Published in final edited form as:

J Abnorm Child Psychol. 2018 August ; 46(6): 1217–1228. doi:10.1007/s10802-017-0361-y.

Do Genetic Factors Explain the Links Between Callous-Unemotional, Attention Hyperactivity and Oppositional Defiant Problems in Toddlers?

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Abstract

Research demonstrates that callous-unemotional (CU) behaviors, Attention Deficit Hyperactivity Disorder (ADHD) and Oppositional Defiant Problems (ODD) are related, but little is known about the sources of covariation among the three externalizing behaviors. The present study looked at genetic and environmental links between all three behavioral domains in twins at ages 2 and 3 years (MZ=145, DZ=169), a time when CU behaviors are beginning to emerge. CU, ADHD, and ODD behaviors as assessed using the Child Behavior Checklist 1.5–5 (Achenbach & Rescorla, 2000) were strongly interrelated at both ages. Genetic factors primarily explained the covariation among the three behavioral domains via a common externalizing factor; however, there were also genetic factors unique to each behavior. Furthermore, the majority of nonshared environmental influences on each externalizing behavior were behavior-specific. The heritable externalizing factor was highly stable across age, largely due to genetic factors shared across ages 2 and 3 years. Despite their extensive phenotypic and genetic overlap, CU, ADHD, and ODD behaviors have unique genetic and nonshared environmental influences as early as toddlerhood. This supports phenotypic research showing that the three are related but distinct constructs in very young children.

Keywords

Callous-unemotional; ADHD; ODD; early childhood; twins; behavior problems

Introduction

Individuals with callous-unemotional (CU) behaviors exhibit a lack of guilt, empathy, and affect (Frick & Morris, 2004). As early as 2 years of age, meaningful differences in CU behaviors can be assessed (e.g., Waller et al., 2015), and are genetically influenced in early childhood and beyond (Flom & Saudino, 2016; for review see Viding & McCrory, 2012). Across development, in both clinical and community samples, CU behaviors are related to other externalizing behavior problems such as Attention-Deficit Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD), Conduct Disorder, and Antisocial

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Conflict of Interest

The authors declare that they have no conflict of interest.

Personality Disorder (Frick, Ray, Thornton, & Kahn, 2014a; Pardini, Obradovi , & Loeber, 2006; Willoughby, Mills-Koonce, Gottfredson, & Wagner, 2014). This pattern of associations is seen as early as 2 years of age (e.g., Waller et al., 2015), though because severe psychopathology has not yet emerged, research in early childhood focuses primarily on the extent to which CU behaviors are related to ADHD and ODD behavior problems.

Despite this consistent pattern of intercorrelations, CU, ADHD and ODD behaviors are distinct constructs in early and middle childhood (Frick, Ray, Thornton, & Kahn, 2014b; Waller, Hyde, Grabell, Alves, & Olson, 2015). Importantly, CU, ADHD and ODD behaviors can be reliably discriminated by parent-report in very young children (Flom & Saudino, 2016; Waller, Shaw, et al., 2015; Willoughby, Waschbusch, Moore, & Propper, 2011), and are differentially related to later developmental outcomes in middle childhood (Willoughby, Mills-Koonce, Waschbusch, & Gottfredson, 2015).

Furthermore, CU behaviors in early childhood through adolescence independently predict later behavior problems, above and beyond other externalizing behaviors such as ADHD and ODD (e.g., Frick et al., 2014b; Waller, Shaw, et al., 2015; Willoughby et al., 2015), demonstrating the unique predictive validity of CU behaviors across development. Early childhood, a period of rapid developmental change, can be particularly informative in exploring etiologic distinctions between CU, ADHD, and ODD. Moral behaviors relevant to CU; emotion regulation implicated in ODD; and inhibitory control and impulsive behaviors salient to ADHD, are all coming online in early childhood, and may represent distinct pathways to early childhood conduct problems (Waller, Hyde, et al., 2015). Indeed, ADHD has been uniquely associated with lower effortful control, attentional focusing, and emotion understanding; CU behaviors with lower moral regulation, guilt and empathy, as well as later externalizing problems and proactive aggression; and ODD behaviors with anger and frustration (Waller, Hyde, et al., 2015). Thus, it was proposed that ADHD and ODD behaviors index “hot” and CU behaviors “cold” domains of CD problems, respectively. CU behaviors viewed as a cold domain are a particularly severe risk factor for later behavior problems, largely because of a disruption in conscience (Waller, Hyde, et al., 2015). Of note, etiologic distinctions between these behaviors can be seen as early as infancy. Specifically, CU behaviors in early childhood are preceeded by a fearless temperament in infancy, whereas ADHD and ODD problems are preceeded by higher emotional dysregulation (Willoughby et al., 2011).

Though specific nomological networks have been found for CU, ADHD, and ODD (Waller et al., 2015), nothing is known, however, about the genetic and environmental contributions to shared and unique etiologies between these three behaviors. In other words, do CU behaviors overlap with ADHD and ODD as a result of genetic effects common to all, overlapping environmental effects, or both? Similarly, to what extent do genes and/or the environment contribute to behavior-specific variance? It is important to understand genetic and environmental links between these behaviors in early childhood, as this is the time when these behaviors are first emerging, and are most receptive to intervention (Olds, Robinson, Song, Little, & Hill, 2005). Identifying the underlying sources of covariance between CU, ADHD and ODD behaviors can help us further understand the factor structure of the behavior problems, comorbidity, and potential avenues for intervention.

No research has examined the genetic and environmental overlap between *all three* constructs (CU, ADHD, and ODD behaviors) at any age, but related twin research in older children and adolescents informs on sources of underlying links between some of these behavior problems. There is only one study that explored the genetic and environmental overlap between CU behaviors and *any* externalizing behavior in childhood or adolescence—which is surprising given the extensive research on CU behaviors and their well-established relations and comorbidity with externalizing behaviors. In 7-year-olds, CU behaviors were related to CD primarily as a result of shared genetic effects, though there were also modest nonshared environmental (i.e., environmental experiences unique to members of a family) contributions to covariation (Viding, Frick, & Plomin, 2007).

