EEG source analysis of chronic fatigue syndrome

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ABSTRACT

Sixty-one dextral, unmedicated women with chronic fatigue syndrome (CFS) diagnosed according to the Fukuda criteria (1994) and referred for investigation by rheumatologists and internists were studied with quantitative EEG (43 channels) at rest with eyes open and during verbal and spatial cognitive activation. The EEGs from the patients were compared with recordings from 80 dextral healthy female controls. Only those subjects who could provide 20 1-s artefact-free segments of EEG were admitted into the study. The analysis consisted of the identification of the spatial patterns in the EEGs that maximally differentiated the two groups and the estimation of the cortical source distributions underlying these patterns. Spatial patterns were analyzed in the alpha (8–13 Hz) and beta (14–20 Hz) bands and the source distributions were estimated using the Borgiotti–Kaplan BEAMFORMER algorithm. The results indicate that the spatial patterns identified were effective in separating the two groups, providing a minimum correct retrospective classification rate of 72% in both frequency bands while the subjects were at rest to a maximum of 83% in the alpha band during the verbal cognitive condition. Underlying cortical source distributions showed significant differences between the two groups in both frequency bands and in all cognitive conditions. Lateralized cortical differences were evident between the two groups in the both frequency bands during both the verbal and spatial cognitive conditions. During these active cognitive conditions, the CFS group showed significantly greater source-current activity than the controls in the left frontal–temporal–parietal regions of the cortex.

1. Introduction

Fukuda et al. (1994) have provided a modern operational definition of chronic fatigue syndrome (CFS): 6 months or more of increased fatigue, severe enough to reduce daily activity below 50% of premorbid level with at least four of the following symptoms present for at least 6 months or more: mild fever, painful lymph nodes, myalgia, nonexudative pharyngitis, sleep disturbance (insomnia or hypersomnia), migratory arthralgia, memory dysfunction, post-exertional fatigue for more than 24h. The above, of course, requires that no primary medical or psychiatric illness be present that could account for the symptomatology. Fibromyalgia (FM) differs from CFS in that pain at particular trigger points is found, whereas fatigue dominates the clinical picture in CFS, but the symptomatic overlap in the two conditions is striking (Goldenberg, 1989). It has now been well established that no single virus is etiological in CFS, but in 70% of cases it is triggered by a viral “flu-like” illness. A preexisting immune vulnerability is probable, given the overwhelming female susceptibility, women being more prone to autoimmune diseases than men, for example, Hashimoto’s thyroiditis, lupus, rheumatoid arthritis, Sjogren’s syndrome, antiphospholipid syndrome, Graves’ disease/hyperthyroiditis, scleroderma, myasthenia gravis, and multiple sclerosis. That the immunologic system is involved is shown by increase in activated T lymphocytes, increase in cytotoxic T cells, increase in circulating cytokines and poor cellular function: low natural killer cell cytotoxicity, poor response to mitogens in culture and frequent immunoglobulin deficiencies: IgG1 and IgG3 (Landay et al., 1991; Lloyd et al., 1988). In recent years it has become increasingly recognized that the brain and the immune system interact in a bidirectional chemical communication through neurotransmitters and cytokines modulating corticotropin releasing factor, in turn regulating the hypothalamic–pituitary–adrenal axis (Black, 1995). One of the most important conveyors of immunological information to the central nervous system (CNS) is the polypeptide cytokine interleukin-1 (Ur et al., 1992). At the subjective level, cognitive impairment is emphasized in patients with CFS, “mental fog”, impaired concentration, poor memory and frequent word finding difficulties. Numerous neuropsychological studies have confirmed the presence of CNS dysfunction, essentially deficits in information processing, memory impairment, and poor learning of information (Marcel et al., 1996; Altay et al., 1990; Deluca and Schmaling, 1995; Moss-Morris et al., 1996). Michiels and Cluydts
symptoms, 52% had muscle weakness and 65% had clear CNS signs. Nervousness and extreme fatigue. Seven years later, 75% had persistent grade fever (not higher than 37.8 °C) with painful muscles, weakness, myelitis, suggesting an autoimmune pathogenesis (Johnson et al., 1995). Changes are similar to those seen in experimental allergic encephalomyelitis that starts, on average, 5 days after the rash with CT.

In all these subjects both adrenal glands were 50% smaller than in controls on examination with computed tomography (CT).

In patients with CFS, we administered the adrenocorticotropin (ACTH) stimulation test in 30 patients with CFS, in each case triggered by a viral infection. The children were investigated with SPECT, which showed that the left temporal and occipital blood flow was strikingly reduced in two of the patients whereas in the third the blood flow in the left basal ganglia and thalamus was increased. MRS revealed “a remarkable elevation of the choline/creatinine ratio.” Chaudhuri et al. (2003) studied eight patients with CFS without psychiatric complications with 1H-MRS and found a very significant increase in choline compounds in the left basal ganglia. They did not, however, study the right basal ganglia. Schwartz et al. (1993) find on SPECT imaging of 45 patients with CFS that they had a similar number of regional defects when compared with 14 patients with unipolar depression.

