Identifying Neural, Genetic, and Behavioral Correlates of the p Factor
by

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Dissertation submitted in partial fulfillment of
the requirements for the degree of Doctor
of Philosophy in the Department of
Psychology and Neuroscience in the Graduate School
of Duke University

2018

ABSTRACT

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Abstract

Accumulating mental health research encourages a shift in focus towards transdiagnostic dimensional features that are shared across categorical disorders. In support of this shift, recent studies have identified a general liability factor for psychopathology – called the 'p factor' – that underlies shared risk for a wide range of mental disorders. Identifying the behavioral, neural, and genetic correlates of this general liability would substantiate its importance in characterizing the shared origins of mental disorders and help us begin to understand the mechanisms through which the p factor contributes to risk. In the current series of studies, I investigate the behavioral, neural, and genetic correlates of the p factor in two independent samples in order to better understand the mechanisms underlying a general liability for mental illness. I first investigate these correlates in the Duke Neurogenetics Study (DNS) comprised of 1,246 young adult volunteers aged 18-22. I then determine whether the correlates identified in the DNS replicate in a subsample of 481 45 year-old members of a birth cohort from the ongoing Dunedin Longitudinal Study (Dunedin). The Dunedin Study includes over 1,000 participants from Dunedin, New Zealand who have been followed since birth.

In Study 1 (Chapter 3), I show that the p factor, which previously has been identified and related to maladaptive behaviors in the Dunedin cohort, is identifiable in the DNS, a high-functioning young adult sample, and demonstrate that p factor scores map onto a broad range of dysfunctional behaviors. In Study 2 (Chapter 4), using high-

resolution multimodal structural neuroimaging in the DNS, I demonstrate that individuals with high p factor scores show reduced structural integrity of pons white matter pathways and reduced gray matter volume in the occipital lobe and left cerebellar lobule VIIb, which is functionally connected with prefrontal regions supporting cognitive control. Consistent with the preponderance of cerebellar afferents within the pons, I observe a significant positive correlation between the white matter integrity of the pons and cerebellar gray matter volume associated with higher p factor scores. In Study 3 (Chapter 5), I replicate these occipital and cortico-cerebellar structural alterations in the Dunedin cohort. I also identify smaller gray matter volumes in prefrontal, insular, anterior cingulate, parietal, and limbic regions in the Dunedin Study. In Study 4 (Chapter 6), I demonstrate that liabilities for internalizing, externalizing, and thought disorders overlap with some structural neural correlates of the p factor, but also have unique correlates with brain structure in both samples. Finally, in Study 5 (Chapter 7), I show that polygenic risk for schizophrenia is associated with higher p factor scores, and that this association is partly mediated by cortico-cerebellar circuitry in the DNS, but not the Dunedin, sample.

Overall, these findings provide initial evidence that structural alterations in occipital and cortico-cerebellar circuitry supporting core functions related to the basic integration, coordination, and monitoring of information may contribute to a general liability for mental disorders and are robust to differences in sample characteristics.

Structural deficits in prefrontal, parietal, and limbic regions in Dunedin are consistent with associations between higher p factor scores and impairments in executive function, interoceptive awareness, conflict monitoring as well as somatosensory and emotional processing. Links between genes, brain, and behavior in the DNS suggest that polygenic risk for schizophrenia may confer increased behavioral risk for general psychopathology through its influence on the capacity to communicate and process information between the cerebrum and the cerebellum through the pons. Failure to replicate these latter associations in the Dunedin cohort suggests important future research directions such as examining more specific genetic influences as well as their interactions with early life experiences on brain structure and general risk for psychopathology.

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1. Introduction

Psychiatric diagnostic systems were developed in order to systematically identify and differentiate abnormal mental conditions and to aid in discovering causes, treatment, and prognosis. In fact, the word "diagnosis" itself is from Greek and literally means, "knowing thoroughly" in that diagnoses are supposed to provide us with a full understanding of abnormal conditions. Its full definition includes "the art or act of identifying a disease from its signs and symptoms" and an "investigation or analysis of the cause or nature of a condition, situation, or problem" (Webster-Merriam). Over the years, since Hippocrates' first diagnostic system in 400 BC of the four humors, we have made enormous strides in the development of in-depth systems for diagnosis of mental disorders. However, although our current diagnostic systems often help us to identify signs and symptoms, they do not necessarily provide us with an understanding of the causes or nature of those signs and symptoms.

There may be several reasons for this incomplete understanding. For one, our current diagnostic systems were not designed primarily to answer questions about etiology. Instead, they were designed to provide a guide for determining treatment of mental disorders to be used in clinical practice. This is because we often do not need to understand exactly why and how disorders develop in order to treat them. For example, we believe that selective serotonin reuptake inhibitors (SSRIs) are effective for treating depression because of their ability to increase the amount of serotonin in the synapse by

decreasing the reuptake of serotonin, which affects our mood. Despite our general knowledge of how SSRIs work to alleviate depressive symptoms, we are still working to determine the exact nature and causes of depression. This is also common in medicine where treatment and causality of illness are not always related. For example, aspirin treats headaches, yet we do not fully understand how it works or what causes headaches. Thus, diagnostic systems are mainly designed to identify the signs and symptoms of a given disorder to determine the proper treatment as opposed to being designed for the purposes of gaining a full understanding of a disorder's etiology.

However, it stands to reason that although treatments developed without a thorough understanding of a disorder's etiology may work relatively well, interventions developed with a full understanding of how and why a disorder develops may be better equipped to treat the signs and symptoms more fully, and perhaps, to prevent relapse, recurrence, or even initial onset. This may be one reason why some of our leading psychopharmacological and psychotherapeutic treatments such as SSRIs and cognitive behavioral therapy range in effectiveness from 40-80% on average (e.g., Hofmann, Asnaani, Vonk, Sawyer, & Fang, 2012) or have small effect sizes (e.g., Kirsch, Moore, Scoboria, & Nicholls, 2002). Having a better understanding of the nature of mental disorders not only may improve our intervention approaches, but also aid in the development of more effective prevention programs.

1.1 History of Psychiatric Diagnosis

Although our current diagnostic systems are not geared towards etiology, some of our earliest diagnostic systems actually were framed in an etiologic perspective. For example, Kraepelin's "Compendium der Psychiatre," originally published in 1883 and revised eight times, was the first modern psychiatric classification system that outlined patterns of symptoms observed in patients (Kraepelin, 1923). Kraepelin believed that studying case histories and identifying the signs and symptoms of mental disorders would help to illuminate the biological causes of such conditions.

The first actual diagnostic manual was developed directly following World War I. The census bureau in collaboration with what is now called the American Psychiatric Association (APA) developed a classification system of mental health called the Statistical Manual for the Use of Institutions for the Insane that was primarily used for administrative purposes in mental hospitals. This system included 22 diagnostic categories of mostly severe mental disorders often seen in mental institutions and was based on the Kraepelinian system. This system was highly biologically based because mental health professionals mainly worked with institutionalized patients with severe mental disorders that seemed to have clearer links to biology (Grob, 1991; Kawa & Giordano, 2012). The APA and the New York Academy of Medicine also developed the "Standard Classified Nomenclature of Disease" referred to as the "Standard" in a psychiatric nomenclature subsection of the U.S. Medical Guide for clinical use.

The emphasis on diagnosing and understanding the biological underpinnings of severe mental disorders began to change during World War II. Many soldiers returned from war with symptoms that did not fit within the "Standard's" criteria and needed outpatient as opposed to inpatient services. As a result, the army took it upon itself to develop its own diagnostic system titled, "The War Department Technical Bulletin, Medical 203," in 1943, which included more common, less severe conditions that were thought to be brought on by environmental stressors as opposed to somatic causes (52 diagnoses in total; Stengel, 1959). Overall, the field began taking a more psychosocial approach to the understanding and diagnosis of mental disorders as opposed to a somatic or Kraepelinian approach (Kawa & Giordano, 2012).

Given these multiple diagnostic systems in use simultaneously, there was no one standard language that all mental health professionals could use in diagnosing and treating their patients, creating confusion. Consequently, members of these different organizations came together to develop the first Diagnostic and Statistical Manual (DSM) as a variant of the International Classification of Diseases (ICD)-6 (APA, 1952) and closely adapted from the Medical 203. It included 128 broadly construed diagnostic categories, which were subdivided into conditions that were thought to be due to somatic causes versus life circumstances (Blashfield, Keeley, Flanagan, & Miles, 2014; Kawa & Giordano, 2012). The DSM-I only had limited bearing on psychiatric practice because of its lack of specific inclusion or exclusion criteria and vague descriptions of

symptoms (Kawa & Giordano, 2012). In 1965, the World Health Organization (WHO) published the ICD-8 and a few years later APA published the DSM-II (APA, 1968). One of the bigger changes in DSM-II was the number of diagnoses, which increased to 193 in order to include more common forms of mental disorder (Kawa & Giordano, 2012).

It was not until DSM-III (APA, 1980) that etiology was more or less removed from the development and categorization of diagnoses. Given that there was much debate as to whether mental disorders were caused by biological versus environmental factors, the APA thought it best to take a more neutral stance on the nature and causes of the disorders included in DSM-III. The DSM-III represented an attempt to improve the reliability of the diagnostic categories and to "re-medicalize" American psychiatry by shifting from a focus on psychological states to discrete, operationally defined disease categories. This revision was heralded as a huge step forward for the field of psychiatry and for the treatment of mental disorders (Blashfield et al., 2014). Subsequent revisions to DSM-III represented changes mostly in the number of diagnostic categories, which steadily increased from 253 diagnoses in the DSM-III-R to 383 in DSM-IV and DSM-IV-TR, and to 541 in DSM-5 (Blashfield et al., 2014), but the manual's relatively neutral stance on etiological underpinnings of diagnoses also remained throughout these revisions.

1.2 Classification Challenges for Research

Given the decrease in focus on etiology in the DSM since 1980, psychopathology researchers have identified some challenges to uncovering the nature and causes of mental disorders using DSM-defined diagnostic criteria. These concerns include issues of severity and comorbidity, and are described below.

Diagnostic criteria typically have not taken into account severity of symptoms, which can pose a problem for research. Historically, much of psychopathology research has employed case-control designs in which differences in performance on a given measure are compared between these groups. However, severity becomes problematic in these kinds of study designs because both cases and controls likely vary on the extent to which they experience symptoms of a given disorder. Controls may actually experience some symptoms with greater severity than cases, but they are still considered controls because they do not technically meet criteria for a given disorder (i.e., they may not endorse all the symptoms necessary for a diagnosis or may not exhibit the symptoms for enough days in a row). Hence, the distinction between cases and controls becomes blurred, which could make it difficult to identify predictors or underlying mechanisms associated with the presence of a given disorder. Another issue is that some of the criteria are arbitrarily defined. For example, the main difference between a manic and hypomanic episode is not a difference in symptomatology, but instead a difference in duration of symptoms (seven vs. four days for a manic vs. hypomanic episode; e.g.,

APA, 2013). Thus, any etiological distinction between these two presentations of bipolar disorder may be difficult to identify when participants display the same symptoms but only for varying lengths of time. Furthermore, examining symptoms on a dimensional scale may provide more statistical power for uncovering underlying mechanisms (e.g., Frances, 1993; Widiger, 1992).

Although our main diagnostic systems always have been largely categorical, we have valued dimensional measurement of symptoms for a long time with the advent and continued use of self-report questionnaires such as the Minnesota Multiphasic Personality Inventory (MMPI; Hathaway & McKinley, 1942), the Personality Assessment Inventory (PAI; Morey, 1991, 2007), and the Child Behavior Checklist (CBCL; Achenbach, 1991). In fact, the term "spectrum" is frequently used throughout the DSM to refer to categories of disorders that clearly range in severity in a dimensional fashion, suggesting an awareness of the dimensional nature of categories of disorders. In DSM 5, the most recent revision (APA, 2013), the APA task forces made an effort to incorporate severity and dimensionality into the system in addition to categories. For example, autistic disorder, Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified were grouped as a dimension along the autism spectrum instead of being categorized as distinct entities. Additionally, the DSM 5 now includes a dimensional assessments section to aid in measuring severity. But on the whole, the DSM 5 remains primarily a categorical system, which may be due to the

fact that it is still unclear where to place cutoff points on these dimensions for diagnosis and treatment purposes (although some suggestions have been proposed; see Kamphuis & Noordhof, 2013). However, as mentioned above, measuring disorders dimensionally may have certain benefits for etiologic research as well as for determining treatment strategies that are likely to be shared by mental conditions along the dimension. Moreover, dimensional approaches are particularly advantageous for prevention efforts in that they can identify individuals in need of early intervention before their symptoms worsen and progress to more impairing conditions along the dimension.

Similarly, comorbidity — the co-occurrence of multiple health conditions — is one of the most vexing clinical and etiologic challenges in mental-health practice and research. Comorbidity rates are very high among mental disorders with approximately half of individuals who meet diagnostic criteria for one disorder meeting diagnostic criteria for a second disorder at the same time (e.g., Clark, Watson, & Reynolds, 1995). Clinically, comorbidity is associated with greater severity of impairment and complexity in treatment planning, compliance, and coordination of services (Newman, Moffitt, Caspi, & Silva, 1998). Comorbidity also is an etiologic challenge because it makes it very difficult to find causes, biomarkers, and treatments with specificity to individual disorders. For example, behavioral genetics studies show that many different disorders share a common genetic etiology (Kendler, 1996; Lichtenstein et al., 2009; Pettersson, Larsson, & Lichtenstein, 2016; Sartor et al., 2010), and treatment studies show that

targeting a specific brain chemistry or cognitive process is often as effective in treating one disorder as another (Barlow et al., 2010; Vaswani, Linda, & Ramesh, 2003). This suggests that mental disorders that are categorized as distinct may not truly present as distinct in real individuals.

1.3 Structure of Psychopathology

The high rates of comorbidity observed among mental disorders suggest that there may be a more parsimonious structure to psychopathology than implied by current psychiatric nosologies, such as DSM-5 or ICD-10. In fact, research on the structure of mental disorders and comorbidity indicates that many different disorders may be manifestations of a smaller number of transdiagnostic latent factors (Achenbach & Edelbrock, 1981; Krueger & Markon, 2006; 2011). Factor-analytic studies of multiple symptoms and diagnoses suggest that the structure of mental disorders can be summarized by three such factors: an "internalizing" liability to depression and anxiety disorders, an "externalizing" liability to antisocial and substance-use disorders, and a "thought disorder" liability to schizophrenia, bipolar disorder, and obsessive-compulsive disorder. These observations have led some to argue that studying the mechanisms underlying transdiagnostic latent factors should be the focus of etiological research and applied practice (e.g., Lahey, Krueger, Rathouz, Waldman, & Zald, 2017).

The empirical observation that even these three transdiagnostic latent factors are positively correlated (Wright et al., 2013) has given rise to a more radical hypothesis,

which is that people may differ from each other in a generalized propensity to experience all forms of mental disorders (Lahey et al., 2012). The work that first confirmed this hypothesis reported a single factor in psychopathology data (Lahey et al., 2012), which has been subsequently replicated and labeled the 'p factor' because it is thought to parallel the 'g factor' that emerges in studies of the latent structure of cognitive abilities (Caspi et al., 2014). Although cognitive abilities are dissociable into separate components, such as verbal skills, visuospatial skills, working memory, or processing speed, the 'g factor' summarizes the observation that individuals who do well on one type of cognitive test tend to do well on all other types of cognitive tests (Deary, 2001; Jensen, 1998; Spearman, 1904). Thus, the 'g factor' accounts for the positive correlation among all cognitive test scores, suggesting that there may be a common etiology that influences or contributes in some way to all cognitive abilities. Analogously, the 'p factor' suggests that there may be a general factor of psychopathology that accounts for the positive correlation (or comorbidity) among psychiatric symptoms (and disorders). As the 'g' dimension reflects low-to-high mental ability, the 'p' dimension represents low-to-high liability to develop any mental disorder. Multiple studies in different parts of the world, in different age groups, using different assessment instruments, now have replicated this p factor (e.g., Blanco et al., 2015; Brodbeck et al., 2014; Castellanos-Ryan et al., 2016; Laceulle, Volleberg, & Ormel, 2015; Lahey et al., 2015; Martel et al., 2016; Neumann et al., 2016; Olino, Doughtery,

Bufferd, Carlson, & Klein, 2014; Patalay et al., 2015; Snyder, Young, & Hankin, 2017; Tackett et al., 2013).

Given the challenges of using our current diagnostic system outlined above, investigating the validity and meaning of a general factor of psychopathology has the potential to address some of these challenges to researching underlying etiology of mental disorders. For one, a p factor takes into account comorbidity by capturing the shared variance underlying a wide range of symptoms and disorders. Instead of having to investigate the etiological underpinnings of hundreds of distinct diagnoses that all have a certain degree of overlap, we can focus research efforts to examine the shared and unique variance of mental disorders, and thus, use comorbidity to our advantage. Similarly, a p factor also takes into account severity, given that it is a dimensional measure of low-to-high liability for developing mental disorders. Thus, the p factor has the potential to help us better understand the shared and unique etiologic processes underlying psychopathology, which ultimately has the potential to improve intervention and prevention efforts.

1.4 Current Theories of the Meaning of the p Factor

Although the possibility of a general risk factor for mental disorders that cuts across diagnostic categories is in keeping with new transdiagnostic perspectives on psychopathology (Brown & Barlow, 2009; Cuthbert, 2014; Lahey et al., 2017), it is not yet clear how to interpret the meaning of such a general psychopathology factor. Some

commentators have wondered whether such a general factor is real and meaningful or merely factor-analytic foolery (McNally et al., 2015). Non-substantive theories for the meaning of the p factor have been proposed such as the hypothesis that a general factor of psychopathology may be a measurement artifact reflecting nothing more than a biased response style in which people systematically endorse (or deny) all symptoms (Lahey et al., 2015). It also is possible that the p factor may reflect a singular outcome of having comorbid, persistent mental illness, which is dysfunction and impairment in multiple life domains (Widiger & Oltmanns, 2017). Additionally, an alternative theory is that high correlations among symptoms may be due to causal processes between symptoms as opposed to a latent etiological factor that influences all symptoms (Borsboom & Cramer, 2013). This theory posits that a central causal symptom may lead to other comorbid symptoms as part of a network and that intervening on this central symptom may break up the network of causation instead of treating an underlying, shared root cause (McNally, 2016).

As has been true in studies of the g factor (Deary, Penke, & Johnson, 2010), examining neural and genetic correlates of the p factor may help to clarify the meaning of a general liability for mental disorders. For example, if the high overlap in symptoms accounted for by the p factor is due to one or more of these non-substantive explanations rather than a latent general factor, then meaningful neurobiological correlates are unlikely to exist. In contrast, the presence of neurobiological correlates not only would

suggest that the p factor is measuring meaningful variance, but also would point to possible mechanisms underlying a general liability for mental disorders.

Multiple substantive theories of the potential etiological meaning of the p factor have been proposed (see Caspi & Moffitt, 2018 for a review). For one, the p factor might account for general negative affectivity (Lahey et al., 2017). Neuroticism has been found to predict multiple mental disorders (Kotov et al., 2010) and common genetic influences have been linked to both neuroticism and general psychopathology (Tackett et al., 2013). Whether neuroticism or general negative affect is a cause of mental disorder or a general risk factor for multiple mental disorders is yet to be determined (Ormel et al., 2013). Another hypothesis is that the p factor reflects poor emotion regulation and impulse control (Carver et al., 2017). Longitudinal research has shown that poor childhood emotion regulation and deficits in executive functioning predict general psychopathology (Snyder et al., 2015). Third, poorer general intelligence has been proposed as a mechanism of the p factor. Prior research has shown that individuals scoring high on the p factor show deficits in cognitive abilities such as attention, concentration, mental control, visuospatial processing speed, and visual-motor coordination (Caspi et al., 2014; Castellanos-Ryan et al., 2016; Martel et al., 2016). Childhood IQ also has been shown to predict future general psychopathology (Caspi et al., 2014), suggesting that cognitive deficits may serve as a common vulnerability for the development of multiple mental disorders. Finally, the p factor might be characterized

by disordered or dysfunctional thinking that is present not only in the more severe thought disorders, but also in extreme presentations of internalizing and externalizing disorders as well. This hypothesis posits that general liability for psychopathology exists on a spectrum with severe thought impairments (i.e., psychotic delusions and hallucinations) at the extreme and all other psychiatric disorders residing at different points on the spectrum (Caspi et al., 2014). This suggests that all disorders have the possibility of developing into severe forms of thought disorder and that disordered thinking may be at the root of even the less severe, more common forms of psychopathology such as anxiety, depression, substance dependence, and antisocial behavior. Indeed, irrational, dysfunctional thoughts such as rumination, intrusive thoughts, irrational fears, suicidal and homicidal ideation, etc., are often present in these psychiatric disorders.

1.5 Present Studies

Examining the behavioral, neural, and genetic correlates of the p factor may help to clarify the meaning of a general liability for common mental disorders and provide support for one or more of the etiological hypotheses described above. In the present series of studies, I systematically examine the behavioral, neural, and genetic correlates of the p factor in order to begin to understand the mechanisms underlying this general liability in two independent samples: the Duke Neurogenetics Study (DNS) and the Dunedin Longitudinal Study (Dunedin). The DNS includes a volunteer sample of 1,246

young adult university students aged 18-22. The Dunedin Study includes an entire cohort of 1,007 individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who have been assessed 13 times throughout their lifetime beginning at age 3 to currently at age 45. Because assessments are still ongoing at age 45, neuroimaging data are available in 481 study members for the current research. The Dunedin cohort is much older and includes participants with a greater range of functioning and greater variability in psychiatric symptoms compared to the DNS participants. If the neural and genetic correlates are consistent across these very different samples, we have greater evidence that the neurobiological mechanisms underlying the p factor generalize to a wide range of adults. If these correlates do not replicate across samples, we can begin to understand how the p factor might confer risk for multiple mental disorders in these different groups of people and at different ages.

In Chapter 2, I present the general methods and materials employed in DNS and Dunedin that are common across the five specific studies described herein. For each subsequent chapter, refer to Chapter 2 for detailed methods information. In Chapter 3, I identify a p factor in the DNS sample using confirmatory factor analysis and examine its behavioral correlates including developmental history, personality, current functioning, and intelligence. I use the same procedures to conduct these analyses as those employed in the previously published study in the Dunedin cohort (see Caspi et al., 2014). In Chapter 4, I use multimodal neuroimaging to investigate the structural neural correlates

(i.e., differences in integrity of white matter tracts and gray matter volume) of the p factor in the DNS sample. I opted to focus on brain structure rather than function because it allows me to explore the neural correlates of general psychopathology without having to test specific hypotheses about brain regions of interest, which functional neuroimaging analyses typically require. Based on the results from Chapter 4, in Chapter 5, I use the same multimodal neuroimaging procedures to examine the structural neural correlates of the p factor in the Dunedin cohort in order to determine whether these structural alterations replicate and to identify any additional alterations present in this sample. In Chapter 6, I investigate the structural neural correlates of liabilities for internalizing, externalizing, and thought disorders and identify their common versus unique alterations in both independent samples. In Chapter 7, I investigate the genetic correlates of the p factor and links with brain structure first in the DNS sample, and then in the Dunedin cohort, to determine whether my findings replicate in an independent sample. Finally, in Chapter 8, I provide conclusions and discuss the meaning and implications of this set of studies.

2. General Methods

2.1 Duke Neurogenetics Study

2.1.1 Participants

Data were available from 1,246 undergraduate students (727 women; mean age: 19.69 +/- 1.26) who had successfully completed the Duke Neurogenetics Study. All participants provided informed consent in accordance with Duke University Medical Center Institutional Review Board guidelines prior to participation. All participants were in good general health and free of the following conditions: 1) medical diagnoses of cancer, stroke, head injury with loss of consciousness, untreated migraine headaches, diabetes requiring insulin treatment, chronic kidney or liver disease; 2) use of psychotropic, glucocorticoid, or hypolipidemic medication; and 3) conditions affecting cerebral blood flow and metabolism (e.g., hypertension).

2.1.2 Measurement of psychiatric symptoms

I assessed symptoms from 11 different psychiatric disorders using both the electronic Mini International Neuropsychiatric Interview (e-M.I.N.I.) and self-report questionnaires. The e-M.I.N.I. is a short, structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders (Sheehan et al., 1998). Clinical psychologists, graduate students, and post-baccalaureate research assistants under the supervision of a licensed clinical psychologist conducted these interviews.

From the final sample, 250 (20%) participants met criteria for at least one Axis I or II disorder, including 136 with alcohol use disorders, 48 with non-alcohol substance use disorders, 59 with major depressive disorders, 35 with bipolar disorders, 22 with panic disorder (no agoraphobia), 21 with panic disorder including agoraphobia, 11 with social anxiety disorder, 22 with generalized anxiety disorder, 15 with obsessive compulsive disorder, 11 with eating disorders, 2 with post-traumatic stress disorder, and 132 with at least one comorbid diagnosis.

2.1.2.1 Internalizing symptoms

Anxiety and depressive symptoms were assessed with the 62-item Mood and Anxiety Symptom Questionnaire—Short Form (MASQ-SF), the 20-item State-Trait Anxiety Inventory—Trait (STAI-T), the 20-item Center for Epidemiological Studies on Depression scale (CES-D), and symptom counts of panic disorder, agoraphobia, and social phobia from the e-M.I.N.I. The MASQ-SF is a well-validated measure (Watson et al., 1995) yielding four subscales assessing symptoms experienced within the last seven days specific to Anxious Arousal, General Distress Anxiety, Anhedonic Depression, and General Distress Depression. The STAI-T was used to assess participants' general tendency to perceive situations as threatening and to respond to such situations with subjective feelings of apprehension and tension (Spielberger, Sydeman, Owen, & Marsh, 1999). The CES-D was used to assess depressive symptoms within the past week (Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977).

