Published in final edited form as:

Am J Psychiatry. 2012 January ; 169(1): 47–54. doi:10.1176/appi.ajp.2011.10101549.

Adolescent irritability: phenotypic associations and genetic links with depressed mood

Argyris Stringaris, MD, PhD^{1,*}, Helena Zavos, MSc^{2,*}, Ellen Leibenluft, MD³, Barbara Maughan, PhD², and Thalia Eley, PhD²

¹Department of Child and Adolescent Psychiatry, King's College London, Institute of Psychiatry, London, United Kingdom

²Social, Genetic and Developmental Psychiatry Centre, King's College London, Institute of Psychiatry, London, United Kingdom

³Section of Bipolar Spectrum Disorders, Mood and Anxiety Programme National Institute of Mental Health, Bethesda, MD, USA

Abstract

Objective—Irritability has been proposed to underlie the developmental link between oppositional problems and depression. However, little is known about the genetic and environmental influences on irritability and its overlap with depression. This paper tests the hypothesis that the association between irritability and depression is accounted for by genetic factors. As such, it draws on the notion of “generalist genes” i.e., genes of general effect that underlie phenotypic overlap between disorders.

Method—The G1219 study, a UK-based twin sample (N=2651), was used in a cross-sectional and longitudinal design. Irritable and headstrong/hurtful dimensions of oppositional behavior were derived using factor analysis. Regression was used to estimate the association between depression and delinquency. Multivariate genetic analyses were used to estimate the genetic overlap between irritability versus headstrong/hurtful behaviors with depression and delinquency respectively.

Results—Irritability showed a significantly stronger phenotypic relationship with depression than delinquency, whereas headstrong/hurtful behaviors were more strongly related to delinquency than depression. In multivariate genetic analyses, the genetic correlation between irritability and depression (0.70; CI: 0.59-0.82) was significantly higher than that between irritability and delinquency (0.57; CI: 0.45-0.69); conversely, the genetic correlation between headstrong/hurtful behaviors and delinquency (0.80; CI: 0.72-0.86) was significantly higher than that between headstrong/hurtful behaviors and depression (0.46; CI: 0.36-0.57). In longitudinal models, the phenotypic association between irritability at Time 1 and depression at Time 2 was accounted for by the genetic association between irritability and depression at Time1.

Conclusions—The findings are consistent with the theory that genes with general effects underlie the relationship between irritability and depression.

Keywords

irritability; depression; oppositional defiant disorder; mood disorders; development

Address for Correspondence: Argyris Stringaris King's College London Institute of Psychiatry Box 085 Denmark Hill London SE5

*AF Tel: +44 (0)20 7848 0302 Fax: +44 (0)20 7708 5800 argyris.stringaris@kcl.ac.uk.

*these authors contributed equally to the work presented in the manuscript

Introduction

Irritable mood, a common and impairing symptom in psychopathology¹⁻³, has been proposed to underlie the developmental link between oppositional problems in youth and depression in adults^{4,5}. However, little is known about the genetic and environmental influences on irritability and its overlap with psychiatric disorders. This paper uses a twin sample to test the hypothesis that the association of irritability and depression is due to genetic factors.

An unexplained aspect of developmental psychopathology concerns the transition from disruptive behavior problems to mood and anxiety problems⁶. A striking example is the recent finding that oppositionality in youth is a potent predictor of depression in young adult life, over and above depression in early life⁷. It has recently been proposed that irritable mood may explain this transition from oppositionality to later depression^{5,7,8}. Data suggest that oppositionality in youth comprises at least two dimensions with differential predictions⁹⁻¹²: an irritable dimension, more strongly associated with depressive disorders than with antisocial behaviors; and a headstrong/hurtful dimension, (capturing argumentative, rule breaking alongside spiteful behaviors), more strongly associated with antisocial behaviors than depressive disorders^{5,11,12}. These differential associations have been demonstrated in a series of longitudinal studies spanning childhood into adulthood^{5,11}.

It remains unknown whether such differential phenotypic links are accounted for by genetic or environmental factors. For example, is the overlap between irritability and depression accounted for by one set of shared genes, whilst a different set of genes explain the link between headstrong/hurtful behaviors and antisociality? Previous genetic studies have found that genetic factors may have broader influences than initially thought; indeed so called “generalist genes” are thought to explain the association between closely linked phenotypes^{13,14}. An alternative explanation for such phenotypic overlap lies in the realm of overlapping environmental factors. Family- or person-specific environmental influences may be associated with both irritability and depression and thus underlie their relationship, while a different set of such overlapping environmental risks may underlie the relationship of headstrong/hurtful behaviors with antisociality. Answering these questions would help understand the mechanisms underlying these key developmental pathways.