There are three diseases characterized by symptomatology that is remarkably similar to that of chronic fatigue syndrome: Addison’s disease, Rickettsial diseases (Scientific American Medicine, 1987. 7: XVII: 1–10), and glucocorticoid deficiency. For example, Addison’s disease is of sudden onset with an overrepresentation of middle-aged women and presents with the following general symptoms: persistent fatigue, debilitation after exercise, weakness, fever, enlarged lymph nodes, myalgia, arthralgia, flu-like symptoms, sore throat, headaches, and dizziness upon standing (Bascbeth, 2000). Hypothension and reduced aldosterone are an integral part of Addison’s disease, and it is probably not coincidental that postural hypotension (Rou-Holihag et al., 1995) and symptomatic relief with fluorocortisone (Florinef) have been described in CFS. Remarkably, Scott et al. (1999) administered the adrenocorticotropin (ACTH) stimulation test in 30 patients with CFS, in each case triggered by a viral influenza-like illness, and found eight who had a blunted response to 1μm intravenously, i.e. failure to achieve a peak cortisol level greater than 600 nmol/l 30 min later. In all these subjects both adrenal glands were 50% smaller than in controls on examination with computed tomography (CT).

Some neurological illnesses may provide insight into the pathogenesis of CFS: meases encephalomyelitis is a neurological disorder of abrupt onset that starts, on average, 5 days after the rash with headaches, generalized seizures, confusion, and motor deficits. The virus is not detected in the brain where the neuropathological changes are similar to those seen in experimental allergic encephalomyelitis, suggesting an autoimmune pathogenesis (Johnson et al., 1984). There was in the small locality of Akureyri in Iceland an epidemic CNS illness in the winter of 1948–49 characterized by low grade fever (not higher than 37.8 °C) with painful muscles, weakness, nervousness and extreme fatigue. Seven years later, 75% had persistent symptoms, 52% had muscle weakness and 65% had clear CNS signs (Goodnick and Sandoval, 1993).

A number of investigations have reported reduced cerebral circulation and hypometabolic changes in CFS, principally in the frontal and temporal regions with single-photon emission computed tomography (SPECT) and positron emission tomography (PET) techniques. Sarkar and Seastrunk (1998) studied 150 patients, half with CFS and half with idiopathic chronic fatigue, with SPECT and magnetic resonance spectroscopy (MRS). With SPECT they found that “the most reproducible area of perfusion abnormality is the left frontal (or orbitofrontal) hyperperfusion in the cortical gray matter both in early and delayed images on almost all patients.” MRS findings were of decreased choline and increased lactate, again in the left frontal lobe, correlating with SPECT hypoperfusion in that region. No such changes were found in the right frontal lobe. In the temporal lobes the metabolites were normal except for a mild lactate increase on the left. Tomoda et al. (2000) reported on three children, ages 11, 12 and 13, with CFS that was triggered by a low grade flu-like illness. The children were investigated with SPECT, which showed that the left temporal and occipital blood flow was strikingly reduced in two of the patients whereas in the third the blood flow in the left basal ganglia was increased. MRS revealed “a remarkable elevation of the choline/creatinine ratio.” Chaudhuri et al. (2003) studied eight patients with CFS without psychiatric complications with 1H-MRS and found a very significant increase in choline compounds in the left basal ganglia. They did not, however, study the right basal ganglia. Schwartz et al. (1993) find on SPECT imaging of 45 patients with CFS that they had a similar number of regional defects when compared with 14 patients with unipolar depression.

