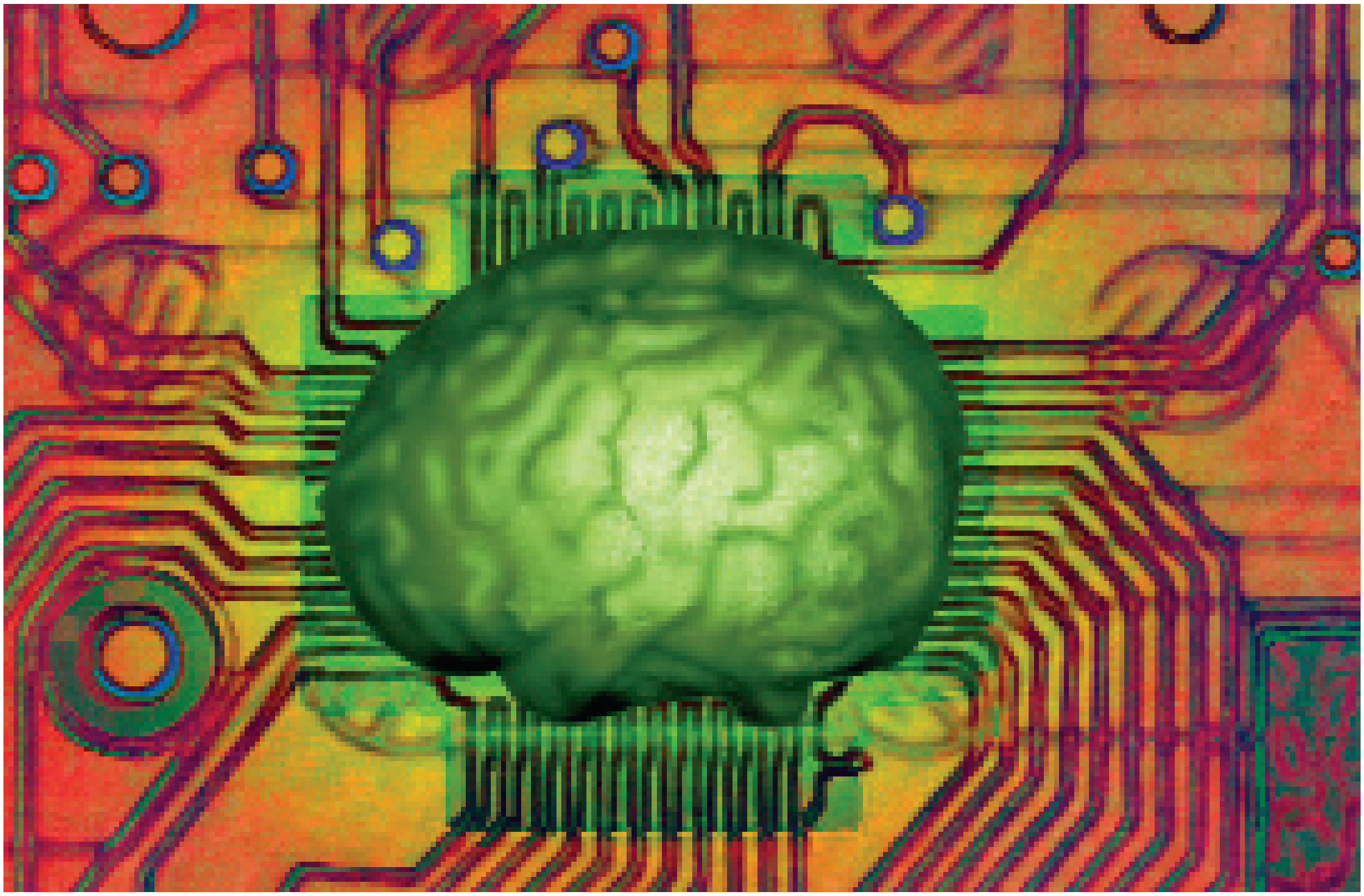


Matters of the Brain

BY FLORIS DE LANGE, F.C. DONDERS CENTRE FOR COGNITIVE NEUROIMAGING, NETHERLANDS

A lead researcher explains findings of gray matter reduction in two CFS brain studies.

