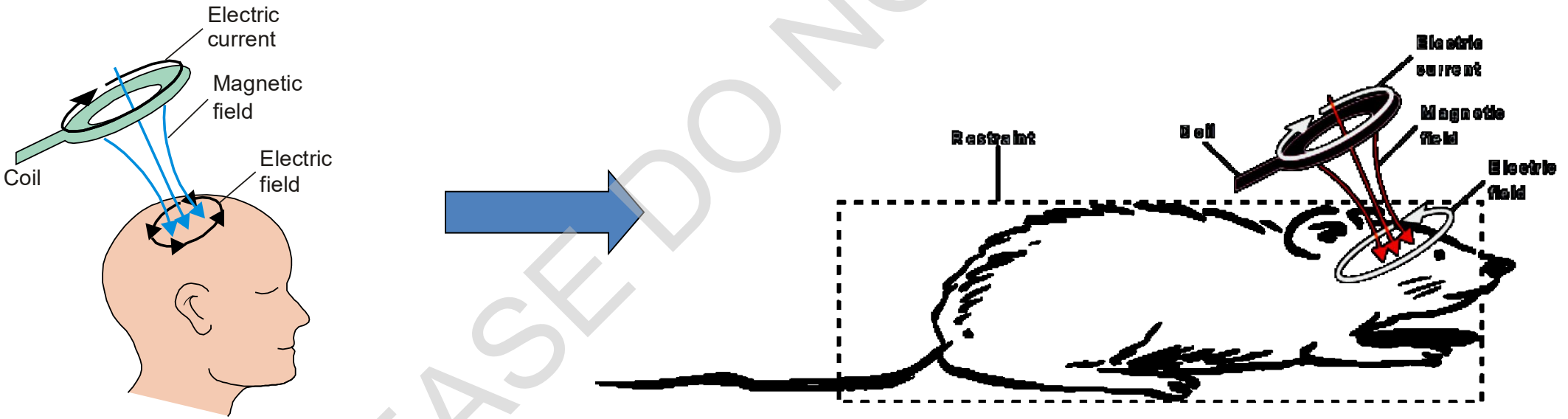
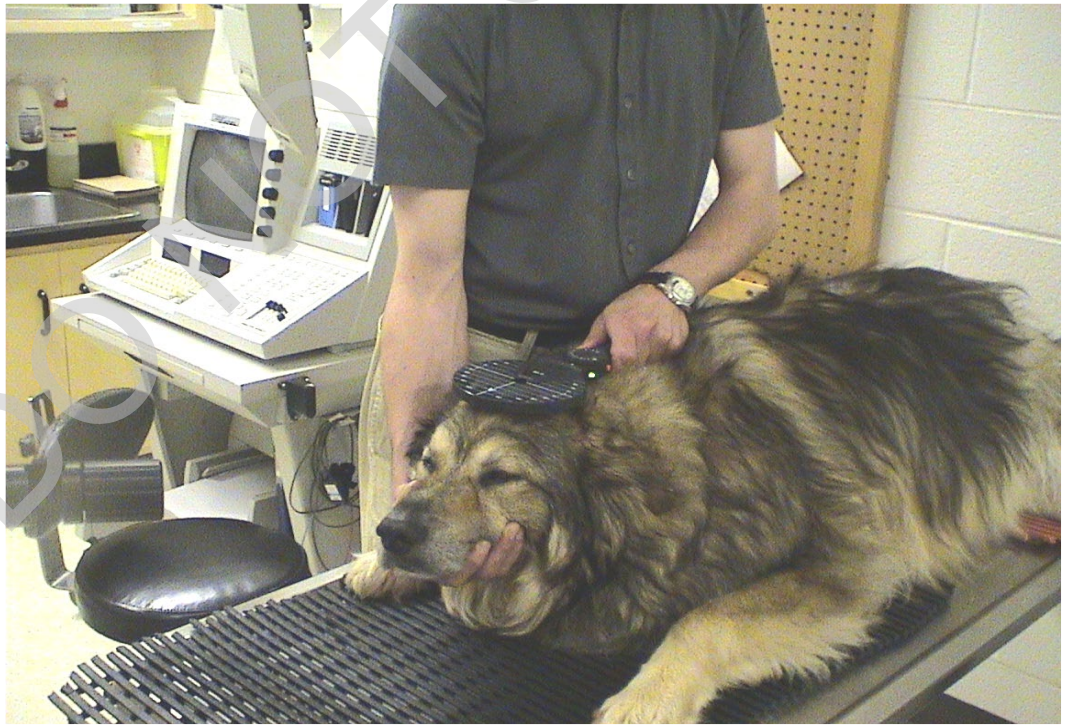
TMS in animal models: Methods and Applications



Why TMS studies in animals?

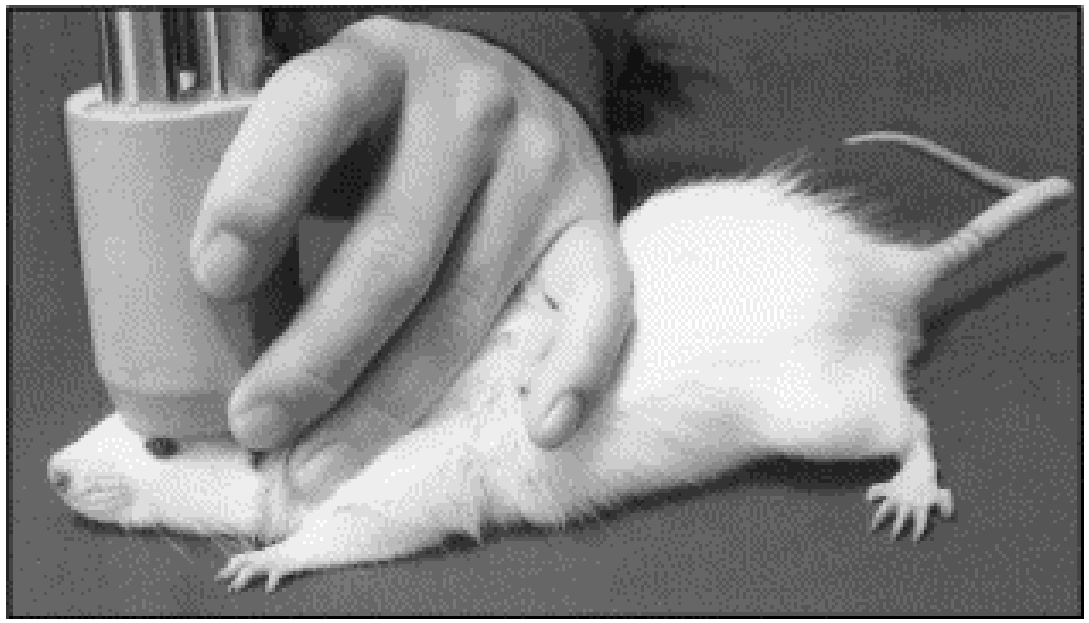
- Basic Science
- Translational Research



Poma et al., 2006

Advantages of animal subjects

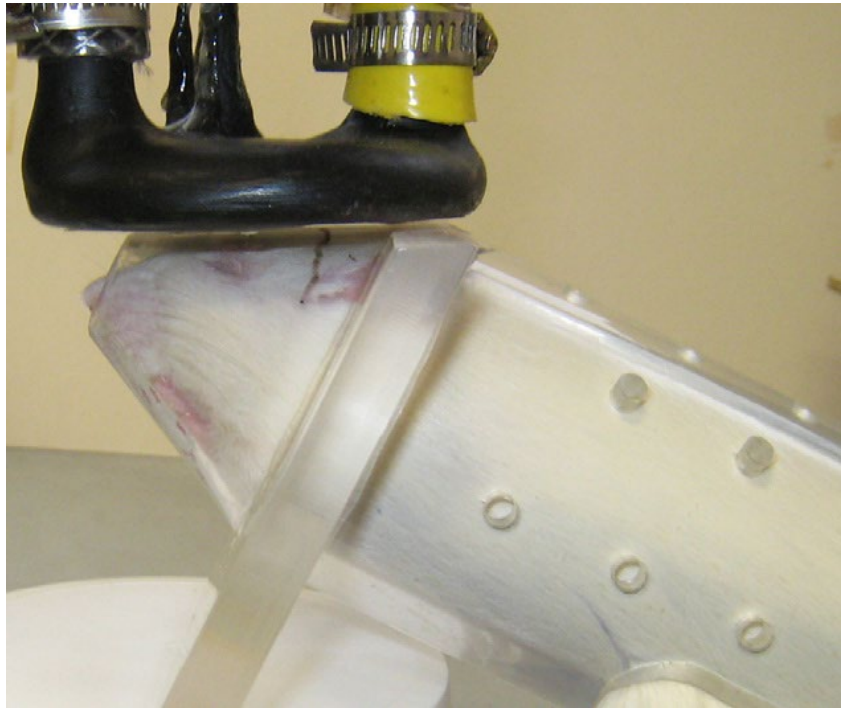
- Homogeneity
- Available histology
- Genetic / disease models



Liebetanz et al., 2003

Translational Relevance

- Disease modeling
- TMS safety
- Neuronal connectivity
- Synaptic plasticity
- Cortical organization

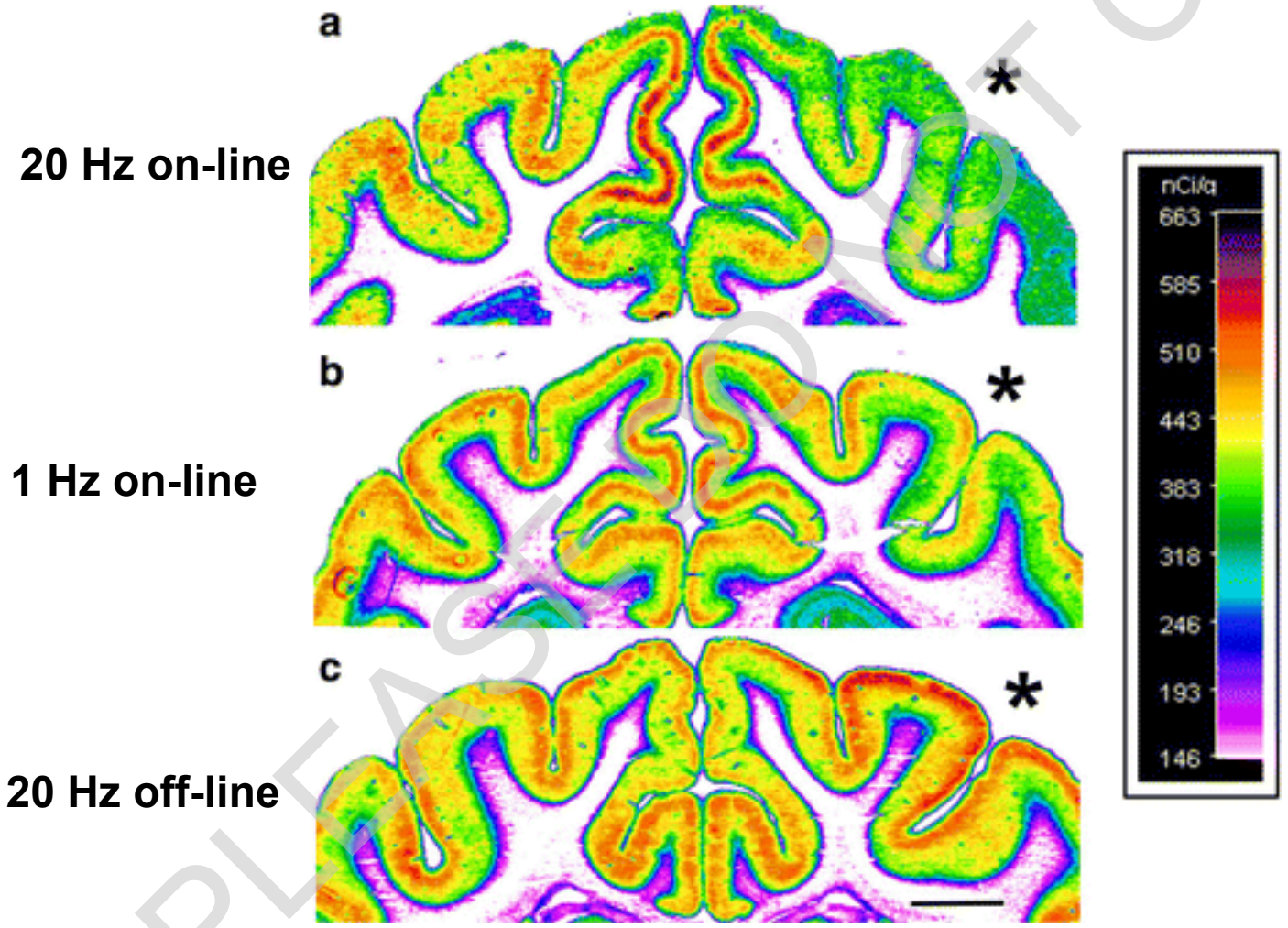


Charlet de Sauvage et al. 2007

Preclinical data indicate noinjury after prolonged rTMS

- Counter, 1995:
  - No deleterious effect on AEP after 1000 pulses at 1Hz n rabbits
- Nishikiori, 1996:
  - No cortical or brainstem lesions after ~1 month of daily TMS in rabbits
- Liebetanz et al., 2003:
  - No MRS or histologic changes after 5 days of 1 Hz rTMS
- Charlet de Sauvage et al., 2007
  - No DNA damage after 2000 TMS pulses

Animal models enable insights into mechanisms (e.g. frequency-dependent 14C-2DG uptake modulated in cat)



20 Hz on-line

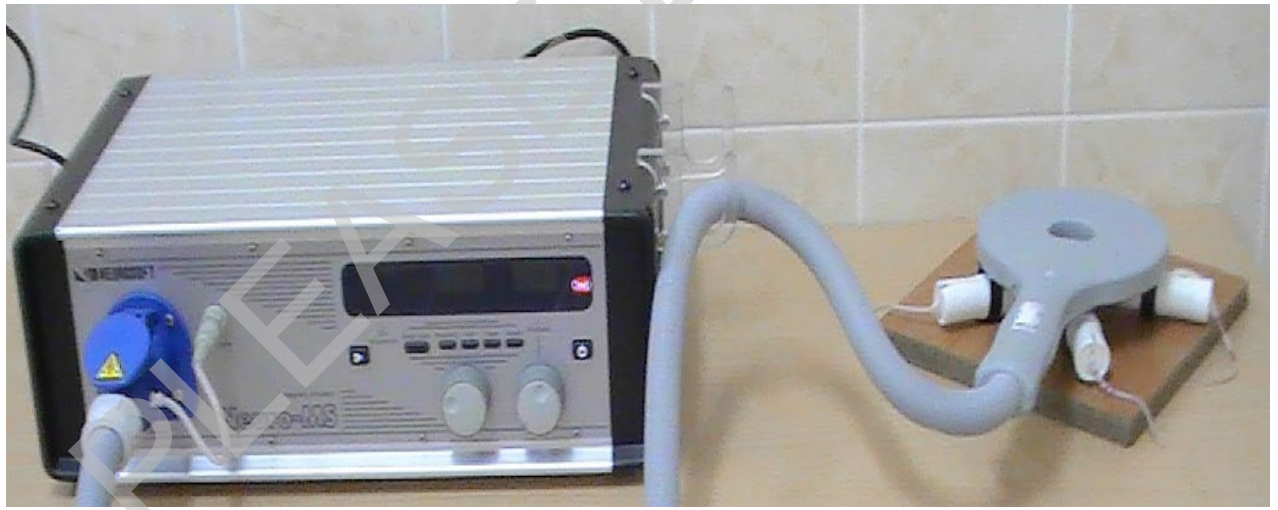
1 Hz on-line

20 Hz off-line

Valero-Cabre et al. 2006

Most translational research is with rodents

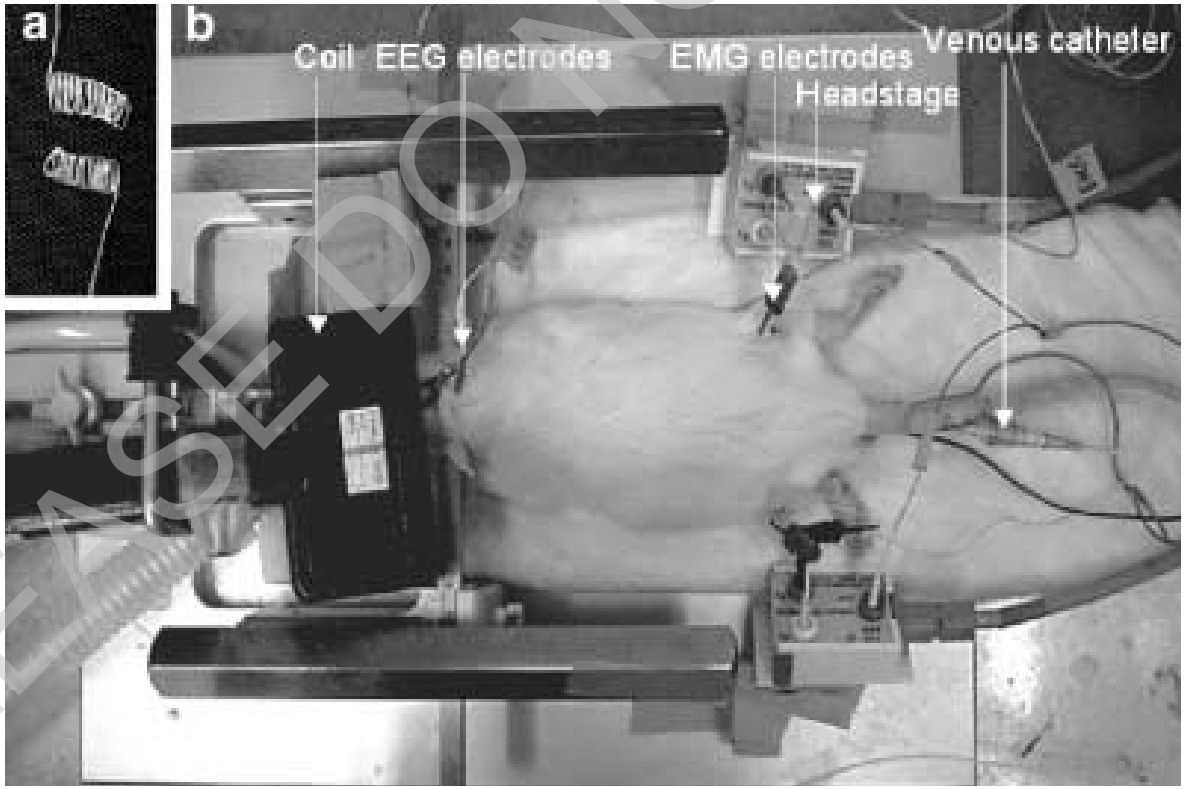
- Well-described disease models
- Inexpensive
- Experiments may be translated to clinical care
- TMS effect can be examined at multiple levels: whole animal, brain slice, single cell, etc.



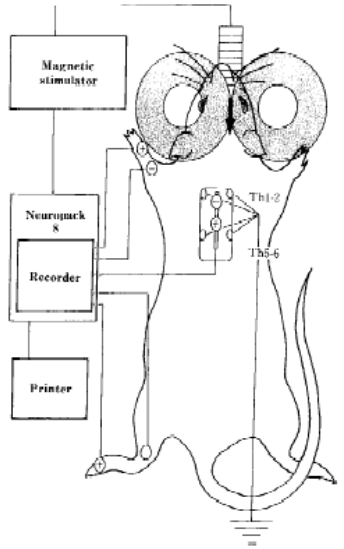
Kistsen et al., personal communication

Disadvantages of rat model

- Compromised stimulus focality
- Slightly more difficult EEG
- Required restraint or anesthesia

