Spectral and Topographic Analysis of EEG in Schizophrenic Patients

E. Michael Kahn, Richard D. Weiner, Richard Coppola, Harold S. Kudler, and Katherine Schultz

The authors performed spectral analysis of electroencephalograms (EEG), recorded awake, with eyes closed, in 13 patients with schizophrenia and 9 age-matched individuals without psychiatric diagnosis. We tested several possible parameterizations of the data, and two data-reduction strategies; these yielded similar results. Comparison of the two groups revealed a relative increase in alpha frequency activity in the frontal regions in the patient group. The authors believe that this finding is consistent with data from neuropsychologic tests, metabolic imaging studies, and evoked potential studies that suggest impaired activation of frontal brain areas in patients with schizophrenia.

Key Words: Computerized EEG, spectral analysis, schizophrenia

Introduction

Investigators have reported a wide range of electroencephalogram (EEG) abnormalities in schizophrenic patients (Shagass 1987; Nuwer 1988). Early studies are flawed by failure to employ standardized diagnostic criteria, incomplete characterization of symptom and medication status of patients, and absence of comparison groups. In the work presented here, the authors attempted to localize differences in the EEG spectrum between a group of schizophrenic patients, symptomatically stable, on medication, and a nonpsychiatric comparison group. Secondarily, we compared the utility of different spectral parameter derivations, and tested anatomic grouping and factor analysis as data-reduction techniques.

Methods

Subjects

Patients with schizophrenia were recruited from the outpatient clinic at a Veterans Administration Hospital. All met DSM-III diagnostic criteria for schizophrenia, were described as symptomatically stable by their outpatient psychiatrist, and were taking antipsychotic medication at conventionally used "maintenance" doses (Table 1). Comparison subjects were drawn from the medical and surgical inpatient units of the hospital, and from hospital support staff. All subjects were men.

Individuals were excluded from the study if they had a history of substantial head trauma, neurological illness, or substantial recent alcohol or substance abuse. A behavioral dominance battery was used to determine handedness, and subjects with left or mixed dominance were excluded. All subjects provided informed consent.

From the Department of Psychiatry, Dartmouth Medical School, Hanover, NH (EMK); Department of Psychiatry, Duke University Medical Center, Durham, NC (RDW, HSK); NIMH Neurosciences Center, St. Elizabeth's Hospital, Washington, DC (RC); Mental Hygiene Clinic, Durham Department of Veterans' Affairs Medical Center, Durham, NC (HSK); Family Practice Program, Moses Cone Hospital, Greensboro, NC (KS).
Address reprint requests to Dr. Kahn, New Hampshire Hospital, 105 Pleasant St., Concord, NH 03301.
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Table 1. Characteristics of Sample

Parameter	Schizophrenic	Comparison
n	13	9
Age (years)	35.0 ± 7.32	36.7 ± 6.33
IQ (Shipley)	96.0 ± 9.07	104.6 ± 15.6
Antipsychotic dose (Chlorpromazine Equivalents)	400–3000 mg median 700 mg	N/A
Antiparkinsonian dose (Benztropine Equivalents)	0–4 mg median 1 mg	N/A
BPRS		
range	23–65	N/A
mean	48.4 ± 15.0	

Medications

Medications and doses were recorded by the research assistant at the time of EEG recording. Medication doses were converted to chlorpormazine and benztropine equivalents using commonly accepted conversion factors (Weiner et al 1983).

Assessments

Brief Psychiatric Rating Scale (BPRS) ratings of schizophrenic subjects were performed by the same study psychiatrist. The Shipley IQ test was administered by a research technician. Both assessments were contemporaneous with the EEG recording.

EEG Technique

EEG recordings were made with a 21 channel Nihon Kohden polygraph interfaced to a Digital Equipment Corporation 11/24 computer using a Data Translation analog-to-digital converted (12 bit conversions). EEG was recorded from 19 scalp electrodes placed according to the International 10–20 system. The ears, linked though 10 K-Ohm resistors, were used as reference, as is commonly the practice in the topographic analysis of EEG. Single channels of oblique eye movement and electrocardiogram (EKG) were also recorded. Recordings were made in a dimly lit, acoustically shielded room, with subjects reclining in a comfortable chair. Subjects were monitored visually throughout the recording (directly or by video camera), and care was taken to maintain the subjects in an awake, alert state throughout the recordings.

