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ADHD: Sibling Interaction or Dominance: An Evaluation of Statistical Power

M. J. H. Rietveld,[1,3] D. Posthuma,[1] C. V. Dolan,[2] and D. I. Boomsma[1]

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Sibling interaction effects are suggested by a difference in phenotypic variance between monozygotic (MZ) twins and dizygotic (DZ) twins, and a pattern of twin correlations that is inconsistent with additive genetic influences. Notably, *negative* sibling interaction will result in MZ correlations which are more than twice as high as DZ correlations, a pattern also seen in the presence of genetic dominance. Negative sibling interaction effects have been reported in most genetic studies on Attention Deficit Hyperactivity Disorder (ADHD) and related phenotypes, while the presence of genetic dominance is not always considered in these studies. In the present paper the statistical power to detect both negative sibling interaction effects and genetic dominance is explored. Power calculations are presented for univariate models including sources of variation due to additive genetic influences, unique environmental influences, dominant genetic influences and a negative sibling interaction (i.e., contrast effect) between phenotypes of twins. Parameter values for heritability and contrast effects are chosen in accordance with published behavior genetic studies on ADHD and associated phenotypes. Results show that when both genetic dominance and contrast effects are truly present and using a classical twin design, genetic dominance is more likely to go undetected than the contrast effect. Failure to detect the presence of genetic dominance consequently gives rise to slightly biased estimates of additive genetic effects, unique environmental effects, and the contrast effect. Contrast effects are more easily detected in the absence of genetic dominance. If the significance of the contrast effect is evaluated while also including genetic dominance, small contrast effects are likely to go undetected, resulting in a relatively large bias in estimates of the other parameters. Alternative genetic designs, such as adding pairs of unrelated siblings reared together to a classical twin design, or adding non-twin siblings to twin pairs, greatly enhances the statistical power to detect contrast effects as well as the power to distinguish between genetic dominance and contrast effects.

KEY WORDS: Statistical power; sibling interaction; genetic dominance; ADHD; power calculation; twin study; heritability.

INTRODUCTION

The effects of phenotypic interaction among twins and siblings to individual differences in behavior was first introduced by Eaves (1976) and later discussed by Carey (1986). This interaction can either be cooperative or competitive. In the former case, behavior in one twin leads to similar behavior in his or her co-twin. In the latter case, behavior in one twin leads to opposite behavior in his or her co-twin. For common childhood psychopathology, cooperation and competition effects have both been reported (for a review, see Garcia *et al.,* 2000). In data obtained from parental ratings the effects of cooperation and competition may be mimicked (Eaves *et al.,* 2000; Neale and Stevenson, 1989; Simonoff *et al.,* 1998). When parents are asked to evaluate and report upon their children's phenotype,

[1] Department of Biological Psychology, Vrije Universiteit, Amsterdam, the Netherlands.
[2] Department of Psychology, Universiteit van Amsterdam, Amsterdam, the Netherlands.
[3] To whom correspondence should be addressed at Vrije Universiteit, Department of Biological Psychology, Van der Boechorststraat 1, 1081 BT Amsterdam, the Netherlands. Tel: +31.20.444.8812. Fax: +31.20.444.8832. E-mail: mjh.rietveld@psy.vu.nl

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they may compare the twins' behavior. In this way, the behavior of one twin becomes the standard against which the behavior of the co-twin is rated. Parents may either stress the similarities or differences between the children, resulting in an apparent cooperation or competition effect. The presence of an interaction effect, either true sibling interaction or rater bias, is indicated by differences in MZ and DZ variances. If the interaction effect is cooperative (either true cooperation or due to rater bias), the variances of MZ and DZ twins are both inflated, and this effect is greatest on the MZ variance. The opposite is observed if the effect is competitive; MZ and DZ variances are both deflated and again this effect is greatest on the MZ variance. In the present paper our main interest is in a *competition* effect (either true competition or due to rater bias), also referred to as a contrast effect. In addition to heterogeneity in MZ and DZ variances, the presence of a contrast effect affects MZ and DZ covariances, resulting in a characteristic pattern of MZ and DZ correlations in which MZ correlations are much larger than DZ correlations. This pattern of correlations is not only consistent with contrast effects, but also with genetic nonadditivity such as dominance effects. In order to distinguish between genetic dominance and contrast effects it is therefore crucial to consider MZ and DZ variance-covariance structures in addition to MZ and DZ correlations.

