

Running Head: Longitudinal genetic analysis of anxiety sensitivity

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Abstract

Background. Anxiety sensitivity is associated with both anxiety and depression and has been shown to be heritable. Little, however, is known about the role of genetic influence on continuity and change of symptoms over time. Our aim was to examine the stability of anxiety sensitivity during adolescence. By using a genetically sensitive design we were also able to investigate the extent to which genetic and environmental factors influence anxiety sensitivity over time. Method. Self-reports of anxiety sensitivity were obtained for over 1300 twin and sibling pairs at 3 time points. Data were analysed using multivariate genetic models. Results. Anxiety sensitivity was moderately heritable at all time points with substantial non-shared environmental contributions. Time 1 genetic factors accounted for continuity of symptoms at times 2 and 3. New genetic factors at time 2 also influenced time 3 symptoms. New non-shared environmental influences emerged at each time point. Analysis of a latent factor of trait anxiety sensitivity revealed some stable non-shared environmental influences. Conclusions. Genetic effects were generally stable over time with new genetic influences emerging in late adolescence. Environmental influences on anxiety sensitivity were, on the whole more time specific, however, some stable environmental influences were also found.

Keywords: Anxiety sensitivity, anxiety, depression, panic, cognitive biases, twins

## Introduction

Anxiety sensitivity refers to sensitivity to the physical and emotional symptoms of anxiety and the belief that these are harmful (Reiss, Peterson, Gursky and McNally, 1986). Originally proposed to explain variation in panic, anxiety sensitivity has been shown to have incremental validity above and beyond measures of trait anxiety, which reflect a tendency to respond with state anxiety in the anticipation of threatening situations, in the prediction of fear and panic (for example, McNally, 1994; Taylor, 1996). Anxiety sensitivity is now widely regarded as a vulnerability factor in the development of anxiety disorders more generally as well as playing a role in depression (Muris, Schmidt, Merckelbach and Schouten, 2001; Pollock, Carter, Avenevoli, Dierker, Chazan-Cohen and Merikangas, 2002; Weems, Hammond-Laurence, Silverman and Ginsburg, 1998). Given the accumulating evidence of a role for anxiety sensitivity in psychopathology, it is important to understand its developmental phenomenology.

Associations between anxiety sensitivity and panic were initially investigated with biological challenges, such as the CO<sub>2</sub> challenge (for review see McNally, 1994). In these challenges, participant's physiological state is manipulated to provoke feelings of panic. Individuals reporting high anxiety sensitivity are more likely to report fear and shortness of breath in comparison to individuals with low anxiety sensitivity in such experiments (Schmidt and Mallott, 2006). Studies taking a longitudinal approach have demonstrated that anxiety sensitivity is predictive of panic and anxiety in both clinical and non-clinical samples (Benítez, Shea, Raffa, Rende, Dyck, Ramsawh, Edelen and Keller, 2009; Plehn and Peterson, 2002; Schmidt, Keough, Mitchell, Reynolds, MacPherson, Zvolensky and Lejuez, 2010; Schmidt, Lerew and Jackson, 1997). One

such study, reported a 3-year follow up of college students who were classified as high or low for levels of anxiety sensitivity (Maller and Reiss, 1992). Those with high levels of anxiety sensitivity were found to be five times more likely to have a DSM-III-R anxiety diagnosis than those with low levels of anxiety sensitivity three years later. It has been suggested that anxiety sensitivity influences anxiety as awareness of anxiety symptoms leads to increased anxiety related to detrimental consequences. This in turn heightens the anxiety symptoms themselves which contributes to an increasing cycle of escalating anxiety (Barlow, Chorpita and Turovsky, 1996).

There are two main theories of the development of anxiety sensitivity, one proposes a trait-like explanation (Reiss and Haverkamp, 1996) the other, however, emphasises the importance of learning processes (Schmidt, Lerew and Joiner, 2000). In order to improve our understanding of the etiology of anxiety sensitivity a developmental approach is required as these different theories suggest different developmental trajectories. For example, in a trait model of anxiety sensitivity, an individual's anxiety sensitivity would be expected to remain relatively stable over time whether high or low. If, however, sensitivity to anxiety is largely learned, changes in the level of anxiety sensitivity over time may occur through cognitive, operant or respondent conditioning. It should be noted that these models are not necessarily mutually exclusive.

One avenue through which learning processes could contribute to the development of anxiety sensitivity is by the occurrence of environmental events. Stressful events (particularly those which are uncontrollable and unpredictable) may, for example, play a role in shaping beliefs about the consequences of anxiety symptoms. Support for this hypothesis comes from a longitudinal study of adults in which high

levels of stress (in the form of basic combat training for military recruits) were related to increases in anxiety sensitivity over a five week period (Schmidt et al., 2000). This effect was also replicated in adolescence, with stressful life events found to be longitudinally associated with increases in anxiety sensitivity (McLaughlin and Hatzenbuehler, 2009). Events related to health and family discord were found to be differentially predictive (McLaughlin and Hatzenbuehler, 2009). This research emphasises the importance of learning processes in the development and maintenance of anxiety sensitivity. However, previous research in adult samples has also shown that anxiety sensitivity is relatively stable over time (e.g. Peterson & Plehn, 1999; Weems, Hayward, Killen and Taylor, 2002) supporting a trait approach to the concept. Another study investigated factors important to the development of sensitivity among adolescents. Through cluster analysis, two groups with stable levels of anxiety sensitivity were identified (both low and high), as well as a small group of individuals whose levels escalated in the 4 year period. This study seems to suggest that both trait (shown by the stable high and low groups) as well as learning processes (shown by the increasing group) may be involved in the development of anxiety sensitivity.

