
Clinical and Biological Concomitants of Resting State EEG Power Abnormalities in Schizophrenia

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Background: *This study investigated the clinical and biological concomitants of electroencephalogram power abnormalities in schizophrenia.*

Methods: *We examined the power characteristics of resting electroencephalograms in 112 schizophrenic patients. Also collected were measures of psychotic symptomatology, brain morphology, ocular motor functioning, electrodermal activity, and nailfold plexus visibility. Seventy-eight nonschizophrenic psychosis patients (e.g., mood disorder patients with psychosis) and 107 nonpsychiatric control subjects were included for comparison.*

Results: *Schizophrenic patients whose electroencephalograms were characterized by augmented low-frequency power and diminished alpha-band power had more negative symptoms, larger third ventricles, larger frontal horns of the lateral ventricles, increased cortical sulci widths, and greater ocular motor dysfunction compared with schizophrenic patients without these electroencephalogram characteristics. In nonschizophrenic psychosis patients, augmented low-frequency and diminished alpha-band powers failed to be associated with any clinical or biological indices.*

Conclusions: *Results suggest that clinical and biological concomitants of low-frequency and alpha-band power abnormalities in schizophrenia are unique, perhaps indicating the presence of thalamic and frontal lobe dysfunction. Biol Psychiatry 2000;48:1088–1097 © 2000 Society of Biological Psychiatry*

Key Words: Schizophrenia, electroencephalogram, psychosis, symptomatology, brain morphology, ocular motor function

Introduction

Since the 1970s, investigators have reliably shown electroencephalograms (EEGs) of schizophrenic patients to contain augmented low-frequency power and

diminished alpha-band power (e.g., Iacono 1982; Itil et al 1972, 1974; Miyauchi et al 1990; Sponheim et al 1994). Nonetheless, the significance of EEG power abnormalities to schizophrenia is unclear. Electroencephalogram anomalies are not a medication phenomenon. Researchers have found EEG anomalies in medication-free (Merrin and Floyd 1996; Miyauchi et al 1996) and neuroleptic naive (Nagase et al 1996; Omori et al 1995) schizophrenic patients. Electroencephalogram power abnormalities of schizophrenic patients are relatively independent of current (Fenton et al 1980) and past medication status (Gattaz et al 1992), as well as type (Sponheim et al 1994) and dosage (Kahn et al 1993; Omori et al 1992) of medication. Also, augmented low-frequency power and diminished alpha-band power appear to be unrelated to chronicity in schizophrenia (Sponheim et al 1994). Although evidence indicates EEG power abnormalities are not due to treatment or the duration of schizophrenia, low-frequency and alpha-band power abnormalities are not specific to the disorder (for a review, see Williamson and Kaye 1989). For instance, patients with bipolar disorder exhibit similar EEG anomalies (Clementz et al 1994). To determine the significance of EEG power abnormalities to schizophrenia, this study examined clinical and biological characteristics of schizophrenic patients who exhibit augmented low-frequency power and diminished alpha-band power. We also studied clinical and biological features of non-schizophrenic psychosis patients to determine whether the significance of EEG power anomalies is similar for a variety of psychotic patients.

Several studies have demonstrated that schizophrenic patients with augmented low-frequency EEG power show more negative symptomatology (Fenton et al 1980; Gattaz et al 1992; Omori et al 1992). The association between low-frequency power and negative symptoms has been found in middle-aged (Fenton et al 1980) and elderly schizophrenic patients (Omori et al 1992), as well as subjects on medications (Omori et al 1992) and off (Fenton et al 1980). Alpha power has been found to be inversely related to negative symptoms (motor retardation, blunted affect, and emotional withdrawal; Merrin and Floyd 1992, 1996), whereas beta power has generally failed to be associated with negative symptoms (Merrin

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and Floyd 1991, 1996; Omori et al 1992). There is little evidence that EEG power abnormalities are related to thought disorganization, delusions, or hallucinations in schizophrenia.

Although some studies suggest that schizophrenic patients with EEG power abnormalities have additional biological anomalies, evidence is too scant to provide an understanding of the biological significance of power abnormalities. Studies have shown delta power to be associated with the area of the third cerebral ventricle (Takeuchi et al 1994), glucose metabolism in frontal brain regions (Alper et al 1998; Guich et al 1989), and abnormalities in visual- and auditory-evoked potentials (Morihisa et al 1983) in individuals with schizophrenia. Diminished alpha power in schizophrenia has been associated with evoked potential abnormalities (Morihisa et al 1983), subcortical metabolism (Alper et al 1998), and high levels of noradrenaline in cerebral spinal fluid (Kemali et al 1990). Changes in alpha peak frequency have been tied to enlargement of the lateral cerebral ventricles (Karson et al 1988). One study identified remitted schizophrenic patients who were electrodermal responders to have lower alpha frequencies and more beta activity than electrodermal nonresponders (Iacono 1982).

