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Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: A BOLD fMRI study of verbal working memory

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Individuals with Chronic Fatigue Syndrome (CFS) often have difficulties with complex auditory information processing. In a series of two Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) studies, we compared BOLD signal changes between Controls and individuals with CFS who had documented difficulties in complex auditory information processing (Study 1) and those who did not (Study 2) in response to performance on a simple auditory monitoring and a complex auditory information processing task (mPASAT). We hypothesized that under conditions of cognitive challenge: (1) individuals with CFS who have auditory information processing difficulties will utilize frontal and parietal brain regions to a greater extent than Controls and (2) these differences will be maintained even when objective difficulties in this domain are controlled for. Using blocked design fMRI paradigms in both studies, we first presented the auditory monitoring task followed by the mPASAT. Within and between regions of interest (ROI), group analyses were performed for both studies with statistical parametric mapping (SPM99). Findings showed that individuals with CFS are able to process challenging auditory information as accurately as Controls but utilize more extensive regions of the network associated with the verbal WM system. Individuals with CFS appear to have to exert greater effort to process auditory information as effectively as demographically similar healthy adults. Our findings provide objective evidence for the subjective experience of cognitive difficulties in individuals with CFS.

Keywords: Chronic Fatigue Syndrome; Blood Oxygen Level Dependent; Functional Magnetic Resonance Imaging; Verbal working memory

Introduction

Chronic Fatigue Syndrome (CFS) is a medically unexplained illness that is diagnosed based on an individual's self-report of symptoms. After first ruling out potential medical explanations for the fatigue, the disorder is clinically defined by the onset of new (not lifelong) fatigue lasting for at least 6 months causing a substantial decrease in activity and the presence of four or more of the following symptoms: sore throat, tender lymph nodes, muscle and/or multi-joint pain, headaches, unrefreshing sleep, post-exertional malaise, and cognitive problems (Fukuda et al., 1994). These symptoms together can result in significant functional disability (Ciccone and Natelson, 2003; Tiersky et al., 2001). Complaints of cognitive problems occur in 85–95% of individuals with CFS (Grafman, 1994; Komaroff and Buchwald, 1991). Objective findings supporting these claims are inconsistent (Afari and Buchwald, 2003; Vercoulen et al., 1998) or subtle (Schmaling et al., 1994). When neuropsychological problems are detected, slowed speed of information processing is often most closely associated with cognitive difficulties in CFS (for review, see Johnson et al., 1999; Tiersky et al., 1997), especially under conditions of increasing complexity (DeLuca et al., 1993, 1995; Dobbs et al., 2001; Johnson et al., 1994). Information processing difficulties can often impair everyday functional status in individuals with CFS (Christodoulou et al., 1998; Tiersky et al., 2001). Since many of these individuals suffer from comorbid major depression (DeLuca et al., 1994; Grafman et al., 1991; Manu et al., 1993), it has been suggested that cognitive difficulties associated with CFS could be behavioral manifestations of depression (Hudson and Pope, 1994). However, neuropsychological evidence has accumulated to suggest that depression alone does not account for the cognitive problems experienced by individuals with CFS (DeLuca et al., 1997; Schmaling et al., 1994) and that these problems may be related to central nervous system (CNS)

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dysregulation (Grafman et al., 1993; Lange et al., 1999, 2001; Schwartz et al., 1994a).

Efficient, timely processing of verbal information is an essential cognitive function that is mediated by the verbal working memory system (Baddeley, 1992; Baddeley et al., 1984). As conceptualized by Baddeley and co-workers (Baddeley, 1992, 2001), verbal working memory (WM) represents an integrated network comprised of an articulatory loop and a central executive. In this model, incoming verbal information is encoded and maintained in a low-capacity, temporary phonological store (i.e., articulatory loop) via sub vocal rehearsal. A 'central executive' function that can be conceptualized as a "supervisory attention system" (SAS) then assists in manipulating the information for further use in a series of online mental operations (Baddeley et al., 2001; Norman and Shallice, 1980). Positron Emission Tomography (PET) and BOLD fMRI techniques have revealed an anatomic basis for this framework in the form of a robust cortical frontal–parietal network of anatomical substrates underlying the functional components of verbal WM (for review, see Fletcher and Henson, 2001; Paulesu et al., 1993; Petrides et al., 1993; Salmon et al., 1996; Smith et al., 1998). Encoding or acquisition of verbal information has been associated with dorsolateral prefrontal areas (BA 9, BA 46; Rypma et al., 2002), active maintenance, and storage of information with ventrolateral prefrontal regions (BA 44, BA45, BA47; Awh et al., 1995, 1996; Posner and Rothbart, 1998; Rypma et al., 2002; Salmon et al., 1996; Smith and Jonides, 1999; Smith et al., 1998), supplementary motor and premotor cortices (BA6, BA8; Fiez et al., 1996), as well as inferior (BA 40) and superior parietal areas (BA 7; Honey et al., 2000; Jonides et al., 1998). The central executive has been isolated and localized to the dorsolateral prefrontal cortex (BA46, BA10, BA9; D'Esposito et al., 1999; Salmon et al., 1996; Smith and Jonides, 1999) as well as the anterior cingulate (BA24, BA32; Barch et al., 2001; Posner and Rothbart, 1998).

Degree of task complexity appears to play a major role in determining the pattern of functional engagement of the verbal WM system (for review, see (Jonides et al., 1998). Initial studies frequently reported left sided lateralization for verbal working memory tasks (i.e., Awh et al., 1995; Paulesu et al., 1993). However, parametric neuroimaging studies manipulating task complexity by increasing verbal WM load have consistently found that the degree or extent of cortico-functional engagement depends on the degree of effort required to process the verbal information efficiently (Jonides et al., 1997; Schumacher et al., 1996; Smith et al., 1998). As the need for efficient auditory information processing increases, so does the engagement of the functional verbal WM network often reflected by bilateral signal changes in homologous anterior and posterior brain regions (Jonides et al., 1997; Rypma et al., 2002). Thus, interpretations of task demands can be made based on the distribution of cortical responses within the verbal WM system.

