TMD, (fatigue), and the autonomic nervous system

James Allison

Wellcome Trust Clinical Research Fellow; School of Dental sciences, Newcastle University, UK

Honorary Clinical Fellow in Oral Surgery; Newcastle upon Tyne Hospitals, UK


Newcastle
University

Newcastle University

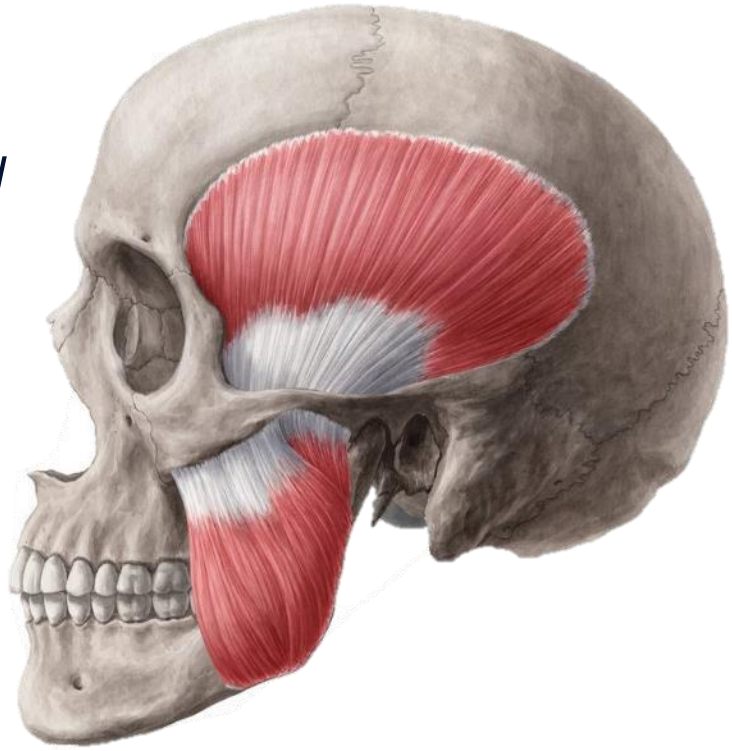
Temporomandibular disorders

"Group of related musculoskeletal conditions affecting the masticatory muscles, temporomandibular joint, and associated structures"[1]

Myogenous

Arthrogenous

Headache



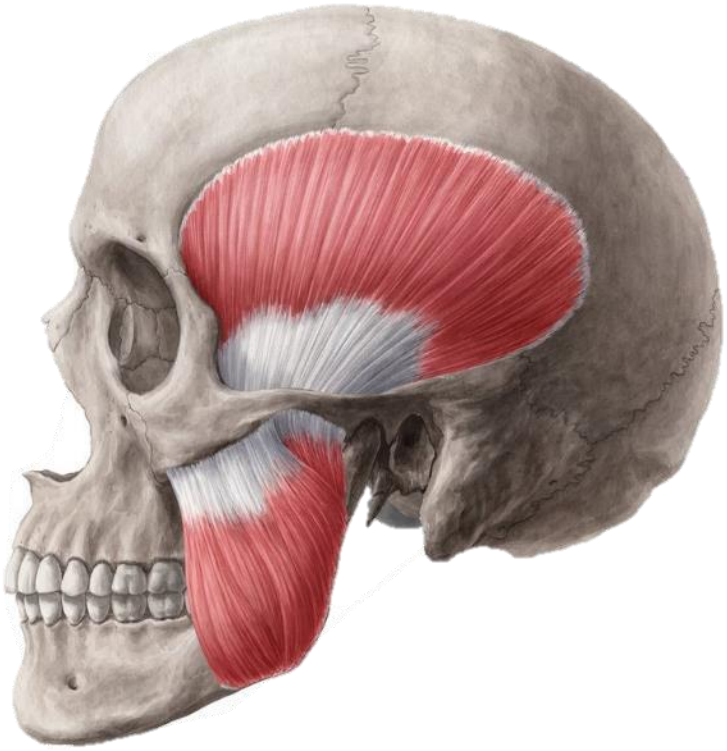
1: Schiffman *et al.*. 2014

Temporomandibular disorders

Pain and dysfunction

Other symptoms

Other conditions



1) A common aetiology?

2) Predictive of TMD incidence?

3) Prognostic value?

4) Therapeutic value?

Fatigue

"Extreme and persistent tiredness, weakness, or exhaustion of mental and/or physical origin that is not relieved by rest"[1]

May be a symptom of dysfunction of the autonomic nervous system

1: Dittner *et al.* **The assessment of fatigue: a practical guide for clinicians and researchers**. *J Psychosom Res.* 2004; 56: 157-170

Fatigue in TMD

Symptoms of fatigue are common in TMD patients.[1]

Not necessarily related to sleep disturbance, quantity, or daytime sleepiness.

May emerge as somatic symptom of depression and somatisation.

1: de Leeuw *et al.* **Fatigue and fatigue-related symptoms in an orofacial pain population.** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2005;99:168-74

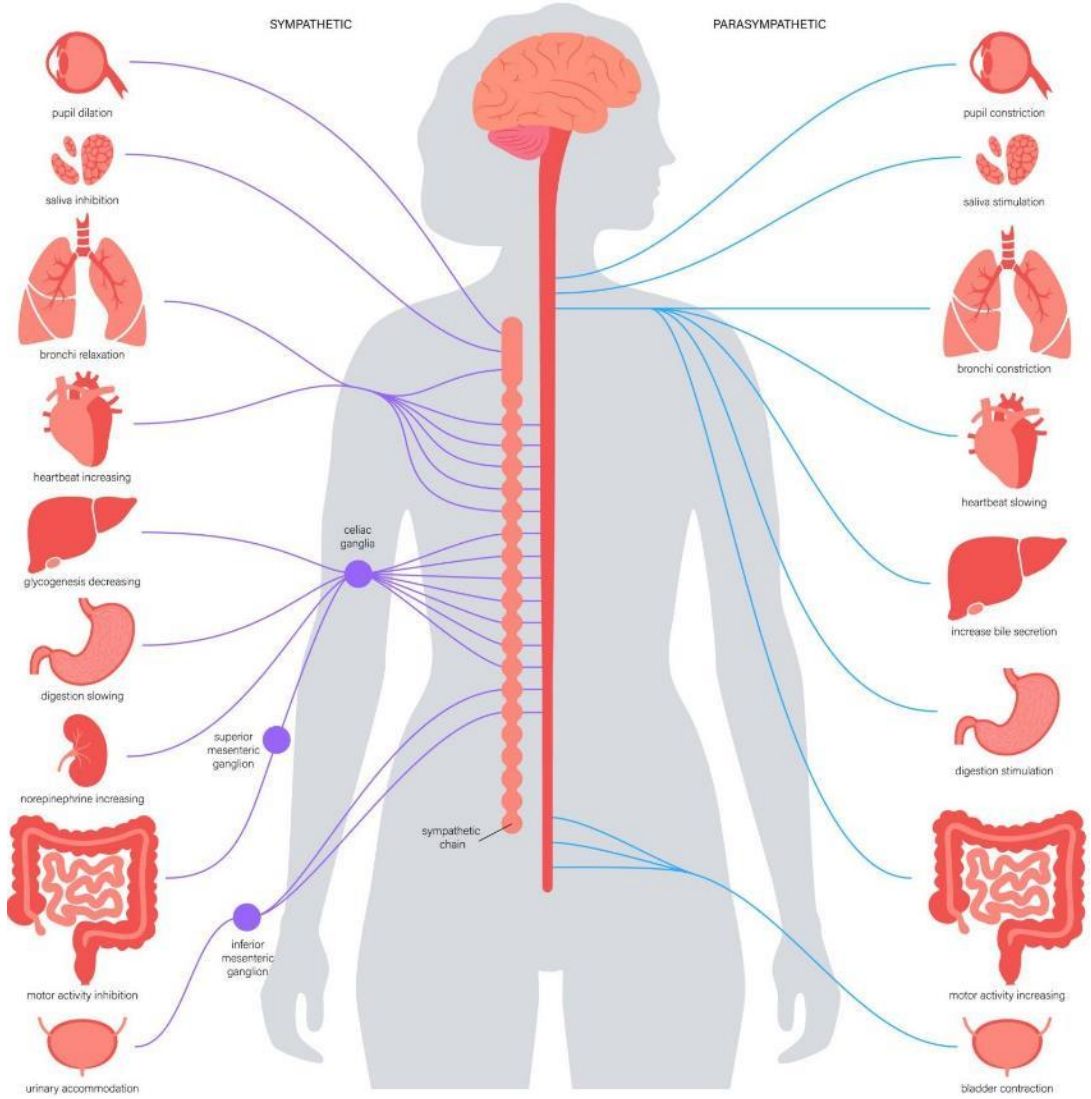
The autonomic nervous system (ANS)

Newcastle University

From Newcastle. For the world.

The ANS constantly receives information, integrates it, and produces outputs

Its function is **homeostasis**



Credit: simplypsychology.org

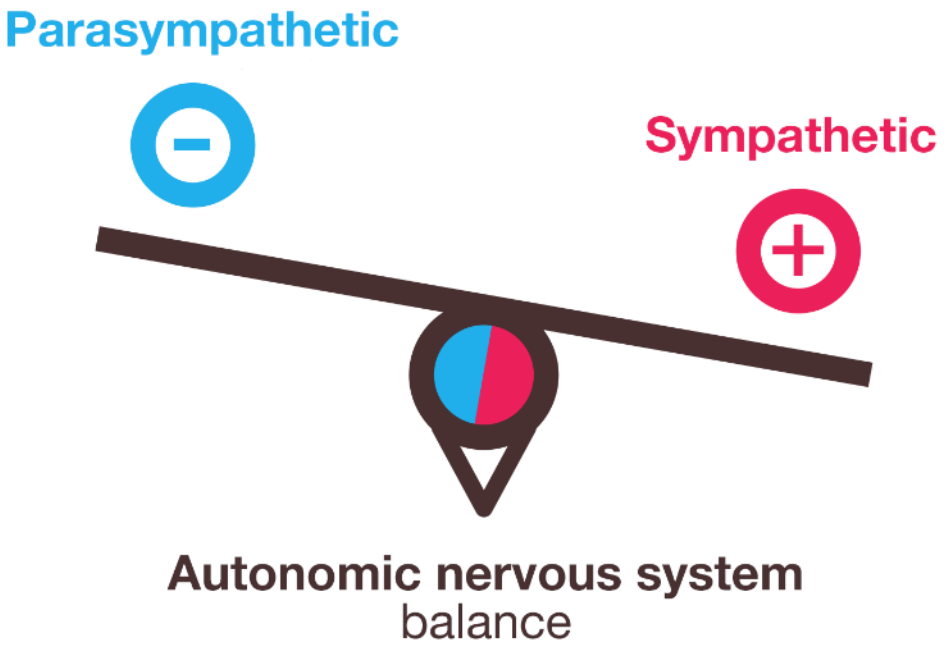
The autonomic nervous system

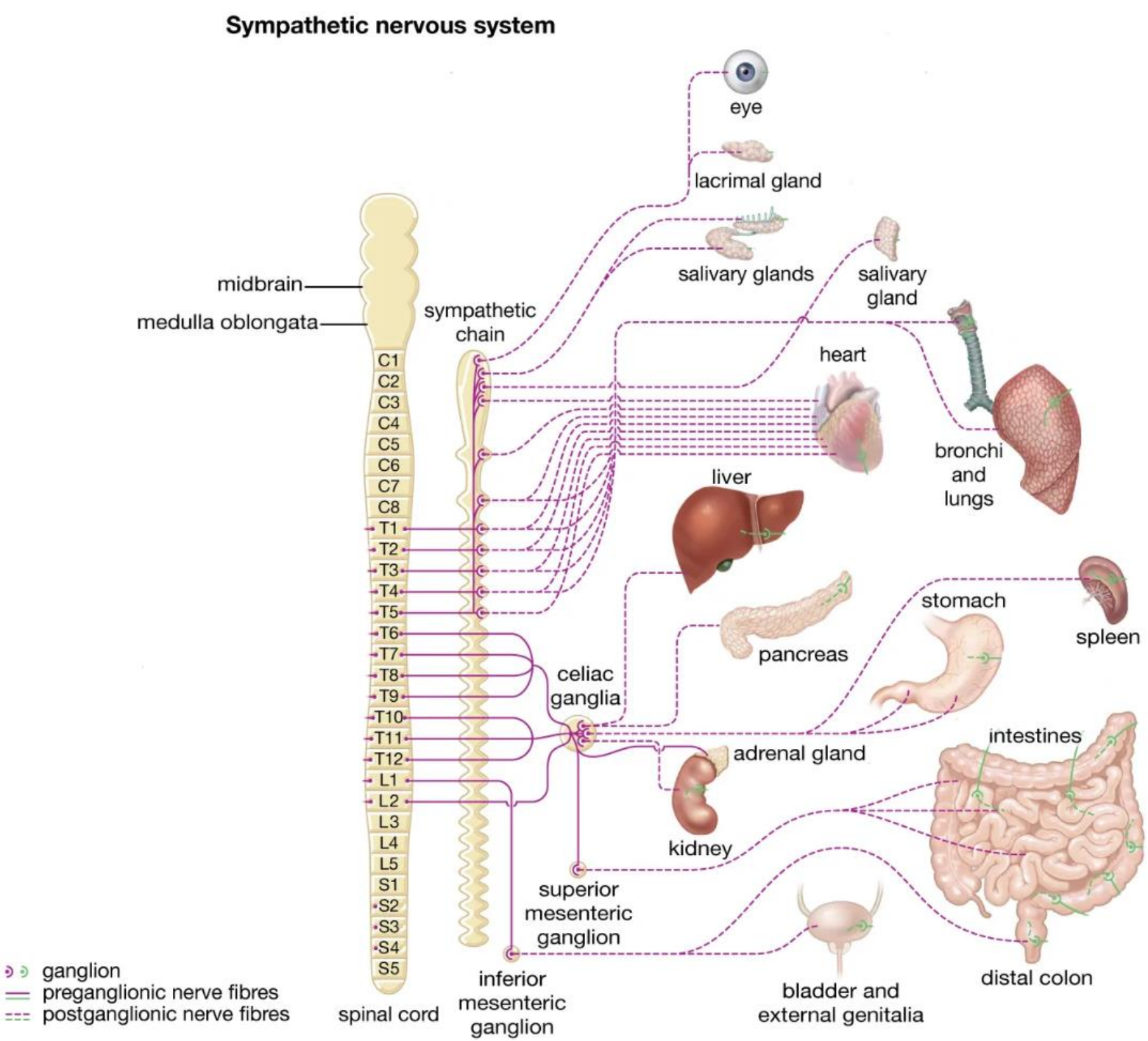
Sympathetic

Parasympathetic

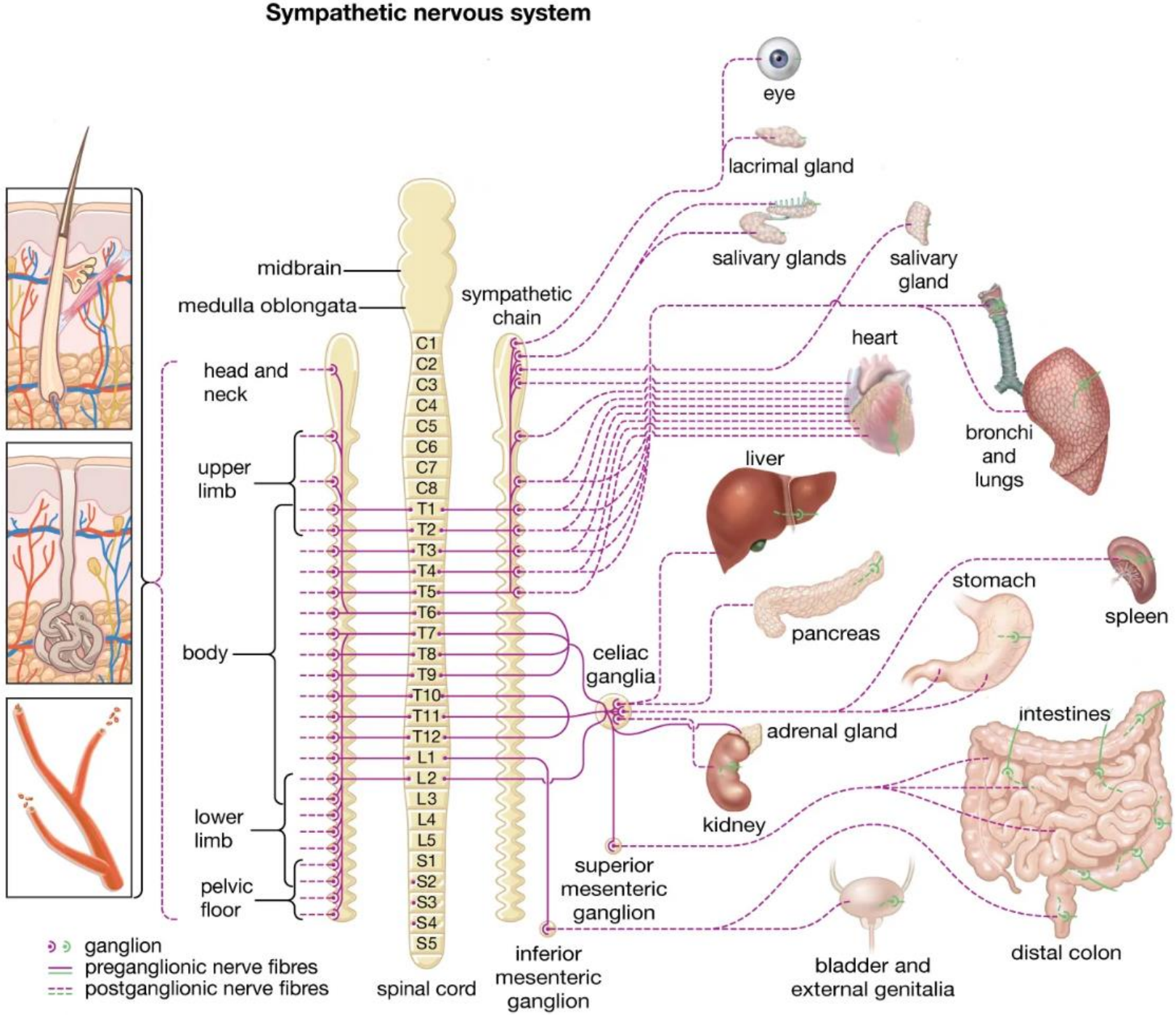
(Enteric nervous system)