Tirelli et al. (1998), in a PET study (fluorodeoxyglucose, FDG) of 18 patients with CFS, reported significant hypometabolism in the right medial frontal cortex and brainstem in these patients when compared with healthy controls. Six psychiatric patients with depression showed more severe hypometabolism bilaterally in the medial and upper frontal regions, with normal brainstem. Machale et al. (2000) compared 30 patients with CFS without depression, 12 psychiatric patients with major depression and 15 healthy controls, measuring cerebral perfusion with SPECT. In patients with CFS and those with depression, there was increased circulation in the right thalamus, pallidum and putamen, the CFS patients in addition having increased perfusion in the left thalamus. Schmaling et al. (2003) studied 15 patients with CFS and 15 healthy controls with SPECT at rest and during the Paced Auditory Serial Addition test (PASAT). Contrary to their hypothesis, there was greater brain activation in the CFS subjects during the PASAT task, which was more diffuse than in the controls, both groups performing equally well on the test. Further, there was greater activation of the left anterior cingulate in the CFS subjects. Siessmeier et al. (2003) evaluated cerebral glucose metabolism with FDG-PET in 26 patients with CFS (13 female; 13 male) and found that 12 of 26 patients were similar to the controls, while 12 had bilateral hypometabolism of the cingulate and mesial cortical regions. In addition, five of these had decreased metabolism in the orbital frontal cortex. Anxiety and depression, but not fatigue, were correlated with reduced glucose metabolism. Interestingly, Ichise et al. (1992), gave the overlap in some of the symptoms found in depression and CFS, found no differences in cerebral circulation in depressed and non-depressed patients with CFS. Schwartz et al. (1994) compared MRI and SPECT in 16 patients with CFS, finding that the magnetic resonance signals were not statistically different from signals in 14 controls, although the SPECT scanning revealed significantly more defects throughout the cortex in the patients (present in 81% of patients and 21% of controls). Abu-Judeh et al. (1998) came to similar conclusions in 18 patients with CFS, finding 13 abnormal SPECT results and 15 normal FDG-PET results in the CFS patients. Abnormalities of cerebral circulation may occur with normal glucose metabolism. The three abnormal PET scans all had hypometabolism of the left parietal region. Brooks et al. (2000), investigating 7 patients with CFS and 10 controls with 1H-MRS, found that the patients had a significant reduction of N-acetylaspartate in the right hippocampus, even although the volume of both hippocampi was similar to that in the normal control subjects. Only the right hippocampus was studied. Strikingly, the left hemisphere was implicated in many of the imaging investigations reviewed above. Thus, we thought it would be of interest to carry out a quantitative EEG analysis (current source density) to see whether a similar lateralization might be found electrophysiologically.
There have been few quantitative EEG investigations of CFS published. Sherlin et al. (2007) reported on a LORETA study of monozygotic twins discordant for CFS. They found that the CFS twins had higher delta values in the left uncus and the left parahippocampal gyrus and higher theta values in the cingulate gyrus and the right frontal gyrus. Their sample consisted of 17 pairs of twins, studied with 19 electrodes. Although their subjects were recorded in the Eyes Open, Eyes Closed condition and during a mental arithmetic task, they only reported the Eyes Closed data. Their twins were unmedicated and they were administered the Diagnostic Interview Schedule. Twenty-four percent of the CFS twins were depressed at the time of study vs. none of the unaffected twins. Forty-seven percent had an acute onset with a mean age of this group was 25.57 (S.D. ± 8.37). These subjects were female. The right hemisphere lateralization found here may reflect the depressive aspect since there is evidence that the electrophysiological correlates of depression are of right fronto-temporal excitation (Flor-Henry et al., 2004). Lewis et al. (2001), however, in the study of 22 monozygotic twins, one of whom had CFS, found that cerebral blood flow (SPECT) was the same in the affected and unaffected twins. Guilleminault et al. (2006), in a sleep study of 14 patients with CFS, found in the CFS group a significant increase in slow delta power relative to findings in normal controls. Siemionow et al. (2004), in only eight CFS patients, observed an increase in omega power found here may also reflect the depressive aspect since there is evidence that the electrophysiological correlates of depression are of right fronto-temporal excitation (Flor-Henry et al., 2004).

2. Methodology

2.1. Subjects

In order to further study the central nervous system characteristics in chronic fatigue syndrome (CFS), quantitative EEG analysis was carried out in a group of patients referred by rheumatologists, internists and general practitioners. All satisfied Fukuda’s criteria (1994), all were dextral and were unmedicated at the time of study. In 67% of these patients the onset was acute. Data were recorded from 61 women suffering from CFS. The mean age of the group was 45.65 (S.D. ± 9.87) years. These subjects were completely right handed as determined by the handedness questionnaires (Annett, 1970; Chapman and Chapman, 1987). All potential control subjects were administered a pretest interview. Any who responded in the affirmative to having a history of neurological disease, birth complications, head trauma, psychiatric illness or substance abuse were excluded from the study. In addition to the pretest interview, the Quick Diagnostic Interview Schedule (Marcus et al., 1989) was systematically administered to these subjects. Those subjects with positive symptom categories were excluded from the study. The Basic Personality Inventory (Jackson, 1996), which compares the subject on 12 personality dimensions to the North American female norms, and the Multidimensional Aptitude Battery (MAB-II), which provides Verbal, Performance and Full Scale IQ, were administered to all patients and controls (Jackson, 1998).

