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Effect of attention on frontal distribution of delta activity and cerebral metabolic rate in schizophrenia

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15 patients with schizophrenia and nine normal volunteers had 32 channel topographic EEG recorded for spectral analysis during the uptake of 18-F-deoxyglucose (FDG) for positron emission tomography (PET). Both patients and controls performed the Continuous Performance Test, a visual vigilance task, during FDG uptake. EEG was also obtained during an initial pre-FDG resting period. Each EEG epoch was individually inspected for eye movement artifacts. Analysis confirmed increased delta activity in the frontal region of patients with schizophrenia in comparison to normal controls, and a significant correlation between increased frontal delta and relative reduction in frontal lobe metabolism among patients with schizophrenia. This finding of increased delta is consistent with PET, blood flow and topographic EEG studies of schizophrenia, suggesting reduced frontal activity.

Key words: Positron emission tomography; Quantitative electroencephalography; Attention; Delta; Continuous Performance Test; Frontal lobe

INTRODUCTION

Increased delta activity in schizophrenia was one of the earliest electroencephalographic findings. Patients never medicated with neuroleptics and untreated had a higher delta index (Hoagland, 1938) and also greater percent frontal slow activity (Jasper et al., 1939). Unmedicated patients showed greater posterior frontal (C_2–C_4) slow activity in another study (Tarrier et al., 1978). Lifshitz and Gradijan (1972) also studied delta and inferred lower arousal in schizophrenics than in normals. In a review of delta findings, Iacono (1985) found increased delta had potential as a genetic marker. Although no specific EEG patterns have as yet been established as pathognomic for schizophrenia (e.g., Itil, 1977), several recent quantitative topographic studies have indicated an increase in delta activity in the frontal regions (Buchsbaum et al., 1982; Morihisa et al., 1983; Morstyn et al., 1983; Guenther and Breitling, 1986). We have suggested that these results parallel the findings of reduced frontal lobe function as assessed by positron emission tomography and cerebral blood flow (see review by Buchsbaum and Haier, 1987). Delta activity over regions of low flow is well known clinically, and has been linked directly to blood flow change in EEG/xenon flow studies by Ingvar et al. (1976) and Tolonen and Sulg (1981). In PET studies, we found that patients with relatively lower metabolic rates in the frontal lobe had increased frontal delta (Buchsbaum et al., 1982).

However, these imaging studies with EEG and blood flow have not been uniform in demonstrating frontal dysfunction (Buchsbaum and Haier, 1987) or increased delta (Buchsbaum et al., 1984b). Two factors, task activation and eye movement artifacts, have been suggested to be important in

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the negative studies (Buchsbaum and Haier, 1987; Weinberger et al., 1988). A critical uncontrolled variable in many studies has been the activity of the patient during the functional study. PET, EEG and cerebral blood flow are extremely sensitive to the mental activity of the subject (Buchsbaum and Haier, 1987). Recent studies have indicated that deficits on attentional and informational processing tasks are among the most consistent neuropsychological abnormalities found to characterize schizophrenia (Cornblatt et al., 1988) and that the diminished function of the frontal lobes is most prominent in patients performing a task which activates the frontal lobe (Cohen et al., 1987; Weinberger et al., 1988). We chose to study the Continuous Performance Test (CPT), because this task has shown particular sensitivity to schizophrenic performance deficit (see review, Nuechterlein et al., 1984) and because it has been associated with reduced frontal metabolic rates on PET scans in schizophrenics (Cohen et al., 1987).

The second criticism, that frontal delta resulted from residual eye movement artifacts which had not been fully deleted (Karson et al., 1987), was addressed with careful visual inspection of records and with the simultaneous examination of metabolic rate of the frontal eye fields with PET. Since voluntary lateral eye movements might most likely appear as increased metabolic rates in active frontal eye fields (area 8), an examination of the correlation between frontal delta and the extent of frontal hypometabolism would address this artifact issue.

METHODS

Patients

The patient group comprised 15 patients with schizophrenia (14 men, one woman, mean $\pm$ SD age of 27 ± 6.4 years). These patients were recruited from the clinical and research programs of the University of California at Irvine and Los Angeles and do not overlap with earlier samples from NIMH (Buchsbaum et al., 1982, 1987a). The PET findings on 13 of these patients are reported elsewhere (Buchsbaum et al., 1989). 13 of the 15 patients were right-handed; two were left-handed. Patients were off all psychoactive medication a minimum of 31 days and a mean of 30 weeks. For long-acting injectable antipsychotic medication, the minimum period off medication was 8 weeks. All patients were in good physical health, and none had noteworthy abnormalities on physical examination or on laboratory tests. Patients with history of seizure disorder, major head trauma or substance abuse were excluded. Psychiatric interviews and assessments of the patients were carried out at UCLA independently of PET laboratory procedures in the week before the scan. The diagnostic workup included the Present State Exam (PSE) (Wing et al., 1974) modified to allow use of DSM-III criteria and an expanded version of the Brief Psychiatric Rating Scale (Overall and Gorham, 1962; Lukoff et al., 1986). The mean BPRS score (sum of first 18 items) was 31.7 (SD = 12); mean score on the hallucinations item was 2.6. Mean educational level was 12.8 years. Patients performed the CPT at the interview as well as during the glucose uptake period.

