EEG Coherence in Unmedicated Schizophrenic Patients

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We have recently shown that electroencephalogram (EEG) coherence data recorded with common reference methods, including those obtained from schizophrenics, are confounded by power and phase effects. Three published reports using bipolar recordings found that EEG coherence was higher in schizophrenics; however, only medicated patients were studied. To extend these findings, we measured EEG coherence from bipolar EEG recordings in unmedicated schizophrenics (n = 10), affective disorder patients (n = 8), and normal controls (n = 13) during resting and task conditions. Seven schizophrenics were restudied after a period of neuroleptic treatment. Schizophrenics had higher across-task interhemispheric (p < 0.05) and intrahemispheric (p < 0.04) coherence in the theta band and tended to have higher intrahemispheric alpha coherence (p < 0.08). Medication treatment was associated with clinical improvement and increases in spectral power, but not with changes in coherence values. These results confirm those obtained by earlier investigations and suggest that increased coherence reflects the presence of anomalous cortical organization in schizophrenics rather than medication effects or transient states related to acute clinical disturbance.

Introduction

A number of investigators have studied brain functioning in schizophrenic patients by measuring electroencephalogram (EEG) coherence. Coherence of the EEG signal recorded from electrodes over different brain regions is assumed to index anatomic or functional coupling between the brain regions under the electrodes (Shaw 1981). Unfortunately, most EEG coherence studies have used common reference recordings. We have recently demonstrated that common reference coherence data are strongly confounded by the spectral power and phase of local activity at both the recording and reference electrode sites (Fein et al. 1988).

Common reference EEG studies of coherence have yielded contradictory results in schizophrenic patients (Giannitrapani 1979; Shaw et al. 1979; Flor-Henry and Koles 1984). Three laboratories that examined EEG coherence in schizophrenics with bipolar recording, which is not subject to the problems of common reference recordings, reported consistent results. Coherence, particularly in lower frequencies, was higher in schizophrenics than in controls (Giannitrapani et al. 1986). However, only medicated patients were studied.

We examined the influence of medication on EEG coherence by studying (1) schizophrenic patients, (2) affective disorder patients, and (3) normal controls. Our results confirm earlier investigations and suggest that increased coherence reflects the presence of anomalous cortical organization in schizophrenics rather than medication effects or transient states related to acute clinical disturbance.

Subjects

Subjects were all right-handed from each prospective subject pool. California and Veterans Administration wards were screened to rule out major medical illness. Ten recently hospitalized DSM-III diagnoses (4 paranoid, 4 schizoaffective, 2 affective disorder) were verified by Schizophrenia (Spitzer and Endicott 1978a). The patients were all medicated for 1 month, and the others were restudied after a period of neuroleptic treatment. Clinical ratings with 24 hr of the initial EEG session were decreasing from 9 days after 9 days of chlorpromazine equi- weight (96 mg). BPRS ratings were down (ranging from 12 to 0.001). Affective disorder patients were restudied after 9 days, and schizophrenic patients were restudied after 1 month, and the others were restudied after 9 days.

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Coherence data recorded with bipolar recordings however, only medicated patients had higher across-band coherence (p < 0.04) coherence in the theta frequency band (p < 0.08). Medication increases in spectral power, but confirms those obtained by earlier studies. The influence of neuroleptic medications on bipolar EEG coherence by studying (1) schizophrenic patients prior to and after neuroleptic treatment, (2) medication-free affective disorder controls, and (3) normal controls.

Method

Subjects

Subjects were all right-handed adult men (Annett 1976). Informed consent was obtained from each prospective subject according to guidelines approved by the University of California and Veterans Administration human experimentation committees.

Ten recently hospitalized schizophrenics (age 43.4 ± 11.9 years) were selected, and DSM-III diagnoses (4 paranoid, 4 undifferentiated, 1 disorganized, and 1 chronic schizoaffective) were verified by administration of the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott 1978a). Two patients had never received neuroleptic medication, and the others had been untreated for 1 month to 2 years. One patient, off medications for 1 month, received two 5-mg doses of oral fluphenazine 62 hr prior to testing. Clinical ratings with the Brief Psychiatric Rating Scale (BPRS), obtained within 24 hr of the initial EEG session, yielded a mean score of 50.5 ± 7.0. Seven patients were res tudied after 9 days to 4 weeks of daily neuroleptic treatment with a mean daily dose in chlorpromazine equivalents (Davis 1976) ranging from 200 to 500 mg (mean 369 ± 106 mg). BPRS ratings were significantly lower at the time of the postmedication EEG session, decreasing from 49.0 ± 6.7 to 32.1 ± 2.8 (paired t-test: t = -5.67, df = 12, p < 0.001).

