

# Is CFS a Brain Disorder?



*The cognitive problems CFS patients report have led to numerous research studies to assess neurocognitive impairments. Although data is not consistent, research confirms both structural and functional brain abnormalities in CFS.*

By Gudrun Lange, PhD, UMDNJ-New Jersey Medical School

Trouble concentrating. Poor memory. Difficulty processing information. Cognitive difficulties are among the most debilitating of CFS symptoms. These problems, often referred to as “brain fog” by patients, are more than just a nuisance or frustrating. They can be functionally disabling and severely limit school or job performance, even contributing to school failure or loss of career in some patients.

measured using objective neuropsychological assessment tools, the deficits detected are often labeled as “subtle” or “not statistically significant.”<sup>1</sup> However, statistical significance can’t be equated with clinical significance.

Most researchers now acknowledge that the central nervous system—the brain and spinal cord—somehow plays a role in CFS. The scientific literature, however, is full of conflicting studies, and the exact nature of the neurocognitive impairment is still unclear.

## What accounts for conflicting results?

Nancy Klimas’s article beginning on page 4 covers the methodological factors—including sample size, makeup of control groups and the need to subtype cohorts—that have plagued CFS research. There are, however, some additional factors contributing to inconsistent results in neurocognitive research.

- ▶ A standard neuropsychological test battery to assess cognitive function isn’t used across studies, prompting differing interpretations of test results.
- ▶ Some studies rely on rater-dependent data analysis techniques that could introduce bias.
- ▶ Technological aspects of the studies often differ, affecting results. SPECT cameras can range from single- to triple-head cameras; MRI scanners can have a field strength of either 1.5 or 3.0T.
- ▶ Investigators using the SPECT technique often use the cerebellum to normalize their data, assuming that flow in this region of the brain is similar between groups. Based on some reports, this may not be the case.
- ▶ Due to technical limitations, some studies only

Cognitive problems have been reported in as many as 85-95% of patients, and neurocognitive studies form a significant body of CFS research to date. Researchers have focused both on the anatomy/structure of the brain and the function of the brain in CFS patients to determine if there are abnormalities that might account for the impaired cognitive function.

Although CFS patients describe their cognitive problems as very prominent and disabling, when



## Two Studies Find Gray Matter Reduction in CFS Patients

Cognitive difficulties are found in 85-95% of CFS patients. Now, cutting-edge research from two independent international groups suggests that the volume of gray matter in the brain is significantly decreased in CFS. This decrease in brain tissue, or cerebral atrophy, may be responsible for cognitive problems in some people with CFS.

The most recent of the studies, conducted in 2005 in the Netherlands, used MRI technology to measure brain volume and tissue concentration, finding that the volume of gray matter in CFS patients was significantly decreased.<sup>6</sup> What is especially interesting about this study is that after researchers found structural abnormalities in a first CFS cohort, they repeated the experiment in a second cohort of equal size and found the same results. In all, 28 patients and 28 healthy controls were tested. The researchers, led by Floris de Lange, report that when results from both cohorts were combined, the reduction in gray matter tissue in CFS patients was 8%.

This echoes the 2004 findings of a Japanese research group led by Tomohisa Okada, MD, PhD, which observed “a significant reduction in gray matter volume in the bilateral prefrontal areas of CFS patients.” Investigators found an 11.8% volume reduction in the 16 CFS patients compared to the 49 healthy controls.<sup>7</sup>

Both studies used a technique called voxel-based morphometry (VBM) to measure the results of the brain scan. Unlike assessment techniques that rely on human observers and rating scales, VBM is an automated procedure that provides unbiased results. While gray matter reduction was found in both studies using VBM, neither study found white matter abnormalities.

Although we don't know if the observed cerebral atrophy is a cause of CFS or a consequence, these findings are alarming some members of the CFS patient community, who are concerned about “brain damage.” It's important to note that the studies are small and need to be replicated by other researchers before definite conclusions can be made. And even if the results are confirmed by future investigators, the brain has a remarkable ability to adapt and to “rewire” itself in compensatory ways. Research shows that people with CFS may use more extensive regions of the brain to process tasks and information, perhaps compensating for deficits in specific areas of the brain. There are rehabilitative techniques patients can employ to help with cognitive problems. (See pages 48-59 for more on treatment.)

have two image slices available for analysis whose thickness is not always noted, while others are able to analyze contiguous slices of the entire brain.

► When neuroimaging studies are task-dependent, the behavioral paradigms used to evaluate brain function are rarely identical or even similar across studies, so they need to be described thoroughly.

It's also possible that we haven't yet discovered what area of the brain to study in CFS, or whether the technology now available can give us the answers we seek.

