Long-COVID /Post COVID-19 Syndrome
An Osteopathic Approach

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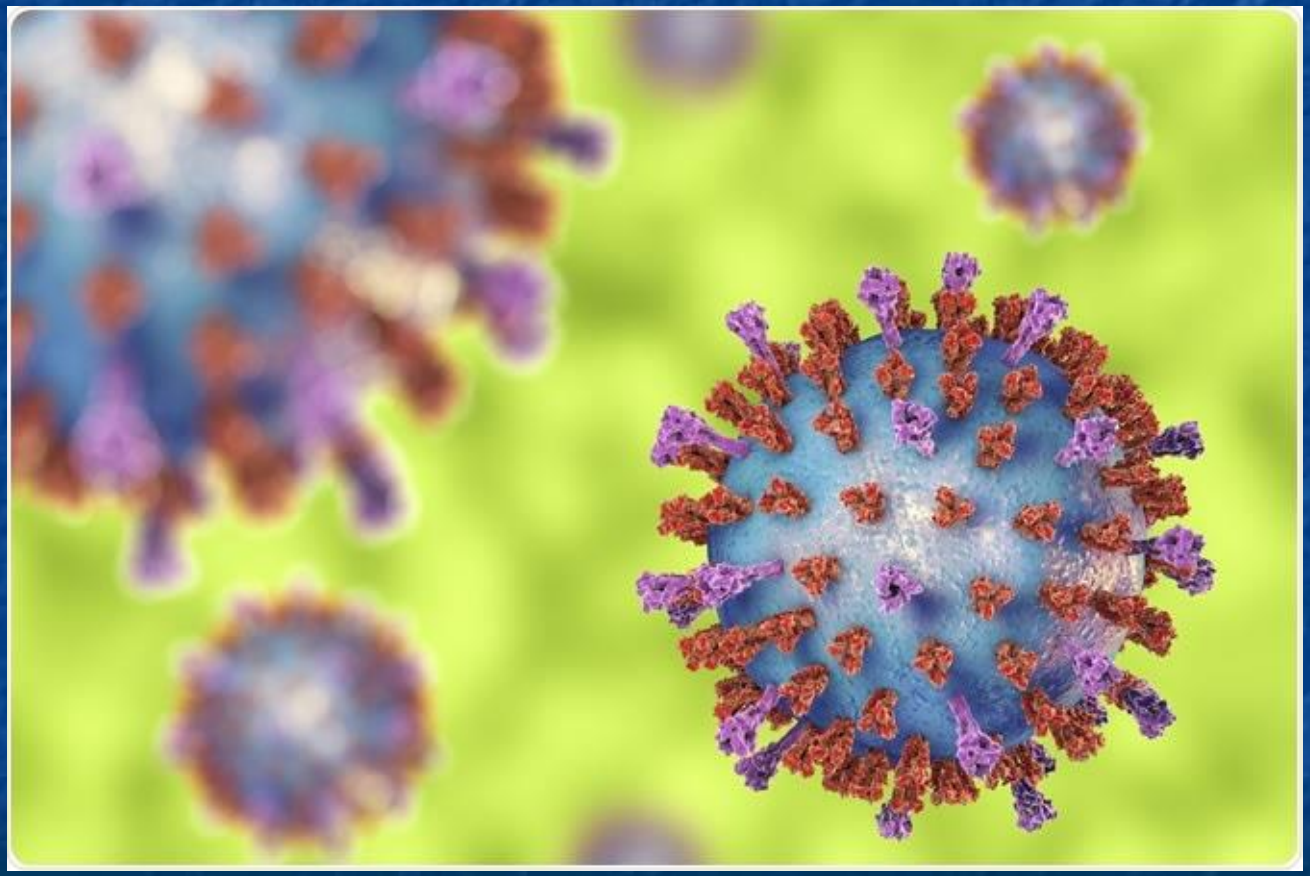
RESEARCH AND PRACTICE AWARD
AWARDS 2015
WINNER

Hon. Clinical Research Fellow
Faculty of Biology Medicine &
Health.
The University of Manchester
Manchester, UK.

Lecturer, International Faculty OSD

Vice Patron: University College of Osteopathy, London.

The common cold virus



Long-COVID

- Some have coined a new term for it: post-acute sequelae SARS-CoV-2 infection

PASC

What is Long-COVID?

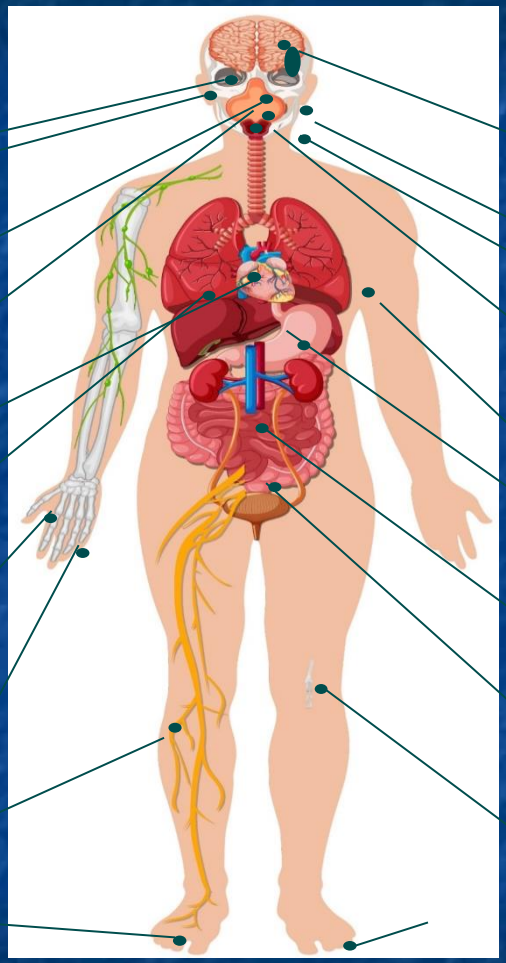
Most people affected by the SARS-CoV-2 virus are feeling back to normal within the first 4 weeks.

However, some people can experience serious health issues that continue even after their initial recovery period

- There are a huge amount of symptoms that people with long covid could experience, but the five most common are
  - fatigue (overall feeling of tiredness or lack of energy)
  - headache
  - Concentration problems (trouble concentrating or 'brain fog')
  - hair loss
  - difficulty breathing

Symptoms

Image courtesy of: brgfx / Freepik



Itchy or sore eyes, blurred vision

Ringing in the ears

Loss of smell;
strange smells (metallic or 'burning')

Loss of taste

Chest pain, fast heart rate (palpitations)

Chest - **Shortness of breath, especially on activity**, cough

Numbness, tingling or pain

Joint pain and swelling in the fingers

Pain and swelling of the knee

Numbness, tingling or pain

Poor sleep

Headache, **poor memory, confused, lightheaded, dizziness, difficulty paying attention, difficulty organising oneself**

Cheek pain

Throat itchy, dry, sore or tight

Hoarse voice

Rashes, including hives, new food allergies

Indigestion, wind

Bloating, pain, diarrhoea, constipation

Changes to periods, swelling of testes

Muscle pain, especially after exercise

Covid toe (like chilblains), rashes

Types of support

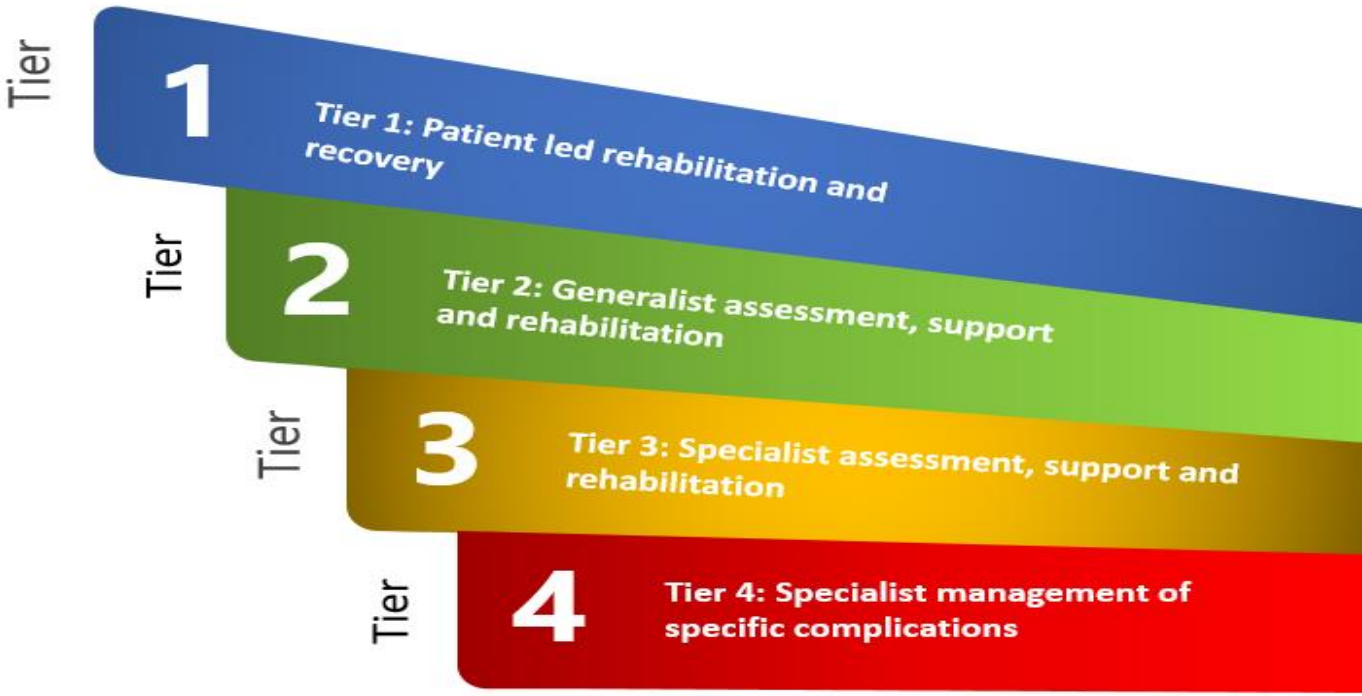
To make sure patients get the right level of support, people can access help at different levels

Advice, information and from www.yourcovidrecovery.nhs.uk

Support from your GP

Assessment and support from your local hospital and community team

Specialist support from a local or other hospital in GM



(Huang C et al. 2021. 6-month consequences of COVID-19 in patients discharged from hospitals: a cohort study. Lancet, 397:220-32 2021)

Largest cohort study (n=1733) with the longest follow-up duration for the consequences of adult patients discharged from hospital recovering

The most common symptoms were fatigue or muscle weakness and sleep difficulties

Journal of Medical Hypotheses

Into the looking glass: Post-viral syndrome post COVID-19

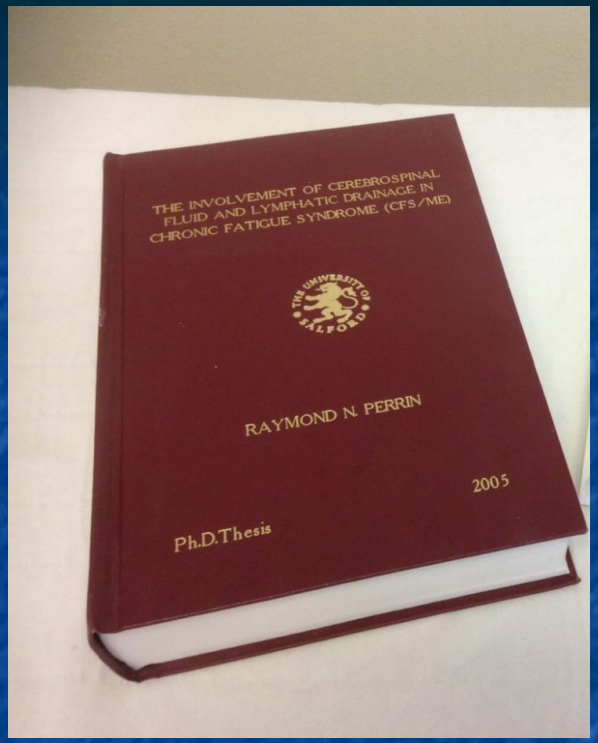
(160+ citations)

Ray Perrin, Lisa Riste, Mark Hann, Andreas Walther, Annice Mukherjee & Adrian Heald

Med Hypotheses. 2020; 144: 110055.

The British School of Osteopathy 1980-84

University of Salford 1994-2005



PhD Thesis 2005

The Involvement of cerebrospinal Fluid and Lymphatic Drainage in Chronic Fatigue Syndrome (ME/CFS)

PRESTON, UK

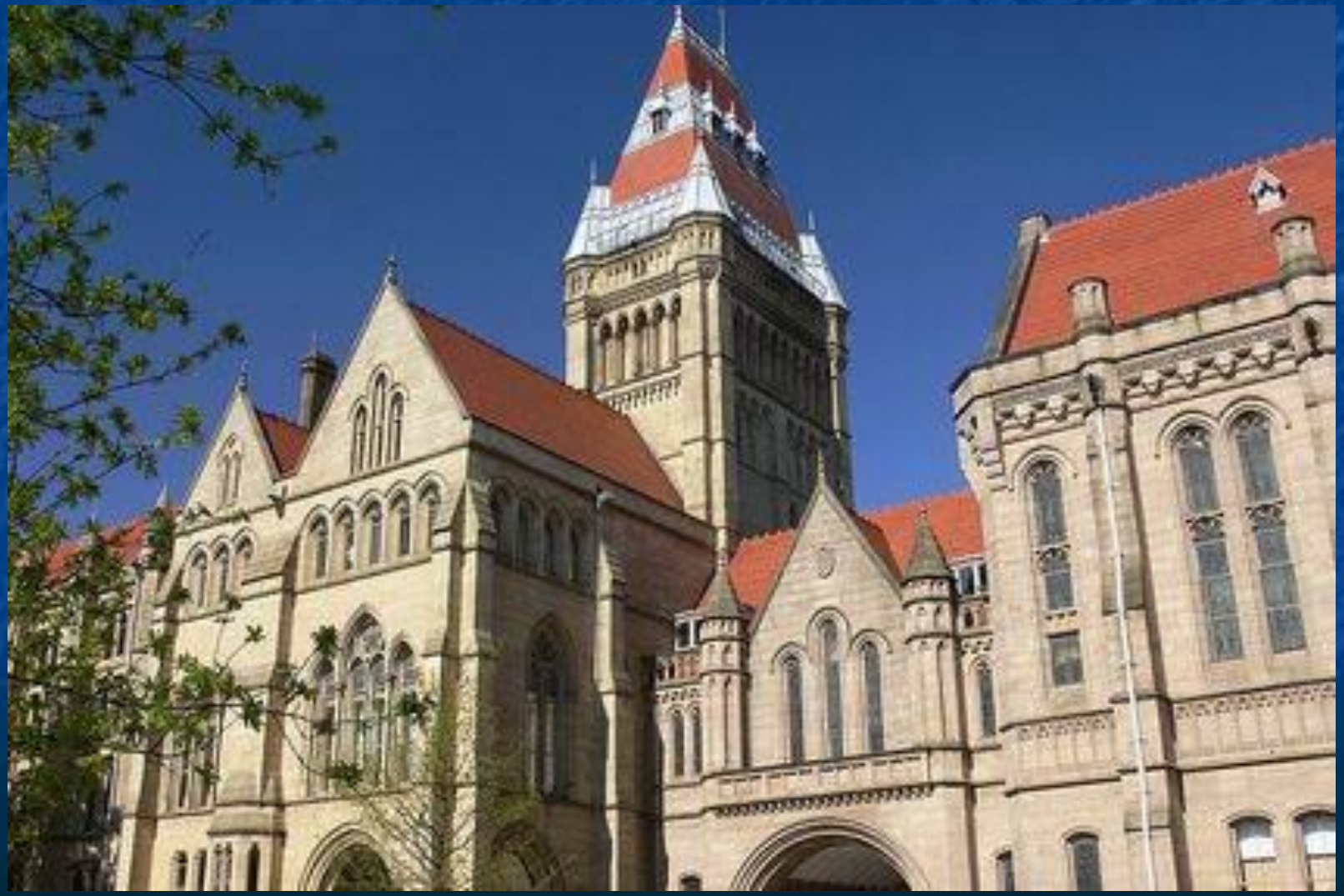

Edinburgh
Glasgow
Newcastle
Belfast
Preston
uclan
York
Manchester
Liverpool
London

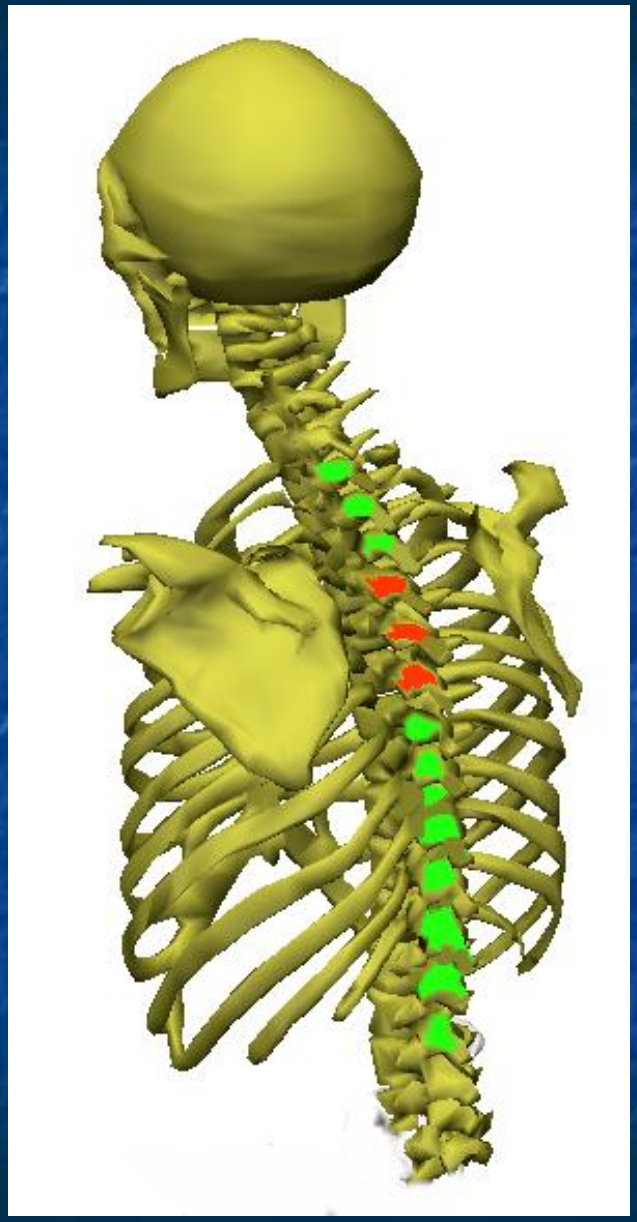

uclan


uclan


uclan
School of
Psychology

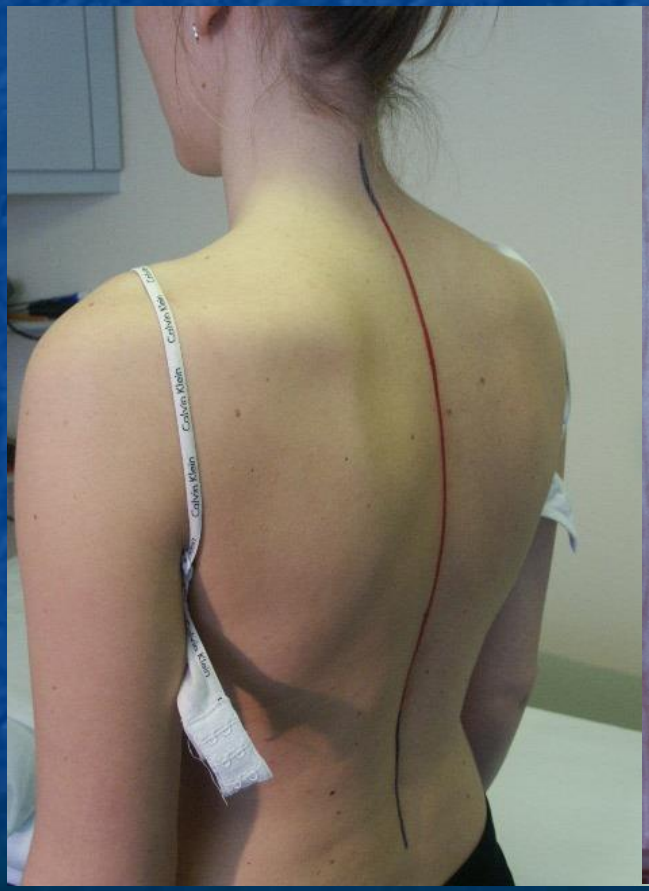
The University of Manchester, UK.

