Quantitative Electroencephalographic Comodulation: An Investigation of Patterns in Chronic Fatigue Syndrome

Tamara D. Lorensen BSc and Grad Dip [a][b] & Kathryn M. Gow PhD [c]

[a] School of Psychology and Counseling, Queensland University of Technology, Faculty of Health , Brisbane, Australia

[b] Neurotherapy Centre , Brisbane, Australia

[c] School of Psychology and Counseling, Queensland University of Technology, Faculty of Health , Carseldine Campus, Brisbane, Australia
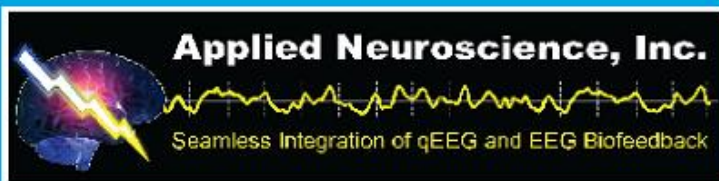Published online: 07 Sep 2008.

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SCIENTIFIC ARTICLE

Quantitative Electroencephalographic Comodulation: An Investigation of Patterns in Chronic Fatigue Syndrome

Tamara D. Lorensen, BSc, Grad Dip
Kathryn M. Gow, PhD

ABSTRACT. *Introduction*. This is a pilot study of quantitative electro-encephalographic (QEEG) comodulation analysis, which is used to assist in identifying regional brain differences in those people suffering from chronic fatigue syndrome (CFS) compared to a normative database. The QEEG comodulation analysis examines spatial-temporal cross-correlation of spectral estimates in the resting dominant frequency band. A pattern shown by Sterman and Kaiser (2001) and referred to as the an-

terior posterior dissociation (APD) discloses a significant reduction in shared functional modulation between frontal and centro-parietal areas of the cortex. This research attempts to examine whether this pattern is evident in CFS.

Method. Eleven adult participants, diagnosed by a physician as having CFS, were involved in QEEG data collection. Nineteen-channel cap recordings were made in five conditions: eyes-closed baseline, eyes-open, reading task one, math computations task two, and a second eyes-closed baseline.

Results. Four of the 11 participants showed an anterior posterior dissociation pattern for the eyes-closed resting dominant frequency. However, seven of the 11 participants did not show this pattern. Examination of the mean 8-12 Hz amplitudes across three cortical regions (frontal, central and parietal) indicated a trend of higher overall alpha levels in the parietal region in CFS patients who showed the APD pattern compared to those who did not have this pattern. All patients showing the pattern were free of medication, while 71% of those absent of the pattern were using antidepressant medications.

Conclusions. Although the sample is small, it is suggested that this method of evaluating the disorder holds promise. The fact that this pattern was not consistently represented in the CFS sample could be explained by the possibility of subtypes of CFS, or perhaps co-morbid conditions. Further, the use of antidepressant medications may mask the pattern by altering the temporal characteristics of the EEG. The results of this pilot study indicate that further research is warranted to verify that the pattern holds across the wider population of CFS sufferers.

INTRODUCTION

Diffuse somatic complaints are commonly expressed by sufferers of anxiety and depressive disorders, sleep disorders, somatoform disorders and chronic fatigue syndrome (CFS). The use of many diagnostic tests including psychological batteries, blood assays, biochemical assays, and various imaging methods, while having contributed to an increased understanding of these various complaints, still leave diagnoses, evaluations and treatment options open to

varied interpretations by professionals. This is due to the very nature of the diffuse problems that patients experience. It has been observed in one imaging method, the quantitative electroencephalographic (QEEG) analysis, that patients presenting with somatic complaints, similar to the diagnosis of CFS, show a unique QEEG pattern (Sterman, 2001). Just what this pattern means, and how it may differentiate this subgroup from normal QEEG patterns, is not yet clear.

This paper explores the QEEG phenomena associated with CFS and aims to instigate an empirically based description of what may be QEEG characteristics of the sub-groups who demonstrate the pattern called the anterior posterior dissociation (APD) pattern. The goal in this study has not been to diagnose or determine causality, but to search for previously unrecognised functional regional brain differences in the central nervous system. Hence an inductive research strategy has been used.