The normal control group for this study consisted of nine right-handed volunteers (mean age 27.8, SD = 8.9, three men and six women). Subjects were screened for health just as the patients were, by physical examination, medical history, laboratory measures, and psychiatric interview at UCI. No subject was taking any medication, had a history of psychiatric illness in self or first-degree relatives, or had current significant medical illness. The BPRS was not done. Patients and normals participated under protocols and consent forms approved by the UCI Human Subjects Committee.

Experimental procedure

Subjects had two IV lines inserted for blood sampling and 18-F-deoxyglucose administration as described elsewhere (Buchsbaum et al., 1987). They were seated in a darkened isolation room and rested with their eyes closed for the first EEG recording. They were next instructed in the Continuous Performance Task, and did 20–40 practice trials. The task began, FDG was injected 1–2 min later, and EEG was again recorded. Subjects received 4–5.2 mCi of FDG. After 30 min, patients were moved to the PET scanner where scans were obtained, as described elsewhere (Buchsbaum et al., 1987; 1989).

Task

Subjects viewed a series of single digits presented at 2 s intervals and were instructed to press a button

with their right thumb each time the digit 0 appeared. Targets are presented irregularly with a probability of 0.25 by a Kodak Carousel slide projector fitted with an Ilex no. 4 synchro-electronic shutter and controlled by a microcomputer. Stimuli were presented in the center of the visual field with a width of 6°. Stimuli are optically degraded by blurring to a degree that requires a 2.8 diopter increase in lens power to refocus sharply. The spatial frequency is approximately 0.5 cycles/cm. Additional details are given in Nuechterlein et al. (1983).

For the contrast condition, subjects rested with their eyes closed. This was chosen for comparability with our earlier studies and those assessing blood flow (Buchsbaum et al., 1982a,b).

EEG recording

For EEG recording, a set of 32 Grass gold disc electrodes were placed with Grass electrode paste on subjects' scalps using 19 standard International 10–20 System leads, three additional midline leads (FF and FC at 10% steps and O_z), two additional temporal leads ($TT_{1,2}$) between T_3-T_5 and T_4-T_6 at 5% steps, and eight additional leads ($FTC_{1,2}$; $CP_{1,2}$; $TCP_{1,2}$ and $PO_{1,2}$) at the centers of squares formed by other electrodes (Fig. 1). Recordings were referenced to linked ears. Two to four 30 s epochs were recorded for each condition.

Data collection and processing

The EEG was recorded using a 32 channel amplifier system designed at the National Institute of Mental Health by Drs. Coppola and Morgan. The amplifier uses a Burr Brown INA-101 direct coupled (0.5 Hz 3 dB single pole RC) to a following stage of amplification at gain 2000. The output is high pass filtered with a corner at 50 Hz using a linear phase Reticon 5613 with rolloff approximately 24 dB/octave. EEG activity was digitized on-line (with a PDP-11/34) at 200 buffer points/s, and low frequency subharmonics were removed by an autoregressive filter (Coppola, 1979). The amplifiers were calibrated by recording a 10 Hz, 100 μV sine wave through all channels and determining the calibration factor for each channel; each channel was then proportionally adjusted before analysis. A window function consisting of a 10% cosine taper was obtained by weighing the 50 buffer points at either end of each 2.56 s epoch by a cosine

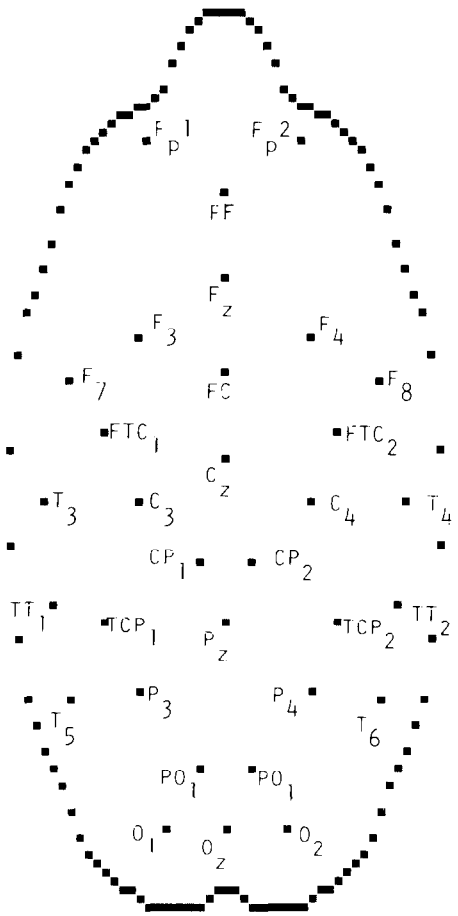

Fig. 1. 32 electrode positions on scalp, using 19 standard International 10–20 System leads, three additional leads (FF, FC and O_z), two additional temporal leads (TT_1, TT_2), and additional leads (FTC_1, FTC_2, CP_1, CP_2, TCP_1, TCP_2, and PO_1, PO_2) at the center of squares formed by electrodes.

bell. A standard fast Fourier transform was applied to the 2.56 s epochs, and the power spectrum estimates computed at 0.39 Hz steps. For smoothing, four adjacent estimates were summed to yield 1.56 Hz resolution, with the final estimates expressed as magnitude values in microvolts (square root of power). The activity estimated for the following bands was computed by summing adjacent values: delta, 0.78–4.30 cps; theta, 4.34–7.80 cps; alpha, 8.20–12.90 cps; and beta I, 13.30 19.90 cps.

