A Pilot Treatment Study for Mild Traumatic Brain Injury: Neuroimaging Changes Detected by MEG after Low-Intensity Pulse-based Transcranial Electrical Stimulation

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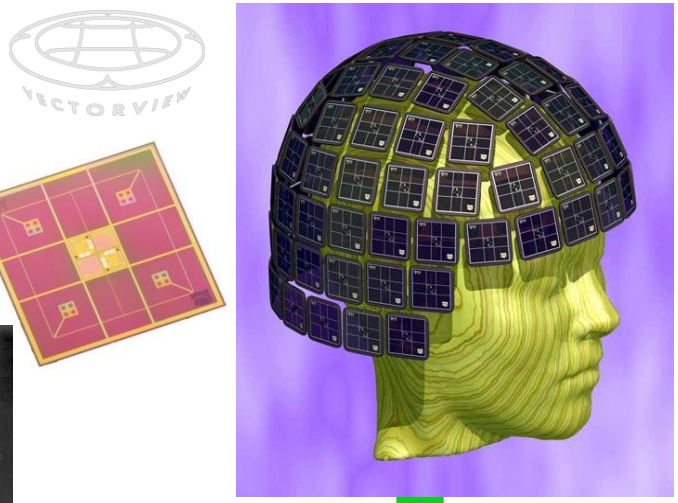
Topics to be covered

- Magnetoencephalography (MEG), MEG slow-wave imaging (delta-waves), and the detection of mild traumatic brain injury (mTBI).
- Potential healing mechanisms associated with delta-waves
- Different models for transcranial electrical stimulation
- A Pilot Treatment Study for mTBI: MEG changes after low-intensity pulse-based transcranial electrical stimulation.

MEG 1 ms time resolution, 2-3 mm spatial resolution

MEG SQUID Sensor Array



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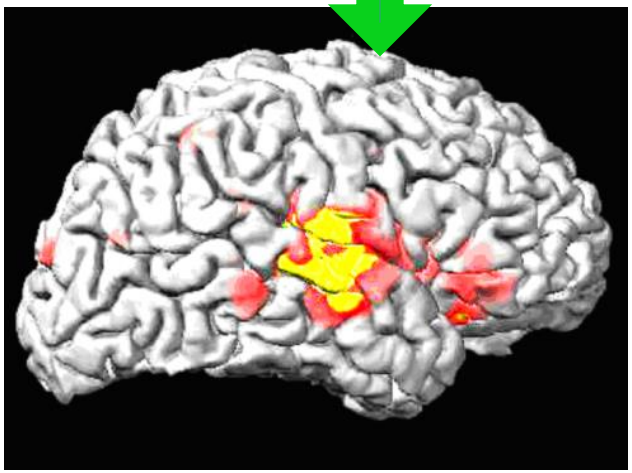
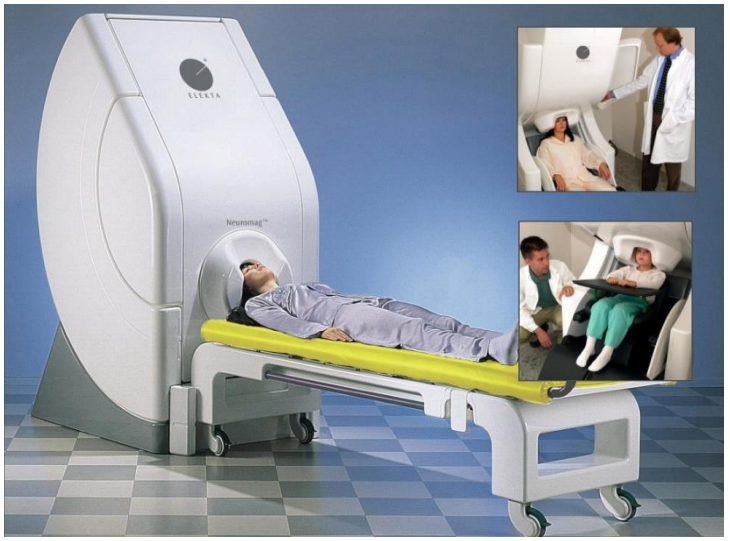
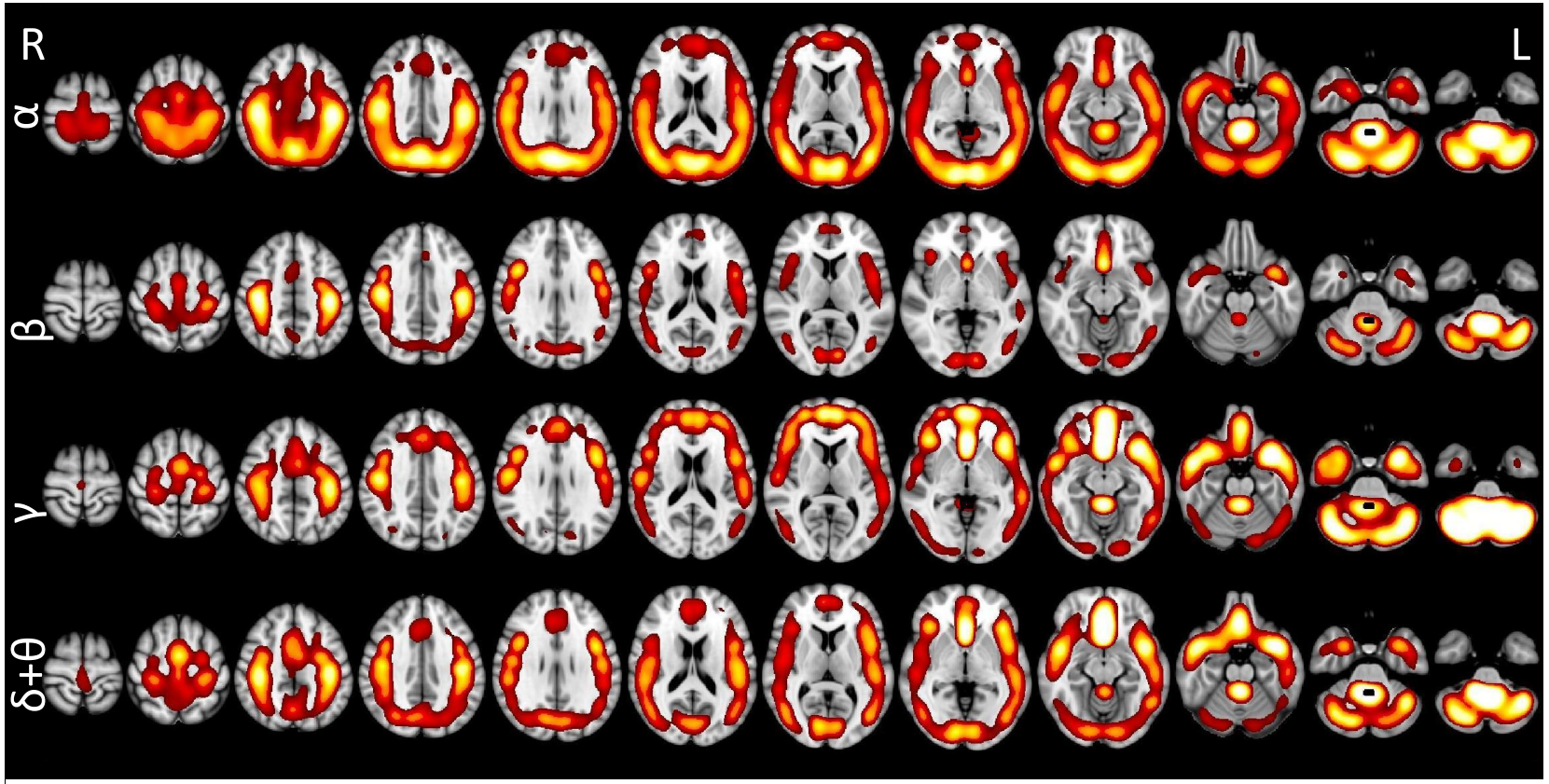




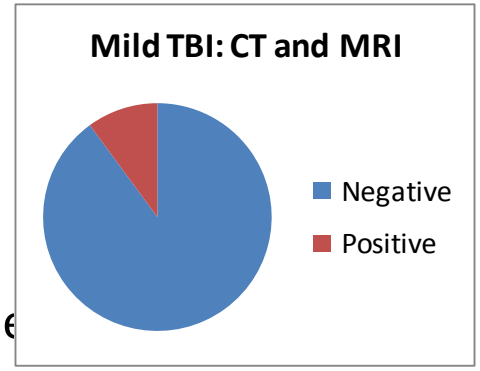
Normative Database: Comprehensive Source Magnitude Images of Resting-state Brain Rhythms for Different Frequency Bands

Huang et al., NeuroImage, 84, 585-604, 2014



Whole brain rs-MEG source-amplitude images averaged from 41 healthy subjects in MNI-152 atlas coordinates from **Fast-VESTAL** in alpha (1st row), beta (2nd row), gamma (3rd row), and low-frequency (delta plus theta, 4th row) bands.

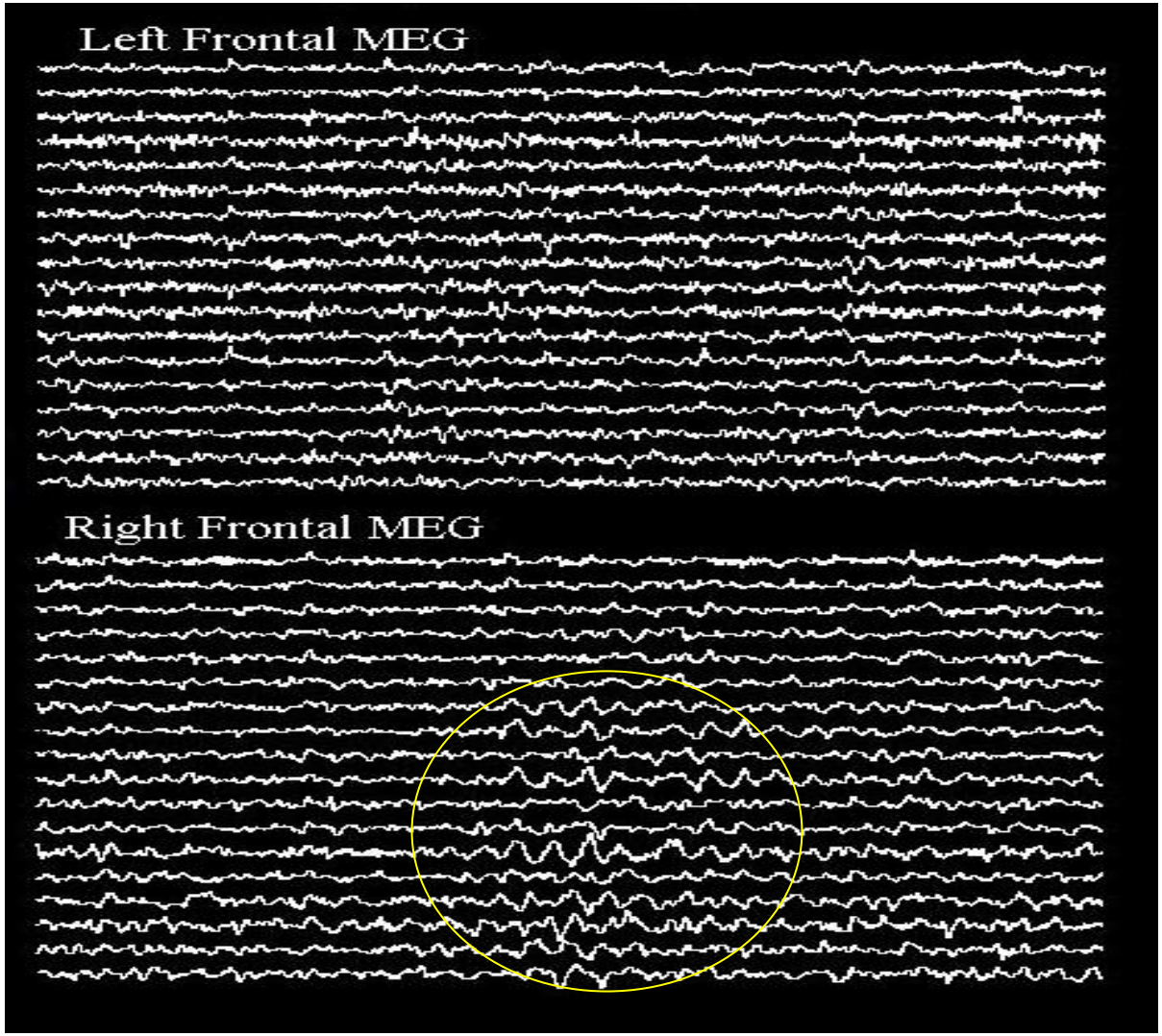
Mild TBI is often referred as *invisible* injuries: Detecting Mild TBI is Challenging using Conventional Neuroimaging Methods



