MEA Summary Review: Whole-brain imaging study suggests brain inflammation in ME/CFS

By: Charlotte Stephens 15th January 2019

"We report metabolite and temperature abnormalities in ME/CFS patients in widely distributed regions. Our findings may indicate that ME/CFS involves neuroinflammation" Younger et al. 2019.

Last week, Dr Jarred Younger and his team – from the University of Alabama, Birmingham, with researchers from the University of Miami, Florida – published results from a long-awaited brain study in ME/CFS.

What they found supports previous theories of the involvement of brain inflammation in ME/CFS. In this summary review, we hope to explain the results, what they might mean and the next steps towards treatment development.

- You might like to listen/watch Dr Younger explain this study in a video he did for Solve ME/CFS Initiative (SMCI) in December 2018.

Key Points

- Using a specialised scanning technique, they measured the levels of 4 metabolites, as well as temperature, inside the brains of 15 ME/CFS patients and 15 controls.
- Raised levels of certain metabolites, as well as increased temperature inside the brains of the ME/CFS patients indicate brain inflammation.
- Youngers next step is to repeat this study in a larger group of patients (around 100) to confirm these findings, as well as explore possible treatment options.

The theory of brain inflammation in ME/CFS

Dr Younger and his team's hypothesis is that ME/CFS represents a state of chronic, low-level neuroinflammation (inflammation of the brain).

Younger believes that immune cells (called microglia) in the brain have become abnormally activated and are releasing chemicals (inflammatory cytokines) that result in symptoms such as fatigue, cognitive disruption, pain and exertional intolerance.

Also, he thinks these activated microglia are now hyper-sensitive and overly responsive to even mild triggers, such as exercise, which cause them to react by releasing chemicals.

His aim is to develop a tool for detecting this neuroinflammation, which can then be used to measure drug effectiveness on targeting inflammation.

The Brain Scan

Brian Inflammation is not often seen in conventional medical scans (MRI), which are mainly used to observe tumours and evidence of meningitis.

Specialised scans are needed in order to detect chemicals (metabolites) that are being produced by brain cells, that demonstrate inflammation.

The scan used in this study is called an MRS (Magnetic Resonance Spectroscopy).

It is a type of MRI that has a series of tests added to it (spectroscopy) in order to measure levels of chemicals (metabolites) in certain areas of the brain.

Image of a patient in an MRI scanner. Copyright: 123RF/zlikovec

The scan is a non-invasive procedure, where patients lie down in a scanner for around 30 minutes. The benefit of this type of scan is that it can be regularly repeated, making it ideal for monitoring progress of drug therapies.

The MRS scan is not currently available via the NHS in the UK.

The Metabolites

The 4 key metabolites examined in this study were:

1. Choline

This is a marker of rapid cell turnover (cells are dying and being created very quickly), which usually means there's an inflammatory process going on.

2. Lactate

You usually don't detect this in the brain at all – and when you do it usually means the chemical reactions in the brain are happening so fast that the blood supply cannot keep up with the demand for oxygen.

When this happens, cells switch to an alternative, less efficient, way of producing energy. This alternative pathway produces lactate as a by-product.

This is similar to when athletes run too fast and burn through the oxygen supply in their muscles. They have to convert to a different means of supplying muscles with energy, which leads to a build-up of lactic acid and causes muscle fatigue and pain.

The only reason for lactate to be building up in the brain is if there's neuroinflammation or if there's a problem with the blood vessels, causing a shortage in supply of oxygen, which has been suggested before in ME/CFS (Biswal *et al*., 2011; Yoshiuchi *et al*., 2006).

3. Myo-inositol

This is found in microglial cells – the immune cells which are believed to be driving inflammation. High amounts of this suggest lots of microglial cells in one area, which is also indicative of neuroinflammation.

4. N-acetylaspartate

This is a marker of neuronal (brain cell) health. High levels tell you there's a lot of neurons in that area and that they're healthy. If this level goes down, it indicates the presence of neurodegeneration (loss or damage of brain cells).

