) and categorical (e.g., the Kiddie Schedule for Affective Disorders and Schizophrenia; K-SADS). Not only is there is evidence to suggest that caregiver- and youth-report regarding mental health symptoms can be vastly disparate in early adolescence, but youth may be even more reliable reporters of their own internal state than their parents (Grills & Ollendick, 2002; Rothen et al., 2009). By examining psychosocial predictors of youth self-reported internalizing symptoms, this study will fill an important gap.

The ABCD Study® provides researchers with ample opportunities to interrogate these fine-grained contextual variables as they relate to emerging depression and anxiety. To that end, the present study employs a competitive modeling approach, with several different penalized regression (LASSO regression, ridge regression, and elastic net) and ensemble learning techniques (random forest and extreme gradient boosted trees), to identify key behavioral, psychosocial, and environmental predictors of internalizing symptomatology in youth. We hypothesized that some of the aforementioned risk factors for depression and anxiety (e.g., parental psychopathology, family conflict, sleep quality, but also sex-assigned at birth and stressful life events - see Section 1.2.3.2) would be among the most important predictors, but that the incorporation of responses to item-level questions would reveal more subtle nuances about how these broad constructs facilitate a vulnerability to internalizing symptoms.

4.3 Methods and Materials

4.3.1 Participants

As described in Section 2.2.1, participants included in the present analysis were part of the ongoing Adolescent Brain and Cognitive Development[SM] Study (ABCD Study®). Details regarding sampling and recruitment for the ABCD Study® (Feldstein Ewing, Chang, et al., 2018; Feldstein Ewing, Bjork, et al., 2018; Garavan et al., 2018; Iacono et al., 2018; Volkow et al., 2018), components of the ABCD Study® protocol (Barch et al., 2018; Casey et al., 2018; C. C. Fan et al., 2021; Lisdahl et al., 2018; Luciana et al., 2018; Palmer et al., 2021; Uban et al., 2018; Zucker et al., 2018), and inclusion/exclusion criteria for the study have all been published previously and are discussed in Section 2.1.

4.3.2 Measures

4.3.2.1 Internalizing Symptoms

Internalizing symptoms were assessed via the Brief Problem Monitor - Youth Form (BPM-Y). A cumulative measure of internalizing symptom burden was generated by summing internalizing subscale scores collected between the first mid-year interview and the 2-year follow-up. Details regarding the calculation of this cumulative score, as well as the BPM-Y itself, can be found in Section 2.2.

4.3.2.2 Psychosocial Predictors (Features)

Detailed descriptions of the assessments and questionnaires administered at baseline have been published previously (Barch et al., 2018; Casey et al., 2018; C. C. Fan et al., 2021; Lisdahl et al., 2018; Luciana et al., 2018; Palmer et al., 2021; Uban et al., 2018; Zucker et al., 2018) and are

summarized in Section 2.1.3.1. For this analysis, individual items from across all of the domains (i.e., culture and environment, physical health, mental health, neurocognition, substance use, and linked external data) were considered as potential predictors. No summary scores were used, with the exception of the sex-specific items from the Pubertal Development Scale. To avoid these items being excluded due to excessive missingness (see Section 4.3.3.2), summary scores for female and male adolescents were calculated separately, and then coalesced into a single variable (Cheng et al., 2021).

4.3.3 Statistical Analysis

4.3.3.1 Data Partitioning

This analysis utilized a nested cross-validation (CV) scheme similar to that of Wang and colleagues (Figure 4.1)(Wang et al., 2023). The discovery dataset was first split into 10 outer folds. Family was used as a grouping variable to ensure that siblings/twins/triplets were kept in the same fold, thus maximizing independence and avoiding false inflation of test performance. For each of the 10 outer train-test splits, Boruta feature selection was applied to narrow down the initial list of predictor variables (Kursa & Rudnicki, 2010). Boruta is a feature selection algorithm that works by permuting the labels for each existing predictor variable to create a corresponding "shadow" variable. Random forests are then trained using all predictors (original and shadow) and permutation importance scores are computed for each predictor. The algorithm then identifies the best performing shadow predictor, and retains all of the original predictors with permutation importance scores that are significantly greater than the best shadow predictor. Subsequently, within each of the outer 10 folds, the data was split into 5 inner folds. Again, family was used as a grouping variable to keep siblings together. For each of the 5 inner train-test splits, hyperparameter

optimization was performed using a grid search approach. This process resulted in 5 estimates of performance for each set of hyperparameters evaluated within each of the 10 outer folds. The optimal set of hyperparameters (i.e., that which minimized prediction error; lowest root mean squared error - RMSE) was identified, and those values were used to re-train and test the model at the outer 10-fold level. This approach yielded 10 estimates of performance for each model based on their best predictor variable set and hyperparameter set, which were then compared to determine the best final model (see Section 4.3.3.4)

4.3.3.2 Feature Engineering

Predictor variables were selected based upon their distribution and missingness within the discovery dataset. Predictor variables with more than 15% missing data were removed, and those with 15% missing data or less were imputed using K-nearest neighbors (k = 7) (for further details, see Section 2.2.5). A more in-depth discussion of the predictor variables that were removed due to missingness, and the implications for this analysis, can be found in Section 4.5. Predictor variables with zero or near-zero variance were also removed. Categorical predictor variables were one-hot encoded, and numeric predictor variables were centered and scaled (mean = 0, standard deviation = 1).

4.3.3.3 Model Training and Hyperparameter Tuning

Six different modeling strategies were compared in this analysis. These models were selected to strike a balance between predictive power and interpretability; although some advanced machine learning techniques (e.g., deep neural networks) are being increasingly harnessed to predict a variety of mental health outcomes, such approaches are often referred to as “black boxes” because

there is not a clear explanation for how the predictor variables interact to produce a particular output (Su et al., 2020). Here, we consider standard linear regression as a baseline, and compare increasingly 'complex' penalized regression methods (i.e., LASSO, ridge, and elastic net regression) as well as several ensemble-based learning methods (i.e., random forest and extreme gradient boosting). A description of the associated hyperparameters for each model and the values explored can be found in Table 4.1.

LINEAR REGRESSION

Linear regression is a traditional parametric modeling approach that is often used to assess the relationship between a continuous outcome variable (here, internalizing symptom scores) and predictor variables that may be either continuous or categorical. The primary advantages of this approach lie in its interpretability, as the coefficients derived from linear regression can be used to explain the relationship between each predictor variable and the outcome of interest. It is also a very fast model to train because it does not have any additional hyperparameters that require tuning. However, the disadvantages of linear regression are that it assumes a linear relationship between the predictor variables and the outcome of interest, which may or may not be the case. Linear regression is also sensitive to outliers and can underfit with small, high-dimensional datasets.

LASSO REGRESSION

LASSO stands for Least Absolute Shrinkage and Selection Operator. This penalized regression approach uses L1 regularization to reduce overfitting and model complexity (Friedman et al., 2010; Tibshirani, 1996). Coefficients of variables that are less important can be reduced to zero because

the penalty term for LASSO (lambda; λ) applies to the absolute value of the magnitude of the coefficients, meaning that this approach performs its own form of internal feature selection by removing uninformative predictors. The advantages of LASSO are that it is less prone to overfitting than linear regression and can handle high-dimensional datasets even when the number of predictor variables exceeds the number of observations. However, this approach may be less interpretable than standard linear regression because it can retain highly correlated predictor variables in the model.

RIDGE REGRESSION

Ridge regression is similar to LASSO; however, L2 regularization is used so the penalty term (lambda; λ) applies to the *squared* absolute value of the magnitude of the coefficients (Cessie & Houwelingen, 1992; Feig, 1978; Friedman et al., 2010). This means that the coefficients of less important variables can be substantially reduced, but not rendered inert (i.e., taken all the way down to zero). Some advantages of ridge regression are that, like LASSO, it is less prone to overfitting than linear regression and can handle multicollinearity between predictor variables. One important disadvantage, though, is that all predictors are kept in the final model - there is no form of internal feature selection.

ELASTIC NET REGRESSION

Elastic net regression can be thought of as a combination of LASSO and ridge regression. Elastic net employs a penalty term to shrink the coefficients of less important predictor variables, but this time the penalty applies to a combination of the L1-norm and L2-norm of the coefficients, weighted by a parameter (alpha; α) that determines the relative contribution of each type of regularization

(Zou & Hastie, 2005). Elastic net regression handles multicollinearity better than LASSO, but can also reduce model complexity better than ridge. However, this approach still may not capture non-linear or more complex interactions between predictor variables.

RANDOM FOREST

Random forest is a type of supervised ensemble learning algorithm that uses bootstrap aggregation (bagging) to combine predictions from multiple individual decision trees (Breiman, 2001). The fundamental idea behind the random forest is that a large number of uncorrelated models (individual decision trees) operating as a committee will outperform any of those individual models. Random forest offers good generalization performance, and reduces overfitting compared to individual decision trees; however, the training complexity is higher than any of the penalized regression methods discussed thus far, and it is not as easily interpretable.

EXTREME GRADIENT BOOSTING

Extreme gradient boosting takes random forests a step further. Instead of building decision trees in parallel and aggregating the results, the algorithm builds a series of shallow decision trees one at a time, and with each iteration the error residuals of the previous model are used to inform the next. This process is called boosting, and it allows each decision tree to make better predictions than the last. The primary advantages of the extreme gradient boosting method are its ability to capture nonlinear relationships between predictor variables and to handle multicollinearity. However, the hyperparameter tuning process for this approach can be complex and computationally expensive, and the algorithm can be sensitive to outliers.

4.3.3.4 Model Comparisons and Final Model Selection

Given that the performance statistics derived from the outer 10-fold CV are not entirely independent (i.e., some of the same participants will be included in the training set across multiple folds), paired, one-sided Wilcoxon Rank Sum tests were used to determine whether any of the more complex models (i.e., LASSO, ridge, elastic net, random forest, or extreme gradient boosting) offered significant improvement over standard linear regression in terms of variance explained (R^2), RMSE, or MAE. The best model was determined on the basis of performance improvement above and beyond linear regression and interpretability, with the simplest model being preferred. A series of permutation tests were also performed to understand whether each model performed better than chance when it came to predicting internalizing symptom scores. For each of the 10 outer folds, the labels (i.e., internalizing symptom scores) were shuffled and the train-test process was repeated. A total of 100 iterations of shuffling, retraining, and re-testing were performed at each of the 10 outer folds. The performance of the models on the original (non-permuted) data was then compared to their performance on the permuted data according to the variance explained (R^2), root mean squared error (RMSE) and mean absolute error (MAE).

4.3.3.5 Performance Evaluation

The best model was retrained on the entire discovery dataset (N = 6,357) and its performance (R^2, RMSE, MAE) was evaluated on the validation dataset (N = 164), which had been held out separately for the entirety of the training and tuning process (see Figure 4.1). Feature importance was evaluated in both a model-specific (via individual feature coefficients) and a model-agnostic framework (via SHapley Additive exPlanations). In a penalized regression model such as an elastic net, the regularized coefficients represent the linear relationship between each feature and the outcome variable of interest, adjusted by the penalty terms. Larger absolute values of these

coefficients imply a stronger effect of that feature on the prediction of the outcome variable. The SHapley Additive exPlanations (SHAP) method is a relatively new, but powerful technique based upon principles from cooperative game theory that aims to lend additional interpretability to more complex machine learning models (Lundberg & Lee, 2017). In this framework, the 'game' is to reproduce the outcome of the model for each observation, and each predictive feature included in the model is a 'player'. By averaging the marginal contribution a given feature ('player') across all possible combinations of other features included in the model (all other possible 'teammates'), the SHAP method can be used to quantify how much that feature contributes to a single prediction ('game'). Importantly, this means that Shapley values are focused on local interpretability. Average absolute Shapley values can be used to evaluate feature importance on a global level (i.e., across all observations in the dataset). All analyses were performed using R version 4.2.0.

4.4 Results

4.4.1 Participant Characteristics

Sociodemographic characteristics for the final sample of 6,521 participants included in this analysis are presented in Table 3.1. As described in Chapter 3, there are significant differences between participants in the discovery dataset (N = 6,357) and participants in the validation dataset (N = 164) with respect to self-reported racial identity.

4.4.2 Model Comparisons

Visual inspection of the distribution of performance measures obtained from the 10 outer folds of nested CV did not yield a clear best-performing model (Figure 4.2). However, the random forest

did appear to perform marginally worse than any of the other models across all three performance metrics considered (R^2, RMSE, MAE). All models performed significantly better on the original, non-permuted data than on permuted data (Figure 4.3).

Results of the paired, one-sided Wilcoxon Rank Sum tests are presented in Table 4.2. All three penalized regression methods performed significantly better than linear regression with respect to explained variance (R^2) and RMSE. Because there were no statistically significant differences in performance between the penalized regression methods, the elastic net model was chosen as the final best model for two reasons: 1) the elastic net model performed the best *on average* across the 10 outer folds of cross validation (i.e., highest mean R^2 and lowest mean RMSE/MAE; Figure 4.2), and 2) the elastic net model was the 'simplest' model with respect to how many features were retained in the final model. Even after Boruta feature selection, the elastic net model reduced the coefficients of several predictor variables to zero, thus creating a model with fewer predictors overall. When applied to the validation set, the elastic net model explained approximately 27.22% of the variance in cumulative internalizing symptom scores, with an RMSE of 0.87 and an MAE of 0.72.

