

AUTONOMIC PATHOLOGY, MECHANISMS & SYMPTOMS IN LONG COVID

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National Academy of Sciences, Engineering and Medicine



Stony Brook **Medicine**

DYSAUTONOMIA INTERNATIONAL



AWARENESS



ADVOCACY



ADVANCEMENT

DISCLOSURES

I have no conflicts/disclosures to report

MANY PATHOGENS KNOWN TO TRIGGER POST- INFECTIOUS DYSAUTONOMIA

PRIOR CORONAVIRUSES (SARS, MERS)

ENTEROVIRUS 71

HERPES VIRUSES

HIV

HTLV-1

INFLUENZA

TICK-BORNE ENCEPHALITIS VIRUS

RABIES VIRUS

WEST NILE VIRUS

ZIKA VIRUS

CAMPYLOBACTER JEJUNI

BORRELIA BURDORGFERI (LYME)

MYCOBACTERIUM LEPRO (LEPROSY)

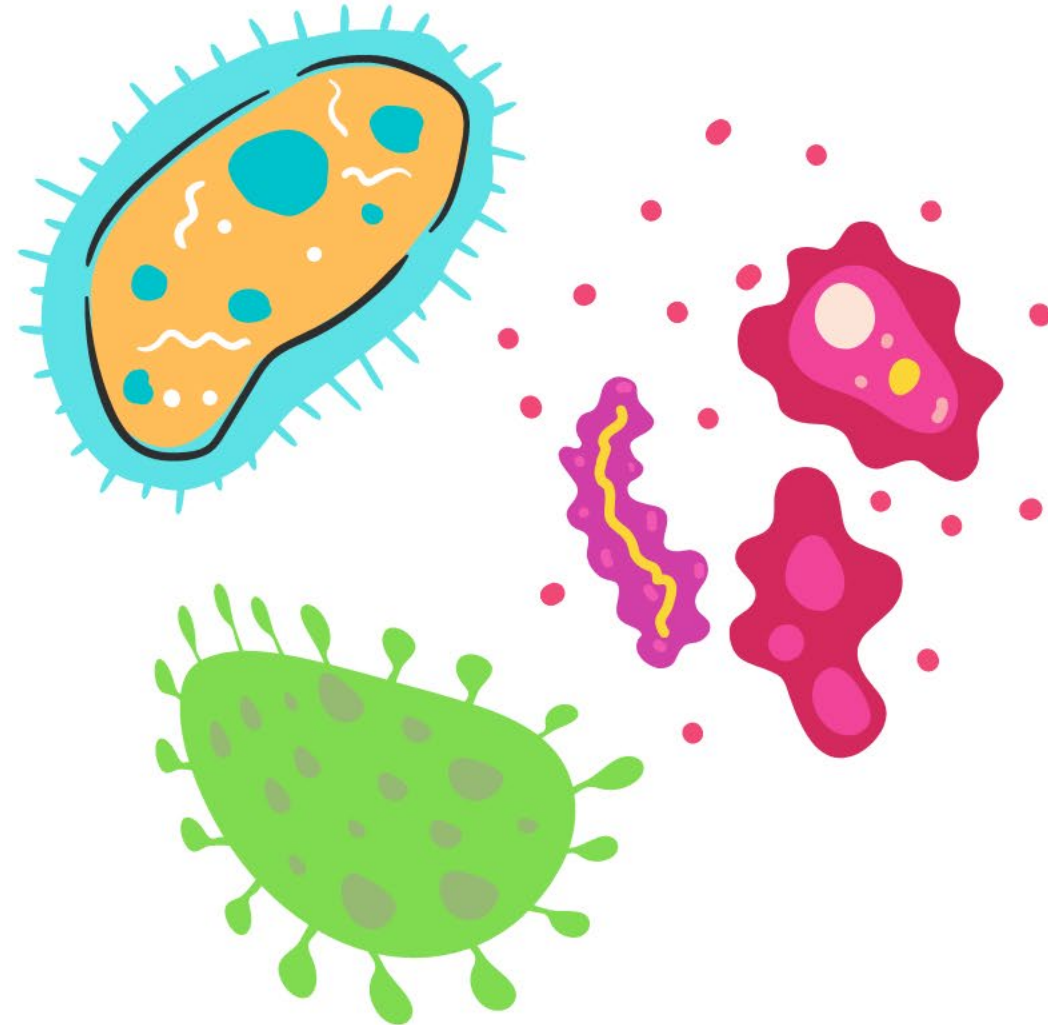
MYCOPLASMA PNEUMONIAE (WALKING PNEUMONIA)

CORYNBACTERIUM DIPHTHERIAE (DIPHTHERIA)

CLOSTRIDIUM TETANI (TETANUS)

CLOSTRIDIUM BOTULINUM (BOTULISM)