EEGs were recorded from all subjects during a passive condition, eyes open (EO), and two active cognitive conditions, Word Finding (WF) and Dot Localization (DL). At least 3 min of recording was obtained from each subject. During the passive condition, the subjects were told to relax, to think of nothing in particular and to fixate on a point across the room. The tasks producing the cognitive challenges were development by (Miller et al., 1995) to be psychometrically matched, in terms of difficulty, item-scale correlations and internal consistency, using a sample of 350 normal subjects. These cognitive challenges were the same as those used by Davidson et al. (1990) and Koles et al. (2001). The test questions were presented to the subjects by slides projected from the rear of the recording chamber. Once having formulated an answer to a question, the subjects were asked to press a button to indicate that they were about to verbalize a response. By using the recording of the button signal, the EEGs were separated into cognitive and motor phases. Only the cognitive phases were analyzed. Generally, the subjects required at least 5 s to formulate their answers and neither the first nor the last second of the EEG recorded during this period was selected for analysis. Also, to ensure compliance, only those EEGs corresponding to correct responses to the test questions were utilized. No rest period was allowed the subjects between the questions.

The DL task contained 25 items with each item consisting of two vertically arranged open rectangles, the top rectangle containing a pair of dots and the bottom rectangle, slightly offset to either the right or the left, containing an array of numbers. The offset of the bottom rectangle differed randomly among items such that half of the items were offset to either the right or the left side. Subjects were asked to indicate which two numbers in the lower rectangle corresponded to the location of the dots in the upper rectangle. Item difficulty is determined by the size of the number arrays, which varied in five levels from 4 to 50 numbers. In the WF task, subjects were asked to correctly identify an object when presented with a written definition of the object. For example, the correct answer for the item a very large piece of floating ice is iceberg. The WF task consisted of 30 items that differed in an ascending order of difficulty.

The research protocol outlined above was reviewed by the Ethics Review Committee of the Alberta Hospital Edmonton and found to be acceptable within the limitations of human experimentation.

2.2. Recordings

EEG recordings were obtained using a 43-lead stretchable electrode cap containing tin electrodes. The 43 electrode sites represented standard electrode positions described in the American Electroencephalography Society Guidelines (Sharbrough et al., 1990). The lead sites were AFz, Fp1, Fp2, F7, F8, T7, T8, C5, C6, P7, P8, O1, and O2. All leads were referenced to the left ear and the impedance at each electrode was adjusted to be below 5 kΩ. Three additional channels were recorded as follows: the electrocardiogram (EKG), a bipolar recording over the external canthus to the supra-orbit of the right eye to monitor vertical and horizontal eye movements.
(EOG), and one bipolar electromyogram (EMG) channel recorded from the temporomandibular region on the right and left sides. All channels were amplified using a Grass Neurodata system and digitized with a 12-bit RC Electronics analog-to-digital converter at a rate of 256 samples/s. The band pass was set at 3–80 Hz with the high pass controlled by a Grass Model 12A5 two-pole Butterworth filter with the 3-dB point set at 3 Hz. The anti-aliasing filter was an eight-pole Bessel function filter with the 3-dB point set at 80 Hz.

2.3. Spectral analysis

The digitized EEG records were visually edited off-line in an attempt to select from each subject 20 non-overlapping, 1-s data segments corresponding to correct responses to the tasks. These were selected randomly from all of the 1-s segments available from the subject. Segments that contained voltage spikes, large eye movements, or muscle activity were not selected for analysis. Rejection of segments was frequent and resulted in 58, 25 and 34 CFS patients being able to contribute 20-segment EEGs during the EO, WF and DL conditions, respectively. Of the control subjects, 79, 44 and 63 were able to contribute 20-segment EEGs during these same conditions. Only those patients and subjects who were able to contribute the 20 segments were admitted into the study.

The Fast Fourier Transform (FFT) was applied to each row of the data matrix formed by the 46 EEG, EKG, EOG and EMG channels (as rows) and 256 time samples (as columns) collected during each second. Prior to the application of the FFT, each row of the data matrix was preprocessed by applying a 50% Hamming taper (Brillinger, 1981, p.55). With 256 samples in each 1-s segment, the frequency resolution of the FFT along the columns of each transformed data matrix, \( V(f) \), was 1 Hz spanning the range of frequencies from 0 to 255 Hz. Since the alpha band (8–13 Hz) and low beta band (14–20 Hz) were investigated in this study, only the columns 9 to 14 and 15 to 21 in \( V(f) \), corresponding to these frequencies, were selected.

The selected columns from the transformed data matrices were characterized in terms of their cross-spectra. The cross-spectral matrices \( \Sigma(\alpha) \) and \( \Sigma(\beta) \) were formed as:

\[
\Sigma(\alpha) = V(\alpha)V^H(\alpha) \quad \text{and} \quad \Sigma(\beta) = V(\beta)V^H(\beta)
\]

where \( V(\alpha) \) and \( V(\beta) \) are the alpha and beta columns from \( V(f) \) and \( T \) is the complex conjugate transpose. An average 46 × 46 complex-valued cross-spectral matrix over the 20 segments available from each subject was then calculated for each frequency band and for each of the EO, WF and DL conditions.

