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EEG Patterns and Chronic Fatigue Syndrome

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This study examined the relationship between EEG recordings of 28 females with Chronic Fatigue Syndrome (CFS) and age matched controls of the same gender. CFS subjects' EEG recordings were also compared to their responses on the Profile of Fatigue Related Symptoms, and two questionnaires developed specifically for this study. EEG electrodes were placed in a monopolar arrangement (active lead at CZ, ground lead in the center of the forehead, and two reference electrodes clipped to the earlobes) according to the international 10-20 system, and impedance was kept below 6 kohms. The data were collected under two conditions: eyes closed and serial sevens (while the subjects silently counted backward from 900 by seven).

CFS EEG microvolt levels were significantly higher in the 5-7 Hz range in both conditions and were significantly lower in the 9-11 Hz range during the serial sevens task. In the eyes closed condition, peak alpha (the frequency between 8 to 13 Hz at which the greatest amount of energy was observed) correlated negatively with the 'fatigue today" rating and the peak frequency (the frequency between 4 to 20 Hz at which the greatest amount of energy was observed) correlated negatively with the theta to beta ratio and the total fatigue score. During the serial sevens task, peak frequency correlated negatively with the total cognitive difficulty rating. No EEG differences were found between employed and non-employed CFS subjects or between CFS subjects who were taking antidepressant medications versus those who were not. Subjective symptom ratings and EEG comparisons suggest that CFS symptomology is displayed physiologically in the EEG. Implications are discussed.

Key Words: Chronic Fatigue Syndrome, CFS, Electroencephalogram, EEG, Fatigue.

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The number of investigations of the degree and extent of cognitive difficulties found in Chronic Fatigue Syndrome (CFS) subjects has increased in recent years. Deficits in speed of information processing, psychomotor activity, semantic processing, logical reasoning, and metabolism of the cerebral cortex (measured using a SPECT scan) all demonstrate the broad array of cognitive difficulties associated with this disorder (DeLuca, Johnson, Beldowicz, & Natelson, 1995; Johnson, DeLuca, Fiedler, & Natelson, 1994; Krupp, Sliwinski, Masur, Friedburg, & Coyle, 1994; Ray, Phillips, &Weir, 1993; Schwartz et al., 1994; Smith, Behan, Bell, Millar, & Bakheit, 1993).

Although current research has yet to establish any etiological factor or combination of factors that characterize a majority of CFS patients, numerous studies have demonstrated psychological differences between CFS patients and controls representing the general population (Hickie, Lloyd, Wakefield, & Parker, 1990; Krupp et al., 1994; Swanink et al., 1995). Hickie et al. (1990) concluded that psychological impairment in CFS is a result of the illness and not a precursor to CFS. They found that the premorbid prevalence of ma or depression (12.5%) and of total psychiatric disorder (24.5%) was no higher than general community estimates. Only 20.5% of the CFS patients studied by Schweitzer, Robertson, Kelly, and Whiting (1994) exceeded the severe depression cutoff on the Beck Depression Inventory In contrast, Manu et al. (1989) claimed that depression is an important antecedent to chronic fatigue. Unfortunately, CDC criteria for CFS were not used in the selection process for subjects in the latter study, making comparisons between this and other studies difficult. Krupp et al. (1994) found that CFS patients rated themselves as significantly more depressed on self-report questionnaires when compared to controls ($p < .001$), with a lifetime prevalence of major depression (determined through psychiatric interview) at 40%. Only CFS subjects who included cognitive symptoms among the major CDC

criteria were used in this study This selection criteria may have indirectly limited CFS inclusion to those subjects who were more depressed.

DeLuca, Johnson, and Natelson (1994) found that both CFS and depressed patients differed significantly from "healthies" in overall neuropsychological performance. When CFS subjects were separated based on high and low depression levels, no difference was found on their Paced Auditory Serial Addition Test Scores. They concluded that "depression is not an adequate explanation for the cognitive difficulties of the CFS group" (p. 517). CFS subjects appear to differ from the clinically depressed subjects only in their subjective rating of fatigue (Schmaling, DiClementi, Cullum, & Jones, 1994), but this may represent a confounding of symptoms between Major Depression and CFS (Ware & Kleinman, 1992).

