How can TMS benefit Veterans with chronic pain and headaches?

HSRD CYBERSEMINAR DEC, 2019

UC San Diego
SCHOOL OF MEDICINE

Albert Leung, M.D.

Professor of Anesthesiology and Pain Medicine

UC San Diego, School of Medicine,

Center for Pain Medicine

VA San Diego Healthcare System, Pain Service

Director, Center for Pain and Headache Research (CPHR)

Director, Center for TMS

VA San Diego
HEALTHCARE SYSTEM

Objectives

- Review the underlying analgesic mechanisms of TMS;
- Discuss the current outcome evidence of TMS for pain and headaches;
- Review the latest consensus panel review and treatment recommendations;
- Discuss relevant technical issues relevant to broader clinical implementation;

What is rTMS?

- Repetitive Transcranial Magnetic Stimulation (rTMS)
- A neurophysiological technique of inducing a localized current in the brain via dynamic magnetic flux passing the scalp and the skull safely and painlessly

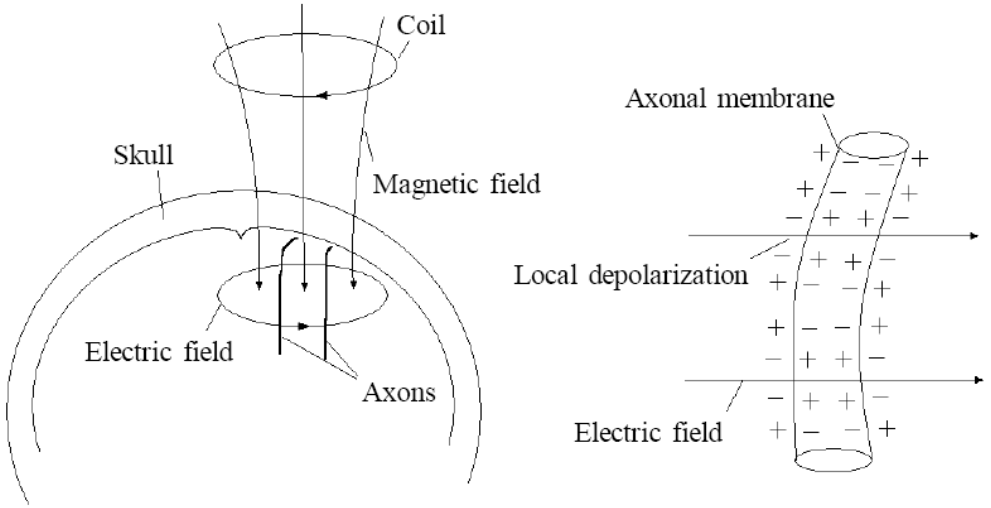
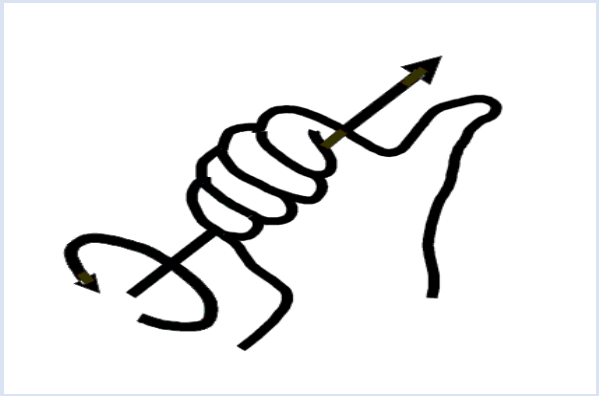


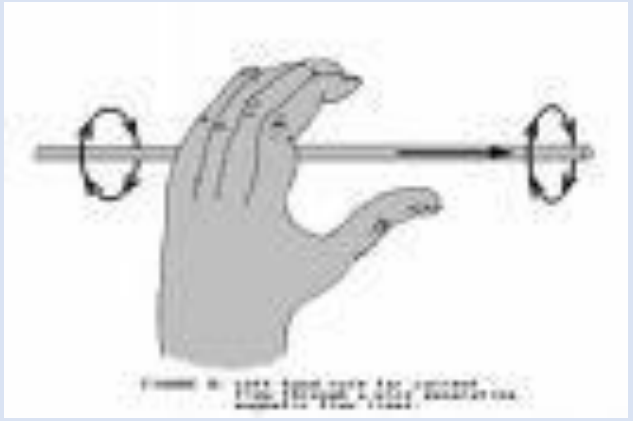
Fig. **Basic principes of transcranial magnetic stimulation**

Ampere's Law: Induction of electric field subsequently induces magnetic field

Faraday's Law: Generation of electric current by changing magnetic field

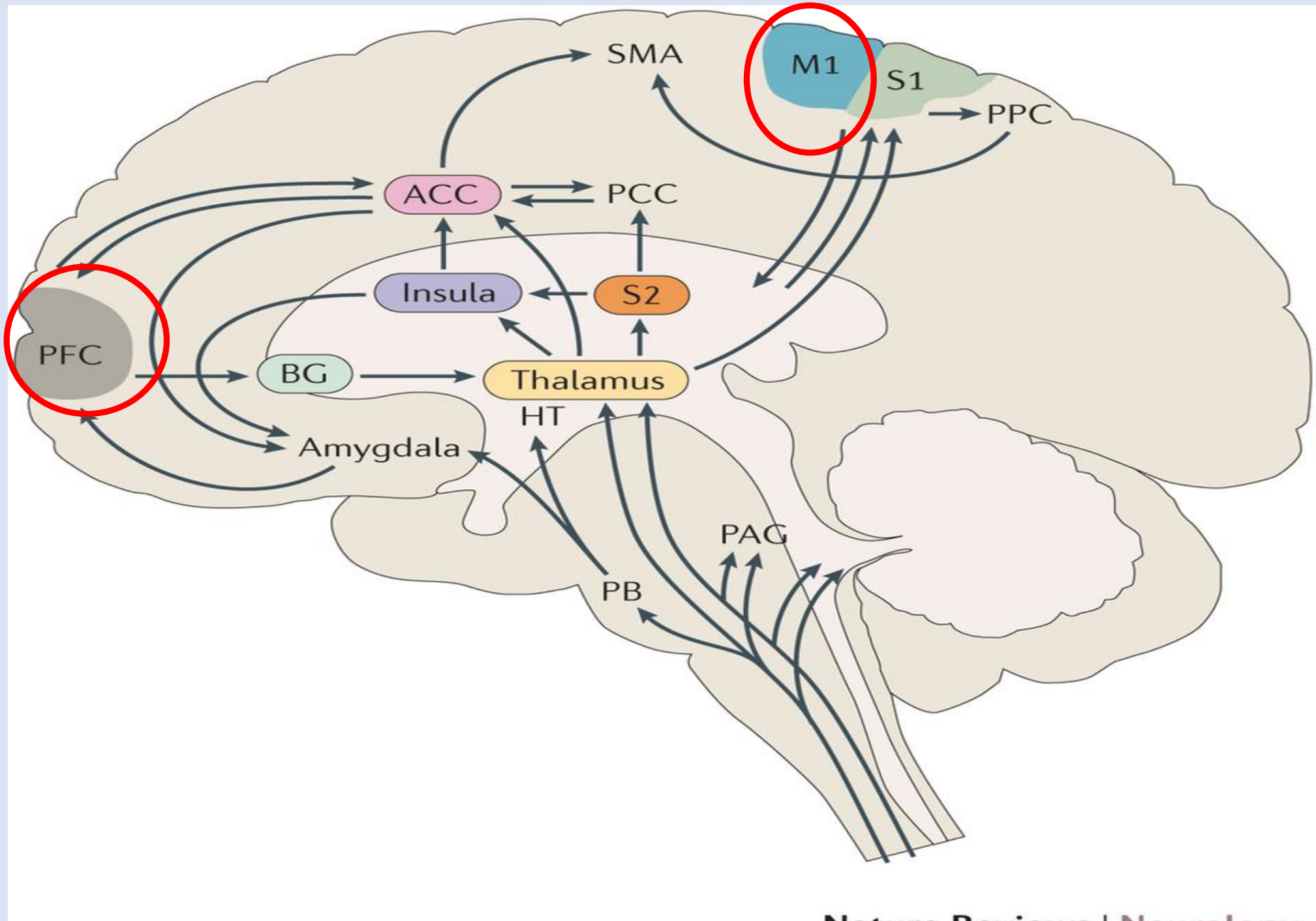
Electromagnetic Coupling



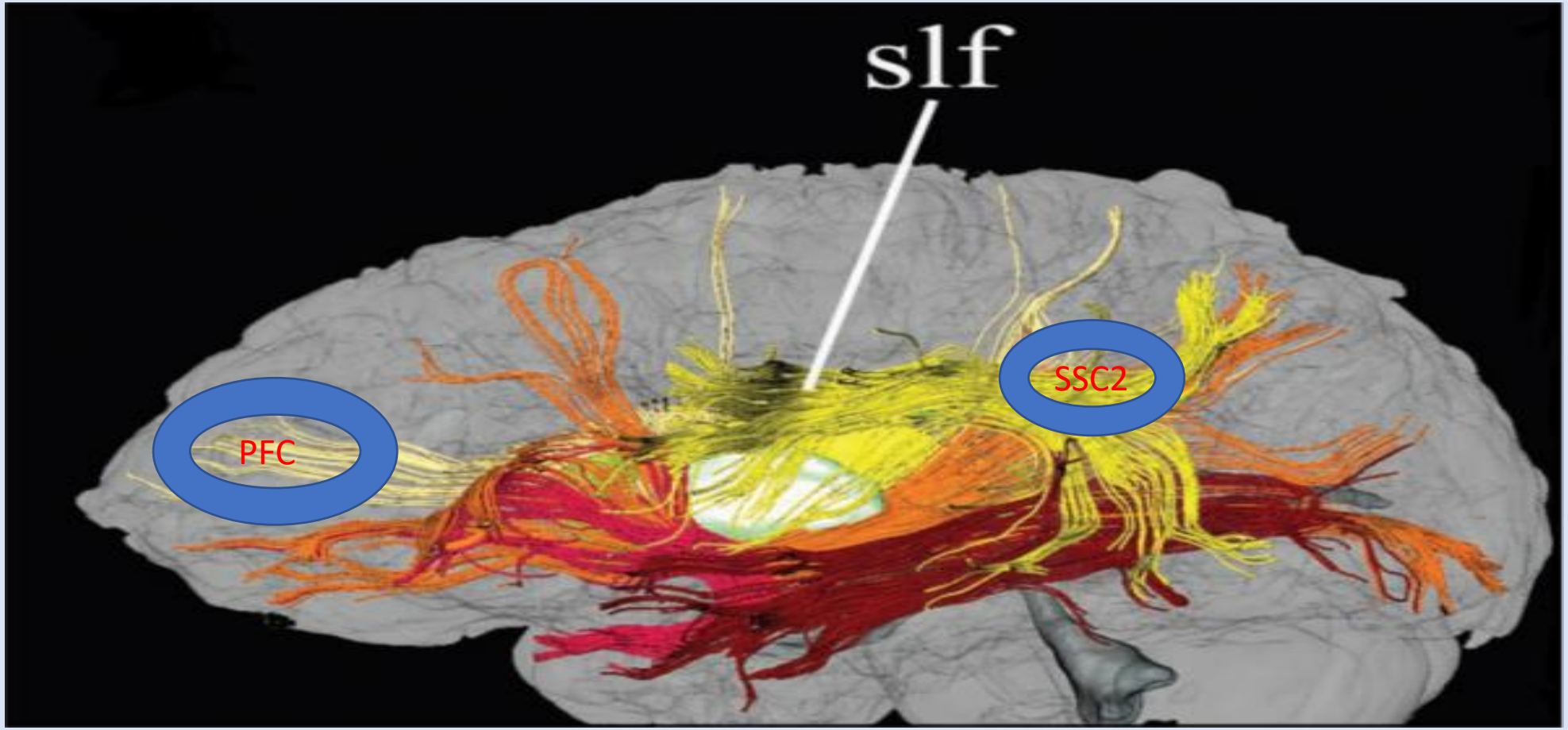


Supraspinal Pain Matrix

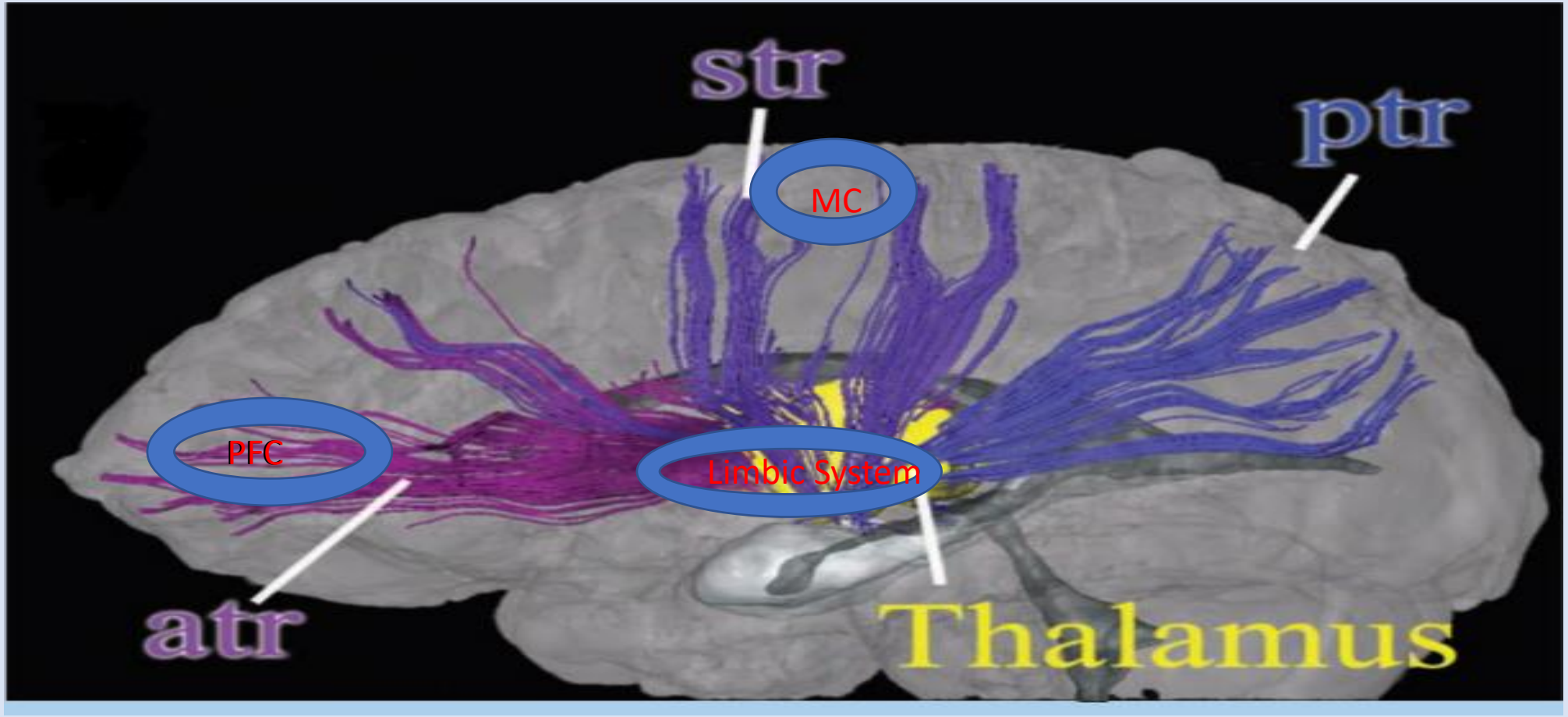
- Sensory Discriminatory
  - Primary Somatosensory Cortices (BA 1-3)
  - Secondary Somatosensory Cortices (BA5, 7)
  - Inferior Parietal Lobe (BA 39, 40)
- Affective & Emotional
  - Anterior Cingulate Cortex (BA 24, 32)
  - Insular (BA 13)
  - Amygdala
- Modulatory
  - Prefrontal cortices (BA 8-10, 46)
  - Premotor (BA 6) and Motor (BA 4)


