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Photobiomodulation Therapy and the Glymphatic - Meningeal Lymphatic System: Promising Applications for Improving Brain Drainage

Denis E Bragin, Ph.D., FAHA

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Review

Photobiomodulation Therapy and the Glymphatic System: Promising Applications for Augmenting the Brain Lymphatic Drainage System

Farzad Salehpour [1,2], Mahsa Khademi [3], Denis E. Bragin [4] and Joseph O. DiDuro [2,*]

Salehpour F, Khademi M, Bragin DE, DiDuro JO. Photobiomodulation Therapy and the Glymphatic System: Promising Applications for Augmenting the Brain Lymphatic Drainage System. *Int J Mol Sci*. 2022 Mar 10;23(6):2975. doi: 10.3390/ijms23062975. PMID: 35328396; PMCID: PMC8950470.

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DOI: 10.1002/tbio.201900036

FULL ARTICLE

TRANSLATIONAL BIOPHOTONICS

Photostimulation of cerebral and peripheral lymphatic functions

Oxana Semyachkina-Glushkovskaya[1] | Arkady Abdurashitov[1] | Maria Klimova[1] | Alexander Dubrovsky[1] | Alexander Shirokov[2] |

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Open Access Review

Sleep as a Novel Biomarker and a Promising Therapeutic Target for Cerebral Small Vessel Disease: A Review Focusing on Alzheimer's Disease and the Blood-Brain Barrier

by Oxana Semyachkina-Glushkovskaya [1,2,*], Dmitry Postnov [1], Thomas Penzel [1,3,4] and Jürgen Kurths [1,2,5]

pharmaceutics

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Article

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Maria Tzoy [2],

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Night Photostimulation of Clearance of Beta-Amyloid from Mouse Brain: New Strategies in Preventing Alzheimer's Disease

Oxana Semyachkina-Glushkovskaya [1,2,*], Thomas Penzel [2,3], Inna Blokhina [2], Alexander Khorovodov [2], Ivan Fedosov [2], Tingting Yu [4,5], Georgy Karandin [2], Arina Evsukova [2], Dariya Elovenko [2], Viktoria Adushkina [2], Alexa
Vasily

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Article

Low-Level Laser Treatment Induces the Blood-Brain Barrier Opening and the Brain Drainage System Activation: Delivery of Liposomes into Mouse Glioblastoma

Oxana Semyachkina-Glushkovskaya [1,2,*], Denis Bragin [3,4], Olga Bragina [3], Sergey Socolovski [5], Alexander Shirokov [2,6], Ivan Fedosov [2], Vasily Ageev [2], Inna Blokhina [2], Alexander Dubrovsky [2], Valeria Telnova [2], Andrey Terskov [2], Alexander Khorovodov [2], Daria Elovenko [2], Arina Evsukova [2], Maria Zhoy [2], Ilana Agranovich [2], Elena Vodovozova [7], Anna Alekseeva [7], Jürgen Kurths [1,2,8] and Edik Rafailov [5]

Adv Exp Med Biol. 2021;1269:57-61. doi: 10.1007/978-3-030-48238-1_9.

Transcranial Photobiomodulation of Clearance of Beta-Amyloid from the Mouse Brain: Effects on the Meningeal Lymphatic Drainage and Blood Oxygen Saturation of the Brain

Oxana Semyachkina-Glushkovskaya [1], M Klimova [2], T Iskra [2], D Bragin [3 4], A Abdurashitov [2], A Dubrovsky [2], A Khorovodov [2], A Terskov [2], I Blokhina [2], N Lezhnev [2], V Vinnik [2], I Agranovich [2], A Mamedova [2], A Shirokov [5], N Navolokin [6], B Khlebsov [5], V Tuchin [2], J Kurths [2 7 8]

ЛИМФАСОН

СГУ

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2. Brain Glymphatic and Meningeal Lymphatic Drainage System
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    3.3. PBM and Neuroprotection
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Introduction

- Transcranial photobiomodulation (tPBM) is the application of low levels of red or near-infrared (NIR) light to stimulate tissues.

- PBM has been demonstrated to be an effective approach for promoting cellular proliferation and microcirculation and for relieving pain and edema in various traumatic, acute, and chronic diseases

- PBM has been also shown to improve brain hemodynamics along with an increase in cerebral oxygenation and metabolic capacity

Introduction

- There is an increasing body of evidence to support that PBM therapy of the brain can ameliorate neuronal oxidative stress, neuroinflammation, and apoptosis, while promoting neurogenesis and synaptogenesis.

- To date, no serious adverse effects have been reported in for brain PBM therapy; however, caution must be considered with high-power laser sources (class 3B and 4) due to the hazard for macular lesions.

Introduction

- The glymphatic system is a glial-dependent waste clearance pathway in the brain, devoted to drain away waste metabolic products and soluble proteins such as amyloid-beta.

- The meningeal lymphatics is a network of lymphatic vessels located parallel to the dural venous sinuses and meningeal arteries of the brain, responsible for draining immune cells, blood, small molecules, and excess fluid from the brain into the deep cervical lymph nodes.

Introduction

- An impaired brain glymphatic system can increase the incidence of neurovascular, neuroinflammatory, and neurodegenerative diseases.

- PBM therapy can serve as a non-invasive neuroprotective strategy for maintaining and optimizing effective brain waste clearance.

- Recent preclinical research in rodents proven the efficiency of PBM for maintaining and optimizing effective brain waste clearance in several models of brain diseases.

Brain Drainage System

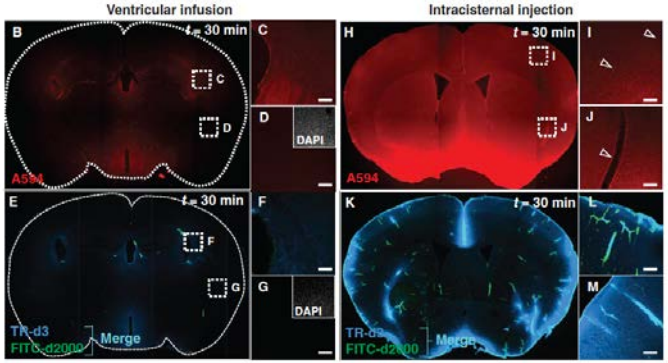
Glymphatic System

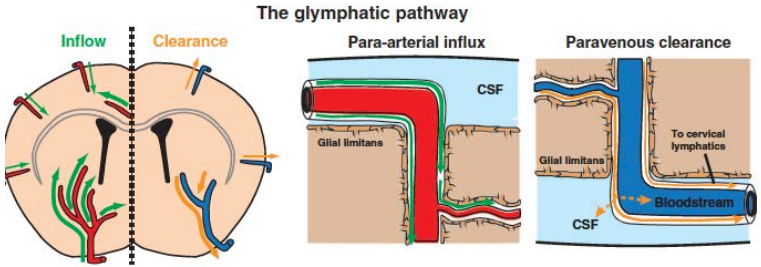
CEREBROSPINAL FLUID CIRCULATION

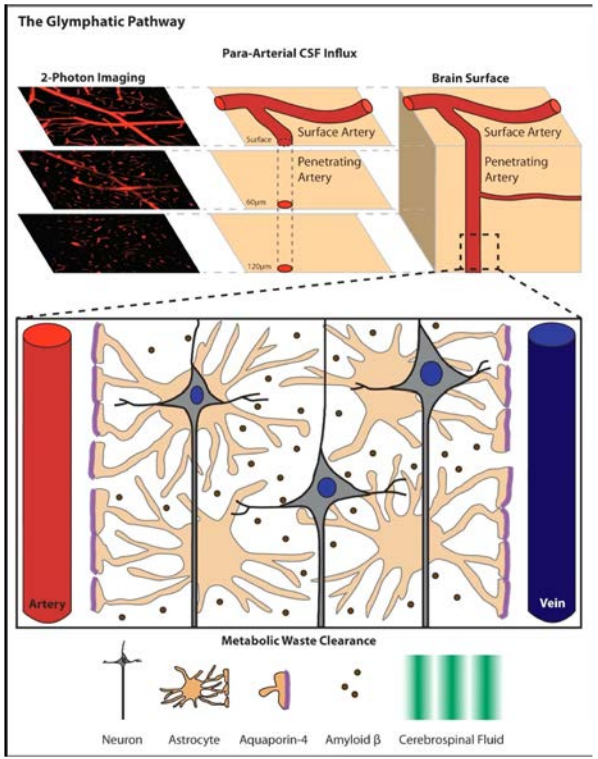
A Paravascular Pathway Facilitates CSF Flow Through the Brain Parenchyma and the Clearance of Interstitial Solutes, Including Amyloid β

Jeffrey J. Iliff,[1]* Minghuan Wang,[1,2] Yonghong Liao,[1] Benjamin A. Plogg,[1] Weiguo Peng,[1] Georg A. Gundersen,[3,4] Helene Benveniste,[5,6] G. Edward Vates,[1] Rashid Deane,[1] Steven A. Goldman,[1,7] Erlend A. Nagelhus,[3,4] Maiken Nedergaard[1]*

Maiken Nedergaard, MD







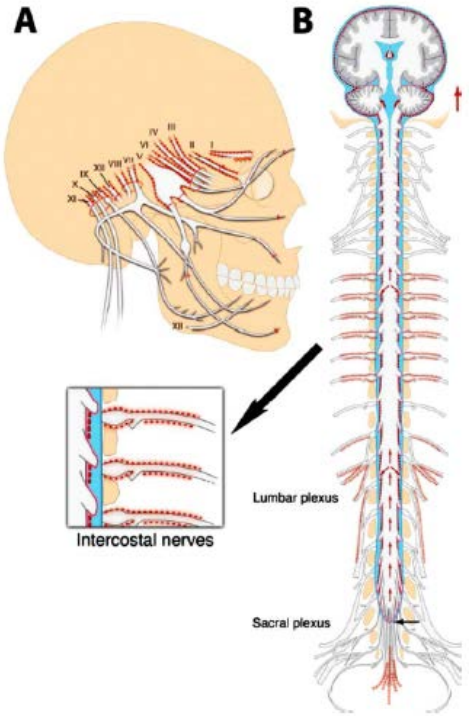
Iliff JJ, et al., 2012, 2013

Brain Drainage System

Glymphatic System

Heinrich Quincke
1842 - 1922

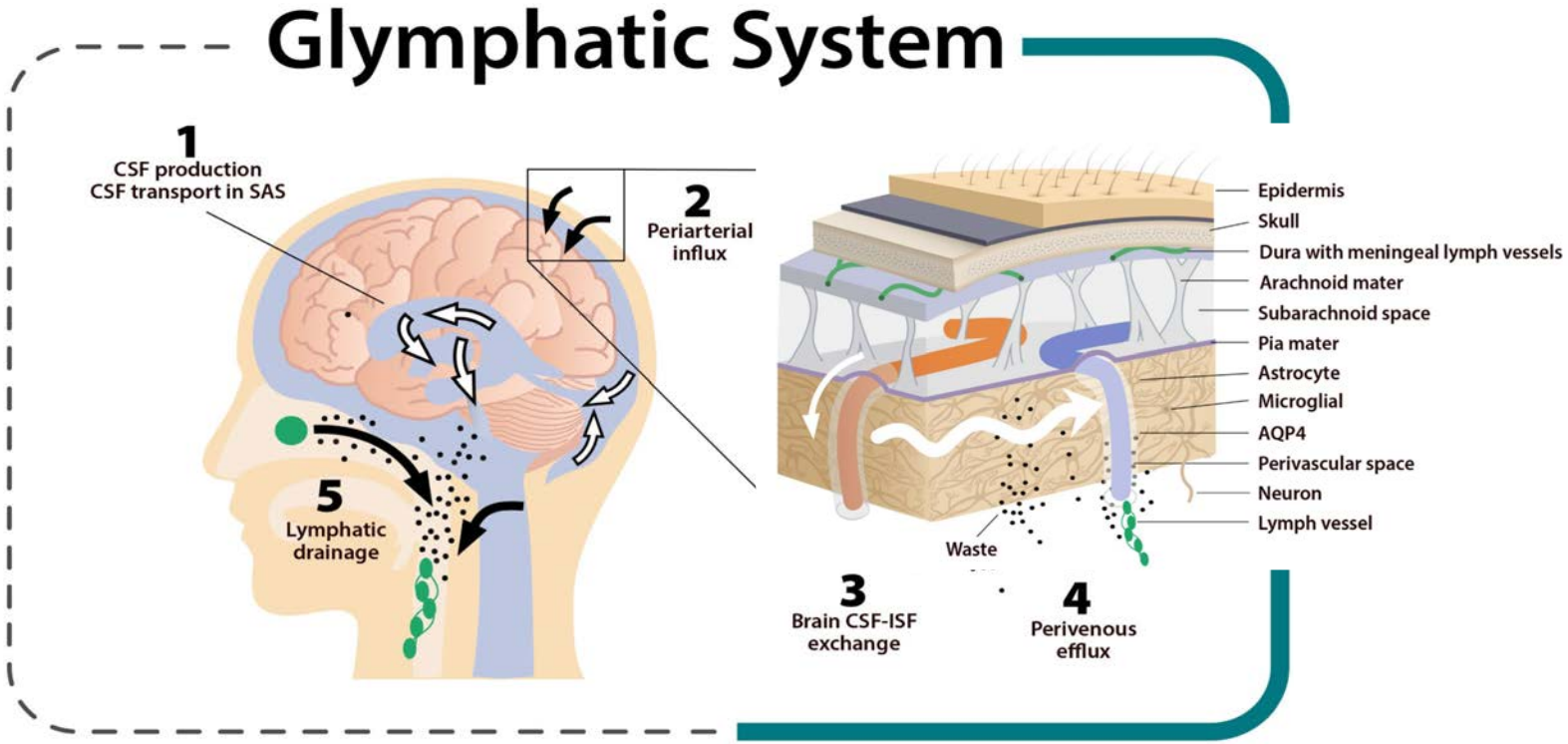
- Characterized brain waste removal via CSF in 1872
- Distribution of cinnabar injected into into the intrathecal spaces in freely moving animals



Benveniste H, et al., Modern cerebrospinal fluid flow research and Heinrich Quincke's seminal 1872 article on the distribution of cinnabar in freely moving animals. *J Comp Neurol.* 2015

