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Correlation of qEEG with PET in Schizophrenia

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Abstract
PET relative metabolism was correlated with quantitative EEG in 9 schizophrenic patients. The PET metabolic regions of interest were the frontal lobes, thalamus and basal ganglia, and right and left temporal lobes. Significant positive correlations were seen for the frontal lobes and delta EEG power, and alpha power with subcortical metabolism. The physiologic plausibility of those correlations is discussed with reference to the possible effect of neuroleptic medication.

Introduction

The correlation of the EEG and metabolism may provide a heuristically useful approach to the question of the generation of the EEG. Electrophysiologic measurements obtained from the scalp are direct consequences of the firing and membrane potential shifts of populations of neurons, events which require metabolic energy. It therefore seems reasonable to expect that electrophysiology and metabolism are correlated and this correlation may contribute some understanding to the generation of the EEG.

A common finding in studies correlating metabolism or regional cerebral bloodflow (rCBF) with quantitative EEG (qEEG) is a significant negative correlation of qEEG slow activity to metabolism or rCBF. However, a simple correlation between qEEG mean frequency content and rCBF or metabolism appears to be more characteristic of states of frank neurologic pathology such as primary dementia or cerebrovascular disease. Across four studies making comparisons between healthy controls and dementia patients [1, 2], or between hemispheres in the presence of a unilateral infarct [3, 4], the variance of qEEG explained by rCBF or metabolism was relatively greater either in the demented subjects or the infarcted hemisphere. The limited investigations that have reported on normals or schizophrenics suggest the lack of a simple relationship or qEEG frequency content to metabolism. Buchsbaum et al. [5] found both positive and negative correlations with either delta or alpha power to positron emission tomography (PET) metabolism in normals in the eyes closed resting state depending on which topographic region was examined. In a subsequent report on schizophrenics [6], PET metabolism measured during a continuous performance task correlated negatively with frontal EEG delta power during the task, and positively with occipital EEG delta power at rest.

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Table 1. Patient characteristics

Patient No.	Age years	Education years	Diagnosis	Duration of illness years	Medication	BPRS	AIMS PET and EEG	Interval (days) between
1	33	12	Undifferentiated	20	Off	42	0	1[a]
2	32	12	Paranoid	10	On	32	12	7[b]
3	36	11	Paranoid	15	On	22	0	7[b]
4	28	9	Undifferentiated	9	On	24	6	7[b]
5	22	10	Paranoid	5	Off	37	0	1[b]
6	43	6	Disorganized	20	On	32	1	6[b]
7	27	11	Undifferentiated	11	On	30	0	1[a]
8	35	12	Paranoid	9	On	26	0	1[a]
9	33	13	Disorganized	14	On	36	18	1[a]

[a] These patients were studied with qEEG once, 1 day after their PET study.
[b] There patients were studied with qEEG twice; simultaneously with PET study and again subsequent to the PET study.

The opportunity to observe correlations between resting EEG and PET metabolism in schizophrenics arose in the context of a study of the metabolic correlates of a motor task in schizophrenia that has been published elsewhere [7]. As this study involved PET measurements obtained at rest in schizophrenics, it was possible to also additionally obtain resting EEG measurements. This present study reports on the correlation of qEEG and PET in a sample of 9 schizophrenics. One objective of this preliminary investigation was to examine the topography of PET and qEEG correlations. In addition, it was also possible to examine the question of the possible effect of the PET laboratory environment on the qEEG by obtaining EEG from the same subjects simultaneously with the PET scan, and again subsequently in the environment of the EEG laboratory.