FAST FACTS

- Magnetic resonance imaging (MRI) technology, combined with new comparison methods, has yielded a novel way to examine brain abnormalities.
- Two studies have uncovered evidence of gray matter reduction in people with CFS, possibly correlating with fatigue and/or activity levels.

In the past year, two studies were published from different laboratories in different parts of the world (Japan and the Netherlands), each using similar methodology and reporting similar results about the brain structure of CFS patients. Using high-resolution magnetic resonance imaging (MRI) technology, both studies found that CFS patients had lower gray matter volume than healthy control subjects. In addition, the studies could relate this gray matter reduction to CFS features and symptoms.

These findings were met with enthusiasm by both CFS researchers and people suffering from CFS, since they added to objective physical evidence of the illness.

But what is gray matter? And what significance do these new findings have?

The anatomy of the brain

When one looks at the brain with the naked eye, it can, roughly speaking, be divided into three elements: gray matter, white matter and cerebrospinal fluid. Figure 1 shows one horizontal slice of the brain and its gray matter.

The gray matter consists mainly of neurons and dendrites (local connections), which can be thought of as the computational units or "computers" of the brain. This is where most thought processing takes place. Each of these computers is connected via the white matter that makes quick electrical transmission possible. The cerebral spinal fluid transports waste and acts as a cushion for the brain.

Magnetic resonance imaging

With the advent of magnetic resonance imaging (MRI), it has become possible to obtain detailed images of the brain in a noninvasive manner. For two decades, MRI technology has been commonly used in the clinical setting to diagnose a variety of neurodegenerative diseases.

Until recently, however, there has not been agreement about whether abnormalities indeed exist in the brain of CFS patients. Some researchers found indications of cerebral abnormalities. For example, several studies in the 1990s found abnormalities in cerebral white matter, which showed up as small hyperintensities on the MRI results. Yet others could not definitely confirm these findings. How can there be such contradictions? One part of the answer likely lies in the way the MRI scans are evaluated in the clinical setting.

During normal analysis of MRI scans, they are rated in a qualitative manner. This means that a rater—typically a neurologist—will visually inspect the scan and indicate possible abnormalities. Although this method works well for focal and relatively large abnormalities (like tumors), it is not possible to detect more subtle and diffuse brain abnormalities with this technique. Recent studies have tried to solve this problem by using techniques that can automatically detect even small and diffuse abnormalities. One of those techniques is called voxel-based morphometry (Ashburner and Friston 2000).

Voxel-based morphometry

Voxel-based morphometry (VBM) is a research tool used to compare the brain anatomy of two or more groups of subjects, or brain anatomy over different points in time.

First, high-resolution anatomical images are collected from a group of patients and a group of comparable controls (typically matched in terms of age, gender and education). Each brain image is then divided into little cubes, called voxels. The size of each voxel is typically one millimeter, and the brain can be divided accordingly into approximately 2.5 million voxels.

Then the brain image is segmented into images of gray matter, white matter and cerebrospinal fluid, using a complicated segmentation method. The gray matter map of each of the subjects is overlaid, one on top of the other, so they can be compared. A comparison of the average amount of gray matter between the two groups is conducted for each of the millions of voxels, making it possible to identify gray matter differences in an automatic and objective fashion.