To investigate the clinical and biological features of schizophrenic patients with EEG power abnormalities, we examined the resting EEGs of a large sample of schizophrenic patients. Psychotic symptoms were studied as possible clinical concomitants of EEG power abnormalities, and brain morphology, ocular motor functioning, electrodermal activity, and nailfold plexus visibility were examined as possible biological concomitants. Previous work has shown schizophrenic subjects to be abnormal on these selected biological variables (Clementz et al 1992; Iacono 1985; Iacono et al 1992, 1999; Sponheim et al 1994). Nonschizophrenic psychosis (e.g., bipolar disorder with psychotic features) and nonpsychiatric control subjects were studied for comparison. If associations between EEG power abnormalities and clinical or biological characteristics are unique to schizophrenia, it would suggest that abnormal brain electrical activity reflects aspects of neuropathology in schizophrenia not shared with other mental disorders.

Methods and Materials

Subjects

The subject sample consisted of 112 schizophrenic patients (54 first episode and 58 chronic), 78 nonschizophrenic first-episode psychosis patients (33 bipolar, 29 major depressive, and 16 other psychosis), and 107 nonpsychiatric control subjects. Table 1 summarizes the characteristics of the subjects. All subjects gave written informed consent to be in the study. Patients received a

Table 1. Characteristics of Subjects

Diagnostic group	N	Percent female	Age	
			Mean	SD
Schizophrenic				
First episode	54	24	22.6	5.01
Chronic	58	12	28.6	4.36
Nonschizophrenic psychosis				
Bipolar	33	39	24.5	6.47
Major depressive	29	31	24.4	5.24
Other psychosis ^a	16	31	28.7	12.22
Nonpsychiatric control	107	45	31.6	14.31

^a7 paranoid psychosis, 8 schizophreniform, 1 schizoaffective.

semistructured interview (the Present State Examination [PSE], 9th edition; Wing et al 1974) by a trained psychiatrist or clinical psychologist. Because all subjects were recruited 1980–1986, diagnoses were originally assigned according to DSM-III criteria (American Psychiatric Association 1980), after a consensus diagnosis was reached by two or more clinicians who had reviewed a patient's data across all time points (first-episode patients) and from all sources including hospital records (first-episode and chronic patients). For this report, DSM-IV (American Psychiatric Association 1994) consensus diagnoses were made by reviewing all interview, symptom checklist, course, and functioning data from which original diagnoses were made.

Patients were excluded if they had a history of substance dependence or head trauma or showed evidence of a neurologic disorder (including tardive dyskinesia) or mental retardation (IQ < 60). Written consent was obtained from each subject after the procedures of the study were explained. (For additional information concerning the diagnostic approach, see Iacono and Beiser 1989.)

First-episode schizophrenic and first-episode nonschizophrenic psychosis patients were referred through a community-wide network consisting of all psychiatric hospitals and community mental health centers in Vancouver, Canada, and referrals from private practice psychiatrists and general practice physicians who agreed to assist in the study. An attempt was made to recruit all persons, between the ages of 16 and 54, who experienced their first episode of psychosis during a 2.5-year period. To be included in the study, subjects had to be experiencing their first episode of disorder and have hallucinations, delusions, or grossly disorganized behavior (i.e., be psychotic; for a full listing of criteria, see Iacono and Beiser 1989). Of 318 potential subjects, 94 refused to participate, 31 could not be located in time to recruit them, 18 were not psychotic, 15 withdrew from the study before their EEGs could be recorded, and 28 patients were excluded due to data collection problems or unavailability of artifact-free EEGs. At the time of EEG testing, first-episode schizophrenic and nonschizophrenic psychosis patients were clinically stable and almost all had been recently hospitalized. Eighty-three percent of first-episode schizophrenic patients and 85% of first-episode nonschizophrenic psychosis patients were on medications.

Chronic schizophrenic patients were recruited from an extended-care mental institution and affiliated board-and-care homes in the Vancouver area. If after reviewing interview and hospital infor-

mation clinicians concluded at a case conference that patients met DSM criteria for chronic schizophrenia, they were included in the study. Of 65 chronic schizophrenic subjects, the EEGs of seven patients were excluded due to recording errors or a lack of artifact-free data. Of the remaining 58 patients, 29 were residing on a male inpatient ward and 29 were recruited from board-and-care homes. Chronic schizophrenic patients were characterized by an early age of onset (mean = 18.7 years, SD = 3.39), extended histories of schizophrenia (mean = 9.9 years, SD = 4.23), and many months of hospitalization (mean = 23, SD = 26.90). Ninety-eight percent of the chronic schizophrenic patients were on medications.

Nonpsychiatric control subjects were volunteers recruited from family practice clinics in low income neighborhoods, employment centers, community centers, and vocational colleges. Nonpsychiatric subjects were excluded if they reported a history of mental health treatment in either themselves or their first-degree relatives. Nonpsychiatric subjects were free of drug or alcohol dependence and any chronic physical illnesses.

EEG Apparatus and Procedure

Subjects were seated in a darkened room and presented binaurally with 55-dB (sound pressure level) white noise over headphones. Subjects were instructed to close their eyes, sit still, and relax for several minutes while their "brain waves" were recorded. Gold electrodes referenced to linked ears were used to record EEGs from three central scalp locations (Cz, C3, and C4), and Ag–AgCl electrodes above and below the right eye registered ocular movements. All electrode connections had impedances below 5 k Ω .