Subjects and Methods

Nine patients meeting DSM-III-R and RDC criteria for schizophrenia were studied in this investigation with PET and EEG. These subjects are a subset of those reported in Günther et al. [7]. Subject characteristics are summarized in table 1. Seven subjects were on neuroleptic medication at the time of the study, in all medicated patients the neuroleptic medication used was haloperidol in either the oral or decanoate form with oral dosages ranging from 10 to 40 mg per day and 1 patient on haloperidol 10 mg per day and decanoate 150 mg every 4 weeks. Two subjects had been off medication for at least 1 year prior to the study. No other psychotropic medication had been used for at least 1 month prior to the study, with the exception of benzodiazepine hypnotics which were withheld the night prior to the study. Subjects with histories of substance abuse, head trauma with loss of consciousness, encephalitis, or other neurologic conditions known to affect the EEG were excluded from the study. Ratings on the Brief Psychiatric Rating Scale (BPRS) [8] and Abnormal Involuntary Movement Scale (AIMS) [9] were obtained the day prior to the PET study.

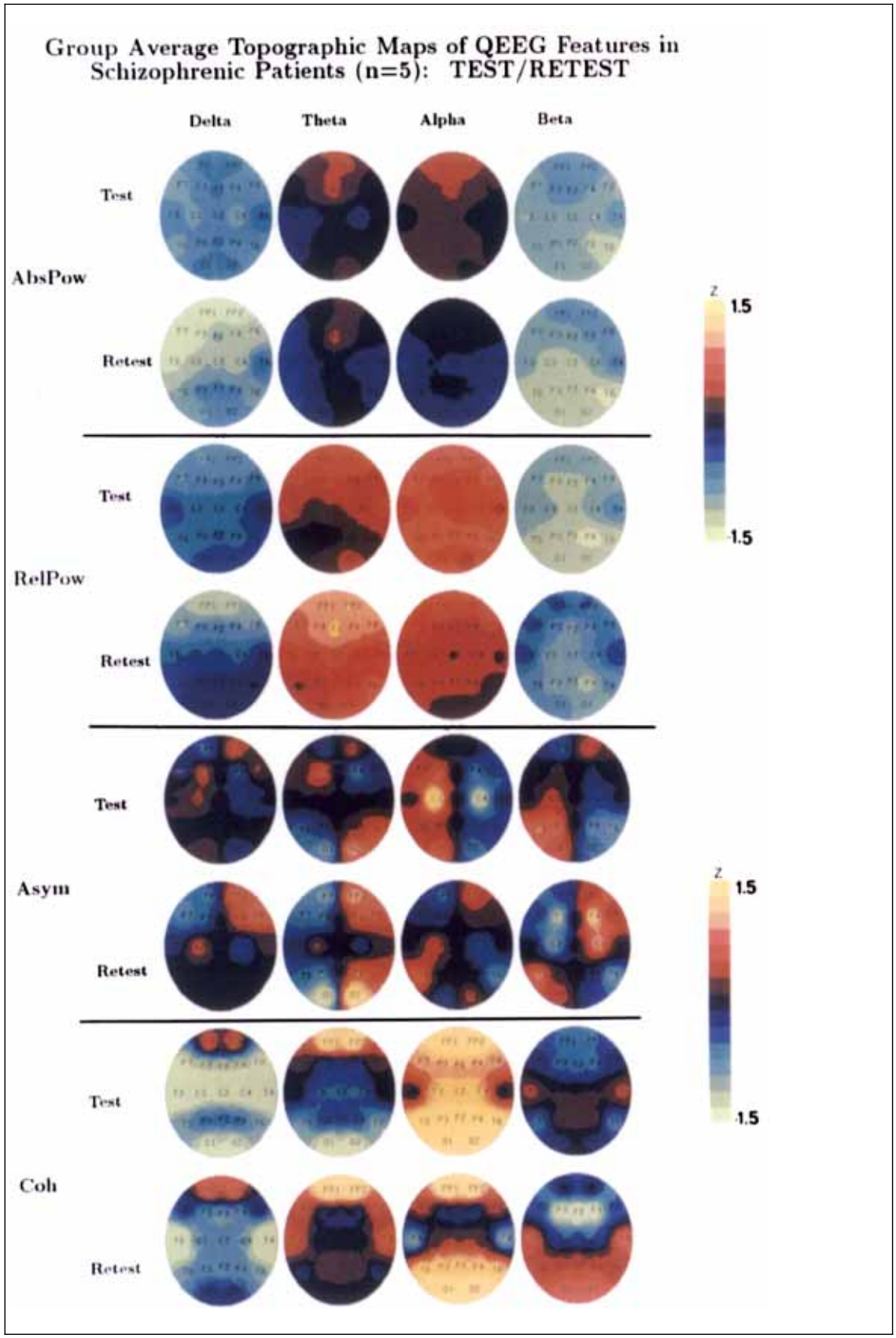
For 5 of the 9 subjects EEG and PET were obtained simultaneously in real time at the Brookhaven National Laboratory. Additionally, EEG data was obtained on all 9 subjects subsequent to the PET scan at Brain Research Laboratories at New York University Medical Center. The interval between the PET study with or without EEG simultaneous at Brookhaven, and the EEG study at Brain Research Laboratories are provided in table 1. For the 5 subjects on whom EEG simultaneous was available, the EEG obtained simultaneously with PET was used to compute PET/EEG correlations. In the 4 subjects without simultaneous EEG, the EEG obtained at Brain Research Laboratories subsequent to the PET scan was used. To address the question of the reliability between EEG simultaneous with PET and EEG obtained subsequent to the PET scan, test-retest comparisons were examined for EEG on subjects for whom both simultaneous and nonsimultaneous EEG data were available. As seen in figure 1, the test-retest comparisons showed generally good replicability of EEG obtained during the PET scan and EEG subsequent to the PET scan.