Brain Drainage System

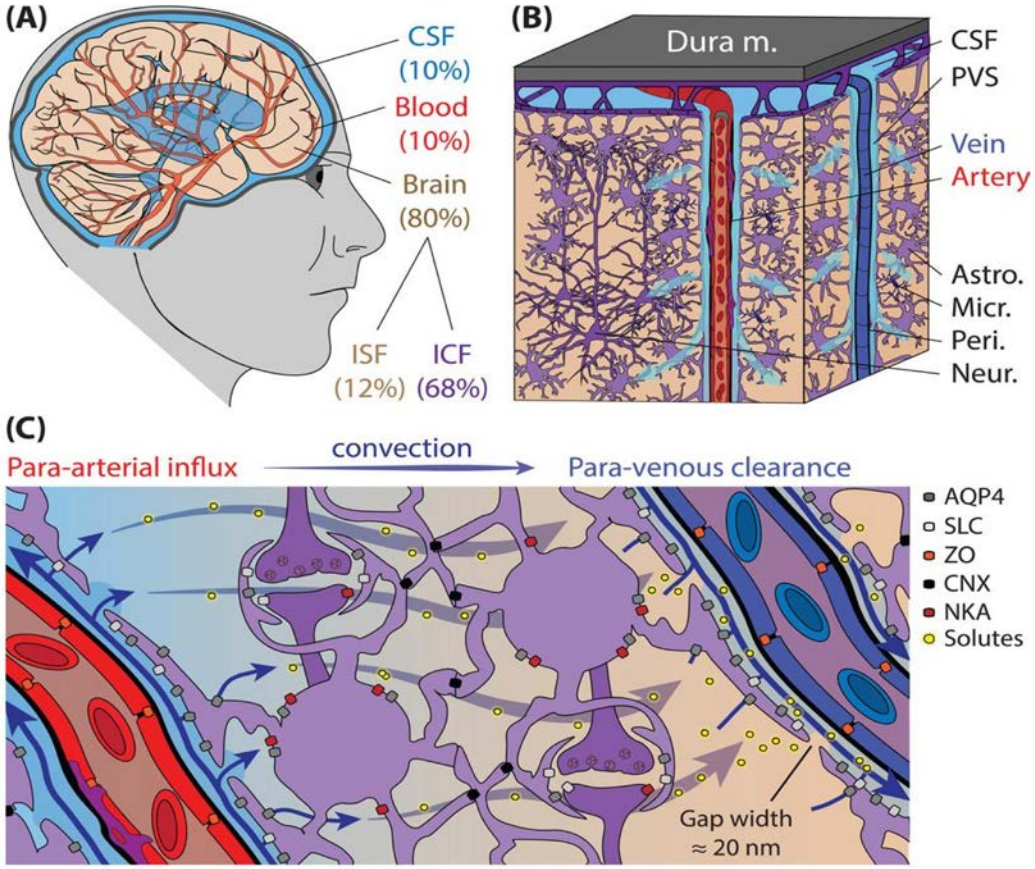
Glymphatic System



Salehpour, et al., *Int J Mol Sci*. 2022

Brain Drainage System

Glymphatic System



Brain Drainage System

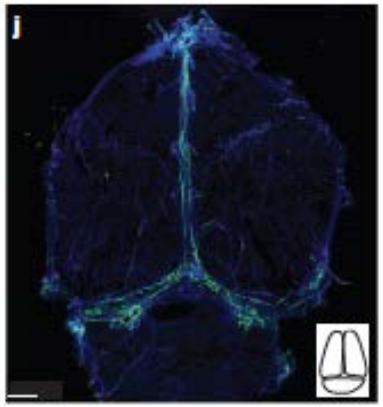
Meningeal Lymphatic System

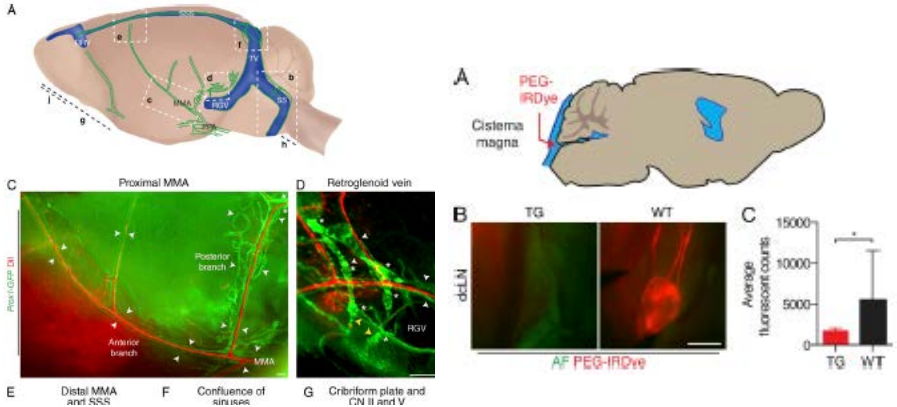
Brain Drainage System

Meningeal Lymphatic System

Jonathan Kipnis

Kari Alitalo





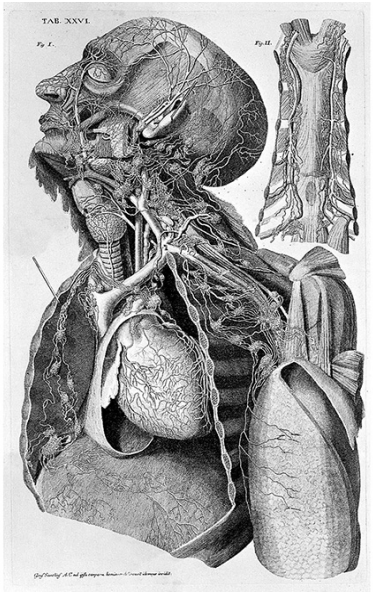
Louveau, et al., *Nature.* 2015.

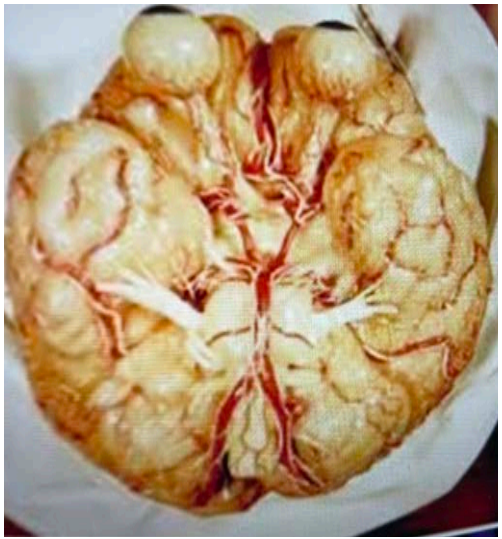
Aspelund, et al., *J Exp Med.* 2015.

Brain Drainage System

Meningeal Lymphatic System

Paolo Mascagni
1755-1815

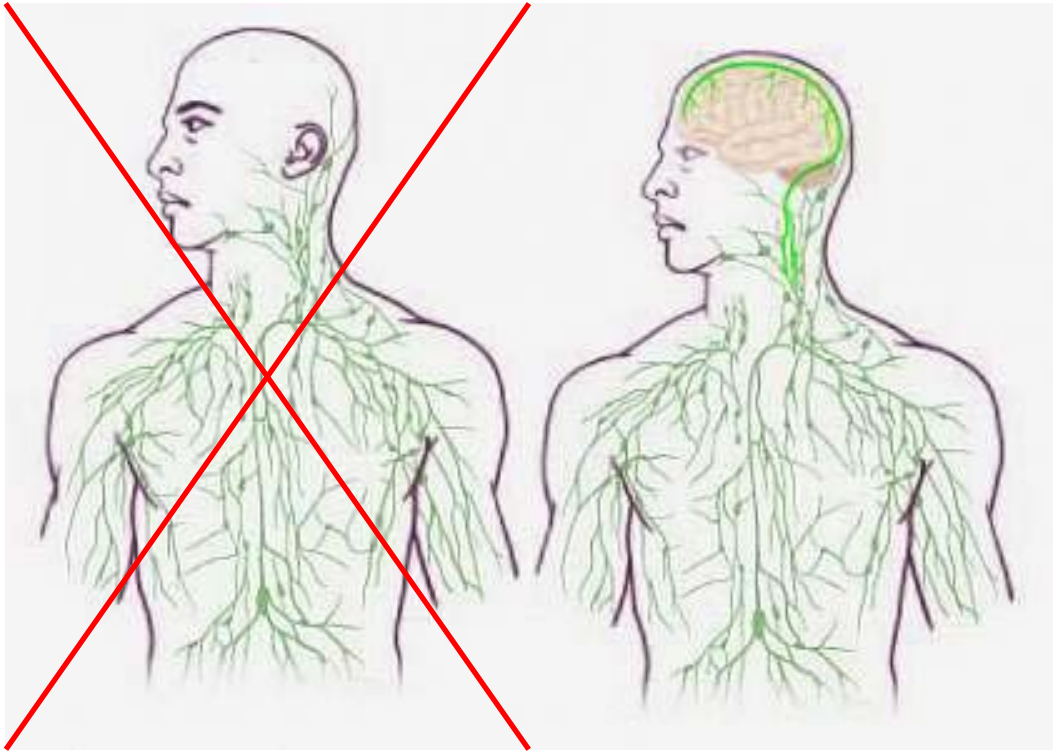




Mascagni P(ed.) (1787) De lymphaticis profundis capitis et colli. Vasorum lymphaticorum corporis humani historia et ichnographia. Pars Prima Section VII, Art. VI. Siena: PazziniCarli.

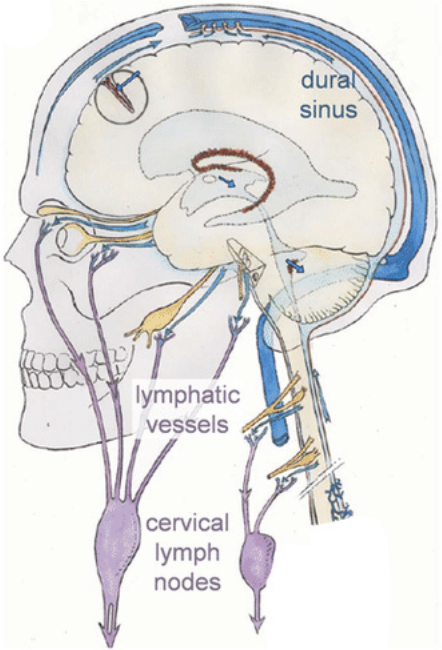
Brain Drainage System

Meningeal Lymphatic System

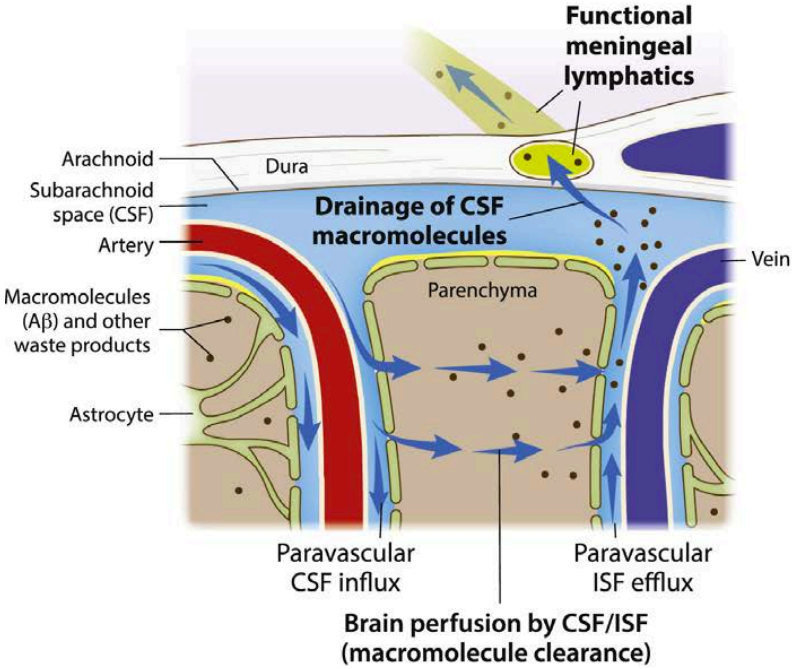


Brain Drainage System

Meningeal Lymphatic System



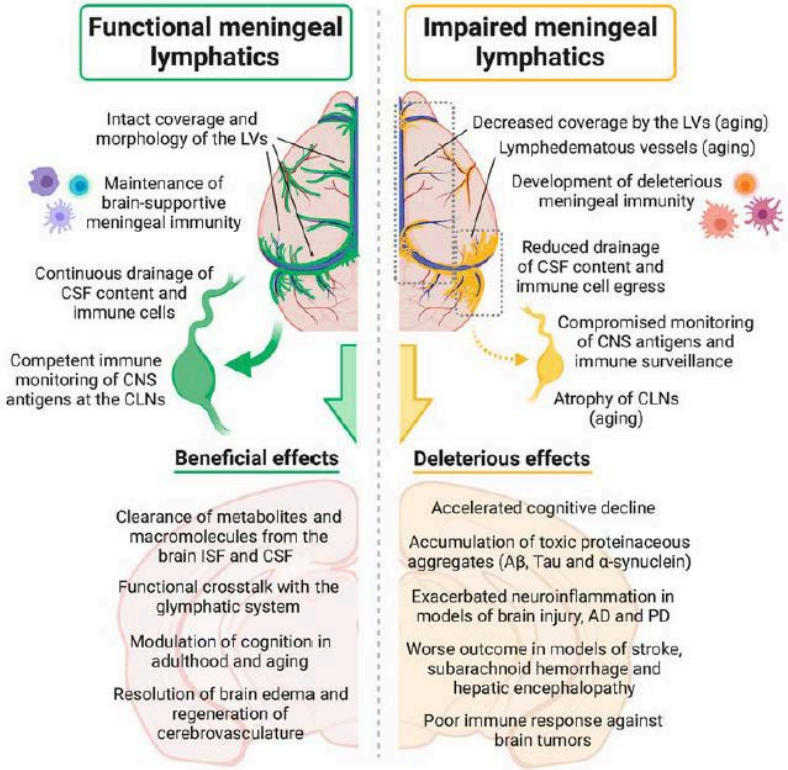
Riba, et al., *Proc Natl Acad Sci U S A*. 2019

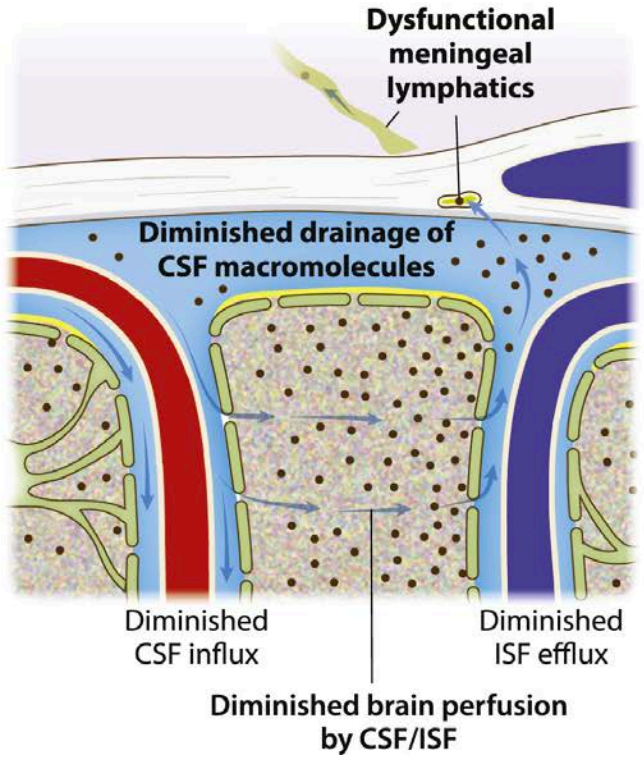


Da Mesquita, et al., *Neuron.* 2018.

