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Genetic Influences on Respiratory Sinus Arrhythmia across Different Task Conditions

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Abstract. Respiratory sinus arrhythmia (RSA) has been shown to be a sensitive index of vagal cardiac control. We studied the genetic and nongenetic influences on individual differences in RSA in a sample of 160 adolescent twins. RSA was measured during rest and across two different tasks. Results show that heritability is task dependent. The amount of genetic variance is the same, however, during rest and task conditions. Because nonshared environmental variance decreases during tasks, heritability is larger for RSA measured under more stressful conditions than for RSA as measured during rest. Multivariate models assessed the continuity of the genetic and environmental influences and show genetic influences to be the same across different conditions, while environmental influences are different. More specifically, a one-factor model is found for genetic influences and a second-order autoregressive model for the environmental factors.

Key words: Respiratory sinus arrhythmia (RSA), Vagal tone, Twins

INTRODUCTION

In this paper we look at the genetic influences on individual differences in cardiac vagal tone as indexed by respiratory sinus arrhythmia (RSA). High RSA is regarded as an index of good health, both with regard to cardiovascular and central-nervous system functioning. In a prospective study Hinkle et al [7] found RSA to be an early predictor of cardiovascular disease and death. Lowensohn et al [10] observed heart-rate variability to be related to the functional state of the nervous system in a study of brain-damaged adults. Porges [14] also demonstrated a relation of RSA with clinical dysfunction and found RSA to be decreased in disordered populations such as children with minimal brain dysfunction or hyperactivity. Based on

these observations, Van der Molen et al [12] proposed to use RSA in cardiovascular neurometric assessment of hyperactive children. In addition, RSA has also been claimed to be related to information processing [13]: RSA goes down, for example, during mental load in laboratory tasks such as reaction time and speeded mental arithmetic.

Heart rate level is the result of intrinsic sinus node function and humoral and nervous effects. Nervous innervation of the heart is both sympathetic and parasympathetic (vagal) and short-term changes in heart rate can result from simultaneous changes in sympathetic influences and vagal tone. To separate the influences of vagal tone from sympathetic effects, it is therefore not sufficient to look at heart rate itself. An increase in heart rate, as observed in many stressful laboratory tasks, for example, can be the result of an increase in sympathetic influence or a decrease in vagal tone, or both. Respiratory sinus arrhythmia has been shown to be a sensitive, noninvasive index of cardiac vagal control. RSA refers to the cyclic variations in heart rate that are related to respiration. Heart rate typically increases during inspiration and decreases during expiration. The stronger these respiration-related variations in heart rate, the larger RSA and the stronger the vagal control of heart rate. The correlation between RSA and independently measured vagal tone has been found to be very high in both animal and human studies ($r > 0.9$) [9,3]. Part of RSA is mediated through the gating of vagal efferents of the heart by respiration, but the precise mechanisms underlying RSA are not understood. Several mechanisms are reviewed by Porges [15] and Grossman [5].

There are large individual differences in RSA, but no research is yet available on its heritability. For that reason, we measured RSA in a sample of 160 twin pairs to establish the influence of genetic factors on RSA. As RSA can be influenced by task manipulation, it was assessed both during rest and during a reaction time and a mental arithmetic task. In addition to estimating heritability under different conditions we also wanted to investigate if the same genetic and environmental influences operate in different tasks.

METHODS

Subjects

This study is part of a larger project in which cardiovascular risk factors are studied in 160 adolescent twin pairs and their parents. Addresses of twins (between 14-20 years of age) living in Amsterdam and neighboring cities were obtained from City Council population registries. Twins still living with both their biological parents were contacted by letter and asked to participate in the study. A family was included in the study only if the twins, as well as both parents, were willing to participate. Between 30% and 40% families complied. In addition, a small number of families who heard of the study from other twins also volunteered to participate. At the time of data collection, 83 families lived in, and 77 outside Amsterdam.

Zygosity was determined by analyzing the following polymorphisms: ABO,

MNS, P, Rhesus, Lutheran, Kell, Duffy, Kidd, Gm, Am and Km. Six twin pairs whose parents still doubted their monozygosity were also typed by DNA fingerprinting [8]. Three series of triplets were included by discarding the data from the middle child.

There were 35 MZ female pairs (average age 16.0, $sd = 2.2$), 35 MZ male pairs (16.6, $sd = 1.8$), 30 DZ female pairs (17.7, $sd = 2.0$), 31 DZ male pairs (17.2, $sd = 1.7$) and 29 DZ opposite sex pairs (16.4, $sd = 1.8$). All subjects were paid Dfl. 25 for their participation.

