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Resting EEG in offspring of male alcoholics: beta frequencies

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Abstract

This study examines the differences in beta (12–28 Hz) band power in offspring of male alcoholics from densely affected alcoholic families. We have attempted to investigate if the increase in beta power is a 'state' or 'trait' marker for alcoholism. This study also explores the gender differences in the expression of this potential risk marker. Absolute beta power in three bands—beta 1(12–16 Hz), beta 2 (16–20 Hz), and beta 3 (20–28 Hz)—in the eyes closed EEG of 171 high risk (HR) subjects who were offspring of male alcoholics and 204 low risk (LR) subjects with no family history of alcoholism, were compared for each gender separately using a repeated measures analysis of variance design. Alcoholic and non-alcoholic subjects within the high risk group were compared using a repeated measures design as a follow-up analysis. The present study demonstrated increased beta power in the resting EEG of offspring of male alcoholics. Male HR subjects had higher beta 1 (12–16 Hz) power and female HR subjects had increased power in beta 2 (16–20 Hz) and beta 3 (20–28 Hz) as compared with low risk participants. Female HR subjects also showed significantly increased beta 2 and beta 3 power if they had two or more alcoholic first-degree relatives when compared with HR females having only an affected father. Risk characteristics are expressed differentially in males and females and may be an index of differential vulnerability to alcoholism. The results indicate that increased EEG beta power can be considered as a likely marker of risk for developing alcoholism and may be used as a predictive endophenotype.

Keywords: Beta; EEG; High risk; Alcoholism; Absolute power; Gender; Inhibition

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1. Introduction

Beta oscillation in the electroencephalogram (EEG) has been extensively studied in resting states of normal and pathological conditions of the central nervous system (Neidermeyer, 1999). Rhythmical activity from 13 to 30 Hz, designated as the beta frequency band, is considered as an index of level of cortical excitation. In vitro and modeling studies have defined beta/gamma (13–50 Hz) oscillations as inhibition-based rhythms (Haenschel et al., 2000; Whittington et al., 2000a). Although a functional role cannot be assigned for each frequency, the beta/gamma oscillation is believed to represent an activated state of the underlying neuronal network. Studies suggest that beta frequencies typically observed in the EEG reflect neuronal activation with $GABA_A$ receptor action as pacemakers (Whittington et al., 2000b). A recent study reporting a significant linkage and linkage disequilibrium between beta frequency and a set of $GABA_A$ receptor genes (Porjesz et al., 2002) strengthens the evidence for the involvement of $GABA_A$ receptors. Lowered benzodiazepine-$GABA_A$ receptor density have been reported in alcoholics (Abi-Dargham et al., 1998) and in addition, abnormal metabolic responses to GABA agonists have been reported in non-alcoholic offspring of alcoholics (Volkow et al., 1995).

Beta power increase in the EEG of alcoholics, particularly in the resting condition has been well documented (Bauer, 1994; Costa and Bauer, 1997; Winterer et al., 1998; Rangaswamy et al., 2002). Several studies report increased beta power in the EEG of relatives of alcoholics (Gabrielli et al., 1982; Pollock et al., 1995; Bauer and Hesselbrock, 1993). However, only a few studies report an absence of pre-ethanol baseline differences in resting EEG between low and high-risk subjects (Pollock et al., 1983; Kaplan et al., 1988; Cohen et al., 1991). The details regarding the specific range of the beta bands examined in the studies cited in this section can be found in Table 1.

Significantly increased fast activity has been reported in both the resting state (Gabrielli et al., 1982; Pollock et al., 1995) and following ethanol consumption (Ehlers and Schuckit, 1990) among relatives of alcoholics as compared with controls. A diagnosis of antisocial personality (ASP) along with a positive family history for alcoholism was shown to be associated with increased beta power in frontal leads (Bauer and Hesselbrock, 1993). Studies have reported EEG beta power differences in high risk samples with only male subjects (Bauer and Hesselbrock, 1993) or in samples including both males and females (Pollock et al., 1995). Pollock et al. (1995) reported elevated beta power in family history positive (FHP) when compared to family history negative (FHN) subjects; this finding was more robust in male high-risk subjects. Gabrielli et al. (1982) attempted to characterize the differences in male and female high risk subjects compared to low risk separately, and demonstrated differences in male subjects only. The lack of differences between high risk and low risk females was attributed to a possible ceiling effect in beta power in females. A later study by Finn and Justus (1999) reporting increased relative power in beta band at frontal and occipital locations, noted no gender differences in the magnitude of increased relative beta power. The reports on high risk/low risk differences in beta power within the genders have, so far, been equivocal.