Until recently, the analysis of twin and sibling data by use of contrast models has received limited attention in the behavior genetic literature. However, this has changed with recent publications on common childhood psychopathology measured in large twin samples of around 1000 pairs and more (Eaves *et al.,* 1997; Nadder *et al.,* 1998, 2001; Price *et al.,* submitted; Rhee *et al.,* 1999; Rietveld *et al.,* 2003; Thapar *et al.,* 2000, Van Beijsterveldt *et al.,* submitted). These studies reported that for behavioral problems like inattention, hyperactivity, and impulsivity the DZ correlation is small and sometimes even negative. Overall, the MZ correlation is large and more than twice the DZ correlation, suggesting either the presence of genetic dominance or the presence of contrast effects (or both). In addition, however, the DZ variance is often reported larger than the MZ variance, favouring the presence of a contrast effect over the presence of genetic dominance. The consistency in finding evidence for contrast effects among studies on ADHD is noteworthy. With the exception of Rhee *et al.* (1999) and Levy *et al.* (1997) the largest twin studies report the presence of contrast for at least one of their measures (Van Beijsterveldt *et al.,* submitted; Eaves *et al.,* 1997; Nadder *et al.,* 1998, 2001; Price *et al.,* submitted; Rietveld *et al.,* in press; Thapar *et al.,* 2000). The estimate for the contrast effect ranges from −.05 to −.25. Consistent with studies of smaller samples (Gjone *et al.,* 1996; Hudziak *et al.,* 2000; Kuntsi *et al.,* 2000; Martin *et al.,* 2002; Schmitz *et al.,* 1995; Spinath and Angleitner, 1998; Thapar *et al.,* 1995, Saudino *et al.,* 2000; Stevenson, 1992), broad heritability for traits related to ADHD is estimated between 60%–85% with the residual variance explained by environmental experiences unique to the individual.

Both genetic dominance and contrast effects may act on a given trait. In such a model, four sources of variance are specified; additive genetic (A), genetic dominance (D), unique environmental (E) and the interaction effect (*b*). Twin models including these effects have sometimes been accused of overparametrization or underidentification (Martin *et al.,* 2002). An empirical examination of the identification of the ADE-b model, however, has previously shown and concluded that the model is indeed identified (Nadder *et al.,* 1998). In the present study the identification of the ADE-b model is explored both formally and empirically.

The exploration of an ADE-b model is hindered by a lack of power. With MZ and DZ twins reared together, parameter estimates are highly correlated. The detection of dominance requires large samples, preferably including pairs of varying genetic relatedness (Eaves, 1972; Posthuma and Boomsma, 2000). Eaves (1976) noted that the inclusion of pairs of unrelated individuals reared together facilitates the detection of contrast effects. In the present study we discuss the statistical power to detect genetic dominance and contrast effects using a classic twin design as well as alternative designs.

METHODS

Model

The algebraic derivation of the expectation for the variances and covariances in the presence of contrast effects is found in Eaves (1976) and Neale and Cardon (1992).[4] The expected twin variance and twin covariance are modeled as follows, see Table I.

The present power study is limited to the analysis of the covariance structure. The sibling interaction as

[4] The expected additive genetic variance and genetic dominance variance are listed incorrectly in Table 10.3 (Neale and Cardon, 1992, p. 208). The α is missing for additive genetic variance (i.e., 1 for MZ twins and 0.5 for DZ twins), and δ is missing for genetic dominance variance (i.e., 1 for MZ twins and 0.25 for DZ twins).

Table I. Algebraic Representation of Expected Variances, Covariances, and Correlation under ADE-b and ADE Models

