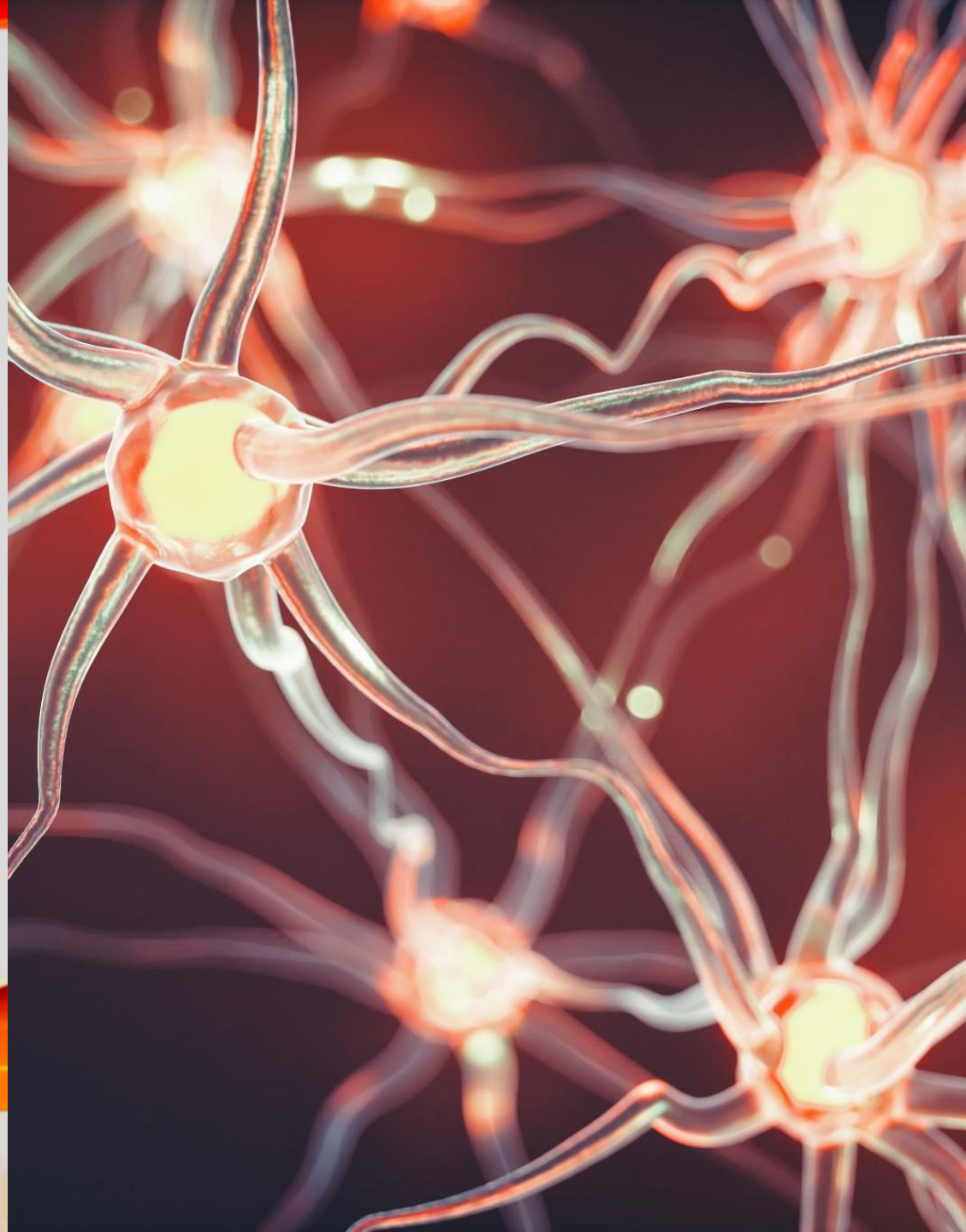
LIGHT ON THE VAGUS NERVE

- Dr. Aaron Nichols, FAAO, FOVDR
- Great Lakes Vision Rehabilitation at Excel est. 2004
- 48189 Van Dyke Ave, Shelby Twp., MI 48317



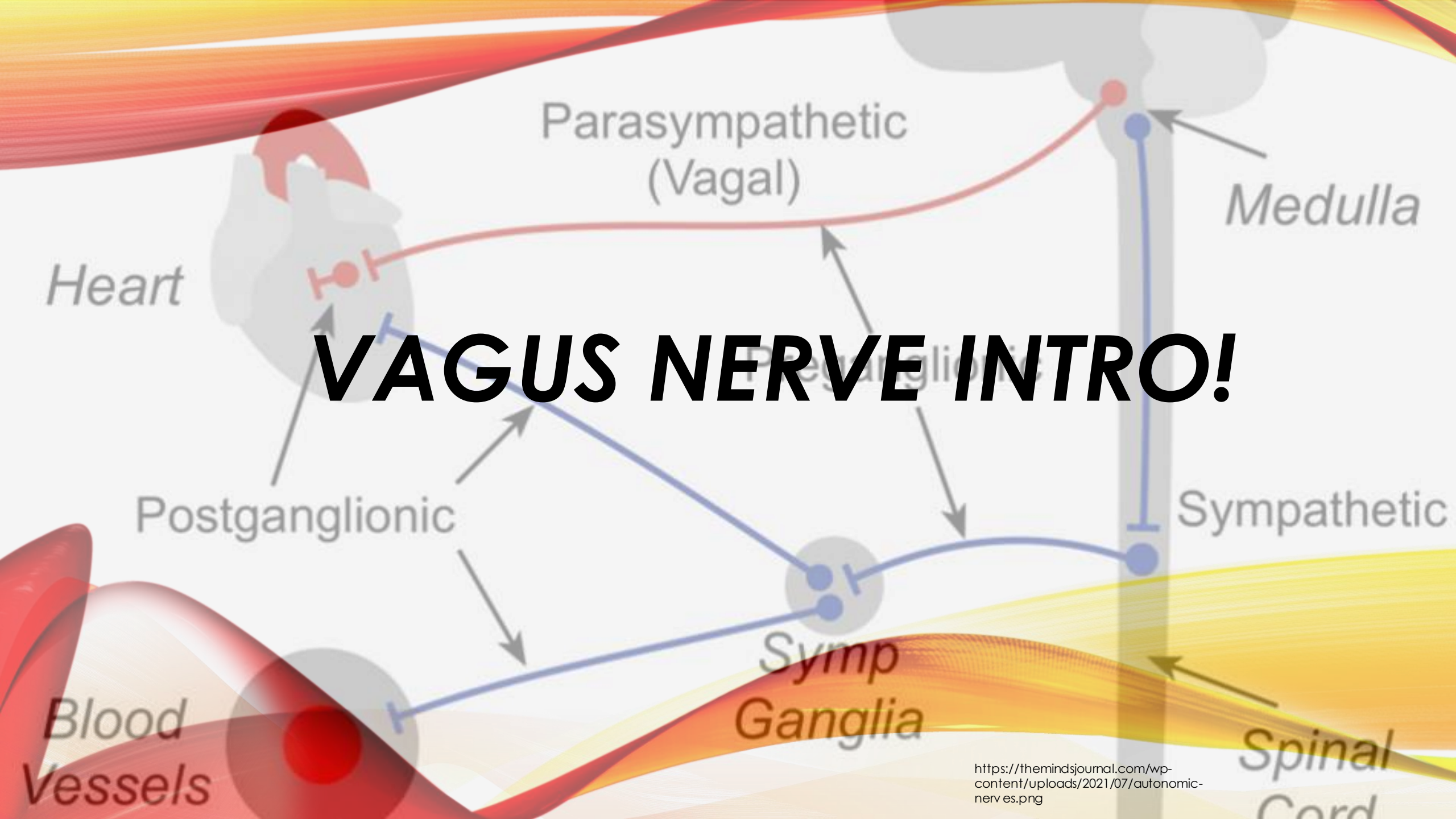
No financial disclosures or conflicts of interest.

OBJECTIVES

- Understand the anatomy and physiology of the vagus nerve
- Understand different stimulation techniques of the vagus nerve
- Understand the process of light absorption from a nerve pathway point of view
- Understand how light affects the autonomic nervous system
  - Emphasis on the heart
- The connection of light to the parasympathetic nervous system
- CSO filters and their relation to motor and sensory nerves

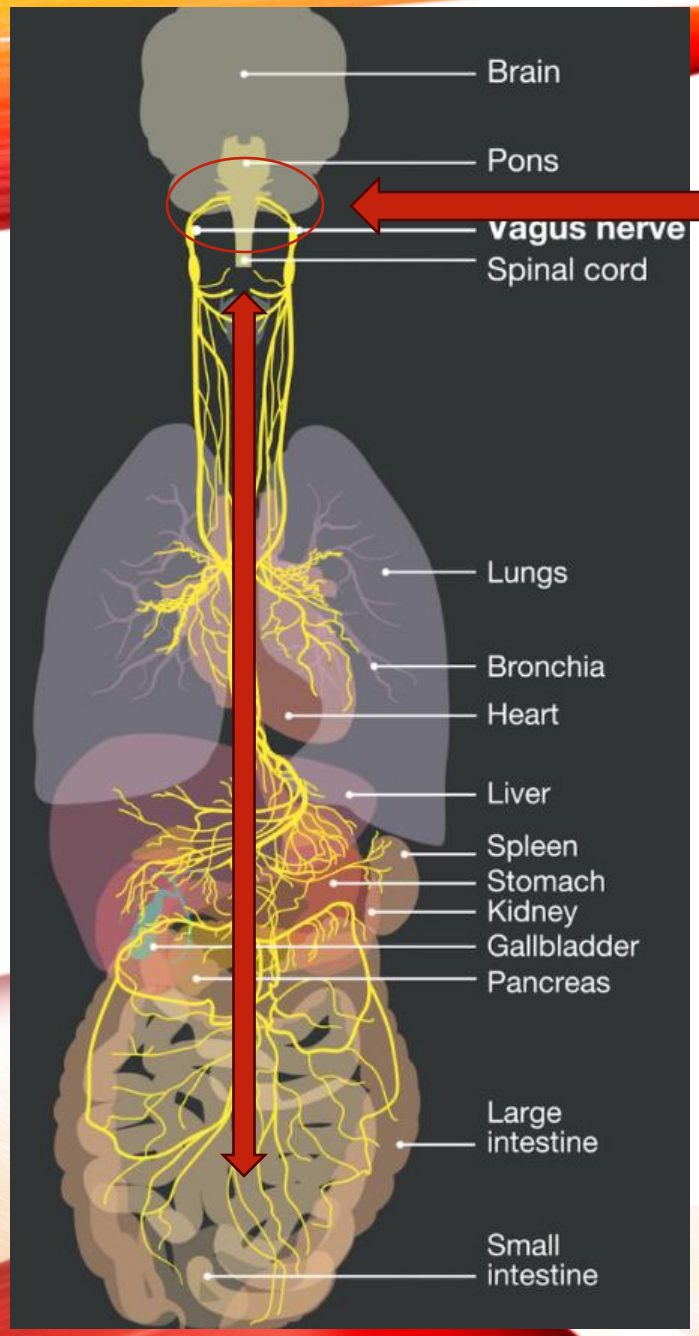
OUTLINE

- *Overview of the vagus nerve*
  - *Anatomy, physiology, innervations, blood supply, stimulation*
- *Light Processing*
  - *Light and the impact on the ANS*
  - *Image versus non-image forming*
  - *The pupil and the ANS*
- *The Heart and the PNS*
  - *Right and Left Vagus Nerve*
  - *Light and the HEART*
  - *Internal Loop connection*
- *Syntonics Filters and the vagus Nerve*
  - ***Spectrochrometry Encyclopedia***
    - ***Dinshah Ghadiali***
  - *Review the Vagus nerve anatomy and physiology and the filters*
- *Red Light and NIH Clinical Trial*
- *Conclusions*
- *Questions*



VAGUS NERVE INTRO!

https://themindsjournal.com/wp-content/uploads/2021/07/autonomic-nerv es.png



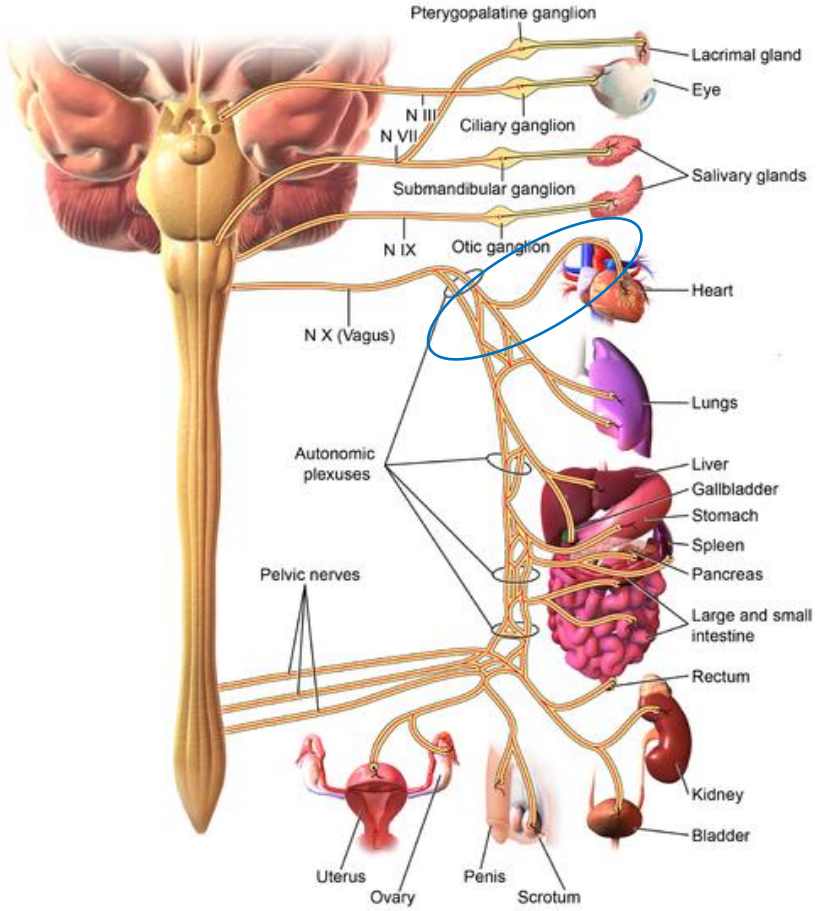
VAGUS NERVE ANATOMY

- Longest Cranial Nerve
- CN X (10)
- Medulla Oblongata
- Motor and Sensory Functions
- Originate from:
  - Dorsal Motor Nucleus (DMN)
  - Nucleus Ambiguous
  - Super Ganglion
  - Inferior Ganglion
- Efferent
  - **Motor**
  - Sensory
- Afferent
  - **Motor**
  - Sensory

https://img.theepochtimes.com/assets/uploads/2022/06/09/vagus-nerve-e1654752459789-1200x1114.jpeg