The correlated effects of the EKG, EOG and EMG with the EEG were removed using a matched filter (Brillinger, 1981 p.299) resulting in 43 × 43 cross-spectral matrices for each subject/frequency band/condition. Each matrix was then normalized by dividing all of its elements by its trace (the sum of its diagonal elements). This procedure was implemented in order to remove the confounding effects of skull thickness on EEG power (Wheeler et al., 1993).

2.4. Reduction of dimensionality

To reduce the effects of measurement noise and to minimize the dependence of the EEG features captured in the cross-spectral matrices on individual subjects, the dimensionality of the measurement space was reduced from 43 × 43 to 30 × 30 by factoring the sum of the average cross-spectral matrices obtained from the CFS and control groups in each frequency band/condition as:

\[
\Sigma_F + \Sigma_C = E \Lambda E^H
\]

where \( \Sigma_F \) and \( \Sigma_C \) are the average cross-spectral matrices for the CFS and control groups, respectively, \( E \) is the matrix of eigenvectors and \( \Lambda \) is the diagonal matrix of corresponding eigenvalues arranged in decreasing order. The reduction in dimensionality of the cross-spectral matrices was obtained by using only the first 30 columns of \( E \) to form:

\[
\Sigma_{FR} = E^H \Sigma_F E \quad \text{and} \quad \Sigma_{CR} = E^H \Sigma_C E
\]

where \( \Sigma_{FR} \) and \( \Sigma_{CR} \) are the dimensionally reduced average cross-spectral matrices of each group and \( E \) contains the first 30 columns of \( E \). The number 30 was chosen arbitrarily but, in every case, the retained components accounted for more than 99% of the combined temporal variances in the cross-spectral matrices from the two groups.

2.5. Separation of the groups

To assess the separation between the EEG features captured in the reduced cross-spectral matrices obtained from the CFS and control groups, the average cross-spectral matrix for each group were then factored as (Koles et al., 2001):

\[
\Sigma_{FR} = C \Psi_F C^T \quad \text{and} \quad \Sigma_{CR} = C \Psi_C C^T
\]

where \( C \) is the matrix of spatial patterns common to the two groups and \( \Psi_F \) and \( \Psi_C \) are diagonal matrices containing the eigenvalues corresponding to each of the spatial patterns. The spatial patterns in the columns of \( C \) are determined from \( C = (\Psi^{-1})^T \) where the matrix \( \Psi \) contains the eigenvectors of either \( \Sigma_{FR} \) or \( \Sigma_{CR} \) both being the same. The columns of \( C \) could be scaled such that \( \Psi_F + \Psi_C = I \), the identity matrix. With this scaling, it is evident that the spatial pattern in \( C \) that accounts for the largest variance in the CFS group (as given by the corresponding eigenvalue in \( \Psi_F \) ) will account for the least variance in the control group. Similarly, the spatial pattern in \( C \) that accounts for the largest variance in the control group (as given by the corresponding eigenvalue in \( \Psi_C \) ) will account for the least variance in the CFS group. Using these decompositions, a measure of the Mahalanobis distance between the CFS and control groups was calculated as:

\[
D^2 = \text{trace}(\Sigma^{-1}_F \Sigma_C) = \text{trace}(\Psi_F^{-1} \Psi_C)
\]

\( D^2 \) in Eq. (5) can be interpreted as the sum of the squared distances, measured in standard deviations, between the CFS and control groups in the direction of each of the common spatial patterns. A \( D^2 \) value of 30 would indicate that the CFS and control groups did not differ in terms of the features captured in their reduced cross-spectral matrices.

Fig. 1 shows the square roots of the elements of the diagonal eigenvalue matrix \( \Psi_F^{-1} \Psi_C \) in Eq. (5) for the CFS and control groups compared in the EO, WF and DL cognitive conditions and in both of the alpha and beta frequency bands. The elements of \( \Psi_C \) were ordered from largest to smallest (and hence \( \Psi_F \) from smallest to largest). All six curves have the same general shape tending to flatten in the middle and to pitch up and down at the left and right ends, respectively. It is evident from the figure that the common spatial patterns corresponding to the first and last eigenvalues account for the greatest variance in one group compared with the other in all cognitive conditions and in both frequency bands.

2.6. Classification of individuals

To assess the level to which the features contained in the cross-spectral matrices obtained from the CFS and control groups would separate the individual subjects in the groups, the classical complex domain quadratic discriminant function was used to retrospectively classify the subjects in each group. Under the assumption that the EEG
is a zero mean Gaussian process, this classifier is given by (Shumway, 1982):

$$QDF = \text{trace}(\Sigma_F^{-1} - \Sigma_C^{-1}) \Sigma_{IR} = \text{trace}(\Psi F^{-1} - \Psi C^{-1}) \Psi^T \Sigma_{IR}$$

(6)

where $\Sigma_{IR}$ is an unclassified subject’s reduced cross-spectral matrix. Group centroids are obtained by setting $\Sigma_{IR}$ in Eq. (6) to $\Sigma_{IR}$ and $\Sigma_{CR}$ respectively. This results in:

$$m_f = \text{trace}(I - \Psi C^{-1} \Psi F)$$

and

$$m_c = \text{trace}(\Psi F^{-1} \Psi C - I)$$

(7)

$\Sigma_{IR}$ is assigned to a group based on a decision line placed between the centroids.