Procedure

Subjects always came to the laboratory in pairs, either the twins together and the parents together or a parent and a child. After arrival in the laboratory, height and weight were measured and electrodes and blood pressure cuff were attached. Subjects were measured during rest and during two task conditions. Testing took place in a sound-attenuated, electrically shielded cabin. The two experimental tasks consisted of a choice reaction time (RT) task and a speeded mental arithmetic (MA) task. Each condition was repeated once and lasted 8.5 minutes. During the resting periods subjects were asked to relax as much as possible. Before actual measurements were taken, subjects first received a practice session for each task. Subjects changed places in the cabin several times. When one subject was tested, the other subject filled in questionnaires. Sequence of events was: practice sessions, pause, Rest1 followed by RT1 and RT2, another break, Rest2 followed by MA1 and MA2. Eleven twin pairs were tested a second time after 18 months.

Tasks

In the RT task, each trial was started with the simultaneous onset of an auditory warning stimulus and the appearance of a vertical bar on the television screen. After 5 sec, a reaction stimulus was heard. Subjects had to react to high tones by pressing a key labeled "Yes" and to low tones by pressing a key labeled "No". Two seconds later, subjects received feedback on the television screen, indicating whether they had pushed the correct key and, in case the response was correct, also their reaction time.

In the MA task, subjects had to add 3 numbers that were presented in succession on the television screen. Five sec after the first number, the answer to the addition problem appeared on the screen. Half of the presented answers were correct, half incorrect. Subjects were required to press the "Yes" key if the presented answer was correct, and the "No" key if it was incorrect. They received the same feedback as in the RT task and after 2 more sec the next trial was started. The MA problems contained 10 levels of difficulty: ranging from 3 1-digit numbers (eg, $9 + 4 + 5$) to 3 2-digit numbers (eg, $85 + 79 + 47$).

All subjects started with a training session of 36 RT and 36 MA trials. The first problem for the MA task always was at the first level of difficulty. The level

of next problems depended on the subjects responses. The level reached by the subject after the 36 practice trials determined the level at which he or she started in the MA task. This procedure was developed so that the MA task would be equally stressful for all subjects. After the training session followed a pause and the first resting period. Next, subjects received 2 blocks of 36 RT trials. After a pause, subjects received the second resting period and two blocks 36 MA trials.

Apparatus

Subjects were seated in a comfortable chair in front of a Barco color television screen, that was used for presentation of visual stimuli. Auditory stimuli were binaurally presented through padded earphones. Two reaction time keys were mounted on either the left or right arm of the chair. Subjects pushed the keys with their preferred hand (278 right handed, 42 left handed).

To obtain electrocardiograms (ECG), Ag-AgCl electrodes were placed on sternum and lateral margin of the chest. ECG was recorded using an amplifier with a time constant of 0.3 sec and 1 M ohm impedance.

To measure respiration, a technique was employed that is based on changes in thorax circumference caused by expiration and inspiration. To assess these changes, subjects wore a small silicone tube around the thorax in which the frequency shift of an audio-tone was measured. These frequency shifts are directly related to changes in thorax circumference.

Data Quantification

ECG and respiration were recorded on a Beckman polygraph and digitized at 250 samples/sec via a 12-bit A-D converter. ECG data were used to determine the time between successive R-waves in msec. The respiration signal was used to identify onset times of inspiration and expiration phase and of the pauses between inspiration and expiration. RSA was quantified by the peak-to-trough method [6]. The shortest interbeat interval during inspiration is subtracted from the longest interbeat interval during expiration yielding a longest-shortest difference in msec. These differences are then averaged across all respiratory cycles of the measurement period. Interactive inspection of the automatic RSA quantification allowed for removal of artifacts. The first 30 sec of each condition were discarded for all subjects.

RESULTS

Table 1 gives means and standard deviations for the oldest and youngest twin of each sex by zygosity group for all task conditions. Multivariate analyses of variance showed no effect of zygosity and sex or of the interaction of sex by zygosity on the 6 RSA measures.