ANATOMY

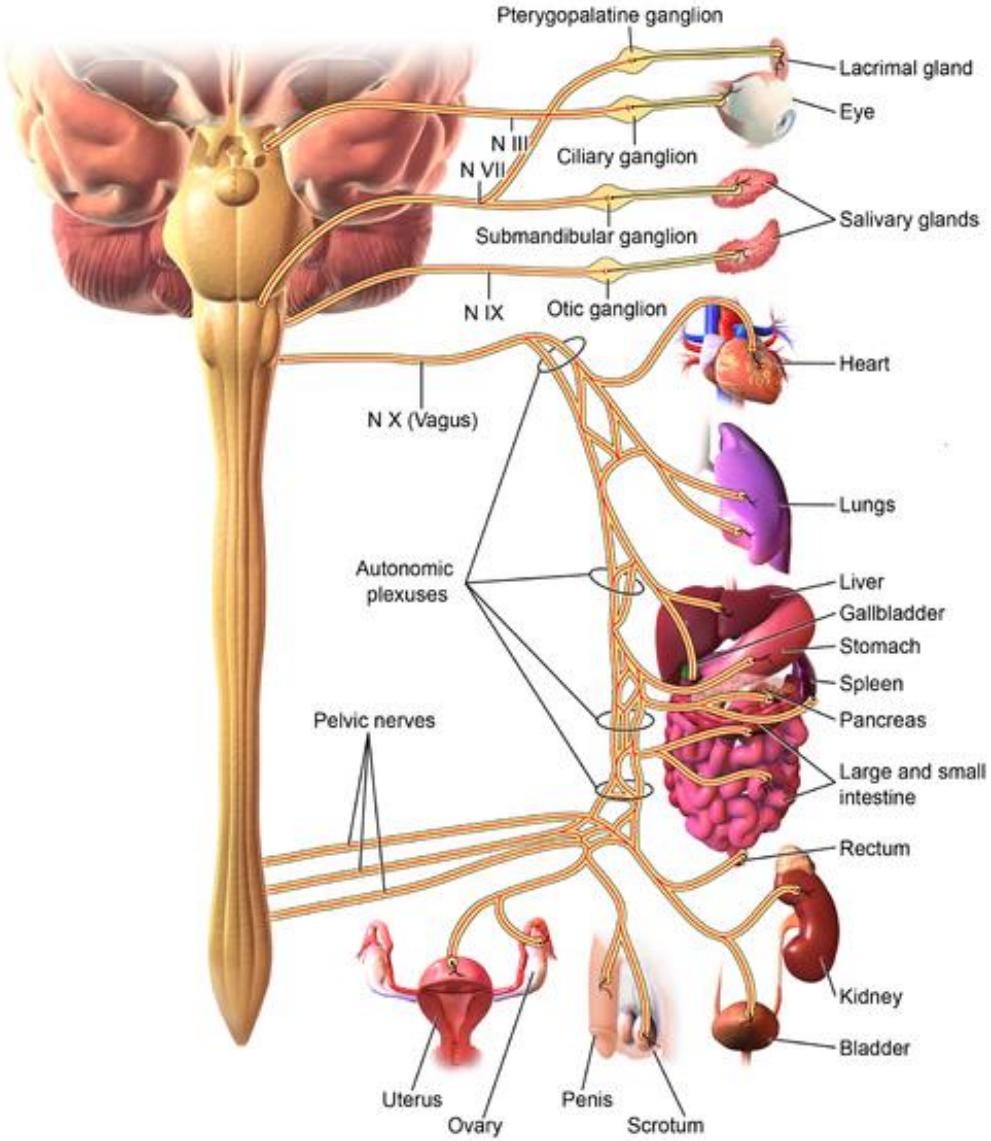
- Jugular Foramen
- Fibrous Connective Tissue
  - Spinal Canal
  - Carotid Sheath
    - Sympathetic Plexus
    - Jugular Vein
    - Carotid Artery
- **Left Vagus**
- **Right Vagus**
- Branch Nerves
  - Pharyngeal
  - Superior Laryngeal
    - Internal and External
  - Gastric
  - Bronchial
  - **Cardiac**
    - Superior



- **Left Vagus**
  - Crosses the subclavian artery
  - Passes along the trachea
    - Near the left common carotid
  - Cross the left lung
- **Right Vagus**
  - Travels in the carotid sheath
  - Forms the esophageal plexus with L. vagus nerve
  - Branches as anterior and posterior bronchial branches
- **Cardiac**
  - Superior Cardiac N
  - **LEFT** nerve sends more branches to the heart
    - More common for stimulation

ANATOMY-BLOOD SUPPLY

- Intracranial
  - Middle Meningeal
  - Posterior Meningeal
    - Also supplies extracranial
- Extracranial
  - Common Carotid
  - Internal Carotid
  - Inferior Thyroid
  - External Carotid
  - Internal Thoracic
  - Bronchial
  - Esophageal



https://www.physio-pedia.com/Vagus_Nerve

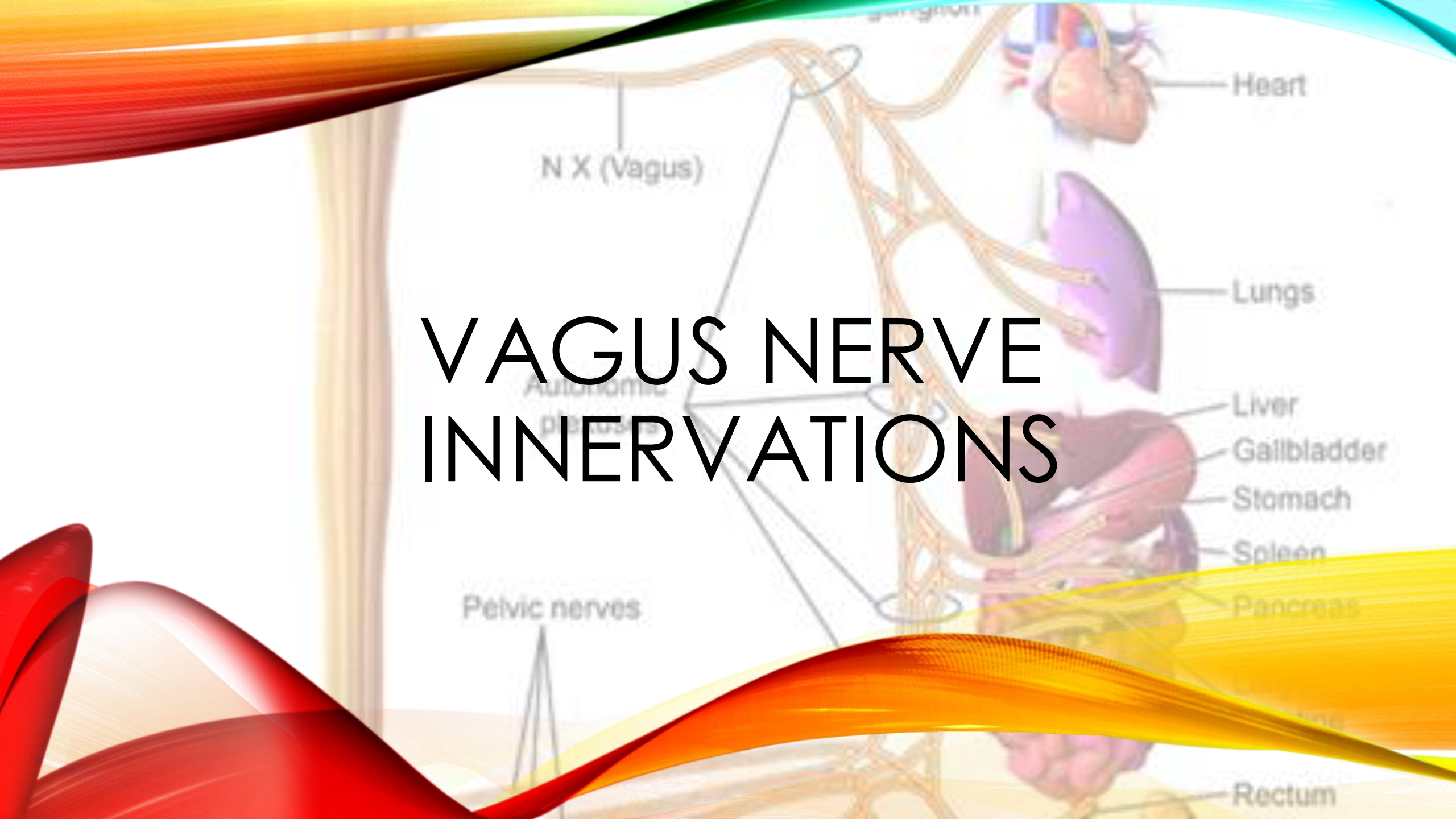
VAGUS NERVE PHYSIOLOGY

- Acetylcholine
  - Pre-ganglionic junction for parasympathetic
  - PRIMARY postganglionic neurotransmitter
  - Cytokine production
    - Anti-inflammatory pathway
- Synapses at MUSCANRIC receptors at the heart
  - M1, M2 (**SA Node**, **AV Node**), M3

- **80% Sensory**
  - Afferent Nuclei
    - Nucleus Tractus Solitarius
    - Dorsal Raphae Nucleus
    - Locus Ceruleus (pons)
    - Amgydyla
    - Hypothalmus
    - Thalmus
    - Bifrontal Cortex
- 20% Motor

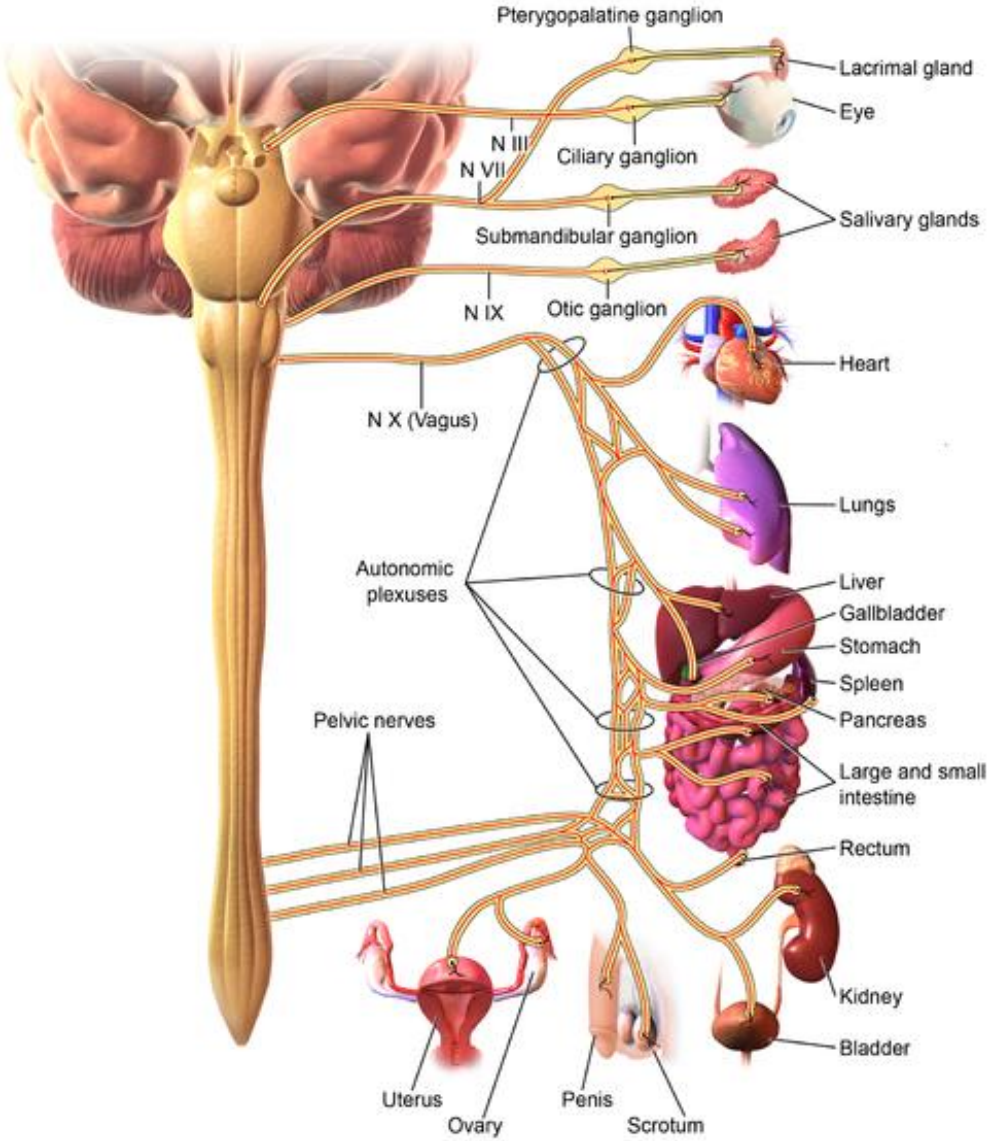
https://university.pressbooks.pub/test456/

VAGUS NERVE INNERVATIONS



PHYSIOLOGY- INNERVATIONS

- Sensory
  - Taste, Vocal Cord
  - Uvula
  - Emotional and Cognitive Function
    - Cortical-Limbic-Thalamic-Striatal= Neural Circuit
- Motor
  - Pharyngeal Muscles
    - Nasopharynx
  - Tongue
- Thoracic and Abdominal Visceral
- GI Tract
- Esophagus
- Liver
- Pancreas
- Lungs
  - Respiratory Tract
- **Heart**



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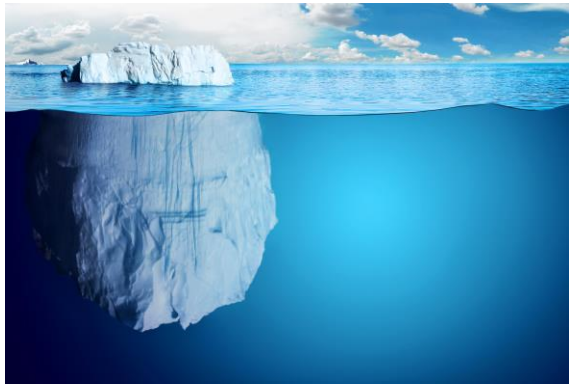
VAGUS NERVE STIMULATION TECHNIQUES

- Manipulation of Carotid Artery (1880's)
- Electrical Activity (1930s and 40's)
  - Mostly left vagus nerve
    - Transcutaneous electrical nerve stimulation (TENS)
    - Through the ear (auricular branch of vagus nerve
    - HA, migraine, medication overuse, cluster HA
- Paced Breathing
  - Deep breathing, yoga, aerobic exercise
- Anti-inflammatory effect
  - Neuro-endocrine-immune axis

- Right Vagus Nerve
  - Cardiac and Seizures
- ***Left Vagus Nerve***
  - Left Upper Chest
  - Subcutaneous surgery
  - Seizure control
- Music
  - Humming, Singing, or Listening
- Cold Water Immersion



VAGUS NERVE STIMULATION TECHNIQUES

- Areas of focus for improvement:
  - Epilepsy
  - **Depression**
  - **Headaches**
  - **Inflammation**
  - Metabolic Disorders
  - **Heart Disease**
    - **Blood Pressure**
  - Obesity
  - **Pain Management**
  - **Stress**
  - *Standard 10-30 hz*

LIGHT AND THE AUTONOMIC NERVOUS SYSTEM

Adv Mind Body Med. 2013 Fall;27(4):7-16.

The impact of modulated, colored light on the autonomic nervous system.

Ross MJ, Guthrie P, Dumont JC.