Individuals with CFS generally perceive complex auditory information processing as more effortful than Controls (i.e., Schmaling et al., 2003), although neuropsychological support for the experience of poor cognitive function is inconsistent across studies (Altay et al., 1990; Moss-Morris et al., 1996; Schmaling et al., 1994; Wearden and Appleby, 1996). We propose that functional neuroimaging during performance of a neuropsychological task has the potential to provide neurophysiological evidence in support of the patient's subjective complaint. Based on parametric neuroimaging studies in healthy adults, we hypothesize that the verbal WM system of individuals with CFS operates as if it were under conditions of greater cognitive challenge than that of Controls in response to the same task demands. Therefore, we expect that individuals with CFS will show more widespread functional engagement in cortical regions of the verbal WM system than Controls. The present study will utilize BOLD fMRI to determine the extent of BOLD signal within defined regions of the verbal WM system in individuals with CFS and healthy Controls.

We first tested our hypothesis that individuals with CFS would display a pattern of more widespread BOLD signal during complex auditory information processing in a pilot study (Study 1) comparing BOLD signal change between a group of seven healthy Controls and six individuals with CFS who were free from psychiatric illness and who had neuropsychologically documented problems in complex auditory information processing as assessed with the Paced Auditory Serial Addition Test (PASAT; Brittain et al., 1991). To control for task performance, a second study (Study 2) followed comparing 15 healthy Controls and 19 individuals with CFS without psychiatric illness and also without documented cognitive difficulties. This design allowed us to better test the extent that CFS affects BOLD signal change during cognitive performance.

General methods

Study participant intake, imaging acquisition procedures, fMRI verbal WM paradigm presentations, and general fMRI data analysis strategies were the same for both studies. Details will be presented below.

Participants

Individuals participating in Study 1 were selected from a database of 172 individuals with CFS and 100 Controls that had undergone the standard intake procedure (see below) of the CFS Cooperative Research Center (CFS CRC) between April 1992 and October 1998. Individuals participating in Study 2 were selected from a cohort of 290 individuals with CFS and 126 Controls that had undergone the standard intake procedure of the CFS CRC between April 1992 and December 2001. None of the participants in Study 1 were used in Study 2.

Standard CFS CRC intake procedure

All individuals with CFS were either self-referred based on media reports about the existence of the CFS CRC or referred by physicians; all Controls were recruited by advertisement in the local community. Once recruited, individuals provided consent, approved by the University of Medicine and Dentistry-New Jersey Medical School (UMDNJ-NJMS) institutional review board (IRB), to be administered the standard intake procedure in order to determine eligibility for participation in CFS CRC research studies. The standard intake procedure included a careful medical evaluation to determine group membership [i.e., healthy individuals versus those who fulfilled the most recent CDC case definition for CFS (Fukuda et al., 1994)], a computerized structured psychiatric interview, the Diagnostic Interview Schedule (DIS; Markus et al., 1990), to determine the presence of lifetime and current DSM III-R Axis-I psychiatric disorders, and a comprehensive neuropsychological testing battery including an estimate of premorbid intellectual ability using the Vocabulary subtest of the Wechsler

Adult Intelligence Scale-Revised (Wechsler, 1981) and an assessment of verbal information processing by PASAT (Brittain et al., 1991). The PASAT is a complex verbal WM task that has been used to uncover verbal information processing difficulties in individuals with CFS (Johnson et al., 1994).

Selection criteria for individuals with CFS and controls participating in Study 1 and Study 2

Participants for Study 1 and Study 2 were selected from the CFS CRC database described above. The total PASAT score was used to determine study eligibility for all participants. In Study 1, we chose CFS participants with verbal working memory difficulties operationally defined as PASAT performance of 1.5 SD or greater below the average score of all healthy individuals that were included in the CFS CRC database at intake. Of the 172 individuals with CFS in the database, six met our PASAT performance criteria and agreed to participate. In Study 2, we chose CFS participants who did not have PASAT performance difficulties as defined above (i.e., less than 1.5 SD below the mean of the healthy database sample). Of the 290 individuals with CFS in the database, 19 met our PASAT performance criteria and agreed to participate. For both studies, we chose healthy participants whose individual PASAT scores were less than 1.5 SD below the average of the total healthy database at time of intake. For Study 1, seven Controls met our criteria and agreed to participate. For Study 2, 18 Controls met our criteria and agreed to participate.

All participants were required to have an estimated premorbid intellectual ability within the average range as assessed by participants' Standard Score on the Vocabulary subtest of the WAIS-R (Wechsler, 1981) obtained as part of the initial standard intake procedure. Participants could not have a history of loss of consciousness for greater than 5 min and could not be on medications other than birth control pills. None of the study participants could have a current or lifetime Axis-I psychiatric disorder. All study participants had to be between 21 and 45 years old, right-handed, and native English speakers.

Once enrolled in either Study 1 or 2, within 3 months prior to their scheduled fMRI acquisition, all prospective study participants were re-administered a brief physical to confirm group membership, the DIS (Markus et al., 1990) to confirm the absence of a lifetime or current psychiatric diagnosis, and the PASAT (Brittain et al., 1991) to ascertain their individual level of verbal information processing ability (see Table 1). Based on these criteria, we included all six individuals with CFS and all seven Controls in Study 1 and all 19 individuals with CFS and all 18 Controls in Study 2. All participants signed informed consent approved by the internal review board committee at the UMDNJ-NJMS prior to participation in either Study 1 or Study 2.

Demographic information on all groups is presented in Table 1. Groups within and between studies were matched on handedness, gender distribution, and estimated premorbid IQ. There was no significant difference in age in Study 1 despite a large effect size (d = .81) suggesting that this finding was likely due to the small sample size studied. Differences in age observed in Study 2 were due to the elimination of data from three Controls secondary to faulty MR image acquisitions. In addition, based on our planned study designs, the total score on the PASAT differed significantly between CFS and control groups in Study 1, but not in Study 2.