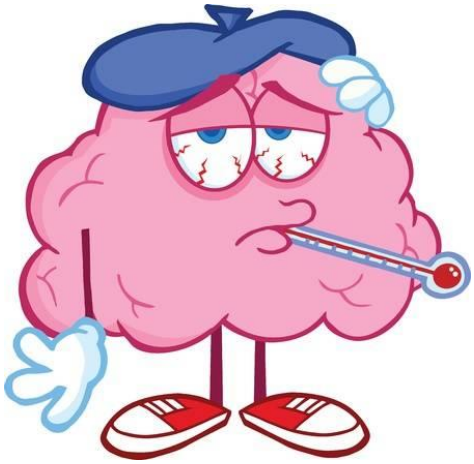
Brain Temperature

Brains are naturally hotter than the rest of our bodies.

Temperature in the brain rises when there is inflammation present, just like body temperature does during an infection.

Blood circulation acts to 'cool' the brain, by taking away 'hot' blood and replacing it with cooler, to try and match the core body temperature.

During neuroinflammation, metabolic reactions are happening so quickly that more heat is being produced, meaning it is less easily taken away by the circulation, as it can't keep up with the heat being produced.



Temperature in the brain rises when inflammation is present. Copyright: 123RF/Chudomir Tsankov

Build-up of heat in the brain can start to cause cognitive problems, balance problems and mood problems, which could explain some of the symptoms of ME/CFS.

Brain temperature is very sensitively controlled and so even a 1-degree difference would be enough to create symptoms.

The Patients

15 ME/CFS patients meeting the Fukuda criteria and 15 controls – all age and gender matched – participated in the study. Fatigue and Depression and Anxiety questionnaires were also completed.

As expected, the fatigue score was higher in the patients than controls. The depression and anxiety scores were also higher in the patients. Average body temperature was slightly higher in the patient group compared to controls.

The Results

Significant differences in metabolite levels and brain temperature were found in several brain regions between the patient and control groups.

These results support Younger's hypothesis of chronic, low-level inflammation in the brain.

- 'Low-level' inflammation means that it's not so severe that it is damaging neurons (brain cells).

Location of the Inflammation

The inflammation observed is located in regions of the brain that would drive the symptoms seen in ME/CFS. Examples include:

- Cingulate – responsible for feelings of general malaise and low mood.
- Hippocampus – where memories are formed and stored (could explain memory problems).
- Thalamus – relays information coming from the body (could be responsible for feeling pain, weird sensations (like tingling or numbness) or sensitivities).
- Cerebellum – area for coordination and motor speed (could explain slow movements).

1. Choline

Choline (a metabolite) levels were increased in several brain areas in the ME/CFS group, and no areas in the control group.

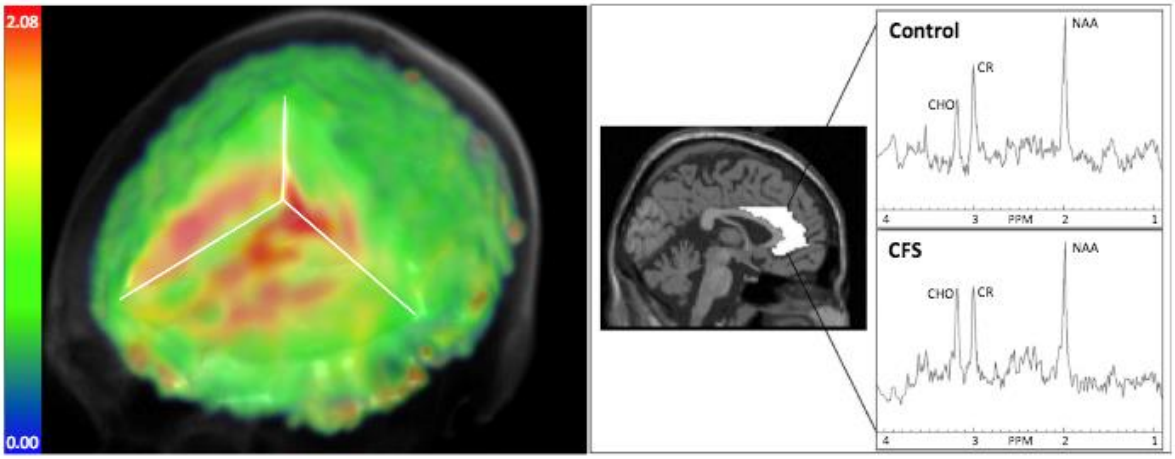
Regions where it was elevated are implicated in 'the sickness response' which drives the feeling of malaise and 'illness behaviours' that are triggered during an infection.

