

# **Augmentation of Cognitive Brain Functions with Transcranial Infrared Laser Stimulation**

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# Introduction to human TILS

- Brain cells are highly dependent on oxygen metabolism.
- **Transcranial infrared laser stimulation (TILS)** at **1064 nm wavelength** is a form of photoneuromodulation that we have successfully developed to **augment cerebrovascular oxygenation** and thereby improve human cognitive functions.
- The molecular target of TILS is the respiratory enzyme **cytochrome oxidase** in the mitochondrial electron transport chain, which reduces oxygen to water during oxidative phosphorylation to produce metabolic energy.
- Safe and non-invasive TILS uses low power ( $\text{mW}/\text{cm}^2$ ) and high fluence ( $\text{J}/\text{cm}^2$ ) laser at 1064 nm wavelength that has estimated penetration of 3-4 cm into the cerebral cortex.

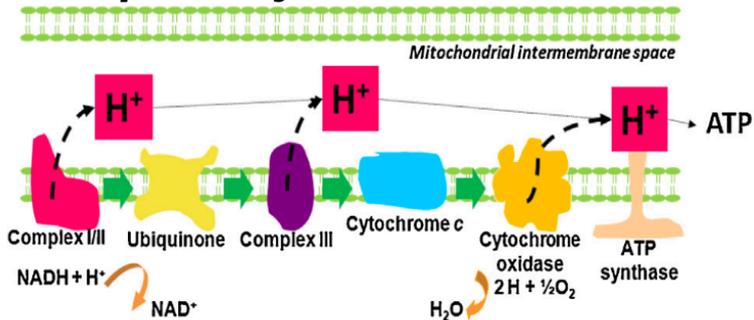
# Central Thesis

**Transcranial infrared laser stimulation (TILS)**  
of the human prefrontal cortex can augment cerebral oxidized cytochrome oxidase and cerebrovascular oxygenation as a new photoneuromodulatory approach to improve neurocognitive functions

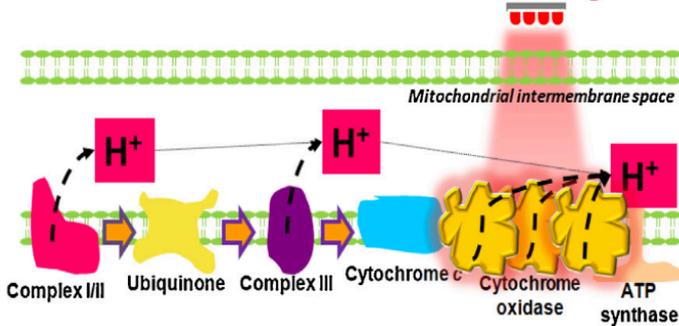
**Infrared Photons → Oxidized Cytochrome Oxidase  
→ Cerebral Oxygenation → Cognitive Enhancement  
and Neuroprotection**

# Molecular effects: Cytochrome c Oxidase (CCO)

## Respiratory Chain



Low-level light

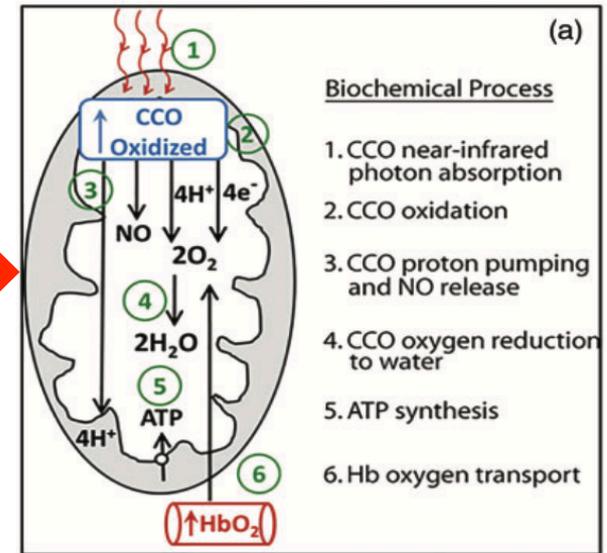


J.C. Rojas & F. Gonzalez-Lima, 2013

## Primary Effects

TILS accelerates CCO catalytic activity:

- Increases rate of  $\text{O}_2$  consumption catalyzing formation of  $\text{H}_2\text{O}$
- Produces NO
- Increases ATP production

