Behav Genet (2007) 37:302–313
DOI 10.1007/s10519-006-9133-0

ORIGINAL PAPER

Heritability of Bipolar EEG Spectra in a Large Sib-pair Population

Yongqiang Tang · David B. Chorlian · Madhavi Rangaswamy · Sean O'Connor · Robert Taylor · John Rohrbaugh · Bernice Porjesz · Henri Begleiter

Received: 6 March 2006 / Accepted: 9 November 2006 / Published online: 19 December 2006

Abstract The additive genetic heritability of both monopolar and bipolar EEG spectral power in a sample of 305 non-twin sibships comprising 690 individuals (age range 7–65) was estimated in order to investigate their regional variation. The heritabilities of the bipolar EEG spectral power ranged from 0.10 to 0.63 in 38 electrode-pairs, and those of monopolar power ranged from 0.23 to 0.68 in 19 electrodes in six frequency bands from theta to high beta. The bipolar data shows significantly greater topographic variation compared to that of the monopolar data. The mean of bivariate genetic correlations were consistently lower for the bipolar data and the coefficients of variation consistently higher when compared to those of the monopolar data for each of the frequency bands. The results from the bipolar derivations are in greater accord with genetic findings in brain anatomy and show the possibility of multiple genetic sources for the phenotypic variability of EEG activity.

Keywords Heritability · Bipolar EEG spectra · Sib-pair · Genetic correlation

Edited by Danielle Posthuma

This work was supported by NIAAA Investigator-Initiated Interactive Research Project Grant (IRPG): AA 12560 at SUNY Downstate Medical Center, AA 12555 at Indiana University School of Medicine, grant AA 12557 at Washington University School of Medicine, and AA 12553 at Howard University.

We would like to dedicate this paper to the memory of Henri Begleiter, who initiated its writing, and whose death during its preparation only inspired us to continue to follow the high scientific standards which his work exemplified.

Y. Tang · D. B. Chorlian (✉) · M. Rangaswamy · B. Porjesz · H. Begleiter
Neurodynamics Laboratory, SUNY Downstate Medical Center, Brooklyn, NY, USA
e-mail: chorlian@cns.hscbklyn.edu

S. O'Connor
Indiana University School of Medicine, Indianapolis, IN, USA

R. Taylor
Howard University, Washington, DC, USA

J. Rohrbaugh
Washington University School of Medicine, St. Louis, MO, USA

Introduction

EEG measures are indices of brain function associated with a variety of behavioral and cognitive traits. Spectral analysis of electro-encephalographic signals provides an accurate quantitative measure which has large intra-individual stability; test-retest reliabilities are around 0.8 for absolute and relative power in the same individual within a 12–16 week interval (Pollock et al. 1991; Salinsky et al. 1991). Considerable topographical variation in EEG activity in different frequency bands has been found by a number of researchers (Niedermeyer 1999; Michel et al. 2001). Understanding interindividual variation in EEG power could provide clues to the underlying neurobiology of various forms of psychopathology where EEG abnormalities have been documented, such as alcoholism (Porjesz et al. 2005; Rangaswamy et al. 2002, 2003), depression (Gotlib et al. 1998; Bruder et al. 1997), anxiety (Blackhart et al. 2006) and ADHD (Clarke et al. 2001; Bresnahan et al. 2002).

It has been shown that EEG spectral power and mean frequency values from biologically related family members are more similar than those obtained from unrelated non-family controls according to a family study (Eischen et al. 1995). In that study, the family versus non-family effects were generally observed across all electrode sites, with somewhat stronger effects for the Pz electrode (See our Fig. 1 for electrode locations). Similar relationships were obtained for the peak frequency data (Posthuma et al. 2001). This indicates that genetic contributions may vary over the scalp; yet very few studies have examined this issue with quantitative EEG phenotypes.

Neurophysiological signals are complex phenotypes and the influence of genetic and environmental factors have been studied in both family and twin models. Twin and family studies provide good evidence for the influence of genetic factors on resting EEG indices in normal subjects (van Beijsterveldt and Boomsma 1994; van Beijsterveldt and van Baal 2002). There are large differences across studies, especially with respect to age, EEG methodology, genetic analysis, and sample size. In a comprehensive review of EEG heritability studies, van Beijsterveldt and van Baal (2002) found comparable heritability estimates in family and twin studies. In the twin studies used in their meta-analysis, heritabilities of alpha band power ranged from less than 50% to near 90%. These findings suggest that variability in EEG power is largely dependent on genetic factors.

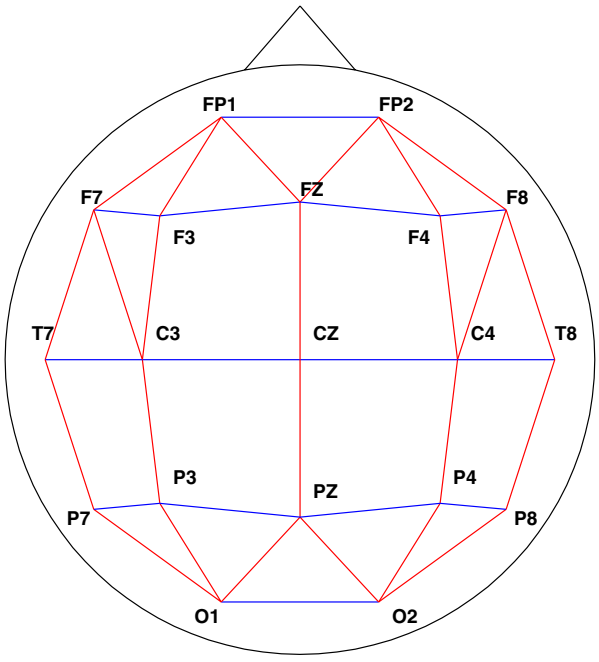

Fig. 1 Schematic representation of the 19 electrode montage indicating the 38 channel bipolar lead configuration. Lines in red joining electrode locations indicate vertical derivations; lines in blue indicate horizontal derivations

Studies designed to estimate the effects of alcohol on heritability of the EEG power spectrum in MZ and DZ twins report an increase in the EEG heritability after alcohol ingestion (Sorbel et al. 1996). This result was associated with a concomitant significant decrease in the within-pair differences of monozygotic twins for all frequency bands except fast beta, indicating that alcohol decreases environmental variation of EEG power spectral density, causing the increase in heritability (Sorbel et al. 1996).

A recent study (Smit et al. 2005) estimated the genetic and non-genetic (environmental) contributions to individual differences in the background EEG power spectrum, ranging from 1.0 to 25.0 Hz, in two cohorts with mean ages of about 26 and 49 years. They studied 19 channel eyes closed EEG from monozygotic and dizygotic twin pairs and their siblings, totaling 760 subjects. There was relatively little difference between heritabilities at different electrodes for most frequency bands and even across frequency bands from theta to beta. The authors concluded that across the scalp and across most of the frequency bands, individual differences in adult EEG are largely determined by genetic factors.