Scheffers, Johnson, Dale, Grafman, and Straus (1992) found no differences in event related potentials and performance data in their comparison of CFS and matched control subjects. In this study, CFS subjects' reaction time was prolonged in comparison to that of controls. Schmaling et al. (1994) compared CFS subjects to subjects experiencing a major depressive episode. They found no neuropsychological differences between the two, both scoring within normal limits on most measures. In contrast to these findings, Smith et al. (1998) found differences between CFS subjects and controls in memory, attention, and psychomotor tasks; they further concluded that the differences could not be attributed to psychopathology.

Comparison of results from chronic fatigue studies has been made difficult by the use of varied selection criteria for inclusion. Apparently, the extent to which neuropsychological impairments in CFS exist lacks clarity and remains a topic of dispute. The present study was designed to attempt to clarify some of the discrepancies relating to neurological impairments in CFS patients. The electroencephalograph was selected as a measurement device as it directly quantifies cortical activity and the electroencephalogram or EEG (brain activity measured by the electroencephalograph) can easily be compared to other quantified data.

The present study also attempted to clarify the neurological discrepancies found in the CFS literature and to assess CFS patients using electrophysiological activity of the brain. The EEG recordings of 28 CFS subjects were compared to 28 non-patient comparison subjects using a single recording cite. Based on previous findings in children with cognitive disorders (Mann et al., 1991), it was predicted that CFS subjects would have EEG signatures that differed from non-patient comparison subjects, and that these differences would be greater while subjects performed a challenging task. More specifically, CFS subjects were expected to have higher theta to beta ratios than age-matched non-patient comparison subjects, and the difference was expected to be greater when both groups of subjects were engaged in challenging mental tasks. Finally, CFS subjects were expected to display higher microvolt levels in the lower Hz frequencies (3-8 Hz), while non-patient comparison subjects were expected to display greater microvolt levels in the higher frequencies (9+ Hz).

It was also predicted that CFS ratings of the degree of sleep difficulty, fatigue, cognitive difficulty, emotional distress, somatic symptoms, and overall symptoms (on the PFRS and global symptom questionnaires) would negatively correlate with the peak alpha (the Hz value within the range of 8-12 Hz at which the most energy is generated) and the overall peak frequency (Hz value within the 4-20 Hz range at which the most energy is generated), and correlate positively with the theta to beta ratio in both conditions. Further, employed CFS subjects were expected to display lower theta to beta ratios (healthier EEGs) than their nonemployed counterparts. This expectation was based on the assumption that CFS subjects who are able to work outside of the home are less

fatigued and healthier.

METHOD

Subjects

Female adult CFS sufferers were recruited by placing advertisements in local newspapers and contacting area CFS support groups. Only females were included as they represent the majority of patients reporting this disorder (Manu, Lane, & Matthews, 1992) and a sufficient sample of males could not be obtained. CFS subjects had to be diagnosed with CFS by a physician (CDC criteria verified in writing; Holmes et al, 1988). Of the 28 subjects who qualified for participation, 8 worked full time, 3 part time, and 17 were not employed outside of the home. Twelve were taking anti-depressant medications at the time of testing. As an incentive, subjects who completed the study received a coupon for a free back massage from a certified massage therapist.

Non-patient comparison subjects were recruited from the University of West Florida and the Pensacola community. In order to account for EEG changes that occur with age, non-patient comparison subjects were matched for age and gender to CFS patients. Although selected to be matched, the CFS subjects were on average 1.3 years younger than the non-patient comparison subjects W = 45.8 and 47.1). This small difference in age was nonsignificant and is not suspected to have skewed the findings (t = .018, *DF* = 54, p >.50). The age of CFS subjects ranged from 26 through 73, while control subjects ranged in age from 24 through 74.

