NEUROPSYCHIATRIC LYME DISEASE: SYMPTOMS, THE IMMUNE RESPONSE, AND THE VAGUS NERVE

Inflammatory Brain Disorders Conference

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DISCLOSURE SLIDE

I will discuss off-label uses of treatments/medications

I report no financial conflict of interest

Outline

- General Intro to Lyme
- Selected findings on Immune markers
- Neuropsychiatric Lyme disease
- Vagal Nerve Stimulation
- Conclusions

Signs of Lyme Disease

- *Early:* ***Erythema Migrans Rash***
  - An expanding rash, usually not painful
  - Greater than 2 inches in diameter
  - **BUT not usually bull's eye in appearance**

- *Early or Late Disseminated:*
  - **Dermatologic:** multiple EMs
  - **Neurologic**
    - Cranial and peripheral nerves
    - Central Nervous System
      - Meningitis, radiculitis, encephalitis, encephalopathy
  - **Arthritis** (pain or swelling)
  - **Cardiac:** heart block, carditis

Diagnostic Evaluation

Blood Tests

- ELISA (standard, C6, C10/VlsE), Western blot
- Sensitivity:
  - 30-50% early LD, 70-90% neurologic LD

Other:

- Spinal Fluid
- Nerve Conduction studies/EMG
- Skin biopsy for small nerve fibers
- Neuroimaging
- Cognitive Testing

Cerebrospinal Fluid Testing for Neuroborreliosis

CSF assays:

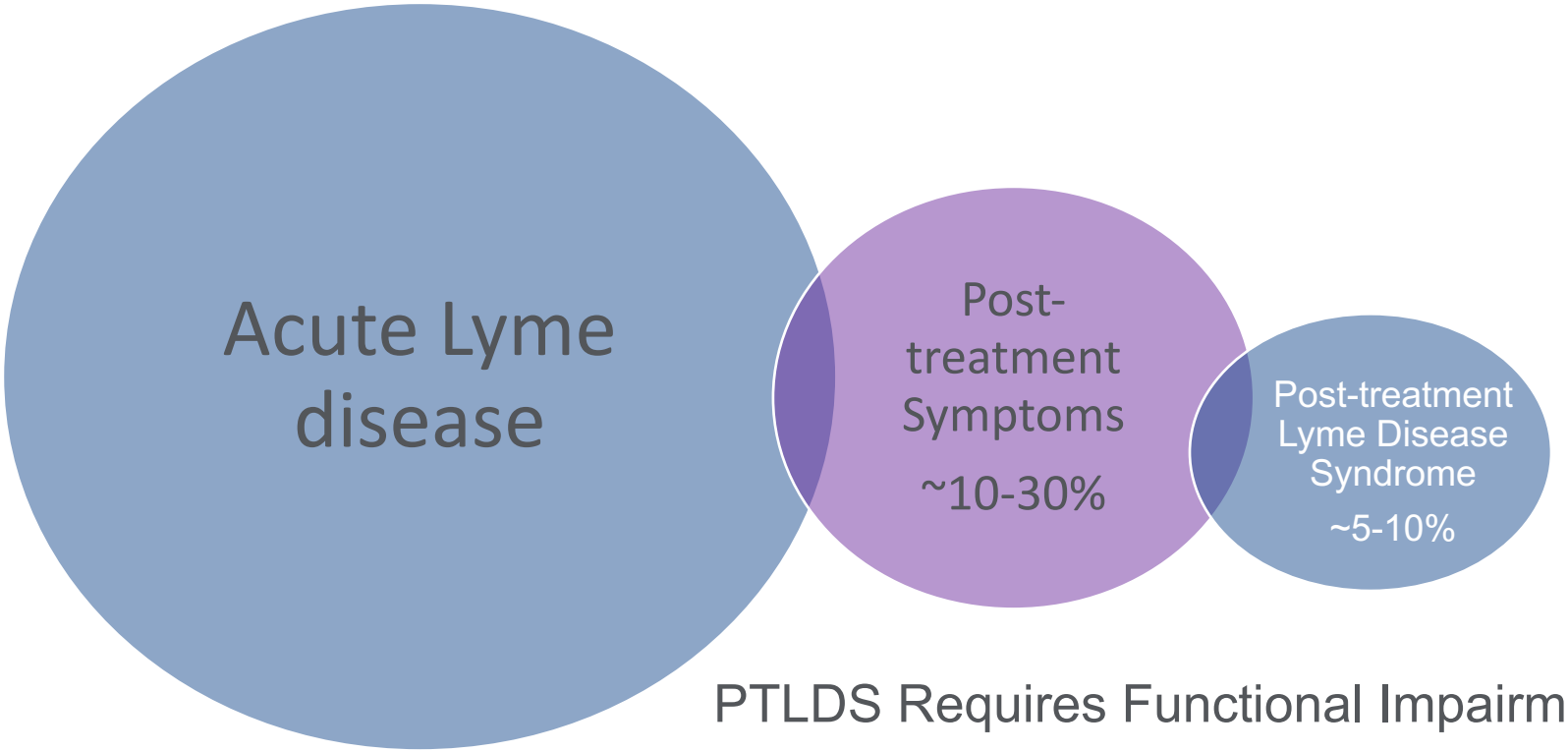
- Intrathecal Antibody production
  - Need paired serum ELISA and CSF ELISA
- Mildly elevated protein & WBC

CSF tests in Neurologic Lyme may be negative in 20% of cases.

- Antibiotic treatment should be given even with a normal CSF if clinical suspicion of neuro Lyme is high (Coyle et al, Neurology, 1995).

Post-treatment symptoms

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



PTLDS Requires Functional Impairment

Inflammation and Lyme

Lots of –itis in Lyme: Arthritis, Cranial Neuritis, Radiculoneuritis, Meningitis, Encephalitis, Myelitis, Vasculitis, Carditis

Borrelia outer surface proteins are 50-500x greater inducers of cytokines than lipoproteins of other organisms, such as E.coli (Weis at al, 1994).

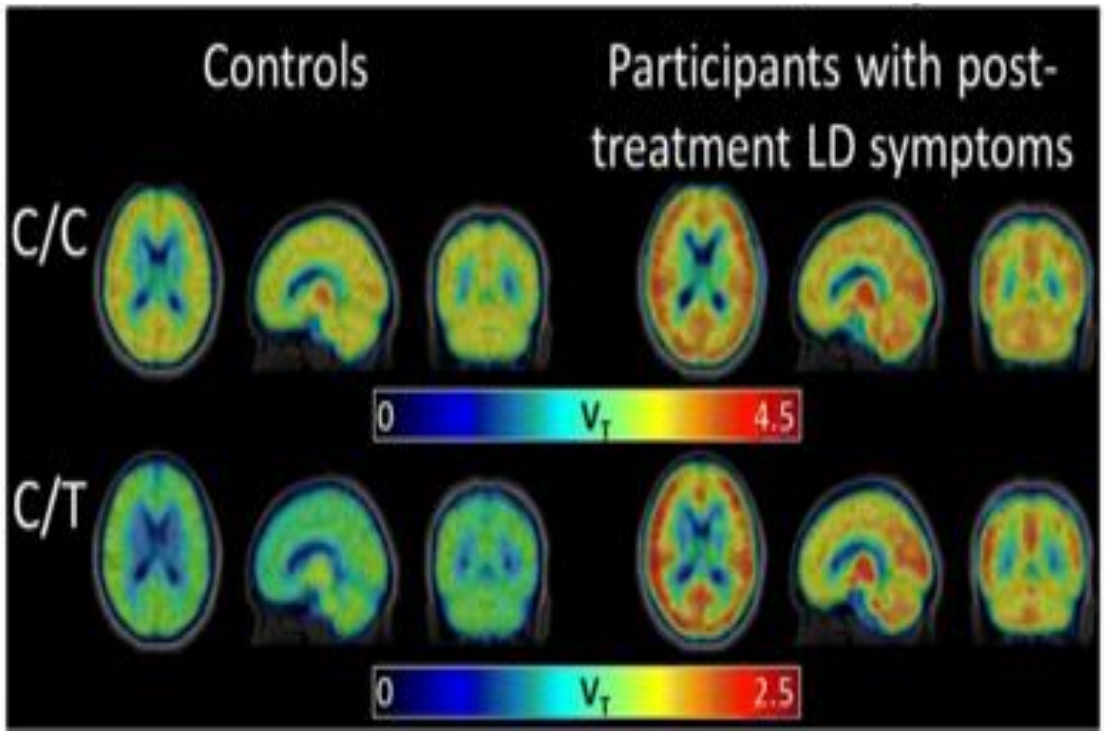
Reported elevations of immune markers

- Cytokines/Chemokines in CSF: IL-6, IL-8, IL-12, IL-18, interferon gamma, CXCl12, CXCL13
- PTLDS: IL6, IF alpha, CCL19, IL-23 (Jacek 2013, Strle 2014, Soloski 2014, Aucott 2016)

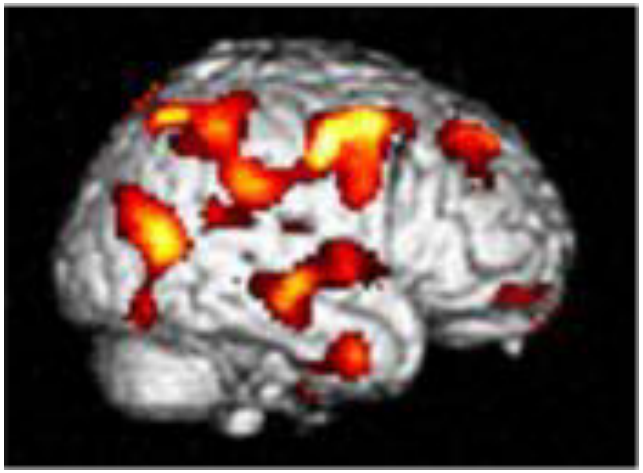
Microglia are activated in post-treatment Lyme disease symptoms/syndrome: A pilot PET study with [^{11}C]DPA-713

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)

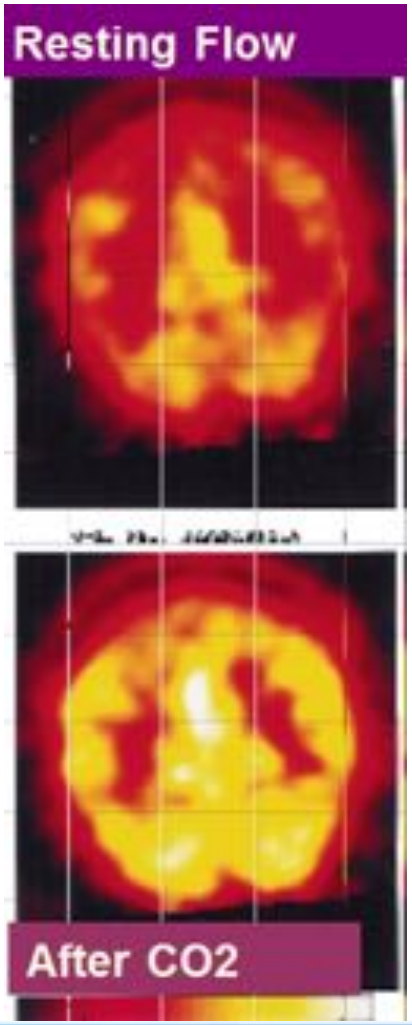


Brain metabolism and blood flow are decreased in Post-treatment Lyme Encephalopathy (Fallon et al, JAMA Psychiatry 2009)