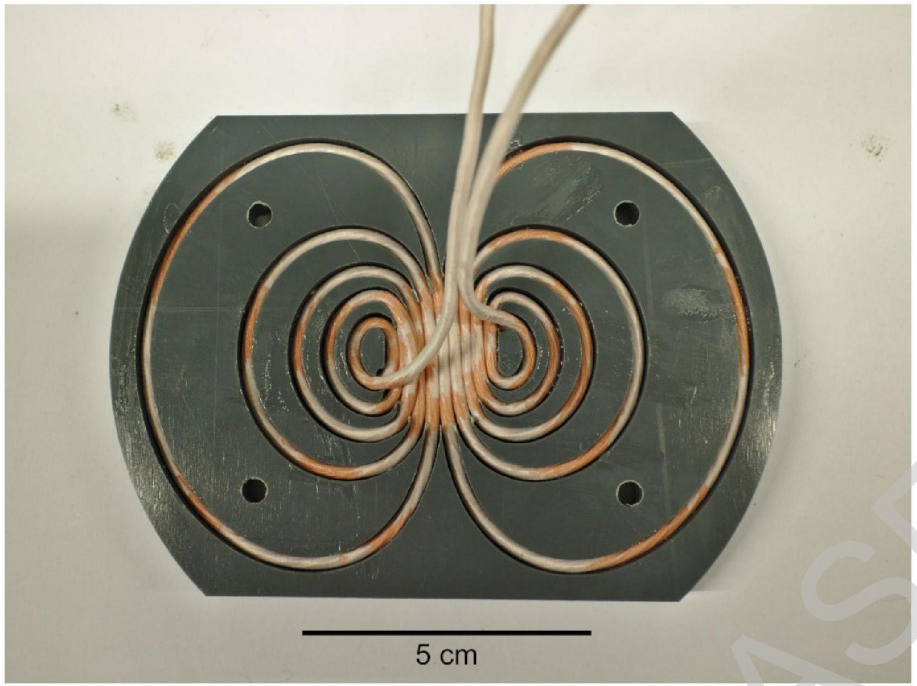


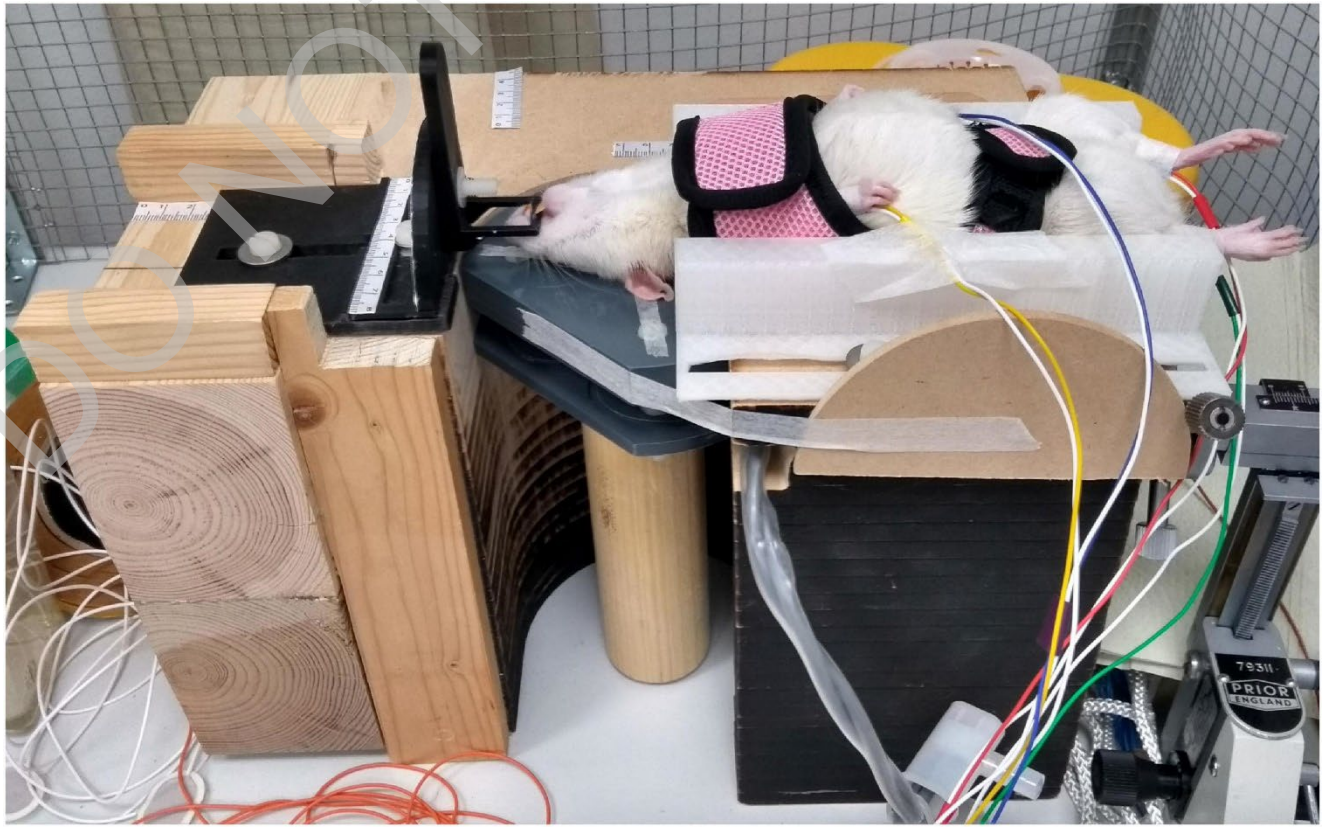
Luft et al., 2001



Kamida et al., 1998

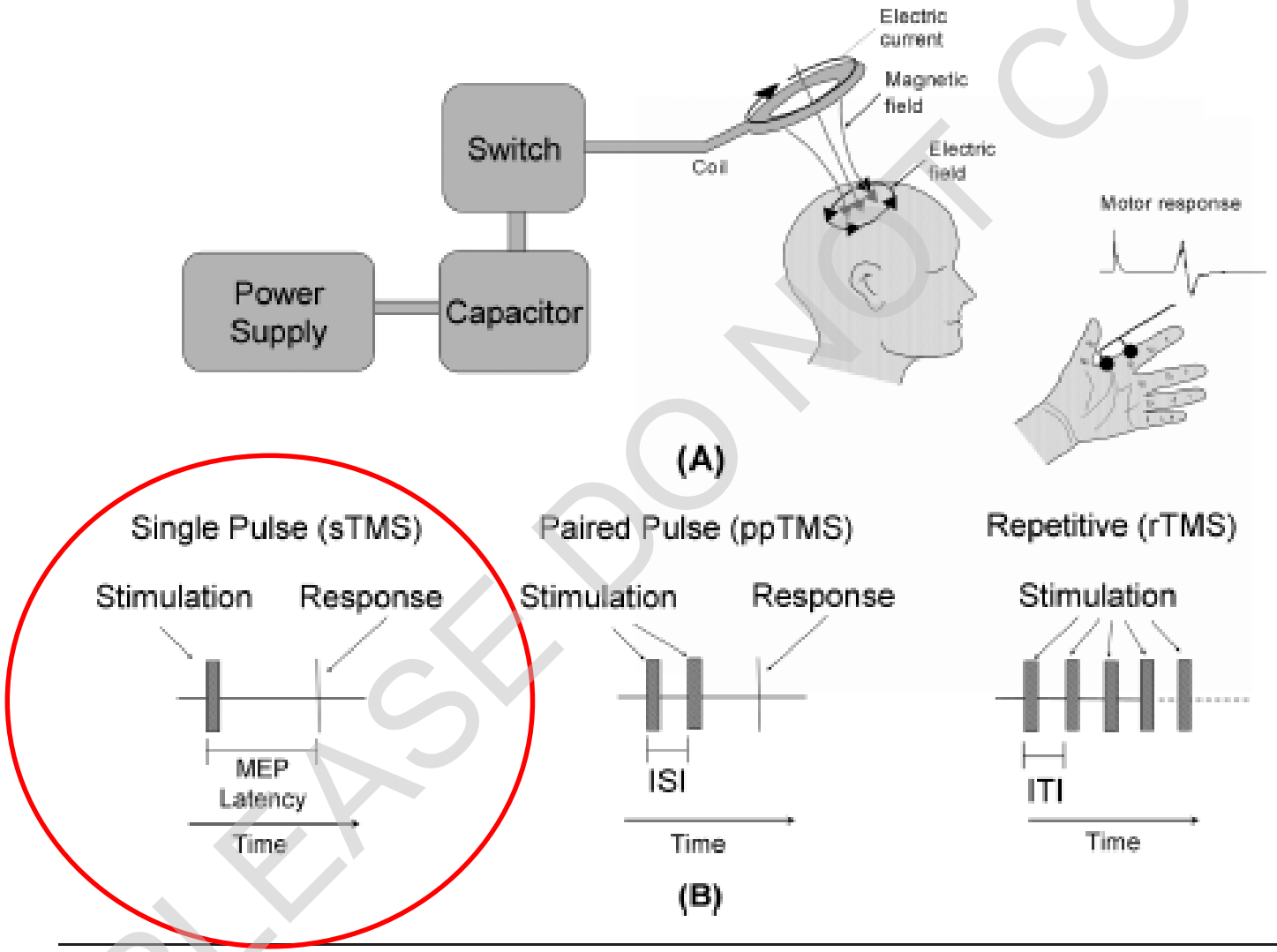
…but, some of these problems are surmountable with adapted equipment





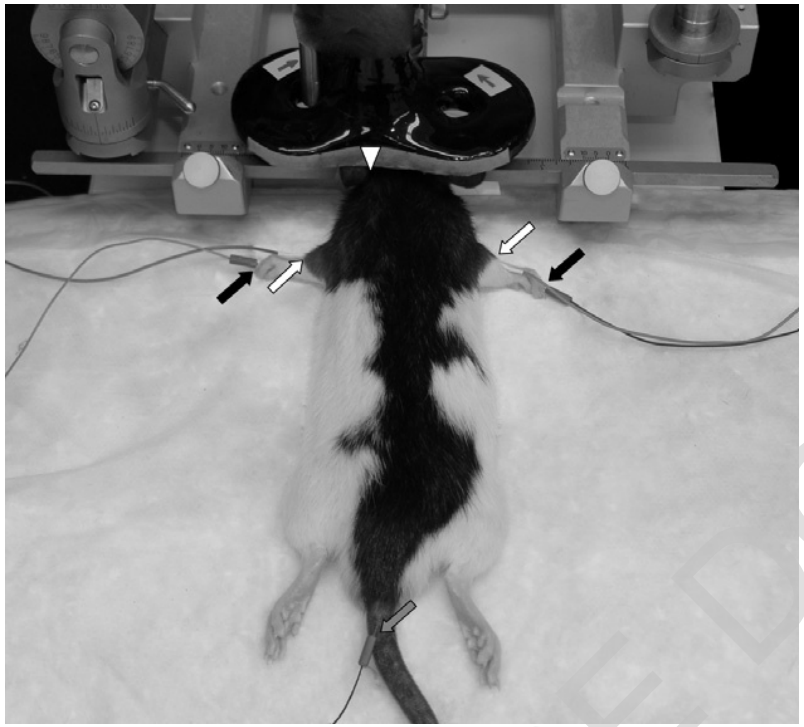
Nieminen et al., 2022

Stimulation protocols

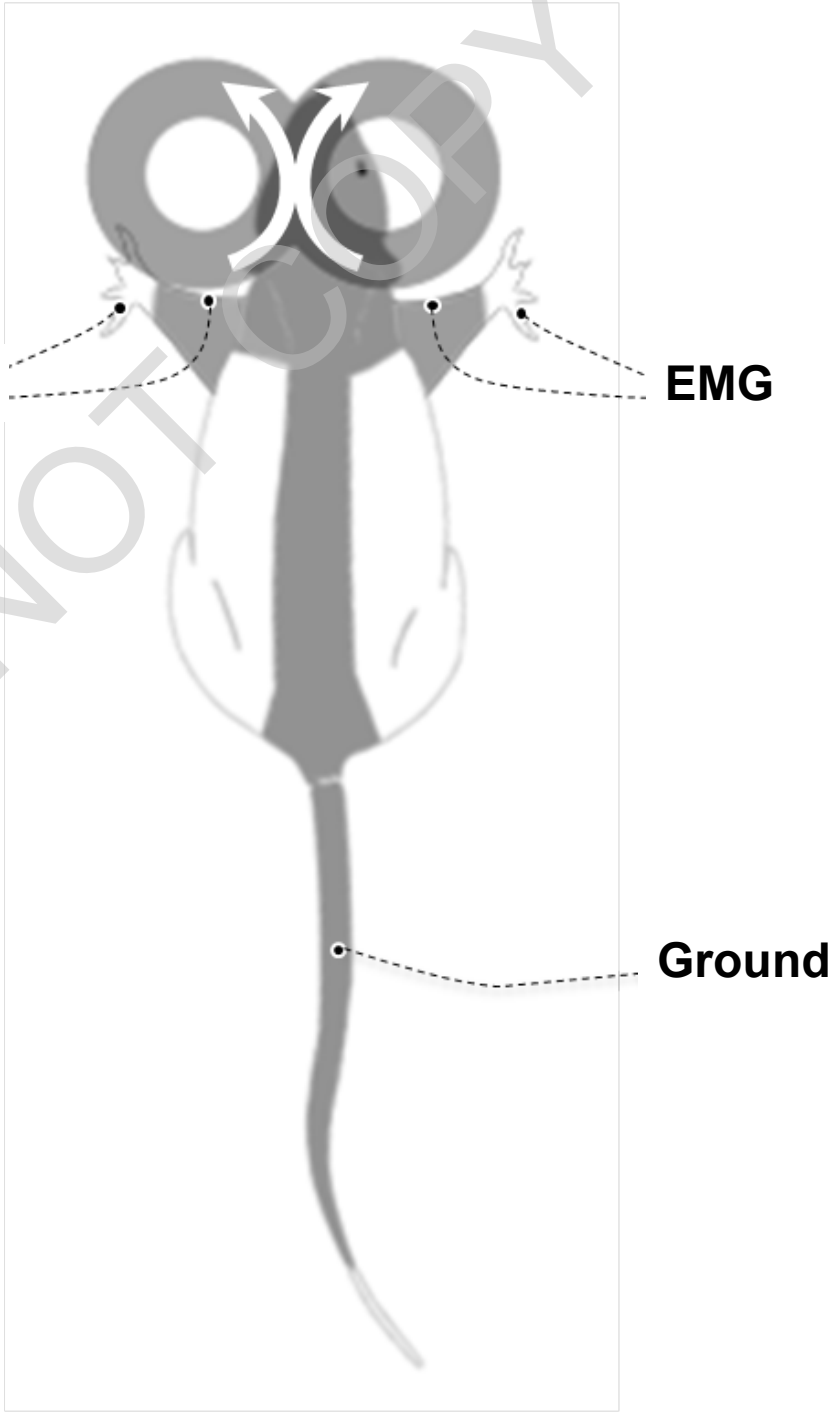


Frye, Rotenberg, et al. Child Neurol 2007

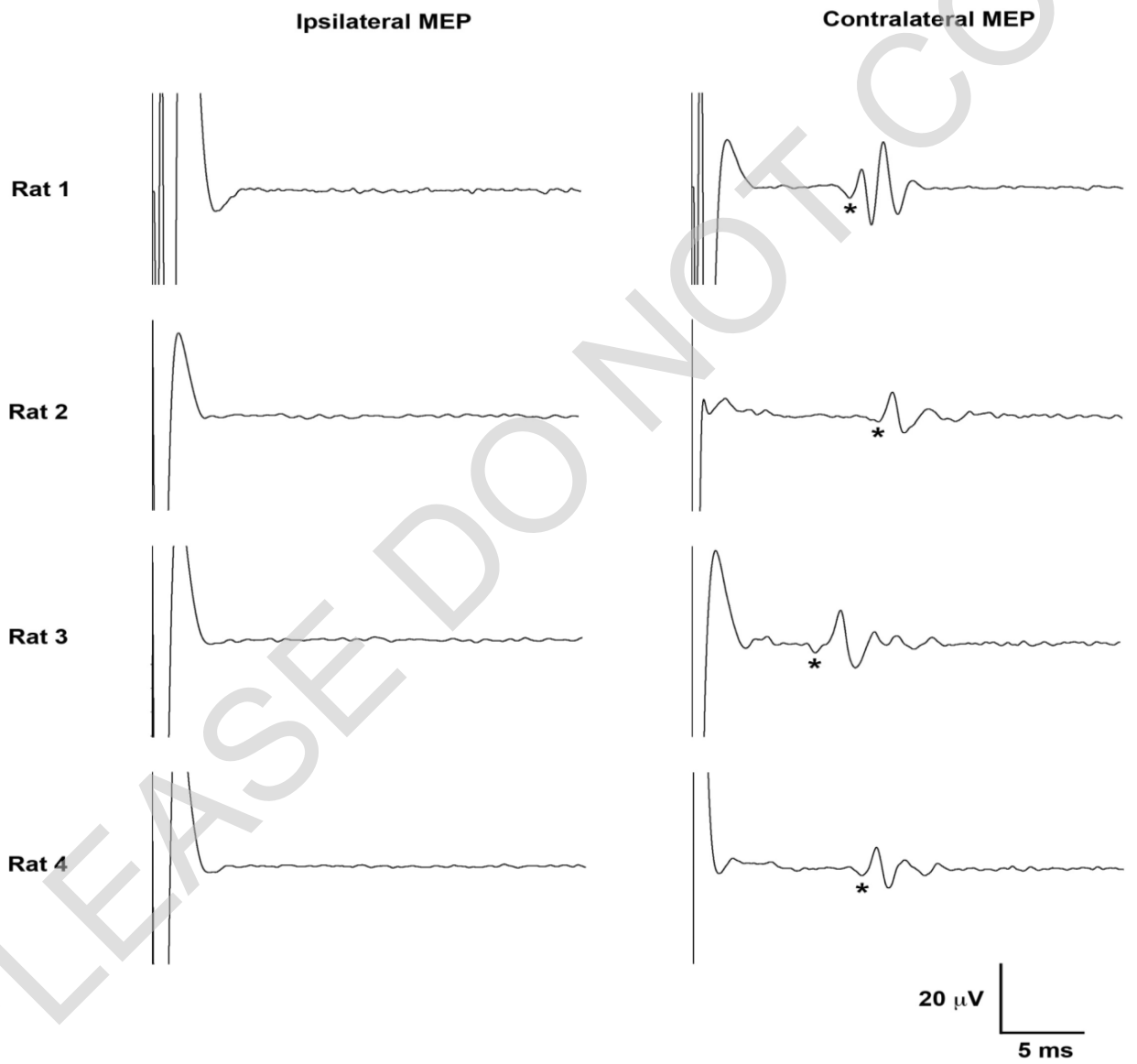
Off-Center Coil



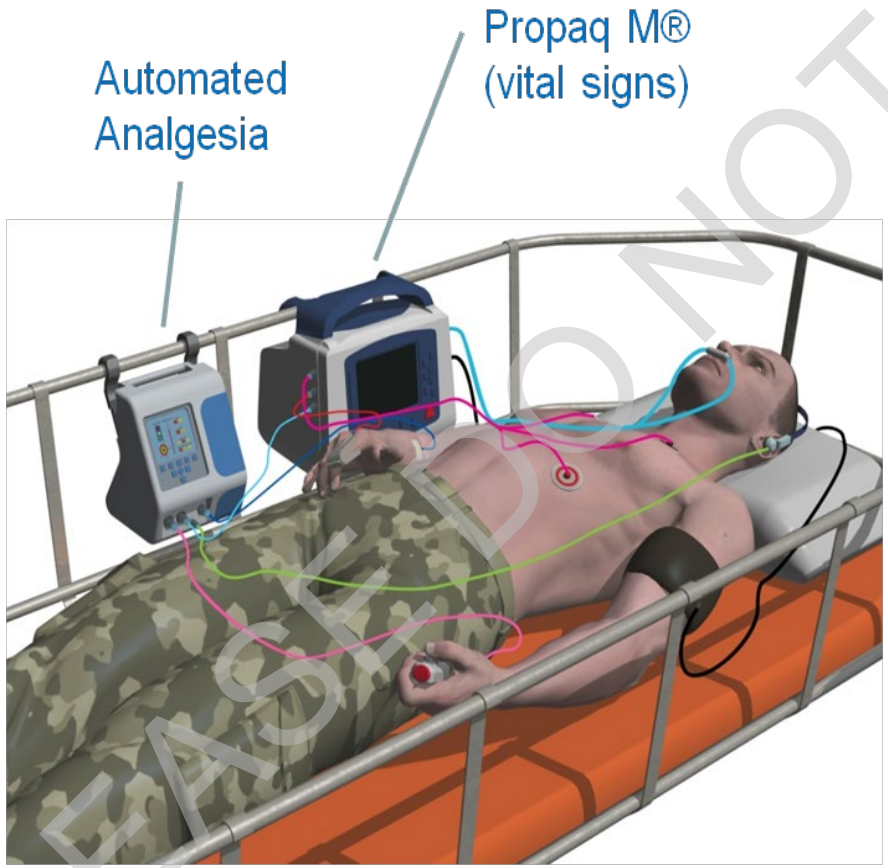
Rotenberg et al., 2009



Lateralized brachioradialis MEP in rat

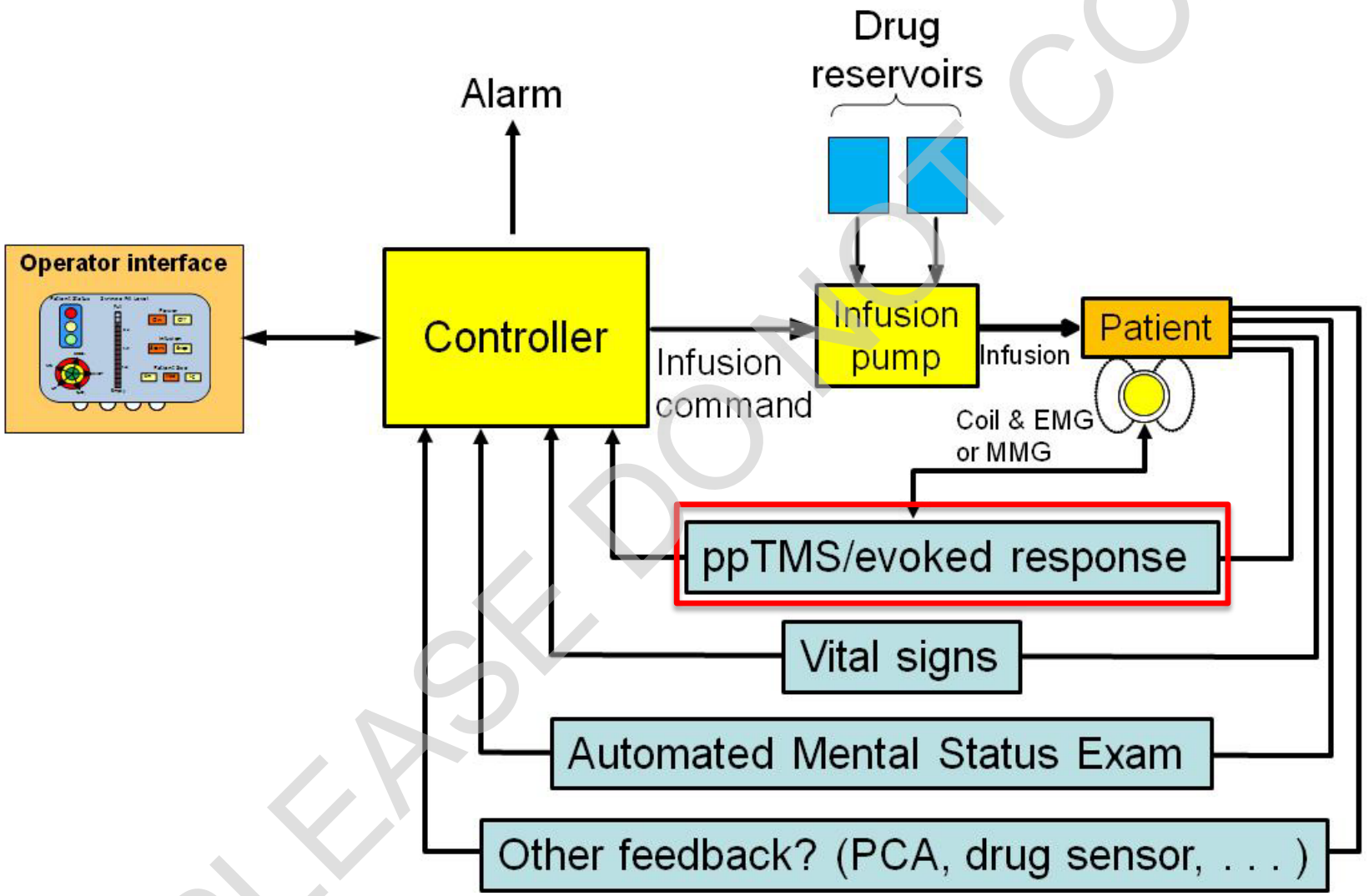


Use case: model TMS in a Deployable Automated Anesthesia Unit (DAAU)



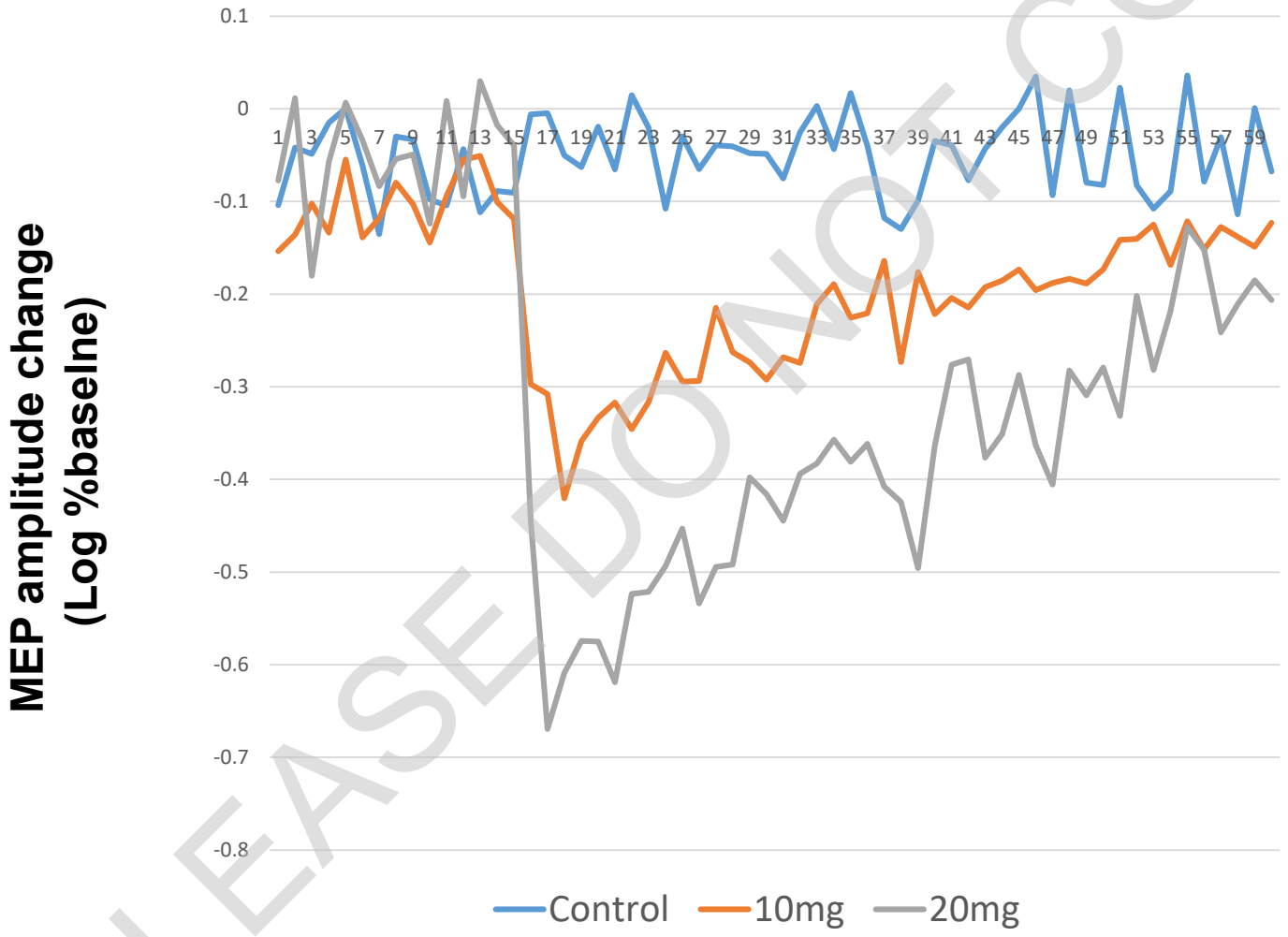
Rotenberg, Goldie, Leroy (Vivonics Inc., and Boston Children's Hospital)

