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Genetics of testosterone and the aggression-hostility-anger (AHA) syndrome: a study of middle-aged male twins

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The aim of this study was to determine the genetic contribution to the variation in testosterone and the aggression-hostility-anger (AHA) syndrome in middle-aged twins. Moreover, the relation between testosterone and this syndrome, and possible common genetic mechanisms were investigated. Towards this end, blood samples were collected at two time points; the AHA syndrome was measured using three questionnaires: the Buss-Durkee Hostility Inventory with seven subscales, the Jenkins Activity Survey and the Spielberger State-Trait Anger Scale. The results showed substantial heritabilities for testosterone (approximately 60%) and moderate to fair heritabilities for the nine measures of the AHA syndrome (23–53%). The best fitting model for testosterone at two time points included a small age component and additive genetic and unique environmental factors, while a multivariate analysis of the nine AHA subscales resulted in an independent pathway model with two common additive genetic and two common unique environmental factors. No correlation between the common genetic factor influencing testosterone and the AHA subscales was found. We did, however, detect a negative correlation between the common environmental factor underlying testosterone and both common environmental factors influencing the nine AHA subscales, which may reflect a tendency for testosterone levels to rise and hostility to drop (or vice versa) after repeatedly experiencing success (or failure). Twin Research (2000) 3, 266–276.

Keywords: hostility, aggression, testosterone, twins, heritability

Introduction

The quest for biological factors underlying the development of hostility and aggression has been aimed at various neuronal and endocrinological variables. Of all the neurotransmitters possibly involved in this complex trait, serotonin has recently attracted most of the attention whilst testosterone is the hormone most frequently investigated.

Testosterone is the male steroid hormone that is synthesized mainly by the Leydig cells of the testes. It exerts a potent anabolic action that is responsible for the post-pubescent growth rate and the subsequent muscle and bone tissue maintenance of the adult male. Studies in rodents have shown that testosterone levels are influenced by genetic factors. For instance, male wild house mice genetically selected for short attack latencies (ie high aggression) show higher testosterone concentrations than males selected for long attack latencies (ie low aggression).[1,2] In humans, testosterone is also heritable. Twin studies have found a substantial genetic contribution to the variation in human testosterone levels (see, for instance, Harris et al,[3] Meikle et al[4,5]). Accordingly, the first aim of this study is to expand these findings by measuring total testosterone (free- + bound) levels at two different time points in a sample of male middle-aged Dutch twins and determine the heritability in a multivariate model to optimise power.[6]

The genetic basis of aggression and hostility has been studied more extensively. These concepts are part of a cluster often referred to as the aggression-hostility-anger (AHA) syndrome.[7] Anger refers to an emotion but can also be considered a personality trait. The term aggression refers to overt verbal or physical aggressive behaviour towards others. Hostility is in itself a multidimensional concept that can be categorised into an attitudinal, an emotional and a behavioural component. The attitudinal (or cognitive) component refers to negative attitudes and appraisals towards others, in other words, mistrust

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and cynicism. The emotional component includes emotions like anger, irritability and annoyance. The behavioural component, also described as reactive or expressive hostility, refers to aggressive, antagonistic behaviour. A number of questionnaires to measure the components of the AHA syndrome have been used and described in the literature. The following five seem to be the most widely used (but see Vernon et al,[8] for other examples).

The Cook-Medley Hostility (Ho) Scale mainly measures cynical hostility although it also contains an expressive and neurotic component. The Jenkins Activity Survey (JAS) measures Type A behaviour, which typically comprises achievement orientation, competitiveness, repressed hostile feelings, excessive impatience, overactivity and a continuous sense of time urgency. Type A individuals show a high potential for hostility and an inability or unwillingness to express anger. Third is the Buss–Durkee Hostility Inventory (BDHI). The Assault, Verbal and Indirect Hostility sub-scales are supposed to measure expressive hostility while Resentment and Suspicion measure neurotic hostility. The fourth questionnaire is the Spielberger State-Trait Anger Scale (STAS). The trait version of this scale measures the predisposition to experience anger.[9] Recently, Buss and Perry[10] have constructed a new list of questions, the Aggression Questionnaire, with four scales: Hostility, Anger, Physical and Verbal Aggression. For an evaluation of this questionnaire, the reader is referred to Harris.[11] Construct validity and psychometric properties of the instruments measuring hostility are discussed in the concise review by Smith.[12]

Results on genetic components of the Cook and Medley Scale have been conflicting, with only the cynicism sub-scale showing a reproducible but moderate genetic component.[13,14] Both BDHI and Type A-like measures show moderate to substantial heritabilities.[15–20] We are not aware of any studies that investigated heritability of the STAS. Recently, Vernon et al[8] reported substantial heritabilities for three of the four sub-scales of the Aggression Questionnaire. In the same study the genetic component to hostility and aggression was confirmed by results from six additional questionnaires. Consequently, the second aim is to investigate whether the genetic contribution to the variation in hostility and aggression in our Dutch twin sample is similar. Towards this end, three of the earlier mentioned questionnaires measuring different aspects of the AHA syndrome were administered to all subjects: the BDHI, the JAS and the STAS.

