**SUPPLEMENTARY MATERIAL**

**Stability and change: Genetic simplex**

A genetic simplex model (Boomsma and Molenaar, 1987) formed the basis to analyze stability and change in symptoms of anxiety and depression (SxAnxDep). Genetic simplex models include latent genetic and environmental factors that underlie the observed outcome variables (phenotypes). Applying the genetic simplex model results in a linear genetic decomposition of phenotypic variance into genetic and non-genetic sources. Such a decomposition is possible in a twin design using the fact that monozygotic (MZ) twins are (nearly) 100% genetically identical, while dizygotic (DZ) twins share on average 50% of their segregating genes (Boomsma *et al.* 2002; Middeldorp and Boomsma, 2009). The genetic simplex makes further use of the information captured by the MZ and DZ twin correlations across age (Tables S1-3), that is the correlation for SxAnxDep of twin 1 at for example age 3 and SxAnxDep of twin 2 at for example age 7. If these correlations are substantial (and positive), and if the twin correlations across ages are stronger in MZ twins than in DZ twins (Figure S2), this suggest that phenotypic stability is (at least in part) due to genetic factors, or in other words the genetic factors at age t are correlated with the genetic factors at the subsequent age at which we measure SxAnxDep (t+1). In a similar vein, environmental factors may be correlated across age (the extent to which the MZ correlations across age differ from the within person correlations across age is an indication for the importance of environmental stability).

In the genetic simplex model, correlations among latent genetic and environmental factors are specified through an autoregression process (see text Figure 1).

Specifically, SxAnxDep at each age t was modeled as follows:

SxAnxDept = At + Et + mt + rest + Ct C,

where At , Et and C denote the (zero-mean) additive genetic, nonshared (unique) environmental and shared environmental values, mt the grand mean of SxAnxDep, and rest the residual term. Subscript t denotes age t=1,…30, where t=1 is the first age bin for which we observed outcome data (age 3-4) and t=30 is the last age bin (61-63 years). Here, A and E are modeled as autoregressive processes and C is modeled as a common factor (see below).

The autoregressive patterns were modeled as:

At = At \* At-1 + At ,

Et = Et \* Et-1 + Et,

where coefficientAt and Et denote the autoregression coefficients, reflecting that genetic and nonshared environmental effects present at the previous age (t-1) influence the next age (t) and are thus carried over. Terms At andEtdenote additive genetic and nonshared effects that arise at age t, and which are called innovations. Effects of innovations are thus not present earlier than age t, but are carried over to subsequent ages.

To model the effects of shared environment in childhood at age 7, 10 and 12, we extended the AE simplex model by allowing the outcome measures at these ages to also load on a common, shared environmental factor: SxAnxDept=Ct C, where Ct represents the factor loading at ages 7, 10 and 12 , and where C is a latent factor (see text Figure 1) with unit variance and SxAnxDept is the phenotype at age t. At age 12, C influences maternal and self-ratings of SxAnxDep.

All genetic and environmental factors are assumed to be independent from each other, such that at each age:

Var(SxAnxDept) = Var(At) + Var(Ct) + Var(Et) + Var(rest),

where

Var(At) = At2 \* Var(At-1) + Var(At),

Var(Et) = Et2 \* Var(Et-1) + Var(Et),

Var(Ct) = Ct2 \* Var(C) = Ct2

At each age, the residual variance Var(rest) in the phenotype was decomposed into genetic and environmental factors, according to a standard behavior genetic model:

rest = resAt + resEt,

such that

Var(rest) = Var(resAt)+ Var(resEt)

This reflects the possibility that the age-specific phenotypic residuals include the effects of age-specific additive genetic, and nonshared environmental factors, i.e. these age-specific effects are not carried over to subsequent ages (and in this respect can be distinguished from innovations). Note that the component Var(resEt) also includes variance due to measurement error.