Though not encompassing CU behaviors, research investigating the overlap between ADHD, ODD and CD in older children and adolescents can provide hints on possible genetic and environmental sources of covariance between ADHD, ODD and CU in early childhood. Overlapping genetic effects primarily explain covariation between ADHD, ODD and/or CD behaviors in middle childhood through adolescence (Dick, Viken, Kaprio, Pulkkinen, & Rose, 2005; Nadder, Rutter, Silberg, Maes, & Eaves, 2002; Tuvblad, Zheng, Raine, & Baker, 2009), though in some cases, environmental factors contribute to covariation as well (Burt, Krueger, McGue, & Iacono, 2001; Dick et al., 2005; Rhee, Willcutt, Hartman, Pennington, & DeFries, 2008; Thapar, Harrington, & McGuffin, 2001). Taken together, research supports a common genetic liability to covariation between ADHD, CD and ODD; and between CU and CD. Molecular genetics research supports this notion. A measured heritability study, which employs data from single nucleotide polymorphisms (SNPs) to estimate variance explained by measured genetic variants (Yang, Lee, Goddard, & Visscher, 2011), found that multiple behavior problems in middle childhood loaded on a general psychopathology factor which was influenced by common genetic variations (Neumann et al., 2016). Though this study did not include CU behaviors, it provides strong evidence for a genetic liability linking common behavior problems in middle childhood. However, it is also possible that environmental factors link behavior problems, which will go undetected in such molecular genetic studies.

Despite research demonstrating strong shared genetic links between ADHD, ODD and CD, and between CU and CD, twin research suggests that common genetic (and environmental) factors rarely fully overlap, signifying genetic and environmental influences unique to each behavior. Thus, it appears that there are certain genes that may serve as general risk factors for psychopathology, as well as others that influence symptoms specific to each behavior problem. The unique environmental effects highlight the relevance of the environment in differentially influencing behavior-specific symptoms. As such, ADHD, ODD, and CD, as well as CU and CD, are distinct from one another, notwithstanding their strong common underlying genetic etiology.

This research hints at the potential of a genetic factor common to CU, ADHD, and ODD, but this remains an empirical question. Furthermore, nothing is known about the genetic and environmental overlap between *any* of these behaviors in early childhood (i.e., CU and ADHD; ODD and ADHD; ODD and CU). Because genetic and environmental influences on individual differences can change across age (Plomin, DeFries, Knopik, & Neiderhiser,

2013), the underlying mechanisms of association between behaviors are not necessarily the same throughout development.

The current study is the first to examine the genetic and environmental links between CU, ADHD, and ODD behavior problems. Using a twin sample at ages 2 and 3 years, we examine the genetic and environmental sources of overlap between the three externalizing behaviors, as well as the potential genetic and environmental effects unique to each behavior. Based on prior twin and molecular research in older children, we hypothesized that genetic factors would primarily explain the phenotypic correlations between the three externalizing behaviors. We also hypothesized unique genetic and environmental effects on each behavior, particularly given that CU, ADHD, and ODD behaviors emerge as distinct constructs in phenotypic factor analyses in early childhood (Flom & Saudino, 2016; Waller, Shaw, et al., 2015; Willoughby et al., 2014), and have unique risk factors and correlates at a young age (Waller, Hyde, et al., 2015; Willoughby et al., 2011). Because we have previously demonstrated phenotypic factor invariance at ages 2 and 3 years (Flom & Saudino, 2016), we expected a similar pattern in the underlying links between CU, ADHD and ODD behaviors at each age.

Methods

Participants

Participants were from the Boston University Twin Project. Twins were assessed within approximately 2 weeks of their second and third birthdays. When families arrived for the first lab visit at age 2, the primary caregiver provided informed consent for the twins' participation. This study was approved by the Institutional Review Board at Boston University. Three hundred and fourteen same-sex twin pairs (145 MZ, 169 DZ) participated in age 2 assessments. Of these, 304 of these (141 MZ, 163 DZ) were reassessed at age 3. Ethnicity of this community sample was generally representative of the Massachusetts population (85.4% Caucasian, 3.2% Black, 2% Asian, 7.3% Mixed, 2.2% Other). Fifty-three percent of the sample was male. Socioeconomic status according to the Hollingshead Four Factor Index (Hollingshead, 1975) ranged from low to upper middle class (range = 20.5–66; $M = 50.9$, $SD = 14.1$). Zygosity was determined via DNA analyses using DNA obtained from cheek swab samples. In the cases where DNA was not available ($n = 3$), zygosity was determined using parents' responses on physical similarity questionnaires, which have been shown to be more than 95% accurate when compared with DNA markers (Price et al., 2000).

Assessment of Behavior Problems

Parent reports (94% mothers) on the *Child Behavior Checklist 1½-5* (CBCL 1½-5; Achenbach & Rescorla, 2000) were used to assess CU, ADHD and ODD behaviors for each twin at both ages. None of the items for the CU, ADHD, and OD scales overlap. Each item on the CBCL is rated as either 0 ("not true"), 1 ("sometimes true"), or 2 ("always true").

CU Behaviors—Following Willoughby et al. (2011), a 5-item screening measure from the CBCL 1½-5 was used to assess CU behaviors for each twin. In our non-clinical sample, scores ranged from 0 – 7. This measure has demonstrated good reliability and validity at

both ages. Specifically, CU at age 2 demonstrates expected behavioral correlates and predictive validity into middle childhood (e.g., Waller, Shaw, et al., 2015) and moderate stability across early childhood ($r=.45$; Flom & Saudino, 2016). Factor analyses of CBCL items from the CU, ADHD and ODD scales in different early childhood samples have demonstrated that the data is best described by a 3-factor model, indicating that parents can differentiate between the three behaviors as early as 2 years of age (Flom & Saudino, 2016; Waller, Shaw, et al., 2015). Furthermore, in the current sample, phenotypic factor invariance across ages 2 and 3 has been established (Flom & Saudino, 2016), indicating that age 2 CU is not structurally different from CU at age 3. Though internal consistency for the present sample was low (age 2 $\alpha=.55$; age 3 $\alpha=.61$), this is consistent with previous research using the same 5-item behavior scale in 3-year-olds ($\alpha=.59$, Waller et al., 2015; $\alpha=.65$, Willoughby et al., 2011; $\alpha=.55$, Willoughby et al., 2014).