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

O-15 PET before and after a CO2 challenge



The PTLE 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)

Autoantibodies and Lyme

- **Lyme neuroborreliosis:** 50% had IgG reactivity to cardiolipin and 29% of patients had serum IgM antibodies that reacted with ganglioside (~ encephalopathies, motor neuron disease, Guillain-Barre Syndrome) (Garcia-Monco et al 1993)

- **PTLDS:** Antibodies against **Endothelial cell growth factor** are increased in some studies of PTLDS compared to recovered patients. If these autoantibodies are present in early infection with a high T_H17 immune response, the risk of developing PTLDS increases. (Strle 2014)

- **PTLDS: Anti-neuronal Ab** are increased comparable to what is seen in systemic Lupus and significantly greater than in recovered Lyme disease (Chandra et al 2010)

Molecular Mimicry and Lyme

- **Ab against flagellin of Bb** cross react with human peripheral nerve axons (Sigal 1988, 1993, 1997)

- **Ab against OspA peptides** cross-react with human brain, spinal cord, and dorsal root ganglia (Alaedini and Latov 2005)

Antineuronal Ab & CaMKinase activation in Post-treatment Lyme and EM

Participants:

All from Lyme endemic areas in Northeastern US

24 with new EM and no prior LD

8 with new EM and past LD

119 with Post-treatment Lyme

28 controls (healthy, never had Lyme, negative on Lyme Ab tests)

Serum Assays were conducted blind to diagnostic group:

Anti-dopamine D1 Receptor Autoantibody

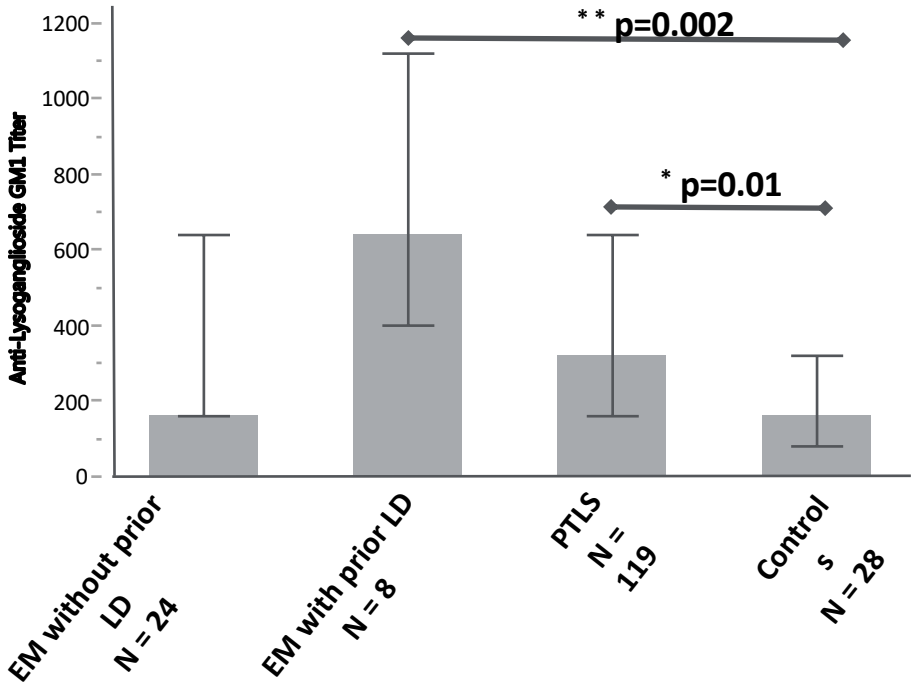
Anti-lysoganglioside Gm1 Autoantibody

Anti-Tubulin Autoantibody

CamKII Activation of Human Neuronal Cell Line

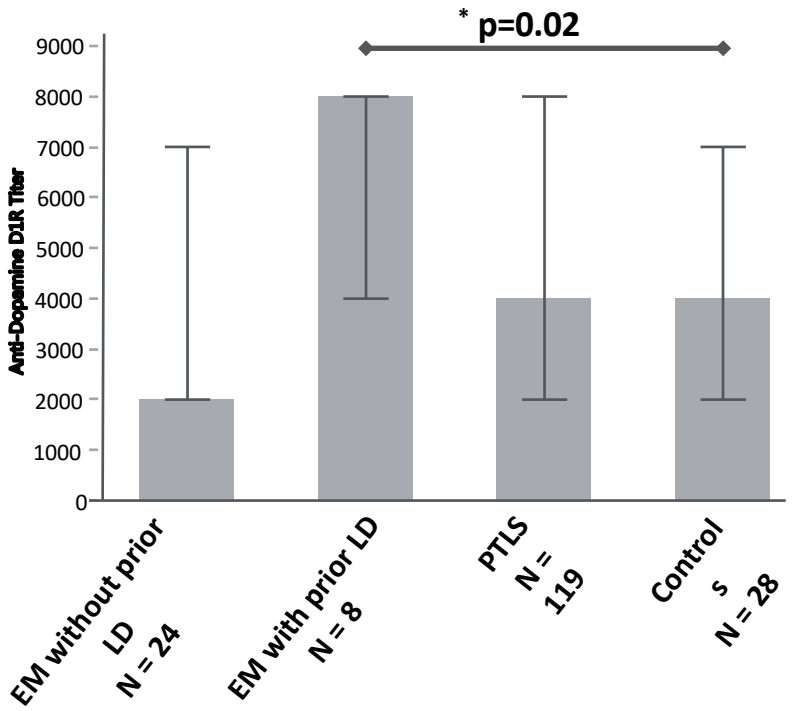
Fallon, Strobino, Reim, Stoner, Cunningham, Brain Behavior Immunity -Health, 2020

Anti-Lysoganglioside GM1 Autoantibody Titers are Significantly elevated in repeated Lyme disease & Post-treatment Lyme compared to Control Sera



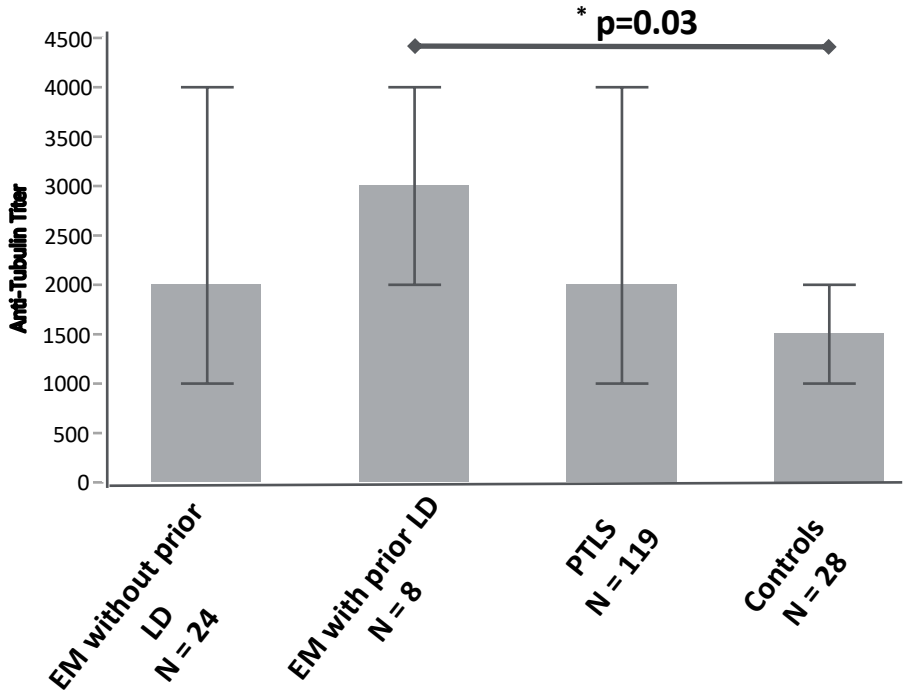
Fallon, Strobino, Reim, Stoner, Cunningham, Brain Behavior Immunity-Health, 2020

Anti-Dopamine D1 Receptor Autoantibody Titers are significantly elevated in repeated Lyme Disease Cohort compared to Control Sera



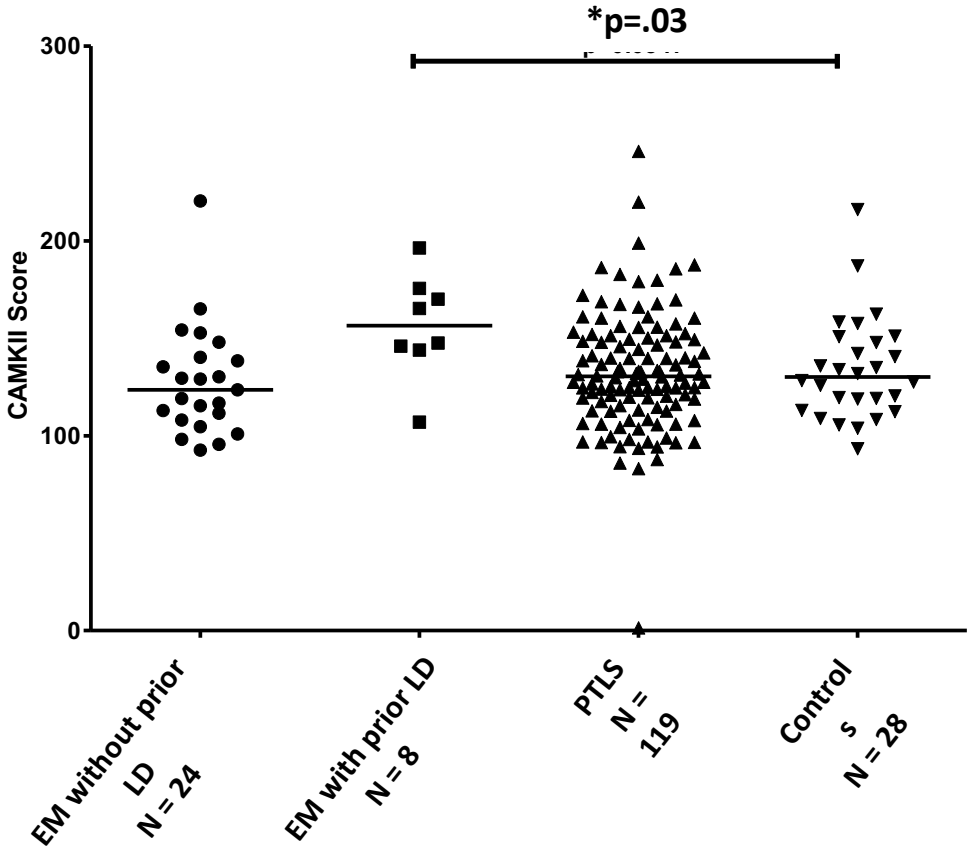
Fallon, Strobino, Reim, Stoner, Cunningham, Brain Behavior Immunity-Health, 2020