We allowed for mean differences in SxAnxDep between males and females by modeling the observations (mt) as a function of sex:

mt = b0t + b1t\*sex,

where b0t denotes the intercept and b1t the effect of dummy coded variable sex (0 = males, 1= females) at age t. The model, as implemented, did not allow for sex differences in heritabilities (Vink *et al.* 2012). To explore whether this was reasonable, the data were divided into 7 larger age bins (3 to 12, 12 to 19, 19 to 27, 27 to 35, 35 to 43, 43 to 53, and 53 to 63 years of age) and heritabilities were estimated for males and females separately each of the larger age bins. The larger bins did not show a difference in heritability between males and females but for age 35-43 (see text Figure 2*b*).

The complete model was implemented in Mplus version 6.11 (Muthén and Muthén, 1998-2010). All scripts may be obtained from the first author. Analyses were carried out using robust full information maximum likelihood, which allows for the presence of missing data and the analysis of non-normally distributed continuous outcome variables. Commonly, comparative model fits of models as the model above are evaluated using likelihood ratio tests (-2\*log-likelihood difference between two models). However, given the oversensitivity for large sample sizes of this test (Tanguma, 2001) and the large sample size in the current study, model fit was assessed by Akaike’s information criterion (AIC) and Bayesian information criterion (BIC).

**Identification, trimming, and evaluation of the genetic simplex model**

At the first age for which we have observed data, At and Et obviously cannot be predicted by data from earlier ages, therefore at this age all variance in the latent additive genetic and latent environmental factor is due to innovation variance: Var(A1) = Var(A1), and Var(E1) = Var(E1).

Residual variances at the first and last age at which we have observed data are only identified when additional assumptions are made. The following constraints were added to the model: Var(resA1)=Var(resA2), Var(resE1)=Var(resE2), Var(resA29)=Var(resA30), and Var(resE29)=Var(resE30). To speed up computation and to avoid empirical identification problems, the variances of the residuals (both E and A residuals) were constrained to be equal over three subsequent age bins: Var(resA1)=Var(resA2)=Var(resA3), Var(resA4)=Var(resA5)=Var(resA6), etc.

Based on the initial results of fitting the simplex model, and in order to arrive at an optimal, parsimonious model, we trimmed the model by allowing for further constraints. The autoregression parameters in the genetic simplex model (βAt) between the age of 18 and 63 all approached 1. Constraining these regression parameters to be 1 proved to be acceptable as judged by the AIC and BIC. We further observed that the innovations (ζAt) of the genetic variables A from age 18 to age 63were close to zero, and often did not reach significance (α=0.05), given their standard error. Restricting these parameters to zero reduced the BIC slightly, but increased the AIC (see Table S2). Effectively, these constraints reduced the genetic model equivalent to a single factor model from age 18 onwards, and rendered the model substantially more parsimonious, the results of which are reported in the main text.

From the final model, standardized coefficients of the contribution of genetic (and environmental) effects were derived for each age (t), including heritability coefficients (*h*2).

*h*t2 = (Var(At)+ Var(resAt))/(Var(At) + Var(Et) + Var(Ct) + Var(resAt)+ Var(resEt))

*c*t2 = Var(Ct)/(Var(At) + Var(Et) + Var(Ct) + Var(resAt) + Var(resEt))

*e*t2 = (Var(Et)+ Var(resEt))/(Var(At) + Var(Et) + Var(Ct) + Var(resAt)+ Var(resEt))

**Additional mean trend analyses.**

Mean trends over age, and sex differences herein were analyzed by post-hoc analyses. Age trends were analyzed using weighted least squares (WLS) on the means. The trends fitted are visible as dashed lines in text Figure 2*a*. Model derived means of males and females are vectorized from age 3 to age 63 and added to a single variable (MV, mean vector). This mean vector is regressed on a sex dummy variable (S), a design variable (D1) that linearly increases between age 12 and 28 and a design variable that monotonically increases from age 30 to 63(D2). These variables are combined in the following regression equation:

MV = I + b1\*S + b2\*D1 + b3\*D2 + b4\* S\*D1 + b5 \* S\*D2

The parameter b1 reflects the intercept difference between male and female means. This intercept, I, reflects the mean SxAnxDep score between the ages of 3 and 12. Parameter b2 reflects the change in SxAnxDep between ages 12 and 28 for male participants. Parameter b3 reflects the change in SxAnxDep for male participants between the ages of 30 and 63. Parameter b4 reflects the change for female participants over and above the change of male participants between the ages of 12 and 28. Parameter b5 reflects the change for female participants over and above the change of male participants between the ages of 30 and 63. The regression is weighted to reflect the differences in sample size used for the mean estimates at the different age points.

