Lyme Aware Delaware
CONFERENCE

Neuropsychiatric Lyme Disease: Manifestations & Treatment

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Outline of Talk

- Diagnosis & Clinical Cases
- Mechanisms of Disease
- Neuropsychiatric Manifestations & Treatment
  - Nationwide Study of Mental Disorders & Suicide after diagnosis of Lyme disease
  - Suggestions for Health Professionals
- Clinical Trials Network for Lyme & other Tick-borne Diseases

Neurologic Manifestations

- 10-15% of untreated patients → neurologic signs
- Early: Meningitis, Cranial Neuritis (e.g.,CNVII), Radiculoneuritis
- Later (months to years) (Logigian et al NEJM 1990):
  - Chronic polyneuropathy (often patchy multi-focal)
    - Paresthesias, radicular pain
  - Encephalopathy
- Less common:
  - Cerebellar ataxia
  - Myelitis – weakness, dysautonomia, sensory loss
  - Encephalomyelitis (White matter changes/MS-like)
  - Children: Pseudotumor cerebri-like
  - Vasculitic changes (seizures or stroke)

Case series: Depression & irritability are common in chronic neurologic Lyme

"Chronic Neurologic Manifestations of Lyme Disease".

Months to years after the initial infection with *B. burgdorferi*, patients with Lyme disease may have chronic encephalopathy, polyneuropathy, or less commonly, leukoencephalitis.

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- Encephalopathy 89%
  - Memory loss 81%
  - Difficulty finding words 19%
- Fatigue 74%
- Headache 48%
- Spinal or radicular pain 41%
- **Depression 37%**
- Sleep disturbances 30%
- Extreme irritability 26%

Logigian EL, Kaplan RF, Steere AC. NEJM 1990

Neurologic Lyme Disease

- Bb reaches the CNS quickly (2 weeks) (Allal 1986) & 50% may not show CNS symptoms (Luft 1992)
- Impact depends on Bb strain neurotropism, spirochetal load, host immune response
- CNS infection (as a relatively sequestered body organ) has treatment implications
- CSF culture and PCR studies have limited value (ie, insensitive or hard to obtain)

Case 1: Dr. A

- 35 year old physician & gardener
- Initial: fatigue, irritability, myalgias, cognitive problems after a tick bite. No rash. Did not meet CDC criteria for Lyme but tested +. Treated with Doxy – 90% better
- 2 relapses: joint pains, stabbing pains, light and sound sensitivity, depression. Her primary doc denied further treatment so she sought colleagues to help.
- She asks: "What is going on? Are the patients right??"

Case 1 Comments
This is not an unusual case

- >20% of patients with LD do not see a rash
- Cognitive problems occur – “brain fog”
  - Slow processing speed, word finding & short-term memory problems
- Other Symptoms are common:
  - Light & sound sensitivity, paresthesias, neuropathic pain, irritability, depression
- What would have happened if she hadn’t had the connections to be retreated?

Case 1 Comments

- Benefit of antibiotic re-treatment.
  - Retreatment of relapsing symptoms is not recommended by the Lyme Disease treatment Guidelines (except for arthritis) (2020)
  - However, ~40% of clinicians in the U.S. do give additional courses of antibiotics (CDC, 2019)
- This case raises question of whether infection can persist after antibiotic therapy
  - Animal model studies demonstrate persistence.

Neuropsychiatric Manifestations can occur

Case 2:
The Bicycle Boy

Pachner A.
Annals of NY Academy of Sciences, 1988

Case 2: Restrictive Eating/OCD
"Borrelia burgdorferi in the Nervous System: The New Great Imitator"

Pachner A. Annals of NY Academy of Sciences, 1988

2. Behavioral Changes

Between 1982 and 1984, a 12-year-old boy had four attacks of swelling of the right knee; the diagnosis of Lyme arthritis was confirmed serologically. After the last attack, he was treated with doxycycline, 100 mg twice a day for 30 days. Two months later, the patient became withdrawn and depressed. He no longer interacted with his friends, spent most of this time alone, and would no longer do his school work. He ate very little and began to exercise compulsively. His weight dropped 14 kg. On admission to a psychiatric hospital, he was grossly depressed and uncommunicative. He was diagnosed as having anorexia nervosa.

Because of the history of Lyme disease, he was transferred to Yale-New Haven Hospital. Serum and CSF antibody titers to *B. burgdorferi* were elevated, but neurologic evaluation was normal. He was treated with intravenous penicillin, 20 million U a day for 14 days, and within several weeks he began to eat more, gain weight, and communicate. During the following several months, his behavior returned to normal, he went back to school, and has remained asymptomatic for the past 2 years.

Comments on Case 2

- Depression and compulsive behaviors emerged 2 years after first bout of Lyme arthritis.
- Lyme disease as a cause of compulsive behaviors & anorexia is rare. The spinal fluid confirmed the CNS infection.
- There were no typical signs of Lyme disease (except for prior arthritis). How many cases of neuropsychiatric Lyme disease are we missing?

Was this a case of PANDAS?

"Pediatric Autoimmune Disorder Associated with Strep"

1. Presence of OCD &/or Tic Disorder
2. Prepubertal Onset
3. Acute onset and episodic course
   - Relapsing/remitting (not waxing/waning)
4. Association with neurologic abnormalities
   - Choreiform ("piano playing") movements
5. Temporal relationship between symptom worsening and GABHS infections

Diagnostic Evaluation

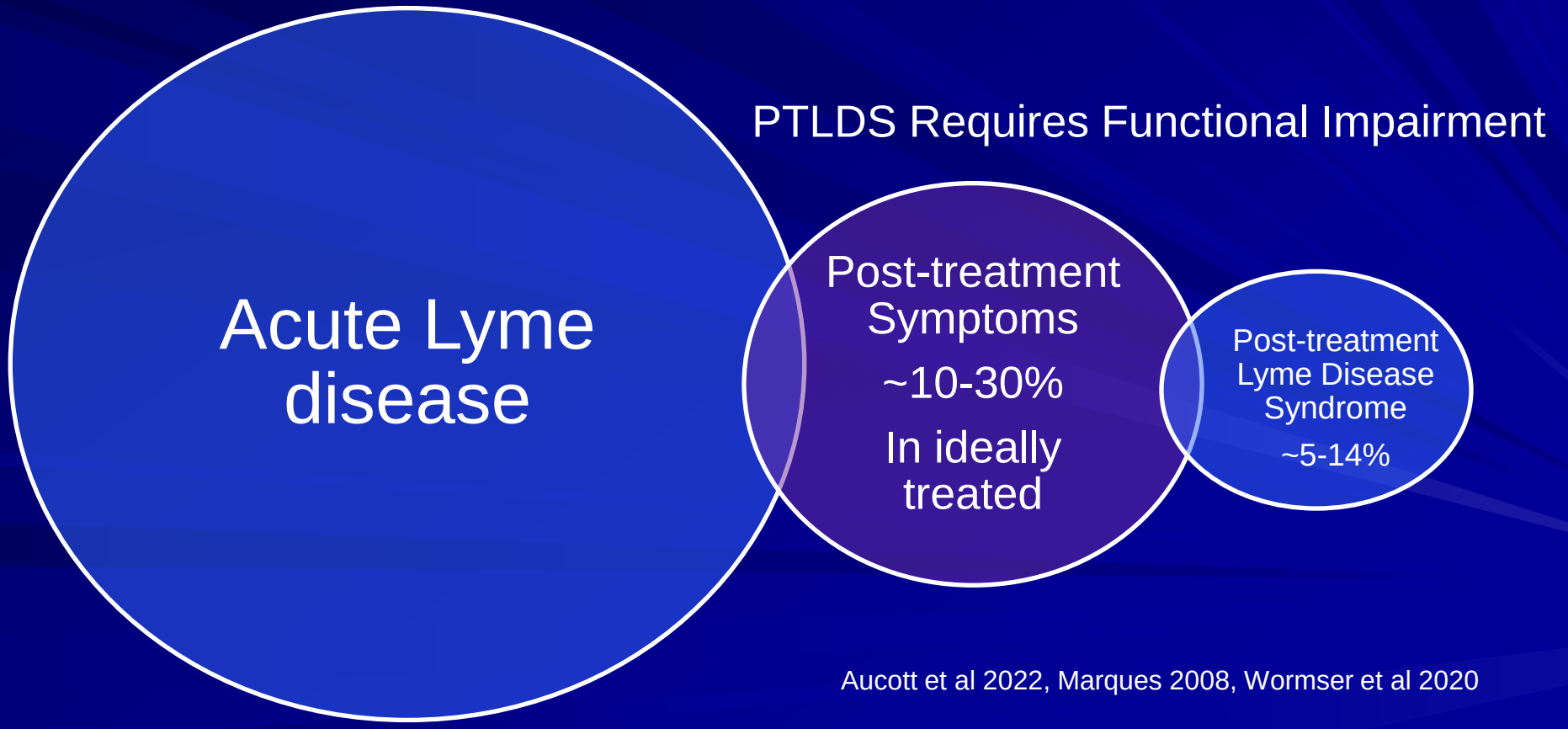
- Blood Tests
- Neurologic:
  - Spinal Fluid (send serum & CSF for Bb intrathecal index)
  - Assessing Nerve Function
    - EMG/Nerve Conduction studies for large nerves
    - Skin punch biopsy to assess small nerve fibers
  - Neuroimaging
    - MRI
    - PET/SPECT
- Cognitive testing