This paper uses a genetically-informative design to address these questions. We begin by examining phenotypic links between the two components of oppositionality (irritability and headstrong/hurtful behaviors) and depressive problems and antisocial behaviors. Consistent with previous findings, we predict a double dissociation, such that adolescent irritability will show differential concurrent and longitudinal relationships to depressive problems, while headstrong/hurtful behaviors will be specifically related to antisocial outcomes. We use young people’s self-reports, thus complementing previous work based on parent- and teacher report^{5,11,12} and re-examining previous negative findings⁵ about the relationship between self-reported irritability and psychopathology. Focusing on adolescence offers the additional advantage that the differential relationships of irritability can be tested at a time when adult mood problems are emerging¹⁵ and antisocial behaviors reach a peak¹⁶.

In the next step, we use multivariate twin modelling to test the paper’s main hypothesis that the genetic findings will show a double dissociation consistent with the phenotypic findings. We expect that genetic factors shared between irritability and depression underlie their phenotypic association and, similarly, that genetic factors shared between headstrong/hurtful and antisocial behaviors explain their phenotypic association. This prediction is based on the notion of “generalist genes”, which are hypothesized not to be disorder specific, but, rather,

to exert wider effects giving rise to closely linked behavioral¹⁷ or cognitive phenotypes^{13, 14}. Indeed, we have recently provided further empirical evidence in support of this theory by showing substantial genetic links between cognitive bias, depression, and anxiety problems¹⁸.

Material and Methods

Sample

Data from the G1219 sample were used as previously described¹⁸. This is a longitudinal study of 3640 adolescent twins and siblings (age range 12–19 at initial contact). Analyses here focus on the second and third waves of the data collection. Data collection for waves 2 and 3 (from hereon referred to as time 1 and time 2) respectively took place approximately 8 (range: 0–24 months) and 33 months (range 24–60 months) after initial contact. At time 1, data were available from 2651 individuals (73% of the original sample at wave 1) whilst corresponding figures for time 2 were 1597 adolescents (44% of the original sample at wave 1). Zygosity was established through a questionnaire measure completed by mothers. The sample consists of 118 monozygotic male, 199 monozygotic female, 138 dizygotic male twin pairs, 190 dizygotic female, 463 opposite-sex dizygotic twin pairs and 109 male sibling pairs, 132 female sibling pairs and 186 opposite-sex sibling pairs. At times 1 and 2, the proportions of boys were 43.9% and 41.3% respectively. The mean ages at times 1 and 2 were 15 years (range 12–21) and 17 years (range 14–23). To handle the effects of initial response and attrition bias, a single weighting variable was included in all genetic analyses as previously described¹⁸. Informed consent was obtained from parents/ guardians of all adolescents under 16 years, and from the adolescents themselves when over 16. Ethical approval was provided by the Research Ethics Committees of the Institute of Psychiatry, South London and Maudsley NHS Trust, and Goldsmiths, University of London.

Measures

Depression Ratings—Depressive symptoms were rated by self report using the Short Mood and Feelings Questionnaire^(19–21). At time 1, a four-point response format (never to always) was used to allow for discrimination at the lower end of the spectrum. The standard three-point scale was used at time 2.

Delinquent Behavior—Using the ASEBA family of instruments^{22, 23}, we formed a delinquency scale from 11 items as previously described²⁴ that capture lacks guilt, deviant peers, lying, preferring older peers, running away from home, setting fires, stealing, swearing, truanting, and use of alcohol/drugs.

Dimensions of oppositionality—Items used to define dimensions of oppositionality were drawn from the Youth Self Report²² (YSR, Ages 11–18) and the Adult Self Report²³ (ASR, Ages 18–59) of the ASEBA family of instruments. At time 1, we used the following items from the YSR: *Argue a lot, mean to others, destroy others' things, disobey parents, disobey at school, have a hot temper, tease others a lot, stubborn, mood/feelings change suddenly*. The last item was included on the basis that mood lability is a commonly used term to describe chronic irritability²⁵. At time 2, we used comparable items with the exception that they did not include the item *disobey parents*, and the item *stubborn* was rephrased as *stubborn, sullen, or irritable*.