On the other hand, studies characterizing the regional variations in heritability of brain anatomy have shown that while global features, such as overall brain volume, are highly heritable, local features, such as the sizes or shapes of specific areas, have a wide range of heritabilities (Bartley et al. 1997; Baare et al. 2001; Wright et al. 2002; Carmelli et al. 2002; Geschwind et al. 2002). While assigning genetic sources on the basis of this evidence is difficult, Wright et al. (2002) find two independently regulated brain systems from the examination of bivariate genetic correlations. This raises the question of why so little topographic variation in the heritabilities of EEG spectral power has been found, particularly when compared to the considerable variation found in the heritabilities of local features, e.g. size in brain anatomy. Is it because there is a single global factor which operates in a fairly uniform manner across all regions in EEG activity, or is it because the choice of monopolar data for analysis results in a reduction of phenotypic variability across regions, and a consequent unrealistically uniform pattern of heritabilities? If the second possibility is the case, then data preprocessing to enhance phenotypic locality (Nunez et al. 1997), such as the use of the bipolar derivations employed in this study, may reveal a more adequate picture of the topographic variation

in heritabilities than the use of monopolar data. The results of this study suggest that there may be regional factors which are under genetic control and contribute to EEG activity.

This study was designed to evaluate EEG heritability and its topographic characteristics in a large population of non-twin sibling pairs. The sample in the present study, from 305 sibships (a total of 690 subjects), had a wide age range (7–65 years), included males and females, and was collected at a number of sites which may differ in population characteristics; hence age, gender and site were included as covariates. To address the issue of topography, spectral power in the frequency bands were computed for 38 bipolar derivations covering the entire scalp. Bipolar derivations were used in preference to monopolar derivations in order to improve the spatial resolution of the electrical sources, and reduce volume conduction effects. For comparative purposes, the 19 monopolar derivations from which the 38 bipolar derivations were obtained were analyzed by the same methods. Differences in the topographic specificity of these measures could shed light on the genetic factors influencing EEG activity. The use of the same subjects with the same EEG recordings means that the topographic differences can only be attributed to the difference between the bipolar and monopolar derivations.

Methods

Participants

Subjects were participants in an Investigator-Initiated Interactive Research Project (IRPG) collaborative study examining novel phenotypes for genetic analysis in alcoholism, at the following sites: (1) Indiana University School of Medicine, (2) SUNY Downstate Medical Center, (3) Washington University School of Medicine, and (4) Howard University. Probands with at least one sibling over 13 years of age were recruited from psychiatric inpatient or outpatient programs for alcohol and/or chemical dependency. Detoxification was complete before the potential proband was approached. Additional family members between the ages of 7 to 70 years were also recruited for the study. The study also included control families which were ascertained as randomly as possible to be representative of the general population; they were recruited from HMOs, drivers license records, and dental clinics. Subjects for the present analysis were all sibling pairs selected from the pool of families described above with two or more siblings. The final dataset contained 690 subjects from 305 families (248 families had 2 sibs, 43 had 3 sibs, 8 had 4 sibs, 6 had 5 or greater number of sibs). The mean age range among sibs was 5.0 years with a standard deviation of 4.0 years. The institutional review board at each site approved the research procedures and written consent was obtained from each individual prior to participation. Subjects were also excluded from the neurophysiological assessment if they manifested uncorrected sensory deficits, hepatic encephalopathy or cirrhosis of the liver, significant head injury or seizures, acute or chronic illness, or if they were on medication that affects brain functioning, or had a positive breath analyzer test for alcohol use, had undergone neurosurgery, tested positive for HIV, or used psychoactive substances in the past 5 days.

Data recording

All four sites used the same experimental procedures and EEG acquisition hardware and software. Each subject wore a fitted electrode cap (Electro-Cap International Inc.; Eaton, OH) using the 19-channel montage as specified according to the 10-20 International system [FP1, FP2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2] (Electrode Position Nomenclature, American Electroencephalographic Association, 1991). The nose served as reference and the forehead was the ground electrode. Electrode impedances were always maintained below 5K ohms. The electrooculogram (EOG) was recorded from electrodes placed supraorbitally at the outer canthus of the eye. Vertical and horizontal eye movements were monitored to perform ocular artifact correction. EEG was recorded from the 19 channels with the subjects seated comfortably in a dimly lit sound-attenuated temperature-regulated booth (Industrial Acoustics Company; Bronx, NY). They were instructed to keep their eyes closed and remain relaxed. Subjects were also cautioned not to fall asleep. Electrical activity was amplified 10,000 times by Sensorium EPA-2 Electrophysiology amplifiers (Charlotte, VT), with a bandpass between 0.02 and 50 Hz and recorded using the Neuroscan software system (Compumedics Limited; El Paso, TX) running on i86 PCs. The sampling rate was 256 Hz and the activity was recorded for 4.25 min.

Data reduction

EEG analysis was performed at SUNY Downstate Medical Center. A continuous interval comprising 256 s of EEG data was used for analysis. Offline raw data were subjected to wavelet filtering and reconstruction to

eliminate high and low frequencies (Bruce and Gao, 1994; Strang and Nguyen 1996). The *s*12 wavelet was used to perform a 6-level analysis, and the output signal was reconstructed using levels *d*6 through *d*3. This procedure is roughly equivalent to applying a band pass filter with a range of 2–64 Hz to the data. Subsequently, eye movements were removed by use of a frequency domain method developed by Gasser (Gasser et al. 1985, 1986). This method subtracts a portion of observed ocular activity from observed EEG to obtain the true EEG, based on the difference between the cross-spectral values of trials with high ocular activity and those with low ocular activity. Visual inspection of corrected data confirmed satisfactory artifact removal characteristics.

The data were subsequently software transformed into 38 bipolar derivations formed by the subtraction of adjacent electrodes in both horizontal and vertical orientations (Fig. 1), and analyzed in 254 overlapping 2-s epochs by use of a Fourier transform and windowed using a Hamming function to improve the accuracy of the spectral results (Hamming 1983). The resulting spectral densities (sampled at 0.5 Hz intervals) were aggregated into bands, divided by the bandwidth and subsequently averaged across epochs. The bands calculated were the theta (3–7 Hz), low alpha (7.5–9 Hz), high alpha (9.5–12 Hz), low beta (12.5–16 Hz), middle beta (16.5–20 Hz) and high beta (20.5–28 Hz) frequency bands. Absolute power spectra were then calculated from these values, giving a total of 228 variables.

