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Genetic influences on bipolar EEG power spectra

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Abstract

The EEG bipolar power spectra provide more localization than spectral measures obtained from monopolar referencing strategies, and have been shown to be useful endophenotypes of psychiatric disorders such as alcoholism. We estimated the additive genetic heritability of resting bipolar EEG power spectra in a large sample of non-twin sibling pairs. The corresponding heritabilities ranged between 0.220 and 0.647 and were highly significant at all 38 electrode pairs for theta (3–7 Hz), low-alpha (7–9 Hz), high-alpha (9–12 Hz), low-beta (12–16 Hz), middle-beta (16–20 Hz) and high-beta (20–28 Hz) frequency bands. The heritabilities were the highest in the high-alpha and low-beta bands at most electrode pairs. The heritabilities were most variable across the head in the three beta bands. Other heritability patterns were also identified within each frequency band. Our results suggest that substantial proportions of the variability in the bipolar EEG measures are explained by genetic factors.

Keywords: Heritability; Bipolar EEG power spectra; Endophenotype

1. Introduction

Resting human electroencephalogram (EEG) power has long been used as a non-invasive measure of spontaneous brain electrical activity. Spectral analysis of EEG signals provides an accurate quantitative measure of the signal that has high intra-individual stability (Pollock et al., 1991) and shows a considerable amount of variation among individuals (Smit et al., 2005, 2006; van Baal et al., 1996). The magnitudes of EEG spectral power have been shown to be related to a number of psychiatric disorders, such as alcoholism (Rangaswamy et al., 2003, 2002), depression (Gotlib et al., 1998; Bruder et al., 1997), anxiety (Blackhart et al., 2006) and attention deficit hyperactivity disorder (Clarke et al., 2001; Bresnahan and Barry, 2002). Understanding the genetic and environmental influences on EEG power could provide clues to the underlying neurobiology of these psychiatric disorders.

Twin and family studies provide powerful method for evaluating the heritability of human behavioral traits, that is, the proportion of the total phenotypic variance attributable to the genetic factors. In traditional twin studies, heritability is evaluated by comparing the resemblance between monozygotic (MZ) and dizygotic (DZ) twins (Falconer, 1960). Since MZ twins share 100% of genes while DZ twins share 50% of their genetic material on average, a higher MZ than DZ resemblance evidences genetic influences. The variance component method via maximum likelihood (ML) techniques has become increasingly popular in recent heritability studies. The ML approach considers all pedigree information jointly so that it is more efficient than classical methods based on pairs of relatives, and is more suitable for data with complex pedigree structure. The ML approach assumes that the trait variance can be partitioned into genetic and environmental components. All parameters

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including heritability, covariate effects, the contribution of genetic and environmental factors can be jointly estimated by modeling the observed genetic resemblance between relatives as a function of the relationship among individuals (i.e., kinship matrix) and modeling the trait mean as a function of covariates. The ML approach also allows a further partition of the genetic components into additive genetic part and nonadditive part (e.g. dominance effect) and a partition of environmental contributions into the part shared by family members and individual specific environmental effects. Interested readers may refer to Neale and Cardon (1992) for more details in the context of twin studies and to Almasy and Blangero (1998) in the context of family studies.

A considerable number of twin and family studies indicate that monopolar EEG power is largely determined by genetic factors. Eischen et al. (1995) observed that the correlations for EEG power between family members were greater than those obtained between non-family members, suggesting EEG characteristics are genetically influenced. In general, the heritability of monopolar EEG powers is large and comparable in family and twin studies. The EEG heritabilities typically ranged from more than 30% to near 90%; see van Beijsterveldt and van Baal (2002) for a comprehensive review and references. Generally, the EEG heritabilities vary across frequency bands and across the scalp (Smit et al., 2005; van Baal et al., 1996). Sorbel et al. (1996) observed that the heritability of EEG power in twins increased after alcohol ingestion, which could be explained by the fact that alcohol decreased environmental variation of EEG power spectra.

