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White Matter Neuroinflammation in ME/CFS

Qiang Yu
University of the Sunshine Coast

Trusted.
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Transforming lives through mental health research, training and treatment.

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)

ME/CFS affects up to *half a million* Australians and *24 million* people worldwide

Distinct white matter impairments were observed in ME/CFS patients with different onsets

Post-infectious ME/CFS (PI-ME/CFS)

- **Inflammation-related swelling** in post-infectious ME/CFS associated with worse physical health

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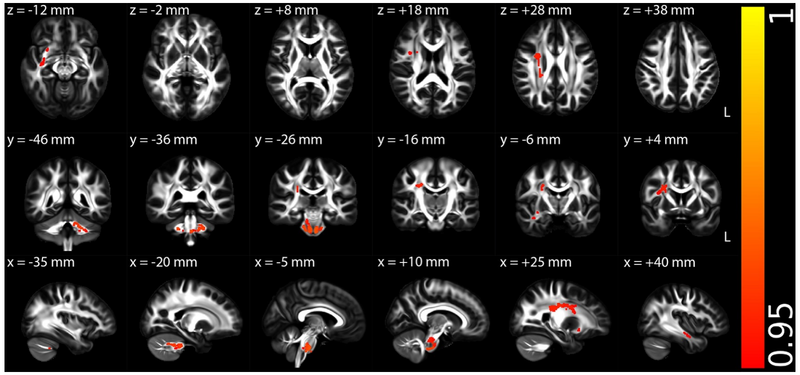

Gradual onset ME/CFS (GO-ME/CFS)

- **Neural fibre atrophy** in gradual onset ME/CFS associated with worse mental health

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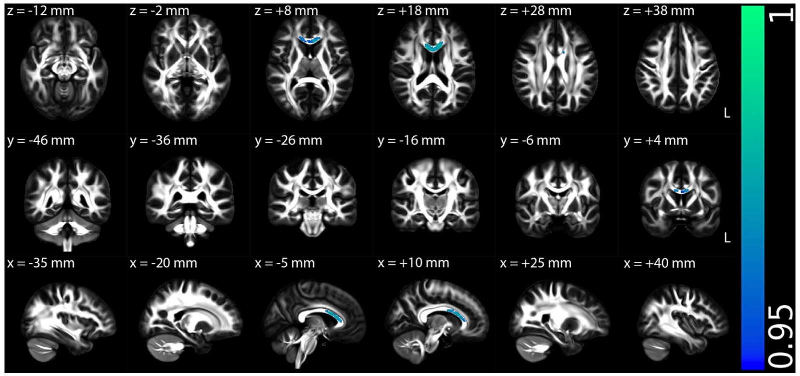
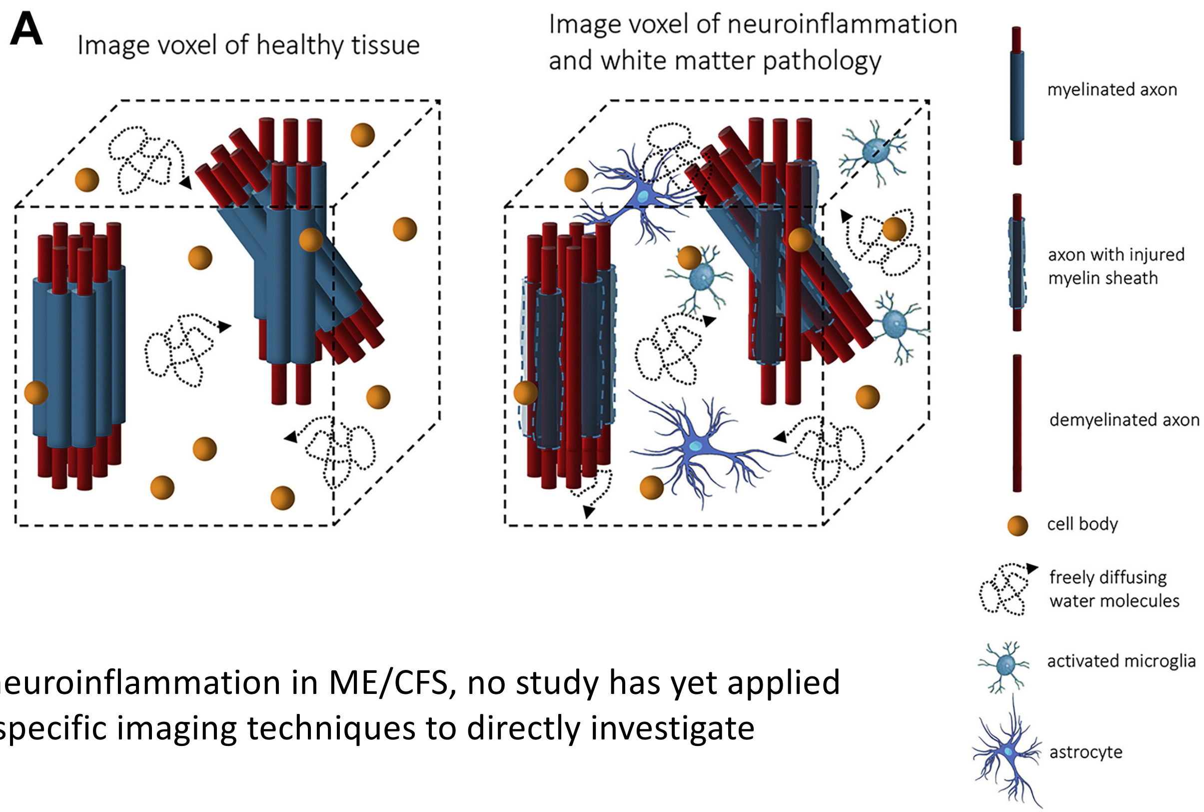


