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Genetic and Environmental Influences on EEG Coherence

C. E. M. van Beijsterveldt,[1-3] P. C. M. Molenaar,[2] E. J. C. de Geus,[1] and D. I. Boomsma[1]

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EEG coherence measures the covariation in electrical brain activity between two locations on the scalp and is used to study connectivity between cortical regions. The aim of this study was to determine the heritability of EEG coherence. Coherence was measured in a group of 213 16-yr-old twin pairs. By including male and female twin pairs in the sample, sex differences in genetic architecture were systematically examined. The EEG was obtained during quiet supine resting. Coherence was estimated for short and long distance combinations of electrode pairs along the anterior-posterior axis within a hemisphere for four frequency bands (delta, theta, alpha and beta). Averaged over all electrode combinations about 60% of the variance was explained by genetic factors for coherence in the theta, alpha and beta bands. For the delta band, the heritability was somewhat lower. No systematic sex differences in genetic architecture were found. All environmental influences were nonshared, i.e., unique factors including measurement error. Environmental factors shared by twin siblings did not influence variation in EEG coherence. These results suggest that individual differences in coherence form a potential candidate for (molecular) genetic studies on brain function.

KEY WORDS: Brain function; cortico-cortical connectivity; sex differences; maturation; twins; heritability.

INTRODUCTION

The aim of this study is to investigate the contributions of genetic and environmental factors to individual differences in the functional connections between human brain areas. The human brain has a modular organization consisting of brain areas which differ markedly in their morphology and in their function. The brain areas do not work isolated but are linked, coordinated and integrated by complex neural circuits. In humans, the number of cortico-cortical connections is very large and their development continues at least until the age of 20. The general program of cortico-cortical pathways development seems to be under genetic control, but, the final number of synapses is far too large to be controlled by a specific genetic program (Changeux and Danchin, 1976). For example, the morphology of the corpus callosum in monozygotic (MZ) twins is more similar than in unrelated subjects but not completely identical (Oppenheim, 1989; Steinmetz *et al.*, 1994), pointing to genetic factors and environmental experiences as co-determinants of its final shape. It seems likely that only the general outlines of neural connectivity are genetically programmed (Huttenlocher, 1994), while the fine-tuning of the pattern of neural connections is determined through the interactions with its en-

[1] Department of Psychophysiology, Vrije Universiteit, Amsterdam, The Netherlands.
[2] Department of Psychology, Universiteit van Amsterdam, Amsterdam, The Netherlands.
[3] To whom correspondence should be addressed at Universiteit Maastricht, Department of Neuropsychology, Postbus 616, 6200MD Maastricht, The Netherlands. Fax: +31433671096. e-mail: t.vanbeijsterveldt@nnp.unimaas.nl.

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vironment (Wiesel, 1994). Growth of the central nervous system (CNS) is an epigenetic process: the CNS develops in interaction with the environment resulting in modification of both the CNS and the environment (Benno, 1990; Molenaar *et al.*, 1993). Therefore, it may be expected that in addition to genetic factors, effects of specific experiences will account for individual differences in the functional connections of the brain.

A noninvasive technique for studying functional connections between brain regions is the electroencephalgraphic (EEG) coherence. The coherence estimates the association between electrophysiological signals recorded from two spatially separated scalp locations. Mathematically it is the squared cross-correlation in the frequency domain between two EEG time series measured simultaneously at different brain locations (Nunez, 1995). Although volume conduction may inflate coherence, phase relations and the fall in coherence with distance suggest that coherence relates to the degree of functional connectedness among distant cortical areas. Thatcher (1994) has speculated that the coherence between two scalp regions reflects the degree to which there are anatomical connections among these brain regions. The type, strength, and number of these axonal connections are reflected by coherence values, such that coherence between neighboring electrode sites reflects the short-fiber system of basal dendrites and axon collaterals, whereas longer distance coherences reflect cortico-cortical connections of the apical dendrites. Empirically, coherence has been associated with both normal and abnormal individual differences in behavior. For example, the coherence patterns during mental activity are predictive of performance in cognitive tasks and even of general intelligence (Duffy *et al.*, 1995; Anokhin and Vogel, 1996). An ongoing study found decreased local EEG coherence in anterior cortical areas in individuals high on novelty seeking and low on harm avoidance (Anokhin, Vedeniapin, Rohrbaugh, Sirevaag, and Cloninger, unpublished). Thus, EEG coherence is a promising tool for the study of individual differences. Complex behavioral traits, like general intelligence, are likely to be related to individual differences in *organization* of brain activity, rather than to the characteristics of activity at isolated cortical sites.

Two recent studies (Ibatoullina *et al.*, 1994; van Baal *et al.*, 1998) provided evidence for genetic influences on EEG coherence in young children. Heritability estimates for coherence ranged from 30 to 71%. In this study we want to investigate the coherence in the adolescent period. Maturation of the brain is strongest in childhood, but continues up to the second and third decades of life. In the period of adolescence and young adulthood there is ongoing increase in myelination (Benes, 1989) and elimination of excess synapses that are not incorporated in functional units (Goldman-Rakic, 1987). These structural changes are particularly pronounced in the connections to the frontal brain areas. In addition to structural changes, several studies demonstrated functional changes in the frontal lobes of the brain as measured by EEG methods (Matoušek and Petersén, 1973; Hudspeth and Pribram, 1992; Buchsbaum *et al.*, 1992). Specifically, in a large cross-sectional study (Thatcher *et al.*, 1987; Thatcher, 1994), coherence showed large changes during cerebral development of normal children in the range from a few months to early adulthood. Periods of increased coherence alternated with periods of decreased coherence, and prominent changes in EEG coherences involving frontal areas were prominent around age 16.