	ADE-b		ADE	
	Expected variance	Expected covariance	Expected variance	Expected covariance
Additive genetic	$\frac{a^2 (1 + 2b\alpha + b^2)}{(1 - b^2)^2}$	$\frac{a^2 (\alpha + 2b + \alpha b^2)}{(1 - b^2)^2}$	a^2	$\alpha\, a^2$
Dominant genetic	$\frac{d^2 (1 + 2b\delta + b^2)}{(1 - b^2)^2}$	$\frac{d^2 (\delta + 2b + \delta b^2)}{(1 - b^2)^2}$	d^2	$\delta\, d^2$
Unique environment	$\frac{e^2 (1 + b^2)}{(1 - b^2)^2}$	$\frac{e^2(2b)}{(1 - b^2)^2}$	e^2	0
Total	$\frac{(1 + b^2)(a^2 + d^2 + e^2) + 2b\,(\alpha\, a^2 + \delta d^2)}{(1 - b^2)^2}$	$\frac{(1 + b^2)(\alpha\, a^2 + \delta d^2) + 2b\,(a^2 + d^2 + e^2)}{(1 - b^2)^2}$	$a^2 + d^2 + e^2$	$\alpha\, a^2 + \delta\, d^2$
Expected correlation	$\frac{(1 + b^2)(\alpha\, a^2 + \delta d^2) + 2b\,(a^2 + d^2 + e^2)}{(1 + b^2)(a^2 + d^2 + e^2) + 2b\,(\alpha\, a^2 + \delta d^2)}$		$\frac{\alpha\, a^2 + \delta d^2}{a^2 + d^2 + e^2}$	

Note: a^2 denotes the additive genetic variance, d^2 denotes the dominant genetic variance, e^2 denotes the unique environmental variance, b denotes the contrast effect, α denotes the additive genetic relation between two individuals of a pair (i.e., 1 for MZ twins and 0.5 for DZ twins), and δ denotes the dominant genetic relation between two individuals of a pair (i.e., 1 for MZ twins and 0.25 for DZ twins).
Adapted from Table 10.3, Neale and Cardon (1992).

considered in this paper does not result in phenotypic mean differences between pairs of relatives varying in genetic relatedness (Carey, 1986, p. 324).

Calculations

Variance-covariance matrices were calculated for MZ and DZ twins for ADE-b models. Because the majority of twin studies on ADHD report no differences in heritability between males and females, evaluation of sex differences were not included in the power calculations. Estimates were 0.50 (a^2), 0.25 (d^2), and 0.25 (e^2) for additive genetic, genetic dominance, and unique environmental sources of variance, respectively. These estimates are usually reported for ADHD phenotypes, after correction of the total variance for the increase in variance due to the contrast effect. In other words, the sum of these three sources of variance equaled 1.00 in the absence of a contrast effect ($b = .00$). The contrast effect b was fixed at varying values, .00, −.05, −.10, −.15 and −.20. We considered univariate phenotypes only. All analyses were carried out using the statistical software package Mx (Neale *et al.,* 1999).

Identification of the ADE-b Model

Identification of parameters in the ADE-b model can be established formally by the method of Bekker *et al.* (1993). This method involves calculating the nullspace of the Jabobian of the covariance structure model. The Jacobian is the matrix of the derivatives of each element in the expected covariance matrices with respect to the parameters in the model. Specifically, this matrix has as many rows as there are elements in the expected covariance matrices, and as many column as there are (to be estimated) parameters. Each entry in the matrix is the derivative of the expected (co-) variance with respect to the parameters. The model is identified if and only if the null space of the Jacobian is zero, that is, if there are no linear dependencies among the columns of the Jacobian. In other words, the Jacobian should have full column rank for the model to be identified. Forming the Jacobian of the ADE-b model and calculating the null space is carried out using the program Maple (Heck, 1997). The formal approach to establish identification does not exclude the possibility that empirical underidentification may be encountered with this model (Kenny, 1979). As empirical underidentification may be apparent in computational difficulties, we also adopted an empirical approach to investigate whether such difficulties were encountered in fitting the ADE-b model (Neale *et al.,* 1999, p. 92). Again, MZ and DZ variance-covariance matrices were calculated with a set of fixed values a^2, d^2, e^2 and varying values for b. In an attempt to retrieve parameter values equal to those which were used as input in the calculation, varying starting values for a^2, d^2, e^2 and b were used. If the true parameter values are recovered regardless of starting values and the chi-square is zero, this provides an indication that empirical underidentification is not a problem.

Power in a Classic Twin Design

Power calculations were carried out by fitting the known model to the exact (population) covariance matrices as described in Neale and Cardon (1992). Constraining a certain set of parameters to zero and refitting the model provides the non-centrality parameter related to that particular constraint. From this non-centrality parameter the sample size required to reject the constrained (i.e. false) model with a probability (i.e., a power) of 0.80 and a significance level α of .05 can be calculated (Martin *et al.,* 1978; Hewitt and Heath, 1988) and is conveniently supplied by Mx. For the true model ADE-b, three series of power analyses were conducted. i) to establish the statistical power to detect contrast effects for given sample sizes, ADE models were fitted to variance-covariance matrices from the true ADE-b model. ii) to establish the statistical power to detect genetic dominance for given sample sizes false AE-b models were fitted. iii) to establish the power to detect a contrast effect after dominance had already been dropped from the model, the fit of an AE model was compared to the fit of an AE-b model while the true model was ADE-b.