- Traumatic brain injury (TBI) is a leading cause of sustained impairment in veterans, military personnel, and civilian populations.
- Mild TBI (mTBI): injuries are difficult to detect (injuries visible on only 10% of conventional MRIs or CTs).
- Diffuse axonal injury and neurochemical damages are leading factors in mTBI. Conventional CT and MRI are mainly sensitive to blood product
- Injured brain tissues in mTBI patients generate pathological slow-wave magnetic signal that can be measured and localized by MEG (Lewine et al., 1999, 2007, Huang et al., 2009, 2012, 2014).

Abnormal resting-state MEG slow-waves in gray matter (1-4 Hz, delta-waves) are characteristics of neurological Injuries in the brain, resulting from white matter injury and/or neuro-chemical (e.g., cholinergic) blockage

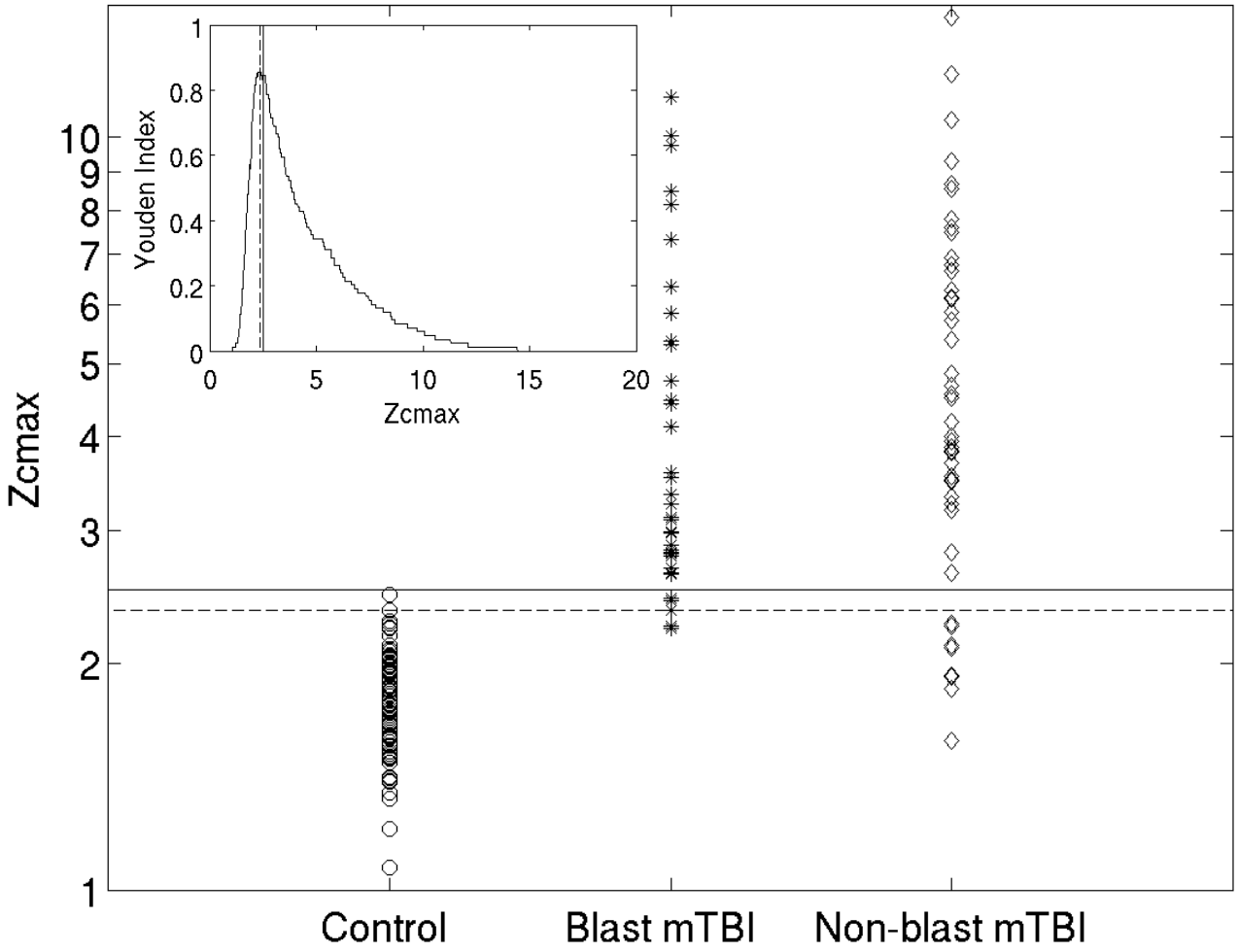
- Stroke
- Brain tumor
- Epilepsy
- Traumatic brain injury



Huang et al., NeuroImage: Clinical, 2014, 5:109-119.

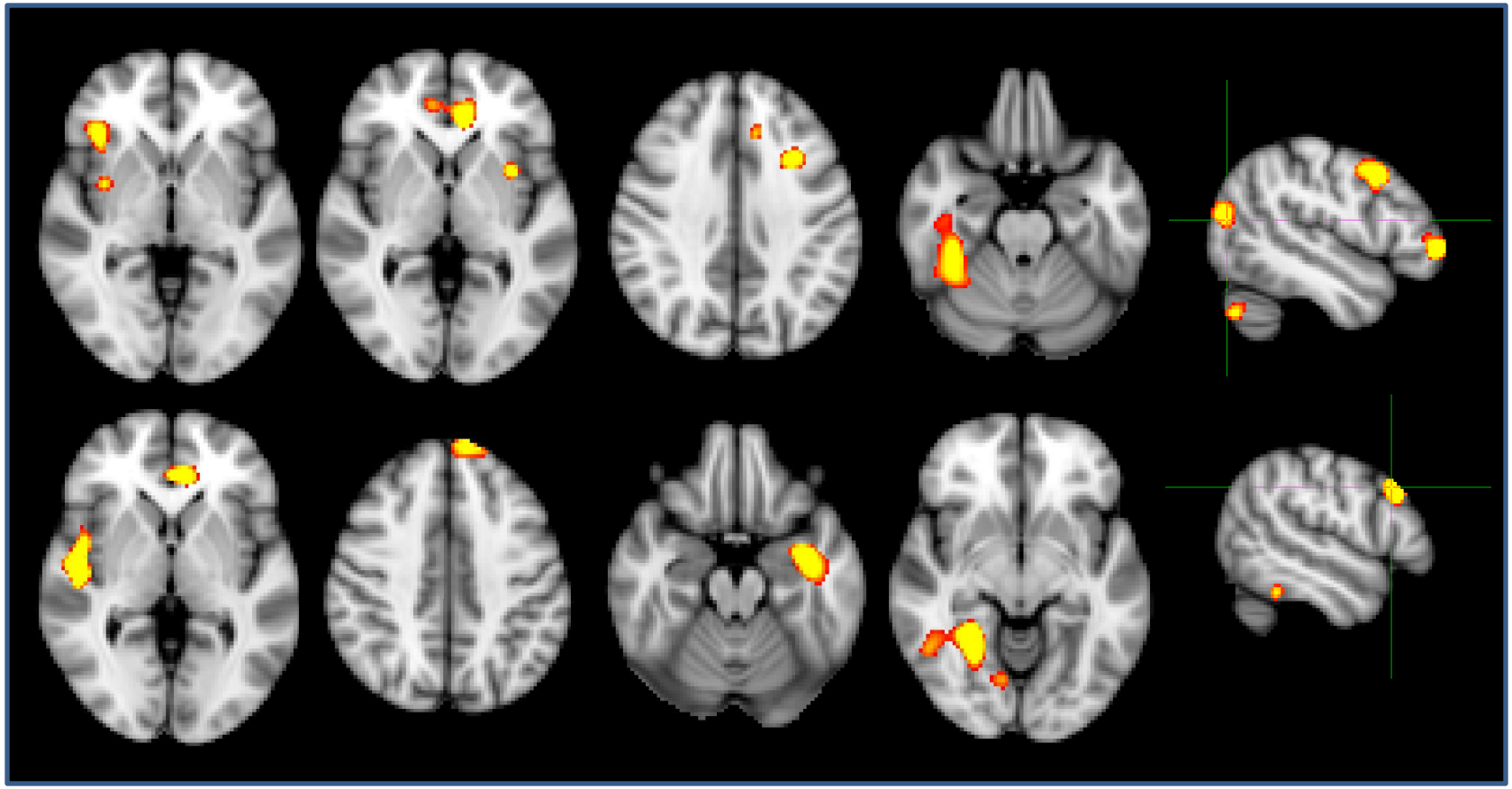
Sensitivity rates of MEG slow-wave imaging for mTBI

- The threshold of 0% false-positive rate in healthy control subjects.
  - ➢In the blast mild TBI group, MEG sensitivity rate was **86.1%**.
  - ➢In the non-blast mild TBI group, MEG sensitivity rate was **83.3%**.
  - ➢In the combined mild TBI group (blast + non-blast), MEG sensitivity rate was **84.5%**.



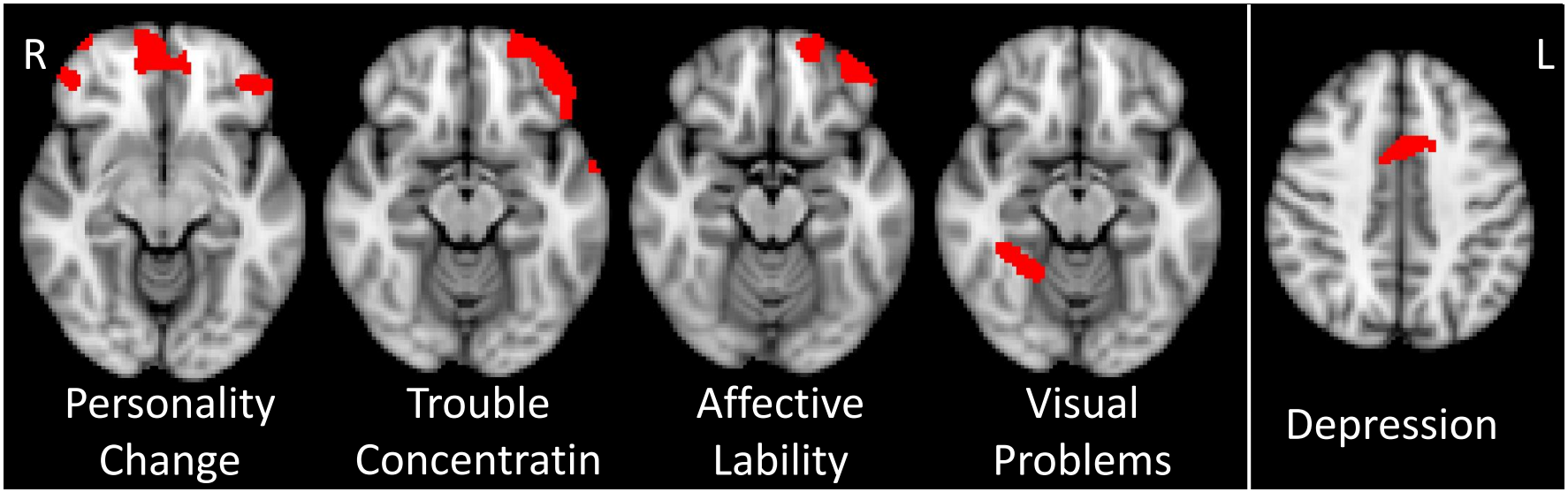
Huang et al., NeuroImage: Clinical, 2014, 5:109-119.