Brain Drainage System

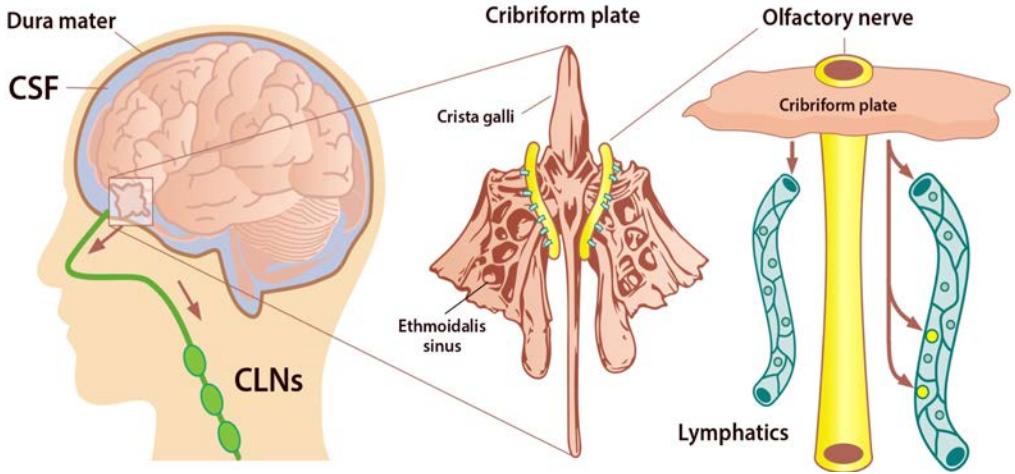
Meningeal Lymphatic System

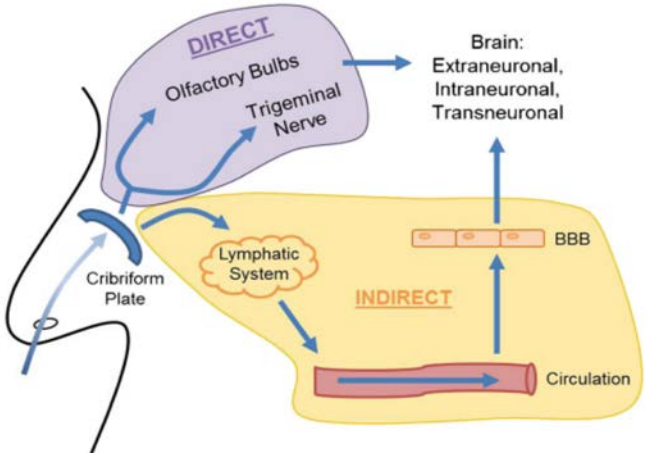




Da Mesquita, et al., *Neuron.* 2018.

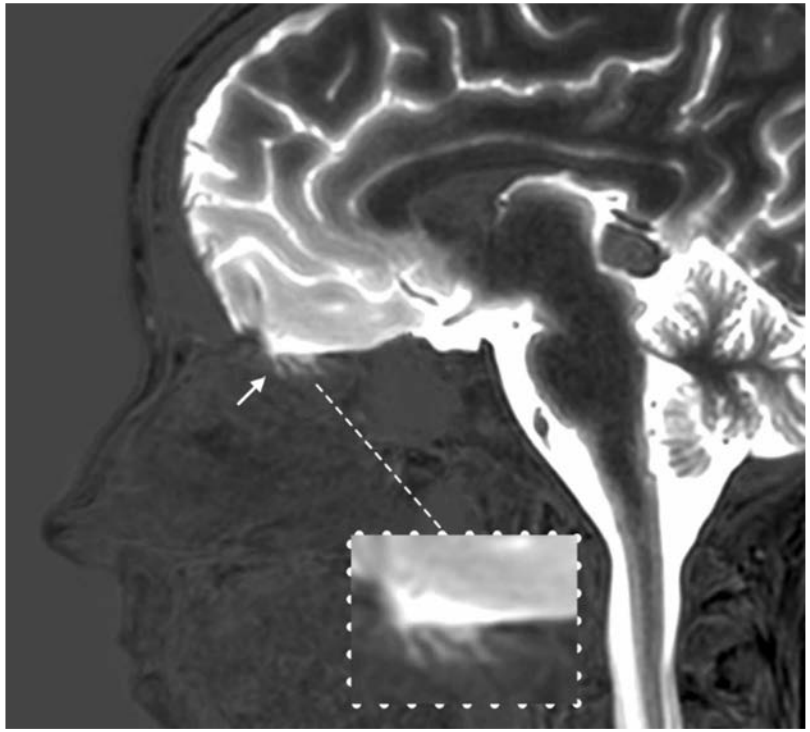
Brain Drainage System





Salehpour, et al., *Int J Mol Sci*. 2022

Brain Drainage System

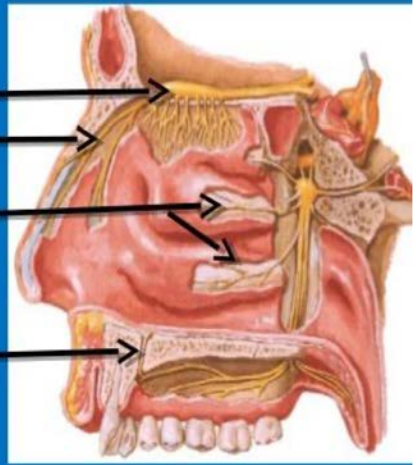


NERVE SUPPLY

External nose –Infra orbital nerve, Infra trochlear, External nasal nerve.

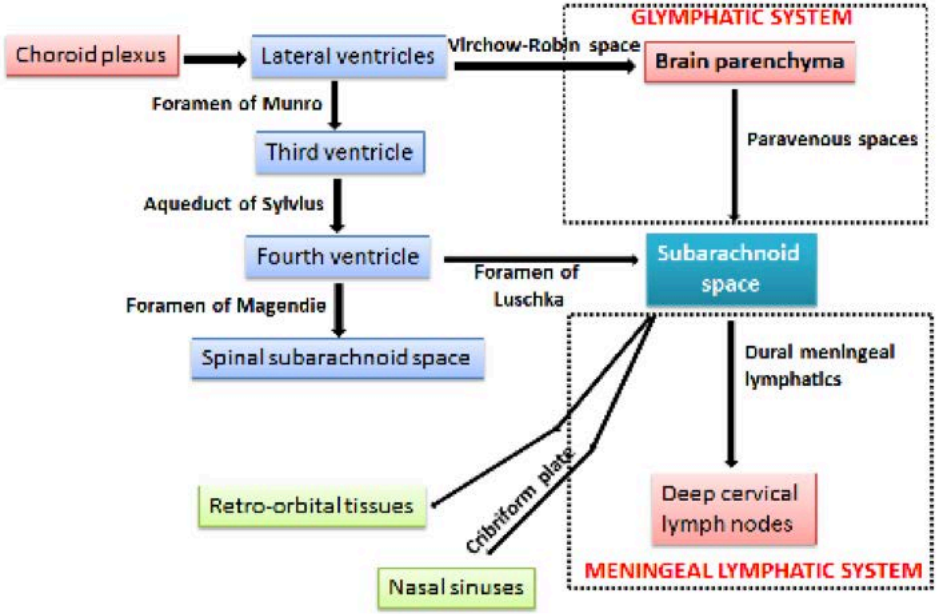
Nerve Supply of the Nasal Cavity

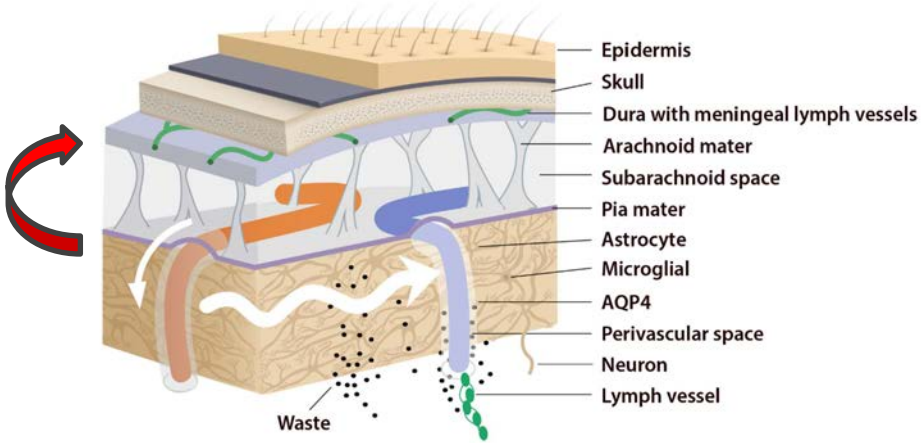
- Olfactory nerve
- Anterior ethmoidal nerve
- Nasal branches of pterigo palatine ganglion
- Nasopalatine nerve



Brain Drainage System

Connection of the Glymphatic and Meningeal Lymphatic System





Balasubramanya, *Mater Methods*, 2022.

Salehpour, et al., *Int J Mol Sci*. 2022

Brain Drainage System

Connection of the Glymphatic and Meningeal Lymphatic System

NewScientist

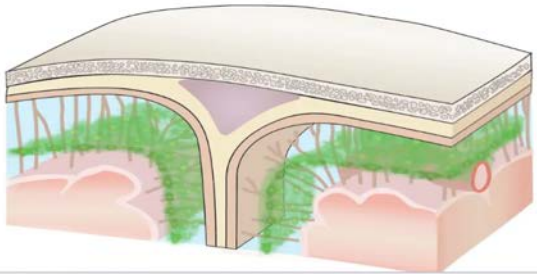
Health

We've just discovered a new part of the brain's waste disposal system

A thin layer of tissue called the subarachnoid lymphatic-like membrane, or SLYM, keeps fresh cerebrospinal fluid separate from fluid containing waste from brain cells

By Clare Wilson

5 January 2023



Science

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RESEARCH ARTICLE | BRAIN ANATOMY

A mesothelium divides the subarachnoid space into functional compartments

KJELD MØLLGÅRD, FELIX R. M. BEINLICH, PETER KUSK, LEO M. MIYAKOSHI, CHRISTINE DELLE, VIRGINIA PLÁ, NATALIE L. HAUGLUND, TINA ESMAIL, MARTIN K. RASMUSSEN, [...] AND MAIKEN NEDERGAARD +2 authors Authors Info & Affiliations

SCIENCE • 5 Jan 2023 • Vol 379, Issue 6627 • pp. 84-88 • DOI: 10.1126/science.adc8810

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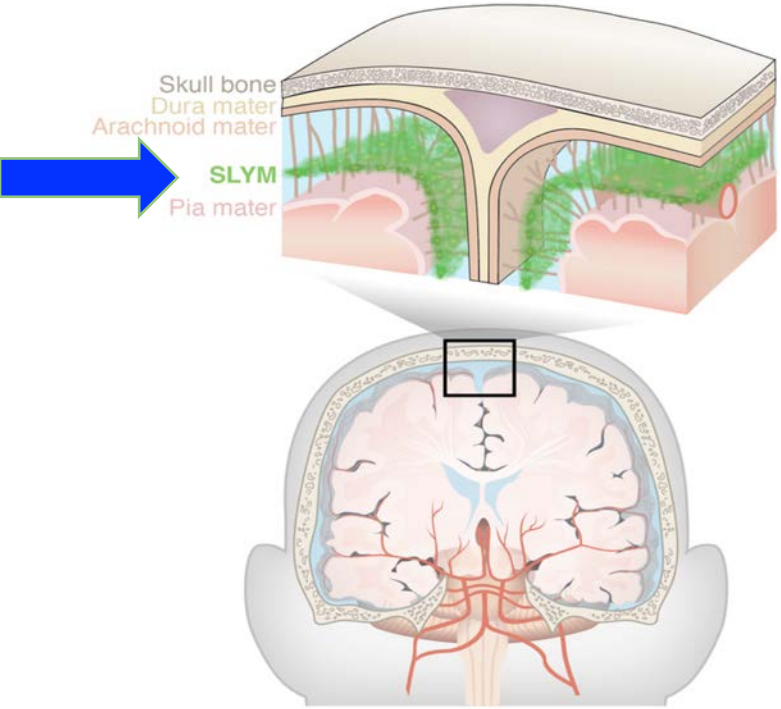
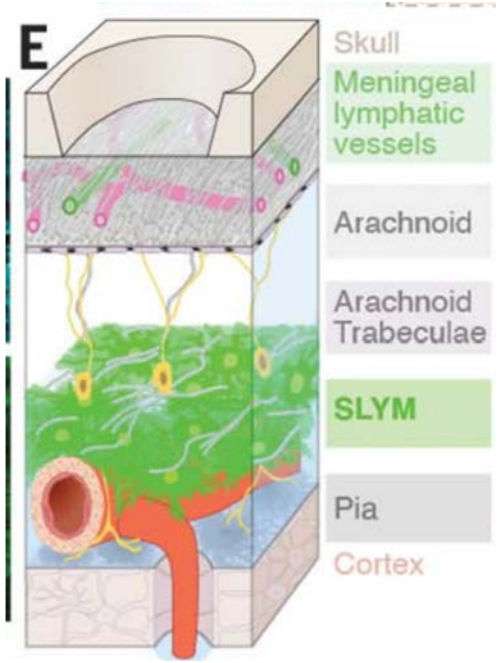
An extra layer lines the brain

Brain Drainage System

Connection of the Glymphatic and Meningeal Lymphatic System

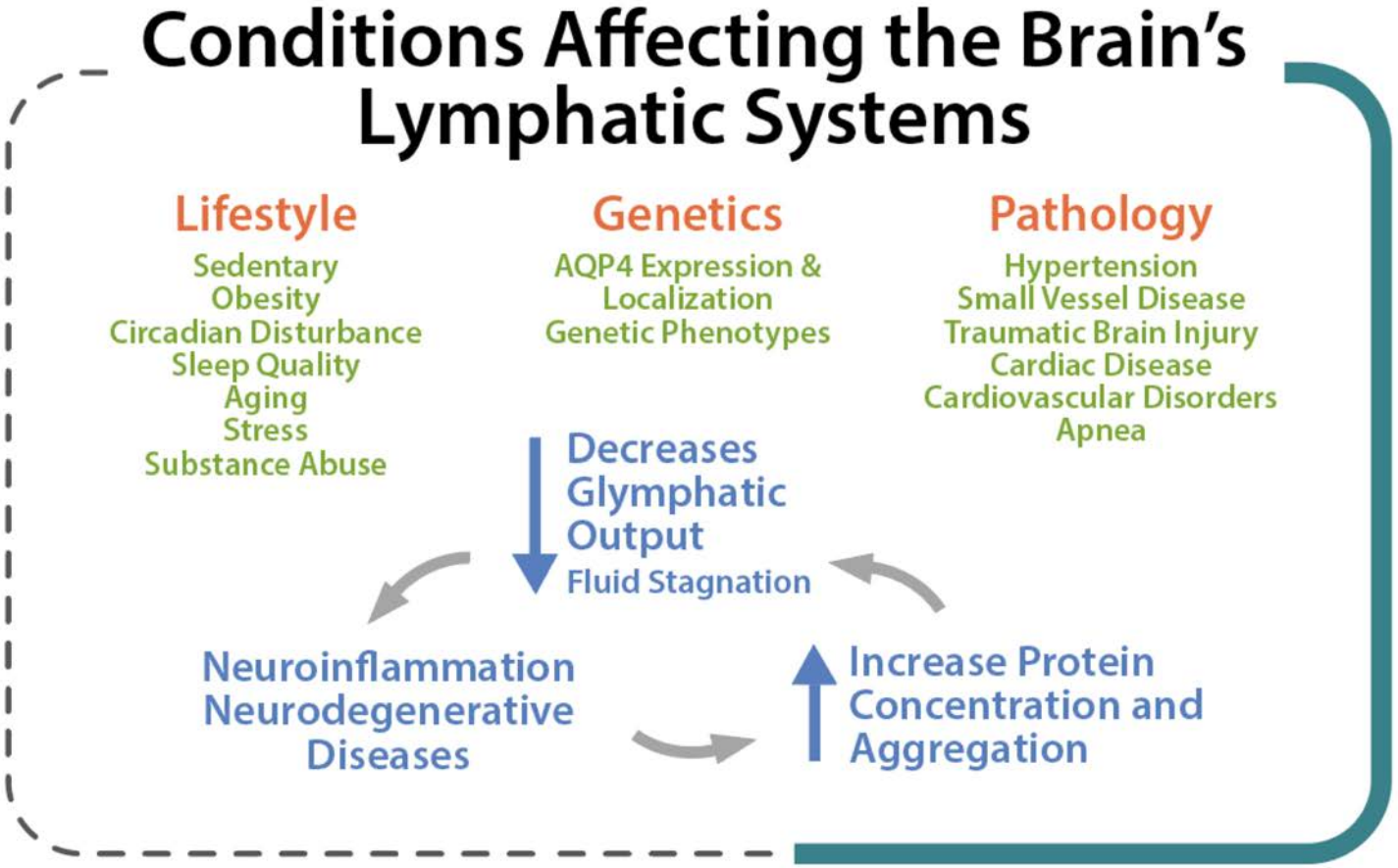




Schematic representations of the immunophenotypical characterization of the meningeal layers, meningeal lymphatic vessels, and arachnoid trabeculations.