4.4.3 Final Model Fit

The elastic net model, after being retrained on the entire discovery dataset (N = 6,357) and applied to the validation dataset (N = 164) explained approximately 27.22% of the variance in cumulative internalizing symptom scores. The model had an RMSE of 0.87 and an MAE of 0.72. This model included only 80 predictor variables out of the original set that were considered prior to feature selection.

4.4.4 Feature Importance

Some of the most important predictor variables (as determined by their regularized coefficients from the final model), tapped into aspects of fearfulness/worry (e.g., “I am very fearful compared to my friends”, “I usually get very tense when I think something unpleasant is going to happen”, “I worry about making mistakes”, “I feel pretty upset when I think someone is angry with me”), family relationships and the family environment (e.g., “Caregiver is easy to talk to”, “We fight a lot in our family”), self-worth and self-esteem (e.g., “I feel I am just as smart as other kids my age”, “Self-conscious or easily embarrassed”), as well as physical activity (e.g., number of days physically active for at least 60 minutes in the past week, hours spent on a computer, cell phone, tablet, or other electronic device on a typical weekend) Figure 4.4. There are also community-level factors that appear to be particularly relevant, including measures from the Social Vulnerability Index (SVI) that reflect per capita income at the primary residential address and annual average of particulate air pollution at the primary residential address.

Panel A of Figure 4.5 displays the mean absolute Shapley values for the top 25 most important predictive features (out of a total of 80 included in the final model). The relative magnitudes of these values indicate, on average, how much each predictive feature contributed to the predicted internalizing symptom scores. Although there are subtle differences, there is a large degree of overlap with the items and constructs that were identified as important by their regularized coefficients. The beeswarm plot in panel B of Figure 4.5 illustrates the distribution of individual Shapley values for each of the top features. Comparing the color distribution of the points across the x-axis provides insight into the directionality of the relationship between the raw values for each predictive feature and their Shapley values. For example, lower values for the item relating to weekend screen time (‘Hours spent on a computer, cell phone, tablet, or other electronic device on a typical weekend day’) have negative Shapley values (the blue points extend to the left of zero on

the y-axis), and higher values have positive Shapley values. This indicates that more weekend screen time is associated with a higher predicted internalizing symptom score. For ordinal and categorical variables, where the data has been dummy coded such that each predictive feature represents a single response option to a given item, a higher feature value (red) would mean that the participant endorsed that response option. Conversely, a lower feature value (blue) would mean that they did not endorse that response option. The distribution of the points along the x-axis is also informative. Considering the screen time example, there is a dense cluster of low screen time instances (blue points) with small but negative Shapley values. Instances of higher screen time (red points) extend further to the right, suggesting that high screen time has a stronger relationship with high internalizing symptom scores, while low screen time has a less strong relationship with low internalizing symptom scores.

4.5 Discussion

This is the first study, to our knowledge, to investigate *item-level* predictors of youth self-reported internalizing symptoms in the ABCD Study® cohort using a multivariate analytic strategy. Importantly, this work expands upon prior analyses that have interrogated multi-level predictors of depressive symptoms in the ABCD Study® sample using primarily summary scores (Ho et al., 2022; Vijayakumar et al., 2023; Zink et al., 2023) in order to improve predictive power and narrow down specific risk factors. Some of the strongest predictors of cumulative internalizing symptom burden across nearly two years of follow-up were features related to fearfulness and worry, self-esteem, and family relationships - especially caregiver-child communication. Penalized regression methods (LASSO, ridge, elastic net) offered the best performance during training, but it is likely that the initial round of Boruta feature selection lessened the benefit of some of the more complex machine

learning methods, such as random forest and extreme gradient boosted trees. The elastic net model was able to explain approximately 27.22% of the variance in internalizing symptom scores using only 80 predictor variables, many of which reflect different response options to the same question.

As with the findings presented in Chapter 3, the intent of applying a multivariate modeling framework was to bolster predictive power by considering many potentially important variables simultaneously. That said, it may be useful to examine the overarching themes that emerge from the most significant predictor variables to shed light on key targets for intervention. Numerous prior studies have demonstrated that excessive worry and low self-esteem are robustly associated with internalizing symptoms, a finding that is mirrored here (Magro et al., 2018; Masselink et al., 2018; Mullan et al., 2023; Ngo et al., 2020; Spitz et al., 2022). The development of self-esteem during adolescence is largely shaped by the availability of support from family and peers, with fluctuations in the level of support being directly related to intra-individual changes in self-esteem (Krauss et al., 2020; Magro et al., 2018). Parental warmth and sensitivity, as well as open and effective communication between the caregiver and their child, are particularly important. Several items relating to the caregiver being "easy to talk to" were highlighted in this analysis, suggesting that creating an environment where children feel safe expressing their thoughts and emotions may be especially protective against internalizing psychopathology. Family environments that are characterized by conflict and aggression and caregiver-child relationships that are generally unsupportive, cold, or neglectful have been shown to have a considerable negative impact on adolescent mental health. It is often the case that witnessing conflict between parents, or being exposed to hostile interactions between family members (e.g., "We fight a lot in our family"), increases feelings of insecurity and fear in youth. This spillover effect has been linked to elevated levels of anxiety and depression symptoms in adolescents (Lin et al., 2023), and has been shown to

impact the formation of emotion regulation capabilities (Fosco & Grych, 2012; Repetti et al., 2002).

In this analysis, we also identified physical activity and weekend screen time as being important predictors of internalizing symptoms. Interestingly, both in childhood and in later adolescence, higher levels of physical activity and sports participation have been found to be associated with lower anxiety- and depression- related symptoms, lower perceived stress, and higher distress tolerance, with some evidence to suggest that these relationships are mediated by higher self-esteem (Rodriguez-Ayllon et al., 2023; Wright et al., 2023). Extensive screen time, particularly at the expense of other activities, has been shown to correlate with diminished psychological well-being (Twenge & Campbell, 2018; Zink et al., 2023). There is also evidence to suggest that time spent on social media is associated with heightened feelings of social comparison, cyberbullying, and poor sleep quality, all of which contribute to the development of internalizing symptoms (Primack et al., 2017; Twenge & Campbell, 2018). The findings presented here, coupled with prior work, would support targeting adolescent self-esteem as a crucial intermediary between several predisposing factors and the manifestation of internalizing symptoms.

Interestingly, although female sex-assigned-at-birth has been one of the most robust risk factors identified for adolescent-emergent internalizing psychopathology, it did not appear to be important in this analysis. For decades, researchers have noted a considerable disparity in the prevalence of depression between female and male adolescents that begins to emerge around the time of puberty (Hankin et al., 1998; Hyde et al., 2008; Soares & Zitek, 2008). However, sex differences in depression- and anxiety-related symptoms are not evident at baseline in the ABCD Study® cohort (Serio et al., 2022). Even by the 2-year follow-up, participants are only between 11 and 12 years of age, whereas the most apparent sex differences in the prevalence of internalizing symptoms are

typically seen later in development (i.e., between 15 and 18 years of age). It's possible that interaction effects between sex-assigned-at-birth and other key predictors have obscured sex-specific phenotypes of risk in this analytic approach. There is evidence to support gendered pathways to internalizing symptoms from early childhood and into adolescence (Gutman & Codiroli McMaster, 2020), so future analyses may endeavor to examine these predictors *separately* by sex with follow-up time points into mid- and late adolescence.

Though the exact ranking of these most important features in this analysis should not be expected to replicate perfectly in an independent sample, the constructs that emerge across several different items are likely strong contributors to internalizing psychopathology. For example, feelings of fear and worry (e.g., "I am very fearful compared to my friends", "I usually get very tense when I think something unpleasant is going to happen") manifest across several different assessments (e.g., the CBCL and the BIS-BAS) as well as different reporters (e.g., caregiver- vs. youth-report). Many of the same features are found to be 'important' according to both the magnitude of their regularized coefficient as well as their Shapley value, further supporting the assertion that these broad domains related to self-esteem and self confidence, worry, and family relationships, are important for predicting internalizing symptoms across the next several years.

There are several limitations to this study that warrant further consideration. First, as alluded to in Section 2.2.5 and Section 4.3.3.2, a number of potentially important predictor variables were excluded from this analysis due to missingness. Upon further investigation, it was determined that for a majority of the instruments with excessive (>15%) missingness, this was due to conditional or branching logic rather than non-response or skipping. Unfortunately, this does mean that potentially important information, such as whether or not youth experience bullying, discrimination, or other problems due to their gender identity, cannot be incorporated into this modeling strategy.

Other variables that were excluded due to intentional missingness from conditional/branching logic included items from the Mexican-American Cultural Values Scale, the PhenX Acculturation Survey, questions about the age at which youth received certain services (e.g. mental health treatment), questions about the severity and age at first TBI, and questions from the Parental Rules on Substance Use Questionnaire (missing if the caregiver had not yet made rules about substance use at the time of the baseline assessment). Constrained analyses that focus only on a subset of the ABCD Study® cohort may be better suited to evaluate the importance of these key constructs for the development of internalizing psychopathology in youth. Along a similar vein, and as with the results presented in Chapter 3, the participants included in this analysis were only selected if their baseline resting-state fMRI scan met quality control criteria. The fact that ABCD Study® participants with low-noise rs-fMRI data (as compared to high-noise) are more likely to come from socioeconomically privileged families, are less racially diverse, score higher on neurocognitive tests, and report better physical and mental health, means that the findings presented here can not necessarily be expected to generalize to youth from disadvantaged or minoritized groups who were disproportionately excluded due to head motion (Cosgrove et al., 2022).

In sum, this study demonstrates that some of the most important predictors of youth self-reported internalizing symptoms are related to being fearful and worrisome, physical activity, feeling safe and smart at school, having caregivers that are easy to talk to, screen time, and family conflict. The elastic net model was able to explain approximately 27.22% of the variance in internalizing symptom scores, suggesting that the combination of item-level predictors within a machine learning framework may be more valuable for prediction that approaches that have examined only one or several summary scores at a time. In considering opportunities for translation to clinical practice, future work may be able to narrow down this list of features, possibly through item-response theory,

to develop a readily accessible screening instrument that can simultaneously provide guidance for intervention strategies.

4.6 Acknowledgements

4.6.1 Funding Statement

Data used in the preparation of this article were obtained from the Adolescent Brain and Cognitive Development Study^{SM} (ABCD Study®; https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multi-site, longitudinal study designed to recruit more than 10,000 children ages 9-10 and follow them over 10 years into early adulthood. The ABCD Study® is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041117, U01DA041028, U01DA041134, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051038, U01DA041148, U01DA041093, U01DA041089, U24DA041123, and U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of study investigators can be found at https://abcdstudy.org/consortium_members/. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or view of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from [NIMH Data Archive Digital Object Identifier (10.15154/1523041)]. Research reported in this publication was also supported by

the National Center for Advancing Translational Sciences of the National Institutes of Health under award number TL1TR002371.

4.6.2 Data Availability Statement

Qualified researchers can request access to ABCD Study® data at https://nda.nih.gov/abcd/request-access. The data used in this report came from the online repository for ABCD Data Release 4.0 and can be found at [NIMH Data Archive Digital Object Identifier (10.15154/1523041)].

Chapter 5

Discussion

5.1 Summary of Findings

The goal of this dissertation work was to characterize both the neural and psychosocial correlates of internalizing psychopathology in a large and demographically diverse sample of early adolescents. By leveraging symptom dimensionality and a novel multivariate prediction method inspired by genomics research, this project lends new insights that will inform future assessment and intervention strategies, as well as pave the way for more granular longitudinal analyses of symptom change over time.

Chapter 3 utilized the BWAS-PNRS framework to identify a phenotype of RSFC that was associated with internalizing symptom burden. Both within- and between-network connectivity of the default mode network (DMN) was particularly relevant for predicting internalizing symptoms, and the PNRS was able to explain approximately 9.47% of the variance in internalizing symptom scores. Not only did this approach yield a remarkable improvement in phenotypic variance

explained over the small contributions of the individual functional connections, but it also revealed key interactions among several different RSNs that are relevant for internalizing psychopathology. Specifically, components of the dorsal attention (DAN), retrosplenial temporal (ReT), cingulo-parietal (CiP), and cingulo-opercular (CiO) networks emerged as being strongly correlated with internalizing symptom burden using the BWAS framework. Importantly, there was substantial heterogeneity in the directionality of these correlations, both within and between networks, which may partially explain discrepant results reported in the literature to date.

Chapter 4 employed a competitive modeling approach to identify psychosocial predictors of internalizing symptoms in the same adolescent sample. Among the most important features in the final elastic net model were items relating to fear and worry, self-confidence and self-esteem, and family relationships. While these findings generally echo prior literature, this study is unique in its synthesis of a wide array of item-level predictor variables from across multiple assessment domains (e.g., culture and environment, mental health, physical health, neurocognition, substance use, etc.). Large consortium projects such as the ABCD Study®, coupled with advanced modeling techniques designed to handle high-dimensional data, are making it possible to integrate many potentially relevant features in a single analytic framework. Using only psychosocial, environmental, and behavioral variables *without* neuroimaging data to predict cumulative internalizing symptom burden yielded an explained variance of approximately 27.22%.