Materials

Various demographic data and symptom reports were collected from CFS subjects. A global symptom questionnaire was developed to track symptoms in four domains on the day of the evaluation: emotional distress, cognitive difficulty, fatigue, and somatic symptoms (physical illness). Subjects were instructed to rate how they were feeling "today" about each symptom, using a seven-point scale where 0 represented "not at all" and 6 "extremely." Subjects were also asked five questions regarding their sleep patterns according to the seven point scale described above. These questions addressed difficulty sleeping in general, getting to sleep, staying asleep, extent of awakening earlier than desired, and the restful quality of sleep. As this questionnaire was developed for use in the present study, reliability and validity data are not available.

CFS subjects also completed the Profile of Fatigue-Related Symptoms (PFRS) which was developed by Ray, Weir, Phillips, and Cullen (1992). This questionnaire consists of 54 items which are divided into four factors: emotional distress, fatigue, somatic symptoms, and cognitive difficulty. Subjects report the extent to which they have experienced each symptom during the past week using a seven point scale (ranging from 0 69not at all," to 6 "extremely"). Test-retest reliability scores range from a high of 0.97 on the fatigue scale to a low of 0.86 for the emotional distress factor. The PFRS hasbeen shown to have acceptable validity (Ray et al., 1992).

EEG frequency and microvolt activity were recorded with Lexicor neurofeedback NRS 2 equipment and the V-151 software interfaced to an IBM compatible computer. Sampling rate was set to 128 samples per second. Four EEG electrodes (one ground [forehead], one active [Cz], and two ear reference clips) were used. Rubbing alcohol, cotton balls, Ten-20 conductive paste, and Nu prep were used for EEG electrode preparation.

Procedure

After reading a description of the study and providing signed consent, CFS subjects completed the demographic questionnaire, the PFRS, and the global symptom and sleep questionnaire. Control subjects completed only the demographic questionnaire and consent form. Subjects were next seated in the neurofeedback room. EEG assessment was thoroughly explained as a noninvasive technique and subjects were afforded the opportunity to ask questions. EEG electrodes were placed at CZ according to the international 10-20 system and impedance was kept below 6K ohms.

A total of 214 epochs (two seconds each) was collected for each subject. For the first 100 epochs, the following instructions were given: "During this period, please close your eyes. Try to remain relaxed and quiet." During the last 114 epochs, data were collected while the subject silently counted backwards from 900 by sevens (serial sevens condition) with eyes closed. Given that the serial sevens task normally produces more artifact, an extra 14 epochs were added to ensure that enough EEG data were recorded.

The raw data were reviewed and artifacted manually Approximately 25% of the data was removed from each group. Any fluctuation in the number of epochs removed was not thought to have had any bearing on the statistical outcome of this study (see Discussion).

The majority of CFS and control subjects' EEG recordings were taken in the evening hours from 6:00-7:30 p.m. Some recordings were taken earlier in the day due to scheduling differences, but this variable is expected to have been even over CFS and control subjects.

RESULTS

Data Reduction

Four bandpass files were entered into the Lexicor software. The first two files averaged the microvolts at each single Hz frequency between 3 and 10 in the first band file, and 11 through 16, plus 20 and 28 in the second band file (16 total data points). The 28-Hz frequency was used as the upper parameter based on preliminary CFS findings of Tansey (1993). The third band file was set to collect the data in intervals from 5-7, 7-9, 9-11, 11-13, 13-15, and 15-17 for a total of six data points, and was established for exploratory purposes. The final band file (default) averaged the data for four different wave forms: delta, 0 to 4 Hz; theta, 4 to 8 Hz; alpha, 8 to 13 Hz; and beta, 13 through 21 Hz. Epochs containing artifacts resulting from eye movements and other muscle movements were removed manually by the first author under the guidance of the second author.

Theta to beta ratios were calculated using the figures in the last (default) band file. For each CFS subject, peak alpha frequency was determined by selecting the single Hz value in the range of 8 through 12 in which the highest magnitude was observed. The peak frequency value was calculated by selecting the Hz frequency in which the highest magnitude was observed in the range of 4-20 Hz. All of the data were averaged separately for the two conditions: eyes closed and serial sevens. Each factor score on the PFRS (emotional distress, cognitive difficulty, fatigue, and somatic symptoms) was separately calculated, then the total score (total of the four factors) was determined. Total scores were also compiled for the global symptom questions and the sleep questions.