It is well known that the choice of EEG reference and data processing have a significant influence on the degree with which calculated values reflect local activity (Nunez et al., 1997). EEG power measures for bipolar electrode pairs provide a higher pass spatial filter than is obtained with monopolar derivations and reduce volume conduction effects (Nunez, 1995; Nunez et al., 1997). 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).

In several genetic studies, the bipolar EEG measures have been shown to be a useful endophenotype for psychiatric disorders such as alcoholism. Porjesz et al. (2002) and Edenberg et al. (2004) detected linkage and association of the bipolar EEG power with a $GABA_A$ receptor gene. Ghosh et al. (2003) also showed the usefulness of the bipolar derivations in linkage analysis. However, bipolar EEG power measures, like all complex traits, involve multiple genes. It has not yet been determined to what extent the bipolar EEG power measures are genetically determined. Hence, in this paper, we aimed to estimate the heritability of bipolar EEG power spectra in various spectral bands across the scalp. By the analysis of a large population of non-twin sibling pairs (442 sibships, 1598 subjects), we confirmed that the bipolar EEG power measures are highly heritable.

2. Methods

2.1. Participants

Subjects included in this study were participants in the Collaborative Study on the Genetics of Alcoholism (COGA), a large multi-center study investigating the genetic predisposition to develop alcohol dependence and related disorders. The six participating centers are located at: SUNY Downstate Medical Center, University of Connecticut Health Center, Washington University School of Medicine in St. Louis, University of California at San Diego, University of Iowa, and Indiana University School of Medicine. The details of the COGA recruitment procedures have been described elsewhere (Begleiter et al., 1995). Alcoholic probands were recruited from inpatient and outpatient treatment facilities, and they met the criteria for DSM-IIIR alcohol dependence and the criteria established by Feighner et al. (1972) for "definite" alcoholism. Probands were excluded from the COGA study if they were habitual intravenous drug users, known to be HIV positive, or had non-alcohol related terminal illness. All probands and their first-degree relatives were interviewed with the SSAGA, a semi-structured diagnostic psychiatric interview schedule developed specifically for COGA (Bucholz et al., 1994; Hesselbrock et al., 1999).

Subjects under the age of 18 years were administered the child/adolescent version of the SSAGA, called the CSSAGA-A for adolescents aged 13 to 17, and the CSSAGA-C for children aged 7 to 12 (Kuperman et al., 1999). Families with three or more alcohol-dependent members were studied further with a more extensive protocol that included drawing blood for genetic analysis, neuropsychological and neurophysiological assessments. Control families were recruited from HMOs, driver's license records, and dental clinics, with the objective of being representative of the general population at each center. Individuals with alcoholism and other psychiatric illnesses were not excluded from the control sample in order to reflect prevalence rates that are similar to those of the population at large. All control subjects were interviewed with the SSAGA and they underwent blood drawing as well as neuropsychological and neurophysiological assessments. The institutional review board at each site approved the research procedures in the COGA study, and written consent was obtained from each individual prior to participation. Subjects were excluded from the neurophysiological assessment if presence of alcohol was detected with the breathanalyzer prior to testing. Subjects with hepatic encephalopathy or cirrhosis of the liver, acute or chronic illness, a significant history of head injury, seizures or neurosurgical procedures, tested positive for HIV or were on medication that affects brain functioning were excluded. Subjects who manifested uncorrected sensory deficits and subjects who had used any psychoactive substances in the past 5 days were also excluded. 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 1598 subjects (age±mean: 28.95±10.95, age range: 7.2–69.1; proportion of males: 50.0%) from 442 families (73 families had 2 sibs, 193 had 3 sibs, 85 had 4 sibs, 91 had 5 or greater number of sibs).

