



## Review: Grey and white matter differences in chronic fatigue syndrome – A voxel-based morphometry study

A [recent study](#) reported differences in brain structure in people with chronic fatigue syndrome (ME/CFS).

This was not the first paper to report such aberrations, but it was the first to report *increased* Grey Matter volume compared to healthy controls.

### **Comment from Dr Charles Shepherd, Hon Medical Adviser, ME Association:**

This study was carried out in Newcastle by Professor Julia Newton and colleagues – a team who have not only achieved a long and distinguished record in ME/CFS research but also have access to patients who have been very carefully assessed from a clinical point of view. So, the results should be taken seriously.

As has been pointed out in this review, three of the main criticisms of previous neuroimaging studies involving people with ME/CFS is that the numbers involved have often been far too small; there has been a lack of information from other control groups that would be relevant in addition to the use of healthy controls; and that different imaging techniques have been used. So, not surprisingly, the results are not always consistent.

Despite these caveats, these results clearly add weight to the findings from previous neuroimaging studies describing white matter abnormalities in ME/CFS but also raise the possibility of grey matter involvement in ME/CFS.

There are several possible explanations for these findings but no clear answer has emerged in the paper. Are they a primary feature of ME/CFS? Or are they secondary to other factors – e.g. duration of illness, decrease in activity, severity of fatigue – that are related to having ME/CFS? The only way to find out is through further research into what is clearly an interesting aspect of neuropathology in ME/CFS.

A fully referenced summary of all the key findings from both functional and structural neuroimaging studies in ME/CFS can be found in the Research section of the ME Association [‘An Exploration of the Key Clinical Issues’](#) available from our online shop.

### **Overview of the study**

42 patients with ME/CFS – who met the Fukuda diagnostic criteria and were pre-screened for comorbid psychological disorders – and 30 healthy controls, had their brains imaged by an MRI scanner.

Comparisons of areas of the brain found that, on average, ME/CFS patients had lower white matter volume overall, consistent with previous findings. However, this study also found

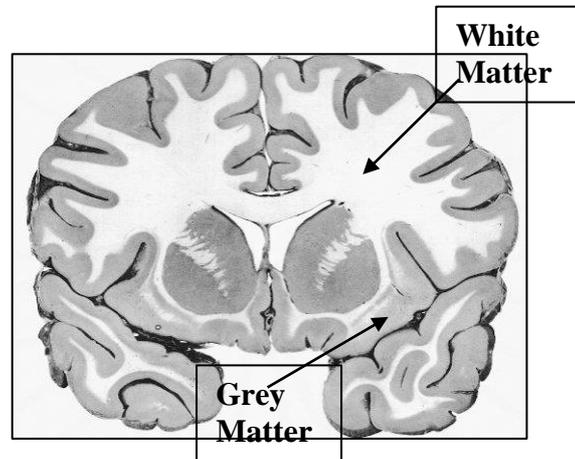
several areas of increased grey matter volume, which was different to other studies in this area.

### A quick lesson on brain structure

The brain is made up of about 60% white matter and 40% grey matter (Dale *et al.* 2008).

These both comprise parts of the central nervous system (CNS) and are made up of cells called neurons, which conduct signals and send messages to and from the brain to the body.

The grey and white colouring is due to differing components (mainly fat content).



#### *Grey matter (GM)*

Grey matter refers to areas of the brain and spinal cord that are composed mainly of neuron cell bodies. It also contains glial cells, which provide nutrients and energy to neurons, help keep them in place and destroy invading pathogens (Robertson 2014).

The grey matter is where most of the processing of information happens and includes regions of the brain involved in muscle control, sensory perception (vision/hearing/touch), memory, emotions and speech.

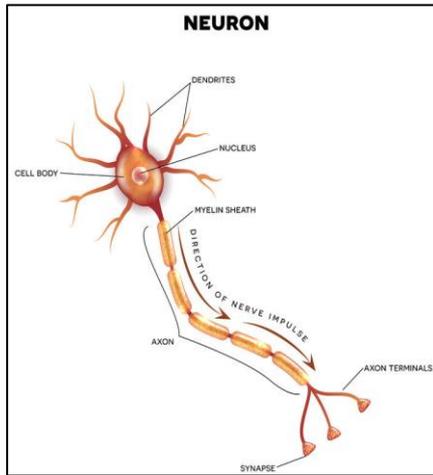
The density of cells (volume of grey matter) appears to correlate with various abilities and skills. This volume can be affected by genetic and environmental factors, so you can be born with differences or develop differences through experience or illness (Robertson 2014).

For example, studies have found decreased grey matter volume in alcoholics and people with memory problems and increased volume in certain areas of the brain in professional musicians and taxi drivers (Robertson 2014).

