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Longitudinal Stability of Genetic and Environmental Influences on Irritability: From Childhood to Young Adulthood

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Abstract

Background: Little is known about genetic influences on juvenile irritability and whether such influences are developmentally stable and/or dynamic. This study examined the temporal pattern of genetic and environmental effects on irritability using data from a prospective, four-wave longitudinal twin study.

Methods: Parents and their twin children (n=2490 children) from the Swedish Twin Study of Child and Adolescent Development reported on twin children's irritability, defined using a previously identified scale from the Child Behavior Checklist.

Results: Genetic effects differed across the sexes, with males exhibiting increasing heritability from early childhood through young adulthood. Genetic innovation was prominent in males with new genetic risk factors impacting irritability in early and late adolescence. By contrast, females expressed a strong genetic effect early in development and genetic innovation during adolescence, with attenuation of genetic influences on irritable mood. Shared environment was not a primary influence on irritability for males or females. Unique, non-shared environment suggested strong effects early for males followed by an attenuating influence whereas unique environmental factors were relatively stable for females.

Conclusions: Genetic effects on irritability are developmentally dynamic from middle childhood through young adulthood, with males and females displaying differing patterns. As males age, genetic influences on irritability strengthen coupled with a weakening of non-shared environmental influences. Genetic contributions are quite strong in females early in life, but decline in importance as they age. In girls, non-shared environmental influences are fairly stable throughout development. Clinical and research implications of results are considered.

Introduction

Studies in youth suggest that irritability is a common (~3%; Althoff, Verhulst, Rettew, Hudziak, & van der Ende 2010; Brotman, Schmajuk, Rich, Dickstein, Guyer, Costello, Egger, Angold, Pine & Leibenluft, 2006), stable (Caprara, Paciello, Gerbino, and Cugini 2007; Olweus, 1979), and often impairing (Fava, Hwang, Rush, Sampson et al 2010; Pickles, Aglan, Rutter et al 2010; Brotman, Schmajuk, Rich, Dickstein, Guyer, Costello, Egger, Angold, Pine & Leibenluft, 2006; Pickles Aglan, Collishaw, Messer, Rutter, Maughan 2009) trait. However, research has yet to explore the genetic and environmental contribution to individual differences in irritability. Indeed, few studies have examined the heritability of irritability per se (Coccaro, Bergeman, Kavoussi, Seroczynski 1997), with most work being done in the context of other traits (e.g., aggression), or related psychiatric disorders (Derks, Dolan, Hudziak, Neale, Boomsma 2007; Hudziak, Derks, Althoff, Copeland, Boomsma 2005; Hudziak, Althoff, Derks, Faraone, Boomsma 2005; Derks, Hudziak, van Beijsterveldt, Dolan, Boomsma 2004; Burt & Klump 2013; Eley, Lichtenstein, Stevenson 1999; Seroczynski, Bergeman, Coccaro 1999; Deater-Deckard & Plomin 1999). These limited available data suggest that irritability is moderately heritable, with estimates of approximately 0.3 (Coccaro, Bergeman, Kavoussi, Seroczynski 1997; Stringaris, Zavos, Leibenluft) and a range from 0.22 to 0.51 (Maughan, Eley 2012; Seroczynski, Bergeman, Coccaro 1999).

Research on pediatric psychopathology, including anxiety, depression, and attention deficit hyperactivity disorder, demonstrates that these clinical phenotypes are developmentally complex, characterized by both continuity and genetic innovation (Kendler, Gardner, Annas, Neale, Eaves, Lichtenstein 2008; Kendler, Gardner, Lichtenstein 2008). This may also be true of irritability, a stable, heritable trait (Caprara, Paciello, Gerbino, and Cugini 2007; Olweus, 1979), which has shown to have both genetic and environmental influences (Seroczynski, Bergeman, Coccaro 1999). Whereas genetic continuity indicates developmental stability in genetic risk factors over time, genetic innovation suggests that new genes, previously without

effect at one developmental age, become influential during subsequent periods (Kendler Gardner, Lichtenstein 2008; Change et al 2013). Research has yet to examine the relative contribution of genetic influences on irritability across the lifespan. Understanding evolving genetic risk factors for irritability has profound research, clinical, and treatment implications.

In this study, we examined irritability in a population-based cohort of Swedish twins assessed four times between age 8 and 20 years using a developmental model which permits us to assess both genetic stability and genetic innovation. We measured irritability using the Achenbach System of Empirically Based Assessment (Achenbach 1991a; Achenbach 1991b; Achenbach 2003) (Lichtenstein, Tuvblad, Larsson, Carlstrom 2007). Our primary goal was to discriminate between two trajectories that might describe the developmental course of genetic risk factors for irritability. A 'developmentally stable' pattern would predict a single set of genetic risk factors that impact on irritability throughout development, while, a 'developmentally dynamic' pattern would suggest that genetic innovation occurs and genetic effects on irritability vary over time. A second goal is to examine environmental effects on irritability to determine whether such influences are stable or dynamic across development.

Our period of observation included puberty, a developmental transition of special interest because genetic mechanisms may come online during fluctuations in gonadal hormones at this time. Indeed, hormonal fluctuations may impact the neural mechanisms mediating irritability (Killgore et al. 2001; Steiner et al. 2003; Toufexis et al. 2006; Walf & Frye, 2006; Koshibu & Levitt, 2008). While extensive research has shown sex differences in the prevalence (Leibenluft 2011; Leibenluft, Cohen, Gorrindo, Brook, Pine 2006; Brotman, Schmajuk, Rich, Dickstein, Guyer, Costello, Egger, Angold, Pine & Leibenluft, 2006) and manifestations (Martin, Neighbors, Griffith 2013; Crick 1995; Bongers, Koot, van der Ende, Verhulst 2004) of irritability, research has yet to examine sex differences in genetic influences on irritability. Thus, our secondary goal was to examine potential sex differences on the developmental trajectory. [maybe mention looking at role of environment – do you expect stable individual env effects? Do you expect c2

to be present and its importance to decline? This seems a bit “too” genetic focused as developmental twin studies can be quite informative about environmental influences].