Affective disorder patients were selected from hospital admissions to serve as non-schizophrenic patient controls. The sample included 8 right-handed patients (aged 55.8 ± 12.2 years) with DSM-III diagnoses of bipolar depressed (2), bipolar manic (2), and unipolar depressed (4). All patients had been off medication at least 2 weeks.

Thirteen right-handed normal controls (aged 41.5 ± 8.1 years), were recruited from hospital employees and represented a range of educational and socioeconomic levels. All were screened to rule out major psychopathology with the SADS-Lifetime (Spitzer and Endicott, 1978b).

Experimental Procedure

Subjects were seated in a sound-attenuated chamber while EEG was recorded during a resting, eyes-open condition (EO) and during two task conditions: copying text (CT) and copying designs (CD). EEG was recorded from electrodes at F3, F4, C3, C4, Cz, T3, T4, P3, and P4, all referenced to Fz or Cz (in two schizophrenics and one affective patient). Eye movements (EOG) were monitored by electrodes at Fpl and the right outer canthus. Impedance was less than 10 kohm for each electrode.

Signals were amplified by a Grass model 7 polygraph with 1/2 amplitude filters set at 1 and 35 Hz, and digitized on-line (at 64 samples per second per channel with a 100 μsec interchannel interval) on an IBM-XT microcomputer. Automatic artifact rejection
software eliminated epochs with EOG signals greater than 50 μV baseline to peak until 60 acceptable 1-sec epochs were obtained. EEGs were later visually screened for artifact and additional contaminated epochs deleted. An average of 49.3 ± 8.4 sec (range 26–60) of EEG remained for the EO condition, 40.0 ± 8.4 sec (range 22–55) for CD, and 43.9 ± 7.4 sec (range 26–60) for CT. There were no differences between groups in the number of EEG epochs remaining after artifact screening.

**Coherence Computations**

The Fz (or Cz) referenced EEG was algebraically transformed to the following bipolar electrode pairs over each hemisphere: (1) frontal–temporal (FT), (2) frontal–parietal (FP), (3) frontal–central (FC), (4) central–parietal (CP), (5) temporal–central (TC), (6) temporal–parietal (TP). Fast Fourier transforms were then performed, and coherences computed between 10 bipolar pairs: four intrahemispheric and six interhemispheric. Intrahemispheric bipolar pairs (FT versus CP, FC versus TP) were selected to avoid using the same electrode in both members of a pair. Interhemispheric coherences were measured between the following homologous regions: (1) FT–IT (F3-T3 and F4-T4), (2) FP–FP (F3-P3 and F4-P4), (3) FC–FC (F3-C3 and F4-C4), (4) CP–CP (C3-P3 and C4-P4), (5) TC–TC (T3–C3 and T4–C4), (6) TP–TP (T3–P3 and T4–P4). Data were banded into delta (0–3 Hz), theta (3.5–7 Hz), alpha (7.5–12.5 Hz), beta1 (13–19.5 Hz) and beta2 (20–32 Hz) frequency bands. The coherence data were normalized prior to analysis by transformation to Fischer's $z'$ scores (Cohen and Cohen 1983). For graphic presentation, means and standard deviations were transformed back to coherence values. Data were analyzed using repeated measures Analysis of Variance (ANOVA).

**Results**

In the theta and alpha bands, both inter- and intrahemispheric coherences were significantly reduced from resting (EO) values during tasks (CD, CT) across subject groups ($p < 0.001$ for both theta and alpha bands). As there were no group-by-condition interactions, data displayed in the figures are the mean coherence averaged over the three conditions.

Coherences tended to be larger in schizophrenics overall, but significant findings were restricted to the theta (3.5–7 Hz) band. Interhemispheric theta coherence (see Figure 1) was higher in schizophrenics ($F = 3.39$, df = 2, $p < 0.05$), particularly for FT–IT and TP–TP placements. Post-hoc t-tests revealed that schizophrenics had higher values than affective patients ($p < 0.02$), but not normal controls. Intrahemispheric theta coherence (see Figure 2) was also increased in schizophrenics ($F = 3.75$, df = 2, $p < 0.04$). Post-hoc t-tests revealed that schizophrenics had higher values than both affective patients ($p < 0.04$) and normal controls ($p < 0.02$). Intrahemispheric alpha coherence were also higher in schizophrenics, but the magnitude of the effect fell short of the 0.05 significance level ($F = 2.75$; df = 2, $p = 0.08$). There were no group x side interactions in any frequency band.