- Different effects between **energizing** (combinations of red, orange, and yellow), **balancing** (equal proportions of all colors), **relaxing** (combination of green, blue, indigo), and **white lights**
- Heart Rate Variability (HRV)
  - Very Low Frequency (VLF)--- SNS Action
  - Low (LF)--- Blood Pressure Maintenance, SNS and PNS Action
  - High (HF)--- Activity from the Vagus nerve, PNS Action
  - LF/HF--- SNS/PNS Balance
- Skin Conductance (SC)
- Profile of Mood States (POMS)
- Randomized, Controlled, Partially blinded study with three intervention groups and one control group
  - 117 participants

Heart Rate Variability and Skin Conductance

HRV

- Can be used to assess the ANS: PNS vs SNS by measuring the variability between R-R variables
  - **Energizing:** Statistically significant for VLF and LF
  - **Balancing:** Statistically significant on the VLF, LF, and LF/HF
  - **Relaxing:** Statistically significant on VLF, LF, and HF
  - **White Light:** Statistically significant for HF (PNS)
- **Heart Rate:** Decreased by Energizing, Balancing***, and Relaxing Light

SC

- Can be used to assess the ANS: PNS vs SNS by measuring the variability between R-R variables
  - **Energizing:** Statistically significant for VLF and LF
  - **Balancing:** Statistically significant on the VLF, LF, and LF/HF
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Profile of Mood States (POMS)

- Subjective questionnaire that has been proven to be statistically significant to determine the mood of the patient
- Determining the "Total Mood Disturbance" with higher values indicating more mood disturbance
- Energizing, ***Balancing***, and Relaxing all had statistically significant lowering effects
  - ***Balancing*** had the most significant lowering effect
  - White was not statistically significant
- Total Mood Disturbance is based on Six Categories:
  - Tension
  - **Depression**
  - Anger
  - Vigor
  - Fatigue
  - Confusion

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Study Take Away Points

- Light can impact the autonomic nervous system
- The visible spectrum ranges from red to blue, with green in the middle
  - **Red**, **blue**, and **green** have different impacts on the ANS
- Choose color frequencies based on what you choose to accomplish

Adv Mind Body Med. 2013 Fall;27(4):7-16.

The impact of modulated, colored light on the autonomic nervous system.

Ross MJ, Guthrie P, Dumont JC.

- 96 subjects between ages 18-60 with essential hypertension
  - 3o minute light session
  - 77 participants randomly assigned to 3 different groups: 1,2 and 3, red, blue and white, respectively
- Studied **BP**, HRV, and Electrocardiogram (ECG)
- **Red Light** increases excitement and **blood pressure (BP)**
- **Blue Light** decreased excitement and BP
- Newer area of research
  - BUT the research is being conducted and looking for alternative options

Original Article

The effect of short-term exposure to red and blue light on the autonomic tone of the individuals with newly diagnosed essential hypertension

Pratibha Modi[1], Kamlesh Jha[1], Yogesh Kumar[1], Tribhuwan Kumar[1], Ramji Singh[1], Abhilasha Mishra[1]

[1]Department of Physiology, All India Institute of Medical Sciences, Patna, Bihar, India

Results

- **Red Light**: Shifted patients to SNS dominance in HF to LF ratio (sympathovagal balance)
  - Found to suppress PNS and stimulate SNS
- **White Light**: Increased PNS dominance; Significant PNS activation compared to red or blue light
  - Statistically significant in HRV VLF and HF
- **Blue Light**: Did not show any statistically significant levels
  - Close to $p < 0.1$ in HRV LF and LF/HF ratio

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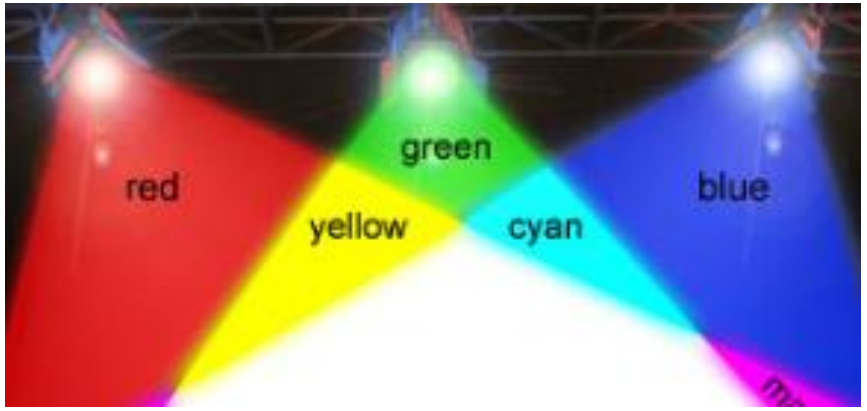
[1]Department of Physiology, All India Institute of Medical Sciences, Patna, Bihar, India

KEY POINTS FROM STUDY

- Light can be useful in changing the ANS
- **Red light** is stimulating of SNS
- **White light** has a statistically significant impact on the ANS
- This was a relatively small study and low duration of light stimulation
- Consider one "dose" of light and that it may not have the full impact of multiple sessions or "doses"



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Concussion

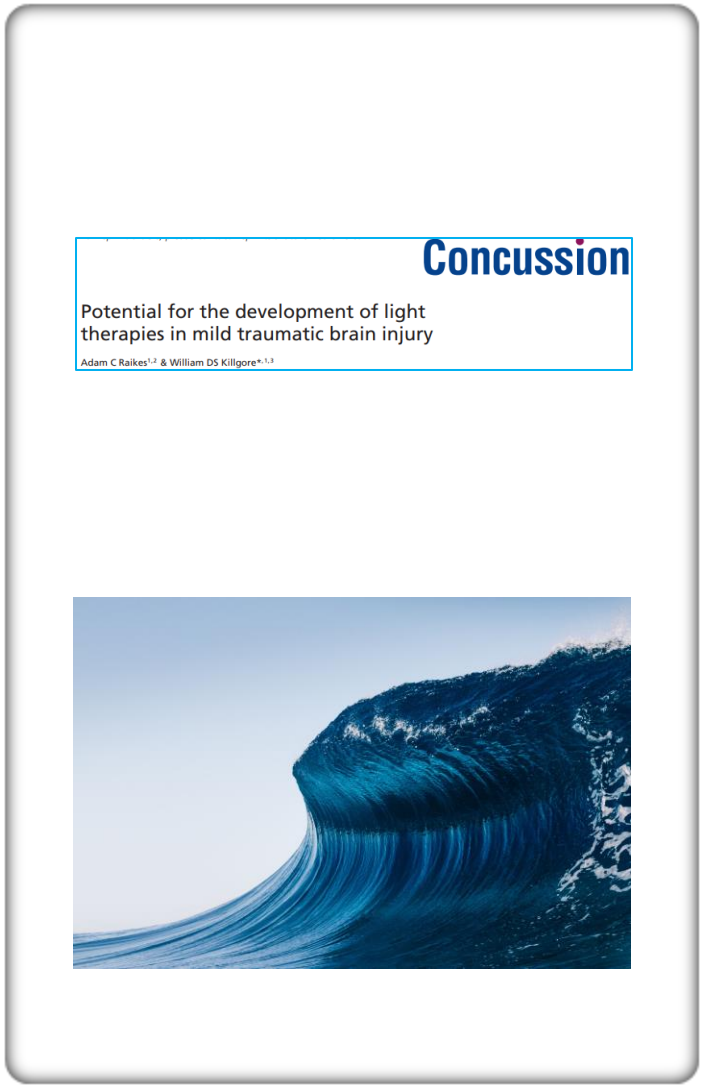
Potential for the development of light therapies in mild traumatic brain injury

Adam C Raikes[1,2] & William DS Killgore*[,1,3]

- **Light Directly stimulates the rods, cones, and ipRGCs**
- **ipRGCs are non-image forming retinal ganglion cells**
  - Project to many areas in the brain:
    - **Suprachiasmatic Nucleus (Circadian Rhythm)**
    - **Pineal Gland (melatonin)**
    - Amygdala (emotional center)
    - Trigeminovascular (pain)
    - Edinger-Westphal (pupils)

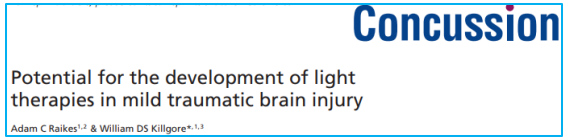
- **White Light:** Includes all colors of the visible spectrum (blue-red)
  - **Has an impact on sleep/circadian rhythm, alertness, reducing depression**
  - **2000 to 10,000 lux**
    - **Higher intensity had more benefits for light therapy**
- **Blue Light:** Most impact on circadian rhythm and melatonin release
  - **Decreases sleepiness and fatigue**
  - **Increasing alertness**
  - **Potentially worsening of headaches/migraines/light sensitivity**
- **Red Light: detected by "L" cones**
  - **Having an alerting effect?**
    - **Evidence is not clear now**
- **Green Light: Has a sleep promoting function**
  - Beneficial in the use for headaches and migraines

- **Blue light** has been applied to mTBI patients to assist with fatigue
- **Blue light** showed significant changes to white matter tracts
  - Using diffusion tensor imaging
  - Improved memory
- ipRGCs are most sensitive to the blue end of the spectrum (~420 nm), therefore, most research is in this range



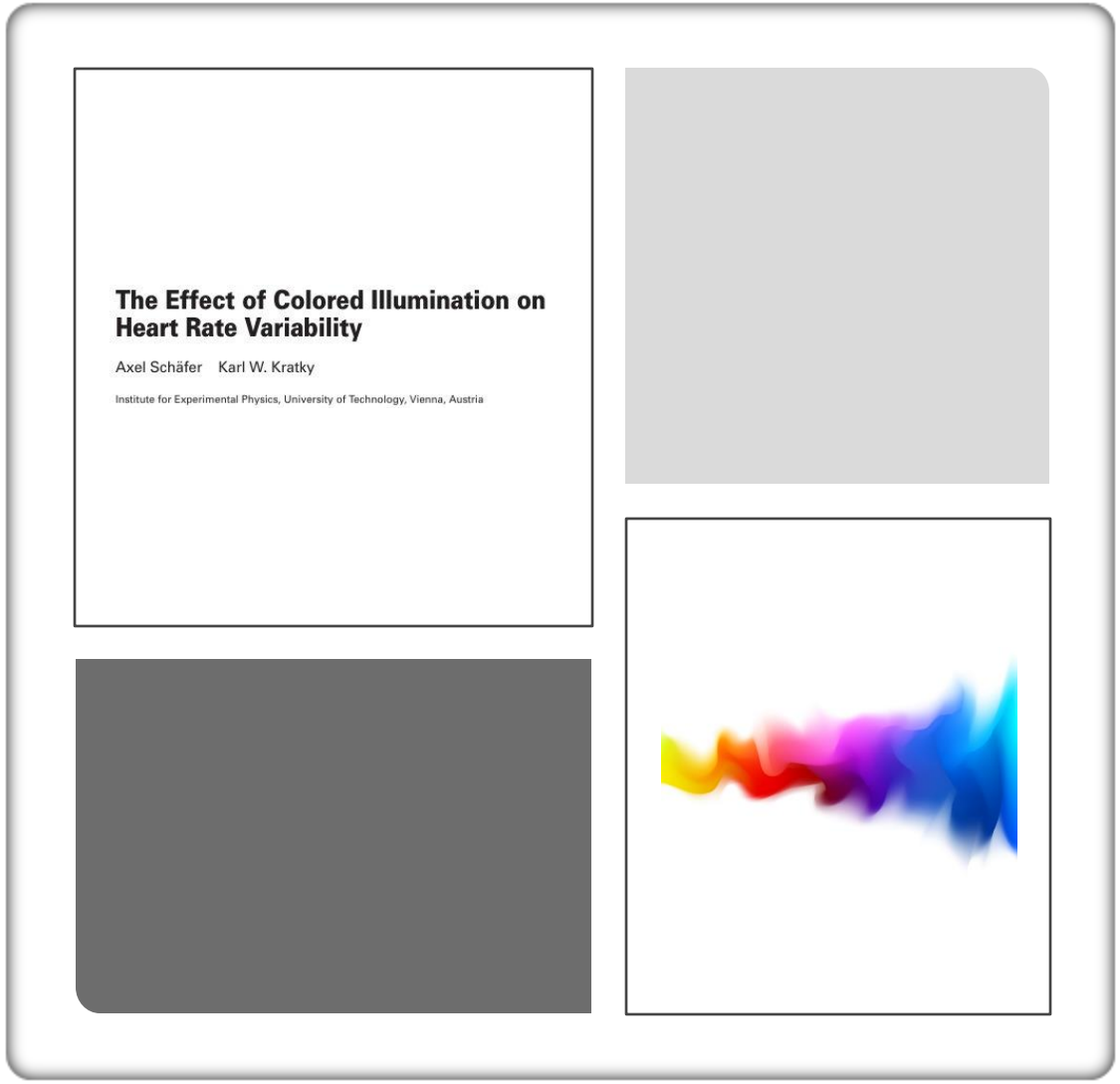
KEY POINTS FROM PAPER

- **Blue light** helps with fatigue and promoting wakefulness
- **Green light** can assist in sleeping
- **Red light** improved alertness
- Most of the evidence is speculative at this point
- More research needs to be performed
- **<u>Light is showing promise as a treatment modality</u>**



METHODS

- 3colored lights: flicker free (700 lux)
  - Red light
  - Green light
  - Blue Light
- 12 healthy subjects
- Dark adapted for 15 minutes, **10-minutes with color**, 15 minutes dark adapted
- HRV measurements



RESULTS

"THE ABSORPTION CURVES OF R+G CONES OVERLAP, WHILE THAT OF BLUE CONES IS LOCATED MORE SEPARATE FROM THE OTHERS."

- SDNN (R-R interval) measure of total HRV
- Following BLUE light there was a decrease in R-R, but it was not statistically significant
- Light can change the HRV in as little as 10-minutes of colored light exposure
- Green and Red are more energizing, while blue subjectively led to a more relaxed state
- Red and green light were more similar, and blue stood alone in the HRV responses

The Effect of Colored Illumination on Heart Rate Variability

Axel Schäfer Karl W. Kratky

Institute for Experimental Physics, University of Technology, Vienna, Austria

Research Article | Open Access
Volume 2021 | Article ID 6697701 | https://doi.org/10.1155/2021/6697701

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Changes in Humans' Autonomic Nervous System under Dynamic Lighting Environment During A Short Rest

Chien-Yu Chen [1], Pei-Jung Wu [2], Yu-Jen Hsiao,[3] and Yu-Wen Tai[4]

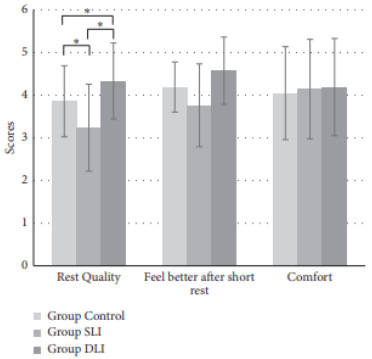

FIGURE 6: The subjective results from the questionnaire (* $p < 0.05$).

Methods

- 21 subjects
- 3 groups:
  - No light (control)
  - Steady and Low-Illuminance light (10 lux) at 2750K white light (SLI)
  - Dynamic and Low-Illuminance (0.5-10 lux)
    - Mainly red light ~630 nm and not affect the melatonin secretion
    - 90 second intervals for dynamic lighting
      - Red, Red+Green, Red+Blue, Red, etc.
- 20 minutes dark adapted, 50 minutes in the luminous setting, 20 minutes for questionnaire
  - 50 minutes of sat in a recliner and relaxed
- Used an electrocardiogram

Results

- DLI group showed improvements in PNS functioning in the first **30 minutes**
- Light stimuli groups did not show a significant change in the comprehensive indicator of the SNS and PNS
- SLI and Control did not show remarkable differences
- *Subjective questionnaire improvements was consistent with objective improvements for PNS and relaxation*

KEY TAKE AWAY POINTS

- Dynamic light may be more beneficial than continuous light
- Changing throughout frequencies was found to be the most important in this study
  - Like standard O.P. protocols with high- or low-frequencies and a balancer
- From the study:
  - "DL environment proposed in the study indeed could efficiently enhance users' activities of the PNS..."

