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A Hierarchical-Spectrum Model of Mental Disorders: Genetic, Developmental, and Interpersonal Perspectives

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A Hierarchical-Spectrum Model of Mental Disorders:

Genetic, Developmental, and Interpersonal Perspectives

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Psychology

by

Christopher Callahan Conway

2013

ABSTRACT OF THE DISSERTATION

A Hierarchical-Spectrum Model of Mental Disorders:

Genetic, Developmental, and Interpersonal Perspectives

by

Christopher Callahan Conway

Candidate for the Degree of Philosophy in Psychology

University of California, Los Angeles, 2013

Professor Constance Hammen, Chair

The current project aimed to determine whether a recently developed explanatory model

for comorbidity patterns—labeled the Hierarchical-Spectrum Model (HSM)—could serve as a

useful organizing framework for research on psychopathology. The HSM accounts for the high

co-occurrence of depressive and anxiety disorders by representing them as facets of an

overarching Internalizing dimension; likewise, the substance use and antisocial behavior

disorders are represented as facets of an Externalizing dimension. In latent variable modeling

terms, the HSM parses the shared and unique variance of disorders into transdiagnostic latent

factors (i.e., Internalizing and Externalizing dimensions) and diagnosis-specific residuals,

respectively. This project integrated the HSM quantitative structure with prominent genetic and

psychosocial theories of psychopathology. Results from Study 1 demonstrated that the

relationship of early environmental adversity with psychopathology in young adulthood is partly

mediated by the transdiagnostic dimensions. At the same time, early adversity was associated

with several residual variances of the HSM, signaling the presence of diagnosis-specific

pathways from early adversity to mental disorder. Study 2 conceptualized the stress generation hypothesis, which posits that people with a history of depression, relative to their never-depressed counterparts, experience more stressful life events dependent at least in part on their own behavior, through the lens of the HSM. Results revealed stress generating effects of the Internalizing and Externalizing dimensions, suggesting that the stress generation phenomenon is not specific to any one diagnostic category. Yet, the diagnosis-specific components of major depression and dysthymia also contributed to stress generation over and above the effects of the transdiagnostic dimensions, suggesting there is some pathology unique to depression that confers vulnerability to stress exposure. In Study 3, a daily diary methodology was used to examine day-to-day fluctuations of HSM symptoms. Consistent with expectations, elevated daily stress levels predicted increases in both Internalizing and Externalizing symptoms. Further, a widely studied polymorphism in the serotonin transporter gene (5-HTTLPR) moderated the relationship between daily stress and Internalizing, but not Externalizing, symptoms. Together, the current findings suggest that the HSM has the potential to be a useful framework for research, treatment, and classification in clinical psychology.

The dissertation of Christopher Callahan Conway is approved.

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PUBLICATIONS AND PRESENTATIONS

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Chapter 1: General Introduction

The Challenge of Comorbidity

For decades, clinicians and researchers have struggled to understand the co-occurrence (or comorbidity) of multiple psychiatric syndromes in the same individual. In clinical settings, it is often unclear how to conceptualize and treat a client suffering from a diversity of symptomatology. Should intervention programs target the various pathologies simultaneously or should they be addressed sequentially? In practice, it may be difficult to access and achieve proficiency in the many treatment protocols tailored to each specific psychiatric and substance use disorder.

From a research standpoint, comorbidity presents a dilemma for the design and interpretation of studies on psychopathology. On one hand, researchers could recruit participants that manifest only one disorder (i.e., "pure" cases) to ensure that any effects are attributable to the disorder of interest. However, owing to the relative infrequency of pure cases, this would be a somewhat unique sample and research findings may not generalize to the entire population of people qualifying for this disorder. An alternative, and more typical, approach is to obtain an optimally representative sample of people diagnosed with a particular disorder, enhancing the validity of statistical inferences to the population under study. Yet, given the presence of comorbid cases in such a sample, any claims concerning causality in this study would be undercut by the possibility that comorbid syndromes accounted, at least in part, for the observed effects.

Additionally, the co-occurrence of syndromes in the same person is not easily reconciled with the categorical conceptualization of psychopathology espoused in official nosologies, such as the *Diagnostic and Statistical Manual of Mental Disorders* (DSM). The DSM represents

mental disorders as discrete (i.e., having clear boundaries defining who is "in" and who is "out") entities, each with a distinct etiology, pathophysiology, and prognosis. The current edition of the DSM (DSM-IV-TR; American Psychiatric Association [APA], 2000) acknowledges that ''a categorical approach to classification works best when all members of a diagnostic class are homogenous, when there are clear boundaries between classes, and when the different classes are mutually exclusive'' (p. xxxi). As described in detail below, there is now sufficient evidence from comorbidity research to challenge each of these assumptions of a categorical system.

Theoretical Models of Comorbidity

Epidemiological research indicates that comorbidity among DSM-IV disorders is the rule rather than the exception, with more than 50% of people who meet criteria for a diagnosis in the past 12 months endorsing more than 1 disorder during that time (Demyttenaere et al., 2004; Kessler, Chiu, Demler, & Walters, 2005). This degree of co-occurrence is not accounted for simply by chance, as might be possible given high base rates of individual syndromes (Frances, Widiger, & Fyer, 1990). Instead, a wealth of research evidence in clinical and community samples demonstrates that virtually all diagnoses are correlated; that is, the presence of one diagnosis increases the odds of meeting criteria for other diagnoses (Kessler et al., 2005; Maser & Cloninger, 1990).

The patterning of intercorrelation among diagnoses has been the topic of growing interest among researchers. Certain sets of syndromes tend to co-occur at particularly high rates. For instance, according to the National Comorbidity Survey Replication (NCS-R), respondents endorsing major depression in the past year are also commonly diagnosed with anxiety disorders (57.5%), in contrast to substantially lower rates of comorbidity with substance use (8.5%) or impulse control (16.6%) disorders (Kessler et al., 2003). In recognition of these consistent

configurations of diagnostic co-occurrence, Clark et al. (1995) commented that "comorbidity, while rampant, is not random" (p. 129).

This realization inspired researchers to develop explanatory models to make sense of common comorbidity patterns. While some of these efforts have focused on how comorbidity may be explained by limitations in diagnostic assessment tools or study recruitment methods (e.g., Caron & Rutter, 1991), a preponderance of evidence indicates that comorbidity is not an artifactual phenomenon (Angold, Costello, & Erkanli, 1999; Seligman & Ollendick, 1998). The majority of recent work has focused on common cause models, in which correlated syndromes are posited to be indicators of the same dimension of liability in much the same way that vocabulary and comprehension subscales on intelligence tests are considered indicators of a higher-order verbal index.

Much of the current research on the structure of comorbidity in adults can be traced to theoretical arguments outlined by Clark and Watson (1991) in the tripartite model of depression and anxiety. These researchers posited that negative affectivity, as a common diathesis for both depression and anxiety symptoms, explains the co-occurrence of these two types of disorder. At the same time, the disorders were distinguished by an anhedonia component characterizing depression and a somatic hyperarousal component unique to anxiety. Barlow and colleagues (Barlow, 1991; Brown & Barlow, 1992) extended this theory in a hierarchical model of anxiety disorders. They argued that somatic hyperarousal could not adequately explain the clustering of anxiety disorders, and hypothesized instead that each disorder contained a unique, distinguishing component, with somatic hyperarousal serving as the unique component for panic disorder (Zinbarg & Barlow, 1996). Key features from these models were subsequently synthesized in an integrative hierarchical model of anxiety and depression (Mineka, Watson, & Clark, 1998).

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The Hierarchical-Spectrum Model (HSM) of Common Mental Disorders

The two main insights gained from early theoretical models of comorbidity were (a) covariance between separate syndromes may be due to their dependence on a shared vulnerability factor, and (b) quantitative methods can be applied to compare the degree to which competing statistical models are able to reproduce the observed structure of comorbidity. Krueger and colleagues (1998) incorporated these ideas into a Hierarchical-Spectrum Model (HSM) of Internalizing and Externalizing syndromes, where hierarchical refers to the distinction between the superordinate (i.e., latent variable) and subordinate (i.e., manifest diagnosis) levels of the model, and spectrum refers to the continuous (as opposed to categorical) metric of the latent liability factors. According to the HSM, disorders are correlated because the liability spectra represent common causes, and putatively distinct disorders (e.g., generalized anxiety versus depressive disorder) are simply different behavioral expressions of a single spectrum of Internalizing (or Externalizing) risk.

Confirmatory factor analysis (CFA) offers a method for evaluating the tenets of the HSM. CFA models assume that directly measured variables serve as indicators, or manifestations, of a latent construct. A causal relationship is assumed between the latent construct and its facets (Borsboom, 2008). With the use of standard fit indices, researchers can determine how well the theoretical model instantiated in the CFA equations accounts for correlations among the observed variables. A theoretical model is supported to the extent that the model-implied correlations approximate the correlations observed in the real data. Moreover, CFA allows the statistical comparison of competing or alternative models. Significance tests can be conducted to decide whether one theoretical model does a better job of recovering observed correlations than another.

In the original study, Krueger et al. (1998) used CFA to ascertain the number and nature of liability spectra underlying 10 common mental disorders assessed in the longitudinal Dunedin birth cohort study using DSM-III-R classifications. The authors compared the fit of three models: first, a one factor model in which all diagnoses were assumed to be indicators of a general maladjustment factor; second, a two-factor model in which major depression (MDD), dysthymia (DYS), generalized anxiety disorder (GAD), agoraphobia (AGO), social phobia (SOP), specific phobia (SPP), and obsessive-compulsive disorder (OCD) were conceptualized as loading on a latent Internalizing dimension, whereas conduct disorder (CD), marijuana dependence (MD), and alcohol dependence (AD) loaded on a latent Externalizing dimension; third, a four-factor model corresponding to the DSM organizational scheme in which MDD and DYS loaded on an affective factor, GAD, AGO, SOP, SPP, and OCD loaded on an anxiety factor, MD and AD loaded on a substance dependence factor, and CD was the sole indicator of a antisocial behavior factor. According to several fit indices, the correlated two-factor model was the optimal representation of the relationships among these 10 syndromes (see Figure 1 for schematic of the best-fitting model).

Krueger (1999) followed up this initial study by examining the latent structure of a similar set of 10 mental disorders in the National Comorbidity Survey (NCS; Kessler et al., 1994), a large ($N = 8,098$), nationally representative survey of US civilians. Lifetime diagnoses were again based on DSM-III-R criteria and assessed by the Composite International Diagnostic Interview (CIDI; Robins, Wing, Wittchen, Helzer, & others, 1988). In addition to the three CFA models evaluated in the original study, Krueger (1999) examined the fit of a three-factor model in which the Internalizing dimension was divisible into two highly correlated anxious-misery and fear factors. Based on preliminary exploratory factor analyses (EFA) of NCS diagnoses, MDD,

DYS, and GAD were designated as facets of the anxious-misery factor and panic disorder (PAN), AGO, SOP, and SPP formed the fear factor. Fit indices suggested that the three-factor model, in which anxious-misery and fear subfactors were indicators of a superordinate Internalizing factor, offered the best approximation of the observed diagnostic correlations in the complete NCS sample (see Figure 2). However, in the treatment-seeking subsample of NCS respondents, the two-factor (correlated Internalizing and Externalizing dimensions) provided the best fit. Echoing conclusions drawn from the Dunedin study, Krueger (1999) interpreted the results as evidence that comorbidity represents a reliable empirical phenomenon that reflects the operation of core psychological processes (i.e., liabilities) shared across multiple DSM syndromes.

Various epidemiological studies have replicated the same basic configuration of latent structures identified by Krueger and colleagues. Using data obtained from the first two waves of the Netherlands Mental Health Survey and Incidence Study (NEMESIS; Bijl, Ravelli, & Van Zessen, 1998), Vollebergh et al. (2001) found the three-factor model from Krueger (1999) to provide the best fit to past 12-month diagnoses ascertained using the CIDI at both time points. Again, the three-factor model provided superior fit relative to a factor model based on the DSM organizational structure. It is noteworthy that the anxious-misery and fear domains were highly correlated, with loadings on the higher-order Internalizing factor ranging from .85 to .96 across waves 1 and 2.

Cox and colleagues (2002) investigated the location of posttraumatic stress disorder (PTSD) in the best-fitting structural model from Krueger's (1999) initial analyses of the NCS data. This study used CIDI interviews of respondents to Phase II of the NCS; PTSD was not assessed in the NCS Phase I. EFA results indicated that PTSD clustered with disorders marking

the anxious-misery factor and had no affinity with either the latent fear or Externalizing liability dimensions. This finding was consistent across past 12-month and lifetime diagnoses. Slade and Watson (2006) applied CFA techniques to data from the Australian National Survey of Mental health and Well-Being (Andrews, Henderson, & Hall, 2001), a population-based sample of over 10,000 community volunteers assessed using the CIDI (WHO, 1997) for DSM-IV past 12-month diagnoses. These analyses replicated the three-factor structure identified by Krueger (1999) in the NCS, although the separation of Internalizing into 2 subfactors appeared questionable (e.g., a standardized loading of the fear subfactor on Internalizing of .99). Finally, in a nationally representative sample (N = 3,021) of German adolescents and young adults, Beesdo-Baum et al. (2009) compared CFA models of the 10 diagnoses, assessed using the CIDI, originally examined in the NCS analyses. They found that the optimal arrangement was a three-factor model in which anxious-misery and fear factors correlate with each other and with Externalizing, but do not load on a higher-order Internalizing factor. They also noted that the two-factor model of Krueger et al. (1998) provided satisfactory fit.

A number of studies have focused on explicating the factor structure of either the Internalizing or Externalizing spectrum in isolation. Krueger and Finger (2001) analyzed data from treatment-seeking respondents (i.e., those who affirmatively endorsed the question "Are you currently seeing any professional about your problems" in the context of an interview covering past year emotional and substance use problems) to Phase II of the NCS (N = 251). Focusing particularly on the 7 Internalizing diagnoses (as specified in Krueger [1999]), the authors posited a one-factor model to explain the diagnostic correlations. The excellent fit of the unidimensional model suggested that these diagnoses could be considered facets of a coherent Internalizing dimension. In a similar set of analyses, Fergusson et al. (2006) investigated the

structure of Internalizing pathology in a birth cohort assessed in young adulthood as part of the Christchurch Health and Development Study. These authors took a symptom-based approach and found that CIDI symptom counts of MDD, GAD, SOP, SPP, and PAN were reliable indicators of a single latent Internalizing continuum across three time points.

Krueger and colleagues (2007) developed 23 unidimensional scales indexing various aspects of the Externalizing spectrum (e.g., physical and relational aggression, substance use, impulsivity, delinquency, excitement seeking, conscientiousness) and administered them in questionnaire form to a mixed sample of prisoners and college students (overall N = 1,787). Of several CFA models that were evaluated, a bifactor model (Gibbons & Hedeker, 1992; Holzinger & Swineford, 1937), in which each scale loaded on a general factor common to all Externalizing scales and one specific factor (see Figure 3 for a visual representation of a hypothetical bifactor model), provided the best fit. Of the two specific factors that emerged in this analysis, one comprised mostly aggression and empathy scales and the other comprised mostly substance use scales. The hierarchical configuration of this model resembles that of the explanatory models of the depressive and anxiety disorders (Mineka et al., 1998; Zinbarg & Barlow, 1996).

Finally, consistent with results of two earlier studies among adults (Krueger, Markon, Patrick, & Iacono, 2005; Markon & Krueger, 2005), Walton and colleagues (2011) recently found a unidimensional latent trait model to fit parent- and child-reports of Externalizing behaviors on the Child Behavior Checklist (CBCL; Achenbach, 1991) in the Tracking Adolescents' Individual Lives Survey (TRAILS). These results suggest that Externalizing behaviors in adolescence may be conceptualized as manifestations of an underlying liability-spectrum of Externalizing problems.

Additional Properties of the HSM

Coverage of Diagnoses. Structural analyses of comorbidity to date have focused predominantly on the most common of the clinical disorders. Many of the less prevalent, and typically more severe, disorders (e.g., bipolar and psychotic disorders) have yet to be incorporated into the same model-testing framework. One exception is a study by Markon (2010) using interview and questionnaire data from the British Psychiatric Morbidity Survey to model the latent structure of Axis I and II symptoms. CFA analyses revealed that a thought disorder dimension emerged as part of a broad four-factor structure, also including Internalizing, Externalizing, and pathological introversion factors. Thought disorder correlated .72 with Internalizing and .58 with Externalizing.

Watson (2005) observed that there is some uncertainty regarding the placement of OCD in these empirical taxonomies. OCD was omitted from structural analyses in most studies due to its low prevalence, which attenuates correlations with other disorders and inflates model standard errors (e.g., Krueger, 1999; Vollebergh et al., 2001). However, OCD was included in the Australian NSMHWB epidemiological study (Slade & Watson, 2006) and loaded significantly on the fear subfactor of the higher-order Internalizing factor. In contrast, according to unpublished results of Watson et al. (2005), OCD failed to load on the fear dimension in exploratory and confirmatory factor analyses of the NEMESIS data.

It is noteworthy that the majority of quantitative studies on the structure of comorbidity include antisocial personality disorder (ASPD), an Axis II disorder that is typically assessed and conceptualized separately from clinical disorders, as an indicator of the Externalizing spectrum. The fact that ASPD hangs together with symptom- and diagnosis-based markers of Axis I Externalizing disorders suggests that the latent Externalizing dimension transcends the multiaxial DSM scheme and implies the presence of psychopathological processes common to all

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manifestations of Externalizing problems. This hypothesis is in agreement with an accumulating body of research evidence showing that clinical and personality disorder constructs are more similar than they are distinct (Krueger, 2005; Shea & Yen, 2003).

Moreover, two recent studies have found that borderline personality disorder (BPD) can be modeled as a facet of latent dimensions responsible for risk for Axis I pathology. James and Taylor (2008) demonstrated that BPD symptoms cross-loaded on the anxious-misery and Externalizing factors in a population-based sample of young adults. Replicating these findings with diagnostic-level BPD data, Eaton and colleagues (2010) found syndromal BPD to be an indicator of the anxious-misery subfactor and Externalizing factor in the US National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Grant, Moore, Shepard, & Kaplan, 2003). Thus, it is plausible that as diagnostic coverage is expanded in quantitative studies of comorbidity to include the full range of Axis II conditions, clinical and personality disorders may be found to be reflective of a limited number of latent traits that cut across the Axis I versus II distinction stipulated in DSM-IV (APA, 1994).

Finally, it can be inferred from the preceding survey of studies that there is no standard set of diagnoses used to define the HSM. For example, ASPD is modeled as an indicator of the Externalizing trait in some studies but not others. In some investigations, certain diagnoses are assessed but not used in model fitting procedures due to prohibitively low base rates (e.g., Griffith et al., 2010). Despite this heterogeneity, studies to date have consistently identified an Internalizing-Externalizing configuration to account for inter-diagnosis correlations. However, it may be important to keep in mind that differences in the "item pools" available for these factor analyses may subtly alter the nature of the latent HSM factors. If this is the case, variability

across studies in the indicators used to form the HSM may complicate the interpretation of correlations of HSM latent dimensions with external criteria.

   Temporal Stability of the Liability Spectra. Longitudinal designs have enabled a number of the previously mentioned studies to estimate the stability of the latent liabilities over time. For instance, Krueger et al. (1998) estimated the continuity of Internalizing and Externalizing dimensions over three years in young adulthood in the Dunedin cohort. Standardized path coefficients representing autocorrelation effects were .69 for Internalizing and .86 for Externalizing. In the NEMESIS study, which found evidence for a three-factor model, stability coefficients were .85 for anxious-misery, .89 for fear, and .96 for Externalizing over a one-year interval (Vollebergh et al., 2001). They did not report the autocorrelation of the higher-order Internalizing factor. In the Christchurch study of Internalizing behaviors across young adulthood, Fergusson et al. (2006) reported continuity estimates of .72 and .76 for the latent Internalizing dimension over two successive three-year intervals. Collectively, these data imply considerable rank-order stability of HSM dimensions over time, with some indication that standing on Externalizing is especially stable. These estimates of the magnitude of stability are comparable to those found previously in latent variable modeling research on the continuity of normal and abnormal personality traits (Shea & Yen, 2003; Warner et al., 2004).

   Applicability across Cultures. The epidemiological studies reviewed above have replicated the same basic Internalizing-Externalizing structure, with some studies reporting better fit for models that distinguish between two highly correlated Internalizing subfactors, in the US, Netherlands, Germany, and Australia, indicating some degree of cross-cultural consistency of the findings. Krueger and colleagues (2003) carried out a CFA on data collected from 14 countries (a mix of Western and non-Western cultures) participating in the WHO Collaborative Study of

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Psychological Problems in General Health Care (Utsun & Sartorius, 1995) to explicitly examine the structure of seven common psychopathological syndromes (depression, somatization, hypochondriasis, neurasthenia, anxious worry, anxious arousal, and hazardous alcohol use) across cultures. In the combined sample, a two-factor model that differentiated Internalizing problems from hazardous alcohol use offered the best fit. When analyses were conducted separately by country, this two-factor model was preferred in all but two countries (US and Germany, in which the Internalizing factor bifurcated into strongly correlated depression-anxiety and somatization subfactors).

   Correlation between Internalizing and Externalizing Factors. The degree of overlap between the Internalizing and Externalizing spectra varies across the studies reviewed above. The correlation between these two factors ranged from 0.41 to 0.66 (median = 0.53), indicating a moderate amount of shared variance. It is instructive to note that studies reporting the largest factor correlations typically constructed the Externalizing factor solely from drug and alcohol use disorders, whereas studies documenting smaller correlations also modeled CD and ASPD as Externalizing facets. This pattern is not entirely surprising given substantial levels of comorbidity between substance use disorders and mood and anxiety pathology (Hasin, Stinson, Ogburn, & Grant, 2007; Kessler, Merikangas, & Wang, 2007). The correspondence between Internalizing and Externalizing factors may be an important feature in studies that examine the ability of HSM dimensions to predict external constructs, a topic discussed in later sections. Greater overlap between latent factors may create a collinearity problem that could limit the efficiency of clinical and etiological research with the HSM.

Implications of the HSM for Official Nosologies

Dimensional versus Categorical Assessment. Beginning with the release of DSM-III

(APA, 1980), the DSM classification system has been aligned with a neo-Kraepelinian

perspective on mental disorder (Klerman, 1990). In this framework, syndromes are

conceptualized as discrete, categorical entities, each with a distinct etiology, pathophysiology,

and prognosis. To a large extent, the comorbidity phenomenon contradicts the premise that

syndromes are qualitatively distinct from each other and from "no disorder" (Lilienfeld,

Waldman, & Israel, 1994; Meehl, 2001). Extensive empirical overlap among separate

syndromes undermines the discriminant validity of categorical diagnoses, diminishing the

plausibility of separate etiologies and pathologies across all disorders.

The HSM supports an alternative, dimensional conceptualization of psychopathology.

This model raises the possibility that apparently distinct syndromes do not reflect true categories

and instead represent different facets of a single continuum. In contrast to the neo-Kraepelinian

view that people either have a disorder (i.e., are members of a true latent class) or not, the HSM

assumes that all individuals possess the Internalizing (or Externalizing) trait in varying amounts.

From this perspective, disorder may be defined as a position on the liability-spectrum in excess

of some clinically meaningful threshold (cf. Cannon & Keller, 2006; Krueger & Markon, 2006).

Various researchers have used model-fitting techniques to compare dimensional and

categorical conceptualizations of disorder. Walton et al. (2011) evaluated the fit of latent class

and latent trait models to adolescent Externalizing behavior problems assessed by the CBCL

(Achenbach, 1991) in the TRAILS study. Latent class models represent the categorical

perspective because they assume that a specific number of mutually exclusive groups underlie

the response data (McCutcheon, 1987), whereas latent trait models assume the presence of a

continuously-distributed liability dimension that is possessed by all individuals to different

degrees (Hambleton, Swaminathan, & Rogers, 1991). According to the Bayesian information criterion (BIC; Schwarz, 1978), a latent trait model provided superior fit to the symptom data when compared with latent class models at both time points in this longitudinal study. Krueger and colleagues (2005) adopted this same analytic strategy to compare categorical and continuous models of Externalizing diagnoses in the Minnesota Twin Family Study (MTFS). As predicted, these authors found a latent trait model to provide superior fit, again supporting a spectrum approach to describe antisocial behavior and substance use disorders.

These studies are unique because they aimed to directly compare the results from quantitative models that map onto competing conceptualizations of psychopathology. This research bolsters confidence in previous studies, many of which are reviewed above, that found a latent trait model to provide a good account of the correlations between Internalizing and Externalizing diagnoses, but did not conduct comparisons with latent class models (e.g., Krueger et al., 1998; Krueger et al., 2007).

An Empirically-Based DSM. The transition to DSM-5 is an opportunity to incorporate research on the empirical organization of psychopathology into our classification system (Krueger, 2005). Clark, Watson, and their associates (e.g., Clark & Watson, 2006; Watson, 2005) have asserted that it is time that the diagnostic system be founded on scientific work, as opposed to "shared phenomenological features" (APA, 1994, p. 10) or a "rational folk system" (Clark & Watson, 2006, p. 482).

As mentioned above, a number of large-scale quantitative studies on the structure of comorbidity have used model-fitting to explicitly compare the DSM organization of disorders to other arrangements suggested by previous empirical work (e.g., Krueger et al., 1998; Krueger, 1999; Vollebergh et al., 2001). In each case, the DSM organization has failed to provide optimal

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fit, relative to other potential organizing schemes. In response to these findings, Watson (2005) proposed a quantitative model for the emotional disorders that clustered GAD and PTSD with MDD and DYS as Distress Disorders (sometimes labeled the anxious-misery domain), whereas PAN and the phobias were subsumed under Fear Disorders. Obviously, placing GAD and PTSD with the mood disorders represents a departure from the current nosology, which distinguishes mood from anxiety disorders. Also noteworthy is that OCD was not included in this hierarchical structure of emotional disorders because existing data are limited and support divergent conclusions (Watson, 2005; Slade & Watson, 2006).

Other researchers have used existing empirical modeling studies of comorbidity to propose similar "meta-structures" to organize DSM-5 Internalizing and Externalizing disorders (Goldberg, Krueger, Andrews, & Hobbs, 2009; Krueger & South, 2009). In addition to noting the high rates of comorbidity within the Internalizing and Externalizing spectra, these proposals highlight that Internalizing disorders tend to be characterized by similar genetic factors, early childhood environment, cognitive and emotional processing, and various other external criteria that are to a large extent separable from those marking Externalizing disorders.

Elaborating the Nomological Network of the HSM

In a commentary accompanying Krueger's (1999) analysis of comorbidity in the NCS data, Wittchen, Höfler, and Merikangas (1999) cautioned that enthusiasm for the HSM should be limited until evidence to support its construct validity is produced. Referring to guidelines offered by Robins and Guze (1970) for establishing diagnostic validity, Wittchen et al. claimed that Krueger had accomplished the first step in the validation process (i.e., articulating a clinical description, or inclusion criteria) for the HSM, but the remaining criteria (i.e., stability, heritability, laboratory markers, and delimitation from other disorders [exclusion criteria]) were

untested. Therefore Wittchen et al. concluded that there was insufficient evidence to support Krueger's recommendation that psychopathology research should focus on the common substrates (i.e., higher-order Internalizing and Externalizing dimensions) of mental disorders. Research findings emerging in response to the commentary of Wittchen et al. that are relevant to construct validity and scientific utility of the HSM higher-order dimensions are the focus of the remainder of this review.