Møllgård, et al., *Science*. 2023.

Brain Drainage System



Brain Drainage System

Glymphatic System

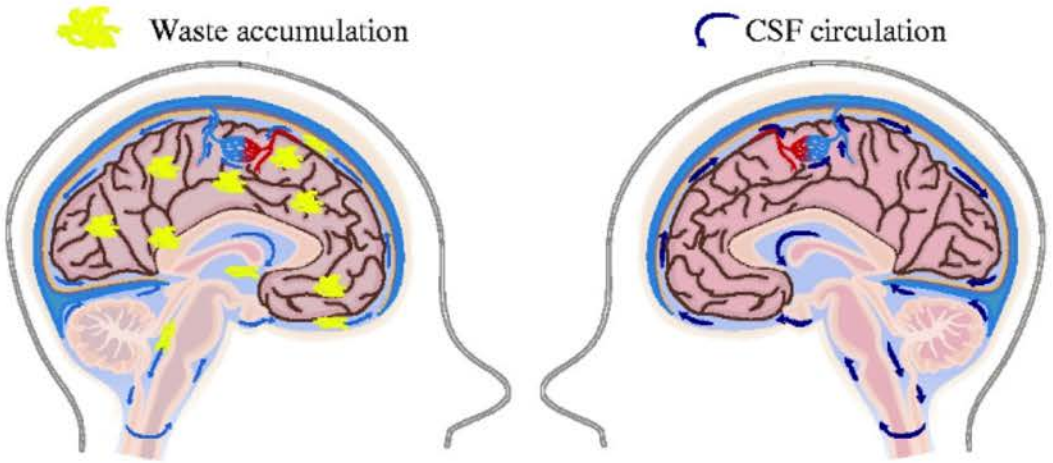
Insuffient
brain clearance

Sleep disturbances

Stress

Hypertension

High levels of alcohol



Effective
brain clearance

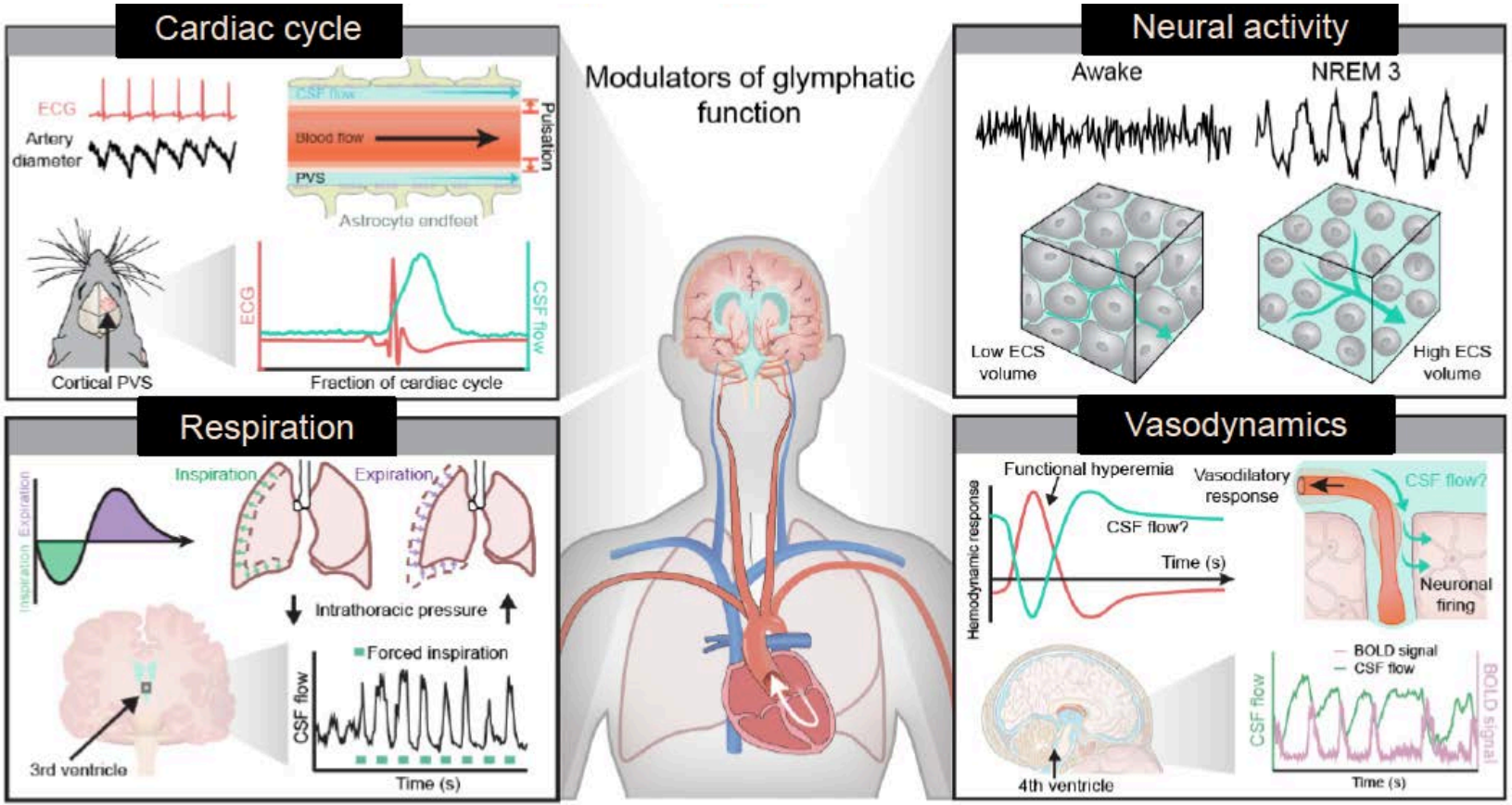
Sleep

Vascular health

Exercise

Low levels of alcohol

Brain Drainage System

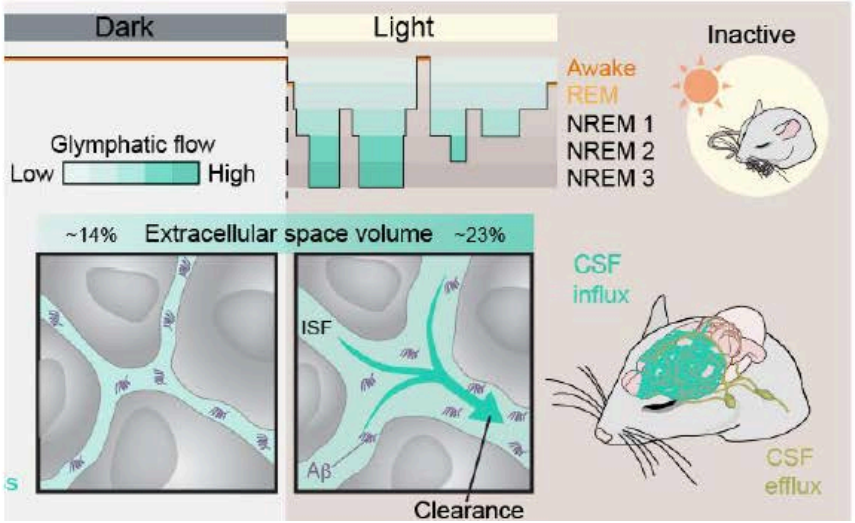


Rasmussen et al. 2021, Physiol Rev, PMID: 33949874

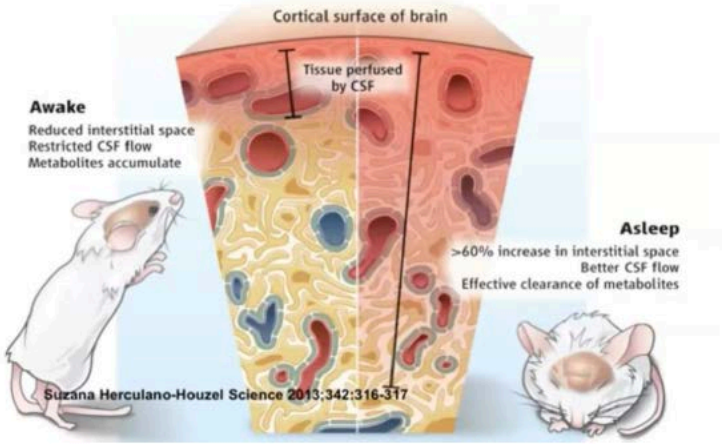
Brain Drainage System

Sleep Drives Metabolite Clearance from the Adult Brain

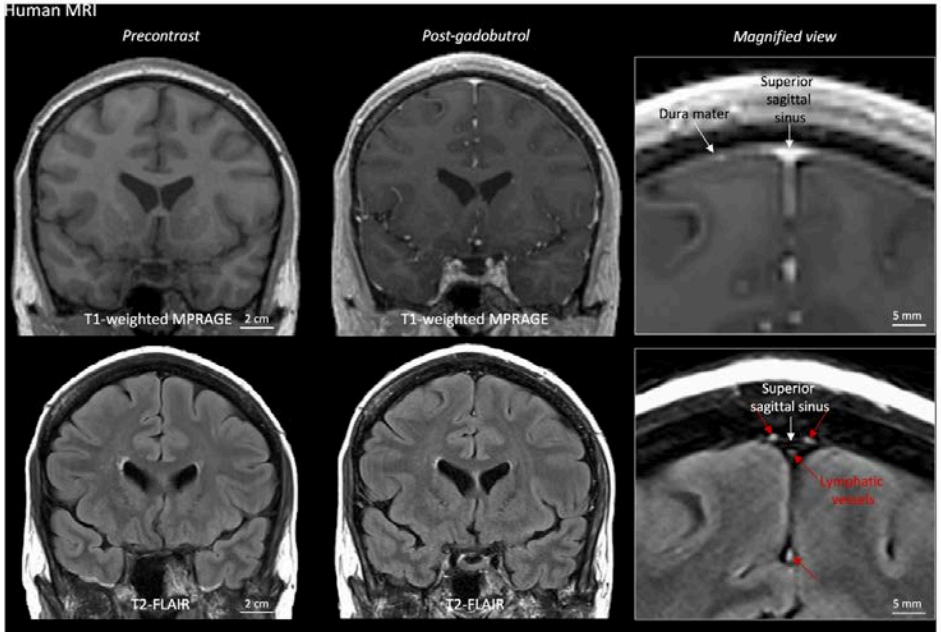
Lulu Xie[1,*], Hongyi Kang[1,*], Qiwu Xu[1], Michael J. Chen[1], Yonghong Liao[1], Meenakshisundaram Thiyagarajan[1], John O'Donnell[1], Daniel J. Christensen[1], Charles Nicholson[2], Jeffrey J. Iliff[1], Takahiro Takano[1], Rashid Deane[1], and Maiken Nedergaard[1]



Volume variation.The extracellular (interstitial) space in the cortex of the mouse brain, through which cerebral spinal fluid moves, increases from 14% in the awake animal to 23% in the sleeping animal, an increase that allows the faster clearance of metabolic waste products and toxins.