EEG Data Acquisition

EEG data were collected using 19 electrodes placed in accordance with the International 10/20 system, referenced to linked earlobes. All electrode impedances were less than 5,000 Ω. Amplifier bandwidth was from 0.5 to 70 Hz (3 dB points), with a 60-Hz notch filter; sampling rate was 200 Hz.

Data Analysis

EEG Feature Extraction. The neurometric EEG feature extraction methods used have been described in detail previously [10]. One to two minutes of artifact-free data were extracted from the EEG


Group Average Topographic Maps of QEEG Features in Schizophrenic Patients (n=5): TEST/RETEST
Delta
Theta
Alpha
Beta
Test
AbsPow
Retest
Test
RelPow
Retest
Test
Asym
Retest
Test
Coh
Retest
Z
1.5
-1.5
Z
1.5
-1.5

recorded for quantitative analysis, with the aid of a computerized artifact detection algorithm. All epochs selected for analysis were visually reviewed by one of the authors to exclude any artifacts which eluded this algorithm. Univariate features were computed for absolute and relative power, coherence and asymmetry in four frequency bands (delta, 1.5–3.5 Hz; theta, 3.5–7.5 Hz; alpha, 7.5–12.5; beta, 12.5–25 Hz) for the 19 monopolar derivations. Each feature was compared with normative age-regression equations to obtain Z scores, after transformations to ensure Gaussianity.

PET Scan Procedures

All subjects were scanned in the low-resolution mode on the PET VI at Brookhaven National Laboratory (spatial resolution at full width of half-maximum = 11.8 mm in the plane of section and 14.4 mm in the axial direction). Prior to the first isotope injection each subject's head was positioned in a plane parallel to the canthomeatal line. Transmission scans were the performed using a $^{68}Ge/^{68}Ga$ ring source. These were used for attenuation correction and to define the size and center of the brain for each PET image. Catheters were inserted into a dorsal vein for isotope administration 45 min before the first injection. Each subject's left hand was heated to maintain skin temperature 44 °C in order to arterialize venous blood [11].

The plasma input function was determined for multiple sampling of the arterialized blood prior to and for 35 min after injection of the ^{11}C-2-deoxyglucose (CDG). Each subject received an injection of a bolus of between 5.8 and 6.5 mCi of CDG each [12], administered at approximately 10.30 a.m. Scans were obtained at 35 min and again at 45 min after injection. Seven simultaneous images were obtained from each scan. After the 35-min scan the subject was moved 7.2 min, which resulted in a set of 14 interleaved PET images slightly displaced in time. Calculation of the normalized regional metabolic rates of glucose metabolism was performed as previously described in Bartlett et al. [13]. The calculation of normalized regional metabolic rates by this method yields measures that have been demonstrated to be highly reproducible on the order of 1%.