To date, the source of individual differences in EEG coherence in adolescence remains unknown. Understanding these individual differences in coherence is important because inadequate development of (frontal) brain connectivity in this period is generally thought to play a crucial role in the vulnerability to psychosis and affective disorders (Saugstadt, 1994). The present study uses a twin design to estimate the contribution of genetic and environmental factors on EEG coherence in adolescents. Since different studies have found sex differences in the structure of the human brain (Gur *et al.*, 1995; Steinmetz *et al.*, 1995) and sex differences in functional organization (Kimura, 1987), sex differences in the genetic architecture of EEG coherence will be specifically modeled. EEG was measured on 14 scalp locations, yielding (14*13)/2 possible electrode combinations. In this paper we will concentrate on intrahemispheric coherences along the posterior-anterior axis. This choice reflects the importance of intrahemispheric connections from and to the frontal lobe in adolescence and keeps our results comparable to those of previous studies (van Baal *et al.*, 1998; Thatcher, 1994; Kaiser and Gruzelier, 1996).

METHODS

Subjects

A group of 213 adolescents twin pairs (mean age = 16.18 SD = .55) participated in the study. Addresses of twin pairs were obtained from participants in a large questionnaire study on health-related behaviors (Boomsma *et al.*, 1994). Subjects were invited by letter to participate in the experiment. As a reward for their participation the subjects received a present and costs they incurred traveling to the laboratory were reimbursed.

The twin pairs were divided into five groups by sex and zygosity: 39 monozygotic male pairs (MZM), 36 dizygotic male pairs (DZM), 52 monozygotic female pairs (MZF), 38 dizygotic female pairs (DZF) and 48 opposite sex (DOS) pairs. For 114 same-sex twin pairs zygosity was determined by blood and DNA typing. For the other same-sex twin pairs zygosity was determined by a questionnaire that was completed by the mother (N = 34) or by the twins themselves (N = 17). The questionnaire contained items about physical similarity (similarity of face, eye color, hair color and skin color) and the frequency of confusion of the twins by family and strangers. Agreement between zygosity based on this questionnaire and zygosity based on blood group and DNA polymorphisms in the 114 twin pairs for whom both types of information was available was 95%.

Six pairs were discarded from further analyses because of recording artifacts in one or more EEG channels. This left 37 MZM, 35 DZM, 52 MZF, 37 DZF and 46 DOS twin pairs for analysis.

Procedure

The measurement session lasted three and a half hours and took place in the morning or in the afternoon. Subjects visited the laboratory on the same day as their cotwin and were tested during the same part of the day. The session consisted of four tests: measurement of the electroencephalogram (EEG), event related potentials (ERP), measurement of nerve conduction velocity (NCV) reaction time and IQ tests (Rijsdijk et al., 1995). After arriving, subjects were given a short explanation of the experimental procedure. One member of the twin pair started with the EEG measurement, the other one with the NCV. After the EEG and

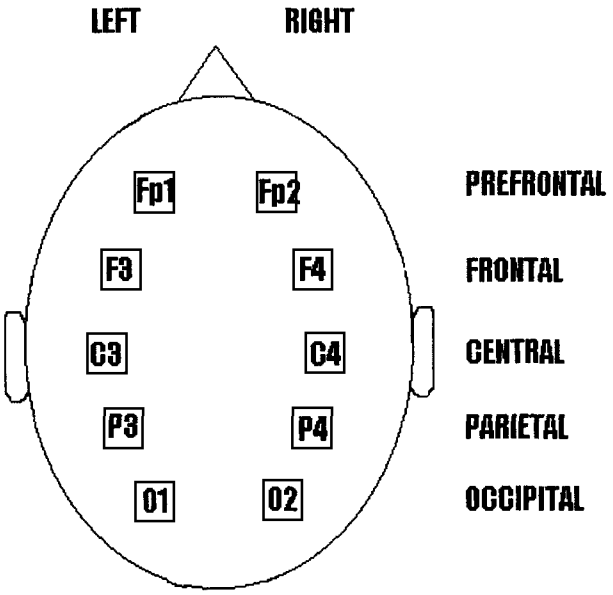

Fig. 1. Scalp locations at which EEG coherence was computed: prefrontal (Fp1, Fp2), frontal (F3,F4), parietal (P3, P4), and occipital (O1, O2).

EOG (electro-oculogram) electrodes were put in place, the subjects laid down on a bed in an electrically shielded and sound proof cabin. After inspection of the EEG and EOG signals, instructions were displayed on a black and white monitor that was attached to the ceiling. EEG was measured during 4 experimental conditions in a fixed order: auditive habituation task, visual oddball task and background-EEG in rest with eyes open and finally with eyes closed. If artifacts occurred during the recording, for example due to movement of the subject or technical problems, the recording period was lengthened until 3 minutes of artifact free EEG was obtained. In the present paper the results of EEG coherence in the supine rest condition with eyes closed are presented.

EEG Recording

Tin electrodes mounted in an electrocap were used for measuring EEG and EOG activity. Scalp locations (depicted in Figure 1) were prefrontal (Fp1,Fp2), midfrontal (F3,F4), frontal (F7,F8), central (C3,C4), parietal (P3,P4), occipital (O1,O2) and temporal (T5,T6), according to the 10–20 system (Jasper, 1958). Linked earlobes were used as

an electric reference according to the method described by Pivik *et al.* (1993). Briefly, two separate preamplifiers with high input impedance were connected to each of the reference electrodes, and their output linked electrically. With the reference electrodes linked this way, the effects of possible electrode impedance introduced by the electrical double layers were prevented. The electrode impedance for EEG and EOG was less than 5 Kohm. Tin electrodes were placed at the canthus of each eye for recording horizontal movements. To detect vertical eye movement, EOG was recorded from intra-orbital and supra-orbital electrodes, in line with the pupil of the left eye. A ground electrode was attached to Fpz (The scalp location between Fp1 and Fp2).

