Patterns of Regional Brain Activity in Alcohol-Dependent Subjects

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Background: Electroencephalographic (EEG) measures of hemispheric asymmetry in anterior brain activity have been related to a variety of indices of psychopathology and emotionality. However, little is known about patterns of frontal asymmetry in alcohol-dependent (AD) samples. It is also unclear whether psychiatric comorbidity in AD subjects accounts for additional variance in frontal asymmetry, beyond a diagnosis of AD alone.

Methods: We compared 193 AD subjects with 108 control subjects on resting brain activity in anterior and posterior regions, as indexed by asymmetries in α band power in the left and right hemispheres. Within the AD group alone, we examined whether comorbid major depressive disorder (MDD) or antisocial personality disorder (ASPD) had effects on regional asymmetry.

Results: Compared with control subjects, AD subjects exhibited lower left, relative to right, cortical activation in anterior regions. Evidence that comorbidity in AD subjects accounted for further variance in EEG asymmetry was mixed; AD subjects with comorbid ASPD were not significantly different from those without ASPD, while AD subjects with a lifetime history of MDD showed less asymmetry in anterior regions than those without MDD.

Conclusions: Our findings indicate that AD subjects exhibit a pattern of frontal asymmetry similar to that found in other psychiatric groups. Results examining the effects of comorbidity in AD on EEG asymmetry were inconclusive. The implications of our findings for future work are described.

Key Words: Alcohol Dependence, Anterior Asymmetry, EEG, Negative Emotionality, Comorbidity.

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IN RECENT DECADES, the importance of cortical structures to emotional experience and regulation has become generally accepted (see Davidson, 2004, for a review), especially with regard to the prefrontal cortex and its roles in cognitive control (Miller and Cohen, 2001) and in attributing emotional significance to stimuli (Rolls et al., 2003). The significance that these structures may have for the development of psychopathology has also risen to the forefront of basic psychopathology research. For example, a large literature has emerged relating electroencephalographic (EEG) measures of resting anterior α asymmetry to individual differences in emotional traits that may be linked to psychopathology vulnerability (Davidson, 2004). The literature examining the relative activity in anterior regions has emphasized α band power, which varies inversely with cortical activity such that lower power indicates greater cortical activity (Coan and Allen, 2004). It has been proposed that activity indexed by α band power in the left anterior cortex reflects the activity of neural substrates that regulate approach behaviors aimed at acquiring rewards and the accompanying positive affect, while activity in the right frontal cortex indexes systems involved in behavioral inhibition in the face of potentially aversive stimuli and fearful emotional responding (Davidson, 1998). An imbalance in activity in these regions could reflect a dysregulation, possibly genetically

based, in neurobehavioral systems that govern emotion and motivation. The precise mechanisms by which such a dysregulation might increase vulnerability are unclear and probably complex; one possibility is that it may reflect a decreased capacity to respond effectively to stressors or to develop adequate support systems to buffer against the effects of negative life events. In any case, such quantifiable indices of neurobehavioral characteristics are potentially valuable as they may serve as novel endophenotypes for psychiatric disorders.

In adult samples, evidence shows that lower left anterior cortical activation, relative to right, is associated with current (Gotlib et al., 1998; Henriques and Davidson, 1991) and lifetime history of depression (Gotlib et al., 1998; Henriques and Davidson, 1990), although inconsistent results have also been reported (Pizzagalli et al., 2002; Reid et al., 1998). Additionally, self-reports of negative emotionality (NE; neuroticism, or the propensity to experience depressive and anxious mood states) have been linked to similar indices of cortical activation (Tomarken et al., 1992). It appears that individual differences in frontal asymmetry may be meaningfully linked to behavior and temperament even early in life; preschoolers who appear inhibited and unoccupied in free-play settings exhibit decreased left frontal activation (Fox et al., 1995), and infants of mothers with depressive symptomatology show reduced left frontal activation during playful interactions with their mothers (Dawson et al., 1992). This pattern of asymmetry in frontal activity has also been associated with infant distress during maternal separation (Davidson and Fox, 1989).