TRYPANOSOMA CRUZI (CHAGAS)



PATHOLOGY OF AUTONOMIC DYSFUNCTION IN LONG COVID

- **viral presence, replication & structural damage to autonomic ganglia (animal model)**¹
 - ganglionitis previously identified in POTS and ME/CFS autopsies²
- **viral infection of vagus nerve**³
- **autonomic small fiber neuropathy**⁴
 - phosphorylated alpha-synuclein⁵
- **GPCR autoantibodies (adrenergic, muscarinic, angiotensin, g-AChR)**⁶
 - same antibodies previously reported in POTS, OH, ME/CFS, Sjogren's and Chagas

1- Bertke, et al. Herpes simplex virus and SARS-CoV-2 infection of autonomic neurons. 320 Clin Auton Res (2022) 32:313–380.

2 - "Pathology of Chronic Fatigue Syndrome: Pilot Study of Four Autopsy Cases. DG O'Donovan, T Harrower, S Cader, LJ Findley, C Shepherd, A Chaudhuri. Presented at the International Science Symposium on ME/CFS, 2010, Bond University, Australia.

3 - Bulfamante, G., Bocci, T., Falleni, M. et al. Brainstem neuropathology in two cases of COVID-19: SARS-CoV-2 trafficking between brain and lung. J Neurol (2021). <https://doi.org/10.1007/s00415-021-10604-8>

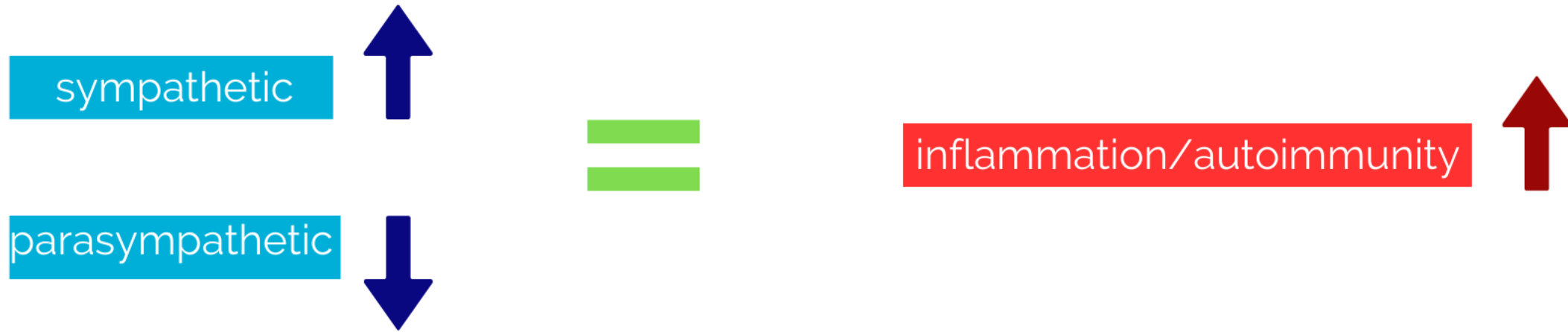
4 - Novak, et al. Network autonomic analysis of post-acute sequelae of COVID-19 and postural tachycardia syndrome. Neurol Sci. 2022 Dec;43(12):6627-6638.

5 - Miglis, et al. A case series of cutaneous phosphorylated α -synuclein in Long-COVID POTS. Clin Auton Res. 2022 Jun;32(3):209-212.

6 - Wallukat G, et al. Functional autoantibodies against G-protein coupled receptors in patients with persistent Long-COVID-19 symptoms. Journal of Translational Autoimmunity. 4 (2021) 100100.