DZ twins usually outnumber MZ twins due to the inclusion of opposite-sex twins. We therefore maintained a 1:2 ratio of MZ to DZ. Sample sizes are 300, 1500, 3000 and 6000 twin pairs, corresponding to empirical sample sizes for ADHD. The largest three sample sizes correspond to publications by the Virginia Twin Study of Adolescent Behavioral Development (Eaves *et al.,* 1997; Nadder *et al.,* 2001) and the Greater Manchester Twin Register (Thapar *et al.,* 2000); the Netherlands Twin Registry (Rietveld *et al.,* 2003); and the Twins Early Development Study (Price *et al.,* submitted), respectively. A sample of 300 twin pairs falls within the range of sample sizes reported upon by several smaller studies (Gjone *et al.,* 1996; Hudziak *et al.,* 2000; Kuntsi *et al.,* 2000; Martin *et al.,* 2002; Saudino *et al.,* 2000; Schmitz *et al.,* 1995; Sherman *et al.,* 1997).

Power in Alternative Twin Designs

Following the suggestion of Eaves (1976), the effects of additionally including pairs of genetically unrelated siblings (UR) reared together on statistical power were investigated. These unrelated siblings were considered as an extra group, not being part of the twin families. Given that shared environment is absent for ADHD, it was assumed that any phenotypic relation between these siblings is due to the contrast effect. These additional power calculations were conducted for the most unfavorable conditions, i.e., for the smaller sized twin studies, using the same fixed parameter values. We also considered the increase in power when non-twin siblings were added to the twin pairs. That is, here we considered the additional siblings being part of the twin families. The ratio of twin pairs with a sibling to twin pairs only was fixed at 2:1 while the ratio MZ to DZ twins was maintained at 1:2.

Positive Interaction

Whereas a negative *b* is confounded with D, a positive *b* is confounded with C. A model including shared environmental variance (C) and a positive *b* (i.e., ACE+b) is expected to encounter more power problems compared to an ADE model with a negative *b*. The expected shared environmental variance derived from the ACE+b model is of equal magnitude for MZ and DZ twins. As a result, the total variances of MZ and DZ twins do not differ as much from one another in the presence of a positive *b* compared to a negative *b*. To illustrate the magnitude of the power problem to detect a positive interaction effect, variance-covariance matrices were calculated with variance estimates of .50 for a^2, .25 for c^2 and .25 for e^2. The interaction effect *b* was fixed at +.15. An ACE model was fit to these variance-covariance matrices.

RESULTS

Expected Descriptives

The consequences of the presence a contrast effect on the total expected variances, covariances and correlations can be deducted from the equations given previously. In Table II the expected values of the MZ, DZ, and UR variances, covariances and correlations are given for each of the five true ADE-b models that are used in the power analyses.

This exercise clearly shows the consequences for variances, covariances and correlations in the presence of a contrast effect. Whereas the DZ variance is only minimally affected by a contrast effect, the DZ covariance reduces rapidly. As opposed to the DZ variance, the MZ variance is greatly affected by the contrast effect. The statistics for the UR pairs illustrate how the contrast effect corresponds to a negative correlation.

Identification of the ADE-b Model

Formal identification of the ADE-b model was established by calculation of the nullspace of the Jacobian

Table II. Expected Variances (Var), Covariances (Cov), and Correlations (Cor) for MZ Twins, DZ Twins, and UR Sibling Pairs in the Presence of a Contrast Effect (*b*)

	True model				MZ			DZ			UR		
	a^2	d^2	e^2	b	Var	Cov	Cor	Var	Cov	Cor	Var	Cov	Cor
(1)	.50	.25	.25	.00	1.00	.75	.75	1.00	.31	.31	1.00	.00	.00
(2)				−.05	.93	.66	.70	.98	.21	.22	1.01	−.10	−.10
(3)				−.10	.88	.57	.65	.97	.12	.12	1.03	−.20	−.20
(4)				−.15	.83	.49	.59	.97	.02	.02	1.07	−.31	−.29
(5)				−.20	.80	.41	.51	.99	−.08	−.08	1.13	−.43	−.38