Anti-Tubulin Autoantibody Titers are Significantly Elevated in repeated Lyme Disease Compared to Control Sera



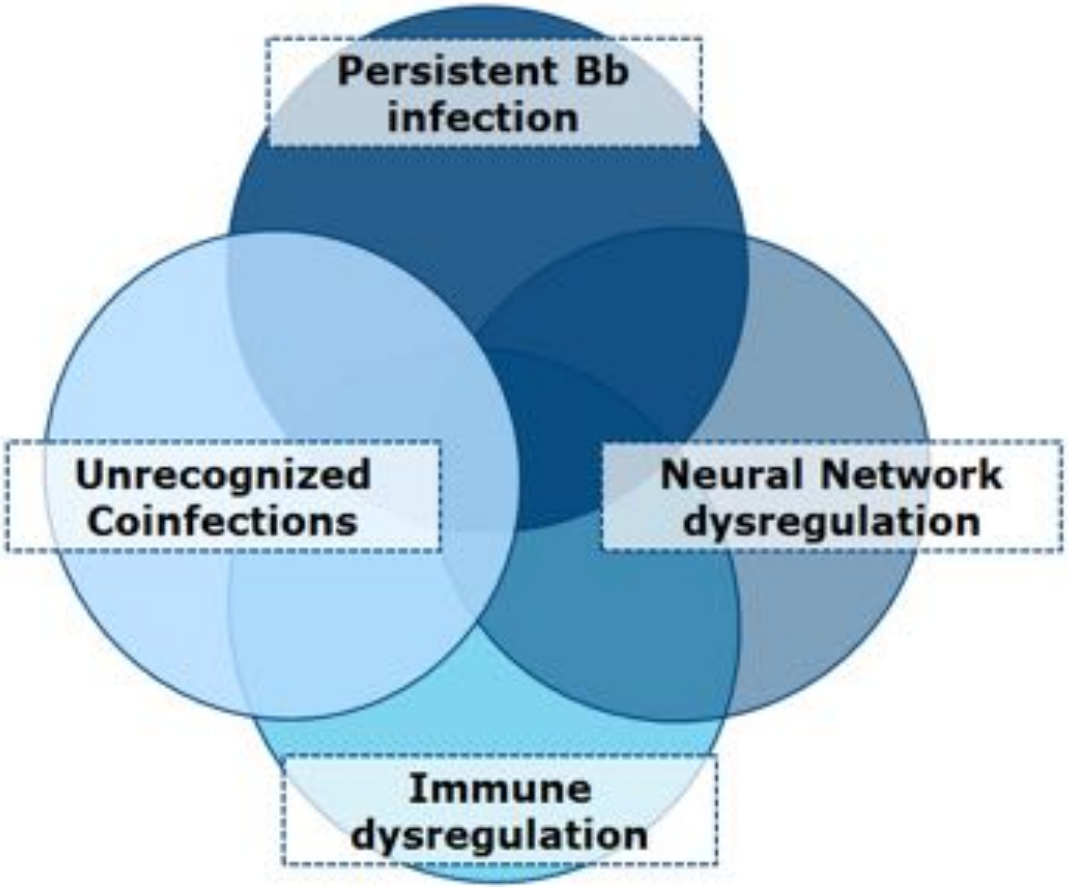
Fallon, Strobino, Reim, Stoner, Cunningham, Brain Behavior Immunity-Health, 2020

Functional Measure of Neuronal Cell Signaling: CaMKII Activation of Human Neuronal Cell Line Significantly Elevated in repeated Lyme Disease compared to Controls



Fallon, Strobino, Reim, Stoner, Cunningham, Brain Behavior Immunity-Health, 2020

Possible causes of Persistent Symptoms



NEUROPSYCHIATRIC MANIFESTATIONS

Selected Psychiatric Presentations

Anxiety Disorders:

- Obsessive Compulsive Disorder, Panic Attacks

Mood Disorders:

- Mood disorders, Mania, Suicidality

Psychosis

Tourette Disorder

Sensory hyperarousal (light, sound…)

Cognitive Deficits in PTLDS

- **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 people with PTLDS have **objective measurable problems. These impact short-term memory, verbal fluency, and processing speed.**(Kaplan et al 1992; Keilp et al 2006; Touradji et al 2018)
- **Known: Cognitive deficits are independent of severity of depression & on average mild in severity** (Westervelt & McCaffrey, 2002; Kaplan et al., 1999; Ravdin et al., 1996)
- Primary Unknown:
  - Optimal treatment for persistent cognitive deficits

Case 1: a 30 yr old encephalopathic man

Initial: paranoia...months later…encephalopathy

Hospital ICU: meningoencephalitis

- CSF & serum: positive for Bb Ab & ⬆ WBC
- **IV Ceftriaxone – 80% better, discharged**

3 weeks later

- arthritic pain starts, encephalopathy returns

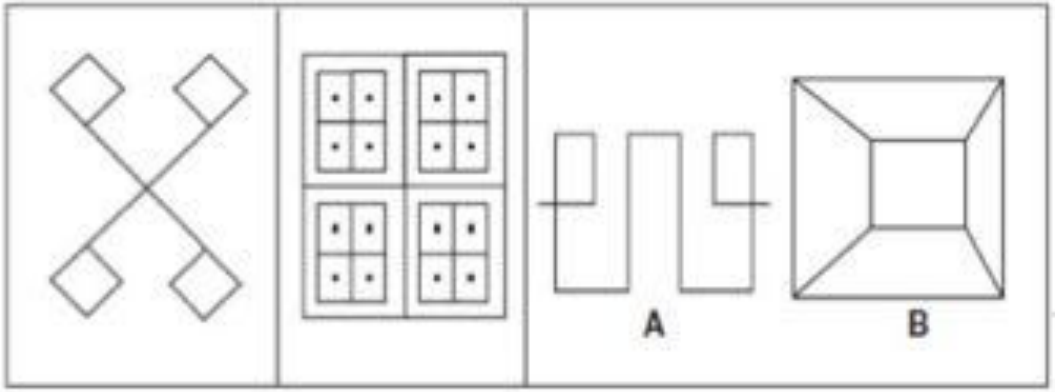
Hosp #2:

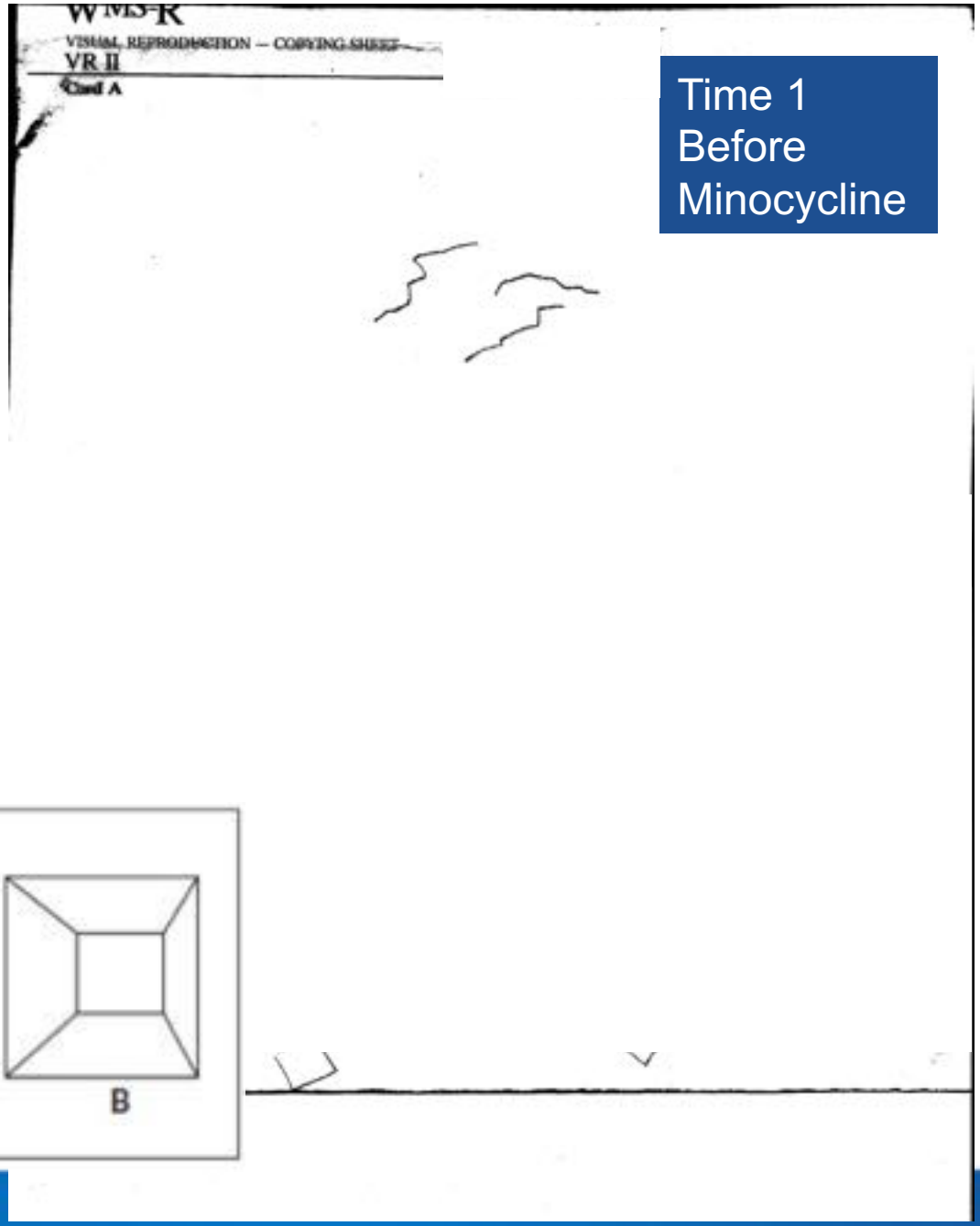
- retreated with IV Ceftriaxone – no benefit
- Conclusion – “This must be a psych problem.”

30 Year old Man with Severe Lyme Encephalopathy

4 more months of outpatient IV Ceftriaxone did not help.