More recently, interest has moved to considering whether anxiety sensitivity is heritable. The first twin study of anxiety sensitivity used a large population-based sample of adults and produced a heritability estimate of around 50% (Stein, Jang and Livesley, 1999), with the remaining variance due to non-shared environment (non-shared environmental influences are those that work so as to make individuals within a family differ). Studies with younger samples estimated heritability to account for 37% of the

variance in childhood (Eley, Gregory, Clark and Ehlers, 2007) and 47% of the variance in adolescence (Zavos, Rijdsdijk, Gregory and Eley, 2010).

Although studies have shown that anxiety sensitivity is heritable, no study has investigated the genetic and environmental structure of anxiety sensitivity over time. By using a genetically informative design it is possible to examine whether developmental continuity or change is due to genetic or environmental influences. This is an important empirical question as it can help us to understand the etiology of anxiety sensitivity and potentially be better placed to reduce symptoms. For example, if environmental influences explain why levels of anxiety sensitivity change over time, this would suggest that research should focus on specifying these environmental influences in order to be in a stronger position to develop techniques to reduce levels of anxiety sensitivity.

Generally, studies looking at the developmental pattern of genetic and environmental effects in child emotional development have found evidence of genetic continuity whilst environmental influences tend to be more specific to developmental periods accounting for change rather than stability of symptoms (e.g. Eaves and Silberg, 2008; Kendler, Gardner, Annas, Neale, Eaves and Lichtenstein, 2008b; Kendler, Gardner and Lichtenstein, 2008c; Lau and Eley, 2006). One of the most relevant of these studies examined the temporal pattern of genetic and environmental effects on the level of fears in a population based cohort from age 8 to 20 years (Kendler et al., 2008c). The findings provided evidence of genetic continuity with genetic attenuation and innovation. So whilst there was evidence of genetic continuity, the influence of genetic factors at age 8-9 years, for example, declined over time (genetic attenuation) and new sets of genetic risk factors were found to ‘come on line’ in early and late adolescence as well as in early

adulthood (genetic innovation). The influence of shared environment (environmental influences which make individuals from the same family more similar) was found to decrease over time whereas non-shared environment was found to be increasingly important. Also consistent with this pattern of effects is an investigation into depression using the current sample (Lau and Eley, 2006). Stable genetic influences at the first time point (mean age 14 years) accounted for continuity of symptoms at the second and third time points (mean ages 15 and 17 years). In addition to this, new genetic effects emerged at the second time point. 'New' non-shared environmental effects were also evident at each time point, and overall non-shared environment contributed to change rather than stability of symptoms across time. If this pattern of influence is observed with respect to anxiety sensitivity it would have important implications with regard to etiology and would suggest that both trait and learning processes are involved in its development and maintenance over time.

The current investigation had two aims. First, given that the trait and learning hypotheses have contrasting predictions as to the stability of symptoms of anxiety sensitivity over time, we sought to investigate the continuity of anxiety sensitivity during adolescence, a time of great environmental as well as biological change.

Second, previous research has tended to find that genetic effects are stable over time and contribute substantially to continuity of symptoms whereas environmental influences are responsible for change over time. We, therefore, investigated the extent to which genetic and environmental factors are involved in the stability of anxiety sensitivity. This was explored in two steps. In the first step, the continuity of genetic and environmental influences on individual measures of anxiety sensitivity was assessed. In

the second step, the genetic and environmental architecture of a latent factor of trait anxiety sensitivity was investigated. In this approach stable environmental influences, free from specific measurement error, can be estimated. By examining these questions we hope to further elucidate the development and etiology of anxiety sensitivity.

## Method

### Participants

The G1219 study is longitudinal study of 3640 adolescent twins and siblings aged between 12-19 years at initial contact. Questionnaires were sent to adolescents at four time points. Informed consent was obtained from parents/guardians of all adolescents under 16 years, and from the adolescents themselves when 16 years or over. Ethical approval for different stages of this study has been provided by the Research Ethics Committees of the Institute of Psychiatry, South London and Maudsley NHS Trust, and Goldsmiths, University of London.