Yu et al., Scientific Reports 2025, 15: 24256.

Limitations

- DTI indices only reflecting **overall integrity** and lacking specificity for neuroinflammatory processes
- Traditional DTI provides limited insights into tissue compartments
- **Novel advanced diffusion model** is needed to investigate white matter neuroinflammation



- Despite the accumulating evidence for neuroinflammation in ME/CFS, no study has yet applied advanced diffusion neuroinflammation-specific imaging techniques to directly investigate inflammatory processes in ME/CFS

Oestreich and O'Sullivan, Biological Psychiatry: Cognitive Neuroscience and Neuroimaging 2022, 7(7): 638-658.

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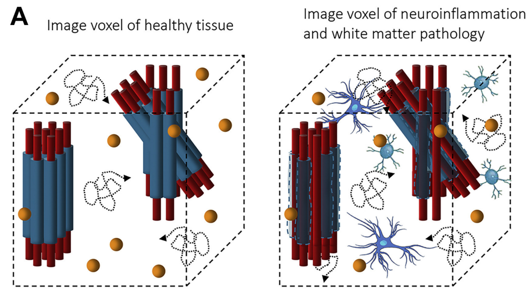


NII model

Diffusion-based neuroinflammation imaging (NII):

$$S_k = \sum_{i=1}^{N_{Aniso}} f_i e^{-|\overrightarrow{b_k}|\cdot\lambda_{\perp\_i}} e^{-|\overrightarrow{b_k}|\cdot(\lambda_{\|\_i}-\lambda_{\perp\_i})\cdot\cos^2\psi_{ik}} + \int_a^b f(D) e^{-|\overrightarrow{b_k}| D} dD$$

multiple anisotropic diffusion tensors **isotropic diffusion components**

where S_k and $|\overrightarrow{b_k}|$ are the signal and b-value of the k-th diffusion gradient; N_{Aniso} is the number of anisotropic tensors; ψ_{ik} the angle between the principal direction of the i-th anisotropic tensor and the k-th diffusion gradient; $\lambda_{\|i}$ and $\lambda_{\perp i}$ are the AD and RD of the i-th anisotropic tensor; f_i is the signal intensity fraction for the i-th anisotropic tensor; and a and b are the low and high diffusivity limits for the isotropic diffusion spectrum $f(D)$.

Wang et al., Brain 2011, 134: 3590-3601.