Statistical Analyses

Derivation of the irritable and headstrong/hurtful dimensions—At each wave, we conducted exploratory factor analyses using the oppositionality items with weighted least

squares estimation (due to the categorical nature of the items) on a random half of the dataset. These yielded two factors with eigenvalues > 1 , corresponding to previously described dimensions of oppositionality^{10-12, 26}. Table 1 shows that (with the exception of the cross-loading *argue a lot* item), all items loaded clearly on either the irritable (*have a hot temper, stubborn* (time 1) or *stubborn, sullen or irritable* (time 2) *mood/feelings change suddenly*) or the headstrong/hurtful (*disobey parents* (only available at time 1), *mean to others, destroy others' things, disobey at school, tease others a lot*) factors.

We note that although the ASR item 'stubborn, sullen or irritable' would be expected to load on the irritability dimension, the YSR version of that item (simply labelled 'stubborn') might be more ambiguous, and reflect headstrong as well as irritable tendencies. Although both versions of the item loaded clearly and consistently on the irritable dimension in the factor analyses, we re-ran all the main analyses excluding this item (as detailed below) to ensure any potential ambiguity did not bias the study's results.

The results of the exploratory factor analyses were further tested in confirmatory factor analyses in the other half of the sample. A single factor model—in which all the items would load—was compared to the two factor—irritable and headstrong/hurtful—model derived by exploratory factor analysis. All fit indices from maximum likelihood estimation and the χ^2 difference score in weighted least squares estimation indicated a better fit for the two-factor versus the single factor model, (Supplementary Table 1 of the appendix). The Cronbach alpha coefficients were 0.67 (time 1) and 0.55 (time 2) for the headstrong/hurtful and 0.61 (time 1) and 0.66 (time 2) for the irritable dimension.

Phenotypic analyses—Cross-sectional associations between variables were explored using correlation and robust regression with either depression or delinquency as the outcome and both dimensions of oppositionality entered simultaneously as predictors. Longitudinal associations between the dimensions of oppositionality at time 1 and psychopathology at time 2 were examined using regression models adjusting for the dimensional psychopathology score measured at baseline. For example, where depression scores at time 2 were the outcome, the predictors were the two dimensions—irritable and headstrong/hurtful behavior—at time 1 and the depression scores at time 1. Robust standard error (sandwich) estimators²⁷ were used to account for dependence of twin observations.

Genetic analyses—The twin design compares the degree of similarity among monozygotic (sharing 100% of their genes), and dizygotic twins (sharing on average 50% of their genes). Relative differences in within-pair correlations are used to estimate additive genetic (A), shared environmental (C), and non-shared environmental (E) effects on measures.

Variables were regressed for age and sex as is standard practice for quantitative genetic model fitting. Variables were transformed to ensure all skew statistics were between the range of 1 and -1 .

Models were fitted in the Mx program²⁸ using raw data maximum likelihood, with weighting corrections to account for selective attrition. The fit statistic provided for raw data modelling (twice the log likelihood $[-2LL]$) of the observations was used to compare the fit of the genetic model to that of a saturated model. Following parsimony, the fit of sub-models was assessed by χ^2 difference tests and the Akaike's Information Criterion ($\chi^2 - 2df$), with lower χ^2 values and more negative Akaike values indicating a better fit.

Multivariate Genetic Models—We used multivariate genetic models to test the paper's hypotheses using both cross-sectional and longitudinal approaches.

In the first, cross-sectional step, we interpreted a Cholesky decomposition as a correlated factors solution to examine whether the genetic findings mirrored the phenotypic associations. We tested whether: a) genetic overlap between irritability and depression is stronger than that between headstrong/hurtful behaviors and depression; and b) genetic overlap between headstrong/hurtful behaviors and delinquency is stronger than that between irritability and delinquency.

In the second, longitudinal, step we used trivariate (3-variable) and then quadrivariate (4-variable) Cholesky decomposition models. The purpose of the trivariate model was to investigate whether any genetic or environmental relationships remained between *irritability at Time 1 and delinquency at Time 2* on the one hand, and *headstrong/hurtful behaviors at Time 1 and depression at Time 2* on the other, after accounting for headstrong/hurtful behaviors and irritability (both at Time 1) respectively. The quadrivariate Cholesky models additionally adjust for depression at *Time 1* when examining depression at *Time 2* as an outcome and for delinquency at *Time 1* when examining delinquency at *Time 2* as an outcome.