MEG slow-wave imaging for individual mild TBI patients



Huang et al., NeuroImage: Clinical, 2014, 5:109-119.

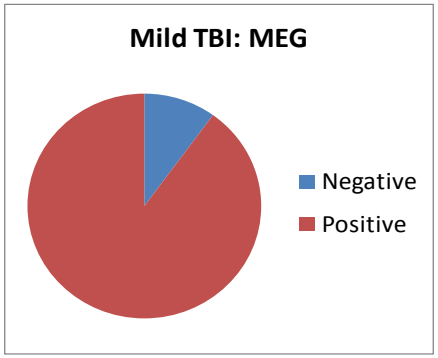
MEG slow-wave source magnitude significantly correlated with PCS



Huang et al., NeuroImage: Clinical, 2014, 5:109-119.

Summary: MEG Slow-wave imaging as a potential imaging marker for mTBI

- MEG slow-waves from gray-matter result from de-afferentation, due to axonal injury and/or neuro-chemical (e.g., cholinergic) blockage in white-matter.
- For mild TBI, automated MEG slow-wave imaging techniques (regional or voxel-based whole brain) show high positive finding rate (~85%).
- MEG slow-wave findings correlated with mTBI symptoms



Are Slow-waves Associated with Healing Mechanisms in the Brain?

- Is slow-wave generation in wakefulness merely a negative consequence of neuronal injury?
- Or, is the slow-wave a signature of ongoing neuronal rearrangement and healing that occurs at the site of the injury?
- Xie et al., (2013). Sleep drives metabolite clearance from the adult brain. Science 342, 373–377.
- Morawska et al., (2016). Sleep Modulation Alleviates Axonal Damage and Cognitive Decline after Rodent Traumatic Brain Injury. J Neurosci 36, 3422–3429.
- Ju et al., (2017). Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. Brain 140, 2104–2111.

Xie et al., (2013). Sleep drives metabolite clearance from the adult brain. Science 342, 373–377.

Sleep Drives Metabolite Clearance from the Adult Brain

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The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

mice, $P < 0.05$, paired t test) (Fig. 1D). To investigate whether the state of brain activity indeed controlled CSF influx, we repeated the experiments in a new cohort of mice in which all experiments were performed when the animals were awake (8 to 10 p.m.). Because mice normally do not sleep at this time of day, we first evaluated CSF tracer influx in the awake state by means of intracisternal infusion of FITC-dextran. CSF tracer influx into the brain was largely absent and only slowly gained access to the superficial cortical layers (Fig. 1, E and F, and fig. S2). After 30 min imaging of CSF tracer in the awake state, the animals were anesthetized with intraperitoneal administration of ketamine/xylazine (KX). Texas red-dextran was administered 15 min later, when a stable increase in slow wave activity was noted (Fig. 1, E and F). Texas red-dextran rapidly flushed in along periarterial spaces and entered the

CSF Tracer

ketamine/xylazine (KX)

Xie et al., (2013). Science 342, 373–377.

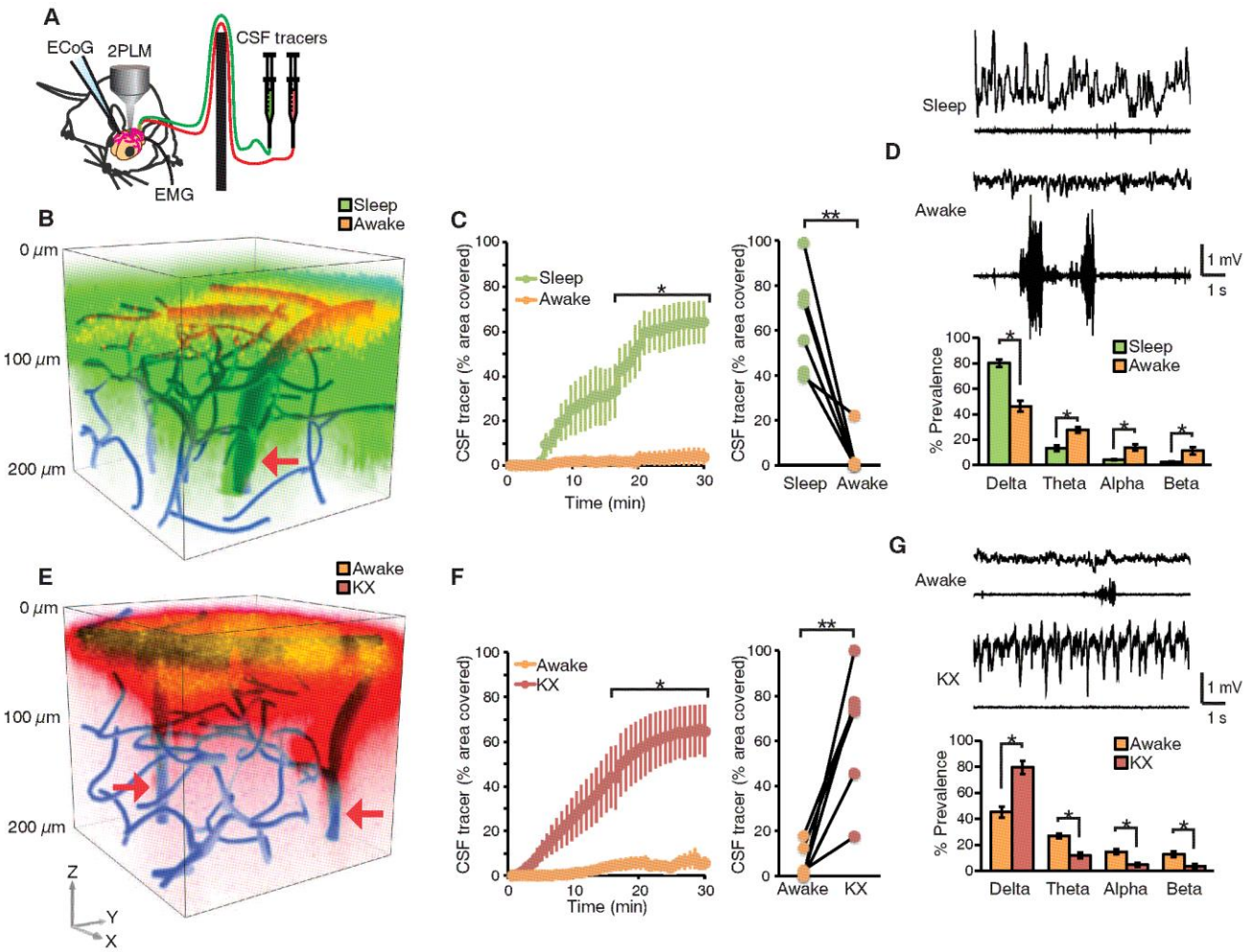


Fig. 1. Wakefulness suppresses influx of CSF tracers. (**A**) Diagram of experimental setup used for two-photon imaging of CSF tracer movement in real time. To avoid disturbing the state of brain activity, a cannula with dual ports was implanted in the cisterna magna for injection of CSF tracers. ECoG and EMG were recorded to monitor the state of brain activity. (**B**) Three-dimensional (3D) vectorized reconstruction of the distribution of CSF tracers injected in a sleeping mouse and then again after the mouse was awakened. The vasculature was visualized by means of cascade blue-dextran administered via the femoral vein. FITC-dextran (green) was first injected in the cisterna magna in a sleeping mouse and visualized by collecting repeated stacks of z-steps. Thirty min later, the mouse was awakened by gently moving its tail, and Texas red-dextran (red) was administered 15 min later. The experiments were performed mostly asleep (12 to 2 p.m.). The arrow points to penetrating arteries. (**C**) Comparison of time-dependent CSF influx in sleep versus awake. Tracer influx was quantified 100 μm below the cortical surface; $n = 6$ mice; $^*P < 0.05$, two-way ANOVA with Bonferroni test. (Right) The tracer intensity within the two arousal states at the 30-min time point was compared. $^{**}P < 0.01$, t test. (**D**) ECoG and EMG recordings acquired during sleep and after the mouse was awakened. Power spectrum analysis of all the animals analyzed in the two arousal states ($n = 6$ mice; $^*P < 0.05$, t test). (**E**) 3D reconstruction of CSF tracer influx into the mouse cortex. FITC-dextran was first injected in the awake stage, and cortical influx was visualized by means of two-photon excitation for 30 min. The mouse was then anesthetized with ketamine/xylazine (intraperitoneally), and Texas red-dextran was injected intracisternally 15 min later. The vasculature was visualized by means of cascade blue-dextran. Arrows point to penetrating arteries. (**F**) Comparison of time-dependent CSF influx in awake versus ketamine/xylazine anesthesia; $n = 6$ mice; $^*P < 0.05$, two-way ANOVA with Bonferroni test. (Right) The tracer intensity during the two arousal states at the 30-min time point was compared. $^{**}P < 0.01$, t test. (**G**) ECoG and EMG recordings in the awake mouse and after administration of ketamine/xylazine. Power spectrum analysis of all the animals analyzed in the two arousal states; $n = 6$ mice; $^*P < 0.05$, t test.