The autonomic nervous system

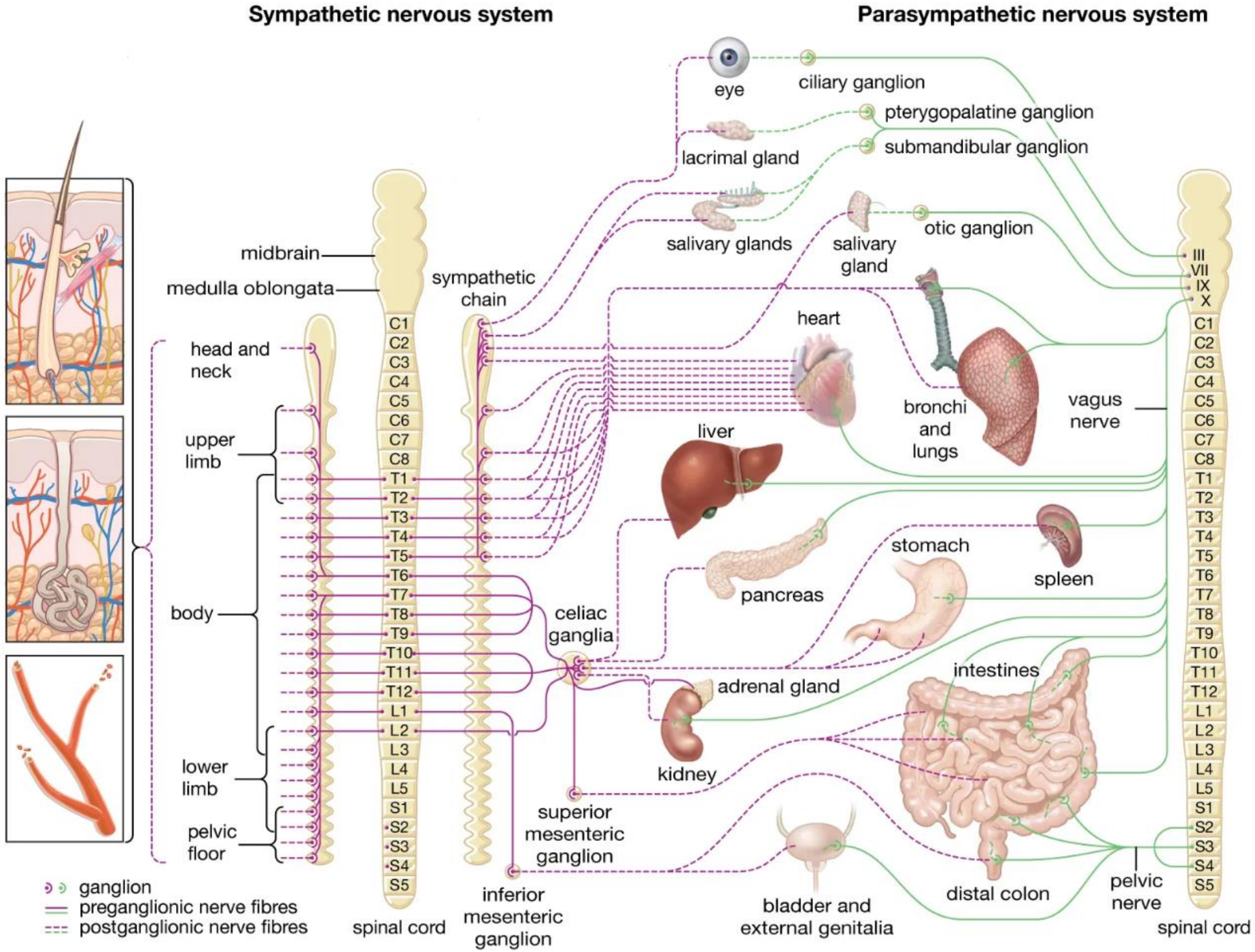




Credit: Encyclopaedia Britannica

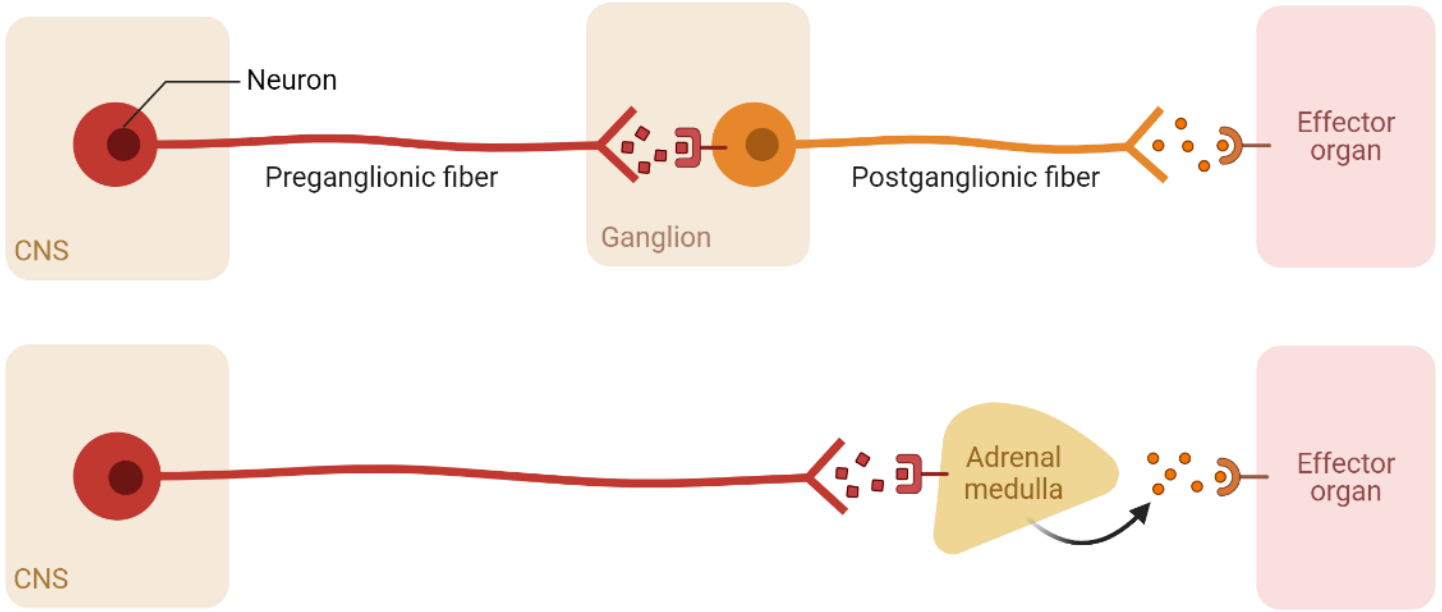


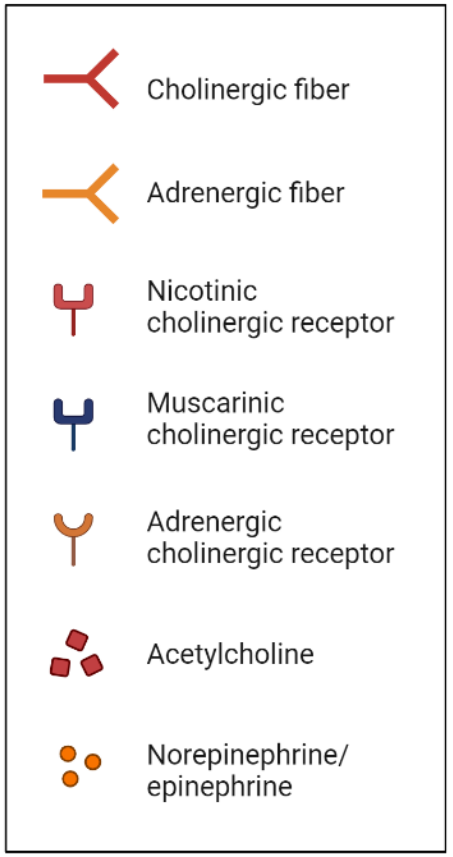
Credit: Encyclopaedia Britannica



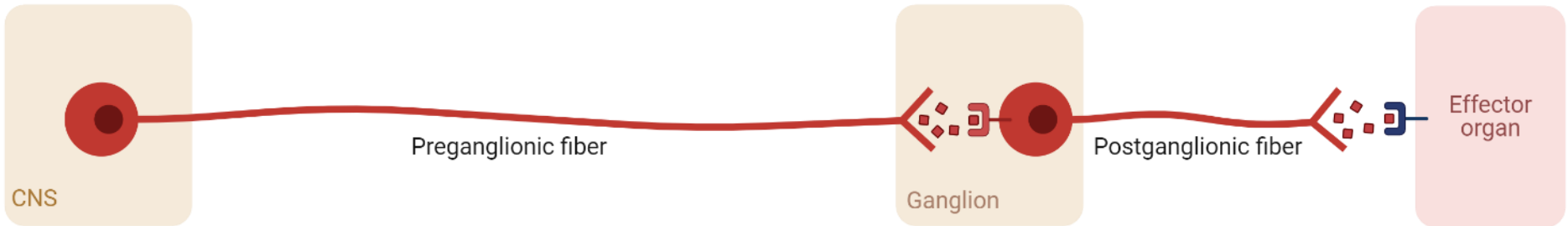
Credit: Encyclopaedia Britannica

Sympathetic nervous system



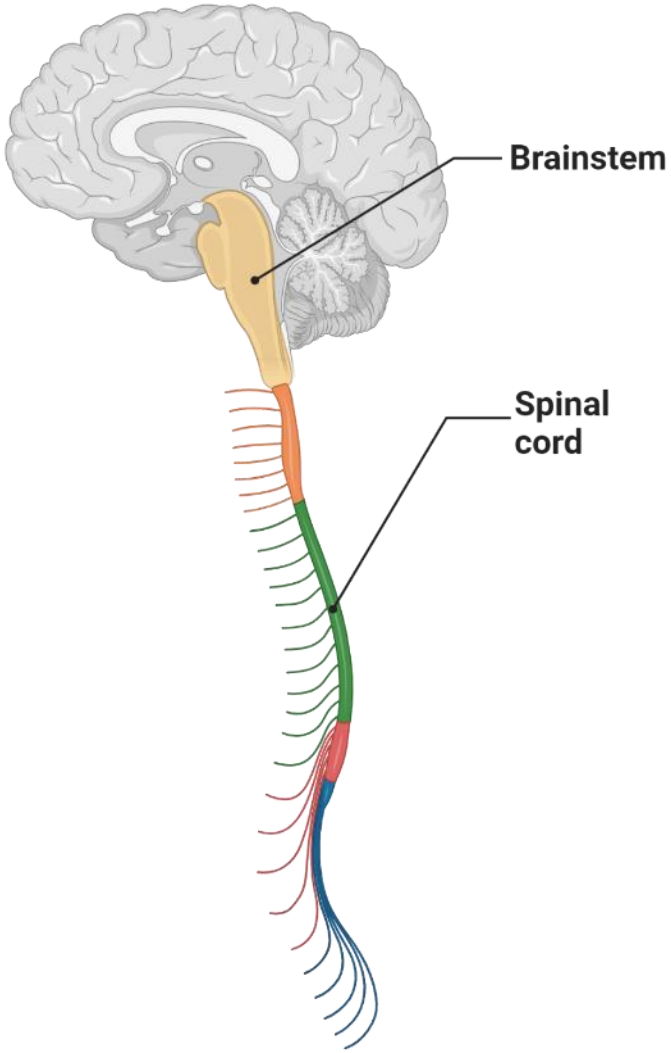


Parasympathetic nervous system



Central pathways of the ANS

Reflexes arcs exist in the **spinal cord** and **brainstem**

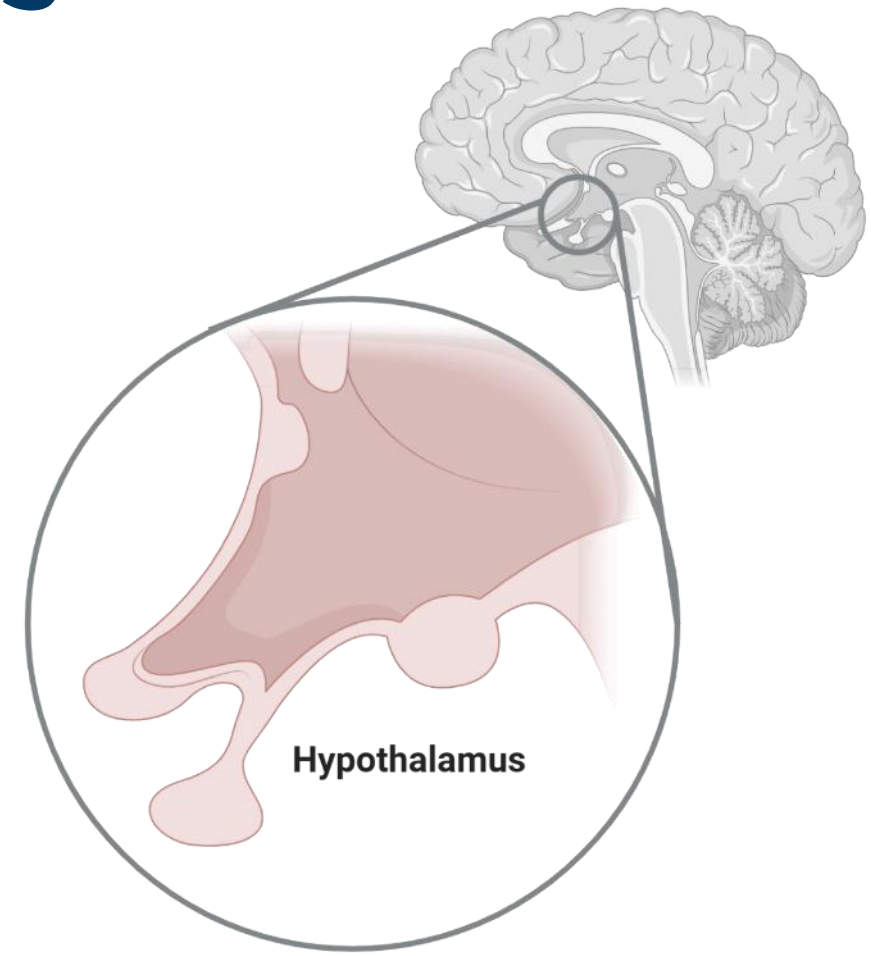


Created with BioRender.com

Central pathways of the ANS

Hypothalamus provides the

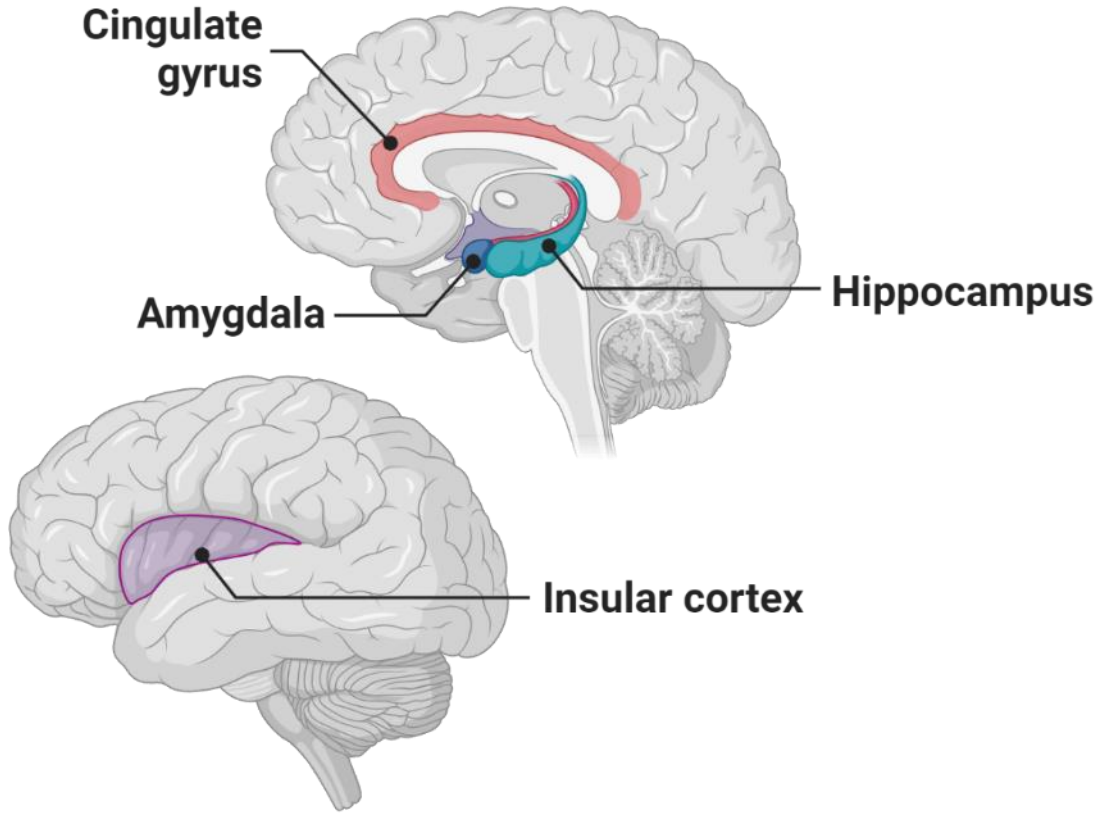
homeostatic nature of the ANS



Created with BioRender.com

Central pathways of the ANS

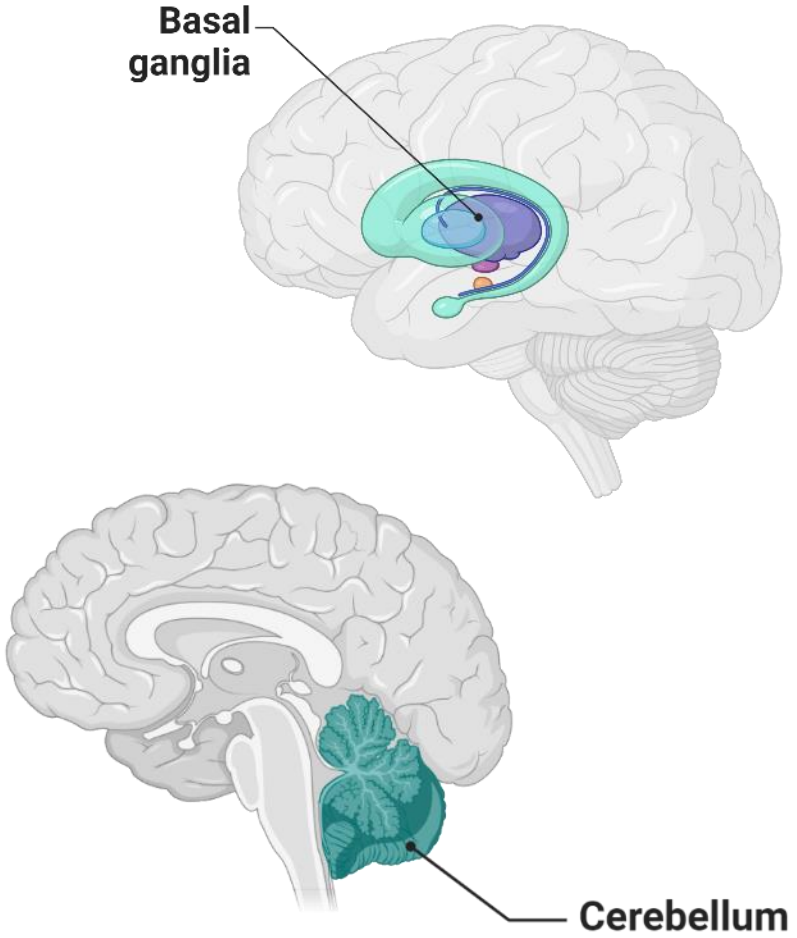
The **limbic system** adds **emotional** and **social significance**



Created with BioRender.com

Central pathways of the ANS

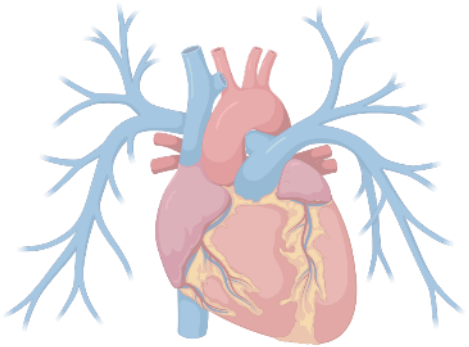
Cerebellum and **basal ganglia** are involved in **coordination** and **initiation** autonomic functions

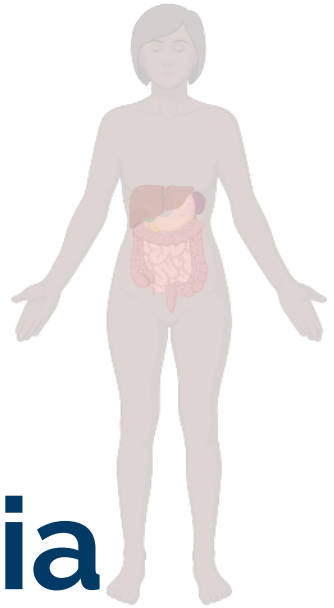


Created with BioRender.com

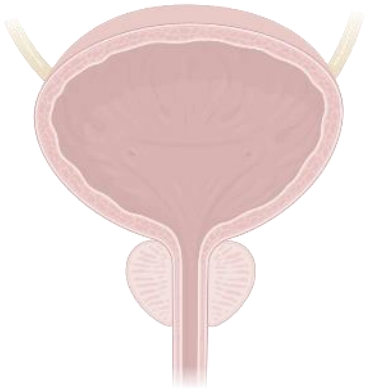

YOU CAN FIGHT..
ME UM FLIGHT!..

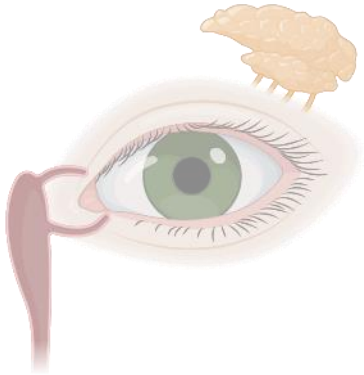

IBM