All EEG- and EOG-signals were displayed and recorded by an 18-channel Nihon Kohden electroencephalograph (type EEG-4414A1K). For EEG and EOG the recording time constant was 5 s and a low pass frequency, with a 35 Hz cut-off frequency used. Signals were sent to a 12-bit analog-to-digital converter and computer-stored for offline processing. The sampling rate of the AD-converter was 250 Hz. A set of 100 microvolt sine waves was used for calibration prior to and after recording.

Data Processing

Preprocessing of the EEG consisted of dividing the EEG signal into epochs of 2 sec. After automatic removal of epochs with clippings and with abnormal EEG patterns (detected during visual inspection), eye movement artifacts in the remaining 2 sec epochs were removed by means of a dynamic regression routine in the frequency domain (Brillinger, 1975). The direct current offset was removed from the data by calculating the mean of the epoch and subtracting it from each point. Fast Fourier Transformation (FFT) was applied, which converted the raw EEG coherence from the time domain into the frequency domain. Per epoch the output yielded power spectra for electrode position and cross spectra. Smoothed power spectra and cross spectra for frequency range from .5 to 30 Hz, with .5 Hz steps, were calculated by averaging the power and cross spectra over the valid epochs. A minimum of 30 epochs was required per subject. For each frequency EEG coherence was estimated from power and cross spectra. The coherence was calculated for the electrode combinations Fp1-O1, Fp1-P3, F3-O1, Fp1-C3, C3-O1, Fp1-F3, and P3-O1, and the same combinations for the right hemisphere: Fp2-O2, Fp2-P4, F4-O2, Fp2-C4, C4-O2, Fp2-F4, and P4-O2. Coherence was computed as

$$\text{coherence} = \frac{Gxy(f)^2}{Gxx(f)Gyy(f)}$$

where Gxy is the cross spectrum of EEG at two electrode locations 'x' and 'y', and Gxx(f) and Gyy(f) are the respective EEG power spectra at these electrode locations. The f indicates the frequency. The coherence is analogous to the usual correlation coefficient and so ranges from 0 to 1.

The resulting coherence values were averaged over broad frequency bands: delta (1.5-3.5 Hz), theta (4-7.5 Hz), alpha (8-12.5 Hz) and beta (13-25 Hz). All values were log transformed with $\log_{10}(\text{Coh}/1\text{-Coh})$ to transform the coherence into a more Gaussian distribution.

Statistical Analysis

Before carrying out the statistical analyses, the data were examined for extreme values of the coherence (larger than 4 * sd). If there were extremes scores, subjects were discarded from further analysis. For the delta band 8 twin pairs were discarded, for theta 3 twin pairs, and for beta 12 twin pairs were discarded, respectively. MANOVA was used to test whether there were any mean differences between males and females or between MZ and DZ twins. For each frequency band, the coherence of all electrode combinations were used as the dependent variables, with electrode combinations (Fp-O, Fp-P, F-O, Fp-C, C-O, Fp-F, and P-O), hemisphere (left, right) and birth order (first, second born) as within pairs factors and with sex and zygosity as between factors. To test for sex and zygosity effects the MANOVA was carried out on data from same-sex twin pairs.

Genetic Analyses

For each electrode combination, the data of twin1 and twin2 were summarized into 2 × 2 variance-covariance matrixes, computed by Prelis (Jöreskog and Sörbom, 1986). Mx (Neale, 1994) was used to test the fit of the univariate twin model for the coherence of each electrode combination by the

method of maximum likelihood. Mx provides a χ^2 goodness-of-fit statistic for the overall model (Heath *et al.*, 1989; Neale and Cardon, 1992). Models were fitted to the covariance matrices that specified variation in coherence to be due to additive genetic (A), unique environmental (E) influences, and genetic non-additive (D) influences. In order to test for sex differences three models were evaluated. The first model tests the possibility of a different magnitude of genetic and environmental factors between the sexes, but for males and females the same genes and/or common environmental factors are expressed. The second model was a scalar model, in which the heritabilities are constrained to be equal across sexes, but in which total variances may differ. In the scalar model, the variance components for males are constrained to be equal to a scalar multiple of the female variance components. The third model tested the possibility that sex specific genes exist, which influence the trait in one sex but not in the other. In this model the genetic correlation between the DOS twins was estimated, instead of fixing it at .5. An estimate of this correlation that is significantly lower than .5 indicates that genetic influences on EEG coherence that are expressed in males are imperfectly correlated with genetic influences that are expressed in females.

Parameters h, d, and e that represent additive, non-additive genetic and unique environmental influences on the phenotype were estimated by maximum likelihood, using the computer program Mx (Neale, 1994). Goodness-of-fit was assessed by the likelihood-ratio Chi-square tests. The overall chi-square tests the agreement between the observed and the predicted variances and covariances in the 5 twin groupings. Submodels, that constrain parameters to be equal to zero or constrain parameter estimates in females to be equal to the estimates in males, were compared by hierarchic chi-square tests, in which the chi-square for the full model is subtracted from that for a reduced model. The degrees of freedom (df) for this test are equal to the difference between the df for the full and the submodel.