Using these measures, five scores of anxiety and depressive symptoms were created: 1) a MASQ-SF anxiety score was created by standardizing (z-scoring) and then averaging the Anxious Arousal and General Distress scales; 2) the sum total score on the STAI-T self-report questionnaire was used as a second measure of trait anxiety; 3) a MASQ-SF depression score was created by z-scoring and averaging the Anhedonic Depression and General Distress Depression scales; 4) the sum total score on the CES-D scale was used as a second measure of depression; 5) e-M.I.N.I. symptom counts of social phobia, panic disorder, and agoraphobia were z-scored and then averaged to create a count of fears/phobias symptoms.

2.1.2.2 Externalizing symptoms

Antisocial personality/psychopathy, delinquency, and substance abuse and dependence symptoms were assessed using the 29-item Self Report of Psychopathy—Short Form scale, the 49-item Self Report of Delinquency scale (revised), the 10-item Alcohol Use Disorders Identification Test, the 13-item Recreational Drug Use questionnaire, and symptom counts of cannabis abuse and dependence from the e-M.I.N.I. I did not include nicotine dependence symptoms in the assessment of externalizing disorders given that less than 2% of the DNS sample reported ever smoking cigarettes. The Self Report of Psychopathy scale assesses the Interpersonal, Affective, Lifestyle, and Antisocial factors of psychopathy (Paulhus, Neumann, & Hare, 2014). The Self Report of Delinquency scale assesses the frequency with which

individuals have engaged in aggressive and delinquent behavior, alcohol and drug use, and related offenses (Elliott, Huizinga, & Ageton, 1985). The Alcohol Use Disorders Identification Test assesses the frequency with which participants report hazardous and harmful use of alcohol as well as alcohol dependence (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). The Recreational Drug Use scale assesses the frequency with which participants report using other substances (e.g., cocaine) in their lifetime.

Using these measures, five scores of antisocial personality/psychopathy and substance abuse and dependence symptoms were created: 1) the Self Report of Psychopathy was used to measure antisocial personality and psychopathy symptoms; 2) the Self Report of Delinquency was used to measure delinquent symptoms; 3) alcohol abuse and dependence symptoms were measured using the Alcohol Use Disorders Identification Test total score; 4) cannabis abuse and dependence symptoms were measured using a symptom count from the e-M.I.N.I.; and 5) other substance use and abuse were assessed using the Recreational Drug Use total score.

2.1.2.3 Thought disorder symptoms

Three scores of obsessive-compulsive disorder, mania, and psychosis were created using symptom counts from the e-M.I.N.I. Mania included counts of both manic and hypomanic symptoms.

2.1.3 MRI acquisition and preprocessing

High-resolution diffusion tensor and structural MRI data were acquired using an eight-channel head coil for parallel imaging on one of two identical research-dedicated GE MR750 3T scanners at the Duke-UNC Brain Imaging and Analysis Center. Diffusion tensor imaging (DTI) was used to assess regional fractional anisotropy (FA) correlates as a metric of the structural integrity of white matter pathways and optimized voxel-based morphometry (VBM) was used to assess regional gray matter volume (GMV) correlates of p factor scores. Out of the 1,246 participants included in the study, DTI analyses were available for 951 participants and VBM analyses were available for 1,200 participants with overlapping structural MRI and clinical symptom data surviving stringent, multilevel quality control procedures.

2.1.3.1 Diffusion tensor imaging to assess white matter integrity

Following an ASSET calibration scan, two 2-min 50-s high angular resolution diffusion imaging acquisitions were collected, providing full brain coverage with 2 mm isotropic resolution and 15 diffusion weighted directions (10-s repetition time, 84.9 ms echo time, b value 1,000 s/mm^2, 240 mm field of view, 90° flip angle, 128 x 128 acquisition matrix, slice thickness 2 mm). DTI analyses were completed using SPM8 implemented in Matlab v7.11.0 (R2010b). All diffusion weighted scans were realigned to the first scan with a b value of 0 to correct for head movement. The two DTI sequences were used in the tensor model to calculate FA values for each voxel and nonbrain tissue

was removed. Each image was normalized to Montreal Neurological Institute (MNI) space by affine registration to the FMRIB58_FA template, taken from FMRIB's Software Library (Smith et al., 2004). After normalization, each image was smoothed using 4-mm FWHM Gaussian kernel. A white matter mask for subsequent analyses was created by thresholding the final stage (6th) IXI template at 0.1.

2.1.3.2 Voxel-based morphometry to assess gray matter volume

T1-weighted images were obtained using a 3D Ax FSPGR BRAVO with the following parameters: TR = 8.148 s; TE = 3.22 ms; 162 sagittal slices; flip angle, 12°; FOV, 240 mm; matrix =256 × 256; slice thickness = 1 mm with no gap; and total scan time = 4 min and 13 s. Regional gray matter volumes were determined using the unified segmentation (Ashburner & Friston, 2005) and DARTEL normalization (Ashburner, 2007) modules in SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Using this approach, individual T1-weighted images were segmented into gray, white, and CSF images, then non-linearly registered to the existing IXI template of 550 healthy subjects averaged in MNI space, available with VBM8 (http://dbm.neuro.uni-jena.de/vbm/). Subsequently, gray matter images were modulated for nonlinear effects of the high-dimensional normalization to preserve the total amount of signal from each region and smoothed with an 8mm FWHM Gaussian kernel. The voxel size of processed images was 1.5 × 1.5 × 1.5 mm. A gray matter mask for subsequent analyses was created by thresholding the final stage (6th) IXI template at 0.1.

2.1.3.3 Spatially Unbiased Atlas Template of the cerebellum and brainstem

The Spatially Unbiased Infratentorial (SUIT) toolbox was used for cerebellar VBM analyses (version 3.0, http://www.icn.ucl.ac.uk/motorcontrol/imaging/suit.htm) (Diedrichsen et al., 2009). For each participant, the Isolate function of the toolbox was used to create a mask of the cerebellum and generate gray and white matter segmentation maps. The masked segmentation maps then were normalized to the SUIT template with non-linear DARTEL normalization. The resulting cerebellar gray matter image was resliced into the SUIT atlas space and smoothed with a 4mm FWHM isotropic Gaussian kernel, a small kernel to preserve precision in the definition of cerebellar structures, in line with previous publications (D'Agata et al., 2011b). All images were visually inspected for quality.

2.1.3.4 Statistical thresholds for neuroimaging analyses

Significance thresholds for the DTI, VBM, and SUIT analyses were set using an overall false detection probability based on 10,000 Monte Carlo simulations. Simulations determined that a cluster size of 132, 567, and 63 contiguous voxels was needed to achieve a threshold of $p < .005$, with an overall family-wise error rate of $\alpha < .05$ for the DTI, VBM, and SUIT analyses, respectively.

2.2 Dunedin Longitudinal Study

2.2.1 Participants

Participants are members of the Dunedin Multidisciplinary Health and Development Study, a longitudinal investigation of health and behavior in a complete birth cohort. Study members (n = 1,037; 91% of eligible births; 52% male, 48% female) were all individuals born between April 1972 and March 1973 in Dunedin, New Zealand, who were eligible for the longitudinal study based on residence in the province at age 3 and who participated in the first follow-up assessment at age 3. The cohort represents the full range of socioeconomic status in the general population of New Zealand's South Island and is primarily White. Assessments were carried out at ages 3, 5, 7, 9, 11, 13, 15, 18, 21, 26, 32, and 38 years when 95% of the 1,007 study members still alive were assessed. Assessments are currently being carried out at age 45 during which 481 study members (219 women) have participated thus far. At each assessment wave, study members (including emigrants and prisoners) are brought to the Dunedin Multidisciplinary Health and Development Research Unit for a full day of interviews and examinations. These data are supplemented by searches of official records and by questionnaires that are mailed, as developmentally appropriate, to parents, teachers, and informants nominated by the study members themselves. The University of Otago Ethics Committee approved each phase of the study.

2.2.2 Measurement of psychiatric symptoms

Detailed descriptions of the measurement of psychiatric symptoms are provided in Caspi et al. (2014). The Dunedin Study longitudinally ascertains mental disorders using a strategy akin to experience sampling: every 2 to 6 years, participants are interviewed about past year symptoms. Past-year reports maximize reliability and validity because recall of symptoms over longer periods has been shown to be inaccurate. Symptom counts for the examined disorders were assessed via private structured interviews using the Diagnostic Interview Schedule (Robins, Cottler, Bucholz, & Compton, 1995) at ages 18, 21, 26, 32, and 38. Interviewers are health professionals, not lay interviewers. DSM-defined symptoms of the following disorders that were repeatedly assessed in the longitudinal study were studied: alcohol dependence, cannabis dependence, dependence on hard drugs, tobacco dependence (assessed with the Fagerström Test for Nicotine Dependence; Heatherton, Kozlowski, Frecker, & Fagerström, 1991), conduct disorder, major depressive episode, generalized anxiety disorder, fears/phobias, obsessive-compulsive disorder, mania, and positive and negative schizophrenia symptoms. Ordinal measures represented the number of the 7 (e.g., mania and generalized anxiety disorder) to 10 (e.g., alcohol dependence and cannabis dependence) observed DSM-defined symptoms associated with each disorder. Fears/phobias were assessed as the count of diagnoses for simple phobia, social phobia, agoraphobia, and panic disorder that a study member reported at each assessment.

Symptoms were assessed without regard for hierarchical exclusionary rules to facilitate the examination of comorbidity. Of the 11 disorders, 4 were not assessed at every occasion, but each disorder was measured at least three times.

Past-year prevalence rates of psychiatric disorders in the Dunedin cohort are similar to prevalence rates in nationwide surveys of the United States and New Zealand (Moffitt et al., 2010). Of the original 1,037 study members, 1,000 study members who had symptom count assessments for at least one age were included (871 study members had present symptom counts for all five assessment ages, 955 for four, 974 for three, and 989 for two). The 37 excluded study members comprised those who died or left the study before age 18 or who had such severe developmental disabilities that they could not be interviewed with the Diagnostic Interview Schedule.

2.2.3 Confirmatory factor analyses

More detailed descriptions of the procedures used to examine the structure of psychopathology in Dunedin are described in Caspi et al. (2014). Confirmatory factor analysis was used to fit three standard models: correlated factors, bi-factor, and one-factor models (Brunner, Nagy, & Wilhelm, 2012; Rindskopf & Rose, 1988). All confirmatory factor analyses were performed in Mplus (Muthén & Muthén, 1998-2013) using the weighted least squares means and variance adjusted (WLSMV) algorithm. The WLSMV estimator is appropriate for categorical and nonmultivariate normal data and provides consistent estimates when data are missing at random with respect to

covariates (Asparouhov & Muthén, 2010). Model fit was assessed using the chi-square value, the comparative fit index (CFI), the Tucker-Lewis index (TLI), and the root-mean square error of approximation (RMSEA). Nonsignificant chi-square tests indicate good model fit; nonetheless, this test is generally overpowered in large sample sizes. CFI and TLI values greater than .90 indicate adequate fit; RMSEA scores less than .08 are considered acceptable (Bollen, & Curran, 2006). Factor scores from the correlated factors and bi-factor models were extracted using the standard regression method and were used in subsequent neuroimaging analyses. Factor scores were standardized to a mean of 100 (*SD* = 15), with higher scores indicating a greater propensity to experience all forms of psychiatric symptoms (see Appendix A for distributions).

2.2.4 MRI acquisition and preprocessing

Each study member was scanned using a Siemens Skyra 3T scanner equipped with a 64-channel head/neck coil at the Pacific Radiology imaging center in Dunedin, New Zealand. DTI was used to assess regional FA correlates as a metric of the structural integrity of white matter pathways and optimized VBM was used to assess regional GMV correlates of p factor scores. Out of the 481 study members at age 45 included in the study, DTI analyses were available for 414 participants and VBM were available for 459 participants with overlapping structural MRI and clinical symptom data surviving stringent, multilevel quality control procedures.

2.2.4.1 Diffusion tensor imaging to assess white matter integrity

Diffusion-weighted images providing full brain coverage were acquired with 2.5 mm isotropic resolution and 64 diffusion weighted directions (4700 ms repetition time, 110.0 ms echo time, b value 3,000 s/mm2, 240 mm field of view, 96×96 acquisition matrix, slice thickness = 2.5 mm). Non-weighted (b = 0) images were acquired in both the encoding (AP) and reverse encoding (PA) directions to allow for EPI distortion correction. Diffusion images were processed in FSL (http://fsl.fmrib.ox.ac.uk/fsl). Raw diffusion-weighted images were corrected for susceptibility artifacts, subject movement, and eddy currents using topup and eddy. Images were then skull-stripped and fitted with diffusion tensor models at each voxel using FMRIB's Diffusion Toolbox (FDT; http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDT). The resulting FA images from all subjects were non-linearly registered to the FA template developed by the Enhancing Neuro Imaging Genetics Through Meta-Analysis consortium (ENIGMA), a minimal deformation target calculated across a large number of individuals (Jahanshad et al., 2013).

2.2.4.2 Voxel-based morphometry and SUIT to assess gray matter volume

High resolution structural images were obtained using a T1-weighted MP-RAGE sequence with the following parameters: TR = 2400 ms; TE = 1.98 ms; 208 sagittal slices; flip angle, 9°; FOV, 224 mm; matrix = 256×256; slice thickness = 0.9 mm with no gap (voxel size 0.9×0.875×0.875 mm); and total scan time = 6 min and 52 s. Regional gray matter volumes were determined using the unified segmentation (Ashburner & Friston,

2005) and DARTEL normalization (Ashburner, 2007) modules in SPM12 (http://www.fil.ion.ucl.ac.uk/spm). Using this approach, individual T1-weighted images were segmented into gray, white, and CSF images, and then non-linearly registered to the existing IXI template of 550 healthy subjects averaged in standard Montreal Neurological Institute (MNI) space, available with VBM8 (http://dbm.neuro.uni-jena.de/vbm/). Subsequently, gray matter images were modulated for nonlinear effects of the high-dimensional normalization to preserve the total amount of signal from each region, and smoothed with an 8mm FWHM Gaussian kernel. The voxel size of processed images was 1.5×1.5×1.5 mm. A gray matter mask for subsequent analyses was created by thresholding the final stage (6th) IXI template at 0.1. The SUIT toolbox also was used for cerebellar VBM analyses (see subsection 2.1.3.3 for more details).

2.2.4.3 Significance thresholds for neuroimaging analyses

Significance thresholds for the DTI, VBM, and SUIT analyses were set using an overall false detection probability based on 10,000 Monte Carlo simulations. Simulations determined that a cluster size of 917, 803, and 55 contiguous voxels were needed to achieve a threshold of $p < .005$, with an overall family-wise error rate of $\alpha < .05$ for the DTI, VBM, and SUIT analyses, respectively.

3. Replication of the p Factor in High-Functioning Young Adults and Links with Developmental History, Personality, Current Functioning, and Intelligence[1]

3.1 Background

Prior research has employed confirmatory factor analyses to identify a latent general psychopathology factor in a variety of samples, using a range of assessment methods, at different ages throughout the lifespan (see Lahey et al., 2017 for a review). These studies compare the fit of three models of the structure of psychopathology: a correlated factor, bi-factor, and one-factor model. The correlated factors model tests the hypothesis that symptoms load onto three distinct latent factors, internalizing, externalizing, and thought disorders, and these factors are allowed to correlate. The bi-factor model tests the hypothesis that symptoms load onto one general factor accounting for shared variance common to all symptoms (i.e., the p factor) and three specific factors accounting for shared variance unique to internalizing, externalizing, and thought disorder symptoms. The one-factor model tests the hypothesis that the majority of the shared variance among symptoms is common to the p factor as opposed to specific to internalizing, externalizing, and thought disorder factors. If a one-factor model fits the data better than a bi-factor model, this would suggest that the p factor completely

[1]Parts of this Chapter are based on the following publication: Romer A. L., Knodt, A. R., Houts, R., Brigidi, B. D., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2018). Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. *Molecular Psychiatry, 23*, 1084-1090.

accounts for symptom covariation without specific internalizing, externalizing, and thought disorder factors.

In this chapter, I examine the structure of psychopathology in the DNS sample using confirmatory factor analysis. I determine whether the p factor will replicate in this high-functioning young adult sample by comparing the model fit of three structural models: correlated factors, bi-factor, and one-factor models. Based on the results of Caspi et al. (2014) in the Dunedin cohort, I hypothesize that the bi-factor model will fit the data best, thus replicating the presence of the p factor in the DNS. I then examine relationships among the p, internalizing, externalizing, and thought disorder factors to determine their interrelationships. Finally, I examine the associations between these disorder-liability factors and measures of developmental history, personality, current functioning, and intelligence. I hypothesize that the p factor will be related to a broad range of dysfunctional behaviors in this sample.

3.2 Methods

Data were available from 1,246 undergraduate students (727 women; mean age: 19.69 +/- 1.26) who had successfully completed the DNS. Using the e-M.I.N.I. and self-report questionnaires, internalizing symptoms including anxiety, depression, and fears/phobias, externalizing symptoms including antisocial personality/psychopathy, delinquency, and substance abuse and dependence, and thought disorder symptoms

including obsessive-compulsive disorder (OCD), mania, and psychosis were assessed (see **Chapter 2** for details).

3.2.1 Measures of behavioral functioning

Table 1 provides descriptive statistics on all the behavioral variables included in subsequent analyses.

Table 1: Descriptive statistics for all measures.

Measures	N	Min	Max	Mean	Std. Dev.
Developmental History					
Parental Education	1217	1	10	7.584	1.947
Perceived Socioeconomic Status	1218	1.33	11	7.458	1.256
Family History of Internalizing Disorders	1218	0	18	3.676	3.562
Family History of Externalizing Disorders	1218	0	16	2.688	3.255
Family History of Thought Disorders	1218	0	16	1.101	1.991
Childhood Trauma	1217	25	76	33.649	8.796
Personality					
Neuroticism	1217	25	169	86.115	22.808
Extraversion	1217	44	174	119.991	20.633
Openness	1217	57	176	123.990	18.395
Agreeableness	1217	48	171	116.775	19.077
Conscientiousness	1217	22	178	118.608	21.224
Impulsivity	1218	37	113	61.805	9.635
Anger	1218	10	40	16.068	4.628
Aggression	1218	30	139	60.539	17.758
Current Functioning					
Current Stress	1217	0	22	4.416	3.179
Reappraisal	1218	1	7	5.174	.891
Suppression	1218	1	7	3.796	1.152
Sleep Problems	1218	0	17	4.969	2.609
Intelligence					
g Score	948	-3.483	3.459	-.008	.994

3.2.1.1 Developmental history

Items from the Social Demographic Questionnaire and Family History (DEMO) were used to assess family history of internalizing (major depression and anxiety),

externalizing (antisocial personality disorder and substance dependence), and thought disorder symptoms (OCD, bipolar disorder, and psychosis) as well as parental education level and perceived socioeconomic status. Participants responded "yes" or "no" to questions about the symptoms present in their biological family (i.e., "Has anyone in your family ever felt sad, blue, or depressed for most of the time for two weeks or more?"). Symptom counts for internalizing, externalizing, and thought disorders were created. Using the DEMO, I also assessed biological, step-, or guardian mother's and father's highest education level before participants turned 18 years old, on a scale from 1, "No high school," to 10, "MD/PhD/JD/PharmD." I averaged participants' mother's and father's education level to create one measure of parental education level. Perceived socioeconomic status was assessed using the DEMO, which asks participants to place themselves and their biological parents on a ladder in which "the people who are best off (most money, education, and most respected jobs) are at the top, while the people who are the worst off (least money, education, and least respected jobs) are at the bottom". Participants are then asked to indicate where they would place themselves and their biological parents compared to others from their country of origin. Participants' responses for themselves and their biological parents were averaged to create a score of perceived socioeconomic status. I assessed history of childhood trauma using a sum of the 28 items from the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), which had adequate internal consistency (α = .685).

3.2.1.2 Personality

The 240-item Neuroticism Extraversion Openness-Personality Inventory Revised (NEO-PI-R; Costa, & McCrae, 1992) was used to assess neuroticism, extraversion, openness, agreeableness, and conscientiousness (α's ranged from .702 to .850). The sum of the 30 items from the Barratt Impulsiveness Scale (Patton, Stanford, & Barratt, 1995) was used to assess non-planning, motor, and cognitive forms of impulsivity (α = .834). The sum of the 10 items from the State-Trait Anger Expression Inventory-Trait Only (STAXI-T; Spielberger, 1988) was used as a measure of trait anger (α = .863). The sum of the 29 items of the Buss Perry Aggression Questionnaire (BPAQ; Buss & Perry, 1992) was used to assess aggressive behavior (α = .920).

3.2.1.3 Current functioning

Measures of current stress, coping, and sleep were used to assess level of current functioning. The sum of the 46 items from the Life Events Scale for Students (LESS; Clements & Turpin, 1996) was used to measure the number of stressful life events within the past year (α = .688). Emotional reappraisal (α = .863) and suppression (α = .769) subscales from the 10-item Emotion Regulation Questionnaire (ERQ; Gross & John, 2003) were used as measures of emotional coping strategies. A sum of the 22 items from the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) was used to assess problems with sleep, with higher scores indicating poorer quality sleep (α = .730).

3.2.1.4 Intelligence

All participants were administered a neuropsychological battery from which the following cognitive measures were utilized to derive a "*g*" score based on Dickinson et al. (2014): 1) California Verbal Learning Test (CVLT-II) Trials 1–5 total, 2) Symbol Digit Modalities Test (SDMT), 3) Trail Making Test, 4) Digit Span, 5) Verbal Fluency, and 6) Wechsler Abbreviated Scale of Intelligence (WASI) subscales of Vocabulary, and Matrix Reasoning. Summary performance scores from each measure were converted to z-scores. These standardized scores were entered into a principal components analysis (PCA) and the first principal component was used as the index of "*g*" (Ree & Earles, 1991; Spearman, 1904).

3.2.2 Statistical analyses

Analyses were conducted in the following steps using the same procedures as Caspi et al. (2014). First, I examined bivariate correlations between the 11 different psychiatric symptom scores. Second, I used confirmatory factor analysis to fit three standard models: correlated factors, bi-factor, and one-factor models (Brunner et al., 2012; Rindskopf & Rose, 1988). All confirmatory factor analyses were performed in Mplus version 7.4 (Muthén & Muthén, 1998-2013) using the weighted least squares means and variance adjusted (WLSMV) algorithm. The WLSMV estimator is appropriate for categorical and nonmultivariate normal data and provides consistent estimates when data are missing at random with respect to covariates (Asparouhov &

Muthén, 2010). I assessed how well each model fit the data using the chi-square value, the CFI, TLI, and RMSEA. Nonsignificant chi-square tests indicate good model fit; nonetheless, this test is generally overpowered in large sample sizes. CFI and TLI values greater than .90 indicate adequate fit; RMSEA scores less than .08 are considered acceptable (Bollen & Curran, 2006). Third, I extracted factor scores from these models using the standard regression method for examining associations with each other and measures of developmental history, personality, current functioning, and intelligence. I standardized the factor scores to a mean of 100 (*SD* = 15), with higher scores indicating a greater propensity to experience psychiatric symptoms.

3.3 Results

3.3.1 Correlations among psychiatric symptoms

As in previous studies, I observed that correlations between different psychiatric symptoms were positive, with a few exceptions. This result indicates that individuals who experienced one set of symptoms (e.g., depression) also were likely to experience other sets of symptoms (e.g., anxiety, alcohol abuse, etc.; see Table 2).

Table 2: Inter-correlations among individual psychiatric symptoms.

	1	2	3	4	5	6	7	8	9	10	11	12	13
(1) Psychosis	1												
(2) Mania	.072	1											
(3) OCD	**.262**	**.490**	1										
(4) Fears	**.154**	**.293**	**.431**	1									
(5) MASQ Depression	**.147**	**.219**	**.199**	**.266**	1								
(6) CES-D	.114	**.256**	**.225**	**.244**	**.842**	1							
(7) MASQ Anxiety	**.129**	**.172**	**.183**	**.240**	**.565**	**.609**	1						
(8) STAI	.075	**.258**	**.250**	**.330**	**.770**	**.727**	**.530**	1					
(9) Psychopathy	**.193**	**.286**	.058	.014	**.193**	**.235**	**.267**	**.209**	1				
(10) Delinquency	.019	**.239**	**.117**	.033	**.135**	**.194**	**.245**	**.130**	**.531**	1			
(11) Cannabis	**.158**	**.408**	**.242**	**.201**	**.137**	**.142**	**.143**	**.202**	**.368**	**.381**	1		
(12) Alcohol	.073	**.149**	-.036	-.006	.033	.055	**.155**	.037	**.373**	**.585**	**.452**	1	
(13) Drug Use	.038	**.240**	.061	-.008	.035	.030	.062	.047	**.357**	**.590**	**.714**	**.566**	1

Correlations with $p < .01$ are shown in bold. OCD = obsessive-compulsive disorder; MASQ = Mood and Anxiety Symptom Questionnaire; CES-D = Center for Epidemiological Studies – Depressive Scale; STAI = State-Trait Anxiety Inventory – Trait Scale.

3.3.2 Structure of psychopathology

Table 3 shows all three models (correlated factors, bi-factor, and one-factor) with standardized factor loadings and the correlations between the three specific factors.

Table 3: Model fit statistics, standardized factor loadings, and factor correlations from three confirmatory factor models.

	Correlated Factors Model				Bi-factor Model				One-Factor Model	
Statistics, Loadings, and Correlations	**Model Fit**	**THT**	**INT**	**EXT**	**Model Fit**	**p**	**INT**	**EXT**	**Model Fit**	**p**
Statistic										
Chi-Square (WLSMV)	620.813				385.084				2696.079	
Df	62				55				65	
CFI	.903				.943				.544	
TLI	.878				.919				.452	
RMSEA [90% CI]	.085 [.079, .091				.069 [.063, .076]				.180 [.174, .186]	
Standardized Factor Loadings										
Psychosis		.338				.307				.197
Mania		.786				.625				.434
OCD		.595				.499				.325
Fears			.343			.303	.193			.299
MASQ Depression			.859			.358	.858			.553
CES-D			.892			.443	.790			.548
MASQ Anxiety			.701			.517	.457			.512
STAI			.811			.406	.715			.521
Psychopath				.640		.491		.410		.535
Delinquent				.782		.404		.644		.719
Cannabis				.569		.300		.498		.566
Alcohol				.703		.206		.718		.563
Drug Use				.749		.150		.822		.664
Factor Correlations										
INT		.652				.356				
EXT		.556	.249			.236	-.125			

THT = Thought Disorders Factor; INT = Internalizing Disorders Factor; EXT = Externalizing Disorders Factor; CFI = Comparative Fit Index; TLI = Tucker Lewis Index; RMSEA = Root Mean Square Error of Approximation; CI = Confidence Interval.