Correlates of HSM Dimensions. In a section of the original report on the HSM titled "What Are Internalizing and Externalizing?", Krueger et al. (1998) speculated that these latent factors may correspond to broadband personality traits. Based on research documenting links between personality dimensions and psychiatric diagnoses (e.g., Trull & Sher, 1994), the authors hypothesized that Internalizing would map onto neuroticism whereas Externalizing would be associated with (low) conscientiousness. In subsequent work, Krueger and colleagues (Krueger et al., 2005; Krueger et al., 2007) have posited that Externalizing overlaps extensively with disinhibition, an amalgam of Disagreeableness and Unconscientiousness from the five-factor model of personality (Markon, Krueger, & Watson, 2005).

The first study to examine these predictions empirically was conducted by Krueger, McGue, and Iacono (2001) in the MTFS. Their analyses revealed moderate correlations between Internalizing and negative emotionality as assessed by the Multidimensional Personality Questionnaire (MPQ), with values of .27 and .22 for men and women, respectively. Internalizing was virtually unrelated to MPQ constraint, an index of cautious behavior and endorsement of traditional values ($r < .04$ for both sexes). In contrast, Externalizing was not significantly associated with negative emotionality (rs $< .04$), but demonstrated a moderate inverse correlation with constraint ($r = -.28$ for men and $-.20$ for women).

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Simms and colleagues (2008) carried out a similar study using bifactor modeling of the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al., 2007) in college student, community, and patient samples. The IDAS was designed explicitly to assess the general and specific components of depression and anxiety (Watson et al., 2008, 2007) and includes ten subscales that reflect relatively specific types of symptoms (e.g., Traumatic Intrusions, Social Anxiety, Panic). In the bifactor model, each symptom on the IDAS was allowed to load on the general factor and one specific factor corresponding to its subscale (e.g., all items on the Panic subscale loaded on the same specific factor). The general factor, representing common variance across all depression and anxiety symptom scales, may be construed as an Internalizing trait. Analyses revealed a strong positive correlation (rs ranged from .51 to .67 across samples) between the Internalizing general factor and Big Five Inventory neuroticism, and moderate negative associations with conscientiousness (rs from -.31 to -.34) and agreeableness (rs from -.25 to -.39). Simms et al. (2008) also reported correlations of the Internalizing factor with the Beck Depression Inventory (Beck, Steer, & Brown, 1996) ranging from .75 to .82 across samples, and correlations between Internalizing and the Beck Anxiety Inventory (Beck & Steer, 1990) of .68 to .72.

Griffith et al. (2010) applied structural equation modeling (SEM) to examine the links between neuroticism and the HSM factors in a high-school sample overselected for high levels of neuroticism. In this study, Internalizing psychopathology included MDD, DYS, PAN, SOP, GAD, SPP, and OCD, whereas the Externalizing factor was formed by alcohol and cannabis use disorders. A design strength was that neuroticism was assessed using multiple measures and both self- and peer-report. In the final model, the latent neuroticism factor correlated .98 and .29 with Internalizing and Externalizing, respectively. Chi-square difference tests indicated that the

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correlation between neuroticism and Internalizing did not significantly differ from unity, indicating nearly complete overlap between these two constructs. The estimate of the association between neuroticism and Internalizing may have been high, in comparison to that found by Krueger et al. (2001) and Simms et al. (2008), due to the elimination of measurement error in the neuroticism construct afforded by the SEM approach. It is also possible that the strength of the neuroticism-Internalizing association varies systematically as a function of age or measurement instrument. Specifically, the study by Griffith et al. (2010) involved high school participants, whereas the other two studies relied on adult samples. Further, in other research areas, different instruments used to measure neuroticism have led to conflicting conclusions (Munafò et al., 2009).

Etiology and Clinical Features. Evidence to support the HSM account of comorbidity is accumulating, yet much of this research has been cross-sectional and virtually silent on the etiology of Internalizing and Externalizing dimensions. Longitudinal research is needed to determine whether the HSM can explain the associations between common vulnerability factors (e.g., childhood adversity, gender) and psychopathology. An intriguing possibility is that some popular risk markers in psychopathology research may confer risk for general Internalizing and Externalizing traits, and could thus be considered indirectly related to manifest diagnoses. For example, a hypothetical cognitive diathesis could predict greater severity of the Externalizing trait (e.g., by promoting a general disinhibitory cognitive style), which may in turn increase risk for ASPD. A complementary hypothesis is that some risk factors are relatively specific to particular disorders and show a statistical association with these diagnoses even after partialling out the variance shared between diagnoses and the common factors. In sum, research focusing on the etiology and clinical consequences of individuals' position on the higher-order

Internalizing and Externalizing factors has the potential to recast risk factors, correlates, and consequences of psychopathology as general (i.e., related to standing on the common factors only), specific (i.e., related to the unique component of one or more diagnoses but not common factors), or hybrid (i.e., related to the common factors and also the unique component of one or more diagnoses). Uncovering the specific and hybrid risk factors of mental disorders may have particularly intriguing implications for research and nosology. As stated by Meehl (1977) and others (e.g., Garber, Frankel, & Street, 2009), identifying the biological and psychosocial etiological factors unique to a particular disorder is the strongest form of construct validation for diagnostic entities. Presented in Figure 4 is a schematic of how general, specific, and hybrid risk factors might interface with the hierarchical structure of the HSM.

Some prior work has attempted to evaluate the generality versus specificity of risk factors for psychopathology. Kramer et al. (2008) conducted a study to determine whether gender differences in common forms of psychopathology could be explained by gender differences on the higher-order factors in the HSM. Participants in the Minnesota Twin Registry (MTR; Lykken, Bouchard, McGue, & Tellegen, 1990) completed the Psychiatric Diagnostic Screening Questionnaire (PDSQ; Zimmerman & Mattia, 2001) to assess MDD, GAD, SOP, PAN, AGO, OCD, hypochondriasis, bulimia, substance use disorders, and adult antisocial behavior (AAB). Consistent with predictions, the authors found evidence for a two-factor Internalizing-Externalizing model. To test the hypothesis that the mean number of symptoms for individual syndromes would not differ for males and females after accounting for gender differences on the latent factors, a series of increasingly stringent factorial invariance models were applied to the two-factor HSM by imposing constraints on factor loadings, factor covariances, factor variances, residual variances, intercepts, and factor means (Meredith, 1993). A strong invariance model

(which assumes invariance across gender in factor structure, factor loadings, and the intercepts in the equations linking the latent factors and observed syndromes) was found to fit the data best, indicating that gender differences in manifest symptom scores were attributable to mean differences in the latent factors across gender. Specifically, men demonstrated higher levels of Externalizing ($d = 0.52$) and lower levels of Internalizing ($d = -0.23$) than women. The interpretation of these results was that etiological mechanisms causing gender differences in psychiatric syndromes may act in large part on Internalizing and Externalizing traits. It is important to keep in mind, however, that observed syndromes have varying levels of overlap with the common factors, and this may reflect different levels of susceptibility to risk factors impacting the higher-order traits (cf. Mineka et al., 1998). For example, Kramer et al. (2008) note that in men, the Internalizing factor accounted for 55% and 16% of the variance in MDD and OCD, respectively. It is thus possible that etiological factors that are not relevant to the Internalizing factor determine the majority of risk to OCD.

Two studies have examined whether the HSM can explain the intergenerational transmission of psychopathology. First, Kendler et al. (1997) evaluated the correspondence between parent and offspring Internalizing and Externalizing trait estimates. Using interviews with NCS Phase II participants and their parents, the authors modeled MDD and GAD as indicators of a latent Internalizing factor and drug abuse/dependence (DAD), alcohol abuse/dependence (AAD), and ASPD as indicators of latent Externalizing. (In parents, DAD was allowed to cross-load on Internalizing and Externalizing.) They found the parental Internalizing factor to affect offspring standing on both Internalizing ($\beta = .36$) and Externalizing ($\beta = .14$) dimensions. Likewise, parental Externalizing had statistically significant effects on offspring Externalizing ($\beta = .21$) and Internalizing ($\beta = .12$) traits. Kendler et al. (1997) did not

directly model residual covariation between parent and offspring manifestations of particular

diagnoses. However, they tested specificity of transmission by statistically controlling for the

presence of all other disorders when computing associations between particular parent and

offspring diagnoses. For MDD, GAD, and AAD, substantial intergenerational transmission

effects remained (as indicated by odds ratios > 1.70) even after controlling for the influence of

comorbid diagnoses in both parent and offspring. This suggests that some unique risk for these

disorders is passed down to offspring, independent of the transmission of general vulnerability to

Internalizing or Externalizing distress.

Second, Hicks et al. (2004) investigated the heritability and familial transmission of a

latent Externalizing trait formed by symptom counts of AAB, CD, DAD, and AAD in the

Minnesota Twin Family Study. Model-fitting results indicated that parent standing on

Externalizing was passed down to offspring (βs = .30 for both mother and father effects on

offspring). In contrast to the Kendler et al. (1997) results, no significant residual correlations

between parent and child diagnoses were detected after controlling for the general transmission

effect, indicating an absence of disorder-specific transmission. Although there were no specific

effects across generations, there was evidence of residual correlations between syndromes among

twins, indicating the existence of diagnosis-specific risk factors. Additionally, these residual

correlations were found to be equal for monozygotic and dizygotic twin pairs, signaling that

these diagnosis-specific risk factors are environmentally mediated.

Patrick and colleagues (2006) conducted a unique study in which the relationship

between the general Externalizing factor—composed of symptom counts of AD, CD, AAB, drug

dependence (DD), and nicotine dependence—and the p300 brain potential response was

examined. The p300 response was historically thought to be a marker of risk to AD, but has

since been associated with all other syndromes of the Externalizing spectrum (e.g., Costa et al., 2000). Hierarchical regression analyses revealed that symptom counts from all diagnoses had significant zero-order relationships with p300 amplitude, but these associations were all found to be negligible once general Externalizing scores were taken into account. The authors suggest that this is evidence that p300 response patterns may not be associated specifically with alcohol problems. More generally, these data indicate that common clinical correlates or consequences of particular syndromes may primarily be associated with what clusters of disorders have in common, rather than their uniquenesses.

In the largest study to document the construct validity of the HSM to date, Kessler et al. (2011) studied the role of latent dimensions in the development of comorbidity among 18 lifetime diagnoses (10 Internalizing, 8 Externalizing) in the WHO World Mental Health Surveys. EFA of all diagnoses produced two broad liability spectra representing Internalizing and Externalizing, with no indication of a subdivision between anxious-misery and fear disorders. Kessler et al. found that the prospective associations between Time 1 disorders and Time 2 onsets of comorbid conditions were mediated by Internalizing and Externalizing latent variables. Only 13 of the 306 total residual across-time diagnostic correlations were significant in the model that posited mediating Internalizing and Externalizing pathways. These results suggest that the HSM is useful not only in describing the structure of comorbidity but also explaining the new onset of comorbid syndromes. However, some additional explanatory mechanisms may be necessary to account for a limited number of diagnosis-specific associations.

Quantitative Genetic Bases. Recently, researchers have begun to address the question of whether disorders that cluster together phenotypically are also genetically coherent. Evidence of a common genetic diathesis underlying a spectrum of disorders would indicate the presence of

shared biological etiological factors. Initial work by Kendler (1996) demonstrated that the genetic correlations among the mood and anxiety disorders mirrored the pattern of phenotypic associations between them. The genetic correlation between MDD and GAD did not differ from unity, suggesting that these disorders have an identical genetic basis, with variation in environmental exposure determining the distinct behavioral manifestations of these disorders. It was later reported that much of this shared genetic diathesis overlapped with genes causing variation in neuroticism (Kendler, Gardner, Gatz, & Pedersen, 2007). On the other hand, MDD and GAD are both genetically distinguishable from the remaining anxiety disorders, showing moderate genetic overlap with panic disorder, agoraphobia, social phobia, and OCD, and a weaker genetic relationship to specific phobias (Hettema, Neale, Myers, Prescott, & Kendler, 2006; Kendler, Neale, Kessler, Heath, & Eaves, 1993; Koenen et al., 2008).

Kendler and colleagues (2003) extended this line of work by modeling the shared genetic and environmental determinants of Internalizing and Externalizing disorders in the population-based Virginia Twin Registry. Biometric analyses identified common genetic factors underlying risk to Internalizing (MDD, GAD, and the phobias) and Externalizing (AAD, DAD, CD, and AAB), producing a structure congruent with phenotypic analyses in epidemiological samples. A second set of analyses focused particularly on Internalizing syndromes and revealed two correlated genetic factors mapping onto anxious-misery (MDD, GAD) and fear (animal and situational phobias) dimensions previously identified in the epidemiological literature. Importantly, the multivariate genetic analyses also showed that the coherence of the Internalizing-Externalizing structure was due mostly to the two common genetic factors; the shared and unique environmental factors were not specific to one set of disorders or the other.

Also using a twin design, Wolf et al. (2010) investigated the genetic structure of a similar

set of diagnoses (MDD, DYS, GAD, PD, PTSD, ASPD, AAD, and DAD). In preliminary

phenotypic analyses, PTSD was shown to load on both Internalizing and Externalizing

dimensions, in contrast to the EFA results of Cox et al. (2002). Replicating findings from

Kendler et al. (2003), satisfactory fit was found for a model distinguishing between two genetic

factors corresponding to the Internalizing and Externalizing spectra. A significant difference

was found in the heritability of the Externalizing ($h^2 = .69$) and Internalizing ($h^2 = .41$)

dimensions. Additionally, shared genetic variance accounted for 67% of the phenotypic

correlation ($r = .52$) between the spectra. Two similar studies, specifying slightly different

combinations of indicator variables for the latent Externalizing dimension, supported the

hypothesis of a highly heritable (h^2 estimates of .84 and .81) latent factor uniting Externalizing

disorders and disinhibitory personality traits (Krueger et al., 2002; Young, Stallings, Corley,

Krauter, & Hewitt, 2000).

Summary and Future Directions. Krueger and Markon (2011), in reviewing the state of

the HSM literature, recently commented that the focus of new research should be on evaluating

how HSM dimensions relate to other psychological phenomena. As stated by Cronbach and

Meehl (1955), "A construct is defined implicitly by a network of associations or propositions in

which it occurs" (p. 299). Thus, to clarify what the HSM dimensions are, a nomological network

for the HSM must be articulated. This entails the examination of predictive relationships with

observed variables (e.g., age, hospitalizations, treatment seeking behavior) and other

hypothetical constructs (MacCorquodale & Meehl, 1948). As of yet, this nomological net

contains few connections, reflecting limited theoretical development of the HSM factors.

Indeed, the process of HSM construct validation is truly in an incipient phase, with only a handful of studies in existence that link the Internalizing and Externalizing spectra with theoretically related variables (e.g., Griffith et al., 2010; Patrick et al., 2006). Thus, while it is clear that a latent variable model provides a viable explanation for comorbidity, it remains relatively uncertain whether the HSM can serve as a useful heuristic for research on psychopathology (cf. Wittchen et al., 1999). Although the studies reviewed above demonstrate that it is possible to frame psychopathological theories and research around the HSM, a much more extensive delineation of its nomological network is necessary before the construct validity of the HSM can be considered robust.

Research to date has yielded only a partial answer to Krueger et al.'s (1998) question "What are Internalizing and Externalizing?" These two dimensions have shown a moderate degree of discriminant validity in studies examining associations with personality constructs. Consistent with expectations, Internalizing correlates substantially with neuroticism, although estimates of this effect size vary widely across different instruments and samples (Griffith et al., 2010; Krueger et al., 2001; Simms et al., 2008). In contrast, Externalizing shows a modest relationship with individual differences in neuroticism, and exhibits a moderate, inverse association with the personality dimension of constraint (Krueger et al., 2001). Even though some estimates of the overlap between HSM factors and broadband personality traits are very high (Griffith et al., 2010), it is likely that multiple psychopathological processes underlie variation in each domain. That is, despite the fact that many models identify only two latent variables in phenotypic and genotypic structures of disorders (e.g., Wolf et al., 2010), it is plausible that a number of processes or constructs operate together to determine individuals' standing on Internalizing and Externalizing (Kessler et al., 2011). No study to date has examined

the predictive power of multiple explanatory variables in HSM frameworks. Construction and testing of multivariate models that evaluate the comparative explanatory value of various theoretically relevant predictors is needed to resolve the range and relative importance of processes impacting HSM dimensions.

As noted at the outset, the comorbidity phenomenon complicates the interpretation of studies attempting to test hypotheses pertaining to particular disorders (Clark et al., 1995). The work of Kessler et al. (2011) provides an empirical demonstration of this dilemma by showing that the majority of pairwise, longitudinal associations between a given syndrome and new onsets of comorbid conditions were mediated by standing on higher-order latent dimensions. This suggests that researchers focusing on a particular diagnosis (or limited set of diagnoses) should be aware that effects may reflect a more general vulnerability common to a range of pathologies. More longitudinal research incorporating the HSM is necessary to enrich our understanding of both the origins and clinical consequences of individual differences in Internalizing and Externalizing traits, and to uncover which of these variables are uniquely related to manifest syndromes, as opposed to general Internalizing or Externalizing vulnerability.

The hierarchical configuration of correlated disorders embodied in the HSM, first developed in the 1990s for comorbid depression and anxiety (e.g., Mineka et al., 1998), offers a valuable framework for elaborating the nomological network of the HSM. Once the hierarchical structure is expressed as a quantitative model (i.e., translated into a system of equations), we are able to address the question "Does the HSM make our theories work better?" That is, we can evaluate whether the relationship between criterion Y and syndrome X is better accounted for by the relationship between criterion Y and the general vulnerability factor of which syndrome X is an indicator. For instance, Patrick et al. (2006) used this strategy to examine whether (a) general

severity of Externalizing pathology (i.e., standing on the latent variable uniting various substance and antisocial behavior disorders) was associated with p300 amplitude; and (b) alcohol use disorder symptomatology was predictive of p300 scores after controlling for general Externalizing severity. These authors found that p300 amplitude was robustly associated with the common Externalizing factor, and that there was no unique relationship between alcohol use disorder and p300 variability. This suggests that the original psychological theory postulating a specific pathway involving the p300 response, executive functioning impairments, and risk for alcohol dependence (e.g., Begleiter & Porjesz, 1999) may be in need of revision. Specifically, the brain-based cognitive impairment indicated by reduced p300 amplitude may confer risk for a general Externalizing trait. Generally, the study by Patrick et al. (2006) represents a method for using the HSM to refine existing theories of psychopathology.

Almost every major theory in psychopathology research could be reevaluated through the lens of the HSM hierarchy. To take one example, much has been written about possible explanations for gender differences in depressive disorders (e.g., Hankin & Abramson, 2001; Nolen-Hoeksema, 2001). An empirical study by Kramer et al. (2008) suggests that the many of the vulnerability factors increasing risk for depression in females may act directly on a general Internalizing vulnerability. These authors showed that after accounting for higher standing among females on Internalizing there were negligible gender differences in the severity levels of all manifest mood and anxiety syndromes.

Prior work has also shown that the HSM has implications for the intergenerational transmission of psychopathology. Again, considerable research has focused on familial transmission of particular disorders, such as depression (e.g., Hammen, Shih, & Brennan, 2004). Studies by Kendler et al. (1997) and Hicks et al. (2004) suggest that what is passed down to

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offspring may be a general vulnerability to common forms of psychopathology, rather than specific risk for one disorder or another. Hicks et al. (2004) explicitly modeled diagnosis-specific effects of Externalizing disorder transmission between parent and offspring and found no evidence of specificity (see also Low, Cui, & Merikangas, 2008). This area of research is in its infancy, and methodologies have not been entirely consistent across studies, limiting the strength of any conclusions to be drawn from them. Nonetheless, it is clear that the hierarchical perspective implicit in the HSM provides a novel framework for evaluating existing theories in psychopathology and generating new research questions.

Regarding the construct validity of different levels of the HSM hierarchy, virtually nothing is known about the external correlates of the anxious-misery and fear dimensions. This is partly because in past work Internalizing is only sometimes divisible into these subfactors (Kendler et al., 2003; Kessler et al., 2011; Wolf et al., 2010). The importance of this issue is not entirely clear, given that even when anxious-misery and fear are empirically distinguishable they are highly correlated and interpretable as subcomponents of the broader Internalizing spectrum (Krueger, 1999). However, it is theoretically possible for these two subfactors to display meaningfully different patterns of associations with relevant constructs, which would argue for the importance of differentiating between them when examining external correlates of the HSM. Indeed, in comparison to statistical model fit indices, empirical results of construct validation studies are likely to provide a much more scientific basis for the decision of whether or not to distinguish between the two subfactors of the Internalizing spectrum (see Lahey et al., 2008). Along these lines, twin data reported in Kendler et al. (2003) indicated that the genetic diathesis underlying Internalizing was separable into two positively correlated components identified by anxious-misery disorders (MDD, GAD) and fear disorders (animal and situational phobias).

Future research into the potentially different origins, correlates, and consequences of the anxious-misery versus fear dimensions is vital to establishing a consistent structure for the HSM and explicating its nomological network.

Quantitative genetics studies have shown the phenotypically coherent liability spectra to also be genotypically coherent. Two separate investigations have now identified distinct genetic components underlying risk for Internalizing and Externalizing traits (Kendler et al., 2003; Wolf et al., 2010). This research has interesting implications for research on the etiology of related disorders. The available data suggest that many of the biological mechanisms predisposing to, say, MDD are shared among the remaining Internalizing disorders. At the extreme, research has consistently found MDD and GAD to have indistinguishable genetic bases (Kendler, 1996). These findings suggest a number of hypotheses for future research. First, genetic and psychobiological pathways known to impact a particular syndrome may be relevant primarily to overall risk on the higher-order dimensions. Second, given evidence showing that disorders cohere primarily due to genetic, and not environmental, causes, testing associations of known environmental risk factors with unique variance in correlated disorders may help establish which environmental vulnerabilities are responsible for the different behavioral manifestations of the same risk dimension. Such a research enterprise would be consistent with a "generalist genes, specialist environments" model, in which environmental influences differentiate between syndromes with highly overlapping genetic liabilities (Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011). For example, it might be hypothesized that stressful events involving loss or humiliation may be specifically associated with residual variance in MDD (and not GAD) after partialling out the overlap of variability between MDD (GAD) and the general Internalizing spectrum (e.g., Kessler, Davis, & Kendler, 1997; Monroe, Rohde, Seeley, & Lewinsohn, 1999).

Quantitative genetic investigations have also been able to ascertain the heritability of the higher-order dimensions of the HSM. The estimated heritability for Internalizing is 41% (Wolf et al., 2010) and estimates range from 69-84% for Externalizing across three studies (Krueger et al., 2002; Wolf et al., 2010; Young et al., 2000). It may be hypothesized that these heritable latent dimensions constitute an endophenotype of the observed Internalizing and Externalizing diagnoses. That is, the continuously-distributed latent trait underlying a set of syndromes may map more closely onto the shared biological substrate that confers risk for these different disorders (Krueger & Markon, 2006). These latent variables may therefore be important targets for future research on the molecular genetics and psychobiology of psychopathology.

Molecular Genetics of the HSM

With the advent of molecular genetic technologies, the investigation of the biological origins of latent psychopathological processes has become a tractable goal. Researchers have only recently begun to integrate the sophisticated statistical techniques used to define the HSM with a molecular genetic approach. This section of the review describes the potential utility of the HSM for gene finding efforts.

The majority of research in psychiatric genetics has focused on identifying genes relevant to a specific, categorically defined diagnosis (Dick et al., 2008). For example, a large amount of funding has been dedicated to projects concentrating on schizophrenia, alcohol dependence, autism, and other syndromes. The efficiency of this research paradigm has been challenged by accumulating data indicating that (a) consistent gene-disorder linkages are extremely rare and (b) single genes influence risk for multiple forms of psychopathology (i.e., pleiotropy). Therefore, it may not be plausible to expect one-to-one correspondences between particular genes and syndromes (Kendler, 2006).

Phenotypic studies supporting the HSM suggest an alternative representation of disorder phenotype that may facilitate molecular genetic research in psychopathology. The superordinate factors of the HSM are continuously-distributed spectra that reflect basic psychopathological processes shared among disorders. It is possible that some genetic variants affect susceptibility for observed disorders by influencing these common processes (Krueger & Markon, 2006). Consistent with this hypothesis, twin studies of the HSM have demonstrated a shared genetic liability across disorders (e.g., Kendler et al., 2003). In fact, the heritability estimates of Internalizing and Externalizing dimensions were generally found to exceed those of individual disorders (Wolf et al., 2010).

The combination of shortcomings of molecular genetic research with categorical phenotypes (e.g., Hamer, 2002) and the substantial heritability of the HSM factors has led some authors to propose the use of these latent traits as endophenotypes in molecular genetic studies (Dick, 2007). The potential utility of endophenotypes—defined as intermediate links on the causal chain from genetic variation to disorder (Bearden et al., 2009)—lies in a simplified etiology. That is, distilling observed syndromes into core psychopathological processes is presumed to restrict the range of causal influences on the phenotype, relative to the breadth of processes acting on a given disorder (Cannon & Keller, 2006). With fewer competing genetic and environmental risk factors, it is possible that HSM endophenotypes are more robustly associated with candidate genes and thus more amenable to molecular genetic analysis (Leboyer et al., 1998).

Molecular Genetic Findings with the HSM. Three empirical studies to date have supplied data to support the notion that HSM dimensions may function as endophenotypes. Stallings et al. (2005) assessed symptoms of substance dependence and CD in a community-based sample of

adolescents and young adults referred to treatment facilities for substance use and delinquency. Genetic analyses indicated that the same chromosomal region (9q34) was associated with both substance dependence and CD behaviors. However, linkage was significantly stronger between 9q34 and a composite of substance use and CD symptoms than with either of these outcomes in isolation. In follow up analyses with the same sample, this research group investigated the association of 1500 single nucleotide polymorphisms (SNPs) across 50 candidate genes with the composite phenotype, which was labeled antisocial drug dependence (Corley et al., 2008). Two genes (neuronal nicotinic receptor alpha 2 [CHRNA2] and the mu opiod receptor gene [OPRM1]) were identified as plausible contributors to the antisocial drug dependence phenotype.

Finally, in the Collaborative Study on the Genetics of Alcoholism, Dick et al. (2008) used principal component analysis (PCA) to show lifetime symptom counts of AD, DD, CD, and ASPD, as well as novelty seeking and sensation seeking personality trait scores, formed a unitary Externalizing factor. The authors examined the association of the general Externalizing spectrum with the muscarinic acetylcholine receptor M2 gene (CHRM2), a gene that had been previously linked with AD in this sample. A number of SNPs in CHRM2 were significantly associated with different Externalizing facets (e.g., CD), but the strongest and most consistent associations were found with the general Externalizing phenotype. This result provides some indication that the Externalizing factor may represent a basic psychological construct that is more proximal to CHRM2 gene action than its various facets.

Summary and Future Directions. To date, 1 linkage and 2 association studies have explored the genetic bases of HSM dimensions. Each of these investigations has found evidence supporting a genetic link to the Externalizing spectrum. The study by Dick et al. (2008) offered the most comprehensive coverage of Externalizing facets and found that the CHRM2 gene was

more strongly related to the Externalizing spectrum than to the individual syndromes and personality traits on which it was based.