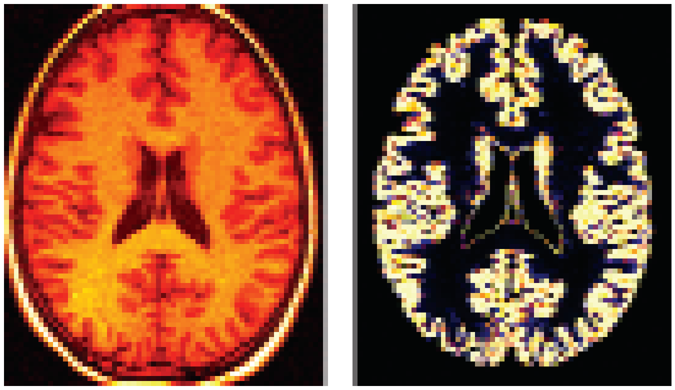
These studies appear to show that brain abnormalities do indeed exist in CFS and that they could be related to fatigue or activity levels.

VBM is an interesting and informative tool in studying CFS because it can expose common disease characteristics in terms of brain abnormality, which could help explain what happens in the brains of patients with CFS.

Gray matter reduction in CFS

What was found by the two groups that have used VBM to investigate differences in gray matter and white matter in CFS? The researchers in Japan (Okada et al.) observed a gray matter reduction in the prefrontal cortex (the most anterior part of the brain) in CFS patients. The 16 subjects with CFS exhibited an average of 11.8 percent volume reduction as compared to the 49 healthy controls. They also found a correlation between the degree of fatigue

Figure 1: In these side-by-side images of the human brain, the left image is a cross section of the entire brain and the right one is an extracted image showing just the gray matter.



experienced and the amount of gray matter reduction in the prefrontal cortex. Patients who were more fatigued had less gray matter.

My research team in the Netherlands also observed a gray matter reduction in a group of 13 CFS patients and was subsequently able to reproduce these findings in a second, similarly sized group with CFS. In each instance the average volume reduction among the CFS patients was approximately 8 percent. Although we did not find a correlation between fatigue levels and gray matter reduction, we *did* find a correlation between the level of daily physical activity of the CFS patients and their gray matter volume. Patients who were more active—measured objectively over a two-week period using a movement-sensing device—had more gray matter.

Together, these studies appear to show that brain abnormalities do indeed exist in CFS and that they could be related to fatigue and/or activity levels. But what do these abnormalities mean for the patient?

Once gone, lost forever?

All studies looking at the brain structure of living human subjects (*in vivo* studies) can only look at the brain in a macroscopic fashion. The resolution is expressed in, at best, tenths of millimeters—fairly large terms given that brain cells are a microscopic fraction of that size. This kind of "big picture" description of the brain lumps together many cell structures: the neuron (nerve cell) and its helper cell, the glia, as well as the local connections between neurons (dendrites) and the cell body of the neuron. This makes it difficult to say what actually happens when a reduction of gray matter has occurred.

Traditionally people thought that gray matter reduction meant a loss of neurons. The belief that we lose many neurons over the course of our life stems from this assumption. From modern neuron counting techniques, however, it seems that we may not be losing so many neurons at all. Rather, our neurons appear to shrink with age. Therefore, reductions of gray matter do not automatically mean cell death, but may mean that the neurons have become smaller. This may be good news for CFS patients since it implies that a reduction in gray matter may be reversible. Indeed, increases in gray matter have been observed in healthy participants as a result of training and learning a new activity (Draganski et al., 2004). In this respect, it is possible that the gray matter reduction in CFS patients is a consequence

Reductions of gray matter do not automatically mean cell death but may mean that the neurons have become smaller.

COMPARISON VS. DIAGNOSIS

While voxel-based morphometry (VBM) sheds light on global, characteristic differences in the brains of CFS patients, it does not allow for individual diagnosis.

As an illustration of this concept, imagine that we would like to know whether CFS patients are taller than healthy subjects.

Let's suppose we measured the height of one CFS patient at 6 feet tall, and the height of one control subject at 5.8 feet tall. Certainly, this particular CFS patient is taller than the control subject. But is this a characteristic of CFS, or does the measured difference merely reflect the variability in height that exists in the general population?