ADHD and ODD Behaviors—The DSM Attention-Deficit Hyperactivity Problems and DSM Oppositional Defiant Problems scales both consist of 6 items. These scales are widely used to assess ADHD and ODD behavior problems in early childhood and have demonstrated good reliability and validity (see Achenbach & Rescorla, 2000; Rescorla, 2005). For example, the ADHD and ODD scales from the *CBCL1½-5* have shown good discriminative ability to identify ADHD and ODD diagnoses from a clinical interview during the preschool years (de la Osa, Granero, Trepát, Domenech, & Ezpeleta, 2016). In our sample, both scales demonstrated good internal consistency (ADHD: Age 2 $\alpha=.78$, Age 3 $\alpha=.79$; OD: Age 2 $\alpha=.79$, Age 3 $\alpha=.81$).

Analyses

Data Transformation—As expected in our normative sample, CU scores were positively skewed, and were log-transformed to create a more normal distribution. ADHD and ODD scores were also positively skewed and were square-root transformed. Because twin covariances can be inflated by variance due to sex, all scores used in the biometric analyses were residualized for sex effects (McGue & Bouchard Jr, 1984).

Correlational Analyses—The twin method involves comparing genetically identical (MZ) twins with fraternal (DZ) twins who share approximately 50% of their segregating genes. Genetic influences are implied when cotwin similarity covaries with the degree of genetic relatedness. If heredity affects a trait, the two-fold greater genetic similarity of MZ twins is expected to make them more similar than DZ twins. Intraclass correlations typically serve as indices of cotwin similarity. An MZ correlation that is greater than the DZ correlation suggests genetic influence on the phenotype. DZ correlations that exceed one-half the MZ correlation suggest the presence of shared environmental influences. Differences within pairs of MZ twins (i.e., the extent to which the MZ intraclass correlation is less than 1.0) are due to nonshared environmental influences and measurement error.

To evaluate genetic and environmental sources of covariance amongst CU, ADHD and OD, cross-twin cross-trait correlations were calculated. The cross-twin cross-trait correlation involves correlating, for example, Twin A's Age 2 CU score with Twin B's Age 2 ADHD score and vice versa. Genetic contributions to the covariance between two traits (i.e., that

both traits are tapping the same genetic factors) are implied when the MZ cross-twin cross-trait correlation is greater than the DZ cross-twin cross-trait correlation.

Model-Fitting Analyses—Although the results of a multivariate twin analysis can be gleaned from twin cross correlations, model-fitting procedures analyze all of the data simultaneously, provide tests of the fit of models, yield confidence intervals for parameter estimates, and test the fit of alternative models (Plomin et al., 2013). Models were fit to raw data using a maximum likelihood pedigree approach implemented in Mx structural equation modeling software (Neale, Boker, Xie, & Maes, 2006). This approach does not yield a χ^2 for assessing the fit of the model, however, the fit of a model can be assessed by calculating twice the difference between the negative log-likelihood ($-2LL$) of the model and that of a saturated model (i.e., a model in which the variance/covariance structure is not estimated and all variances and covariances for MZ and DZ twins are estimated). The difference in $-2LL$ is asymptotically distributed as χ^2 with degrees of freedom equal to the difference in the number of parameters in the full model and that in the saturated model.

To examine cross-trait and trait-specific genetic effects on parent-reported externalizing problems we fit two multivariate models to the data separately at each age. Both models decompose the phenotypic variance of each trait and the phenotypic covariances *between* traits into additive genetic effects (A), shared environmental effects (C), and nonshared environmental effects (E); however, each model makes different assumptions about the reasons for covariance between traits. Based on the degree of genetic relatedness, the A factors correlate 1.0 and .5 for MZ and DZ twins, respectively. Because all twins were reared in the same family, C factors correlate 1.0 for both MZ and DZ twins. E factors, which reflect experiences unique to each member of a twin pair, are uncorrelated for both MZ and DZ twins.

The ***Independent Pathway model*** (Kendler, Heath, Martin, & Eaves, 1987) assumes that genetic and environmental factors contribute to covariance between behaviors through separate genetic and environmental pathways (see Figure 1). This model decomposes the genetic, shared environmental and nonshared environmental variance of CU, ADHD, and ODD into genetic and environmental effects that are common to all three behavior problem domains (i.e., cross-domain effects), and genetic and environmental effects that are unique to each domain (i.e., domain-specific effects). For example, in Figure 1 the latent variables A, C, and E represent additive genetic, shared environmental, and nonshared environmental effects, respectively, that are common to all three domains. The latent variables denoted in subscripted lowercase represent genetic and environmental effects that are unique to a specific behavior problem domain (e.g., a_{CU} , c_{CU} , and e_{CU} refer to genetic and environmental influences unique to CU behaviors). Under this model, covariance between behaviors can arise due to different factors. That is, although CU, ADHD, and ODD may be intercorrelated across all behaviors, the sources of covariance between any two behavioral domains may differ (e.g., the correlation between CU and ADHD could have a different source than the correlation between ADHD and ODD). This model is considered to be “agnostic” in that it does not specify that the same common phenotype operates across different behavioral domains, rather it just allows that the domains being assessed are correlated (Hewitt, Silberg, Neale, Eaves, & Erickson, 1992).

The *Common Pathway model* (Kendler et al., 1987; McArdle & Goldsmith, 1990), is more restrictive positing that genetic and environmental factors influence covariation between behaviors through a *single* common pathway. Thus, this model suggests that correlations between behavioral domains arise because of a common externalizing phenotype (EXT in Figure 2) operating across all domains. This common phenotype is then influenced by genetic and environmental influences. As is the case with the Independent Pathway Model, this model also allows genetic and environmental effects specific to each behavioral domain. Under this model, genetic and environmental sources of covariance are the same across all domains. Covariance between behavior problem domains arises because they tap the same latent phenotype (i.e., they are assessing the same behaviors; in this case, externalizing). Differences between behavioral domains arise because, to some extent, these different behaviors are also somewhat etiologically distinct.

Results

Descriptive Statistics

Table 1 lists the means and standard deviations by sex and zygosity. We evaluated the mean differences using generalized estimating equations (GEE) implemented in the SAS GENMOD procedure to account for dependence in the data due to the fact that our sample comprised pairs of twins. GEE are an extension of the standard generalized linear models that allow modeling of correlated data (Liang & Zeger, 1986; Zeger & Liang, 1986). Boys had higher ADHD scores than girls at both ages (age 2: $z=-2.97$, $p=.003$; age 3: $z=-2.77$, $p=.006$). No significant sex differences emerged at either age for CU or ODD behaviors, but means were in a direction consistent with the literature (i.e., higher for males). MZ and DZ twins did not differ on any behaviors.