Bipolar derivations were used in preference over monopolar derivations to improve the spatial resolution of the electrical sources (Nunez 1995; Nunez et al. 1997). Bipolar arrangements using close electrodes provide a higher pass spatial filter than is obtained with reference recordings. This method counteracts part of the smearing of cortical potentials and has also been shown to be more effective in capturing a greater amount of cerebral energy output than other referencing strategies (Cook et al. 1998), as well as capturing topographical features not seen with monopolar data (Baranov-Krylov and Shuvaev 2005). Bipolar derivations have previously shown their usefulness in both linkage and single-nucleotide polymorphism (SNP) analysis (Porjesz et al. 2002; Edenberg et al. 2004; Ghosh et al. 2003). A logarithmic transformation of the values was applied to the bipolar absolute power data to normalize their distributions. The spectral densities for the monopolar data were obtained by the identical procedure for comparative purposes. The topographic pattern of the observed (monopolar) data was that in the frontal channels the peak of the spectrum was located in the theta band, in the fronto-central channels power was relatively constant from theta to high alpha, and in the parietal and occipital channels there was a pronounced peak in high alpha. In all areas the beta bands had considerably lower activity than either theta or alpha. In all bands power increased from anterior to posterior, but the increase was much greater in the alpha bands than in the theta and beta bands. The bipolar derivations exhibited much greater phenotypic variability with no clear topographic or frequential pattern.

Genetic modeling

Additive genetic heritabilities and their standard errors were calculated using the robust variance component model implemented in Sequential Oligogenic Linkage Analysis Routines (SOLAR) (Almasy and Blangero 1998). The univariate variance component method (Almasy and Blangero 1998) was used to evaluate the heritabilities of EEG traits, where the phenotypic variance of the EEG were decomposed as the sum of its additive genetic and environmental variance components. The observed phenotypic vector $y_i = (y_{i1}, \ldots, y_{in_i})^{\mathrm{T}}$ from ith pedigree is assumed to follow a multivariate t-distribution

$$\boldsymbol{y_i} \sim \boldsymbol{t_{n_i}}(\mathbf{x}_i\beta, 2\Phi_i\sigma_{\mathrm{g}}^2 + \boldsymbol{I_{n_i}}\sigma_{\mathrm{e}}^2, \boldsymbol{v}),$$

where n_i denotes the pedigree size, $\mathbf{x}_i$ is a matrix of covariates including the intercept terms, β is a vector containing the covariate effects, Φ_i is the kinship matrix, σ_{g}^2 is proportional to the variance due to additive genetic factors, σ_{e}^2 is proportional to the variance resulting from individual-specific environmental effects, and I_{n_i} is an identity matrix, and $t_k(\mu,\Psi,v)$ denotes the k-variate t-distribution (Lange et al. 1989) with location vector μ, scale matrix Ψ and v degrees of freedom. The robust approach based on t-distributions is particularly suitable for modelling data with longer-than-normal tails and may effectively mute the impact of residual outliers (Lange et al. 1989). Age, gender, and site were included in the analyses as covariates and retained only if the associated P-value was less than 0.05. Since our data consist of only sib-pairs, the additive genetic effect may be confounded with early common environment (Falconer and Mackay 1996). Various studies (Smit et al. 2005; van Baal et al. 1996) indicate that the EEG traits are more likely to be influenced by genetic factors and less likely by common environment. It is reasonable to assume that this holds also for our data. So throughout the paper, we still use the word ''heritability'' although it may be more proper to use ''familial effect''.

The bivariate variance component model (Almasy et al. 1997) was used to estimate the pairwise genetic correlations between all 38 bipolar derivations and all 19 monopolar derivations in each frequency band. The method decomposes the covariation between two phenotypes into the portion due to shared genetic factors and that due to shared environment. Prior to the bivariate analysis, all phenotypes were adjusted for covariate effects determined in the univariate approach. The genetic correlation measures the extent to which two traits are affected by shared genetic effects. A smaller genetic correlation between the EEG measures at two scalp locations implies that the EEG measures are mainly influenced by the genetic factors specific to each location. On the other hand, a larger genetic correlation indicates that common genetic factors play a major role in determining the EEG measures. For our purposes the relatively large confidence limits for genetic correlations less than 0.3 are irrelevant, since the exact values are not crucial to our analysis and the statistical tests subsequently performed involving genetic correlations are all non-parametric.

To test whether the heritabilities of EEG were different at two leads, we use the following Wald test:

$$Z = \frac{\widehat{h_1^2} - \widehat{h_2^2}}{\sqrt{\mathrm{var}\left(\widehat{h_1^2} - \widehat{h_2^2}\right)}} = \frac{\widehat{h_1^2} - \widehat{h_2^2}}{\sqrt{\mathrm{var}\left(\widehat{h_1^2}\right) - 2\,\mathrm{cov}\left(\widehat{h_1^2}, \widehat{h_2^2}\right) + \mathrm{var}\left(\widehat{h_2^2}\right)}},$$

where $\hat{h}_1^2$ and $\hat{h}_2^2$ are the heritability estimates at the two leads from the bivariate analysis, and the sampling variance of $\widehat{h_1^2} - \widehat{h_2^2}$ is evaluated based on the maximum likelihood estimation. The test statistic Z is asymptotically distributed as $N(0,1)$ under the null hypothesis that $h_1^2 = h_2^2$ (provided neither the true heritability h_1^2 nor h_2^2 is 0).

Results

Monopolar and bipolar heritabilities

The heritabilities of the bipolar EEG spectral power ranged from 0.10 to 0.63 and were highly significant for 224 of the 228 combinations of 38 electrode-pairs across theta, low alpha, high alpha, low beta, middle beta, and high beta frequency bands. The heritabilities of the monopolar EEG spectral power ranged from 0.23 to 0.68 and were highly significant for all of the combinations of 19 electrodes and 6 frequency bands. For both derivations, age effects were highly significant across the scalp in the theta and alpha bands and were weakly significant if at all in the beta bands. Site effects were significant at nearly all scalp locations and frequency bands, except that they were relatively weak around low-alpha and high-alpha bands for both monopolar and bipolar data. Gender effects were significant for all monopolar traits and for 150 of 228 bipolar traits; the pattern of gender effects was less obvious than that of age and site effects. In the model for the bipolar data, the mean of the coefficients for age was –0.0036/year; only 8 of the 228 coefficients were positive. The mean of the coefficients coding for females as compared to males was 0.0337; only 20 of the coefficients were negative. Site was modeled by comparing sites 1 through 3 to site 4, so that the coefficients for sites 1 through 3 represent the mean of that site relative to the mean of site 4, while simultaneously accounting for age and gender. Mean coefficients for site were far larger than those for age or gender, with values 0.1441, 0.0932, and 0.0953; only one coefficient was negative. We speculate that these relatively large coefficients are a function of the differences between sites in the ethnic composition of the subjects tested, as well as slight differences which are the result of different levels of experience in administering the test protocol and collecting the data.

The mean heritabilities were the highest in the low alpha, high alpha and low beta bands for both bipolar and monopolar values. The monopolar data shows relatively little regional variation compared to the bipolar data, as can be seen by examining the coefficients of variation displayed in Table 1. An important feature of the heritabilities is that the maximum values in each frequency band are not significantly different between the monopolar and bipolar derivations, while the minimum values are often quite different. In addition, we report on the number of pairs of derivations for which the difference in heritabilities is statistically significant (“Bivariate analysis” section). The large difference between the monopolar and bipolar data is the result of the presence of the very low heritability values in the bipolar data. The mean heritabilities over bipolar electrode pairs for theta, low alpha, high alpha, low beta, mid beta and high beta bands are displayed in Table 1. Heritabilities, as estimated by SOLAR, for all frequency bands and electrode pairs are displayed in Fig. 2.