RESULTS

Mean Data

Table I presents the mean coherence for the electrode combinations for each frequency band in the left and right hemisphere across all subjects. The mean coherences of all frequency bands decreased as the interelectrode distance increased. Higher coherences were found for the shorter distances. The coherences in the left and right hemisphere showed no mean differences. MANOVA showed no significant main effect of hemisphere on any of the frequency bands. A significant sex effect was found for all bands (alpha, $F(1/157) = 6.91$, $p < .009$; delta, $F(1/151) = 5.65, p < 0.019$; theta, $F(1/155) = 19.57$, $p < .000$; beta, $F(1/149) =$

Table I. Mean Values of the Untransformed Coherence Estimates of Electrode Combinations for 4 Frequency Bands (Delta, Theta, Alpha and Beta)[a]

	Males		Females	
	Left	Right	Left	Right
		Delta		
Fp-O	.03	.03	.03	.03
Fp-P	.06	.05	.06	.06
F-O	.06	.06	.07	.07
Fp-C	.17	.19	.18	.20
C-O	.22	.22	.27	.26
Fp-F	.50	.51	.51	.52
P-O	.59	.62	.67	.69
		Theta		
Fp-O	.03	.03	.03	.03
Fp-P	.05	.05	.05	.05
F-O	.05	.05	.06	.06
Fp-C	.17	.20	.20	.22
C-O	.18	.17	.21	.20
Fp-F	.53	.56	.54	.57
P-O	.54	.57	.61	.63
		Alpha		
Fp-O	.15	.15	.15	.14
Fp-P	.08	.08	.08	.08
F-O	.09	.10	.09	.09
Fp-C	.21	.22	.25	.25
C-O	.12	.12	.14	.13
Fp-F	.62	.64	.64	.66
P-O	.54	.59	.60	.64
		Beta		
Fp-O	.03	.03	.03	.03
Fp-P	.04	.04	.04	.06
F-O	.03	.03	.03	.03
Fp-C	.13	.13	.15	.16
C-O	.10	.09	.11	.10
Fp-F	.39	.42	.41	.44
P-O	.48	.50	.53	.55

[a] Coherence scaling is from 0 to 1. Electrode combinations are ordered by decreasing electrode distance.

13.97, $p < .000$). For most electrode combinations in all frequency bands the coherence in females was larger than the coherence in males. There were no significant main effects of birth order and zygosity and no significant interactions of zygosity by sex, except a small sex by zygosity interaction for coherence in the delta frequency band ($F(1/151) = 4.17$, $p < .043$).

Reliability

Estimates of reliability of EEG coherence were obtained by using a split-half approach. The EEG coherence epochs were divided in two series, an odd and an even series. The correlation between these two series served as an estimate of reliability of the EEG coherences. As shown in Table II the reliability was high for most electrode combinations and frequency bands. In the delta and theta frequency bands reliability decreased with increasing electrode distance. Some care is needed in interpreting the genetic results of delta and theta coherence across the longer distances.

Genetic Analyses

The MZ and DZ, female and male, twin pair correlations are given in Table II. Generally, for all electrode combinations in all frequency bands, the correlations for MZ twins were higher than the DZ correlations, pointing to the influence of genetic factors. The DOS correlations were for the most part similar to the same-sex DZ correlations, suggesting no sex differences in the genetic architecture. Table III presents the χ^2's for the best fitting models for each electrode combination of the left and right hemisphere. In addition, the table gives the comparison between (1) ADE model with sex differences and an ADE model without sex differences (test for sex differences in parameter estimates), and (2) and ADE model and an AE model (test for dominance). The E only model never gave an adequate description of the data. The χ^2's indicate the goodness-of-fit, the smaller the χ^2 the better the agreement of the observed data with the model. For most electrode combinations the fit of the model was fairly good (χ^2 of 6.26, gives a probability of .85) to reasonable (χ^2 of 15, gives a probability of .30). The heritability estimates and their confidence intervals (Miller and Neale, 1997) are displayed in Table IV. Only additive heritabilities are given since most tests for dominance showed no significance. The details for each frequency band are discussed below.

Delta. For all electrode combinations an AE model gave the best fit to the observed data, suggesting that genetic influences play a role in the individual differences in coherence. No sex differences in genetic architecture were found, as indicated by the nonsignificant decreases in χ^2 comparison to the reduction in the degrees of freedom. Heritability of the coherences over short and intermediate distances in the left and right hemisphere averaged 48%. For three of the longer distances (right and left Fp-O, Fp-P left), only 29% of the variance in individual differences in delta coherence was explained by genetic factors. Confidence intervals of these three long connections did not overlap with those of five of the shorter distances. The lower reliability of long distance delta coherence most likely explains its lower heritability.

Theta. The MZ correlations for EEG coherence in the theta frequency band were about twice the DZ correlations and in general twin correlations were higher than those found for the delta band. Some DZM correlations were near zero and formal testing indicated genetic dominance for coherence between right Fp and O leads. No evidence of genetic dominance was found for all other theta coherences. For most combinations of electrode pairs the best fitting models were AE models, indicating an additive genetic mode of transmission. The fit of these models was passably good. The percentage of variance explained by genetic factors, averaged over all electrode combinations, was around 60% for both hemispheres. Inspection of the confidence intervals yields two clusters of electrode combinations that had comparable within-cluster heritability, but little between cluster overlap in confidence intervals: heritability in Fp-P, F-O and P-O coherence was about 50%, whereas Fp-O, Fp-C, C-O and Fp-F had average heritability of 68%. This pattern was observed in both hemispheres and was unrelated to reliability. No sex differences were found, except for the right F-O electrode combination for which an AE scalar model gave the best fit ($\chi^2 = 12.109$, df = 12).

