



Published in final edited form as:

Am J Psychiatry. 2015 July ; 172(7): 630–637. doi:10.1176/appi.ajp.2015.14070818.

The intergenerational transmission of anxiety: a children-of-twins study

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Abstract

Objective.—The transmission of anxiety within families is well-recognised, but the underlying processes are poorly understood. Twin studies of adolescent anxiety demonstrate both genetic and environmental influence, and multiple aspects of parenting are associated with offspring anxiety. To date, the Children-of-Twins design has not been used to evaluate the relative contributions of genetic versus direct transmission of anxiety from parents to their offspring.

Method.—Anxiety and neuroticism measures were completed by 385 monozygotic and 486 dizygotic same-sex twin families (37% male twin pair families) from the Twin and Offspring Study in Sweden (TOSS). Structural equation models tested for the presence of both genetic and environmental transmission from one generation to the next.

Results.—For both anxiety and neuroticism the models provide support for significant direct environmental transmission from parents to their adolescent offspring. In contrast there was no evidence of significant genetic transmission.

Conclusions.—The association between parental and offspring anxiety largely arises due to a direct association between parents and their children independent of genetic confounds. The lack of genetic transmission may reflect there being different genetic effects on these traits in adolescence and adulthood. Direct environmental transmission is in line with developmental theories of anxiety suggesting that children and adolescents learn anxious behaviours from their parents via a number of pathways such as modelling. Future analyses should combine children-of-twins data with child twin data in order to examine whether this direct effect solely represents parental influences on the offspring or whether it also includes child/adolescent anxiety evoking parental anxiety.

Anxiety disorders are the most common group of disorders, with a life-time prevalence of about 30% (1). They are associated with a wide array of personal, financial and societal costs (2) making research into their aetiology a priority. A notable feature of anxiety disorders is that they start early in life, with a mean age at onset of 11 years (1). It is therefore crucial to understand the development of anxiety symptoms in young people.

One of the most robust features of anxiety disorders is that they run in families (3). This association has been widely explored and there is evidence for a number of contributing

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mechanisms. First, children and adolescents can develop symptoms of anxiety by vicarious learning, whereby offspring watching anxious behaviour in their parent then model these behaviours themselves (4). Second, anxious mothers may have a more anxious parenting style including holding more negative expectations, and showing greater intrusiveness, overprotection and expressed anxiety (5, 6), though it should be noted that most studies that find this association focussed on families where the child also had an anxiety disorder, or heightened anxiety symptoms. Third, as well as the parent influencing their offspring, there is evidence for the reverse effect. Specifically, parents of offspring with anxiety disorders show higher levels of parental overprotection, rejection, and lower levels of emotional warmth (7, 8). However, these studies do not take into account another possibility, whereby genes that affect parent anxiety and child/adolescent anxiety also influence parenting, thus leading to a confounding of genetic and environmental influences.

Twin studies consistently reveal modest to moderate genetic influences on a wide range of child and adolescent anxiety measures including trait anxiety (9), disorder-related symptoms assessed by self-report (10) and parent-report (11), and anxiety disorders (12, 13). Similarly, studies in adults reveal modest to moderate genetic influence on trait anxiety (14), anxiety symptoms (15) and disorders (16). This suggests that the transmission of anxiety phenotypes from parents to their children could be explained, at least partially, by genetic influences. Of note, there is considerable genetic over-lap across symptoms reflecting different anxiety diagnoses (such as separation anxiety, social anxiety and general anxiety) in child (17, 18), adolescent (10), and adult (10, 19) samples. Furthermore, epidemiological studies find evidence for substantial heterotypic continuity within the anxiety disorders (i.e. continuity of anxiety over time does not sit within diagnostic boundaries (20)). Thus a child who presents with separation anxiety may develop generalized anxiety in adolescence and panic disorder in adulthood. This heterotypic continuity, combined with the genetic over-lap found between different types of anxiety measures suggests that for examination of transmission of anxiety one should use a broad measure of anxiety symptomatology reflecting general vulnerability to anxiety disorders.