The EEG was recorded with a 35-Hz, half-amplitude, low-pass filter and a 1-sec time constant and stored on reel-to-reel tape with a Vetter (Vetron Technology, Rebersburg, PA) Model A recorder. To ensure that the power of the frequency spectrum could be accurately determined, a calibration pulse was recorded with the EEG. The EEG data were digitized through 0.1-Hz high-pass and 40-Hz low-pass filters (24 dB/octave) at a rate of 256 Hz. The digitized EEG for each subject was divided into 21 8-sec segments. A digital high-pass autoregressive filter (filter parameter = .975; Coppola 1979) was applied to reduce low-frequency artifacts.

EEG Analysis

Procedures were implemented to reduce the contributions of bioelectric artifacts to the data. Although subjects were advised to keep their eyes closed and not talk during the EEG recordings, these instructions were not necessarily followed. From an audio track of the session recorded with the EEG, times when subjects spoke were identified and these EEG segments were eliminated from analyses. By inspecting digitized electro-oculogram (EOG) records, occasions were identified when some subjects, counter to instructions, opened their eyes (as indicated by the presence of blinks) during EEG recording. Electroencephalogram segments were rejected if they contained blink events greater than 100 μ V in amplitude and were from 285 to 340 msec in duration. When subjects kept their eyes closed, rolling eye movements occasion-

ally contaminated the EEG. To remove these eye movements, the EOG signal was mathematically subtracted from the EEG according to the method of Gratton et al (1983). Lastly, EEG segments were visually inspected, and those identified as containing high-frequency artifacts were excluded from analyses. All subjects with less than 32 sec of artifact-free data were excluded from analyses. In prior research, we have found that reliable EEG power values can be obtained from nonpsychiatric control subjects and schizophrenic subjects using 32-sec epochs (Lund et al 1995; Sponheim 1993). These previous analyses revealed internal consistencies (α ; Cronbach 1951) above .83 for all frequency bands except delta, which had an internal consistency of .61 for schizophrenic patients and .77 for nonpsychiatric control subjects.

For each subject's data, fast-Fourier transforms were computed on every artifact-free segment using a Hanning window with 100% taper length, and frequency spectra were averaged across segments within each scalp location. Square roots of EEG power values were computed; divided into delta (1–3 Hz), theta (3.125–8 Hz), alpha (8.125–13 Hz), beta 1 (13.125–20 Hz), beta 2 (20.125–25 Hz), and beta 3 (25.125–30 Hz) power bands; and divided by the total spectrum area.

Assessment of Symptomatology

Psychosis (delusion and hallucinations), Disorganization (formal thought disorder), and Negative Symptom scores were rationally derived using items from the PSE intake interview and the guidelines of Andreasen (1981, 1983) and Andreasen et al. (1995). The Psychosis score was the total number of symptoms endorsed out of eight hallucinations and 27 delusions. The Disorganization score referred to the number on a five-point scale that was derived from ratings of neologisms and idiosyncratic use of language (PSE no. 135), incoherence of speech (PSE no. 136), and pressure of speech (PSE no. 131). A score of 0 meant all symptoms were rated as not present, a score of 2 meant that more than one symptom was rated as present in a fairly severe degree, and a score of 4 meant more than one symptom was rated as being present in a very severe degree. The Negative Symptom score referred to the number on a five-point scale that was derived from two affective flattening symptoms (PSE nos. 128 and 129), four alogia symptoms (PSE nos. 130, 133, 134, and 138), two avolition/apathy symptoms (PSE nos. 108 and 110), two anhedonia/asociality symptoms (PSE nos. 21 and 28), and two attentional impairment symptoms (PSE nos. 102 and 114). A score of 0 meant all symptoms were rated as not present, a score of 2 meant that more than one symptom was rated as present in a fairly severe degree, and a score of 4 meant that more than two symptoms were rated as being present in a very severe degree.

Brain Morphology Assessment

Procedures for computed tomography scanning and measurement of brain morphology are detailed elsewhere (Iacono et al 1988). Scanning for all subjects was accomplished using a high-resolution, third generation, total body scanner. Thirteen to 16 cross-sections of the brain, each 8 mm thick, were obtained. Lateral ventricle size was indexed by calculating the ventricle-

to-brain ratio (i.e., lateral ventricle area divided by the total brain area and multiplied by 100). The size of the frontal horns of the lateral ventricles was measured by computing the frontal horn-to-brain ratio (i.e., frontal horn area divided by total brain area and multiplied by 100). A traveling microscope was used to measure third ventricle width at the widest point where continuous ventricle walls could be discerned, and cortical atrophy ratings were made on a three-point scale anchored at each level by exemplars (1, no visible sulci; 2, visible but not extensive sulci; 3, sulci clearly visible and extensive). For each index the scan that maximally revealed the ventricle area of interest was selected for measurement, with the exception being cortical atrophy ratings, which were made from the scan three above the scan that maximally revealed the lateral ventricles.

Assessment of Ocular Motor Functioning

Ocular motor functioning was assessed by having subjects track a moving dot with their eyes while their head was immobilized (Iacono et al 1992). The dot was driven by a sine wave generator, horizontally traversing 20° of visual arc, at a frequency of .4 Hz for 20 cycles. Ag–AgCl electrodes attached to the outer canthi of both eyes with an earlobe ground were used to record ocular motion. Both eye-tracking and target signals were digitized and corrected for phase differences. The root-mean-square difference between the signals was calculated for the best 16 consecutive cycles of eye tracking. The median root-mean-square error of the 16 cycles was used as the dependent measure. The \log_{10} of the root-mean-square error values was computed to correct for positive skew in their distribution.