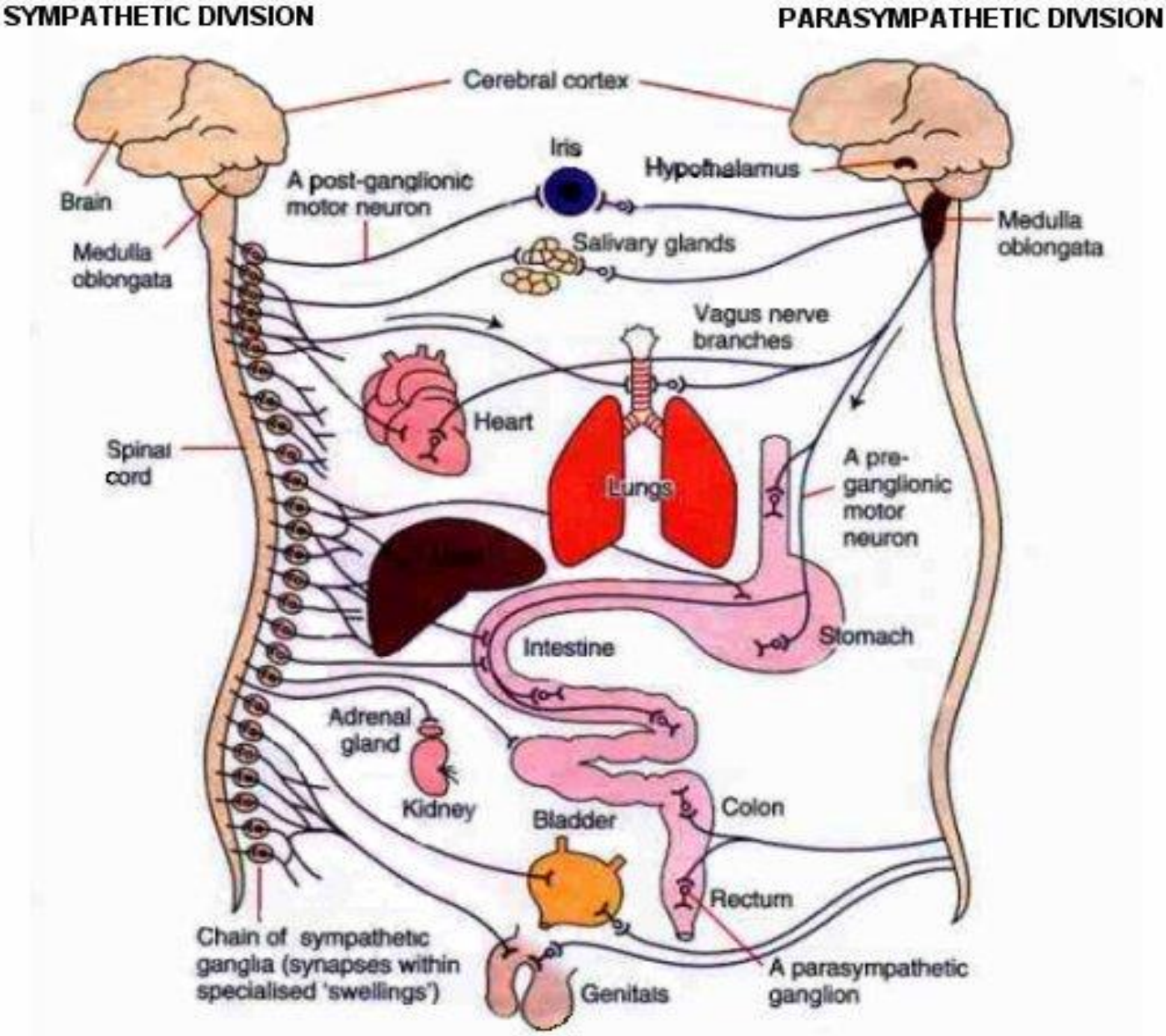




Thoracic Spine (dorsal spine)
Area most affected in ME/CFS

Postural strain in the thoracic spine

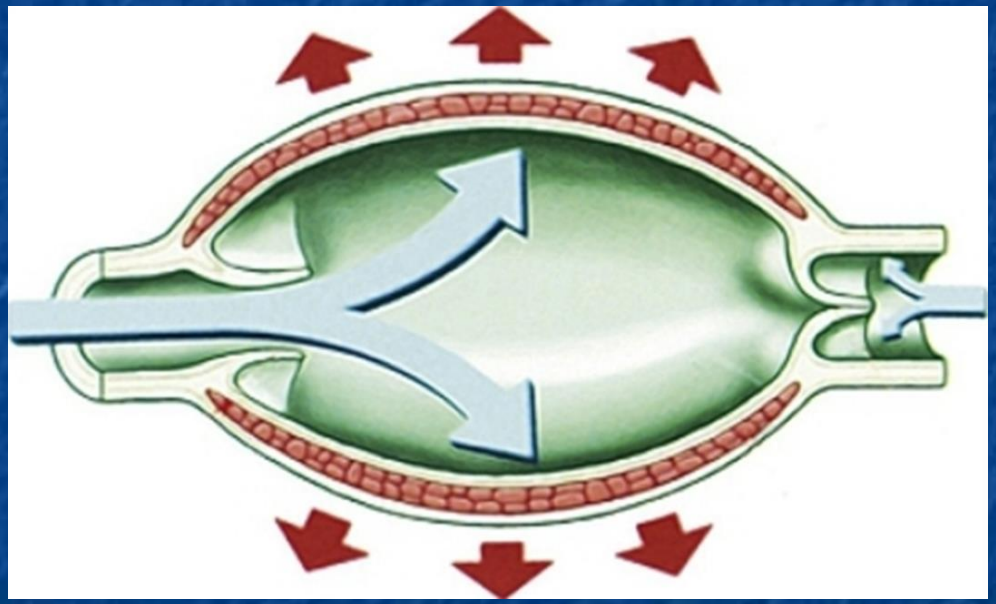


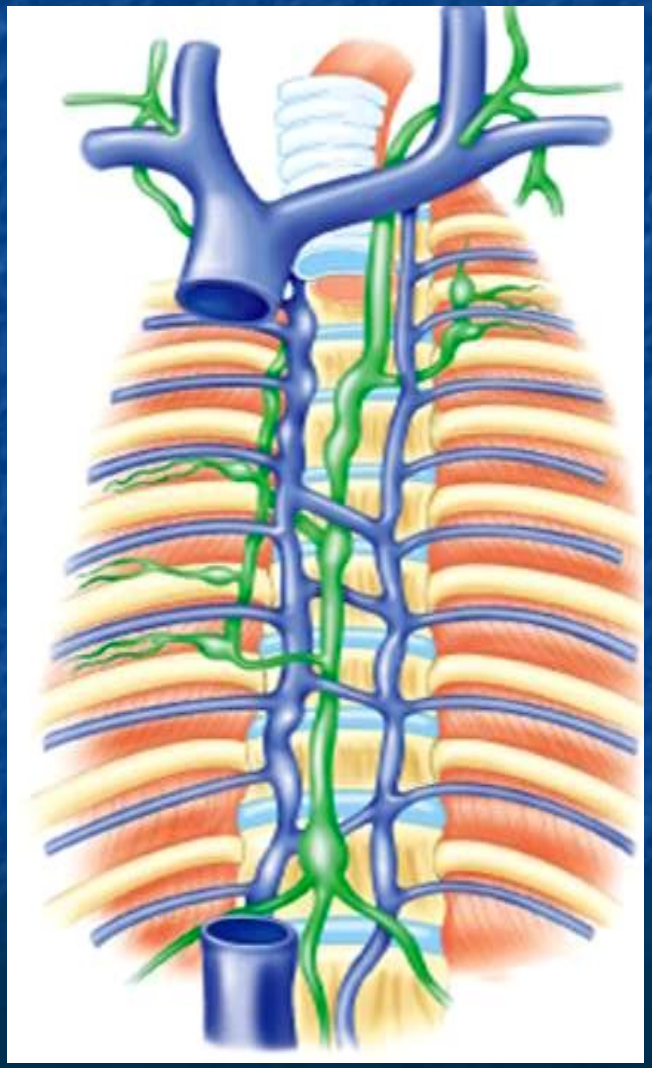

SYMPATHETIC DIVISION
PARASYMPATHETIC DIVISION
Cerebral cortex
Iris
Hypothalamus
Brain
A post-ganglionic motor neuron
Medulla oblongata
Salivary glands
Medulla oblongata
Vagus nerve branches
Heart
Spinal cord
Lungs
A pre-ganglionic motor neuron
Intestine
Stomach
Adrenal gland
Kidney
Bladder
Colon
Rectum
Chain of sympathetic ganglia (synapses within specialised 'swellings')
Genitals
A parasympathetic ganglion

SYMPATHETIC- SOMATIC

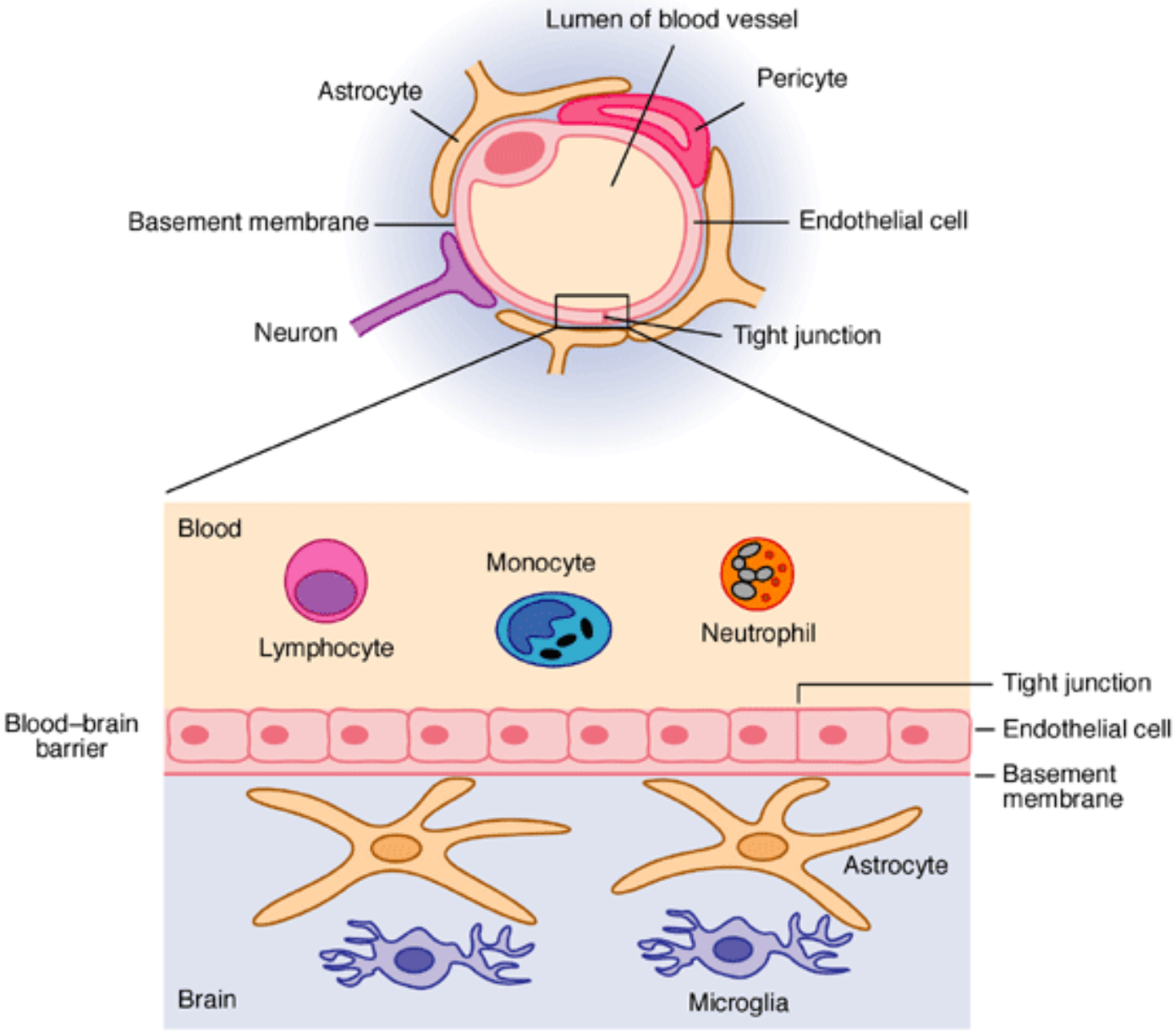
The connection between peripheral somatic nociceptive afferent fibres and sympathetic nerves has been observed in pathological mechanisms (Janig, 1988).

Lymphatic System



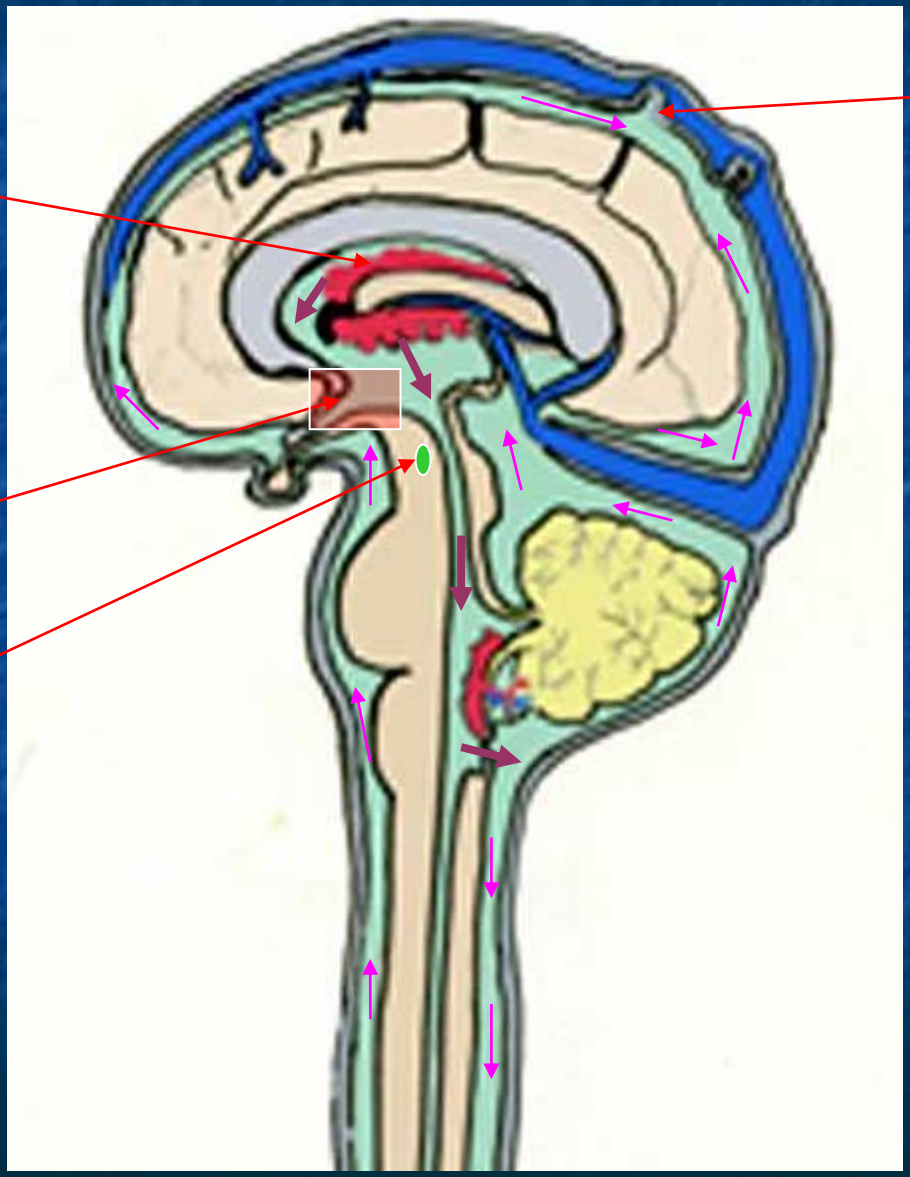


WHAT IS REALLY GOING ON IN THE BRAIN?