3.3.2.1 Correlated factors model

Using this model, I tested the hypothesis that there are latent trait factors, each of which influences a subset of the diagnostic symptoms. In this case, I tested three factors representing externalizing (with loadings from alcohol, cannabis, other drugs, and antisocial personality disorder/psychopathy, and delinquency), internalizing (with loadings from MASQ depression, CES-D, MASQ anxiety, STAI-T, and fears/phobias), and thought disorder (with loadings from OCD, mania, and psychosis). This model allows the externalizing, internalizing, and thought disorder factors to be correlated.

I found that the model provided a moderately adequate fit to the data: $\chi^2(62, n = 1{,}246) = 620.813$, $p < .001$, CFI = .903, TLI = .878, RMSEA =.085, 90% confidence interval (CI) = [.079, .091]. Loadings on the three factors were all positive and statistically significant (all $p < .001$). Correlations between the three factors were all positive and ranged from .249 between internalizing and externalizing to .652 between internalizing and thought disorder.

3.3.2.2 Bi-factor model

Using this model, I tested the hypothesis that the symptom measures reflect both the general p factor and three specific forms of psychopathology that are orthogonal to the p factor. For example, depression symptoms loaded on both the p factor and on the

internalizing factor. The specific factors represented the constructs of externalizing, internalizing, and thought disorder.

This model had a Heywood case, an estimated variance that was negative for one of the lower-order symptom factors (specifically, fears/phobias), suggesting this was not a valid model. Inspection of the results revealed the source of the convergence problem. The model was respecified to be consistent with Caspi et al. (2014) in which thought disorders were subsumed in the general p factor. In this model, the p factor served as a general factor and internalizing and externalizing factors served as additional unique sources of variation apart from the p factor. This revised model fit the data well: χ^2 (55, n = 1,246) = 385.084, $p < .001$, CFI = .943, TLI = .919, RMSEA = .069, 90% CI [.063, .076]. Loadings on the p factor were all positive and statistically significant (all $p < .05$). The highest standardized loadings were for mania (.625) and MASQ anxiety (.517). Similarly, the loadings for the two specific factors were all positive and statistically significant (all $p < .001$).

3.3.2.3 One factor model

Using this model, I tested whether the specific factors are needed in a simple structural model that assigned each diagnostic symptom only to the p factor. Loadings on the p factor were all positive and statistically significant (all $p < .001$). However, this

model did not fit the data well: $\chi^2(65, n = 1,246) = 2696.079$, $p < .001$, CFI = .544, TLI = .452, RMSEA = .180, 90% CI [.174, .186].

3.3.3 Factor correlations

Factor scores were extracted for subsequent analyses (see Appendix A for distributions of factor scores) using the standard regression method in Mplus. After extracting factor scores from the correlated factors and bi-factor models, their inter-correlations were calculated. Table 4 shows that p factor scores are most highly correlated with thought disorders ($r = .845$) and least highly correlated with externalizing disorders ($r = .585$). As expected, internalizing and externalizing factor scores from the bi-factor model are highly related to internalizing and externalizing factor scores from the correlated factors model, respectively. Internalizing factor scores from the bi-factor model are unrelated to externalizing factor scores from the correlated factors model and vice versa.

Table 4: Factor correlations between the correlated factors model and the bi-factor model.

	Bi-factor Model		
Correlated Factors Model	Externalizing	Internalizing	p
Externalizing	.921	.035	.585
Internalizing	-.010	.928	.671
Thought Disorders	.293	.420	.845

In addition to the correlations between the bi-factor and correlated factors models, Table 3 shows correlations among factors within the bi-factor model (p and internalizing: r = .356; p and externalizing: r = .236). These correlations are particularly high given that the bi-factor model specifies these factors to be orthogonal, which is likely due to factor indeterminancy when estimating factor scores (Grice, 2001). Thus, from now on, I will focus my analyses on the p factor from the bi-factor model, and the three factors, internalizing, externalizing, and thought disorders from the correlated factor model.

3.3.4 Behavioral correlates of disorder liability

Table 5 displays associations between disorder-liability factor scores from the bi-factor and correlated factors models with measures of developmental history, personality, current functioning, and intelligence. The p factor score is significantly related to a broad range of these behavioral correlates. In terms of developmental history, individuals with high p factor scores reported that they came from lower socioeconomic backgrounds, had greater family history of internalizing, externalizing, and thought disorders, and greater histories of childhood trauma. There was no association between p factor scores and parental education level, which serves as a proxy for socioeconomic status. In terms of personality, individuals with high p factor scores reported high levels of neuroticism and low levels of extraversion, agreeableness,

and conscientiousness, as well as higher levels of impulsivity, anger expression, and aggression. In terms of current functioning, individuals with high p factor scores reported greater frequency of current stressful life events, less use of reappraisal and greater use of suppression coping, and poorer sleep quality. In terms of intelligence, interestingly, the p and g factors are only slightly related to one another, suggesting that these two constructs are not highly overlapping. Similar to associations with the p factor, the internalizing, externalizing, and thought disorder factors from the correlated factors model are also related to these broad behavioral dysfunctions.

3.4 Discussion

Results indicated that a bi-factor model that includes one general factor accounting for shared variance common to all symptoms and two specific factors accounting for shared variance unique to internalizing and externalizing symptoms fit the data well. The general factor replicated the presence of a shared liability for mental illness in the DNS sample. This alone is important as it further suggests that the p factor is relatively robust to different samples and measures of psychiatric symptoms. Furthermore, these results suggest that a general factor of psychopathology is present in a high-functioning student population and maps onto a broad range of dysfunctional behaviors, underscoring its potential value for identifying at-risk individuals.

Table 5: Correlations between disorder-liability factor scores and developmental history, personality, current functioning, and intelligence.

	Correlated Factors Model			Bi-Factor Model
Measures	**INT**	**EXT**	**THT**	**p**
Developmental History				
Parental Education	-.016	.043	-.017	-.025
Perceived Socioeconomic Status	-.176***	.069*	-.117***	-.114***
Family History of INT	.325***	.215***	.337***	.346***
Family History of EXT	.183***	.258***	.266***	.274***
Family History of THT	.217***	.200***	.295***	.329***
Childhood Trauma	.456***	.199***	.365***	.444***
Personality				
Neuroticism	.722***	.178***	.477***	.487***
Extraversion	-.318***	.119***	-.087**	-.076**
Openness	-.028	.104***	.088**	.053
Agreeableness	-.201***	-.371***	-.271***	-.384***
Conscientiousness	-.403***	-.346***	-.386***	-.362***
Impulsivity	.426***	.414***	.447***	.502***
Anger	.430***	.320***	.408***	.533***
Aggression	.465***	.409***	.456***	.605***
Current Functioning				
Current Stressful Life Events	.278***	.288***	.327***	.375***
Reappraisal	-.234***	-.088**	-.126***	-.088**
Suppression	.245***	.070*	.166***	.190***
Sleep Problems	.530***	.298***	.428***	.468***
Intelligence				
g score	-.135***	-.012	-.074*	-.098**

* $p < .05$, ** $p < .01$, *** $p < .001$. INT = Internalizing Disorders Factor; EXT = Externalizing Disorders Factor; THT = Thought Disorders Factor.

In particular, I find that p factor scores are related to worse perceived socioeconomic status, greater family history of mental illness, higher neuroticism and lower extraversion, agreeableness and conscientiousness, greater impulsivity, anger, and aggressive behaviors, greater history of childhood trauma, current stress, less use of adaptive emotion regulation strategies, poorer sleep quality, and lower intelligence. Consistent with the p factor accounting for shared variance among internalizing, externalizing, and thought disorder factors, these three factors each were associated with these same behavioral correlates. The only exceptions to this were that liability for externalizing disorders was associated with greater perceived socioeconomic status and was unrelated to general intelligence. Many of these findings replicate those found in other studies as described below.

3.4.1 Developmental history

In terms of family mental illness, previous research found that individuals with high p factor scores had greater family history of major depression, anxiety, conduct disorder/antisocial personality disorder, substance dependence, and psychosis (Caspi et al., 2014; Lahey et al., 2012). Previous studies also have found that individuals who score high on the p factor have experienced greater histories of childhood maltreatment (Caspi et al., 2014; Lahey et al., 2012). In terms of socioeconomic status, previous studies have found that individuals with high p factor scores come from lower socioeconomic

backgrounds and more deprived neighborhoods (Caspi et al., 2014; Patalay et al., 2015). Interestingly, in the current study, I found that individuals who scored high on the p factor believed they came from lower socioeconomic backgrounds compared to others in the country; however, there was no association between p factor scores and parental education level as a proxy for socioeconomic status. This finding suggests that in the DNS sample, individuals with high p factor scores had socioeconomic backgrounds equivalent to those with lower p factor scores, but believed that they were more socioeconomically disadvantaged than others. The lack of association between p factor scores and parental education level as a proxy for socioeconomic status may be due to the restricted range of parental education level for participants who attend an elite university. In fact, individuals scoring high on externalizing showed associations with higher perceived socioeconomic status.

3.4.2 Personality

In general, prior research has shown that individuals with high p factor scores demonstrate a personality profile of high negative affect and low agreeableness/prosociality and effortful control/conscientiousness (Caspi et al., 2014; Olino et al., 2014; Tackett et al., 2013), which is consistent with the current study findings of high neuroticism, low extraversion, agreeableness, and conscientiousness as associated with p factor scores. The current study also found that individuals with high

p factor scores reported higher levels of impulsivity, anger expression, and aggression. In fact, out of all of these measures, p factor scores were most strongly related to these personality traits. Individuals who are highly impulsive, angry, and aggressive will likely experience problems interacting with others and show difficulty functioning in society, which may be consistent with prior research showing that individuals scoring high on the p factor have more incarcerations and violence convictions (Caspi et al., 2014; Lahey et al., 2012).

3.4.3 Current functioning

Previous research has shown that p factor scores are associated with greater life impairment in terms of suicide attempts, reliance on social-welfare benefits, lower personal income, psychiatric hospitalizations, and problems with the law (Caspi et al., 2014; Lahey et al., 2012). Although I did not have measures of these forms of life impairment, I was able to show that individuals with high p factor scores have had more stressful life events in the past year, greater problems with sleep, and less use of adaptive emotion regulation strategies. Not surprisingly, poor sleep quality has been associated with a wide range of mental health problems (Ford & Kamerow, 1989; Baglioni et al., 2016; Benca, Obermeyer, Thisted, & Gillin, 1992). In terms of emotion regulation coping strategies, individuals with high p factor scores reported using more cognitive suppression and less reappraisal. Cognitive reappraisal is the process of

changing the interpretation of negative emotions or experiences in an attempt to be more neutral or objective; whereas, expressive suppression involves inhibiting one's negative emotional response (Gross & John, 2003). Use of cognitive reappraisal has been linked to greater experience and expression of positive emotions and lesser negative emotions and better interpersonal functioning; whereas, use of suppression is related to the opposite (Gross & John, 2003). Thus, in the current study, individuals with greater general psychopathology tended to use suppression as opposed to reappraisal to cope with negative emotions, suggesting poorer ability to regulate emotions in everyday life.

3.4.4 Intelligence

In the current study, the g factor accounts for the shared variance among cognitive tests of declarative memory, processing speed, visuospatial skills, working memory, verbal fluency, and IQ. I found that the g factor of intelligence was negatively related to the p factor of psychopathology, suggesting that individuals with greater general liability for psychopathology possess lower intelligence and executive functioning abilities. However, this g-p factor association is one of the weakest associations obtained, suggesting that the p and g factors are largely non-overlapping constructs. Prior research also has shown negative associations (with relatively small effect sizes) with IQ, executive functioning, and memory (Caspi et al., 2014; Lahey et al., 2015; Neumann et al., 2016).

In sum, the current study results add to the growing body of literature identifying and replicating a general psychopathology factor in a range of samples across the world. In addition to the other studies investigating a general psychopathology factor, these results continue to provide validity for the p factor as a meaningful measure of general liability for mental illness and demonstrate the vast behavioral impairments present in individuals with severe, comorbid psychopathology. Next, in Chapter 4, I begin to investigate the neural underpinnings of the p factor in order to better understand the mechanisms underlying a general liability for psychopathology in the DNS sample.

4. Structural Alterations within Cerebellar Circuitry are Associated with the p Factor in Young Adults[1]

4.1 Background

In the current chapter, I use multimodal neuroimaging to study the structural neural correlates of the p factor in the DNS sample. I conducted these analyses in the following step-wise fashion. First, I conducted exploratory whole-brain analyses of the structural integrity of white matter pathways and regional gray matter volume correlates of p factor scores identified from diffusion tensor and high-resolution structural imaging data, respectively. Second, I examined relationships between white matter and gray matter correlates of the p factor emerging from these exploratory analyses in an effort to better understand the possible neural mechanisms for a general liability for mental disorders.

4.2 Methods

Data were available from 1,246 undergraduate students (727 women; mean age: 19.69 +/- 1.26) who had successfully completed the DNS. p factor scores described in Chapter 3 were used in subsequent neuroimaging analyses and standardized to a mean

[1] Parts of this Chapter are based on the following publication: Romer A. L., Knodt, A. R., Houts, R., Brigidi, B. D., Moffitt, T. E., Caspi, A., & Hariri, A. R. (2018). Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders. *Molecular Psychiatry, 23*, 1084-1090.

of 100 (*SD* = 15), with higher scores indicating a greater propensity to experience all forms of psychiatric symptoms (sample range = 75 - 205).

DTI was used to assess regional FA correlates as a metric of the structural integrity of white matter pathways and optimized VBM was used to assess regional GMV correlates of p factor scores. Out of the 1,246 participants included in the study, DTI analyses were available for 951 participants and VBM analyses were available for 1,200 participants with overlapping structural MRI and clinical symptom data surviving the stringent, multilevel quality control procedures (see Chapter 2 for more details).

4.2.1 MRI follow-up analyses

Differences in integrity of specific white matter tracts were examined based on the results from the whole-brain analyses. Preprocessing of diffusion data was completed in FSL (http://www.fmrib.ox.ac.uk/fsl) (Smith et al., 2004). For each of the two acquisitions, the diffusion weighted scans were corrected for eddy currents using the initial b = 0 scan of the respective acquisition as a reference. Non-brain tissue was removed, tensors were calculated, and the resulting two FA maps were linearly registered to each other and then averaged. Tract-wise average FA values were extracted using the ENIGMA-DTI protocols (Jananshad et al., 2013; Kochunov et al., 2014; Kochunov et al., 2015). Briefly, FA images from all participants were non-linearly registered to the ENIGMA-DTI target FA map, a minimal deformation target calculated

across a large number of individuals (Jananshad et al., 2013). The data were then processed using the tract-based spatial statistics (TBSS) analytic method (Smith et al., 2006) modified to project individual FA values on the ENIGMA-DTI skeleton. Following the extraction of the skeletonized white matter and projection of individual FA values, ENIGMA-tract-wise regions of interest, derived from the Johns Hopkins University (JHU) white matter parcellation atlas (Mori et al., 2008), were transferred to extract the mean FA across the full skeleton and average FA values for a total of 25 (partially overlapping) regions. Using the SUIT toolbox (for details, see Chapter 2 subsection 2.1.3.3), I also examined cerebellar-specific GMV differences based on results from the whole-brain exploratory VBM analyses.

4.2.2 Statistical analyses

I conducted my analyses in three steps. First, to identify structural neural correlates of the p factor, I conducted exploratory whole-brain analyses of white matter integrity and GMV using voxel-based estimates of FA and optimized VBM, respectively. Second, based on the results from the exploratory DTI analyses, I conducted whole-brain analyses of differences in white matter integrity predicting differences in GMV in order to determine how these two modalities relate to one another. Third, based on the results of the whole-brain exploratory analyses of white matter integrity and GMV, I conducted

follow-up analyses of the structural integrity of specific white matter tracts and GMV differences in order to better understand these neural correlates.

For all analyses, I conducted linear regressions of differences in FA and GMV controlling for age, sex, and average whole-brain FA values for the DTI and total intracranial volume for the VBM analyses. I verified that resulting associations were not unduly affected by extreme p factor scores by conducting sensitivity analyses wherein outlier values (defined as values > ±3 standard deviations from the mean) were winsorized before testing (Wilcox, 2005). Furthermore, all analyses were conducted using Monte Carlo simulation-derived whole-brain corrected thresholds with an overall family-wise error rate of $\alpha < .05$. For the follow-up analyses of FA regressed onto whole-brain GMV, simulations determined that a cluster size of 713 contiguous voxels was needed to achieve a threshold of $p < .005$.

4.3 Results

4.3.1 Exploratory analyses of structural neural correlates of the p factor

Whole-brain analyses of FA revealed that individuals with higher p factor scores had significantly reduced white matter integrity exclusively within the right and left pons as indexed by lower FA values (Figure 1A, Table 6). Whole-brain analyses of GMV revealed that individuals with higher p factor scores had significantly less volume

within the right and left lingual gyrus and right intracalcarine cortex of the occipital lobes (Figure 1B), as well as the left posterior cerebellum (Figure 1C) (Table 6). There were no significant positive associations between p factor scores and FA or GMV. Interestingly, white matter pathways encompassing afferent connections between the cerebrum and cerebellum pass through the pons (Middleton & Strick, 2001). Thus, the lower FA observed within the pons among participants with higher p factor scores suggests that individuals with higher liability to general psychopathology exhibit decreased structural integrity and, possibly, impaired functional communication between structures within the cerebrum and the cerebellum.

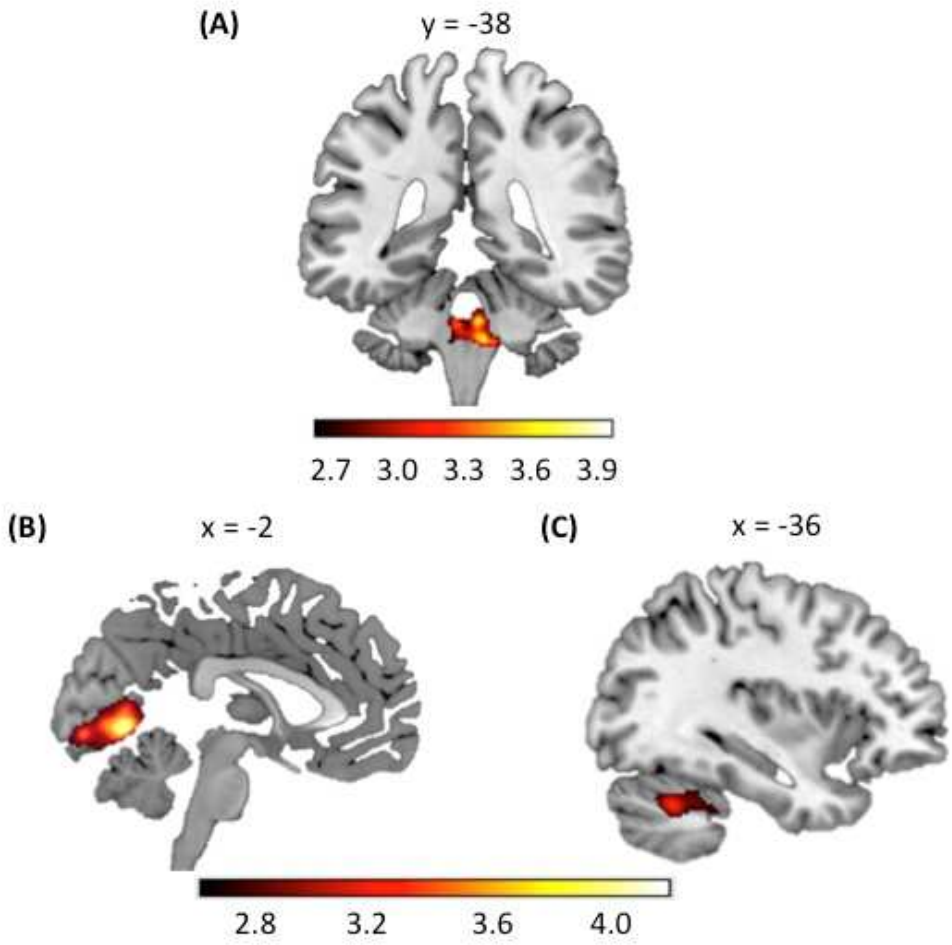

Figure 1: Structural alterations associated with p factor scores.

Statistical parametric maps from whole-brain exploratory analyses are shown to illustrate voxels exhibiting a significant negative correlation with p factor scores. (A) DTI analyses show poorer FA in the bilateral pons. VBM analyses show reduced GMV in (B) bilateral occipital lobe and (C) left posterior cerebellum. Colorbars reflect *t* scores.

Table 6: Differences in fractional anisotropy and gray matter volume associated with p factors scores.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (p Factor)
		x	y	z		
Diffusion Tensor Imaging Analysis						
272	Right pons	12	-39	-42	3.96	.016
	Right pons	5	-37	-33	3.62	.014
	Left pons	-5	-37	-35	3.30	.011
Voxel-Based Morphometry Analysis						
2,353	Left lingual gyrus	-2	-69	-2	4.28	.015
	Right intracalcarine cortex	11	-74	17	4.06	.014
	Left lingual gyrus	-2	-89	-5	3.46	.010
710	Left posterior cerebellum	-36	-57	-33	3.26	.009
	Left posterior cerebellum	-41	-41	-35	3.15	.008

4.3.2 Associations between white matter integrity and gray matter volume

Given that the pons acts as a structural bridge between the cerebrum and cerebellum (Middleton & Strick, 2001), I hypothesized that pons FA would be associated with cerebellar GMV. To test this hypothesis, I used linear regressions to examine whether differences in FA of white matter tracts in the pons predict differences in cerebellar GMV, effectively linking the two structural neuroimaging modalities. As such, I extracted FA cluster-wise values from the bilateral pons found to be associated

with p factor scores to predict differences in GMV using whole-brain voxel-based morphometry (n = 951) controlling for age, sex, average whole-brain FA, and total intracranial volume. I found that pons FA was associated with larger GMV in the bilateral cerebellum and fusiform cortex, as well as right precentral gyrus/supplementary motor area (Figure 2A, Table 7). Pons FA also was associated with smaller GMV in the right occipital cortex (Figure 2B, Table 7). Importantly, I identified a 203-voxel cluster in left posterior cerebellum (x = -29, y = -66, z = -30; $T = 5.44$, $p < .005$; $R^2 = .03$) wherein GMV correlated with both pons FA and p factor scores (Figure 2C).

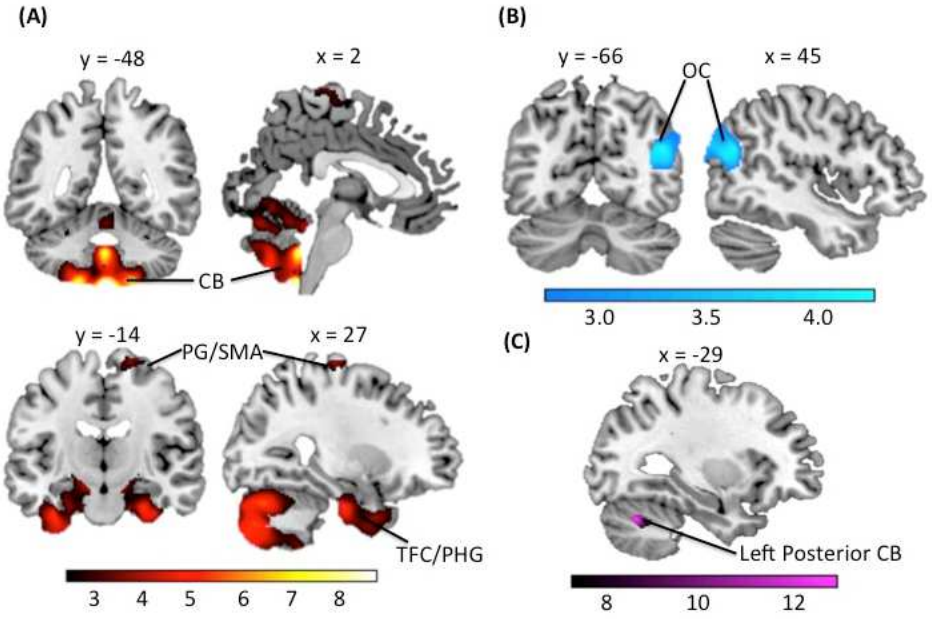

Figure 2: Pons FA is related to differences in GMV.

(A) Shows larger GMV associated with higher pons FA in the bilateral cerebellum (CB), temporal fusiform cortex (TFC)/parahippocampal gyrus (PHG), and

precentral gyrus (PG)/supplementary motor area (SMA). (B) Shows smaller GMV associated with pons FA in the occipital cortex (OC). (C) Depicts the 203-voxel overlapping gray matter cluster in the left posterior cerebellum (in violet) found to be associated both with p factor scores and pons FA. Colorbars reflect *t* scores.