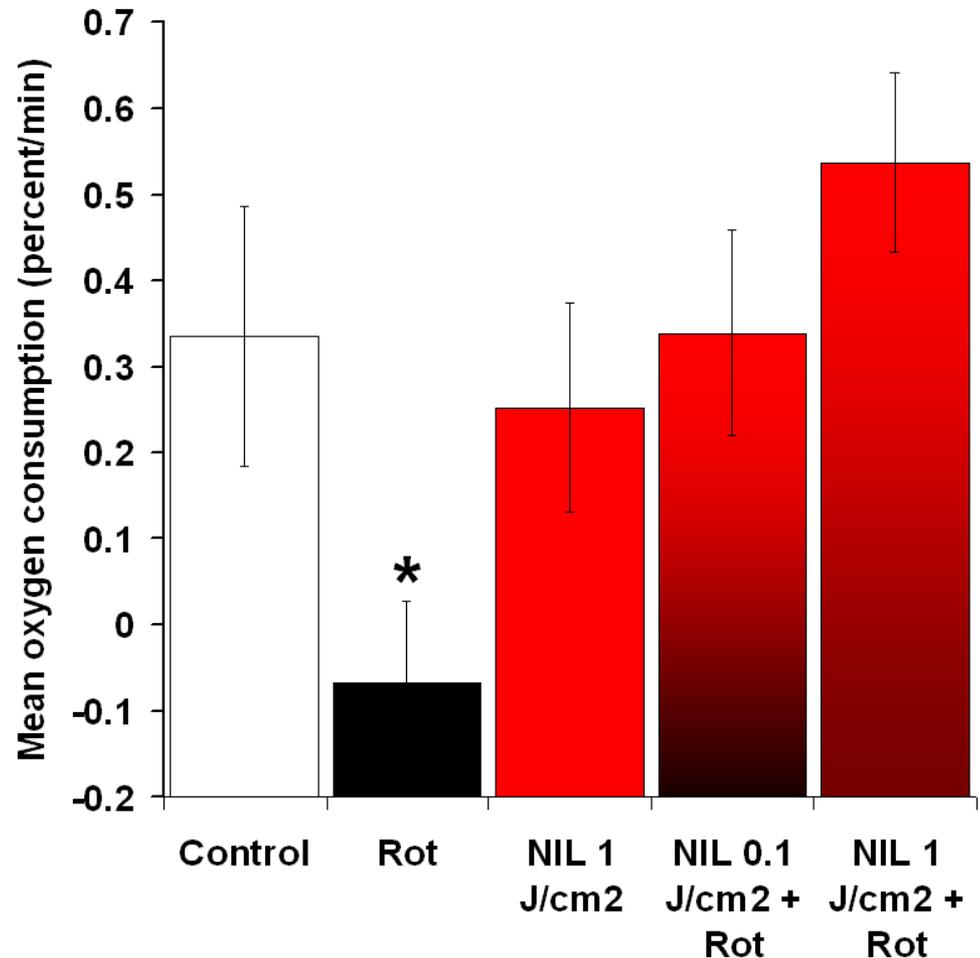


X. Wang et al., 2017

# Near Infrared Light Mechanism of Action

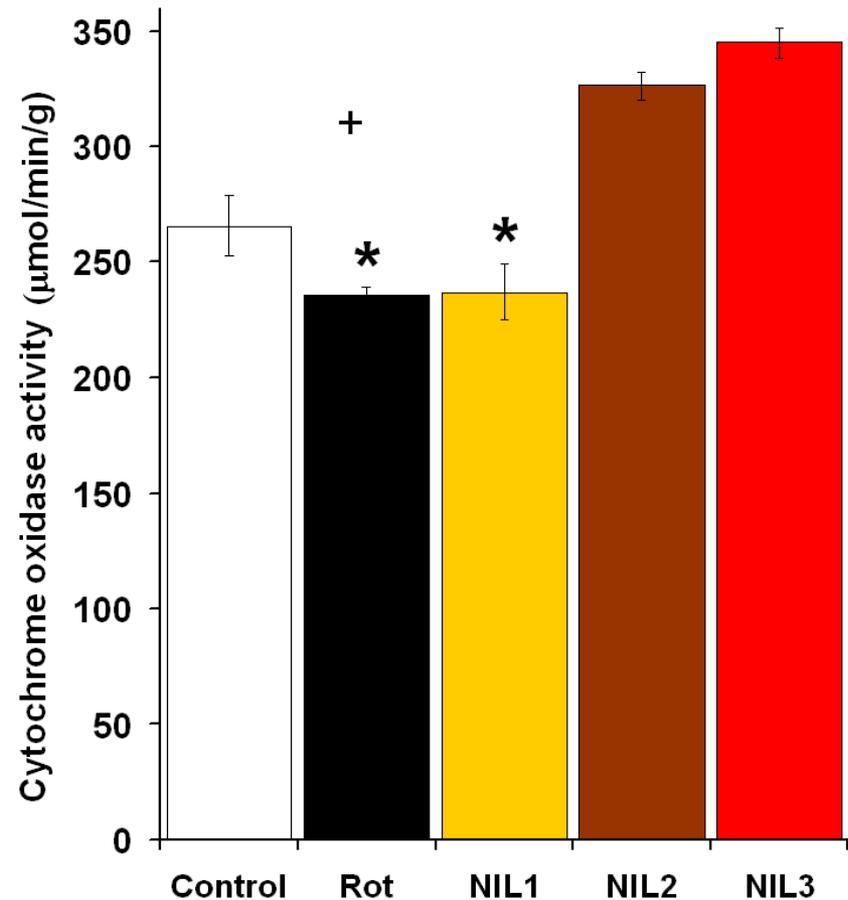
## ➤ Does NIL directly improve cell respiration?

- *In vitro* oxygen consumption in whole-brain homogenates, as calculated by changes in partial pressure of oxygen measured by dynamic fluorescence quenching.

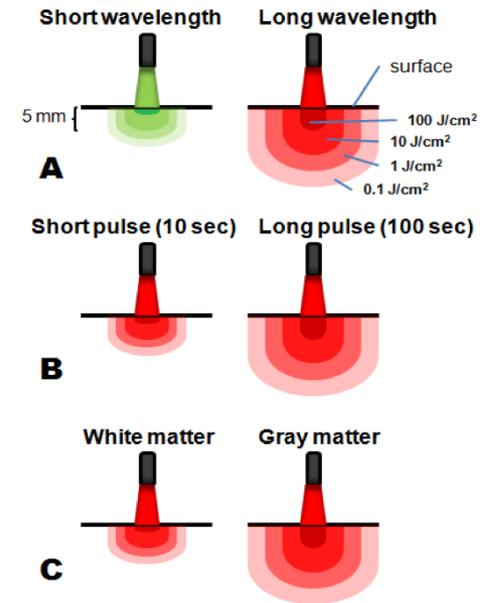
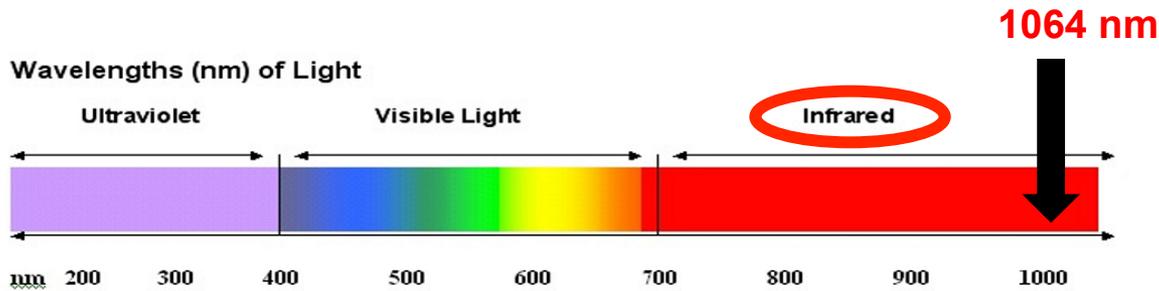