Brain Drainage System



PBM Therapy

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FULL ARTICLE

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by Oxana Semyachkina-Glushkovskaya [1,2,*], Dmitry Postnov [1], Thomas Penzel [1,3,4] and Jürgen Kurths [1,2,5]

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Maria Tzoy [2],

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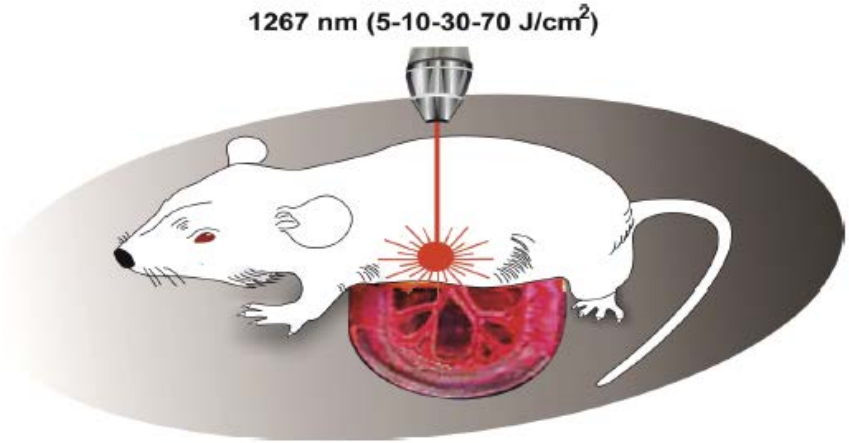
PBM Therapy

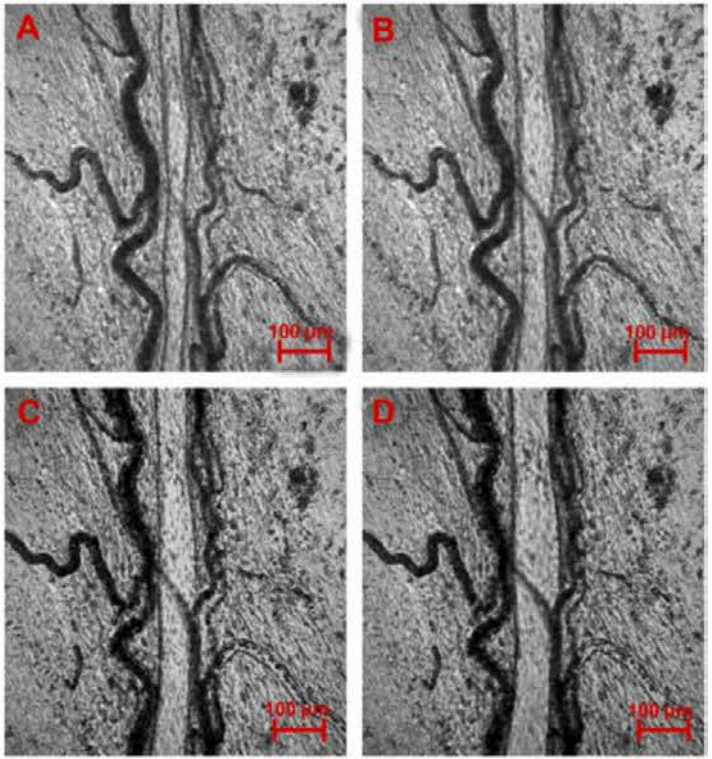


Before PBM

After PBM

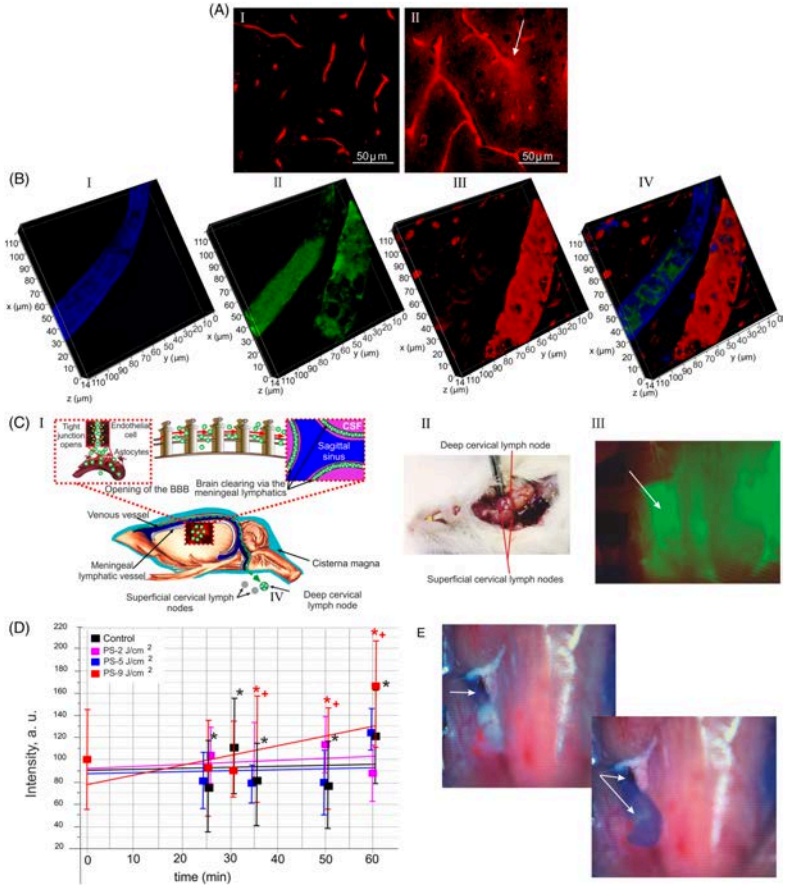
Systole

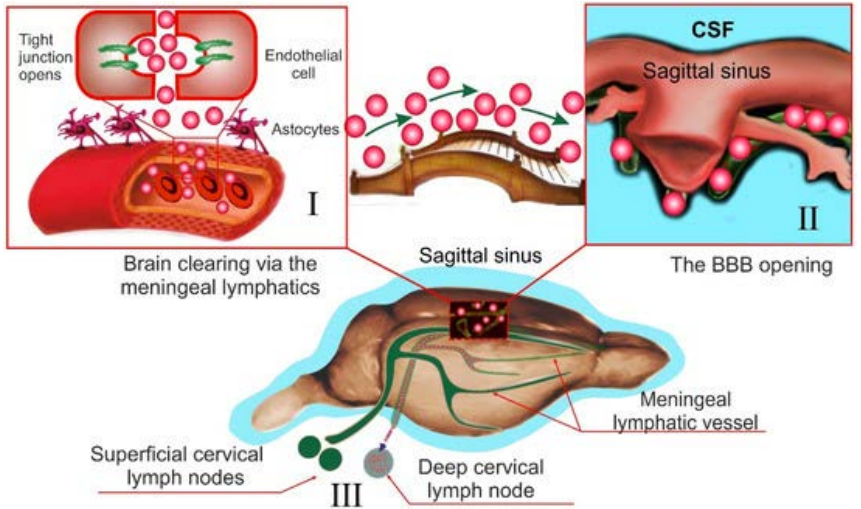
Diastole



O. Semyachkina-Glushkovskaya, et al., "Photobiomodulation of lymphatic drainage and clearance: perspective strategy for augmentation of meningeal lymphatic functions," *Biomed. Opt. Express,* 2020

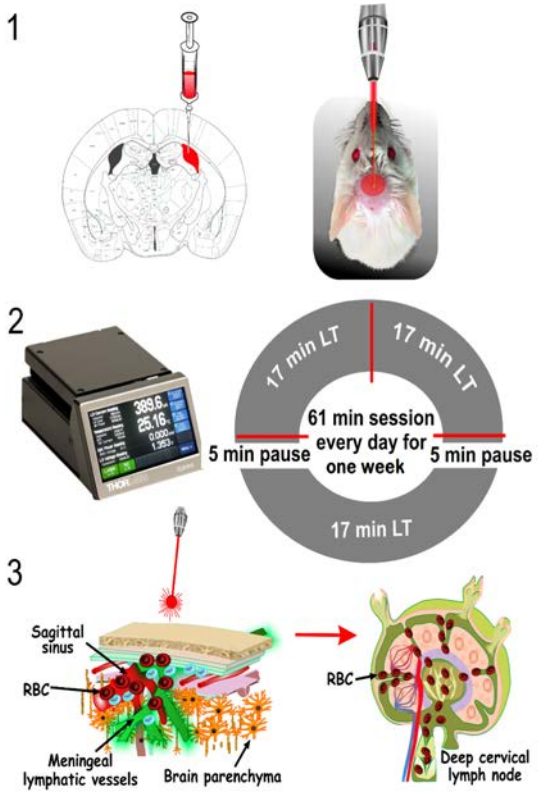
PBM Therapy

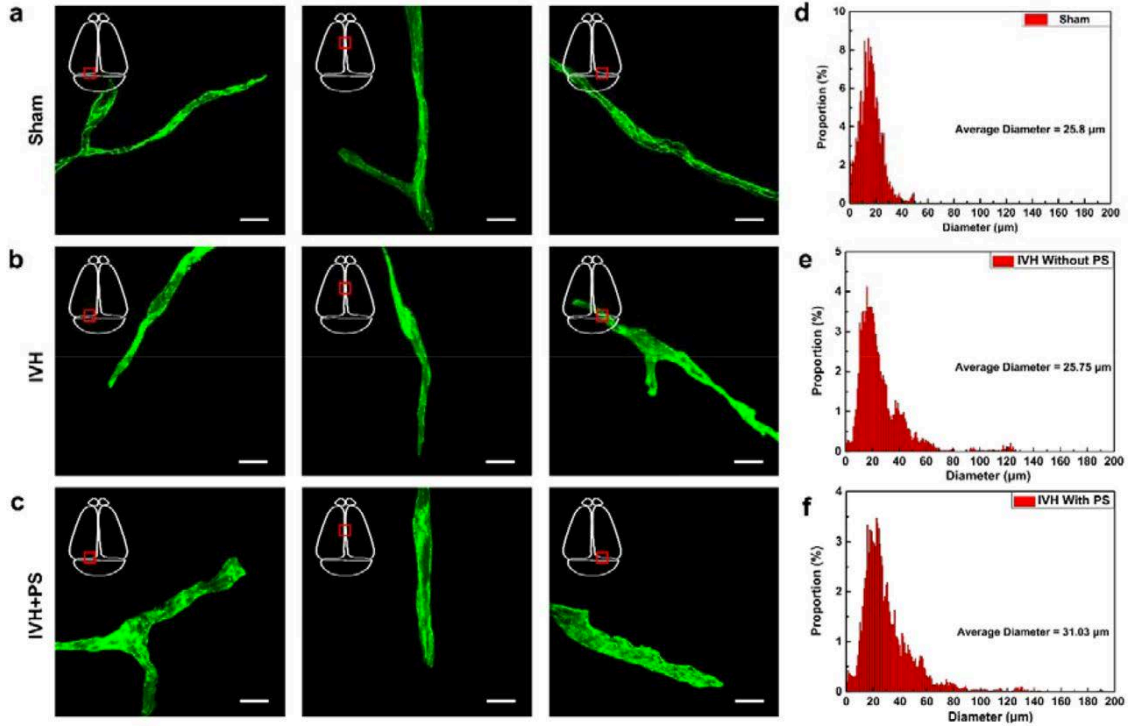




Semyachkina-Glushkovskaya, et al. Photostimulation of cerebral and peripheral lymphatic functions. *Translational Biophotonics*. 2020

PBM Therapy





bioRxiv 2020.11.16.384149; doi: https://doi.org/10.1101/2020.11.16.384149 (under review in Nature Communications)

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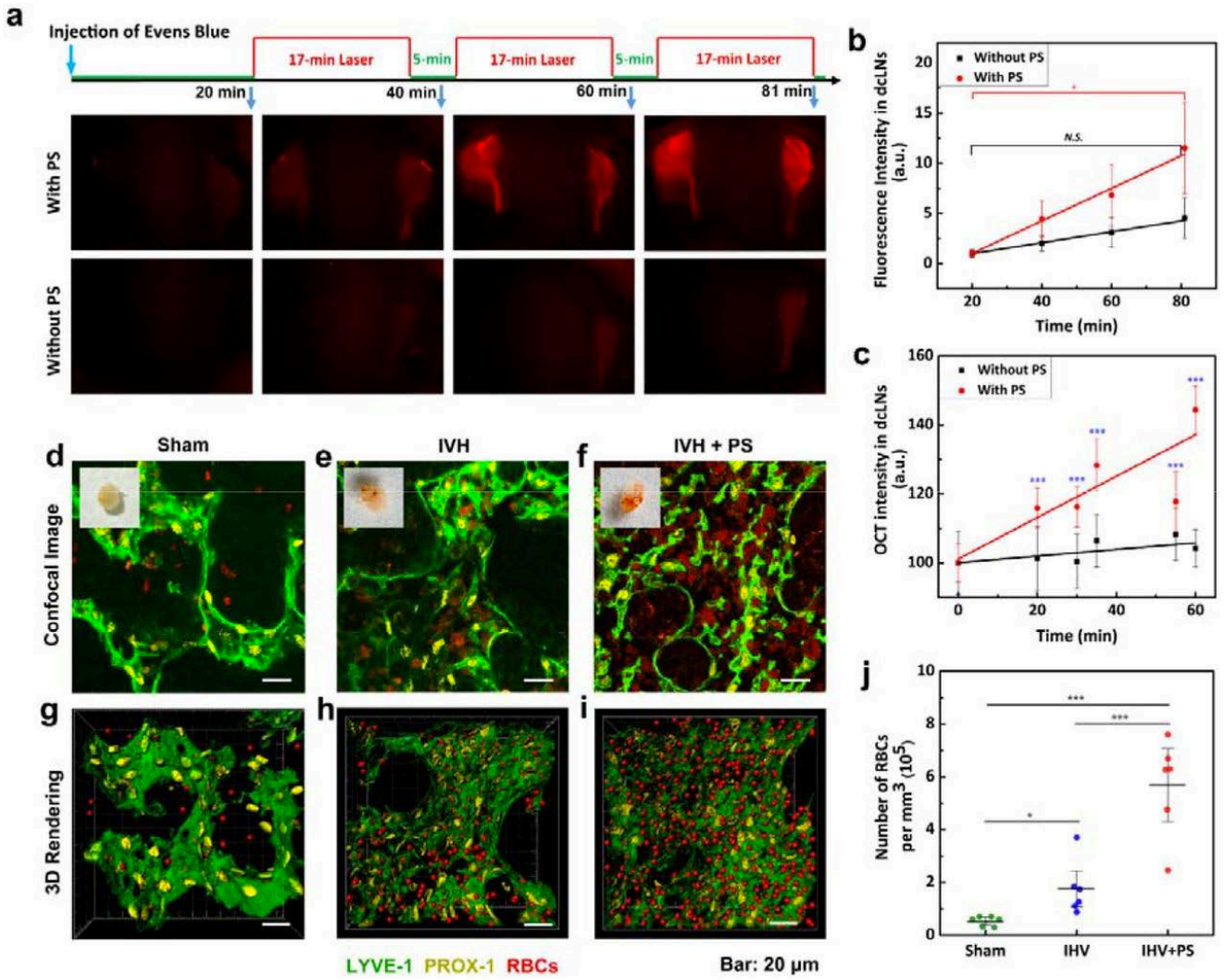

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Nitric Oxide 130 (2023) 58–68

Contents lists available at ScienceDirect

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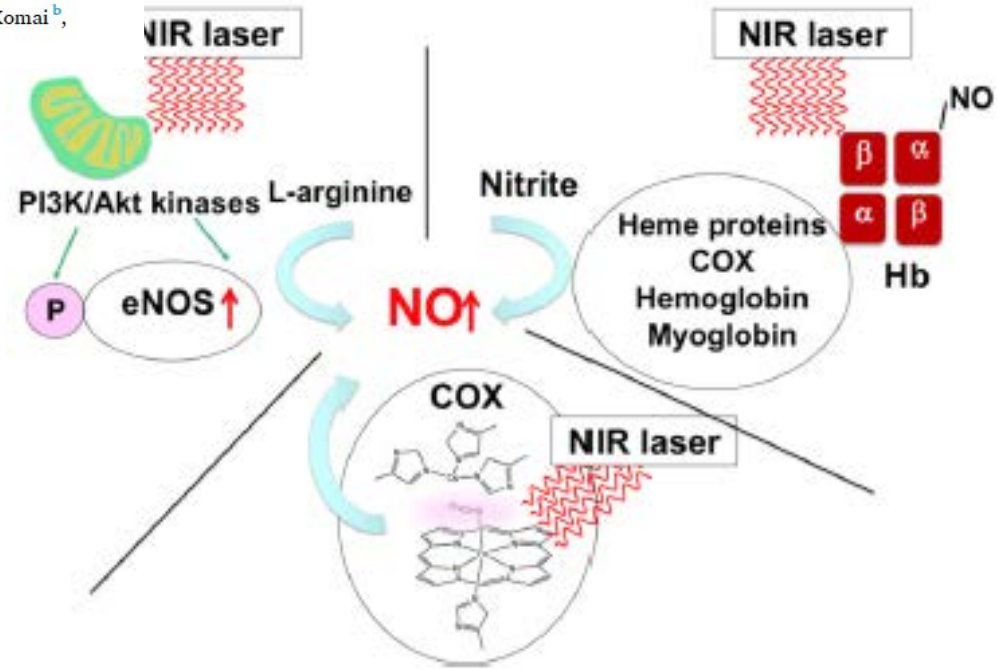
journal homepage: www.elsevier.com/locate/yniox