In general bipolar heritabilities showed higher values in the left side of the scalp extending from temporal to occipital areas, and in the fronto-central

Table 1 Summary of heritability results by band

Method	Theta	Low alpha	High alpha	Low beta	Mid beta	High beta
Monopolar						
Mean	0.44	0.54	0.49	0.51	0.43	0.42
CV	0.12	0.09	0.11	0.16	0.17	0.15
Min	0.32	0.45	0.37	0.36	0.27	0.23
Max	0.53	0.61	0.59	0.68	0.57	0.54
N pairs different	5	0	0	12	3	2
Bipolar						
Mean	0.30	0.42	0.46	0.42	0.40	0.41
CV	0.32	0.23	0.23	0.26	0.24	0.22
Min	0.10	0.22	0.17	0.23	0.21	0.25
Max	0.55	0.58	0.62	0.63	0.60	0.60
N pairs different	60	37	57	66	32	27

CV = coefficient of variation; *N* pairs different = the number of pairs such that the difference between their heritabilities is statistically significant

areas. Relatively lower values were found in the right frontal and right central-parietal areas. The theta band did not have the high heritabilities in the central occipital region typical of the other bands. Low and high alpha bands had the highest values for the parieto-occipital pairs, extending into the right parieto-temporal regions. Beta bands had high heritabilities in the right temporal area and relatively lower heritabilities in the frontal area. The monopolar heritabilities were more uniform but not inconsistent with the bipolar heritabilities.

Bivariate analysis

A bivariate variance component approach was used to assess the significance of pairwise comparisons of heritabilities between all 38 bipolar derivations and between all 19 monopolar derivations in 6 frequency bands. Examining the pairwise comparisons individually, we find a considerable difference between monopolar and bipolar data. For monopolar EEG traits, among all 1,026 pairwise comparisons (171 comparisons in each band), only 22 comparisons were significant at the 0.05 level, and 1 comparison at the 0.01 level. For bipolar power, among all 4,218 pairwise comparisons (703 in each band), 279 comparisons were significant at the 0.05 level. (The distribution of these values by band can be found in Table 1.)

We also calculated the genetic correlation matrices for all pairs of both monopolar and bipolar data. The means of the bivariate genetic correlations of the bipolar EEG spectral power ranged from 0.72 to 0.83, while the mean of the genetic correlations of the monopolar EEG spectral power ranged from 0.79 to 0.88, with the monopolar values being greater than the bipolar in all frequency bands (see Table 2 for details). The difference was statistically significant, using the Wilcoxon Rank Sum test in the theta ($P < 0.0001$), low alpha ($P < 0.0001$), and high beta ($P = 0.0024$) frequency bands. In addition, the Ansari–Bradley test of difference in variances showed statistically significant differences in theta ($P < 0.0001$), low alpha ($P < 0.0001$), and low beta ($P = 0.0002$) between monopolar and bipolar genetic correlations. Thus the statistical comparison between bipolar and monopolar genetic correlations further demonstrates the presence of greater topographical variation in the bipolar data as compared to the monopolar data. We also note that two symmetrically placed inter-hemispheric derivations often have higher genetic correlations between themselves than either has with a non-symmetrically placed adjacent derivation. The lower mean and greater variance of the bipolar genetic correlations is the result of the presence in them of a large number of values which are smaller than the smallest values of the corresponding monopolar genetic correlations. The presence of these low values suggests the possibility of multiple genetic sources, if the heritabilities are significant at the pairs of bipolar derivations whose correlation is low. In fact, there are clear anterior and posterior clusters of bipolar derivations in the low alpha, low beta, and mid beta bands such that the genetic correlations between bipolar derivations within each cluster are high, and the genetic correlations between bipolar derivations in different clusters are low. No clustering was found in the high alpha band, and the clusters in the theta and high beta bands had very few members. The bipolar derivations F7-F3, FP1-F3, FP1-F7, and FP2-F8 were found in at least 4 of the 5 anterior clusters; C3-P3, C4-P4, P8-O2, PZ-P3, PZ-P4, and T8-P8 were found in at least 4 of the 5 posterior clusters; no derivation was present in both an anterior and a posterior cluster.

The clustering process was driven by the insight that if there was a low genetic correlation between a particular derivation and a group of other derivations, we should be able to find other derivations which had low genetic correlations with members of that group.

