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Translational insights into the genetic etiology of mental health disorders: Examining risk factor models, neuroimaging, and current dissemination practices

Jessica L. Bourdon
Virginia Commonwealth University

Translational insights into the genetic etiology of mental health disorders: Examining risk factor models, neuroimaging, and current dissemination practices

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy of Clinical and Translational Sciences – Psychiatric, Behavioral, and Statistical Genetics concentration at Virginia Commonwealth University.

by

Jessica Lynn Bourdon

Bachelor of Science, Psychology, University of Richmond, May 2010
Bachelor of Arts, Cognitive Science, University of Richmond, May 2010
Doctor of Philosophy, Clinical and Translational Sciences, Virginia Commonwealth University, May 2019

Director: John M. Hettema
Associate Professor
Department of Psychiatry
Virginia Institute for Psychiatric and Behavioral Genetics
Virginia Commonwealth University

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*Indicates manuscripts that have either been accepted for publication or are currently under review. They have been modified to be included in this dissertation.

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List of Abbreviations

-2LL: Minus twice the log-likelihood
A: Additive genetic factors
ADHD: Attention deficit hyperactivity disorder
AIC: Akaike information criteria
AFNI: Analysis of functional neuroimages
ANOVA: Analysis of variance
ASD: Autism spectrum disorder
AUD: Alcohol use disorder
BI: Behavioral inhibition
BIQ: Behavioral Inhibition Questionnaire
BOLD: Blood oxygen level dependent
C: Shared / familial environmental factors
CBCL: Child Behavior Checklist
CI: Confidence interval
CFA: Confirmatory factor analysis
CP: Common pathway model
D: Dominant genetic factors
D&I: Dissemination and implementation science
DSM-IV: Diagnostic and Statistical Manual - 4th edition
DSM-5: Diagnostic and Statistical Manual - 5th edition
DZ: Dizygotic
E: Unique / individual environmental factors
EFA: Exploratory factor analysis
EFAT: Emotional fact activation task
FDR: False discovery rate
FWER: Family-wise error rate
fMRI: Functional magnetic resonance imaging
GWAS: Genome-wide association study
IP: Independent pathway model
JAS: Juvenile Anxiety Study
LRT: Likelihood ratio test
MATR: Mid-Atlantic Twin Registry
MZ: Monozygotic
NCATS: National Center for Advancing Translational Sciences
NVS: Negative valence systems

OLS: Ordinary least squares
PBI: Parental Bonding Instrument
SCARED: Screen for Child Anxiety Related Disorders
SCARED-C: Screen for Child Anxiety Related Disorders - Child Version
SCARED-P: Screen for Child Anxiety Related Disorders - Parent Version
SD: Standard deviation
SEM: Structural equation modeling
SUD: Substance use disorder
VCU: Virginia Commonwealth University

Abstract

TRANSLATIONAL INSIGHTS INTO THE GENETIC BASIS OF MENTAL HEALTH DISORDERS: EXAMINING RISK FACTOR MODELS, NEUROIMAGING, AND CURRENT DISSEMINATION PRACTICES

By Jessica Lynn Bourdon, Ph.D.

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy of Clinical and Translational Sciences – Psychiatric, Behavioral, and Statistical Genetics concentration at Virginia Commonwealth University.

Virginia Commonwealth University, 2019.

Director: John M. Hettema, Associate Professor, Department of Psychiatry, Virginia Institute for Psychiatric and Behavioral Genetics

Psychiatric genetics is a basic science field that has potential for practical application and effective translation. To date, translational frameworks utilized by this field have been linear (e.g., sequential) in nature, focusing on molecular genetic information. It is proposed that non-linear (e.g., socio-ecological) frameworks are a better way to immediately translate non-molecular genetic information. This dissertation explored the translation of psychiatric genetic information in two ways. First, a survey was sent to academic stakeholders to assess the state of the science regarding the translation of genetic information to the clinical care of mental health disorders. Findings from this indicate a translation-genetic competence gap whereby genetic knowledge reinforces linear frameworks and genetic competence is needed to achieve effective translation in this content area. Second, a new risk factor model for social anxiety was created

that incorporated genetic, environmental, and neurophysiological risk factors (behavioral inhibition, parental bonding, emotion reactivity). Findings indicate that genetic etiology is more informative knowledge that can influence risk factor models and possibly prevention and intervention efforts for social anxiety. Overall this dissertation paves the way for examining the translational capacity of psychiatric genetics in a clinical setting. It constitutes the first examination of barriers to and a potential solution for the most effective translation of psychiatric genetic information.

Chapter 1: The Intersection of Translational Science and Psychiatric Genetics

Introduction

Effective development and translation of genetically-informed models is key to leveraging our knowledge of the etiology of psychiatric diseases and improving treatment (International Society of Psychiatric Genetics, 2017). As we enter a post-genome-wide association study (GWAS) era, it is time to reflect upon the breadth and application of genetic information to maximize its impact (Dick et al., 2018). While genetically-informed research utilizes data from epidemiological (twin, family) and molecular (linkage, GWAS, genome-wide complex trait analysis, next-generation sequencing, polygenic risk scores, epigenetics) sources (Kendler & Eaves, 2005), the latter has been the primary focus of any genetics-related translational efforts (Fernandez et al., 2013; Kimball, Nowakowski, Maschke, & McCormick, 2014; Klitzman et al., 2013; Sullivan et al., 2018). Translation of this type of information has been effective for chronic, physical disorders such as cardiovascular disease (Arnett et al., 2007; Ebomoyi, 2013; Vornanen et al., 2016; Khera & Kathiresan, 2017), breast cancer (Cornel & El, 2017; Gil et al., 2003; Macdonald, Sarna, Weitzel, & Ferrell, 2009; Norman & Brain, 2005; Phillips et al., 2006), macular degeneration (Black & Clark, 2016), and other similarly complex disorders. However, it has had little effect on the care of psychiatric conditions (International Society of Psychiatric Genetics, 2017; Sullivan, Daly, & O'Donovan, 2012; Sullivan et al., 2018; Visscher et al., 2016). There are several key barriers that have prevented forward momentum in translating genetic information to the care of mental health disorders.

Barriers to translating genetic information broadly, regardless of disorder type, include education and training, stigma, overall engagement of stakeholders (Sperber et al., 2017; Zhou et al., 2014), and disagreement over whose responsibility it is to discuss genetic information with

patients (Sullivan et al., 2012; Visscher et al., 2016; Finn & Smoller, 2006). These barriers are amplified in the context of mental health care. This is likely due to the assumption that the translational frameworks that have been effective for chronic, physical conditions will be equally effective for psychiatric disease. Such an assumption has been bolstered by recent success in identifying and replicating genetic variants associated with Schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; International Schizophrenia Consortium, 2009), bipolar disorder (International Schizophrenia Consortium, 2009), and autism spectrum disorder (ASD) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). (For broader discussions also see: Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Dick et al., 2018; Sullivan et al., 2012; Visscher et al., 2016). However, these disorders are the exception rather than the norm for what is currently understood about psychiatric disorders at the molecular genetic level. The mental health conditions for which we know the most at a molecular level tend to display higher heritability. This means that at the population level, most of the variance that is associated with development of the disorders can be currently attributable to genetic risks. However, most psychiatric disorders have at least equal influences of genetic and environmental factors, if not more influences of the environment (Polderman et al., 2015). The vast majority of psychiatric disorders have little-to-no known replicated molecular genetic variants. There have been some replicated variants associated with alcohol use disorder (AUD) (Bierut et al., 2012; Gelernter et al., 2014), cannabis use disorder (Agrawal et al., 2018), and depression (CONVERGE Consortium, 2015), but these variants account for such little genetic variance and are likely not actionable anytime in the near future. What *is* known about *all* psychiatric disorders, though, derives from twin and family sources (i.e., non-molecular genetic epidemiological data).

By shifting focus from molecular to epidemiological sources of genetic information, there should be an accompanying shift in translational frameworks used when approaching research-to-practice in this area. There should also be a shift toward determining the translational applicability of not just psychiatric genetic information broadly, but information specific to common mental health conditions where more epidemiological than molecular information is known (i.e., shift from focusing on molecular to non-molecular information). It is in these shifts that appropriate examination of how best to incorporate genetic information into the care of mental health disorders can occur.

This dissertation examines these shifts both broadly and specifically. The first aim assesses the state of the science regarding the translation of genetic information to the clinical care of mental health disorders. The second develops a genetically-informed risk factor model for pre-adolescent social anxiety by examining its relationship with behavioral inhibition and parental bonding. The final aim is an extension of the second, assessing the inclusion of neurophysiological data into the risk factor model for pre-adolescent social anxiety. Together, these aims will constitute the first examination of barriers to and a potential solution for the most effective translation of psychiatric genetic information.

Translational Science Frameworks

There are many approaches of translational science, each with specific purposes and foci. When considering how best to translate genetic studies for use in mental health care, five approaches are commonly considered: (a) bench-to-bedside, (b) precision medicine, (c) dissemination and implementation science, (d) prevention science, and (e) research-to-policy. The first two frameworks are traditional and linear in nature (van der Laan & Boenink, 2012) having been commonly used when translating genetic information as already mentioned and with

little effect for psychiatric conditions (Visscher et al., 2016). The latter three take a socio-ecological approach to translation and as such, may be better suited for translation of non-molecular genetic information in treating mental health conditions.

Bench-to-bedside is an approach that begins with basic bench science aimed at identifying mechanisms for disease and moves through a structured series of studies to examine the applicability of basic findings to treatment of disease (Waldman & Terzic, 2010; Khoury et al., 2007). Personalized medicine is broadly the use of any biological information about an individual patient to improve their health that may be acquired from the bench or beyond (i.e., family history of disease, known drug allergies, etc.) (Collins & Varmus, 2015; Jameson & Longo, 2015). More often than not, it is the application of bench-to-bedside findings (i.e., techniques or drugs deemed effective and efficacious in clinical trials). Both bench-to-bedside and precision medicine utilize biological information and thus, in the context of psychiatric disorders, rely heavily on gene-finding efforts that have thus far been unsuccessful (Visscher et al., 2016; Sullivan et al., 2016) except for the aforementioned highly heritable diseases (Schizophrenia, bipolar disorder, ASD) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014; International Schizophrenia Consortium, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). They also focus on treatment and intervention with a patient-level perspective.

Dissemination and implementation science (D&I) is another approach to translation. Similar to the former two approaches, D&I embraces an individualized view of translation by focusing on treatment and intervention more than prevention, although this is beginning to change (Collins & Varmus, 2015). Unlike the bench-to-bedside and precision medicine, D&I uses multiple lenses to understand and model how scientific findings can influence services

downstream. Most D&I frameworks emphasize building interventions with the ecology of the service system in mind including the perspectives of multiple stakeholders. For example, interventions specific to mental health must consider patient, family, provider, agency, and broader systemic perspectives to achieve the most beneficial public health effects (Atkins, Rusch, Mehta, & Lakind, 2016; Schoenwald & Hoagwood, 2001; see also Cox, Martinez, & Southam-Gerow, 2019). The ecological approach of D&I science relies more heavily on collaborations among stakeholders and assumes a non-linear path to translation (van der Laan & Boenink, 2012; Chambers & Azrin, 2013; Glasgow et al., 2012). This deep communication and collaboration improves the flow of information between stakeholders and brings a focus to both persons and settings in the socio-ecology (Atkins et al., 2016), ultimately leading to more informed treatment and improved patient outcomes.

Prevention science is a translational approach similar to D&I science in that also focuses on collaboration and involvement of multiple stakeholders. However, prevention science focuses on general public health with a strong emphasis on prevention efforts more so than treatment or intervention (Bradshaw & Haynes, 2012). Examples can be found in community-based participatory research (Minkler & Wallerstein, 2008), public health genomics (Arnett et al., 2007; McBride et al., 2010), and school-based programs (Conrod et al., 2013; Schuckit et al., 2012). Here, emphasis is placed on screenings, health education, and similar public health approaches to identify individuals who are at risk of a disorder. Finally, research-to-policy is the translation of knowledge into policy changes at the local, state, or federal level. While the remainder of the dissertation will not focus on this framework, it still deserves mention. There are no specific policies about genetic information specific to mental health. Even 23andMe does not offer testing for mental health conditions (the most closely related variant that they test for is

the one responsible for the alcohol flush reason) and strongly advise against using their tests for health reasons (23andMe Inc., 2019). However, organizations such as the American Society for Human Genetics have made official statements warning patients about the results of direct-to-consumer marketing of genetic tests (Hudson, Javitt, Burke, & Byers, 2007). There is also a lively research base investigating the ethics of biobanking (Kimball et al., 2014) and the return of incidental findings to patients (Fernandez et al., 2013; Klitzman et al., 2013; Ramoni et al., 2013; Wilson et al., 2016), issues which will likely lead to official policy in the near future.

A Brief Overview of Psychiatric Genetic Information

Psychiatric genetics is a basic science field but has potential for practical application and translation. There are three key questions that comprise the foundation of the field: (a) do genes affect a trait, (b) how much do genes affect a trait, and (c) where/what are the genes. The first two questions fall under the non-molecular, genetic epidemiology umbrella while the latter utilizes molecular genomic techniques (Kendler & Eaves, 2005). It is widely accepted that for complex traits such as psychiatric disorders, each trait is the product of the effects of hundreds (if not thousands) of genes that themselves are inherited by Mendel's traditional laws of inheritance (infinitesimal model) (Fisher, 1918). The effect of each gene will contribute little to the overall variation of the trait, but all of the genes create a cumulative effect (i.e., the trait) with a normal distribution (central limit theorem) (Neale, Ferreira, Medland, & Posthuma, 2008). This normal distribution likely represents an additive model whereby the effect of each individual gene aggregates to form the likelihood of disease when also combined with environmental factors. In biometrical modeling (Neale & Cardon, 1992), the averaged cumulative effects at each quantitative trait locus (i.e., the alleles of a gene) are estimated based on the expected correlations between varying types of related individuals, in particular twins. Using this basic

knowledge, heritability estimates, family history and aggregation of a trait, gene-environmental interplay, endophenotypes (intermediate phenotypes), sibling contrast effects, cultural transmission, genetic attenuation and innovation, and more (Neale & Cardon, 1992) can be estimated without needing to rely on molecular techniques. The specific epidemiological techniques for these types of analyses will be discussed in subsequent chapters.

Shifting Focus to a Specific Disorder: Social Anxiety

Due to the fact that most psychiatric disorders are common and the product of the environment plus hundreds or thousands of genes (i.e., polygenic effects), additional questions that focus on the translation of information need to be posited in the field of psychiatric genetics which complement the core three. These are: (a) is this information actionable, (b) if so, for whom is this information actionable, (c) how can this information be used, and (d) what are the barriers to using this information. Such questions make the field of psychiatric genetics, and genetic information in general, more approachable for all stakeholders involved in translating such information to clinical care. Instead of focusing on rare psychiatric disorders, this dissertation examines these questions in the context of pre-adolescent social anxiety, a common mental health concern.

Social anxiety is a major public health concern affecting 9.1% (Merikangas et al., 2010) of adolescents with a mean age of onset of 10-13 years. (Rapee & Spence, 2004). It is associated with several negative outcomes (Chansky & Kendall, 1997; Erath, Flanagan, & Bierman, 2007; Spence, Donovan, & Brechman-Toussaint, 1999) and treatment and/or early intervention are usually needed to help with symptoms (Hirshfeld-Becker & Biederman, 2002). Despite the fact that social anxiety has a pre-adolescent mean age of onset, only the genetic epidemiology of social anxiety in adults has been well-researched using twin methodology (Hettema, Neale, &

Kendler, 2001; Hettema et al., 2005; Kendler, Gardner, & Lichtenstein, 2008). In addition, neurophysiology is broadly of interest due to its biological nature and implicit ties to genetic information (Moore, Sawyers, Adkins, & Docherty, 2017). Specific to social anxiety, while its neurophysiology is widely studied, there is little research on the neurophysiology of the disorder in pre-adolescents and in relation to other phenotypic risk factors. To our knowledge, no comprehensive risk factor model exists for pre-adolescent SOC that incorporates genetic epidemiology or neurophysiological data. This lack of inclusion of all available biological information inhibits the flow of information to other researchers, clinicians, patients, and other key stakeholders. Thus, there is currently no way to assess whether such information is actionable, for whom, and how it can be used.

The standard treatment for pediatric social anxiety is cognitive behavioral therapy or parent-based therapy (Aune & Stiles, 2009; Gould et al., 1997; Hirshfeld-Becker et al., 2010; Spence, Donovan, & Brehcman-Toussaint, 2000), neither of which take genetically- or neurologically-informed findings into account. The risk factor model in this dissertation may serve as the first step toward creating a preventative intervention for social anxiety that takes these new factors into account. To date, prevention efforts for pediatric social anxiety also utilize cognitive behavioral therapy (Aune & Stiles, 2009) or focus on parental intervention (Gould et al., 1997; Bayer et al., 2010). It is not unreasonable to think that non-molecular genetic or neurological information in the form of a risk factor model could inform treatment or prevention efforts and thus patient outcomes (Dick et al., 2018). This can be accomplished by focusing on a few key risk factors (e.g., Degnan, Almas, & Fox, 2010) where the mechanisms of the relationship between the risk factors and disorder of interest can be examined in more depth. This is in contrast to broad models that may not provide much detail (e.g., Acarturk et al., 2009;

Ollendick & Benoit, 2012; Rapee & Hemberg, 1997; Rapee & Spence, 2004). Thus, this dissertation will focus on the relationship between one key risk factor for social anxiety disorder, behavioral inhibition, and two other factors related to both phenotypes, parental bonding and emotion reactivity (the latter constitutes a neurophysiological risk factor). Both are highly associated with pediatric SOC (Rapee & Spence, 2004; Bayer et al., 2011; Bayer, Sanson, & Hemphill, 2006; Fox et al., 2005) but the specific genetic and neuroimaging mechanisms surrounding these relationships are not well understood.

Dissertation Roadmap

This dissertation is made up of two key sections. The first focuses on translational insights into psychiatric genetic research. It is comprised of two chapters that provide a literature review on translational science in the context of psychiatric genetics and a description of a survey designed to assess the translation of genetic information into mental health care (aim 1), respectively. The next section dives into translating from the ground up; in other words, beginning with basic science research questions with potential implications for practice. This section ends by discussing potential ecological perspectives on translating non-molecular information into mental health care. In total, this section has five chapters that create a risk factor model of pre-adolescent social anxiety by examining its relationship with BI from biometrical (aim 2) and neuroimaging (aim 3) perspectives.

Overall, this dissertation will examine global and specific aspects of translating psychiatric genetic information to the clinical care of mental health disorders. Results will identify global barriers to this translational practice as well as create a risk factor model with potential implementation capability specific to one common disorder. All efforts will be made to

maintain a collaborative, socio-ecological perspective of translation throughout this dissertation, although admittedly aims 2 and 3 have more of a linear flavor than desired.

Dissertation Aims

The aims and corresponding hypotheses, steps, and research questions for this dissertation can be found below in Table 1.1.

Table. 1.1. Outline of dissertation aims.

Aim	Hypothesis, Step, and/or Research question	Chapter(s)
Aim 1: Assess the state of the science regarding the translation of genetic information to the clinical care of mental health disorders from an academic perspective.	Step 1: Descriptive statistics for each variable to get overview of the state of the science Step 2: Examine hypotheses / research questions from step 1 (see below) Step 3: Analysis of key open-ended questions Step 4: Limited psychometrics Hypothesis 1.1: There will be positive relationships between genetic competence and questions about (a) current translational practices, (b) the importance of translation, (c) willingness to improve own translational skills, and (d) impact on care. In other words, the stronger participants' genetic competence then the more thoroughly they can think about translating genetic information. Hypothesis 1.2: There will be positive relationships between genetic knowledge and questions about (a) current translational practices, (b) the importance of translation, (c) willingness to improve own translational skills, and (d) impact on care, but these relationships will not be as strong as those for genetic competence. In other words, the stronger participants' genetic competence then the more thoroughly they can think about translating genetic information. Stronger genetic knowledge is a likely barrier that prevents stakeholders from thinking in non-linear ways about translating genetic information. Research question 1.1: Are there differences in genetic knowledge and competence among participants based on job type (researcher, clinician, both, neither)?	3
Aim 2: Develop a genetically-informed risk factor model for pre-adolescent social anxiety disorder.	Hypothesis 2.1: The relationship between childhood behavioral inhibition and pre-adolescent social anxiety is causal. Hypothesis 2.2: Parental bonding moderates the relationship between behavioral inhibition and social anxiety. Hypothesis 2.3: Parental bonding is a measured/specified common environment variable in the biometrical model of behavioral inhibition and social anxiety.	6, 7

Aim 3: Assess the inclusion of neurophysiological data into the risk factor model for pre-adolescent social anxiety disorder.	Hypothesis 3.1: Heightened emotion reactivity to threatening faces will be associated with increased symptoms of pre-adolescent social anxiety. Hypothesis 3.2: Heightened emotion reactivity to faces will be associated with increased symptoms of childhood behavioral inhibition. Hypothesis 3.3: Increased emotion reactivity moderates the relationships between behavioral inhibition and social anxiety.	8

Chapter 2: The State of Translating Psychiatric Genetics Research: A Review[1]

Introduction

Psychiatric disorders are a major burden in the U.S. resulting in over $300 billion annually in cost from healthcare expenses, loss of wages, and disability benefits (Centers for Disease Control and Prevention, 2011). Among adults, over a quarter of the population has been diagnosed with one or more psychiatric disorders (Kessler, Chiu, Demler, & Walters, 2005). Costs will only continue to increase without effective prevention, detection, treatment, and support for these conditions. The translation of molecular genetic information to the clinical realm has helped in the prevention and treatment of several chronic, physical disorders such as cardiovascular disease, cancer, and more recently diabetes (Vornanen et al., 2016). Thus, assessing the translation of genetic information to the care of psychiatric disorders is a necessary step toward possibly reducing mental health morbidity and mortality (Visscher et al., 2016; Sullivan, Daly, & O'Donovan, 2012).

Unfortunately, the application of genetic information – whether it be non-molecular genetic epidemiological (family history, population level information) or molecular genomic data – is absent in prevention and treatment strategies for psychiatric disorders when compared to other chronic medical conditions. For example, the incorporation of genomics testing for *BRCA* variants in the clinical setting has led to applications for the diagnosis of breast cancer and more effective treatment (Phillips et al., 2006). Progress in the area of breast cancer has also been made in understanding how patients, researchers, and clinicians feel about complex topics such as the return of incidental genomic findings and biobanking of DNA samples (Kimball, Nowakowski, Maschke, & McCormick, 2014; Fernandez et al., 2013). This level of research knowledge (e.g., genomic findings, insights into stakeholders' attitudes) continues to expand for

[1]Modified version of the manuscript Bourdon, J. L., Davies, R., Overstreet, C. M., Langi, G., & Long, E. C. (In Review). The state of translating psychiatric genetics research: An brief review. *Translational Issues in Psychological Science.*

many physical disorders but is not yet available for psychiatric disorders. This has lead many to conclude that the application of genetic information to mental health is years away (Sullivan et al., 2016; Sullivan et al., 2018; Visscher et al., 2016). It is likely that there is no "one size fits all" approach to translation.

The type of translational framework utilized is to inform and expedite the ways in which genetic information is integrated into the clinical care of psychiatric disorders. A proper understanding of such frameworks and their applications, both broadly and in the context of psychiatric genetics genetics, are a necessary first step to explore this possibility. Translational frameworks can be divided into two broad categories, linear and non-linear / socio-ecological (van der Laan & Boenink, 2012) (see Figure 2.1). The first are those that follow a linear structure, such as bench-to-bedside (research that begins at the biological level and can eventually lead to clinical trials or other patient-focused initiatives) (Khoury et al., 2007; Waldman & Terzic, 2010) and precision medicine (the use of biological information to improve patient health that may be acquired from the bench or beyond) (Collins & Varmus, 2015; Jameson & Longo, 2015). These frameworks are highly prevalent across all health-related research fields but are particularly relevant within fields possessing a medical or biological focus. They have been largely effective for the translation of molecular genetic information about chronic, non-psychiatric diseases such as breast cancer (Andreassen, 2017; Cornetta & Brown, 2013), type 2 diabetes (Chan & Ginsberg, 2011), and coronary heart disease (Ginsberg & Willard, 2009).

The second category of translational frameworks are those that require simultaneous integration of information from many stakeholders, such as (a) dissemination and implementation (D&I), which focuses on the ecology of service delivery (Chambers & Azrin,

2012; Glasgow et al., 2012; van der Laan & Boenink, 2012), and (b) prevention science, which incorporates risk factors in a trans-disciplinary manner into the prevention of behavioral disorders (Fishbein, 2016). These frameworks have been shown to be effective for assessing community needs (Kimball et al., 2014), evaluating mental health service delivery (Rodriguez, Southam-Gerow, O'Connor, & Allin Jr., 2014), and targeting interventions towards individuals at risk for alcohol use disorders (Schuckit et al., 2016). They are socio-ecological and non-linear in nature, meaning that they integrate the simultaneous perspective of stakeholders to further research and clinical needs.

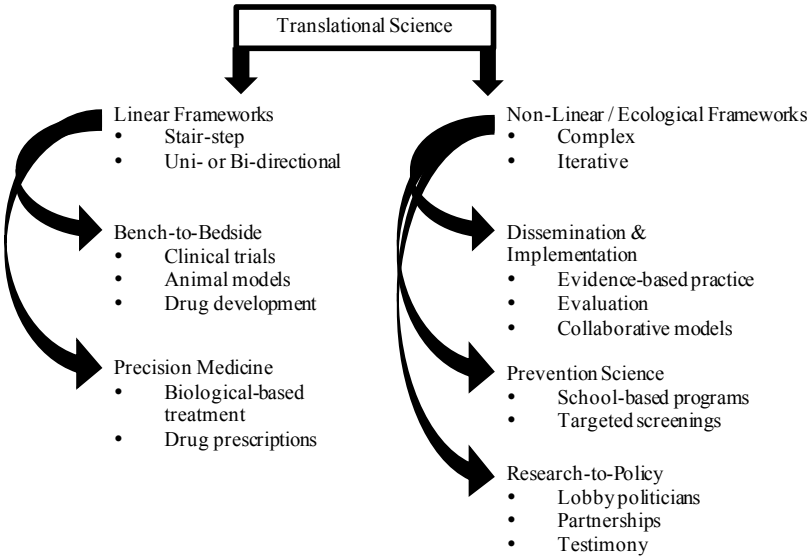

Figure 2.1. Flowchart of translational frameworks.

It has been suggested that frameworks following traditional linear views of translation may not be as effective for psychiatric conditions as they are for other illnesses (van der Laan & Boenink, 2012), a viewpoint that aligns with calls to shift focus from the application of genetics to the study and care of psychiatric disorders (Sullivan et al., 2012; Wittchen et al., 2014). With such a shift, genetic findings from all sources would be carefully and mindfully applied to

psychiatric disorders and can even be included in prevention efforts instead of current efforts that solely focus on finding genomic variants.

Specific Aims

It is necessary to understand the state of the science regarding the translation of psychiatric genetic information. The current study will provide a comprehensive overview of the literature in this area. The primary goal is to examine which frameworks/models are most commonly utilized when translating genetic information (family history, heritability estimates, molecular genomic data) about psychiatric disorders. Secondary analyses will examine trends in the type of genetic information used (broad, molecular, epidemiological, epigenetics) and disorder of interest (anxiety, alcohol use, Schizophrenia, mood, etc.) in each study. Finally, overall benefits/challenges to such translation will be discussed.

Methods

Review

A thorough literature review was conducted in multiple steps. First, all combinations of terms from three groups were searched in EBSCOhost, Google Scholar, and PubMed. The first group of terms named translational frameworks ("translation;" "personalized medicine" OR "precision medicine;" "bench to bedside;" "implementation science"), the second group specified the illness type ("mental health;" "psychiatr*"), and the final group indicated types of genetic information ("genetic OR genomic;" "twin OR family OR heritability"). Search results were limited through December 2017 when the review began. The abstracts from all potentially relevant articles were downloaded.

Next, each abstract was assigned to two reviewers who independently completed an inclusion/exclusion checklist for each assigned abstract. Inclusion criteria were that the abstract

must name or imply a translational framework, explicitly mention genetic information, and focus on mental health (i.e., name a psychiatric disorder or be a broad discussion of mental health). Exclusion criteria were not meeting one or more of these criteria, not being a peer-reviewed article, and not being in English. Conference abstracts, short commentaries, dissertations, book chapters, and editorials were automatically excluded. If abstracts were too brief due to journal restrictions, reviewers were allowed to download full articles to complete the checklist.

The final step involved the lead author closely reviewing the included abstracts to settle disagreements among reviewers, confirm that included abstracts met all inclusion criteria, and organize abstracts into clear categories with appropriate coding. The categories of the articles were: translational framework (precision medicine, bench-to-bedside, D&I, prevention science, broad discussion of translation, other, multiple frameworks), type of genetic information (epidemiology - i.e., family, twin, heritability studies; molecular genetic information - i.e., candidate genes, sequencing, genome wide analysis studies [GWAS], copy number variation, knockout genes, polygenic risk scores; epigenetics; broad discussion), psychiatric disorder (anxiety, mood, schizophrenia, neurodevelopmental [e.g., Autism Spectrum Disorder; ASD], attention deficit hyperactivity disorder [ADHD], alcohol and substance use disorders [AUD/SUD] and addiction, other, broad discussion of mental health, multiple disorders), and whether the study utilized animal models (yes, no).

Analyses

Basic frequencies and cross tabulations were utilized to summarize the type(s) of genetic information, psychiatric disorders, and translational frameworks utilized by the included papers. Weighted Cohen's Kappa (Fleiss & Cohen, 1973; Koo & Li, 2016; Mandrekar, 2011) was

calculated to confirm agreement among reviewers for the abstracts as a whole. All analyses were done in R (R Development Core Team, 2015).

Results

Search Results

The first step of the review process ended with 325 abstracts that were loosely related to the aims of this paper. After reviewers completed the checklist and the lead author confirmed the articles, 100 abstracts met criteria for inclusion. Overall, reviewers agreed 82% of the time with whether an article should be included, which resulted in a weighted Cohen's Kappa value of 0.67 (confidence interval [CI] = 0.59-0.74). Kappa values between specific pairs of reviewers ranged from 0.47 (CI = 0.31-0.64) to 0.83 (CI = 0.71-0.96). See Table 2.1 for a list of articles included in the review.

Table 2.1. Articles that met inclusion criteria for the literature review.

Citation	Translational Framework	Genetic Information	Psychiatric Disorder
Kong, C., Dunn, M., & Parker, M. (2017). Psychiatric genomics and mental health treatment: Setting the ethical agenda. *American Journal of Bioethics, 17,* 3-12.	Broad	Broad	Broad
deLeon, J. (2009). The future (or lack of future) of personalized prescription in psychiatry. *Pharmacological Research, 59,* 81-89.	Precision Medicine	Broad	Broad
Patriquin, M. A., Bauer, I. E., Soares, J. C., Graham, D. P., & Nielsen, D. A. (2015). Addiction pharmacogenetics: A systematic review of the genetic variation of the dopaminergic system. *Psychiatric Genetics, 25*, 181-193.	Precision Medicine	Molecular	AUD/SUD & Addiction
Evanoff, B. & Bierut, L. (2017). M7 - Achieving the promise of translational genomics in psychiatric care. *European Neuropsyhopharmacology, 27,* S370-S371.	Multiple	Molecular	Broad
Malter, C. M., Tottneham, N., & Casey, B. J. (2013). Translational developmental studies of stress on brain and behavior: Implications for adolescent mental health and illness. *Neuroscience, 249,* 53-62.	Bench-to-Bedside	Molecular	Other
Jurgens, G., Jacobsen, C. B., Rasmussen, H. B., Werge, T., Nordentoft, M., & Andersen, S. E. (2012). Utility and adoption of CYP2D6 and CYP2C19 genotyping and its translation into psychiatric clinical practice. *Acta Psychiatrica Scandinavica, 125,* 228-237.	Precision Medicine	Molecular	Broad
Ostergren, J. E., Hammer, R. R., Dingel, M. J., Koenig, B. A., McCormick, J. B. (2014). Challenges in Translational Research: The Views of Addiction Scientists. *PLoS ONE, 9*, 1-6.	Prevention	Broad	AUD/SUD & Addiction
Drury, S., & Cuthbert, B. (2015). Advancing pediatric psychiatry research. *Therapeutic Innovation & Regulatory Science, 49*, 643-646.	D&I	Broad	Broad
Lobo, D. S. S., Aleksandrova, L., Knight, J., Casey, D. M., el-Guebaly, N., Nobrega, J. N., & Kennedy, J. L. (2015). Addiction-related genes in gambling disorders: new insights from parallel human and pre-clinical models. *Molecular Psychiatry, 20,* 1002-1010.	Bench-to-Bedside	Molecular	AUD/SUD & Addiction
Addington, A. M., & Rappaport, J. L. (2012). Annual Research Review: Impact of advances in genetics in understanding developmental psychopathology. *Journal of Child Psychology & Psychiatry, 53*, 510-518.	D&I	Molecular	Multiple
Donaldson, Z. R., & Hen, R. (2015). From psychiatric disorders to animal models: A bidirectional and dimensional approach. *Biological Psychiatry, 77*, 15-21.	Bench-to-Bedside	Broad	Broad
Phillips, J. M., Siegel, S. J., Shields, A. E., Pattersonm, F., Gould, T. J., Strasser, A. A. ... Lerman, C. (2007). Translating basic science to improve pharmacotherapy for nicotine dependence. *Nicotine & Tobacco Research, 4*, 583-598	Precision Medicine	Broad	Neuro
Driscoll, A. C., Barr, C. S. (2016). Studying longitudinal trajectories in animal models of psychiatric illness and their translation to the human condition. *Neuroscience Research, 102*, 67-77.	Bench-to-Bedside	Molecular	Multiple
DrVries, J., Stein, D. J., & Kamuya, D. (2017). Psychiatric Genomics: Ethical Implications for Public Health in Lower- and Middle-Income Countries. *American Journal of Bioethics, 17*(4), 17-19.	Broad	Broad	Broad

Luoni, A., & Riva, M. A. (2016). MicroRNAs and psychiatric disorders: From aetiology to treatment. *Pharmacology & Therapeutics, 167*, 13-27.	Precision Medicine	Epigenetics	Broad
Papassotiropoulos, A., de Quervain, D. (2015). Failed drug discovery in psychiatry: Time for human genome-guided solutions. Tr*ends in Cognitive Sciences, 19*, 183-187.	Precision Medicine	Broad	Broad
Heizen, E. L., Neale, B. M., Allen, A. S., & Goldstein, D. B. (2015). the genetics of neuropsychiatric diseases: Looking in and beyond the exome. *Annual Review of Neuroscience, 38*, 47-68.	Broad	Broad	Broad
Bubier, J. A., & Chelser, E. J. (2012). Accelerating discovery for complex neurological and behavioral disorders through systems genetics and integrative genomics in the laboratory mouse. *Neurotherapeutics, 9*, 338-348.	Bench-to-Bedside	Molecular	Broad
Visscher, P. M., Wray, N. R., Zhang, Q., Sklar, P., McCarthy, M. I., Brown, A., & Yang, J. (2017). 10 Years of GWAS Discovery: Biology, Function, and Translation. *American Journal of Human Genetics, 101*(1), 5-22.	Precision Medicine	Molecular	Multiple
Fraguas, D., Diaz-Caneja, C. M., State, M. W., O'Donovan, M. C., Gur, R. E., & Arango, C. (2017). Mental disorders of known aetiology and precision medicine in psychiatry: A promising but neglected alliance. *Psychological Medicine, 47*, 193-197.	Precision Medicine	Molecular	Neuro
Klein, D. A., & Walsh, B. T. (2005). Translation approaches to understanding anorexia nervosa. *International Journal of Eating Disorders, 37*(1), S10-S14.	Broad	Molecular	Broad
Veenstra-VanderWeele, J., & Blakely, R. D. (2012). Networking in Autism: Leveraging Genetic, Biomarker and Model System Findings in the Search for New Treatments. *Neuropsychopharmacology, 37,* 196-212.	Bench-to-Bedside	Molecular	Neuro
Vinkers et al. (2008). Translational aspects of pharmacological research into anxiety disorders: The stress-induced hyperthermia (SIH) paradigm. *European Journal of Pharmacology, 585*, 407-425.	Bench-to-Bedside	Molecular	Anxiety
Damiano, C. R., Mazefsky, C. A., White, S. & Dichter, G. S. (2014). Future Directions for Research in Autism Spectrum Disorders. *Journal of Clinical Child & Adolescent Psychology, 43*, 828-843.	Bench-to-Bedside	Broad	Neuro
Restifo, K., & Bogels, S. (2009). Family processes in the development of youth depression: Translating the evidence to treatment. *Clinical Psychology Review, 29*, 294-316.	Precision Medicine	Epidemiology	Mood
Daws, S. (2017). Ethical Application of Precision Medicine to Schizophrenia Management. *New Bioethics, 23*, 147-153.	Precision Medicine	Broad	Schizophrenia
Bloss, C. S., Jeste, D. V., & Schork, N. J. (2011). Genomics for disease treatment and prevention. *Psychiatric Clinics of North America, 34*, 147-166.	Precision Medicine	Epidemiology	Multiple
Jia, F., Shan, L., Wang, B., Li, H., Miao, C., Xu, Z. … Saad, K. (2017). Bench to bedside review: Possible role of vitamin D in autism spectrum disorder. *Psychiatry Research, 6*, 360-365.	Bench-to-Bedside	Molecular	Neuro
Uher, R. (2011). Genes, Environment, and Individual Differences in Responding to Treatment for Depression. *Harvard Review of Psychiatry, 19*, 109-124.	D&I	Molecular	Mood
Plesnicar, B. K. (2016). Personalized treatment of schizophrenia in everyday clinical practice: reality or fiction? *Psychiatria Danubina, 27*, 314-318.	Precision Medicine	Molecular	Schizophrenia

Plummer, J. T., Gordon, A. J., & Levitt, P. (2016). The genetic intersection of neurodevelopmental disorders and shared medical comorbidities - Relations that translate from bench to bedside. *Frontiers Psychiatry, 7:*142.	Bench-to-Bedside	Molecular	Multiple
Delude, C. M. (2015). Deep phenotyping: The details of disease. *Nature, 527,* s7576, s14-s15.	Precision Medicine	Broad	Broad
Stahl, S. M. (2017). Psychiatric pharmacogenomics: How to integrate into clinical practice. *CNS Spectrums, 22,* 1-4.	Precision Medicine	Broad	Broad
Malhotra, A. K., Lencz, T., Correll, C. U., & Kane, J. M. (2007). Genomics and the future of pharmacotherapy in psychiatry. *International Review of Psychiatry, 19*, 523-530	Precision Medicine	Molecular	Schizophrenia
Helton, S. G., Lohoff, F. W. (2015). Pharmacogenetics of alcohol use disorders and comorbid psychiatric disorders. *Psychiatry Research, 230,* 121-129.	Precision Medicine	Broad	Multiple
Hsin-Ya, L., Jih-Heng, L., Uuh-Ling, T., Wei-Chiao, C., Tze-Chun, T. … Liu, R.-H. (2013). Moving toward personalized medicine in the methadone maintenance treatment program: A pilot study on the evaluation of treatment responses in Taiwan. *BioMed Research International, 2013*, 1-11.	Precision Medicine	Molecular	AUD/SUD & Addiction
Mrazek, D. A., Smoller, J. W., de Leon, J., & de Leon, J. (2006). Incorporating pharmacogenetics into clinical practice: Reality of a new tool in psychiatry. Current issues in clinical implementation. *CNS Spectrums, 11*, 1-16.	Precision Medicine	Molecular	Broad
Hariri, A. R., & Holmes, A. (2015). Finding translation in stress research. *Nature Neuroscience, 18*, 1347-1352.	Prevention	Molecular	Multiple
Geschwind, D. H., & State, M. W. (2015). Gene hunting in autism spectrum disorder: on the path to precision medicine. *Lancet Neurology, 14*, 1109-1120.	Precision Medicine	Broad	Neuro
Lett, T., Walter, H., & Brandl, E. J. (2016). Pharmacogenetics and imaging-pharmacogenetics of antidepressant response: Towards translational strategies. *CNS Drugs, 30*, 1169-1189.	Precision Medicine	Molecular	Mood
Drake, R. E., Cimpean, D., & Torrey, W. C. (2009). Shared decision making in mental health: prospects for personalized medicine. *Dialogues in Clinical Neuroscience, 11,* 455-463.	Precision Medicine	Molecular	Broad
Cuthbert, B. N. & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: The seven pillars of RDoC. *BMC Medicine, 11:126*.	Precision Medicine	Broad	Broad
Bickman, L., Lyon, A. R., & Wolpert, M. (2016). achieving precision mental health through effective assessment, monitoring, and feedback processes. *Administration and Policy in Mental Health and Mental Health Services Research, 43*, 271-276.	Precision Medicine	Broad	Broad
Gardner, P. O., Tapper, A. R., King, J. A., DiFranza, J. R., & Ziedonis, D. M. (2009). The neurobiology of nicotine addiction: Clinical and public policy implications. *Journal of Drug Issues, 39*, 417-441.	Bench-to-Bedside	Broad	AUD/SUD & Addiction
Hendershot, C. S. (2014). Pharmacogenetic approaches in the treatment of alcohol use disorders: addressing clinical utility and implementation thresholds. *Addiction Science & Clinical Practice, 9:20*.	D&I	Molecular	AUD/SUD & Addiction