FMRI verbal WM paradigm

The fMRI paradigm consisted of a set of two auditory information processing tasks. Task 1 was an auditory monitoring test measuring simple attention. Task 2 was the mPASAT, a challenging auditory verbal WM test. Both tasks were administered as two separate time-series in a fixed sequence with Task 1 always preceding Task 2. As shown in Fig. 1, each task was presented within a blocked design consisting of five blocks: a baseline period and two "ON-periods" alternating with two "OFF-periods". The two experimental tasks were presented during "ON-periods". In each of the tasks, numbers were presented once every 2 s for 500 ms. No task was presented during "OFF-periods" in any of the time-series and the participants were instructed to rest quietly.

Task 1—auditory monitoring: a simple attention task requiring monitoring of the aurally presented numeric information. During the auditory monitoring task, study participants heard a sequence of numbers ranging from 1 to 9 presented at a rate of one number every 2 s. Whenever the number "7" was presented, participants were required to use the thumb of their right hand to press a button on a box placed at their right thigh. The response was transmitted to and recorded on a laptop computer outside the scanning chamber.

Task 2—mPASAT: a modified version of the PASAT that has been used in previous studies (Christodoulou et al., 2001; Lange et al., 1998). This task requires encoding, maintenance, and manipulation of verbal information. During the mPASAT, study participants heard a sequence of numbers, ranging from 1 to 9 presented at the same rate as in Task 1. Study participants were instructed to add the 1st number they heard to the 2nd, the 2nd to the 3rd, and so on. Instead of answering aloud as in the standard PASAT procedure, participants were told to *silently* add the number dyads and to press a button with the thumb of their right hand whenever the dyad's sum equaled 10. This modification was designed to limit head movement artifacts during image acquisition. Both tasks presented to study participants were temporally and spatially balanced and differed from each other in only one dimension — task difficulty.

Table 1
Summary of demographic data for groups in Study 1 and 2

	Study 1 (n = 13)			Study 2 (n = 34)		
	CFS (n = 6)	Controls (n = 7)	P	CFS (n = 19)	Controls (n = 15)	P
Age	38.17 (9.0)	30.71 (9.6)	.18	37.53 (8.0)	30.80 (7.5)	.02
Female	100%	57%	.19	84%	68%	.42
Premorbid IQ[a] (mean SS[a])	10.80 (2.2)	11.20 (3.3)	.82	12.1 (2.3)	11.17 (2.0)	.27
Total PASAT[a] score	102.00 (27.7)	144.80 (24.8)	.03	128.18 (29.7)	126.73 (32.4)	.90

[a] IQ, Intelligence Quotient; SS, Standard Score; PASAT, Paced Auditory Serial Addition Test.

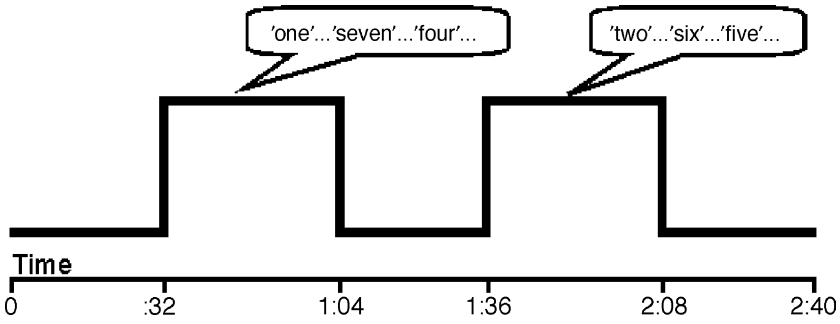

Fig. 1. Representation of the stimulus design presented to each subject. Timing was the same for each of the two task conditions, auditory monitoring and mPASAT, with two cycles of 32 s of stimulation and 32 s of rest after a 32 s introduction period.

Participants received task instructions and engaged in brief task practice before entering the magnet to ensure familiarity with the task protocol. The purpose of this study was to document brain activity during auditory information processing and not to image a learning effect. The audibility of both tasks (80 db) was well within the range of normal human auditory perception. It has been shown that the ambient noise level in the MR scanner does not impact on the hearing threshold of subjects. That is, subjects consistently obtained thresholds for pure tones and speech that ranged from 20 db to 30 db (Millen et al., 1995). The pitch of the auditory stimuli was randomly varied from 200 Hz to 1200 Hz to avoid adaptation. All stimuli were delivered simultaneously to both ears.

fMRI and conventional image acquisition

Imaging was performed on a 1.5 T Signa Scanner (General Electric Medical Systems, Milwaukee, WI). Study participants were positioned supine on the MRI table with their head resting in the padded radio frequency head coil. To avoid possible BOLD signal changes due to motion artifacts, bands of tape across the forehead and chin in conjunction with the padding restricted head motion. Study participants also wore MR compatible headphones to reduce scanner noise and to allow for the auditory presentation of the verbal WM tasks during fMRI acquisition.

First, an initial T1-weighted sagittal localizer was acquired to determine the location of the MR images. Second, T1-weighted axial images encompassing the whole brain were acquired (TE/TR = 20/4500 ms, 256 × 256 pixel matrix, FOV = 24 cm, slice thickness = 5 mm). Third, a gradient echo planer T2*-weighted sequence was used at the same slice locations to acquire data sensitive to the BOLD signal (TE/TR = 60/4000, 64 × 64 pixel matrix, FOV = 24 cm, slice thickness = 5 mm).

fMRI data analysis

The functional neuroimaging data were analyzed using SPM99 (Wellcome Department of Cognitive Neurology, http://www.fil.ion.ucl.ac.uk/spm). To account for magnetic saturation effects, the first three scans of each time-series were discarded. The remaining images for each time-series were realigned to the first image of the first series to correct for movement related artifacts. The time-series was co-registered to the structural T1 volume and all images were spatially normalized using 12 parameter affine basis functions and non-linear warping into the standard Montreal Neurological Institute (MNI) space (Ashburner and Friston, 1999; Friston et al., 1995). Locations of signal change are reported in Talairach and Tournoux space (Talairach and Tournoux, 1988) after appropriate spatial correction (Brett et al., 2002). All functional images were spatially smoothed with an 8 mm isotropic Gaussian kernel to account for anatomic variability between study participants. Using the general linear model, statistical maps were computed for each time-series at the single subject level to reflect the differences between the ON and the OFF conditions of the blocked paradigm. After creation of the individual brain maps, within and between groups statistical comparisons were performed.