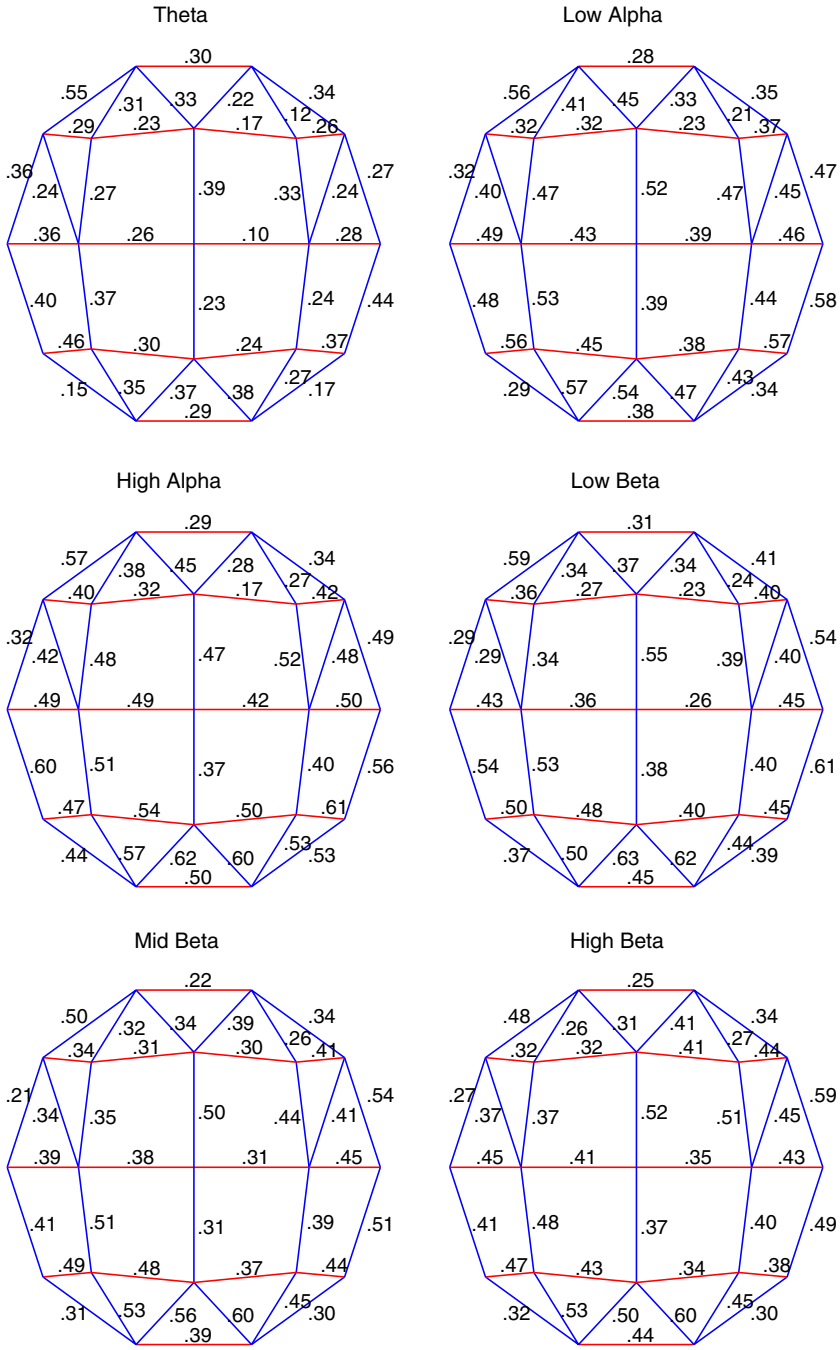

Fig. 2 Heritabilities for all frequency bands and bipolar electrode pairs. Heritabilities 0.17 and below (in the theta band) are not significant

Conversely, each derivation in that group would have its own group of derivations with which it had low correlations, and these groups should have considerable overlap. We also wished to eliminate non-significant groups, so the groups could not be too small. Exactly how many groups would emerge from the clustering process, if any at all, was simply a function of the data itself. We then implemented an algorithm to determine the groups; clusters were found by the following procedure: First, all derivations whose heritability was not significant were eliminated from the analysis. Working within each frequency band, for each bipolar derivation we found its ''opposite'' set, the set of bipolar derivations such that the pairwise genetic correlation between that derivation and each of the members of the set was lower than the lowest monopolar genetic correlation in that frequency band. We then eliminated each bipolar derivation whose opposite set contained fewer than two elements. For each remaining bipolar derivation, we calculated the size of the intersection of its opposite set with each other opposite set. We then separated the bipolar derivations

Table 2 Summary of genetic correlation results by band

Method	Theta	Low alpha	High alpha	Low beta	Mid beta	High beta
Monopolar						
Mean	0.86	0.88	0.85	0.85	0.79	0.80
Standard deviation	0.10	0.09	0.13	0.11	0.13	0.15
Number < 0.5	0	0	1	0	4	8
Bipolar						
Mean	0.72	0.80	0.83	0.80	0.75	0.76
Standard deviation	0.21	0.15	0.14	0.17	0.19	0.18
Number < 0.5	116	39	32	41	79	70
P values for Wilcoxon rank sum test for equality of medians						
P	0.0001	0.0001	0.2294	0.0522	0.0783	0.0024
P values for Ansari–Bradley test for equality of variances						
P	0.0001	0.0001	0.2893	0.0002	0.0635	0.0545

into clusters such that if the intersection of two opposite sets was empty, the corresponding derivations would be placed in different clusters. We found that in all frequency bands except for high alpha and low beta, two clusters, anterior and posterior, would suffice. In high alpha, there were no derivations which met the criteria for inclusion because the number of low genetic correlations was small. In low beta, because of the large number of eligible low genetic correlations, we eliminated each bipolar derivation whose opposite set contained fewer than three elements, and separated the derivations if the intersection of their two opposite sets was empty or had only one element; with these criteria, two clusters, anterior and posterior, also would suffice.

Discussion

The results show that the bipolar EEG power spectra in the different frequency bands are highly heritable, although we report heritabilities which are lower than those reported by other researchers such as Smit et al. (2005) and Anokhin et al. (2006), and at the low end of those reported in van Beijsterveldt and van Baal (2002). A number of factors may partly explain the difference of heritability estimates between our family study and previous twin studies. Our sample was collected from 4 sites and had a very wide age range (7–65 years). The age-EEG relationship is very complex across the scalp over the life span and is not necessarily linear. An imprecise specification of the age-EEG relationship may overestimate the within-family (environmental) variation and hence underestimate the heritability if the between sibling age range is large (mean ± SD: 5.0± 4.0 in our sample); twin studies suffer no such problem because of the identity of age in twins. It is also possible that the EEG heritability changes with age, which can not be evaluated due to the wide age range and limited sample size in our data. It should be noted that excluding subjects under the age of 15 had little effect on heritability estimates. Similarly, dropping site from the model leads to a large increase in heritability estimates especially in the low-beta, mid-beta and high-beta bands since sites act as common environmental influences. This also indicates the beta power is more sensitive to environmental variation.

In particular, our results show that degree of genetic influence has considerable topographic specificity. Although the mean heritability for each frequency band is lower in the bipolar derivations compared to the monopolar derivations, it should be emphasized that the maxima of heritabilities do not differ between derivations, but the minima are much lower in the bipolar derivations. Information about heritability is not being lost through the use of bipolar derivations, as shown by the comparable values of the maxima. The reason for the difference in the minima and the consequent difference in topographical variation is that whatever neurophysiological factors are responsible for the largest electrical potentials are the most heritable as observed in our data. Thus in the monopolar derivations the phenotypic similarities are widespread because of the volume conduction effects of the large potentials, while in the bipolar derivations the phenotypic similarities are much reduced, enabling factors which are phenotypically more local to affect the heritability values. This is evident in the genetic correlation matrices, where the difference in variance between monopolar and bipolar derivations is even more apparent.

Topographic variation in heritability by itself does not imply multiple genetic sources; rather spatially separated areas of high heritability call for further investigation. If spatially separate areas of significant heritability have low genetic correlations between themselves and relatively high genetic correlations

within themselves, then we may infer that distinct local genetic sources may be superimposed upon more global sources. This is the case with the bipolar genetic correlations in the theta, low alpha, and beta bands. What is known about the neurophysiological sources of EEG activity is that both global and local factors are involved: neurotransmitter levels, distribution of neurotransmitter receptors, local and global patterns of neural connectivity, and levels of thalamic activity, to mention only a few (Niedermeyer 1999; Porjesz et al. 2005; Begleiter and Porjesz 2006). Since exactly the same subjects and recordings are used in the monopolar and bipolar data sets, the differences in the heritabilities and the genetic correlations can only be a function of the difference in the derivations.