The blood–brain barrier (BBB)

The Hypothalamus



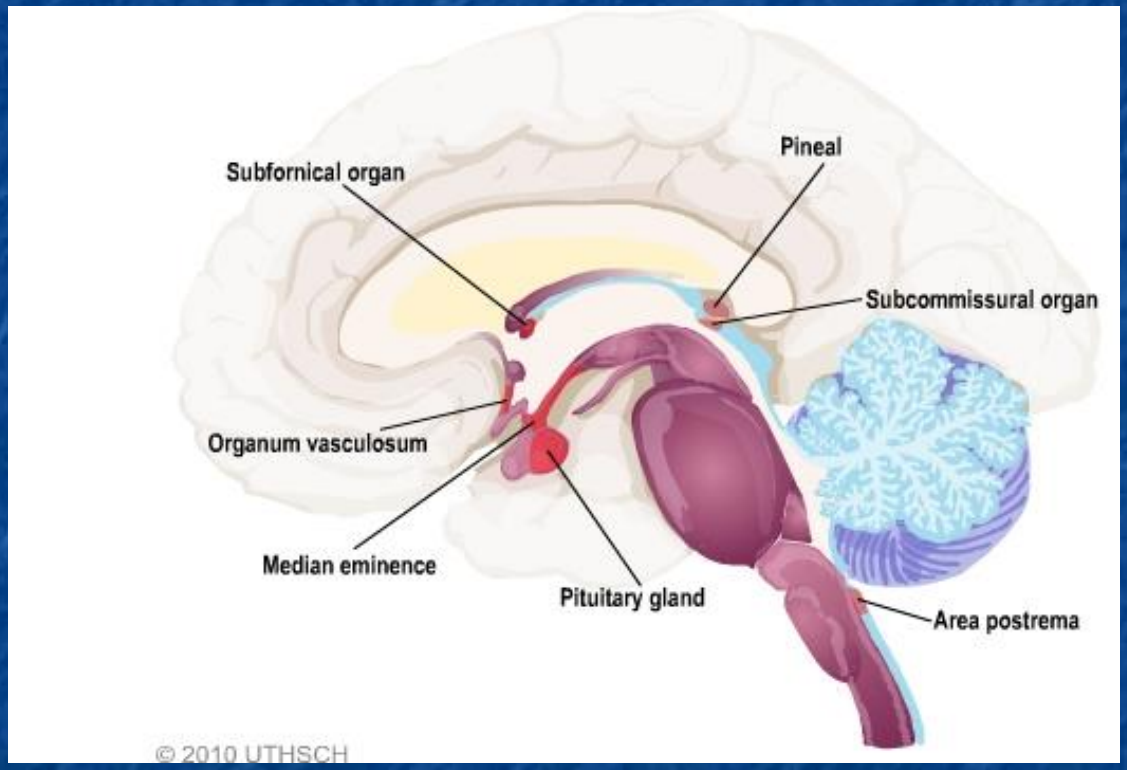
- The human insulin protein is composed of 51 amino acids and has a molecular weight of 5808 Da.
-
- 5808 Daltons is whapping!
- Molecular weight of water= $M(H_2O) \approx$ 18 **Daltons**

Circumventricular Organs

- Pineal Gland
- Pituitary Gland
- Area Postrema
- Subcommissural Organ
- Subfornical Organ
- Median Eminence

& Organ Vasculosum

(part of Hypothalamus)

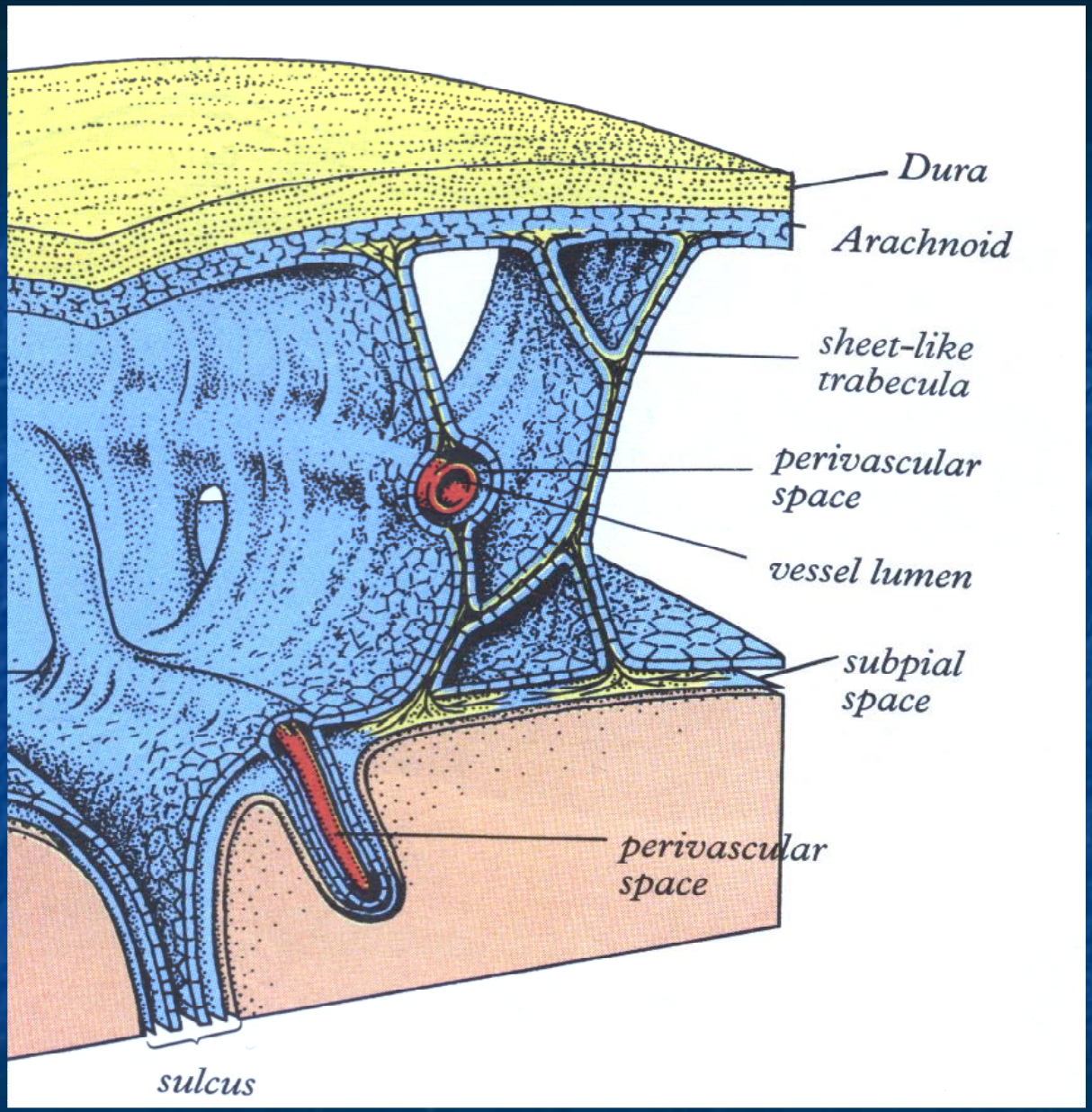


- Dr Still admitted, "Possibly less is known of the lymphatics than any other division of the life-sustaining machinery of man."

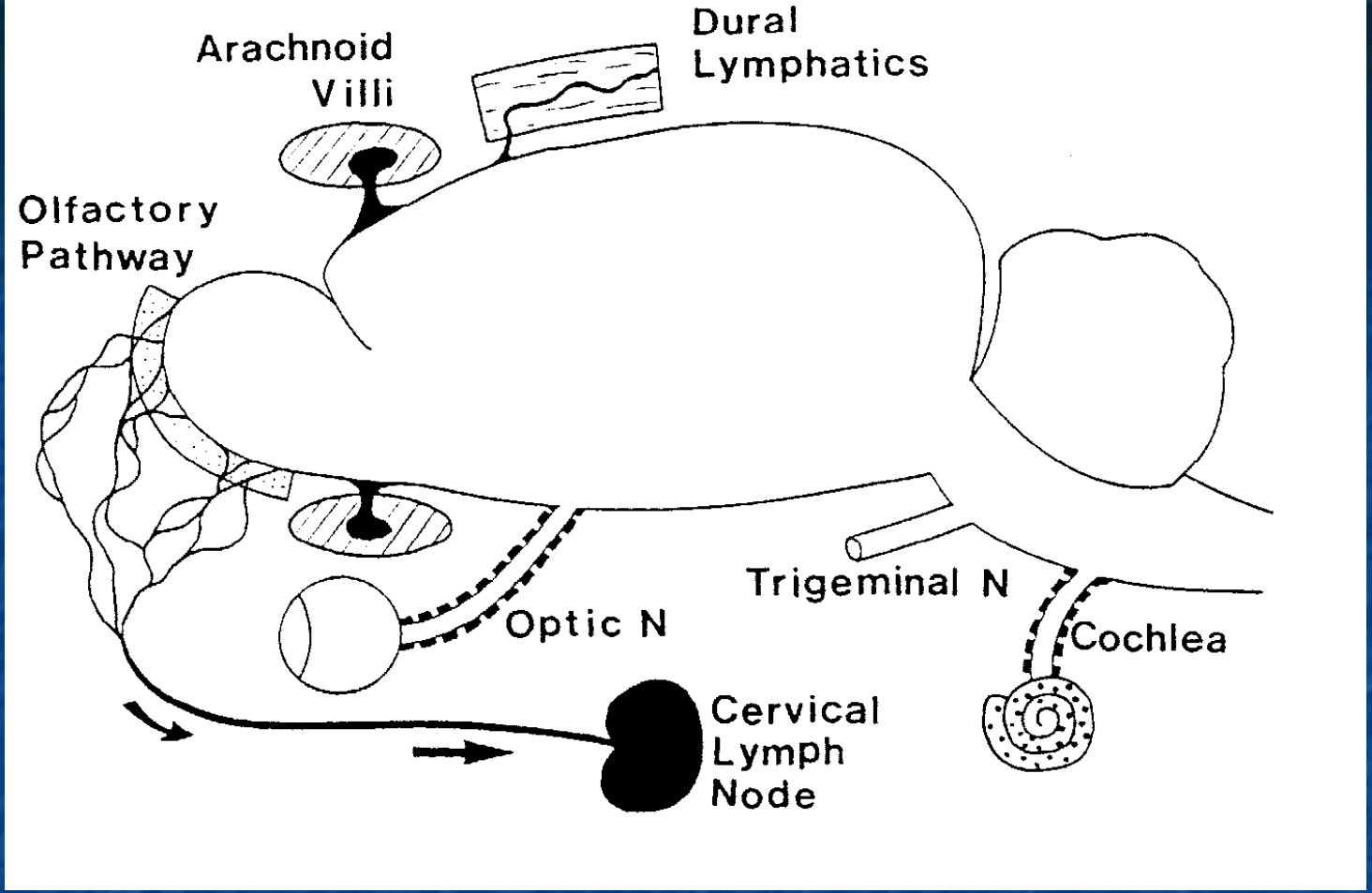
- Still AT. *The Philosophy and Mechanical Principles of Osteopathy*. Kansas City, Mo: Hudson-Kimberly Pub Co;1902 : 65,66.

- When asked about the "eternal truths" of osteopathy, Dr Still responded, "[Those truths] are found in the spinal column with all of its intricate bony framework, plus the beautiful circulation of blood and lymph through the nerve centers of the spinal cord and throughout the whole body."

- Hildreth AG. *The Lengthening Shadow of Dr Andrew Taylor Still*. Macon, Mo: Arthur Grant Hildreth; 1938:342 ,409



Section of the meninges illustrating perivascular spaces
(Illustration from Gray's Anatomy 38th Edition p.1213, Zhang *et al.*, 1990)

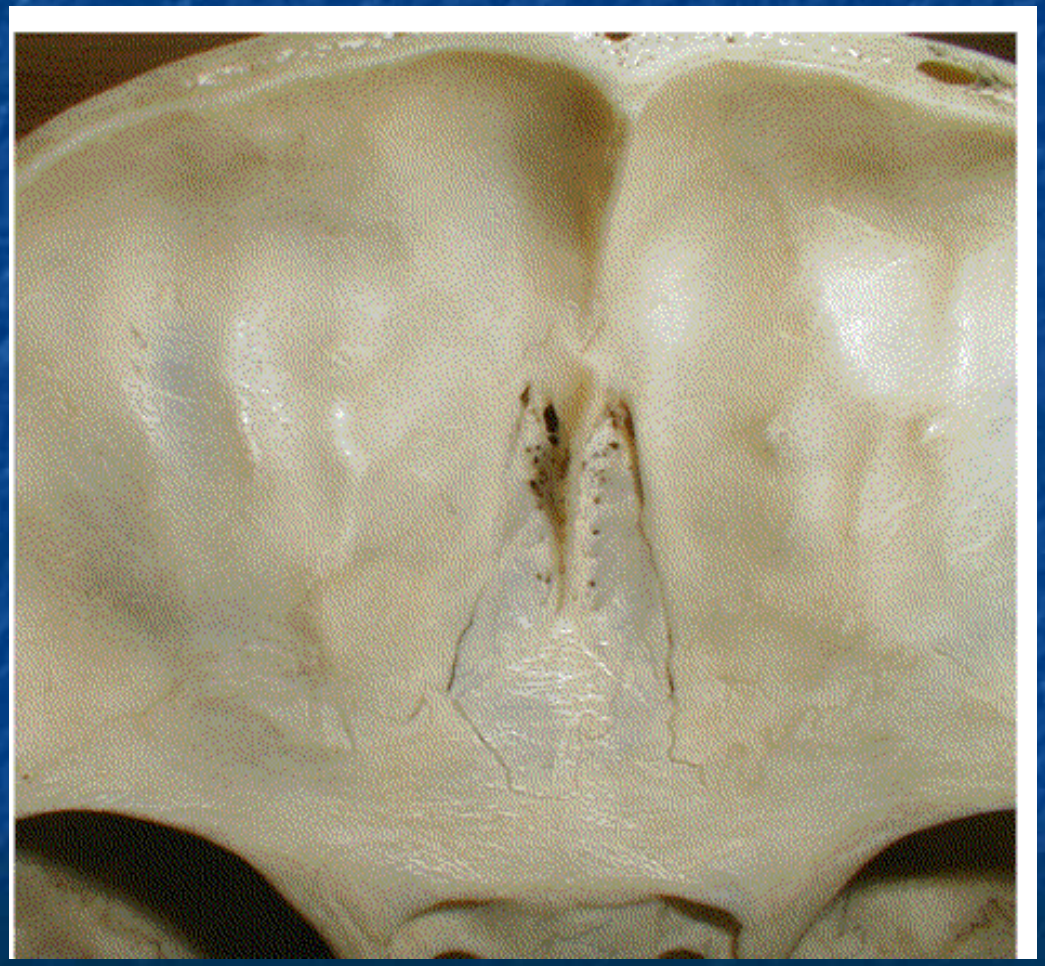


The lymphatic drainage of the rat's brain

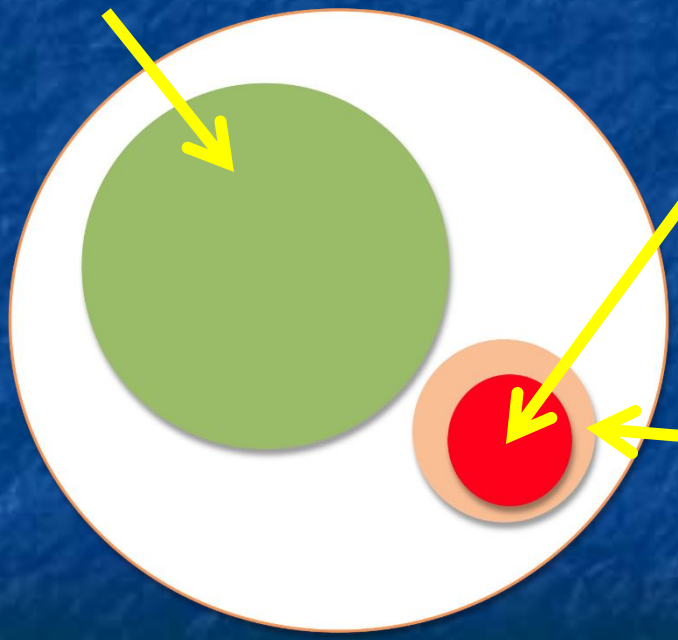
Kida S, Pantazis A, Weller RO. 1993

Neuropathology, Faculty of Medicine, University of Southampton, UK.