SMA
M1
S1
PPC
ACC
PCC
Insula
S2
PFC
BG
Thalamus
HT
Amygdala
PAG
PB

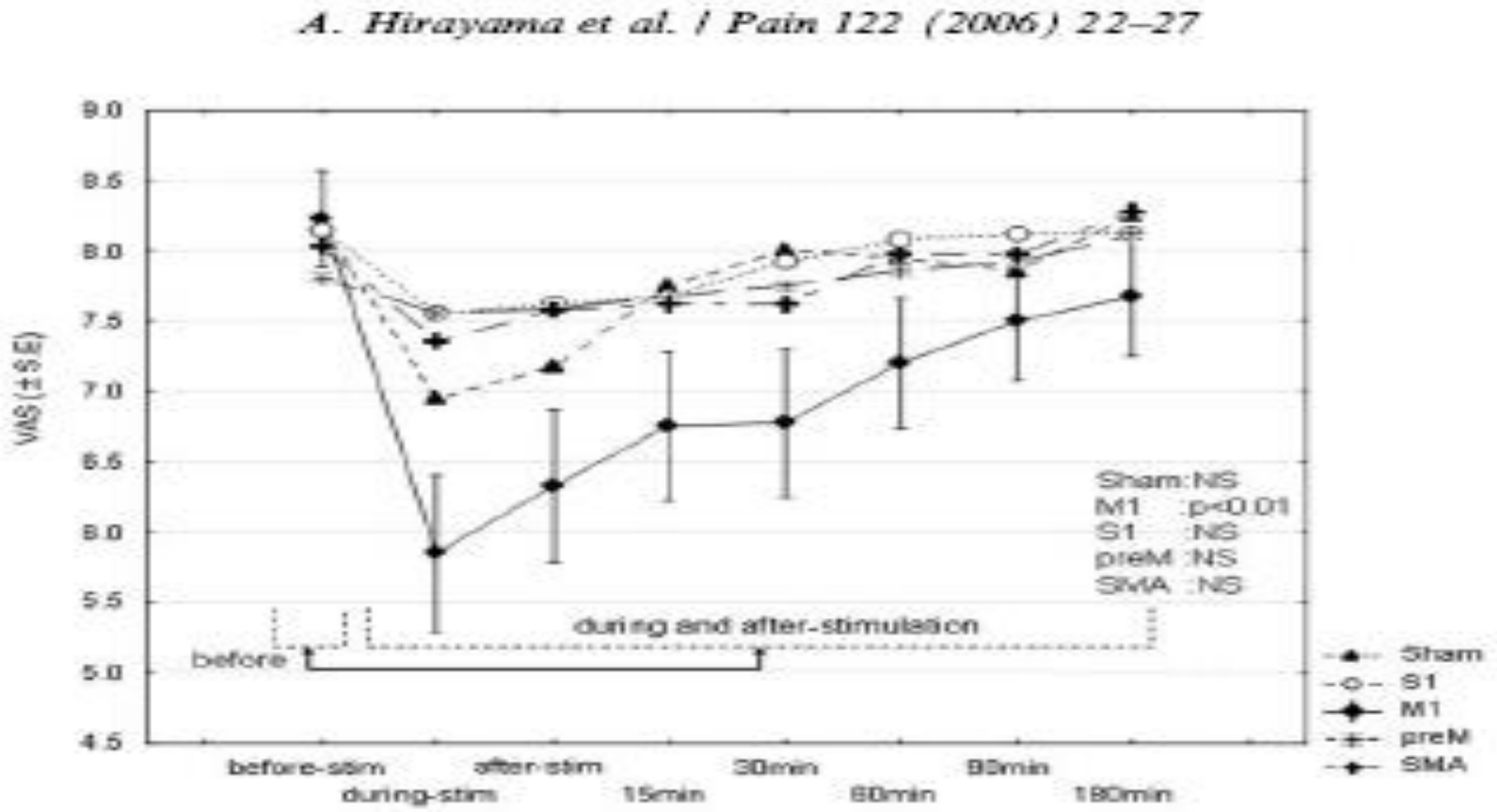
Superior Longitudinal Fasciculus



Anterior Thalamic Radiation Tract

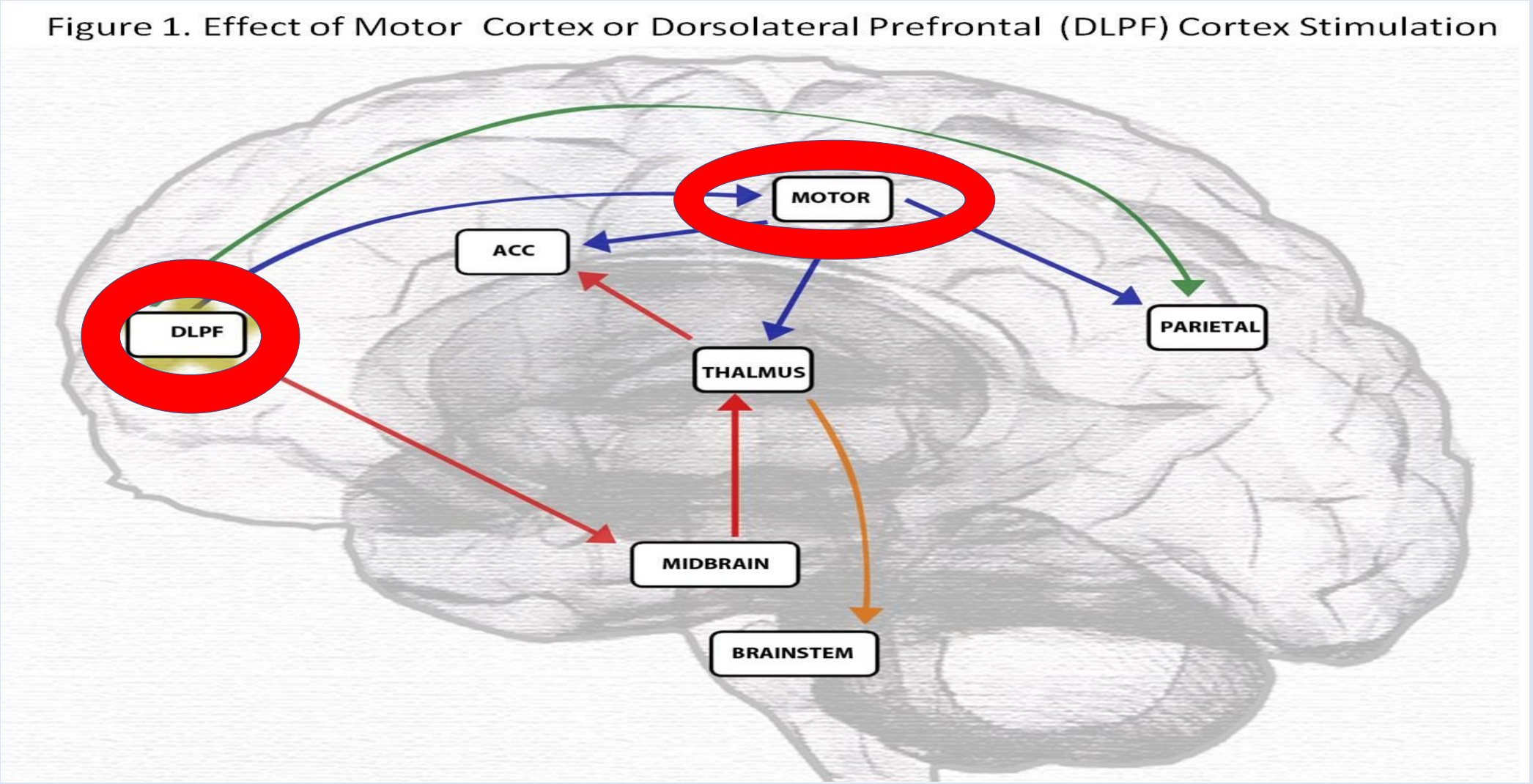


Site Specificity



Saitoh, Y., et al., *Stimulation of primary motor cortex for intractable deafferentation pain.* Acta Neurochir Suppl, 2006. **99**: p. 57-9.

Neuromodulatory Pathway of rTMS



PAIN® 152 (2011) 320–326

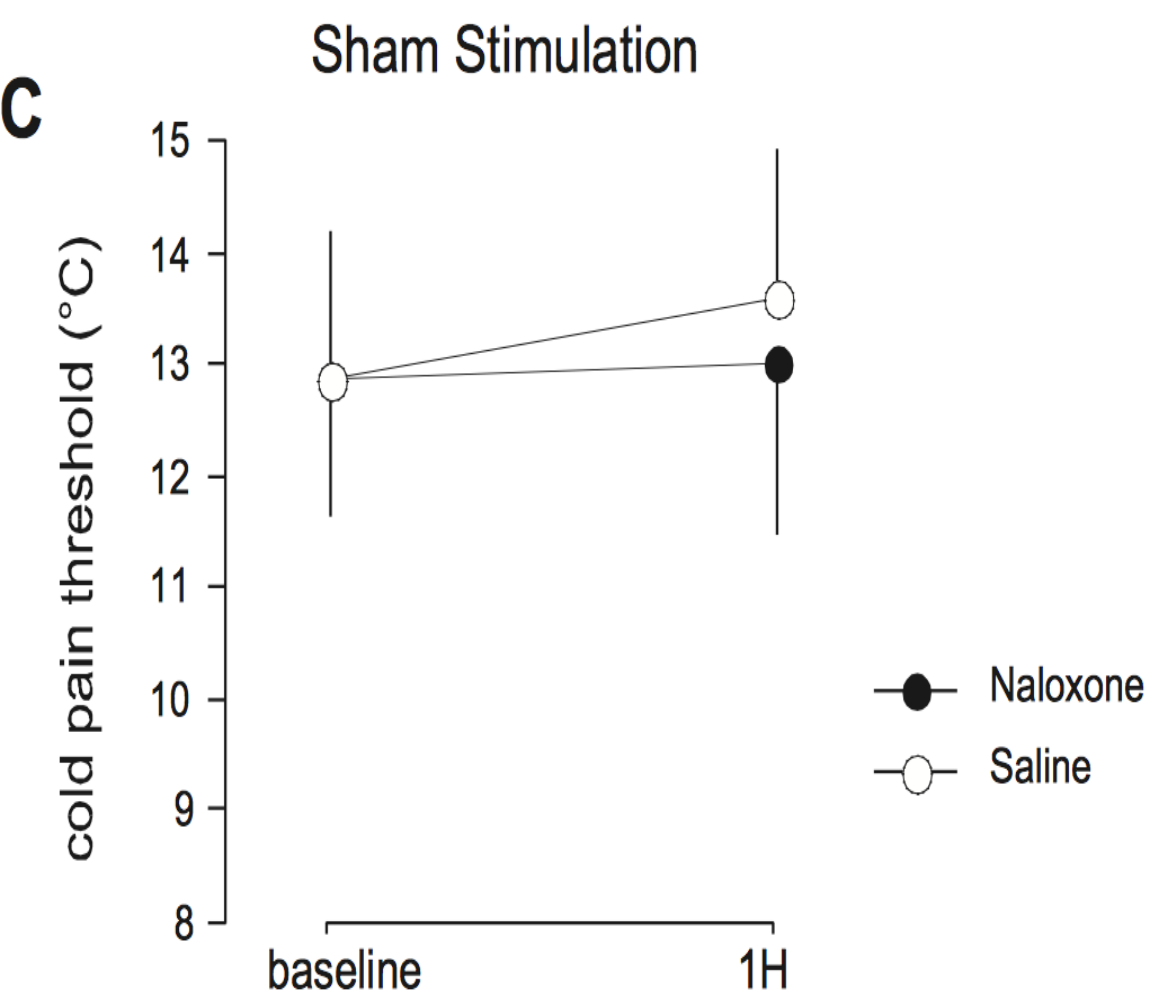
PAIN®

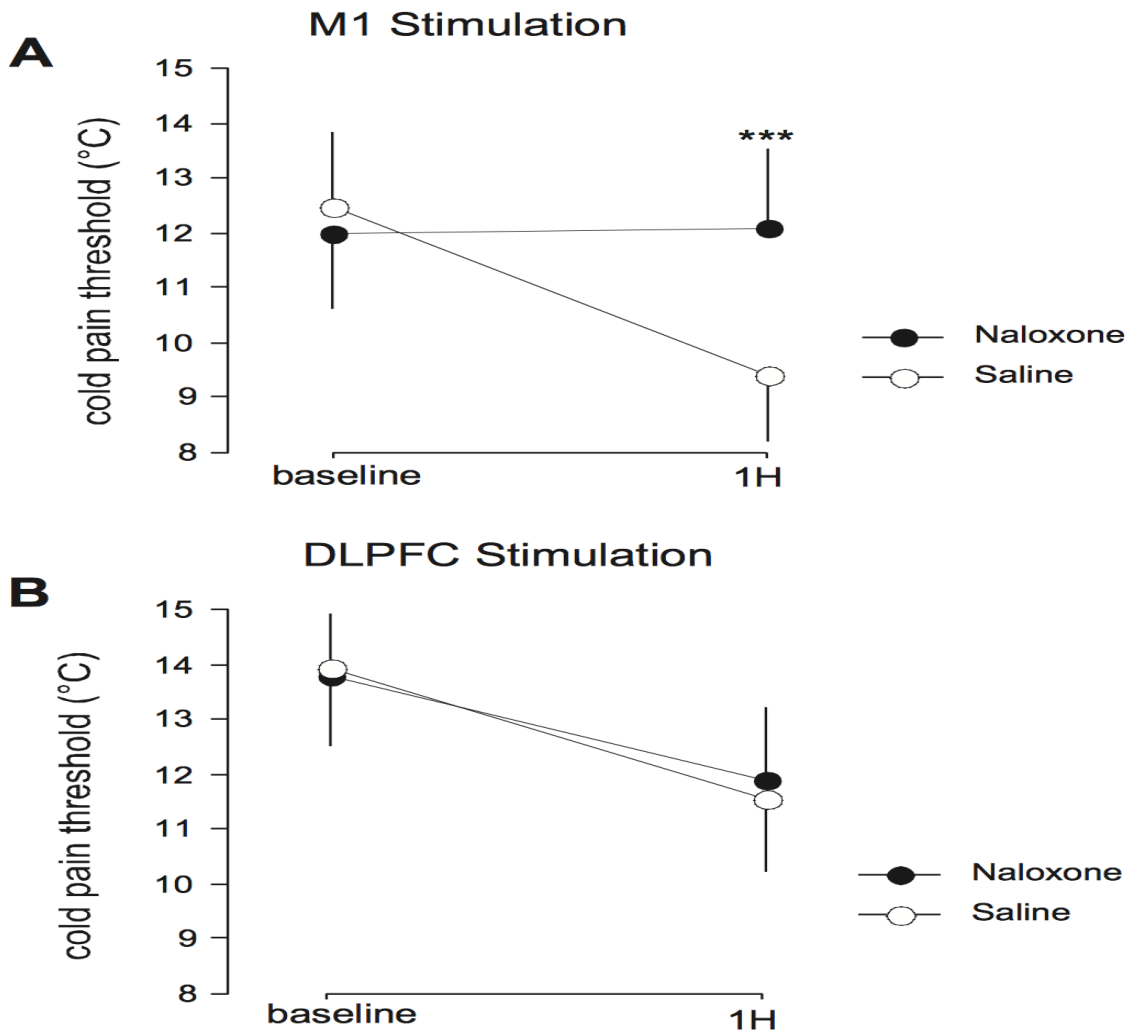
www.elsevier.com/locate/pain

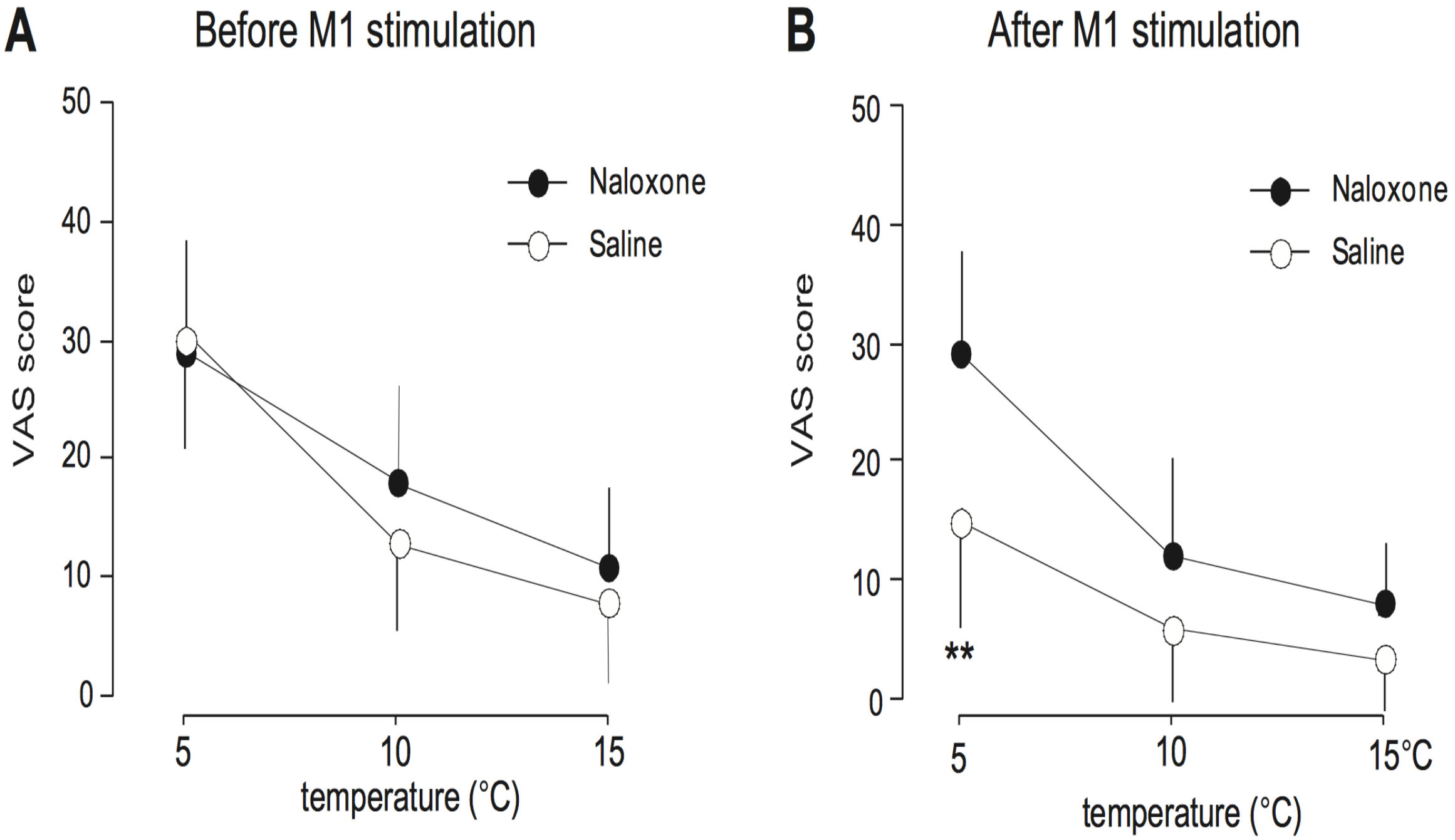
Neuropharmacological basis of rTMS-induced analgesia: The role of endogenous opioids

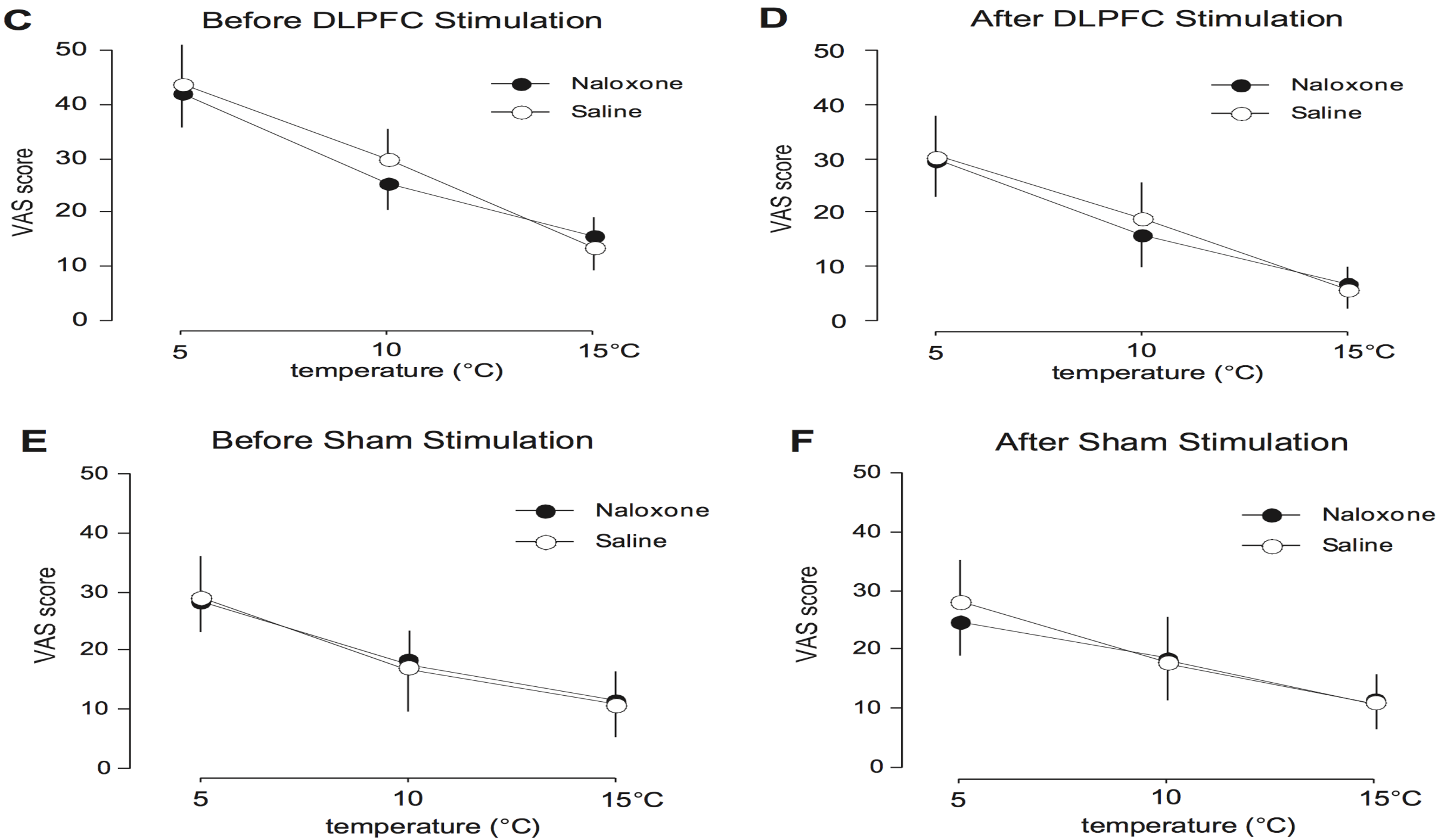
Daniel Ciampi de Andrade [a,b], Alaa Mhalla [a], Frédéric Adam [a], Manoel Jacobsen Texeira [b], Didier Bouhassira [a,*]

[a] INSERM U-987, Centre d'Evaluation et de Traitement de la Douleur, Ambroise Paré, Boulogne-Billancourt, France
[b] Department of Neurology, Hospital das Clinicas, University of São Paulo, Brazil






A
Before M1 stimulation
B
After M1 stimulation
VAS score
50
40
30
20
10
0
Naloxone
Saline
**
5
10
15
15°C
temperature (°C)