Note: Expected variances and covariances were calculated in Mx. Due to rounding errors the listed descriptives may vary slightly from those calculated by hand.

of the covariance structure (the Maple input is available upon request). Data were generated assuming broad heritability of .75 with the values of the contrast effect *b* varying between −.05 and −.20. The calculated variance – covariance matrices were used as input data in a series of modeling in which starting values were varied for *b* and A, D, and E. Occasionally, we found that Mx converged to the incorrect maximum. This is perhaps due to the fact that Mx optimizes the log-likelihood using only function values. The specification of appropriate bounds ($-1 < b < 1$) avoided these problems and identical parameter values with zero chi-square were retrieved. We therefore conclude that the ADE-b model is empirically identified.

Power in a Classic Twin Design

For our first series of analyses, the effect of interest is the contrast effect *b*. As presented in Table III, a small contrast effect of −.05 remains undetected, irrespective of the number of twin pairs. Even with 6000 pairs, the power is only .30 to detect this effect. A large contrast effect (−.20) is detected reliably with a sample size of only 300 pairs. Comparison of the difference between estimates (see footnote, Table III) and the true values for A, D, and E indicates that when a contrast effect is ignored, estimates for the remaining sources of variance deviate from the true values, most notably when the true value of the contrast effect is larger than −.05.

In the second series of analyses, the power to detect genetic dominance was investigated by using the non-centrality parameter from the AE-b model, fitted to MZ and DZ covariance matrices generated from the ADE-b model. The requirement of very large sample sizes to detect D was confirmed (Table IV). The power to detect D is independent of the size of the contrast effect, clearly illustrated by identical power estimates within each twin design with varying values for *b*.

The third series of power calculations were based on a presumed 'realistic' scenario (Table V). The true parameters, again, are a^2 (.50), d^2 (.25), e^2 (.25) and *b* (.00, −.05, −.10, −.15, and −.20).

Following the usual procedure of comparing nested submodels to a full model (ADE-b), one may first decide that the variance due to D may be omitted from the model. Inability to detect D happens even with the largest sample size of 6000 twin pairs (see Table IV). The estimates that result from the fit of the AE-b model are slightly biased (these are identical to those listed in the footnote of Table IV). Dropping D from the ADE-b

Table III. Power to Detect a Contrast Effect *b* (*df* = 1)

	True model				100 MZ 200 DZ	500 MZ 1000 DZ	1000 MZ 2000 DZ	2000 MZ 4000 DZ
	a^2	d^2	e^2	b				
(1)	.50	.25	.25	−.05	.06	.11	.17	.30
(2)				−.10	.16	.59	.87	.99
(3)				−.15	.61	1.00	1.00	1.00
(4)				−.20	.94	1.00	1.00	1.00

Note: Estimates are (1) $a^2 = .16$, $d^2 = .55$, and $e^2 = .29$; (2) $a^2 = .00$, $d^2 = .66$, and $e^2 = .34$; (3) $a^2 = .00$, $d^2 = .60$, and $e^2 = .40$; (4) $a^2 = .00$, $d^2 = .51$, and $e^2 = .49$.

Table IV. Power to Detect Dominant Genetic Variance (*df* = 1)

	True model							
	a^2	d^2	e^2	b	100 MZ 200 DZ	500 MZ 1000 DZ	1000 MZ 2000 DZ	2000 MZ 4000 DZ
(1)	.50	.25	.25	.00	.06	.08	.12	.18
(2)				−.05	.06	.08	.12	.18
(3)				−.10	.06	.08	.12	.18
(4)				−.15	.06	.08	.12	.18
(5)				−.20	.06	.08	.12	.18

Note: Estimates are $a^2 = .78$, and $e^2 = .22$ for each model, (1) $b = -.04$; (2) $b = -.09$; (3) $b = -.14$; (4) $b = -.19$; (5) $b = -.24$.

model increases power to detect the contrast effect, which is slightly biased upwards. Interestingly, *b* may be detected when *b* is truly absent. Even with data from 3000 twin pairs available, there is a chance of .89 to estimate *b* at .04 when the true value of *b* is .00.