Polygraph channels were filtered with a band pass of 1–70 Hz, and were digitized at a rate of 102.4 Hz. Three minutes of EEG were recorded in both the eyes-open and eyes-closed states. These "runs" were segmented into contiguous 5-sec intervals ("epochs") for storage, editing, and analysis. Epochs contaminated by eye movement, muscle, drowsiness, electrode, or other artifacts were rejected from analysis after visual review by a clinical electroencephalographer, who was blind to subject identity and experimental group.

Spectral analyses were performed using the Fast Fourier Transform (FFT) technique with a cosine window taper. Frequency bands were defined as: Delta 2.2–5.0 Hz, Theta 5.2–8.0 Hz, Alpha 8.2–13.0 Hz, Beta 1 13.2–18.0 Hz, and Beta 2 18.2–30.0 Hz. Results were displayed topographically using techniques described by Kahr et al (1988).

Data Analysis Strategy

There is a lack of consensus as to the most meaningful of the parameters to be derived from the FFT (Kahn et al 1988). We considered four sets of EEG parameters in statistical evaluations:

1. amplitude spectrum coefficients (uV) derived from the FFT ("amplitude spectrum content"),
2. log-transformed amplitude spectrum coefficients,
3. amplitude spectrum coefficients standardized by total amplitude across all bands ("relative amplitude content"), and
4. the weighted average frequency (Hz) across the spectral band 0.2–30.0 Hz ("mean frequency").

To reduce the massive number of paired comparisons involved in a parameter by lead analysis (Oken and Chiappa 1986), we aggregated data by anatomic regions: Frontal (Fp1, Fp2, F3, F4), Temporal (F7, F8, T3, T4, T5, T6), Central (C3, C4), Occipital (P3, P4, 01, 02), and the Vertex (Fz, Cz, Pz). We performed factor analysis on lead data to assess these groupings (Locatelli et al 1991). We computed "symmetry indices" to test for lateralized findings.*

Statistical analyses were performed using the SPSS system (Norusis, 1986). The t-statistic was used for comparisons of means. Two-tailed tests were used for comparisons of means. Other statistical tests are described explicitly at their point of occurrence in the text. Unless otherwise specified, an alpha level of 0.05 or less was accepted as "significant".

* The general formula for the symmetry index is:

Asymmetry Index = (Left − Right)/(Left + Right)

For example, the asymmetry index for a parameter for the Frontal region would be:

Asymmetry Index = (Fp1 − Fp2 + F3 − F4) / (Fp1 + Fp2 + F3 + F4)

Results

Matched Comparison Group

Schizophrenic and comparison subjects did not differ significantly with regard to mean age or I.Q. (Table 1).

Artifact

There was extensive eye-movement artifact in the "eyes open" recordings. Therefore, only data recorded in the "eyes closed" condition will be presented here.

In the eyes-closed records, of a maximum possible 36 5-sec epochs per subject, an average of 14.5 ± 10.1 epochs were acceptable for schizophrenic subjects, and an average of 10.6 ± 9.29 were acceptable for comparison subjects (t_{19} = 0.906, NS).

Inspection of z-transformed amplitude spectrum coefficients revealed that Beta 1 and Beta 2 activity were highly variable, even across adjacent leads, in both schizophrenic and comparison groups. We suspected that residual muscle artifact contributed to this variability. This interpretation was confirmed on visual examination of the records, and we excluded these bands from further analysis.

Spectral Parameters

Results from analyses of amplitude spectrum content, log-transformed amplitude content, and relative amplitude content were congruent, revealing differences of similar location and magnitude between the patient and comparison groups. For the sake of simplicity, only the results from the analysis of amplitude spectrum content will be presented here. There were no differences in mean frequency, in the bandwidth 0.2–30 Hz, by anatomic region between schizophrenic patients and the comparison group. Also, we did not find differences between schizophrenic and comparison subjects using the symmetry indices.