Taken as a whole, EEG indices of lower left relative to right frontal brain activity have been interpreted as reflecting an early emerging vulnerability to NE and depressive disorders. Given the inclusion of young children and remitted samples in this literature, these patterns of frontal asymmetry are thought to be trait-like and show at least modest evidence of heritability (Anokhin et al., 2006), although there are state effects on variance in resting EEG asymmetry as well (Hagemann et al., 2005).

Little is known about whether a relationship exists between resting anterior α asymmetry and alcohol dependence (AD). This is surprising, given that the propensity to experience NE may have important significance in this disorder. For example, higher levels of self-reported trait NE are associated with alcoholism (McGue et al., 1999). Also, NE predicts the course of adolescent alcohol use (Chassin et al., 2002; Colder et al., 2002) and distinguishes heavy drinkers from light (Chassin et al., 2004). Although these studies are based upon self-report measures of NE, they suggest the potential value of examining EEG indices of anterior cortical activity in alcoholism. For resting EEG, 1 study examining a sample of Native American youths (Ehlers et al., 2001) reported no association between EEG indices of frontal α activity and a family history of alcoholism. However, it is unclear whether these measures might predict more direct indices of problematic drinking, such as a diagnosis of AD.

Equally unclear is whether psychiatric comorbidity in AD would be associated with different patterns of frontal α band activity. The bulk of the literature looking at EEG asymmetry has focused on depression and related constructs (e.g., behavioral inhibition) and suggests that internalizing patterns of behavior are associated with lower left (or higher right) relative activation (Allen et al., 1993; Henriques and Davidson, 1990, 1991; Wiedemann et al., 1999). Other studies suggest that high behavioral activation and approach-related emotions such as anger are associated with the opposite pattern of frontal asymmetry: that is, higher left activation relative to right (Coan and Allen, 2003; Harmon-Jones and Allen, 1998). These findings suggest that AD subjects with comorbid externalizing psychopathology, such as antisocial personality disorder (ASPD), may show opposing patterns of resting asymmetry than those with comorbid depression.

To explore these issues, we examined patterns of resting α activity in a sample of adults with a diagnosis of AD and a community sample of controls with no psychiatric history. We expected that subjects with AD would differ from control subjects on anterior α asymmetry, showing a pattern of activity that has been previously linked to negative emotional states and psychopathology (i.e., left frontal hypoactivation). We also predicted that AD subjects with comorbid major depressive disorder (MDD) would show an especially pronounced pattern of lower left frontal activation relative to right, while AD subjects with a comorbid diagnosis of ASPD would show increased left frontal activation relative to right frontal areas, compared with AD subjects without these comorbid diagnoses.

MATERIALS AND METHODS

Subjects were a subset of participants in the ongoing Collaborative Study on the Genetics of Alcoholism (COGA) project, a multisite study of families affected with alcoholism and a control sample of families ascertained to be representative of the general population. Participating sites were Indiana University School of Medicine, University of Iowa, University of Connecticut, State University of New York Health Sciences Center in Brooklyn, University of California—San Diego, and Washington University at St. Louis. Greater details on recruitment of the COGA sample have been provided elsewhere (Nurnberger et al., 2004; Rice et al., 2003). Briefly, alcoholic subjects were drawn from inpatient and outpatient treatment facilities, while controls were recruited through a variety of channels, including health and dental clinics and motor vehicle registries. This study was approved by institutional review boards at all sites.