## Cognitive deficits

In spite of methodological limitations and conflicting studies, there are some consistent findings about brain function from neuropsychological testing. Impairments in numerous cognitive domains—acquiring new information, processing information, attention, concentration, verbal memory, visual memory, reaction time and psychomotor function—can be found in the scientific literature on CFS. The most consistent findings, however, are slower reaction time, poorer performance on complex attentional and memory tasks and slowness in acquiring new information. This suggests that slowed cognitive and motor speed appears to be a basic underpinning of cognitive difficulties in CFS.<sup>2,3</sup>

## Neuroimaging study results

Investigators have used brain imaging technology to examine whether people with CFS have structural and/or functional abnormalities. Both have been found. Here are some of the key findings:

► Several structural MRI studies conducted in the 1990s found abnormalities in cerebral white matter, usually small hyperintensities (bright white spots or lesions).<sup>4</sup> It appears that CFS patients who don't also have a psychiatric disorder like depression are much more likely to have white matter abnormalities than CFS patients with depression.

► Three recent studies have found evidence of cerebral atrophy. This means the brain has decreased in size, possibly due to the death of brain tissue. Our UMDNJ group found indirect evidence for white matter loss,<sup>5</sup> and two recent studies reported a significant reduction in cerebral gray matter (see boxed story on this page).<sup>6,7</sup>

► Numerous dynamic imaging studies have now shown reduced cerebral blood flow, called hypoperfusion, in CFS patients.<sup>8,9,10,11</sup> Reduced cerebral blood flow has been found globally<sup>9,10,11</sup> as well as in the lateral frontal, lateral temporal and medial temporal lobes.<sup>12,13</sup> The research suggests that CFS patients, particularly those without concurrent psychiatric conditions, suffer from widespread cerebral hypoperfusion.

► Several studies have found abnormal brain metabolism in CFS patients. Abnormal cerebral glucose metabolism,<sup>14,15</sup> decreased acetylcarnitine uptake<sup>10</sup> and abnormalities in the serotonergic neurotransmitter system are the reported

findings.<sup>16,17</sup>

► Our UMDNJ research team used BOLD fMRI in a 2005 study which found that CFS patients are able to process challenging information, but they utilize more extensive cerebral networks and have to exert greater effort to process auditory information. Brain activation in CFS, particularly in patients without concurrent psychiatric illness, is significantly more diffuse than normal.

► A 2005 study found that 30% of CFS patients had higher protein levels and/or white blood cell counts in spinal fluid than normal.<sup>18</sup> CFS patients without depression or other psychiatric comorbidity were more likely to have abnormal spinal fluid, suggesting that this subset of patients may suffer from central nervous system immune dysfunction.

► Due to work from our research group and many others, it appears that CFS patients who don't have a concurrent psychiatric disorder are the ones with the most severe cognitive difficulties and the most pronounced abnormalities in neuroimaging studies. This suggests subtyping CFS cohorts by the presence or absence of depression and other psychiatric disorders may be very useful in subsequent studies.

## What can we say for sure?

We know CFS patients, especially those without concurrent psychiatric illnesses, are generally slower mentally as well as motorically, but often not to a "statistically significant" degree. This slowness can impact higher cognitive functions, such as memory and executive function.

What we don't know is what causes the slowed latencies observed in CFS patients. Hypotheses abound. Some investigators claim that an infectious process may be responsible, while others suggest cardiovascular problems may be at the root of the cognitive problems. Could the reduced cerebral blood flow found in CFS be linked to the cerebral atrophy and cognitive problems found in some patients? We don't know at this point whether the brain abnormalities observed are caused by underlying immunological or physiological processes or

## Will Technology Reveal the Answer?

New neuroimaging techniques are revealing more and more about CFS. The integrity of the brain in CFS patients is being evaluated using both static and dynamic imaging tools. There is hope that utilizing a combination of these tools under strict study protocols may someday give us conclusive answers about the role of the brain in CFS.

**MRI**, magnetic resonance imaging, is the static technique most often used in CFS. It's used to detect brain lesions, the presence of white and gray matter abnormalities and decreases in brain volume.

**fMRI**, functional MRI, a newer dynamic technique, is used to assess the functional integrity of the brain in CFS patients.

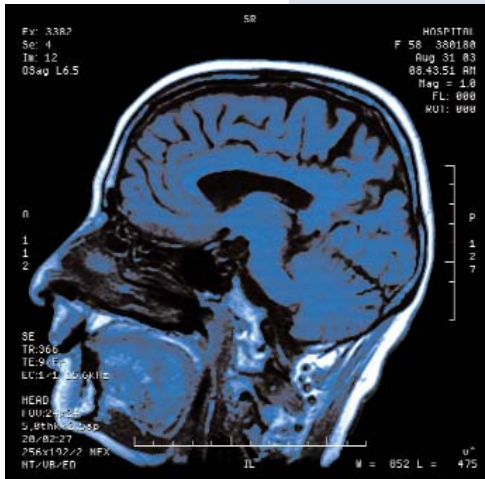
**BOLD fMRI**, blood oxygen level dependent functional MRI, is not invasive since no radioligands are involved, so task-related activity can be imaged multiple times.