Table 7: Differences in gray matter volume associated with pons fractional anisotropy.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Pons FA)
		x	**y**	**z**		
Increased Gray Matter Volume						
30,591	Right brainstem	2	-48	-62	8.40	.069
	Vermis X	0	-47	-41	7.61	.058
	Right lobule VIIIb	20	-51	-63	7.52	.056
5,983	Right temporal fusiform cortex (posterior division)	39	-23	-33	5.31	.029
	Right parahippocampal gyrus (anterior division)	27	-14	-30	5.22	.028
	Right temporal fusiform cortex (posterior division)	18	-5	-41	4.37	.020
6,241	Left temporal fusiform cortex (posterior division)	-35	-15	-36	5.31	.029
	Left temporal fusiform cortex (anterior division)	-35	-3	-47	5.30	.029
	Left temporal pole	-30	8	-38	5.15	.027
842	Right precentral gyrus	29	-20	72	3.81	.015
	Right precentral gyrus/supplementary motor area	11	-18	68	3.74	.015
	Right precentral gyrus/superior frontal gyrus	18	-14	72	3.63	.014
Decreased Gray Matter Volume						
2,351	Right lateral occipital cortex	45	-66	24	4.42	.020
	Right occipital pole	35	-93	14	3.84	.015
	Right occipital pole	26	-92	14	3.80	.015

In addition to showing a statistical association between pons FA and cerebellar GMV, I also investigated whether the structural integrity of specific white matter tracts within the pons and cerebellum was associated with p factor scores. To do this, I extracted average FA values from white matter tracts in the right and left medial lemniscus, right and left inferior cerebellar peduncles, and right and left superior cerebellar peduncles. I was unable to measure FA within the middle cerebellar peduncles, which are the afferent white matter tracts that connect the pons and cerebellum, as they typically fall out of the field of view, and thus, are difficult to reliably image (Jahanshad et al., 2013).

I conducted partial correlations of p factor scores predicting average FA within these six white matter tracts controlling for sex, age, and average whole-brain FA values. I found that higher p factor scores were associated with poorer integrity of the right and left medial lemniscus as well as the left superior cerebellar peduncle (Table 8). In contrast, p factor scores were unrelated to the bilateral inferior and right superior cerebellar peduncles.

Table 8: Partial correlations between p factor scores and fractional anisotropy of pons and cerebellar white matter tracts.

White Matter Tracts	Partial r Score	P-Value
Right Medial Lemniscus	-.116	<.001
Left Medial Lemniscus	-.120	<.001
Right Inferior Cerebellar Peduncle	-.029	.368
Left Inferior Cerebellar Peduncle	-.041	.211
Right Superior Cerebellar Peduncle	-.049	.130
Left Superior Cerebellar Peduncle	-.070	.031

4.3.3 Cerebellar-specific differences in gray matter volume associated with p factor scores

Given the above convergent evidence from the exploratory analyses that p factor scores are associated with alterations in cerebellar circuitry, I employed follow-up analyses of GMV within the cerebellum to clarify the nature of the associations using the SUIT (Diedrichsen, 2006) to improve the anatomical localization of gray matter correlates of p factor scores.

As with the whole-brain analyses, I conducted a linear regression with p factor scores predicting differences in cerebellar GMV. I found that p factor scores were associated with smaller GMV within a 156-voxel cluster in the left lobule VIIb (x = -22 y = -68 z = -45; $T = 3.47$, $p < .005$; $R^2 = .010$; Figure 3), a cerebellar region that has been found to be functionally connected with orbitofrontal, dorsolateral, and medial prefrontal cortex regions supporting cognitive control (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Yeo et al., 2011).

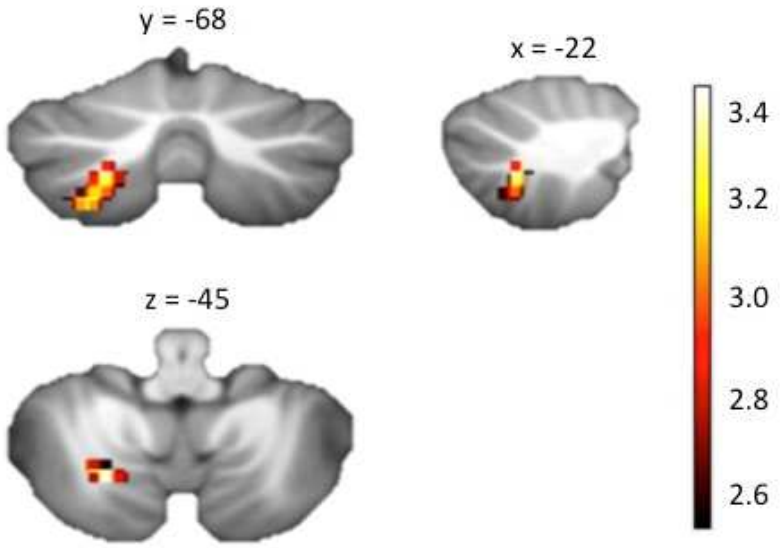

Figure 3: Cerebellar-specific GMV reductions.

A statistical parametric map from the SUIT cerebellar-specific analysis is shown to illustrate voxels exhibiting a significant negative correlation with p factor scores within the left cerebellar lobule VIIb. Colorbar reflects *t* scores.

As with the more general correlation between cerebellar GMV and pons FA, this left lobule VIIb GMV found to be associated with p factor scores, also was correlated with pons FA (standardized $B = .105$, $p < .01$) controlling for age, sex, average whole-brain FA, and intracranial volume.

4.4 Discussion

Some commentators have questioned the utility of a general factor that underlies shared risk for a wide range of mental disorders by suggesting that it is analogous to arguing that all forms of physical illness can be represented as a general state of being

"unwell" (McNally et al., 2015). But this analogy ignores the fact that all mental disorders are expressed through dysfunction of the *same* organ, whereas physical diseases such as atherosclerosis, emphysema, and diabetes are manifest through dysfunction of *different* organ systems. Collectively, the current findings provide initial evidence that the p factor may capture a neural mechanism underlying a general liability for mental disorders.

The results implicate alterations in the structure of cerebellar circuitry as a transdiagnostic biomarker of a general liability for mental disorders in the form of reduced white matter integrity of pontine pathways encompassing cerebellar afferents and smaller cerebellar GMV. Although the cerebellum is most widely known as a region involved in basic motor processing and coordination, it has been long implicated in higher-order cognitive and emotional processes through its structural and functional connectivity with various cerebral structures (Buckner, 2013; D'Angelo & Casali, 2013; Keren-Happuch, Chen, Ho, & Desmond, 2014). This dynamic communication occurs through what are known as cerebello-thalamo-cerebro-cortical circuits (CTCCs) (D'Angelo & Casali, 2013; Strick, Dum, & Fiez, 2009). As part of these CTCCs, the cerebellum has been found to be activated during a number of complex cognitive and affective tasks, such as working memory, set-shifting, associative fear learning, and recognizing emotional facial expressions (Berman et al., 1995; Desmond, Gabrieli,

Wagner, Ginier, & Glover, 1997; Fusar-Poli, Placentino, Carletti, Landi, & Abbamonte, 2009; Sachetti, Scelfo, & Strata, 2005). More generally, investigators have theorized that the cerebellum functions as a general "forward controller" creating internal models of how a given output will fit with contextual information (Ito, 1993; 2008). As such, the cerebellum may compute models that provide a representation of future action plans, thoughts, and emotions and subsequently modify these models based on external feedback; in effect, comparing intention with execution (D'Angelo & Casali, 2013; Ghez, 1991). Thus, reduced cerebellar GMV and pontine white matter integrity associated with higher p factor scores may reflect impaired processing and communication of information, respectively, necessary to guide behavior.

Not surprisingly, there is evidence of cerebellar dysfunction in specific categorical disorders including major depressive disorder, mania, OCD, autism spectrum disorders, and schizophrenia (e.g., Bauman & Kemper, 2005; Lazaro et al., 2014; Mills, DelBello, Adler, & Strakowski, 2005; Peng et al., 2011). In patients with psychosis, for example, studies have found global cerebellar atrophy (D'Angelo & Casali, 2013), lower FA in the left cerebellar peduncle (Kyriakopoulos, Vyasa, Barkerb, Chitnisb, & Frangoua, 2008), and a recent meta-analysis showed relatively decreased activation of the cerebellum during a variety of cognitive and affective tasks (Bernard & Mittal, 2015). Interestingly, in cerebellar cognitive affective syndrome, which results

from damage to the cerebellum, patients experience symptoms across cognitive and affective domains including executive function impairment, difficulties with spatial cognition, personality change (i.e., blunting of affect and/or disinhibited and inappropriate behavior), and language deficits (Schmahmann, 2004; Schmahmann, Weilburg, Sherman, 2007). These symptoms, typically referred to as "dysmetria of thought," bear resemblance to the symptoms of schizophrenia and other thought disorders (Andreasen, Paradiso, & O'Leary, 1998). Although cerebellar dysfunction has been reported in association with several specific mental disorder categories, this study provides initial evidence that abnormal cerebellar structure and potential dysfunctional communication with the cerebrum through the pons may underlie a general liability for psychopathology more broadly.

Of particular interest, the region of the cerebellum in which I found the strongest GMV association with p factor scores (lobule VIIb) is part of a cognitive control network including orbitofrontal, dorsolateral, and medial prefrontal cortex (Buckner et al., 2011; Yeo et al., 2011). Similarly, meta-analyses of fMRI studies show that lobule VIIb is activated during cognitive control tasks (e.g., Keren-Happuch et al., 2014; Stoodley & Schmahmann, 2009), which is consistent with the hypothesis that poorer cortico-cerebellar communication may manifest behaviorally as reduced ability to regulate bottom-up drives. Furthermore, I also found that lower FA of the left superior cerebellar

peduncle was associated with higher p factor scores. Anatomically, the superior cerebellar peduncles are efferent white matter tracts that send information to the cerebrum through the thalamus, whereas the inferior cerebellar peduncles are primarily afferent tracts that receive proprioceptive and motor information from the spinal cord and medulla oblongata (Mori et al., 2008). These results are consistent with the hypothesis that individuals with higher p factor scores may show poorer communication between the cerebellum and cerebral cortex. Whether the deficits are specific to efferent pathways to the cerebrum through the thalamus or afferent pathways from the cerebrum to the pons, or some combination of both, remains to be determined.

In addition to the findings of impairments in cortico-cerebellar circuitry as a potential biomarker of general psychopathology, I also found reduced GMV within regions of the occipital lobes in individuals with high p factor scores. I found the strongest association with p factor scores in the lingual gyrus, a region supporting visual attention and memory processing (Bogousslavsky, Miklossy, Deruaz, Assal, & Regli, 1987) with direct connections to the corticolimbic circuit (Conrad & Stumpf, 1975). Volumetric studies have shown that depressed individuals exhibit relatively less GMV in the lingual gyrus (Du et al., 2012; Yang et al., 2015). Another study found that smaller volume of the lingual gyrus was associated with poorer response to antidepressants and poorer cognitive functioning in depression (Jung et al., 2014). One hypothesis is that the

lingual gyrus may be involved in top-down attentional control of frontoparietal and corticolimbic circuits (Hopfinger, Buonocore, & Mangun, 2000; Jung et al., 2014), such that smaller GMV in the lingual gryus may manifest as dysregulated cognition and emotion contributing to risk for a wide range of disorders. Furthermore, recent research on the functional connectivity of neural regions demonstrate that higher p factor scores uniquely map onto hyper-connectivity between visual association cortex and both frontoparietal and default mode networks (Elliott et al., 2018), which is consistent with this hypothesis and suggests impairments in executive functioning and self-referential processes.

Overall, these findings both support the significance of the p factor as a meaningful dimension of general risk for multiple forms of psychopathology, and provide initial evidence for circumscribed neuroanatomical correlates of this general liability. In particular, this exploratory work suggests that structural alterations in cortico-cerebellar circuitry are associated with a general liability for mental disorders and sets the stage for future hypothesis-driven, region of interest analyses.

5. Replication and Extension of Brain Structural Correlates of the p Factor in a Representative Birth Cohort

5.1 Background

In Chapter 4, I identified differences in cortico-cerebellar and occipital circuitry structure as associated with a general liability for mental illness. In this chapter, I aim to examine whether these cortico-cerebellar and occipital structural alterations will replicate in the Dunedin study members in order to determine whether the findings from Chapter 4 are robust to different samples and ages. I also aim to examine whether Dunedin study members with high p factor scores demonstrate structural alterations in white matter integrity and GMV in regions other than those identified in Chapter 4 by conducting whole-brain exploratory analyses of FA and GMV.

5.2 Methods

Participants include 481 (219 females) 45 year-old study members who completed behavioral and neuroimaging assessments as part of the ongoing Dunedin Study. Psychiatric symptoms were measured using the Diagnostic Interview Schedule (Robins et al., 1995). Confirmatory factor analyses of symptom data were conducted using the same procedures as in the DNS sample (as described in Chapter 2 subsection 2.2.3). p factor scores, extracted using the standard regression method, were

standardized to a mean of 100 (*SD* = 15), with higher scores indicating a greater propensity to experience all forms of psychiatric symptoms (sample range = 68 – 151). Out of the 481 study members at age 45 included in the study, DTI analyses were available for 414 and VBM analyses were available for 459 study members with overlapping structural MRI and psychiatric symptom data surviving the multilevel quality control procedures (see Chapter 2 for details).

5.2.1 Statistical analyses

I examined differences in FA of the pons and GMV of the cerebellum and occipital cortex (i.e., lingual gyrus) as regions of interest (ROIs) based on the findings from Chapter 4 in the DNS sample. I created masks of the significant clusters within the pons, cerebellar lobule VIIb, and lingual gyrus to restrict analyses of FA and GMV to the regions I found to be associated with p factor scores in Chapter 4. To examine differences in FA of the pons and GMV of the cerebellum and lingual gyrus, I conducted linear regressions with p factor scores predicting differences in FA and GMV controlling for sex and average whole-brain FA values for the DTI and total intracranial volume for the VBM analyses. To examine differences in GMV of the cerebellum, I used SUIT to improve the anatomical localization of gray matter correlates of p factor scores. I also conducted exploratory analyses within the cerebellum using SUIT in order to determine whether differences in GMV of other cerebellar lobules might also be associated with

higher p factor scores in Dunedin. All ROI analyses were conducted using Monte Carlo simulation-derived whole-brain corrected thresholds with an overall family-wise error rate of $\alpha < .05$. Simulations determined that a cluster size of 11, 42, and 54 contiguous voxels were needed to achieve a threshold of $p < .005$ for the DTI, VBM, and SUIT ROI analyses, respectively.

In addition to these ROI analyses, I conducted exploratory whole-brain analyses of white matter integrity and GMV using voxel-based estimates of FA and optimized VBM, respectively. Specifically, I conducted linear regressions with p factor scores predicting differences in FA and GMV controlling for sex and average whole-brain FA values for the DTI and total intracranial volume for the VBM analyses. Whole-brain exploratory analyses were conducted using Monte Carlo simulation-derived whole-brain corrected thresholds with an overall family-wise error rate of $\alpha < .05$ (see Chapter 2 subsection 2.2.4.3 for more details).

5.3 Results

5.3.1 Structural alterations in regions of interest associated with p factor scores

Results from the ROI SUIT analysis showed that p factor scores were not significantly associated with left cerebellar lobule VIIb GMV. The exploratory analysis of cerebellar GMV more broadly revealed that p factor scores were associated with smaller

volume of a 110-voxel cluster within the right cerebellar Crus II (x = 38, y = -70, z = -43; T = 4.13, $p < .005$; $R^2 = .036$) (Figure 4), a cerebellar region that has been found to be involved in language, working memory, and spatial processing (Stoodley & Schmahmann, 2009) and functionally connected with dorsolateral, medial, and frontopolar prefrontal cortex regions supporting cognitive control (Krienen & Buckner, 2009; Yeo et al., 2011).

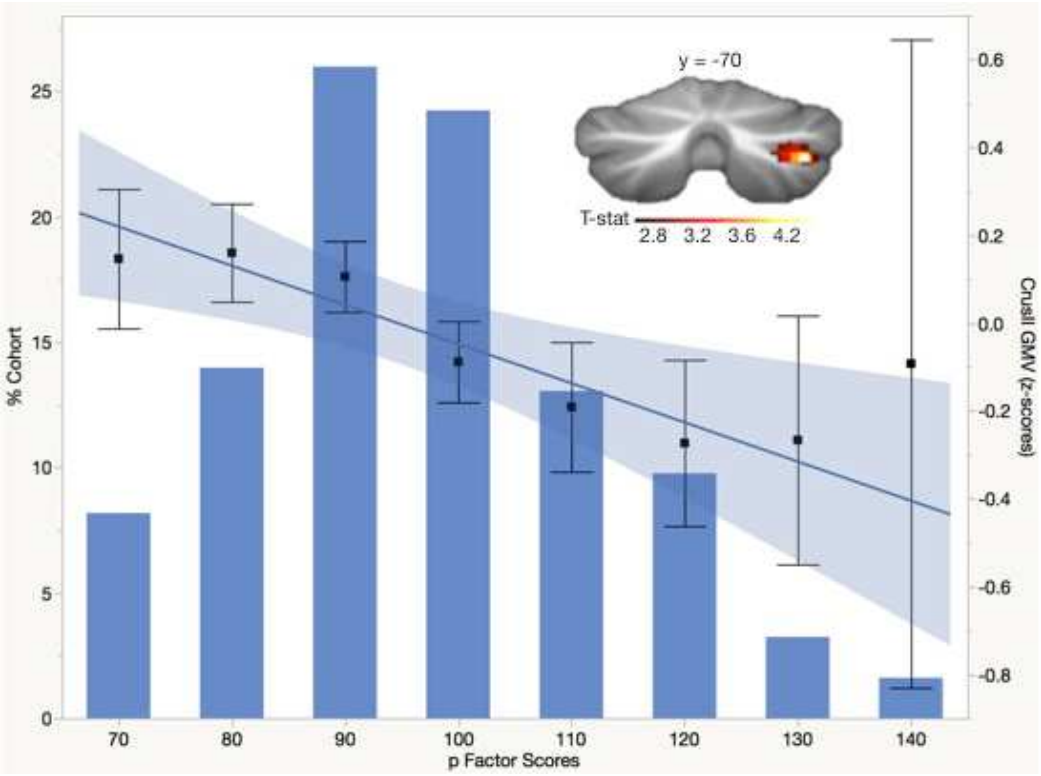

Figure 4: Plot of association between p factor scores and cerebellar Crus II gray matter volume.

Bars indicate percent of the cohort with p factor scores within the range shown. Colorbar reflects t scores.

Results from the ROI analyses of pons FA and occipital GMV showed that p factor scores were significantly associated with reduced white matter integrity of a 24-voxel cluster within the pons (x = -7, y = -42, z = -32; $T = 3.34$, $p < .005$; $R^2 = .026$) (Figure 5) and smaller GMV of a 352-voxel cluster within the lingual gyrus (x = 0, y = -92, z = -5; $T = 4.07$, $p < .005$; $R^2 = .035$) (Figure 6).

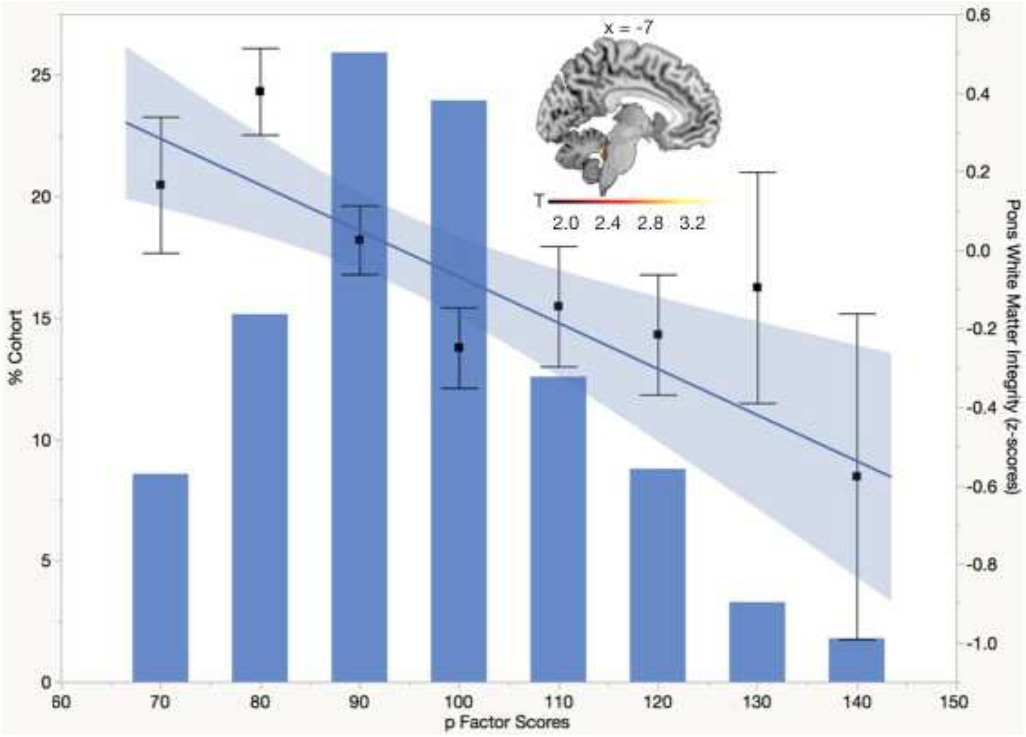

Figure 5: Plot of the association between p factor scores and fractional anisotropy in bilateral pons.

Bars indicate the percent of the cohort with p factor scores within the range shown. Colorbar reflects *t* scores.

5.3.2 Exploratory analyses of structural neural correlates of the p factor

Whole-brain analyses of FA revealed no significant differences in white matter integrity associated with p factor scores. Whole-brain analyses of GMV showed that individuals with higher p factor scores had reduced volume of prefrontal cortex regions within the middle and inferior frontal gyri, paracingulate gyrus, and orbital frontal cortex, which include portions of Brodmann Areas (BA) 9, 10, 11, 32, 44, 45, 46, and 47. These BAs include dorsolateral, frontopolar, dorsomedial, ventrolateral,

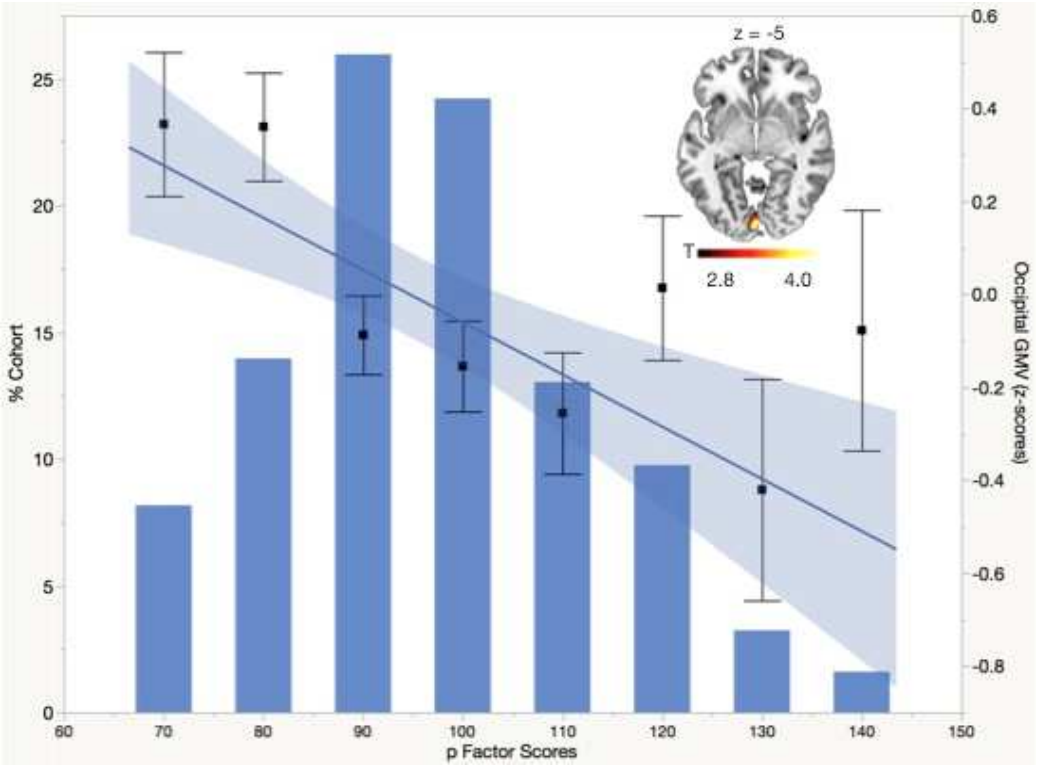

Figure 6: Plot of association between p factor scores and lingual gyrus gray matter volume.

Bars indicate percent of the cohort with p factor scores within the range shown. Colorbar reflects *t* scores.

ventromedial, and dorsal anterior cingulate prefrontal regions. In addition to these prefrontal cortex GMV correlates, individuals with higher p factor scores had less volume within the parietal lobe (e.g., postcentral and supramarginal gyri), insular cortex, temporal lobe (e.g., amygdala, hippocampus, and thalamus), occipital cortex (e.g., lingual and fusiform gyri and the occipital pole), and the posterior cerebellum (Figure 7, Table 9). There were no significant positive associations between p factor scores and FA or GMV.

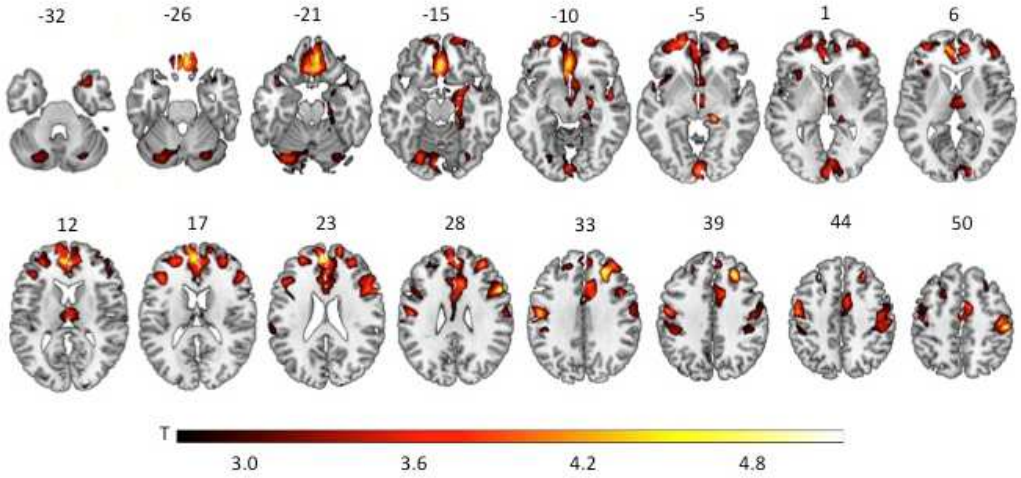

Figure 7: Reductions in gray matter volume associated with higher p factor scores in Dunedin (colorbar reflects *t* scores).