Photobiomodulation and nitric oxide signaling

Satoshi Kashiwagi [a,*], Atsuyo Morita [b], Shinya Yokomizo [a,c], Emiyu Ogawa [d], Eri Komai [b], Paul L. Huang [b], Denis E. Bragin [e,f,***], Dmitriy N. Atochin [b,**]



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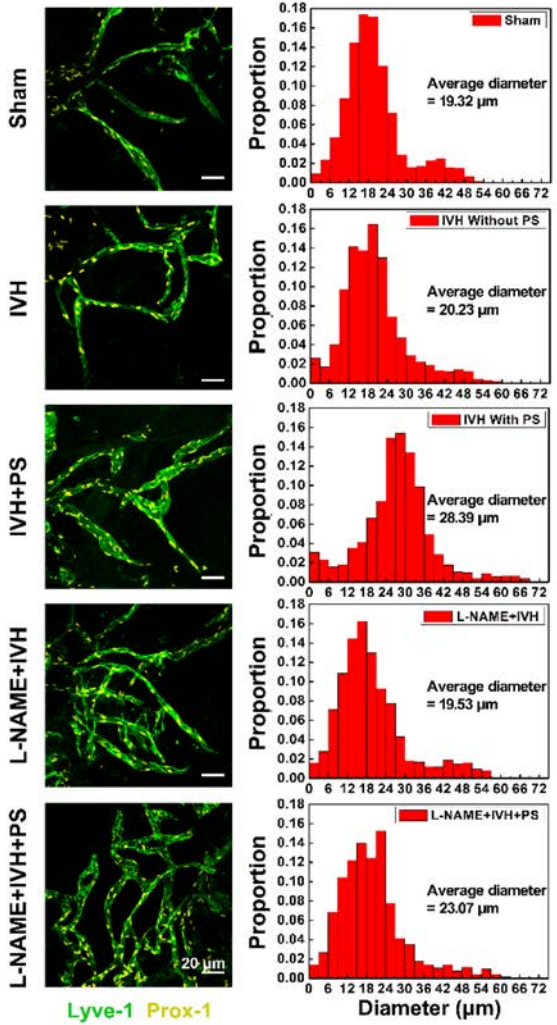

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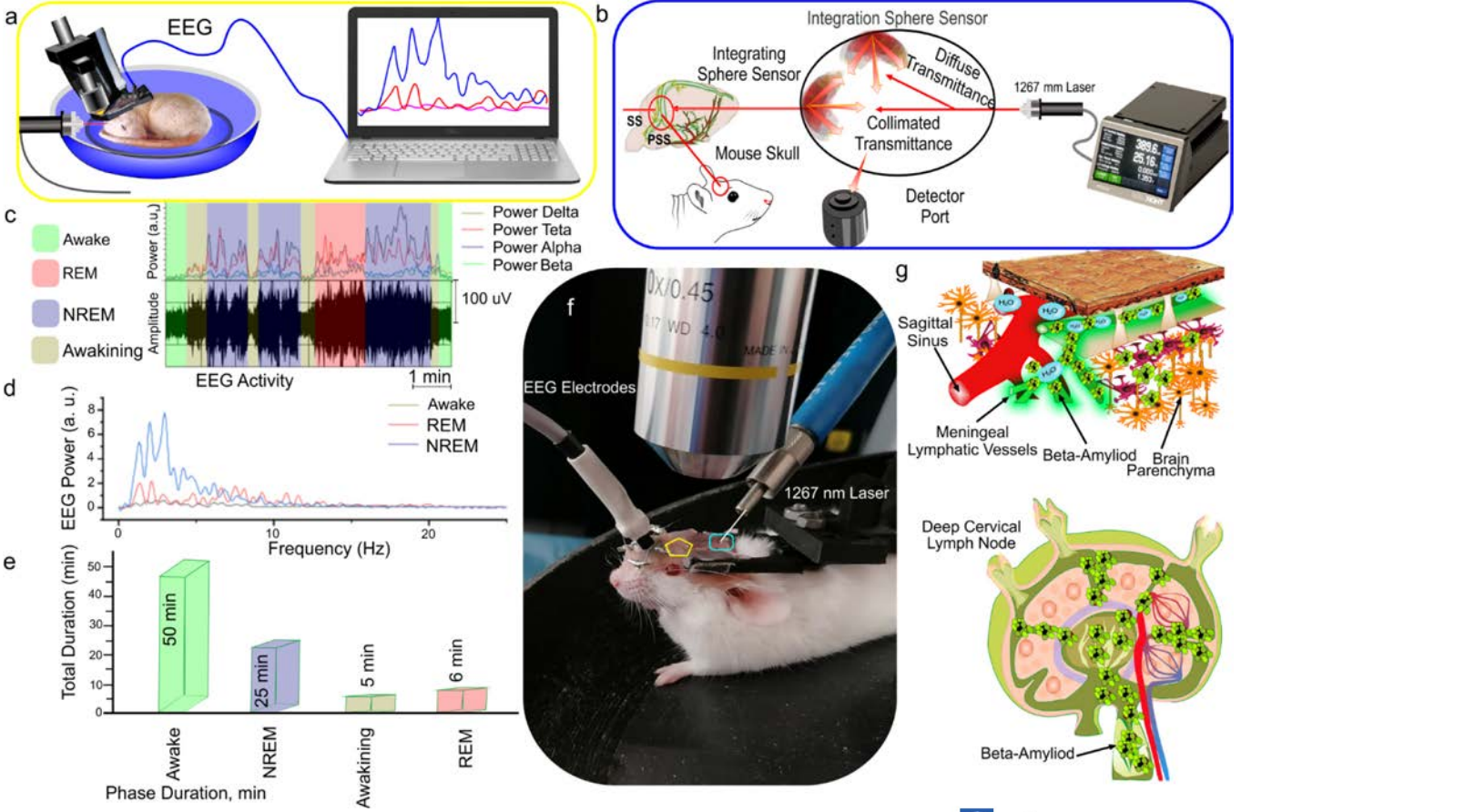

cells

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Article

Night Photostimulation of Clearance of Beta-Amyloid from Mouse Brain: New Strategies in Preventing Alzheimer's Disease

Oxana Semyachkina-Glushkovskaya [1,2,*], Thomas Penzel [2,3], Inna Blokhina [2], Alexander Khorovodov [2], Ivan Fedosov [2], Tingting Yu [4,5], Georgy Karandin [2], Arina Evsukova [2], Dariya Elovenko [2], Viktoria Adushkina [2], Alexander Shirokov [2,6], Alexander Dubrovskii [2], Andrey Terskov [2], Nikita Navolokin [2,7], Maria Tzoy [2],

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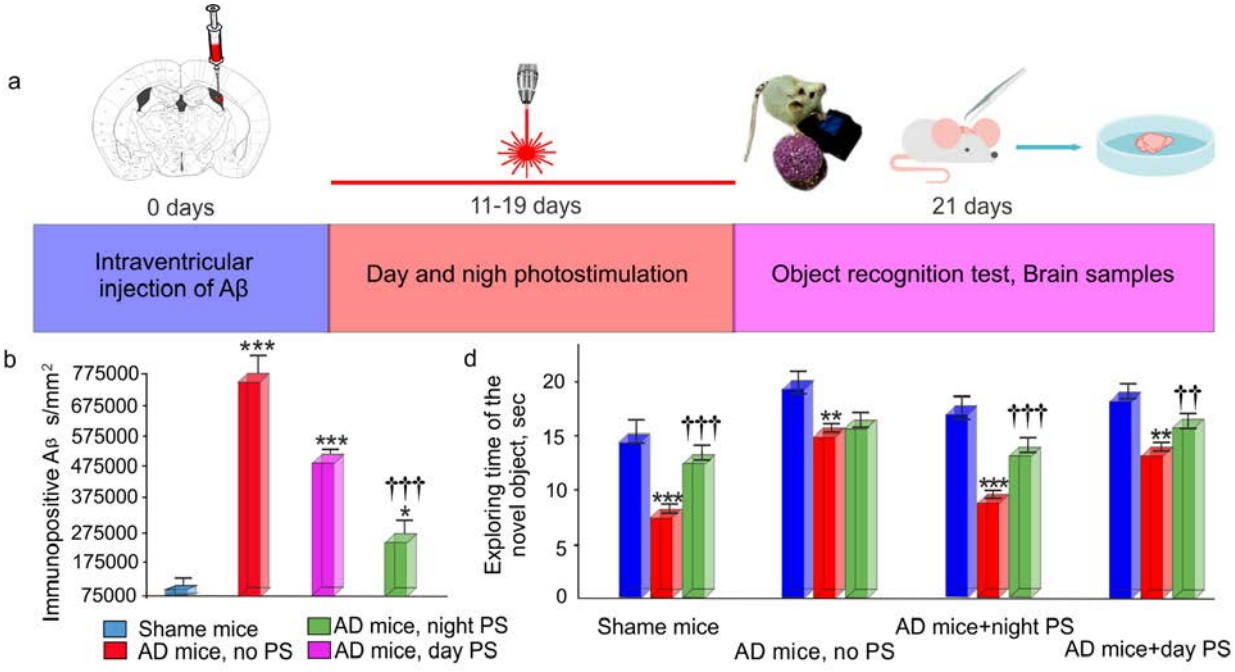

cells

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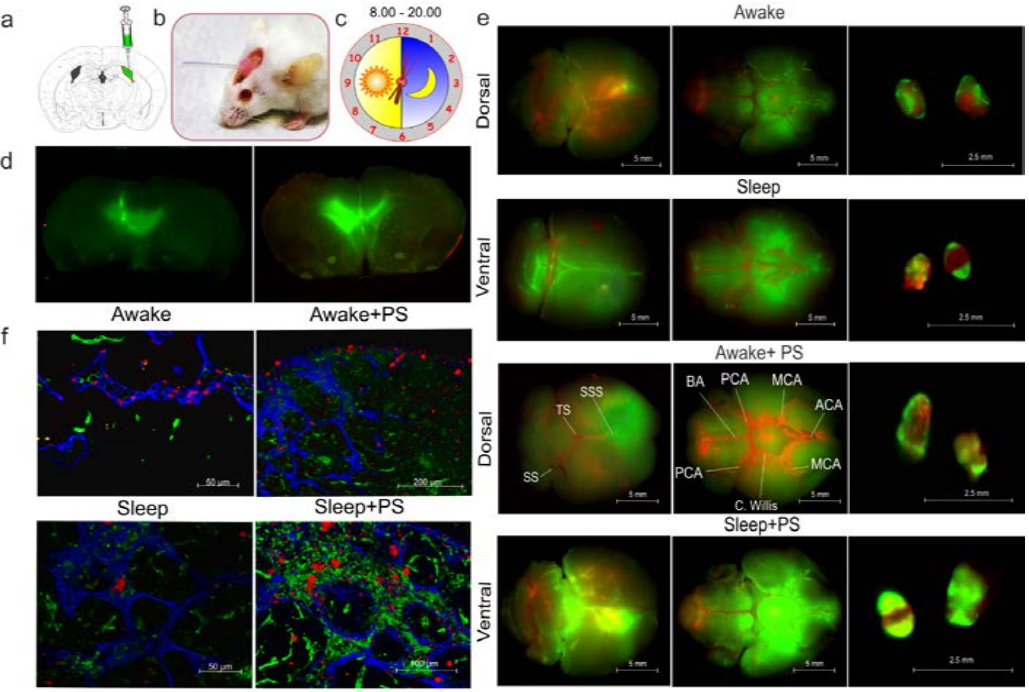

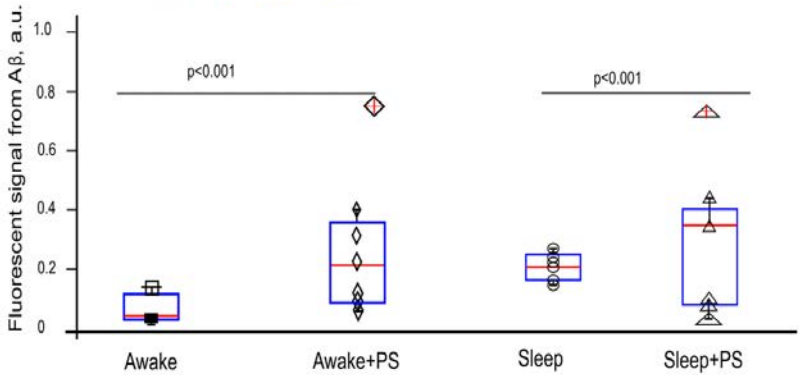

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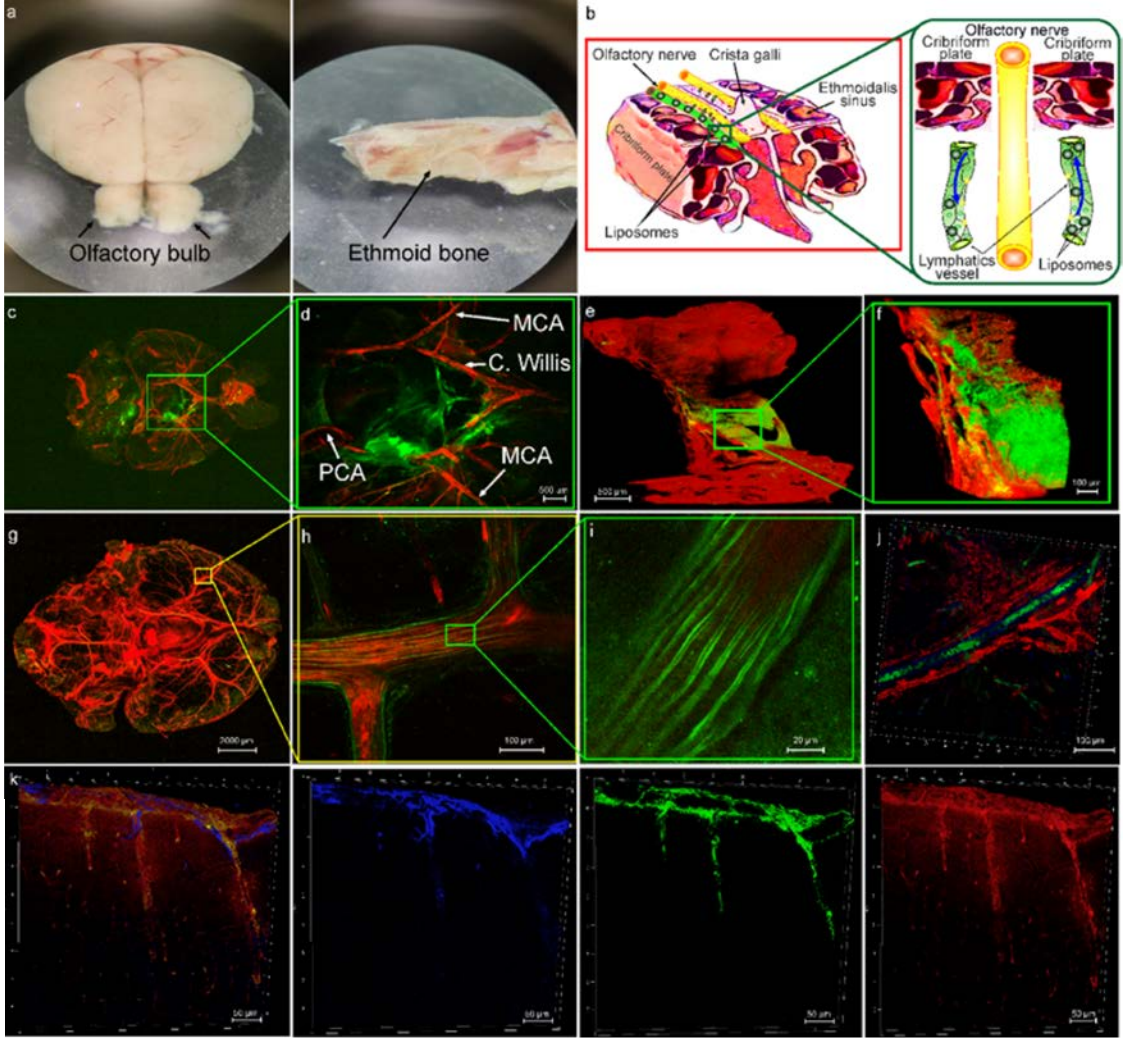