2.2. Data recording

All collaborative sites used the same experimental procedures. Each subject wore a fitted electrode cap (Electro-Cap International Inc.; Eaton, OH) using the 19-channel montage (Fig. 1) 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]. The nose served as reference and the forehead was the ground electrode. Electrode impedances were always maintained below 5 kΩ. 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 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 Hz and 50 Hz. The output from the amplifiers was digitized and recorded using either the Neuroscan software system (Compumedics Limited; El Paso, TX) running on i86 PCs or the COGA software system (Neurodynamics Laboratory, SUNY Downstate Medical Center) running on Concurrent 5550 computers (Concurrent Computer Corporation, Atlanta, GA). The sampling rate was 256 Hz and the activity was recorded for 4.25 min.

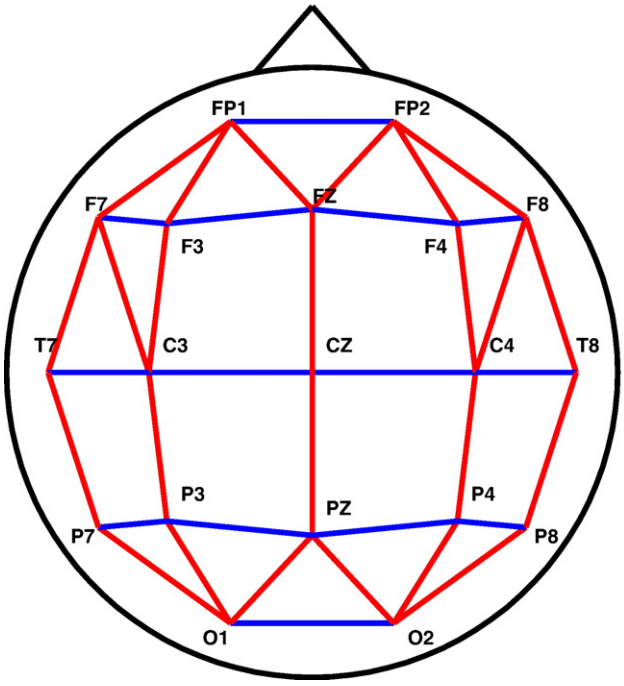

Fig. 1. Schematic representation of the 19 electrode montage indicating the bipolar lead configuration. Lines in red joining electrode locations indicate vertical derivations; lines in blue indicate horizontal derivations.

2.3. 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 bandpass 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 (overlapping by 1 s) 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. Absolute power spectra were then calculated from these values. A logarithmic transformation of the values was applied to the bipolar absolute power data to normalize their distributions.

2.4. Genetic modeling

Additive genetic heritabilities of absolute bipolar EEG power spectra in theta (3–7 Hz), low alpha (7–9 Hz), high alpha (9–12 Hz), low beta (12–16 Hz), middle beta (16–20 Hz) and high beta (20–28 Hz) frequency bands were calculated using the robust variance component model implemented in SOLAR (Almasy and Blangero, 1998). The observed phenotypic vector $\boldsymbol{y}_i=(y_{i1}, \ldots, y_{in_i})^T$ from *i*-th pedigree is assumed to follow a multivariate *t*-distribution

$$\boldsymbol{y}_i \sim t_{n_i}(\boldsymbol{x}_i\beta, 2\Phi_i\sigma_g^2 + I_{n_i}\sigma_e^2, \nu),$$

where n_i denotes the pedigree size, $\boldsymbol{x}_i$ 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_g^2 is proportional to the variance resulting from individual-specific environmental effects, and I_{n_i} is an identity matrix, and $t_k(\mu, \Psi, \nu)$ denotes the *k*-variate *t*-distribution (Lange et al., 1989) with location vector μ, scale matrix Ψ and ν 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, age^2, gender, sites and their interactions were included in

Table 1
Mean and range of bipolar heritabilities by frequency bands

Frequency	Mean	Min–max	Range
Theta	0.462	0.351–0.565	0.214
Low-alpha	0.487	0.410–0.564	0.154
High-alpha	0.560	0.448–0.644	0.196
Low-beta	0.532	0.360–0.643	0.283
Mid-beta	0.499	0.314–0.626	0.312
High-beta	0.445	0.217–0.633	0.416

the analysis as covariates and retained if it was significant at the 0.05 level. *P*-values for heritability were obtained by comparing a model in which additive genetic heritability was estimated with one in which that parameter was fixed at zero. Twice the difference in log-likelihood between these two models is distributed as a mixture of a chi-square distribution with one degree of freedom and a point mass at zero (Self and Liang, 1987).

