Neuroimaging Findings
in ME/CFS and PCS

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Why Neuroimaging in ME/CFS?

- **Objective evidence of brain alterations**
  - Connectivity (fMRI)
  - Volumes (structural MRI)
  - Microstructure (DTI)
  - Perfusion (ASL)

- **Understanding pathophysiology**
  - Brain networks dysfunction (fMRI)
  - Neuroinflammation (PET)
  - Energy metabolism (MRS)

- **Identify biomarkers**
- **Identify treatment targets**

Main Neuroimaging Modalities

Method	Key Measure	ME/CFS Focus
Structural MRI: Volumetry	Brain structure volumes	Whole brain and regional atrophy patterns

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Arterial Spin Labeling (ASL)	Cerebral blood flow	Hypoperfusion / altered perfusion
Magnetic Resonance Spectroscopy (MRS)	Metabolites (e.g. N-acetylaspartate, choline, lactate, glutamate)	Detect brain metabolite abnormalities

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Positron Emission Tomography (PET)	Metabolism (glucose) & inflammation	Altered metabolism, neuroinflammation

Magnetic Resonance Imaging (MRI)

What is it?

- Non-invasive brain imaging
- Strong magnetic fields + radiofrequency pulses
- Detects hydrogen signals in tissue water
- High-resolution structural and functional data

Different tissue properties = **different signal contrasts**

What can it measure?

- **Structure** → anatomy (gray/white matter)
- **Function (fMRI)** → blood oxygenation (BOLD)
- **Chemistry (MRS)** → metabolites
- **Perfusion** → blood flow (ASL)

Berlin Center for Advanced Neuroimaging (BCAN)
Charité – Universitätsmedizin Berlin

Structural MRI: Volumetry

What it mesures

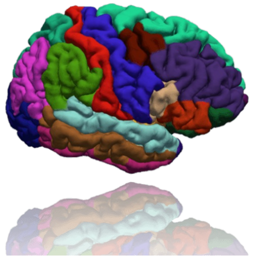
- Gray matter
- White matter
- Specific regions (e.g., thalamus, hippocampus)

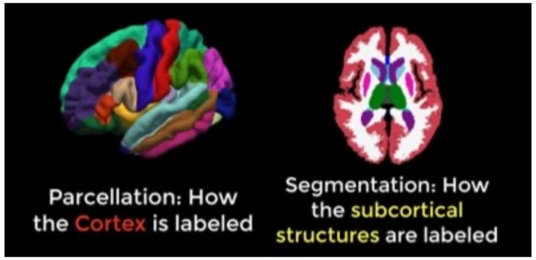
Methodology

- T1-weighted MRI
- Automated segmentation
- Group comparisons:
    - patients vs controls
    - regional volume differences

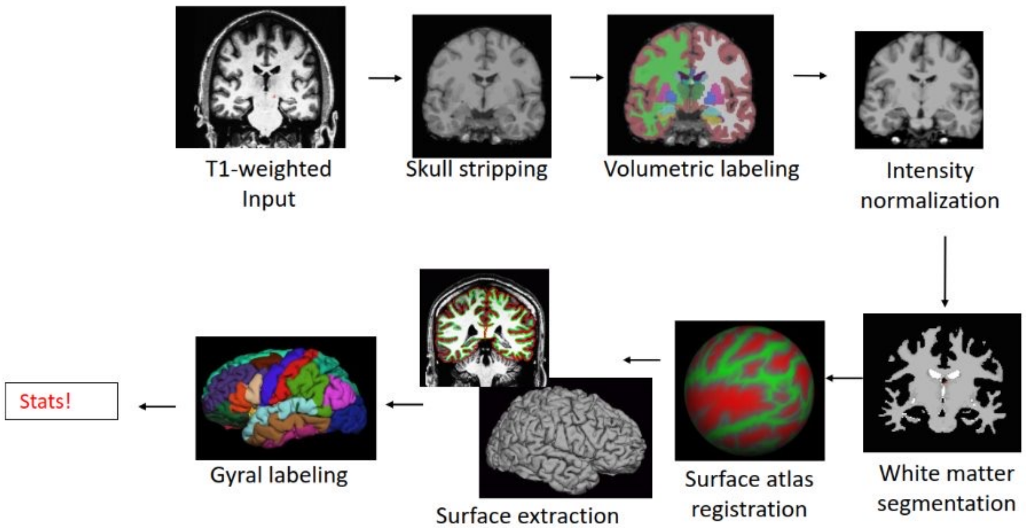
Clinical insights

- Structural changes (atrophy, hypertrophy)
- Disease progression





Overview of automated processing stream "recon-all"