Wittchen, H. U., Knappe, S., Andersson, G., Araya, R., Banos Rivera, R. M., Barkham, M., ... & Berrocal, C. (2014). The need for a behavioural science focus in research on mental health and mental disorders. *International Journal of Methods in Psychiatric Research, 23(S1),* 28-40.	Other	Broad	Broad
Singh, A. B., Bousman, C. A., Ng, C., & Berk, M. (2014). Antidepressant pharmacogenetics. *Current Opinion in Psychiatry, 27(1),* 43-51.	Prevention	Broad	Mood
Shamy, M. C., Zai, C., Basile, V. S., Kennedy, J. L., Muller, D. J., & Masellis, M. (2011). Ethical and policy considerations in the application of pharmacogenomic testing for tardive dyskinesia: case study of the dopamine D3 receptor. *Current Pharmacogenomics and Personalized Medicine, 9(2*), 94-101.	Bench-to-Bedside	Molecular	Schizophrenia
Breen, G., Li, Q., Roth, B. L., O'Donnell, P., Didriksen, M., Dolmetsch, R., ... & Edenberg, H.J. (2016). Translating genome-wide association findings into new therapeutics for psychiatry. *Nature Neuroscience, 19,* 1392-1396.	Bench-to-Bedside	Molecular	Broad
Roos, J. L. (2011). Genetics of schizophrenia: Communicating scientific findings in the clinical setting. *African Journal of Psychiatry, 14(2),* 105-111.	D&I	Molecular	Schizophrenia
Ursano, R. J., Zhang, L., Li, H., Johnson, L., Carlton, J., Fullerton, C. S., & Benedek, D. M. (2009). PTSD and traumatic stress: From gene to community and bench to bedside. *Brain Research, 1293*, 2-12.	Bench-to-Bedside	Molecular	Other
Kumra, S. Asarnow, R., Grace, A., Keshavan, M., McClellan, J., Sikich, L., & Wagner, A. (2009). From bench to bedside: Translating new research from genetics and neuroimaging into treatment development for early-onset schizophrenia. *Early Intervention in Psychiatry, 3*, 243-258.	Bench-to-Bedside	Molecular	Schizophrenia
de Leon, J. (2014). AmpliChip CYP450 Test: personalized medicine has arrived in psychiatry. *Expert Review of Molecular Diagnostics, 6*, 277-286.	Precision Medicine	Broad	Broad
Evers, K. (2009). Personalized medicine in psychiatry: Ethical challenges and opportunities. *Dialogues in Clinical Neuroscience, 11*, 427-434.	Precision Medicine	Broad	Broad
Prendez-Alvarez, S., & Nemeroff, C. B. (2018). Personalized medicine: Prediction of disease vulnerability in mood disorders. *Neuroscience Letters, 16(669):* 10-13. [Note: During the literature search, a corrected 2016 proof was available online; this citation is for the final published manuscript.]	Precision Medicine	Broad	Mood
Hess, G. P., Fonseca, E., Scott, R., & Fagernes, J. (2015). Pharmacogenomic and pharmacogenetic-guided therapy as a tool in precision medicine: current state and factors impacting acceptance by stakeholders. *Genetics Research, 97*, e13.	Precision Medicine	Molecular	Multiple
Shin, C., Han, C., Pae, C., & Patkar, A. A. (2016). Precision medicine for psychopharmacology: A general introduction. *Expert Review of Neurotherapeutics, 16*, 831-839.	Precision Medicine	Molecular	Broad
Dalvie, S., Koen, N., McGregor, N., O'Connell, K. Warnich, L., Ramesar, R. … Stein, D. J. (2016). Toward a global roadmap for precision medicine in psychiatry: Challenges and opportunities. *OMICS: A Journal of Integrative Biology, 20*, 557-564.	Precision Medicine	Molecular	Broad
Gerretsen, P., Muller, D. J., Tiwari, A., Mamo, D., & Pollock, B. G. (2009). The intersection of pharmacology, imaging, and genetics in the development of personalized medicine. *Dialogues in Clinical Neuroscience,*	Precision Medicine	Broad	Multiple

11, 363-376.			
Beversdorf, D. Q. (2016). Phenotyping, etiological factors, and biomarkers: Toward precision medicine in Autism Spectrum Disorders. *Journal of Developmental & Behavioral Pediatrics, 37*, 659-673.	Precision Medicine	Broad	Neurodevelop mental
Ozomaro, U., Wahlestedt, C., & Nemeroff, C. B. (2013). Personalized medicine in psychiatry: Problems and promises. *BMC Medicine, 11:132*.	Precision Medicine	Broad	Multiple
Costa, J. A. (2013). Personalized medicine in psychiatry: New technologies and approaches. *Metabolism Clinical and Experimental, 62*, S40-S44.	Precision Medicine	Molecular	Broad
Hutchison, K. E. (2010). Substance use disorders: Realizing the promise of pharmacogenomics and personalized medicine. *Annual Review of Clinical Psychology, 6*, 577-589.	Precision Medicine	Broad	AUD/SUD & Addiction
Finucane, B., Challman, T. D., Martin, C. L., & Ledbetter, D. H. (2016). Shift happens: Family background influences clinical variability in genetic neurodevelopmental disorders. *Genetics in Medicine, 18*, 302-304.	Precision Medicine	Epidemiology	Multiple
Harold, G. T., Leve, L. D., & Sellers, R. (2017). How can genetically informed research help inform the next generation of interparental and parenting interventions? *Child Development, 88*, 446-458.	Prevention	Broad	Broad
Alhajji, L., & Nemeroff, C. B. (2015). Personalized medicine and mood disorders. *Psychiatric Clinics of North America, 38*, 395-403.	Precision Medicine	Molecular	Broad
Murck, H., Laughren, T., Lamers, F., Picard, S., Walther, S., Goff, D., & Sainati, S. (2015). Taking personalized medicine seriously: Biomarker approaches in phase IIb/III studies in major depression and schizophrenia. *Innovation Clinical Neuroscience, 12*, 26S-40S.	Precision Medicine	Broad	Multiple
Niculescu, A., Le-Niculescu, H., Levey, D. F., Phalen, P. L., Dainton, H. L., Roseberry, K. … Salomon, D. R. (2017). Precision medicine for suicidality: From universality to subtypes and personalization. *Molecular Psychiatry, 22*, 1250-1273.	Precision Medicine	Molecular	Multiple
Blum, K., Modestnio, E. J., Gondre-Lewis, M. C., Neary, J., Siwicki, D., Hauser, M. … Badgaiyan, R. D. (2017). Global opioid epidemic: doomed to fail without genetically based precision addiction medicine (PAM™): Lessons learned from America. *Precision medicine (Balgalore), 2(1)*, 17-22.	Precision Medicine	Molecular	AUD/SUD & Addiction
Myers, A. J., & Nemeroff, C. B. (2010). New vistas in the management of treatment-refractory psychiatric disorders: Genomics and personalized medicine. *Psychopharmacology: Treatment-Resistant Disorders, 8*, 525-535.	Precision Medicine	Molecular	Broad
Allenby, C. E., Boyland, K. A., Lerman, C., Falcone, C. (2016). Precision medicine for tobacco dependence: Development and validation of the nicotine metabolite ratio. *Journal of Neuroimmune Pharmacology, 11*, 471-483.	Precision Medicine	Broad	AUD/SUD & Addiction
Ragia, G., Manolopoulos, V. (2017). Personalized medicine of alcohol addiction: Pharmacogenomics and beyond. *Current Pharmaceutical Biotechnology, 18*, 221-230.	Precision Medicine	Epigenetics	AUD/SUD & Addiction
Falk, A., Heine, V. M., Harwood, A. J., Sullivan, P. F., Peitz, M., Brustle, O … Djurovic, S. (2016). Modeling psychiatric disorders: From genomic findings to cellular phenotypes. *Molecular Psychiatry, 21*, 1167-1179.	Broad	Broad	Multiple

Gandal, M., Leppa, V. Won, H., Parikshak, N. N., & Geschwind, D. H. (2016). The road to precision psychiatry: Translating genetics into disease mechanisms. *Nature Neuroscience, 19*, 1397-1407.	Precision Medicine	Broad	Broad
Foley, C., Corvin, A., Nakagome, S. (2017). Genetics of schizophrenia: Ready to translate? *Current Psychiatry Reports, 19:61*	Bench-to-Bedside	Broad	Schizophrenia
Kaiser, T., Feng, G. (2015). Modeling psychiatric disorders for developing effective treatments. *Nature Medicine, 21*, 979-988.	Prevention	Broad	Broad
Garner, M. Mohler, H., Stein, D. J., Mueggler, T., & Baldwin, D. S. (2009). Research in anxiety disorders: From the bench to the bedside. *European Neuropsychopharmacology, 19*, 381-390.	Bench-to-Bedside	Broad	Anxiety
Walden, L. M., Brandl, E. J., Changasi, A., Sturgess, J. E., Notario, J. F. D. … Kennedy, J. L. (2015). Physicians' opinions following pharmacogenetic testing for psychotropic medication. *Psychiatry Research, 229,* 913-919.	Precision Medicine	Molecular	Broad
LeFoll, B., Pushparaj, A., Pryslawsky, Y., Forget, B., Vemuri, K., Makriyannis, A., & Trigo, J. M. (2014). Translational strategies for therapeutic development in nicotine addiction: Rethinking the conventional bench to bedside approach. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 52*, 86-93.	Bench-to-Bedside	Molecular	AUD/SUD & Addiction
Insel, T. R., Voon, V., Nye, J. S., Brown, V. J., Altevogt, B. M., Bullmore, E. T., ... & Marston, H. M. (2013). Innovative solutions to novel drug development in mental health. *Neuroscience & Biobehavioral Reviews*, *37*, 2438-2444.	Bench-to-Bedside	Broad	Multiple
Costain, G., Esplen, M. J., Toner, B., Scherer, S. W., Meschino, W. S., Hodgkinson, K. A., & Bassett, A. S. (2012). Evaluating genetic counseling for individuals with schizophrenia in the molecular age. *Schizophrenia Bulletin, 40(1),* 78-87.	Bench-to-Bedside	Epidemiology	Schizophrenia
Rutter, M., & Solantaus, T. (2014). Translation gone awry: differences between commonsense and science. *European Child & Adolescent Psychiatry, 23*, 247-255.	Broad	Broad	AUD/SUD & Addiction
State, M. W. (2010). The genetics of child psychiatric disorders: focus on autism and Tourette syndrome. *Neuron, 68,* 254-269.	Bench-to-Bedside	Molecular	Broad
Borgelt, E. L., Buchman, D. Z., Weiss, M., & Illes, J. (2014). In search of "anything that would help": Parent perspectives on emerging neurotechnologies. *Journal of Attention Disorders, 18,* 395-401.	D&I	Molecular	ADHD
Finn, C. T., & Smoller, J. W. (2006). Genetic counseling in psychiatry. *Harvard Review of Psychiatry, 14(2),* 109-121.	Precision Medicine	Epidemiology	Broad
Need, A. C., & Goldstein, D. B. (2016). Neuropsychiatric genomics in precision medicine: Diagnostics, gene discovery, and translation. *Dialogues in Clinical Neuroscience, 18*, 237-252.	Bench-to-Bedside	Molecular	Broad
Smoller, J. W. (2016). The genetics of stress-related disorders: PTSD, depression, and anxiety disorders. *Neuropsychopharmacology, 41*, 297-319.	D&I	Epidemiology	Multiple
Beirut, L. J., Johnson, E. O., & Saccone, N. L. (2014). A glimpse into the future: Personalized medicine for smoking cessation. *Neuropharmacology, 76,* 592-599.	Precision Medicine	Molecular	AUD/SUD & Addiction

Rende, R., & Slomkowski, C. (2008). Incorporating the family as a critical context in genetic studies of children: implications for understanding pathways to risky behavior and substance use. *Journal of Pediatric Psychology, 34,* 606-616.	Broad	Epidemiology	Other
Glatt, C. E., & Lee, F. S. (2016). Common polymorphisms in the age of Research Domain Criteria (RDoC): Integration and translation. *Biological Psychiatry, 79(1),* 25-31.	Bench-to-Bedside	Molecular	Broad
Geschwind, D. H. (2003). DNA microarrays: Translation of the genome from laboratory to clinic. *The Lancet Neurology, 2,* 275-282.	Precision Medicine	Molecular	Schizophrenia
Vorstman, J. A., Parr, J. R., Moreno-De-Luca, D., Anney, R. J., Nurnberger Jr, J. I., & Hallmayer, J. F. (2017). Autism genetics: Opportunities and challenges for clinical translation. *Nature Reviews Genetics, 18,* 362-376.	D&I	Molecular	Neuro
Holsboer, F. (2008). How can we realize the promise of personalized antidepressant medicines? *Nature Reviews Neuroscience, 9*, 638-646.	Precision Medicine	Molecular	Mood
Rujescu, D., Genius, J., Benninghoff, J., & Giegling, I. (2012). Current progress in the genetic research of schizophrenia: Relevance for drug discovery? *Current Pharmaceutical Biotechnology, 13*, 1614-1621.	Bench-to-Bedside	Broad	Schizophrenia
Amare, A. T., Schuberg, K. O., & Baune, B. T. (2017). Pharmacogenomics in the treatment of mood disorders: Strategies and opportunities for personalized psychiatry. *EPMA J, 8*, 211-227.	Precision Medicine	Molecular	Mood
Chen, L. A., Zawertailo, L., Piasecki, T. M., Kaprio, J., Foreman, M., Elliott, H. R. … Saccone, N. L. (2017). Leveraging genomic data in smoking cessation trials in the era of Precision Medicine: Why and how. *Nicotine Tobacco Research, 20*, 414-424.	Precision Medicine	Molecular	AUD/SUD & Addiction
Lee, B. S., McIntyre, R. S., Gentle, J. E., Park, N. S. Chiriboga, D. A., Lee, Y. … McPherson, M. A. (2017). A computational algorithm for personalized medicine in schizophrenia. *Schizophrenia Research, 192*, 131-136.	Precision Medicine	Molecular	Schizophrenia
Lally, J., Gaughran, F., Timms, P., & Currna. S. R. (2016). Treatment-resistant schizophrenia: Current insights on the pharmacogenomics of antipsychotics. *Pharmacogenomics and Personalized Medicine, 7(9)*, 117-129.	Precision Medicine	Molecular	Schizophrenia
Sweatt, J. D., & Tamminga, C. A. (2016). An epigenomics approach to individual differences and its translation to neuropsychiatric conditions. *Dialogues in Clinical Neuroscience, 18*, 189-198.	Bench-to-Bedside	Epigenetics	Schizophrenia
Wium-Andersen, I. K., Vinberg, M., Kessing, L. V., & McIntyre, R. S. (2016). Personalized medicine in psychiatry. *Nordic Journal of Psychiatry, 71(1)*, 12-19.	Precision Medicine	Broad	Broad

Translational Frameworks

Most (53%) of the articles were from a precision medicine perspective, followed by bench-to-bedside (25%), D&I (8%), and a broad discussion of translational science (7%). While prevention-focused translational frameworks were not the focus of this review, a few of the articles included this perspective (5%). Finally, 2% of articles discussed either another framework not already mentioned or multiple frameworks.

Genetic Information

Molecular genetic information was mentioned in a majority of the articles (51%). Many articles also discussed genetics more broadly (39%); in other words, the article simultaneously discussed many types of genetic information or used the term "genetics" to mean all genetic information. Neither genetic epidemiology (heritability, family history; 7%) or epigenetics (3%) made up a substantial percentage of the genetic information discussed.

Psychiatric Disorders

Many articles discussed psychiatric conditions in a broad manner (36%) or examined multiple psychiatric conditions (16%). Among specific disorders mentioned, AUD/SUD and addiction were the most commonly mentioned (14%), followed by schizophrenia (13%), and neurodevelopmental disorders (8%). Internalizing disorders (anxiety, 2%; mood, 7%) were largely underrepresented and ADHD (1%) made up the smallest percentage. Three percent of papers discussed other mental health conditions (e.g., stress, risky behaviors).

Other Trends

Most articles discussing precision medicine (49%), bench-to-bedside (64%), and D&I (75%) focused on molecular genomics. A notable proportion of papers discussing each of these

frameworks also discussed genetics broadly (40%, 28%, and 13%, respectively). Finally, a majority (71%) of articles that discussed translation broadly also discussed genetics broadly.

Fewer obvious trends appeared when examining which psychiatric disorders were most commonly translated among specific frameworks. A broad discussion of mental health was the most common psychiatric context for all frameworks (24%-100%) with the exception of D&I (13%) where discussion of multiple disorders was more common (25%). A broad discussion of mental health was also the most common context for molecular (31%) and broad genetic (46%) studies. A combination of multiple psychiatric disorders the most prevalent context when translating genetic epidemiology (43%) information. Conditions for which epigenetic information was translated were evenly split (33% each) among schizophrenia, AUD/SUD and addictive disorders, and broad mental health.

Discussion

To date, multiple frameworks and models have been proposed for how to translate scientific findings broadly (Collins & Varmus, 2010; Gray & Bonventre, 2002; Waldman & Terzic, 2010) and genetic information specifically (Collins, 2011; Collins & Varmus, 2015). Little attention has been placed on how to translate genetic information within the context of psychiatric disorders, although there have been several proposed frameworks to help with this (e.g., a division of translation into two phases focused on clinical trials and community engagement (Brekke, Ell, & Palinkas, 2007) or the Translational Science Benefits Model that evaluates resources, scientific activities, outcomes, and health/societal benefits (Luke et al., 2017)). By studying trends among the intersection of translational frameworks, genetic information, and psychiatric disorders, this review provides insight into the ways in which communication regarding the genetics of psychiatric disorders is occurring. Overall, trends

identified within the present review further highlight the need for change in how psychiatric genetic information is translated to non-research stakeholders (McBride et al., 2010; Visscher et al., 2016). This may be accomplished by shifting away from linear views of translation so that *all* genetic information (especially non-molecular information) is better incorporated into the care of these complex psychiatric disorders.

Historically, linear translational frameworks such as bench-to-bedside and precision medicine have spearheaded advancements in medicine, specifically the translation of molecular genetic information about chronic, non-psychiatric conditions (Cornetta & Brown, 2013; Legare et al., 2016). Such frameworks have also been applied to the genetics of psychiatric disorders to little effect (Sullivan et al., 2012; Visscher et al., 2016; Wittchen et al., 2014). The current findings support this pattern, as most articles included in this review focused on linear frameworks. These frameworks are limiting, as they present barriers to translating genetic information to all stakeholders. Namely, there is an emphasis on molecular genomics and familiarity with this type of genetic information may be limited, many facilities lack technology to test genomic information of patients, and these forms of translation are notoriously slow (Cornel & El, 2017; Sperber et al., 2017).

Recent public health efforts have somewhat shifted this narrative in regard to the translation of genetic information broadly (Belsky, Moffitt, & Caspi, 2012; Cornel & El, 2017; Doerr & Teng, 2012) but rarely for the genetics of mental health conditions (Dick, 2017; McBride, 2018). This shift has occurred in two key ways. First, translational frameworks such as D&I and prevention science are being recognized as having more reach and immediate impact (Bradshaw & Haynes, 2012; Sperber et al., 2017). This may better motivate behavior change by clinicians, patients, and other stakeholders by engaging at more levels of the translational

process. Second, these shifts also turn attention away from molecular genomic and epigenetic information and open up the possibility of utilizing family history, heritability, and other non-molecular genetic epidemiological sources of information either singularly or in tandem with genomic information (Dick, 2017; Doerr & Tend, 2012). This information is relevant and may present genetic information in a more readily accessible form, improving the likelihood of understanding (Bradshaw & Haynes, 2012; Dick, 2017) and thereby reducing a significant barrier to the translation of genetic information.

A notable trend in the current findings was the large number of articles that discussed translation, genetics, and/or mental health in broad terms. Such articles were largely not cross-sectional or experimental designs but in-depth inquiries into the topic at hand. Without diminishing the importance of such studies, it should be noted that the field of psychiatric genetics will not advance without clear and purposeful investigations of the best translational frameworks for specific disorders. Some examples of this exist (Arar, Delgado, Lee, & Abboud, 2012; Bradshaw & Haynes, 2012; Dick, 2017), but they are the exception rather than the standard approach. This was especially true when focusing explicitly on psychiatric disorders. Most of disorders specifically studied in the articles included in this review (e.g., AUD/SUD, schizophrenia, neurodevelopmental) are those that have the most molecular genetic information known about them, perpetuating a linear view of translation that is inextricably tied to a belief that molecular genomic and epigenetic findings are the best sources of genetic information to translate due to their historic role in linear translational frameworks. Little genetic translation has even been attempted for disorders such as anxiety or ADHD where little molecular genomic information is known despite the fact that heritability, family history, and other genetic

epidemiological information could be communicated to stakeholders and potentially incorporated into care.

It is hoped that these findings will help all stakeholders who are affected by, study, or treat psychiatric conditions (researchers, clinicians, administrators, patients, families, community members) to think more deeply about this issue. Namely, there is a need to push forward and study potential impacts of non-molecular genetic epidemiological information in practice, prevention, and policy. It needs to be acknowledged that linear forms of translation are not the most effective for psychiatric disorders, and a deep investigation into how frameworks such as D&I or prevention science can utilize genetic information is crucial. Relatedly, knowledge and competence surrounding these three interrelated topics is needed. Lack of genetic knowledge has already been cited as a key barrier to translation (Cornel & El, 2017; McBride, 2018), but most individuals are also not well-versed in different translational frameworks, appropriate stakeholder groups, or specific mental health conditions.

Limitations

There are a few limitations to note from the current study. First, the search terms used were not exhaustive, and some key translational frameworks and key words were omitted. As already stated, research-to-policy was intentionally left out of the terms given that policy is a more advanced translational framework, and psychiatric genetics is arguably not ready for that. However, mention of policy appeared in several articles included in the final list. This implies that a search specific to policy is warranted, perhaps to explicate the intricacies of insurance, biobanking, family history communication, and other related topics. Also, "research-to-practice" was not used because it is often used as a catchall term and is not specific. Second, by design this study did not require reading each article in depth but rather summarized across articles. This

does not detract from the current conclusions but does prevent further analysis and additional nuances to be gleaned. Third, the Kappa values between pairs of reviewers fluctuated (although all were within an acceptable range). This may be due to the fact that reviewers purposefully came from different training backgrounds to facilitate interdisciplinary study and translation. Finally, reviewers had to often use their knowledge of translational science to determine which framework(s) articles were working under. This admittedly allowed some bias into the review as interpretations of translational frameworks and terms are somewhat fluid.

Implications

The purpose of this review was to understand which translational frameworks guide the application of genetic information to the clinical care of psychiatric disorders. It has direct implications for service delivery and findings may help to relieve some burden from clinicians by improving communication with researchers. Such work is only a small part of what is needed to ensure proper translation among all stakeholder groups, namely researchers and clinicians. This review complements the work currently underway to open genetic counseling centers for psychiatric disorders, as such counseling has been shown to be efficacious for patients (Moldovan, Pintea, & Ausin, 2017). It also highlights that there is no one-size-fits-all approach to translation and the application of a given framework in any context needs to be carefully evaluated. These conclusions imply that linear frameworks should not necessarily be applied to translating psychiatric genetic information, nor should socio-ecological frameworks be used in all contexts. Future research is still needed to determine which frameworks are best for which psychiatric disorders and for which types of genetic information.

Chapter 3: Assessing Stakeholder Perceptions of the Utility of Genetic Information for the Clinical Care of Mental Health Disorders[1]

Overview

The purpose of this chapter is to assess the state of the science regarding the translation of genetic information to the clinical care of mental health disorders from an academic perspective and constitutes aim 1 of this dissertation. This was accomplished by designing and implementing a survey on this topic. Given the overall lack of knowledge on this topic, a qualitative / inductive approach was taken (Strauss & Corbin, 1998). This means that the purpose of the survey, and hence the aim as a whole, was to be hypothesis-generating and gauge the state of the science of the topic at hand. The purpose was not to create a psychometrically sound measure for assessing attitudes and practices related to translation, although this chapter lays the groundwork for such a future endeavor. The purpose was also not to go into the survey with clear hypotheses in a traditionally deductive manner.

This chapter is presented in five parts because this dissertation aim took on a different form than the others. There were no *a priori* hypotheses or research questions (see chapter 1). The purpose of this aim was to assess the state of the science regarding the translation of genetic information to the clinical care of mental health disorders from an academic perspective. Part 1 presents the rationale for this dissertation aim, survey methodology, and basic descriptive and frequency statistics with a brief discussion. Part 2 tests hypotheses generated in part 1, provides a few additional analyses, and concludes with a brief discussion. Part 3 includes the analyses of key open-ended questions. Part 4 discusses the limited psychometrics of the survey, which were not viewed as crucial to the study but are included for completeness. Part 5 provides a global discussion and ending to this chapter.

[1]Modified version of the manuscript Bourdon, J. L., Hettema, J. M., Prom-Wormley, E. C., & Southam-Gerow, M. A. (In Review). Assessing stakeholder perceptions of the utility of genetic information fo the clinical care of mental health disorders: We have a will but need to see the way. *Translational Behavioral Medicine.*

Part 1: Aim rationale, survey methodology, basic descriptive statistics, discussion[1]

Introduction

There is widespread agreement that the translation of basic scientific findings to the benefit of public health represents a critical goal in scientific research (Collins & Varmus, 2015; Sullivan, Daly, & O'Donovan, 2012; Centers for Disease Control, 2007; Belsky, Moffitt, & Caspi, 2012). Incorporation of genetic information specifically (e.g., family history, sequencing results) is important for the the creation of evidence-based treatment across a range of disorders (Collins & Varmus, 2012; Sullivan et al., 2012; Visscher et al., 2016). Impressive progress has been made to document the role that molecular genetic information plays in the risk reduction, identification, prevention, and treatment of physical, chronic conditions such as cardiovascular disease (Arnett et al., 2007; Ebomoyi, 2013; Vornanen et al., 2016; International Consortium for Blood Pressure Genome-Wide Association Studies, 2011; Khera & Kathiresan, 2017), breast cancer (Cornel & El, 2017; Gil et al., 2003; Macdonald, Sarna, Weitzel, & Ferrell, 2009; Norman & Brain, 2005; Phillips et al., 2006), and other similarly complex disorders. Unfortunately, gene-finding for mental health conditions has proven more difficult than initially expected (Sullivan et al., 2012; Sullivan et al., 2018; Visscher et al., 2016) and these conditions have consequently been largely overlooked in genetic-focused translational efforts. Translation can incorporate more than molecular information. However, it rarely does despite the fact that non-molecular genetic epidemiological information (e.g., family history, twin information, gene-environment interplay) has been shown to impact perceived risk across a range of complex disorders (Vornanen et al., 2016; Prom-Wormley et al., 2019). Considering that over a quarter of the U.S. adult population has lived with a psychiatric disorder in the past year (Kessler et al., 2005) and that not enough is known yet about the molecular risks and mechanisms, incorporating non-

molecular genetic information into mental health care could improve the outcomes of millions of individuals.

Part of the challenge of effectively translating any genetically-informed research into clinical practice for mental health conditions rests in the use of linear translational frameworks (van der Laan & Boenink, 2012) over socio-ecological models (Belsky et al., 2012). Whereas such linear views have had demonstrable effects for the aforementioned chronic conditions (Arnett et al., 2007; E, 2013; Vornanen et al., 2016; International Consortium for Blood Pressure Genome-Wide Association Studies, 2011, 2011; Khera & Kathiresan, 2017; Cornel & El, 2017; Gil et al., 2003; Macdonald et al., 2009; Norman & Brain, 2005; Phillips et al., 2006) and will continue to do so for the foreseeable future (Kahn, Cooper, & Del Prato, 2014), they have not provided much benefit to their mental health counterparts (Sullivan et al., 2018; Visscher et al., 2016; Wittchen et al., 2014). These linear views include *bench-to-bedside* with its structured translational steps (i.e., basic science aimed at identifying mechanisms for disease that moves through a structured series of studies to examine the applicability of basic findings to treatment of disease [Waldman & Terzic, 2010; Khoury et al., 2007]) and *precision medicine* (i.e., the use of biological information to inform treatment, typically information from bench-to-bedside findings [Collins & Varmus, 2015; Jameson & Longo, 2015]). In a genetics context, these frameworks rarely incorporate the viewpoints of multiple stakeholders simultaneously and focus almost exclusively on molecular genetic information. This presents several key barriers that are amplified in a mental health context. For example, these frameworks almost solely rely on gene-finding efforts to complete their translational pipeline - efforts that are not currently possible for mental health conditions except possibly schizophrenia (Sullivan et al., 2012; Sullivan et al., 2018; Visscher et al., 2016). These linear frameworks also tend to discuss but rarely address the

common barrier of whose responsibility it is to discuss genetic information with patients seeking treatment (Sullivan et al., 2012; Visscher et al., 2016; Finn & Smoller, 2006), with separate arguments made that clinicians (psychiatrists, genetic counselors, nurses, etc.) (Sperber et al., 2017; Zhou et al., 2014; International Society of Psychiatric Genetics, 2017) and researchers (Klitzman et al., 2013; Ramoni et al., 2013) should bear this burden. These barriers are further subsumed by larger issues of education/training, stigma, and overall engagement of stakeholders both across disorders (Sperber et al., 2017; Zhou et al., 2014).

Psychological disorders are thus largely seen through the strict genes-researcher-clinician-patient linear vantage point instead of a cooperative or collaborative lens. This is even true of the National Center for Advancing Translational Sciences' (NCATS) translational spectrum which appears visually collaborative but is described in very familiar, linear terms (NCATS, 2016). It is important for all translational efforts, especially genetically-informed ones, to simultaneously integrate multiple perspectives across disciplines and stakeholders (e.g., researchers, clinicians, patients, administrators, policy makers) in collaborative ways (Collins & Varmus, 2015; Waldman & Terzic, 2010; Kon, 2008; Sperber et al., 2017) in order to improve patient outcomes related to mental health care. This will likely open the door for stakeholders considering the use of non-molecular genetic information in translational efforts. It is likely that the solution lies in utilization of frameworks such as *dissemination and implementation science* (a socio-ecological-focused framework that uses multiple lenses to understand and model how scientific findings can influence downstream services, considering all stakeholders in the process [Chambers & Azrin, 2013; Glasgow et al., 2012; Schoenwald & Hoagwood, 2001; Southam-Gerow, Ringeisen, & Sherrill, 2006; Southam-Gerow, Rodriguez, Chorpita, & Daleiden, 2012]) and *prevention science* (similar to D&I with a strong focus on general public health with a strong

emphasis on prevention efforts vs. treatment [Bradshaw & Haynes, 2012; Fishbein, 2016]). Neither of these approaches would be burdened by needing molecular genetic information to assist patients. Population level data such as heritability estimates or gene-environment interplay as well as family history information may suffice (Doerr & Teng, 2012). For example, such information could inform how often clinicians decide that a patient should come in for treatment, patients learning about the roles genes and environment may help them cope with their disorder (Inglis et al., 2015), and such information can be used to proactively and preventatively refer individuals for services (Dick, 2017; Schuckit et al., 2012). It needs to be examined how these different lines of non-molecular genetic information can be made accessible and disseminated to appropriate stakeholders in the most effective ways possible. The end goal is that mental health care (treatment, recovery, or prevention) will be positively impacted, although more research is needed to determine the impact of this information.

Through an appreciation of such diverse perspectives, multi-faceted, targeted translation plans can be developed to reflect the expertise and needs of the stakeholders involved in the prevention and treatment of mental health conditions. To date there has only been one study that compared the attitudes of psychiatrists and genetic counselors on their training, education, and competency related to discussing genetic information with patients who have mental health disorders (Zhou et al., 2014). This study found similar barriers to those that are common in linear frameworks (i.e., discrepancies in training, education, and competency). However, this study argued for enhanced training opportunities that includes all health professionals, focuses on family history, and includes a patient-oriented approach to risk communication. This is in line with a collaborative, socio-ecological perspective to the incorporation of genetic information into mental health care more than a linear translational framework.

Current Study

In short, the slow progress of translation in the area of genetics and mental health care may be a result of adopting frameworks that skew perceptions of how communication around genetic information should occur. The current study seeks to provide preliminary data to help guide a path forward. This was done by exploring the perspectives of academic stakeholders in mental health fields, mainly researchers and clinicians, concerning the utility of genetic information broadly. These groups were queried on their professional translational practices, self-rated genetic knowledge and competence, and attitudes regarding specifically the translational of genetic information related to mental health. The purpose of this study was to describe trends in stakeholders' responses across these domains.

Method

Participants

Participants were actively recruited via direct email to 432 individuals across 11 mental health related departments at Virginia Commonwealth University (VCU) (including some individuals with dual appointment in affiliated local organizations and private practice) and 68 individuals in the Psychology Department at Michigan State University. Recruitment was limited to faculty and staff only. Passive advertisement of the study was also used and included two announcements in VCU's daily email blast to all faculty/staff and four announcements in the lead investigator's weekly department email. Sixty-four individuals completed the survey (see Table 3.1 for full demographic information; 12.80% response rate based on active recruitment only). Most participants were over the age of 35 (47.62%), white (92.19%), and identified as women (54.69%). All but one participant held a graduate degree, either a Ph.D. (57.14%), master's degree (23.81%), M.D. (14.29%), or Psy.D. (3.17%). About the same number of

participants identified primarily as researchers (41.67%) or clinicians (31.67%) with the remaining nearly split between being both (11.67%) or neither (15.00%). Those who identified as neither identified as administrators, general research support, policy specialists, public health professionals, or preventionists. Most (67.65%) individuals with a Ph.D. identified as researchers while most participants with an M.D. (66.67%) or master's (64.29%) primarily identified as clinicians. Demographic categories that were under-powered (i.e., made up less than 10% of the variable) (de Vaus, 2002) were excluded from those analyses (Psy.D., another degree, gender non-conforming, Asian, Black were changed to missing).

Table 3.1. Demographic information on the full sample.

Category	*n*	Percentage
Age		
18-35	30	47.62%
36-55	13	20.63%
56+	20	31.75%
Race		
American Indian / Alaskan Native / Native Hawaiian	0	0.00%
Asian	3	4.69%
Black	1	1.56%
White	59	92.19%
Another	0	0.00%
Choose not to respond	1	1.56%
Ethnicity		
Hispanic	0	0.00%
Gender		
Woman	35	54.69%
Man	29	43.75%
Transgender	0	0.00%
Non-conforming	1	1.56%
Another	0	0.00%
Chose not to respond	0	0.00%
Highest degree obtained		
Master's	15	23.81%
Ph.D.	36	57.14%
Psy.D.	2	3.17%
M.D.	9	14.29%
Another	1	1.59%
Job type		

Researcher	25	41.67%
Clinician	19	31.67%
Both	7	11.67%
Neither	9	15.00%

Survey Instrument

A survey consisting of four sections was sent to participants. These sections assessed professional translational practices, self-rated genetic knowledge and competence, translation of genetic information related to mental health, and demographic information. See the Appendix for a PDF of the full survey.

Professional Translational Practices. This section of the survey was designed to assess broad translational practices in the context of one's profession. Participants answered five questions related to familiarity with translational science terms and five questions about their network of collaborators (translational science does not occur in a vacuum, and collaborators are a key component to each framework to varying degrees).

Genetic Knowledge and Competence. Education/training are an oft-cited barrier to the translation of genetic information (Zhou et al., 2014). Accordingly, the second section of the survey inquired about participants' genetic knowledge and competence separately. Participants were asked familiarity with terms related to genetic content areas (six questions - family history/aggregation, heritability, gene-environment relationship, twin studies, molecular genomics, epigenetics) as a way to gauge genetic knowledge. Competence was assessed via nine pointed questions asking how competent participants felt about discussing, reading articles, authoring papers, and mentoring students on projects that utilized genetic information. Finally, they were also queried on their genetics training (one question).

Translation of Genetic Information Related to Mental Health. The third section of the survey queried participants' agreement on four statements that asked how important the translation of genetic information about mental health disorders is, how much it would improve their field, whether it is important for professionals in their field to understand this information, and whether it would benefit students' training. They then had to rank their likeliness of attending five hypothetical training opportunities where they would learn about how to improve their involvement in the translation of genetic information about mental health disorders. Participants were also directly asked how much they believe that increased knowledge of genetic information would improve nine different aspect of mental health research, prevention, treatment, and recovery. They had to answer the same question in relation to each of the 13 Diagnostic and Statistical Manual - 5th edition's (DSM-5) categories of disorders.

Demographic Information. Participants were asked about their age, race, ethnicity, gender, highest degree obtained, and job type.

Procedure

The current instrument was administered online via REDCap (Harris et al., 2009) using both active and passive methods that were approved by VCU's Institutional Review Board. Individuals recruited by active methods were emailed the survey link with a brief explanation of the study. A reminder email was sent out approximately two weeks later. Those recruited via passive methods were provided with the survey link in the advertisement.

Data Plan

The purpose of the survey was to be hypothesis-generating for future projects in this research area, and qualitative, inductive analytical approaches were taken (Strauss & Corbin, 1998). This allowed for the emergence of themes and identification of key points to be explored

in further studies. Thus, only frequency counts for each question were examined. All analyses were done in R (R Development Core Team, 2015).

Results

Professional Translational Practices

In regard to broad translational concepts in a professional context, participants were the most familiar with personalized medicine (see Table 3.2). Over ninety percent of participants had at least heard of the term, followed by research-to-policy (89.75%), D&I (87.30), research-to-practice (79.89%) and bench-to-bedside (76.51%). Between a third and half of participants could define and give an example of each translational science term. Finally, more participants reported actively participating in research-to-practice (36.15%) than any other form of translation.

Measures of breadth and depth of collaborators revealed that most participants (54.58%) had a network of collaborators that included at least 10 people. Participants reported meeting regularly with their collaborators (61.29%) and that their collaborators span many job types (i.e., researcher, nurse, teacher) and fields (i.e., psychology, statistics, social work, etc.).

Table 3.2. Frequencies for individual questions from the "Professional Translational Practices" section.

Select the answer that best describes your experience with these terms related to translational science				
	I have not heard of this	I have heard of this	I can define this and give an example	I actively participate in this form of translation
Research-to-practice	11.11%	19 .05%	33.33%	36.51%
Research-to-policy	11.11%	30.02%	37.51%	22.22%
Bench-to-bedside	23.44%	23.44%	48.38%	4.69%
Dissemination and Implementation	12.70%	20.63%	38.10%	28.57%
Personalized medicine	9.38%	20.31%	53.03%	17.19%

The size of my network of collaborators is…			
I do not have a network of collaborators	Less than 10	10 or more	20 or more
15.63%	28.13%	54.58%	1.56%

I have collaborators that are… [check all that apply]				
Researchers	Clinicians	Nurses	Teachers	Other
82.81%	81.25%	39.06%	53.13%	20.31%

My collaborators span the following disciplines… [check all that apply]								
Social/ Behav. Health	Social Work	Public Health	Other	Psychology	Psychiatry	Statistics	Psychiatric / Behav. Genetics	Human / Molecular Genetics
56.25%	50.00%	48.44%	29.69%	79.69%	56.25%	48.44%	48.44%	37.50%

How often do you meet/consult with individuals from your network of collaborators?		
Several of us meet/consult regularly	I meet/consult with individuals on an as-needed basis	Other
61.29%	38.71%	0.00%

Genetic Knowledge and Competence

Over half (64.06%) of participants were not active in any field of genetics with about a quarter (23.44%) not reporting any formal genetics training (see Table 3.3). Nevertheless, participants were quite familiar with genetic terms; many were able to at least define and give an example of each term. Specifically, participants were the most familiar with twin studies (90.63%) followed by heritability (89.07%), gene-environment relationship (85.94%), family history (81.25%), epigenetics (72.88%), and molecular genomics (43.75%). More participants reported utilizing content related to family history (31.25%) in their everyday work than other forms of genetic information.

Participants' self-rated competence fluctuated depending on the content area. They were the most comfortable reading articles that either mention genetic information (98.39%) or where genetics is the focus of the paper (79.36%) followed by discussing genetic information with collaborators (76.19%), trainees/students (69.84%), and patients (47.62% - note this question was not applicable to many participants). They were the least comfortable co-authoring (29.10%) or leading (37.09%) a paper where the genetics of a mental health disorder was the focus. Most were also not comfortable mentoring a trainee/student who wants to study the genetics of a mental health disorder (37.09%).

Table 3.3. Frequencies for individual questions from the "Genetic Knowledge and Competence" section.

Experience in the field of genetics					
Currently active in a field of genetics	Not active but had training within last 2 years	Not active but had training within last 3-5 years	Not active but had training 6-10 years ago	Not active and had training more than 10 years ago	No genetics training of any kind
35.94%	9.38%	7.81%	9.38%	14.06%	23.44%

Select the answer that best describes your experience with each of the following content areas of genetics				
	I have never heard of this	I have heard of this but cannot define it	I can define this and give an example	I utilize content related to this in my everyday work
Family history / aggregation	3.13%	15.63%	50.00%	31.25%
Heritability	1.56%	9.38%	60.94%	28.13%
Gene-environment relationship (i.e., interaction or correlation)	0.00%	14.06%	60.94%	25.00%
Twin studies	0.00%	9.38%	78.13%	12.50%
Molecular genomics	7.81%	48.38%	17.19%	26.56%
Epigenetics	4.69%	23.44%	60.94%	10.94%

Rank how much you agree/disagree with the following statements					
	Strongly Disagree	Disagree	Agree	Strongly Agree	Not Applicable
I feel competent discussing genetic information regarding mental health disorders with my network of collaborators	4.76%	12.70%	47.62%	28.57%	6.35%
I feel competent discussing genetic information regarding mental health disorders with trainees/students	7.94%	17.46%	44.44%	25.40%	4.76%
I feel competent discussing genetic information regarding mental health disorders with patients	4.76%	11.11%	38.10%	9.52%	36.51%
I feel competent reading a scholarly article that mentions genetic information (i.e., in the intro or discussion as potential implications)	0.00%	1.61%	38.71%	59.68%	0.00%
I feel competent reading a scholarly article that utilizes genetic information as a the focus of the overall purpose of the study (i.e., heritability study, genome-wide association study)	1.59%	19.05%	39.68%	39.68%	0.00%
I feel competent being a CO-author on a scholarly article where the genetics of a mental health disorder is the focus of the study	20.63%	36.51%	19.05%	10.05%	4.76%
I feel competent being a LEAD author on a scholarly article where the genetics of a mental health disorder is the focus of the study	55.56%	10.98%	24.19%	12.90%	1.61%
I feel competent mentoring/advising a trainee/student who wants to study the genetics of a specific mental health disorder (i.e., cumulative project, thesis, dissertation)	40.32%	20.98%	24.19%	12.90%	1.61%

Note: The genetic experience questions were not part of the knowledge or experience variables directly but needed to be assessed and were logically put into that section.

Translation of Genetic Information Related to Mental Health

A large majority of participants agreed or strongly agreed with all statements regarding the importance and benefit of translating genetic information about mental health disorders in various professional contexts (84.12-96.82%) (see Table 3.4). They agreed the most with the broad statement that the translation between research and practice related to mental health is important (96.82%). However, they were less enthusiastic about hypothetical activities related to improving their own translation of genetic information about mental health disorders. Most were not likely or very not likely to attend any of the suggested events (65.08-92.06%). The exception was a 2-hour seminar at a conference they already planned to attend; 60.32% were likely or very likely to do this.

Participants were in the most agreement that increased knowledge of genetic information about mental health disorders would moderately influence care in regard to creating biological or pharmacological therapies (56.45%), discovering new and better treatments (49.21%), and improving diagnostic clarification of affected patients (46.78%). Otherwise, they reported that increased knowledge of genetic information would have weak or no influence on clinical care in the rest of the posited areas (60.65-78.93%). Accordingly, specific disorders that participants felt would moderately benefit from increased genetic information are those that we currently know the most about biologically – schizophrenia spectrum and other psychotic disorders (63.49%), neurodevelopmental disorders (including ASD; 68.25%), and bipolar disorder (58.73%). Otherwise, they reported that the translation of genetic information into clinical care would have some or no benefit for the remaining DSM-5 disorder categories (53.95-90.47%).

