Interstitial Medicine and Dysautonomia
Seeing the Whole Elephant

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"Play in a band where everyone is better than you" attributed to Dave Grohl

Objectives

- Discuss a group of overlapping patients with multisystem symptoms related to autonomic nervous system dysfunction
- Discuss the complex associations with dysautonomia
- Describe what we mean by a “functional” disorder
- Explain why we need interdisciplinary medical care for patients with dysautonomia

Disclosure of conflicting interests

- none

Holistic understanding of medicine

- Everything in the human body has an effect on everything else.
- We see patients through the lens of our specialty
- The division between medical illness and psychiatric illness is an illusion.
- Medicine has created “silos” that are barriers to a holistic view.
- Patients from complex co-morbid disorders need an interdisciplinary team to care for them

Many physicians have observed a group of patients with complex comorbid complaints who do not fit our diagnostic “system-based” understanding of medical disorders and fail to respond to our treatments

Familial Immune Dysregulation

Sympathetic overactivation

Autoimmune disease

Infectious Insult

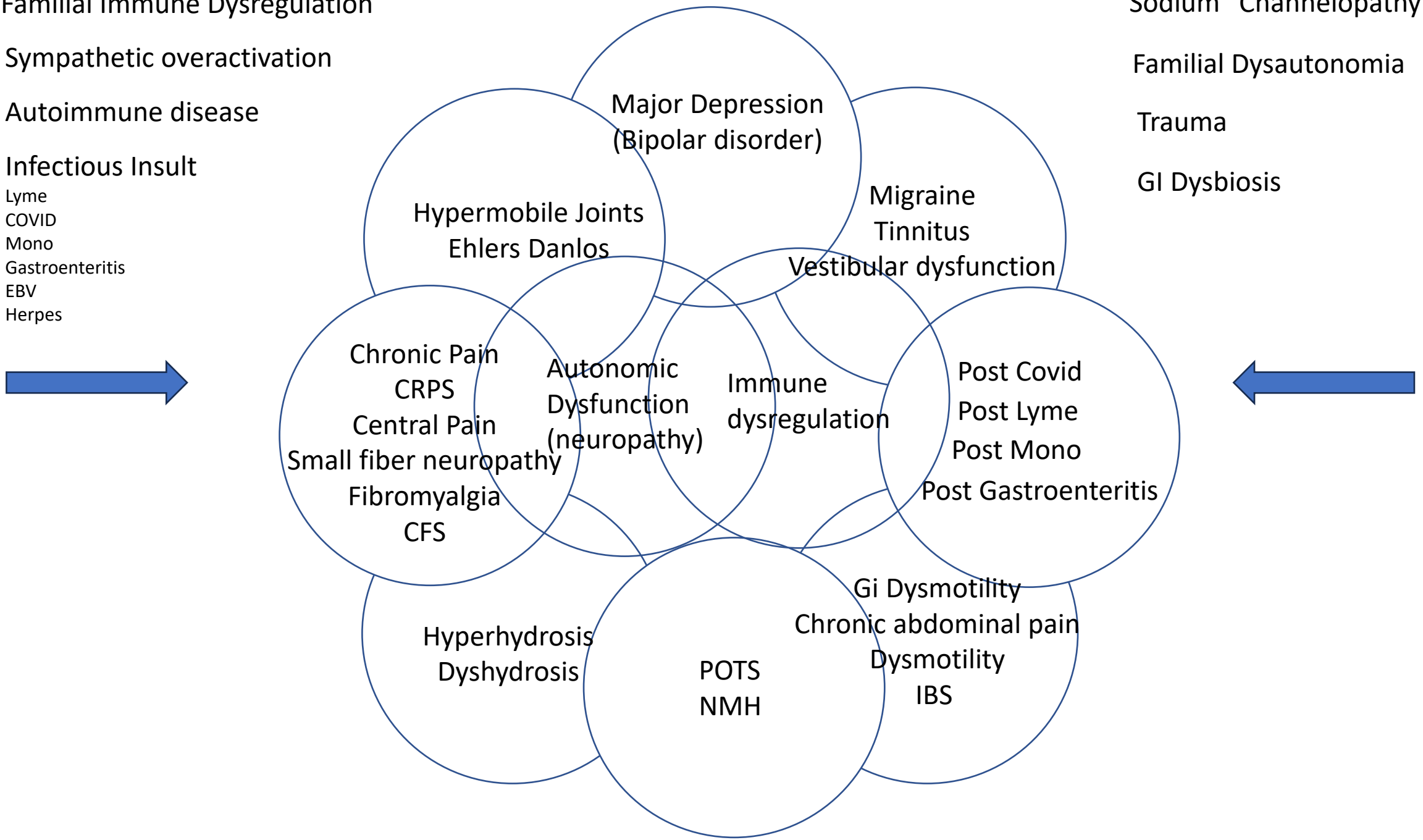
Lyme
COVID
Mono
Gastroenteritis
EBV
Herpes

Sodium "Channelopathy"

Familial Dysautonomia

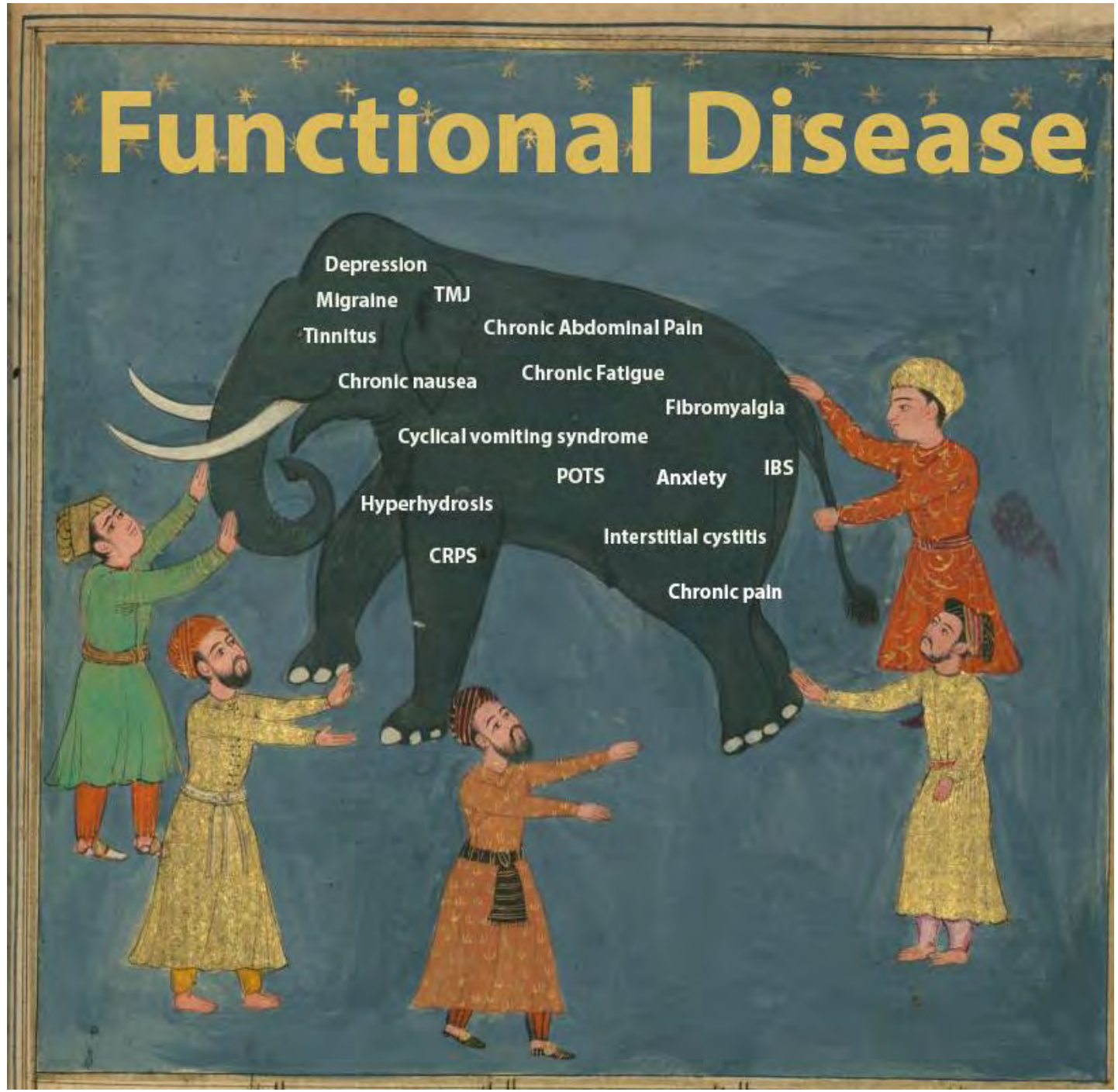
Trauma

GI Dysbiosis



These conditions are often labeled as “functional’

- A medical condition characterized by unexplained symptoms that cannot be attributed to a specific underlying structural or biochemical abnormality
- A disorder in which the physical symptoms have a psychological function in the patient-psychosomatic (Something the patient is doing)
- A newer use of the term is a disorder of function rather than structure


Functional Disease
Depression
Migraine
TMJ
Tinnitus
Chronic Abdominal Pain
Chronic nausea
Chronic Fatigue
Fibromyalgia
Cyclical vomiting syndrome
POTS
Anxiety
IBS
Hyperhydrosis
Interstitial cystitis
CRPS
Chronic pain

- **Briquet’s syndrome (Briquet P, Traité clinique et therapeutique de l'hystérie. Paris J.B. Bailliere et fils:1859**