Regional Grouping

Factor analysis of the amplitude spectrum content, by lead, using the principal components method with varimax rotation, yielded three factors groupings, Anterior (Fp1, Fp2, F3, F4, F7, F8, Fz), Central (C3, C4, T3, T4, Cz), and Posterior (P3, P4, T5, T6, Pz, 01, 02). In the delta range, these factors accounted for 91.2% of the variance, in the theta range, 96.2% of the variance, and in the alpha range, 92.5% of the variance.* Because the results using these groups were similar to those attained with the anatomic groups, we will present only the results from the anatomic groups.

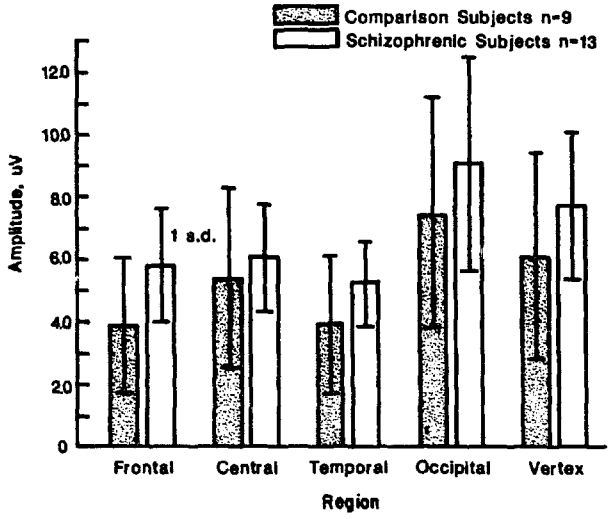

Figure 1. Mean amplitude of alpha frequency EEG activity averaged over leads by scalp region. For frontal areas, schizophrenic subjects, X = 5.82 ± 1.78 uV, comparison subjects, X = 3.89 ± 2.10, t_{20} = 2.32, p = 0.031.

Age, IQ and Medication Effect

Amplitude spectrum content, by region and frequency band, did not vary significantly with age or IQ. Nor did we find differences in amplitude spectral content, by region and frequency band, between schizophrenic subjects receiving doses of antipsychotic medication above the median, and those receiving doses below it. In addition, we did not observe differences between schizophrenics receiving high and low doses of antiparkinsonian medication.

Schizophrenics Versus Controls

As shown in Figures 1 through 4, schizophrenic subjects had higher amplitudes of activity in both the delta and alpha frequency bands in the frontal areas. Theta frequency activity did not differ statistically by region between these groups. Delta frequency differences were localized to the frontopolar regions, suggesting an ocular etiology.

Discussion

Methodologic Issues

TECHNICAL CONSIDERATIONS. Use of the linked ear reference can, in some instances, lead to reference effects, such as the transposition of temporal alpha frequency ac-

* The authors will provide interested parties with a table of factor loadings on request.

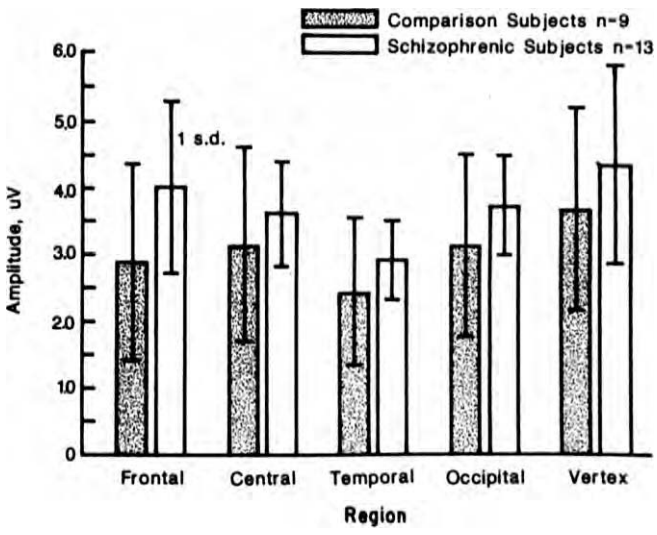

Figure 2. Mean amplitude of delta frequency EEG activity averaged over leads by scalp region. For frontal areas, schizophrenic subjects, X = 3.85 ± 1.13 uV, comparison subjects, X = 2.80 ± 1.35, t_{20} = 1.97, p = 0.062.