# Neuroprotective Metabolic Action

- Does NIL enhance the overall brain energy metabolism capacity?
  - *In situ* whole-brain cytochrome oxidase activity measures



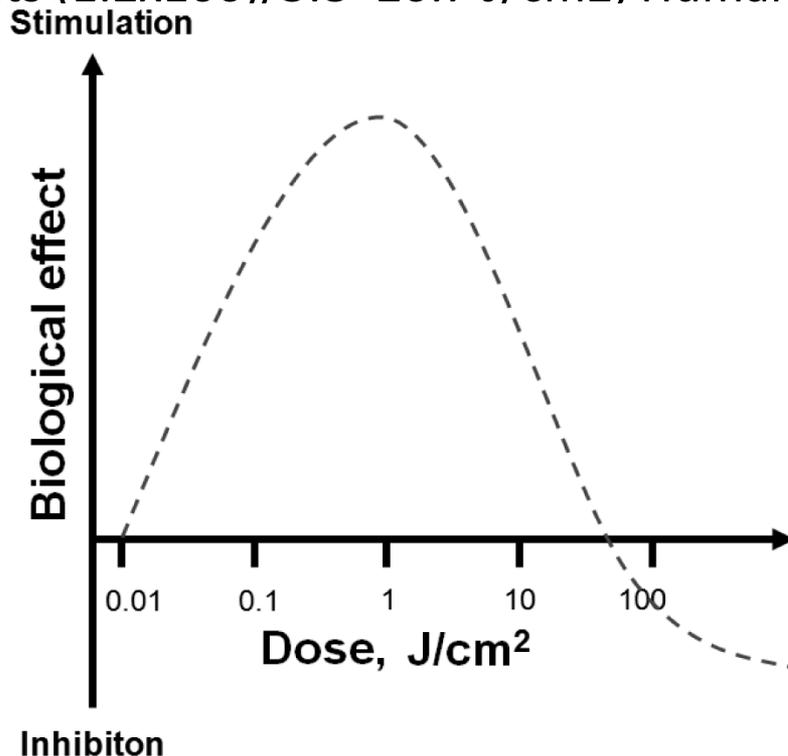
# Transcranial Infrared Laser Stimulation (TILS)



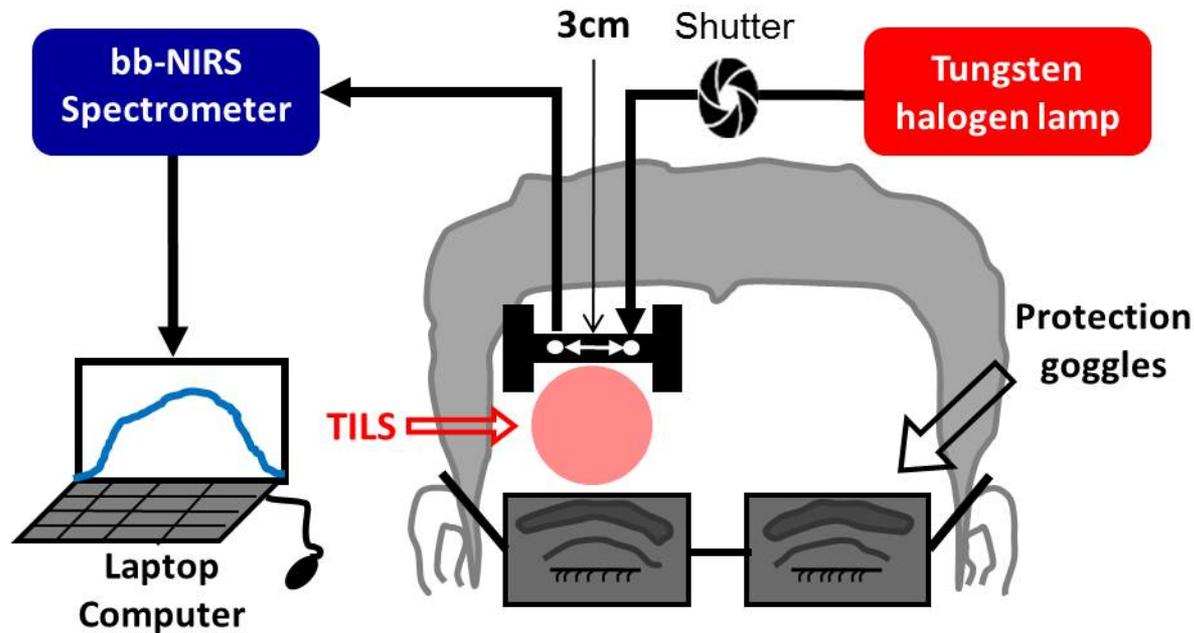
Julio C. Rojas, F. Gonzalez-Lima, 2011

# Hormetic dose-response

- Inverted U-shaped, biphasic or bell-shaped curve: *in vitro* near infrared photonic stimulation of brain cytochrome oxidase activity with low (0.01 – 10 J/cm<sup>2</sup>) and inhibition with high (> 10 J/cm<sup>2</sup>) energy densities, with **peak at 1.2 J/cm<sup>2</sup>**
- **Transcranial 1064 nm transmission 5.8% rats (21x), 2% humans (60x)**
- Calculation: Rats  $(1.2 \times 100) / 5.8 = 20.7$  J/cm<sup>2</sup>; Humans  $(1.2 \times 100) / 2 = 60$  J/cm<sup>2</sup>



