Evidence for CNS Involvement in Post-treatment Lyme disease

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MRI AND PET IMAGING OF PERSISTENT LYME ENCEPHALOPATHY

Supported by NINDS

To see further details:

Cognition: Keilp et al J International Neuropsychological Society 2006

Treatment: Fallon et al Neurology 2008

Neuroimaging; Fallon et al Archives of General Psychiatry 2009

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These patients met highly conservative criteria for Post-treatment Lyme Disease

- Age 18-65

- Lyme participants:
  - Historically well-documented Lyme disease based on CDC surveillance clinical and laboratory criteria
  - Prior treatment with at least 3 weeks of IV ceftriaxone
  - Memory problems confirmed by cognitive testing
  - Current positive IgG Western blot at our reference lab

- Healthy Controls: age-, sex-, education-matched

Final Study Entry Sample Size

Total: 55

- **Lyme patients: 37**
  - 23 randomized to ceftriaxone
  - 14 randomized to placebo
- **Healthy controls: 18**

Of 3700 evaluated, 1% were enrolled

- Results may not be generalizable to larger sample of persistently symptomatic patients who do not meet the narrow study criteria

  (Additional research is needed for these other patients)

Enrolled Sample of 37 Patients with Chronic Lyme Encephalopathy

Age: 45.1 yrs,

Gender: 59% female

Delay between symptoms and treatment: **1.2 yrs**

Amount of Prior Treatment: this is a particularly chronic sample

- **Mean IV: 2.3 months**
- **Mean oral: 7.7 months**

Assessments

Structural Imaging (MRI)

Functional Imaging (PET)

- FDG to assess metabolism
- O-15 to assess flow (3 scans: resting, room air, hypercapnea)

Neurocognitive Testing

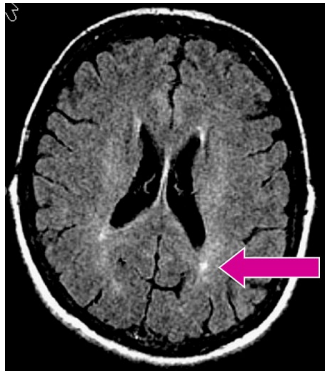
Self-reports

- Fatigue, Pain, Functional Status

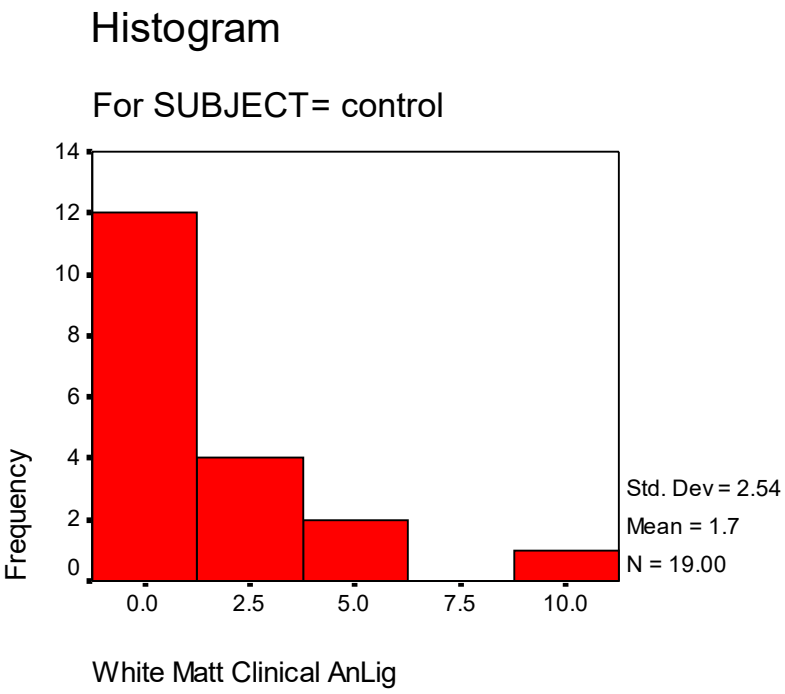
CSF Results at baseline (n=33)

- Few Routine abnormalities:
  - Mildly increased WBC (n=2), protein (n=4)
  - Oligoclonal bands: none
- CSF Bb Antibodies:
  - CSF Bb ELISA positive: 66.7%
  - CSF Bb IgM WB positive: 0%; IgG WB positive: 84.8%
  - **Intrathecal Bb Ab Production:**
    - **CSF Whole cell sonicate ELISA Index positive: 12.1%**
    - **CSF C6 ELISA Index positive: 62.5%**
- CSF PCR positive: None using OspA based PCR
- CSF Culture positive: 1 sample (false positive)