Phenotypic and Twin Correlations

As seen in Table 2, CU, ADHD, and ODD behaviors were all highly correlated at both ages. All three behaviors were moderately to highly stable across age (CU: $r=.46$, 95% CI=.38–.52; ADHD: $r=.57$, 95% CI=.51–.63; ODD: $r=.58$, 95% CI=.52–.64). For all three traits at both ages, the intraclass correlations for MZ twins exceeded those for DZ twins, suggesting genetic influences on these externalizing behaviors (Table 3). Cross-twin cross-trait correlations for MZ twins were consistently higher than those for DZ twins, indicating that genetic factors contribute to the phenotypic correlation between the three types of externalizing behaviors.

Model-fitting Analyses

Table 4 presents the fit statistics for the multivariate model-fitting analyses. As indicated by the nonsignificant chi-square statistics for the overall fit of the model, both multivariate models adequately described the data. Because the Common Pathway model is nested within the Independent Pathway model, it is possible to determine the relative fit of the two models by comparing the difference in χ^2 between the two models. Imposing the more restrictive Common Pathway model to the data did not result in a significant decrement in the fit of the model at age 2 ($\chi^2 = 6.578$, $df = 4$, $p = .16$) or at age 3 ($\chi^2 = .63$, $df = 4$, $p = .96$). Moreover, its lower AIC provides additional evidence for the Common Pathway model as

the best-fitting overall model at both ages. At both ages the C paths were non-significant and could be dropped from the models without a significant detriment in fit (Age 2: $\chi^2=1.057$, $df=4$, $p=.90$; Age 3: $\chi^2=.621$, $df=4$, $p=.96$).

After determining the Common Pathway model best described the data at each age, a longitudinal Bifactor Common Pathway model was fit to the data, post-hoc, to investigate the stability of the common latent factor from age 2 to 3 years. In addition to providing the genetic, shared, and nonshared environmental components contributing to the latent factor at each age, this model also estimates the genetic and environmental effects persisting from the latent factor at age 2 (i.e., stability effects) and those specific to age 3 (i.e., change). Given that this longitudinal model includes the same information as the two cross-sectional models and also provides novel information on sources of stability and change in the latent factor across age, we focus on the results from the longitudinal model. Consistent with the cross-sectional models, in the longitudinal model, all C variances were estimated at or near zero; in addition the E covariance between the latent factors across age was also non-significant, and these paths could be dropped from the model without a significant decrement in fit ($\chi^2=3.218$, $df=10$, $p=.97$). No other parameters could be dropped from the model without worsening the fit of the model.

Figure 3 presents the path estimates from the reduced longitudinal Bivariate Common Pathway model. The full model is presented in supplementary materials (Figure S.1). For ease of interpretation, the path estimates in the model, which are standardized partial regressions indicating the relative influence of the latent variables on the phenotypes, have been squared to represent the proportion of variance for each measure accounted for by the latent variable. The total genetic variance for CU behaviors at age 2 is the heritability of the latent externalizing factor times the variance in CU behaviors that is due to the common factor (i.e., square of the factor loading), plus unique genetic variance (i.e., $[(.92 \times .48) + .27 = .71]$). Total specific and common variances for each behavior are presented in Table 5. All three types of externalizing behaviors were significantly heritable, with genetic effects accounting for approximately 60–80% of the total variance at each age. The remaining variance for CU, ADHD and ODD behaviors was explained by nonshared environmental factors.

Genetic and environmental influences on latent EXT phenotype—The significant factor loadings on the common latent externalizing factor (EXT) indicate that CU, ADHD and ODD behaviors tap a common EXT phenotype at each age. This common EXT factor explained 56% (i.e., $[(.48 + .60 + .61) \div 3 = .56]$) of the variance in our externalizing behavior measures at age 2 and 57% (i.e., $[(.50 + .60 + .61) \div 3 = .57]$) at age 3. Variation in the common EXT phenotype was due to genetic influences (age 2=92%; age 3=83%) and, to a lesser extent, nonshared environmental influences (age 2=8%; age 3=17%). In other words, covariance between different types of externalizing behavior problems (i.e., cross-trait consistency) arises mostly because of common genetic influences, and somewhat as a result of common nonshared environmental influences. Furthermore, as seen in Figure 3, this latent externalizing factor is highly stable across age ($r=.79$; 95% CI=.73–.85), and this was largely due to genetic influences. The genetic correlation, which indicates the extent to which genetic effects on the common phenotype at age 2 correlate with genetic effects on

the phenotype at age 3, *independent of the heritability of each*, was .90 (95% CI=.82–.96). Nonshared environmental influences on the externalizing factors were entirely age-specific (i.e., contributed to change in the factor across age, rather than stability).

Sources of covariance between behaviors within age—The genetic effects on CU behaviors correlated .69 (95% CI=.61–.76) with ADHD at age 2 and .66 (95% CI=.57–.74) at age 3, and .70 (95% CI=.62–.77) with ODD at age 2 and .69 (95% CI=.61–.77) at age 3. Similarly, the genetic correlation between ADHD and ODD was .76 (95% CI=.69–.83) at age 2 and .69 (95% CI=.62–.77) at age 3. Nonshared environmental correlations were moderate but significant. At age 2, the nonshared environmental effects on CU behaviors correlated .15 (95% CI=.06–.25) with ADHD, .14 (95% CI=.06–.24) with ODD, and ADHD and ODD correlated .17 (95% CI=.06–.28). At age 3 the nonshared environmental correlations amongst the different types of externalizing behaviors were higher but the confidence intervals overlap suggesting that there was no significant difference across age. The nonshared environmental effects on CU behaviors correlated .32 (95% CI=.22–.42) with ADHD and .28 (95% CI=.19–.38) with ODD, and the nonshared environmental correlation between ADHD and ODD was .39 (95% CI=.27–.50).