A positive family history of alcoholism has been recognized as a robust and consistent predictor of alcoholism risk. The first-degree relatives of alcoholics have been reported to show a seven-fold elevation in vulnerability to alcoholism (Goldman, 1993). Cotton (1979), reviewing several published family studies, concluded that alcoholics were 4 to 6 times more likely to have a parent who also was alcohol-dependent than were non-alcoholic controls.

Family, twin and adoption studies that highlight genetic contributions to alcoholism suggest that both genders are equally vulnerable (McGue and Slutske, 1996; Prescott et al., 1999). However, behavioral genetic studies estimating the heritability of alcoholism reveal more consistent estimates for males (0.50 to 0.60) and a highly variable estimate for females (0.0 to 0.56), providing a firm case for differential heritability of alcoholism for the two genders. Meta analysis of seven non-twin family studies of alcoholism indicates that the rate of cross-gender transmission of alcoholism is comparable to the within-gender transmission,

Table 1
Frequency range of Beta bands examined in EEG studies cited in our article

Authors	Beta band/s range
Gabrielli et al. (1982)	8–26 Hz
Kaplan et al. (1988)	13–20 Hz
Ehlers and Schuckit (1990)	12–20 Hz
Cohen et al. (1991)	13.2–19.5 Hz (slow beta); 19.75–26 Hz (fast beta)
Bauer and Hesselbrock (1993)	13.2–17.9 Hz (slow beta); 18.6–27.64 Hz (fast beta)
Bauer (1994)	13.2–27.6 Hz
Pollock et al. (1995)	12.09–15.99 Hz (Beta 1); 16.38–30.3 Hz (Beta 2)
Costa and Bauer (1997)	13–19 Hz (low beta); 19–30 Hz (high beta)
Winterer et al. (1998)	12.5–18 Hz (Beta 1); 21–30 Hz (Beta 3)
Finn and Justus (1999)	13–25 Hz
Rangaswamy et al. (2002)	12–16 Hz (Beta 1); 16–20 Hz (Beta 2); 20–28 Hz (Beta 3)

which in turn implies that the extent to which inherited factors are shared is roughly the same (McGue and Slutske, 1996). Nevertheless, the results of most genetic studies are equivocal about gender differences, especially owing to a lack of consistency in studies reporting about females. In their detailed review of the family genetic studies, McGue and Slutske (1996) suggest that inconsistencies of results across the various studies probably reflect limited statistical power due to the sample sizes used in the studies, and strongly recommend studying larger samples and reporting results separately by gender.

Apart from the risk of developing alcoholism, some authors have discussed the possibility of females having higher vulnerability to adverse consequences of alcohol use, higher blood-alcohol concentrations and greater alcohol-related organ damage (Urbano-Marquez et al., 1995; Zhang et al., 1999). The two genders also differ in their EEG spectral profile. Authors who have studied the EEG spectral profile in a population of normal healthy females and age-matched healthy males report gender differences in beta power (Wada et al., 1994; Duffy et al., 1993). Female subjects have higher power in the beta band of the EEG. These existing gender differences in the spectral properties of EEG further underscore the importance of studying risk indicators within the context of gender.

Our recent EEG study of alcoholics from the Collaborative Study on the Genetics of Alcoholism (COGA) demonstrates that the elevation of all three bands of beta power is a strong feature in the resting EEG of alcoholics when compared to age matched controls (Rangaswamy et al., 2002). Male alcoholics manifest this difference more clearly than female alcoholics, perhaps because physiological variables in females, such as stage of menstrual cycle, add to the variability of the data (Solis-Ortiz et al., 1994; Kaneda et al., 1997). The female alcoholics did show a significantly higher beta 3 (20–28 Hz) power and an almost significant increase in beta 2 (16–20 Hz) at the midline frontocentral location. The elevation of beta power in alcoholics has a largely anterior topography, especially in the higher frequency beta 3 band (20–28 Hz). It is important to determine if this beta power elevation is a feature that becomes apparent during the development of alcoholism ('state' related condition) or is found prior to alcohol exposure ('trait' related condition), particularly in the subjects with a high risk for developing alcoholism.