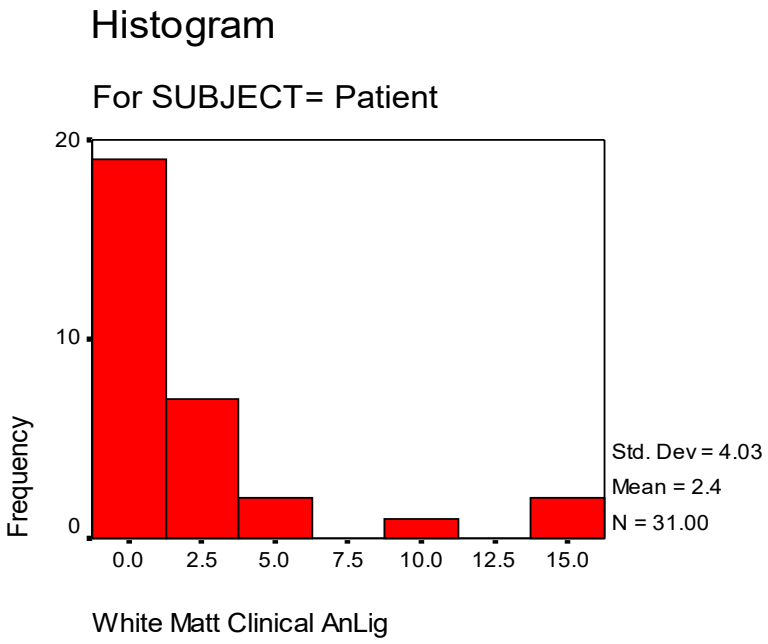
Brain MRI: Deep White Matter Hyperintensities: Controls vs Patients



DWMH in Controls

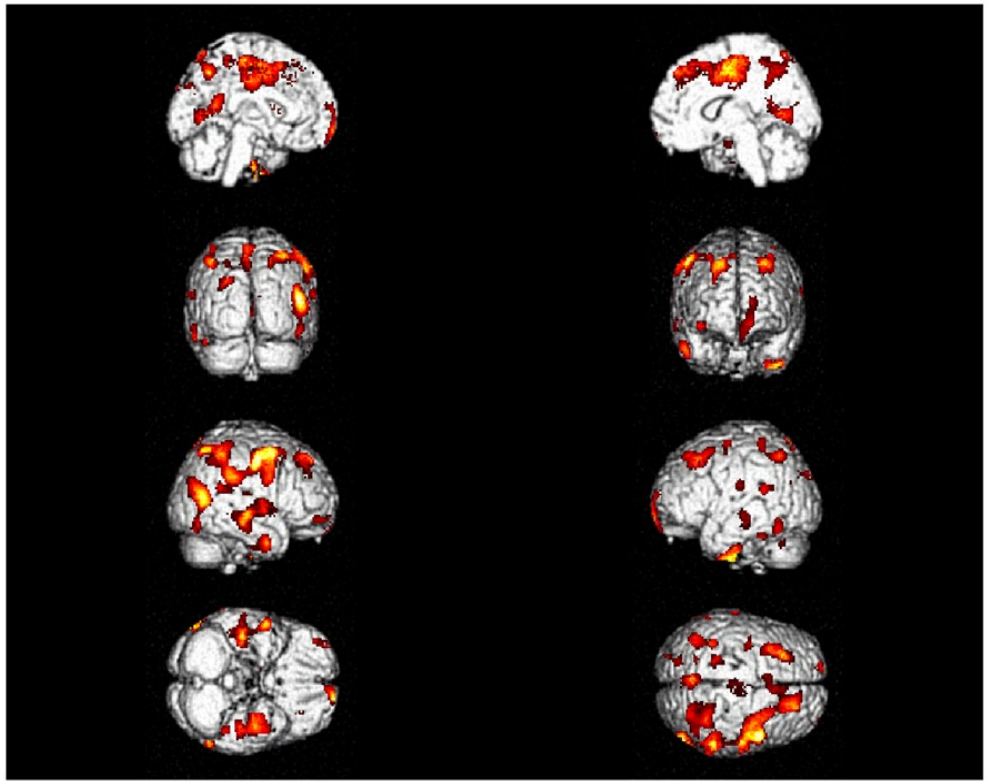


DWMH in Patients



Note: No diff. in WMHI Score between 2 groups

FDG Imaging: are there regional metabolic differences between patients & controls? Yes.



- Large clusters of specific areas of decreased metabolism in Gray matter and White matter
- This was not a random distribution…most abnl areas on metabolic scan were also abnl on the 3 blood flow scans.