Proposed use: a closed loop autonomous analgesia system



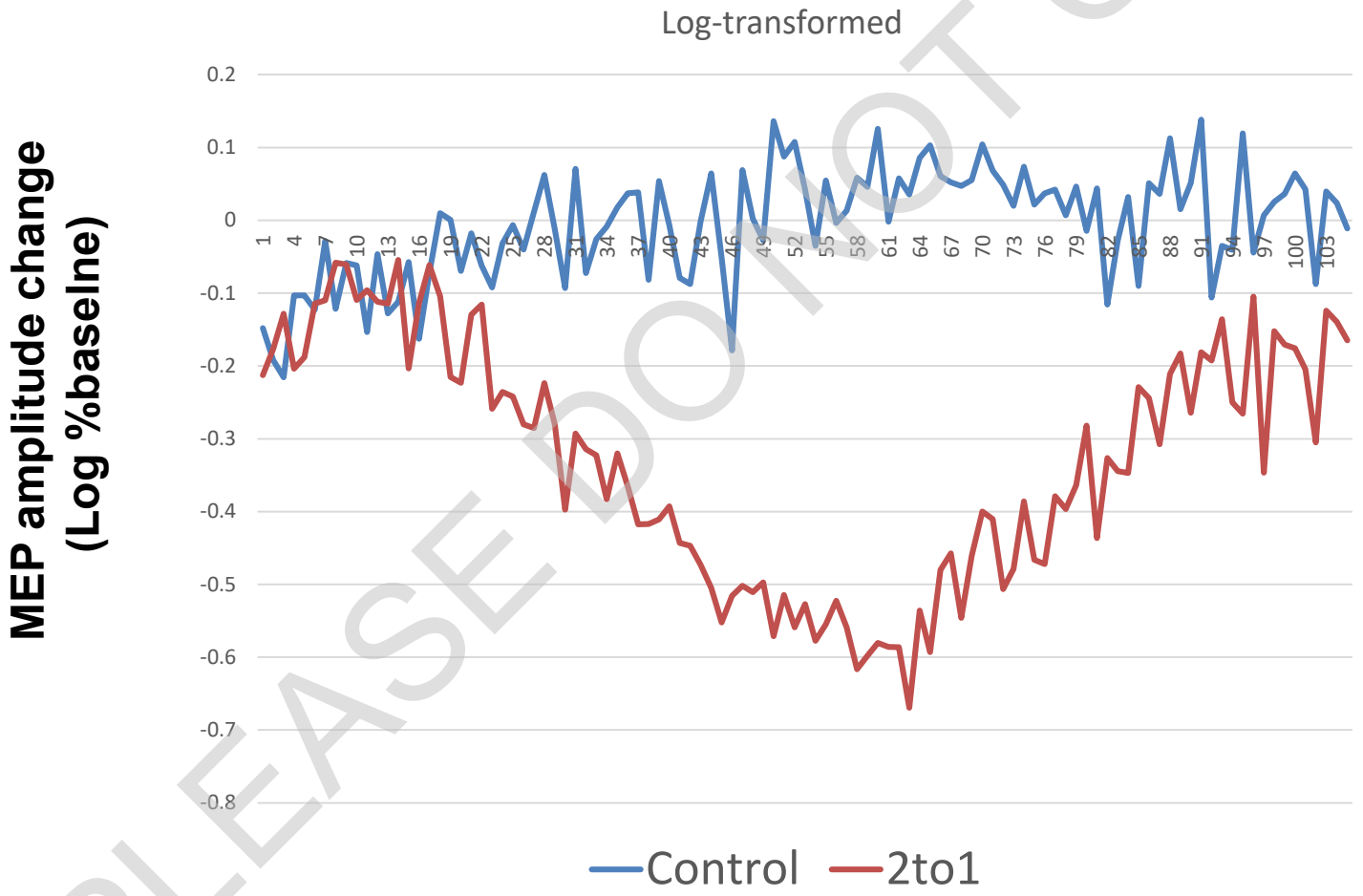
Rotenberg, Goldie, Leroy (Vivonics Inc., and Boston Children's Hospital)

MEP response to propofol bolus

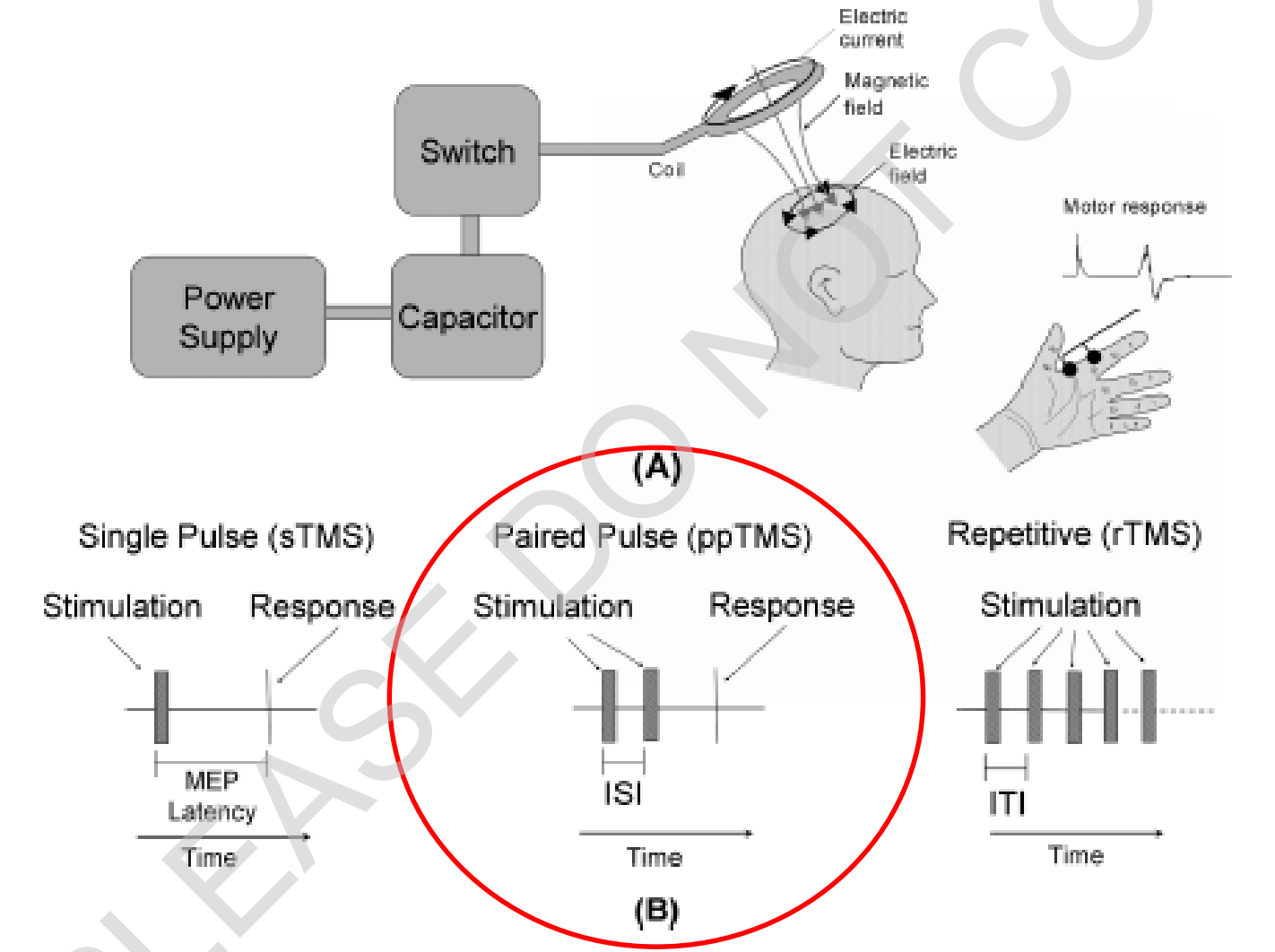


Gersner et al., 2020

MEP response to propofol rate change

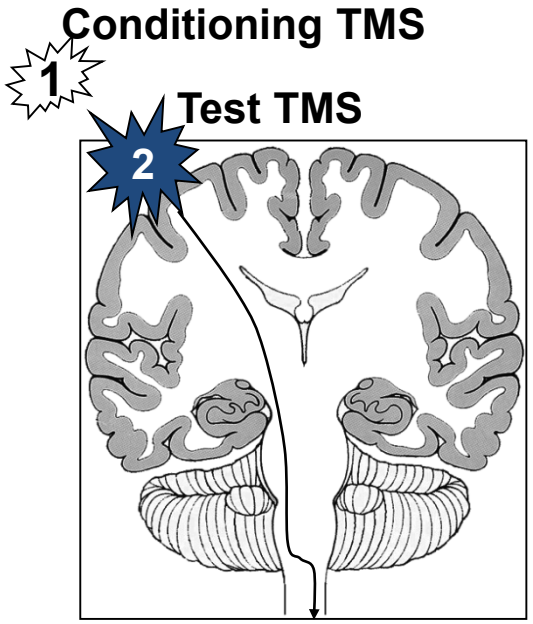


Stimulation protocols

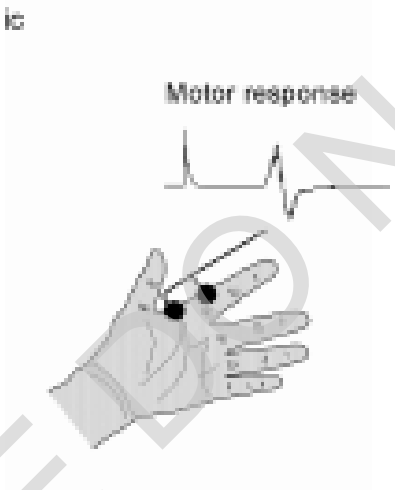


Frye, Rotenberg, et al. Child Neurol 2007

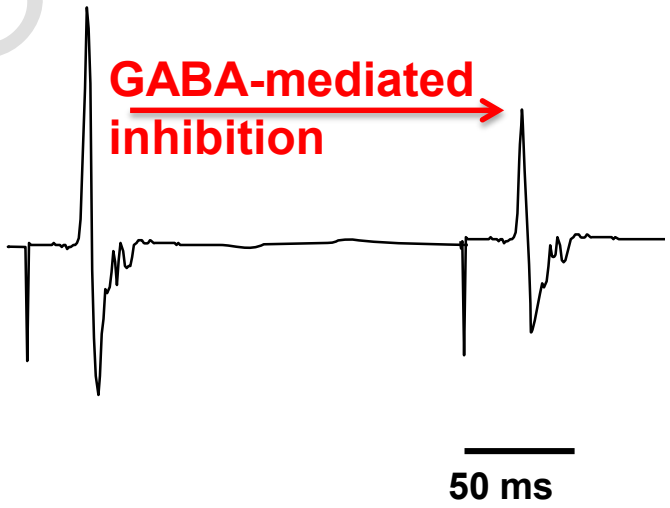
GABAergic cortical inihibition measures by paired-pulse TMS (ppTMS)



Rotenberg and Pascual-Leone, 2010



Paired-pulse MEP inhibition

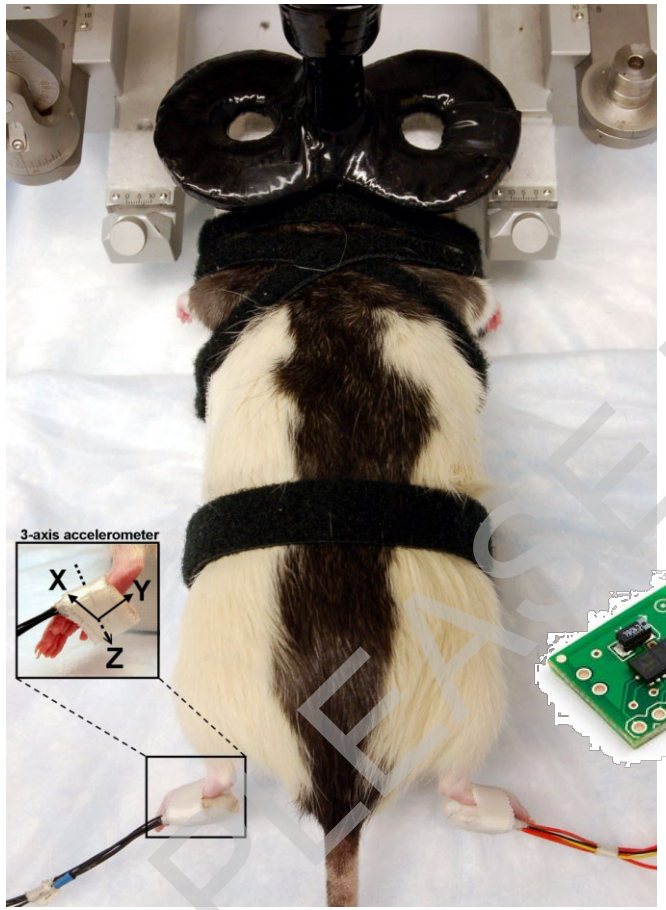


J Neurophysiol 107: 966–972, 2012.
First published October 19, 2011; doi:10.1152/jn.00690.2011.

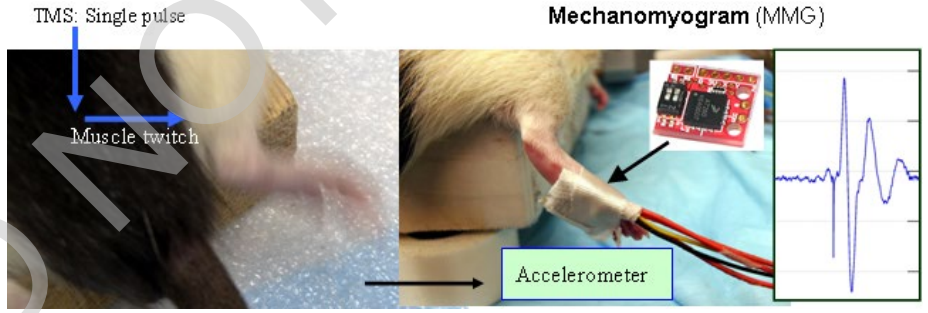
A new measure of cortical inhibition by mechanomyography and paired-pulse transcranial magnetic stimulation in unanesthetized rats

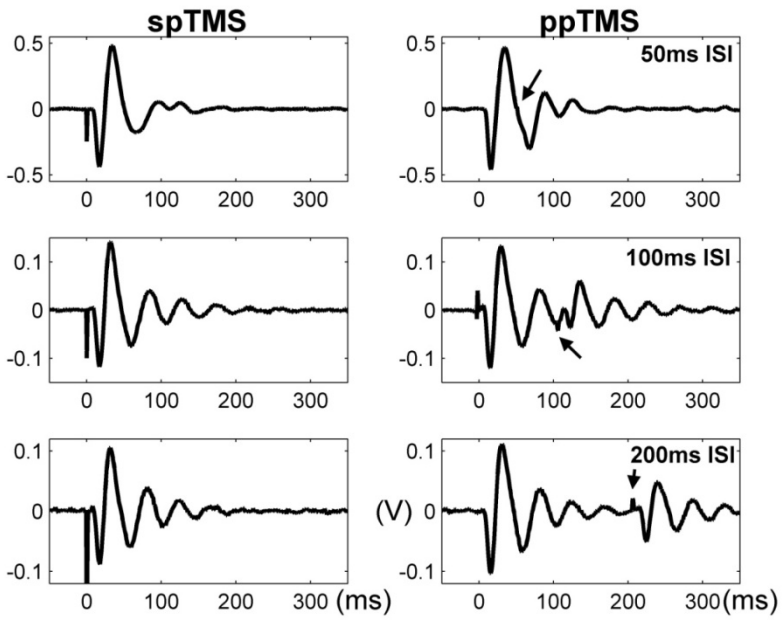
Tsung-Hsun Hsieh,[1,2] Sameer C. Dhamne,[1] Jia-Jin J. Chen,[2] Alvaro Pascual-Leone,[3,4] Frances E. Jensen,[1,5] and Alexander Rotenberg[1,3]

MMG (Mechanomyography)

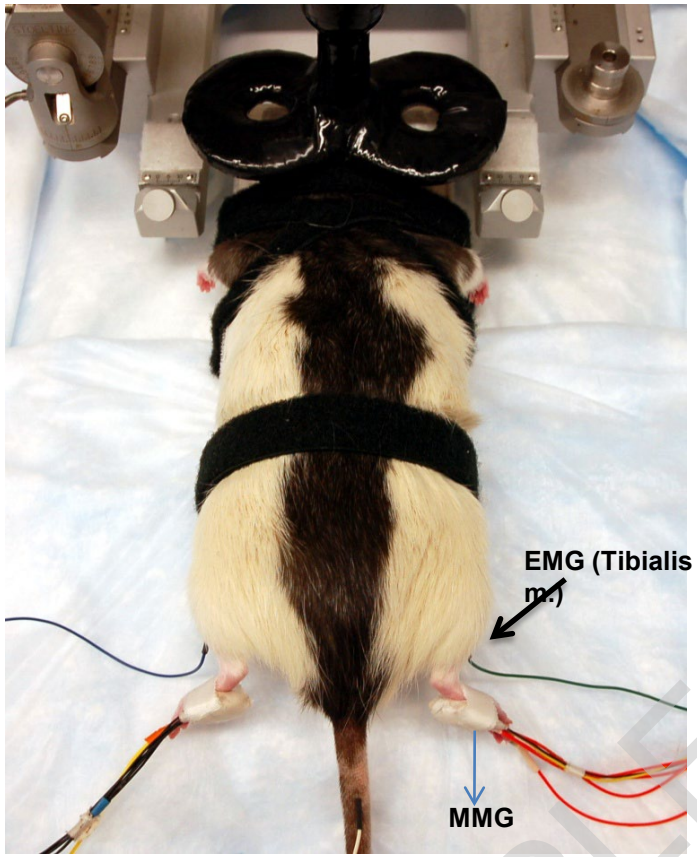


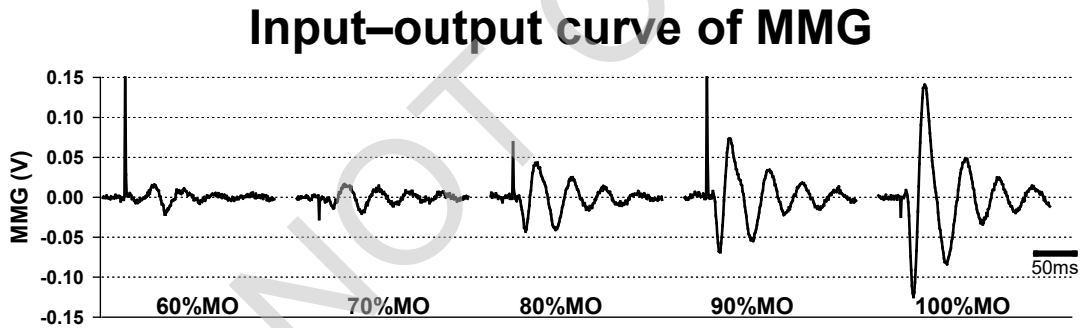
Accelerometer

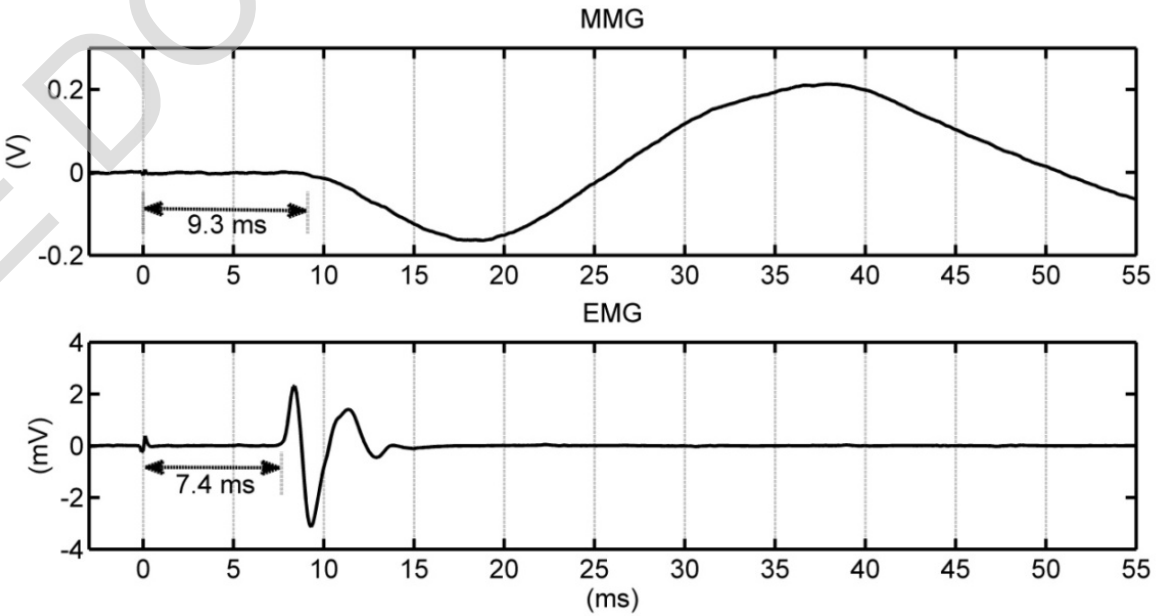




EMG vs MMG

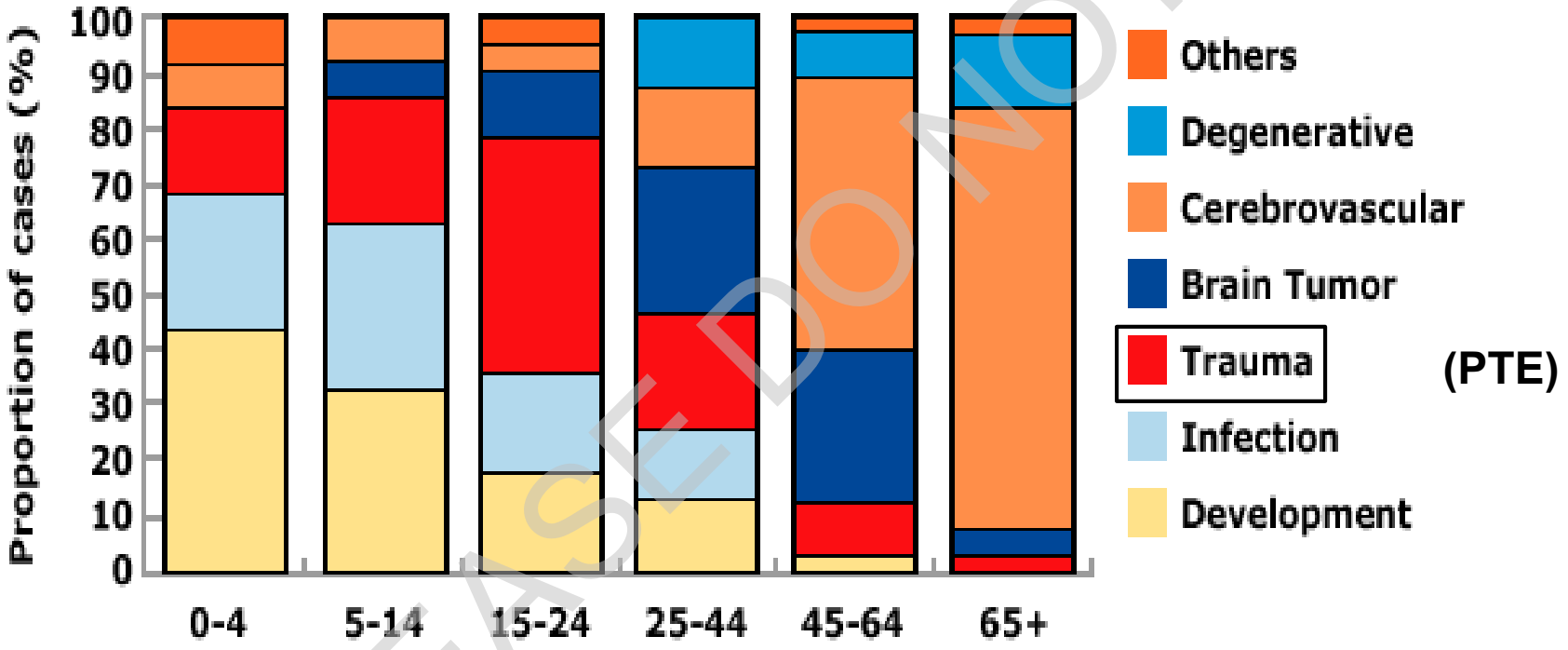






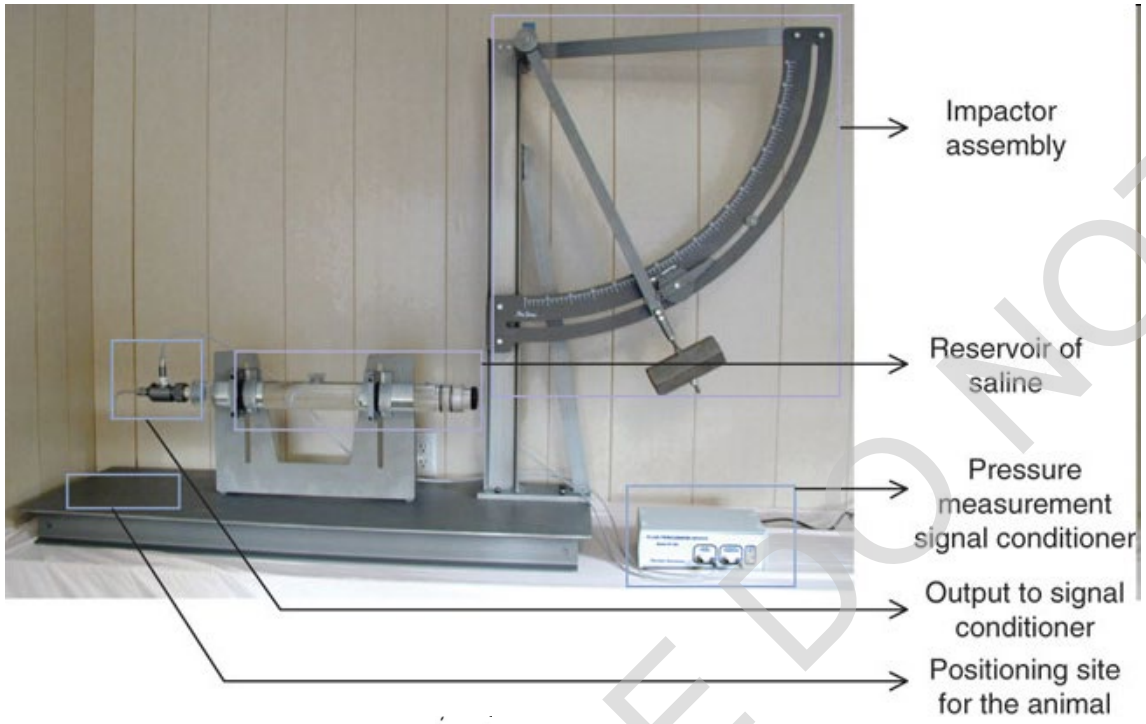
TBI: The most common cause of acquired epilepsy in young adults

- Causes of Epilepsy:

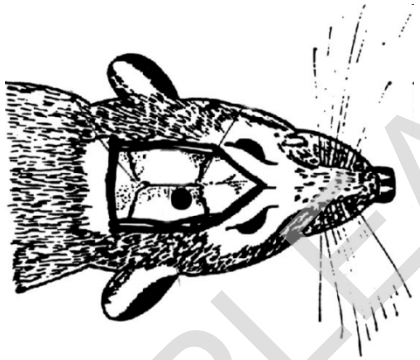


Annegers JF. Lippincott Williams & Wilkins, 2001:165-72.