Based on our a priori hypothesis, we employed an ROI analysis including gray matter in the following brain regions: Brodmann areas 9/10/46, 45/47, 44, 6/8, 7, 40, 24/32. ROIs were created using the automated Talairach Daemon (TD; Lancaster et al., 2000) thereby eliminating any operator biases. All within group ROI results were then corrected for multiple voxel-wise comparisons with the False Discovery Rate (FDR) method (Genovese et al., 2002) and analyzed at the corrected P level of <.05. Between groups analysis was conducted at an uncorrected P level set at < .01. This procedure was consistent with that used by Cook et al. (2004). Briefly, we only admitted those predetermined ROIs into the between groups analysis that had shown significant BOLD signal change (at an FDR-corrected level of $P < .05$) at the between groups level. This effectively limited the within group search volume to those locations utilized by either group at the within group level. The results for this limited search volume were thresholded at an uncorrected significance level of $P < .01$. We chose the uncorrected threshold, because the between group search volume was based on the FDR-corrected within groups statistics.

Study 1

Comparison between healthy Controls and individuals with CFS who have neuropsychologically documented problems in verbal information processing as assessed with the PASAT.

Methods

Behavioral assessments and data analysis

Just prior to acquisition of the functional MRI data, we administered the Beck Depression Inventory (BDI; Beck, 1987) to all participants to document potential symptoms of depression present during the week before participation in the study. The BDI is widely used in clinical settings to screen for depression and has well-established psychometric properties (Beck, 1961; Beck et al., 1988). Each of the 21 items on the BDI consists of four statements arranged in increasing order of severity. Participants are instructed to choose the one that 'best describes the way you have been

feeling over the past week, including today'. Total scores range from 0 to 63 with a cut-off for clinical depression usually set at 18. At the same time, we also administered the State component of the Spielberger's Anxiety Inventory (STAI; Spielberger, 1983) to measure the level of anxiety just prior to MR scanning. The 20-item State component of the STAI is used to assess an individual's level of anxiety at a specific moment in time: (1) not at all, (2) somewhat, (3) moderately so, (4) very much so. Each item is given a weighted score of 1 through 4. Total scores range from 20 to 80. The scale has found to reliably reflect changes in level of anxiety over time (Spielberger, 1983). For both auditory information processing tasks, percent total errors were recorded during task performance in the MR scanner. All behavioral data were analyzed using Students t test with the significance level set at $P < .05$.

fMRI image acquisition and data analysis

Each of the two information processing tasks described above was presented in a blocked paradigm consisting of five 32-s blocks. Each time-series lasted 2 min and 40 s and resulted in the acquisition of 40 scans for each study participant for each task. After removal of the first three scans, 37 scans were admitted into the analysis. Due to the small number of participants in Study 1, we used a fixed effects model to analyze our within and between groups functional data. Thus, our results are limited to inferences about the specific groups of individuals with CFS and Controls imaged for this study.

Results and discussion

Behavioral assessments

The mean BDI score of the CFS group was significantly higher ($M = 17.83$, SD = 12.5) than that of Controls ($M = .29$, SD = .5; $t = -3.42$, $P < .02$). Likewise, the CFS group scored significantly higher on the State component of the STAI prior to fMRI data acquisition ($M = 51$, SD = 9.1) than Controls ($M = 27.86$, SD = 8.3; $t = -4.8$, $P < .001$). As shown in Fig. 2, the error rate of the Study 1 CFS group on the mPASAT during fMRI acquisition was significantly higher than that of Controls (CFS percent mean total errors = 45.83%, SD = 23.8%; control percent mean total errors = 13.00%, SD = 10.6%; $t = -3.1$, $P < .02$). In contrast, no significant group difference was observed on the simple auditory monitoring task (CFS percent mean total errors = 9.67%, SD = 23.7%; control percent mean total errors = 4.71%, SD = 12.5%; $t = -.48$; $P < .64$).

Neuroimaging data

To determine the BOLD signal change over and above the working memory demands required by a simple attention task (auditory monitoring task), we generated within group contrasts by subtracting signal change in response to the auditory monitoring task from that of the mPASAT task. Once the BOLD signal change in response to the auditory monitoring task was factored out, regions specifically engaged in individuals with CFS during mPASAT performance included: bilateral dorsolateral prefrontal (BA9/46), bilateral inferior frontal (BA44), left ventrolateral prefrontal (BA45/47), bilateral supplemental and premotor (BA6/8), bilateral superior parietal (BA7), bilateral inferior parietal regions (BA40), and the bilateral anterior cingulate regions (BA24/32). The same contrast in Controls engaged regions including: left dorsolateral prefrontal (BA9/46), left inferior frontal (BA44), left supplemental and premotor (BA6/8), and bilateral superior parietal regions (BA7) (for detailed results of both groups, see Table 2).