- **Dramatic or complicated medical history beginning before the age of thirty-five**
- **15 of the following symptoms in 9/10 of the groups**
  - feeling sickly for most of **her** life, headache
  - blindness, paralysis, anesthesia, aphonia, fits or convulsions, unconsciousness, amnesia, deafness, hallucinations or urinary retention
  - fatigue, lump in the throat, fainting spells, visual blurring, weakness or dysuria
  - breathing difficulty, palpitation, anxiety attacks, chest pain or dizziness
  - anorexia, weight loss, marked fluctuations in weight, nausea, abdominal bloating, food intolerances, diarrhea or constipation
  - abdominal pain or vomiting
  - dysmenorrhea, menstrual irregularity, including amenorrhea for at least two months, or excessive menstrual bleeding
  - Sexual indifference, sexual frigidity, dyspareunia, other sexual difficulties or vomiting for all nine months of pregnancy
  - back pain, joint pain, extremity pain, burning pains of the sexual organs, mouth or rectum or other bodily pains
  - nervousness, fears, depressed feelings, need to quit working or inability to carry on regular duties because of feeling sick, crying easily, feeling life was hopeless, thinking a good deal about dying, wanting to die, thinking of suicide or suicide attempts

Da Costa’s Syndrome (1871) (soldier’s heart)
(originally thought to be cardiac but reclassified as “hysteria”)

- Often developed after a bout of fever or diarrhoea
- The pulse was always greatly and rapidly influenced by position
- Chest pains
- Palpitations
- Breathlessness
- Fatigue in response to exertion
- Used digitalis (sodium-potassium ATPase inhibitor)
  - Called "*irritable heart”* by Da Costa who studied 300 cases

Symptoms reported by 195 Long COVID patients

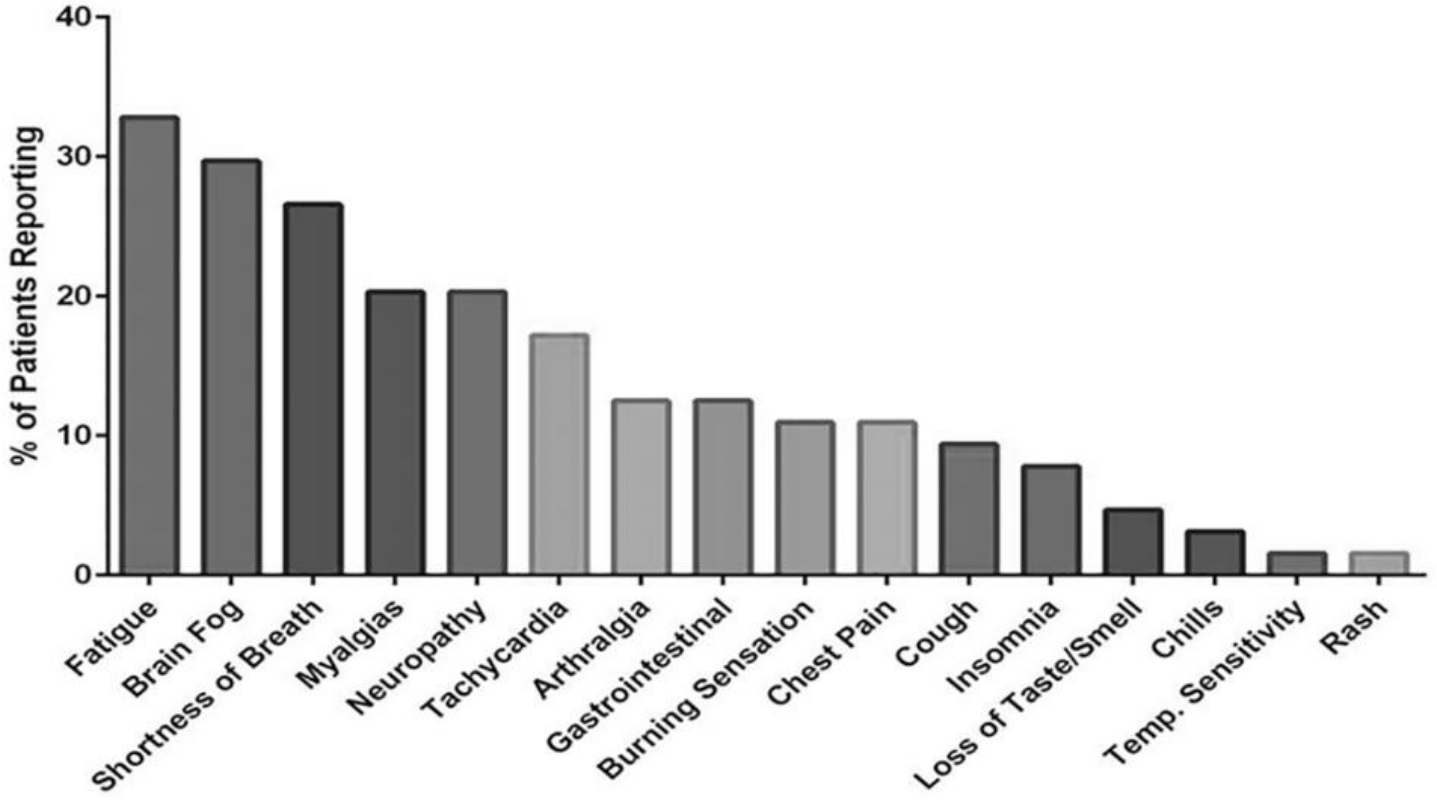
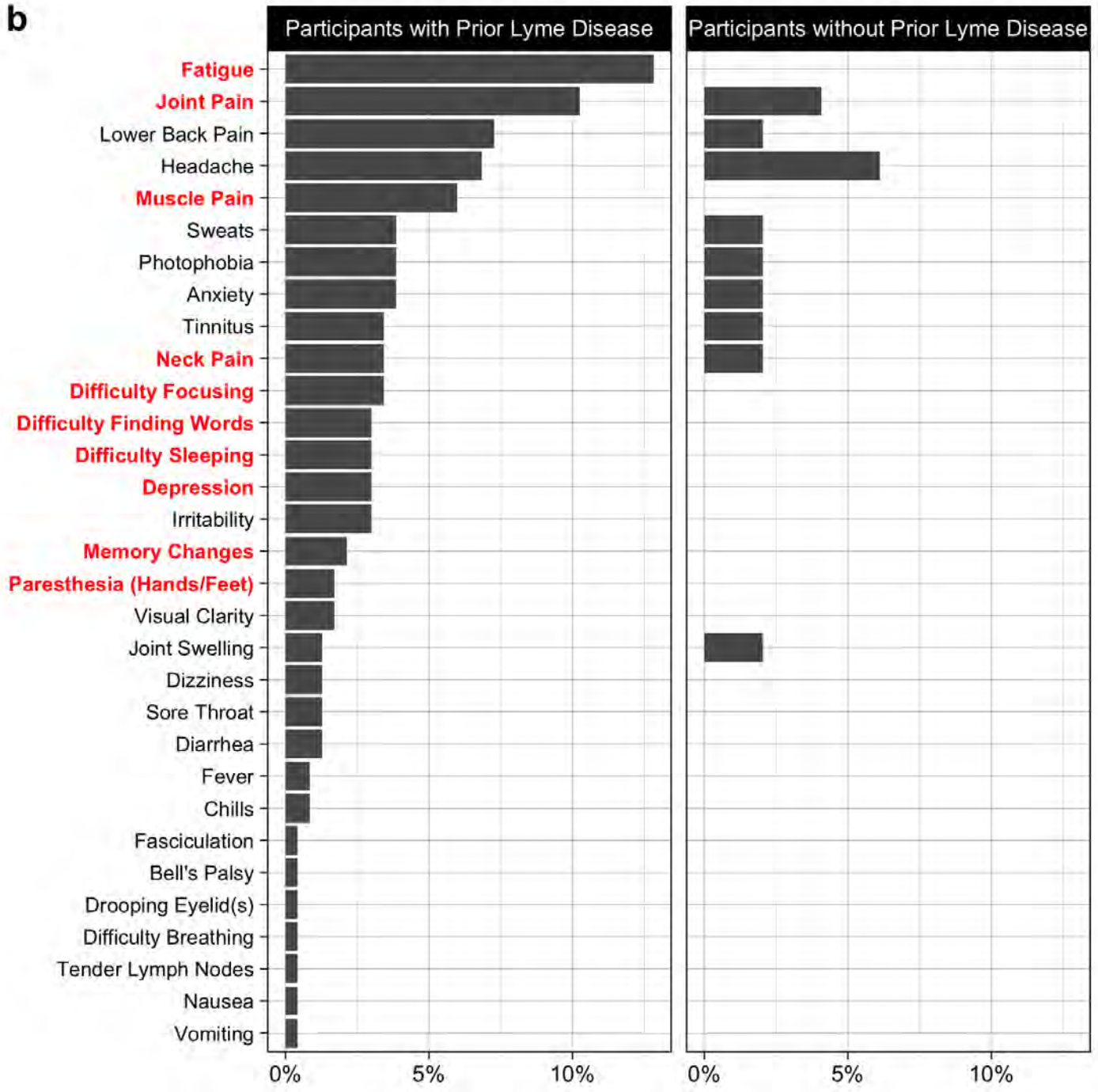


FIGURE 1 | Symptoms reported by PASC patients enrolled in the study.

Patterson BK, Guevara-Coto J, Yogendra R, Francisco EB, Long E, Pise A, Rodrigues H, Parikh P, Mora J and Mora-Rodrı´guez RA (2021) Immune-Based Prediction of COVID-19 Severity and Chronicity Decoded Using Machine Learning. Front. Immunol. 12:700782.