More importantly, testosterone and hostility might be related. Evidence for this relation has mainly come from studies on non-primate animals where aggression is dependent on testosterone (see, among others, Albert et al[21]). Generally, higher testosterone levels are associated with increased aggressive behaviour (see, for instance, Van Oortmerssen et al[1]). Whether this testosterone-dependent aggression is actually present in humans is still unclear. Although quite a few studies have dealt with this subject in the past, the evidence for a relation between testosterone and aggression in humans is yet inconclusive. In the beginning of the 1990s two reviews exploring the testosterone–aggression relationship emerged. Archer[22] was moderately positive about testosterone being the biological basis of human aggression whilst Albert et al[23] were plainly negative. However, recently there has been some evidence that testosterone and aggression are related in both physically and psychologically healthy subjects.[24,25] Hence, the third aim is to investigate whether testosterone levels and (aspects of) the AHA syndrome are related. We hypothesise that higher level of testosterone are associated with higher scores on the three questionnaires reflecting the AHA syndrome. If this is the case, we will examine to what extent the covariance between hormone levels and this cluster of personality traits is due to common genes (pleiotropy) or common environment.

Methods

Subjects

This study is part of a larger project in which cardiovascular risk factors were studied in 213 middle-aged twin pairs (aged between 34 and 63)[26–29] Twins were recruited by a variety of means, including advertisement in the media, advertisement in the information bulletin of the Netherlands Twin Registry[30] and solicitation through the Dutch Twin Club. In addition, a small number of twins who heard from the study in another way volunteered to participate. Informed consent obtained from all subjects. Data from one twin pair was excluded because no blood could be obtained from one of the twins. In total 164 males were included in the study: 45 monozygotic (MZ) and 37 dizygotic (DZ) pairs. Zygosity was determined by DNA fingerprinting.

Blood sampling and testosterone assay

Twins arrived at the Department of Biological Psychology in Amsterdam at about 10.00 am. They were requested to fast, refrain from smoking and the use of alcohol, coffee and tea after 11.00 pm the preceding night. Blood was collected by venipuncture and sampled in citrate tubes. The tubes were placed on ice and centrifuged promptly (30 min, 2000 g) at 4°C to separate plasma from cells. Aliquots of plasma

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were snap-frozen using liquid nitrogen and stored at –20°C until processing.

Blood samples were collected at two distinct time points. The first sample was taken at 10.30 am, the second one at 2.00 pm. This procedure takes into account the variability in testosterone due to its circadian rhythm. Testosterone concentrations were determined using a standard radioimmunoassay (Equate, Portland, Maine, USA). For this assay, the minimal detectable dose of testosterone was found to be 1.8 ng/dl. Intra-assay and inter-assay coefficients of variation were 7.6% and 4.6%, respectively. Cross reactivity was 1.7% with dihydrotestosterone, 0.059% with 17β-estradiol and < 0.001% with progesterone. Citrate plasma samples were found to correlate perfectly (r = 0.996) with serum samples in the Equate radioimmunoassay, although mean values were systematically lower by 12.2%. All samples were assayed in duplicate and average values were used in all analyses. Total testosterone concentrations (free and bound) were measured. Previous to all data analysis testosterone levels were log transformed to obtain a normal distribution.

Questionnaires

The AHA syndrome was measured using three different questionnaires.

(1) The Dutch validated version of the Buss–Durkee Hostility Inventory (BDHI), which is a self-rating scale with 75 true-false items providing information on seven sub-classes of hostility: physical assault, indirect hostility, irritability, negativism, resentment, suspicion and verbal hostility.[31,32] These seven sub-scales are summed to yield a total hostility score. The BDHI also contains a guilt scale, which shares no items with any of the hostility scales and was, therefore, excluded from the genetic analysis.

(2) The Jenkins Activity Survey (JAS), which is a self-report measure of Type A behaviour.[33,34] The characteristic elements of Type A behaviour pattern are achievement orientation, competitiveness, repressed hostile feelings, excessive impatience, overactivity and a continuous sense of time urgency. Hostility is thought to be an important component of the heterogeneous concept of Type A behaviour.[7]

(3) The Spielberger State-Trait Anger Scale (STAS).[9] We used the Dutch validated version and from this only the trait items.

Total scores on the JAS (ie Type A behaviour), Spielberger's Trait-Anger questionnaire and scores on the seven sub-scales of the BDHI were all regarded as reflecting (different aspects of) the AHA syndrome. These nine measures were all included in the multivariate model-fitting analysis.

