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Low-resolution electromagnetic brain tomography (LORETA) of monozygotic twins discordant for chronic fatigue syndrome[☆]

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Background: Previous work using quantified EEG has suggested that brain activity in individuals with chronic fatigue syndrome (CFS) and normal persons differs. Our objective was to investigate if specific frequency band-pass regions and spatial locations are associated with CFS using low-resolution electromagnetic brain tomography (LORETA).

Methods: We conducted a co-twin control study of 17 pairs of monozygotic twins where 1 twin met criteria for CFS and the co-twin was healthy. Twins underwent an extensive battery of tests including a structured psychiatric interview and a quantified EEG. Eyes closed EEG frequency-domain analysis was computed and the entire brain volume was compared of the CFS and healthy twins using a multiple comparison procedure.

Results: Compared with their healthy co-twins, twins with CFS differed in current source density. The CFS twins had higher delta in the left uncus and parahippocampal gyrus and higher theta in the cingulate gyrus and right superior frontal gyrus.

Conclusions: These findings suggest that neurophysiological activity in specific areas of the brain may differentiate individuals with CFS from those in good health. The study corroborates that slowing of the deeper structures of the limbic system is associated with affect. It also supports the neurobiological model that the right forebrain is associated with sympathetic activity and the left forebrain with the effective management of energy. These preliminary findings await replication.

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Introduction

Chronic fatigue syndrome (CFS) is an illness characterized by profound fatigue lasting at least 6 months accompanied by disturbances of sleep, mood, musculoskeletal pain, and other symptoms (Fukuda et al., 1994). CFS patients are often depressed (Manu et al., 1998; Wood et al., 1991; Katon et al., 1991) and report problems with forgetfulness, attention, and information processing (Komaroff and Buchwald, 1991; Buchwald et al., 1996). Investigators have sought, mostly unsuccessfully, to characterize these complaints by linking them to specific changes on objective measures of brain function. Recently, EEG methods have been used to examine central nervous system function in which brain wave electrical patterns from multiple scalp electrodes are quantified by computer programs. In one study using quantified EEG, CFS patients had higher theta power than healthy control subjects (Billiot et al., 1997). In another, spectral analysis suggested that physical activity-induced EEG signal changes might serve as physiological markers for CFS (Siemionow et al., 2004). Although not diagnostic, abnormalities were observed that distinguished the ill and healthy groups.

We have conducted a co-twin control study of monozygotic twins discordant for CFS to examine the pathophysiology of this illness. Among the 21 pairs of twins examined with quantified EEG, we observed that the magnitude of the delta and theta bands at Fz, Cz, and Pz was significantly higher in CFS twins than their healthy co-twins (T. Budzynski, personal communication, June, 2005). The co-twin control methodology is a matched pair analysis that adjusts for many genetic and environmental factors not generally considered in case-control studies (Hrubec and Robinette, 1984). This design offers a powerful alternative to traditional approaches that compare CFS patients to healthy, depressed, or sedentary control subjects. It is particularly valuable in studies of electrophysiological parameters because the number of data points generated is large, the range of values observed in normal

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individuals is wide, and many features appear to be heritable (Stassen et al., 1988; Christian et al., 1996).

In this analysis, we used data from 17 of the 21 pairs to extend our findings using low-resolution electromagnetic tomography (LORETA) (Pascual-Marqui, 1999; Pascual-Marqui et al., 1994). LORETA is an inverse solution technique that estimates the distribution of electrical neuronal activity in a 3-dimensional space. It has been extensively used in electrophysiological research (Pascual-Marqui et al., 2002) and evaluated independently in several laboratories (Fuchs et al., 1999; Worrell et al., 2000; Winterer et al., 2001). Our objective was to investigate if specific frequency band-pass regions and spatial locations are associated with CFS.