In addition to providing evidence for genetic influences, twin studies also provide support for a significant role of the shared environment (21), non-genetic influences that contribute to family members resembling one another, and the non-shared environment, that which leads to differences amongst family members. The contribution of shared environment to variation in anxiety is consistent with the evidence described above for the importance of family environment in the development of anxiety in children. For example, siblings may show similar levels of anxiety because they were both exposed to the same level of parental expressed anxiety. In sum, there is evidence to support a role for both genetic and environmental influences on anxiety in adults and in children and adolescents, but to date, no study has explicitly tested the relative contribution of genetic and environmental influences to the transmission of anxiety within families. This is important because we might target interventions for pediatric anxiety differently if intergenerational transmission is largely due to genes versus resulting from the family wide environment.

Although pediatric twin studies are able to ascertain the proportion of variance in child/adolescent phenotypes due to genetic and environmental influences, they cannot specify the

extent to which genes and the environment contribute to transmission from parents to their children. For this, other genetically sensitive designs are needed. The Children-of-Twins is one such design, and involves adult twin pairs and their offspring (22). By comparing correlations between children and their parent and contrasting this with correlations between children and their parent's identical co-twin, we can learn about the influence of living with one's parent over and above simply receiving 50% of their genes. Furthermore, by comparing the extent to which correlations between children and their twin uncle/aunt (avuncular correlations) differ for monozygotic and dizygotic twin families, we can infer the extent to which genetic and environmental factors influence transmission from one generation to another. Children share a greater level of genetic influence with their uncle/aunt when in monozygotic families than when in dizygotic families (see Figure 1). Thus if children resemble their uncle/aunt to a greater extent in monozygotic than dizygotic families this implies a genetic influence on transmission of the trait of interest. In contrast, if these two sets of correlations are similar, and are significantly lower than the parent-child correlations, this is indicative of an environmental mode of transmission. Whilst transmission of both depression and internalizing symptoms within families has been found to be due to environmental transmission independent of genetic effects (23–25), the transmission of anxiety-related traits within families has yet to be explored using the Children-of-Twins design.

In the present study we used the Children-of-Twins design to examine the relative contribution of genetic and environmental influences to transmission of broadly assessed anxiety from one generation to another. For this analysis we use a measure of anxious personality in parents, and a measure of anxiety symptoms in the offspring. For simplicity, from herein we use the word “anxiety” alone when referring to the transmission of parental anxious personality to offspring anxiety symptoms whilst specifying all other types of anxiety as applicable. As a comparison we also repeated analyses for Neuroticism, given that this personality trait shows strong phenotypic and genetic correlations with anxiety (26).

Method

Participants

Data were drawn from the Twin and Offspring Study of Sweden (TOSS) and comprised information on 387 monozygotic twin families and 489 dizygotic twin families. A twin family comprised a twin pair, each twin's spouse and one of each of their adolescent children. Only same-sex twin pairs were used and twin offspring were selected so that cousins were the same sex as one another and did not differ in age by more than 4 years. 37% of twin pairs were male and 52% of offspring were male. At the time of data collection the mean age of offspring in the TOSS sample was 15.7 years ($SD=2.4$; range 11-22). The mean age of twins in the sample was 44.8 years ($SD=4.9$; range 32-60), and for spouses the mean age was 45.5 ($SD=5.4$; range=25-65). After complete description of the study to the subjects, written informed consent was obtained. Further information on the TOSS sample is given elsewhere (27).

Measures

Parental Anxious Personality was self-reported by twins using 20 items from the Karolinska Scales of Personality (28, 29). Items were oriented towards either social (“I often feel uncertain when I meet people I don’t know very well”), or physical (“sometimes my heart beats hard or irregularly for no particular reason”) aspects of anxiety, in addition to general worry (“I often worry about little things which others see as unimportant”). Respondents used a likert scale ranging from 0 (not at all) to 3 (very) true. Item scores were summed to give an overall anxiety rating. Cronbach’s alpha was .90.