Electrodermal Activity Assessment

The electrodermal activity of subjects was assessed during the presentation of two sound effects and two series of 0.5-sec, 1000-Hz tones with 40-msec rise and fall times (for details, see Iacono et al 1999). One tone series consisted of eight tones at 85 dB, and the other series contained 12 tones at 105 dB. Scores were calculated for each subject on a single factor identified through a principal components analysis (varimax rotation) of number of skin conductance responses, log-transformed skin conductance response amplitude to the first stimulus, log-transformed mean skin conductance level calculated as the average of the individual levels measured at the onset of each stimulus, log-transformed frequency of nonspecific fluctuations during the tone series, and a categorical index of response status (responder, responded to at least one tone; nonresponder, responded to none of the tones). To achieve an overall index of electrodermal activation deviance, the absolute value of factor scores minus the nonpsychiatric control group mean was computed (Ficken 1991). The use of such a score is consistent with findings indicating that psychotic patients tend to be either electrodermally hypo- or hyperresponsive in habituation studies. For instance, Iacono et al (1999) have noted that elevated rates of electrodermal nonresponding have been consistently observed in schizophrenia and mood disorder, and psychotic patients who are electrodermal responders appear to be hyperaroused. This hyperarousal is evidenced by elevated skin conductance levels, high rates of skin

conductance responding, and frequent nonspecific electrodermal fluctuations.

Nailfold Plexus Visibility Assessment

Maricq's Scale for Plexus Visualization was used to quantify the visibility of the capillary plexus at the base of the nailfolds (for a detailed overview of this assessment, see Clementz et al 1992). Plexus visibility refers to the degree to which the capillaries at the base of the nailfold can be visualized on each finger with the aid of a low-power stereo microscope. Visualization scores were assigned without knowledge of diagnosis and according to a nine-point scale anchored by reference photographs; 0 represented no visible plexus, 4 was extensive plexus visibility, and halfpoints were given for intermediate visibilities. The \log_{10} of ratings summed across all fingers was used to compute the plexus visibility score. The intraclass test-retest reliability of nailfold plexus visibility ratings on a subset of these subjects was greater than .95 over an interval of 9 months (Clementz et al 1992).

Results

Because previous analyses (Sponheim et al 1994) failed to produce a recording site effect (Cz–C3–C4) for group differences in EEG power values, analyses were limited to data collected from site Cz. Electroencephalogram power bands were corrected for age using linear coefficients derived from nonpsychiatric control group data. Factor analyses of EEG power bands were carried out to identify common sources of variance in the dependent variables. Analyses of schizophrenic, nonschizophrenic psychosis, and nonpsychiatric groups identified two factors with eigenvalues exceeding 1. The two factors accounted for nearly three quarters of the power band variance in each subject group (variance accounted for: schizophrenia = 75%, nonschizophrenic psychosis = 72%, and nonpsychiatric = 71%). Coefficients of congruence (Wrigley and Neuhaus 1955) for the factors were above .96 across groups, indicating that the covariant structures of power bands were similar for schizophrenic, nonschizophrenic psychosis, and nonpsychiatric groups. Subject groups were combined and a factor analysis of these data identified two factors with eigenvalues greater than 1. The two factors accounted for 73% of the variance in the power bands. After varimax rotation, the first factor was interpreted as a beta factor because beta 1, beta 2, and beta 3 bands had strong positive loadings on the factor. The second factor was interpreted as an augmented-low-frequencies-diminished-alpha (LFA) factor, since it had strong positive loadings of delta and theta bands and a strong negative loading of the alpha band. Figure 1 depicts

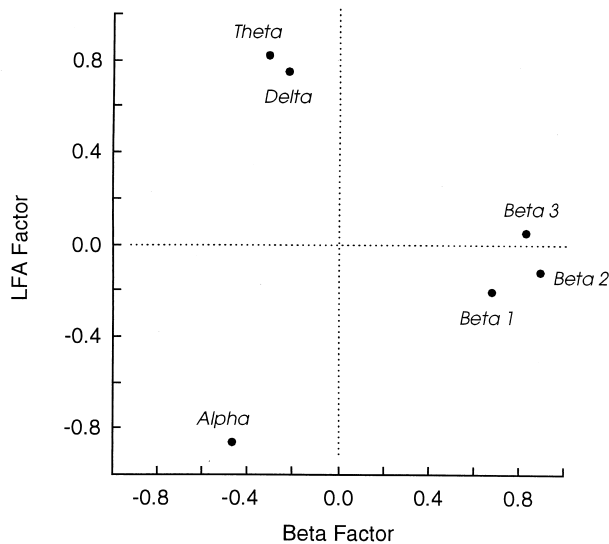


Figure 1. Factor loadings of electroencephalogram power bands on beta and augmented-low-frequencies-diminished-alpha (LFA) factors. Factors were identified by a factor analysis with varimax rotation using data from schizophrenic, nonschizophrenic psychosis, and nonpsychiatric subjects ($n = 297$).

the factor loadings of EEG power bands.¹ Medication effects were examined by performing comparisons within diagnostic categories of individuals on and off a particular drug. These tests failed to yield a single Medication Status or Medication Status-by-Diagnosis effect, indicating that medication status was unrelated to scores on beta and LFA factors.