Results

Phenotypic findings

Irritability was significantly higher in girls than in boys (2.27 ± 1.57 vs 1.86 ± 1.54 , $t=6.6$, $p<0.001$) and headstrong/hurtful behaviors were more common in boys than girls (1.84 ± 1.85 vs 1.38 ± 1.53 , $t=6.9$, $p<0.001$).

The correlations between the study's main variables are shown in Table 2. Inspecting the coefficients and confidence intervals, irritability showed a stronger association with depressive ratings than did headstrong/hurtful behaviors. Conversely, headstrong/hurtful behaviors showed a stronger association with delinquency than did irritability. Figure 1a shows the findings of cross-sectional robust regression models, with either depression or delinquency as the outcome and with the two dimensions of oppositionality entered simultaneously as predictors. It illustrates a double dissociation, in which irritability is significantly more strongly associated with depression than with delinquency, whereas, in contrast, headstrong/hurtful behaviors are significantly more strongly associated with delinquency than with depressive problems. Controlling for gender and age did not alter the pattern of the results.

Longitudinal robust regression models showed the same pattern. Irritability, but not headstrong/hurtful behaviors, at time 1 was a significant predictor of self-reported depression symptom scores at time 2, after controlling for self-reported depression symptom scores at time 1 (0.14 [0.08 to 0.20] and 0.01 [-0.05 to 0.07] respectively). Conversely, headstrong/hurtful behaviors, but not irritability, were significant predictors of self-reported delinquency scores at time 2, even after adjusting for self-reported delinquency scores at time 1 (0.19 [0.12 to 0.27] and 0.05 [-0.00 to 0.10] respectively). The pattern of results was unchanged when the reduced irritability scale (omitting the 'stubborn' item) was used instead (Suppl. Table 2).

Genetic analyses

Genetic overlap between irritability and both depression and delinquency was first assessed cross-sectionally. A saturated model was fit which estimates variances, covariances and means for the raw data to get a baseline index of fit ($\chi^2=22733.580$, $df=9337$). Subsequent models were compared to the saturated model to determine the best fitting model. We found that a model without sex differences in A, C and E parameters but allowing for variance difference across the sexes, fit the data best ($\chi^2=22848.251$, $df=9648$, $p<0.01$ Akaike

information criterion=-155.481). However, shared environment was small and non-significant; we therefore present results from an AE model.

Heritability ranged from 0.31 for irritability to 0.56 for delinquency, shown in the diagonal of Table 3. Genetic correlations (shown in the off diagonals of Table 3 and in figure 1b) ranged from 0.46 (between headstrong/hurtful behaviors and depression) to 0.80 (between headstrong/hurtful behaviors and delinquency). Genetic correlations between headstrong/hurtful behaviors and depression (0.46) were significantly lower than between headstrong/hurtful behaviors and delinquency (0.80). Genetic correlations between irritability and delinquency were significantly lower (0.57) than between irritability and depression (0.70). These results didn't change when using the time 2 data, with the exception that the genetic correlations between irritability and delinquency did not differ significantly from those between irritability and depression (Suppl Table 3).

Next, we explored the extent to which longitudinal genetic associations showed a similar pattern to the phenotypic associations. We first explored whether there was shared genetic variance between headstrong at Time 1 and depression at Time 2, over and above the genetic association already identified between each of these variables and irritability at Time 1. This is akin to testing whether there is a partial genetic correlation between headstrong/hurtful behaviors and depression that accounts for their longitudinal association, independent of associations with irritability. Similarly we tested whether there was any shared genetic variance between irritability at Time 1 and delinquency at Time 2 independent of headstrong/hurtful behaviors at Time 1. To test this we used two separate trivariate Cholesky models. The results are shown in Figures 2a and 2b. Headstrong/hurtful behaviors at Time 1 and depression at Time 2 shared no genetic variance after accounting for irritability at Time 1 (Figure 2a). Similarly, irritability at Time 1 and delinquency at Time 2 shared no genetic variance after accounting for headstrong/hurtful behaviors at Time 1 (Figure 2b). Again these remain unchanged when the 'stubborn' item was omitted from the irritability scale (see Suppl. Figures 1a and b).

We then asked whether the genetic relationship between irritability at Time 1 and depression at Time 2 was explained through shared genetic effects between irritability and depression at Time 1. As shown in Figure 3a, the genetic association between irritability and depression at Time 1 fully accounted for the longitudinal association between irritability at Time 1 and depression at Time 2. Similarly, the relationship between headstrong/hurtful behaviors at Time 1 and delinquency at Time 2 was explained through the genetic association of headstrong/hurtful behaviors and delinquency at Time 1 (Figure 3b).

