

# Advanced Imaging Analysis Reveals Altered Volume Segmentation, Structural Characteristics, and Fractional Anisotropy in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome and Long COVID Patients.

Christof Peter Ziaja<sup>1,2,3</sup> PhD1 Susanne Young<sup>3,4</sup> PhD2; Jan Sedlaczik<sup>5</sup>; Thomas Lindner<sup>2</sup>; Michael Sadre Chirazi-Stark<sup>3</sup>.  
1 Akademia Wychowania Fizycznego im Polskich, University of Breslau, Al. Paderewskiego 35, PL 51-617 Wrocław Poland. 2 UKE Department of Neuroradiology Hamburg, Martinstraße 52, WEST 14, Room 57, 20251 Hamburg. 3 Institut of Stress Diagnostic and Interventional Fatigue Science, Prof Stark, Beim Schlump 29, 20144 Hamburg. Email kontakt@prof-stark.de, 4 South African PTSD Research Program of Excellence, Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Email 16073371@sun.ac.za. 5 Biomedical Engineering Department and Centre for the Brain, School of Biomedical Engineering and Imaging Sciences, King's College London, London UK

Long Covid  
2. KONGRESS  
24.-25. November 2023 | Jena

Teilnahme mit Long COVID: COVID-19, Sepsis und entzündungsassoziierte Folgeerkrankungen



## ABSTRACT

The onset of Long COVID (LC) and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) may be related to a virus-or immune mediated disruption. Such inflammatory processes have an impact on the brain's interconnectivity. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) represents a complex condition whose onset is potentially linked to viral infections or immune-mediated disturbances, instigating inflammatory processes with repercussions on brain interconnectivity. This case study explores the intricate relationship between viral infections and vector markers within diverse brain networks, employing Fractional Anisotropy (FA) imaging as a primary investigative tool. A comprehensive analysis of 120 brain volumes is conducted, tracking changes over time and capturing unique characteristics. Automated fibre quantification facilitates the comparison of FA along 4 specific tracts.

## METHODS

- We analyzed four main fiber tracts out of a total of 42 in the Diffusion MRI White-Matter Tract Atlas, and we examined 16 volume segmentations of various brain regions.
- The tract atlas, acquired from the Center for Biomedical Imaging at Massachusetts General Hospital and Harvard Medical School, underwent manual annotation.
- TRACULA, FREESURFER, CONN functional connectivity toolbox version 21a, HOROS, and FSLeye software were utilized for the reconstruction of the tracts based on the atlas.
- Diffusion Tensor Imaging (DTI), a modified form of magnetic resonance imaging, was employed to assess the movement of water molecules in the brain, enabling the visualization of nerve fibres in white matter.
- In the data processing phase, DCM files were imported into Horos and converted for subsequent analysis using TRACULA and FreeSurfer.
- Fractional Anisotropy (FA) was utilized to measure the diffusion of water molecules in the tissue. Parameters such as anisotropy (FA Avg), representing myelin sheath inflammation and conductivity, were subjected to analysis.
- Various brain regions, including the amygdala, hypothalamus, lateral ventricles, cerebellum white matter volume, cerebellum cortex, hippocampus, thalamus, and fornix, underwent examination.

## RESULTS

- The average age of participants was 35 years (with a standard deviation of ±15 years), and all participants were right-handed.
- Measurements were conducted on 10 participants with Long Covid in both 2021 and 2023, focusing on changes in the FA Avg conductivity and volume of specific brain regions.
- Individuals diagnosed with ME/CFS and Long Covid exhibited significant increases in the right posterior hypothalamic segmentation, along with a decrease and deformation anomaly in the structural integrity of the interior anterior region.
- Enlargement of the tubular right of the tegmentum of the caudal part of the hypothalamus (mammillothalamic tract) was associated with the speed of skeletal muscle tremors.
- The reduction in amygdala volume played a central role in the emotional evaluation of mechanoreceptive information, leading to a decrease in sensorimotor interaction and neuromuscular interaction with the central body of the corpus callosum, accompanied by a reduction in FA Avg (Fig. 3).
- Significant volume increases were observed in the White Matter Segmentation Fiber Tracts of the Fornix on both the left and right sides from 2021 to 2023 in the Long Covid group.
- The thickening of these fibre bundles contributed to a reduction in FA Avg conductivity of the Fornix vectors from front to back, impacting the volume of the Amygdala and Hippocampus and disrupting the balance in Fornix function.
- The Fornix, a crucial component of the limbic system, plays a role in the storage of short-term and long-term memory, learning, and modulation of neurotransmitters (dopamine, serotonin, and acetylcholine).
- These findings provide insights into the persistent symptoms of Long Covid and ME/CFS, emphasising the need for further patient data for validation.