Sleep and anesthesia increase the volume of extracellular space in cortex: Xie et al., (2013). Science 342, 373–377

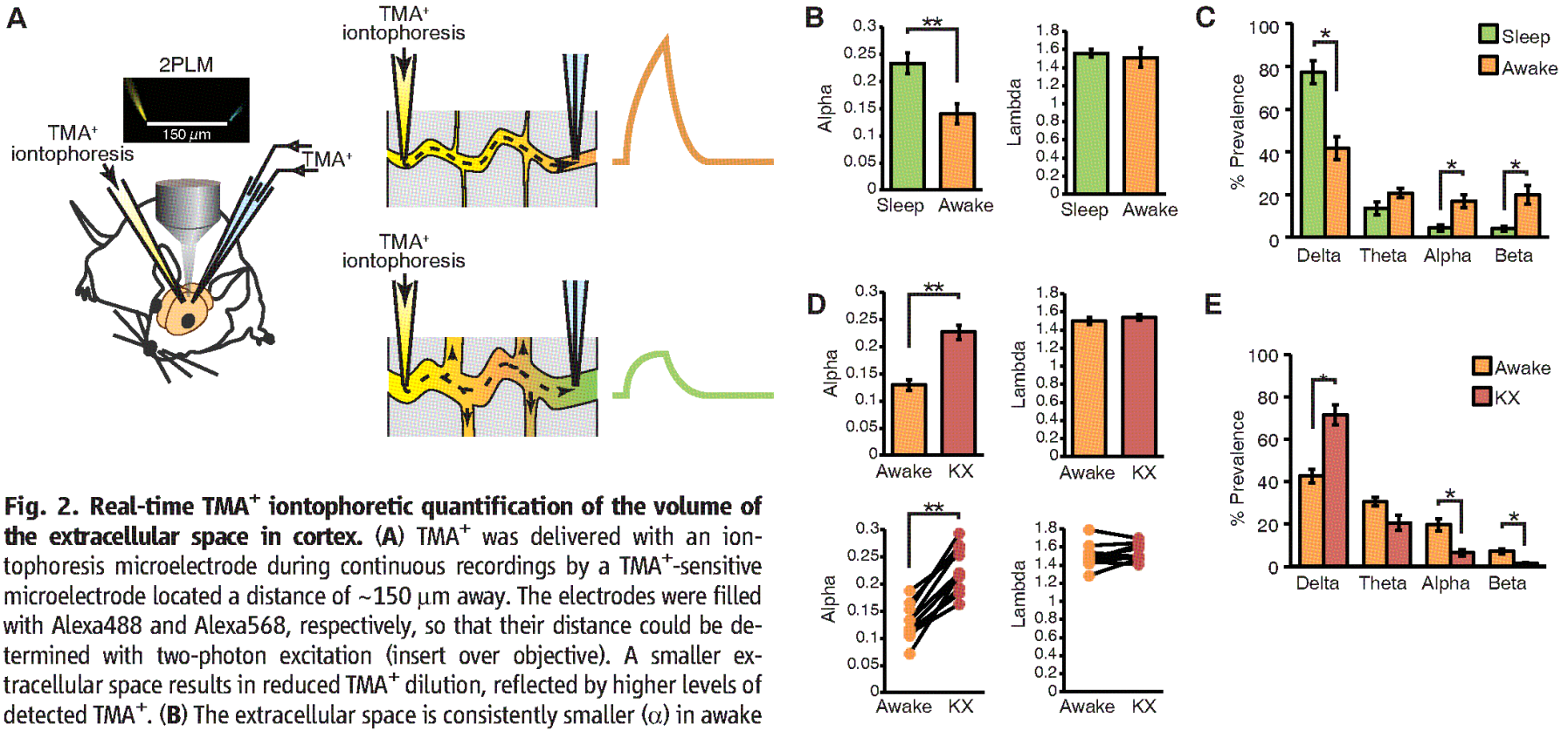
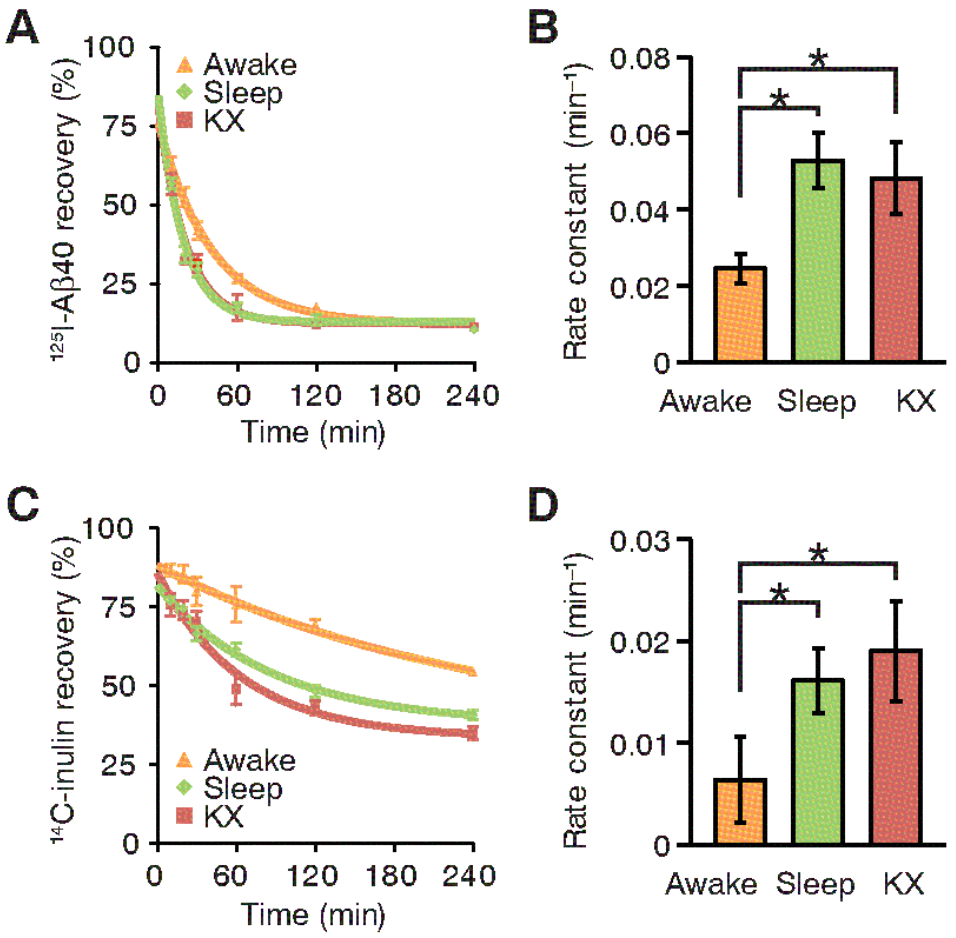


Fig. 2. Real-time TMA$^+$ iontophoretic quantification of the volume of the extracellular space in cortex. (**A**) TMA$^+$ was delivered with an iontophoresis microelectrode during continuous recordings by a TMA$^+$-sensitive microelectrode located a distance of ~150 μm away. The electrodes were filled with Alexa488 and Alexa568, respectively, so that their distance could be determined with two-photon excitation (insert over objective). A smaller extracellular space results in reduced TMA$^+$ dilution, reflected by higher levels of detected TMA$^+$. (**B**) The extracellular space is consistently smaller (α) in awake than in sleeping mice, whereas the tortuosity remained unchanged (λ); $n = 4$ to 6 mice; $^{**}P < 0.01$, t test. (**C**) Power spectrum analysis of ECoG recordings; $n = 6$ mice; $^{*}P < 0.05$, t test. (**D**) The extracellular space was consistently smaller in the awake state than after administration of ketamine/xylazine in paired recordings within the same mouse, whereas tortuosity did not change after anesthesia; $n = 10$ mice; $^{**}P < 0.01$, t test. (Bottom) TMA measurements obtained during the two arousal states compared for each animal. (**E**) Power spectrum analysis of ECoG; $n = 6$ mice; $^{*}P < 0.05$, t test.

Amyloid-Beta clearance: Xie et al., (2013). Science 342, 373–377

Fig. 3. Sleep improves clearance of Aβ. (**A**). Time-disappearance curves of ^{125}I-Aβ_{1-40} after its injection into the frontal cortex in awake (orange triangles), sleeping (green diamonds), and anesthetized (red squares, ketamine/xylazine) mice. (**B**) Rate constants derived from the clearance curves. (**C**) Time-disappearance curves of ^{14}C-inulin after its injection into the frontal cortex of awake (orange triangles), sleeping (green diamonds), and anesthetized (red squares, ketamine/xylazine) mice. (**D**) Rate constants derived from the clearance curves. A total of 77 mice were included in the analysis: 25 awake, 29 asleep, and 23 anesthetized, with 3 to 6 mice per time point. *$P < 0.05$ compared with awake, ANOVA with Bonferroni test.



Adrenergic inhibition increase CSF influx in **awake mice** using norepinephrine (NE) receptor antagonists: Xie et al., (2013). Science 342, 373–377

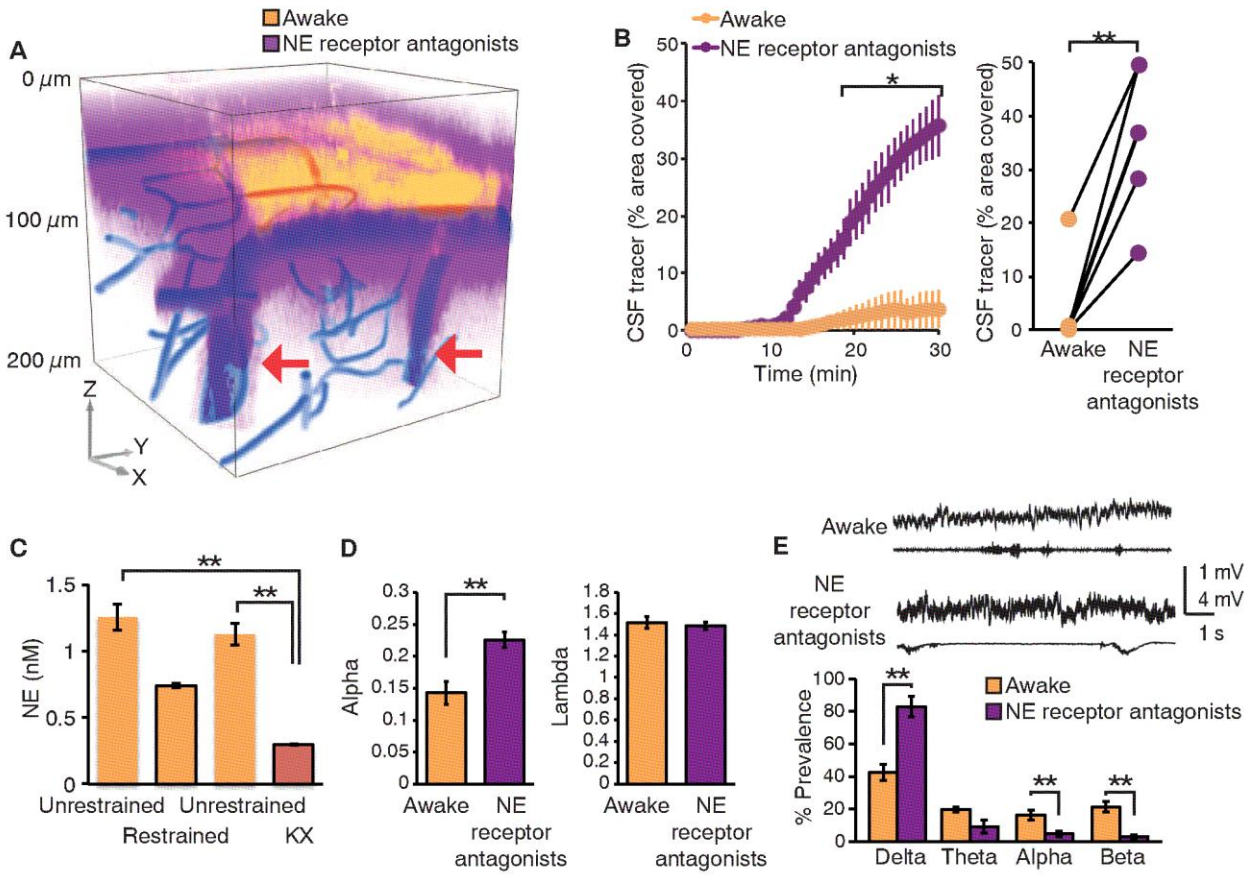


Fig. 4. Adrenergic inhibition increases CSF influx in awake mice. (A) CSF tracer influx before and after intracisternal administration of a cocktail of adrenergic receptor antagonists. FITC-dextran (yellow, 3 kD) was first injected in the cisterna magna in the awake mouse, and cortical tracer influx was visualized by means of two-photon excitation for 30 min. The adrenergic receptor antagonists (prazosin, atipamezole, and propranolol, each 2 mM) were then slowly infused via the cisterna magna cannula for 15 min followed by injection of Texas red-dextran (purple, 3 kD). The 3D reconstruction depicts CSF influx 15 min after the tracers were injected in cisterna magna. The vasculature was visualized by means of cascade blue-dextran. Arrows point to penetrating arteries. **(B)** Comparison of tracer influx as a function of time before and after administration of adrenergic receptor antagonists. Tracer influx was quantified in the optical section located 100 μm below the cortical surface; $n = 6$ mice; $^{*}P < 0.05$, two-way ANOVA with Bonferroni test. (Right) The tracer intensity during the two arousal states at the 30-min time point was compared. $^{**}P < 0.01$, t test. **(C)** Comparison of the interstitial concentration of NE in cortex during head-restraining versus unrestrained (before and after), as well as after ketamine/xylazine anesthesia. Microdialysis samples were collected for 1 hour each and analyzed by using high-performance liquid chromatography. $^{**}P < 0.01$, one-way ANOVA with Bonferroni test. **(D)** TMA^{+} iontophoretic quantification of the volume of the extracellular space before and after adrenergic inhibition; $n = 4$ to 8 mice; $^{**}P < 0.01$, t test. **(E)** Power spectrum analysis, $n = 7$ mice; $^{**}P < 0.01$, one-way ANOVA with Bonferroni test.