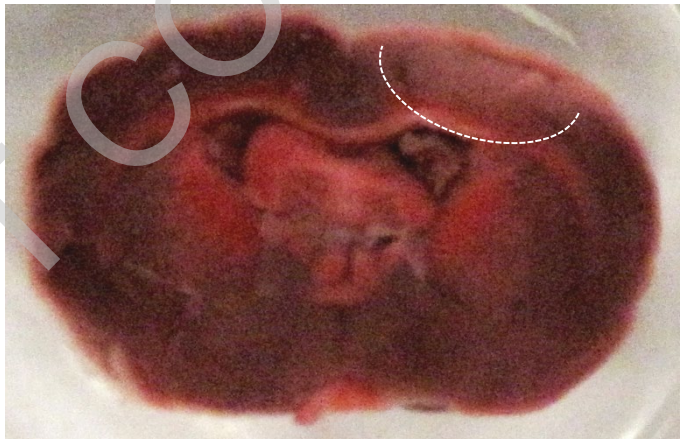
Fluid Percussion Injury: a post-traumatic epilepsy model

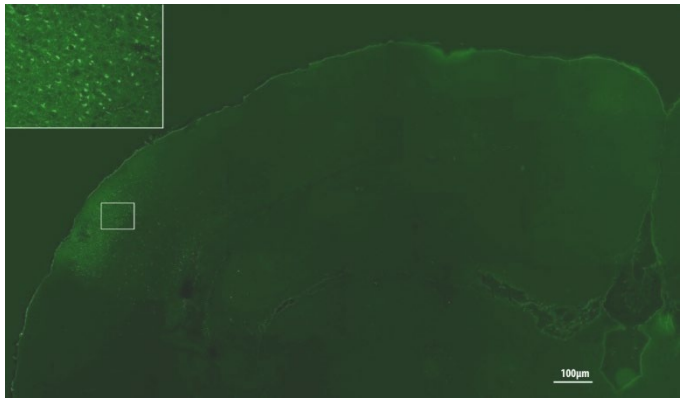


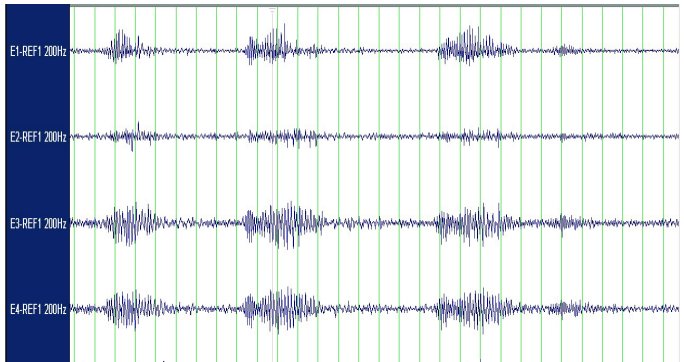
Nature Protocols, 2011



McIntosh et al., 1989







OXFORD

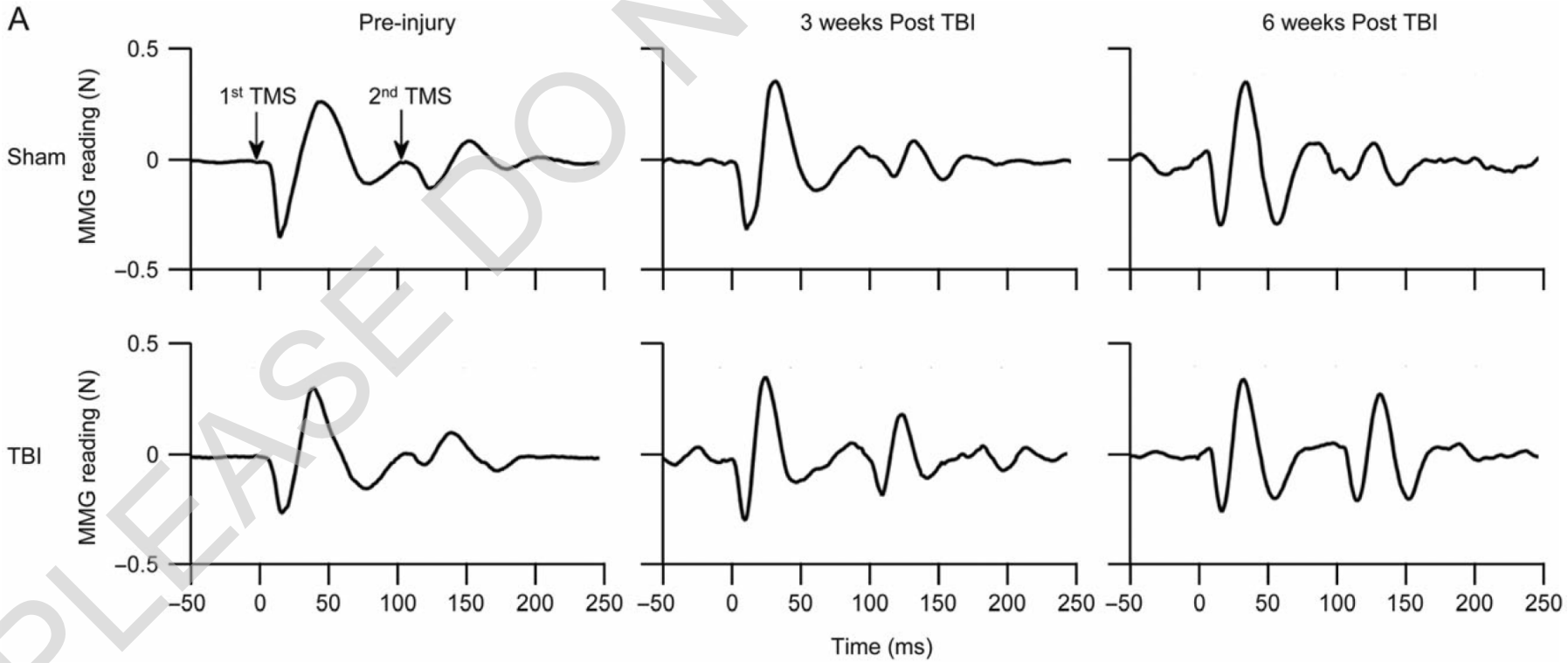
Cerebral Cortex, 2016; 1–16

doi: 10.1093/cercor/bhw318
Original Article

ORIGINAL ARTICLE

Trajectory of Parvalbumin Cell Impairment and Loss of Cortical Inhibition in Traumatic Brain Injury

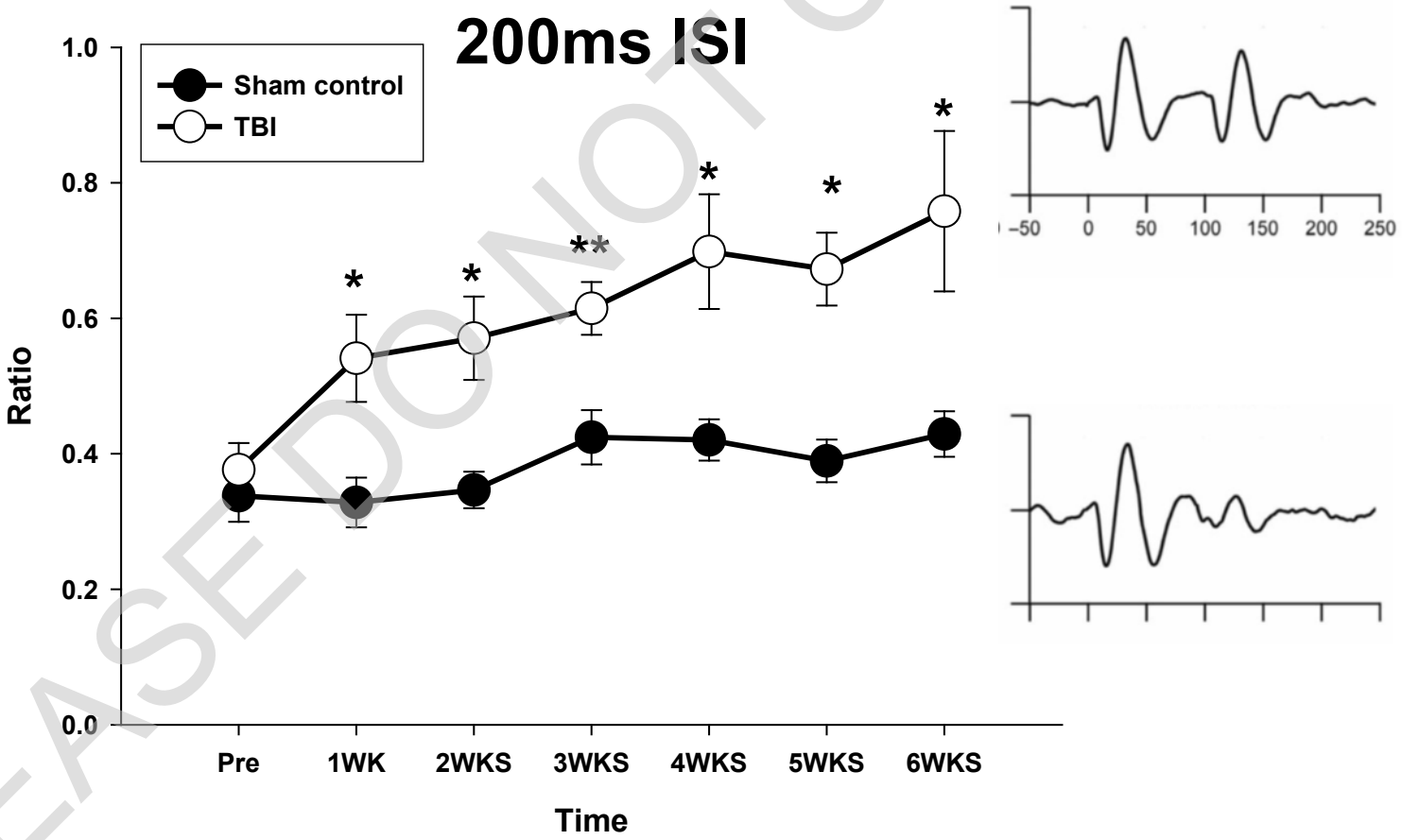
Tsung-Hsun Hsieh[1,2,3,†], Henry Hing Cheong Lee[4,†], Mustafa Qadir Hameed[1,4,5], Alvaro Pascual-Leone[6], Takao K. Hensch[4,7] and Alexander Rotenberg[1,4,6]



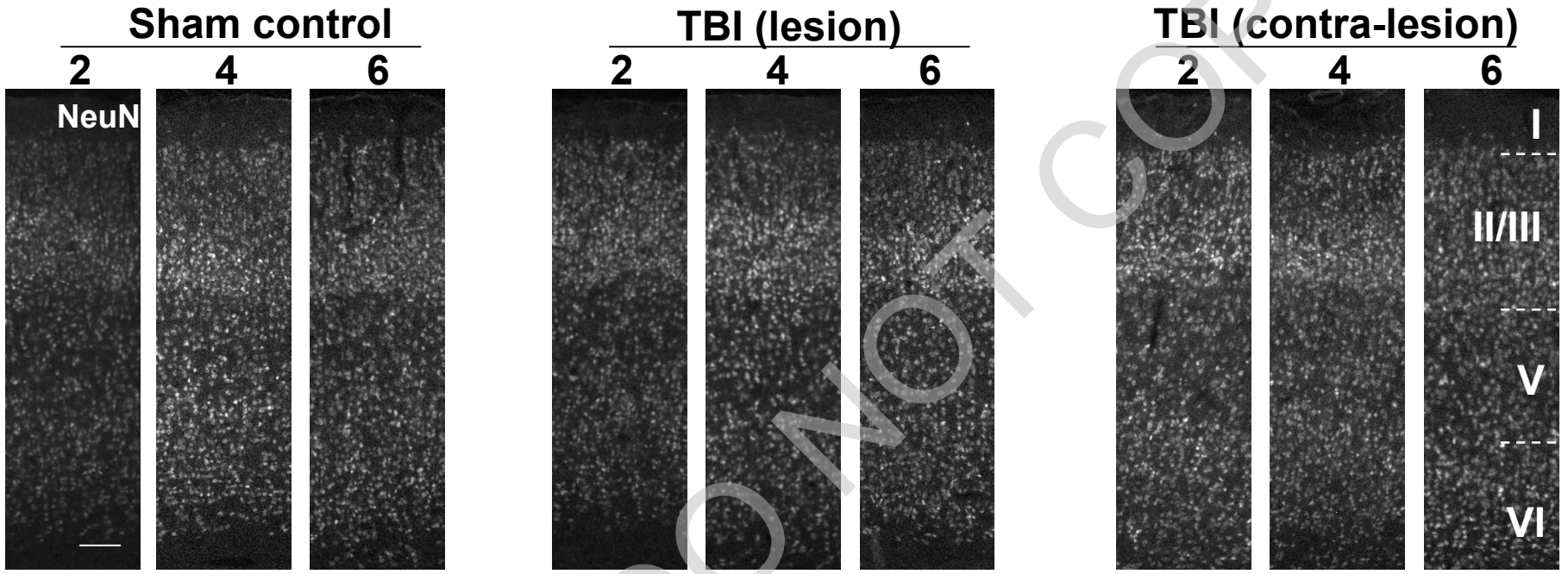
Loss of cortical paired-pulse inhibition after TBI

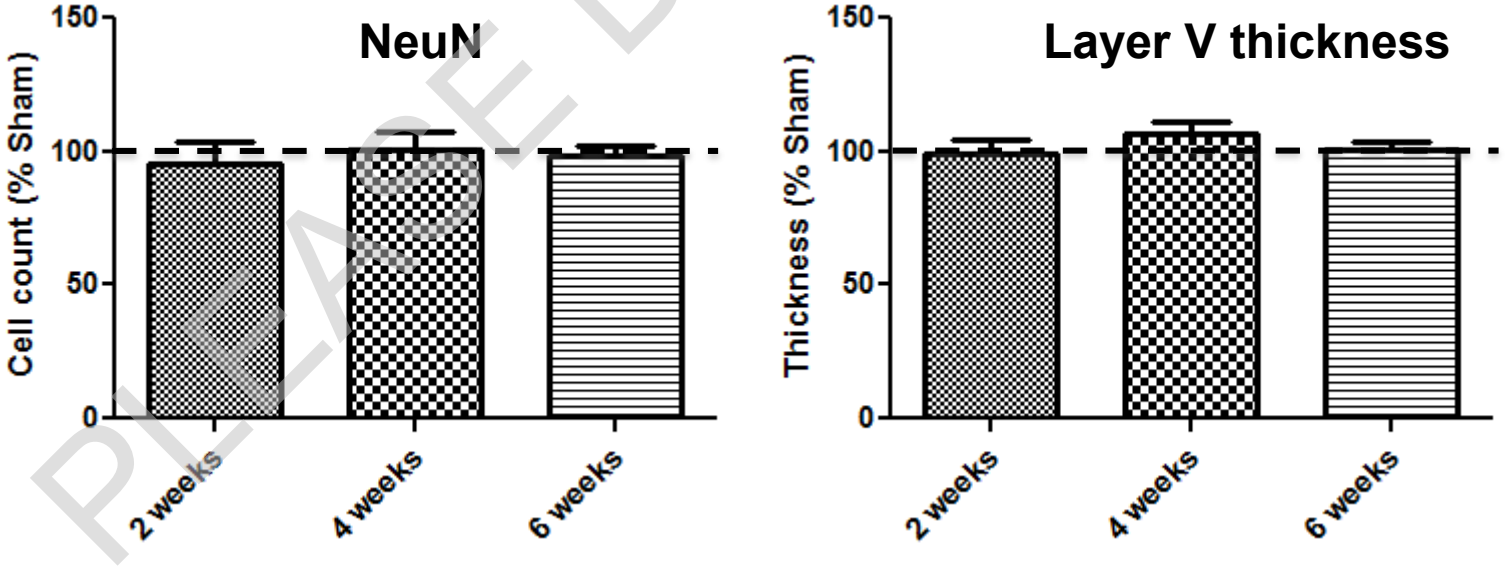
Min GABA inhibition

Max GABA inhibition

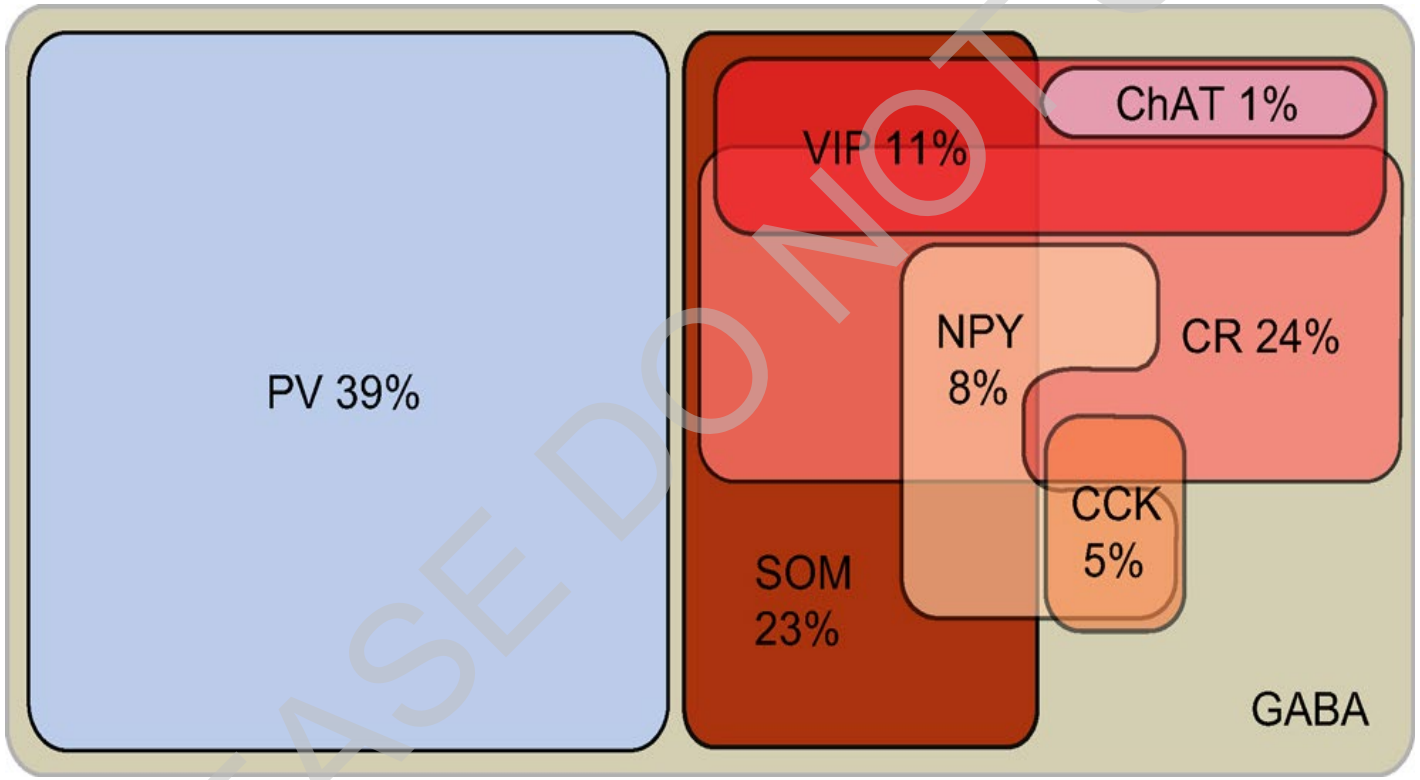


General cortical architecture was not affected by TBI



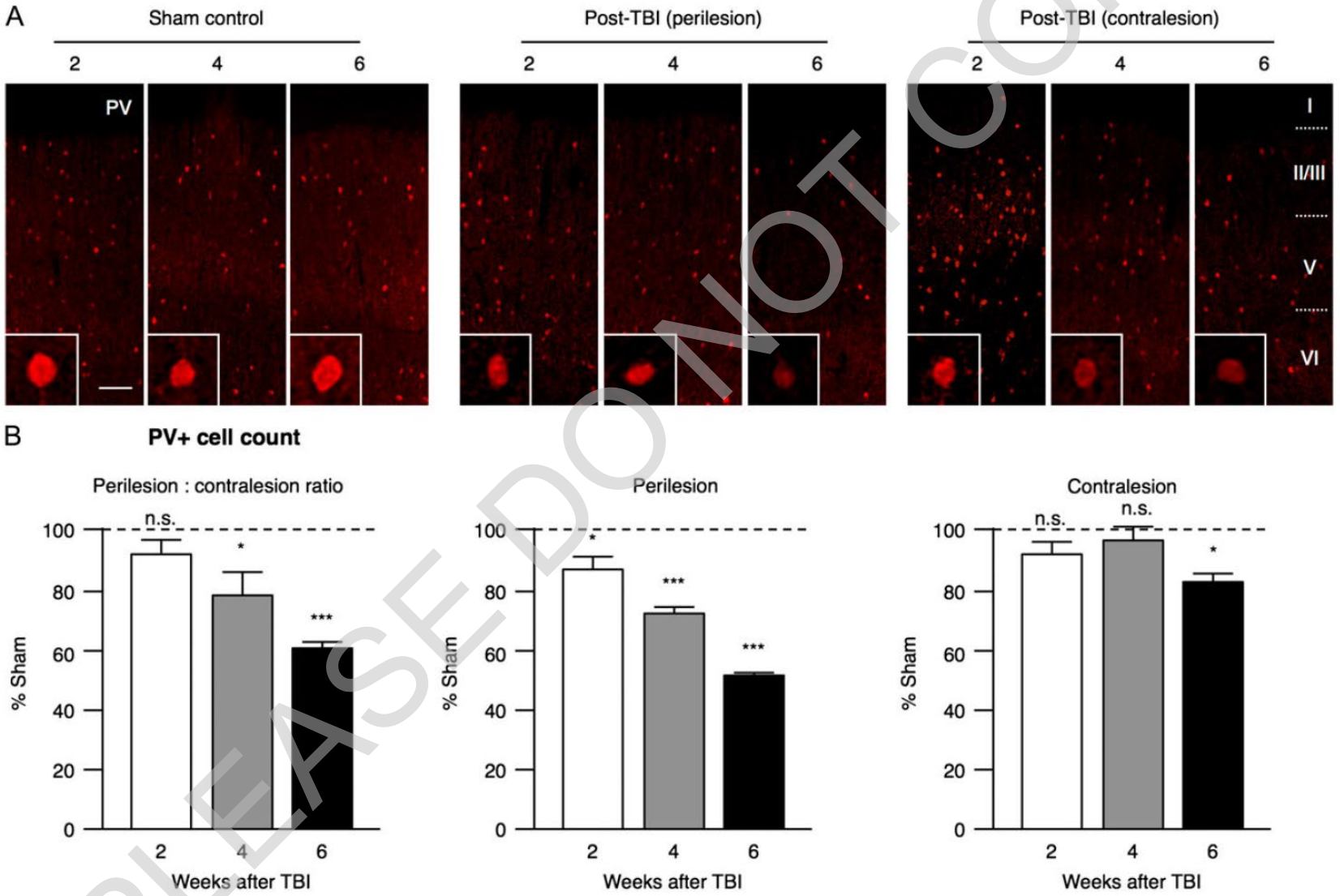


Parvalbumin (PV) interneurons are the major sub-type of cortical inhibitory neuron… and vulnerable to oxidative stress