Regions of interest (ROIs) were obtained from nine contiguous images located between approximately 10.3 and 4.7 cm above the canthomeatal line. MRI or CT images from approximately the same planes of section were transferred by computer software onto corresponding metabolic images. The ROIs utilized in this paper are derived from those utilized by Günther et al. and are composites that subsume the smaller ROIs presented in Günther et al. [7]. In the present study 'frontal' combines the mesial frontal region anterior to the central sulcus, and the right prefrontal and left prefrontal regions. 'Subcortical' combines the right and left thalamus and basal ganglia, and 'right temporal' and 'left temporal' are the same as the correspondingly named ROIs in Günther et al. [7]. A detailed figure illustrating the boundaries of those ROIs utilized by Günther et al. [7] is available in that paper.

Correlations between PET ROIs and neurometric Z scores were computed using the Pearson r. For n = 9 (d.f. = 7), at p = 0.05, r = 0.67.

Results

Figure 1 shows the test-retest comparison for EEG obtained on 5 subjects during PET scan, and then subsequent to the PET scan at the EEG lab. The issue of test-retest reliability between qEEG measures is relevant to the validity of including the 4 subjects without EEG obtained simultaneously with PET in the calculation of PET/EEG correlations. The test-retest interval for EEG on the 5 subjects obtained during and after the PET scan was 5.6 (range 1–7) days. The test-retest interval for each of the other 4 subjects whose EEG was only obtained subsequent to PET was 1.0 ± 0 days.

As is evident from figure 1, there is little change in qEEG values for the 5 subjects examined both simultaneously with and subsequent to PET. The apparent lack of change indicates that there is little difference between qEEG values obtained under the conditions and environment of the PET scan and a mean of 5.6 days later in the EEG lab. The time interval between PET and retest qEEG in these 5 subjects is greater than the 1 day separating the PET and EEG studies of the other 4 subjects. It can be argued, therefore, that the test-retest results for the 5 subjects with EEG in both states is conservative in providing evidence for the validity of including EEG data obtained from the other subjects whose EEG was obtained only subsequent to the PET study.

Figure 2 shows maps of the correlations between relative PET metabolism in each of 4 PET ROIs and qEEG for all 9 subjects. The correlations for relative power are divided into the delta, theta, alpha and beta bandwidths, and the correlations with mean frequency are for the entire frequency spectrum of 1.5–25 Hz. The PET ROIs, each of which is correlated separately with the 4 relative power measures and 1 overall EEG frequency measure, are frontal, subcortical, and left and right temporal (see PET methodology).

For the delta bandwidth, there is an apparently positive correlation with the frontal PET ROI in anterior leads. There is generally negative correlation of relative delta power with subcortical metabolism. For the cortical PET ROIs (frontal, left temporal and right temporal) there is a general topographic pattern of positive correlations anteriorly and negative correlations posteriorly. The topography of correlations of relative theta power shows a rough similarity to those for relative delta power.

For the alpha relative power bandwidth, there is a general topographic pattern of PET/qEEG correlation that is the inverse of that for delta and theta. The cortical PET regions generally correlate negatively with relative alpha

Fig. 1. Test-retest EEG data on 5 subjects evaluated simultaneously with PET scanning and again subsequently a mean of 5.6 days later in the EEG lab.