The research has several objectives: (a) to investigate whether the APD pattern is a non-random event and/or is reliably associated with CFS, (b) to determine whether this QEEG pattern is consistent in its variation from the normative database, and (c) to investigate other factors that may interact with the expression of this pattern.

The patient populations suffering from CFS, somatic disorders, diffuse anxiety and pain as well as poor sleep are poorly defined and the clinical disorders show significant overlap in subjective complaints (Demitrak & Greden, 1991; Kruesi, Dale, & Straus, 1989; Manu, Lane, & Matthews, 1989). Therefore, these groups are particularly homogeneous with respect to subjective complaints and concerns and evaluations made by professionals.

A recent review by Evengard, Schacterle, and Komaroff (1999) provides an extensive overview of the current state of affairs in the understanding of CFS. It is clear that the origin of chronic fatigue is variable and complex, and debate continues to occur around its aetiology and diagnosis. The United States Centers for Disease Control and Prevention (Fukuda, 1994) provides a case definition of CFS, which is summarized below. These authors suggest that patients can often receive either inadequate or excessive evaluations of CFS by various professionals. While some professionals diagnose CFS in isolation, there is also a significant overlap with other disorders (Kruesi et al., 1989; Manu et al., 1989). Research has been conducted using comparative groups in which CFS has been shown to have no significant differences (Marshall, 1997), and conversely significant differences (Sandman, 1993) between control groups and psychiatric groups. Treatment outcome studies also show variable results similar to the results of studies of initial evaluations and diagnosis. Such variations amongst individuals lead us to question whether this may be indicative of sub-types of CFS, or whether an extended evaluation may reveal other types of pathology.

The United States Centers for Disease Control and Prevention provides a current case definition for chronic fatigue syndrome and stresses the appearance of somatic symptoms (see Table 1).

In the literature examined to date there is some agreement among treating professionals and researchers about the symptoms experienced (Kruesi et al., 1989; Manu et al., 1989; Michiels & Cluydts, 2001) by CFS sufferers. This includes not only debilitating fatigue, but also somatic (muscle pain, sore throat), psychopathological (depression and anxiety), and neuropsychological symptoms (poor memory and attention), all of which vary in severity and subjective focus or concern.

Many of the symptoms of CFS also suggest involvement of the central nervous system (CNS). Researchers have attempted to look for objective evidence utilising neuroimaging methods. Primarily this has occurred through the use of magnetic resonance imaging (MRI), which has shown evidence that there are white matter abnormalities in CFS groups that are not present in nor-

TABLE 1. United States Centers for Disease Control and Prevention Current Case Definition for Chronic Fatigue Syndrome.

Severe fatigue that persists or relapses for $\geq$ 6 months
Exclude if patient found to have:
1. Active medical condition that may explain the chronic fatigue, such as untreated hypothyroidism, sleep apnoea, narcolepsy;
2. Previously diagnosed medical conditions that have not clearly fully resolved, such as previously treated malignancies or unresolved cases of hepatitis B or C infections;
3. Any past or current major depressive disorder with psychotic or melancholic features; bipolar affective disorders, schizophrenia, delusional disorders, dementias, anorexia nervosa, or bulimia nervosa;
4. Alcohol or other substance abuse within two years before the onset of chronic fatigue and at any time afterward; and
5. Severe obesity as defined by BMI
Classify as chronic fatigue syndrome if:
Sufficiently severe: of new or definite onset (not lifelong) not substantially alleviated by rest, and results in substantial reduction in previous levels of occupational, educational, social or personal activities; and Four or more of the following symptoms are concurrently present for $\geq$ 6 months:
1. impaired memory
2. sore throat
3. tender cervical or axillary lymph nodes
4. muscle pain
5. multi-joint pain
6. new headaches
7. unrefreshing sleep
8. post-exertional malaise

mal controls (Natelson, Cohen, Brasselhoff, & Lee, 1993). Single photon emission computed tomography (SPECT) research has also demonstrated abnormalities in perfusion or CNS cellular function in CFS groups compared to normal controls (Ichise, Salit, & Abbey, 1992). Again, the findings showed mixed results (Michiels, 2001), with no conclusive patterns arising that are consistently associated with CFS. In addition, Evengard (1999) has stated that neural imaging techniques have not been widely used and therefore the optimal use of imaging methods in increasing our understanding of CFS is not yet known.