The most notable region found to be elevated was the cingulate cortex, which has been noted as critically important for mediating cytokine-induced fatigue and mood deterioration (Capuron *et al.,* 2005; Harrison *et al.,* 2009).

Raised Choline was the only result that remained significant after statistical corrections for multiple comparisons. This result also supports previous reports of increased Choline in ME/CFS (Puri et al., 2002).

Choline levels were 'moderately positively correlated' with anxiety and depression, meaning that higher levels of choline were observed in those with higher scores for anxiety and depression.

However, correlation does not always mean causation. To clarify this, a larger study would need to be carried out on many more patients.



Example of a whole-brain metabolite map of choline from a patient with ME/CFS, along with a spectra comparing a region of the brain, showing raised Choline in patients compared to controls. Younger et al. 2019

2. Lactate

Lactate (a metabolite) was elevated in the most regions of the brain in ME/CFS patients, at about 4x higher levels than in controls. Lactate is produced by various immune cells under inflammatory conditions.

The form of energy metabolism that lactate is produced by (anaerobic glycolysis) is not the preferred method and is very inefficient in terms of cellular energy (ATP) production. This could explain energy deficits at the cellular level and in turn the experience of extreme fatigue in ME/CFS.

These results support several previous reports of elevated lactate in the brains of ME/CFS patients (Brooks *et al*., 2000; Mathew *et al.* 2009; Murrough *et al.* 2010; Natelson *et al.* 2017; Shungu *et al*. 2012).

3. Myo-inositol

Myo-inositol (a metabolite) was only found to be raised in one area of the brain; the right pallidum, which is located in the basal ganglia. Involvement of the basal ganglia has been highlighted in ME/CFS before (Chaudhuri *et al.,* 2003; Miller *et al*., 2014).

4. N-acetylaspartate

There was little evidence of decreased N-acetylaspartate (a metabolite), which is a good thing as it shows that there is no neurodegeneration (brain cells are not being damaged and destroyed) and that the neurons are healthy, despite the inflammation. It also separates ME/CFS from neurodegenerative disorders, such as Multiple Sclerosis (MS) and Alzheimer's.

Brain temperature

> "It is not certain that the observed temperature differences are associated with neuroinflammation.
>
> "However, we note that three out of the five regions with elevated brain temperature in individuals with ME/CFS also contained elevated lactate: the right insula, right thalamus, and cerebellum."
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> "The convergence of elevated lactate and elevated temperature in the same regions suggest heightened metabolism that may be related to neuroinflammation."
>
> Younger et al. 2019

Brain temperature was elevated in 5 regions in patients compared to controls. Interestingly, 3 of these 5 regions were the same as regions with raised Lactate levels. Furthermore, these matching regions are all involved in so-called 'sickness behaviours'.

The elevated lactate levels, along with the elevated temperature in the same region, suggest heightened metabolism that may be related to neuroinflammation. However, both of these things could also be caused by reduced blood flow to the brain or mitochondrial dysfunction.

The researchers carried out a statistical test that showed the elevated brain temperature was not a consequence of raised body temperature.

They also measured cerebral perfusion (blood supply to the brain) and said that the raised brain temperature is also not attributable to differences in this between the groups.

A note of caution in interpreting the results

Although one explanation for these results could be brain inflammation, there are also other possible explanations:

Reduced blood flow – this would also result in increased brain temperature, as well as increased lactate levels; as there would be a reduced supply of oxygen to brain cells, resulting in anaerobic glycolysis. Reduced blood flow to the brain has been shown in ME/CFS in previous studies (Biswal *et al.,* 2011; Yoshiuchi *et al*., 2006)

> "We note that while metabolite and temperature abnormalities in ME/CFS patients are consistent with the presence of neuroinflammation, there are other mechanisms, such as mitochondrial dysfunction or aberrant neuronal communication, that may be contributing to these changes." Younger et al. 2019

Dysfunctional mitochondria – or defects in cellular energy metabolism, as many current metabolomics studies are pointing towards.