The purpose of this study was to examine the differences in magnitude and distribution of the EEG beta band in a large sample of male and female offspring of male alcoholics in the COGA database and to determine if the elevation of beta observed in alcoholics (Rangaswamy et al., 2002) is a consequence of alcohol use or a predisposing factor. Owing to existing differences in the spectral properties of EEG and progression, pathology and heritability of alcoholism, we have proposed to analyze the male and female subjects independently and discuss the profiles in the context of

each other. The study also investigates the influence of having more than one alcohol-dependent first-degree relative on the beta power of the EEG, separately, in males and females.

2. Methods and materials

2.1. Subjects

Subjects were participants in the ongoing Collaborative Study on the Genetics of Alcoholism (COGA), a multisite multi-stage national consortium designed to study the genetics of alcoholism. The collaborative sites are located at: SUNY-Health Science Center at Brooklyn, 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. A detailed description of the COGA recruitment procedure has been described previously (Begleiter et al., 1995). 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. Alcoholic probands were recruited from inpatient and outpatient treatment facilities, and they and their first degree relatives were interviewed with the SSAGA (Semi Structured Assessment of Genetics of Alcoholism), a semi-structured diagnostic psychiatric interview schedule designed expressly by COGA investigators (Bucholz et al., 1994; Hesselbrock et al., 1999). Subjects under the age of 18 years were administered the child/adolescent version of SSAGA, called the CSAGA/ASAGA respectively. Families in which the proband and two additional first-degree relatives met lifetime criteria for alcohol dependence by both Feighner and DSM-IIIR criteria were designated Stage II, and extended family members were also interviewed. From the Stage II family members, blood was drawn for establishing lymphoblastoid cell lines and biochemical analyses, and neurophysiological and neuropsychological assessments were conducted. Control families were recruited from HMOs, drivers' license records, and dental clinics, with the objective of being representative of the general population at each site. The control families were interviewed with the SSAGA, and underwent the full Stage II protocol.

Subjects were excluded from the neurophysiological assessment if presence of alcohol was detected when tested with the breathanalyzer. Subjects with hepatic encephalopathy/cirrhosis of the liver, acute/chronic illness, a significant history of head injury, seizures or neurosurgical procedures were excluded. Subjects who manifested uncorrected sensory deficits were also excluded. Subjects who tested positive for HIV or were on medication that affects/influences brain functioning or had used any psychoactive substances in the past 5 days were excluded.

For this study, 204 low risk (LR) subjects were culled from the control families and 171 high risk (HR) subjects from the alcoholic families. All subjects in the present study were in the age range of 16 to 25 years. Subjects with any history of psychoses were excluded from the sample. Subjects were categorized low risk if they and all their first degree relatives were diagnosed negative for DSM IIIR alcohol dependence by direct interview. Subjects assigned to the high risk category were offspring of male alcoholics from the alcoholic families whose mothers were not alcohol dependent. The sample was limited to offspring of male alcoholics to rule out confounding effects of Fetal Alcohol Syndrome (FAS) or fetal alcohol effects (FAE). The high risk sample was not confined to pure unaffected subjects (see Table 2).

2.2. Data recording

All six collaborating sites used identical experimental procedures and EEG acquisition hardware and software. Subjects were seated comfortably in a dimly lit sound-attenuated temperature-regulated booth (Industrial Acoustics Company; Bronx, NY), and instructed to keep their eyes closed and remain relaxed. Subjects were instructed not to fall asleep. 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,

Table 2
Sociodemographic and clinical characteristics of the sample

	High risk		Low risk	
	Males	Females	Males	Females
Number of subjects (*n*)	94	77	89	115
Mean Age	19.6	19.9	19.6	20.2
% Alcohol dependence-DSM IIIR	47	31	–	–
% cocaine dependence-DSM IIIR	8.5	5.2	0	0
% marijuana dependence-DSM IIIR	33.0	13.0	5.6	1.7
% stimulant dependence-DSM IIIR	4.3	5.2	0	0
% sedative dependence-DSM IIIR	2.1	3.9	0	0
% lifetime depression-DSM IIIR	6.4	24.7	9.0	26.0
% ASP-DSM IIIR	14.9	1.3	3.4	0
% Anxiety Disorders-DSM IIIR	1.1	9.1	6.7	6.1

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 and at the outer canthus of the left eye. Vertical and horizontal eye movements were monitored to perform ocular artifact correction. Electrical activity was amplified 10 000 times by Sensorium EPA-2 Electrophysiology amplifiers (Charlotte, VT), with a band pass between 0.02 Hz to 50 Hz and digitized on a Concurrent 5550 computer (Concurrent Computer Corp. Atlanta, GA). The sampling rate was 256 Hz and the activity was recorded for 4.25 min.