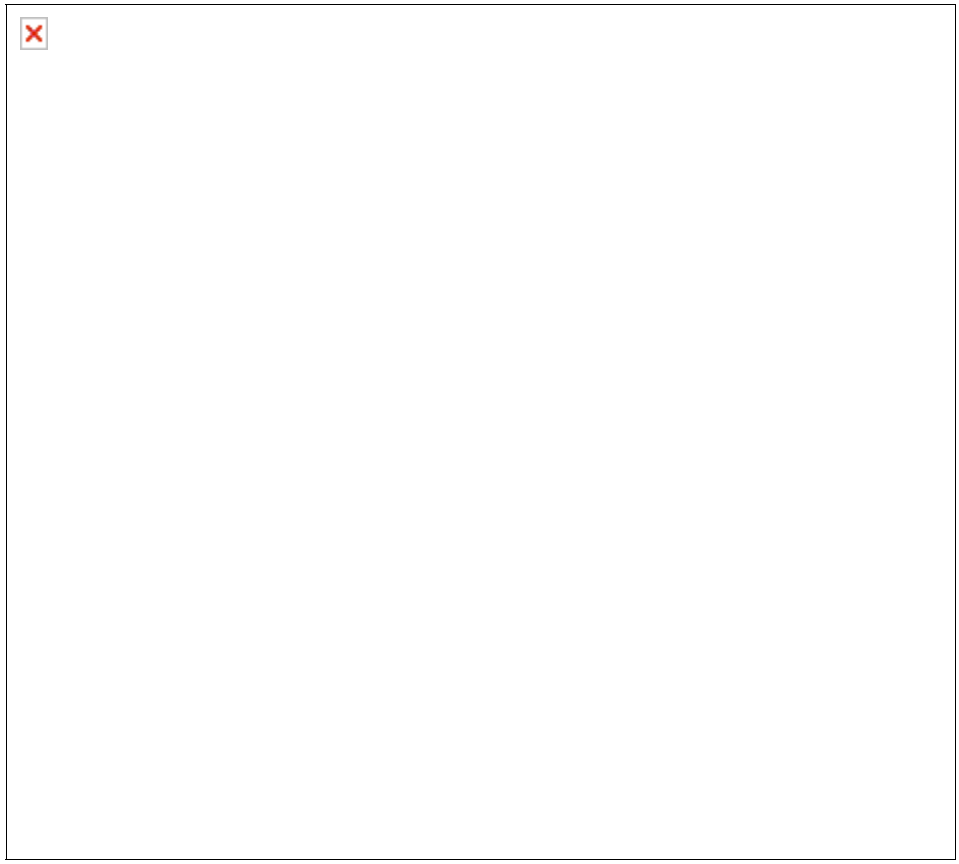
Statistical Approach

T-tests were performed to compare the two groups at each parameter mentioned above, and the

theta to beta ratios were also compared in this manner for the two conditions. To test the relationship between EEG parameters and various CFS subject symptom scores, the theta to beta ratios, peak alpha, and peak frequency values were correlated with cognitive difficulty (past week and today), emotional distress (past week and today), fatigue (past week and today), somatic symptoms (past week and today), the total score for the PFRS, and the total of the five sleep questions, using the Pearson r correlation coefficient (30 comparisons total). This statistic was also used to compare peak frequency and peak alpha with the theta to beta ratios of the CFS subjects.

In order to determine the relationship between working status of CFS subjects (employed versus non-employed) and EEG, a t-test was calculated for the theta to beta ratios, alpha peak, and peak frequency values. The same statistic was used for comparing those CFS subjects who were taking antidepressant medications and those who were not. The use of a theta to beta ratio was based on research by Lubar (1991) which demonstrated that this ratio may be more appropriate than the use of independent percentages of theta or beta alone as it provides one overall figure to use for statistical comparisons. Because of the exploratory nature of this study, alpha was set at .05 for all analyses.

