Integrative Healthcare SYMPOSIUM

The Hyperoxic-Hypoxic Paradox: Unraveling Its Potential in Regenerative Medicine

Shai Efrati, MD

The Hyperoxic-Hypoxic Paradox: Unraveling its Potential in Regenerative Medicine

Shai Efrati, MD

January 2024

SAGOL NEUROSCIENCE NETWORK

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Sagol School of Neuroscience
Tel Aviv University

Performance

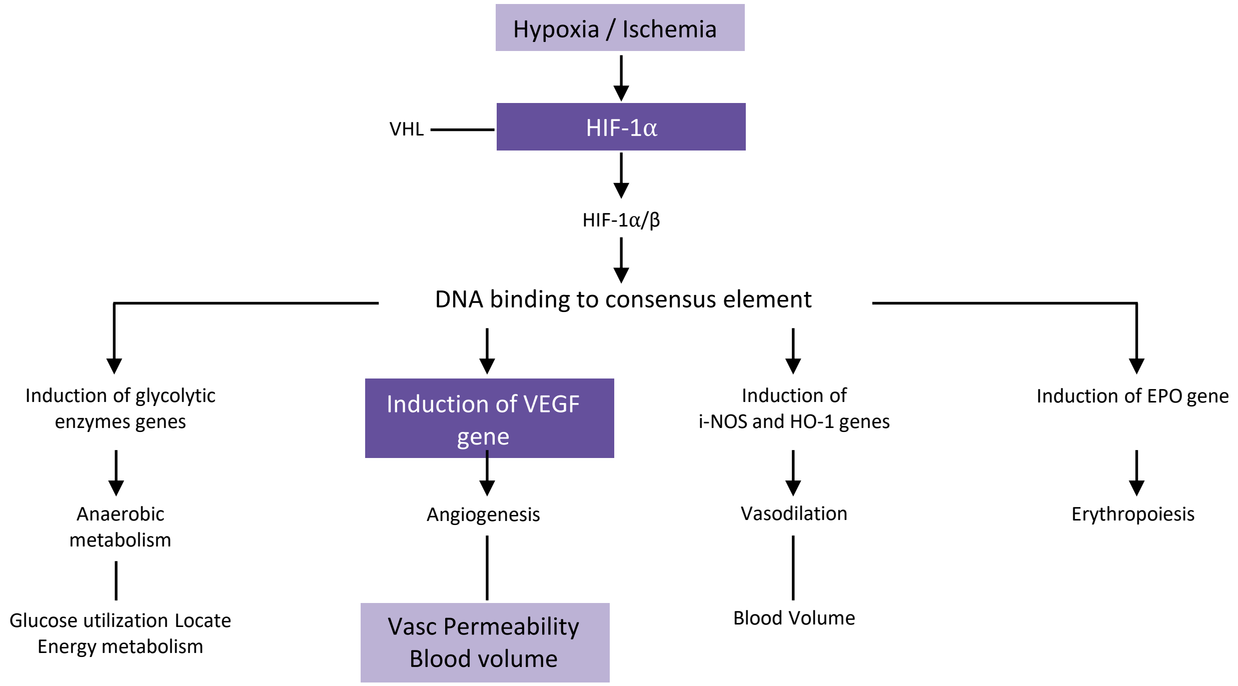
Regenerative vs. Degenerative


PIT-
STOP

What do we need for regeneration?

- Trigger
- Stem cells
- Energy
  - Oxygen
  - Improve mitochondrial function
- Angiogenesis

Trigger - HIF



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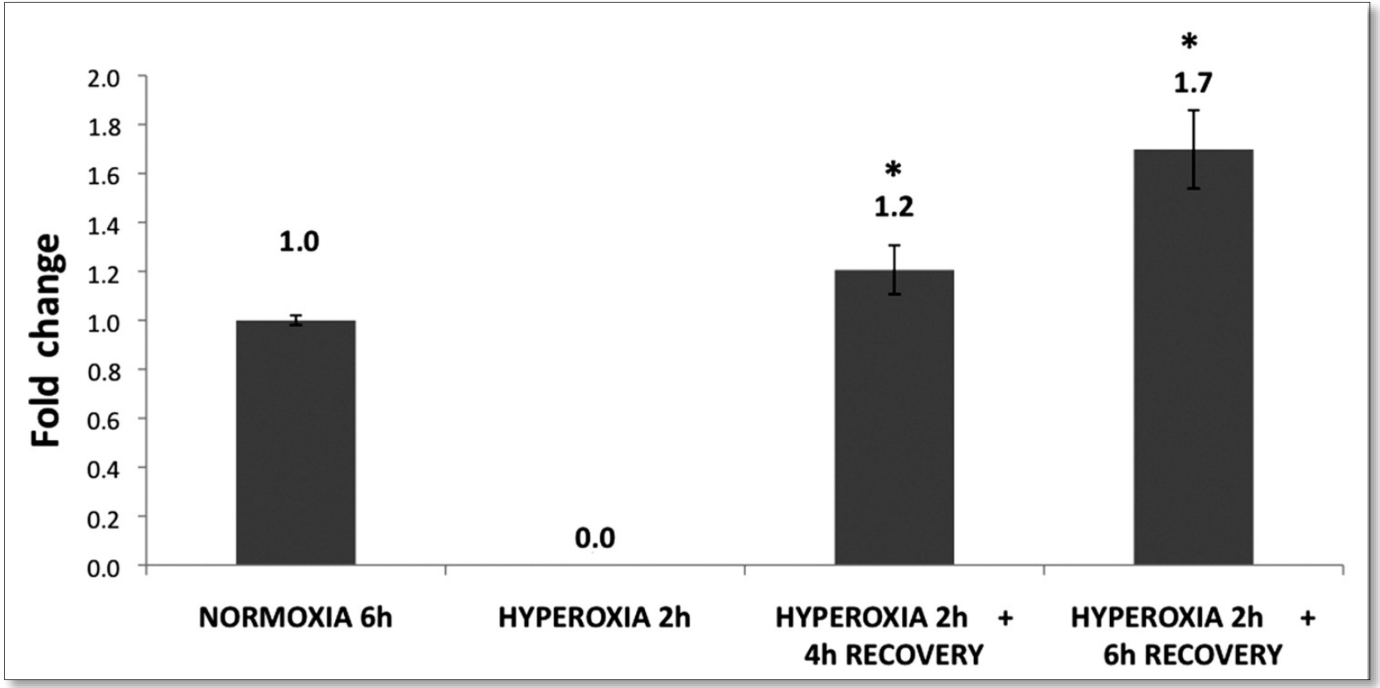
Hyperbaric Oxygen Therapy

The Hyperoxic-Hypoxic Paradox

Trigger: Hyperbaric Oxygen Suite

Hyperoxic - Hypoxic Paradox
HIF 1α in HUVEC



F. Cimino et al J Appl Physiol. 2012

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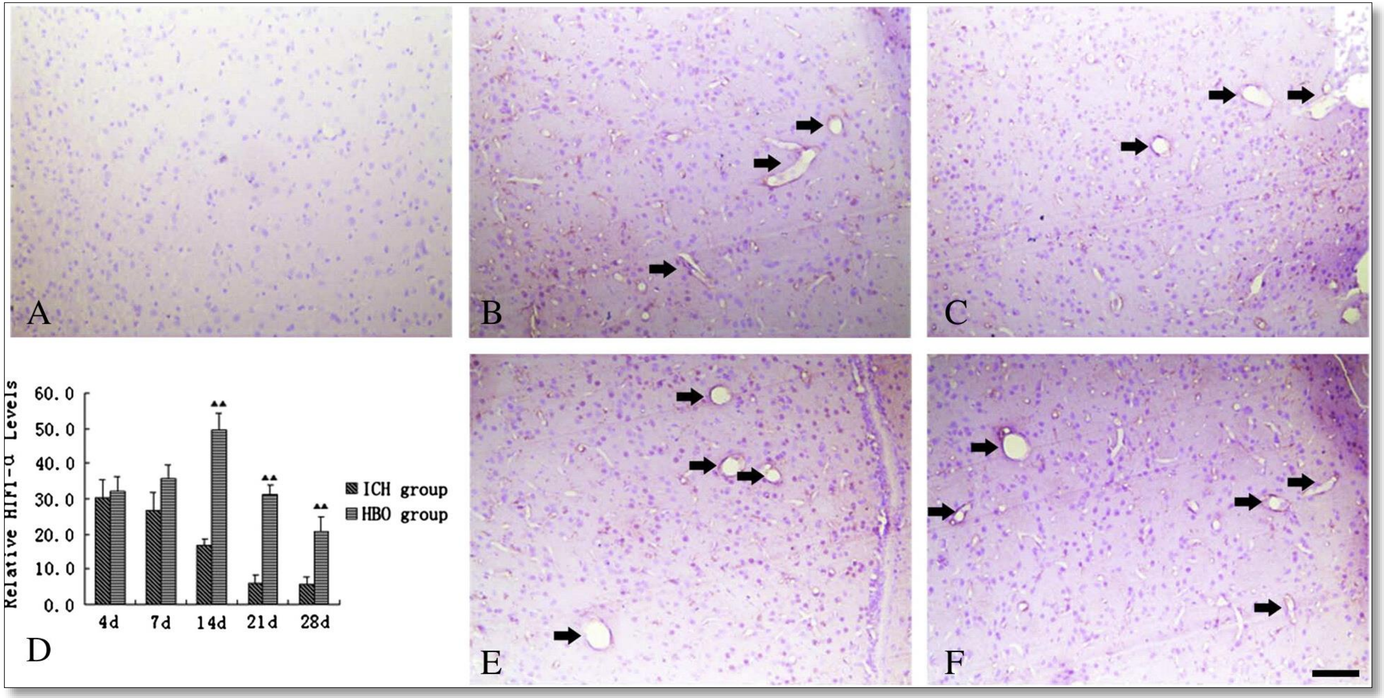
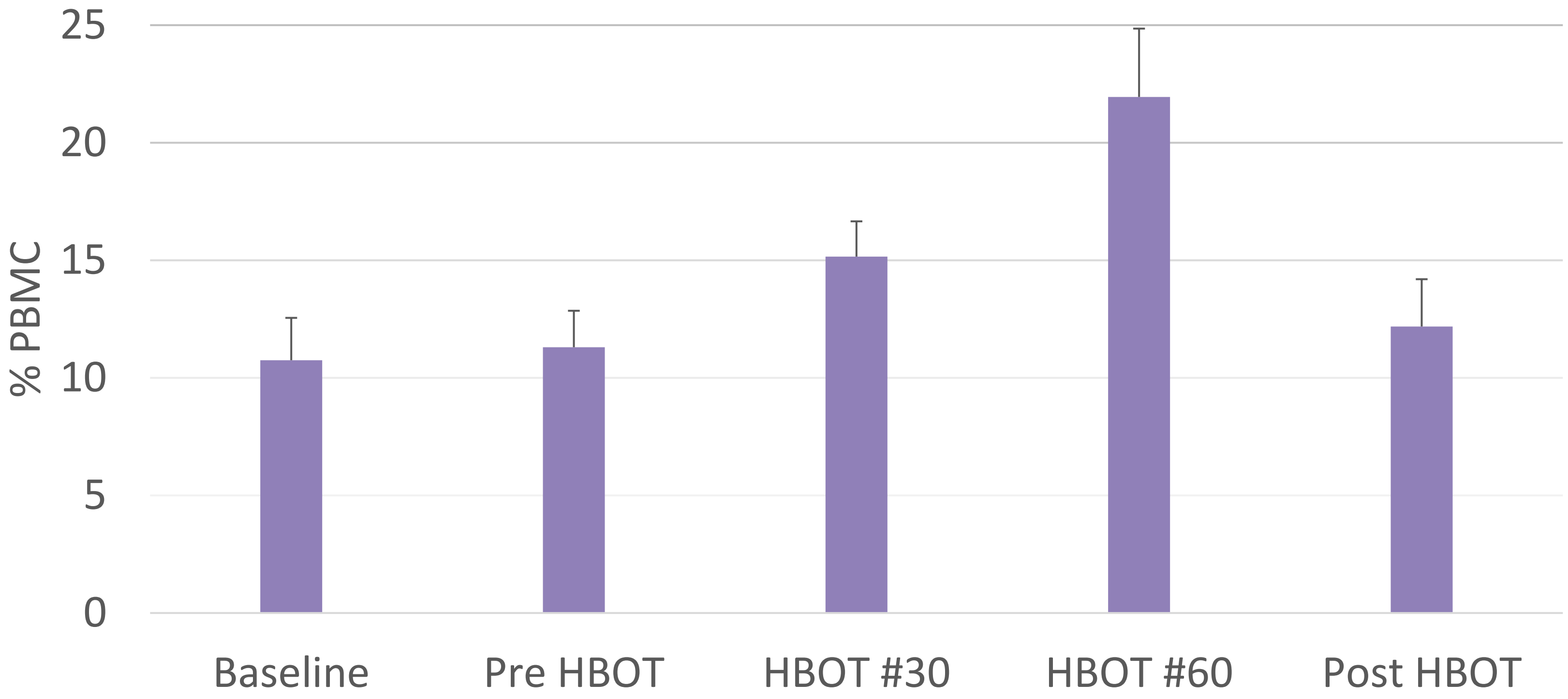
Hyperoxic - Hypoxic Paradox
HIF in the Brain (animal model)



Peng et al. J Neurol Sci. 2014

Hyperoxic - Hypoxic Paradox
HIF 1α in Humans PBMC



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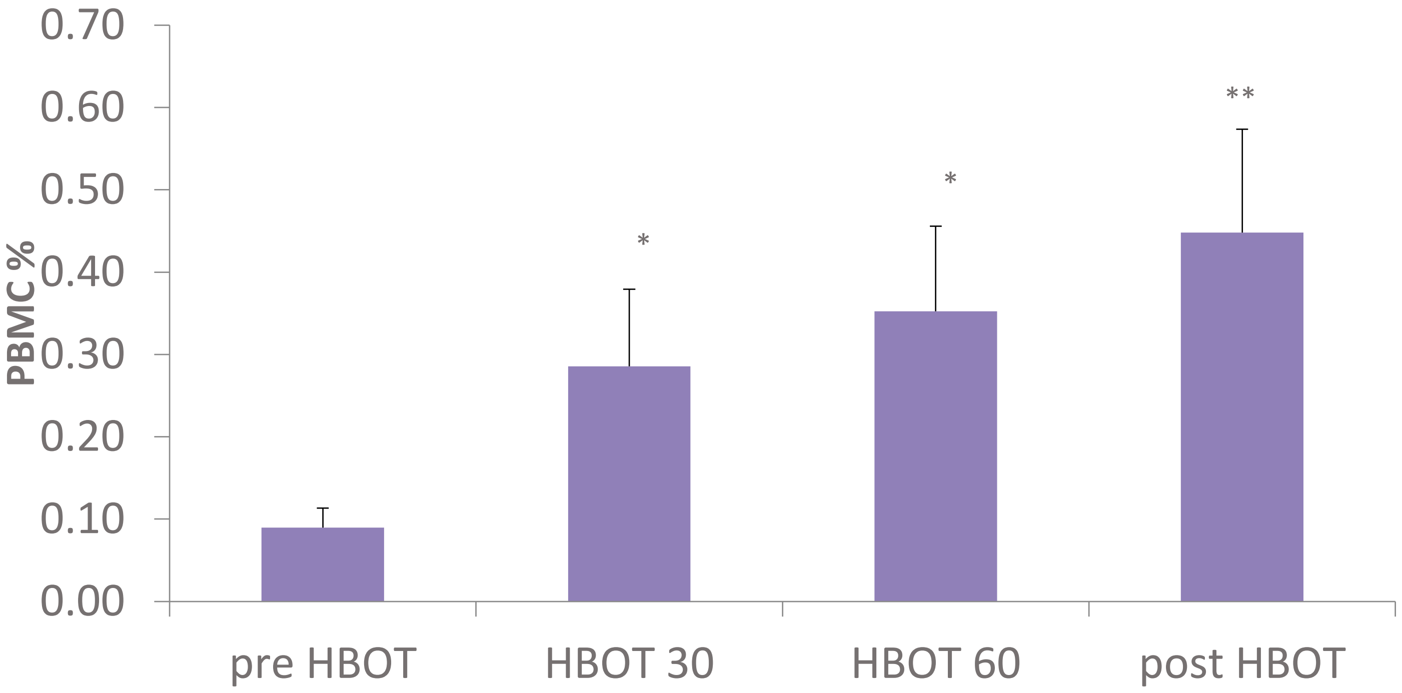
What do we need for regeneration?