5.2 Comparing 'Brain' vs. 'Behavior' Models

In order to synthesize the findings from these two analyses, and begin to explore the added utility of neuroimaging for prediction of mental health conditions above and beyond what can be gleaned

from questionnaires alone, this dissertation project included a supplementary exploratory analysis. Briefly, the performance of the 'brain-only' model from Chapter 3 (the polyneuro risk scores) was compared to the 'behavior-only' model from Chapter 4 (the psychosocial and environmental variables) as well as a 'brain-plus-behavior' model that included *all* of the aforementioned predictors. The results of this comparison are presented in Table 4.3. The combined 'brain-plus-behavior' model explained approximately 30.59% of the total variance in internalizing symptom scores, meaning that most, but not all, of the explanatory power of the PNRS overlaps with information that is already captured in the psychosocial and environmental variables. There is some unique contribution from the resting-state fMRI, but it is only about 3% above and beyond what can be assessed with simple questionnaires. These findings seem to suggest that, at least insofar as the field is currently able to measure and analyze resting-state brain function, using neuroimaging for the prediction of internalizing psychopathology may not be worth investment. Neuroimaging is extremely time-consuming and expensive, and as such it may be better equipped to interrogate the neurobiological mechanisms associated with psychopathology or to determine which treatment strategies are likely to be most beneficial for which individuals (i.e., 'precision' psychiatry) (Etkin, 2019; Grzenda & Widge, 2024). For these reasons, it is imperative that the scientific community think critically about which methodological approaches are best suited to answering prediction-based questions in the mental health space.

5.3 Conceptualizing Neural Predictors of Internalizing Psychopathology

The findings presented in Chapter 3 are consistent with the hypothesis that aberrant functioning of the DMN may be a transdiagnostic risk marker for multiple types of psychopathology (Albertina et al., 2022; Karcher et al., 2021). Given the role of the DMN in self-referential thought and rumination (Hamilton et al., 2015; McLaughlin & Nolen-Hoeksema, 2011), it has been posited that this particular RSN plays a role in the cognitive features of depression and anxiety, including perseverative negative thought patterns and excessive worry. Using data from the ABCD Study®, Karcher and colleagues found associations between a general psychopathology 'p' factor and *lower* functional connectivity within the DMN (Karcher et al., 2021). In looking at the β-weights estimated from the discovery set in Chapter 3, a majority of the β-weights for within-network DMN connections were indeed negative (Figure 3.4). However, this is not the case for *all* within-network DMN connections. It is important to recognize that, at the ages of 9 and 10 when the neuroimaging sessions were conducted, the different components of the DMN would have been undergoing substantial normative developmental changes (see Section 1.2.2) (F. Fan et al., 2021).

In general, though, these findings likely indicate that an overall lower within-network functional connectivity of the DMN is predictive of greater internalizing symptoms. This is in line with most prior research (Albertina et al., 2022; Karcher et al., 2021; Son et al., 2023), although it does contradict several studies (Chahal et al., 2021; Y. Lee et al., 2023). In addition to the aforementioned normative neurodevelopmental changes, the reason for this discrepancy may have to do with whether internalizing symptoms were already present at the time of the scan, the severity of those symptoms, and/or sex differences in internalizing symptoms or DMN maturation (Y. Lee et al., 2023). It should be noted that sex differences in the prevalence of internalizing symptoms are

not apparent in the ABCD Study® cohort at baseline (Serio et al., 2022). At the 2-year visit, youth are predominately between the ages of 11 and 12 years, and the most significant divergence in symptom prevalence typically occurs later in adolescence, between the ages of 15 and 18 years (Hankin et al., 1998; Salk et al., 2017). The fact that alterations of within- and between-network DMN functional connectivity are apparent largely before the onset of puberty is interesting, as it would suggest that differential functioning of this RSN is not a product of puberty-related changes. It's possible that the cascade of hormonal fluctuations interact with this pre-existing neural phenotype to exacerbate internalizing symptoms in female adolescents after the onset of puberty.

Even though there is a significant amount of comorbidity between internalizing and externalizing symptoms in the ABCD Study® sample (Schettini et al., 2021), and that is reflective of the broader population (Angold, Costello, & Erkanli, 1999; Krueger & Markon, 2006; Lahey et al., 2017), the analysis presented in Chapter 3 found robust associations of within-network DMN connectivity and internalizing symptoms *specifically*, whereas externalizing symptoms were characterized by a more globally distributed RSFC phenotype (see Figure 3.6). The degree of comorbidity in the sample could also contribute to some discrepant findings in the literature to date. For the purposes of this work, externalizing symptom scores from the BPM-Y were not included as a covariate in any of the predictive models due to concerns that the variance remaining after this adjustment would not be as clinically meaningful. However, future research would benefit from a more granular examination of the unique and overlapping neural phenotypes that give rise to internalizing and externalizing features along a continuum of severity.

One of the major advantages of the BWAS-PNRS framework is that it has revealed the involvement of several other key networks that are associated with internalizing symptomatology in youth. For example, connectivity between the DMN and the cingulo-opercular network (CiO) emerged among

the most significant features in the discovery dataset. The CiO, working in tandem with the FPN, is known to play a role in maintaining task-focused attention, coordinating task processes, and error detection (Sadaghiani & D'Esposito, 2015; Sestieri et al., 2014). In relation to internalizing symptoms, differential functioning of the DMN with the CiO, as well as with the DAN, could contribute to difficulties with cognitive control and directing attention away from ruminative thought patterns. Also important were connections involving the ReT and other "unassigned" parcels, which likely plays a role in the attentional bias toward negative information and events, which then become the focus of rumination. In other analyses of the ABCD Study® cohort, several CBCL dimensions have been shown to be associated with reduced within-network connectivity of one or more of these networks (Wainberg et al., 2022). The most significant connection identified in the BWAS was between the precuneus and medial temporal cortex. Although this specific connection may not be reproducible (i.e., it may not persistently emerge as being the *top* predictor) in an independent sample, the consistent involvement of the DMN with other components of attentional and memory-related circuitry is striking. These features are aligned with both increased rumination and difficulties with managing or directing attention away from negative emotional experiences - key features of both anxiety and depression. These findings underscore the importance of considering the intricate interplay between multiple RSNs in understanding the neurobiological basis of internalizing psychopathology, particularly during adolescence.

Notably, the BWAS-PNRS framework yielded greater predictive power using only resting-state fMRI data than other network-based approaches (Ho et al., 2022). While it is likely that this multivariate approach is the source of the improvement, there are several key differences in this dissertation work that may also contribute. Perhaps most importantly, the analyses presented here utilize youth self-report on the BPM-Y as the primary outcome measure for internalizing symptomatology, whereas a majority of other published work in the ABCD Study® sample has

focused on caregiver-report from the CBCL. There is evidence to suggest that caregiver- and youth-report regarding mental health symptoms diverge in early adolescence, and that youth may be more reliable reporters of their own internal state (Grills & Ollendick, 2002; Rothen et al., 2009). Preliminary, unpublished work from our lab has corroborated this finding. Initial attempts at using the BWAS-PNRS framework to identify brain-behavior associations using the caregiver-report on the CBCL were largely unsuccessful, with a mere 1%-2% of variance in symptomatology explained - a dramatic difference from the 9.47% explained by youth self-report. Given that a caregiver's own mental health may influence their perceptions of their child's symptoms, or otherwise affect their behavior and interpersonal interactions with their child, special care should be taken when comparing analyses that use outcome measures from different sources. Future work may endeavor to disentangle neural and psychosocial features that are predictive of concordant vs. discordant reports of youth mental health, as this could lend further insight into how the relationship between the caregiver and their child impacts psychopathology. As discussed in Chapter 4, one of the most important predictors for internalizing symptom burden was the approachability of the caregiver (e.g., "Caregiver is easy to talk to"), suggesting that open communication is of particular relevance.

5.4 Conceptualizing Psychosocial Predictors of Internalizing Psychopathology

Chapter 4 demonstrated that a predictive model comprised primarily of item-level psychosocial variables was able to explain approximately 27.22% of the variance in internalizing symptoms across a nearly two-year follow-up period. As with Chapter 3, this is a substantial improvement

over recent studies in the same ABCD Study® sample that have relied on summary scores for prediction (Ho et al., 2022). However, this improvement cannot be automatically attributed to the use of item-level predictive features, as again there are several other distinguishing features of this dissertation work, including the use of youth self-report as the outcome variable of interest.

Several of the most important predictors identified in the final elastic net model touched on different aspects of the family environment and relationships. Specifically, greater family conflict and less open communication with the caregiver were both associated with greater internalizing psychopathology (see Figure 4.5). A negative or stressful family climate may amplify risk for internalizing symptoms by creating a strained or otherwise unsafe caregiver-child relationship (Deardorff et al., 2013; Rudolph & Troop-Gordon, 2010). Indeed, exposure to frequent, hostile interactions between parents is thought to dampen a child's emotional stress response, which may be a mechanism for the development of internalizing psychopathology (Cummings & Davies, 2002; Lucas-Thompson, 2012). Additionally, a parenting style that is characterized by high affectionless control (i.e., lack of care coupled with overprotection) has been shown to predict depression in youth (S. H. Goodman & Gotlib, 1999; Grant et al., 2012; Weissman & Jensen, 2002), and there is also evidence to suggest that a parent's capacity for emotion regulation influences youth's ability to learn emotion regulation (Lin et al., 2023; Rutherford et al., 2015).

These findings dovetail nicely with the results presented in Chapter 3 which highlighted RSNs that are known to be involved in emotion regulation. Although this dissertation work did not specifically address mediation, it is conceivable that greater family conflict or distant relationships with the caregiver could lead to difficulties managing negative emotions, or excessive feelings of anxiety or worry via alterations to the neural circuitry that guides internally focused attention and emotion. Likewise, difficulties with emotion regulation and internalizing psychopathology could add strain

that either leads to or reinforces a negative or stressful family dynamic. With additional waves of data from the ABCD Study® cohort being released annually, future analyses should examine longitudinal changes in internalizing symptoms in association with neurodevelopmental trajectories and fluctuations in family environment and relationship factors to better disentangle these temporal relationships.

The importance of predictor variables that reflect high levels of fear and worry (e.g., "I am very fearful compared to my friends", "I usually get very tense when I think something unpleasant is going to happen", "I worry about making mistakes", "I feel pretty upset when I think someone is angry with me") and low levels of self-esteem (e.g., "I feel I am just as smart as other kids my age", "Self-conscious or easily embarrassed") are unsurprising, yet still very relevant. First, it is well-understood that beliefs about one's own goodness or worth are a major risk/protective factor for mental health outcomes. Mostly irrespective of sex, low self-esteem significantly predicts internalizing and externalizing symptoms in adolescence and adulthood (Masselink et al., 2018; Spitz et al., 2022). But what's most interesting about these findings is that the items identified here are somewhat overlapping with the BPM-Y internalizing symptom sub-scale that was used to generate the cumulative internalizing symptom score outcome measure in the first place. The fact that the predictive features from Chapter 4 were assessed at the baseline visit, and were found to be significantly associated with cumulative internalizing symptom burden across the next two years of data, highlights the high degree of homotypic continuity of internalizing problems in adolescence (for further discussion, refer to Section 1.1.1). It is also worth noting that the constructs of excessive worry and low self-esteem emerged out of both caregiver- (CBCL) and youth-report (BIS-BAS) measures. These attributes may be ripe targets for early intervention via cognitive therapy and supportive parenting.

So much of the recent work in the arena of developmental psychology has aimed to find new and sophisticated methods for leveraging neuroimaging data to predict future mental health outcomes. Unfortunately, based on the phenotypic variance explained, the findings presented here would suggest that RSFC (at least insofar as we have been able to measure and analyze it) is less useful for predicting internalizing symptoms when compared to psychosocial, environmental, and behavioral variables. While there appears to be some unique contribution of RSFC that is not captured by the psychosocial variables (i.e., the difference in variance explained between the 'behavior-only' and the 'brain-and-behavior' model in Table 4.3), it is relatively small. Given the cost and time-intensive nature of neuroimaging, this particular kind of assessment may have more utility for stratifying individuals according to likelihood of treatment response or guiding the selection of therapeutic intervention.

5.5 Limitations and Caveats

Although this dissertation work presents important findings with regard to both the neural and psychosocial correlates of internalizing psychopathology during the early adolescent period, there are several caveats that warrant further discussion.