pharmaceutics

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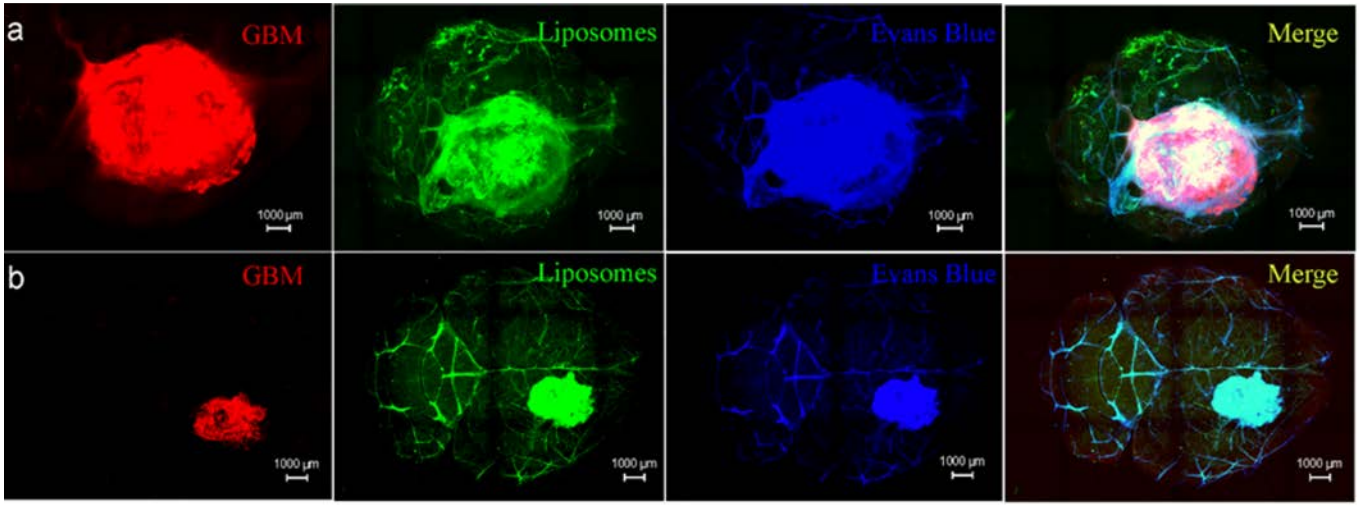
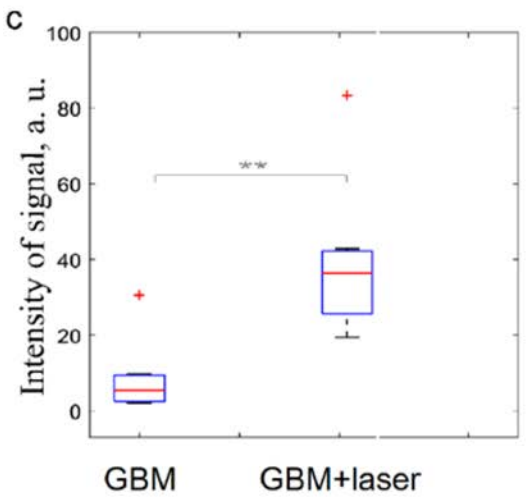
Article

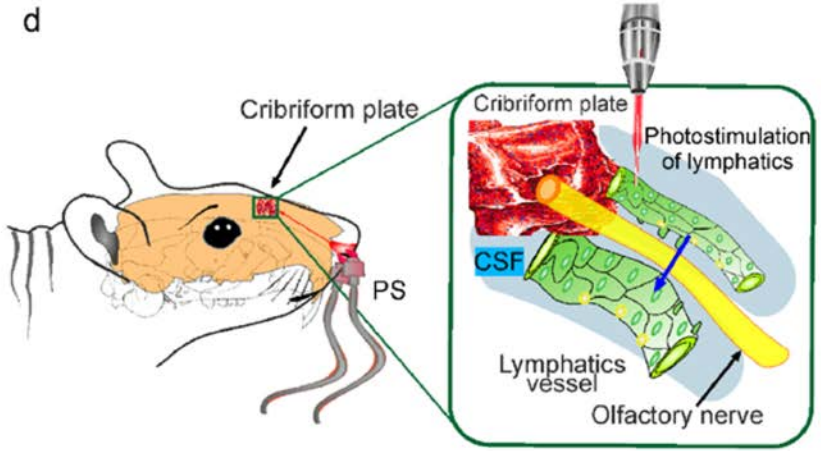
Intranasal Delivery of Liposomes to Glioblastoma by Photostimulation of the Lymphatic System

Oxana Semyachkina-Glushkovskaya [1,2,*], Alexander Shirokov [2,3], Inna Blokhina [2], Valeria Telnova [2], Elena Vodovozova [4], Anna Alekseeva [4], Ivan Boldyrev [4], Ivan Fedosov [2], Alexander Dubrovsky [2], Alexandr Khorovodov [2], Andrey Terskov [2], Arina Evsukova [2], Daria Elovenko [2], Viktoria Adushkina [2], Maria Tzoy [2], Ilana Agranovich [2], Jürgen Kurth [1,2,5] and Edik Rafailov [6]

PBM Therapy







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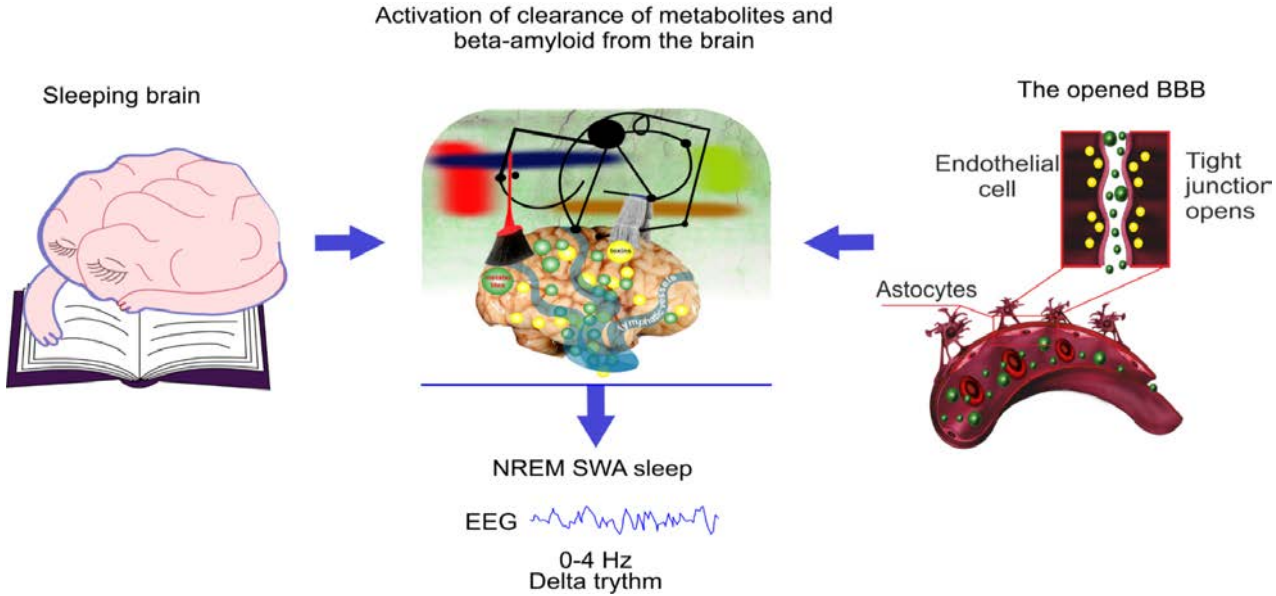
International Journal of Molecular Sciences

Open Access Review

Sleep as a Novel Biomarker and a Promising Therapeutic Target for Cerebral Small Vessel Disease: A Review Focusing on Alzheimer's Disease and the Blood-Brain Barrier

by Oxana Semyachkina-Glushkovskaya [1,2,*], Dmitry Postnov [1], Thomas Penzel [1,3,4] and Jürgen Kurths [1,2,5]



International Journal of
Molecular Sciences

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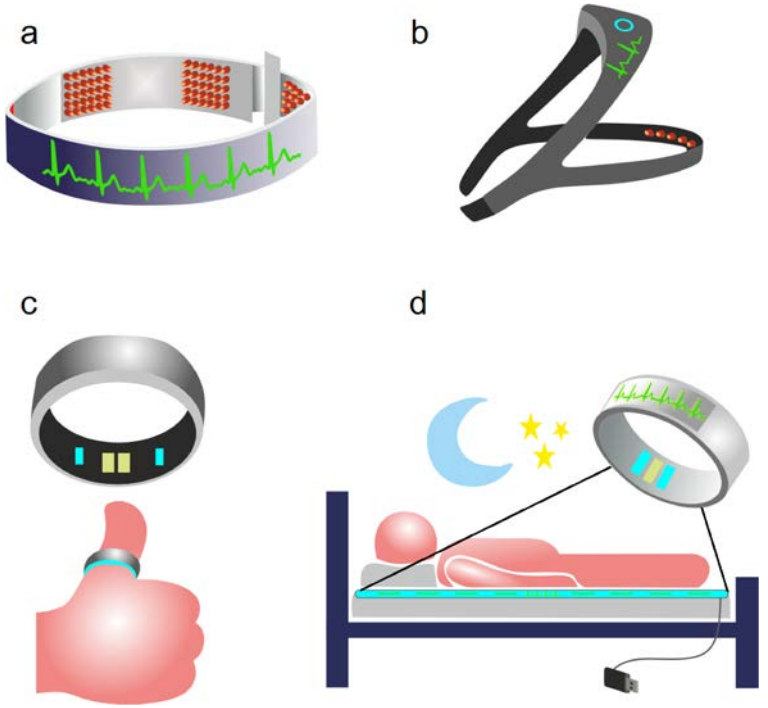
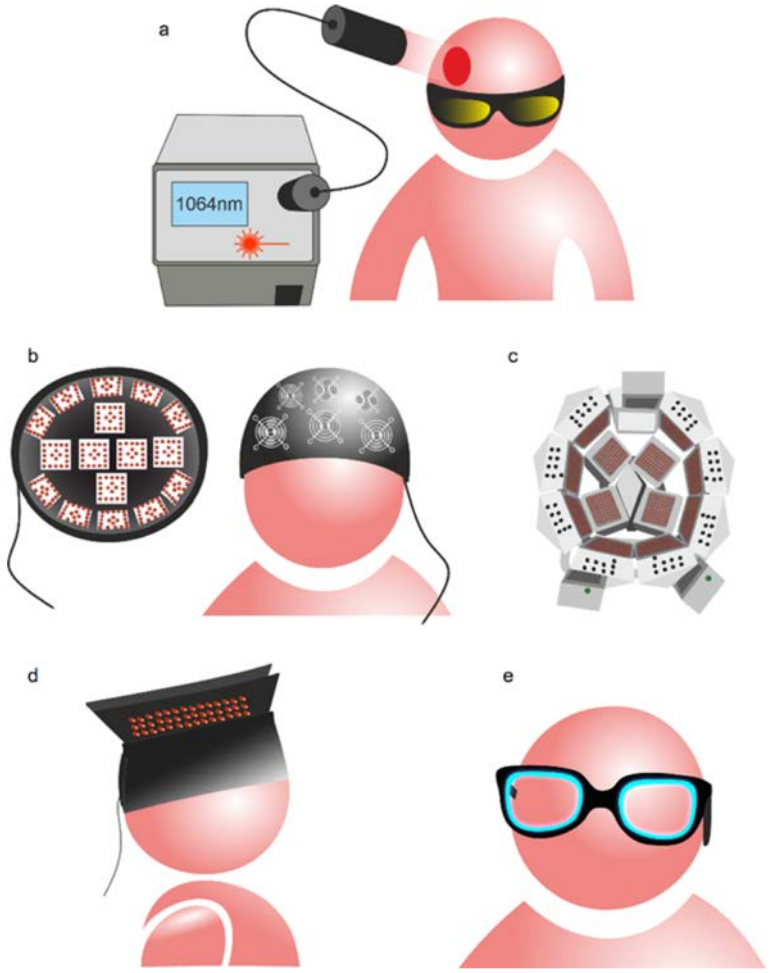
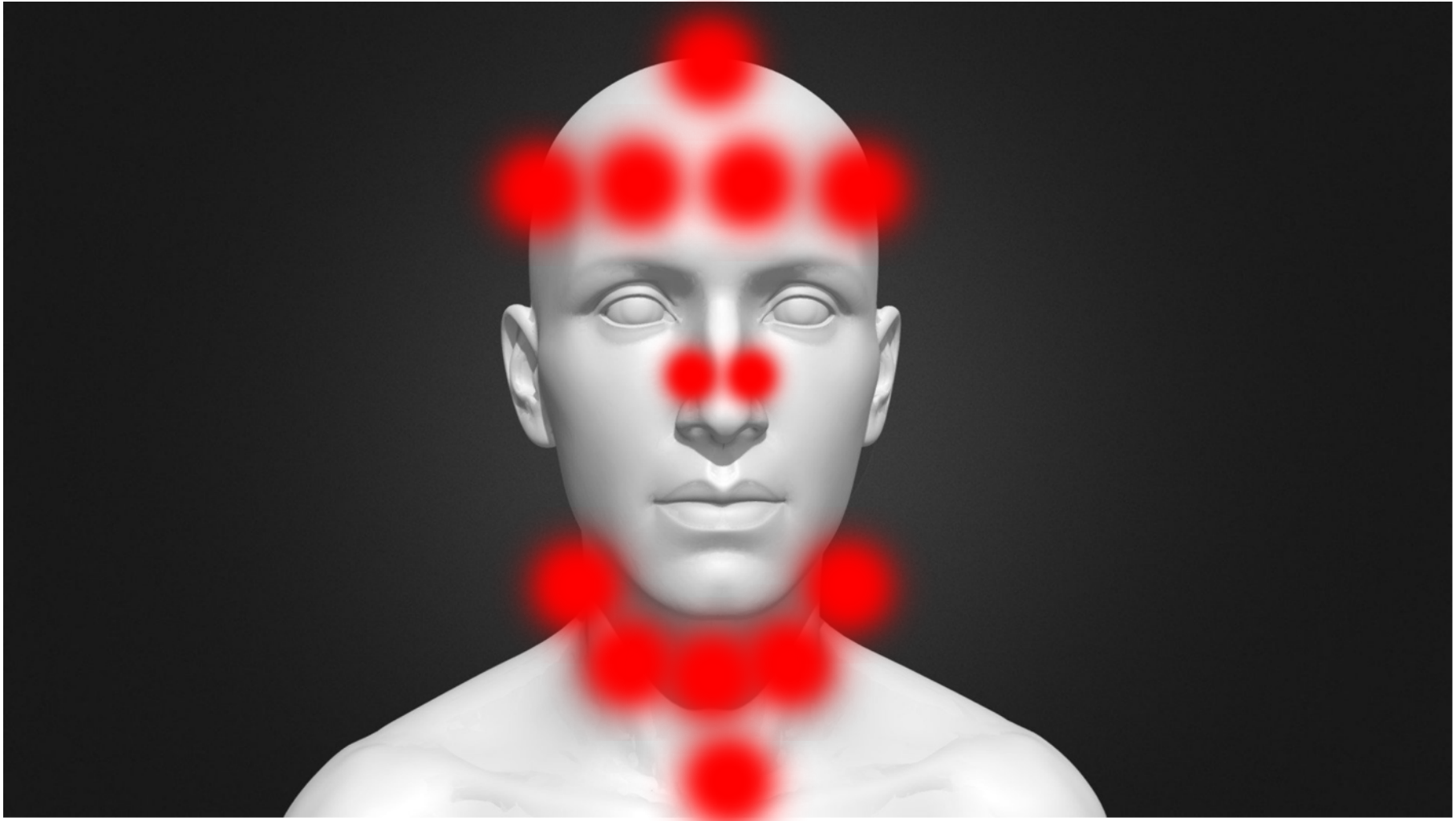
Review