Discussion

Several new findings emerge from this paper about the phenotypic and genetic correlates of irritability. Heritability of irritability by adolescent self report is relatively low, consistent with previous data in adults²⁹. Phenotypically, irritability was specifically related to subsequent depressive symptoms, whereas the headstrong/hurtful dimension was associated with delinquency. The paper's main hypothesis was that the same pattern of double dissociation would be found in the multivariate genetic analyses, and this was found to be the case. The genetic relationship between headstrong/hurtful behaviors and depression was entirely due to the overlap with the irritable dimension. Conversely, the genetic relationship between irritability and delinquency was entirely due to the overlap with headstrong/hurtful behaviors. Also, the concurrent genetic relationship between irritability and depression at Time 1 accounted for the genetic relationships between irritability at Time 1 and depression at Time 2. The same pattern of results was found for the relationship between headstrong/hurtful behaviors at Time 1 and delinquency at Time 2. In previous longitudinal

analyses^{10-12, 26}, headstrong items have been shown to be differentially strongly related to ADHD and conduct problems, whereas hurtful items were preferential predictors of more aggressive conduct problems and callous and unemotional traits. However, in this paper, headstrong and hurtful emerged as a common factor, in keeping with another recent epidemiologic study¹⁰, possibly reflecting the limited number of items available.

Irritability has traditionally been studied in the context of antisocial behavior in both early life and adult studies^{30, 31}. However, it is debated whether disruptive behaviors form a unitary construct. Consistent with our previous findings^{5, 11, 12}, we show that the relationship between irritability and antisociality may be because of their correlation with headstrong/hurtful behaviors. Our findings support a model whereby irritability is linked with depression, forming part of a nexus of negative mood with common genetic underpinnings. The finding that strong phenotypic links between syndrome constellations or disorders may be explained by genetic, as opposed to environmental, overlap is consistent with prior theory^{13, 14} and empirical data¹⁸.

Our findings have numerous implications. First, they are relevant for understanding developmental transitions. Recent evidence suggests that oppositional behaviors are the most robust early predictors of depression in young adult life⁴, even after adjusting for conduct disorder or early depression. Our findings go a step further by showing that the relationship between oppositional problems and depressive symptoms may be due to the irritability component of oppositionality, rather than to disruptive headstrong and hurtful behaviors. The findings of this study are based on adolescent self report and thus extend previous findings based on parent and teacher report^{5, 11, 12}. In contrast to the present study, in past work we did not find that self reported irritability predicted psychiatric disorders⁵. These different findings might be due to the considerably smaller size of the previous study, differences in length of follow up, and the different instruments used.

Second, our findings may have implications about the aetiology of depression. We found that the relationship between irritability and depression is largely explained by common genes. By contrast, we found only a small overlap in non-shared environmental factors between irritability and depression. It will be important to characterize the shared genetic mechanisms between irritability and depression, which may include affective processing mechanisms.

Third, our findings support clinical notions that irritability is a presenting symptom of depression, and that patients presenting with irritability should be screened carefully for depression^{2, 32-34}. This thinking is reflected in the youth, but not adult, criteria for depression in the DSM-IV. Whether treatments targeting irritability would treat and/or prevent depressive symptoms is a topic for future research.

This study has several limitations. First, there was considerable attrition at follow up. However, while attrition bias poses a problem for estimating prevalences, it is less likely to bias associations between variables³⁵. Second, the study relied on an existing measure out of which the irritability and headstrong/hurtful items were extracted. However, the modest internal consistencies of the scales would reduce the power of detecting differences. Given the double dissociations we found in this study, it seems unlikely that internal consistency has had differential effects on the study's results. Third, our use of age-appropriate versions of the ASEBA scales (ref) at times 1 and 2 meant that one item in the irritability scale was differently worded at the two study sweeps ('stubborn, sullen or irritable' at time 2, 'stubborn' at time 1). Although both versions of this item loaded clearly and consistently on the irritability factor, we repeated all the main analyses excluding this item to ensure that

any potential ambiguity in the simpler (time 1) wording had not biased the findings. All of the key findings remained unchanged.