First, at the time of this analysis, complete data from the ABCD Study® cohort had only been released for the baseline visit through the 2-year follow-up visit. The BPM-Y was administered a total of four times during this interval (i.e., at 6 months, 1 year, 18 months, and 2 years). Importantly, the BPM-Y is designed to assess symptoms that have occurred in the past week, meaning that this questionnaire only provides a brief snapshot of youth mental health at each of the aforementioned timepoints. In an attempt to generate a more robust summary of internalizing

symptoms, this dissertation work aggregated BPM-Y internalizing symptom scores across several years, rather than focusing on any individual follow-up timepoint. However, internalizing psychopathology, and depression in particular, is known to follow an episodic course during adolescence, so it is entirely possible that participants who have continuously experienced severe symptoms throughout the follow-up period just happened to be asymptomatic at the time of assessment. Conversely, it may be that some individuals rarely exhibit symptoms, but happened to fill out the questionnaire on a day when they were experiencing particularly low mood. Such prolonged gaps between assessments makes it difficult to comprehensively measure internalizing symptom burden. Ideally, more frequent measurements would allow for a more robust characterization of brain-behavior relationships as well as an in-depth investigation of temporal patterns in symptom variability.

Secondly, this dissertation work does not draw inferences about whether the neural and psychosocial predictors identified here are also predictive of meeting clinical diagnostic criteria for an internalizing disorder (e.g., major depressive disorder, generalized anxiety disorder, obsessive compulsive disorder, etc.). At the time this analysis was conducted, errors in the KSADS-5 scoring algorithm meant that accurate data regarding clinical diagnoses were unavailable. Even though there are national norms and thresholds for the BPM-Y that can be used to delineate clinically significant symptoms from symptoms in the sub-clinical and normative ranges, it is still the case that low base rates of clinical depression and anxiety in this age range would likely have made a categorical prediction underpowered. It is understood that the phenotypes identified here likely exist on a continuum, but there may be unique risk factors that differentiate the most severe cases from individuals who fall in a more normative symptom range. The analyses presented here do not make any conclusions in that regard. Additionally, because the BPM-Y was not administered at baseline, it is not possible to determine whether these neural and psychosocial characteristics

precede onset of internalizing psychopathology, occur as a *result* of experiencing internalizing psychopathology, or simply *coincide with* internalizing psychopathology. There are some environmental factors where a reciprocal relationship (i.e., internalizing symptoms leading to a particular characteristic) is unlikely. For example, environmental exposure to air pollution would more likely contribute to, or coincide with, the emergence of internalizing symptoms, not evolve as a result. Nevertheless, this project does not have the temporal resolution to be able to differentiate the sequence between events.

Thirdly, some instruments that were administered as part of the ABCD Study® protocol were not able to be included in the predictive models in Chapter 4 due to excessive missingness. Importantly, the large majority of this missing data was intentional missing due to branching logic as described in Section 4.3.3.2 and Section 4.5. For this reason, the results of this analysis should be interpreted with caution. Potentially important variables pertaining to cultural values, traumatic brain injury, and parental rules on substance use, which may very well be relevant for internalizing psychopathology in youth, have not been investigated here. Also with regard to missing data, the imputation method used in Chapter 3 is not ideal because it does not take advantage of the unique ability for multiple imputation to capture variability and uncertainty in imputed values. Further methodological work to determine how best to implement Rubin's rules within the BWAS-PNRS framework would be needed, but are outside the scope of this project. While combining results from multiple iterations of imputation, using auxiliary variables, results in imputed values being treated with the same certainty as values that were actually measured, this approach is still likely to be an improvement over simple mean imputation or last-observation-carried-forward.

Fourthly, although there is a good rationale for combining ARMS-1 and ARMS-2 for a single large discovery set across both aims of this dissertation (Marek et al., 2022), the trade-off is that the

demographically matched samples cannot be used to examine replicability of the findings presented here (Feczko et al., 2021). An independent sample will be required to determine to what degree these neural and psychosocial phenotypes generalize. While the exact order of importance for individual features may not be reproducible in an independent dataset, the intent of using such a large discovery sample was to identify core constructs (e.g., within-DMN functional connectivity, family relationships, self-esteem/self-worth) associated with internalizing psychopathology and estimate those relationships as accurately as possible (Marek et al., 2022).

The last, and perhaps the most important caveat to the results presented here, is the impact of motion censoring criteria. It is well documented that head motion confounds the interpretation of fMRI analyses, as even sub-millimeter movements can significantly distort functional connectivity estimates (Power et al., 2012; Satterthwaite et al., 2012). Not only that, but motion has been shown to alter functional connectivity estimates in a *spatially-dependent* manner - artificially inflating estimates for short-range connections and reducing estimates for long-range connections (Power et al., 2012), which has important implications for studying brain-behavior associations within and across spatially distributed resting-state networks. Even after using a regression-based approach to motion correction, these artifacts persist, necessitating the use of stringent quality assurance criteria. Typical motion censoring thresholds for rs-fMRI data range between a framewise displacement (FD) value of 0.2mm and 0.5mm, and the analyses presented here utilized a threshold of 0.2mm with at least eight minutes of data. However, this criterion has been shown to disproportionately exclude participants belonging to marginalized and underrepresented groups (Cosgrove et al., 2022; Ricard et al., 2023). In spite of efforts to balance data quality with generalizability, it is still true that the sample analyzed here is significantly different from the rest of the ABCD Study® cohort with respect to nearly all sociodemographic characteristics examined (e.g., sex-assigned-at-birth, race, ethnicity, parental education, household income) (Table 3.3).

There are a myriad of contextual factors that likely contribute to these systematic differences in head motion, including, but not limited to, a very valid mistrust of academic institutions and healthcare systems among marginalized populations. The historical atrocities perpetrated by medical and academic establishments, amplified by pervasive racial and ethnic discrimination, inequities in healthcare treatment, and barriers to access, continue to have profound consequences for the clinical research that is being done today. It is incumbent upon the scientific community both to understand the limits to generalizability that result from current field-standard approaches, and to actively work to rectify these issues so as to avoid drawing biased conclusions that further perpetuate harmful practices. Some methodological changes that could help to mitigate bias and ensure that data collection is truly representative might be to oversample certain demographic groups, perform better pre-scan training and intentionally work with participants to assuage any anxiety or discomfort, consider the demographics of research staff (Does et al., 2018), collect excess data, or find ways to interpolate neuroimaging data that would otherwise have too much motion. It is our responsibility as researchers to address these issues, and further work on our part is necessary to ensure that our procedures maximize participant inclusion and safety.

5.6 Conclusions

This dissertation project has taken advantage of several new opportunities in the field of developmental psychology to advance our understanding of adolescent internalizing psychopathology. By employing a novel multivariate approach that takes into account the non-sparse nature of the explanatory signal in the brain (the BWAS-PNRS framework), the analyses presented in Chapter 3 identified a phenotype of resting-state functional connectivity that was associated with internalizing symptomatology across nearly two years of follow-up. This

phenotype was characterized by heavy involvement of the DMN, further underscoring the contributions of this RSN to emerging psychopathology. Then, the analyses of Chapter 4 identified key behavioral, psychosocial, and environmental predictors of internalizing symptomatology in the same sample. Among the strongest predictors of internalizing symptom scores were fearfulness and worry, self-esteem, and family conflict. In comparing the relative predictive power of the 'brain vs. behavior', this work demonstrates that a majority of the explanatory power of RSFC can already be captured with psychosocial variables and appears to offer only modest improvements in prediction. However, later waves of data that are released from the ABCD Study® cohort will allow for a more nuanced investigation of trajectories of symptom change (both severity and chronicity). These findings may be particularly useful for informing the development of targeted intervention strategies that seek to either modify RSFC within and between specific networks (e.g., the default mode network and its connections) or address specific psychosocial and environmental risk factors (e.g., caregiver-child communication, family conflict, self-esteem and self-worth).

Figures

Figure 2.1: Inclusion criteria for the present study. *After excluding ABCD Study ® participants for missing rs-fMRI data at baseline, for rs-fMRI data that did not pass quality control procedures, and for missing mental health data during follow-up, there was a final sample of N = 6,521 participants.*

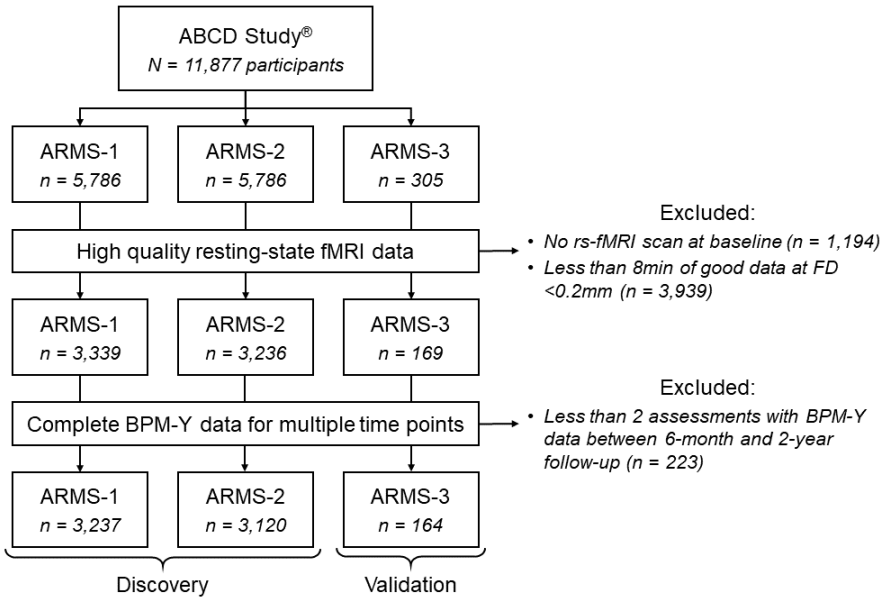


Figure 3.1: Brain-wide association study (BWAS) framework. *First, for each participant in the discovery set, mass univariate parameter estimates (β-weights) for the relationship between functional connectivity of each ROI-x-ROI pair and behavior were estimated. A linear model was applied such that the outcome measure (cumulative BPM-Y internalizing symptom score) was modeled as a function of the weighted contribution of a given functional connection, controlling for covariates (see Equation 3.1). This process was repeated for all functional connections, and for all participants in the discovery set. Functional connections were ordered according to their p-value (most significant to least significant) in the discovery set, and various thresholds of the top connections (e.g., top 0.1%, top 0.2%, top 0.5%, etc.) were used to generate polyneuro risk scores (PNRS) and applied to the validation set.*

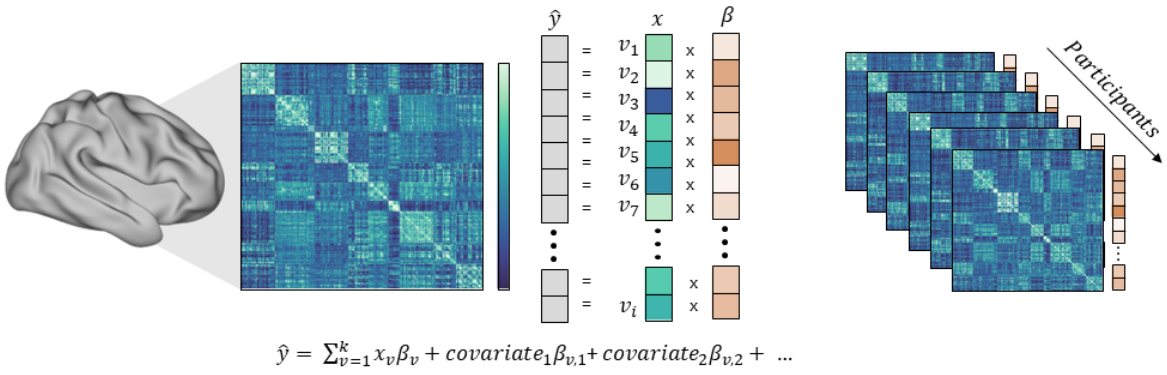


Figure 3.2: Key functional connections identified by BWAS for **internalizing** symptom scores. *Manhattan plot in logarithmic scale displays the significance value for each functional connection as identified in the discovery set. More significant features appear higher on the y-axis. Functional connections are grouped along the x-axis according to their network assignment in the Gordon parcellation scheme (network abbreviations correspond with the Gordon parcellation and can be found in Figure 3.3). Along the right-hand axis are horizontal gray lines that denote the various thresholds of top connections (e.g., top 0.1%, top 0.2%, etc.). A selection of the most strongly implicated network pairs are colored and labeled to facilitate visualization.*