The Cribriform Plate

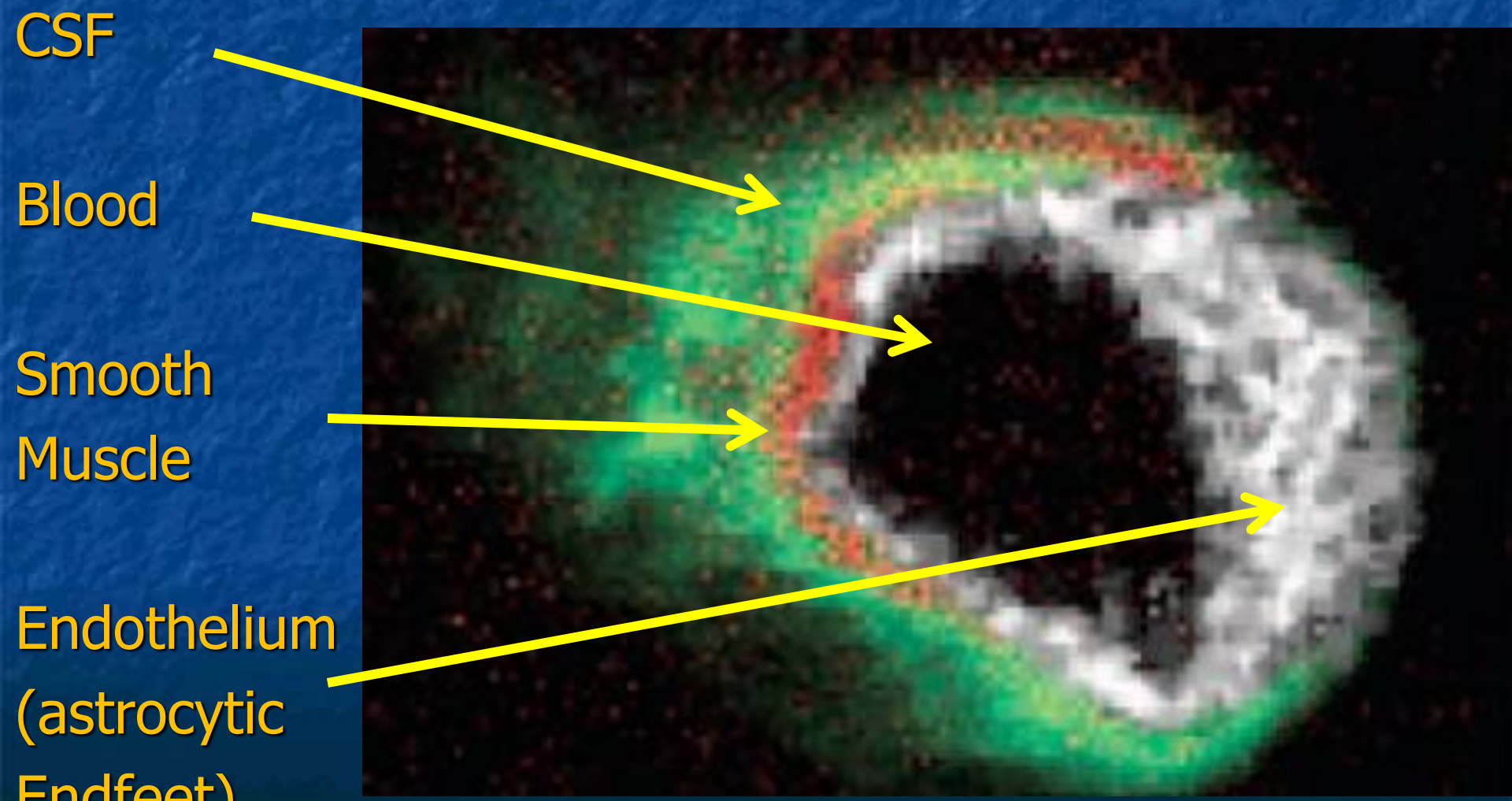


PERFORATION THROUGH THE CRIBRIFORM PLATE

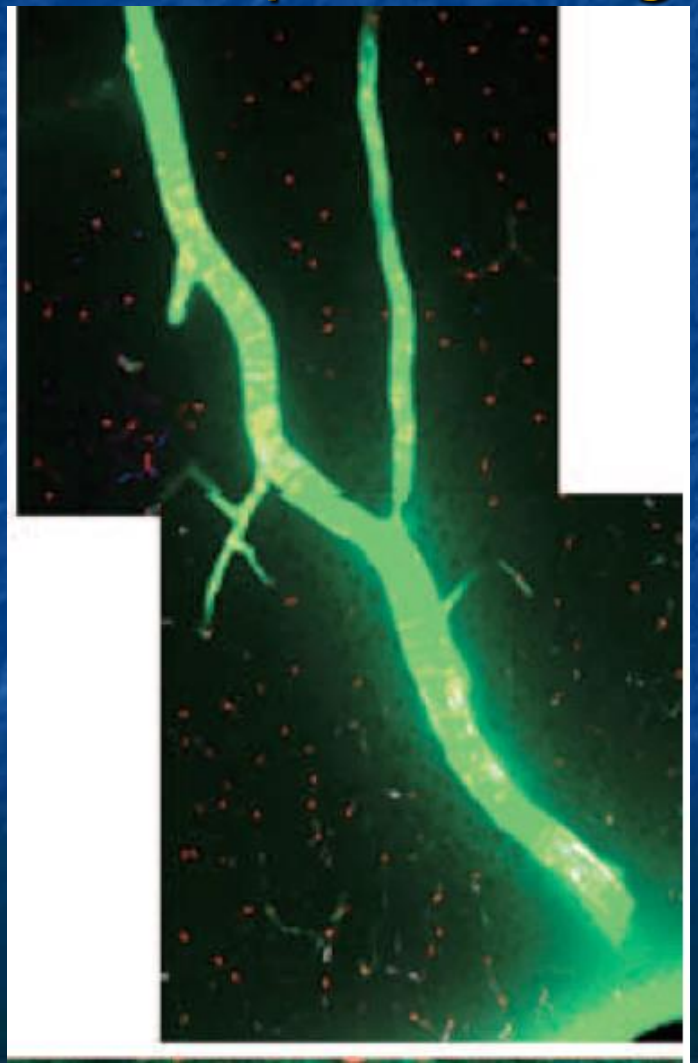


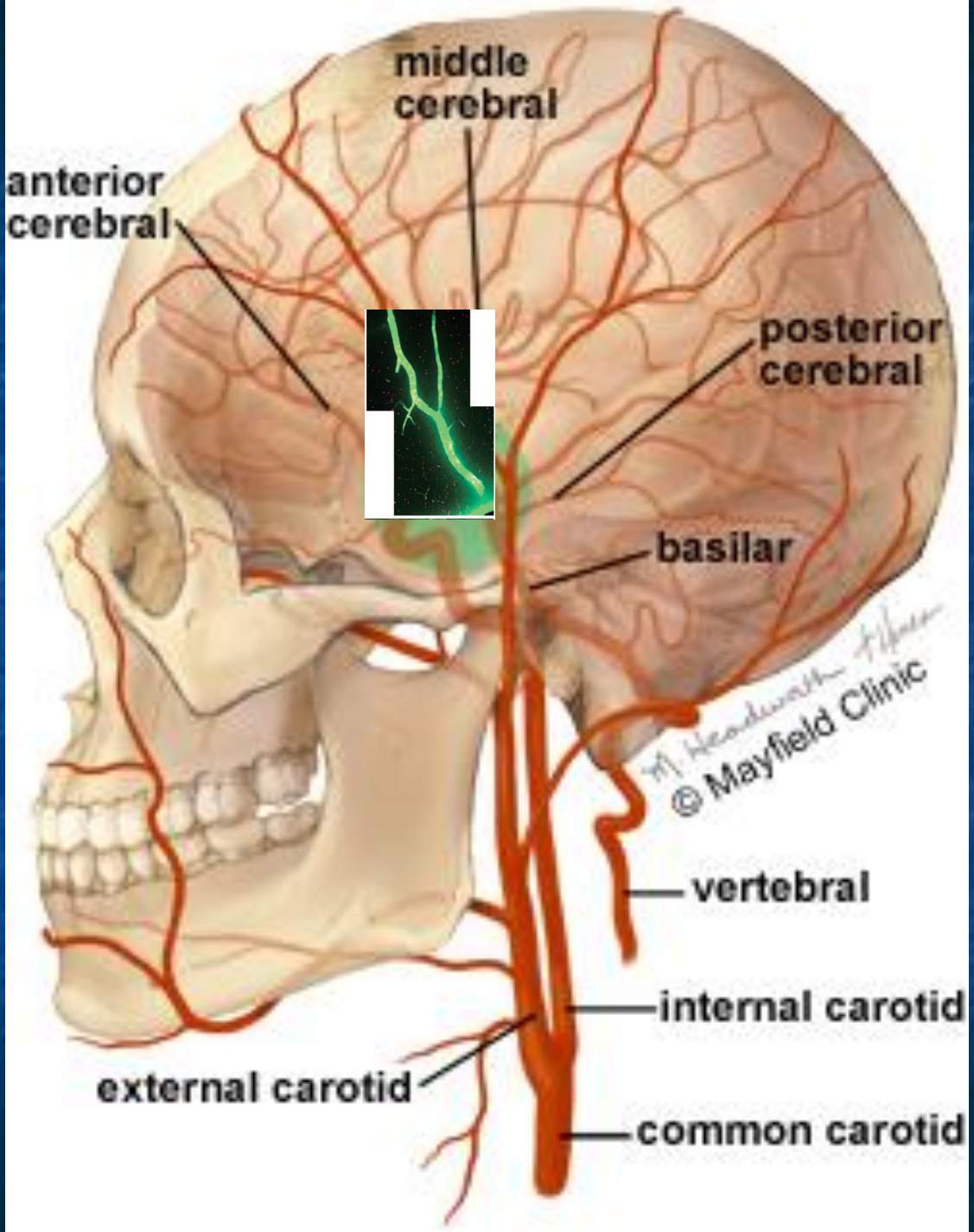
CSF tracer (Green) moves along the paravascular space around an arteriole in the brain.

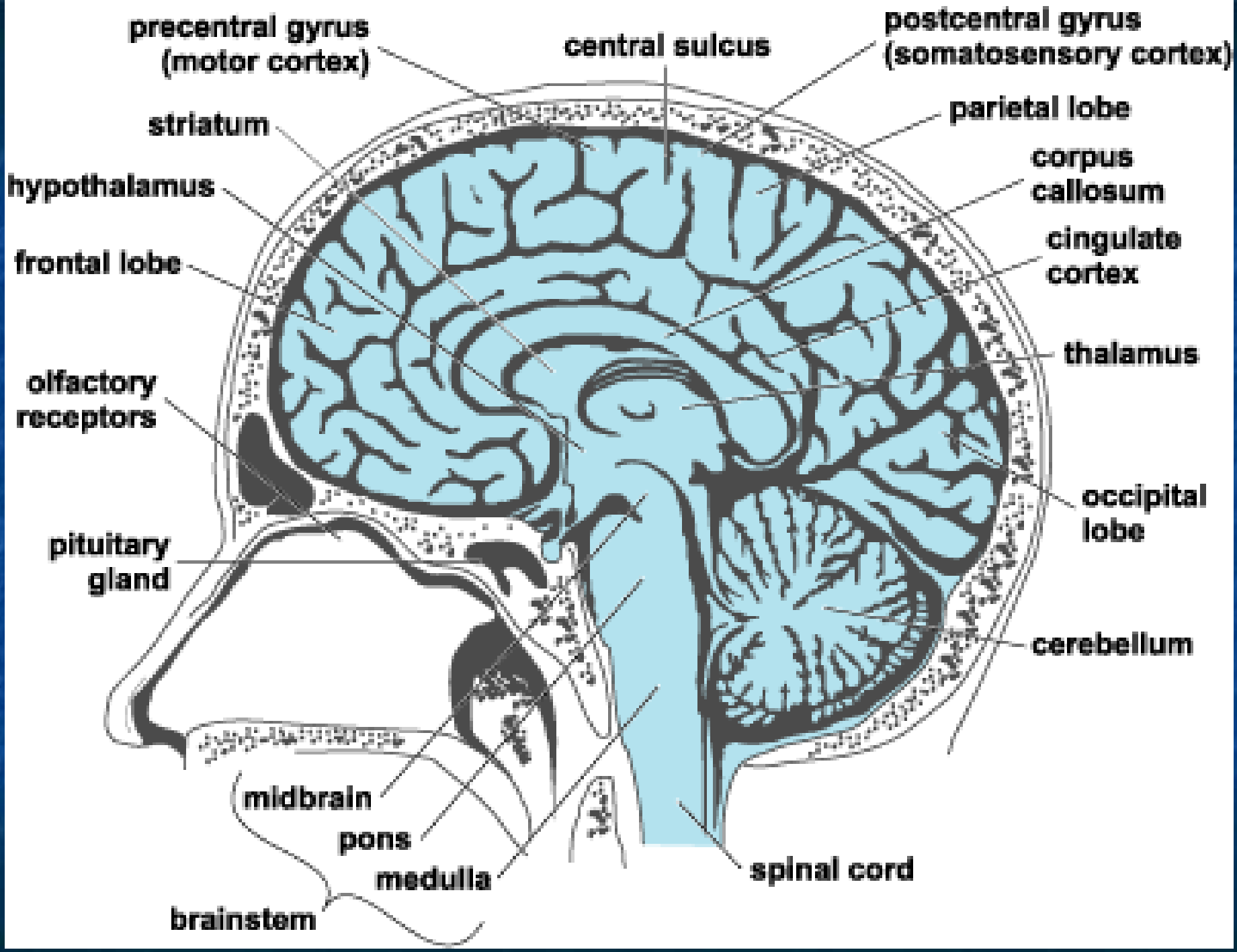
Iliff J et al. August 2012



Large amounts of tracer are observed in the basal ganglia and thalamus, entering along large ventral perforating arteries




middle cerebral
anterior cerebral
posterior cerebral
basilar
© Mayfield Clinic
vertebral
internal carotid
external carotid
common carotid


precentral gyrus
(motor cortex)
central sulcus
postcentral gyrus
(somatosensory cortex)
striatum
parietal lobe
hypothalamus
corpus
callosum
frontal lobe
cingulate
cortex
thalamus
olfactory
receptors
occipital
lobe
pituitary
gland
cerebellum
midbrain
pons
medulla
spinal cord
brainstem

The Basal Ganglia

NOT GLUTAMATE

gamma-Aminobutyric acid

MAINLY

GABA

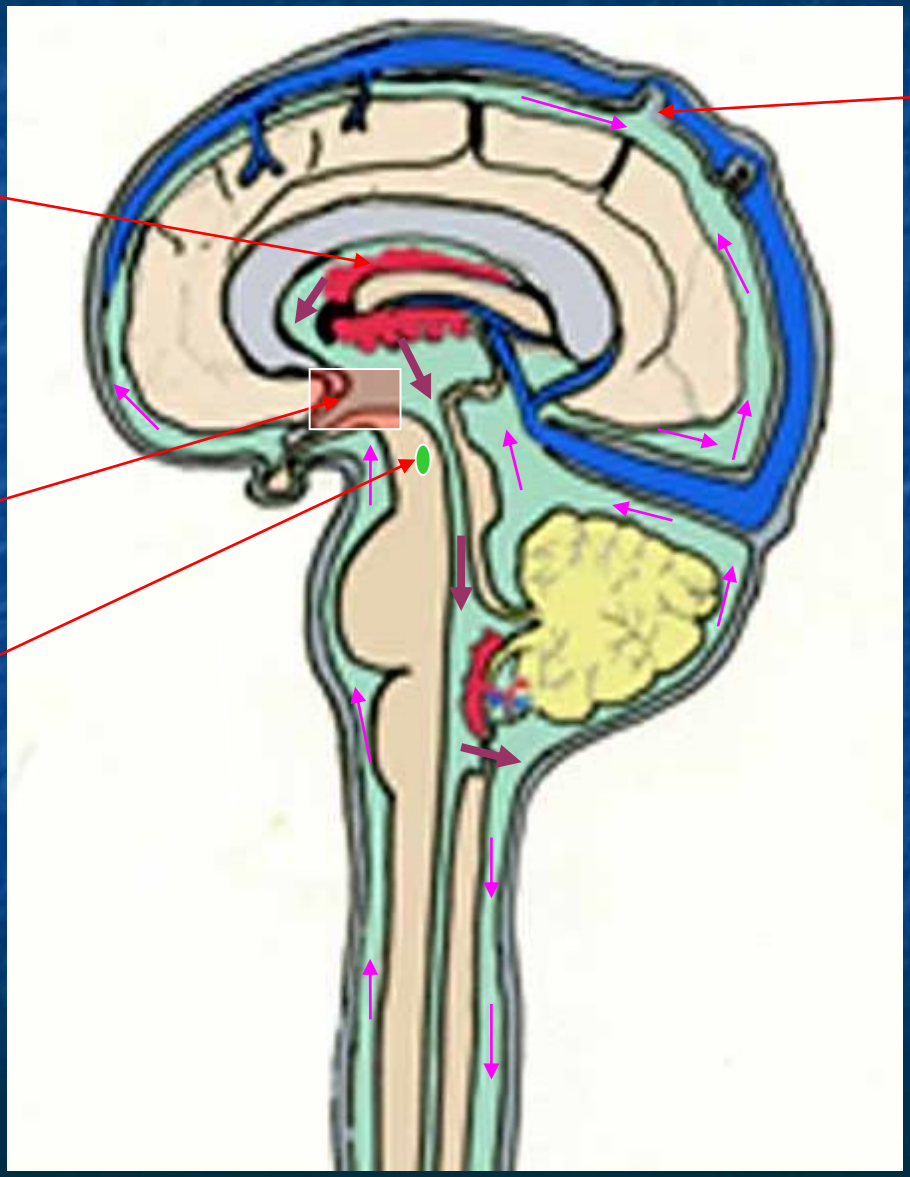
a group of subcortical nuclei responsible primarily for, motor control, as well as other roles such as motor learning, cognitive functions, emotions and pain control.

The Thalamus

RELAYING SENSORY AND MOTOR SIGNALS TO CEREBRAL CORTEX

THE REGULATION OF CONSCIOUSNESS ,SLEEP ALERTNESS AND PAIN.