Table 3.4. Frequencies for individual questions from the "Translation of Genetic Information Related to Mental Health" section.

Rank how much you agree/disagree with the following statements				
	Strongly Disagree	Disagree	Agree	Strongly Agree
Translation between research and practice related to mental health disorders is important	0.00%	3.17%	50.79%	46.03%
My field would benefit from improved translation of genetic information related to mental health disorders	3.17%	6.35%	50.79%	39.68%
It is important for all professionals in my field (researchers, teachers, practitioners) to understand the genetic risk associated with specific mental health disorders	1.59%	14.29%	50.79%	33.33%
It is important for students to be taught how to utilize information regarding the genetic risk associated with specific mental health disorders, regardless of field	0.00%	11.11%	50.79%	38.10%

Below are potential ways to improve the translation of genetic information about mental health disorders in an academic setting. Please rank the following activities in terms of how likely you would be to utilize them if they were available to you right now. Assume the event would be geared toward your primary role at your university (i.e., researcher, practitioner, teacher, combination thereof).					
	Not Very Likely	Not Likely	Likely	Very Likely	I Already Do / Have Done Something Like This
Attend a one-day in-person workshop at VCU	33.33%	31.75%	33.33%	1.59%	0.00%
Attend a in-person course at VCU that meets once a week for four weeks	58.73%	33.33%	7.94%	0.00%	0.00%
Take an online training module that can be spread out over multiple sittings	27.42%	40.32	29.03%	3.23%	0.00%
Attend a special 2-hour seminar presentation at a conference you already plan to attend	15.87%	23.81%	49.21%	11.11%	0.00%
Attend regular meetings with your network of collaborators	31.75%	33.33%	23.81%	11.11%	0.00%

To what extent do you believe that increased knowledge of genetic information regarding the basis of mental health disorders will influence the following?				
	No Influence	Weak Influence	Moderate Influence	Strong Influence
Discovering new and better treatments for mental health disorders	1.59%	49.21%	49.21%	0.00%
Improving diagnostic clarification of affected patients with mental health disorders	1.61%	51.61%	46.78%	0.00%
Identifying asymptomatic patients at risk of developing mental health disorders	11.47%	49.18%	39.34%	0.00%

Targeting of resources to at-risk populations	11.29%	51.61%	37.10%	0.00%
Prenatal testing to guide reproductive choices	27.42%	46.77%	25.81%	0.00%
Stigma of mental health disorders	16.13%	46.77%	37.10%	0.00%
Insurance to patients with a high-risk genetic profile for mental health disorders	19.67%	47.54%	32.79%	0.00%
Interest in psychosocial therapies for mental health disorders	20.87%	58.06%	20.975	0.00%
Interest in biological or pharmacological therapies for mental health disorders	3.23%	40.32%	56.45%	0.00%

Which of the following do you think will benefit the most from increased translation of genetic information?

	No Benefit	Some Benefit	Moderate Benefit	Significant Benefit
Schizophrenia spectrum and other psychotic disorders	0.00%	36.51%	63.49%	0.00%
Anxiety disorders (generalized, social, panic, separation, phobias)	4.76%	63.49%	3.17%	0.00%
Bipolar disorder	0.00%	41.27%	58.73%	0.00%
Depression disorders (major depression, melancholia)	3.17%	50.79%	46.03%	0.00%
Obsessive-compulsive disorder	0.00%	63.92%	36.51%	0.00%
Post-traumatic stress disorder	11.11%	73.02%	15.87%	0.00%
Eating disorders (anorexia, bulimia, binge eating disorder)	9.52%	65.08%	25.40%	0.00%
Personality disorders	12.70%	68.25%	19.05%	0.00%
Neurodevelopmental disorders (autism spectrum disorder, communication disorders, intellectual developmental disorder)	1.59%	30.16%	68.25%	0.00%
Sleep-Wake disorders (insomnia disorder, narcolepsy)	6.35%	53.97%	39.68%	0.00%
Sexual dysfunction	22.22%	68.25%	9.52%	0.00%
Disruptive, impulse-control, and conduct disorders	11.11%	61.90%	26.98%	0.00%
Substance use disorders (alcohol, gambling, cocaine, other substances)	1.61%	56.45%	41.94%	0.00%

Discussion

The use of genetic information in mental health care is lacking. The current study took a broad, inductive approach to examining the potential role that genetic information may have in the care of mental health disorders. Academic stakeholders in mental health fields were queried about their professional translational practices, genetic knowledge and competence, and attitudes specific to the translation of genetic information to mental health care. Findings indicate overall enthusiasm for the translation of genetic information into the care of mental health disorders that dissipated as more hypothetical effort was required from participants (e.g., more genetic

competence, more time put into training, etc.). This enthusiasm diminished as scenarios became more specific, though (e.g., asking about the utility of genetic information for anxiety disorders compared to asking if students should be trained more in communicating genetic risk of mental health disorders). Thus, participants held many dissonant views on the topic at hand.

Specifically, on one hand participants engage with broad translational practices in a satisfactory way. This was most clear by the breadth and depth of collaborators that they regularly meet with as well as actively engaging in different translational frameworks. They were also in agreement that in the context of mental health, translation between research and practice is important, that their field would benefit from improved translation of genetic information, and that it is important for professionals and students to be trained on how to communicate genetic risk. On the other hand, participants reported less favorable attitudes when asked about whether they were willing to increase their own translational practices, whether genetic information would impact treatment-related outcomes, or about benefits that genetic information would have for specific DSM-5 disorders. In other words, participants appear to like the idea of translation but when pushed further, were not willing to take steps toward improving their own translational capacity and did not believe that translating genetic information would have large impacts on mental health care.

This finding must be discussed in light of the findings regarding genetic knowledge versus competence, as the dissonance noted may be rooted in moderate levels of knowledge but lower levels of competence. Specifically, participants reported a range of experience with genetics - about half had formal training within the last five years or were active in a field of genetics and half had little-to-no formal genetics training. Notably, they had high levels of self-reported genetic knowledge (information known about a topic) and variable levels of competence

(ability to apply knowledge to a new context). The more application of genetic information that was required in a hypothetical scenario, the less competent participants felt. Interesting, there were two exceptions to this. The areas where participants felt that genetic information would have the greatest impact on mental health care were (a) interest in biological or pharmacological therapies for mental health disorders and (b) disorders for which we know the most about biologically (schizophrenia spectrum and other psychotic disorders, neurodevelopmental disorders, and bipolar disorder). These exceptions highlight a linear perspective that echoes the translation of genetic information related to chronic, physical conditions (Arnett et al., 2007; Cornel & El, 2017; Ebomoyi, 2013; Vornanen et al., 2016; International Consortium for Blood Pressure Genome-Wide Association Studies, 2011, 2011; Gil et al., 2003; Khera & Kathiresan, 2017; Macdonald et al., 2009; Norman & Brain, 2005; Phillips et al., 2006) and older views that such frameworks would also work for psychiatric disorders (Sullivan et al., 2012; Visscher et al., 2016). They also are examples of participants' genetic knowledge at work, as participants were likely taught or inferred throughout their careers that the only way genetic information can inform care is by first uncovering underlying biological mechanisms of disease and then creating biological or pharmacological therapies based on those mechanisms.

The lower genetic competence for more genetic-intense scenarios aligns with participants' disagreement that translating genetic information will have large benefits for mental health care. This lack of competence is likely preventing participants from thinking beyond a linear framework when answering questions related to other ways that genetic information may be of impact (e.g., improving diagnostic clarification for affected patients with mental health disorders) and for disorders for which the underlying molecular genomic architecture is unclear (i.e., anxiety disorders). In other words, there is a translation-genetic competence gap in the

context of mental health among academic stakeholders. An immediate next step along this line of research should therefore be to examine the relationship between genetic knowledge and competence and the translation-focused questions of this survey. It should also be examined whether there are differences in genetic knowledge and competence among academic stakeholders (researchers, clinicians, both, neither) as has been noted in another study that examined attitudes about communicating the genetic risk of mental health disorders (Zhou et al., 2014). These are explored in part 2 of this chapter. Differences in genetic knowledge and competence among stakeholders should also be assessed for specific types of genetic information (i.e., molecular vs. epidemiological) in a future study.

These findings reiterate two key barriers to translating genetic information broadly and in a mental health context - education/training and proper engagement of all stakeholders (Gray & Bonventre, 2002; Sperber et al., 2017; Sperber, Brosenitsch, Levine, & Kanter, 2008; Zhou et al., 2014). While education/training have already been a noted barrier to the communication of genetic risk about mental health disorders specifically (Zhou et al., 2014), the current findings extend the literature. There is now tentative evidence that delineating genetic knowledge from genetic competence in the context of mental health is critical to addressing barriers related to translation. Efforts to enhance the translation of genetic information about mental health disorders need to emphasize the difference between knowledge and competence and ensure that stakeholders are able to generalize their knowledge to new situations, not simply know details about genetic information (although that is still a noted barrier in past studies [Cornel & El, 2017; Dick, 2017; Howe, Breach, Brody, & Wyman, 2016; Sperber et al., 2017; Sullivan et al., 2012; Sullivan et al., 2018; Visscher et al., 2016; Wittchen et al., 2014]). A key way for this to occur is through non-linear translational frameworks such as D&I and prevention science that

emphasize collaboration and communication with a socio-ecological perspective. A natural by-product of such a shift would be an emphasis on non-molecular genetic information which may aid in the incorporation of genetic information into mental health care.

Findings also highlight that participants have a healthy number of diverse collaborators with whom they communicate regularly. This is to be commended, and future work needs to leverage this information carefully. For example, the current study did not assess how participants engage with their collaborators. It is possible that they already take a holistic approach to collaboration or that they engage in a linear view of translation and only rely on specific collaborators when certain areas of expertise are needed. Knowing this information would greatly help to bridge the translation-genetic competence gap among academic mental health stakeholders. It is critical that collaborators be engaged in all aspects of projects and translation in a collaborative and cooperative manner. Again, overcoming these barriers is not insurmountable, especially if shifts away from linear views of translation and molecular-only genetic data occur occur.

Limitations

This study should be interpreted in the context of seven limitations. First, most findings presented here are novel and thus not comparable to past literature and must be evaluated in and of themselves. Second, these findings are likely not generalizable outside of academia, and to that end, a large institution. The issues discussed in this paper are complex, and inquiries into them must start somewhere; hopefully future studies will fill in gaps such as extensions to other stakeholders. In that vein, there is no input from patients or trainees, stakeholder groups who can also be found at large universities with a medical campus and other training facilities. Third, inquiries into academics' roles were restricted to asking about their degree, primary job type, and

primary areas of research and/or clinical expertise. We were understandably not permitted to ask specific department affiliations, although such information may have provided additional insights. Fourth, care was taken to ensure that concepts such as genetic knowledge and genetic competence were captured by this survey. However, psychometric analysis was limited, and the validity of this survey is not known (see part 4). Fifth, participants were queried across a range of genetic concepts and often, "genetic information" was used broadly in the survey. This was to gauge participants' views on this topic but admittedly did not directly address issues brought up in this study – namely, that different translational approaches should be taken for molecular and non-molecular genetic information. Sixth, the survey did not query participants on their familiarity with prevention science, a major translational framework. Finally, a major purpose was for this survey to be ideas-generating for future projects. This is one step of many into this line of research. That said, this paper somewhat fell into the trap of focusing on what to do in the future instead of what can be done in the present because of this limitation.

Conclusions

Translation has been more attainable for certain fields and types of genetic information than others and it has become clear over the past decade that there is no one-size-fits-all approach to the translation of genetic information (Khoury et al., 2007; Kon, 2008; Waldman & Terzic, 2010). The current study sheds light on academic mental health stakeholders' translational practices and attitudes as well as their genetic knowledge and competence by taking a broad, inductive approach to studying the topic at hand. Findings extend past research and highlight a translation-genetic competence divide that may be able to be addressed by applying collaborative and inclusive translational frameworks to the incorporation of genetic information in mental health care.

Part 2: Hypotheses and research question generated from the survey

Introduction

To recap from part 1, a translation-genetic competence gap was noted. Participants supported broad level translation but displayed lower enthusiasm for translating genetic information related to specific mental health treatment scenarios and disorder examples. They also reported lower competence for more genetic-intense scenarios. This indicates that genetic competence, which is properly applying knowledge to a new context, is needed above and beyond genetic knowledge to thoroughly assess the translation of genetic information into the care of mental health disorders. That is because genetic knowledge likely teaches linear views of translation and pharmacological-based views of translating genetic information with examples that rely on chronic, physical conditions (Spencer et al., 2008; van der Laan & Boenink, 2012).

Hypotheses and Research Questions

Accordingly, there are two hypotheses and one research question designed to be a follow-up to part 1. They are as follows:

Hypothesis 1: There will be positive relationships between genetic competence and questions about (a) current translational practices, (b) the importance of translation, (c) willingness to improve own translational skills, and (d) impact on care. In other words, the stronger participants' genetic competence then the more they can think thoroughly about translating genetic information.

Hypothesis 2: There will be positive relationships between genetic knowledge and questions about (a) current translational practices, (b) the importance of translation, (c) willingness to improve own translational skills, and (d) impact on care, but these relationships will not be as strong as those for genetic competence. In other words, the stronger participants'

genetic competence, then the more they can think thoroughly about translating genetic information. Stronger genetic knowledge may prevent stakeholders from thinking in non-linear ways about translating genetic information.

Research question 1: Are there differences in genetic knowledge and competence among participants based on job type (researcher, clinician, both, neither)?

Methods

All methodology except the specific analyses from part 1 apply to part 2. A summated score (Fink et al., 2017) was used to generate composite variables across questions that had multiple components. For example, participants answered the question "which of the following do you think will benefit from increased translation of genetic information" for 13 DSM-5 disorders. The sum score was created for a composite variable that represents *overall* attitudes on "benefit of translation of genetic information for specific mental health disorders."

Specifically, eight composite variables were created (see Table 3.5 below for details): "experience with translational science terms," "breadth and depth of network of collaborators," "genetic knowledge," "genetic competence," "importance of translating genetic information about mental health disorders," "willingness to improve own translational competency," "influence of translating genetic information on mental health care," and "influence of translating genetic information of specific mental health disorders."

Table 3.5. Composite variables created from the translational survey.

Original Questions	Original Answers	Score for the Answer Option That Went Into Sum Score
Experience With Translational Science Terms		
Select the answer that best describes your experience with these terms related to translational science:* Research-to-practice Research-to-policy Bench-to-bedside Dissemination and Implementation Precision Medicine	I have not heard of this	0
	I have heard of this	1
	I can define this and give an example	2
	I actively participate in this form of translation	3
Breadth and Depth of Network of Collaborators		
The size of my network of collaborators is…	I do not have a network of collaborators	0
	Less than 10	1
	10 or more	2
	20 or more	3
I have collaborators that are… [check all that apply]	Researchers Clinicians Nurses Teachers Other (please specify)	1 point per different type of collaborator
My collaborators span the following disciplines… [check all that apply]	Psychology Psychiatry Statistics Psychiatric and behavioral genetics Human and molecular genetics Social and Behavioral Health Social work Public health Other (please specify)	1 point per different type of discipline
How often do you meet/consult with individuals from your network of collaborators?	Several of us meet/consult regularly	2
	I meet/consult with individuals on an as-needed basis	1
	Other (please specify)	1
Genetic Knowledge		
Select the answer that best describes your experience with each of the following content areas of genetics Family history / aggregation Heritability	I have never heard of this	0
	I have heard of this but cannot define it	1
	I can define this and give an example	2

Gene-environment relationship (i.e., interaction or correlation) Twin studies Molecular genomics Epigenetics	I utilize content related to this in my everyday work	3
Genetic Competence		
Rank how much you agree/disagree with the following statements • I feel competent discussing genetic information regarding mental health disorders with my network of collaborators • I feel competent discussing genetic information regarding mental health disorders with trainees/students • I feel competent discussing genetic information regarding mental health disorders with patients • I feel competent reading a scholarly article that mentions genetic information (i.e., in the intro or discussion as potential implications) • I feel competent reading a scholarly article that utilizes genetic information as the focus of the overall purpose of the study (i.e., heritability study, genome-wide association study) • I feel competent being a CO-author on a scholarly article where the genetics of a mental health disorder is the focus of the study • I feel competent being a LEAD author on a scholarly article where the genetics of a mental health disorder is the focus of the study • I feel competent mentoring/advising a trainee/student who wants to study the genetics of a specific mental health disorder (i.e., cumulative project, thesis, dissertation)	Strongly Disagree	0
	Disagree	1
	Agree	2
	Strongly Agree	3
	Not Applicable	0
Importance of Translating Genetic Information About Mental Health Disorders		
Rank how much you agree/disagree with the following statements • Translation between research and practice related to mental health disorders is important	Strongly disagree	0
	Disagree	1

• My field would benefit from improved translation of genetic information related to mental health disorders • It is important for all professionals in my field (researchers, teachers, practitioners) to understand the genetic risk associated with specific mental health disorders • It is important for students to be taught how to utilize information regarding the genetic risk associated with specific mental health disorders, regardless of field	Agree	2
	Strongly agree	3
Willingness to Improve Own Translational Competency		
Rank how much you agree/disagree with the following statements • Attend a one-day in-person workshop at VCU • Attend an in-person course at VCU that meets once a week for four weeks • Take an online training module that can be spread out over multiple sittings • Attend a special 2-hour seminar presentation at a conference you already plan to attend • Attend regular meetings with your network of collaborators	Not very likely	0
	Not likely	0
	Likely	1
	Very likely	2
	I already do this / have done something like this	3
Influence of Translating Genetic Information On Mental Health Care		
To what extent do you believe that increased knowledge of genetic information regarding the basis of mental health disorders will influence the following? • Discovering new and better treatments for mental health disorders • Improving diagnostic clarification of affected patients with mental health disorders • Identifying asymptomatic patients at risk of developing mental health disorders • Targeting of resources to at-risk populations • Prenatal testing to guide reproductive choices • Stigma of mental health disorders • Insurance to patients with a high-risk genetic profile for mental health disorders • Interest in psychosocial therapies for mental health disorders	No influence	0
	Weak influence	1
	Moderate influence	2
	Strong influence	3

• Interest in biological or pharmacological therapies for mental health disorders		
Influence Of Translating Genetic Information Of Specific Mental Health Disorders		
Which of the following do you think will benefit the most from increased translation of genetic information? • Schizophrenia spectrum and other psychotic disorders • Anxiety disorders (generalized, social, panic, separation, phobias) • Bipolar disorder • Depression disorders (major depression, melancholia) • Obsessive-compulsive disorder • Post-traumatic stress disorder • Eating disorders (anorexia, bulimia, binge eating disorder) • Personality disorders • Neurodevelopmental disorders (autism spectrum disorder, communication disorders, intellectual developmental disorder) • Sleep-Wake disorders (insomnia disorder, narcolepsy) • Sexual dysfunction • Disruptive, impulse-control, and conduct disorders • Substance use disorders (alcohol, gambling, cocaine, other substances)	No benefit	0
	Some benefit	1
	Moderate benefit	2
	Significant benefit	3

Next, Pearson correlations were run to calculate the correlations among these eight composite variables. This not only answered hypotheses 1 and 2 but provided some additional information. There were three components to these two hypotheses - that genetic competence and genetic knowledge (respectively) would be positively correlated with a) current translational practices, b) the importance of translation, c) willingness to improve own translational skills, and d) impact on care. Here, "current translational practices" entailed the "experience with translational science terms" and "breadth/depth of network of collaborators" composite variables of the survey. "The importance of translation" and "willingness to improve own translational skills" were represented by the composite variables with the same titles (above). "Impact on

care" was also represented by two composite variables, those related to the importance of genetic information on mental health care scenarios and specific mental health disorders.

Finally, a 1-factor ANOVA was run to assess differences in the sum scores for genetic knowledge and genetic competence across the ordinal variable of job type (four levels - researchers, clinicians, both, and neither).

Results

Hypothesis 1: Relationship Between Genetic Competence and Translation

This hypothesis was mostly unsupported and should be rejected (see Table 3.6). Out of the six correlations assessed, only one was significantly associated with genetic competence. The "importance of translating genetic information about mental health disorders" variable had a strong, positive relationship with genetic competence ($r = .58$; $p < .01$).

Table 3.6. Results for hypothesis 1 - assessing the relationship between genetic competence and translational variables.

	Experience with translational science terms	Breadth/ depth of network	Importance of translating genetic information about mental health disorders	Willingness to improve translational skills	Influence of genetic information on mental health care scenarios	Influence of genetic information on specific mental health disorders
Genetic competence	-.20	.10	.58*	.15	.07	.00

*$p < .01$

Hypothesis 2: Relationship Between Genetic Knowledge and Translation

This hypothesis was also mostly unsupported and should be rejected (see Table 3.7). Two of the six correlations had a relationship with genetic knowledge, although one was in the opposite direction. As hypothesized, the correlation between genetic knowledge and "importance of translating genetic information about mental health disorders" was positive but not as strong (*r*

= .30; p <.05) as the variable's relationship with genetic competence. Interestingly there was a negative relationship between genetic knowledge and "experience with translational science terms" (r = -.29; p < .05). None of the other variables were related to genetic knowledge.

Table 3.7. Results for hypothesis 2 - assessing the relationship between genetic knowledge and translational variables.

	Experience with translational science terms	Breadth/ depth of network	Importance of translating genetic information about mental health disorders	Willingness to improve translational skills	Influence of genetic information on mental health care scenarios	Influence of genetic information on specific mental health disorders
Genetic knowledge	-.29*	.07	.30*	.03	-.07	-.19

*p < .05

Research Question 1: Differences by Job Type

There were significant differences found in genetic knowledge and competence based on job type. See Table 3.8 for the mean scores of genetic knowledge and competence by job type.

Table 3.8. Mean scores (standard deviation) of genetic knowledge and genetic competence by job type.

	Researchers	Clinicians	Both	Neither
Genetic knowledge	11.72 (3.13)	12.05 (2.55)	14.57 (2.64)	9.67 (3.67)
Genetic competence	12.04 (5.50)	12.53 (4.06)	17.14 (5.08)	9.67 (6.87)

The ANOVA for genetic knowledge was significant (F = 3.570; df = 3; p < .05) and a Tukey Posthoc test revealed that the significant differences was between those who were both clinicians and researchers and those who were neither (see Table 3.9). A second ANOVA that removed those who were neither (due to such individuals being the most different from the other three categories) revealed no further significant differences (F = 2.772; df = 2; p > .05).

Table 3.9. ANOVA results for genetic knowledge.

	F (*df*); *p*	Researcher Differences	Clinician Differences	Both Differences
ANOVA	3.570 (3); .020	--	--	--
Tukey Posthoc	--	Researcher vs. Clinician: .333 (*p* = .983) Researcher vs. Both: 2.851 (*p* = .128) Researcher vs. Neither: 2.053 (*p* = .301)	Clinician vs. Both: 2.519 (*p* = .238) Clinician vs. Neither: 2.386 (*p* = .212)	Both vs. Neither: 4.905 (*p* = .010)

The ANOVA for genetic competence was not significant ($F = 2.736$; $df = 3$; $p > .05$) however a Tukey Posthoc test was conducted anyway for completeness (see Table 3.10). The posthoc test revealed significant differences between those who were both clinicians and researchers and those who were neither. A second ANOVA that removed those who were neither (due to such individuals being the most different from the other three categories) revealed no further significant differences ($F = 2.996$; $df = 2$; $p > .05$).

Table 3.10. ANOVA results for genetic competence.

	F (*df*); *p*	Researcher Differences	Clinician Differences	Both Differences
ANOVA	2.736 (3); .052	--	--	--
Tukey Posthoc	--	Researcher vs. Clinician: .486 (*p* = .990) Researcher vs. Both: 5.103 (*p* = .119) Researcher vs. Neither: 2.373 (*p* = .655)	Clinician vs. Both: 4.617 (*p* = .208) Clinician vs. Neither: 2.859 (*p* = .542)	Both vs. Neither: 7.476 (*p* = .033)

Additional findings

As stated in the methods, a correlation matrix was completed for all of the variables in the survey based on their sum scores. The full matrix is below and includes some information not discussed in the above sections (see Table 3.11). The variables are in the same order as the survey. Additionally, a Spearman correlation was run between the nine composite survey variables and job type.

Table 3.11. Correlations among all composite variables and job type.

	1.	2.	3.	4.	5.	6.	7.	8.	9.
1. Experience with translational science terms	1								
2. Breadth and depth of network of collaborators	.11	1							
3. Genetic knowledge	-.29*	.07	1						
4. Genetic competence	-.20	.10	.63**	1					
5. Importance of translating genetic information about mental health disorders	.00	.14	.30*	.58**	1				
6. Willingness to improve own translational competency	.00	.05	.03	.15	.20	1			
7. Influence of translating genetic information on mental health care	.10	.00	-.07	.07	-.12	.14	1		
8. Influence of translating genetic information of specific mental health disorders	.12	-.11	-.19	.00	-.09	.08	.60**	1	
9. Job type	.26	.27*	-.08	-.02	.24	-.06	-.03	.15	1

*$p < .05$; **$p < .01$; ***$p < .001$

Note: Job type is ordinal and thus Spearman correlations were used; all other correlations were done with Pearson correlation. Job type was ordered in the following ascending way: researcher, clinician, both, neither.

As seen from the correlation matrix above, there were few significant correlations across these variables. Unsurprisingly, there is a strong correlation among all genetic variables. The

strongest correlation is between attitudes about the perceived impact of genetic information on mental health care and mental health disorders, which is also unsurprising given that the two variables are two components of the same topic. Finally, there was a positive correlation between job type and breadth/depth of participants' network of collaborators. This implies that those who are only researchers and clinicians are least likely to have a stronger network of collaborators.

Conclusions

Despite preliminary, descriptive evidence from part 1 of a translation-genetic competence gap among participants, there are few relationships between the translational variables from the survey and genetic competence or knowledge. Hypotheses 1 and 2 stated that genetic competence and knowledge, respectively, would be positively associated with translation variables with competence having stronger relationships. Both genetic competence and knowledge were moderately associated with how important participants viewed the overall translation of genetic information about mental health disorders; genetic competence had the stronger correlation. However, genetic competence was not associated with any other translation variables and genetic knowledge was negatively associated with experience with translational terms. Together, these results lead to the rejection of both hypotheses 1 and 2.

The two associations between the importance of translating genetic information about mental health disorders and genetic competence and knowledge are notable. The strength of the relationships aligns with the proposed translation-genetic competence gap from part 1. Even though there was only an association with one translation variable, it was still stronger for genetic competence than knowledge. This adds some evidence that genetic competence is a bigger driving force behind thinking outside of the box and holding positive views about the translation of genetic information into the care of mental health disorders. Genetic knowledge

likely comes form and hence reinforces linear views of translation that hinder translation in a mental health context. The rationale behind this gap is further reinforced by the finding that as genetic knowledge increases, experience with translational science terms decreases.

Finally, significant differences were found between those who identify as both and neither researchers and clinicians in regard to their amount of genetic knowledge and competence. Those who identified as both reported higher levels of both. Otherwise, there is no evidence that genetic knowledge or competence differ based on job type. This is especially good to know when comparing researchers and clinicians, as differences between those two groups would have arguably had the most implications for this line of research.

Overall, it is clear that while part 1 provides some intriguing insights into the current state of the science regarding the translation of genetic information, there is only so much to be gleaned from this survey. There is much more to examine about this topic, but utilizing the survey for anything more than descriptive statistics and ideas for future projects seems fruitless.

Part 3: Analysis of key open-ended questions

Introduction & Methods

Finally, there were several open-ended questions in the survey. Many of these were options for participants to give responses if they selected "other" for a question, but a few were purposeful and will be discussed in turn. These question was analyzed using the qualitative content analysis approach of open coding whereby the responses were read, ideas were labeled, codes were created, and themes were identified across responses (Strauss & Corbin, 1998).

Current Translational Experiences

At the end of the *Professional Translational Experiences* section of the survey, participants were asked "What else should I know about your current professional behaviors and experiences related to translational science (i.e., organizations you are a part of, specific details of your collaborative efforts, ways you integrate science, practice, and teaching, etc.)?" Fifteen people responded to this question and two key themes emerged. First, most people who answered this question clearly felt that they were meeting translational expectations and doing the right thing within their respective fields, whether it be research- or clinical-related. On the research side, participants cited grants, research studies, reading articles, mentorship, and being a reviewer for journals as translational activities that they engage in. On the clinical side, many cited efforts to improve service, increase evidence-based practice, and develop new programs. The second and more surprising theme was the discussion of bridging the research-to-practice gap via collaborations, committees, and interdisciplinary relationships. No matter the translational framework utilized, this is the end goal of translational science.

Influence On Mental Health Care

Toward the end of the final section of the survey, *Translational of Genetic Information to Mental Health*, participants were asked "What are other ways you think genetic information can influence mental health?" Only four participants answered this question but their responses were all along the same theme and are worth mentioning. Specifically, each response discussed the negative consequences of utilizing genetic information in clinical care - consequences such as stigma, insurance concerns, and additional barriers. It should be noted that such a theme implies that participants assumed that the genetic information that would be translated to the care of mental health disorders is molecular genetic information. Most of these negative consequences would not be a concern when translating non-molecular genetic information. Additionally, one

participant mentioned a positive influence could be policy changes to support increased research related to this topic.

Final Thoughts About Given Topic

At the end of the survey, participants were asked two questions. The first was "What are your final thoughts about the translation of the genetic information to the clinical care of mental health disorders?" Thirteen participants answered this question and three themes emerged from the responses. First, participants thought that there was a strong need to consider the ethical and moral implications as we continue to examine the genetic etiology and eventual clinical implementation of such data into the care of mental health disorders. This echoes responses from the previous question ("What are other ways you think genetic information can influence mental health?"). Second, on a more positive note, participants were hopeful that translating genetic information would help overcome barriers to care, such as medication adherence, less self-blame, and overall benefits. Finally, participants were vocal about the fact that so far, there is no evidence that genetic information will help with mental health disorders due to few findings that are potentially translatable (again, a molecular-only perspective is implied in such responses - only one person explicitly mentioned heritability). Many participants were negative about the potential utility while many held out hope that future research will lead to findings that can positively impact care.

Translational Science Definition

The second question asked at the end of the survey was "I carefully avoided giving you a specific definition of translational science during this survey. Please let me know what translational science means to you in one sentence." A definition of translational science was purposefully not provided during the survey. Twenty-seven participants responded and despite

this being the most-answered open-ended question, only one major theme was present. That theme was that translational science is the application of basic science to clinical practice and policy in a linear fashion. Across these responses, key words such as "disseminate," "implement," and "research-to-practice" were used but in a linear context. Variations of the word "translation" were also often used in the definition. One response did not give a definition of translation science and instead stated that it is an over-used term. Another participant stated that translational science is broader in scope and is the application of knowledge across fields. It must be noted that other than this one response, a participatory / collaborative perspective of translation was not upheld by participants. Discussion of collaborators and effective communication were missing, as well as ways to think outside of the box and use socio-ecological perspectives to implement non-molecular information (for example).

Conclusions

Analysis of the open-ended questions reaffirmed that participants hold a very linear view of translation and assume that the "genetic information" to be translated into mental health care is molecular genetic information. This aligns with findings from chapters 2 and 3 that participants hold more knowledge than competence and future studies will have to examine that further.

Part 4: Limited psychometrics of the translational survey

Introduction

As a reminder, this section is included for completeness. The survey was designed to be hypothesis-generating and inductive, not deductive. The purpose was never to create a permanent measure but set the groundwork for a future line of research that eventually includes an updated

survey. This would require overhauling the current survey, administering it to a larger sample size, and conducting proper psychometric analyses. Thus, the current analyses are what could be performed given limitations of the current survey.

Typically, psychometric evaluation of a measure includes assessing reliability, validity, and factor structure. These will be discussed in turn.

Reliability

Reliability is the extent to which a measure produces consistent results. Internal consistency was calculated for individual sections of the survey as well as the composite variables via Cronbach's alpha. Results are in Table 3.12. Overall, both the sections and composite variables are reliable throughout the survey with the exception of section 1, which has low internal consistency.

Table 3.12. Internal consistency for the three sections of the survey and their eight associated composite variables.

	Cronbach's alpha (confidence interval)
Section 1: Professional Translational Practices	
Overall section	.31 (.09 - .53)
Experience with TS terms*	--
Network	.54 (.40 - .68)
Section 2: Genetic Knowledge and Competence	
Overall section	.85 (.80 - .90)
Genetic knowledge	.84 (.78 - .89)
Genetic competence	.81 (.75 - .88)
Section 3: Translation of Genetic Information to Mental Health Care	
Overall section	.88 (.84 - .93)
Importance of translating MH	.80 (.72 - .88)
Willingness to improve translation of MH	.73 (.62 - .83)
Influence translation of genetic info will have on MHC	.82 (.76 - .89)
Benefit translation of genetic info will have on specific disorders	.88 (.84 - .92)

TS = translational science; MH = mental health; MHC = mental health care

*Cannot assess reliability for one question

Due to the structure and nature of how the survey was constructed and administered, it was not possible to assess inter-rater reliability or test-retest reliability.

Validity

Validity is how well a measure assesses what it is supposed to assess. While content and face validity can be measured to a certain degree, establishing criterion validity would have more of an impact for the survey. Unfortunately, there are no comparable measures to the current survey by which to show criterion validity (i.e., convergent and/or divergent validity). Subjectively, the survey has face validity. It includes one section for each key topic in question - translation, genetics, and the intersection of those two in a mental health context. It is likely that

the content validity is weaker than the face validity. The survey could have included different types of questions about translation and genetics especially. For example, both of those sections of the survey ask participants to rank their familiarity with translation and genetics terms but those terms are never defined for participants nor used again in the survey. There are likely better ways to assess experience with translational science and genetic knowledge and competence.

Factor Structure

Factor structure is important to know because it is possible that there are redundant responses in a measure, items do not load the way the measure's creators think that they do, and so on. Ways to assess this include an exploratory factor analysis (EFA), confirmatory factor analysis (CFA), and item response theory (IRT) modeling. Unfortunately, none of these options were appropriate for the data in the survey. The survey comprised three sections, nine key composite variables, and dozens of individually coded questions. These questions were asked in different ways (i.e., check all that apply, Likert) that made conducting an EFA or CFA impossible. Additionally, the purpose of IRT modeling such as an item characteristic curve is to describe the relationship between a latent ability and performance on a test item. The purpose of this survey was <u>not</u> to gauge "right" or "wrong" responses about the translation of genetic information into the care of mental health disorders. Thus, there were no "right" or "wrong" answers by which to discriminate and the parameters of an IRT model do not apply to this survey (ability level, correct response, discrimination, difficulty, guessing).

Conclusions

Limitations of assessing the psychometrics of this survey were discussed along with the few results. Overall, this survey served its purpose in being hypothesis-generating but strong conclusions should not be made. Given the plentiful limitations (essentially the lack of any

psychometrics except for internal consistency), the descriptive results from this survey are the only informative results. Future studies should build upon what this survey attempted to do by being more targeted, conducting focus groups before creating the survey, doing more pilot testing, and putting measures in place to be able to thoroughly assess the psychometrics of the measure (e.g., consistently asking questions the same way to be able to conduct an EFA, A/B testing or testing in waves to assess reliability more thoroughly, including some questions for which IRT modeling would be appropriate)

Part 5: Global discussion - What have we learned about the translation of genetic information into the care of mental health disorders?

Impressive progress has been made to document the role that genetic information plays in the risk reduction, identification, prevention, and treatment of physical, chronic conditions such as cardiovascular disease (Arnett et al., 2007; Ebomoyi, 2013; Khera & Kathiresan, 2017; International Consortium for Blood Pressure Genome-Wide Association Studies, 2011; Vornanen et al., 2016), breast cancer (Cornel & El, 2017; Gil et al., 2003; Macdonald, Sarna, Weitzel, & Ferrell, 2009; Norman & Brain, 2005; Phillips et al., 2006), macular degeneration (Black & Clark, 2016), and other similarly complex disorders. While it has long been assumed that such linear ways of translating genetic information would carry over to psychiatric disorders (Sullivan et al., 2012), that has not occurred (Sullivan et al., 2018; Visscher et al., 2016). The current dissertation aim was a way to gauge attitudes and practices surrounding the translation of genetic information into the care of mental health disorders. Findings shed light on a translation-genetic competence gap among participants that likely stems from the fact that many (if not all) hold a linear view of translation. This view communicates that molecular information is the

"genetic information of choice" and given the state of the science (Visscher et al., 2016), we are decades away from any level of implementation. Relatedly, participants like the idea of translation but do not seem quite sure how to act upon that.

Despite a lack of depth to this area of research, survey results somewhat align with the dearth of extant literature and serve to push the field forward. This is all discussed in the context of three barriers to translating the genetic information of mental health disorders: (1) Whether explicitly or implicitly stated, linear frameworks of translation abound when discussing any disorder, even those of a psychiatric nature. (2) The lack of training and continuing education across academic fields related to the ever-changing field of genetics and its sub-fields (psychiatric, behavioral, human, molecular, counseling). (3) The exclusion of mental health / psychiatry from widespread discussion of translational practices.

First, as already stated, linear frameworks abound when discussing any form of translation in a genetic context because it is assumed that "genetic information" equals "molecular genetics." This is misleading because there are many types of genetic information that may be useful to clinicians and health educators that are not molecular (e.g., heritability, family history, gene-environment interplay, the concept of genes vs. environment involved in a disorder). It is likely that such linear ways of thinking stem from stronger genetic knowledge than genetic competence. It has been hypothesized during this chapter that genetic competence is necessary for the type of translation that is necessary to integrate non-molecular genetic information into the clinical care of mental health disorders. It is time that we move beyond waiting for science to catch up with practice and find new, collaborative, communicative, and socio-ecological frameworks that allow us to ask the next set of questions about incorporating genetic information into the clinical care of mental health disorders.

Second, despite moderate self-reported levels of genetic knowledge, participants largely did not report having much genetic experience. This is in line with oft-cited barriers to translation (both general translation and translation specific to genetics) - training and education. On one hand, continuing education, workshops, and other outlets are necessary to assist mid-to-late career professionals with simply discussing the translation of non-molecular information into mental health care, let alone actually doing the translation. Increased education would likely lead to increased communication among stakeholder groups (Sperber et al., 2017). Getting participants to come to these events may be difficult, though, as the survey showed.

On the other hand, translation, genetics, and mental health need to be taught together. For example, if an individual is earning a master's in genetic counseling, they should be taught about the risks of psychiatric conditions and how to inform patients, collaborate with psychiatrists, and so on. If a person is earning a doctorate in clinical psychology, a program which already emphasizes translation via evidence-based practice, then genetics should also be part of that training. Finally, more programs that specialize in training the next generation to be translational specialists are necessary. One study found that translational training (especially as it related to behavioral health) need to be organized into research-related, translational, and societal impacts (Baldwin et al., 2017). Such broadening frees stakeholders from the traditional linear viewpoints that are associated with the term "translational science."

Finally, mental health conditions have been largely overlooked in translational efforts. For example, the White House's Precision Medicine Initiative (Collins & Varmus, 2015) clearly leaves mental health conditions out of national efforts to broadly apply precision medicine with a top-down, federal initiative. Additionally, the National Center for Advancing Translational Science focuses on GWAS for physical, chronic conditions (Collins, 2011). It does not focus

heavily on non-molecular approaches or psychiatric disorders. There is widespread agreement that the translation of basic scientific findings to the benefit of public health represents a critical goal in scientific research (Centers for Disease Control, 2007; Collins & Varmus, 2015; Sullivan, Daly, & O'Donovan, 2012). To accomplish that goal, some have argued for the importance of integrating multiple perspectives across disciplines (psychiatry, psychology, social work, genetics, statistics) and stakeholders (e.g., researchers, clinicians, patients, administrators, policy makers) (Kon, 2008; Waldman & Terzic, 2010). Those efforts should naturally include non-molecular information and mental health care. Through an appreciation of such diverse perspectives, multi-faceted, targeted translation plans can be developed reflecting the expertise and needs of the stakeholders involved.

Limitations

Limitations have been discussed throughout each part of this chapter and will not be repeated here. However, a few words must be given to what is simultaneously the survey's biggest strength and limitation. The survey purposefully did not provide participants with definitions of "genetic information" or "translational science." On one hand, this decision likely contributed to ambivalence and negativity about exactly how translation could impact mental health care and participants' hypothetical roles in this process. On the other, this lack of direction also meant that little creator bias was introduced into the survey, thus it represents the state of the science.

Similarly, the survey tackled abstract concepts that participants might not have previously thought much about. It is possible that the pattern of results in parts 1 and 2 are due to a general misunderstanding of the topic at hand and not true genetic knowledge / competence or translational attitudes / practices. This is why the most attention was given to the descriptive part

1 - it would be foolish to read too much into the results from the quantitative part 2 or to dig any deeper without proper input from stakeholders. Thus, the broad scope of the survey was simultaneously a necessary first step toward examining this topic area and also a major limitation. Future studies need to seek stakeholder input in the creation of a survey (with focus groups or interviews preceding it) and find a way to give more context to the survey. This might mean focusing specifically on one psychiatric disorder, defining key terms from the beginning, and/or finding new ways to assess knowledge and competence.

Final Thoughts

This survey served as the first step toward the integration of non-molecular information into mental health care. Such integration is a multi-step process and will require first examining even *if* such a step should be taken by consulting with a wider range of stakeholders. Current findings support moving forward with this line of research. See chapter 9 for a more thorough discussion of next steps.

Chapter 4: Pediatric Social Anxiety: Etiology, Risk Factor Models, and Best Treatment Practices

Overview

This chapter is a transition from discussing translational science in a broad manner (chapters 2 and 3) to a specific manner via social anxiety. In this context, the translational end-goal will be the creation of a risk factor model (presented in chapter 9) based on the work done in the next few chapters. Chapters 4 through 8 thus include aims 2 and 3 from the dissertation with a chapter dedicated to an overview of social anxiety (current chapter) and summative methodology chapter (chapter 5).

Introduction

Social anxiety disorder is a major public health concern affecting 9.1% (Merikangas et al., 2010) of adolescents, 6.8% of adults (Kessler et al., 2005), and has up to 13% lifetime prevalence (Rapee & Spence, 2004). The mean age of onset is 10-13 years (Rapee & Spence, 2004) and so logically, symptoms often present throughout childhood and pre-adolescence. Social anxiety is a complex disorder meaning that its etiology is an uncertain mix of a multitude of genes, environment, and likely the interplay between the two. The heritability of social anxiety is 52-55% in pre-adolescents (Lahey et al., 2011; Ogliari et al., 2006) and remains stable into adulthood (Hettema et al., 2001), implying a lack of genetic attenuation. This complex etiology highlights the need to study both genetic and environmental risk factors associated with the disorder and ultimately mitigate its onset.