Offspring Anxiety Symptoms were measured using items from the Child Behaviour Checklist (30). Twins, their spouses and offspring all reported on offspring behaviour over the previous 6 months. A previous study aimed at developing DSM-oriented scales from Child Behaviour Checklist items (31) was used to guide the selection of items included in our anxiety scale, and as with the parental anxiety symptoms, the focus was on items that reflect social (“clings to adults or too dependent”) and physical (“I’m nervous, high strung or tense”) aspects of anxiety as well as general worry (“I worry quite a lot”; for a full list of items see SI). Items were scored on a scale ranging from 0 (not) to 2 (very/often) true. Items from all three reporters (which correlated from .25-.45) were summed to create an overall anxiety score, to provide the broadest and most objective measure possible. Cronbach’s alpha was .73.

Neuroticism was self-reported for both twins and offspring using the neuroticism scale of the Eysenck Personality Inventory (32). The scale comprised 9 yes/no items such as “are you often worried without knowing why?”, scored 1/0 for yes/no. Item scores were summed to give an overall neuroticism rating. Cronbach’s alpha was .72/.67 for parents/offspring.

Analyses

Analyses on anxiety include 385 monozygotic twin families and 486 dizygotic twin families. However, the neuroticism measure was only included in the second cohort of the study, resulting in a reduced sample comprising 222 monozygotic families and 293 dizygotic families for the neuroticism analyses.

Genetic analyses were conducted in the structural equation modelling programme OpenMx (33). Prior to analyses residuals were taken to control for twin sex and age as is standard practise in twin analyses (34). All variables were log transformed to correct for skew. We fitted structural equation models to the data using maximum likelihood estimation. Models allowed us to quantify the effects of additive genetic (A), common environmental (C; non-genetic effects that make members of a nuclear family similar to one another) and non-shared environmental effects (E; environmental effects that make members of a family different to one another) on parental anxiety. By comparing the magnitude of monozygotic twin correlations (attributable to the combined effects of A+C) to dizygotic twins (attributable to (.5*A) + C), genetic and environmental influences can be estimated. Comparing monozygotic and dizygotic avuncular correlations and parent-child correlations allows for the estimation of genetic and non-genetic intergenerational pathways. Comparing correlations between cousins from monozygotic families with those of dizygotic families

allows for the estimation of the role of familial and non-shared environmental effects on offspring anxiety.

The model used is shown in Figures 2 and 3. Of note, the path from parent-phenotype to offspring phenotype reflects the direct influence of a parent's behaviour on their offspring. As this is manifested through the environment, we describe it as "environmental" transmission, but it should be noted that this pathway also reflects gene-environment correlation if there is genetic influence on the parent phenotype. Second, as in all Children-of-Twins models, there is no shared environment factor for the offspring part of the model, as this would result in there being too many paths for the data available. The significance of the environmental (from parent to offspring phenotype) and genetic (from A1' to offspring phenotype) intergenerational pathways were tested by creating sub-models in which they were fixed to zero. Both χ^2 difference tests and Akaike's Information Criterion (AIC) were used to assess whether sub-models were a significantly worse fit to the data than the full model. All analyses were repeated controlling for assortative mating but results were substantively similar (see supplementary information).

Results

The correlation between the anxiety measures and neuroticism was .70 for parents and .42 for offspring. Table 1 provides the correlations between twin parents and their offspring for both anxiety measures and neuroticism. Several findings from this table are worth noting. First, there is evidence for genetic effects on both anxious personality and neuroticism in the parents, as indicated by the larger monozygotic than dizygotic correlations (e.g. .51 versus .17 respectively for anxiety). Second, there is evidence for genetic influence on offspring anxiety symptoms and neuroticism given the larger correlations for cousins from monozygotic as compared to dizygotic families (e.g. .17 versus .08 respectively for anxiety). Third, there is marginal evidence for genetic effects on transmission of anxiety given the larger avuncular correlations (offspring 1-parent2 and vice versa) for monozygotic as compared to dizygotic families (.11 versus .02 respectively). However, these values are both small, and for neuroticism, this pattern is not seen (.03 versus .07 for monozygotic and dizygotic families respectively). Over-all, these data do not suggest substantial genetic transmission of broadly assessed anxiety or neuroticism. Finally, there is modest evidence for environmental transmission of both anxiety and neuroticism given the larger parent-offspring than avuncular correlations in both monozygotic and dizygotic families. For example, in monozygotic families, whilst the avuncular correlation for anxiety is .11, the parent-offspring correlation is .20.