Methods

Participant recruitment

A total of 600 twins were mailed an intake questionnaire; 426 (71%) were returned, and complete data were available for both members of 193 twin pairs (386 individuals). Twins were recruited through patient support group newsletters (58%), CFS electronic bulletin board notices (15%), practitioners/researchers familiar with CFS (11%), twin organization and researchers (6%), relatives and friends (3%), and other sources (8%). Each twin completed a mailed questionnaire that collected extensive data on demographics, zygosity, life style and habits, psychiatric and physical health conditions, the nature, extent, and consequences of fatigue, and a checklist of the symptoms of CFS (Fukuda et al., 1994). For the non-fatigued twin, a control version of questions was used that did not reference fatigue. A more comprehensive description of the CFS twin registry can be found elsewhere (Buchwald et al., 1999).

Psychiatric disorders

To determine psychiatric diagnoses, the Diagnostic Interview Schedule, Version III-A (DIS) (Robins and Helzer, 1985) was administered via telephone interview to Registry participants. The Diagnostic Interview Schedule assigns current and lifetime diagnoses by computer algorithm based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Version III-Revised (American Psychiatric Association, 1987). A trained research assistant administered modules on major depression, dysthymia, generalized anxiety, panic, agoraphobia, post-traumatic stress disorder, mania, bipolar affective disorders, schizophrenia, eating disorders, somatization, and substance abuse/dependence.

Subjects

From the twin registry, 22 sets of monozygotic twins discordant for CFS were chosen for a 7-day in-person evaluation based on registry information and additional telephone screenings. Twins were required to (1) be at least 18 years of age; (2) be reared together; (3) be discordant for CFS (1 twin met the Centers for Disease Control and Prevention CFS criteria, the other was healthy); (4) discontinue alcohol, caffeine, and all medications known to affect sleep or cognition at least 2 weeks prior to evaluation; and (5) travel to Seattle together. One set of twins did not complete the EEG evaluation and the data from 3 others could not be used in this analysis.

Twins were classified as meeting CFS criteria (Fukuda et al., 1994) according to their responses to a CFS symptom checklist and the diagnoses generated by the Diagnostic Interview Schedule. The same inclusion and exclusion criteria (e.g., body-mass index, specific psychiatric disorders) and review processes were applied to the fatigued and healthy twins. Medical records for the last 5 years were reviewed by a physician knowledgeable about CFS for exclusionary medical conditions (including recurrent head trauma with prolonged loss of consciousness). A psychologist and an infectious disease specialist also independently reviewed the medical charts to verify illness/health status and approve twins for participation. Prior to the scheduled visit, we confirmed that the ill twin still met CFS criteria and the control twin was healthy and not fatigued.

Zygosity was initially determined using validated self-report methods (Torgersen, 1979; Eisen et al., 1989), then confirmed by restriction fragment length polymorphisms. DNA was extracted from peripheral blood mononuclear cells, digested with *HaeIII*, separated by agarose electrophoresis, blotted onto a nylon membrane, and hybridized with 6 variable number repeat tandem probes to determine monozygosity with a certainty of $\geq 99.9\%$ (Keith and Machin, 1997).

EEG data collection

EEGs on each twin pair were obtained back-to-back in a fully lighted room with each twin sitting upright in a small chair. The researchers were blinded to which twin had CFS. The actual testing took approximately 3 min for each of 3 periods, with instructions between each period, minimizing the possibility for napping or drowsiness to occur. The EEG was sampled with 19 electrodes in the standard 10–20 International placement referenced to linked ears. Data were collected for 100 2-s epochs in each of 3 conditions: eyes open, eyes closed, and eyes closed while performing a mental mathematics task (serial 7s). Eyes closed task data were then transported into the Eureka! software (Congedo, 2002), plotted, and carefully inspected for manual artifact-rejection. All episodic artifacts including eye blinks, eye movements, teeth clenching, body movements, or EKG artifact were removed from the stream of the EEG. Seventeen of the twin pairs had acceptable quality data after performing the artifacting procedure. Average cross-spectral matrices were computed for bands delta (2–3.5 Hz), theta (4–7.5 Hz), alpha1 (8–10 Hz), alpha2 (10–12), beta1 (12–16 Hz), beta2 (16–20 Hz), beta3 (20–24 Hz), beta4 (24–28 Hz), and beta5 (28–32 Hz).