**SPECT**, single photon emission computed tomography, is a dynamic technique used to measure global and regional cerebral blood flow either at a resting state or during task performance.

**PET**, positron emission tomography, has been used to provide data on cerebral blood flow and metabolism in CFS.

**H-MRS**, proton magnetic spectroscopy, is used to assess the concentration of brain metabolites in CFS patients.

**VBM**, voxel-based morphometry, is a technique for computational analysis of differences in global and local gray and white matter volume from MRI images. Unlike many morphological assessment tools, which require human observers and subjective ratings, VBM is fully automated, so results are more objective.



whether these neurological problems are the cause of other abnormalities observed in CFS.

In my opinion, it's premature to conclusively point to specific brain abnormalities, whether of a structural or functional nature. Better characterization of study samples and imaging protocols, as well as replicating and combining different techniques, is necessary before we can be conclusive about brain abnormalities in CFS and the role the central nervous system plays in this illness. ■

## References

1. Altay HT, Toner BB, Brooker H, Abbey SE, Salit IE, Garfinkel PE. The neuropsychological dimensions of postinfectious neuromyasthenia (chronic fatigue syndrome): a preliminary report. *Int J Psychiatry Med* 1990;20:141-149.
2. Lange G, Steffener J, Cook DB, Bly BM, Christodoulou C, Liu WC et al. Objective evidence of cognitive complaints in Chronic Fatigue Syndrome: a BOLD fMRI study of verbal working memory. *Neuroimage* 2005;26:513-524.
3. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JW et al. Neural correlates of the chronic fatigue syndrome--an fMRI study. *Brain* 2004b;127:1948-1957.
4. Lange G, DeLuca J, Maldjian JA, Lee H, Tiersky LA, Natelson BH. Brain MRI abnormalities exist in a subset of patients with chronic fatigue syndrome. *J Neurol Sci* 1999;171:3-7.
5. Lange G, Holodny AI, DeLuca J, Lee HJ, Yan XH, Steffener J et al. Quantitative assessment of cerebral ventricular volumes in chronic fatigue syndrome. *Appl Neuropsychol* 2001;8:23-30.
6. Okada T, Tanaka M, Kuratsune H, Watanabe Y and Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol* 2004;4:14.
7. de Lange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Meer JW, Toni I. Gray matter volume reduction in the chronic fatigue syndrome. *Neuroimage* 2005;26:777-781.
8. Yoshiuchi K, Farkas J and Natelson BH. Patients with Chronic Fatigue Syndrome Have Reduced Absolute Cortical Blood Flow. *Clinical Physiology and Functional Imaging* In Press.
9. Abu-Judeh HH, Levine S, Kumar M, el Zeftawy H, Naddaf S, Lou JQ et al. Comparison of SPET brain perfusion and 18F-FDG brain metabolism in patients with chronic fatigue syndrome. *Nucl Med Commun* 1998;19:1065-1071.
10. Schmaling KB, Lewis DH, Fiedelak JI, Mahurin R, Buchwald DS. Single-photon emission computerized tomography and neurocognitive function in patients with chronic fatigue syndrome. *Psychosom Med* 1990;65:129-136.
11. Kuratsune H, Yamaguti K, Lindh G, Evengard B, Hagberg G, Matsumura K et al. Brain regions involved in fatigue sensation: reduced acetylcarnitine uptake into the brain. *Neuroimage* 2002;17:1256-1265.
12. Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA et al. Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT. *AJR Am J Roentgenol* 1994a;162:935-941.
13. Costa DC, Tannock C and Brostoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *QJM* 1995;88:767-773.
14. Siessmeier T, Nix WA, Hardt J, Schreckenberger M, Egle UT and Bartenstein P. Observer independent analysis of cerebral glucose metabolism in patients with chronic fatigue syndrome. *J Neurol Neurosurg Psychiatry* 2003;74:922-928.
15. Tirelli U, Chierichetti F, Tavio M, Simonelli C, Bianchin G, Zanco P et al. Brain positron emission tomography (PET) in chronic fatigue syndrome: preliminary data. *Am J Med* 1998;105:54S-58S.
16. Cleare AJ, Messa C, Rabiner EA and Grasby PM. Brain 5-HT1A receptor binding in chronic fatigue syndrome measured using positron emission tomography and [11C]WAY-100635. *Biol Psychiatry* 2005; 57:239-246.
17. Yamamoto S, Ouchi Y, Onoe H, Yoshikawa E, Tsukada H, Takahashi H et al. Reduction of serotonin transporters of patients with chronic fatigue syndrome. *Neuroreport* 2004;15:2571-2574.
18. Natelson BH, Weaver SA, Tseng CL and Ottenweller JE. Spinal fluid abnormalities in patients with chronic fatigue syndrome. *Clin Diagn Lab Immunol* 2005; 12(1):52-55.