Repeated measures ANOVAs were performed on pre- and posttreatment data from seven schizophrenic subjects. There were no significant session effects. In contrast, spectral power analysis revealed a significant increase in theta power after treatment ($f = 7.50$, df = 1, $p < 0.04$). Figure 3 displays the pre- and posttreatment inter- and intrahemispheric alpha and theta coherence data.

**Discussion**

Measuring bipolar EEG coherence-free, schizophrenic pat comparable to those obtained and Montagu 1979; Ford et a not changed after treatment w

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Figure 1. Interhemispheric Theta Coherence

Means are collapsed across conditions ($p < 0.001$).
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150 µV baseline to peak until visually screened for artifact of 49.3 ± 8.4 sec (range 26–55) for CD, and differences between groups in the

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Figure 1. Interhemispheric Theta Coherence in Schizophrenics, Affective Patients and Animals. Means are collapsed across conditions; error bars are 95% confidence intervals. Coherence was higher in schizophrenics overall (p < 0.05) and higher in schizophrenics than affective patients (p < 0.02).

Discussion

Measuring bipolar EEG coherences in a modest-sized sample of newly admitted, medication-free, schizophrenic patients and controls, we obtained increased coherence values comparable to those obtained by two other laboratories with medicated subjects (Weller and Montagu 1979; Ford et al. 1986). In addition, EEG coherence measurements were not changed after treatment with antipsychotic agents, despite an increase in theta power.

We found a large decrease in theta and alpha coherence during task performance relative to resting states across all bipolar coherence pairs. With common reference recordings, engagement in tasks has been reported to either increase (Busk and Galbraith 1975; Beaumont et al. 1978; Ford et al. 1986a) or decrease (Koles and Flor-Henry 1981; Tucker et al. 1985) coherence between brain regions in normal subjects. It is noteworthy that Shaw et al. (1983), recording from both common reference and bipolar arrays simultaneously, found that task activity increased coherence in the former but decreased coherence in the latter. It is possible that when using common reference recordings, increases in coherence during task performance may have been a consequence of the effect of task activation on spectral power at the reference and recording sites, rather
Electrode Pairs

Figure 2. Intrahemispheric Theta Coherence in Schizophrenics, Affective Patients and Animals. Means are collapsed across conditions; error bars represent 95% confidence intervals. Coherence was higher in schizophrenics ($p < 0.04$) than in affective patients ($p < 0.04$) or normals ($p < 0.01$).

than a consequence of changes in coherence between true measures of local activity. Another possibility is that our findings are a function of the size of the cortical areas sampled by our bipolar lead pairs. Further empirical studies are needed to explore these issues.

Higher coherence values in schizophrenic patients might reflect a pattern of more diffuse, undifferentiated cortical organization. Although there is little direct evidence to support this hypothesis, Feinberg (1983) has speculated that a neurodevelopmental failure to lose redundant synaptic connections during adolescence underlies schizophrenia. Increased numbers of synaptic connections would be consistent with higher coherence values. The absence of medication effects on coherence in the context of improved BPRS scores suggests that increased EEG coherence reflects anomalous patterns of cortical organization rather than transient states related to acute clinical disturbance. This finding also suggests that further EEG coherence studies can be pursued with larger samples of more readily available medicated patients.

Unfortunately, the limited bipolar montage we used is not ideal for studying patterns of cortical organization. The large areas of cortical surface sampled by bipolar electrode
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Figure 3. Inter- and Intrahemispheric Theta and Alpha Coherence in Schizophrenics (n = 7) Before and After Neuroleptic Treatment. Means are collapsed across conditions; error bars represent 95% confidence intervals. There were no significant changes with treatment.
pairs based on the standard 10-20 system may obscure local effects. Future studies of EEG coherence should have enough channels to sample the EEG at its spatial frequency, using bipolar montages, current source derivation recordings (Nunez 1981), or other reference-free recording methods.

References
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Serum Thyroxine (FT4) in Psychiatric Inpatients

Steven Southwick, John Thomas R. Kosten

Serum free thyroxine (FT4, BPRS) measurements were during hospitalization in affective disorders. A and for FT4 (p < 0.005), symptom severity was linked found the relationship not three patient subgroups for synchron level, as well as the The hormonally defined thyroxine levels that then rose substantially, but then decreased was not the poor recovery group suggest that a "normalization" of overall recovery levels appear to have clinical sign a variety of psychiatric disorder.

Introduction

Although there is a variety of disorders (Hoskins and Slel thyroid hormonal levels in The primary purpose of this search for clinical or subcl particularly hypothyroidism.