



Published in final edited form as:

Child Dev Perspect. 2015 March 1; 9(1): 26–31. doi:10.1111/cdep.12102.

Comorbidity Among Dimensions of Childhood Psychopathology: Converging Evidence from Behavior Genetics

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Abstract

In this article, we review evidence from recent behavior genetic studies that examined the covariance among common childhood psychopathological conditions and tested specific hypotheses regarding common and broadband-specific underlying features of childhood psychopathology. Specifically, we review the distinction between internalizing and externalizing disorders, the support for the generalist genes and specialist environments model, negative emotionality as a heritable underlying feature common to both internalizing and externalizing disorders, and daring as a heritable broadband-specific underlying feature that distinguishes externalizing disorders from internalizing disorders. We also discuss the implications of research in the search for specific genes that influence childhood psychopathology and suggest avenues for new research.

Keywords

behavior genetics; comorbidity; internalizing; externalizing

Comorbidity in Childhood Psychopathology

Comorbidity, or the co-occurrence of two disorders in the same individual, is the norm rather than the exception across common psychiatric disorders and development. Comorbidity among childhood psychiatric disorders often exceeds the rate expected by chance, with a meta-analysis reporting odds ratios ranging from 3.0 to 10.7, and noting that comorbidity cannot be attributed to methodological artifacts such as referral bias, rater expectancies, or nonspecific symptoms (1). Significant comorbidity appears as early as the preschool years—odds ratios of 1.81 to 18.44 in one study (2) and 4.4 to 26 in another (3), with few exceptions of nonsignificant comorbidity. Comorbidity is associated with greater impairment and less optimal course and prognosis. For example, comorbid symptoms of oppositional defiant disorder or conduct disorder (CD) in children with attention deficit

hyperactivity disorder (ADHD) are associated with less optimal course and prognosis of ADHD itself, family dynamics, and educational outcomes, and greater risk for other disorders (4).

Researchers have posed alternative hypotheses for comorbidity (e.g., 5–6) and used different methods designed to identify the correct model (e.g., 7–8). Genetically informative research (e.g., twin and adoption studies) is useful in examining the etiology and comorbidity among psychiatric disorders. In this article, we review recent behavior genetic studies that examined the covariance among common childhood psychopathological conditions and tested specific hypotheses regarding common and broadband-specific underlying features of childhood psychopathology, and we explore how these results inform the search for specific genes that influence childhood psychopathology.

Twin studies take advantage of the fact that monozygotic (MZ) twins share 100 percent of their genes, whereas dizygotic (DZ) twins share 50 percent of segregating genes on average. Comparing the similarity of a trait in MZ versus DZ twins allows us to estimate the magnitude of variance of that trait in a population that is explained by genes (i.e., heritability), environmental influences leading to similarity between siblings (shared environment), and environmental influences leading to differences between siblings (nonshared environment). The magnitude of these influences on the covariance among disorders can be estimated by examining in MZ and DZ twins the correlation between the first disorder in one twin and the second disorder in the other twin. The hypothesis of genetic influences on the covariance between two disorders is supported if the correlation is greater in MZ than in DZ twins. In interpreting findings such as these, we must remember that twin studies are limited in their ability to detect nonadditive genetic influences and assume that the environment of MZ twin pairs is no more similar than that of DZ twin pairs.

Heritability increases significantly with age (e.g., see 9 for a meta-analysis), which may reflect individuals' increasing ability and tendency to select their own environments as they grow older (i.e., active genotype-environment correlation). We should also consider the interaction between genotype and the environment because unrecognized interactions may lead to overestimating heritability in twin studies (10).

Evidence for the Internalizing-Externalizing Model

Multivariate studies of behavior problems provided the first evidence for the internalizing-externalizing model of psychopathology, supporting two broadband syndromes: internalizing or overcontrolled behavior characterized by anxiety and depression, and externalizing or undercontrolled behavior characterized by hyperactivity, aggression, and delinquency (e.g., 11). Much of the early work on the factor structure of psychiatric disorders examined adults. For example, one meta-analysis (12) reported separate but moderately correlated internalizing and externalizing latent factors. More recently, studies examining psychiatric disorders in children and adolescents (e.g., 13–14), including preschool children (15), have distinguished internalizing from externalizing disorders.

Two behavior genetics studies tested alternative models explaining comorbidity among many common psychiatric disorders in childhood and adolescence (13–14). Despite

differences in the methods used and the specific phenotypes examined, they reached similar conclusions. One study examined three internalizing and three externalizing disorders in 12- to 18-year-old twins (13). A bivariate common factor model fit the data well, with a large genetic correlation between the latent internalizing and externalizing factors ($r = .72$) that was mostly due to common genetic influences (62 percent). Disorder-specific causes were mostly nonshared environmental influences. Another study, of 9- to 17-year-old twins that examined scores for 11 disorders, found separate but highly correlated ($r = .89$) internalizing and externalizing genetic factors (14). An alternative model including a general factor reflecting global genetic risk for psychopathology fit the data significantly better. As in the study of 12- to 18-year-old twins (13), dimension-specific genetic influences typically were modest. The results of both studies are consistent with the view of significant common genetic influences on all psychopathology but mostly nonshared environmental influences on specific disorders, which has been called the generalist gene and specialist environments model (16). Researchers examining common psychiatric disorders in adults have concluded similarly (e.g., 17).