These studies are representative of a movement toward endophenotype research in clinical psychology and psychiatry that began in response to failures to consistently identify molecular genetic causes of categorical disorders (Hamer, 2002). Research on the HSM has raised the possibility that higher-order factors may represent core processes that mediate genetic risk for observed psychiatric syndromes (Krueger & Markon, 2006). The latent factors, especially Externalizing, are more heritable than their constituent diagnostic indicators (Krueger et al., 2009) and may be linked to theoretically relevant candidate genes (e.g., Dick et al., 2008). Clearly, however, researchers are only just beginning to explore the viability of HSM endophenotypes.

One final consideration is that, based on a rapid proliferation of gene-environment interaction (G × E) findings in the clinical literature, environmental factors are likely to be play an important role in molecular genetic research on HSM endophenotypes (see Lau & Eley, 2010; Caspi et al., 2010; Rutter, 2008). Most notably, a recent meta-analysis supported the hypothesis that a polymorphism in the serotonin transporter gene (5-HTTLPR) predicts risk for MDD, but only under stressful environmental circumstances (Karg, Burmeister, Shedden, & Sen, 2011). This emerging evidence supports the possibility that the monoaminergic candidate genes and stressful environments act in concert to determine individual differences on the Internalizing and Externalizing dimensions.

<center>Project Overview</center>

In view of the far-reaching implications of the HSM for theory, research, classification, and treatment in clinical psychology, further empirical attention to the construct validity of the

HSM is an urgent task for the field. The majority of research to date has endeavored to determine the number of latent spectra needed to explain the co-occurrence of common psychiatric syndromes without a great deal of consideration of the nature of these spectra. As a result, very little is known about the origins of individual differences on the Internalizing and Externalizing dimensions. A corollary is that prior work has not delineated which etiological factors are specific to individual syndromes (e.g., GAD), as opposed to those that confer general risk for the Internalizing and Externalizing traits. Likewise, more research is needed to elucidate the clinical features and consequences (e.g., suicide attempts, interpersonal difficulties) of the higher-order HSM dimensions and create a taxonomy of which of these variables are characteristic of specific syndromes versus general liability factors. Generally speaking, the nomological network of the HSM remains unpopulated (Cronbach & Meehl, 1955).

The current dissertation is designed to address these gaps in our understanding of the HSM. Several questions about the origins, correlates, and consequences of higher-order HSM dimensions and their facets will be explored in a series of three studies, two of which rely on prospective, longitudinal data from a community sample of young adults oversampled for a history of maternal depression. The first study addresses the developmental antecedents— including genetic, temperamental, and environmental influences—of standing on the HSM factors. The second study examines the ability of the HSM to explain recent findings regarding the stress generation phenomenon, which is the tendency for people with a history of depression, relative to their never-depressed counterparts, to experience more stressful life events dependent at least in part on their own behavior or characteristics (Hammen, 1991). The third study investigates the joint effects of genetic and environmental factors in generating Internalizing and

Externalizing behaviors on a within-person basis with the use of a daily diary methodology. The primary questions to be addressed in the project are as follows:

1. What are the optimal number and configuration of higher-order HSM dimensions to explain the covariation of common psychiatric syndromes?

This question is addressed in all three studies. Past research has produced inconsistent results regarding the number of latent spectra that provides the best account of diagnostic correlations. In particular, results are mixed regarding the possibility that the broad Internalizing spectrum bifurcates into anxious-misery and fear subfactors. The first two studies will use standard fit indices to evaluate how well two- and three-factor models reproduce correlations among syndromes. If anxious-misery and fear subfactors can be reliably differentiated, a comparison of their correlations with other constructs (e.g., developmental risk factors) will provide an indication as to whether there is any practical benefit of distinguishing between them. The daily diary study will also inform this debate by comparing the cross-day associations between prototypical symptoms of the anxious-misery (e.g., depressed mood) and fear (e.g., physiological signs of panic) dimensions. If the fear symptoms are substantially more highly correlated with subsequent fear, as opposed to anxious-misery, symptoms, this would represent evidence of a meaningful distinction between the two Internalizing subfactors.

2. Do monoaminergic genes play a role in determining individual differences on Internalizing and Externalizing dimensions?

Genetic questions will be examined in Studies 1 and 3. In Study 1, 5-HTTLPR and a common variant in the catechol-*O*-methyltransferase (COMT) gene are studied as risk factors for HSM dimensions both in isolation and in conjunction with childhood adversity. In Study 3, the

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role of 5-HTTLPR in potentiating the effects of daily stress on Internalizing and Externalizing symptoms is examined.

3. What are the early childhood predictors of the HSM latent factors?

This question is addressed specifically in Study 1. This study among high-risk young adults evaluates the prospective effects of childhood adversity and early manifestations of the Internalizing and Externalizing spectra on HSM dimensions derived in young adulthood. Additionally, both of these developmental factors, as well as gender, will be examined for specific links with individual syndromes, after partialling out variance shared between these syndromes and general HSM factors.

4. What is the role of HSM Internalizing and Externalizing dimensions in the stress generation phenomenon?

Stress generation refers to the tendency of people with a history of depression, relative to never-depressed counterparts, to experience more stressful events that are caused at least in part by characteristics or behaviors of the person (Hammen, 2006). The role of the liability spectra and their facets in stress generation is the focus of Study 2, in which the HSM will be constructed based on onsets of diagnoses before participant age 19, and associations between HSM dimensions and acute stressors occurring in the 12 months prior to participants' age 20 will be examined. Of particular interest is whether MDD will show unique stress generation effects after accounting for the link between the general Internalizing factor and later stress.

Chapter 2: Integrating genetic and environmental risk factors into a Hierarchical-Spectrum

Model of mental disorders

The primary purpose of the first study is to examine several possible etiological factors related to the HSM dimensions. As mentioned above, longitudinal research using the HSM hierarchical framework is needed to delineate which etiological factors are common to a spectrum of Internalizing or Externalizing diagnoses and which are specific to a particular syndrome. This type of investigation is relevant to efforts to revise the organization of current nosologies to reflect etiological, as opposed to phenomenological, similarities among disorders (e.g., Goldberg et al., 2009; Krueger & South, 2009). It also has the potential to reshape etiological research by informing a taxonomy of risk factors that is based on their degree of specificity to a given form of psychopathology. For example, risk factors could be classified as general (i.e., predisposing to standing on the common factors only), specific (i.e., affecting risk for the unique component of one or more diagnoses but not common factors), or hybrid (i.e., affecting risk for the common factors and also the unique component of one or more diagnoses).

Despite the importance of this question for classification and research in psychopathology, only one study to date has investigated the impact of a known risk factor for various forms of psychopathology on the general and specific levels of the HSM hierarchy. Kramer and associates (2008) found significant gender differences on both the Internalizing and Externalizing dimensions of the HSM in expected directions. Moreover, gender had no effect on risk for any observed syndrome after partialling out its effect on the latent factors, suggesting that gender acts as a general risk factor.

The current study attempts to replicate these findings of gender differences in standing on the liability dimensions. The influence of several other risk factors is explored on the basis of

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their consistent associations with various forms of psychopathology. Specifically, the current study investigates, for the first time, the prospective effect of early environmental adversity on the HSM dimensions. Further, the effects of two extensively studied candidate genes in psychopathology and psychiatric genetics research (5-HTTLPR and the COMT) on Internalizing and Externalizing propensities are investigated. In addition to direct genetic effects, the joint contributions of candidate gene variability and childhood adversity are assessed in gene-stress interaction models. Finally, the current study examines the continuity of the HSM dimensions by estimating the effect of early childhood Internalizing and Externalizing behavior problems on HSM standing in young adulthood. This last analysis will address the question of whether HSM dimensions can be conceptualized as traitlike, that is, core psychopathological processes that remain relatively stable across developmental stages.

Hypotheses

1. A correlated two-factor (Internalizing and Externalizing) CFA model will provide adequate fit to the correlations among 11 common psychiatric syndromes assessed at age 20. Diagnoses include MDD, DYS, GAD, PTSD, PAN, SOP, SPP, CD, ASPD, AAD, and DAD. No a priori hypotheses are made concerning the bifurcation of the Internalizing factor into anxious-misery and fear subfactors due to inconsistent findings in prior work.

2. In agreement with previous findings (Kramer et al., 2008), gender differences will be observed in the latent dimensions. Females will evidence significantly higher levels of Internalizing and lower levels of Externalizing, relative to males. After controlling for the variance shared with the latent factors, individual syndromes will not be statistically associated with gender.

3. Early environmental adversity—assessed at age 5—will have a positive, prospective association with standing on both Internalizing and Externalizing dimensions at age 20. Previous epidemiological research has shown that most forms of early adversity, and especially those concerning marital and family functioning, are related to future risk for all classes of psychopathology (Green et al., 2010; McLaughlin et al., 2010). These results imply that there is very little specificity between early adversity and particular forms of disorder. Therefore, we hypothesize that early adversity will show general effects on HSM dimensions, but will not be related to residual variation in observed syndromes after controlling for common factor variance.

4. Although the HSM dimensions have been proposed as endophenotypes, and thus may be more likely to be directly associated with candidate genes (e.g., Dick et al., 2008; Krueger et al., 2007), it is still unclear whether a direct effect of 5-HTTLPR on Internalizing will be detectable given the involvement of many (genetic and environmental) etiological factors in determining Internalizing risk. Thus we are agnostic as to whether 5-HTTLPR will be directly associated with Internalizing risk. However, we expect to observe an interaction between 5-HTTLPR and early environmental adversity, such that the 5-HTTLPR S allele will be associated with elevated standing on the Internalizing spectrum, but only among those exposed to relatively high levels of adversity. This hypothesis is based on recent meta-analytic findings suggesting significant 5-HTTLPR $G \times E$ in MDD (Karg et al., 2011). Additionally, studies appear to show that the interactive effect of 5-HTTLPR with early environmental adversity, as opposed to other forms of environmental stress, is particularly strong (Karg et al., 2011; Uher & McGuffin, 2010). The COMT val158met polymorphism, previously implicated

in susceptibility to Externalizing disorders (e.g., Brody et al., 2006; Eisenberg et al., 1999), is similarly expected to be associated with the Externalizing spectrum under high levels of exposure to early environmental adversity. In accordance with past research (e.g., Brennan et al., 2011), the COMT val158 allele is expected to increase risk for Externalizing problems in the context of early adversity.

5. We predict that maternal reports of participants' Internalizing and Externalizing problem behaviors on the CBCL (Achenbach, 1991) at age 5 will be prospectively associated with standing on HSM dimensions at age 20. Specifically, the age 5 Internalizing subscale is expected to be linked with the Internalizing spectrum, and the Externalizing subscale should be linked with the Externalizing spectrum. Previous studies (e.g., Krueger et al., 1998; Vollebergh et al., 2001) have demonstrated relatively high rank-order stability of the HSM dimensions over the course of 1 to 3 years, but continuity with early childhood manifestations of Internalizing and Externalizing traits has not yet been explored. Heterotypic associations (e.g., early Externalizing predicting later Internalizing) are possible, but are predicted to be smaller than homotypic correlations (e.g., early Externalizing predicting later Externalizing).

Method

Participants

Data will be drawn from a previously conducted high-risk community-based longitudinal study following a population of adolescents into young adulthood. Participants were recruited from the Mater-University Study of Pregnancy (MUSP) in Brisbane, Australia (Keeping et al., 1989), which followed a birth cohort of 7,223 mothers and their offspring born between 1981 and 1984 at the Mater Misericordiae Mother's Hospital to study children's health and

development. Mothers were assessed for depression using the Delusions-Symptoms-States Inventory (DSSI; Bedford & Foulds, 1978) during pregnancy, post-partum, 6 months after birth, and 5 years after birth. The present study selected and followed up 815 of the original families when the child reached age 15, oversampling for mothers with probable diagnosable depression varying in severity and chronicity, as well as random sample of women with no significant depression. Diagnoses of maternal depression were subsequently confirmed using structured clinical interviews, as described below. When youth reached age 20, all families were recontacted regarding participation in a second assessment, with 705 youth and mothers consenting to complete further interviews and questionnaires (2 were deceased, 51 refused, 52 could not be located or scheduled, 1 withdrew after data collection). The majority of this sample was Caucasian (92.1% White, 3.6 Asian, 1% Australian Aborigine, 0.8% Maori) and median family income fell in the lower-middle class (Keenan-Miller, Hammen, & Brennan, 2007).

Out of the 705 youth participating at the age 20 assessment, 512 provided DNA for genetic analyses between ages 22-25. Unavailable participants had either withdrawn from follow-ups, moved, could not be scheduled, had major medical problems, or were deceased. The 512 youth providing blood samples did not differ from the 193 participating at age 20 that did not provide blood with respect to youth depression history by age 20 or maternal history of depression by age 15, χ^2s < 1, ps > .10, but were less likely to be male, $\chi^2(1, 705) = 17.80$, $p <$ .01.

Current genetic analyses were based on 384 and 472 randomly-selected DNA samples for 5-HTTLPR and COMT, respectively, from the 512 youth who participated in the genotyping assessment. Economic and procedural constraints prevented genotyping of all 512 available DNA samples. Three samples produced an invalid reading at 5-HTTLPR, resulting in a final

sample of 381 for analyses involving this locus. The youth genotyped for 5-HTTLPR and/or COMT did not differ from the youth whose DNA samples were unanalyzed in terms of maternal depression status, $\chi^2(1, 512) < 1$, $p > .10$, but males were less likely to have their sample analyzed than females, $\chi^2(1, 512) = 16.49$, $p < .01$.

Procedure

In the initial phase of the MUSP, researchers invited women to participate in a study on pregnancy upon arrival for their first antenatal hospital visit. Women completed self-report questionnaires on health problems, psychosocial constructs, daily activities, and attitudes toward pregnancy. Approximately 3 to 5 days after their child's birth, mothers completed an additional questionnaire that assessed changes occurring during pregnancy. Obstetric data were also collected from hospital records and medical charts. At child age 6 months, and again at age 5 years, mothers were mailed further questionnaires assessing health and psychosocial changes for themselves and their children.

Interviews at the age 15 phase of data collection were conducted in the homes of the families at a time when both the mother and child would be available. Two interviewers blind to the mother's depression status conducted interviews with mothers and youth separately and independently. When the youth turned 20, participants were again interviewed and completed a battery of questionnaires in their homes. Youth were contacted in 2006 about participation in the genotyping study when they were between ages 22 and 25. The mean interval between assessments was 3.32 years ($SD = 1.02$). Participants who agreed to the blood collection study were mailed consent forms, a blood collection pack, and questionnaires, and were instructed to have the blood drawn at a local pathology lab. The blood samples were picked up by courier from the individual and transported to the Genetic Epidemiological Laboratory of the

Queensland Institute of Medical Research, where the genotyping procedures were conducted. Procedures were approved by the Institutional Review Boards of the University of Queensland; University of California, Los Angeles; and Emory University. Participants provided written informed consent and were compensated for their time.

Early Childhood Measures

Early Environmental Adversity. Information on adverse environmental conditions before the age of 5 was collected in self-report questionnaires administered to mothers during the first four phases of MUSP (pregnancy through child's age 5). Five domains of adversity were assessed in this study: economic hardship, parental separation, parental criminality, severe childhood health problems, and maternal psychopathology.

Economic hardship was defined using maternal reports of family income across the first five years of the child's life. At the prenatal, 6 month, and 5 year waves, mothers reported family income on a 7-point scale as part of questionnaire data collection. These responses were averaged and families falling in the upper third of the resulting distribution were considered as experiencing significant hardship.

At the fourth wave of MUSP data collection, mothers indicated on the general questionnaire whether they had experienced a divorce, separation, or partner change during the previous five years. Parental separation was operationalized as the presence of any of these events during the offspring's first five years.

Also in the fourth wave at age 5, questionnaires asked mothers whether they had "been in trouble with the police" in the previous 5 years and answered the same question about their partners. If either the mother or her partner endorsed involvement with the police in the past 5 years, parental criminality was scored as present.

Early childhood health problems were assessed from maternal reports in two areas. First, mothers were asked "has your child had any of these conditions or symptoms continuing longer than three months" (items included asthma, seizures, anemia, heart defect, cancer, and other serious conditions), and responded on a 3-point scale (1—not present for 3 months, 2—present and limited child's activities somewhat, 3—present and limited activities a lot). An impairing chronic illness was judged to be present if mothers reported that the offspring's activities were limited "somewhat" or "a lot" by one or more illnesses. Second, mothers indicated whether offspring had been hospitalized for medical reasons more than once over the previous 5 years. Participants were judged to have early health problems if they had experienced either an impairing chronic illness or multiple hospitalizations.

The presence of maternal depression or anxiety diagnoses was determined using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995) administered to mothers at offspring age 15. Other types of maternal diagnoses were not included in the current analyses due to low base rates (e.g., there were a total of 10 cases of substance abuse/dependence and 12 cases of alcohol abuse/dependence). Attempting to include either alcohol or drug use diagnoses in structural equation models led to convergence problems. For the current analyses, we only included diagnoses present between birth and age 5. Although reliability data are not available for the subset of maternal diagnoses present in the offspring's first five years, the weighted kappas, computed using blind clinician ratings of 52 taped interviews, for maternal lifetime diagnoses prior to offspring age 15 were all above 0.80.

Childhood Internalizing and Externalizing Behaviors. An abbreviated form of the Child Behavior Checklist (Achenbach, 1991), a widely used and well-validated measure of behavioral problems in children, was completed in questionnaire format by mothers at offspring age 5. The

modified version of the CBCL used in the current study included 33 of the original 113 items from the original CBCL, chosen for appropriateness for a 5-year-old sample (Najman et al., 2008). The Internalizing subscale (comprising withdrawn, anxious, and depressed behaviors, as well as somatic complaints) consisted of 10 items, whereas the Externalizing subscale (comprising delinquent and aggressive behaviors) consisted of 11 items. Previous research indicates that this modified CBCL has psychometric properties comparable to the original measure (Najman et al., 2001), and strong correlations have been found between long and short form CBCL Internalizing and Externalizing subscales in mothers completing both forms (Najman et al., 1997). In the current sample, Cronbach's alpha estimates for the abbreviated Internalizing and Externalizing subscales were 0.77 and 0.84, respectively.

Genotyping

Assays for the COMT val158met SNP were designed using MassARRAY Assay Design software (version 3.0; Sequenom Inc., San Diego, CA) and typed using iPLEX™ chemistry on a Compact MALDI-TOF Mass Spectrometer (Sequenom). Forward and reverse PCR primers and primer extension probes were purchased from Bioneer Corporation (Daejeon, Korea). Genotyping was carried out in standard 384-well plates with 12.5 ng genomic DNA used per sample. A modified Sequenom protocol was followed, using half reaction volumes in each of the PCR, SAP and iPLEX stages giving a total reaction volume of 5.5 µL. The iPLEX reaction products were desalted by diluting samples with 18 µL of water and 3 µL SpectroCLEAN resin (Sequenom) and then were applied to a SpectroChip (Sequenom), processed and analyzed on a Compact MALDI-TOF Mass Spectrometer by MassARRAY Workstation software (version 3.3) (Sequenom). Allele calls for 384-well plates were reviewed using the cluster tool in the SpectroTYPER software (version 3.3; Sequenom) to evaluate assay quality. In the present

sample, genotype frequencies at val158met were VV = 113, VM = 242, MM = 117, and were in

Hardy-Weinberg Equilibrium, χ^2 (1, 381) = 0.04, p = 0.83.

The 5-HTT 43 basepair deletion polymorphism was assayed using previously reported

methods (Wray et al., 2009). Most samples were subject to triplicate gel analysis. A minimum

of two independent results in agreement was required for inclusion which gave a final call rate of

96.4%. In the present sample the genotype frequencies were LL = 101, LS = 189, and SS = 91,

and in Hardy-Weinberg equilibrium, χ^2 (1, 381) = 1.61, p = 0.20.

The minor allele of the rs25531 SNP in the L allele has been reported to render the L

allele functionally equivalent to S (Wendland et al., 2006). This SNP was assayed using the

protocol of Wray et al. (2009), and the current analyses were performed reclassifying L_G alleles

as S.

Offspring Lifetime Diagnoses to Age 20

The Schedule for Affective Disorders and Schizophrenia in School-Aged Children (K-

SADS-E; Orvaschel, 1995) was administered during the age 15 data collection to determine

offspring current and lifetime diagnoses of Axis I psychiatric disorders. The K-SADS-E is a

widely used and validated semi-structured interview for assigning Axis I diagnoses in children

and adolescents. Trained clinicians interviewed adolescents and their mothers separately and

privately during the age 15 assessment. Diagnoses were assigned if either the adolescent or

maternal interview indicated that the adolescent qualified for a given syndrome. Interrater

reliability was assessed using a random sample of 75 K-SADS-E interview recordings evaluated

by clinicians blind to the original diagnostic ratings. Weighted kappas were in the acceptable

range (i.e., greater than .75) for depressive, anxiety, substance use, and disruptive behavior

disorders.

The SCID was administered at offspring age 20 to assess for onsets of Axis I syndromes since the age 15 assessment. To determine interrater reliabilities for diagnoses, a sample of 55 interviews were selected and reviewed by a second trained clinician blind to the original diagnoses. Weighted kappas for depressive, anxiety, substance use, and disruptive behavior disorders were all above 0.79.

Antisocial personality disorder symptoms (occurring since age 15) were assessed using the Structured Clinical Interview for DSM-IV Axis II Personality Disorders, Version 2.0 (SCID-II; First, Spitzer, Gibbon, Williams, & Benjamin, 1994) at the age 20 data collection. The SCID-II is a semistructured interview containing 140 items organized by Axis II diagnosis. The interview probed each of the 7 DSM-IV ASPD criteria. The mean number of ASPD criteria endorsed in the entire sample was 0.36 ($SD = 1.21$), and the number of ASPD diagnoses was 50 (7.14%). ASPD diagnosis was used as a further indicator of the Externalizing spectrum. Cronbach's alpha for the set of 7 criteria was 0.90. Kappas representing the interrater reliability for each symptom across a randomly-selected sample of 34 respondents ranged from 0.76 to 1.0 (median = .96).

Data Analytic Procedures

All analyses were conducted within a structural equation modeling (SEM) framework. First, the fit of the two-factor (correlated Internalizing and Externalizing) HSM and three-factor (in which Internalizing is divisible into anxious-misery and fear subfactors) models was tested. In the two-factor model, the Internalizing factor was defined by major depressive disorder (MDD), dysthymia (DYS), generalized anxiety disorder (GAD), post-traumatic stress disorder (PTSD), panic disorder (PAN), social phobia (SOP) and specific phobia (SPP) diagnoses from the SCID, and the Externalizing factor was defined by conduct disorder (CD), alcohol

abuse/dependence (AAD), drug abuse/dependence (DAD) diagnoses from the SCID and ASPD diagnoses from the SCID-II. In the three-factor model, the anxious-misery subfactor was defined by MDD, DYS, GAD, and PTSD, whereas the fear subfactor was defined by PAN, SOP, and SPP (see Watson, 2005). Model fit was evaluated with the likelihood ratio chi-square test, the comparative fit index (CFI; Bentler, 1990), the root-mean-square error of approximation (RMSEA; Browne & Cudeck, 1993), and weighted root-mean-square residual (WRMR), which represents the average differences between the sample and model-estimated correlations.

Next, we estimated the effects of the risk factors on HSM components. These analyses proceeded in several steps. First, we examined the continuity in Internalizing and Externalizing from childhood to young adulthood by regressing the HSM components on childhood CBCL scores, with gender included in this model as a covariate. Second we examined the associations between an environmental adversity composite and the HSM. That is, we summed the five separate environmental risk factors to produce an overall index of environmental risk (range 0-5) to be used as the independent variable in SEM analyses. In this model, both transdiagnostic factors and all residual variances of the manifest disorders were regressed on the adversity composite. The transdiagnostic and diagnosis-specific effects of gender were estimated as part of this model. Third, we added COMT and 5-HTTLPR as predictors to this model and estimated their effects on the latent factors and residual variances in the subsample of participants with genetic data. Notably, the HSM did not converge when 5-HTTLPR was included as a predictor, presumably due to difficulties with estimating a complex model in such a small sample ($n = 384$). As a result, 5-HTTLPR was omitted from all analyses reported herein. Fourth, we added the product term representing the interaction between COMT and environmental adversity to evaluate G × E effects, again in the genetics subsample. To account for the numerous

significance tests performed on diagnosis-specific associations, we applied a Bonferroni correction to the tests of association between these three primary risk factors (environmental adversity composite, COMT, and COMT × adversity) and the diagnosis-specific outcomes. More precisely, these significance tests were evaluated with respect to an alpha value of .0015 (i.e., .05 / 33).

Finally, we conducted a set of exploratory analyses in an attempt to understand the relationship between early environmental adversity and disorder with greater precision. We evaluated a model in which each of the five types of environmental adversity predicted the HSM components while controlling for the effects of all other forms of adversity. All five forms of adversity were allowed to intercorrelate.

Preliminary analyses indicated that the relationships of all risk factors with the Internalizing and Externalizing factors did not significantly differ across gender. Thus, to increase statistical power, analyses were run in the full sample of males and females, and gender was controlled in all models. All analyses were performed in Mplus 5.0 using the WHSMV estimator (Muthén & Muthén, 2007). Since all latent variable outcomes are scaled on a *z*-score metric, we interpret unstandardized regression coefficients as effect size measures in standard deviation (SD) units (e.g., a regression coefficient of 0.50 indicates that for a 1 unit increment in the predictor, a 0.50 SD increase in the outcome is expected).

<div align="center">Results</div>

Structure of the HSM

A tetrachoric correlation matrix of all diagnoses is presented in Table 1. A visual inspection of diagnostic correlations indicates that the co-occurrence of diagnoses within the Internalizing and Externalizing spectra is greater than that of Internalizing diagnoses with

Externalizing diagnoses, offering preliminary support for the distinction between the transdiagnostic dimensions. Model fit indices demonstrated that the two-factor HSM provided an excellent fit to the data ($\chi^2(29) = 37.18$, $p = .14$; CFI = .98; RMSEA = .02; WRMR = .89). The two latent factors were moderately correlated ($r = .37$). Table 2 displays the factor loadings, which were all significant at the .01 level, from this model.

The attempt to fit the three-factor model resulted in a Heywood case (i.e., out of range parameter estimate). Specifically, the factor loading of the fear dimension on the superordinate Internalizing dimension was found to be greater than 1.0. Exploratory analyses omitting the higher-order Internalizing dimension revealed that the correlation between the fear and anxious-misery dimensions was extremely high ($r = .97$). A LRT indicated that this factor correlation did not significantly differ from unity ($\chi^2(1) = 0.56$, $p = .45$). Given that the two Internalizing subfactors in the three-factor model could not be reliably differentiated in the current sample, the two-factor model was used in subsequent analyses.

Continuity of Internalizing and Externalizing Dimensions

As presented in Table 3, analyses revealed that, after controlling for CBCL Externalizing scores, CBCL Internalizing was not significantly associated with either of the transdiagnostic dimensions. However, CBCL Internalizing scores were related to the unique variance in panic disorder. CBCL Externalizing scores, after controlling for CBCL Internalizing, predicted standing on the Externalizing factor and also 3 diagnosis-specific components (COND, DAD, and SOP).