Each 2.56 s epoch was visually inspected by SMG without information on diagnostic group for artifacts and any epoch containing artifacts was eliminated. Pilot data collected before our 1982

study (Buchsbaum et al., 1982a) indicated that leads Fp_1 and Fp_2 detected horizontal eye movements of 2° or greater and were quite sensitive to blinks. This was determined by having subjects make eye movements between targets at 1°, 2°, 3°, and 6° apart. The power spectral values for the artifact-free 2.56 s epochs (8–12 epochs/person/condition) were then averaged to yield one representative 2.56 s epoch of power spectral values for each subject in each condition.

Map technique

Topographic maps were computed by linear interpolation from the four nearest electrodes (Buchsbaum et al., 1982). Values were displayed on an approximately equal area map of the cortical surface using dot density representation of power value. The map was developed from sagittal sections of the brain. The maps are scaled in nine shades of gray with a 4×4 dot matrix in a 1–16 dot range.

PET measures

Regional brain activity changes were imaged as glucose metabolic rate using sterile, pyrogen-free ^{18}F-2-deoxyglucose, prepared at the Crocker Nuclear Laboratory, University of California, Davis. Batches containing 90–100 mCi of ^{18}F-2-deoxyglucose dissolved in 0.9% isotonic saline were synthesized from ^{18}F made in a 2 h bombardment, by the ^{20}Ne(d,a)^{18}F reaction using a 27.5 MeV external deuteron beam (20 μA) from the 76 inch isochronous cyclotron. Radiochemical purity and pyrogen testing were performed before injection of the ^{18}F-2-deoxyglucose using a Varian 5000 HPLC and a *Limulus* amebocyte lysate gelation test, respectively. The USP sterility test was performed on the ^{18}F-2-deoxyglucose after administration due to the 14 day incubation time. All quality assurance procedures confirmed the ^{18}F-2-deoxyglucose to be within specifications and of pharmaceutical quality.

Prior to PET scanning, an individually molded, thermosetting plastic head holder was made for each subject to minimize head movement. After 30–35 min of FDG uptake, the right arm IV was removed, the subject was allowed to void, and then transferred to the adjacent scanning room. Nine planes (CTI NeuroECAT) at 10 mm increments and parallel to the canthomeatal line (CM) were done between 45 and 100 min after FDG injection. Scans were performed with both shadow and septa shields in a configuration with measured in plane resolution of 7.6 mm and 10.9 mm resolution in the z dimension (axial). A calculated attenuation correction and smoothing filter were used. The scanner was calibrated each scan day, with a cylindrical phantom, and compared to well counter data.

Scan slice processing and selection. Scans were transformed to glucose metabolic rate according to the model of Sokoloff (1977) using our adaptation of a program developed by Sokoloff. Kinetic constants and the lumped constant from Phelps et al. (1979) were used. The supraventricular slice was selected exactly following our previously described technique (Buchsbaum et al., 1982, 1984). This slice was chosen because these earlier reports found the frontal/occipital ratio calculated from it to separate normals and schizophrenics. The slice was outlined with a boundary-finding algorithm, and a 2 cm thick ring of cortex identified. The frontal/occipital ratio was obtained by dividing the supraventricular slice metabolic rate frontal sector by the occipital sector exactly as described elsewhere (Buchsbaum et al., 1984).

Statistical analysis

Statistical analyses were performed using three way analysis of variance (ANOVA) with the BMDP2V program (Dixon, 1981) with a one grouping factor and two within factors design: group (normal, schizophrenic) by lead (32 channels) by condition (rest, CPT) for each of four frequencies: delta, theta, alpha, and beta-1. This design was employed on both microvolt and normalized values. Normalization (z transformation) was done by calculating the mean and standard deviation across the 32 leads for each condition in each subject and then expressing the 32 lead values as the value minus the mean divided by the standard deviation. Normalization yields similar results to the common practice in cerebral blood flow and PET studies of calculating relative values (region/mean of brain or slice), but incorporated each person's own range of variation into a common metric as well. To test more specifically for anterior/posterior and lateral gradient differences, 20 leads were selected to make up a 4×5 electrode matrix (Table 1). A four way ANOVA was then performed on a design of group by row (five rows

TABLE 1

Normalized delta activity in normals and in schizophrenic patients for our 4 × 5 (anteroposterior, mediolateral) lead array

	Rest	*CPT*
Normals		
F_7-F_3-F_4-F_8	−0.22	0.07
T_3-C_3-C_4-T_4	−0.50	−0.58
TT_1-TCP_1-TCP_2-TT_2	−0.64	−0.74
T_5-P_3-P_4-T_6	−0.07	−0.24
O_1-PO_1-PO_2-O_2	0.29	0.11
Schizophrenics		
F_7-F_3-F_4-F_8	0.11	−0.19
T_3-C_3-C_4-T_4	−0.64	−0.57
TT_1-TCP_1-TCP_2-TT_2	−0.91	−0.86
T_5-P_3-P_4-T_6	−0.30	−0.18
O_1-PO_1-PO_2-O_2	0.29	0.38

of four leads for anterior/posterior gradient) by column (four columns of five leads for left/right gradient) by condition. This analysis was also done for both microvolt and normalized power spectral values. Post hoc *t* test maps are only presented if lead by condition or lead by group interactions are significant. Since the replication of the finding of increased delta in the frontal lobes was tested with the *F* for the anteroposterior (AP) by group and AP by group by task ANOVA, *t* tests were used to identify the area of greatest effect rather than as exploratory and atheoretical tests; for this reason the Bonferroni correction was not used.