Common and specific variance components—The genetic, shared, and nonshared genetic variances for each type of externalizing behavior domain were decomposed into effects common across behavioral domains and those that are unique to each domain (see Table 5). CU, ADHD and ODD behaviors all showed a similar pattern of unique sources of variance. At age 2 approximately 80% of the nonshared environmental variance, which includes child specific effects and measurement error, was trait specific for all three types of externalizing behaviors (i.e., CU: .25/.29=.86; ADHD: .22/.27=.81; ODD: .23/.28=.82), whereas the proportion of genetic variance that was trait specific was lower, ranging from about 20–40% for all three traits (e.g., ADHD=.18/.73=.25). At age 3 a similar pattern emerged; however, not surprisingly given the higher nonshared environmental correlations amongst the traits at this age, the proportion of trait specific nonshared environmental variance was slightly lower, ranging from approximately 60–75% (e.g., CU: .28/.37=.76). Approximately 30% of the total genetic variance for each behavior was trait specific (e.g., CU=.21/.62=.34). Overall, about 40–50% of the total variance in each behavior was behavior-specific (i.e., despite high intercorrelations between the behaviors, roughly half of the variation in CU, ADHD and ODD behaviors could be explained by genetic and environmental factors unique to each).

Discussion

This was the first study to investigate the links between CU, ADHD, and ODD behaviors. We explored this etiologic overlap at ages 2 and 3 years, an important developmental period when many of these behaviors are beginning to come online. Consistent with research in older children exploring the overlap between CU behaviors and CD, and between ADHD, ODD and CD, genetic factors primarily explained the phenotypic association between the three behaviors. Genetic and nonshared environmental effects *specific to each behavior* provide additional support to phenotypic research demonstrating the ability to differentiate CU behaviors from other externalizing behavior problems in very young children. Lastly, the

pattern of results at ages 2 and 3 was similar, further highlighting the validity of assessing CU behaviors as early as 2 years of age.

As with work looking at links between ADHD, ODD, and CD (e.g., Dick et al., 2005; Nadder et al., 2002; Tuvblad et al., 2009), it appears that CU, ADHD, and ODD behaviors are also related due to common genetic factors linking all three. At both ages a common pathway model provided the best fit to the data indicating that all three behaviors tap a highly heritable common latent externalizing phenotype. A similar latent phenotype has emerged in studies of related behaviors (ADHD, ODD, and CD) in older children (Burt et al., 2001; Tuvblad et al., 2009). As with our study, both found support for a common externalizing factor, though one was primarily influenced by environmental factors (Burt et al., 2001) and the other by genetic factors (Tuvblad et al., 2009). On the basis of the present findings and the body of research looking at sources of covariation between other distinct externalizing behaviors, there appears to be a genetically-influenced externalizing phenotype. We would add that this phenotype includes CU behaviors, and further, is highly stable across early childhood due to overlapping genetic effects. Because our interest was in exploring the sources of covariation between three specific externalizing behaviors that have been found to be intercorrelated in the phenotypic literature, we view the common variance as an externalizing phenotype. We acknowledge, however, that it is possible that it may be part of a more general psychopathology phenotype reflecting a genetic liability to psychopathology more broadly.

The finding of a heritable common externalizing factor linking CU, ADHD and ODD behaviors has several important implications. First, this suggests a general genetic liability to the three externalizing behaviors, with environmental experiences likely determining which disorder is expressed in an individual (Kendler et al., 1987). Second, the high heritability of the common externalizing factor highlights its potential relevance, rather than specific externalizing behaviors such as CU, in molecular genetic work. Third, though this study did not explicitly explore the etiology of comorbidity, the highly heritable common factor linking the three behaviors would suggest that comorbidity between them is more likely to be a result of an additive combination of genetic liability to the behaviors, rather than a distinct disorder. Indeed, this has been indicated for comorbidity between ADHD and ODD/CD (Nadder et al., 2002; Rhee et al., 2008), though there is also research supporting classification as a distinct disorder (Thapar et al., 2001). Lastly, despite high heritability of the common externalizing factor, this is not to say the environment is irrelevant. The heritability of the common factor is only explaining why the three behaviors are *linked* to one another, not the unique etiologic effects on the behaviors or the overall genetic and environmental contributions to variance in each behavior. Furthermore, genetic estimates can also include gene-environment correlations and interactions, which should be explored in future research.

Despite the highly heritable common externalizing factor, the three behaviors have distinct etiologies as well. In fact, approximately 50% of the variance is specific to each behavior at both ages. It is these unique effects that may explain differences in hot and cold paths to conduct problems. Consistent with phenotypic factor structure indicating support for a 3-factor model of CU, ADHD, and ODD behaviors across different samples in early childhood

(Flom & Saudino, 2016; Waller, Shaw, et al., 2015; Willoughby et al., 2011), behavior-specific genetic and nonshared environmental effects offer support at the level of etiology for the ability of parent report to differentiate between the three behaviors as early as 2 years of age. This is also consistent with work demonstrating unique early risk factors for CU, ADHD and ODD behaviors (e.g., Willoughby et al., 2011), and differential socio-emotional and behavioral correlates in early childhood (Waller, Hyde, et al., 2015). Thus, this work provides further support for the construct validity of assessing CU behaviors in very young children. Genetic variance that is unique to a behavior has been suggested to imply some independence in underlying biological substrates (Taylor, Loney, Bobadilla, Iacono, & McGue, 2003), indicating that the three are partially distinct in early childhood at the level of etiology. Nonshared environmental effects were largely responsible for differentiation among the behaviors rather than overlap between them, yet it is important to remember that nonshared environmental influences on each behavior includes measurement error. To the extent that these behavior-specific estimates do not reflect measurement error, they highlight the need to consider each externalizing behavior separately, as the environment is mostly responsible for differentiation among the behaviors rather than overlap between them. Moreover, the influence of the nonshared environment points to the need to target experiences that *differ* among family members, such as differential parenting, keeping in mind that these environmental effects may be largely independent across behaviors. However, because it is not possible to distinguish unique nonshared environmental factors from measurement error, it may also be that each behavior is prone to distinct issues with measurement and that “true” unique environmental effects are less relevant.