- ✓ Trigger
- Stem cells
- Energy
  - Oxygen
  - Improve mitochondrial function
- Angiogenesis

Hematopoietic Stem Cells (CD34+/CD90+)



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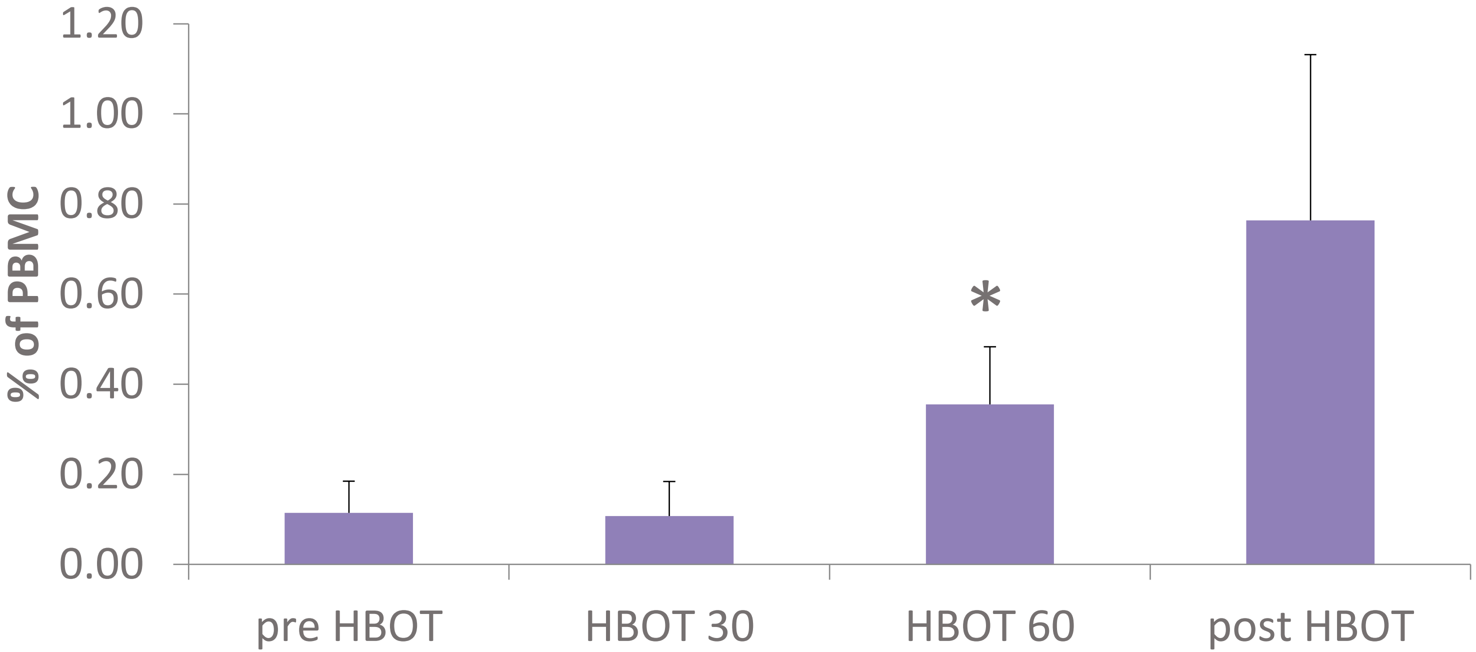
Mesanchimal Stem Cells (CD34-/CD45-/CD73+/CD90+/CD105+)



What Do We Need For Regeneration?

Supporting Environment

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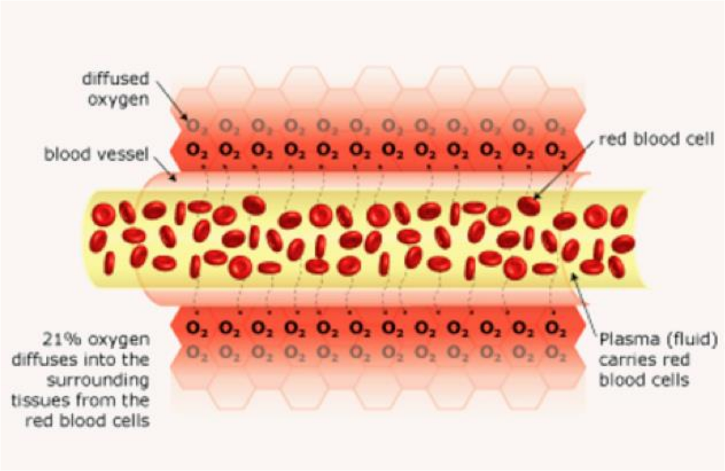
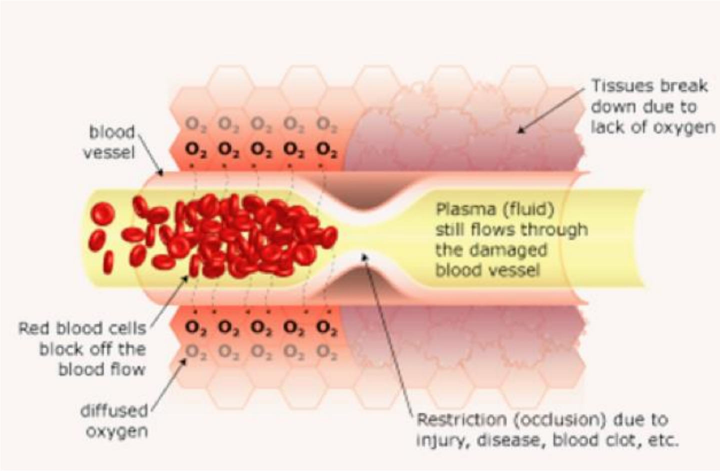
Environment

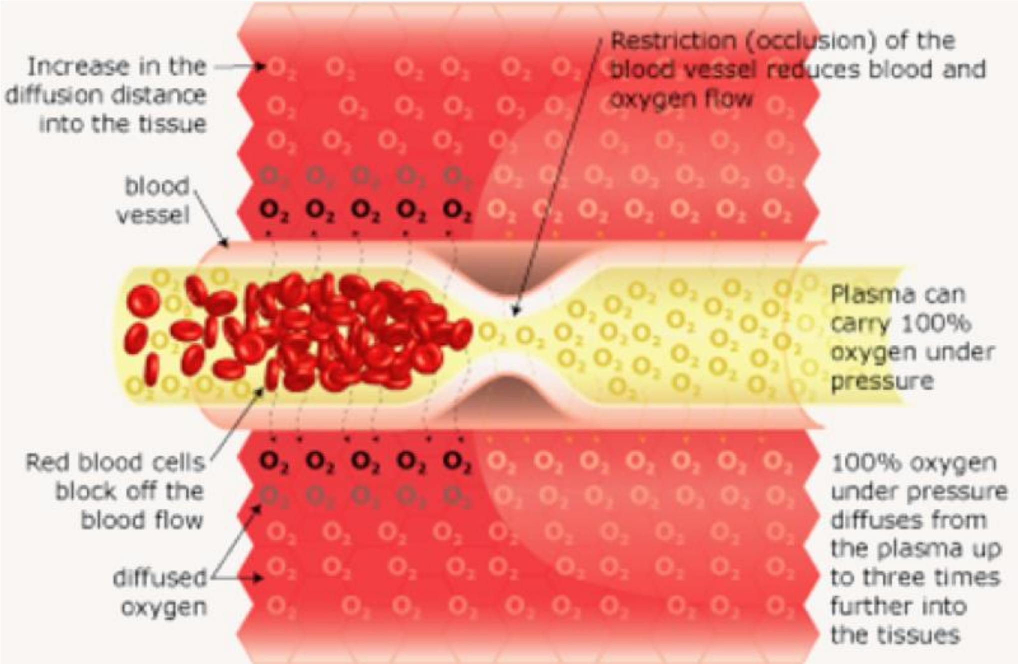
Normal Perfusion



Hypoperfusion



Supporting Environment



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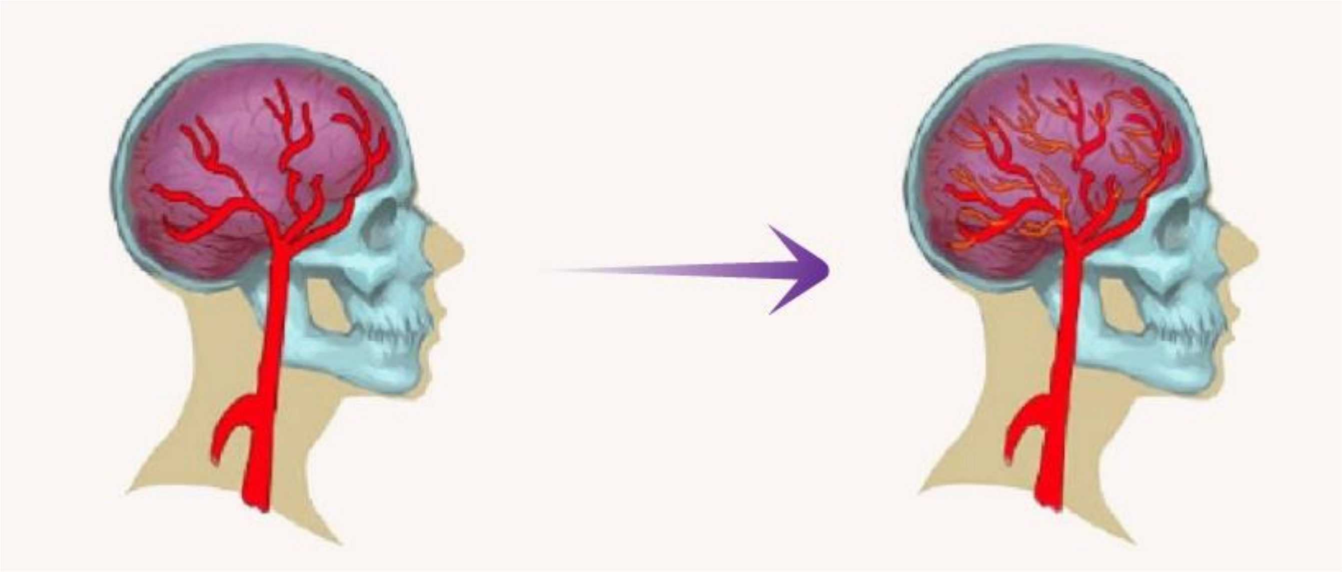
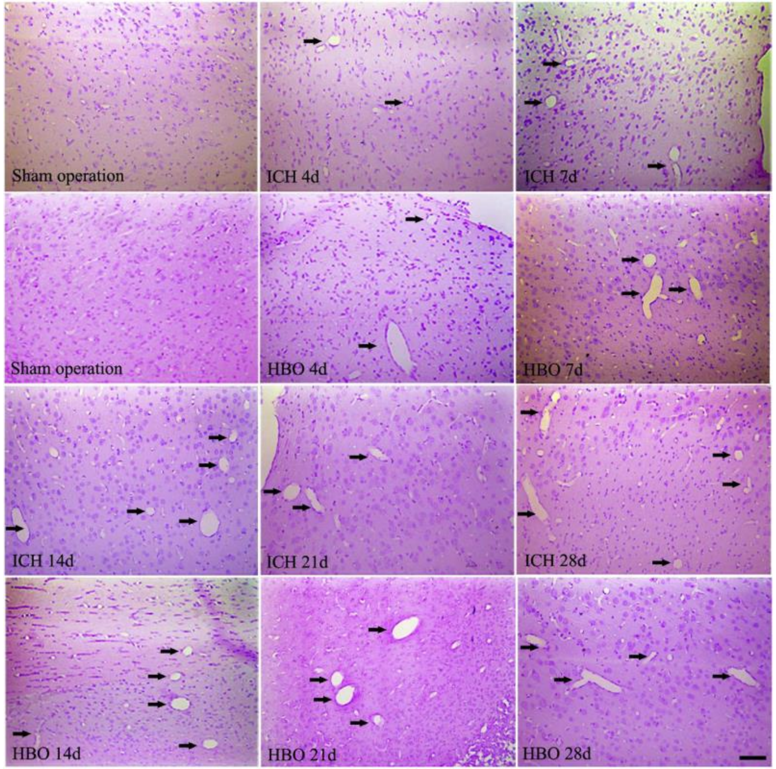
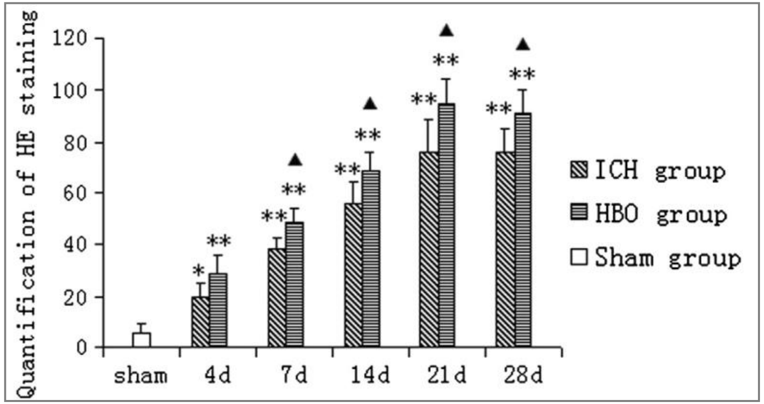
Supporting Environment

Angiogenesis



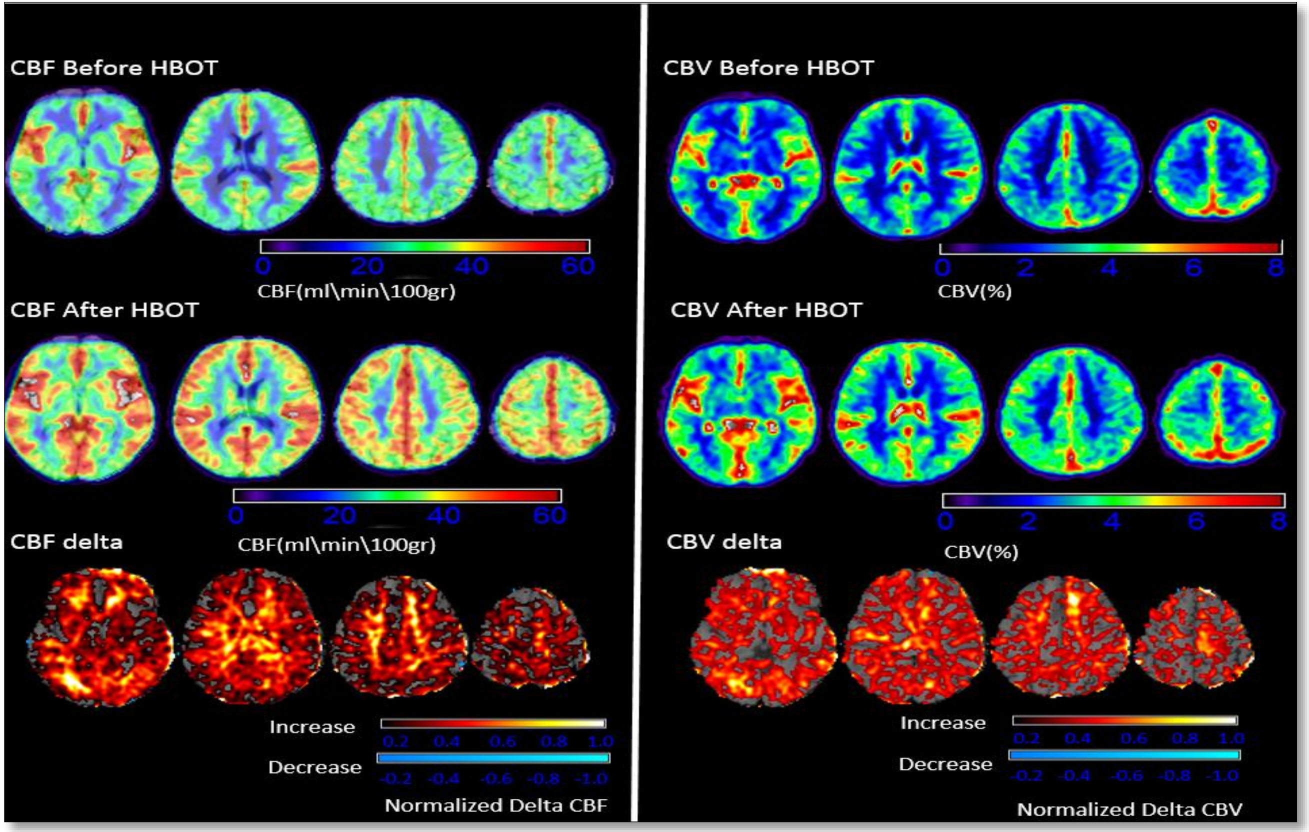
Hyperbaric Oxygen Therapy induce Brain Angiogenesis - Post Stroke rat





Peng et al. J Neurol Sci. 2014

Perfusion MRI of Post TBI Patients
(10±3 yrs after the acute event)

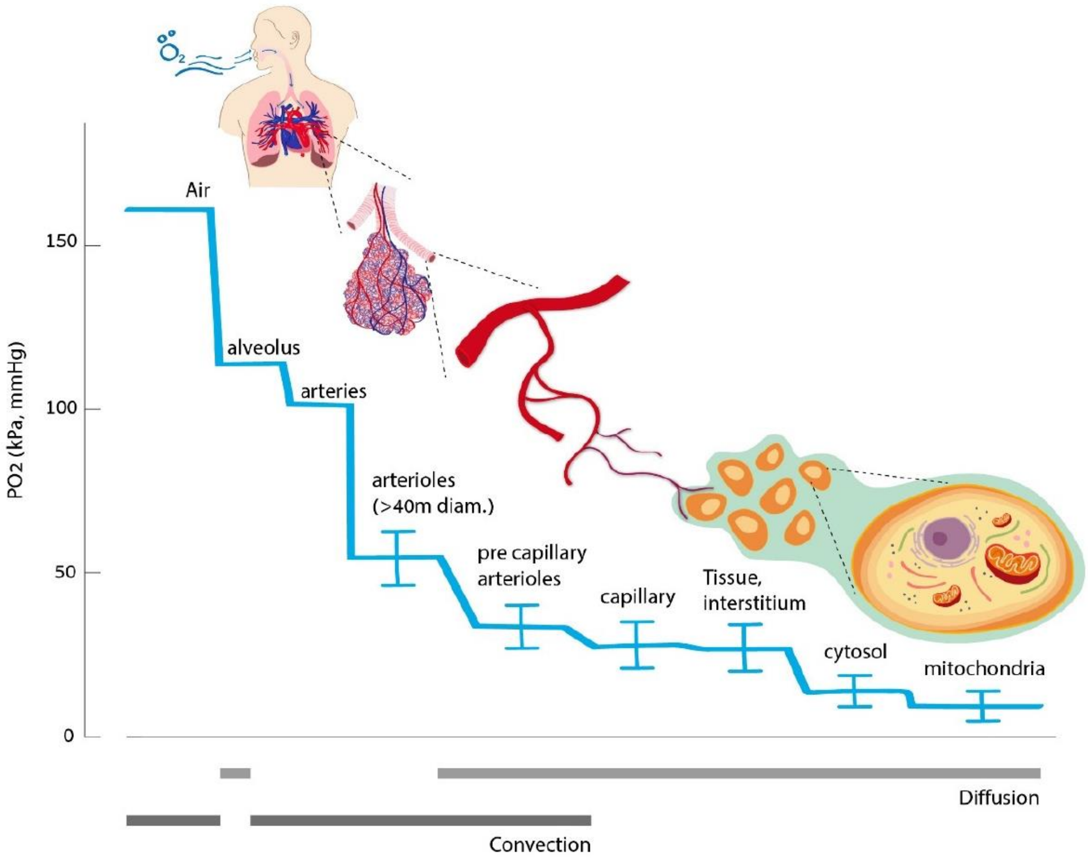


Restor Neurol Neurosci. 2015

What do we need for regeneration?