Initial recruitment of the sample was from two different sources. First, the offspring of adults participating in a large scale population based study (GENISiS) were contacted and invited to participate in this study or another study of hyperactivity (Curran, Rijdsdijk, Martin, Marusic, Asherson, Taylor and Sham, 2003). Of the 3,600 responses a total of 1,818 of adolescents (20%) from 1,294 families agreed to participate in G1219 of which 445 were full siblings pairs living at home and with an age gap of 5 years or less. A second source of recruitment was random selection of twin pairs from live twin births between 1985 and 1988 identified by the UK Office of National Statistics. Health Authorities and General Practitioners contacted 2,947 families of who

1,381 (47%) participated. Both samples were sent two postal reminders, and only respondents aged 12- to 19-years were included.

Contact invitations included questionnaires to be completed by adolescents and their parents at wave 1. At Wave 2, 8 months after initial contact, data were available from 2,651 individuals (73% of the twin and sibling pairs recruited at Wave 1) whilst corresponding figures for Wave 3, 25 months after wave 2, were 1,597 adolescents (44% of the twin and sibling pairs at Wave 1). At wave 4 we traced participants who had taken part in either waves 2 or wave 3 primarily by using websites/databases dedicated to providing information (e.g. phone numbers and postal addresses) about members of the population. We successfully traced 2,550 individuals of whom 1,556 responded (61% of those targeted; 74% of those participating at wave 3). For a flow diagram detailing participation rates, please see **Figure 1**.

The proportion of girls in the sample was 52%, 56%, 60% and 61% at waves 1, 2, 3, and 4 respectively. The mean ages at waves 1, 2, 3 and 4 were 14 years (range 12-19), 15 years (range 12-21), 17 years (range 14-23) and 20 years (range 18-27 years). The majority of participants (90%) were in a tighter age-range (e.g. 18-22 years at wave 4), but inclusion of sibling pairs inevitably created some age-spread. Zygosity was assessed at waves 2 and 3 through maternal-report of physical similarity (Cohen, Dibble, Grawe and Pollin, 1975). This technique produces high accuracy results, for example, one study using DNA demonstrated that parent-rated questionnaires had a 97% accuracy level (Price, Freeman, Craig, Petrill, Ebersole and Plomin, 2000). When zygosity was only available at one or other wave, this rating was used. If there was disagreement between zygosity ratings at the two time points, DNA was obtained (N = 26 pairs) before final

classifications were made. The number of twin and sibling pairs changed at each wave due to attrition. Specifically, wave 1 comprised of 367 MZ; 791 DZ; and 427 sibling pairs. Wave 2 comprised of 350 (345 complete) MZ; 647 (632 complete) DZ; and 330 (263 complete) sibling pairs. Wave 3 comprised of 324(212 complete) MZ; 439 (348 complete) DZ; and 182 (121 complete) sibling pairs. At wave 4, the sample comprised of 230(190 complete) MZ; 446 (327 complete) DZ; and 201 (128 complete) sibling pairs. Sibling type was uncertain for a remaining 235, 45 (39 complete), 11 (8 complete) and 19 (15 complete) pairs at waves 1, 2, 3 and 4. Ninety eight percent of the sample reported their ethnic origin as white.

Levels of parental education were somewhat higher (39% educated to A-level or above) than in a large nationally represented sample of parents (Meltzer, Gatward, Goodman and Ford, 2000) where 32% were educated to A-level or above. G1219 parents were also somewhat more likely to own their own houses (82%) than in the nationally representative sample (68%) (Meltzer et al., 2000). We re-weighted the sample to match the distribution of educational qualifications in the nationally representative sample of parents to reduce the impact of any initial response bias, associated with educational qualifications in a nationally representative sample. To account for any attrition between Waves 1 and 2, a second weight was created by assigning scores based on Wave 1 predictors of non-response at wave 2. Predictors of response included sex of the child (response was more likely from girls), housing tenure (response was more likely from parents reporting home ownership) and parental education (response was more likely from individuals with parents reporting higher qualifications). Anxiety was a significant predictor of response, however, once sex was included as a covariate, anxiety was no

longer a significant predictor of response. This suggests that the association between anxiety and response is driven by sex, anxiety was therefore not incorporated into the weight. These scores were then multiplied with the Wave 1 weight to incorporate initial response bias. We used this weight in the analysis as weights created for latter waves required previous response at both waves and therefore increases the amount of missing data. Effectively, weighting involves assigning lower weights to individuals from over-represented categories and higher weights to individuals from under-represented categories in the sample relative to the population distribution. The weights were created to be family-general, such that in model-fitting analyses, the weights did not incur any additional individual-specific effects between members of the same family. The current investigation uses data from the second, third and fourth wave of data collection and will be referred to as time 1, 2 and 3 respectively from hereon for ease of presentation.

### Measures

Anxiety sensitivity was measured at times 1 and 2 by the Child Anxiety Sensitivity Index (CASI: Silverman, Fleisig, Rabian and Peterson, 1991), designed for use with school-aged children (6-17 years). The CASI is an eighteen item questionnaire which requires children to rate their level of fear to the same types of anxiety-related sensations or experiences that are represented on the adult version. Participants rate each item on a 3 point Likert scale (1=*none* to 3=*a lot*). A total CASI score can be computed by summing items. The CASI has good psychometric properties similar to those of the adult ASI (Silverman et al., 1991). In the current sample, internal consistency at time 1 and 2 was .82 and .86 respectively.