Limitations of this research should be acknowledged. First, as is the case with most research in early childhood where using other reporters (e.g., teachers) is often not possible, we relied on parent-report. When both members of a twin pair are assessed by the same rater, there is the potential problem of shared rater variance which would act to inflate estimates of shared environmental variance (Saudino, 2017). That is, there is covariance between the biases that affect the ratings of each twin such that the rater tends to consistently overestimate or underestimate the behavior of both cotwins. Because there was no significant shared environmental variance on any of the behaviors examined, this does not appear to be a problem in the present study. Future research should utilize different reporters at different ages when possible. Second, our CU scale had lower internal consistency than the ADHD and ODD scales. The lower reliability of the CU scale is consistent with CU research in early childhood and beyond (e.g., Waller, Hyde, et al., 2015; Willoughby et al., 2011). Nonetheless, the remarkable consistency of our findings across age and with prior phenotypic research (e.g., Waller, Shaw, et al., 2015; Willoughby et al., 2014) suggests that the lower reliability is likely not a problem. More importantly, the latent factor is free of measurement error (Saudino, 2017); consequently, genetic and nonshared environmental influences on the common externalizing factor are not affected by the lower reliability of the CU scale. In addition, because unreliability cannot result in the systematic effects necessary to estimate genetic influences, the specific genetic effects represent real effects that are unique to each behavior problem domain (Saudino, 2017; Van der Valk, Van den Oord, Verhulst, & Boomsma, 2001).

In conclusion, the overlap between CU, ADHD, and ODD behaviors can be explained by a highly heritable common externalizing factor, suggesting a genetic liability to externalizing behavior problems in early childhood. This genetic liability likely interacts with the environment to influence specific manifestation of certain behaviors, though this remains an empirical question. Despite strong genetic links between the three behaviors, the behavior-specific genetic and nonshared environmental effects provide further support to phenotypic research indicating the construct validity of parent-reported CU behaviors in very young children.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The Boston University Twin Project (BUTP) is supported by grants from the National Institute of Mental Health (MH062375) and the National Institute of Child Health and Human Development (HD068435) to Dr. Saudino. The twins' and families' participation is gratefully acknowledged.

References

- Achenbach TM, Rescorla LA. Manual for the ASEBA preschool forms & profiles: An integrated system of multi-informant assessment; Child behavior checklist for ages 1 1/2-5; Language development survey; Caregiver-teacher report form University of Vermont; 2000
- Burt SA, Krueger RF, McGue M, Iacono WG. Sources of covariation among attention-deficit/hyperactivity disorder, oppositional defiant disorder, and conduct disorder: The importance of shared environment. *Journal of Abnormal Psychology*. 2001; 110(4):516–525. DOI: 10.1037/0021-843X.110.4.516 [PubMed: 11727941]
- De la Osa N, Granero R, Trepal E, Domenech JM, Ezpeleta L. The discriminative capacity of CBCL/1½-5- DSM5 scales to identify disruptive and internalizing disorders in preschool children. *European Child & Adolescent Psychiatry*. 2016; 25(1):17–23. DOI: 10.1007/s00787-015-0694-4 [PubMed: 25715996]
- Dick DM, Viken RJ, Kaprio J, Pulkkinen L, Rose RJ. Understanding the Covariation Among Childhood Externalizing Symptoms: Genetic and Environmental Influences on Conduct Disorder, Attention Deficit Hyperactivity Disorder, and Oppositional Defiant Disorder Symptoms. *Journal of Abnormal Child Psychology*. 2005; 33(2):219–229. DOI: 10.1007/s10802-005-1829-8 [PubMed: 15839499]
- Flom M, Saudino KJ. Callous-unemotional behaviors in early childhood: Genetic and environmental contributions to stability and change. *Development and Psychopathology* 2016
- Frick PJ, Morris AS. Temperament and developmental pathways to conduct problems. *Journal of Clinical Child and Adolescent Psychology*. 2004; 33(1):54–68. DOI: 10.1207/S15374424JCCP3301_6 [PubMed: 15028541]
- Frick PJ, Ray JV, Thornton LC, Kahn RE. Annual research review: A developmental psychopathology approach to understanding callous-unemotional traits in children and adolescents with serious conduct problems. *Journal of Child Psychology and Psychiatry*. 2014a; 55(6):532–548. DOI: 10.1111/jcpp.12152 [PubMed: 24117854]
- Frick PJ, Ray JV, Thornton LC, Kahn RE. Can callous-unemotional traits enhance the understanding, diagnosis, and treatment of serious conduct problems in children and adolescents? A comprehensive review. *Psychological Bulletin*. 2014b; 140(1):1–57. DOI: 10.1037/a0033076 [PubMed: 23796269]
- Hewitt JK, Silberg JL, Neale MC, Eaves LJ, Erickson M. The analysis of parental ratings of children's behavior using LISREL. *Behavior Genetics*. 1992; 22(3):293–317. DOI: 10.1007/BF01066663 [PubMed: 1616461]