Table 2 provides the fit indices from the model-fitting analyses for twin parents and their offspring for both anxiety and neuroticism. Note that the power to detect genetic effects in the child part of the model is low, given that the genetic resemblance between cousins from monozygotic versus dizygotic families is .25 versus .125. In both cases, the model restricted to environmental transmission only, from which the genetic transmission path has been removed (model 3) provides a good fit to the data indicating that genetic transmission is not a significant contributor to overall model fit. In contrast, for both anxiety and neuroticism, the genetic transmission only model, in which the environmental transmission path has

been dropped, provides a significantly poorer fit to the data providing support for the environmental transmission pathway. However, given the complexity of these models, we provide the results for the full model rather than the most parsimonious model in Figures 2 and 3. Examination of the confidence intervals for the environmental transmission and genetic transmission paths for both anxiety and neuroticism reveals that the confidence interval for the environmental transmission pathway, going from parent to offspring, do not include zero. In contrast, in both cases, the genetic transmission path (from A1' to offspring phenotype) do include zero.

Discussion

This is the first paper to examine the transmission of anxiety using a children-of-twin design. These analyses provide support for the direct, environmental mediated transmission of anxiety from parents to their adolescent offspring over and above any genetic confounding of this association. Of note, the analyses do not provide support for genetic transmission being a significant influence, given the assumptions of our model that the same genetic factors influence both adolescent and adult anxiety. These two findings will be discussed in turn.

There are three potential interpretations of the environmental influence on the association between parent and offspring anxiety. The first is that parental anxiety itself results in a rearing environment that is conducive to the development of anxiety in young people. This could operate through a number of mechanisms. One is vicarious learning (4), whereby the young person learns to be fearful of certain environmental stimuli by observing the presence of that fear in their parent(s). For example, if an adolescent witnesses repeated examples of parental anxiety in response to ambiguous or only mildly threatening behaviour they will learn that the world is an unsafe place. Such learning can also take place through hearing explanations or interpretations of ambiguous or mildly negative experiences that emphasise the threat content of that experience, reflecting anxiety-related information processing on the part of the parent (35, 36). In both these instances, whilst there may be a genetic influence on the parent's expressed anxiety (as seen in the models here), the way in which the anxiety is transmitted is through a direct environmental pathway between the behaviour of the parent and their offspring. The second interpretation of this environmental pathway is that it reflects anxious parents engaging in negative parenting behaviours that promote anxiety in their offspring. However, although anxious parents have been shown to be more likely to display over-controlling behaviour (37) (5), and to be more negative and critical of their offspring (5), this is most commonly found in the context of the child/adolescent displaying high anxiety. This leads to the third interpretation, that anxiety in the offspring influences the parenting they receive. This is compatible with findings that parents of anxious children/adolescents display parenting behaviours that exacerbate the anxiety symptoms (8, 37). Of note, one study of anxious children found that associations between negative parenting behaviours and child expressed anxiety during a task were far stronger for mothers who were also anxious as compared to mothers who were not (5). This suggests that there are likely to be effects in both directions. Whatever the mechanism, the present study is the first to demonstrate that the association between parent and child anxiety persists after accounting for genetic confounding.

The lack of evidence for genetic transmission of anxiety within families may at first appear surprising given the heritability estimates found for both anxiety and neuroticism. Of note, however, it is consistent with other findings on internalizing problems, that similarly find evidence only for environmental transmission (23–25, 38). There are at least three possible explanations for this apparent lack of genetic transmission for anxiety-related phenotypes within families. The first relates to the assumptions of our model, that the same genes influence both adult and adolescent anxiety. At present, the twin literature is inconclusive on this issue. Two studies, one of mixed anxiety/depression (39) the other of anxious cognitions (40), both across adolescence and into young adulthood, identified considerable continuity of genetic factors. In contrast, two studies of mixed anxiety/depression (41) and fears (42) from adolescence into young adulthood found only modest stability with considerable genetic innovation. Thus it remains unclear the extent to which the same genes affect both adolescent and adult anxiety-related phenotypes. Given this, it is plausible that whilst parental anxiety is genetically influenced, these genes are different from those relevant to the development of adolescent anxiety. Testing this hypothesis would require Children-of-Twins data in which we had measures from *adolescence* on the adult parent twins. At present no such dataset exists although the number of longitudinal child twin studies where the children are entering young adulthood is encouraging from this perspective (43, 44). Second, it is also possible that the heritability estimate for anxiety phenotypes obtained from child/adolescent twin studies includes interactions between genetic factors and the shared environment. Such interactions would in a traditional twin design be included in the heritability estimate (45), but in the Children-of-Twins design we use this would not be the case because the effects of the shared environment cannot be estimated in the offspring generation. Given that shared environment is found to be significant more often in child anxiety phenotypes than in other types of psychopathology this is another plausible explanation. Third, it is possible that measurement error reduced the paths between the generations thus reducing our ability to detect genetic transmission. However, the study used relatively standard questionnaire measures for which there is at least adequate reliability.