# Measurement of TILS effect on CCO by broadband near infrared spectroscopy (bbNIRS)

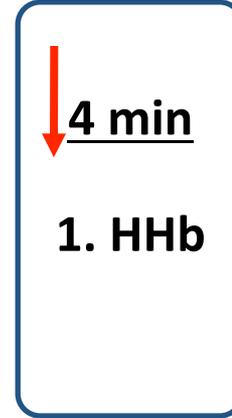
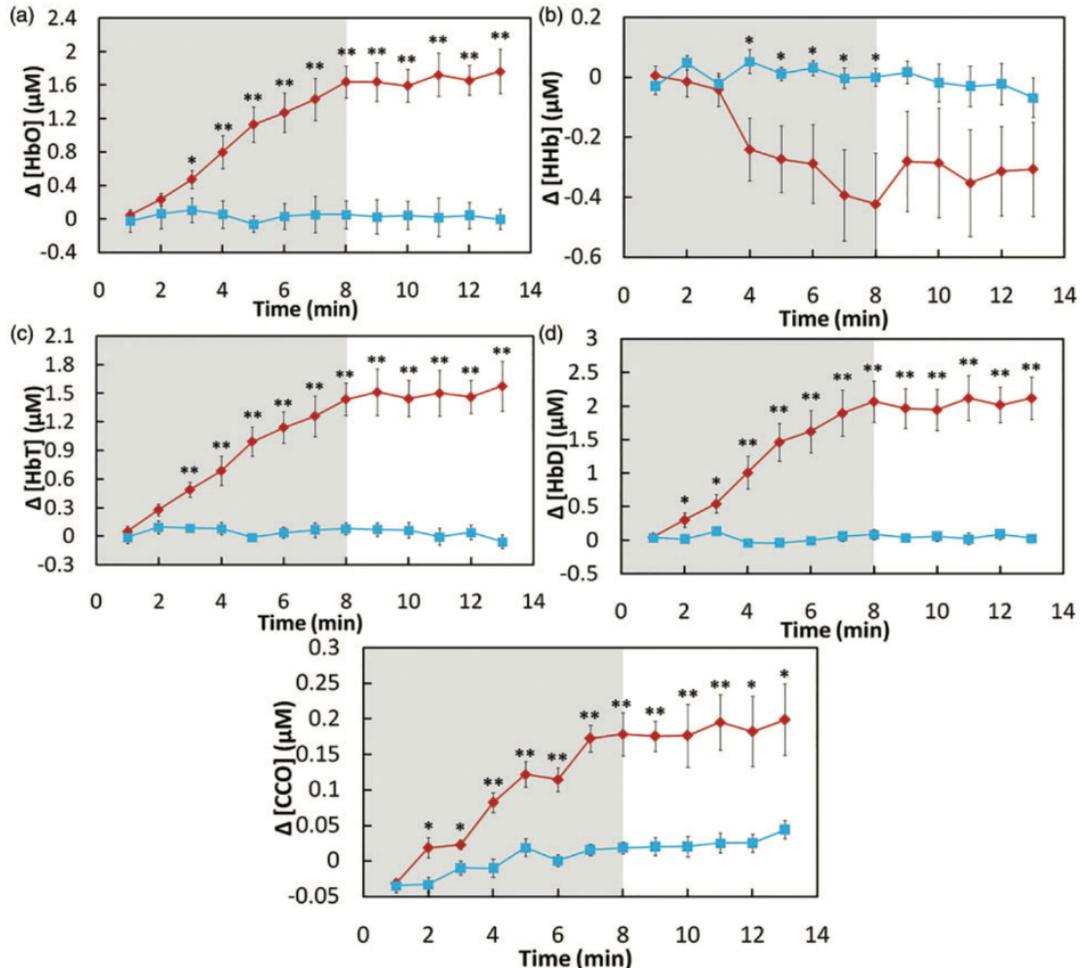


X. Wang et al., 2017

# Human brain effects measured with bb-NIRS

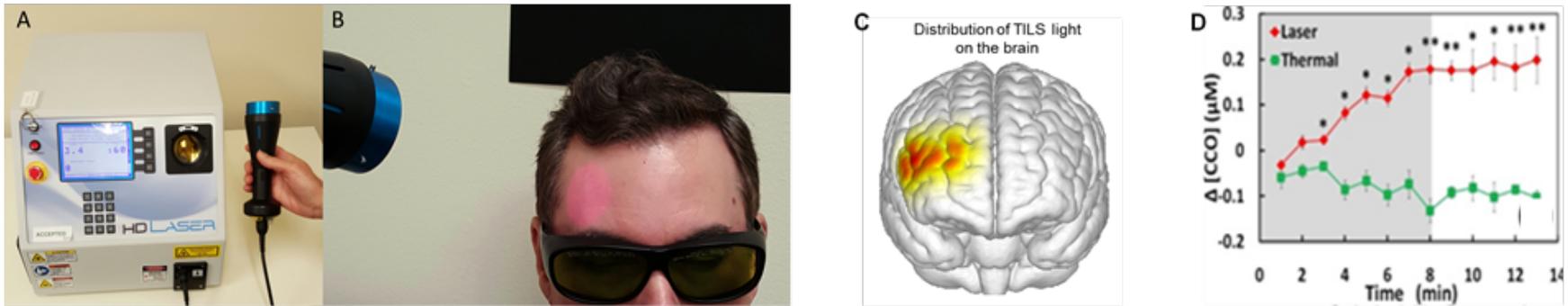
## *Prefrontal TILS-induced Cytochrome Oxidase & Hemodynamic Changes in Humans*