SLICE Study

Patient reported Moderate-Severe symptoms in Lyme disease participants vs. controls



Because of “medical silos” appreciation of co-morbidity is often missed

• POTS/NMH	Cardiology
• Migraine	Neurology
• Brain fog	Neurology
• Gut dysmotility	GI
• IBS	GI
• Fibromyalgia	Rheumatology
• MCTD	Rheumatology
• Chronic Fatigue	Inf Disease
• Tinnitus	ENT
• Interstitial cystitis	Urology
• Chronic pain	Anesthesia
• CRPS/RSD	Anesthesia
• Depression	Psychiatry
• Ehlers-Danlos	PMR
• Lyme	Inf Disease
• Long COVID	Many clinics

Complex comorbidities may lead clinicians towards psychological explanations

How can one patient have all these different conditions?

Psychological vulnerabilities

- Poor coping
- Trauma history
- Mood disorders
- TBI and ADHD
- Emotional instability

Pathological findings

- Tilt table
- Small fiber neuropathy
- Chronic immune activation
- Chronic inflammation
- Functional MRI

Patient with “functional GI disorder”

- 22 year old young woman with Fibromyalgia, POTS, TMJ syndrome, IBS with alternating diarrhea and constipation, migraine headaches with multiple food triggers, dysmenorrhea, chronic abdominal pain, back pain and depression on 6-8 mg of clonazepam a day. Intolerant of all psychotropic drugs and diagnosed with “borderline personality”)
- GI workup shows slowed colonic transit
- Tilt table shows moderate to severe POTS.
- ANA pos to 640 but no clear diagnostic antibodies
- Exposure to antidepressants demonstrated Bipolar II
- Developed ITP on VPA and responded to steroids with a mixed state

Med list

failed meds

- Aripiprazole
- Buspirone
- Doxycycline
- Escitalopram
- Nortriptyline
- Fludrocortisone
- Gabapentin
- Pregabalin
- Doxepin
- Dicyclomine
- Guanfacine
- Hyoscyamine
- Iloperidone
- Liothyronine
- Naltrexone
- Pramipexole
- Propranolol
- Pyridostigmine
- Quetiapine
- Risperidone
- Vortioxetine
- Vilazodone
- Venlafaxine
- Ziprasidone
- desvenalfaxine

current meds

- Protriptyline 30
- Lamotrigine 300 mg
- Lithium 750
- Cariprazine 6
- Asenapine 5
- Topiramate 150/ 150
- Vpa 250/500
- Midodrine

Patient now 29, in grad school and stable for 6 years on these medications

JAG-A syndrome described by Jay Pasricha



Amos Food Mind Body Center
Amos CIM scholar

- **Joint hypermobility** or any type of connective tissue disease, such as Ehlers-Danlos syndrome
- **Autonomic dysfunction** such as postural orthostatic tachycardia syndrome, or POTS, which involves an abnormal heart rate increase upon standing
- **Gastrointestinal dysmotility** such as gastroparesis or slow-transit constipation
- **Autoimmunity** or predisposition to any underlying autoimmune disease
- “Describing the JAG-A syndrome and the criteria by which a patient may fit into the group has helped us identify patients who may have an underlying autoimmune problem that is contributing to or causing their motility disorder,”

Amos Food Mind Body Center

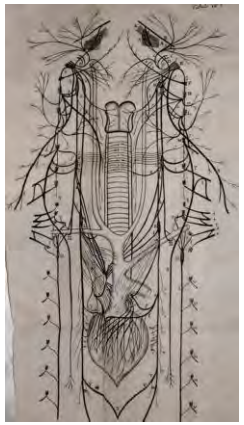
Major depression



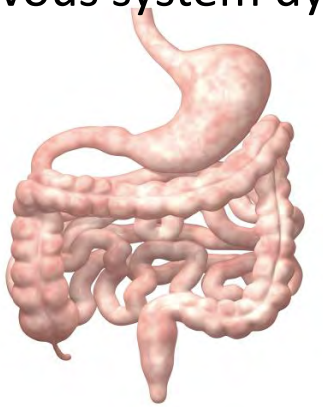
Stress Axis



Dysautonomia



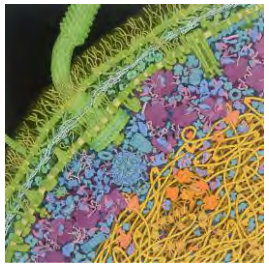
Functional bowel disorders
Enteric Nervous system dysfunction



Immune dysregulation



Microbiome Dysbiosis



E coli by David S. Goodsell

Of approximately 500 patients seen in the AMOS food mind body center:



- About 90 % have clinical evidence of abnormal GI function
- **About 85 % have depression by clinical examination**
- **About 3/4 have other autonomic issues**
- About half have hypermobile joints (EDS or spectrum)
- About 1/3 have clear evidence of autoimmunity
- About 2/3 have a family history of a related condition (GI/dysautonomia/autoimmune)
- Of those with clear autoimmunity we have given IVIG to about 30 patients with 10 “miracle” resolutions of nearly all their symptoms and 15 patients with significant benefit

An experiment which argues against a “functional” explanation



Irritation of the colon

IBS Model

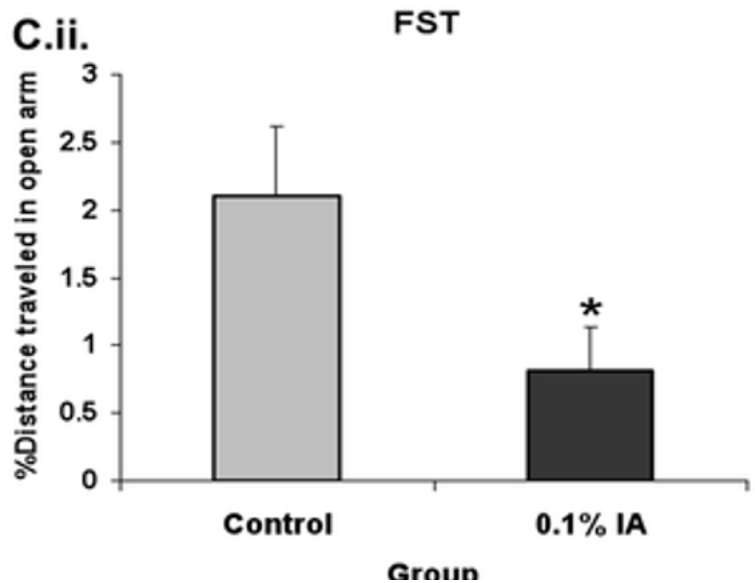
Increased visceral pain sensitivity (allodynia and hyperalgesia) and alternating diarrhea and constipation