This study has a number of notable strengths. It is the first Children-of-Twins analysis of transmission of anxiety from parents to their adolescent offspring. It uses a relatively large dataset which provides good statistical power. Finally, we provide an internal replication by considering neuroticism in addition to anxiety. There are however a number of limitations. First, whilst the study was fairly large, one always achieves greater power with larger samples. In Table 1, we see a modest difference between the avuncular correlations for anxiety from monozygotic versus dizygotic families (.11 and .02 respectively), which suggest modest genetic influence, that may have proved significant with a larger sample. For neuroticism there was no indication of genetic transmission even in the correlational data. Second, although these findings provide support for direct transmission, the use of cross-sectional data means that they do not indicate the direction of effect. Finally, it is possible that parents with higher levels of anxiety would over-report anxiety in their offspring resulting in a bias in parent-offspring correlations at the upper end of the distribution. However, mean levels of anxiety do not differ across our monozygotic versus dizygotic families, so any bias associated with higher anxiety should not impact on our estimates of genetic and environmental influences or on the direct transmission pathway.

In sum, the association between parental and offspring anxiety remains after accounting for genetic transmission. These results are consistent with a direct, environmentally mediated effect of parent anxiety on offspring anxiety, or could reflect anxious adolescents eliciting anxiety in their parent. Longitudinal analyses using an extended children-of-twins design will be useful in exploring these questions further.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Preparation of this manuscript was supported by the Leverhulme Trust (RPG-210). The Twin and Offspring Study in Sweden was supported by Grant R01MH54610 from the National Institute of Mental Health.

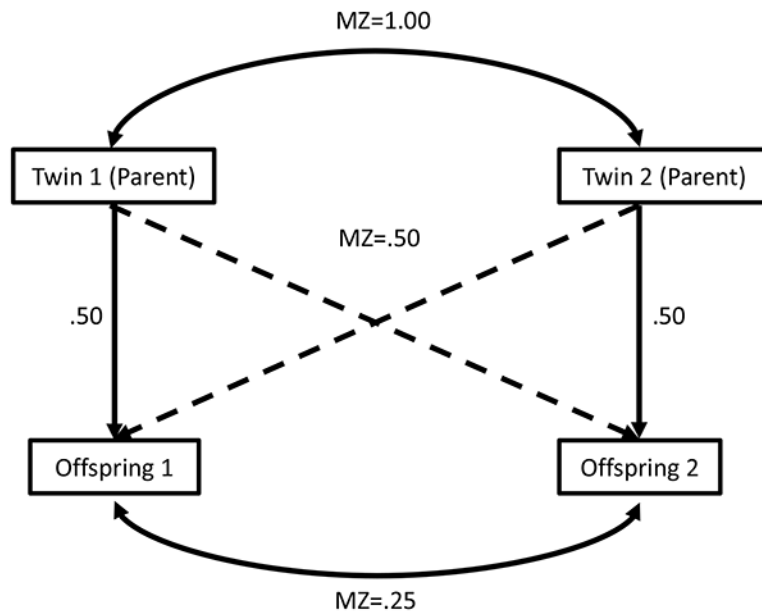
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Section a