### 2.7. Estimation of cortical source-current density

The estimate of the cortical source-current density in each subject, $s_i^2$, in each cognitive condition and frequency band was obtained similarly to Koles et al. (2001):

$$s_i^2 = \text{diag}(GE_i^T C^P \sum_{j,k} P^C E_k^T G)$$

(8)

where $G$ is the Borgiotti–Kaplan (BK) BEAMFORMER solution to the EEG inverse problem (Sekihara et al., 2001). The $\text{diag}$ operator in the equation indicates that only the diagonal elements of the matrix inside the brackets are used. $G$ is a matrix with 43 rows and 51197 columns and $s_i^2$ is a column vector with 51197 elements containing the estimates of the magnitude of the source-current density at locations in the cerebral cortex of the head model used for this study.

The matrix product $C^P$ in Eq. (8) was included prior to the BEAMFORMER transformation to eliminate the components in the EEGs that were common to the CFS and control groups. To do this, only those columns from $G$ and $P$ were retained that corresponded to the largest and smallest values of $\Psi$ (or the smallest and largest values of $\Psi$). These columns were chosen because they account for maximally different proportions of the temporal variances in the CFS and control groups. The full matrix product $C^P$ yields the identity matrix; however, with only two selected columns, this is not the case and, while the product matrix in this case has dimensions $30 \times 30$, its rank is only 2. The reduced eigenvector matrix $E_b$ is used to transform the 30-dimensional space back to 43 dimensions.

### 2.8. The BEAMFORMER transformation

Transformation of the cross-spectral matrices, filtered with $CP^T$ and $E_b$ to source-current densities was implemented using the Borgiotti–Kaplan Beamformer (Sekihara et al., 2001). The BK Beamformer differs from the LORETA Transformation (LORETA-KEY®) in that it is not only dependent on the lead-field matrix of the head model but also on the cross-spectral matrix of the EEG. It has been shown (Russell and Koles, 2007) that the BK Beamformer is generally superior to LORETA in terms of both the accuracy and the dispersion of source-current estimates.

The BK Beamformer was implemented in a realistic head model obtained as a digitized MRI from the Brain Imaging Centre, Montreal Neurological Institute (MNI). The model contains 4,079,350 cubic elements and was segmented into five tissue compartments, scalp, skull, CSF, gray matter, and other brain tissue. The elements contained in each tissue compartment were assumed to be isotropic with conductivities assigned according to Haueisen et al. (1997). The solution space consisted of 51,197 current dipoles distributed as a sheet in the gray matter compartment of the head model. The lead-field matrix for the head model was obtained using a variation of the preconditioned conjugate-gradient method developed by Neilson et al. (2005). The MNI head model was used, without any modification, to estimate the cortical source-current density for all of the subjects involved in this study.

To locate the positions of the electrodes on the head model, a sphere that best approximated the scalp surface of the MNI model was used to locate a center point for the sphere. Radial lines from the center point were then projected toward the standard electrode locations on the sphere and the electrodes placed on the model at the points where the radial lines intersected the scalp surface. The same electrode locations on the head model were used for all subjects.

Following the calculation of the estimates of the source-current density vectors underlying the cross-spectral matrices for all of the subjects, the elements of these vectors from the CFS and control groups were statistically compared to identify brain regions that contained statistically significant differences. The method used is based on randomized $t$-tests of each element of the source-current density vectors (Holmes et al., 1996). This method has the advantage of not relying on underlying distributional assumptions while simultaneously reducing the probability of obtaining false-positive results. The Holmes method was used to determine the critical value of $t$, $t_{c}$, such that if $t > t_c$ the probability that there is no significant difference (two sided) between the CFS and control groups is less than the chosen value of 0.05 ($P = 0.05$). The results of the statistical comparisons were summarized by displaying the statistically significant $t$ scores on a three-dimensional rendering of the cerebral cortex of the head model.