Blue Gene/P

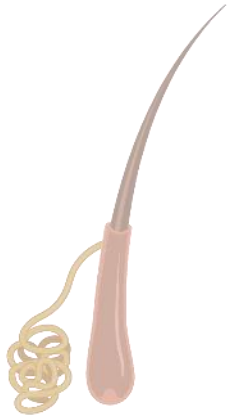




Dysautonomia







Cardiovascular

Orthostatic intolerance

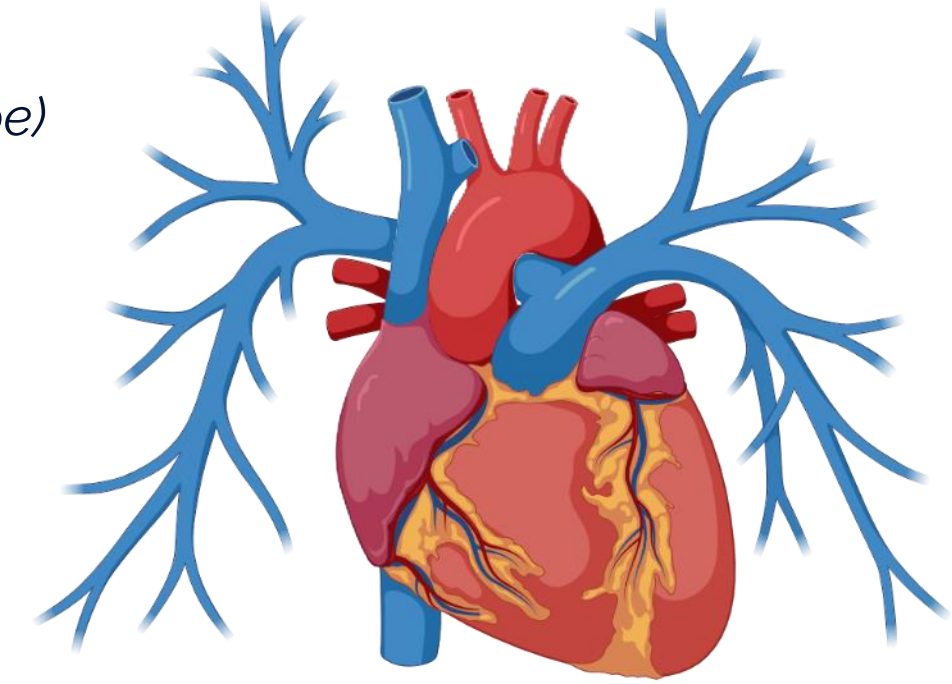
(Orthostatic hypotension/ POTS/ neurally-mediated syncope)

Tachycardia/ palpitations

Chest discomfort

Shortness of breath

Blood pooling in extremities



Central nervous system

Fatigue

Cognitive impairment (“brain fog”)

Anxiety

Dizziness

Insomnia

Vertigo

Weakness

Gastrointestinal

Nausea

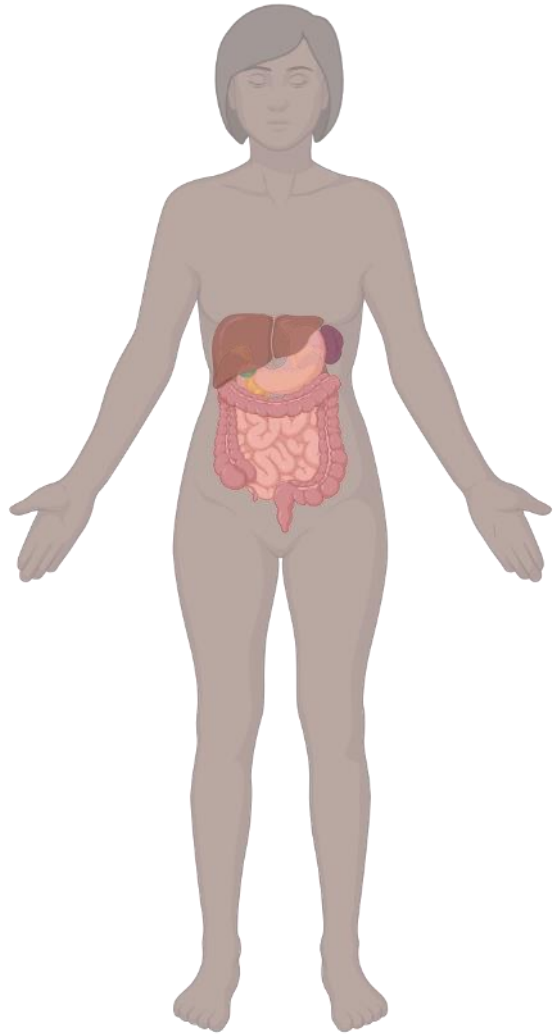
Vomiting

Constipation

Diarrhoea

Abdominal pain

Reflux/ heartburn



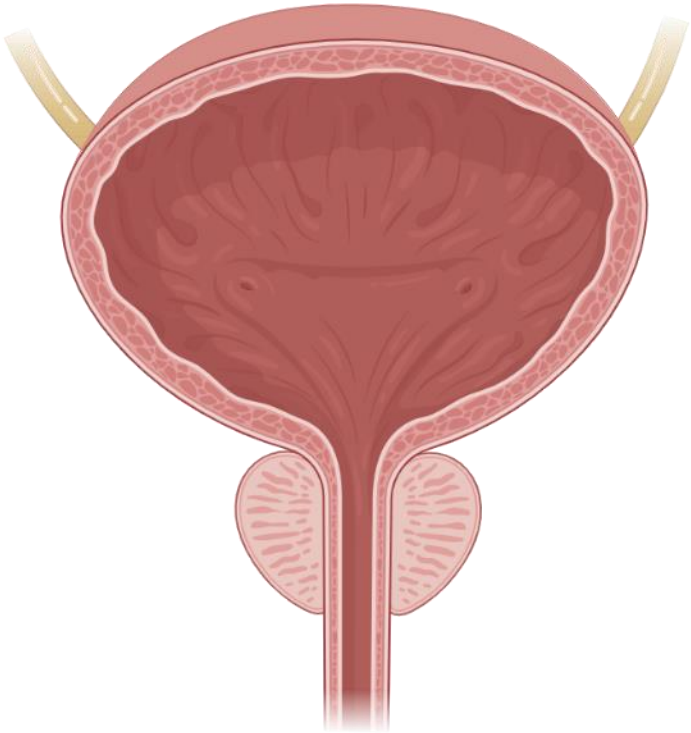
Genitourinary

Bladder dysfunction

Urinary retention

Incontinence

Impotence



Eye

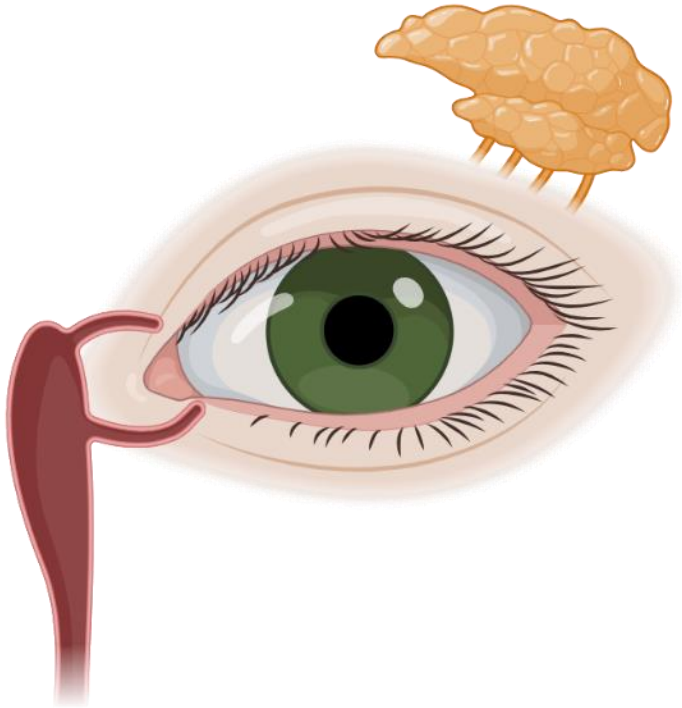
Blurred vision

Intolerance of bright light

Poor vision in dark

Dry eyes

Anisocoria



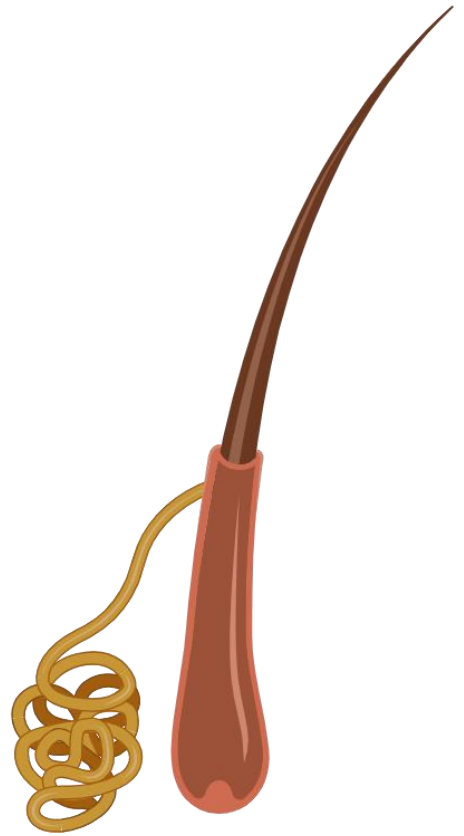
Sudomotor

Hypohidrosis

Hyperhidrosis

Anhidrosis

Gustatory sweating



Management of ANS symptoms

Management by the patient's physician

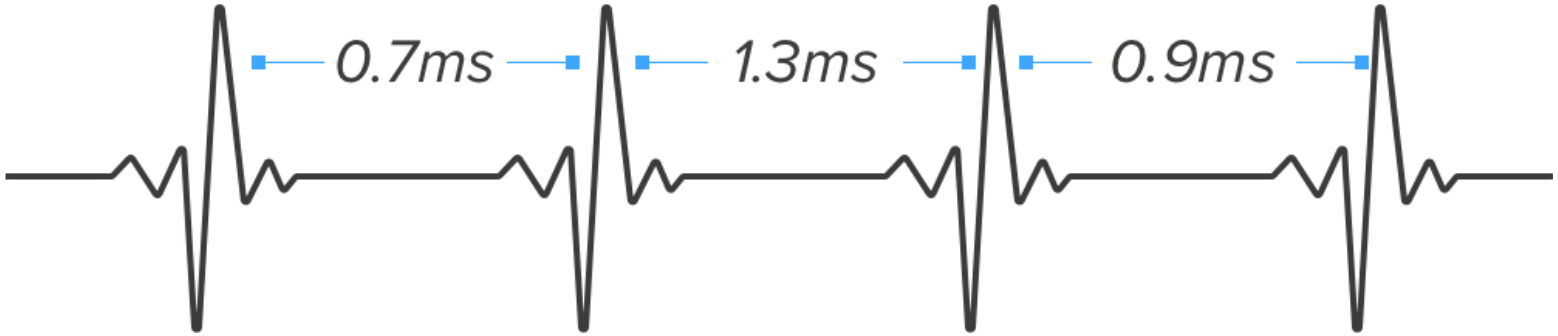
Non-pharmacologic: fluid and salt intake, compression garments, coping strategies

Pharmacologic: beta blockers, alpha agonists, mineral corticoids

Assessment of the autonomic nervous system

From Newcastle. For the world.