Analytical approach

Model fitting to twin data

Details of model fitting to twin data have been described elsewhere.[28,35] In short, the technique is based on the comparison of the variance–covariance matrices in MZ and DZ twin pairs and allows separation of the observed phenotypic variance into additive (A) or dominant (D) genetic components and shared (C) or unique (E) environmental components. The latter also contains measurement error. Dividing each of these components by the total variance yields the different standardised components of variance, for example the heritability (h^2) which can be defined as the ratio of additive genetic variance to total phenotypic variance. By incorporating age into the model, the influence of age on the phenotype can also be quantified.[36] Extension of univariate to multivariate models additionally allows exploration of the question whether the origin of the covariance between the different variables is genetically and/or environmentally determined.

Multivariate analysis of testosterone and the AHA syndrome

A bivariate Cholesky decomposition[37,38] including age was used to analyse testosterone at the two measurement occasions. Subsequently this model was further simplified to obtain the most parsimonious solution. The Cholesky decomposition allows calculation of the genetic and environmental correlation between testosterone at time 1 and at time 2.

For the analysis of the nine selected scales of the AHA syndrome three multivariate models were used: the Cholesky decomposition, the independent pathway model and the common pathway model. Whilst all these models decompose the variance into the respective components of variance (A, C, D or E), each represents different ways in which genes and the environment may affect the observed covariations between the outcome measures. The Cholesky model allows exploration of the extent to which the different factors (A, C, D or E) can explain the variance and covariance of the outcome measures. The number of latent factors equals the number of variables: the first factor loads on all nine hostility measures, the second factor loads on the eight remaining measures, the third on the seven remaining measures etc. The independent pathway model is a submodel of the Cholesky model, assuming one

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or more common factors of each possible type (A, C, D or E) loading on all the outcome measures. Besides these common factors, each of the nine outcome measures is influenced by genetic and environmental factor loadings specific to each of those nine measures. In the common pathway model, both genes and the environment are assumed to contribute to one or more latent (unmeasured) variables (eg 'AHA syndrome'), which is or are responsible for the observed covariation between the scales. Genetic and environmental factors specific to each measure are also incorporated in the model.

The following strategy was used in the multivariate analysis of the AHA syndrome to find the most parsimonious model. First, a Cholesky decomposition was used to explore the significance of the contributions of the different factors (A, C, D or E) to the variance and covariance of the outcome measures. Next, exploratory factor analysis was performed on the correlation matrices of the latent factors derived from the best fitting Cholesky model to determine the likely number of common factors. Subsequently a range of independent pathway models was fitted to determine the number of common latent factors constituting the best fitting model. Finally, we examined whether this best fitting model could be further simplified by constraining the relative importance of genetic and environmental influences to be equal in all nine outcome variables. That is, we fitted a common pathway model with two common factors.

To ensure the identification of models with multiple common A and E factors (and of the common pathway model with two common factors) we used orthogonal rotations (ie uncorrelated common factors) with reference variables.[39] For example, for the case of two common factors we first identified a variable that loaded high on one factor and low on the other. This reference variable was obtained from a varimax rotated exploratory factor model with the same number of common factors and the A or E correlation matrices derived from the Cholesky decomposition as input. Next, in our genetic modelling analyses the loading of the reference variable on the intended common factor was estimated, but the loading of the reference variable on the other common factor was fixed to zero. In a similar fashion 3 and 6 factor loadings were fixed to zero for models with three and four common factors respectively.

Model fitting procedure

A series of models was fitted to the multivariate–covariance matrices. The significance of variance components A, C and D was assessed by testing the deterioration in model fit after each component was dropped from the full model, leading to a model in which the pattern of variances and covariances is explained by as few parameters as possible. Submodels were compared with the full model by hierarchic χ^2 tests. The difference in χ^2 values between sub-model and full model is itself approximately distributed as χ^2, with degrees of freedom (df) equal to the difference in df of sub-model and full model. Model selection was also guided by Akaike's Information Criterion (AIC = $\chi^2 - 2df$). The model with the lowest AIC reflects the best balance between goodness of fit and parsimony.

Statistical software

Data handling and preliminary analyses were done with STATA Version 5.0.[40] Exploratory factor analysis was done with LISCOMP.[41] All genetic modelling was carried out with Mx.[37]

Results

Means of testosterone levels at the two time points and hostility measures are shown in Table 1 for the total sample and for MZ and DZ twins separately. Testosterone levels showed a significant fall between time 1 and time 2 (paired t-test: $P < 0.001$). Mean values of age, testosterone levels and hostility scales

Table 1 Means (sd) of testosterone levels and measures of the aggression-hostility-anger (AHA) syndrome in monozygotic (MZ) and dizygotic (DZ) twins and the total twin sample