RESULTS

Delta distribution in normals and schizophrenics

The frontal delta excess in schizophrenics we observed earlier was statistically confirmed in this new sample with the critical interaction of group by anteroposterior position by condition using the normalized data ($F = 6.97$, df = 2.4, 43.2, $P = 0.001$) (Fig. 2). The four way interaction, group by condition by anteroposterior by mediolateral, was also significant ($F = 2.01$, df = 8.1, 145.0, $P = 0.048$). Using all 32 leads in a three way (group by condition by lead) ANOVA also yielded a significant group by condition by lead interaction ($F = 3.30$, df = 2.91, 52.4, $P = 0.028$). Since the ANOVA revealed significant interactions, follow up *t* tests are presented (Fig. 3) revealing delta differences in frontal areas during rest, and a different pattern of

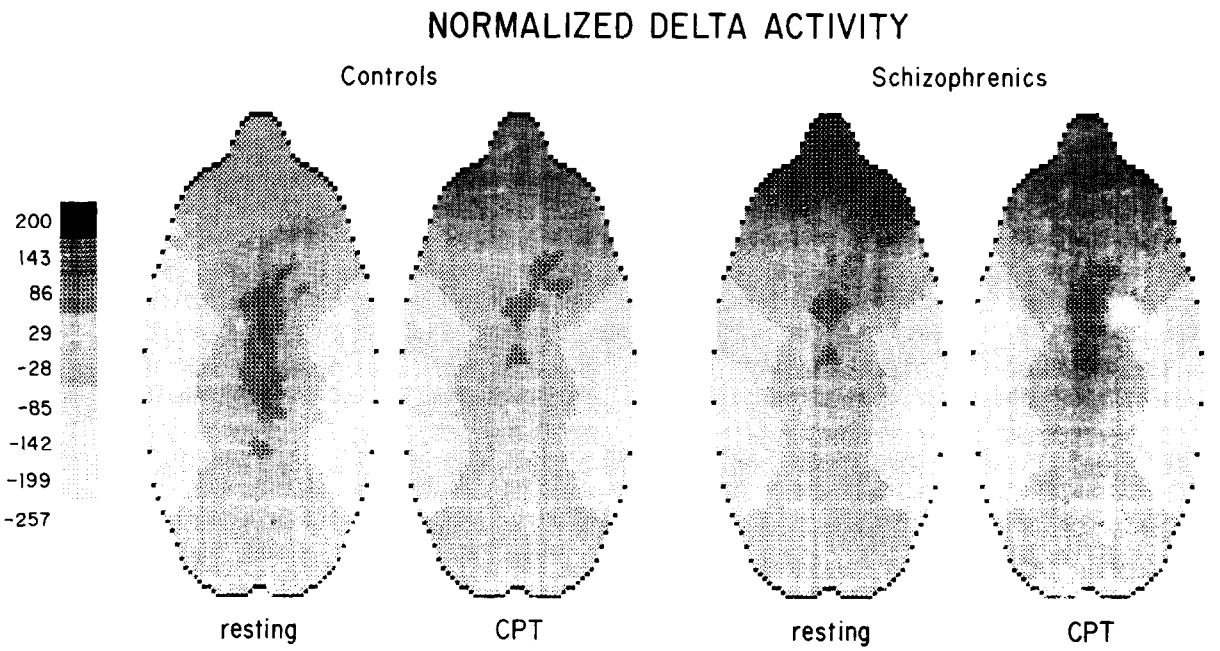

Fig. 2. Comparison of normalized delta in controls and patients with schizophrenia while resting and during Continuous Performance Test and positron emission tomography 18 F-deoxyglucose (FDG) uptake. Scale shows *z* values (× 100), with black indicating 2.00 and above. Note darker coloration (greater relative delta) in frontal region of patients.