The solving of NII model

$$S_k = \sum_{i=1}^{N_{Aniso}} f_i e^{-\left|\vec{b}_k\right| \cdot \lambda_{\perp\_i}} e^{-\left|\vec{b}_k\right| \cdot (\lambda_{\parallel\_i} - \lambda_{\perp\_i}) \cdot \cos^2 \psi_{ik}} + \int_a^b f(D) e^{-\left|\vec{b}_k\right| D} dD \quad (k = 1, 2, \ldots, K)$$

→

$$s = \begin{bmatrix} s_1 \\ \vdots \\ s_K \end{bmatrix} = \begin{bmatrix} m_{1,1}, & \ldots & m_{N_{Aniso},1}, & m_{1+N_{Aniso},1}, & \ldots & m_{L+N_{Aniso},1} \\ \vdots & \cdots & \vdots & \vdots & \cdots & \vdots \\ m_{1,K}, & \cdots & m_{N_{Aniso},K}, & m_{1+N_{Aniso},K}, & \cdots & m_{L+N_{Aniso},K} \end{bmatrix} \times \begin{bmatrix} f_1 \\ \vdots \\ f_{N_{Aniso}} \\ f(a) \\ \vdots \\ f(b) \end{bmatrix} = Mf$$

$$m_{1,1} = e^{-|\vec{b}_1| \cdot \lambda_{\perp-1}} e^{-|\vec{b}_1| \cdot (\lambda_{\parallel-1} - \lambda_{\perp-1}) \cdot \cos^2 \theta_{1,1}}$$

$$m_{N_{Aniso},1} = e^{-|\vec{b}_1| \cdot \lambda_{\perp-N_{Aniso}}} e^{-|\vec{b}_1| \cdot (\lambda_{\parallel-N_{Aniso}} - \lambda_{\perp-N_{Aniso}}) \cdot \cos^2 \theta_{N_{Aniso},1}}$$

$$m_{1,K} = e^{-|\vec{b}_K| \cdot \lambda_{\perp-1}} e^{-|\vec{b}_K| \cdot (\lambda_{\parallel-1} - \lambda_{\perp-1}) \cdot \cos^2 \theta_{1,K}}$$

$$m_{N_{Aniso},K} = e^{-|\vec{b}_K| \cdot \lambda_{\perp-N_{Aniso}}} e^{-|\vec{b}_K| \cdot (\lambda_{\parallel-N_{Aniso}} - \lambda_{\perp-N_{Aniso}}) \cdot \cos^2 \theta_{N_{Aniso},K}}$$

$$m_{1+N_{Aniso},1} = e^{-|\vec{b}_1| a} \quad m_{1+N_{Aniso},K} = e^{-|\vec{b}_K| a}$$

$$m_{L+N_{Aniso},1} = e^{-|\vec{b}_1| b} \quad m_{L+N_{Aniso},K} = e^{-|\vec{b}_K| b}$$

Wang et al., Brain 2011, 134: 3590-3601.

Parameter estimation: a modified hybrid Nelder-Mead simplex search and particle swarm optimisation (MH-NMSS-PSO)

- Want et al. (2011) using the **regularised non-negative least-squares optimisation** which relies on **repeated executions with different initial values** to achieve consistent results by generalised pattern search.

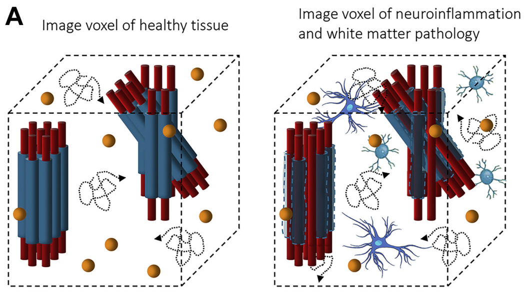
- The **NMSS** focuses on the exploitation of the **current solution space** with pre-determined initial points and then **moves towards** those points that have **better objective function values**.

- The **PSO** is used to explore the **unknown space** using a set of random initial points and **moves away** from those points that have **worse performance**.

- NMSS is likely to be trapped in a local optima and PSO has a slow convergence rate, but the **combination** of the two methods is superior to both NMSS and PSO methods in terms of **solution quality and convergence rate**.

Wang et al., Brain 2011, 134: 3590-3601.
Yu et al., Applied Mathematics and Computation 2022, 427: 127188.