Came for a study in which WAIS & WMS-R tests were done before and after outpatient treatment

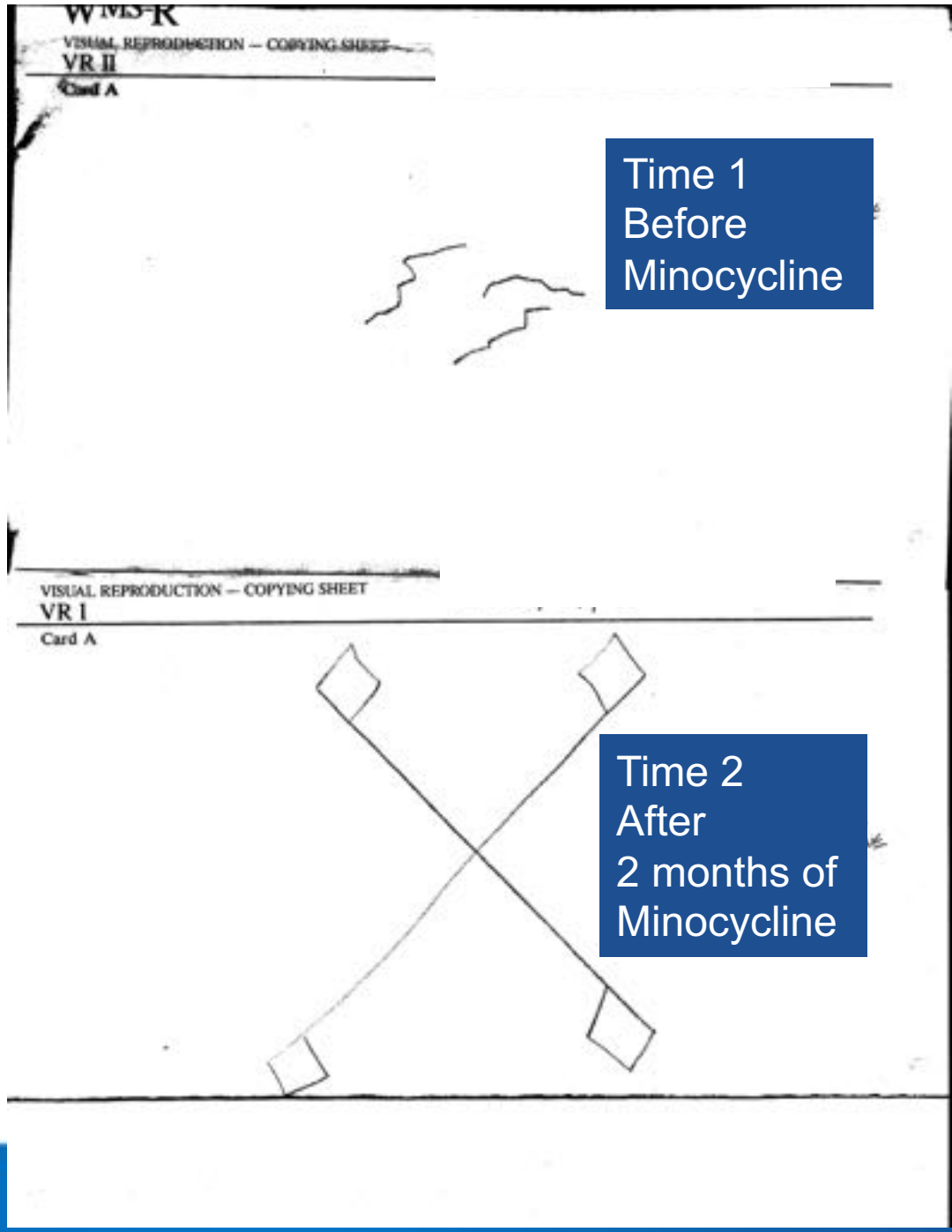




Time 1
Before
Minocycline

30 year old Man with Severe Lyme Encephalopathy

- After 4 months of outpatient IV Ceftriaxone, a switch to minocycline led to marked improvement.
- Minocycyline has anti-inflammatory and antimicrobial effects.
- NOTE: Paranoia was the first symptom in this patient



Lyme Encephalitis 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.

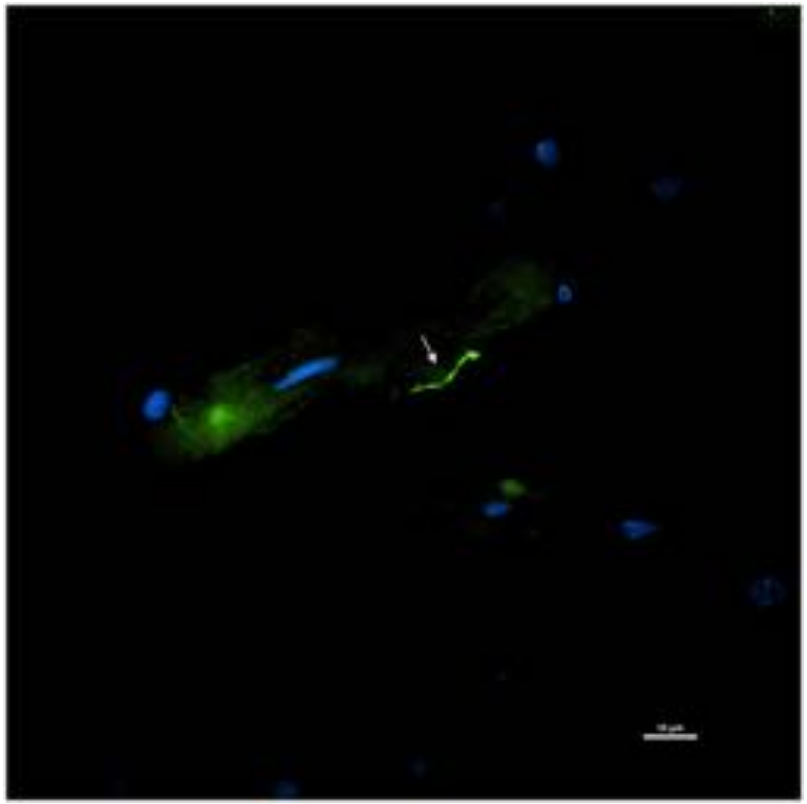
A 42 year old woman presents with new onset schizophrenia-like disorder (Hess et al, Biol. Psychiatry 1999)

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 sx of LB were present. Full recovery after Abx.

Rare Borrelia can persist in humans despite treatment – quiescent or disease inducing?

Borrelia burgdorferi found in amygdala & spinal cord



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

2 yrs later – sleep behavior disorder

4 yrs later – cognitive and anxiety problems

Partial non-sustained response to IV ceftriaxone

Neurodegenerative dementia

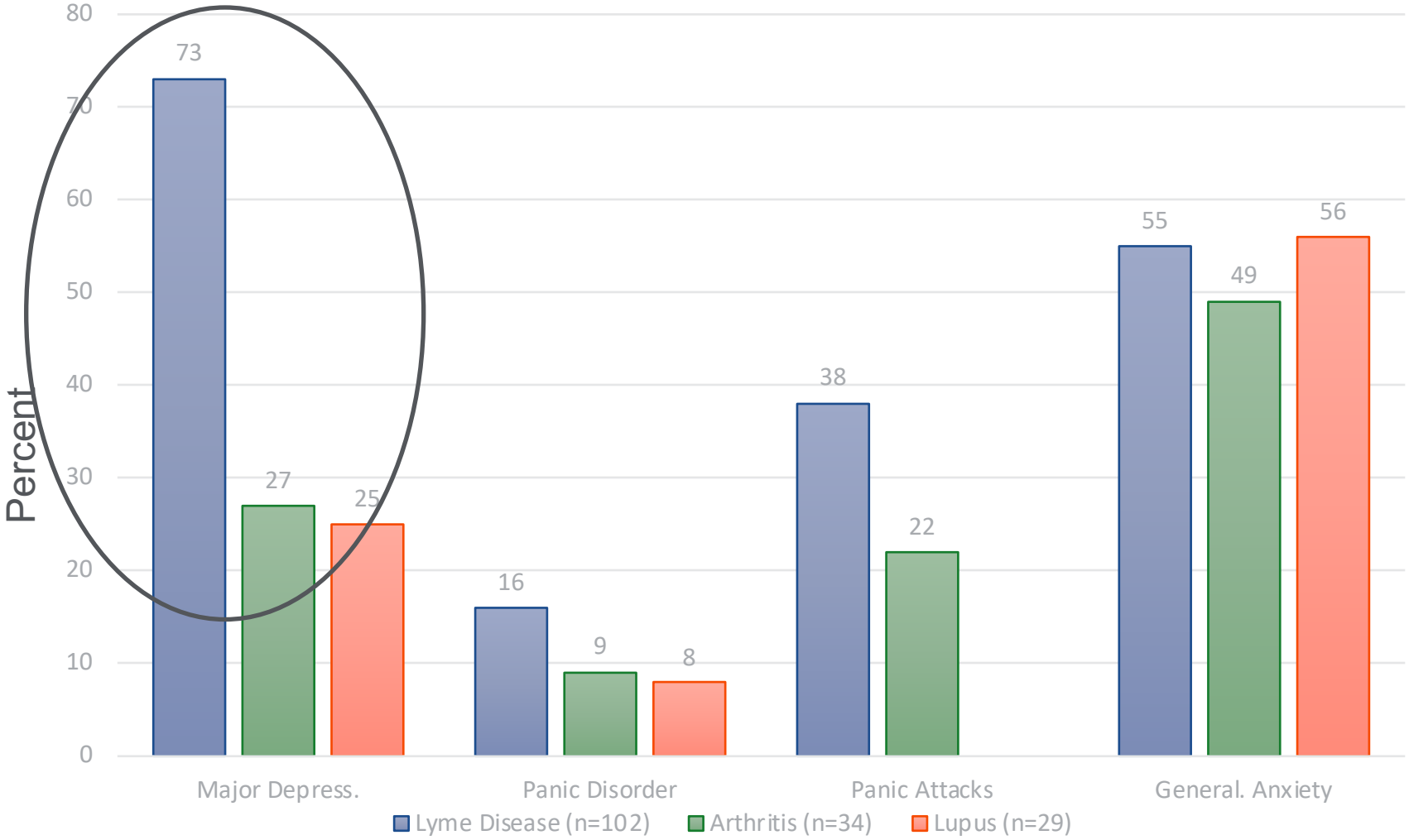
Died age 69

Embers et al, Frontiers in Neurology, 2021

WHAT IS THE FREQUENCY OF PSYCHIATRIC DISORDERS AMONG PATIENTS WITH PREVIOUSLY TREATED LYME DISEASE?