#### *White matter (WM)*

White matter is made up of the axons that extend from the neuron bodies of Grey matter. These nerve axons are the infrastructure of the brain, connecting different areas together like wires in a circuit and coordinating communication between them (Fields 2008).

The axons are coated in a fatty layer called myelin, which is what gives the white colour. Myelin acts as an electrical insulation to the 'wires', protecting them and helping to make the transmission of messages much faster.



A lack or loss of myelin disrupts nerve transmissions and causes neurological problems, affecting your ability to move, use your sensory faculties, or react appropriately to external stimuli (Fields 2010).

Several diseases can affect white matter including multiple sclerosis and dementia (Filley 2012).

Destruction of myelin can also result from inflammation, blood vessel problems, immune disorders, nutritional deficiencies, stroke, poisons, and alcohol abuse (Monnig *et al.* 2013).

### What is “Voxel-based morphometry” (VBM)?

This is the most popular neuroimaging analysis technique used to measure the local concentration of grey and white matter in the same space.

A voxel is a value, a unit of measurement used in the context of measuring volume, and is used to visualise and analyse data.

Morphometry is the process of measuring the external shape or dimensions of something; in this case, the brain (Dale *et al.* 2008).

### What made this study different?

1. This study had a larger sample size than previous studies, with other studies having <30 patients.
2. The paper stated that, ‘not all studies explicitly excluded patients with a psychiatric comorbidity, which may have affected findings,’ and so the patients in this study, were ‘meticulously screened for psychiatric comorbidities’.
3. The VBM analysis followed a recently revised protocol which aimed to improve the quality of the results over previous implementations.

### The Results

#### *Whole-brain volume measurements*

The study measured the overall brain segment volume in terms of:

1. Total intracranial volume (TIV),
2. Grey matter (GM) volume,
3. White matter (WM) volume, and,
4. Cerebral Spinal Fluid (CSF) volume.

TIV is a measure of the total space within the skull and CSF is the liquid surrounding the structures of the brain and spinal cord.

These measurements were taken as absolute (on their own separately) and when adjusted to take account of the total intracranial volume (TIV) of each person.

This adjustment is important as people with smaller skull size could naturally have less volume, and vice-versa in people with larger skulls.

When looking at the absolute values on their own:

- The average TIV of patients was ~5% lower than the healthy controls (1487ml vs 1560ml).
- The average WM volume was ~8% lower in patients than healthy controls (517ml vs 559ml).
- There was no significant difference in absolute GM volumes between the two groups (667ml vs 669ml).
- There was a trend for lower absolute CSF volume in patients than in healthy controls, by ~9% (303ml vs 332ml). However, this trend is not significant as the p-value was 0.08 and the cut off for significance is <0.05.

After adjusting for total intracranial volume (TIV):

- The average GM volume was ~3% higher in patients than the healthy controls (676ml vs 655ml).
- The average WM volume was ~3% lower in patients than healthy controls (527ml vs 542ml).
- There was no significant difference in the CSF volume (313ml vs 318ml) between the two groups.

### *Voxel-based morphometry results*

#### *Grey Matter (GM)*

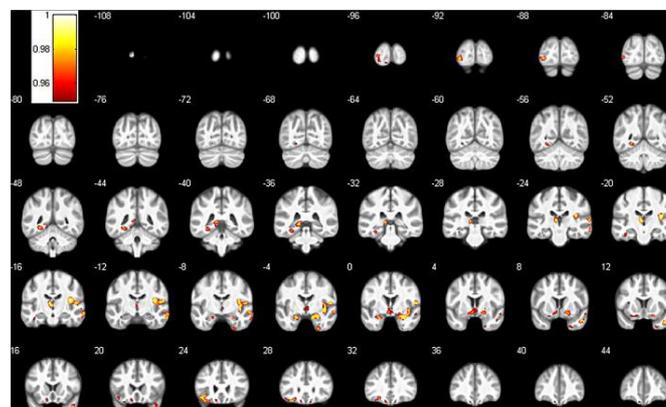


Figure 1. Areas of significantly increased grey matter in the ME/CFS group compared to the control group.

‘The VBM analysis showed significant differences in GM volume in several regions throughout the brain (Figure 1). Patients showed higher GM in widespread areas of the right [temporal lobe](#) including the [insular cortex](#), in various subcortical areas such as the bilateral [amygdala](#), [putamen](#), [thalamus](#) and [hippocampus](#), parts of the left inferior [frontal lobe](#) and left [occipital lobe](#).’

‘There were no significant areas with reduced GM volume in the patient group.’