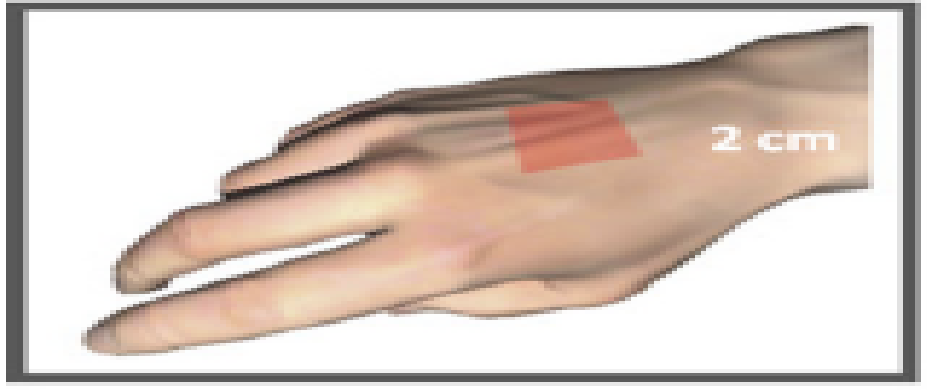

C
Before DLPFC Stimulation
VAS score
50
40
30
20
10
0
Naloxone
Saline
5
10
15°C
temperature (°C)
D
After DLPFC Stimulation
VAS score
50
40
30
20
10
0
Naloxone
Saline
5
10
15°C
temperature (°C)
E
Before Sham Stimulation
VAS score
50
40
30
20
10
0
Naloxone
Saline
5
10
15°C
temperature (°C)
F
After Sham Stimulation
VAS score
50
40
30
20
10
0
Naloxone
Saline
5
10
15°C
temperature (°C)

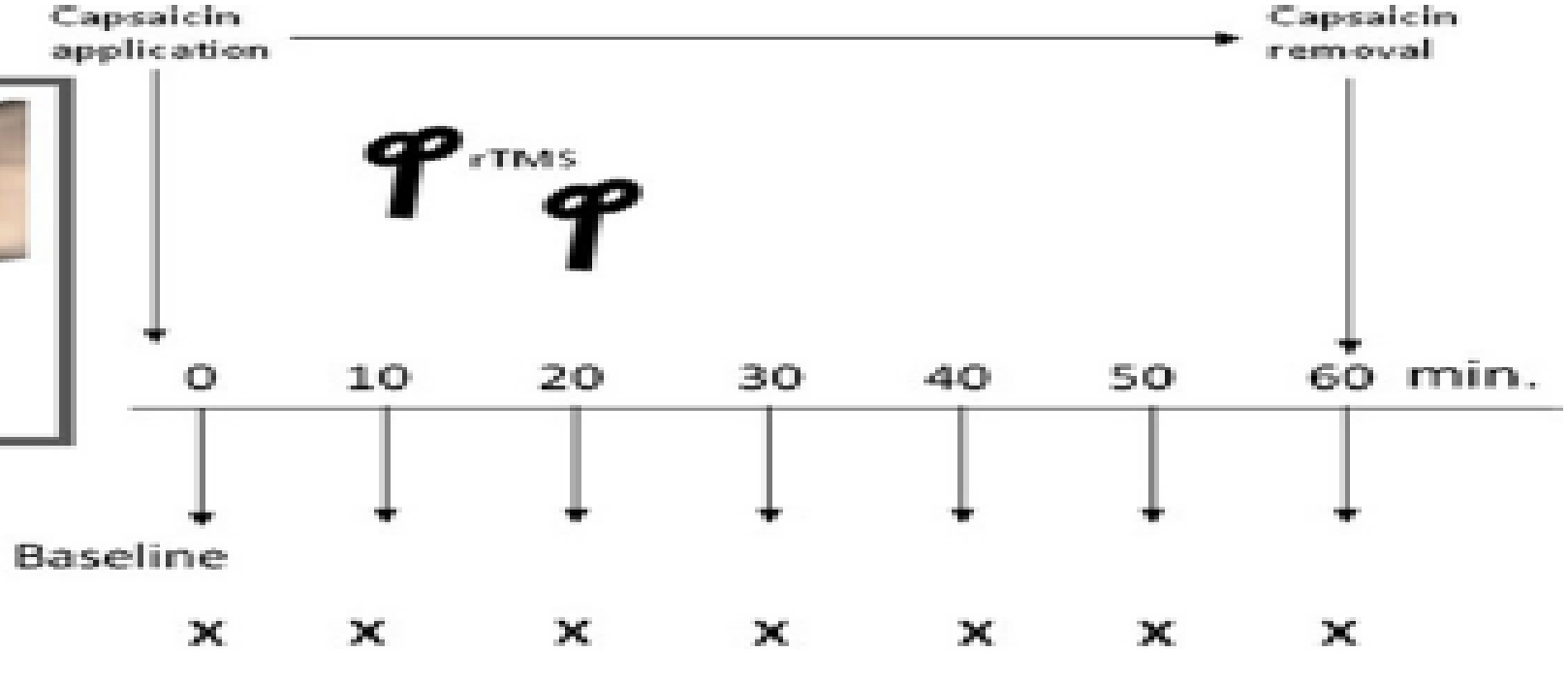
J Headache Pain (2011) 12:185–191
DOI 10.1007/s10194-011-0322-8

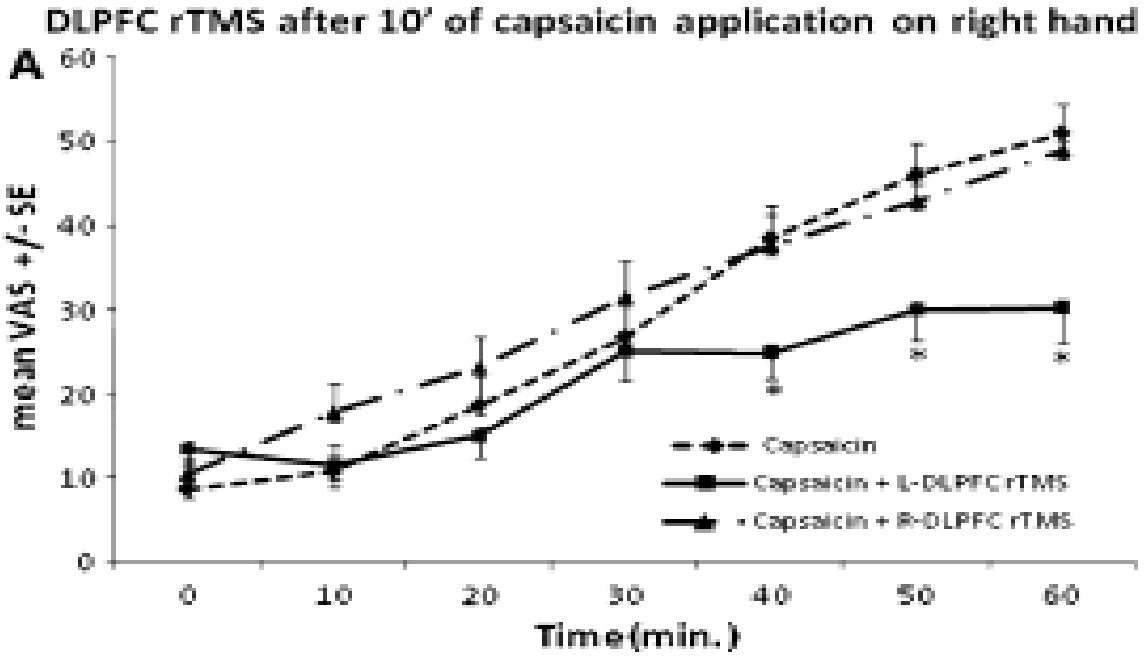
ORIGINAL

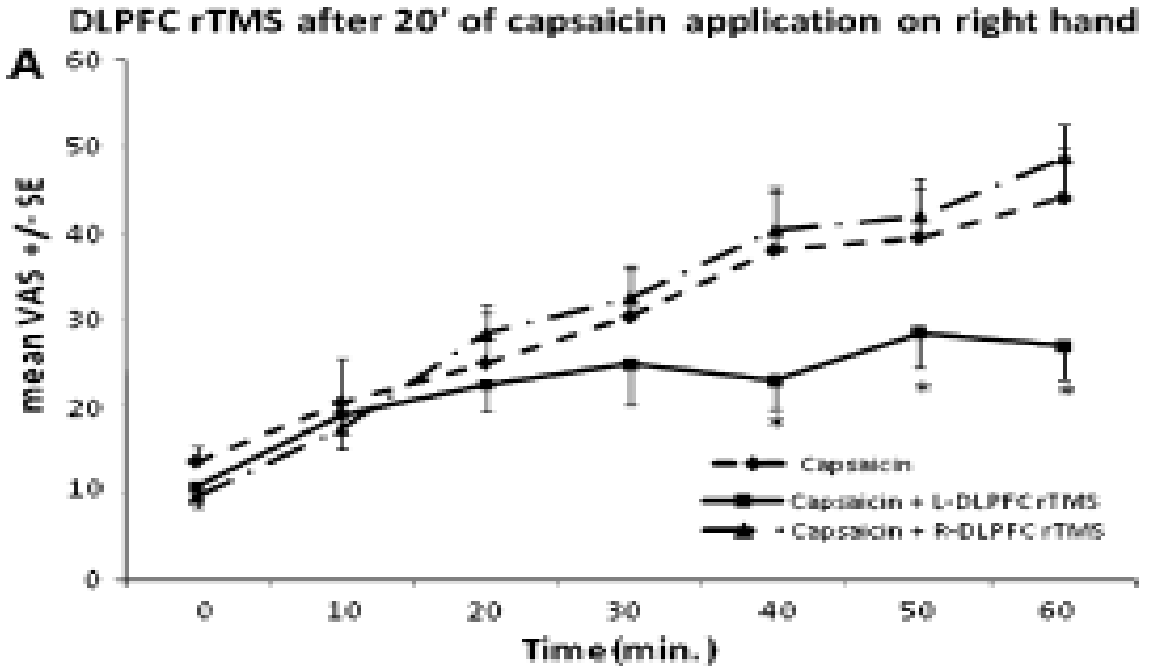
Modulation of pain perception by transcranial magnetic stimulation of left prefrontal cortex

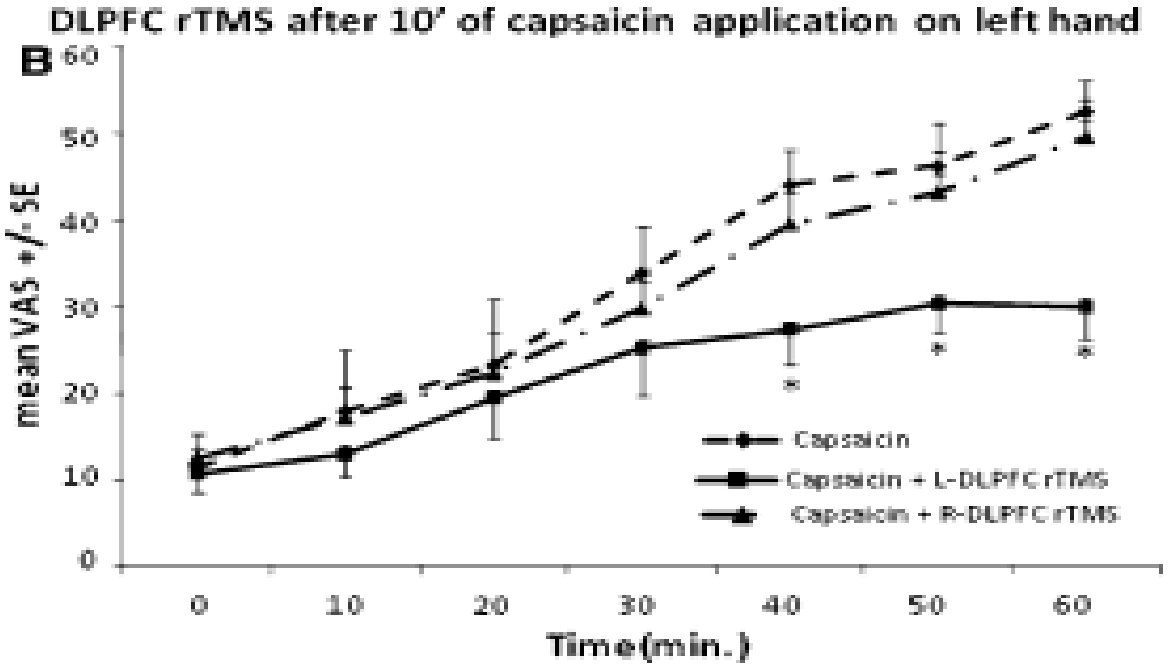
Filippo Brighina · Marina De Tommaso · Francesca Giglia · Simona Scalia · Giuseppe Cosentino · Angela Puma · Maristella Panetta · Giuseppe Giglia · Brigida Fierro

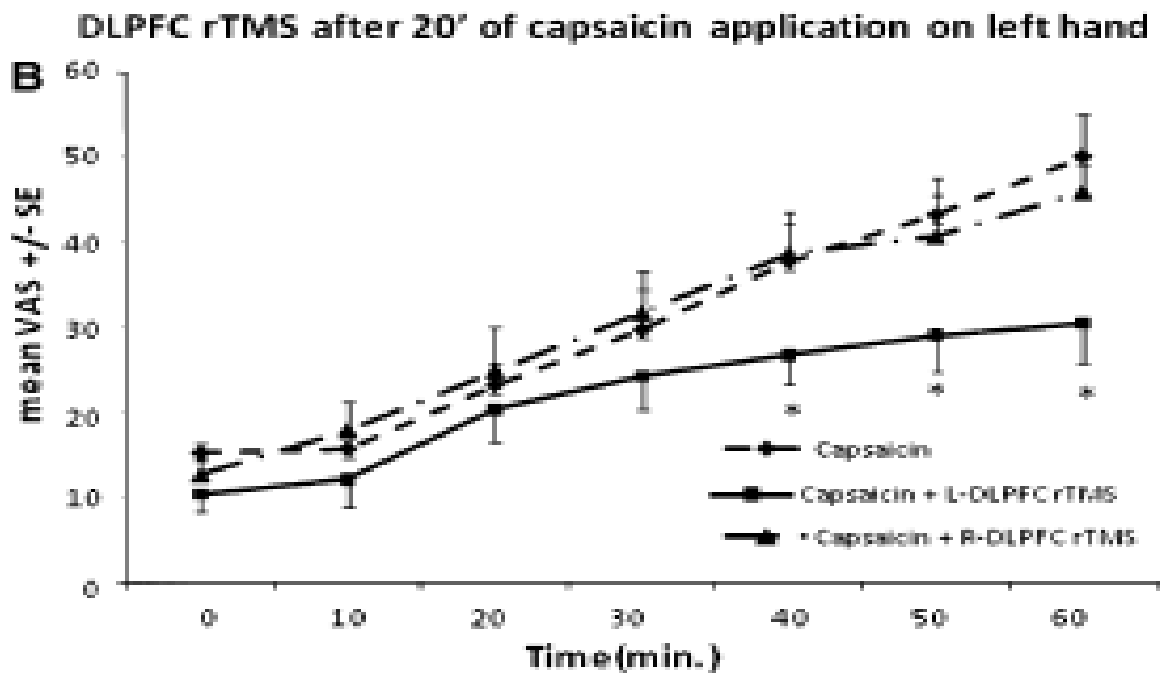





DLPFC rTMS after 10' of capsaicin application on right hand
A
mean VAS +/- SE
Time (min.)
Capsaicin
Capsaicin + L-DLPFC rTMS
Capsaicin + R-DLPFC rTMS


DLPFC rTMS after 20' of capsaicin application on right hand
A
mean VAS +/- SE
Time (min.)
Capsaicin
Capsaicin + L-DLPFC rTMS
Capsaicin + R-DLPFC rTMS


DLPFC rTMS after 10' of capsaicin application on left hand
B
mean VAS +/- SE
Time (min.)
Capsaicin
Capsaicin + L-DLPFC rTMS
Capsaicin + R-DLPFC rTMS


DLPFC rTMS after 20' of capsaicin application on left hand
B
mean VAS +/- SE
Time (min.)
Capsaicin
Capsaicin + L-DLPFC rTMS
Capsaicin + R-DLPFC rTMS

PubMed Literature

- Depression (US FDA APPROVED)~2,040
- Acute and chronic Pain~1,000
- Migraine (US FDA APPROVED)-199
- Headache~196
- Schizophrenia~497
- Parkinson~439
- Motor neuron disorder~247
- Movement disorder~514
- Autism~92

EARLY META-ANALYSIS

The Journal of Pain, Vol 10, No 12 (December), 2009: pp 1205-1216
Available online at www.sciencedirect.com

ELSEVIER

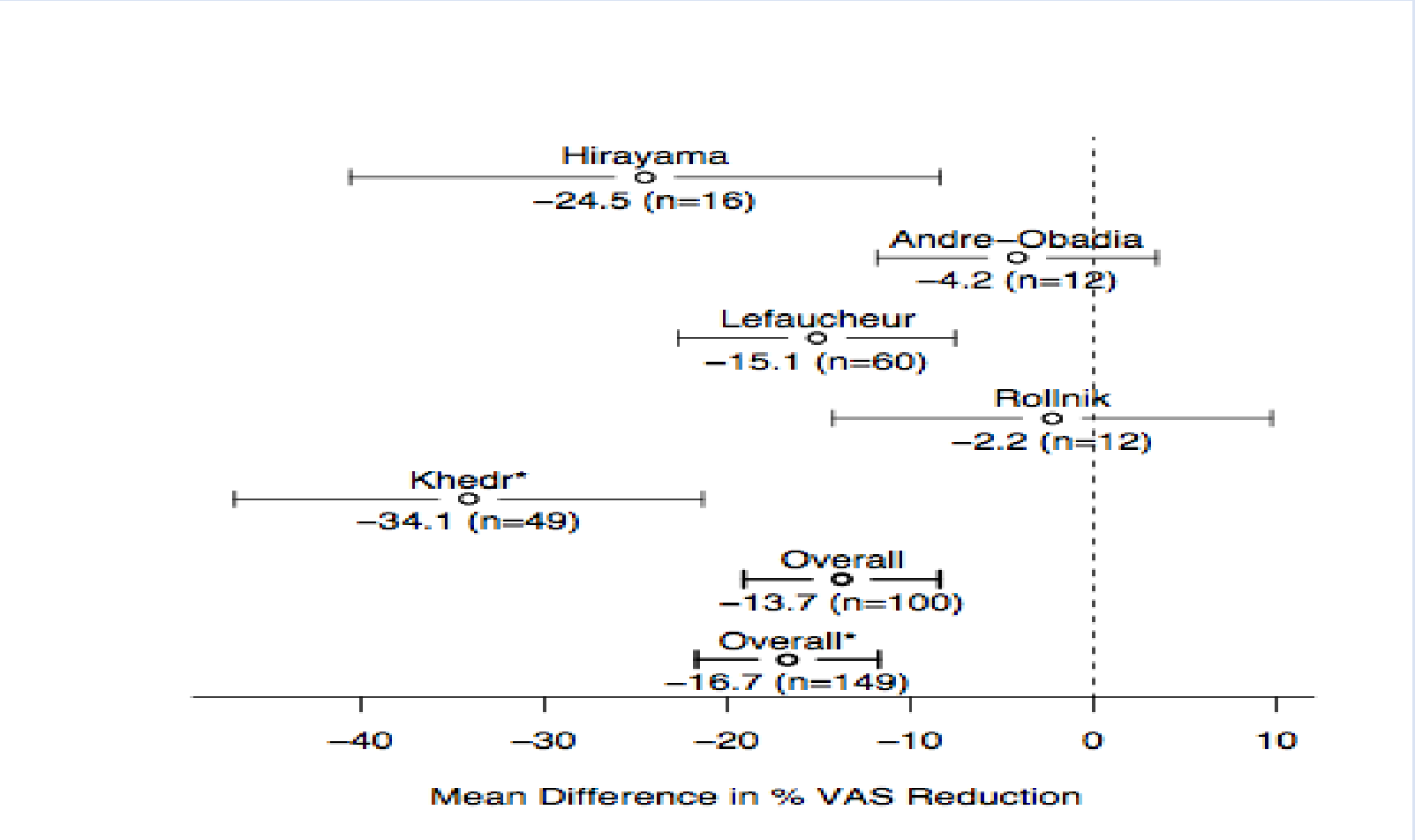
Review Article

rTMS for Suppressing Neuropathic Pain: A Meta-Analysis

Albert Leung,[*] Michael Donohue,[†] Ronghui Xu,[‡] Ryan Lee,[§] Jean-Pascal Lefaucheur,[¶] Eman M. Khedr,[‖] Youichi Saitoh,[**] Nathalie André-Obadia,[††] Jens Rollnik,[‡‡] Mark Wallace,[§§] and Robert Chen[¶¶]