Social anxiety can lead to negative outcomes such as attentional and cognitive biases toward negative stimuli (Heinrichs & Hoffman, 2001), social deficits (Chansky & Kendall, 1997; Erath, Flanagan, & Bierman, 2007; Spence, Donovan, & Brechman-Toussaint, 1999), and peer

victimization (Erath et al., 2007). Without treatment, symptoms typically do not abate and can result in continued social anxiety and adult-onset comorbid disorders such as alcohol misuse and major depression (Axelson & Birmaher, 2001; Bosquet & Egeland, 2006; Carrigan & Randall, 2003; Kendall, Safford, Flannery-Schroeder, & Webb, 2004; Kessler, Stang, Wittchen, Stein, & Walters, 1999; Weichold, Weisner, & Silbereisen, 2014; Wittchen et al., 2000). A lifetime struggle with social anxiety has been shown to lead to disability in routine functions, reduced quality of life, and suicide (Wittchen et al., 2000; Stein & Kean, 2000; Weiller et al., 1996). To best understand the risks that may lead to social anxiety as an adult, studying its onset and related problems in childhood and pre-adolescence are key steps.

Existing Risk Factor Models

To date, few risk factor models exist for pediatric social anxiety despite the public health risk that it poses. Those that do exist each have their strengths and weaknesses which will be discussed in turn. Rapee and Heimberg (1997) presented a comprehensive but less detailed risk factor model for social phobia (see Figure 4.1). This broad model includes cognitive processes such as allocation of attentional resources, negative valence systems, and overall perception of external factors (i.e., audience, cues). Its core includes one's self perception of how others view them which eventually can lead to behavioral, cognitive, and physical symptoms. The cognitive focus of this model is likely due to it being published at the beginning of the implementation of the Diagnostic and Statistical Manual – 4th edition (DSM-IV) (American Psychiatric Association, 2000). The DSM-IV included a name change from "social phobia" to "social anxiety disorder" as well as generalized and specific versions of the disorder. Thus, such a model should be seen as an opportunity to legitimize newer conceptualization of social anxiety (Rapee & Heimberg, 1997). Overall this model is vague; for example, it lists "external indicators of negative valence"

but does not specify what those indicators are. Further, no environmental or genetic factors are discussed, nor are the sources of covariance between the model's elements.

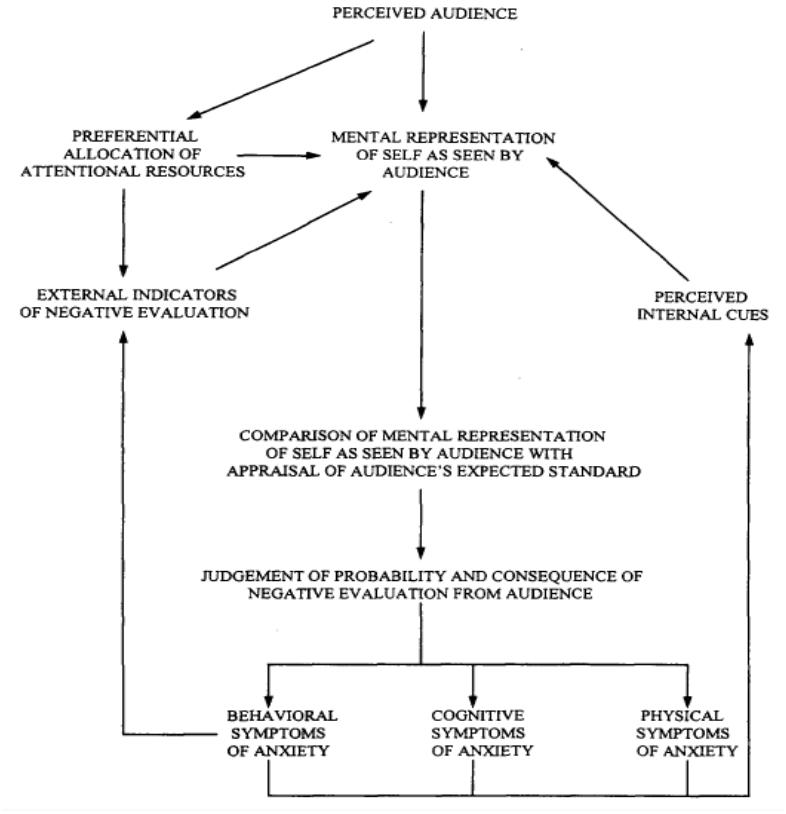

Figure 4.1. Rapee and Heimberg's (1997) cognitive behavioral model of social phobia.

Rapee and Spence revised their risk factor of social anxiety disorder to include more external risks and broad genetic influences conceptualized along a continuum of social anxiety disorder (Rapee & Spence, 2004). It is a more comprehensive model, however, specific influences are still lacking (see Figure 4.2). For example, it is unclear from the model what is meant by "parent influences" or "peer influences." These influences are explained well in the accompanying manuscript, but clinical or public health applications of this work based on the model alone are unclear.

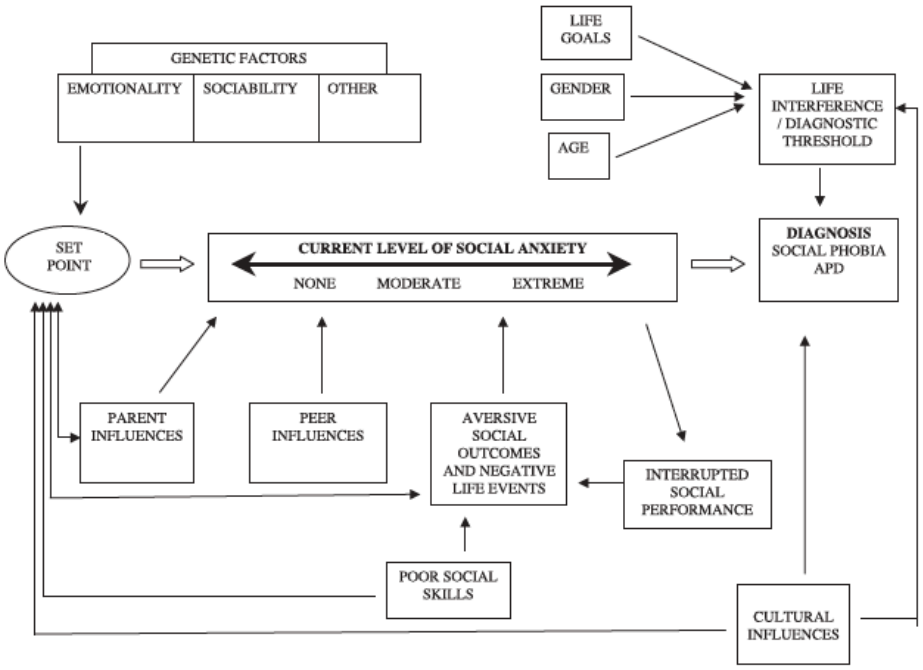

Figure 4.2. Rapee and Spence's (2004) risk factor model for social anxiety disorder, highlighting broad development of the disorder.

While taking a slightly different approach, Ollendick and Benoit (2012) created a model centered on the parent-child relationship. This served to focus the risk factor model and make it less broad than past models (see Figure 4.3). The model identifies processes, including behavioral inhibition and parental practices (bonding), which can increase the risk of developing pediatric social anxiety disorder. This dissertation will focus this risk factor even more, highlighting the nuances of the relationships between behavioral inhibition and parental bonding with social anxiety disorder in order to create a pointed risk factor model (see Chapter 9).

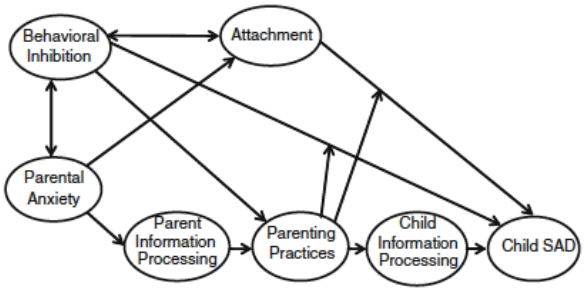

Figure 4.3. Ollendick and Benoit's (2012) risk factor model for social anxiety disorder, highlighting a parent-child interactional process.

Finally, Degnan and colleagues (2010) focused specifically on the relationship between behavioral inhibition and anxiety in their risk factor model for anxiety (see Figure 4.4). They were careful to be specific in the focus of this model by zoning in on this relationship. Yet, within the context of behavioral inhibition and anxiety, the model is quite comprehensive. It includes risk factors such as parenting styles, caregiving contexts, and peer relationships. It also includes the possibility of mediation and moderation of the causal pathways to social anxiety. Their model emphasizes the need to examine *how* these risk factors combine to elevate the risk of social anxiety, which is where the present aims come into play.

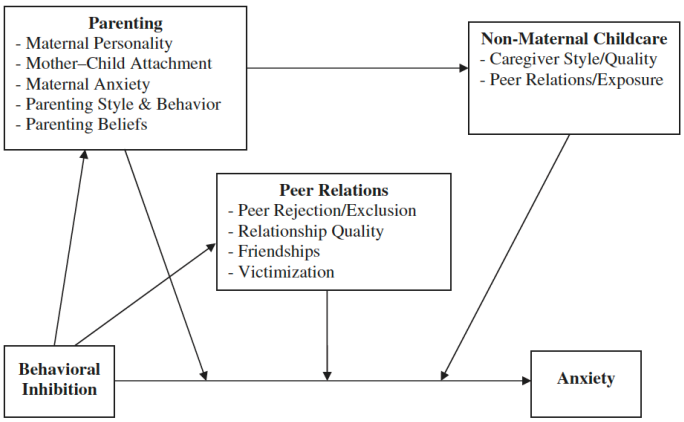

Figure 4.4. Degnan and colleagues' (2010) risk factor model for social anxiety disorder, highlighting its relationship with behavioral inhibition and intermediate factors.

Developing a New Risk Factor Model

A more exhaustive and plausible risk factor model ought to include biological information, namely genetic and neurophysiological information. Apart from helping to predict future behavior, the purpose of a risk factor model is to be translational by informing clinical intervention and prevention efforts and conversely, include new research ideas and updates to the model via clinical findings (Zvolensky, Schmidt, Bernstein, & Keough, 2006). While many prevention efforts exist for internalizing problems (Aune & Stiles, 2009; Spence et al., 2000; Zvolensky et al., 2006; O'Leary-Barrett et al. 2013) and social anxiety specifically (Aune & Stiles, 2009; Hirshfeld-Becker et al., 2010; Bayer et al., 2010), none include detailed genetic epidemiological nor neurophysiological information.

To date, prevention efforts for pediatric social anxiety focus on universal, selective, and indicated populations, ideally in the preschool years (Bayer et al., 2010). Universal approaches are given to all children regardless of risk. Selective prevention efforts are aimed at children with etiological risks for anxiety while indicated efforts are reserved for children who have some symptoms of anxiety but do not yet meet diagnosable criteria (Bayer et al., 2010). An example of a selective program includes one by Rapee (2002) which educated parents of children with elevated behavioral inhibition over several sessions by teaching them about inhibition, anxiety, and parenting behaviors (namely overprotection). This education reduced children's anxiety symptoms and later internalizing disorders. This (Rapee, 2002) and similar programs (Bayer et al., 2010; Kennedy, Tapee, & Edwards, 2009) have been shown to be effective in reducing anxiety symptoms when compared to control groups who received no prevention sessions.

Effective intervention efforts utilize cognitive behavioral therapy (CBT) and occasionally medication, although the former has been found to be more effective than the latter in the pre-

adolescent age group when treating anxiety (Aune & Stiles, 2009; Gould et al., 1997; Rapee, Schniering, & Hudson, 2009). There are many CBT options, including skill-based learning, exposure therapy, and cognitive restructuring (Gould et al., 1997; Rapee et al., 2009). Most styles are individual or group therapy, although some CBT sessions have a family-based focus (Rapee et al., 2009).

The specifics of prevention and intervention efforts for pediatric anxiety are outside the scope of this dissertation. However, they are relevant because risk factor models inform these efforts via translational science. Temperament and parental bonding have robust associations with social anxiety (Shamir-Essakow, Ungerer, & Rapee, 2005; Rapee et al., 2009; Fox et al., 2005) and are even included in some prevention (Kennedy et al., 2009; Rapee, 2002) efforts for anxiety and internalizing disorders broadly. However, the field would benefit from a concerted focus on building a risk factor model for pediatric social anxiety - specifically pre-adolescent social anxiety - that includes temperament and parental bonding that can potentially be widely included in eventual prevention and intervention efforts which includes delineations of genetic, environmental, and neurophysiological risk. The choice of temperament and parental bonding are purposeful. Temperament, specifically behavioral inhibition (BI), is predominantly a genetically influenced risk factor that may have neurophysiological ties to social anxiety (Fox et al., 2005). Parental bonding is a predominantly environmental risk factor (Kendler, 1996; Otowa, Gardner, Kendler, & Hettema, 2013; see Chapter 5) that does likely interplay with genetic factors (correlation and interaction) in its risk for a child's social anxiety development and maintenance. Together, these encompass significant etiological risk.

Behavioral Inhibition

One temperament which serves as a significant developmental risk factor for pediatric social anxiety is behavioral inhibition (BI), where children express significant fear or distress toward novel people, places, or environments (Rapee & Spence, 2004; Biederman et al., 2001; Chronis-Tuscano et al., 2009; Clauss, Avery, & Blackford, 2015; Clauss & Blackford, 2012; Coll, Kagan, & Reznick, 1984; Essex et al., 2009; Fox, et al., 2005; Hirshfeld-Becker et al., 2007; Hirshfeld-Becker, Micco, & Simoes, 2008; Muris, van Braken, Arntz, & Shouten, 2011; Rapee, 2014; Schwartz, Snidman, & Kagan, 1999). BI occurs in 10-15% of children (Muris et al., 2011), 43% of whom later develop SOC (Coll et al., 1984). It has also appeared in many discussions of social anxiety disorder (Fox et al., 2005; Degnan et al., 2011; Ollendick and Benoit, 2012). Unfortunately, the genetic and environmental covariance and the direction of causation between social anxiety and BI remain unknown. These questions are examined in this dissertation (see Chapter 6).

There are also significant knowledge gaps surrounding the underlying neurophysiological mechanisms in this relationship. Specifically, adults with social anxiety show a robust heightened emotion reactivity (as assessed via amygdala activation) specific to threatening (fearful, angry, sad) faces (Birbaumer et al., 1998; Cooney et al., 2006; Evans et al., 2008; Phan et al., 2005; Stein et al., 2002; Stein, Simmons, Feinstein, & Paulus, 2007). This effect has only been shown in a single study of adolescents with social anxiety (Killgore & Yurgelun-Todd, 2005) and not in pre-adolescents. The strong risk that childhood BI poses for later social anxiety implies that in addition to underlying genetic mechanisms, there might be similar neurophysiological mechanisms linking the two - specifically amygdala activation (Fox et al., 2005). However, associations between BI and emotion reactivity have been mixed in adult and adolescent samples, with significant findings not specific to an emotion but faces in general

(Clauss, Benningfield, Rao, & Blackford, 2016; Perez-Edgar et al., 2007; Schwartz et al., 2003). Thus, not only has a direct assessment of the relationship between emotion reactivity and childhood BI not been conducted, but neither has the potential moderating effect of emotion reactivity between BI and social anxiety. There are two possible explanations for the neurophysiological developmental mechanisms between BI and social anxiety: (1) individuals with a history of BI eventually become more selective toward threatening faces or (2) individuals with social anxiety who have a history of BI generally show broader emotional responses, but extant studies have not been sufficiently sensitive to differentiate those individuals.

Parental Bonding

Parental bonding is highly associated with both BI (Fox et al., 2005) and pediatric social anxiety (Rapee & Spence, 2004; Bayer et al., 2010; Bayer, Sanson, & Yemphill, 2006) and has been shown to be a key moderating factor between the two (Rubin, Burgess, & Hastings, 2002). It includes the domains of overprotection, coldness, and authoritarianism, with high levels of each broadly associated with internalizing problems (Bayer et al., 2006). The mechanisms of the relationship between BI, parental bonding, and social anxiety in adolescents have never been determined. Such information will serve to create a targeted risk factor model for social anxiety disorder that focuses on depth (Ollendick & Benoit, 2012), not breadth (Rapee & Heimberg, 1997; Rapee & Spence, 2004).

Translating Risk Factor Models

There is little point to creating an abundance of risk factor models for common disorders if there is no plan for how to utilize such information. Unfortunately, there is no clear consensus on the best practice for translating these models. As already discussed, there are many translational frameworks that need to be utilized in the appropriate context for a given disorder

(see Chapters 2-3). Specific to pediatric health, as with psychiatric disorders broadly, linear frameworks such as that by Szilagyi (2009) are common. Szilagyi's specific framework includes bi-directional but still linear pathways between potential application, efficacy, effectiveness, and population-based stages, reminiscent of Khoury and colleagues' (2007) T1-T4 stages of translation. In regard to BI and social anxiety, we have already moved into an efficacy stage with prevention programs such as the Turtle Program (Chronis-Tuscano et al., 2015) and others (Hirshfeld-Becker et al., 2008; Rapee et al., 2010). The goal of this dissertation is to demonstrate that even the linear nature of basic science where such risk factor models are created can actually be non-linear (i.e., collaborative and socio-ecological) (see Chapters 2 and 3). By including detailed genetic, neurophysiological, and environmental risk factors, such a risk factor model may be more informative for clinicians. This cannot be assumed, though, and the global discussion of this dissertation (chapter 9) will review this more thoroughly.

Conclusion

The translation of basic science findings into clinical practice has not been addressed systematically in mental health fields (Glasgow et al., 2012). Translation should be collaborative and socio-ecological in focus, but it still must begin with basic science. The next four chapters will use pre-adolescent social anxiety to highlight the first steps toward true translation from a field that historically solely relies on bench-to-bedside and precision medicine translational frameworks (Sullivan et al., 2012; Visscher et al., 2016; Sullivan et al., 2018). This will be done by using key genetic, neurophysiological, and environmental risk factors for social anxiety to create an updated risk factor model. Not only will individual findings and the risk factor model as a whole be novel, but it offers suggestions for how to move this line of work forward within a new translational framework is unprecedented.

Chapter 5: Methodology of the Juvenile Anxiety Study and Measures Used in the Current Dissertation

Introduction

Aims 2 (chapters 6 and 7) and 3 (chapter 8) of this dissertation draw from the same dataset, the Juvenile Anxiety Study (JAS). Thus, this chapter is dedicated to providing details about the JAS such that all chapters hereafter will only reference it. This chapter will also serve to provide details on the specific measures from the JAS that were used in this dissertation. Many psychometric examinations of these measures were conducted that, while outside the immediate scope of aims 2 and 3, directly influenced how these aims were conceptualized. Additionally, this chapter will serve as a thorough review of biometrical modeling. This type of modeling is frequently used to assess the psychometric properties of included measures as well as in aim 2. All analyses were conducted in R (R Development Core Team, 2008). Biometrical genetic structural equation models (SEM) were completed in the OpenMx package (Neale et al., 2016).

This chapter is presented in three parts. Part 1 presents an overview of the JAS, including its purpose, information on the sample, and brief overview of included measures. Part 2 provides an overview of biometrical modeling, one of the main analyses used in the rest of this dissertation. Part 3 then gives details about preliminary analyses on the JAS measures used in this dissertation, most of which utilize biometrical modeling. This part also includes a brief discussion.

Part 1: Overview of the Juvenile Anxiety Study

The Juvenile Anxiety Study

The purpose of the JAS was to study the relationship between measures related to negative valence systems (NVS) and symptoms of internalizing disorders (Carney et al., 2016). NVS constructs include acute threat (fear), potential threat (anxiety), sustained threat, loss, and frustrative non-reward (Cuthbert & Insel, 2013). Additional constructs included in the JAS that are not strictly NVS constructs were temperament, risk/protective factors, and demographics (sex, age). Specific phenotypes of interest for this dissertation were anxiety symptoms, behavioral inhibition (BI), parental bonding, and emotion reactivity (see Part 3 below for an explanation of preliminary analyses involving all measures except emotion reactivity; see chapter 8 for an explanation of the neuroimaging protocol). Measures were a combination of questionnaires, experimental paradigms, and neuroimaging paradigms (see Table 5.1). The JAS is a cross-sectional study.

Table 5.1. Overview of measures in the JAS.

Construct	Paradigm	Measure
Acute Threat	Questionnaire	Fear Survey Schedule for Children - Revised Threat and Fearlessness Questionnaire - 20 item version Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (phobias) Child Behavior Checklist*
	Experimental	Fear Potentiated Startle Skin Conductance Response
	Neuroimaging	Emotion Face Matching Task*
Potential threat	Questionnaire	Screening for Childhood Anxiety Related Disorders* Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (anxiety)
	Experimental	Baseline Startle
Sustained threat	Questionnaire	Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (post-traumatic stress disorder)
	Experimental	Face-Emotion Processing (threat) Facial Expression Labeling Task
	Experimental and Neuroimaging	Extinction Recall
Loss	Questionnaire	Short Mood and Feelings Questionnaire Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (depression)
	Experimental	Face-Emotion Processing (sadness)
Frustrative non-reward	Questionnaire	Affective Reactivity Index
	Experimental and Neuroimaging	Affective Posner 2
Temperament	Questionnaire	Junior Eysenck Personality Questionnaire Childhood Anxiety Sensitivity Index Behavioral Inhibition Questionnaire (retrospective)* Behavioral Inhibition System / Behavioral Activation System Inventory of Callous-Unemotional Traits
Risk / protective factors	Questionnaire	Parental Bonding Instrument* Multidimensional Peer Victimization Scale Traumatic Events Screening Inventory - Parent Report Revised Pubertal status
Demographics	Questionnaire	Age* Sex*

* Indicates measure used in this dissertation

Protocol

Data collection occurred from February 2013 to March 2016. Participants were recruited from the Mid-Atlantic Twin Registry (MATR), a database of twins, other higher order multiples, and their family members (Lilley & Silberg, 2013). Specifically, research assistants were provided with the contact information of individuals on the MATR registry. These individuals were called up to three times by the research assistants for recruitment. If they agreed to be in the study, a time was scheduled for Visit 1. It was at Visit 1 when full consent was obtained per Institutional Review Board protocol. During Visit 1, participants completed a full set of questionnaires and laboratory paradigms. A portion of the families were invited back for a second visit 2 to 4 weeks later to collect reliability data on a subset of the protocol measures (reported for the measures of interest for this dissertation below in Part 3). Twins and parents were separated during Visits 1 and 2. Protocols were counter balanced across twins, who completed all procedures in separate rooms. Parents completed questionnaires about themselves and their children in a waiting area away from their children. Neuroimaging data was collected during a third visit on a small subset of participants who met eligibility criteria (see chapter 8 for more details). The criteria included not having braces or other metal attached to the body, behaviorally able to sit still and not cause motion artifacts, overall willingness (lack of claustrophobia, not afraid of task, etc.).

Participants

Families with twins ages 9-13 and at least one parent ($N_{families}$ = 398, $N_{children}$ = 796) were surveyed as part of the JAS. They were administered an array of measures which included experimental tasks and dimensional questionnaires (see above). In total, there are data on 796 twins (N_{pairs} = 398; monozygotic [MZ] = 128; dizygotic [DZ] = 245; unknown zygosity = 21;

M_{age} = 11.20; female = 52.6%) available for the proposed analyses, all of whom were Caucasian. Note that at the time these analyses were run, there were 21 individuals with unknown zygosity. Since that time, the zygosity of these individuals is now known but due to timing, those individuals were still left out of the sample used in these analyses. Zygosity was measured via parent report and an algorithm calculated similarity within a twin pair based on the parent report (Carney et al., 2016). There some few pairs for whom the parent report of zygosity was incomplete and those twins' blood samples were tested using molecular genomic methods to confirm zygosity.

Eleven percent of the sample included reports from fathers. Father's reports of their children consistently correlate lower with actual child behavior / mental health than mother's report (e.g., Bishop, Spence, & McDonald, 2003) and were removed from all analyses. Additionally, except when assessing reliability, only data from Visit 1 was utilized. Thus, in all analyses for this dissertation, only data from child and maternal reports from Visit 1 were utilized. For the preliminary analyses of the measures used, the final analytical sample included 352 families and 704 children (M_{age} = 11.22; standard deviation [SD_{age}] = 1.41; female = 53%; MZ = 114 pairs; DZ = 238 pairs; 88% of full sample).

Measures of Interest

Measures from the JAS that are used in either primary or preliminary analyses for this dissertation include the following: Screen for Child Anxiety Related Disorders (SCARED; Birmaher et al., 1997), Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001), Behavioral Inhibition Questionnaire (BIQ; Bishop et al., 2003) and Parental Bonding Instrument (PBI; Parker, Tupling, & Brown, 1979; Parker, 1990). See Part 3 for details of the preliminary analyses performed using these measures before the primary analyses (see chapters 6-8).

Part 2: Biometrical modeling overview

Introduction

Before explaining details of the measures included in this dissertation and the preliminary analyses conducted on them, an overview of biometrical modeling must be presented. This is for simplicity and ease of readership. Biometrical modeling is used in several preliminary analyses and it is easier to provide an overview in Part 2 below and then present the preliminary analyses in part 3.

Biometrical Modeling Premise

Biometrical structural equation modeling (SEM; Neale & Cardon, 1992) was performed at various times during this dissertation to analyze the JAS data. In this process, the variance in each phenotype is decomposed into additive genetic (A), shared (familial) environmental (C), and unique environmental (E) risk factors. The A variance reflects the additive effect of individual alleles at genetic loci influencing a trait. On average, MZ twins share 100% of their segregating genes whereas DZ twins share 50%. In phenotypes where familial aggregation is entirely explained by additive genetics, MZ twin pair correlations will be twice their DZ counterparts. The C variance reflects environmental influences that make family members more alike compared to random pairs of individuals. Consequently, where familial aggregation is entirely explained by common environmental risks, MZ and DZ twin pair correlations will be equal or non-significantly different or the DZ correlation will be more than half of the MZ correlation. The E variances are uncorrelated between twins and reflect aspects of the environment that are specific to each individual including measurement error.

In standard analyses, the approach is to begin by testing for equal means across twin order, equal means and variance across twin order, and then equal means and variance across twin order and zygosity. This ensures that there is no bias in the data and that all basic assumptions are met. The assumptions of all biometrical modeling are: equal environments of MZ and DZ pairs, random mating, no gene-environment interplay, no age or sex effects (Neale & Cardon, 1992).

Next, all three components of variance (ACE) are tested, known as saturated model fitting. Finally, a series of nested submodels are tested in which A, C, or both are constrained to zero to examine the significance of their contributions to phenotypic variation. Model fit is compared using the likelihood ratio test (LRT) (Wilks, 1938) and Akaike information criteria (AIC) statistic (Akaike, 1987). These statistics test whether there is a significant decrease in model fit after parameters in the full model are constrained to zero, indicative of the importance of the constrained parameter(s).

Models that were fit in this dissertation include univariate, multivariate, common pathway, and independent pathway. Each of these will briefly be discussed in turn (Neale & Cardon 1992).

Univariate Biometrical Modeling

Univariate biometrical models entail decomposing the variance of a single phenotype into A, C, and E (see Figure 5.1). The purpose of such a model is to calculate the proportion of variance due to genetic versus environmental factors of a single phenotype.

This model was fit in this dissertation to examine the structure of the PBI (see Part 3 below).

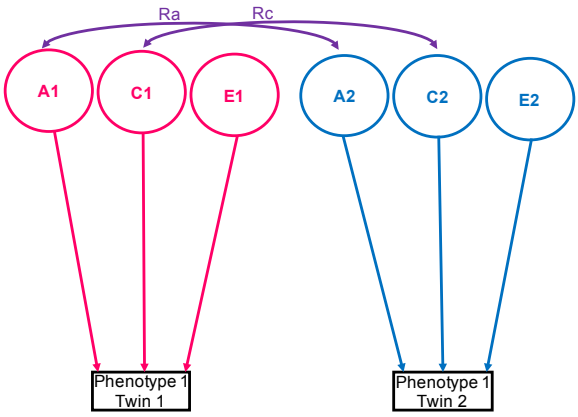

Figure 5.1. Example of a univariate biometrical model (variance paths left out for simplicity). Ra = 1.00 for MZ twins and .50 for DZ twins. Rc = 1.00 for all twins. A1/C1/E1 = factors for phenotype 1.

Multivariate Biometrical Modeling

Multivariate biometrical models allow for the examination of covariance between two or more phenotypes. In the absence of any theory explaining covariance structure, this is typically achieved by fitting a lower triangular Cholesky decomposition (Neale & Cardon, 1992). They allow for the genetic versus environmental variance to be decomposed across phenotypes, showing how much of which type of variance is shared among the phenotypes. In other words, it is possible to see how much of one phenotype's variance is due to shared genetic or environmental factors with another phenotype - if the two phenotypes are related at all. Alternative theoretical models or, if there is evidence to suspect a more complicated relationship across the phenotypes, include common pathway and independent pathway models can also be explored (see below).

Multivariate biometrical models were used in this dissertation to assess the relationship between BI and various pre-adolescent anxiety clusters (generalized, social, panic, separation) in aim 1 (chapter 6) as well as to estimate the heritability of each construct. The latter was done using multivariate instead of univariate to avoid running multiple univariate models because

heritability can be calculated for each phenotype in a multivariate model by adding all of its additive genetic variance (both unique and shared). Multivariate modeling was also used to examine the relationship between BI, overprotectiveness, and social anxiety (chapter 7).

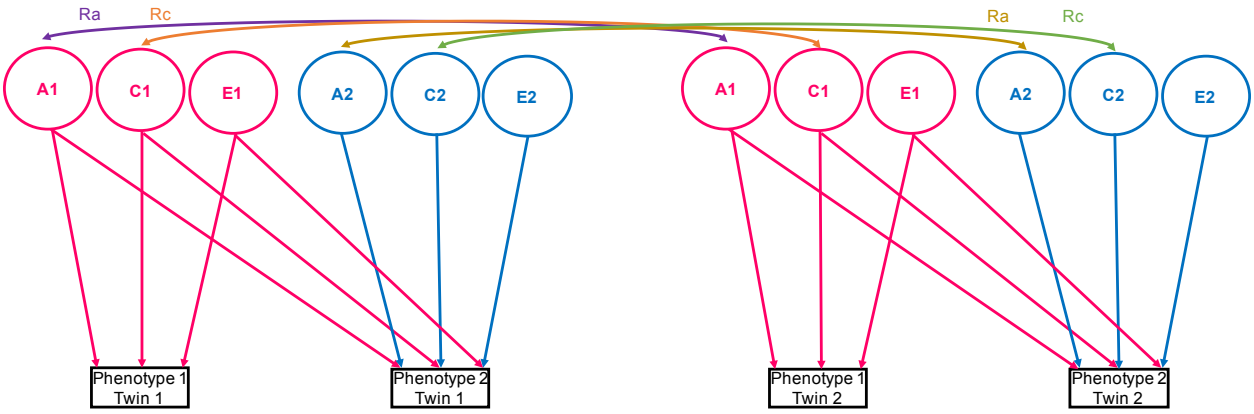

Figure 5.2. Example of a multivariate biometrical model (variance paths left out for simplicity). Ra = 1.00 for MZ twins and .50 for DZ twins. Rc = 1.00 for all twins. A1/C1/E1 = factors for phenotype 1. A2/C2/E2 = factors for phenotype 2.

Common Pathway Biometrical Model

A common pathway biometrical model allows for the measured phenotypes to load onto one ore more common (hierarchical), latent variables that are decomposed into A, C, and E sources of variance (see Figure 5.3). Specific A, C, and E variances are allowed to load into individual phenotypes to account for residual variance. This model is useful when examining whether there is a higher level, latent construct through which the genetic and environmental factors load and which account for the variance of multiple phenotypes at once. It is also helpful when examining if there are multiple indicators for a variable.

In the current dissertation, this type of model was fit twice in preliminary work (see Part 3). First, it was used to assess whether there was a common / latent phenotype that subsumed child and parent scores on the SCARED subscales. Second, it was used to examine whether

scores from the three PBI scales could be loaded onto a larger "parent" factor (similar to Gillespie et al., 2003).

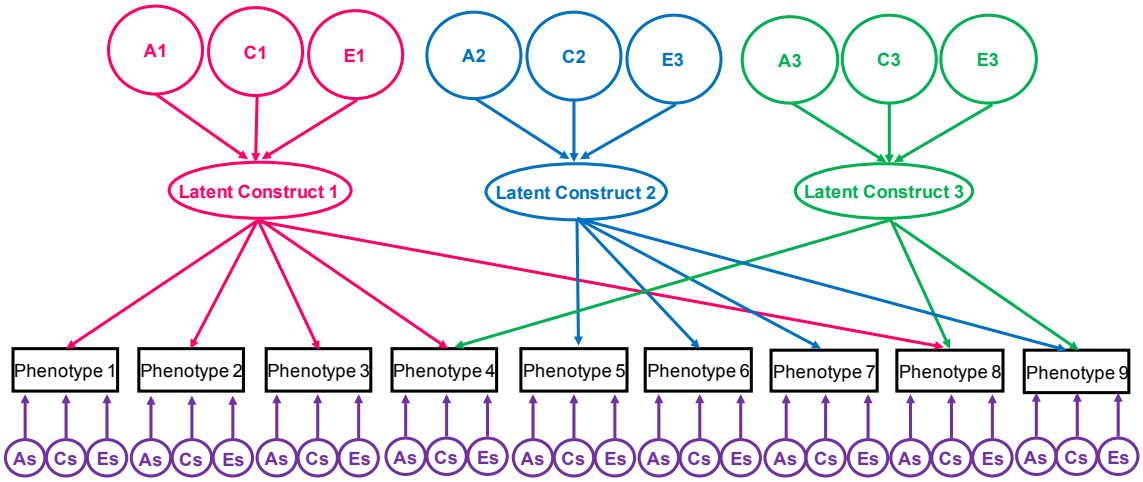

Figure 5.3. Example of a common pathway biometrical model (single twin only; variance paths left out for simplicity). A1/C1/E1 = factors for latent construct 1. A2/C2/E2 = factors for latent construct 2. A3/C3/E3 = factors for latent construct 3. As/Cs/Es = specific factors not shared with the other phenotypes.

Independent Pathway Biometrical Model

Independent pathway biometrical models allow for measured phenotypes to load onto multiple A, C, and E latent variables directly instead of going through latent phenotypes (see Figure 5.4). This model is useful in examining whether there are a unique number of genetic and environmental factors influencing the phenotypes. In univariate and multivariate models, there are the same number of A, C, and E variance estimates in the models. In an independent pathway model, different numbers of A, C, and E factors are tested until the best fitting model is found. Each factor may load onto one or more phenotypes, adding more nuance to the final model.

This model was used to examine the structure of the PBI (similar to Gillespie et al., 2003).

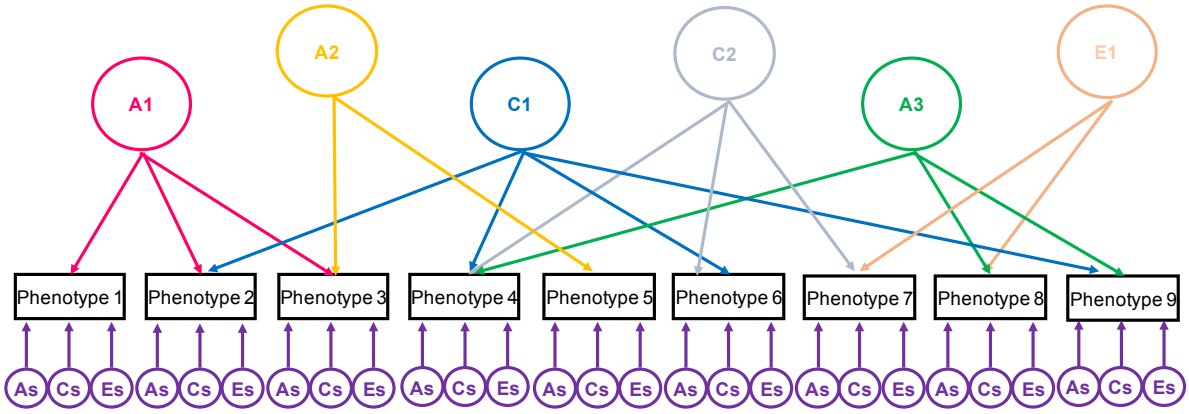

Figure 5.4. Example of an independent pathway model (single twin only; variance paths left out for simplicity). A1/A2/A3 = the three distinct additive genetic factors in this model. C1/C2 = the two distinct familial environmental factors in this model. E1 = the one distinct unique environmental factor in this model. As/Cs/Es = specific factors not shared with the other phenotypes.

Part 3: Preliminary analyses

The Screen for Child Anxiety Related Disorders

The Screen for Child Anxiety Related Disorders (SCARED) is a 41-item scale that assesses various recent anxiety disorder symptoms in children that breaks down into five clinical subscales (generalized anxiety, panic, separation anxiety, social phobia, school avoidance) (Birmaher et al., 1997). Subjects rated statements regarding their own and their children's behavior in the past three months on a scale from 1 ("not true or hardly ever true") to 3 ("very true or often true"). Example questions include "My child worries about how well he/she does things" or "I am shy". The SCARED has strong internal consistency (α = .90 - .94) and test-retest reliability (r = .70 - .90) in both prior studies and the current one (Birmaher et al., 1997; Carney et al., 2016). Both parent and child responses to the SCARED were collected because both types of reporting by themselves are limited and potentially biased (De Los Reyes & Kazdin, 2005). In order to confirm whether or not one or both raters were necessary for primary

analyses, a common pathway model (i.e., multiple rater model) was tested to examine and account for potential rater bias (if necessary). As already discussed in Part 2 above, this model allows for the hierarchical testing of latent factors. In this model, that is child and parent scores on the SCARED. Different submodels of this model could be tested - one where child and parent scores were allowed to freely load and one where they were constrained to be equal.

Data Analysis: The SCARED

Parent and child SCARED scores were included as indicators for a latent "anxiety" variable in multivariate SEM. This was done for each anxiety symptom cluster (social, generalized, separation, panic), and two models per cluster were tested: one where parent and child scores were allowed to freely load on the latent variable and another where they were constrained to be equal (i.e., the variances were constrained) (see Figure 5.5). The best-fitting model (as determined via AIC fit statistic; see Part 2 above) was used in all further analyses to index each anxiety symptom cluster, respectively. Additionally, sex was treated as a covariate in all biometrical models due to its known association with various anxiety domains (Hettema et al., 2005; Rapee, 2004).

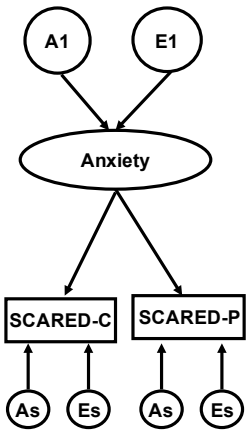

Figure 5.5. Example of the common pathway model used to test for parent and child anxiety. Variance estimates left off for simplicity.

Results: The SCARED

For all anxiety clusters, parent and child SCARED scores could be constrained to be equal in their common pathway / multiple indicator models (see Table 5.2). In other words, the average of the parent and child SCARED sum scores provided a reasonable representation of these anxiety domains for analyses with parent-rated BI and were used in all analyses.

Table 5.2. Model fit statistics from common pathway (CP) analyses assessing child and parent indicators on each anxiety symptom cluster

Model	EP	-2 LL	DF	AIC	Δ LL	Δ DF	*p*
Social Anxiety							
Full CP model with child and parent indicators set to be free	17	6651.303	1265	4121.303	-	-	-
CP model with child and parent indicators constrained to be equal *	16	6651.465	1266	4119.465	.162	1	.687
Generalized Anxiety							
Full CP model with child and parent indicators set to be free	17	6859.450	1265	4329.450	-	-	-
CP model with child and parent indicators constrained to be equal *	16	6859.450	1266	4327.450	<.001	1	.999
Separation Anxiety							
Full CP model with child and parent indicators set to be free	17	6252.353	1264	3724.353	-	-	-
CP model with child and parent indicators constrained to be equal *	16	6252.597	1265	3722.597	<.001	1	.999
Panic							
Full CP model with child and parent indicators set to be free *	17	6421.260	1264	3893.260	-	-	-
CP model with child and parent indicators constrained to be equal *	16	6421.260	1265	3891.260	.245	1	.621

* Indicates best-fitting model(s) from that series of nested sub-models
EP = Estimated Parameters; -2LL = twice the negative log likelihood; DF = degrees of freedom; AIC = Akaike Information Criteria; p = p-value statistic; delta (triangle) = change in

The Child Behavior Checklist

The Child Behavior Checklist (CBCL) provides an overall snapshot of current child behavior with 112 questions divided into eight subscales, four of which were used in the current study (anxious/depressed, withdrawn/depressed, somatic complaints, social problems; Achenbach & Rescorla, 2001). Parents rate behaviors that describe their children in the past 6 months on a scale of 1 (not true) to 3 (very true or often true). Example items include "Acts too young for his/her age" and "Fears he/she might think or do something bad." Subscales used in the current analyses have good internal consistency (Cronbach's alpha = .82) and test-retest reliability (r = .81). The CBCL was used in this dissertation to assess validity of the BIQ (see below).

The Retrospective Behavioral Inhibition Questionnaire

The BIQ is a 30-item Likert-style measure given to parents to assess their child's behaviors related to inhibition. It has previously demonstrated reliability and validity (Bishop et al., 2003; Broeren & Muris, 2010) and adequate correlation with the gold standard behavioral assessment of BI (r = .46 among maternal raters, Bishop et al., 2003; 74% agreement rate, Hudson & Dodd, 2012). The BIQ has been successfully used in multiple studies of inhibition and anxiety in childhood, including assessing their neurophysiological and cognitive underpinnings (Clauss, Benningfield, Rao, & Blackford, 2016; Fu, Taber-Thomas, & Perez-Edgar, 2015; Morales, Taber-Thomas, & Perez-Edgar, 2016; Taber-Thomas, Morales, Hillary, & Perez-Edgar, 2016), predicting anxiety symptoms (Edwards, Rapee, & Kennedy, 2010) and evaluating early interventions (Kennedy, Rapee, & Edwards, 2009).