### 3. Results

At the time of testing, the CFS patients were normal on all personality dimensions except hypochondriasis, this reflecting the somatic symptoms characteristic of CFS; notably, they did not indicate depression (see Fig. 2). From the Quick Diagnostic Interview Schedule it was found that over a lifetime 21 (or 34.4%) of the patients had experienced depressive episodes, 7 (or 11.5%) social phobias, 10 (or 16.4%) agoraphobia, 9 (or 14.7%) generalized anxiety, 7 (or 11.5%) panic attacks, 8 (or 13.1%) somatiform, 15 (or 24.6%) obsessive-compulsive features, 2 (or 3.2%) bulimia, and 1 patient in the past had experimented with stimulants, sedatives, cocaine, and heroin. Hickie et al. (1990) evaluated the prevalence of psychiatric disorder in 48 patients with CFS. The premorbid prevalence of major depression was 12.5% and of total psychiatric disorder was 24.5%, which was not higher than general community estimates. They further found that the pattern of psychiatric symptoms in the CFS patients was similar to what is seen in other medical disorders and different from what was found in psychiatric patients.
In the female controls the mean verbal IQ was 115.5, performance IQ 113.5, and full scale IQ 115.6. In the CFS patients, the verbal IQ was 111.2, performance IQ 111.9, and full scale IQ 112.1. There was no statistically significant difference between the two groups. The women with chronic fatigue are significantly older than the female controls (Table 1). However, we expect that the normalization of the cross-spectral matrix from each subject by its trace (total EEG power in the band) will help to eliminate any dependence of EEG power on age.

Klimesch (1999), discussing alpha and theta oscillations that reflect cognitive and memory functions in a review of the relevant literature, concludes that with increasing age absolute power in the alpha and theta band decreases whilst upper alpha power increases. Alpha frequency increases from early childhood to adulthood and then progressively decreases with age. Consequently, we analyzed the peak alpha frequency of the patients and controls. Across all leads on average the patients were 0.3 Hz slower than the controls—which was non-significant (Hotelling T-squared value: 14.919; F = 1.14, d.f. = (12 128), sig. = 0.33).

Fig. 2 shows the BPI profile of 63 women with chronic fatigue syndrome and 39 with fibromyalgia. (There are 2 extra women with CFS who were not included in the study as they were tested after the analysis.) It is notable that outside of the hypochondriasis scale (because of somatic symptoms) both women with CFS and fibromyalgia are similar to normal controls on 11 of the 12 dimensions. In particular neither the fibromyalgia nor the CFS subjects were depressed at the time of testing.

Table 1
Demographics of unmedicated, dextral patients suffering from chronic fatigue syndrome versus dextral controls.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Female controls</th>
<th>Female chronic Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes open*</td>
<td>N = 79</td>
<td>N = 58</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26.01</td>
<td>45.60</td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td>8.69</td>
<td>9.84</td>
<td></td>
</tr>
<tr>
<td>Eyes closed*</td>
<td>N = 80</td>
<td>N = 61</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.57</td>
<td>45.65</td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td>8.37</td>
<td>9.87</td>
<td></td>
</tr>
<tr>
<td>Dot localization*</td>
<td>N = 63</td>
<td>N = 34</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.48</td>
<td>45.62</td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td>8.41</td>
<td>10.68</td>
<td></td>
</tr>
<tr>
<td>Word Finding</td>
<td>N = 44</td>
<td>N = 25</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.82</td>
<td>45.44</td>
<td></td>
</tr>
<tr>
<td>S.D.</td>
<td>8.02</td>
<td>9.50</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.01.

Table 2
The percentage of the subjects in the CFS and control groups correctly classified using only the two common spatial patterns that account for maximally different proportions of the variance in the EEGs from the two groups in each of the alpha (8–13 Hz) and beta (14–20 Hz) bands.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alpha band</th>
<th>Beta band</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eyes open</td>
<td>72%</td>
<td>71%</td>
</tr>
<tr>
<td>Word finding</td>
<td>83%</td>
<td>80%</td>
</tr>
<tr>
<td>Dot localization</td>
<td>74%</td>
<td>74%</td>
</tr>
</tbody>
</table>

The decision line between the two group centroids was placed so that the subjects in each of the two groups were correctly classified at the same rate.
Fig. 3. Statistical $t$ maps ($t$-value at $P<0.05$) of the cortical regions where the source current density is significantly greater in the CFS group than in the control group (red hues) and significantly greater in control group than in the CFS group (blue hues) in the alpha (8–13 Hz) band during the eyes open (EO) cognitive condition.

Fig. 4. Statistical $t$ maps ($t$-value at $P<0.05$) of the cortical regions where the source current density is significantly greater in the CFS group than in the control group (red hues) and significantly greater in control group than in the CFS group (blue hues) in the alpha (8–13 Hz) band during the word finding (WF) cognitive condition.

Fig. 5. Statistical $t$ maps ($t$-value at $P<0.05$) of the cortical regions where the source current density is significantly greater in the CFS group than in the control group (red hues) and significantly greater in control group than in the CFS group (blue hues) in the alpha (8–13 Hz) band during the dot localization (DL) cognitive condition.