Structural MRI: Volumetry Studies

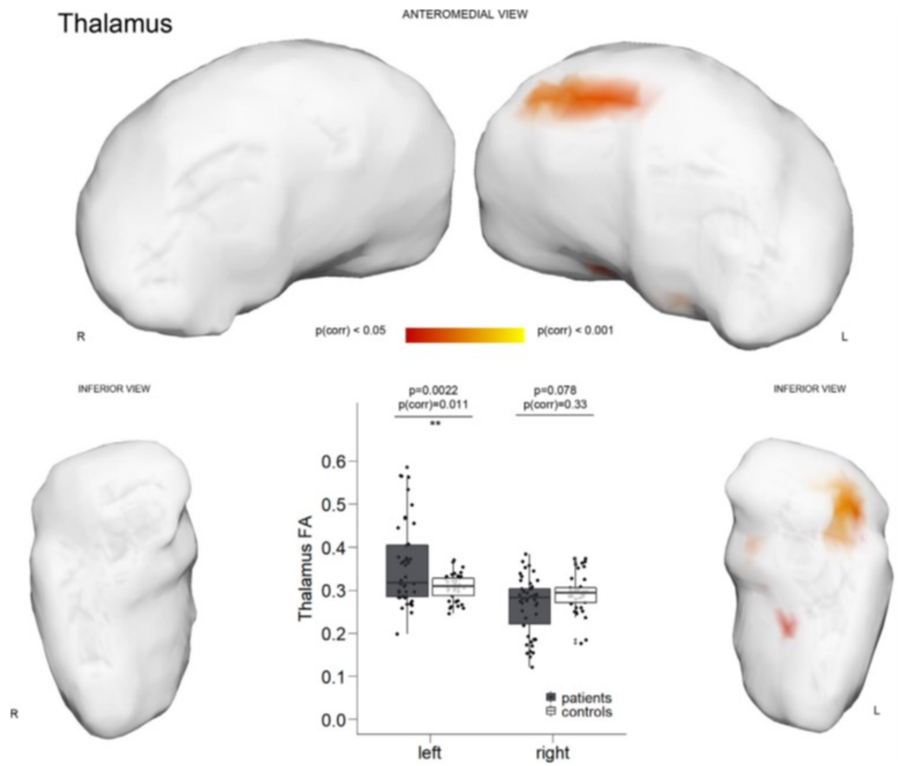
Heine et al. 2023 - eClinicalMedicine: Thalamic & basal ganglia volume reduction in post-COVID fatigue

Study

- N = 47 post-COVID patients with fatigue (median 7.5 months post-infection) (29% met ME/CFS criteria**)**
- n = 47 matched healthy controls
- MRI: T1 volumetry + diffusion imaging (DTI)

Findings

- Volumetry: Redced thalamus & basal ganglia volumes
- DTI: Microstructural alterations (FA) in thalamus and pallidum
- Clinical correlations:
  - Thalamic FA ↔ physical fatigue, Bell score, daytime sleepiness
  - Subcortical volumes ↔ short-term memory deficits



Magnetic Resonance Spectroscopy (MRS)

What is it?

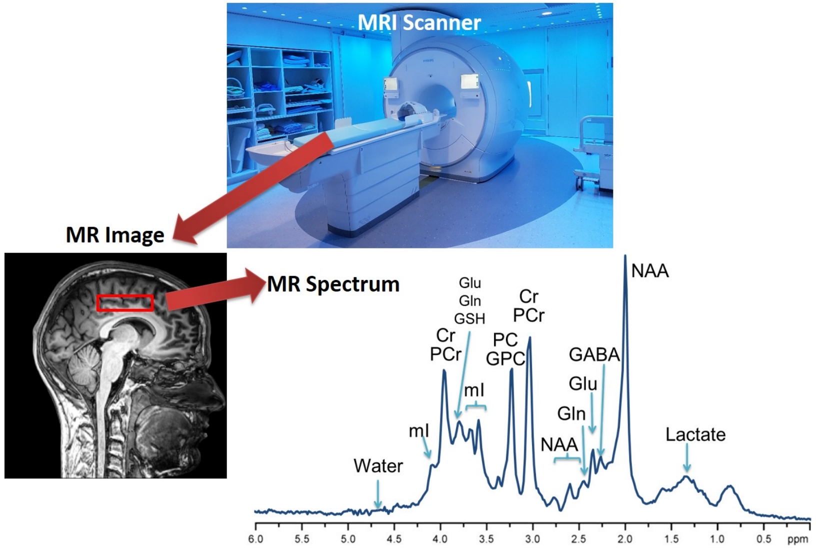
- MRI technique measuring brain chemistry (metabolites) rather than structure or connectivity
- Non-invasive window into **neuroinflammation & metabolic dysfunction**

What it measures

In vivo markers of:

- neuronal integrity (NAA)
- Glial activation / inflammation (choline, myo-inositol)
- Energy metabolism (lactate)

Image from *https://blogs.ubc.ca/erinlmacmillan*



Findings in ME/CFS & PCS

- ↑ Lactate in brain & muscle (energy dysfunction)[1]
- ↑ Glutamate (excitotoxicity)[2]
- ↓ Choline (glial changes)[1]
- ↑ NAA (neuronal compensation)[2],[3]
- ↓ Myo-inositol (glial dysfunction)[4]

Major 7T studies: *[1]Godlewska et al. Front Neurosci 2025, [2]Thapaliya et al. Am J Med 2025, [3]Kaur et al. Medicina 2024, [4]Godlewska et al. J Psychopharmacol 2022, [5]Pajuelo et al. MAGMA 2024*

MRS Studies

Godlewska et al. 2025 - Molecular Psychiatry

7T MRS in ME/CFS (n=24) and Long COVID (n=25) vs controls (n=24)

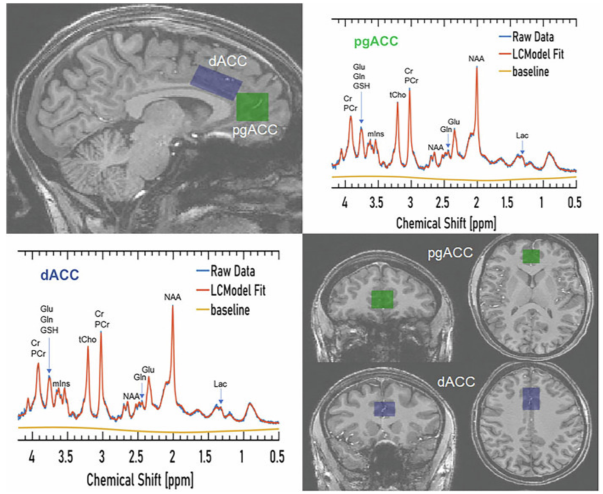
Voxel placement:

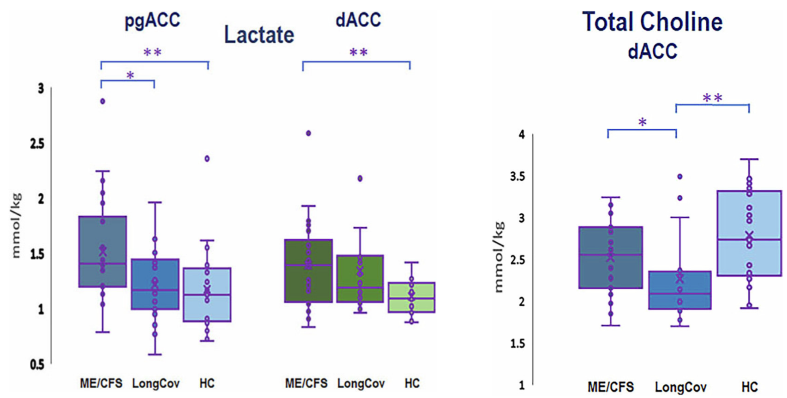
- Brain → Pregenual anterior cingulate cortex (**pgACC**) and dorsal anterior cingulate cortex (**dACC)**
- Muscle → Calf

Key findings

- ↑ **Lactate in ME/CFS** (Impaired oxidative energy metabolism / mitochondrial dysfunction)
- ↓ **Total choline in Long COVID** (May relate to coagulation abnormalities and "brain fog“)
- No differences in glutathione, glutamate, or creatine
- No significant muscle metabolite differences at rest

Both groups had similarly high fatigue scores
Chalder Fatigue Scale: ME/CFS 23.0 vs long COVID 23.8





Arterial Spin Labeling (ASL)

What is it?

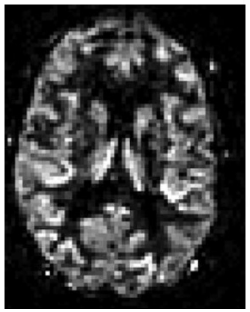
- **Non-invasive perfusion imaging:** measures tissue blood flow by using magnetically "labeled" arterial blood water as endogenous tracer