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LIGHT AND THE PARASYMPATHETIC AND SYMPATHETIC NERVOUS SYSTEM

- Dementia is usually associated with a dysfunction in the PNS
- >SNS activity at night is associated with poorer cognition and sleep quality
- Sympathovagal balance
  - LF/HF ratio quantifies the sympathovagal balance
- Using **BRIGHT** morning light as a non-invasive, simple, easy to operate, and cost-effective therapy
- Side note: "brainstem structures supposedly generate output to the **heart."**

healthcare MDPI

Healthcare (Basel). 2023 Mar; 11(6): 793. PMCID: PMC10048435
Published online 2023 Mar 8. doi: 10.3390/healthcare11060793 PMID: 36981450

Bright Morning Lighting Enhancing Parasympathetic Activity at Night: A Pilot Study on Elderly Female Patients with Dementia without a Pacemaker

Chuen-Ru Liu,[1] Terry B. J. Kuo,[2] Jwo-Huei Jou,[3,*] Chun-Ting Lai Lai,[2] Yu-Kai Chang,[4] and Yiing Mei Liou[5,*]

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Methods

- Non-randomized controlled pilot study with convenience sampling
- Bright morning light (2500 lux) and general light (neutral density filter with decreased lux= 600-800) for a control group
- >/= 60-year female patients
- 22 patients
- Assessed heart rate variability
- 25 hours of BML

Results

- HF power (commonly associated with PNS) significantly improved
- BML caused an increase in PNS versus general lighting
- SNS was significantly decreased in the BML versus general lighting group
- Cognition was also improved in the BML group

STUDY TAKE AWAY POINTS

- This was not optometric phototherapy; however, it showed the power of light on the vagus nerve!
  - INCREASE IN GAMMA-AMNIOBUTRYIC ACID (**GABA**)
  - GABA IS A KEY REGULATOR OF THE **VAGUS** NERVE FOR PNS
- BML increases the amplitude of SCN signals
- BML has positive effects on the ANS and cognition

healthcare MDPI

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LIGHT PROCESSING

- Light and the autonomic nervous system (ANS)
- The pupil and the ANS (brief overview)
- Image versus Non-Image Forming Pathways

LIGHT ABSORPTION (OVERVIEW)

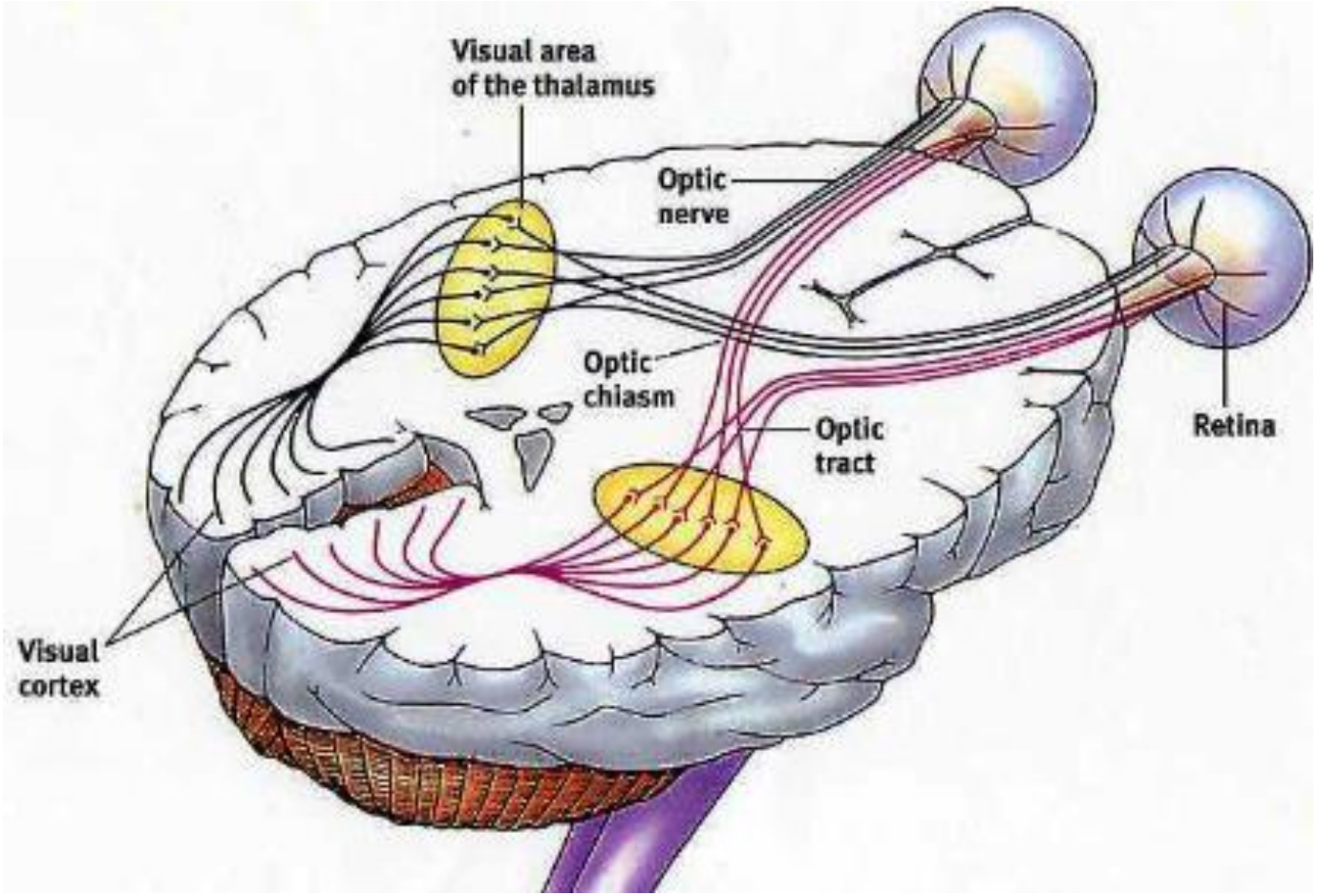
- Photon is the basic unit of light
  - Absorbed by the chromophore (on the opsin)
- A photon hit an object and it gets absorbed
- **ENERGY**
  - The shorter the wavelength, the higher the energy
  - Ranges from 1.8 electron volts (eV) (red) to 3.1 eV (purple(ish))
  - *Per single photon, but the human eye cannot detect a single photon
- Retinal cells absorb light energy and transmits the electrical impulses
  - Induces an action potential
- Phototransduction…

LIGHT ABSORPTION (OVERVIEW)

- Phototransduction
  - Occurs inside the photoreceptor cells
  - Can lead to hyperpolarization (-,-,-)
    - Unlike normal neuronal cells (i.e., depolarization (+,+,+))
  - This leads to a complex biochemical cascade
    - **LIGHT PERCEPTION**
- Review the reference for a comprehensive review.

IMAGE FORMING PATHWAY

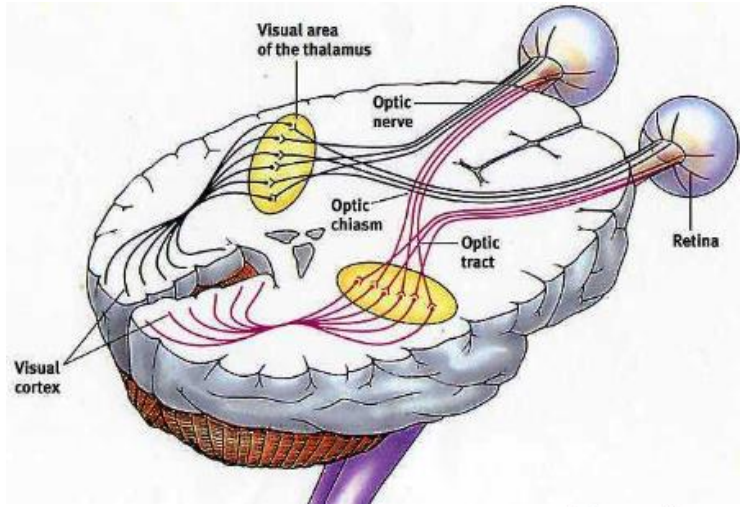
- Retina absorbs the light
  - Ganglion Cell Layer and Nerve Fiber layers=foundation for the optic nerve
- Temporal and Nasal Fibers
  - Control the opposite visual fields
- Retinal fibers join at the optic disc and form the orbital part of the optic nerve
- Fibers exit the skull and go to the optic chiasm
- LATERAL GENINCULATE NUCLEUS (Midbrain)
  - Thalamus
- Genico-calcarine tracts
  - Parietal and temporal lobes
    - Meyer's Loop
- Primary Visual Cortex
- **PATTERN RECOGNITION**

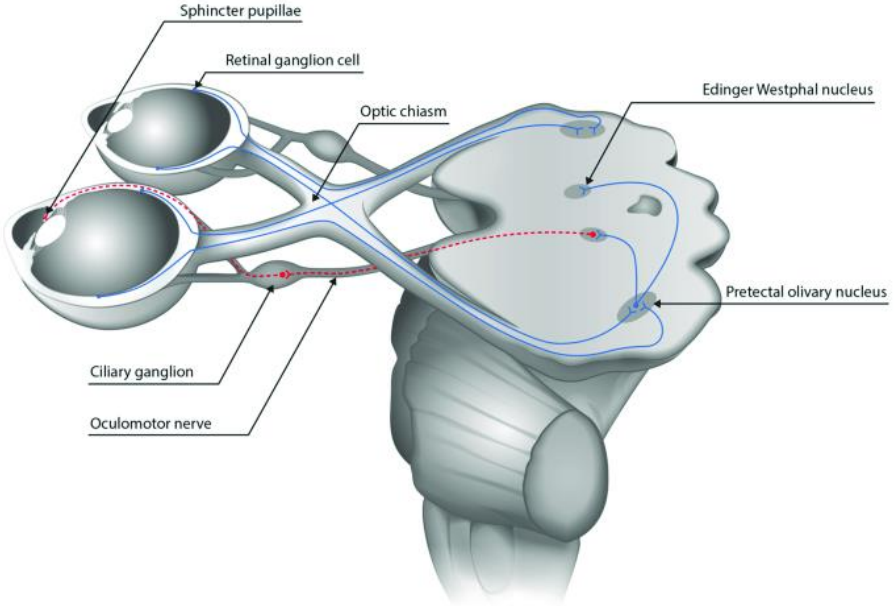


https://www.edoctoronline.com/medical-atlas.asp?c=4&id=21878#google_vignette

PUPILLARY PATHWAY

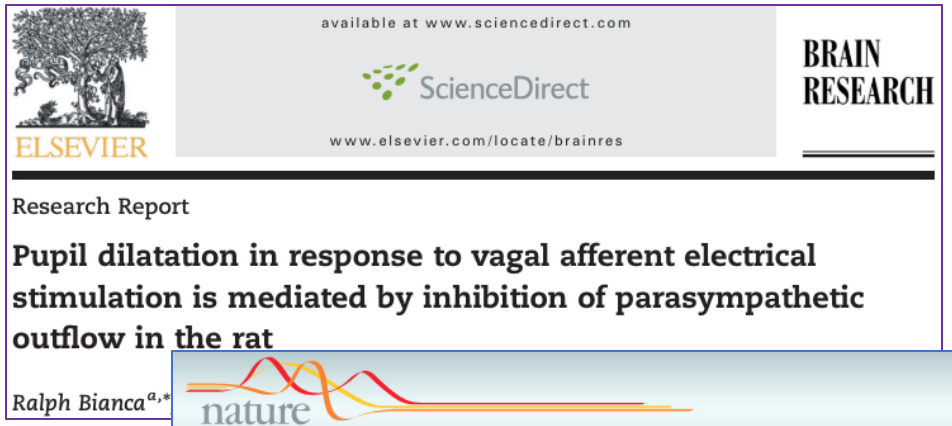
- **The parasympathetic constricts the pupil**
- **The sympathetic dilates the pupil**
- **Retinal fibers via the optic nerve transmit information to the Edinger-Westphal Nucleus**
  - **Pre-Ganglionic**
- **Information is passed on to the ciliary ganglion**
  - **Post-ganglionic**
- **Fibers travel via CN3 (oculomotor nerve) to the sphincter muscle**
- Sympathetic fibers
  - Originate in the hypothalamus
  - Ascending fibers carry info through the upper thoracic spinal cord
  - Second-order neurons travel to the superior cervical ganglion
  - Third order neurons travel via the long ciliary nerves and innervate the pupil dilator and Muller's muscle





1.https://www.edoctoronline.com/medical-atlas.asp?c=4&id=21878#google_vignette
2.https://www.researchgate.net/figure/The-pupillary-pathway-The-afferent-pupillary-pathway-comprises-the-retinal_fig1_331279771

VAGUS NERVE STIMULATION AND THE PUPIL?



available at www.sciencedirect.com

ScienceDirect

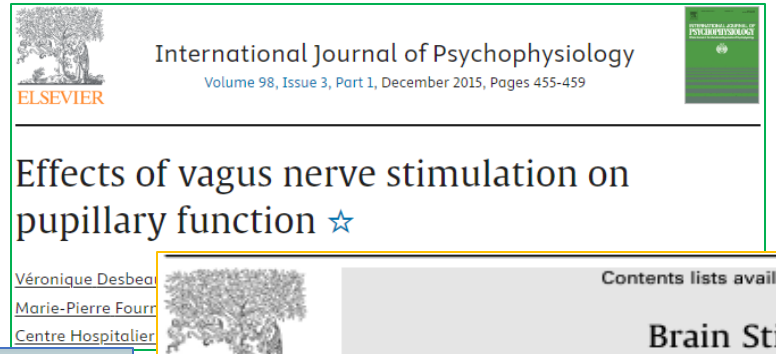
www.elsevier.com/locate/brainres

BRAIN RESEARCH

Research Report

Pupil dilatation in response to vagal afferent electrical stimulation is mediated by inhibition of parasympathetic outflow in the rat

Ralph Bianca[a,*]



ELSEVIER

International Journal of Psychophysiology

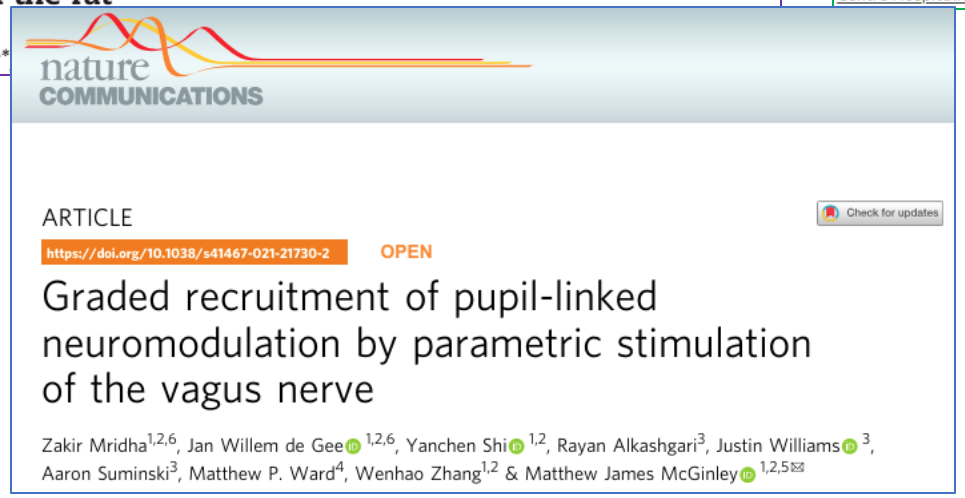
Volume 98, Issue 3, Part 1, December 2015, Pages 455-459

