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Cerebral Blood Flow Is Reduced in Chronic Fatigue Syndrome As Assessed by Arterial Spin Labeling

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Abstract

Background—Chronic fatigue syndrome is diagnosed by a set of clinical criteria and therefore is probably heterogeneous. Earlier reports tested the hypothesis that the syndrome had a neurological substrate by doing studies of cerebral blood flow (CBF) but with discrepant results. One possible reason for the discrepancy was that relative CBF was assessed. We found reduced CBF in an earlier study of absolute CBF using xenon-CT. The purpose of this study was to use a second method of assessing CBF and to look within the study group for heterogeneity of responses.

Method—Eleven CFS patients and 10 age matched healthy controls underwent neuro-imaging using arterial spin labeling to determine their regional and global absolute CBF. A template was constructed based on the control data, and individual patient montages were compared on a case by case basis to determine if differences in regions of interest occurred.

Results—The patients as a group had significantly lower global CBF than the controls. The reduction in CBF occurred across nearly every region assessed. Nine of the 11 patients showed these reductions compared to the average control data, while two patients showed actual increases relative to the controls.

Conclusion—The data extend our earlier observation that CFS patients as a group have broad decreases in CBF compared to healthy controls. However, as expected, the effect was not homogeneous in that 2 of the 11 patients studied showed actual increases in CBF relative to controls.

Keywords

fatigue; cerebral blood flow; heterogeneous; absolute; relative; syndrome

INTRODUCTION

Chronic fatigue syndrome (CFS) is a medically unexplained illness characterized by debilitating fatigue accompanied by infectious, rheumatological and neuropsychiatric symptoms. While earlier work had suggested that the severe fatigue of CFS was due to

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problems in muscle, more recent work does not confirm this [1]. Our own findings of impaired neuropsychological function [2] and abnormal brain MR scans [3] in CFS patients without comorbid psychiatric illness pointed to the brain as the target organ producing fatigue. One mechanism for this might be globally reduced cerebral blood flow (CBF). A number of early studies using single-photon emission computerized tomography (SPECT) have reported global cerebral hypoperfusion [4;5]. However, three studies – one in carefully matched monozygotic twins discordant for CFS – found no differences in cerebral blood flow (CBF) between patients and controls [6–8].

One explanation for this apparent discrepancy is a methodological issue. SPECT scanning provides information about whole brain blood flow relative to some other site – usually the cerebellum. If some CFS patients had reduced blood flow to cerebellum, this occurrence might greatly confound the results. Because of this, we turned to a method that provided information on absolute CBF – xenon-CT. In that study [9], we found a statistically significant group effect: CBF was significantly lower in the patients than in matched healthy controls.

A second method that produces data uses arterial spin labeling (ASL), a method of functional neuroimaging using magnetic resonance (MR) methodology. One major advantage of this technique compared to xenon-CT is that this form of functional neuroimaging allows the collection of data without the need for patients to be exposed to radiation. Therefore, we decided to determine if we could replicate our earlier finding of reduced CBF using this alternative method and then to extend that work to determine if individual differences in CBF existed among CFS patients.

MATERIALS AND METHODS

Protocol

Eleven patients who fulfilled the 1994 case definition [10] for CFS and ten age matched (±5years) healthy volunteers were scanned for this study after obtaining signed informed consent approved by the Institutional Review Board of the New Jersey Medical School. Subjects were positioned supine on the MRI bed of 3 T research Siemens Allegra scanner with head in a midline location in the coil and were instructed not to move their head during the session.

Images were acquired using a 3-axis asymmetrically balanced-torque head gradient coil with end capped birdcage RF coils. In all experiments, the radio frequency power deposition and field-switching rate was kept below levels specified by the U.S. Food and Drug Administration.

A pulsed arterial spin labeling technique, that uses endogenous water as a tracer by alternating between slice selective and non-slice selective inversion, was used. For each subject, resting-state time courses of 90 ASL images were acquired using a TR = 2500 ms, TE = 40 ms, and slice-selective inversion width = 14 mm. Other imaging parameters were FOV = 22 cm, matrix size = 64 × 64, and slice thickness = 6 mm. The Tl value was 1400 ms, which suppresses signal at 3T from CSF and blood. Even-numbered nonslice selective images were BOLD-weighted and all odd-numbered images in the image sequence were slice-selective BOLD- plus flow-weighted. Subtracting every odd-numbered image from the succeeding even-numbered image resulted in a time series of images that was flow-weighted.

Data Analysis

The functional MRI (fMRI) raw data were transferred from the MRI scanning area to a linux workstation for offline processing and analysis. All the reconstructed images were analyzed using an Analysis of Functional Neuroimaging (AFNI) software [11]. Custom software was also developed for additional analysis.