## RESULTS

### FORNIX WM VOLUME SEGMENTATION AND FA

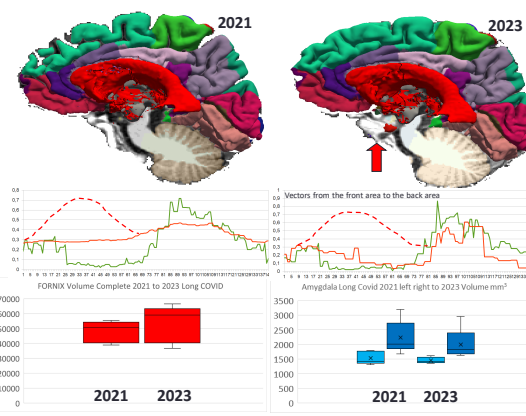


Fig. 2 displays the volumetric data increase in both Fornix Segmentation and FA Avg in white matter (wm) on both sides (left/right) from 2021 to 2023. The observed thickening of these fiber bundles results in a decrease in the conductivity of the FA Avg (Average), impacting the overall fractional anisotropy.

### ANTERIOR COMMISSURE AND CC body CENTRAL FA

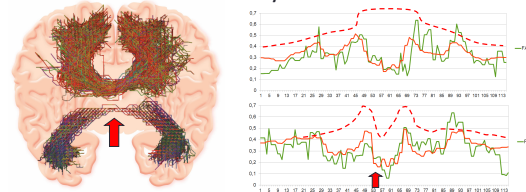


Fig. 3. Fig. 3 illustrates the networks of the Anterior Commissure and the central body of the Corpus Callosum. The Anterior Commissure spans the two temporal lobes and intersects with olfactory pathways. Within this region, fibers of stem cells transition from Nociceptors to secondary afferent neurons and from Alpha motor neurons. This complex process contributes to the sensitive processing of smells and raises suspicions of a potential association with small fiber neuropathy, particularly in nociceptors.

### HYPOTHALAMUS VOLUME SEGMENTATION AND STRUCTURAL CHANGES

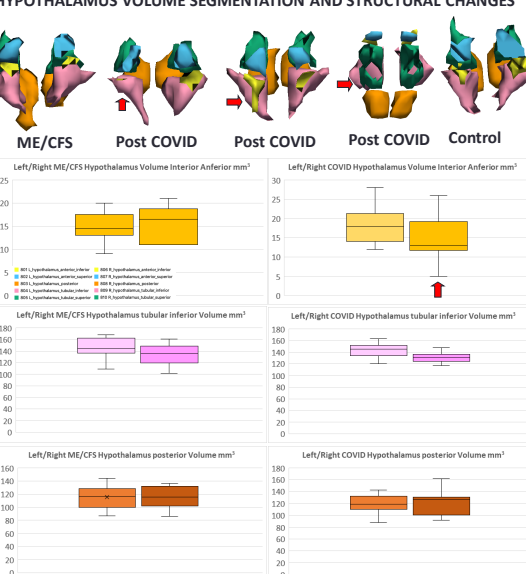


Fig. 4. Illustrates the Hypothalamus, subdivided into nuclei for neuroendocrine, behavioural, and autonomic homeostasis (Shapiro et al., 2022). The anterior regulates thermoregulation and sleep, while the posterior promotes arousal. Left dominance in circadian rhythm, thyroid activity, thermoregulation, and immune responses; right dominance in cardiovascular responses to stress (Xavier et al., 2009). Yellow shading highlights volume changes in the interior anterior right side, associated with bedridden status in Long Covid patients.