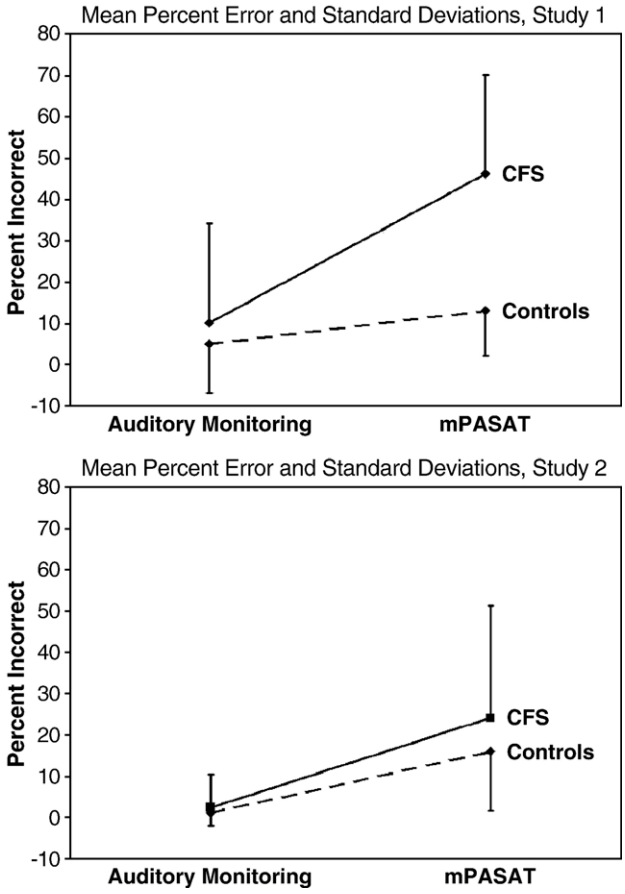

Fig. 2. Both plots show mean percent error and standard deviations for CFS and Controls during performance on the auditory monitoring and mPASAT tasks while in the MRI scanner. The top plot shows data from Study 1 and the bottom plot reflects performance on Study 2.

When compared directly to Controls using a fixed effects analysis, the CFS group showed significantly greater BOLD signal change in bilateral premotor (BA6; left hemisphere: $x = -26$, $y = 22$, $z = 47$; peak Z score = 2.73; number of gray matter voxels = 8; right hemisphere: $x = 28$, $U = -4$, $z = 44$, peak Z score = 2.58; number of gray matter voxels = 4) and left superior parietal regions (BA7; $x = -22$, $y = -58$, $z = 45$; peak Z score = 4.05, number of gray matter voxels = 46). Controls did not exhibit any BOLD signal change greater than CFS in any of the ROIs studied.

Discussion

When complex auditory information processing was required, the pattern of BOLD signal change in individuals with CFS that had difficulties with complex verbal information processing extended to homologous bilateral brain areas that have previously been associated with the functional verbal WM network. The ROI analysis showed that the CFS group engaged dorsolateral and ventrolateral prefrontal, supplemental motor, and premotor regions bilaterally to an equal degree. The same pattern held true for the inferior and superior parietal lobes, as well as the anterior cingulate. In contrast and consistent with previous imaging studies of healthy individuals, the demographically matched, but cognitively significantly better performing control group utilized dorso- and ventrolateral prefrontal, supplementary

Table 2
Study 1 within groups analysis mPASAT versus auditory monitoring using a fixed effects model, FDR-corrected at $P < .05$

Region of interest Brodmann area	Peak voxel	Peak Z score	Number of gray matter voxels in cluster	Peak voxel	Peak Z score	Number of gray matter voxels in cluster
	Left hemisphere—CFS			Right hemisphere—CFS		
9/46	−54 6 36	5.72	274	34 32 16	3.08	68
45/47	−46 20 12	2.91	16			
44	−44 14 8	3.08	16	60 6 18	2.62	11
10						
6/8	−32 6 56	6.29	270	32 −6 50	6.00	313
6/8	−2 6 52	4.01	137	20 −16 68	3.79	14
7	−24 −70 44	INF	1119	24 −62 52	6.67	761
40	−36 −56 52	7.44	610	46 −36 38	6.42	566
24/32	−4 12 46	4.08	352	4 2 48	3.62	239
	Left hemisphere—Controls			Right hemisphere—Controls		
9/46	−44 6 38	4.50	33			
45/47						
44	−54 6 16	4.16	7			
10						
6/8	−42 0 54	3.99	7			
6/8						
7	−6 −66 54	4.94	41	28 −60 46	3.96	3
40						
24/32						

motor, and premotor regions exclusively in the left hemisphere and only engaged the superior parietal regions bilaterally. Total PASAT scores of the CFS group in Study 1 were significantly associated with error rate on the mPASAT during fMRI acquisition ($r = -.676$, $P < .03$) suggesting that both tasks posed a similar level of difficulty for these individuals. In support of our hypothesis, the findings of Study 1 suggest that the low performing CFS group required more extensive, bilateral recruitment of brain regions associated with verbal WM function to process the task demands presented by this complex and difficult information processing task (mPASAT).

It is possible that the observed BOLD signal change in this pilot study could be at least partially attributed to factors unrelated to fatigue including lack of effort to perform well, anxiety, or depression. Therefore, we empirically controlled for this possibility in a larger follow-up study (Study 2), using a comparable protocol, with study participants that were demographically matched to those that participated in Study 1 (see Table 1). However, in Study 2, we also statistically controlled for symptoms of anxiety and depression and most importantly for the level of cognitive performance. Individuals with CFS did not have objectively measured problems in auditory complex information processing as defined above. Thus, if the pattern of verbal WM function observed in Study 1 was due to the impact of CFS on brain function, we should observe similar bilateral BOLD signal changes in a CFS group without auditory information processing difficulties.

Study 2

Comparison between healthy Controls and individuals with CFS *who do not have* neuropsychologically documented problems in auditory information processing as assessed with the PASAT.