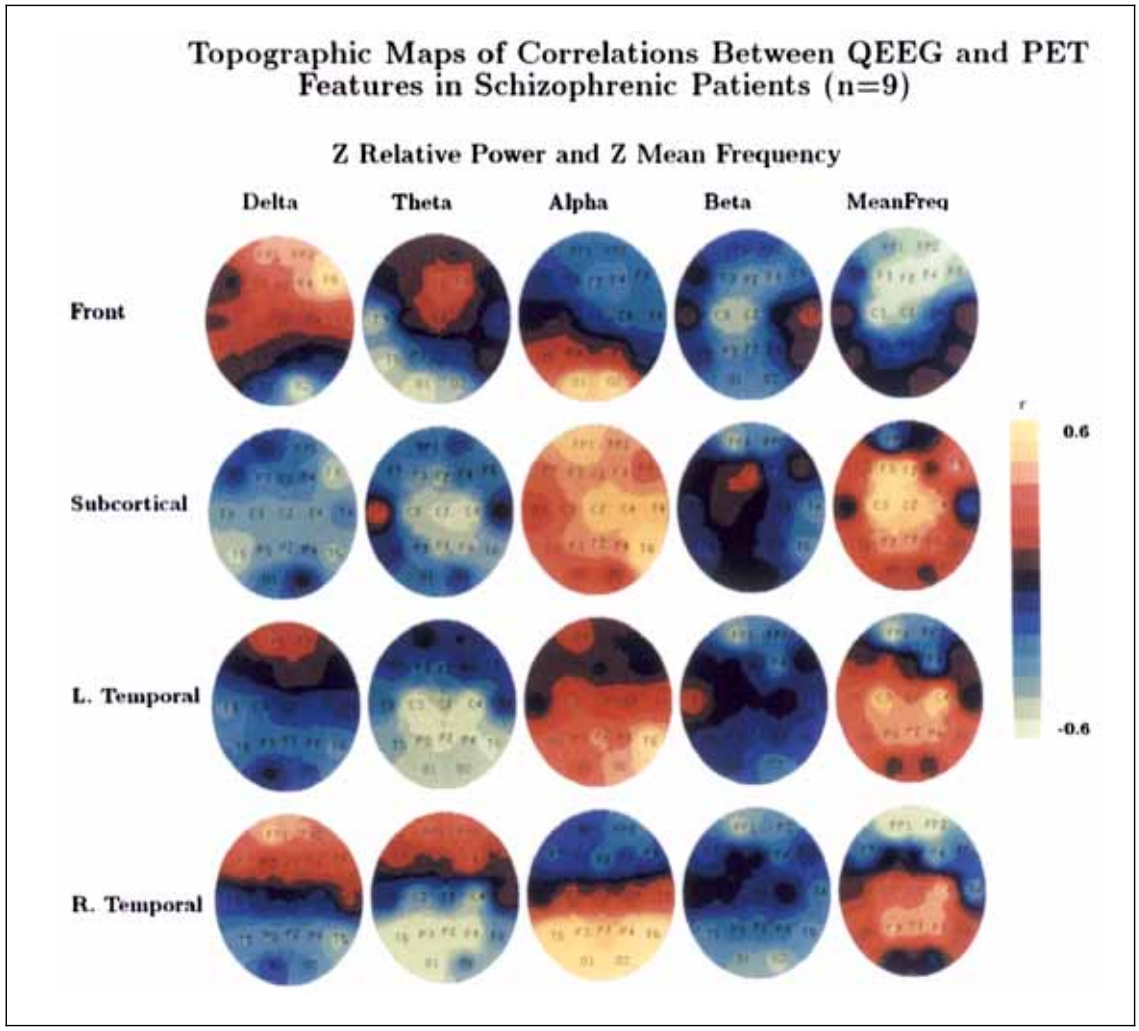


Fig. 2. Correlations of each of the 4 PET ROIs with absolute and relative power in the delta, theta, alpha, and beta bandwidths, and mean frequency across the frequency spectrum of 1.5–25 Hz.

anteriorly and positively posteriorly. Beta relative power tends to correlate negatively with all PET ROIs, however the magnitude of most correlations is low.