3. Results

The bipolar EEG power spectra were found to be quadratically related with age and significantly higher in female subjects for all of the combinations of 38 electrode pairs and 6 frequency bands. The diagnostic status was significant mainly at high-alpha and beta bands. Site effects were significant at nearly all scalp locations and frequency bands. Exclusion of site effects from the model leads to a slight increase in heritability estimates since sites act as common environmental influences.

Table 1 displays the mean and range of the bipolar EEG heritabilities across all electrode pairs by frequency bands. Clearly, on average, the mean heritabilities were the highest in the high-alpha band. Theta, low-alpha, high-alpha bands produced a narrower range of heritability values than the low-beta, mid-beta and high-beta bands.

Heritabilities of the bipolar EEG are displayed in Fig. 2. The bipolar heritabilities were highly significant (all *p*-values <0.000001) at all 38 electrode pairs in all 6 frequency bands. Fig. 3 uses color to display the bipolar EEG heritability for better visualization. Theta had higher heritabilities at predominantly fronto-central locations. The heritabilities at the low-

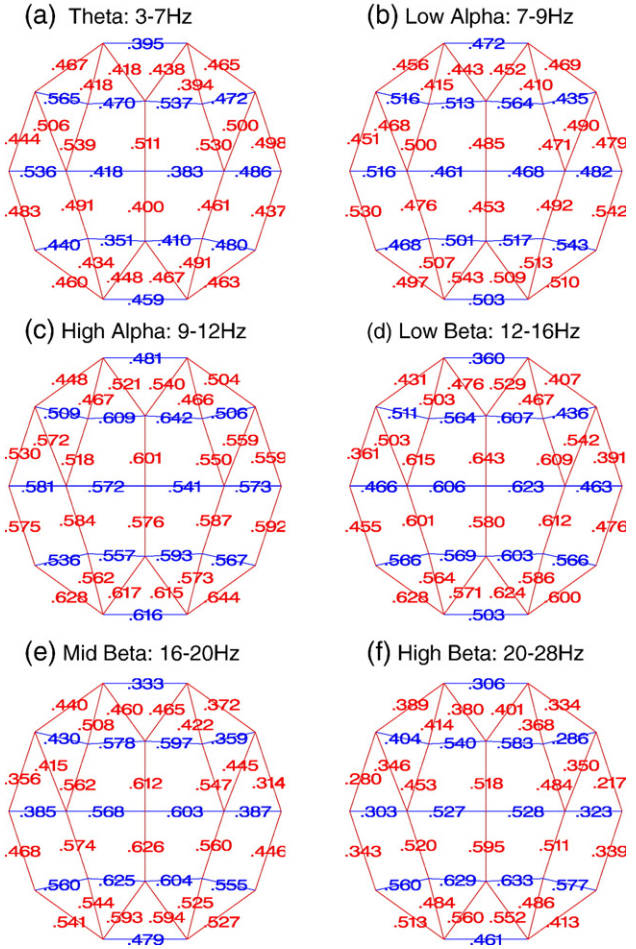

Fig. 2. Estimated heritabilities for all frequency bands and electrode pairs. The standard errors of all estimated heritabilities ranged between 0.057 and 0.065. All heritabilities were highly significant with *p*-values <0.00001.

