Computerized EEG in Schizophrenia

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Abstract

Despite advances in the processing and display of electroencephalographic (EEG) data, the utility of this inexpensive and noninvasive technique in the investigation of schizophrenia has not been well established. We studied the resting EEG in 19 medication-free patients with chronic schizophrenia and 21 normal controls. Patients with schizophrenia had increased delta activity which was not specific to the frontal regions. Schizophrenic patients also had increased fast activity, and this increase was left sided for the fast beta frequency. Alpha frequency was reduced (<10.2 Hz) in 7 of 16 schizophrenic patients. Moreover, those patients with an alpha frequency reduction had a significantly larger mean cerebral ventricular size. These results indicate that the EEG does detect neurophysiological changes in schizophrenia. Our understanding of these changes may be enhanced by other neuroimaging techniques such as computed tomography.

Eye Movement

The eyes, like the brain, generate electrical potentials. Large and discrete potentials occur during blinking and vertical eye movements. EEG recordings containing such potentials can be easily recognized and discarded. Horizontal eye movements (EOM), however, constitute a more difficult problem. Undetected, they introduce slow frequencies (delta) into the EEG, particularly in the frontal regions (Gasser et al. 1985) (see figure 1). This problem is compounded in studies using frequency analysis (power spectrum analysis), which amplifies artifact because the amplitude of a given frequency is summed over time. EOMs are of high amplitude. Moreover, patients with schizophrenia have more EOMs than normal controls and are less able to limit such movement with maneuvers such as visual fixation (Matsue et al. 1986). Hence, undetected EOMs could account for the increase in frontal...
delta in schizophrenic patients reported in earlier EEG mapping studies (Buchsbaum et al. 1982; Morihisa et al. 1983; Morstyn et al. 1983; Guenther et al. 1986). In a study that used one channel of the EEG to detect horizontal eye movements, we were unable to confirm a specific increase of frontal delta activity in patients with schizophrenia (Karson et al. 1987). Overall delta activity, however, was increased.

Methods

Subjects. The subjects were 16 male and 3 female psychiatric inpatients who met DSM-III criteria (American Psychiatric Association 1980) for chronic schizophrenia. All had been withdrawn from medications for a minimum of 4 weeks. The mean age for the group of patients was 30 ± (SD) 5 years. Sixteen patients reported that they were right-handed and three that they were left-handed. Eight paid volunteers recruited by advertisement and 13 members of the clinical and research staff of the William A White Building served as normal controls. The mean age for the control group, which included 15 males and 6 females, was 31 ± (SD) 7 years. Seventeen were right-handed and four were left-handed.

We have thus added four patients with schizophrenia and eight normal subjects to those in our initial report (Karson et al. 1987).

EEG Recording and Analysis. The methods for recording EEGs and performing power spectral analysis and the subsequent topographic EEG mapping data have been described elsewhere (Coppola 1979; Coppola et al. 1982; Karson et al. 1987). The subjects were seated comfortably at rest in a darkened sound-proofed room. Twenty electrodes were applied to the scalp using standard methods in accordance with the 10-20 system and referenced to linked ears. Filter settings were 1 and 70 Hz. The frequency bands examined were delta (4-3.9 Hz), theta (4.3-7.8 Hz), alpha (8.2-12.9 Hz), beta 1 (13.2-19.9 Hz) and beta 2 (20.3-27.3 Hz). To reiterate for emphasis, horizontal eye movements were recorded on a separate channel by recording the potential between electrodes placed at the outer canthus of each eye. The filter settings for this amplifier were at 1 and 70 Hz. In addition to visual inspection, power spectral analysis was carried out on this channel to measure the amount of eye movement.

Subjects were recorded for 5 minutes separately with eyes open and closed. In the eyes-open condition, the mean (±SD) number of artifact-free epochs (1 epoch = 2.56 seconds) obtained for the patients was 25 ± 2.3 (1 minute) and 62 ± 34 (2.5 minutes) for the controls. In the eyes-closed state, the mean (±SD) number of artifact-free epochs for the patients was 32 ± 26 (a little over 1 minute) compared with 64 ± 37 (2.5 minutes) for normal controls. Three patients were unable to stop their eye movements in the eyes-closed state sufficiently to produce enough artifact-free EEG recordings for statistical analysis. The same was true for four different patients and two controls in the eyes-open state. Hence, data were obtained from 16 patients and 21 controls with the eyes closed and from 14 patients and 19 normals with the eyes open.

Following the initial power spectrum analysis, a more complete assessment of alpha activity was made for recordings from the eyes-closed state. The dominant frequency was defined as the frequency of the spectrum estimate with maximum amplitude in the eyes-closed condition. If the dominant frequency was in the alpha range and less than 10.2 Hz, the subject was classified as having reduced alpha frequency. This cutoff point was derived from a study of 16 normal controls employing topographic analysis (Coppola and Chassy 1986).

Measurement of Cerebral Ventricular Size. CT scans were obtained for each subject on a fourth generation CT scanner. The lateral ventricles were measured with a fixed arm planimeter using a modification of the method of Synek and Reuben (1970). The slice examined was that in which the lateral ventricles appeared largest. The ventricles and brain were separately outlined with the planimeter and the ventricular-brain ratio (VBR) determined by dividing the area of the ventricles by that of the brain and multiplying by 100.

Results

Power Spectral Analysis and Topographic Mapping. Patients with schizophrenia had increased delta activity at the vertex and O2 in the eyes-open state (overall comparison of the midline cluster, Hotelling’s $T^2 = 19.41, F = 3.38, df = 5, 27, p < .02$, multivariate analysis of variance. Delta activity was also increased in the right hemispheric regions of the patients in the eyes-closed condition (Hotelling’s $T^2 = 20.29, F = 2.40$.
Figure 1. Increased frontal slowing (delta) during blinks and horizontal eye movements in the averaged record of 9 normal controls.