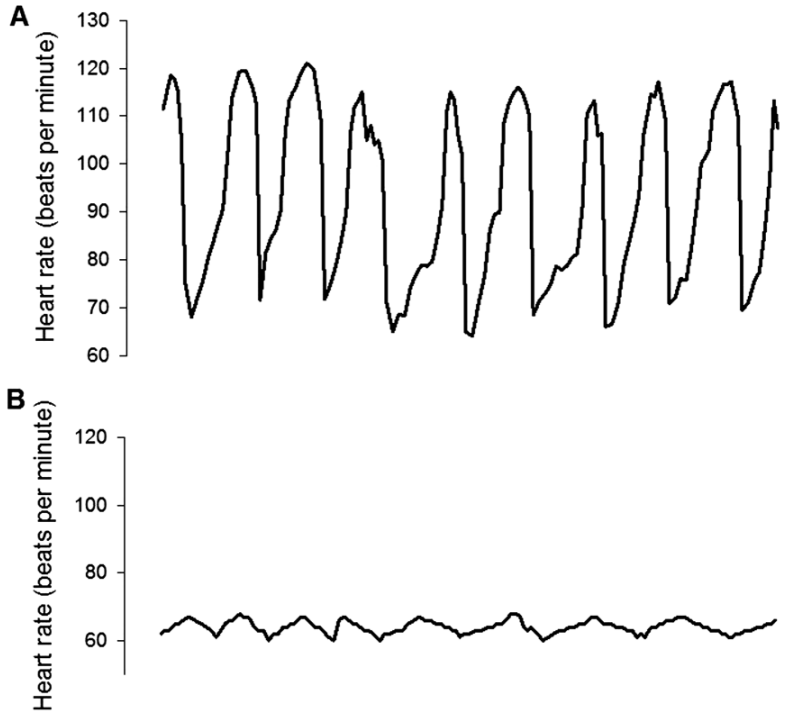
Heart rate variability



Heart rate variability

Heart rate fluctuates over time:

- **High frequency** (>0.15 Hz) caused by respiration - mediated by vagus
- **Low frequency** (<0.04 – 0.15 Hz) caused by slow fluctuations in blood pressure – sympathetically mediated

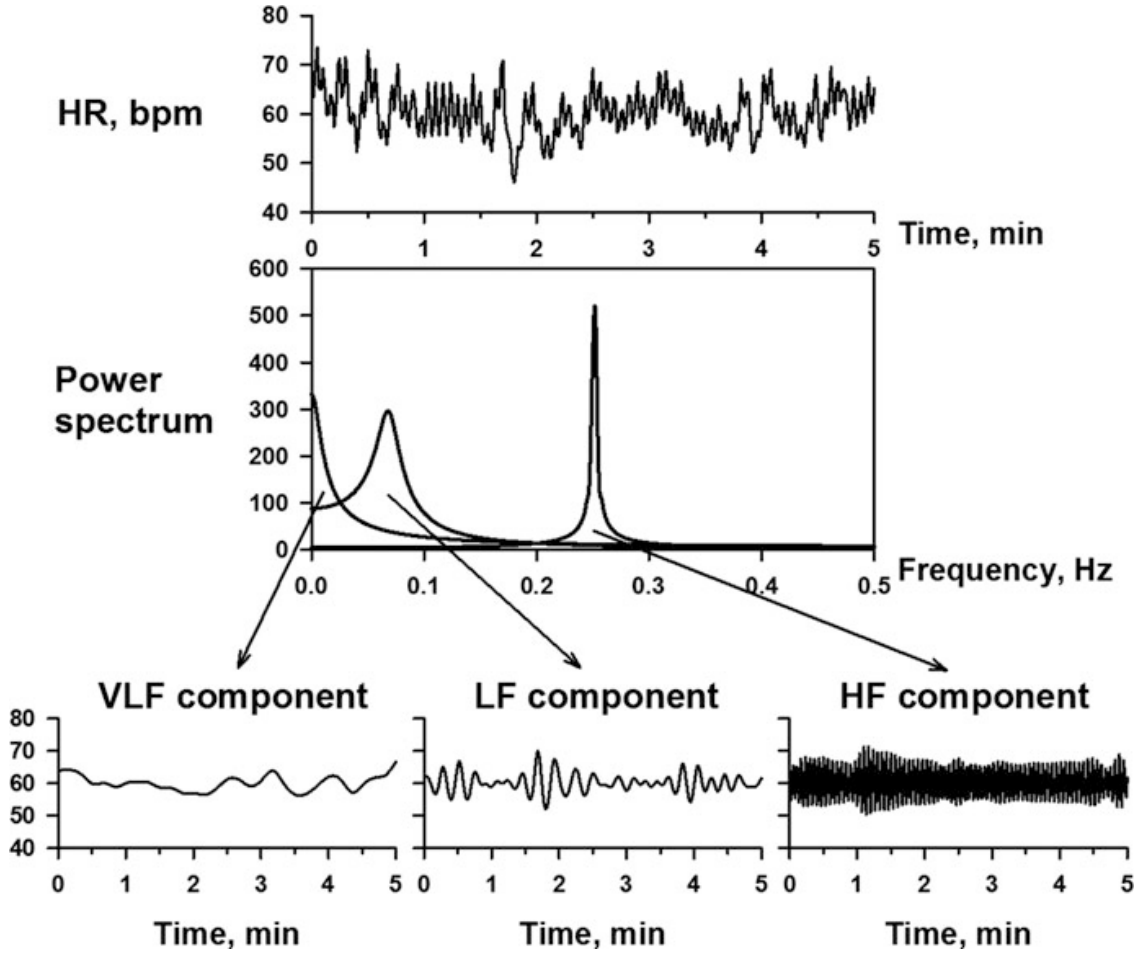


Swenne, CA. Baroreflex sensitivity: mechanisms and measurement. *Neth Heart J*. 2013;21(2):58-60. DOI: 10.1007/s12471-012-0346-y

Heart rate variability

Frequency analysis looks at each component:

- **Low frequency (LF) variation**
- **High Frequency (HF) variation**
- **Ratio (LF/HF)**



Iwase *et al.* Clinical Assessment of the Autonomic Nervous System. 2017. Springer: Tokyo

Valsalva manoeuvre

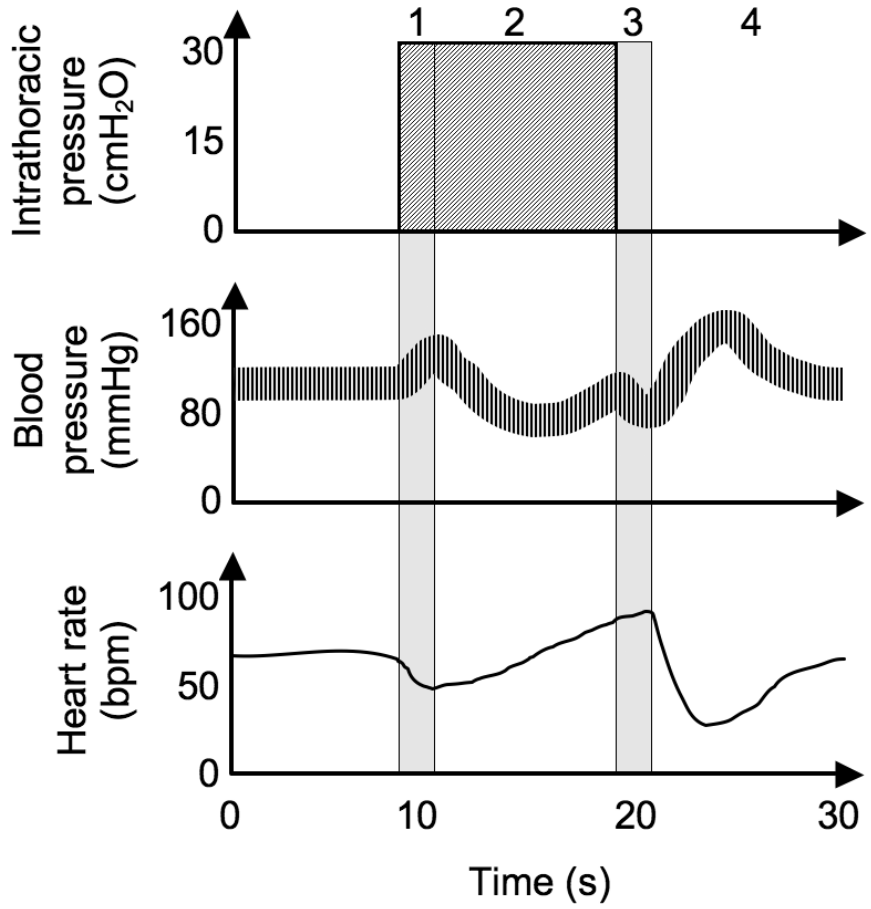
1: Initial BP rise

2: Reduced venous return & compensation

3: Pressure release

4: Return to baseline

Valsalva ratio: Max HR / Min HR (within 30s release)



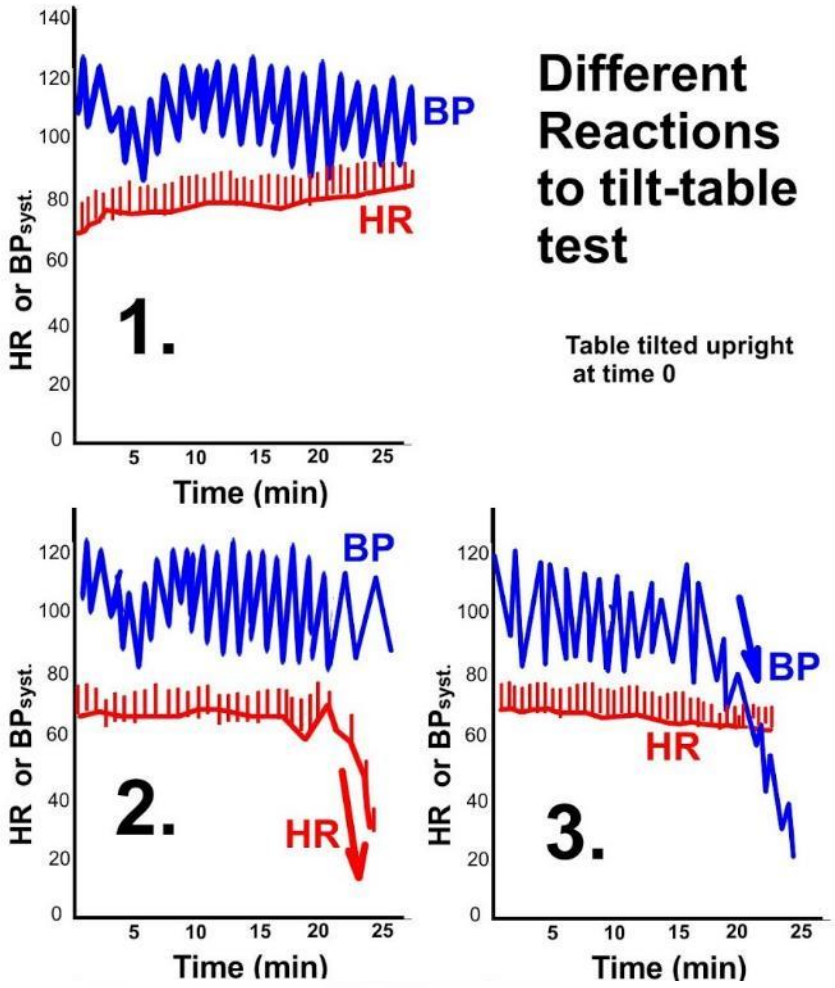
Cross ME, Plunkett EVE. The Valsalva manoeuvre. In: *Physics, Pharmacology and Physiology for Anaesthetists: Key Concepts for the FRCA*. Cambridge University Press; 2014:274-275.

Tilt table test

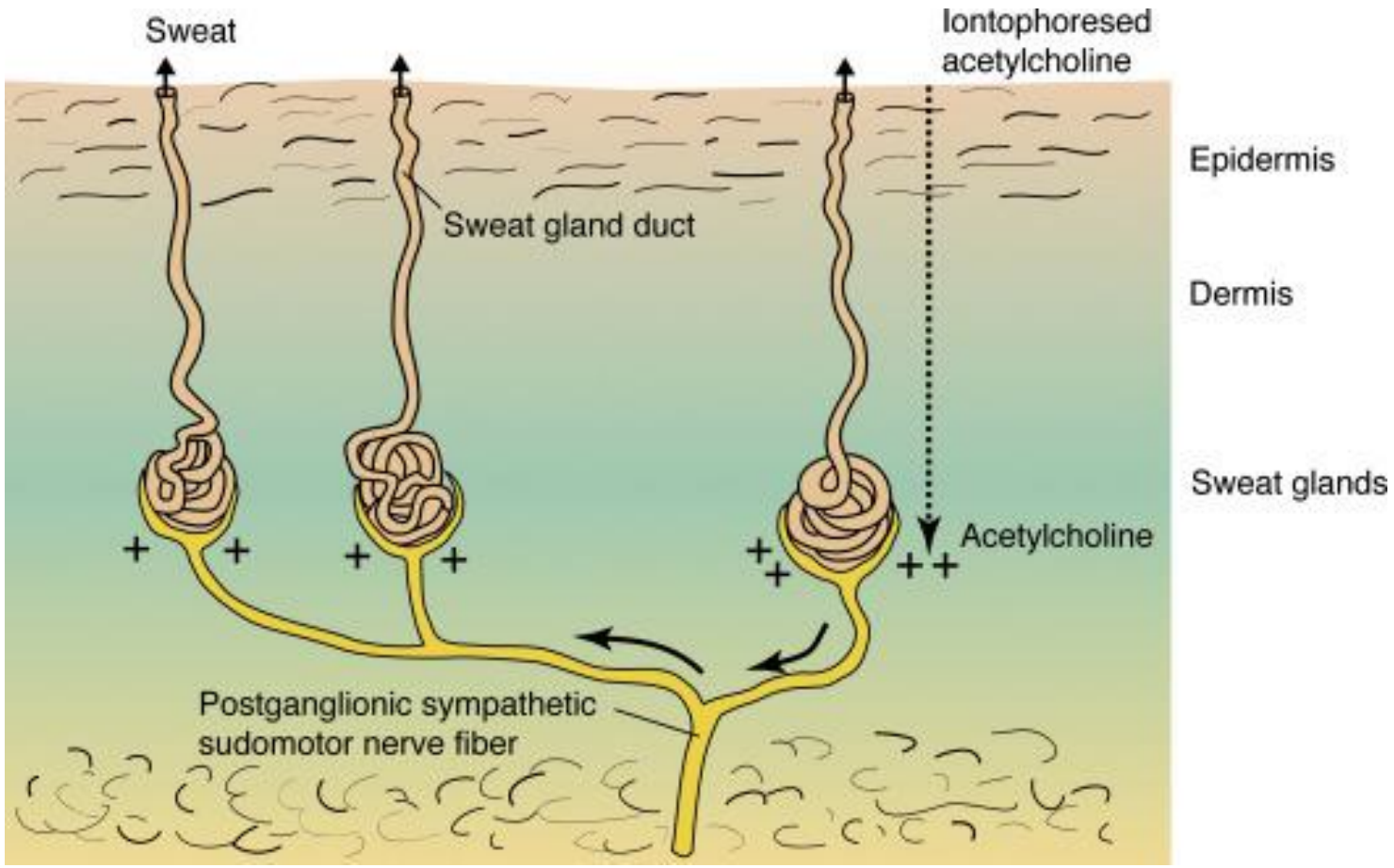
Supine 5–30 mins

Tilt 60–90˚ for 15–45 min

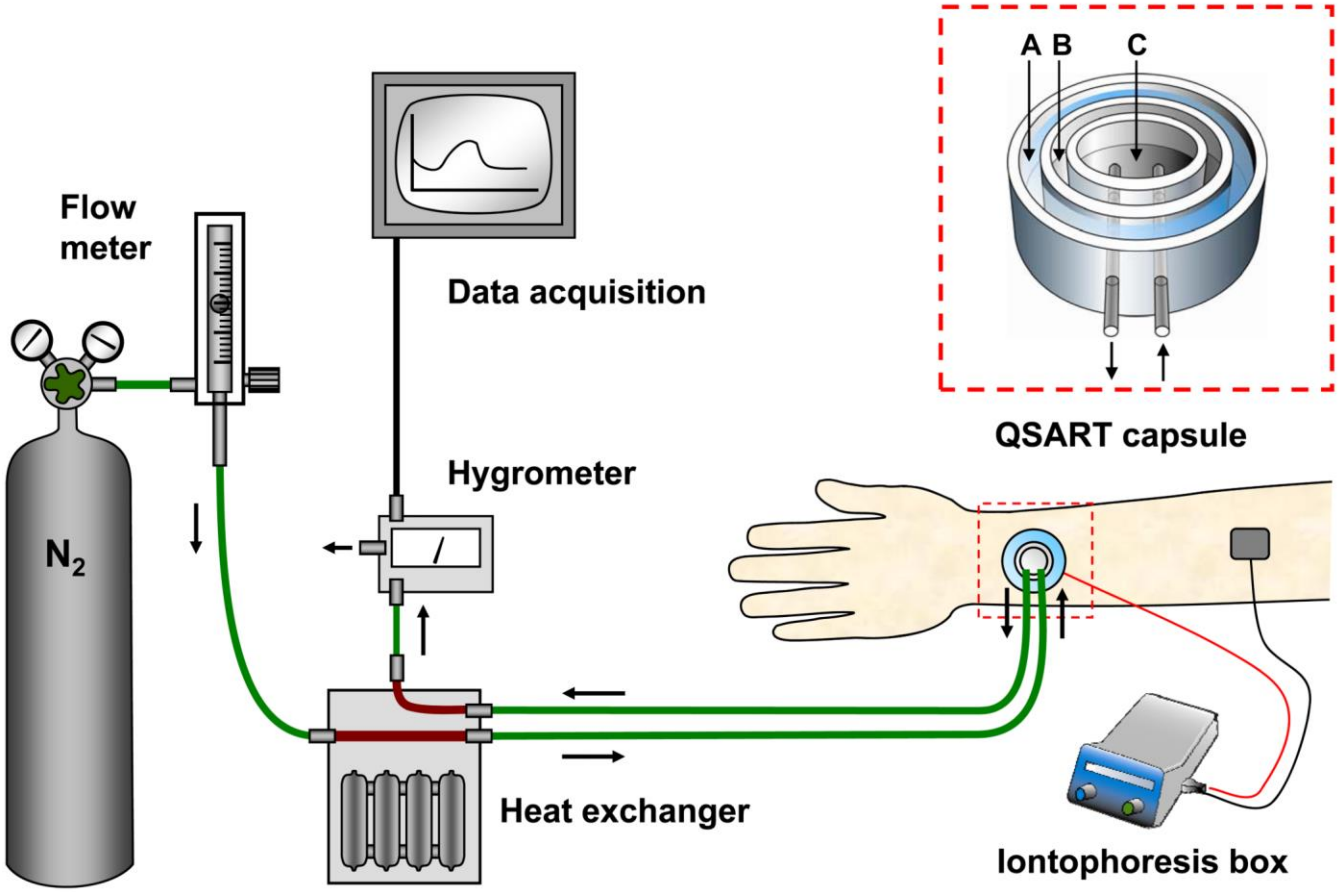
- **Vasovagal** (neurally-mediated) **syncope**
- **Orthostatic hypotension**
- **POTS**
- **Negative response**