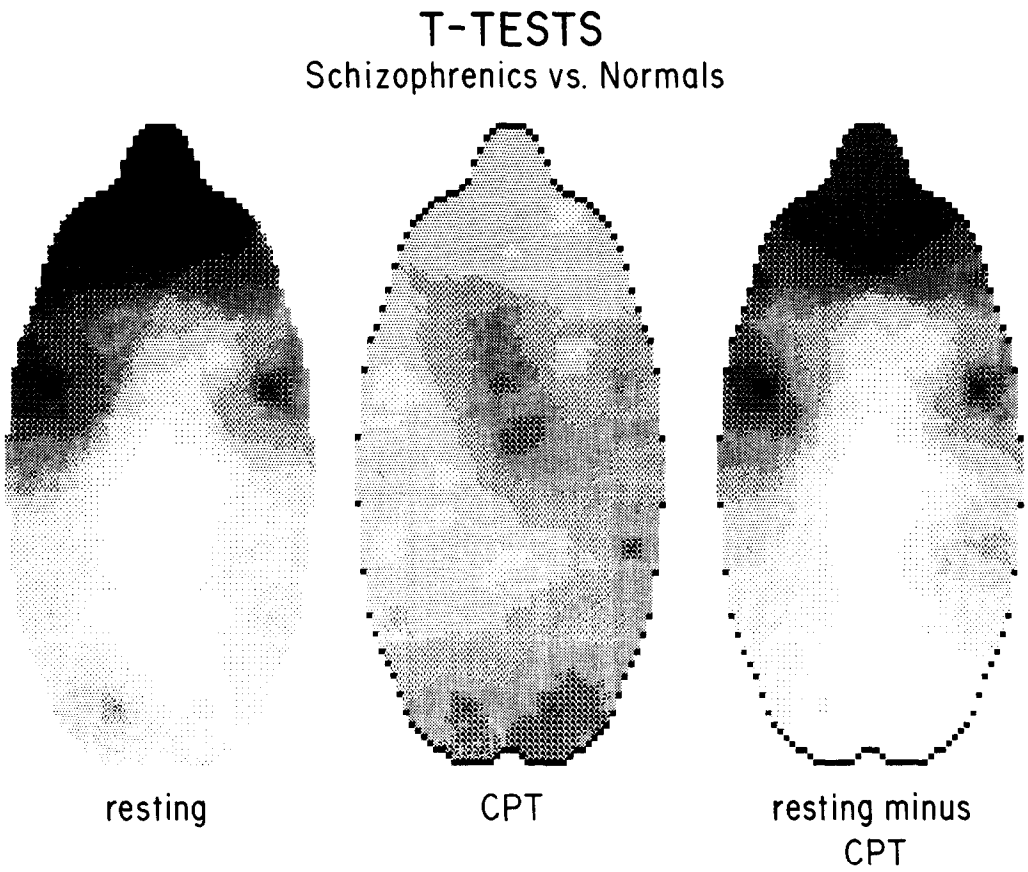

Fig. 3. Comparison of normals and schizophrenics by t test for resting, Continuous Performance Test (CPT), and resting minus CPT scores for normalized EEG. Post hoc t values done following a significant group by lead by condition interaction on analysis of variance. Black is $P<0.05$ for schizophrenics greater than controls.

activation. Normals showed a significant decrease in delta with task over the motor areas C_z and C_4 (although the left side, C_3, did not show the decrease significantly). In contrast, schizophrenics showed a significant decrease in delta with task in the right inferior frontal region (Fp_2, F_8) and no region showed a significant (delta) increase with task.

Using microvolt values, we found delta activity to be highest over the midline and frontal regions of the brain in both groups and for both conditions. Three way ANOVA revealed a significant lead effect ($F=23.0$, df$=2.67, 48.4$, $P<0.001$) but no main effects of condition or group, and no interactions. The 4×5 grid design with a four way ANOVA (five anteroposterior rows, four right to left columns, two conditions, two groups) detected regional but not group effects. Significant anteroposterior gradients ($F=26.1$, df$=2.05, 36.9$, $P<0.0001$) were observed, with lowest values in the mid position (16.0 μV, row TT_1-TT_2) and highest in the posterior (19.0 μV, row O_1-O_2).

Alpha distribution in normals and schizophrenics

Using microvolt values, alpha was highest in the occipital regions for both groups and for both conditions. Analysis of variance yielded a significant condition effect ($F=23.8$, df$=1.0$, $P=0.0001$), a significant lead effect ($F=22.9$, df$=5.1$, $P<0.00005$) and a significant lead by condition interaction ($F=11.2$, df$=4.7, 84.8$, $P<0.00005$) but no significant interactions by group. Using our 4×5 grid design, we found significance for condition ($F=22.1$, df$=1.0, 18.0$, $P=0.0002$), for anteroposterior lead array ($F=38.4$, df$=1.5, 28.0$, $P<0.00005$), for mediolateral lead array ($F=9.9$, df$=2.3, 41.0$, $P=0.0002$),

and for all interactions between these factors: condition by anteroposterior ($F=21.2$, df$=1.5$, 28.2, $P<0.00005$), condition by mediolateral ($F=6.0$, df$=2.4$, 44.5, $P=0.0028$), anteroposterior by mediolateral ($F=5.4$, df$=6.5$, 116.3, $P<0.00005$), and condition by anteroposterior by mediolateral ($F=2.4$, df$=5.3$, 96.2, $P=0.042$). But again we found no significant interaction between any of these factors and the grouping factor.

Statistical analysis of our normalized data for alpha did not uncover any significant effects for group or group by factor interactions, for either the 32 lead array or the 4×5 grid design. As would be expected with alpha blocking, the occipital regions for both groups showed the largest decline in alpha activity during the CPT task.

Correlations with regional glucose metabolic rate

We have previously reported that these patients with schizophrenia showed relative glucose metabolic hypofrontality, more marked on the right side (Buchsbaum et al., 1982, 1984, 1989). This has been tested both in our report (Buchsbaum et al., 1989) and in the original blood flow study (Ingvar and Franzen, 1974) by computing the frontal/occipital ratio. To examine whether the patients with elevated frontal delta were the same ones with metabolic hypofrontality, we correlated delta amplitude at our frontal leads during the CPT with the frontal/occipital PET ratios obtained from the supraventricular slice. The correlations were -0.58 ($P<0.02$, one tailed) for Fp_1 (right side) and -0.49 ($P<0.05$, one tailed) for Fp_2 (left side). The correlations at other frontal leads were: $F_4=-0.59$; $F_3=-0.38$; $F_7=-0.40$; $F_8=-0.54$; $FF=-0.57$ (all $P<0.025$). Correlations for occipital delta were all nonsignificant (0.40 at O_z, 0.43 at O_1, 0.36 at O_2). During rest, the frontal correlations were not significant, but posterior leads showed significant positive correlations: $O_z=0.59$, $O_1=0.55$, and $O_2=0.67$ (all $P<0.02$). Since PET FDG uptake was obtained during CPT, not rest, it is not surprising that correlations with metabolic rate were best with subjects' EEG from the activated condition.