Power in Alternative Twin Designs

Based on Table III, it was decided to perform power analyses for the most unfavorable conditions. Variance-covariance matrices were calculated for 50, 100, and 200 pairs of UR which were combined with the twin data sets including 300 and 1500 pairs. A small contrast of −.05 remained undetected, even if data from 6000 twin pairs and 200 UR pairs are collected (power estimated at .56). We have therefore limited our analyses for a contrast effect of −.10 and −.15. Outcomes are listed in Table VI.

Comparing the results in Table III to the results in Table VI, it is apparent that the power to detect a contrast effect is greatly enhanced by the inclusion of genetically unrelated pairs. To detect a contrast effect of −.10, a small twin study of 300 pairs benefits most from additional information measured in more than 100 UR pairs. Due to the inclusion of pairs of UR siblings reared together, power increases from .16 to .64 (100 UR pairs) and .88 (200 UR pairs). Quite notable, a design including 300 twin pairs and 200 UR pairs is equally powerful as a design including 3000 twin pairs without additional UR siblings (Table III; third twin design). Also, adding 50 UR pairs to a twin study of 1500 pairs rapidly increases the statistical power to detect a contrast effect of −.10 from .59 to .76. Further, when a small twin study is extended with UR pairs, the difficulty to detect a contrast effect of −.15 is no longer encountered.

The increase in power due to the inclusion of non-twin siblings was explored for a contrast effect of −.10 and −.15. To enable a comparison with results shown in Table VI, analyses were performed for sample sizes, identical in number of participating individuals. Irrespective of sample size, power to detect a contrast effect of −.10 is insufficient when only twins and non-siblings are participating. A study of twins and non-twin siblings consisting of 700 individuals from 300 families has sufficient power to detect a contrast effect of −.10. This compares favourable to the power (.61) available in a study of equal family size, consisting of twins only (Table III, third row, first column).

Table V. Power to Detect a Contrast Effect *b* after Dropping D from the ADE-b Model (*df* = 1)

	True model							
	a^2	d^2	e^2	b	100 MZ 200 DZ	500 MZ 1000 DZ	1000 MZ 2000 DZ	2000 MZ 4000 DZ
(1)	.50	.25	.25	.00	.17	.61	.89	.99
(2)				−.05	.56	1.00	1.00	1.00
(3)				−.10	.89	1.00	1.00	1.00
(4)				−.15	.98	1.00	1.00	1.00
(5)				−.20	1.00	1.00	1.00	1.00

Note: Estimates are (1) $a^2 = .74$, $e^2 = .26$; (2) $a^2 = .68$, $e^2 = .32$; (3) $a^2 = .60$, $e^2 = .40$; (4) $a^2 = .47$, $e^2 = .53$.; (5) $a^2 = .31$, $e^2 = .69$.

Table VI. Power to Detect a Contrast Effect ($df = 1$) when Genetically Unrelated Sib Pairs (UR) Are Included

	True model							
	a^2	d^2	e^2	b	100 MZ 200 DZ +50 UR	100 MZ 200 DZ +100 UR	100 MZ 200 DZ +200 UR	500 MZ 1000 DZ +50 UR
(1)	.50	.25	.25	−.10	.43	.64	.88	.76
(2)				−.15	.89	.97	1.00	1.00

Power to Detect Positive Interaction

Expected variances calculated from the ACE +b are 1.31 and 1.23 for MZ and DZ twins, respectively. Expected covariances are 1.12 and .85 for MZ and DZ twins, respectively. The power is .43 to detect an interaction effect of $b = +.15$ with a twin sample of 2000 MZ and 4000 DZ pairs. This suggests that the detection of a positive interaction effect is not feasible given any sample size.

DISCUSSION

The use of models that incorporate interactions between phenotypes has become a popular method to analyze twin data. For overactivity, hyperactivity, impulsivity, inattention, and other phenotypes related to ADHD negative interactions or contrast effects have been reported. For some traits, positive interactions have been observed (Carey, 1992; Patterson, 1984; Rowe *et al.,* 1992). These reports most often concern antisocial tendencies. A single power calculation was performed to illustrate the mission impossible to detect a positive interaction effect. As opposed, the detection of a negative interaction is a feasible operation given a certain sample size. Here, we present power calculations for the detection of genetic dominance and contrast effects in the context of ADHD phenotypes. Sample sizes were fixed at 300, 1500, 3000, and 6000 twin pairs and a MZ to DZ ratio of 1 to 2, based on sample sizes from published reports on ADHD.