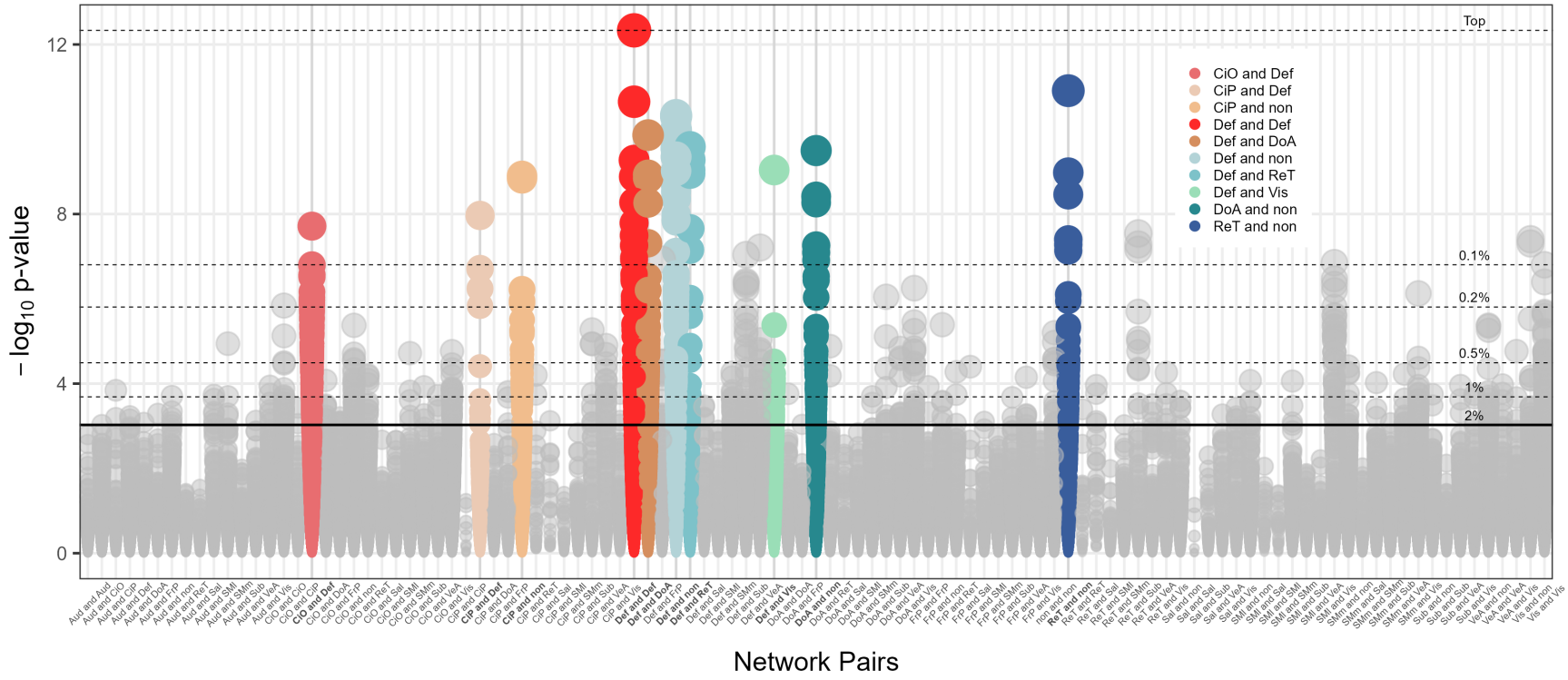


Figure 3.3: Topographical distribution of the most significant functional connections for the prediction of **internalizing** symptom scores. *For each threshold, the brain regions that contribute to those connections are mapped to their topographical location. (a) Colors represent the sum of the absolute values of all estimated β-weights for each region. (b) Colors represent the network assignment of each region according to the Gordon parcellation scheme.*

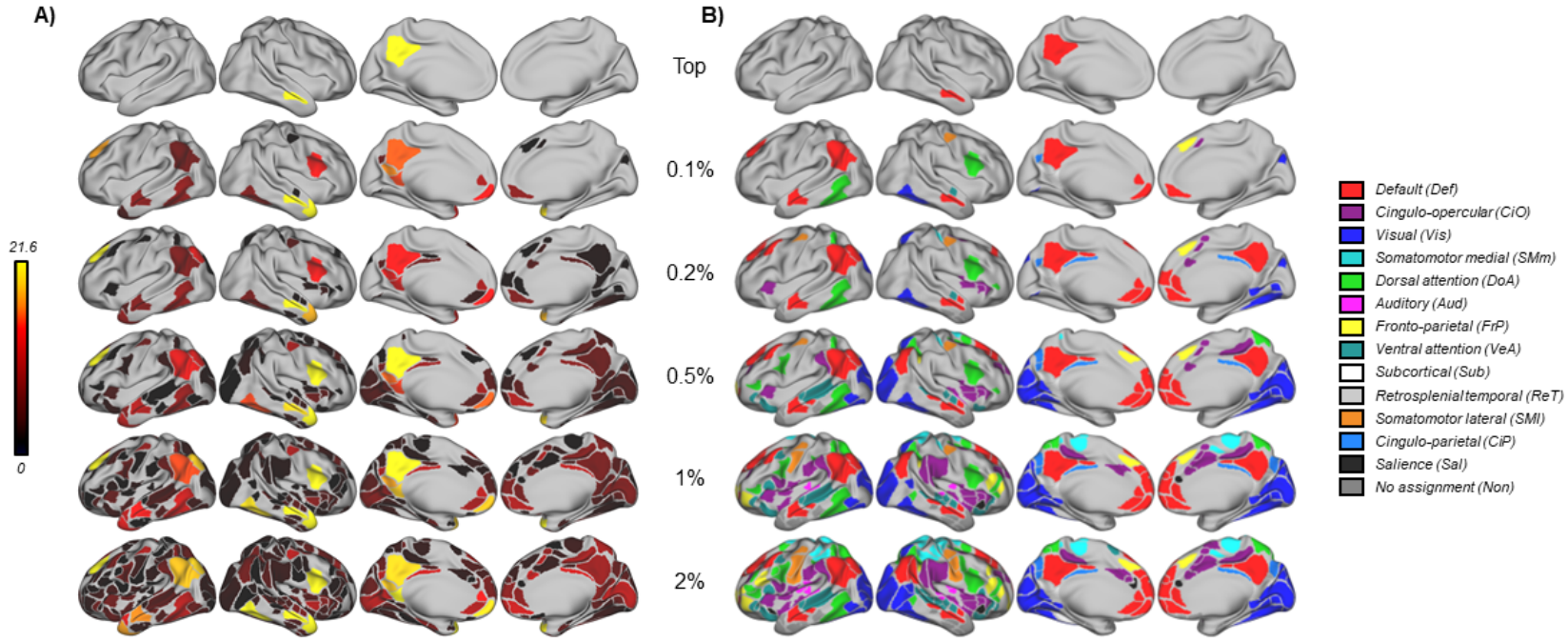


Figure 3.4: Distribution of positive vs. negative β-weights by network assignment for the prediction of **internalizing** symptom scores. *Functional connections are grouped according to their network assignment in the Gordon parcellation scheme. For each network pair, the percentage of functional connections with positive (red) vs. negative (blue) β-weights, as determined by the BWAS, are displayed in a horizontal bar chart. The highlighted network pairs correspond to the most strongly implicated network pairs (i.e., most significant) from Figure 3.2.*

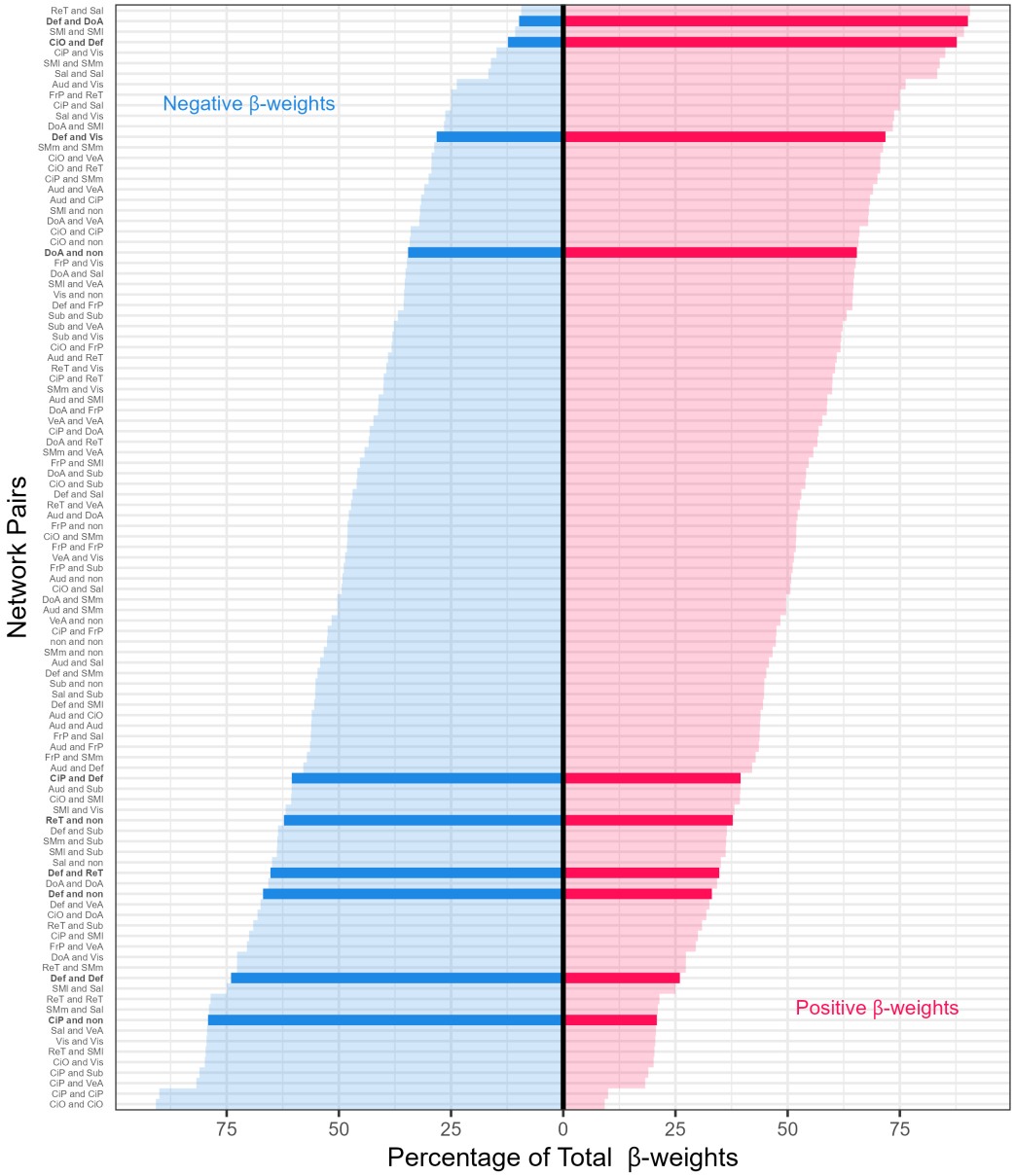


Figure 3.5: Observed vs. predicted **internalizing** symptom scores derived from the PNRS. *The PNRS performance peaked when the top 2% of significant connections identified in the discovery set were retained. At this threshold, the PNRS was able to explain 9.47% of the variance in internalizing symptom scores in the validation set. Scores were normalized using a Box-Cox transformation. The shaded region surrounding the line of best fit represents the 95% confidence interval.*

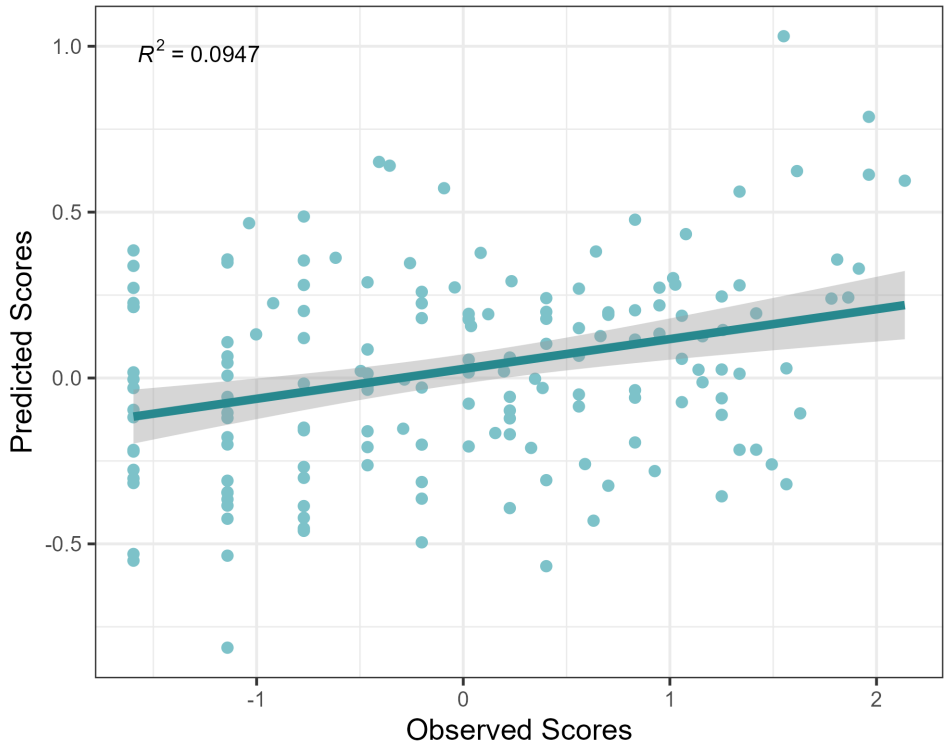


Figure 3.6: Key functional connections identified by BWAS for **externalizing** symptom scores. *Manhattan plot in logarithmic scale displays the significance value for each functional connection as identified in the discovery set. More significant features appear higher on the y-axis. Functional connections are grouped along the x-axis according to their network assignment in the Gordon parcellation scheme (network abbreviations correspond with the Gordon parcellation and can be found in Figure 3.3). Along the right-hand axis are horizontal gray lines that denote the various thresholds of top connections (e.g., top 0.1%, top 0.2%, etc.). The most strongly implicated network pairs from the analysis of internalizing symptom scores are colored and labeled to facilitate comparison.*