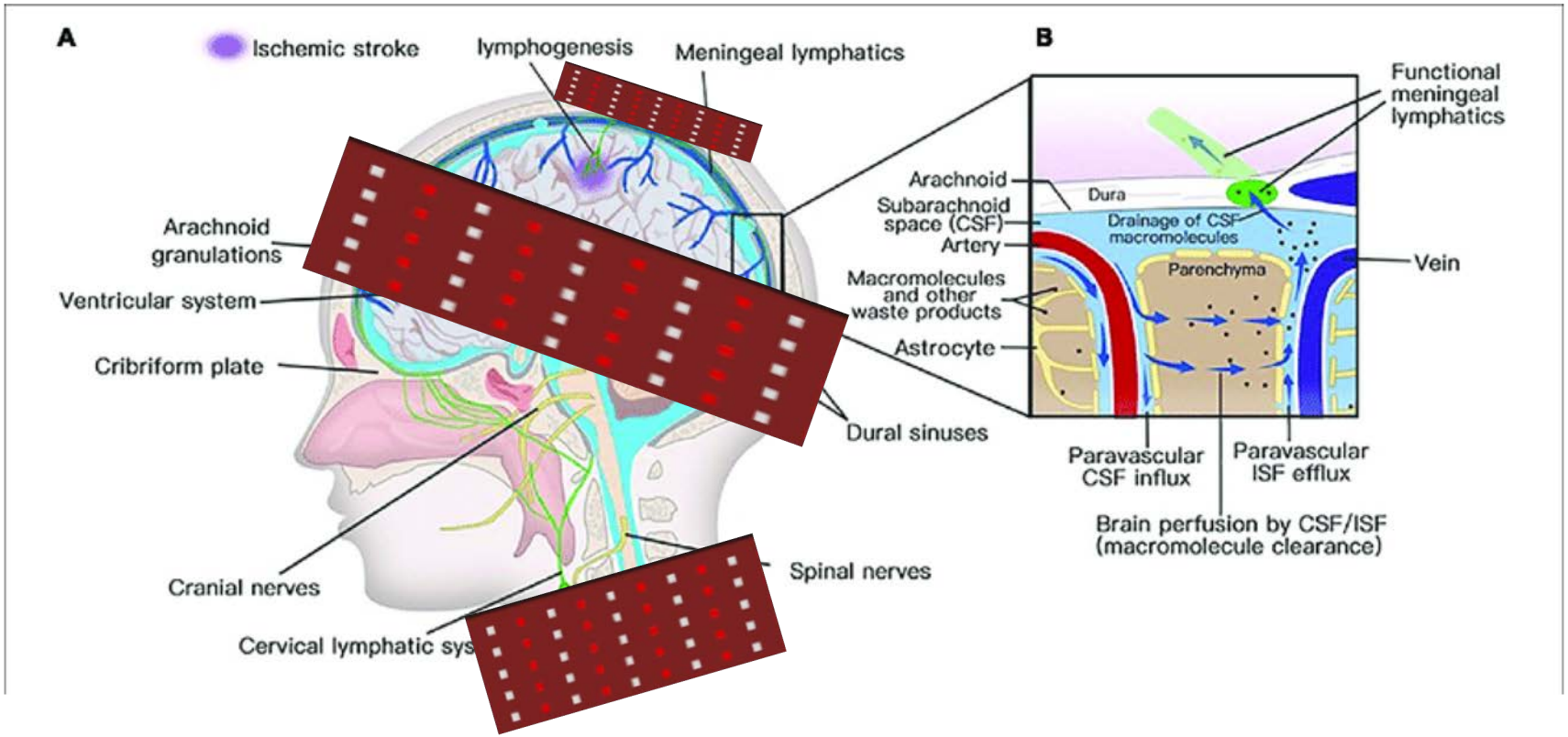
Brain Waste Removal System and Sleep: Photobiomodulation as an Innovative Strategy for Night Therapy of Brain Diseases

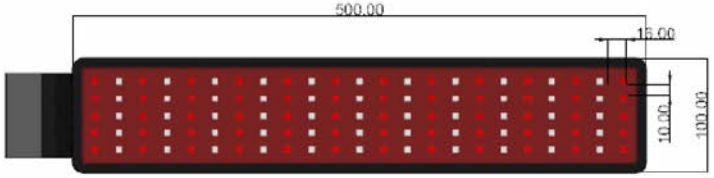
Oxana Semyachkina-Glushkovskaya [1,2,*], Ivan Fedosov [2], Thomas Penzel [2,3], Dongyu Li [4,5], Tingting Yu [4,6], Valeria Telnova [2], Elmira Kaybeleva [2], Elena Saranceva [2], Andrey Terskov [2], Alexander Khorovodov [2], Inna Blokhina [2], Jürgen Kurths [1,2,7] and Dan Zhu [4,6]







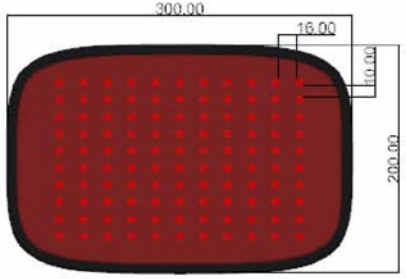

A
Ischemic stroke
lymphogenesis
Meningeal lymphatics
Arachnoid granulations
Ventricular system
Cribriform plate
Dural sinuses
Cranial nerves
Spinal nerves
Cervical lymphatic sys
B
Functional meningeal lymphatics
Arachnoid
Dura
Subarachnoid space (CSF)
Drainage of CSF macromolecules
Artery
Vein
Parenchyma
Macromolecules and other waste products
Astrocyte
Paravascular CSF influx
Paravascular ISF efflux
Brain perfusion by CSF/ISF (macromolecule clearance)



Neckwrap NW-03B

Size: 500mm x 100mm

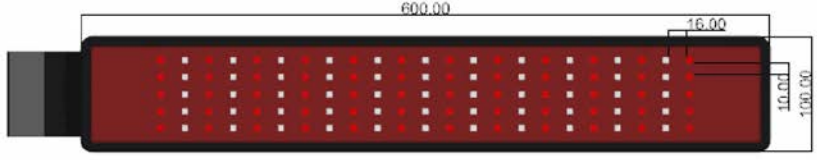
- Dual chip:635+904nm
- Dual chip:810+810nm



Bodywrap LW-03B

Size: 300mm x 200mm

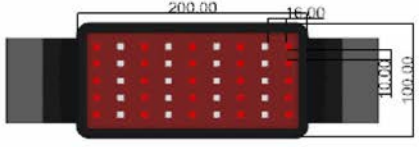
- Dual chip: 635+810nm



Headwrap BW-03B

Size:600mm*100mm

- Dual chip:635+904nm
- Dual chip: 810+1064nm



Topwrap TW-03B

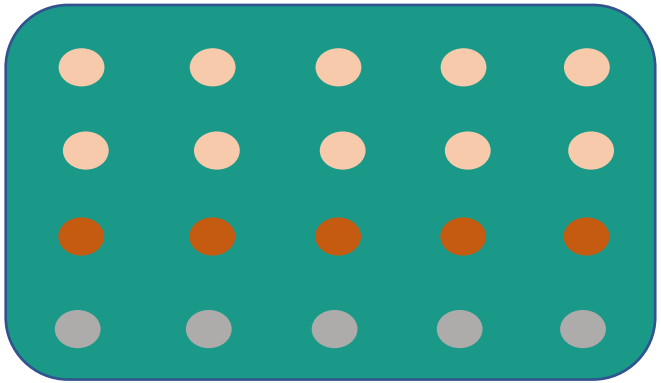
Size:200mm*100mm

- Dual chip:635+904nm
- Dual chip: 810+1064nm

PBMT set up

Head + Neck + body pads

Schematic of a pad with various LEDs



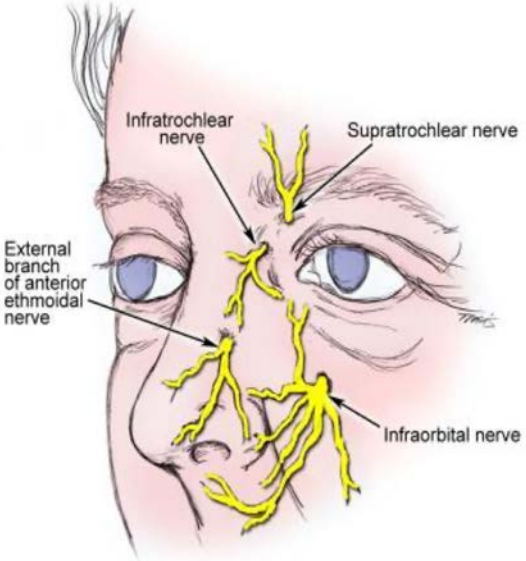
904 nm

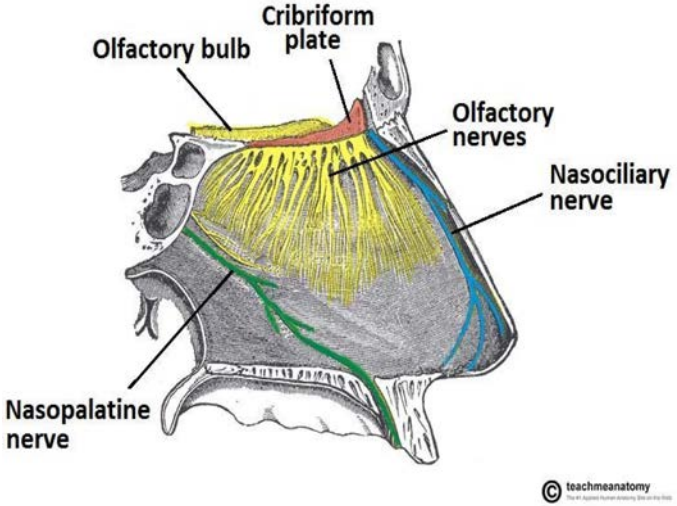
810 nm

635 nm

1064nm

PBM Therapy

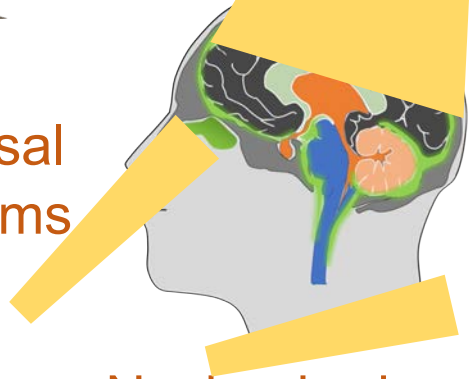

Infratrochlear nerve
Supratrochlear nerve
External branch of anterior ethmoidal nerve
Infraorbital nerve


Olfactory bulb
Cribriform plate
Olfactory nerves
Nasociliary nerve
Nasopalatine nerve
© teachmeanatomy

PBMT SEGMENTAL: Overview

Transcranial paradigms

Intranasal paradigms



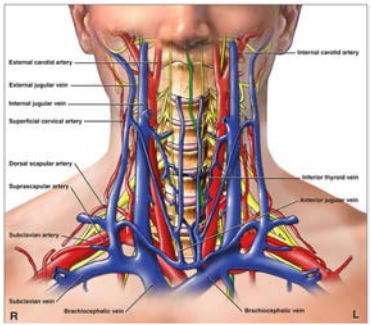
Neck + body pads

ProNeuroLIGHT - Red Light Therapy Devices

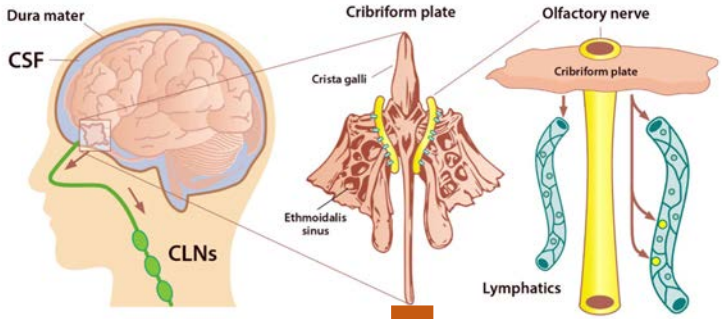
tPBMT & the Brain fluid homeostasis

Head Wrap

Neck Wrap



Intranasal probes



Modulation of cerebral autoregulation (e.g., CBF & CSF flow)?

Reduce cerebral edema by enhancing interstitial fluid drainage from CNS to periphery and alleviate imminent neurodegeneration?

Anatomy of the Arteries Veins and Nerves of the Cervical Neck Spine Region Stock Photo - Alamy

Salehpour et al., 2021

Conclusions

- Brain drainage system (glymphatic and meningeal lymphatic) plays an important role in maintaining water and ion balance of the ISF and CSF, waste clearance, and reabsorption of macromolecular solutes.

- A second physiological function includes communication with the immune system modulating immune surveillance and responses of the brain.

- PBM of the cranial and the extracranial lymphatics may be a promising approach for the treatment of brain disorders.