Depression-like behaviors

Irritation of the colon
Cut the Vagus nerve

Elevated Plus Maze



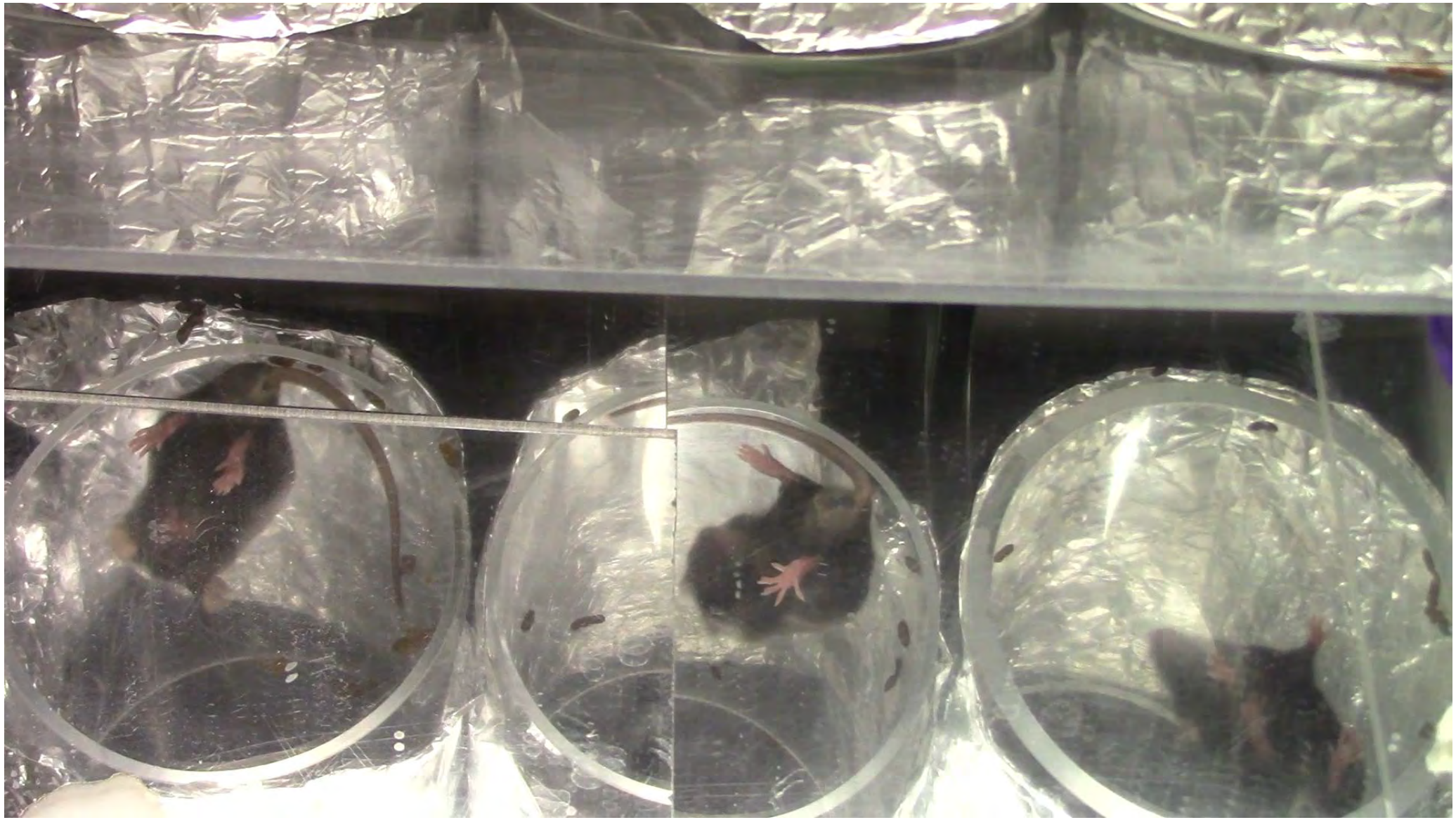


43 y.o. patient with anxiety and hyperhidrosis



Malcolm Brock

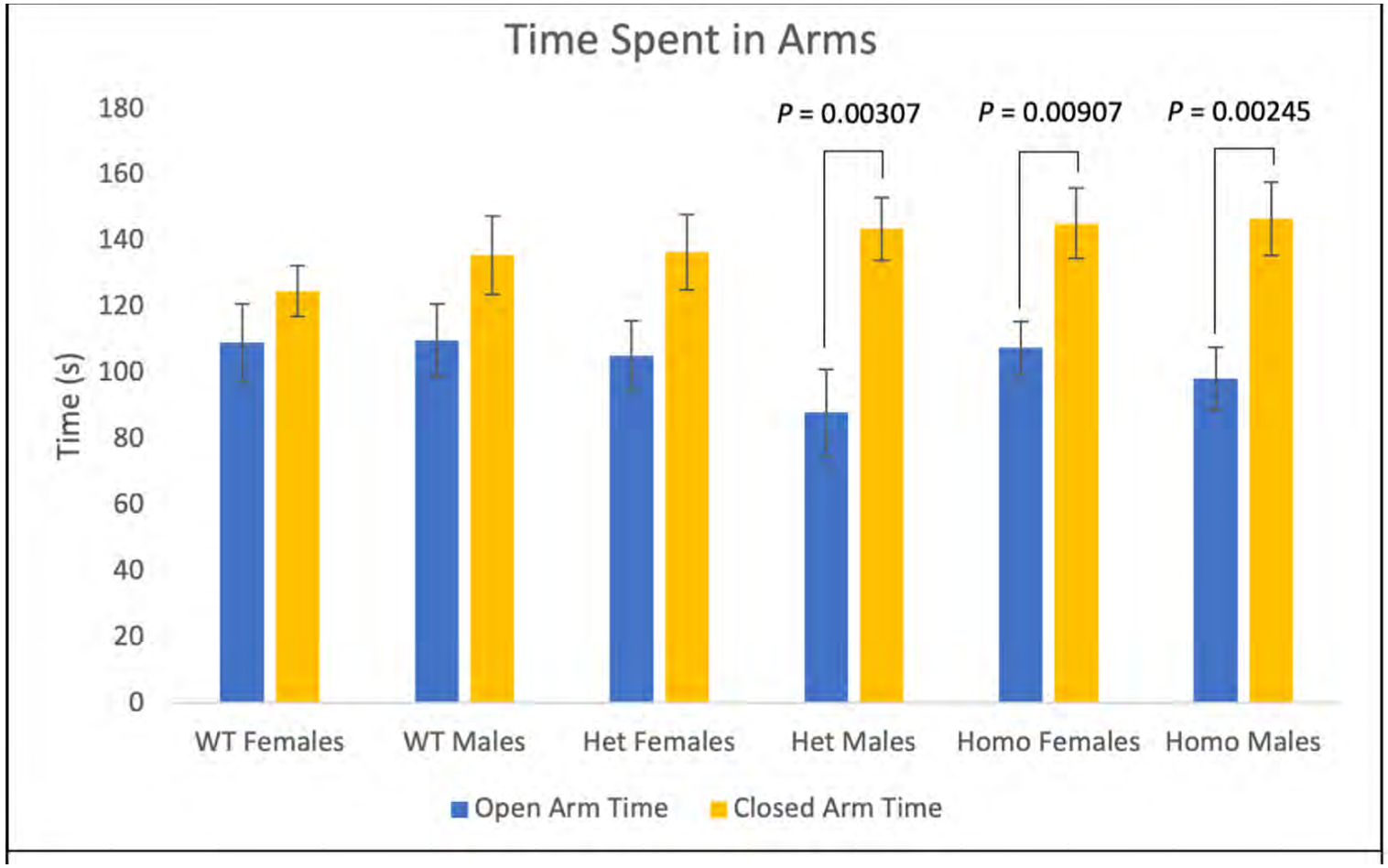
- On evaluation he had multiple autonomic dysfunctions
- On genetic testing he had a sodium channel ‘gain of function’ NAV 1.8 mutation
- Malcolm Brock et al. cloned the sodium channel gene into a mouse and made both heterozygous and homozygous mutants





Nav1.8 – Behavior - EPM







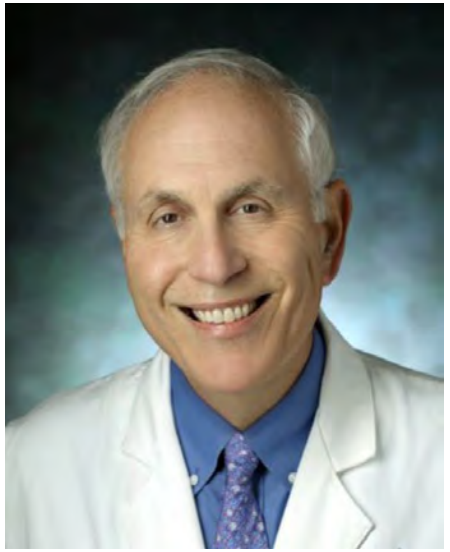
Study of Lyme Disease Immunology and Clinical Events Post Treatment Lyme Disease PTLD

- 234 Lyme patients (Erythema Migrans)
- 49 controls without Lyme disease.
- EM patients were treated with 21 days of doxycycline

- 14 % of treated Lyme patients developed symptoms of PTLD
- 4.1% of controls develop the symptoms associated with PTLD
- Risk of meeting PTLD criteria was also independently increased among females and those with higher exposure to prior traumatic life events



John Aucott



Jonathan Zenilman

***Aucott JN**, Yang T, Yoon I, Powell D, Geller SA, Rebman AW. Risk of post-treatment Lyme disease in patients with ideally-treated early Lyme disease: A prospective cohort study. Int J of Inf Dis, 2022 V116, p 230-237.*