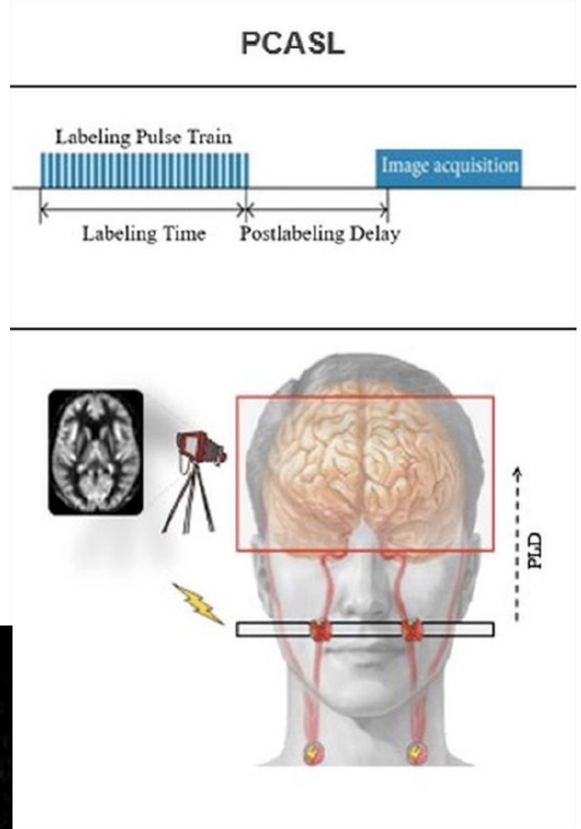
How does it work?

- **Control–label subtraction:** images with and without magnetic labeling of inflowing blood
- **Quantitative output:** Absolute cerebral blood flow (CBF) values (e.g., mL/100 g/min) → useful for comparing across patients, time points, and sites

Clinical application

- Assessment of perfusion deficits or hyperperfusion
- (i.e. strokes, brain tumors)





Clement et al., Front Radiol 2022

ASL Studies

***Boissoneault et al. 2016 - Magnetic Resonance Imaging*:** Abnormal resting state functional connectivity in patients with chronic fatigue syndrome: an arterial spin-labeling MRI study

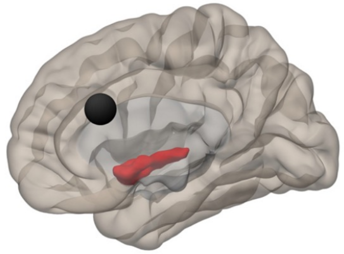


Fig. 1. *ACC seed* (black circle); ***Cluster 1*** (red: connectivity higher in HC than ME/CFS → right insula, planum polare, temporal pole, putamen, Heschl's gyrus)

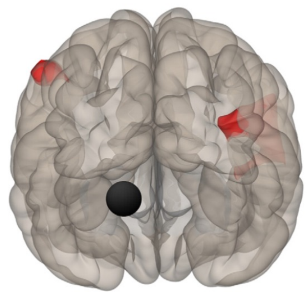


Fig. 2. Left *PaHCG seed* (black circle); ***Cluster 1*** (connectivity higher in HC than ME/CFS → right precentral gyrus, middle frontal gyrus, inferior frontal gyrus); **Cluster 2** (connectivity higher in HC than ME/CFS (left postcentral gyrus and left supramarginal gyrus)

Study

- 3T ASL + seed-to-voxel resting state fMRI (12 a priori seed regions)
- used **spontaneous cerebral blood-flow fluctuations over time** to infer connectivity between brain regions (rather than BOLD)
- ME/CFS (Fukada) (n=17) vs healthy controls (n=17)

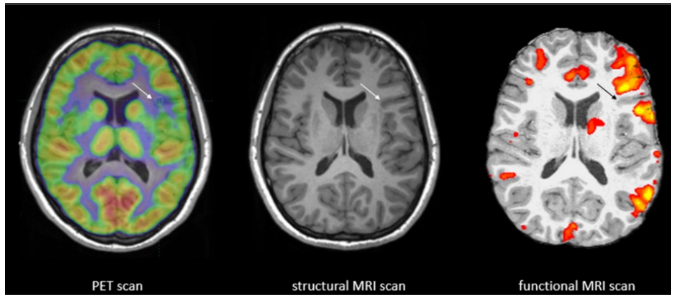
Key findings

- Reduced rCBF in brain regions associated with memory, cognition, affect, and motor function
- Altered connectivity between:
    - Parahippocampal gyrus (memory) ↔ somatosensory cortex
    - Pallidum (motor) ↔ occipital cortex (visual processing)
    - ACC (emotion/cognition) ↔ multiple brain networks
- Cerebral hypoperfusion correlated with fatigue severity

Functional MRI (fMRI) – Task-Based

What it measures

- Brain activity via blood oxygen levels (BOLD signal)
- Functional connectivity between brain regions
- **Task-related activation patterns (task-based fMRI)**
- Resting-state network organization (resting-state fMRI)



Task-based fMRI

- Brain activity during controlled cognitive or sensory tasks
- **“How brain networks respond under demand”**
- In fatigue disorders, often used to probe attention, working memory, cognitive effort
- Possible confounders: motivation, fatigue level during task, strategy differences