By time 3, as participants were 18 years or older, the Anxiety Sensitivity Index (ASI: Reiss et al., 1986) was used to assess participants anxiety sensitivity. This consists of 16 items with participants rating their level of agreement on a 4-point likert scale (from 1=*very little* to 4=*very much*). Total ASI scores are, like the CASI, computed by summing items. The ASI has sound psychometric properties (Peterson and Reiss, 1987) and extensive validity estimates (Cox, Parker and Swinson, 1996). Test–retest reliability has been reported at .75, and various studies have estimated Cronbach’s alpha coefficient of internal reliability at between .82 and .91 (see Reiss, Silverman and Weems, 2001 for a review). In the current sample, internal consistency of the ASI was .87.

The main difference between the child and adult versions of the questionnaire concerns the simplicity of the language used in the items. For example, in the child version, items include ‘It scares me when my heart beats fast’, the adult equivalent being ‘It scares me when my heart beasts rapidly.’ As compared to the child version, the adult version has two less items and a greater choice of options on the likert scale. Total scores were used as they provide an overall estimate of an individual’s sensitivity to anxiety (e.g. Weems et al., 2002). Furthermore, the majority of confirmatory factor analyses of CASI provide evidence for a hierarchical structure where factors are all associated to a common general factor (Wright, Asmundson, McCreary, Stewart, McLaughlin, Comeau and Walsh, 2009).

### Statistical Analysis

#### Model-Fitting Analyses

The rationale of the twin and sibling design is to compare the degree of similarity of resemblance among monozygotic (MZ) twins, who share 100% of their genetic make-

up, with dizygotic (DZ) twins, who share on average 50% of their segregating genes and 25% of non-additive genetic influences (D). Relative differences in within-pair correlations are then used to estimate additive genetic (A) shared environmental (C), dominance (D) and non-shared environmental (E) effects on measures. Where correlations are higher for MZ as compared to DZ twins and full sibling (FS) pairs, genetic influence is assumed to be playing a role. Within-pair similarity that is not due to genetic factors is attributed to shared environmental influences (C), which is thus defined as aspects of the environment that contribute to resemblance between family members. Non-shared environment (E) accounts for individual specific factors that create differences among siblings from the same family. These are estimated from within-pair differences between MZ twins. Any measurement error present is included in this term. Where correlations between DZ are less than half that of MZ twins non-additive genetic effects are tested using an ADE model (for further information see Plomin et al., 2008).

Statistical analysis was conducted in Mx (Neale, Harvey, Maes, Sullivan and Kendler, 2006). Variables were age and sex regressed as is standard practice for quantitative genetic model fitting (McGue and Bouchard, 1984). Variables were transformed using the square root function to ensure skew statistics were within the range of -1 and 1.

#### Selecting Models of best fit.

Models were fitted using raw data maximum likelihood, incorporating appropriate weighting corrections. The fit statistics provided by Mx for raw data modelling is minus twice the log likelihood (-2LL) of the observations. This is not an overall measure of fit, but provides a relative measure of fit, since differences in -2LL between models are

distributed as  $\chi^2$ . Therefore, to examine the overall fit of the genetic model it is necessary to compare the -2LL to that of a saturated model. Consistent with the principle of parsimony, the fit of sub-models was assessed by  $\chi^2$  difference tests and the Akaike's Information Criterion ( $AIC = \chi^2 - 2df$ ) with lower  $\chi^2$  values and more negative AIC values suggesting better fit. Generally, a difference in AIC between two models of less than 2 suggests substantial evidence for both models (chose the most parsimonious), a difference of at least 3 indicates that the higher AIC model has considerably less support and a difference of more than 10 indicates that the higher AIC model is very unlikely (Wagenmakers and Farrell, 2004). The 95% confidence intervals of parameter estimates were obtained by maximum likelihood.

Model-fitting analyses can also test for sex differences in the patterns of etiological factors by comparing models which vary in their assumptions and specifications of the genetic and environmental parameters in males and females.

#### Univariate Models.

Univariate models examined the influences of additive genetic (A), shared environment (C), non-additive genetic effects (D) and non-shared environment (E) on anxiety sensitivity. Univariate analyses were performed in order to inform the multivariate models in terms of sex differences. Several models were tested beginning with a saturated model to which the full ACE and ADE models were compared. Quantitative sex differences were examined by evaluating the significance of fit reduction when male and female variance components were equated. If quantitative sex differences were found, a scalar model was fitted to see if this difference could be due to variance differences in the measure (variance differences between males and females, rather than

differences in genetic and environmental parameters). Where there were quantitative differences that were not due to variance differences, qualitative sex differences were also tested by freeing up the genetic correlations between DZOS (opposite sex dizygotic twins) and seeing whether it was a significantly worse fit. Qualitative sex differences were not found so are not discussed further.