The Hypothalamus



Sleep Drives Metabolite Clearance from the Adult Brain

Xie L. et al

2013 VOL 342 SCIENCE 373-377

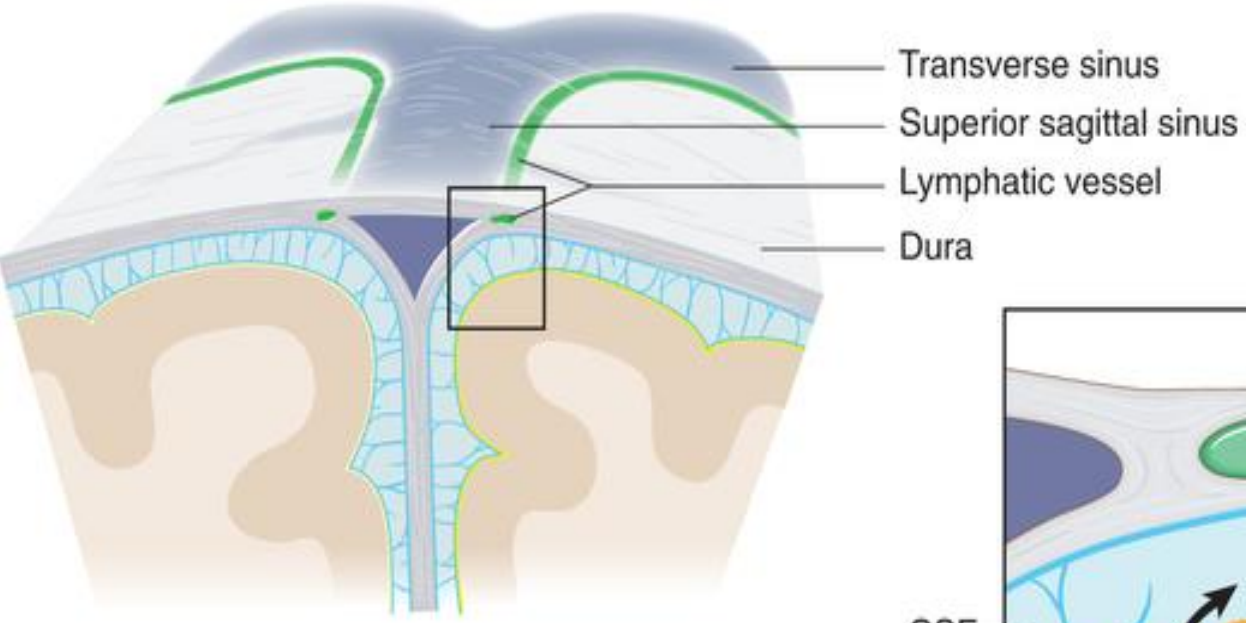
Same Rochester University team as previous study by Jeffrey J. Iliff

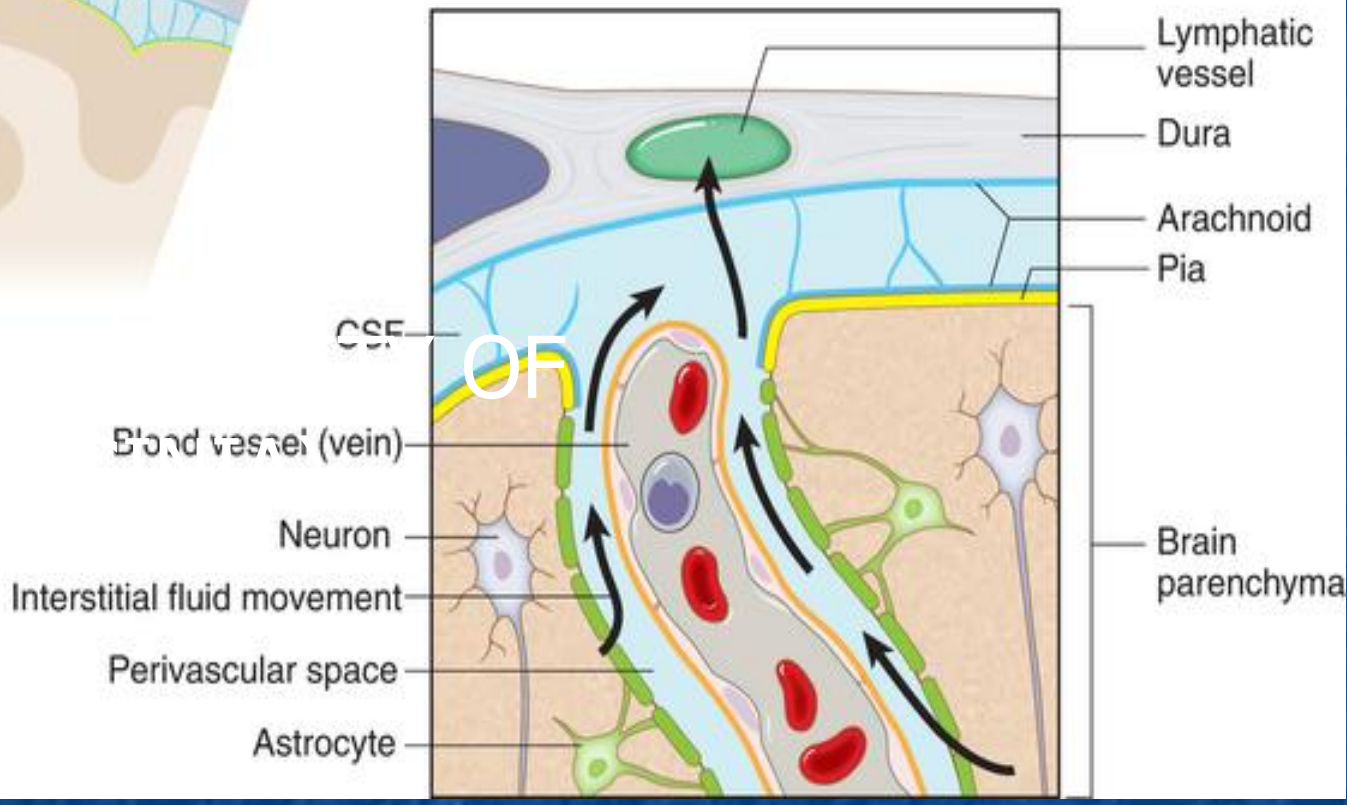
Under Prof. Maiken Nedergaard

Alpha Wave Intrusion in ME/CFS

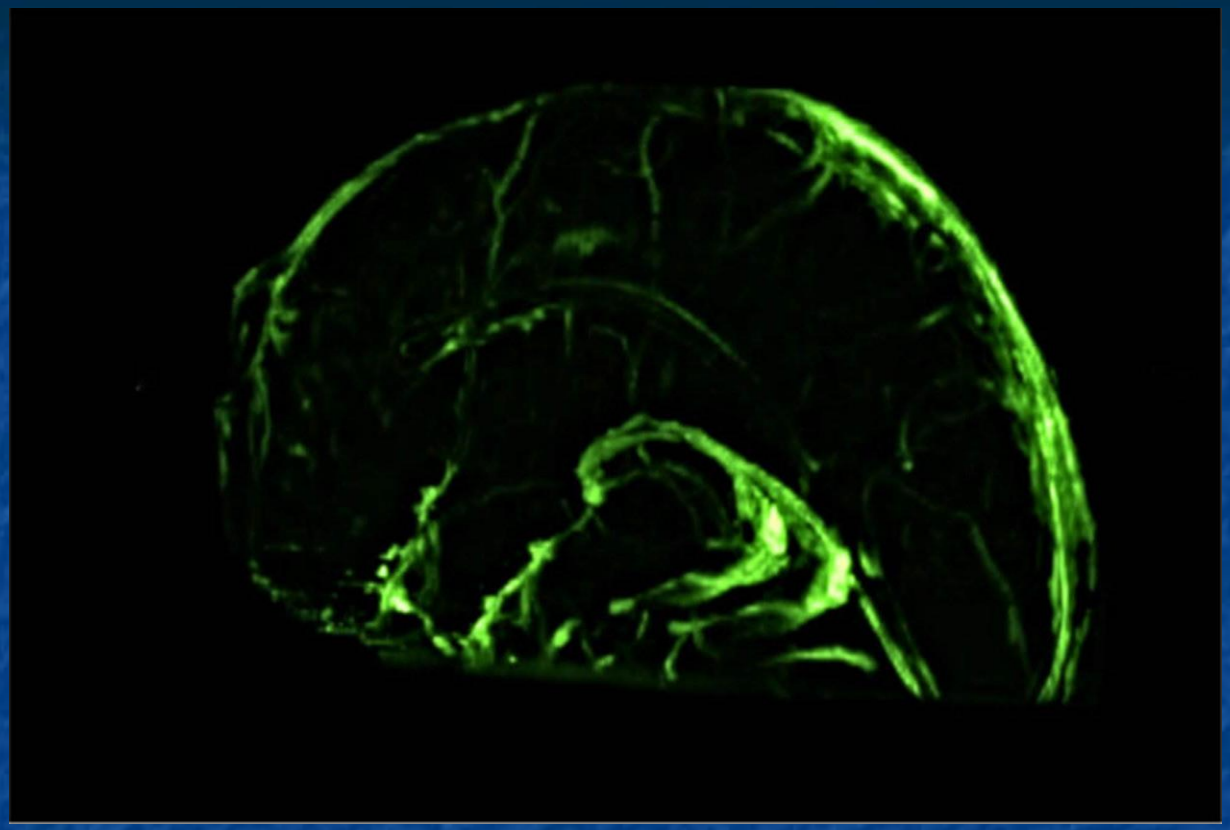
Van Hoof E, De Becker P, Lapp C, Cluydts R, De Meirleir K. Defining the occurrence and influence of alpha-delta sleep in chronic fatigue syndrome. Am J Med Sci. 2007 Feb;333(2):78-84

“wired and fired” or Shattered





Antoine Louveau et al. **Structural and functional features of central nervous system lymphatic vessels.** *Nature*, 2015; DOI: 10.1038/nature14432



3D-rendering of dural lymphatics (green) in a 47 year old woman.

Absinta, Ha et al. Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI, October 3, 2017 eLife: 10.7554/eLife.29738.

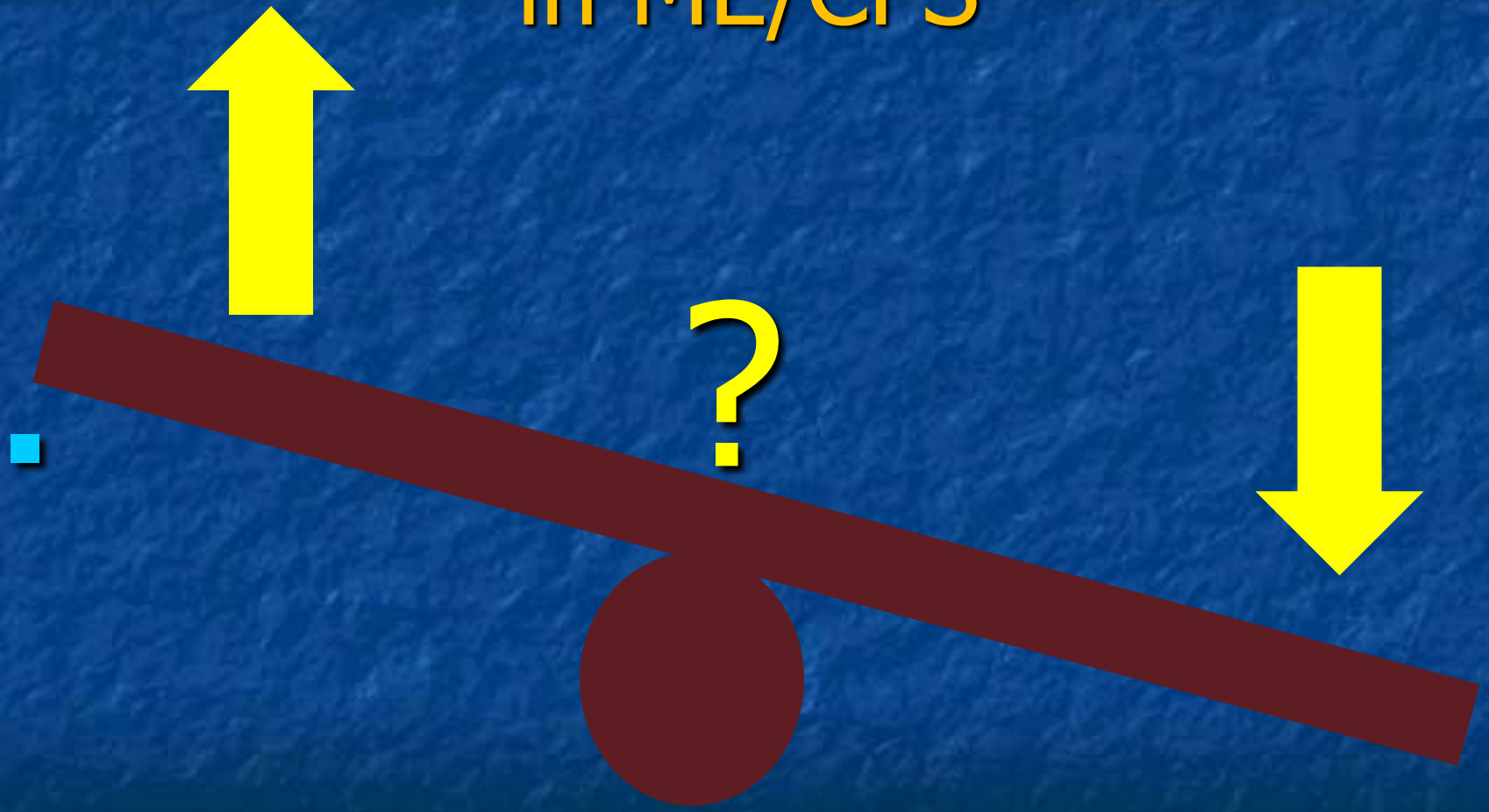
2013:Muscle fatigue in ME/CFS The Reason Uncovered!

20 times as much lactic acid detected when exercised and related directly to central autonomic control.

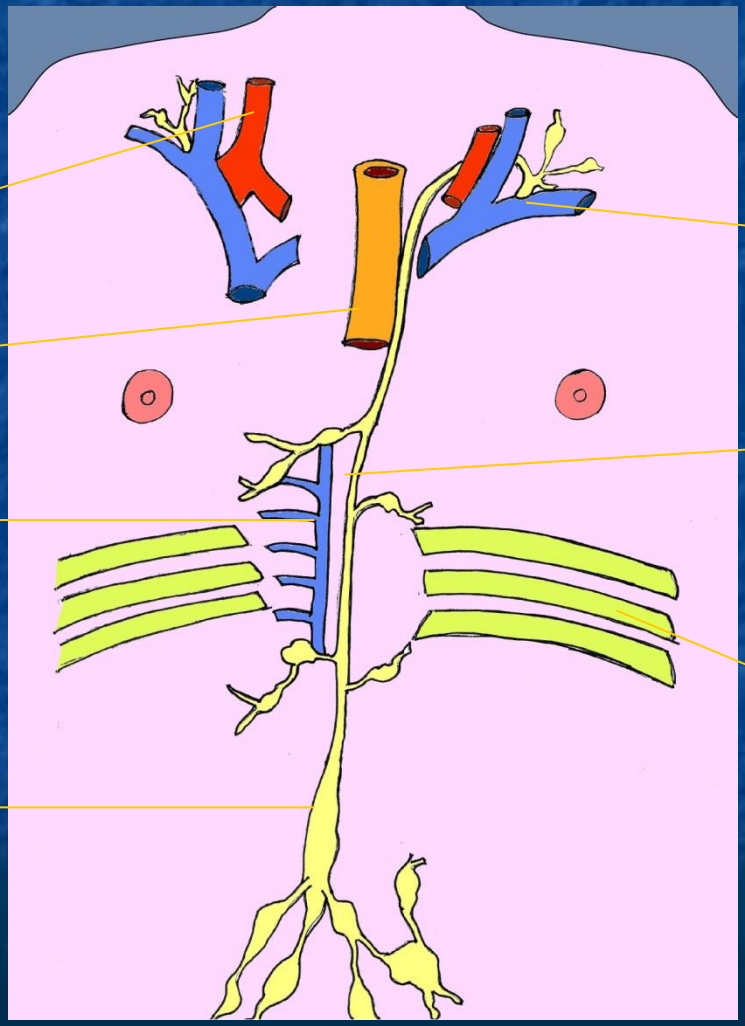
Is there a possible underlying neuro-lymphatic cause for the myalgia?

He J, Hollingsworth KG, Newton JL, Blamire AM. Cerebral vascular autonomic control is associated with skeletal muscle pH in chronic fatigue syndrome patients both at rest and during dynamic stimulation. Neuroimage Clin. 2013 Jan 5;2:168-73