Morawska et al., (2016). Sleep Modulation Alleviates Axonal Damage and Cognitive Decline after Rodent Traumatic Brain Injury. J Neurosci 36, 3422–3429.

Sleep Modulation Alleviates Axonal Damage and Cognitive Decline after Rodent Traumatic Brain Injury

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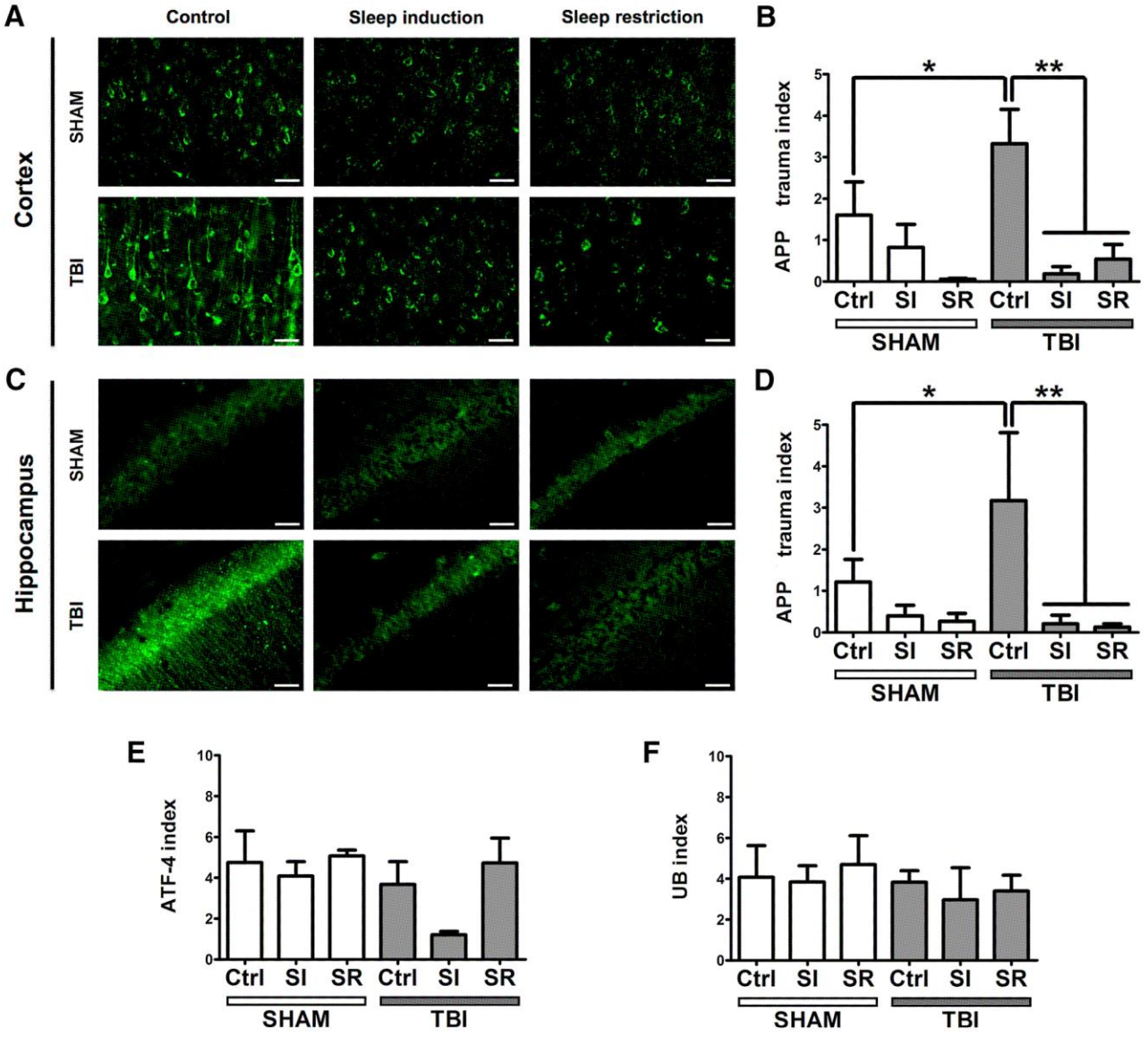
Traumatic brain injury (TBI) is a major cause of death and disability worldwide. It produces diffuse axonal injury (DAI), which contributes to cognitive impairment, but effective disease-modifying treatment strategies are missing. We have recently developed a rat model of closed skull TBI that reproduces human TBI consequences, including DAI and clinical sequelae such as memory impairment. Here, we investigated whether sleep modulation after trauma has an impact on DAI and memory outcome. We assessed cognition with the novel object recognition test and stained for amyloid precursor protein, a DAI marker. We found that both sleep induction and restriction acutely after TBI enhanced encephalographic slow-wave activity, markedly reduced diffuse axonal damage in the cortex and hippocampus, and improved memory impairment 2 weeks after trauma. These results suggest that enhancing slow-wave sleep acutely after trauma may have a beneficial disease-modifying effect in subjects with acute TBI.

Key words: diffuse axonal damage; memory; sleep; traumatic brain injury

Significance Statement

Traumatic brain injury (TBI) is a clinically important entity. Cognitive deficits belong to the most prevalent chronic posttraumatic symptoms, most likely due to diffuse axonal injury (DAI). A growing body of evidence suggests a role of sleep in the clearance of waste products in the brain, possibly including amyloid precursor protein (APP), a marker of DAI. In this study, we provide evidence that enhancement of slow-wave oscillatory activity in the delta-frequency range decreases the APP-immunoreactivity and preserves cognitive abilities after trauma, potentially offering novel, noninvasive treatment options for traumatic injury.



amyloid precursor protein (APP)

Morawska et al., (2016). J Neurosci 36, 3422–3429.

Figure 4. Effect of sleep modulation on histological markers after TBI. ***A***, ***C***, Representative images from sham and TBI animals (all groups) showing cortical (***A***) and hippocampal (***C***) APP staining. Only the non-sleep-modulated control TBI group showed marked axonal staining. ***B***, ***D***, Quantification of APP-immunoreactive cells in cortex (***B***) and hippocampus (***D***). All charts show the number of positive grid squares of one section divided by the area of cortex (number of positive squares per square millimeter of cortex). The TBI control group shows the highest APP trauma index (reflecting the highest expression of APP), which is significantly different from the sham group ($p < 0.05$). Sleep modulation resulted in decrease of APP expression in cortex and hippocampus, as indicated by the decreased APP trauma index in the sleep-induced TBI group ($p < 0.01$) and the sleep-restricted TBI group ($p < 0.01$). ***E***, Quantification of ATF-4-immunoreactive cells in cortex. No difference was noted in ATF-4 immunoreactivity between the groups. ***F***, Quantification of UB immunoreactivity in cortex. There was no difference in UB immunoreactivity between the groups.

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BRAIN
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REPORT

Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels

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*These authors contributed equally to this work

See Mander *et al.* (doi:10.1093/awx174) for a scientific commentary on this article.

Sleep deprivation increases amyloid-β, suggesting that chronically disrupted sleep may promote amyloid plaques and other downstream Alzheimer's disease pathologies including tauopathy or inflammation. To date, studies have not examined which aspect of sleep modulates amyloid-β or other Alzheimer's disease biomarkers. Seventeen healthy adults (age 35–65 years) without sleep disorders underwent 5–14 days of actigraphy, followed by slow wave activity disruption during polysomnogram, and cerebrospinal fluid collection the following morning for measurement of amyloid-β, tau, total protein, YKL-40, and hypocretin. Data were compared to an identical protocol, with a sham condition during polysomnogram. Specific disruption of slow wave activity correlated with an increase in amyloid-β_{40} ($r = 0.610$, $P = 0.009$). This effect was specific for slow wave activity, and not for sleep duration or efficiency. This effect was also specific to amyloid-β, and not total protein, tau, YKL-40, or hypocretin. Additionally, worse home sleep quality, as measured by sleep efficiency by actigraphy in the six nights preceding lumbar punctures, was associated with higher tau ($r = 0.543$, $P = 0.045$). Slow wave activity disruption increases amyloid-β levels acutely, and poorer sleep quality over several days increases tau. These effects are specific to neuronally-derived proteins, which suggests they are likely driven by changes in neuronal activity during disrupted sleep.

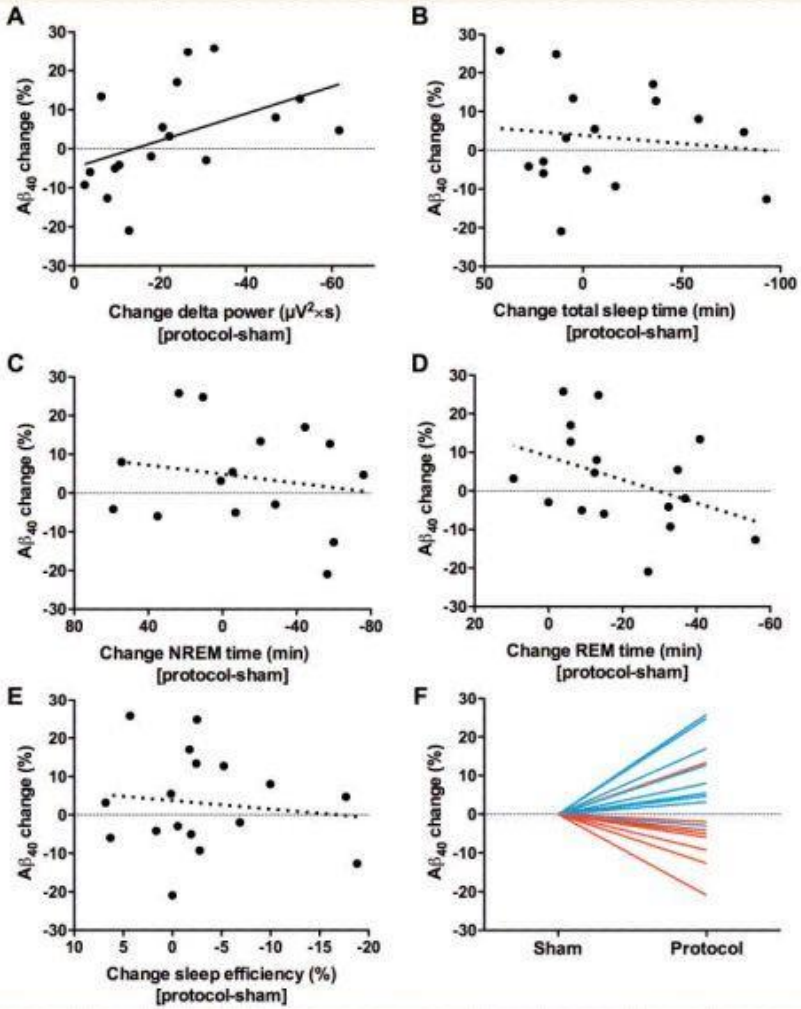


Figure 1 Decreased slow wave activity is associated with increased CSF amyloid-β. (**A**) Suppression of slow wave activity, as measured by the change in delta spectral power, was strongly correlated with increased amyloid-β_{40} ($r = 0.610$, $P = 0.009$). There was no correlation between change in amyloid-β_{40} levels and (**B**) total sleep time ($r = -0.075$, $P = 0.782$), (**C**) time in non-REM sleep ($r = -0.156$, $P = 0.564$), (**D**) time in REM sleep ($r = -0.351$ $P = 0.168$), or (**E**) sleep efficiency ($r = -0.007$, $P = 0.978$). (**F**) When participants are divided at the median (20 $\mu V^2 \times s$) amount of slow wave activity disruption, the 'responders' to SWA disruption (blue lines) had a significant increase in amyloid-β_{40} ($n = 9$, 11562 ± 2603 versus 10562 ± 2868 pg/ml, 95% confidence interval difference 315 to 1686 pg/ml, $P = 0.010$) while 'non-responders' (red lines) did not. *X*-axes in **A–E** are more negative to the right, i.e. values to the right indicate more disruption of slow wave activity or less sleep.