In summary, our findings provide further evidence that irritable mood may underlie the relationship between oppositionality and depression and suggest that the association between irritability and depression is due to genetic overlap.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Brotman MA, Schmajuk M, Rich BA, Dickstein DP, Guyer AE, Costello EJ, Egger HL, Angold A, Pine DS, Leibenluft E. Prevalence, clinical correlates, and longitudinal course of severe mood dysregulation in children. *Biol Psychiatry*. 2006; 60(9):991. [PubMed: 17056393]
2. Fava M, Hwang I, Rush AJ, Sampson N, Walters EE, Kessler RC. The importance of irritability as a symptom of major depressive disorder: results from the National Comorbidity Survey Replication. *Mol Psychiatry*. Mar 10.2009
3. Pickles A, Aglan A, Collishaw S, Messer J, Rutter M, Maughan B. Predictors of suicidality across the life span: The Isle of Wight study. *Psychol Med*. Nov 26.2009 :1–14. [PubMed: 19335938]
4. Copeland WE, Shanahan L, Costello EJ, Angold A. Childhood and adolescent psychiatric disorders as predictors of young adult disorders. *Arch Gen Psychiatry*. Jul; 2009 66(7):764–772. [PubMed: 19581568]
5. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. *Am J Psychiatry*. Sep; 2009 166(9):1048–1054. [PubMed: 19570932]
6. Kim-Cohen J, Caspi A, Moffitt TE, Harrington H, Milne BJ, Poulton R. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry*. 2003; 60(7):709–717. [PubMed: 12860775]
7. Copeland W, Shanahan L, Costello EJ, Angold A. Configurations of common childhood psychosocial risk factors. *J Child Psychol Psychiatry*. Apr; 2009 50(4):451–459. [PubMed: 19220623]
8. Stringaris A, Maughan B, Goodman R. What's in a Disruptive Disorder: Temperamental Antecedents of Oppositional Defiant Disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2010; 49:474–483. [PubMed: 20431467]
9. Aebi M, Asherson P, Banaschewski T, Buitelaar J, Ebstein R, Eisenberg J, Gill M, Manor I, Miranda A, Oades RD, Rothenberger A, Sergeant J, Sonuga-Barke E, Thompson M, Taylor E, Faraone SV, Steinhausen HC. Predictability of oppositional defiant disorder and symptom dimensions in children and adolescents with ADHD combined type. *Psychol Med*. 2010; 40:2089–2100. [PubMed: 20380783]
10. Rowe R, Costello J, Angold A, Copeland WE, Maughan B. Developmental pathways in Oppositional Defiant Disorder and Conduct Disorder. *Journal of Abnormal Psychology*. 2010 in press.
11. Stringaris A, Goodman R. Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry*. Apr; 2009 48(4):404–412. [PubMed: 19318881]
12. Stringaris A, Goodman R. Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry*. Mar; 2009 50(3):216–223. [PubMed: 19166573]
13. Eley TC. General genes: a new theme in developmental psychopathology. *Current Directions in Psychological Science*. 1997; 6:90–95.
14. Plomin R, Kovas Y. Generalist genes and learning disabilities. *Psychol Bull*. Jul; 2005 131(4):592–617. [PubMed: 16060804]