Other Blood testing

- Other Neurotropic Tick-related pathogens
  - Borrelia miyamotoi
    - Emerging pathogen
  - Bartonella henselae (mainly flea borne)
    - Associated with neuropsychiatric disorders
  - Powassan Virus
    - Rare but can be deadly

Post-treatment symptoms

- Symptoms that persist for >6 months after treatment are not uncommon. Risk of chronic symptoms increase with delayed treatment



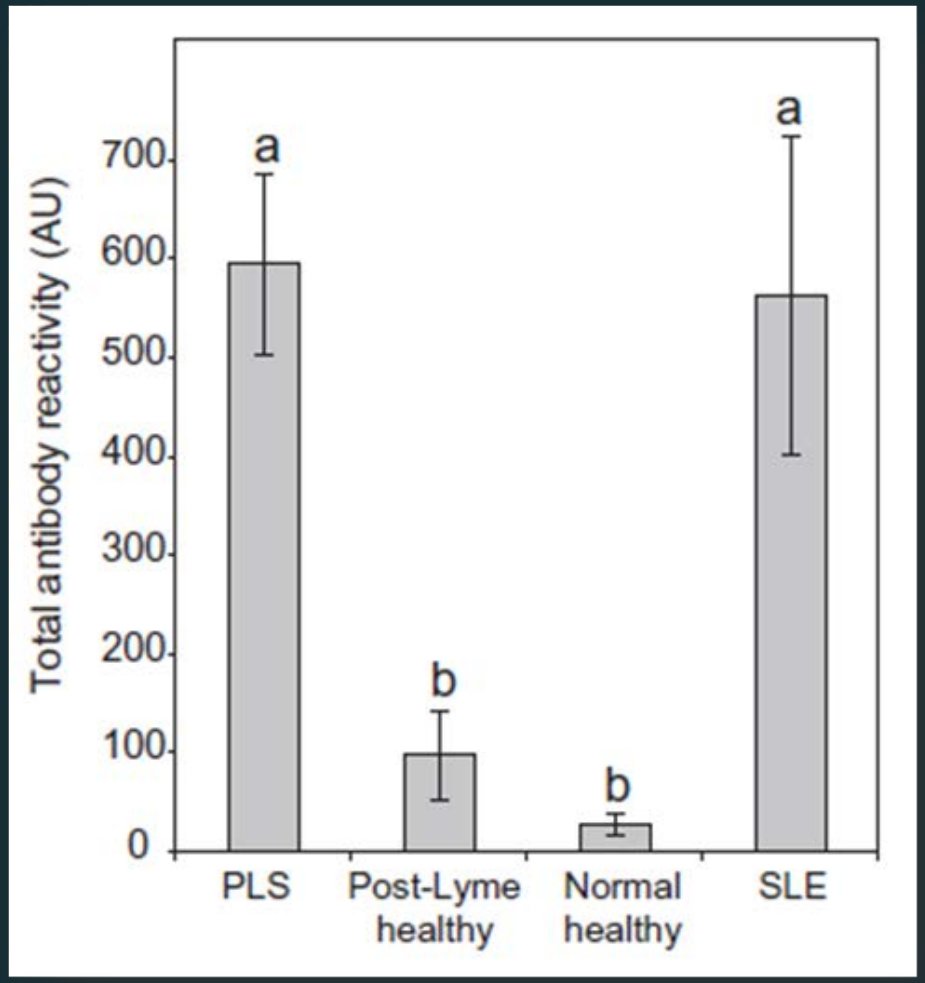
Aucott et al 2022, Marques 2008, Wormser et al 2020

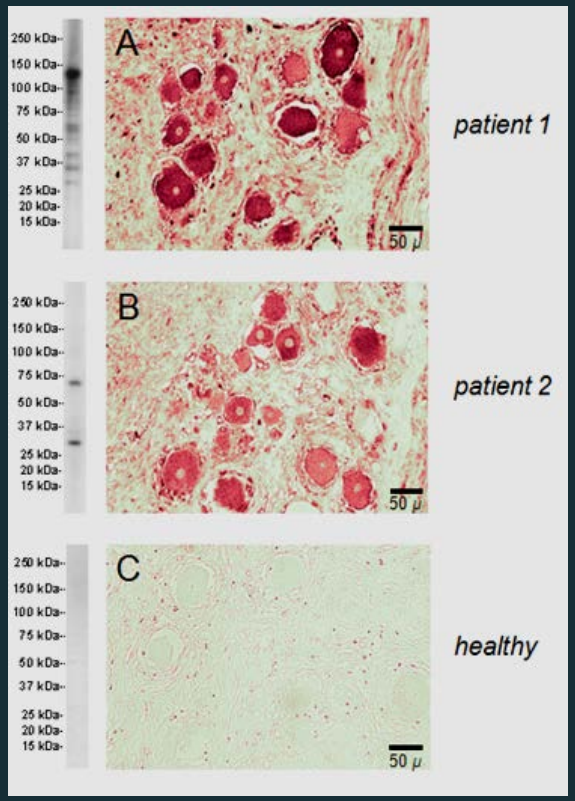
Post Treatment Lyme Disease Syndrome has biological correlates

Immune biomarkers of PTLDS:

- Autoimmunity/Molecular mimicry:
  - anti-neuronal Ab – comparable to Systemic Lupus
  - Endothelial cell growth factor antibody
- Inflammation:
  - IL6 & expression of IF alpha
  - Chemokine CCL 19
  - CSF Complement cascade proteins

Persistent symptoms are associated with increased antibodies against neural proteins