NII-derived indices



$$S_k = \sum_{i=1}^{N_{Aniso}} f_i e^{-|\vec{b_k}| \cdot \lambda_{\perp\_i}} e^{-|\vec{b_k}| \cdot (\lambda_{\parallel\_i} - \lambda_{\perp\_i}) \cdot \cos^2 \psi_{ik}} + \int_a^b f(D) e^{-|\vec{b_k}| D} dD$$

Isotropic diffusion components:

- Hindered water ratio (**NII-HR**), is the hindered **fraction of non-restricted** isotropic diffusion [***f(D) at*** $0.3 < D \leq 2.5$ ***μm²/ms***], refers to water diffusion in the extracellular space with **intermediate diffusivity**.
- Hindered **fraction of restricted** isotropic diffusion (**NII-RF**) [***f(D) at*** $D \leq 0.3$ ***μm²/ms***] refers to the **low-diffusivity** water diffusion in restricted cellular environments, like intracellular or tightly packed small-cell spaces.

Multiple anisotropic diffusion tensors:

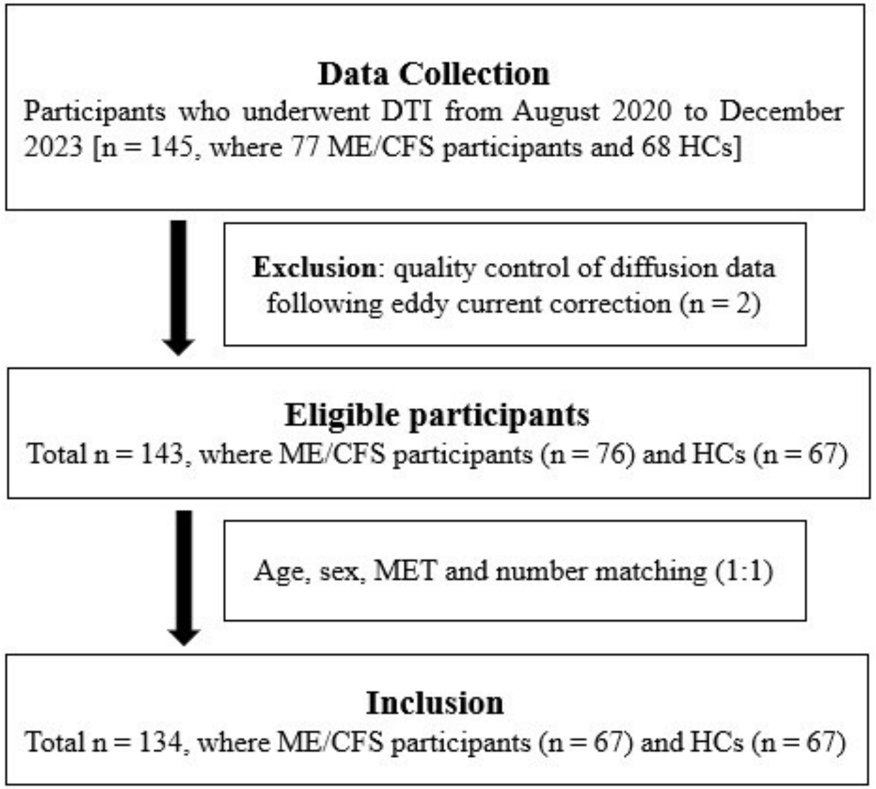
- **Fibre fraction (NII-FF)**: indicates apparent axonal density.
- Other NII-derived indices: NII-derived axial diffusivity (**NII-AD**), NII-derived radial diffusivity (**NII-RD**), NII-derived mean diffusivity (**NII-MD**), NII-derived fractional anisotropy (**NII-FA**).

Wang et al., Brain 2011, 134: 3590-3601.

NII study - participants

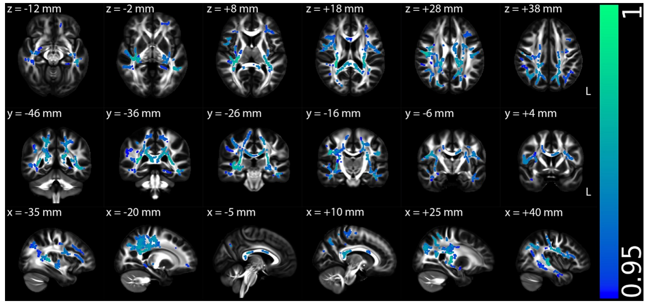
- We investigated white matter neuroinflammation in a **unified cohort** of ME/CFS patients, without subgrouping by onset type, to identify common pathological features.
- DTI data from 134 participants were analysed, including **67** participants with **ME/CFS** (mean age, 41.06 ± 12.50 [SD, standard deviation]; 54 women) and **67 HCs** (mean age, 37.51 ± 11.57 [SD]; 52 women).
- In our study, there are **no significant group differences** between ME/CFS patients and HCs in **sex, age, body mass index (BMI), metabolic equivalents (MET) rate, or MRI scan time** (all $p > 0.05$).