Fig. 6. Statistical $t$ maps ($t$-value at $P<0.05$) of the cortical regions where the source current density is significantly greater in the CFS group than in the control group (red hues) and significantly greater in control group than in the CFS group (blue hues) in the beta (14–20 Hz) band during the eyes open (EO) cognitive condition.
The essential findings in this investigation suggest that the features in the EEG which best separate chronic fatigue syndrome from normal brain function in females are the result of cortical source-current activity that is generally suppressed in the alpha band and beta bands in the Eyes Open condition in CFS. Further, during the Word Finding task there are increased sources in the left frontal region in the alpha band and during Dot Localization in the beta band. In both cognitive tasks, and in both bands the sources of the right hemisphere are reduced. It is noteworthy that the best classification, in both alpha and beta bands, is during the Word Finding task. It has been generally accepted in the past that decreased EEG power in the alpha band and increased power in the beta frequency band correspond to increased functional activation in the cerebral cortex. However, study of theta (4–8 Hz) and gamma (28–64 Hz) oscillations show a significant increase in power during encoding predicted subsequent recall (Sederberg et al., 2003). Hanslmayr et al. (2009) reports that successful encoding in a semantic task is related to power decrease in the alpha (8–12 Hz) as would be expected, but to beta power decrease in the low beta (12–20 Hz) and increase in the gamma band (55–70 Hz). Similarly, Sederberg et al. (2007), who studied in epileptics with implanted intracranial electrodes during verbal memory recall tasks report an increase in gamma band oscillations (44–64 Hz) with a decrease in other bands. However, with respect to the alpha frequency band the physiological meaning of alpha oscillations is more complex. As Basar et al. (1997) comments: “Alpha as
a universal code or universal operator...the major physiological meaning of 10 Hz oscillations which may be comparable to the putative universal role of gamma responses in brain signaling.\" The fact that alpha does not necessarily reflect passive states or idling of the brain is shown by the evoked 10 Hz oscillations that can be generated after sensory stimulation and by event related alpha rhythms that can be induced by cognitive processing. These findings are consistent with the fMRI study of verbal working memory in CFS which shows increased cerebral circulation in the left superior parietal region (and bilateral activation in the prefrontal regions) in CFS during the processing of complex verbal information (Lange et al., 2005). In view of these complexities the precise interpretation of our findings is complex: in line with the more generally accepted view that reduction of alpha power corresponds to increased cortical activation, then in the Eyes Open and during the Dot Localization condition the CFS group differs from controls in having increased cortical activation bilaterally. During Word Finding there is increased activation bilaterally, together with reduced activation in the left frontal region. If one accepts these general premises, in the beta band, the reduced bilateral sources in the Eyes Open condition imply increased bilateral activation and in the Word Finding condition the reduced sources in the right hemisphere similarly imply increased activation of that hemisphere. In Dot Localization task the right hemisphere sources are reduced and the left hemisphere sources are increased over the whole of the left hemisphere, i.e. activation of the right and extensive relative hypofunction of the left hemisphere.

In a remarkable series of publications, Renoux and Bziere have shown in right and left cortical lesioned rats, that in the mammalian brain the T-cell immunological system is underlateralized in left brain cortical control: with left hemisphere lesions there is a complete collapse of T-cell mediated events, but this is under feedback inhibition from the right hemisphere. Animals with right brain lesions have normal T-cell immunological reactivity and are similar to healthy animals; however, with left brain lesions, there is atrophy of the thymus, whereas with right brain lesions there is hypertrophy of the thymus (Renoux et al., 1983a,b; Bziere et al., 1985; Renoux and Bziere, 1986). These findings were confirmed by Neveu (1988), who found that large lesions of the left cerebral cortex depressed whereas lesions of the right hemispheric cortex enhanced T-cell immunity. Interestingly, Davidson et al. (2003) studied 25 subjects before and after an 8-week training course in meditation with quantitative EEG. These subjects and a control group were then vaccinated with influenza vaccine. The meditators had a significant increase in left brain activation (C3, C4) on an asymmetry index in the 8–13 Hz band. Further, the meditators also had a significantly greater rise in influenza antibody titers compared to the compared with the controls that was significantly correlated to the degree of left-sided anterior activation.

5. Conclusion

Thus, it would appear that dysregulation of the cortical hemispheric controls of immunological functional systems (left hemisphere) and hypothalamic–pituitary–adrenocortical axis is the underlying pathophysiology of CFS. The best discrimination from controls is during cognitive activation of the left hemisphere during the Word Finding task, over 80% correct (8–13 Hz). At the same time cognitive activation of the right hemisphere in the spatial task, presumably through transcallosal interaction, also induces increased sources in the left hemisphere, (14–20 Hz). Quantitative EEG analysis would appear to be a promising diagnostic indicator for this disorder.

References


Jackson, D.N., 1996. Basic Personality Inventory Manual, 2nd ed. Sigma Assessments Systems, Port Huron, MI.