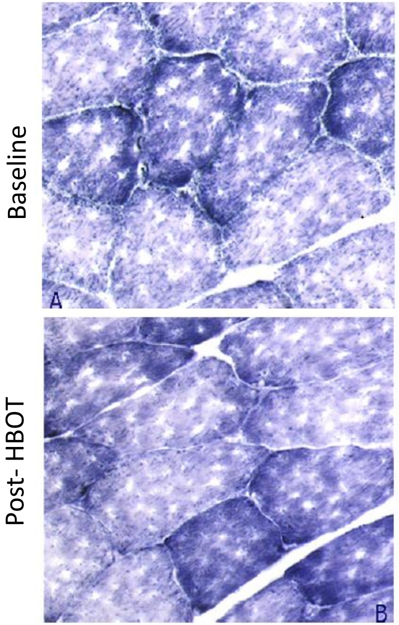
- ✓ Trigger
- ✓ Stem cells
- ✓ Energy
  - ✓ Oxygen
  - ✓ Angiogenesis
  - Improve mitochondrial function

Mitochondria



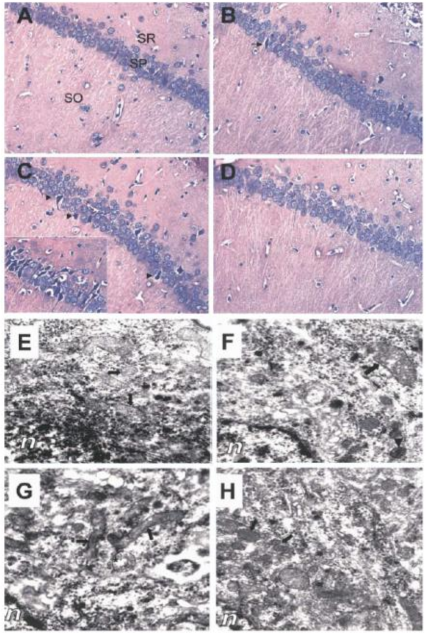
HBOT induced Mitochondrial Biogenesis

Rat Muscle



Kurt et al. Clinical neuroscience 2007

Rat Hippocampus



Gutsaeva et al. Neuroscince 2006

HBOT and Mitochondrial

J Neurosurg 106:687–694, 2007

Protection of mitochondrial function and improvement in cognitive recovery in rats treated with hyperbaric oxygen following lateral fluid-percussion injury

ZHENGWEN ZHOU, M.D.,[1,2] WILSON P. DAUGHERTY, M.D., PH.D.,[1] DONG SUN, M.D., PH.D.,[1] JOSEPH E. LEVASSEUR, M.S.,[1] NABIL ALTEMEMI, B.S.,[1] ROBERT J. HAMM, PH.D.,[3] GAYLAN L. ROCKSWOLD, M.D., PH.D.,[4] AND M. ROSS BULLOCK, M.D., PH.D.[1]

Departments of [1]Neurosurgery and [3]Psychology, Virginia Commonwealth University School of Medicine, Richmond, Virginia; [4]Department of Neurosurgery, Hennepin County Medical Center, Minneapolis, Minnesota; and [2]Department of Neurosurgery, RenJi Hospital, Shanghai Second Medical University, Shanghai, China

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Journal of Clinical Neuroscience 15 (2008) 445–450
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Journal of Clinical Neuroscience
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Laboratory Study

Effects of hyperbaric oxygen on energy production and xanthine oxidase levels in striated muscle tissue of healthy rats

Bülent Kurt[a,*], Yasemin Kurt[a,b], Yıldırım Karslıoğlu[a], Turgut Topal[a,c], Hüsamettin Erdamar[d], Ahmet Korkmaz[a,c], Nurten Türközkan[d], Halil Yaman[a,b], Zeki Odabaşı[a,e], Ömer Günhan[a]

[a] Department of Pathology, Gulhane Military Medical Academy and Medical School, Ankara, Turkey
[b] Department of Biochemistry, Gulhane Military Medical Academy and Medical School, Ankara, Turkey
[c] Department of Physiology, Gulhane Military Medical Academy and Medical School, Ankara, Turkey
[d] Department of Biochemistry, Faculty of Medicine, Gazi University, Ankara, Turkey
[e] Department of Neurology, Gulhane Military Medical Academy and Medical School, Ankara, Turkey

Hyperbaric Oxygen Treatment Suppresses MAPK Signaling and Mitochondrial Apoptotic Pathway in Degenerated Human Intervertebral Disc Cells

Chi-Chien Niu,[1,2] Song-Shu Lin,[1,3] Li-Jen Yuan,[1,2] Lih-Huei Chen,[1,2] I-Chun Wang,[1,2] Tsung-Ting Tsai,[1,2] Po-Liang Lai,[1,2] Wen-Jer Chen[1,2]

[1]Department of Orthopaedic Surgery, Hyperbaric Oxygen Therapy Center, Chang Gung Memorial Hospital, Taoyuan, Taiwan, [2]College of Medicine, Chang Gung University, Taoyuan, Taiwan, [3]Graduate Institute of Biomedical Sciences, Chang Gung University, Taoyuan, Taiwan

BRAIN RESEARCH 1221 (2008) 126–133
available at www.sciencedirect.com
ScienceDirect
www.elsevier.com/locate/brainres
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BRAIN RESEARCH

Research Report

Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties☆

*Eilam Palzur, Menashe Zaaroor[1], Eugene Vlodavsky, Felix Milman, Jean F. Soustiel**

Acute Brain Injury Research Laboratory, Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel

HYPERBARIC OXYGEN PRECONDITIONING REDUCES ISCHEMIA–REPERFUSION INJURY BY INHIBITION OF APOPTOSIS VIA MITOCHONDRIAL PATHWAY IN RAT BRAIN

J.-S. LI,[a1] W. ZHANG,[a1] Z.-M. KANG,[b] S.-J. DING,[a*] W.-W. LIU,[b] J. H. ZHANG,[c] Y.-T. GUAN[a] AND X.-J. SUN[b*]

[a]Department of Neurology, Changhai Hospital, 168 Changhai Road,
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...hina
...ity, Loma Linda,

moda et al., 2007) and observed in clinical cases after multiple transient ischemic attacks (Sitzer et al., 2004). However, the safety concerns and practical feasibility have limited the application of preconditioning in practice.

Hyperbaric oxygen (HBO) has been used for multiple neurological diseases (Lou et al., 2004; Al-Waili et al., 2005; Rosenthal et al., 2003; Ostrowski et al., 2006) and proved a safe treatment modality in all age and gender groups, includ-

OXYGEN-INDUCED MITOCHONDRIAL BIOGENESIS IN THE RAT HIPPOCAMPUS

D. R. GUTSAEVA,[a,b] H. B. SULIMAN,[a] M. S. CARRAWAY,[a] I. T. DEMCHENKO[a,b] AND C. A. PIANTADOSI[a*]

[a]*Departments of Medicine and Anesthesiology and Center for Hyperbaric Medicine and Environmental Physiology, Duke University Medical Center, Box 3315, Durham, NC 27710, USA*

[b]*Institute of Evolutionary Physiology and Biochemistry Russian Academy of Science, St. Petersburg, Russia*

1972; Balentine, 1982). The mechanisms of CNS O_2 toxicity, although not fully understood, involve the generation of reactive oxygen and nitrogen species (ROS and RNS) that disrupt the brain's oxidant/antioxidant balance (Demchenko et al., 2002). This imbalance promotes macromolecule oxidation, including lipids, enzymes, and nucleic acids, which in theory produces the neurochemical alterations and manifestations of toxicity (Jamieson, 1989;

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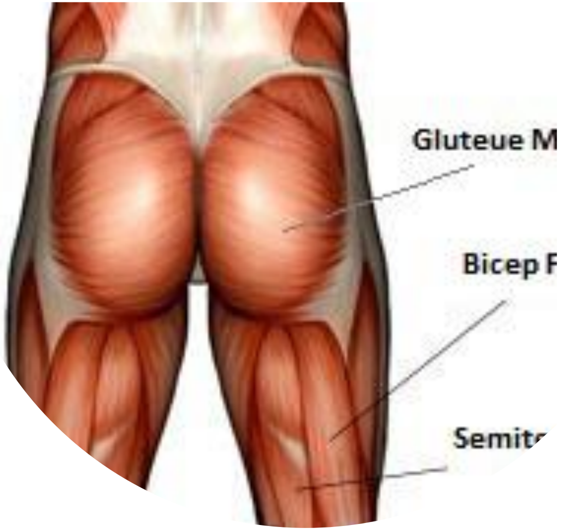
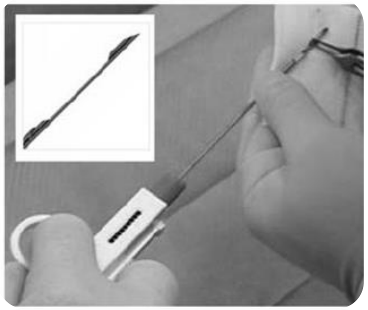
Mitochondrial Respiratory Function



- Gluteus Maximus muscle biopsy
- Sterile Trucut biopsy
- *Blinded biologist:*
- Muscle fibers handling
- O2K (Oxygraph) respiratory measurements
- Respiratory chain complexes staining



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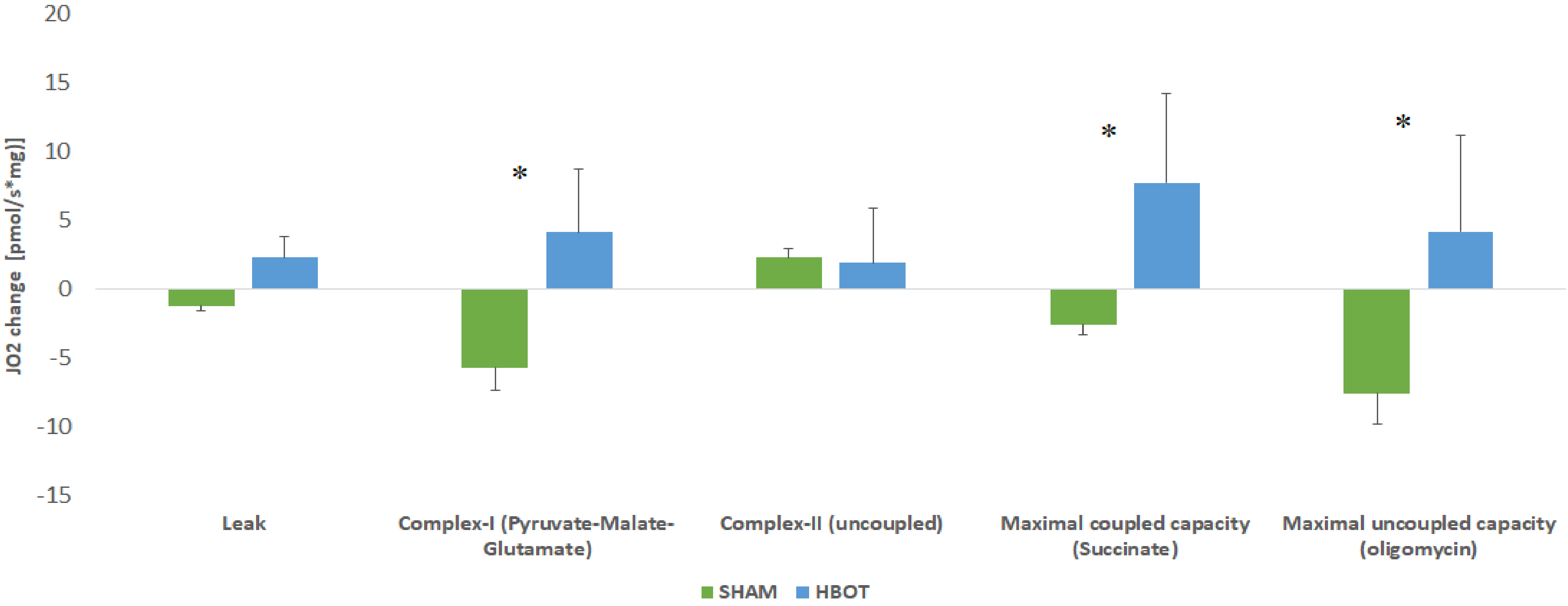
Mitochondrial Functional Change



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* p<0.05, Mean±SE

Efrati et al. Sports Med. 2022

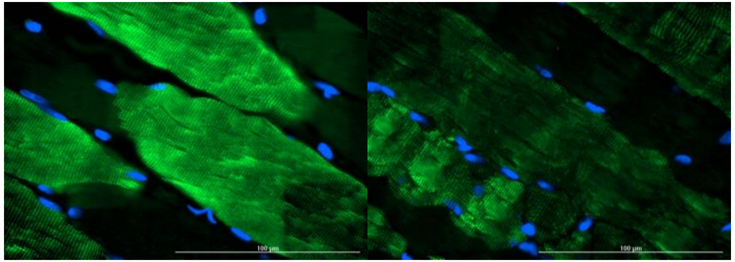
Mitochondria Biogenesis

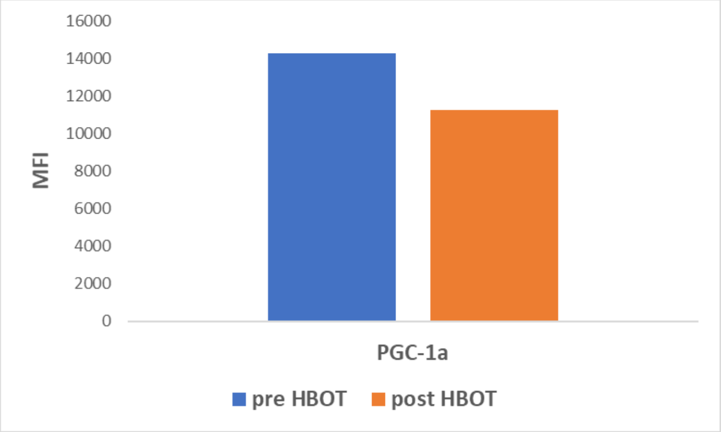
PGC1 alpha- a Marker for Mitochondrial Biogenesis

SHAM

Pre SHAM

Post SHAM

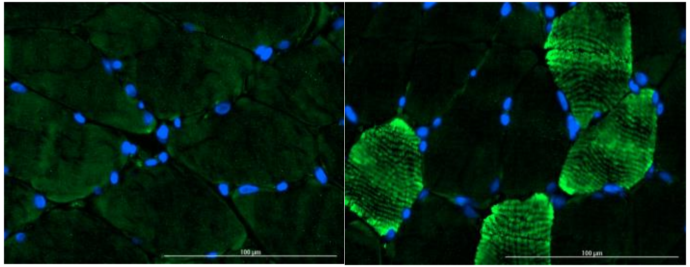


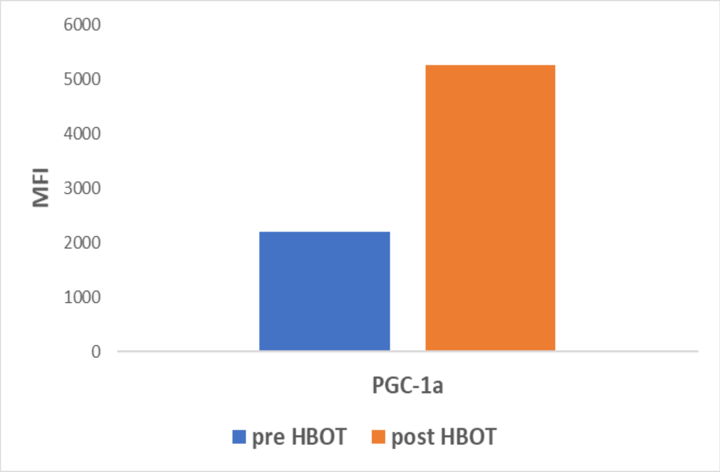


HBOT

Pre HBOT

Post HBOT





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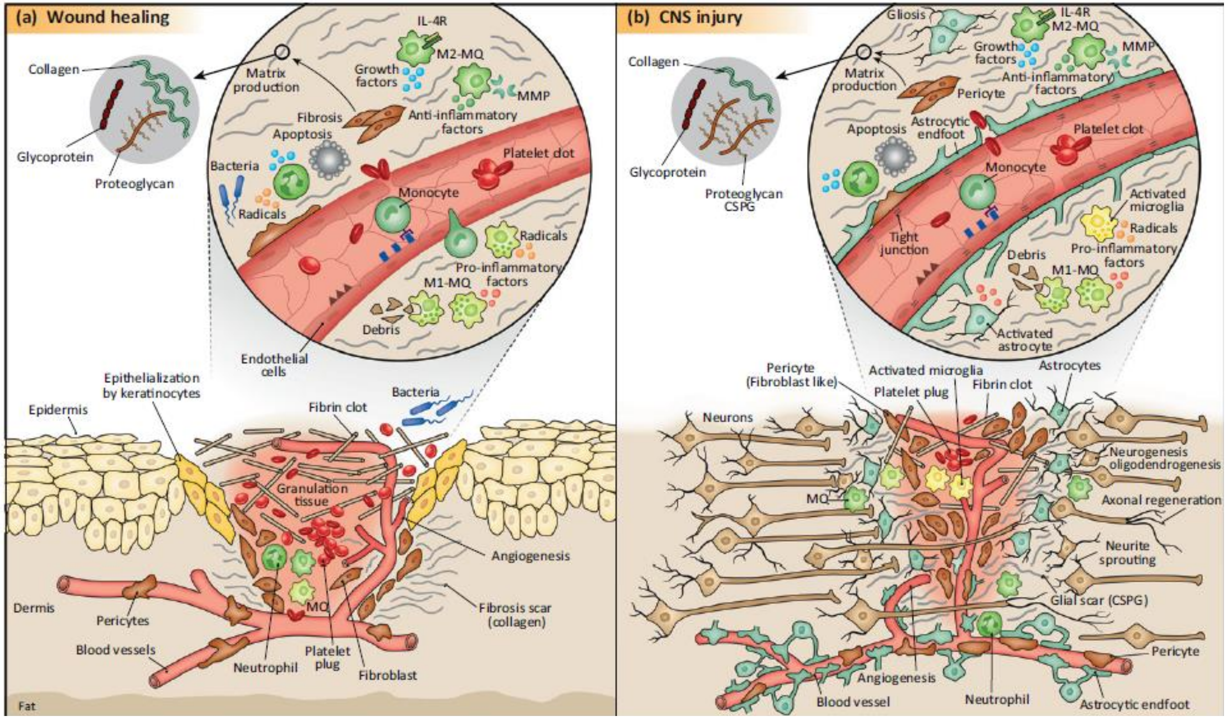
Efrati et al. Sports Med. 2022

What do we need for regeneration?