Summary: metabolic cleaning mechanism is associated with slow-wave generation during **NREM-delta sleep**, **delta-sleep by anesthesia**, and **awake with adrenergic inhibition**

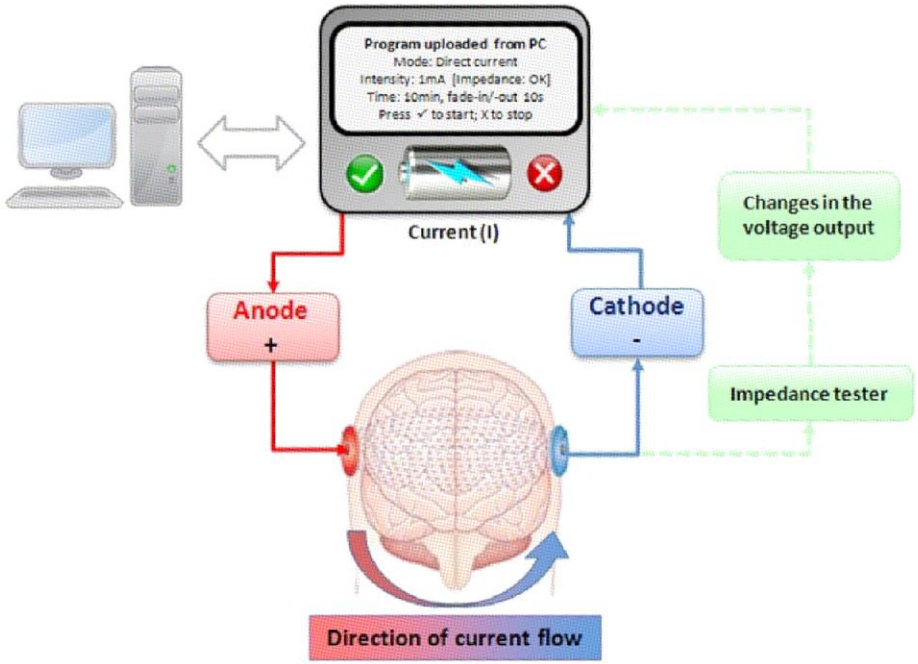
- Slow-wave generation is associated with metabolite clearance during natural NREM-delta sleep, delta-sleep by anesthesia, and adrenergic inhibition-induced delta waves during awake (Xie et al., 2013).
- Amyloid-beta after TBI can be effectively cleaned during delta-wave sleep induction and modulations (Morawska et al., 2016)
- Slow-wave sleep disruption increases cerebrospinal fluid amyloid-beta levels (Ju et al., 2017).
- However, taking anesthesia or adrenergic inhibition medicines without clinical monitoring will not be an option for mTBI patients
- Are there any alternative ways to potentiate the slow-wave generation for enhancing the cleaning / healing process at the site of the injury?
- How about transcranial electrical stimulation?

Transcranial Electrical Stimulation:

Box 1.

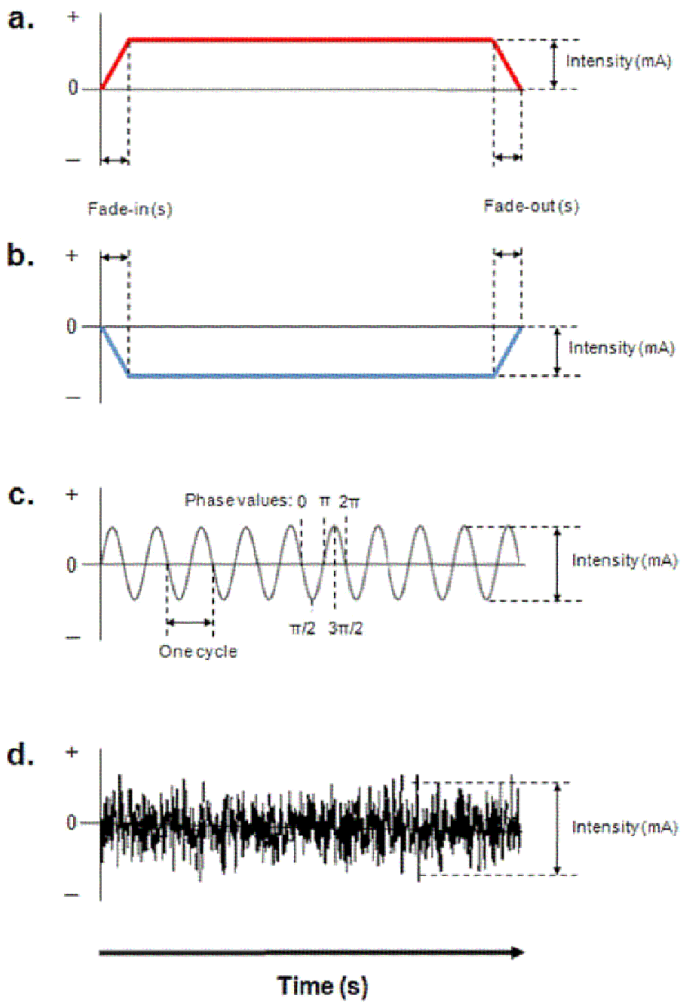
Schematization of the transcranial electrical stimulation (tES) stimulating device.

The technique involves the delivery of a low-level intensity (~1-2 mA) current by a battery-driven stimulator between two electrodes (anode and cathode) that are placed on the scalp. The electrodes are typically large, conductive-rubber sheets inserted in saline-soaked sponges (20-35 cm^2). The current passes through the scalp and crosses the extracortical layers to reach the cortex, which modulates the membrane polarity of the neurons within a region of underlying neural tissue. In the case of direct current delivery, the current flow direction is from the anode to cathode. This current induces changes in the electrical activity of the neurons, and it consequently modifies the neurons' synaptic efficiencies. This modification is insufficient to induce action potentials; however, it is adequate to introduce variation in the response threshold of the stimulated neurons (Bindman and others 1964; Brunoni and others 2011; Creutzfeldt and others 1962) (Fig. 2). To maintain a constant current, the impedance is regularly verified by an impedance tester to establish whether it is necessary to vary the voltage delivered from the stimulator.



Fertonani and Miniussi , Neuroscientist, 2017, 23(2): 109-123

Transcranial Electrical Stimulation: a) and b) tDCS; c) tACS; d) tRNS



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Conventional Models for Transcranial Electrical Stimulation (tES: tDCS, tACS, tRNS)

- Anodal tDCS and tRNS increase neuronal excitability and may consequently enhance behavioral performance,
- Cathodal tDCS decreases neuronal excitability and subsequently worsens behavioral performance,
- tACS increases neuronal excitability via entrainment of the desired neuronal firing frequency and consequently modulates performance
- However, such a simplistic, sliding-scale reasoning (from excitation to inhibition or vice versa) does not always explain the results at either the neurophysiological or the behavioral level

Paulus W. Transcranial electrical stimulation (tES - tDCS; tRNS, tACS) methods. Neuropsychol. Rehabil. 2011;21:602–617.

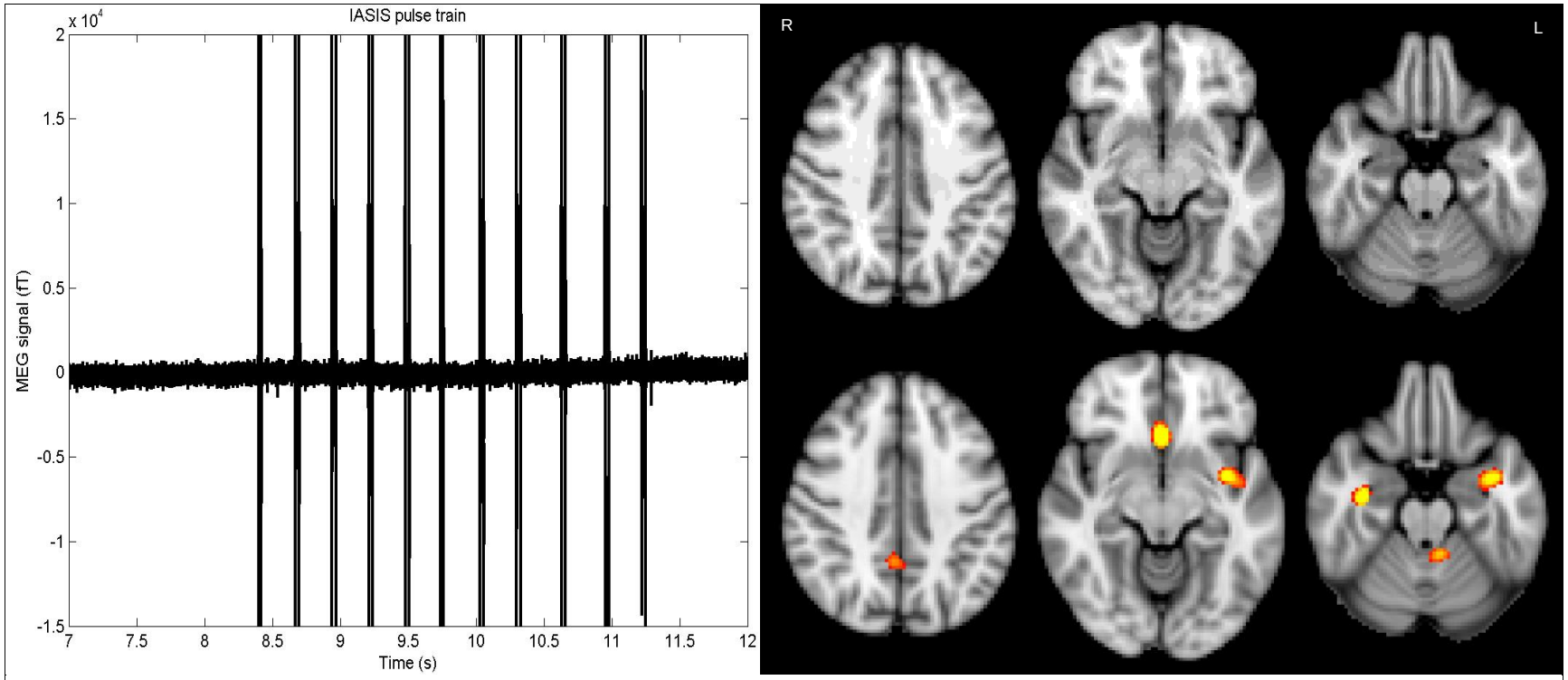
Fertonani and Miniussi , Neuroscientist, 2017, 23(2): 109-123

Advanced Models for Transcranial Electrical Stimulation (tES: tDCS, tACS, tRNS)

- Stimulation-Dependent Model
- Activity-Dependent Model
- Network Activity-Dependent Model
- Excitation-Inhibition Balance Model
- Zero-Sum Model
- **Stochastic Resonance (SR) Model**: endogenous oscillatory brain signals that are normally too weak / last too short, but can be boosted by adding to the brain some noise or electrical / magnetic inputs, which contains a wide spectrum of frequencies.