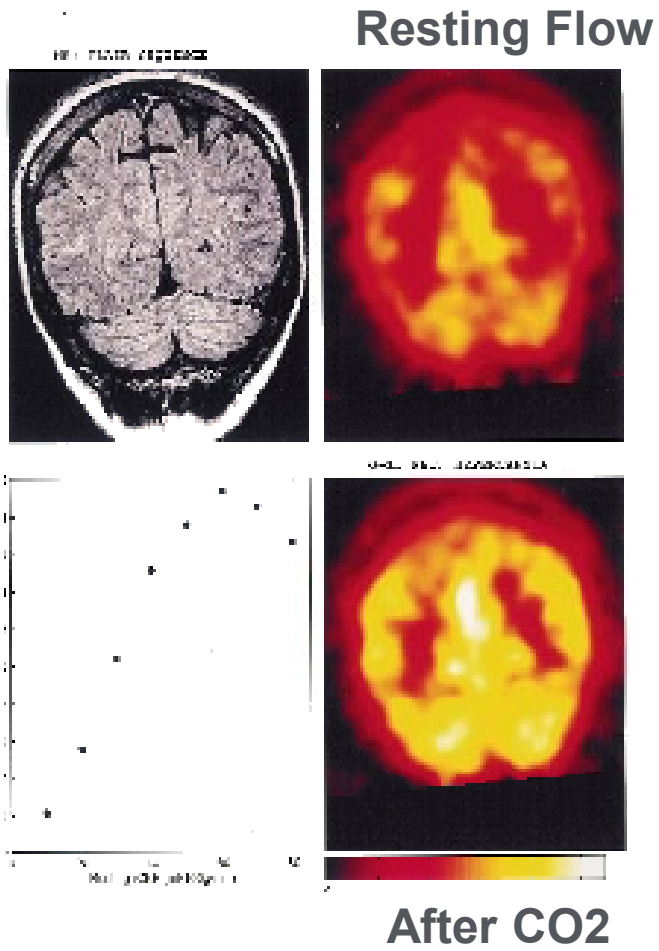
Patients have lower metabolism in 12 clusters (3049 voxels)

Left Hemisphere: Temporal (1199v), Frontal (527v), claustrum (539v), Parietal (139v);
Right Hemisphere: Cingulate (487 v), Parietal (265 v), Insula (154v)

Patients have higher metabolism in 3 clusters (680 voxels)

Fallon et al, JAMA Psychiatry 2009

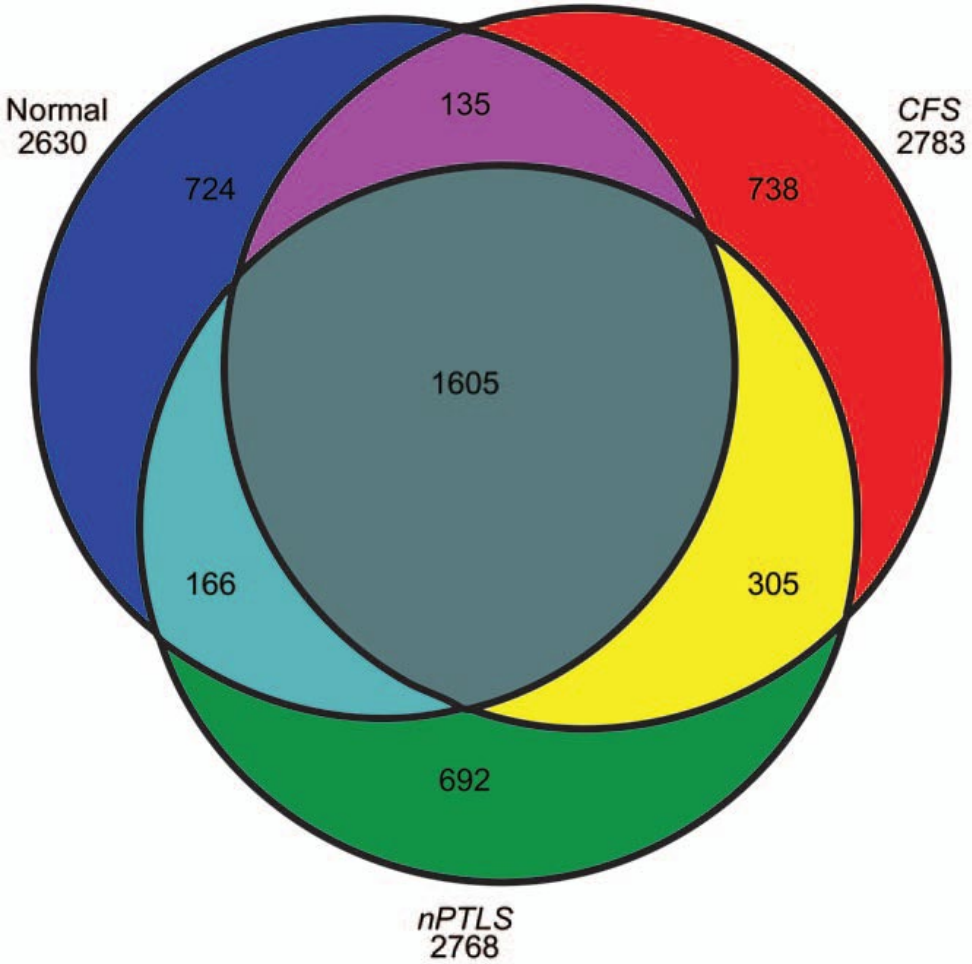
Global Cerebral Blood Flow: is there a difference in vasodilation capacity between patients and controls?