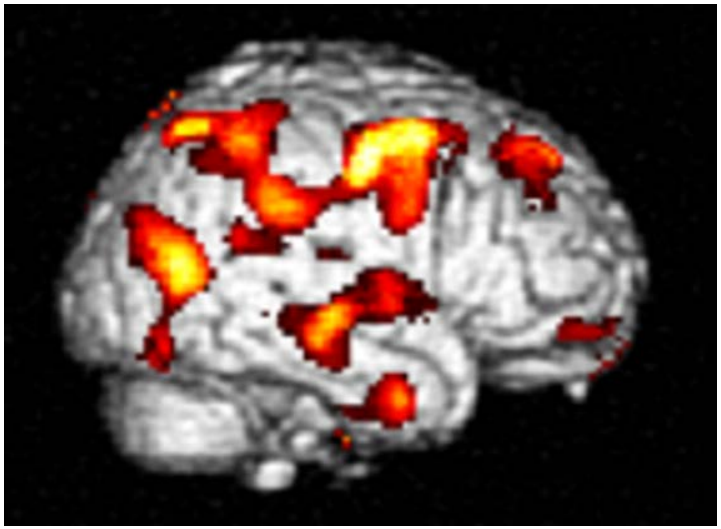




Chandra et al, 2010

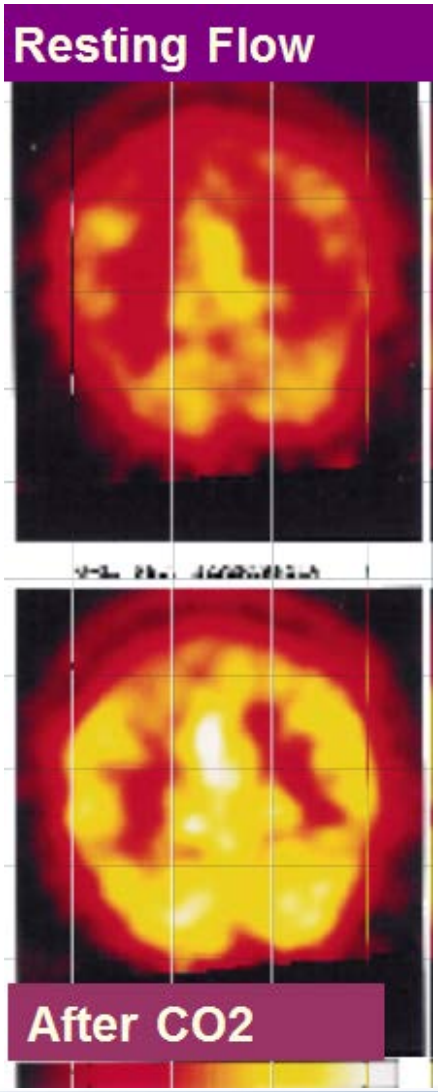
Brain metabolism and blood flow are decreased in Post-treatment Lyme Encephalopathy

(Fallon et al, JAMA Psychiatry 2009)



Metabolism: FDG PET (37 pts vs 18 matched controls)

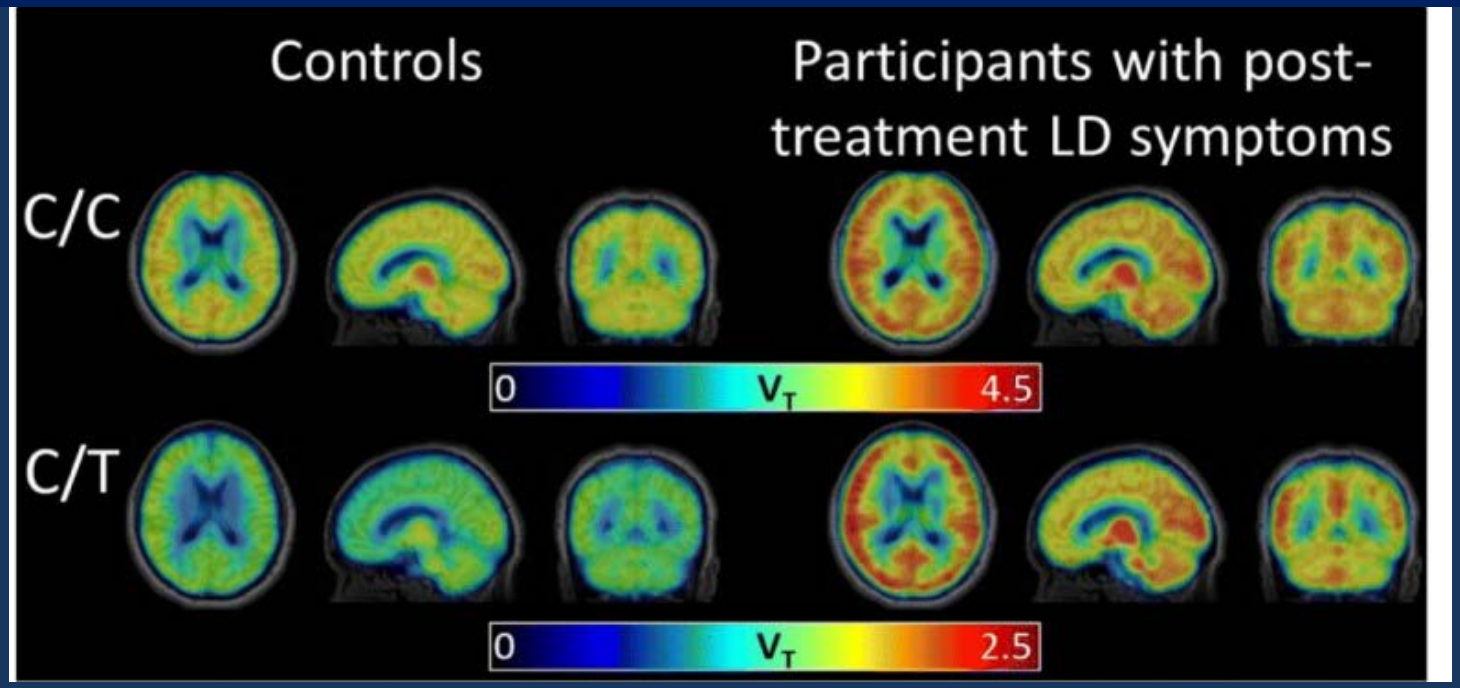
O-15 PET before and after a CO2 challenge



The LYME group showed decreased regional metabolism & a diminished ability to enhance blood flow compared to controls. (**8.2% for patients vs 28.1% for controls**, p<.02)

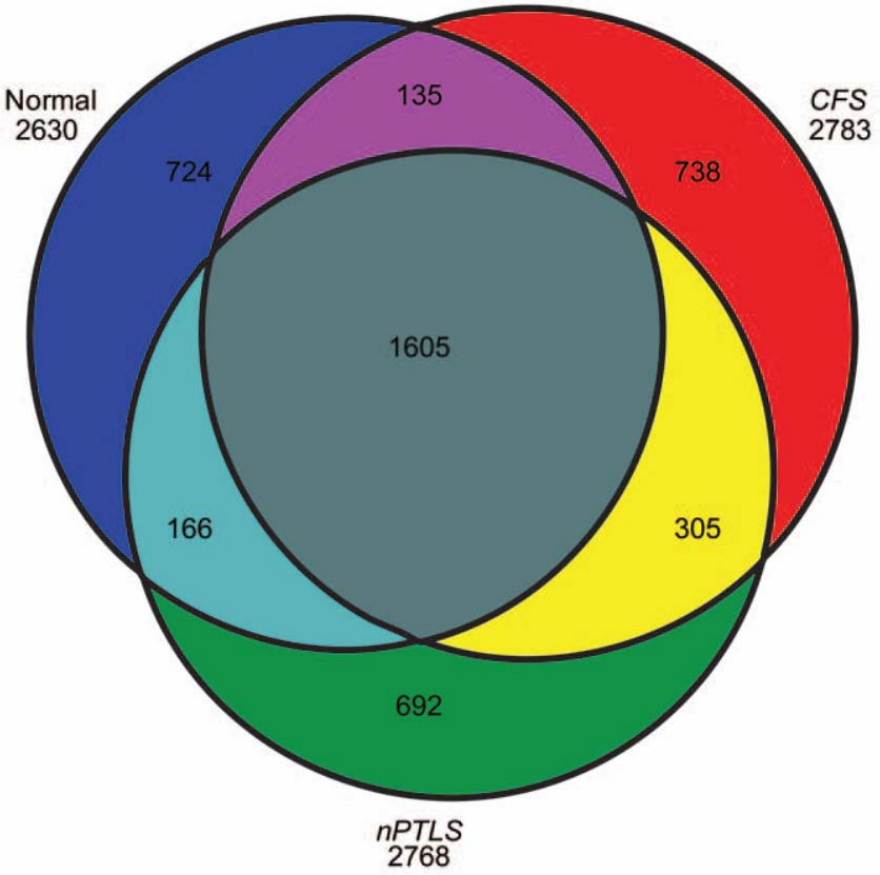
Microglia are activated in post-treatment Lyme disease symptoms/syndrome: A pilot PET study with [^{11}C]DPA-713