The imaging method of QEEG holds promise for examining this difficult-to-define disorder because of its features of normative database comparison, non-invasive methods of data acquisition, and cost effectiveness.

In the late 1980s, a report published by researchers John (1989) and Fisch and Pedley (1989) attempted to debate the 'pros' and 'cons' with respect to the efficacy of quantitative EEG mapping. These include concerns such as the type of instrumentation utilized, the actual data reduction methods, the normative database used, and other methodological issues. More recently, Kaiser (2000) has suggested that it is not a lack of methodological rigor, but a lack of methodological standards appropriate to EEG analyses that reinforces any erroneous characterization of QEEG.

Likewise, Hughes and John (1999) report that QEEG mapping in the last decade has shown itself to remain highly reliable. This review pointed out that the electrical activity of the brain is homeostatically regulated which results in a predictable frequency composition of the background EEG. Several other studies have also shown that the quantitative values in normal healthy functioning individuals have little deviation and are independent of ethnicity. When similar methodologies have been compared, there has been good agreement between the different studies and high specificity and sensitivity of the QEEG (Kaiser, 2000).

Sterman and Kaiser (Sterman-Kaiser Imaging Laboratory, 2000), in a continued effort to address any shortcomings in quantitative electroencephalographic (QEEG) evaluation, developed a program that has further improved the quality, reliability and sensitivity of evaluation. This has included the ability to adjust for time of day diurnal rhythms, the ability to remontage the recorded data to offset the possible distortions caused by common-mode rejection when ear references are used, and the ability to specify frequency widths in the analysis (Kaiser, 2000). Included in the metric evaluation is the ability to quantify temporal synchrony between recording sites, which Sterman labelled 'comodulation.' This metric uses a multi-site cross correlation coefficient analysis of sequential spectral density estimates in frequency bands between 1-23 Hz. This differs from the previously available method of coherence measures, which determine coincident frequency and waveform characteristics. Comod-

ulation evaluates both the frequency and time domain or temporal correspondence of variation in spectral density between sites. The ability to use this metric allows investigation of putative thalamocortical comodulation of the EEG and provides insight into the neural dynamic network.

Sterman (2001) has empirically identified a specific comodulation pattern. This anterior-posterior dissociation (APD) pattern occurs primarily in the alpha (8-12 Hz) range, but is found to be most evident in the individual's true mean peak frequency range, as determined by single hertz analysis of data collected during the eyes-closed condition. While the sample is small, common features among the client presenting problems are somatisizing, anxiety, diffuse pain, sleep problems and anxiety. These subjects showed a lack of the normal or expected degree of shared comodulation between anterior and posterior regions when compared to a normative database.

Demitrak and Greden (1991) clearly stated that what is necessary for a more complete understanding of CFS and associated disorders is an integrative interdisciplinary approach to studies in this area, and this is further supported by Lawrie, Machale, Power, and Goodwin (1997), who state that there is a polarization of psychiatric explanations and physical explanations. Lawrie et al. (1997) considered that the addition of neuroscience to the study of CFS would result in a more unifying understanding of the condition. It appears that the new metric of comodulation may shed light on our understanding of this condition and particularly in the investigation of the anterior posterior comodulation pattern as it relates to CFS.

It is expected that the QEEG patterns of interest will not be consistently represented in the CFS sample, because of the heterogeneity of the population as indicated in the literature.

METHODS

Participants. The participants were seven female and four male subjects with CFS (N = 11) as diagnosed by their specialist physicians' clinics in Brisbane, Queensland, Australia. Their ages ranged from 37 to 63 years (*M* = 48 years). Physicians were provided with an introductory letter detailing the research and requesting that an invitation to participate be passed on to potential participants. Included in the physician's letter was a requirement that the patient had been diagnosed with CFS and that those patients who were minors, intellectually impaired, non-English speaking, or with psychiatric diagnoses were to be excluded.