Genetic and Environmental Predictors of the HSM

The regression of the HSM dimensions on the environmental adversity composite revealed significant positive effects of adversity on both latent factors even after controlling for

gender, which was strongly associated with Internalizing and Externalizing, as well as 8

diagnosis-specific components, in the predicted directions (see Table 4). The regression

coefficients in Table 4 indicate that for a one unit increase in the adversity variable (i.e., with the

addition of one form of environmental adversity), an increment of approximately 0.17 SD in

Internalizing and 0.18 SD in Externalizing is expected. A quadratic term representing a

nonlinear effect of environmental adversity on the HSM outcomes was evaluated but did not

approach significance for either Internalizing or Externalizing (ts < 1.00, ps > .10).

Aside from its effects on the latent factors, environmental adversity was significantly

associated with elevations in the unique components of 4 out of 11 diagnoses after applying a

Bonferroni correction. As seen in Table 4, environmental adversity was significantly related to

the diagnosis-specific variance of CD, AAD, and DAD on the Externalizing spectrum and GAD

on the Internalizing spectrum, with the largest effects observed for CD and GAD.

When COMT val158met was entered as a predictor, along with gender and

environmental adversity, it did not exhibit any associations with the latent factors of the HSM.

COMT variation was, however, significantly related to the unique component of SPP ($b = 0.38$,

$SE = 0.12$, $p < .001$). Specifically, the number of val158 alleles present was positively associated

with SPP-specific pathology. The effect of COMT did not approach significance for any other

diagnosis-specific component.

We then examined the joint effect of COMT and environmental adversity in predicting

the various HSM components. Analyses revealed significant G × E for Externalizing ($b = 0.13$,

$SE = 0.06$, $p < .05$) but not Internalizing ($b = 0.01$, $SE = 0.08$, $p = .90$). Further, no G × E effects

were observed for the diagnosis-specific components. Multiple group SEM analyses, which

estimate the path from environmental adversity to Externalizing for each genotype group

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separately, were carried out to examine simple effects (Muthén & Muthén, 2007). These analyses showed that the adversity-Externalizing association was significant for the val/val group ($b = 0.20$, $SE = 0.08$, $p < .05$) but not the val/met ($b = 0.08$, $SE = 0.06$, $p = .19$) or met/met ($b = -0.01$, $SE = 0.06$, $p = .82$) groups. The form of this interaction is depicted in Figure 5.

Exploratory Analysis

In light of the robust effect of the environmental adversity composite on the transdiagnostic dimensions, we decided to perform an exploratory analysis that would provide some insight into the unique effects of the different components of environmental adversity on the HSM dimensions. We therefore fit a model in which all five types of adversity, along with gender as a covariate, were entered simultaneously into a model predicting the components of the HSM (see Figure 6). This exploratory model provided an excellent fit to the data ($\chi^2(60) = 70.56$, $p = .16$; CFI = .98; RMSEA = .02; WRMR = .88).

As presented in Table 5, analyses revealed an effect of maternal depression/anxiety on both Internalizing and Externalizing factors, as well as several diagnosis-specific components. After controlling for the other adversities, economic hardship and childhood health problems were related to Internalizing, but not Externalizing, and did not affect standing on any diagnosis-specific components. In contrast, parental criminality had no effect on either latent factor, but predicted unique variance in AAD. Finally, parental separation was related to the Externalizing factor, as well as the unique component of AAD. Taken together, these early environmental predictors accounted for 10.0% of the variation in Internalizing and 9.30% of the variation in Externalizing.

<div style="text-align:center">Discussion</div>

The purpose of the current study was to examine the general and specific connections of several genetic and early environmental risk factors with psychopathology in a young adult sample. Both exposure to early environmental adversity and monoaminergic candidate gene variation have been implicated in risk for a variety of disorders (see Craddock et al., 2006; Kessler et al., 1997), but previous research has not established whether their nonspecific effects are best accounted for by (a) a limited number of transdiagnostic pathways or (b) numerous diagnosis-specific pathways to mental illness. Using latent variable modeling to parse the shared and unique variance of commonly co-occurring disorders, the HSM allows investigators to simultaneously estimate the effects of a given risk factor on transdiagnostic and diagnosis-specific pathology (Krueger & Markon, 2011). Within the HSM framework, we were able to characterize the effects of gender, childhood Internalizing and Externalizing behavior, early environmental adversity, and COMT in terms of general (i.e., transdiagnostic), specific (i.e., diagnosis-specific), or hybrid (i.e., a mixture of transdiagnostic and diagnosis-specific) patterns of risk for psychopathology.

Consistent with two previous studies (Eaton et al., 2010; Kramer et al., 2008), we detected gender differences in the two latent dimensions of the HSM, with females exhibited higher levels of Internalizing and lower levels of Externalizing. Specifically, females were estimated to possess approximately half a standard deviation more Internalizing than males, whereas males were nearly half a standard deviation higher on the Externalizing spectrum than females. This result could be interpreted as suggesting that gender differences in diagnoses are simply markers of a more general gender difference in transdiagnostic pathology. However, in contrast to previous latent variable modeling studies, we also found diagnosis-specific effects of gender on multiple Internalizing and Externalizing diagnoses, suggesting that there are gender

differences in diagnosis-specific forms of pathology. One possible explanation for the

discrepancy between the current result and prior studies is a difference in the statistical

approaches to testing for gender differences. Extant research on this topic has used factorial

invariance models to probe for gender differences, whereas the current study estimated the

regression of the residual variance terms on gender in the context of a larger explanatory model.

The current analyses provided some evidence for the continuity of the Externalizing, but

not Internalizing, spectrum from childhood to young adulthood. Maternal reports of offspring

Externalizing behavior at age 5 significantly predicted standing on the Externalizing factor of the

HSM, as well as the diagnosis-specific components of COND, DAD, and SOP. In contrast,

CBCL Internalizing scores did not predict individual differences in the Internalizing factor.

However, they were significantly related to panic-specific pathology. These findings are

consistent with several previous studies that have documented greater continuity of the

Externalizing, as compared to Internalizing, spectrum in the HSM context (e.g., Krueger et al.,

1998) and suggest there may be a diagnosis-specific pathway from early Internalizing behavior

to panic disorder later in life.

Elevated exposure to early environmental adversity was significantly associated with

standing on both the Internalizing and Externalizing factors. At the same time, it was also

related to the unique components of 3 out of 4 Externalizing diagnoses and 1 out of 7

Internalizing diagnoses. These results are generally consistent with a wealth of epidemiological

and clinical data that reveal effects of early adversity on a broad range of depressive, anxiety,

substance use, and antisocial personality disorders (e.g., Cicchetti & Toth, 2005; Green et al.,

2010; Maniglio, 2009; Monroe, 2008). It extends this previous work by demonstrating that the

pattern of multifinality documented in these literatures is likely due to a combination of

transdiagnostic and diagnosis-specific effects. In terms of our taxonomy of risk factors, cumulative exposure to early environmental adversity confers a hybrid pattern of risk for psychopathology.

Following up on the highly significant associations that we observed for the composite measure of early adversity with transdiagnostic and diagnosis-specific outcomes, we evaluated an exploratory model that distinguished the unique effects of each type of environmental adversity on risk for disorder by statistically controlling for the presence of all other environmental risk factors. Results from this model indicated that not all forms of adversity conform to a hybrid pattern of risk. Maternal depression/anxiety by offspring age 5 most closely resembled the early adversity composite in that it influenced both transdiagnostic factors, as well as several diagnosis-specific components. Similarly, parental separation, while related to only 1 factor (Externalizing) and 1 diagnosis-specific component (alcohol abuse/dependence), demonstrated a hybrid pattern. In contrast, both economic hardship and childhood health problems predicted Internalizing, but none of the diagnosis-specific components, indicating a general pattern of risk. Finally, parental criminality was significantly associated with only the residual portion of alcohol abuse/dependence, consistent with a specific pattern of risk.

Our primary conclusion from this model of early adversities is that there is likely to be variation across early environmental risk factors in their patterns of association with transdiagnostic and diagnosis-specific forms of psychopathology. Some may be related to multiple disorders because they instigate multiple diagnosis-specific risk processes, whereas others may be related to multiple disorders because they set the stage for a limited number of transdiagnostic risk processes. Additionally, when controlling for all other risk factors, it appears that certain adversities predispose exclusively to Internalizing pathology, whereas others

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confer vulnerability exclusively to Externalizing pathology. Thus, it is possible that different transdiagnostic dimensions can be differentiated with respect to antecedent risk factors. For instance, our results suggest that parental separation during the offspring's first 5 years may be uniquely related to variation on the Externalizing dimension.

According to our taxonomy of risk factors, COMT exemplified a specific pattern of risk. It was robustly associated with the residual variance of specific phobia, whereas it exhibited small, nonsignificant correlations with each of the common factors. To our knowledge, no previous research has directly examined the relationship between the COMT val158met polymorphism and specific phobia, but several related findings can be brought to bear on the current results. One previous study examined the association between COMT and phobic anxiety, which was measured using a questionnaire that included items regarding fear of heights, crowds, and enclosed spaces (McGrath et al., 2004). The investigators found that the val158 allele was linked with elevations in phobic anxiety, generally consistent with our result. Further, indirectly supporting the plausibility of the diagnosis-specific relationship between COMT and specific phobia, several quantitative genetics studies have demonstrated that specific phobia is characterized by a unique genetic component that is uncorrelated with genetic risk for the rest of the Internalizing disorders (Czajkowski, Kendler, Tambs, Røysamb, & Reichborn-Kjennerud, 2011; Hettema, Prescott, Myers, Neale, & Kendler, 2005; Kendler et al., 2003). These studies suggest that the genetic etiology of specific phobia is largely distinct from that of other depressive and anxiety disorders (Czajkowski et al., 2011), a possibility that is congruent with the residual association between COMT and specific phobia detected here.

While we did not observe a main effect of COMT on either of the common factors, $G \times E$ analyses revealed a significant interaction between COMT and environmental adversity in

predicting standing on the Externalizing factor such that the adversity-Externalizing association was significant for the val/val genotype group, but not the val/met or met/met groups. The stress-sensitizing effects of the val158 allele found here are consistent with a number of previous reports of COMT G × E in Externalizing disorders (e.g., Brennan et al., 2011; Wagner et al., 2010). Given that no diagnosis-specific effects were observed in the current study, our findings raise the possibility that prior studies on COMT G × E that focused on individual Externalizing diagnoses may have been detecting the nonspecific effect of COMT, in combination with environmental stress, on the Externalizing dimension (see Dick, 2007).

Another way to interpret the COMT G × E effect is that the direct effect of COMT on Externalizing pathology is only evident under conditions of environmental adversity. From this perspective, COMT could be viewed as conferring a hybrid pattern of risk, influencing both the common factor and residual variance levels of the HSM, in that it predicts the Externalizing factor in certain contexts and also predicts the residual component of specific phobia. More generally, this result provides partial support for the hypothesis that HSM factors can serve as intermediate phenotypes that are more proximal to gene action than DSM-defined diagnoses (Dick, 2007). Further, our findings suggest that, as in the genetic association literature as a whole (Rutter, 2007), relationships between candidate genes and HSM dimensions may only be detectable under certain environmental conditions.

Limitations and Conclusions

A number of limitations of the current study should be borne in mind when interpreting the results. First, the coverage of Axis I diagnoses was incomplete. It is possible that when more infrequent and severe forms of pathology (e.g., bipolar and psychotic disorders) are incorporated into the HSM framework the number and/or nature of the latent dimensions may be

altered. Along these lines, one previous investigation modeled the latent structure of an extensive array of Axis I and II symptoms and found evidence for Internalizing and Externalizing factors, in addition to factors representing thought disorder and pathological introversion (Markon, 2010).

Second, this study was conducted in a sample of young adults, who at age 20 had not completely passed through the periods of highest risk for many Axis I disorders (e.g., Kessler et al., 2003). Consequently, the prevalence of some of the diagnoses assessed in this study was likely lower than those that would be obtained from an older sample of adults. Nevertheless, model fitting procedures have identified a correlated Internalizing-Externalizing configuration of diagnoses in previous studies of adolescents and young adults (e.g., Griffith et al., 2010). Moreover, prior longitudinal HSM research has shown that these latent dimensions are highly stable over time (Fergusson et al., 2006; Vollebergh et al., 2001).

Third, participants were oversampled for maternal depression. As a result, correlations among the Internalizing disorders, or covariation between the latent Internalizing and Externalizing dimensions, may have differed from those typical of unselected samples. However, a two-factor model has been reported to provide acceptable fit to diagnostic intercorrelations in previous high-risk samples (Griffith et al., 2010; Krueger, 1999). Further, it is important to note that when the presence of maternal depression was entered into these models as a covariate, the pattern and significance of results was unaltered.

Fourth, all analyses involving the COMT gene were conducted in a subsample of 471 participants who provided blood samples for genetic analysis. Although the fit of the HSM model to the data did not deteriorate when the reduced sample was used, this sample size is relatively small for the purposes of genetic association studies. Given the danger of false

positives in genetic research (Munafò, 2006), these findings should be interpreted with caution until replications in large-scale studies are available.

Fifth, the set of environmental adversities examined in this study was not comprehensive. Notably, we did not assess various types of childhood abuse that are consistently associated with psychopathology in adolescence and adulthood (e.g., Maniglio, 2009). In addition, there are several other popular genetic variants in research on psychopathology (e.g., 5-HTR1A, BDNF, DRD4) that were not assessed in this study but may be related to various transdiagnostic and diagnosis-specific components of the HSM (e.g., see Lau & Eley, 2011).

Finally, we reiterate that we did not correct for multiple testing when modeling the unique effects of 5 environmental adversities on the HSM. As such, caution is recommended in the interpretation of those SEM results.

In sum, our results demonstrate that gender and early environmental adversity affect individuals' standing on both transdiagnostic Internalizing and Externalizing dimensions, as well as several diagnosis-specific components of the HSM, suggesting that a hybrid pattern of risk most accurately describes the relationship between these risk factors and psychopathology. However, other patterns of risk are possible, as exemplified by the diagnosis-specific effects of the COMT val158 allele and age 5 Internalizing behavior. Together, these findings highlight that common risk factors for psychopathology may lead to disorder through transdiagnostic pathways, diagnosis-specific pathways, or a mixture of both.

Chapter 3: Expanding stress generation theory:

Test of a transdiagnostic model

Whereas Study 1 examines predictors of HSM dimensions, Study 2 focuses on the

consequences of individuals' standing on these dimensions, with the specific goal of

understanding the relevance of the liability spectra to stress generation, a phenomenon originally

thought to be unique to major depression. Stress generation describes a process whereby

individuals contribute to the occurrence of stressful events and circumstances—especially

interpersonal stressors—in their environment (Hammen, 1991; Liu & Alloy, 2010).

As described above, the interpretation of studies on psychopathology can be complicated

by comorbidity to the extent that effects attributed to a particular syndrome may have been

caused in part by other diagnoses that co-occur with the syndrome of interest (Clark et al., 1995).

The HSM provides a framework that can be used to circumvent this problem. By examining the

relationships of both the general vulnerabilities (i.e., higher-order factors) and particular

diagnoses with external constructs, researchers can establish whether outcomes are related (a)

only to latent liability spectra, (b) only to specific facets of the liability spectra, or (c) both.

Prior work on the HSM demonstrates the importance of this type of clinical research. For

instance, Kessler et al. (2011) found that the majority of pairwise associations between a given

syndrome and new onsets of comorbid conditions were mediated by standing on higher-order

latent Internalizing and Externalizing dimensions. The implication of this finding for research in

psychopathology is that core vulnerability factors shared by various disorders may in fact

account for the statistical associations between individual disorders, which are manifestations of

these core vulnerabilities, and clinical outcomes. Supporting this notion, Patrick and associates

(2006) found that reduced p300 amplitude was no longer associated with alcohol problems (or

symptoms of any other Externalizing syndrome) after accounting for the shared variance between alcohol problems and a latent Externalizing spectrum.

The present study applies the HSM paradigm to stress generation theory in depression. Stress generation refers to the tendency of people with a history of depression, relative to never-depressed counterparts, to experience more stressful events that are caused at least in part by characteristics or behaviors of the person (Hammen, 2006). A history of MDD is not expected to influence rates of independent or fateful events (e.g., illness of a family member) that are out of a person's control. The stress generation effect has been demonstrated previously in community (Cui & Vaillant, 1997; Hammen & Brennan, 2001) and clinical (Chun, Cronkite, & Moos, 2004; Harkness, Monroe, Simons, & Thase, 1999) samples, as well as among children and adolescents (Rudolph & Hammen, 1999; Rudolph et al., 2000).

The original formulation of the stress generation theory recognized that stress generation is not necessarily a result of the major depression syndrome per se, with early evidence showing that stress generation occurred even during periods of MDD remission (Hammen, 1991). Therefore it has been hypothesized that personality characteristics, interpersonal styles, and cognitive schemas of depression-prone individuals bring about dependent stressors, but the exact mechanisms remain unknown (Eberhart & Hammen, 2009).

Consistent with this theoretical framework, recent work has shown that shown that stress generation is not unique to MDD. Other forms of psychopathology are associated with higher rates of dependent stress. For example, anxiety disorders have been linked with greater exposure to future dependent events (Connolly, Eberhart, Hammen, & Brennan, 2010) and the personality trait of anxiety sensitivity, theorized to be a diathesis for all anxiety disorders, has been found to predict frequency of subsequent dependent stressors (Riskind, Black, & Shahar, 2010).

Moreover, research has shown neuroticism, a trait believed to be a common characteristic of depressive and anxiety disorders, to confer risk for future exposure to dependent events (Ellenbogen & Hodgins, 2004; Kercher, Rapee, & Schniering, 2009). Additionally, there are preliminary data that suggest higher levels of Externalizing psychopathology may portend increased exposure to dependent stressors among adolescents (Carter, Garber, Ciesla, & Cole, 2006; Rudolph, 2008; Rudolph et al., 2000).

Especially relevant to an HSM approach to stress generation, comorbidity of MDD with other syndromes has been found to augment the stress generation effect. Daley and colleagues (1997) initially demonstrated that the objectively-rated threat associated with dependent stressors was higher among individuals with comorbid, relative to pure, depression. Harkness and Luther (2001) subsequently found that comorbid anxiety and dysthymia intensified the stress generation effect among a clinical sample of individuals diagnosed with MDD. Specifically, a stress generation effect was most pronounced for people with both anxiety and dysthymia diagnoses (in addition to MDD), as compared to people with only comorbid anxiety or dysthymia. From a HSM perspective, these findings may be interpreted as demonstrating that higher standing on the Internalizing spectrum (as indicated by endorsement of more diagnoses) predisposes to higher rates of future dependent stress (see Krueger & Finger, 2001).

The present study will use the hierarchical framework of the HSM to evaluate the degree of specificity of stress generation to MDD. The associations between the latent Internalizing and Externalizing factors with future dependent stress exposure will be examined and compared with the associations between the individual facets (i.e., diagnoses) of the higher-order dimensions and future dependent stress. Thus, the role of the unique part of MDD (i.e., residual variation

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remaining after accounting for its dependence on the common Internalizing factor) in the stress generation phenomenon can be identified.

Hypotheses

1. As in study 1, it is hypothesized that a correlated two-factor (Internalizing and Externalizing) CFA model will provide adequate fit to the correlations among 10 common psychiatric syndromes occurring up to age 19. Diagnoses include MDD, DYS, GAD, PTSD, PAN, SOP, SPP, CD, AAD, and DAD.

2. Both the Internalizing and Externalizing dimensions will be positively associated with future interpersonal dependent stress and noninterpersonal dependent stress. They are not, however, expected to be related to independent stress threat.

3. MDD will show a significant residual correlation with interpersonal dependent stress (Hammen, 2006; Rudolph et al., 2000).

Method

Participants and Procedure

The full sample of 705 youth participating in the age 20 follow up, described above, was used for the present analyses.

Measures

Lifetime Axis I Diagnoses. The Schedule for Affective Disorders and Schizophrenia in School-Aged Children (K-SADS-E; Orvaschel, 1995) was administered during age 15 data collection to determine offspring current and lifetime diagnoses of Axis I psychiatric disorders. The K-SADS-E is a widely used and validated semi-structured interview for assigning Axis I diagnoses in children and adolescents. Trained clinicians interviewed adolescents and their mothers separately and privately during the age 15 assessment. Diagnoses were assigned if

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either the adolescent or maternal interview indicated that the adolescent qualified for a given syndrome. Interrater reliability was assessed using a random sample of 75 K-SADS-E interview recordings evaluated by clinicians blind to the original diagnostic ratings. Weighted kappas were in the acceptable range (i.e., greater than 0.75) for all Internalizing and Externalizing disorders.

The Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1995) was administered at offspring age 20 to assess for onsets of Axis I syndromes since the age 15 assessment. Diagnostic information from the K-SADS-E and SCID interviews was combined to determine the lifetime presence of Internalizing and Externalizing diagnoses. However, for the current analyses diagnoses with onsets occurring in the 12 months prior to the age 20 assessment were omitted in order to ensure that the onsets of all diagnoses preceded the occurrence of acute stressors. Therefore, although diagnosis onsets always preceded stress exposure, the amount of time elapsed between disorder onset and stress occurrence was variable across participants and across disorders within participants. To determine interrater reliabilities for SCID diagnoses, a sample of 55 interviews were selected and reviewed by a second trained clinician blind to the original diagnoses. Weighted kappas for Internalizing and Externalizing disorders were all above 0.79.

At the age 15 assessment, the SCID was also used to evaluate mothers' lifetime history of depression, which served as a covariate in supplementary stress generation analyses described below. Based on a sample of 33 interviews reviewed by multiple raters, a kappa value of 0.79 was computed for ratings of maternal depression history, indicating adequate interrater reliability.

Acute Stressful Life Events. At age 20, participants were administered the semi-structured UCLA Life Stress Interview (LSI; Hammen, Henry, & Daley, 2000). Modeled after

the contextual threat assessment methods of George Brown and colleagues (e.g., Brown & Harris, 1978), the interview uses standard general probes to elicit specific life events in the past 12 months and follow-up queries to establish the dating of each event and circumstances surrounding its occurrence. Written narratives of each event were then presented to a rating team that was blind to youths' actual response to the event. For each event, the team then assigned a severity rating representing the impact this event would be expected to have on an average person in identical circumstances. Severity ratings ranged from 1 (*no impact*) to 5 (*extremely severe*). Each event was also rated in terms of its dependence (i.e., the extent to which it was caused by the participant's behavior or characteristics) on a 1 (*fateful or completely independent*) to 5 (*completely dependent*) scale; events with a rating greater than or equal to 3 (*partly dependent*) are considered to be dependent, as previously reported by Hammen and colleagues (2000). The rating team also determined whether or not each event was interpersonal in nature, based on identification of the primary content. For instance, dependent interpersonal events focused on a relationship with another person and included disputes, losses, or separations due at least in part to the participant's behaviors, whereas noninterpersonal dependent events were commonly related to work or school performance, person-determined injuries, or financial challenges. For each participant, a cumulative objective stress score was created for each class of event (i.e., independent, noninterpersonal dependent, interpersonal dependent) by summing the objective threat ratings across all events. The number of stressful life events reported per participant ranged from 0 to 11 (*M* = 3.22, *SD* = 1.95). Reliability and validity data for the UCLA Life Stress Interview have been reported in other studies of adolescents and young adults (e.g., Hammen et al., 1995). In the present sample, the interrater reliability analyses for 89 cases

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yielded intraclass correlations of 0.95 and 0.97 for severity and dependence ratings, respectively, and a kappa of 0.89 for the interpersonal (versus noninterpersonal) rating.

Chronic Stress. The LSI was also used at the age 15 assessment to gather information about the ongoing difficulties in at least the prior 6 months in several domains: best friendship, romantic relationship, relationships with family members, finances, health (self), health of family members, academic performance, and school behavior. Interviewers assigned a rating to each domain according to a set of behaviorally-specific anchors. Ratings ranged from 1 (no stress; superior circumstances) to 5 (severe stress; major difficulties). The chronic stress interview attempts to ascertain an objective assessment of ongoing stressful conditions that is independent of the individual's subjective experience of stress. The stability of the LSI chronic stress ratings has been established in previous longitudinal investigations (e.g., Daley, Hammen, & Rao, 2000; Hammen, Kim, Eberhart, & Brennan, 2009), and its convergent validity—in terms of significant agreement with other measures of functioning in typical roles such as academic performance, successful peer relations, and quality of parent-child relationships—has been documented consistently (Hammen, 2005; Hammen et al., 2009). In the present study, reliability analyses using independent raters yielded intraclass correlations of 0.77 and higher for each chronic stress domain. The chronic stress score used in the present analyses was computed by summing interviewer ratings across all domains.

Data Analytic Plan

Data analyses using structural equation modeling proceeded in three parts. First, the fit of the two-factor (Internalizing and Externalizing) and three-factor (in which the Internalizing factor is divisible into anxious-misery and fear subfactors) models was compared using the same

methods as in Study 1. Given that the correlation between anxious-misery and fear subfactors was again equivalent to unity, the two-factor model was used in stress generation analyses.

Second, the predictive associations between the latent dimensions and all three classes of stress (i.e., independent, noninterpersonal dependent, and interpersonal dependent) were examined in three separate models. That is, the sum of contextual threat ratings within a particular class of stress was regressed on the factors from the best fitting factor model (see Figure 7). Importantly, in these regressions, the effect of the factors on stress occurrence above and beyond the effects of other factors was estimated (e.g., shared variance between Internalizing and Externalizing factors was partialled out in the regression of stress on the Internalizing factor).

Multiple group structural equation modeling was carried out to examine gender as a moderator of the stress generating effects of the Internalizing and Externalizing dimensions given previous research reporting gender differences in rates of exposure to dependent stressors (Rudolph & Hammen, 1999; Shih, 2006). Two models were compared in tests of moderation. In one, the regression of acute stress on the latent dimensions was constrained to be equal across gender. In the other, these parameters were allowed to vary for males and females. A likelihood ratio test (LRT) was used to compare the fit of these two models (Chou & Bentler, 2002). Significant LRT values would indicate that constraining the structural paths to equality across gender degrades model fit, reflecting statistically significant moderation. LRTs for gender moderation revealed no significant differences for males and females for any of the 3 types of stress (all χ^2s < 1, ps > .10). As such, all results presented below reflect analyses conducted in the full sample. However, gender was included as a covariate in all stress generation models in light of prior research in young adult (e.g., Achenbach, 1997) and epidemiological samples

(Kessler et al., 2003) demonstrating prominent gender differences in susceptibility to both Internalizing and Externalizing pathology.

Third, each class of stress was regressed on the residual variances of all observed syndromes (see Figure 8). Again, separate models were estimated to evaluate the residual associations of diagnoses with independent, noninterpersonal dependent, and interpersonal dependent stress. These analyses were carried out to determine whether the unique portions of the various manifest syndromes (i.e., variance not shared with other disorders) predicted stress occurrence. It is useful to reiterate here that only diagnoses with onsets that preceded the 12 month period prior to the age 20 data collection point were included in the present analyses in order to establish the appropriate temporal ordering between syndrome and stress occurrence.

Chronic stress assessed at age 15 was included as a covariate in all stress generation analyses given its associations with both acute stress (Hammen et al., 2009) and psychopathology (Paykel & Cooper, 1992). That is, we wanted to isolate the portion of the relationship between psychopathology and acute stress exposure that was independent of the effects of chronic stress. All analyses were performed in Mplus 5.0 using the WLSMV estimator (Muthén & Muthén, 2007).