Prior to the power calculations, it was formally and empirically established that the ADE-b model is identified when using data from MZ and DZ twins. A model including both these effects as well as additive genetic effects and unique environmental effects was subsequently used as a true model for the power calculations. First, power was calculated for four values of the contrast effect (−.05, −.10, −.15, and −.20). Even with a sample size of 6000 twin pairs it was difficult to detect a relatively small contrast effect of −.05. Larger contrast effects could easily be detected using 3000 twin pairs ($b = -.10$), 1500 twin pairs ($b = -.15$) or even 300 twin pairs ($b = -.20$). The statistical power to detect genetic dominance accounting for 25% of the variance, remained as low as 0.18 even for sample size of 6000 twin pairs, confirming results of previous power analyses (Eaves, 1972; Posthuma and Boomsma, 2000). The difficulty to detect dominance is independent of the presence of either small or large contrast effects. Genetic dominance is estimated by differences in MZ and DZ covariances only and not by differences in MZ and DZ variances.

Usually, in an attempt to explain the data by the most plausible and parsimonious model, each individual source of variance is evaluated for its contribution to the observed total variance. Although reduced models are indeed more parsimonious, these models may give a biased account of the data. If a contrast effect is present but ignored, estimates for genetic dominant sources of variance are inflated whereas estimates for additive genetic sources of variance are deflated. The discrepancies between true values and resulting estimates are large, with unrealistic values for the additive genetic source of variance. Whereas large twin studies have the potential to detect a contrast effect, genetic dominance is more likely to go undetected given any sample size. Under these circumstances, the power to detect the contrast effect is much higher compared to the situation where genetic dominance is not omitted from the model. A small study of 300 pairs has sufficient power (.89) to detect a contrast effect of −.10 when genetic dominance is rejected from the model. This compares to a power estimate of .16 to detect the same effect of *b* when the genetic dominance is still included in the model. An accompanying result of ignoring the presence of genetic dominance is that A, E, and *b* deviate from the actual values. However, this bias is relatively small. When broad heritability is considered, the true values of A and D add up to 75% com-

pared to 78% obtained after fit of the reduced AE-b model. This bias is much smaller compared to the bias that results from rejecting a contrast effect prior to evaluating the presence of genetic dominance. From this we argue that the evaluation of genetic dominance should precede the evaluation of a contrast effect in a sequence of model fitting. If it is decided to exclude D from the model, estimates are close to true values and the likelihood to detect *b* is largely increased. However, with any reduced model, the researcher should be cautioned that the newly obtained estimates are biased.

We showed the advantage of extending the twin design with data from genetically unrelated siblings reared together. The power calculations indicated that a contrast effect is considerably easier to detect when data from such an additional group of informative pairs is available. Here we have assumed that the contrast effect for UR pairs is identical to the effect for twins. This assumption may not always be tenable. For instance, the magnitude of a contrast effect may vary as a function of the age difference between siblings. Since twins are of the same age, and UR most likely not, the magnitude of the contrast effect may differ between twin pairs and sibling pairs. Not only may the magnitude of the effect differ, the interaction may be limited to a one-way effect in UR pairs (e.g., Abramovitch *et al.,* 1979). If the contrast effect in UR pairs may not be constrained to the effect in twin pairs, there is obviously no advantage of including such an extra group of sibling pairs. So, ideally, the UR siblings are close in age. Segal (2000) has reported on such siblings as virtual twins who were either two adoptees, or one biological and one adopted child. Of course, unrelated siblings reared together may also apply to two children with different biological parents who live in the same household because their parents re-married. Although the search for these virtual twins may be troublesome, the increase in power is worth the effort, as are the financial benefits of not having to collect data from a large number of twins. We demonstrated that, in order to detect a moderate contrast effect, a study with 300 twin pairs and 200 sibling pairs has just as much power as a twin study of six times the sample size. The advantage of including UR pairs in the twin study also became evident when we explored the effects on statistical power of adding one non-twin sibling in the twin study (see also Posthuma and Boomsma, 2000).

In conclusion, the detection of a contrast effect is achievable given a certain sample size and composition. Researchers of ADHD and related traits are encouraged to search for unrelated sibling pairs to enhance power to detect a contrast effect. If present twin studies are small and suffer from minimal power to detect a contrast effect, we propose that genetic dominance is evaluated prior to the contrast effect.

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