The values for overall mean frequency tend to conform with the expectation that would be derived from inspection of the maps for delta and alpha. Where alpha tends to correlate positively with PET, mean frequency also tends to correlate positively with PET. Where PET and delta relative power correlated positively, the correlations for mean frequency and PET tend to be negative.

Discussion

The results presented in figure 1 indicate good test-retest reliability between qEEG measures obtained simultaneously with PET and those obtained subsequent to PET in the EEG lab. These results are consistent with previous work on the test-retest reliability of the qEEG [14–16]. The neurometric methodology may be particularly helpful in this regard. The normative data, from which the confidence limits of neurometrics Z scores are derived, intentionally does not control for certain factors and treats them as normal variance. For example, the normal subjects in the neurometric data base were tested without controlling rigorously for time of day and at several differ-

ent sites. Such an approach increases the confidence limits of the normal data which mitigates against falsely positive values deriving from overly rigid or specific testing parameters. The multiple replications of the neurometric norms [17–22] provide substantiative empirical justification for this approach. In the present study, the inclusion of the incidental effects of differing laboratory environments in the confidence limits of the norms against which the qEEG data was referenced may have mitigated against spurious changes due to laboratory environment. The test-retest reliability of the data obtained from the 5 subjects simultaneous and subsequent to PET supports the validity of having included the other 4 subjects whose data was only obtained subsequent to PET.

One result that might be viewed as somewhat surprising is that a positive relationship was seen between frontal PET metabolism and relative delta qEEG power. The well known entity of pathological polymorphic delta has been correlated with anoxia and functional deafferentation of the cortex [23, 24], and often leads to the assumption of a general association of delta activity with depressed cerebral metabolism. However, approximately 20–30% of the voltage of awake normal humans in anterior leads is in delta as revealed by multiple replicated studies [17–22]. Increased delta activity has been correlated with a number of presumably metabolically activating states in normal awake humans such as the performance of calculations [25], reaction time tests [26], abstract thought [27] or an omitted stimulus paradigm [28]. The frontal localization of the apparently positive correlation between delta and PET also may be regarded as consistent with the contention that this may be a valid reflection of physiology and not accidental artifact. Such a contention receives support from the putative role of the forebrain in the normal generation of delta power and from studies utilizing dipole analysis that place the site of maximum delta generation in normals in the frontal cortex [27, 29].

The apparent phenomena whereby metabolism and EEG appear to correlate more strongly in the presence of ischemic or primary dementia injury than in the absence of frank neurologic pathology [1–4] also suggest the possibility that normal physiologic determinants of slow activity exist that are part of the normative frequency content of the EEG and not of exclusively pathological origin. This view appears to receive some support from the literature on normal controls and psychiatric patients. Okyere et al. [30] reported a significant positive correlation of qEEG amplitude, as opposed to frequency with CBF in normals, and did not observe a significant relationship of CBF to qEEG frequency. Modulations of qEEG amplitudes by normal metabolism could produce changes in the correlation of the spectral content of the qEEG with metabolism in a way different from that which has been reported for dementia. Metabolic modulation of qEEG amplitude could be logically expected to permit the dissociation of qEEG slowing from decreased metabolism and could even possibly account for a positive correlation of qEEG slow activity with metabolic activation.

The positive correlation of alpha power with subcortical metabolism may well be an epiphenomenon related to neuroleptic medication. Reduced alpha power in schizophrenia is a well replicated finding in the qEEG literature [31]. Neuroleptic medication reportedly increases alpha [32–35], and also subcortical metabolism [36]. The apparently positive correlation between subcortical metabolism and alpha power seen in this study may simply reflect neuroleptic-related increases in both alpha power and subcortical metabolism and not necessarily a direct causal association.

The small number of subjects and the medicated state of most of the patients are significant limitations of this present study. Nonetheless, the correlation of metabolism with EEG is an arguably interesting heuristic approach to understanding the metabolic basis of the EEG. Logical directions for extending the results presented here include studying PET and EEG in normal subjects, medication-free patients and of course independently replicating the preliminary results on the small sample of patients presented here.

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