Comparisons of Diagnostic Groups on EEG Factors

Two analyses of variances (ANOVAs) were carried out to determine whether subgroups within the schizophrenic and nonschizophrenic psychosis groups exhibited differences on EEG factor scores. Between-subjects effects were Group (for schizophrenic patients: chronic and first-episode; for nonschizophrenic psychosis patients: major depressive, bipolar, and other psychosis), Gender (male and female), and the interaction of Group and Gender. Figure 2 depicts means of EEG factor scores as a function

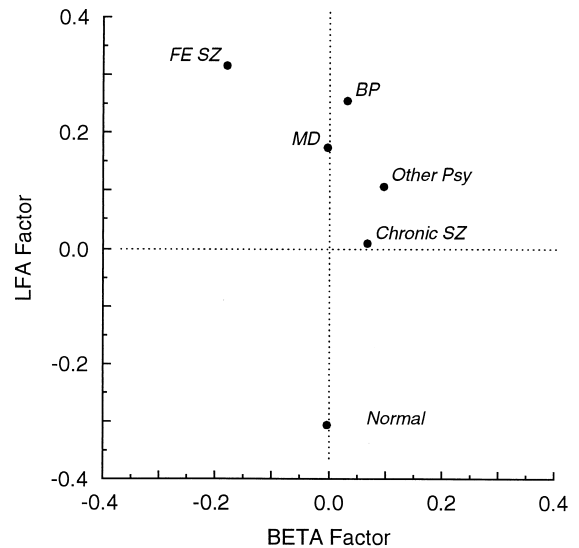


Figure 2. Factor score means for schizophrenic (FE SZ, first-episode [$n = 54$]; Chronic SZ, chronic [$n = 58$]), nonschizophrenic psychosis (MD, major depressive [$n = 29$]; BP, bipolar [$n = 33$]; Other Psy, other psychosis [$n = 16$]), and nonpsychiatric ($n = 107$) groups on beta and augmented-low-frequencies-diminished-alpha (LFA) factors.

of group. For schizophrenic subgroups and nonschizophrenic psychosis subgroups, analyses of beta and LFA factor scores failed to yield any effects involving Group or Gender, thus indicating that EEG factor scores did not differ among schizophrenic subgroups (i.e., first-episode and chronic) or among nonschizophrenic psychosis subgroups (i.e., bipolar, major depressive, and other psychosis).

To determine whether there were differences between schizophrenic, nonschizophrenic psychosis, and nonpsychiatric groups on EEG factor scores, ANOVAs were carried out using beta and LFA factor scores as dependent variables. Each ANOVA included Group (schizophrenic, nonschizophrenic psychosis, and nonpsychiatric), Gender, and the interaction of Group and Gender as between-subjects effects. Analyses yielded a Group main effect for LFA factor score [$F(1,291) = 7.00, p = .001$] and a Group-by-Gender effect for beta factor score [$F(2,291) = 4.83, p = .009$]. Follow-up t tests revealed that both schizophrenic patients [$t(217) = 3.47, p = .001$] and nonschizophrenic psychosis patients [$t(183) = 3.59, p < .001$] had higher LFA scores than nonpsychiatric subjects, but no difference was identified between schizophrenic and nonschizophrenic psychosis groups for LFA factor scores [$t(188) = -.25, p > .05$]. Follow-up t tests for the Group-by-Gender effect showed that female schizophrenic patients had lower beta scores (mean = $-.418, SD = 0.94$) than female nonpsychiatric subjects [mean = $.318, SD = 1.16; t(66) = -2.51, p = .015$] and female

¹ See Sponheim et al (1994) for details regarding analyses of covariation between EEG power bands. Alpha dropout and the appearance of other frequencies is a common phenomenon in the EEG (for a review, see Niedermeyer 1999). Research suggests that alpha and low-frequency activity are generated by well-defined networks of pyramidal cells in layers IV and V of the cortex. The generation of alpha is dependent on the integrity of anatomically and functionally distinct thalamic-cortical circuits in which the reticular nucleus of the thalamus serves as a pace maker for cortical pyramidal neurons. Pathologic low-frequency activity results from thalamic or midbrain reticular formation lesions, and more generally from partial deafferentation of the cerebral cortex through white matter pathology. Excess low frequency and diminished alpha power noted in schizophrenic patients is consistent with subcortical disruption of thalamic-cortical circuits. See Steriade et al 1990 and Steriade 1999 for reviews of the cellular basis of cerebral rhythmic electrical activity.

nonschizophrenic psychosis patients (mean = .201, SD = 1.09; $t(45) = -2.03$, $p = .048$). Beta scores for male schizophrenic patients (mean = .029, SD = 0.97) did not differ from those of nonpsychiatric males [mean = $-.189$, SD = 0.84; $t(149) = 1.41$, $p > .05$] or nonschizophrenic psychosis males [mean = $-.078$, SD = 0.97; $t(141) = 0.64$, $p > .05$].