Method

Participants

Data analyzed in this study are from the Swedish Twin Study of Child and Adolescent Development (TCHAD). All twin pairs born in Sweden between May 1985 and December 1986, where both twins were alive and residing in Sweden in 1994, were contacted for study participation (Lichtenstein et al. 2007). Data from 2719 twin individuals were available, although zygosity was not known for some twin pairs or only one member of the pair participated. This resulted in 1310 pairs (2,620 individuals) for the current twin analyses. Of these pairs, there were 267 female-female monozygotic (MZ) pairs, 199 female-female dizygotic (DZ) pairs, 254 male MZ pairs, 182 male DZ pairs, and 408 opposite-sex (OS) DZ pairs.

Twins were assessed at four waves via a mailed questionnaire. Twin ages at the time of the assessments included 8–9 years (Wave1 [W1], parent report only; n=1109 or 75% response rate), 13–14 years (Wave2 [W2] parent report, n=1063 or 73% response rate; child report, n=2263 or 78% response rate), 16–17 years (Wave3 [W3] parent report, n=1067 or 74% response rate; child report, n=2369 or 82% response rate), and 19–20 years (Wave4 [W4] parent report, n=619 or 78% response rate; child report, n=1705 or 59% response rate). The Ethics Committee of the Karolinska Institute, Stockholm, Sweden, approved questionnaires. Zygosity was determined using well-validated questions to twins and parents chosen from a discriminant analysis of 106 pairs where zygosity was determined using DNA markers (Lichtenstein et al. 2007).

Measures

Parent report of twin irritability was obtained using items from the Child Behavior Checklist (CBCL; Achenbach, 1991a) when the twins were ages 8 to 21 years. Twins completed the Youth Self-Report CBCL (Achenbach, 1991b) at ages 13-14 and 16–17, and the Adult

Behavior Checklist at ages 19–20 (Achenbach & Rescorla, 2003). All items were scored on a three-point scale where 0=not true, 1=somewhat or sometimes true, and 2=very true or often true.

Derivation of the irritability dimension

The irritability dimension analyzed here, identified previously by Stringaris et al. (Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012), was derived from the CBCL oppositionality items using exploratory factor analysis. Exploratory, rather than confirmatory, methods were preferred because there is only one previous study of the CBCL irritability factor structure. These analyses yielded two factors: Headstrong/Hurtful and Irritability, with eigen values ≥ 1 (Aebi et al, 2010; Rowe, Costello, Angold, Copeland, Maughan, et al., 2010, Stringaris & Goodman, 2009a,b). The irritability items identified previously include: 1. stubborn, sullen or irritable, 2. Sudden changes in mood, and 3. temper tantrums or hot temper. [maybe give the items – were there only three?]

First, we determined whether we could replicate this factor structure for each wave and each informant. To do this, we conducted seven separate exploratory factor analyses using the CBCL Oppositionality items (see Table 1 isnt this supplement table 1?). These analyses indicated that all three irritability items loaded strongly on the Irritability factor for parent (range .61-.91) and child self-report (range .52-.88) on the Irritability factor (see Supplement Table 1a). We then created an Irritability score by summing the three irritability items to create an Irritability score at each wave for each informant. This repeated measure, multi-informant Irritability score served as the primary variable in biometric twin models. Irritability scores were standardized given the complexity of the model. EFA analyses were performed in Mplus (Muthen & Muthen, 2007), using the weighted least squares mean variance estimator, while biometric twin models were conducted in Mx (Neale et al. 2003).

Data analysis

A Cholesky Decomposition was used to address questions regarding the magnitude of genetic and environmental influences on longitudinal measurement of irritability. Twin models, such as the Cholesky Decomposition, allow for the determination of the degree of similarity/dissimilarity between monozygotic (sharing 100% of their genes) and dizygotic twins (sharing on average 50% of their genes, by descent). Multiple measures of irritability may be correlated because they share common genes and/or common environmental influences. Twin data allow for the partitioning of the covariation between measures into genetic and environmental components. Specifically, Cholesky Decomposition allows for the disaggregation of the covariance into additive genetic (A), common (shared) environmental (C), and unique or non-shared environmental (E) components.

The longitudinal Cholesky Decomposition is presented in Figure 1 (for simplicity, only additive genetic effects (A) are illustrated). The model contains four major elements. First, the model includes four latent Irritability scores (T1–T4), which reflect the ‘true’ level of Irritability at W1 (ages 8–9), W2 (ages 13–14), W3 (ages 16–17) and W4 (ages 19–20). These latent variables are indexed by ratings of Irritability made by parent (P) and self-report (S) by twins. Both reporters provided ratings at W2–W4, with only parental report available at W1. The paths λ_P and λ_S reflect the degree to which the parent- and self-reported Irritability Scores index the latent level of irritability. Next, the genetic and environmental influences on the latent levels of irritability at W1–W4 are modeled using a Cholesky Decomposition. This approach divides genetic risk into four factors (F1–F4), with the first (F1) beginning in childhood (ages 8–9) and potentially remaining active over the entire developmental period. The strength of this factor at each age is reflected in the path coefficients f_{11} , f_{12} , f_{13} and f_{14} . The second factor (F2) begins in early adolescence (ages 13–14) and influences irritability assessed at W2–W4 via paths f_{22} , f_{23} and f_{24} . The third factor onsets in late adolescence (ages 16–17) and effects W3–4 via paths f_{33} and f_{34} . The fourth and final factor impacts only at W4 when twins are in young adulthood (ages 19–20) via path f_{44} . The ‘developmentally stable’ (Kendler et al., 2008)

hypothesis predicts that genetic liability to irritability originates solely in the first factor with no significant subsequent genetic innovation. By contrast, the ‘developmentally dynamic’ (Kendler et al., 2008) hypothesis predicts both genetic innovation (new genetic variation impacting on irritability emerging later in development) and genetic attenuation (declining impact over time of the genetic factors acting early in development).