Quantitative sudomotor axon reflex testing



Quantitative sudomotor axon reflex testing

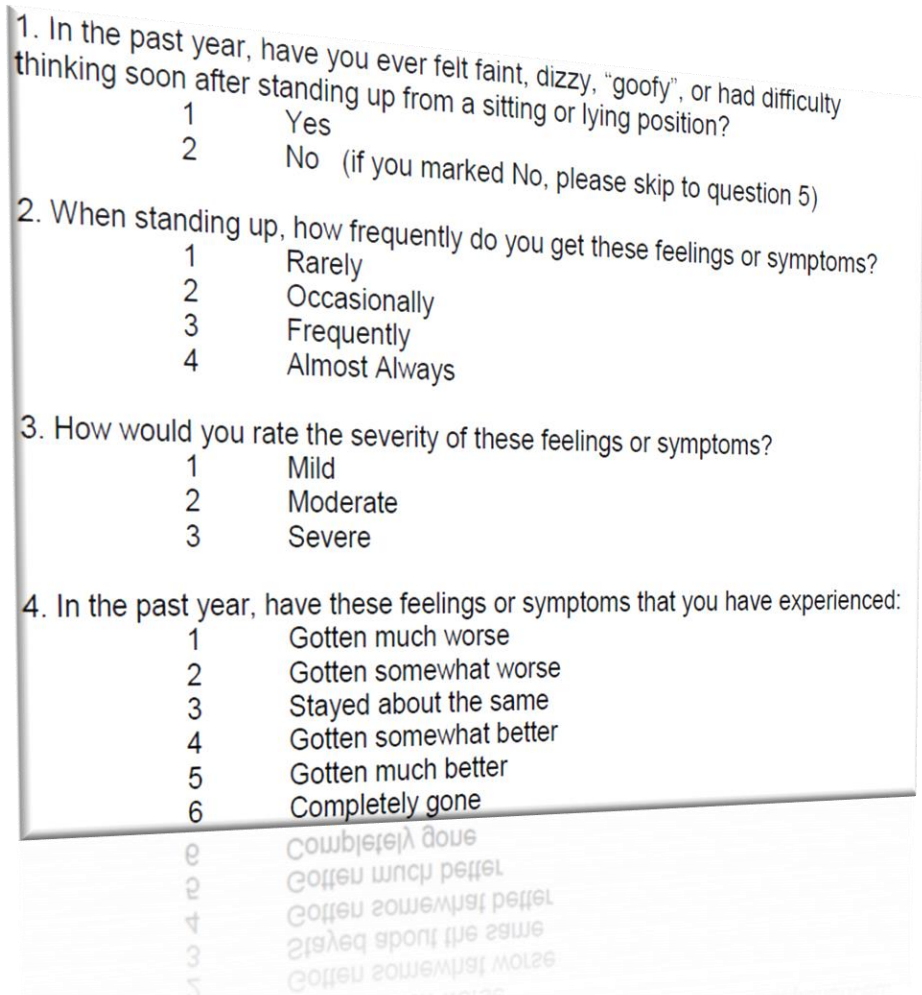


Illigens BM and Gibbons CH. **Sweat testing to evaluate autonomic function**. *Clin Auton Res.* 2009;19:79-87

COMPASS 31

31-item questionnaire:[1]

- Orthostatic intolerance
- Vasomotor
- Secretomotor
- Gastrointestinal
- Bladder
- Pupillomotor



1. In the past year, have you ever felt faint, dizzy, "goofy", or had difficulty thinking soon after standing up from a sitting or lying position?
   1 Yes
   2 No (if you marked No, please skip to question 5)

2. When standing up, how frequently do you get these feelings or symptoms?
   1 Rarely
   2 Occasionally
   3 Frequently
   4 Almost Always

3. How would you rate the severity of these feelings or symptoms?
   1 Mild
   2 Moderate
   3 Severe

4. In the past year, have these feelings or symptoms that you have experienced:
   1 Gotten much worse
   2 Gotten somewhat worse
   3 Stayed about the same
   4 Gotten somewhat better
   5 Gotten much better
   6 Completely gone

1: Sletten *et al.* **COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score.** *Mayo Clin Proc.* 2012;87(12):1196-1201

COMPASS 31

Good reliability (test-retest: r_s=0.886) & internal validity (Cronbach's α=0.919)[1]

Correlates with autonomic testing[2]

Predictive of small fibre neuropathy on biopsy[3]

Healthy norm: 8.6 – 8.9

1: Treister *et al.* **Validation of the composite autonomic symptom scale 31 (COMPASS-31) in patients with and without small fiber polyneuropathy**. *European Journal of Neurology* 2015, 22: 1124–1130
2: Vincent *et al.* **Patients With Fibromyalgia Have Significant Autonomic Symptoms But Modest Autonomic Dysfunction.** *PM&R*. 2016;8:425-35
3: Meling *et al.* **The Composite Autonomic Symptom Score 31 Questionnaire: A Sensitive Test to Detect Risk for Autonomic Neuropathy.** *J Diab Res*. 2023;2023:4441115

Dysautonomia

- Fibromyalgia
- Chronic Fatigue Syndrome (CFS)
- Other chronic overlapping pain conditions
- Ehlers-Danlos syndrome
- *Neurological:* Parkinson's disease, Multiple sclerosis, Guillain-Barre
- *Endocrine:* Diabetes, thyroid, adrenal
- *Autoimmune:* Lupus, Sjögren's
- *Infection:* Lyme disease, HIV

Fibromyalgia

Pain in multiple body sites, fatigue, sleep disturbance, cognitive issues.[1]

Many TMD patients fulfil criteria for fibromyalgia (**32.7%** [95%CI:4.5–71.0%])[2]

1: Wolfe *et al*. **Revisions to the 2010/2011 fibromyalgia diagnostic criteria**. *Semin Arthritis Rheum.* 2016;46:319–329
2: Yakkaphan *et al* . **Temporomandibular Disorders and Fibromyalgia Prevalence: A Systematic Review and Meta-Analysis.** *J Oral Facial Pain Headache.* 2023;37(3):177-193

Fibromyalgia

Patients report widespread ANS symptoms[1]

Increased sympathetic activity, correlates with symptom severity[2]

TMD + FM = lower HRV[3]

1:Vincent *et al.* **Patients With Fibromyalgia Have Significant Autonomic Symptoms But Modest Autonomic Dysfunction.** *PM&R*. 2016;8:425-435.
2: On *et al.* **Relationships of autonomic dysfunction with disease severity and neuropathic pain features in fibromyalgia: is it really a sympathetically maintained neuropathic pain?** *Korean J Pain*, 2022;35:327-335.
3: Eisenlohr-Moul, *et al.* **Parasympathetic reactivity in fibromyalgia and temporomandibular disorder: associations with sleep problems, symptom severity, and functional impairment.** *J Pain*. 2015;16:247-57

Chronic Fatigue Syndrome (CFS)/ Myalgic Encephalomyelitis (ME)

"Persistent debilitating fatigue, not . . . explained by other conditions, and results in substantial reduction in activity"[1,2]

Debilitating fatigue

Post-exertional malaise

Unrefreshing sleep/ sleep disturbance

Cognitive difficulties

1: Fukuda *et al*. **The Chronic Fatigue Syndrome A Comprehensive Approach to Its Definition and Study**. *Ann Intern Med.* 1994;121:953-959
2: NICE. **Myalgic encephalomyelitis (or encephalopathy)/chronic fatigue syndrome: diagnosis and management, NICE guideline [NG206].** 2021. Available at: https://www.nice.org.uk/guidance/ng206. Accessed: 27/08/2024

Chronic Fatigue Syndrome (CFS)

Orthostatic intolerance and other **autonomic symptoms**

Pain

Temperature hypersensitivity

Flu-like symptoms

Chronic Fatigue Syndrome (CFS)

CFS prevalence: ~0.2%[1]

0-10% of patients with TMD report CFS[2]

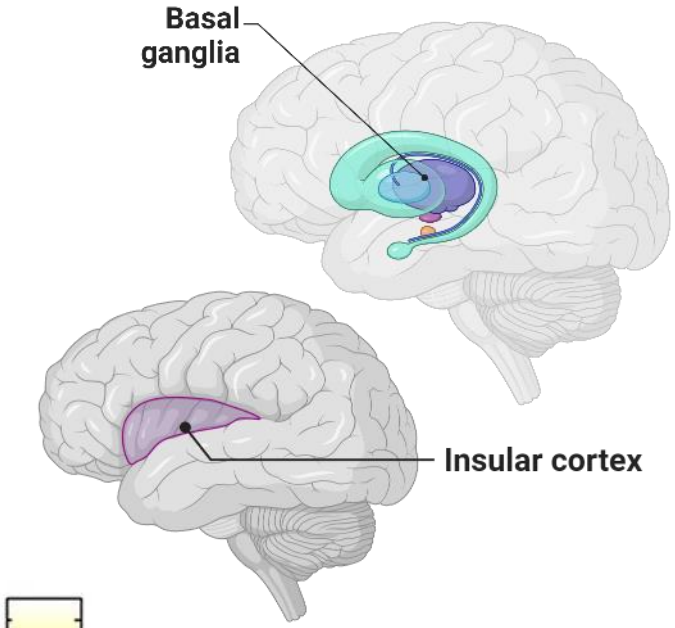
20-30% of patients with CFS report TMD[2,3]

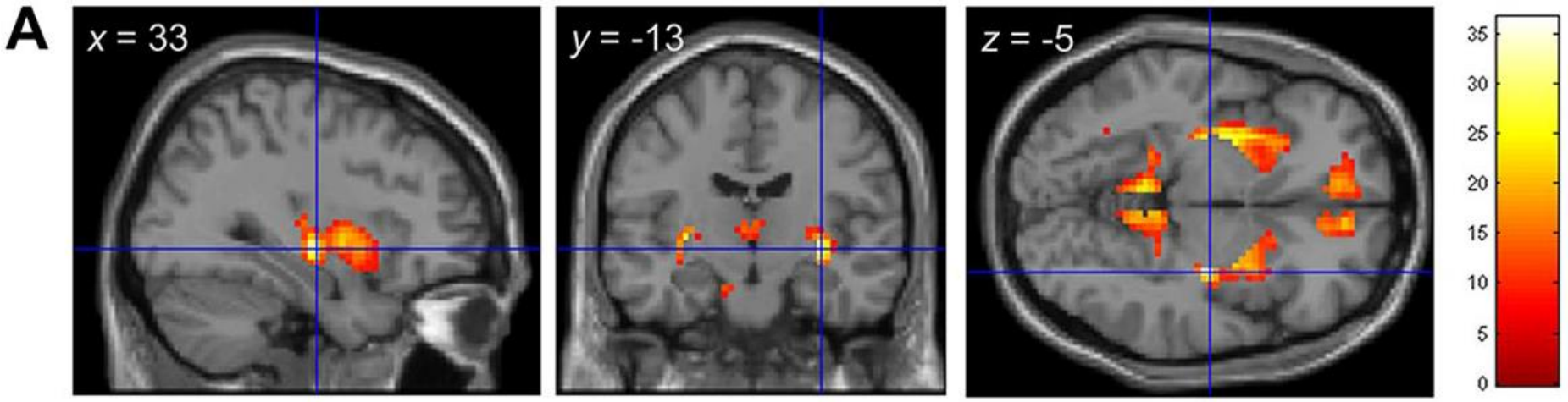
CFS + TMD = greater subjective & objective dysautonomia[3]

1: Nacul *et al.* **Prevalence of myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) in three regions of England: a repeated cross-sectional study in primary care.** *BMC Medicine.* 2011;9:91
2: Robinson *et al.* **A systematic review of the comorbidity between Temporomandibular Disorders and Chronic Fatigue Syndrome.** *J Oral Rehab.* 2016;43:306-16
3: Robinson *et al.* **Autonomic function in chronic fatigue syndrome with and without painful temporomandibular disorder.** *Fatigue.* 2015;3:205-219

Brain Responses in CFS and TMD to Autonomic Challenges: An Exploratory fMRI Study

Q.C. Vuong[1], J.R. Allison[2], A. Finkelmeyer[1], J. Newton[3,4], and J. Durham[2,5,6]

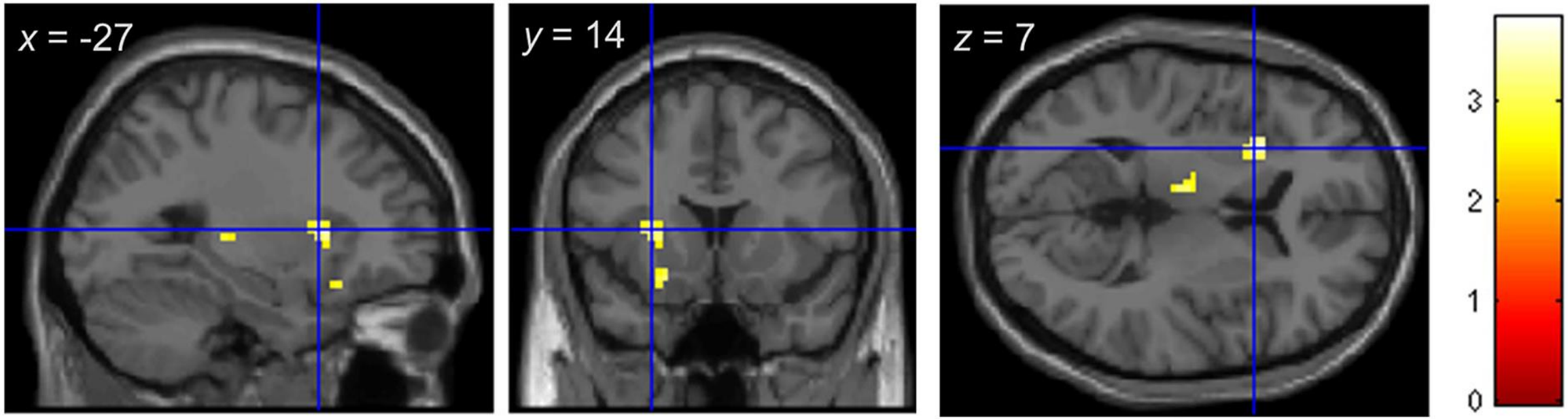




Control (*n* = 10)
CFS-TMD (*n* = 16)
CFS+TMD (*n* = 26)