Clinical and Biological Concomitants of EEG Abnormalities

To examine the clinical and biological characteristics of schizophrenic patients with augmented low-frequency power and diminished alpha-band power, subjects were split into two groups defined by LFA factor scores. Because both schizophrenic and nonschizophrenic psychosis groups exhibited EEG power abnormalities, the median LFA factor score for all patients (.1541) was used to divide the subjects of each diagnostic category into high LFA and low LFA groups. High and low LFA groups were then compared on collateral indices to determine whether patients with augmented low-frequency power and diminished alpha-band power (i.e., high LFA group) differed from patients who did not exhibit these EEG characteristics (i.e., low LFA group).

A consistent approach was taken toward testing differences between high and low LFA groups on clinical and biological variables.² For each clinical or biological index high and low LFA groups were simultaneously contrasted within first-episode and chronic schizophrenic samples to determine whether the dependent variable(s) were associated with the presence of low-frequency and alpha-band power abnormalities in schizophrenia, and whether the association was related to disorder chronicity. Between-subjects effects were LFA Score (high and low), Group (first-episode and chronic), and the interaction of LFA Score and Group. High and low LFA groups within the bipolar, major depressive, and other psychosis groups were also compared on the dependent variable(s). This contrast tested whether the dependent variable(s) were associated with the presence of EEG power abnormalities in the nonschizophrenic psychosis groups, and whether the associations were different among major depressive, bipolar, and other psychosis patients. Between-subjects effects were LFA Score (high and low), Group (bipolar, major depressive, and other psychosis), and the interaction of

LFA Score and Group. When group comparisons yielded effects involving LFA Score, follow-up tests were conducted to detail the nature of the effect. Table 2 presents means, SDs, and comparisons of high and low LFA Score subjects on indices of symptomatology, brain morphology, and other biological features.

To ascertain whether schizophrenic patients with augmented low-frequency power and diminished alpha-band power presented with distinct symptoms, we carried out analyses of symptomatology indices in schizophrenic and nonschizophrenic psychosis groups. A multivariate ANOVA (MANOVA) of Psychosis, Disorganization, and Negative Symptom scores for schizophrenic subjects yielded an LFA Score effect [Wilks $\lambda = .91$, $F(3,94) = 3.18$, $p = .028$] and a Group effect [Wilks $\lambda = .89$, $F(3,94) = 3.96$, $p = .010$]. Follow-up analyses revealed that high LFA schizophrenic subjects exhibited more negative symptomatology than low LFA subjects. First-episode schizophrenic patients had higher scores than chronic patients on the Psychosis [$F(1,96) = 6.20$, $p = .014$] and Negative Symptom [$F(1,96) = 7.73$, $p = .010$] indices. In the nonschizophrenic psychosis group multivariate and univariate analyses of symptomatology indices failed to yield any effects involving LFA Score.

To determine whether the brain morphology of subjects with augmented low-frequency power and diminished alpha-band power was different than that of subjects without these EEG power characteristics, we conducted analyses of brain morphology indices in schizophrenic and nonschizophrenic psychosis patients. A MANOVA of four brain morphology indices in schizophrenic patients yielded a main effect for LFA Score [Wilks $\lambda = .84$, $F(1,74) = 3.75$, $p = .008$]. Follow-up analyses revealed high LFA schizophrenic subjects had wider third ventricles, larger frontal horns of the lateral ventricles, and larger cortical sulci than low LFA subjects. Multivariate and univariate analyses of brain morphology indices for nonschizophrenic psychosis failed to yield any main or interaction effects.

To ascertain whether subjects with augmented low-frequency power and diminished alpha-band power had unique ocular motor, electrodermal, or nailfold plexus visibility features we carried out analyses of the other biological indices under study. For schizophrenic patients, high LFA first-episode subjects exhibited worse ocular motor function than low LFA first-episode subjects [$t(51) = 2.82$, $p = .007$]. Also, high LFA chronic schizophrenic patients had more deviant electrodermal activity than low LFA chronic patients [$t(48) = 3.16$, $p = .003$]. For nonschizophrenic psychosis patients the only effect was a Group-by-LFA Score interaction for the electrodermal activation index, but follow-up analyses

² Depending on the clinical or biological variable under examination, sample sizes for the subject groups varied across analyses. In most instances variations in sample size were modest; however, when more than 20% of the members in a subject group had missing data, a two-way ANOVA (with Availability of Data and Diagnosis as factors, and LFA factor scores as the dependent variable) was carried out to determine whether individuals with and without data differed in their low-frequency and alpha-band powers. Analyses revealed that the availability of data for clinical and biological variables was never a factor that differentiated groups.

Table 2. Comparisons of High and Low LFA Score Subjects on Indices of Symptomatology, Brain Morphology, and Other Biological Features as a Function of Diagnostic Groups