Our argument for the preferential use of the bipolar derivations is built on five main points:

- The basic facts of EEG measurement imply that phenotypic variability will be lower with monopolar than with bipolar derivations, thus contributing to the lesser variability of the monopolar heritabilities.
- We find brain anatomy analogous to resting EEG because each can be regarded as providing a substrate for task-related brain activity. Results from the studies of heritability of brain anatomy show considerable variation in the heritabilities of local features. Since functional features are closely associated with structural features, they could share a similar pattern of variation. The variation in the heritabilities of local features raises the question of why the monopolar results are so uniform.
- A number of genetic studies of particular EEG features show localization or independence of genetic sources. So it is possible that EEG power spectra have local genetic sources in addition to global ones.
- Genetic studies using bipolar EEG values have contributed to identification of genes controlling neurotransmitter receptors.
- Analysis of the genetic correlation matrices suggests that low genetic correlations in the bipolar data not found in the monopolar data define clusters of bipolar derivations which have spatial patterns consistent with local sources.

We will treat each of these in turn.

Before any further discussion, it is necessary to stress the fundamental fact of the measurement of EEG activity by scalp electrodes: the neural generator which is recorded at one electrode is also recorded at adjacent electrodes (Nunez et al. 1997). This non-independence of results in the measuring process in conjunction with the possibility that some sources of EEG activity are considerably stronger than others has the consequence that the use of ''raw'' values in an analysis may lead to the obliteration of local variability. Without some compensating strategy to restore that variability such as the use of bipolar derivations or surface Laplacians, important information can be lost. We interpret the reduced variance in the monopolar derivations reported here, comparable to the variance of other monopolar EEG studies, to the reduction of local phenotypic variability inherent in the use of the monopolar data. We note that Tenke and Keyser (2005) using surface Laplacian derivations, which ensure even greater localization than bipolar derivations, find multiple factors involved in alpha band EEG production. The primary sources of alpha band production were found to be posterior, but a secondary source of low alpha was located along the frontal midline.

It is instructive to compare the results reported here with studies of the heritability features of brain anatomy, particularly of the sizes and shapes of brain regions. In the most comprehensive study, Wright et al. (2002) report a wide range of heritability values, from 0 to 1 (mean 0.31; standard deviation 0.3), for the volumes of 92 distinct cerebral regions. In examining bilaterally symmetric regions with high heritability for volumes, the left and right specific genetic effects were small compared to the common genetic effect. In addition, Mechelli et al. (2005) report patterns of covariance in gray matter density in between variously aligned regions in the two hemispheres. Many positive and no negative correlations were found between homotopic regions in the two hemispheres, except for visual cortex. The topography of genetic correlations observed in our data is consistent with these findings. A clear correspondence between brain structure and function is shown in a study in adolescents and young adults, in which the normal reduction in EEG power with age is attributed to a reduction in the amount of gray matter in the brain (Whitford et al. 2006). For an example of direct structural effect on EEG production, we note that Begre et al. (2003) found a significant correlation between more anterior alpha EEG activity and lower fractional anisotropy of both hippocampi in schizophrenics, but not in controls.

Several studies have indicated a possible stronger genetic influence on posterior rather than frontal regions. A twin study on EEG spectral bands by Meshkova and Ravich-Shcherbo (1982) reported stronger genetic influences for occipital and parietal areas than for frontal, central and temporal leads. Higher genetic influences on posterior as compared to frontal regions have also been demonstrated in a

study on schizophrenic families (Trubnikov et al., 1993) and is suggested by a small twin study on EEG bispectrum (Whitton et al. 1985). Alpha bands have the highest heritability in the parieto-occipital region and this is in agreement with the studies that have shown that there are multiple generators of alpha activity in the posterior parts of the cerebrum, with activity arising near the parieto-occipital areas and in the calcarine sulcus (Hari and Salmelin 1997; Salenius et al. 1997; Liljestrom et al. 2005). Smit et al. (2006), in a study of adolescent twins, find high heritability for both alpha power and the frequency at which alpha power was greatest. More significantly for our purposes, the genetic influences on these features were independent.

We know of few studies which connect EEG spectral power with specific genes: Enoch et al. (2003) found an association in women between low-voltage alpha power and Met158/Met158 allele of the catechol-O-methyltransferase genotype, the enzyme that metabolizes dopamine and norepinephrine in females. Using bipolar data which had been processed in a manner similar to that applied to the data used in this study, Porjesz et al. (2002) found linkage and linkage disequilibrium between a beta phenotype which was a linear combination of values (obtained by trilinear analysis (Wang et al. 2000)) from eleven bipolar horizontal derivations and a cluster of $GABA_A$ receptor genes on chromosome 4*p*; Ghosh et al. (2003), using a novel non-parametric multipoint linkage technique on mid beta bipolar data also gave strong evidence for linkage in this region. Edenberg et al. (2004) identified variations in the *GABRA2* receptor gene which accounts for the linkage/linkage disequilibrium findings of Porjesz et al. (2002) and Ghosh et al. (2003) (for a concise review of these and other genetic results, consult Begleiter and Porjesz (2006)). Since the studies done with bipolar data did not have contrasting ones done with monopolar data, one can only speculate about the relative efficacy of the bipolar approach. Nevertheless, assuming that there are multiple genetic sources of EEG activity, as is suggested by the results of this study, and that the phenotypes at any bipolar derivation are a function of both local and global sources, the underlying phenotypic variation may lead a decompositional procedure such as trilinear analysis performed on the phenotypic data to isolate the effects of different genetic sources in different components. While a decompositional procedure performed on the monopolar data might also isolate the effects of different genetic sources in different components, the lesser variability of the monopolar data would make this less likely.

In contrast to our work, a recent study of the heritability of EEG power spectrum in younger and older adults suggests that power at different frequency bands share a common genetic source (Smit et al. 2005, p. 696). The ''heritability spectra'' computed for 1 Hz bins for the entire spectrum indicated highest values for the alpha range in both age groups, with a drop in heritability frontocentrally for the theta and delta bands in the older age group. Most significantly, the regional variation in heritability was quite small in the theta and alpha bands, the largest coefficient of variation being 0.04, while the largest coefficient of variation in the beta band was 0.16. The present study reports a wider range of heritability values for bipolar EEG spectral power, ranging from 0.10 to 0.63, and large topographic variations in heritability within frequency bands, with coefficients of variation ranging from 0.22 to 0.32. Differences in the methodology employed for EEG spectrum calculation probably account for the differences in our results when compared to that of Smit DJ et al. In that study, the EEG spectrum was calculated for monopolar derivations referenced to linked earlobes, while the present study employed bipolar derivations which function as a high pass spatial filters and counteract the smearing of cortical potentials. The lack of topographic variation in Smit DJ et al. is probably partially the effect of volume conduction which is present in data recorded from a monopolar montage. Our study also uses a robust approach based on t-distributions instead of normal distributions. This is particularly suitable for modeling data with longer-than normal tails and may effectively mute the impact of residual outliers (Lange et al. 1989).