- ✓ Trigger
- ✓ Stem cells
- ✓ Energy
  - ✓ Oxygen
  - ✓ Angiogenesis
  - ✓ Improve mitochondrial function

What is the “standard clinical practice” today ?

Current clinical practice



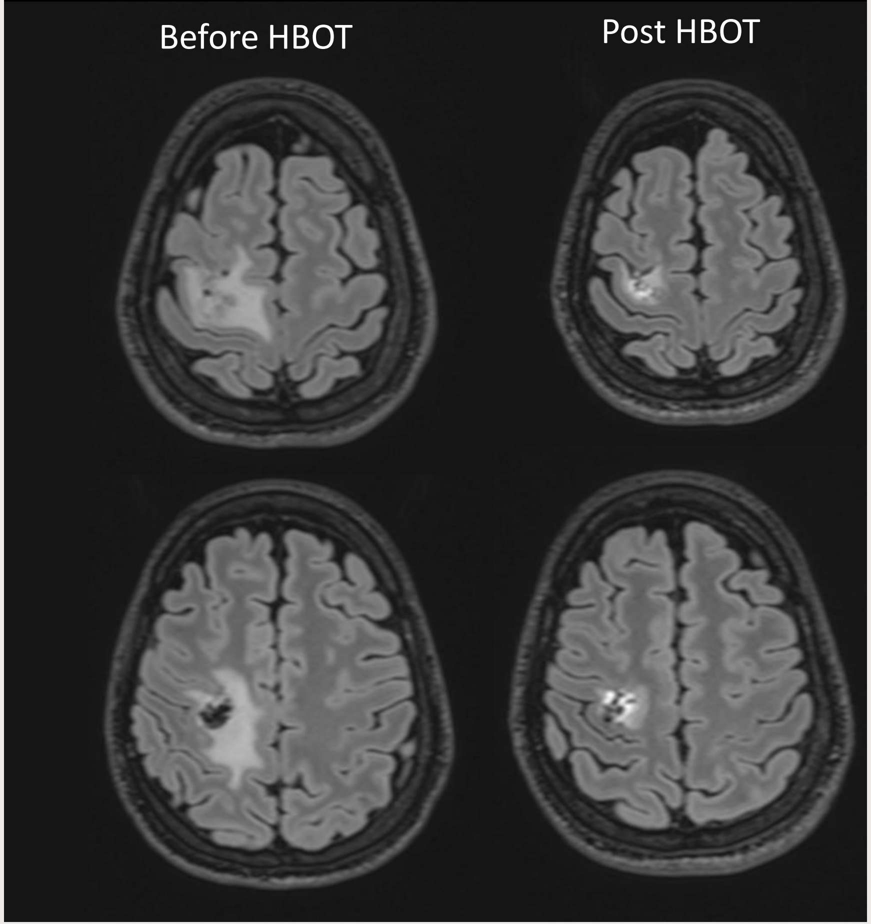
Michal Schwartz at all

Non-Healing peripheral wounds

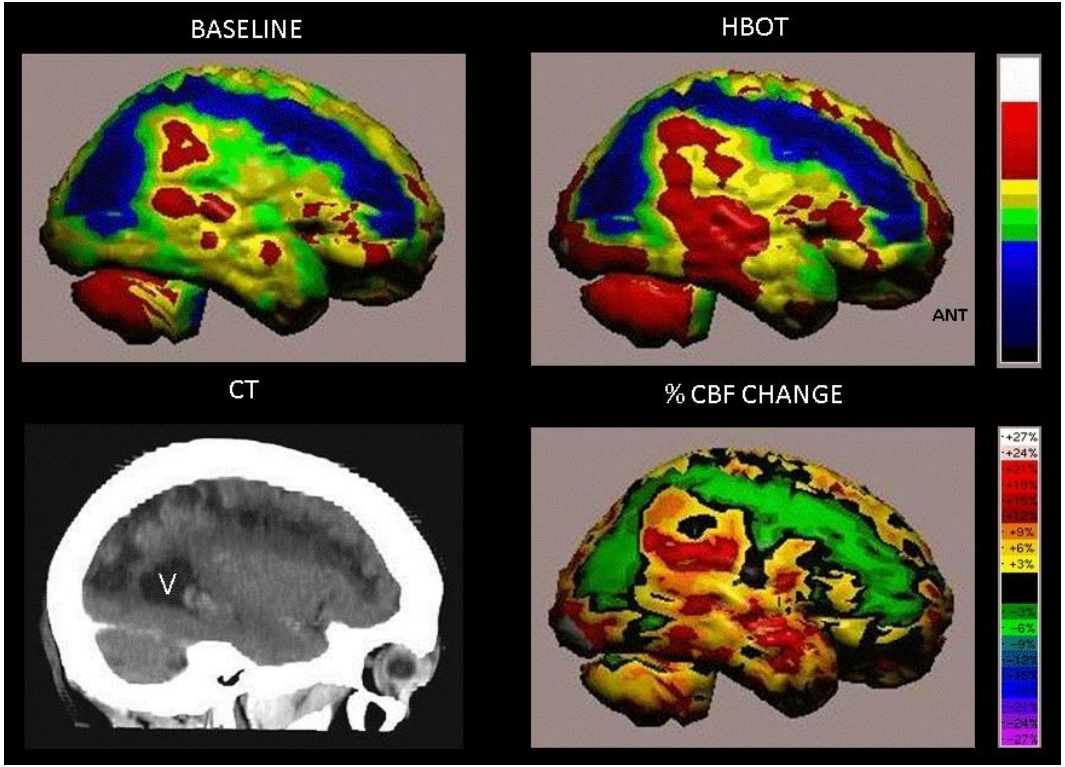
Before HBOT | Post HBOT

Current clinical practice of Hyperbaric Oxygen Therapy

Non-Healing post radiation brain wounds (2 years after the radiation)

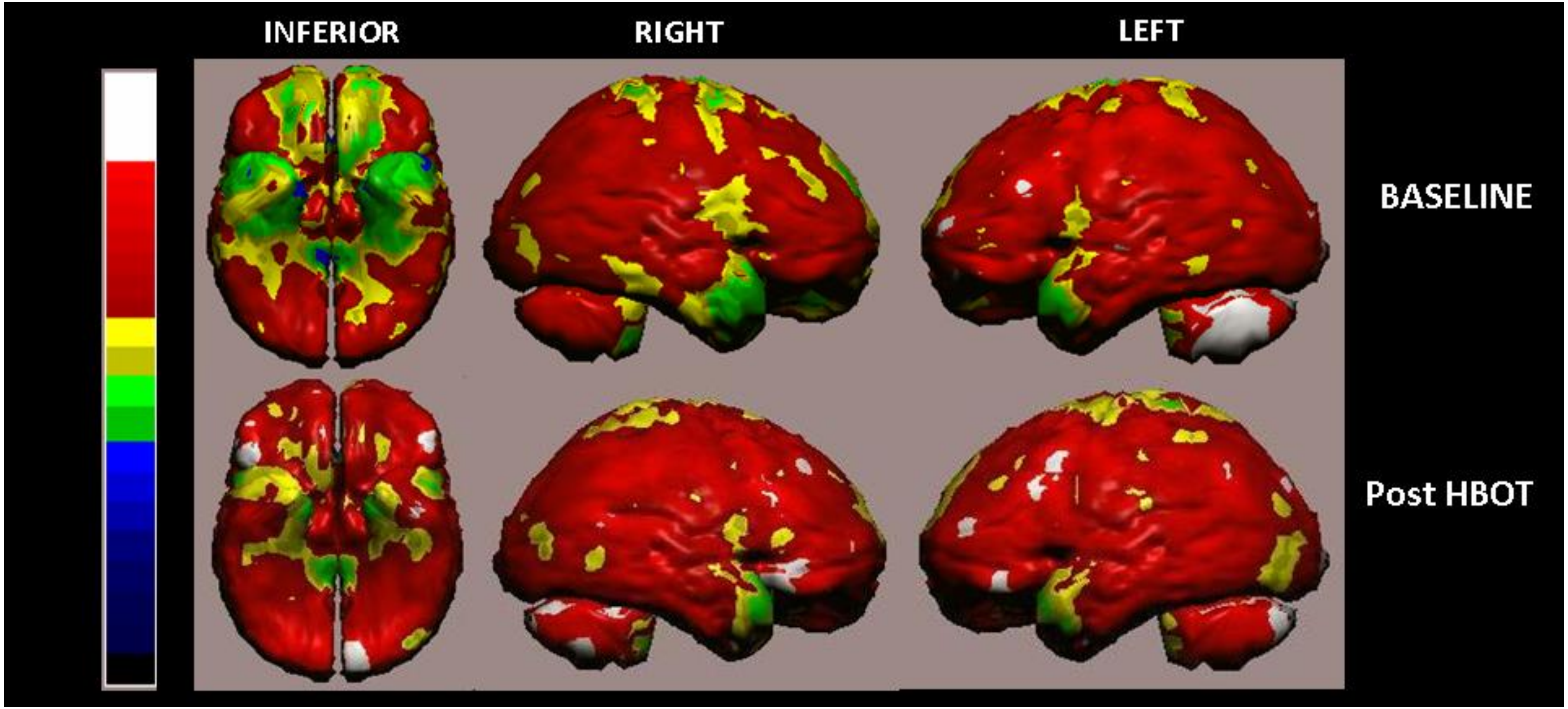


64-year-old woman, suffering from left hemiparesis due to ischemic stroke that occurred 26 months prior to inclusion in the study.



Efrati et al. Plos 2013

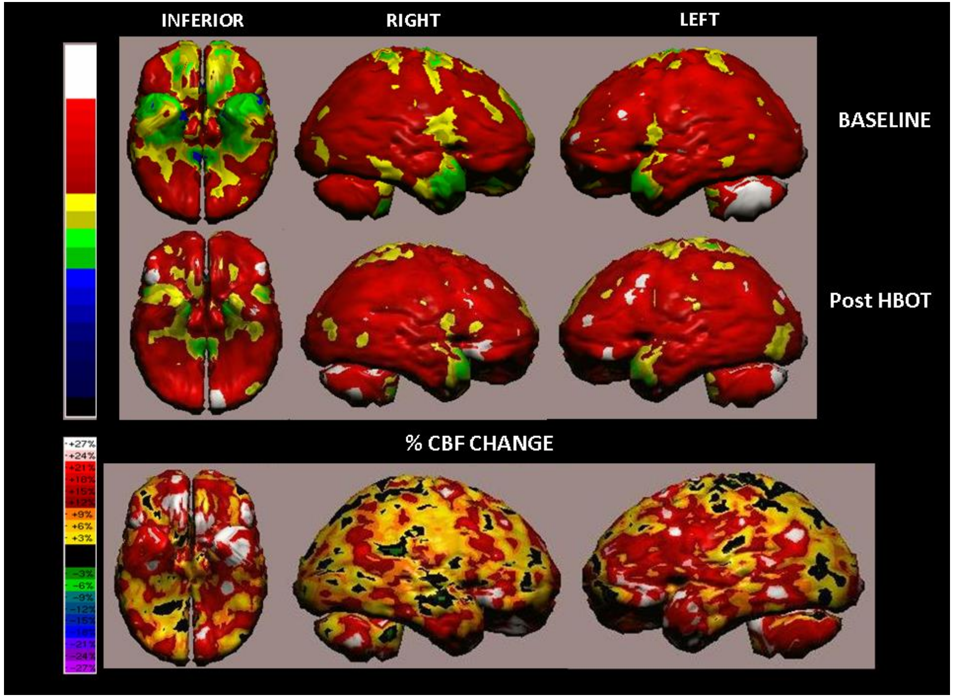
51-year-old woman that had mTBI (fall from a bus)
2 years prior to her inclusion



Efrati et al. Plos 2013

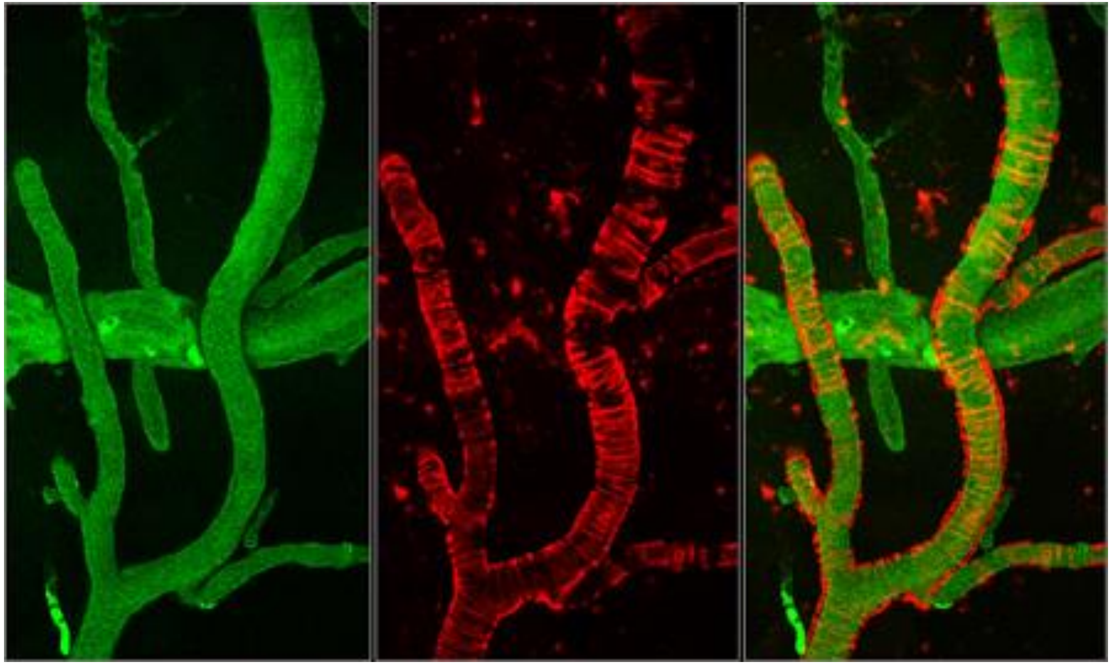
Case Example

51-year-old woman that had mTBI (fall from a bus)
2 years prior to her inclusion



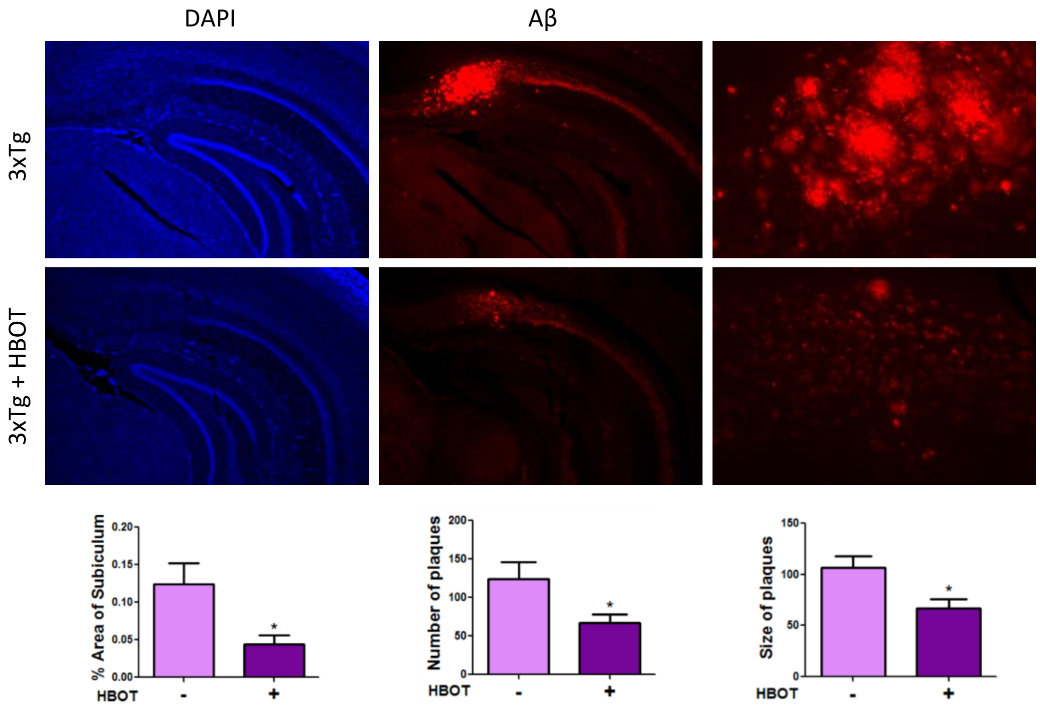
	Baseline	Post HBOT
Memory	56	108
Attention	47	81
Executive Function	65	85
Information processing speed	85	95