Methods

Behavioral assessments and data analysis

As in Study 1, the BDI and the State Component of the STAI (Spielberger, 1983) were administered just prior to MRI acquisition. However, in contrast to Study 1, all study participants now also completed the State component of the STAI after MRI data acquisition to determine whether context related levels of anxiety for each group were significantly different pre- and post MR acquisition. If so, level of State anxiety would be considered as a confounding variable possibly affecting within group differences in the pattern of BOLD signal change. We also assessed the degree of perceived mental fatigue as measured by the Multidimensional Fatigue Inventory-20 (MFI-20; Smets et al., 1995), a 20-item self-report questionnaire with good psychometric properties. On this instrument, participants are instructed to put a cross in one of five continuing boxes ranging from "yes, that is true" (statement to left of the boxes) to "no, that is not true" (statement to right of the boxes) when responding to a statement placed next to the row of boxes such as: "Thinking requires effort". Each item is given a weighted score of 1 through 5. Total scores range from 20 to 100. As in Study 1, we recorded percent total errors on both verbal WM tasks. Additionally, we measured the latency to respond on a laptop computer outside of the scanner chamber during task performance in the MR scanner. All behavioral data were analyzed using Students t test with the significance level set at $P < .05$.

fMRI image acquisition and data analysis

We acquired 43 scans per task for each study participant by increasing the duration of the baseline period from 32 s in Study 1 to 44 s. Thus, after removing the first three scans to account for magnetic saturation effects, we were able to submit 40 scans per task per study participant for analysis. Increasing the number of scans by increasing the length of the baseline period was an

improvement over our design in Study 1, because it kept all blocks in the time-series at the same duration of 32 s.

We also modified the fMRI analysis in Study 2. Due to the greater sample size, we employed a within groups random effects model, thus were able to account for within-subject as well as between-subject variance. The between groups analysis was conducted consistent with the procedure used by Cook et al. (2004) described above. Since groups significantly differed on age, as well as mood, anxiety, and mental fatigue scores, we employed an Analysis of Covariance to the between groups data to account for these differences. We used STAI pre-scores as the anxiety covariant since we considered them to be reflective of the general state of anxiety during fMRI acquisition.

Results and discussion

Behavioral assessments

Compared to Controls, individuals with CFS experienced significantly greater mental fatigue (CFS: $M = 15.58$, SD = 3.6, Controls: $M = 6.00$, SD = 2.7, $t = -8.74$, $P < .001$). We separated the total BDI scores into subcategories reflecting the cognitive–affective (items 1 through 13) and somatic components (items 14 through 21) of the BDI (Beck and Steer, 1993). While scores of the CFS group in both components were significantly different from that of Controls (BDI mean cognitive–affective score CFS = 3.7, SD = 3.4; BDI mean cognitive–affective score Controls = 1.2, SD = 2.0; $t = -2.53$, $P < .02$; BDI mean somatic score CFS = 5.9, SD = 2.9; BDI mean somatic score Controls = 0.8, SD = 1.4; $t = -6.66$, $P < .001$), we only chose to correlate the cognitive–affective scores to the BOLD signal, since the items on the somatic component are consistent with symptoms of CFS. The CFS group was more anxious during study participation (mean pre STAI total score = 33.68, SD = 9.6; mean post STAI total score = 34.47, SD = 10.0) than the Controls (mean pre STAI total score = 26.93, SD = 6.7, $t = -2.30$, $P < .03$; mean post STAI total score = 24.20, SD = 4.8, $t = -3.65$, $P < .001$), but pre and post scores were not significantly different for both groups.

As intended by the design for Study 2, the error rates on the auditory monitoring (CFS mean percent error = 2.43%, SD = 8.0% and control mean percent error = 1.19%, SD = 3.0%; $t = -.55$; $P < .58$) and mPASAT tasks (CFS mean percent error = 24.16%, SD = 27.2% and control mean percent error = 16.10%, SD = 14.4%; $t = -1.10$; $P < .28$) were similar for CFS and control groups (see Fig. 2). Consistent with Study 1, percent mean total errors on the mPASAT task were significantly correlated with the total score on the PASAT ($r = .375$, $P < .04$) suggesting a similarity in task demands. On average, compared to Controls, the CFS group was slower to indicate their responses to the simple auditory monitoring task (Controls = 0.96 s, SD = .07, CFS = 1.13 s, SD = .22, $t = -2.29$, $P < .03$), but reached a response speed comparable to that of Controls when more attentional effort was required in order to solve the mPASAT (Controls = 1.34 s, SD = .29; CFS = 1.42 s, SD = .32, $P < .54$; see Fig. 3).

Neuroimaging data

Under conditions of effortless auditory processing (auditory monitoring), CFS and Controls engaged the same brain regions underlying the verbal WM network including: bilateral dorsolateral prefrontal (BA9/46), bilateral ventrolateral prefrontal (BA45/47), bilateral inferior frontal (BA44), right anterior frontal (BA10), bilateral supplemental and premotor (BA 6/8), bilateral inferior parietal (BA40), as well as bilateral anterior cingulate regions (BA24/32). Subsequent between groups comparison (CFS > Controls and vice versa) with an uncorrected P level set at .01 confirmed our initial impression.

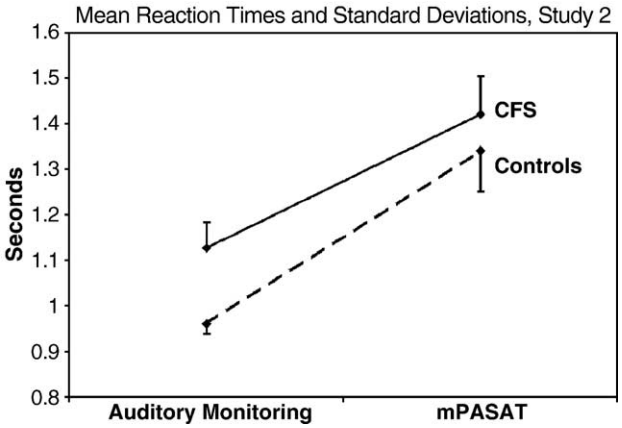

Fig. 3. Study 2 mean reaction times and standard errors of CFS and Controls during performance on the auditory monitoring and mPASAT tasks while in the MRI scanner.

After factoring out the BOLD responses to the simple auditory monitoring task over rest, BOLD signal change in response to the mPASAT in Controls was only observed in bilateral dorsolateral prefrontal (BA9/46), bilateral supplemental motor and premotor regions (BA6/8), and right superior parietal cortex (BA7). In addition to these brain regions, the CFS group also engaged left ventrolateral prefrontal (BA45/47), left inferior frontal (BA44), right anterior frontal (BA10), bilateral supplemental and premotor (BA 6/8), left superior (BA7) and inferior parietal cortex (BA40), as well as bilateral anterior cingulate regions (BA24/32) when processing complex auditory information (see Table 3 and Fig. 4).