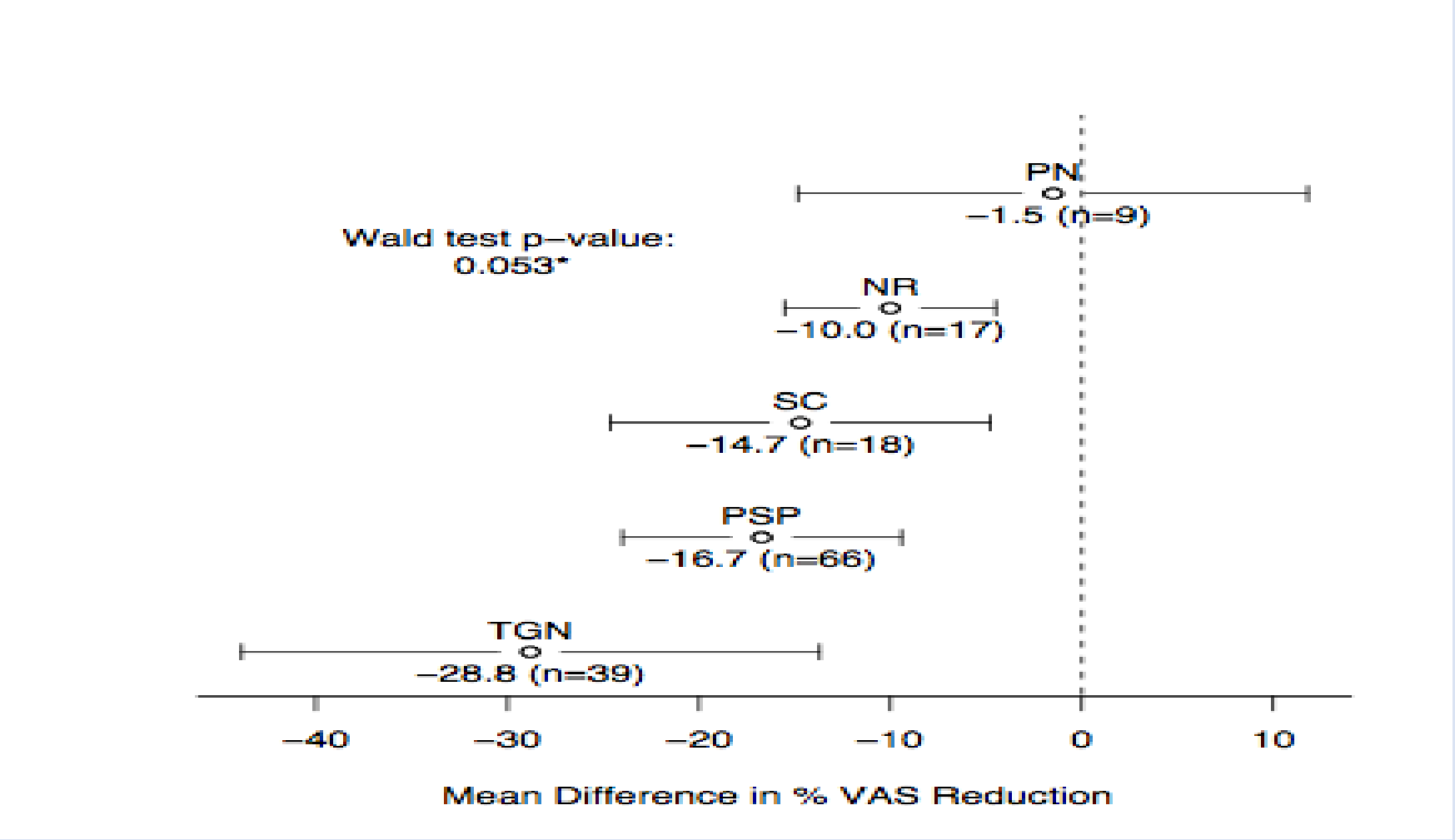
[*] *Department of Anesthesiology, The University of California, San Diego, School of Medicine, VA San Diego Healthcare System.*
[†] *Department of Family and Preventive Medicine, The University of California, San Diego, School of Medicine.*
[‡] *Department of Family and Preventive Medicine, and Department of Mathematics, The University of California, San Diego, School of Medicine.*
[§] *The University of California, San Diego.*
[¶] *Department of Physiology, Henri Mondor University Hospital, Créteil, France.*
[‖] *Department of Neurology, Assiut University Hospital, Assiut, Egypt.*
[**] *Department of Neurosurgery, Osaka University Graduate School of Medicine, Osaka, Japan.*
[††] *Department of Neurology, University Hospital Lyon Sud, Lyon, France.*
[‡‡] *Department of Neurology and Clinical Neurophysiology, Medical School of Hannover, Germany.*

Overall Treatment effect



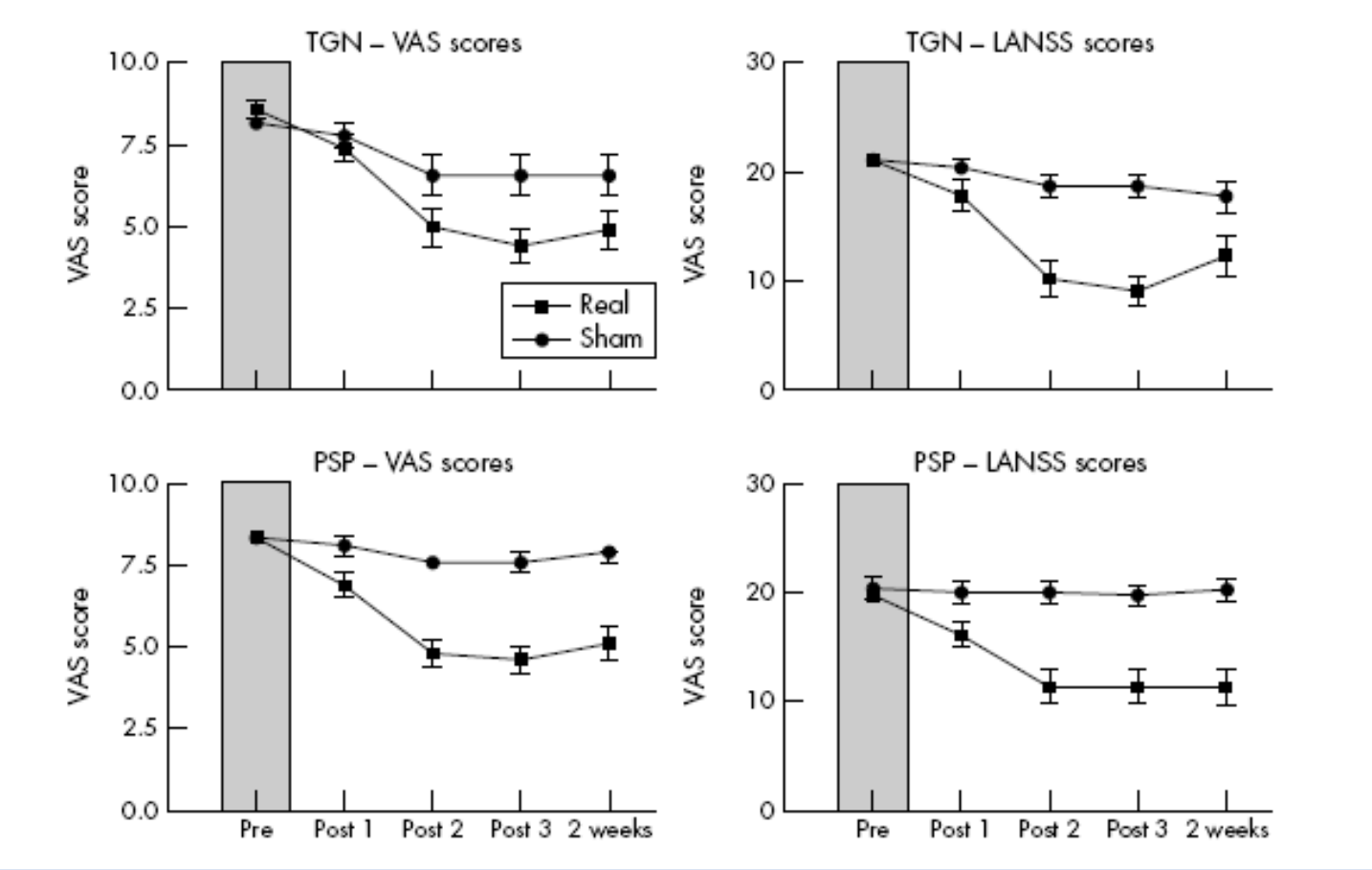
Leung et al., Journal of Pain,2009

Neuroanatomical Etiology and Treatment Effect



Leung et al., Journal of Pain,2009

Long-Term Benefit



Follow-up Meta-analysis and Guideline

Clinical Neurophysiology 125 (2014) 2150–2206

Contents lists available at ScienceDirect

Clinical Neurophysiology

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

Guidelines

Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS)

Jean-Pascal Lefaucheur [a,b,*], Nathalie André-Obadia [c,d], Andrea Antal [e], Samar S. Ayache [a,b], Chris Baeken [f,g], David H. Benninger [h], Roberto M. Cantello [i], Massimo Cincotta [j], Mamede de Carvalho [k], Dirk De Ridder [l,m], Hervé Devanne [n,o], Vincenzo Di Lazzaro [p], Saša R. Filipović [q], Friedhelm C. Hummel [r], Satu K. Jääskeläinen [s], Vasilios K. Kimiskidis [t], Giacomo Koch [u], Berthold Langguth [v], Thomas Nyffeler [w], Antonio Oliviero [x], Frank Padberg [y], Emmanuel Poulet [z,aa], Simone Rossi [ab], Paolo Maria Rossini [ac,ad], John C. Rothwell [ae], Carlos Schönfeldt-Lecuona [af], Hartwig R. Siebner [ag,ah], Christina W. Slotema [ai], Charlotte J. Stagg [aj], Josep Valls-Sole [ak], Ulf Ziemann [al], Walter Paulus [e,1], Luis Garcia-Larrea [d,am,1]

2014 Evidence Based Ranking

LEVEL A (Definite)

- HF C-M1:NP
- HF Lt. F3: Depression

LEVEL B (Probable)

- HF Lt. F3:NP
- LF Rt.F3: Depression
- HF Lt. F3: Schizophrenia
- LF M1: Motor Stroke

LEVEL C (Possible)

- LF TP: Tinnitus /Auditory Hallucination

NP: Neuropathic Pain; HF: High Frequency (>1 hz); LF: Low Frequency (≤Lobe1 hz); M1: Primary Motor Cortex; F3: Dorsolateral Prefrontal Cortex; TP: Temporal Parietal; C: contralateral

Top Responding NP Conditions

- Post-Stroke Central Pain
- Trigeminal Neuralgia
- Phantom Limb Pain

- Lefaucheur, J.P., et al., *Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS).* Clin Neurophysiol, 2014. **125**(11): p. 2150-2206.

Updated Evidence Ranking

- Level A Evidence
  - HF-rTMS of the left dorsolateral prefrontal cortex (DLPFC) using a figure-of-8 or a H1-coil for depression;
  - Low-frequency rTMS of contralesional M1 for hand motor recovery in the post-acute stage of stroke.

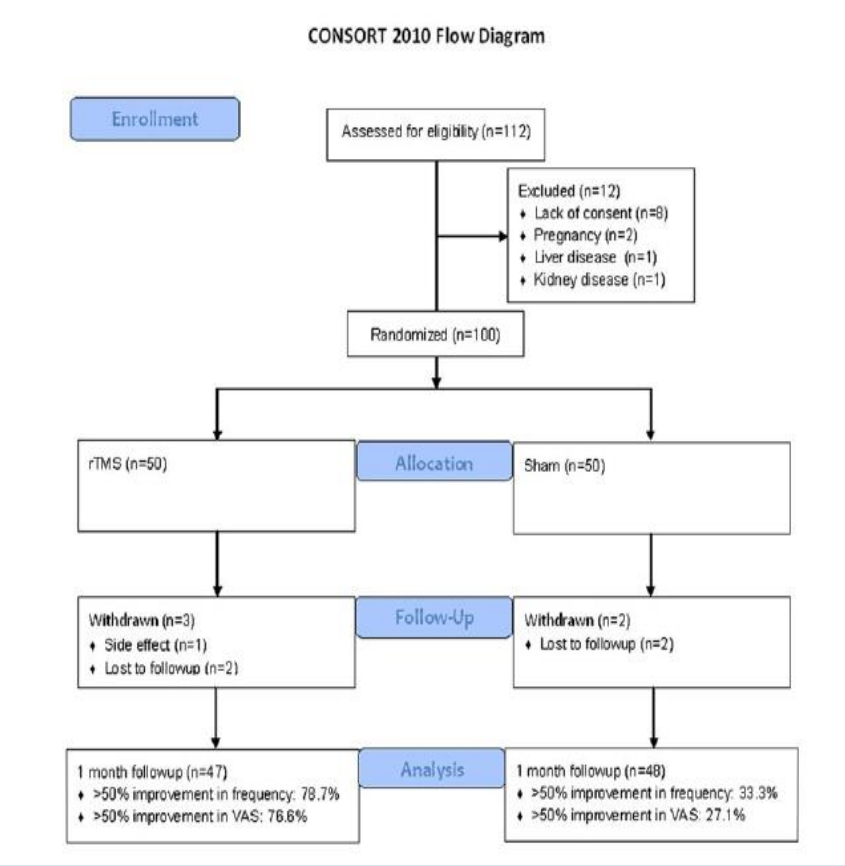
Updated Evidence Rankings

- Level B (Probable) Evidence
  - HF-rTMS of the left M1 or DLPFC for improving quality of life or pain, respectively, in fibromyalgia;
  - HF-rTMS of bilateral M1 regions or the left DLPFC for treating motor impairment or depression, respectively, in Parkinson's disease;
  - HF-rTMS of ipsilesional M1 in motor stroke at the post-acute stage of stroke; intermittent theta burst stimulation targeted to the leg motor cortex for lower limb spasticity in multiple sclerosis;
  - HF-rTMS of the right DLPFC in posttraumatic stress disorder; LF-rTMS of the right inferior frontal gyrus in chronic post-stroke non-fluent aphasia;
  - LF-rTMS of the right DLPFC in depression;
  - Bihemispheric stimulation of the DLPFC combining right-sided LF-rTMS (or continuous theta burst stimulation) and left-sided HF-rTMS (or intermittent theta burst stimulation) in depression;

Got Headaches?

rTMS RCT in Migraine prophylaxis

Study Design

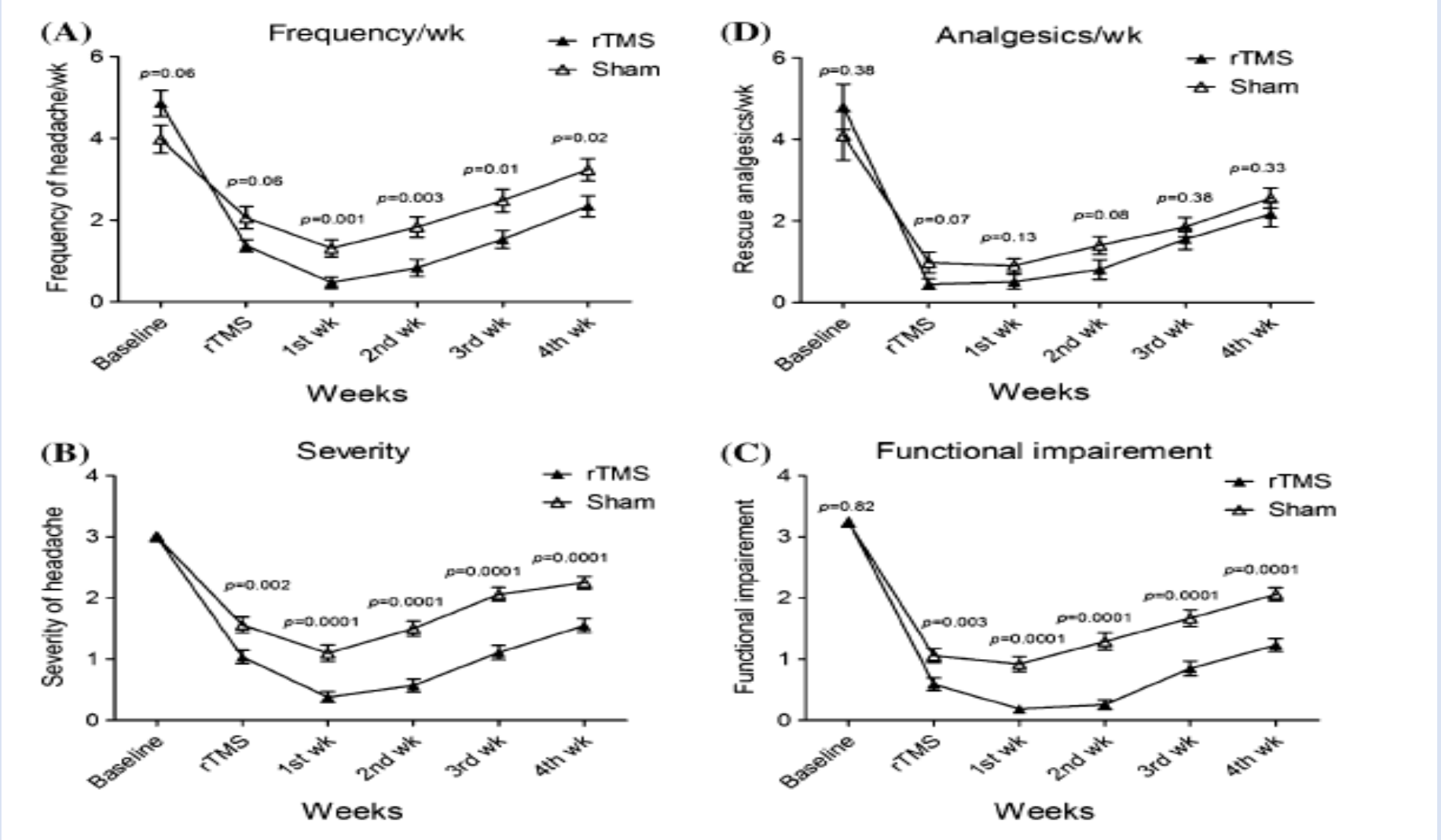


Protocol

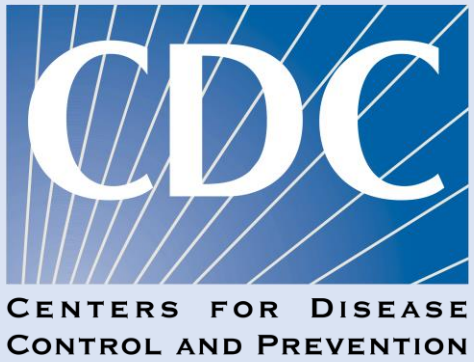
- 3 sessions in alternate days at PFC
- 10Hz, 600 pulses in 6 trains
- 80% MT
- Anatomical landmark based
- Weekly assessment up to one month

Mirsa et al., J Neurol, 2013

Outcomes


(A)
Frequency/wk
rTMS
Sham
Frequency of headache/wk
p=0.06
p=0.06
p=0.001
p=0.003
p=0.01
p=0.02
Baseline
rTMS
1st wk
2nd wk
3rd wk
4th wk
Weeks
(D)
Analgesics/wk
rTMS
Sham
Rescue analgesics/wk
p=0.38
p=0.07
p=0.13
p=0.08
p=0.38
p=0.33
Baseline
rTMS
1st wk
2nd wk
3rd wk
4th wk
Weeks
(B)
Severity
rTMS
Sham
Severity of headache
p=0.002
p=0.0001
p=0.0001
p=0.0001
p=0.0001
Baseline
rTMS
1st wk
2nd wk
3rd wk
4th wk
Weeks
(C)
Functional impairement
rTMS
Sham
Functional impairement
p=0.82
p=0.003
p=0.0001
p=0.0001
p=0.0001
p=0.0001
Baseline
rTMS
1st wk
2nd wk
3rd wk
4th wk
Weeks

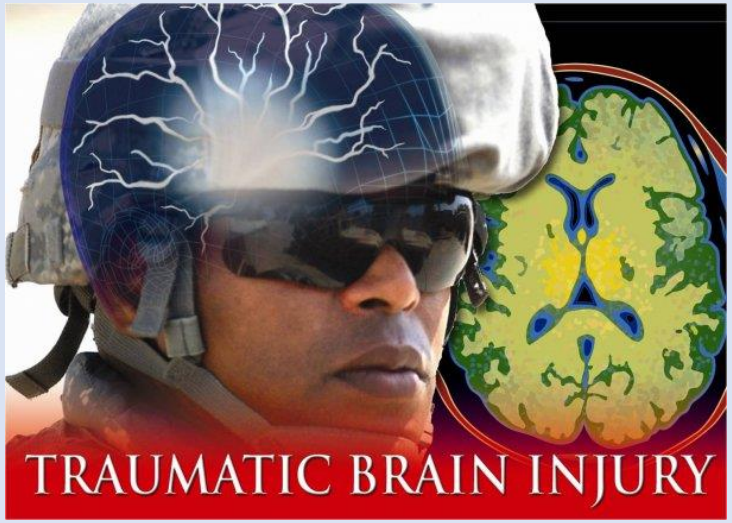
Traumatic Brain Injury

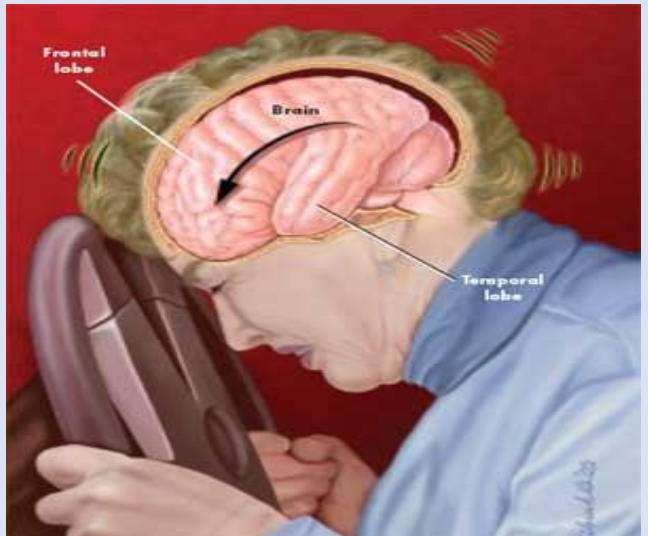


- An estimated **1.7 million people** sustain a TBI annually.