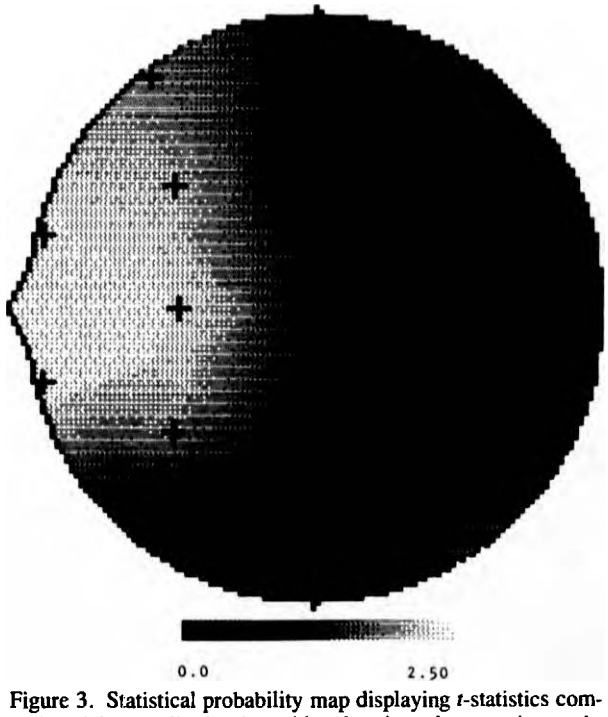

Figure 3. Statistical probability map displaying t-statistics comparing delta amplitudes for schizophrenic and comparison subjects. For this number of subjects, t-statistic values > 2.09 are associated with p values < 0.05. Schizophrenic subjects have significantly higher alpha activity anteriorly.

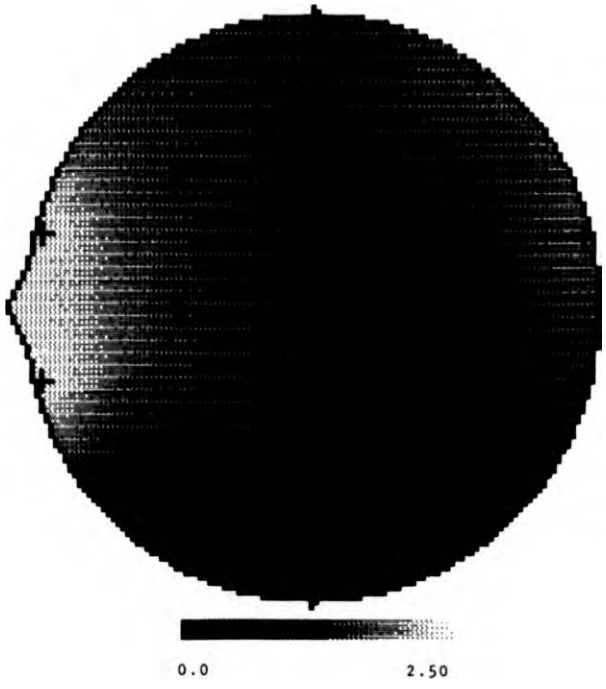

Figure 4. Statistical probability map displaying t-statistics comparing delta amplitudes for schizophrenic and comparison subjects. For this number of subjects, t-statistic values > 2.09 are associated with p values < 0.05. Schizophrenic subjects tend to have higher delta activity anteriorly; this is tightly localized to leads Fp1 and Fp2. At Fp1, for schizophrenic subjects, X = 3.96 ± 1.35 uV, and comparison subjects, X = 2.53 ± 1.31, t_{20} = 2.47, p = 0.023. At Fp2, for schizophrenic subjects, X = 4.05 ± 1.44, and comparison subjects, X = 2.61 ± 1.32, t_{20} = 2.39, p = 0.027. The t-statistic for similar comparisons at Fz, F3, F4, F7, and F8 did not attain significance at the 0.05 level.

tivity to other areas. However, our data (Figure 1) demonstrate a typical frontal to occipital gradient in the distribution of alpha-frequency activity. Therefore, we do not believe that reference effect would account for the localization of the alpha frequency differences we found.