It is typically given to parents to assess concurrent behavior when their child is between the ages of 2-6 (toddlerhood through early childhood). However, given the pre-adolescent nature of the JAS sample, the BIQ was altered to be retrospective. Wording of the instructions and questions were changed such that parents reported on behaviors related to BI when their child was 2-6 years old. Past studies of the BIQ have shown moderate correlation with the gold standard behavioral assessment of BI (r = 0.46, Bishop et al., 2003; 74% agreement rate, Hudson & Dodd, 2012). However, a recent study in older children and adolescents reported a modest but significant correlation of total parent-report retrospective BIQ score with BI defined by observational laboratory protocols at ages 2-6 (r = .21; p = .05) and individual subscales of the retrospective BIQ showed similar correlations (r = 0.22-0.32, p <.05, Hirshfeld-Becker et al., 2016). However, the psychometric characteristics of this retrospective BIQ in a normative sample of developing children have not been examined. Preliminary examination of this version of the BIQ examined its (1) reliability, (2) validity, and (3) factor structure.

Data Analysis: The Retrospective BIQ

Reliability. Reliability was assessed in two ways. Internal consistency was estimated via Cronbach's alpha for Visit 1 data, and test-retest reliability was estimated via intraclass correlation between data from Visits 1 and 2.

Validity. Construct validity was assessed via correlations between sum scores of the total retrospective BIQ and subscales of the SCARED parent subscales (SCARED-P for simplicity) and CBCL using the R software package. Spearman correlations were chosen due to the positive skew of the SCARED-P and CBCL scores.

Factor Structure. To examine the factor structure of the retrospective BIQ and assess whether this version of the measure aligns with past BIQ iterations, exploratory factor analyses

(EFA) and confirmatory factor analyses (CFA) were conducted in Mplus (MPLUS, version 7) using a randomized split-sample procedure, and twins were clustered within families. Where appropriate, BIQ items were reverse-coded to have positive factor loadings. To maximize the power to estimate model parameters, the final CFA models included data from the full analytical sample. Two models were tested: (1) oblique, geomin rotated correlated factor model (simple structure); and (b) orthogonal, bifactor model. The correlated model is consistent with previous analyses exploring the psychometric properties of the BIQ (Bishop et al., 2004; Broeren & Muris, 2010; Kim et al., 2011; Vreeke et al., 2012). The bifactor model consists of one overall factor capturing the common aspects of BI across all of the indicators plus uncorrelated, residual factors that capture the specific components (Reise, 2012). The bifactor model was chosen as a potential model because it is well-suited for representing broad constructs simultaneously with distinct domains that may be present in the data (Reise, 2012). However, it does not allow for the domains to correlate with each other or with the general domain due to its orthogonal nature, presenting a potential limitation of the model (e.g., correlations that may be present in the data across domains are not captured). While a structure that had not been tested in previous analyses of the BIQ, the bifactor structure is a common psychometric model (Reise, Moore, & Haviland, 2010). See Figures 5.7 and 5.8 for an abbreviated correlated factors and bifactor CFA from the BIQ.

Items with loadings above 0.3 in the EFA were chosen for inclusion in the preliminary CFA model. Item information curves were examined following the first iteration of the CFA such that items providing little information were deleted from the model to see if fit would improve. To assess model fit, χ^2, Root Mean Square Error of Approximation (RMSEA), Comparative Fit Index (CFI), and Tucker-Lewis Index (TLI) were used. Specifically, we applied

the recommendations for RMSEA < 0.08 and CFI/TLI > 0.95 (Hu & Bentler, 1999). Finally, reproducibility of the final factor structure model across sexes was conducted via tests for configural (same loading pattern across groups), metric (same meaning assigned to latent constructs, and hence same responses, across groups), and scalar (the relationship between latent constructs and observed variables is the same across groups) invariance (Hong, Malik, & Lee, 2003).

Reliability (internal consistency) then was assessed for each factor of the best-fitting model via Cronbach's alpha from the full sample CFA. Finally, the validity of the best-fitting model from the full sample CFA was assessed using SEM. Representative items were selected from the SCARED (parent version) that had similar content to each of the factors in the final model. Using SEM, each selected item was correlated with each factor to test discriminant validity (criterion via predictive validity and content via convergent and divergent validity). In addition, one item was chosen for the overall model to test convergent validity.

Results: The Retrospective BIQ

Reliability. Reliability for the overall retrospective BIQ was estimated in two ways: Cronbach's alpha was 0.96 (excellent) for the overall BIQ suggesting high levels of internal consistency for the measure as a whole. The intraclass correlation used to estimate test-retest reliability between Visits 1 and 2 was also high (*ICC* = 0.87; CI = 0.84 – 0.89).

Validity. Content validity was tested via convergent and divergent validity for the BIQ's sum score was assessed via correlations with the CBCL and SCARED-P subscales. A forest plot of the correlations is presented in Figure 5.6. As expected, the retrospective BIQ was most highly correlated with measures related to social anxiety, such as the SCARED-P social anxiety and CBCL social problems subscales, and only modestly correlated with subscales related to other

forms of anxiety, depression, or somatic complains, such as the SCARED-P school avoidance or CBCL somatic complaints subscales. Importantly, the two social anxiety constructs had significantly higher correlations with the BIQ than the non-social anxiety constructs, with the exception of the CBCL-anxious/depressed facet and the SCARED-P total sum (which includes the social anxiety subscale items).

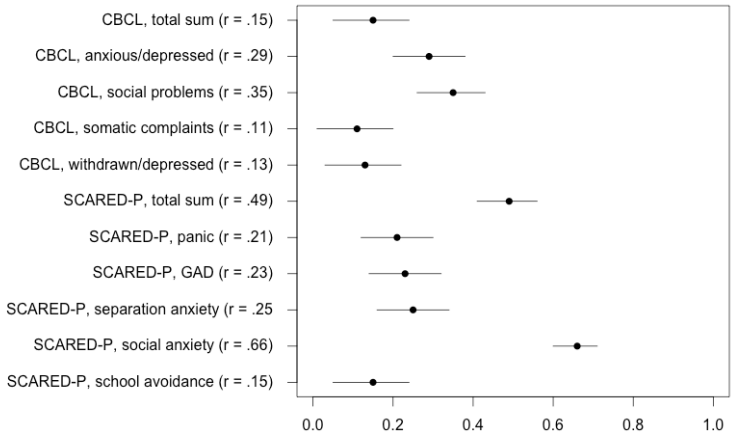

Figure 5.6. Forest plot of the correlations between the retrospective BIQ and other parent report measures. Error bars depict 95% confidence intervals. All correlations are significant at minimum $p < 0.05$.

Notes on Fit Indices. For the next several sections, many fit indices will be referred to (Hu & Bentler, 1999). RMSEA measures how well a model with ideal parameters would fit a variance-covariance matrix. The lower the number, the better; anything below 0.70 is considered a good fit, 0.80-1.00 is a mediocre fit, and more than 1.0 is a bad fit. χ^2 shows the discrepancy between different submodels and a significant p-value indicates a change in model fit. A significant p-value typically indicates a decrease in model fit. GFI is an alternate to χ^2 and provides the proportion of variance and covariance accounted for by the model. A score more than 0.90 is considered a good fit. TLI/NFI compare the model χ^2 to the null χ^2 and values more

than 0.95 are considered a good fit. CFI takes sample size into account with TLI/NFI and again, values more than 0.95.

Correlated Factor Model. Consistent with previous studies that have validated a 6-factor solution for the BIQ, EFAs with 1-4 factors did not achieve acceptable fit. While the correlated EFAs for 5-7 factors provided increasingly improved fit, models with more than 5 factors did not provide interpretable solutions. Applying Kaiser's rule to the scree plot of keeping factors with eigenvalues greater than 1 (Kaiser, 1960), a 5-factor solution was supported (eigenvalues = 15.97, 2.80, 2.19, 1.13, 1.04). It was the only model with reasonable fit and a valid factor structure for the correlated EFA (χ^2 = 950.676, *df* = 295; $p < 0.001$; *RMSEA* = 0.081; *CFI* = 0.969; *TLI* = 0.954). All items had loadings above 0.3 and clustered according to Bishop and colleagues' (2003) BIQ subscales with the exception of "Unfamiliar Situations." This scale did not define its own factor; instead, its items loaded onto all remaining factors except "Performance." See Figure 5.7 for an abbreviated version of this model.

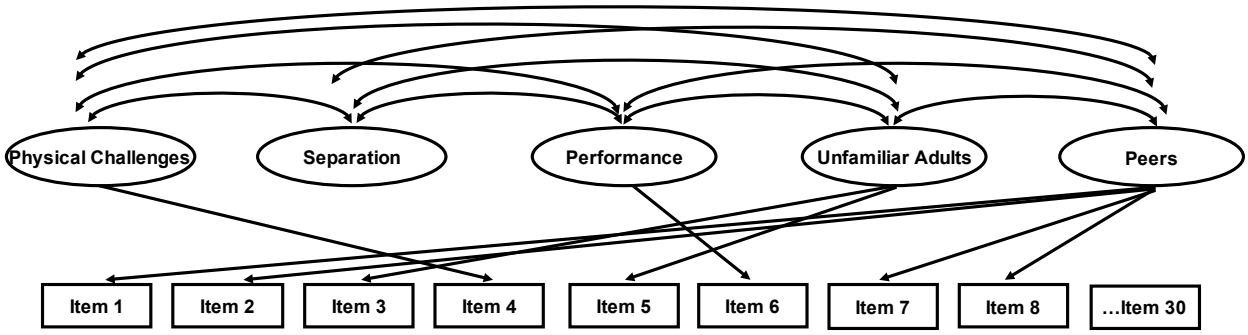

Figure 5.7. Abbreviate correlated CFA from the BIQ.

CFA performed in the other half of the sample using the item loadings from the EFA revealed a slightly worse fit (χ^2 = 2544.176, *df* = 395; $p < 0.001$; *RMSEA* = 0.127, CI = 0.122 – 0.132; *CFI* = 0.899; *TLI* = 0.800). However, the model had interpretable factor structure with strong item loadings. The item information curves revealed only item 14 as potentially

uninformative. When the model fit was assessed without this item, the fit worsened (χ^2 = 3850.588, *df* = 396; $p < 0.001$; *RMSEA* = 0.161, CI = 0.156 – 0.165; *CFI* = 0.838; *TLI* = 0.822), so all items were retained in the correlated 5-factor model. The CFA performed using the full sample yielded a similar fit to the preliminary CFA (χ^2 = 4650.863, *df* = 395; $p < 0.001$; *RMSEA* = 0.126, CI = 0.123 – 0.123; *CFI* = 0.880; *TLI* = 0.868), with identical items as factor indicators (see Table 5.3).

Table 5.3. Item indicators for the original BIQ (Bishop et al., 2003) and the Retrospective BIQ (current study).

BIQ			
Broad Domains	Specific Categories	Number of Items	Items (Question Numbers)
Social Novelty	Unfamiliar Adults	4	3, 16, 26, 30
	Approaching Peers	6	2, 7, 8, 12, 19, 20
	Performance	4	6, 10, 21, 28
Situational Novelty	Unfamiliar Situations	8	1, 5, 14, 15, 22, 23, 24, 25
	Separation/School	4	9, 11, 18, 27
Novel Physical Activity	Physical Activities	4	4, 13, 17, 29
Retrospective BIQ			
Model	Factors	Number of Items	Items (Question Numbers)
5-factor Correlated	Peers	8	1, 2, 7, 8, 12, 19, 20, 24
	Physical Challenges	6	4, 13, 17, 22, 23, 29
	Separation	7	9, 11, 14, 15, 18, 25, 27
	Performance	4	6, 10, 21, 28
	Unfamiliar Adults	5	3, 5, 16, 26, 30
5-factor Bifactor*	General Factor	30	All Items
	Physical Challenges	4	4, 13, 17, 29
	Separation	6	9, 11, 14, 15, 18, 27
	Performance	4	6, 10, 21, 28
	Unfamiliar Adults	4	3, 16, 26, 30

* Indicates final model in current study

Bifactor Model. Consistent with information from the prior analysis, bifactor EFAs were run only for the 5-, 6-, and 7-factor models. Again, the 5-factor solution had the best combination of theory-driven loadings and fit (χ^2 = 950.676, *df* = 295; $p < 0.001$; *RMSEA* = 0.081, CI = .075 -

.087; *CFI* = 0.969; *TLI* = 0.954). All items had loadings above 0.3 and also clustered according to Bishop and colleagues' (2003) BIQ subscales with the exception of "Unfamiliar Situations" and "Approaching Peers." These items were absorbed into the "General" and "Separation" factors. See Figure 5.7 for an abbreviated version of this model.

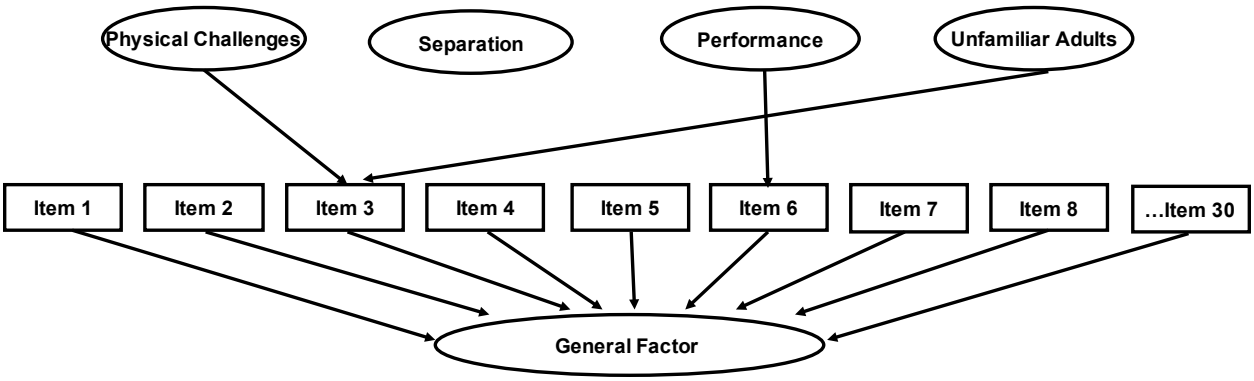

Figure 5.8. Abbreviated bifactor CFA from the BIQ.

CFA performed with the other half of the split sample revealed a similar fit (χ^2 = 1463.216, *df* = 387; $p < 0.001$; *RMSEA* = 0.091, CI = .086 – 0.96; *CFI* = 0.950; *TLI* = 0.943) with a highly interpretable factor structure that confirmed the results from the EFA. The item information curves revealed items 3, 14, and 15 as potentially uninformative. Again, when the model fit was assessed without these items, the fit worsened (χ^2 = 1724.585, *df* = 390; $p < 0.001$; *RMSEA* = 0.101, CI = 0.096 – 0.105; *CFI* = 0.937; *TLI* = 0.930), so all items were retained in the 5-factor bifactor model.

The CFA performed using the full sample yielded a similar fit to that of the preliminary CFA (χ^2 = 2426.747, *df* = 387; $p < 0.001$; *RMSEA* = 0.088, CI = .085 – 0.92; *CFI* = 0.942; *TLI* = 0.935) (see Table 5.4) with identical items as factor indicators (Table 5.3).

Table 5.4. Factor structure fit indices from studies exploring the psychometrics of the BIQ and Retrospective BIQ (current study).

Study	χ^2, *df*	*df*	χ^2/df	*p*	*RMSEA*	*CFI*	*TLI/NFI*	*GLI*	N
Previous Studies									
Bishop et al., 2003	1835	390	--	<0.001	0.08	0.88	0.87	--	613
Broeren & Muris, 2010	--		1.74-2.34		0.07-0.08	0.88-0.91	--	--	531
Kim et al., 2011	1382.610	390	--	<0.001	0.075	0.903	--	--	495
Vreeke et al., 2012*	--		--	--	0.05	0.98	0.96	0.97	2,343
Current Study									
5-factor Correlated Model	4650.863	395	--	<.001	0.126	0.880	0.868	--	681
5-factor Bifactor Model**	2462.747	387	--	<.001	0.088	0.942	0.935	--	681

*Indicates that a short version of the BIQ was used. **Indicates final best-fitting model in the current study.

This fit was better than that obtained for the correlated factor model; as such, the 5-factor bifactor model was chosen as the final model (see Table 5.5). Tests for configural, metric, and scalar invariance were significant (*ps* < 0.001), implying that the bifactor model fit results are equal across sex in this sample. Configural invariance assesses whether there is the same pattern of factors and loadings across groups. Metric invariance tests whether the factor loadings are the same across factor loadings. Scalar invariance determines if the residual variances are also the same across loadings (Waldaman & Reise, 1997).

Table 5.5. Model loadings (SE) for the best-fitting 5-factor bifactor CFA model using the full sample – all are significant at $p<0.001$.

Items	General	Physical Challenges	Separation	Performance	Unfamiliar Adults
1. Approached new situations or activities very hesitantly	.781 (.018)				
2. Would happily approach a group of unfamiliar children to join in their play	-.851 (.013)				
3. Was very quiet around new (adult) guests to our home	.753 (.020)				.425 (.026)
4. Was cautious in activities that involved physical challenge (e.g., climbing, jumping from heights)	.437 (.032)	.743 (.023)			
5. Settled in quickly when we visited the homes of people we didn't know well	-.807 (.016)				
6. Enjoyed being the center of attention	-.681 (.022)			-.483 (.025)	
7. Was comfortable asking other children to play	-.865 (.012)				
8. Was shy when first meeting new children	.852 (.012)				
9. Happily separated from parent(s) when left in new situations for the first time (e.g., kindergarten, preschool, childcare)	-.506 (.032)		-.733 (.023)		
10. Was happy to perform in front of others (e.g., singing, dancing)	-.692 (.022)			-.591 (.023)	
11. Quickly adjusted to new situations (e.g., kindergarten, preschool, childcare)	-.558 (.028)		-.683 (.023)		
12. Was reluctant to approach a group of unfamiliar children to ask to join in	.816 (.014)				
13. Was confident in activities that involved physical challenge (e.g., climbing, jumping from heights)	-.474 (.029)	-.770 (.023)			
14. Was independent	-.576 (.028)		-.333 (.031)		

15.	Seemed comfortable in new situations	-.847 (.013)		-.269 (.019)	
16.	Was very talkative to adult strangers	-.752 (.022)			-.554 (.027)
17.	Was hesitant to explore new play equipment	.540 (.027)	.432 (.026)		
18.	Got upset at being left in new situations for the first time (e.g., kindergarten, preschool, childcare)	.489 (.032)		.782 (.021)	
19.	Was very friendly with children he or she had just met	-.752 (.022)			
20.	Tended to watch other children, rather than join in their games	.772 (.016)			
21.	Disliked being the center of attention	.687 (.022)			.507 (.022)
22.	Was clingy when we visited the homes of people we didn't know well	.780 (.017)			
23.	Happily approached new situations or activities	-.864 (.012)			
24.	Was outgoing	-.875 (.011)			
25.	Seemed nervous or uncomfortable in new situations	.853 (.013)			
26.	Happily chatted to new (adult) visitors to our home	-.732 (.022)			-.561 (.025)
27.	Took many days to adjust to new situations (e.g., kindergarten, preschool, childcare)	.581 (.029)		.690 (.025)	
28.	Was reluctant to perform in front of others (e.g., singing, dancing)	.662 (.023)			.631 (.022)
29.	Happily explored new play equipment	-.635 (.028)	-.516 (.027)		
30.	Was very quiet with adult strangers	.741 (.022)			.563 (.026)

Factor Structure Reliability. Cronbach's alpha was calculated for the final bifactor model. Since the first factor of this model included all items, that reliability is the same as for the overall retrospective BIQ previously reported (alpha = 0.96). Reliability for the sub-factors was also quite good and was as follows: "Physical Challenges" (alpha = 0.81), "Separation" (alpha = 0.91), "Performance" (alpha = 0.89), "Unfamiliar Adults" (alpha = 0.94).

Factor Structure Validity. To assess the criterion and content validity of the final bifactor model, four items from SCARED-P were identified that are uniquely representative of each factor; an appropriate item could not be identified for "Physical Challenges". The correlation coefficients from the SEM are presented in Table 5.6. It was expected that each factor would correlate with one specific SCARED-P item to demonstrate discriminant (predictive and divergent) and convergent validity. In addition, the item chosen for the "General" factor was also used to show convergent validity for the BIQ as a whole. All factors were included in each structural equation model as covariates (estimates not shown).

As expected, the "Separation" factor alone correlated with the SCARED-P item "My child follows his/her parents everywhere they go" ($r^2 = 0.204$; SE = 0.067; $p < 0.01$) while the other factors were not significantly associated with this item. Similarly, the "Unfamiliar Adults" factor correlated with the item "It is hard for my child to talk with people he/she doesn't know very well" ($r^2 = 0.255$; SE = 0.046; $p < 0.001$), while the "Performance" factor correlated with the item "My child feels nervous when he/she is with other children or adults and he/she has to do something while they watch him/her" ($r^2 = 0.236$; SE = 0.044; $p < 0.001$). Finally, all of the factors except "Physical Challenges" correlated with the item "My child is shy," with the "General" factor having the strongest relationship ($r^2 = 0.659$; SE = 0.030; $p < 0.001$).

Intriguingly, the "Separation" factor negatively correlated with this item, indicating possible multicollinearity with the "General" factor.

Table 5.6. Discriminant and convergent validity for each factor of the final 5-factor bifactor model. Values represent SEM correlation estimates (SE).

Factor	My child follows his/her parents everywhere they go	It is hard for my child to talk with people he/she doesn't know very well	My child feels nervous when he/she is with other children or adults and he/she has to do something while they watch him/her	My child is shy
General	.182 (.052)***	.626 (.031)***	.497 (.036)***	.659 (.030)***[p,c]
Physical Challenges	.041 (.055)[d]	-.092 (.041)*[d]	.057 (.041)[d]	-.020 (.041)[d]
Separation	.204 (.067)**[p]	-.163 (.044)***[d]	.056 (.047)[d]	-.177 (.041)***
Performance	-.089 (.057)[d]	.079 (.042)[d]	.236 (.044)***[p]	.150 (.040)***[c]
Unfamiliar Adults	-.019 (.060)[d]	.255 (.046)***[p]	-.007 (.046)[d]	.207 (.045)***[c]

Notes: p = predictive; d = divergent; c = convergent

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

The Parental Bonding Instrument

The PBI is an instrument designed to assess overall relationship or bond between parents and children using three scales: authoritarianism (discouragement of independence in child), coldness (distance from and affection toward child), and overprotectiveness (control of child) (Kendler, 1996; Parker, 1990; Parker, Tupling, & Brown, 1979). The original version of the PBI was intended to be administered to children and had two scales, care (now coldness) and overprotectiveness (now split into authoritarianism and protectiveness) (Parker, 1990; Parker et al., 1979). The version used in the current dissertation is a reduced, 16-item scale (Kendler,

1996). This reduced scale was originally developed with the purpose of administering the PBI to parents instead of to children, which aligns with how it was administered in the JAS, although it has been administered to a variety of contexts (i.e., adults giving a retrospective account, children, etc.) (Kendler, 1996; Otowa, Gardner, Kendler, & Hettema, 2013; see Gillespie et al., 2003 for a slightly different 14-item scale). In the current sample, the three PBI scales have appropriate inter-item reliability (α = .63-.74) and test-retest reliability (r = .57-.68) (Carney et al., 2016). The sum scores for each scale were utilized in all analyses.

Biometrical Analyses. Past analyses have examined the biometrical structure of the shortened PBI with mixed results (see Table 5.7). Kendler (1996) first examined the overall genetic epidemiology of parental bonding using the PBI. This was done by first conducting a factor structure of the PBI, revealing three scales (authoritarianism, coldness, overprotectiveness). Next, they examined the best-fitting univariate biometrical model for each scale for several different informants (fathers, mothers, co-twin, self), of whom only the mother was relevant to the current studies. Gillespie and colleagues (2003) went a step further to examine the structure of the PBI using adult female informants to retrospectively report on their childhood bonding with their parent. These analyses revealed that the factor structure of the PBI is indeed three factors, unlike Parker's original two (note – Gillespie and colleagues named the factors autonomy, coldness, and overprotection which map onto Kendler's authoritarianism, coldness, and protectiveness). However, when analyzed as a whole composite representation of parental bonding, a common pathway model fit the data better than an independent pathway. This provides evidence for a universal "parenting" latent factor that holds all three scales of the PBI together. Finally, Otowa and colleagues (2013) examined the univariate structure for each PBI scale in adult male twins who were also retrospectively reporting on their past parental

bonding. Both twins and co-twins served as informants in that co-twins also reported on bonding for their sibling; only the former is reported below. Otowa and colleagues' results somewhat differed from the previous two studies (see Table 5.5).

Table 5.7. Proportion of variance accounted for by genes and environment from the best-fitting models for the PBI scales across studies, including the current analyses (95% confidence intervals).

Study	Informant	A	C	E
Authoritarianism				
Kendler, 1996	Mother	.00	.85	.15
Gillespie et al., 2003	Self (female)	.33	.17	.51
Otowa et al., 2013	Self (male)	.31 (.14 - .37)	.00 (.00 - .14)	.60 (.63 - .76)
Current analyses	**Mother**	**--**	**.76 (.71 - .80)**	**.24 (.20 - .29)**
Coldness				
Kendler, 1996	Mother	.12	.71	.17
Gillespie et al., 2003	Self (female)	.61	.00	.39
Otowa et al., 2013	Self (male)	.30 (.09 - .45)	.09 (.00 - .26)	.62 (.55 - .69)
Current analyses	**Mother**	**.25 (.11 - .41)**	**.58 (.44 - .70)**	**.16 (.12 - .22)**
Overprotectiveness				
Kendler, 1996	Mother	.05	.83	.12
Gillespie et al., 2003	Self (female)	.22	.24	.54
Otowa et al., 2013	Self (male)	.07 (.00 - .30)	.26 (.06 - .37)	.67 (.61 - .73)
Current analyses	**Mother**	**--**	**.81 (.77 - .84)**	**.19 (.16 - .23)**

Notes: A = additive genetic latent factor; C = familial environment latent factor; E = unique environment latent factor.

Bold indicates current analyses.

Given the variation in informants and results, similar analyses to Kendler (1996), Gillespie and colleagues (2003), and Otowa and colleagues (2013) were conducted on the PBI using the current sample of pre-adolescent twin and their mothers. Note that only one previous study (Kendler, 1996) also examined mothers as informants about their bonding with their children. Specifically, preliminary analyses for this dissertation examined the PBI in two ways:

first with the scales separate (per Kendler, 1996, Gillespie et al., 2003, and Otowa et al., 2013) and then with them combined (per Gillespie et al., 2003). After confirming equal means and variances across twins and zygosity, univariate Cholesky decompositions were fit to the authoritarianism, coldness, and protectiveness scales. It was found that a CE fit the data best for authoritarianism (C = .76; E = .24), ACE for coldness (A = .25; C = .58; E = .06), and CE for protectiveness (C = .81; E = .19). These results most closely follow Kendler (1996), which is logical since the informants are the same for these two inquiries into the PBI. See Table 5.7 for comparison of these results to other studies and Table 5.8 for full model fit statistics.

Table 5.8. Model fit statistics for univariate Cholesky models assessing PBI scales Models

Model	EP	-2 LL	DF	AIC	Δ -2LL	Δ DF	*p*
Overprotectiveness							
Full	5	2548.625	613	1322.625	-	-	-
Drop C	4	2632.249	614	1404.249	83.624	1	<.001
Drop A *	4	2550.021	614	1322.021	1.295	1	.237
Drop A and C	3	2877.552	615	1647.552	328.927	2	<.001
Coldness							
Full *	5	2457.329	613	1231.329	-	-	-
Drop C	4	2496.699	614	1268.699	39.370	1	<.001
Drop A	4	2468.142	614	1240.142	10.813	1	.001
Drop A and C	3	2726.321	615	1496.321	268.992	2	<.001
Authoritarianism							
Full	5	2435.652	613	1211.652	-	-	-
Drop C	4	2501.021	614	1275.021	65.368	1	<.001
Drop A *	4	2436.121	614	1210.121	.469	1	.494
Drop A and C	3	2696.346	615	1468.346	260.694	2	<.001

Notes: EP = Estimated Parameters; -2LL = twice the negative log likelihood; DF = degrees of freedom; AIC = Akaike Information Criteria; p = p-value statistic; delta (triangle) = change in

* Indicates final model in that section

To assess whether an overall latent "parent" factor is present in the current sample, multivariate Cholesky, independent pathway (IP), and common pathway (CP) models were fit to the data. The final fit of each model type were not distinguishable from one another based on AIC values (see Table 5.9) and thus, there is no evidence for a latent "parent" factor in the

current data. The study that found that utilized a different informant, which might explain this discrepancy.

Table 5.9. Model fit statistics across the multivariate models tested for the PBI.

Model	EP	-2LL	DF	AIC	Δ -2LL	Δ DF	*p*
Cholesky							
1a. Full	22	7392.051	1831	3730.051	-	-	-
1b. Drop A	16	7579.378	1837	3905.378	187.327	6	<.001
1c. Drop C	16	7405.159	1837	3731.159	13.108	6	.041
1d. Drop A and C	20	8237.043	1843	4551.043	844.992	12	<.001
1e. Drop all shared parameters	13	7443.611	1840	3763.611	51.560	9	<.001
1f. Drop shared A	19	7392.362	1834	3724.362	0.311	3	.958
1g. Drop shared C	19	7420.240	1834	3752.240	28.189	3	<.001
1h. Drop shared E	19	7396.305	1834	3728.305	4.254	3	.235
1i. Drop shared A and E *	**16**	**7402.797**	**1837**	**3728.797**	**10.746**	**6**	**.966**
Independent Pathway							
2a. Full model	21	7393.553	1832	3729.553	-	-	-
2b. Full model drop latent A	18	7394.050	1935	3724.050	.497	3	.920
2c. Full model drop latent C	18	7422.945	1835	3752.945	29.392	3	<.001
2d. Full model drop latent E	18	7397.787	1835	3727.787	4.234	3	.237
2e. Full model drop latent A, latent E *	**15**	**7404.678**	**1838**	**3728.678**	**11.125**	**6**	**.085**
2e1. Drop specific A	12	7417.431	1841	3735.431	12.953	3	.005
2e2. Drop specific C	12	7511.981	1841	3829.981	107.302	3	<.001
2e3. Drop specific A and C	9	7962.552	1844	4274.552	557.874	6	<.001
Common Pathway							
3a. Full model	18	7402.858	1836	3730.858	-	-	-
3b. Full model drop common A	17	7402.858	1837	3728.858	<.001	1	1.000
3c. Full model drop common C	17	7427.113	1837	3753.113	24.155	1	<.001
3d. Full model drop common E	17	7404.143	1837	3730.143	1.284	1	.257
3e. Full model drop latent A, latent E *	**16**	**7404.68**	**1838**	**3728.678**	**1.820**	**1**	**.403**
3e1. Drop specific A	13	7417.43	1841	3735.431	12.7530	3	.005
3e2. Drop specific C	13	7511.98	1841	3829.981	107.302	3	<.001
3e3. Drop specific A and specific C	10	7962.55	1844	4274.552	557.874	6	<.001

Notes: EP = Estimated Parameters; -2LL = twice the negative log likelihood; DF = degrees of freedom; AIC = Akaike Information Criteria; p = p-value statistic; delta (triangle) = change in

Models 2e1, 2e2, and 2e3 were compared to model 2e, not 3a and 3e1, 3e2, and 3e3 were compared to model 3e, not 3a.

* **bold** indicates final model of for a given model type

Discussion

Multiple models were utilized in aims 2 and 3 of this dissertation. While the primary analyses will be discussed in Chapters 6-8, this chapter provided an overview of biometrical

modeling as well as the results of preliminary analyses. There are a few limitations to note specifically for our analyses of the BIQ.

Limitations: The Retrospective BIQ Preliminary Analyses

First, the fit statistics (χ^2, RMSEA, CFI, TLI) of the final model were marginal and did not meet standard minimum thresholds in the full sample (see Table 5.4). Such thresholds are somewhat arbitrary, and fit statistics from other studies of the BIQ were similar except for the study by Vreeke and colleagues (2012) (see Table 5.4). They utilized the more restricted BIQ-Short Form with a substantially larger sample, making it difficult to directly compare to the fit statistics of the retrospective BIQ or previous BIQ studies. This limitation highlights the need for scale assessment and improvement for BI measures. Second, because of its retrospective nature, parent report of their now older child's prior behavior is limited in reliability. In particular, state-dependent recall could bias parents of high-anxiety children to report higher levels of early BI. Third, there were limited potential external validators available in JAS that specifically tapped into BI-related constructs. We restricted these to other parent report measures since these weakly correlated with relevant child report measures, a notorious problem in child psychopathology research. Nevertheless, using the available items it was possible to demonstrate both convergent and divergent validity for all factors except for "Physical Challenges." The retrospective BIQ has shown limited correlation with the behavioral observation in another study (Hirshfeld-Becker et al., 2016) and the original BIQ shows similar properties (Bishop et al., 2003). The issue of strong construct validity for the entire retrospective BIQ remains an issue of the assessment. Fourth, there was evidence of multicollinearity between factors in the bifactor model, meaning that the "General" factor does not account for all of the variance in the subscales. This makes the subscales necessary for the overall fit of the retrospective BIQ but reduces their independent

interpretability and use. The most severe limitation, common to most measures of BI, is the retrospective BIQ's potential to validly assess a stable, reliable, construct of BI beyond early childhood. As noted previously, a recent study in older children and adolescents found rather modest correlation ($r = 0.21$) between the parent-report retrospective BIQ with BI defined by observational laboratory protocols at ages 2-6 (Hirshfeld-Becker et al., 2016). Yet, other studies of the non-retrospective BIQ report higher correlations with the behavioral observation assessment ($r = .46$, Bishop et al., 2003; 74% agreement rate, Hudson & Dodd, 2012).

Points to Remember

There are points to note from this chapter that should be remembered while reading the rest of this dissertation. First, the JAS sample used throughout this dissertation was limited to mother and child report only for visit 1. Father reports of their children and all visit 2 analyses (except for calculating reliability) were omitted. Second, the parent and child scores for the SCARED were averaged together to reflect the fact that pre-adolescence is a time when parents still know a great deal about their children but may not have total insight into their mental health and related behaviors. Third, the retrospective version of the BIQ is a valid, reliable way to measure early childhood BI. Finally, the PBI scales are best analyzed separately; no evidence for a latent "parent" factor was found in the current sample.

Chapter 6: Psychiatric Genetic Perspective on the Relationship Between Behavioral Inhibition and Anxiety[1]

Introduction

First characterized by Kagan and colleagues, childhood behavioral inhibition (BI) is a temperamental trait whereby children express shyness, restraint, or other negative affect in response to novel people, objects, or environments (Garcia Coll, Kagan, & Reznick, 1984; Fox et al., 2005; Kagan, Reznick, & Snidman, 1987). Roughly 20% of children initially scored as having high BI continue to exhibit elements of inhibition as they age into adolescence (Kagan, 2012), and approximately 40% later develop social anxiety (Clauss & Blackford, 2012; Clauss, Avery, & Blackford, 2015). While BI is a well-documented risk factor for later social anxiety disorder in adolescents and adults (Clauss & Blackford, 2012; Chronis-Tuscano et al., 2009; Hirshfeld-Becker et al., 2007; Hirshfeld-Becker et al., 2008; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010; Kagan, Reznick, & Snidman, 1987; Muris, van Braken, Arntz, & Schouten, 2011; Schwartz, Snidman, & Kagan, 1999), it is also associated with other forms of anxiety-related psychopathology such as specific phobia, panic disorder, separation anxiety, generalized anxiety, and avoidant disorder earlier in childhood (Biederman et al., 2001; Dyson et al., 2011; Frenkel et al., 2015; Muris, Merckelbach, Wessel, & van de Ven, 1999; Paulus, Backes, Sander, Weber, & von Gontard, 2015). Development of any disorder, namely anxiety, is complex with many possible branching points and outcomes, but a hypothetical example could be that a child with elevated BI presents as more generally anxious during childhood. However, when they get to middle school, a time of increased social pressure, social anxiety symptoms become more prominent, and they are diagnosed with social anxiety disorder as an adolescent. Conversely, it is possible for a child to exhibit elevated BI and continue on a linear progression to develop later

[1]Modified version of the manuscript Bourdon, J. L., Savage, J. E., Verhulst, B., Carney, D. M., Brotman, M. A., Pine, D. S. … Hettema, J. M. (2019). The genetic and environmental relationship between childhood behavioral inhibition and pre-adolescent anxiety. *Twin Research Human Genetics, 1-8*. doi:10.1017/thg.2018.73

social anxiety. However, as they age further, they may learn to hide or better manage many of their symptoms and not meet criteria for a diagnosis. Thus, the overall goal of the present study is to clarify the etiological relationship between childhood BI and pre-adolescent anxiety domains using novel genetic epidemiological approaches.

BI has been well studied from developmental and clinical perspectives over the last three decades, but genetic epidemiological approaches have been underutilized. Past studies of singletons have examined childhood and/or adolescent and adult ages (i.e., Chronis-Tuscano et al., 2009; Frenkel et al., 2015; Schwartz et al., 1999), leaving pre-adolescence less well understood from a developmental perspective. Prior twin studies report moderate heritability through age 2 for BI (42-56%; Emde et al., 1992; Plomin et al., 1993; Robinson, Kagan, Reznick, & Corley, 1992) and similar estimates for all childhood anxiety disorders (28-60%; Lahey, Van Hulle, Singh, Wadman, & Rathouz, 2011; Scaini, Belotti, & Ogliari, 2014; Ogliari et al., 2006; Ogliari et al., 2010). However, no twin studies have directly examined the sources of shared genetic and environmental risk factors between BI and anxiety disorders in children. Further, a twin design allows for the examination of possible causal pathways from BI to strongly related anxiety domains even using a cross-sectional design. Pertinently, there is ongoing debate as to whether BI is a distinct construct or simply an earlier version of social anxiety (Clauss & Blackford, 2012).

Pre-adolescence is a key time to elucidate these shared genetic and environmental risks, as symptoms of anxiety disorders, while common, remain largely still at pre-clinical levels in this developmental period (Rapee, Schniering, & Hudson, 2009; Rapee & Spence, 2004). Understanding this shared risks would complement prior work by further elaborating the etiology of anxiety disorders from a trans-diagnostic, genetic perspective (i.e., Kagan, Snidman, Zentner,

& Peterson, 1999; Rapee & Spence, 2004) and possibly inform future prevention/intervention efforts. The current study specifically addresses two key knowledge gaps regarding the shared etiologic pathways between childhood BI and related anxiety domains by dissecting their developmental and phenotypic relationships at the genetic epidemiological level. The first aim of this study is to clarify the exact relationship between BI and key anxiety domains. For example, previously reported associations between BI and generalized anxiety, separation anxiety, or panic symptoms (Biederman et al., 2001; Dyson et al., 2011; Frenkel et al., 2015; Muris et al., 1999; Paulus et al., 2015) may be indirect effects of correlations between these symptoms and social anxiety rather than the direct result of shared genetic and environmental effects. The second aim is to disaggregate the overlapping sources of liability between the anxiety domains for which BI shares the most genetic and environmental variance. Specifically, it will be tested whether shared genetic and environmental factors are simply correlational, or if evidence for causal pathways can be identified. This aligns with dissertation aim 2.1.

Materials and Methods

Participants

Participants were part of the Virginia Commonwealth University Juvenile Anxiety Study (JAS; Carney et al., 2016). See chapter 5 for an overview of this study and its sample. As a reminder, the final analytical sample included 352 families and 704 children (M_{age} = 11.22; standard deviation [SD_{age}] = 1.41; female = 53%; monozygotic [MZ] = 114 pairs; dizygotic [DZ] = 238 pairs; 88% of full sample).

Measures

This study utilized two measures, a retrospective version of the Behavioral Inhibition Questionnaire (BIQ; Bishop, Spence, & McDonald, 2003) and the Screen for Child Anxiety

Related Emotional Disorders – Parent and Child Versions (SCARED) (Birmaher et al., 1997). A series of preliminary analyses confirmed their validity, reliability, and appropriate usage in the primary analyses as discussed in chapter 5.

Both parent and child responses to the SCARED were collected since both types of report for any form of psychopathology are limited and potentially biased (De Los Reyes & Kazdin, 2005). As expected, parent-rated BI more strongly correlates with parent-rated than child-rated recent anxiety (see Table 6.1), yet pre-adolescent children potentially offer additional insight into their own symptomology. Information was combined across raters by including the average of the parent and child SCARED sum scores for each subscale in analyses with parent-rated BI.

Analyses

An overview of biometrical modeling is provided in chapter 5.

Descriptive Statistics. The mean, standard deviation, and range were calculated for each phenotype. Pearson correlations estimated the within-individual (i.e., phenotypic) associations between anxiety clusters and BI. MZ and DZ twin correlations were calculated individually for each phenotype as well as the cross-twin, cross-trait correlations between phenotypes (see Table 6.1). This information roughly predicts how the variance of the measures will decompose at the univariate and multivariate levels (Neale & Cardon, 1992).

Table 6.1. Pearson correlations between the BIQ and parent measures of child anxiety and child measures of child anxiety ("C" indicates child report; "P" indicates parent report).

Measure	1	2	3	4	5	6	7	8	9
1. BIQ	--								
2. SCARED-C, social anxiety	.26**	--							
3. SCARED-C, generalized anxiety	.05	.40**	--						
4. SCARED-C, separation anxiety	.04	.43**	.41**	--					
5. SCARED-C, panic	.04	.41**	.49**	.51**	--				
6. SCARED-P, social anxiety	.67**	.29**	.03	.05	.00	--			
7. SCARED-P, generalized anxiety	.25**	.07	.20**	.09*	.08*	.48**	--		
8. SCARED-P, separation anxiety	.22**	.05	.06	.26**	.08*	.39**	.59**	--	
9. SCARED-P, panic	.19**	.04	.03	.05	.10*	.43**	.61**	.61**	--

*$p < .05$; **$p < .001$

Covariates. Univariate linear regression was used to assess for the need to include sex (male, female) as a covariate due to its known association with anxiety domains (Hettema et al., 2005; Rapee, 2004).

Primary Analyses. For the first aim, biometrical SEM was used to fit a multivariate Cholesky decomposition of BI and all anxiety clusters to assess which etiological latent genetic and environmental factors are shared between phenotypes. The order of the clusters in the model was based on the strength of the phenotypic associations between each cluster and BI. At the multivariate level, each source of variance (A, C, E) was estimated as well as its contributions to the covariance between phenotypes. A series of nested submodels tested whether the shared

variance (covariance) paths could be eliminated from the model using likelihood ratio chi-square tests and Akaike information criteria fit statistics.