- https://www.cdc.gov/traumaticbraininjury/pdf/bluebook_factsheet-a.pdf

Mild Traumatic Brain Injury (MTBI)





MTBI

- A traumatically induced physiological disruption of brain function, as manifested by at least one of the following:
- 1) any loss of consciousness;
- 2) any loss of memory for events immediately before or after the accident;
- 3) any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused) and focal neurologic deficit (s) that may or may not be transient but where the severity of the injury does not exceed the following:
  - 1) loss of consciousness of approximately 30 min or less;
  - 2) after 30 min, an initial Glasgow Coma Scale score of 13–15;
  - 3) post-traumatic amnesia not greater than 24 hrs.

Persistent Headaches in Patients with MTBI

- Persistent headaches is one of the most common debilitating symptoms in patients with mild traumatic brain injury (MTBI)

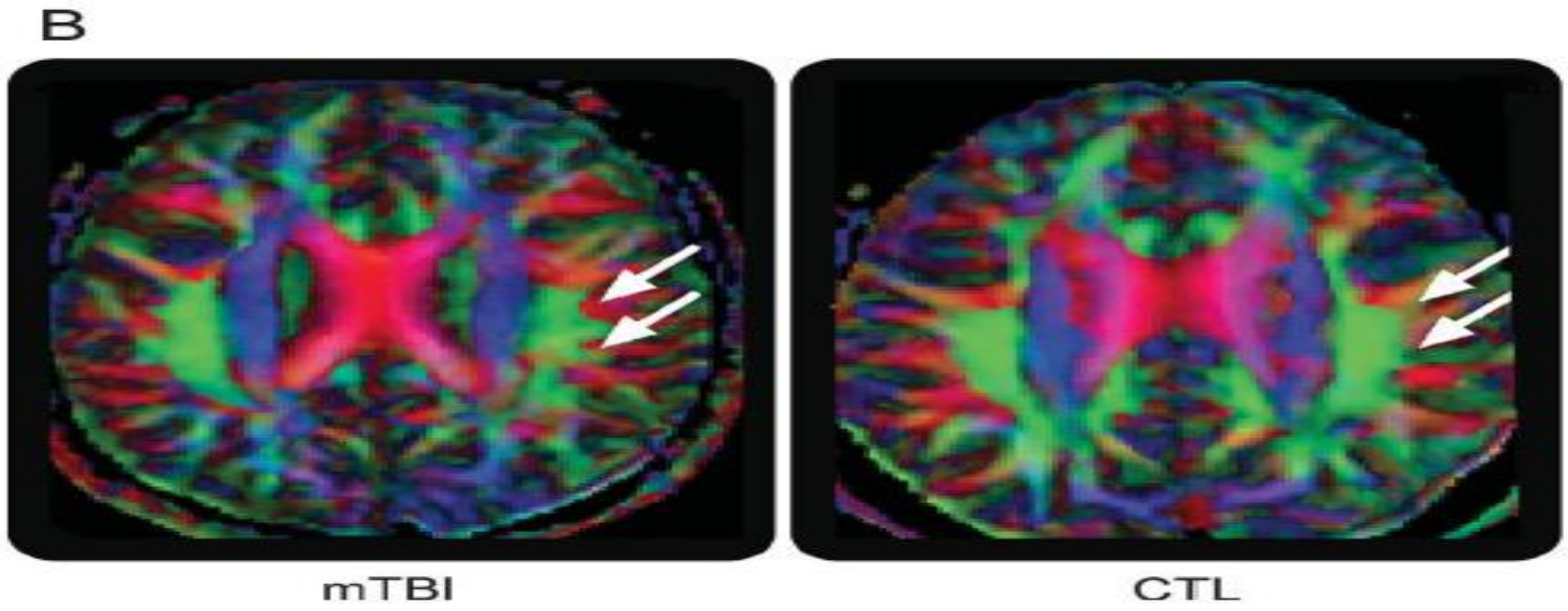
- The prevalence of headache (HA) in the general TBI population is estimated to be around 57.8%.
  - Patil et al., 2011

- **Overall incidence of persistent HA in Veterans with MTBI is even higher (over 90%) than the general population.**

- High prevalence of chronic HA is closely associated with neuropsychological dysfunction in mood, attention and memory.

Patil, V.K., et al., *Prevalence and treatment of headaches in veterans with mild traumatic brain injury.* Headache, 2011. **51**(7): p. 1112-21.

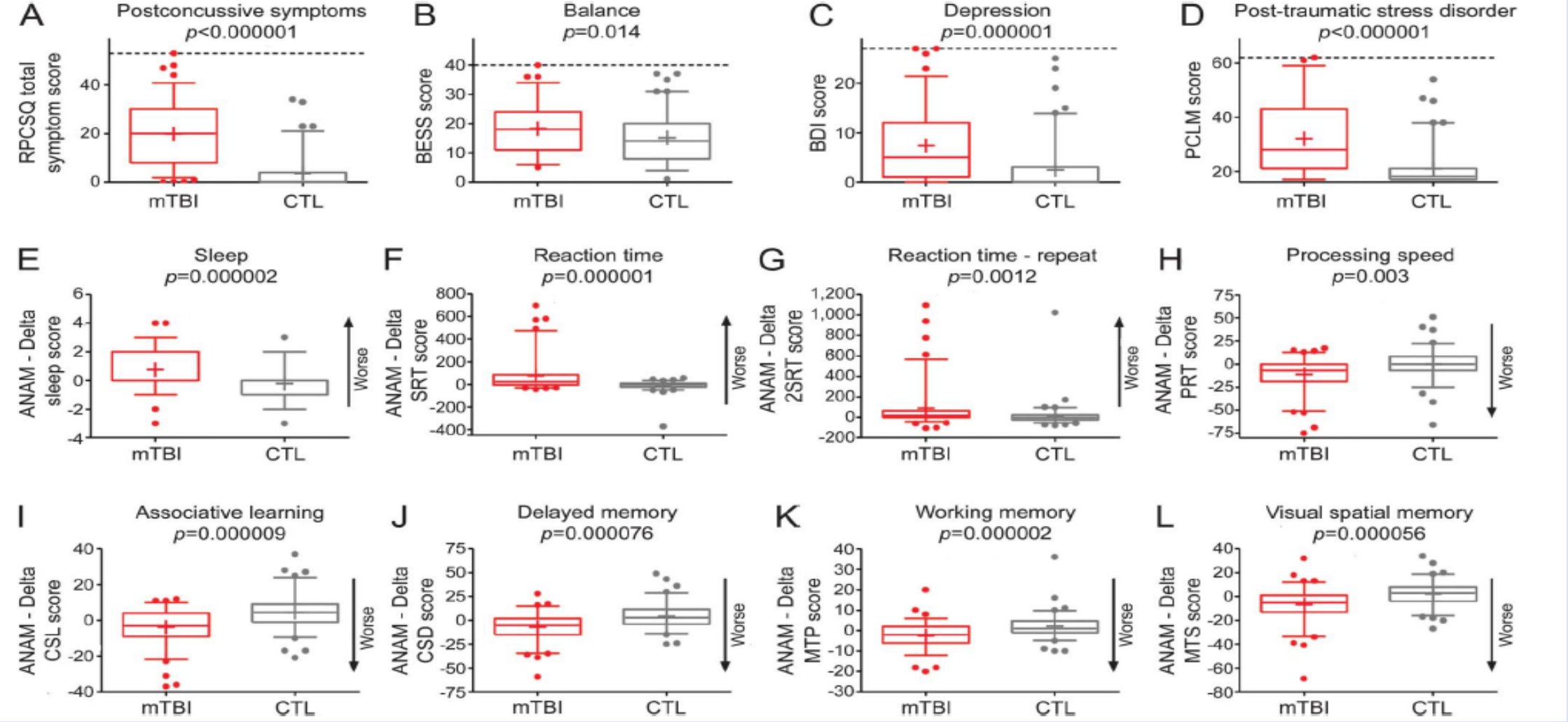
Loss of Fractional Anisotropy (FA) in the Superior Longitudinal Fasciculus



(A) Scatterplot of fractional anisotropy values for each participant. Solid horizontal lines represent the means and the SDs. The dotted horizontal line marks 2 SDs below the mean for CTL. Solid symbol points (triangles for mTBI, squares for CTL) represent participants below this level. (B) Diffusion tensor fractional anisotropy images displaying signal loss in the right superior longitudinal fasciculus in a participant with mTBI compared with a CTL (arrows). Images are displayed in anatomical convention. CTL = controls; mTBI = mild traumatic brain injury.

Adam et al., Neurology, 2015

Mood, Motor and Cognitive Functional Deficits



Cortical Excitability

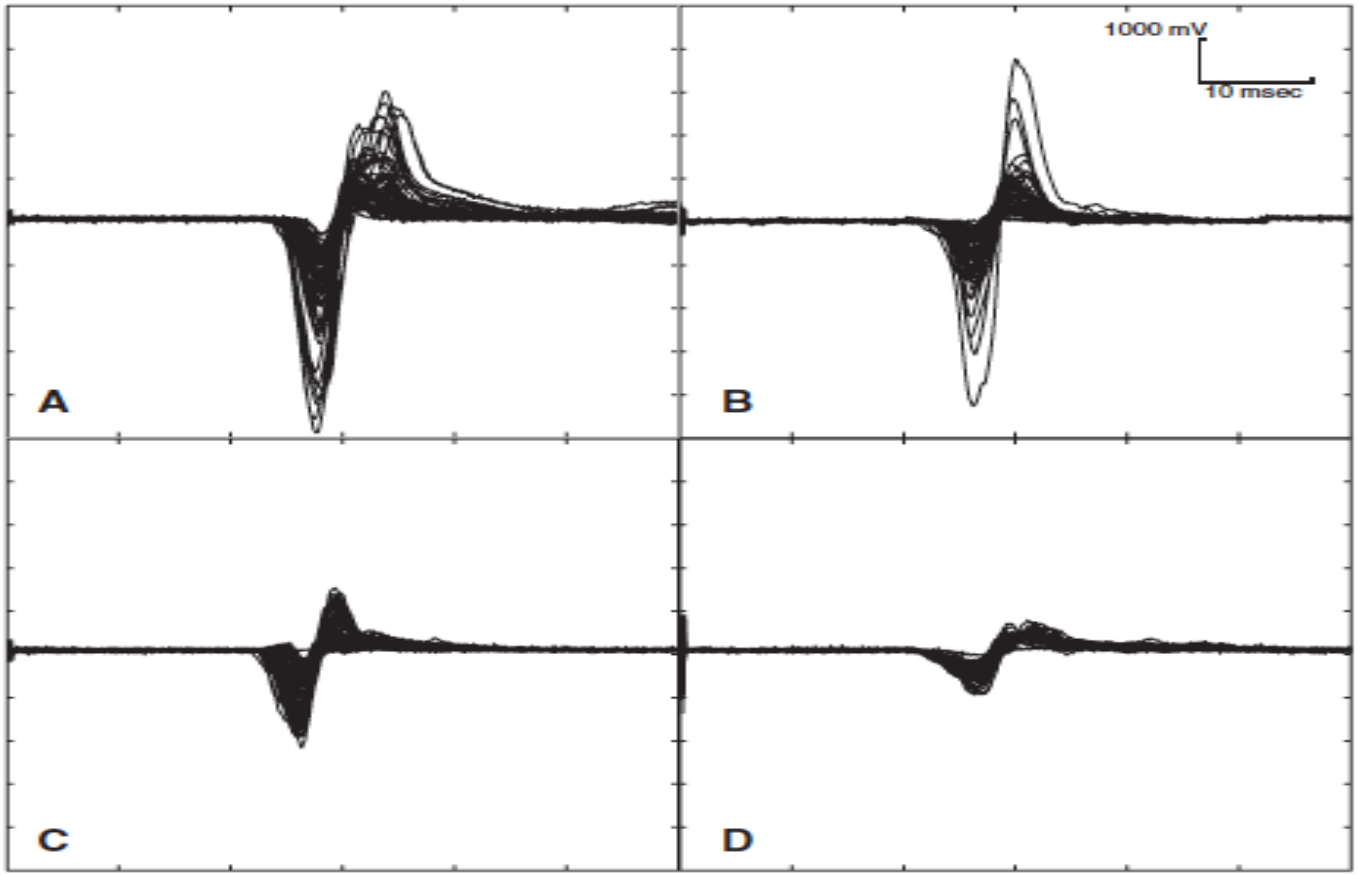


FIG. 2. Superimposed MEPs demonstrate distinct patterns of variability in motor responses: **(A)** control, **(B)** mild DAI without paresis, **(C)** severe DAI without paresis, and **(D)** severe DAI with paresis.

Bernabeu et al., 2009

Pain mechanisms???

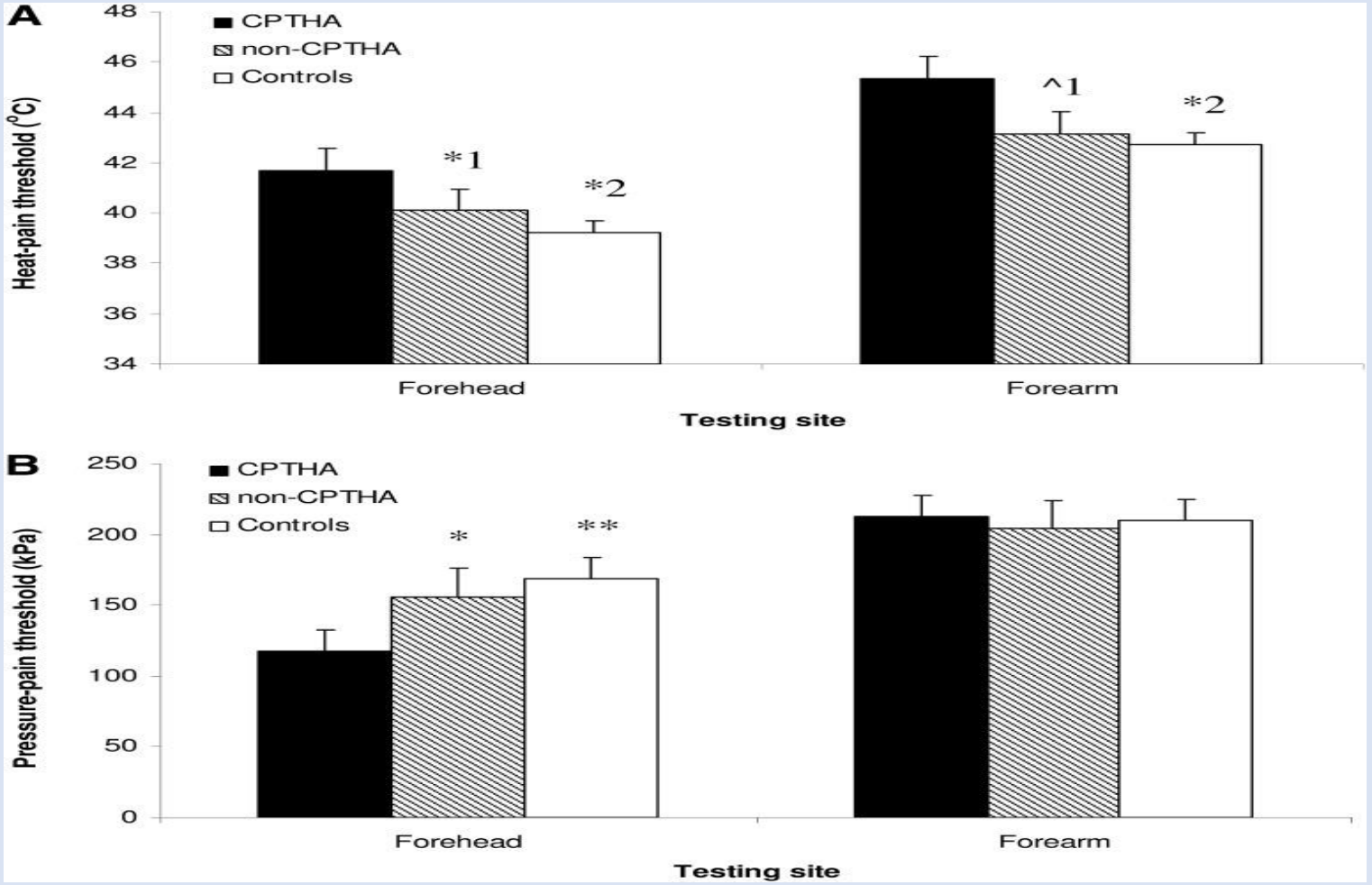
JOURNAL OF NEUROTRAUMA 32:28–37 (January 1, 2015)