15. Angold A, Costello EJ. Puberty and depression. *Child Adolesc Psychiatr Clin N Am*. Oct; 2006 15(4):919–937. ix. [PubMed: 16952768]
16. Moffitt TE, Arseneault L, Jaffee SR, Kim-Cohen J, Koenen KC, Odgers CL, Slutske WS, Viding E. Research review: DSM-V conduct disorder: research needs for an evidence base. *J Child Psychol Psychiatry*. Jan; 2008 49(1):3–33. [PubMed: 18181878]
17. Kendler KS, Neale MC, Kessler RC, Heath AC, Eaves LJ. Major depression and generalized anxiety disorder. Same genes, (partly) different environments? *Arch Gen Psychiatry*. Sep; 1992 49(9):716–722. [PubMed: 1514877]
18. Zavos HM, Rijdsdijk FV, Gregory AM, Eley TC. Genetic influences on the cognitive biases associated with anxiety and depression symptoms in adolescents. *J Affect Disord*. Jul; 2010 124(1-2):45–53. [PubMed: 19945751]
19. Angold A, Costello EJ, Messer SC, Pickles A, Winder F, Silver D. The development of the short questionnaire for use in epidemiological studies of depression in children and adolescents. *Int J Methods Psychiatr Res*. 1995; 5:1–12.
20. Costello EJ, Angold A. Scales to assess child and adolescent depression: checklists, screens, and nets. *J Am Acad Child Adolesc Psychiatry*. Nov; 1988 27(6):726–737. [PubMed: 3058677]
21. Costello EJ, Benjamin R, Angold A, Silver D. Mood variability in adolescents: a study of depressed, nondepressed and comorbid patients. *J Affect Disord*. Dec; 1991 23(4):199–212. [PubMed: 1791265]
22. Achenbach, TM. Manual for the YSR and 1991 profile. University of Vermont Department of Psychiatry; Burlington, Vt: 1991.
23. Achenbach, TM.; Rescorla, LA. Manual for the ASEBA Adult Forms and Profiles. An integrated System of Multi-informant Assessment. ASEBA; Burlington, VA: 2003.
24. Rowe R, Maughan B, Eley TC. Links between antisocial behavior and depressed mood: the role of life events and attributional style. *J Abnorm Child Psychol*. 2006; 34(3):293. [PubMed: 16718539]
25. Leibenluft E, Charney DS, Towbin KE, Bhangoo RK, Pine DS. Defining clinical phenotypes of juvenile mania. *Am J Psychiatry*. 2003; 160(3):430. [PubMed: 12611821]
26. Aebi M, Muller UC, Asherson P, Banaschewski T, Buitelaar J, Ebstein R, Eisenberg J, Gill M, Manor I, Miranda A, Oades RD, Roeyers H, Rothenberger A, Sergeant J, Sonuga-Barke E, Thompson M, Taylor E, Faraone SV, Steinhausen HC. Predictability of oppositional defiant disorder and symptom dimensions in children and adolescents with ADHD combined type. *Psychol Med*. Apr 12.2010 :1–12.
27. STATA 10.1 [computer program]. StataCorp; College Station, Texas: 2009. Version
28. Neale, MC. Mx: Statistical Modeling. Version 1.1. Department of Psychiatry; Richmond, VA 23298: 1997. Box 710 MCV
29. Coccaro EF, Bergeman CS, Kavoussi RJ, Seroczynski AD. Heritability of aggression and irritability: a twin study of the Buss-Durkee aggression scales in adult male subjects. *Biol Psychiatry*. Feb 1; 1997 41(3):273–284. [PubMed: 9024950]
30. Achenbach TM, McConaughy SH, Howell CT. Child/adolescent behavioral and emotional problems: implications of cross-informant correlations for situational specificity. *Psychol Bull*. Mar; 1987 101(2):213–232. [PubMed: 3562706]
31. Eley TC, Lichtenstein P, Moffitt TE. A longitudinal behavioral genetic analysis of the etiology of aggressive and nonaggressive antisocial behavior. *Dev Psychopathol*. 2003; 15(2):383–402. Spring. [PubMed: 12931834]
32. Carlson GA, Cantwell DP. Unmasking masked depression in children and adolescents. *Am J Psychiatry*. Apr; 1980 137(4):445–449. [PubMed: 7361930]
33. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression, Part 1: Clinical correlates and response to fluoxetine treatment. *Am J Psychiatry*. Aug; 1993 150(8):1158–1163. [PubMed: 7848377]
34. Ryan ND, Puig-Antich J, Ambrosini P, Rabinovich H, Robinson D, Nelson B, Iyengar S, Twomey J. The clinical picture of major depression in children and adolescents. *Arch Gen Psychiatry*. Oct; 1987 44(10):854–861. [PubMed: 3662742]

35. Wolke D, Waylen A, Samara M, Steer C, Goodman R, Ford T, Lamberts K. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. *British Journal of Psychiatry*. 2009; 195:249–256. [PubMed: 19721116]

CLINICAL DESCRIPTION

A typical presentation of a young person scoring high on **irritability** would be:

Jack is a 15 year-old boy who reports having difficulties controlling his feelings of anger. He describes often feeling annoyed “at everyone and everything” right from the start of the day and mostly for no apparent reason. He has frequent arguments with his girlfriend where he can go “into a right rage” and stay like that for hours after that. He tells you that “it feels weird” to be so angry, but is not sure what to do about it.

A typical presentation of a young person scoring high on **headstrong/hurtful** would be:

Alfie is a 16 year-old boy who openly tells you that he “couldn’t care less” about rules recently laid out for him at school. He describes how he gets antagonistic in his relationships to other young people at school and that he thinks some of them are “plainly stupid” and that he has no problem telling them so. He tells you how he recently splashed water on his sister’s iPod because she “deserved it”.