AMYLOID & BLOOD FLOW IN ALZHEIMER DISEASE MICE



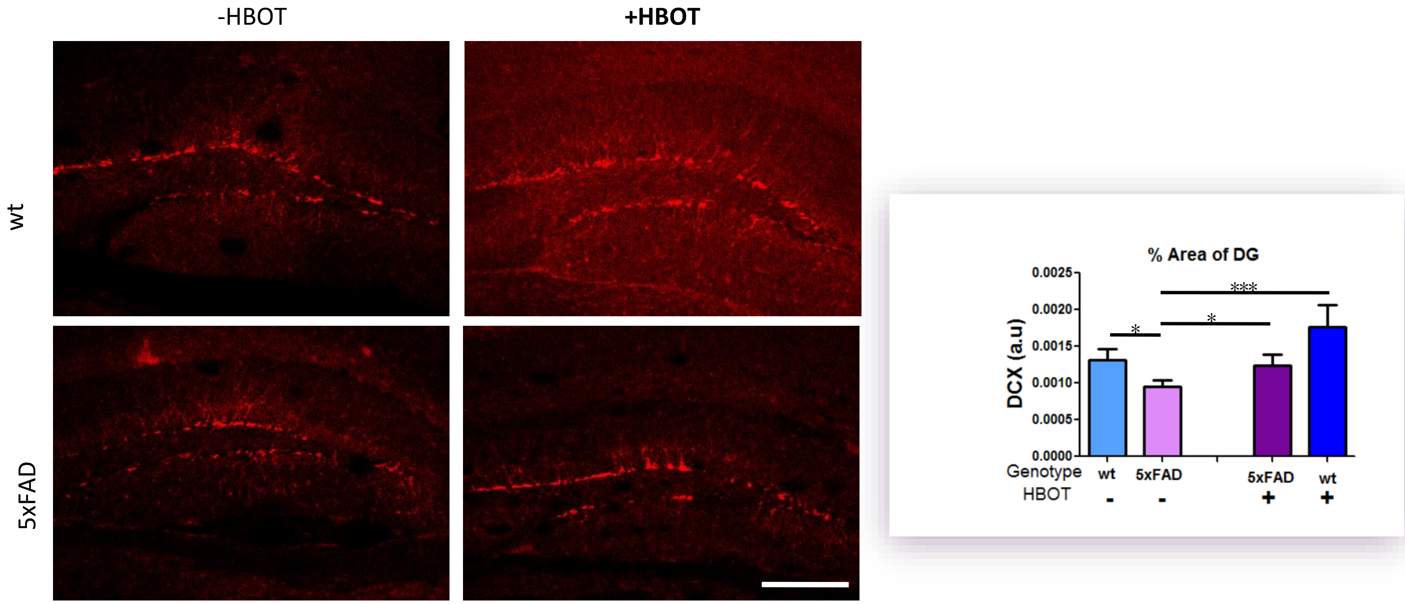
The images were taken using a multiphoton microscope and illustrate the vasculature of an Alzheimer's disease mouse. Green shows blood flow and red amyloid deposition. The ring-like structures surrounding the blood vessels represent cerebral amyloid angiopathy.

HBOT REDUCES AMYLOID LOAD IN THE OLD 3XTG MICE



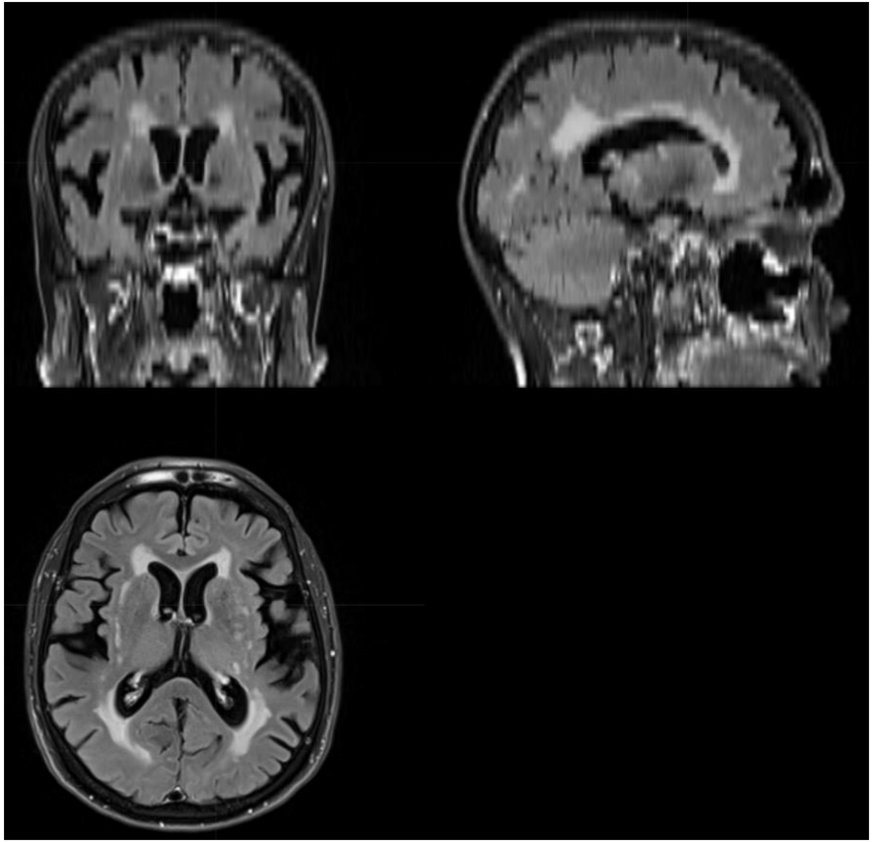
Neurobil Aging 2018 Feb:62:105-119.

HBOT INCREASE SURVIVAL OF NEW-BORN NEURONS IN CONTROL AND 5XFAD MICE



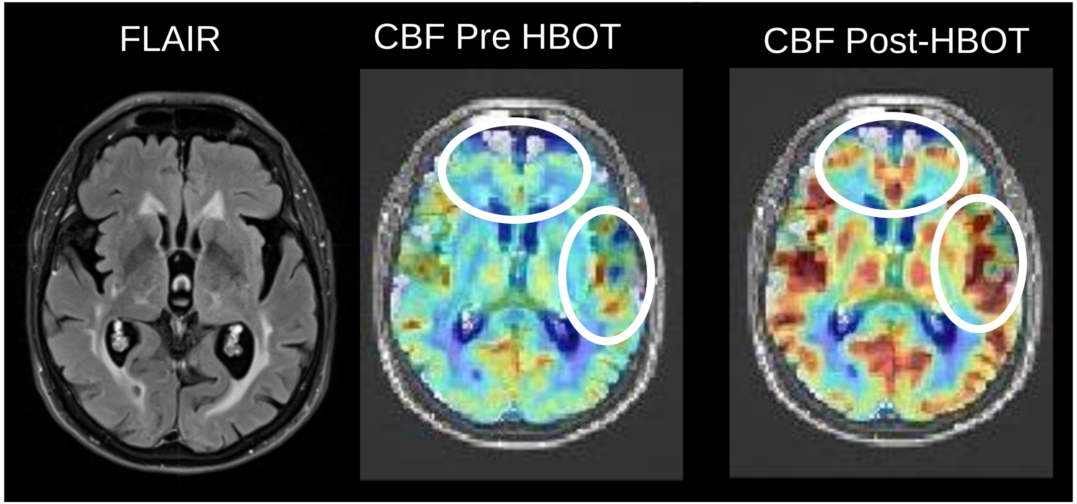
Neurobil Aging 2018 Feb:62:105-119.

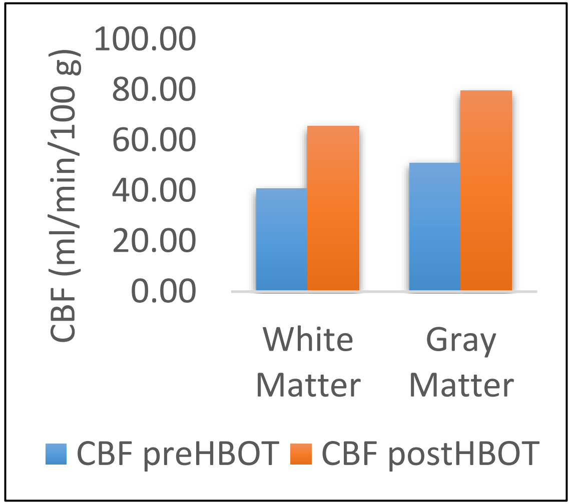
Age Related Mild Cognitive Impairment
Case example



84 yr female, with MCI
(memory loss, shortness of attention span)

Perfusion in Mild Cognitive Impairment Following HBOT
Case example





Brain region	Brain function	% change
Anterior cingulate cortex	Attention	67.40%
Hippocampus	Long term memory, Spatial memory	65.53%

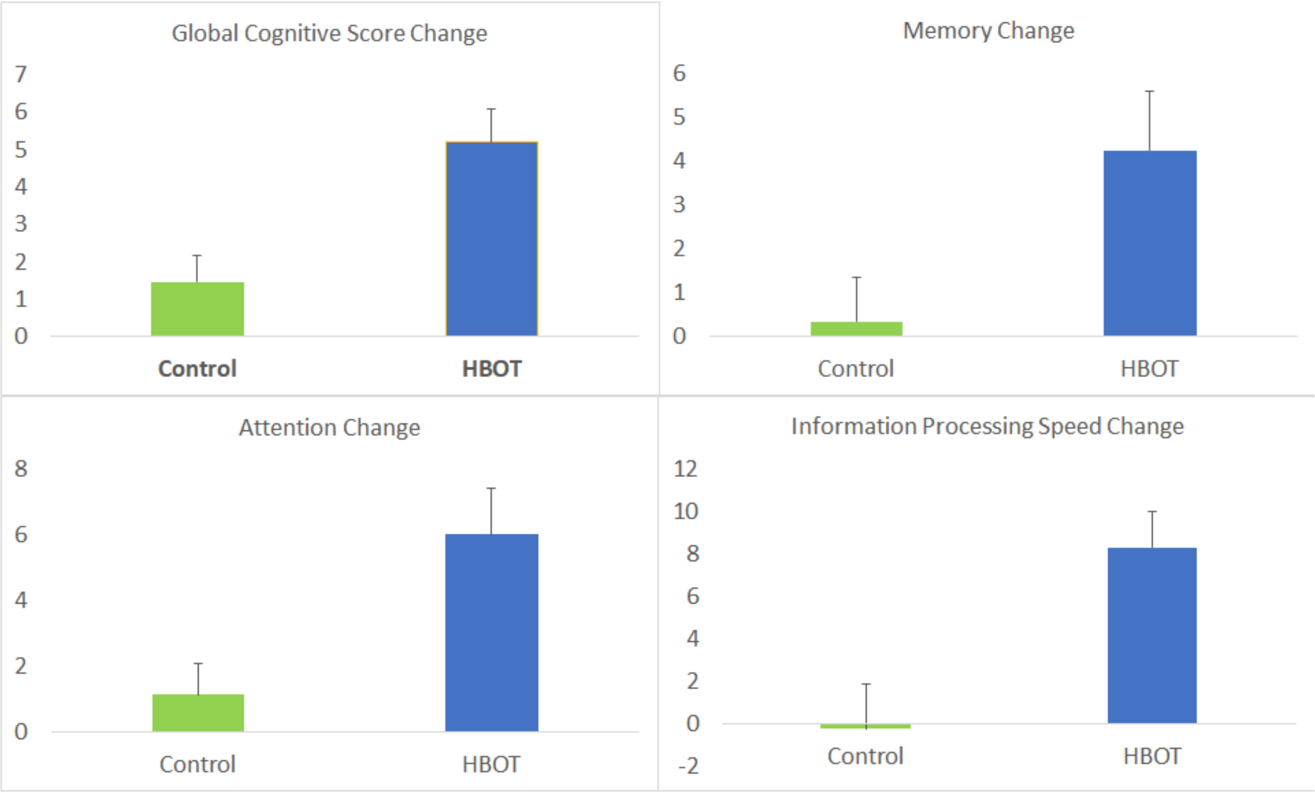
Post HBOT cognitive assessments show significant improvement in:

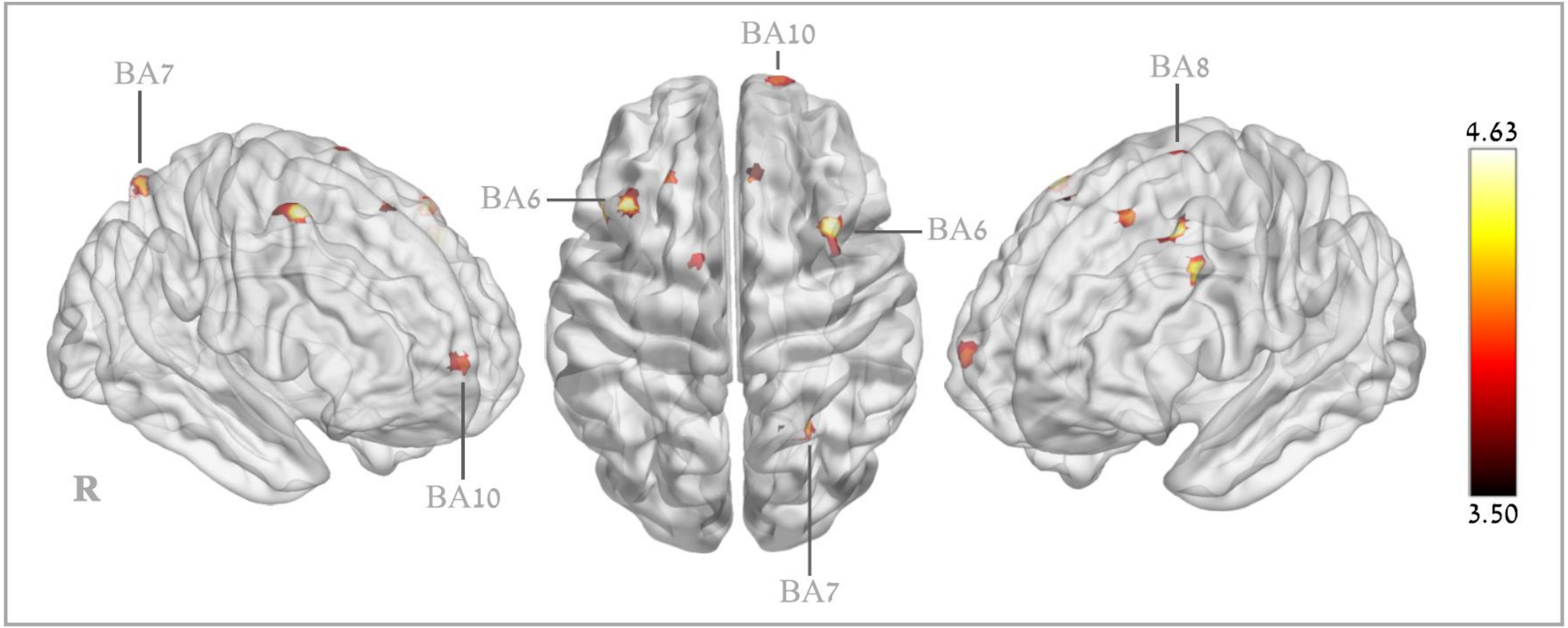
- Attention
- Memory
- Overall cognitive function

Reverse Aging Program Target Population

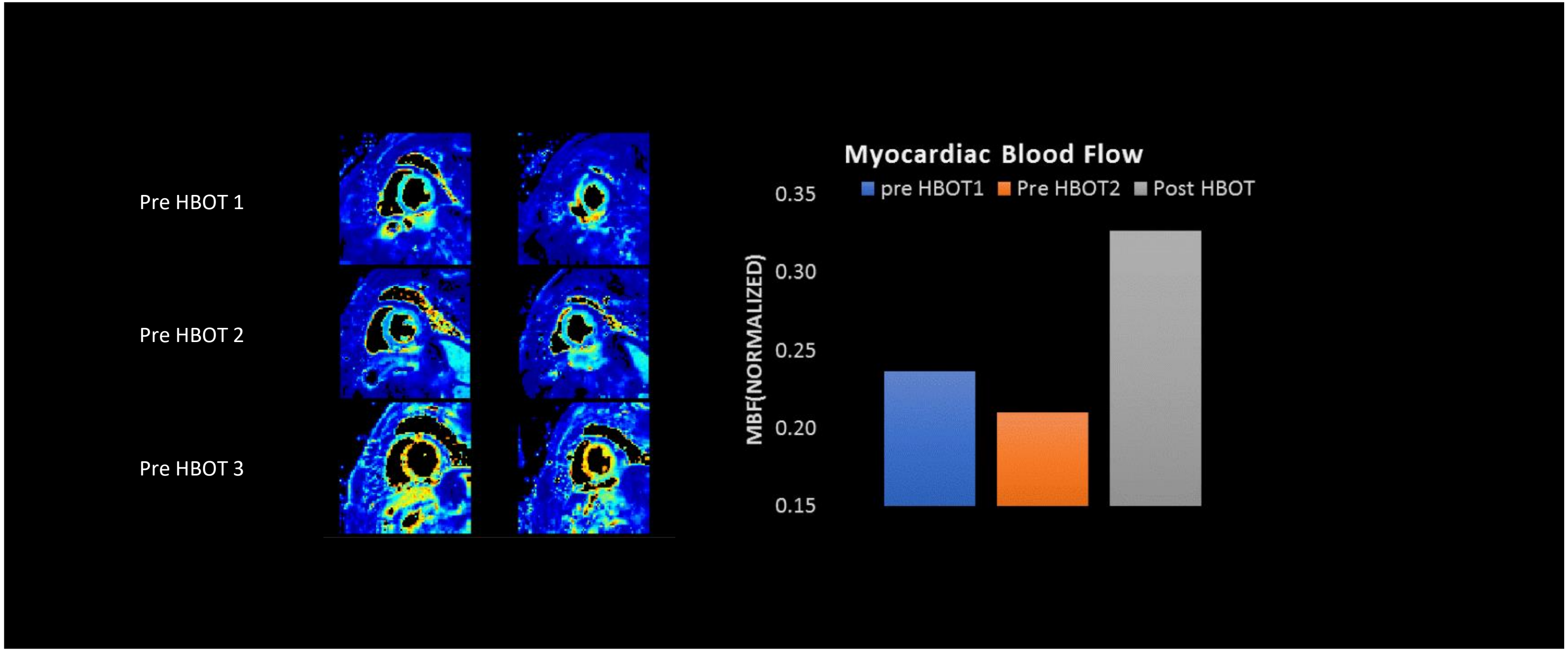
Age 65 years or older
Medically stable population
Fully function in their daily life activity
Non- obese
Nonsmokers