DOI: 10.1089/neu.2014.3359

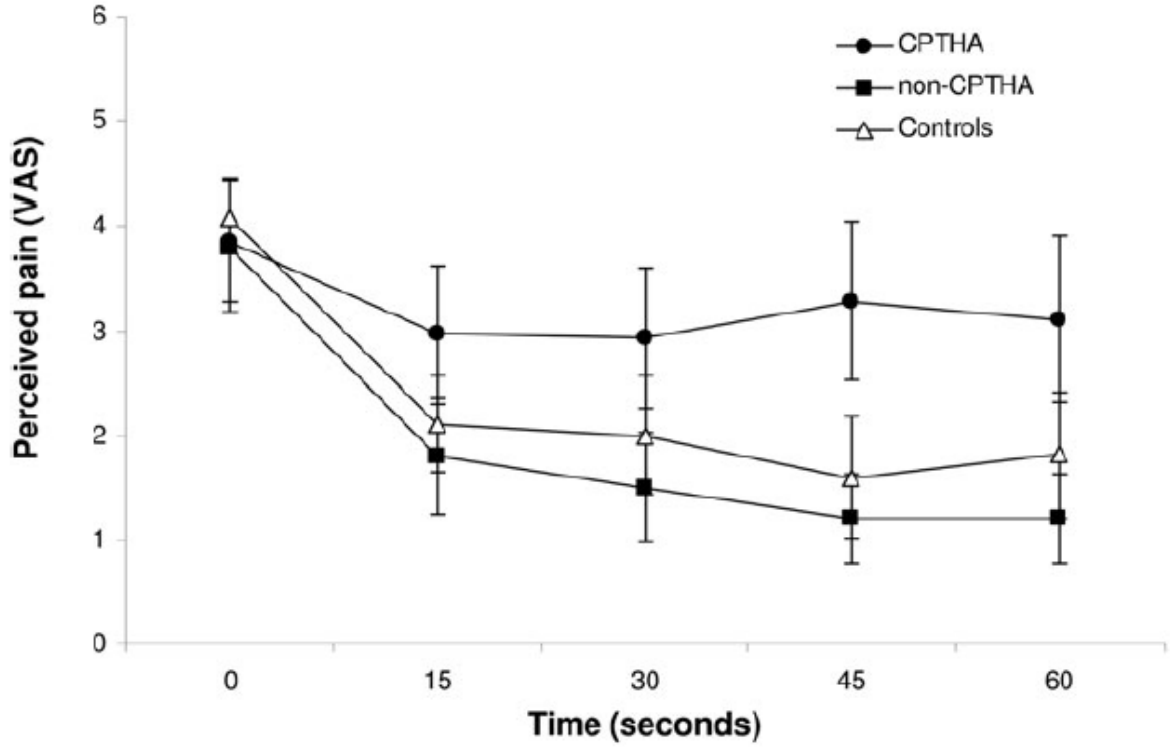
Deficient Pain Modulatory Systems in Patients with Mild Traumatic Brain and Chronic Post-Traumatic Headache: Implications for its Mechanism

Ruth Defrin,[1] Miri Riabinin,[2] Yelena Feingold,[3] Shaul Schreiber,[4] and Chaim G. Pick[2]

Change of thermal and tactile thresholds



DEFICIENT PAIN MODULATION IN CPTHA



Research Article

MOLECULAR PAIN

Molecular Pain
Volume 12: 1–13

DOI: 10.1177/1744806916662661
mpx.sagepub.com

SAGE

Diminished supraspinal pain modulation in patients with mild traumatic brain injury

Albert Leung, MD[1,2], Shivshil Shukla, BS[1,2], Eric Yang, BS[3], Bryan Canlas, BS[3], Mawj Kadokana, BS[3], Jason Heald, BS[4], Ariea Davani, BS[5], David Song, MD[2,6], Lisa Lin, MD[2], Greg Polston, MD[1,2], Alice Tsai, DO[2] and Roland Lee, MD[2,7]

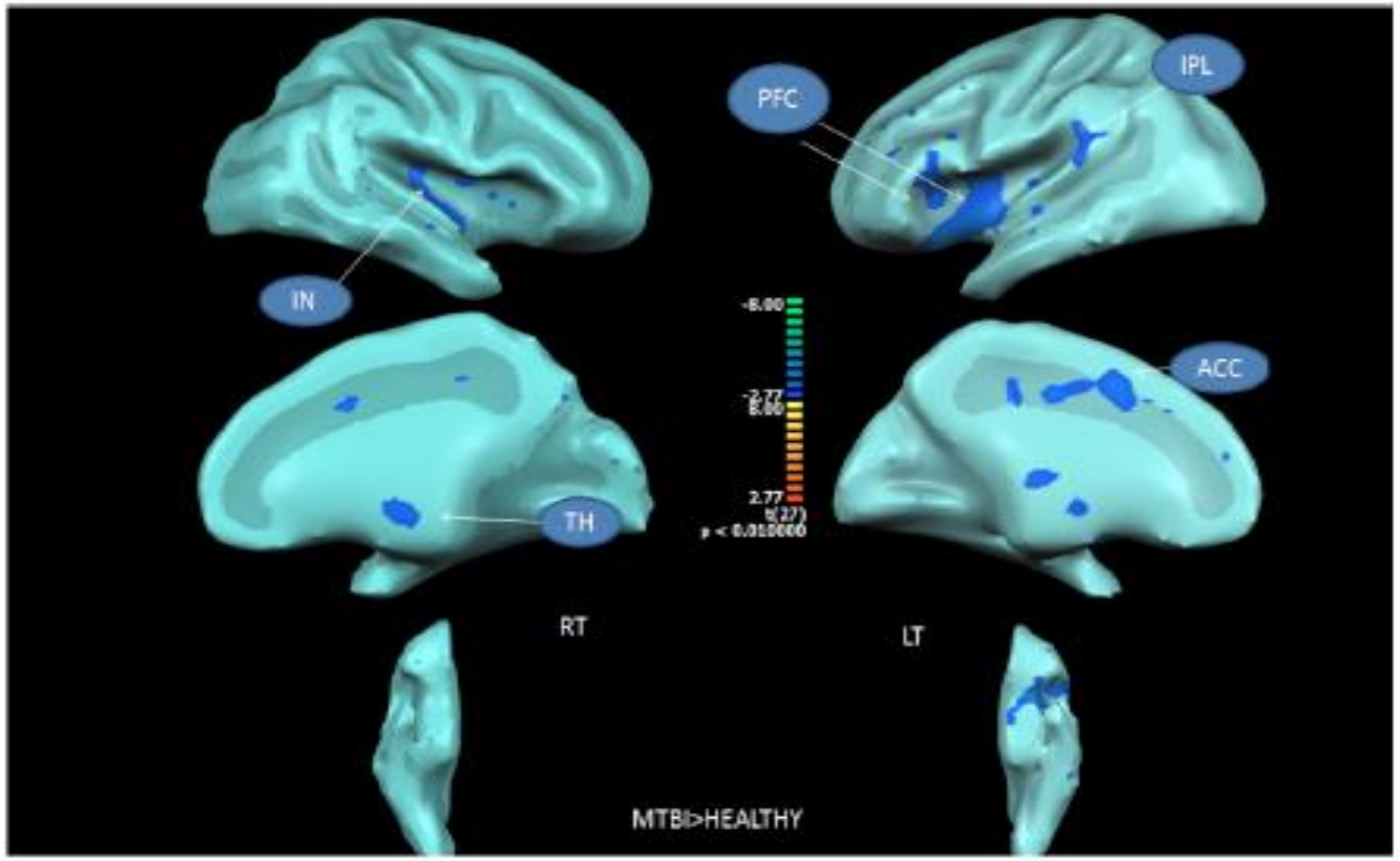


Figure 1a. MTBI minus Healthy (MTBI>Healthy) between group random effect analysis; PFCs : Medial Prefrontal Cortices; IPL: Inferior Parietal Lobe; ACC: Anterior Cingulate Cortex; TH: Thalamus; IN: Insula; P<0.01; Cluster threshold>150 voxels

Leung et al., Molecular Pain, 2016

Resting State Functional Connectivity with Left Prefrontal Cortex as the seed region

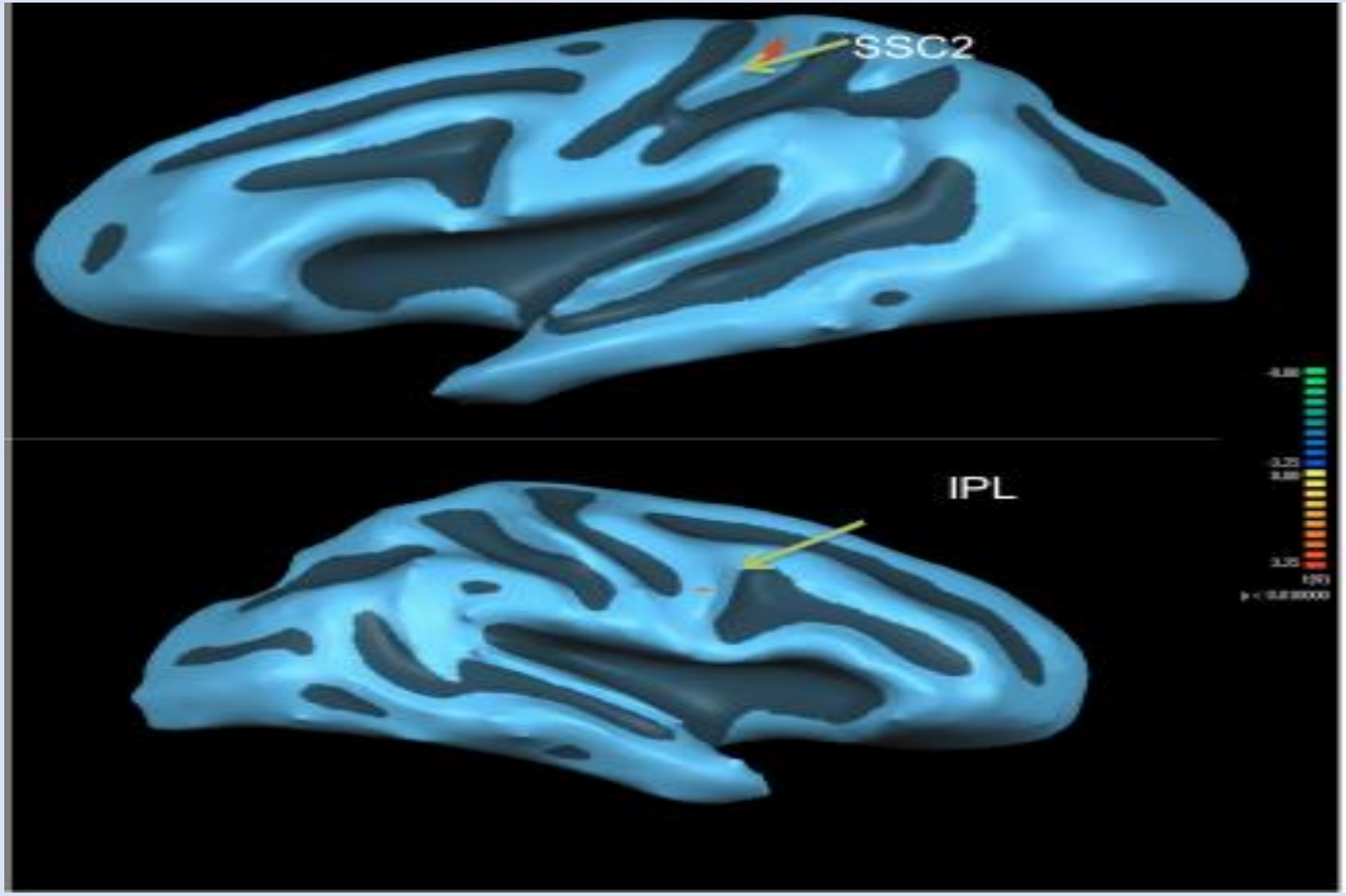


Figure 2a. Resting state functional connectivity difference with the left prefrontal cortex (seeded region) of the Healthy Controls (N=15) demonstrating more significant (P<0.01) Connectivity to the left Secondary Somatosensory Cortex (SSC2) and right inferior Parietal Lobe (IPL) than subjects with Mild Traumatic Brain Injury Related Headache (N-15)

Leung et al., Molecular Pain, 2016

Decrease FA in the SLF

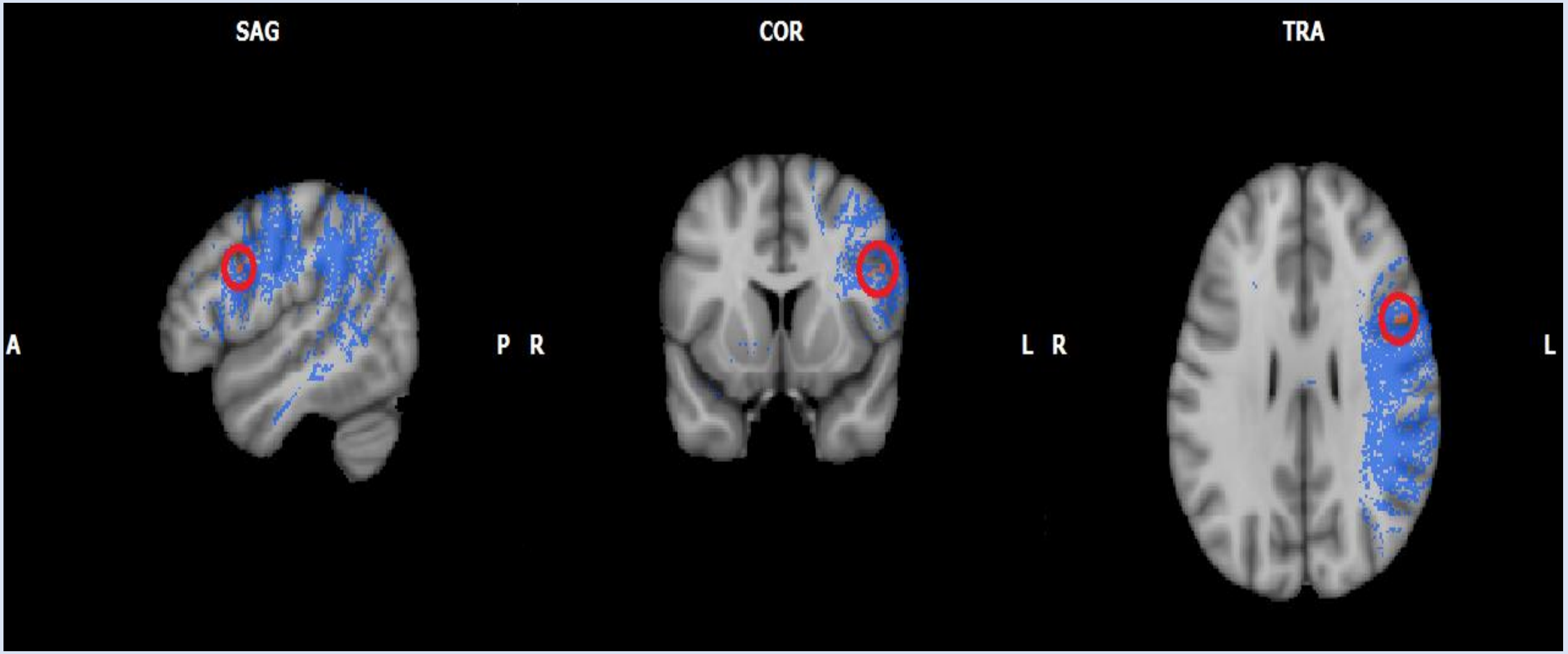


Figure1. Area (red circle) of white matter tract fractional anisotropy deficit (P<0.01, Cluster Threshold>50 voxels, F value=16.76, Peak voxel coordinates: X=-49, Y=8, Z=29) found in the Superior Longitudinal Fasciculus (blue) of patients with MTBI related headache in comparison with healthy controls;

Decrease of FA in the ATR

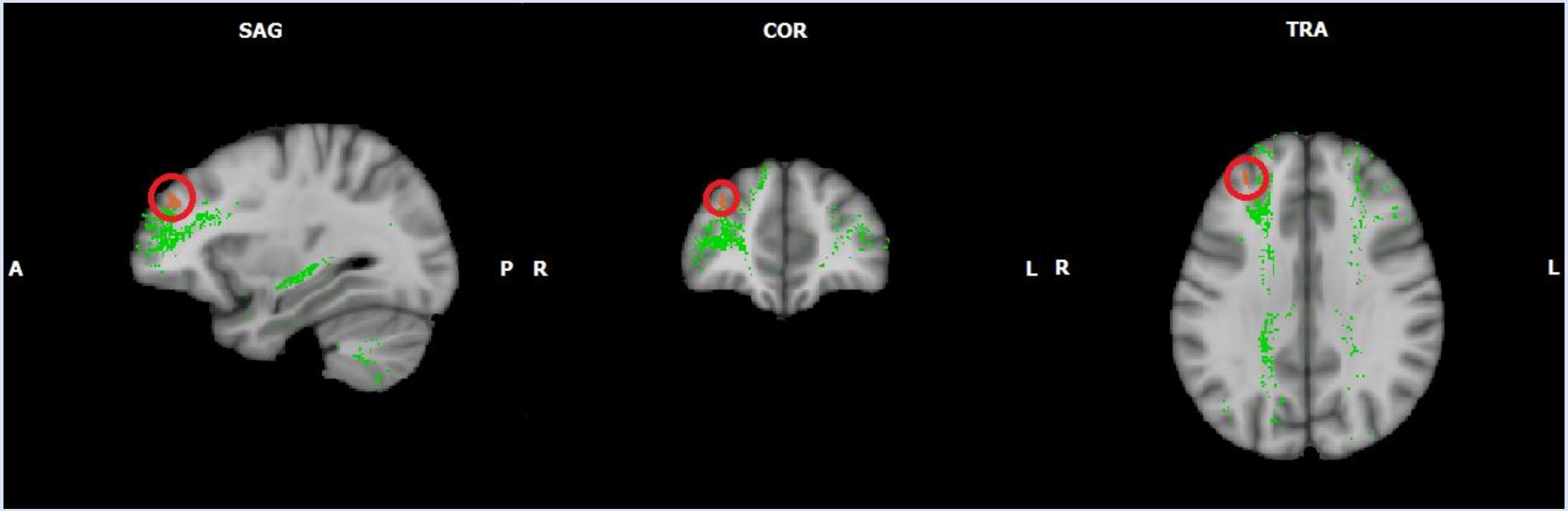
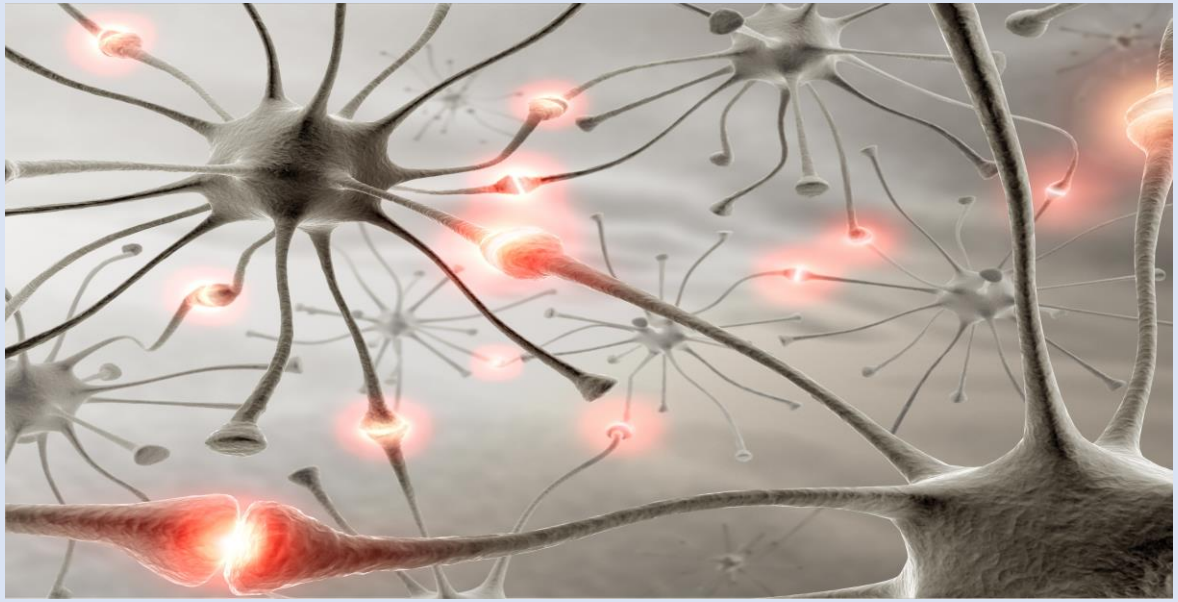


Figure 2. Area (red circle) of white matter tract fractional anisotropy deficit (P<0.01, Cluster Threshold>50 voxels, F=16.57, Peak voxel coordinates: X=35, Y=50, Z=33) found in the Anterior Thalamic Radiation (green) patients with MTBI related headache in comparison with healthy controls;

What is Neuropathic Pain (NP)?