<div align="center">Results</div>

Structure of the HSM

Table 6 displays the frequencies of Axis I diagnoses in the current sample as well as a tetrachoric correlation matrix for all diagnoses. A visual inspection of Table 6 reveals that the Externalizing disorders tended to co-occur more often with each other than with Internalizing disorders, providing a preliminary indication of the distinction between Internalizing and Externalizing spectra.

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The two-factor model provided an excellent fit to the data ($\chi^2(24) = 28.24$, $p = .35$; CFI = .99; RMSEA = .01; WRMR = .86). The factor loadings from the two-factor configuration are presented in Table 7. A correlation between the Internalizing and Externalizing factors of .46 indicated moderate overlap between the two latent constructs. All factor loadings on both dimensions were significant at an alpha level of .01.

HSM Dimensions, Syndrome-Specific Components, and Stress Generation

    Independent Stress. In the baseline model, independent stress load was regressed on Internalizing, Externalizing, gender, and chronic stress. This model fit the data extremely well ($\chi^2(32) = 32.48$, $p = .44$; CFI = .99; RMSEA = .01; WRMR = .82). Equivalent or superior levels of model fit were observed in the interpersonal dependent and noninterpersonal dependent stress models and will not be reported below. Gender was significantly related to Internalizing ($r = -.30$) and Externalizing ($r = .19$) in expected directions, with males averaging higher scores on Externalizing and lower scores on Internalizing. In addition, chronic stress was strongly associated with both the Internalizing ($r = .35$) and Externalizing ($r = .49$) dimensions. As summarized in Table 8, the Internalizing and Externalizing dimensions were not significantly related to independent stress occurrence in the past 12 months. Next, independent stress was regressed on the residual variances of each of the syndromes of the HSM. This model also provided a good fit to the observed data ($\chi^2(26) = 26.14$, $p = .45$; CFI = .99; RMSEA = .01; WRMR = .75). Analyses revealed that none of the residual associations with independent stress were significant (ps > .05).

    Interpersonal Dependent Stress. Consistent with hypotheses, the regression of dependent stress on the transdiagnostic dimensions revealed a significant effect for the Internalizing dimension after partialling out its covariance with Externalizing, gender, and chronic stress.

Higher scores on the Internalizing dimension were associated with greater generation of interpersonal dependent stress ($b = 0.76$, $SE = 0.25$, $p < .01$, $\beta = 0.29$). In contrast, the Externalizing dimension was not significantly associated with interpersonal dependent stress.

Even after removing variance due to the Internalizing dimension, both major depression and panic disorder were related to future interpersonal dependent stress (see Table 8). As hypothesized, the presence of prior depression predicted an increase in interpersonal stress during the 12 months before the age 20 assessment ($b = 0.49$, $SE = 0.16$, $p < .01$, $\beta = 0.24$). Interestingly, panic disorder was inversely related to interpersonal stress ($b = -0.76$, $SE = 0.34$, $p < .05$, $\beta = -0.21$). This is an example of a suppressor effect (Cohen & Cohen, 1983), given that the zero-order association between panic disorder and interpersonal stress was small and positive ($r = .03$). Thus, it appears that the variance shared between panic disorder and the other Internalizing disorders obscured the moderate negative association between panic disorder and interpersonal stress occurrence.

Noninterpersonal Dependent Stress. Standing on the Externalizing, but not Internalizing, dimension was positively associated with noninterpersonal dependent stress ($b = 0.43$, $SE = 0.21$, $p < .05$, $\beta = 0.17$). In fact, after partialling out its association with Externalizing, Internalizing was weakly negatively related with noninterpersonal dependent stress in this model. After controlling for these effects, gender was not significantly related to stress exposure, although males tended to experience higher levels of noninterpersonal dependent stress. Chronic stress was positively associated with the occurrence of later noninterpersonal dependent stress ($b = 0.14$, $SE = 0.04$, $p < .01$, $\beta = 0.14$).

As presented in Table 8, analyses examining the predictive power of specific syndromes, after partialling out variance due to the transdiagnostic factors, revealed that dysthymia was

associated with increased noninterpersonal dependent stress ($b = 0.25$, $SE = 0.10$, $p < .05$, $\beta = 0.13$). No other Internalizing or Externalizing syndromes demonstrated unique effects on noninterpersonal dependent stress.

Discussion

The present study proposed to expand stress generation theory to include the complementary stress generating effects of (a) transdiagnostic Internalizing and Externalizing dimensions of psychopathology and (b) distinct Axis I syndromes. Even after controlling for gender and chronic stress levels, both the Internalizing and Externalizing dimensions were found to play a role in stress generation, supporting the hypothesis that stress generation is not a specific feature of any one diagnostic category. At the same time, after accounting for variance due to the latent dimensions, several syndromes continued to predict dependent stress levels, indicating that diagnostic boundaries in our current nosologies capture unique clinical information that may be necessary for a complete understanding of stress generation patterns.

The Internalizing and Externalizing dimensions were implicated in the generation of different types of stressful events. The Internalizing dimension predicted levels of interpersonal, but not noninterpersonal, dependent stress. This result is consistent with separate lines of research demonstrating that neuroticism is a nonspecific vulnerability factor for depressive and anxiety disorders (Clark & Watson, 1991) and that elevated neuroticism predicts higher levels of interpersonal dependent stress (e.g., Kercher et al., 2009). Additionally, this finding is in agreement with previous life stress research that has found depression to be most strongly associated with the generation of interpersonal conflict events, as compared to noninterpersonal dependent or independent stressors (Hammen, 2006).

The observation of a stress generation effect for the Internalizing dimension raises the possibility that the relationship between depression and interpersonal stress generation may simply be a marker of a more general connection between a transdiagnostic Internalizing trait and interpersonal stress generation. However, results also revealed that the specific component of major depression predicted increased rates of interpersonal conflict stress above and beyond the effect of the Internalizing dimension. This residual association indicates that some set of attributes unique to depression (e.g., excessive reassurance seeking [Prinstein et al., 2005], negative feedback seeking [Joiner, 1995], hopelessness [Abramson, Metalsky, & Alloy, 1989], and/or co-rumination [Rose, 2002]) promotes conflict in interpersonal relationships. Indeed, the development of depression in adolescents and adults has been linked most robustly to interpersonal disruption and loss events, as compared to noninterpersonal stressful events (see Joiner & Coyne, 1999; Rudolph et al., 2000). The current investigation extends this previous empirical work by clarifying that the transdiagnostic Internalizing dimension does not completely account for interpersonal dysfunction characterizing depression; some unique vulnerability associated with the depression syndrome further increases risk for conflictual interpersonal encounters.

The unique component of panic disorder also had a significant effect on subsequent interpersonal dependent stress. Despite a non-negative zero-order correlation between panic disorder and interpersonal dependent stress, panic disorder was significantly inversely related to interpersonal dependent stress after partialling out variance due to the Internalizing dimension. Thus, the covariance between panic disorder and the other Internalizing syndromes masked its true role in the stress generation process (cf. Brown, Chorpita, & Barlow, 1998). Specifically,

panic disorder appears to produce a "stress inhibition" effect, such that the presence of this syndrome reduces rates of interpersonal conflict events.

It is possible that the unique elements of panic disorder reflect an avoidance of autonomic arousal (Kircanski, Craske, Epstein, & Wittchen, 2009). Anxiety sensitivity, or the belief that anxiety and related physical sensations are dangerous, has been linked theoretically and empirically to panic disorder (Reiss et al., 1986) and may account in part for its relationship with interpersonal conflict stress in the current study. Due to the somatic arousal accompanying interpersonal conflict events, individuals with elevated anxiety sensitivity may experience arguments and controversy as particularly alarming and threatening. Thus, potentially due to its overlap with the anxiety sensitivity construct, the unique element of panic disorder may cause individuals to actively avoid discord within relationships and thus create a buffer from interpersonal dependent stress.

Noninterpersonal dependent stress was related to individual differences on the Externalizing, but not Internalizing, dimension. Higher Externalizing scores predicted subsequent elevations in noninterpersonal stress levels, with no evidence that any syndrome-specific components of the substance use and disruptive behavior disorders had an incremental stress generating effect. This result supports a more extensive incorporation of Externalizing disorders into stress generation theory. To date, only a limited number of studies has examined the contribution of Externalizing pathology to the stress generation effect (Carter et al., 2006; Rudolph et al., 2000). Consistent with the current results, when noninterpersonal and interpersonal stressors have been distinguished in past research, Externalizing symptoms have been shown to predict an excess of noninterpersonal dependent stress only (Rudolph, 2008).

Although the latent Internalizing dimension did not have a significant impact on noninterpersonal dependent stress, dysthymia was associated with elevations in noninterpersonal dependent stress once variance shared with the Internalizing factor was removed. Given that the specific component of dysthymia was independent of variance shared with major depression, it could be speculated that this specific component represents attributes distinctive to chronic, mild depressive conditions. In support of a unique connection between chronic depression and stress generation, recent large-scale studies have reported that chronic (i.e., duration greater than 2 years), relative to nonchronic, depressions are associated with higher rates of unemployment, medical illness, hospitalizations, and suicide attempts (Gilmer et al., 2005; Satyanarayana, Enns, Cox, & Sareen, 2009). Indicating that chronic depression may confer vulnerability to noninterpersonal stress occurrence in particular, additional studies have reported that occupational and financial functioning may be especially impaired among those with chronic depressions, relative to those experiencing a single depressive episode (e.g., DeLisio et al., 1986), possibly due to a failure to achieve key vocational milestones (Evans et al., 1996). Given that much of the prior research on the stress generating effects of depressive disorders has not distinguished between major depression and dysthymia (Liu & Alloy, 2010), our findings underscore the importance of comparing the stress generation patterns of these two disorders, especially with respect to the types of stressful life events precipitated by major depression versus dysthymia.

Implications for Stress Generation Research

By integrating the HSM and stress generation theory, the current study provides a blueprint for a hierarchical model of stress generation in which the superordinate transdiagnostic level is distinguished from the subordinate syndrome level. This hierarchical model illuminates

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the general and specific influences of Internalizing and Externalizing syndromes on exposure to diverse classes of stressful life events. It is hoped that this model may enhance the efficiency of future stress generation research, which might otherwise be difficult to design or interpret due to high rates of comorbidity among mental disorders. That is, in most representative samples, the presence of comorbidity can undercut claims that a particular disorder (e.g., major depression) caused a stress generation effect due to the possibility that stress generation was attributable, at least in part, to one or more co-occurring syndromes. On the other hand, recruiting participants who manifest only one disorder (e.g., pure cases of major depression) ensures that effects are attributable to the disorder of interest, but, owing to the relative infrequency of pure cases, the results may not generalize to the entire population of individuals qualifying for this disorder. The present model circumvents this dilemma by distinguishing the shared and specific components of mental disorders in relation to stress generation.

The validity of the hierarchical model is supported by its ability to accommodate prior theory and empirical findings in the stress generation literature. For example, recent studies have demonstrated that other Internalizing syndromes besides depression produce a stress generation effect (e.g., Connolly et al., 2010). From an HSM perspective, this result is explained by the shared dependence of all Internalizing syndromes on the latent Internalizing dimension, which is in turn associated with interpersonal dependent stress. Moreover, the finding that comorbidity amplifies the stress generation effect (Harkness & Luther, 2001) is consistent with the hierarchical model. In this framework, the co-occurrence of multiple Internalizing diagnoses within the same person indicates that this person possesses a higher level of the Internalizing trait, relative to individuals with pure depression or no disorder (cf. Krueger & Finger, 2001).

In addition to organizing previous findings within a parsimonious theoretical framework, the hierarchical model may also elucidate new pathways to stress generation. That is, results from the current study indicate for the first time that the specific components of various Internalizing syndromes may have unique effects on stress exposure. For example, after controlling for variance due to the Internalizing spectrum, major depression, unlike all other disorders, predicted higher rates of interpersonal dependent stress. Further empirical work is needed to clarify the nature of the unique component of depression and identify the psychological mechanisms through which it affects stress generation. Additionally, this model revealed that the specific component of panic disorder produces a "stress inhibition" effect, whereby the presence of this diagnosis reduces exposure to interpersonal conflict.

The current findings with the HSM also suggest a number of directions for future stress generation research. First, results affirm that more empirical attention on the role of Externalizing pathology in stress generation is needed. In particular, future work would benefit from a detailed investigation of potential differences in content between stressors generated primarily by Internalizing versus Externalizing pathology (e.g., Hammen, 2006). Second, the findings highlight the importance of differentiating between the anxiety disorders when examining patterns of stress generation. The current data suggest that panic disorder can be distinguished from other anxiety disorders with respect to the magnitude, and even direction, of its effects on stress generation. This may be a main reason that studies assessing anxiety symptoms globally (Joiner, Wingate, Gencoz, & Gencoz, 2005), or the physiological aspects of anxiety specifically (Wingate & Joiner, 2004), have failed to detect stress generation effects.

Limitations and Conclusions

Many of the limitations of Study 1 also apply to Study 2, given the overlap of samples and model-fitting procedures between the two studies. However, there are a number of notable limitations that are specific to Study 2. First, due to the use of lifetime, as compared to current, diagnoses in these analyses, the time elapsed between disorder onset/offset and acute stress exposure varied across participants and diagnoses. Thus, while this study addresses the specificity of stress generation with regard to various Axis I syndromes, it does not address specificity with regard to the clinical course of these syndromes. In other words, the relative strength of stress generation effects in the premorbid, manifest psychopathology, and recovery/remission time periods remains unknown.

Second, it is acknowledged that there might be different patterns of stress generation in individuals at different stages of life (Rudolph & Hammen, 1999). For example, it is speculated that young adults may be particularly prone to stress generation as they are expected to make significant life changes by gaining geographic, emotional, and financial independence from family, establishing intimate relationships, and developing work and career paths. Individuals who are older and in more established and stable relationships, occupations, and housing situations may experience fewer life events, including those to which they have contributed (cf. Kendler et al., 2011). Further research is needed to explore differences in stress generation patterns in different life epochs.

Third, numerous syndrome-specific stress generation effects were estimated (see Table 3). Caution is therefore warranted in the interpretation of syndrome-specific stress generation results given the increased probability of Type I error, especially with regard to the less prevalent forms of psychopathology in this sample. Although the unique stress generating effect of MDD was highly significant, the corresponding effects for panic disorder and dysthymia were

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significant at the .05 alpha level and were thus more likely to be due to chance. Future replication studies in larger samples and more targeted research on the construct validity of the unique components of the syndromes studied here are recommended to evaluate the robustness of the current results.

Finally, it is important to note some alternative methods for conceptualizing and quantifying stress occurrence. For instance, while stress generation analyses in the present study used total objective threat scores summed across events (Brown & Harris, 1978; Hammen, 1991), other studies have used a count of stressful events or the number of events reaching a particular threshold of severity. Further research on the most reasonable metric for characterizing acute event impact may be necessary. Additionally, although we controlled for chronic stress in all analyses, we were unable to explore the possibility that chronic stress mediates the association between disorder and acute stress. Certain chronic stressors (e.g., poor peer relationship quality) may come about as a direct result of disorder onset and, in turn, increase the likelihood of acute stress occurrence (e.g., major fights or disputes among friends). Generally, more longitudinal research is needed to disentangle the dynamic interactions between chronic stress, acute life events, and psychopathology.

In spite of these limitations, this study offers a significant contribution to theory on the relationship between stress and psychopathology. The integration of structural modeling of Axis I diagnoses with stress generation theory presents an opportunity for a hierarchical model of stress generation that has the flexibility to explain emerging findings and illuminate avenues for future stress generation research. Further empirical work is needed to evaluate the explanatory power of hierarchical models of stress generation in other samples and to examine the specific effects of clinical syndromes not studied here (e.g., eating disorders, psychotic disorders).

Chapter 4: Serotonin transporter polymorphism (5-HTTLPR) status predicts Internalizing and Externalizing symptoms in response to daily life stress

There are two primary objectives to the current study. The first is to explore the covariation of the hypothesized anxious-misery (AM), fear (F), and Externalizing (E) dimensions on a within-person basis. As described earlier, previous HSM research—conducted exclusively on a between-subjects level—has produced inconsistent results regarding the question of whether AM and F constitute separate subdivisions of a higher-order Internalizing (I) factor. Therefore, it remains unclear whether these two dimensions should be considered distinct constructs in research and classification efforts framed around the HSM. One approach to resolving this issue is to examine the associations between AM and F with external criteria on a within-person level. For instance, if AM and F demonstrate different relationships with daily stress, this would be evidence that they should be distinguished when examining correlates (i.e., elaborating the nomological network) of the HSM (cf. Lahey et al., 2008).

Investigating the relationships between the HSM dimensions on a daily basis may also help explain why the I and E (or AM, F, and E) factors are correlated in cross-sectional research. For instance, it is possible that a similar array of risk factors confers risk to both I and E disorders, and this common cause accounts for their covariation. Alternatively, it may be that the I and E domains are functionally related, such that fluctuations in one generate change in the other. Lending support to this latter notion, Kendler et al. (2011) reported that I disorders predicted subsequent onsets of E disorders, and vice versa. However, these relationships between HSM dimensions have not yet been explored over daily intervals. The current study involves a reformulation of these HSM questions in terms of within-person processes (cf. Borsboom, Mellenbergh, & Van Heerden, 2003). Such an approach will help address the

question of whether the causes and consequences of I and E pathology described in large epidemiological studies are equivalent to those operating on a within-person basis. This information would be able to advance efforts to utilize the HSM framework in clinical assessment and nosology (e.g., Goldberg et al., 2009).

The second objective of the study is to examine the roles of stressful events and 5-HTTLPR genotype in daily manifestations of I and E pathology. It is not known whether daily stress precipitates I and E (or AM, F, and E) reactions to the same degree. Further, the joint contribution of stress and 5-HTTLPR to daily I and E is of interest to researchers seeking to elucidate the mechanisms through which this polymorphism confers risk to various psychiatric syndromes (Caspi et al., 2010; Rutter, 2008). That is, 5-HTTLPR moderates stress-disorder associations on a macro-scale, but the effects of 5-HTTLPR on the micro-scale that lead to these findings on the diagnostic level remain unclear. One possibility is that exaggerated or prolonged daily I and E reactions to stressful events among 5-HTTLPR S allele carriers may account for the relationship between 5-HTTLPR, stress, and full-blown disorders. Thus, extending recent endophenotype research involving 5-HTTLPR (e.g., Beevers et al., 2007; Conway et al., in press), the current study examines whether the 5-HTTLPR S allele promotes stress reactivity on a daily basis. Moreover, the specificity of 5-HTTLPR gene-stress interactions to I (or AM and F) versus E is examined, allowing a test of theories linking 5-HTTLPR, in combination with environmental stress, to both I and E pathology (Carver et al., 2011).

<div align="center">Hypotheses</div>

1. Stressful circumstances on Day$_t$ will have a positive, significant association with AM, F, and E on Day$_{t+1}$, consistent with previous work using daily diary methodologies to investigate daily influences on specific forms of I and E psychopathology (e.g., Bylsma,

Taylor-Clift, & Rottenberg, 2011). Stress is expected to have an equal prospective effect on AM and F.

2. The S allele at 5-HTTLPR will amplify the effect of Day$_t$ stress on Day$_{t+1}$ AM, F, and E. This hypothesis is based on prior research showing 5-HTTLPR gene-stress interaction effects for various disorders on the between-person level (reviewed in Caspi et al., 2010). Additionally, S allele carriers have been found to report elevated anxiety on days following stressful events (Gunthert et al., 2007); in contrast, L homozygotes appear relatively non-reactive to daily stress. Experimental evidence documenting exaggerated increases in hypothalamic-pituitary-adrenal axis activity among S allele carriers following stressful tasks also supports the notion that these individuals will report more I and E maladaptive behaviors in the face of daily stressors (Gotlib, Joormann, Minor, & Hallmayer, 2008; Way & Taylor, 2010).

Method

Participants

Participants were 104 UCLA undergraduate students enrolled in an introductory psychology course. Prior to enrollment in the study, all students in introductory psychology courses completed a brief measure of I or E behaviors online. During the first half of data collection (corresponding to the Fall academic quarter), students completed the Anxious/Depressed subscale of the Young Adult Self Report questionnaire (YASR; Achenbach, 1997). During the second half of data collection (Winter quarter), students completed the Aggressive and Delinquent subscales of the YASR. These scales were intended to identify individuals with above-average Internalizing and Externalizing pathology, respectively, in order to ensure sufficient variability in the daily outcome measures of these constructs. Students

scoring above the sample mean on the screening questionnaire were invited by email to participate in the present study. At the same time, those students scoring in the lower half of the screening sample—who were not contacted by email to invite them to participate—were still able to participate by signing up for the study through the departmental website. Thus, the screening instruments were intended to increase the percentage of participants scoring in the clinical range on the YASR, but elevated scores on the instruments were not necessary for inclusion in the study. Additionally, in an effort to reduce the effects of racial heterogeneity on the genetic analyses, participation was restricted to those students who identified themselves as Caucasian or Latino/a during the screening assessment. Students were awarded course credit in exchange for participation.

The final sample included 76 females (73.1%) and 28 (26.9%) males. The mean age for participants was 19.64, with a standard deviation of 4.61; 90% of participants were between the ages of 18 and 22. At a baseline interview, 47 (45.2%) of participants self-identified as Caucasian, 45 (43.3%) as Latino/a, 5 (4.8%) as biracial, 3 (2.9%) as Asian, 1 (1.0%) as Native American, and 3 (3.0%) as other.

Procedures

Following recruitment, participants provided informed consent, completed the YASR, and supplied a saliva sample for genotyping procedures at a baseline assessment meeting. Participants were then instructed on how to use the daily online diary. The diary data were collected on the day of the baseline assessment and the following 13 days. The 14 day length of the study was chosen so that participants would not vary on the number of weekend days during the daily data collection period. Participants were asked to complete the diary as late at night as was convenient for them (from 8PM to 2AM). An automated email was sent to participants each

evening with a link to the diary website, and a reminder email was sent at 9AM the next morning

to those participants who did not fill out a scheduled survey the night before.

Measures

Baseline Assessment

     Internalizing and Externalizing Symptoms. The full version of the YASR was

administered to assess individual differences in I and E. The YASR consists of 119 items

tapping the I and E spectra, as well as some other problem behavior dimensions (e.g., somatic

complaints, thought problems). The I scale is composed of Anxious/Depressed and Withdrawn

subscales, and the E scale is composed of Intrusive, Aggressive Behavior, and Delinquent

Behavior subscales. Each item is rated on a scale of 0-2, representing responses of "not true,"

"somewhat or sometimes true," and "very true or often true." Achenbach (1997) has provided

data to support the internal consistency, test-retest reliability, and criterion validity of YASR I

and E scales. Clinical cutoffs recommended by Achenbach (1997) based on a nationally-

representative sample of treatment-referred and non-referred young adults were used to

determine the percentage of participants with clinically meaningful levels of I and E in the

present study for descriptive purposes (see Results).

Daily Diary

     Daily Internalizing. Daily I symptoms were assessed using selected items from the

YASR I subscale and the Inventory of Depression and Anxiety Symptoms (IDAS; Watson et al.,

2007). To allow coverage of both AM and F dimensions, 6 items were chosen from each

domain. Example AM items are "I worried," "I felt inadequate," and "I had little interest in my

usual hobbies or activities." Example F items are "I was worried about embarrassing myself

socially," "My heart was racing or pounding," and "I was afraid that I might think or do

something bad." Participants were prompted to respond on a 5 point Likert-type scale according to "how much you have felt or experienced things this way today." Response options ranged from "not at all" to "extremely." The sum of ratings across all symptoms in the AM and F domains was used to represent daily AM and F severity, respectively. Daily AM and F items are presented in Appendix A.

Daily Externalizing. The same prompt and response format was used to assess daily severity of E behaviors. Again, items to assess the E spectrum were adapted from the YASR. Nine items were used to form the daily E scale. Examples include "I was mean to others," "I used drugs (e.g., marijuana) for nonmedical purposes," and "I broke or threw things." At least one item was included to represent each common E disorder (e.g., ASPD, alcohol abuse, drug abuse). A complete list of daily E items is presented in Appendix B.

Stressful Events. Daily stressors were assessed with an 18-item inventory developed for this study. Items were selected from previous instruments designed to elicit self-reports of recent stressful life events, such as the Objective and Subjective Event Checklist (Seidlitz & Diener, 1993), the Brief Adolescent Life Event Scale (Shahar, Henrich, Reiner, & Little, 2003), and the Inventory of Small Life Events (Zautra, Guarnaccia, & Dohrenwend, 1986). An effort was made to exclude events that are subjective in nature and may overlap with symptoms of I and E disorders, given that any such overlap could artificially inflate the correlation between the reports of stressful events and daily I and E problems (Dohrenwend, 2006). Items were sampled from multiple life domains, including interpersonal, achievement, financial, and health events. Example items include "a friendship ended," "failed to achieve an important school-related goal," "did not have enough money to do something or buy something," and "was sick or had a medical issue." Participants indicated whether each event occurred over the course of the current

day, and if so, how many times it occurred. The total count of stressors was used in analyses to represent daily stress exposure. The full daily inventory of stressful events is presented in Appendix C.

Genotyping

Saliva samples were collected under researcher observation for DNA analyses using Oragene saliva collection kits. Genotyping was performed at the UCLA Genotyping and Sequencing (GenoSeq) Core. Polymerase chain reaction (PCR) primers were labeled with fluorescent dye (6-FAM, VIC, or NED), and PCR was performed on Applied Biosystems dual block PCR thermal cyclers. Microsatellite genotypes were run on an AB 3730 capillary DNA sequencer and analyzed using the AB GeneMapper software version 4.0. The 5-HTTLPR polymorphism at the *SLC6A4* locus was assayed on an AB 7900HT Fast Real-Time PCR System and analyzed using the Sequence Detection Systems (SDS) software version 2.3. Each run included two positive control samples (individual 2 in CEPH family 1347; Coriell Institute). Genotypes were automatically scored by the allele calling software, and each genotype was verified by visual inspection. In process validation checks, the UCLA GenoSeq Core has average call, reproducibility, and concordance rates of 96, 99.7, and 99.8%, respectively. Quality values were computed for each genotype call in this sample, using a standard algorithm that combines various quality metrics. Genotype calls with a quality score of less than 95% were set to fail. The genotype frequencies in the current sample were LL = 34, SL = 42, SS = 28, and did not deviate from Hardy-Weinberg equilibrium.

Data Analytic Plan

Data analyses were conducted using a hierarchical linear modeling (HLM) approach. HLM is appropriate for diary studies because observations at multiple timepoints are nested

within individuals, resulting in dependencies among residuals. Standard (ordinary least squares)

regression methods assume independence of errors and can thus produce misleading results—

specifically, inflated type I error rates—in nested data contexts (Snijders & Bosker, 1999). HLM

adjusts for correlations among residuals by using estimates of within-person (Level 1) and

between-person (Level 2) error variance in significance testing.

Hypothesis 1 was examined using the following HLM functions,

$$I_t = \pi_0 + \pi_1(S_{t-1}) + e_t$$
$$\pi_{0j} = \beta_{00} + \beta_{01}(\text{Gender}_j) + \beta_{02}(\text{YASR}_j) + \beta_{03}(5\text{-HTTLPR}_j) + u_{0j}$$
$$\pi_{1j} = \beta_{10} + u_{1j}$$

where S_{t-1} represents the count of stressful events on Day_{t-1}. Gender and trait levels of I and E

were controlled in this analysis by including them as between-subjects predictors of the overall

intercept (π_0) on Level 2. All Level 1 variables were group mean centered, such that S_{t-1}

indicates the difference between the number of stressors occurring on Day_{t-1} for a given

participant and this participant's mean number of daily stressful events. Gender and genotype

were entered uncentered into Level 2 equations. The baseline YASR scores were entered grand-

mean centered into Level 2 equations.