5.4 Discussion

In this study, I obtained replication of occipital and cortico-cerebellar circuitry as structural correlates of the p factor in the Dunedin cohort. These findings suggest that structural alterations in cerebellar circuitry and occipital cortex are robust to differences in sample, age, and background. They also suggest that deficits in the basic processing and monitoring of information supported by these circuits may be associated with a general liability for mental illness.

In addition, I identified smaller volumes within the prefrontal cortex, postcentral and supramarginal gyrus, insula, amygdala, hippocampus, and thalamus in the Dunedin study members that were not present in the DNS participants from the whole-brain exploratory analysis. Differences in results between these two studies may be due to differences in sample characteristics. The DNS participants are highly selected young adults who are predominantly healthy and high-functioning, whereas study members from Dunedin were included as part of a birth cohort, and thus, exhibit a more normal distribution of p factor scores than those in the DNS. Another stark difference between these samples is the difference in age. One hypothesis is that cerebellar and occipital alterations may be present at a younger age and that more global prefrontal, parietal, and limbic deficits may develop as individuals age and accumulate more symptomatology.

Table 9: Differences in gray matter volume associated with p factor scores.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (p Factor)
		x	**y**	**z**		
31,042	Right middle frontal gyrus	23	35	36	5.05	.053
	Left paracingulate gyrus	-6	51	23	4.90	.050
	Right inferior frontal gyrus	53	15	29	4.86	.049
3,335	Right postcentral gyrus	51	-24	50	4.53	.043
	Right postcentral gyrus	57	-11	30	3.53	.027
	Right postcentral gyrus	27	-32	63	3.29	.023
2,537	Left postcentral gyrus	-53	-14	32	4.50	.043
	Left postcentral gyrus	-54	-9	44	4.14	.036
	Left supramarginal gyrus	-45	-35	41	3.26	.023
5,116	Right occipital pole	2	-92	-5	4.07	.035
	Left lingual gyrus	-6	-83	-17	3.91	.032
	Left occipital fusiform gyrus	-26	-77	-17	3.79	.031
1,116	Left inferior frontal gyrus	-42	27	20	3.96	.033
	Left inferior frontal gyrus	-50	20	26	3.87	.032
	Left inferior frontal gyrus	-41	32	8	3.44	.025
1,055	Left orbital frontal cortex	-38	14	-17	3.53	.027
	Left insula	-42	12	-6	3.33	.024
	Left insula	-35	24	9	3.24	.023
854	Right posterior cerebellum	26	-75	-26	3.12	.021
	Right occipital fusiform gyrus	32	-75	-17	3.04	.020
	Right posterior cerebellum	29	-69	-41	2.81	.017

Smaller volumes within prefrontal cortex regions suggest impairments in cognitive control and executive functioning in individuals with high general liability for psychopathology. This is consistent with the hypothesis that the p factor may reflect disordered thought processes that are common across forms of psychopathology (Caspi & Moffitt, 2018). These findings also are consistent with individuals with higher p factor scores performing less well on executive functioning tasks in the Dunedin Study (Caspi

et al., 2014). Furthermore, reduced prefrontal cortex GMV has been implicated in a variety of mental disorder categories including major depression, bipolar disorder, schizophrenia, and anxiety disorders (Haijma et al., 2013; Shang et al., 2014; Wise et al., 2017).

These findings of smaller prefrontal GMV also are consistent with a recent investigation into GMV differences in a sample of young children (mean age = 7.9; Snyder, Hankin, Sandman, Head, & Davis, 2017). In this study, researchers used confirmatory factor analysis of parent-reported internalizing and externalizing symptoms to replicate a general psychopathology factor using bi-factor modeling. They then used an ROI approach to investigate reductions in GMV in dorsal, ventrolateral, and orbital prefrontal cortex as well as in medial temporal lobe, amygdala, hippocampus, and insula. They chose these ROIs based on previous research that indicated that multiple mental disorders were associated with smaller GMV of these brain regions. They found that the p factor was associated with less volume within the dorsal prefrontal cortex (superior frontal gyrus, rostral middle frontal gyrus), ventrolateral prefrontal cortex (inferior frontal gyrus), and lateral and medial orbital frontal cortex, which is consistent with my findings in the Dunedin Study. They also found that p factor scores were unrelated to differences in GMV of the medial temporal lobe, amygdala, insula, and occipital lobe, which is inconsistent with my findings.

Instead, they find that the specific internalizing factor from the bi-factor model was negatively related to GMV within these temporal and limbic regions.

There are a few hypotheses for why the results differ between these two studies. First, these researchers took an ROI approach to examining associations with p factor scores as opposed to employing a data-driven exploratory approach, which allows for a more complete investigation into potential GMV differences that were not hypothesized in advance. Thus, it is possible that they would have identified smaller volumes within the occipital lobes and posterior cerebellum if they had taken this whole-brain exploratory approach. It also is possible that the differences in ages between the samples could explain the differences in results. Finally, the absence of thought disorders from the bi-factor model in the Snyder et al. (2017) study might have contributed to the differences in results with the current study. Occipital and cerebellar GMV may be associated with p factor scores in the DNS and Dunedin samples in part because of the inclusion of thought disorders, which are subsumed entirely by the p factor.

In addition to associations with prefrontal GMV, I also found that individuals with high p factor scores showed reduced GMV of the insula and dorsal anterior cingulate, which are regions involved in interoceptive awareness and conflict monitoring, respectively. These findings are consistent with a recent meta-analysis of smaller insula and dorsal anterior cingulate volumes present in six diagnostic groups

(schizophrenia, bipolar disorder, OCD, depression, anxiety, and addiction) as part of an attentional and cognitive control network (Goodkind et al., 2015). Another large study of adolescents and young adults also found that higher p factor scores were associated with altered intrinsic connectivity of the anterior cingulate cortex (Kaczkurkin et al., 2017).

Smaller volumes also were identified in parietal regions including the postcentral and supramarginal gyri, which encompasses the primary somatosensory cortex and association area. Reduced postcentral gyrus GMV has been predominantly identified in schizophrenia (Ferro et al., 2015; Glahn et al., 2008; Zhou et al., 2007); however, smaller parietal lobe volume also has been shown in GAD (Makovac et al., 2016), pediatric bipolar disorder (Frazier et al., 2005), and autism spectrum disorder (Liu et al., 2017).

Finally, GMV reductions were found in limbic regions including the amygdala, hippocampus, and thalamus, which are responsible for salience and emotional processing, declarative memory, and relaying sensory information, respectively. Interestingly, the thalamus is part of the cerebello-thalamo-cerebral circuitry (CTCC), which relays information from the cerebellum to the prefrontal cortex (Middleton & Strick, 2001). Reductions in thalamic GMV further suggest deficits in this cortico-cerebellar circuitry associated with general psychopathology. Additionally, meta-analyses have shown less GMV in these limbic regions as implicated in multiple mental

disorders including major depression (Du et al., 2014; Zhang et al., 2016), conduct disorder (Rogers & De Brito, 2016), bipolar disorder (Yu et al., 2010), and schizophrenia (Ellison-Wright et al., 2008; Guo et al., 2014; Nelson, Saykin, Flashman, & Riordan, 1998; Shepherd et al., 2012). Overall, these results suggest that smaller volumes of occipital and cortico-cerebellar circuitry are associated with a general liability for mental illness in two independent samples. Furthermore, greater liability for psychopathology is associated with widespread GMV reductions in prefrontal, parietal, and limbic regions.

6. Common and Unique Brain Structural Correlates of Liabilities for Internalizing, Externalizing, and Thought Disorders

6.1 Background

In addition to investigating the structural neural correlates of the p factor, accounting for what is shared across liabilities for internalizing, externalizing, and thought disorders, it also is important to examine differences in brain structure uniquely associated with each of these liabilities. In the current chapter, I examine the differences in white matter integrity and GMV associated with internalizing, externalizing, and thought disorders from the correlated factors model in the DNS and Dunedin samples. I compare the structural alterations of these three liabilities with those found to be associated with the p factor in order to determine the structural neural correlates in common with the p factor, as well as those unique to internalizing, externalizing, and thought disorders in both independent samples.

6.2 Methods

Participants included 1,246 undergraduate students (727 women; mean age: 19.69 +/- 1.26) and 481 (219 females) 45 year-old study members from the DNS and Dunedin samples, respectively. p factor scores from the bi-factor model and internalizing, externalizing, and thought disorder factor scores from the correlated factors model were

used in subsequent neuroimaging analyses in both samples. Out of the 1,246 DNS participants, DTI analyses were available for 951 participants and VBM analyses were available for 1,200 participants. Out of the 481 Dunedin study members, DTI analyses were available for 414 participants and VBM analyses were available for 459 participants with overlapping structural MRI and psychiatric symptom data surviving the stringent, multilevel quality control procedures (see Chapter 2 for details).

6.2.1 Statistical analyses

I conducted ROI and whole-brain exploratory analyses of white matter integrity and GMV differences associated with internalizing, externalizing, and thought disorder factors from the correlated factors model in the DNS and Dunedin samples. For the ROI analyses, I extracted pons FA and occipital and cerebellar GMV from significant clusters in both samples based on findings from Chapters 4 and 5 to examine associations with internalizing, externalizing, and thought disorder factor scores. For the ROI analyses, I conducted partial correlations, and for the whole-brain analyses, I conducted separate linear regressions of differences in FA and GMV controlling for sex and average whole-brain FA values for the DTI and total intracranial volume for the VBM analyses. Age was included as an additional covariate in the analyses conducted in the DNS sample. All whole-brain analyses were conducted using Monte Carlo simulation-derived whole-

brain corrected thresholds with an overall family-wise error rate of $\alpha < .05$ (for details, see Chapter 2).

6.3 Results

6.3.1 Region of interest analyses

ROI analyses revealed that internalizing, externalizing, and thought disorder factors from the correlated factor model showed similar associations with pons FA and occipital and cerebellar GMV as did the p factor in the DNS and Dunedin samples (Table 10). The only exception to this was the externalizing factor in the DNS sample, which was negatively associated with cerebellar lobule VIIb GMV, but was unrelated to pons FA and occipital GMV. This may be due to the fact that the externalizing factor is the least highly correlated with the p factor. In general, this pattern of associations is consistent with the hypothesis that p factor scores reflect what is shared across liabilities to internalizing, externalizing, and thought disorder symptoms.

Table 10: Associations of the correlated factors model and the p factor with pons fractional anisotropy and cerebellar and occipital gray matter volume in DNS and Dunedin Samples.

Factors	Pons FA	Cerebellar GMV	Occipital GMV
Duke Neurogenetics Study			
Internalizing	-.137***	-.085***	-.064**
Externalizing	-.032	-.044*	-.038^{+}
Thought Disorders	-.143***	-.062**	-.058**
p	-.134***	-.066**	-.077***
Dunedin Longitudinal Study			
Internalizing	-.151**	-.175***	-.147**
Externalizing	-.112*	-.121**	-.138**
Thought Disorders	-.174***	-.174***	-.176***
p	-.174***	-.175***	-.177***

$^{+}p < .06$, $*p < .05$, $**p < .01$, $***p < .001$. Partial *r* values are reported. Cerebellar GMV is specific to the left lobule VIIb in the DNS sample and the right Crus II in the Dunedin cohort.

6.3.2 Exploratory Analyses

I examined differences in brain structure associated with internalizing, externalizing, and thought disorder factors from the correlated factors model and compared their patterns of structural alterations with those associated with the p factor. Figures show differences in FA and GMV related to both p and internalizing, externalizing, and thought disorder factors (overlap shown in green), versus differences in FA and GMV that are uniquely related to these factors (shown in hot colors) (see Appendix B for structural differences related to these factors without marking overlap

with the p factor). Tables list differences in FA and GMV associated with internalizing, externalizing, and thought disorder factor scores. There were no positive associations between brain structure and these three factors.

6.3.2.1 Duke Neurogenetics Study

6.3.2.1.1 Internalizing

Whole-brain analyses of FA revealed that individuals with higher internalizing scores had significantly reduced white matter integrity in the pons, similar to the lower pons FA associated with p factor scores (Figure 8A, Table 11). In fact, Figure 8A shows that reduced pons FA is largely overlapping between internalizing and p factor scores.

Whole-brain analyses of GMV revealed that individuals with higher internalizing scores had significant reductions in GMV within the temporal lobe (e.g., parahippocampal gyrus, middle temporal gyrus, pole, and fusiform cortex), the occipital cortex (e.g., lingual gyrus, occipital fusiform gyrus, and intracalcarine cortex), the supramarginal gyrus, and the posterior cerebellum (see Table 11). Out of those regions, Figure 8B shows that reduced GMV of clusters within the lingual gyrus, intracalcarine cortex, and the posterior cerebellum were found to be associated both with p and internalizing factor scores. Alternatively, smaller GMV of clusters within the temporal lobe were found to be uniquely related to internalizing factor scores and unrelated to p

factor scores. Although both internalizing and p factor scores were related to GMV reductions within portions of the supramarginal gyrus, those clusters did not overlap.

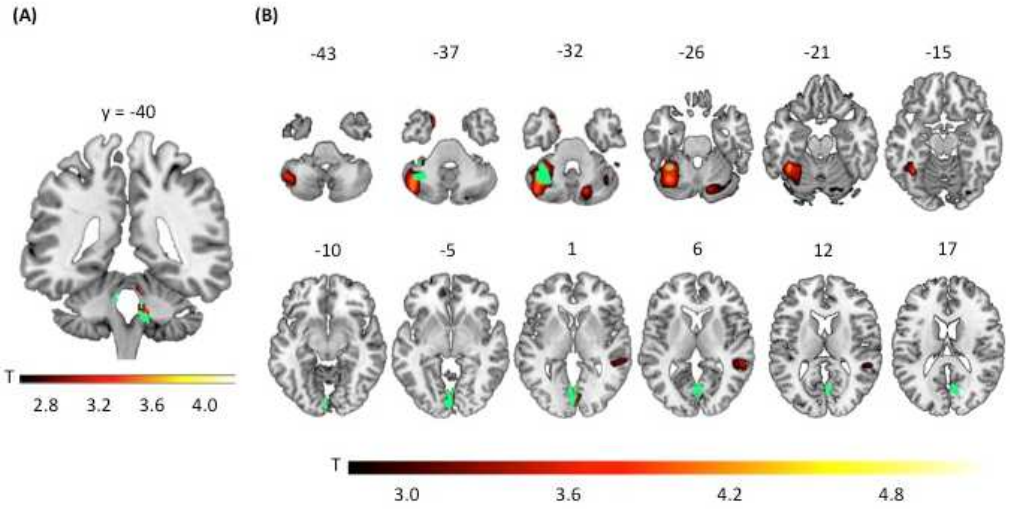

Figure 8: Common and unique structural correlates of internalizing and p factor scores in the DNS.

Green indicates overlap in GMV reductions related to internalizing and p factor scores. Hot colors indicate unique associations between GMV and internalizing factor scores (colorbars reflect *t* scores). (A) DTI analyses show largely overlapping differences in pons FA related to internalizing and p factor scores. (B) VBM analyses show smaller GMV within the occipital cortex and posterior cerebellum is related to both internalizing and p factor scores. GMV reductions in the temporal lobe are uniquely related to internalizing factor scores.

Table 11: Differences in white matter integrity and gray matter volume associated with internalizing factor scores in the DNS.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Factor Score)
		x	**y**	**z**		
White Matter Integrity						
437	Right pons	12	-40	-42	4.30	.019
	Right pons	9	-39	-35	4.15	.018
	Left pons	-3	-37	-35	3.99	.017
Gray Matter Volume						
726	Left parahippocampal gyrus	-14	2	-33	4.81	.019
	Left temporal pole	-18	12	-38	3.62	.011
	Left temporal fusiform cortex	-18	0	-47	3.57	.011
5,526	Left posterior cerebellum	-38	-60	-32	4.24	.015
	Left temporal occipital fusiform	-39	-48	-21	4.00	.013
	Left posterior cerebellum	-45	-71	-35	3.93	.013
1,536	Left lingual gyrus	-2	-71	-3	3.84	.012
	Left lingual gyrus	0	-81	-2	3.84	.012
	Right intracalcarine cortex	11	-71	17	3.03	.008
1,095	Right posterior cerebellum	15	-74	-32	3.45	.010
	Right posterior cerebellum	41	-60	-32	2.92	.007
	Right occipital fusiform gyrus	30	-80	-15	2.82	.007
800	Right supramarginal gyrus	56	-39	8	3.26	.009
	Right middle temporal gyrus	48	-47	6	2.85	.007

6.3.2.1.2 Externalizing

Individuals with higher externalizing scores showed significantly reduced white matter integrity in the left calcarine (i.e., optic radiation) as well as in the right corpus callosum (Table 12). Figure 9A shows that there was no overlapping differences in FA

associated with both externalizing and p factor scores (no green), suggesting that poorer FA in the calcarine and corpus callosum was uniquely associated with liability for externalizing disorders.

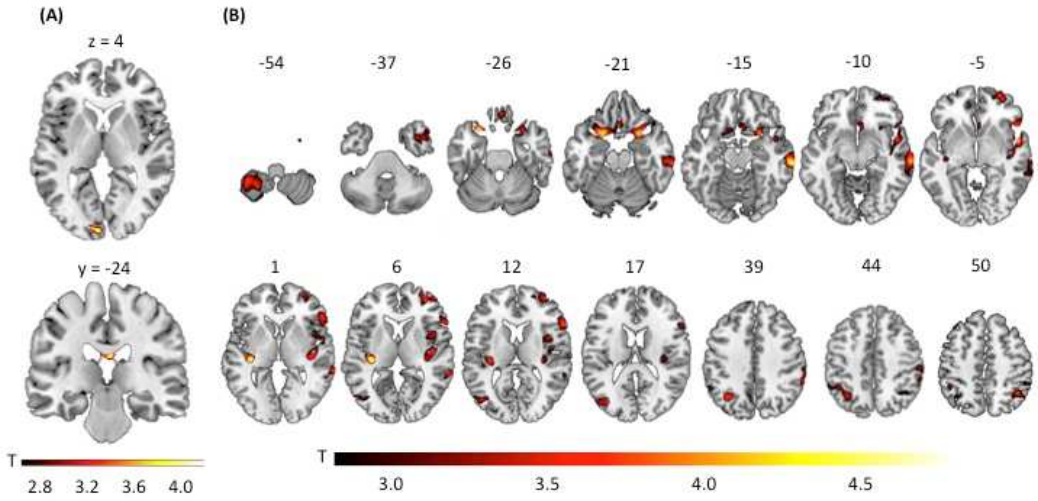

Figure 9: Common and unique structural correlates of externalizing and p factor scores in the DNS.

There were no overlapping differences in FA and GMV associated with both externalizing and p factor scores. (A) DTI analyses show that poorer FA in the bilateral pons is uniquely related to externalizing factor scores. (B) VBM analyses show reduced GMV in the prefrontal cortex, temporal lobe, parietal lobe, occipital cortex, and the posterior cerebellum are uniquely related to externalizing factor scores. Colorbars reflect *t* scores.

Whole-brain analyses of GMV showed that individuals with higher externalizing factor scores had smaller volumes within the prefrontal cortex (e.g., orbital and medial frontal cortex and frontal pole), temporal lobe (e.g., middle and inferior temporal gyri and pole), parietal lobe (e.g., superior parietal lobule, supramarginal, and angular gyri),

insular cortex, lateral occipital cortex, and posterior cerebellum (Table 12). Figure 9B shows that there were no overlapping GMV reductions associated with both externalizing and p factor scores, suggesting that smaller GMV of these regions are uniquely associated with liability for externalizing disorders. Although externalizing and p factor scores both were related to GMV reductions within the occipital cortex and posterior cerebellum, there were no overlapping GMV reductions within those regions.

Table 12: Differences in white matter integrity and gray matter volume associated with externalizing factor scores in the DNS.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Factor Score)
		x	**y**	**z**		
White Matter Integrity						
181	Left calcarine (optic radiation)	-5	-94	4	4.12	.018
140	Right corpus callosum	2	-24	21	4.01	.017
Gray Matter Volume						
658	Left insula	-35	-26	3	4.64	.018
2,026	Left orbital frontal cortex	-24	14	-24	4.37	.016
	Right medial frontal cortex	2	38	-33	3.83	.012
	Subcallosal cortex	0	24	-23	3.31	.009
1,970	Right middle temporal gyrus	68	-26	-17	4.34	.016
	Right middle temporal gyrus	60	-23	-17	4.09	.014
	Right middle temporal gyrus	63	-42	8	3.60	.011
4,707	Right orbital frontal cortex	26	11	-20	4.13	.014
	Right superior temporal pole	51	3	-5	4.01	.013
	Right inferior frontal gyrus	59	23	9	3.75	.012
964	Left lateral occipital cortex	-36	-62	35	4.13	.014
	Left superior parietal lobule	-36	-57	47	3.38	.009
	Left supramarginal gyrus	-45	-47	48	3.20	.008
755	Right temporal pole	38	8	-36	3.75	.012

	Right inferior temporal gyrus	41	-2	-41	3.42	.010
	Right temporal pole	53	15	-33	2.92	.007
	Left posterior cerebellum	-27	-54	-59	3.63	.011
1,731	Left posterior cerebellum	-36	-47	-53	3.60	.011
	Left posterior cerebellum	-39	-57	-59	3.40	.010
	Right frontal pole	33	51	6	3.56	.010
1,217	Right frontal pole	30	60	-3	3.56	.010
	Right frontal pole	45	54	8	3.46	.010
	Right supramarginal gyrus	62	-42	35	3.54	.010
1,634	Right angular gyrus	41	-54	51	3.46	.010
	Right supramarginal gyrus	57	-39	29	3.42	.010
	Left lateral occipital cortex	-36	-75	18	3.46	.010
752	Left lateral occipital cortex	-44	-72	12	3.23	.009
	Left lateral occipital cortex	-53	-71	8	3.04	.008

6.3.2.1.3 Thought disorders

Thought disorder factor scores were associated with significant reductions in white matter integrity of the pons, similar to those found to be associated with p and internalizing factor scores (Figure 10A, Table 13). Similar to Figure 8A, Figure 10A shows that the differences in white matter integrity associated with both thought disorder and p factor scores are largely overlapping.

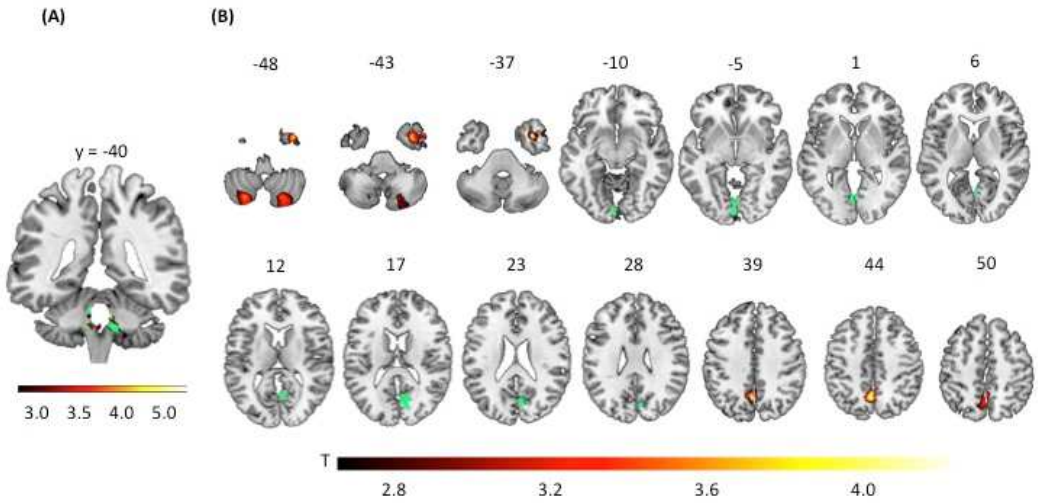

Figure 10: Common and unique structural correlates of thought disorder and p factor scores in the DNS.

Green indicates overlap in GMV reductions related to thought disorder and p factor scores. Hot colors indicate unique GMV associations with thought disorder factor scores (colorbars reflect *t* scores). (A) DTI analyses show that lower pons FA is related to both thought disorder and p factor scores. (B) VBM analyses show smaller GMV in occipital cortex and posterior cerebellum are related to both thought disorder and p factor scores. GMV reductions in the precuneus and temporal lobe are uniquely related to thought disorder factor scores.

Whole-brain analyses of GMV showed that thought disorder factor scores were associated with less volume of the inferior temporal gyrus and pole, precuneus, lingual gyrus, intracalcarine cortex, and the posterior cerebellum (Table 13). Figure 10B shows that out of those regions, reduced GMV in the lingual gyrus and intracalcarine cortex was found to be associated both with p and thought disorder factor scores. Smaller

GMV of clusters within the precuneus and inferior temporal gyrus and pole was found to be uniquely related to thought disorder factor scores and unrelated to p factor scores.