Only right-handed subjects were included in these analyses, as is standard practice in studies of anterior α asymmetry. We examined 193 unrelated subjects with a diagnosis of AD and 108 control subjects without a lifetime history of major affective illness, eating disorder, anxiety disorder, alcohol or drug dependence, or ASPD. Diagnoses were made following DSM-III-R criteria (American Psychiatric Association, 1987) and were established using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994). The most recent and comprehensive clinical interview data available were used, either from the baseline interview

($N = 53$) or from follow-up ($N = 140$). For the AD group, the number of symptoms met for a diagnosis of AD from the clinical interview was used as a dimensional measure of AD severity. Of the control subjects, 56 (52%) were male and most were white ($N = 90$, 84%). Nine control subjects were African American (8%), and the 9 remaining subjects (8%) were of other ethnic backgrounds. The average age of control subjects was 41 years old (SD = 14 years). Alcohol-dependent subjects were mostly male ($N = 144$, 75%) and were also mostly white ($N = 144$, 75%). Eighteen percent ($N = 35$) were African American and the remaining 7% were of other ethnic backgrounds ($N = 18$). Alcohol-dependent subjects were an average of 43 years old (SD = 11 years). Twenty-six of the AD subjects (14%) had a lifetime history of MDD (excluding subjects with substance-induced episodes), and 37 (19%) had a diagnosis of ASPD. Three subjects had both ASPD and MDD.

All collaborative sites used the same 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). Subjects 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). The nose served as reference and the forehead was the ground electrode. Electrode impedances were always maintained below 5 kΩ. An electrooculogram was recorded from electrodes placed supraorbitally and on the outer canthus of the eye. Vertical and horizontal eye movements were monitored to perform ocular artifact correction. Electrical activity was amplified 10,000 times by EPA-2 electrophysiology amplifiers (Sensorium, Charlotte, VT), with a band pass between 0.02 and 50 Hz and digitized on a Concurrent 5550 computer (Concurrent Computer Corp., Atlanta, GA).

Electroencephalographic data were collected for a period of 256 seconds at 256 samples per second while subjects' eyes were closed and open, for a total of 512 seconds. The raw data were subjected to wavelet filtering and reconstruction to eliminate very high and low frequencies. The s12 wavelet was used to perform a 6-level analysis, and the output signal was reconstructed with levels $d6$ through $d3$. Eye movements were removed by use of a frequency domain method developed by Gasser et al. (1985, 1986). This method subtracts a portion of the observed ocular activity from the observed EEG to obtain the true EEG, where the proportionality is based on the difference between the cross-spectral values of trials with high ocular activity and those with low ocular activity. The data were analyzed in 254 overlapping 2-second intervals using of a Fourier transform. A Hamming window was used to improve the accuracy of the spectral results. The resulting values were aggregated into bands, and the aggregates were divided by the bandwidth and then averaged.

α-Band power (8–12.5 Hz) was computed and log-transformed to address positive skew. Regional asymmetry was approximated by comparing log-transformed α band power at 2 frontal (F3, F4) and posterior (P3, P4) scalp loci. An asymmetry metric was computed as the logarithm of right cortical activity in the α band minus the logarithm of the analogous left site. Although the present study is concerned with asymmetry in frontal regions, a similar metric was also calculated for posterior regions to examine whether evidence for regional specificity of asymmetrical activation was present. These logarithmic difference scores are interpreted as analogous to ratiometric scores of the raw data (Miller et al., 2002). As α band power varies inversely with cortical activity (i.e., lower α band power indicates greater cortical activity), lower asymmetry scores are interpreted as reflecting decreased left relative to right cortical activity (Coan and Allen, 2004; Davidson, 1988; Miller et al., 2002).

RESULTS

To test our hypotheses regarding asymmetric frontal α band power, a repeated-measures analysis of variance (ANOVA) was used with eyes (open vs closed) and region (anterior vs posterior) as within-group variables and sex and group (control vs AD) as between-group variables. Pillai's trace statistic was used. As neither the eyes factor nor the sex factor interacted with group, both were dropped from the model, and asymmetry metrics were examined averaged across the 2 eye conditions. The expected Group×Region interaction did not reach significance [$F(1, 300) = 1.67$, $p = 0.20$, $\eta^2 = 0.005$]; nonetheless, because of an a priori hypothesis regarding asymmetries in specific regions, simple effects analyses were used to evaluate asymmetries in frontal and posterior regions separately (see Fig. 1). Comparison of asymmetry scores in frontal regions showed a main effect of group [$F(1, 300) = 9.04$, $p = 0.003$, $\eta^2 = 0.029$], with AD subjects having significantly more negative frontal asymmetry scores ($M = -0.03$, SD = 0.07) than controls ($M = -0.01$, SD = 0.08).[1] There was no significant group effect on posterior asymmetry scores [$F(1, 300) = 2.03$, $p = 0.16$, $\eta^2 = 0.007$].