Figure 1



Magnitude at single frequency bands in the eyes closed (top) and serial 7's conditions (bottom).

Statistical Findings

CFS versus Controls-Eyes Closed condition

CFS microvolt levels were significantly higher at the 3-, 4-, and 6-Hz frequencies and lower at 28 Hz ($t = 2.02$, $p < .05$; $t = 2.25$: $p < .05$; $t = 2.46$, $p < .05$, $t = -2.38$, $df = 54$, $p < .05$; see Figure 1). Additionally, CFS microvolt levels were significantly higher in the 5-7 Hz range in the eyes closed condition ($t = 2.09$, $p < .05$, $df = 54$, $p < .05$).

CFS versus Controls-Serial Sevens condition

CFS microvolt levels were significantly higher at 6 Hz and lower at 28 Hz ($t = 2.46$, $p < .05$, $t = -2.59$, $df = 54$, $p < .05$; see Figure 1). No significant differences were found at the other 14 data points. CFS microvolt values were also significantly higher in the 5-7 Hz range ($t = 2.16$, $df = 54$, $p < .05$), and the 9-11 Hz magnitude of the CFS group was significantly lower during the serial sevens task ($t = 2.04$, $df = 54$, $p < .05$).

CFS - EEG, questionnaire ratings, and demographic data

In the eyes closed condition, peak alpha correlated negatively with the fatigue today rating ($r = -.46$, $df = 26$, $p < .05$), but not with the overall (past week) fatigue rating. Additionally, peak frequency correlated negatively with the theta to beta ratio and the PFRS total fatigue score ($r = -.49$, $df = 26$, $p < .05$; $r = -.41$, $p < .05$) during this condition.

During the serial sevens task, the peak frequency correlated negatively with both the theta to beta ratio and also with the PFRS cognitive difficulty rating ($r = -.54$, $p < .01$; $r = -.45$, $df = 26$, $p < .05$; see Table 1). Comparisons of employment status and anti-depression medication status revealed no significant results ($p > .05$).

Table 1
Peak Frequency Correlations with Theta to Beta Ratios and PFRS Results

		Condition	
Subscale	Eyes closed		Serial 7's
Theta/Beta	-0.4887 *	CFS EEG	-0.5364 **
Fatigue past week Cognitive difficulty past week Emotional distress past week Somatic symptoms past week	-0.4100 -0.3478 -0.3433 -0.1874	Profile of Fatigue Related Symptoms	-0.2991 -0.4524 * -0.1730 -0.1509

Note: Table values are Pearson ***r*** values. *$p < .05$, **$p < .01$

DISCUSSION

Given the exploratory nature of this study, only one active EEG channel was employed and no adjustments were made for repeated tests. Even within this simple paradigm, interesting and suggestive results were found; further research which incorporates a full cap measurement and addresses this statistical short-coming seems warranted. Furthermore, given the overlap between CFS and depression, the addition of a group of clinically depressed subjects could potentially clarify the distinction between the two. As the CDC criteria indicate that the symptoms of CFS should not be accounted for by other clinical conditions, the authors assumed that other possible etiological agents had been ruled out by the CFS subjects' physicians, but this was not verified independently.

CFS subjects displayed greater impairment than non-patient comparison subjects in that they generated higher microvoltage activity in the lower frequencies (5-7 Hz) under both conditions (see Table 2). This display of excess theta is assumed to reflect the cognitive difficulties associated with CFS. The expected difference at each single Hz frequency in the alpha range (8-12 Hz) was not found, but during the serial sevens task, the EEG microvolt levels in the 9- to 11-Hz band were significantly lower in the CFS group when compared to non-patient comparison subjects. The increased microvolt levels found in the lower frequencies in CFS subjects may be indicative of deficits in information processing speed, psychomotor activity, attention, retrieval of information from semantic memory, and logical reasoning, and the metabolism of the cerebral cortex found in earlier studies between CFS patients and other disorders (DeLuca et al., 1995; Johnson et al., 1994; Krupp et al., 1994; Ray et al., 1993; Schwartz et al., 1994; Smith et al., 1993).