The International Association for the Study of Pain (IASP) defined Neuropathic Pain (NP) as “pain originated from a lesion or disease of somatosensory systems



Post Traumatic Headache as a Neuropathic Pain State

Typical Neuropathic Pain Conditions

- Persistent pain after tissue healing
- Allodynia (pain with non-painful stimuli)
- Hyperalgesia (Enhanced pain perception)
- Hyperpathia (Enhanced emotion response to pain)
- Altered motor or sensory functions
- Enhanced Sympathetic Activity/Mediated Pain
- Mood: Depression

MTBI related Headache

- Persistent head pain long after the injury
- Frequent Debilitating Exacerbation (Pain without painful provocation)
- Tinnitus (Altered sensory function)
- Light sensitivity (Altered sensory function)
- Balance problem (motor)
- Easily agitated (sympathetic involvement)
- Altered neuronal functions (memory and attention)
- PTSD (sympathetic involvement)
- Depression (mood)

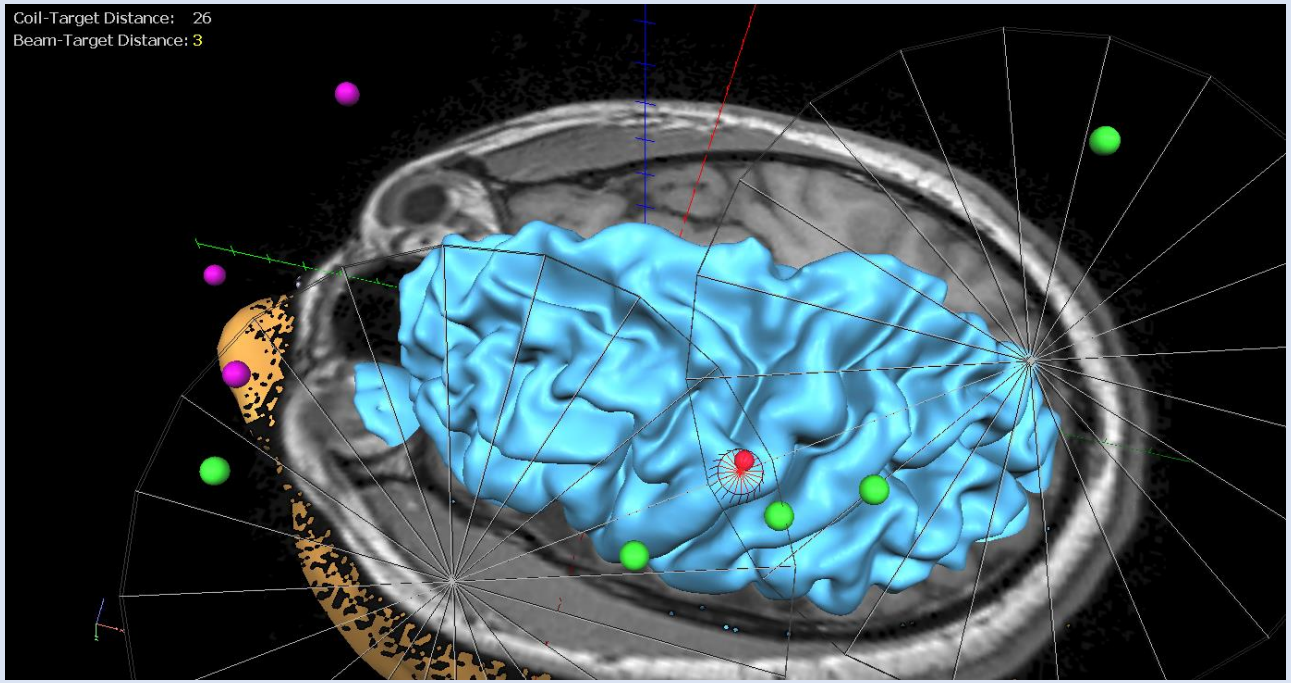
Neuromodulation: Technology at the Neural Interface

Received: July 17, 2015 Revised: September 7, 2015 Accepted: September 15, 2015

(onlinelibrary.wiley.com) DOI: 10.1111/ner.12364

Repetitive Transcranial Magnetic Stimulation in Managing Mild Traumatic Brain Injury-Related Headaches

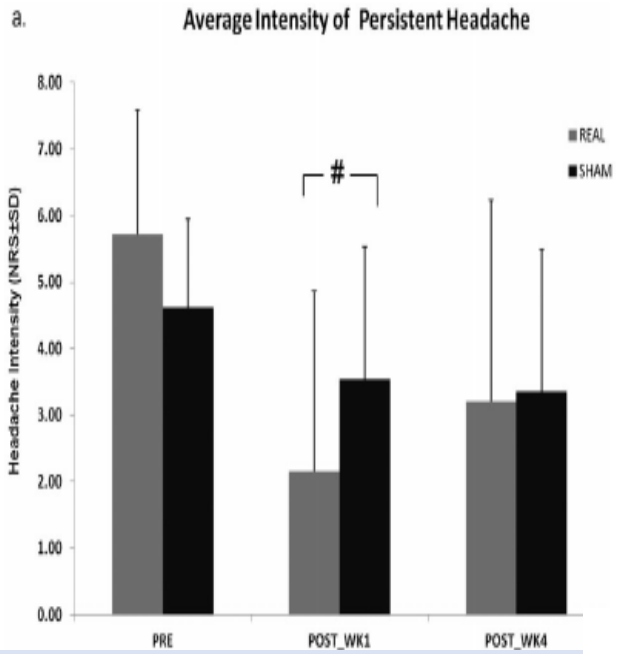
Albert Leung, MD*; Shivshil Shukla, BS*; Amir Fallah, BS*; David Song, MD, PhD*; Lisa Lin, MD*; Shahrokh Golshan, PhD*,†; Alice Tsai, DO*; Amy Jak, PhD*; Greg Polston, MD*; Roland Lee, MD*



Neuronavigation Guided rTMS at the Motor Cortex

Clinically feasible treatment paradigm

- 3 sessions (>24 and <72 hours) 10 hz, 80% RMT, 2000 pulses/session
- Pre- and post-treatment one- and four- week assessments for headache, attention, mood and memory



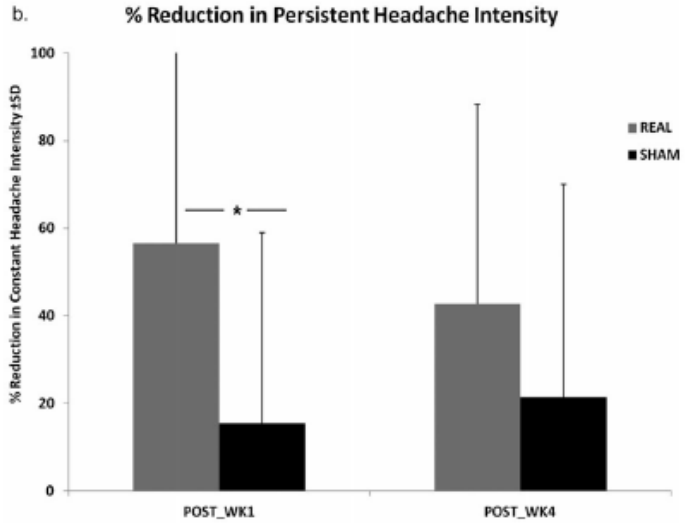


Figure 3. Change of persistent headache. a. Intensity of persistent headache in numerical rating scale (NRS), # $p = 0.06$. b. Percentage of reduction in persistent headache.*$p < 0.05$. Post_WK1: posttreatment one week; Post_WK4: posttreatment four weeks.

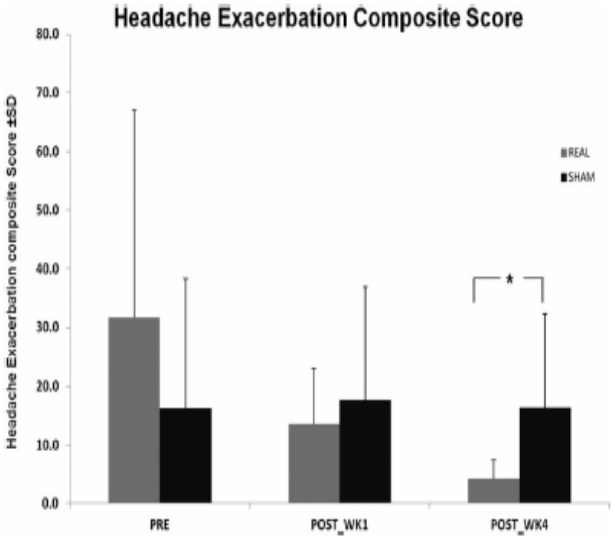


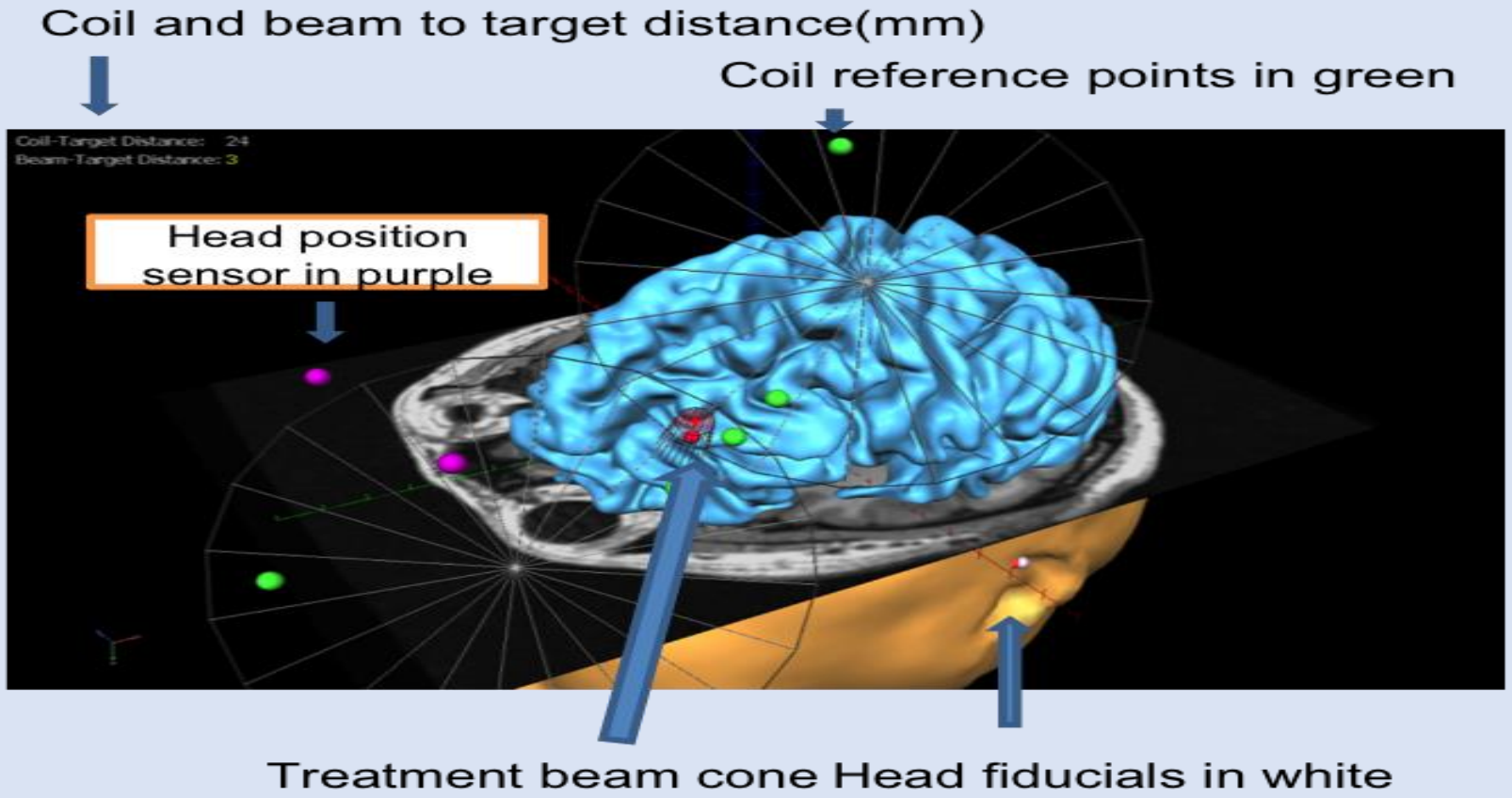
Figure 4. Debilitating headache exacerbation composite score. Pre: pretreatment; Post_WK1: posttreatment one week; Post_WK4: posttreatment four weeks; *$p < 0.05$.

Received: January 2, 2017 Revised: March 22, 2017 Accepted: April 10, 2017

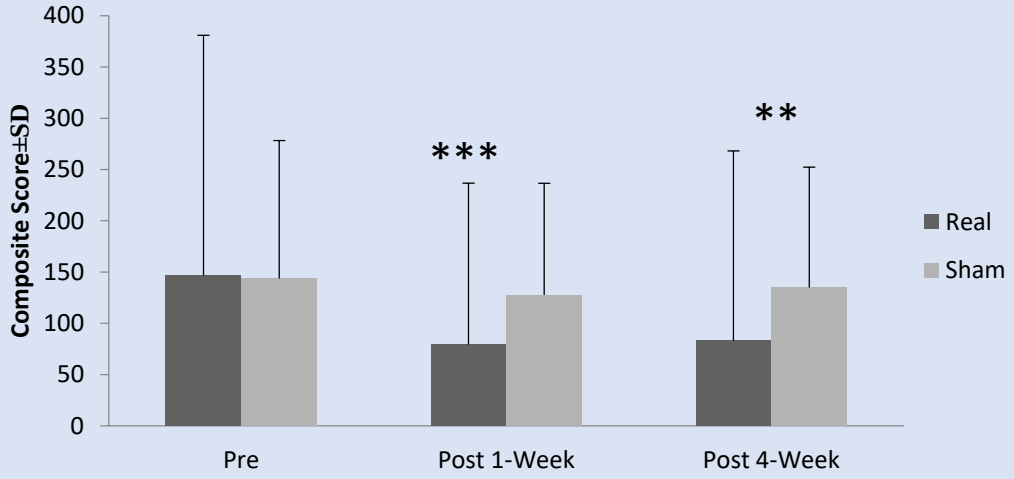
(onlinelibrary.wiley.com) DOI: 10.1111/ner.12615

Left Dorsolateral Prefrontal Cortex rTMS in Alleviating MTBI Related Headaches and Depressive Symptoms

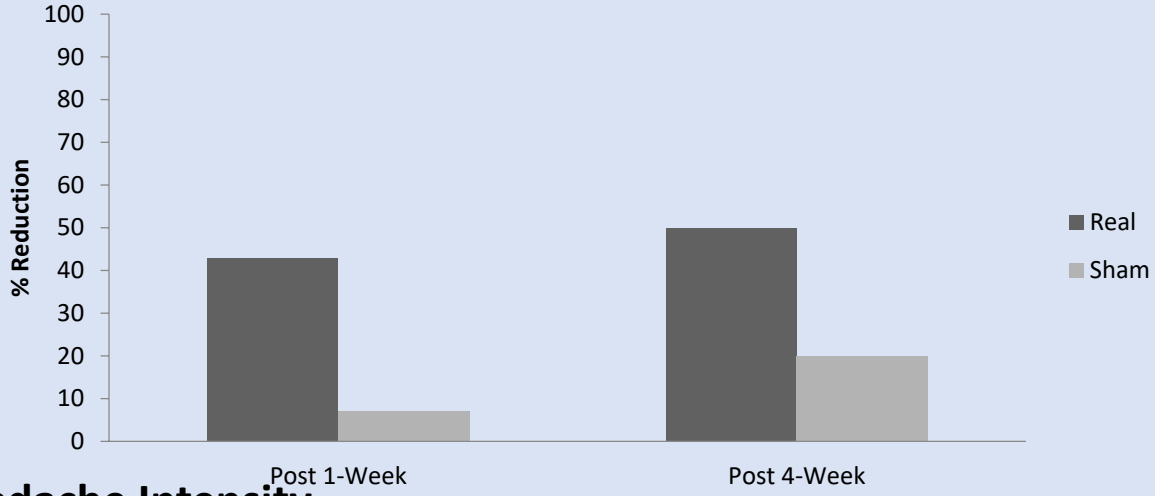
Albert Leung, MD*†; Valerie Metzger-Smith, BS†; Yifan He†; James Cordero, BS†; Brandon Ehlert, BS†; David Song, MD, PhD†‡; Lisa Lin, MD†; Shahrokh Golshan, PhD§; Alice Tsai, DO†; Michael Vaninetti, MD*†; Thomas Rutledge, PhD†¶; Greg Polston, MD*†; Robert Sheu, MD; Roland Lee, MD†††**