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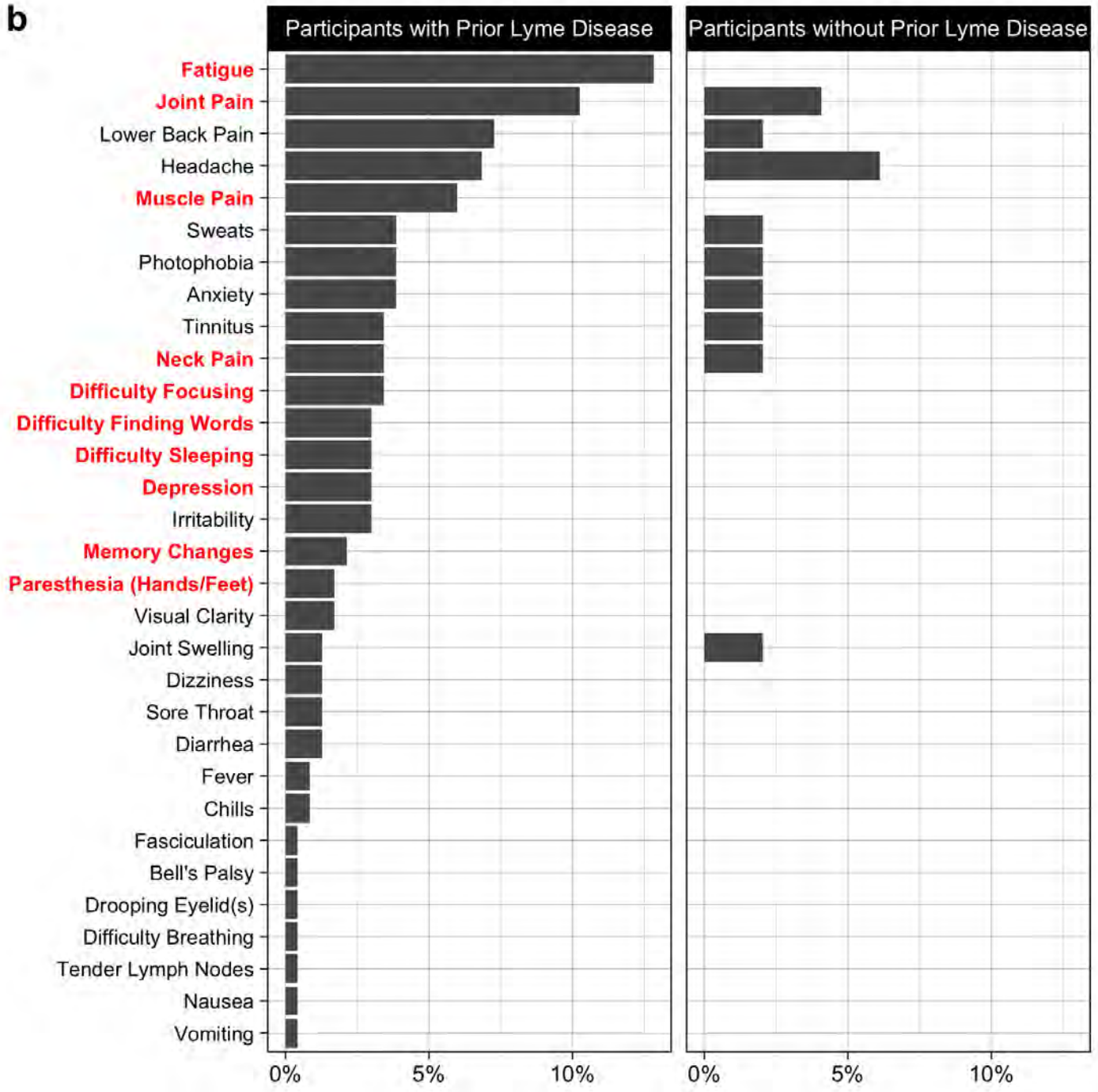
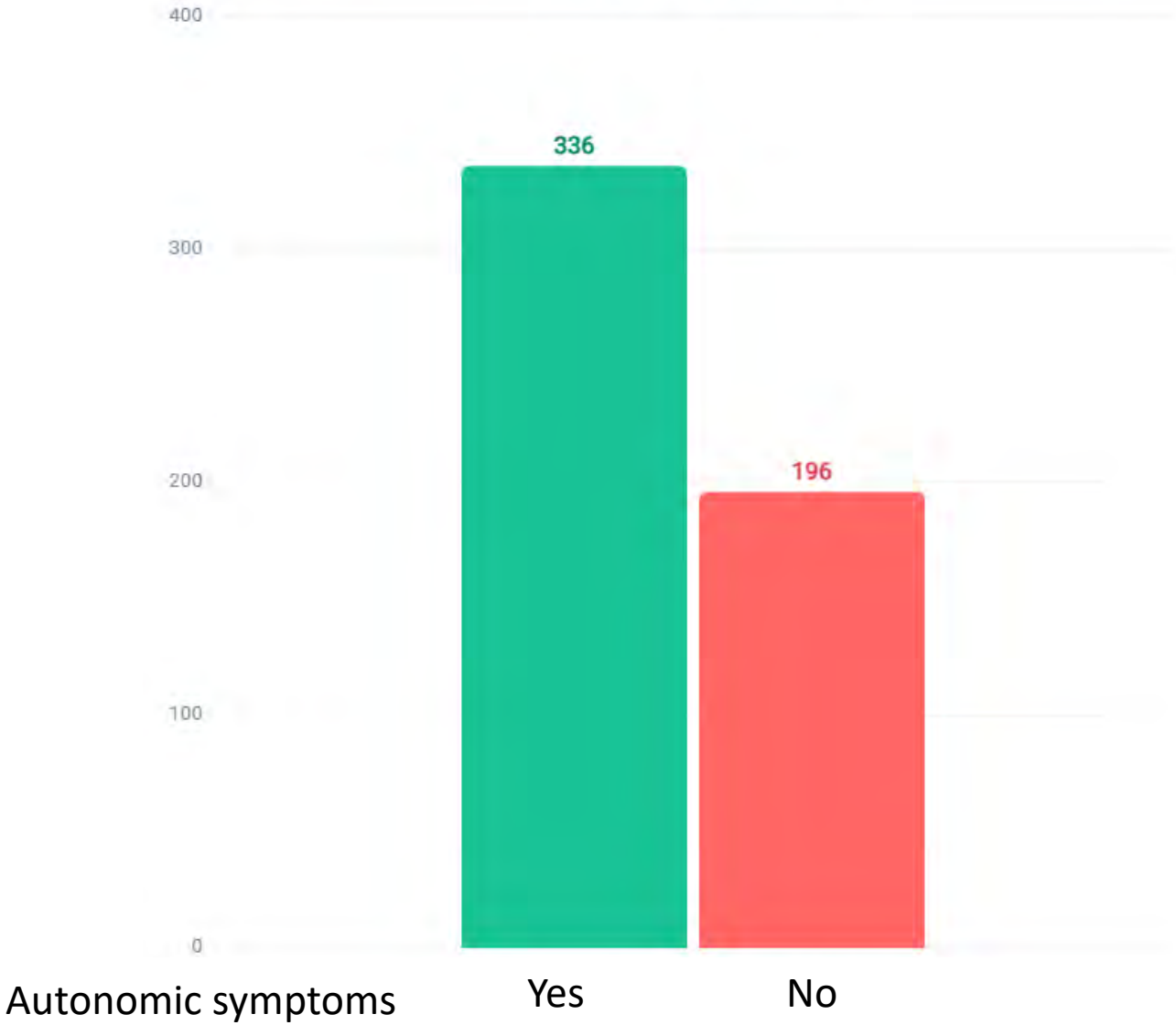




John Carey ENT
Superior canal dehiscence

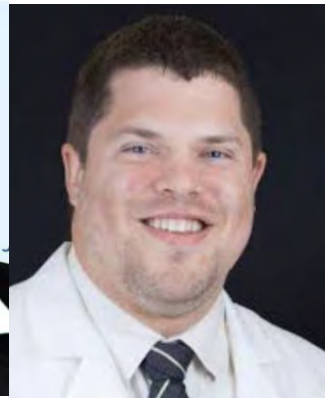
Patients with Superior Canal Dehiscence Syndrome
With and without other autonomic disturbances



There is a large network of collaborative clinicians working with dysautonomia patients



Britt Adler



John Miller

Autoimmune disease



Paul Auwaerter



Traci Speed



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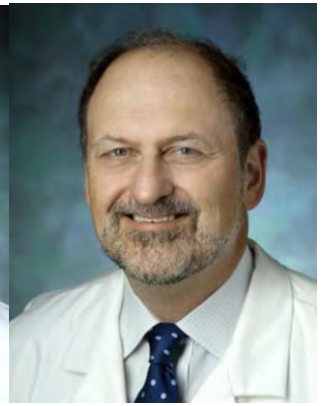


Bob Bulat

Chronic abdominal pain

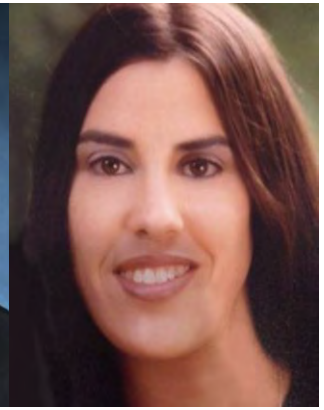


Tae Chung



Peter Rowe

POTS
Dysautonomia



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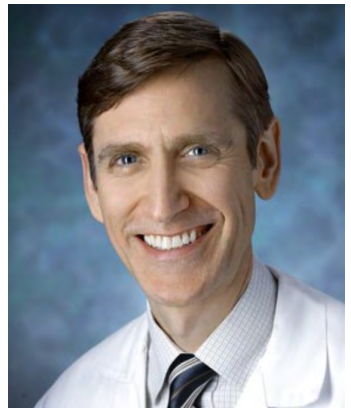


John Carey

Vestibular dysfunction

How do we unite these diverse symptoms in multiple systems?

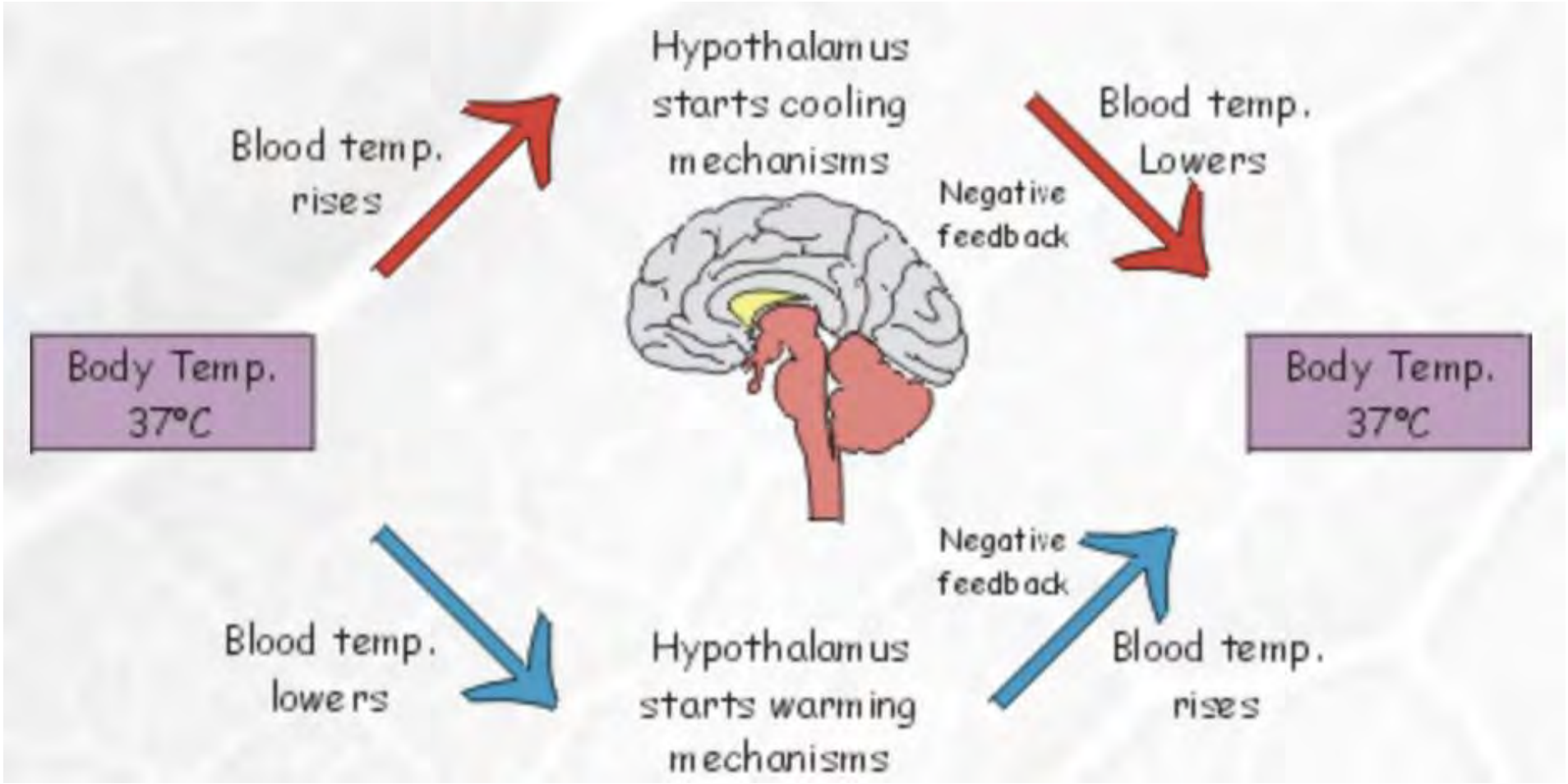
- Most of these symptoms can be manifestations of the autonomic nervous system dysregulation