Sympathetic Nervous System in ME/CFS



The Thoracic Duct

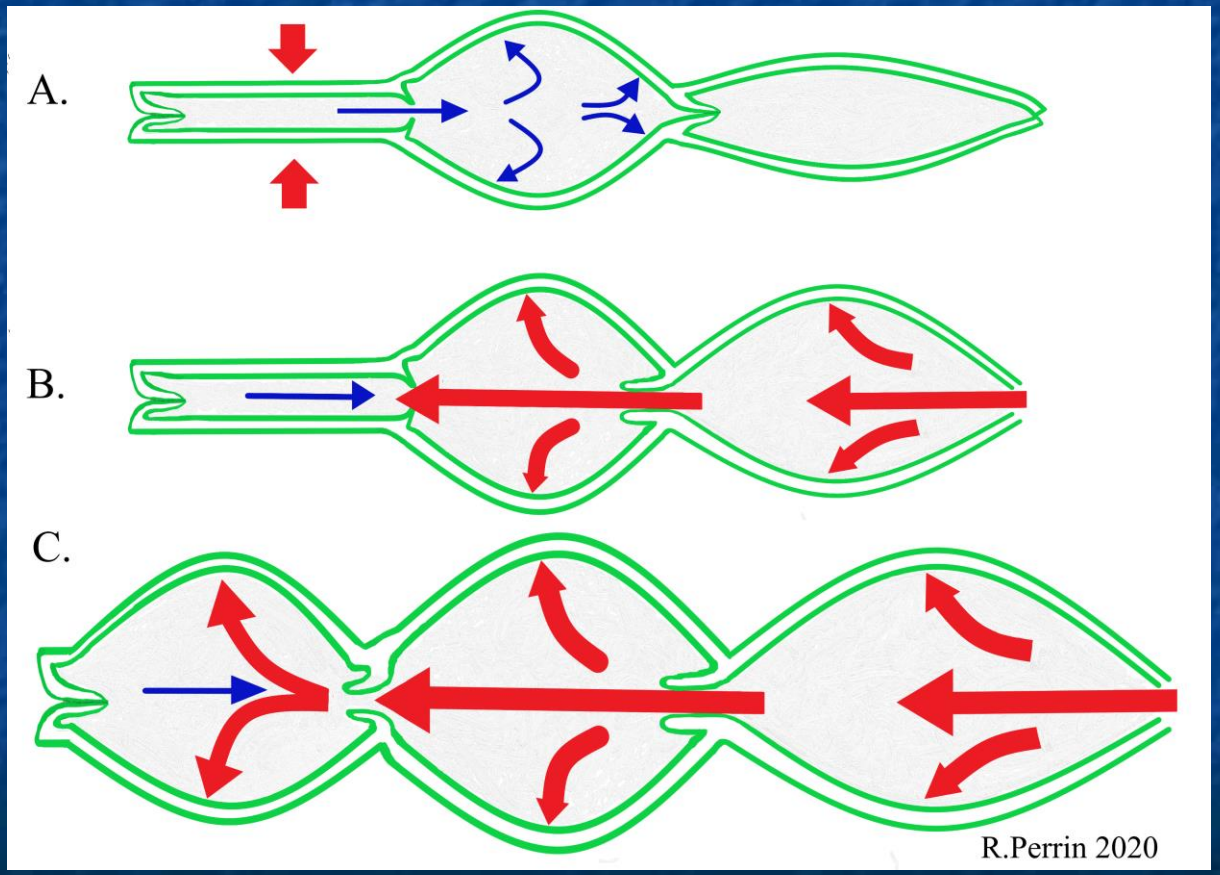


- Professor John Kinmonth
- Guys and St Thomas Medical School

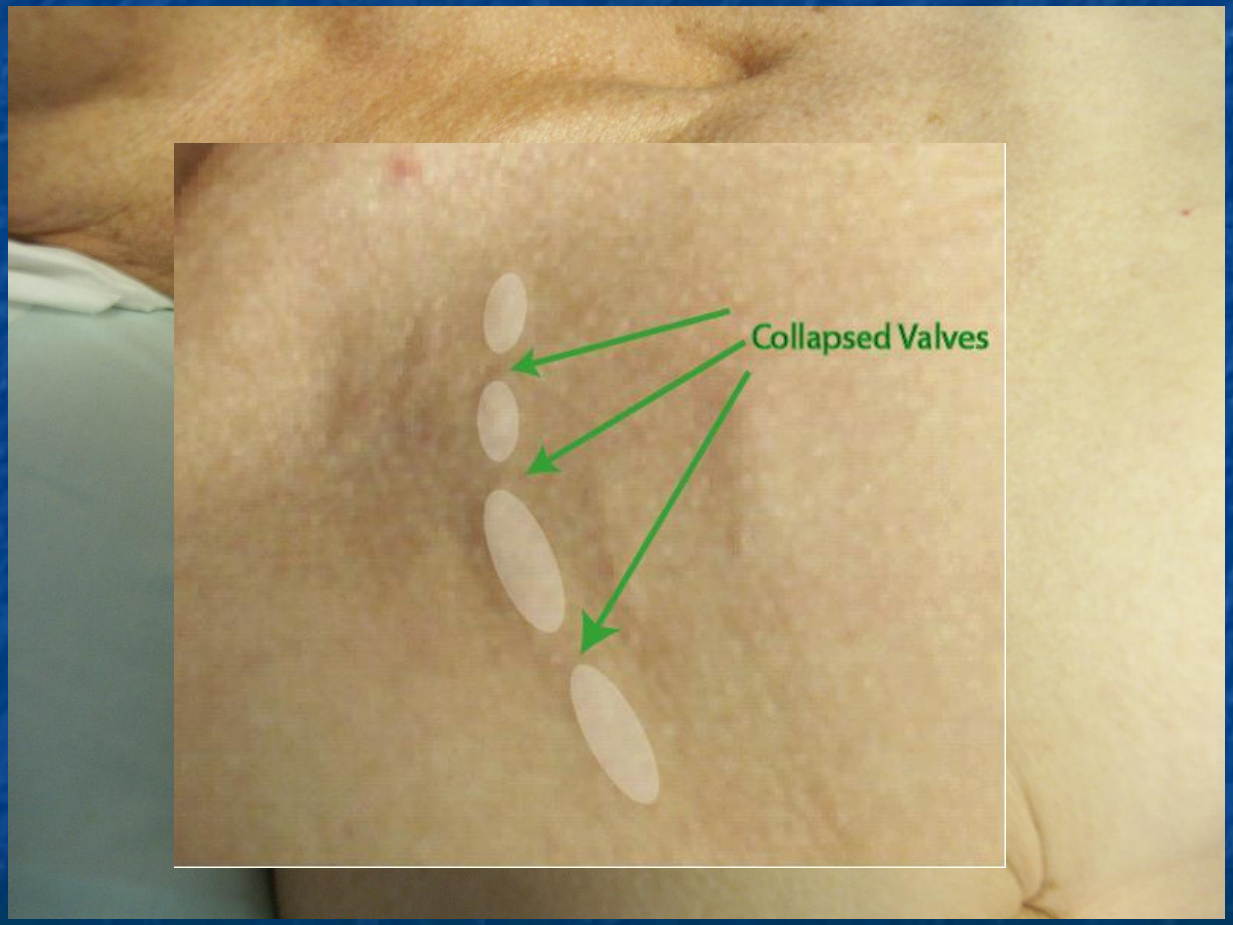
Kinmonth JB. 1982. *The Lymphatics*, 2nd Edition. Edward Arnold, London. p. 80.

Browse NL. 1968. Response of lymphatics to sympathetic nerve stimulation. *J. Physiol.* (London) **19**: 25.

The formation of Varicose Megalymphatics

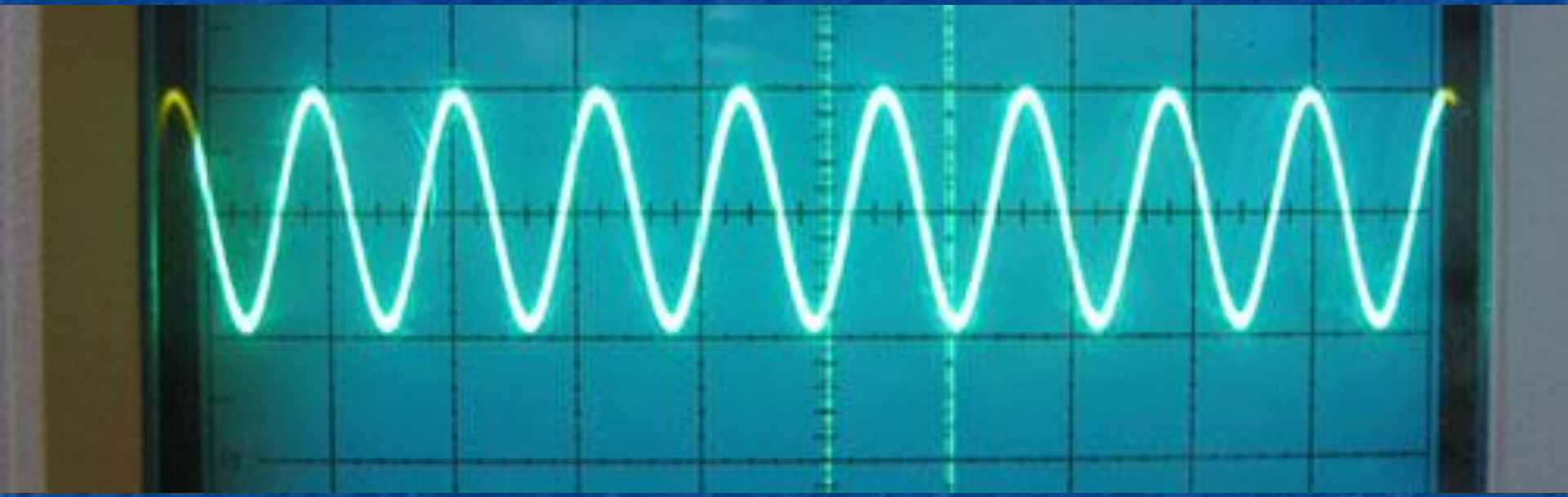


Varicose Mega-Lymphatic Vessels

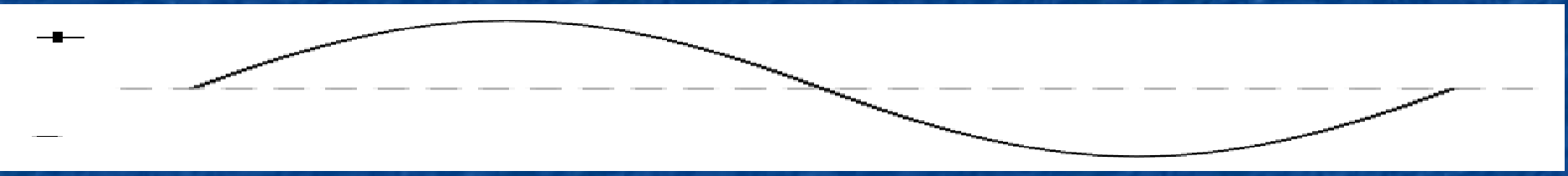


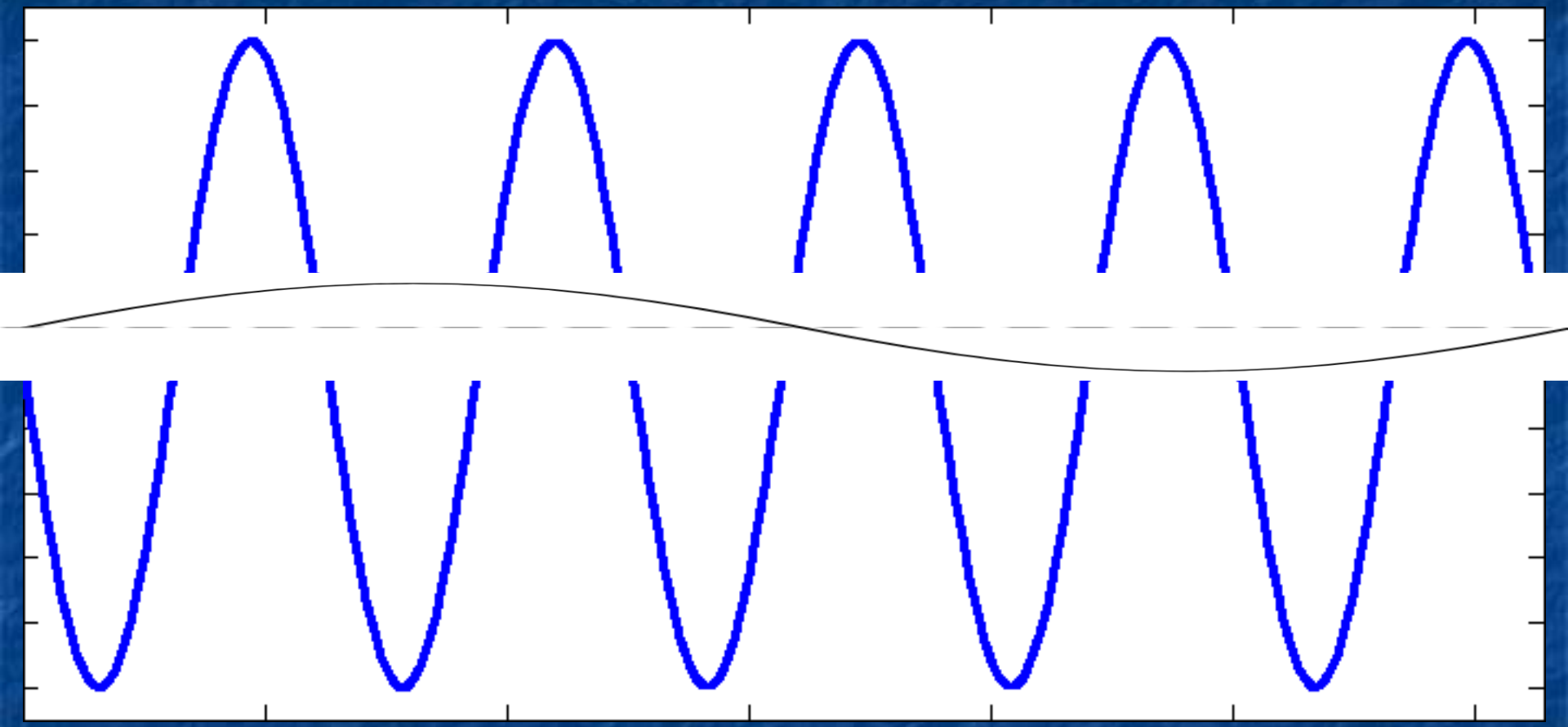
Varicose Lymphatic Vessels

HR =intracranial CSF pulse 50-100bpm

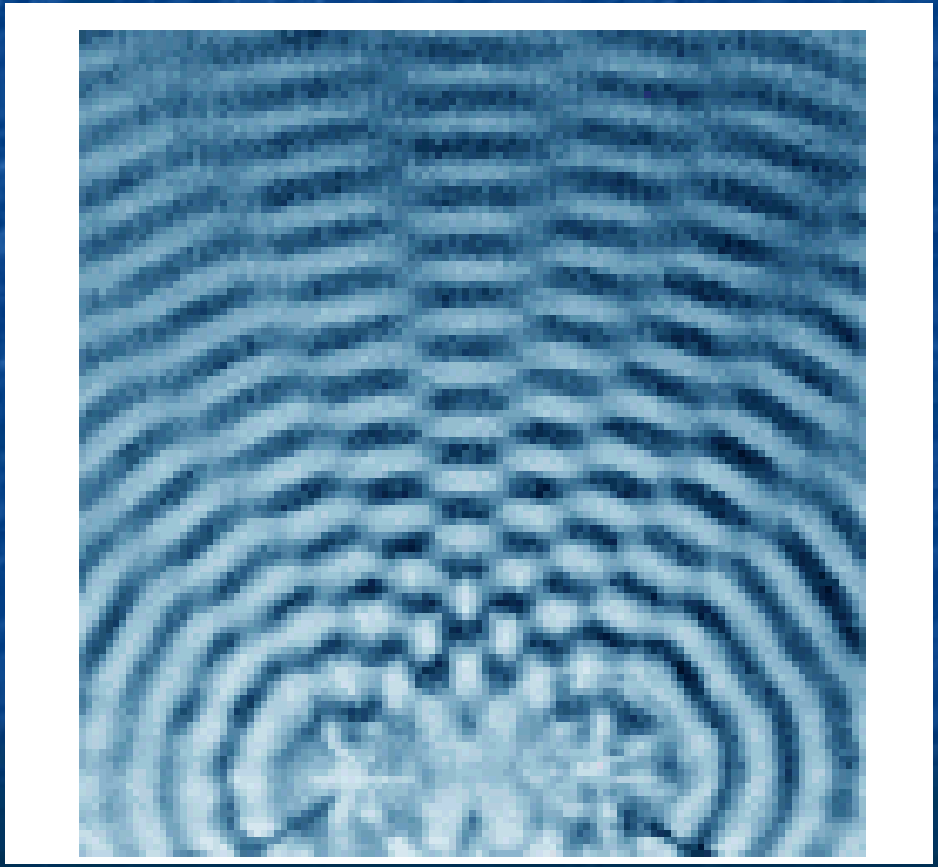


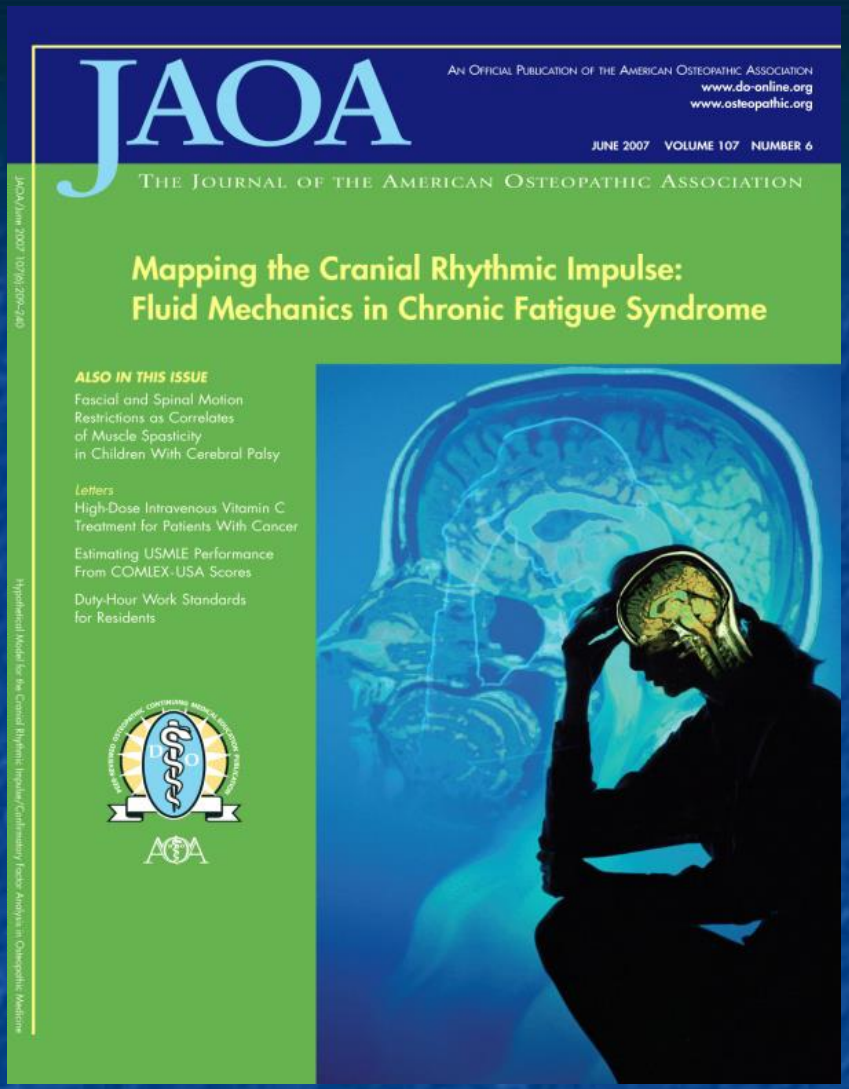
Thoracic duct Pump = 4bpm





The Interference Wave = The Cranial Rhythmic Impulse 8-12 BPM





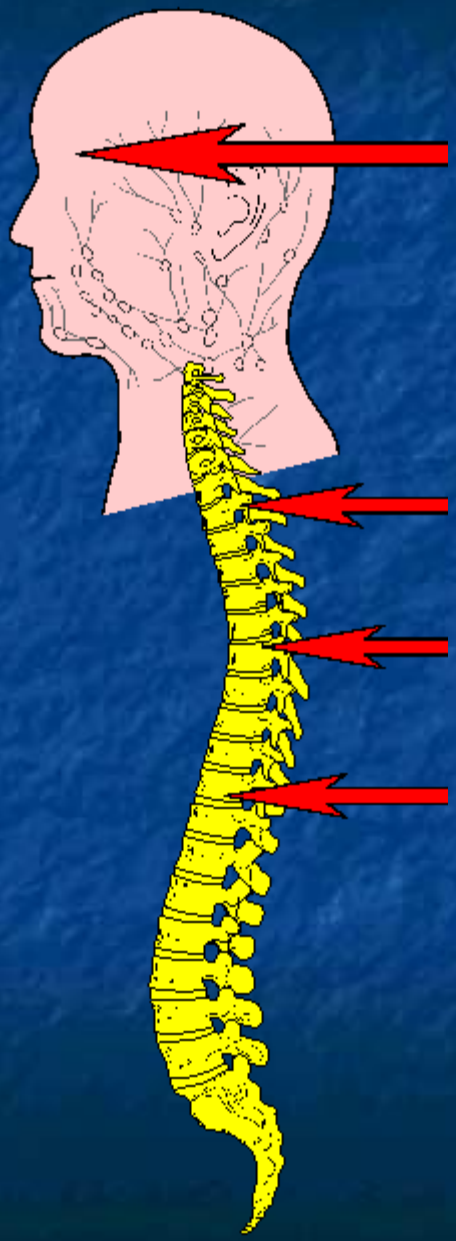
Perrin RN. 2007

Lymphatic Drainage of the Neuraxis in Chronic Fatigue Syndrome: A Hypothetical Model for the Cranial Rhythmic Impulse.