Table 1 - Means and standard deviations for RSA in msec for oldest and youngest twins during mental arithmetic (MA), reaction time (RT) and rest

RSA	MA1	MA2	RT1	RT2	Rest1	Rest2
MZM t1	82 (50.6)	79 (50.7)	91 (48.0)	83 (42.3)	114 (74.0)	114 (59.7)
MZM t2	77 (40.0)	69 (38.2)	88 (46.9)	81 (43.2)	110 (52.5)	105 (54.7)
DZM t1	81 (40.9)	77 (40.0)	95 (44.9)	88 (41.7)	102 (51.5)	98 (42.5)
DZM t2	85 (64.5)	79 (58.8)	92 (61.1)	86 (60.4)	106 (65.8)	103 (55.7)
MZF t1	93 (53.8)	91 (47.7)	106 (55.4)	99 (49.5)	130 (61.2)	127 (64.5)
MZF t2	88 (48.2)	85 (46.3)	100 (44.9)	94 (46.3)	114 (52.0)	116 (53.7)
DZF t1	83 (56.7)	80 (51.9)	88 (50.6)	90 (50.4)	109 (64.0)	112 (70.6)
DZF t2	77 (43.8)	75 (44.9)	88 (47.8)	83 (43.4)	104 (51.2)	107 (64.0)
DZOS M	88 (38.0)	85 (37.4)	99 (41.1)	93 (36.1)	109 (52.5)	114 (46.6)
DZOS F	86 (42.2)	83 (40.9)	104 (51.5)	99 (54.1)	116 (58.7)	116 (58.3)
Total	84 (48.2)	80 (45.9)	95 (49.3)	89 (47.0)	111 (58.7)	111 (57.4)

Correlations between RSA and age were not significantly different from zero.

Average long-term test-retest correlations computed for the 22 subjects that performed the experiment twice were 0.59 for Rest, 0.53 for RT and 0.60 for MA.

Analysis of variance for repeated measures tested the effects of task (3), trial (2, ie, the repetition of each condition), and task \times trial. Probabilities for the within-subjects factors were adjusted with the Greenhouse and Geisser [4] correction. There were significant (at the 5% level or better) effects of task and trial as well as of the interaction between the two. These effects did not interact with sex or zygosity. The effect of task is in the expected direction: RSA decreases under task conditions as compared with rest and more so in the more demanding MA task than in the RT task. As can be seen in Table 1, the effects of trial and task \times trial, though significant, are very small.

Genetic Analyses

Table 2 gives the intraclass correlations for the 5 twin groups, and for all MZ and all DZ pairs together. The correlations are dependent on the measurement condition: for both MZ and DZ twins correlations are higher under task conditions than during rest. With the possible exception of the rest conditions, there is no suggestion of different heritabilities for boys and girls.

Table 3 gives chi-squared statistics for univariate models fitted to each task condition. Models that have only a random environment parameter (E) do not fit the data in the task conditions, but do give a nonsignificant χ^2 for rest. For all conditions, however, there is a significant improvement in fit if genetic (G) or common environmental (C) factors are added to the model. This improvement is somewhat larger for the EG than for the EC model. When both G and C are specified, estimates for C go to zero and an EG model remains. The second part of

Table 3 gives parameter estimates from the best fitting (EG) model and heritability estimates, again for each condition. Genetic factors explain almost 50% of the variance in RSA under task conditions and roughly half of that during rest. As can be seen, the amount of genetic variance is almost the same in each situation, and the differences in heritability are caused by a larger amount of specific environmental variance in the resting conditions.

Table 2 - Intraclass correlations for RSA during mental arithmetic (MA), reaction time (RT) and rest

RSA	MA1	MA2	RT1	RT2	Rest1	Rest2
MZM	0.48	0.51	0.42	0.47	0.15	0.19
DZM	0.32	0.33	0.19	0.22	0.14	0.03
MZF	0.48	0.48	0.51	0.49	0.45	0.36
DZF	0.21	0.20	0.12	0.12	0.04	0.05
DZOS	0.24	0.17	0.20	0.24	0.07	0.19
All MZ	0.50	0.51	0.47	0.49	0.30	0.29
All DZ	0.25	0.23	0.16	0.19	0.07	0.06

Table 3 - Univariate model fitting: Chi-squared statistic and probability level

	MA1	MA2	RT1	RT2	Rest1	Rest2
E	26.88 (0.00)	24.32 (0.00)	19.71 (0.02)	21.34 (0.01)	9.07 (0.43)	12.04 (0.21)
EC	8.96 (0.35)	6.88 (0.55)	6.83 (0.56)	7.86 (0.44)	5.07 (0.75)	8.66 (0.37)
EG	6.21 (0.62)	3.74 (0.88)	2.27 (0.97)	2.82 (0.95)	3.98 (0.86)	7.44 (0.49)
EGC	6.20 (0.52)	3.73 (0.81)	2.27 (0.94)	2.82 (0.90)	3.98 (0.78)	7.44 (0.38)

Input is mean squares between and within twin pairs; degrees of freedom are 9 (E), 8 (EC and EG) and 7 (EGC).