The model also includes two reporter-specific common factors, one for parent (F_p) and one for twin self-report (F_s), as well as rater- and time-specific residuals. The reporter-specific common factors allow the model to estimate genetic and environmental influences on ratings that are unique to the parents or to the child.

Our analyses focused on the latent measures of irritability (i.e., upper portion of Figure 1) reported by parents and children, separately, (T1–T4) because these measures are likely to be most valid, reflecting both the subjective and objective manifestations of irritability. Reporter-specific factors (F_p , F_s) are part of the model (i.e., lower portion of Figure 1) and are briefly reviewed herein.

Estimates of heritability and shared environmental effects obtained in this model are not comparable to those obtained from standard twin models because in standard twin models, errors of measurement contribute to individual-specific environment effects, thereby reducing estimates of heritability and shared environment. Our use of multiple raters permits us to distinguish true individual-specific environment effects, which impact on the latent Irritability scores (T1–T4), from measurement error, which contributes to the rater-specific effects (P1–P4 and S2–S4).

Qualitative and quantitative sex effects on Irritability scores also were examined. Qualitative sex effects, which arise when genetic factors influencing a trait are not identical in males and females, are measured by the genetic correlation, r_g , which can vary from zero (i.e., entirely distinct sets of genes in the two sexes) to unity (i.e., identical genetic factors impacting on males and females). Quantitative sex effects arise when the same genetic factors impact in

males and females but to different degrees. These were identified estimating all path coefficients separately by sex.

When interpreting common (shared) and unique (non-shared) environment, an important point to remember is that of the objective and effective environment (Turkheimer and Waldron 2000; Goldsmith 1993). Objective environments “refer to environmental events as they might be observed by a researcher, as opposed to how they affect family members” whereas effective environments “are defined by the outcomes they produce” (Turkheimer and Waldron, 2000, p.79). The common (shared) environment reflects the effective environment (i.e., the effect of the environment). Turkheimer and Waldron (2000) cite the example of divorce where both twins reared together would be objectively exposed to the divorce of their parents, but this event may not affect the two individuals in the same way. Estimates of common (shared) and unique (non-shared) environment capture effective shared and unshared environment, respectively, rather than the objective conditions that produced the outcomes.

Irritability scores were fairly normally distributed and were treated as a continuous trait. To evaluate the fit of our entire model, we used the Akaike Information Criterion (AIC; Akaike, 1974). The lower the AIC value, the better the balance of explanatory power and parsimony.

Results

Descriptive Results

Table 1 lists the mean (\pm standard error [SE]) of the raw Irritability scores by sex, age and reporter. Higher Irritability scores were observed for females versus males by both parent and self-report except at age 8-9. Moreover, twins generally self-reported higher levels of irritability compared to parent report. After W2, irritability symptoms generally decreased with age in females and males by both parent and self-report. Table 1A (available in online Appendix) contains Pearson correlations between self-report and parent report of Irritability scores within and across time. Parent report was moderately correlated over time (range $r=.32-.49$), with the correlations declining in a monotonic fashion across waves. This same pattern was observed for

twin self-report (range $r=.31-.45$). Parent and twin report of twin irritability demonstrated significant, albeit weak, levels of association (range $r=.19-.20$). Confused – the table shows a twin-parent correlation of .32, .36 and .23 at waves 2, 3 and 4??

Twin-twin correlations are presented in Table 2. Stronger associations were found for Irritability Scores between MZ twins compared to DZ twins. Parent rated Irritability Scores for same and opposite-sex twins were similar in strength whereas twin self-report of irritability is slightly higher in same-sex DZ twins relative to opposite- sex DZ twins. No evidence of dominance was observed (that is MZ correlations much greater than twice the DZ correlation). Therefore, an ACE model (additive genetics [A], common (shared) environment [C], and unique (non-shared) environment [E]) was fit to the data.

Longitudinal Cholesky Decomposition

The longitudinal Cholesky Decomposition, where repeated measures of Irritability Scores were modeled, suggested that the best AIC value was obtained for a model with quantitative, but not qualitative, sex effects (see Table 3). Thus, models were fitted separately for males and females. You also need to say that ACE model fitted best.

Males. In males, genetic factors play a strong role in influencing irritability, as indexed by both self and parent ratings. Overall, both genetic innovation and stability were observed, with these two processes culminating in a substantial increase in heritability of irritability over development. For males, heritability at each sequential wave was estimated at 36% ($.60^2$), 68% ($.55^2+.61^2$), 76% ($.47^2+.62^2+.39^2+$), and 89% ($.69^2+.11^2+.63^2+-.01^2$).