J Coughlin et al, J Neuroinflammation 2018



Higher TSPO Binding (glial activation) was found in 12 participants with post-treatment Lyme disease symptoms (< 6 months) or syndrome, compared to 19 healthy control participants, accounting for TSPO genotype (C/C vs. C/T)

Post-treatment Lyme disease (encephalopathy) is associated with a distinct Cerebrospinal Fluid protein profile (692 unique proteins)

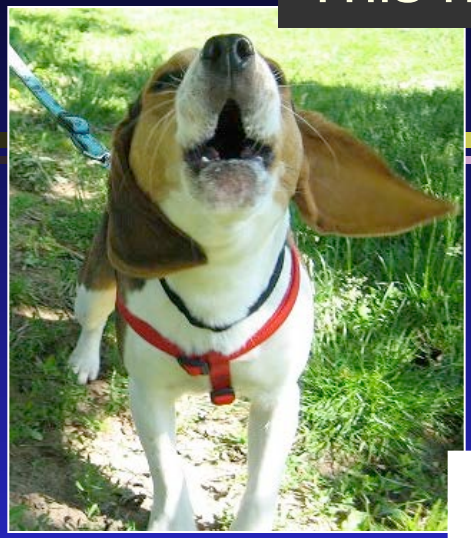


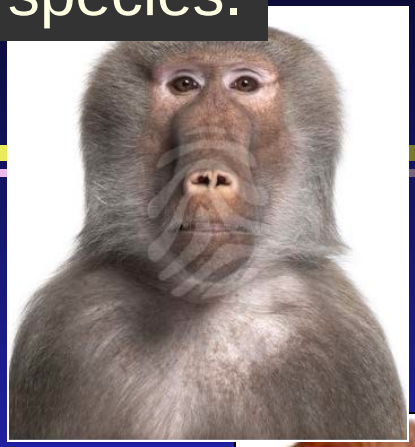
- This proteomic CSF profile differentiated post-treatment Lyme disease from ME/CFS
- Greater overlap in proteins between Lyme and ME/CFS than between either and controls
- Both disorders were associated with an increase in complement cascade proteins

(Schutzer et al 2010)

Do Spirochetes persist despite antibiotic treatment?

Borrelia persist despite antibiotics.
This has been shown in many species.









Often with minimal or No Disease

Slide courtesy of Stephen Barthold, UC Davis

NEUROPSYCHIATRY

Key Message

Most mental disorders have nothing to do with Lyme disease.

But some do…..

Why neuropsychiatric symptoms?

Acute or persistent Borrelia or Bb remnants can trigger

- Inflammation – systemic &/or central
- Autoimmune - Molecular Mimicry
- Altered neurocircuitry (e.g., central sensitization)

What might amplify biologic mechanisms?

- Prior trauma
- Current stressors (pain, economic, interpersonal)
- Uncertainty about diagnostic tests & treatment options

Cognitive Deficits in Post-treatment Lyme Disease

Up to 90 percent of people who meet criteria for PTLDS complain of cognitive difficulties (Aucott et al., 2013; Touradji et al., 2018).

A smaller percent (7-30%) of PTLDS have **objective measurable problems.** These impact short-term memory, verbal fluency, and processing speed (”brain fog”) (Kaplan et al 1992; Keilp et al 2006; Touradji et al 2018)

Unknown: Optimal treatment for persistent cognitive deficits

Lyme Encephalitis - though rare - can present with severe psychiatric disorders

A 55-year old woman presents with new onset manic psychosis (Pasareanu, Mygland, Kristensen, J Norwegian Medical Assoc 2012)

Note: **Mania was the initial symptom** followed several days later by radicular pain and weakness. **CSF Ab index wasn't positive until 8 wks after onset.** Mania, radicular pain, weakness resolved with Abx.

A 42 year old woman presents with new onset schizophrenia-like disorder (Hess et al, Biol. Psychiatry 1999)

Note: Cognitive problems and irritability followed by paranoia and hallucinations for 8 months – finally after a LP, NB was diagnosed.

No systemic physical signs or symptoms suggestive of LB were present. Full recovery after Antibiotic therapy.

Note: **~15% of the time, CSF intrathecal antibody studies may be positive for neurologic Lyme disease but blood tests are negative** (Knudtzen Clinical Infectious Disease 2017)

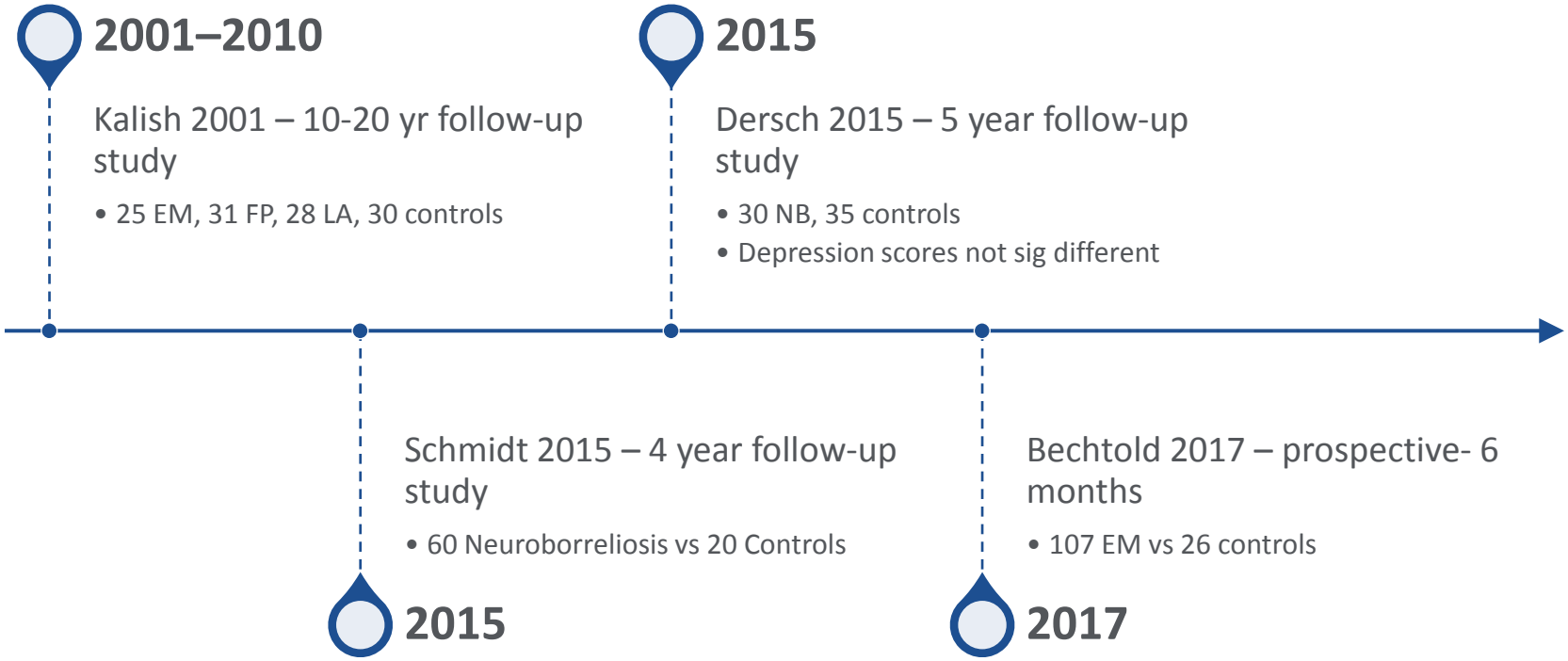
Suicidal Ideation is common in patients with persistent symptoms related to Lyme disease