Alpha. The MZ and DZ correlations for EEG coherence are comparable to those of the theta band; the MZ correlation was twice the DZ correlation. AE models without sex differences were the

Table II. Split-Half Reliability and Twin Correlations for the Coherence Estimates of Combinations of Electrode Pairs in the Left and Right Hemisphere, for Each Frequency Band (Delta, Theta, Alpha, and Beta)[a]

	Reliability (left/right)	Mzm (left/right)	Dzm (left/right)	Mzf (left/right)	Dzf (left/right)	Dos (left/right)
Delta		(35)	(34)	(50)	(36)	(44)
Fp-O	.47/.37	.21/.30	.39/.31	.29/.31	.29/.19	.10/−.01
Fp-P	.63/.65	.39/.53	.05/.17	.31/.39	.20/.09	.08/.35
F-O	.72/.77	.60/.51	.14/.28	.34/.36	.46/.36	.12/.05
Fp-C	.72/.71	.70/.51	.14/.22	.50/.49	.22/.13	.13/.21
C-O	.87/.86	.67/.58	.10/.05	.43/.47	.34/.41	.37/.36
Fp-F	.78/.80	.51/.50	.32/.29	.56/.55	.28/.39	.15/.53
P-O	.91/.87	.63/.18	−.01/.10	.45/.46	.36/.25	.41/.26
Theta		(37)	(35)	(51)	(36)	(45)
Fp-O	.58/.60	.79/.74	.26/.02	.62/.64	.34/.28	.24/.24
Fp-P	.72/.73	.36/.38	.53/.31	.55/.54	.27/−.04	.23/.28
F-O	.74/.75	.58/.62	−.04/.02	.59/.54	.26/−.07	.10/.18
Fp-C	.86/.81	.59/.64	.58/.35	.76/.78	.23/.16	.40/.48
C-O	.86/.86	.73/.75	.20/.11	.58/.64	.38/.39	.37/.49
Fp-F	.89/.86	.66/.62	.58/.47	.76/.74	.41/.44	.41/.48
P-O	.90/.90	.61/.58	.20/.28	.50/.51	.28/.48	.26/.36
Alpha		(37)	(35)	(52)	(37)	(46)
Fp-O	.93/.93	.76/.89	.25/.25	.73/.72	.33/.29	.24/.34
Fp-P	.89/.87	.80/.81	.12/.15	.64/.60	.47/.38	.08/.02
F-O	.86/.88	.70/.86	.19/.19	.71/.73	.35/.41	.25/.32
Fp-C	.94/.93	.71/.68	.23/.12	.69/.82	.32/.37	.45/.53
C-O	.90/.89	.59/.59	.03/.10	.54/.63	.07/.05	.00/.15
Fp-F	.94/.94	.71/.71	.26/.19	.80/.88	.30/.47	.43/.44
P-O	.93/.95	.67/.73	.41/.21	.52/.48	.21/.23	.01/.27
Beta		(34)	(33)	(50)	(36)	(42)
Fp-O	.75/.81	.49/.61	.30/.27	.66/.69	.53/.34	.28/.36
Fp-P	.82/.80	.72/.72	.35/−.04	.54/.51	.44/.48	.23/.14
F-O	.74/.71	.51/.53	.11/.12	.59/.44	.09/.04	.17/.06
Fp-C	.90/.91	.70/.69	.46/.06	.68/.67	.50/.61	.21/.20
C-O	.89/.90	.57/.61	.29/.35	.64/.59	.55/.37	.22/.39
Fp-F	.93/.93	.51/.75	.26/−.13	.59/.65	.43/.31	.11/.05
P-O	.93/.93	.52/.57	.25/.43	.55/.51	.14/.29	.17/.31

[a] Above each column the number of twin pairs is given. Electrode combinations are ordered by decreasing electrode distance.

best fitting models for most electrode combinations. For the right Fp-O, right P-O and left Fp-P and right Fp-P combinations females showed higher heritabilities than males. For the right C-O, an AE scalar sex model was found to fit best, indicating that there was a significant difference in variance for males and females, but the heritabilities were the same. Averaged over all electrode combinations the contribution of the genetic factors to the variance was around 65% for the left and right hemisphere. Most confidence intervals overlapped, but lower heritabilities were suggested for C-O, C-P and P-O connections in both hemispheres.

Beta. The MZ correlations for the EEG coherence in the beta band were almost the same as the MZ correlations for alpha and theta. AE models were again the best fitting models. Averaged over all electrode combinations, 60% of the variance was explained by genetic factors. A large overlap of confidence intervals for heritability was found for most connections with the exception of right F-O coherence that was lower than most. This was, however, also the electrode combination with low-

Table III. Model-Fitting Results for the Coherence in the Left and Right Hemisphere, for Each Frequency Band (Delta, Theta, Alpha, and Beta)[a]

	df	Fp-F	Fp-C	Fp-P	Fp-O	F-O	C-O	P-O
Delta								
Left								
Test for sex diff	3	0.795	2.733	2.772	2.135	5.096	1.334	0.555
Test for *D*	1	0.019	1.053	0.247	0.000	0.000	0.000	0.000
χ^2	13	7.610	11.796	15.779	19.320	14.858	16.002	13.386
Right								
Test for sex diff	3	0.318	1.993	1.763	4.553	1.818	0.998	3.135
Test for D	1	0.000	0.015	0.000	0.000	0.044	0.000	0.000
χ^2	13	18.218	23.359	20.798	19.857	16.684	14.557	15.289
Theta								
Left								
Test for sex diff	3	1.815	1.738	0.825	2.967	1.969	3.042	0.312
Test for D	1	0.000	0.000	0.000	0.914	2.440	0.000	0.000
χ^2	13	9.780	14.569	10.805	9.679	13.979	23.165	14.775
Right								
Test for sex diff	3	2.544	0.543	0.631	0.668	6.121	1.685	0.651
Test for D	1	0.000	0.014	0.000	4.324	4.152	0.000	0.000
χ^2	13^	14.093	8.268	10.067	10.153^	12.109+	18.383	14.156
Alpha								
Left								
Test for sex diff	3	2.844	1.319	7.479	0.827	2.482	1.682	4.703
Test for D	1	0.394	0.000	2.116	0.691	0.865	3.578	0.401
χ^2	13*	13.990	9.684	11.211*	8.331	7.719	23.965	20.152
Right								
Test for sex diff	3	4.450	1.935	8.118	7.613	4.064	5.785	6.173
Test for D	1	0.112	0.000	3.826	0.894	0.381	4.502	0.093
χ^2	13*+	23.277	17.800	13.492*	4.830*	18.473	12.712+	18.734*
Beta								
Left								
Test for sex diff	3	6.654	1.106	2.269	2.303	0.243	1.208	0.366
Test for D	1	0.659	0.000	0.000	0.000	1.989	0.000	1.214
χ^2	13+	29.987+	15.250	8.391	12.694	16.832	7.279	11.141
Right								
Test for sex diff	3	3.636	3.256	4.911	0.747	2.974	0.870	1.165
Test for D	1	0.238	0.208	0.302	0.166	1.672	0.000	0.000
χ^2	13	16.217	21.642	17.894	6.119	27.632	10.358	5.203