Consistent with the “developmentally stable” hypothesis, genetic factors that first appeared pre-pubertally continued to influence irritability significantly throughout adolescence and into young adulthood (see Figure 2 [upper]). Indeed, stable genetic influences on irritability constituted a majority of the total genetic effect after age 8 to 9 years. Specifically, the genetic factor measured during childhood (F_1) accounted for significant genetic variance in childhood ($f_{11}=36\%$), early adolescence ($f_{12}=30\%$), late adolescence ($f_{13}=22\%$), and young adulthood

($f_{14}=48\%$). Genetic effects emerging during early adolescence also explained significant genetic variation in late adolescence ($f_{23}=38\%$) and there were generic contributions associated with late adolescence on young adult life irritability ($f_{34}=40\%$). However, evidence of genetic innovation was also found, with new genetic influences becoming active during early adolescence ($f_{22}=37\%$) and, to a modest degree, late adolescence ($f_{22}=15\%$). There were no new genetic effects activated after late adolescence.

Unlike genetic factors, shared environmental influences on irritability were very small, accounting for only 1-5% of variance in liability across waves. Shared environment effects were observed in the reporter-specific portion of the model, where parent report yielded stronger shared-environment effects than twin self-report. By contrast, non-shared environmental factors demonstrated a robust influence early in development, followed by considerable attenuation, accounting for 58%, 30%, 24%, and ultimately 10% of the variance in irritability. Innovation also was noted, with a new set of unique environmental factors emerging during early adolescence ($f_{22}=29\%$).

Examination of reporter-specific estimates (i.e., lower portion of Figure 1 you mean supplemental figure 1?) for the parent and child report indicate that the λ_p (parent) path was somewhat higher than the λ_s (child self-report) path, suggesting that parental ratings were a better index of irritability than twin self-report. More consistent reporter specific genetic factors were seen for self-ratings than for parent ratings.

Females. Although females exhibited robust genetic liability for irritability earlier in development, temporal attenuation occurred such that total heritability estimates declined from childhood into young adult life i.e., 66%, 64%, 56%, to 46%. Genetic stability was found, with genetic effects assessed during childhood (F_1) and earlier adolescence (F_2) predicting significant genetic variance through adolescence into young adulthood (i.e., $f_{12}=38\%$ $f_{13}=29\%$

$f_{14}=24%$; $f_{23}=27%$, $f_{24}=22%$, respectively). These genetic processes are illustrated in Figure 2 (lower).

Similar to males, shared environmental influences on irritability were nearly absent, with the exception of shared environmental influences measured during early adolescence, which explained a significant portion of the shared environment effect during young adulthood ($f_{24}=18%$). Reporter-specific effects for shared environment also were found, with parents reporting stronger common, shared environment effects compared to twin self-report. By contrast, at each sequential wave, unique environmental factors accounted for 35%, 34%, 35%, and 28% of the variance in irritability as reported by both parent and child, demonstrating temporal stability.

Unique environmental influences measured at ages 13-14 contributed modestly to environment effects on irritable mood at ages 16-17 ($f_{23}=13%$). Similarly, unique environmental factors at ages 16-17 contributed to irritable mood during young adult life ($f_{34}=22%$), suggesting stability of unique environmental exposures during late adolescence on irritable mood assessed in young adulthood. Moreover, new unique environmental influences emerged during early and late adolescence ($f_{22}=31%$ and $f_{33}=22%$, respectively).

The λ_p path was somewhat higher than the λ_S path, again suggesting that parental ratings were a better index of irritability than female self-report. Parameter estimates for the parent- and self-report factors for irritability are seen in Table 3. More consistent reporter specific genetic factors were found for self-ratings compared with parent ratings.

Discussion

Our primary aim was to clarify the developmental nature of genetic and environmental risk factors for irritability. To do this, we examined data from a general population twin sample where both parent and child reported on irritability from childhood through the adolescent years where important pubertal changes occur into young adulthood. Quantitative sex differences for irritability were found, indicating that the *magnitude* of genetic and environmental effects differed

in males and females. Our results provided clear support for both stable and dynamic genetic effects in males, where genetic influences expressed early in childhood were stable into young adulthood and new genetic influences emerged during adolescence. The total of these stable and new genetic influences culminated in a consistent increase in of heritability of irritability for males over development. A different pattern of additive genetic influences was observed for females. Specially, females exhibited a very robust genetic effect early in development that diminished over time. Although total heritability decreased over time, significant new genetic influences came online during early adolescence, and these emergent genetic effects continued to exert influence through adolescence into young adult life. Thus, irritability was associated with strong genetic effects in both males and females, although the precise patterns of these effects differed by sex.

We also examined common (shared) and unique (non-shared) environmental contributions to the longitudinal course of irritability. Common environment did not contribute appreciably to the expression of irritability in males or females, suggesting that familial environmental factors that affect twins similarly are not critical in the pathogenesis of irritable mood. Stronger effects were observed for unique environmental influences (i.e., environmental factors that cause twins to be dissimilar) on irritable mood. Males and females both exhibited a strong unique environmental contribution to irritable mood early in childhood, but this effect attenuated substantially from childhood into early adolescence. This suggests that the environmental effects that impact irritability early in life ceased to influence irritability from adolescence into young adulthood. New environmental influences also were detected during early adolescence for both sexes, but this effect also weakened substantially over time. For females, an innovative environmental contribution to irritability emerged during late adolescence and remained stable into young adulthood. Thus, neither unique environmental exposures occurring during early childhood or those that emerged during adolescence impacted on

irritability in adulthood; however, unique environmental influences emerging during late adolescence did have lasting impact on irritability expression during the young adult years.