Seemingly Paradoxical Results Regarding the Covariance Between Internalizing and Externalizing Disorders

Associations between internalizing and externalizing disorders sometimes differ. The meta-analysis mentioned earlier (1) suggests greater comorbidity between depression and externalizing disorders (odds ratios of 5.5 to 6.6) than between anxiety disorders and externalizing disorders (odds ratios of 3.0 to 3.1), and studies examining co-occurrence of diagnoses in preschool children found nonsignificant comorbidity between anxiety disorders and ADHD (2–3). Having an internalizing disorder, particularly anxiety disorders and symptoms, may protect against externalizing disorders. In two other studies, boys with comorbid CD and anxiety symptoms had fewer conduct problems than boys with CD alone (18), and inhibited and fearful children were at greater risk of developing internalizing symptoms but at decreased risk for developing externalizing symptoms (19). Also, the presence of internalizing symptoms predicted less risk of reoffending among juvenile delinquents (20). In two other studies, children with reduced levels of anxiety had more callous-unemotional traits, a strong predictor of antisocial behavior (21), and social anxiety was associated negatively with symptoms of conduct disorder among children and adolescents with ADHD (22).

A Hierarchical Model of the Etiology of Childhood Psychopathology

Weiss, Süsser, and Catron (23) conceptualized the underlying causal factors influencing childhood psychopathology in three levels: common features distinguishing both internalizing and externalizing disorders from normality, broadband-specific features distinguishing internalizing disorders from externalizing disorders, and narrow-band-specific features that discriminate disorders within the internalizing and externalizing categories. Lilienfeld (24) suggested that the disposition toward negative emotionality, or the pervasive disposition to experience unpleasant affective states of many kinds, is a common underlying feature that increases the risk for both internalizing and externalizing disorders. Broadband-specific underlying features that may distinguish internalizing from

externalizing disorders include child unadaptability for internalizing disorders (e.g., 19), peer rejection for externalizing disorders and peer neglect for internalizing disorders (e.g., 19), and behavioral disinhibition for externalizing disorders (e.g., 25).

Lahey and Waldman (26) proposed similar hypotheses. Their model also suggests negative emotionality (also referred to as neuroticism) as a common feature underlying all childhood psychopathology. Daring, characterized by being adventurous and enjoying loud, rough, and risky activities, may be a broadband-specific underlying feature for externalizing disorders that is either unrelated to or associated negatively with internalizing disorders. Daring is similar to behavioral disinhibition and novelty seeking, and is associated inversely with harm avoidance, shyness, and behavioral inhibition. This model may explain the seemingly paradoxical relations between internalizing and externalizing disorders. That is, internalizing problems that reflect negative emotionality may be associated positively with externalizing problems, whereas internalizing problems that reflect low daring may protect against developing conduct problems. Lahey et al. (27) expanded their hypotheses to differentiate depression from anxiety, with anxiety symptoms predicted to be associated negatively with daring, whereas depressive symptoms were predicted to be uncorrelated with daring.

Negative Emotionality as a Common Underlying Feature and Daring as a Broadband-Specific Underlying Feature

Studies of children, adolescents, and adults support Lahey and Waldman's (26) model. Negative emotionality or neuroticism has been associated significantly with both internalizing and externalizing behavior or disorders in several studies (e.g., 19, 28–29), whereas daring and similar constructs have been associated significantly with externalizing behavior or disorders in other studies (e.g., 25). Also, other studies have found common genetic influences between neuroticism and both internalizing and externalizing disorders, including a significant genetic correlation between negative emotionality or neuroticism and depression (e.g., 30–31), neuroticism and symptoms of anxiety (e.g., 30), and negative emotionality and externalizing behaviors and disorders (e.g., 32–33). Studies have also found common genetic influences between novelty seeking/daring and externalizing disorders (32–33).

Studies examining the degree to which temperament and personality traits explain the comorbidity between internalizing and externalizing disorders provide additional support for the Lahey and Waldman model (26). Children with high levels of neuroticism have higher rates of comorbid internalizing and externalizing behaviors (19), and negative emotionality predicted more accurately having both internalizing and externalizing disorders than pure internalizing or externalizing disorders in children (28). In a study of adults, neuroticism explained 20–45 percent of the comorbidity among internalizing disorders, 10–12 percent of the comorbidity among externalizing disorders, and 19–88 percent of the comorbidity between internalizing and externalizing disorders (34). In contrast, novelty seeking accounted for 7–14 percent of the comorbidity among externalizing disorders, but not among internalizing disorders or between internalizing and externalizing disorders. Also, in a study of 6- to 18-year-old twins, genetic influences on the comorbidity between major

depressive disorder (MDD) and CD were shared entirely with those influencing negative emotionality, at least for males (31).