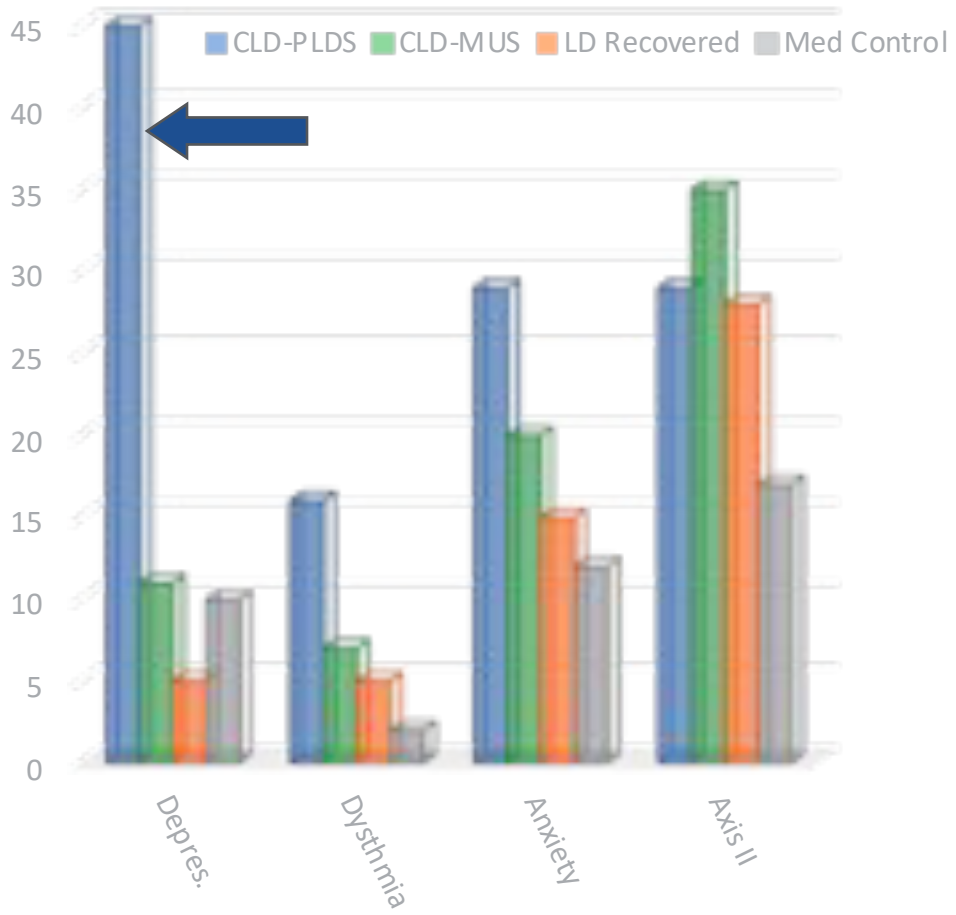
A Survey of psychiatric problems in adults after acquiring Lyme Disease – 2.5x higher frequency of depression

(Fallon, Nields 1994)



Depression in PTLS was 4x more common than in other groups

Hassett et al, Arthr & Rheum 2008



Depressive co-morbidity was 4x more frequent in patients with definite prior LD vs those with medically unexplained symptoms who did not have a good history of LD but self-identified as having chronic Lyme

Some studies have also reported increased suicidal Ideation associated with LB

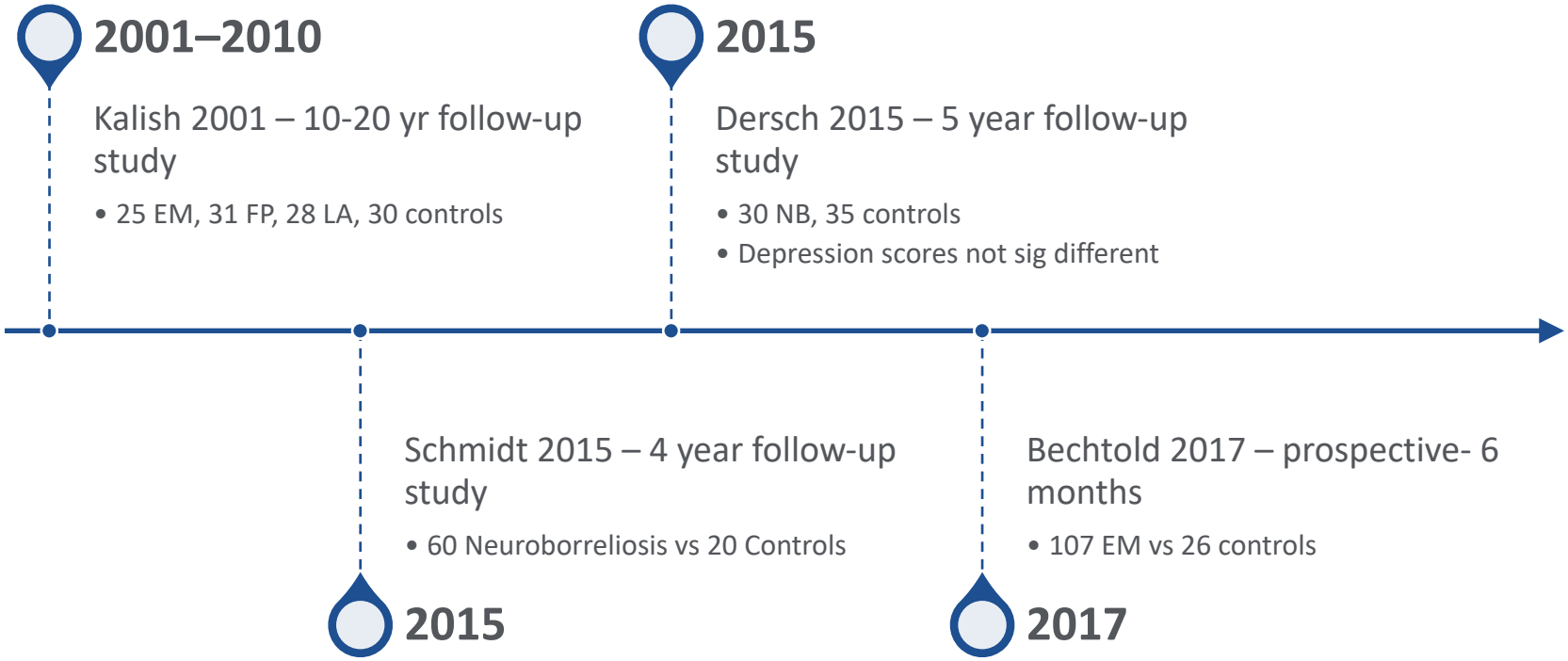
Clinical case series from a private practice:

- Bransfield (2018): A retrospective chart review from a psychiatric practice – a very heterogeneous group of patients with possible and confirmed TBD
  - **n=253, 44% suicidal**

Case-control studies of Lyme borreliosis:

- Tager (2001)
  - 20 children with PTLS vs 20 control
  - **41% suicidal thoughts & 11% attempts vs 0% in controls**
  - But referral bias may have led to inflated rates
- Doshi (2018) - all came for a study unrelated to depression
  - 81 PTLS, 70 HIV+, 44 controls
  - **Suicidal ideation: 20% PTLS, 27% HIV, 5% controls**

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:
2 Nationwide Cohort Studies

Study 1 (Tetens et al, JAMA Psychiatry, 2020)

Is the frequency of mental disorders greater after neuroborreliosis vs those without neuroborreliosis?

Study 2 (Fallon et al, Amer J Psychiatry 2021)

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

Denmark is a small country (~ 6 million) with a medical registry of all citizens

Study #1: Danish Cohort Study of Neuroborreliosis (Tetens 2020)

Design:

- Nationwide matched cohort study of all CSF Bb Index positive cases from 1995-2015 (n= 2897 CSF+patients & 28,970 controls) (total: 31,876).
- Dx of NB was based on CSF (not clinically confirmed)

Three Main Outcomes:

- Any hospital diagnosed mental disorder
- Any inpatient psychiatric hospitalization
- Receipt of prescription for psychiatric medication

Study 1 Results: Neuroborreliosis

- No increased risk of hospital-based psychiatric diagnosis or of psychiatric hospitalizations

- There was an increased risk of psychiatric medication prescriptions during the year after the CSF Borrelia index positive result. (anxiolytics, hypnotics, sedatives, and antidepressant medications). Reason? Pain, Sleep, Mood?

- Authors concluded: *"The short-term affective symptoms of Lyme neuroborreliosis warrant further investigation"*

Study #2

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?

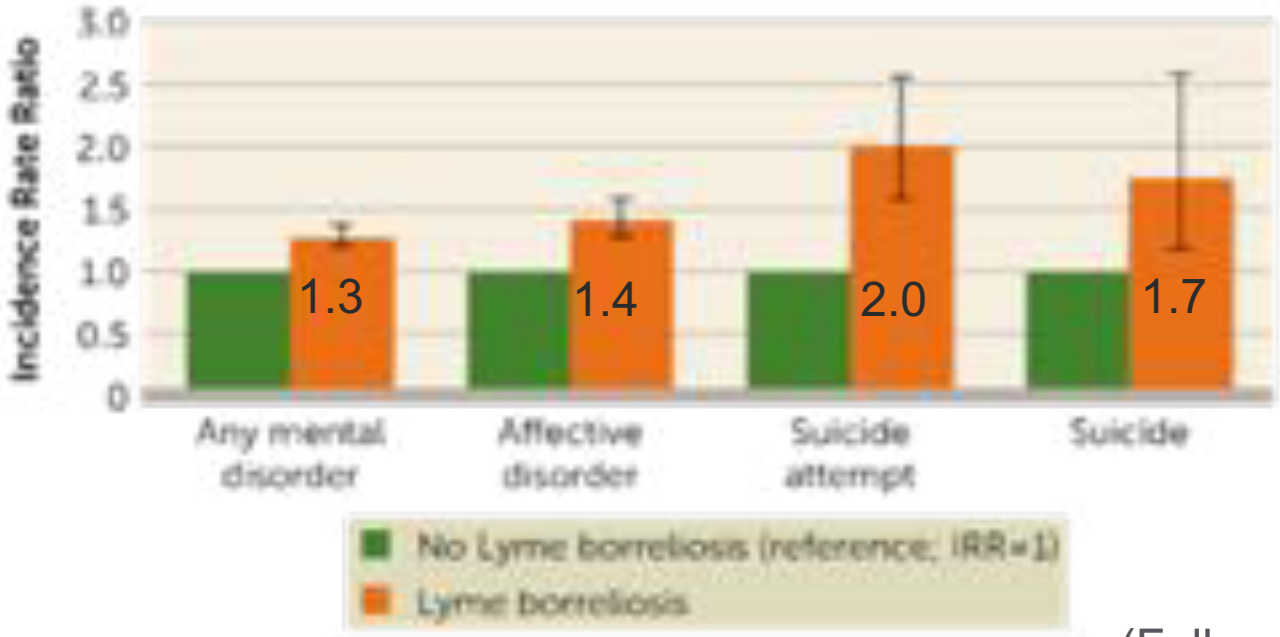
# of Persons in Study: **6,945,837**

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

(Fallon, Madsen, Erlangsen, Benros, Amer J Psychiatry 2021)