Journal of the American Osteopathic Association, 107(06), 218-224.

STAGES LEADING UP TO ME/CFS

1



Trauma/ Congenital

Physical damage/abnormality affecting perivascular spaces.

olfactory; optic; trigeminal; auditory

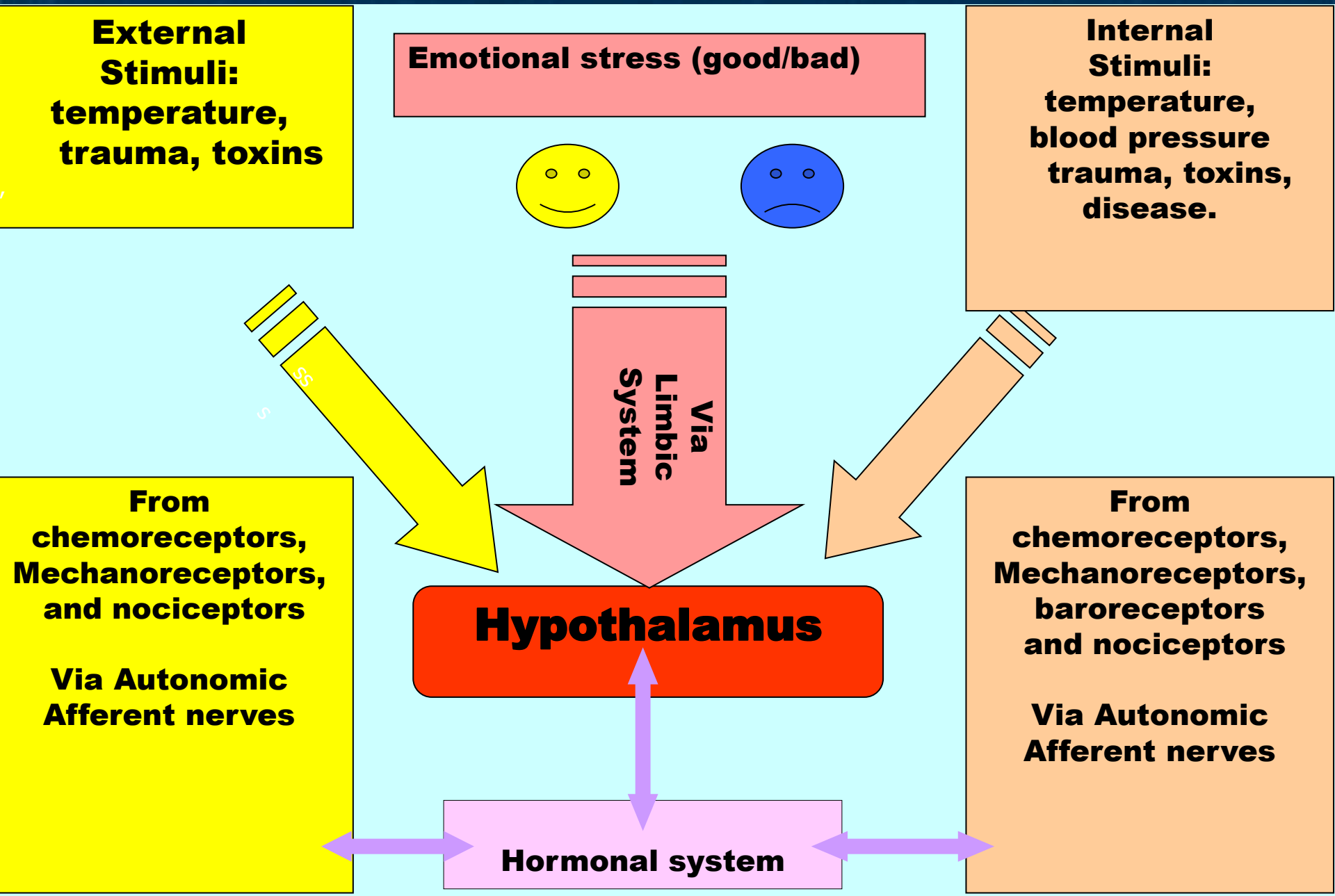
Spinal Canal and alongside Spinal Nerve Roots

STAGES LEADING UP TO ME/CFS

Build Up of Stress:

- Emotional Trauma
- Physical Trauma/Pain
- Immunological Trauma
  (Infections or Sensitivities/ Allergies)
- Environmental Trauma (Pollution)
- Other Pathologies

STAGES LEADING UP TO ME/CFS



STAGES LEADING UP TO ME/CFS

SYMPATHETIC OVERLOAD

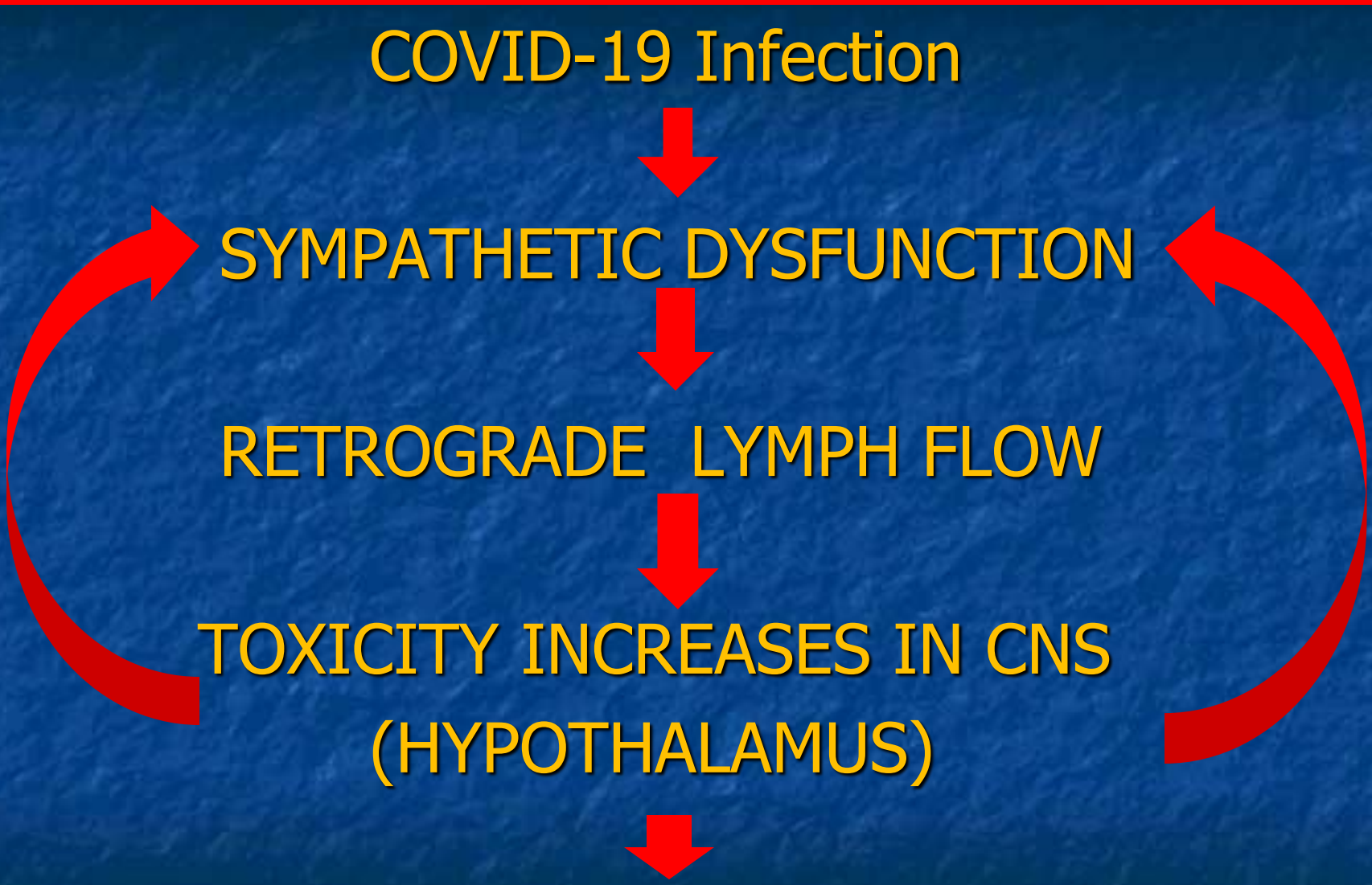
SYMPATHETIC DYSFUNCTION

RETROGRADE LYMPH FLOW

TOXICITY INCREASES IN CNS (HYPOTHALAMUS)

CFS/ ME

STAGES LEADING UP TO Long-COVID



Post COVID-19 Syndrome

Perrin R et al. 2020

There is a potential for a major outbreak of post-viral syndrome to manifest following COVID-19 infection as previously reported following Severe Acute Respiratory Syndrome (SARS) infection , also a coronavirus.

Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565–74.

Prof Harvey Moldofsky

- Severe Acute Respiratory Syndrome

Once an acute COVID-19 infection has been overcome, a subgroup of remitted patients are likely to experience long-term adverse effects resembling ME/CFS symptomatology such as persistent fatigue, diffuse myalgia, depressive symptoms, and non-restorative sleep.

Post-mortem research into the SARS outbreak of 2003, indicated the virus had crossed the blood brain barrier into the hypothalamus via the olfactory pathway (Moldofsky & Patcai, 2021). The pathway of the virus seemed to follow that previously suggested in ME/CFS patients, involving disturbance of lymphatic drainage from the microglia in the brain (Hives et al., 2017).

One of the main pathways of the lymphatic drainage of the brain is via the perivascular spaces along the olfactory nerves through the cribriform plate into the nasal mucosa (Kida, Pantazis &Weller 1993) If the pathogenesis of coronavirus affects a similar pathway, it could explain the anosmia observed in a proportion of COVID-19 patients.

Cytokine Storm

ME/CFS is often triggered by a virus and it is the build up of cytokine activity in the CNS that leads to many of the post viral symptoms due to the toxins ie the pathogen and pro-inflammatory cytokines passing through the blood brain barrier in circumventricular organs such as the hypothalamus. (Perrin 2005)

This leads to autonomic breakdown and also very high fever due to the infection and cytokines overstimulating the median preoptic nucleus of the hypothalamus.

In November 2020 electron microscope images showed intact coronavirus particles inside the olfactory mucosa, demonstrating that the main entry of SARS-CoV-2 into the brain is via the olfactory nerve pathway. They also suggest that migration of SARS-CoV-2 across the blood–brain barrier (BBB) is a valid possibility as they found immunoreactivity to SARS-CoV S protein in leptomeningeal endothelial cells, a main pathway in the neuro- lymphatic drainage (Meinhardt., et al 2021). There is further evidence that the spike protein of the virus crossing the blood-brain barrier (Rhea J et al., 2020)

This disturbance leads to a build-up of pro-inflammatory agents, especially post-infectious cytokines such as interferon gamma, and interleukin 7 which may affect the neurological control of the 'Glymphatic System' as observed in ME/CFS

Montoya JG, Holmes TH, Anderson JN, et al. Cytokine signature associated with disease severity in chronic fatigue syndrome patients. Proc Natl Acad Sci 2017; 114: E7150–8.

“The lymphatics are closely and universally connected with the spinal cord and all other nerves, and all drink from the waters of the brain” A T STILL

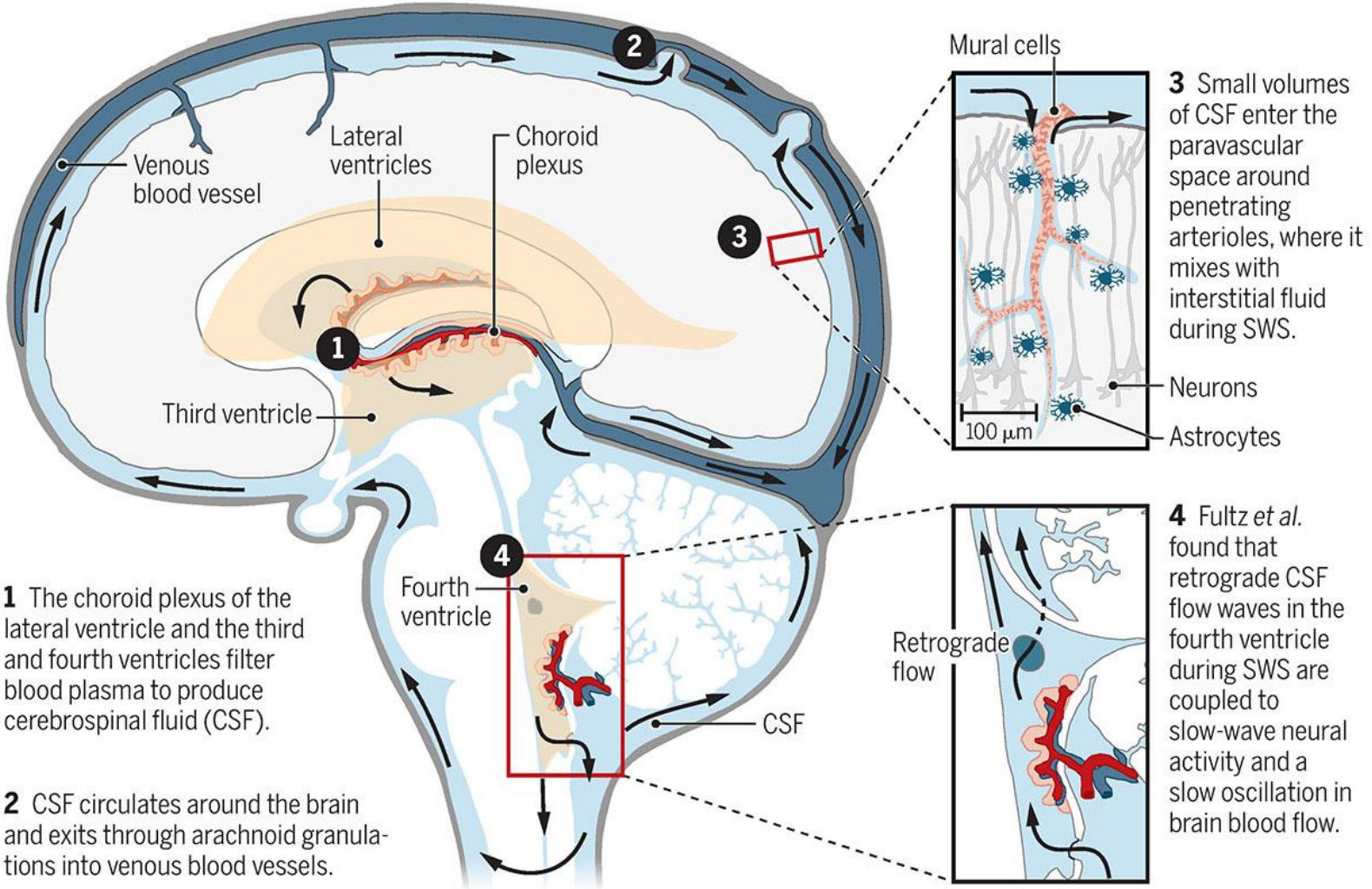
“When you tap the waters of the brain by compressing the fourth ventricle see what happens in the lymphatic system. Visualise the lymph node that is holding some poison that has gathered there, changing the constituency before the lymph is moved along into the venous system”

William Garner Sutherland

(1873–1954)

Brain fluid flow switches direction in deep sleep

Fultz *et al.* show that retrograde brain fluid waves follow the fluctuations in neural activity and brain blood volume in slow-wave sleep (SWS).



1 The choroid plexus of the lateral ventricle and the third and fourth ventricles filter blood plasma to produce cerebrospinal fluid (CSF).

2 CSF circulates around the brain and exits through arachnoid granulations into venous blood vessels.

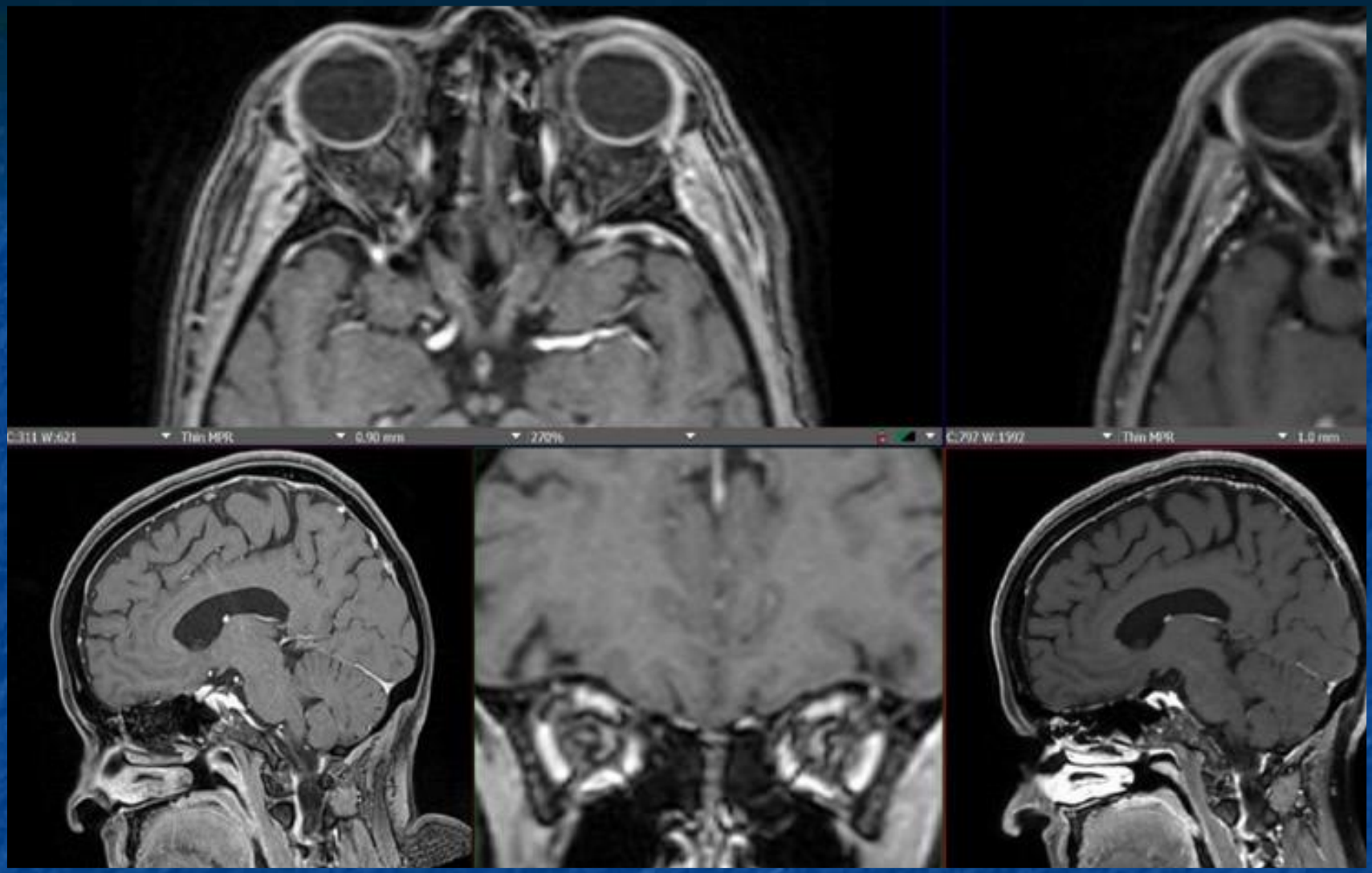
3 Small volumes of CSF enter the paravascular space around penetrating arterioles, where it mixes with interstitial fluid during SWS.