Red = TILS    Blue = Sham Placebo



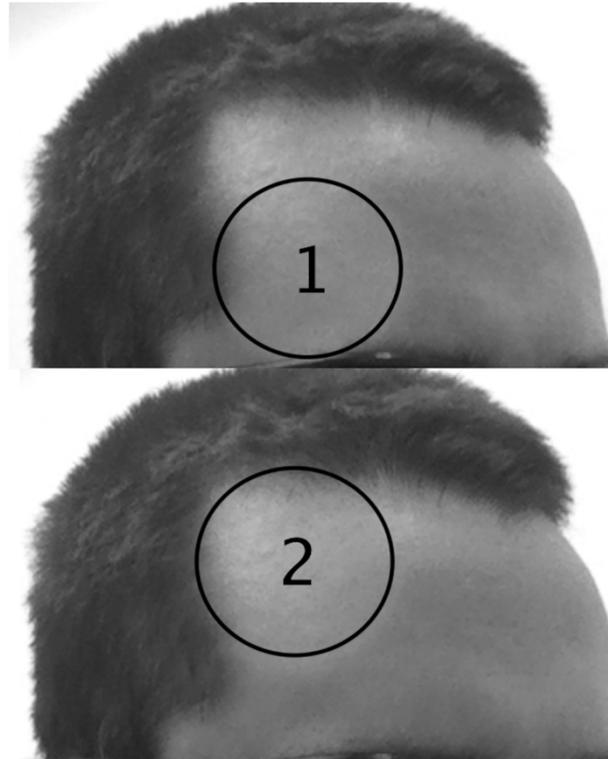
X. Wang et al., 2017

# TILS system and prefrontal cortex target

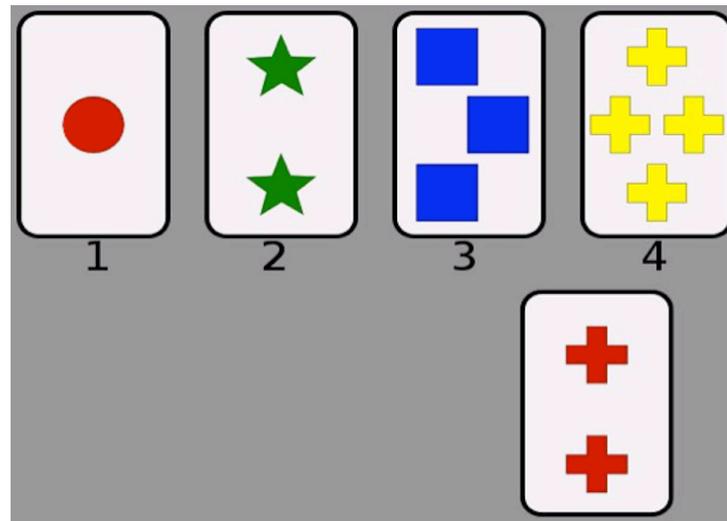


- A. Laser device.** The FDA-cleared Class IV laser device (HD Laser, Cell Gen Therapeutics, Dallas, Texas) consists of a control unit (16"x14"x13") with a fiber optic cable coupled to a handpiece.
- B. Laser delivery.** For illustration purposes, the largest laser aperture aims at the PI's forehead using an internal red diode aiming light. The laser aperture can be adjusted to a desired spot size from 1 to 45 mm diameter. We used a 4-cm diameter laser beam size to match the size of the **prefrontal cortex (PFC)** area we aim to stimulate.
- C. Cortical target.** Model of intensity distribution of treatment light on the right PFC (orange indicates effective light intensity).
- D. Molecular target.** Oxidized [CCO] increases during laser (red; n=11) but not thermal (green; n=11) stimulation measured *in vivo* by bbNIRS. "\*" p<0.05 and "\*\*\*"p<0.01 laser vs. thermal stimulation (mean  $\pm$  SE). Wang et al, *Neurophotonics* 5(1), 011004, 2018.