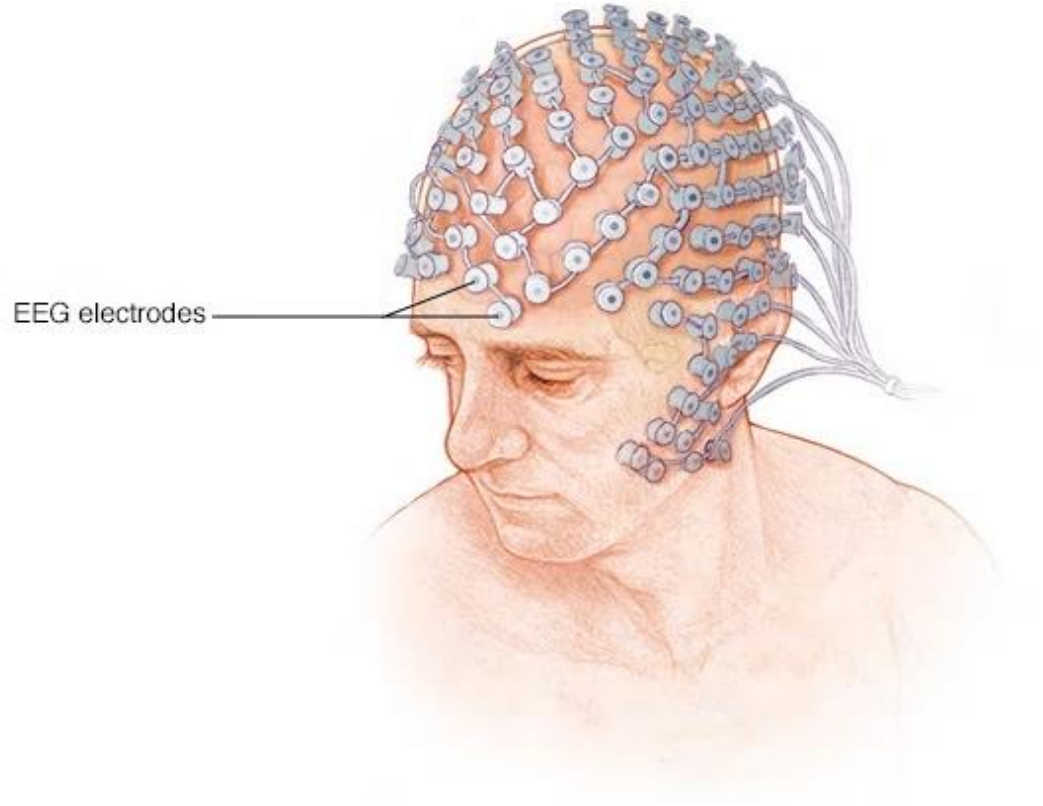
Vuong *et al.* **Brain Responses in CFS and TMD to Autonomic Challenges: An Exploratory fMRI Study.** *JDR Clin Trans Res.* 2020;5;224-232

CFS+TMD vs CFS-TMD

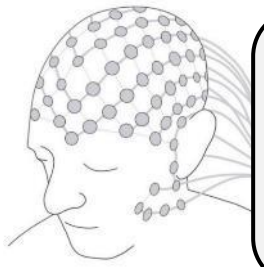


Vuong *et al.* **Brain Responses in CFS and TMD to Autonomic Challenges: An Exploratory fMRI Study.** *JDR Clin Trans Res.* 2020;5;224-232

Elucidate: Exploring pain and autonomic dysfunction in ME/CFS and TMD



Elucidate



Control (*n*=15)

EEG Visit

Resting / painful stimulation

sent visit
ue, ANS symptoms,
easures

(*n*=30)

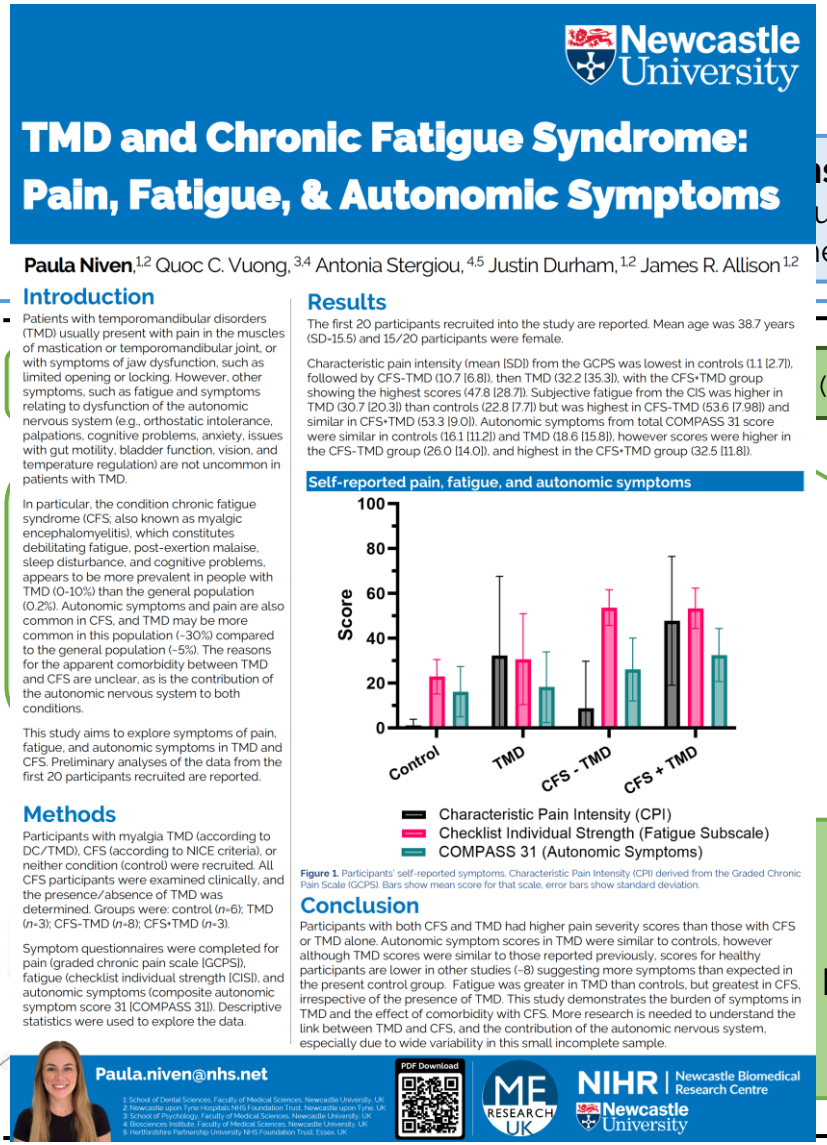
TMD (*n*=15)

EEG Visit

Resting / painful stimulation

EEG Visit

Resting / painful stimulation



Newcastle University

TMD and Chronic Fatigue Syndrome: Pain, Fatigue, & Autonomic Symptoms

Paula Niven,[1,2] Quoc C. Vuong,[3,4] Antonia Stergiou,[4,5] Justin Durham,[1,2] James R. Allison[1,2]

Introduction

Patients with temporomandibular disorders (TMD) usually present with pain in the muscles of mastication or temporomandibular joint, or with symptoms of jaw dysfunction, such as limited opening or locking. However, other symptoms, such as fatigue and symptoms relating to dysfunction of the autonomic nervous system (e.g., orthostatic intolerance, palpations, cognitive problems, anxiety, issues with gut motility, bladder function, vision, and temperature regulation) are not uncommon in patients with TMD.

In particular, the condition chronic fatigue syndrome (CFS; also known as myalgic encephalomyelitis), which constitutes debilitating fatigue, post-exertion malaise, sleep disturbance, and cognitive problems, appears to be more prevalent in people with TMD (0-10%) than the general population (0.2%). Autonomic symptoms and pain are also common in CFS, and TMD may be more common in this population (~30%) compared to the general population (~5%). The reasons for the apparent comorbidity between TMD and CFS are unclear, as is the contribution of the autonomic nervous system to both conditions.

This study aims to explore symptoms of pain, fatigue, and autonomic symptoms in TMD and CFS. Preliminary analyses of the data from the first 20 participants recruited are reported.

Methods

Participants with myalgia TMD (according to DC/TMD), CFS (according to NICE criteria), or neither condition (control) were recruited. All CFS participants were examined clinically, and the presence/absence of TMD was determined. Groups were: control (*n*=6); TMD (*n*=3); CFS-TMD (*n*=8); CFS+TMD (*n*=3).

Symptom questionnaires were completed for pain (graded chronic pain scale [GCPS]), fatigue (checklist individual strength [CIS]), and autonomic symptoms (composite autonomic symptom score 31 [COMPASS 31]). Descriptive statistics were used to explore the data.

Results

The first 20 participants recruited into the study are reported. Mean age was 38.7 years (SD=15.5) and 15/20 participants were female.

Characteristic pain intensity (mean [SD]) from the GCPS was lowest in controls (1.1 [2.7]), followed by CFS-TMD (10.7 [6.8]), then TMD (32.2 [35.3]), with the CFS+TMD group showing the highest scores (47.8 [28.7]). Subjective fatigue from the CIS was higher in TMD (30.7 [20.3]) than controls (22.8 [7.7]) but was highest in CFS-TMD (53.6 [7.98]) and similar in CFS+TMD (53.3 [9.0]). Autonomic symptoms from total COMPASS 31 score were similar in controls (16.1 [11.2]) and TMD (18.6 [15.8]), however scores were higher in the CFS-TMD group (26.0 [14.0]), and highest in the CFS+TMD group (32.5 [11.8]).

Self-reported pain, fatigue, and autonomic symptoms

Figure 1. Participants' self-reported symptoms. Characteristic Pain Intensity (CPI) derived from the Graded Chronic Pain Scale (GCPS). Bars show mean score for that scale, error bars show standard deviation.

Conclusion

Participants with both CFS and TMD had higher pain severity scores than those with CFS or TMD alone. Autonomic symptom scores in TMD were similar to controls, however although TMD scores were similar to those reported previously, scores for healthy participants are lower in other studies (~8) suggesting more symptoms than expected in the present control group. Fatigue was greater in TMD than controls, but greatest in CFS, irrespective of the presence of TMD. This study demonstrates the burden of symptoms in TMD and the effect of comorbidity with CFS. More research is needed to understand the link between TMD and CFS, and the contribution of the autonomic nervous system, especially due to wide variability in this small incomplete sample.

Paula.niven@nhs.net

1: School of Dental Sciences, Faculty of Medical Sciences, Newcastle University, UK
2: Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK
3: School of Psychology, Faculty of Medical Sciences, Newcastle University, UK
4: Biosciences Institute, Faculty of Medical Sciences, Newcastle University, UK
5: Hertfordshire Partnership University NHS Foundation Trust, Essex, UK

PDF Download

NIHR | Newcastle Biomedical Research Centre

Newcastle University

1) Do autonomic symptoms point to a common aetiology?

Newcastle University
UK | Malaysia | Singapore

Autonomic dysfunction in TMD

From our University. For the world.

TMD is associated with ANS dysfunction

Large case control studies: TMD= ↑**HR,** ↓**HRV**[1]

↓**HRV during sleep**, esp. parasympathetic[2]

↓**parasympathetic response** during a non-stressful task, correlated with pain intensity[3]

↓**HRV** (↓HF and ↑LF) after recalling a stressful life event[4]

1: Maixner *et al.* **Potential autonomic risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study.** *J Pain.* 2011;12:T75-91
2: Eze-Nliam *et al.* **Nocturnal heart rate variability is lower in temporomandibular disorder patients than in healthy, pain-free individuals.** *J Orofac Pain.* 2011;25:232-9
3: Chinthakanan *et al.* **Reduced heart rate variability and increased saliva cortisol in patients with TMD.** *Arch Oral Biol.* 2018;90:125-129
4: Schmidt *et al.* **A controlled comparison of emotional reactivity and physiological response in masticatory muscle pain patients.** *J Orofac Pain.* 2009;23:230-42

TMD is associated with ANS dysfunction

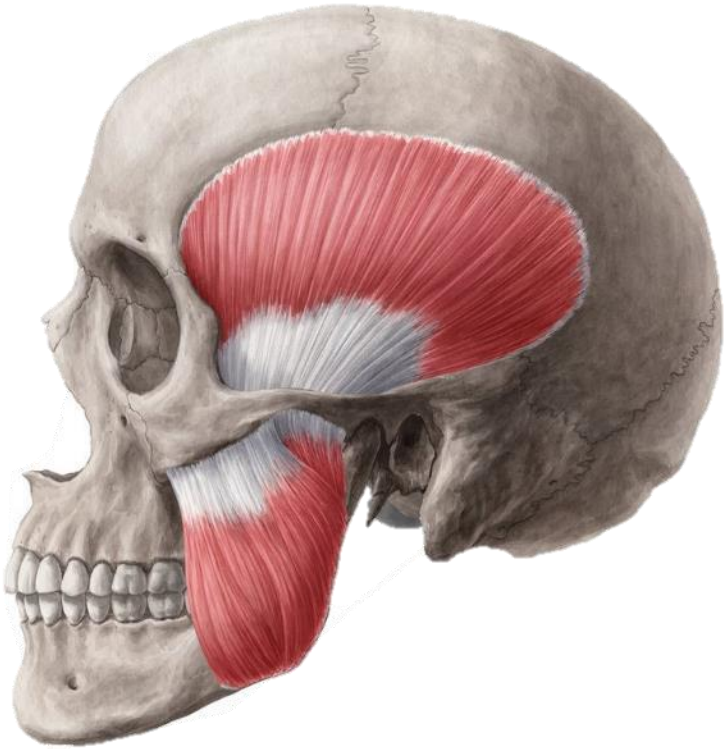
Table 2. Demographics and descriptive scores of COMPASS 31 of 71 patients with TMD.

		Mean	SD
Demographics	Age (years)	35.76	14.00
	Symptom duration (months)	11.94	26.26
COMPASS 31 questionnaire	Orthostatic intolerance	8.45	9.40
	Vasomotor	0.10	0.56
	Secretomotor	2.83	3.04
	Gastrointestinal	3.15	2.83
	Bladder	0.46	0.93
	Pupillomotor	0.63	0.85
	Total score	15.65	10.48

1: Jeong *et al.* **Temporomandibular disorders and autonomic dysfunction: Exploring the possible link between the two using a questionnaire survey.** *Cranio.* 2023;41:467-477

Reduction in parasympathetic tone &

bias towards **sympathetic dominance**

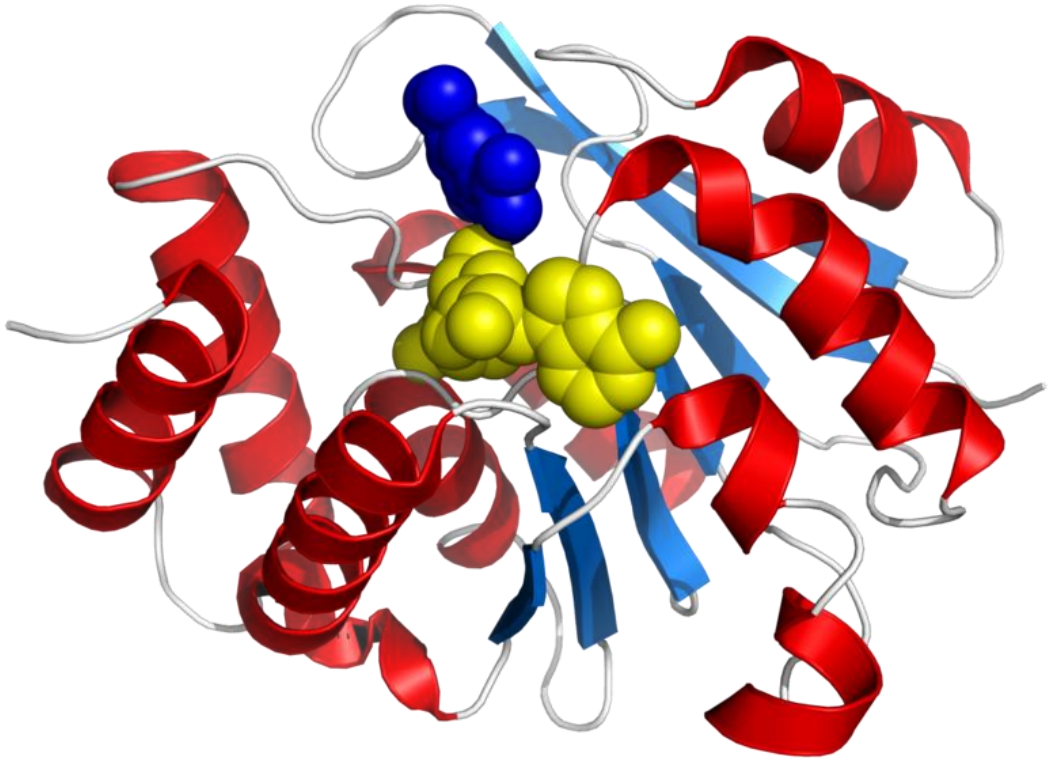


Is dysautonomia a predictive factor for TMD?

COMT determines pain sensitivity, and risk of TMD[1]

Some genetic predictors of TMD status are involved in ANS[2]

Cardiovascular autonomic measures **don't predict TMD onset**[3]



Catechol-O-methyltransferase (COMT)

1: Diatchenko *et al.* **Genetic basis for individual variations in pain perception and the development of a chronic pain condition.** *Hum Mol Genet.* 2005;14:135-43
2: Smith *et al.* **Potential genetic risk factors for chronic TMD: genetic associations from the OPPERA case control study.** *J Pain.* 2011;12:T92-101
3: Greenspan *et al.* **Pain sensitivity and autonomic factors associated with development of TMD: the OPPERA prospective cohort study.** *J Pain* . 2013;14:T63-74.e1-6

Is dysautonomia a predictive factor for TMD?

8-fold TMD risk: **bodily pain**, **psychological distress**, **sleep disturbance**[1]

↑**HR** and ↓**HF HRV** = reduced parasympathetic activity[2]

1: Smith *et al.* **Chairside risk assessment for first-onset temporomandibular disorders: Result from the Orofacial Pain: Prospective Evaluation and Risk Assessment data set.** *J Am Dent Assoc.* 2021;152:505-513.e2
2: Chen *et al.* **Triad multisystem phenotype with high risk for developing temporomandibular disorders-characteristics and potential pathophysiology results from the Orofacial Pain: Prospective Evaluation and Risk Assessment dataset**. *Pain.* 2023;164:1027-1038

Is dysautonomia a predictive factor for TMD?