[a] Electrode combinations are ordered left to right by decreasing electrode distance. Tests for sex differences give the difference in χ^2 for an ADE model with sex differences and an ADE model without sex differences. The test for D gives the difference in χ^2 for an ADE model and an AE model. The last line gives the overall χ^2 for the best-fitting model. Unless indicated otherwise, the best fitting model was an AE model.

^ Best model ADE, df = 12.

* Best model AEsex, df = 11.

+ Best model AEscalar, df = 12.

est reliability of coherence. No sex differences were found. Differences in variance between the sexes were found for the left Fp-F combination, but the heritabilities were the same.

DISCUSSION

This study examined the contribution of genetic and environmental influences to individual differences in EEG coherence. Sex differences in heritability were systematically examined by including male and female twin pairs in the analyses. The main finding of this study is that averaged across all electrode combinations and all frequency bands 58% of the variance in coherences between individuals was explained by genetic factors. The lowest heritability was found in the delta frequency band across the longest distance connections (29%)

Table IV. Heritabilities and Their 80% Confidence Intervals for Coherence in the Left and Right Hemisphere, for Each Frequency Band (Delta, Theta, Alpha, and Beta)[a]

	Fp-O	Fp-P	F-O	Fp-C	C-O	Fp-F	P-O
Left							
Delta	28	30	44	52	55	52	52
	(18–38)	(18–40)	(34–59)	(42–60)	(46–63)	(43–60)	(43–60)
Theta	69	47	53	69	60	73	50
	(62–75)	(38–55)	(43–61)	(62–75)	(52–66)	(67–78)	(42–58)
Alpha	71	61/76*	68	67	47	77	54
	(64–76)		(61–74)	(60–73)	(37–55)	(72–82)	(45–62)
Beta	65	62	50	71	61	58	53
	(57–72)	(54–69)	(40–59)	(63–76)	(52–67)	(48–66)	(43–62)
Right							
Delta	28	41	43	43	56	54	36
	(17–38)	(30–50)	(32–53)	(33–52)	(47–64)	(46–61)	(25–45)
Theta	68	43	49	73	68	69	52
	(60–75)	(33–52)	(38–58)	(67–78)	(61–74)	(62–74)	(44–59)
Alpha	70/88*	50/75*	74	73	55	82	43/70*
			(68–79)	(67–78)	(46–64)	(77–85)	
Beta	68	55	40	66	62	61	54
	(60–74)	(45–63)	(30–50)	(59–73)	(53–69)	(51–69)	(45–62)

[a] Electrode combinations are ordered left to right by decreasing electrode distance.

* Model with sex differences (males/females). Confidence interval for left Fp-P (50–69)/(64–83), for right Fp-O (61–77)/(82–91), for right Fp-P (43–66/67–84), and for right P-O (30–54)/(59–78).

and highest heritability was found in the alpha frequency across short distance fronto-frontal connections (79%). Inspection of the confidence intervals suggested clear regional differences in heritability, mainly in alpha and theta bands, that were seen in both hemispheres. These regional differences in heritabilities of coherence were not systematically related to electrode distance.

Only two previous studies reported genetic and environmental influences on intrahemispheric coherences. Both studies measured the EEG in young children. Ibatoullina *et al.* (1994) estimated heritabilities for coherence from 20 MZ and 17 DZ pairs. They found low genetic contributions to coherence on most combinations of electrodes. This may have been due the small number of subjects used as well as their method of coherence assessment. Only five 5-sec epochs were used, which may not be enough for reliable estimation of coherence (Nunez, 1995). In a large sample of 200 4-6 year old twin pairs van Baal *et al.* (1998) averaged coherence over ninety 2-sec epochs. Between 30% and 71% of the variance in EEG coherence was explained by genetic factors with a mean heritability of 49% across all frequencies and electrode combinations. This figure for childhood coherence suggests a somewhat lower heritability than in adolescence.

The observed heritabilities for coherence are somewhat lower than the heritabilities for EEG power spectra in this same group of adolescent twins, which are around 85% for all electrode positions and frequency bands (Van Beijsterveldt *et al.*, 1996). Heritability is calculated as the variance accounted for by genetic factors divided by the total variance, including measurement error. Reliability of coherence measurement sets an upper bound to estimated heritability. Model fitting clearly suggested that the variance could be attributed entirely to genetic and unique environmental factors, and measurement error loads entirely on the unique environmental factor. Thus, a possible explanation of the lower heritability of coherence in comparison to power could be its lower reliability. Inspection of split-half reliability did suggest some contribution of measurement error to the low heritabilities of long distance delta, theta and beta coherence, but for short distance coherences and long distance alpha coherence excellent split-half reliability was found. The substantial contribution of E in the models, therefore, seems to reflect true nonshared environmental influences. The possible nature of these influences has been discussed in some detail in studies on the interaction of genetic programs with specific experiential input during the development of the brain (Benno, 1990; Wiesel, 1994).