Effects of vagus nerve stimulation on pupillary function ☆

Véronique Desbea

Marie-Pierre Fourr

Centre Hospitalier



nature COMMUNICATIONS

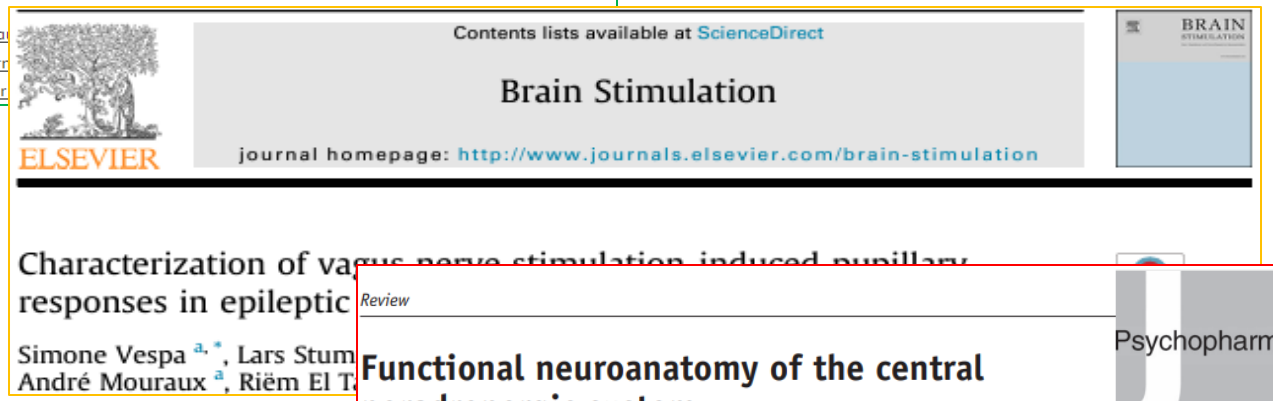
ARTICLE

Check for updates

https://doi.org/10.1038/s41467-021-21730-2 OPEN

Graded recruitment of pupil-linked neuromodulation by parametric stimulation of the vagus nerve

Zakir Mridha[1,2,6], Jan Willem de Gee[1,2,6], Yanchen Shi[1,2], Rayan Alkashgari[3], Justin Williams[3], Aaron Suminski[3], Matthew P. Ward[4], Wenhao Zhang[1,2] & Matthew James McGinley[1,2,5]✉



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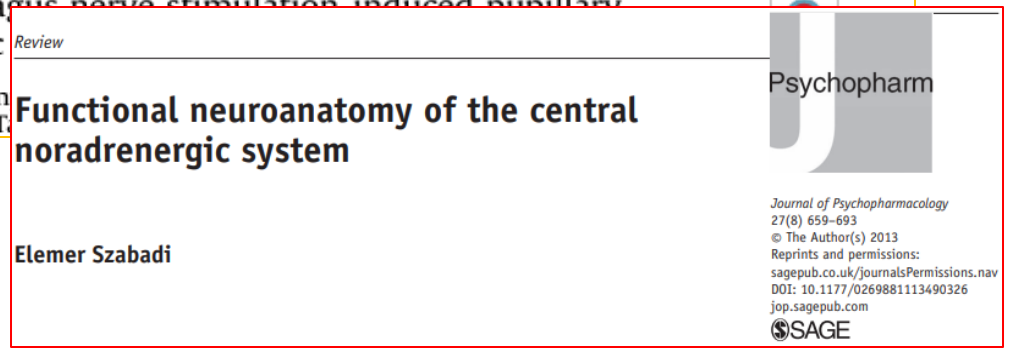
Characterization of vagus nerve stimulation-induced pupillary responses in epileptic

Simone Vespa [a,*], Lars Stum

André Mouraux [a], Riëm El T



Review

Functional neuroanatomy of the central noradrenergic system

Elemer Szabadi

Psychopharm

Journal of Psychopharmacology
27(8) 659–693
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DOI: 10.1177/0269881113490326
jop.sagepub.com

SAGE

INTRODUCTION TO LIGHT, THE LC, AND THE VAGUS NERVE

The SNS and PNS do not function in isolation

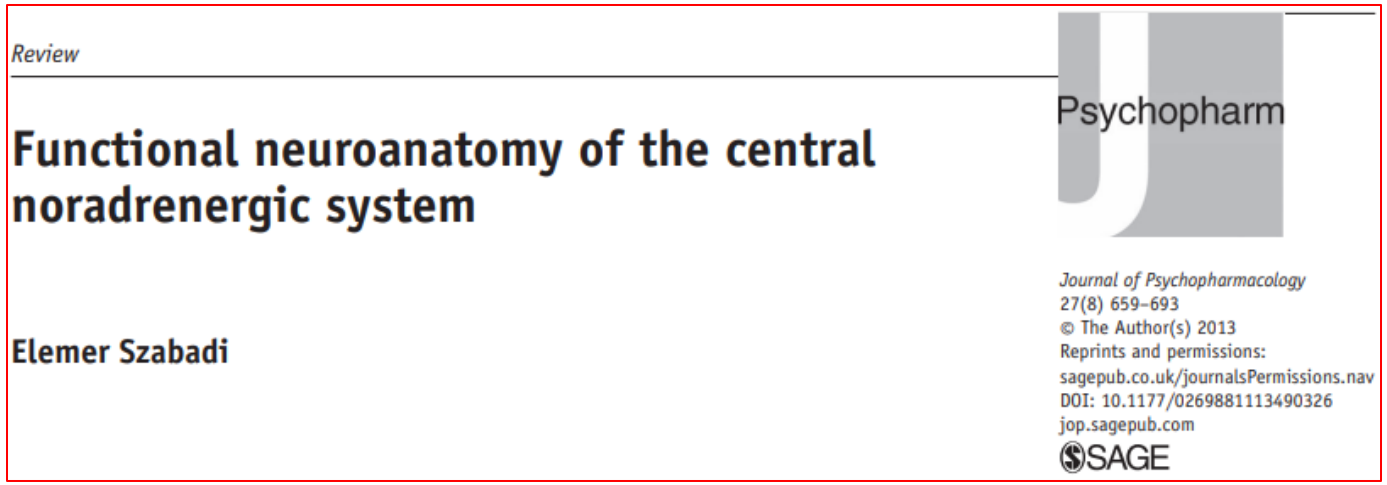
- Cross talk in the medulla oblongata and the paraventricular nucleus
  - PNS premotor neurons are in the LC (doi.10.3389/fneur.2018.01069)

Recall two Vagus Nerve Nuclei

- Dorsal Motor Nucleus (DMV)
- Nucleus Ambiguous (NA)
  - More associated with cardiac function

Coeruleovagal Pathway

- Pontine Nuclei
  - A5 noradrenergic projects pre-ganglionic PNS to the DMV and the NA
- The Locus Coeruleus is a major relay center for pupillary control



Review

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Journal of Psychopharmacology
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DOI: 10.1177/0269881113490326
jop.sagepub.com
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METHODS

- Animal Study with Rats
  - Female rats
- Surgical Stimulation of R or L vagus nerve
- Pupil Measured in dim lighting and assessed for pupillary constriction related to the stimulation
- Two Experiments:
  - 1: 3 groups:
    - Intact
    - Bilateral Resection of the SCG
    - Combination of BR and transection of the brain at the mid-pontine level
  - 2: Vagus Nerve and Sympathetic Chains were isolated
    - Unilateral electrical stimulation to the SNS
    - Unilateral electrical signal to VN

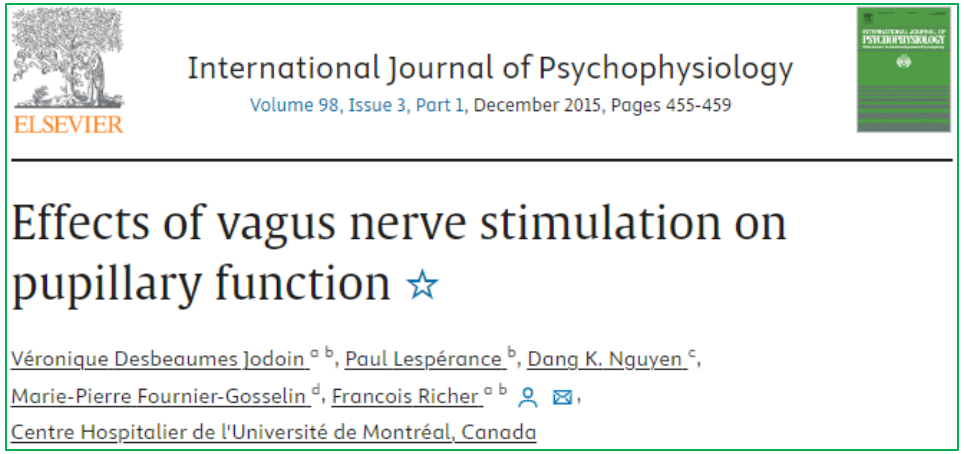
- Hypothesis:
  - 1.if PD occurs after bilateral resection of SCG, it would necessarily be attributable only to inhibition of PNS outflow to the pupil
  - 2. Bilateral resection of the SCG, mid-pontine transection, would eliminate the remaining PNS-mediated PD and thereby abolish any response of the pupil to **AFFERENT** vagal activation

RESULTS

- *PARADOXICALLY: stimulation of the Vagus Nerve (PNS) inhibits PNS output and results in pupillary dilation*
  - *HOWEVER, this assessed the AFFERENT, not the EFFERENT vagus nerve connections*
- The study confirms the PNS is a complex system (polyvagal theory) characterized by both afferent and efferent pathways to and from brain regions that control facilitation and inhibition

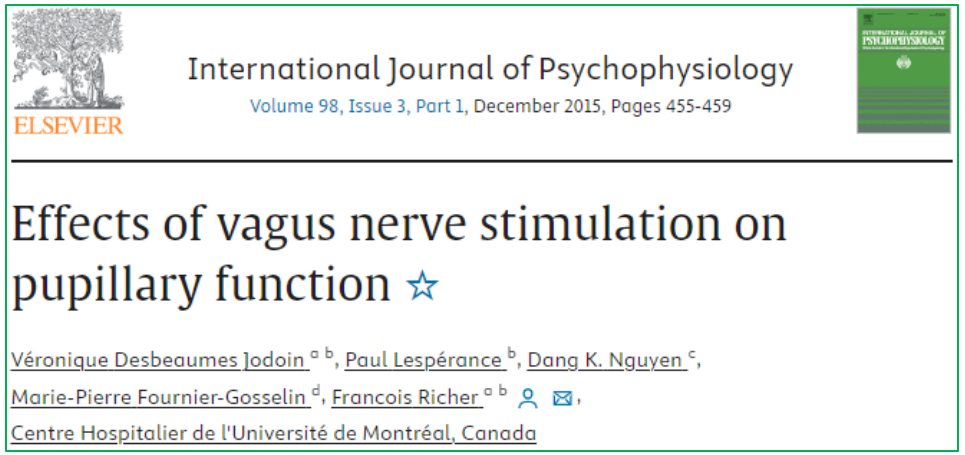
METHODS

- 21 Patients (7 with depression and 14 with epilepsy)
  - No caffeine for 4 hours
  - No eye diseases or anticholinergic or psychostimulant medications
    - *HOWEVER, patients used antidepressants, anticonvulsants, antipsychotics, and anxiolytics*
- 30 seconds ON and 3-5 minutes off stimulation
  - Cyberonics model 102 pulse generator
  - **Left Vagus Nerve** at the level of the neck
- Resting pupil size and light reflex measures
  - Resting pupil (OS) diameter, constriction latency, latency of peak constriction, constriction amplitude, maximum constriction velocity, and maximum constriction acceleration
    - **VCmax** and **ACmax** are sensitive to **parasympathetic** function
  - Dark room setting (340 lux) and 5-minute dim illumination adaptation
  - White disc flashed on the screen for 500ms
  - Pupillary recordings occurred for 1.95s
- Symptom Improvement Monitored with Montgomery-Asberg Depression Rating Scale



RESULTS

- No clinical significance with **ACmax** or **VCmax**
- Resting pupil diameter was significantly larger during the ON conditions
- LIMITATIONS:
  - Small Sample Size
  - Restricted intensity range (0.25 mA-2.25 mA)
    - FDA approved range for study population
  - Dim illumination versus true dark adaptation
    - "Dark adaptation and higher flash intensities may help reveal small effects of VNS on the light reflex"
  - Patients were on medications that could have affected the results



ELSEVIER

International Journal of Psychophysiology

Volume 98, Issue 3, Part 1, December 2015, Pages 455-459

Effects of vagus nerve stimulation on pupillary function ☆

Véronique Desbeaumes Jodoin [a b], Paul Lespérance [b], Dang K. Nguyen [c], Marie-Pierre Fournier-Gosselin [d], Francois Richer [a b],

Centre Hospitalier de l'Université de Montréal, Canada

Methods:

- VNS with an ON duration of 11s, separated by OFF phases of 18s
- 3 blocks with different intensities and 6 trials in each block (18 total)
  - 3 minutes total
  - VNS at current clinical output (mid)
  - Clinical+0.25 mA (high)
  - Clinical-0.50 mA (low)
  - And control stimulation
- 3 Pupil Measures:
  - Peak Dilation Velocity
  - Early Sustained Pupil Dilation Response (PDR) (first 2.5 seconds)
  - Late PDR (pupil size between >2.5-seconds)

- *VNS modulates the LC via an ascending pathway from the vagus nerve (nucleus of the solitary tract-the main afferent of CNX)*
  - *Excitatory inputs reach the LC via nucleus paragigantocellularis*
  - *Has been shown to cause pupil dilation*

Contents lists available at ScienceDirect

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ELSEVIER

Characterization of vagus nerve stimulation-induced pupillary responses in epileptic patients

Simone Vespa [a, *], Lars Stumpp [a], Giulia Liberati [a], Jean Delbeke [a], Antoine Nonclercq [b], André Mouraux [a], Riëm El Tahry [a, c]

Key Take Away Points:

"The early PDR might reflect a phasic, rapid, saliency-driven activation of the LC, while the late PDR could depend on a possibly tonic, more sustained LC activation related to the vagus nerve afferent input, graded by VNS intensity rather than by the perception of the stimulus."