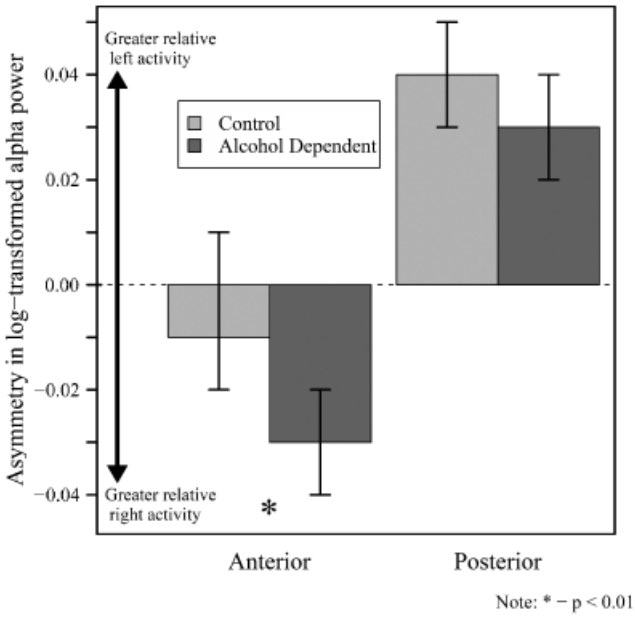

Fig. 1. Mean anterior and posterior log-transformed α band power asymmetry scores in control and alcohol-dependent subjects (error bars are standard errors).

To examine whether comorbidity had an effect on cortical asymmetries in the AD group, another repeated-measures ANOVA was used with Eyes (open vs closed) and Region (anterior vs posterior) as within-group variables and MDD (present vs absent) and ASPD (present vs absent) as between-group variables. This analysis was aimed at clarifying whether comorbidity had additional effects on frontal α asymmetry, above and beyond a diagnosis of AD alone, and therefore included only the AD subjects. The majority of the AD group was male, which

[1]Analyses examining male and female subjects separately yielded identical results.

meant that the number of female AD subjects with comorbid ASPD and MDD was low ($N = 4$ for ASPD and $N = 8$ for MDD). Because of the small number of females with these diagnoses, only male AD subjects were included in these analyses. Severity of AD (indexed by number of AD symptoms met from the clinical interview) did not differ between male AD subjects with comorbid depression or comorbid ASPD compared with those without depression [$t(1, 142) = 0.00$, $p = 1.00$] or ASPD [$t(1, 142) = -1.67$, $p = 0.10$]. Also, severity of AD was not significantly correlated with either the anterior or the posterior asymmetry metric [$r(N = 193) = -0.08$, $p = 0.26$] and [$r(N = 193) = 0.11$, $p = 0.14$], respectively. As the Eyes factor did not interact with the comorbidity variables, it was dropped from the model, and corresponding asymmetry metrics were averaged across the 2 eye conditions. ASPD comorbidity did not interact significantly with region in predicting asymmetry scores ($F = 0.18$, $df = 1, 140$, $p = 0.67$, $\eta^2 = 0.00$). Comorbidity with MDD, however, showed a trend level interaction with region ($F = 3.71$, $df = 1, 140$, $p = 0.06$, $\eta^2 = 0.03$). The interaction term of both types of comorbidity did not interact significantly with region ($F = 1.07$, $df = 1, 140$, $p = 0.30$, $\eta^2 = 0.01$).