2.3. Data reduction and analysis

EEG analysis was performed at SUNY. A continuous interval comprising 256 s of EEG data was used in the 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). Wavelet filtering was employed because the signal being filtered had 2^{-16} samples and both very high and very low frequencies had to be eliminated; the long-term non-stationarity of EEG makes fixed length FFT filtering methods inappropriate. Wavelet filtering adjusts the length of filter to the frequency being filtered, rather than using a fixed length for all frequencies. The s12 wavelet was used to perform a 6 level analysis, and the output signal was reconstructed with levels d6 through d3. 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., 1986, 1987). 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 showed satisfactory artifact removal characteristics.

The data were subsequently software transformed into 20 vertical bipolar derivations (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. Absolute power spectra were then calculated for beta 1 (12–16 Hz), beta 2 (16–20 Hz) and beta 3 (20–28 Hz) bands, from these values. Bipolar derivations were used in preference over monopolar derivations to improve the spatial resolution of the electrical sources (Nunez, 1995; Nunez et al., 1997) especially because the 19-channel montage used in the study would not be appropriate for current source density analysis. Bipolar arrangements using close electrodes provide a higher pass spatial filter than is obtained with reference recordings. This method counteracts part

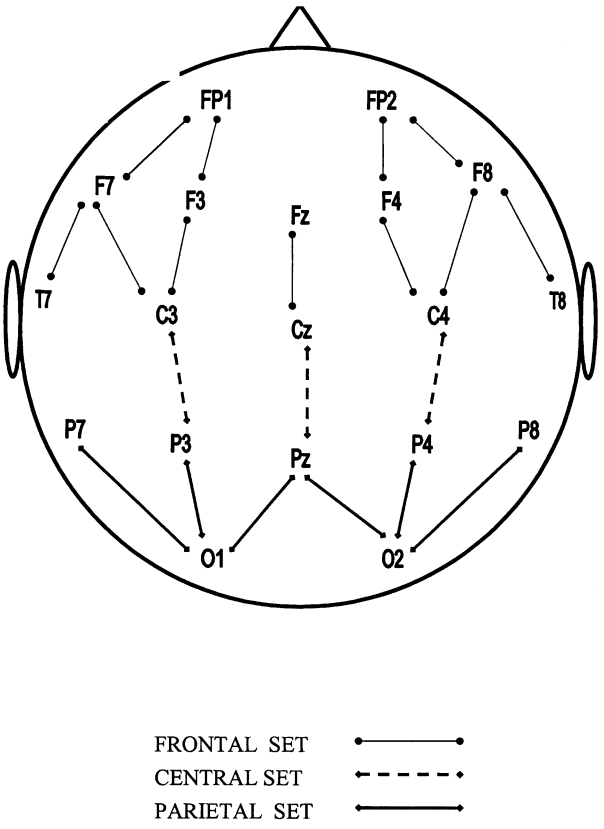

Fig. 1. Topographical diagram of the bipolar electrode-pairs used in the analysis.

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). A logarithmic transformation of the values was applied to the bipolar absolute power data to normalize their distributions.

2.4. Statistical analysis

2.4.1. Primary analysis

The three beta bands were analyzed independently. The normalized absolute beta 1 (12–16 Hz), beta 2 (16–20 Hz) and beta 3 (20–28 Hz) band power data were analyzed for group differences, separately for the two genders using six 2×20 repeated measures of analyses of variance (RMANOVA) designs (SAS, v6.11).

2.4.2. Secondary analysis

1. In order to characterize regional differences for each gender, three region-wise groups of the electrode-pairs were determined and the absolute beta power at each of these arrays was used as the dependent vector for comparisons between the two groups. Post hoc comparisons were made in the regions that were significantly different. The three sets were (Fig. 1):
   a FRONTAL-11 electrode pairs (FP1-F3, FP2-F4, FP1-F7, FP2-F8, F3-C3, F4-C4, Fz-Cz, F7-C3, F8-C4, F7-T7, F8-T8)
   b CENTRAL-3 electrode pairs (Cz-Pz, C3-P3, C4-P4)
   c. PARIETAL-6 electrode pairs (P7-O1, P8-O2, P3-O1, P4-O2, PZ-O1, PZ-O2)
2. In an attempt to explore any possible contribution of (a) status of the high risk individual (affected vs. unaffected) and (b) family density (as defined by the number of first degree relatives who are alcoholic), follow-up RMANOVAs were conducted using beta power as the dependent vector, for the high risk group only.