- Some of the symptoms are manifestations of damaged nerves
- Some of the symptoms are manifestations of immune system dysregulation

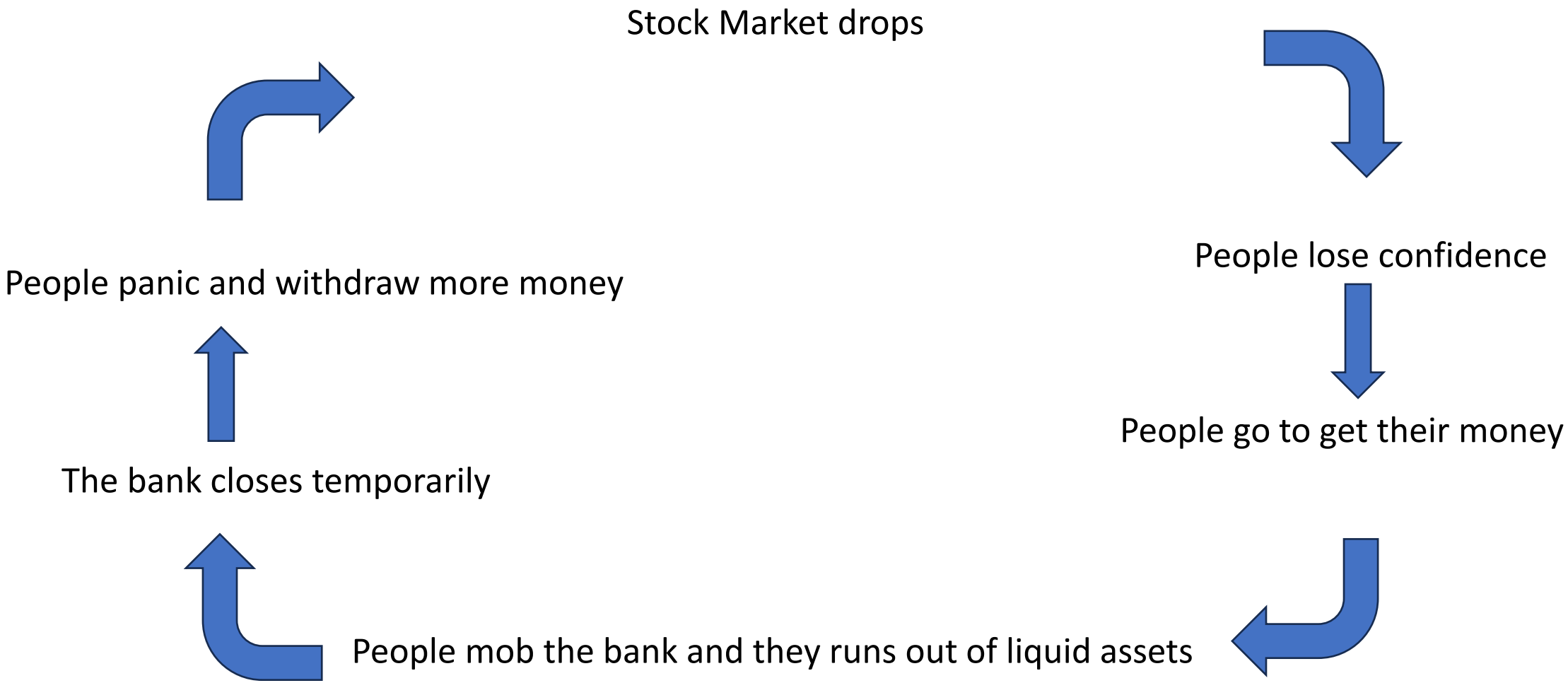
Homeostasis

- The balancing of body functions back to an optimal baseline
- The body adapts to changing circumstances- a lion is chasing you
- Your body adapts to fight or flight mode
- You escape the lion
- Your body must now return to the baseline state