Parameter estimates and SE for univariate EG models						
G	33.52 (3.82)	31.88 (3.66)	33.25 (3.99)	32.57 (3.69)	28.73 (6.64)	27.84 (6.57)
E	35.28 (2.78)	33.72 (2.66)	36.57 (2.87)	34.12 (2.69)	51.36 (3.77)	50.46 (3.70)
h^2	0.47	0.47	0.45	0.48	0.24	0.23

Table 4 - Phenotypic correlations for RSA between tasks for oldest (upper half) and youngest twins (lower half)

	Rest1	RT1	RT2	Rest2	MA1	MA2
Rest1	1.000	0.827	0.817	0.900	0.755	0.739
RT1	0.806	1.000	0.953	0.819	0.895	0.868
RT2	0.812	0.958	1.000	0.817	0.905	0.886
Rest2	0.861	0.827	0.835	1.000	0.823	0.793
MA1	0.741	0.888	0.909	0.783	1.000	0.976
MA2	0.721	0.859	0.906	0.764	0.957	1.000

Phenotypic correlations between the six RSA measures are high (see Table 4). The highest correlations are between the replications of a condition, while correlations between rest and task are somewhat lower. To the 6×6 matrices of crossproducts between and within twin pairs we first fitted a factor model with one genetic and one environmental common factor [11] and a simplex model with one first-order autoregressive genetic and one first-order autoregressive environmental series [2]. In the factor model, correlations between observations are explained by their loadings on the same genetic and environmental factors. In addition, unique genetic and environmental factors can be specified for that part of the variance that is not shared between measures. In the simplex model, correlations are explained by the autocorrelation among genes and among environmental factors that influence the phenotype at each different time point. In this model the variance unique to each observation is accounted for by an innovation term that can come into play at each time point. Both these models did not fit the data, even after some allowance was made for the bad condition of the input matrices. When working with input matrices that are nearly singular because of the high intercorrelations between measures (ie, have a small determinant), chi-squared statistics become biased and parameter estimation can be difficult [1]. Numerical optimization can be greatly improved by adding a small constant to the diagonal of the input matrices that is subsequently corrected for in the model. Since the constant is corrected for in the model, parameter estimates themselves remain unbiased.

With these provisions, the simplex model showed a smaller χ^2 than the factor model, χ^2 for the factor model was 370.55 ($df = 192$, $p < 0.000$) and for the simplex model it was 270.49 ($df = 187$, $p < 0.000$). Inspection of the residuals for the simplex model (ie, the differences between estimated and observed variances and covariances) showed that the largest residuals were for the covariances of Rest1 and Rest2 and for the covariances of RT and MA tasks. Looking at the phenotypic correlations, we see that the correlations among tasks are higher than the correlations between resting conditions and tasks. This suggests that a first-order autoregressive process may not give a good explanation of the data and that we have to look for additional influences specific to task and rest conditions. Therefore, second-order autoregressive models were fitted to the data with additional paths from Rest1 to Rest2 and from RT2 to MA1. Here, in addition to a direct path from time i to time $i + 1$, separate paths test whether there is a significant independent influence from the first to the second resting period, that is, influences specific to rest and not to task, and if there also is an independent influence from the RT to the MA task that is not mediated by the rest in between the two. Models were specified where there was a second-order process for the genetic or the environmental series. The model with a second-order simplex for the environment showed the best fit. The model with a second-order process for G gave a χ^2 of 266.83 ($df = 185$, $p < 0.000$), whereas a second-order process for E gave a χ^2 of 203.11 ($df = 185$, $p < 0.172$). Parameter estimates for this last model are given in Table 5A. Loadings of the 6 observations on unique environmental factors were constrained to be equal (the square of these estimates represents variance of measurement errors and other occasion specific environmental influences). The autoregressive coefficients for the

Table 5 - Parameter estimates and SE for

A: simplex model for E (second-order) and G (first-order)