Functional MRI (fMRI) – Task-Based Studies

Inderyas et al. 2026 - Journal of Translational Medicine

Study

- 7T task-fMRI during Stroop cognitive test
- ME/CFS (n=27), Long COVID (n=17) vs controls (n=24)
- Pre (fatigue buildup) vs Post (fatigue set-in)

Purple Red Brown
Red Green Blue

Key Findings

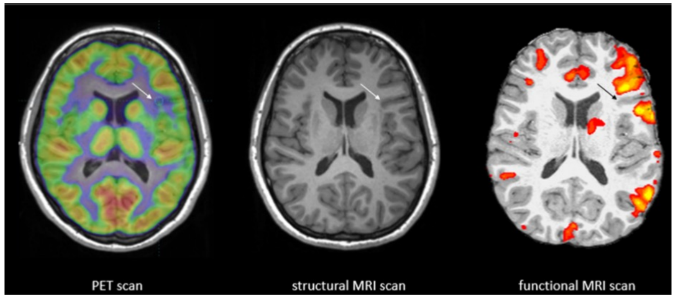
- **Healthy Controls** → Brain networks coordinate better during challenge: increased connectivity in subcortical from pre to post
- **ME/CFS** → Aberrant connectivity in core networks (DMN, SN)
  - ↓ hippocampus-nucleus accumbens (memory + motivation pathway)
- **Long COVID** → Impaired reward/motivation circuit
  - ↓ Nucleus accumbens ↔ Cerebellum (blunted dopaminergic reward)
  - ↓ Medulla ↔ Hippocampus (Memory-autonomic connection)

- Distinct patterns between ME/CFS and Long COVID
- FC differences correlate with cognitive impairment severity

Functional MRI (fMRI) – Resting State

What it measures

- Brain activity via blood oxygen levels (BOLD signal)
- Functional connectivity between brain regions
- Task-related activation patterns (task-based fMRI)
- **Resting-state network organization (resting-state fMRI)**



Resting-state fMRI

- Intrinsic brain activity **during rest** (no task performed)
- Identifies functional networks through **synchronized neural activity** (correlated BOLD signal patterns)
- Reveals baseline connectivity patterns and network organization

Key Brain Networks

Default Mode Network (DMN)
Self-reflection, memory

Salience Network (SN)
Attention to important stimuli

Central Executive Network
Cognitive control, working memory

Sensorimotor Networks
Movement, sensation

Functional MRI (fMRI) – Resting State

Díez-Cirarda et al. 2023, Brain: Multimodal neuroimaging in post-COVID syndrome and correlation with cognition

Study

- Multimodal MRI (resting-state fMRI, structural, DTI)
- Long COVID with cognitive impairment (n=86) vs. controls (n=36) at 11 months post-infection

Key findings

Functional connectivity:

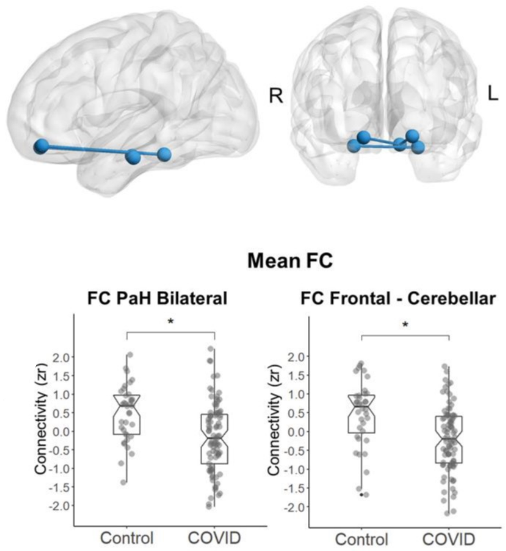
- Reduced connectivity between left & right parahippocampal & between orbitofrontal & cerebellar regions
- Correlates with memory deficits (learning & recall)

Structural changes:

- Grey matter volume reduction: parahippocampal, frontal, cerebellar, temporal regions
- Strong correlations with attention, processing speed, working memory deficits

White matter:

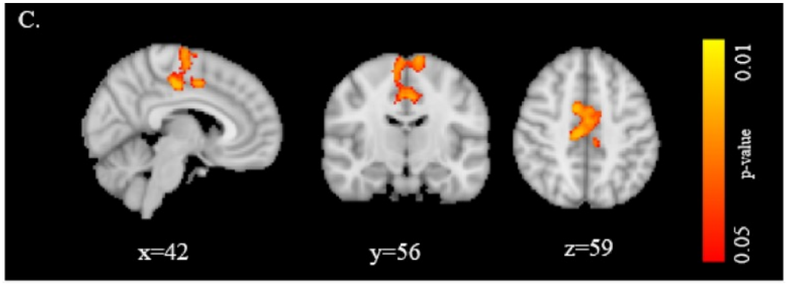
- ↓ axial & mean diffusivity (suggests axonal injury)