Returning to the question we raised in the introduction as to the topographic uniformity of heritability found in the studies based on monopolar data, we could attribute this uniformity to the presence of a single genetic source, or to low phenotypic variability. Finding more variability in genetic correlations and in heritabilities derived from bipolar data, we would discount the possibility that a single genetic source was involved. Instead we would hypothesize the existence of several genetic sources of EEG power based on topographic variations in heritability within frequency bands and in the topographic structure of the corresponding genetic correlations. The presence of anterior and posterior clusters separated by low genetic correlations is strong evidence that a single genetic source model is inadequate. In the interpretation of the anterior and posterior clusters we must add a third set of derivations; those which have overall high genetic correlations, including high correlations with members of both

anterior and posterior clusters. The phenotypic values at these derivations are primarily manifesting the global genetic influences; the phenotypic values at the clusters are manifesting the effects of both local and global genetic influences. The membership of the clusters reflects the fact that, as we noted previously, two symmetrically placed inter-hemispheric derivations often have higher genetic correlations between themselves than either has with a non-symmetrical adjacent derivation. It is possible that studies using denser electrode arrays and more sophisticated analyses of the genetic correlations would provide further support for the existence of multiple genetic sources acting locally in addition to globally acting sources.

Our study also confirms that bipolar EEG power is a very heritable complex trait in human subjects, confirming the results from previous studies of monopolar EEG power from small twin samples (Lykken et al. 1982; McGuire et al. 1998; Christian et al. 1996), a large twin study (Smit et al. 2005) and adolescent studies (van Beijsterveldt and van Baal 2002; van Beijsterveldt et al. 1996). The present findings also suggest that bipolar EEG spectral power measures have value in indicating the topographic variability in the genetics of EEG production, a variability which monopolar measures are unlikely to reveal. Thus bipolar EEG spectral power measures may serve as important traits in quantitative genetic analysis.

Acknowledgments We would like to thank our colleagues in the Neurodynamics Lab for their help in preparation of the data, particularly Arthur Stimus and Chamion Thomas. We would also like to thank two anonymous reviewers whose insightful comments led us to expand our horizons in the course of writing this paper.

References

Almasy L, Blangero J (1998) Multipoint quantitative-trait linkage analysis in general pedigrees. Am J Hum Genet 62:1198–1211

Almasy L, Dyer TD, Blangero J (1997) Bivariate quantitative trait linkage analysis: pleiotropy versus co-incident linkages. Genet Epidemiol 14(6):953–958

Anokhin AP, Heath AC, Myers E (2006) Genetic and environmental influences on frontal EEG asymmetry: a twin study. Biol Psychol 71(3):289–295

Baare WF, Hulshoff Pol HE, Boomsma DI, Posthuma D, de Geus EJ, Schnack HG, van Haren NE, van Oel CJ, Kahn RS (2001) Quantitative genetic modeling of variation in human brain morphology. Cereb Cortex 11(9):816–824

Baranov-Krylov IN, Shuvaev VT (2005) Effects of selective visual attention in the parietal and temporal areas of the human cortex using evoked potential data. Neurosci Behav Physiol 35(2):159–164

Bartley AJ, Jones DW, Weinberger DR (1997) Genetic variability of human brain size and cortical gyral patterns. Brain 120 (Pt 2):257–269

Begleiter H, Porjesz B (2006) Genetics of human brain oscillations. Int J Psychophysiol 60(2):162–171

Begre S, Federspiel A, Kiefer C, Schroth G, Dierks T, Strik WK (2003) Reduced hippocampal anisotropy related to anteriorization of alpha EEG in schizophrenia. Neuroreport 14(5):739–742

Blackhart GC, Minnix JA, Kline JP (2006) Can EEG asymmetry patterns predict future development of anxiety and depression? A preliminary study. Biol Psychol 72(1):46–50

Bresnahan SM, Barry RJ (2002) Specificity of quantitative EEG analysis in adults with attention deficit hyperactivity disorder. Psychiatry Res 112:133–144

Bruce A, Gao H (1994). S+ wavelets user's manual. Mathsoft Inc., Seattle, WA

Bruder GE, Fong R, Tenke CE, Leite P, Towey JP, Stewart JE, McGrath PJ, Quitkin FM (1997) Regional brain asymmetries in major depression with or without an anxiety disorder: a quantitative electroencephalographic study. Biol Psychiatry 41:939–948

Carmelli D, Swan GE, DeCarli C, Reed T. (2002) Quantitative genetic modeling of regional brain volumes and cognitive performance in older male twins. Biol Psychol. 61(1&2):139–155

Christian JC, Morzorati S, Norton JA Jr, Williams CJ, O'Connor S, Li TK (1996) Genetic analysis of the resting electroencephalographic power spectrum in human twins. Psychophysiology 33:584–591

Clarke AR, Barry RJ, McCarthy R, Selikowitz M (2001) EEG-defined subtypes of children with attention-deficit/hyperactivity disorder. Clin Neurophysiol 112:2098–2105

Cook IA, O'Hara R, Uijtdehaage SH, Mandelkern M, Leuchter AF (1998) Assessing the accuracy of topographic EEG mapping for determining local brain function. Electroencephalogr Clin Neurophysiol 107:408–414

Edenberg HJ, Dick DM, Xuei X, Tian H, Almasy L, Bauer LO, Crowe RR, Goate A, Hesselbrock V, Jones K, Kwon J, Li TK, Nurnberger JI Jr, O'Connor SJ, Reich T, Rice J, Schuckit MA, Porjesz B, Foroud T, Begleiter H (2004) Variations in GABRA2, encoding the alpha 2 subunit of the GABA(A) receptor, are associated with alcohol dependence and with brain oscillations. Am J Hum Genet 74(4):705–714

Eischen SE, Luckritz JY, Polich J (1995) Spectral analysis of EEG from families. Biol Psychol 41:61–68

Enoch MA, Xu K, Ferro E, Harris CR, Goldman D (2003) Genetic origins of anxiety in women: a role for a functional catechol-O-methyltransferase polymorphism. Psychiatr Genet 13:33–41

Falconer DS, Mackay TFC (1996) Introduction to quantitative genetics. Addison Wesley Longman, Harlow, Essex, UK

Gasser T, Sroka L, Mocks J (1985) The transfer of EOG activity into the EEG for eyes open and closed. Electroencephalogr Clin Neurophysiol 61:181–193

Gasser T, Sroka L, Mocks J (1986) The correction of EOG artifacts by frequency dependent and frequency independent methods. Psychophysiology 23:704–712

Geschwind DH, Miller BL, DeCarli C, Carmelli D (2002) Heritability of lobar brain volumes in twins supports genetic models of cerebral laterality and handedness. Proc Natl Acad Sci USA 99(5):3176–3181