	MZ		DZ		Total	
Number of pairs[a]	45		37		82	
Age (yr)	42.8	(5.6)	44.6	(7.2)	43.6	(6.4)
Testosterone time 1 (ng/dl)	470.5	(132.0)	456.1	(172.6)	464.0	(151.4)
Testosterone time 2 (ng/dl)	383.1	(109.1)	362.3	(134.1)	373.8	(121.1)
Type A	11.9	(5.7)	12.3	(5.1)	12.1	(5.4)
Trait-Anger	15.8	(3.5)	15.8	(4.4)	15.8	(3.9)
Assault	5.6	(3.8)	5.2	(4.0)	5.4	(3.9)
Indirect hostility	7.2	(3.7)	6.1	(3.5)	6.7	(3.7)
Irritability	7.7	(4.0)	8.0	(3.8)	7.8	(3.9)
Negativism	4.4	(2.4)	4.1	(2.4)	4.3	(2.4)
Resentment	2.7	(3.0)	2.8	(3.0)	2.7	(3.0)
Suspicion	5.2	(3.4)	5.1	(3.3)	5.2	(3.4)
Verbal hostility	13.1	(4.8)	13.7	(3.6)	13.4	(4.3)
Guilt	7.2	(3.2)	7.2	(3.5)	7.2	(3.3)
Total hostility	45.9	(15.9)	45.0	(15.8)	45.5	(15.8)

[a]Hostility measures were not available in one MZ twin pair.
Testosterone time 1 reflects the concentration at 10.30 am, testosterone time 2 the concentration at 2.00 pm. Type A represents the score on the Jenkins Activity Survey (JAS). Trait-Anger the score on the trait version of the Spielberger State-Trait Anger Scale (STAS), whereas Assault up to Verbal Hostility inclusive represent the seven sub-scales of the Buss–Durkee Hostility Inventory (BDHI). These seven sub-scales are summed to yield a total hostility score.

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were all highly similar for MZ and DZ twins. No significant differences in variances of log transformed testosterone values were found between MZ and DZ pairs (χ^2[2] = 3.08; P = 0.21) and time1 and time2 (χ^2[1] = 2.62; P = 0.11).

For testosterone levels at the two time points and for all hostility measures, twin correlations in MZ twin pairs were larger than those in DZ twin pairs, indicating substantial genetic influences on all traits (Table2).

Table3 shows phenotypic correlations between age, testosterone levels, hostility scales, guilt and total hostility. Testosterone levels showed a weak negative association with age. The correlation between testosterone at the two time points was 0.83. Hostility scales showed no relation with age or testosterone levels. Intercorrelations between the nine hostility scales ranged from 0.16 to 0.62. Correlations between testosterone and the different indicators for hostility were equal for the two time points (χ^2[9] = 6.68; P = 0.67) and not significantly different from zero (χ^2[9] = 5.98; P = 0.74). Due to the absence of an association between testosterone and the different indicators for hostility we decided in the first instance not to include both testosterone and hostility measures into the same multivariate model (ie to test for common genes). Instead we first used different models to investigate the genetics of testosterone levels and hostility scales separately.

Table 2 Twin correlations for monozygotic (MZ) and dizygotic (DZ) twin pairs

	MZ	DZ
Testosterone time 1 (ng/dl)	0.58	0.20
Testosterone time 2 (ng/dl)	0.58	0.40
Type A	0.69	0.19
Trait-Anger	0.29	0.07
Assault	0.50	–0.10
Indirect hostility	0.26	0.06
Irritability	0.43	0.15
Negativism	0.13	0.04
Resentment	0.53	0.38
Suspicion	0.55	0.09
Verbal hostility	0.49	0.05
Guilt	0.07	0.30
Total hostility	0.63	–0.03

For explanation see Table 1.

Table4 shows the results of modelling testosterone at the two measurement occasions. Both C and D could be dropped from the model without a significant reduction in fit. Thus the best fitting model included A and E. The influence of age was also significant (χ^2[2] = 6.67; P < 0.05) and different for the two time points (χ^2[1] = 3.46; P = 0.06). Both the genetic and environmental structure of this AE model could be simplified further, leading to the most parsimonious model (see Figure1). In this best-fitting model, testosterone at time1 and time2 is influenced by one common genetic factor and a unique environmental part that contains both common and specific influences. Unlike both the common and specific environmental influences, the genetic factor loadings in this model could not be set equal for time1 and time2 (χ^2[1] = 5.11; P < 0.05). Thus, the environmental variance remains the same on both occasions, whereas the genetic variance increases from time1 to time2. The genetic and unique environmental correlations between testosterone at time1 and time2 in this model were 1.0 and 0.55, respectively. These results confirm the expectation that testosterone at the two measurement occasions is influenced by the same genes and that variation in levels between the two points can be attributed to unique environmental factors. Heritability estimates for testosterone levels were somewhat lower for time1 (0.56) compared with time2 (0.65) (see Table5).

Results of multivariate model fitting of the AHA syndrome using the Cholesky decomposition are shown in Table6. Both C and D could be dropped from the model without a significant reduction in fit, ie the AE model provided the best fit.