Table 13: Differences in white matter integrity and gray matter volume associated with thought disorder factor scores in the DNS.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Factor Score)
		x	**y**	**z**		
White Matter Integrity						
442	Right pons	12	-40	-42	4.72	.023
	Left pons	-9	-40	-42	3.76	.015
	Left pons	-5	-37	-35	3.74	.015
Gray Matter Volume						
1,103	Left precuneus	-3	-60	42	4.30	.015
1,110	Right temporal pole	36	8	-38	4.28	.015
	Right temporal pole	36	5	-48	3.74	.012
	Right inferior temporal gyrus	51	8	-45	3.65	.011
1,191	Left lingual gyrus	-2	-69	-3	3.89	.012
	Left lingual gyrus	-2	-90	-6	3.42	.010
	Right intracalcarine cortex	11	-72	18	3.39	.010
1,339	Left posterior cerebellum	-26	-81	-53	3.67	.011
	Left posterior cerebellum	-26	-72	-50	3.56	.010
	Left posterior cerebellum	-42	-60	-57	3.35	.009
1,378	Right posterior cerebellum	21	-71	-45	3.52	.010
	Right posterior cerebellum	27	-78	-53	3.40	.010

6.3.2.2 Dunedin Longitudinal Study

6.3.2.2.1 Internalizing

Whole-brain analyses of GMV revealed that individuals with higher internalizing scores showed significant GMV reductions in the prefrontal cortex (e.g.,

middle and inferior frontal gyrus, frontal pole, and paracingulate gyrus), parietal lobe (e.g., postcentral and precentral gyri), limbic lobe (e.g., hippocampus and amygdala), and occipital cortex (e.g., lingual gyrus and occipital pole) (Table 14). Figure 11 shows that smaller GMV of clusters within these regions are completely overlapping with those found to be associated with p factor scores, suggesting there were no GMV reductions uniquely associated with internalizing disorders that were unrelated to the p factor.

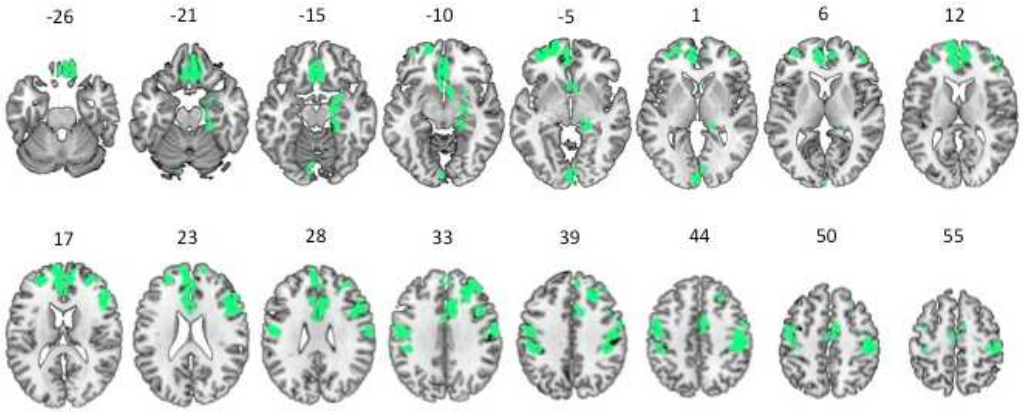

Figure 11: Common gray matter correlates of internalizing and p factor scores in the Dunedin Study.

Green indicates overlap in GMV reductions related to internalizing and p factor scores. The absence of hot colors indicates that there were no unique GMV associations with internalizing factor scores that were unrelated to p factor scores. Smaller volumes of clusters within the prefrontal cortex, parietal lobe, limbic lobe, and occipital cortex were correlated with both internalizing and p factor scores.

Table 14: Differences in gray matter volume associated with internalizing factor scores in the Dunedin Longitudinal Study.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Factor Score)
		x	**y**	**z**		
1,020	Right middle frontal gyrus	23	35	36	5.00	.052
	Right frontal pole	39	39	36	3.93	.033
2,048	Right inferior frontal gyrus	53	15	29	4.73	.047
	Right inferior frontal gyrus	51	30	20	3.67	.029
	Right middle frontal gyrus	42	12	35	3.36	.024
9,679	Left paracingulate gyrus	-6	51	23	4.38	.040
	Left paracingulate gyrus	-12	53	6	4.04	.035
	Left paracingulate gyrus	-2	33	-14	4.02	.034
2,221	Left postcentral gyrus	-53	-14	32	4.36	.040
	Left precentral gyrus	-53	-11	44	3.68	.029
	Left precental gyrus	-53	-3	47	3.37	.024
1,330	Right hippocampus	18	-30	-5	4.18	.037
	Right amygdala	23	-14	-11	3.66	.029
	Right brainstem	14	-17	-23	3.58	.027
2,658	Right postcentral gyrus	50	-26	50	3.95	.033
	Right postcentral gyrus	57	-11	30	3.62	.028
	Right postcentral gyrus	48	-17	38	3.53	.027
1,414	Left frontal pole	-18	57	-6	3.65	.028
	Left Frontal Pole	-32	51	-3	3.55	.027
	Left frontal pole	-29	51	23	3.47	.026
886	Left occipital pole	0	-95	-3	3.55	.027
	Left lingual gyrus	-6	-83	-17	3.50	.026
	Right lingual gyrus	6	-81	-2	3.01	.020

6.3.2.2.2 Externalizing

Individuals with higher externalizing scores showed significant reductions in GMV within the prefrontal cortex (e.g., frontal pole, paracingulate and inferior frontal

gyri), insular cortex, parietal lobe (e.g., postcentral, precentral, and supramarginal gyri), temporal pole, occipital cortex (e.g., lingual and fusiform gyri), and the posterior cerebellum (Figure 12, Table 15). Out of those regions, reduced GMV within the paracingulate and inferior frontal gyri, postcentral, precentral, and supramarginal gyri, lingual and fusiform gyri, and posterior cerebellum are related to both externalizing and p factor scores. Clusters within the frontal pole, orbital frontal cortex, cingulate gyrus, insula, superior parietal lobule and superior temporal gyrus and pole were found to be uniquely related to externalizing factor scores and unrelated to p factor scores.

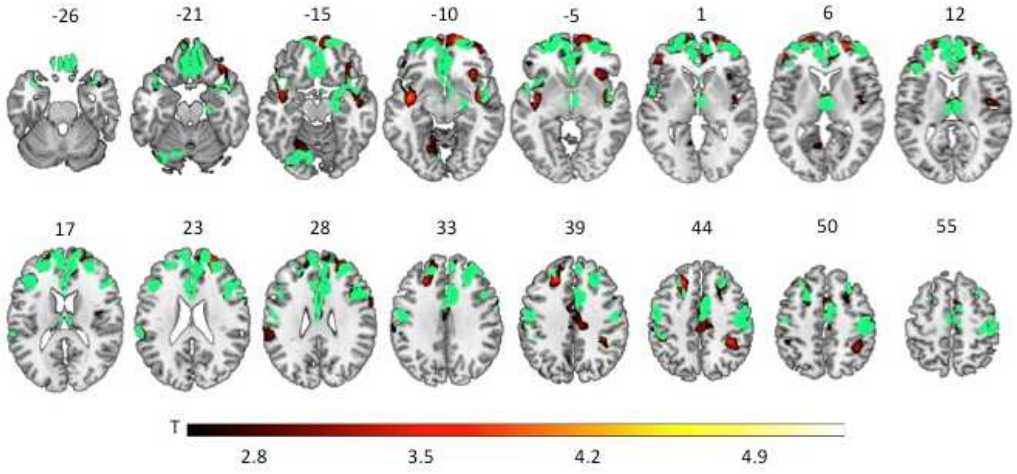

Figure 12: Common and unique structural correlates of externalizing and p factor scores in the Dunedin Study.

Green indicates overlap in GMV reductions related to externalizing and p factor scores. Hot colors indicate unique GMV associations with externalizing factor scores (colorbar reflects *t* scores). VBM analyses show overlapping reductions in GMV within regions of the prefrontal cortex, parietal lobe, occipital cortex, and posterior cerebellum

related to both externalizing and p factor scores. Smaller GMV in the frontal pole, orbital frontal cortex, cingulate gyrus, insula, superior parietal lobule, and superior temporal gyrus and pole are uniquely related to externalizing factor scores.

Table 15: Differences in gray matter volume associated with externalizing factor scores in the Dunedin Longitudinal Study.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Factor Score)
		x	**y**	**z**		
3,961	Left inferior frontal gyrus	-42	30	18	5.38	.060
	Left insula	-41	-5	-9	4.22	.038
	Left temporal pole	-42	6	-17	4.14	.036
4,024	Right postcentral gyrus	54	-24	50	5.14	.055
	Right postcentral gyrus	47	-20	51	4.10	.036
	Right inferior frontal gyrus	60	14	24	3.91	.032
31,673	Right frontal pole	18	63	23	5.12	.054
	Left paracingulate gyrus	-12	53	8	5.11	.054
	Right frontal pole	29	45	27	4.74	.047
4,150	Right insula	45	-3	-8	4.74	.047
	Right temporal pole	41	9	-17	4.43	.041
	Right superior temporal pole	45	3	-14	4.04	.035
851	Left precentral gyrus	-53	-11	44	3.91	.032
	Left postcentral gyrus	-53	-14	33	3.79	.031
1,994	Left occipital fusiform gyrus	-35	-80	-18	3.77	.030
	Left lingual gyrus	-11	-56	-5	3.69	.029
	Left anterior cerebellum	-18	-69	-15	3.39	.025
1,212	Left supramarginal gyrus	-47	-38	45	3.72	.030
	Left supramarginal gyrus	-60	-30	23	3.56	.027
	Left postcentral gyrus	-60	-24	41	3.16	.021

6.3.2.2.3 Thought disorders

Thought disorder factor scores were associated with less GMV within regions of the prefrontal cortex (e.g., middle and inferior frontal gyri, and paracingulate gyrus),

insular cortex, parietal lobe (e.g., postcentral and precentral gyri), temporal pole, occipital cortex (e.g., lingual and fusiform gyrus and calcarine sulcus), and the posterior cerebellum (Figure 13, Table 16). Figure 13 shows that similar to internalizing disorders, GMV reductions related to thought disorder factor scores were completely overlapping with reductions found to be associated with p factor scores. Thus, there were no unique GMV differences related to thought disorder factor scores that were not also related to p factor scores.

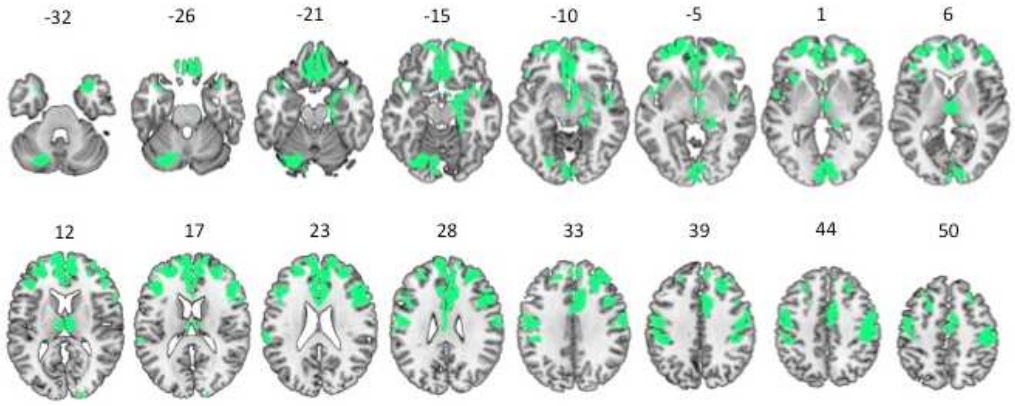

Figure 13: Common gray matter correlates of thought disorder and p factor scores in the Dunedin Study.

Green indicates overlap in GMV reductions related to internalizing and p factor scores. The absence of hot colors indicates that there were no unique GMV associations with thought disorder factor scores that were unrelated to p factor scores. Smaller volumes of clusters within the prefrontal cortex, parietal lobe, limbic lobe, and occipital cortex were correlated with both internalizing and p factor scores.

Table 16: Differences in gray matter volume associated with thought disorder factor scores in the Dunedin Longitudinal Study.

Cluster Size (k)	Peak Region	MNI Coordinates			T score	R^2 (Factor Score)
		x	**y**	**z**		
29,283	Left paracingulate gyrus	-6	51	23	4.98	0.052
	Right middle frontal gyrus	23	35	36	4.92	0.050
	Right inferior frontal gyrus	53	15	29	4.81	0.048
3,073	Right postcentral gyrus	51	-24	50	4.50	0.043
	Right postcentral gyrus	57	-12	29	3.54	0.027
	Right postcentral gyrus	27	-32	63	3.20	0.023
2,504	Left postcentral gyrus	-53	-14	32	4.47	0.042
	Left postcentral gyrus	-53	-11	44	4.11	0.036
	Left precentral gyrus	-54	-2	45	3.84	0.031
4,398	Left calcarine sulcus	0	-93	-3	4.04	0.035
	Left lingual gyrus	-6	-83	-17	3.81	0.031
	Left occipital fusiform gyrus	-26	-77	-17	3.74	0.030
1,005	Left inferior frontal gyrus	-42	27	20	3.92	0.033
	Left inferior frontal gyrus	-51	21	26	3.79	0.031
	Left inferior frontal gyrus	-41	32	8	3.37	0.024
874	Left temporal pole	-41	14	-20	3.50	0.026
	Left temporal pole	-51	8	-5	3.16	0.021
	Left insula	-42	12	-6	3.13	0.021

6.4 Discussion

In the current study, I identified reduced white matter integrity and GMV associated with liabilities for internalizing, externalizing, and thought disorders in two independent samples. In both samples, I demonstrated that these three liabilities are associated with poorer white matter integrity of the pons and smaller volumes of the lingual gyrus and neocerebellum. This is important in and of itself because it suggests

that structural alterations of occipital and cortico-cerebellar regions are shared across liabilities for internalizing, externalizing, and thought disorders, reflective of general psychopathology, in two very different independent samples.

Using whole-brain analyses, I also identified structural alterations that are in common with the p factor versus those that are unique to each of these three liabilities. In both samples, the gray and white matter reductions associated with internalizing and thought disorder factors, compared to the externalizing factor, were much more closely overlapping with those found to be associated with the p factor. In fact, the structural alterations associated with internalizing and thought disorder factor scores in the Dunedin cohort were completely overlapping with those found to be associated with p factor scores. The overlap in structural correlates between p, internalizing, and thought disorders is consistent with the strong positive interrelationships between these factors. Alternatively, externalizing factor scores are less strongly correlated with p factor scores, which may account for why there were more unique structural neural correlates associated with liability to externalizing disorders.

In terms of unique white matter alterations, externalizing factor scores were associated with poorer FA of the calcarine and corpus callosum, which were unrelated to p factor scores in the DNS sample. No other differences in white matter integrity were uniquely associated with internalizing and thought disorders in both samples. Poorer

calcarine FA likely reflects reduced integrity of the geniculocalcarine tract, also known as the optic radiation, which is a white matter tract that carries visual information from the lateral geniculate nucleus of the thalamus to the visual cortex (terminates in the lingual gyrus) along the calcarine fissure (Mori et al., 2008). In addition, the corpus callosum is a white matter tract that connects the left and right cerebral hemispheres, allowing communication between the left and right sides of the brain. Poorer FA of the corpus callosum has been found to be associated with externalizing disorders such as antisocial behavior (Waller, Dotterer, Murray, Maxwell, & Hyde, 2017) and attentional deficit hyperactivity disorder (ADHD; Chen et al., 2016; Wu et al., 2017). Reduced FA of the optic radiation has been found to be associated with ADHD (Pastura et al., 2016) as well. These findings suggest that individuals with externalizing disorders may show poorer communication of visual information between the thalamus and lingual gyrus and deficient interhemispheric communication.

In the DNS sample, smaller GMV within the temporal pole was found to be uniquely related to internalizing, externalizing, and thought disorder factor scores. Similarly, unique GMV reductions within the temporal pole also were found to be associated with externalizing factor scores in the Dunedin cohort. The temporal pole is an association cortex involved in semantic and emotional memory processing, on the right and left hemispheres, respectively, with strong connections to the amygdala and

orbital frontal cortex (Olson, Plotzker, & Ezzyat, 2007). These findings are consistent with prior research, which has shown reduced temporal pole GMV in individuals with depression (Webb, Weber, Mundy, & Killgore, 2014), social anxiety disorder (Talati et al., 2013), ADHD (Sasayama et al., 2010), and schizophrenia (Lee et al., 2016). Interestingly, externalizing and thought disorder factor scores were uniquely associated with smaller GMV in the right temporal pole responsible for semantic memory; whereas, internalizing factor scores were uniquely associated with left temporal pole deficits involved in emotional memory.

GMV reductions also were found in the right middle temporal gyrus associated with both internalizing and externalizing factor scores, but unrelated to p factor scores in the DNS sample. Smaller right inferior temporal gyrus GMV was associated with externalizing and thought disorder factor scores in the DNS sample as well. The middle temporal gyrus is involved in language and semantic memory processing (Cabeza & Nyberg, 2000; Chao, Haxby & Martin, 1999; Tranel Damasio, & Damasio, 1997) and the inferior temporal gyrus is implicated in visual perception (Herath, Kinomura, & Roland, 2001; Ishai, Ungerleider, Martin, & Haxby, 2000). These results are consistent with prior research, which shows smaller middle temporal gyrus GMV is associated with depressive and ADHD symptoms (Villemonteix et al., 2015; Webb et al., 2014) and

reductions in inferior temporal gryus GMV in individuals with substance dependence and schizophrenia (Delvecchio et al., 2017; Moreno-Lopez et al., 2012).

In addition to white matter reductions of the optic radiation and corpus callosum and smaller GMV of the temporal lobe, liability to externalizing disorders also was uniquely associated with GMV reductions in the orbital frontal cortex and superior parietal lobule in both samples. The orbital frontal cortex is involved in decision-making and emotion processing (Bechara, Damasio, & Damasio, 2000) and the superior parietal lobule is implicated in visuospatial, attentional, and working memory processing (Koenigs, Barbey, Postle, & Grafman, 2009). Orbital frontal cortex GMV reductions have been shown in individuals with externalizing disorders such as antisocial personality, substance dependence, and ADHD (Bralten et al., 2016; Dalwani et al., 2015; Francx et al., 2016; Raine, Yang, Narr, & Toga, 2011; Wang et al., 2016); however, there have not been any studies showing less GMV in superior parietal lobule in individuals with externalizing disorders. These results suggest that unique liability to externalizing disorders may be linked to poorer decision-making, emotion regulation, visuospatial, attention, and working memory as supported by the orbital frontal cortex and superior parietal lobule.

In the DNS sample, thought disorder factor scores were uniquely associated with smaller GMV within the precuneus in addition to the temporal lobe described above.

The precuneus is a parietal region within the "default mode network" that acts as a hub between the parietal and prefrontal cortices and is involved in self-referential processing (Fransson & Marrelec, 2008). GMV reductions in the precuneus have been found in individuals with OCD (Tang et al., 2015) and psychosis-spectrum symptoms (Satterthwaite et al., 2016).

Internalizing factor scores also were uniquely associated with reduced GMV of the parahippocampal gyrus in the DNS sample in addition to smaller middle temporal gyrus volume. The parahippocampal gyrus surrounds the hippocampus and is responsible for contextual associations and episodic memory (Aminoff, Kveraga, & Bar, 2014). Parahippocampal GMV reductions have been found in individuals with depression (Wang et al., 2015) and social anxiety disorder (Liao et al., 2011). This result suggests that liability to internalizing disorders may be uniquely associated with impaired contextual and episodic memory processing as supported by the parahippocampal gyrus.

In sum, liabilities to internalizing, externalizing, thought disorders, and general psychopathology are each associated with structural alterations in occipital and cortico-cerebellar circuitry in both independent samples. Consistent with their relationships with the p factor, structural alterations associated with liabilities for internalizing and thought disorders were closely overlapping with those associated with a general liability

for psychopathology. Structural alterations unique to internalizing, externalizing, and thought disorder liabilities were found in the temporal lobe in the DNS and Dunedin samples. Poorer white matter integrity of the optic radiation and corpus callosum were uniquely associated with liability to externalizing disorders, suggesting deficient communication between the thalamus and lingual gyrus and between prefrontal hemispheres in individuals with externalizing disorders. Similarly, liability to externalizing disorders was uniquely related to gray matter reductions in orbital frontal cortex and superior parietal lobule, suggesting impairments in decision-making, emotion regulation, and visuospatial, attentional, and working memory abilities. Reduced GMV of the precuneus was uniquely associated with liability to thought disorders, suggesting poorer self-referential processing in individuals with thought disorders. Finally, smaller GMV in the parahippocampal gyrus was uniquely associated with internalizing disorder liability, suggesting poorer contextual and episodic memory processing.

7. Does Cortico-Cerebellar and Occipital Circuitry Link Polygenic Risk for Schizophrenia and the p Factor?

7.1 Background

Thus far, I have identified behavioral and structural neural correlates of a general liability for psychopathology as well as liabilities for internalizing, externalizing, and thought disorders. In the current chapter, I examine the genetic correlates of these disorder-liability factors due to accumulating evidence suggesting that the p factor may reflect common genetic risk for psychopathology. Consistent with twin studies documenting that the latent genetic risk for various forms of psychopathology is largely shared (Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011; Pettersson, Anckarsater, Gillberg, & Lichtenstein, 2013), genome-wide association studies (GWAS) have shown that common single nucleotide polymorphisms (SNP) and genetic pathways confer risk for a diverse array of psychiatric disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Further, polygenic risk scores (PRS) for one disorder are associated with risk for other disorders (Carey et al., 2016; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), and SNP-based heritability estimates suggest that the p factor is moderately heritable (i.e., 38%; Neumann et al., 2016). Collectively, this evidence suggests that common polygenic variability confers pleiotropic risk for various forms of psychiatric dysfunction represented by the p factor.

In Chapters 4 and 5, I provided evidence for discrete neural correlates of the p factor in a large volunteer sample of young adult university students (Romer et al., 2018) and in a birth cohort from Dunedin, New Zealand. Specifically, I found that higher p factor scores uniquely map onto reduced GMV in the occipital cortex and neocerebellum and decreased structural integrity of white matter pathways within the pons, which communicate information from the cerebrum to the cerebellum (Middleton & Strick, 2001) in both samples. Within the occipital cortex, I found the strongest association with p factor scores in the lingual gyrus, a region supporting visual attention and memory with direct connections to the corticolimbic circuit (Conrad & Stumpf, 1975). This pattern of structural alterations associated with the p factor suggests that diminished capacity for monitoring and information processing supported by cortico-cerebellar circuitry (Buckner, 2013; D'Angelo & Casali, 2013; Ghez, 1991; Ito, 1993; 2008) and top-down visual attentional control supported by lingual gyrus may contribute to higher general liability for mental illness. This pattern is further consistent with evidence for cortico-cerebellar circuit and occipital cortex dysfunction in disorders principally characterized by poor executive control and disorganized thought such as schizophrenia (e.g., Bernard & Mittal, 2015) as well as the emergence of executive dysfunction referred to as "dysmetria of thought" in individuals with cerebellar cognitive affective syndrome

following damage to the neocerebellum (Andreasen et al., 1998; Schmahmann, 2004; Schmahmann et al., 2007).

Interestingly, I found in Chapter 3 that the p factor also is highly correlated with thought disorders (~.85) including psychosis, mania, and OCD, consistent with findings in the Dunedin cohort (Caspi et al., 2014) and an adolescent sample (Laceuelle et al., 2015). Other studies have found that the p factor is most highly correlated with internalizing symptoms of depression and anxiety (e.g., Lahey et al., 2012; Lahey et al., 2015; Olino et al., 2014; Tackett et al., 2013); however, these studies typically did not include thought disorders in their factor-analytic models. Furthermore, studies have found that individuals with high p factor scores exhibit poorer cognitive and executive functioning (Caspi et al., 2014; Lahey et al., 2015), which is consistent with reduced neurocognitive abilities present in individuals with thought disorders, and suggests that these deficits may underlie risk for psychopathology more broadly.

In the current chapter, I examine the relationships between higher genetic risk for thought disorders, p factor scores, and cortico-cerebellar circuit and lingual gyrus anatomy in the DNS and Dunedin samples. Specifically, I hypothesized that p factor scores would be positively correlated with genetic risk for schizophrenia, one form of thought disorder. To this end, schizophrenia PRS were derived for each participant in both samples from meta-analytic GWAS summary statistics provided by the Psychiatric

Genomics Consortium (PGC; http://www.med.unc.edu/pgc/) and I tested whether these are associated with p factor scores and variability in cortico-cerebellar circuit and lingual gyrus anatomy. Based on converging evidence that: (1) common polygenic risk is shared across different forms psychopathology (Lahey et al., 2011; Pettersson et al., 2013), (2) the p factor is heritable (Neumann et al., 2016), (3) the p factor wholly subsumes thought disorders (Caspi et al., 2014; Lacuelle et al. 2015; Romer et al., 2018), and is associated with executive dysfunction (Caspi et al., 2014; Lahey et al., 2015), and (4) cortico-cerebellar circuit and lingual gyrus anatomy are associated with the p factor (Romer et al., 2018), executive function (e.g., Buckner, 2013), and disorders of executive function (Bernard & Mittal, 2015; Andreasen et al., 1998; Schmahmann, 2004; Schmahmann et al., 2007), I hypothesized that cortico-cerebellar and lingual gyrus anatomy would mediate associations between genetic (schizophrenia PRS) and behavioral (p factor) risk.

7.2 Methods

7.2.1 Duke Neurogenetics Study

p factor scores, structural MRI, and genomic data were available from 475 (257 females) 18-22 year-old (mean age: 19.76 +/- 1.24) non-Hispanic university students of European ancestry who had successfully completed the DNS. DTI was used to assess differences in pons FA as a metric of the structural integrity of pons white matter pathways and optimized VBM was used to assess differences in occipital GMV.

Cerebellar GMV was assessed using the SUIT toolbox (Diedrichsen et al., 2009). Out of the 475 non-Hispanic Caucasian participants with genetic and psychiatric symptom data, DTI data surviving the stringent, multilevel quality control procedures was available for 365 participants (77%). High quality VBM data was available in all 475 participants (see Chapter 2 for details).