Experimental evidence linking coherence with the development of brain structure (cortico-cortical pathways, synaptic density, axonal myelination, etc.) is still scarce. The available evidence from developmental studies suggests a link between coherence and the degree of axonal connectivity among brain areas and/or the ratio of gray and white matter (Thatcher, 1994). This link is corroborated in cross-hemisphere comparison studies. Larger coherence in the right hemisphere than in the left hemisphere has been found in various studies (Thatcher *et al.*, 1986; Tucker *et al.*, 1986). Tucker *et al.* (1986) calculated multiple coherences (representing variance in one channel shared with all other channels together), measured at rest, for right-handed males, and found larger coherences in the right hemisphere. In a large group of children, Thatcher *et al.* (1986) also found higher coherences in the right hemisphere. It was suggested that coherence is larger in the right hemisphere because the proportion of white matter to gray matter is larger than it is for the left hemisphere (Gur *et al.*, 1980). In contrast to these studies, we did not find a significant main effect of hemisphere on any of the electrode combinations.

In our study, a significant main effect of sex was found for average coherence in all frequency bands. Comparison of coherence mean values of males and females revealed higher coherences in females for most combinations of electrode pairs. The finding of sex differences for mean coherences agrees with previous findings (Flor-Henry *et al.*, 1987; Marosi *et al.*, 1993). Using subjects with different ages or using different methods of EEG recording and processing, the general finding of these studies is that females have higher EEG coherence. A possible explanation for higher coherence in females might be a sex-related higher white-to-gray matter ratio. Robust sex differences have been suggested in the size and shape of the human corpus callosum, a main indicator of the bulk of interhemispheric white matter (Steinmetz *et al.*, 1995) and in the amount of gray matter (Gur *et al.*, 1982). This could suggest the existence of sex-specific genetic factors influencing brain connections. The highly similar pattern of male and female heritabilities on virtually all intrahemispheric coherences in our data do not provide support for this. Alternatively, in our age group, the higher short-distance coherence of female adolescents might simply reflect a sex-linked difference in the speed of brain maturation. A temporary lead in the development of functional brain connections could explain the higher mean coherences in females without the need to invoke sex-specific genetic influences. Contraintuitively, however, *early* maturation in puberty has been associated with *lower* coherence (Kaiser and Gruzelier, 1996). Thus, higher coherence in the female twins would suggest a lag rather than a lead in brain maturation. Analysis of the longitudinal follow-up data that are being collected in this group may shed more light on this matter.

In conclusion, we have given a description of intrahemispheric coherence in anterior-posterior electrode combinations for the 4 classic EEG frequency bands. This large study (213 twin pairs) yielded a consistent picture on adolescent EEG coherence. For all electrode combinations in the four frequency bands, a substantial part of the individual differences in coherence is explained by additive genetic factors. Unique environmental factors make up the rest of the variance. No sex differences in genetic architecture were found. The high additive genetic contribution to variance in coherence of these 16-year olds confirms it as a potential candidate to study adolescent brain function from a genetic perspective, for instance, in linkage analysis (Boomsma *et al.*, 1997).

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REFERENCES

Anokhin, A., and Vogel, F. (1996). EEG alpha rhythm frequency and intelligence in normal adults. *Intelligence* **23**: 1–14.

Anokhin, A. P., Vedeniapin, A. B., Rohrbaugh, J. W., Sirevaag, E. J., and Cloninger, C. R. (1997). Frontal EEG asymmetry and personality, Unpublished manuscript. Institute of Psychology, Russian Academy of Sciences, Moscow.

Benes, M. (1989). Myelination of cortical-hippocampal relays during late adolescence. *Schizophr. Bull.* **15**:585–593.

Benno, R. (1990). Development of the nervous system: Genetics, epigenetics, and phylogenetics. In Hahn, M., Hewitt, J., Henderson, N., and Benno, R. (eds.), *Development Behavior Genetics. Neural, Biometrical and Evolutionary Approaches*, Oxford University Press, New York, pp. 113–143.

Boomsma, D. I., Koopmans, J., VanDoornen, L., and Orlebeke, C. (1994). Genetic and social influences on starting to smoke: A study of dutch twins and their parents. *Addiction* **89**:219–226.

Boomsma, D. I., Anokhin, A., and de Geus, E. J. C. (1997). Genetics of electrophysiology: Linking genes, brain, and behavior. *Curr. Direct. Psychol. Sci.* **6**(4):106–110.

Brillinger, D. R. (1975). *Time Series. Data Analyses and Theory*, Holt, Rinehart and Winston, London.

Buchsbaum, M., Mansour, G. S., Teng, D. G., Zia, A. D., Siegel, J., Benjamin, and Rice, D. M. (1992). Adolescent developmental change in topography of EEG amplitude. *Schizophr. Res.* **7**:101–107.

Changeux, J. P., and Danchin, A. (1976). Selective stabilisation of developing synapses as a mechanism for the specification of neuronal networks. *Nature* **264**:705–712.

Duffy, F. H., Jones, K. J., McAnulty, G. B., and Albert, M. S. (1995). Spectral coherence in normal adults: Unrestricted principal components analysis; Relation of factors to age, gender, and neuropsychologic data. *Clin. Electroencephalogr.* **26**:30–46.

Flor-Henry, P., Koles, Z., and Reddon, J. (1987). Age and sex related configurations in normal subjects. In Glass, A. (ed.), *Individual Differences in Hemisphere Specialization* Plenum Press, New York, pp. 121–148.

Goldman-Rakic, P. S. (1987). Development of cortical circuitry and cognitive function. *Child Dev.* **58**:601–622.