Table 3 Intraindividual phenotypic correlations between age, testosterone and measures of the AHA syndrome (n=162)

	Age	Test 1	Test 2	Type A	Anger	Ass	Indh	Irrit	Negat	Res	Susp	Verbh	Guilt
Age													
Testosterone time 1	–0.18												
Testosterone time 2	–0.09	0.83											
Type A	–0.03	–0.03	–0.03										
Trait-anger	0.07	–0.09	–0.04	0.57									
Assault	–0.01	–0.15	–0.07	0.17	0.29								
Indirect hostility	–0.19	0.01	0.00	0.26	0.45	0.30							
Irritability	0.02	–0.10	–0.09	0.50	0.62	0.18	0.33						
Negativism	–0.12	–0.08	–0.08	0.16	0.23	0.35	0.28	0.21					
Resentment	–0.07	0.00	–0.05	0.24	0.35	0.24	0.38	0.62	0.26				
Suspicion	0.02	–0.03	–0.08	0.20	0.33	0.18	0.28	0.42	0.31	0.50			
Verbal hostility	–0.13	–0.05	–0.01	0.23	0.38	0.38	0.33	0.31	0.36	0.27	0.17		
Guilt	0.21	–0.16	–0.15	0.18	0.21	0.20	0.10	0.31	0.24	0.24	0.32	0.01	
Total hostility	–0.11	–0.09	–0.08	0.40	0.61	0.60	0.65	0.69	0.54	0.71	0.62	0.66	0.30

For explanation see Table 1.

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Table 4 Results of model fitting of (log transformed) testosterone at time 1 and time 2

Model	χ^2	df	P	AIC
ACE	33.10	18	0.02	–2.90
ADE	32.94	18	0.02	–3.06
AE	33.22	21	0.04	–8.78
AE best model	33.22	23	0.08	–12.78
CE	38.81	21	0.01	–3.20
E	60.82	24	0.00	12.82

χ^2: chi-square goodness of fit statistic; df: degrees of freedom; P: probability; AIC=Akaike's Information Criterion. See text for further abbreviations. All models included age.

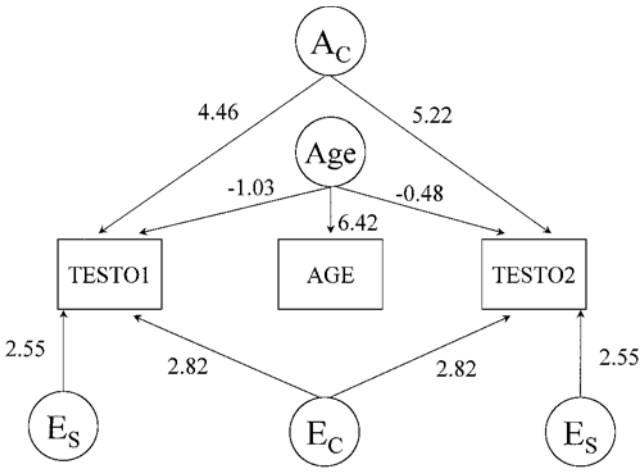

Figure 1 Most parsimonious bivariate model for testosterone levels measured on two occasions. For clarity only one twin is depicted. Non-standardised factor loadings are shown. testo1: testosterone level at time 1; testo2: testosterone level at time 2; A_C: common additive genetic factor; E_C: common unique environmental factor; E_S: specific unique environmental factor

Table 5 Parameter estimates and 95% confidence intervals of the best-fitting model of (log transformed) testosterone measured at two time points

	a^2	95% CI	e^2	95% CI	age^2	95% CI
Testosterone time 1						
non-standardised	19.9	11.4–30.8	14.3	10.6–20.8	1.1	0.0–4.7
standardised	0.56	0.36–0.71	0.41	0.27–0.61	0.03	0.0–0.12
Testosterone time 2						
non-standardised	27.3	17.3–40.4	14.3	10.6–20.8	0.2	0.0–3.0
standardised	0.65	0.48–0.77	0.34	0.23–0.52	0.01	0.0–0.07

a^2=additive genetic variance component (heritability); e^2=unique environmental variance component; age^2=variance component due to age. For the standardized results variance components were divided by the total variance.

Table 6 Results of multivariate model fitting of the nine selected measures of the aggression-hostility-anger (AHA) syndrome using a Cholesky decomposition. Comparisons of models are shown and P-values and differences in chi-squares ($\Delta\chi^2$) and df (Δdf) for these comparisons indicated

Model	χ^2	df	AIC	vs	$\Delta\chi^2$	Δdf	P
Cholesky models							
1. ACE	341.03	207	–72.97				
2. ADE	344.38	207	–69.62				
3. AE	352.65	252	–151.35	1	11.62	45	ns
4. CE	367.56	252	–136.44	1	26.53	45	ns
5. E	462.51	297	–131.49	1	121.48	90	<0.025

ns=non significant; vs=versus and indicates with which model the submodel is compared. For other abbreviations see Table 4.