Antidepressants – 10 out of the 15 ME/CFS patients were taking antidepressant medication. Such medications have been shown to have an impact on metabolites and can lead to adjustments in mitochondrial metabolism (Villa *et al*., 2016).

Depression – Patients had higher scores on the depression and anxiety questionnaire than controls, which correlated with the areas of raised Choline. Depression has also been linked to neuroinflammation and activation of microglia in the brain (Abbot, 2018; Brites and Adelaide, 2015; Furtado and Katzman, 2015).

> "Because anxiety and depressed mood were elevated in the ME/CFS group compared to controls, it is possible that metabolite or temperature differences between groups were related to these variables. In fact, we found moderate correlations between anxiety and depression and the metabolite ratios in some brain regions." Younger et al 2019

No diagnostic markers – because other conditions have been shown to express abnormalities in these metabolites, the researchers note that "they are not specific markers of neuroinflamation and cannot likely provide a unique diagnostic test for ME/CFS."

Treatment options

Younger's end goal is to develop a treatment that targets the root cause of ME/CFS, not one that simply covers up the symptoms.

His theory of the best treatment for ME/CFS is an anti-inflammatory drug that has the ability to cross the blood brain barrier – decreasing the inflammation in the brain.

There is currently no FDA approved drug that is designed specifically to do this. However, there are drugs designed for different purposes that seem to achieve the same thing.

Botanicals could also provide a treatment for neuroinflammation in ME/CFS
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For example, Low-dose Naltrexone (LDN) has shown evidence of reducing brain inflammation. The research team are currently testing similar drugs to see if they can reduce brain inflammation.

They have also just completed a study looking into 9 different botanicals (natural plant-based supplements like herbs and spices), including curcumin, that could reduce brain inflammation. They are analysing the data from the study and will publish in due course.

Another possible method of reducing neuroinflammation could be 'cooling the brain'. However, this is usually only done in an emergency situation to try and slow down any damage the inflammation may cause to the neurons. Younger said he's never seen it used for chronic disease and so they would need to run a clinical trial to see if this would be practical or safe.

Finally, Vagus nerve stimulation, using a special implant, can produce anti-inflammatory chemicals in the brain which can counteract the inflammation. Younger said this may be another option that they may look into testing in clinical trials.

- The ME Association has a previous Research Review that covered some natural ways to stimulate the vagus nerve which might be of interest.

Next steps

These are encouraging results to get from a pilot study – demonstrating significant differences in areas of the brain that correlate with symptoms – and it adds support to the belief that neuroinflammation exists in ME/CFS.

The results justify carrying out this study in a much larger group of people, which is what Younger and his team intend to do next.

They are also trying to get funding to develop clinical trials looking into available medications, as well as the design of new drugs, brain cooling devices and vagus nerve stimulations.

Younger has received funding to look at leukocyte infiltration in the brain in ME/CFS. What he thinks might be happening is that B and T cells (immune cells) are getting into the brain when they're not supposed to and contributing to the inflammatory response.

Conclusion

This was the first study to investigate whole-brain MRS markers of neuroinflammation in ME/CFS. Metabolite and temperature differences were observed in several areas of the brain and the results largely agree with findings from previous publications.

However, the study was very small and there are a lot of questions that need to be clarified by repeating the study on a much larger scale, in order to confirm if this truly is evidence of neuroinflammation.

Jarred Younger and his team are clearly very passionate about ME/CFS research and are working hard looking into the causes of ME/CFS from different angles and also exploring many approaches to treatment. His work provides hope for us all.

- Read all of the ME Association Research Summaries in the Research section of our website.

The ME Association

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References

Abbot A (2018) Depression: the radical theory linking it to inflammation. *Nature* 557: 633-634.

Biswal B, Kunwar P and Natelson B (2011) Cerebral Blood Flow is Reduced in Chronic Fatigue Syndrome As Assessed by Arterial Spin Labeling. Journal of *Neurological Science* 301 (1-2): 9-11.