- Hollingshead AB. Four factor index of social status 1975 Retrieved from http://www.academia.edu/download/30754699/yjs_fall_2011.pdf#page=21
- Kendler KS, Heath AC, Martin NG, Eaves LJ. Symptoms of Anxiety and Symptoms of Depression: Same Genes, Different Environments? *Archives of General Psychiatry*. 1987; 44(5):451–457. DOI: 10.1001/archpsyc.1987.01800170073010 [PubMed: 3579496]
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986; 73(1):13–22. DOI: 10.1093/biomet/73.1.13
- McArdle JJ, Goldsmith HH. Alternative common factor models for multivariate biometric analyses. *Behavior Genetics*. 1990; 20(5):569–608. DOI: 10.1007/BF01065873 [PubMed: 2288547]
- McGue M, Bouchard TJ Jr. Adjustment of twin data for the effects of age and sex. *Behavior Genetics*. 1984; 14(4):325–343. DOI: 10.1007/BF01080045 [PubMed: 6542356]
- Nadder TS, Rutter M, Silberg JL, Maes HH, Eaves LJ. Genetic effects on the variation and covariation of attention deficit-hyperactivity disorder (ADHD) and oppositional-defiant disorder/conduct disorder (ODD/CD) symptomalogies across informant and occasion of measurement. *Psychological Medicine*. 2002; 32(1):39–53. DOI: 10.1017/S0033291701004792 [PubMed: 11883729]
- Neale MC, , Boker SM, , Xie G, , Maes HH. *Mx: Statistical Modeling (Version 7th Edition)*: VCU Box 900126 Richmond, VA: 2006 23298
- Neumann A, Pappa I, Lahey BB, Verhulst FC, Medina-Gomez C, Jaddoe VW, Tiemeier H. Single nucleotide polymorphism heritability of a general psychopathology factor in children. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2016; 55(12):1038–1045. DOI: 10.1016/j.jaac.2016.09.498 [PubMed: 27871638]
- Olds DL, , Robinson J, , Song N, , Little C, , Hill P. Reducing risks for mental disorders during the first five years of life: A review of the literature Substance Abuse and Mental Health Services Administration; Rockville, MD: 2005
- Pardini D, Obradovi J, Loeber R. Interpersonal Callousness, Hyperactivity/Impulsivity, Inattention, and Conduct Problems as Precursors to Delinquency Persistence in Boys: A Comparison of Three Grade-Based Cohorts. *Journal of Clinical Child and Adolescent Psychology*. 2006; 35(1):46–59. DOI: 10.1207/s15374424jccp3501_5 [PubMed: 16390302]
- Plomin R, , DeFries J, , Knopik V, , Neiderhiser J. *Behavioral Genetics Vol. 6*. Worth Publishers; 2013
- Price TS, Freeman B, Craig I, Petrill SA, Ebersole L, Plomin R. Infant zygosity can be assigned by parental report questionnaire data. *Twin Research*. 2000; 3(03):129–133. DOI: 10.1375/twin.3.3.129 [PubMed: 11035484]
- Rescorla LA. Assessment of young children using the Achenbach System of Empirically Based Assessment (ASEBA). *Developmental Disabilities Research Reviews*. 2005; 11(3):226–237. DOI: 10.1002/mrdd.20071
- Rhee SH, Willcutt EG, Hartman CA, Pennington BF, DeFries JC. Test of alternative hypotheses explaining the comorbidity between attention-deficit/hyperactivity disorder and conduct disorder. *Journal of Abnormal Child Psychology*. 2008; 36(1):29–40. DOI: 10.1007/s10802-007-9157-9 [PubMed: 17636436]
- Saudino KJ. *Wiley StatsRef: Statistics Reference Online* 2017 Rater Bias Models.
- Taylor J, Loney BR, Bobadilla L, Iacono WG, McGue M. Genetic and environmental influences on psychopathy trait dimensions in a community sample of male twins. *Journal of Abnormal Child Psychology*. 2003; 31(6):633–645. DOI: 10.1023/A:1026262207449 [PubMed: 14658743]
- Thapar A, Harrington R, McGuffin P. Examining the comorbidity of ADHD-related behaviours and conduct problems using a twin study design. *The British Journal of Psychiatry*. 2001; 179(3):224–229. DOI: 10.1192/bjp.179.3.224 [PubMed: 11532799]
- Tuvblad C, Zheng M, Raine A, Baker LA. A common genetic factor explains the covariation among ADHD ODD and CD symptoms in 9–10 year old boys and girls. *Journal of Abnormal Child Psychology*. 2009; 37(2):153–167. DOI: 10.1007/s10802-008-9278-9 [PubMed: 19015975]
- Van der Valk JC, Van den Oord E, Verhulst FC, Boomsma DI. Using Parental Ratings to Study the Etiology of 3-year-old Twins' Problem Behaviors: Different Views or Rater Bias? *Journal of Child Psychology and Psychiatry*. 2001; 42(7):921–931. DOI: 10.1017/S0021963001007648 [PubMed: 11693587]

- Viding E, Frick PJ, Plomin R. Aetiology of the relationship between callous-unemotional traits and conduct problems in childhood. *The British Journal of Psychiatry*. 2007; 190(Suppl 49):s33–s38. DOI: 10.1192/bjp.190.5.s33
- Waller R, Hyde LW, Grubel AS, Alves ML, Olson SL. Differential associations of early callous-unemotional, oppositional, and ADHD behaviors: multiple domains within early-starting conduct problems? *Journal of Child Psychology and Psychiatry*. 2015; 56(6):657–666. DOI: 10.1111/jcpp.12326 [PubMed: 25251938]
- Waller R, , Shaw DS, , Neiderhiser JM, , Ganiban JM, , Natsuaki MN, , Reiss D, , Hyde LW. Toward an Understanding of the Role of the Environment in the Development of Early Callous Behavior. *Journal of Personality* 2015
- Willoughby MT, Mills-Koonce WR, Gottfredson NC, Wagner NJ. Measuring callous unemotional behaviors in early childhood: Factor structure and the prediction of stable aggression in middle childhood. *Journal of Psychopathology and Behavioral Assessment*. 2014; 36(1):30–42. DOI: 10.1007/s10862-013-9379-9 [PubMed: 24729655]
- Willoughby MT, Mills-Koonce WR, Waschbusch DA, Gottfredson NC. An examination of the Parent Report version of the Inventory of Callous-Unemotional Traits in a community sample of first-grade children. *Assessment*. 2015; 22(1):76–85. DOI: 10.1177/1073191114534886 [PubMed: 24820529]
- Willoughby MT, Waschbusch DA, Moore GA, Propper CB. Using the ASEBA to screen for callous unemotional traits in early childhood: Factor structure, temporal stability, and utility. *Journal of Psychopathology and Behavioral Assessment*. 2011; 33(1):19–30. DOI: 10.1007/s10862-010-9195-4 [PubMed: 21483647]
- Yang J, Lee SH, Goddard ME, Visscher PM. GCTA: A Tool for Genome-wide Complex Trait Analysis. *The American Journal of Human Genetics*. 2011; 88(1):76–82. DOI: 10.1016/j.ajhg.2010.11.011 [PubMed: 21167468]
- Zeger SL, Liang KY. Longitudinal Data Analysis for Discrete and Continuous Outcomes. *Biometrics*. 1986; 42(1):121–130. DOI: 10.2307/2531248 [PubMed: 3719049]

Figure 1.
Independent Pathway Model, One Twin Only

Figure 2.
Common Pathway Model, One Twin Only

Figure 3.

Reduced Longitudinal Bivariate Common Pathway Model. 95% confidence intervals are presented in parentheses. EXT represents the common externalizing factor; A=additive genetic influences on the common factor; E=nonshared environmental influences on the common factor; a=unique genetic influences on each behavior (CU, ADHD and ODD); e=unique nonshared environmental influences on each behavior.