Table 7 Submodels of the AE independent pathway model with four common factors for both A and E

Model	χ^2	df	AIC	vs	$\Delta\chi^2$	Δdf	P
1. 4 A_C & 4 E_C	360.89	264	–167.11				
2. 3 A_C & 4 E_C	368.82	270	–171.18	1	7.93	6	0.243
3. 4 A_C & 3 E_C	368.25	270	–171.75	1	7.36	6	0.298
4. 3 A_C & 3 E_C	376.43	276	–175.57	1	15.54	12	0.213
5. 2 A_C & 3 E_C	390.68	283	–175.32	4	14.25	7	0.047
6. 3 A_C & 2 E_C	386.60	283	–179.40	4	10.17	7	0.170
7. 2 A_C & 2 E_C	399.98	290	–180.02	4	23.55	14	0.052
8. 1 A_C & 2 E_C	422.36	298	–173.64	7	22.38	8	0.004
9. 2 A_C & 1 E_C	422.32	298	–173.68	7	22.34	8	0.004
10. 1 A_C & 1 E_C	465.10	306	–146.90	7	65.12	16	<0.001

A_C=common additive genetic factor; E_C=common unique environmental factor. For further explanation see Table 6. Most parsimonious solution is in bold.

Exploratory factor analysis with the A correlation matrix derived from the Cholesky decomposition as input, showed two factors with an eigenvalue >1. The situation for E was less clear with four eigenvalues >1, but three of those only just >1. Based on these results we decided to test a range of submodels of an AE independent pathway model with four common factors for both A and E. The most parsimonious model (with the lowest AIC) included, beside the obvious specific influences of A and E, two common genetic and two common unique environmental factors (Table 7). We further tried to simplify this model by testing a common pathway model with two common factors. This sub-model, however, showed a fit that was significantly worse ($\chi^2[15] = 62.66$; $P < 0.001$).

Table 8 shows the standardised solution of the best-fitting independent pathway model, ie the total variance of each variable was standardised to 1. The first common genetic factor is characterised by high loadings of Type A, anger, irritability and resentment, whereas assault, negativism and verbal hostility load high on the second common genetic factor. Indirect hostility and suspicion load on both common factors. The structure of the environmental

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Table 8 Standardised solution (total variance of each variable standardised to 1) of the best fitting AE independent pathway model

	First common factor		Second common factor		Specific factors	
	A	E	A	E	A	E
Type A	0.49	0.00[a]	0.04	0.36	0.50	0.57
Trait-Anger	0.50	0.24	0.07	0.72	0.00	0.41
Assault	0.00[a]	0.24	0.57	0.29	0.41	0.63
Indirect hostility	0.29	0.27	0.31	0.29	0.22	0.77
Irritability	0.65	0.37	0.10	0.28	0.16	0.58
Negativism	0.19	0.07	0.54	0.13	0.00	0.80
Resentment	0.61	0.66	0.27	–0.18	0.28	0.00
Suspicion	0.48	0.19	0.35	–0.03	0.41	0.65
Verbal hostility	0.09	0.24	0.46	0.33	0.41	0.67

[a]These factor loadings were fixed at zero.

Table 9 Parameter estimates and 95% confidence intervals of measures of the aggression-hostility-anger (AHA) syndrome in the best-fitting AE independent pathway model

	a^2	95% CI	e^2	95% CI
Type A	0.52	0.28–0.70	0.48	0.30–0.72
Trait-Anger	0.25	0.07–0.50	0.75	0.50–0.93
Assault	0.48	0.21–0.68	0.52	0.32–0.79
Indirect hostility	0.23	0.04–0.46	0.77	0.54–0.96
Irritability	0.46	0.24–0.63	0.54	0.37–0.76
Negativism	0.33	0.13–0.51	0.67	0.49–0.87
Resentment	0.53	0.28–0.69	0.47	0.31–0.72
Suspicion	0.53	0.27–0.70	0.47	0.30–0.73
Verbal hostility	0.39	0.14–0.59	0.61	0.41–0.86

For abbreviations see Table 5.

common factors is quite different with most variables showing moderate loadings on both factors and only resentment loading strongly on the first and anger strongly on the second.

The two testosterone measurements were subsequently included in this final model to test whether there would be any correlation between the two common A and E influencing the AHA syndrome and the single common A and E influencing the two testosterone measurements. Correlations between the common A for testosterone and the first and second common A for the AHA syndrome were 0.03 and 0.17 respectively, both non-significant. For the common Es these correlations were –0.22 and –0.42, respectively. These correlations could not simultaneously be set to zero ($\chi^2[2] = 8.38$; $P = 0.015$), which probably explains the (non-significant) tendency for negative correlations between AHA variables and testosterone as shown in Table 3.

For the best fitting independent pathway model of the AHA syndrome, overall heritability estimates and 95% CIs are shown in Table 9. Heritabilities range from 23% for indirect hostility to 53% for both resentment and suspicion.