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

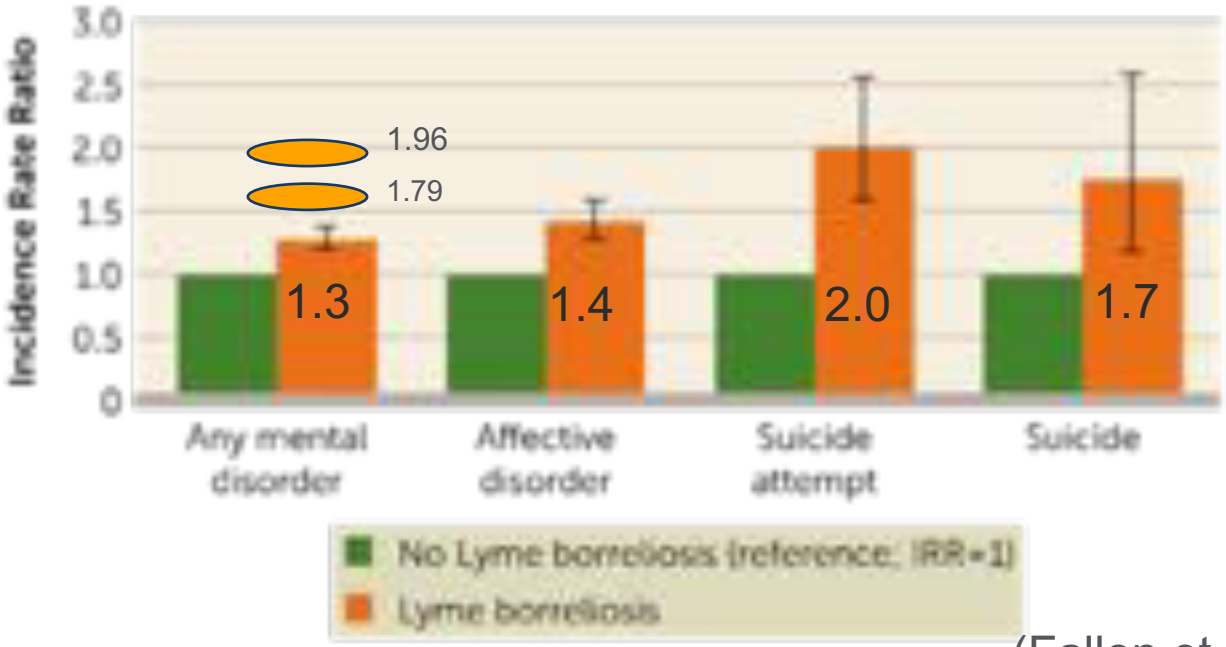
FIGURE 1. Incidence rate ratios for any mental disorder, affective disorder, suicide attempt, and suicide among individuals with Lyme borreliosis compared with individuals with no Lyme borreliosis in Denmark (1994–2016)[a]



(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)

Danish Nationwide Cohort Study of all Lyme manifestations

Additional Analysis

Is it possible that another comorbid condition accounted for the elevated rates of mental disorders?

Unlikely, as these increased rates of mental disorders remained even after we removed individuals in the Lyme group who had another serious comorbid medical condition

(Fallon et al, AJP, 2021)

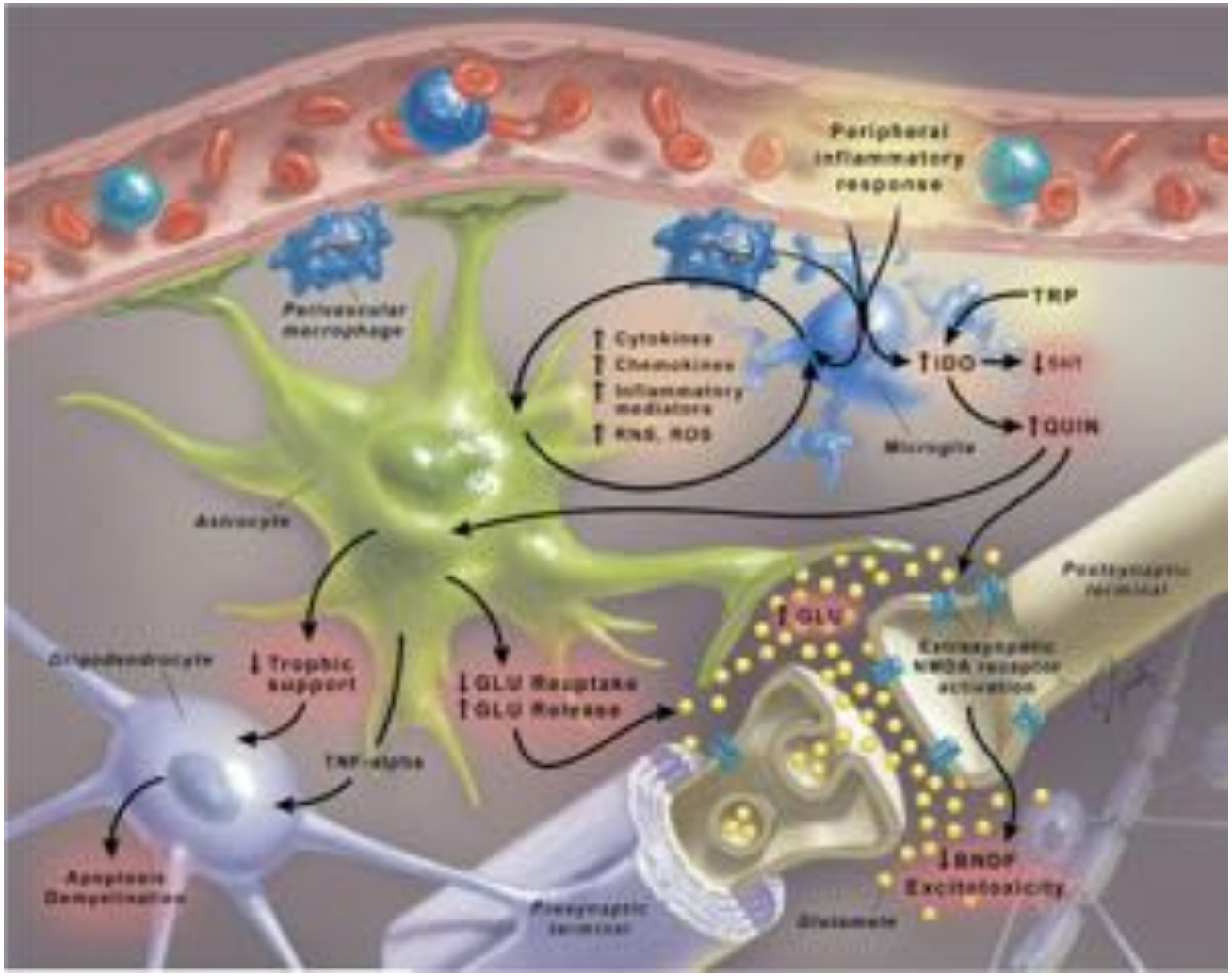
Are these results surprising? No

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.

Peripheral inflammation stimulates microglial inflammatory cascade leading to depression



Miller, Raison…Biological Psychiatry 2009; Nature Rev Immunology 2016

Clinical Recommendations for primary care clinicians

- Monitor patients for mental health sequelae after Lyme disease, especially during the 1st year

- Consider incorporating a mental health screening tool in practice
  - PHQ-9 for depression and suicidal ideation
  - Columbia Suicide Severity Rating Scale (C-SSRS)

- Refer to mental health clinicians
  - Can help in many ways
  - Suicide Prevention Lifeline Phone: 1-800-273-TALK (8255)

Psychosis and Bartonella: a pilot Case-Control Study. Lashnitz et al, Vector Borne & Zoonotic Diseases, 2021

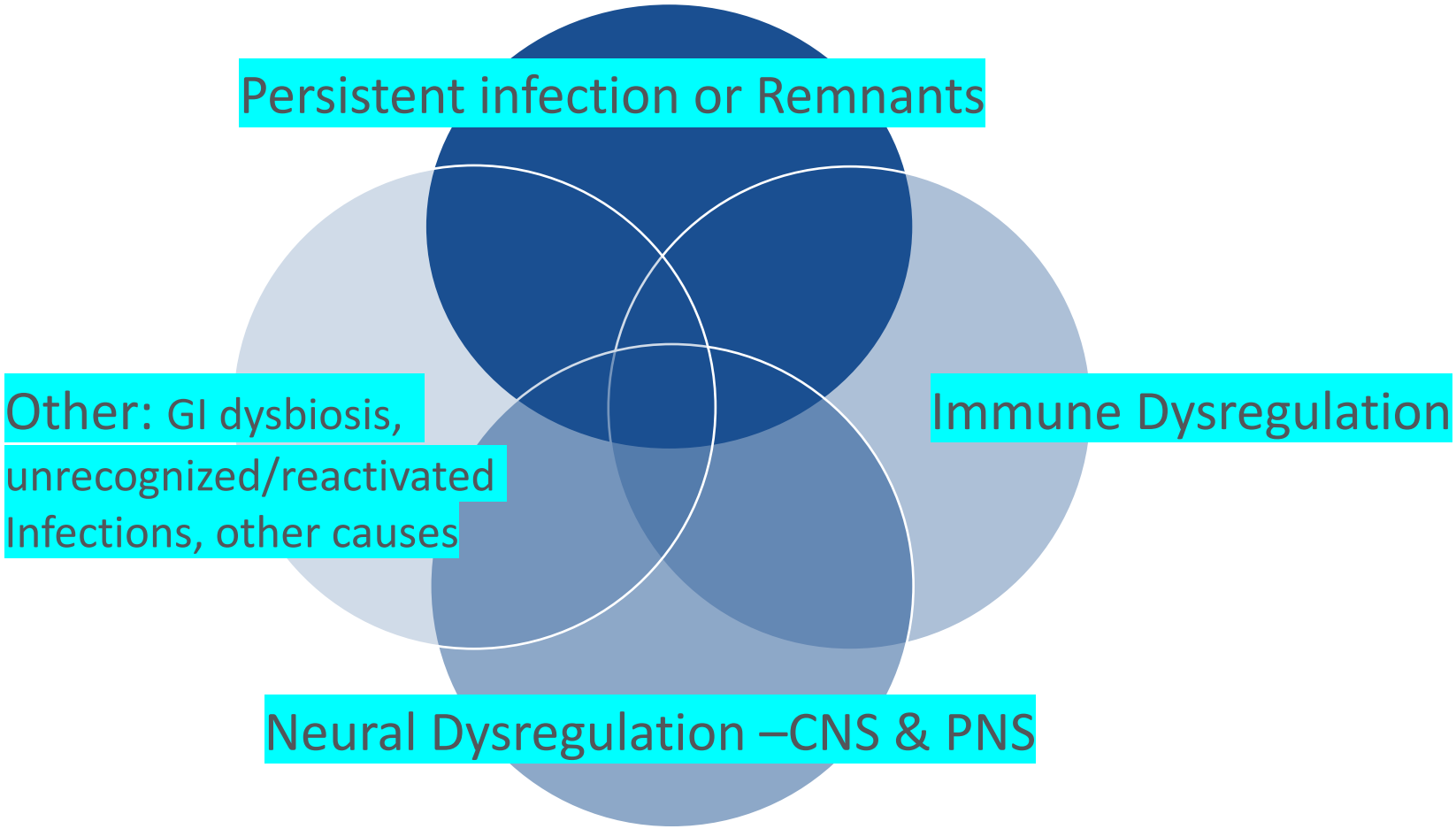
Question: is there an association between schizophrenia/schizoaffective disorder and Bartonella species infection?