Section b

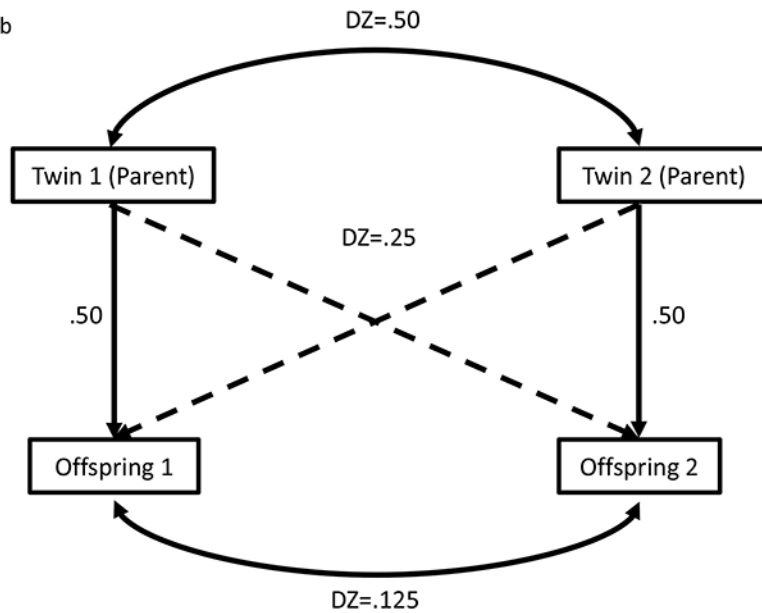


Figure 1. Genetic correlations between family members in the Children of Twins study design for both monozygotic (MZ, section a) and dizygotic (DZ, section b) families. Note. Twin parents share 50% of their genes with their own children. They also share 100% or 50% of their genes with their co-twin depending on whether they are monozygotic or dizygotic twins. Finally, twins share either 50% or 25% of their genes with their niece/nephew.