We took great care to eliminate muscle artifact through management of the subjects during recording and censoring of contaminated epochs after visual review of the records. Still, our statistical review of the data showed considerable variability in beta 1 and beta 2 frequency activity, suggesting residual muscle artifact. For this reason, we did not conduct further analyses for the data in these frequency ranges. Could this residual muscle artifact effect data in other frequency ranges? With a sampling rate of 102.4 Hz, muscle artifact on the order of 90 Hz would alias to the alpha frequency range. The 70-Hz Nihon-Kohden filter employed would attenuate 90-Hz activity about 35%. If the 90-Hz activity was comparable to the alpha-frequency activity in magnitude, then error caused

by aliasing could be substantial. We would counter this possibility with two observations. First, the statistical analysis that suggested residual muscle artifact did not find similar variability in the alpha-frequency data. Second, the alpha-frequency differences identified are distributed relatively broadly in the frontal areas, particularly F3, F4, F7, and F8. Were aliasing the source of the apparent differences, we would expect it to be localized tightly to the most prominent sources of anterior-muscle artifact, Fp1, Fp2, F7, and F8. We would recommend use of a higher digitization rate and use of a filter with higher attenuation to future investigators.

A final caution in the interpretation of the results of this study regards the use of multiple statistical comparisons (Oken and Chaippa 1986). In principle, if many statistical tests are conducted, then there is a substantial chance that false positives will occur. We attempted to avoid this problem by reducing the number of comparisons made through use of regional lead groupings. This accomplishes approximately a four-fold reduction in the number of comparisons, from 19 (leads) to 5 (groups). A more conservative approach to this difficulty is to raise the standard of statistical significance by adjusting for the number of comparisons made, often referred to as the "Bonferroni" correction. The differences that we observed in frontal alpha-frequency activity would not be significant under such stringent criteria. This method is not commonly used in computerized electroencephalogram (CEEG) studies, and it would not be misleading to compare our results with those others have reported. Still, the reader must bear this qualification of our findings in mind in interpreting this report.

DATA REDUCTION AND ANALYSIS STRATEGY. Amplitude spectrum content for alpha and delta activity differed, by region, between schizophrenic and comparison subjects. Analysis of log-transformed and standardized spectral amplitude coefficients did not reveal additional differences. The strategy of grouping lead data by anatomic region was supported by factor analysis. These observations suggest that a simplified analysis strategy may be quite adequate for spectral data in future studies.

Topographic display of selected data was a useful adjunct to statistical review, aiding recognition of possible artifact, and facilitating comparison of findings with those from other laboratories, or other imaging modalities (e.g., magnetic resonance imaging, positron emission tomography).

"Negative" Findings

We did not find differences in lateralization of activity. These have been reported principally in beta frequencies, and we were not able to analyze the data for these bands because of presumed artifact. We did not find age-related differences; however, the detection of such effects could have been impeded by the small number of subjects, and their relatively narrow span of ages. Medication effects were not evident. This, too, might reflect the small number of subjects, and the wide range of medication doses. A larger sample and paired comparison of subjects premedication and postmedication would facilitate detection of medication effects.

Are Delta Differences "Real"?

Statistical probability maps (Duffy et al 1981) computed from the delta-frequency data (Figure 4) show very tight localization of amplitude differences to leads Fp1 and Fp2. The appearance of the delta map contrasts sharply with that for alpha activity (Figure 3), which demonstrates the rounded contours usually associated with electrophysiologic activity of cerebral origin. For this reason, we suspect that the delta differences may be caused by residual eye-movement artifact in schizophrenic subjects, rather than bona fide differences in brain activity.