- Yes, the response to hypercapnic CBF challenge differed:
  - The patient group showed a diminished ability to enhance blood flow compared to controls (8.2% v 28.1%, p<.02)
  - This finding suggests vascular compromise in the patient group (not attributable to CVD risk factors)

Fallon et al, JAMA Psychiatry 2009

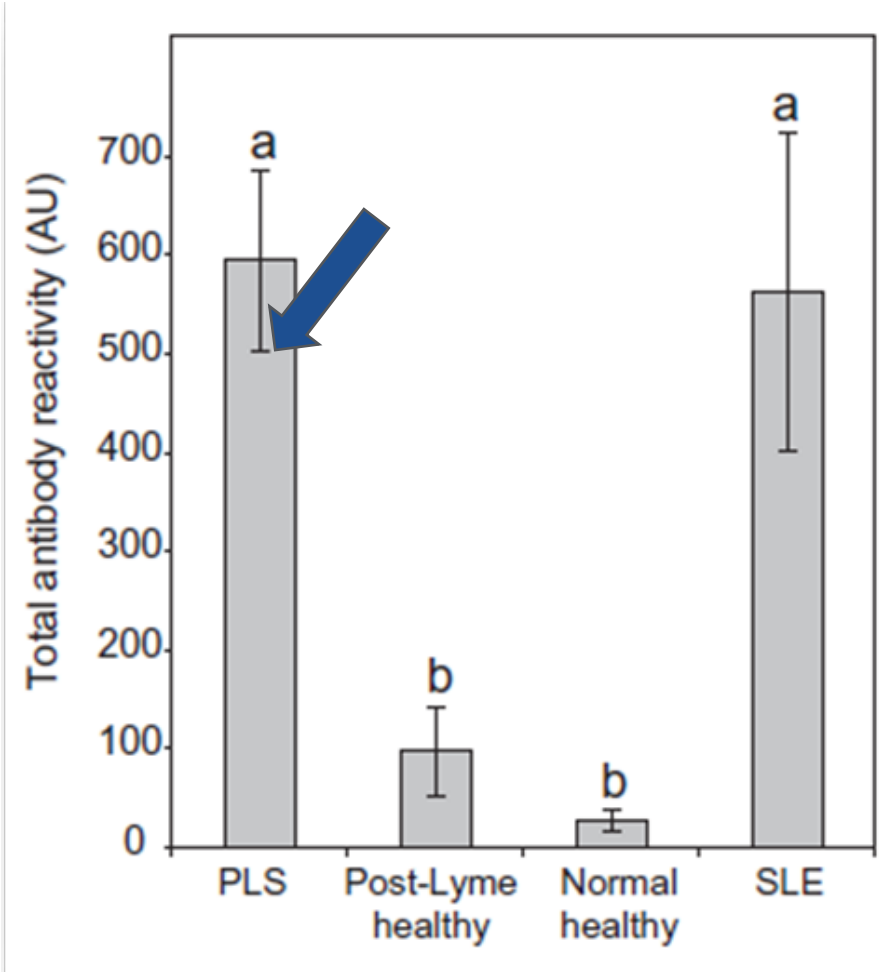
Is there a difference in the CSF Proteome? Yes, unique proteins differentiate post-treatment Lyme vs ME/CFS vs Normal