The inclusion of parent and child self-report in one model is a strength of looking at latent irritability indexed by two raters – reduce rater specific effect then that parental reports index latent liability better – why might that be? See below

Irritability is a transdiagnostic dimensional construct that lends itself well to exploration with multiple methods across numerous levels of analysis in human and model organisms. For this reason, studies of irritability are consistent with the Research Domain Criteria (RDoC) approach, and a scientific focus on irritable mood is likely to generate tractable and clinically relevant critical questions about the etiology, pathophysiology, and development of mood disorders and other psychiatric conditions. To date, longitudinal data indicates that chronic irritability predicts increased risk for major depression, dysthymia, and generalized anxiety disorder in young adulthood (Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006). Since irritability manifests early in life, it would be important to elucidate critical developmental periods during which chronic irritability segues into an internalizing disorder, and how genetic and environmental factors contribute to this shift. Pubertal development also likely plays a primary role in the transition from irritability to internalizing disorder, particularly for depression given its robust association with pubertal stage (Angold et al., 1998). Another developmentally relevant observation was that no new genetic or environmental effects emerged in young adulthood for males or females. This finding reinforces the importance of early identification and delivery of empirically supported interventions for children with impairing irritable mood.

This study relied on items of the CBCL items to generate a previously identified irritability construct measure. Although high factor loadings were observed in this study and a previous one (Stringaris, et al., 2012), construct validation of this phenotypic measure is lacking. Moreover, our outcomes pertain to the irritability phenotype as defined by the CBCL; additional research into the genetic and environmental contributions to juvenile irritable mood using other

measures (e.g., Affective Reactivity Index, Stringaris et al.) is needed. Also, this study did not include a child report of irritability at ages 8-9 and, therefore, we relied on parent report only. However, parental ratings appeared to be better indices of latent levels of irritable mood than twin self-ratings, this finding may reflect better insight of parents regarding their child's irritability levels.

Irritability is common, impairing, and presents in the context of a number of psychiatric conditions. Given its transdiagnostic nature, a better understanding of the genetic and environmental contributions to its expression could inform the extant literature and promote development of psychological and pharmacological therapeutics. In all, genes appear to impart robust and dynamic effects on irritability throughout development while the environment is a strong force primarily during childhood. These effects are worthy foci of future research inquiry.

Note

Additional tables and figures accompany this paper on the Journal's website.

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References

Rowe R, Costello EJ, Angold A, Copeland WE, Maughan B: Developmental pathways in oppositional defiant disorder and conduct disorder. *J Abnorm Psychol* 2010; 119:726–738

Stringaris A, Goodman R: Longitudinal outcome of youth oppositionality: irritable, headstrong, and hurtful behaviors have distinctive predictions. *J Am Acad Child Adolesc Psychiatry* 2009; 48:404–412

Stringaris A, Goodman R: Three dimensions of oppositionality in youth. *J Child Psychol Psychiatry* 2009; 50:216–223

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* 2010; 40:2089–2100.

Leibenluft E, Cohen P, Gorrindo T, Brook JS, Pine DS. Chronic versus episodic irritability in youth: A community-based, longitudinal study of clinical and diagnostic associations. *J Child Adolesc Psychopharmacol* 2006;16:456-466.

Table 1. Mean (\pm SE) for Irritability Scores by Sex, Informant, and Age.

	Males		Females	
Wave 1, Age 8-9	Mean	S.E.	Mean	S.E
Parent Report	1.07	0.04	1.04	0.04
Wave 2, Age 13-14				
Parent Report	3.86	0.04	4.09	0.04
Offspring Self-Report	4.72	0.05	5.13	0.05
Wave 3, Age 16-17				
Parent Report	3.77	0.04	4.04	0.04
Offspring Self-Report	4.43	0.04	5.08	0.05
Wave 4, 19-20				
Parent Report	3.49	0.05	3.82	0.05
Offspring Self-Report	3.80	0.04	4.55	0.05

Table 2. Irritability Score Correlations Between Twins By Zygosity.

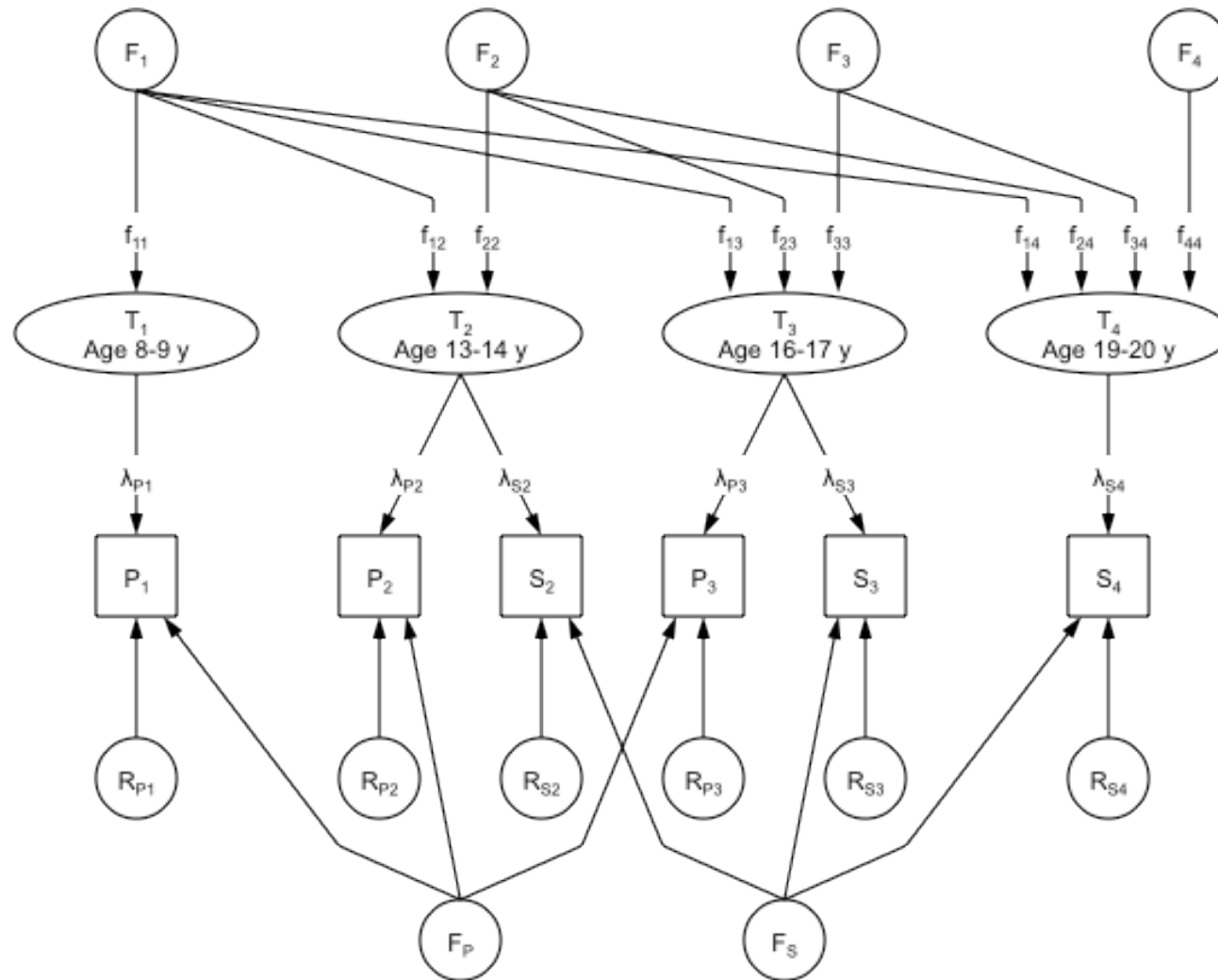
	Female-Female MZ	Female-Female DZ	Male-Male MZ	Male-Male DZ	Male-Female DZ
W1, Parent	0.77	0.30	0.55	0.29	0.39
W2, Parent	0.80	0.49	0.64	0.44	0.45
W3, Parent	0.69	0.54	0.80	0.44	0.49
W4, Parent	0.63	0.48	0.62	0.39	0.31
W2, Self-report	0.40	0.18	0.49	0.24	-0.06
W3, Self-report	0.44	0.16	0.48	0.12	0.02
W4, Self-report	0.41	0.05	0.33	-0.11	0.23