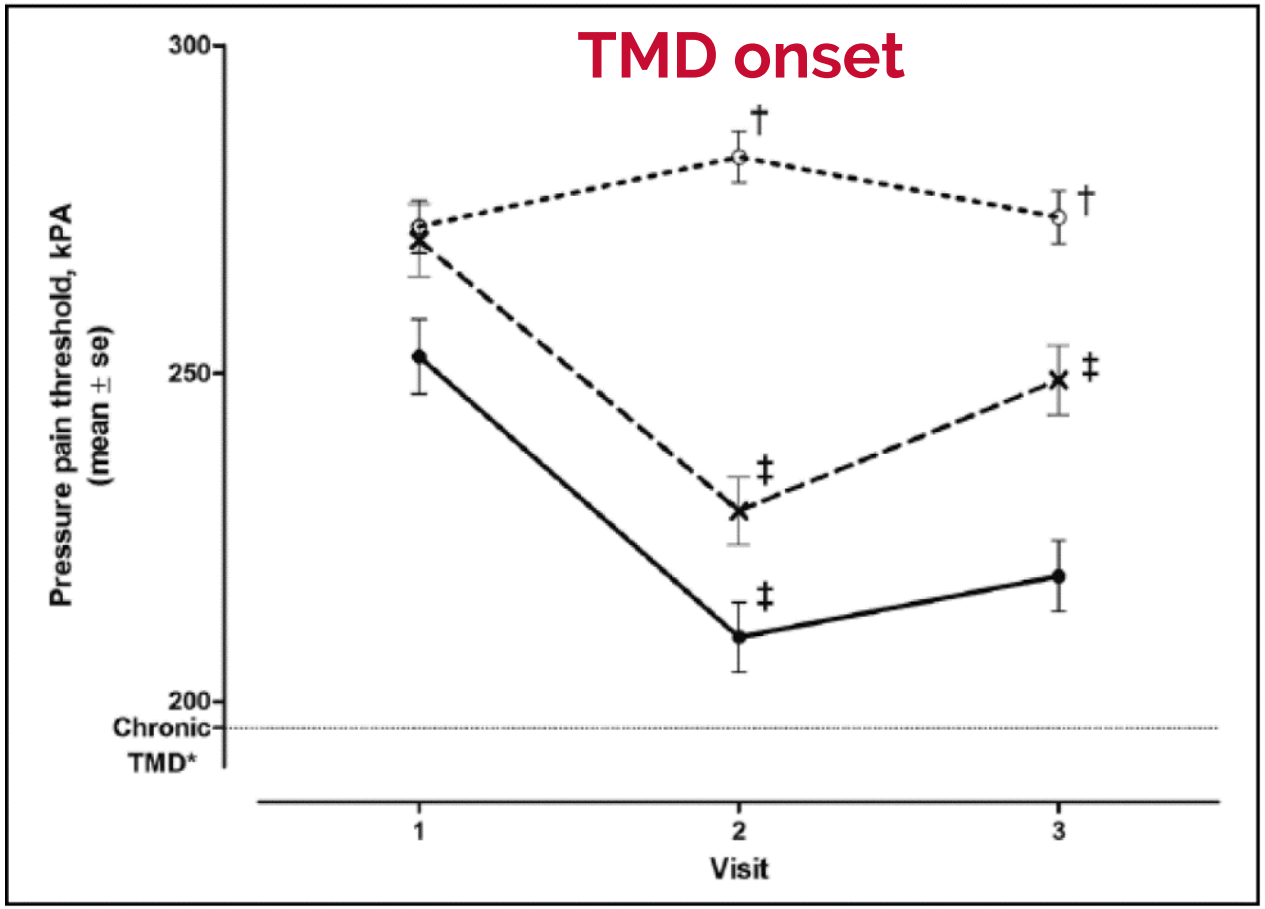
Experimental masseter pain = ↓HRV healthy participants.[1,2]

Beta-blocker (propranolol) doesn't reduce experimental pain[2]

Beta-agonist agonist (terbutaline) doesn't increase masseter pain[3]

1: Bendixen *et al* . **Experimental stressors alter hypertonic saline-evoked masseter muscle pain and autonomic response.** *J Oral Facial Pain.* 2012;26:191-205.
2: Bendixen *et al* . **Effect of propranolol on hypertonic saline-evoked masseter muscle pain and autonomic response in healthy women during rest and mental arithmetic task.** *J Oral Facial Pain.* 2013;27:243-255.
3: Ried *et al.* **Influence of a sympathomimetic amine on masticatory and trapezius pain/pressure thresholds and electromyographic levels.** *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1996;82:525-531

Is dysautonomia a predictive factor for TMD?



Pain-free (*n* = 126)

Transient TMD (*n* = 75)

Persistent TMD (*n* = 72)

Slade *et al.* **Painful Temporomandibular Disorder: Decade of Discovery from OPPERA Studies.** *J Dent Res.* 2016;95:1084-1092

2) Is dysautonomia predictive of TMD incidence?

1) A common aetiology?

2) Predictive of TMD incidence?

3) Prognostic value?

4) Therapeutic value?

3) Is dysautonomia a prognostic indicator?

Transition to chronic TMD & TMD severity?

ANS dysfunction as a marker of greater disease burden?

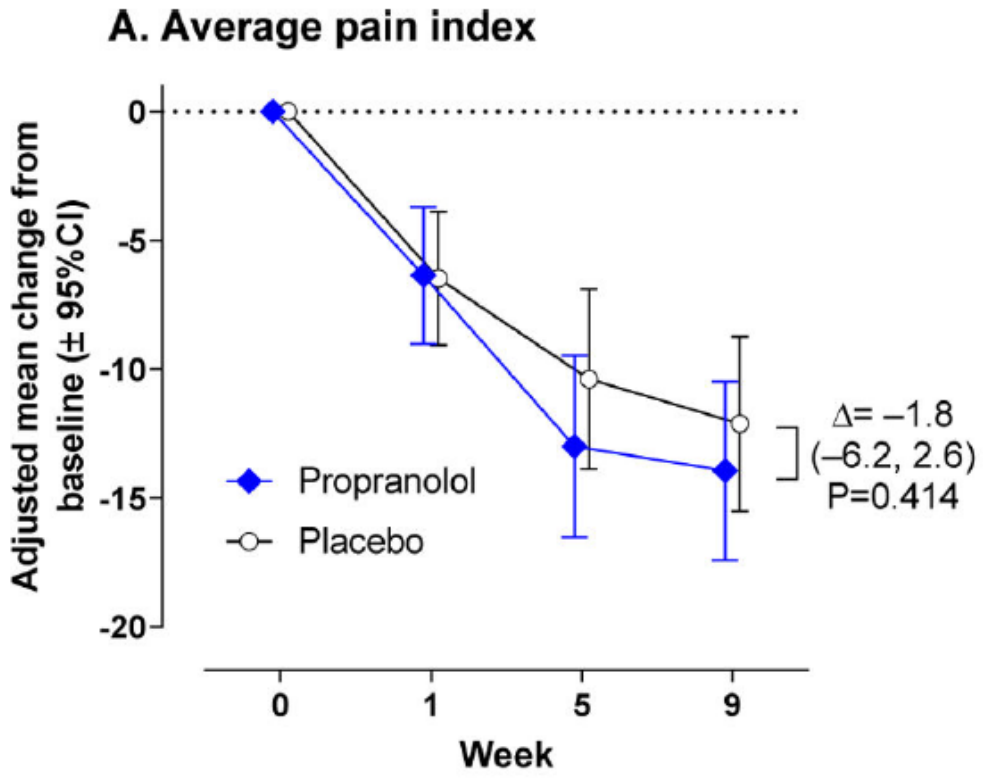
Can we target the ANS to treat TMD?

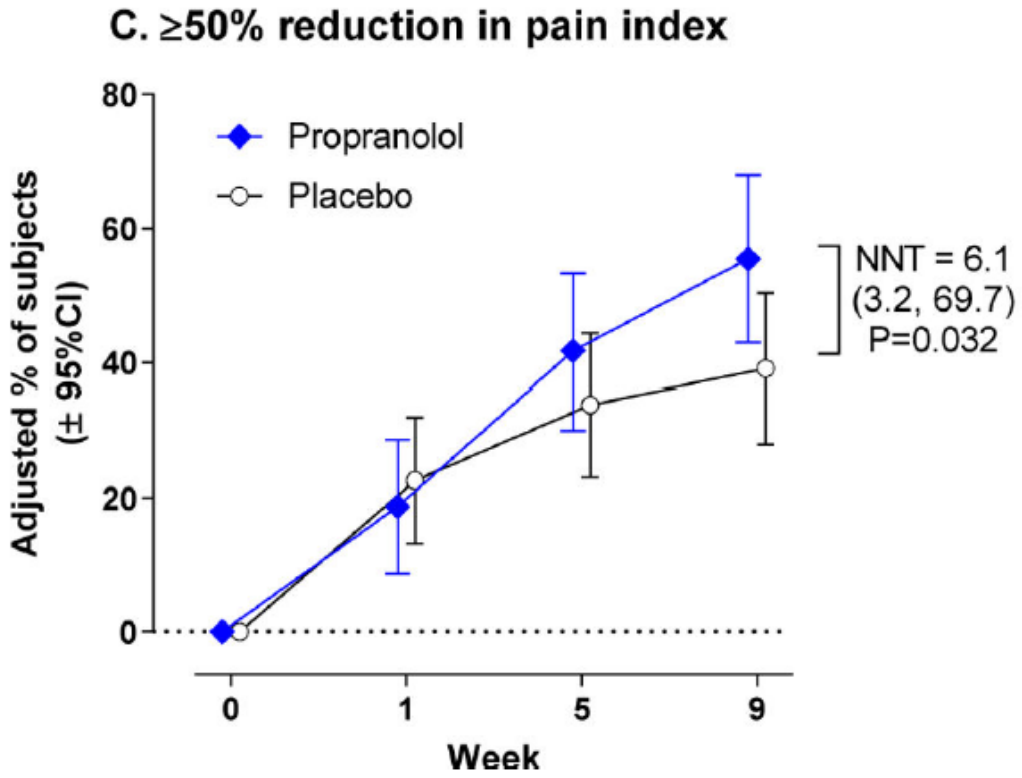
Propranolol eliminates ANS differences in TMD and reduces number of painful body sites[1]

Some evidence of improvement in TMD pain with propranolol.[2]

1: Light *et al* . **Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder** *J Pain.* 2009;10:542-52
2: Tchivileva *et al.* **Effect of catechol-O-methyltransferase polymorphism on response to propranolol therapy in chronic musculoskeletal pain: A randomized, double–blind, placebo-controlled, crossover pilot study.** *Pharmacogenet Genomics.* 2010;20:239-48

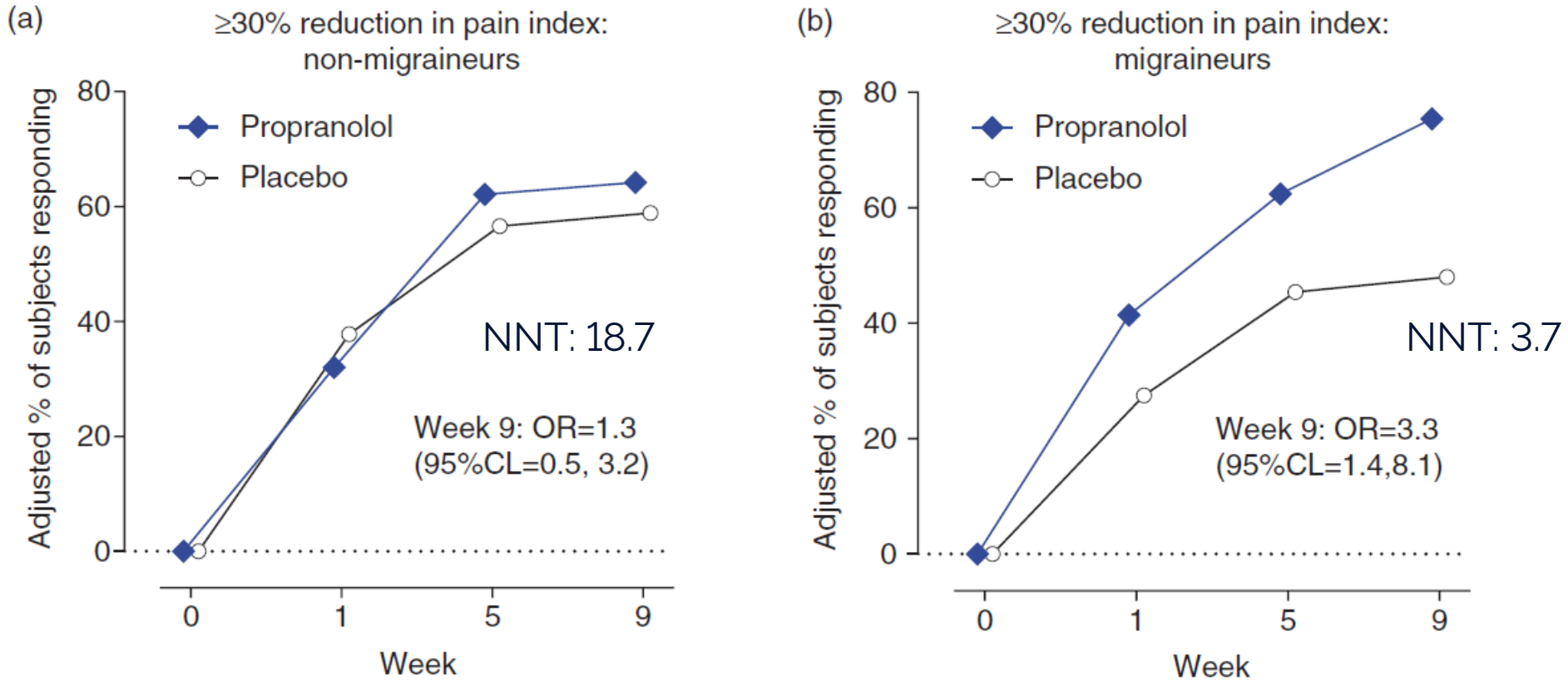
Can we target the ANS to treat TMD?





Tchivileva *et al* . **Efficacy and safety of propranolol for treatment of TMD pain: a randomized, placebo-controlled clinical trial.** *Pain.* 2020;16:11755–1767.

Can we target the ANS to treat TMD?



Tchivileva *et al* . **Effect of comorbid migraine on propranolol efficacy for painful TMD in a randomized controlled trial.** *Cephalgia.* 2021;41:839-850.

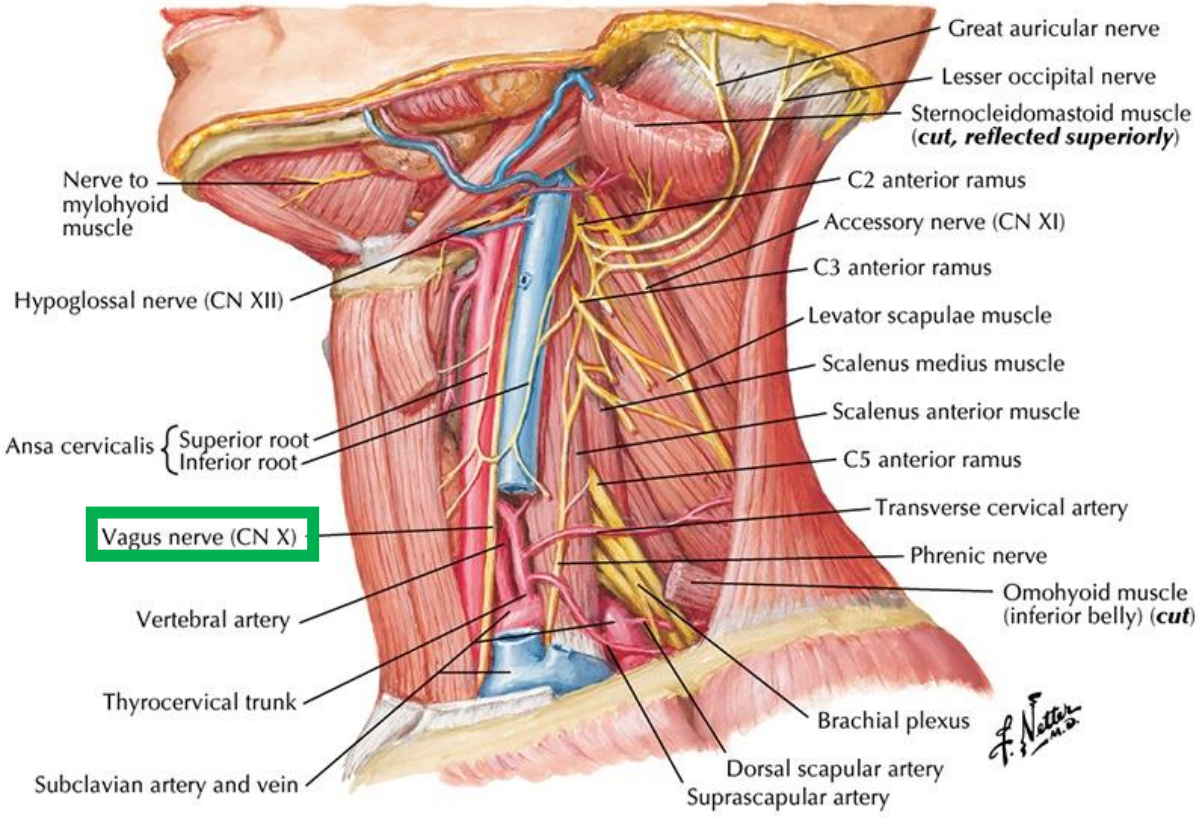
Can we target the ANS to treat TMD?