Ghosh S, Begleiter H, Porjesz B, Chorlian DB, Edenberg H, Foroud T, Reich T, Goate A (2003) Linkage mapping of

beta 2 EEG waves via non-parametric regression. Am J Med Genet 118B:66–71
Gotlib IH, Ranganath C, Rosenfeld JP (1998) Frontal EEG alpha asymmetry, depression, and cognitive functioning. Cogn Emot 12:449–478
Hari R, Salmelin R (1997) Human cortical oscillations: a neuromagnetic view through the skull. Trends Neurosci 20:44–49
Hamming R (1983) Digital filters. Prentice-Hall, Englewood Cliffs, NJ
Lange KL, Little RJA, Taylor JMG (1989) Robust Statistical Modeling Using the t distribution. JASA 84:881–896
Liljestrom M, Kujala J, Jensen O, Salmelin R (2005) Neuromagnetic localization of rhythmic activity in the human brain: a comparison of three methods. Neuroimage 25:734–745
Lykken DT, Tellegen A, Iacono WG. (1982) EEG spectra in twins: Evidence for a neglected mechanism of genetic determination. Physiol Psychol 10:60–65
Michel CM, Thut G, Morand S, Khateb A, Pegna AJ, Grave de Peralta R, Gonzalez S, Seeck M, Landis T (2001) Electric source imaging of human brain functions. Brain Res Brain Res Rev 36(2–3):108–118
McGuire KA, Katsanis J, Iacono WG, McGue M (1998) Genetic Influences on the Spontaneous EEG: an examination of 15-year-old and 17-year-old twins. Dev Neuropsychol 14:7–18
Mechelli A, Friston KJ, Frackowiak RS, Price CJ (2005) Structural covariance in the human cortex. J Neurosci 25(36):8303–8310
Meshkova T, Ravich-Shcherbo I (1982) Influence of the genotype on the determination of individual features of the human EEG at rest. In: Schmidt H, Tembrock G (eds) Evolution and determination of animal and human behavior. VEB Deutscher Verlag der Wissenschaft, Berlin, pp 92–107
Niedermeyer E (1999) The normal EEG of the waking adult. In Niedermeyer E, Lopes da Silva F (eds) Electroencephalography, 4th ed. Lippencott Williams & Wilkins, Philadelphia, pp 149–73
Nunez PL (1995) Quantitative states of neocortex. In: Nunez PL (eds) Neocortical dynamics and human EEG rhythms. Oxford University Press, New York/Oxford, pp 3–67
Nunez PL, Srinivasan R, Westdorp AF, Wijesinghe RS, Tucker DM, Silberstein RB, Cadusch PJ (1997) EEG coherency. I. Statistics, reference electrode, volume conduction, Laplacians, cortical imaging, and interpretation at multiple scales. Electroencephalogr Clin Neurophysiol 103:499–515
Pollock VE, Schneider LS, Lyness SA (1991) Reliability of topographic quantitative EEG amplitude in healthy late-middle-aged and elderly subjects. Electroencephalogr Clin Neurophysiol 79:20–26
Porjesz B, Almasy L, Edenberg HJ, Wang K, Chorlian DB, Foroud T, Goate A, Rice JP, O'Connor SJ, Rohrbaugh J, Kuperman S, Bauer LO, Crowe RR, Schuckit MA, Hesselbrock V, Conneally PM, Tischfield JA, Li TK, Reich T, Begleiter H (2002) Linkage disequilibrium between the beta frequency of the human EEG and a GABAA receptor gene locus. Proc Natl Acad Sci USA 99(6):3729–3733
Porjesz B, Rangaswamy M, Kamarajan C, Jones KA, Padmanabhapillai A, Begleiter H (2005) The utility of neurophysiological markers in the study of alcoholism. Clin Neurophysiol 116(5):993–1018
Posthuma D, Neale MC, Boomsma DI, de Geus EJ (2001) Are smarter brains running faster? Heritability of alpha peak frequency, IQ, and their interrelation. Behav Genet 31(6):567–79
Rangaswamy M, Porjesz B, Chorlian DB, Wang K, Jones KA, Bauer LO, Rohrbaugh J, O'Connor SJ, Kuperman S, Reich T, Begleiter H (2002) Beta power in the EEG of alcoholics. Biol Psychiatry 52(8):831–842
Rangaswamy M, Porjesz B, Chorlian DB, Choi K, Jones KA, Wang K, Rohrbaugh J, O'Connor S, Kuperman S, Reich T, Begleiter H (2003) Theta power in the EEG of alcoholics. Alcohol Clin Exp Res 27(4):607–615
Salenius S, Portin K, Kajola M, Salmelin R, Hari R (1997) Cortical control of human motoneuron firing during isometric contraction. J Neurophysiol 77:3401–3405
Salinsky MC, Oken BS, Morehead L (1991) Test-retest reliability in EEG frequency analysis. Electroencephalogr Clin Neurophysiol 79:382–392
Smit DJ, Posthuma D, Boomsma DI, Geus EJ (2005) Heritability of background EEG across the power spectrum. Psychophysiology 42:691–697
Smit CM, Wright MJ, Hansell NK, Geffen GM, Martin NG (2006) Genetic variation of individual alpha frequency (IAF) and alpha power in a large adolescent twin sample. Int J Psychophysiol 61(2):235–243
Sorbel J, Morzorati S, O'Connor S, Li TK, Christian, JC (1996) Alcohol effects on the heritability of EEG spectral power. Alcohol Clin Exp Res 20:1523–1527
Strang G, Nguyen T (1996) Wavelets and filter banks. Wellesley-Cambridge Press, Wellesley, MA
Tenke CE, Kayser J (2005) Reference-free quantification of EEG spectra: combining current source density (CSD) and frequency principal components analysis (fPCA). Clin Neurophysiol 116(12):2826–2846
Trubnikov V, Uvarova L, Alfimova M, Orlova V, Ozerova N, Abrosimov N (1993) Neurophysiological and psychological predictors of genetic risk for schizophrenia. Behav Genet 23:455–459
van Baal GC, De Geus EJ, Boomsma DI (1996) Genetic architecture of EEG power spectra in early life. Electroencephalogr Clin Neurophysiol 98(6):502–514
van Beijsterveldt CE, Boomsma DI (1994) Genetics of the human electroencephalogram (EEG) and event-related brain potentials (ERPs): a review. Hum Genet 94:319–330
van Beijsterveldt CE, Molenaar PC, de Geus EJ, Boomsma DI (1996) Heritability of human brain functioning as assessed by electroencephalography. Am J Hum Genet 58(3):562–573
van Beijsterveldt CE, van Baal GC (2002) Twin and family studies of the human electroencephalogram: a review and a meta-analysis. Biol Psychol 61:111–138
Whitton JL, Elgie SM, Kugel H, Moldofsky H (1985) Genetic dependence of the electroencephalogram bispectrum. Electroencephalogr Clin Neurophysiol 60:293–298
Wang K, Begleiter H, Porjesz B (2000) Trilinear modeling of event-related potentials. Brain Topogr 12:263–271
Whitford TJ, Rennie CJ, Grieve SM, Clark CR, Gordon E, Williams LM (2006) Brain maturation in adolescence: Concurrent changes in neuroanatomy and neurophysiology. Hum Brain Mapp, in press
Wright IC, Sham P, Murray RM, Weinberger DR, Bullmore ET (2002) Genetic contributions to regional variability in human brain structure: methods and preliminary results. Neuroimage 17(1):256–271