### Multivariate Models

We used multivariate genetic models to test our main hypothesis in two steps. In the first step, a multivariate cholesky decomposition was fitted to the data to test whether there was evidence of either stable genetic or stable environmental influences over adolescence. A cholesky decomposition of three variables, partitions genetic, shared environmental effects into three sets of factors.  $A_{T1}$ ,  $C_{T1}$ , and  $E_{T1}$  act on all the variables,  $A_{T2}$ ,  $C_{T2}$ , and  $E_{T2}$  act on the second and third variables and  $A_{T3}$ ,  $C_{T3}$ , and  $E_{T3}$  act on the third variable only. Variables were ordered according to the time sequence with which they were collected allowing for inferences of direction of effects in the results (Rijsdijk and Sham, 2002).

In the second step, we tested a common pathway model to establish the genetic and environmental architecture of a stable latent variable trait anxiety sensitivity. In this model the variance in behaviours is decomposed into that which is shared - a single underlying 'phenotypic' latent variable, and that which is unique to each behaviour. This latent variable has genetic and environmental components of variance but there are still variable specific genetic and environmental sources of variances (Rijsdijk and Sham, 2002). The non-shared environmental component of the latent variable will be free from time-specific measurement error but not from shared measurement error.

## Results

### Descriptive Statistics

Moderate phenotypic correlations were evident between measures of anxiety sensitivity at the 3 time points (see **Table 1**). Highest correlations were between times 1 and 2 ( $r=.47$ ) and between times 2 and 3 ( $r=.48$ ).

Table 2 presents within-pair twin and sibling correlations. Correlations were in the main suggestive of additive genetic effects as DZ correlations were generally half that of the MZ correlations. There were, however, some cases where the DZ correlation was less than half that of the MZ correlation (for example, the male DZ correlations at time 1) implicating dominant genetic effect. We therefore compared the relative fit of both ACE as well as ADE models.

### Univariate analysis

Univariate results for the best fitting model are reported in **Table 2**. No sex differences were evident in genetic and environmental estimates of anxiety sensitivity at the three time points. There were, however, differences in variances between males and females. Univariate models included a scalar to account for this difference in variance. Both ACE and ADE models provided a good description of the data, however, neither C nor D was significant, we therefore present an AE model (see electronic appendix 1 for details of model fit). Moderate genetic influences were indicated at all times, ranging from .33 at time 2 to .46 at time 1 (Zavos et al., 2010). There was however, also substantial influence of non-shared environmental factors.

### Multivariate analysis

### Cholesky Decomposition

A cholesky decomposition was found to provide a good description of the data (**Table 3**). Again both an ADE and ACE model were tested, however neither was found to provide a significantly better fit. We therefore chose to present an AE model where the A component may be regarded as a ‘broad sense heritability’ estimate. The cholesky model informs us about the effects of stable and new genetic and environmental factors across the three time points in adolescence and early adulthood. Parameter estimates are presented in **Table 4**. As there was no evidence of gender differences in the size of the genetic and environmental parameters in univariate genetic models, a single set of parameters for the whole sample was presented for this model too. Total genetic and environmental estimates can be derived by summing the contributions of common and specific elements. Thus, the estimated heritability of anxiety sensitivity at time 2 is estimated by summing  $A_{T1}$  and  $A_{T2}$  and at time 3,  $A_{T1} + A_{T2} + A_{T3}$ . Total genetic and environmental estimates were generally found to be consistent with those derived from univariate models, see **Table 2**. Results show a stable genetic factor ( $A_{T1}$ ) which influences anxiety sensitivity at all three time points. At time 2, it accounts for 41% of the total genetic variance and 44% at time 3. A new genetic factor, suggesting different etiological influences, emerges at time 2 which accounts for 56% of genetic variance at time 3. No new genetic influences were apparent at time 3. Environmental effects were largely specific to each time point.

### Common Pathway Model

The common pathway model estimates the genetic and environmental influences on a reliable, stable, higher order factor. Results of the common pathway models are

shown in **Figure 2**. The common pathway model did not fit the data as well as the scalar cholesky model, but still provided a well fitting solution (see **Table 3**). Trait anxiety sensitivity is reliably measured by the anxiety sensitivity questionnaires at each time point indicated by the factor loadings which ranged from .36-.59. The variance in the latent factor of adolescents trait anxiety sensitivity, representing the underlying trait over time, was influenced by genetic factors (61%) and non-shared environmental factors (39%). Results also suggest that variation in anxiety sensitivity at each time point is mainly accounted for by non-shared environment or measurement error (41-54% of the specific variance) with specific genetic influences only significantly influencing variation at time 1 in line with results from the cholesky decomposition.

### Discussion

We examined the genetic and environmental structure of anxiety sensitivity from adolescence into early adulthood. Two main findings emerged. First, the moderate phenotypic correlations between variables at each time point suggests that anxiety sensitivity is relatively stable over time. Second, continuity of anxiety sensitivity was largely due to stable genetic influences. Environment conversely was largely time specific. Results support both a learning (significant influence of non-shared environment) and trait hypothesis (continuity of genetic influences) for the development of anxiety sensitivity. Before discussing the implications of these results, we first consider the studies limitations.