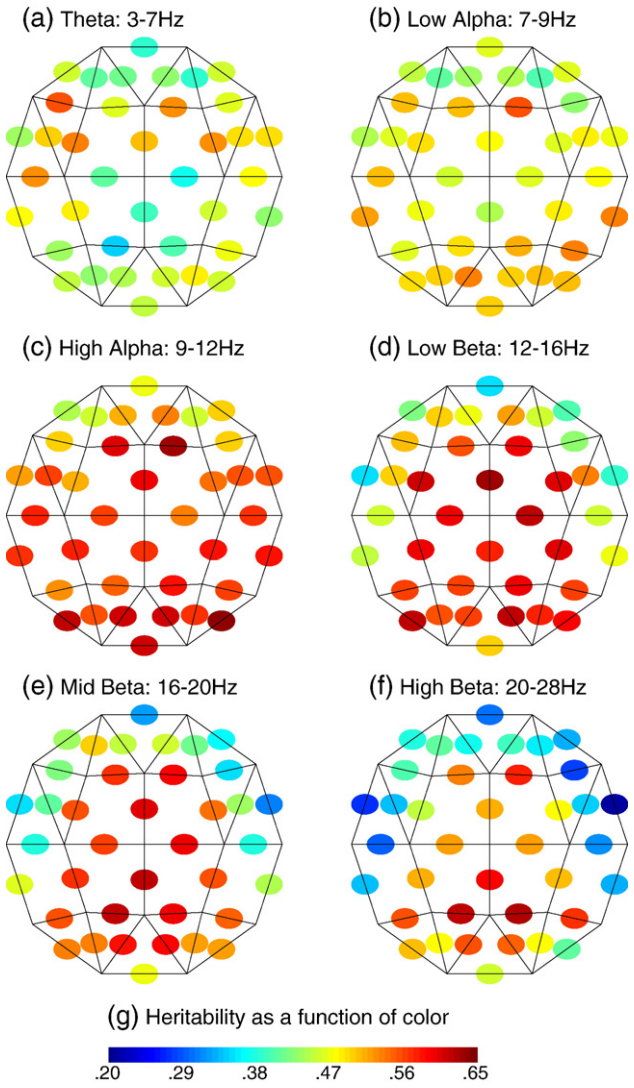

Fig. 3. Representation of heritability by color.