Discussion

The heritabilities of total plasma testosterone concentrations and anger, hostility and aggression were determined in middle-aged twins. The results show that testosterone levels are heritable in middle-aged men, with approximately 60% of the variation due to genetic factors. The genetic contribution to the variation in the AHA syndrome (measured by the BDHI, JAS and STAS) ranges from 23% to 53% depending on the different sub-scales. The best-fitting model for testosterone at two time points included a small age component and additive genetic and unique environmental factors, whilst a multivariate analysis of the nine AHA sub-scales resulted in an independent pathway model with two common additive genetic and two common unique environmental factors. No correlation between the common genetic factors influencing testosterone and the AHA subscales was found. We did, however, detect a negative correlation between the common environmental factor underlying testosterone and both common environmental factors influencing the nine AHA subscales.

To optimise the power of our relatively small sample of male twins and use all available information the two measurements of testosterone were modelled in a multivariate way.[6] The single common genetic factor for the two measurements (implying a perfect genetic correlation) confirmed that the same genes are responsible for the variance in testosterone at the two time points. The environmental variance remained the same on both occasions, whereas the genetic variance showed a small increase from time 1 to time 2. The heritability of testosterone we found is in agreement with previous findings. Up till now three twin studies have thoroughly investigated the genetics of testosterone. In one study Meikle et al[5] found that genetic factors accounted for approximately 85% of the variation in testosterone production rate, while another study by the same group revealed that the variance in free and bound testosterone was explained for 34% and 26% by genetic factors, respectively.[4] A more recent study also measured total plasma testosterone levels in young-adult twins (13–21 years) from the same twin registry we used, and found that 66% of the variance in testosterone concentrations in young-adult men can be accounted for by genetic factors.[3] The similarity of this heritability to our estimates (time point 1: 56%; time point 2: 65%) is striking. In addition, Harris et al[3] did not find a correlation between fathers and sons ($r = 0.04$), suggesting either that distinct genetic mechanisms influence testosterone levels over time or that plasma testosterone concentrations are not heritable at the fathers' age (48 ± 6 years). Our results on middle-aged male twin

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pairs (mean age: 44 ± 6 years) strongly suggest the first assumption to be true. Hence, different genes seem to determine testosterone concentrations in different periods of life.

The total testosterone concentrations of the middle-aged men fell in the normal range as reported by the supplier of the testosterone assay. Older men showed lower testosterone levels than younger ones, hereby confirming previous findings.[42] The decrease is minimal in our sample, however. Furthermore, we find higher testosterone levels at time point 1 (10.30 am) compared with point 2 (2.00 pm). This decrease is in line with previous studies which demonstrated that testosterone is highest in the morning and then slowly decreases during the day (see, among others, Ahokoski et al[43]).

The heritability of the different subscales of hostility vary from 23% for indirect hostility to 53% for resentment and suspicion in the BDHI questionnaire, while Type A (JAS) and Trait-Anger (STAS) yielded 52% and 25%, respectively. The best-fitting multivariate model of the nine AHA syndrome scales was an AE independent pathway model with two common genetic and two common environmental factors. Our best-fitting model suggests two common sets of genes and two common sets of unique environmental effects are responsible for the relations between different scales measuring aspects of the AHA syndrome. This seems to be in agreement with previous studies that have suggested that the hostility concept consists of two or maybe even three factors.[7,32] It has been argued that the multidimensional concept of hostility can be categorised into an attitudinal, an emotional and a behavioural component. Our best multivariate model suggests that the first common genetic factor is primarily an emotional factor (Type A, anger, irritability and resentment) and the second primarily a behavioural factor (assault, negativism and verbal hostility). Attitudinal traits (indirect hostility and suspicion) seem to load on both factors. The environmental common factors showed a different structure with most variables showing moderate loadings on both factors and only resentment loading strongly on the first and anger strongly on the second.

For most hostility scales, DZ twin correlations were smaller than half the MZ correlation, which would be suggestive of dominance genetic effects. However, tested univariately only assault and suspicion showed a non-significant trend towards a dominance effect. Inspection of the MZ and DZ cross-correlations also showed little evidence of dominance, which was confirmed by the multivariate modelling.

Our results are in concordance with previous studies. Coccaro et al[16] focused on the 'motor aggression' sub-scales of the Buss–Durkee Hostility Inventory and found that irritability, indirect, verbal and physical assault showed significant heritabilities, varying from 28% to 47%. Using different questionnaires Coccaro et al[15] also demonstrated genetic influences on assertiveness/aggression in a study of twins reared together and reared apart. Rushton et al[19] even found heritabilities of 64% and 72% for assertiveness and aggressiveness. The results we found on Type A behaviour are generally in line with former studies,[17,20,44,45] which showed heritabilities ranging from 28% to 39% in the Jenkins Activity Survey (JAS). Recently, Vernon et al[8] estimated variance components for a total of 18 (sub)scales reflecting different aspects of hostility and aggression from seven different questionnaires. Fourteen sub-scales showed a significant heritability and five of those a substantial dominance component. Their multivariate analysis confirmed our results by showing that there is considerable overlap between the genes operating on different types of aggressive behaviour.