Task

Mean CPT d' scores in normals were 2.2, SD$=0.85$ and in patients 1.72, SD$=0.92$ ($t=1.26$, $P=$ ns). In three patients a valid performance score was not obtained due to a computer error and these patients are omitted from this analysis. Three patients with schizophrenia performed below the $d'=1.0$ level. Two patients with schizophrenia scored at levels which could not be distinguished from chance by χ^2 and 5% confidence (less than 17 targets detected from the total of 40 targets in the 160 stimuli; expected random performance would be 10/40).

DISCUSSION

In this study, as in our previous report (Buchsbaum et al., 1982), we found greater levels of delta activity in the frontal lobes of patients with schizophrenia than in normal controls. This is consistent with the quantitative topographic reports of Morstyn et al. (1983), Morihisa et al. (1983), and Guenther and Breitling (1985). It is also consistent with the data presented in two other studies. Williamson and Mamelak (1987) studied 12 acutely ill schizophrenics (six unmedicated) and 12 normal volunteers; frontal but not temporal or occipital delta was significantly elevated in the patients while ill (tested, as appropriate in replication, with a one-tailed t test) but not after all patients were treated. Karson et al. (1987) similarly found frontal delta significantly higher in schizophrenics than normals using a MANOVA on sets of four or five leads. They did not report on the critical group by electrode position interaction effect, however. They do present a table of univariate tests on 14 electrodes for schizophrenics and normals for eyes open and closed. Of the 28 possible t test comparisons for delta, 11 are significant and of these, six are in the frontal lobe. In our PET data, the relative hypofrontality (Buchsbaum et al., 1982, 1984) was strongest in the right frontal region; our EEG correlations were strongest there as well. Examining the right-sided leads in Karson's table, we note that the schizophrenics had delta 11.1 μV higher than controls over the frontal lobe (F_4) but only 4.9 μV higher over the occipital lead (O_2).

Karson et al. (1987) suggest that our results (Buchsbaum et al., 1982) as well as those of Morihisa et al. (1983) and Guenther and Breitling (1985) are flawed due to inclusion of eye movement

artifacts. The current data are not consistent with this interpretation. While our records are individually inspected for eye movement artifacts, it is often argued that the process was not sufficiently selective. But the correlation between measured cortical metabolic rate and delta cannot so easily be explained as an artifact. If our delta were only due to eye movements, we might have expected a positive correlation between electrical activity and increased metabolism in the frontal lobe eye fields (e.g., area 8) or no correlation at all. The negative correlation observed between delta and metabolism is consistent with the hypothesis of reduced activity in the frontal lobes being non-artifactually reflected in increased delta. Note also that we obtained our right-sided hypofrontality ratio correlations only with right-sided EEG leads; strongest at F_8. Saccadic eye movement artifacts would be mostly bilateral. Furthermore, there was a larger and more significant delta increase with task in leads F_7 and F_8 than in leads Fp_1 and Fp_2, respectively. This also is inconsistent with an eye movement artifact interpretation; topographic maps of delta activity during deliberate eye movements show greatest amplitude at Fp_1 and Fp_2 (Lee and Buchsbaum, 1987).

Some effects of task were similar to those of Guenther et al. (1988). In their data, normals showed anterior frontal delta increases with task but schizophrenics did not. In our data, a similar pattern appeared during task with the normal-schizophrenic difference in delta task effect (Fp_1, Fp_2), significant only one-tailed ($t=1.91$, $P=0.035$; $t=2.02$, $P=0.028$, respectively, one-tailed in replication). However, in our data, delta increases with task were not significant (two-tailed) for any of the frontal leads (see Table 2), although the delta increase at F_7, contralateral to the right-hand motor task, did reach one-tailed significance ($P<0.05$ paired $t=2.00$). Our difference data show that normals increase anterior frontal delta (Fp_1, Fp_2, F_7, F_8) but decrease midline (C_z) and right posterior (C_4) delta with task; Breitling et al. (1986) also present relative data maps and show a not dissimilar pattern in normals (although they do not record C_z, F_3 and F_4). In contrast, the schizophrenics seem to increase posterior frontal midline delta and decrease anterior and lateral frontal delta. Other brain lobes showed little significant delta change with task, reinforcing the importance of the frontal lobes in attentional processes, and the need to consider the motor and prefrontal areas of the frontal lobe separately in EEG studies. Thus, the largest differences between normals and schizophrenics (Table 2) are in inferior and lateral areas of the prefrontal region (F_7 and F_8) rather than over the motor area for right hand movement (C_3). This is more consistent with a difference in attentional mechanisms than with a motor performance deficit. Interestingly, the large 'eyes closed minus CPT' difference at leads F_7 and F_8 between normals and schizophrenics, approximately overlying the inferior frontal gyrus, corresponds to the area of greatest difference in glucose metabolic rate on the PET scan (Buchsbaum et al., 1989). Note that in no area did we confirm a significant delta increase with task (Table 2), although a larger sample may reveal this. Thus the possibility that

TABLE 2

Frontal lobe EEG changes in delta with task (eyes closed minus Continuous Performance Test)