A least-squares motion correction algorithm was applied to the data sets in the x, y and z directions. After the raw image data were reconstructed, data sets were de-trended to eliminate linear drifts caused by scanner related influences, global physiological factors, and motion using the 3dvolvreg function [12]. Next, the fMRI statistical maps were created. To facilitate direct comparison between the individual cortices and compensate for variations in anatomy, data sets of each subject were transformed into Talairach coordinates. The Talairach transformation was performed using a process in which the anterior commisure (AC) and posterior commisure (PC) line of the high resolution anatomical images was initially identified. The longitudinal (inter-hemispheric or mid-sagital) fissure was next aligned to the yz plane to define the z-axis. After identifying the five landmarks on the high-resolution images, the anatomical images were scaled to the Talairach-Tournox Atlas which allowed for the designation of anatomical regions in the transformed images. An affine transformation was then used to align the two image data sets. Using the Talairach images as a reference, images across subjects could be compared both spatially and temporally.

Individual parametric maps were generated for each subject during the rest scan. A group stistical map was obtained for the healthy controls by averaging the statistical maps across all the healthy controls. For each CFS patient, a percent change across each of the ROIs was then calculated. The percent difference across the whole brain was also tabulated. For each ROI, parametric differences between the two groups were computed and only ROIs exceeding a threshold value of $P = 0.05$ were recognized as statistically significant regions of activation.

RESULTS

Motion was not found to be significant in any of the runs for each of the subjects, and no significant difference in motion was observed between the two groups.

Spatial maps of arterial spin labeled images were obtained for each of the subjects (both CFS and matched controls). A number of anatomical regions had significant differences between the two groups. The CFS group had a significant reduction compared with matched controls on whole brain blood flow as well as on the following areas of regional flow: Frontal (both left and right), Parietal (right) and Temporal (left and right) regions. Table 1 provides a list of the ROIs and the percent difference from the pooled matrix of healthy subjects for matched CFS patients. There was a significant reduction across many anatomical regions. The percent reduction in the left frontal, right frontal, left parietal, right parietal, left temporal, and right temporal was found to be 22.1%, 21.1%, 16.8%, 16.9%, 14.3% and 14.0% respectively. Table 2 shows the averaged blood flow (mean in ml/min/100 g ± SD) for the healthy controls and for the 9 patients shown in Table 1 to have reduced CBF. Even when correcting for tissue volume, those patients showed diminished CBF relative to the controls.

DISCUSSION

This paper confirms and extends our earlier observation that patients with chronic fatigue syndrome as a group have diminished cerebral blood flow relative to matched controls – even when the data are corrected for volume of brain tissue. Importantly, both this paper and

our earlier one using xenon-CT [9] used a method that assessed absolute CBF rather than the relative measure used in earlier studies with other methodologies. The reduction in CBF was quite diffuse sparing only the right temporal area. Because we have found diffuse reduction in CBF using two methodologies, we conclude that CBF is reduced in general in CFS. These data support the previously done SPECT studies as well as a study using PET technology which also showed diminished brain blood flow [13]. However, the other reason for our doing this study was to look at subject-to-subject variability in CBF. When we compared each CFS patient to a composite map comprised of data from our control subjects, we found that 9 of 11 of the patients showed reduction in CBF. However, two of the patients showed actual increases in CBF relative to controls. This result encourages this approach and documents the idea that CFS is by definition a heterogeneous illness because it is diagnosed using a clinical case definition and has no specific diagnostic test. We have hypothesized that some CFS patients have neurological underpinnings to their illness. An important next step will be to determine if patients with low CBF have some phenotypic difference in the presentation of their illness relative to those with normal CBF: we hypothesize that patients in the group with the lowest global CBF comprise the same group as those with abnormal brain neuroimaging results and objective evidence of brain dysfunction in the form of reduced cognitive testing scores.

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Table 1

Differences in regional and whole brain blood flow when individual patient data are subtracted from a montage comprised of averaged controls.

		L-Frontal	R-Frontal	L-Parietal	R-Parietal	L-Temporal	R-Temporal	Whole
	1	14	15	9	8	6	5	14
	2	18	15	11	12	8	7	13
	3	21	23	16	15	11	12	12
	4	32	28	17	18	9	14	16
	5	25	24	16	14	11	10	17
	6	32	34	21	23	16	14	18
	7	28	27	23	27	32	32	31
	8	22	19	21	16	19	21	18
	9	23	18	22	26	22	21	24
	10	−13	−16	−12	−16	−15	−12	16
	11	−16	−14	−17	−11	−9	−7	7
Paired-T-test		0.0028	0.0048	0.0110	0.0097	0.210	0.0106	0.020

Table 2

Cerebral Blood Flow (mean in ml/min/100 g tissue ± SD) for healthy controls and the 9 CFS patients with reduced CBF

	Lt Frontal	Rt Frontal	Lt Parietal	Rt Parietal	Lt Temporal	Right Temporal	Whole
Controls	53.3±7.8	48.7±8.2	44.3±6.7	45.8±5.9	57.2±9.1	55.6±7.4	51.4±12.6
Patients	40.4±3.1	37.7±3.1	36.6±2.2	37.7±3.0	48.6±0.7	47.2±4.7	42.1 ±3.1