LORETA variables

For each twin, cross-spectral matrices were computed and averaged over 4-s epochs resulting in one cross-spectral matrix for each twin and for each of the discrete frequencies within each band. Based on previous LORETA analyses (e.g., Lubar et al., 2003), we used a rectangular window. Sliding overlapping windows (overlap 93.8%) allowed reliable and smooth spectral estimates. The LORETA-Key software package (Pascual-Marqui et al., 1994) was used to compute LORETA current density in the frequency domain directly from the average cross-spectral matrix (Frei et al., 2001). This LORETA implementation incorporates a 3-shell spherical head model registered to a recognized anatomical brain atlas (Talairach and Tournoux, 1988), and makes use of EEG electrode coordinates derived from cross-registration between

spherical and realistic head geometry (Towle et al., 1993). The solution space is restricted to cortical gray matter using the digitized probability atlas of the Brain Imaging Center at the Montreal Neurological Institute (Collins et al., 1994), divided in 2394 voxels measuring $7 \times 7 \times 7$ mm.

Data analysis

For every frequency band and subject, the current density modules at each voxel (current density amplitude) were smoothed with a 10.5 mm 3-dimensional moving average filter, normalized, and finally log-transformed. Log-transformation of power estimates is routinely performed in EEG and LORETA to approximate data gaussianity (John et al., 1987). With LORETA, some smoothing is advisable to reduce anatomical and localization errors due to inter-individual differences in head geometry and electrodes placement. In general, local maxima can be visualized in slightly different locations. Spatial normalization consists of normalizing the square root of the sum of squared current density values for each subject at all voxels to equal unity. This manipulation eliminates confounding variables such as the inter-individual variability in skull thickness and electrode impedance, without constraining the analysis on relative power measures, which is the solution usually adopted in EEG studies. Current density amplitude estimates computed and pre-processed as described provided the data for statistical analysis.

To compare the current density amplitude of the CFS and healthy twins, we used the randomization–permutation multiple comparison t -sum approach (Congedo et al., 2004). Data-permutation approaches can adaptively account for the correlation structure of the variables, an embedded feature of all electrophysiological measurements (Holmes et al., 1996). We performed one test for each of the 9 frequency band-pass regions (delta, theta, alpha1, alpha2, beta1, beta2, beta3, beta4, and beta5). For the whole data set (2394×9 variables), voxel-by-voxel paired (twin-matched) t -tests were computed. A threshold of significance (if the global null hypothesis was false) was then computed by the t -sum method. For all bands, we tested the hypothesis that the mean LORETA current density amplitude of the 2 groups differed by subtracting the values for each CFS twin from that of their healthy co-twin (Congedo et al., 2004).

Results

The average age for the 17 pairs of twins was 40.6 years, 88% were female, and 100% were white. CFS twins differed from their co-twins in the frequency of being employed (53% versus 88%, $p=0.034$), current depression (24% versus 0%, $p=0.046$), and in educational level (13.7 versus 14.4 years, $p=0.048$). Among the twins with CFS, 47% reported an acute onset with a flu-like illness with an average fatigue duration of 7.4 years.

The majority of the frequency band parameters were similar in the CFS and healthy twins: alpha1 (-1.83 t -max difference), alpha2 (-2.46 t -max difference), beta1 (2.01 t -max difference), beta2 (-0.42 t -max difference), beta3 (-0.34 t -max difference), beta4 (2.52 t -max difference), and beta5 (-1.94 t -max difference). Fig. 1 illustrates that the LORETA current source density in the delta (2–3.5 Hz) band was higher in the CFS twins than among the healthy twins in the left uncus and parahippocampal gyrus (Brodmann areas 28, 36, 38, and 20). Fig. 2 illustrates that theta was also higher in the CFS group in the cingulate gyrus (Brodmann areas 24 and 32) and right precentral gyrus of the frontal lobe (Brodmann areas 6 and 8). The maximum t -statistic, or maximum t -value across the entire volume was 3.61 and 6.08 for delta and theta, respectively, which suggests that the effect for theta is much stronger than the effect for delta.