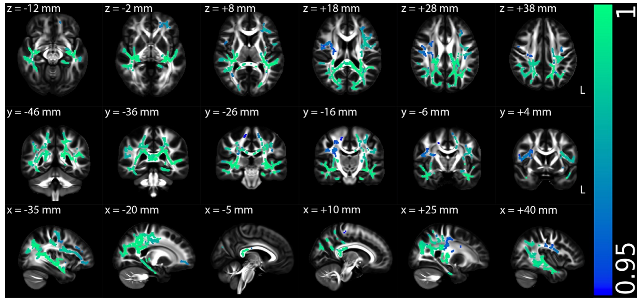
Yu et al., Human Brain Mapping 2026, 47: e70505.

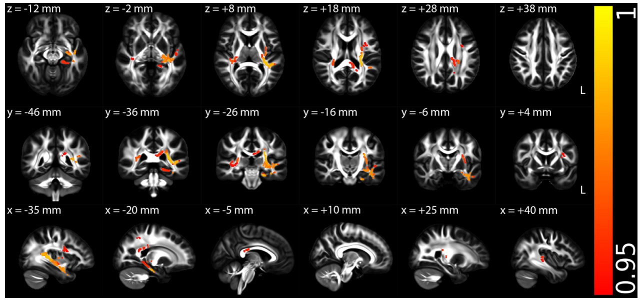


NII study results – group comparison

- **Reduced** hindered water ratio of non-restricted isotropic diffusion (**NII-HR**) in ME/CFS: indicates the brain is not experiencing vasogenic edema (which would increase extracellular water) but rather a form of **cellular swelling or "cytotoxic-like" edema**.
- **Reduced** hindered fraction of restricted isotropic diffusion (**NII-RF**) in ME/CFS. Rather than large, focal inflammatory lesions, ME/CFS may involve a subtle and chronic activation of microglia that causes the cells to change shape (e.g., from ramified to amoeboid) without necessarily increasing their number. The decreased NII-RF may reflect the **shape changes of activated microglia or a chronic depletion of microglia**.
- **Increased** fibre fraction (**NII-FF**) in ME/CFS: may reflect **increased apparent axonal density or a reduced extracellular space** due to neuroinflammatory processes.







Yu et al., Human Brain Mapping 2026, 47: e70505.

NII study - other results

Group comparison:

- Compared to HCs, ME/CFS patients exhibited widespread white matter abnormalities, including significantly **higher NII-AD, NII-MD, and NII-FA** across major tracts.
- Some regions also showed **decreased NII-AD and NII-MD** in ME/CFS.

Multiple regression:

- **Lower NII-RF** (hindered fraction of restricted isotropic diffusion), **NII-AD, and NII-MD were associated with worse mental health**, while **lower NII-RF was associated with greater disability.**
- **Higher NII-FF** (fibre fraction) **was associated with lower disease severity**.

Conventional DTI-derived metrics (DTI-AD, DTI-MD, DTI-RD, and DTI-FA):

- Compared to HCs, ME/CFS patients showed significantly **higher DTI-AD** in several white matter fibre tracts.
- **No significant associations** between DTI-derived metrics and **clinical measures**.

Yu et al., Human Brain Mapping 2026, 47: e70505.

Limitations

- First, although the NII model offers biologically informed metrics, it is still an indirect measure of neuroinflammation and does not differentiate between specific inflammatory cell types or processes.

- Second, this study did not collect biological samples alongside neuroimaging data, preventing an investigation of potential peripheral biomarkers associated with the observed findings.

Yu et al., Human Brain Mapping 2026, 47: e70505.

Conclusions

- This study investigates white matter neuroinflammation in ME/CFS, characterised by **cerebral edema (reduced NII-HR), cell shape change or a chronic depletion of microglia (reduced NII-RF), and axonal reorganisation (increased NII-FF)**.
- NII-derived indices may serve as sensitive biomarkers for neuroinflammation in ME/CFS.
- This study advances understanding of ME/CFS neuropathology, offering objective markers to validate patient experiences and inform diagnostics.

Yu et al., Human Brain Mapping 2026, 47: e70505.

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