B: simplex model for E (second-order) and Factor Model for G

C: environmental and genetic variances based on model B

A	Autoregressive coefficients (E)	Innovations (E)	Autoregressive coefficients (G)	Innovations (G)	Error
Rest1		2710.26 (328.9)		696.44 (295.1)	7.08 (1.06)
RT1	0.58 (0.04)	480.64 (83.8)	1.15 (0.19)	52.24 (108.9)	7.08 (1.06)
RT2	0.91 (0.04)	69.55 (37.4)	0.97 (0.05)	14.75 (23.3)	7.08 (1.06)
Rest2	0.52 (0.12)	465.84 (75.0)	0.79 (0.12)	27.79 (28.2)	7.08 (1.06)
	0.60 (0.07) ^a				
MA1	0.15 (0.06)	209.24 (46.0)	1.32 (0.22)	49.97 (67.1)	7.08 (1.06)
	0.72 (0.10) ^b				
MA2	0.92 (0.04)	27.62 (33.5)	0.97 (0.04)	24.10 (23.5)	7.08 (1.06)

B	Autoregressive coefficients (E)	Innovations (E)	Factor loadings	
			G	Error
Rest1		2492.73 (283.3)	32.63 (3.42)	6.65 (1.19)
RT1	0.57 (0.04)	569.21 (70.8)	32.63 (3.42)	6.65 (1.19)
RT2	0.87 (0.03)	87.13 (30.6)	32.63 (3.42)	6.65 (1.19)
Rest2	0.45 (0.08)	544.17 (60.6)	32.63 (3.42)	6.65 (1.19)
	0.61 (0.05) ^a			
MA1	0.14 (0.04)	315.70 (38.9)	32.63 (3.42)	6.65 (1.19)
	0.74 (0.07) ^b			
MA2	0.90 (0.03)	58.57 (30.1)	32.63 (3.42)	6.65 (1.19)

C	Environmental innovation	Total E variance	Genetic variance	Error variance	h ²
Rest1	2492.73	2492.73	1064.70	44.22	0.29
RT1	569.21	1376.10	1064.70	44.22	0.43
RT2	87.13	1128.70	1064.70	44.22	0.48
Rest2	544.17	1700.26	1064.70	44.22	0.37
MA1	315.70	967.11	1064.70	44.22	0.51
MA2	58.57	841.93	1064.70	44.22	0.51

^a Independent influence of Rest1 on Rest2^b Independent influence of RT2 on MA1

environmental part of the model show that, in addition to significant paths from time i to time $i + 1$, there are independent influences from environmental factors at Rest1 to environmental factors at Rest2, representing environmental influences specific to "resting" RSA. The independent influences from environmental factors at RT2 to environmental factors at MA1 can be regarded as task specific. As can be seen, the genetic simplex strongly suggests a one-factor solution with the autoregressive coefficients approaching 1, and nonsignificant genetic innovations. Thus, as a last model, we took the same second-order autoregressive environmental process and a one-factor model for G, with loadings on the genetic factor constrained to be equal (see Figure). The χ^2 for this last model was 215.73 ($df = 195$, $p < 0.147$). Parameter estimates are given in Table 5B and the total amounts of genetic

and environmental variance in 5C. The estimate of 1700.26 for the environmental variance in RSA during Rest2 is thus in part shared with the environmental variance during RT2 ($0.45^2 * 1128$), in part with the environmental variance during Rest1 ($0.61^2 * 2492$), and is partly new environmental variance entering into the process at that point in time (544). As can be seen in Table 5, the error variance is relatively small as compared to the total environmental variance. Heritabilities as computed from this multivariate model, finally, are somewhat larger than in the univariate analyses. By having 6 indicators for G and constraining the factor loadings on G to be the same across all conditions, there is more power to estimate heritabilities than in the univariate case.