Participants then contacted the researcher for inclusion in the study. Signed consent forms were obtained from all participants. Details of the demographic, medical, and work-status data are included in Table 2.

TABLE 2. Demographic Information.

Client	Meds.	Time with CFS	Age at Onset	Work Impaired	AP Pattern
R1 F	Nil	5 yrs	32	Yes	No
R2 F	Antidep.	13 yrs	33	Disability	No
R3 M	Antidep.	6 yrs	41	Disability	No
R4 F	Nil	6 yrs	50	Disability	No
R6 M	Antidep.	8 yrs	48	Disability	No
R7 F	Antidep.	5 yrs	50	Disability	No
R8 F	Antidep.	6 yrs	57	Retired	No
R9 M	Nil	3 yrs	35	Working	Yes
R10 F	Nil	9 yrs	43	Working	Yes
R11 M	Nil			Working	Yes
R12 F	Nil			Working	Yes

Design. To determine systematic differences between subject variables, a natural groups design was selected. Using this design, a comparison could be made against a selected normative database to determine evidence of the APD pattern. The objective of this study was not to determine causality, but to investigate incidence. Participants were matched for age and recording time of day against the normative database. To reduce any possibility of confounding by environmental factors, all participants were recorded at the same time of the day (9:30 a.m. to 11:00 a.m.), in the same room, and by the same technician. All procedures were standardized with respect to the sequence of the procedures.

Materials. The Symptom Checklist-90-R (Derogatis, 1994) was used. It is a 90 item self-report inventory designed to evaluate a current point in time (the past seven days including the current day psychological distress). Each item is rated on a five-point scale of distress (0-4) ranging from "Not at All" to "Extremely." The test is scored and interpreted with respect to nine primary symptom dimensions. These include: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. There are also three global indices: global severity index, positive symptom distress index and positive symptom total. The global indices were developed to provide flexibility in overall assessment and the ability to summarise the levels of symptomatology and psychological distress. The manual provides norms for non-patient as well as inpatient groups.

Reliability has been established through two methods: internal consistency and test-retest reliability. Internal consistency coefficients ranged across the nine dimensions from .77 for Psychoticism (lowest) to .90 for Depression

(highest). The test-retest coefficients ranged between .80 and .90 for measures of symptom constructs.

Electrophysiological Procedures. EEG was acquired and digitized on a Lexicor NRS-24 (USA) using software version 1.5. The QEEG recording system used a sampling rate of 128 Hz resulting in two-second epochs and high and low pass filtering at 2 Hz and 37 Hz, respectively. Data were stored on computer disk for later analysis. Data files were then transported to a custom program for the analysis described below.

EEG spectral analysis was completed on the Sterman-Kaiser Imaging Laboratory (SKIL) software version 2.05. This software allows for automatic artifacting, time-of-day corrected spectral analysis, state comparison analysis, and comodulation analysis. Data can be compared to an adult database consisting of two baseline and two challenge task conditions. Results can be displayed as means, percent change, or as time-of-day corrected database comparisons within, and between, conditions for selected frequency bands.

Comodulation analysis includes both the generation of a within-subject and cross-correlation coefficients to the Sterman-Kaiser Imaging Laboratory (SKIL) normative database. The cross correlation of each recording site with all other sites is calculated for a given frequency band. In this case the normal resting dominant frequency in the eyes closed condition, which is generally between 8-12 Hz. Within subject analysis of regional correlation has values ranging from -1 to +1. Cross correlations of each site with itself produce coefficients of exactly +1, while comparisons to other sites show progressive diminishing of correlation with increasing distance from the site of interest. This aids in defining the regional localization of function over the cortical mantle. Statistical comparison of the coefficient with the correlation coefficient SKIL database identifies areas of functional homogeneity or heterogeneity that deviate from normal. The metric of comodulation in this study will be expressed as a parametric statistical comparison between a given individual and the SKIL database.