Cognitive Functions - Reverse Ageing Population




BA7
BA10
BA8
BA6
BA6
BA10
BA7
R
4.63
3.50

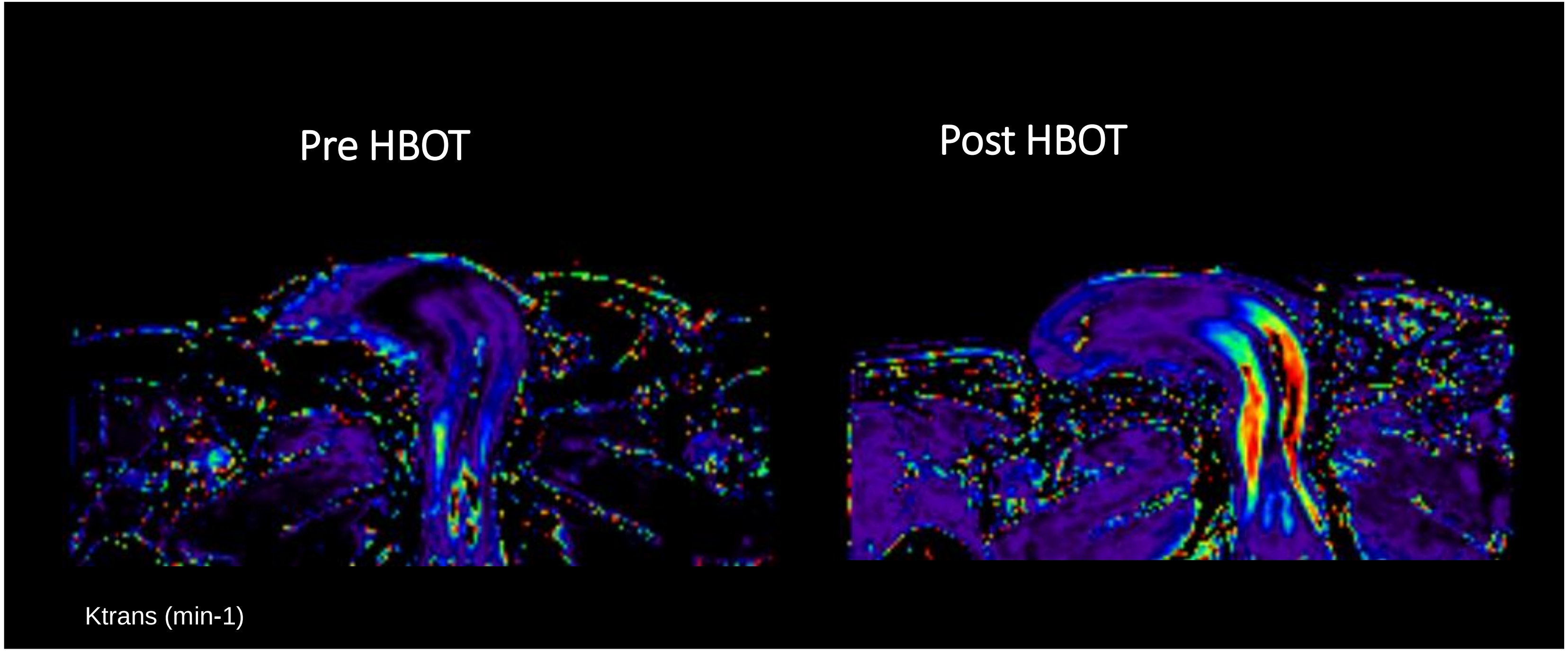
Cardiac MRI – Myocardial Blood Flow



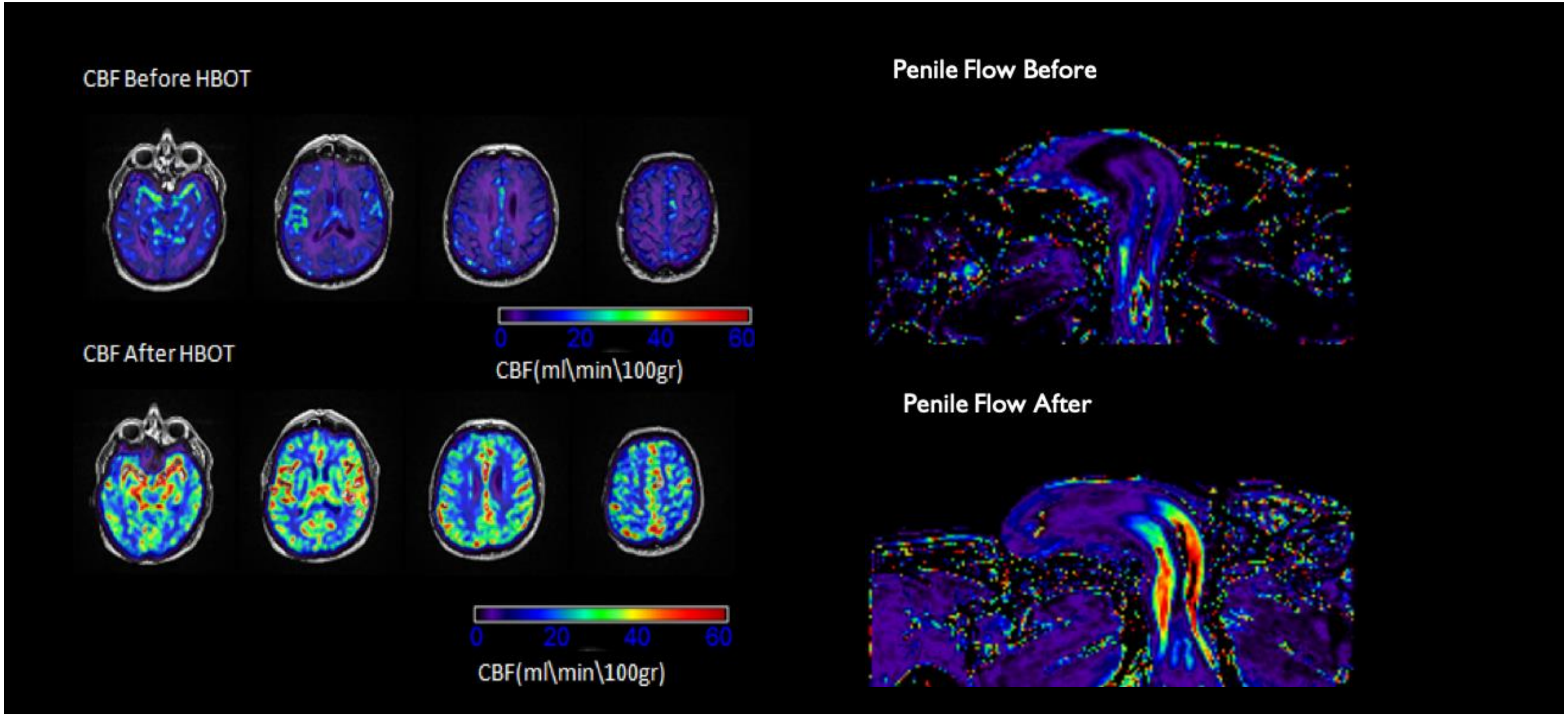
Cardio-Pulmonary Exercise Test (VO2 max test)

15% improvement in the
Anaerobic Threshold (AT)

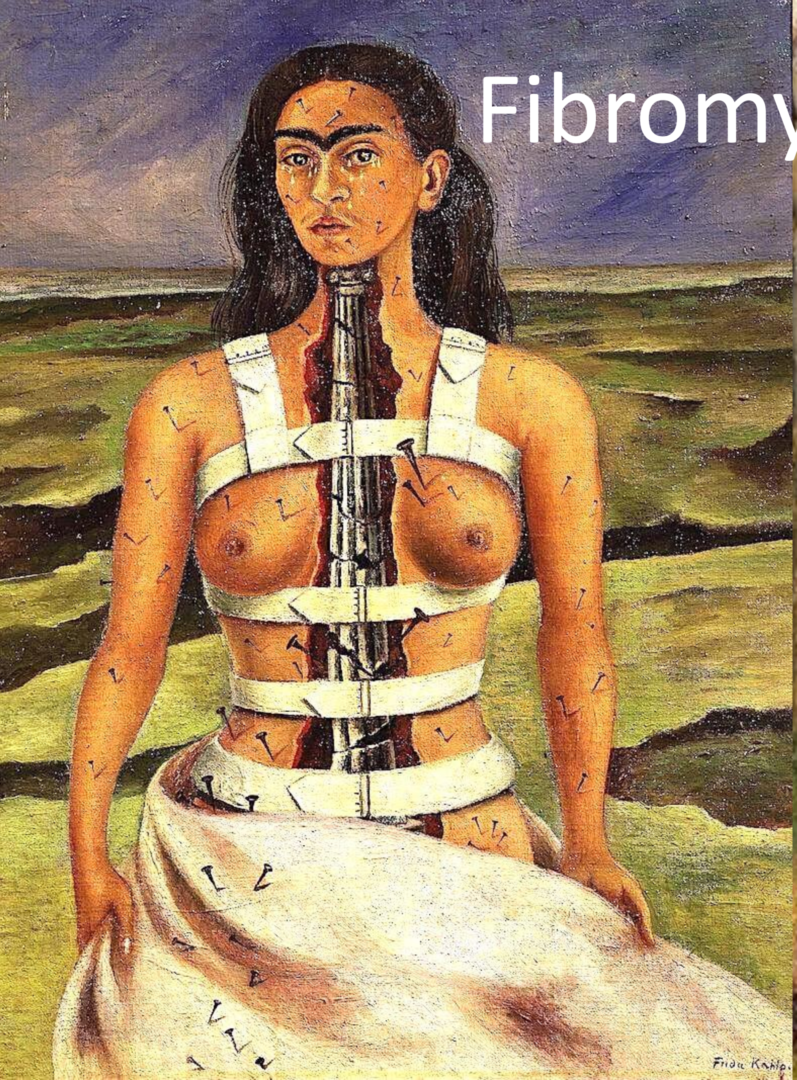
The Penile



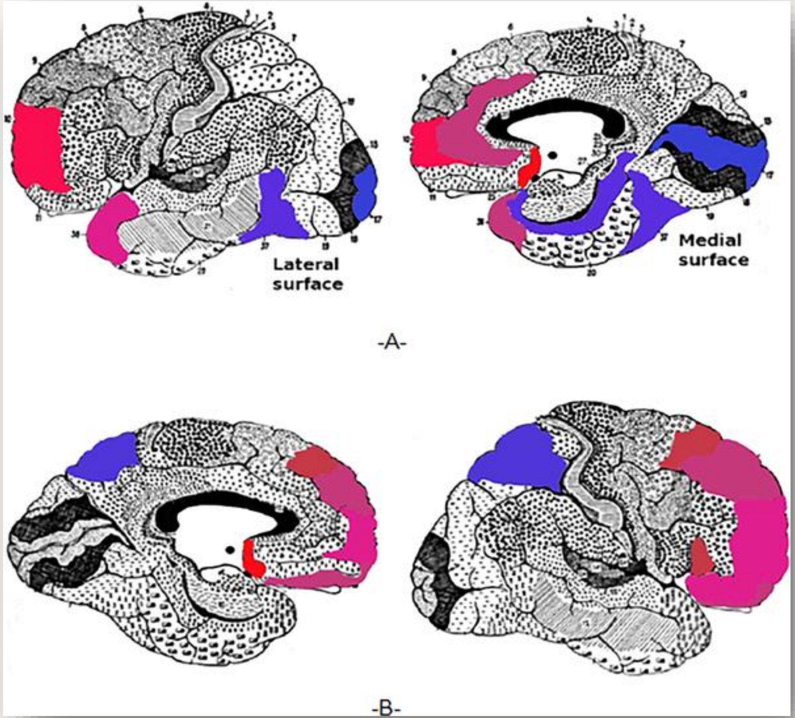
78 Years Old Male Pre and Post Hyperbaric Oxygen Therapy

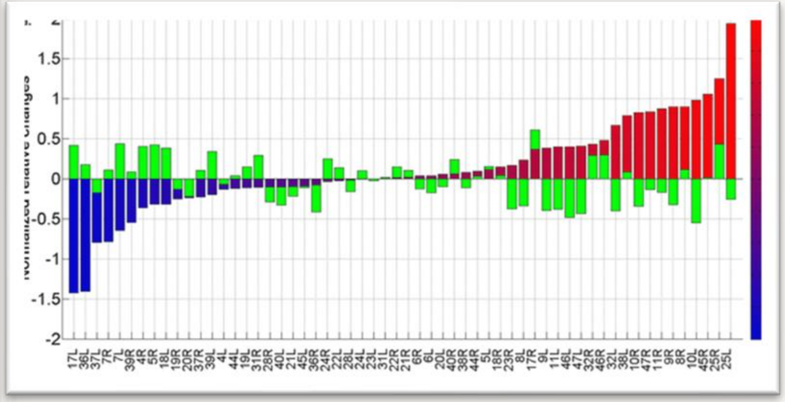


Fibromyalgia

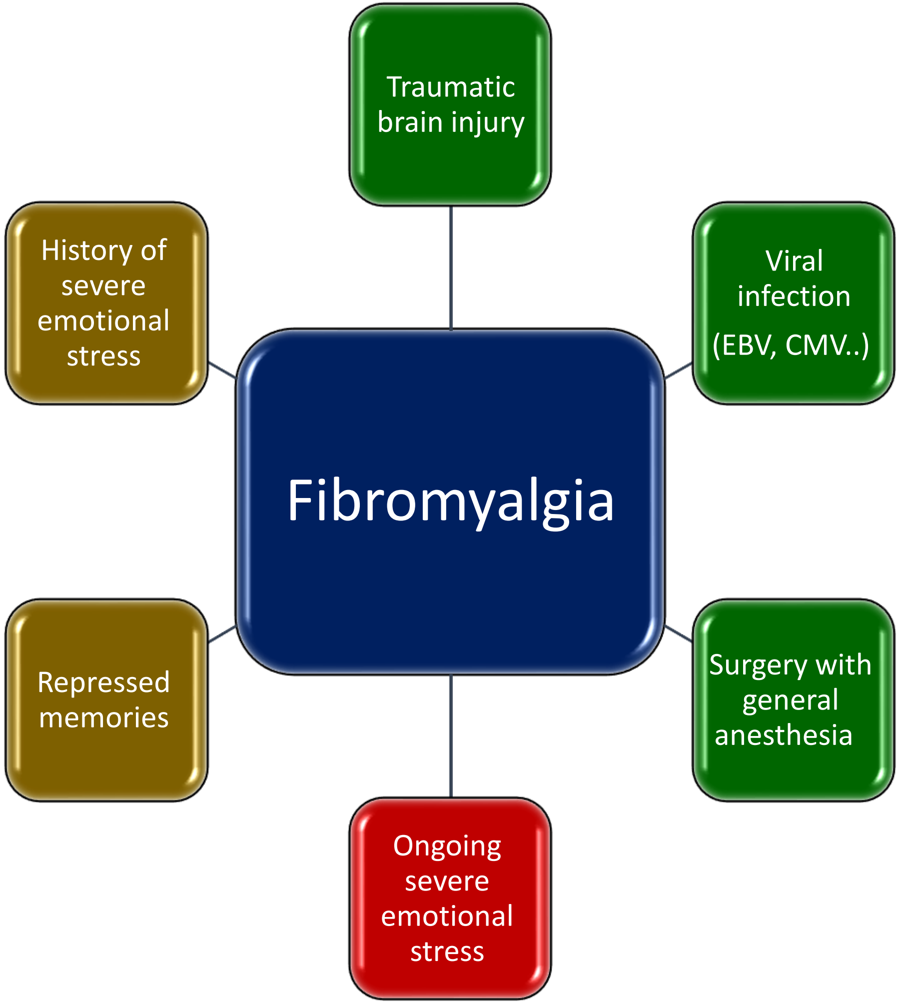


FRIDA KAHLO





PLSo One. 2015


Traumatic brain injury
History of severe emotional stress
Viral infection
(EBV, CMV..)
Fibromyalgia
Repressed memories
Surgery with general anesthesia
Ongoing severe emotional stress

A drawing made by a 53-years-old participant, who had been sexually abused by her father

Baseline

Phase II of the treatment

End of the treatment

Frontiers in psychology 2018

A drawing drawn by a 32-years-old participant, who had been sexually abused during childhood by a family member

