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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 24 h. 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

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(2001) and Tiersky et al. (1997) have reviewed these findings. Joyce et al. (1996) further found that patients with CFS were also impaired on verbal tests of unrelated word association learning and letter fluency. Interestingly, Lange et al. (2005) found in a functional magnetic resonance imaging (fMRI) study of verbal working memory that although individuals with CFS could process auditory information as accurately as controls, they utilized more extensive regions of the network associated with the verbal working memory system and that mental fatigue accounted largely for the increased blood-oxygen-level-dependent (BOLD) signal change in the left superior parietal region as well as increased activation bilaterally in the supplementary and premotor regions. Numerous publications document a down-regulation of the hypothalamic–pituitary–adrenal axis in chronic fatigue (Parker et al., 2001; Demitrack et al., 1991; Demitrack, 1994; Bearn et al., 1995; Poteliakhoff, 1981). Some 30–40% of CFS patients have hypocortisolism. Abnormalities in serotonin neurotransmission have been found in CFS: serotonin agonists lead to an increase in serum prolactin in CFS that is not seen in depressed or healthy controls, i.e. in CFS there is an up-regulation of serotoninergic neurotransmission, while in depression the opposite is found, hypercortisolism and suppressed serotonin-mediated prolactin response (Demitrack and Crofford, 1995). Excellent reviews of the general characteristics of CFS have been provided by Wessely (1995), Afari and Buchwald (2003), and Prins et al. (2006).

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 (Baschetti, 2000). Hypotension and reduced aldosterone are an integral part of Addison's disease, and it is probably not coincidental that postural hypotension (Bou-Holaigah et al., 1995) and symptomatic relief with fludrocortisone (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-type illness, and found eight who had a blunted response to 1 μm 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: measles 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) hypoperfusion 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 and thalamus was increased. MRS revealed "a remarkable elevation of the choline/creatine 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 (flurorodeoxyglucose, 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 in 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), given 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.