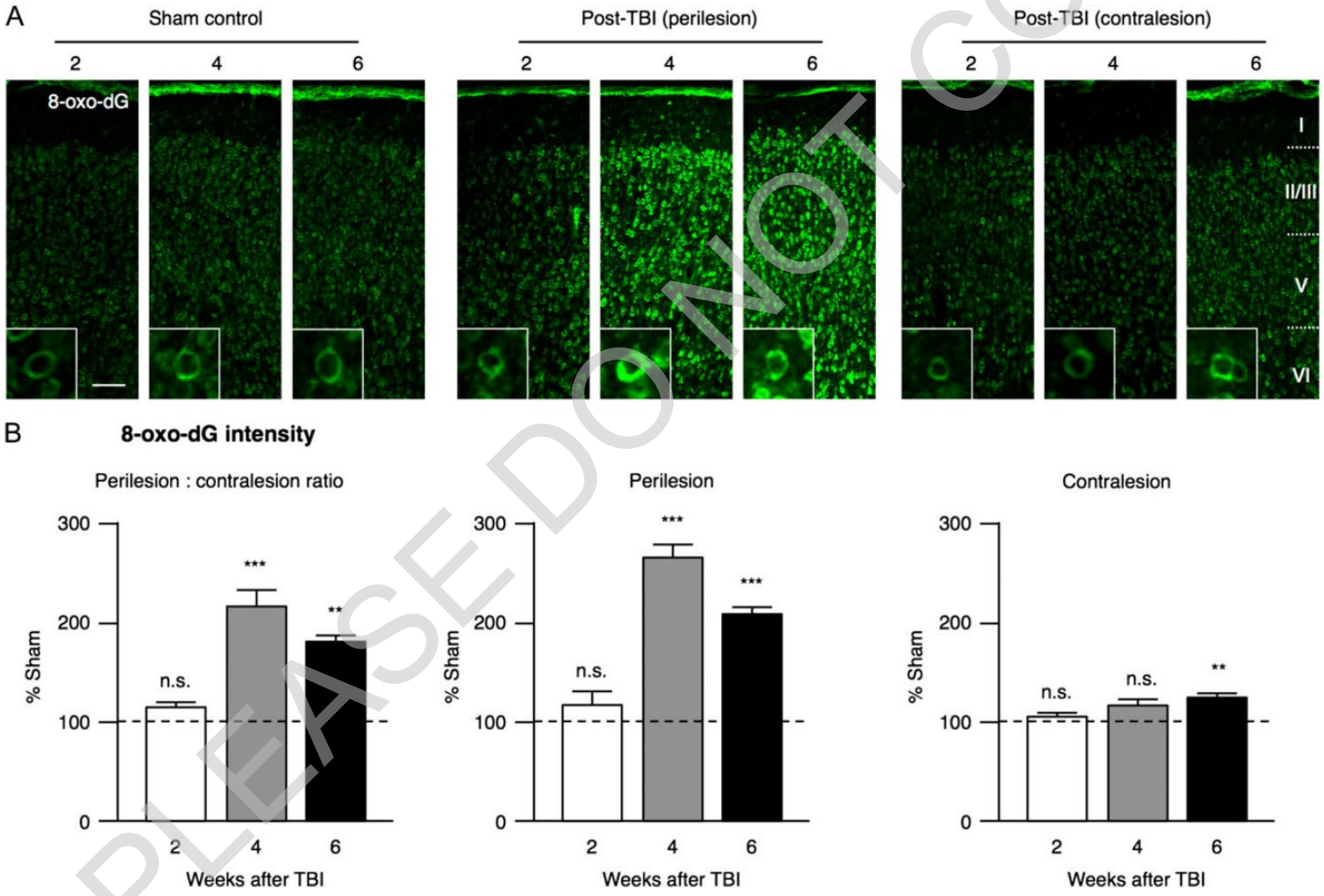


Gonchar et al., 2007, Front Neuroanat.

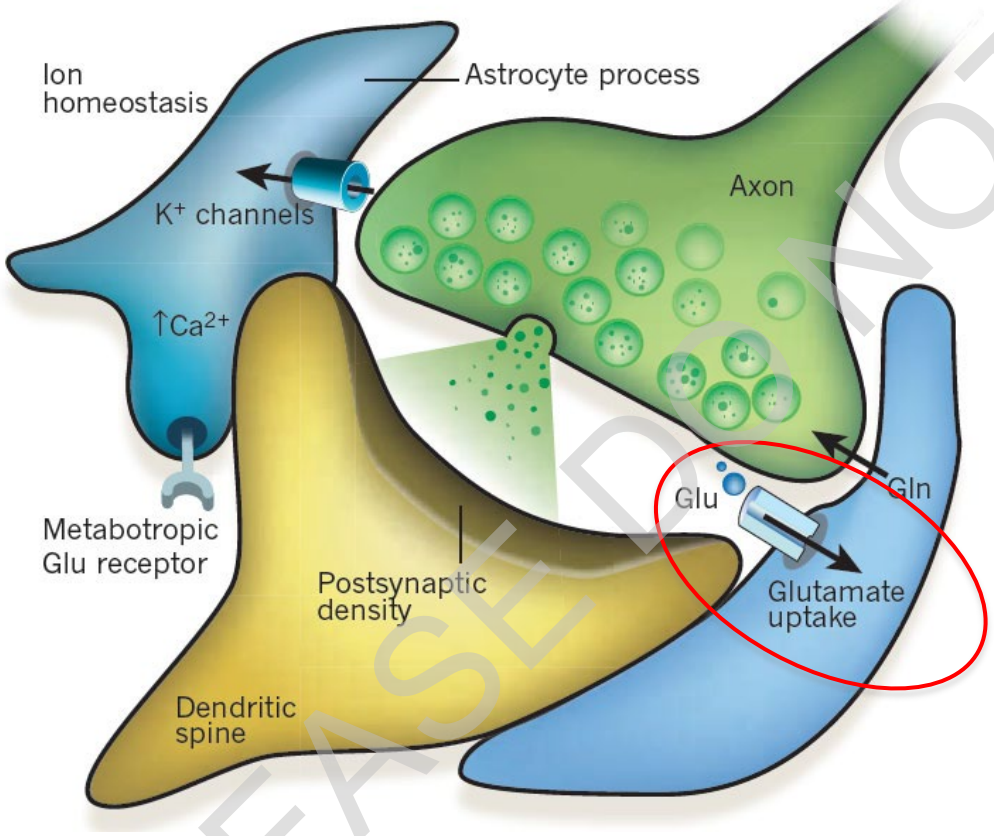
Progressive PV loss after TBI



Progressive oxidative stress after TBI



Astrocytic glutamate transporter as a druggable target in epileptogenesis

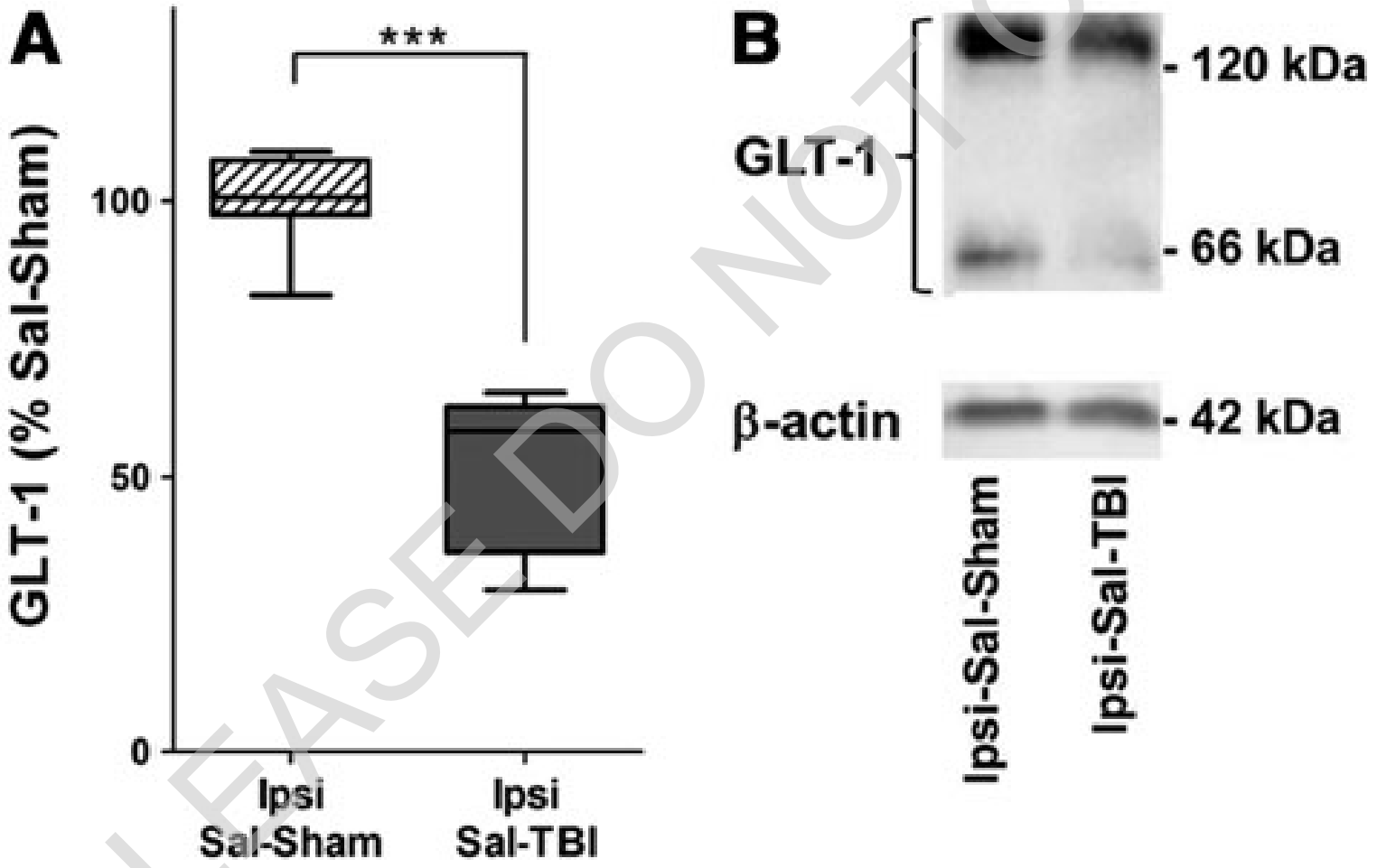


Astrocytes in the tripartite synapse

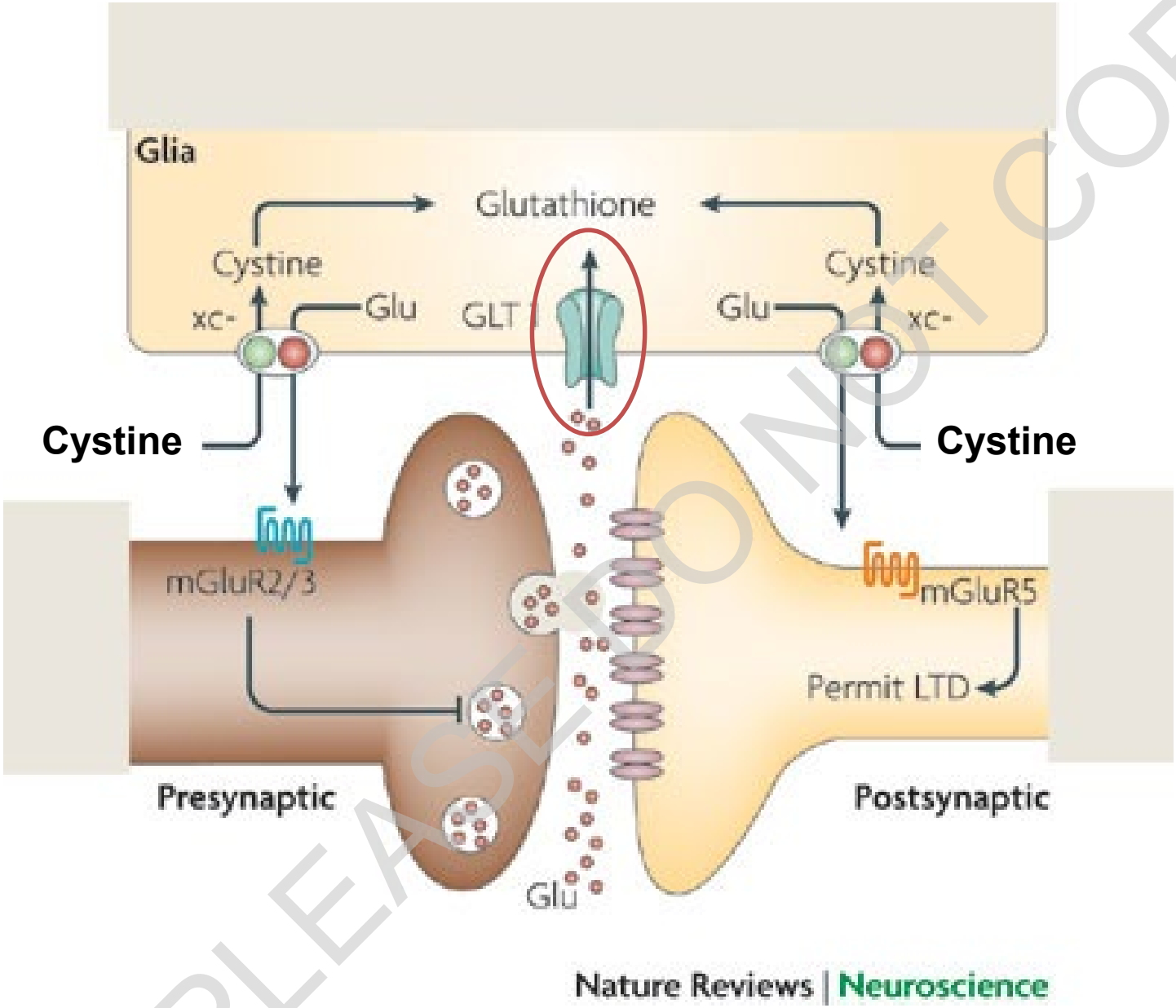
- K+ buffering
- **Glutamate homeostasis**
- GABA synthesis

Courtesy of P. Rosenberg

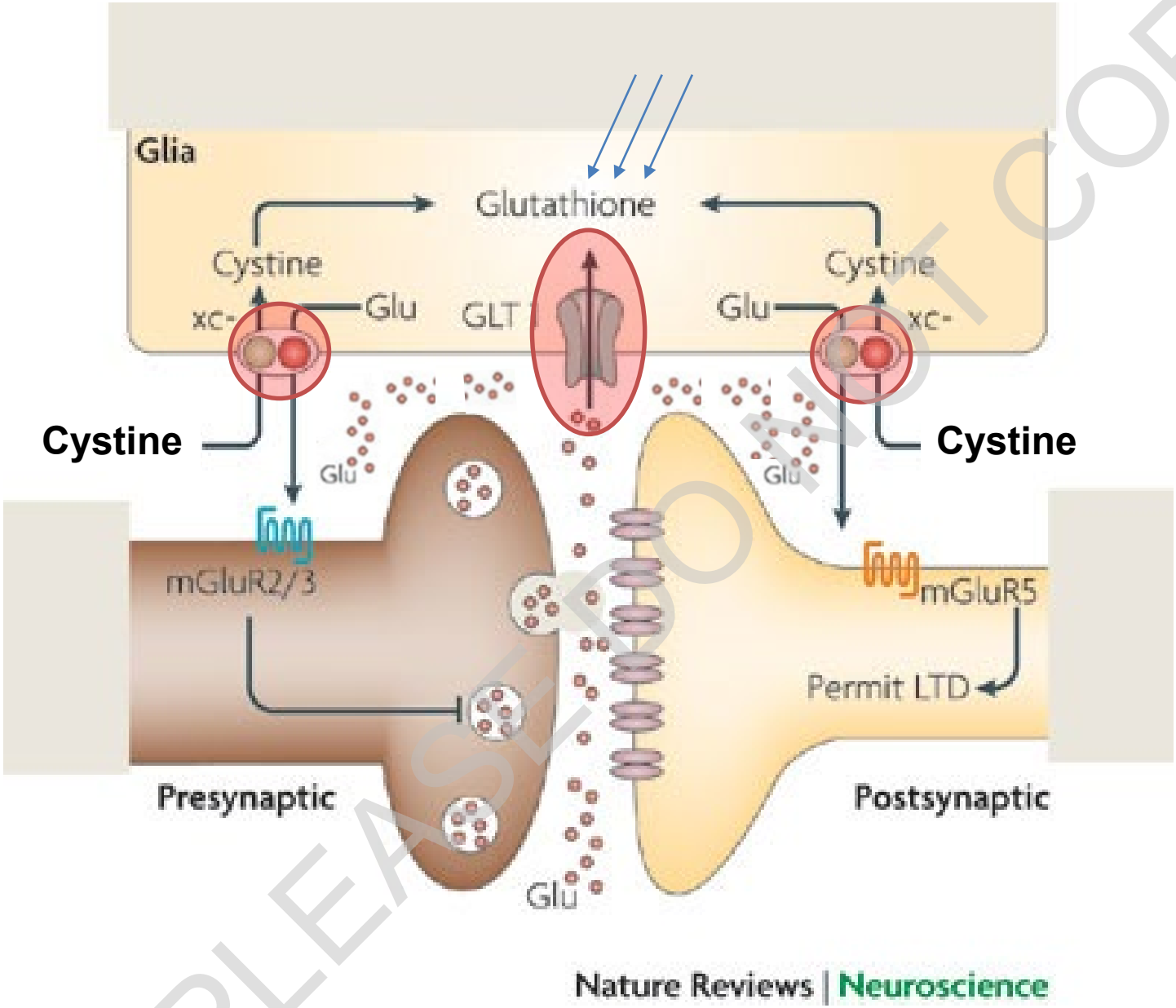
Cortical GLT-1 is depressed after epiletogenic TBI



Goodrich et al., J. Neurotrauma 2013



Kalivas 2009



Kalivas 2009

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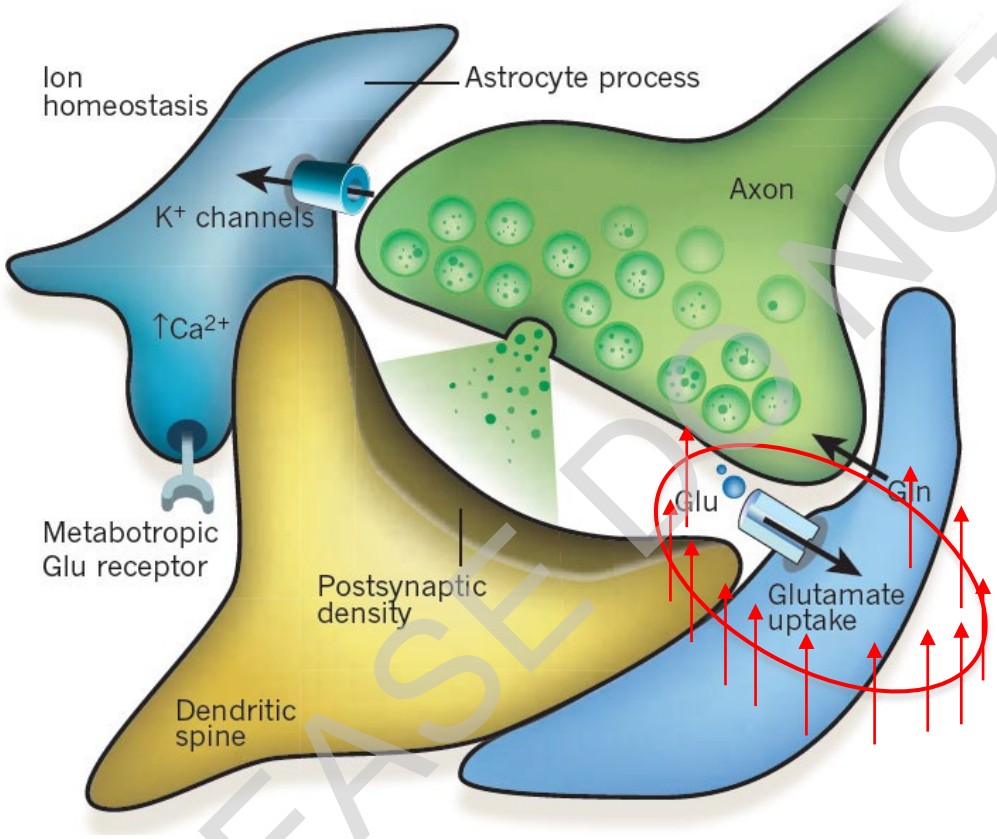


Glutamate clearance can be enhanced by BETA LACTAMS (!)