4 Fultz *et al.* found that retrograde CSF flow waves in the fourth ventricle during SWS are coupled to slow-wave neural activity and a slow oscillation in brain blood flow.

Nina E. Fultz et al. Science 2019;366:628-631

During Slow Wave Sleep the cerebral blood flow is reduced by 25% which lowers cerebral blood volume by @ 10%. This reduction in CBV allows inflow of CSF to the 3rd and 4th Ventricles which may facilitate the neurolymphatic (Glymphatic) clearance.

Nina E. Fultz et al. Science 2019;366:628-631



Prominent perivascular spaces in the right greater than left basal ganglia were visualised on MRI.

(Grach SL, et al. 2022)

Mild olfactory enhancement noted on initial MRI, resolved on follow-up.

MRI of the brain repeated 8 months later demonstrated non-enhancing T2 signal changes in the white matter of the anterior left frontal lobe (higher cognitive functions) especially along the frontal horn of the lateral ventricle

PET CT of the brain for metabolic evaluation revealed nonspecific scattered areas of low-level hypometabolism at:
bilateral frontal lobe (Social/emotional Skills, Cognitive Skills)

left precuneus (memory)

occipital lobe(sight and processing of visual perceptions.)

and parietal regions (processing tactile sensory information)

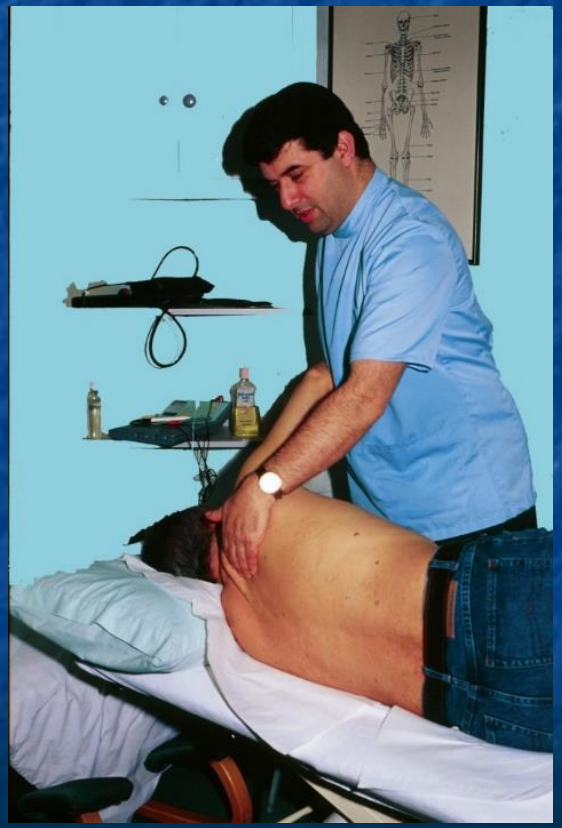
Also heart rate responses to deep breathing were reduced on autonomic reflex screening

Grach SL, Ganesh R, Messina SA, et al.

Post-COVID-19 syndrome: persistent neuroimaging changes and symptoms 9 months after initial infection

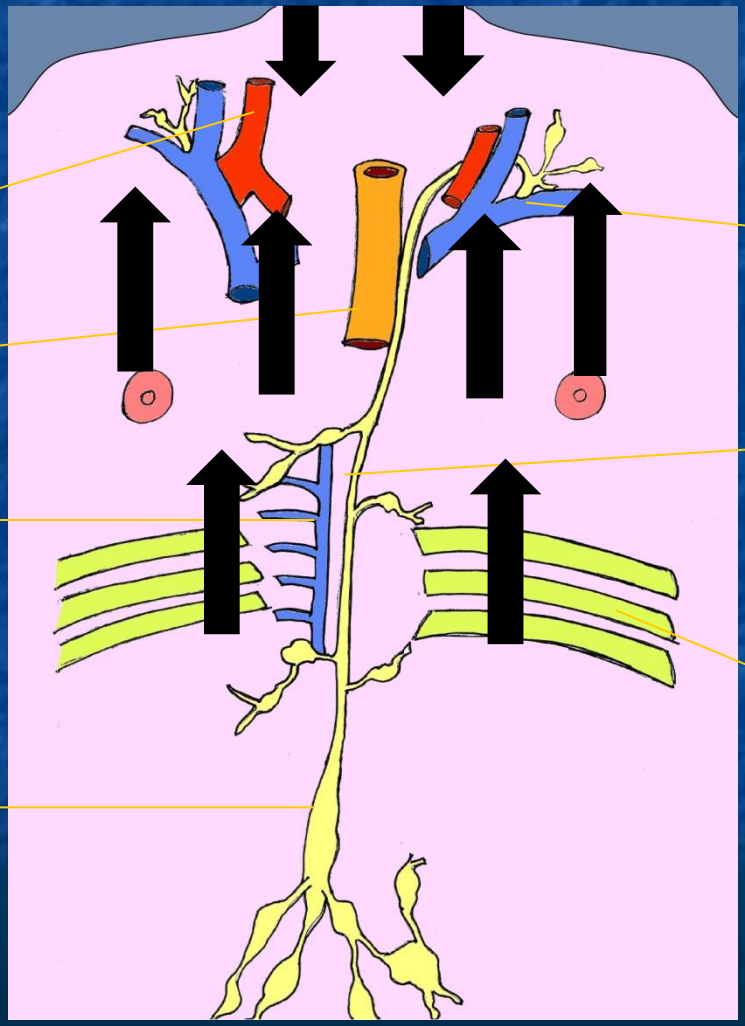
BMJ Case Rep 2022;**15**:e248448. doi:10.1136/bcr-2021-248448

HOW CAN OSTEOPATHY HELP?



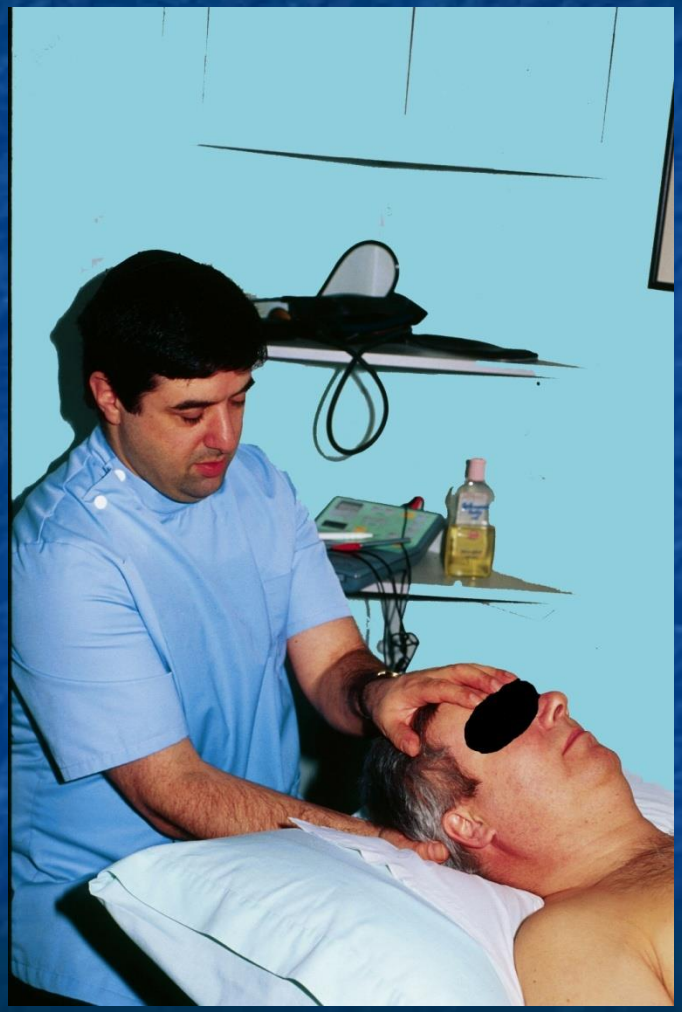
The Concertina Affect

The Concertina Affect



Treatment
Lymph Massage and Gentle Muscle Stretching

Cranial Treatment



New paper just published

Reducing fatigue-related symptoms in Long COVID-19: a preliminary report of a lymphatic drainage intervention.

Heald H, Perrin R, Walther A et al. Cardiovasc Endocrinol Metab. 2022 Jun; 11(2): e0261.

Clinically, practitioners across the UK trained in the manual intervention of ME/CFS symptoms are already treating and helping patients with the Long Covid/ chronic post COVID-19 symptoms as demonstrated in the reduction of the symptom severity in the Profile of Fatigue Related States scores (Ray et al , 1992).

Ray C, Weir WRC, Phillips L, Cullen S. 1992. Development of a measure of symptoms in chronic fatigue syndrome: the profile of fatigue related symptoms (PFRS). Psychology and Health. 7: 27-43.

Patients of a group of osteopaths and physiotherapists were asked to complete the Profile of Fatigue Related States (PFRS) prior to entry (baseline) and again around 3 months after receiving a manual treatment protocol for fatigue related to Long COVID. We asked practitioners to submit this as anonymised data by the end of January 2021.

Intervention:

Treatment sessions with the practitioners involving effleurage of the neck back and chest plus soft tissue stretching of paravertebral thoracic muscles, trapezii and levator scapulae, suboccipital muscular and gentle cranial osteopathic techniques were completed, once a week.

The individuals being treated also followed a daily self-massage routine of the head, neck and chest and alternating warm and cool gel packs on the upper spine to encourage a reduction of spinal inflammation and further aid lymph drainage of the brain and spine. These were performed along with regular gentle mobility exercises involving rotational movement of the thoracic region that improve spinal mobility

None of the individuals had any prior diagnosis of chronic fatigue syndrome. All were new attendees to the clinic at the time of initial assessment.

Outcome measures: Practitioners collected and recorded symptom severity using self-reported 54-item PFRS.

Responses are scored according to a seven point Likert-scale ranging from 0 (not at all) through 3 (moderately) to 6 (extremely).

Variables pre- and post treatment were compared by ANOVA.The mean age of the men was 41.8 years with a range of 29.1-53.1 years with the corresponding mean age for women being 39.3 years with a range of 28.3-50.4 years.

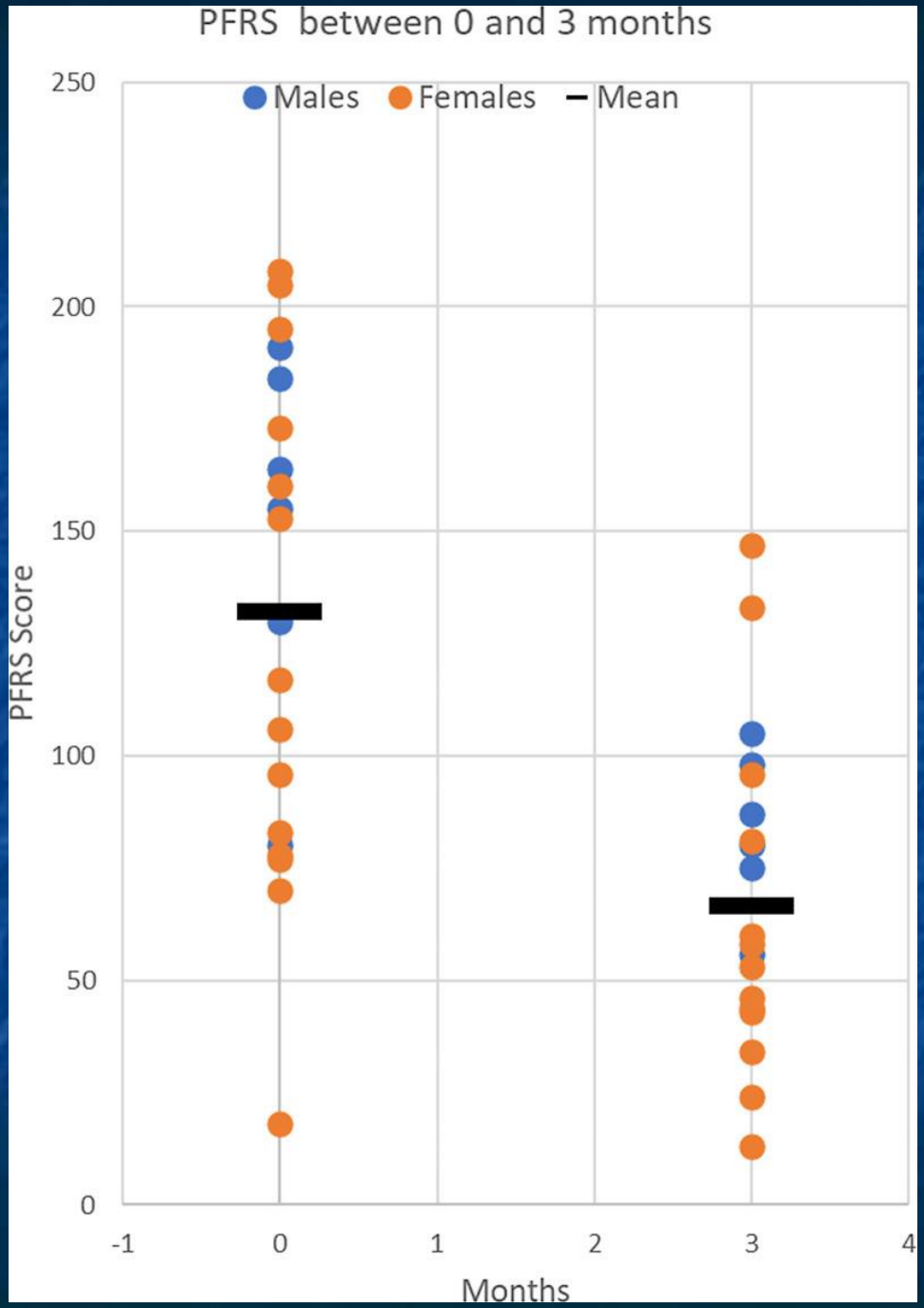
The mean time interval between onset of Coronavirus symptoms and start of treatment for Long COVID was similar between men and women at just over 20 weeks. The average number of treatment sessions was similar at 9.7 in men and 9.4 in women (with a maximum of 12 weekly treatment sessions).

The change in PFRS score was similar in men (-67.2, standard deviation 4.1)
and in women (-64.8, standard deviation 3.8).
The fall in PFRS was highly statistically significant (F 4.8, $p<0.001$)

50.0% fall in scores for men and women combined.

Our results indicate that this intervention helped reduce fatigue related symptoms as indicated by the PFRS in the chronic post COVID patients.

(Months refers to months after start of treatment.)



It may be that early intervention and supportive treatments at the end of the acute phase of COVID-19 can help overcome acute phase symptoms and prevent them becoming longer-term consequences.

The best results for most would be a multidisciplinary approach as suggested by Halpin and colleagues (Halpin,O'Connor & Sivan, 2020) ……..

……and hopefully including osteopathic treatment of the neuro-lymphatic system (Perrin et al., 2020).

Reducing fatigue in Long COVID-19: A feasibility study of a self-help intervention to reduce fatigue-related symptoms among patients in general practice.

IRAS project ID: 291940

REC reference: 21/LO/0809

100 people experiencing longer-term symptoms will be invited to take part in this research which will assess the feasibility of the osteopathic self-help intervention (The Perrin Technique) to help reduce symptoms of fatigue in Long-COVID……

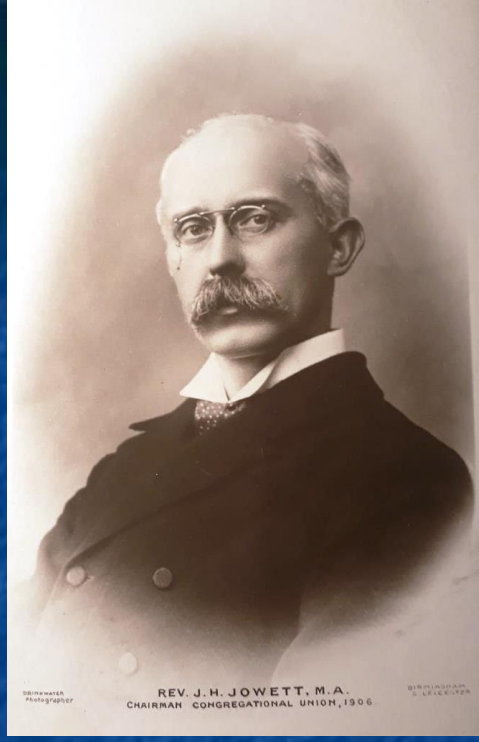
…… to be continued!

Thanks to my research colleagues at The University of Manchester and Salford Royal Foundation NHS Trust). Lisa Riste, Mark Hann, Annice Mukherjee, and especially Adrian Heald.

& Thanks to the grant from the Fund for Osteopathic Research into ME charity trust.

"Gratitude is a vaccine, an antitoxin, and an antiseptic."

Rev John Henry Jowett (1863-1923)



Thanks again to the OIA for the invitation.

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