Simple effects analyses were used to evaluate the effects of comorbid depression and ASPD on asymmetries in frontal and posterior regions separately. Antisocial personality disorder did not have a significant effect on asymmetry scores in anterior regions (see Fig. 2) [$F(1, 141) = 0.059$, $p = 0.81$, $\eta^2 = 0.00$], although its effects on posterior regions approached significance [$F(1, 141) = 3.45$, $p = 0.07$, $\eta^2 = 0.02$]. Comorbid MDD did not have a significant effect on posterior asymmetry scores [$F(1, 141) = 0.09$, $p = 0.77$, $\eta^2 = 0.00$]; however, it did have a significant effect on anterior regions (see Fig. 2) [$F(1, 141) = 6.35$, $p = 0.01$, $\eta^2 = 0.04$]. Surprisingly, this effect was in the opposite direction anticipated: AD subjects with MDD tended to have *less* asymmetry in frontal regions ($M = 0.00$, SD = 0.05) than AD subjects who were not comorbid ($M = -0.04$, SD = 0.06).

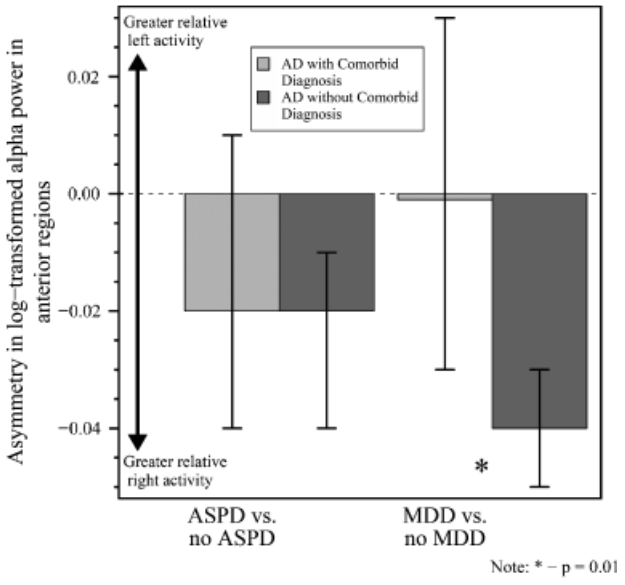

Fig. 2. Mean anterior log-transformed α band power asymmetry scores in male alcohol-dependent (AD) subjects with and without comorbid major depressive disorder (MDD) and antisocial personality disorder (ASPD) (error bars are standard errors).

DISCUSSION

As predicted, we found that AD subjects showed significantly more negative anterior asymmetry scores than control subjects, as indexed by EEG α band power measured at scalp locations F3 and F4, indicating a pattern of decreased left relative to right frontal activation. We also predicted that AD subjects with comorbid MDD would show an especially pronounced pattern of lower left frontal activation relative to right, while AD subjects with comorbid ASPD would show increased left frontal activation relative to right frontal areas, compared with AD subjects without these comorbid diagnoses. However, evidence that comorbidity in AD subjects accounted for further variance in EEG asymmetry was mixed; AD subjects with comorbid ASPD were not significantly different from those without ASPD on indices of anterior asymmetry. Contrary to our hypothesis, AD subjects with a lifetime history of MDD showed less asymmetry in anterior regions than those without MDD.

To our knowledge, this study is the first to characterize resting anterior activation in AD subjects. Regarding our finding of decreased left anterior activation relative to right in AD subjects, it is noteworthy that similar patterns of frontal EEG activity have been noted in MDD. Replication of this finding in other AD samples is critical as our sample size was relatively large for studies of this kind, and the obtained effect size was small. However, should this pattern be established as consistent, frontal α asymmetry may prove a useful phenotype for genetic studies of AD, as well as other forms of psychopathology. Our findings, taken with the larger research on regional asymmetry in psychopathology, suggest that commonalities may exist across disorders for the EEG patterns observed in the present study. If so, anterior asymmetry may prove to be a quantitative index of a general vulnerability to psychopathology that interacts with other genetic and environmental factors to predict the development of specific disorders, including AD. It may be the case that similarities in asymmetries of α band power in AD and mood disorders reflect shared genetic variance in these forms of psychopathology (Kendler et al., 1993).