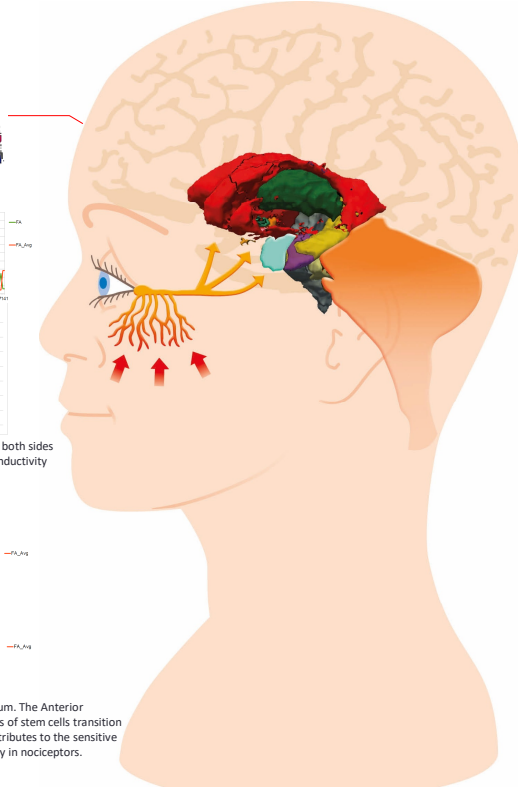


Fig. 1 The figure above depicts the interaction among specific brain regions, with their network traversing segments of the olfactory pathways. The interaction unfolds from the Anterior Commissure to the Amygdala, Fornix, Hippocampus, and the Thalamus/Hypothalamus Network.

## REFERENCES

Baraniuk James N. et al.: Differential Effects of Exercise on fMRI of the Midbrain Ascending Arousal Network Nuclei in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Gulf War Illness (GWI) in a Model of Postexertional Malaise (PEM). In: Brain Sci. 12, 78 <http://doi.org/10.3390/brainsci12010078>, 2022

Barnes-Goraly N. et al.: White Matter Development During Childhood and Adolescence: A Cross-Sectional Diffusion Tensor Imaging Study. In: Cerebral Cortex 15, 5, 1848-1854, 2005

Billot B. et al.: Automated segmentation of the hypothalamus and associated subunits in brain MRI, in Print, 2023

Byrne H. et al.: Hypothalamus volumes in adolescent Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS): impact of self-reported fatigue and illness duration. In: Brain Structure and Function, May 2023

Maffei C. et al.: Using diffusion MRI data acquired with ultra-high gradients to improve tractography in routine-quality data. In: Neuroimage 245:118706, 2021

Shapiro N. et al.: In vivo hypothalamic regional volumetry across the frontotemporal dementia spectrum. Neuroimage Clin 35:103084. j.nid.2022

Xavier Ch. Et al.: Functional asymmetry in the descending cardiovascular pathways from dorsomedial hypothalamic nucleus. Neuroscience 164:1360-1368. jneuroscience, 2009

Zeineh M.M. et al.: Right Arcuate Fasciculus abnormality in chronic fatigue syndrome. Radiology, Volume 274, Number 2 February 2015

Ziaja P.C. et al.: Autonomic Nervous System Functioning in Patients with Post Viral Syndrome: A Case-Series Study of a Healthy Control Subject, a Long Covid patient and a ME/CFS patient. In: 2022 Clinical & Scientific Conference Stony Brook University, NY, USA

Ziaja P.C., Young S, Sedlaczik J, Lindner T, et al. (2023) Comparing Fractional Anisotropy Diffusion Tensor Imaging of Patients with Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, Long COVID and Healthy Controls. 2nd International Meeting of the CFS – Charité Fatigue Center Berlin 11 May – 12 May at the Universitätsmedizin 2023 Berlin

## CONCLUSIONS

- The observed volume increases in both sides of the Fornix, coupled with right-sided hypothalamic inflammation and a reduction in the right Amygdala, indicate potential microstructural alterations in white matter. This suggests a progressive decline in the conductivity of Fractional Anisotropy (FA) over time in the Anterior Commissure, Fornix, and the central body of the Corpus Callosum in individuals with ME/CFS and LC. These findings not only hold promise as biomarkers for identifying both conditions but also offer potential insights for therapeutic interventions. Furthermore, the demonstrated utility of fractional anisotropy as a diagnostic biomarker suggests its applicability in distinguishing and diagnosing ME/CFS and LC.

## ACKNOWLEDGEMENTS

We would like to thank the patients at Prof Stark Institut, for their participation and making available of their patient data for the advancement of our knowledge of CNS dysregulation in ME/CFS and PCS