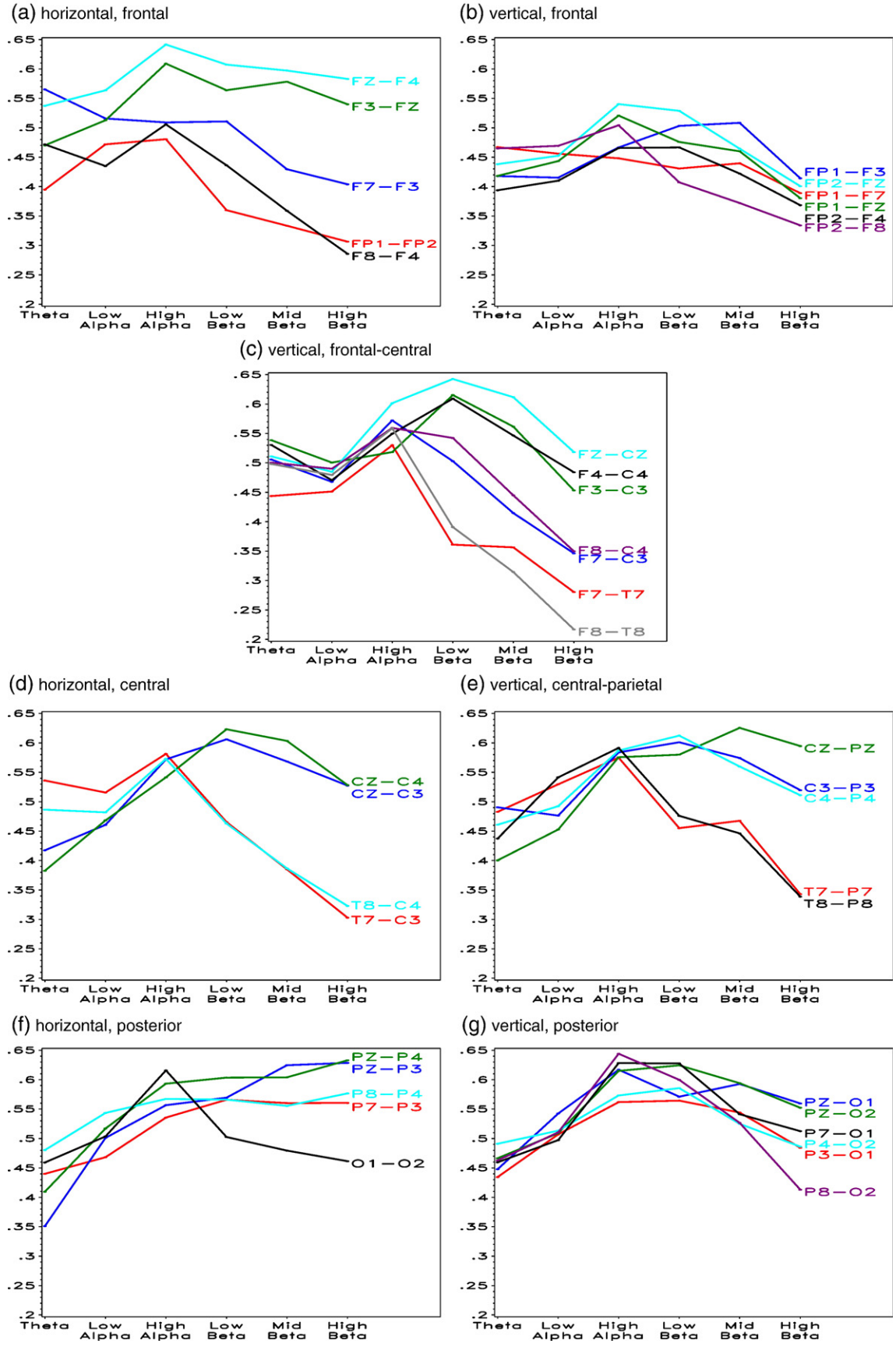

Fig. 4. Heritability spectra by region and orientation. In order to clearly display the heritability spectra, we split the plots by orientation. There seems no difference between the magnitude of the heritability estimates in the vertical and horizontal directions in each region.

alpha, high-alpha and low-beta bands were relatively high in the fronto-central regions as well and showed trends that increased from the central to the parietal and occipital regions. At mid-beta and high-beta bands, the electrode pairs closer to the center (electrode Cz) tended to have higher heritabilities than those electrode-pairs at the periphery.

Fig. 4 shows plots of the heritability spectra (heritability versus frequency) by regions. At most electrode pairs, the heritabilities increased in the theta, low-alpha and high-alpha bands, and then decreased in the low-beta, mid-beta and high-beta bands. Fig. 4 also shows that the heritabilities in the three beta bands were more variable than that in the theta, low-alpha and high-alpha bands across electrode pairs in all regions, particularly at horizontally oriented central pairs and vertically oriented central–parietal regions where there are large central–peripheral differences.

4. Discussion

The objective of the present study was to evaluate the genetic influence on bipolar EEG power spectra. By analyzing a large population of sibling pairs (442 sibships, 1598 subjects), we show that the bipolar EEG power spectra are highly heritable in all frequency bands across the scalp. Although the bipolar measures have previously been used in genetic linkage and association studies (Ghosh et al., 2003; Porjesz et al., 2002; Edenberg et al., 2004), our findings represent the first report of a large heritability analysis of the bipolar measures.

Reviewing the topography of heritability estimates, we find the following spatial patterns. In the theta band, the bipolar heritability estimates were the highest at the fronto-central locations. In the low-alpha, high-alpha and low-beta bands, the heritabilities increase from the central to the parietal and occipital regions. In the mid-beta and high-beta bands, the central electrode pairs produce higher heritability estimates than peripheral pairs. Overall, the mean heritabilities are the highest around the parietal/parieto-occipital region at all frequency bands except theta, and this is consistent with the previous studies on monopolar traits (Meshkova and Ravich-Shcherbo, 1982; Trubnikov et al., 1993; Smit et al., 2005; van Baal et al., 1996). Alpha band has 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).