Comparing BOLD signal change in response to the mPASAT, over and above that elicited by simple auditory monitoring over rest, directly to Controls, the CFS group showed significantly greater BOLD signal change in bilateral supplemental and premotor (BA 6/8; left hemisphere: $x = -26$, $y = 22$, $z = 47$; peak Z score = 2.73; number of gray matter voxels = 8; right hemisphere: $x = 28$, $y = -4$, $z = 44$; peak Z score = 2.58; number of gray matter voxels = 4) and left superior parietal regions (BA7; $x = -22$, $y = -58$, $z = 45$, peak Z score = 4.05, number of gray matter voxels in cluster = 46). Analysis of Covariance with age, anxiety, or the cognitive–affective symptoms of the BDI as the covariant did not eliminate the group differences. However, mental fatigue as measured by the MFI accounted to a large degree for BOLD signal change in the left superior parietal region (BA7) and enhanced activation in bilateral supplemental and premotor regions (BA 6/8). Controls did not exhibit any BOLD signal change greater than CFS in any of the ROIs studied. Thus, we obtained evidence that the CFS group needs to engage the verbal WM system more extensively than Controls when greater effort is required to process complex verbal information, but not when auditory information processing is simple.

Discussion

Based on the results of the present investigation, Chronic Fatigue Syndrome (Fukuda et al., 1994) may have a significant effect on brain function when people are required to process complex auditory information quickly and efficiently. Utilization

Table 3
Study 2 within groups analysis mPASAT versus auditory monitoring using a random effects model, FDR-corrected at $P < .05$

Region of interest Brodmann area	Peak voxel	Peak Z score	Number of gray matter voxels in cluster	Peak voxel	Peak Z score	Number of gray matter voxels in cluster
	Left hemisphere—CFS			Right hemisphere—CFS		
9/46	−48 30 21	4.71	38	42 42 20	3.73	16
	−44 3 27	4.05	125	46 23 32	3.40	96
	−40 33 30	3.75	11	34 46 27	2.87	4
45/47	−50 18 14	3.21	10			
44	−50 18 14	3.21	45			
10				42 42 20	3.73	7
6/8 Middle	−26 11 57	4.11	43	24 11 55	3.85	143
	−44 3 27	4.05	6	46 23 32	3.40	17
	−26 4 46	3.57	68			
	−22 24 49	3.10	26			
6/8 Superior				2 22 49	4.42	62
				24 11 55	3.85	18
7	−22 −60 47	4.89	218	28 −56 45	4.18	155
	−32 −60 45	3.87	19	34 −58 43	3.65	5
40	−22 −60 47	4.89	95	28 −56 45	4.18	90
24/32	−2 21 41	3.10	26	4 18 41	3.47	14
				8 34 22	2.98	16
	Left hemisphere—Controls			Right hemisphere—Controls		
9/46	−46 6 33	4.36	31	46 17 34	4.55	52
45/47						
44						
10						
6/8 Middle	−26 4 46	3.27	3	32 6 49	4.22	18
6/8 Superior	−2 14 51	5.02	22			
7				8 −62 51	3.33	4
40						
24/32						

of the verbal WM system in response to a complex auditory information processing task was more extensive in the CFS group than in Controls and occurred independent of objectively measured information processing difficulties. Importantly, anxiety and cognitive–affective mood symptoms did not explain the observed differences. In contrast, the degree of mental fatigue experienced accounted for most of the between group differences in the left superior parietal cortex (BA7), part of the "posterior attention system" implicated in attentional shifts from one target to another (for review, see Posner and Petersen, 1990) and selectively involved in sustained attention tasks (Coull et al., 1996; Honey et al., 2000; LaBar et al., 1999).

In the CFS groups, the shift of BOLD signal change toward more bilateral engagement (Study 1) as well as increased engagement of brain regions known to support verbal WM was consistent with previous verbal WM studies. These studies included the examination of the effects of load on verbal working memory in healthy adults (i.e., Braver et al., 1997; Jonides et al., 1997; Seidman et al., 1998), as well as in individuals with traumatic brain injury (Christodoulou et al., 2001; Manoach et al., 1997; McAllister et al., 1999, 2001) and multiple sclerosis (Chiaravalloti et al., 2003; Hillary et al., 2003; Staffen et al., 2002). Taken together, these results suggest that the pattern of BOLD signal change observed in individuals with CFS may be a reflection of the networks operation under conditions of increased mental effort (Christodoulou et al., 2001; Cohen et al., 1997; Gould et al., 2003; Woodard et al., 1998) in response to or in order to overcome the experience of mental fatigue. Our results would also explain the inconsistencies observed between subjective reports of cognitive difficulties (i.e., more effortful information processing) and objective findings. Individuals with CFS can process complex auditory information successfully, therefore not show any difficulties on neuropsychological testing. However, they do so "working harder" which may lead to the perception of mental fatigue (i.e., cognitive complaints). Behavioral, neuropsychological testing may not be sensitive enough to uncover this problem in individuals with CFS. Functional neuroimaging provides a window to the brain during the process of auditory information processing showing that the problem for individuals with CFS is not only "what" is processed, but "how" it is processed. Thus, our results provide objective evidence in support of the subjective report of cognitive difficulties in individuals with CFS and demonstrate an important role for functional neuroimaging in understanding the pathophysiology of CFS symptoms.

In general, the pattern of BOLD signal change in Controls across both studies is consistent with that seen in response to other complex numeric verbal WM tasks in healthy adults (e.g., Schumacher et al., 1996). To accommodate the cognitive demands imposed by the task chosen in this study, the mPASAT, over and above those necessary to solve the less demanding auditory monitoring task, controls engaged dorsolateral (BA 9/46) and ventrolateral prefrontal (BA 44), supplementary motor and premotor (BA 6/8), and superior parietal (BA7) regions. The left dorsolateral prefrontal region is known to be involved when high working memory loads are processed and can extend bilaterally when latency to respond increases (Rypma and D'Esposito, 1999).