7.2.1.1 Genotyping

DNA was isolated from saliva derived from Oragene DNA self-collection kits (DNA Genotek) customized for 23andMe (www.23andme.com). DNA extraction and genotyping were performed by the National Genetics Institute (NGI), a CLIA-certified clinical laboratory and subsidiary of Laboratory Corporation of America. One of two different Illumina arrays with custom content was used to provide genome-wide SNP data, the HumanOmniExpress or HumanOmniExpress-24. Genotype imputation was run separately for all DNS participants with genome-wide chip data using the pre-phasing/imputation stepwise approach implemented in SHAPEIT (Delaneau, Marchini, & Zagury, 2012) and IMPUTE2 (Howie, Fuchsberger, Stephens, Marchini, & Abecasis, 2012) using only biallelic SNPs and the default value for effective size of the population (20,000), and chunk sizes of 3Mb and 5Mb for the respective arrays. Within each array batch, genotyped SNPs used for imputation were required to have missingness < 0.02, Hardy-Weinberg equilibrium $P > 10^{-6}$, and minor allele frequency (MAF) > 0.01. The

imputation reference set consisted of 2,504 phased haplotypes from the full 1000 Genomes Project Phase 3 dataset (May 2013, over 70 million variants, release "v5a"). Imputed SNPs were retained if they had high imputation quality (INFO > 0.9), low missingness (< 5%), and MAF > 0.01.

7.2.1.2 Polygenic risk scores

A PRS was generated based on the 108 schizophrenia-associated loci reported in the PGC's most recent GWAS meta-analysis of the disorder, which included 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics, 2014). Of the 108 loci, three were located on the X chromosome and two additional loci could not be imputed in the DNS, leaving 103 autosomal loci for inclusion in the PRS. For each of these 103 loci, the most significant SNP from the GWAS meta-analytic summary statistics available in the DNS was selected.

Schizophrenia PRSs also were constructed based on PGC GWAS meta-analysis summary statistics for the following p-value thresholds: 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1.0 (http://www.med.unc.edu/pgc/results-and-downloads). SNPs were required to have a MAF > 0.02, genotyping rates > 0.98, and HI p-values > 10^{-6}. SNPs within the MHC region (chr6: 25000000:35000000) were excluded due to their complex patterns of linkage disequilibrium. All remaining SNPs were then pruned using p-value-informed clumping (i.e., grouping linked SNPs; R^2 = .10, 500kb window), leaving 121,232

SNPs for analysis. For each threshold, using the --score method in Plink (v.1.07; Purcell et al., 2007), the log odds-ratio for each component SNP was multiplied by the number of reference alleles for that SNP before being summed and divided by the total number of contributing SNPs to produce a single metric for each participant representing cumulative risk for schizophrenia. All PRSs were normally distributed.

7.2.2 Dunedin Longitudinal Study

p factor scores and genetic data were available in 918 (448 women) study members, whereas DTI and VBM/SUIT data were available in 414 and 459 study members, respectively. DTI was used to assess differences in pons FA as a metric of the structural integrity of pons white matter pathways and optimized VBM was used to assess differences in occipital GMV. The SUIT toolbox was used to assess differences in cerebellar GMV (for details, see Chapter 2).

7.2.2.1 Genotyping and imputation

Illumina HumanOmni Express 12 BeadChip arrays (Version 1.1; Illumina, Hayward, CA) were used to assay common SNP variation in the genomes of our cohort members. We imputed additional SNPs using the impute2 software (Version 2.3.1; https://mathgen.stats.ox.ac.uk/impute/impute_v2.html; Howie, Donnelly, & Marchini, 2009) and the 1000 Genomes Phase 3 reference panel (1000 Genomes Project, 2016). Imputation was conducted on autosomal SNPs appearing in dbSNP (Version 140;

http://www.ncbi.nlm.nih.gov/SNP/; Sherry et al., 2001) that were "called" in more than 98% of the Dunedin Study samples. Invariant SNPs were excluded. Prephasing and imputation were conducted using a 50-million-base-pair sliding window. The resulting genotype database included genotyped SNPs and SNPs imputed with 90% probability of a specific genotype among the non-Maori members of the Dunedin cohort (n = 918). SNPs were analyzed in Hardy-Weinberg equilibrium ($p > .01$).

7.2.2.2 Polygenic scoring

Polygenic scoring was conducted following the method described by Dudbridge (2013) using PRSice (Euesden, Lewis, & O'Reilly, 2015). Briefly, 108 SNPs reported in the results of the most recent genome-wide association study released by the PGC (Schizophrenia Working Group of the Psychiatric Genomics, 2014) were matched with SNPs in the Dunedin database. For each SNP, the count of schizophrenia-associated alleles was weighted according to the effect estimated in the GWAS. Weighted counts were averaged across SNPs to compute polygenic scores. All matched SNPs were used to compute polygenic scores irrespective of nominal significance for their association with schizophrenia and linkage disequilibrium between SNPs. To control for possible population stratification, a principal component analysis was conducted of the genome-wide SNP database using PLINK (Version 1.9; Chang et al., 2015). The 10 principal components explained 1.2% in the Dunedin cohort. The PRS was residualized for the

first 10 principal components estimated from the genome-wide SNP data. The residualized score was normally distributed and was standardized (M = 0, SD = 1) for analysis.

7.2.3 Statistical analyses

I conducted my analyses first in the DNS as the discovery sample, and second, in Dunedin as the replication cohort. First, I examined the relationship between p factor scores and schizophrenia (SCZ) PRS including the 108 top associated loci and PRSs at 0.0001, 0.001, 0.01, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, and 1.0 p-value thresholds. Associations between the SCZ PRS and internalizing, externalizing, and thought disorders from the correlated factors model also were examined in order to determine whether each of these factors is related to schizophrenia polygenic risk as well. Partial correlations were used to assess the associations between SCZ PRS and disorder-liability factor scores controlling for sex and ancestry in the DNS sample and sex in the Dunedin cohort; 475 and 918 participants had genetic data available for these analyses in the DNS and Dunedin samples, respectively.

Second, I examined associations between the SCZ PRS representative of the top associated loci and brain structure. In Chapters 4 and 5, I identified reduced cerebellar and lingual gyrus GMV and poorer pons white matter integrity as structural neural correlates of the p factor in both the DNS and Dunedin samples. Based on these previous

analyses, for the current chapter, I created masks of significant clusters within the pons, lingual gyrus, and cerebellum as regions of interest to restrict analyses of PRS associations with FA and GMV to these regions I found to be associated with p factor scores. I conducted linear regressions of SCZ PRS on pons FA and lingual gyrus and cerebellar GMV controlling for sex, age, and ancestry in the DNS sample and sex in the Dunedin cohort. Third, based on the results of these analyses, follow-up mediation analyses were conducted to determine whether differences in brain structure mediate the association between SCZ PRS and p factor scores. For these analyses, DTI data were available in 365 of the 475 DNS participants and 414 of the 918 Dunedin study members. VBM data were available in all 475 DNS participants and 459 of the 918 Dunedin study members.

7.3 Results

7.3.1 Duke Neurogenetics Study

7.3.1.1 Genetic correlates of the p factor

I found a positive correlation (r = .092, p = .047) between the SCZ PRS including the top associated loci and p factor scores. In addition, I found a consistent pattern of positive associations between multiple p-value thresholds of the SCZ PRS and p factor scores (Figure 14). Specifically, the SCZ PRS was significantly associated with p factor scores at the 0.001 and 0.01 p-value thresholds and marginally associated ($p < .1$) at the

0.0001, 0.05, 0.2, 0.3, 0.4 thresholds. The thought disorder factor scores from the correlated factors model also was significantly related to the SCZ PRS including the top associated loci (r = .106, p = .022); however, the internalizing (r = .070, p = .131) and externalizing factor scores (r = .033, p = .481) were not related to this SCZ PRS. The PRS indicative of the top associated loci was used in subsequent analyses.

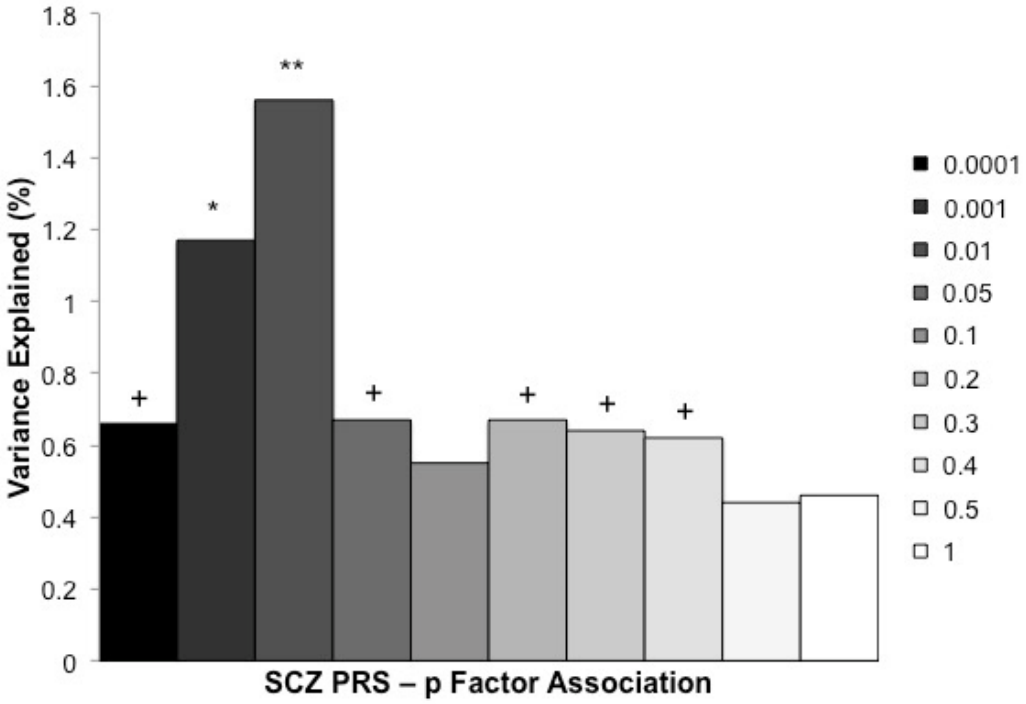

Figure 14: Polygenic risk for schizophrenia accounts for significant variability in p factor scores in the DNS sample.

Y-axis depicts the percent of variation in p factor scores explained by the SCZ PRSs plotted along the X-axis. Shades of gray in the legend indicate the p-value threshold at which the risk score was calculated. $^{+}$ $p < .1$; * $p < .05$; ** $p < .01$.

7.3.1.2 PRS and brain structure associations

The region of interest DTI analysis identified a 93-voxel cluster within the pons wherein reduced FA was significantly correlated with higher SCZ PRS (Figure 15). There was no significant relationship between SCZ PRS and lingual gyrus and cerebellar GMV. I extracted FA values from the 93-voxel cluster identified above for subsequent mediation analyses described below.

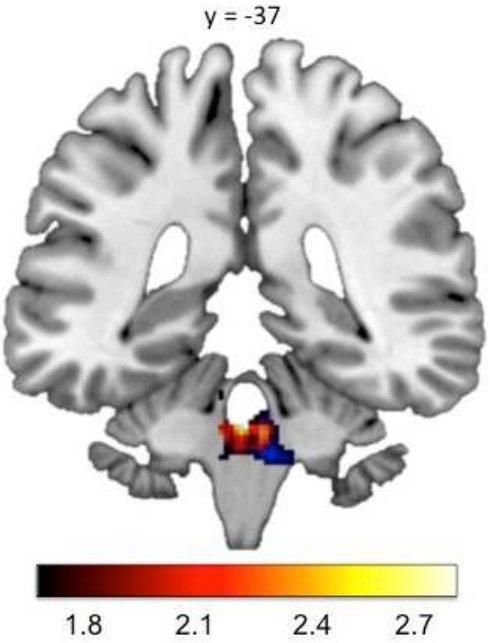

Figure 15: Reduced white matter integrity of the pons is associated with both greater polygenic risk for schizophrenia and higher p factor scores.

A statistical parametric map is shown to illustrate that pontine FA is significantly negatively correlated with both p factor scores and SCZ PRS (as shown in hot colors; x = -2, y = -37, z = -33; $T = 2.65$). Pontine FA only correlated with p factor scores is shown in blue. Colorbar reflects *t* scores.

7.3.1.3 Brain structure as mediator of PRS and p factor associations

Based on the correlations between pontine FA and polygenic risk for schizophrenia, I conducted mediation analyses to determine whether the association between SCZ PRS representative of the top associated loci and p factor scores is mediated by differences in FA of the pons. To do this, I used path analysis in Mplus (Muthén & Muthén, 1998-2013) with robust standard errors to define the model. Indirect effects were computed using bias-corrected bootstrapping procedures with 5,000 samples (MacKinnon, Lockwood, & Williams, 2004). Standard methods for assessing goodness of fit were used, including the maximum likelihood goodness-of-fit chi-square test ($p > .05$), the comparative fit index (CFI > .95), the standardized root mean square residual (SRMR < .05), and the root mean square error of approximation (RMSEA < .08) (Kline, 2011). To address the missing FA data, I used full information maximum likelihood to estimate missing pons and average whole-brain FA scores for the 23% of the sample who did not have data available. This procedure is recommended when data are missing at random (Enders, 2010), an assumption that was reasonable given that there were no demographic differences between participants with or without DTI data (see Appendix C). Sex, age, ancestry, and average whole-brain FA were included as covariates.

After dropping nonsignificant paths, the model of SCZ PRS to pons FA to p factor scores demonstrated overall good fit ($X^2(2) = 1.87$, $p = .39$; RMSEA < .001; SRMR = .011; CFI = 1.00). Within the full model, SCZ PRS negatively predicted pons FA ($\beta_{PRS} = -.188$, 95% CI [-.341, -.026]), which, in turn, negatively predicted p factor scores ($\beta_{Pons} = -.552$, 95% CI [-.934, -.171]). The indirect pathway from SCZ PRS to p factor scores through pons FA was significant ($\beta_{IND} = .104$, 95% CI [.019, .266], Figure 16), suggesting that pons FA is a potential mediator of the SCZ PRS – p factor association. Furthermore, the direct relation between SCZ PRS and p factor scores was no longer significant controlling for the mediated path, ($\beta_{DIR} = .428$, 95% CI [-.148, .979]), suggesting that pons FA could completely account for the relation between SCZ PRS and p factor scores.

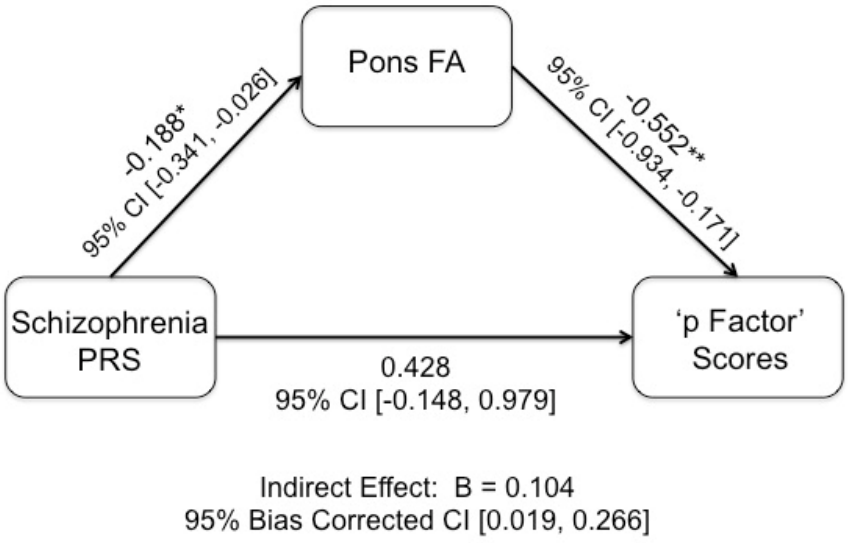

Figure 16: Mediation model showing the association between polygenic risk for schizophrenia and p factor scores, as mediated by pons FA.

Unstandardized regression coefficients are shown. The direct effect is reported along the lower path. * $p < .05$; ** $p < .01$. CI = confidence interval.

7.3.2 Dunedin Longitudinal Study

7.3.2.1 Genetic correlates of the p factor

I found that the SCZ PRS including the top associated loci was not significantly related to p factor scores ($r = .040$, $p = .222$). Internalizing ($r = .040$, $p = .229$), externalizing ($r = .044$, $p = .187$), and thought disorder factors ($r = .041$, $p = .217$) from the correlated factors model also were not significantly associated with the PRS. Additionally, region of interest analyses indicated no significant correlations between SCZ PRS and brain structure (pons FA: $r = .062$, $p = .222$; lingual gyrus GMV: $r = .053$, $p = .271$; cerebellar GMV: $r = -.021$, $p = .688$). Given these nonsignificant results, follow-up mediation analyses were not conducted in the Dunedin cohort.

7.4 Discussion

Here I showed that broad behavioral risk for mental illness, as indexed by higher p factor scores, is associated with higher polygenic risk for schizophrenia in the DNS, but not the Dunedin Study. Moreover, in the DNS sample only, I found that reduced white matter integrity within cortico-cerebellar pathways represents a potential neural bridge between increased polygenic risk for schizophrenia and p factor expression. This finding suggests that polygenic risk for schizophrenia may confer increased behavioral

risk for general psychopathology through its influence on the capacity to communicate and process information between the cerebrum and the cerebellum through the pons. Given that the DNS sample was unmedicated and did not include any individuals meeting diagnostic criteria for schizophrenia by design, these results in combination with findings from Chapter 4 suggest the hypothesis that impaired communication of higher-order cognitive and affective information through the cerebello-thalamo-cerebro-cortical circuits may be a premorbid risk marker of individuals with high genetic risk for schizophrenia as well as for mental illness more broadly.

Failure to replicate these findings in the Dunedin cohort may be due to the following reasons. First, it is possible that the positive association between schizophrenia polygenic risk and the p factor in the DNS is a false positive finding. Although the DNS sample is large for neuroimaging analyses (n = 475), it is relatively small for genetic association analyses, which can increase the risk of both false positive and false negative findings and result in imprecise effect estimates (Bogdan, Pagliaccio, Baranger, & Hariri, 2016). The fact that the Dunedin cohort is much larger (n = 918), suggests that the significant finding in the DNS sample may be a false positive.

Second, if the association between schizophrenia polygenic risk and the p factor is a false positive, it is possible that polygenic risk for internalizing or externalizing disorders, which were not tested, might be more strongly associated with the p factor in

both samples. The PGC GWAS meta-analysis from which SCZ PRS was derived was quite large (n_{case}=36,989, $n_{control}$=113,075) and yielded 108 genome-wide significant loci; however, the GWAS meta-analyses for other internalizing and externalizing disorders were much smaller (e.g., MDD: n_{case}=9227, $n_{control}$=7383; ADHD: $n_{triocase}$=1947, $n_{pseudocontrol}$=1947, n_{case}=840, $n_{control}$=688) and failed to yield any genome-wide significant loci (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). As the sample sizes for GWAS of these and other disorders continue to increase and generate more robust estimates of their polygenic architecture, future research can re-examine the specificity of the polygenic risk and the p factor. Third, there are large differences in sample characteristics that could account for the positive PRS – p factor association in the DNS and a failure to replicate that finding in the Dunedin Study.

Fourth, it is possible that the schizophrenia PRS contains some SNPs that are unrelated to the p factor, thus providing excess noise in detecting an association in both samples. For example, new research has examined the convergence of schizophrenia polygenic risk and placental biology (Ursini et al., in press). In particular, Ursini et al. (in press) identified two novel PRSs associated with increased risk for schizophrenia based on genes that are dynamically modulated and highly expressed in placenta. These two PRSs split the total schizophrenia PRS into two components: SNPs that are dynamically modulated and highly expressed in placenta (called "PlacPRS") and SNPs that are not

expressed in placenta (called "NonPlacPRS"). Preliminary analyses in the DNS show a slightly stronger positive association between the PlacPRS and p factor scores (r = .105, p = .023) than the association between the full schizophrenia PRS and p factor scores (r = .092, p = .047) is noteworthy because the PlacPRS has many fewer loci underlying the PRS calculation than the full schizophrenia PRS. Additionally, the NonPlacPRS was unrelated to p factor scores (r = .020, p = .647), suggesting that genes specifically expressed in placenta related to schizophrenia risk are predictive of p factor scores in the DNS. Because the PlacPRS includes only those SNPs that are specifically expressed in placental biology and associated with increased risk for schizophrenia, I may be more likely to detect an association between PlacPRS and the p factor in the Dunedin Study. Investigating associations between the p factor and PlacPRS also may provide us with a better understanding of how genetic risk for schizophrenia and early life environment might interact leading to greater psychopathology expression. In future research, I hope to investigate this question in the Dunedin Study.

In sum, there is substantial evidence to suggest that common polygenic variability confers pleiotropic risk for general psychopathology. However, whether schizophrenia polygenic risk is specifically associated with the p factor is still unclear given the above discrepant results. It is possible that polygenic risk for internalizing or externalizing disorders also may be related to general psychopathology and warrants

future testing once GWAS sample sizes become more robust. Finally, future research into polygenic risk for schizophrenia as expressed through placental biology is a promising future direction to better determine the genetic mechanisms underlying a general liability for mental illness.

8. Conclusions

In this dissertation, I investigated the behavioral, neural, and genetic correlates of a general liability for mental illness in two independent samples. Results from Chapter 3 showed that the p factor is identifiable in a high-functioning young adult volunteer sample and is related to a wide range of behavioral impairments, consistent with prior research. In Chapters 4 and 5, I demonstrated that occipital and cortico-cerebellar circuitry supporting core functions related to the basic integration, coordination, and monitoring of information may contribute to a general liability for mental disorders. Indeed, alterations in these circuits were present in both independent samples, which provides strong evidence for their relevance to understanding the mechanisms underlying a general psychopathology factor and suggests that they are robust to differences in sample characteristics. Reduced GMV also was present in prefrontal, insular, parietal, and limbic regions in the Dunedin cohort suggesting that individuals with greater liability for general psychopathology demonstrate poorer cognitive, interoceptive, sensorimotor, and emotional processing.

In Chapter 6, I showed that liabilities to internalizing, externalizing, and thought disorders also were related to deficits in occipital and cortico-cerebellar circuitry in both samples, consistent with the hypothesis that the p factor captures shared variance among these three disorder-liability factors. Internalizing, externalizing, and thought disorder liabilities also were associated with unique structural alterations in temporal gyrus and pole, parahippocampal gyrus, orbital frontal cortex, superior parietal lobule, and precuneus. Finally, in Chapter 7, I found that cortico-cerebellar circuitry mediated polygenic risk for schizophrenia and general liability for psychopathology in the DNS, but not the Dunedin sample. The failure to replicate the genetic correlates of the p factor in Dunedin suggests that the association found in the DNS sample may be a false positive due to lack of power in a relatively small sample for genetic analyses. Future research examining genes related to schizophrenia that are highly expressed in placenta and their interactions with early life complications may more robustly relate to the p factor.

The identification of meaningful structural neural correlates in two independent samples rebuts hypotheses that the p factor is due to response biases, measurement artifact, or central causal symptoms as part of a network. The structural alterations in occipital and cortico-cerebellar circuitry present in individuals with comorbid mental disorders is consistent with the hypothesis that disordered thought processes present in

most, if not all, mental disorder categories serves as a common mechanism underlying a general liability for psychopathology. Cortico-cerebellar circuitry deficits are typically found in individuals with thought disorders such as schizophrenia, but this research suggests that the mechanisms underlying risk for the most severe forms of disorder (i.e., thought disorders) also may predispose individuals to internalizing and externalizing disorders.

The additional gray matter reductions found in prefrontal, insula, anterior cingulate, parietal, and limbic structures supporting cognitive and emotional processing in the Dunedin cohort also are consistent with the "dysfunctional thinking" hypothesis, but do not preclude alternative hypotheses of poorer intellectual function, emotion dysregulation, and greater negative affect as common mechanisms underlying a general liability for mental illness. Future research examining differences in brain function can better distinguish which of these proposed mechanisms underlie the p factor. For example, one could examine differences in cerebellar activation and cortico-cerebellar functional connectivity during cognitive control tasks as associated with p factor scores to determine whether there is support for the "dysfunctional thinking" hypothesis. One such task is the Stroop (Peterson et al., 1999), which would likely activate cortico-cerebellar circuits because it relies on the ability to monitor errors and continuously update internal models based on task performance feedback. p factor scores also may be

related to differences in brain function during tasks that tap into emotion regulation, intellectual function, and negative affect. Assessing differences in brain function during tasks that assess these psychological processes will help to determine whether one or more of these proposed mechanisms might underlie the p factor.

The larger number of gray matter reductions found in the Dunedin cohort as compared to the DNS sample suggests a few hypotheses. For one, the Dunedin study members have greater variability in symptoms and are less highly selected than the DNS sample, which affords greater power to detect effects. This is consistent with the larger effect sizes found in the Dunedin cohort compared to the DNS sample. It is also possible that the differences in ages between the two samples is what contributed to the more profound gray matter reductions present in the middle adult Dunedin study members compared to the young adult DNS participants. Although the current research is cross-sectional, these findings suggest a developmental hypothesis of increasing structural gray matter alterations as people age and accumulate symptoms. Future longitudinal research should examine this question. In fact, because the Dunedin cohort is followed longitudinally, it will be possible to test whether differences in brain structure at age 45 predict future p factor scores.

Moreover, it will be important to determine whether these structural alterations are present in young children. The p factor has been identified in a sample as young as

3-5 years (Olino et al., 2015), suggesting the possibility that we can identify young children who are at risk for developing persistent, severe, comorbid psychopathology prior to the onset of such mental illness. Identifying neural correlates of the p factor in children and adolescents also may help us better determine whether alterations in occipital and cortico-cerebellar circuitry may be present earlier in life or whether they are a consequence of comorbid mental illness. If so, we may be able to use this information to inform more targeted prevention efforts to those youth who are likely to develop multiple forms of mental disorder prior to their onset.