- 81 adults with well-documented treated LD & persistent cognitive symptoms evaluated at our Lyme Center at Columbia
- 1 in 5 reported suicidal thoughts (20%).
- Of the post-treatment Lyme patients with > mild depression, 63% had suicidal ideation

This sample is biased against suicidal ideation, as they were not hopeless – coming to a Research Center to obtain treatment. This frequency is comparable to research patients with HIV at our site.

Doshi et al., Psychosomatics, 2018

Other studies have not found an increased risk of depression



Limitations in Some of the Studies

- Small sample size
- Unclear diagnostic criteria (e.g., Chronic Lyme)
- Ascertainment bias
  - Patients from psychiatric practices or research clinics
- Lack of an appropriate control group
- How do we resolve these issues?

To address these limitations:

A Nationwide Cohort Study in Denmark of the entire population over a 22-year period

Is Lyme Borreliosis (all manifestations) associated with a higher rate of mental disorders, affective disorders, suicide attempts, & suicide?

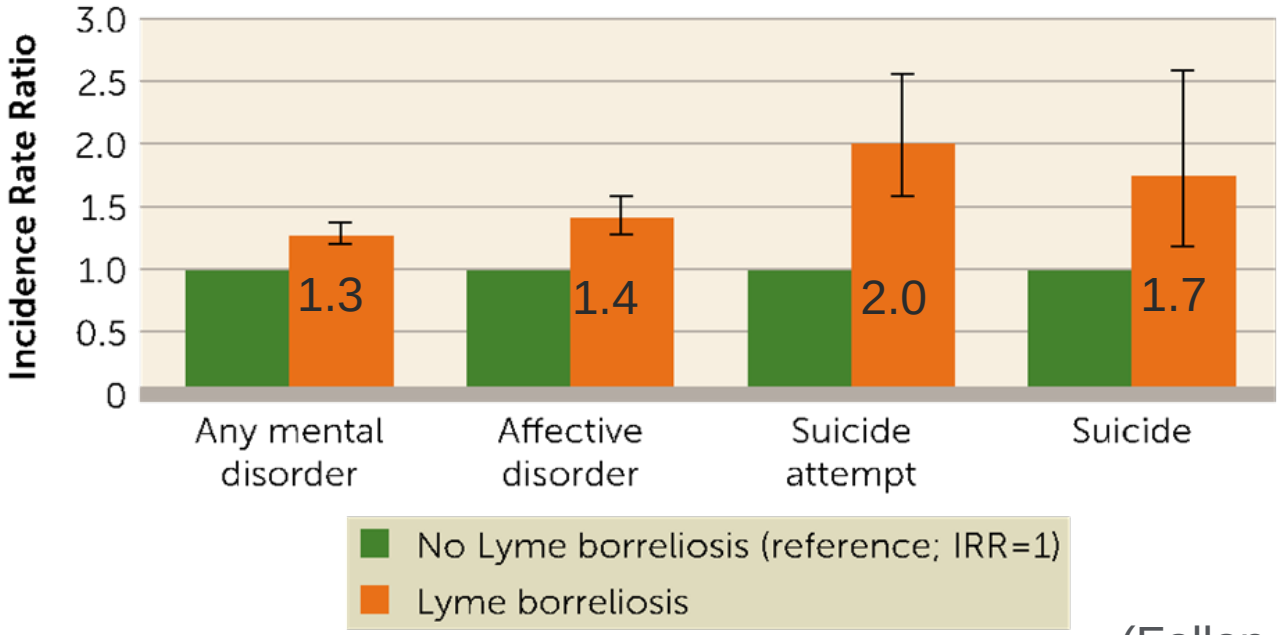
# of Persons in Study: **6,945,837**

with Lyme Disease (no prior mental disorder diagnosis): **n=12,616**

Fallon et al, Amer J Psychiatry 2021

Is a hospital-based diagnosis of Lyme disease associated with a subsequently increased risk of mental disorders? YES

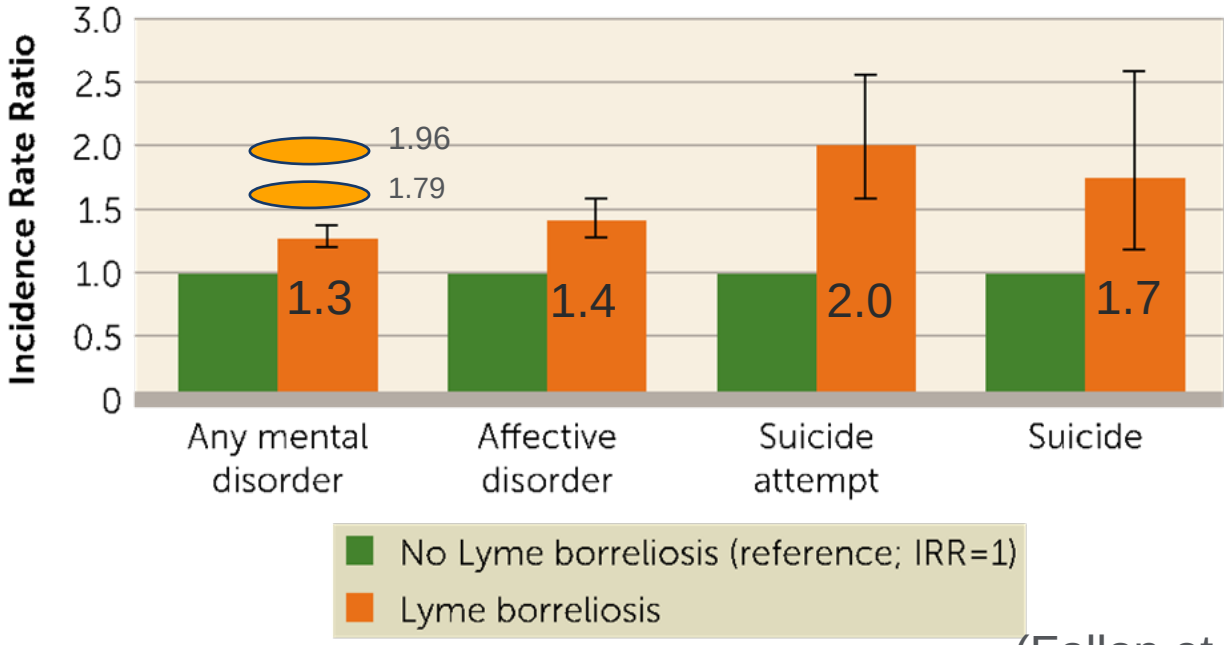
FIGURE 1. Incidence rate ratios for any mental disorder, affective disorder, suicide attempt, and suicide among individuals with Lyme borreliosis compared with individuals with no Lyme borreliosis in Denmark (1994–2016)[a]



(Fallon et al, AJP, 2021)

There was a temporal and dose relationship. The rate of mental disorders was 96% higher in the 6 months after Lyme diagnosis and 79% higher if there was more than one episode of LD.