3. Results

3.1. Subject characteristics

All subjects studied were in the range of 16–25 years. Table 2 shows the gender-wise description of demographic and clinical variables in the study sample. The table also lists the various co-morbid conditions and lifetime prevalence as per DSM IIIR criteria. The sample of the present study differs from most published high risk studies with respect to the following points: (a) The status of alcoholism in all the index subjects and their first-degree relatives have been diagnosed and confirmed by individual assessment using the SSAGA, and corroborated with the family history assessment module (FHAM) In contrast, family history assessments in most published EEG studies have been obtained from index subject reports/assessments (Bauer and Hesselbrock, 1993; Finn and Justus, 1999; Ehlers et al., 1995). In the present study status of second degree relatives was not counted. However, all the family history positive subjects came from densely affected families.; and

(b) the co-morbid conditions (DSM IIIR diagnoses of Axis I conditions) have not been controlled for by matching their rates in the low and high risk samples. The percentages of occurrence of the co-morbid conditions in the present sample are reported in Table 2. The rationale for not matching the samples on drug use and other Axis I conditions, is that the reported rates for some conditions particularly anxiety and depressive disorders in subjects with family history of alcoholism, are elevated over normal population levels (Sher et al., 1991; Cuijpers et al., 1999). In keeping with one aspect of the COGA study, the present study attempts to define a stable endophenotype in a heterogeneous sample population.

3.2. Beta power differences between high risk (*HR*) and low risk (*LR*)

The estimates of log-transformed mean absolute power in the beta 1 (12–16 Hz); beta 2 (16–20 Hz) and beta 3 (20–28 Hz) bands were analyzed using repeated measures analyses of variance (RMANOVA) with group as the between-subjects factor and electrode location as the within-subjects factor. The two genders were analyzed separately. For each gender, four RMANOVAs were performed on the entire set of vertical electrode pairs and three sets of regional arrays viz. Frontal, Central and Parietal. The *F* values and significance levels for the group main effect have been summarized in tabular form following a short description of results (Table 3). The power increase in the HR subjects had a central focus.

3.2.1. Beta 1

Males: The HR males had higher beta 1 log power at all locations as reflected by a significant group main effect ($F=4.60$; $P=0.033$). This significant difference was largely due to the log beta 1 power increase in the central ($F=5.17$; $P=0.024$) and parietal ($F=6.09$; $P=0.014$) regions. The Cz-Pz electrode pair in the high risk group demonstrated the most significant increase of beta 1 log power in post hoc univariate tests ($P=0.006$).

Females: The HR females were not significantly different from LR females in the log beta 1 power distribution. The Cz-Pz electrode pair in the high risk group did not demonstrate any significant increase of beta 1 log power in post hoc univariate tests.

Table 3
LR vs. HR-RMANOVA *F* and *P* values for males and females

Data set	Males main effect-group		Females main effect-group	
	F	*P*	*F*	*P*
Beta 1 (12–16 Hz)				
All 20 pairs of electrodes	4.60	**0.033**	1.52	0.219
FRONTAL	2.73	0.100	0.087	0.353
CENTRAL	5.17	**0.024**	1.81	0.180
PARIETAL	6.09	**0.014**	2.04	0.155
Beta 2 (16–20 Hz)				
All 20 pairs of Electrodes	2.61	0.108	9.71	**0.002**
FRONTAL	2.07	0.151	8.34	**0.004**
CENTRAL	3.26	0.072	9.17	**0.003**
PARIETAL	2.95	0.087	8.25	**0.005**
Beta 3 (20–28 Hz)				
All 20 pairs of Electrodes	1.55	0.215	10.42	**0.0015**
FRONTAL	1.72	0.191	9.65	**0.002**
CENTRAL	4.39	**0.038**	13.36	**0.0003**
PARIETAL	0.95	0.332	6.10	**0.014**

3.2.2. Beta 2

Males: The HR males manifested higher log power, especially in the central ($P=0.072$)and parietal ($P=0.087$) regions, in the beta 2 band when compared to the LR males, but the difference was in trend only and not statistically significant.