- The authors indicate this warrants investigation beyond the 5s period
- Low intensity trended to have a potential **pupillary constriction response**

- Results:
- Statistically significant slower dilation response and lesser amplitude for early PDR with VNS conditions versus control
- Sensation of the VNS is not as important in pupillary responses for late PDR versus early PDR
  - Early PDR did not prove significant dependency on intensity, BUT a positive relationship with PERCEPTION intensity
  - Late PDR is more impacted by VNS intensity
- VNS affected the late PDR (**<u>for vagal afferents</u>**)

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BRAIN STIMULATION

Characterization of vagus nerve stimulation-induced pupillary responses in epileptic patients

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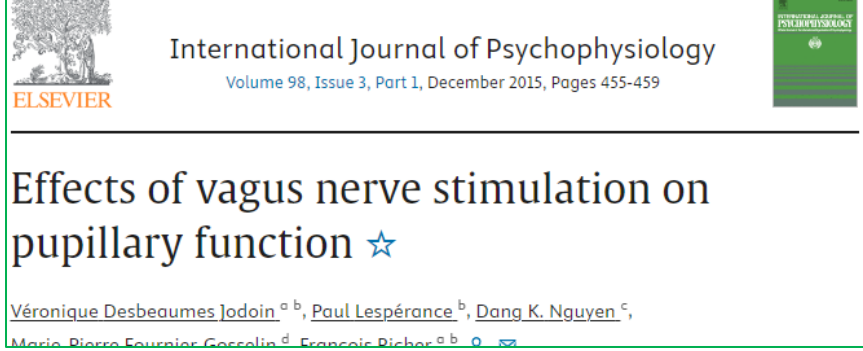
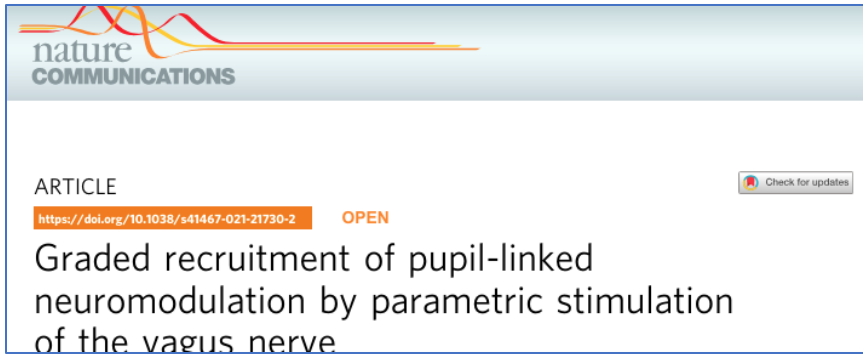
TAKE AWAY POINTS

- The Vagus Nerve and the Pupil are connected
- Continued research must be carried out in humans
  - Stricter criteria
  - Efferent input versus afferent
- Assessing for efferent vagus nerve input with light is warranted
- The main effects of VNS on the brain are thought to be mediated by vagus nerve sensory afferents activating nucleus tractus soltarii, which in turn activates the reticular activating system and other brain areas (Mridha, Nature Communications)





NON-IMAGE FORMING PATHWAY: THE BIOCHEMISTRY (REVIEW)

- IpRGCs have a light evoked large depolarization with fast action potentials
- IpRGCs of a single cell to narrow-band stimuli
  - 400-600 nm (in 20-30 nm steps)
  - Looking for peak depolarization (also assessed increasing energy)
  - Peak sensitivity at 484 nm
- Melanopsin photopigment
- Innervate the suprachiasmatic nucleus (SCN)

Phototransduction by Retinal Ganglion Cells That Set the Circadian Clock

DAVID M. BERSON, FELICE A. DUNN, AND MOTOHARU TAKAO Authors Info & Affiliations

SCIENCE · 8 Feb 2002 · Vol 295, Issue 5557 · pp. 1070-1073 · DOI: 10.1126/science.1067262

NON-IMAGE FORMING PATHWAY

- 5 different types of ipRGCs (M1-M5)
  - Contralateral and ipsilateral input
- SCN receives mostly from M1, also **M2**
  - SCN is in the anterior hypothalamus
  - Core and Shell
    - **Core**= light responsive (ventral region)
      - Vasoactive intestinal polypeptide (VIP)
      - Gastrin-releasing peptide (GRP)
    - Shell= circadian oscillators
      - Arginine Vasopressin (AVP)
      - Calretinin
- IpRGCs project to the brain to influence light mediated behaviors

hitecture of retinal projections
adian pacemaker

arlos Fernandez[a,1], Yi-Ting Chang[b,1], Samer Hattar[a,c], and Shih-Kuo C

ent of Biology, Johns Hopkins University, Baltimore, MD 21218; [b]Department of Life Scier
ent of Neuroscience, Johns Hopkins University, Baltimore, MD 21218; and [d]Genome and S
and Academia Sinica, Taipei 10617, Taiwan

Joseph S. Takahashi, Howard Hughes Medical Institute, University of Texas Southwestern
or review November 30, 2015)

NON-IMAGE FORMING PATHWAY

- **Input**
  - Calcium/cAMP response element binding protein (CREB)
  - CREB is essential for photic resetting of the SCN clock
    - Modulated by non-photic inputs, notably:
      - Thalamic intergeniculate leaflet (IGL)
      - Midbrain raphe
- **Output**
  - Core and shell send EFFERENT projections to local primary targets: medial areas in the hypothalamus and thalamus
  - Master pacemaker, synchronizes other oscillators throughout the brain
    - Autonomic neural connections
    - **Hormones**

Annu Rev Physiol. 2010 ; 72: 551–577. doi:10.1146/annurev-physiol-021909-135919.

Suprachiasmatic Nucleus: Cell Autonomy and Network Properties

David K. Welsh[1,2], **Joseph S. Takahashi**[3], and **Steve A. Kay**[4]

NON-IMAGE FORMING PATHWAY

- Light enters the retina and courses to the Suprachiasmatic Nucleus (SCN)
  - Retinohypothalamic Pathway
  - Biochemical cascade...previous reference
- This pathway relates to the autonomic nervous system
- Light can affect the ANS via oscillating light
- The SCN sends parasympathetic information to the paraventricular nucleus and eventually the thyroid
  - The thyroid releases thyroid releasing hormone (TRH)
    - Light processed via the SCN was found in rostral part of the **dorsal motor nucleus of the vagus nerve**
      - First order neurons
    - **Light releases hormones from the thyroid gland because of the input of light**

Endocrinology. 2000 Oct;141(10):3832-41. doi: 10.1210/endo.141.10.7709.

Functional connections between the suprachiasmatic nucleus and the thyroid gland as revealed by lesioning and viral tracing techniques in the rat

A Kalsbeek [1], E Fliers, A N Franke, J Wortel, R M Buijs

NON-IMAGE FORMING PATHWAY

- Role of the **Core** (ventral and dorsal)
  - (Synchronizes the shell)
  - Locomotor activity
  - Body temperature
  - **HEART RATE**
  - Melatonin
  - Cortisol

Annu Rev Physiol. 2010 ; 72: 551–577. doi:10.1146/annurev-physiol-021909-135919.

Suprachiasmatic Nucleus: Cell Autonomy and Network Properties

David K. Welsh[1,2], **Joseph S. Takahashi**[3], and **Steve A. Kay**[4]

THE HEART

- Parasympathetic Focus
- Right and Left Vagus Review
  - Anatomy and Physiology Slides
- Light and the HEART
- Internal Loop Connection

ON TO THE HEART…

- 22 participants
- Lighting Situations:
  - 13-minutes of <5lux (dim light) @3520K
  - Different light situations each week
    - 500 lux
      - 7434k, 2564k, 3730k
- 4 consecutive weeks
  - Morning and afternoon sessions
- Measured electrocardiogram (ECG) and electroencephalogram (EEG)

JOURNAL OF CIRCADIAN RHYTHMS

Askaripoor, T, et al. 2018 Non-Image Forming Effects of Light on Brainwaves, Autonomic Nervous Activity, Fatigue, and Performance. *Journal of Circadian Rhythms*, 16(1): 9, pp. 1–13. DOI: https://doi.org/10.5334/jcr.167

RESEARCH ARTICLE

Non-Image Forming Effects of Light on Brainwaves, Autonomic Nervous Activity, Fatigue, and Performance

Taleb Askaripoor*, Majid Motamedzadeh†, Rostam Golmohammadi‡, Maryam Farhadian§, Mohammad Babamiri† and Mehdi Samavati‖

RESULTS

- All 3 lighting temperatures had significant effects to the HRV compared to DL
- 2564K (warmer light) showed significant changes to LF/HF (sympatho-vagal balance) compared to DL
- 2564k and 7343k both decreased alpha power on the EEG, subjective fatigue, and sleepiness during the morning session.

Take-Away Points

- Paying attention to the CCT (light temperature) may be more practical to human neurobehavioral functions compared to white bright light in work environments
- Light can improve well-being and productivity for indoors lighting
  - *Including learning abilities in the classroom*
- The heart plays a major factor in light processing

JOURNAL OF CIRCADIAN RHYTHMS

Askaripoor, T, et al. 2018 Non-Image Forming Effects of Light on Brainwaves, Autonomic Nervous Activity, Fatigue, and Performance. *Journal of Circadian Rhythms,* 16(1): 9, pp. 1–13. DOI: https://doi.org/10.5334/jcr.167

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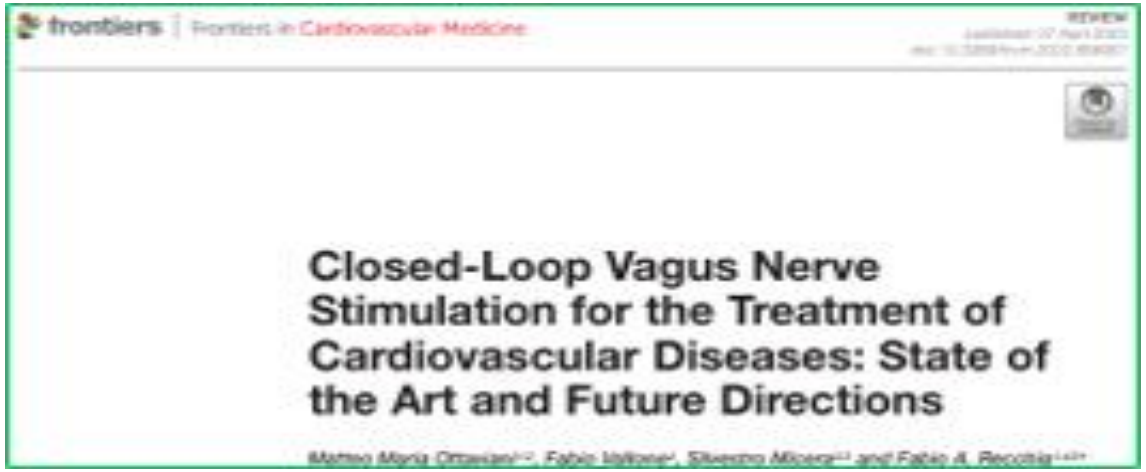
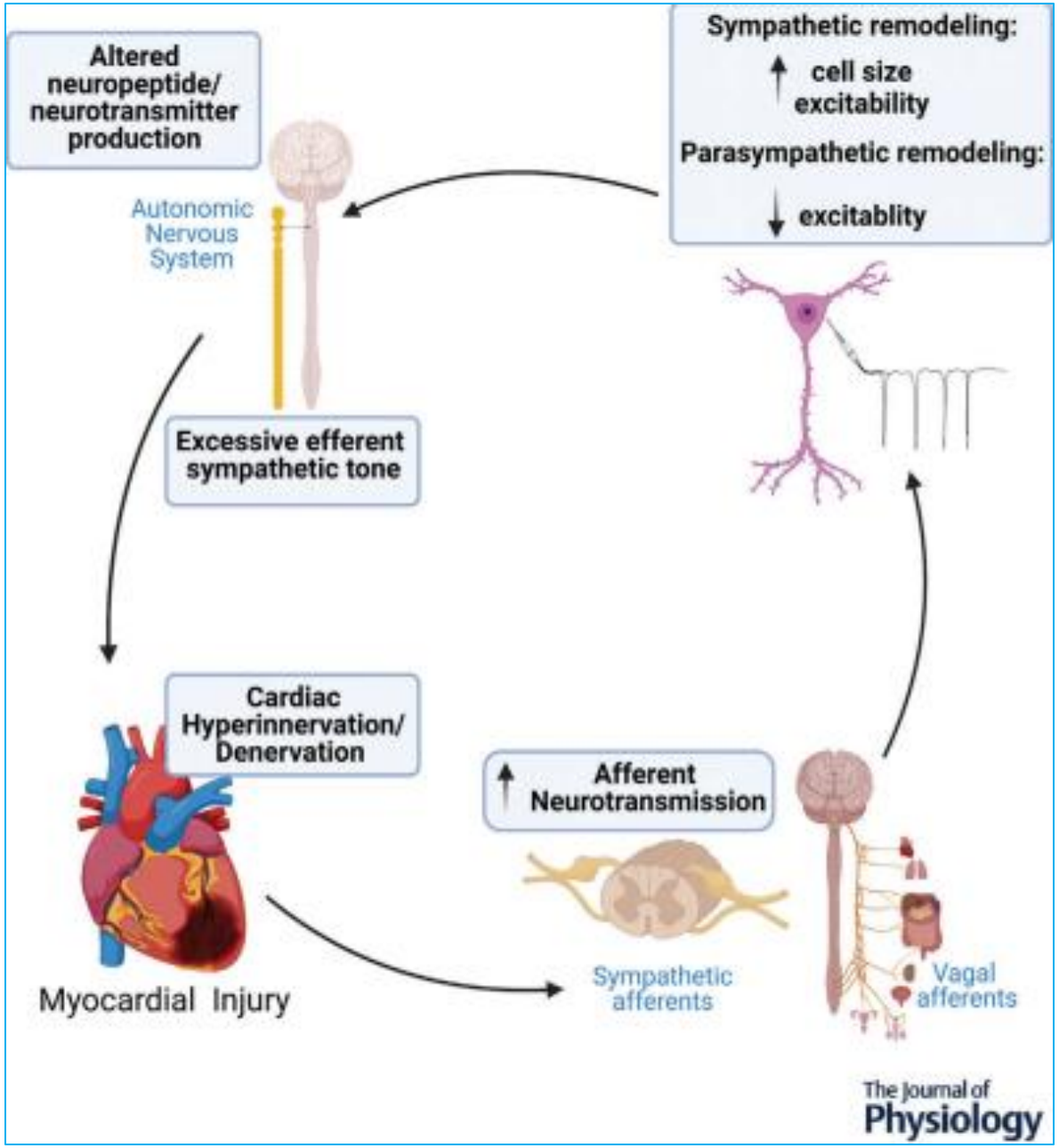
J Physiol 600.3 (2022) pp 451–461

TOPICAL REVIEW

What gets on the nerves of cardiac patients? Pathophysiological changes in cardiac innervation

Courtney Clyburn, Joseph J. Sepe and Beth A. Habecker





WHAT GETS ON THE NERVES…

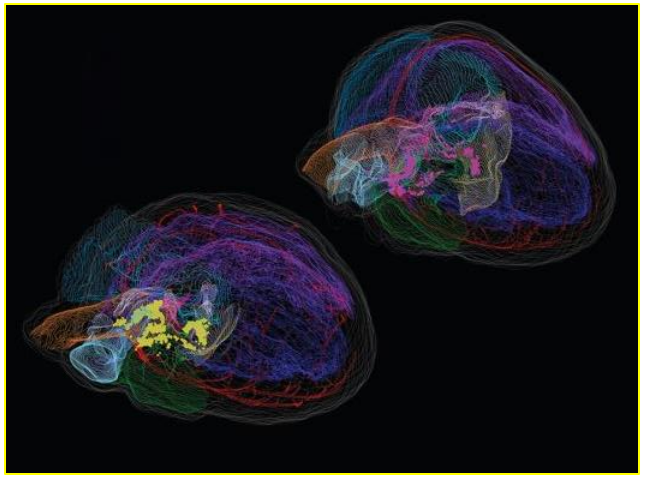
- PNS control on the heart originates in the nucleus ambiguous and the dorsal motor nucleus
- PNS and SNS are influenced by descending neurons from higher cortical nuclei
  - relayed through the nucleus tractus solitarus
- Preganglionic PNS neurons project to the heart via the vagus nerve and form cholinergic synapses with the postganglionic neurons
- ACh is released and activates M2 muscarinic neurons in the SA node, AV node, atria, and ventricles
  - Decreases HR (chronotropy) and conduction velocity (dromotropy)
  - L Vagus mostly AV node
  - R Vagus mostly SA node