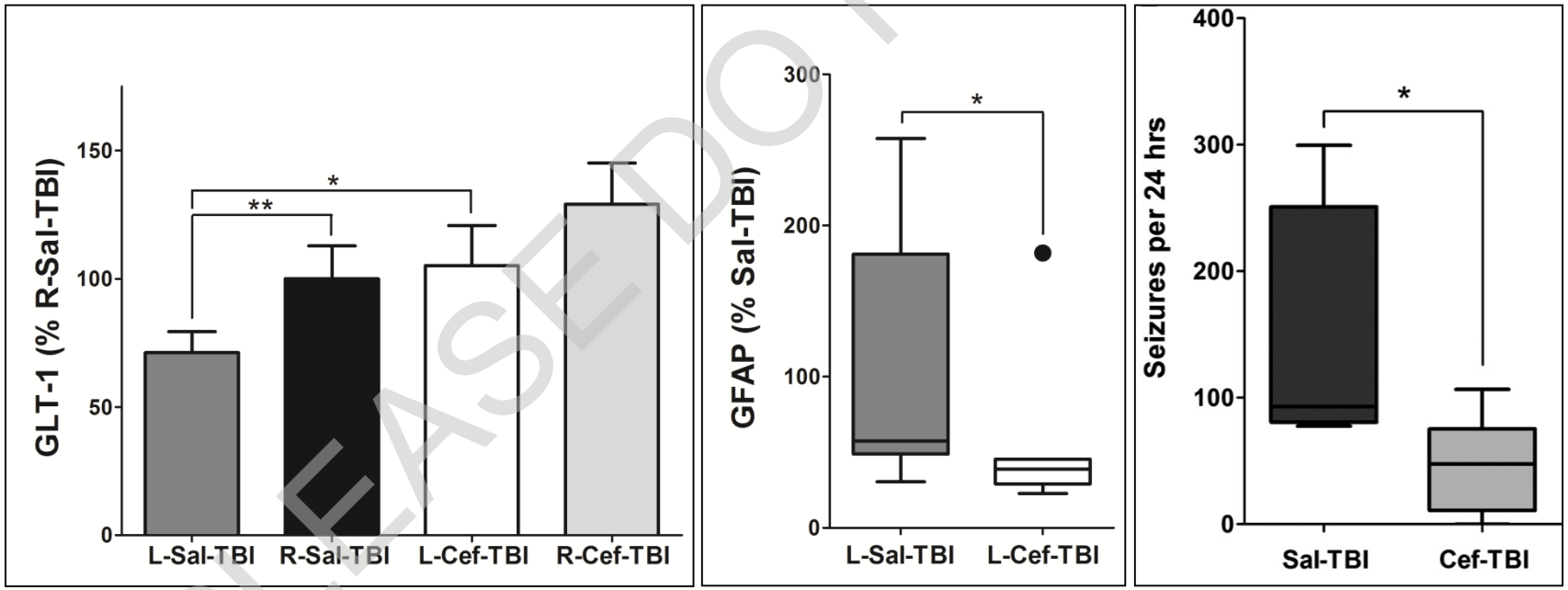
Courtesy of P. Rosenberg

JOURNAL OF NEUROTRAUMA 30:1434–1441 (August 15, 2013)

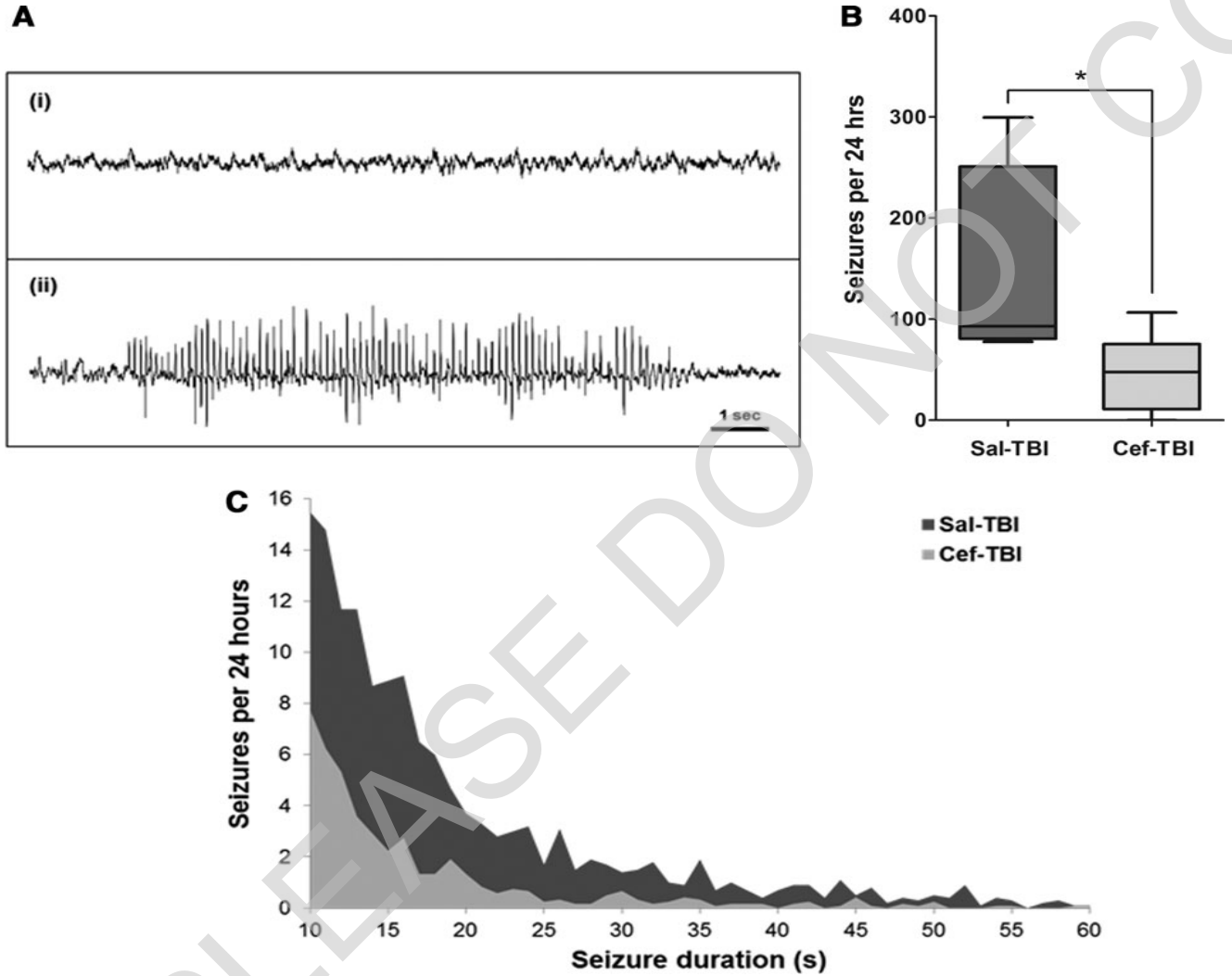
DOI: 10.1089/neu.2012.2712

Ceftriaxone Treatment after Traumatic Brain Injury Restores Expression of the Glutamate Transporter, GLT-1, Reduces Regional Gliosis, and Reduces Post-Traumatic Seizures in the Rat

Grant S. Goodrich,[1,*] Anatoli Y. Kabakov,[1,*] Mustafa Q. Hameed,[1,2] Sameer C. Dhamne,[1] Paul A. Rosenberg,[1] and Alexander Rotenberg[1]

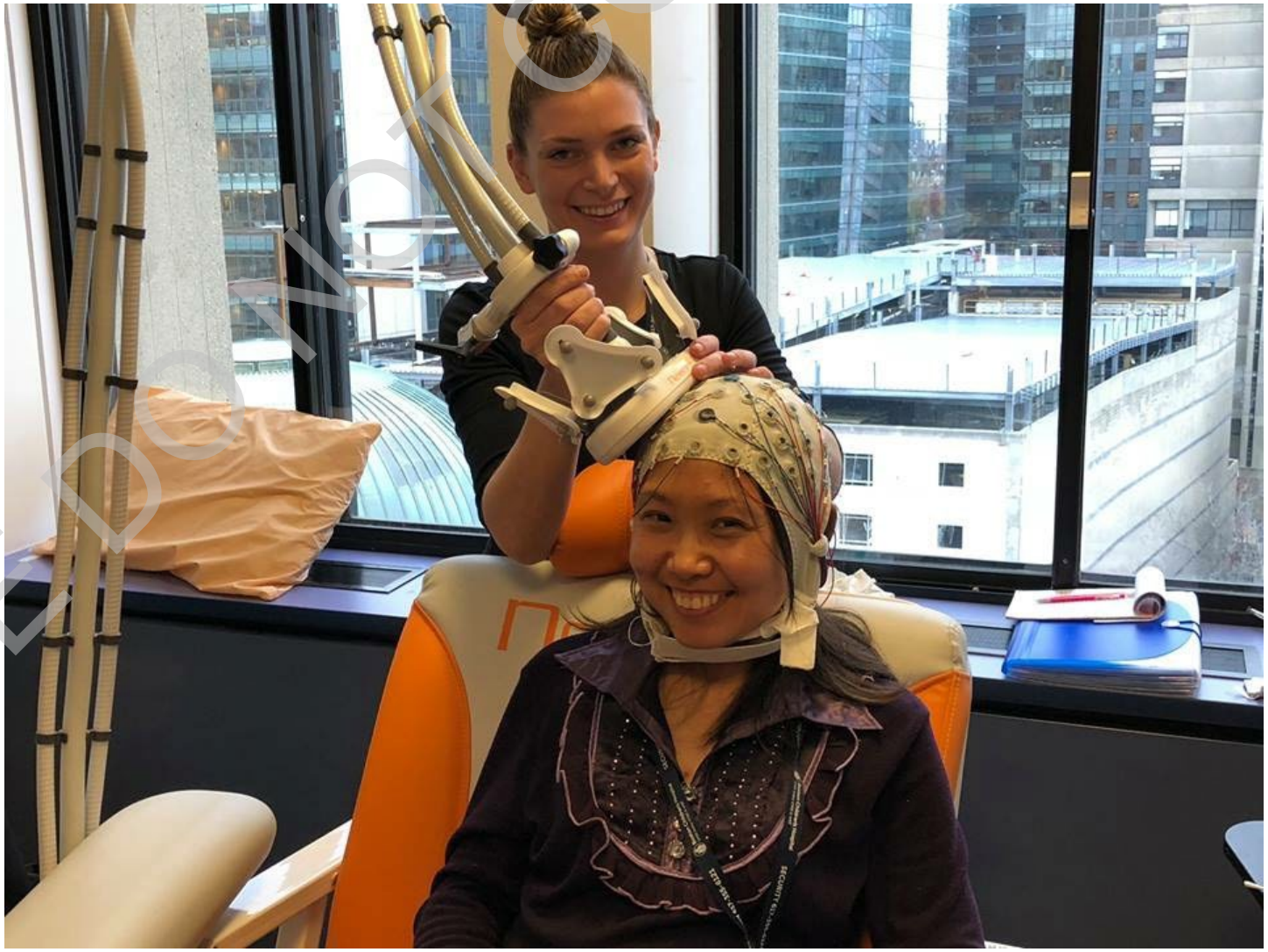


Ceftriaxone treatment prophylaxes against posttraumatic seizures

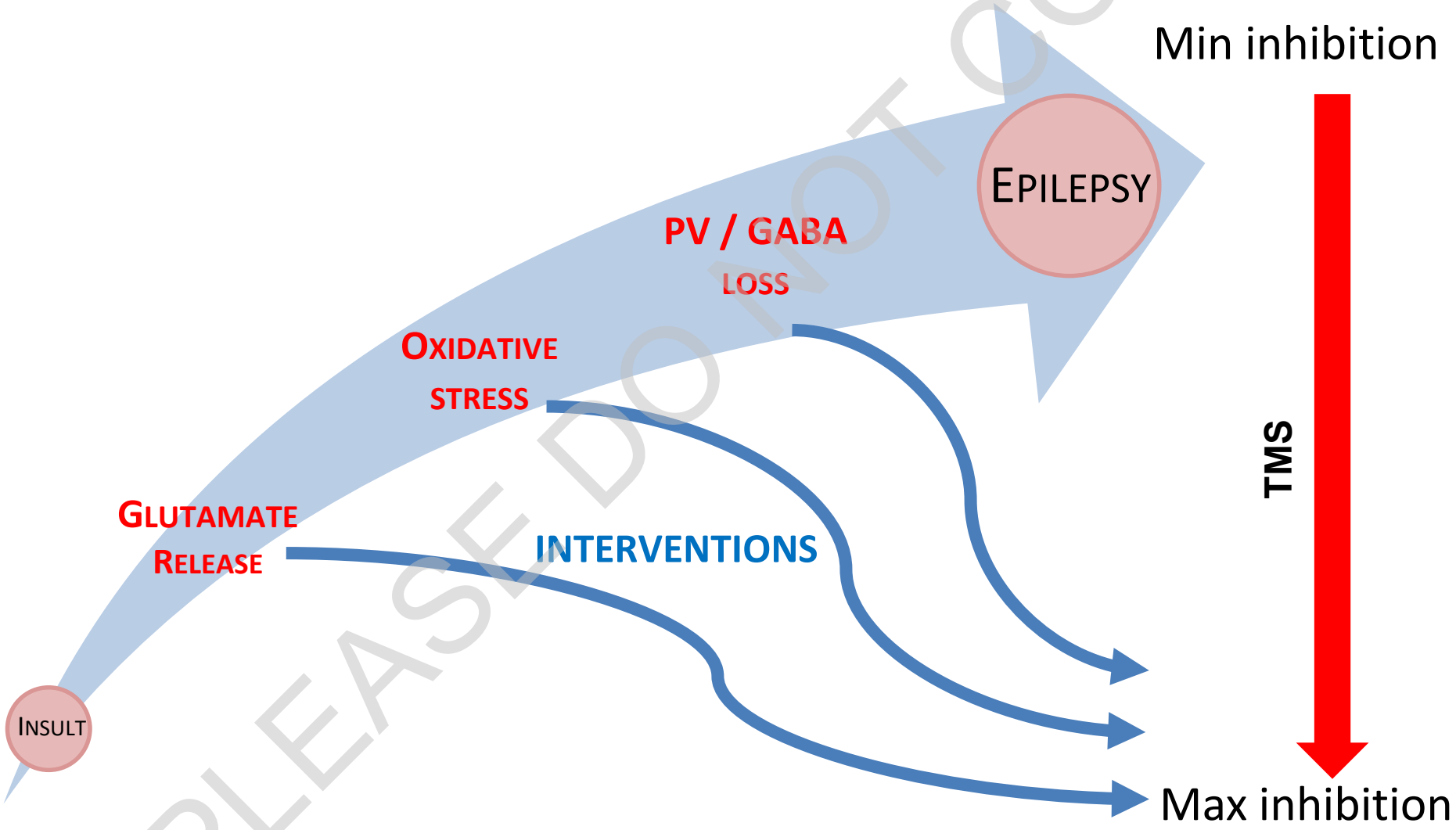


Goodrich et al., J. Neurotrauma 2013

So why is this interesting to a TMS lab?



Post Traumatic Epileptogenesis



OXFORD

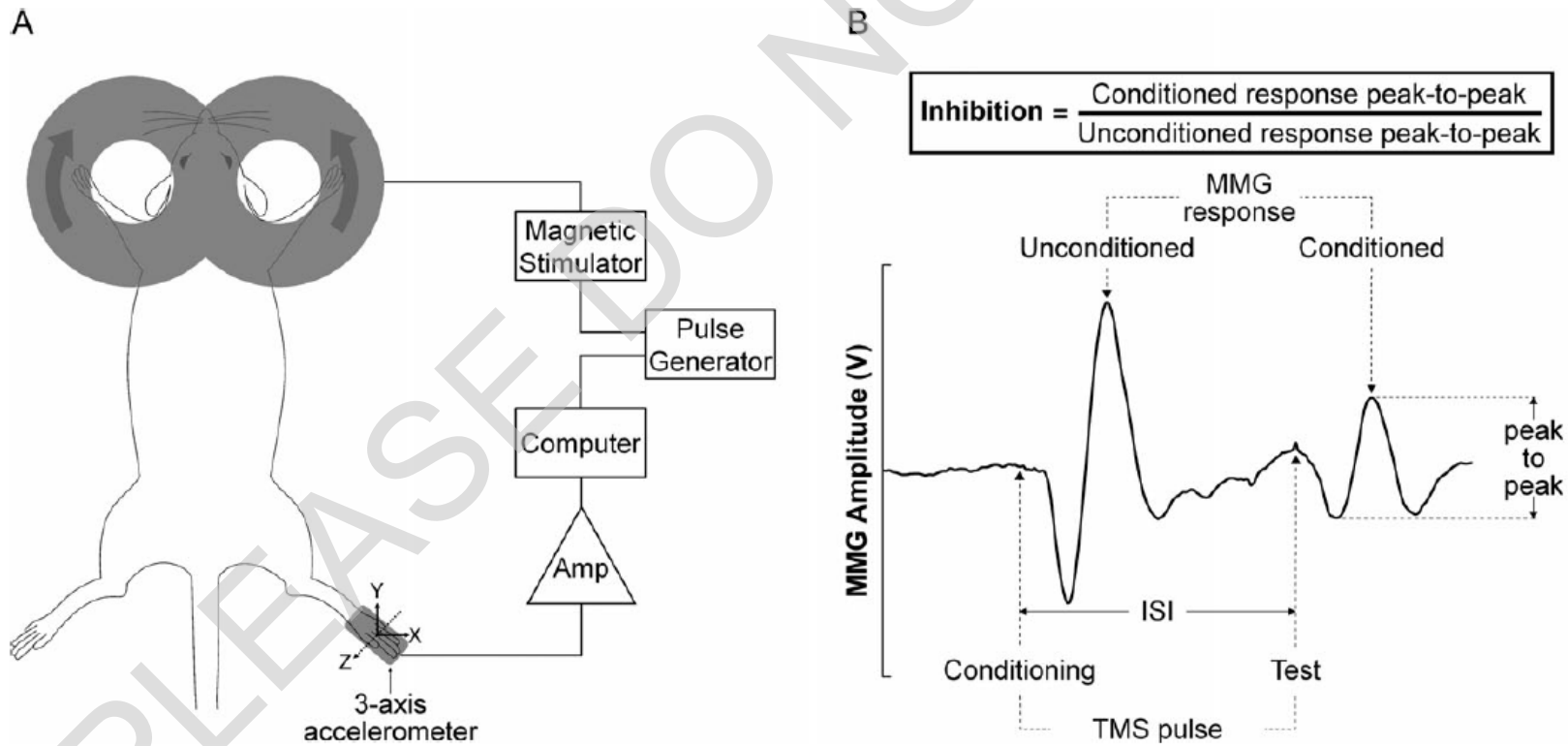
Cerebral Cortex, 2018; 1–13

doi: 10.1093/cercor/bhy328
Original Article

ORIGINAL ARTICLE

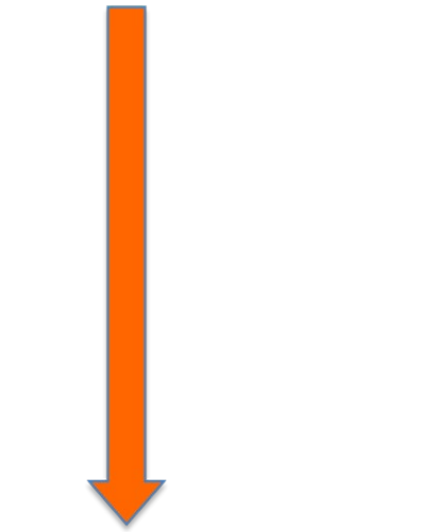
Ceftriaxone Treatment Preserves Cortical Inhibitory Interneuron Function via Transient Salvage of GLT-1 in a Rat Traumatic Brain Injury Model

Mustafa Q. Hameed[1,2,3], Tsung-Hsun Hsieh[1,4,5], Leon Morales-Quezada[6], Henry H. C. Lee[2], Ugur Damar[1,2], Paul C. MacMullin[1,2], Takao K. Hensch[2,7] and Alexander Rotenberg[1,2]