Females: The HR females had higher log beta 2 power when compared to LR females. The group main effect was highly significant ($F=9.71$; $P=0.002$). This effect was seen at all locations frontal ($F=8.34$; $P=0.004$), central ($F=9.17$; $P=0.003$) and parietal ($F=8.25$; $P=0.005$). The Cz-Pz electrode pair in the high risk group demonstrated the most significant increase of beta 2 log power in post hoc univariate tests ($P=0.004$).

3.2.3. Beta 3

Males: The HR males manifested higher log power in the beta 3 band when compared to the LR males only in the central ($F=4.39$; $P=0.038$) region. The differences were not significant between the groups in either the frontal or the

Table 4
Mean age and sample size of HR subgroups compared on the basis of family density

	Only father alcoholic		2 or more alcoholic relatives	
	Mean Age	Number	Mean Age	Number
Males	19.2	44	19.8	50
Females	19.2	39	20.5	38

parietal regions. The Cz-Pz electrode pair in the high risk group demonstrated the most significant increase of beta 3 log power in post hoc univariate tests ($P=0.022$).

Females: The HR females had higher log beta 3 power when compared to LR females. The group main effect was highly significant ($F=10.42$; $P=0.0015$). This effect was seen at all locations–frontal ($F=9.65$; $P=0.002$), central ($F=13.36$; $P=0.0003$) and parietal ($F=6.10$; $P=0.014$). The Cz-Pz electrode pair in the high risk group demonstrated the most significant increase of beta 3 log power in post hoc univariate tests ($P=0.0002$).

3.3. Effect of alcoholism status within the HR sample

Log power in each of the three beta bands in HR subjects with a positive diagnosis of alcohol dependence was not significantly different from log beta power values in unaffected HR for both males and females.

3.4. Effect of family density (number of first-degree alcoholic relatives)

Age and sample sizes of subjects used in this analysis are reported in Table 4.

Males: 44 male offspring with only alcoholic fathers when compared with 55 male offspring with two or more alcohol-dependent first-degree relatives (including the father), showed no significant differences in log power of all three beta bands.

Females: 39 female offspring of alcoholic fathers only were compared with 38 female offspring with two or more alcohol-dependent first-degree relatives (including the father), The female offspring with two or more first-degree alcohol-dependent relatives had significantly higher power in beta 2 (16–20 Hz) ($F=5.68$; $P=0.020$) and beta 3 (20–28 Hz) ($F=5.50$; $P=0.022$) bands and an almost significant increase in beta 1 (12–16 Hz) power ($F=3.83$; $P=0.054$).

4. Discussion

The present study demonstrates increased beta power in the resting EEG of high risk subjects compared to low risk subjects. There were gender differences in the profile of beta power increases in high risk subjects. Male HR subjects had higher log power in the beta 1 band only and female high-risk subjects had higher beta 2 and beta 3 log power. At the regional level male HR subjects showed significantly increased beta 1 log power at the central and parietal regions, nearly significant increase beta 2 at central and parietal regions and beta 3 log power at the central region. Female HR subjects showed significantly higher values at all regions (frontal, central, parietal) for beta 2 and beta 3 log power.

This enhancement was neither found to vary as a function of status (affected vs. unaffected) for both males and females nor as a function of family density (number of affected first degree relatives) for males. The female offspring however, had greater increases in the beta 2 and beta 3 log power when they had two or more alcohol dependent first-degree relatives. The topographical locus of power increase in all three beta bands (12–16 Hz, 16–20 Hz, 20–28 Hz) was largely central.

The findings in male HR subjects in this study are consistent with existing reports of higher beta power in the resting EEG of FHP subjects (Bauer and Hesselbrock, 1993; Pollock et al., 1995). In an alcohol challenge study on non-alcoholic male subjects (Ehlers et al., 1989), moderate social drinkers had significantly higher peak frequency and power in the beta bands at baseline and at 90 min post alcohol intake when compared to low drinkers. The power increase was prominent particularly in the posterior region. Pollock et al. (1995) and Gabrielli et al. (1982) reported robust findings of elevated beta power in male high-risk subjects. The latter study attributed the lack of

differences between females to a possible ceiling effect in beta power in females. The study by Finn and Justus (1999) noted no gender differences in the magnitude of relative beta power increase in HR subjects. As discussed earlier in the Introduction, reports in the literature are clearer regarding the male high risk population than the female high risk individuals.