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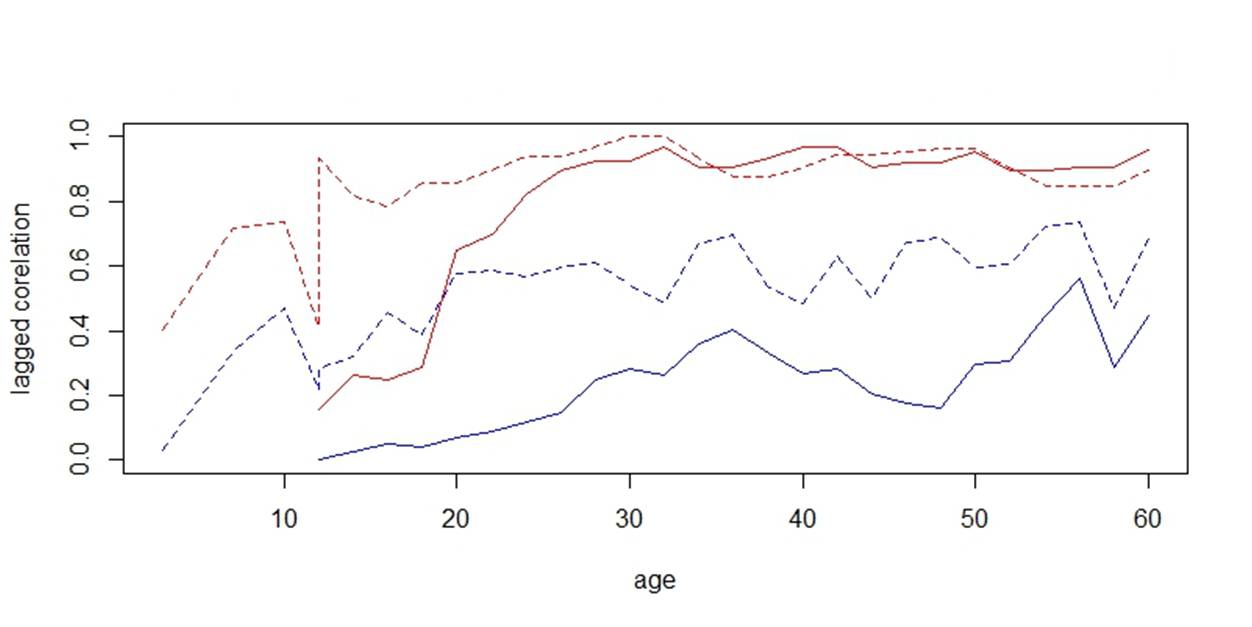
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**Figure S1:** Maximum Likelihood estimates of correlations within and across age for SxAnxDep. For each age, correlations are given with the 3 preceding and 3 subsequent ages. Diagonal: within-person longitudinal correlations. Above diagonal (right upper corner): MZ correlations. Below diagonal (left lower corner): DZ correlations. Within-person across-age correlations are higher than MZ twin across-age correlations, indicating a role for unique environment on stability. MZ across-age correlations are higher than DZ across-age correlations, indicating a role for genetic influences on stability.

**eFigure1.tif**

**Figure S2:** Pairwise genetic (A, red) and Environmental (E, blue) correlations between observations 2 years (dashed) and 10 years (solid) apart.