Procedure. The appointment commenced with a verbal account describing in full the background of the study and the procedures used to acquire both EEG data and completion of the paper and pencil tests. Participants were also shown the acquisition apparatus and associated materials. Participants were then given the opportunity to ask any questions and to mark on their consent forms whether they wanted a report sent to their doctor. Demographic data were collected including age, occupation, and handedness. Further data collected included a brief history of the onset and course of CFS in the form of a structured interview. Participants then completed the SCL-90-R according to the instructions.

A fitted electrode cap (Electro Cap International), with leads placed according to the International 10/20 System, was applied to achieve a standardized

19-channel EEG recording with linked ears reference. Electrode impedance of less than 5 Kohms was required at all sites prior to the initiation of recording.

The client was seated in a comfortable upright chair placed approximately 2.5 meters in front of a video monitor screen. A series of standardized tests, each lasting approximately three minutes was administered. These included: (a) resting eyes closed, (b) resting eyes open, (c) reading, (d) a standardized math test, and (e) a second resting eyes closed.

Digitized data were subjected to a custom automatic artifact detection program that identified and deleted eye-blink and movement artifact. This was supplemented by a visual review of the record for removal of residual undetected eye and head movement artifact, as well as muscle activity of potential consequence to the analysis. A manual cursor was used to selectively identify and delete only those brief segments affected. Atypical transients in the EEG signal were noted for subsequent analysis during this procedure.

Corrected EEG data were then analyzed for frequency content using Fast Fourier Transform. Evaluation of these data employed various descriptive and statistical displays with a variety of frequency band formats. These included spectral maps, individual frequency band topometric analysis (providing both within and between state evaluations), topographic maps, and comodulation analysis. Statistical analysis compared subject data with an adult normative database corrected for significant time-of-day variations and state transitions. Data also were evaluated for percentage change across states and compared with a normative database for state modulation. Finally, topographic maps showing covariance between all sites at relevant frequencies were compared with a normative database to evaluate the status of functional cortical interactions. Participants were assigned to pattern versus no pattern groups, according to the results of QEEG analysis.

After the QEEG analysis, tables were generated to provide magnitude values for all sites and frequencies between 1-23 Hz. Due to the large number of data collected in QEEG, magnitude values in the 8-12 Hz frequency range were averaged within subject across three cortical regions, including a frontal strip (F3, FZ, F4), a central strip (C3, CZ, C4), and a parietal strip (P3, PZ, P4).

Prior to examining the data for general trends, participants' recordings on the QEEG for frontal, central and parietal amplitudes were examined using the Statistical Package for Social Sciences (SPSS) Version 10 to identify any missing values or errors in data entry. Participant amplitudes were examined to determine whether the distributions of scores adequately matched the assumptions of t-tests that were intended for use.

Examination through SPSS (Statistical Package Social Sciences–Australasia) Frequencies revealed that there was some missing data. The pattern of missing data was for the Task 1 condition and was the result of two participants

being unable to sustain task requirements during QEEG recording, resulting in inadequate data. These data were not included in subsequent analyses.

RESULTS

Examination of the QEEG magnitude revealed that individual site amplitudes did not extend beyond the univariate criteria $z > 3.39$, as recommended by Tabachnick and Fidell (1996), indicating that no outliers were present.

Assessment of normality through SPSS (Statistical Package Social Sciences–Australasia) Explore revealed that amplitude for eyes-closed conditions within the mean alpha range (8-12 Hz) for the frontal, central, and parietal sites was positively skewed, but well within the critical level of three standard deviations. Further examination revealed the presence of kurtosis on mean alpha scores for the frontal, central, and parietal regions. While the breaches were high for the parietal region particularly, a decision was made not to transform the data due to the possibility that these transforms would undermine interpretation of meaningful clinical information (Tabachnick & Fidell, 1996).

A decision was made to avoid running any parametric analyses beyond what was available for comparisons against the SKIL normative database on the existing data due to the small sample size, particularly for the group with the anterior posterior dissociation pattern. Although the data appeared to meet many of the assumptions of parametric tests, the limited sample size reduced the available power necessary for detecting any effect if it were present (Keppel, 1992) between groups. Since the current analyses were based on a small sample size, the decision was made to highlight some important trends, without drawing inferences beyond those that are meaningful without adequate statistical support.