Discussions

LORETA is a technique that facilitates a deeper understanding of the neurological findings present in the EEG (Pascual-Marqui et al., 2002). LORETA does not assume a limited number of dipolar point sources or a distribution on a known surface, but directly computes a current distribution throughout the full brain volume. The result is a true 3-dimensional tomography with localization that is preserved with a relatively low spatial resolution. A direct comparison of results obtained from fitting one and 2 dipoles with LORETA shows that the latter provides physiologically meaningful results in many situations where dipolar solutions fail (Pascual-Marqui, 1995). LORETA also offers new hypotheses on the location of higher cognitive functions in the brain (Pascual-Marqui, 1995), an area of great interest to CFS patients and investigators. LORETA results are reference-free, whereas surface EEG results inherently depend upon

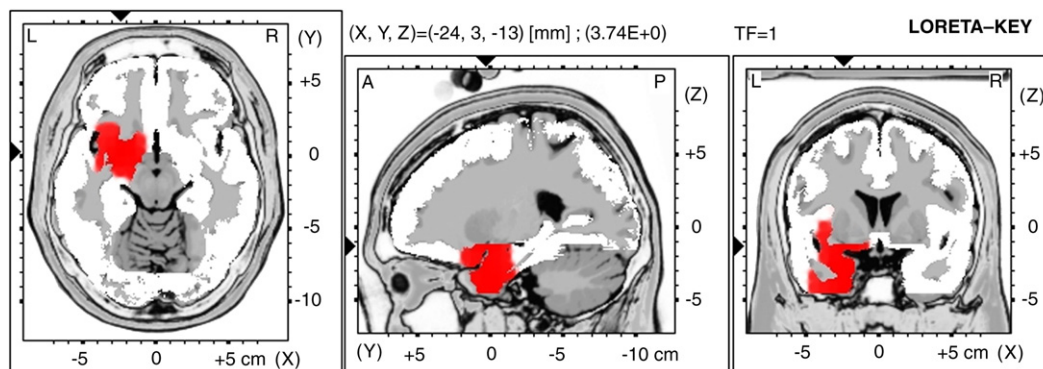


Fig. 1. Significant results for current density amplitude analysis in the delta band. LORETA current source density in the delta (2–3.5 Hz) band was higher in the CFS twins than among the healthy twins in the left uncus and parahippocampal gyrus (Brodmann areas 28, 36, 38, and 20). Coordinates and t -values for this voxel are printed above the picture of the sagittal section. All t -statistics are positive, are displayed in red (the mean of CFS group is greater than the mean of the control group). Displayed are the horizontal (left), sagittal (middle), and coronal (right) sections through the voxel with maximal t -statistic. This image shows significant results only.

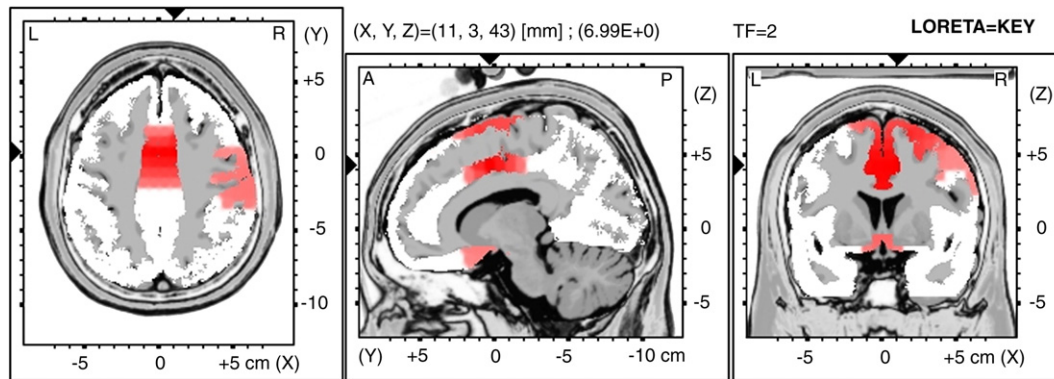


Fig. 2. Significant results for current density amplitude analysis in the theta band. LORETA current source density in the theta (4–7.5 Hz) band was higher in the CFS group in the cingulate gyrus (Brodmann areas 24 and 32) and right precentral gyrus of the frontal lobe (Brodmann areas 6 and 8). Coordinates and t -values for this voxel are printed above the picture of the sagittal section. All t -statistics are positive and are displayed in red (the mean of CFS group is greater than the mean of the control group). Displayed are the horizontal (left), sagittal (middle), and coronal (right) sections through the voxel with maximal t -statistic. This image shows significant results only.