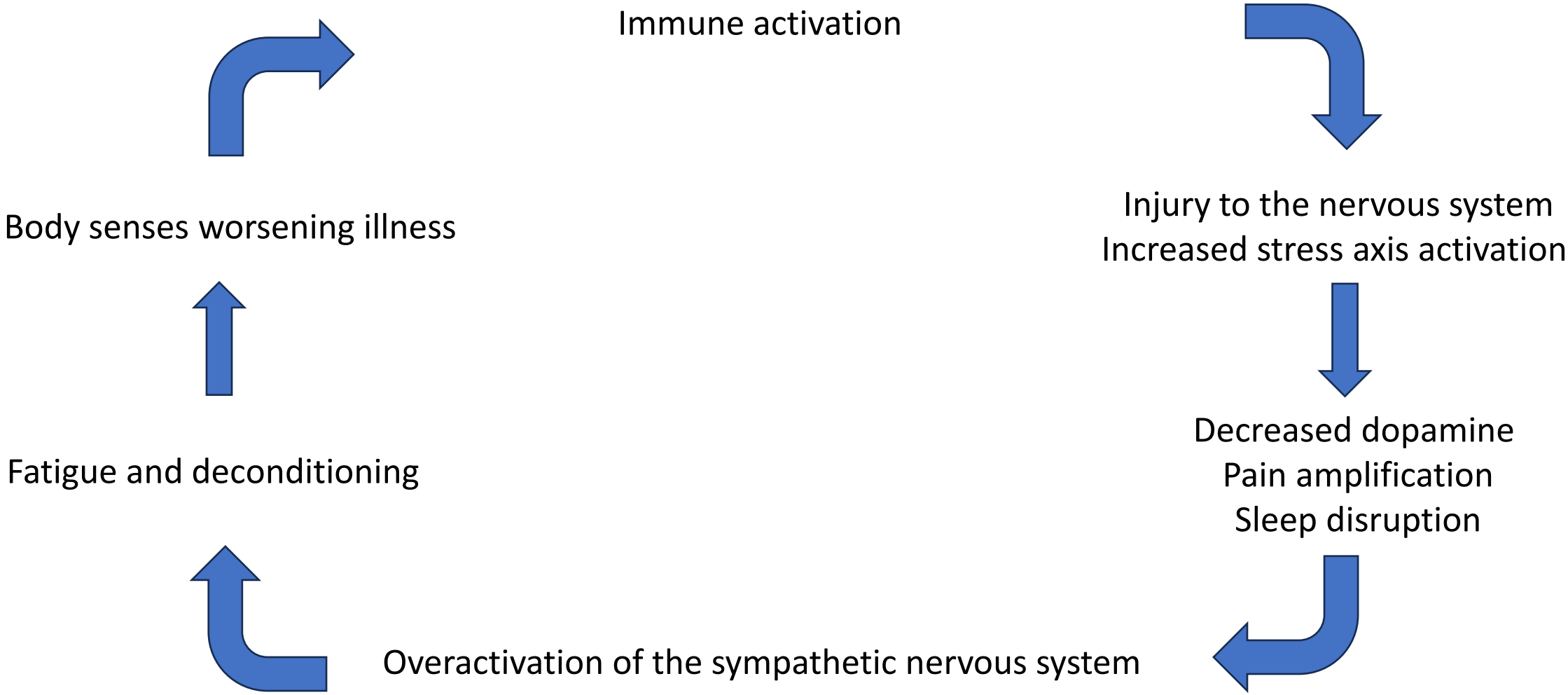
Negative Feedback maintains homeostasis



Positive Feedback causes a loss of homeostasis



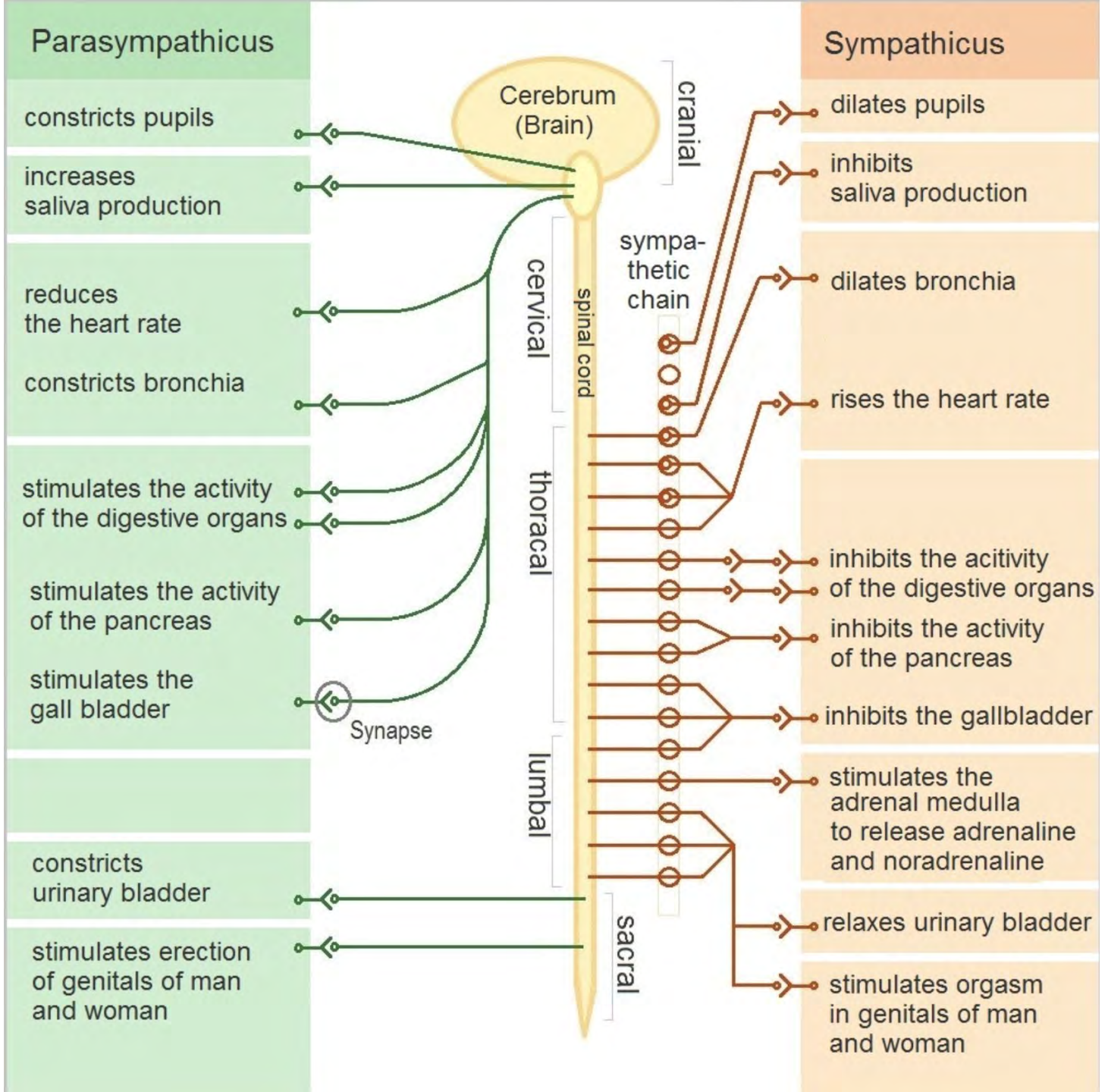
Hypothetical Positive Feedback loop in dysautonomia



Autonomic Nervous System

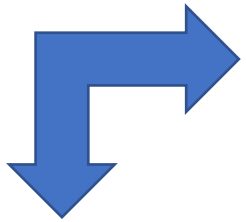
Sympathetic “fight or flight”

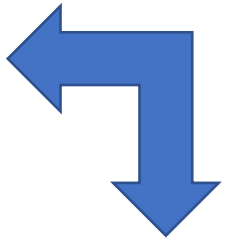
Parasympathetic-relax and digest



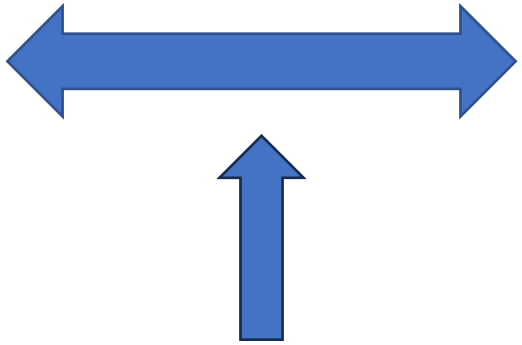
My fundamental hypothesis for this condition

Central Dopamine dysfunction
Stress axis activation





Autonomic dysfunction
Chronic sympathetic activation

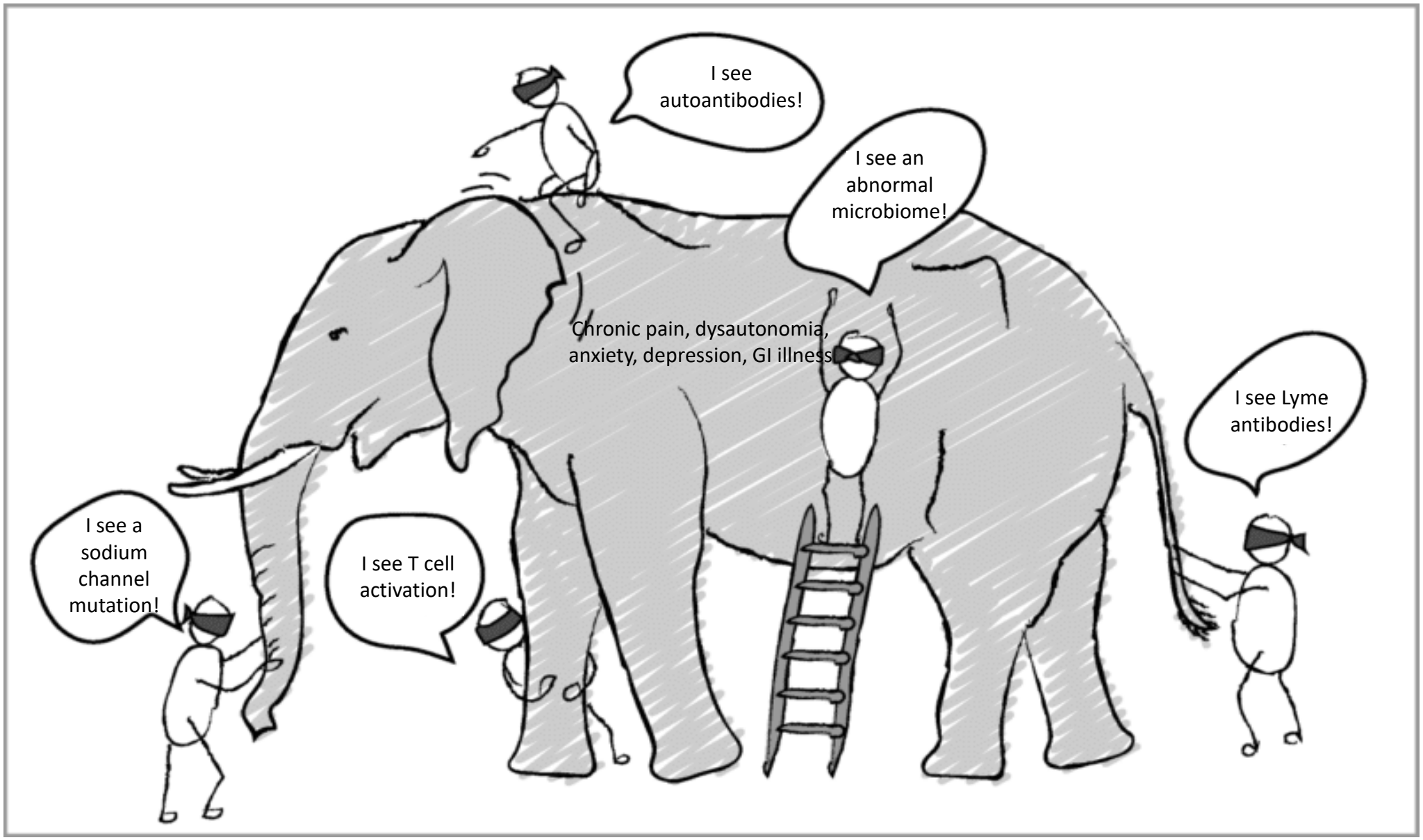


Chronic Immune Activation
Chronic Inflammation

Vulnerabilities
Abnormal sodium channels
Infection
Hypermobile joints

Dysautonomia-Key questions

- Who gets it?
  - Genetic and environmental vulnerabilities
- Why do they get it?
  - Precipitating causes
- What is the pathological mechanism for the syndrome?
  - Sodium channel mutations
  - Neuropathic injury
  - Immune dysregulation
  - Dysbiosis?
  - CNS stress axis and dopamine system?
- What are the factors that determine who gets what symptoms?



Slide courtesy of Susan Eshleman

Adapted from: https://ideascale.com/blog/breaking-down-silos-collaborative-innovation-in-large-organizations/

Rational Therapeutics

- All treatments have potential risks and benefits
- **All medical conditions have risks if not treated**
- **The goal of rational therapeutics is to provide the best possible risk/benefit ratio**
- **Clinicians make life and death decisions based on inadequate information**

What does treatment look like for the complex patient with multiple medical issues?

- Try to come up with a diagnostic formulation (hypothesis)
- Trial and error (Lots of errors-do the errors inform the formulation?)
- Ideally-a cure
- Rehabilitation (physical, social, psychological)
- Pharmacologically reduce of pathological process
- Behavioral Goals:
  - Function
  - Quality of life
  - Longevity

Therapeutic targets

- Improved neuronal ”signal to noise ratio”
  - Membrane stabilizers
  - Physical activation
- Down-regulate signaling amplifiers of
  - Decrease sympathetic activation
  - Treat depression
  - Diminish focus on noxious sensation (catastrophizing)
- Mitigate the nerve damaging process
  - Immunomodulators
  - Improve diet
  - Treat inflammatory provocation

Pharmacology for dysautonomia (and how I think they might work)

- Neuromodulators
  - Drugs that downregulate sympathetic tone (TCA's, SNRI's, Alpha 2 agonists, B-blockers, mirtazapine)
  - Drugs that decrease neuronal excitability (anticonvulsants, calcium channel blockers, antiarrhythmics)
  - Drugs that improve dopamine function (TCA's, SNRI's, mirtazapine, atypical neuroleptics)
  - Drugs that improve parasympathetic activity (cholinergic agonists, acetylcholinesterase inhibitors)
- Immunomodulators
  - Biologics
  - Immuno-inhibitors
  - Steroids
  - Non-steroidal anti-inflammatories