Examination of the comodulation findings revealed the existence of two separate populations in this group of subjects. Four of the subjects showed a clear APD pattern, while seven did not. Table 3 displays the means and standard deviations of spectral magnitude values for subjects showing the APD pattern and no pattern whose mean alpha for eyes-closed conditions were scored across three specific regions: frontal, central, and parietal regions.

Examination of the data for the pattern and no-pattern groups suggest that there are no obvious differences in the overall mean alpha for eyes closed conditions in the frontal region. Further inspection of mean differences between the APD pattern and non-pattern groups for eyes-closed conditions also appears to indicate that both groups may not retain any apparent differences across this site. However, in the parietal region, trends in the mean alpha scores for the APD pattern group suggest that their alpha levels overall may be higher than overall alpha levels of the non-pattern group. Without appropriate statistical tests,

however, there is insufficient evidence to conclude whether apparent differences in the overall means between the two groups have statistical meaning.

Figure 1 illustrates the eyes-closed comodulation non-pattern group data topometric compared to the normative database. The frequency range examined was 8-12 Hz. It can be seen that the group is within the two standard deviations range but that the group is also below the database mean.

Conversely, the APD pattern group displayed consistently higher posterior magnitudes compared to the normative database as shown in Figure 2.

TABLE 3. Means and Standard Deviations of CFS Pattern and CFS Non-Pattern Participants. Overall Measures of EEG Alpha (8-12Hz) for Eyes-Closed Conditions in the Frontal, Central, and Parietal Areas of the Cortex.

CFS Category	Frontal	Central	Parietal
No Pattern Sub-Type	3.24 (1.59)	3.62 (1.69)	4.35 (1.82)
Pattern Sub-Type	3.35 (.78)	4.33 (1.36)	7.43 (3.04)

FIGURE 1. Shows the comodulation non-pattern group data topometric compared to the normative database. The frequency range examined was 8-12 Hz. It can be seen in four selected QEEG files that the group is within the range of two standard deviations but that also this group is below the database mean.
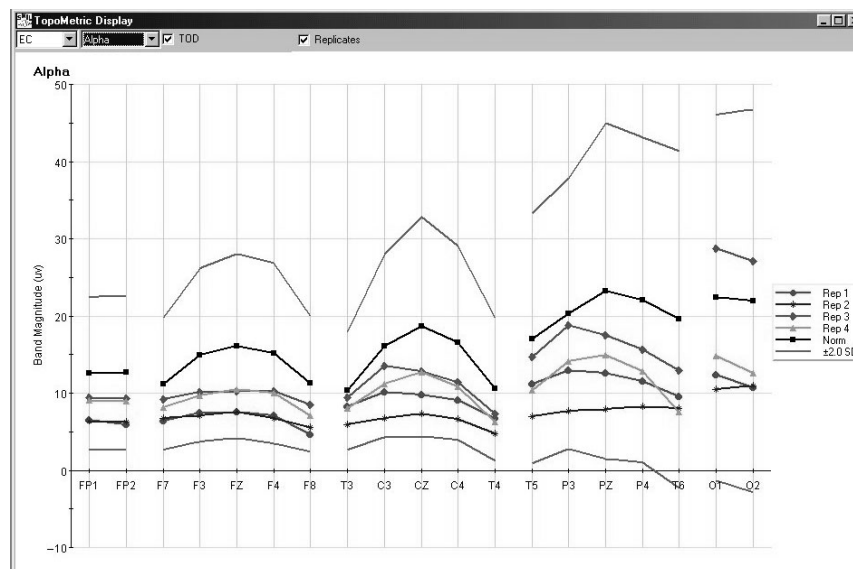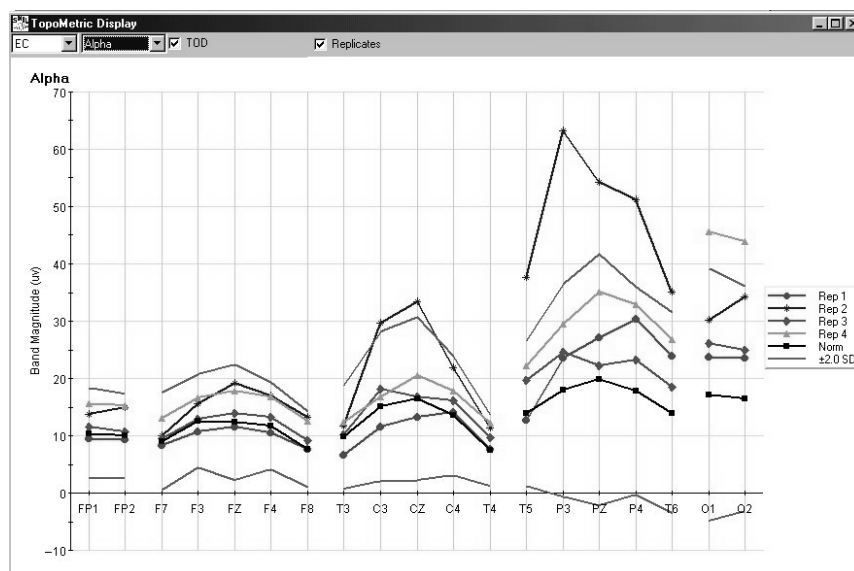
FIGURE 2. Grouped topometric data for the pattern group compared to the database in the 8-12 Hz frequency range. Conversely in Figure 3, the pattern group shows consistently higher posterior magnitudes compared to the normative database.