Table 3. ACE Model Fit Statistics and Parameter Estimates for Latent Irritability by Males and Females (upper table). Parameter estimates for males and females (lower table).

Variables	Qual / Quan	Rg	-2LL	DF	AIC	$\Delta(-2LL)$	ΔDF	ΔAIC
ACE	+ / +	1.00	34488.964	13419	7650.964	-	-	-
ACE – need to note this is best fit model	- / +		34488.919	13420	7648.919	-0.045	1	-2.045
ACE	+ / -	0.64	34611.159	13473	7665.159	122.195	54	14.195
ACE	- / -		34617.768	13474	7669.768	128.804	55	18.804
AE	- / +		34503.228	13420	7663.228	14.264	1	12.264
CE	- / +		34641.908	13420	7801.908	152.944	1	150.944
Parameters Estimates								
Males	Genetic	Total a^2 (%)	1	2	3	4		
		36	.60					
		68	.55	.61				
		76	.47	.62	.39			
		89	.69	-.11	.63	-.01		
	Shared Envir.	Total c^2 (%)						
		5	-.23					
		3	.00	-.18				
		1	-.10	.02	.00			
		2	.15	.00	.00	-.01		
	Non-Shared Envir.	Total e^2 (%)						
		59	.77					
		30	.10	.54				
		24	.20	.39	.21			
		10	.10	.28	-.06	-.01		
Females	Genetic	Total a^2 (%)	1	2	3	4		
		66	.81					
		64	.62	.51				
		56	.54	.52	.05			
		46	.49	.47	.0	.0		
	Shared Envir.	Total c^2 (%)						
		0	.07					
		1	-.10	.01				
		9	.27	-.11	.0			
		26	.27	.43	.0	.03		
	Non-Shared Envir.	Total e^2 (%)						
		35	.59					
		34	.17	.56				
		35	-.04	.36	.47			
		28	.13	.21	.47	-.01		

Notes: Qual=Qualitative; Quan=Quantitative; For qualitative effect, “+” indicates that R_g is estimated and equals the genetic correlation between opposite sex twins. For qualitative effect, “-” indicates that R_g is fixed at 1.0. For quantitative effect, “+” indicates that separate path estimates are computed for males and females. For quantitative effect, “-” indicates that the path estimates are held equal for males and females.