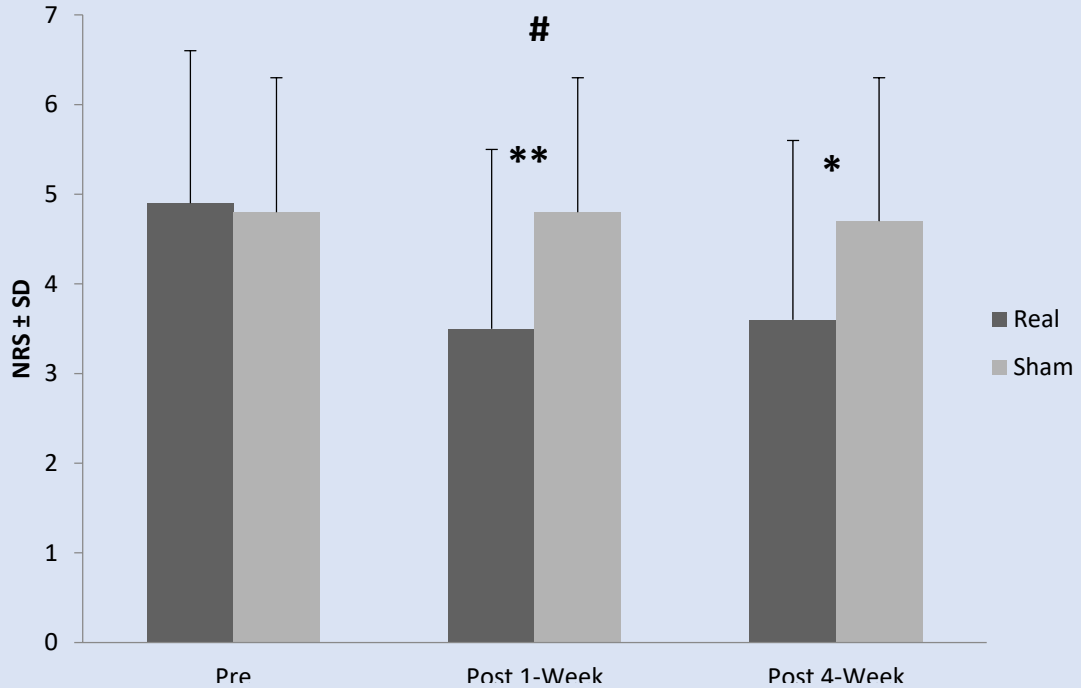
DB Headache Composite Score



% Reduction in the Prevalence of Persistent Headaches

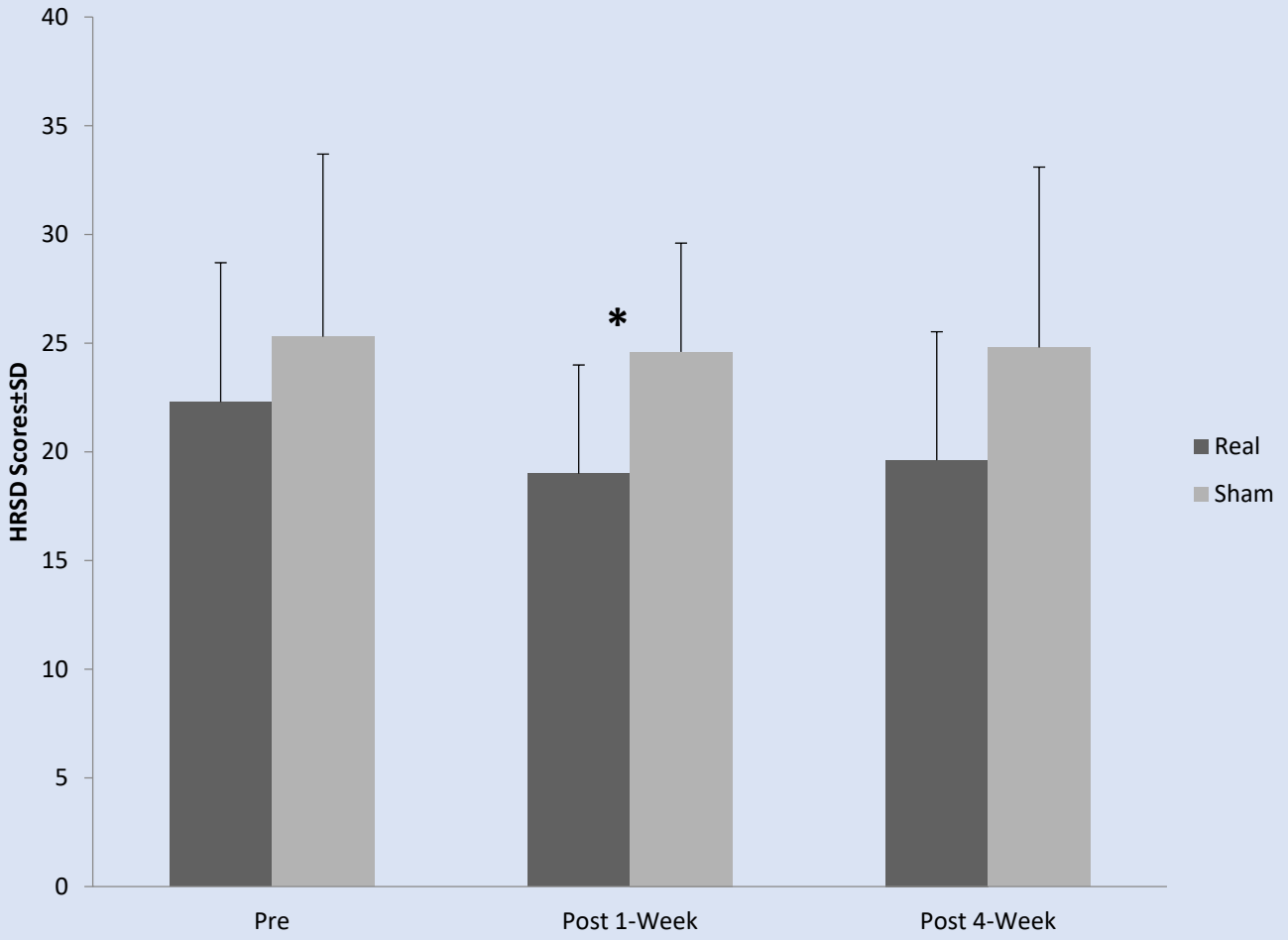


Average Daily Persistent Headache Intensity



*** P<0.001,
** P<0.01; *P<0.05

Hamilton Rating Scale for Depression (HRSD)



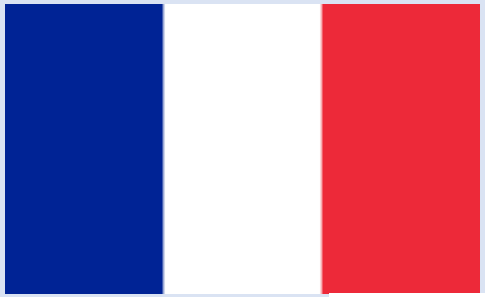
*P<0.05

Leung et al., Neuromodulation, 2017

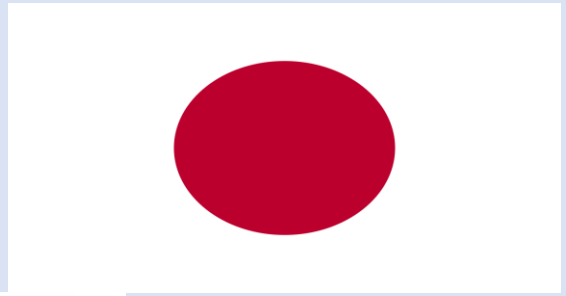
Outcome Evidence

Clinical Implementation

30-member Multinational Multidisciplinary Consensus Panel(>20 institutions)



- 1) Neuropathic pain
- 2) Acute/ Perioperative Pain
- 3) Traumatic Headache
- 4) Primary Headaches
- 5) Pain related co-morbid conditions
- 6) Technical issues
- 7) Cost-effectiveness



North American Neuromodulation Society ·est 1994·

VA HEALTH CARE Defining EXCELLENCE in the 21st Century

NIH

International Association for the Study of Pain IASP Working together for pain relief

ins International Neuromodulation Society

CLINICAL TMS SOCIETY

Table 1. Hierarchy of Studies by the Type of Design (U.S. Preventive Services Task Force) [8].

Evidence Level	Study Type
I	At least one controlled and randomized clinical trial, properly designed
II 1	Well-designed, controlled, non-randomized clinical trials
II 2	Cohort or case studies and well-designed controls, preferably multicenter
II 3	Multiple series compared over time, with or without intervention, and surprising results in noncontrolled experience
III	Clinical experience-based opinions, descriptive studies, clinical observations, or reports of expert committees

Leung et al., Neuromodulation; in press

Table 2. Level of Certainty Regarding Net Benefit Based on Evidence Strength [8].

Level of Certainty	Description
High	The available evidence usually includes consistent results from well-designed, well-conducted studies in representative populations. These studies assess the effects of the preventive service on health outcomes. This conclusion is therefore unlikely to be strongly affected by the results of future studies.
Moderate	The available evidence is sufficient to determine the effects of the preventive service on health outcomes, but confidence in the estimate is constrained by such factors as the number, size, or quality of the individual studies.
	Inconsistency of findings across individual studies.
	Limited generalizability of findings to routine practice.
	Lack of coherence in the chain of evidence.
	As more information becomes available, the magnitude or direction of the observed effect could change, and this change may be large enough to alter the conclusion.
Low	The available evidence is insufficient to assess the effects on health outcomes. Evidence is insufficient because of: · the limited number or size of the studies; · important flaws in the study design or methods; · inconsistency of finding across individual studies; · gaps in the chain of evidence; · findings not generalized to routine practice; · lack of information on important health outcomes. More information may allow estimation of effects on health outcomes.

Leung et al., Neuromodulation; in press

Table 3. Meaning of Recommendation Degrees (U.S. Preventive Services Task Force) [8].

Degree of Recommendation	Meaning
A	Extremely recommendable (high-level evidence that the measure is effective and benefits outweigh the harms)
B	Recommendable (at least moderate level evidence that the measure is effective and benefits exceed harms)
C	The USPSTF recommends selectively offering or providing this service based on professional judgement and patient preferences; there is at least moderate certainty that the net benefit is small
D	Inadvisable (at least moderate evidence that the measure is ineffective or that the harms exceed the benefits)
I	Insufficient, low-quality, or contradictory evidence; the balance between benefit and harms cannot be determined

Leung et al., Neuromodulation; in press

Table 4. Evidence Rankings from the Centers of Disease Control and Prevention [9].

IA	Strongly recommend for implementation and supported by well-designed experimental, clinical, or epidemiological studies
IB	Strongly recommended for implementation and supported by some experimental, clinical, or epidemiological studies and strong theoretical rationale
II	Suggested for implementation and supported by suggestive clinical or epidemiological studies or theoretical rationale
No recommendation/ unresolved issue	Practices for which insufficient evidence or no consensus regarding efficacy exists

NP Task Group Assessment and Recommendation

	Study Design (I, II-1, II-2, II-3, III)	Level of Certainty in Evidence (H, M, L)	USPSTF Recommendation Score (A-F)	CDC Recommendation Score (1A, 1B, II)
	I	H	A(Extremely Recommendable)	IA(Strongly Recommended)
	I	M	B(Recommendable)	IB(Strongly Recommended)

Post-traumatic Headache Task Group Assessment and Recommendation

	Study Design (I, II-1, II-2, II-3, III)	Level of Certainty in Evidence (H, M, L)	USPSTF Recommendation Score (A-F)	CDC Recommendation Score (1A, 1B, II)
	I	H	A (Extremely recommendable)	1A (Strongly recommended)

	Treatment location	Stimulation Protocol (Design)	Pain Conditions	Effect on pain	Effect on Depression	Quality of Life measures	
	Motor Cortex (M1) Stimulation						
	M1 (NNG)	10 sessions (2 wks..) at 10 Hz, 100% RMT, 2500 pulses/session (RCT)	Complex Regional Pain Syndrome Type I	Significant improvement noted in VAS scores during treatments in the Active group	HDRS-21 items: no improvement in depression between Active and Sham groups	Significant improvement in DASH, affective subscores of SF-36, QOL and MPQ in the Active Group	Class II
	M1 (NNG)	Induction: 5 consecutive daily sessions ; Maintenance: 3 weekly sessions + 3 fortnightly session + 3 monthly sessions; at 10 Hz, 80% RMT, 1500 pulses/session (RCT)	Fibromyalgia	Significant improvement in BPI in the Active group	HDRS 21-item : no effect; BDI: no effect	Sensory and affective subscores of MPQ QoL and PCS scores improvement in the Active group	Class I
	M1 (NNG)	10 daily sessions at 10 Hz, 80% RMT, 2000 pulses/session (RCT)	Fibromyalgia	Significant Improvement in BPI pain intensity and Interference, MPQ, and FIQ at day 15 in the Active group	HDRS, BDI, HADS: no change	BPI -interference and FIQ score significantly decreased through day 30 in the Active group	Class I
	M1 (NNG)	10 daily session at 5Hz, 90% RMT, 500 pulses/session (RCT)	Neuropathic Pain	Mean VAS score reduction immediately after stimulation in the Active Group; No cumulative effect during daily stimulation.	BDI: no change	SF-MPQL decrease in short term but no cumulative long-term effects in the Active group	Class I
	M1 (NNG)	10 induction (2 wks.) and 4 biweekly maintenance sessions at 10 Hz, 90% RMT, 2000 pulses/session (RCT)	Fibromyalgia	not measured	no significant change in BDI in the sham or treatment group	Patients of the active rTMS group had greater QoL improvement in the FIQ and in the mental component of the SF-36	Class I
	DLPFC Stimulation						
	L-DLPFC (NNG)	4 sessions (1-2wks) at 10 Hz, 80% RMT, 2000 pulses/session session (RCT)	Mild Traumatic Brain Injury related Headaches	Active group revealed a significant decrease in average daily persistent headache intensity compared to sham	Significant improvement in HDRS score in treatment group		Class I
	R-DLPFC	10 sessions (2 wks.) at low frequency (1 Hz), 110% RMT over R-DLPFC (1600 pulses per session) or high frequency (10Hz), 80% RMT over the left M1 (2000 pulses/session) vs. Sham (RCT)	Fibromyalgia	Pain VAS, K-FIQ improved with H and LF stim, but was maintained after 1 month only with LF TMS	Depression (BDI): Both LF and HF groups had significantly lower BDI scores, but only the LF group maintained at one month.	FIQ, QOL improved after LF and HF TMS and was maintained after 1 month with low frequency TMS	
	L-DLPFC	10 sessions (2 wks.) at 10Hz, 120% RMT, 4000 pulses/session (RCT)	Fibromyalgia	Pain scores improved from baseline but did not differ from sham	difference (sham vs active).	No sig difference in BPI, FIQ	

Potential Cost Savings

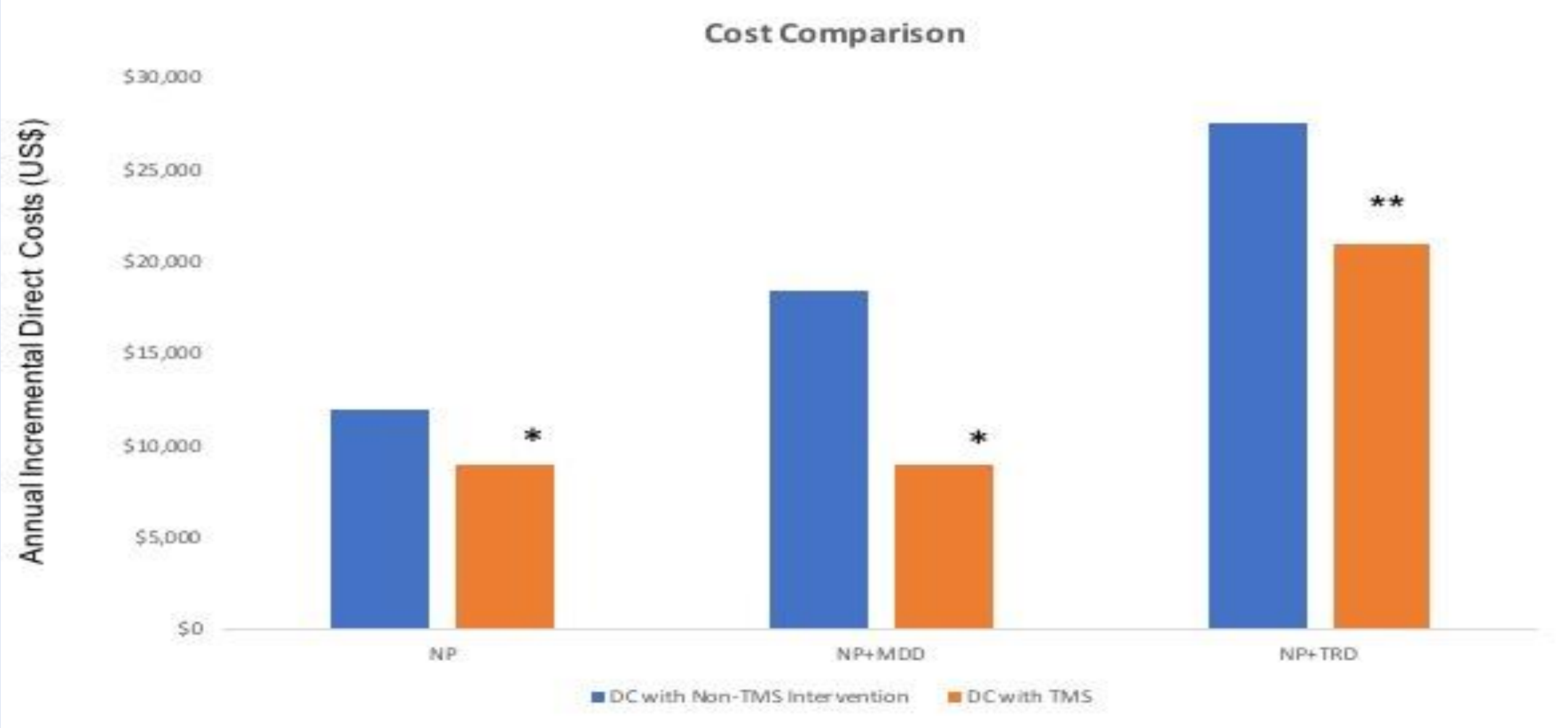


Figure 2: Annual Incremental Cost Comparison for TMS for Neuropathic Pain (NP) alone, with Co-Morbid Major Depressive Disorder (MDD) or Treatment-Resistant Depression (TRD); *30 sessions; **70 sessions

Leung et al., in preparation

Technical Task Group A&E

- "Clinical research data suggest that a significant advantage of TMS treatment delivered with MRI based neuronavigation is in the clinical outcome."

- "In depression, erroneously targeting in premotor cortex rather than dorsolateral prefrontal cortex led to treatment failures."
  - Herbsman et al., 2009
  - Johnson et al., 2013

- "TMS delivery to unintended cortical regions can result in exacerbation of pain instead of reductions in pain, especially if the TMS mode being used is not suited for the unintended target (e.g. an excitatory protocol being delivered to the somatosensory cortex causing increased pain).
  - Kanda et al., 2003

Parameter	Non-neuronavigated TMS	Neuronavigated TMS
Initial costs	Lower	Higher
Long-term costs	Likely higher	Likely lower
Time efficiency	Higher initially, possibly lower long term	Lower initially, possibly higher long term
Location accuracy / treatment reliability	Lower	Higher
Treatment reproducibility	Lower	Higher

Table 15. Likely characteristics of non neuronavigation-guided vs. neuronavigation-guided TMS for chronic pain.

Summary

- Strong mechanistic and outcome evidence supports the use of TMS for NP;
- Strong mechanistic and outcome evidence supports the use of TMS for MTBI-HA;
- Strong outcome evidence support the use of TMS for both pain and co-morbid depression;
- TMS for appears to have cost-saving benefit , especially when used to pain and other co-morbid condition;
- Neuronavigation-guided TMS may have long-term therapeutic, cost-effectiveness, and medical-legal benefits;
- Clinical implementation for pain and headache treatment is imminent;

Leung et al., Neuromodulation; in press

What is next for clinical implementation?

- Center for TMS at the VASDHS;
- Proposal for a VA roll-out program in progress;
- Ongoing research to assess long-term efficacy ;

Thank You!!!!

- Research funding:
  - VA Office of Research & Development
    - Rehabilitation
    - Clinical Science
  - Department of Defense Congressionally Directed Medical Research Program

Research Team

Center for Pain and Headache Research
VA San Diego Healthcare System

Karen Lei, B.S.
Study Coordinator

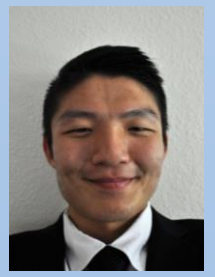
Valerie Metzger Smith, B.S.
Manager

Alphonsa Kunnel, B.S.
Associate Manager

Matthew Flowers, B.S.
Sr. Data Analyst

Naomi Lin, B.S.
Research Assistant II

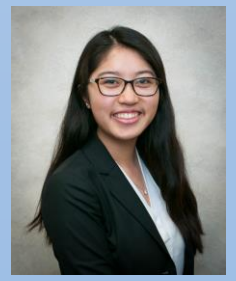
Clinical Research Assistant
UC San Diego Students



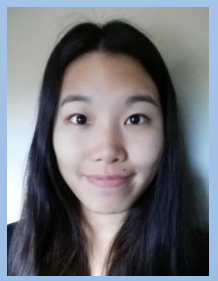
Mike Lim

Aladdin Khalaf

Natalee DeBruin



Emily Nguyen



Yifan He

Brandon Doan

Angeline Wong

Gabriel Jensen

Co-Investigators

1. Thomas Rutledge, Ph.D. Clinical Psychologist – VASDHS; Professor of Psychiatry, UCSD
2. Michael Vaninetti, M.D. Staff Physician, VASDHS; Assistant Clinical Professor of Anesthesiology at UCSD
3. Jay Pyo, D.O. Physiatrist and current Assistant Chief of Physical Medicine and Rehabilitation Service and Polytrauma Amputation Network Site Medical Director – VASDHS
4. Lisa Lin, M.D., Staff Physician for Physical and Rehab Medicine, VASDHS
5. Alice Tsai, D.O., Staff Physician for Physical and Rehab Medicine, VASDHS
6. Jennifer Javors, M.D.; Associate Clinical Professor in Internal Medicine at UCSD, Staff Physician at VASDHS
7. Jennie Wei, M.D.; Director of the environmental Health Clinic at VASDHS
8. Roland Lee, M.D., Professor of Radiology, UCSD; Chief of Neuroradiology, VASDHS
9. Shahrokh Golshan, Ph.D. , Biostatistician, Director of the Methodology, Biostatistics and Data Management Unit