DYSAUTONOMIA IS A MECHANISM, NOT A SYMPTOM

- autonomic modulation of immune function¹



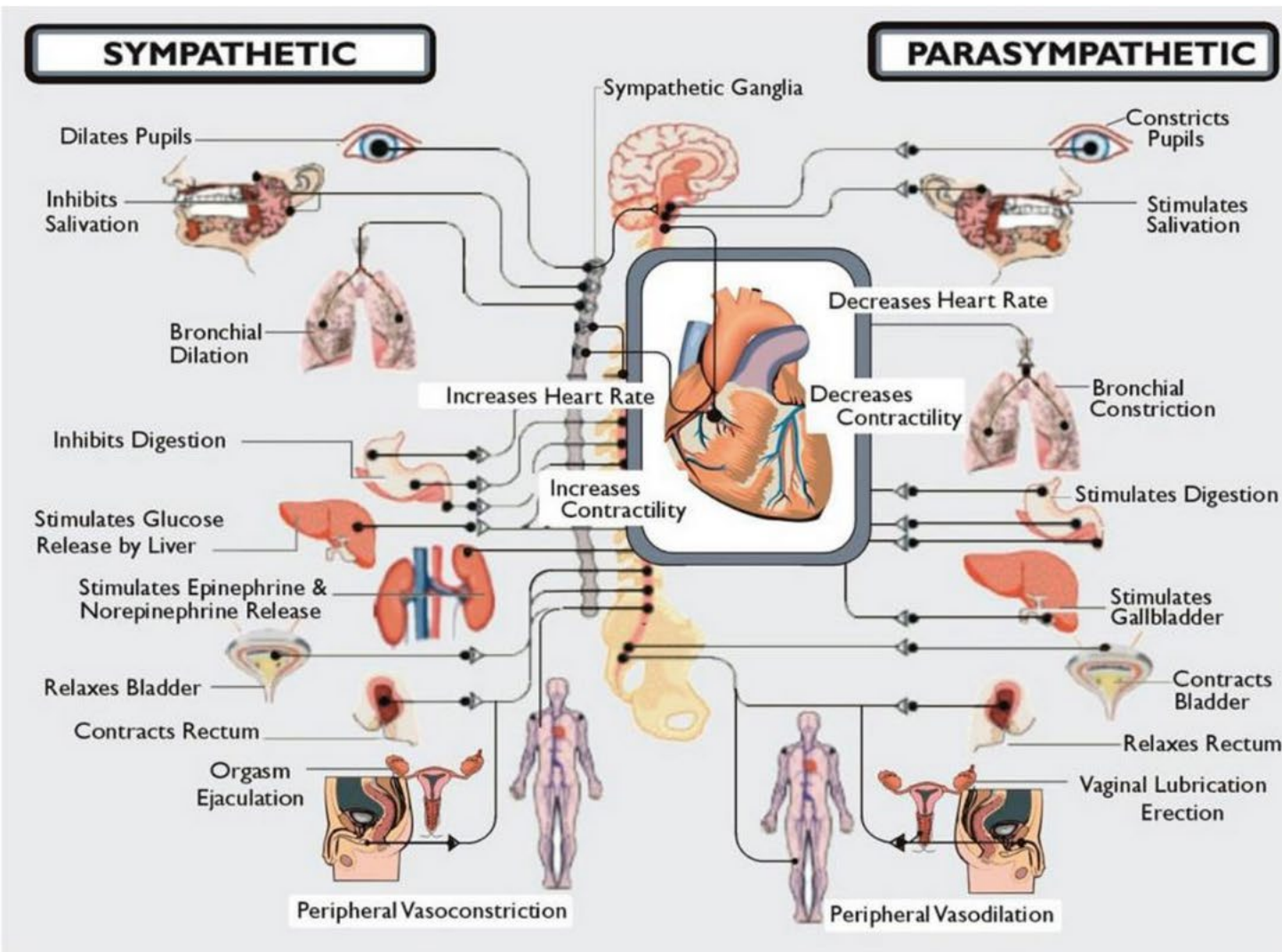
- autonomic modulation of coagulation²



1 - Pavlov, et al. The cholinergic anti-inflammatory pathway: a missing link in neuroimmunomodulation. Mol Med. 2003 May-Aug;9(5-8):125-34

2 - Preckel D, von Kanel R. Regulation of Hemostasis by the Sympathetic Nervous System: Any Contribution to Coronary Artery Disease? Heartdrug. 2004; 4(3): 123-130.

THE ANS REGULATES ALMOST EVERYTHING, THUS AUTONOMIC DYSFUNCTION CAUSES MANY SYMPTOMS



The ANS also regulates:

- immune function
- connective tissue synthesis & repair
- coagulation
- tear production
- saliva production
- all exocrine glands
- bone health
- hormone secretion
- pain sensitivity
- and much more

CHARACTERIZATION OF AUTONOMIC SYMPTOM BURDEN IN LONG COVID: A GLOBAL SURVEY OF 2,314 ADULTS

- **Composite Autonomic Symptom Score-31**

- **COMPASS-31 Autonomic Domains:**

- **orthostatic intolerance**
- **vasomotor**
- **secretomotor**
- **gastrointestinal**
- **bladder**
- **pupillomotor**

Variables	Test Confirmed Hospitalized (N=182)	Test Confirmed Non-hospitalized (N=1067)
Age	49,15.75 [39.25, 55]	43,17 [35, 52]
BMI	31.15,13.7 [24.53, 38.23]	26.62,9.66 [22.80, 32.46]
Sex M:F (%F)	31:151 (83%)	151:928 (87%)
Duration from symptom onset to survey completion	162,116 [91.75, 207.75]	133,137 [66, 203]
Total COMPASS-31 Score	28.95,30.98 [15.62, 46.60]	26.4,28.35 [13.75, 42.10]

67% of our Long COVID cohort had moderate to severe dysautonomia on COMPASS-31

GERMAN CLINICAL STUDY

- 42 patients with Long COVID who had persistent fatigue 6 months after mild infection
- 76% had COMPASS-31 scores suggesting moderate to severe dysautonomia

THE MOST COMMON LONG COVID SYMPTOMS ARE SYMPTOMS OF AUTONOMIC DYSFUNCTION

- RECOVER's first effort at a definition recently published in JAMA
 - Among participants with PASC, the most common symptoms were:
 - PEM (87%)
 - fatigue (85%)
 - brain fog (64%)
 - dizziness (62%)
 - GI (59%)
 - palpitations (57%)
- 
- these are all symptoms of dysautonomia

Figure S10.3. Proportion of individuals diagnosed with conditions by severity of mental fatigue.