In addition to informing prevention efforts, the meaningful behavioral, neural, and genetic correlates of the p factor as identified in this research provide continued support for transdiagnostic interventions, which target psychological processes that have been found to be associated with symptoms from multiple disorder categories. For example, Barlow and colleagues (2010) have created a unified protocol for treating anxiety and depressive disorders, which has been adapted for children and adolescents (Ehrenreich et al., 2008; Ehrenreich-May & Bilek, 2012). Preliminary results provide support for the effectiveness of these transdiagnostic treatments (Newby et al., 2015) and their use in preventing the onset of future disorders (Ehrenreich-May & Bilek, 2012). This kind of approach not only would be extremely cost- and time-efficient, but also could conceivably have benefits for prevention of future psychopathology by targeting

psychological processes across disorder categories prior to their onset. One possibility for streamlining intervention efforts is to administer transdiagnostic treatments to individuals with high p factor scores as the first-line treatment and then subsequently target remaining symptoms with specific evidence-based treatments. This of course would require valid and reliable assessment measures of a general liability for psychopathology.

The current research also suggests that the integration of external feedback into internal models and error monitoring as supported by cortico-cerebellar circuitry may be common psychological processes that are deficient in individuals with multiple, comorbid mental disorders and could be targeted in transdiagnostic interventions. Furthermore, biologically-based interventions such as transcranial magnetic stimulation and transcranial direct current stimulation (tDCS) on cerebellar and prefrontal regions could be used as a transdiagnostic treatment to reduce general symptoms. Preliminary research suggests that tDCS of cerebellar and prefrontal regions may improve cognitive functioning in psychosis (Gupta et al., 2017) and bipolar disorder (Minichino et al., 2015), as well as reduce symptoms of OCD (Bation et al., 2016).

Of course, this research is not without limitations. First, the cross-sectional design of the studies precludes establishing temporal order among the observed links between disorder-liability factor scores, polygenic risk, white matter integrity, regional

gray matter volume, and indicators of behavioral impairments. Future longitudinal research should examine this question. Second, I conducted these studies using a large volunteer sample of university students and a birth cohort from Dunedin, New Zealand, which might limit generalizability to patient populations. Third, the effect sizes were small; however, the associations between brain structure and p factor scores did replicate in the two independent and very different samples. Fourth, because the measurement of psychiatric symptoms was not exhaustive in both samples, I have an incomplete view of people's liability to psychiatric disorders and the findings need to be replicated with a more ethnically diverse sample of participants and an even more comprehensive assessment of psychiatric symptoms. Fifth, the region of interest and whole-brain analyses of brain structure were conducted in a subsample of the Dunedin cohort (approximately half of the cohort) due to ongoing data collection in the remaining study members. It will be important to conduct the analyses with the full cohort once data collection is complete. Finally, the extracted factor scores for 'p' undoubtedly contain error, which is not systematically modeled in subsequent regression analyses, possibly resulting in biased standard errors. As the aim of this research was to identify regions of interest for future studies, replication, including in studies using latent modeling, is imperative.

Despite these limitations, this research is an important initial step in identifying transdiagnostic biomarkers underlying multiple mental disorder categories. It guides future research directions on differences in neural function and functional connectivity of neural circuits, influences of early life stressors on polygenic risk for general psychopathology, and the development of the p factor throughout the lifespan. Further, this research demonstrates that comorbidity and severity, issues that have posed significant challenges to the fields of psychiatry and clinical psychology, can be used as an advantage by examining the etiology of a general liability for mental illness. Results are promising for being able to identify shared etiological mechanisms while also isolating the unique differences between internalizing, externalizing, and thought disorders. Ultimately, the hope is that using these disorder-liability factors will help identify shared and unique etiological mechanisms thereby streamlining research efforts and improving translation into effective prevention and intervention approaches.

Appendix A

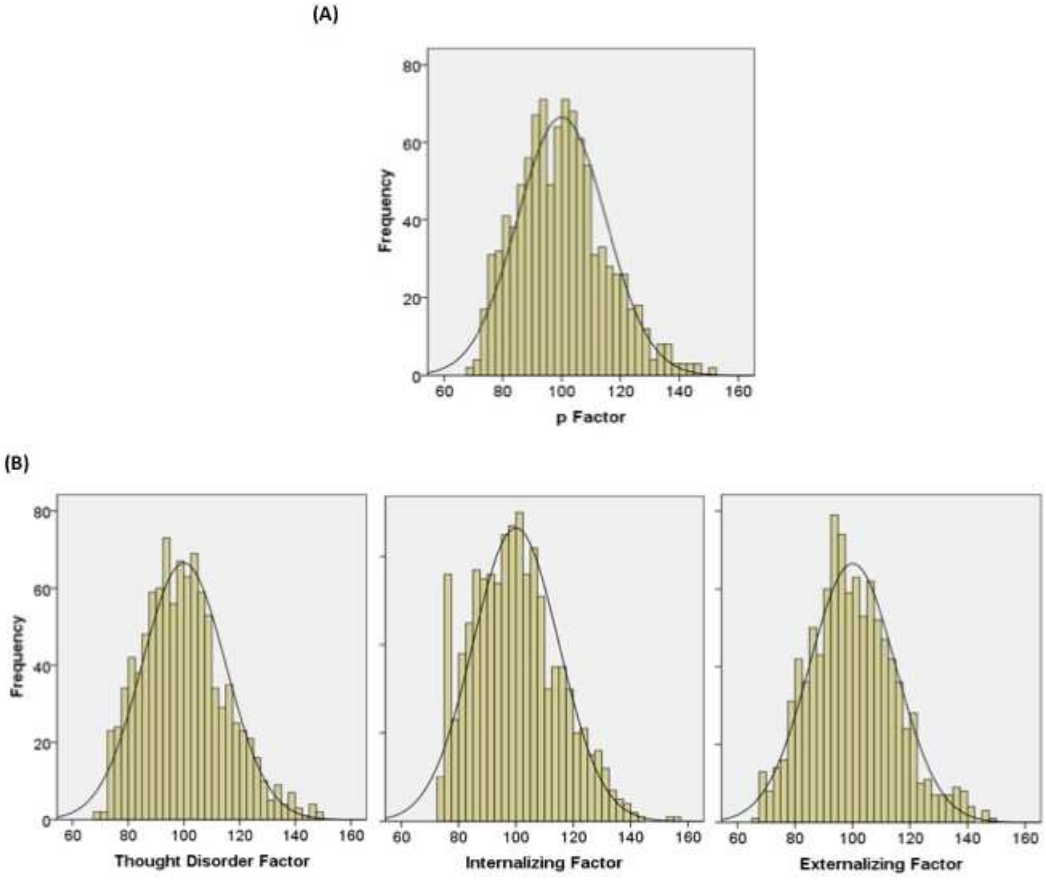

Figure 17: Distributions of (A) p factor scores from the bi-factor model and (B) thought disorder, internalizing, and externalizing factor scores from the correlated factors model in the full Dunedin cohort (n = 1,000).

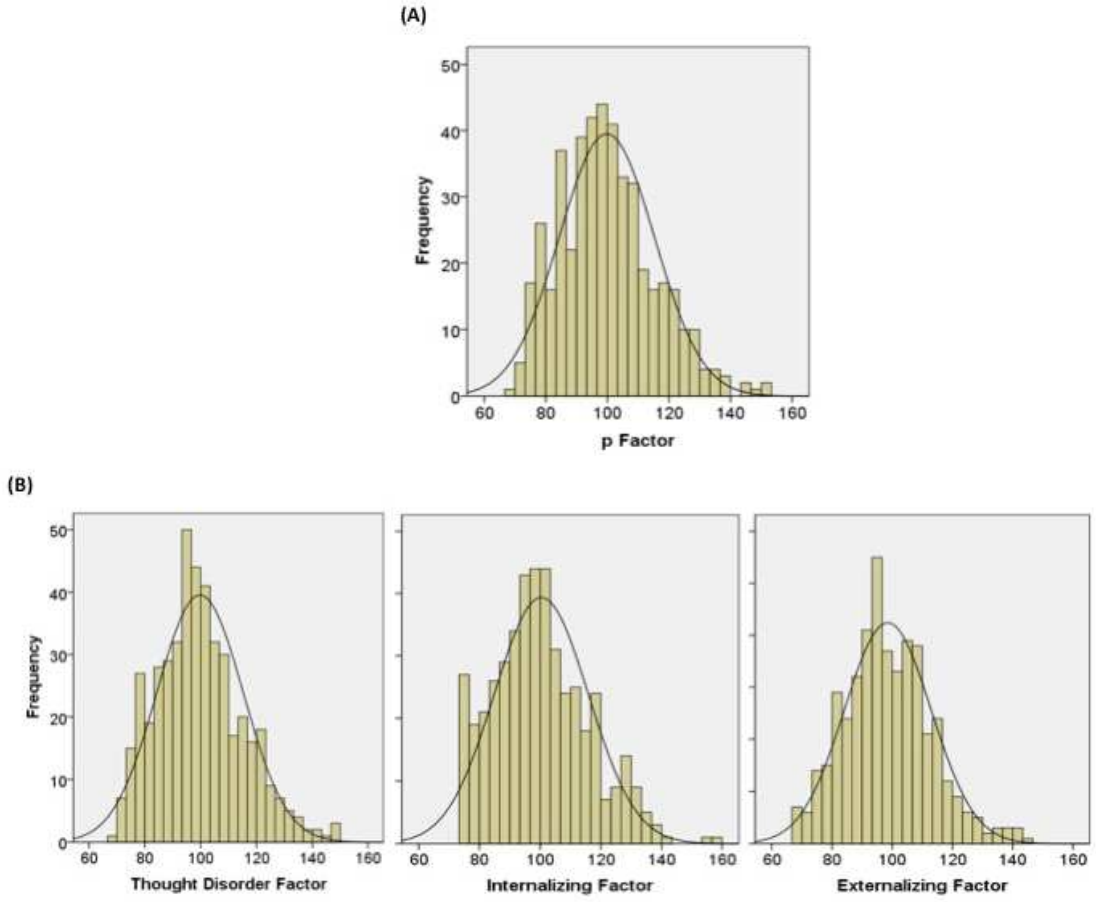

Figure 18: Distributions of (A) p factor scores from the bi-factor model and (B) thought disorder, internalizing, and externalizing factor scores from the correlated factors model in the Dunedin subsample with neuroimaging data available (n = 459).

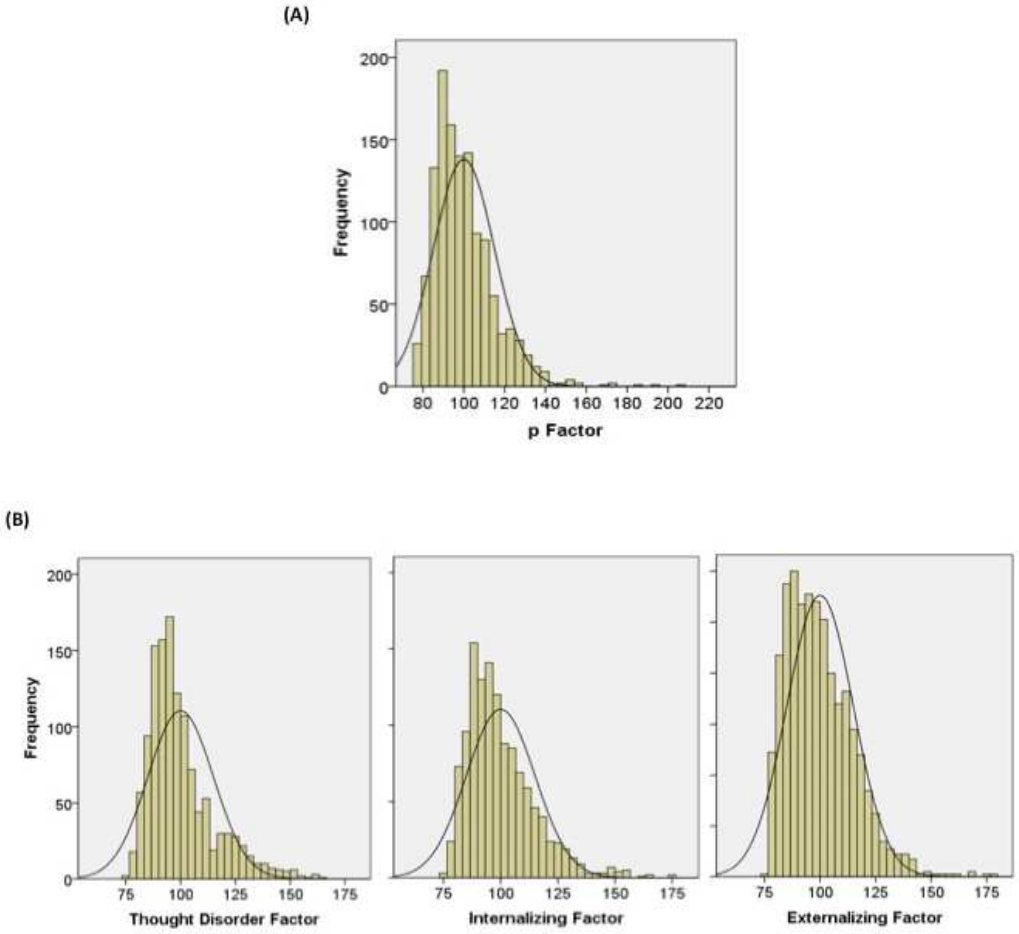

Figure 19: Distributions of (A) p factor scores from the bi-factor model and (B) thought disorder, internalizing, and externalizing factor scores from the correlated factors model in the DNS sample (n = 1,246).

Appendix B

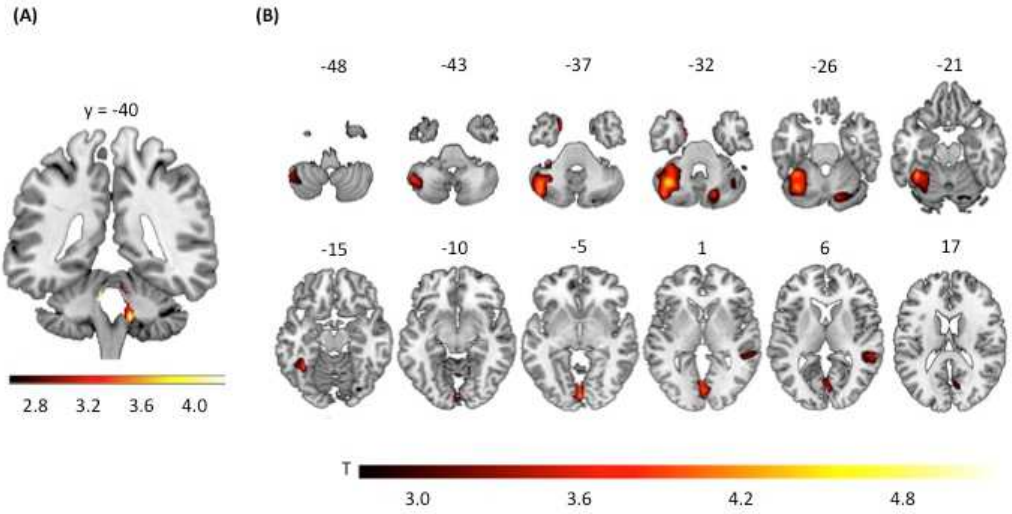

Figure 20: Statistical parametric maps from whole-brain exploratory analyses are shown to illustrate voxels exhibiting a significant negative correlation with internalizing factor scores from the correlated factors model in the DNS sample.

(A) DTI analyses show that poorer FA in the bilateral pons is related to internalizing factor scores. (B) VBM analyses show reduced GMV in occipital lobe, posterior cerebellum, and temporal lobe is related to internalizing factor scores. Colorbars reflect *t* scores.

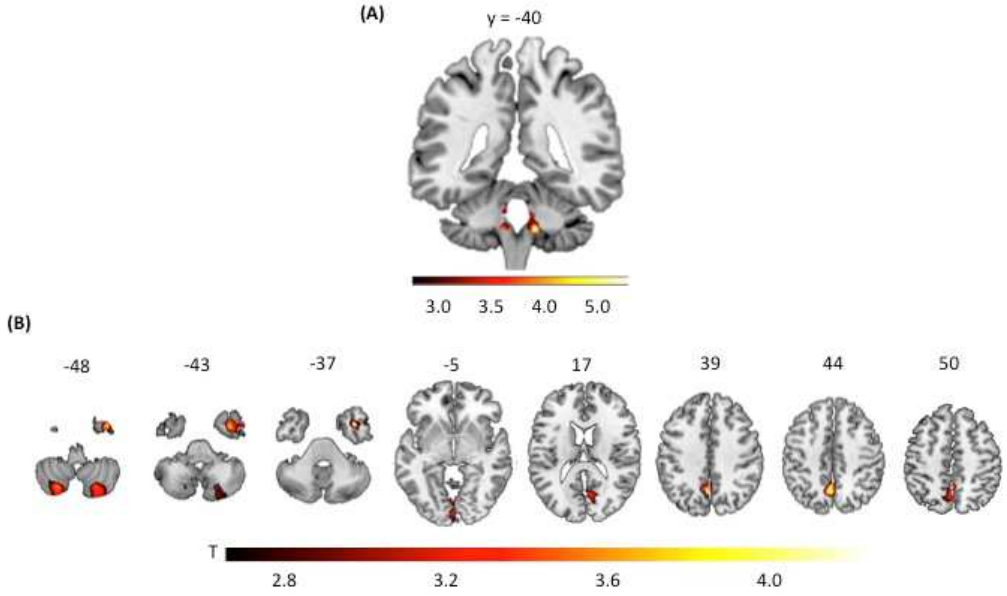

Figure 21: Statistical parametric maps from whole-brain exploratory analyses are shown to illustrate voxels exhibiting a significant negative correlation with thought disorder factor scores from the correlated factors model in the DNS sample.

(A) DTI analyses show that poorer FA in the bilateral pons is related to thought disorder factor scores. (B) VBM analyses show reduced GMV in the occipital lobe, posterior cerebellum, precuneus, and temporal lobe are related to thought disorder factor scores. Colorbars reflect *t* scores.

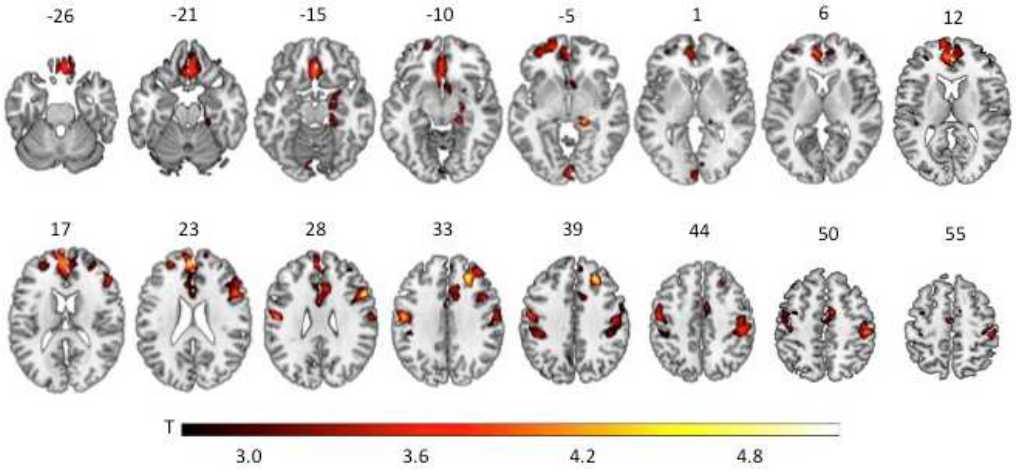

Figure 22: Statistical parametric maps from whole-brain exploratory analyses are shown to illustrate voxels exhibiting a significant negative correlation with internalizing factor scores from the correlated factors model in the Dunedin cohort.

GMV reductions in prefrontal, parietal, limbic, and occipital regions were associated with internalizing factor scores. Colorbar reflects *t* scores.

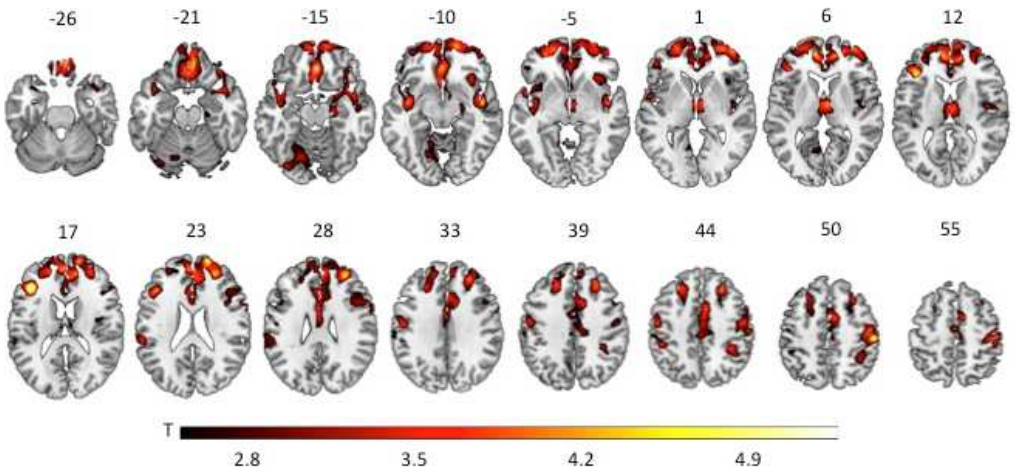

Figure 23: Statistical parametric maps from whole-brain exploratory analyses are shown to illustrate voxels exhibiting a significant negative correlation with externalizing factor scores from the correlated factors model in the Dunedin cohort.

GMV reductions in the prefrontal, parietal, temporal, occipital, and anterior cerebellar regions are related to externalizing factor scores. Colorbar reflects *t* scores.

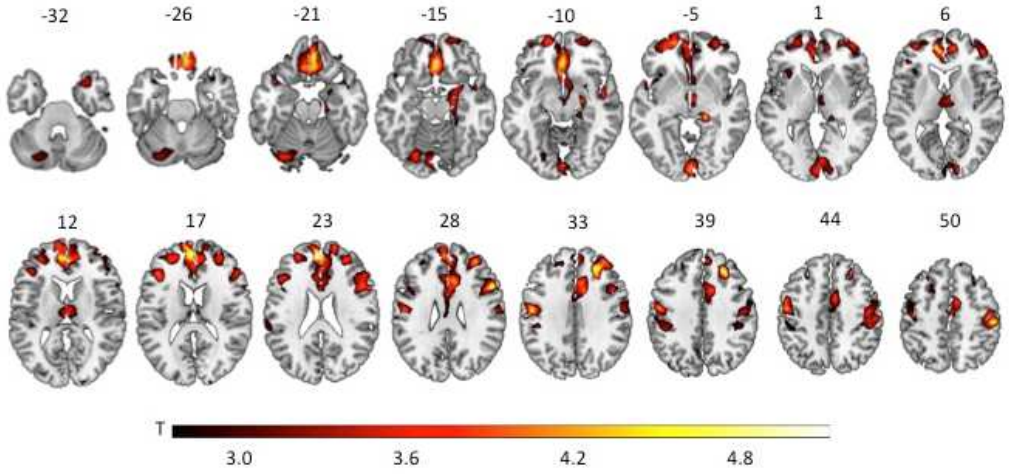

Figure 24: Statistical parametric maps from whole-brain exploratory analyses are shown to illustrate voxels exhibiting a significant negative correlation with thought disorder factor scores from the correlated factors model in the Dunedin cohort.

GMV reductions in prefrontal, parietal, limbic, occipital, and posterior cerebellar regions were related to thought disorder factor scores. Colorbar reflects *t* scores.

Appendix C

Table 17: Test of differences of demographic and ancestry variables between DNS participants with and without diffusion tensor imaging data.

Demographic Variables	DTI Data Present			DTI Data Absent			P-value
	N	**Mean**	**St. Dev.**	**N**	**Mean**	**St. Dev.**	**T**
p Factor Scores	365	98.486	13.134	110	97.958	12.854	0.710
SCZ PRS	365	-5.907	2.189	110	-5.782	2.009	0.591
MDS 1	365	0.352	12.700	110	-1.042	12.239	0.309
MDS 2	365	-0.167	5.754	110	0.466	4.456	0.225
	% Sample			% Sample			X^2
Sex							0.231
Male	47.4			40.9			
Female	52.6			59.1			
Age							0.634
18	18.6			20.0			
19	27.9			23.6			
20	20.3			23.6			
21	24.4			27.3			
22	8.8			5.5			

Independent samples t-tests were used for the continuous variables p factor scores, SCZ PRS, and MDS 1 and 2. Chi-square tests were used for categorical variables sex and age. SCZ PRS = schizophrenia polygenic risk score; MDS = Multidimensional scaling component (top two ancestry-informative components).

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Biography

Adrienne Lynn Romer was born in Chicago, Illinois on August 25th, 1989. She attended Cornell University in Ithaca, NY, USA, and received her Bachelor of Science in Human Development with distinction in May 2011. Following her undergraduate studies, she worked as a research assistant in the Section on Development and Affective Neuroscience at the National Institute of Mental Health with Daniel Pine. Her work in that laboratory resulted in co-authored publications on neural functioning in children with anxiety disorders in *Developmental Cognitive Neuroscience* and *NeuroImage*. In 2013, she began her studies in clinical psychology at Duke University in Durham, NC, USA, and she will receive her Doctor of Philosophy in Psychology and Neuroscience in August 2019. During her tenure at Duke, she published two first-author articles, "Are rash impulsive and reward sensitive traits distinguishable? A test in young adults" (*Personality and Individual Differences*, 2016) and "Structural alterations within cerebellar circuitry are associated with general liability for common mental disorders" (*Molecular Psychiatry*, 2018), and she has co-authored publications in *Brain*, *Biological Psychiatry*, and *Emotion* (accepted for publication). She was awarded a Graduate Research Fellowship from the National Science Foundation in 2015 and the Society for a Science of Clinical Psychology Student Poster Award and the Association for Psychological Science Student Researcher Award in 2017.