FIGURE 1. Incidence rate ratios for any mental disorder, affective disorder, suicide attempt, and suicide among individuals with Lyme borreliosis compared with individuals with no Lyme borreliosis in Denmark (1994–2016)[a]



(Fallon et al, AJP, 2021)

Are these results surprising? No

Prior nationwide studies demonstrate that serious infections are associated with increased rate of mental disorders & suicide (Lund-Sorenson 2016; Kohler-Forsberg 2019)

Many infections have been associated with neuropsychiatric disorders (HIV, EBV, SARS COV2, Strep, Toxo, Treponema pallidum)

Peripheral inflammation is known to lead to depression.

What should trigger consideration of Lyme disease in a patient with mental health (MH) issues?

- Poor response to standard MH treatments
- Concomitant multisystem symptoms
  - Neuropathies, Joint pain, migrating arthralgias
  - Marked fatigue
  - Cognitive problems (eg: word finding, short-term memory, slowed processing speed)
- History of MH disorder onset after viral-like illness &/or after exposure to a Lyme endemic area (ticks)
- Highly suggestive or positive Lyme serologic tests

Clinical Recommendations

- Monitor patients for mental health sequelae from Lyme disease, especially during the 1st year or among those with chronic symptoms
- Incorporate mental health screening tools in your practice
  - PHQ-9 for depression
  - Columbia Suicide Severity Rating Scale (C-SSRS)
- Inform patients with suicidal thoughts about the Suicide Prevention Lifeline Phone#: 988
- Includes tests for Lyme disease (ELISA, Immunoblot) in the medical work-up of patients with mental illness not responding to standard therapies. Consider tests for other neurotropic infections, including Bartonella henselae and Borrelia miyamotoi. A spinal tap may also be valuable.

Key Message: Both Under-diagnosis & Over-diagnosis can be problematic

Underdiagnosis. If a psychiatric disorder is present but a LB infection is not treated, then mental health interventions will be less effective or ineffective.

Overdiagnosis. If tick-borne diagnosis is incorrectly applied as the primary cause of a psychiatric disorder, then the patient's psychiatric disorder may be overlooked or not addressed.

Both Overdiagnosis and Underdiagnosis can lead to increasing anxiety, hopelessness, and treatment delays.

In most cases of Lyme with neuropsychiatric symptoms, concurrent mental health treatment can enhance recovery.

Columbia Suicide Severity Rating Scale

(Free APP: "Columbia Protocol")

Questions for primary care screening

In the last month,

1. **Have you wished you were dead?**
2. **Have you had thoughts of killing yourself?**
3. **Have you been thinking about how you might do this?**
4. **Have you had intention to act on these thoughts?**
5. **Have you worked out the details of a suicide plan?**
6. **Have you started to act on your plan? (ie, behaviors)**

Potential causes of Post-treatment Lyme Symptoms

Borrelia Persistence

Immune dysregulation

- Ongoing activation/inflammation (e.g., peptidoglycan-triggered)
- Autoimmune mechanisms

Dysfunctional Neurologic Signaling:

- Dysautonomia
- Altered Brain metabolism/blood flow/microglial activation
- Altered neural circuits/neurotransmitters

Altered GI microbiome

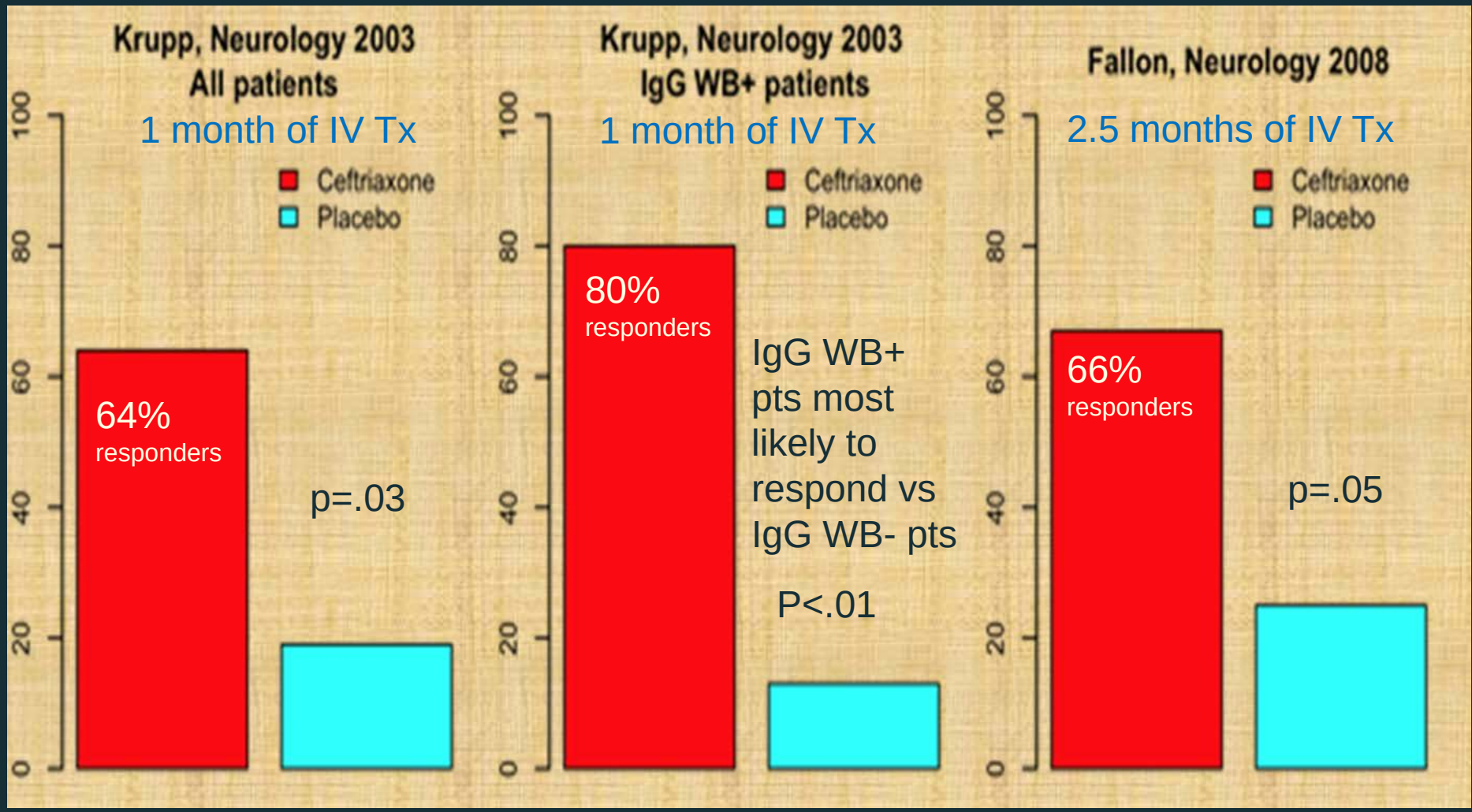
Coinfections

Therapeutic Approaches

- Targeting persistent Infection
  - Repeated antibiotic therapy
- Targeting immune activation
  - Consideration of IV Ig? (e.g, autoimmune neuropathies)
- Targeting altered neurotransmitter systems
  - Glutamate, GABA, Serotonin, Norepinephrine
- Stress reduction and Psychotherapy
  - Meditation/Yoga, Coping Skills Training, CBT
- Physical Reconditioning
- Neurofeedback

Two Small studies with similar findings:

IV Ceftriaxone significantly reduced fatigue in two RCTs of Previously treated Lyme patients



Kundalini Yoga Group Therapy for Persistent Pain &/or Fatigue after antibiotic treatment for Lyme disease

Murray et al,
Healthcare 2022

Random assignment to 8 weeks of KY or a wait-list. N=29.