#### White Matter (WM)

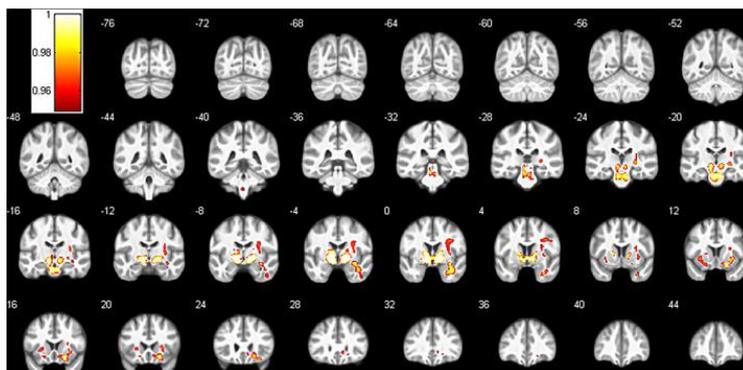


Figure 2. Areas of significantly reduced [white matter](#) in the ME/CFS group compared to the control group.

‘Significant voxel-wise differences were also seen in several [white matter](#) regions (see Figure 2). Patients showed reduced WM compared to controls in bilateral areas of the [internal and external capsule](#) and anterior [midbrain](#), extending caudally into the bilateral [pons](#), dorsally into the right prefrontal lobe and anteriorly into inferior frontal lobe WM.’

‘Additional areas of reduced WM were seen in anterior parts of the right temporal lobe. No areas showed increased WM in the [patient] group compared to the control group.’

#### Relationship to clinical characteristics

The authors examined the different volumes in relation to clinical characteristics, such as severity of ME/CFS, which was measured via self-report questionnaires.

They found a negative association between total intracranial volume (TIV) and almost all the questionnaire measures, meaning the lower the TIV volume, the higher the symptom severity.

A negative association was also seen for GM and CSF volume, but not for WM volume, which did not show an association to clinical characteristics.

## Implications of the results

With regards to the differences seen in total intracranial volume (TIV) as they relate to symptom severity, the paper suggests that, ‘patients with smaller TIV are vulnerable to experiencing more severe symptoms’.

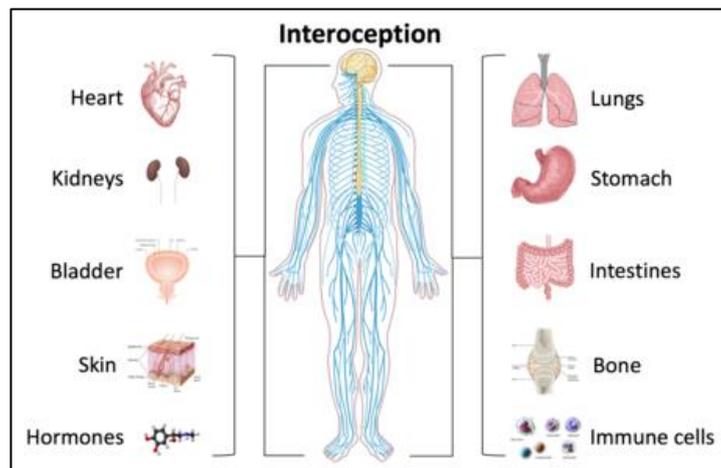
However, the authors gave a note of caution, ‘no previous brain volumetric study in ME/CFS has reported either group differences to healthy participants in TIV or associations of TIV with symptom severity’.

Although Grey matter was found to be increased in several areas of the brain – involved in everything from memory to speech to visual processing – the paper mainly discussed the increased volume in areas called the Amygdala and Insula, as they, ‘appeared to be of most direct relevance to ME/CFS symptomology’.

The amygdala is linked to a variety of different functions, including emotional processing, fear conditioning and memory processes. The amygdala is responsible for triggering our ‘fight or flight’ reactions and links emotions to memories, especially fear or anxiety-triggering events (Dale *et al.* 2008).

Interestingly, increased volume in the amygdala has also been shown in people with joint hypermobility (Eccles *et al.* 2012), a connective tissue disorder which has been linked to ME/CFS (Nijas *et al.* 2006). However, as joint hypermobility was not assessed in this study, the degree to which this may have affected the findings is unclear.

The insula is involved in a variety of functions, including interoceptive, cognitive (memory/attention/learning) and affective (emotional) functions.



Interoception is where various physiological systems in the body – including the respiratory, gastrointestinal, nociceptive (skin), endocrine (hormones) and immune systems – relay information to the brain about their ‘state’ and the brain then uses that information to react appropriately and help maintain a balanced system.