- Johns Hopkins School of Public Health
- 7,926 US adults with long COVID
- online survey

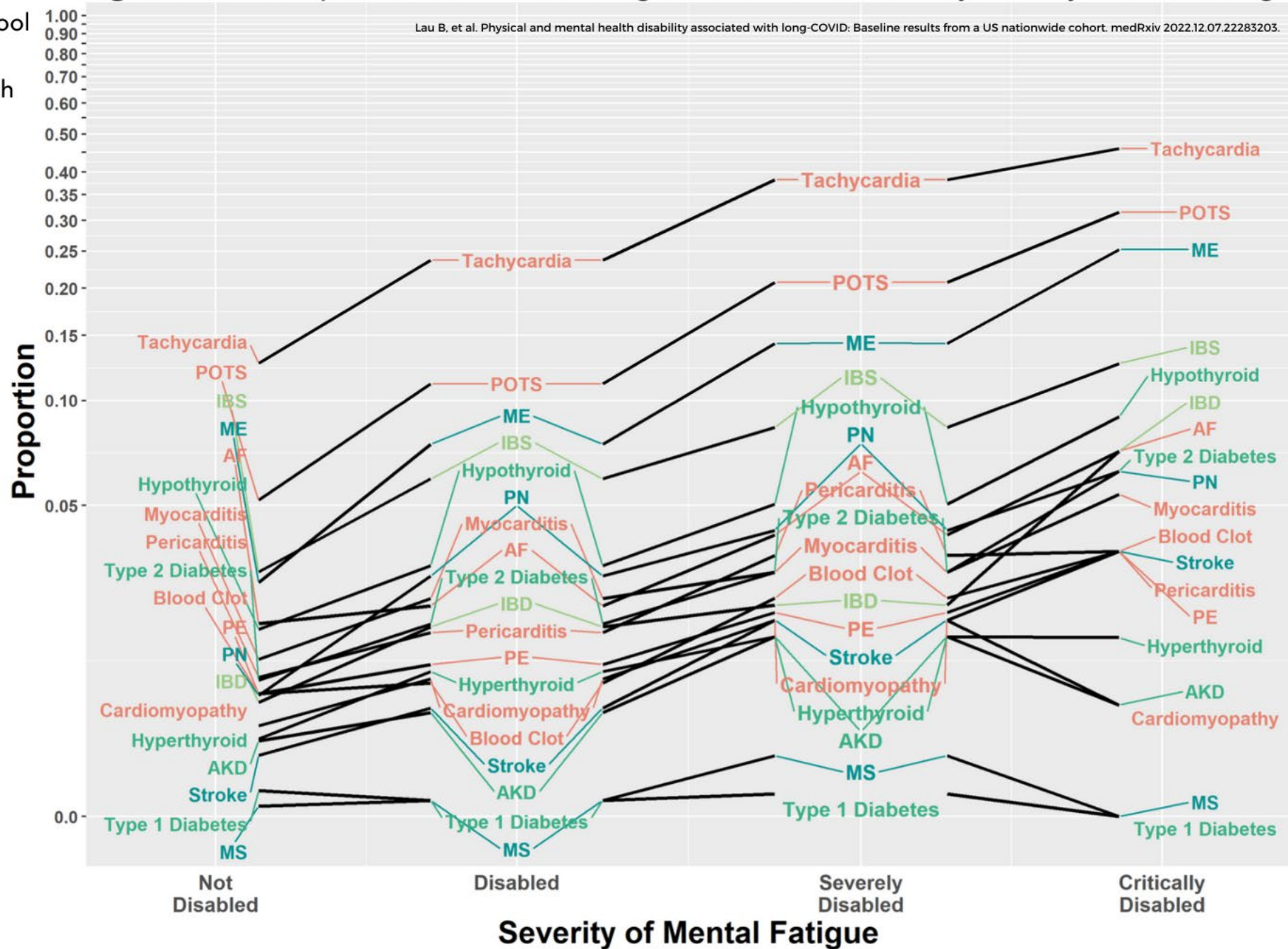


Figure S10.1. Proportion of individuals diagnosed with conditions by severity of mobility disability.