Results: Symptom severity and cognitive complaints decreased, but pain and fatigue did not improve enough to be significant.

Pharmacologic Approaches

- Fatigue:
  - Bupropion
  - Modafinil
- Central Pain/Neuropathies:
  - Tricyclics
  - SNRIs
  - Pregabalin or Gabapentin
  - ?Low dose naltrexone
  - ?Cannabinoids
- Light/Sound Sensitivity:
  - Gabapentin
  - Clonazepam
- Mood dysregulation:
  - Lamotrigine
  - Atypical Neuroleptics
- Depression/Anxiety
  - SSRI/SNRI/Bupropion
- Attention
  - Bupropion/Stimulants

How do we convey to patients that mental health care can be beneficial?

- Anxiety/depression may have been triggered by the Lyme infection, but require brain-modulating treatments for return to normal function

- Many psychiatric medications are helpful in treating arthritic and neuropathic pain (often used by rheumatologists & neurologists). The mood and pain circuits overlap.

The bad news is...you have Lyme disease. The good news is, I don't believe in that disease so you're fine!

INVALIDATION CAN BE TRAUMATIC

The bad news is...you have Lyme disease. The good news is, I don't believe in that disease so you're fine!

CLINICAL TRIALS NETWORK

For Lyme and other Tick-borne diseases

www.lymectn.org

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Clinical Trials Network Coordinating Center

Main Functions:

- **Build a national network of research nodes to collaborate on clinical trials**
  - **Current nodes: Columbia, Johns Hopkins, Childrens National Hospital**
  - **Future nodes?**

- **Support High Quality Research using the Clinical Trials Expertise at Columbia (Research Design, Biostatistics, Network management & coordination)**
  - Provide funds to support nodes and pilot studies to assess safety and impact
  - Goal is to conduct multi-site clinical trials to test leading hypotheses
  - Assist investigators in pilot study design, data analysis, manuscript publication, grant preparation

A Map of the CTN nodes (2021-2023)

Mount Sinai

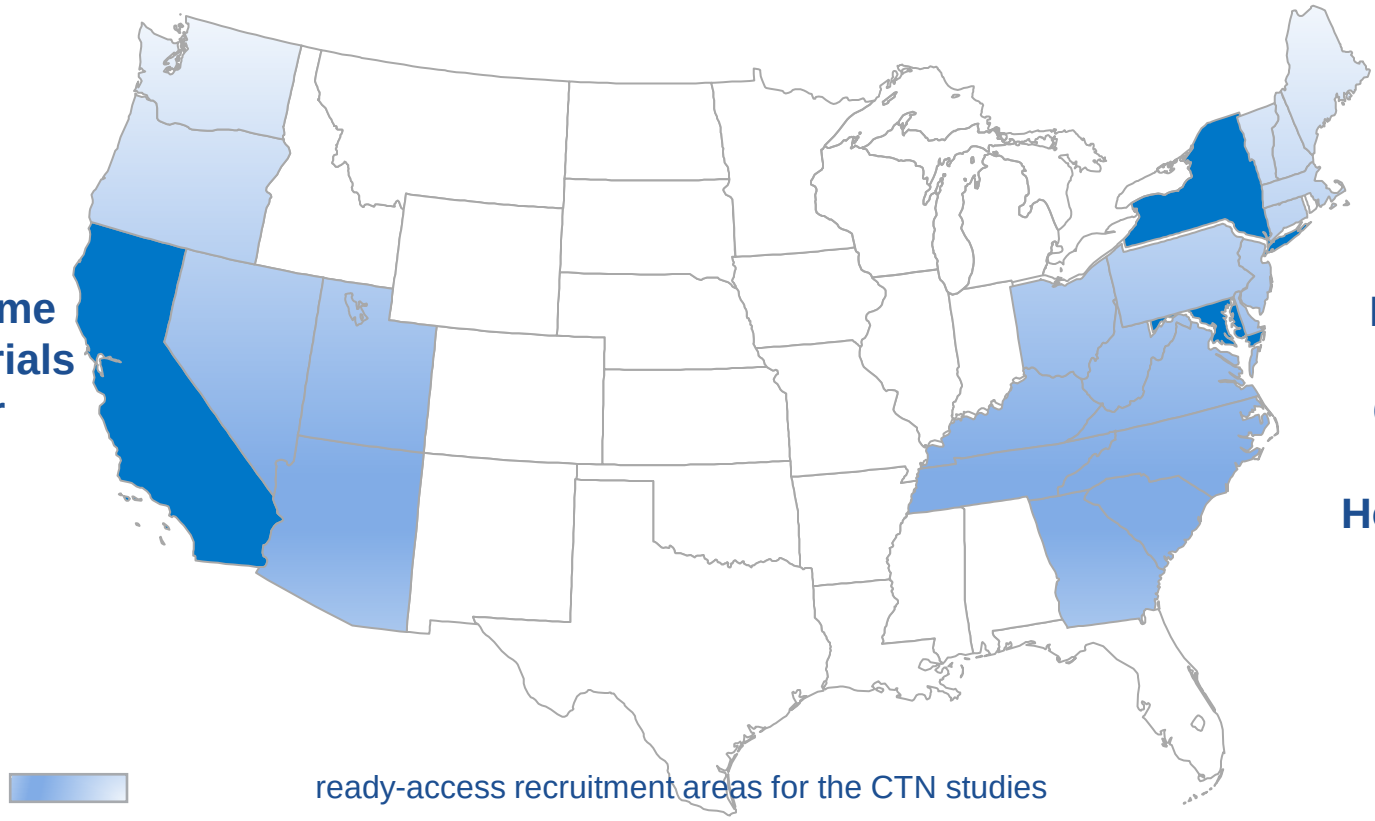
Columbia University

SUNY Upstate

Johns Hopkins (MD)

Children's National Hospital (DC)

UCSF Lyme Clinical Trials Center



ready-access recruitment areas for the CTN studies

Mechanisms of Disease in CTN Pilot studies

Persistent Infection and inflammation

Tetracycline (PI: Aucott; Hopkins)

Pulse IV Ceftriaxone (PI: Paolino, SUNY Upstate Medical)

Dysautonomia, Inflammation, and CNS Network dysregulation

Transauricular Vagus nerve stimulation (PI: Fallon & Kuvaldina, Columbia)

CNS Neural Network dysfunction

Transcranial direct current brain stimulation & Cognitive retraining

(PI: Gorlyn, NYSPI; Co-PIs- Chiu, Chow, UCSF)

Immune Dysregulation related to Post-tick bite Illness

Mast Cell modulation (PI: Commins, UNC)

Microclots & platelet hyperactivation

Proteolytic Enzyme (PI: Putrino, Mount Sinai, NYC)

Prenatal Bb infection and neurodevelopmental outcomes

Pregnancy observational study (PI: Mulkey, Children's National, DC)