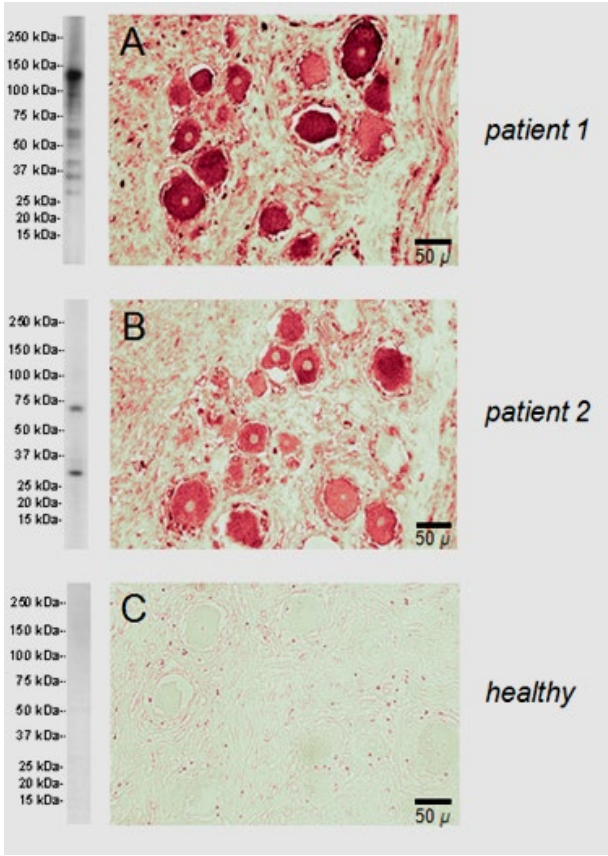


- Unique Proteins:
  - 738 in ME/CFS
  - 692 in post-treatment Lyme
- Proteins in the complement cascade were elevated in abundance in Lyme and CFS.

Schutzer, Angel, Liu…Fallon, Natelson, PLoS-One, 2011

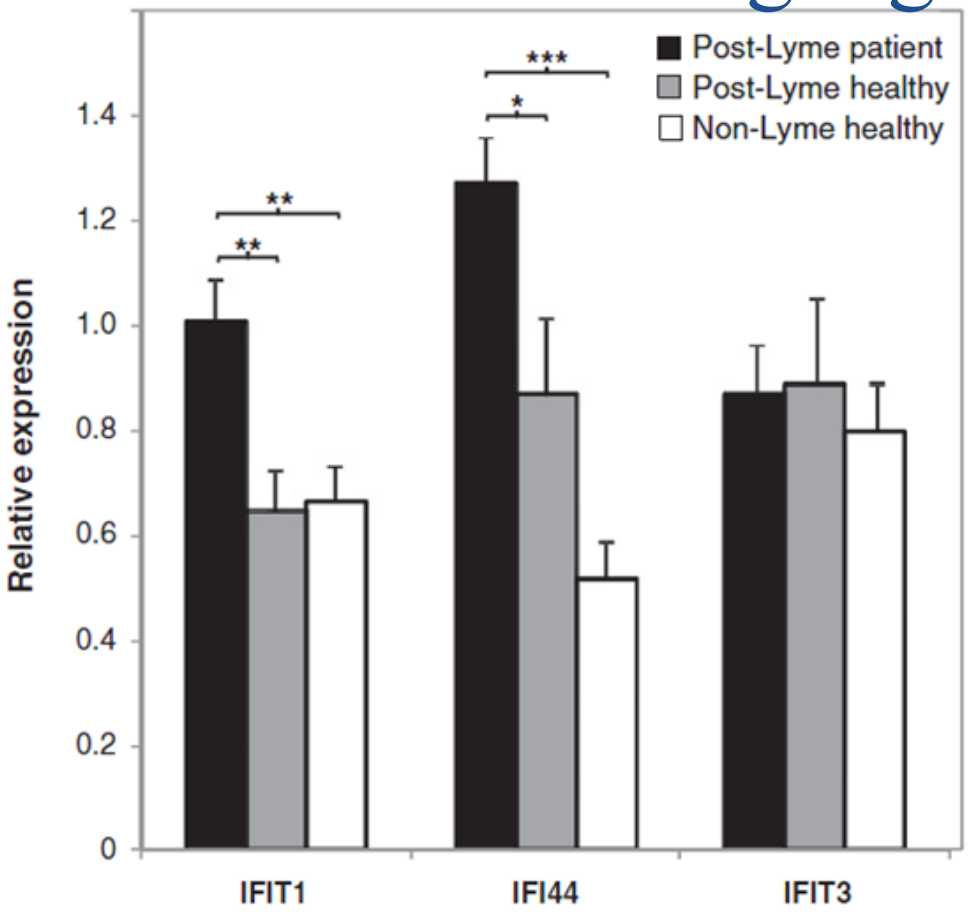
Are there antibodies that target neural tissue? Yes, persistent symptoms are associated with increased antibodies against neural proteins





Chandra et al, 2010

Sera from PTLS patients induce higher expression of IFNα-target genes.