Baseline

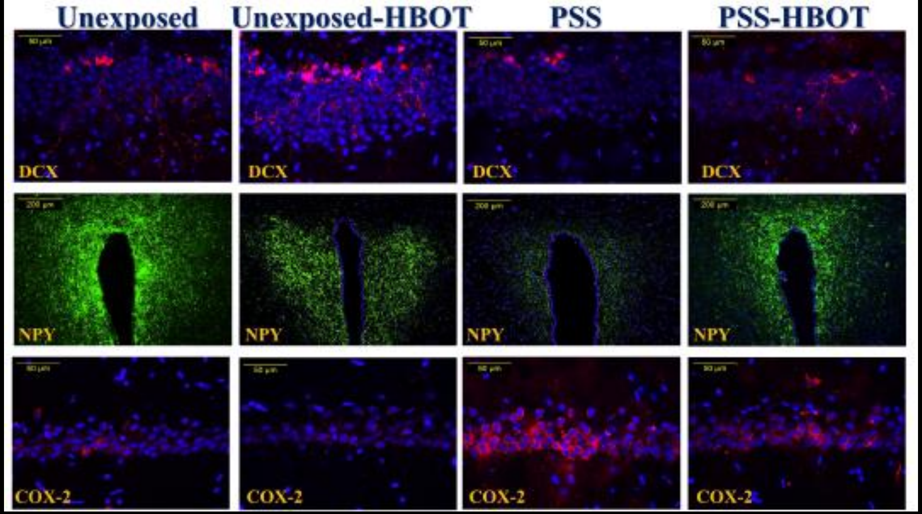
Phase II of the treatment

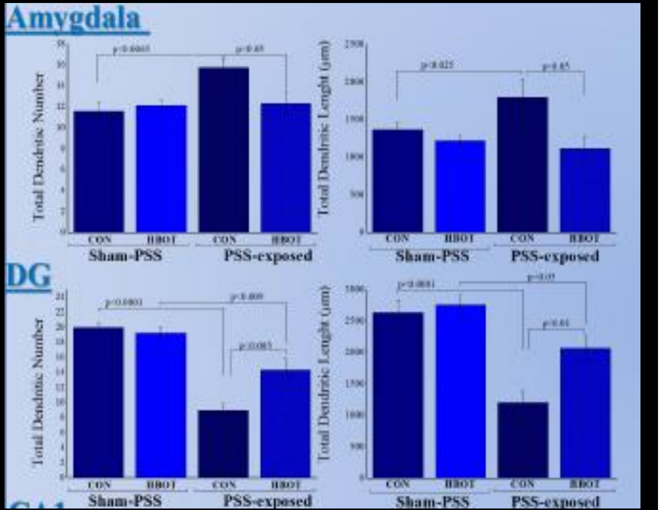
End of the treatment

Frontiers in psychology 2018

Post Traumatic Stress Disorder

Hyperbaric Oxygen Therapy as a potent treatment for Post Traumatic Stress Disorder in ad animal mode

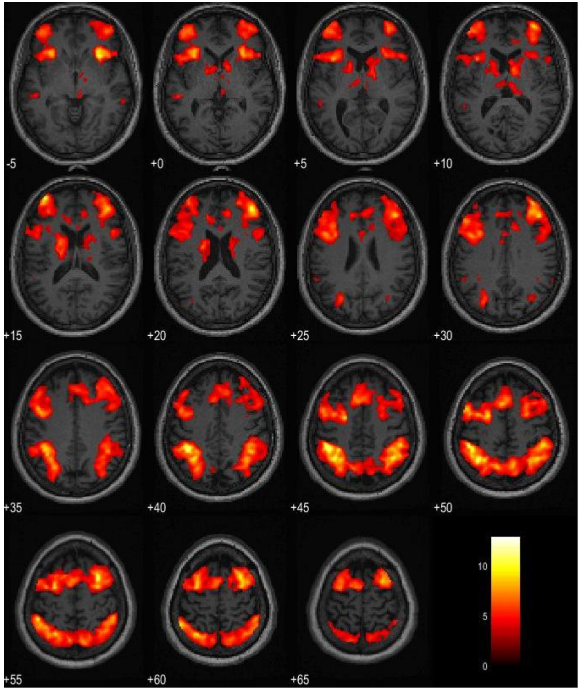




Hagit Cohen 2020

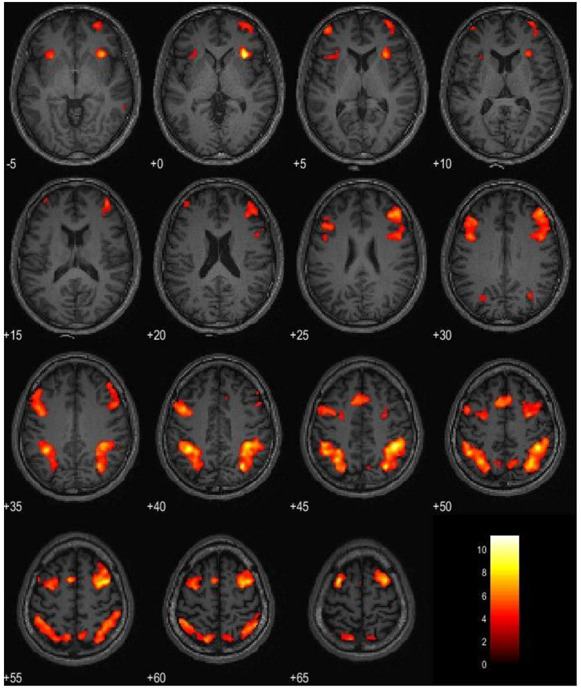
BOLD fMRI responses in a verbal working memory task

Healthy (244-16-ASF), M, N=23



N = 23; Mean Age 38.8 ± 9.5 [21.8.. 51.7]

PTSD, PRE-HBOT, M, N=30

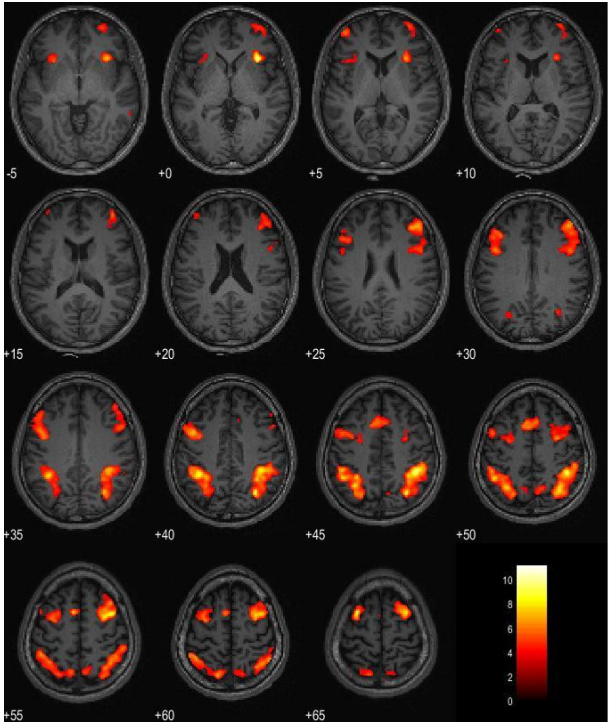


N = 30; Mean Age 37.5 ± 9.1 [24.5.. 58.9]

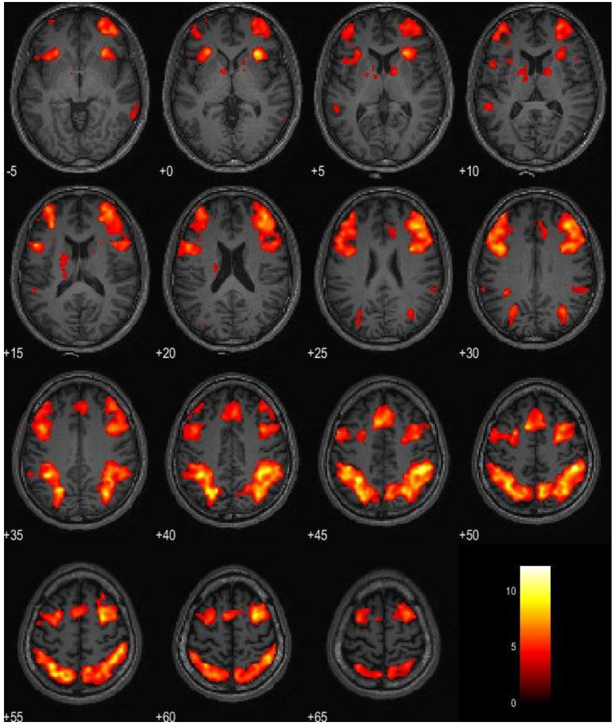
PloS One 2022

BOLD fMRI responses in a verbal working memory task

PTSD, mean PRE-HBOT



PTSD, mean POST-HBOT



PloS One 2022

Post COVID-19 Condition

(Long COVID)

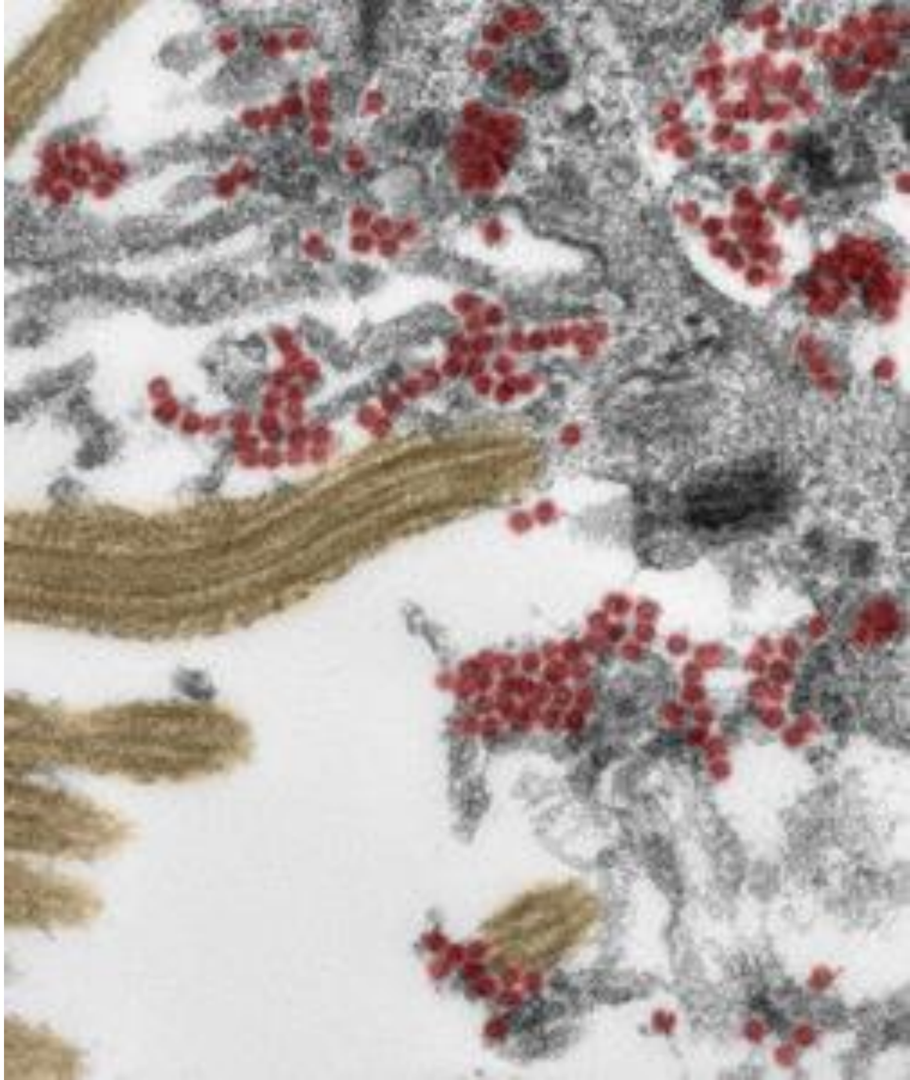
SHAMIR MEDICAL CENTER

Sagol School of Neuroscience
Tel Aviv University

An electron microscope image (ultrathin section, artificially colored) shows a section of a ciliated cell in the olfactory mucosa.

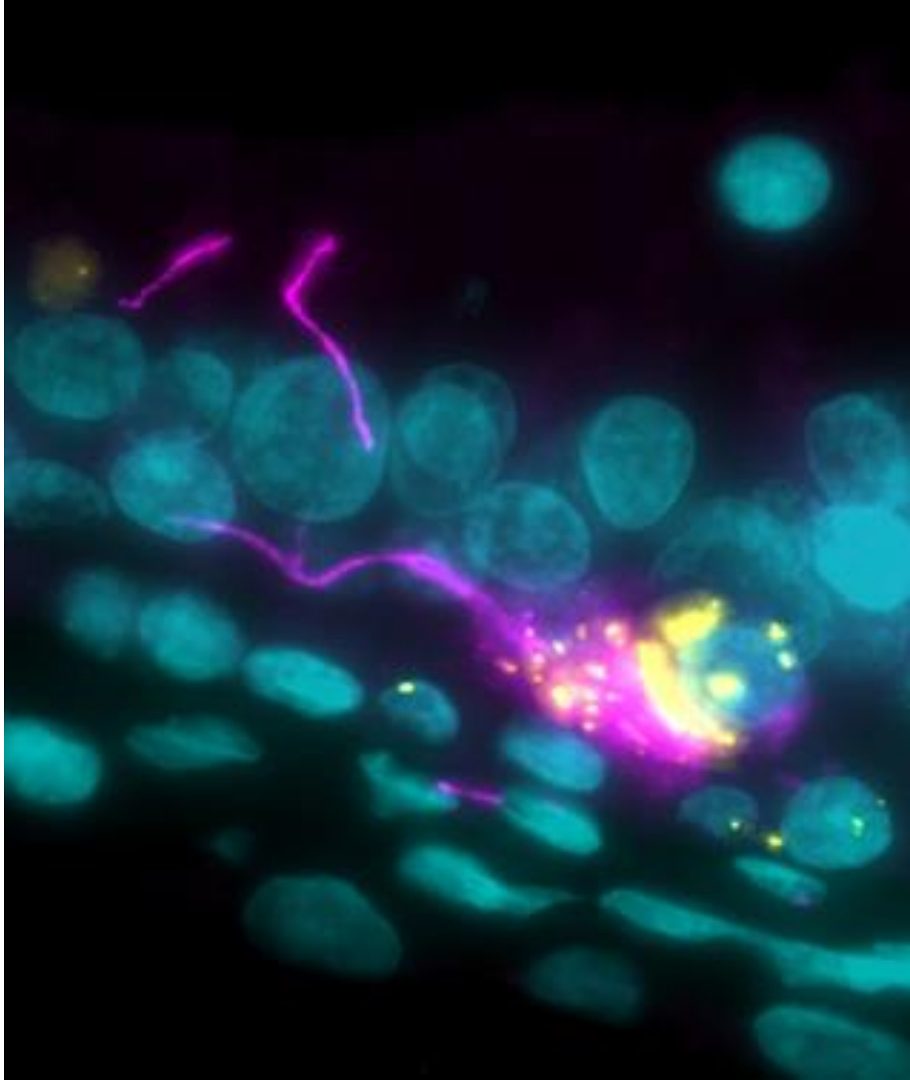
Large numbers of intact SARS-CoV-2 particles (red) are found both inside the cell and on cellular processes. Yellow: kinocilia.

Photo: Michael Laue/RKI & Carsten Dittmayer/Charité



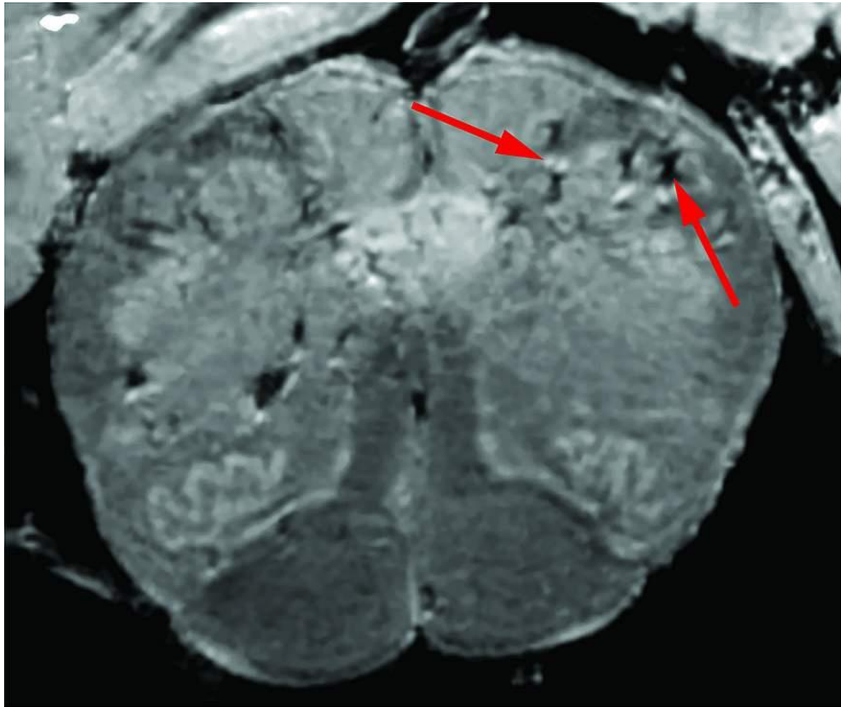
Immunofluorescence staining shows a nerve cell (pink) inside the olfactory mucosa which has been infected with SARS-CoV-2 (yellow). Supporting (epithelial) cells appear blue.