The inclusion of siblings in the sample means there were large age ranges at each wave. This makes it difficult to attribute the emergence of developmental influences to specific ages or stages of development. However, given that 72% of the whole G1219

sample were twins, the majority of the sample had a tighter age range. Time points were described as roughly reflecting mid adolescence, late adolescence and early adulthood, in line with the age of the majority of the sample at each wave.

A second issue concerns the use of self-report data. Analyses for the current study were conducted on data collected from questionnaires which may therefore fail to capture the intricacy of the phenotype in question. This is a necessary result of collecting a wide range of measures in such a large sample. Furthermore, as the sample spanned adolescence to young adulthood, both child and adult versions of the anxiety sensitivity index were used. The main difference between scales was in complexity of the language used for items which may imply more serious symptoms or behaviours. This may be why we observed a lower mean at time 3 than at times 1 or 2. This is an unavoidable limitation in longitudinal designs which span childhood into adulthood.

Despite our best efforts to recruit all study members for participation at all waves, there was also evidence of selective attrition. This was taken into account to some extent by using a weight which assigned greater value to those who were under-represented in the sample and less to those who were over represented.

Finally, the sample consists primarily of twins and there are limitations associated with their use. Concerns surrounding the twin methodology centre around issues including; chorionicity; the equal environments assumption; and generalizability. These limitations are likely to only have small effects in different directions, and as such, derived estimates of heritability and environmental influences should be taken as indicative rather than absolute (for a more comprehensive discussion of limitations of twin studies, see Plomin, Defries, McClearn and McGuffin, 2008).

In spite of these limitations, the results reported have significant implications. First, in line with other studies (Peterson & Plehn, 1999; Weems et al., 2002) we found substantial phenotypic stability of anxiety sensitivity. This makes it a good candidate to focus on in intervention studies on the prevention of disorders such as anxiety and depression (Muris et al., 2001; Weems, Hammond-Laurence, Silverman and Ferguson, 1997). Stability of anxiety sensitivity is supportive of a trait like component to the etiology of this bias.

Second, we found that anxiety sensitivity was moderately heritable at all 3 time points. Longitudinal genetic analysis provided evidence of genetic continuity with environmental specificity. This genetic architecture is in line with results from studies looking at other psychological disorders, for example depression (Lau and Eley, 2006), suggesting that cognitive biases have a similar pattern of genetic and environmental influences to the disorders with which they are associated. Our longitudinal genetic analysis has several implications.

Our finding of genetic continuity in individual measures of anxiety sensitivity and a latent factor of trait anxiety sensitivity suggests that genes are shared across development to a greater extent than they are specific. This supports the ‘generalist genes hypothesis’ (Eley, 1997). This hypothesis posits that genetic factors act as general influences with environmental factors resulting in specific manifestations of symptoms. Continuity of genetic influences and the overall influence of genes at each time point can be taken as support for trait theories of anxiety sensitivity.

Although we found substantial stable genetic influences, we also found that new genetic influences ( $A_{T2}$ ) emerged at the second time point. This could mean that while

our DNA sequence is stable across our life-course, the effects of certain genes may only be apparent at different stages of development, for example after the onset of puberty. Indeed, certain genes may influence anxiety sensitivity at one developmental stage and not another. These new genetic influences were equally important to those from time 1 in accounting for proportions of variance at time 3. There are several possible explanations for the genetic innovation apparent over development. It could represent new gene environment correlations (rGE) which occur as the adolescent is exposed to new experiences. rGE is based on the premise that the genes can to some extent control exposure to the environment (Plomin, DeFries and Loehlin, 1977). Alternatively, or perhaps in addition to rGE, genetic innovation might represent certain maturational steps in the brain which were not previously important but become pertinent during puberty (Pickles, Pickering, Simonoff, Silberg, Meyer and Maes, 1998). Interestingly, no new genetic influences were found by time 3 where mean age of participants was 20 years indicating that the most substantial period of genetic flux was from 15 – 17 years.

With respect to the study of the environment, although shared environmental influences were non-significant, non-shared environment accounted for over half of the variance in anxiety sensitivity at each time point. The importance of environmental influence is supportive of the hypothesis that learning processes are involved in the pathogenesis of anxiety sensitivity. Unlike genetic factors, however, non-shared environmental factors showed little continuity and accounted for most of what was different between measures of anxiety sensitivity over time. Many non-shared environmental influences, for example stressful life events (Goodyer, Kolvin and Gatzanis, 1987), are unlikely to be continuous, as such experiences will tend to be

relatively time-specific. Moving to a new school, for example, is likely to have only a short-lived effect, and will thus tend to influence mood for a number of months afterwards, but probably not several years later. Thus the specificity of these non-shared environmental influences is likely to reflect, in part, the varied social environments adolescents and young adults encounter as they are confronted with novel socialisation practices both in the family and in their peer group.