As part of the second aim, a direction of causation model was utilized to further explicate the relationship between BI and anxiety constructs with which it shared substantial variance (as revealed from the multivariate biometrical model in the first aim). Traditionally in non-twin samples, direction of causation models require longitudinal or experimental data to show causality. In a cross-sectional, biometrical context, direction of causation models leverage known differences between MZ and DZ twins' shared genetics and environments. Specifically, these models utilize cross-twin, cross-trait correlations across three unique sources of variance (A, C, E, or dominance [D]) (Heath et al., 1993; Gillespie & Martin, 2005; Verhulst & Estabrook, 2012). To the extent that the sources of variance differ across the phenotypes (or that the magnitudes of the same sources of variance differ substantially), inferences can be made about whether a beta regression coefficient (as opposed to a correlation) best explains the relationship between two phenotypes. This is tested via five scenarios that are nested within a full Cholesky decomposition model (see Figure 6.1) (Verhulst & Estabrook, 2012): (a) phenotype 1 causes phenotype 2, (b) phenotype 2 causes phenotype 1, (c) reciprocal causation between phenotypes, (d) an external factor causes both (correlated liabilities), and (e) no association between the two phenotypes. Additionally, the proportion of variance accounted for in the "outcome" phenotype in each direction of causation model was estimated and compared to the proportion of variance accounted for by the default correlated liability model (here, the bivariate Cholesky decomposition). The direction of causation model is then compared to a correlated liability model (i.e., a bivariate Cholesky decomposition with shared sources of variance) using likelihood ratio test and Akaike information criteria fit statistics.

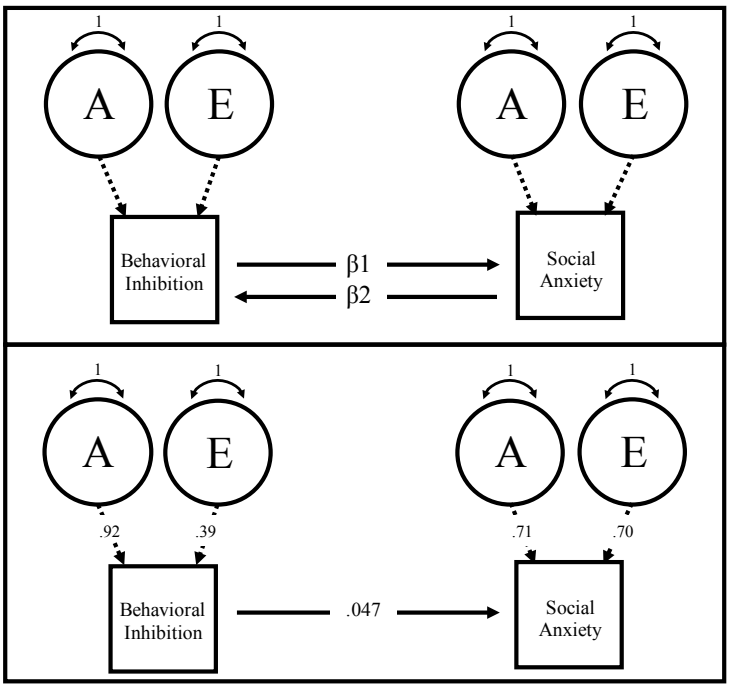

Figure 6.1. Top: Full direction of causation model tested within a nested Cholesky decomposition model. Bottom: Final model found in the present study.

Results

Correlations and Heritability Estimates

For all anxiety clusters, parent and child SCARED scores could be constrained to be equal in their multiple indicator models (see chapter 5, Table 5.2). In other words, the average of the parent and child SCARED sum scores provide a reasonable representation of these anxiety domains for analyses with parent-rated BI and were used in all analyses.

Within-person correlations among BI and each anxiety domain were consistent with past findings (see Table 6.2; Dyson et al., 2011; Muris et al., 1999; Paulus et al., 2015). Consistent with prior reports, childhood BI had the strongest association with pre-adolescent social anxiety symptoms ($r = .57$, $p < .001$) and smaller but significant correlations with generalized anxiety, separation anxiety, and panic symptoms ($r = .11$ - $.18$, $p < .05$).

Table 6.2. Within-person correlations between behavioral inhibition and anxiety symptom clusters.

Measure	1	2	3	4	5
1. Behavioral Inhibition	--				
2. Social Anxiety	.57**	--			
3. Generalized Anxiety	.18**	.40**	--		
4. Separation Anxiety	.15*	.36**	.47**	--	
5. Panic	.11*	.35**	.52**	.51**	--

*$p < .05$; **$p < .001$

All twin correlations for BI and each anxiety domain were significant except for the DZ correlations for BI and social anxiety symptoms (see Table 6.3 and Figure 6.2 for these data and other descriptive statistics on these measures).

Table 6.3. Descriptive and twin statistics for behavioral inhibition and anxiety symptom clusters.

Measure	Applicable Age Range	Report	Mean (SD); SE	Median; Range	MZ Correlation	DZ Correlation	Heritability
Behavioral Inhibition	2-6	**Parent**	**95.24 (35.29); 1.37**	**92.00; 30-199**	**.84****	**.05**	**.76**
Social Anxiety	8-13	Parent	4.06 (3.59); .14	4.00; 0-19	.70**	.03	.61
		Child	5.00 (3.91); .15	6.00; 0-14	.44**	.21*	.42
		Average	**5.01 (2.75); .11**	**4.96; 0-14**	**.64****	**-.02**	**.52**
Generalized Anxiety	8-13	Parent	3.97 (3.74); .14	3.00; 0-19	.63**	.13*	.57
		Child	5.84 (3.63); .14	5.00; 0-16	.43**	.26**	.47
		Average	**4.91 (2.86); .11**	**4.50; 0-15.5**	**.56****	**.19***	**.49**
Separation Anxiety	8-13	Parent	2.21 (2.81); .11	1.00; 0-14	.83**	.36**	.35
		Child	5.17 (3.38); .13	5.00; 0-16	.44**	.38**	.45
		Average	**3.70 (2.46); .09**	**3.00; 0-13.5**	**.62****	**.36****	**.62**
Panic	9-13	Parent	1.53 (2.70); .10	1.00; 0-19	.84**	.56**	.84
		Child	5.18 (3.91); .15	4.00; 0-24	.41**	.25**	-
		Average	**3.35 (2.48); .10**	**3.00; 0-14**	**.68****	**.39****	**.68**

*p<.05; **p<.001; **bold** indicates model used in primary analyses

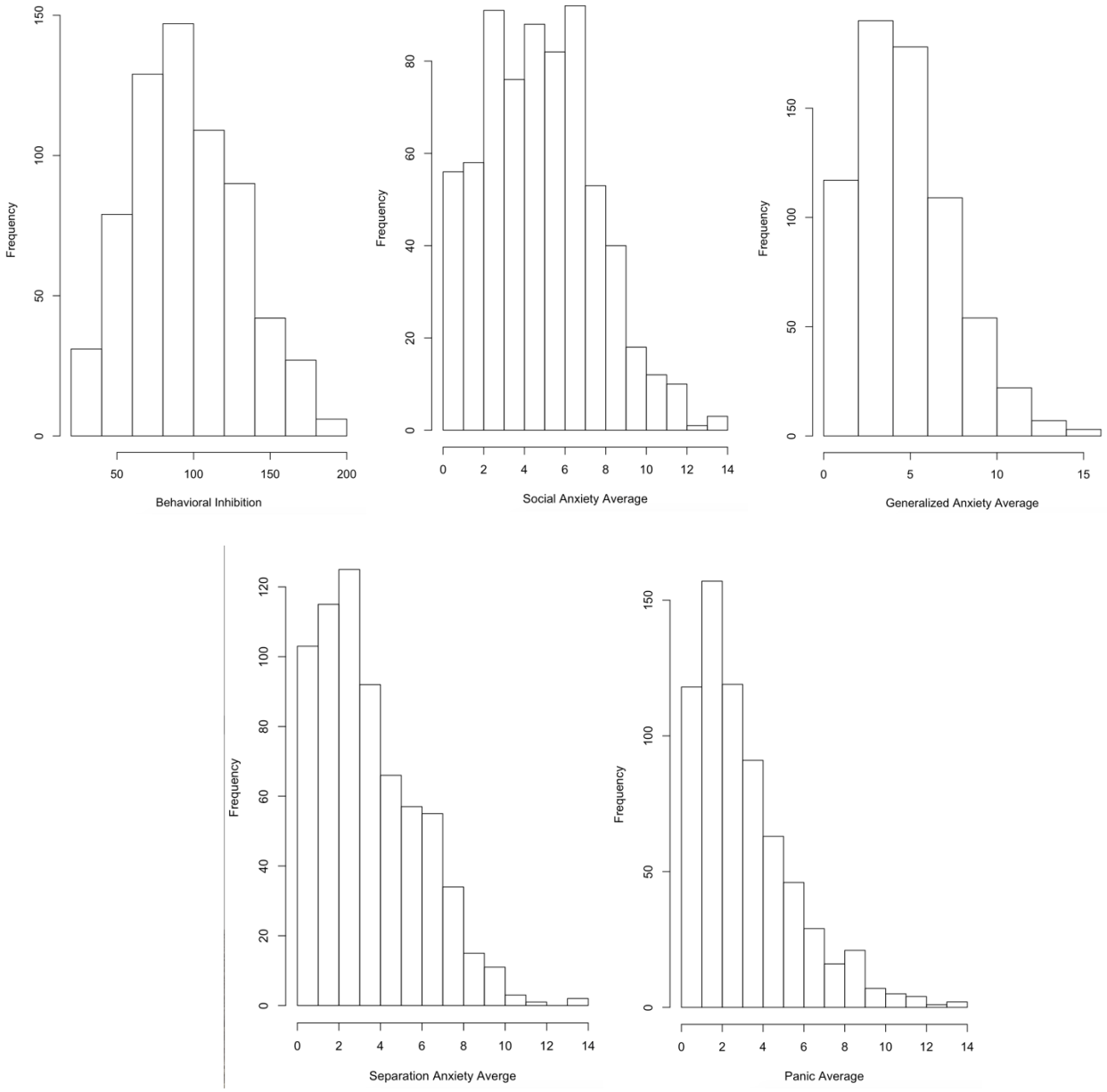

Figure 6.2. Histograms of key variables.

For some scales, the DZ correlations were less than half of the MZ correlations, indicating possible influence of non-additive genetic factors such as genetic dominance or epistasis (denoted as D). ADE models which estimate non-additive genetic influences were tested but did not significantly improve model fit over ACE models for any of the phenotypes tested. This is unsurprising, as the power to detect non-additive genetic variance factors is typically poor in

practical twin sample sizes (Martin, Eaves, Kearsey, & Davies, 1978). The magnitudes of the remaining correlations indicated the possibility of both genetic and common environmental contributions to the variance of each phenotype. The cross-twin, cross-trait genetic correlations followed the same patterns of weaker cross-twin DZ correlations across phenotypes (see Table 6.4).

Table 6.4. Cross-twin, cross-trait genetic correlations between BI and anxiety symptom clusters.

Measure	1	2	3	4	5	6	7	8	9	10
MZ Twins										
1. Behavioral Inhibition – Twin 1	--	--	--	--	--	--	--	--	--	--
2. Behavioral Inhibition – Twin 2	.81	--	--	--	--	--	--	--	--	--
3. Social Anxiety – Twin 1	.50	.42	--	--	--	--	--	--	--	--
4. Social Anxiety – Twin 2	.44	.60	.60	--	--	--	--	--	--	--
5. Generalized Anxiety – Twin 1	.06	.04	.34	.21	--	--	--	--	--	--
6. Generalized Anxiety – Twin 2	-.09	.10	.10	.42	.47	--	--	--	--	--
7. Separation Anxiety – Twin 1	.10	.05	.39	.32	.51	.23	--	--	--	--
8. Separation Anxiety – Twin 2	-.04	.04	.07	.37	.33	.49	.57	--	--	--
9. Panic – Twin 1	-.07	-.13	.24	.15	.46	.27	.46	.38	--	--
10. Panic – Twin 2	.04	.13	.08	.36	.25	.49	.38	.58	.60	--
DZ Twins										
1. Behavioral Inhibition – Twin 1	--	--	--	--	--	--	--	--	--	--
2. Behavioral Inhibition – Twin 2	.02	--	--	--	--	--	--	--	--	--
3. Social Anxiety – Twin 1	.52	-.15	--	--	--	--	--	--	--	--
4. Social Anxiety – Twin 2	-.06	.64	-.02	--	--	--	--	--	--	--
5. Generalized Anxiety – Twin 1	.14	.001	.34	.12	--	--	--	--	--	--
6. Generalized Anxiety – Twin 2	-.002	.26	.05	.40	.17	--	--	--	--	--
7. Separation Anxiety – Twin 1	.15	-.05	.34	.02	.43	.13	--	--	--	--
8. Separation Anxiety – Twin 2	.05	.20	.10	.31	22	.44	.35	--	--	--
9. Panic – Twin 1	.14	.06	.33	.12	.47	.13	.46	.23	--	--
10. Panic – Twin 2	-.01	.18	.19	.31	.26	.53	.25	.49	.34	--

*$p < .05$; **$p < .001$

There was a significant effect of sex on BI ($\beta = 5.791$, $p = .035$), social anxiety ($\beta = .634$, $p = .003$), generalized anxiety ($\beta = .682$, $p = .002$), separation anxiety ($\beta = .565$, $p = .003$), and panic ($\beta = .446$, $p = .019$). Sex was included as a covariate in all biometrical analyses.

Heritability estimates were calculated for each phenotype within the multivariate Cholesky decomposition (see below) to assess consistency with past literature. The estimated heritability of retrospective childhood BI was higher than that of concurrent BI in toddlers (see Table 6.3; h^2 = .76; confidence interval = .65 - .84;) (Emde et al., 1992; Plomin et al., 1993; Robinson, et al., 1992). For the anxiety clusters, heritability estimates were slightly different than previously reported (Lahey et al., 2011; Scaini et al., 2014; Ogliari et al., 2006; Ogliari et al., 2010) except for social anxiety, which was consistent with past studies (h^2 = .52). Specifically, heritability was slightly lower for generalized anxiety (h^2 = .49) and slightly higher for both separation anxiety (h^2 = .62) and panic (h^2 = .68).

Relationship Between BI and All Anxiety Clusters

The phenotypic ordering in the multivariate model was based on decreasing magnitude of correlations found between BI and each anxiety domain (Table 6.2): BI, social anxiety, generalized anxiety, separation anxiety, and panic (see Tables 6.5-6.6 and Figure 6.3).

Table 6.5. Variance and covariance components for the best-fitting multivariate model between BI and anxiety symptom clusters (95% confidence intervals).

BI (Trait 1)	*Social (Trait 2)*		*Generalized (Trait 3)*		*Separation (Trait 4)*		*Panic (Trait 5)*		
Additive Genetic (A) Components Shared Between BI and Anxiety Symptom Clusters									
A_{11}	A_{21}	A_{22}	A_{31}	A_{33}	A_{41}	A_{44}	A_{51}	A_{55}	-
.76 (.65 - .84)	.20 (.10 - .30)	.32 (.22 - .41)	-	.43 (.29 - .55)	-	.42 (.29 - .53)	.01 (.001 - .04)	.29 (.18 - .40)	-
Unique Environment (E) Components Shared Between BI and Anxiety Symptom Clusters									
E_{11}	E_{21}	E_{22}	E_{31}	E_{33}	E_{41}	E_{44}	E_{51}	E_{55}	-
.24 (.16 - .35)	.16 (.07 - .28)	.32 (.25 - .42)	.07 (.03 - .14)	.40 (.29 - .52)	.05 (.02 - .10)	.29 (.22 - .39)	-	.26 (.20 - .34)	-
Additive Genetic (A) Components Shared Between the Anxiety Symptom Clusters									
-	-	-	-	A_{32}	A_{42}	A_{43}	A_{52}	A_{53}	A_{54}
-	-	-	-	.06 (.01 - .16)	.06 (.01 - .15)	.14 (.54 - .26)	.10 (.03 - .20)	.20 (.09 - .33)	.08 (.02 - .17)
Unique Environment (E) Components Shared Between the Anxiety Symptom Clusters									
-	-	-	-	E_{32}	E_{42}	E_{43}	E_{52}	E_{53}	E_{54}
-	-	-	-	.04 (.01 - .09)	.03 (.01 - .07)	.01 (<.001 - .04)	.03 (.01 - .07)	.03 (.01 - .08)	.004 (<.001 - .02)

Notes on variance component naming:
A_{11}/E_{11} = Behavioral Inhibition symptoms
A_{22}/E_{22} = Social anxiety symptoms; A_{21}/E_{21} = Shared between BI and social anxiety symptoms
A_{33}/E_{33} = Generalized anxiety symptoms; A_{31}/E_{31} = Shared between BI and generalized anxiety symptoms
A_{44}/E_{55} = Separation anxiety symptoms; A_{41}/E_{41} = Shared between BI and separation anxiety symptoms
A_{55}/E_{55} = Panic symptoms; A_{51}/E_{51} = Shared between BI and panic symptoms
All other paths represent shared variance between the anxiety symptom clusters

Notes: Variance components above are equal to the squares of the standardized path estimates seen in Figure 2. Within each phenotype, these should add up to 1.00 but may not due to rounding error.

Table 6.6. Model fit statistics for from multivariate analyses between BI and anxiety symptom clusters.

Model	EP	-2LL	DF	AIC	Δ LL	Δ DF	*p*
Full ACE Parameters							
Full ACE	55	17200.516	3109	10982.516	-	-	-
ACE drop all C *	40	17204.918	3124	10956.918	4.401	15	.996
ACE drop all A	40	17306.158	3124	11058.158	105.642	15	<.001
ACE drop all A and C	25	17498.420	3139	11220.420	297.904	30	<.001
Final Model from Above – Drop Parameters Shared with BI							
Full AE	40	17204.918	3124	10956.918	-	-	-
AE drop all shared A	36	17240.292	3128	10984.292	35.374	4	<.001
AE drop all shared E	36	17244.994	3128	10988.994	40.076	4	<.001
AE drop all shared A and E	32	17474.040	3132	11210.040	269.122	8	<.001
AE drop E_{51} *	39	17205.620	3125	10955.620	.702	1	.402
AE drop A_{31} *	39	17206.437	3125	10956.437	1.519	1	.218
AE drop A_{41} *	39	17207.393	3125	10957.393	2.475	1	.116
AE drop A_{51}	39	17209.877	3125	10959.877	4.960	1	.026
AE drop E_{41}	39	17213.725	3125	10963.725	8.807	1	.003
AE drop E_{31}	39	17215.306	3125	10965.306	10.388	1	.001
AE drop E_{21}	39	17255.350	3125	11005.350	50.433	1	<.001
AE drop A_{21}	39	17237.923	3125	10987.923	33.005	1	<.001
Full AE – Drop Non-Significant Parameters from Above							
Full AE	40	17204.918	3124	10956.918	-	-	-
AE drop E_{51}, A_{31}, A_{41} **	37	17209.341	3127	10955.341	4.422	3	.219

* Indicates best-fitting model(s) from that series of nested sub-models; ** Indicates final best-fitting model overall

EP = Estimated Parameters; -2LL = twice the negative log likelihood; DF = degrees of freedom; AIC = Akaike Information Criteria; p = p-value statistic; delta (triangle) = change in

Notes on path naming:
A_{21}/E_{21} = Shared between BI and social anxiety symptoms
A_{31}/E_{31} = Shared between BI and generalized anxiety symptoms
A_{41}/E_{41} = Shared between BI and separation anxiety symptoms
A_{51}/E_{51} = Shared between BI and panic symptoms

Consistent with past findings for each individual phenotype, only additive genetic (A) and unique environment (E) significantly contributed to this multivariate relationship (Lahey et al., 2011; Robinson et al., 1992; Scaini et al., 2014; Ogliari et al., 2006; Ogliari et al., 2010). At least some proportion of genetic or environmental risk of each anxiety cluster was shared with BI (see Figure 6.2). Specifically, social anxiety shared the most of its variance with BI (A = .20; E =

.16), followed in smaller magnitudes by generalized anxiety (E = .07), separation (E = .05), and panic (E = .01).

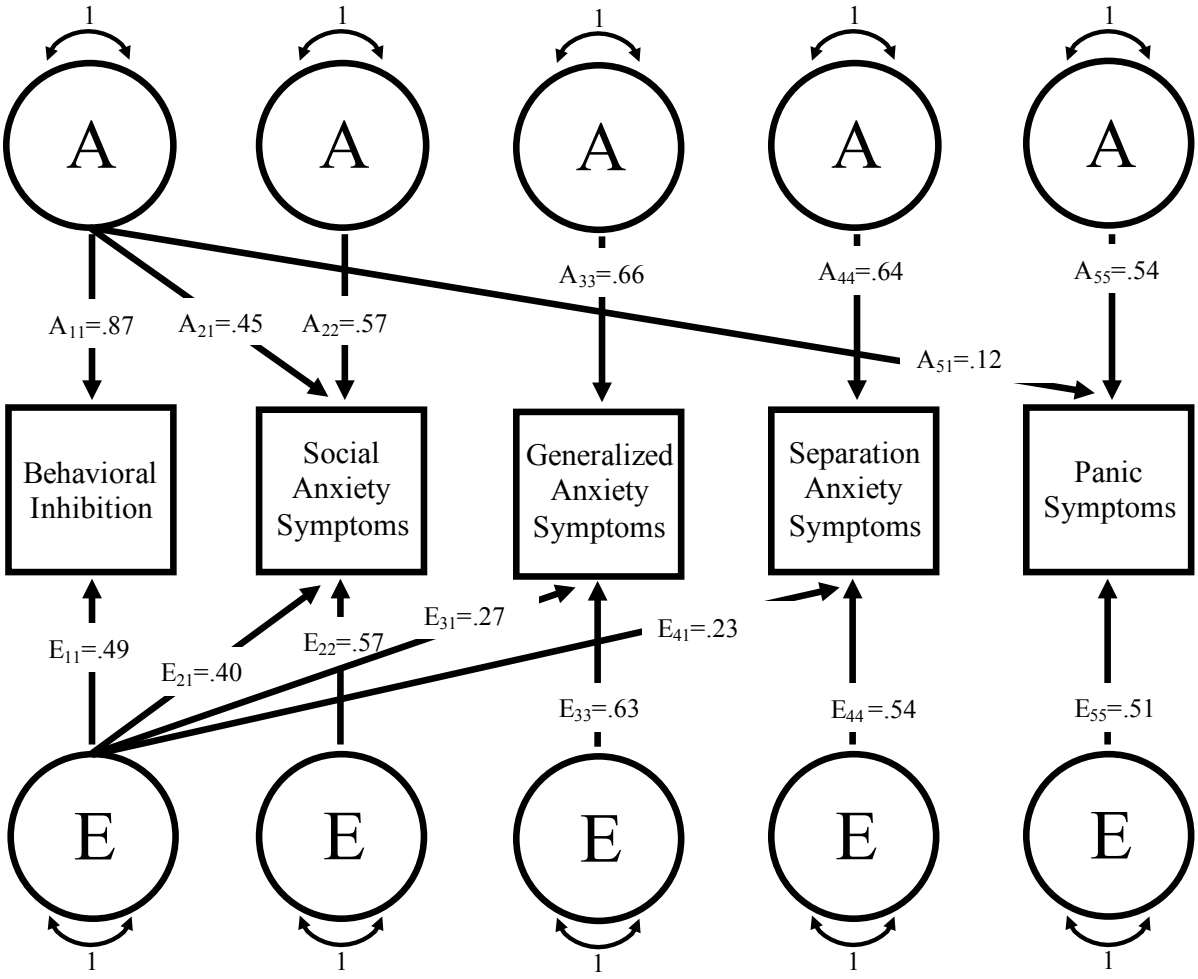

Figure 6.3. Standardized path estimates from the final multivariate model depicting the shared paths between BI and anxiety symptom clusters and unique paths only (shared inter-anxiety paths not included for simplicity but can be found in Table 6.7).

There was also significant shared variance between the anxiety clusters (see Table 6.5) although not as much as previously reported in this age group (Ogliari et al., 2010). Generalized and separation anxiety shared the most genetic variance (A = .14) while social and generalized anxiety shared the most environmental variance (E = .04). A Cholesky decomposition of the anxiety measures alone revealed that, except for social anxiety, these lower between-domain

covariance estimates are not due to residual covariance accounted for by including BI in the model (see Table 6.7).

Table 6.7. Variance and covariance components for the best-fitting multivariate model between anxiety symptom clusters.

Social	*Generalized*		*Separation*			*Panic*			
Additive Genetic (A) Components									
A_{11}	A_{21}	A_{22}	A_{31}	A_{32}	A_{33}	A_{51}	A_{52}	A_{53}	A_{54}
.49	.06	.44	.06	.15	.42	.09	.19	.10	.30
Unique Environment (E) Components									
E_{11}	E_{21}	E_{22}	E_{31}	E_{32}	E_{33}	E_{51}	E_{52}	E_{53}	E_{54}
.52	.09	.41	.06	.01	.29	.03	.03	<.001	.27

Notes on variance component naming:
A_{11}/E_{11} = Social anxiety symptoms
A_{22}/E_{22} = Generalized anxiety symptoms
A_{33}/E_{33} = Separation anxiety symptoms
A_{44}/E_{55} = Panic symptoms
All other paths represent shared variance between the anxiety symptom clusters

Notes: Within each phenotype, these should add up to 1.00 but may not due to rounding error.

Relationship Between BI and Social Anxiety

Due to the modest but significant amounts of additive genetic and unique environmental variance shared between BI and social anxiety but not with other anxiety clusters, the direction of causation model was only tested between these two phenotypes. This model with social anxiety symptoms regressed onto BI fit significantly better than the other direction of causation models tested (BI regressed onto social anxiety, joint causation, no association), notably ruling out these other three possibilities as explanations for the relationship between BI and social anxiety. When compared to the correlated liabilities model, which represents an external unmeasured factor causing both phenotypes, the model with BI causing social anxiety was not significantly worse; it estimated a small but notable regression coefficient ($\beta = .047$; see Tables 6.8-6.9, Figure 6.1). Both models had comparable parameter estimates and fit indices, making it

important to assess the amount of social anxiety's variance accounted for by BI in each model to further explain their relationship from a genetically-informed perspective.

Table 6.8. Variance components and proportion of social anxiety's variance accounted for by BI in the best-fitting correlated liabilities and direction of causation models.

Correlated Liabilities Model with Cross Paths Between Phenotypes					
	Unique A	Unique E	R^2 for A (A_{21})	R^2 for E (E_{21})	Total R^2
Behavioral Inhibition	.79	.21	-	-	-
Social Anxiety	.32	.31	.24	.13	.37

Direction of Causation Model with Causal Beta Paths Between Phenotypes						
	Unique A	Unique E	β_1 Causal Path	R^2 for A	R^2 for E	Total R^2
Behavioral Inhibition	.85	.15	.047	-	-	-
Social Anxiety	.51	.49		.30	.08	.38

Notes: Variance components above are equal to the squares of the standardized path estimates. Within each phenotype, these should add up to 1.00 but may not due to rounding error

Notes on path naming:
A_{21}/E_{21} = Shared between BI and social anxiety symptoms
β_1 = Causal path from BI to social anxiety symptoms
R^2 = Amount of social anxiety's variance that is accounted for by BI

Table 6.9. Model fit statistics for from the direction of causation and correlated liabilities models between BI and social anxiety symptoms.

Model	EP	-2LL	DF	AIC	Δ LL	Δ DF	*p*
Model with Correlated Liabilities (Cross Paths) Between Phenotypes							
Full AE with A_{21} and E_{21} *	10	8911.565	1245	6421.565	--	--	--
AE drop A_{21}	9	8944.554	1246	6452.554	32.989	1	<.001
AE drop E_{21}	9	8947.257	1246	6455.257	35.691	1	<.001
AE drop A_{21} and E_{21} **	8	9172.122	1247	6678.122	260.557	2	<.001
Direction of Causation Model with Causal Beta Paths Between Phenotypes							
Full AE with β_1 and β_2	10	8912.351	1245	6422.351	--	--	--
AE drop β_1	9	9116.040	1246	6624.040	203.689	1	<.001
AE drop β_2 *	9	8913.621	1246	6421.621	1.270	1	.260
AE drop β_1 and β_2 **	8	9172.122	1247	6678.122	259.771	2	<.001
Comparing Final Models							
Full AE with A_{21} and E_{21}	10	8911.565	1245	6421.565	-	-	-
AE drop β_2 *	9	8913.621	1246	6421.621	2.055	1	.152

* Indicates best-fitting model(s) from that series of nested sub-models; ** Indicates identical models

EP = Estimated Parameters; -2LL = twice the negative log likelihood; DF = degrees of freedom; AIC = Akaike Information Criteria; p = p-value statistic; delta (triangle) = change in

Notes on path naming:
A_{21}/E_{21} = Shared between BI and social anxiety symptoms
β_1 = Causal path from BI to social anxiety symptoms
β_2 = Causal path from social anxiety symptoms to BI

BI in both models accounted for a similar proportion of social anxiety's variance. Specifically, 37% of social anxiety's variance (24% of the A and 13% of the E variance) was accounted for by BI in the correlated liabilities model compared to 38% (30% of the A and 8% of the E variance) in the direction of causation model. Taken together with their comparable fit to these data, this implies that a direction of causation model with a single beta coefficient from BI to social anxiety symptoms modestly informs their relationship beyond the correlated risk structure.

Discussion

Using novel approaches that complement existing developmental research, the current study examined the shared genetic and environmental influences between BI and anxiety

symptomology. The first aim of the study sought to clarify the etiology between BI and related anxiety domains, and the second examined potential causality between BI and the anxiety domain(s) with most substantial genetic and environmental overlap with BI from the first aim. Findings explicate prior reported phenotypic associations of BI with various anxiety symptoms in childhood and its role as a particular risk factor for later social anxiety. It was found that retrospectively-reported childhood BI shared both genetic and environmental variance with pre-adolescent social anxiety symptoms, but there was little-to-no genetic overlap between BI and other domains of anxiety symptomatology. Tentative evidence was also found for causality between BI and social anxiety.

These findings clarify that associations between childhood BI and pre-adolescent anxiety symptoms other than social anxiety are primarily a function of shared environmental influences and not simply indirect effects from the correlations between social anxiety and other anxiety clusters. The residual variance of social anxiety increased when BI was taken out of the model, but the genetic and environmental components for the rest of the anxiety clusters and their interrelationships remained unchanged. This implies that associations found in the model that included BI are fairly robust. If the relationship between BI and the other clusters was due to correlations with social anxiety, then their variance components should have differed in the model without BI. Given the generally more stable effects of genetic versus environmental influences across development, this finding helps clarify the more robust, longitudinal relationship seen between early BI and later social anxiety disorder compared with other anxiety disorders.

Further, there is tentative evidence that the relationship between BI and social anxiety is causal. A significant proportion of the variance of pre-adolescent social anxiety symptoms was

explained by childhood BI, specifically about a quarter of the additive genetic variance and a tenth of the unique environmental variance. While it had been previously shown that about 40% of children with BI later develop social anxiety (Clauss & Blackford, 2012; Clauss et al, 2015), the current findings suggest a particularly strong, etiologically-relevant link. Our twin direction of causation model provided a potential approach for distinguishing correlation and direct causation between etiological sources of covariance between BI and social anxiety. The model fits were not significantly worse, and variance estimates were on par with those of the correlated model, implying that either is an appropriate way to represent the relationship between BI and social anxiety disorder. The direction of causation model provides an etiologically informed twin version of a linear regression, bridging the gap between genetically-informed and behavioral-based studies.

These findings contribute to two key threads in the BI and social anxiety literature. There has been a long-standing debate regarding the developmental distinction between BI and social anxiety disorder (Clauss & Blackford, 2012). The current study adds a genetically-informed perspective to this discussion by demonstrating that both shared genetic and environmental factors partially, yet substantially, underpin the relationship between BI and social anxiety. This expands upon past longitudinal studies and expert reviews (Kagan et al., 1999; Fox et al., 2005; Rapee & Spence, 2004). Importantly, these findings also suggest that there are etiologic distinctions, supporting the hypothesis that these phenotypes are not two measures of the same underlying construct.

In addition, these results add to the growing evidence that childhood BI is a putative endophenotype for later social anxiety. Endophenotypes are “intermediate” phenotypes that lie in the etiological pathway between genetic variation and a disorder (Cannon & Keller, 2006;

Gottesman & Gould, 2003). BI has previously been shown to meet a subset of the basic requirements as an endophenotype for social anxiety, including association with the disorder and being itself heritable. The present study adds further support to these two criteria and provides the first firm evidence for a third requisite criterion: co-segregation of the two phenotypes within families (instantiated here as cross-phenotype correlations within twin pairs). Furthermore, these results suggest that this familial coaggregation is primarily due to additive genetic factors. This is the first study conducted on a substantially-sized, genetically-informative sample that includes measures of both phenotypes since Kagan's longitudinal studies of BI (Kagan et al., 1988).

There are additional potential strengths and insights provided by this study design. We modified the BIQ to a retrospective parent report in an attempt to, at least partially, capture the mother's recollection of her child's BI at an earlier age. That version was shown to be similarly reliable and valid as prior versions of the BIQ (however, also see limitations below). Additionally, treating the included phenotypes as quantitative traits provides unique advantages. Statistical power to detect effects with this method is generally increased compared to binary categories. The use of quantitative measures of psychopathology is consistent with recent efforts by the National Institute of Mental Health to shift research towards dimensional constructs that potentially cut across diagnostic boundaries (Cuthbert & Insel, 2013; Insel et al., 2010). Finally, our finding suggests that retrospective parent report of BI assesses a strongly heritable form of inhibited temperament in this age group. This adds genetic evidence to existing rationale for measuring BI in early childhood and provides further support that parent report is a viable approach to assessing the trait when direct laboratory assessment is unavailable (Bishop et al., 2003; Smith et al., 2012).

Limitations

The results of this study should be interpreted in the context of several limitations. First, using a retrospective report of BI could limit the reliability and validity of the measured trait due to recall biases such as parents of high-anxiety pre-adolescents reporting higher levels of early BI (McPhail & Haines, 2010). However, there is little evidence that such potential bias in retrospective reports outweighs their utility (Hardt & Rutter, 2004). This limitation, together with moderate stability of BI over development (Fox et al., 2005), suggests that our assessment likely provides a compromise between past and current inhibition severity. Second, use of the BIQ to index BI only moderately aligns with BI obtained by behavioral observation methods. As already mentioned, however, the BIQ is a reliable measure of inhibited temperament that has been used most often in recent studies of BI (i.e., Bishop et al., 2003; Broreren & Muris, 2010; Clauss et al., 2016; Edwards et al., 2010; Fu et al., 2015; Hudson & Dodd, 2012; Kennedy et al., 2009; Kim et al., 2011; Morales et al., 2016; Taber-Thomas et al., 2016; Vreeke et al., 2012). Third, findings may not be generalizable to a wider population since the sample is made up of entirely Caucasian participants selected to limit genetic variance for the larger aims of the study (Carney et al., 2016). Fourth, twin direction of causation models ideally should examine phenotypes with different sources of variance (Heath et al., 1993; Gillespie & Martin, 2005; Verhulst & Estrabrook, 2012). The sources of variance between BI and social anxiety symptoms were the same (additive genetics and unique environment) but of sufficiently different magnitudes to make the model appropriate for use in the current study. Fifth, it is not possible with the current final direction of causation model to eliminate error from the causal parameter. It is possible that the causal parameter includes measurement error from the BIQ. Sixth, the translational implications are not known. Specifically, it is assumed that the final model chosen, the direction of causation model, has more translational capacity. However, it is possible that the correlated

liabilities model is easier for stakeholders to understand. Given that both models had nearly identical fit, this is a point that needs to be explored in further detail in the future. Finally, the DZ correlations for BI and social anxiety symptoms were low and not significantly different from zero (see Table 6.2). This has also been reported in past studies in which BI was assessed via behavioral observation (Plomin et al., 1993; Robinson et al., 1992; Smith et al., 2012), suggesting this is likely inherent in various measures of BI. There are a few possible explanations for this which we discuss below.

There are several possible explanations for the vastly different MZ and DZ correlations for BI and social anxiety symptoms. The first is sibling contrast effects. These can be ruled out because the means and variances for these phenotypes could be constrained to be equal within twin pairs and across zygosity. The second is a violation of the equal environments assumption (EEA). The EEA, upon which all twin studies are predicated (Neale & Cardon, 1992), states that MZ and DZ twins are equally correlated for their exposure to environmental influences that are of etiologic importance to the trait under study. Thus, while most prior investigations of the EEA have supported its validity (Eaves, Foley, & Silberg, 2003), we cannot rule out the possibility of some level of violation here for BI and social anxiety that is driven by parent report. This could occur if parents of MZ twins inflate similarities of a trait and parents of DZ twins deflate similarities, introducing a pseudo unequal environment across zygosity (Emde et al., 1992). In the current study, this trend is seen for parent-report BI and social anxiety symptoms but not for child self-report measures. Such effects have been noted in a previous study of BI (Smith et al., 2012) and, thus, could present a limitation for any twin study of BI and, possibly, social anxiety. Parent and child measures offer their own unique insights and limitations into underlying psychopathology (Cole, Hoffman, Tram, & Maxwell, 2000), including BI (Muris, Meesters, &

Spinder, 2003) yet are often minimally correlated (Birmaher et al., 1997; Muris et al., 2003), so we obtained reports from both types of informants. After testing more complex multi-rater models, we used the average of the parent and child SCARED scores to provide an optimal compromise in the main analyses.

Conclusions

This chapter (and first part of aim 2) presents the first study to examine the relationship between childhood BI and a broad array of pre-adolescent anxiety symptom clusters from a genetic epidemiological perspective. Of the anxiety symptoms examined, only social anxiety shared a significant proportion of genetic and environmental factors with childhood BI. It also found tentative evidence for a potentially causal pathway that partially explains the relationship between these two phenotypes, expanding extant knowledge about the progression of BI and etiology of social anxiety. Current findings support and extend past research indicating that childhood BI is most robustly a risk factor for later social anxiety despite associations with other anxiety domains. They also suggest that childhood BI and later social anxiety disorder are related but distinct phenotypes, with early BI functioning as a potential developmental endophenotype for later social anxiety. Unfortunately, the full range of translational impact is unclear, namely treatment implications are not known. Yet, such research adds etiological insight into anxiety risk prediction that may be useful for clinicians to consider. Future studies in this line of research could expand the clinical impact of this work by informing clinicians' treatment decisions. For example, the specific mechanisms of the relationship between BI and social anxiety need further exploration, including the developmental progression to social anxiety disorder in adolescence. Such knowledge can help to guide early intervention and prevention efforts aimed at social anxiety outcomes in middle-to-late childhood.

Chapter 7: The Role that Parental Bonding Plays in the Relationship Between Behavioral Inhibition and Social Anxiety[1]

Introduction

Social anxiety disorder typically emerges during the pre-adolescent years (Rapee & Spence, 2004), and by adolescence the lifetime prevalence in the U.S. is 9.1% (Merikangas et al., 2010). Thorough examination of all risk factors, their pathways, and their relative effects is necessary to inform intervention and prevention efforts (Degnan, Almas, Fox, 2010). Behavioral inhibition (BI) is a well-documented, robust childhood risk factor for later development of social anxiety (Clauss & Blackford, 2012; Chronis-Tuscano et al., 2009; Hirshfeld-Becker et al., 2007; Hirshfeld-Becker et al., 2008; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010; Kagan, Reznick, & Snidman, 1987; Muris, van Braken, Arntz, & Schouten, 2011; Schwartz, Snidman, & Kagan, 1999). It persists in approximately 20% of children (Kagan, 2012), and roughly 40% of those who have high BI in childhood later develop social anxiety disorder (Clauss & Blackford, 2012; Clauss, Avery, & Blackford, 2015). The relationship between BI and social anxiety has been thoroughly investigated at both the phenotypic (i.e., Fox et al., 2005) and genetic epidemiological levels (see chapter 6). In fact, previous analyses that examined the relationship between BI and social anxiety revealed a partially causal link between the two (chapter 6; Bourdon et al., 2019).

It has long been thought that parental bonding plays a key role in the development from BI to social anxiety. Examination of the relationship between these three phenotypes to date has been based on behavioral data and uninformed by genetic insights. Specifically, parental bonding is associated with both inhibited temperament and related behaviors (Bayer, Sanson, & Hemphill, 2006; Chorpita et al., 1998; Coplan & Armer, 2007; Hastings et al., 2008; Rapee,

[1]Modified version of the manuscript Bourdon, J. L., Gillespie, N. A., Roberson-Nay, R., & Hettema, J. M. (In Review). The phenotypic and genotypic effects of parental bonding on the relationship between behavioral inhibition and social anxiety. *Journal of Abnormal Child Psychology.*

2004), social anxiety (Arrindell, Emmelkamp, Monsma, & Brilman, 1983; Greco & Morris, 2002), and the trajectory between the two (Fox et al., 2005; Rubin, Burgess, & Hastings, 2002; Degnan et al., 2010). Specifically, parental bonding is believed to have a broadly reciprocal relationship with childhood temperament (Kiff, Lengua, & Zalewski, 2011; Van Zalk & Kerr, 2011), implying a gene-environment interplay. For example, a child's temperament is at least partially due to genes they inherited from their parents (who also raise them). The same heritable components of their personality when manifest may evoke certain responses from their parents, further influencing parental bonding. This reciprocal relationship between temperament and individual differences in parental bonding can in turn can affect expression/development of temperamental outcomes such as BI and later social anxiety. Accordingly, several studies have documented that mothers who are overly anxious tend to have children who are also inhibited and/or anxious (Aktar, Majdandzic, de Vente, & Bogels, 2014; Degnan et al., 2010; Hudson & Dodd, 2012; Rapee, 2004). Such anxiogenic genes and environmental exposures position parenting bonding as an important influence in the development from BI to social anxiety (Fox et al., 2005; Rubin et al., 2002; Degnan et al., 2010). Further, several prevention and intervention that have been effective in reducing later social anxiety and other internalizing syndromes by targeting childhood BI (Chronis-Tuscano et al., 2015; Hirshfeld-Becker et al., 2010; Kennedy, Rapee, & Edwards, 2009; Rapee et al., 2010; Rapee, 2013) have either assessed (Chronis-Tuscano et al., 2015) or targeted (Kennedy et al., 2009) aspects of bonding.

Despite some variation in item content, measures of parental bonding typically include overprotection (intrusion, encouragement of dependence on parent), coldness (lack of involvement, rejection), and authoritarianism (power-assertive parenting, controlling) (Bayer et al., 2006). Despite the studies showing its association with BI and social anxiety, only a few

studies have investigated how parental bonding directly affects the relationship between the two (Degnan et al., 2010). More broadly, parenting has been shown to moderate the relationship between BI and internalizing problems. One study found that toddlers with BI who were exposed to higher levels of permissive parenting had more internalizing symptoms (Williams et al., 2009). More topically, increased maladaptive levels of maternal bonding behaviors (intrusion, control, derision) strengthened the relationship between BI and social reticence (Rubin et al., 2002), and increased maternal over-control lead to higher levels of social anxiety in adolescence among children with elevated BI (Lewis-Morrarty et al., 2012). A limitation of these reports is their inability to determine if the moderating effects of parental bonding are acting on the genetic and/or environmental risks shared between measures of BI and anxiety.