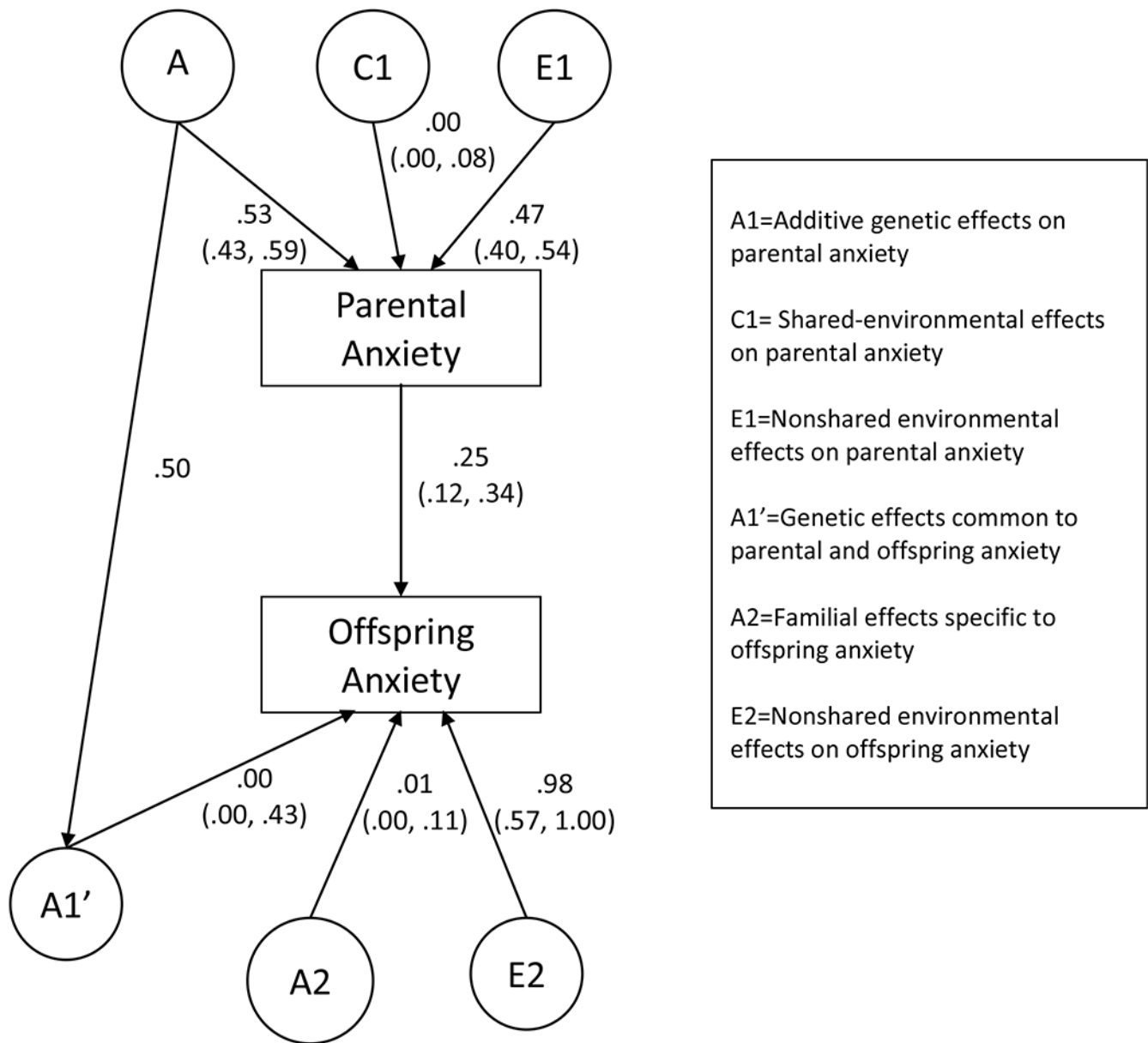


Figure 2. Results from full unconstrained model for anxiety. Note that the pathway between A1 and A1' is fixed to .50 because parents and offspring share 50% of their genome.