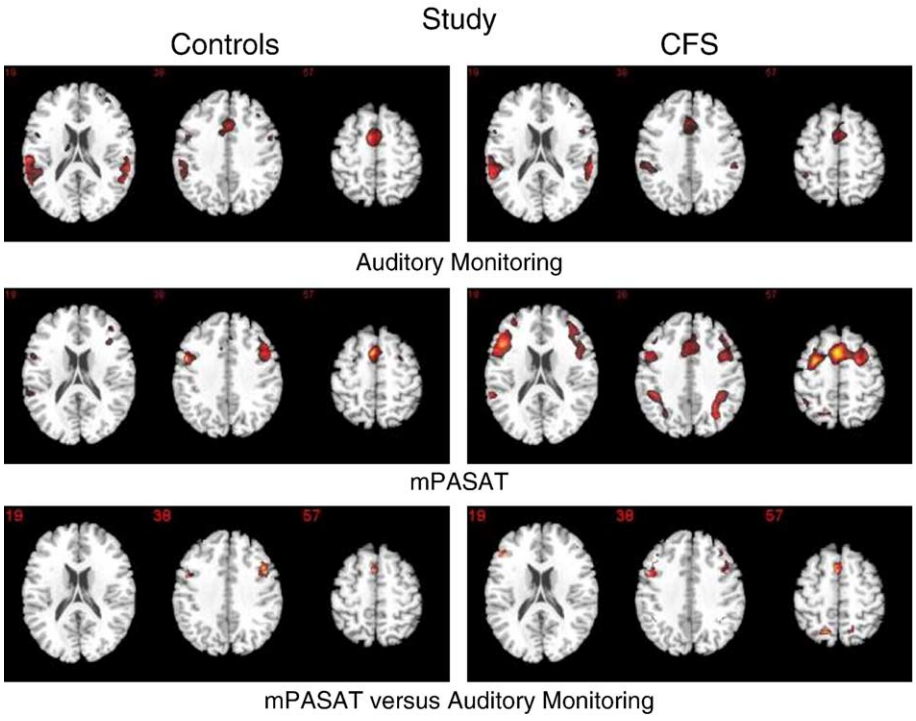

Fig. 4. Within group comparison for CFS and Control groups in Study 2 for auditory monitoring (top row), mPASAT (middle row), and the direct comparison of mPASAT > auditory monitoring (bottom row). The threshold was set at an FDR-corrected level of $P < .05$. The data are overlaid on the standard image provided with MRICro (Rorden and Brett, 2000) software. The slice locations are (from left to right): $z = 18$, 38, and 57 mm.

Rypma et al. (Rypma and D'Esposito, 1999) suggest that the latency to respond may be an indicator of the efficiency with which mnemonic scanning occurs prior to a response. Left ventrolateral cortex is thought to be involved in maintenance and rehearsal of information (for review, see D'Esposito et al., 2000). Bilateral supplemental motor and premotor regions have been implicated in the planning and production of speech (Smith and Jonides, 1998), time processing (Macar et al., 2002), maintenance of temporal order (Rowe and Passingham, 2001), verbal rehearsal strategies (Fiez et al., 1996), as well as automatic information processing (Jansma et al., 2001). Previous studies showed that bilateral superior parietal cortices (BA7) were associated with attentional processes (Posner and Rothbart, 1998).

The evidence supporting a CNS pathophysiological process for some individuals with CFS is mounting. Specifically, small white matter hyperintensities on brain MR imaging have been found in the frontal lobes of a group of individuals with CFS without coexisting psychiatric disorder (Lange et al., 1999) and these brain abnormalities are significantly related to subjective reports of decreased physical function in CFS (Cook et al., 2001). SPECT studies have found significantly lower relative blood perfusion (Ichise et al., 1992; Schwartz et al., 1994b) and glucose levels (Siessmeier et al., 2003; Tirelli et al., 1998) in bilateral frontal brain regions, the anterior cingulate, and also in temporal, parietal, and occipital areas as well as the brainstems of individuals with CFS (Costa et al., 1995). Recently, Schmaling and colleagues (Schmaling et al., 2003) reported comparatively lower relative brain blood flow in the anterior cingulate of individuals with CFS free of psychiatric illness during response to a cognitive challenge. Using PET, Kuratsune and co-workers (Kuratsune et al., 2002) showed that compared to Controls, individuals with CFS without psychiatric histories had significantly lower absolute global and regional levels of blood flow including bilateral dorsolateral (BA 9) and left ventrolateral (BA 44) prefrontal, as well as bilateral anterior cingulate brain regions (BA 24/32).

Limitations of this study

The results of this study must be interpreted in light of possible methodological limitations. First, the mean total PASAT score for Controls in Study 2 was lower than that for Controls in Study 1. However, a comparison of Controls across studies shows that PASAT performance of the Control group in Study 1 was similar to that in Study 2 (mean total PASAT score Study 1: 144.80, SD = 24.8; mean total PASAT score Study 2: 126.73, SD = 32.4, $P < .23$). Thus, although sample sizes differed greatly, both Control groups were characterized by the same degree of variability in PASAT performance (Study 1: $n = 7$, range: 115–183; Study 2: $n = 15$, range: 68–190). Removing outliers out of the statistical analysis did not alter patterns of BOLD signal change. Second, although BOLD fMRI is an accepted and well-validated neuroimaging method, it does not provide a measure of absolute flow and therefore differences in resting baseline flow are a potential limitation. Future research should be conducted that determines whether differences in baseline blood flow are related to changes in BOLD signal during challenging cognitive tasks.

Conclusions

The results of the present study are further evidence that symptomatology associated with a severe fatiguing illness may have an effect on brain function. Our studies do not support the notion that difficulties in cognitive function in individuals with CFS are related to poor motivation, but instead provide evidence of

increased neural resource allocation when processing more complex auditory information, a task often encountered in everyday life.

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