Method: 17 cases & 13 controls tested for evidence of Bartonella infection.

Results: Cases were significantly more likely to have Bartonella spp DNA in their blood stream than controls using ddPCR (11/17 cases vs 1/13 controls, p=.002). Serologic positivity was similar for cases and controls (12/17 vs 12/13). Within the case group, there was no relationship between severity of psychosis and ddPCR positivity.

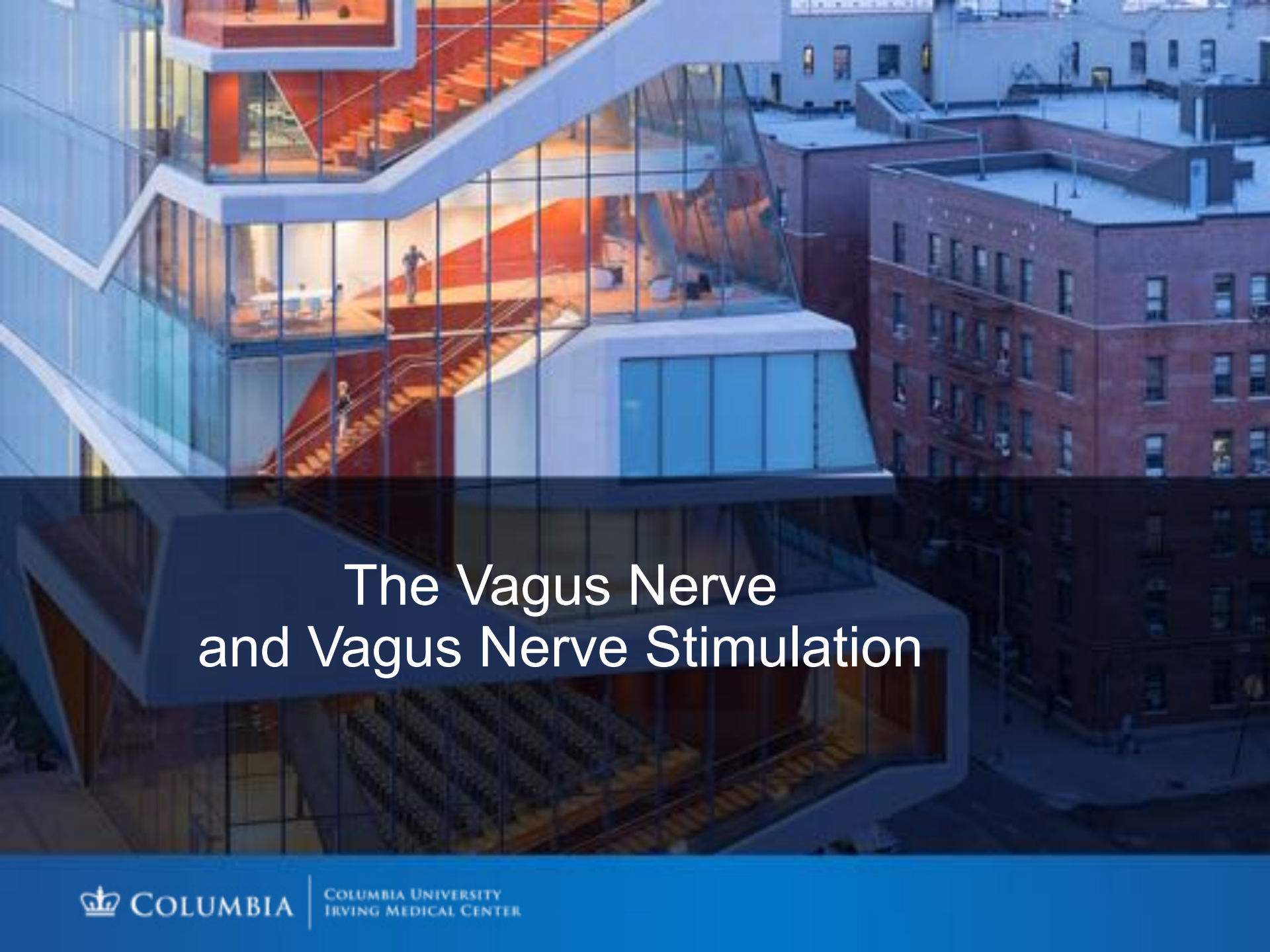
Conclusions: this small pilot study supports further investigation of a possible relationship between psychosis and bartonella species infection .

Potential causes that guide treatment choices for infection-triggered neuropsychiatric syndromes



Potential Therapies

- Targeting persistent Infection
  - Repeated antimicrobial therapy
- Targeting immune activation
  - Consideration of IV Ig? (e.g, autoimmune neuropathies)
- Targeting altered neurotransmitter systems
  - Glutamate, GABA, Serotonin, Norepinephrine
- Targeting an altered microbiome
- Neuromodulation: tDCS, taVNS
- Stress reduction and Psychotherapy
  - Meditation/Yoga, Coping Skills Training, CBT
- Rehab: cognitive and physical



The Vagus Nerve and Vagus Nerve Stimulation

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Why present on the Vagus Nerve?

- Innervates multiple organ systems
- Modulates Inflammation and neural activation
- Patients need additional options for improvement
- Over 400 vagus nerve studies listed on clinicaltrials.gov
  - GI: ulcerative colitis, irritable bowel syndrome
  - Heart: hypertension, heart failure, atrial fibrillation
  - Neuro: stroke, epilepsy
  - Neuropsych: PTSD, major depression, cognitive impairment
  - Rheum: rheumatoid arthritis, fibromyalgia
  - Pain – headaches, back pain
  - Infection-triggered Sequelae – COVID-19
  - Other: Ehlers Danlos Syndrome, POTS, Sleep Disorders

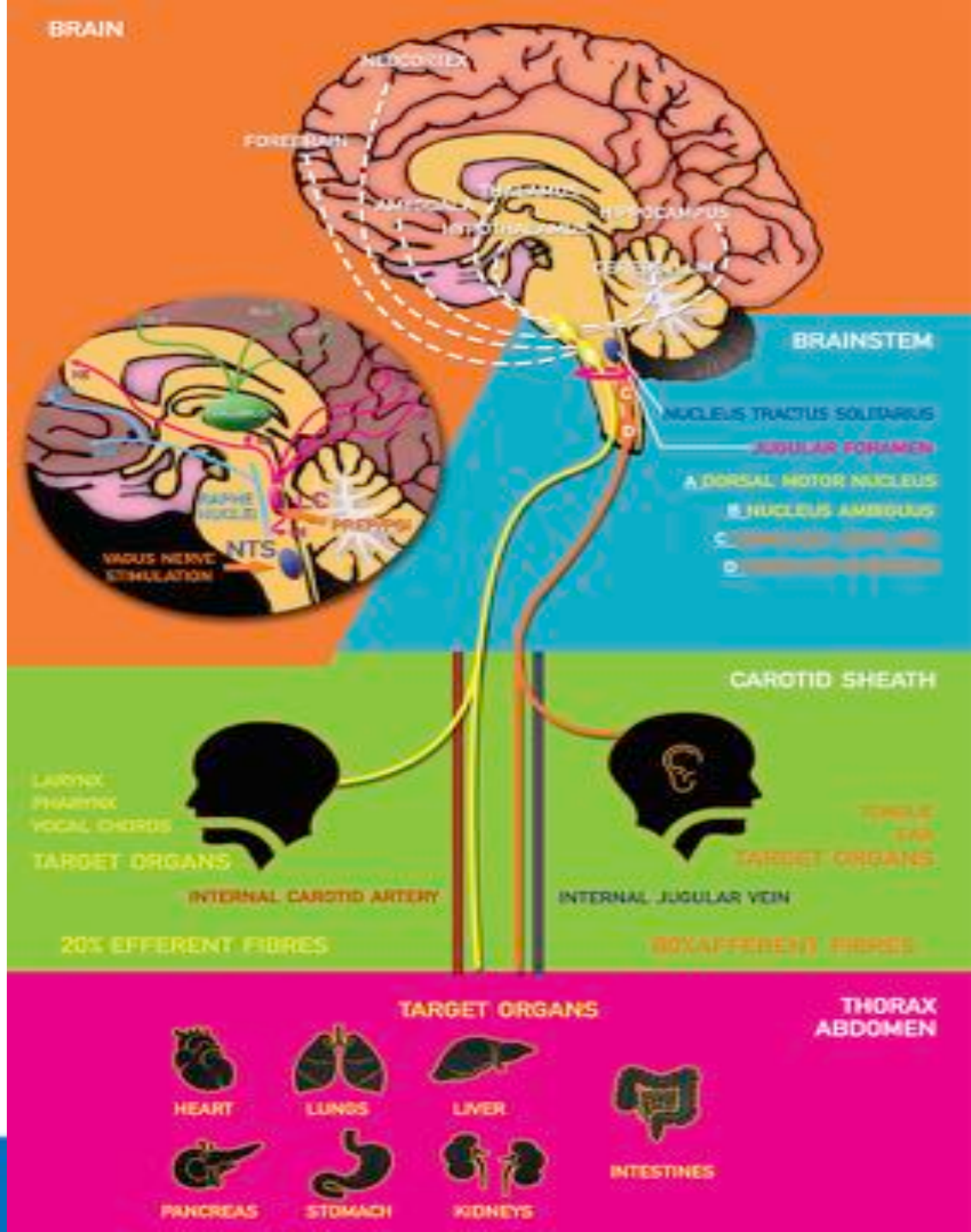
Afferent and efferent pathways of the vagus nerve

Neurotransmitters involved when activating the vagus nerve.

- 5HT, serotonin;
- GLU, glutamate;
- NE, norepinephrine.

Both the autonomic and central nervous system can be modified by vagus nerve stimulation.

From: Vonck, K. E., & Larsen, L. E. (2018). Vagus Nerve stimulation: mechanism of action. In *Neuromodulation* (pp. 211-220). Academic Press.



VNS: history of application

J. Corning, late 19th century, used a ‘fork” for carotid suppression to prevent future epileptic seizures

J. Zabara, 1980+, showed that chemically induced seizures in animal models could be terminated via VNS within seconds.

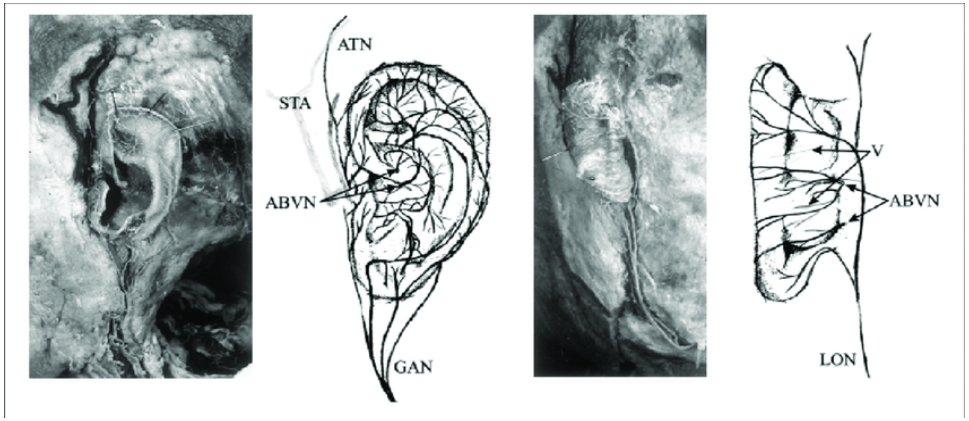
FDA, 1997, approved VNS for treatment of adults with medically refractory epilepsy.