There is a need to further elucidate the moderating role that parental bonding plays between BI and social anxiety specifically (Degnan et al., 2010). To date, no study has investigated the moderating effect of parental bonding in the context of a genetically informative design. Given the strong, potentially causal etiological link between BI and social anxiety (chapter 6; Bourdon et al., 2019) and role of parental bonding, the second part of aim 2 assessed how parental bonding (overprotectiveness, coldness, and authoritarianism) affects this relationship at both the phenotypic and genotypic levels. First, it was hypothesized that the effects of BI on social anxiety will be greater at higher levels of overprotection, coldness, and /or authoritarianism. Second, an exploratory aim examined how the incorporation of parental bonding into a genetic model between BI and social anxiety affected the model fit and total variance explained. These align with the current dissertation's aims 2.2 and 2.3. Findings will contribute to a genetically-informed risk factor model for pediatric social anxiety (see chapter 9) that may eventually inform prevention and intervention efforts.

Methods

Participants

Participants were part of the Virginia Commonwealth University Juvenile Anxiety Study (JAS; Carney et al., 2016). See chapter 5 for an overview of this study and its sample. As a reminder, the final analytical sample included 352 families and 704 children (M_{age} = 11.22; standard deviation [SD_{age}] = 1.41; female = 53%; monozygotic [MZ] = 114 pairs; dizygotic [DZ] = 238 pairs; 88% of full sample).

Measures

This study utilized three measures, a retrospective version of the Behavioral Inhibition Questionnaire (BIQ) (Bishop, Spence, & McDonald, 2003), the Screen for Child Anxiety Related Emotional Disorders – Parent and Child Versions (SCARED) (Birmaher et al., 1997), and the parental bonding instrument (PBI) (Parker, Tupling, & Brown, 1979; Parker, 1990). A series of preliminary analyses confirmed their validity, reliability, and appropriate usage in the primary analyses as discussed in chapter 5. As a reminder, the BIQ and PBI are parent reports and the average of parent and child scores were used for the SCARED in these analyses.

Analyses

Descriptive Statistics and Correlations. Basic descriptive statistics (mean, range) for each variable were calculated as well as the Pearson correlation among all key variables.

Covariates. Univariate linear regression was used to assess for the need to include sex (male, female) as a covariate due to its known association with anxiety domains (Hettema et al., 2005; Rapee, 2004).

Aim 1: Phenotypic Moderation. Per standard moderation analyses (Baron & Kenny, 1986), four linear regressions were tested for each measure of parental bonding

(overprotectiveness, coldness, authoritarianism): (a) social anxiety regressed onto BI; (b) social anxiety regressed onto parental bonding; (c) social anxiety regressed onto both BI and parental bonding; and (d) social anxiety regressed onto the interaction between BI and parental bonding. If the interaction term in this fourth series of regressions is significant, then there is evidence for moderation. There can still be main effects but those do not negate the significant moderation (Baron & Kenny, 1986). Holm's family-wise error rate was used to correct p-values within each scale to account for the number of regressions tested.

The treatment of twins as individuals in the current study means that there are dependent relationships between twins within pairs. This can introduce bias, namely autocorrelation or the phenomenon where the error terms of cases within a variable are dependent on each other (i.e., correlated). This violates ordinary least squares (OLS) estimator assumptions of independence among the error terms of a variable used in a regression. This can often be allowed with OLS estimators, as it only affects the standard errors and not the beta estimates. However, in this study the cause of potential autocorrelation is known *a priori* and can be anticipated and corrected. The Durbin-Watson test was used to assess autocorrelation due to the relatedness between the subjects. If this test was significant for a given regression, then the Cochrane-Orcutt method was applied to correct for the autocorrelation (R package *orcutt*; Spada, Quartagno, Tamburini, & Robinson, 2017). This method iteratively estimates transformed standard errors until convergence.

Aim 2: Genetic Effects. Biometrical genetic structural equation modeling was used to decompose the variance in each phenotype into additive genetics (A), familial environment (C), and unique environment (E) components (Neale & Cardon, 1992). As already stated in chapter 6, previous analyses examining the relationship between BI and social anxiety revealed that a

causal model provided the best fit to the data (Bourdon et al., 2019). Specifically, independent A and E variance components were significant for BI (A = .85; E = .15) and social anxiety (A = .51; E = .49) as was a single directional beta coefficient from BI to social anxiety (β = .047) explicating the developmental relationship between them. The current analyses expanded upon this work by assessing how parental bonding further informs this relationship. This was done in two ways.

First, parental bonding was regressed out of both BI and social anxiety sum scores across participants, and then the final direction of causation biometrical model was re-fit. Specifically, linear regression was used to regress BI and social anxiety separately onto parental bonding. The residuals from each regression were then calculated and used for the biometrical modeling re-fitting. This option allowed for the effect of parental bonding on BI and social anxiety to be taken into account without being explicitly modeled as a covariate.

Second, parental bonding was explicitly added as a variable into the biometrical model as an additional phenotype. Previous studies have noted various biometrical structures and differing variance estimates for the PBI scales, but these studies vary in rater (self, parent) and population (adult male, adult female) (Kendler, 1996; Gillespie et al., 2003; Otowa et al., 2013) and do not overlap with the current sample or measure (parent report of pre-adolescent children of both sexes). To ensure that the correct biometrical structure for PB was added into the model in step 2, preliminary univariate biometrical analyses were conducted to assess the basic ACE structure of the PBI scales (see chapter 5).

In both steps, the amount of social anxiety's variance accounted for by BI in each model was calculated to serve as an indicator of best fit in addition to traditional fit indices (minus

twice the log-likelihood [-2LL] and Akaike Information Criteria [AIC]) (Akaike, 1987; Neale & Cardon, 1992).

Results

Descriptive Statistics, Correlations, and Covariates

The means and ranges for each variable can be found in Table 7.1 and Figure 7.1 (note that histograms for BI and social anxiety are in chapter 6, Figure 6.2). The highest correlations among the variables was between BI and social anxiety ($r = .56$; $p < .001$) (see Table 7.2). Among the parental bonding behaviors, overprotectiveness was the only measure that had any associations with BI ($r = .08$; $p < .05$) and social anxiety ($r = .09$; $p < .05$). Thus, all further analyses were conducted between BI, social anxiety, and overprotectiveness. Sex was significantly associated with BI ($\beta = 5.791$; $p < .05$) and social anxiety ($\beta = .634$; $p < .05$) and was included in analyses due to its effect on the outcome variable (social anxiety). It was not significantly associated with authoritarianism ($\beta = .113$, $p > .05$), coldness ($\beta = -.173$; $p > .05$), or overprotectiveness ($\beta = -.022$; $p > .05$).

Table 7.1. Descriptive information for variables.

Measure	Type	Applicable Age Range	Mean (SD); SE	Median	Sample Range (Min-Max)
Behavioral Inhibition	Parent report	2-6	95.11 (35.30); 1.37	92.00	30 - 199
Social Anxiety	Mean of parent & child report	Current	5.00 (2.75); .11	4.96	0 - 14
Authoritarianism	Parent report	Current	4.01 (2.18); .08	4.00	0 - 10
Coldness	Parent report	Current	19.47 (2.16); .08	20.00	9 - 21
Overprotectiveness	Parent report	Current	3.46 (2.52); .10	3.00	0 - 14

Notes: Sample range is not the total possible range. Coldness reflects warmth but is worded to be consistent with the other scales.

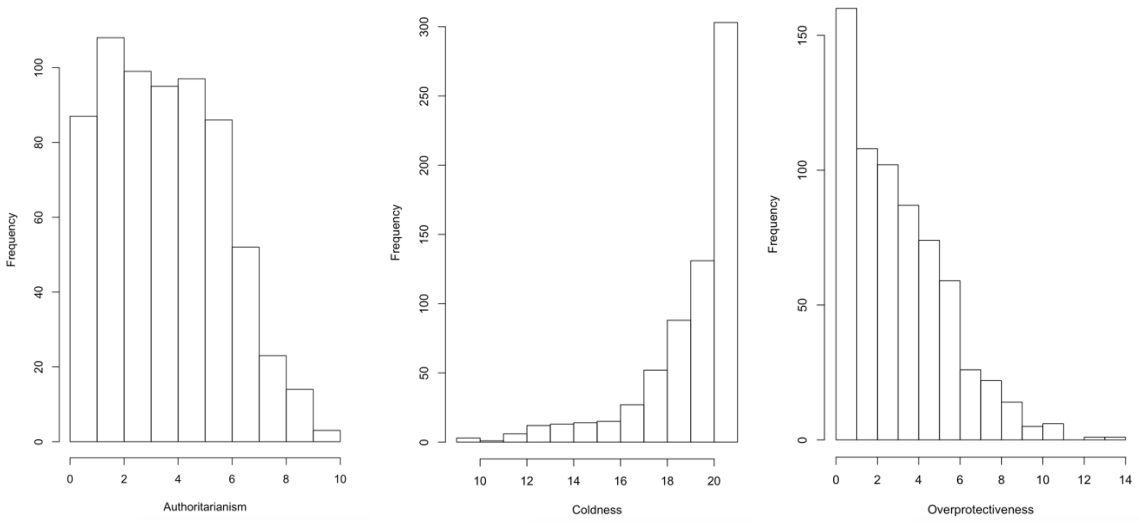

Figure 7.1. Histograms of parental bonding scale variables.

Table 7.2. Correlations between key variables.

	Behavioral Inhibition	Social Anxiety	Authoritarianism	Coldness	Protectiveness
Behavioral Inhibition	--				
Social Anxiety	.56**	--			
Authoritarianism	.03	.01	--		
Coldness	.07	.06	.15**	--	
Overprotectiveness	.08*	.09*	.30**	-.03	--

*p <.05; **p<.001

Aim 1: Phenotypic Moderation

After correcting for multiple tests, BI (β_{BI} = .044; p < .001) independently and significantly predicted social anxiety but overprotectiveness did not (β_{OP} = .090; p > .05) (see Table 7.3). Accordingly, model 3 revealed no effect of overprotectiveness on social anxiety when combined with BI (β_{OP} = .044; p > .05), whereas the effect of BI remained significant (β_{BI} = .043; p < .001). Finally, Model 4 confirmed that overprotectiveness does not significantly interact with BI to predict anxiety (β_{BI*OP} = -.001; p > .05).

Table 7.3. Moderation analysis of the influence of behavioral inhibition and overprotectiveness on social anxiety disorder symptoms.

	Estimate (95% Confidence Interval)	Standard Error	*p*-value (Corrected)	Durbin-Watson Value
Model 1: Behavioral Inhibition				
Behavioral Inhibition	**.044 (.039 - .049)**	**.002**	**<.001 (<.001)**	DW = 1.992, $p = 0.456$
Sex	.311 (-.037 - .660)	.178	.080 (.452)	
Model 2: Protectiveness				
Overprotectiveness	.090 (.005 - .175)	.043	.038 (.268)	DW = 2.006, $p = .523$
Sex	.586 (.166 – 1.006)	.214	.006 (.052)	
Model 3: Behavioral Inhibition and Overprotectiveness				
Behavioral Inhibition	**.043 (.039 - .048)**	**.002**	**<.001 (<.001)**	DW = 1.992, $p = .454$
Overprotectiveness	.044 (-.026 - .115)	.036	.221 (.452)	
Sex	.316 (-.032 - .664)	.178	.076 (.452)	
Model 4: Behavioral Inhibition * Overprotectiveness				
Behavioral Inhibition	**.048 (.040 - .056)**	**.004**	**<.001 (<.001)**	DW = 1.991, $p = .450$
Overprotectiveness	.179 (-.018 - .375)	.100	.075 (.452)	
Behavioral Inhibition *Overprotectiveness	-.001 (-.003 - .001)	.001	.152 (.452)	
Sex	.293 (-.056 - .643)	.178	.101 (.452)	

Note: All models violated the Durbin-Watson test for autocorrelation ($p < .001$) and were corrected. Models presented in this table have all been corrected for autocorrelation and multiple testing. The dependent variable in all analyses was social anxiety disorder symptoms.

* indicates moderation

Bolded estimates are significant at $p < 0.01$

Aim 2: Genetic Effects

Direction of Causation Model with Overprotectiveness Regressed Out. After regressing the contribution of overprotectiveness to the variation in BI and social anxiety and refitting the causal BI-to-social anxiety model, the model using this residualized data fit better (AIC = 6216.626) than the original model (AIC = 6480.200) that did not remove the contribution of overprotectiveness. This modified model accounted for nearly the same amount of social anxiety's variance (37% compared to 38%) (see Chapter 6; Bourdon et al., 2019). There was no significant effect on the genetic or environmental variance components of BI or social anxiety in the residualized model. See Table 7.4 for the full twin modeling results.

Direction of Causation with Overprotectiveness Added. Univariate biometrical modeling for overprotectiveness revealed significant familial (C = .81) and unique (E = .19) environmental components (see chapter 5). Thus, for the second model tested, overprotectiveness with these two latent factors were added to the original BI-to-social anxiety direction of causation model. The final fit of this model included a regression coefficient between BI and overprotectiveness but not between overprotectiveness and social anxiety. This model fit was worse (AIC = 7810.449) than the original one (AIC = 6480.200). However, it accounted for more of SOC's variance (43% compared to 38%). Table 7.4 and Figure 7.2 display the results for this aim.

Table 7.4. Model fit statistics and final parameter estimates for the direction of causation models between behavioral inhibition, overprotectiveness, and social anxiety disorder symptoms.

Model	EP	-2LL	DF	AIC	Δ LL	Δ DF	*p*	A_{BI}	A_{SOC}	C_{OP}	E_{BI}	E_{OP}	E_{SOC}	BI_2SOC	BI_2OP	OP_2SOC
Best-fitting direction of causation model between behavioral inhibition and social anxiety																
1. Original model	7	8976.200	1248	6480.200	--	--	--	.85	.51	--	.15	--	.49	.047	--	--
New model with protectiveness regressed out																
2. Modified model	**7**	**8628.539**	**1205**	**6218.539**	**--**	**--**	**--**	**.80**	**.49**	**--**	**.21**	**--**	**.51**	**.046**	**--**	**--**
New model with protectiveness added																
3. Original model + CE for overprotectiveness + BI_2PB + PB_2SOC	12	11533.852	1861	7811.852	--	--	--	.85	.51	.81	.15	.19	.49	.047	.004	.031
3a. Drop BI_2PB, PB_2SOC	10	11539.538	1863	7813.539	5.685	2	.058	.85	.51	.82	.15	.18	.49	.047	--	--
3b. Drop BI_2PB	11	11538.973	1862	7814.973	5.120	1	.024	.85	.51	.82	.15	.18	.49	.047	--	.030
3c. Drop PB_2SOC *	11	11534.449	1962	7810.449	.560	1	.440	.85	.51	.81	.15	.19	.49	.047	.004	--

Notes: A = additive genetics; C = familial environment; E = unique environment; BI = behavioral inhibition; SOC = social anxiety disorder symptoms; OP = overprotectiveness (parental bonding); BI_2SOC = regression path from behavioral inhibition to social anxiety; BI_2PB = regression path from behavioral inhibition to protectiveness; PB_2SOC = regression path from protectiveness to social anxiety; EP = estimated parameters; -2LL = negative twice the log likelihood; DF = degrees of freedom; AIC = Akaike information criteria; *p* = p-value statistic.

Sex was treated as a covariate (definition variable on the means) in all analyses

* Indicates best-fitting model in that section

Bold indicates best overall fitting model

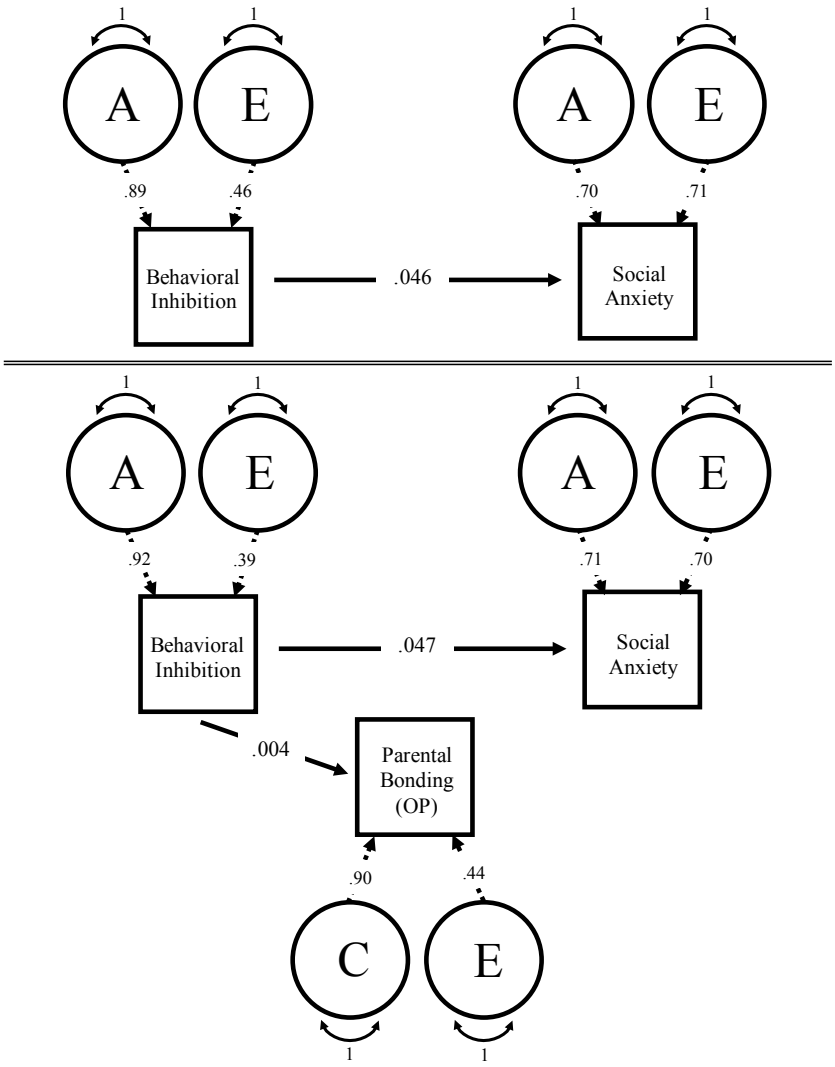

Figure 7.2. Top: Modified direction of causation model between BI and social anxiety that takes overprotectiveness into account (regressed out of both phenotypes - residualized model). Bottom: Final model that includes overprotectiveness (OP) with BI and social anxiety.

Discussion

This was the first study to examine the effects of parental bonding on the relationship between BI and social anxiety at both the phenotypic and genetic levels in a large sample of pre-adolescents. Among the three parental bonding dimensions, only overprotectiveness correlated with BI and social anxiety. This was not surprising given that overprotection has consistently correlated more strongly with measures of BI and social anxiety (Bayer et al., 2006; Rubin 2002;

Rapee, Schniering, & Hudson, 2009). Nevertheless, other studies have found associations between these phenotypes and authoritarianism (often referred to as "control") and coldness (Fox et al., 2005; Lewis-Morrarty et al., 2012; Rapee, 2004; Rapee et al., 2009). Moreover, there was no statistical evidence that overprotectiveness moderates the causal pathway from BI to social anxiety although it needed to be taken into account when examining the genetic etiological pathway from BI to social anxiety.

The first hypothesis that parental bonding would moderate the effect of BI on social anxiety was not supported. While two past studies have found a moderating effect of parenting on the relationship between these two phenotypes, these studies did not use the same standardized measure (the PBI; Parker et al., 1979) and thus had different conceptualizations of bonding (Lewis-Morrartay et al., 2012; Rubin et al., 2002), which could account for the discrepant findings. Also, these studies relied on much smaller sample sizes (Lewis-Morrartay et al., 2012; Rubin et al., 2002). Nevertheless, some interesting trends should be noted related to this first hypothesis. Of the three parental bonding dimensions, only overprotectiveness had small phenotypic correlations with BI and social anxiety. Yet, the effect of overprotectiveness on social anxiety was non-significant when analyzed independently and also when jointly analyzed with BI and controlling for sex. BI consistently exerted significant, direct effects on social anxiety. Contrary to previous non-genetically informed studies based on smaller samples, the findings here imply that the influence of parental bonding is of far less importance than inhibited temperament in the development of social anxiety. These phenotypic findings provide clarity to the small literature on this topic.

The second exploratory aim sought to examine the genetic effects of parental bonding in the relationship between BI and social anxiety. This was done in two different ways. The first

way regressed overprotectiveness out of the two key phenotypes and re-fit the models from chapter 6. This residualized model was a better fit to the data than the model that did not take overprotectiveness into account, but the genetic and environmental variance estimates were almost identical and BI accounted for about the same amount of social anxiety's variance. The second model added overprotectiveness as a third variable in the model and was not a better fit to the data. Overall, these findings indicate that the evidence of a causal relationship from BI to social anxiety was not confounded by parental bonding, although taking it into consideration when examining this relationship may be best. The weak phenotypic correlations between overprotectiveness and the other two traits is of little consequence when examining the development of BI to social anxiety from a research or clinical perspective. There is not much of an impact of taking overprotectiveness into consideration at the genetic level.

Comparison to Past Association Studies

The current findings provide evidence that the causal relationship from BI to social anxiety was not confounded by parental bonding in addition to finding little correlation among the three phenotypes. This is antithesis to the previously noted strong links between parental bonding and BI (Bayer et al., 2006; Chorpita et al., 1998; Coplan & Armer, 2007; Hastings et al., 2008; Rapee, 2004), social anxiety (Arrindell et al., 1983; Greco & Morris, 2002), and the development between the two (Degnan et al., 2010; Fox et al., 2005; Lewis-Morrarty et al., 2012; Rubin et al., 2002; Williams et al., 2009). These disparate finding can likely be somewhat explained by differences in sample age, instruments used, and classification of the sample (i.e., high/low BI). First, in regard to age, most studies that previously found an association between parental bonding and either BI, social anxiety, or both assessed young children that were younger than the current sample (infancy through age 8 across the studies) (Bayer et al., 2006; Greco &

Morris, 2002; Hastings et al., 2008; Rubin et al., 2002). While BI was retroactively assessed for children aged 2-6 in the current sample, anxiety and parental bonding were assessed concurrently with the children's current ages of 8-13 years. This developmental shift from young childhood to pre-adolescence might bring with it a decrease in the importance of parental bonding in the development of social anxiety.

Second, there was much variation in how parental bonding and BI were assessed across past studies. Only one study also used the PBI (Greco & Morris, 2002). The other studies had some overlapping parental bonding constructs with the current study (i.e., overprotection, coldness), but they were typically measured via behavioral observation instead of a paper-based assessment (Bayer et al., 2006; Hastings et al., 2008; Lewis-Morrarty et al., 2012; Rubin et al., 2002; Williams et al., 2009). BI was not assessed the same way in any of the past studies as with the current one. Three studies conceptualized of BI in the same way but they used the behavioral observation method to assess it (Lewis-Morrarty et al., 2012; Rubin et al., 2002; Williams et al., 2009). The other studies measured temperamental inhibition, social wariness, or similar behaviors via behavioral observation (Bayer et al., 2006; Hastings et al., 2008). Some studies also did not use anxiety as an outcome measure but broader internalizing problems or social reticence (Hastings et al., 2008; Rubin et al., 2002; Williams et al., 2009). Finally, a couple of the studies separated children into categories based on their inhibition or anxiety scores (Greco & Morris, 2002; Rubin et al., 2002) which the current study did not do due to the desire to assess dimension constructs of mental health concerns and the fact that the JAS draws from a community sample, not a case-control sample.

Comparison to Past Prevention/Intervention Studies

A few of these inconsistencies in study design and analysis are also present in studies assessing prevention/intervention efforts for anxiety. The current findings imply that if BI symptoms are present, prevention/intervention efforts should focus on BI rather than parental bonding in this pre-adolescent age group. Some programs have successfully reduced internalizing symptoms by targeting childhood BI or related behaviors (Chronis-Tuscano et al., 2015; Hirshfeld-Becker et al., 2010) as well as both BI and parental bonding simultaneously (Bayer et al., 2010; Kennedy et al., 2009; Rapee et al., 2010; Rapee, 2013). One of the studies targeting only BI also found an effect of parental warmth (the opposite of coldness) in the reduction of childhood anxiety among children with high BI, but they found no effect of negative control (authoritarianism) and did not assess overprotection (Chronis-Tuscano et al., 2015). This study did not specifically target parental bonding but simply assessed its role in the relationship between BI and anxiety in children. Thus, the level of success of the prevention can still be attributed to targeting BI.

The studies that targeted both BI and parental bonding were from the same series of randomized control trials (Kennedy et al., 2009; Rapee et al., 2010; Rapee, 2013) or were a review (Bayer et al., 2010). Here, overprotection was part of the prevention program for anxiety. Children with high BI were selected into the trials during young childhood and in addition to educating parents on the development from BI to anxiety, parents were taught about overprotectiveness and ways to reduce it. Parents' levels of overprotectiveness were not assessed before or after the trials, though, so it is impossible to say which educational component of the prevention program made it effective. It is possible that overprotectiveness education had little effect and the main effects came from educating parents about the development of anxiety as a whole.

Limitations

A key limitation compared to some studies is the retrospective parental report of BI instead of a longitudinal behavioral observation. Using a retrospective report of BI could limit the reliability and validity of the measured trait due to recall biases such as parents of high-anxiety pre-adolescents reporting higher levels of early BI (McPhail & Haines, 2010). However, the BI measure used in this study has been used in neurophysiological, genetically-informed, and prevention studies (Bourdon et al., 2019; Clauss et al., 2016; Edwards, Rapee, & Kennedy, 2010; Fu et al., 2015; Kennedy et al., 2009). However, there is little evidence that such potential bias in retrospective reports outweighs their utility (Hardt & Rutter, 2004). The current study also did not explicitly test genetic correlations or model reciprocal relationships in the exploratory aim. Future studies should consider explicitly assessing gene-environment interplay once those methods are more robust (e.g., passive gene-environment correlation). As discussed, there are also multiple discrepancies across reports in terms of sample ages, measurements, and varying thresholds of classification (e.g., high vs low BI) that might explain the lack of findings noted in past studies. Finally, this study did not re-fit all of the models run in chapter 6 with overprotectiveness regressed out. There is little reason to believe that it would significantly changing findings from those analyses given the improved but still similar fit estimates.

Conclusions

The current findings significantly expand past research on the development from BI to social anxiety by examining the influence of parental bonding and serve as the second part to aim 2 of this dissertation (see chapter 6 for part 1 of aim 2). At the phenotypic level, overprotectiveness was weakly correlated with these two variables and does not appear to moderate the relationship between them. At the genetic level, accounting for the minor

contribution of overprotectiveness in the causal model between BI and social anxiety significantly improved fit to these data, but the parameter estimates and variance accounted for in the model did not change. It is possible that such findings could influence translational prevention/intervention efforts aimed at pre-adolescent social anxiety.

Chapter 8: A Neurologically-Informed Insight into The Relationship Between Behavioral Inhibition and Social Anxiety

Introduction

Thoroughly understanding the relationship between behavioral inhibition (BI) and social anxiety is key to prevention and intervention efforts, as 43% of children with BI later develop social anxiety (Clauss & Blackford, 2012; Clauss, Avery, & Blackford, 2015). While associated factors surrounding the relationship at the phenotypic level have been well documented (i.e., developmental trajectories, risk predictions; Clauss & Blackford, 2012; Chronis-Tuscano et al., 2009; Hirshfeld-Becker et al., 2007; Hirshfeld-Becker et al., 2008; Essex, Klein, Slattery, Goldsmith, & Kalin, 2010; Kagan, Reznick, & Snidman, 1988; Muris, van Braken, Arntz, & Schouten, 2011; Schwartz, Snidman, & Kagan, 1999), the specific mechanisms involved are not thoroughly understood. Additional inquiry ought to include biological domains, namely genetic and neurophysiological factors that play a role in this relationship. Results from chapter 6 indicated the importance of shared genetic and environmental variance between BI and social anxiety as well as a causal path from BI to social anxiety (aim 2.1). These results encourage the study of the biological measures that may intervene between BI and social anxiety, such as brain function.

Inquiries into the neurophysiological level of this relationship remain unexplored. Amygdala activation has long been thought to play a role in the development from BI to social anxiety (Kagan & Snidman, 1991; Fox et al., 2005). Specifically, the amygdala has been implicated in animal studies for behaviors related to BI in humans (Kagan & Snidman, 1991). One circuit involving the amygdala relates to motor response in animals that are often seen in infants and toddlers with BI (e.g., tense muscles). The second circuit involving the amygdala has

been shown to be activated in animals who are in distress (e.g., crying), which also relates to infant and toddler BI. Thus, amygdala sensitivity (i.e., an overactive amygdala) among those with BI has long been an assumption in the field, as stated by Kagan himself, for these reasons as well as the brain area's association with fear (Kagan & Snidman, 1991; Fox et al., 2005). This amygdala sensitivity sets the stage for an enhanced fear response to people, places, and objects that are novel (Fox et al., 2005). Emotion reactivity is a key way to tap amygdala activation and is itself a logical place to begin investigating the relationship between BI and social anxiety from a neurophysiological perspective.

Neurophysiology of Social Anxiety and Behavioral Inhibition

Emotion Reactivity. Emotion reactivity is the human response to highly stimulating emotions, namely fear and threat (Hariri et al., 2002). This reactivity likely stems from evolutionary necessity and has been shown in response to emotionally-charged faces and threatening or fearful scenes such as snakes and explosions (Hariri et al., 2002). A validated method of assessing emotion reactivity is to directly activate the amygdala using face-specific emotional responses (i.e., the emotional face activation task [EFAT]; Hariri et al., 2002; Phan et al., 2008; Swartz et al., 2014).

Social Anxiety. Heightened emotion reactivity, as assessed via amygdala activation, has long been implicated in anxiety broadly (Ressler & Mayberg, 2007) and is robustly associated with social anxiety in adults (Birbaumer et al., 1998; Cooney et al., 2006; Evans et al., 2008; Phan, Fitzgerald, Nathan, & Tancer, 2005; Stein et al., 2002; Stein et al., 2007). The association between social anxiety and emotion reactivity via amygdala activation has been shown across tasks, whether engaging participants' attention directly in the task (i.e., asking for a response during imaging data collection; Cooney et al., 2006; Phan et al., 2005; Stein et al., 2002; 2007;

Swartz et al., 2014) or passively (i.e., passive view of images during task; Birbaumer et al., 1998; Evans et al., 2008; Killgore & Yurgelun-Todd, 2005). Most evidence of the robust relationship between emotional reactivity and social anxiety has been found in adult samples (Birbaumer et al., 1998; Cooney et al., 2006; Evans et al., 2008; Phan et al., 2005; Stein et al., 2002; Stein et al., 2007), although two studies have examined this in adolescents to mixed effects (Killgore & Yurgelun-Todd, 2005; Swartz et al., 2014). While there is a lack of evidence associating emotion reactivity and anxiety overall (Swartz et al., 2014), an association has been found between heightened amygdala activation in response to the passive viewing of threatening faces and social dimensions of anxiety (Killgore & Yurgelun-Todd, 2005). To date, evidence of this effect is lacking for younger samples, raising the question of when this neurophysiological response to emotions among those with social anxiety develops. The current study will seek to replicate past findings (Killgore & Yurgelun-Todd, 2005) of an association between increasing social anxiety symptoms and emotion reactivity in pre-adolescents using a direct measure of the amygdala, the EFAT.

Behavioral Inhibition. Comparatively, associations between BI and emotion reactivity have been mixed and are possibly task-dependent rather than due to consistent neurological patterns across individuals with BI. Only a handful of studies examining the neurophysiological correlates of BI have assessed amygdala activation. Methods have been split across studies between passive viewing of faces (Schwartz et al., 2003), attentional tasks focused on threat (Fu, Taber-Thomas, & Perez-Edgar, 2017; Jarcho et al., 2014; Perez-Edgar et al., 2007), and anticipation tasks (Clauss et al., 2016) to assess amygdala activation. Only some of these studies (Clauss et al., 2016; Perez-Edgar et al., 2007; Schwartz et al., 2003) probed the amygdala via emotional reactivity and are thus the most relevant to the current study's second aim of

examining the correlation between levels of BI and emotion reactivity using a direct amygdala activation task (the EFAT).

Specifically, heightened amygdala activation in individuals with a history of BI and those with currently high levels of the trait across development have been found (Perez-Edgar et al., 2007; Schwartz et al., 2003). In adults previously diagnosed as having high BI in toddlerhood, such activation was evident when passively viewing novel versus familiar faces (Schwartz et al., 2003). When attending to internal levels of threat while viewing faces, it has been noted that adolescents previously identified as having high BI had heightened amygdala activation regardless of the emotion of the face (Perez-Edgar, 2007). Finally, a similar trend was recently noted for children with currently high levels of BI who were anticipating faces regardless of emotion (Clauss et al, 2016).

It must be noted, however, that neurophysiological studies designed to elicit attentional bias toward threat and not emotion reactivity have not found heightened amygdala response in those with BI or a history of BI. Specifically, a dot probe task (Fu et al., 2017; Morales, Taber-Thomas, & Perez-Edgar, 2017) in adolescents and a unique attentional task in adults (Jarcho et al., 2014) did not elicit amygdala activation, although other areas of the brain were engaged during these tasks. Thus, paradigms that assess emotion reactivity and the amygdala directly, as opposed to attentional tasks, may be key to understanding the role of neurological mechanisms of BI and its relationship with social anxiety. The use of differing methods when examining BI and amygdala activation in prior studies likely contributes to the variability of findings.

Social Anxiety and Behavioral Inhibition. Of studies that have found significantly heightened amygdala activation in those with elevated BI (Clauss et al., 2016; Perez-Edgar et al., 2007; Schwartz et al., 2003), findings were not emotion-specific. Coupled with the fact that a

key component of BI is novelty more so than threat (Fox et al., 2005), there is reason to believe that amygdala activation in those with BI would be more global to faces as a whole, as well as possibly be more pronounced during the beginning of an imaging task (similar to findings from individuals with social anxiety). Additionally, it has been established that emotion reactivity among those with social anxiety is emotion-specific to threat, fear, or other negative valence stimuli. Therefore, it follows that there are two possible mechanisms through which amygdala activation developmentally changes in the progression of BI to social anxiety: (a) individuals with a history of BI eventually become more selective toward threatening faces, or (b) individuals with social anxiety who have a history of BI generally show broader emotional responses but extant studies have not differentiated such individuals from those without a history of BI. Accordingly, it is possible that emotion reactivity moderates the relationship between BI and social anxiety. Due to the fact that both BI and social anxiety have been associated with emotion reactivity, a mediation model is not being tested. This model would assume a causal path from BI to emotion reactivity to social anxiety, which does not appear to be the case. Instead, a moderation effect is most likely whereby the effect of BI on social anxiety changes depending on the level of emotion reactivity.

Study Hypotheses

No study to date has used emotion reactivity as a way to examine the neurophysiological relationship between childhood BI and later social anxiety, although many studies have investigated reactivity in each construct separately. The purpose of the current study (aim 3 of this dissertation) is to assess the neurophysiological mechanisms between childhood BI and pre-adolescent social anxiety with the following hypotheses. First, heightened emotion reactivity to threatening faces will be correlated with increased symptoms of social anxiety in pre-

adolescents, a replication of past findings. Second, heightened emotion reactivity to any face (regardless of emotion) will be positively associated with early childhood symptoms of BI. Third, emotion reactivity to threatening faces will moderate the relationship between BI and social anxiety such that higher levels of reactivity to threatening faces will lead to a stronger relationship. These align with the dissertation aims 3.1, 3.2, and 3.3, respectively, and will inform the overall risk factor model for social anxiety disorder (see chapter 9).

Methods

Participants

Participants were part of the Virginia Commonwealth University Juvenile Anxiety Study (JAS; Carney et al., 2016). See chapter 5 for an overview of this study and its sample. A subset of participants from the JAS were invited back to be part of a pilot study investigating the relationship between negative valence systems (NVS) and internalizing disorders at the neurophysiological level using functional magnetic resonance imaging (fMRI). This subset of participants comprises the current study (N = 41; M_{age} = 11; female = 59%). Note that participants in this study are part of twin pairs but were treated as individuals for these analyses due to the small number of pairs (monozygotic = 11 twins; dizygotic = 29 twins; singleton = 1 individual).

Behavioral Measures

Two behavioral measures were used in the current study: The Screen for Child Anxiety Related Disorders – Parent and Child Versions (SCARED; Birmaher et al., 1997) and a retrospective version of the Behavioral Inhibition Questionnaire (BIQ; Bishop, Spence, & McDonald, 2003). The SCARED subscale of interest was the social anxiety scale. See chapter 5 for more details about both of these measures.

Differences Between Samples

There were no statistically significant demographic or behavioral differences between the full JAS sample and the fMRI-specific sample recruited for the current study. Differences in age (t = 1.717; df = 42.977; p = .093), sex (t = -.807; df = 43.716; p = .424), SCARED social anxiety subscale score (t = .953; df = 42.445; p = .346), and BIQ score (t = .831; df = 45.428; p = .410) were assessed using independent sample t-tests. While the participants included in the current sample were also part of the larger JAS study, the samples were treated as independent due to their size and the fact that measures were not assessed at different time points. The purpose was to see if restricting the sample to 41 participants biased the behavioral measures, which it does not appear to have done.

Neuroimaging Acquisition

All fMRI data was collected at the VCU Collaborative Advanced Research Imaging facility using a 3.0T Philips Ingenia magnetic resonance image scanner with a 32-channel head coil. Imaging protocol included Series 5 Face Match with the following parameter settings: flip angle = 68 degrees; FOV = 25.6cm; slices = 38; slice thickness = 3mm; 256x256 matrix; repetition time = 8.1ms; echo time = 3.7ms. Data underwent standard preprocessing which included illuminating related voxels at voxelwise $p < .001$ false discovery rate (FDR) threshold and then a $p < .05$ FDR threshold across all images. The regions of interest were voxels covering the right and left amygdala.

Neuroimaging Measures

fMRI data was collected while participants completed the Emotional Face Assessment Task (EFAT) (Hariri et al., 2002). The EFAT was programmed and presented to participants using E-Prime Version 2.0. The EFAT uses faces from a standardized sample (Gur et al., 2002)

and has been well-validated across multiple studies as a way to directly assess amygdala activation via emotion reactivity (Hariri et al., 2002; Swartz et al., 2014; Phan et al., 2008). The EFAT consisted of six 20 second trials within each block. Each full block was repeated three times each over two runs. During each trial, participants were shown either four series of faces or shapes. These objects were presented in a triangular manner. One object was in the top row and two were in the second row (see Figure 8.1).

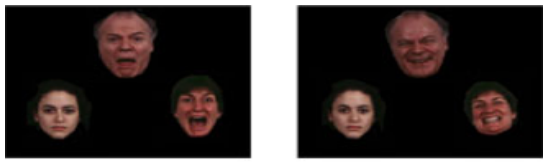

Figure 8.1. Example of two trials in the EFAT.

Participants were instructed to match the object at the top to one of the objects on the bottom. For face conditions, participants were instructed to match based on the emotion of the face in the top row. Matching faces were one of four emotions: angry, fearful, sad, or happy. The non-matching face was always neutral. The identity of each face was never the same within a trial. Shape trials were the same as face trials except participants matched based on shape, which was either a circle, square, or triangle. Emotion and shape trials were counter-balanced across participants and data was collapsed across runs. The accuracy and reaction time of each response was recorded with a button box. The variables of interest to this study included blood oxygen level dependent (BOLD) signals in the right or left amygdala to: (a) faces overall, (b) fear, and (c) threat (see Table 8.1). These BOLD signals measure blood flow to active areas of the brain, changing the ratio of oxygenated to deoxygenated blood that can be detected using magnetic imaging.

Table 8.1. Overview of neuroimaging variables.		
Variable	Subtraction	Amygdala Activation Representation
Left Hemisphere		
Faces overall	Faces – Shapes	Overall emotion reactivity
Fear	Fear – Happy	Emotion reactivity specific to fear
Threat	(Fear + Anger) – Happy	Emotion reactivity specific to threat
Right Hemisphere		
Faces overall	Faces – Shapes	Overall emotion reactivity
Fear	Fear – Happy	Emotion reactivity specific to fear
Threat	(Fear + Anger) – Happy	Emotion reactivity specific to threat

Statistical Analyses

Differences Across Time. After both neuroimaging runs were combined, significant differences and equal variance were assessed between the 1st third, 2nd third, and 3rd third of responses for each imaging variable (left/right faces overall, fear, threat) using an independent samples t-test. This was done to assess potential sensitization to the task whereby the signal would become weaker over time. If no differences were detected within a variable, then the data across time could be combined in further analyses.

Basic Descriptives and Normality. The mean, standard deviation, and range were noted for all variables of interest (BOLD left/right faces overall, fear, and threat; social anxiety; BI). Subsequently, variables were assessed for normality using the Shapiro-Wilks test of normality. Any variables with a non-normal distribution were log-transformed due to the small sample size of this study. (Note that variables were not log-transformed for other dissertation aims that used the same data because those sample sizes were larger, eliminating the need to transform because the tests are more robust against skew in larger samples) (Field, Miles, & Field, 2012).

Covariates. Age and sex were tested as potential covariates of all key variables using multiple linear regressions. Significant covariates were incorporated into later analyses as appropriate.

Main Analyses. It must be noted that the current study took a dimensional approach to psychopathology, treating symptoms continuously instead of categorizing pre-adolescents as having high vs. low BI and social anxiety vs. no anxiety. This is atypical of imaging studies and thus, analytic approaches not usually found in such projects were used. To replicate past findings that heightened emotion reactivity to threatening faces is correlated with increased symptoms of social anxiety, Pearson correlation coefficient was estimated between the BOLD threat response and the SCARED social anxiety sum score. Similarly, a Spearman correlation coefficient was used to determine the degree to which heightened BOLD emotion reactivity to any face, using the overall faces variable, was associated with symptoms of BI. Finally, a moderation relationship was tested via three general linear regression models: social anxiety regressed onto BI, social anxiety regressed onto overall face activation, and social anxiety regressed onto BI, overall face activation, and the interaction of the two (Baron & Kenny, 1986).