CTN Measure of Symptom Burden – Global Symptom Questionnaire – 30 items

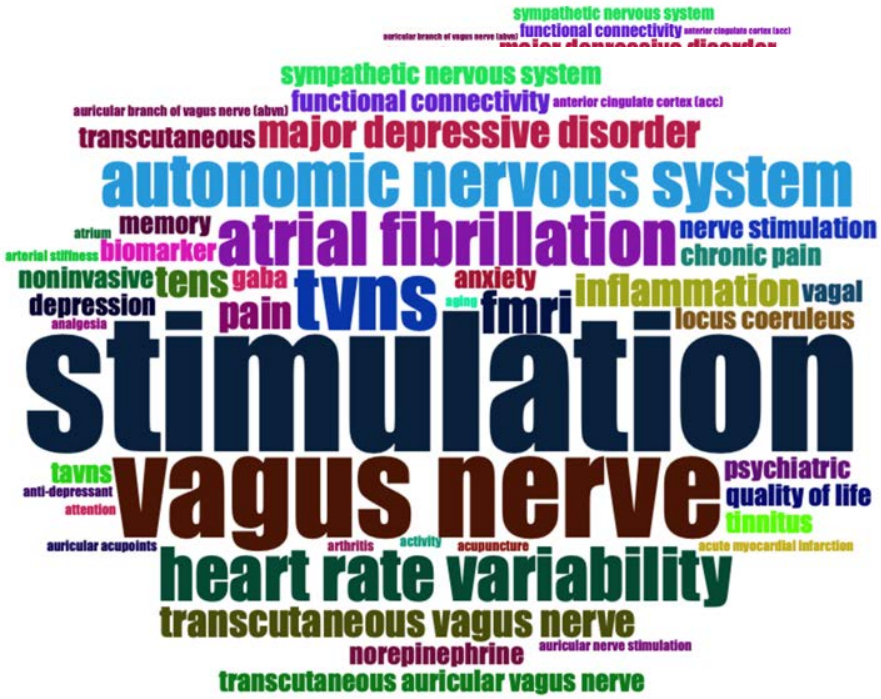
(Fallon et al, Frontiers in Medicine 2019) (in collaboration with Drs. Aucott and Zubcevik)

Validated infection-associated multisystem burden questionnaire – sensitive to detecting change over time – symptom burden is associated with functional impairment.

SYMPTOMS. During the past 2 weeks, how much have you been **bothered** by any of the following?

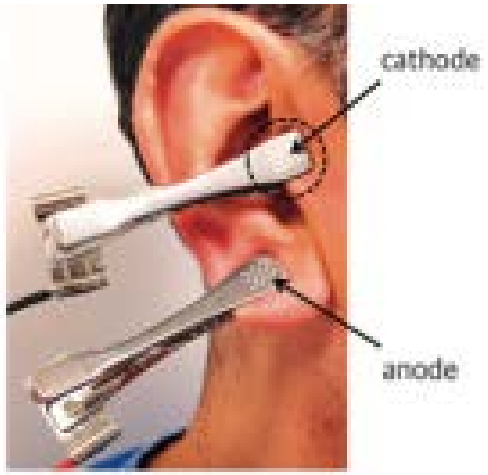
Rate "bother" for the past 2 weeks	Not at all	A little bit	Somewhat	Quite a bit	Very much
1. Shortness of breath	0	1	2	3	4
2. Feeling feverish	0	1	2	3	4
3. Sweats and/or chills	0	1	2	3	4
4. Nausea and/or vomiting	0	1	2	3	4
5. Back pain	0	1	2	3	4
6. Headaches	0	1	2	3	4
7. Stiff or painful neck	0	1	2	3	4
8. Muscle aches or pains	0	1	2	3	4
9. Joint pain or swelling	0	1	2	3	4
10. Muscle weakness	0	1	2	3	4
11. Feeling fatigued or having low energy	0	1	2	3	4
12. Feeling worse after normal physical exertion	0	1	2	3	4
13. Trouble falling or staying asleep	0	1	2	3	4
14. Needing more sleep than usual	0	1	2	3	4
15. Not feeling rested on awakening	0	1	2	3	4
16. Numbness or tingling	0	1	2	3	4
17. Shooting, stabbing or burning pains	0	1	2	3	4

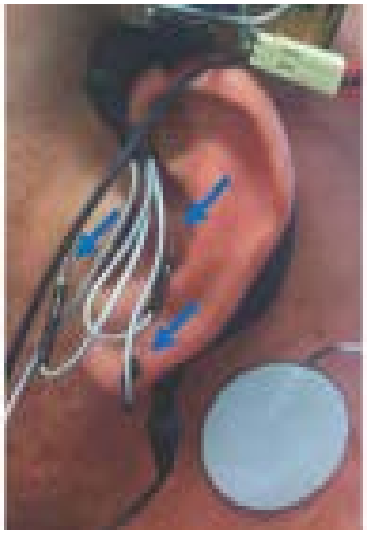
Why the Vagus Nerve?



- Innervates multiple organ systems
- Modulates Inflammation & neural activation
- Over 300 VNS studies underway: neurologic, psychiatric, rheumatologic GI, cardiac, peri-infectious, pain

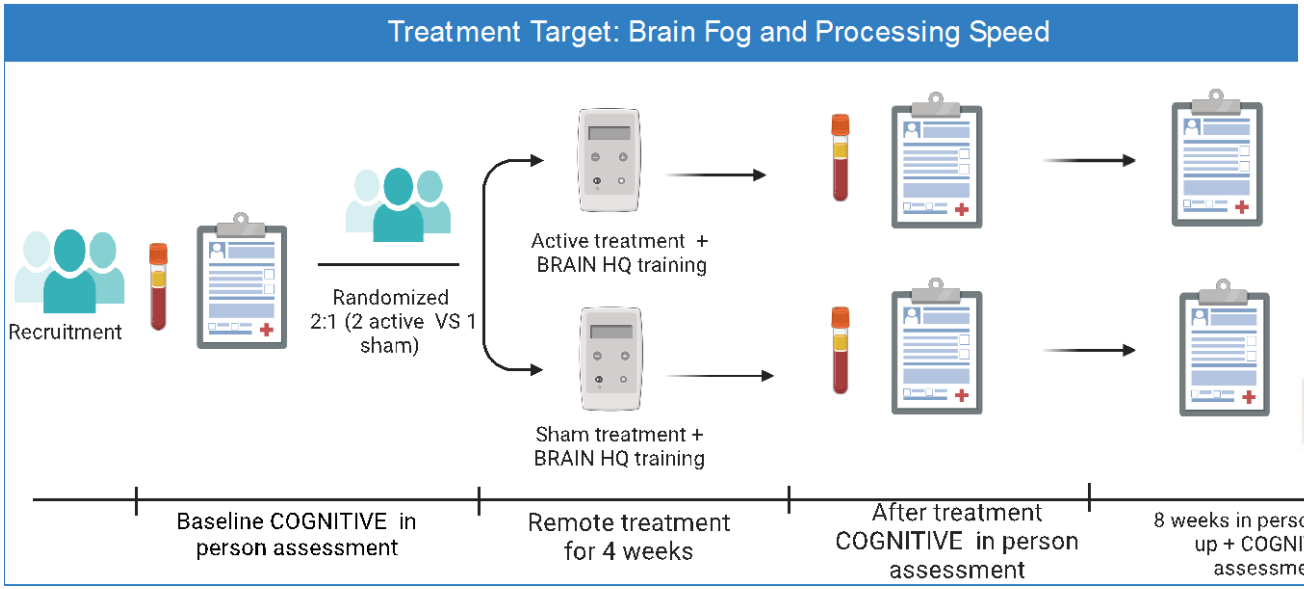
The electrode montage for transauricular VNS





CTN Pilot Neuromodulation: transcranial direct current stimulation with cognitive retraining for Lyme Brain Fog

Multi-site study: Columbia (PIs: Gorlyn, Fallon) and **UCSF** (Pis: Chiu, Chow)



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Rationale: tDCS combined with cognitive retraining can enhance processing speed

Summary of Neuropsychiatric Lyme

- Symptoms:
  - Mood, cognitive problems, suicidal thoughts, sensory arousal - common
  - Screen for depression and suicidal thoughts (C-SSRS)
  - May also have neuropathic or arthritic symptoms
- Course of neuropsychiatric symptoms:
  - Can occur early or late in infection
  - Most individuals show marked improvement or recovery over time
- Mechanism: multiple potentially interacting causes
- Treatment:
  - Focus on the most burdensome symptoms
  - Do not avoid standard mental health treatment – these can enhance brain function and recovery.
  - New treatment approaches offer hope for the future

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