Figures 3 and 4 show the topographic comodulation of the APD pattern and no-pattern group, respectively. This compared each group to the normative database in the 8-12 Hz frequency range. This statistical mode provides a color-coded representation of up to two standard deviations from the normative database.

The comparison of demographic data in Table 2 was based on the identification of these two subgroups. It can be seen that 100% of the APD pattern group was unmedicated whereas only 29% of the no-pattern group was not using medication. Further, all subjects in the APD pattern group were gainfully employed while no one in the no-pattern group was working.

DISCUSSION AND CONCLUSION

As expected, the data revealed that the QEEG patterns of interest were not consistently represented in this subjectively defined CFS sample. Instead, two distinct groups were identified by the empirical QEEG metric used here. These

FIGURE 3. Grouped topographic comodulation map of the anterior-posterior pattern in the 8-12 Hz frequency range. This is the grouped comparison to the normative database.
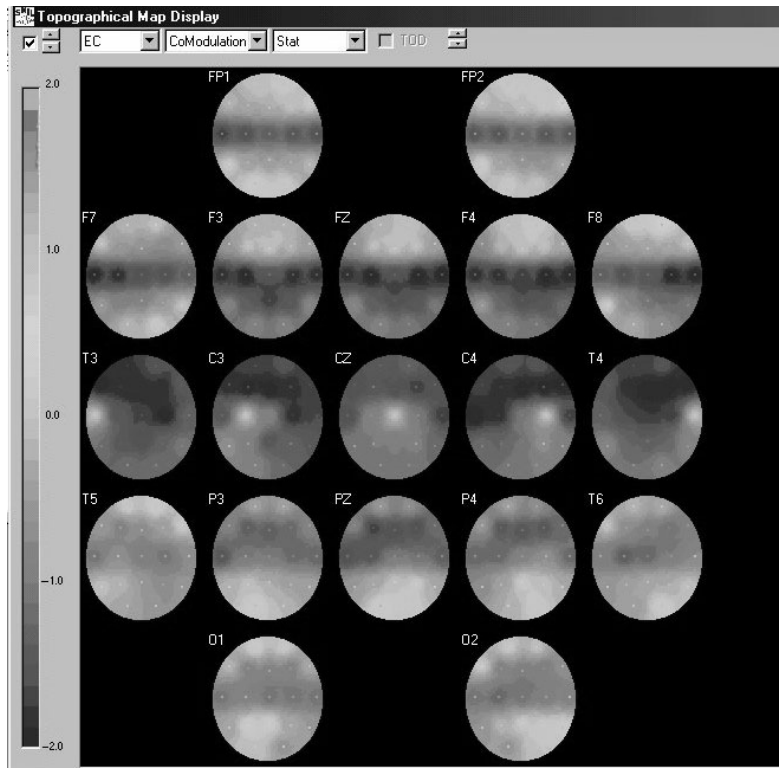

included a distinctive subgroup of four who consistently showed a statistically significant dissociation between anterior and posterior cortical regions in the temporal modulation of dominant frequency expression when the eyes were closed. This group also showed a consistent trend toward elevated dominant activity in the parieto-occipital cortex. A second subgroup of seven subjects failed to show the APD pattern and had low posterior dominant frequency activity.