# Lateral prefrontal stimulation to target executive functions

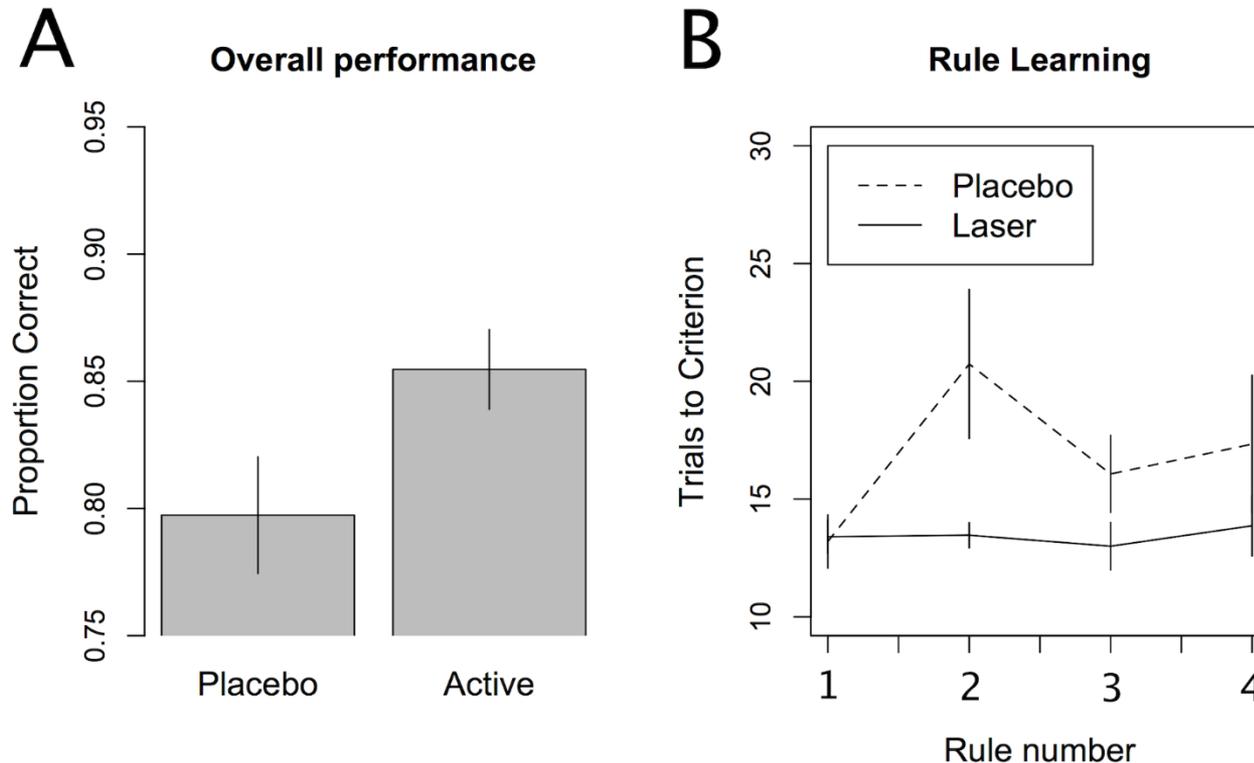


# Wisconsin Card Sorting Task



Gold-standard neuropsychological measure of executive function

# Laser-enhanced executive functions



- A. Overall WCST accuracy.** The laser group correctly sorted the cards more often than the placebo group.
- B. Trials to criterion for each of the first four rules learned.** The placebo group (n=15) took significantly longer to reach criterion on the second rule than the laser group (n=15), suggesting a benefit in set shifting ability in the laser group.

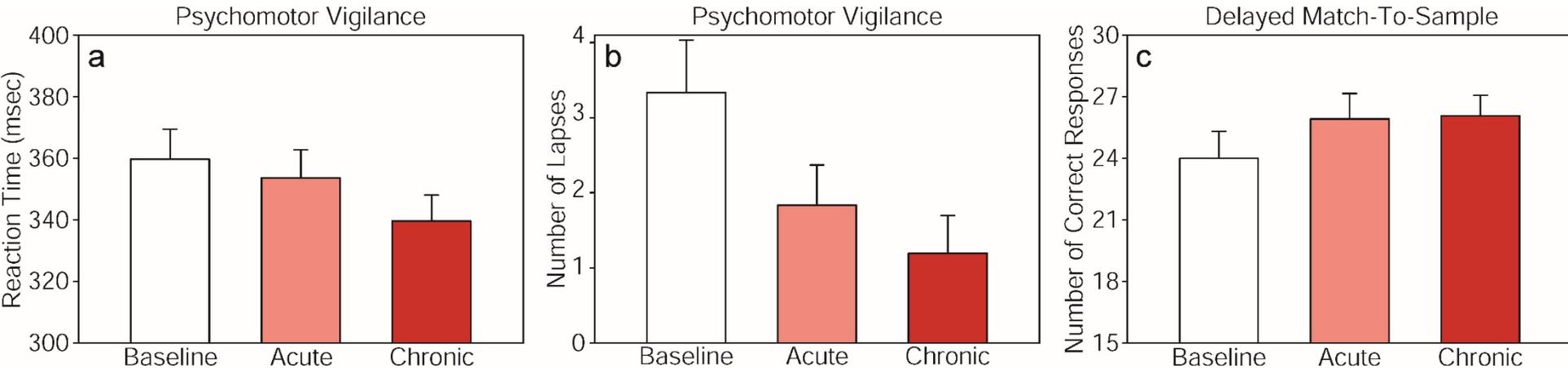
# Attention and memory in older adults

- **Hypothesis:** Transcranial infrared laser stimulation would produce beneficial effects on prefrontal cortex measures of attention and memory in individuals **49-90 years old** with subjective memory complaint (N = 12).
- **Treatment:** transcranial laser protocol to right forehead, targeting prefrontal cortex-based cognitive tasks before and after TILS for 5 weekly sessions
- **Tasks:**
  - 1) Sustained Attention: **psychomotor vigilance task (PVT)**
  - 2) Working Memory: **delayed match-to-sample memory task (DMS)**

The two tasks were conducted:

- immediately before the first laser treatment (Baseline: week 1),
- immediately after the first laser treatment (Acute: week 1),
- on subsequent weeks after additional laser treatments (Chronic: weeks 2, 3, 4, 5).