Figure 2. Left-sided increase of fast beta (beta 2) in patients with schizophrenia.
different in 5 of 7 electrode locations used in this cluster. While the overall comparison was not different on the left, the corresponding univariate comparisons were. The ratio of frontal to occipital (FZ/OZ) delta activity for the eyes-open condition in the midline was 1.11 and 1.15 in the patients and the normals, respectively; in the eyes-closed condition, the corresponding values were 1.15 and 1.07. Despite careful visual screening for records contaminated with horizontal eye movement, the patients had significantly increased delta activity at the horizontal electro-oculogram (EOG) with eyes open ($p < .005$) and closed ($p < .05$).

With the eyes open, the patients also had increased slow beta activity (beta 1) in the occiput (overall for midline leads: Hotelling's $T^2 = 17.60, F = 3.03$; $df = 5,27, p < .05$; at PZ: $F = 8.19, p < .01$; for the right hemisphere locations: Hotelling's $T^2 = 25.83, F = 2.98; df = 7,25; p < .05$; at PO: $F = 8.58; df = 7,25; p < .01$, and increased fast beta (beta 2) on the left side (side x diagnosis comparison: Hotelling's $T^2 = 23.37, F = 2.69; df = 7,25; p < .05$; with significant left over right increases detected at the P3-P4, FC5-FC6, and CP1-CP2 electrode pairs) (figure 2).

**Alpha Analysis (Dominant Frequency Analysis).** Seven of sixteen patients had an alpha frequency below 10.2 Hz. One patient had alpha above 10.2 Hz, and two other patients had two dominant frequencies in the alpha range, above and below the 10.2 Hz cutoff. Six patients had no dominant frequency in the alpha range. In contrast, the alpha frequency in 13 of 21 normal controls was above 10.2 Hz. Reduced alpha frequency was present in only five controls, and three controls had a dominant frequency outside the alpha range. Hence, 13 of 21 normal controls had a dominant frequency in the alpha band above 10.2 Hz compared with only 1 of 16 patients ($p = .001$, Fisher's Exact Test). This significant difference in distribution between the two groups was due primarily to the high number of schizophrenic patients with an alpha frequency below 10.2 Hz ($p = .009$) rather than a high proportion of patients with a dominant frequency outside the alpha range ($p < .11$).

The mean VBR was significantly increased in the patients with reduced alpha frequency compared with other patients ($9.8 \pm 1.9$ vs. $5.0 \pm 2.4$, respectively, $p < .01$).

**Discussion**

**Power.** This group of patients with chronic schizophrenia had diffuse EEG slowing (increased delta activity) that was not specific to the frontal regions. This frequently replicated result supports the notion of functional brain pathology in schizophrenia, as delta is usually a sign of disturbed (usually depressed) function. Moreover, increased delta activity in schizophrenia was reported before neuroleptics became available (Hoagland et al. 1937; Gibbs et al. 1938) and therefore cannot be solely attributed to treatment with these drugs. The magnitude of these results, however, is vitiated to a degree, as the patients had more delta activity at the horizontal EOG and, hence, probably more eye movement.

Fast (beta) activity was also increased as has previously been reported (Itil et al. 1972). Since muscle activity can mimic fast EEG frequencies, it is entirely possible that this increase represents increased muscle tension on the part of the patients. This explanation may not be adequate, however, to explain the increase of fast beta (beta 2) over the left hemisphere in schizophrenia which has been previously reported (Itil et al. 1972; Morihisa et al. 1983). This was not apparent in our original report (Karson et al. 1987) but became evident as we added more subjects.

**Alpha Frequency.** A dominant frequency in the alpha range above 10.2 Hz was found in a majority of our normal controls. In contrast, nearly half (44 percent) of the schizophrenic patients had reduced alpha frequency. Moreover, reduced alpha frequency was associated with a near doubling of lateral ventricular size compared with other schizophrenic patients. We are currently studying more normal controls to establish whether the 10.2 Hz cutoff is optimal or whether it could be as low as the 10 Hz cutoff used by others (Itil et al. 1972).

Another issue is the contribution of persistent concentrations of neuroleptics in the central nervous system (CNS) to the reduced alpha frequencies found in the patients, even though they had been medication free for at least 4 weeks. These medications reportedly increase the amount of alpha activity below 10 Hz (Itil 1977), and haloperidol and its active metabolite, reduced haloperidol, have been found in measurable concentrations in the brain of one subject who died 72 days after his last dose of this drug (Korpi et al.
This question cannot be currently addressed except by studying medication-naive subjects. Nevertheless, the return of normal D$_3$ receptor binding in a normal human, as measured by radio-labeled raclopride, only 2 weeks after the cessation of chronic neuroleptic treatment (Sedvall et al. 1986) suggests that persistent neuroleptic concentrations in the CNS may have limited functional importance. Moreover, it is difficult to see the bearing this issue has on the association of large VBR and reduced alpha frequency which occurs strictly among patients.

Conclusions

Inhibiting eye movement and muscle activity is very difficult for medication-free patients with schizophrenia. This factor remains a severe limitation in quantitative studies of EEG in this disorder, especially with computerized analysis of EEG power spectra. In our study, there is more slow activity (delta) and a left-sided increase of fast activity in schizophrenia. The frequency of alpha activity is reduced in schizophrenia, and this reduction is associated with cerebral ventricular enlargement. These findings indicate that the EEG does detect neurophysiological changes in schizophrenia which may be more readily interpretable in conjunction with other neuroimaging techniques such as the CT scan.

References


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