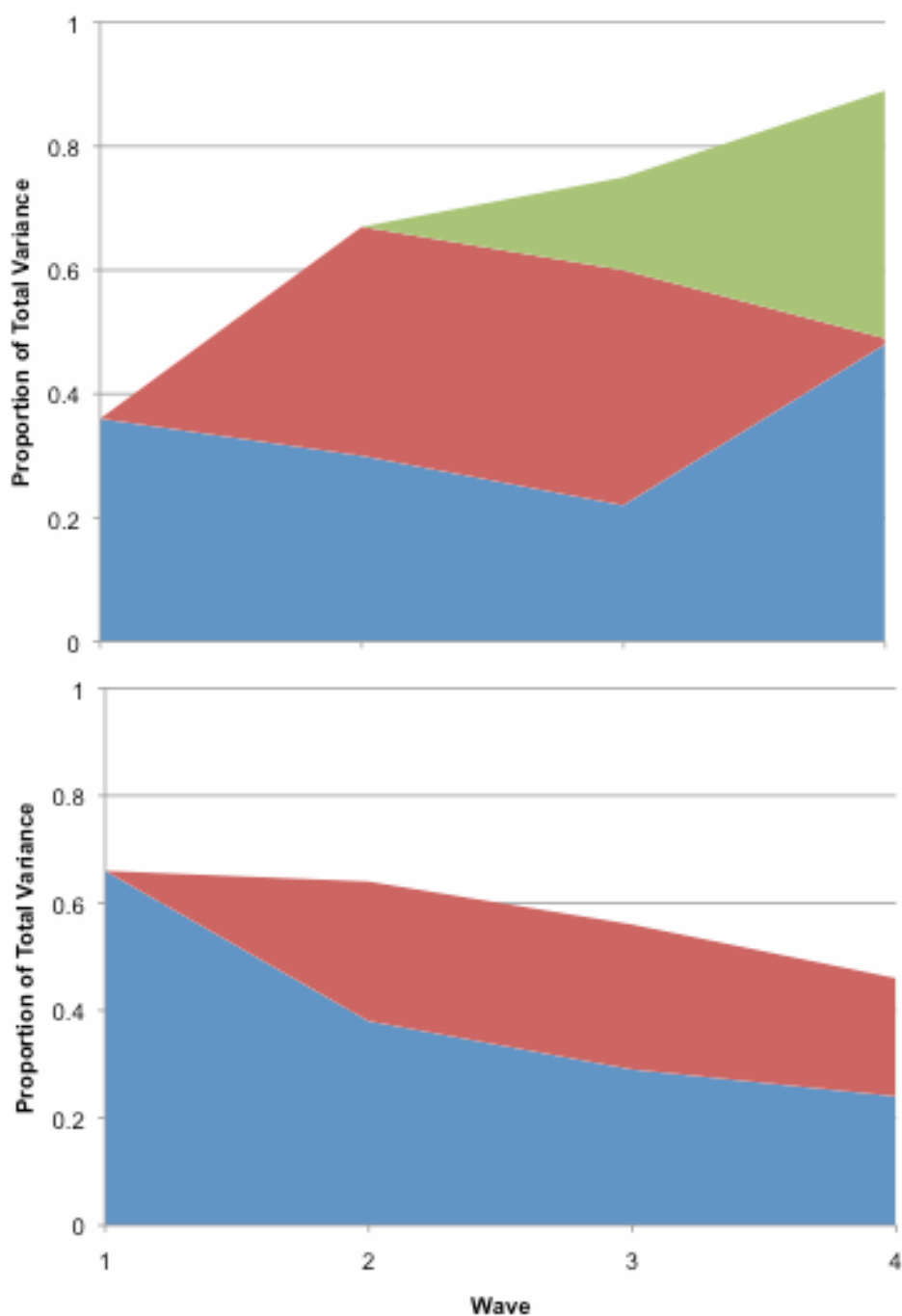
Figure 1. Longitudinal Cholesky Decomposition



The longitudinal Cholesky Decomposition with reference to additive genetic effects. Common (shared) and unique (non-shared) environmental factors are not modeled for simplicity. The model contains 4 latent irritability scores (T_1 - T_4) reflecting irritability at Wave

1 (age 8-9 years), Wave 2 (age 13-14 years), Wave 3 (age 16-17 years), and Wave 4 (age 19-20years). These latent variables are indexed by ratings of irritability by parent report (P) (available for Waves 1-4) and by self-report (S) (available for Waves 2-4). The degree to which the parent- and self-reported irritability ratings index the latent irritability level is reflected by the paths λ_P and λ_S . See text for details. F indicates the four genetic risk factors; f, the path from the genetic factors to the latent irritability scores at each of the four waves; R, residual effects.

Figure 2. The proportion of total variance in irritability accounted for by genetic factors through development. The y-axis represents the total phenotypic variance so the sum of all genetic factors equals total heritability. The upper figure reflects the proportion of total variance for males, which shows an increasing trend in heritability whereas the lower figure represents females, who demonstrate a declining trend in heritability. Blue represents the first genetic factor, starting at age 8-9 years. Red represents the second genetic factor starting at age 13-14 years. Green (for males only) represents the third genetic factor, starting at age 16-17 years.



Supplemental Table1a. Loadings of the Exploratory Factor Analysis of CBCL Oppositionality Items Yielding the Irritability and Headstrong/Hurtful Factors. Items Were Assessed Across Waves 1-4 by Parent and Child Report.

CBCL Content Item	Wave1-Parent		Wave2-Parent		Wave3-Parent		Wave4-Parent	
	Headstrong /hurtful	Irritability	Headstrong /hurtful	Irritability	Headstrong /hurtful	Irritability	Headstrong /hurtful	Irritability
	Factor1	Factor2	Factor1	Factor2	Factor1	Factor2	Factor1	Factor2
Argues a lot	0.48	0.30	0.52	0.31	0.32	0.52	0.72	-0.05
Cruelty, bullying, or meanness to others	0.71	0.14	0.50	0.33	0.24	0.58	0.57	0.59
Destroys things belonging to his/her family or others	0.68	0.14	0.68	0.06	0.48	0.33	0.59	0.06
Disobedient at home	0.87	-0.01	0.92	-0.02	0.96	0.03	----	----
Disobedient at school	0.83	-0.09	0.71	0.00	0.88	-0.05	----	----
Teases a lot	0.51	0.19	0.41	0.23	0.22	0.41	0.05	0.34
Stubborn, sullen or irritable	0.26	0.61	0.27	0.61	0.16	0.71	0.14	0.73
Sudden changes in mood	-0.01	0.87	-0.03	0.90	-0.13	0.95	-0.11	0.90
Temper tantrums or hot temper	0.21	0.68	0.03	0.84	0.00	0.87	-0.11	0.91