However, with that said, analysis of a latent factor of trait anxiety sensitivity indexing what is common and stable between measures of anxiety sensitivity over time revealed a moderate influence of non-shared environment (39%). This is a particularly interesting result and could reflect the stable way in which individuals perceive their environments through development (Turkheimer, 2000). In other words, the environment people experience over time changes, however, the ways in which individuals interpret the environment does not. This is particularly pertinent and suggests cyclical processes in the maintenance of biases such as anxiety sensitivity.

Another possibility is that the stable as well as time specific non-shared environmental influences on anxiety sensitivity are due in part to gene-environment interactions (positive interactions will be estimated in E, see Rijdsdijk and Sham, 2002). Gene-environment interactions occur when environmental risks change as a function of genetic risk, or indeed vice versa when genetic risks are only expressed in the certain environments. Interestingly, previous research has found evidence to suggest that gene-environment interactions are present in the development of anxiety sensitivity (Stein, Schork and Gelernter, 2008). Specifically, the effect of childhood maltreatment on anxiety sensitivity was found to be moderated by variation in the serotonin transporter

gene (5HTTLPR). In other words maltreatment in childhood has an effect on anxiety sensitivity in individuals who also possess genetic risk for such biases.

Given the involvement of anxiety sensitivity in disorders such as anxiety and depression and the recent evidence suggesting the importance of it in the maintenance of anxiety symptoms it is important to understand the developmental architecture of this cognitive bias. With regards to the question of whether anxiety sensitivity is inherent to the individual or largely developed through learning, our results can be interpreted as providing evidence for both. The high genetic continuity seen over this period of study can be taken as evidence of an underlying sensitivity to anxiety. However, the large influence of non-shared environment at each time point and evidence of a modest stable environmental component on trait anxiety sensitivity suggests that learning experiences are also central to its development. Our results are in line with previous studies into anxiety which demonstrated that genetic effects are developmentally stable (Kendler, Gardner, Annas and Lichtenstein, 2008a; Lau and Eley, 2006) with environmental influences tending to be developmentally specific with little continuity over time – largely accounting for the change in symptoms.

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Table 1. Phenotypic correlations & descriptive statistics for anxiety sensitivity (times 1 to 3).

<b>Anxiety Sensitivity</b>	N	Mean (SD)	Correlations		
			Time 1	Time 2	Time 3
			<u>(CI 95%)</u>	<u>(CI 95%)</u>	<u>(CI 95%)</u>
Time 1	2630	28.73 (5.55)	-		
Time 2	1586	25.65 (5.71)	.47 (.43-.51)	-	
Time 3	1548	15.52 (9.41)	.37 (.33-.42)	.48 (.44-.52)	-

Note. N, number of individuals, SD, Standard Deviation; CI, Confidence intervals. The CASI was used at time 1 and 2 whereas the ASI was used at time 3 .

Table 2. Within-pair twin and sibling correlations & univariate estimates for anxiety sensitivity at times 1 to 3 (with 95% confidence intervals).

Within-pair twin and sibling correlations			
	Time 1	Time 2	Time 3
MZ Males	.40 (.26-.51)	.36 (.19-.50)	.48 (.32-.61)
DZ Males	.14 (-.04-.30)	.24 (.04-.41)	.17 (-.08-.39)
MZ Females	.48 (.37-.57)	.26 (.11-.40)	.37 (.20-.51)
DZ/Sibling Females	.26 (.14-.36)	.33 (.17-.46)	.24 (.10-.37)
DZ/Sibling Opp-sex	.24 (.14-.32)	.08 (-.05-.21)	.08 (-.04-.20)
Univariate results			
A	.46 (.26-.52)*	.33 (.23-.42)*	.36 (.18-.46)
E	.54 (.48-.62)*	.67 (.58-.77)*	.64 (.54-.74)

Note. DZ and sibling correlations were equated after testing for any significant differences. MZ, monozygotic twins; DZ, Dizygotic twins; DZ Opp-sex, DZ opposite sex twins; A, Additive genetic effects; E, Non-shared Environmental effects

\* Results previously reported (see Zavos et al., 2010)

Table 3. Model fits for multivariate analysis

Model	-2ll	Df	$\chi^2$	df	p	AIC	$\Delta\chi^2$	$\Delta$ df	p	Comparison Model
1. Saturated	12458.18	5222	-	-	-	-	-	-	-	-
Cholesky Decomposition										
2. ACE Scalar	12675.852	5411	217.672	189	0.074	-160.328	-	-	-	-
<b>3. AE Scalar</b>	<b>12677.608</b>	<b>5417</b>	<b>219.428</b>	<b>195</b>	<b>0.110</b>	<b>-170.572</b>	<b>1.756</b>	<b>6</b>	<b>0.94</b>	<b>2</b>
4. ADE Scalar	12673.304	5411	215.124	189	0.093	-162.876	-	-	-	-
Common Pathway										
5. ACE Scalar	12686.552	5415	228.372	193	0.041	-157.628				
<b>6. AE Scalar</b>	<b>12687.894</b>	<b>5416</b>	<b>229.714</b>	<b>194</b>	<b>0.040</b>	<b>-158.286</b>	<b>1.342</b>	<b>1</b>	<b>0.25</b>	<b>5</b>
7. ADE Scalar	12685.264	5415	227.084	193	0.046	-158.916				