Gur, R., Packer, I., Hungerbuhler, J., Reivich, M., Obrist, W., Amarnek, W., and Sackeim, H. (1980). Differences in the distribution of gray and white matter in human cerebral hemisphere. *Science* **207**:1226–1228.

Gur, R., Obrist, W., Hungerbuhler J., Skolnick, B., and Reivich, M. (1982). Sex and handedness differences in the cerebral blood flow during rest and cognitive activity. *Science* **217**:659–660.

Gur, R., Mozley, L., Mozely, P., Resnick, S., Karp, J., Alavi, A., Arnold, A., and Gur, R. (1995). Sex differences in regional cerebral glucose metabolism during a resting state. *Science* **267**:528–531.

Heath, A. C., Neale, M. C., Hewitt, J. K., Eaves, L. J., and Fulker D. W. (1989). Testing structural equation models for twin data using LISREL. *Behav. Genet.* **19**:9–29.

Hudspeth, W. J., and Pribram, K. H. (1992). Psychophysiological indices of cerebral maturation. *Int. J. Psychophysiol.* **12**:19–29.

Huttenlocher, P. R. (1994). Synaptogenesis in human cerebral cortex. In Dawson, G., and Fischer, W. (eds.), *Human Behavior and the Developing Brain*, Guilford Press, New York, London, pp. 137–152.

Ibatoullina, A., Vardaris, R. M., and Thompson, L. (1994). Genetic and environmental influences on the coherence of background and orienting response EEG in children. *Intelligence* **19**:65–78.

Jasper, H. (1958). Report of the committee on methods of clinical examination in electroencephalography. *Electroencephalogr. Clin. Neurophysiol.* **10**:370–375.

Jöreskog, K., and Sörbom D. (1986). *Prelis: A Preprocessor for LISREL*, National Educational Resources, Chicago.

Kaiser, J., and Gruzelier, J. (1996). Timing on puberty and EEG coherence during photic stimulation. *Int. J. Psychophysiol.* **21**:135–149.

Kimura, D. (1987). Are men's and women's brains really different. *Can. Psychol.* **28**:133–147.

Marosi, E., Harmony, T., Becker, J., Bernal, J., Reyes, A., Rodriguez M., and Fernandez, T. (1993). Sex differences in EEG coherence in normal children. *Int. J. Neurosci.* **72**:115–121.

Matoušek, M., and Petersén, I. (1973). Frequency analysis of the EEG in normal children and adolescents. In Kellaway, P., and Peters, I. (eds.), *Automation of Clinical Electroencephalography*, pp. 75–102.

Miller, M. B., and Neale, M. C. (1997). The use of likelihood-based confidence intervals in genetic models. *Behav. Genet.* **27**:113–120

Molenaar, P., Boomsma, D., and Dolan, C. (1993). A third source of developmental differences. *Behav. Genet.* **23**: 519–524.

Neale, M. C. (1997). *Mx: Statistical Modelling*, Department of Human Genetics, Box 3, MCV, Richmond, VA.

Neale, M. C., and Cardon, L. R. (1992). *Methodology for Genetic Studies of Twins and Families*, NATO ASI Series: Behavioral and Social Sciences, Kluwer Academic, Dordrecht.

Nunez, P. (1995). *Neocortical Dynamics and Human EEG Rhythms*, Oxford University Press, New York.

Oppenheim, J., Skerry, J., Tramo, M., and Gazzaniga, M. (1989). Magnetic resonance imaging morphology of the corpus callosum in monozygotic twins. *Ann. Neurol.* **26**: 100–104.

Pivik, R., Broughton, R., Coppola, R., Davidson, Fox, N., and Nuwer, M. (1993). Guidelines for the recording and quantitative analysis of electroencephalographic activity in research contexts. *Psychophysiology* **30**:547–558.

Rijsdijk, F., Boomsma, D., and Vernon, P. (1995). Genetic analysis of peripheral nerve conduction velocity in twins. *Behav. Genet.* **25**:341–348.

Saugstadt, L. F. (1994). The maturational theory of brain development and cerebral excitability in multi-factorially inherited manic-depressive psychosis and schizophrenia. *Int. J. Psychophysiol.* **18**:112–123.

Steinmetz, H., Herzog, A., Huang, Y., and Hacklander, T. (1994). Discordant brain surface anatomy in monozygotic twins. *N. Engl. J. Med.* **331**: 952–953.

Steinmetz, H., Staiger, J., Schlaug, G., Huang, Y., and Jäncke, L. (1995). Corpus callosum and brain volume in women and men. *NeuroReport* **6**:1002–1004.

Thatcher, R. (1994). Cyclic cortical reorganization. Origins of human cognitive development. In Dawson, G., and Fischer, W. (eds.), *Human Behavior and the Developing Brain*, Guilford Press, New York, London, pp. 232–266.

Thatcher, R. W., Krause, P., and Hrybyk, M. (1986). Cortico-cortical associations and EEG coherence: A two-compartmental model. *Electroencephalogr. Clin. Neurophysiol.* **64**:123–143.

Thatcher, R. W., Walker, R. A., and Guidice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science* **236**:1110–1113.

Tucker, D. M., and Roth, D. L. (1986). Functional connections among cortical regions: Topography of EEG coherence. *Electroencephalogr. Clin. Neurophysiol.* **63**:242–250.

van Baal, C., de Geus, E., and Boomsma, D. (1998). Genetic influences on EEG coherence in 5-year-old children. *Behav. Genet.* **28**:9–19.

Van Beijsterveldt, C., Molenaar, P., Geus, E., and Boomsma, D. (1996). Heritability of human brain functioning as assessed by electroencephalography. *Am. J. Hum. Genet.* **58**:562–573.

Wiesel, T. N. (1994). Genetics and behavior. *Science* **264**: 1648.

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