To answer this question, we'd need to measure the height of a population of CFS patients, as well as a population of healthy control subjects. Then, we could statistically compare and determine whether the average height of the CFS patients is significantly higher than that of the control subjects, taking into account the variability in height of both groups.

If it would turn out that CFS patients are on average indeed taller than healthy control subjects, this would be an interesting finding, allowing us to start investigating why this might be the case. But it would not allow us to say that a tall person therefore has CFS. In fact, it would not even mean that all CFS patients are taller than all healthy control subjects.

Similarly, VBM is producing interesting and informative findings about the global characteristics of the gray matter in CFS patients.

of fatigue or inactivity, and that improvements in health could lead to an increase in gray matter (see sidebar below).

Evidence has been accumulating over the last decade that CFS is associated with brain abnormalities. However, what these abnormalities mean is still not well understood. Are they the cause or the result of CFS? Are they permanent or reversible? These are questions that we hope to tackle in the coming years. No matter what the answers will be, it is obvious that the abnormalities associated with CFS are real. Just as it should now be obvious that the complaints of CFS patients are real.

Floris de Lange is the lead author of the Netherlands' neuroimaging-based study of CFS published in a report titled "Gray matter volume reduction in the chronic fatigue syndrome." He is a PhD candidate at F.C. Donders Centre for Cognitive Neuroimaging.

References

Ashburner J, Friston KJ. Voxel-based morphometry: the methods. *Neuroimage* 2000; 11:805-821.

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.

Draganski B, Gaser C, Busch V, Schuierer G, Bogdahn U, May A. Neuroplasticity: changes in grey matter induced by training. *Nature* 2004; 427:311-312.

Okada T, Tanaka M, Kuratsune H, Watanabe Y, Sadato N. Mechanisms underlying fatigue: a voxel-based morphometric study of chronic fatigue syndrome. *BMC Neurol* 2004; 4:14.

This article originally appeared in the Summer 2006 *CFIDS Chronicle*. The *CFIDS Chronicle* is a quarterly magazine published by the CFIDS Association of America as a benefit to Association members. Visit http://www.cfids.org/support/membership.asp to learn more about subscribing.

IS IT POSSIBLE TO REVERSE GRAY MATTER REDUCTION?

Reduction is not the only option for gray matter evolution over time.

Neuroplasticity refers to the brain's ability to reorganize itself by forming new neural connections, allowing the brain's nerve cells to adjust their activities in response to new situations—sometimes even altering the structure of the brain. In fact, the science of neuroplasticity has uncovered a number of situations where gray matter has increased or where cognitive processing has migrated to other alternate portions of the brain.

For example, recent studies have documented an increase in gray matter from learning new skills as diverse as juggling and foreign language. The acquisition of new and initially abstract information may be related to gray matter changes and supports the belief that learning new skills and exercising the mind can have positive benefits. You don't have to enroll in school to test this theory. Certain word games—like Scrabble, Boggle and Perquacky—that exercise both language and spatial skills may also be beneficial.

Other research has documented an increase in gray matter from regular meditation. Not only do Buddhist monks show an extraordinary increase in higher brain functioning during this practice, but brain imaging has also shown that gray matter actually thickens in working-class people who meditate an average of 40 minutes a day. It's speculated that the focus practiced through meditation actually strengthens the right hemisphere, which is associated with sustaining attention.

Specific to CFS, research suggests that some people with the illness may employ alternate neural pathways for information processing as compared to those without CFS. In effect, some CFS patients may be experiencing a "rewiring" of processing function—further demonstrating the plasticity of the brain.

The main thing to know is that even the adult brain is not "hard-wired" with fixed and immutable circuits. There is no set period of time after which plasticity is lost. There is now even evidence that neurogenesis—the formation of new nerve cells—is possible in the adult brain. We simply do not yet know all of the conditions that can enhance plasticity and increase gray matter and functioning.