Another interesting similarity is that people with autism have also been shown to have more grey matter, as well as reduced areas of white matter, in their brains than healthy controls (Aoki *et al.* 2013). Autism has been linked to ME/CFS in several theories (Konynenburg 2012, Teitelbaum 2011).

The reduced white matter seen in many areas may be due to loss or destruction of myelin or it could be loss or damage of glial cells, which help to repair myelin. Due to the 'job' of white matter, loss of white matter may mean that the transmission of signals is slow in those areas of decreased volume.

White matter abnormalities have been found in many different diseases. Of note, MS (multiple sclerosis) is caused by a loss of myelin (the fat that makes white matter white) and is associated with white matter volume changes (Sastre-Garriga *et al.* 2005) and MS is like ME/CFS in many of its symptom presentations.

There are also white matter abnormalities seen in Alzheimer's disease (Filley 2012).

Destruction of myelin can result from many different causes, such as inflammation, blood vessel problems, immune disorders, nutritional deficiencies, stroke, poisons, and alcohol (Monnig *et al.* 2013).

### **Observations**

It may have been more useful in this study to have a control group who were unhealthy, with a similar chronic illness (e.g. MS or Lupus) as people with chronic illness who are faced with physical adversities may have similar brain anomalies.

Alternatively, they could have chosen healthy but sedentary controls as these results could be reflecting for example, a sedentary behaviour, or even prolonged periods of disturbed sleep.

The average age of the participants was 45. Several studies have found structural differences in the brain which occur naturally with ageing and so it would be useful to look at the brains of younger patients with ME/CFS to see if the same findings apply (Marnier *et al.* 2003).

Previous studies have shown that cardiorespiratory exercise can increase white matter and that exercise decreases the risk of dementia (Fields 2008; Filley 2010; Torres *et al.* 2015).

Could it be that these patients have not been exercising for years because of ME/CFS and this has led to early decline in white matter? This is perhaps another reason to have a sedentary or diseased control group, as well as a healthy one.

The authors have employed some 'cherry picking' in their abstract and discussion, as there was increased grey matter volume in many different areas of the brain, yet they chose to only mention the Amygdala and Insula – regions perhaps best known for the regulation of emotions and anxiety.

This could have been because these areas fit with previous theories, including the psychosomatic model for ME/CFS. However, choosing to only talk about these areas of the brain, instead of discussing all the results equally, is a form of confirmation bias, or selective exposure, and could have been avoided.

### **How does this study compare to others?**

There have been many neuroimaging studies in ME/CFS, usually demonstrating inconsistent findings and no conclusive overall results. This could be because of small sample sizes and differences in imaging and analysis methods.

Studies examining cerebrospinal fluid (CSF) have been limited, although Perrin *et al.* (2010) found no difference in CSF volume in 18 patients with ME/CFS when compared to controls.

However, there is a lot of research about low CSF volume causing pressure headaches, and, given the emerging trend for lower CSF volume in ME/CFS, this may warrant further research to discover if this is a common finding or a random chance result.

In the study that we are reviewing, patients were found to have reduced white matter volume overall, and, unusually, several areas of increased grey matter volume, compared to healthy controls.

Puri *et al.* (2012) did a similar study – again employing voxel-based morphometry – but found *decreased grey and white matter volume*, which was also found in an earlier voxel-based study by Okada *et al.* in 2005.

Shan *et al.* (2015) found *decreased white and grey matter* that correlated with the symptoms associated with ME/CFS, and Zeineh *et al.* (2015) also found *reduced white matter*.

The common finding among most of these studies is a reduction in white matter volume, which is consistent with this current study. Also, the location of the white matter abnormalities in this study appear to overlap considerably with the white matter changes seen in other studies.

However, most previous studies have found either *reduced or unchanged Grey matter volumes*, whereas this study found *increased Grey matter*.

### **Conclusion**

It is hard to draw any meaningful conclusions from this study, given the relatively small sample size and the highly variable results from other studies. Our knowledge of the brain is quite limited and neuroimaging techniques and analyses are still in their infancy – so it is also hard to draw any firm conclusions from brain studies in general.

There does seem to be a clear theme of decreased white matter among patients with ME/CFS and this warrants further exploration. Other diseases, such as multiple sclerosis have demonstrated similar findings which have led to a much better understanding of causation,

the development of diagnostic tools, and treatments – therefore studies of this nature are well worth pursuing.

The finding of increased grey matter in several areas was novel and could suggest an anomaly or that imaging and/or analysis techniques in previous studies were not as good. Unfortunately, we cannot conclude what increased grey matter volume might mean in terms of causation or of symptoms in relation to ME/CFS.

As always, what is needed is a better definition of the study group, larger sample sizes and for all studies to be using the same techniques to enable easier comparison and replication.

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