Functional MRI (fMRI) – Resting State Studies

Leitner et al. 2024 - NeuroImage

Study
- Resting-state fMRI in Long COVID patients with fatigue (n=15) vs. without fatigue (n=24)
- Seed-based analysis with **thalamus** as a seed region



Key findings
- Altered thalamo-cortical connectivity
- Changes are network-specific & fatigue-dependent
  - Fatigued patients: reduced connectivity between thalamus and motor regions
  - Non-fatigued patients: Positive functional coupling in same regions

Motor cortex (M1) Supplementary motor area (SMA)Anterior cingulate cortex (ACC)

- **Interpretation**
  - Fatigue linked to thalamo-cortical circuit dysfunction
  - Relevance for ME/CFS
  - Supports shared neurobiological mechanism

Why the thalamus?
- Central relay + integration hub
- Key role in attention, sensory processing, effort regulation

HBOT-40 Study

Kim & Cammà et al. medRxiv 2025; (under review)

Article

Hyperbaric oxygen therapy improves clinical symptoms and functional capacity and restores thalamic connectivity in ME/CFS

Dr. Laura Kim [1*,#], Guido Cammà [4,#], Dr. Claudia Kedor Peters [1], Maron Mantwill [4], Oliver Müller [2], Nadège Leprêtre[1], Cornelia Heindrich [1], Dr. Rebekka Rust [1,3], Dr. Moritz Krill [4], Dr. Tim J. Hartung [4], Lukas G. Reeß [5,6], Dr. Stephan Krohn [4], Prof. Christian von Heymann [2], Dr. Kirsten Wittke [1], Prof. Carsten Finke [4,#] and Prof. Carmen Scheibenbogen [1,#]

Aims of the study

1. Explore brain changes after Hyperbaric Oxygen Therapy (HBOT) and their association with therapeutic response
2. Investigate differences in brain structure and function between ME/CFS patients and healhy subjects

HBOT-40 Study: Methods

Participants

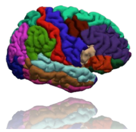
N = 30 patients (Canada Consensus Critera, PEM ≥14h)

- 42.3 ± 11.7 years
- 19 Females
- *Bell score* (mean ± SD) = 38.00 ± 10.95 -> moderate to severe degree of disability
- In 90% SARS-CoV-2 identified as the disease trigger

N = 30 age- and sex-matched healthy controls

MRI data acquisition & analysis

- pre-treatment (<4 weeks before HBOT)
- post-treatment (<4 weeks after HBOT)
- ***Structural***: Whole-brain volumetric analyses -> *FreeSurfer*



- ***Functional***: Seed-based resting state functional connectivity (FC) with thalamus as seed region -> *CONN Toolbox*

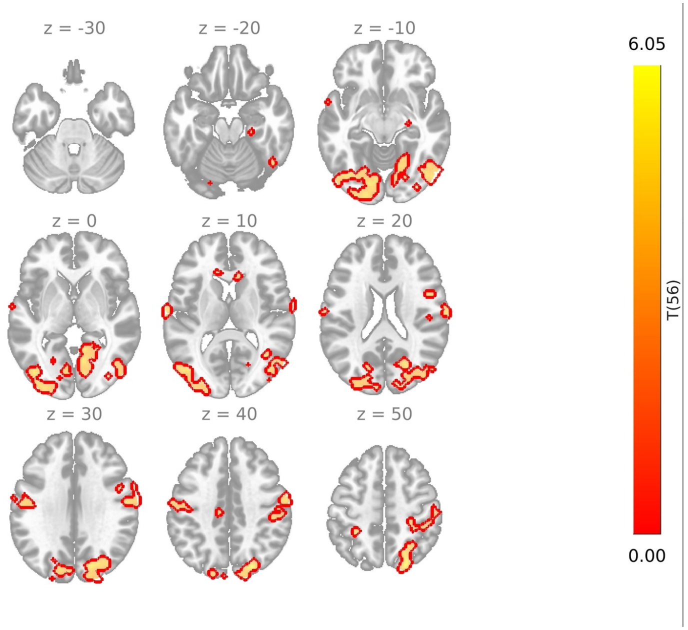
Results HBOT-40: functional analyses

a) Patients vs HC (pre-treatment)

Seed: *thalamic subcluster for sensorimotor integration**
voxel threshold p < 0.001; cluster threshold p < 0.05