	Normals			*Schizophrenics*		
Lead	*Left*	*Mid*	*Right*	*Left*	*Mid*	*Right*
Fp_1-Fp_2	−0.82		−0.82	0.95		1.02[b]
FF		−0.44			0.26	
F_z		0.09			−0.01	
C_z		0.40[a,b]			−0.31[c]	
F_3-F_4	−0.03		0.04	0.04		−0.23
F_7-F_8	−0.63[b]		−0.34	0.68[b,c]		0.76[a,c]
C_3-C_4	0.15		0.30[a]	−0.05		−0.18[c]

[a]Different between eyes closed and Continuous Performance Task (CPT), $P<0.05$, two-tailed.
[b]Different between eyes closed and Continuous Performance Task (CPT), $P<0.05$, one-tailed.
[c]Different from normal controls, $P<0.05$.

normals used more eye movements successfully to solve the CPT task and it is this eye movement masquerading as delta which appears in Table 2, is not clearly supported by the data. Finally it should be noted that with the 40 ms stimulus exposure duration, eye movements cannot be exploited to identify the stimulus.

These results, obtained in the process of replicating earlier findings of significant frontal delta increase in patients with schizophrenia, have a wider implication for future EEG studies. Our data demonstrate that different areas of the frontal lobe vary widely in their delta levels, in the effect of task on delta and perhaps even the physiological significance of the delta signal. Multilead recordings focusing on attentional task effects, separating motor and cognitive task components, and examining individual differences will need to be part of future studies. In the current study we contrast eyes closed with eyes open CPT performance; thus the condition differences may reflect non-specific changes with opening the eyes rather than a specific attention effect. Control conditions with, for example, subjects passively observing the stimuli, counting stimuli, and pressing a button in response to all stimuli, would help to separate the topographic components of vigilance.

However, our non-significant group by condition alpha effects do not support an eyes closed/open effect as the primary source of our patient group by task effect, since alpha is highly sensitive to eye closure.

Delta activity is a normal component of scalp activity in children and decreases from childhood to adulthood (Matousek and Petersen, 1973; Duffy et al., 1984). Feinberg (1982) noted that delta amplitude during sleep declines dramatically during adolescence and suggests that a defect in the maturational process (perhaps deficits in synaptic pruning) may underlie the emergence of schizophrenia at this age. Hypofrontality on PET and cerebral blood flow could be correlates of this process. However, delta activity also can appear as a pathological finding in adults. Niedermeyer and Lopes da Silva (1982) suggest that pathology in the underlying white matter and associated deafferentation of the cortex are important in this process. Thus increased delta in the frontal lobes might also be consistent with the concept of hypofrontality resulting from decreases in the mesocortical dopamine neurons that project to the prefrontal cortex (Weinberger et al., 1988). Interestingly, in topographic EEG studies (Saletu et al., 1987) the neuroleptic chlorprothixene increased microvolt delta power at all leads except three frontal leads and relative power at all leads again except three frontal and the left occipital lead. Both topographic studies of the effects of neuroleptics and longitudinal studies of patients with schizophrenia will now be increasingly important in pursuing the mechanisms of hypofrontality.

REFERENCES

Breitling, D., Guenther, W. and Rondot, P. (1986) Motor responses measured by brain electrical activity mapping. Behav. Neurosci. 100, 104–116.

Buchsbaum, M.S. and Haier, R.J. (1987) Functional and anatomical brain imaging: Impact on schizophrenia research. Schizophren. Bull. 13, 115–132.

Buchsbaum, M.S., Cappelletti, J., Coppola, R., Regal, F., King, A.C. and Van Kammen, D.P. (1982) New methods to determine the CNS effects of antigeriatric compounds: EEG topography and glucose use. Drug Dev. Res. 2, 489–496.

Buchsbaum, M.S., Rigal, F., Coppola, R., Cappelletti, J., King, C. and Johnson, J. (1982) A new system for gray-level surface distribution maps of electrical activity. Electroencephalogr. Clin. Neurophysiol. 53, 237–242.

Buchsbaum, M.S., DeLisi, L.E., Holcomb, H.H., Cappelletti, J., King, A.C., Johnson, J., Hazlett, E., Dowling-Zimmerman, S., Post, R.M., Morihisa, J., Carpenter, W., Cohen, R., Pickar, D., Weinberger, D.R., Margolin, R. and Kessler, R.M. (1984a) Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. Arch. Gen. Psychiatry 41, 1159–1166.

Buchsbaum, M.S., Mirsky, A.F., DeLisi, L.E., Morihisa, J., Karson, C.N., Mendelson, W.B., King, A.C., Johnson, J. and Kessler, R. (1984b) The Genain quadruplets: electrophysiological, positron emission and X-ray tomographic studies. Psychiatry Res. 13, 95–108.

Buchsbaum, M.S., Wu, J., Haier, R., Hazlett, E., Ball, R., Katz, M., Sokolski, K., Lagunas-Solar, M. and Langer, D. (1987) Positron emission tomography assessment of effects of benzodiazepines on regional glucose metabolic rate in patients with anxiety disorder. Life Sci. 40, 2393–2400.

Buchsbaum, M.S., Nuechterlein, K.H., Haier, R.J., Wu, J., Sicotte, N., Hazlett, E., Asarnow, R., Potkin, S. and Guich, S. (1989) Glucose metabolic rate in normals and schizophrenics during the continuous performance test assessed by positron emission tomography. Br. J. Psychiatry, in press.

Cohen, R.M., Semple, W.E., Gross, M., Nordahl, T.E., DeLisi, L.E., Holcomb, H.H., King, C.A., Morihisa, J.M. and Pickar, D. (1987) Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. Life Sci. 40, 2031–2039.