The most extensive study of the heritability of monopolar EEG features is that of Smit et al. (2005), and it is instructive to compare the results reported here with those reported in that paper. Smit et al. (2005) estimate the heritabilities of monopolar traits for 1 Hz bins for the entire spectrum in two age cohorts with mean ages of 26.2 and 49.4. Our results on bipolar measures share some similarity with that of Smit et al. (2005) on monopolar measures in that the heritabilities (1) are generally higher in alpha band than in theta band and (2) typically decrease with increasing frequency especially in the temporal regions in the beta bands. We also observe the difference between the two studies. In our study, the highest bipolar heritabilities are typically observed at alpha bands or the low-beta band while in Smit et al. (2005), the monopolar heritability were highest around the alpha peak. Since the bipolar measures are more localized than the monopolar EEG, it may be expected that bipolar traits which differ between two brain regions are influenced, to a larger extent, by independent genetic sources rather than the common genetic factor. This issue is being explored in detail in a different sample from an IRPG (Investigator-Initiated Interactive Research Project) collaborative study, which examined novel phenotypes for genetic analysis in alcoholism (Tang et al., in press). Although the Laplacian derivation would be a more effective localization method than bipolar derivations, the substantial amount of data recorded with only 19 scalp channels did not permit the use of that method (Nunez, 1995; Nunez et al., 1997).

Our results further demonstrate the potential usefulness of the bipolar EEG power measures as endophenotypes for psychiatric disorders such as alcoholism. A good endophenotype should be not only highly heritable, but also meaningfully associated with the disorder (Porjesz et al., 2005; Gottesman and Gould, 2003; Tsuang and Faraone, 2000). With regard to alcoholism, bipolar EEG measures have been reported to differentiate between individuals who are affected or unaffected (Rangaswamy et al., 2003, 2002), as well as between high risk offspring of alcoholics and low risk offspring of unaffected individuals (Rangaswamy et al., 2004). It is generally believed that the quantitative endophenotypes have a more simple genetic architecture than the disease status of psychiatric disorders and therefore provide more power in gene finding approaches (Porjesz et al., 2005; Gottesman and Gould, 2003; Tsuang and Faraone, 2000). Ghosh et al. (2003) performed linkage studies of the mid-beta bipolar measures and found that the mid-beta waves were linked to some regions on chromosomes 1, 4 and 15. The study of Ghosh et al. (2003) also suggests that the bipolar measures are complex traits involving multiple genes. Porjesz et al. (2002) and Edenberg et al. (2004) detected linkage and association of the bipolar measures with a $GABA_A$ receptor gene on chromosome 4, namely GABRA2. Studies are underway to explore other associated genetic variants.

Compared to other genetic studies on EEG power measures, our sample was collected from 6 sites and consists of a larger number of families (442 sibships, 1598 subjects) with a wider age range (7.2 to 69.1 years) than others reported in the literature. We assume that the traits follow *t*-distributions instead of normal distributions so that the results produced by SOLAR are more robust to residual outliers (Lange et al., 1989). One limitation of our study is that the dominance effect and early common environment effect may be confounded with additive genetic effect (Neale and Cardon, 1992) and cannot be reliably assessed since our data consist mainly of sib-pairs. Although non-additive genetic effects and common environmental effect might explain individual differences in EEG power, many of the existing studies may have lacked the power to discriminate additive from non-additive genetic effect or to

separate genetic from common environmental influences (see van Beijsterveldt and van Baal, 2002 for review and references).

In conclusion, we have shown that genes play a major role in determining the variance of the bipolar EEG power in the COGA population collected from 6 sites. Further studies of genetic linkage and candidate gene association are warranted to identify the specific genetic variants associated with this useful endophenotype of alcoholism and other psychiatric disorders.

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