Autocorrelation. The treatment of twins as individuals in the current study means that there are dependent relationships between twins within pairs. This can introduce bias, namely autocorrelation or the phenomenon where the error terms of cases within a variable are dependent on each other (i.e., correlated). This violates ordinary least squares (OLS) estimator assumptions of independence among the error terms of a variable used in a regression. This can often be allowed with OLS estimators, as it only affects the standard errors and not the beta estimates. However, in this study the cause of potential autocorrelation is known *a priori* and can be anticipated and corrected. The Durbin-Watson test was used to test for autocorrelations in all regression models and corrected with the Cochrane-Orcutt method (R package *orcutt*; Spada, Quartagno, Tamburini, & Robinson, 2017). This method iteratively estimates transformed standard errors until convergence.

Results

All statistical analyses were performed in the R software package (version 1.0.136; R Development Core Team, 2015). Pre-processing of fMRI data was done using analysis of functional neuroimages (AFNI; https://afni.nimh.nih.gov/) and Freesurfer.

Descriptive Statistics

Differences Across Time. Testing for significant differences across each "third" of BOLD signals both within and across hemispheres revealed few significant differences (see Table 8.2). Holm's Family-Wise Error Rate (FWER) method was used to correct for the fact that three tests were run per variable. For faces overall, there were no significant differences across time in either hemisphere, and data from all three time points was used in subsequent analyses. The same was true for threat and fear in the left hemisphere but not the right hemisphere. For the right activation from these latter two variables, significant differences were evident, and only the first and second time points were collapsed and used in subsequent analyses.

Table 8.2. Results of testing for significant differences across time points within hemispheres.

Variable	Left Amygdala			Right Amygdala		
	1st vs. 2nd	2nd vs. 3rd	3rd vs. 1st	1st vs. 2nd	2nd vs. 3rd	3rd vs. 1st
Faces overall	*t* = .793 df = 79.854 *p* = .430 *p-c* = 1.000	*t* = -.119 df = 78.858 *p* = .906 *p-c* = 1.000	*t* = .621 df = 77.949 *p* = .536 *p-c* = 1.000	*t* = .297 df = 77.764 *p* = .767 *p-c* = 1.000	*t* = .537 df = 79.914 *p* = .593 *p-c* = 1.000	*t* = .870 df = 76.8 *p* = .387 *p-c* = 1.000
Fear	*t* = .514 df = 2.000 *p* = .880 *p-c* = 1.000	*t* = .689 df = 79.564 *p* = .493 *p-c* = 1.000	*t* = .888 df = 79.889 *p* = .377 *p-c* = 1.000	*t* = -.608 df = 78.577 *p* = .545 *p-c* = .545	*t* = 2.928 df = 79.834 ***p* = .004** ***p-c* = .013**	*t* = 2.517 df = 77.514 ***p* = .014** ***p-c* = .028**
Threat	*t* = -.186 df = 79.659 *p* = .853 *p-c* = .853	*t* = 1.131 df = 79.999 *p* = .262 *p-c* = .785	*t* = .981 df = 79.632 *p* = .330 *p-c* = .785	*t* = -.727 df = 79.558 *p* = .469 *p-c* = .469	*t* = 3.086 df = 78.913 ***p* = .003** ***p-c* = .008**	*t* = 2.505 df = 77.206 ***p* = .015** ***p-c* = .003**

Notes: *p*-c indicates corrected *p*-value using Holm's FWER method. **Bold** indicates significance.

Basic Descriptives and Normality. The mean, standard deviation, standard error, and range for all of the main variables (neuroimaging and behavioral) can be found in Table 8.3.

Table 8.3. Descriptive information for behavioral and neuroimaging variables.

Measure	Type	Applicable Age Range	Mean (SD); SE	Median	Range (Min-Max)
Behavioral Inhibition	Behavioral	2-6	90.54 (34.16); 5.34	88.00	30 - 186
Social Anxiety	Behavioral	9-13	4.51 (3.21); .51	4.00	0 - 13.5
Faces Overall – Left	Neuroimaging	Current	.13 (.10); .02	.14	-.44 - .41
Faces Overall – Right	Neuroimaging	Current	.17 (.12); .02	.17	-.11 - .39
Fear – Left	Neuroimaging	Current	.02 (.23); .04	.10	-.40 - .50
Fear – Right	Neuroimaging	Current	.04 (.22); .03	.02	-.40 - .69
Threat – Left	Neuroimaging	Current	.02 (.19); .03	.07	-.44 - .41
Threat – Right	Neuroimaging	Current	.02 (.19); .03	.00	-.33 - .55

A significant Shapiro-Wilks test of normality indicates significant difference from a normal distribution and hence non-normality. Only BI scores were not normally distributed ($W = .934$; $p < .05$; see Table 8.4). To account for this, a Spearman test was used with correlations involving BI, and the data was log-transformed for use in regression analyses only (not correlations). Specifically, Spearman correlation coefficient is appropriate for skewed distributions, however, OLS is sensitive to non-normality.

Table 8.4. Shapiro-Wilks test for normality.

Measure	*W*	*p*
Behavioral Inhibition	.934	**.019**
Behavioral Inhibition – log transformed	.957	.126
Social Anxiety	.953	.100
Faces Overall – Left Amygdala	.991	.982
Faces Overall – Right Amygdala	.984	.806
Fear – Left Amygdala	.954	.096
Fear – Right Amygdala	.972	.402
Threat – Left Amygdala	.959	.144
Threat – Right Amygdala	.981	.708

Note: **Bold** indicates significance.

Finally, BI and social anxiety were highly correlated ($r = .58$; $p < .001$), which aligns with past literature.

Covariates. Age and sex were tested as potential covariates on all main variables (see Table 8.5). Neither was found to have a significant effect on the key variables of interest. BI was sensitive to autocorrelation in this regression (DW = 1.512, $p < .05$) which was corrected using the Cochrane-Orcutt method. Only corrected regressions are presented in the table below.

Table 8.5. Effect of covariates on main outcome variables.

Variable	β	Standard Error	*p*	Durbin-Watson Score	*p*
Social Anxiety					
Age	-.375	.337	.273	1.852	.267
Sex	1.231	1.035	.242		
Behavioral Inhibition					
Age	.046	.047	.339	1.958	.417
Sex	.117	.129	.369		
Faces Overall – Left					
Age	.004	.011	.709	1.962	.394
Sex	.051	.033	.139		
Faces Overall – Right					
Age	.006	.013	.658	2.001	.442
Sex	.033	.040	.415		
Fear – Left					
Age	-.025	.023	.291	1.067	.526
Sex	.076	.072	.299		
Fear – Right					
Age	-.019	.024	.438	1.979	.414
Sex	.012	.075	.871		
Threat – Left					
Age	-.024	.020	.240	2.393	.867
Sex	.039	.061	.533		
Threat – Right					
Age	-.010	.021	.620	2.181	.666
Sex	-.017	.063	.787		

Main Results – Behavior and Neurophysiology

Overall, results did not clarify the mixed extant literature as originally hoped (see Table 8.6). Hypothesis 1 sought to replicate past findings that heightened emotion reactivity to threatening faces as measured by BOLD signal in the amygdala is correlated with increasing

symptoms of social anxiety. There were no significant correlations between these variables for either hemisphere. Subsequently, hypothesis 2 was designed to test the degree to which heightened emotion reactivity to any face is associated with symptoms of BI. In the right hemisphere, there was a significant association between BI and fear (r = -.33, p < .05), but this went away after correcting for multiple tests.

Table 8.6. Correlations between social anxiety, BI and neuroimaging variables.

Behavioral Measure	Neuroimaging Variable	Left Amygdala			Right Amygdala		
		r	*p*	*p-c*	*r*	*p*	*p-c*
Social Anxiety	Faces overall	-.11	.4869	1.00	-.03	.8741	1.00
	Fear	-.05	.7623	1.00	-.02	.9129	1.00
	Threat	-.05	.7730	1.00	.00	.9780	1.00
Behavioral Inhibition	Faces overall	-.04	.7864	.7864	.07	.6500	.6500
	Fear	-.29	.0629	.1887	-.33	**.0324**	.0972
	Threat	-.22	.1616	.3232	-.29	.0672	.1344

Notes: *p*-c indicates corrected *p*-value using Holm's FWER method. **Bold** indicates significance.

Even though hypothesis 3 should not have progressed based on results from aims 1 and 2, analyses were conducted for completeness (see Table 8.7). First, univariate linear regression analyses unsurprisingly revealed that BI significantly predicts social anxiety but that overall emotion reactivity in either hemisphere does not. The moderated regression analysis was not significant, with level of emotion reactivity not influencing the degree to which BI impacts social anxiety. Both of the multivariate regressions were corrected for autocorrelation (initial DW for left hemisphere = 1.352, p = .015; initial DW for right hemisphere = 1.350, p = .016).

Table 8.7. Results of moderated regression analyses.

Variable	β	SE	*p*	*p-c*	DW Score	*p*
Univariate Regressions						
BI	6.105	1.020	**<.001**	**<.001**	1.867	.342
Faces Overall – Left	-3.537	5.037	.487	.974	1.740	.199
Faces Overall – Right	-.699	4.380	.874	.974	1.761	.223
Multivariate Regression – Left Hemisphere						
BI	7.311	1.544	**<.001**	**<.001**		
Faces overall	32.467	31.574	.311	1.00	1.903	.419
BI x Faces overall	-8.068	7.435	.285	1.00		
Multivariate Regression – Right Hemisphere						
BI	7.139	1.598	**<.001**	**<.001**		
Faces overall	21.983	27.610	.432	1.00	1.874	.399
BI x Faces overall	-5.072	6.233	.421	1.00		

Notes: BI is log transformed in all analyses. The multivariate regressions have been corrected for autocorrelation using the Cochrane-Orcutt method. SE indicates standard error; DW indicates Durbin-Watson test score. *p*-c indicates corrected *p*-value using Holm's FWER method. **Bold** indicates significance

Discussion

Insight into the relationship between BI and social anxiety from a neurologically-informed perspective is weak, with no studies to date utilizing a sample which has included measures on both phenotypes. The current study sought to replicate past findings showing the effect of emotion reactivity on BI and social anxiety in a sample of pre-adolescents as well as assess whether emotion reactivity moderates the relationship between BI and social anxiety. Unfortunately, all findings were non-significant. The robust effects previously seen between emotion reactivity and social anxiety at the adolescent and adult levels (Birbaumer et al., 1998; Cooney et al., 2006; Evans et al., 2008; Killgore & Yurgelen-Todd, 2005; Phan et al., 2005; Stein et al., 2002; Stein et al., 2007) were not replicated in this pre-adolescent sample. Likewise, no correlation was found between emotion reactivity and BI, which had been demonstrated in the past (Clauss et al., 2016; Perez-Edgar et al., 2007; Schwartz et al., 2003). These initial null results limit statistical ability to further examine the relationship between BI and social anxiety at the neurophysiological level.

Difference with Past Association Studies

It must be stressed that this does not indicate that a relationship does not exist at this biological level, but that a different study design is necessary to examine it. There are many factors to consider. First, while the current sample size is quite large for an fMRI study and there was power to detect significant main and moderation effects, the sample is from a community sample of pre-adolescents. They were not selected via a case-control design, which is what most fMRI studies do. Thus, an even larger sample size may be needed to reduce the signal-to-noise ratio when using a community sample and dimensional constructs of mental health concerns. This concern is further exacerbated by the selection bias that went into asking families to come back for the fMRI part of the JAS. Children with mild temperaments who could sit still (among other requirements - see Methods section) may have been less likely to display a high number of BI and social anxiety-related physiology (even if they display behavioral symptoms). Second, past studies that found associations between BI and/or social anxiety and emotion reactivity were in childhood (Clauss et al., 2016), adolescent (Killgore & Yurgelun-Todd, 2005; Perez-Edgar, 2007; Schwartz et al., 2003) or adult samples (Birbaumer et al., 1998; Cooney et al., 2006; Evans et al., 2008; Phan et al., 2005; Stein et al., 2002; Stein et al., 2007). It is possible that developmentally, the neurophysiological trends associated with pre-adolescence may be different. However, confounding this developmental consideration is again the fact that the current sample is not case-control. Third, as stated earlier (see Introduction section), it is possible that the association between BI and emotion reactivity is task dependent. While studies that have found associations have used emotion reactivity in their tasks, no study has used the EFAT.

Future Directions

Thus, in seeking to clarify the literature, the current study only raises more questions. First, it is still unclear when the emotional reactivity response in those with social anxiety becomes robust. One study has shown it in adolescents (Killgore & Yurgen-Todd, 2005). The current study's goal of expanding this work in a slightly younger sample highlights the need for more neurophysiological studies across development. Second, findings emphasize the differences in effects found in case-control versus community samples. While understanding etiology and developmental relationships at the pre-disorder level is critical, this may not be possible at the neurophysiological level without extremely large sample sizes. Finally, additional results revealed a direct relationship between BI and social anxiety, which is supported by multiple past studies. Findings also revealed a lack of influence of age or sex as covariates, the latter of which is a bit surprising. Sex differences have not been widely noted for BI and have been consistently noted for social anxiety in adolescents (Rapee, 2004) but not adults (Hettema et al., 2005). It is possible that the age of the sample diminished sex differences that will become apparent later.

Limitations and Strengths

The current study is not without need for improvement. First, examining neurophysiological differences in a non-clinical, community sample likely affected our ability to detect significant effects. Even though phenotypes present clinically on continuums and not "yes/no" or "high/low" categories, such categorization may be necessary to examine these research questions in the future. Second, the retrospective nature of assessing BI may be subject to recall bias. Third, it would be best to examine the neurophysiological relationship between BI and social anxiety developmentally over time, allowing for differences between those who exhibit social anxiety symptoms and those who have no symptoms (but who all have a history of

BI) to be better assessed. Finally, the sample included only Caucasian participants due to limitations in other aspects of the larger JAS (see Carney et al., 2016 for a full explanation).

Nevertheless, this study is novel and with design changes, this critical research question could be more fully investigated. The use of emotion reactivity to gauge BI and social anxiety in a sample of pre-adolescents has not previously been done. Even though few insights occurred, understanding this relationship is key to better prevention and intervention efforts in a translational manner. For example, understanding the nature of the relationship between BI and social anxiety at the endophenotypic level, and the role that neurophysiology plays, can inform identification of risk in children and pre-adolescents. This information can also guide researchers and clinicians when expanding risk models for social anxiety, as the purpose of such models is to inform prevention and intervention efforts (Zvolensky, Schidt, Bernstein, & Keough, 2006). Additionally, current risk factor models for social anxiety do not include detailed neurophysiological insights (Degnan et al., 2010; Ollendick & Benoit, 2012; Rapee & Heimberg, 1997; Rapee & Spence, 2004). Future studies should take these findings into consideration when designing neurophysiological experiments that assess the relationship between BI and social anxiety.

Conclusions

The ultimate goal of research into mental health conditions is to improve patient outcomes. An immediate goal of examining biological etiology of disorders is to someday combine the genetics and neurophysiology into well-powered studies. The field of imaging genetics is improving daily mostly by way of increasing sample sizes (Moore, Sawyers, Adkins, & Docherty, 2017). The current study did not find strong neurophysiological links between social anxiety and a strong risk factor for it, BI. Nevertheless, null findings can be clinically

useful by providing insights into what type of information is not ready to be translated. Perhaps the field of imaging genetics is not the way forward for research into the etiology of pre-adolescent social anxiety.

Chapter 9: Final Risk Factor Model for Social Anxiety Disorder and Translational Implications

Recap of Purpose and Findings

The purpose of this dissertation was to examine the translational capacity of psychiatric genetic research in broad and specific ways. It was divided into three aims. Aim 1 assessed the state of the science regarding the translation of the genetic information to the clinical care of mental health disorders from an academic perspective. Aim 2 examined the genetic and environmental risk factors of social anxiety disorder and developed a genetically-informed risk factor model for the disorder. Aim 3 assessed the inclusion of neurophysiological data into the risk factor model for pre-adolescent social anxiety disorder.

Aim 1 (chapter 3) was accomplished via a survey that was sent to academic stakeholders in mental health-related fields. The survey queried participants across three areas: professional translational practices, genetic knowledge and competence, and the translation of genetic information related to mental health. Overall, participants had moderate levels of self-reported translational practices and were familiar with translational science. They also reported moderate levels of genetic knowledge but weaker levels of genetic competence. Accordingly, they did not have strong positive attitudes toward the impact that translating genetic information could have on mental health care except for disorders for which there is more biological knowledge or understanding. This indicates a translation-genetic competence gap whereby genetic knowledge reinforces linear ways of viewing translation that include solely the inclusion of molecular genetic information. Genetic competence is needed to think outside the box and utilize non-molecular genetic information in non-linear frameworks (e.g., dissemination & implementation [D&I], prevention science).

Aim 2 (chapters 6 and 7) focused the translational scope to pre-adolescent social anxiety, as all translation still requires basic science information and must start somewhere. The mechanisms of specific genetic and environmental risk factors for social anxiety were disentangled and contributed to a detailed risk factor model that may have more translational capacity. Specifically, it was found that there is a robust biometrical relationship between social anxiety and behavioral inhibition (BI) that is potentially causal. When adding an additional risk factor into this model, parental bonding (specifically overprotectiveness), it was found that overprotectiveness did not have a direct effect on social anxiety nor a moderating effect on the relationship between BI and social anxiety.

Aim 3 (chapter 8) attempted to examine the neurophysiological connection between BI and social anxiety as a way to provide additional biological insight. Specifically, the relationship between each phenotype and emotional reactivity (assessed via amygdala activation) as well as the moderating effect of emotion reactivity were examined. No strong neurophysiological links were found between BI and social anxiety. These null findings do provide clarification to past literature and indicate that pre-adolescence may be too early in development to detect these neurophysiological connections between the phenotypes. They also imply that genetic etiology is more informative knowledge that can influence risk factor models and eventual prevention and intervention efforts for social anxiety (see chapters 6 and 7).

Together the findings from aims 2 and 3 provide evidence that childhood BI is a putative endophenotype for later social anxiety. Endophenotypes are "intermediate" phenotypes that lie in the etiological pathway between genetic variation and a disorder (Cannon & Keller, 2006; Gottesman & Gould, 2003). The results from aim 2 (chapter 6) add further support to this claim. The five criteria of an endophenotypes are: (a) the endophenotypes is associated with illness in

the population; (b) the endophenotypes is heritable; (c) the endophenotype is state-independent; (d) the endophenotype and illness co-segregate in families; (e) the endophenotype is found in non-affected family members at higher rates than the general population (optional criteria). BI has previously been shown to meet the first three requirements across various studies. The current study adds to these first three criteria and adds substantial evidence for the fourth (instantiated here as cross-phenotype correlations within twin pairs which show that the co-aggregation is primarily due to genetically-informative factors). No study to date has provided evidence for the fifth criteria. The fifth criteria could be tested using a more expansive set of questionnaires or behavioral measures. For example, parents of twins in the current study could have been queried about their history of BI (although this is not the best measure of the trait) or questionnaires could have been given to parents to fill out about their non-twin children's history of BI, social anxiety, and related constructs.

Risk Factor Model

A goal of this dissertation was to provide a new risk factor model for social anxiety that could be easily expanded in the future after investigation of other risk factors and which also included genetic and neurophysiological information. Such a risk factor model could have translational implications for those preventing and treating pre-adolescent social anxiety, although right now the true translational implications are unknown (see *Translational Implications - Social Anxiety Risk Factor Model* below). Figure 9.1 presents the final risk factor model for pre-adolescent social anxiety based upon the findings from this dissertation. As a reminder, past risk factor models have been broad in their included factors (Degnan et al., 2010; Ollendick & Benoit, 2012; Rapee & Heimberg, 1997; Rapee & Spence, 2004). The current

dissertation took the opposite approach and is meant to complement these past models, not serve as a competing model.

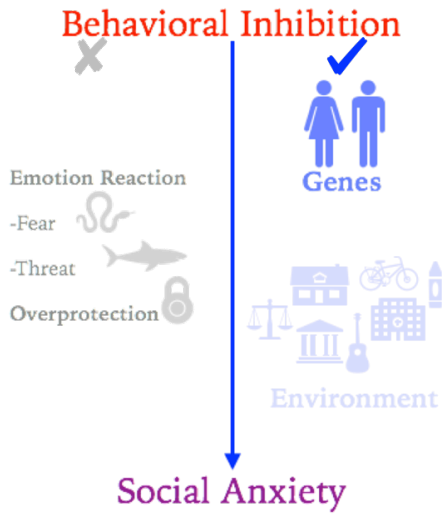

Figure 9.1. Final risk factor model for aim 2 of this dissertation.

Specifically, the model depicts the relationships found in this dissertation in a visually engaging manner. The goal is to examine the development from BI, red, to social anxiety, purple. All risk factors of importance are in varying degrees of blue shading on the right. Risk factors that were not found to be important are in gray on the left. It is hoped that this risk factor model may be expanded in the future. There are many other risk factors that impact both BI and social anxiety that were not discussed in this dissertation. These include parental anxiety (Ollendick & Benoit, 2012), parent information processing (Ollendick & Benoit, 2012), child information processing (Ollendick & Benoit, 2012), attachment (Ollendick & Benoit, 2012), and peer relations (Degnan et al., 2011). The structure of the current risk factor model would make it easy to update given new etiological insights into the relationship between BI and social anxiety.

Translational Implications

This dissertation examined translation first at a broad level by examining the translational implications of psychiatric genetic research and second at a specific level by creating a social anxiety risk factor model. To discuss the translational implications of this dissertation, it is crucial to return to the foundational questions of the field of psychiatric genetics. The three key questions of the field are: (a) do genes affect a trait, (b) how much do genes affect a trait, and (c) where/what are the genes. As discussed in chapter 1, most psychiatric disorders are common and the product of the environment plus hundreds or thousands of genes. Thus, additional questions need to be posited which complement the core three. These are: (a) is this information actionable, (b) if so, for whom is this information actionable, (c) how can this information be used, and (d) what are the barriers to using this information. Such questions make the field of psychiatric genetics, and genetic information in general, more approachable for all stakeholders involved in translating such information to clinical care. The next two sections reflect upon and discuss these questions in the context of the translational survey and social anxiety risk factor model.

Translation of Non-Molecular Genetic Information into Mental Health Care

The findings from the survey in aim 1 (chapter 3) are immediately actionable information, albeit in a small way. Steps should be taken to continue this research and ultimately examine the translational capacity of non-molecular information in mental health care. This would involve perspectives from all possible stakeholders over many stages of research development. Stakeholders may include public heath specialists, health educators, psychologists, psychiatrists, therapists, social workers, researchers, patients and their families, and administrators. To avoid the barrier likely created by the survey of asking an overly broad question, this line of work should limit its scope. This research should focus on a specific

disorder moving forward to help facilitate involvement of stakeholders with key areas of expertise.

For example, a broad idea of how this line of research could be carried out is as follows: (a) Create a new instrument that specifically assesses the incorporation of non-molecular genetic information into treatment and recovery efforts for alcohol use disorder (AUD) on a college campus. This step will involve building partnerships with collegiate recovery groups, campus health educators, and researchers. It will also require qualitative, inductive approaches such as focus groups and interviews prior to the creation of a new survey instrument. (b) Based upon findings from step 1 as well as known barriers to the incorporation of genetic information in clinical care, a research agenda that involves many stakeholders will be created next. This may involve experimentally testing the incorporation of non-molecular information into on-campus treatment settings, creating workshops about the genetic epidemiology of AUD, deducing which components of genetic information are most effective in which settings, testing which stakeholder groups utilize the information the most, and so on. (c) Finally, application of these findings to other common mental health disorders and different environments would be explored.

Thus, this information is actionable and for the key stakeholders mentioned above. How the information can be used as outlined above is hypothetical and will change based on collaboration and communication from future stakeholders per a socio-ecological-focused translational perspective. The possibilities are endless. For example, patients could find great meaning from learning basic psychiatric genetic information in a clinical setting, workshops may help individuals with certain disorders or be used to train stakeholders, patients may want this information to guide reproductive decisions, and there are also ethical implications that should be explored. However, it might not be wise to incorporate genetic information into clinical care

(Lebowitz & Ahn, 2017; Lebowitz & Applebauk, 2017) and any attempts to do so need to be carefully researched. Future work in this area is contingent on addressing multiple barriers to this process. A key main barrier, which was found in the survey, is the translation-genetic competence gap. This ties heavily into the already cited education and engagement of stakeholder gaps. There is a big need to overcome the assumptions made about genetic information, namely that non-molecular information holds much promise. Again, this is likely best accomplished through socio-ecological translational frameworks such as D&I and prevention science where the emphasis will be on the prevention, intervention, treatment, and/or recovery of a specific disorder.

Social Anxiety Risk Factor Model

Findings from aims 2 and 3 (chapters 6-8) provide less of an immediate, actionable product. There is a need to step away from the traditional academic model of not only relying on linear frameworks, but relying on traditional academic translational methods of discussing the model with peers and publishing. A big hurdle in translating knowledge to practice is the gap between academic publishing goals and policy-oriented interest of public / behavioral health (Baldwin et al., 2017). There is a need to overcome this academic barrier; only then will this model (or a version of it) be implemented into care. There is a need to emphasize factors and stakeholders that are outside of this academic impact, such as community engagement, network building, and practical application of evidence (Baldwin et al., 2017). It also needs to be explored how well a risk factor like the current one aligns with current best practices.

Thus, D&I or prevention science frameworks will allow for this linear-appearing model to be collaborative and socio-ecological. This can only happen by not simply publishing the risk factor model and hoping that pediatric clinicians utilize the information. The use of focus groups,

clinical stakeholders from academic and non-academic environments, patients, and families need to be consulted. This can happen through focus groups, targeted surveys, and a more inductive approach. To summarize, this information is potentially actionable for researchers, clinicians, and/or patients if it can be used in a clinical setting and key barriers can be overcome.

Final Thoughts

After thinking about translational science broadly and in the context of psychiatric genetics for many years, it is only appropriate to end this dissertation with a novel and inclusive definition of the term. To me, *translational science is a way of approaching science and practice that, at minimum, integrates perspectives from researchers, clinicians, and patients. Specific behaviors vary by framework, but broadly translational science involves constant communication, cooperation, and partnership between all interested parties to further patient outcomes.* It is my sincere hope that all stakeholders embrace this definition, but especially those in the field of psychiatric genetics. If even a fraction of the emphasis can be removed from molecular genetic information and efforts and put toward non-molecular genetic information, perspectives can shift. Through such a shift, true partnerships and dialogues can be formed that will propel the field forward and usher in an era of genetically-informed mental health care.

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Appendix

Appendix Item 1. PDF copy of the full translational survey (chapter 3, part 1).

An academic perspective on the translation of genetic information to the clinical care of mental health disorders

As a VCU faculty/staff member in a field related to mental health, you have a unique perspective on the relationship between science and practice.

This survey is designed to assess your knowledge of, comfort with, and ideas for the improvement of the translation of genetic information related to mental health disorders.

I am interested in your opinion on this topic regardless of whether you are a researcher, teacher, mentor, practitioner, or combination thereof.

This survey constitutes human subjects research and your participation is completely voluntary. You likely found this survey through a variety of ways - this project employs direct recruitment via identification of VCU faculty/staff email addresses, use of the VCU telegRAM, and department email blasts.

If you have any questions or concerns at any point during this survey, please email Jessica at jlbourdon@vcu.edu or (804) 818-6772.

Thank you!

This first section will ask you questions about your professional behaviors and experiences.

Select the answer that best describes your experience with these terms related to translational science.

	I have not heard of this	I have heard of this	I can define this and give an example	I actively participate in this form of translation
Research-to-practice	○	○	○	○
Research-to-policy	○	○	○	○
Bench-to-bedside	○	○	○	○
Dissemination and Implementation	○	○	○	○
Personalized medicine	○	○	○	○

For the next few questions, collaborators are defined as other professionals with whom you work or consult across all of your roles (i.e., clinical, research, and teaching). They may or may not be within your department or university. How you define your collaborators beyond this broad definition is up to you.

The size of my network of collaborators is...	◯ I do not have a network of collaborators ◯ Less than 10 ◯ 10 or more ◯ 20 or more
I have collaborators that are...	☐ Researchers ☐ Clinicians ☐ Nurses ☐ Teachers ☐ Other (please specify)
If you chose "Other" above, please specify	_____
My collaborators span the following disciplines...	☐ Psychology ☐ Psychiatry ☐ Statistics ☐ Psychiatric and Behavioral Genetics ☐ Human and Molecular Genetics ☐ Social and Behavioral Health ☐ Social Work ☐ Public Health ☐ Other (please specify)
If you chose "Other" above, please specify	_____
How often do you meet/consult with individuals from your network of collaborators?	◯ Several of us meet/consult regularly ◯ I meet/consult with individuals on an as-needed basis ◯ Other (please specify)
If you chose "Other" above, please specify	_____
What else should I know about your current professional behaviors and experiences related to translational science (i.e., organizations you are a part of, specific details of your collaborative efforts, ways you integrate science, practice, and teaching, etc.)?	_____

This second section will ask you questions about your self-rated knowledge and competence of genetic information.

Are you active in a field of genetics (behavioral, psychiatric, human, molecular) as either a researcher, practitioner, teacher, or any combination thereof?	◯ Yes ◯ No

How long ago was your most recent course, workshop, or formal training in any field of genetics (behavioral, psychiatric, human, molecular)?	◯ Within the last 2 years ◯ 3-5 years ago ◯ 6-10 years ago ◯ More than 10 years ago ◯ No genetics training of any kind

Select the answer that best describes your experience with each of the following content areas of genetics.

	I have never heard of this	I have heard of this but cannot define it	I can define this and give an example	I utilize content related to this in my everyday work
Family history / aggregation	◯	◯	◯	◯
Heritability	◯	◯	◯	◯
Gene-environment relationship (i.e., interaction, correlation)	◯	◯	◯	◯
Twin studies	◯	◯	◯	◯
Molecular genomics	◯	◯	◯	◯
Epigenetics	◯	◯	◯	◯

Rank how much you agree/disagree with the following statements.

Please only choose the "Not Applicable" option if the scenario does not pertain to you - i.e., you do not see patients. Do not choose that option to reflect lack of comfort, knowledge, or competence.

I feel competent...

	Strongly disagree	Disagree	Agree	Strongly agree	Not applicable
...discussing genetic information about mental health disorders with my network of collaborators	◯	◯	◯	◯	◯
...discussing genetic information about mental health disorders with trainees/students	◯	◯	◯	◯	◯
...discussing genetic information about mental health disorders with patients	◯	◯	◯	◯	◯
...reading a scholarly article that mentions genetic information about a mental health disorder (i.e., in the intro or discussion as potential implications)	◯	◯	◯	◯	◯
...reading a scholarly article where the genetics of mental health disorders is the focus study (i.e., heritability study, genome-wide association study)	◯	◯	◯	◯	◯

...being a CO-author on a scholarly article where the genetics of a mental health disorder is the focus of the study	○	○	○	○	○
...being a LEAD author on a scholarly article where the genetics of a mental health disorder is the focus of the study	○	○	○	○	○
...mentoring/advising a trainee/student who wants to study the genetics of a specific mental health disorder (i.e., cumulative project, thesis, dissertation)	○	○	○	○	○

What else should I know about your current knowledge and competence related to the genetic basis of mental health (i.e., which content area(s), in what context, etc.)? _____

This third section will ask you questions about the translation of genetic information related to mental health.

Rank how much you agree/disagree with the following statements:

	Strongly disagree	Disagree	Agree	Strongly agree
Translation of genetic information about mental health disorders from research to practice is important	○	○	○	○
My field would benefit from improved translation of genetic information related to mental health disorders	○	○	○	○
It is important for all professionals in my field (researchers, teachers, practitioners) to understand the genetic risk associated with specific mental health disorders	○	○	○	○
It is important for students to be taught how to utilize information regarding the genetic risk associated with specific mental health disorders, regardless of field	○	○	○	○

You said that you "strongly disagree" or "disagree" with the statement "Translation of genetic information about mental health disorders from research to practice is important."

_____

Please elaborate.

You said that you "strongly disagree" or "disagree" with the statement "My field would benefit from improved translation of genetic information related to mental health disorders."

_____

Please elaborate.

You said that you "strongly disagree" or "disagree" with the statement "It is important for all professionals in my field (researchers, teachers, practitioners) to understand the genetic risk associated with specific mental health disorders."

_____

Please elaborate.

You said that you "strongly disagree" or "disagree" with the statement "It is important for students to be taught how to utilize information regarding the genetic risk associated with specific mental health disorders, regardless of field."

_____

Please elaborate.

Below are potential ways to improve the translation of genetic information about mental health disorders in an academic setting. Please rank the following activities in terms of how likely you would be to utilize them if they were available to you right now. Assume the event would be geared toward your primary role at VCU (i.e., researcher, practitioner, teacher, combination thereof).

	Not likely	Somewhat likely	Very likely	I already do / have done something like this
Attend a one-day in-person workshop at VCU	○	○	○	○
Attend an in-person course at VCU that meets once a week for four weeks	○	○	○	○
Take an online training module that can be spread out over multiple sittings	○	○	○	○
Attend a special 2-hour seminar presentation at a conference you already plan to attend	○	○	○	○
Attend regular meetings with your network of collaborators	○	○	○	○

What other translational activities would you attend to expand your knowledge and skills in this area (the genetics of mental health disorders)? _____

To what extent do you believe that increased knowledge of genetic information will influence the following?

	No influence	Some influence	Strong influence
Discovering new and better treatments for mental health disorders	○	○	○
Improving diagnostic criteria of patients with mental health disorders	○	○	○
Identifying asymptomatic patients at risk of developing mental health disorders	○	○	○
Targeting of resources to at-risk populations	○	○	○
Prenatal testing to guide reproductive choices	○	○	○
Stigma of mental health disorders	○	○	○
Insurance to patients with a high-risk genetic profile for mental health disorders	○	○	○
Interest in psychosocial therapies for mental health disorders	○	○	○
Interest in biological or pharmacological therapies for mental health disorders	○	○	○

What other ways can genetic information influence mental health?

_____

Which of the following do you think will benefit the most from increased translation of genetic information?

	No benefit	Some benefit	Significant benefit
Schizophrenia spectrum and other psychotic disorders	○	○	○
Anxiety disorders (generalized, social, panic, separation, phobias)	○	○	○
Bipolar disorder	○	○	○
Depression disorders (major depression, melancholia)	○	○	○
Obsessive-compulsive disorder	○	○	○
Post-traumatic stress disorder	○	○	○
Eating disorders (anorexia, bulimia, binge eating disorder)	○	○	○
Personality disorders	○	○	○
Neurodevelopmental disorders (autism spectrum disorder, communication disorders, intellectual developmental disorder)	○	○	○
Sleep-Wake disorders (insomnia disorder, narcolepsy)	○	○	○
Sexual dysfunction	○	○	○
Disruptive, impulse-control, and conduct disorders	○	○	○
Substance use and addictive disorders (alcohol, gambling, cocaine, other substances)	○	○	○

What are your final thoughts about the translation of genetic information to the clinical care of mental health disorders?

_____

I carefully avoided giving you a specific definition of translational science during this survey. Please let me know what translational science means to you in one sentence.

_____

Last section! Please tell me a bit about yourself.

What is your age?

- ◯ 18-25
- ◯ 26-35
- ◯ 36-45
- ◯ 46-55
- ◯ 56-65
- ◯ 66-75
- ◯ 76+
- ◯ Prefer not to answer

How do you identify?

- ◯ Female
- ◯ Male
- ◯ Transgender
- ◯ Non-binary
- ◯ Other (please specify)
- ◯ Prefer not to answer

If you answered "Other" above, please specify. _____

What is your race?

- ◯ African American / Black
- ◯ American Indian, Alaskan Native, or Native Hawaiian
- ◯ Asian or Pacific Islander
- ◯ Biracial or Multiracial
- ◯ White
- ◯ Other (please specify below)
- ◯ Prefer not to answer

If you answered "Other" above, please specify. _____

Are you of Hispanic or Latino(a) descent?

- ◯ Yes
- ◯ No
- ◯ Prefer not to answer

What degree(s) do you hold (check all that apply)?

- ☐ Master's
- ☐ Ph.D.
- ☐ Psy.D.
- ☐ M.D.
- ☐ Other (please specify below)
- ☐ Prefer not to answer

If you answered "Other" above, please specify. _____

How would you classify yourself (check all that apply)?

- ☐ Researcher
- ☐ Teacher
- ☐ Mentor / Advisor
- ☐ Clinician / Practitioner
- ☐ Other (please specify)
- ☐ Prefer not to answer

If you answered "Other" above, please specify. _____

What population is your primary clinical focus?

- ◯ Children
- ◯ Adolescents
- ◯ Emerging adults
- ◯ Adults
- ◯ Older adults
- ◯ Other (please specify)
- ◯ Prefer not to answer

If you answered "Other" above, please specify. _____

What disorder(s) is your primary clinical focus? Please choose no more than two responses.

- ☐ Schizophrenia spectrum and other psychotic disorders
- ☐ Anxiety disorders (generalized, social, panic, separation, phobias)
- ☐ Bipolar disorder
- ☐ Depression disorders (major depression, melancholia)
- ☐ Obsessive-compulsive disorder
- ☐ Post-traumatic stress disorder
- ☐ Eating disorders (anorexia, bulimia, binge eating disorder)
- ☐ Personality disorders
- ☐ Neurodevelopmental disorders (autism spectrum disorder, communication disorders, intellectual developmental disorder)
- ☐ Sleep-Wake disorders (insomnia disorder, narcolepsy)
- ☐ Sexual dysfunction
- ☐ impulse-control, and conduct disorders
- ☐ Substance use and addictive disorders (alcohol, gambling, cocaine, other substances)
- ☐ Other (please specify)
- ☐ Prefer not to answer

If you answered "Other" above, please specify. _____

What population is your primary research focus?

- ◯ Children
- ◯ Adolescents
- ◯ Emerging adults
- ◯ Adults
- ◯ Older adults
- ◯ Other (please specify)
- ◯ Prefer not to answer

If you answered "Other" above, please specify. _____

What disorder(s) is your primary research focus? Please choose no more than two responses.

- ☐ Schizophrenia spectrum and other psychotic disorders
- ☐ Anxiety disorders (generalized, social, panic, separation, phobias)
- ☐ Bipolar disorder
- ☐ Depression disorders (major depression, melancholia)
- ☐ Obsessive-compulsive disorder
- ☐ Post-traumatic stress disorder
- ☐ Eating disorders (anorexia, bulimia, binge eating disorder)
- ☐ Personality disorders
- ☐ Neurodevelopmental disorders (autism spectrum disorder, communication disorders, intellectual developmental disorder)
- ☐ Sleep-Wake disorders (insomnia disorder, narcolepsy)
- ☐ Sexual dysfunction
- ☐ impulse-control, and conduct disorders
- ☐ Substance use and addictive disorders (alcohol, gambling, cocaine, other substances)
- ☐ Other (please specify)
- ☐ Prefer not to answer

If you answered "Other" above, please specify. _____

Vita

Jessica Lynn Bourdon was born on June 16, 1988 in Fairfax County, Virginia and is an American citizen. She graduated from Riverbend High School and Commonwealth Governor's School, Spotsylvania, Virginia, in 2006. Thereafter she graduated from the University of Richmond, magna cum laude, in 2010 with her Bachelor of Science in Psychology (honors) and Bachelor of Arts in Cognitive Science. Jessica worked in the Psychology Department at the University of Richmond for one year as a research assistant and in the Department of Physical Medicine and Rehabilitation at Virginia Commonwealth University for four years as a program coordinator before attending graduate school. During her time earning her doctorate, she worked as a research specialist at the Wellness Resource Center at Virginia Commonwealth University, founded the Translational Partnership for Mental Health, and assisted with the College Behavioral and Emotional Health Institute's course offerings, annual town hall, and translational activities. She graduated from Virginia Commonwealth University with a doctorate in philosophy in Clinical and Translational Sciences (concentration in Psychiatric, Behavioral, and Statistical Genetics) in 2019. Her list of publications can be found below.

1. **Bourdon, J. L.,** & Hancock, L. C. (In Press). Using electronic audience response technology to track e-cigarette habits among college freshmen. *Addictive Behaviors.* doi:10.1016/j.addbeh.2019.02.019

2. Prom-Wormley, E. C., Clifford, J., **Bourdon, J. L.,** Barr, P., Blondino, C., Ball, J. … Wilson, D. (In Press). Developing community-based strategies with family health history: Assessing the association between community resident family history and interest in health education. *Social Science & Medicine.* doi:10.1016/j.socscimed.2019.02.011

3. **Bourdon, J. L.,** Savage, J. E., Verhulst, B., Carney, D. M., Moroney, E., Machlin, L. … Hettema, J. M. (2019). The genetic and environmental relationship between childhood behavioral inhibition and pre-adolescent anxiety. *Twin Research Human Genetics.* doi:10.1017/thg.2018.73

4. Savage, J. E., Moore, A. A., Sawyers, C. K., **Bourdon, J. L.,** Verhulst, B., Carney, D. M., Moroney, E., Machlin, L., Kaabi, O., Vrana, S., Grillon, C., Brotman, M. A., Leibenluft, E., Pine, D. S., Roberson-Nay, R., & Hettema, J. M. (2019). Fear-potentiated startle response as an endophenotype: Evaluating metrics and methods for genetic applications. *Psychophysiology.* doi:10.1111/psyp.13325

5. **Bourdon, J. L.,** Moore, A. A., Long, E. C., Kendler, K. S., & Dick, D. M. (2018). The relationship between on-campus service utilization and common mental health symptoms in undergraduate college students. *Psychological Services*. doi:10.1037/ser0000296

6. **Bourdon, J. L.,** Moore, A. A., Eastman, M., Savage, J. E., Hazlett, L., Vrana, S. R., Hettema, J. M., & Roberson-Nay, R. (2018). The heritability of resting heart rate variability (HRV) in adolescents and young adults. *Behavior Genetics.* doi:10.1007/s10519-018-9915-1

7. **Bourdon, J. L.,** Saunders, T. R., & Hancock, L. C. (2018). Acknowledgement and support matter: A brief report on gender identity and sexual orientation at a large, urban university. *Journal of American College Health, 66(8*). doi:10.1080/07448481.2018.1432627

8. Cusak, S., Hicks, T., **Bourdon, J. L.,** Sheerin, C., Overstreet, C., Dick, D., Kendler, K. S., & Amstadter, A. B. (2018). Prevalence, predictors, and outcomes of PTSD symptomology in a college undergraduate sample. *Journal of American College Health.* doi:10.1080/07448481.2018.1462824

9. Graham, C. W., West, M. D., **Bourdon, J. L.,** & Inge, K. J. (2016). Employment interventions for return to work in working aged adults following traumatic brain injury (TBI): A systematic review. *Campbell Systematic Reviews, 12(1),* 1-33. doi:10.4073/csr.2016.6

10. Bukach, C. M., Cottle, J., Ubiwa, J., & **Miller, J.** (2012). Individuation experience predicts other-race effects in holistic processing for both Caucasian and Black participants. *Cognition, 123*, 319-324. doi:10.1016j/j.cognition.2012.02.007