Most studies have focused on EEG changes only in male subjects, probably because the prevalence of alcoholism is higher in men than in women (Grant, 1996). Heritability in males with early onset drinking (<20 years) is significantly high and the late onset males and females have a much lower non-significant value (McGue et al., 1992). Family studies examining transmission of alcoholic traits find that both genders have an almost equal transmission to the offspring of both genders (McGue and Slutske, 1996). Studies have shown strong correlation of age at first drink with indicators of disinhibited behavior (McGue et al., 2001), and the association of age at first drink with alcoholism and disinhibitory psychopathology reflects a common underlying vulnerability (Prescott and Kendler, 1999; McGue et al., 2001). However, the basis of the association of age of first drink with disinhibitory psychopathology varies by gender (McGue et al., 2001), and if disinhibitory psychopathology and alcoholism share a common underlying vulnerability, it is likely that it may vary by gender. There seems to be evidence in the literature to suggest a possibility of gender differences in expression of risk characteristics. The characterization of the nature of differences, especially electrophysiological, between the genders has proved to be a difficult task. Owing to increased variability introduced into the female electrophysiological data by physiological variables such as the time point of the menstrual cycle (Solis-Ortiz et al., 1994; Kaneda et al., 1997), the task is made more difficult especially with small samples. In our study we have sufficiently large samples to separate out the effects of gender by examining the profiles independently in males and females.

We have observed the beta power increases in female HR to be more global and affecting the higher frequency sub-bands (16–28 Hz). This suggests increased vulnerability in women and is strengthened by our additional finding of higher beta power in the 16–28 Hz range in females with a higher family density of first-degree alcohol-dependent relatives. Female alcoholics drink less than males but drink to intoxication more often (Rubin et al., 1996), and are also more impaired than men after drinking similar quantities of alcohol, even when adjusted for body weight, due to differential alcohol pharmacokinetics and physiological responsiveness (Mumenthaler et al., 1999). First-degree relatives of alcoholics have been reported to show up to a seven-fold elevation in vulnerability (Goldman, 1993).

An examination of the co-morbidity status of the males and females in the present study (Table 2) reveals slightly higher anxiety rates for high risk females over the low risk female population, and the depression rates are high in both groups yet comparable. In males however, the ASP and drug use (marijuana and cocaine) rates are elevated in high risk when compared to low risk subjects. This distribution is consistent with reports in the literature of co-morbidity rates in early onset vs. late onset type. In an indirect manner, these population statistics indicate that we have probably succeeded in including a large percentage of Type 2/early onset alcoholics in our study sample. The strength of the present study comes from the vast COGA database that allows the parsing of family history and diagnostic variables without a severe attrition in sample sizes. A longitudinal study would provide more information about (a) the time-course of changes in beta power in subjects at risk and (2) if the beta power could be used as a predictive measure in determining if the high risk subject would eventually become alcoholic.

4.1. Theoretical aspects of increased beta power in HR individuals

Two questions arise from the results of the present study: – (a) Is the gender difference in the beta sub-bands affected physiologically significant?

Beta activity is indicative of background excitation that involves a frequency potentiating mechanism at the level of synapses in a network

(Whittington et al., 1997; Wrobel, 2000). Beta rhythm has been observed experimentally where there is an extensive recruitment of excitatory neurons. The potentiation between the excitatory neurons (e–e potentiation) in a single area disrupts the synchrony in the subsequent oscillations by uncoupling the synchronized assemblies (Whittington et al., 2000b). In general, the frequency of the neuronal networks becomes slower and the amplitude larger with increasing extent of synchronized neuronal assemblies (Singer, 1993; von Stein and Sarnthein, 2000). Experimental and modeling studies suggest that the frequency of the oscillations in the fast (gamma and beta) range is dependent on the relative refractory period of the neurons involved in producing them (Whittington et al., 2000a). Few of the important modulators of the refractory period are intrinsic after-hyperpolarization in the neuron, synaptic inhibitory potentials and the network inhibitory' postsynaptic potentials (IPSP).

We speculate that the potentiation between excitatory connections and modulatory drive affecting the refractory periods of the cortical neurons is different in the male and female high risk subjects. This means that the vulnerability in a high risk individual could be due to an increased excitatory drive and a deficient inhibitory tone as envisioned in the model for alcoholism proposed by Begleiter and Porjesz (1999), especially in the light of a recent study reporting significant linkage and linkage disequilibrium between beta frequency and a $GABA_A$ receptor gene (Porjesz et al., 2002). Recent findings also indicate that the same $GABA_A$ receptor gene associated with beta frequency is also involved in alcohol dependence (Edenberg et al., 2003) suggesting that this gene affects level of neural excitability, which affects predisposition to develop alcohol dependence. Lowered benzodiazepine-$GABA_A$ receptor density have been reported in alcoholics (Abi-Dargham et al., 1998) and evidence of an abnormal metabolic response to GABA agonists in non-alcoholic offspring of alcoholics (Volkow et al., 1995) supports a possibility of a reduction in such a modulatory drive. There is however, not much evidence in the literature about the gender differences in the $GABA_A$ receptor density and activity, and most studies report results on male alcoholics or mixed samples. Further studies exploring the gender differences at the receptor level would provide insights in this regard.