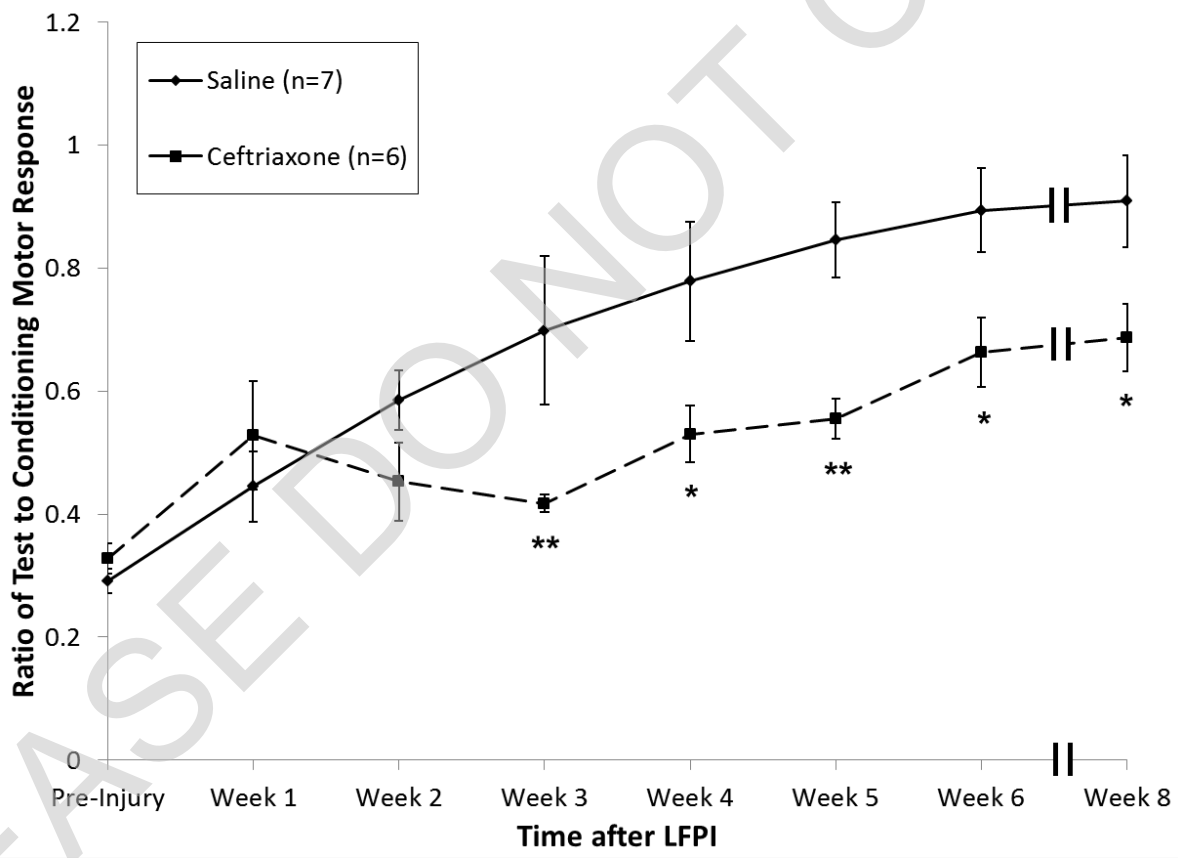


ppTMS as a biomarker and marker of target engagement in epileptogenesis

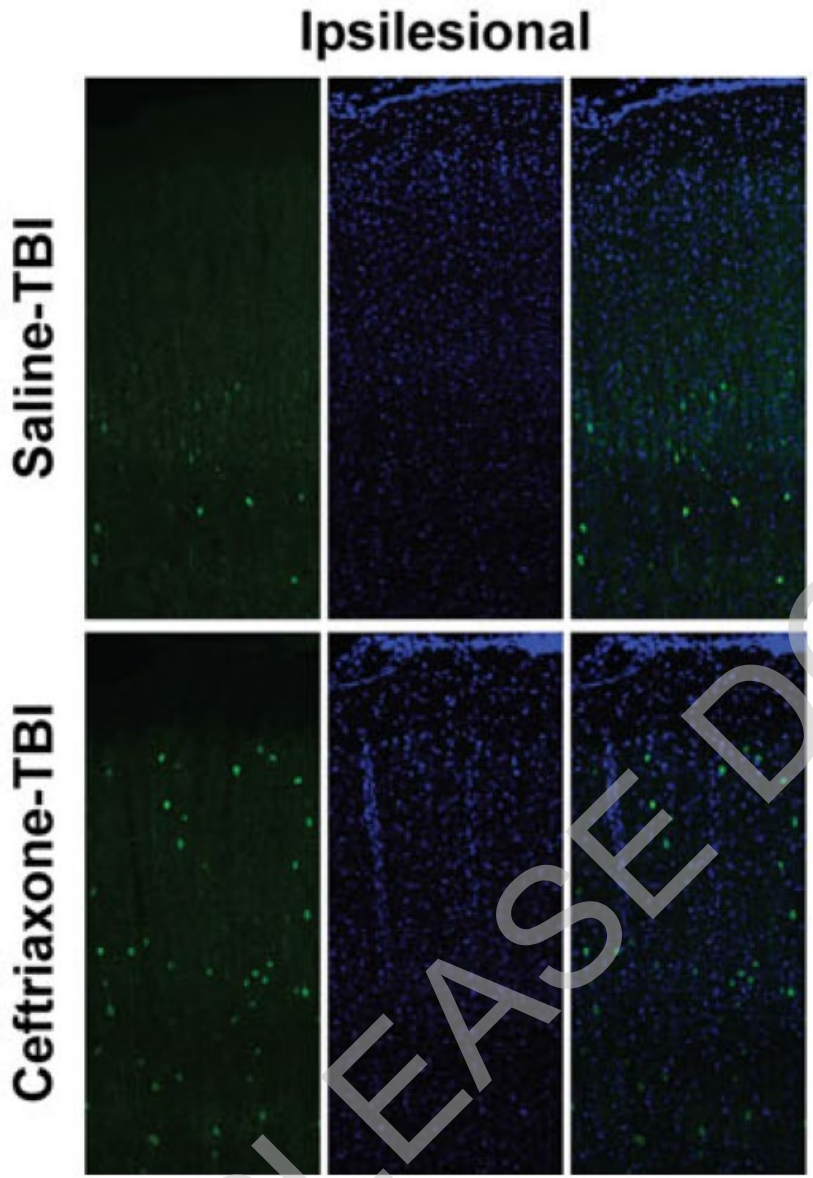
Min GABA inhibition

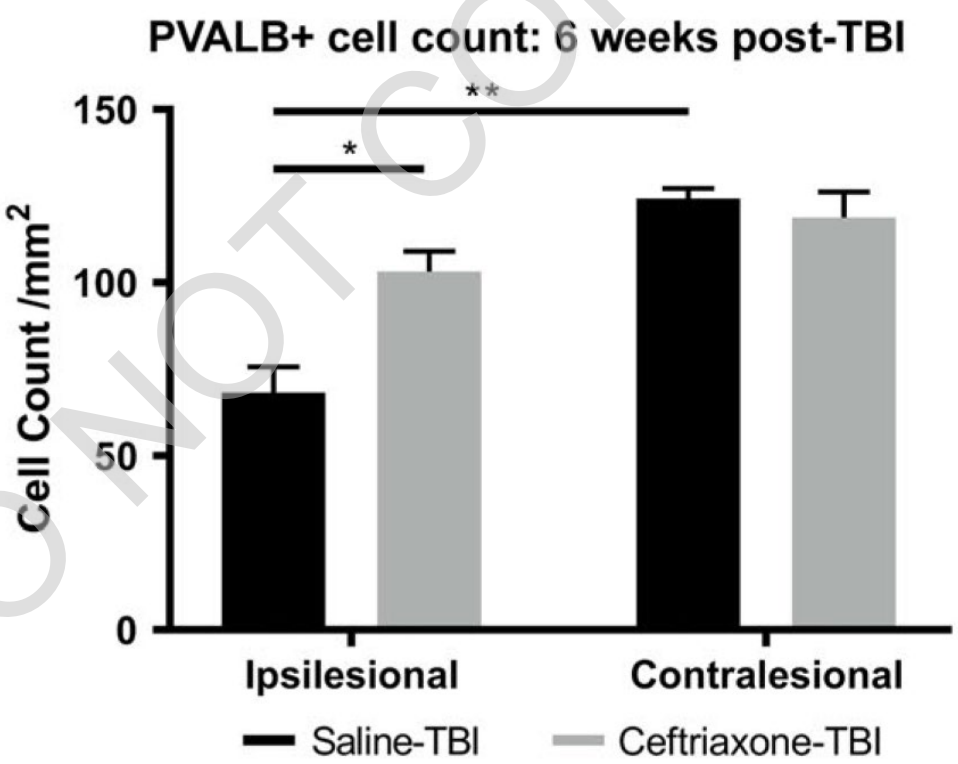


Max GABA inhibition



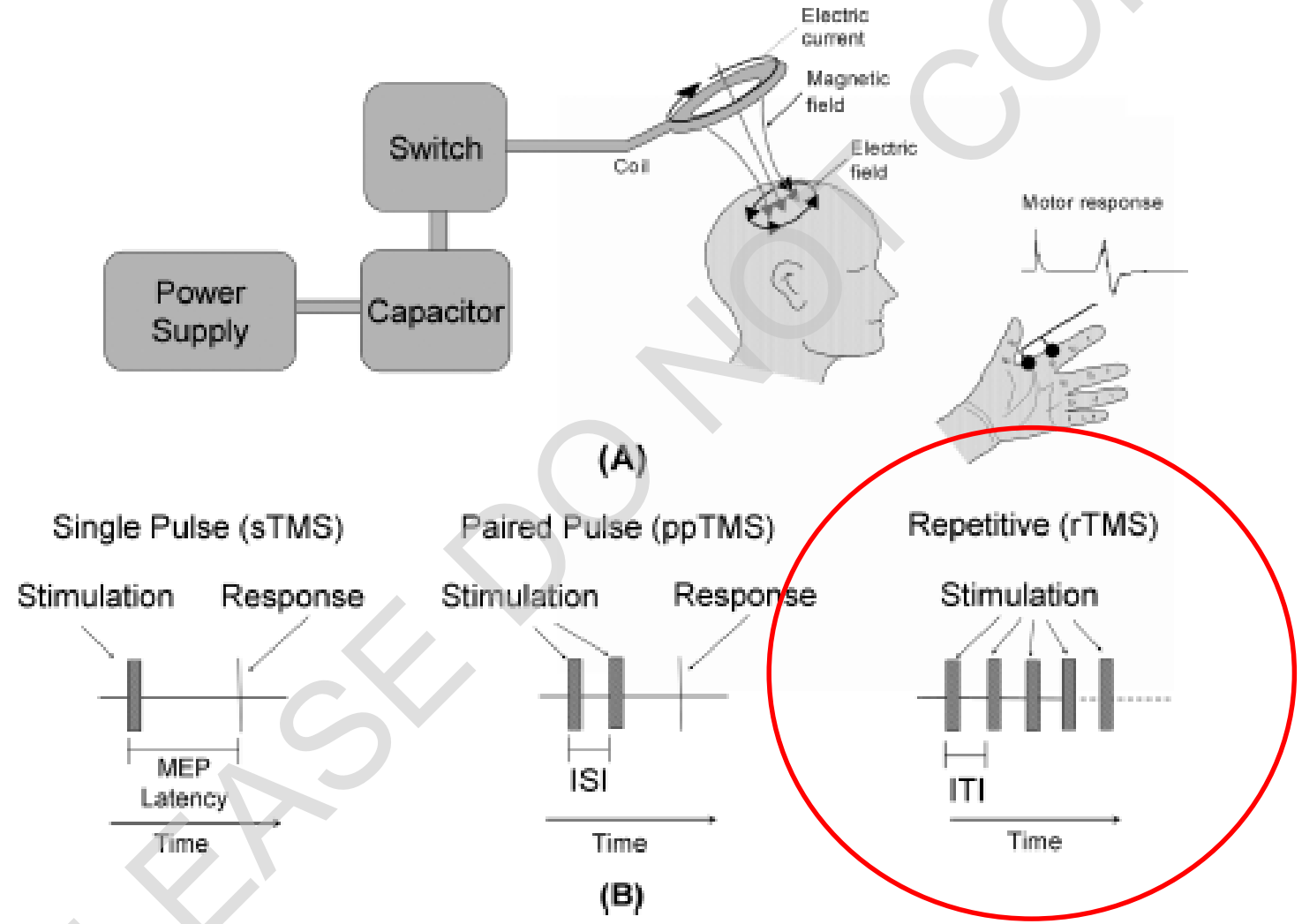
Hameed et al., SFN 2017
Hameed et al., Cerebral Cortex 2018





Hameed et al., Cerebral Cortex, 2018

Stimulation protocols



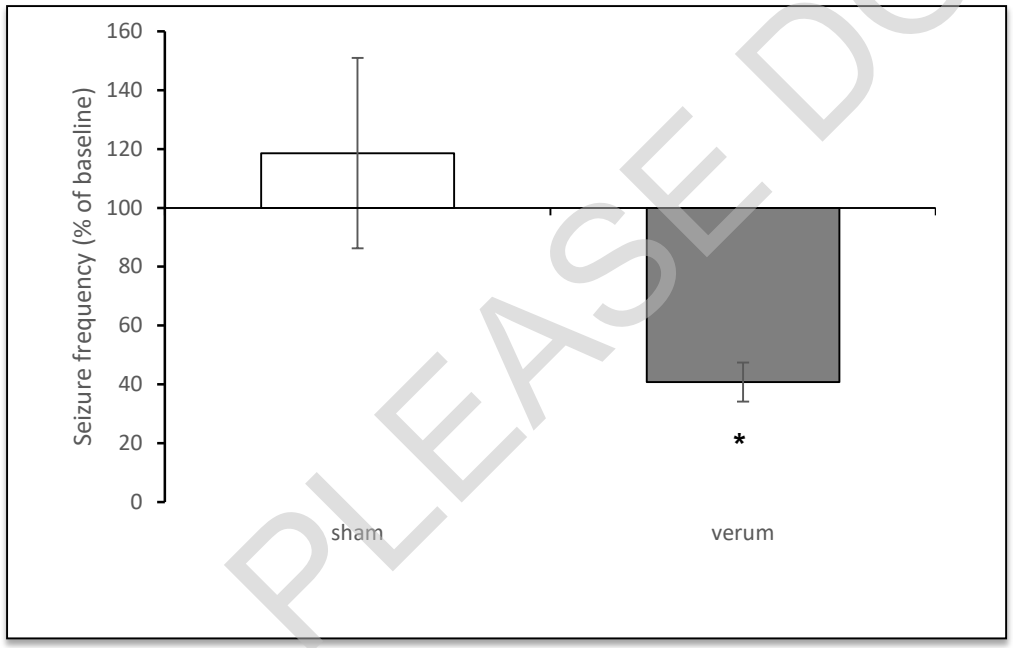
Frye, Rotenberg, et al. Child Neurol 2007

Why rTMS in rats?

1 Hz rTMS in temporal lobe epilepsy, trial in progress

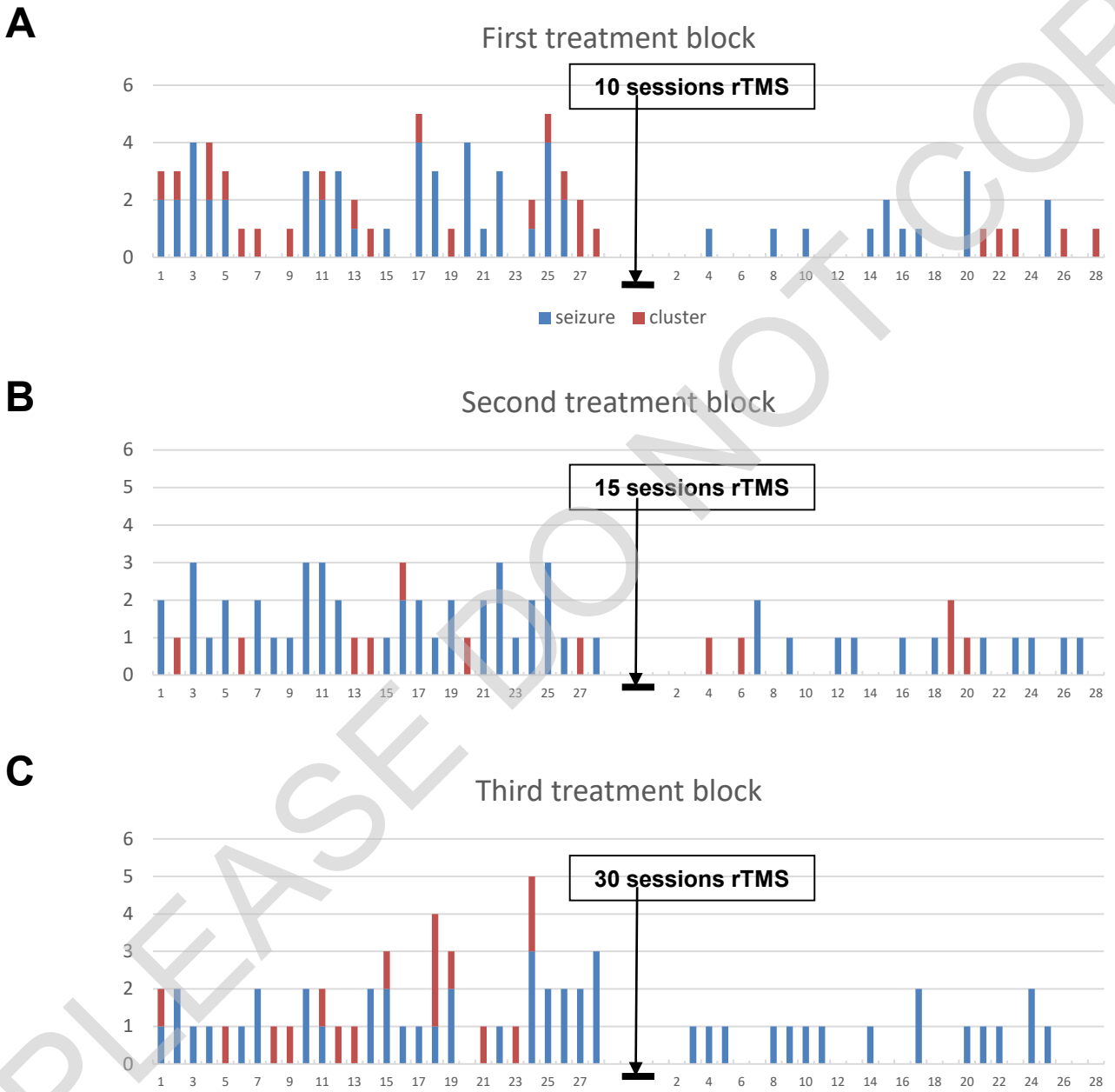
epilepsy therapy project

Boston Children's Hospital
Neuromodulation Program



TMS H-Coil System

Figure 1



Gersner et al., 2016

Clinical Neurophysiology 119 (2008) 2697–2702

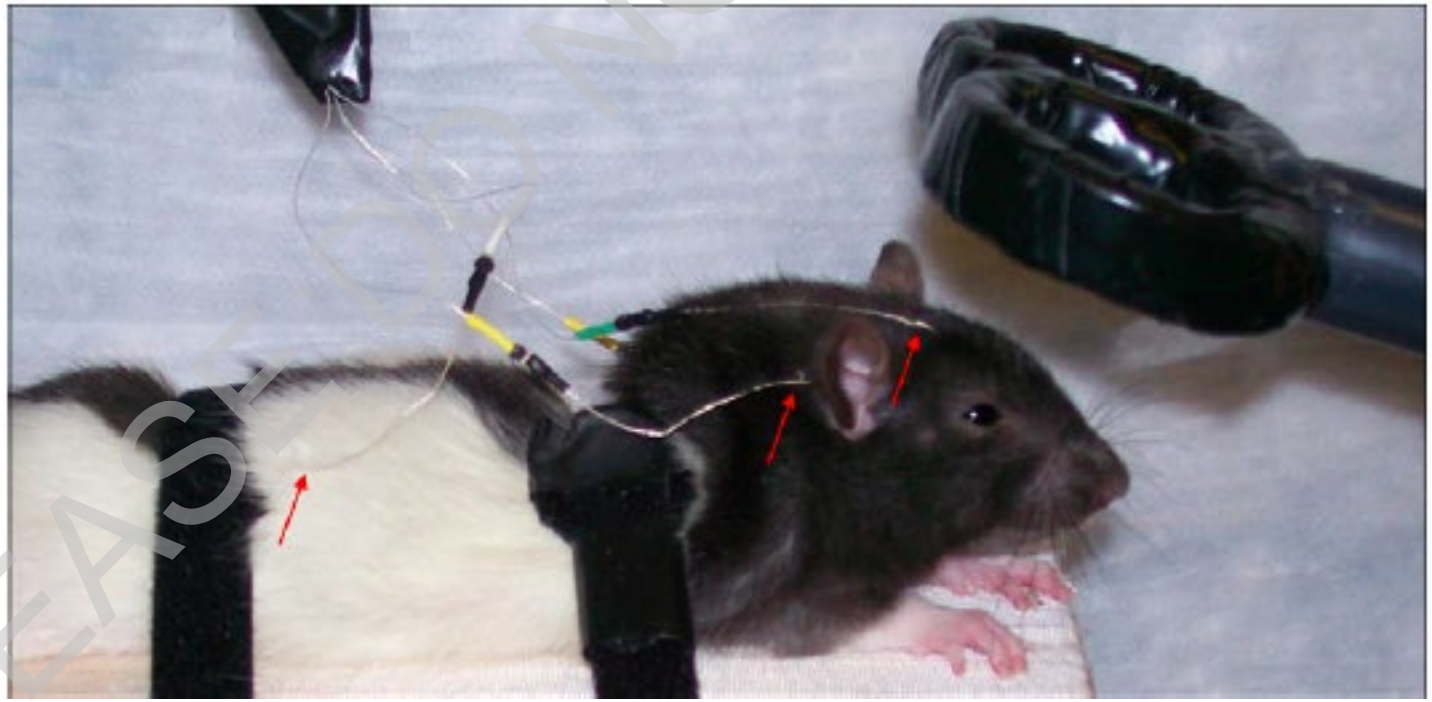
Contents lists available at ScienceDirect

Clinical Neurophysiology

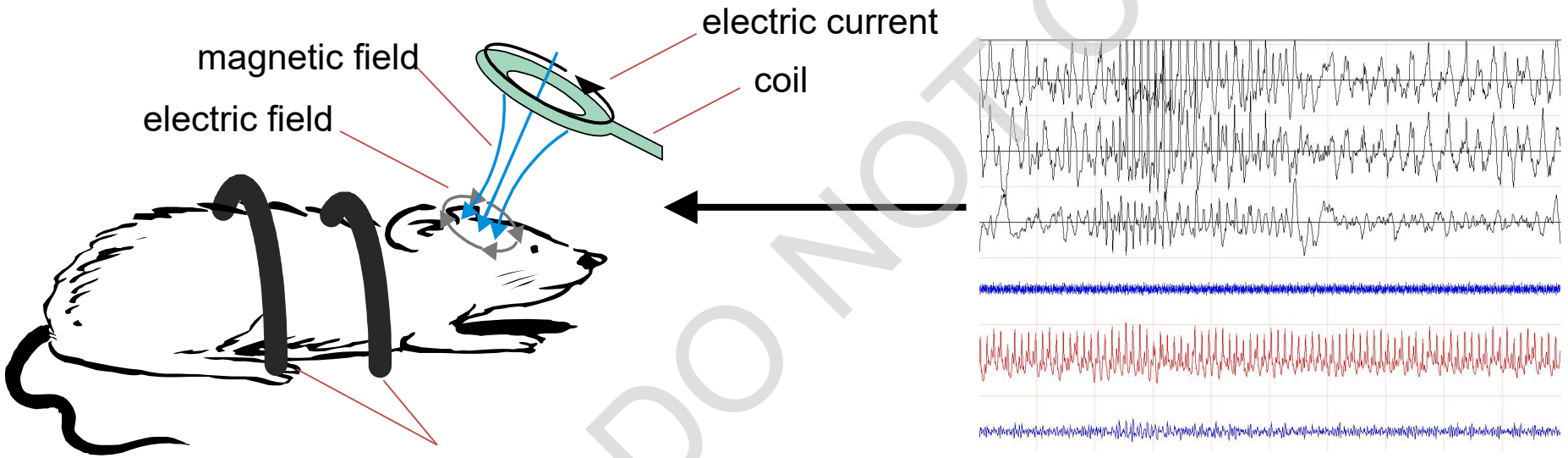
journal homepage: www.elsevier.com/locate/clinph

Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat

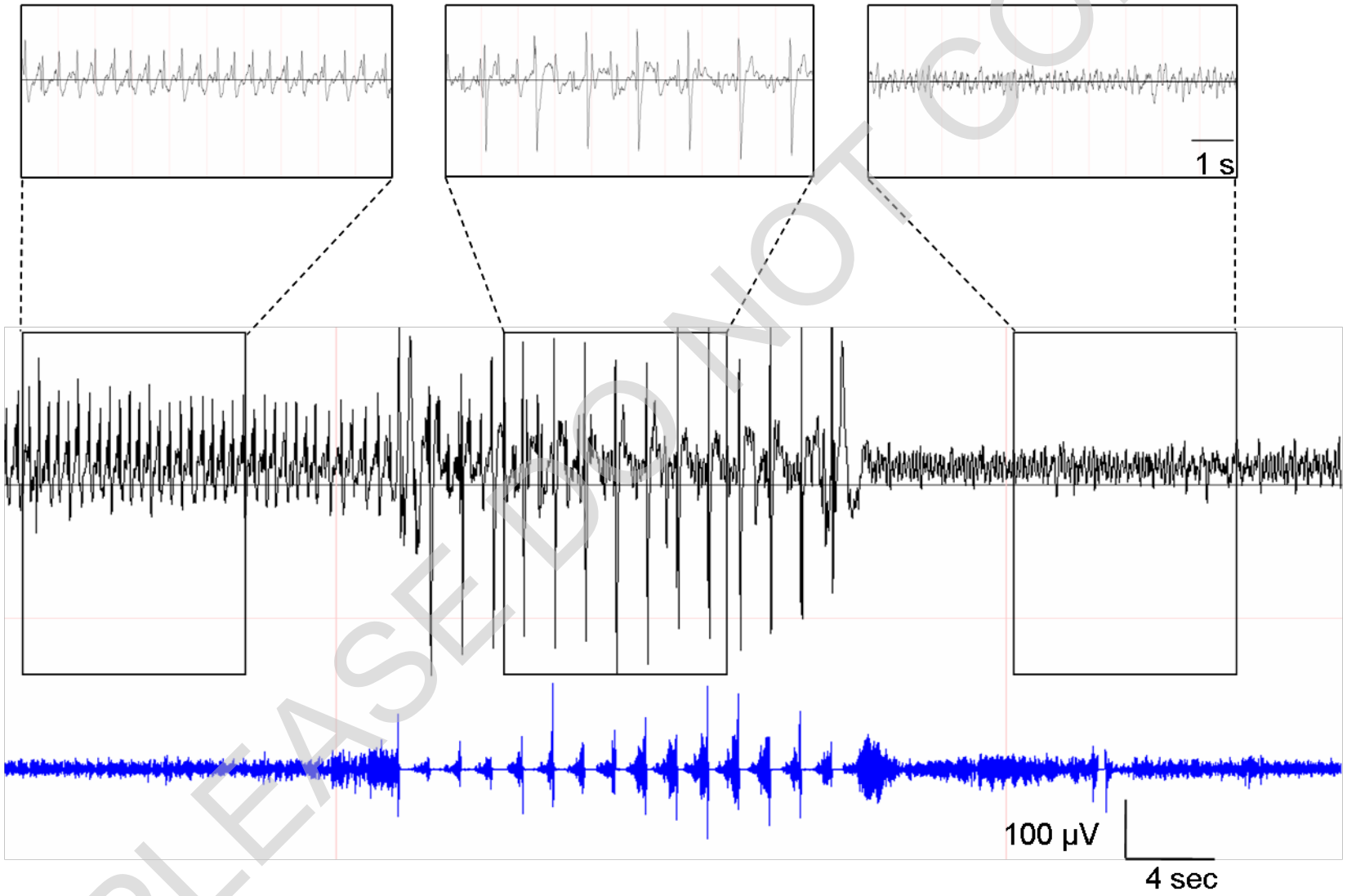
Alexander Rotenberg [a,b,*], Paul Muller [a], Daniel Birnbaum [a], Michael Harrington [a], James J. Riviello [c], Alvaro Pascual-Leone [b], Frances E. Jensen [a]