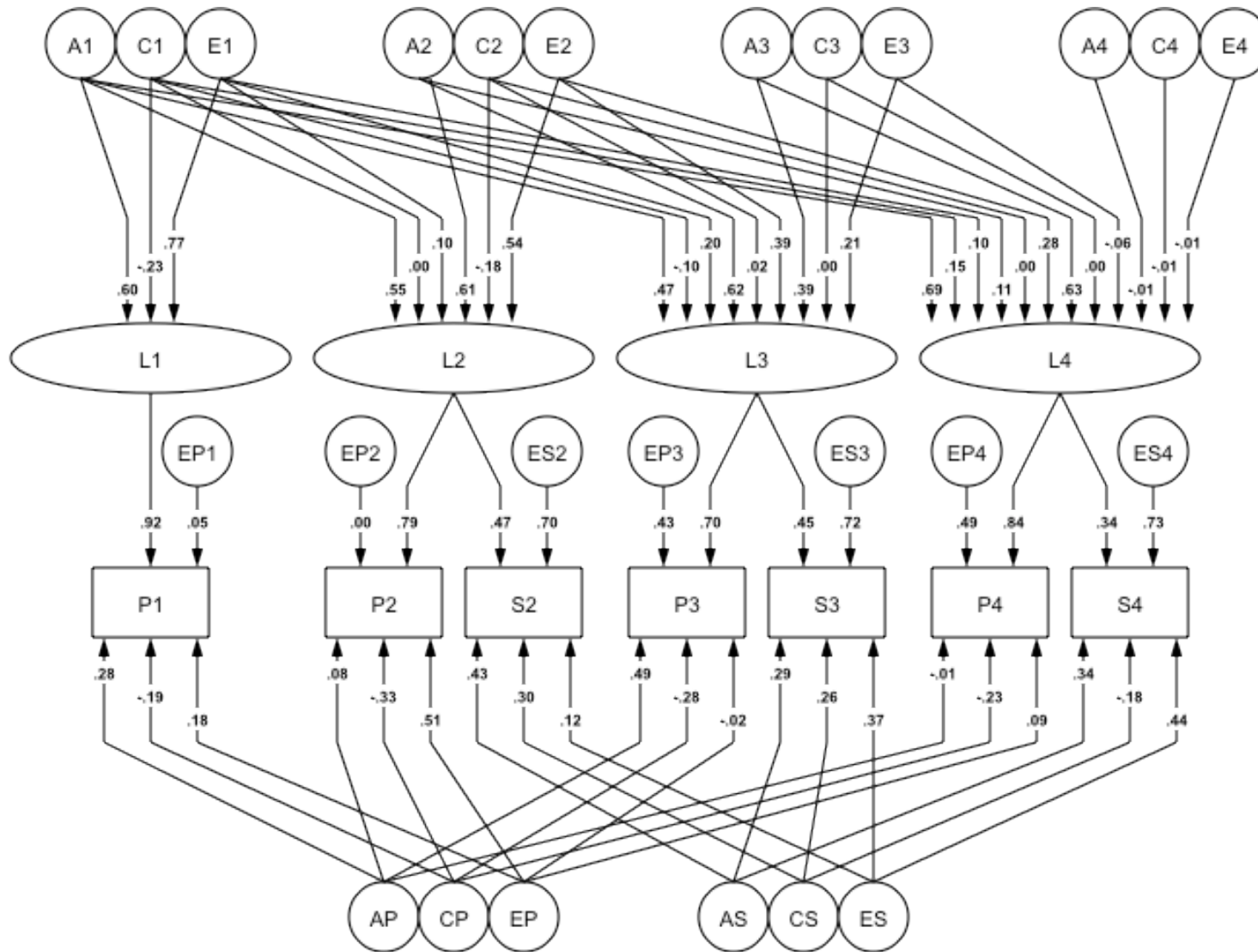
CBCL Content Item	Wave2-Child		Wave3-Child		Wav4-Child	
	Headstrong /hurtful	Irritability	Headstrong/hurtful	Irritability	Headstrong/hurtful	Irritability
	Factor1	Factor2	Factor1	Factor2	Factor1	Factor2
Argues a lot	0.03	0.18	0.12	0.14	0.31	-0.05
Cruelty, bullying, or meanness to others	0.43	0.32	0.41	0.29	0.70	0.02
Destroys things belonging to his/her family or others	0.45	0.11	0.61	0.03	0.64	-0.03
Disobedient at home	0.72	0.05	0.79	-0.01	----	----
Disobedient at school	0.90	-0.04	0.84	0.00	----	----
Teases a lot	0.31	0.33	0.28	0.26	0.66	0.03
Stubborn, sullen or irritable	0.00	0.52	0.15	0.42	0.22	0.61
Sudden changes in mood	0.07	0.81	0.009	0.76	-0.02	0.84
Temper tantrums or hot temper	0.01	0.79	-0.01	0.88	0.26	0.65

Supplemental Table 2. Pearson Correlations Between and Within Parent Report and Self-Report of Irritability Across Waves 1 to Wave 4.

	W1 (8-9) Parent	W2 (12-13) Parent	W3 (16-17) Parent	W4 (19-20) Parent	W2 (12-13) Self-report	W3 (16-17) Self-report	W4 (19-20) Self-report
W1, Parent	-----	.49	.46	.32	.20	.19	.19
W2, Parent		-----	.59	.46	.32	.31	.23
W3, Parent			-----	.48	.25	.36	.23
W4, Parent				-----	.13	.28	.23
W2, Self-report					-----	.44	.31
W3, Self-report						-----	.45

All correlations are significant at $p < 0.01$.

Supplemental Figure 1a. Parameter Estimates for the Best-Fit Model for Irritability (Males).



Supplemental Figure 1b. Parameter Estimates for the Best-Fit Model for Irritability (Females).