Variable	Schizophrenic Subjects				Nonschizophrenic Psychotic Subjects			
	High LFA ^a [Mean (SD)]	Low LFA ^a [Mean (SD)]	LFA Score effect	LFA Score × Group effect	High LFA ^a [Mean (SD)]	Low LFA ^a [Mean (SD)]	LFA Score effect	LFA Score × Group effect
Symptomatology^b								
Psychosis (delusions/ hallucinations)	First episode: 7.24 (5.02) Chronic: 4.67 (4.67)	9.27 (5.74) 6.49 (5.83)	F(1,96) = 3.23 ns	F(1,96) = 0.01 ns	Bipolar: 4.50 (4.32) MD: 4.00 (3.21) Other: 7.86 (5.05)	3.60 (3.68) 3.00 (4.95) 5.14 (4.06)	F(1,66) = 2.14 ns	F(2,66) = 0.25 ns
Disorganization (formal thought disorder)	First episode: 0.54 (0.95) Chronic: 0.23 (0.51)	0.09 (0.42) 0.25 (0.64)	F(1,99) = 2.68 ns	F(1,99) = 3.18 ns	Bipolar: 0.18 (0.39) MD: 0.00 (NA) Other: 0.29 (0.49)	0.13 (0.35) 0.00 (NA) 0.00 (NA)	F(1,67) = 2.35 ns	F(2,67) = 1.22 ns
Negative symptoms	First episode: 3.11 (1.99) Chronic: 1.61 (2.22)	1.83 (1.34) 1.36 (1.63)	F(1,99) = 4.54 <i>p</i> < .05	F(1,99) = 2.01 ns	Bipolar: 2.00 (1.94) MD: 2.61 (1.39) Other: 1.71 (1.11)	1.07 (1.03) 2.86 (2.14) 1.00 (1.53)	F(1,67) = 1.32 ns	F(2,67) = 1.00 ns
Brain morphology								
Third ventricle width (mm)	First episode: 4.16 (1.31) Chronic: 4.47 (0.96)	3.15 (1.08) 4.05 (1.21)	F(1,83) = 7.94 <i>p</i> < .01	F(1,83) = 1.36 ns	Bipolar: 3.54 (0.52) MD: 3.62 (0.84) Other: 2.90 (0.03)	3.30 (1.16) 3.39 (1.00) 3.63 (0.61)	F(1,32) = 0.07 ns	F(2,32) = 0.80 ns
Frontal horn-to-brain ratio	First episode: 1.85 (0.66) Chronic: 2.13 (1.22)	1.53 (0.77) 1.71 (0.81)	F(1,88) = 3.80 <i>p</i> = .05	F(1,88) = 0.07 ns	Bipolar: 1.47 (0.66) MD: 1.79 (0.76) Other: 1.40 (0.89)	1.42 (0.36) 1.61 (0.83) 2.35 (0.77)	F(1,32) = 0.98 ns	F(2,32) = 1.63 ns
Cortical atrophy rating (three-point scale)	First episode: 2.15 (0.74) Chronic: 2.27 (0.77)	1.81 (0.75) 1.93 (0.78)	F(1,84) = 4.09 <i>p</i> = .05	F(1,84) = 0.00 ns	Bipolar: 1.56 (0.88) MD: 2.25 (0.89) Other: 1.67 (1.15)	2.10 (0.88) 2.00 (1.00) 2.00 (1.00)	F(1,32) = 0.38 ns	F(2,32) = 0.70 ns
Ventricle-to-brain ratio	First episode: 6.63 (2.20) Chronic: 7.19 (1.47)	6.57 (2.98) 6.65 (2.03)	F(1,89) = 0.43 ns	F(1,89) = 0.28 ns	Bipolar: 5.71 (1.94) MD: 6.40 (3.06) Other: 6.51 (4.72)	6.45 (1.86) 5.40 (3.70) 6.27 (2.23)	F(1,33) = 0.30 ns	F(2,33) = 0.41 ns
Other biological features								
Eyetracking (log root- mean-square error)	First episode: 2.29 (0.26) Chronic: 2.21 (0.20)	2.12 (0.19) 2.20 (0.25)	F(1,107) = 4.47 <i>p</i> < .05	F(1,107) = 3.81 <i>p</i> < .05	Bipolar: 2.15 (0.21) MD: 2.20 (0.21) Other: 2.12 (0.20)	2.14 (0.28) 2.18 (0.24) 2.23 (0.20)	F(1,68) = 0.19 ns	F(2,68) = 0.47 ns
Electrodermal activation (factor score)	First episode: 0.93 (0.56) Chronic: 1.30 (0.41)	1.09 (0.51) 0.96 (0.34)	F(1,97) = 0.99 ns	F(1,97) = 7.02 <i>p</i> < .01	Bipolar: 0.86 (0.43) MD: 0.80 (0.43) Other: 0.74 (0.46)	0.71 (0.47) 0.83 (0.32) 1.62 (0.71)	F(1,57) = 3.71 ns	F(2,57) = 4.06 <i>p</i> < .05
Plexus visibility score (log of score)	First episode: 0.65 (0.50) Chronic: 0.73 (0.43)	0.61 (0.37) 0.61 (0.43)	F(1,107) = 0.83 ns	F(1,107) = 0.29 ns	Bipolar: 0.40 (0.40) MD: 0.41 (0.47) Other: 0.34 (0.46)	0.44 (0.44) 0.35 (0.35) 0.47 (0.44)	F(1,69) = 0.15 ns	F(2,69) = 0.19 ns

LFA, augmented-low-frequencies-diminished-alpha factor; MD, major depressive; Other, other psychosis.

^aHigh LFA represents subjects with an LFA factor score greater than .1541, all other subjects are classified as Low LFA.^bRationally derived using items from the Present State Exam interview and the guidelines of Andreasen (1981, 1983) and Andreasen et al (1995).

failed to reveal any significant differences between high and low LFA groups within the bipolar, major depressive, and other psychosis groups.