Brites D and Adelaide F. (2015) Neuroinflammation and Depression: Microglia Activation, Extracellular Microvesicles and microRNA Dysregulation. *Frontiers in Cellular Neuroscience 9: 476.*

Brooks J, Roberts N, Whitehouse G and Majeed T (2000) Proton magnetic resonance spectroscopy and morphometry of the hipocampus in chronic fatigue syndrome. *The British Journal of Radiology* 73 (875): 1206-1208.

Capuron L, Pagnoni G *et al. (*2005) Anterior cingulate activation and error processing during interferon-alpha treatment. *Biological Psychiatry* 58 (3): 190-196.

Chaudhuri A, Condon B, Gow W, Brennan D and Hadley M (2003) Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. *Neuro Report* 14 (2): 225-228.

Furtado M and Katzman M (2015) Examining the role of neuroinflammation in major depression. *Psychiatry Research* 229 (1-2): 27-36.

Harrison N, Brydon L, Walker C, Gray M, Steptoe A and Critchley H (2009) Inflammation causes mood changes through alterations in subgenual cingulate activity and mesolimbic connectivity. *Biological Psychiatry* 66 (5): 407-414.

Hungu, D. C., Weiduschat, N., Murrough, J. W., Mao, X., Pillemer, S., Dyke, J. P., et al. (2012). Increased ventricular lactate in chronic fatigue syndrome. III. Relationships to cortical glutathione and clinical symptoms implicate oxidative stress in disorder pathophysiology. NMR in Biomedicine, 25(9), 1073–1087.

Komaroff A, Takahashi R, Yamamura T and Sawamura M (2018) Neurologic Abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: A review. *Brain and Nerves* 70 (1): 41-54.

Mathew S, Mao X, Keegan K, Levine S, *et al*. (2009) Ventricular cerebrospinal fluid lactate is increased in chronic fatigue syndrome compared with generalised anxiety disorder. *NMR in Biomedicine* 22 (3): 251-258.

Miller A, Jones J, Drake D, Tian H, Unger E and Pagnoni G (2014) Decreased Basal Ganglia Activation in Subjects with Chronic Fatigue Syndrome: Association with Symptoms of Fatigue. *PLoS One* 9 (5).

Murrough, J. W., Mao, X., Collins, K. A., Kelly, C., Andrade, G.,Nestadt, P., *et al.* (2010) Increased ventricular lactate in chronic fatigue syndrome measured by 1H MRS imaging at 3.0 T. II: Comparison with major depressive disorder. *NMR in Biomedicine* 23(6): 643–650.

Nakatomi Y, Mizuno K, Ishii A, *et al.* (2014) Neuroinflammatrion in Patients with Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis: An C-(r)-PK11195 PET study. *The Journal of Nuclear Medicine* 55 (6): 945-950.

Natelson, B. H., Weaver, S. A., Tseng, C. L., and Ottenweller, J. E. (2005) Spinal fluid abnormalities in patients with chronic fatigue syndrome. *Clinical and Diagnostic Laboratory Immunology* 12(1): 52–55.

Puri, B. K., Counsell, S. J., Zaman, R., Main, J., Collins, A. G., Hajnal, J.V., & Davey, N. J. (2002) Relative increase in choline in the occipital cortex in chronic fatigue syndrome. *Acta PsychiatricaScandinavica* 106(3): 224–226

Shungu, D. C., Weiduschat, N., Murrough, J. W., Mao, X., Pillemer, S.,Dyke, J. P., *et al.* (2012). Increased ventricular lactate in chronicfatigue syndrome. III. Relationships to cortical glutathione and clinical symptoms implicate oxidative stress in disorder pathophysiology. *NMR in Biomedicine* 25(9): 1073–1087.

Villa RF, Ferrari F, Gorini A, Brunello N and Tascedda F (2016) Effect of desipramine and fluoxetine on energy metabolism of cerebral mitochondria. *Neuroscience* 330: 326-34.

Yoshiuchi K, Farkas J and Natelson B (2006) Patients with chronic fatigue syndrome have reduced absolute cortical blood flow. *Clinical physiology and functional imaging* 26 (2): 83-86.