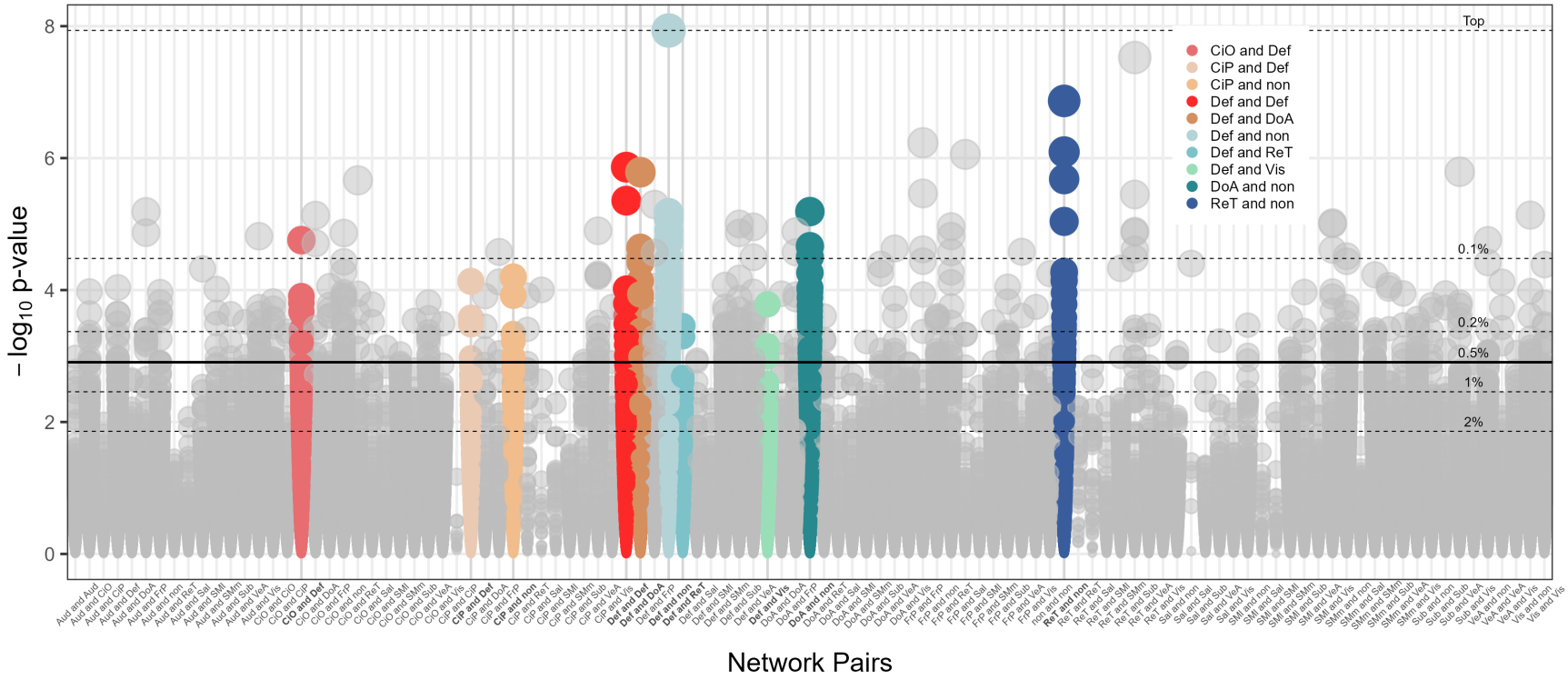


Figure 3.7: Observed vs. predicted **externalizing** symptom scores derived from the PNRS. *The PNRS performance peaked when the top 2% of significant connections identified in the discovery set were retained. At this threshold, the PNRS was able to explain 5.14% of the variance in externalizing symptom scores in the validation set. Scores were normalized using a Box-Cox transformation. The shaded region surrounding the line of best fit represents the 95% confidence interval.*

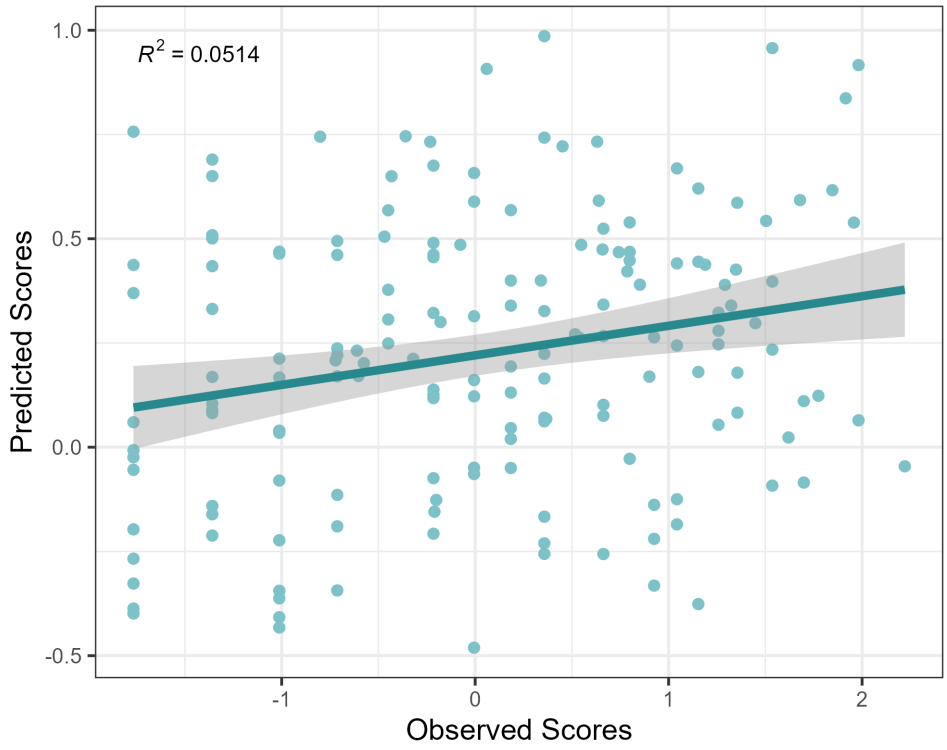


Figure 4.1: Data partitioning scheme for nested cross-validation. *Ten outer folds were used to perform Boruta feature selection. Within each of the 10 train-test splits, the data was further divided into 5 inner folds for hyperparameter optimization. Once a best performing set of hyperparameters was identified, those values were used to retrain and test the model at the outer fold level. Ten estimates of model performance were derived for each model type.*

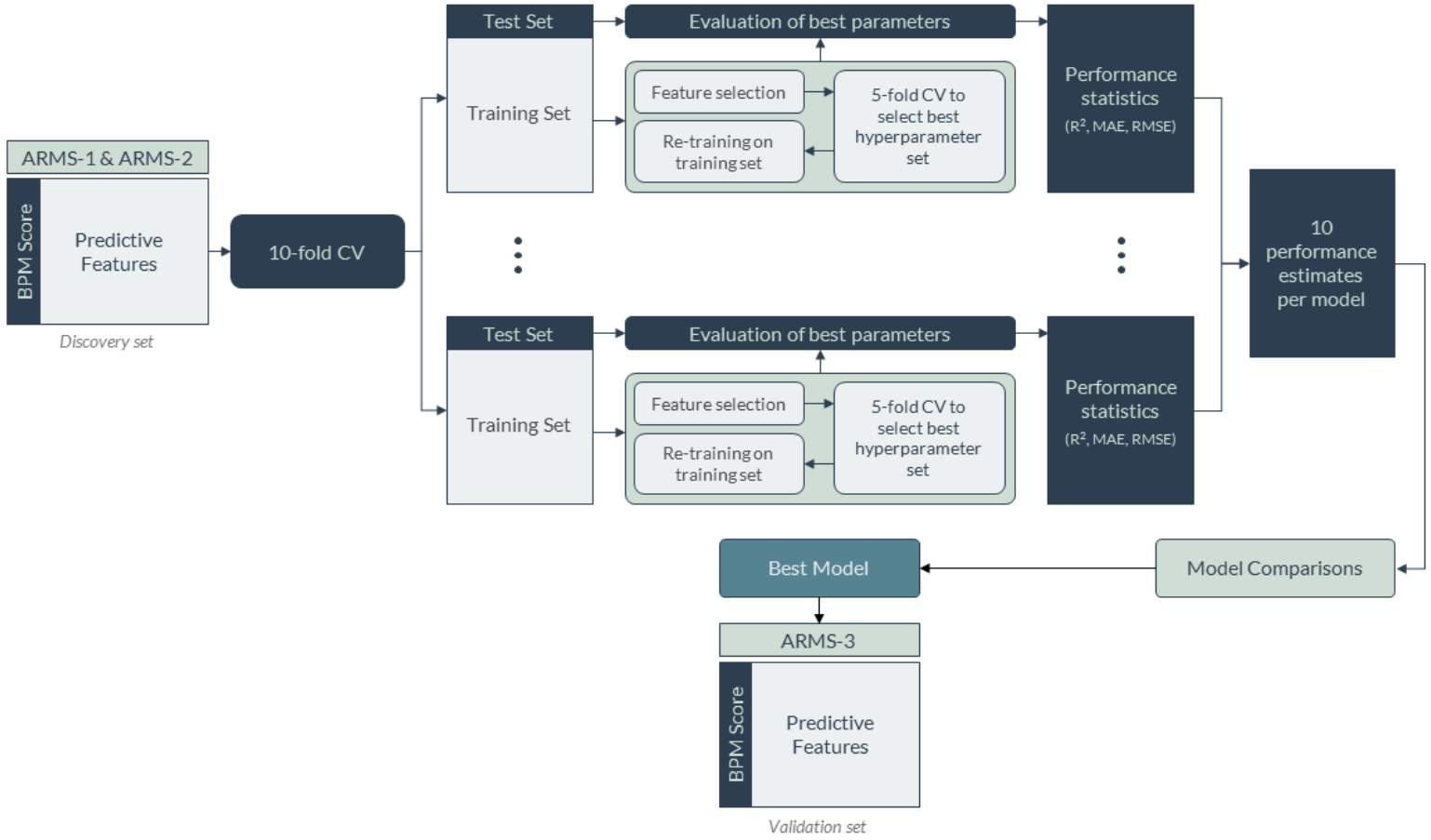


Figure 4.2: Distribution of performance metrics for each model type. *Box-plots display the distribution of model performance metrics (R^2, RMSE, MAE) across the 10 outer folds of nested-cross validation.*

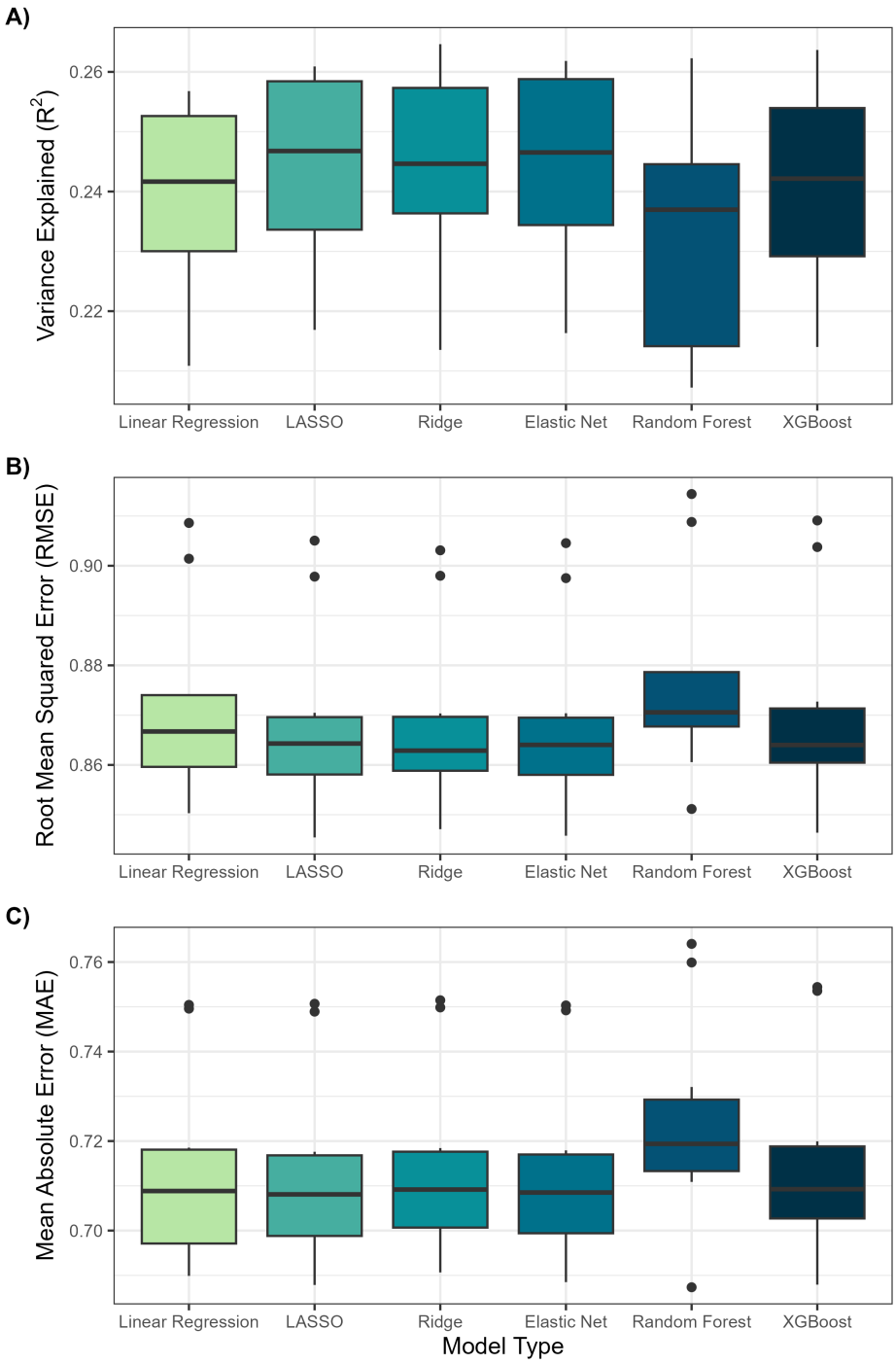


Figure 4.3: Distribution of performance metrics for each model type compared to performance on permuted data. *Box-plots display the distribution of model performance metrics (R^2, RMSE, MAE) across the 10 outer folds of nested-cross validation as in Figure 4.2. Model performance metrics derived from permuted data are displayed in grayscale for comparison.*