THE HEARTS "LITTLE BRAIN"

The Heart's "Little Brain"

By Karuna Meda

Researchers develop the first ever 3D map of the heart's nervous system, providing a foundation for understanding the complexities of heart health.



https://research.jefferson.edu/2022-magazine/the-hearts-little-brain.html

...LITTLE BRAIN

- The heart receives input from the brain about the environment and maintains HR, BP, etc.
- The heart has an internal loop that functions as its own "brain"
- Research discovered when the NIH funded "Stimulating Peripheral Activity to Relieve Conditions" (SPARC)
  - Researchers investigate different organs and their communication with the brain=interoception
  - Regulates vital bodily functions
    - Digestion, breathing, cognition, etc.
    - Much research has been done on the vagus nerve
      - Can affect the heart, lungs, liver, etc.
- Clustered around the SA node (regulates heartbeat)

frontiers in Neurology

MINI REVIEW
published: 20 October 2017
doi: 10.3389/fneur.2017.00541

In a Heartbeat: Light and Cardiovascular Physiology

*Sarah L. Chellappa[1,2], Ruta Lasauskaite[3] and Christian Cajochen[3]**

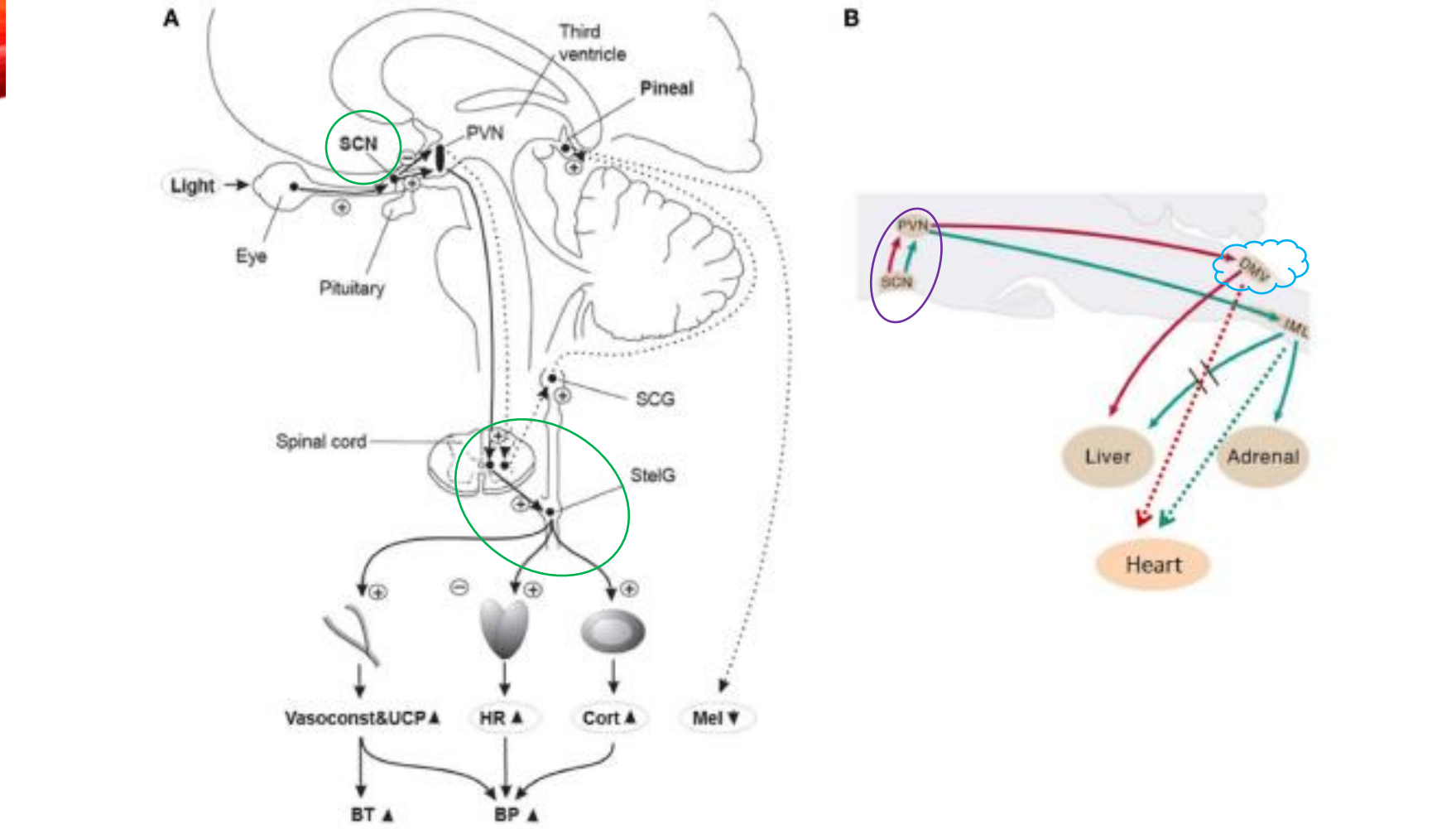
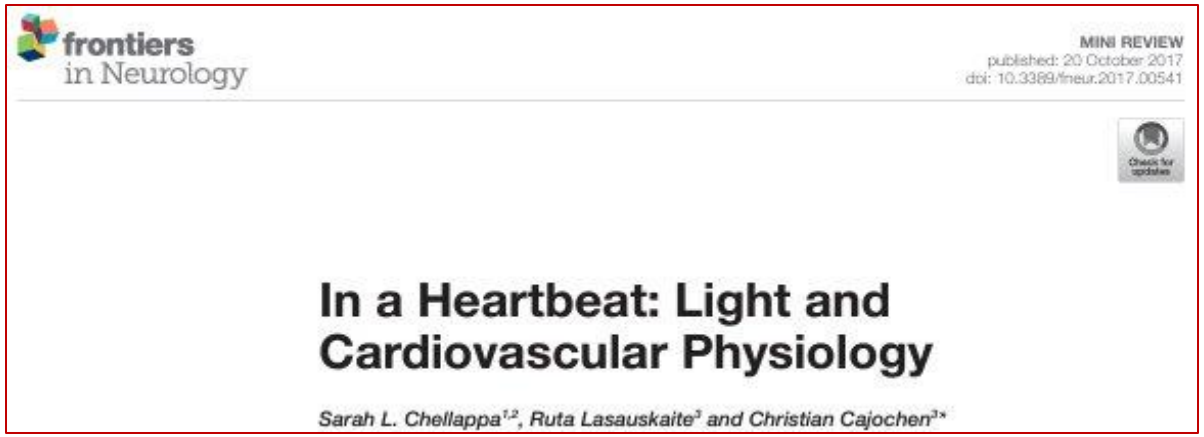


FIGURE 1 | **(A)** Putative light mechanisms on human cardiovascular system *via* the suprachiasmatic nuclei (SCN). Human SCN potentially sends different projections to different parts of the PVN to inhibit melatonin in the pineal gland, while stimulating most other SCN-driven rhythms (e.g., HR and cortisol) after light exposure. BP, blood pressure; BT, body temperature; Cort, cortisol; HR, heart rate; Mel, melatonin; PVN, paraventricular hypothalamus nucleus; SCG, superior cervical ganglion; StelG, stellate ganglion; Vasoconstr & UCP, vasoconstriction and uncoupling protein. Continuous lines: active pathways, dotted lines: suppressed pathways. "Plus" signs: stimulation; "minus" signs: inhibition. Reproduced with permission from Scheer et al. (42). **(B)** Putative sympathetic and parasympathetic outputs from the SCN to peripheral organs *via* neurons of the rat brainstem. DMV, dorsal motor nucleus of the vagus; IML, intermediolateral spinal cord column. Red lines: parasympathetic output. Green lines: Sympathetic output. Dashed red and green lines correspond to *potential* output pathways. Modified from Kalsbeek et al. (34).

LIGHT AND ITS PATH TO THE HEART

- IpRGCs (NIF) cells respond to environmental irradiance
- Integrate photic energy beyond the duration of given light
- Directly project via the retino-thalamic tract to the SCN
  - Multi-synaptically to the pineal gland and other numerous brain regions
- SCN influences PNS output to the HEART via pre-autonomic neurons within the hypothalamus

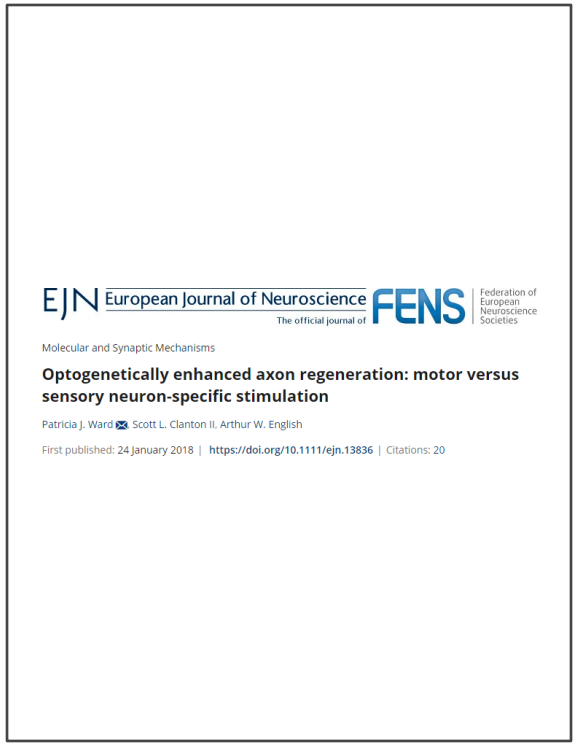


SYNTONIC FILTERS

- Spectrochrometry Encyclopedia- Dinshah Ghadiali
- Connection with the filters?

SPECTROCHROMETRY ENCYCLOPEDIA- DINSHAH GHADIALI

- Modern medicine and research advocating for Dinshah's work
- Dinshah:
  - Nerves are conductors and do not produce energy
  - Page 225 (CH.10)
    - Sensory Impulse converts to a motor impulse
    - Red= oscillating frequency, stimulating
    - Red + Green= Yellow
      - Motor Stimulant
    - **Medulla Oblongata**
      - **Posterior= Sensory Root**
      - **Anterior= Motor Root**
      - VAGUS NERVE REVIEW:
        - Dorsal **MOTOR** Nucleus
        - Nucleus Ambiguous= Motor
        - Afferent and Efferent **motor** and **sensory**
  - Page 52-71 review of the colors
  - Page 89, Figure 59
    - Stimulants and Depressants


EJN European Journal of Neuroscience FENS Federation of European Neuroscience Societies
The official journal of
Molecular and Synaptic Mechanisms
Optogenetically enhanced axon regeneration: motor versus sensory neuron-specific stimulation
Patricia J. Ward, Scott L. Clanton II, Arthur W. English
First published: 24 January 2018 | https://doi.org/10.1111/ejn.13836 | Citations: 20

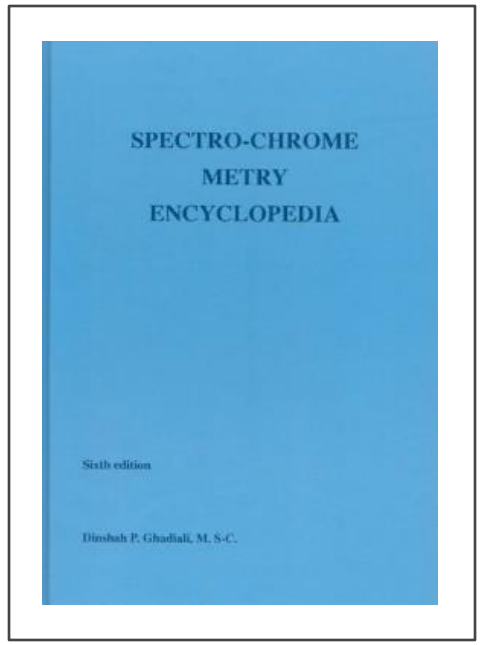


Figure 34

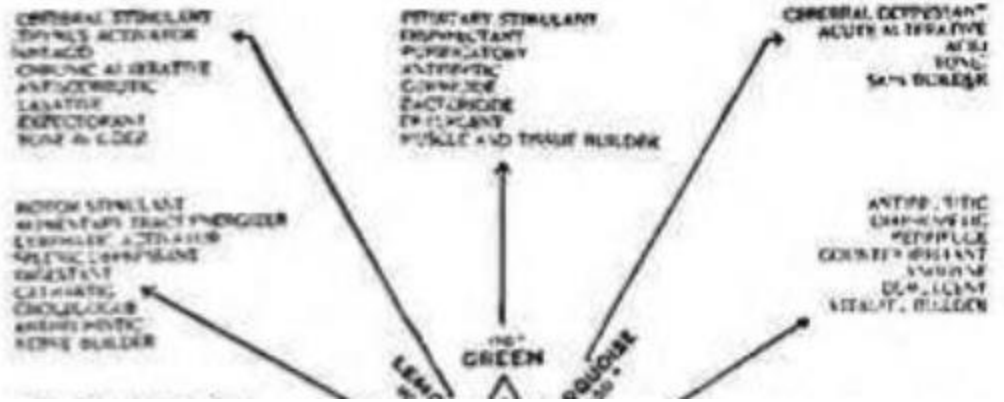
Origination Of Spectro-Chrome Tertiary Colors

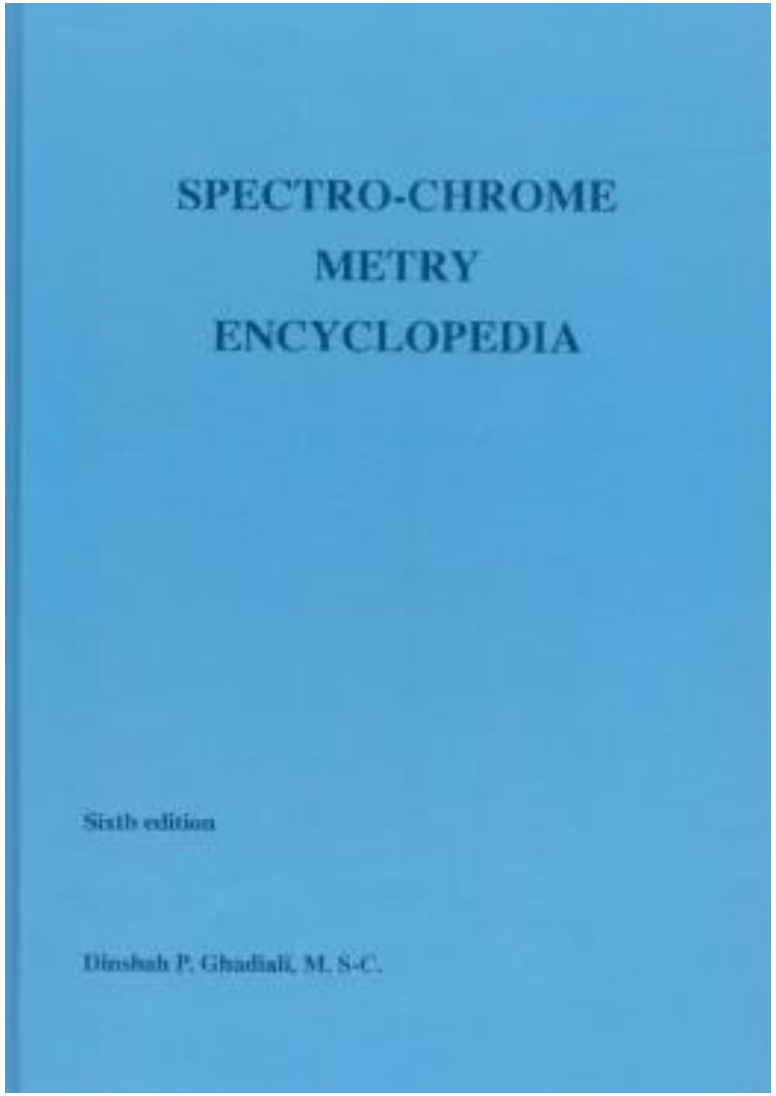
Figure 38

Attuned Color Waves Of Dinshah

Figure 59

Spectro-Chrome Tonation System





MODERN MEDICINE AND MOTOR VERSUS SENSORY

- "Selectively activated either sensory or motor axons using light stimulation combined with transection and repair of the sciatic nerve"
- "Tailoring treatment strategies to engage motor or sensory neurons selectively may facilitate better axon regeneration and the desired functional outcomes"
  - Most therapies focus on motor neuron regeneration
- Optogenetic study approach with mice tracing ChR2 (light sensitive cation channel) to motor and sensory neurons
  - Activated via BLUE light
  - *Not optometric phototherapy as the light was directly shone on the sciatic nerve*