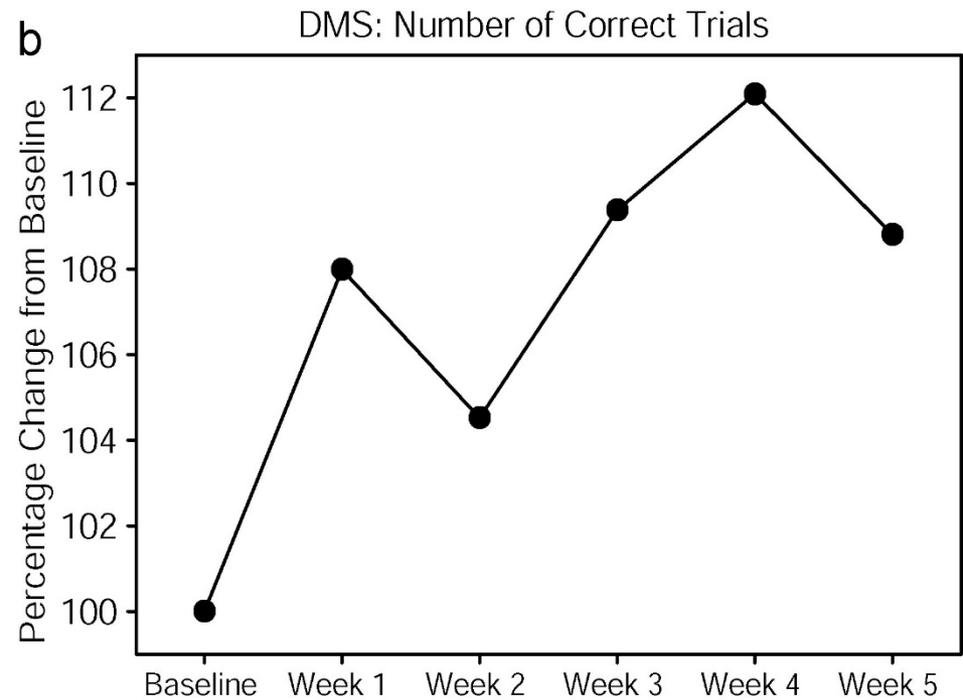
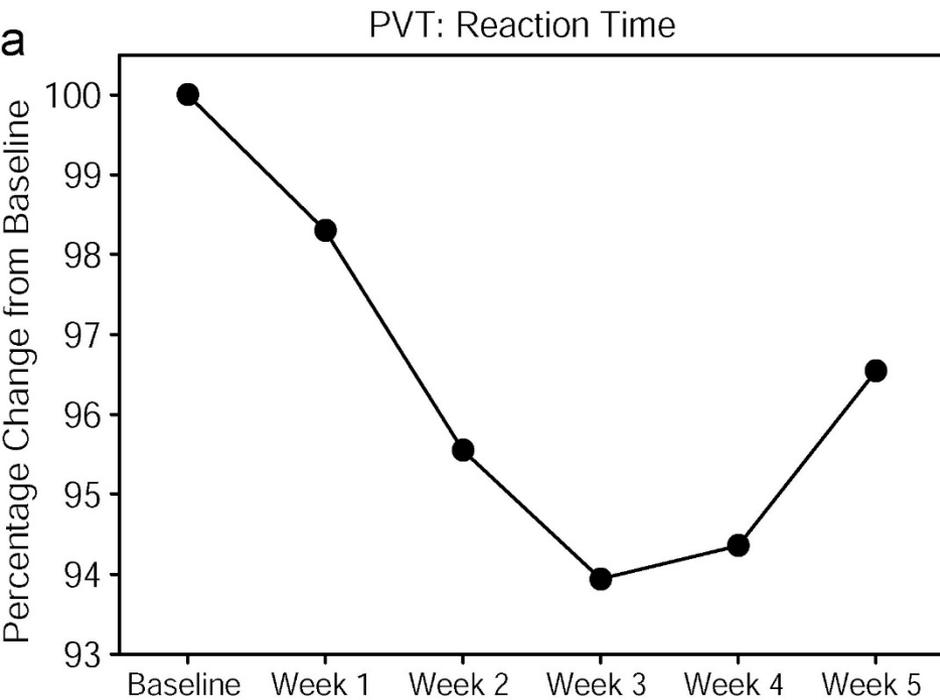
# Acute and Chronic Cognitive Improvement After TILS



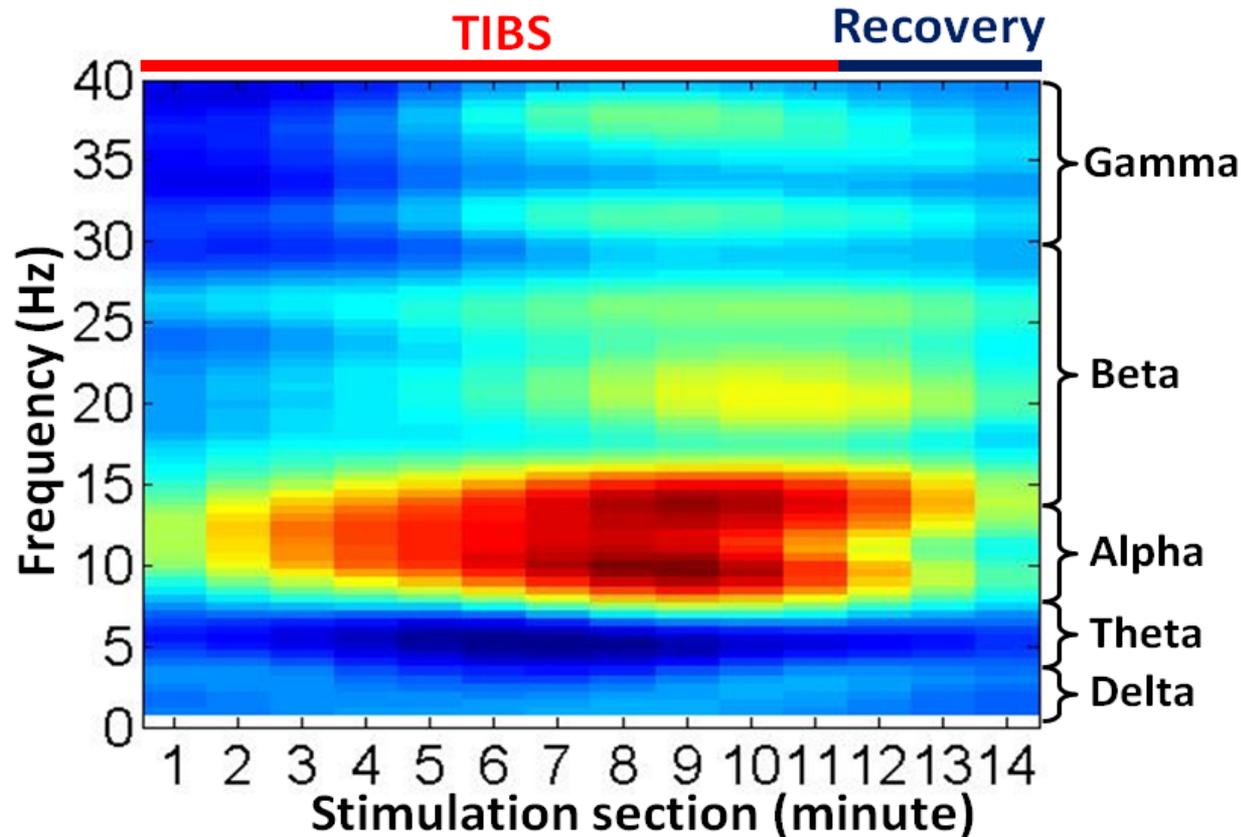
Baseline vs. 5 weekly sessions (8 minutes each) comparisons of mean cognitive scores all showed improvements, significant for PVT reaction time ( $p < 0.001$ ), PVT lapses ( $p < 0.001$ ), and DMS correct responses ( $p < 0.05$ ).