Fertonani and Miniussi , Neuroscientist, 2017, 23(2): 109-123

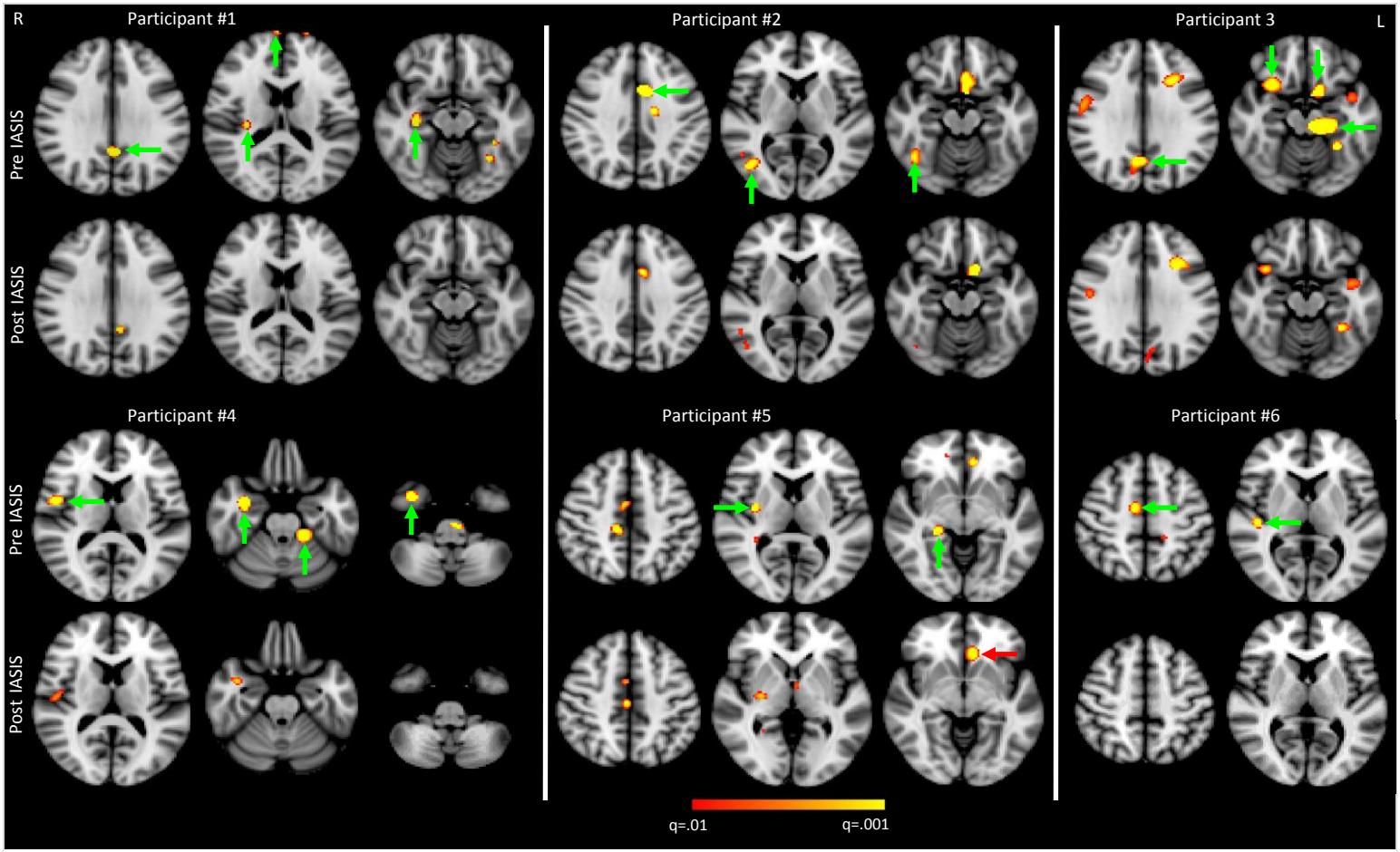
IASIS: Low-intensity pulse-based transcranial electrical stimulation potentiates typical sleep slow-wave network measured by rs-MEG



Left panel: IASIS pulse train at 3.6 Hz. Right panel: in a HC subject, abnormal slow-wave generation was absent right-before IASIS and 96 hours after IASIS (top row). MEG exam immediately after IASIS showed abnormal slow-waves (bottom row).

Huang et al., Brain Injury, 2017; 31(13-14):1951-1963.

IASIS reduced abnormal slow waves in 6 mTBI patients



Changes in abnormal MEG slow-waves between pre- and post-IASIS MEG exams in six mTBI participants. Green arrows indicate areas with abnormal slow-waves at the baseline but markedly reduced (> 30%) after IASIS. Red arrow indicates an area with markedly increased (> 30%) slow-wave after IASIS in mTBI Participant #5, who completed only 4 of 12 scheduled sessions. The hot spots without arrows indicate abnormal slow-waves that did not show marked change (< 30%) after IASIS treatment.

Huang et al., Brain Injury, 2017; 31(13-14):1951-1963.

Changes in post-concussion symptoms pre- and post-IASIS treatment

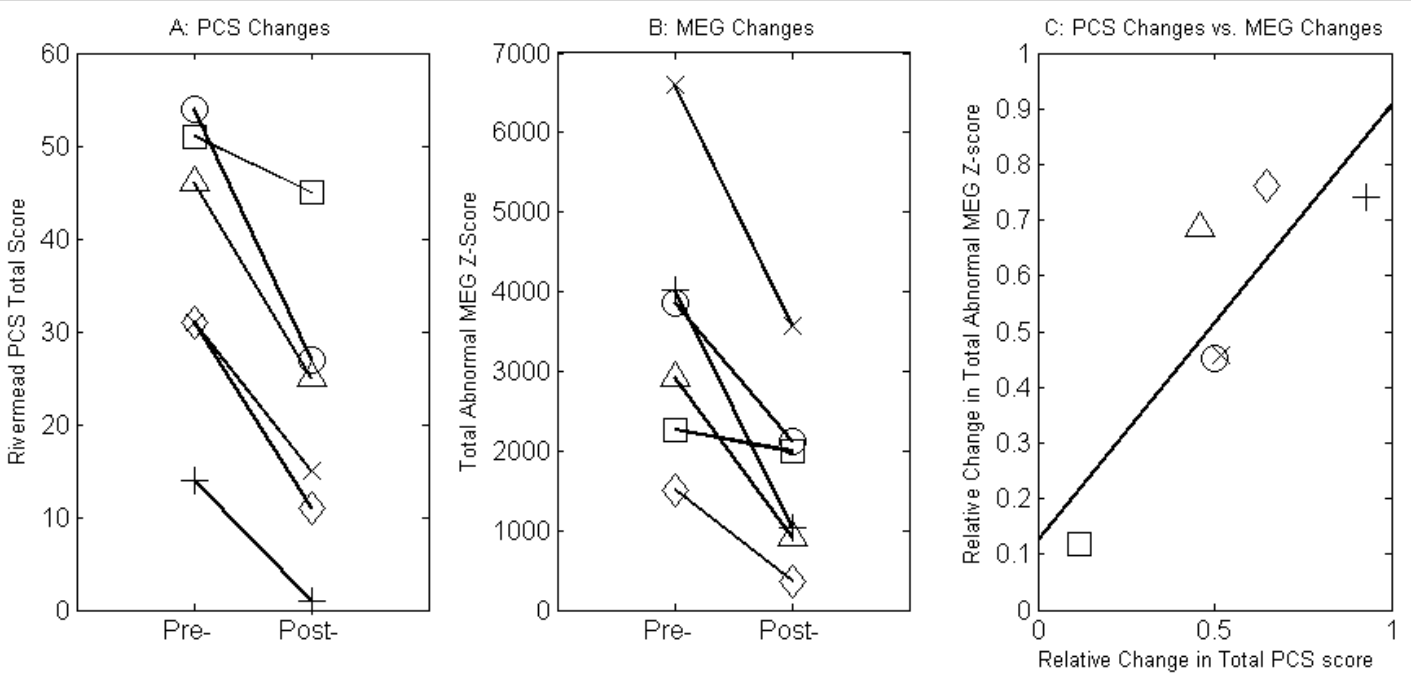
Table 2. Rivermead post-concussion symptom scores from pre- and post-IASIS assessments in six participants with mTBI.

	Participant #1		Participant #2		Participant #3		Participant #4		Participant #5		Participant #6	
Rivermead PCS Questionnaire	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
Headaches	3	1	4	3	4	1	0	0	4	4	3	1
Feelings of Dizziness	3	2	4	2	0	0	0	0	3	3	1	0
Nausea and/or Vomiting	2	1	4	0	0	0	0	0	3	3	0	0
Noise Sensitivity, Easily Upset by Loud Noise	2	2	4	1	2	1	2	1	4	4	4	1
Sleep Disturbance	4	2	4	1	0	0	2	0	3	3	3	1
Fatigue, Tiring More Easily	2	1	0	0	2	0	0	0	3	2	2	1
Being Irritable, Easily Angered	3	1	4	1	2	1	1	0	4	4	3	1
Feeling Depressed or Tearful	2	1	4	3	0	0	1	0	3	3	0	0
Feeling Frustrated or Impatient	4	2	4	3	3	1	1	0	4	3	2	1
Forgetfulness, Poor Memory	4	1	4	2	4	3	2	0	3	3	4	1
Poor Concentration	4	1	4	3	4	3	2	0	3	3	2	1
Taking Longer to Think	3	1	4	3	4	3	2	0	3	3	3	1
Blurred Vision	2	2	3	3	0	0	0	0	3	0	1	0
Light Sensitivity, Easily Upset by Bright Light	2	2	4	1	4	2	0	0	4	4	2	1
Double Vision	2	2	3	1	0	0	0	0	1	0	0	0
Restlessness	4	3	0	0	2	0	1	0	3	3	1	1
TOTAL	46	25	54	27	31	15	14	1	51	45	31	11

Scores on the RPCSQ range from 0 to 4 for individual symptoms where 0 = not experienced, 1 = no more of a problem, 2 = mild problem, 3 = moderate problem, and 4 = severe problem. *Participant #5 did not complete the scheduled protocol: He did only four sessions.

Huang et al., Brain Injury, 2017; 31(13-14):1951-1963.

IASIS reduced post-concussion score (PCS) and overall abnormal slow waves in 6 mTBI patients



Significant reduction in total Rivermead PCS scores between pre- and post-IASIS assessments ($p<0.01$). B: Significant reduction in total abnormal Z-score MEG slow-wave source imaging between pre- and post-IASIS MEG exams ($p<0.01$). C: Relative change in total abnormal MEG Z-score correlates with relative change in total PCS score ($p<0.05$). "Δ", "O", "×", "+", "□", and "◊" represent Participants #1, #2, ..., and #6, respectively.