Hypothesis 2 was evaluated using the same Level 1 and Level 2 equations specified

above, except that 5-HTTLPR genotype and gender were added as Level 2 predictors of the

slope of the outcome on stress (π_1), as shown below:

$$I_t = \pi_0 + \pi_1(S_{t-1}) + e_t$$
$$\pi_{0j} = \beta_{00} + \beta_{01}(\text{Gender}_j) + \beta_{02}(\text{YASR}_j) + \beta_{03}(5\text{-HTTLPR}_j) + u_{0j}$$
$$\pi_{1j} = \beta_{10} + \beta_{11}(\text{Gender}_j) + \beta_{12}(5\text{-HTTLPR}_j) + u_{1j}$$

The cross-level interaction between 5-HTTLPR and daily stress was of primary interest in $G \times E$

analyses. Allele coding for 5-HTTLPR was used, such that S allele carriers were compared with

L homozygotes in a single dummy variable. This approach is consistent with previous stress

reactivity research demonstrating the functional equivalence of the SS and SL genotypes (Hariri & Holmes, 2006; Thomason et al., 2010). However, the significance of the interaction terms was unaltered if genotype coding was used instead of allele coding at 5-HTTLPR. G × E hypotheses were tested for all outcomes.

Results

Descriptive Statistics

The average scores on the YASR I and E scales at baseline were 15.77 (SD = 7.56) and 7.90 (SD = 4.62), respectively. According to Achenbach's (1997) guidelines, 20 out of 104 (19.2%) participants were in the borderline clinical or clinical range for I, and 4 (3.8%) were in the borderline clinical or clinical range for E. Generally consistent with previous research, the Pearson correlation between the I and E scales was .29 (p < .01). No significant gender difference was detected in E symptoms (t[102] = 0.35, p = .73), whereas females tended to report more I symptoms (t[102] = 1.67, p = .09).

Descriptive statistics for the daily variables are presented in Table 9. Averaged across 14 days, all daily symptom scales demonstrated acceptable levels of internal consistency, with Cronbach's alpha values of .91 for I, .91 for F, .93 for AM, and .78 for E. An average of 11.63 out of 14 (83.1%) diaries were completed on time (i.e., before 2AM the day after they were mailed), a rate comparable to that of previous diary studies in college student samples (e.g., Covault et al., 2007; Sahl, Cohen, & Dasch, 2009). Compliance was not related to genotype or the YASR scales, and the pattern and significance of results were unaltered when participants who missed more than 3 surveys were omitted. Therefore, all results presented below reflect analyses that were conducted in the full sample.

Preliminary Analyses

The same-day and cross-lagged relationships between the different symptom scales were examined in order to determine whether the pattern of correlations among HSM dimensions observed in cross-sectional research could be reproduced on a daily time scale. The results of these analyses are summarized in Table 10. I symptoms on Day_t and E symptoms on Day_t were significantly associated, mirroring the significant correlation between these two dimensions on the YASR in the baseline assessment. When I was decomposed into F and AM, E was significantly associated with same-day F but not AM symptoms.

Regarding cross-day associations, I, but not E, on Day_{t-1} predicted I on Day_t. In contrast, I on Day_{t-1} was inversely associated with E on day_t, whereas there was no statistically significant continuity of E across days.

F, but not AM, on Day_{t-1} was significantly related to F on Day_t. Likewise, AM, but not F, on Day_{t-1} was related to AM on Day_t. There were no significant cross-day associations between E and either F or AM symptoms.

Association of Daily Stress with Next-Day Symptoms

The relationship between stress on Day_{t-1} and symptoms on Day_t was examined to test Hypothesis 1. In these analyses, gender, baseline YASR scores, and 5-HTTLPR genotype were covaried at Level 2. For equations predicting daily I (including F and AM) symptoms, the baseline YASR I scale was used as a covariate, whereas for daily E analyses the YASR E scale was used as a covariate. As shown in Table 11, stress did not have a significant effect on any next-day outcome.

The possibility of gene-environment interaction (G × E) was evaluated in models that included the cross-level interaction between 5-HTTLPR and stress. Gender was included as a

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Level 2 covariate to control for gender differences in stress-symptom associations. As seen in Table 12, analyses revealed no evidence for $G \times E$ effects on next-day outcomes.

Association of Daily Stress with Same-Day Symptoms

After observing null effects of stress on next-day symptoms, the same-day effects of stress on HSM symptoms were examined. Table 13 demonstrates that stress on Day_t was robustly positively associated with I and E symptoms on Day_t. Additionally, when separate analyses were performed for AM and F symptoms, stress had a highly significant effect on both symptom dimensions. All stress effects remained significant in supplementary analyses that controlled for symptoms on Day_{t-1} (e.g., I_{t-1} was controlled in analyses predicting I_t), suggesting that the influence of same-day stress was not due to the association of stress on Day_t with symptoms on Day_{t-1}.

Tests for $G \times E$ involving same-day stress and 5-HTTLPR revealed significant moderation for I but not E (see Table 14). Specifically, the relationship between stress and I was significantly stronger for participants carrying a 5-HTTLPR S allele ($b = 1.68$, $SE = 0.23$, $p < .001$), as compared to L allele homozygotes ($b = 0.60$, $SE = 0.35$, $p = .08$). This result was consistent across F and AM symptoms. Figure 9 depicts the form of 5-HTTLPR $G \times E$ with respect to I symptoms.

Discussion

There were two primary objectives to Study 3: (a) determine whether the pattern of covariation among HSM dimensions documented in cross-sectional research is evident on an intraindividual level, and (b) test for the existence of 5-HTTLPR $G \times E$ in relation to daily I and E symptoms. Results partially supported the compatibility of the cross-sectional HSM configuration with relationships between HSM symptom dimensions on a daily time scale. First,

the I and E dimensions were found to be significantly positively associated on the same day, consistent with the moderate positive correlation between these two factors in between-subjects analyses (Krueger et al., 1998). Second, time-lagged results showed that I was inversely related to next-day E, whereas E was not significantly related next-day I. This result suggests that, on a daily basis, the relationship between I and E pathology may be different from what is implied by the positive correlation between them in between-subjects research. While factor correlations from between-subjects HLM studies imply that the probability of having a lifetime E diagnosis is increased among those with an I diagnosis (Krueger & Markon, 2006), on the daily (i.e., micro-process) level, the probability of severe E symptoms may actually be diminished on days after elevations in I symptomatology.

Third, time-lagged results appeared to be congruent with the distinction between F and AM evident in some (but not all; see Kessler et al., 2011) between-subjects representations of the HSM (Krueger, 1999; Krueger & Markon, 2006). For instance, F, but not AM, predicted next-day F in the current study. Likewise, AM, but not F, predicted next-day AM. These significant autocorrelation effects indicate some degree of stability and distinctiveness between the two symptom dimensions, suggesting that F and AM may be reliably differentiated on an intraindividual level. As further evidence for the distinction between F and AM, the E dimension was significantly related to same-day F but not AM. This result stands in contrast to between-subjects HSM research, which typically reveals approximately equal correlations of F and AM with E (see Beesdo-Baum et al., 2009), and may reflect a functional relationship between F and E symptoms. For example, drug and alcohol use may serve to regulate panic symptomatology for some individuals (Zvolensky, Bernstein, Marshall, & Feldner, 2006).

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Together, these findings are generally consistent with the statistical maxim that covariation among traits or dimensions at the between-subjects level does not necessarily imply an equivalent pattern of covariation among these dimensions on a within-subjects level (Borsboom et al., 2003; Molenaar, 1985). Thus, researchers should be aware that theories about comorbidity formulated in between-subjects studies may not be relevant to understanding intraindividual patterns of comorbidity or symptom expression. This observation suggests that future research should investigate how HSM dimensions are related to each other—and, perhaps more importantly, to external constructs (e.g., cognitive biases, interpersonal difficulties)—at the within-person level.

Regarding G × E analyses, no support was found for Hypothesis 1 or 2. That is, Day_{t-1} stress did not predict I or E symptoms on Day_t, and the cross-day association between stress and HSM symptoms was not moderated by variation at 5-HTTLPR. One possible explanation for the absence of a stress-symptom association across days is that delayed reactivity to stress is relatively uncommon among healthy college student populations. In fact, the majority of previous research in non-clinical samples has demonstrated that the timeframe for symptomatic responses to stress is relatively narrow, rarely extending into subsequent days (Bolger, DeLongis, Kessler, & Schilling, 1989; Stone & Neale, 1984). In contrast, delayed reactivity to daily stressors is more frequently observed in clinical populations (e.g., Bylsma et al., 2011; Dasch et al., 2008). Thus, the current sampling procedures (i.e., use of non-clinical participants) may have made it more difficult to detect cross-day stress effects.

Consistent with one previous study examining 5-HTTLPR G × E on a daily basis (Gunthert et al., 2007), there was evidence to support an effect of stress on same-day symptoms and moderation of the stress-I association by 5-HTTLPR genotype. Specifically, individuals

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carrying at least one S allele were found to have a stronger relationship between stress and same-day I symptoms. This result is in line with the original finding of 5-HTTLPR G × E in relation to depression reported by Caspi and colleagues (2003), which has since been partially replicated by numerous studies (Karg et al., 2011; but see Risch et al., 2009, for a contrasting account of the literature). It also extends a growing body of research on 5-HTTLPR and stress sensitivity endophenotypes in which the 5-HTTLPR S allele has been linked to amygdala hyperreactivity in response to emotional cues (Drabant et al., 2012; Hariri et al., 2002, 2005), selective allocation of attention to anxious words and negative self-referent adjectives (Beevers et al., 2007; Hayden et al., 2008; for meta-analytic evidence, see Pergamin-Hight, Bakermans-Kranenburg, van Uzendoorn, & Bar-Haim, 2012), and exaggerated appraisals of threat associated with naturally occurring stressful life events (Conway et al., in press). The current study adds to this list of potential psychological mechanisms that account for enhanced I reactions in the face of stress among S carriers. That is, it is possible that daily stress sensitivity represents one link on the causal chain from 5-HTTLPR genotype to disorder.

The finding of G × E for both F and AM dimensions is significant for theories about the boundaries of 5-HTTLPR G × E. The majority of extant 5-HTTLPR G × E research has targeted depressive disorders (Caspi et al., 2010), and the few studies on anxiety disorders have yielded mixed results (Fergusson, Horwood, Miller, & Kennedy, 2011; Klauke et al., 2011; Stein et al., 2007). Given the association of the S allele with stress sensitivity endophenotypes that have been linked with a wide range of depressive and anxiety disorders in previous research (see Drabant et al., 2012; Hariri & Holmes, 2006), it is plausible that the joint effect of 5-HTTLPR and life stress plays a role in the development of fear-based disorders, in addition to depression and generalized anxiety disorder. Yet, this hypothesis has seldom been examined in the

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literature on 5-HTTLPR. The current results indicate that, at least on a daily basis, the 5-HTTLPR S allele potentiates the effects of stress on multiple forms of I pathology.

On the other hand, G × E effects did not extend to the E domain. The prediction that 5-HTTLPR G × E would apply equally to I and E symptoms (Hypothesis 2) was based on the theory that the combination of stress and 5-HTTLPR vulnerability can eventuate in either I or E responses, depending on preexisting social and psychological characteristics of the individual (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009; Carver et al., 2008). Consistent with the hypothesis that 5-HTTLPR confers a nonspecific deficit in emotion regulation capabilities, several experimental and observational studies have reported 5-HTTLPR G × E for E pathology (Carver et al., 2011; Conway et al., 2012; Verona et al., 2006). It is possible that the G × E effect for E was not statistically significant in the current study because the baseline level of E problems in the college student sample was relatively low. As noted earlier, only 4% of participants were in the clinically significant range for E problems according to the YASR norms. Additional research in clinical populations is therefore recommended to investigate 5-HTTLPR G × E in relation to E symptoms.

Limitations and Conclusions

Several limitations of the current study are noted. First, given that this is the first study to examine relationships among HSM dimensions with stress and with each other on a daily basis, the scales used to measure daily I and E symptoms have not been validated in prior research. While an effort was made to represent the cardinal symptoms from the most common I and E diagnoses on the daily symptom scales, the coverage of symptoms was necessarily incomplete due to time constraints in the administration of daily measures. To cite a few examples, compulsions, sleep disturbance, and criminal behavior were all not included in daily symptom

measures. Second, it was impossible to determine whether stress always preceded symptoms in same-day analyses. Therefore, the same-day results should be interpreted with some degree of caution. At the same time, supplementary analyses demonstrated that results remained the same when controlling for same-day E in tests of the stress-I association and when controlling for same-day I in tests of the stress-E association. Thus, there is some evidence that stress occurrence was not simply a result of symptoms experienced earlier in the day. Third, the sample size for between-subjects analyses, including tests of gene-stress interaction, was relatively modest ($n = 104$). Therefore, the current results should be considered tentative until replications in larger samples are available. Fourth, daily stressors were not assessed using gold standard interviewer- or team-based rating systems and were not validated against any objective criterion. As such, the threshold designating what constituted a stressor likely varied across participants. However, this measurement issue was at least partially addressed by the fact that the effect of stress was analyzed on a within-person level. As such, fluctuations in stress exposure were compared to a participant's average level of stress over the 14 days and not to the average level of stress in the entire sample.

Despite these limitations, the current study has important implications for HSM theory and research on 5-HTTLPR. Results demonstrate that intraindividual relationships between HSM dimensions may not line up with HSM factor correlations derived from between-subjects analyses. Additionally, the relationship between daily stress and I symptomatology was stronger among 5-HTTLPR S allele carriers, consistent with previous research linking the S allele to various neural, endocrine, and information-processing indices of stress sensitivity (Caspi et al., 2010). Together, these findings suggest that knowledge about transdiagnostic processes and

molecular genetics in psychopathology can be enriched by studying HSM symptoms on a within-person level.

Chapter 5: General Discussion

The overarching goal of this dissertation project was to determine whether the HSM can be a useful organizing framework for research on psychopathology. More than a decade of psychometric research on comorbidity has shown that the HSM provides a satisfactory explanation for the pattern of covariation observed among syndromes (Watson, 2009). Yet, the potential of the HSM to answer fundamental questions about etiology, treatment, and classification remains untested (Krueger & Markon, 2011; Wittchen et al., 1999). The current project integrated the HSM quantitative structure with prominent genetic and psychosocial theories of psychopathology to investigate the construct validity—a prerequisite for widespread application of the HSM in research and treatment settings (cf. Cronbach & Meehl, 1955)—of the HSM.

Having presented a series of distinct papers addressing this topic, it is possible to return to the questions set out in the introduction and present answers drawn from the results as a whole:

1. What are the optimal number and configuration of higher-order HSM dimensions to explain the covariation of common psychiatric syndromes?

This question was addressed in all three studies. Standard model fit indices in the between-subjects analyses suggested that the correlated two-factor HSM provided an excellent fit to the diagnostic data. The factor correlation in these models was estimated to be .47 in Study 1 and .36 in Study 2, indicating a moderate degree of overlap between the Internalizing and Externalizing dimensions. Attempts to fit the three-factor model, in which the Internalizing factor bifurcated into Fear and Anxious-Misery subfactors, were unsuccessful. Specifically, the factor loading of the Fear dimension on the superordinate Internalizing dimension was found to

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be greater than 1.0, suggesting that Fear and Anxious-Misery could not be reliably differentiated in the young adult sample of Studies 1 and 2. This result is consistent with a number of previous latent variable modeling studies that have supported the two-factor solution (Kessler et al., 2011; South et al., 2011) and one study that reported a standardized factor loading of .99 of Fear on the higher-order Internalizing factor (Slade & Watson, 2006). One disadvantage of being unable to estimate the three-factor model is that it was impossible to compare the associations of the Fear and Anxious-Misery subfactors with early predictors of psychopathology and stress generation. Uncovering distinct sets of causes and consequences for each subfactor would present strong evidence—arguably stronger evidence than favorable model fit statistics—that these dimensions should be distinguished, when possible, in research on the HSM (see Lahey et al., 2008).

Although factor analyses were not conducted in Study 3, cross-day stability of the Fear and Anxious-Misery symptom dimensions in a non-clinical college student population suggested a meaningful distinction between the two. That is, there were significant autocorrelation effects across days, but Fear on Day_{t-1} did not predict Anxious-Misery on Day_t and vice versa. Further, Fear and Anxious-Misery had contrasting associations with same-day Externalizing symptoms. Together, these findings suggest that all Fear and Anxious-Misery symptoms may have distinct effects on a daily process level.

2. Do monoaminergic genes play a role in determining individual differences on Internalizing and Externalizing dimensions?

In Study 1, the COMT val158met polymorphism was studied as a risk factor for Internalizing and Externalizing pathology, both in isolation and in conjunction with childhood adversity. Identical analyses were planned for 5-HTTLPR, but were ultimately not conducted because the HSM failed to converge in the subsample available for analyses with that genotype.

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COMT was found to have an effect on the Externalizing dimension under conditions of high early environmental adversity, such that carriers of the val158 allele were more susceptible to Externalizing pathology in adverse contexts. The COMT val158 allele was also directly associated with the unique component of specific phobia, consistent with one previous study that reported an association of the val158 allele with phobic anxiety (i.e., fear of heights, crowds, and enclosed spaces; McGrath et al., 2004).

In Study 3, variation at 5-HTTLPR was associated with the strength of relationship between daily stress and HSM symptoms. Carriers of the S allele responded to daily stress with higher levels of Internalizing, but not Externalizing, pathology, presumably putting them at increased risk for developing Internalizing disorders. This gene-stress interaction was consistent across the Fear and Anxious-Misery subdomains of Internalizing symptoms. These results are consistent with a growing body of research linking 5-HTTLPR with stress sensitivity endophenotypes on neural, endocrine, and cognitive-affective levels of analysis (Conway et al., in press; Drabant et al., 2012; Gotlib et al., 2008; Pergamin-Hight et al., 2012).

3. What are the early childhood predictors of the HSM latent factors?

Results from Study 1 demonstrated that maternal reports of offspring Internalizing behavior at age 5 were not related to standing on either of the transdiagnostic dimensions in young adulthood. However, Internalizing scores at age 5 were highly significantly associated with the unique component of panic disorder, suggesting that risk for panic may be detectable early in childhood. Consistent with several previous studies (e.g., Krueger et al., 1998; Fergusson et al., 2006), the Externalizing dimension showed a higher degree of continuity over time. That is, age 5 reports of offspring Externalizing behavior on the CBCL were significantly related to subsequent standing on the HSM Externalizing dimension. Early childhood

Externalizing was also linked with the unique components of conduct disorder, drug abuse/dependence, and social phobia.

Early childhood adversity—indexed by a composite of maternal history of depression or anxiety, economic hardship, parental criminality, parental separation, and childhood health problems—was strongly associated with both Internalizing and Externalizing dimensions. Each additional form of adversity was estimated to produce a 0.17 standard deviation increase in Internalizing and a 0.18 standard deviation increase in Externalizing. Further, early adversity was associated with 3 out of 4 diagnosis-specific components on the Externalizing spectrum and 1 out of 7 on the Internalizing spectrum. This pattern of associations was referred to as a hybrid pattern of risk, given that early adversity affected liability to disorder through a mixture of transdiagnostic and diagnosis-specific pathways.

4. What is the role of HSM Internalizing and Externalizing dimensions in the stress generation phenomenon?

Study 2 reconceptualized stress generation theory, which has historically been used to understand the recurrence of MDD (Hammen, 1991), through the lens of the HSM. Higher standing on the Internalizing dimension predicted increased exposure to interpersonal dependent stress (e.g., romantic relationship breakup, argument with a boss), suggesting that the stress generation phenomenon is not unique to MDD. At the same time, the diagnosis-specific component of MDD was significantly associated with interpersonal dependent stress even after accounting for the effect of the Internalizing dimension, indicating that some psychopathological processes unique to MDD portend disruptions in interpersonal relationships. Additionally, the unique component of panic disorder was inversely related to interpersonal dependent stress

exposure. This finding was labeled a "stress inhibition" effect, and it suggests that some unique feature of panic disorder reduces rates of interpersonal conflict events.

Highlighting the need for an increased focus on Externalizing pathology in the stress generation literature, Study 2 also demonstrated that the Externalizing factor was linked with the occurrence of noninterpersonal dependent stress (e.g., being fired due to poor job performance, financial difficulties due to inappropriate spending). Further, the unique portion of dysthymia was associated with elevations in noninterpersonal dependent stress, consistent with prior reports of impaired occupational and financial functioning among individuals with chronic depression, possibly due to a failure to achieve key vocational milestones (e.g., Evans et al., 1996).

Implications for Nosology and Treatment

Recent years have seen the emergence of several novel approaches to classification and treatment in clinical psychology that are based on the concepts of transdiagnostic processes, diagnosis-specific psychopathology, and/or endophenotypes. The findings from this dissertation—and, more generally, the idea of using the HSM as a research framework—are briefly discussed in this context.

Leaders in clinical psychology are calling for a shift from a purely descriptive diagnostic classification system to one based on an understanding of etiology (Craddock & Owen, 2010; Kupfer & Regier, 2011). It is theorized that compiling disorders on the basis of distinct genetic, biological, and psychological features will address concerns about the validity of diagnostic entities in the current DSM (Hyman, 2008; Watson, 2005), which defines disorders according to polythetic sets of observed symptoms (American Psychiatric Association, 2000).

Research using the HSM can inform this process by identifying associations of diagnosis-specific pathology with a variety of external criteria, including genetic variation, neurobiology,

psychophysiology, personality, and treatment response (Krueger & Markon, 2011; Nolen-Hoeksema & Watkins, 2011). As stated by Meehl (1977) and others (e.g., Garber et al., 2009), delineating the biological and psychosocial etiological factors unique to a particular disorder is the strongest form of construct validation for diagnostic categories. Along these lines, results from Study 1 suggest that COMT val158met variation may be uniquely associated with pathology distinctive to specific phobia. Findings such as these may eventually be useful to diagnosticians attempting to define disorders according to unique sets of antecedents or correlates. Future work would do well to further elaborate the nomological network (cf. Cronbach & Meehl, 1955) of diagnosis-specific components within the HSM framework.

Similarly, an understanding of the differential relationships between risk factors and various forms of psychopathology can help in efforts to construct diagnostic clusters, or sets of related disorders. For example, the DSM-5 Diagnostic Spectra Study Group was charged with developing a scientifically-based organization of mental disorders that moves beyond shared phenomenology. In a series of articles, this Study Group proposed a "metastructure" of disorders that was based on an understanding of causal risk factors and clinical features shared across disorders (see Andrews et al., 2009). Two of the external validators that the Study Group used to assess the degree of relatedness among disorders were specific genetic and environmental risk factors, both of which were examined in Study 1. From the exploratory analysis of five early environmental adversities, it could be hypothesized that the Internalizing cluster is distinguished by its correlation with childhood health problems, for example, whereas the Externalizing cluster might be specifically related to parental separation early in the offspring's life. Further work using latent variable modeling to examine associations of latent Internalizing and Externalizing

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dimensions with a more complete set of genetic and environmental risk factors would help the field move toward an empirical organization of psychopathology.

The current project also has implications for the design and implementation of transdiagnostic psychotherapies (e.g., Barlow, Allen, & Choate, 2004; Mansell, Harvey, Watkins, & Shafran, 2009). The associations of the HSM dimensions with both interpersonal and noninterpersonal impairment in Study 2 support the validity of these transdiagnostic dimensions as targets of intervention. For instance, a one standard deviation increase in Internalizing pathology was associated with a 0.75 point increase (on a 5-point scale) on the interpersonal stress severity rating assigned by the objective rating team.

Clearly, treatments ameliorating the shared pathology of multiple disorders would be expected to enhance the efficiency of mental health service delivery (Barlow et al., 2004). At the same time, results from the dissertation provide a preliminary indication that transdiagnostic therapies may need to incorporate diagnosis-specific interventions to be optimally effective in the treatment of certain disorders. For example, results from Study 2 suggest that some unique pathology of MDD leads to a greater risk of interpersonal problems. Indeed, a standard deviation increment in MDD-specific pathology predicted a full half point increase in the objective severity of interpersonal stress exposure. It is possible that a supplementary focus on interpersonal skills training and/or the elicitation and modification of interpersonal schemas would improve the efficacy of transdiagnostic treatments for individuals diagnosed with MDD. Statistical modeling of the HSM in future treatment outcome studies has the potential to address such hypotheses.

Future Directions

A number of questions regarding the structure of the HSM and its potential utility for guiding research were not tested in this dissertation but are important topics for future study. First, future research within the HSM framework is needed to clarify the nature of the transdiagnostic dimensions. We still do not have an adequate answer to the question "What are the Internalizing and Externalizing spectra?" posed by Krueger and colleagues (1998) in the original formulation of the HSM. Studies to test the construct validity of the Internalizing and Externalizing factors should help uncover the nature of the biological systems, cognitive styles, and personality traits that comprise these transdiagnostic dimensions (Kessler et al., 2011).

Second, future studies would benefit from explicating the causal pathways through which genetic and distal environmental risk factors lead to transdiagnostic and diagnosis-specific pathology. That is, the exact mechanisms accounting for the statistical associations between risk factors and the HSM were not examined here. It is of prime importance to illuminate the links in the causal chain from early environmental and genetic risk to both transdiagnostic and diagnosis-specific pathology so that the HSM can be more completely integrated with existing etiological accounts of psychopathology. It is likely that several biological and psychological processes intervene between vulnerabilities that are inherited or present early in life and proximal risk for disorder (e.g., Nolen-Hoeksema & Watkins, 2011). For example, childhood health problems may lead to social withdrawal and, in turn, higher neuroticism, a construct that has been hypothesized to have substantial overlap with the transdiagnostic Internalizing dimension (e.g., Griffith et al., 2010).

Third, more research is needed on the within-person level to establish whether the structure and predictive validity of the HSM reported in between-subjects analyses are present at the intraindividual level. This is an important task because psychopathological processes (e.g.,

stress generation) involving the HSM dimensions inferred from between-subjects research may not operate at the within-person level; this is an assumption that must be tested empirically (Borsboom et al., 2003). Along these lines, within-person factor analysis (e.g., Molenaar, 1985) may be useful in determining whether the structure of the HSM is invariant across individuals and whether the transdiagnostic traits are indeed working (e.g., accounting for comorbidity, predicting interpersonal functioning) in ways that are consistent with existing between-subjects theories.

Although much work remains to be done, the current project was able to expand the nomological network of the HSM. Connections were made between the transdiagnostic HSM dimensions and psychological phenomena in ways that are consistent with existing theory. Further, the capacity of the HSM to isolate pathology unique to a given syndrome allowed the discovery of several diagnosis-specific pathways to risk for disorder. Overall, the dissertation results support the utility of the HSM as an organizational framework for future genetic and psychosocial research on psychopathology.