Discussion

Results of this investigation demonstrate that schizophrenic patients with augmented low-frequency power and diminished alpha-band power (i.e., high LFA scores) have more negative symptomatology, more deviant brain morphology, worse ocular motor function, and greater electrodermal deviation than schizophrenic patients without these EEG power characteristics. Specifically, schizophrenic patients who exhibited augmented low-frequency and diminished alpha-band power had widened third ventricles, enlarged frontal horns of the lateral ventricles, and increased cortical sulci widths. First-episode schizophrenic patients with high LFA scores showed worse overall eyetracking than low LFA first-episode patients as measured by root-mean-square error between phase-corrected target and eye signals. Chronic schizophrenic patients with high LFA scores had more deviant electrodermal activation than low LFA chronic patients. Although nonschizophrenic psychosis patients had EEG power abnormalities similar to those of schizophrenic patients, low frequency and alpha-band power were not associated with psychotic symptomatology or biological features.

Perhaps the strongest set of findings from this study points to the presence of structural brain abnormalities in schizophrenic patients with augmented low-frequency power and diminished alpha-band power in their EEGs. Both subcortical and cortical pathologies are suggested in schizophrenic patients with EEG power abnormalities. Third ventricle enlargement in schizophrenic patients with augmented low-frequency power and/or diminished alpha-band power, as demonstrated by our study and Takeuchi et al (1994), may indicate that the thalamus plays a role in EEG power abnormalities. Since the third ventricle is bordered on both sides by the medial dorsal thalamic nuclei, enlargement of the third ventricle may reflect structural alterations in these nuclei. Neuropathology research has revealed reductions in neuron and glial cell numbers and the volume of medial dorsal nuclei in schizophrenic patients (Pakkenberg 1990). More generally, neuroimaging studies have shown schizophrenic patients to have reduced thalamic volumes (Andreasen et al 1994; Buchsbaum et al 1996; Gur et al 1998; Staal et al 1998) and metabolism (Buchsbaum et al 1996). Because EEG power abnormalities failed to be associated with brain morphology indices in nonschizophrenic psychosis patients, the neuropathology underlying deviation in EEG power may be different in schizophrenic and nonschizophrenic psychosis.

A brain dysfunction involving frontal cerebral areas may also accompany brain wave anomalies in schizophrenia. First, the frontal horns of the lateral ventricles were enlarged in schizophrenic patients with low-frequency and alpha-band power abnormalities. Second, frontal lobe metabolic activity has been associated with low-frequency power in schizophrenic patients (Alper et al 1998). Third, because schizophrenic patients with EEG power abnormalities in our study had more negative symptoms, and investigators have shown negative symptoms in schizophrenia to be associated with metabolic and structural frontal lobe anomalies (cf. Buchsbaum and Hazlett 1998; Gur and Pearlson 1993). Finally, an association between frontal lobe dysfunction and low-frequency and alpha-band power abnormalities is suggested by the positive relationship between brain wave anomalies and ocular motor dysfunction in first-episode schizophrenia. Schizophrenic patients with ocular motor dysfunction have been shown to perform poorly on tasks that tap frontal lobe abilities (Bartfai et al 1985; Katsanis and Iacono 1991; Sweeney et al 1992), and frontal lobe structures have been suggested to play a role in the generation of smooth-pursuit ocular motion required to perform eye-tracking tasks (Grawe and Levander 1995; Levin 1984; MacAvoy and Bruce 1995; Ross et al 1995). Because ocular motor dysfunction is also a candidate marker for a genetic vulnerability to schizophrenia (Grove et al 1992), the association between ocular motor dysfunction and brain wave anomalies is consistent with abnormal EEGs resulting from a genetically based neuropathology and not an environmental pathogen (Sponheim et al 1997). Genetically based neuropathology is to be distinguished from genetically influenced brain-based vulnerability for schizophrenia. Electroencephalogram power abnormalities appear not to reflect genetic vulnerability for schizophrenia (Clementz et al 1994; Stassen et al 1999).

Taken together, the associations between EEG power abnormalities and negative symptoms, third and frontal horn ventricular enlargement, and ocular motor dysfunction lend credence to recent hypotheses identifying thalamic and prefrontal cortical involvement in schizophrenia (e.g., Jones 1997). Researchers have highlighted the likely importance of thalamic–cortical projections from medial dorsal nuclei to prefrontal cortical areas in the organized processing of information and suggest that disruption of these networks could lead to symptomatology and information-processing deficits evident in schizophrenia (Andreasen et al 1994; Jones 1997). Augmented low frequency and diminished alpha-band power in schizophrenic patients is consistent with dysfunction in thalamic–cortical circuits (for a review, see Steriade et al 1990). In addition, the associations between EEG power abnormalities and third ventricle enlargement and frontal lobe

dysfunction (i.e., poor ocular motor functioning and increased frontal horn of the lateral ventricle size) in our study are consistent with thalamic–cortical disruption in medial dorsal–prefrontal networks. Medial dorsal–prefrontal pathology in schizophrenia is also consistent with low-frequency and alpha-band anomalies being most evident over frontal brain regions (Sponheim and Kodalen 1997). For future studies to test hypotheses regarding the integrity of medial dorsal–prefrontal networks in schizophrenia, they will need to employ EEG methods and brain imaging measures that allow for more precise localization of anomalies in EEG and brain morphology than those used in this study.

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