the chosen reference. Taken together, the advantages of LORETA over surface EEG analysis include the ability to visualize anomalies in the deeper brain structures, and to specify anomalies in frequency band and spatial location.

Our study found that the CFS twins had significantly higher levels of current source density in the delta band in the left uncus and parahippocampal gyrus, cingulate gyrus, and right precentral gyrus of the frontal lobe. These findings are consistent with those obtained with quantified surface EEG techniques both in our experience (T. Budzynski, personal communication, 2005) as well as in the literature (Billiot et al., 1997). Previous studies have found that slowing of the deeper structures of the limbic system is associated with effect. Limbic inputs from the amygdala, entorhinal and perirhinal cortex, and subiculum, may serve as a visceromotor system to provide frontal cortical influence over autonomic and endocrine function. This system appears to be involved in guiding behavior and regulation of mood. It has been suggested that the right forebrain is associated with sympathetic activity that includes negative affect, withdrawal, and survival emotions (Craig, 2005). Findings of increased theta in the specific Brodmann areas mentioned may indicate blunted emotional processing, apathy, attention difficulties, and motivation. Although these Brodmann areas are less often correlated with increases in delta frequency, the left forebrain has been implicated in the effective management of energy, both mental and physical (Craig, 2005). Functional imaging studies indicate that many of these areas also show volume changes and decreased glial number and density in mood-disordered subjects (Price, 1999).

One aspect of this study that deserves emphasis is the fact that the participants were carefully chosen illness discordant twins. To our knowledge, no previous studies of LORETA involving families or twins have been published. However, previous twin studies have demonstrated that many EEG features are predominantly determined by heredity (Stassen et al., 1988; Christian et al., 1996; Martinovic et al., 1997), including peak alpha frequency (Posthuma et al., 2001). Of additional relevance, in a study of older adults, 11% of “normal” control subjects exhibited an abnormal EEG (Leuchter et al., 1993), underscoring the value of exceedingly well-matched controls such as the ones we used in this study.

This co-twin control study has several limitations related to our sample selection and methods. Solicitation by advertisement

resulted in a volunteer sample of twin pairs with the potential for ascertainment problems. However, the more desirable strategy of systematically identifying twins from a well-defined population-based twin registry is not readily accomplished in the United States. Thus, how representative the twins in this study were either of twins in general, or of persons with CFS, is not known. Because our twins were adults, primarily female, drawn from community practices, and the ill twins met strict criteria for CFS, we cannot generalize our findings to other samples and more specialized settings. Nonetheless, the demographic and clinical characteristics of our sample are similar to those previously described in the CFS literature. Fourth, the order of testing of the twins was not formally randomized, so that even though technicians and investigators were blinded, some unrecognized and unaccounted for biases might have resulted. Finally, of concern given the high rates of depression in CFS, we were not able to control for major depression. Due to the constraints of the procedure implemented, no other factors entered into the statistical design.

In conclusion, objective measures of delta and theta current source density differed in twins with CFS and their healthy co-twins. Because twin studies are especially well suited to the study of illnesses for which the appropriate comparison groups are not clearly defined (Hrubec and Robinette, 1984), they offer an alternative approach to examine possible patterns of brain activity in CFS. Future research should focus on investigating larger groups of patients and control subjects. Although these results await replication by others, they provide preliminary evidence that objective electrophysiological parameters may help identify persons with CFS. If alterations in LORETA patterns in CFS can be confirmed, this technique could find clinical applications.

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