Review and Interpretation—Alpha Differences

Computerized techniques for EEG analysis (CEEG) offer increased quantitative sensitivity in the study of brain function (Coppola 1982; Nuwer 1988; Kahn 1992). Most frequently, CEEG studies of patients with schizophrenia have found increases in delta and theta activity (Giannitrapani and Kayton 1974; Itil 1977; Morihisa et al 1983; Morstyn et al 1983; Guenther and Breitling 1985; Makudan 1986; Jin et al 1990), especially in frontal areas. This slowing has been thought to correspond to "hypofrontality" in studies of cerebral blood flow and metabolic activity, which has been interpreted to be an indication of frontal-lobe dysfunction. Frontal slowing has not, however, been a universal finding (Williamson and Mamelak 1987), and some investigators have suggested that the apparent difference between schizophrenic patients and comparison groups is related to increased eye-movement artifact in the schizophrenics (Karson et al 1987; Small et al 1987).

Investigators have also reported decreases in alpha activity or lowering of mean alpha frequency, and increases in beta activity, especially postcentrally and on the left (Giannitrapani and Kayton 1974; Itil 1977; Karson et al 1988 a,b; Miyauchi et al 1990). These changes have been thought to correspond to deficits in the modulation of attention and arousal commonly observed in such patients.

Subsequent investigators have attempted to characterize electrophysiologic aberrancies in schizophrenic patients during task performance (Guenther et al 1986), to differentiate medication and symptom related aspects of EEG

changes (Small et al 1989; Kahn et al 1989), to identify changes associated with subtypes of schizophrenia (Guenther et al 1988), and to link EEG data with information from other imaging modalities (Karson et al 1988b; Williamson et al 1989; Gambini et al 1990). These investigations suggest that in medicated, symptomatically stable schizophrenics, there is cerebral hypoactivity at rest, and hyperactivity in response to activating tasks (Guenther et al 1989). These phenomena are reflected in the EEG as increased delta activity and decreased variability in the resting state, and increased alpha activity during task performance. Some investigators have suggested that these changes are lateralized, with an overactive right hemisphere attempting to compensate for an underactive left hemisphere (Flor-Henry et al 1979). Efforts to link these patterns to functional neuroanatomy have been undertaken (e.g., Williamson et al 1989).

Our finding of increased alpha activity in anterior regions in schizophrenic patients, relative to the comparison group, contrasts sharply with the diffuse alpha reductions that others have reported (Giannitrapani and Kayton 1974; Itil 1977; Karson et al 1988 a,b; Miyauchi et al 1990). We would suggest that this difference might be related to the fact that our patients were stable symptomatically, and able to function in the community, whereas others have generally studied acutely or severely ill inpatients.

The significance of increased anterior alpha activity in this sample of patients with schizophrenia remains unclear, a topic for further research. This finding *is* consistent with data from other investigations of brain activity in schizophrenic patients, and theories regarding the nature of brain dysfunctions in schizophrenia. In neuropsychological studies and imaging studies involving indices of metabolic activity, investigators have found deficits in frontal activation in schizophrenic patients (Weinberger 1987; Szymanski et al 1991). In normal subjects, cortical activation is associated with suppression of alpha activity, in response to both internal and external stimulation (Markand 1990). In schizophrenic patients, we might expect deficits in intrinsic levels of frontal activation to be associated with reduced suppression of alpha activity in this region. This failure of activation could result from intrinsic dysfunction of anterior thalamocortical pathways, with diminished responsiveness to modulating inputs, or from faulty modulation of these projections by diencephalic *or* brainstem centers (Buchsbaum 1990; Csernansky et al 1991; Weinberger 1987).

The result of such lesions would be impaired filtering of afferent inputs to frontal areas—areas that would then be flooded with sensory inputs, yet unable to focus on or select meaningful ones. The existence of these phenomena is supported experimentally by Adler and colleagues (1990), who have observed diminished sensory "gating" of the P50 evoked potential in response to repeated auditory stimuli, and many others (e.g., Pritchard 1986; Pfefferbaum et al 1989) who have observed diminished P3-evoked responses in stimulus-discrimination tasks in their studies of schizophrenic patients who are symptomatically stable.

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Richard Ulrich, MS, WPIC, University of Pittsburgh assisted in the statistical analyses.

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