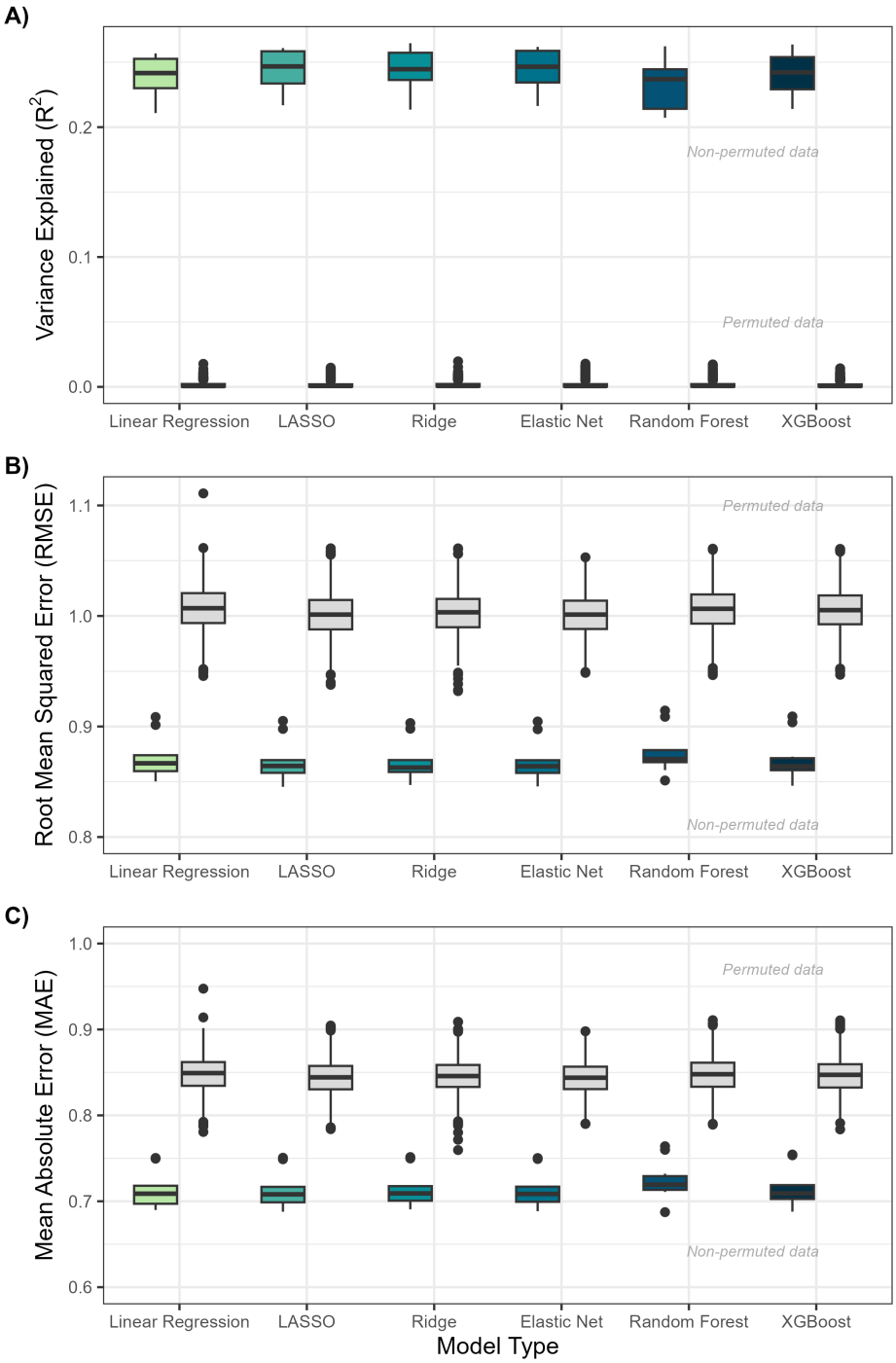


Figure 4.4: Important features ranked by regularized coefficient from the final elastic net model. *The top 25 predictive features with the largest regularized coefficients from the final model are displayed in decreasing order. For numeric features, positive values (red) indicate a positive relationship between the feature and internalizing symptom scores, whereas negative values (blue) indicate an inverse relationship. For categorical features, positive values indicate a positive relationship between endorsement of the specified response option (specified in parentheses) and internalizing symptom scores, whereas negative values indicate an inverse relationship.*

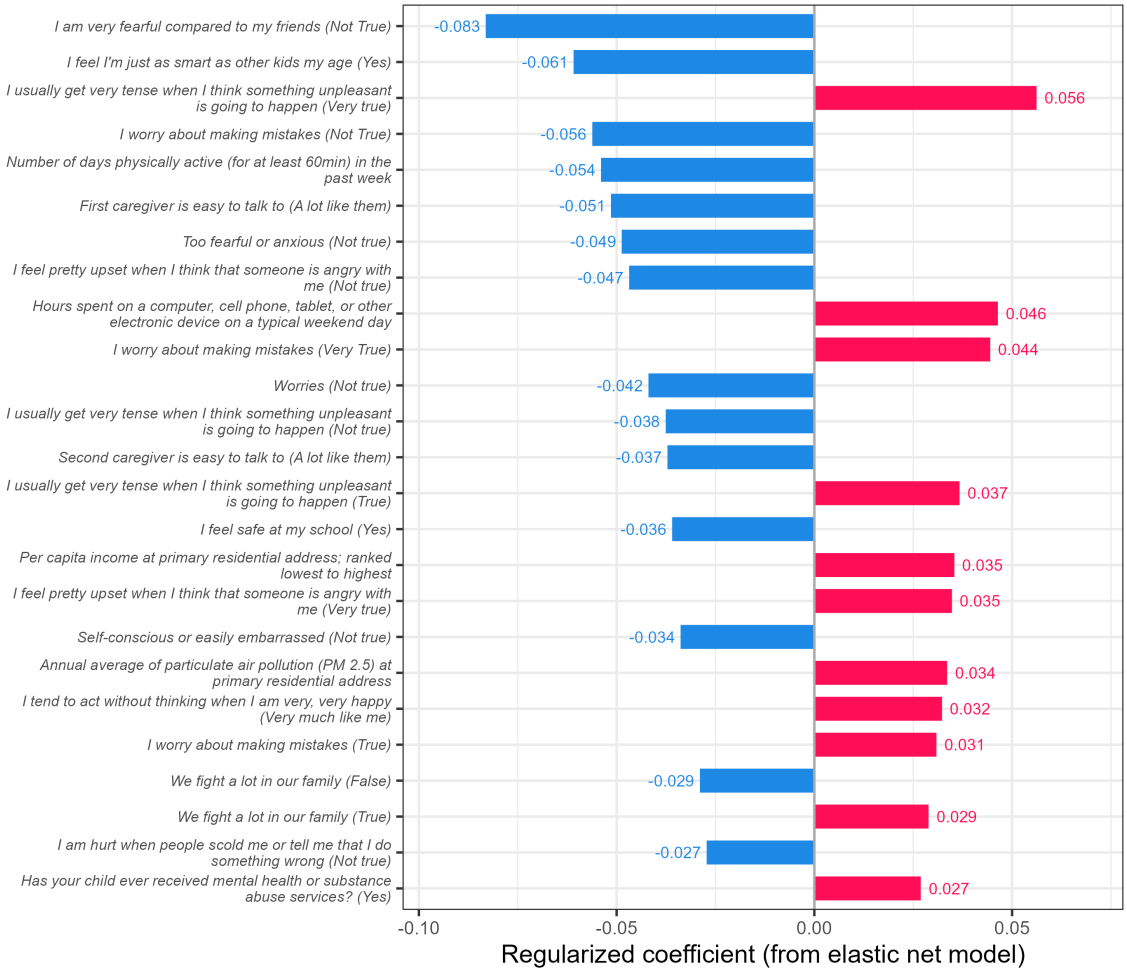
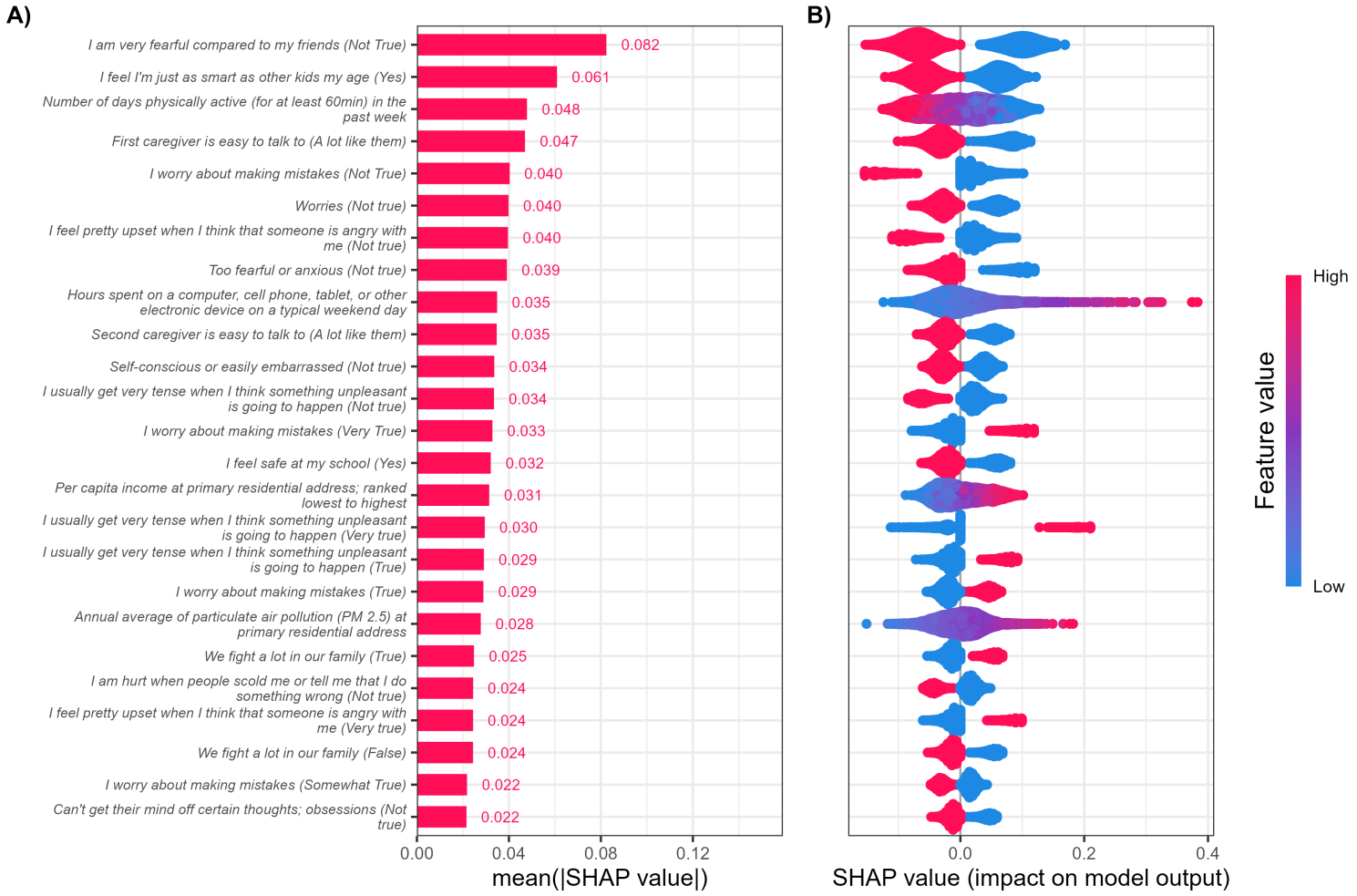


Figure 4.5: Important features ranked by Shapley values from the final elastic net model. *The top 25 predictive features with the largest average Shapley values are displayed in decreasing order. A) Global feature importance - the absolute magnitude of the average Shapley value for each feature. B) Local explanations - summary plots where each point represents a Shapley value for a single feature for a single participant. The position of the point on the x-axis denotes the Shapley value and the color of the point denotes the value of the feature from low (blue) to high (red).*



Tables

Table 3.1: Participant sociodemographic characteristics.