2000, Mood effects of VNS in epilepsy were found in a trial of antiepileptic drugs with and without VNS.

VNS group had more improvement in mood (Harden et al., 2000)

FDA, 2005, approved VNS for the treatment of major depressive disorder

The anatomical basis for transcutaneous auricular vagus nerve stimulation



Cadaver study:

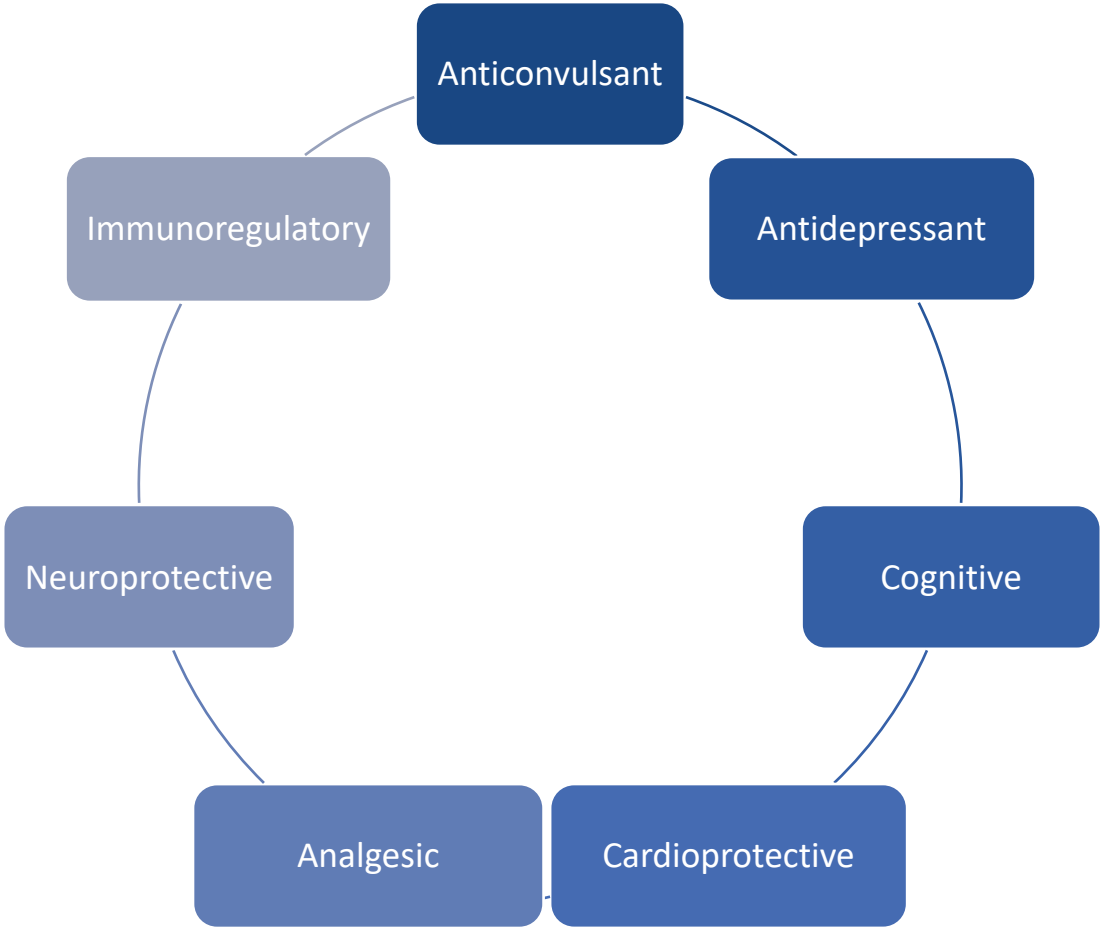
Inner tragus and skin surrounding the cymba concha are innervated by the auricular branch of the vagus nerve (ABVN).

Butt, M. F., Albusoda, A., Farmer, A. D., & Aziz, Q. (2020). The anatomical basis for transcutaneous auricular vagus nerve stimulation. *Journal of anatomy*, *236*(4), 588-611.

Peuker, E. T., & Filler, T. J. (2002). The nerve supply of the human auricle. *Clinical Anatomy*, *15*(1), 35-37.

The electrode montage

Clinical effects of VNS/taVNS: result of a complex interplay of many mechanisms



The Inflammatory Reflex: The Cholinergic Anti-inflammatory pathway

The pathway Is a centrally integrated mechanism in which afferent vagus nerve signaling, activated by cytokines or pathogen-derived products, is functionally associated with efferent vagus nerve-mediated output to **decrease proinflammatory cytokine production and inflammation**.

(Pavlov & Tracey, 2012)

Transcutaneous auricular Vagus Nerve study: Lupus erythematosus

A randomized, double-blind, sham- controlled trial of 18 patients with SLE and pain

12 with taVNS and 6 with sham stimulation

Results:

In this small study, taVNS led to a significant reduction of fatigue and of pain and of joint swelling compared to sham taVNS after only 4 sessions.

Substance P was decreased to a greater extent in taVNS compared to sham taVNS.

(Aranow et al, Annals of Rheumatic Disease 2021)

tVNS and COVID

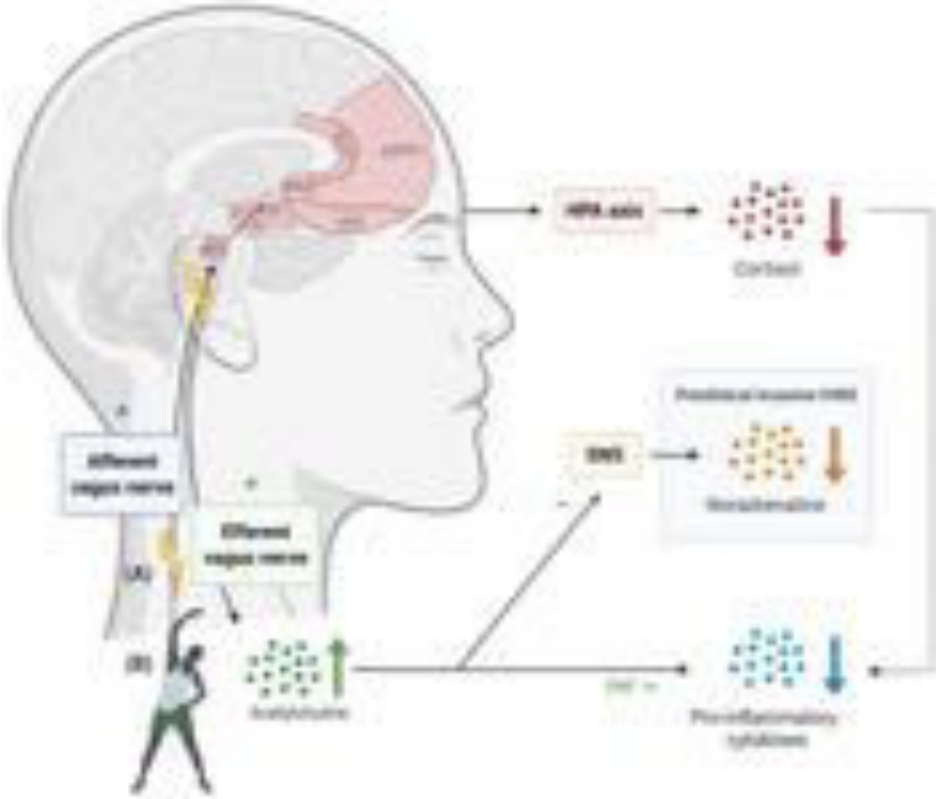
Case studies report subjective improvement in symptoms: *Staats P et, Neuromodulation. 2020*

Clinical Trials:

- ***Pilot open label at home taVNS for Long COVID with ME/CFS*** *(Natelson 2022)*. ***8/14 (57%) were ME/CFS responders*** *with no adverse events*

- ***Pilot-randomized at home taVNS for Long COVID*** *(Badran et al 2022) –* ***n=13*** *taVNS was* ***feasible, safe, trend in reducing mental fatigue***

- ***Randomized Controlled Trial of non-invasive Vagus Nerve Stimulation for acute hospitalized CoViD-19 Respiratory Symptoms*** *(Tornero SAVIOR I, 2022)- USA* ***(n=97)*** *VNS led to* ***sig reduction in inflammatory markers (CRP and procalcitonin) but not in respiratory outcomes***



Pathways by which vagal function-enhancing interventions can normalize biological functioning and improve mental health (from Dedonker et al., 2021)

Dedoncker et al Mental health during the COVID-19 pandemic and beyond: The importance of the vagus nerve for biopsychosocial resilience. *Neuroscience & Biobehavioral Reviews*, 2021

Limitations of knowledge about taVNS

What is the optimal location of electrode placement –

- concha vs tragus vs both vs side of neck?

What are the optimal taVNS stimulation parameters:

- Varying stimulation frequencies (between 0.5 and 30 Hz)
- Varying pulse width (50–500 μs)
- Varying intensities (0.5–50 mA)

How many minutes each day? 15? 30? 60?

How many sessions/day?

What is the optimal activity during VNS to maximize the effect?

(Farmer et al., 2021l Badran, Mithoefer, et al., 2018, Butt et al., 2019)

Current and Upcoming Clinical Trials Network Studies for Lyme & other Tick-borne diseases

Columbia and NYSPI:

Long Lyme Fatigue: taVagus Nerve Simulation (Fallon/Kuvaldina)

Long Lyme Brain Fog: Transcranial Direct Current Stimulation with Cognitive Retraining (Gorlyn)

Long Lyme Depression: Intravenous Ketamine with Cognitive Retraining (Keilp)

Hopkins: Tetracycline for Post-Treatment Lyme Dis (Aucott)

Children's National Hospital: Early neurodevelopmental outcomes of exposure to Lyme disease when treated during pregnancy (Mulkey/DeBiasi)

University of North Carolina: Mast Cell Treatments for post-tick bite illness (Commins)

Conclusions

- Disturbances of cognition and mood are common in post-treatment Lyme disease
- Clinicians need to ask about suicidal thoughts
- Treatment approaches should address the most likely underlying mechanism of disease
- Randomized controlled trials are needed to address the physical and mental symptom complexes

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&
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