Symptomatic treatment for

Migraine
GI motility
Nausea
Orthostasis
Depression

Neuromodulators for neuropathic dysautonomia

Drug	NE reuptake	5HT reuptake	DA reuptake	Gastric emptying	Sleep	Constipation Dry mouth	Orthostasis	Membrane stabilizer	Cardiac	Weight	Pain
Nortriptyline	++++	++++	-	+/-	+++	++	+	Y	++	++	Y
Protriptyline	++++	++++	-	+	+/-	+	+	Y	++	+/-	Y
Doxepin	++++	++++	-	+/-	++++	+	++	Y	++	++	Y
Venlafaxine	++	++++	-	+++	-	-	-	N	N	-	Y
Duloxetine	++	++++	+/-	++	-	-	-	N	N	-	Y
Mirtazapine	-	-	-	?	++++	+/-	-	N	N	++++	Y
Sertraline	-	++++	-	+++	-	-	-	N	N	-	N

Neuromodulators for neuropathic dysautonomia

Drug	Mechanism	Probably helps with	Biggest issue
Lamotrigine	Membrane stabilizing	Autonomic neuropathy	Slow titration and rash
Topiramate	Unknown	Autonomic neuropathy	Cognitive impairment
Gabapentin	Voltage gated Ca channel α2δ Subunit	Autonomic neuropathy	Modest efficacy alone
Pregabalin	Voltage gated Ca channel α2δ Subunit	Autonomic neuropathy	Modest efficacy alone
Valproic acid	Membrane stabilizing	Autonomic neuropathy	Weight gain and toxicity
Carbamazepine	Membrane stabilizing	Autonomic neuropathy	Sedation
Verapamil	Calcium channel blocker	Unclear	Constipation decreased BP
Clonidine?	Alpha 2 adrenergic agonist	Sympathetic modulation	Orthostasis
Olanzapine	Unclear to me	Amplifying other drugs	Weight gain
Cannabinoids?			

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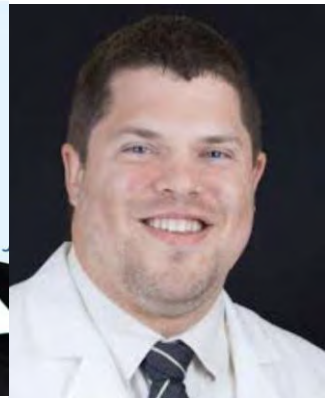

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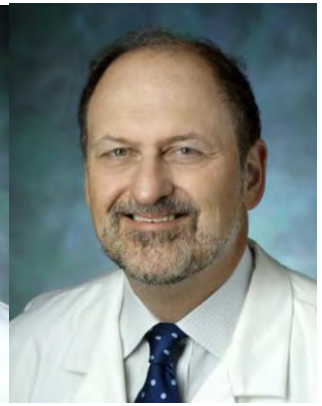

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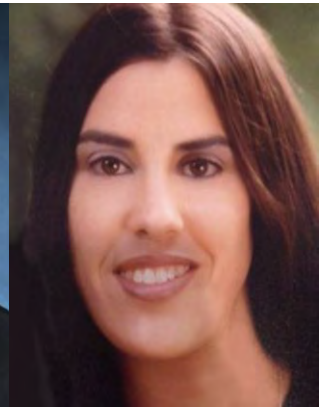

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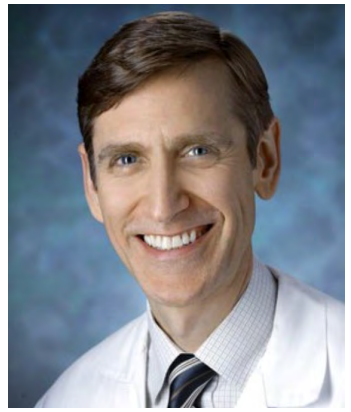


John Carey

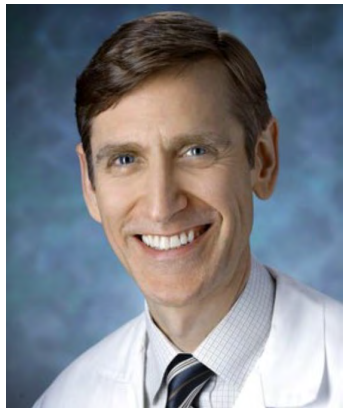
Vestibular dysfunction



John Aucott



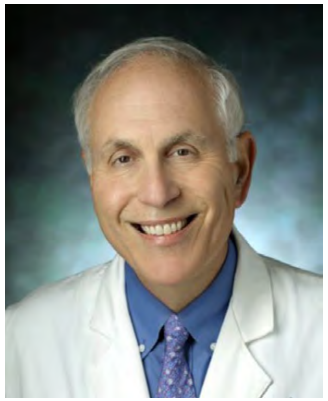
Susan Eshleman



John Carey



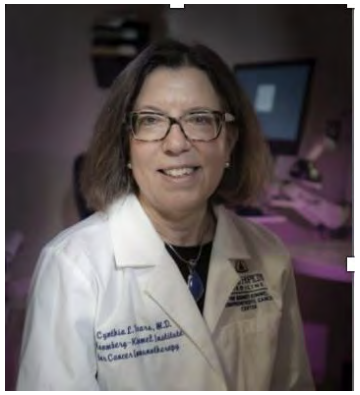
Malcolm Brock



Jonathan Zenilman



Traci Speed



Cindy Sears



Mahya Faghih



Frank Bosemans



Pegah Touradji



Cheryl Novak



Anna Moukouri Kouoh NP



Leah Young



Susan Joseph

Essential information for patients

- You have a real disease
- Your tissue is not being injured when you feel pain
- Depression is a disease
- Anti-depressants reduce pain and help your other symptoms even if you do not have depression (which you have)
- Physical activation will help improve the signal to noise ratio as much as the medicine

Conclusions

- Everything in the human body has an effect on everything else.
- The division between medical illness and psychiatric illness is an illusion.
- Medicine has created “silos” that are barriers to a holistic view.
- Patients who suffer (often for years) from these disorders need interdisciplinary clinics to effectively treat them

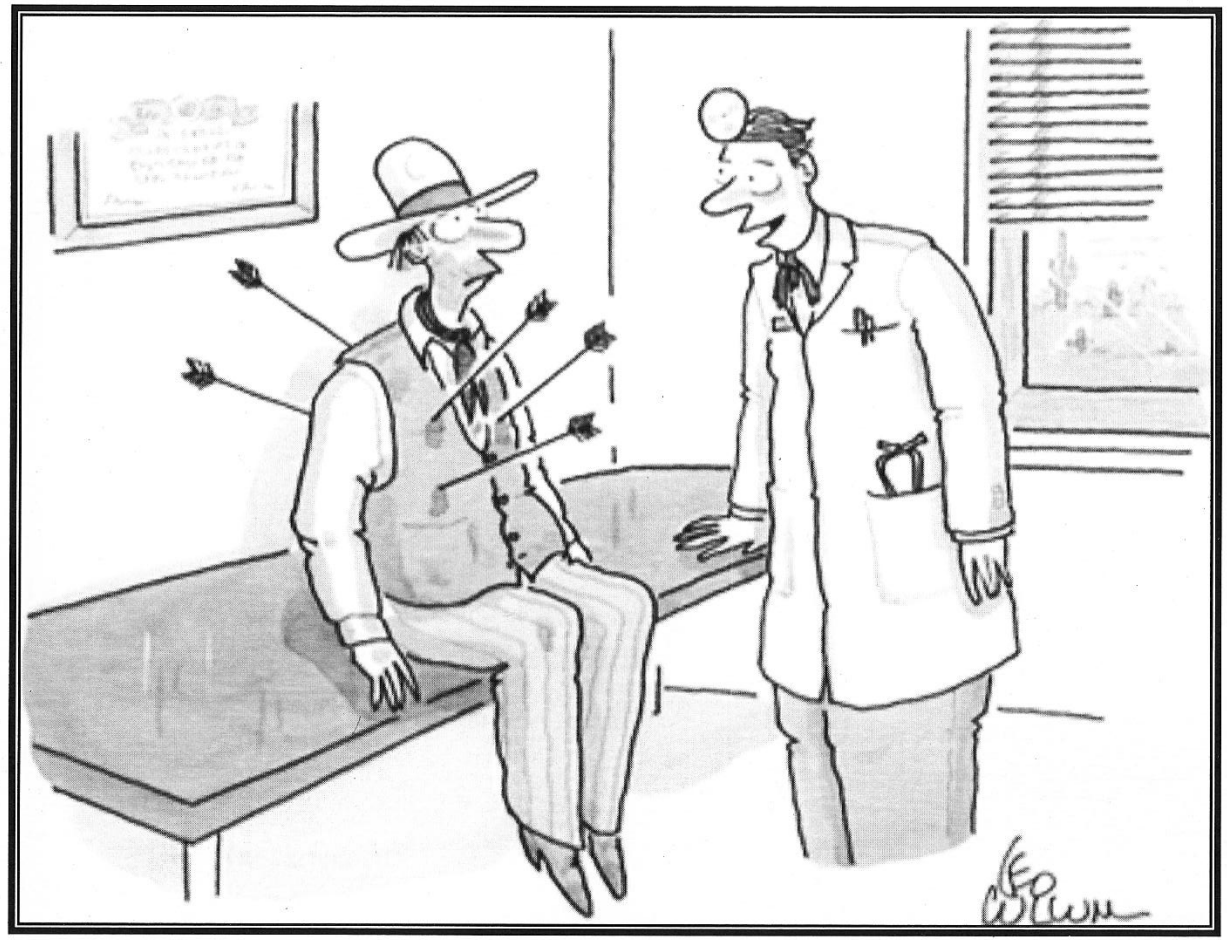
- **While many patients have psychiatric elements as part of their dysautonomia, these conditions are not “functional” and it is difficult to imagine the frustration patients experience when they are referred to psychiatry**

Be a therapeutic optimist

Never, never, never, never, never give up

- Winston Churchill

We already tried nothing and it didn’t help, let’s try something



Your insurance company only authorized me to take out one. You pick.