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**Table S1: Number of subjects per number of repeated observations**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Number of observations | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Subjects | 20987 | 9940 | 6588 | 7015 | 2812 | 1690 | 405 | 87 |

Table S2: Model fitting results based on the longitudinal simplex model

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Model: | Parameters | BIC | AIC | ΔBIC vs Full |
| Full AE simplex | 199 | 564233.711 | 562629.486 | - |
| A-transmission fixed at 1 in adulthood, | 171 | 563989.625 | 562603.059 | -244 |
| A-innovations fixed at 0 in adulthood | 156 | 563912.402 | 562654.819 | -77 |

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| MZ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Age** | **3** | **7** | **10** | **12** | **12** | **14** | **16** | **18** | **20** | **22** | **24** | **26** | **28** | **30** | **32** |
| Upper bound | 0.72 | 0.60 | 0.60 | 0.65 | 0.56 | 0.59 | 0.57 | 0.61 | 0.62 | 0.55 | 0.66 | 0.64 | 0.65 | 0.56 | 0.36 |
| correlation | 0.70 | 0.58 | 0.58 | 0.62 | 0.48 | 0.55 | 0.53 | 0.57 | 0.57 | 0.48 | 0.60 | 0.55 | 0.56 | 0.44 | 0.20 |
| lower bound | 0.69 | 0.56 | 0.55 | 0.60 | 0.40 | 0.51 | 0.48 | 0.53 | 0.51 | 0.40 | 0.52 | 0.45 | 0.45 | 0.30 | 0.02 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Age** | **34** | **36** | **38** | **40** | **42** | **44** | **46** | **48** | **50** | **52** | **54** | **56** | **58** | **60** | **62** |
| Upper bound | 0.60 | 0.70 | 0.65 | 0.56 | 0.64 | 0.67 | 0.69 | 0.58 | 0.83 | 0.69 | 0.77 | 0.63 | 0.59 | 0.89 | 0.67 |
| correlation | 0.47 | 0.58 | 0.51 | 0.34 | 0.44 | 0.52 | 0.55 | 0.37 | 0.71 | 0.51 | 0.59 | 0.36 | 0.32 | 0.76 | 0.35 |
| lower bound | 0.30 | 0.43 | 0.33 | 0.08 | 0.20 | 0.33 | 0.36 | 0.11 | 0.51 | 0.25 | 0.34 | 0.02 | -0.02 | 0.49 | -0.07 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| DZ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Age** | **3** | **7** | **10** | **12** | **12** | **14** | **16** | **18** | **20** | **22** | **24** | **26** | **28** | **30** | **32** |
| Upper bound | 0.36 | 0.38 | 0.37 | 0.38 | 0.40 | 0.26 | 0.30 | 0.29 | 0.29 | 0.35 | 0.27 | 0.33 | 0.25 | 0.38 | 0.34 |
| correlation | 0.34 | 0.36 | 0.34 | 0.36 | 0.32 | 0.22 | 0.25 | 0.23 | 0.22 | 0.27 | 0.17 | 0.21 | 0.10 | 0.22 | 0.16 |
| lower bound | 0.32 | 0.34 | 0.32 | 0.33 | 0.23 | 0.17 | 0.21 | 0.18 | 0.15 | 0.19 | 0.06 | 0.09 | -0.05 | 0.06 | -0.02 |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| **Age** | **34** | **36** | **38** | **40** | **42** | **44** | **46** | **48** | **50** | **52** | **54** | **56** | **58** | **60** | **62** |
| Upper bound | 0.36 | 0.48 | 0.39 | 0.34 | 0.54 | 0.62 | 0.56 | 0.69 | 0.83 | 0.58 | 0.40 | 0.59 | 0.87 | 0.70 | 0.64 |
| correlation | 0.13 | 0.26 | 0.12 | 0.03 | 0.27 | 0.37 | 0.31 | 0.46 | 0.62 | 0.29 | 0.05 | 0.16 | 0.57 | 0.37 | 0.19 |
| lower bound | -0.11 | 0.02 | -0.17 | -0.29 | -0.05 | 0.07 | 0.01 | 0.14 | 0.25 | -0.06 | -0.31 | -0.33 | -0.04 | -0.08 | -0.36 |

**Table S3**: Twin correlations for monozygotic (MZ) and dizygotic (DZ) pairs at ages 3, 7, … , 62 years. The middle row gives the correlation estimate, and the first and third row give the upper and lower bound for the 95% confidence intervals.