	Discovery	Validation	p-value
n	6357	164	
Cumulative BPM-Y internalizing symptom scores (mean (SD))	1.10 (1.02)	1.10 (1.04)	0.993
Age in months (mean (SD))	119.56 (7.54)	119.25 (7.71)	0.601
Sex assigned at birth (%)			**0.886**
Female	3216 (50.6)	86 (52.4)	
Intersex Male	1 (0.0)	0 (0.0)	
Male	3140 (49.4)	78 (47.6)	
Research site (%)			**0.206**
Icahn School of Medicine at Mount Sinai	19 (0.3)	0 (0.0)	
Medical University of South Carolina	225 (3.5)	10 (6.1)	
Oregon Health & Science University	344 (5.4)	20 (12.2)	
SRI International	183 (2.9)	4 (2.4)	
University of California Los Angeles	238 (3.7)	7 (4.3)	
University of Michigan	330 (5.2)	7 (4.3)	
University of Utah	807 (12.7)	14 (8.5)	
University of Vermont	273 (4.3)	5 (3.0)	
Virginia Commonwealth University	256 (4.0)	8 (4.9)	
Washington University in St. Louis	415 (6.5)	9 (5.5)	
Yale University	336 (5.3)	7 (4.3)	
Children's Hospital of Los Angeles	65 (1.0)	1 (0.6)	
Florida International University	395 (6.2)	6 (3.7)	
Laureate Institute for Brain Research	414 (6.5)	9 (5.5)	
University of California San Diego	293 (4.6)	9 (5.5)	
University of Colorado Boulder	407 (6.4)	12 (7.3)	
University of Florida	265 (4.2)	7 (4.3)	

(continued)

	Discovery	Validation	p-value
University of Maryland at Baltimore	107 (1.7)	3 (1.8)	
University of Minnesota	408 (6.4)	8 (4.9)	
University of Pittsburgh Medical Center	197 (3.1)	8 (4.9)	
University of Rochester	189 (3.0)	4 (2.4)	
University of Wisconsin Milwaukee	191 (3.0)	6 (3.7)	
Racial identity			
White = Yes (%)	5037 (79.2)	99 (60.4)	<0.001
Black, African-American = Yes (%)	1122 (17.6)	36 (22.0)	0.187
Asian = Yes (%)	400 (6.3)	8 (4.9)	0.565
Native American, Alaska Native = Yes (%)	202 (3.2)	3 (1.8)	0.453
Native Hawaiian, Pacific Islander = Yes (%)	38 (0.6)	2 (1.2)	0.617
Other not listed = Yes (%)	347 (5.5)	20 (12.2)	<0.001
Multi-racial = Yes (%)	747 (11.8)	10 (6.1)	0.035
Ethnicity (%)			**0.953**
Hispanic	1144 (18.0)	28 (17.1)	
Not Hispanic	5133 (80.7)	134 (81.7)	
NA	80 (1.3)	2 (1.2)	
Parental education (%)			**0.333**
Less than high-school diploma	195 (3.1)	7 (4.3)	
High-school diploma or GED	467 (7.3)	19 (11.6)	
Some college	1590 (25.0)	38 (23.2)	
Bachelor's degree	1753 (27.6)	39 (23.8)	
Post-graduate degree	2349 (37.0)	61 (37.2)	
NA	3 (0.0)	0 (0.0)	
Combined annual household income (%)			**0.116**
Less than $50,000	1453 (22.9)	50 (30.5)	
$50,000 to $100,000	1728 (27.2)	36 (22.0)	
Greater than $100,000	2683 (42.2)	65 (39.6)	
NA	493 (7.8)	13 (7.9)	

Note: Racial identity categories are self-reported and several have been collapsed as follows: Asian includes participants who self-identify as Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or other Asian; Native Hawaiian and/or Pacific Islander includes participants who self-identify as Native Hawaiian, Guamanian, Samoan, or other Pacific Islander. Categories do not sum to 100% of the sample because participants identifying with multiple racial identities are included in the multi-racial group as well as other groups with whom they identify.

Table 3.2: Performance of PNRS for BPM-Y **internalizing** symptom scores using different thresholds of top functional connections.

Features	Components	MAE	R	R-squared (%)	Cohen's d
Top 0.1%	4	0.926	0.216 **	4.687	0.026
Top 0.2%	4	0.938	0.137	1.877	0.021
Top 0.5%	2	0.885	0.229 ***	5.230	0.054
Top 1.0%	4	0.832 ***	0.283 ***	8.018	0.052
Top 2.0%	2	0.832 ***	0.308 ***	9.474	0.080
Top 5.0%	4	0.83 ***	0.262 ***	6.843	0.051
Top 10.0%	4	0.863 **	0.232 ***	5.392	0.119
Top 25.0%	3	0.856 **	0.249 **	6.209	0.150

Note: *p<0.05, **p<0.01, ***p<0.001

Table 3.3: Sociodemographic characteristics of participants included in the present analysis (included) compared to the rest of the ABCD Study® cohort (excluded).

	Included	Excluded	p-value
n	5355	6521	
Age in months (mean (SD))	118.28 (7.38)	119.55 (7.55)	<0.001
Sex assigned at birth (%)			**<0.001**
Female	2379 (44.4)	3302 (50.6)	
Intersex Male	2 (0.0)	1 (0.0)	
Male	2974 (55.5)	3218 (49.3)	
Research site (%)			**<0.001**
Icahn School of Medicine at Mount Sinai	17 (0.3)	19 (0.3)	
Medical University of South Carolina	143 (2.7)	235 (3.6)	
Oregon Health & Science University	220 (4.1)	364 (5.6)	
SRI International	163 (3.0)	187 (2.9)	
University of California Los Angeles	188 (3.5)	245 (3.8)	
University of Michigan	391 (7.3)	337 (5.2)	
University of Utah	190 (3.5)	821 (12.6)	
University of Vermont	301 (5.6)	278 (4.3)	
Virginia Commonwealth University	286 (5.3)	264 (4.0)	
Washington University in St. Louis	283 (5.3)	424 (6.5)	
Yale University	257 (4.8)	343 (5.3)	
Children's Hospital of Los Angeles	340 (6.3)	66 (1.0)	
Florida International University	230 (4.3)	401 (6.1)	
Laureate Institute for Brain Research	322 (6.0)	423 (6.5)	
University of California San Diego	437 (8.2)	302 (4.6)	
University of Colorado Boulder	139 (2.6)	419 (6.4)	
University of Florida	178 (3.3)	272 (4.2)	
University of Maryland at Baltimore	494 (9.2)	110 (1.7)	
University of Minnesota	190 (3.5)	416 (6.4)	
University of Pittsburgh Medical Center	253 (4.7)	205 (3.1)	
University of Rochester	146 (2.7)	193 (3.0)	
University of Wisconsin Milwaukee	187 (3.5)	197 (3.0)	
Racial identity			
White = Yes (%)	3668 (68.5)	5136 (78.8)	<0.001
Black, African-American = Yes (%)	1360 (25.4)	1158 (17.8)	<0.001
Asian = Yes (%)	343 (6.4)	408 (6.3)	0.770
Native American, Alaska Native = Yes (%)	205 (3.8)	205 (3.1)	0.047
Native Hawaiian, Pacific Islander = Yes (%)	34 (0.6)	40 (0.6)	0.975
Other not listed = Yes (%)	433 (8.1)	367 (5.6)	<0.001
Multi-racial = Yes (%)	677 (12.6)	757 (11.6)	0.091
Ethnicity (%)			**<0.001**
Hispanic	1239 (23.1)	1172 (18.0)	

(continued)

	Included	Excluded	p-value
Not Hispanic	4045 (75.5)	5267 (80.8)	
NA	71 (1.3)	82 (1.3)	
Parental education (%)			**<0.001**
Less than high-school diploma	391 (7.3)	202 (3.1)	
High-school diploma or GED	646 (12.1)	486 (7.5)	
Some college	1451 (27.1)	1628 (25.0)	
Bachelor's degree	1223 (22.8)	1792 (27.5)	
Post-graduate degree	1633 (30.5)	2410 (37.0)	
NA	11 (0.2)	3 (0.0)	
Combined annual household income (%)			**<0.001**
Less than $50,000	1720 (32.1)	1503 (23.0)	
$50,000 to $100,000	1307 (24.4)	1764 (27.1)	
Greater than $100,000	1816 (33.9)	2748 (42.1)	
NA	512 (9.6)	506 (7.8)	

Note: Racial identity categories are self-reported and several have been collapsed as follows: Asian includes participants who self-identify as Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, or other Asian; Native Hawaiian and/or Pacific Islander includes participants who self-identify as Native Hawaiian, Guamanian, Samoan, or other Pacific Islander. Categories do not sum to 100% of the sample because participants identifying with multiple racial identities are included in the multi-racial group as well as other groups with whom they identify.

Table 3.4: Performance of PNRS for BPM-Y **externalizing** symptom scores using different thresholds of top functional connections.

Features	Components	MAE	R	R-squared (%)	Cohen's d
Top 0.1%	4	0.936	0.195 *	3.790	0.012
Top 0.2%	2	0.866 *	0.193 **	3.726	0.026
Top 0.5%	3	0.864 *	0.227 ***	5.139	0.061
Top 1.0%	2	0.854 ***	0.21 **	4.414	0.138
Top 2.0%	3	0.883	0.183 *	3.365	0.121
Top 5.0%	3	0.898	0.173 *	2.985	0.099
Top 10.0%	4	0.892 *	0.14 *	1.955	0.122
Top 25.0%	2	0.894	0.144	2.084	0.204

Note: *p<0.05, **p<0.01, ***p<0.001

Table 4.1: Hyperparameters tuned for each model.

Model	Hyperparameters	Description	Values explored
Linear regression	NA	NA	NA
LASSO	lambda	Strength of L1 regularization	range(0.00008, 0.2)
Ridge	lambda	Strength of L2 regularization	range: (0.02, 200)
Elastic net	alpha	Relative weight of LASSO vs. ridge penalties	range: (0.1, 1.0)
Elastic net	lambda	Strength of L1 and L2 regularization	range: (0.00002, 0.36)
Random forest	num.trees	Number of trees per forest	1000
Random forest	mtry	Number of variables to possibly split at each node	range: (2, 108)
Random forest	splitrule	Splitting rule	['Variance', 'Extra Trees']
Random forest	min.node.size	Minimal node size to split at	5
XGBoost	eta	Learning rate	[0.3, 0.4]
XGBoost	gamma	Minimum loss reduction required to make a further partition on a leaf node of the tree	0
XGBoost	max_depth	Maximum depth of a tree	[1, 2, 3, 4, 5, 6, 7, 8, 9, 10]
XGBoost	colsample_by_tree	Percentage of columns used for each tree construction	[0.6, 0.8]
XGBoost	min_child_weight	Minimum sum of instance weight needed in a child (prevents the creation of too small leaves)	1
XGBoost	subsample	Percentage of rows used for each tree construction	range: (0.5, 1)
XGBoost	nrounds	Maximum number of boosting iterations	[50, 100, 150, 200, 250, 300, 350, 400, 450, 500]

Note: Values explored are approximate. Most of the tuning algorithms determine their own 'warm start' from the data.

Table 4.2: Wilcoxon Rank Sum tests comparing model performance to a baseline of linear regression across 10 folds of cross-validation.

	R-squared			RMSE			MAE		
Model	Statistic	p-value	Alternative	Statistic	p-value	Alternative	Statistic	p-value	Alternative
LASSO	1	0.00195	greater	54	0.00195	less	33	0.31250	less
Ridge	1	0.00195	greater	52	0.00488	less	14	0.91992	less
Elastic Net	1	0.00195	greater	54	0.00195	less	31	0.38477	less
Random Forest	40	0.90332	greater	12	0.94727	less	2	0.99805	less
XGBoost	28	0.53906	greater	31	0.38477	less	10	0.96777	less

Table 4.3: Comparison of performance for 'brain-only' vs. 'behavior only' predictive models.

Model	R-squared (%)	RMSE	MAE
Brain Only (Chapter 3: Polyneuro risk scores)	9.474	NA	0.832
Behavior Only (Chapter 4: Psychosocial variables)	27.221	0.873	0.719
Brain & Behavior	30.592	0.852	0.695

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