EJN European Journal of Neuroscience
The official journal of FENS
Federation of European Neuroscience Societies

Molecular and Synaptic Mechanisms

Optogenetically enhanced axon regeneration: motor versus sensory neuron-specific stimulation

Patricia J. Ward, Scott L. Clanton II, Arthur W. English

First published: 24 January 2018 | https://doi.org/10.1111/ejn.13836 | Citations: 20

MODERN MEDICINE AND MOTOR VERSUS SENSORY

- Sensorimotor misdirection of regenerating axons can result to long-term dysfunction
- Blue light in this current study activated **sensory** but not **motor** axons
  - Results are presented cautiously
  - More research is needed
- Sensory axon stimulation seems to impact sensory
  - Motor was not inhibited or affected in this study

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Molecular and Synaptic Mechanisms

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The Transformative Impact of Red Light Therapy on the Vagus Nerve Harmony

January 19, 2024

The Impact of Red Light Therapy on the Vagus Nerve

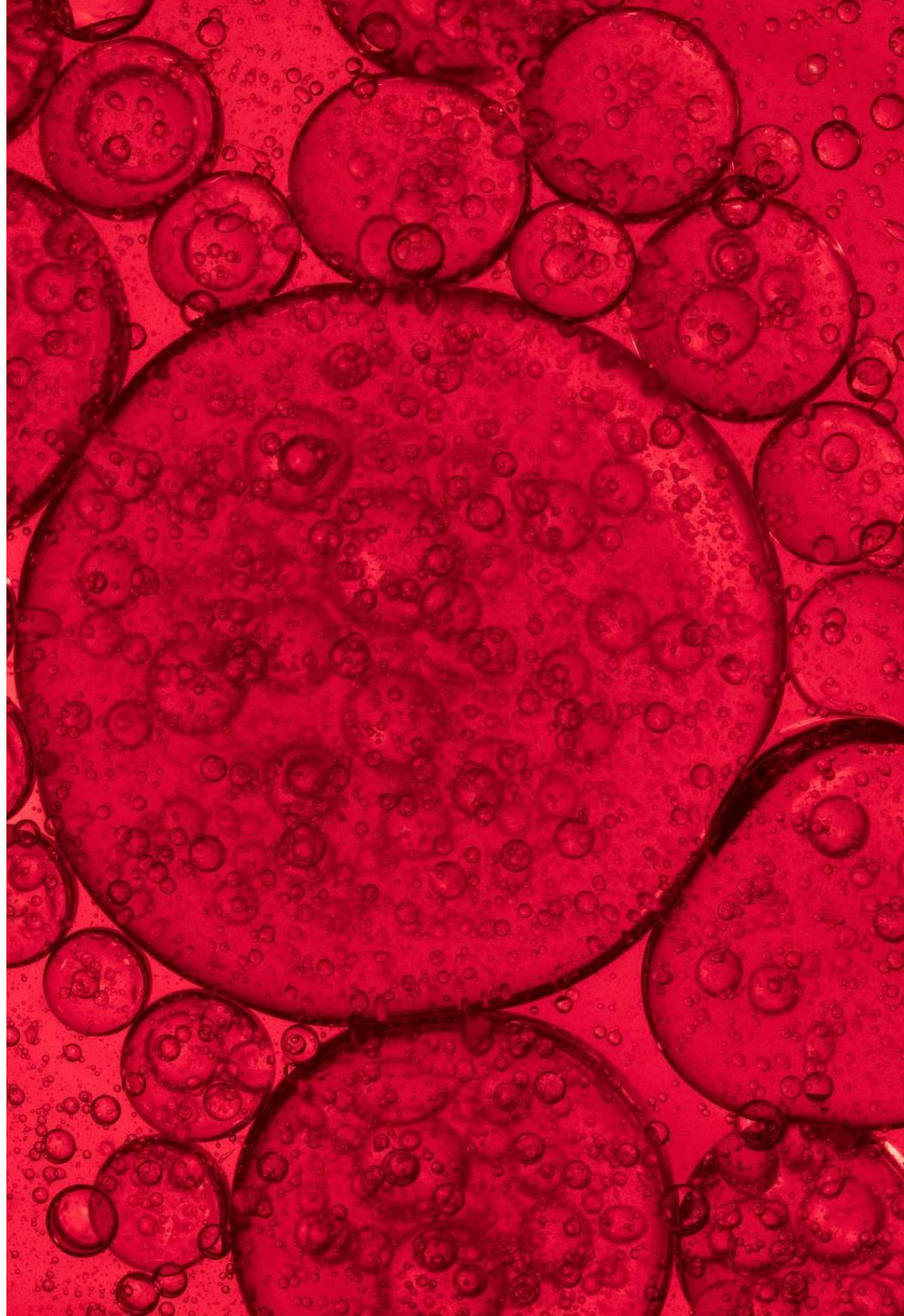
By adminVN | January 12, 2024 | No Comments

NIH U.S. National Library of Medicine

ClinicalTrials.gov

RED LIGHT ON CNX

- Red light via photo biomodulation and stimulates the mitochondria of the cell and neuromodulation via auricular nerves
  - Increases the production of ATP
- Low-level red-light wavelengths
  - Penetrates the skin and is absorbed by the cells
  - Red light can stimulate the vagus nerve by the production of ATP
    - May enhance the communication between nerve cells
  - Increases the production of nitrous oxide (NO)
    - A crucial role in regulating blood flow and reducing inflammation
    - NO has a positive impact on vagus nerve function
- https://vagusnerve.com/the-impact-of-red-light-therapy-on-the-vagus-nerve/
- https://rouge.care/blogs/rouge-red-light-therapy-blog/illuminating-the-transformative-impact-of-red-light-therapy-on-the-vagus-nerve-harmony#:~:text=The%20Transformative%20Impact%20of%20Red%20Light%20Therapy%20on%20the%20Vagus%20Nerve%20Harmony&text=While%20red%20light%20therapy%20is,of%20our%20overall%20well%2Dbeing.



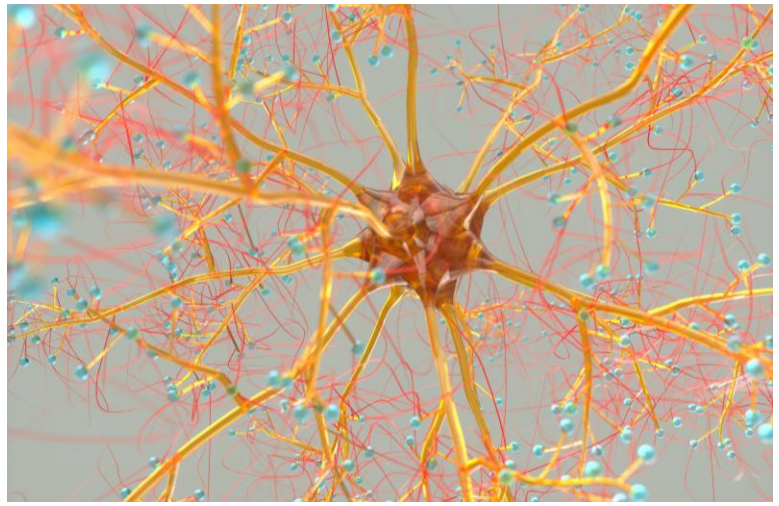
BACK TO CLINICAL TRIALS…

Study Design

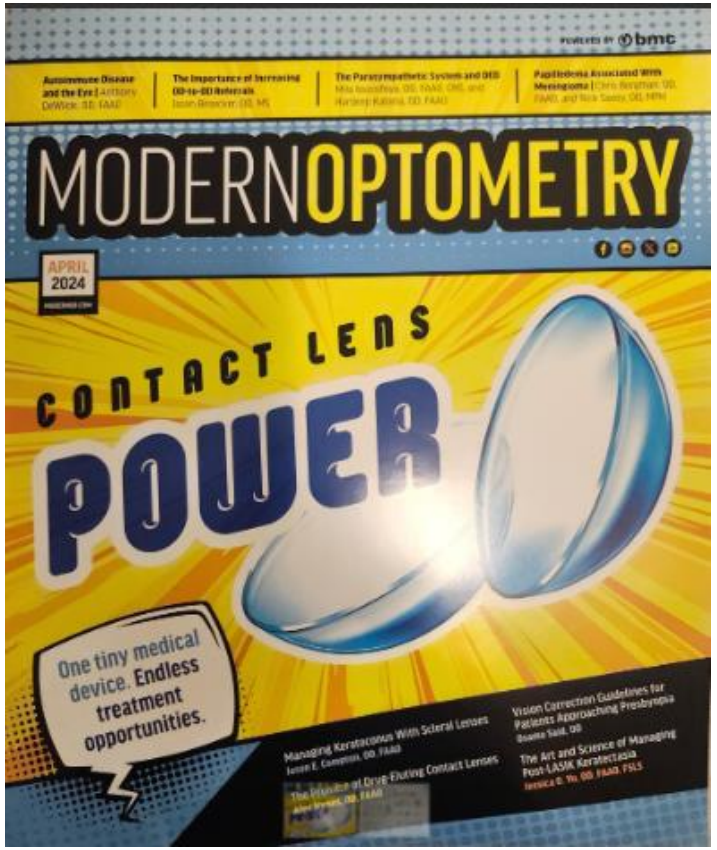
Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	34 participants
Allocation:	Non-Randomized
Intervention Model:	Parallel Assignment
Intervention Model Description:	Patients with refractory epilepsy (divided in non responders & responders), and healthy subjects
Masking:	Single (Participant)
Primary Purpose:	Basic Science
Official Title:	Effect of Blue Light on Vagus Nerve Stimulation in Patients With Refractory Epilepsy
Actual Study Start Date :	July 1, 2023
Actual Primary Completion Date :	July 1, 2023
Estimated Study Completion Date :	April 2026

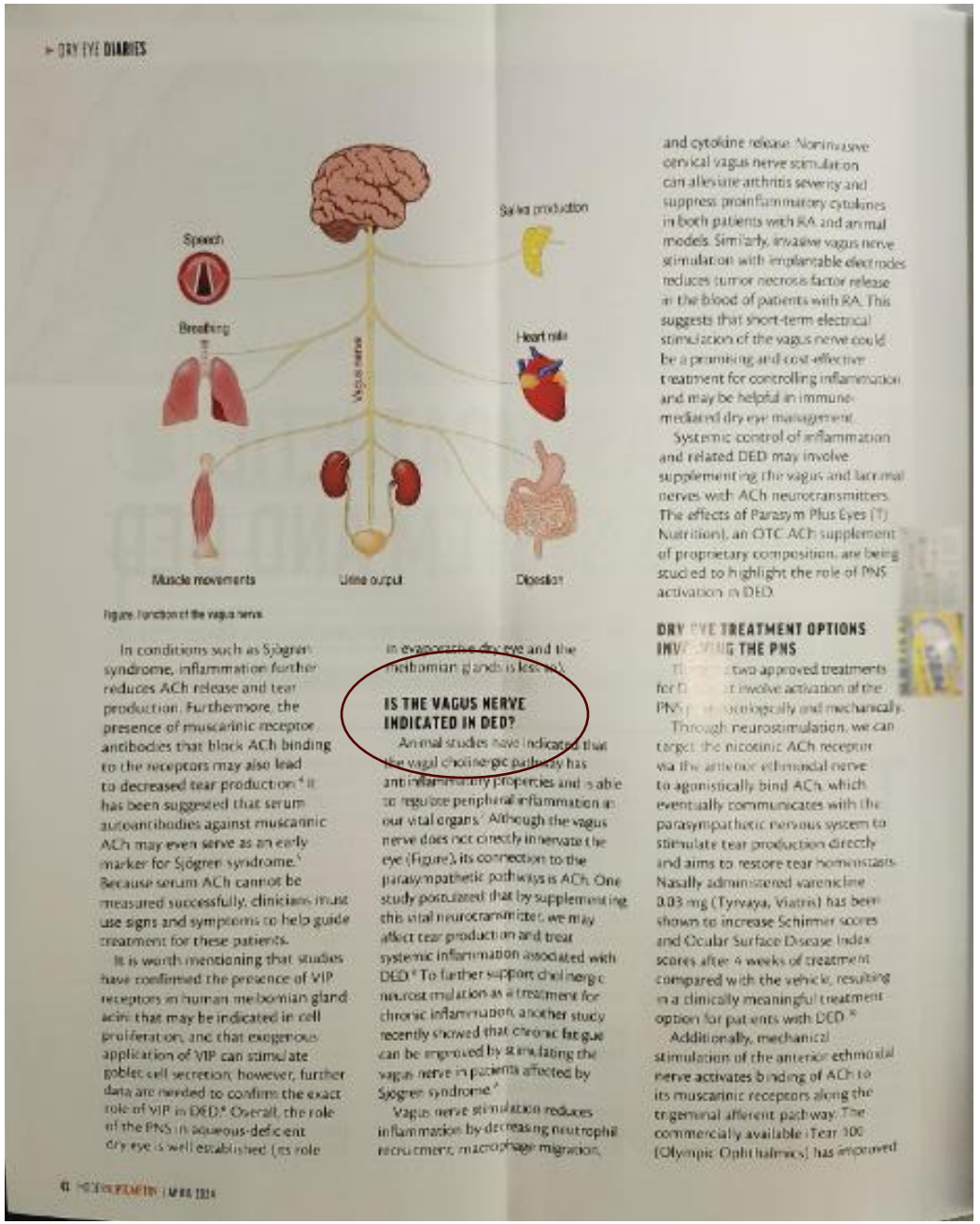
CONTINUED RESEARCH

- There is plenty of light research, but optometric phototherapy or Syntonics requires more research
- Current clinic research is undergoing:
  - Western University College of Optometry
  - Ohio State University
  - Private Practices
- Research into Vagus Nerve and O.P. in the future?
  - Clinical studies, investigative studies, HRV studies, etc.
- Consult with Universities and share ideas to promote the understanding with evidence-based medicine
- Today's idea is 2+ years information...



IN OTHER NEWS





CONCLUSION

References provided upon request


QUESTIONS