Increased thalamic FC

- Visuo-occipital regions right (t = 6.36, p_FDR < 0.001)
- Visuo-occipital regions left (t = 5.34, p_FDR < 0.001)
- Motor and somatosensory regions right (t = 5.39, p_FDR < 0.001)
- Motor and somatosensory regions left (t = 4.87, p_FDR < 0.001)



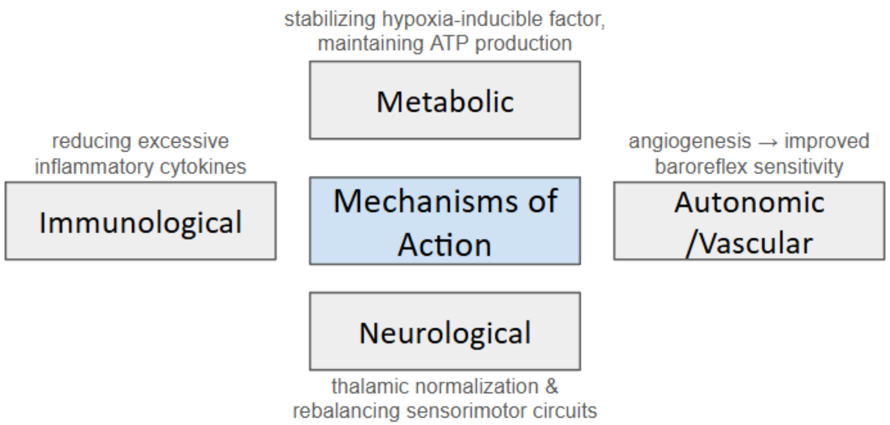
Increased thalamic connectivity with **sensorimotor** and **occipital** regions in ME/CFS patients compared to HCs

*Thalamic subcluster based on connectivity-based thalamic parcellation
(Boeken et al., Brain Struct Funct, 2023)

All analyses controlled for age and sex and FDR-corrected

HBOT-40 Study

2. Explore brain changes after Hyperbaric Oxygen Therapy (HBOT) and their association with therapeutic response



- 40 HBOT sessions over 8-16 weeks (up to 5/week, outpatient)
- Hyperbaric chamber: 2 ATA, 90 min, 5-min air breaks every 20 mins

Results HBOT-40: functional analyses

b) Patients vs HC (post-treatment) → **No significant differences**

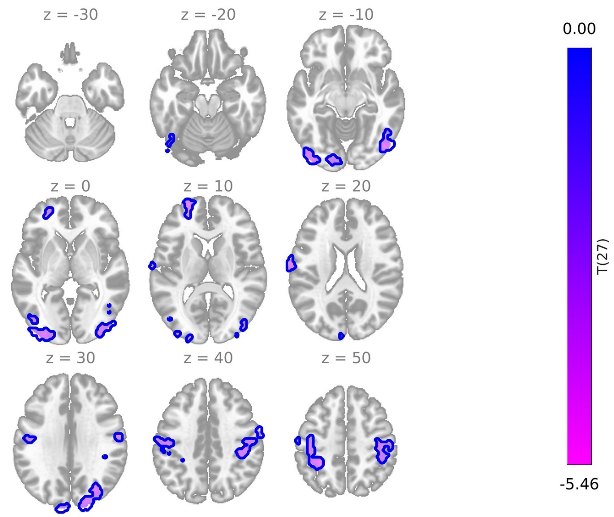
c) Patients longitudinal (pre- vs post-treatment)

Decreased thalamic FC

- Left sensorimotor cluster (t = -6.05, p_FDR < 0.001)
- Left visuo-occipital cluster (t = -4.27, p_FDR < 0.001)
- Right sensorimotor cluster (t = -6.04, p_FDR < 0.001)
- Right visuo-occipital cluster (t = -4.09, p_FDR < 0.001)

Baseline hyperconnectivity normalizes after 40 HBOT sessions

Seed: *thalamic subcluster for sensorimotor integration*
voxel threshold p < 0.01; cluster threshold p < 0.05



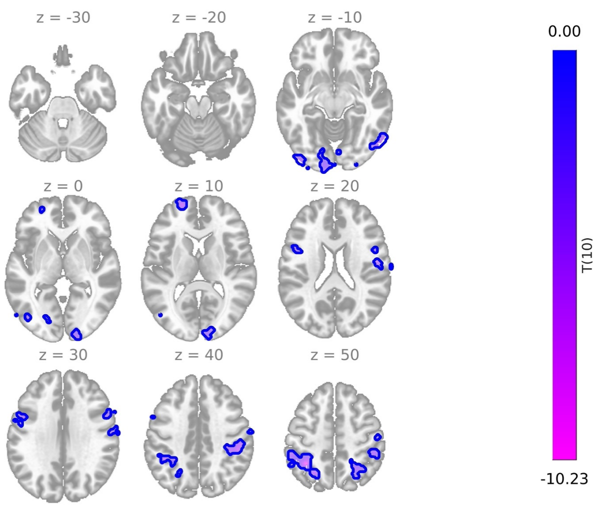
All analyses FDR-corrected

Results HBOT-40: functional analyses

Responders (≥ 10-point increase in SF-36 PF* at 4 weeks post-HBOT)