Photo: Jonas Franz/Universitätsmedizin Göttingen

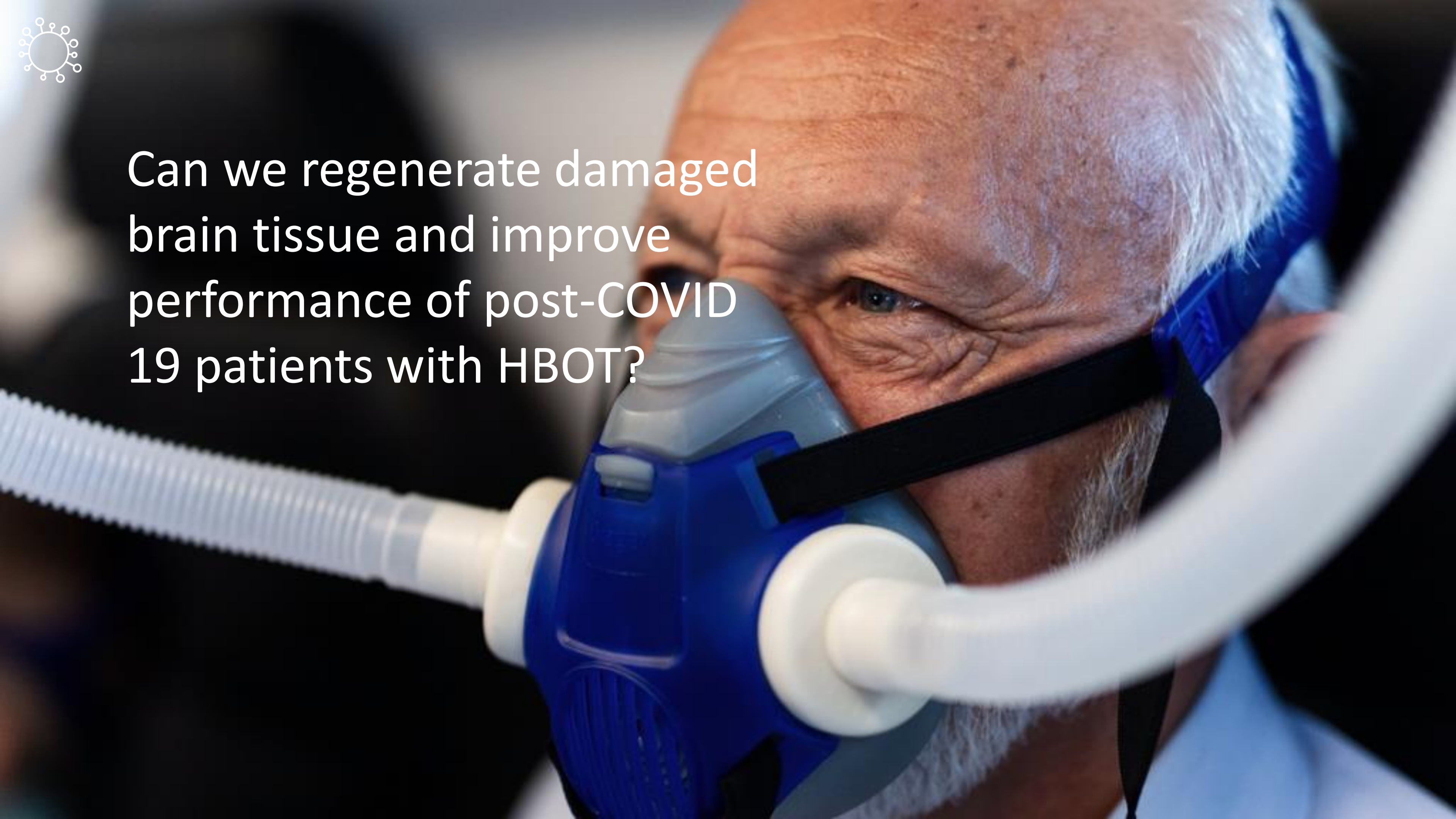


Blood Vessels

NIH researchers consistently found blood vessel damage in the brains of COVID-19 patients but no signs of SARS-CoV-2 infections. Arrows point to light and dark spots that are indicative of blood vessel damage observed in the study.



Can we regenerate damaged brain tissue and improve performance of post-COVID 19 patients with HBOT?

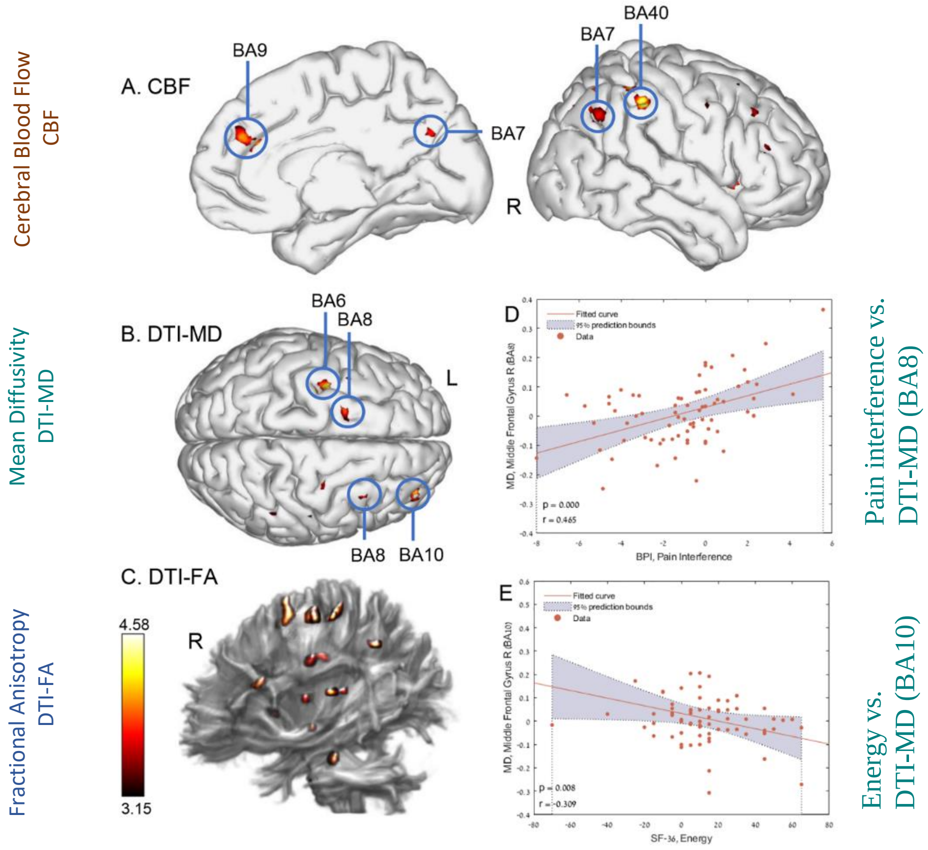


	HBOT				CONTROL				ANOVA (Group-by-Time) Interaction			
	PRE	**POST**	**Two months P-value**	**CHANGE**	**PRE**	**POST**	**Two months P-value**	**CHANGE**	**P-value Baseline**	**Net effect size***	**F**	**P-value**
N	37				36							
Global Score	98.3±11.1	104.1±7.2	**0.0001**	5.8±7.9	98.9±8.5	101.3±8.9	0.0105	2.4±5.4	0.821	0.495	4.469	0.038
Memory	93.7±13.4	102.0±10.9	**0.0001**	8.3±11.2	94.9±12.2	102.1±8.7	**0.0000**	7.2±8.5	0.695	0.111	0.226	0.636
Executive Function	103.5±13.1	109.0±8.2	**0.0029**	5.6±10.6	102.5±10.3	103.8±10.5	0.2526	1.3±6.8	0.725	0.477	4.159	0.045
Attention	97.3±16.0	101.9±9.0	0.0292	4.6±12.4	99.6±8.2	99.4±10.1	0.8495	-0.3±8.3	0.434	0.463	3.914	0.052
Information Processing Speed	94.8±14.2	102.4±13.0	**0.0003**	7.6±11.4	94.4±14.2	98.3±17.7	0.0734	3.9±12.7	0.910	0.303	1.673	0.200
Motor Skills	102.4±12.6	105.3±8.3	0.0827	2.9±10.0	102.9±8.4	102.9±9.0	0.9639	0.1±6.7	0.858	0.338	2.079	0.154

Data are presented as mean ± SD; Bold, significant after Bonferroni correction;
* Cohen's d net effect size

Sci Rep. 2022

Brain Regions with Significant post-HBOT Changes Compared to Control



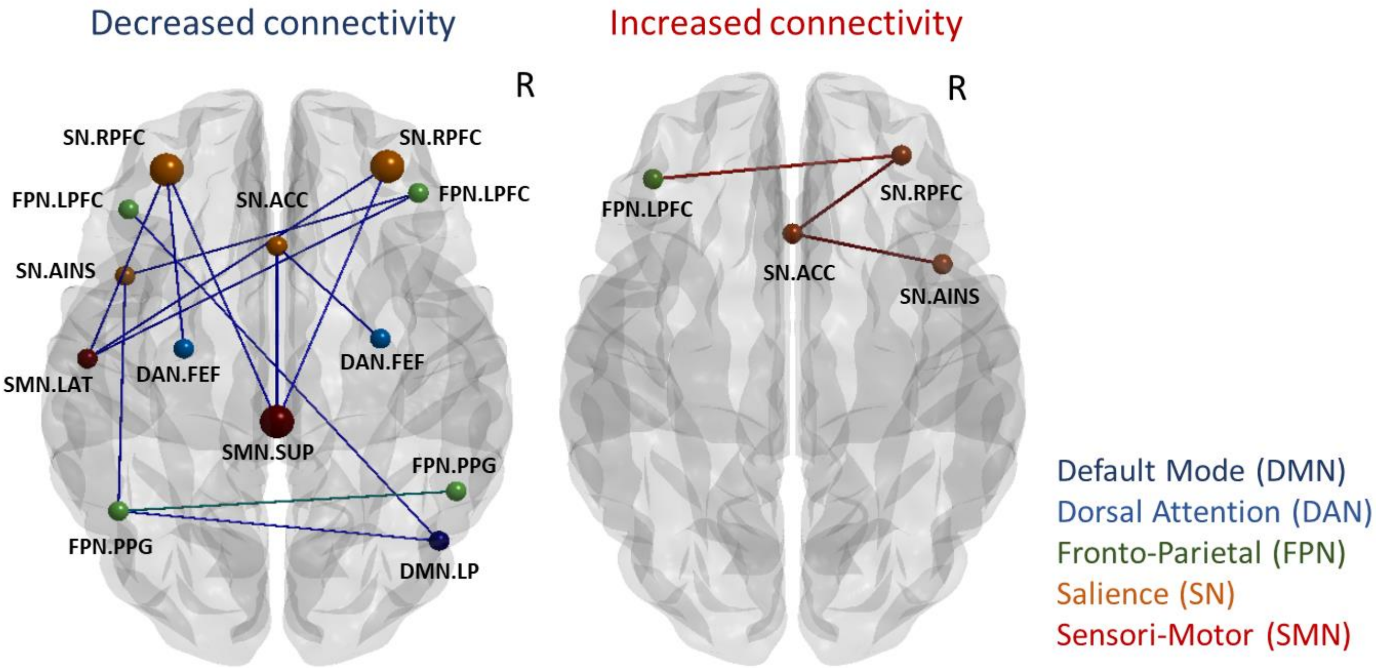
Group-by-time interaction ANOVA model

Anatomical location	BA	P value
CBF (GM)		
Supramarginal Gyrus R (Parietal)	40	0.000008*
Superior Parietal Lobule R (Parietal)	7	0.000008*
Parahippocampal Gyrus L		0.000009*
Insula R	13	0.000012*
Supplementary Motor Area L (Frontal)	6	0.000013*
Anterior Cingulate Gyrus\ Medial Superior Frontal Gyrus L	10/32	0.000026*
Anterior Cingulate Gyrus\ Dorsal Prefrontal R	32/9	0.000037
Putamen R		0.000039
Hippocampus L		0.000137
DTI-MD (GM)		
Frontal Precentral Gyrus L	6	0.000005*
Middle Frontal Gyrus R	10	0.000013*
Middle Frontal Gyrus R	8	0.000052*
DTI-FA (WM)		
Superior Corona Radiata R (Frontal)		0.00006*
Superior Corona Radiata L (Frontal)		0.00006*
Superior Longitudinal Fasciculus L (Parietal)		0.00010

*significant after correction to multiple comparisons, p<0.05

Sci Rep. 2022

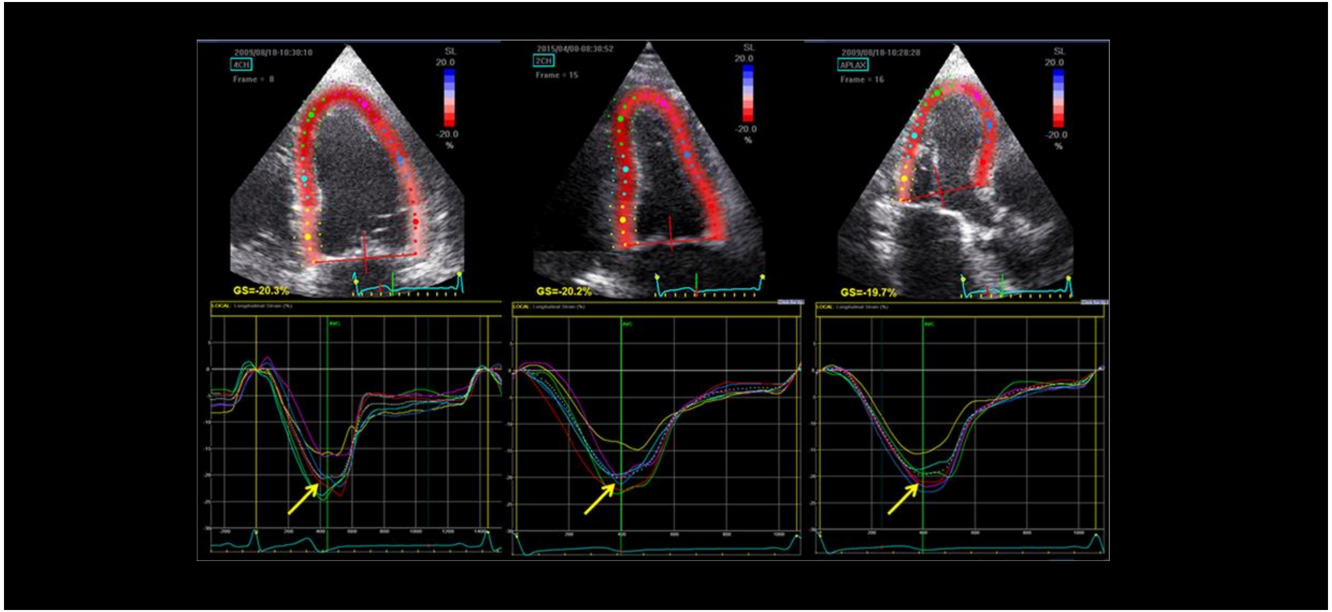
ROI-to-ROI network analysis longitudinal group differences



Changes in post-treatment functional connectivity in the HBOT group compared to controls. Node color - network, node size – significance (see Table 2). Edge color: blue, inter-network connectivity; green, intra-network connectivity. Brain images were created using BrainNet Viewer software

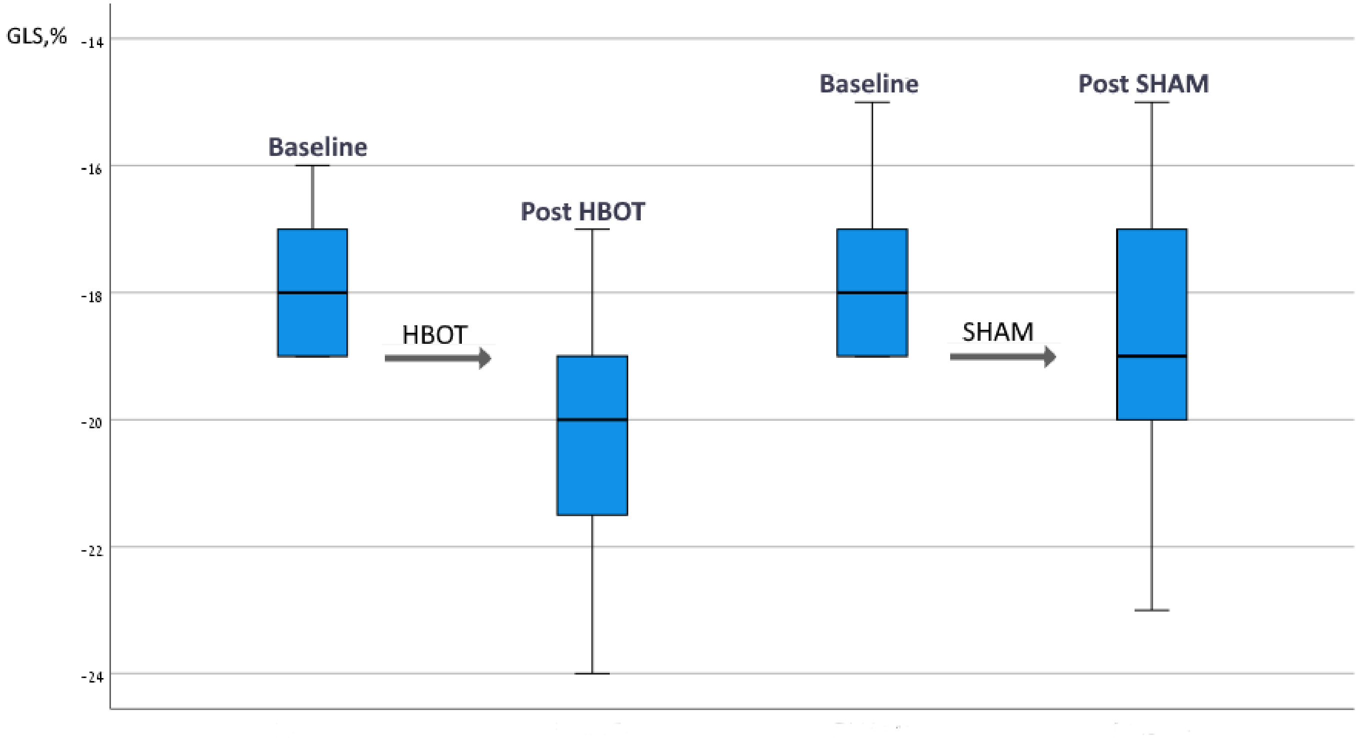
Neuroimage Clin. 2022

Cardiac functions - Global Longitudinal Strain (GLS)



Sci Rep. 2023

Global longitudinal strain in the group of patients with reduced strain at baseline



Sci Rep. 2023

The Hyperoxic-Hypoxic Paradox in regenerative medicine

- Trigger
- Stem cells
- Energy
  - Oxygen
  - Improve mitochondrial function
- Angiogenesis

Vs.

That is not HBOT and cannot deliver the Hyperoxic-Hypoxic Paradox

Thursday 11:00am – 12:00pm

The Hyperoxic-Hypoxic Paradox: Unraveling Its Potential in Regenerative Medicine

Please scan this QR code on you mobile

or tablet device to access the session feedback survey

The Hyperoxic-Hypoxic Paradox: Unraveli
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