Appendices

Daily Fear Items
1. I was worried about embarrassing myself socially

2. My heart was racing or pounding

3. I was afraid that I might think or do something bad

4. I felt self-conscious knowing that others were watching me

5. I had disturbing thoughts of something bad that happened to me

6. I felt panicky

Daily Anxious-Misery Items
7. I worried

8. I felt depressed

9. I felt discouraged about things

10. I felt nervous

11. I felt inadequate

12. I had little interest in my usual hobbies or activities

Appendix B. Daily Externalizing Symptoms.

    13. I was mean to others

    14. I used drugs (e.g., marijuana) for nonmedical purposes

    15. I broke or threw things

    16. I screamed or yelled

    17. I broke rules at school, work, or elsewhere

    18. I drank too much alcohol or got drunk

    19. I spread rumors or gossiped about someone

    20. I intentionally ignored someone

    21. I lied to get what I wanted

1. Problems at work (e.g. didn't get the schedule that you requested, couldn't find someone to fill in for you)

2. Problems with co-workers or boss (if different from above)

3. Did poorly on, or failed, an important exam or major project

4. Failed to achieve an important school related goal that does not involve GPA

5. Did not have enough money to do something or buy something

6. Lost money or something important

7. Property was damaged or stolen

8. Was sick or had a medical issue

9. An event that happened today related to a family member or close friend having a medical or emotional problem

10. Had an argument/problem with significant other

11. Had an argument/problem with a friend

12. Had an argument/problem with family member

13. Had an argument/problem with a professor, or project group

14. Fight or argument among social group to which you belong

15. Was rejected or excluded by others (group, significant other, friend, etc.)

16. Was criticized by others (project group, significant other, friend, professor, etc.)

Tables

Table 1

Correlations and Descriptive Statistics for Risk Factors and Diagnoses

[Table presented on next 2 pages.]

All correlations among diagnoses are tetrachoric correlations. Correlations greater than |.07| are significant at the .05 level; correlations greater than |.10| are significant at the .01 level.

	1	2	3	4	5	6	7	8	9	10	11	12
1. Major Depression	—											
2. Dysthymia	.44	—										
3. Generalized Anxiety Disorder	.55	.38	—									
4. Panic Disorder	.60	.51	.52	—								
5. Social Phobia	.27	.25	.43	.24	—							
6. Specific Phobia	.14	.17	.33	.22	.26	—						
7. Post-Traumatic Stress Disorder	.57	.34	.36	.40	.08	.25	—					
8. Conduct Disorder	.25	.35	.10	.29	.20	.04	-.02	—				
9. Alcohol Abuse/Dependence	.17	.01	.21	.12	.21	-.03	.17	.46	—			
10. Drug Abuse/Dependence	.19	.22	.19	.31	.17	-.04	.28	.61	.62	—		
11. Antisocial Personality Disorder	.17	.35	.13	.26	.16	-.09	.19	.61	.59	.52	—	
12. Economic Hardship	.03	.02	.11	.20	.02	.04	..21	.17	.02	.13	.13	—
13. Parental Criminality	.08	.07	.15	.06	.03	.08	.14	.38	.15	.15	.18	.33
14. Parental Separation	.03	-.01	.19	.05	.09	.06	.12	-.02	.17	.13	.06	.34
15. Health Problems	.06	.15	.14	.09	.03	.09	.09	.17	.14	.02	.06	.07
16. Maternal Depression/Anxiety	.12	.18	.20	.20	.22	-.03	.16	.17	.17	.19	.19	.11
17. Environmental Composite	.10	.14	.27	.21	.14	.08	.23	.33	.22	.22	.20	.67
18. Gender	-.35	-.13	-.15	-.08	.07	-.29	-.29	.31	.22	.19	.30	-.02
19. COMT val158met	.04	.10	.21	-.13	.06	-.24	-.06	-.11	-.01	-.15	-.13	-.02
N (% of sample)	220 (31.2)	71 (10.1)	56 (7.9)	24 (3.4)	144 (20.4)	110 (15.6)	48 (6.8)	21 (3.0)	198 (28.1)	177 (25.1)	61 (8.6)	234 (32.8)
Mean (SD)	—	—	—	—	—	—	—	—	—	—	—	—

	13	14	15	16	17	18	19
13. Parental Criminality	—						
14. Parental Separation	.35	—					
15. Health Problems	.05	.07	—				
16. Maternal Depression/Anxiety	.18	.16	.04	—			
17. Environmental Composite	.68	.66	.39	.49	—		
18. Gender	-.01	-.02	.01	.06	.01	—	
19. COMT val158met	.07	-.01	.05	.08	.06	.01	—
N (% of sample)	176 (24.6)	158 (22.1)	117 (16.4)	127 (18.4)	—	—	—
Mean (*SD*)	—	—	—	—	1.14 (1.19)	0.51 (0.50)	1.01 (0.70)

Table 2

Factor Loadings of Mental Disorders on the Internalizing and Externalizing Factors of the

Hierarchical-Spectrum Model

	Internalizing	Externalizing
Major Depression	.75	—
Dysthymia	.60	—
Generalized Anxiety Disorder	.73	—
Panic Disorder	.76	—
Social Phobia	.44	—
Specific Phobia	.29	—
Post-Traumatic Stress Disorder	.62	—
Alcohol Abuse/Dependence	—	.75
Drug Abuse/Dependence	—	.80
Conduct Disorder	—	.76
Antisocial Personality Disorder	—	.74

All factor loadings are significant at the .01 alpha level.

Table 3

Regression of Transdiagnostic and Diagnosis-Specific Outcomes on Age 5 CBCL Scores

Risk Factors	Transdiagnostic Outcomes			Diagnosis-Specific Outcomes										
	INT	EXT	COND	AAD	DAD	ASPD	MDD	PAN	GAD	SOP	PTSD	DYS	SPEC
CBCL Internalizing	.03	.01	.04	.00	-.01	.03	.02	.10**	.03	-.01	.04	.03	.02
	(.02)	(.02)	(.04)	(.02)	(.02)	(.02)	(.02)	(.04)	(.03)	(.02)	(.03)	(.03)	(.02)
CBCL Externalizing	.02	.04**	.08*	.03	.04*	.02	..01	-.03	.03	.05**	.04	.01	.02
	(.01)	(.01)	(.03)	(.02)	(.02)	(.02)	(.02)	(.04)	(.03)	(.02)	(.03)	(.02)	(.02)

Gender was covaried in these analyses. * $p < .05$; ** $p < .01$

Table 4

Regression of Transdiagnostic and Diagnosis-Specific Outcomes on Environmental and Genetic Risk Factors

Risk Factors	Transdiagnostic Outcomes		Diagnosis-Specific Outcomes										
	INT	EXT	COND	AAD	DAD	ASPD	MDD	PAN	GAD	SOP	PTSD	DYS	SPEC
Step 1													
Gender	-.49**	.56**	.40	.57**	.50**	.63**	-.49**	-.36	-.47*	.05	-.71**	-.30*	-.68**
	(.09)	(.11)	(.24)	(.10)	(.11)	(.15)	(.10)	(.20)	(.15)	(.11)	(.17)	(.14)	(.13)
Early Adversity Composite	.17**	.18**	.30**	.13**	.18**	.13*	.08*	.19*	.25**	.12*	.16*	.16*	.08
	(.04)	(.04)	(.08)	(.04)	(.04)	(.05)	(.04)	(.07)	(.06)	(.04)	(.06)	(.06)	(.04)
Step 2													
COMT val158met	.01	.06	.15	-.02	.13	.13	.02	.18	-.16	-.04	-.02	-.10	.38**
	(.08)	(.07)	(.25)	(.45)	(.09)	(.57)	(.09)	(.16)	(.11)	(.10)	(.14)	(.11)	(.12)
COMT × Adversity	.01	.13*	-.20	-.16	-.18	.05	-.02	.20	.01	.01	.03	.01	-.02
	(.08)	(.06)	(.35)	(.09)	(.10)	(.14)	(.09)	(.18)	(.09)	(.08)	(.11)	(.10)	(.10)

* $p < .05$, ** $p < .0015$. In each cell, the top value is the unstandardized regression coefficient, which can be interpreted in a *z*-score metric, and the bottom value is its standard error. Step 1 analyses were performed in the full sample; Step 2 analyses were performed in the subset of 471 participants who were genotyped for COMT. Gender and early adversity were covaried in Step 2 analyses. For gender, 0 = female, 1 = male. COMT val158met is coded according to the number of val158 alleles present.

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Table 5

Regression of Transdiagnostic and Diagnosis-Specific Outcomes on Five Early Environmental Risk Factors

Risk Factors	Transdiagnostic Outcomes		Diagnosis-Specific Outcomes										
	INT	EXT	COND	AAD	DAD	ASPD	MDD	PAN	GAD	SOP	PTSD	DYS	SPEC
Maternal depression/anxiety	.44**	.24*	.41	.07	.31*	.28	.22	.60**	.34	.28	.42*	.71**	-.04
	(.11)	(.11)	(.26)	(.14)	(.14)	(.19)	(.14)	(.23)	(.19)	(.15)	(.21)	(.17)	(.19)
Economic hardship	.26*	.04	.11	-.12	.19	.10	.09	.31	.31	.07	.29	.28	.13
	(.11)	(.11)	(.40)	(.13)	(.13)	(.19)	(.13)	(.22)	(.18)	(.14)	(.21)	(.16)	(.16)
Parental criminality	.05	.19	.26	.26*	.12	-.05	.13	-.02	.28	-.04	-.01	.03	.18
	(.11)	(.09)	(.32)	(.12)	(.14)	(.18)	(.13)	(.22)	(.18)	(.13)	(.24)	(.16)	(.15)
Parental separation	.06	.30*	.39	.35*	.22	.21	.03	.03	.23	.22	.03	-.29	-.04
	(.12)	(.12)	(.35)	(.14)	(.15)	(.20)	(.14)	(.25)	(.18)	(.14)	(.25)	(.20)	(.17)
Health problems	.28*	.16	.52	.18	-.03	.20	.11	.29	.33	.12	.32	.30	.26
	(.13)	(.13)	(.28)	(.15)	(.16)	(.22)	(.15)	(.27)	(.19)	(.16)	(.22)	(.20)	(.17)

*$p < .05$, ** $p < .01$. In each cell, the top value is the unstandardized regression coefficient, which can be interpreted in a *z*-score metric, and the bottom value is its standard error. Gender was accounted for as a covariate in all analyses.

Table 6

Correlations and Descriptive Statistics for Study Variables

[Table presented on next page.]

All correlations among diagnoses are tetrachoric correlations. Correlations greater than |.07| are significant at the .05 level; correlations greater than |.10| are significant at the .01 level. For gender, 0 = female, 1 = male. N = number of participants qualifying for a diagnosis.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Major Depression	—														
2. Dysthymia	.36	—													
3. Generalized Anxiety Disorder	.57	.32	—												
4. Panic Disorder	.53	.51	.47	—											
5. Social Phobia	.21	.24	.41	.10	—										
6. Specific Phobia	.16	.20	.28	.19	.23	—									
7. Post-Traumatic Stress Disorder	.54	.32	.46	.25	.08	.24	—								
8. Obsessive-Compulsive Disorder	.04	-.06	.33	.08	-.05	.15	.33	—							
9. Conduct Disorder	.11	.26	.01	.39	.24	.19	.01	.03	—						
10. Oppositional Defiant Disorder	.25	.07	.30	.06	.39	-.15	.30	.37	.15	—					
11. Alcohol Abuse/Dependence	.28	.02	.25	.21	.17	.03	.25	.30	.40	.53	—				
12. Drug Abuse/Dependence	.24	.21	.23	.19	.27	.06	.31	.29	.54	.36	.59	—			
13. Interpersonal Stress	.28	.16	.18	.03	.04	.15	.24	.17	-.03	.08	.15	.14	—		
14. Noninterpersonal Stress	.03	.15	.11	.11	.07	.02	-.01	-.08	.20	.13	.08	.23	.07	—	
15. Independent Stress	.15	.15	.03	-.08	.04	.07	.08	.18	.02	.06	.12	.06	.25	.01	—
16. Gender	-.26	-.14	-.18	-.11	.09	-.24	-.34	-.15	.23	.16	.09	.18	-.12	.10	-.10
N (% of sample)	204 (28.6)	63 (8.9)	37 (5.2)	14 (2.0)	112 (15.8)	79 (11.2)	39 (5.5)	16 (2.3)	22 (3.1)	22 (3.1)	139 (19.7)	146 (20.6)	—	—	—
Mean (*SD*)	—	—	—	—	—	—	—	—	—	—	—	—	3.05 (3.02)	1.74 (2.16)	3.06 (2.91)

Table 7

Factor Loadings of Axis I Syndromes on the Internalizing and Externalizing Factors of the

Hierarchical-Spectrum Model

	Internalizing	Externalizing
Major Depression	.73	—
Dysthymia	.52	—
Generalized Anxiety Disorder	.76	—
Panic Disorder	.61	—
Social Phobia	.43	—
Specific Phobia	.31	—
Post-Traumatic Stress Disorder	.65	—
Alcohol Abuse/Dependence	—	.75
Drug Abuse/Dependence	—	.80
Conduct Disorder	—	.60
Oppositional Defiant Disorder	—	.57

All factor loadings are significant at the .01 alpha level.

Table 8

Regression of Stress on Latent Internalizing and Externalizing Dimensions and Specific

Syndromes

[Table presented on next page.]

For gender, female = 0, male = 1. * $p < .05$. ** $p < .01$. Separate models were estimated for each

class of stress.

Predictors	Interpersonal Dependent Stress			Noninterpersonal Dependent Stress			Independent Stress		
	b	SE	β	b	SE	β	b	SE	β
Latent Dimensions									
Internalizing	0.76	0.25	.29**	-0.07	0.13	-.03	0.17	0.23	.06
Externalizing	0.32	0.34	.09	0.43	0.21	.17*	0.37	0.33	.10
Syndrome-Specific Components									
Major Depression	0.49	0.16	.24**	-0.10	0.14	-.07	0.31	0.23	.15
Dysthymia	0.18	0.17	.07	0.25	0.10	.13*	0.32	0.19	.11
Generalized Anxiety Disorder	0.06	0.21	.03	0.13	0.19	.09	-0.14	0.24	-.07
Panic Disorder	-0.76	0.34	-.21*	0.13	0.27	.07	-0.43	0.30	-.16
Social Phobia	-0.25	0.18	-.09	-0.07	0.12	-.04	0.03	0.18	.01
Specific Phobia	0.23	0.17	.08	0.01	0.14	.01	0.04	0.17	.01
Post-Traumatic Stress Disorder	0.36	0.21	.15	-0.09	0.17	-.05	0.03	0.22	.01
Alcohol Abuse/Dependence	0.16	0.15	.08	0.04	0.26	.01	0.23	0.14	.12
Drug Abuse/Dependence	0.14	0.16	.07	0.46	0.28	.15	-0.01	0.15	-.01
Conduct Disorder	-0.30	0.43	-.11	0.09	0.23	.04	-0.02	0.26	-.01
Oppositional Defiant Disorder	0.08	0.31	.03	0.02	0.12	.01	0.02	0.39	.02
Gender	-0.24	0.31	-.04	0.38	0.23	.09	-0.59	0.32	-.10
Chronic Stress	-0.10	0.07	-.07	0.14	0.04	.14**	0.07	0.05	.07

Table 9

Descriptive Statistics for Daily Variables

Variable	Mean	SD	Minimum	Maximum
Internalizing	18.99	5.56	12.07	41.43
Fear	8.57	2.55	6.00	19.43
Anxious-Misery	10.42	3.40	6.00	22.00
Externalizing	9.98	1.19	9.00	17.79
Stress	1.27	1.07	0.00	5.57

The scale for each symptom ranged from 1 through 5, with 12 items indexing Internalizing and 9

indexing Externalizing. The scale for each stressor ranged from 0 through 3. Descriptive

statistics were computed by first taking the within-person mean for each participant on each

variable across all time points, and then computing descriptive statistics across participants. As a

result, the minimum and maximum columns reflect the minimum and maximum for individual

participants aggregated across time points, not the minimum/maximum of the actual responses.

Table 10

Relationships between HSM Symptom Dimensions

Predictors	INT$_t$			FEAR$_t$			AM$_t$			EXT$_t$		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
EXT$_t$	0.48	0.17	.004	0.30	0.07	< .001	0.18	0.11	.105			
INT$_{t-1}$	0.14	0.05	.004							-0.02	0.01	.018
EXT$_{t-1}$	0.16	0.13	.214							0.03	0.04	.511
FEAR$_{t-1}$				0.10	0.05	.032	-0.08	0.07	.238	-0.02	0.03	.504
AM$_{t-1}$				0.01	0.03	.640	0.21	0.05	< .001	-0.02	0.02	.346
EXT$_{t-1}$				0.03	0.06	.656						
FEAR$_{t-1}$				0.11	0.04	.014						
EXT$_{t-1}$							0.13	0.09	.116			
AM$_{t-1}$							0.18	0.05	< .001			

EXT = Externalizing; INT = Internalizing; AM = Anxious-Misery

Table 11

Effects of Stress on Next-Day HSM Symptom Dimensions

Predictors	INT$_t$			FEAR$_t$			AM$_t$			EXT$_t$		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
Overall Intercept π_0												
Intercept β_{00}	18.35	0.81	< .001	7.97	0.27	< .001	10.38	0.44	< .001	10.13	0.30	< .001
Gender β_{01}	-0.72	0.98	.470	0.20	.044	.653	-.91	0.52	.083	-0.20	0.21	.351
YASR INT/EXT β_{02}	0.45	0.06	< .001	0.18	0.02	< .001	0.27	0.03	< .001	0.11	0.03	< .001
5-HTTLPR β_{03}	0.92	0.02	.321	0.67	0.36	.064	0.24	0.50	.628	-0.15	0.28	.590
Stress$_{t-1}$ π_1												
Intercept β_{10}	0.03	0.08	.736	-0.03	0.05	.517	0.06	0.07	.335	-0.05	0.04	.189

YASR = Young Adult Self Report; EXT = Externalizing; INT = Internalizing; AM = Anxious-Misery

Table 12

Gene-Environment Interaction Effects on Next-Day HSM Symptom Dimensions

Predictors	INT_t			$FEAR_t$			AM_t			EXT_t		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
Overall Intercept π_0												
Intercept β_{00}	18.35	0.63	< .001	7.97	0.27	< .001	10.38	0.44	< .001	10.16	0.31	< .001
Gender β_{01}	-0.71	0.91	.435	0.20	0.44	.653	-0.91	0.52	.083	-0.16	0.21	.449
YASR INT/EXT β_{02}	0.45	0.05	< .001	0.18	0.02	< .001	0.27	0.03	< .001	0.03	0.02	.111
5-HTTLPR β_{03}	0.92	0.77	.234	0.67	0.46	.144	0.24	0.50	.628	-0.20	0.31	.525
Stress$_{t-1}$ π_1												
Intercept β_{10}	-0.08	0.09	.351	-0.07	0.04	.080	-0.02	0.09	.835	-0.11	0.09	.193
Gender β_{11}	0.03	0.19	.862	0.10	0.11	.387	-0.06	0.12	.592	0.04	0.08	.643
5-HTTLPR β_{12}	0.18	0.19	.336	0.02	0.10	.839	0.16	0.12	.194	0.09	0.09	.325

YASR = Young Adult Self Report; EXT = Externalizing; INT = Internalizing; AM = Anxious-Misery

Table 13

Effects of Stress on Same-Day HSM Symptom Dimensions

Predictors	INT_t			$FEAR_t$			AM_t			EXT_t		
	b	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*	*b*	*SE*	*p*
Overall Intercept π_0												
Intercept β_{00}	18.56	0.61	< .001	8.05	0.26	< .001	10.53	0.44	< .001	10.53	0.44	< .001
Gender β_{01}	-0.56	0.90	.534	0.24	0.43	.572	-0.78	0.52	.133	-0.78	.52	.133
YASR INT/EXT β_{02}	0.45	0.05	< .001	0.18	0.02	< .001	0.27	0.03	< .001	0.27	0.03	< .001
5-HTTLPR β_{03}	0.85	0.75	.255	0.67	0.35	.060	0.14	0.49	.782	0.14	0.49	.782
$Stress_t$ π_1												
Intercept β_{10}	1.39	0.19	< .001	0.39	0.07	< .001	0.99	0.15	< .001	0.99	0.15	< .001

YASR = Young Adult Self Report; EXT = Externalizing; INT = Internalizing; AM = Anxious-Misery

Table 14

Gene-Environment Interaction Effects on Same-Day HSM Symptom Dimensions

Predictors	INT$_t$			FEAR$_t$			AM$_t$			EXT$_t$		
	b	SE	p	b	SE	p	b	SE	p	b	SE	p
Overall Intercept π_0												
Intercept β_{00}	18.44	0.62	< .001	8.03	0.26	< .001	10.41	0.44	< .001	10.11	0.28	< .001
Gender β_{01}	-0.62	0.90	.491	0.23	0.43	.591	-0.87	0.51	.095	-0.12	0.22	.590
YASR INT/EXT β_{02}	0.46	0.05	< .001	0.18	0.02	< .001	0.27	0.03	< .001	0.10	0.02	< .001
5-HTTLPR β_{03}	1.06	0.75	.164	0.71	0.35	.047	0.35	0.49	.483	-0.13	0.27	.630
Stress$_t$ π_1												
Intercept β_{10}	0.82	0.23	< .001	0.23	0.09	.017	0.58	0.15	< .001	0.11	0.06	.106
Gender β_{11}	-0.47	0.31	.130	-0.10	0.14	.468	-0.39	0.21	.065	0.12	0.13	.347
5-HTTLPR β_{12}	1.00	0.33	.004	0.28	0.13	.044	0.73	0.24	.003	0.11	0.09	.205

YASR = Young Adult Self Report; EXT = Externalizing; INT = Internalizing; AM = Anxious-Misery

Figures

Figure 1. Configuration of the best-fitting model of Krueger, Caspi, Moffitt, and Silva (1998).
MDD = major depression; DYS = dysthymia; GAD = generalized anxiety disorder; AGO =
agoraphobia; SOP = social phobia; SPP = specific phobia; OCD = obsessive-compulsive
disorder; ASPD = antisocial personality disorder; MD = marijuana dependence; AD = alcohol
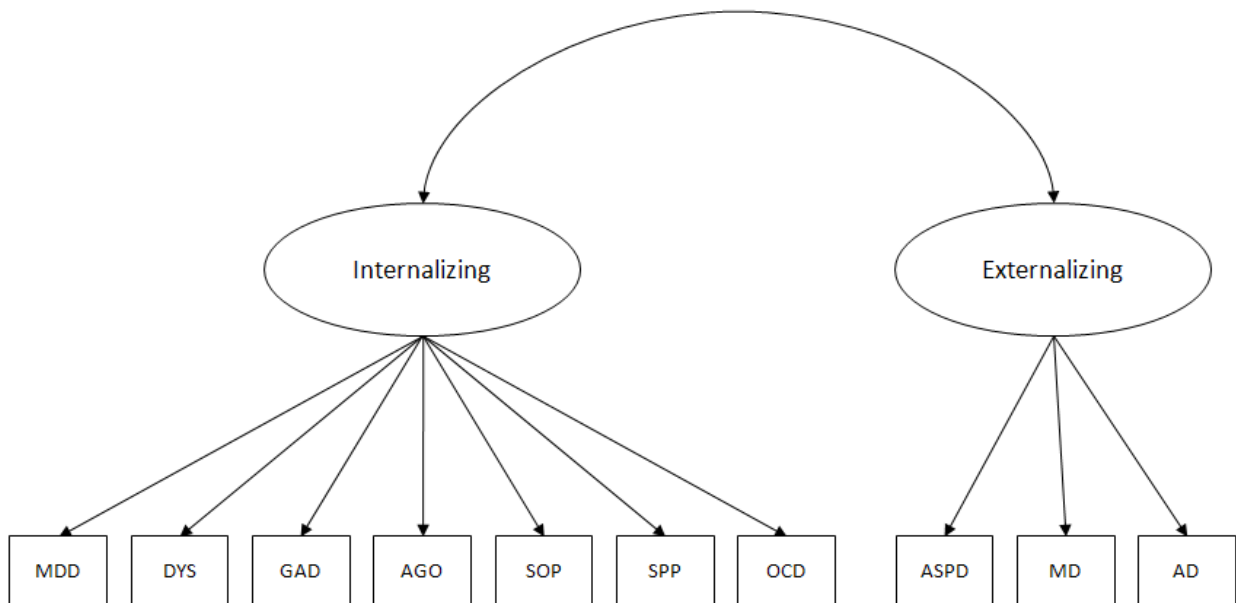dependence.

Figure 2. Configuration of the best-fitting model in the complete sample of Krueger (1999).