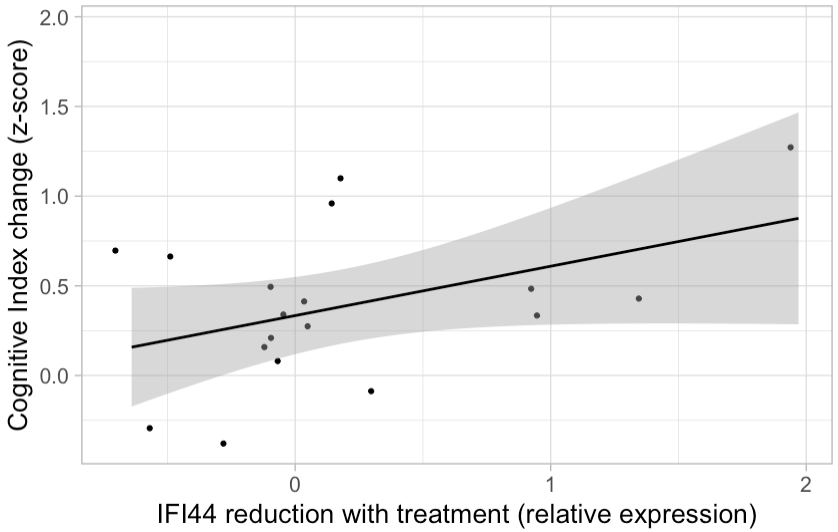


Jacek, Fallon, Chandra, Crown, Wormser, Alaedini, J Neuroimmunology 2013

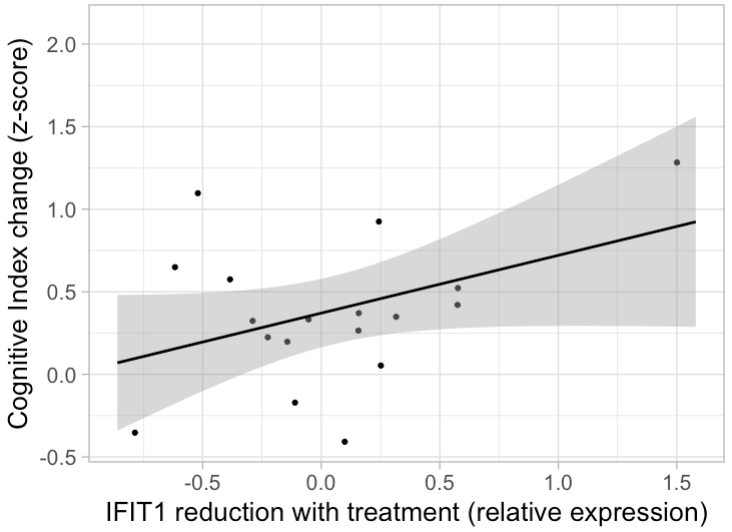
Is IFα alpha associated with Cognitive change in Post-treatment Lyme Disease?

Assessed at baseline and after 12 weeks of study participation

Improvement on cognitive index change score correlated moderately with larger reduction in IFNα target gene expression



R=0.425, p=.004 (one-sided), N=18



R=0.428, p=.004 (one-sided), N=18

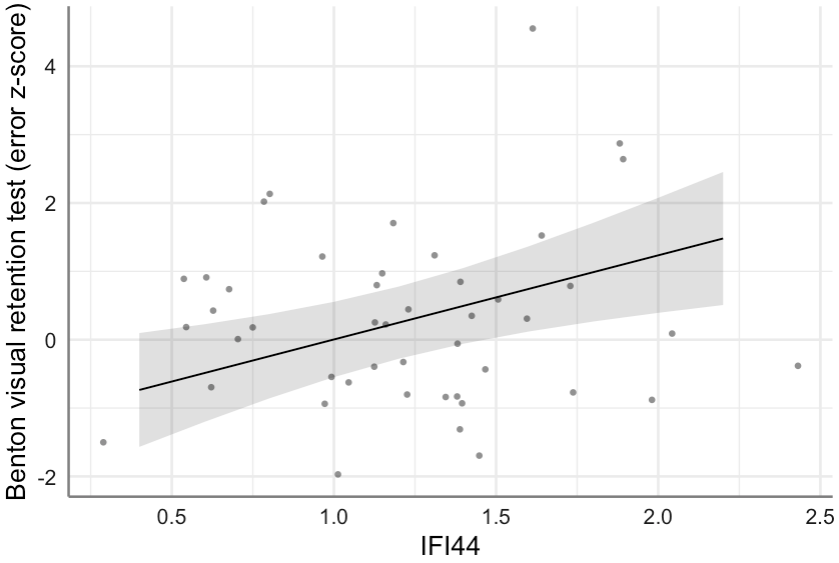
(Kuvaldina et al, manuscript in preparation)

Is IFN-α target gene expression associated with impaired memory in Post-treatment Lyme disease?