Table 1

Means (and Standard Deviations) for CU, ADHD and ODD Behaviors at Both

Age 2	Males		Females		Effect Size	
	MZ	DZ	MZ	DZ	Sex	Zygosity
CU	1.67 (1.52)	1.59 (2.45)	1.40 (1.45)	1.50 (2.10)	.11	.01
ADHD	4.78 (2.68)	4.58 (2.80)	3.68 (2.40)	4.02 (4.10)	.29*	-.03
ODD	3.25 (2.35)	3.08 (2.48)	2.65 (2.29)	2.74 (6.86)	.19	.02
n	148	183	142	154		

Age 3	Males		Females		Effect Size	
	MZ	DZ	MZ	DZ	Sex	Zygosity
CU	1.35 (1.35)	1.43 (1.46)	.94 (1.07)	1.31 (1.30)	.17	-.16
ADHD	4.34 (2.74)	4.23 (2.90)	2.98 (2.41)	3.98 (2.62)	.28*	-.17
ODD	3.54 (2.63)	3.22 (2.50)	2.73 (2.57)	3.29 (2.45)	.15	-.06
n	148	183	142	154		

Note. Effect size estimated as Cohen's *d* express group differences in standard deviation units.

Means presented are of the nontransformed variables to allow for ease of interpretation.

* $p < .01$.

Table 2

Phenotypic Correlations and (95% Confidence Intervals)

	CU	ADHD	ODD
CU	–	.54 (.47–.60)	.55 (.48–.61)
ADHD	.57 (.51–.63)	–	.61 (.55–.66)
ODD	.56 (.50–.62)	.60 (.54–.65)	–

Age 2 = values above the diagonal; Age 3 = below the diagonal.

Table 3

Twin Intraclass and Cross Correlations

Age 2	CU		ADHD		ODD	
	MZ	DZ	MZ	DZ	MZ	DZ
CU	.72 (.63-.78)	.41 (.28-.52)				
ADHD	.49 (.42-.56)	.29 (.18-.39)	.74 (.66-.79)	.39 (.25-.50)		
ODD	.52 (.44-.59)	.30 (.19-.39)	.55 (.48-.62)	.32 (.21-.41)	.72 (.64-.78)	.41 (.28-.52)

Age 3	CU		ADHD		ODD	
	MZ	DZ	MZ	DZ	MZ	DZ
CU	.63 (.52-.71)	.41 (.28-.52)				
ADHD	.49 (.41-.56)	.27 (.16-.37)	.78 (.72-.83)	.28 (.13-.41)		
ODD	.44 (.35-.52)	.36 (.25-.45)	.47 (.39-.54)	.28 (.17-.39)	.66 (.56-.73)	.41 (.27-.53)

Note. Intraclass correlations are in bold. Cross-twin, cross-trait correlations are below the diagonal. All correlations are significant at $p < .05$.

Table 4

Fit statistics for cross-sectional and longitudinal multivariate models of CU, ADHD and ODD Behaviors

Age 2	Overall Fit of Model ^a				Relative Fit of Model			
	-2LL	df	χ^2	df	p	AIC	χ^2	df
Overall Model (Saturated -2LL=1176.734, 1813)								
Independent Pathway model	1184.466	1837	7.732	24	1.00	-40.268		
Common Pathway Model	1185.096	1841	8.362	28	1.00	-47.638	.63^b	4
Age 3	Overall Fit of Model ^a				Relative Fit of Model			
	-2LL	df	χ^2	df	p	AIC	χ^2	df
Overall Model (Saturated -2LL=1117.925, 1720)								
Independent Pathway model	1152.588	1744	34.663	24	.074	-13.337		
Common Pathway Model	1159.166	1748	41.241	28	.051	-14.759	6.578^b	4
Longitudinal	Overall Fit of Model ^a				Relative Fit of Model			
	-2LL	df	χ^2	df	p	AIC	χ^2	df
Overall Model (Saturated -2LL=1871.364, 3461)								
Bivariate Common Pathway Model	2105.077	3580	233.713	119	.000	-4.287		
Reduced Bivariate Common Pathway Model	2108.295	3590	236.931	129	.000	-21.069	3.218^c	10

Note. -2LL=Likelihood Statistic. χ^2 =Chi-square fit statistic. df=Degrees of freedom. AIC=Akaike's Information Criterion. Best fitting model indicated in bold.

^aOverall fit of the model is determined by the difference in -2LL of the model and that of a saturated model.

^b χ^2 difference between the Independent Pathway model and Common Pathway model.

^c χ^2 difference between the full and reduced longitudinal models.

Table 5

Multivariate Estimates of Genetic and Environmental Variance (and 95% Confidence Intervals) from the Longitudinal Bivariate Common Pathway Reduced Model

Age 2	Variance Components										
	Latent EXT Phenotype										
Loading on EXT Phenotype		a^2	c^2	e^2	Specific Variance					Total Variance	
CU	.69 (.63–.75)	.45 (.37–.52)	–	.04 (.01–.07)	.27 (.18–.35)	–	.25 (.19–.32)	.72 (.55–.87)	–	.29 (.20–.39)	
ADHD	.77 (.72–.82)	.55 (.47–.63)	–	.05 (.02–.08)	.18 (.11–.26)	–	.22 (.16–.29)	.73 (.58–.89)	–	.27 (.18–.37)	
ODD	.78 (.73–.82)	.56 (.48–.64)	–	.05 (.02–.08)	.16 (.09–.24)	–	.23 (.17–.30)	.72 (.57–.88)	–	.28 (.19–.38)	
Age 3	Variance Components										
	Latent EXT Phenotype										
Loading on EXT Phenotype		a^2	c^2	e^2	Specific Variance					Total Variance	
CU	.71 (.65–.76)	.41 (.34–.49)	–	.09 (.06–.13)	.21 (.13–.30)	–	.28 (.22–.37)	.62 (.47–.79)	–	.37 (.28–.50)	
ADHD	.78 (.72–.82)	.50 (.41–.58)	–	.10 (.07–.15)	.26 (.18–.35)	–	.14 (.09–.20)	.76 (.59–.93)	–	.24 (.16–.35)	
ODD	.78 (.73–.83)	.51 (.42–.59)	–	.11 (.07–.16)	.19 (.11–.27)	–	.20 (.14–.27)	.70 (.53–.86)	–	.31 (.21–.43)	

Note. a^2 = genetic variance, c^2 = shared environmental variance, e^2 = nonshared environmental variance