Coppola, R. (1979) Isolating low frequency activity in EEG spectrum analysis. Electroencephalogr. Clin. Neurophysiol. 46, 224–226.

Cornblatt, B.A., Risch, M.J., Farris, G., Friedman, D. and Erlenmeyer-Kimling, L. (1988) The CPT, identical pairs version (CPT-IP): I. New findings about sustained attention in normal families. Psychiatry Res. 26, 223–238.

Dixon, W.J. (1981) BMDP Statistical Software. University of California Press, Berkeley, CA, pp. 388–412.

Duffy, F.H., Albert, M.S., McAnulty, G. and Garvey, A.J. (1984) Age-related differences in brain electrical activity of healthy subjects. Ann. Neurol. 16, 430–438.

Feinberg, I. (1982) Schizophrenia: Caused by a fault in programmed synaptic elimination during adolescence? J. Psychiatr. Res. 17, 319–334.

Guenther, W. and Breitling, D. (1985) Predominant sensorimotor area left hemisphere dysfunction in schizophrenia measured by brain electrical activity mapping. Biol. Psychiatry 20, 515–532.

Guenther, W., Davous, P., Godet, J.-L., Guillibert, E., Breitling, D. and Rondot, P. (1988) Bilateral brain dysfunction during motor activation in type II schizophrenia measured by EEG mapping. Biol. Psychiatry 23, 295–311.

Hoagland, H. (1938) Electro-encephalograms in schizophrenia. Am. J. Psychiatry, Vol. 95.

Ingvar, D.H. and Franzen, G. (1974) Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. Acta Psychiatr. Scand. 50, 425–462.

Ingvar, D.H., Sjolund, B. and Ardo, A. (1976) Correlation between dominant EEG frequency, cerebral oxygen uptake and blood flow. Electroencephalogr. Clin. Neurophysiol. 41, 268–276.

Itil, T.M. (1977) Qualitative and quantitative EEG findings in schizophrenia. Schizophren. Bull. 3, 61–79.

Jasper, H.H., Fitzpatrick, C.P. and Solomon, P. (1939) Analogies and opposites in schizophrenia and epilepsy. Electroencephalographic and clinical studies. Am. J. Psychiatry 95, 835–851.

Karson, C.N., Coppola, R., Morihisa, J.M. and Weinberger, D.R. (1987) Computed electroencephalographic activity mapping in schizophrenia. The resting state reconsidered. Arch. Gen. Psychiatry 44, 514–517.

Lee, S. and Buchsbaum, M.S. (1987) Topographic mapping of EEG artifacts. Clin. Electroencephalogr. 18, 61–67.

Lifshitz, K. and Gradijan, J. (1972) Relationships between measures of the coefficient of variation of the mean absolute EEG voltage and spectral intensities in schizophrenic and control subjects. Biol. Psychiatry 5, 149–163.

Lukoff, D., Nuechterlein, K.H. and Ventura, J. (1986) Manual for expanded brief psychiatric rating scale (BPRS). Schizophren. Bull. 12, 594–602.

Matousek, M. and Petersen, I. (1973) Frequency analysis of the EEG in normal children and adolescents. In: P. Kellaway and I. Petersen (Eds.), Automation of Clinical Electroencephalography. Raven Press, New York, pp. 75–102.

Morihisa, J.M., Duffy, F.H. and Wyatt, R.J. (1983) Brain electrical activity mapping (BEAM) in schizophrenic patients. Arch. Gen. Psychiatry 40, 719–728.

Morstyn, R., Duffy, F.H. and McCarley, R.W. (1983) Altered topography of EEG spectral content in schizophrenia. Electroencephalogr. Clin. Neurophysiol. 56, 263–271.

Niedermeyer, E. and Lopes da Silva, L. (1982) Electroencephalography. Urban and Schwarzenberg, Baltimore, MD, pp. 152–153.

Nuechterlein, K.H. and Dawson, M.E. (1984) Information processing and attentional functioning in the developmental course of schizophrenic disorders. Schizophren. Bull. 10, 160–203.

Nuechterlein, K.H., Parasuraman, R. and Jiang, Q. (1983) Visual sustained attention: Image degradation produces rapid decrement over time. Science 220, 327–329.

Overall, J.E. and Gorham, D.R. (1962) The brief psychiatric rating scale. Psychol. Rep. 10, 799–812.

Saletu, B., Anderer, P., Kinsperger, K. and Grunberger, J. (1987) Methods Find. Exp. Clin. Pharmacol. 9, 385–408.

Tarrier, N., Cooke, E.C. and Lader, M.H. (1978) The EEG's of chronic schizophrenic patients in hospital and in the community. Electroencephalogr. Clin. Neurophysiol. 44, 669–673.

Tolonen, U. and Sulg, I.A. (1981) Comparison of quantitative EEG parameters from four different analysis techniques in evaluation of relationships between EEG and CBF in brain infarction. Electroencephalogr. Clin. Neurophysiol. 51, 177–185.

Weinberger, D.R., Berman, K.F. and Illowsky, B.P. (1988) Physiological dysfunction of dorsolateral prefrontal cortex in schizophrenia. III. A new cohort and evidence for a monoaminergic mechanism. Arch. Gen. Psychiatry 45, 609–615.

Williamson, P. and Mamelak, M. (1987) Frontal spectral EEG findings in acutely ill schizophrenics. Biol. Psychiatry 22, 1021–1024.