(b) What is indicated by the lack of differences observed between affected and unaffected high-risk subjects?

For the purpose of this study electrophysiological correlates of risk has been conceptualized as being expressed within the 16–25 years age range. Evidence from existing literature on HR studies suggests that the upper limit of the risk age group is approximately 25 years. The rationale for using both affected and unaffected subjects is substantiated by reports examining the predictive capacity of the age at first drink. An examination of age at first drink as a risk factor indicated that the highest risk for developing alcoholism exists for individuals who used alcohol in the 11–14 years range (Dewit et al., 2000). This report also found that the distinctive risk characteristics became clear 6 to 8 years after the age of first use. Age at first drink has also been correlated with a broad range of indicators of disinhibited behavior (McGue et al., 2001), and studies also suggest that the association of age at first drink with alcoholism reflects a common underlying vulnerability (Prescott and Kendler, 1999).

It has also been observed that an early onset of alcoholism is associated with increased likelihood of antisocial behavior (Babor et al., 1992; Cloninger, 1987b) and disinhibitory behaviors (McGue et al., 1997, 1999; Tarter, 1988). In our study sample we see evidence of similar co-morbidity status (see Table 2). ASP and drug use rates are elevated in the high risk study population. The lack of differences between the unaffected and affected high risk subjects supports a possibility that beta power elevation is a risk marker for alcoholism. Owing to the fact that the age group of this sample is 16–25 years, the duration of alcohol use in affected subjects is likely to be short. It would be of interest to examine the change in the characteristics of beta power elevation with increasing chronicity of alcohol use. We have as yet not examined this aspect in our sample. In our earlier report on elevation of beta power (Rangaswamy et al., 2002), we have studied alcoholics in

the age range of 18–50 years. Those subjects are likely to have been exposed to alcohol for longer durations than the subjects in the present study. The observed elevation in beta power had a more anterior topography in male and female alcoholics when compared to the respective age-matched controls. Male alcoholics had significantly higher power in all three beta bands and the female alcoholics had significantly higher beta 3 power and a strong trend for beta 2 increase at the Fz-Cz location. These findings in alcoholics provide an interesting contrast to those reported in the current HR sample.

The topography of beta power elevation as observed in the present HR sample, viz. elevated beta 1 band power in male HR and elevated beta 2 and beta 3 band power in female HR, is likely to be an antecedent profile prior to chronic alcohol exposure. In contrast to the topography observed in alcoholics (Rangaswamy et al., 2002), the beta power elevation is more central and posterior for the HR subjects, and the Cz-Pz electrode in particular showing consistent differences between the groups. Male high risk subjects have a significantly higher beta power in all three bands [beta 1: $P=0.006$; beta 2: $P=0.031$; beta 3: $P=0.022$] at the Cz-Pz location, which is similar to the profile observed for main effect of group in the male alcoholic sample. The strongest elevations in beta power, however, are observed only in the beta 1 band for the HR males. HR females show significant increases in the beta 2 and beta 3 bands only, while no significant elevations could be demonstrated at the global level for the female alcoholics.

These comparisons seem to suggest that prolonged alcohol exposure serves to normalize the beta power levels in the females and exacerbate the levels in males, leading to a more global and pronounced effect in male alcoholics and less prominent one in female alcoholics.

5. Conclusions

In summary our study indicates (a) Elevation in beta power could be a likely marker for risk of developing alcoholism and may be used as a predictive variable.

(b) Gender differences in the reactive frequency band within the beta range (12–28Hz) could be a marker for differential vulnerability to alcohol effects in the two genders.

A longitudinal gender differentiated study in younger high risk individuals, who are unaffected, would provide further information regarding the changes in the beta power profile and is underway in the COGA project. This follow-up study, assessing how many of the high risk subjects will eventually become alcoholic, will also clarify the predictive capacity of the elevation in beta power observed in the present study.

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