MDD = major depression; DYS = dysthymia; GAD = generalized anxiety disorder; AGO = agoraphobia; SOP = social phobia; SPP = specific phobia; PAN = panic disorder; ASPD = antisocial personality disorder; DD = drug dependence; AD = alcohol dependence.
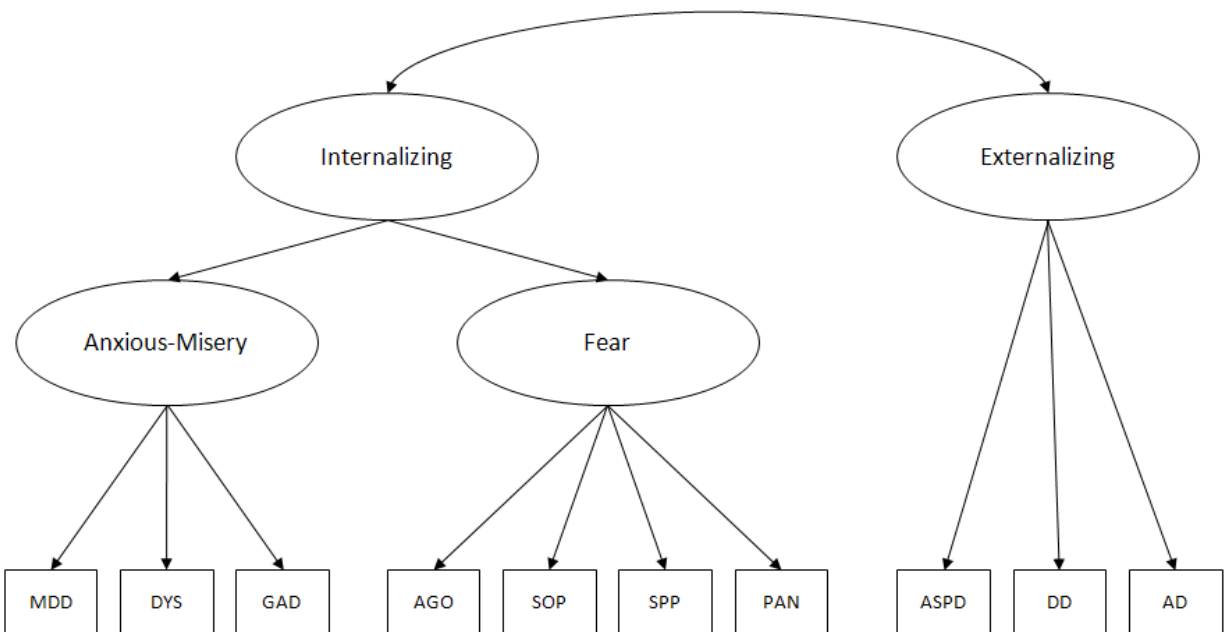
Figure 3. An example of a bifactor model. Note that each specific factor is uncorrelated with all other specific factors and the general factor. SX1 through SX9 represent different symptoms.
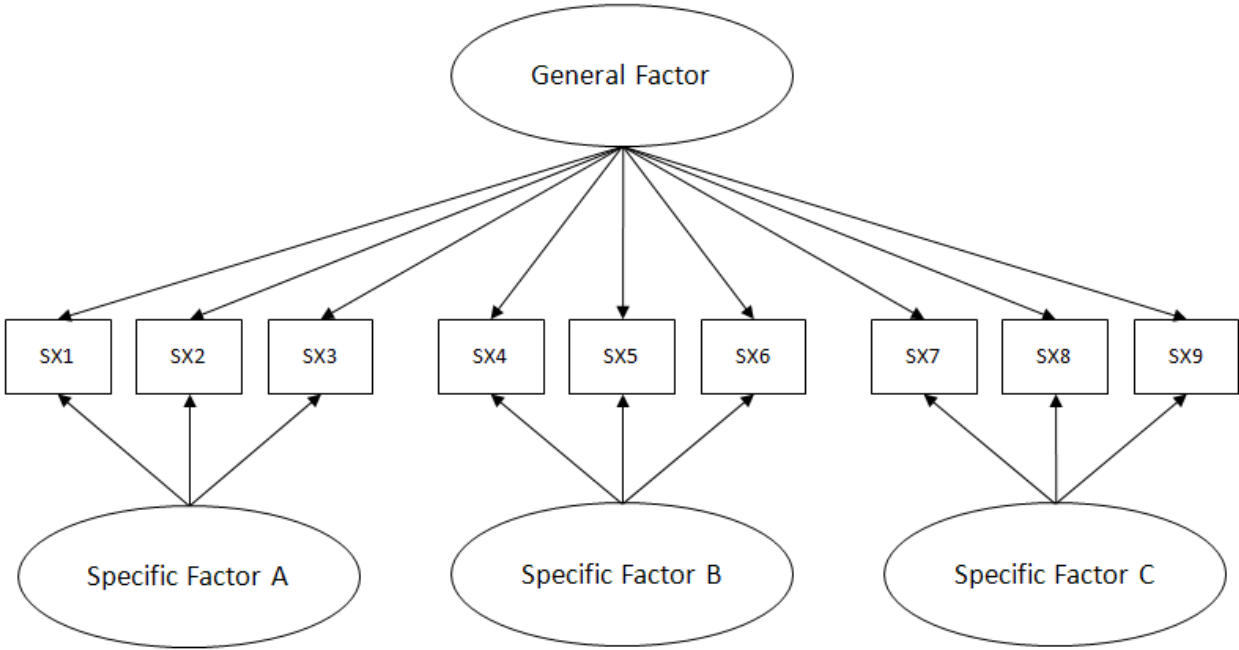
Figure 4. A schematic of a liability-spectrum model of Internalizing disorders and hypothetical

risk factors. G represents a risk factor for the common variance among the Internalizing

diagnoses; S_{MDD} represents a specific risk factor for major depressive disorder diagnoses; H_{OCD}

represents a hybrid risk factor affecting both the higher-order Internalizing factor and also the

unique portion (after partialling out variance shared between the obsessive-compulsive disorder

indicator and the common factor) of obsessive-compulsive disorder diagnoses.
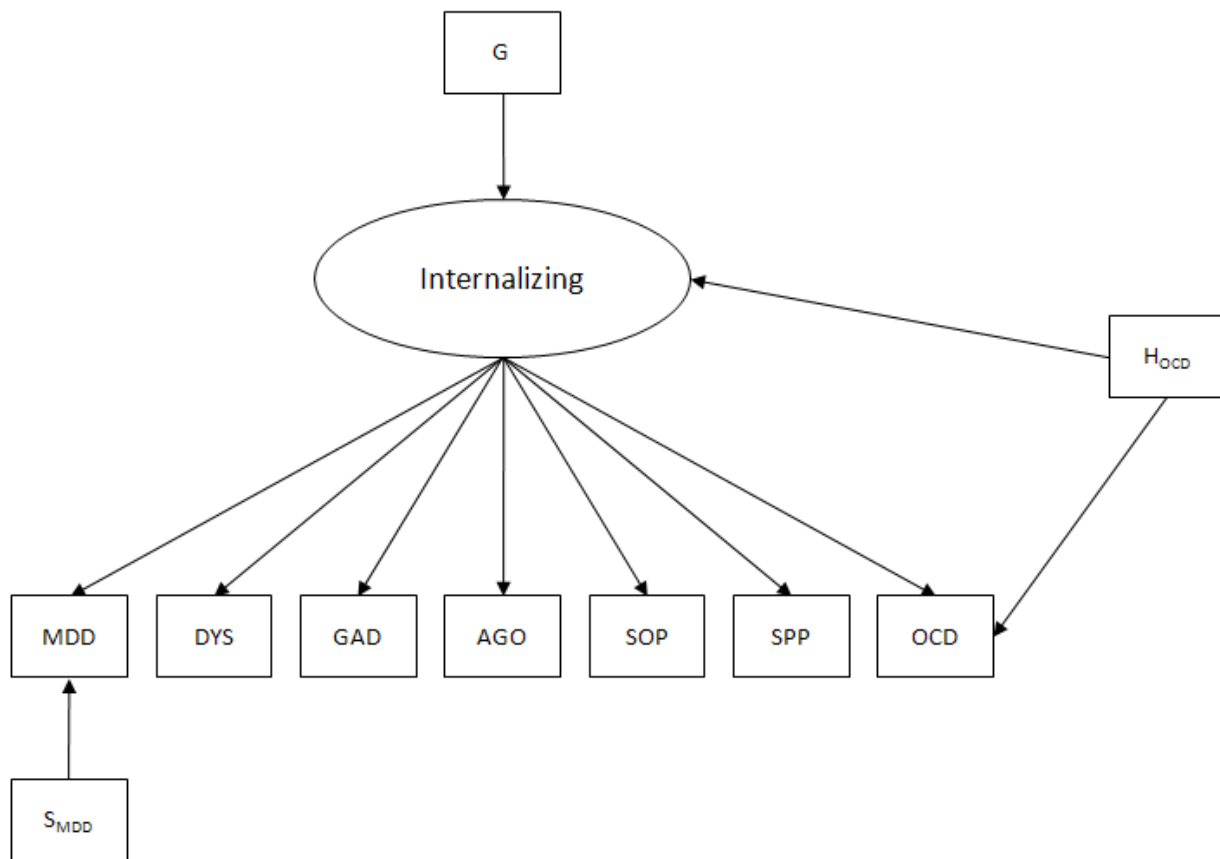
Figure 5. The effect of early environmental adversity on Externalizing scores as a function of

catechol-*O*-methyltransferase genotype. VV = val/val, VM = val/met, MM = met/met.

Externalizing scores on the *y*-axis can be interpreted in a *z*-score metric.
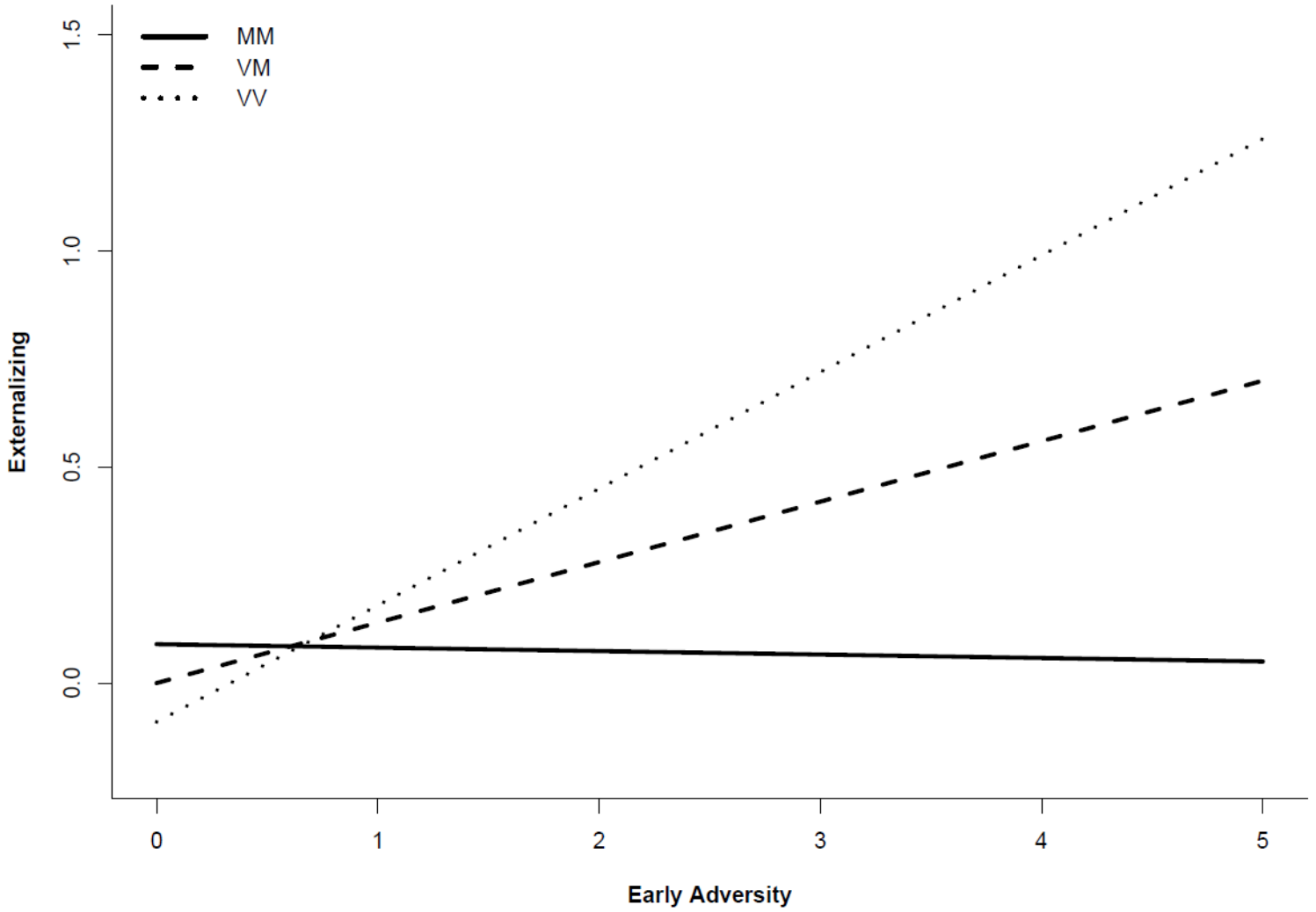
Figure 6.

[Presented on the next page.]

Path diagram of the effects of five environmental risk factors on the transdiagnostic dimensions of the hierarchical-spectrum model. For clarity of presentation, the residual associations of risk factors with diagnosis-specific components are omitted. All exogenous variables were allowed to intercorrelate. Dashed paths are not significant at the .05 alpha level. $*p < .05$, $**p < .01$. INT = Internalizing; EXT = Externalizing; COND = conduct disorder; AA/D = alcohol abuse or dependence; DA/D = drug abuse or dependence; ASPD = antisocial personality disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder; SOP = social phobia; SPEC = specific phobia; PTSD = post-traumatic stress disorder; DYS = dysthymia; PAN = panic disorder; DEP/ANX = depression or anxiety.
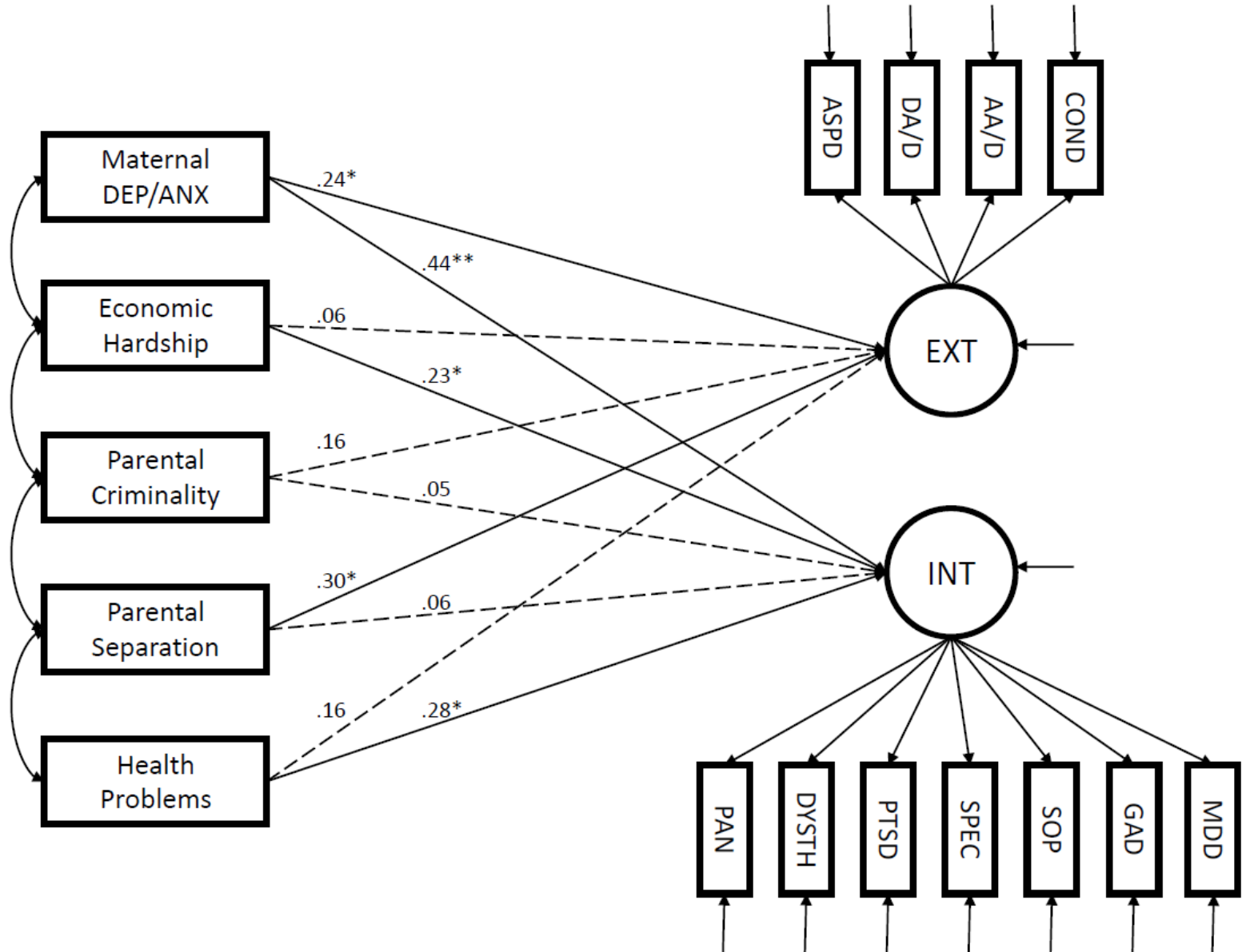
Figure 7.

[Presented on the next page.]

 Path diagram of the stress generating effects of the Internalizing and Externalizing dimensions. INT = Internalizing; EXT = Externalizing; COND = conduct disorder; AA/D = alcohol abuse or dependence; DA/D = drug abuse or dependence; ODD = oppositional defiant disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder; SOP = social phobia; SPEC = specific phobia; PTSD = post-traumatic stress disorder; DYSTH = dysthymia; PAN = panic disorder. Unlabeled circles represent residual variances.
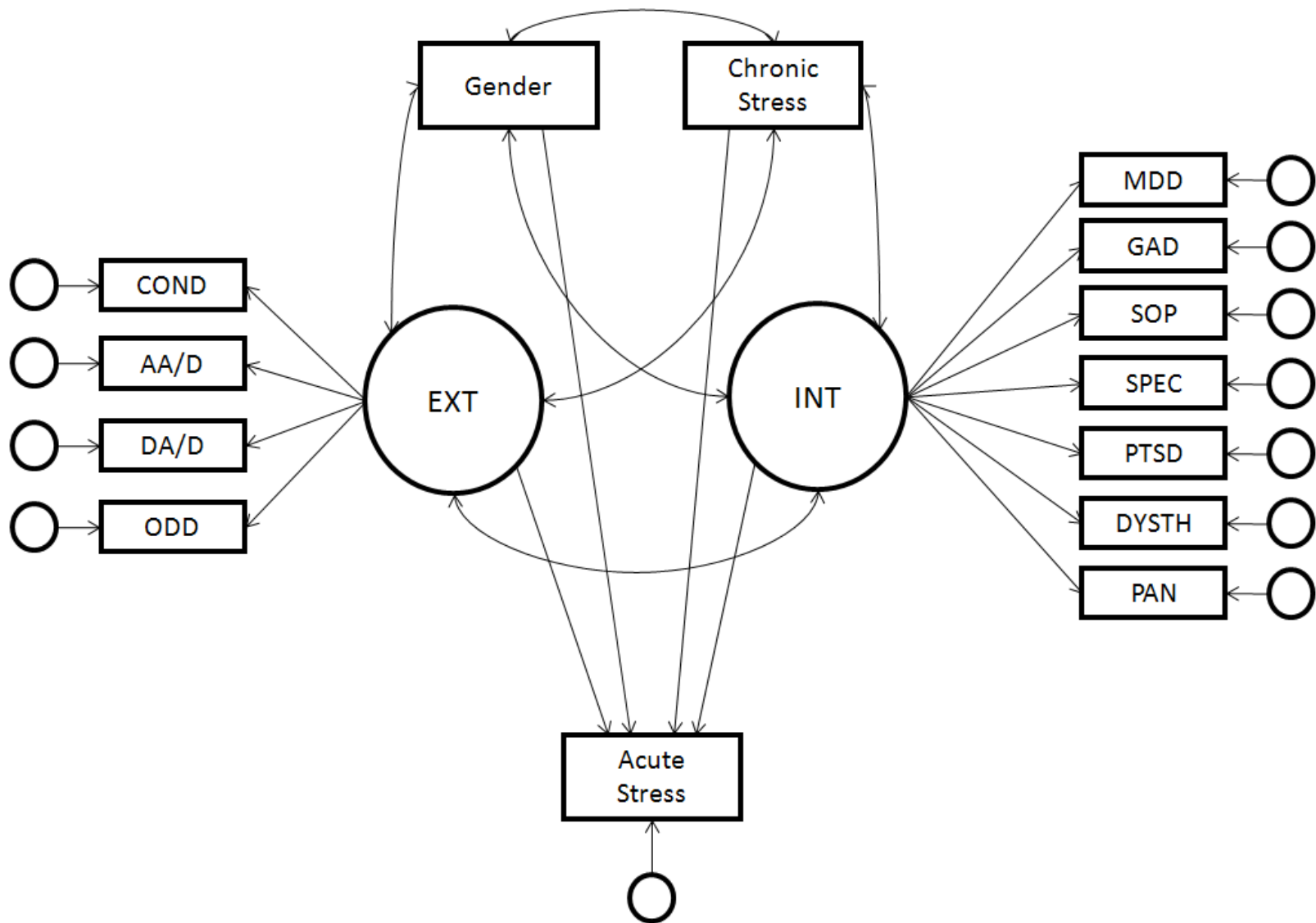
Figure 8.

[Presented on the next page.]

 Path diagram of the stress generating effects of the unique components of Axis I syndromes. For clarity of presentation, the effects of covariates (i.e., gender, chronic stress) are omitted from this diagram. INT = Internalizing; EXT = Externalizing; COND = conduct disorder; AA/D = alcohol abuse or dependence; DA/D = drug abuse or dependence; ODD = oppositional defiant disorder; MDD = major depressive disorder; GAD = generalized anxiety disorder; SOP = social phobia; SPEC = specific phobia; PTSD = post-traumatic stress disorder; DYSTH = dysthymia; PAN = panic disorder. Unlabeled circles represent residual variances.
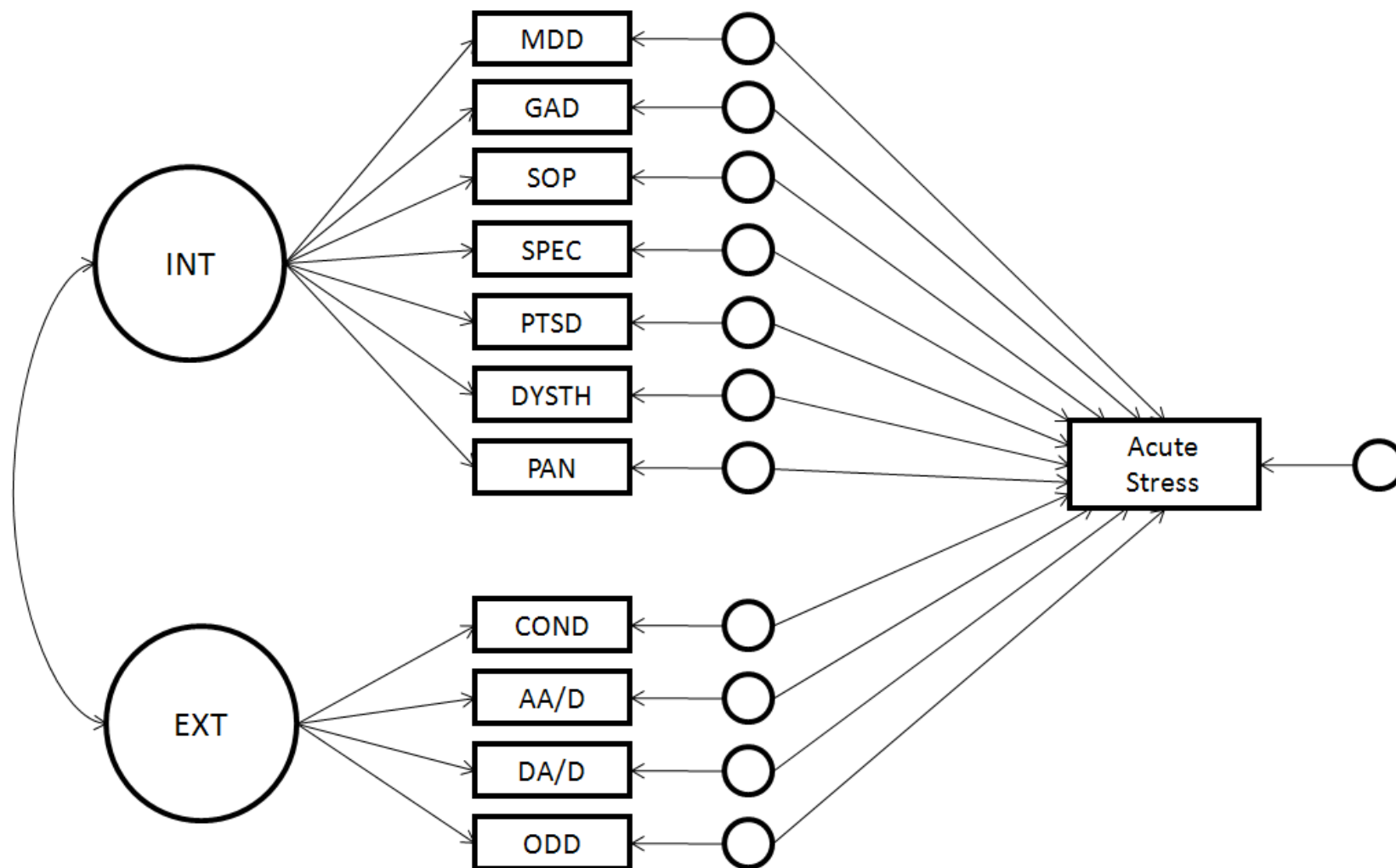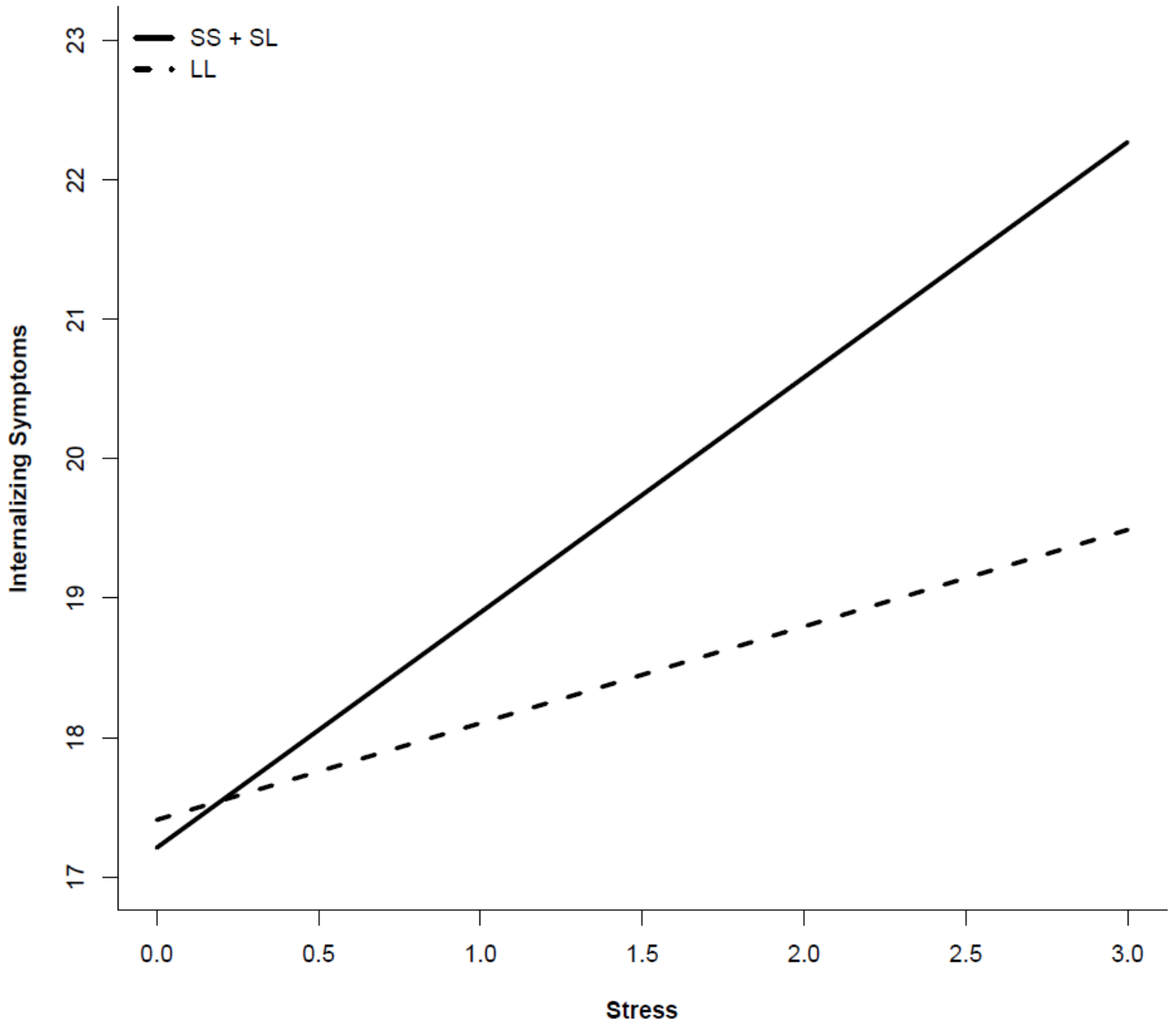
Figure 9. Regression of Internalizing symptoms on same-day stress as a function of serotonin transporter (5-HTTLPR) genotype.

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