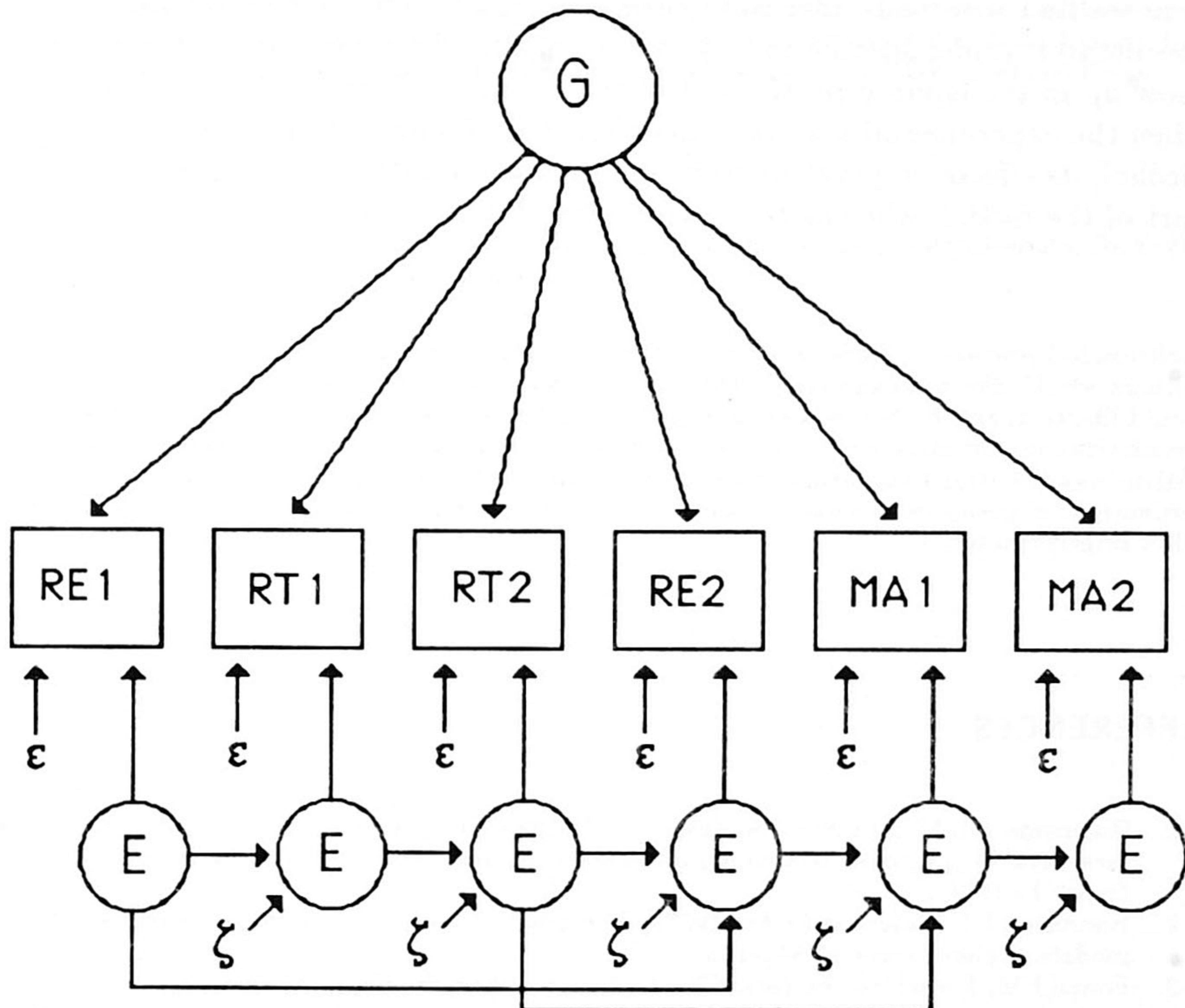


Figure. Final model for RSA measured during rest (RE), reaction time (RT) and mental arithmetic (MA). Genetic influences (G) show a one factor structure. The environmental process is described as a second-order autoregressive model, with independent influences from Rest1 to Rest2 and from RT2 to MA1. ϵ represents measurement errors and ζ innovations.

DISCUSSION

Univariate analyses of the 6 RSA measures show heritabilities to be task dependent. During 2 stressful laboratory tasks, roughly 50% of the variance is explained by genetic factors, while during an 8-minute resting period, only 25% is accounted for by genetic influences. The amount of genetic variance is the same, however, during all conditions and the reason that h^2 is larger during tasks, is that the specific environmental variance decreases. There is no evidence for influence of common environment. Of even more interest are the results from the multivariate analyses. These not only show equal amounts of genetic variance in all conditions, but also that the same genetic factors are expressed under task and rest conditions. This implies that individual differences in vagal tone that are genotype dependent are better assessed during task than during resting conditions. The effects of experimental manipulations only show up in the environmental part of the variance, and here we find a second-order autoregressive process with environmental influences specific to rest and specific to task. Experimental manipulations do not necessarily show up in the environmental part of the variance. Boomsma et al [1] found that when the experimental manipulation consisted of administering a standard dose of alcohol, its effects on psychomotor performance showed up in the genetic (simplex) part of the model, whereas the environmental part showed a one-factor structure.

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