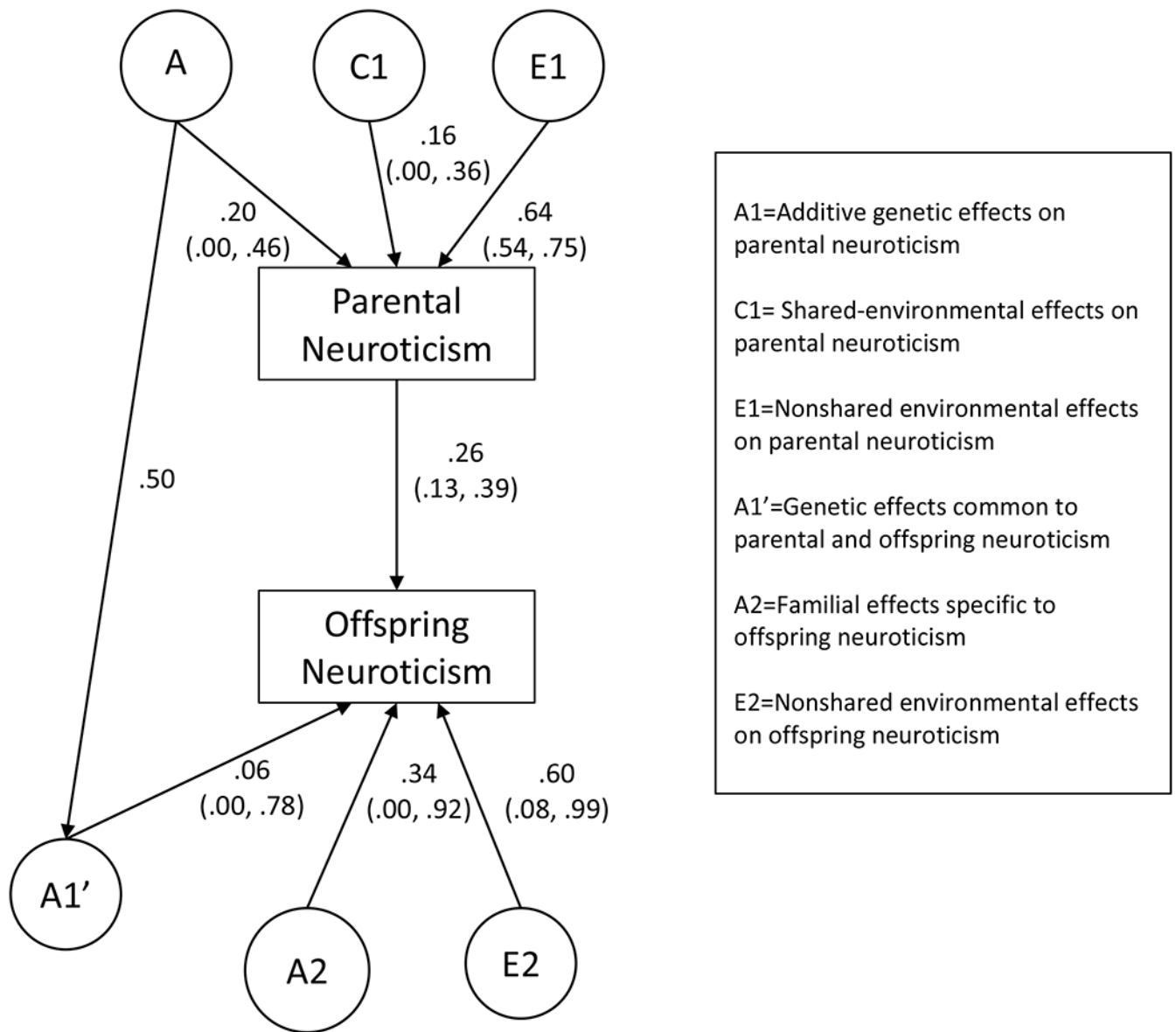


Figure 3. Results from full unconstrained model for neuroticism. Note that the pathway between A1 and A1' is fixed to .50 because parents and offspring share 50% of their genome.

Table 1.

Correlations between twin parents and their offspring for anxiety and neuroticism (95% confidence intervals).

	Monozygotic twin families			Dizygotic twin families		
	Twin Parent 1	Twin Parent 2	Offspring 1	Twin Parent 1	Twin Parent 2	Offspring 1
<u>Anxiety</u>						
Twin Parent 2	.55 (.48, .61)			.20 (.11, .28)		
Offspring 1	.20 (.16, .25)	.11 (.04, .18)		.20 (.16, .25)	.02 (-.05, .08)	
Offspring 2	.11 (.04, .18)	.20 (.16, .25)	.08 (-.03, .19)	.02 (-.05, .08)	.20 (.16, .25)	-.03 (-.12, .05)
<u>Neuroticism</u>						
Twin Parent 2	.36 (.25, .46)			.26 (.15, .36)		
Offspring 1	.21 (.15, .27)	.03 (-.06, .12)		.21 (.15, .27)	.07 (-.02, .15)	
Offspring 2	.03 (-.06, .12)	.21 (.15, .27)	.16	.07 (-.02, .15)	.21 (.15, .27)	.03 (-.09, .15)

Note. Parent-child correlations constrained to be equal across zygosity types.

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Table 2.

Fit indices from model-fitting for twin parents and their offspring on anxiety and neuroticism

Model	-2LL	AIC	df	χ^2	<i>P</i>
<u>Anxiety</u>					
1. Saturated	9582.91	2704.91	3439		
2. Full model*	9610.65	2694.65	3458	27.74 (19)	.09
3. Direct Transmission Only	9611.16	2693.16	3459	0.51 (1)	.47
4. Genetic Transmission Only	9625.15	2707.15	3459	14.5 (1)	<.001
<u>Neuroticism</u>					
1. Saturated	5717.71	1649.71	2034		
2. Full model*	5741.33	1635.33	2053	23.62 (19)	.21
3. Direct Transmission Only	5742.06	1634.06	2054	0.73 (1)	.39
4. Genetic Transmission Only	5756.44	1648.44	2054	15.12 (1)	<.001

Note.

* The most parsimonious model. The overall model fit is assessed by -2LL, which is minus twice the log likelihood. AIC is the Akaike Information Criterion, another measure of fit. The chi-square (χ^2) for model 2 each time is the difference in minus twice the log likelihood (-2LL) between the full genetic and the phenotypic saturated model. In contrast, the chi-square for models 3 and 4 is the difference in -2LL between each model and the full genetic model (model 2).