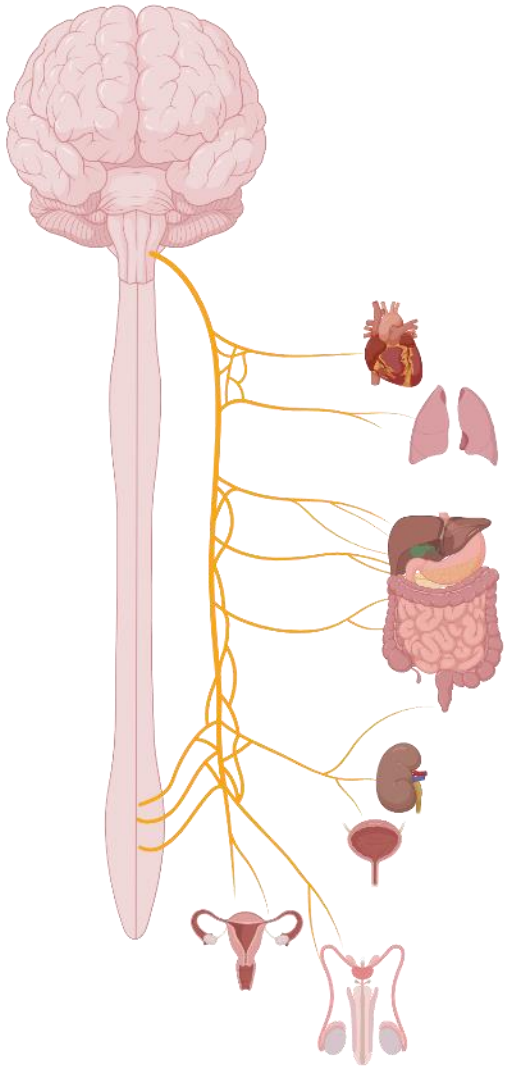
Newcastle University

The vagus nerve

From Newcastle. For the world.

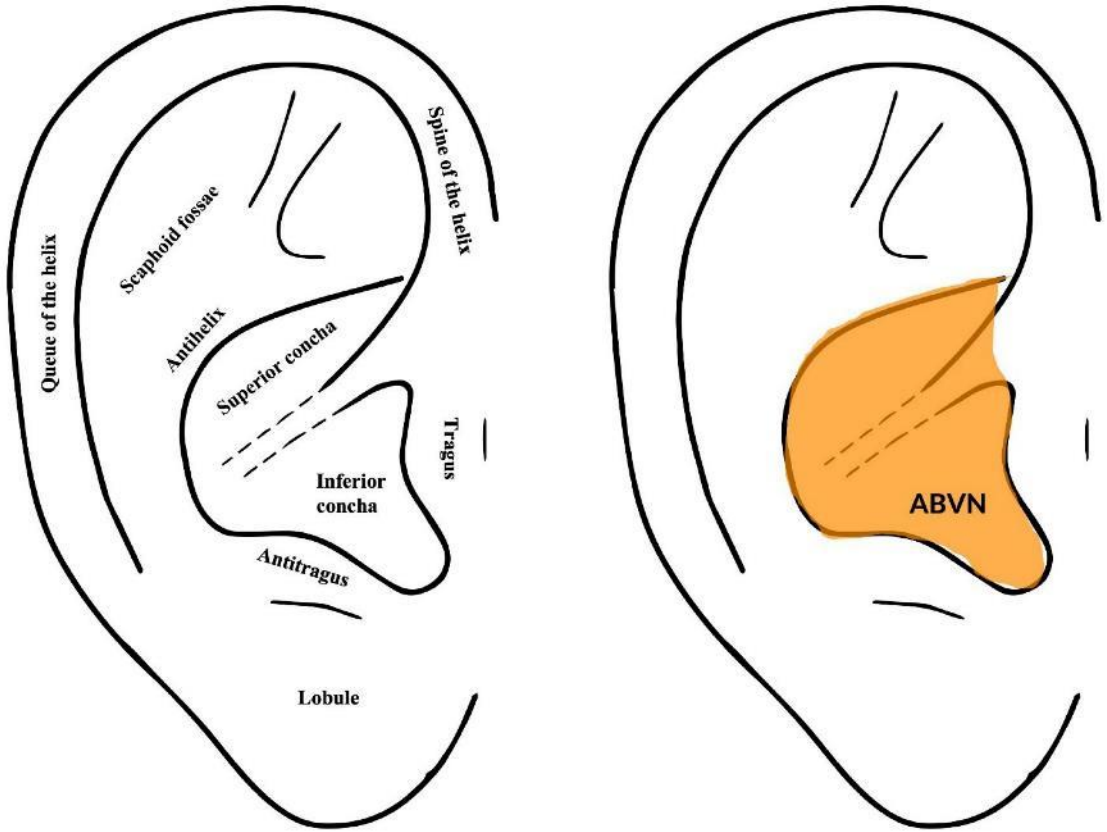
The vagus nerve

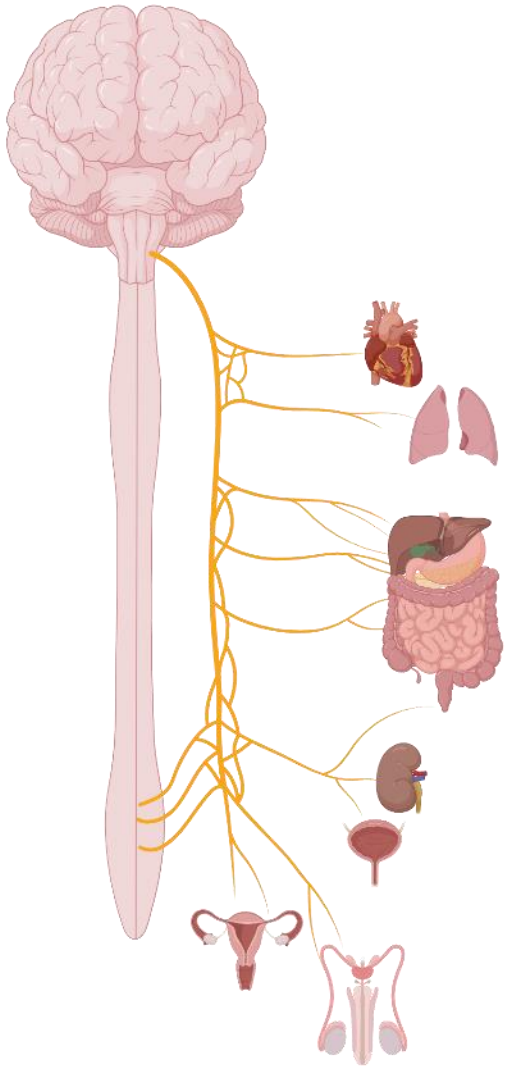




Created with BioRender.com
Credit: Sant'Anna *et al.* 10.1590/1806-9282.20230345

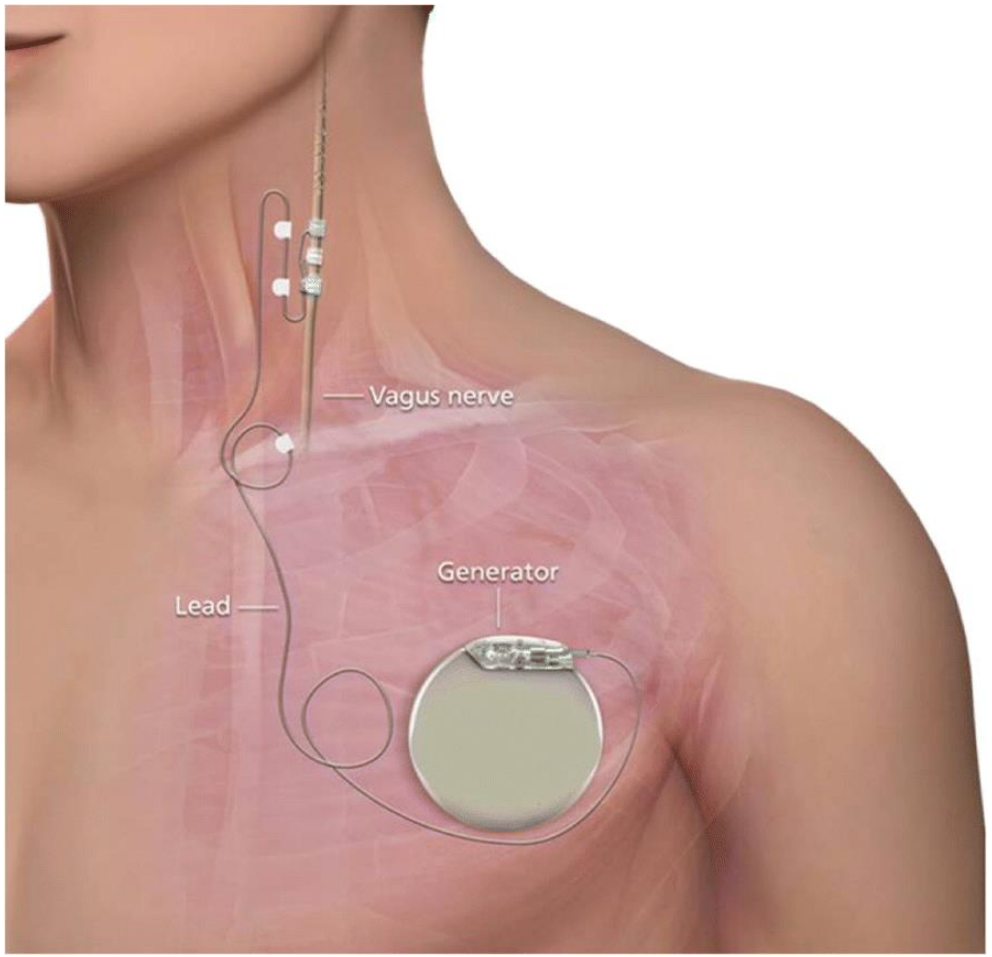
The vagus nerve

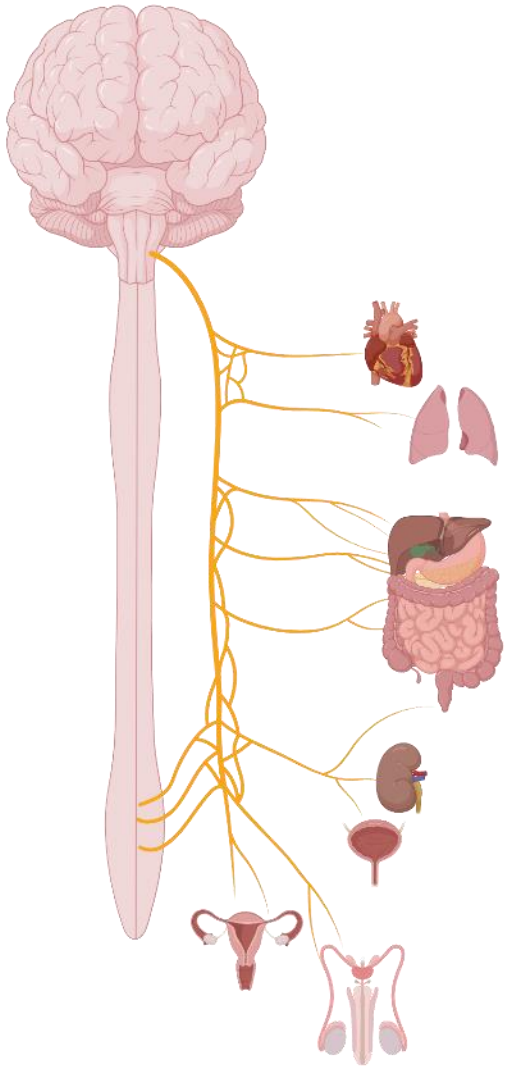




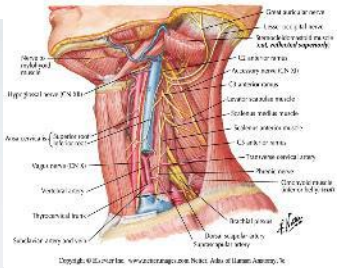
Created with BioRender.com
Credit: Sant'Anna *et al.* 10.1590/1806-9282.20230345

Vagus nerve stimulation





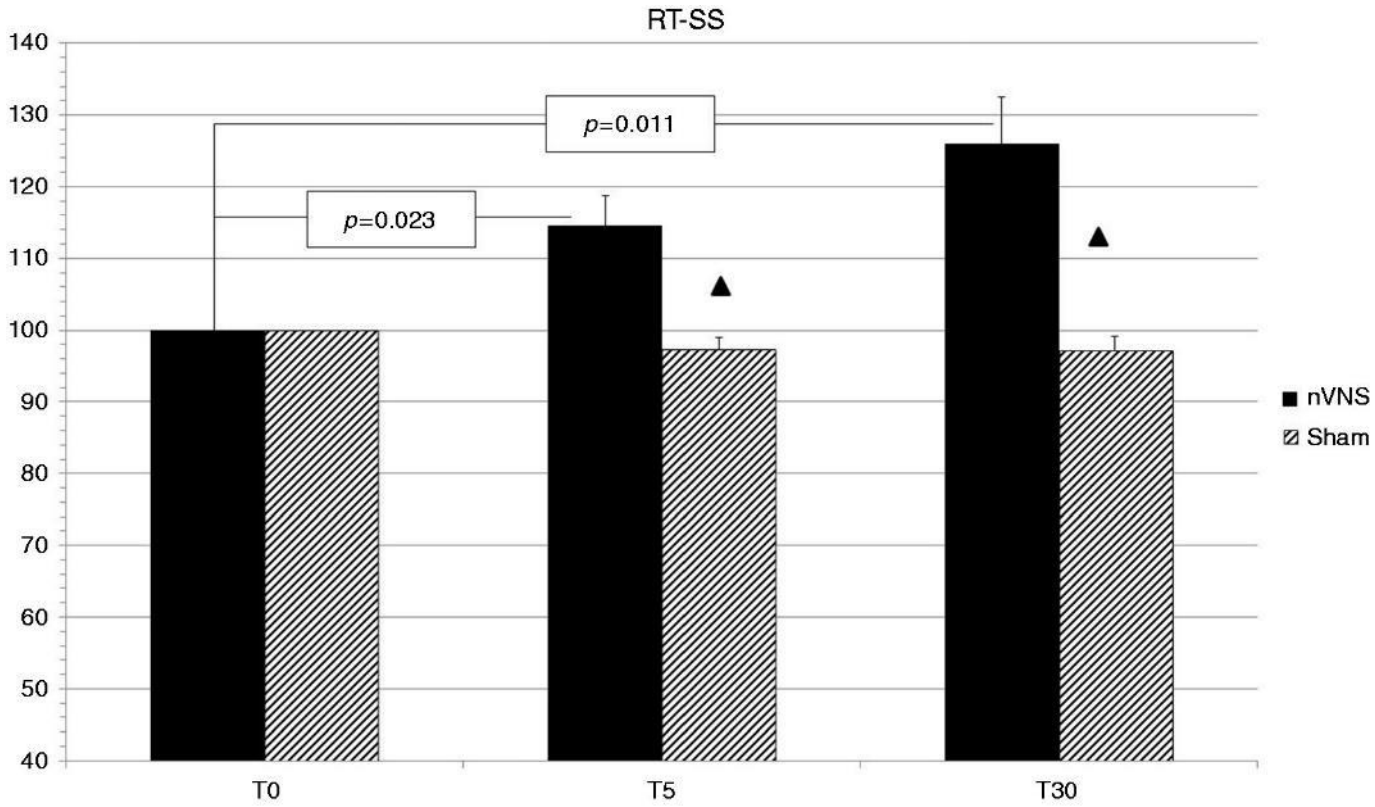
Vagus nerve stimulation



gammaCore (electroCore Inc.)

Nurosym (Parasym Ltd.)

VNS in pain



De Icco *et al*. **Peripheral vagal nerve stimulation modulates the nociceptive withdrawal reflex in healthy subjects: A randomized, cross-over, sham-controlled study**. *Cephalalgia.* 2018;38:1658-1664

VNS in pain conditions

Cluster headache ↓ frequency, ↓ severity, ↓ duration[1]

Recommended as a treatment for Cluster headache in the UK[2]

Migraine ↓ pain at 30-60 min[3]

Some evidence in migraine prevention[4]

1: Marin *et al.* **Non-invasive vagus nerve stimulation for treatment of cluster headache: early UK clinical experience.** *J Headache Pain.* 2018;19:114
2: NICE. **gammaCore for cluster headache (MTG46)**
3: Tassorelli *et al.* **Noninvasive vagus nerve stimulation as acute therapy for migraine: The randomized PRESTO study.** *Neurology.* 2018;91:e364-e373
4: Silberstein *et al.* **Chronic migraine headache prevention with noninvasive vagus nerve stimulation: The EVENT study.** *Neurology.* 2016;87:529-38

4) Can we target the ANS therapeutically?

Newcastle University

The future

Pathophysiology

Prognosis

Therapy

Newcastle University

Acknowledgements

Dr Quoc Vuong

Professor Justin Durham

Antonia Stergiou

Dr Paula Niven

Dr Brendan Payne

Dr Elizabeth Offen

Dr Paul Dorman

Professor Julia Newton

ME RESEARCH UK

NIHR | Newcastle Biomedical Research Centre

NHS The Newcastle upon Tyne Hospitals NHS Foundation Trust

From Newcastle. For the world.