The discrepancy that was documented between these two groups in the use of medication and in work status may be significant. The APD pattern subjects tended to be unmedicated and working. Conversely, the no-pattern group tended to be medicated and unemployed. Thus, the following options may be considered:

1. Medications, and particularly antidepressants, may alter the temporal modulation of dominant frequency activity, imposing also a general suppression of dominant activity. This effect could mask the APD pattern.
2. The no-pattern subgroup consists of patients with more severe and disabling symptoms and/or multiple pathologies.
3. The APD pattern subgroup represents patients with an empirical physiological basis to their symptoms while the no-pattern subgroup suffers from functional psychological disturbances instead.

The pilot study aimed to investigate the possibility of CFS subtypes or differentiation, and determine whether the anterior posterior pattern occurs in

FIGURE 4. Grouped topographic comodulation map of the non-pattern group in the 8-12 Hz frequency range compared to the normative database.
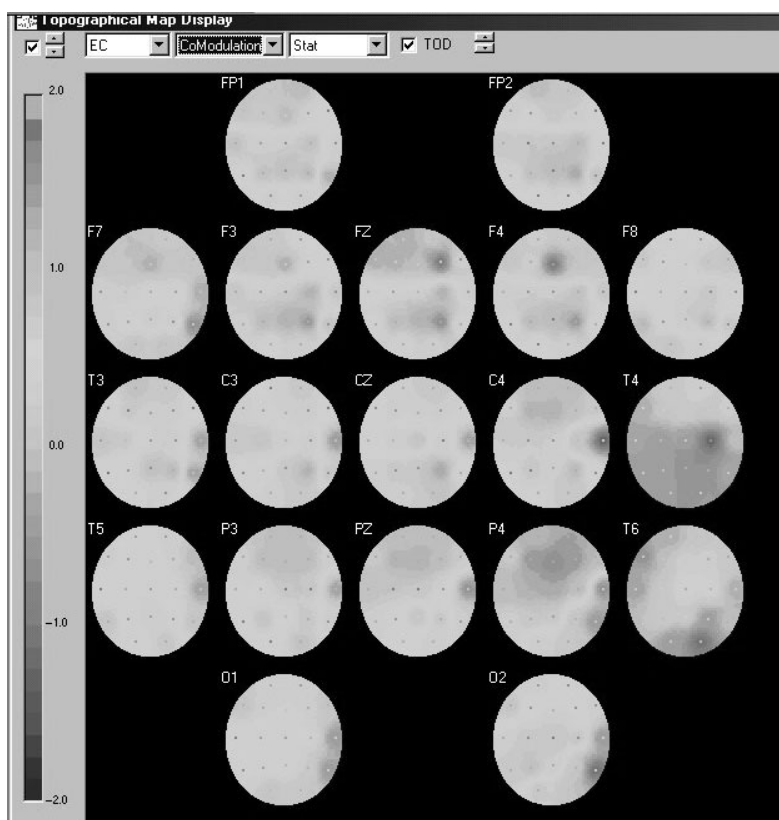
those with chronic fatigue syndrome. The resulting trends suggest that this may be the case. The major limitation of the study is in the limited number of participants used to explore and describe the EEG phenomena of interest.

A future investigation may reveal in support of the difficulties currently facing the evaluation of the condition, that all CFS sufferers experience a similar measure of distress and this is at the very core of what makes CFS difficult to assess. Differences in QEEG findings, however, show some promise of providing a more complete understanding of CFS and bridging the polarization between psychiatric and/or physical explanations.

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