Assessed at 3 times points: baseline, 12 weeks, 24 weeks

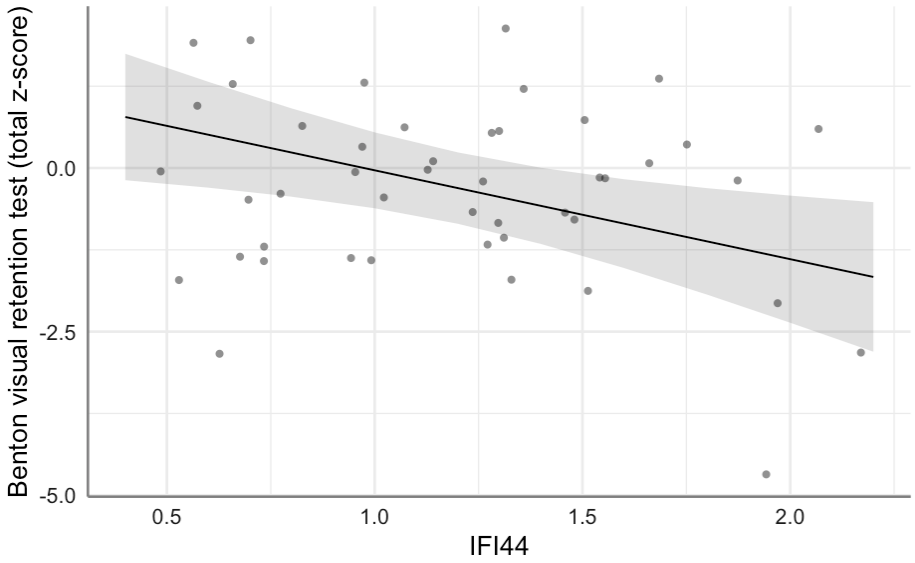
(Kuvaldina et al, manuscript in preparation)

Higher IFN-α target gene expression is moderately associated with poorer visuospatial memory – more errors and lower total visual memory score



Visual Retention Errors

1.23, CI[.4,2.06], p=.005, R^2=0.13, N=18

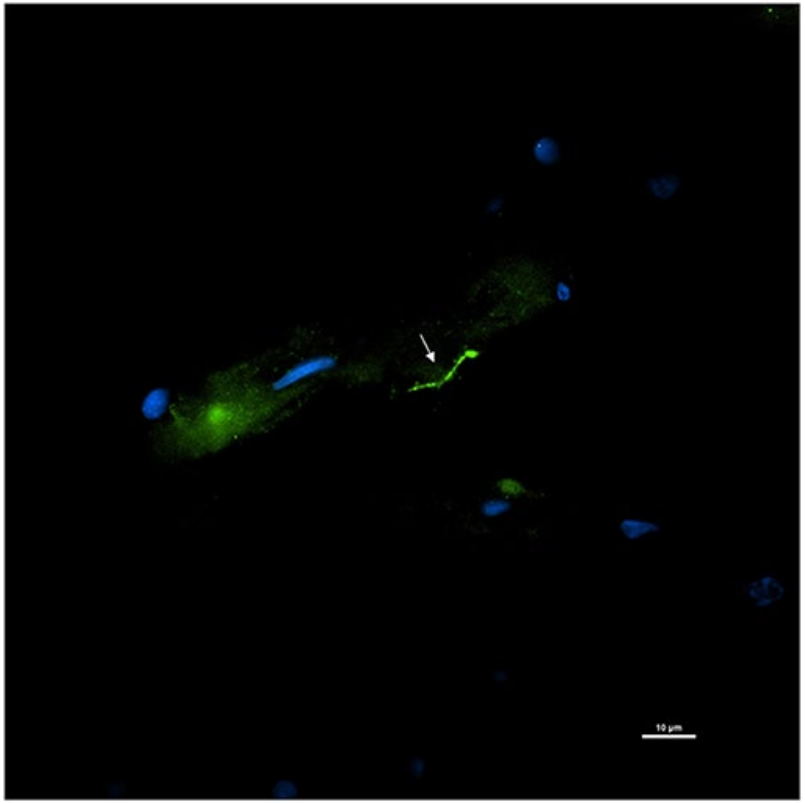


Visual Retention Total

-1.36, CI[-2.38,-.33], p=.012, R^2=0.145, N=18

Rarely, Borrelia may persist in CNS despite treatment – quiescent or disease inducing?