It should be noted that irritability and headstrong/hurtful should be seen as dimensions, rather than separate diagnostic categories. This has two implications. Firstly, such behaviours shouldn’t necessarily be seen as pathological. Secondly, young people may show behaviors from both dimensions (as indicated by the fact that irritability and headstrong/hurtful are correlated dimensions) and outcomes may depend on the relative mix of intensity of these two dimensions

Figure 1a.
Phenotypic associations (cross-sectional)
Differential phenotypic relationships for irritability and headstrong/hurtful behaviors with depression and delinquency

Figure 1b.
Genetic associations (cross-sectional).
Differential genetic relationships for irritability and headstrong/hurtful behaviors with depression and delinquency

Figure 2a.

Longitudinal Cholesky decomposition with depression as part of the model.

Path coefficients and respective confidence intervals are shown. "A" denotes genetic effects, "E" denotes non-shared environmental effects. $\sqrt{}$ stands for square root.

Figure 2b.

Longitudinal Cholesky decomposition with delinquency as part of the model.

Path coefficients and respective confidence intervals are shown. “A” denotes genetic effects, “E” denotes non-shared environmental effects. $\sqrt{}$ stands for square root.

Figure 3a.

Longitudinal Cholesky decomposition with depression as part of the model (adjusted for depression at Time 1).

Path coefficients and respective confidence intervals are shown. “A” denotes genetic effects, “E” denotes non-shared environmental effects. $\sqrt{}$ stands for square root.

Figure 3b.

Longitudinal Cholesky decomposition with delinquency as part of the model (adjusted for delinquency at Time 1).

Path coefficients and respective confidence intervals are shown. "A" denotes genetic effects, "E" denotes non-shared environmental effects. $\sqrt{}$ stands for square root.

Table 1

Factor loadings for the exploratory factor analysis at times 1 and 2.

	Time 1		Time 2	
	irritability	headstrong/hurtful	irritability	headstrong/hurtful
Argue a lot	0.473	0.514	0.509	0.402
Mean to others	0.313	0.648	0.296	0.651
Destroy things belonging to others	0.163	0.688	0.266	0.689
Tease others a lot	0.262	0.558	0.212	0.580
Have a hot temper	0.709	0.320	0.674	0.330
Mood or feelings change suddenly	0.636	0.133	0.695	0.151
Disobey at school	0.159	0.712	0.229	0.618
Disobey parents [†]	0.283	0.640	-	-
Am stubborn, sullen, or irritable ^{††}	0.573	0.217	0.604	0.313

[†] Note: this item is only available in time 1.

^{††} Note: this item is phrased "am stubborn" in time 1 and "am stubborn, sullen, or irritable" in time 2.

Table 2

Cross-sectional phenotypic correlations.

	N	Irritability	Headstrong/ hurtful	Depressive Ratings Time 1	Delinquency Time 1	Depressive Ratings Time 2	Delinquency Time 2
Irritability	2417	-	.46 (.42 to .49)	.45 (.42 to .48)	.40 (.37 to .44)	.33 (.28 to .37)	.27 (.22 to .31)
Headstrong/ hurtful	2400		-	.36 (.32 to .40)	.61 (.59 to .64)	.20 (.15 to .25)	.44 (.40 to .48)
Depression Ratings Time 1	2445			-	.36 (.32 to .40)	.49 (.45 to .53)	.26 (.21 to .31)
Delinquency Time 1	2427				-	.21 (.16 to .26)	.53 (.49 to .56)
Depression Ratings Time 2						-	.33 (.28 to .37)
Delinquency Time 2							

Table 3

Cross-sectional multivariate genetic model results at time 1.

Cholesky Model	Irritability	Headstrong/hurtful	Depressive Ratings	Delinquency
<i>Genetic Influences</i>				
Irritability	.31 (.23-.39)	.66 (.53-.77)	.70 (.59-.82)	.57 (.45-.69)
Headstrong/hurtful		.45 (.38-.52)	.46 (.36-.57)	.80 (.72-.86)
Depression Ratings			.51 (.45-.57)	.54 (.45-.63)
Delinquency				.56 (.49-.62)
<i>Non-Shared environmental influences</i>				
Irritability	.69 (.61-.77)	.34 (.26-.41)	.29 (.21-.37)	.29 (.21-.37)
Headstrong/hurtful		.55 (.48-.62)	.25 (.17-.33)	.44 (.36-.51)
Depression Ratings			.49 (.43-.55)	.15 (.06-.23)
Delinquency				.44 (.38-.51)

Genetic and environmental influences (adding up to 1) on each variable given in bold on the diagonal of each table section (**AE model**). Genetic and environmental correlations are given above the diagonal.