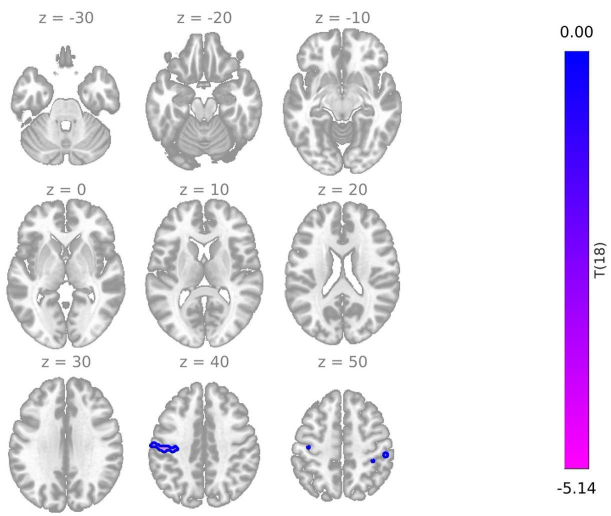
***Responders** (40) longitudinal (pre- vs post-treatment)* (N = 11)

Seed: *thalamic subcluster for sensorimotor integration*
voxel threshold $p < 0.01$; cluster threshold $p < 0.05$



***Non-Responders** (40) longitudinal (pre- vs post-treatment)* (N = 17)

Seed: *thalamic subcluster for sensorimotor integration*
voxel threshold $p < 0.01$; cluster threshold $p < 0.05$

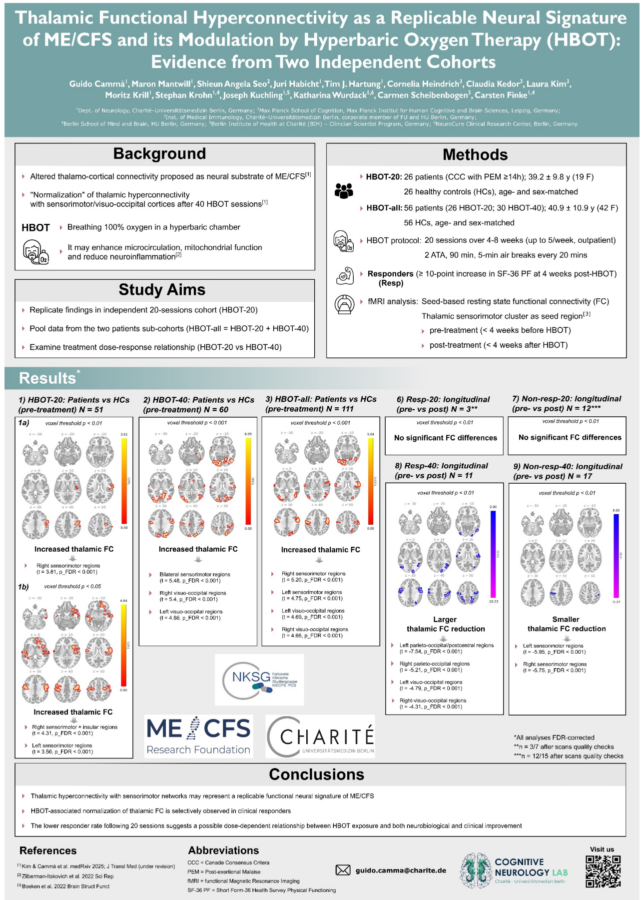


Larger FC normalization in **Responders**

*SF-36 PF = Short Form-36 Health Survey Physical Functioning

All analyses FDR-corrected

HBOT-20 Study



Cammà et al., 2026 - Poster Presentation

Aims of the study

1. Replicate baseline findings in an independent 20-sessions cohort (HBOT-20)
2. Examine treatment dose-response relationship (HBOT-20 vs HBOT-40)

Participants

N = 26 patients (Canada Consensus Critera, PEM ≥14h)

- *Females* (n, %) = 19 (73.07%)
- *Mean age* (mean ± SD) = 39.15 ± 9.8 years
- *Bell score* (mean ± SD) = 37.39 ± 8.64 -> moderate to severe degree of disability

N = 26 age- and sex-matched healthy controls

Thank you!

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ME CFS Research Foundation

NKSG Nationale Klinische Studiengruppe MECFS PCS

COGNITIVE NEUROLOGY LAB Charité - Universitätsmedizin Berlin