Table 2
Mean Microvolt Values and Standard Deviations at Single Hz Frequencies

The expected differences in the upper single Hz range were not found at all data points (9-16, 20,

and 28) as predicted: although at the 28-Hz frequency, decreased CFS microvolt levels recorded during both conditions were significant (see Table 2). However, as noted above, compared with normals the CFS group showed a significant decrease in 9-11 Hz microvolt levels during the serial sevens task.

In the CFS group, strong negative correlations were evidenced between peak frequency and the theta to beta ratios in both conditions. The strength of the correlation increased between the two conditions respectively This supports the hypothesis that subjects who displayed increased energy at higher frequencies would also display lower theta to beta ratios and that the difference would increase when subjects performed a difficult task requiring sustained concentration.

Comparisons between the EEGs and PFRS ratings of CFS subjects provided some interesting results. In the eyes closed condition, the subjective rating of "fatigue today" increased as the alpha peak decreased and the peak frequency decreased as the subjective rating of fatigue in the past week increased (worsened). These expected results indicate not only that CFS subjects appeared to subjectively rate their fatigue today and in the past week appropriately, but also that their fatigue was displayed physiologically in their EEGs. In the serial sevens condition, past week cognitive difficulty increased as the peak frequency decreased. It was expected that cognitive impairments would become more apparent during the serial sevens task, which requires an increased ability to focus. Those subjects who rated themselves as having greater cognitive impairments in the past week tended to produce lower peak frequencies than subjects who rated themselves as having less cognitive difficulty.

The subjects taking antidepressant medications were expected to differ from those who were not. In the absence of baseline depression measurements, the lack of significant findings regarding antidepressant medications is difficult to assess, but perhaps significance was not reached due to the limited number of CFS subjects available for this comparison. This is an area that needs to be explored in greater depth with a larger sample size. Prior to data collection, the authors attempted to obtain a sufficient number of CFS subjects who were not taking medications. Unfortunately, only 16 subjects were antidepressant free, 8 of whom were taking no prescribed medications at the time of testing. In the interest of obtaining an adequate sample size, the authors agreed to test subjects who were adhering to a prescribed medication regimen.

Surprisingly, sleep ratings did not correlate with any of the EEG features tested. This may have resulted from the lack of variation in these ratings. Twenty-one subjects rated at least one item on the sleep survey as "most extreme," and eight of these answered all the questions with the highest rating possible ("most extreme"). As control subjects were not given the sleep questionnaire, comparisons between the two groups could not be made. Though none of the correlations were significant, every CFS subject reported some difficulty with sleep. This information is consistent with previous findings regarding sleep and CFS (Buchwald, Pascualy, Bombardier, & Kith, 1994; Manu et al., 1994; Morriss et al., 1993), although Flanigan, Morehouse, and Shapiro (1995) were unable to find an alpha anomaly in CFS patients during sleep.

As artificating was not performed blindly, the possibility of author bias should be considered. The removal of approximately equal numbers of epochs from both groups suggests that the artifacting was not biased.

The data may have been skewed in the direction of "normalcy" by the large number of the CFS subjects who canceled testing appointments (some as many as four times) due to illness and conflicts with doctor's appointments. Two of the subjects who initially agreed to participate failed

to do so stating that they were "too sick." This exemplifies the difficulty in studying disorders such as CFS in a research setting and suggests the need for in-home or minimal demand assessments and treatment studies.

Whether or not the EEG differences found in this study are a manifestation of CFS remains to be determined. Research utilizing pre- and post-morbid EEGs is needed to address this issue. In any event, the EEG differences between the two groups appear to be reliable and may justify pursuit of treatment studies designed to "normalize" CFS brainwave activity. A neurofeedback protocol in which CFS subjects are trained to increase alpha frequency and power with eyes closed, and reduce the amount of lower frequency EEG activity may prove to be successful in reducing at least some of the symptomology associated with this disorder.

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