Three recent twin studies examined the covariance between personality dimensions and many internalizing and externalizing disorders. The first, a study of 7- to 13-year-old twins, examined negative affect and symptoms of six internalizing disorders and three externalizing disorders (35). The negative affect, internalizing, and externalizing latent factors had significant common genetic, shared environmental, and nonshared environmental influences. The study also found unique shared environmental influences on the negative affect factor, unique genetic influences on the internalizing factor, and unique genetic and shared environmental influences on the externalizing factor.

A second twin study examined parent and self reports of personality and psychopathology symptoms in 6- to 17-year-olds (36). The model included a general factor influencing all psychopathology and specific externalizing and internalizing factors. Negative emotionality was associated significantly with the general factor at the phenotypic level, and genetic influences on the general factor correlated significantly with those influencing negative emotionality for both parent and self reports. Daring was associated positively with the specific externalizing factor and negatively with the specific internalizing factor for both parent and self reports. Results from the genetic models were not as consistent across parent and self reports. The correlation between the genetic influences on the general factor and daring was significant only for parent reports, whereas the correlation between genetic influences on the specific externalizing factor and daring was significant only for self reports. Genetic influences on the specific internalizing factor did not correlate with those on daring.

A third twin study, of 12- to 18-year-olds, examined the covariance among self-reported neuroticism, novelty seeking, and six psychiatric disorders (37). Genetic and nonshared environmental influences on neuroticism explained the covariance among internalizing disorders, among externalizing disorders, and between internalizing and externalizing disorders. Genetic influences shared in common with novelty seeking explained the covariance among externalizing disorders and the covariance between major depressive disorder and externalizing disorders, but not covariances within internalizing disorders or between anxiety disorders and externalizing disorders. Influences shared by neuroticism and novelty seeking explained completely the covariance among the six psychiatric disorders.

The results of these three studies support the hypothesis that neuroticism or negative emotionality is a heritable common underlying feature explaining the overlap between internalizing and externalizing disorders. In addition, the results support the hypothesis that daring is a broadband-specific underlying feature that is associated with externalizing disorders and differentiates internalizing and externalizing disorders (36). They also support the hypothesis that daring may distinguish anxiety and externalizing disorders more than depression and externalizing disorders (37). However, results were not as clear as those for negative emotionality. In the second twin study (36), genetic influences on the general factor were related to daring for parent reports, and in the third study (37), genetic influences on

novelty seeking explained the covariance between major depressive disorder and externalizing disorders.

Summary and Looking Ahead

Comorbidity among psychiatric disorders is the norm rather than the exception across development. The nature of this comorbidity has been clarified by examining temperament or personality dimensions as predictors of psychopathology in genetically informative samples. Several lines of evidence converge across studies examining comorbidity in childhood psychopathology. First, studies support distinguishing internalizing from externalizing disorders from the preschool years to adulthood. Second, research also supports the model of generalist genes and specialist environments, with disorder-specific influences being mostly nonshared environmental influences. Third, negative emotionality is a heritable common underlying feature explaining the overlap between internalizing and externalizing disorders. Fourth, although evidence is less consistent, daring is a heritable broadband-specific underlying feature that distinguishes externalizing from internalizing disorders.

Looking ahead, several lines of research will increase our understanding of the covariance between internalizing and externalizing disorders. First, additional studies need to examine whether fear and distress disorders can be distinguished in childhood and adolescence. Second, we need additional studies examining broadband-specific underlying features for internalizing disorders. Third, we need to learn more about narrow-band-specific underlying features differentiating specific disorders within the internalizing and externalizing classes, although studies suggest that these are likely influenced by the nonshared environment.

The evidence from the twin studies reviewed in this article is starting to be confirmed by other research designs that do not have the same assumptions, such as genome-wide association scans (GWAS) and sequencing studies. Several studies suggest that single nucleotide polymorphisms on current GWAS platforms explain a significant proportion of genetic variance for both internalizing (e.g., 38) and externalizing (e.g., 39) phenotypes and neuroticism, a common feature underlying both internalizing and externalizing disorders (e.g., 40). Also, GWAS data have demonstrated common additive genetic influences on many psychiatric disorders, including a modest overlap between those influencing MDD and ADHD (41).

The search for genes that influence psychopathology may be facilitated by a hierarchical perspective (e.g., 14), in which some genes are hypothesized to influence risk for psychopathology nonspecifically through underlying common features such as negative emotionality, whereas others are hypothesized to be specific to a certain dimension. The focus on dispositional traits is consistent with the National Institute of Mental Health's Research Domain Criteria initiative, which was motivated in part by the understanding that common genetic influences underlie many psychiatric disorders (e.g., 42). The initiative aims to shift research from clinical description toward identifying trait-like psychological constructs that cut across psychiatric disorders (e.g., 43). It also endorses genetic studies that use a dimensional approach agnostic to contemporary diagnostic classifications, starting

with major domains hypothesized to link directly to psychopathological mechanisms, including negative affect (e.g., 44).

Acknowledgments

This work was supported by National Institutes of Health grants HD050346, DA011015, and P50MH94267.

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