Huang et al., Brain Injury, 2017; 31(13-14):1951-1963.

Participant #1 was a Marine who experienced an mTBI due to a mortar blast

- During and following the IASIS treatment, he reported that his symptoms greatly abated, going from severe to no problem or mild. His overall RPCSQ score went from 46 to 25, a reduction of 45.7%.
- He also mentioned that he had completely discontinued his use of nicotine after the IASIS treatments, which he claimed was a beneficial result of the treatments.
- At 6 months after IASIS, he stated that the treatment effects had persisted and that he still did not use nicotine.
- Compared with pre-IASIS MEG, his post-IASIS MEG showed marked reduction of 68.6% in total abnormal MEG Z-score.
- Abnormal slow-waves were markedly reduced from frontal pole, posterior cingulate cortex (PCC), right insula, and right hippocampus.
- In studies of headaches and migraine, activation of the insula, which is a component of the “pain matrix”, is attributed to the processing of pain and unpleasantness. The PCC is also a part of the pain matrix. Following treatment, his headaches were reduced, as were slow-waves in both the insula and the PCC.
- The MEG findings were also compatible with reduced PCS for memory function (related to hippocampus).

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Participant #2 was rear-ended in a multi-vehicle accident that resulted in a loss of consciousness

- She had mTBI with widespread moderate to severe symptoms.
- Halfway through the IASIS sessions, she reported a reduction in stuttering, anxiety, headaches, and less visual and auditory overstimulation (particularly reduction of photophobia). After the completion of all IASIS treatments, she reported an even greater reduction of symptoms (i.e., by 50.0%). Her overall score for RPCSQ went from 54 to 27.
- Her total abnormal MEG Z-score post-IASIS was markedly reduced by 45.1% relative to the baseline MEG exam.
- Specifically, markedly reduced MEG slow-waves after treatment were found in anterior cingulate cortex (ACC), and right occipital areas including the right lateral occipital cortex and right occipital fusiform gyrus spanning the lingual gyrus.
- Reduced slow-waves in the ACC, which is also part of the pain matrix, was compatible with her reduced headaches following treatment. Additionally, her reduced slow-waves after treatment in the right fusiform gyrus and lingual gyrus were compatible with the decrease in photophobia, a symptom that is linked with the lingual gyrus, a visual processing area.

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Participant #3 was involved in a car accident.

- After IASIS, his symptoms drastically reduced by 51.6% from an initial RPCSQ total score of 31 to 15. Light sensitivity was reported as only mild whereas headaches, noise sensitivity, irritability, and frustration no longer a problem. Importantly, initially severe symptoms were more moderate after treatment (i.e., forgetfulness / poor memory, poor concentration, and taking longer to think).
- Compared with the pre-IASIS exam, his post-IASIS total abnormal MEG Z-scores decreased by 45.8%.
- Specifically, striking decreases in abnormal slow-waves were notable in the PCC, bilateral OFC, and left hippocampus. The MEG findings are compatible with reduced PCS for memory problems (hippocampus) and headaches (PCC).

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Participant #4 was an Army soldier who experienced an IED blast while riding in an Mine-Resistant Ambush Protected vehicle

- After 3 visits and throughout the remaining IASIS sessions, he reported that his quality of sleep had improved, leaving him well rested with a positive change in attitude. Upon finishing all IASIS sessions, he recorded an overall score of 1 on the RPCSQ, a reduction of 92.9% in total RPCSQ score. He noted that noise sensitivity was no more of a problem for him. All other symptoms were listed as absent, which meant that he was essentially symptom-free.
- The pre- and post-IASIS MEG exams show that the total abnormal MEG Z-scores were reduced by 74.2%.
- Reductions of abnormal slow-waves were striking in the right inferior-lateral parietal area and superior temporal gyrus/auditory cortex, right hippocampus and amygdala, right inferior temporal pole, and left cerebellum.
- Changes in the central auditory system may play an important role in hyperacusis, an intolerance of normal environmental sound. Following treatment, he had less noise sensitivity, consistent with the observed reduction of slow-waves in the superior temporal gyrus/auditory cortex. Additionally, MEG findings were compatible with reduced PCS for memory loss (hippocampus).

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Participant #5 was a Marine who experienced blunt head trauma when a piece of furniture struck his head. He experienced another blunt head trauma when a chair that he was sitting broke, intensifying his previous symptoms.

- **He only finished 4 out of the 12 required IASIS treatment sessions**. From the beginning, he missed or rescheduled multiple sessions. Because it appeared likely that he might not (actually he did not) finish his IASIS treatment, an MEG exam was performed following his 4th visit, and that MEG was used for this paper. After his 4th IASIS visit, there was a 11.8% reduction in total RPSCQ symptoms (51 in pre-IASIS exam to 45 after the 4th session), which was not nearly as remarkable as that of individuals who completed all sessions.
- The pre-IASIS MEG exams show that he had abnormal slow-wave generation from right ACC and PCC, right striatum / insular cortex, right parahippocampus, and left ventro-medial prefrontal cortex (vmPFC). Following the 4th IASIS treatment visit, his total abnormal MEG Z-score only showed only a marginal reduction of 12.0%.
- Specifically, his abnormal slow-wave generation from the right ACC and PCC remained essentially the same. Reduced slow-waves were observed from his right striatum / insular cortex and his right parahippocampus, but increased slow-wave generation was found from his left vmPFC . The MEG findings were compatible with his persistent and ongoing PCS at his 4th visit for headache (ACC and PCC). Dysfunction in vmPFC can impair modulation of emotional reactions, resulting in increasing irritability and impairing decision making, which was consistent with his severe symptom of irritability.

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Participant #6 was an Army soldier who experienced a blast due to an IED while riding in a Humvee.

- Throughout the IASIS sessions, he noted improvement with sleep quality, accompanied by feeling more energetic. By the end of the sessions, his symptoms were all scored as no more of a problem. The total RPCSQ score reduced by 64.5%.
- After treatment, his total abnormal MEG Z-scores decreased by 76.1%.
- Notable decreases in abnormal slow-wave generation were observed from the right auditory cortex and the right supplementary motor area (SMA) and ACC.
- The SMA is also a component of the pain matrix. Following treatment, the abatement of his headaches was compatible with reduced slowing in both the SMA and the ACC. The MEG findings were also compatible with reduced PCS for noise sensitivity (auditory cortex in the superior temporal gyrus).

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Summary: MEG to assess the mTBI treatment with transcranial electrical stimulation

- IASIS (Low-intensity pulse-based transcranial electrical stimulation) potentiates slow-wave initially.
- IASIS eventually brought down the abnormal slow-wave in mTBI after the subjects finished the treatment.
- IASIS treatment also reduced the total mTBI symptom score.
- Reduction in total mTBI symptom score correlates with reduction in total MEG slow-wave generation.
- Self-report clinically: 5 participants felt substantially better, 1 felt about the same (Participant #5).

Huang et al., Brain Injury, 2017; 31(13-14):1951-1963.

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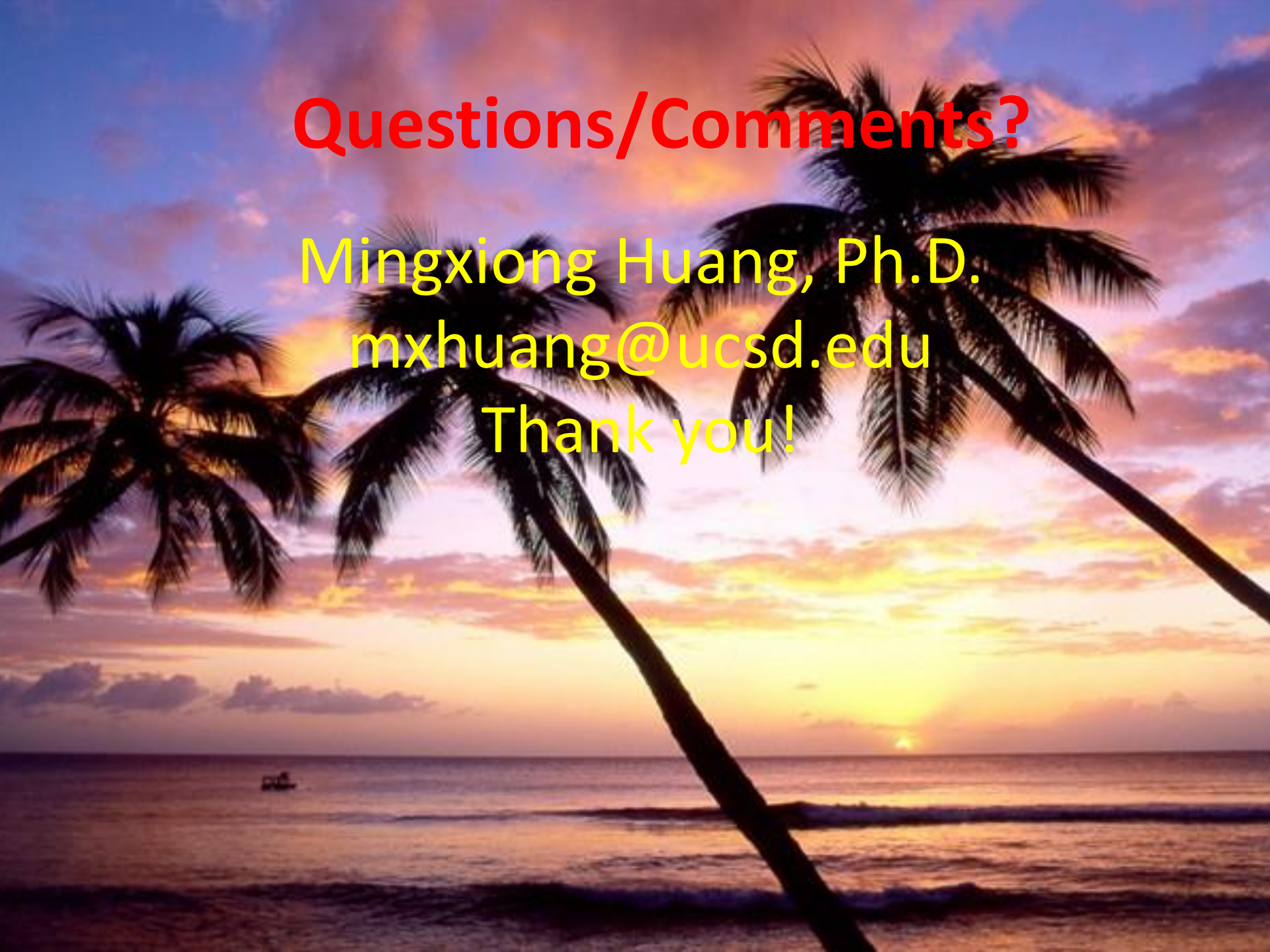
Resources

- “Invisible Injuries become not so Invisible” TV Interview with Col G.I. Wilson by KPBS: http://www.youtube.com/watch?v=uhlANIGAJXA
- National Public Radio interview “War Studies Suggest A Concussion Leaves The Brain Vulnerable To PTSD”: http://www.npr.org/sections/health-shots/2016/09/26/495074707/war-studies-suggest-a-concussion-leaves-the-brain-vulnerable-to-ptsd
- More publications from our lab: http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/48074704/?sort=date&direction=descending


Questions/Comments?
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Thank you!

Poll Question

- Which field(s) describes your interests in TBI (select all that apply)?
  - __ diagnosing TBI
  - __ treating TBI
  - __ animal research of TBI
  - __ human research of TBI SD
  - __ social work or other support to TBI