We did not find the expected positive correlation between testosterone and the different AHA syndrome scales. As has been mentioned in the introduction, the relation between testosterone and aggression has always been somewhat equivocal, partly because of the variation in populations from which subjects were sampled. Research in the 1970s mainly concentrated on either physically or psychologically abnormal subjects (eg alcoholics, rapists, child molesters, wife beaters) and is therefore hard to compare with our findings. Albert et al[23] reviewed and critically re-examined the literature on testosterone levels in high- and low-aggression groups, most of them originating from prison populations. They concluded that only two out of eight studies, one with a methodological weakness and one with internal inconsistencies, confirmed the hypothesis that high aggressiveness and high testosterone actually go together. Also, in two studies BDHI questionnaires were administered to both groups. No relation between testosterone and BDHI scores was detected. However, in this context it is important to mention that in an investigation of human trans-sexuals, van Goozen and colleagues[46,47] reported that anger and aggression proneness increased when female-to-male trans-sexuals were administered androgens orally.

Contemporary research has often centred more on normal healthy volunteers and the administration of steroids, among which testosterone, in different doses. Similar to the relation between testosterone levels and hostility in specific populations the findings are far from unequivocal. Generally, steroid administration increased the scores on hostility-like sub-scales of different questionnaires.[48,49] The only

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study, however, that was used the BDHI did not find an effect of testosterone.[50]

For naturally circulating testosterone concentrations in healthy volunteers, our findings are partly in line with previous studies. They agree with those from Doering et al,[51] who measured plasma testosterone levels, hostility, anxiety, and depression in 20 young men every second day for 2 months. They merely found a tendency for a relation between depression and testosterone and not between hostility and testosterone. However, our results are not in agreement with those from Harris et al[25] who found that salivary testosterone was positively correlated to self-report aggression. Gerra et al[24] also observed a positive relationship between plasma testosterone concentrations and hostility. However, in this study hostility was measured both by self-report (BDHI) and by semi-structured interviews with first-degree relatives and spouses. It appeared that testosterone did correlate with the total aggression scores reported by first-degree relatives and spouses, and with the (self-reported) BDHI sub-scales irritability and resentment, but not with the other sub-scales. The latter study is in accordance with a meta-analysis performed on 24 genetically informative studies using various personality measures of aggression and/or antisocial behaviour.[52] Its main conclusion was that the genetic architecture of aggression appears to be a function of the mode of reporting (self-report vs parental report vs observational report).

We did, however, observe a negative relation between the common environments influencing testosterone and the AHA syndrome. Opposite to our hypothesis, this resulted in a (non-significant) tendency towards negative correlations between AHA variables and testosterone. In line with research showing a relation between testosterone levels and the experience of success or failure this result may indicate that a positive life event (societal success) increases testosterone levels and decreases hostility and anger. On the other hand, a negative life event (failure or humiliation) would do exactly the opposite: testosterone levels drop and hostility arises. In either case (success or failure) there is likely to be a tendency towards a spiralling effect, with a given outcome tending to promote more instances of the same outcome. For instance, decreases in testosterone after a failure may cause a person to feel less assertive and avoid new competition, which, in turn, may lead to more failure.[53]

The question remains, which genes are responsible for the variation in aggression and hostility. Up till now there is only one study, which indisputably located a gene that affected social behaviour. A point mutation in the monoamine oxidase A (MAO-A) gene is associated with a behavioural phenotype that includes disturbed regulation of impulsive aggression.[54] Two years later the involvement of this gene was confirmed in an animal study. Mice that did not express the MAO-A gene ('knock-outs') were far more aggressive than control males.[55] However, most genetic variation in the hostility scores (and plasma testosterone concentrations) of natural populations is more likely to come from polygenic influences instead of devastating single-gene disorders like the MAO-A point mutation. More information may come from animal research. Currently, eleven genes are identified which affect at least one type of mouse aggression (see Maxson[56]). Since there are homologous genes in the human genome, they may be considered as candidate genes.

Especially the genes affecting serotonin (5-HT)-dependent neurotransmission may be strong candidates. Recently, three studies were published which combined measurement of the subscales of the BDHI with serotonergic variables. First, Coccaro et al[57] showed that the Assault sub-scale is inversely correlated with post-synaptic and 'net'-synaptic (5-HT) activity as measured by m-chlorophenylpiperazine and fenfluramine challenges. Second, using blood platelets the same group found that Assault covaried with increasing numbers, but decreasing affinity, of 5-HT2A receptors in personality disorder patients but not in healthy volunteers.[58] Third, New et al[59] found that patients with a specific homozygous tryptophane hydroxylase (the rate limiting enzyme for serotonin) genotype show higher impulsive aggression scores than patients with heterozygous or 'opposite' homozygous genotypes.

In summary, both testosterone and the cluster of personality traits centred around hostility and aggression seem to have a solid genetic basis as indicated by evidence from this and other studies. However, the lack of evidence for a genetic relation between the two suggests that future studies need to explore other avenues to uncover the biological basis of hostile and aggressive human behaviour.

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