E. Vargas, D. W. Barrett, C. L. Saucedo, L. D. Huang, J. A. Abraham, H. Tanaka, A. P. Haley, and F. Gonzalez-Lima, *Lasers in Medical Science*, 2017

# Percent Change After TILS



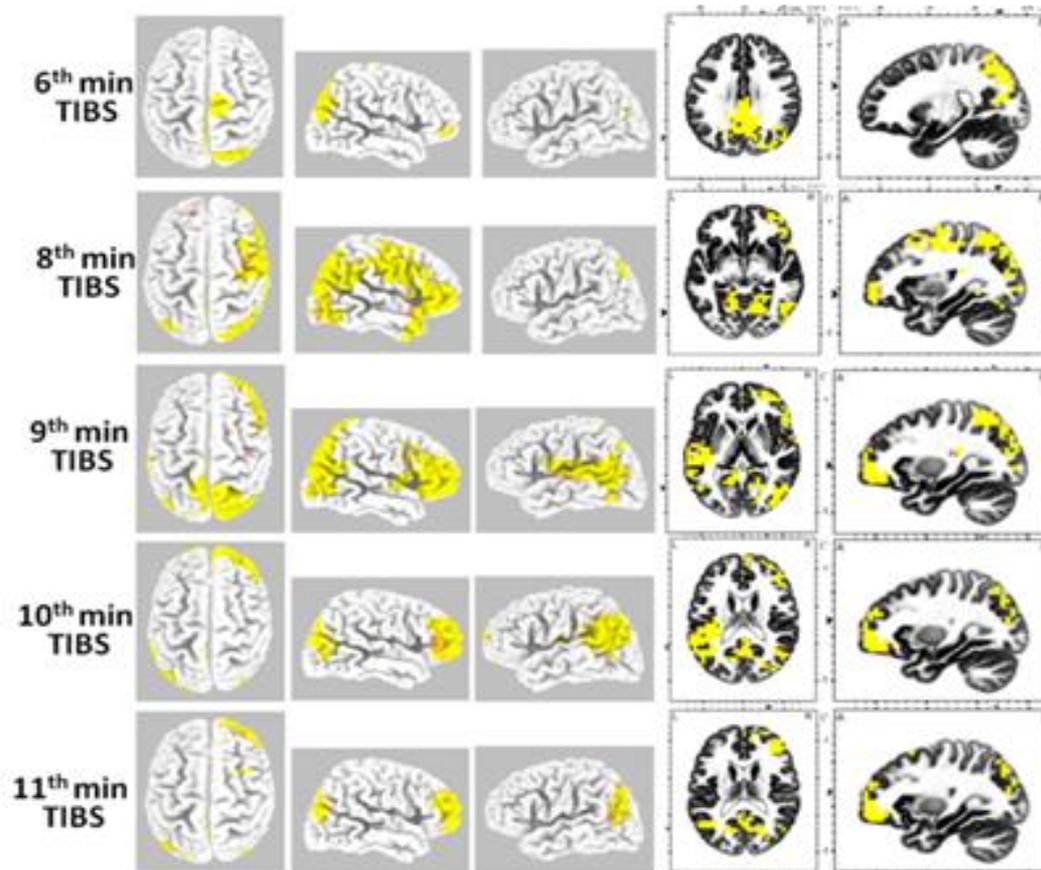
# Prefrontal TILS of EEG Power Spectra



The neural studies showed for the first time that TILS increases resting-state EEG alpha, beta and gamma power, and promotes more efficient prefrontal BOLD-fMRI response (n=20).

Y. Wang et al., 2017

# TILS modulates a large-scale fronto-parieto-occipital network for attention/memory/executive functions



3D views of t-maps (yellow= $p < 0.01$ ) between TILS and placebo conditions based on eLORETA Alpha-band (8-13 Hz) power density at 6, 8, 9, 10, and 11 min after right PFC TILS started (n=20)

X. Wang et al., *Brain Stimulation*, 2017

# Conclusions

- These data imply that transcranial infrared laser stimulation could be used as a non-invasive and efficacious approach to increase cerebral cytochrome oxidase and oxygen metabolism and support neurocognitive functions in humans.
- This safe and innovative neuromodulatory approach could lead to the development of non-invasive interventions in healthy humans and in those in need of neuropsychological rehabilitation.
- Potential applications: age-related cognitive decline, attention and memory disorders, brain trauma, brain ischemia and many other psychological and neurological disorders with compromised cognition.

# Acknowledgements of Coauthors

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