We had expected that AD subjects with comorbid MDD would have lower left frontal activation, relative to right, than those without depression. Our analyses, however, did not support this; surprisingly, AD subjects with comorbid depression had less marked asymmetry in frontal regions than those with AD alone. Given the literature indicating that left frontal hypoactivation is a marker of both state

levels of depression (Gotlib et al., 1998; Henriques and Davidson, 1991) and lifetime history of the disorder (Gotlib et al., 1998; Henriques and Davidson, 1990), this finding is puzzling. The etiological heterogeneity of MDD is widely acknowledged; thus, it is possible that the present finding reflects unknown differences in underlying processes important in depression that cooccurs with AD, as opposed to factors that influence depression without comorbid AD. On a related note, it is crucial to reiterate that this finding pertains only to male subjects; due to the small number of females in our study, only males were examined in the analyses looking at comorbid depression and AD. In contrast, as depression disproportionately affects females, much of the literature looking at frontal asymmetry and depression has examined female subjects, and at least one group (Miller et al., 2002) found the hypothesized left frontal hypoactivation–depression association in females only and not in male subjects. Male subjects with comorbid AD and depression, such as those used in the present study, may constitute a subgroup of depression for which anterior asymmetry is less relevant.

We did not find that AD subjects with comorbid ASPD differed from those with AD alone on anterior α asymmetry. However, our ability to examine the effects of antisocial personality traits on frontal asymmetry may have been hampered by our relatively gross index of behavior relevant to such traits, the DSM-III-R criteria for ASPD, which have been criticized for overemphasizing criminal behavior rather than personality traits (Hare et al., 1991). Future work that uses a more fine-grained index of disinhibitory psychopathology may reveal differences in patterns of regional asymmetry that we were unable to detect using DSM-III-R criteria, which likely capture a broad range of antisocial behaviors driven by diverse etiological factors.

Our study had several strengths, including the use of electrophysiological measures and structured clinical interview assessments of controls and AD subjects. However, our study did have a number of limitations. The obtained effect size was small, raising the possibility that we capitalized on a relatively large sample size for studies of this kind and detected mean differences with minimal implications for behavior and emotion. Analyses of comorbidity were restricted to males only, due to the small number of female subjects with comorbid psychopathology. Although we used diagnostic comorbidity as a way of creating more homogeneous subgroups within the AD sample, such diagnostic categories are still relatively broad and coded as present/absent, which may have led us to miss important distinctions that might exist between more narrowly defined clinical groups.

In an effort to be consistent with the extant literature looking at regional asymmetry, we elected to limit our analyses to those examining α power and not other frequency bands. Although this approach is standard in the field, it was recently reported that other frequency bands besides α may correspond more closely to other indices of cortical activity, such as regional glucose metabolism (Oakes et al., 2004). Future investigations of frontal EEG asymmetry should broaden their scope to include other frequency bands in analyses.

We used difference scores between logarithms of right and left frontal α band power collected during a ''resting'' (i.e., inactive) baseline period as our dependent variable in the present study. This approach is widely used in this area of research, which permits our findings to be incorporated into the larger literature examining anterior asymmetry in psychopathology and temperament. The use of difference scores increases statistical power (Coan and Allen, 2004) and mitigates the influence of individual differences in skull thickness on recorded signal amplitude (Eshel et al., 1995). Also, asymmetry scores correct for individual differences in overall α power, which can be confounded with the magnitude of asymmetry (Allen et al., 2004). However, this approach can be criticized on several grounds. First, participants may exhibit greater variability during a resting task in which no instructions are provided, as opposed to tasks with more explicit demands. Also, difference scores can be criticized on a conceptual level as the same score can reflect very different patterns of right and left frontal activity (Schmidt, 1999); in our study, for example, the use of a difference score makes it unclear whether obtained differences are due to low left frontal activity, high right frontal activity, or a combination of the two. Analyses examining the effects of frontal activity in individual hemispheres separately did not find significant group differences on either hemisphere (data available upon request), leading us to conclude that activities in both left and right frontal regions are contributing to the group differences obtained in our sample.

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