Borrelia burgdorferi found in amygdala & spinal cord



54 yo woman with EM rash with + IgM WB and +IgG Ab WB treated with doxycycline.

2 yrs later – sleep behavior disorder.
4 yrs later – cognitive and anxiety problems

Partial non-sustained response to IV ceftriaxone…further decline

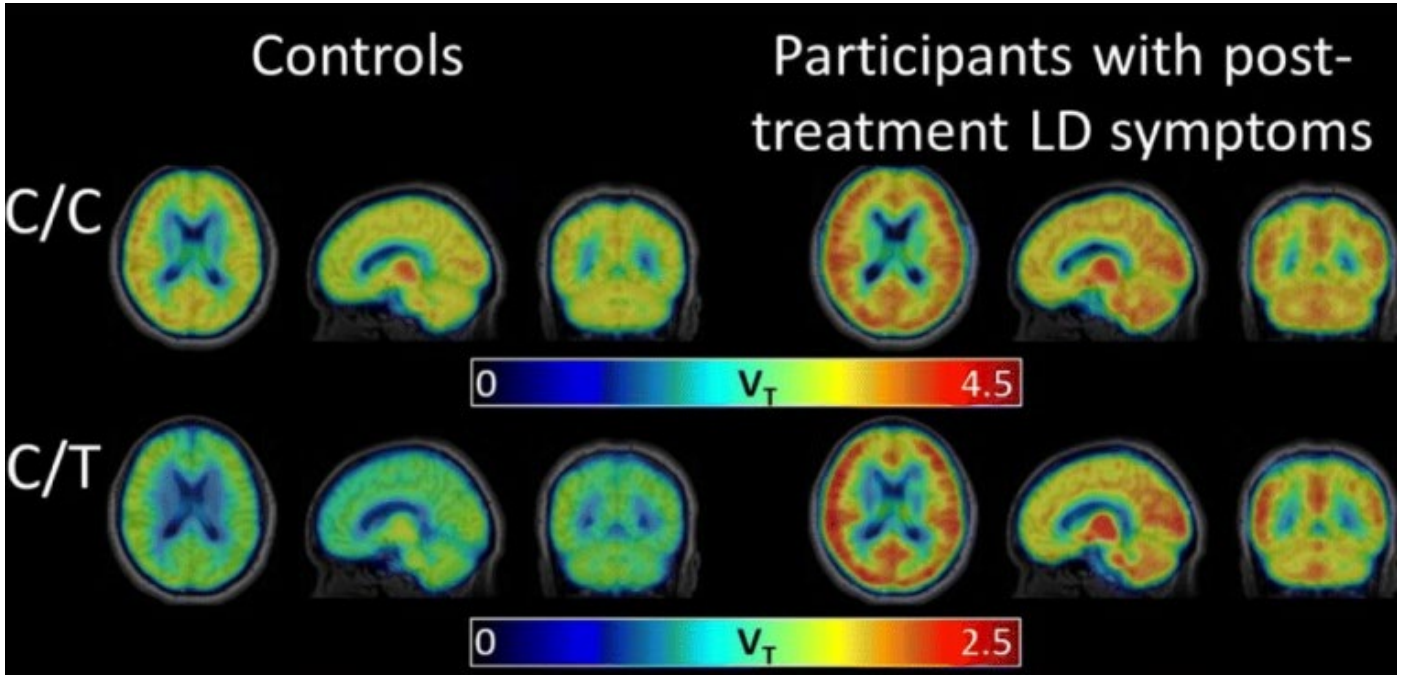
DX: Neurodegenerative dementia

Died age 69

Embers et al, Frontiers in Neurology, 2021

Microglia are activated in post-treatment Lyme disease symptoms/syndrome: A pilot PET study with [11C]DPA-713

Higher TSPO Binding (glial activation) was found in 12 participants with post-treatment Lyme disease compared to 19 healthy control participants



J Coughlin et al, J Neuroinflammation 2018

Summary of Neurologic Evidence in PTLD -

- PET imaging: ↓ cerebral blood flow
  ↓ brain metabolism (Gray & White matter)
- TSPO PET: ↑ microglia activation
- MRI: no difference in white matter hyperintensities
  Functional differences in central neural activation (Marvel 2022)
- CSF Proteome has unique proteins
- Borrelia can persist, including rarely in CNS
- Serum Antineuronal Ab ↑
- Serum Interferon α ↑ (Strle 2023; Jacek 2013)
- Cognitive function ↓

Acknowledgments

NASEM

Research Participants

NINDS

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- Lyme Disease Association
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Research Collaborators

Our Lyme Center Research Team