Note. -2ll = minus twice the log likelihood; AIC= Akaike's Information Criterion; Df = degrees of freedom;  $\chi^2$  = Chi-squared; p= Probability;  $\Delta$ = Change; A= Additive genetic influences; D= Dominant genetic influences; C = Shared environmental influences; E= Non-shared environmental influences

Table 4. Parameter estimates for multivariate longitudinal genetic models of anxiety sensitivity between time 1, 2 and 3 (with 95% confidence intervals)

	Time 1 Factors		Time 2 Factors		Time 3 Factors	
	A <sub>T1</sub>	E <sub>T1</sub>	A <sub>T2</sub>	E <sub>T2</sub>	A <sub>T3</sub>	E <sub>T3</sub>
Time 1	.45 (.37-.51)	.55 (.49-.64)	-	-	-	-
Time 2	.13 (.07-.20)	.09 (.06-.16)	.19 (.10-.27)	.59 (.52-.68)	-	-
Time 3	.20 (.12-.30)	.01 (.001-.04)	.14 (.04-.25)	.03 (.01-.07)	.01 (.00-.13)	.61 (.52-.69)

Note. A, additive genetics; E Non-shared environment; T1, time 1; T2, time 2; T3; time 3. Estimates presented in the table are variance components, estimates should be square rooted in order to obtain path coefficients.

**Figure Captions**

Figure 1. Flow chart of participation in G1219

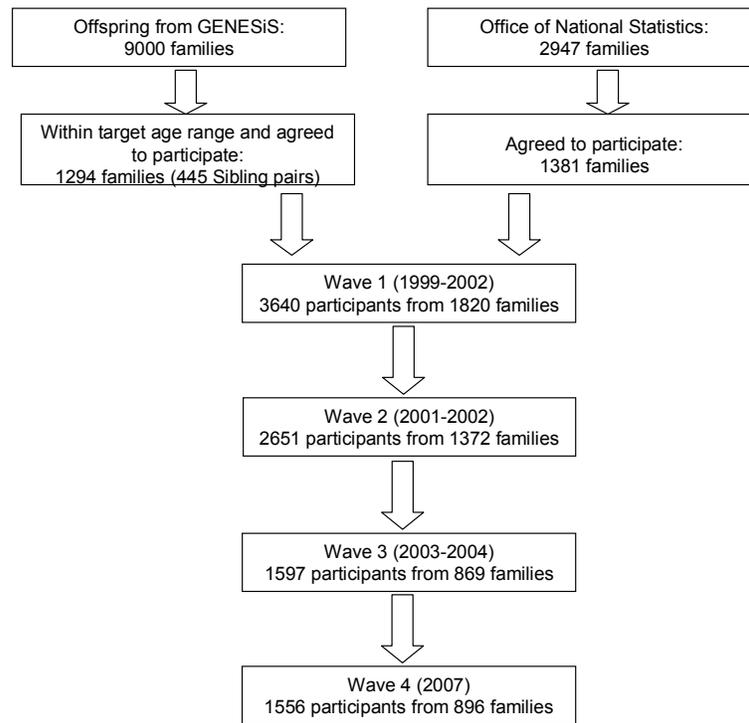
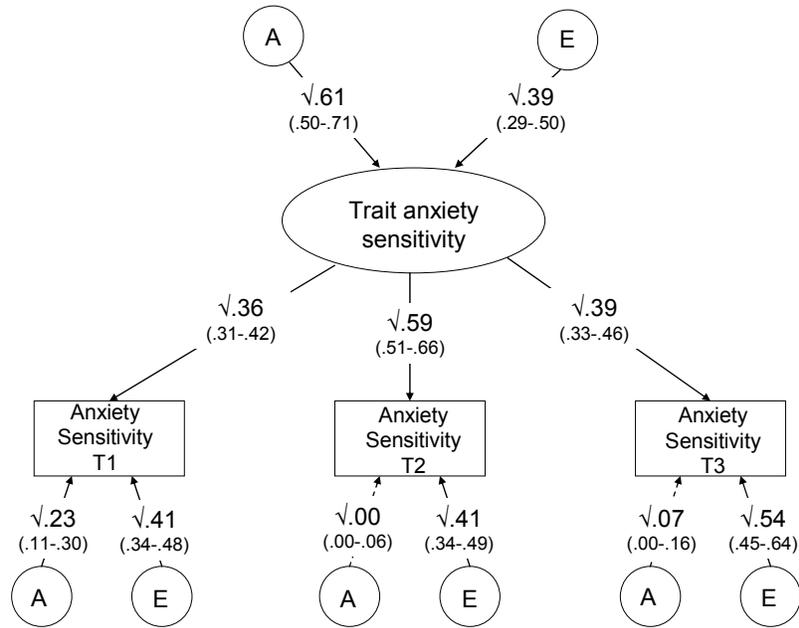


Figure 2. Results for common pathway model.



Note. A, additive genetics; E Non-shared environment; T1, time 1; T2, time 2; T3; time 3