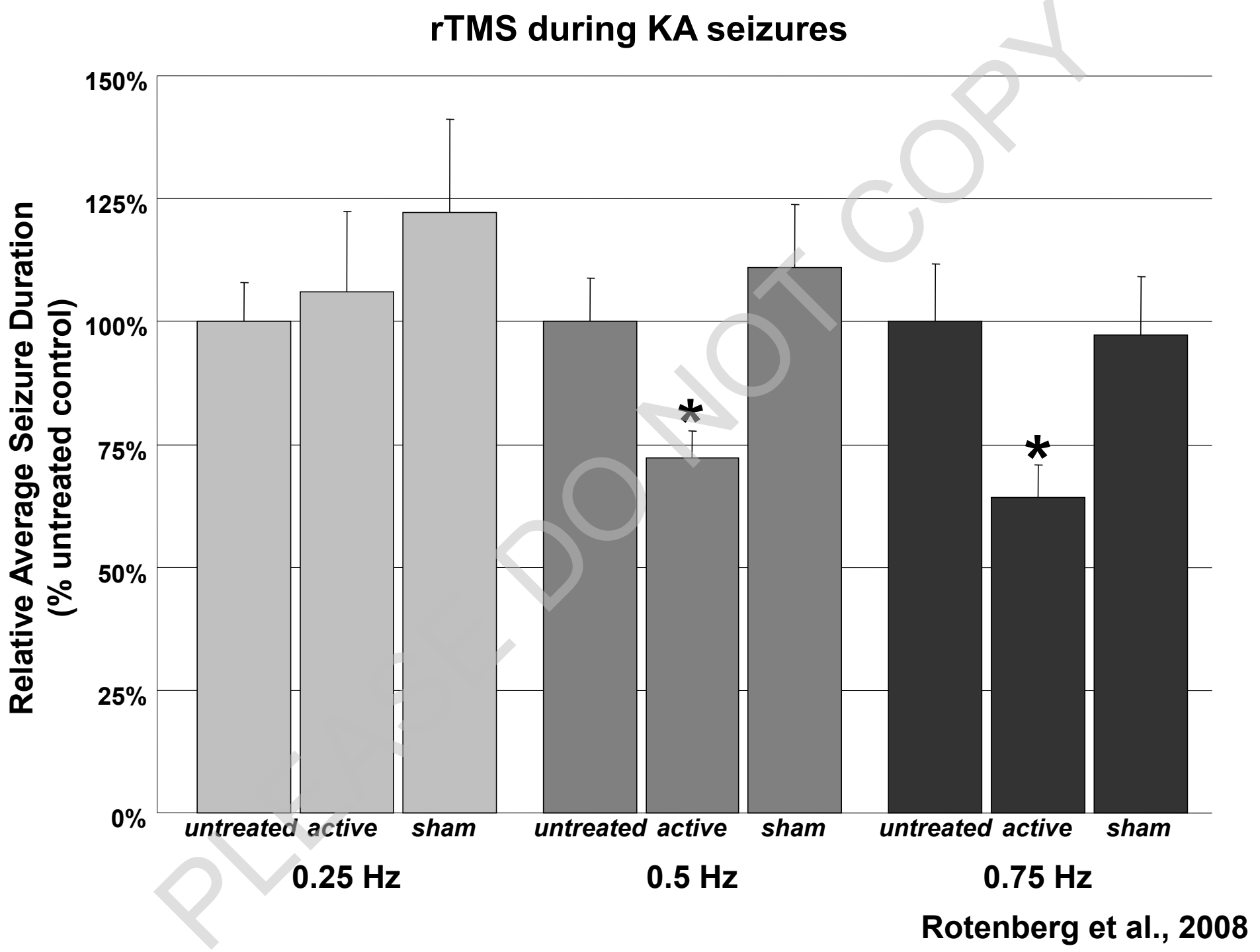
Rat “deep” TMS during seizure



rTMS during KA seizure

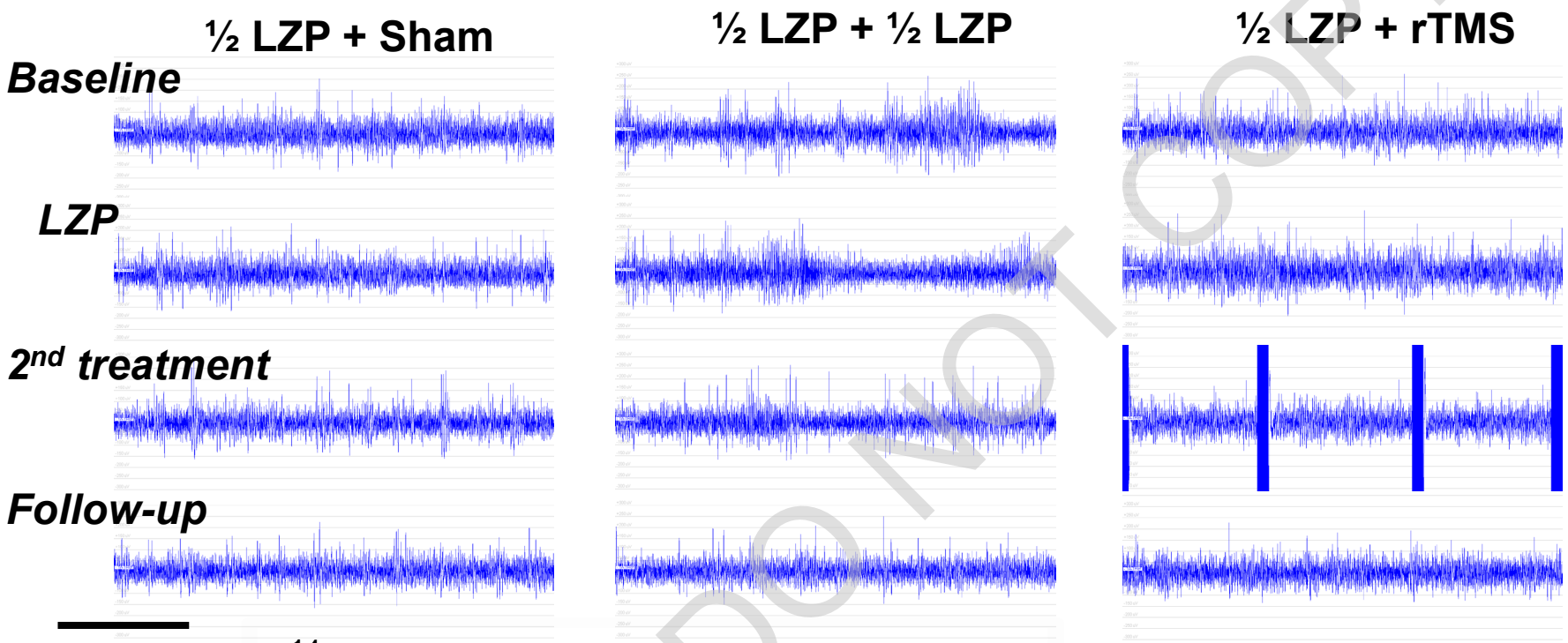


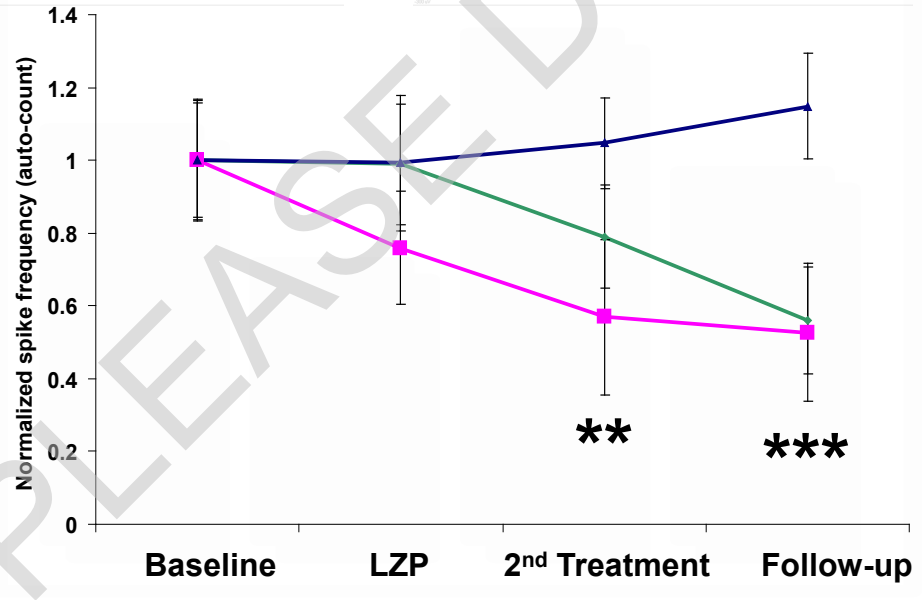
Rotenberg et al., Clin Neurophys 2008



Rotenberg et al., 2008

Combination therapy: lorazepam + rTMS in seizure suppression

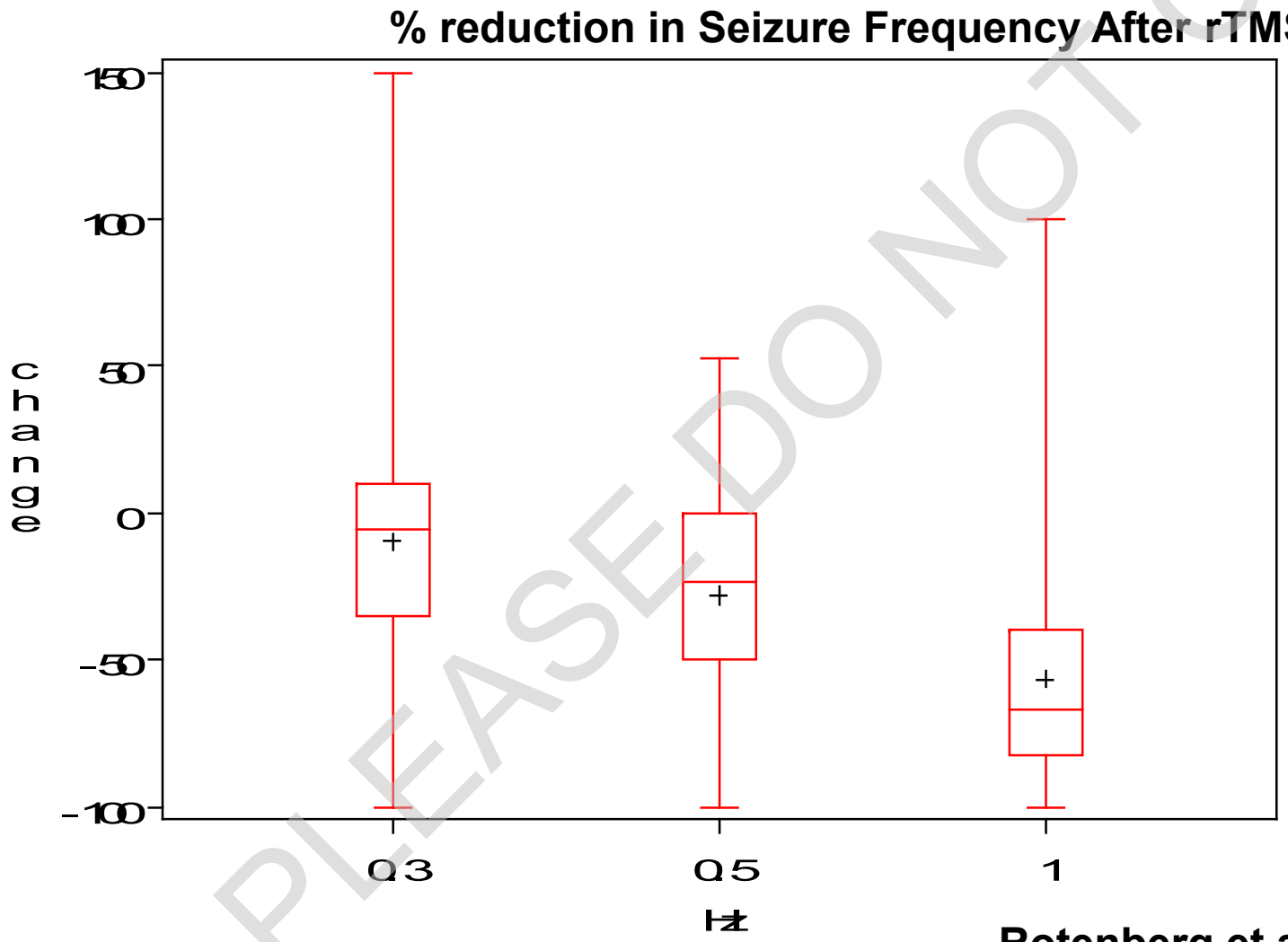




½ LZP + sham TMS
½ LZP + ½ LZP
½ LZP + rTMS

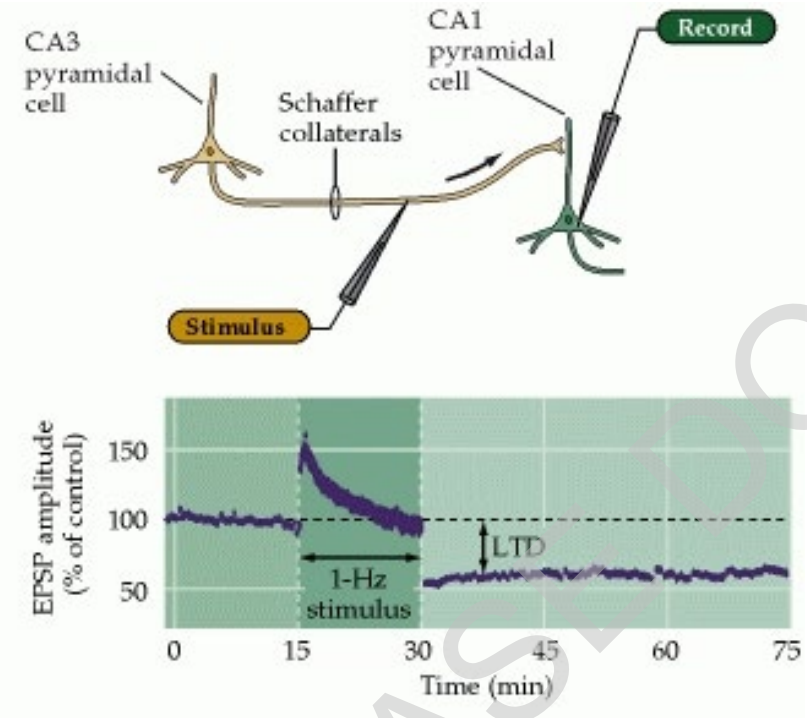
Gersner et al., 2016.

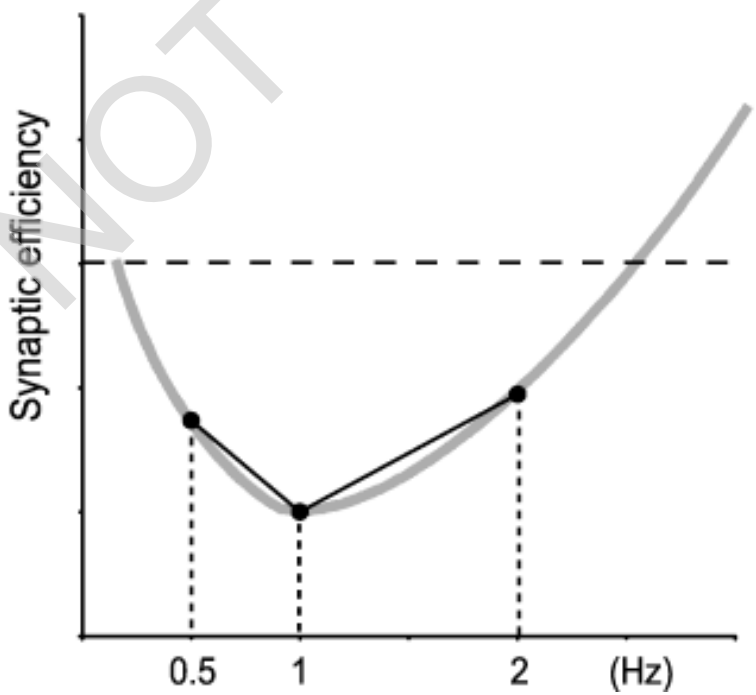
Better seizure suppression in humans with 1 Hz



Rotenberg et al., unpublished data

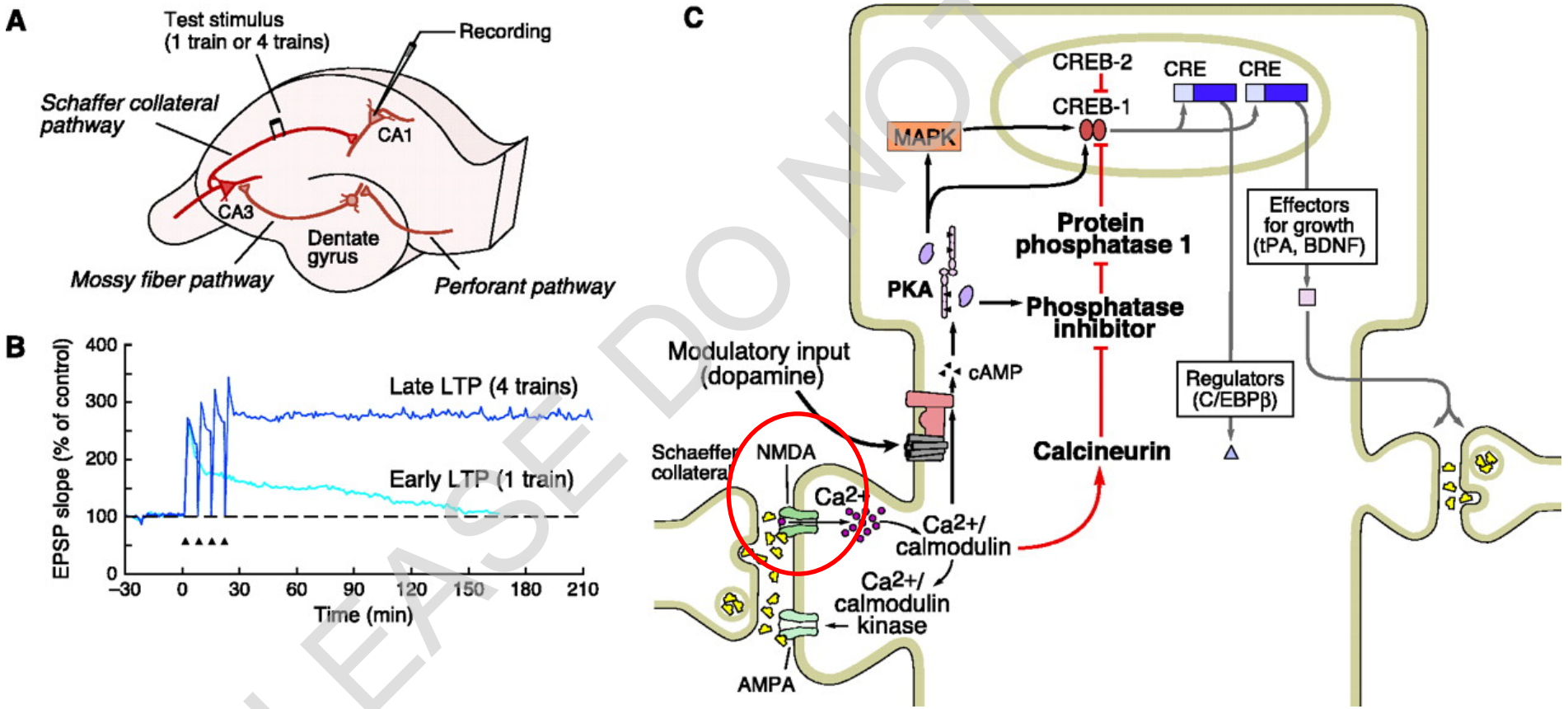
Frequency-response *in vitro* LTD approximates rTMS data





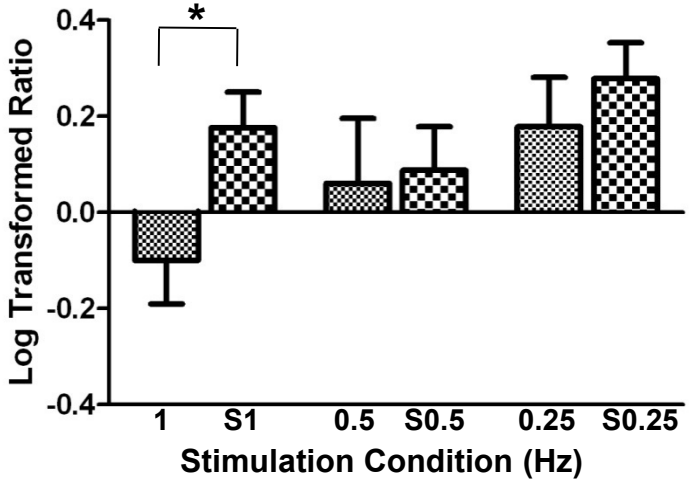
Nakano et al., 2004

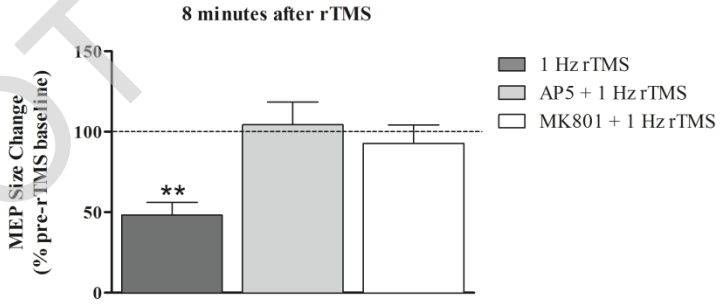
Molecular Basis: Does rTMS induce LTP/LTD?

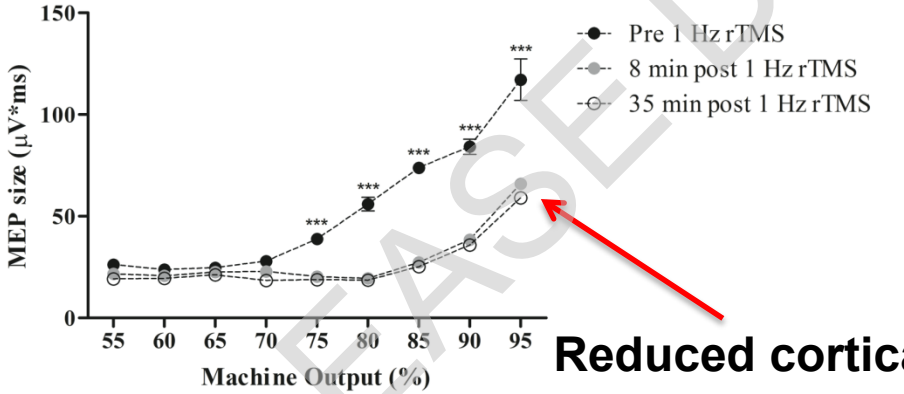


Kandel, 2001

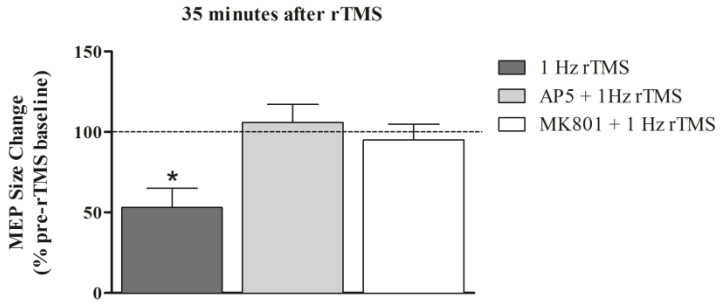
Can 1 Hz TMS suppresses motor excitability rats anesthetized with *pentobarbital*?







Reduced cortical excitability



Muller et al., PLOS One 2014

G Model
YSEIZ-2185; No. of Pages 4
ARTICLE IN PRESS

Seizure xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

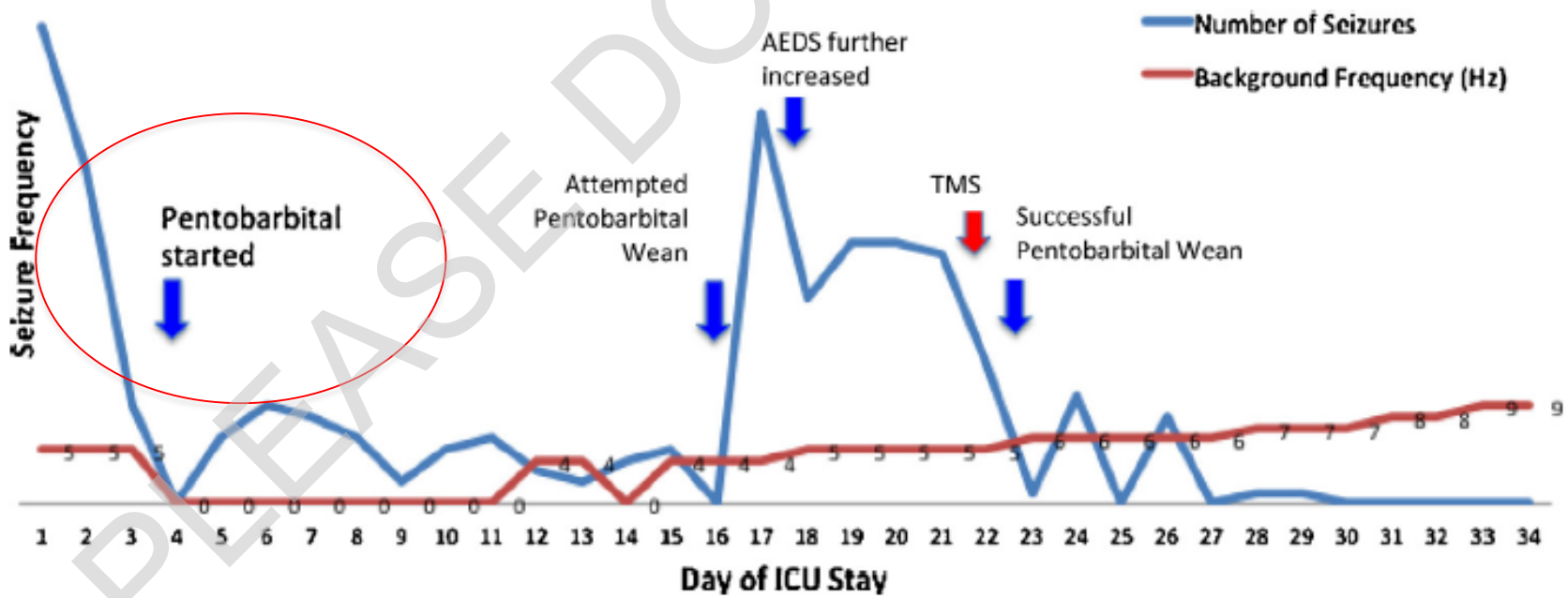
Seizure

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

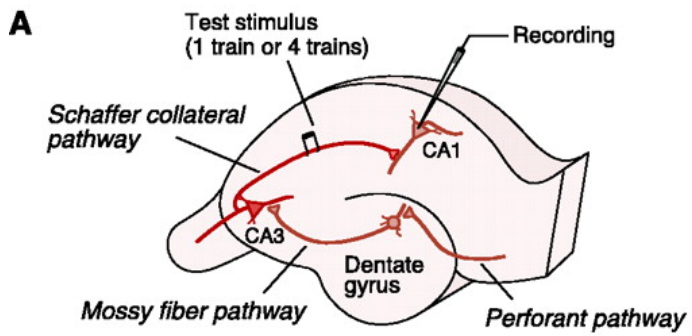
Short Communication

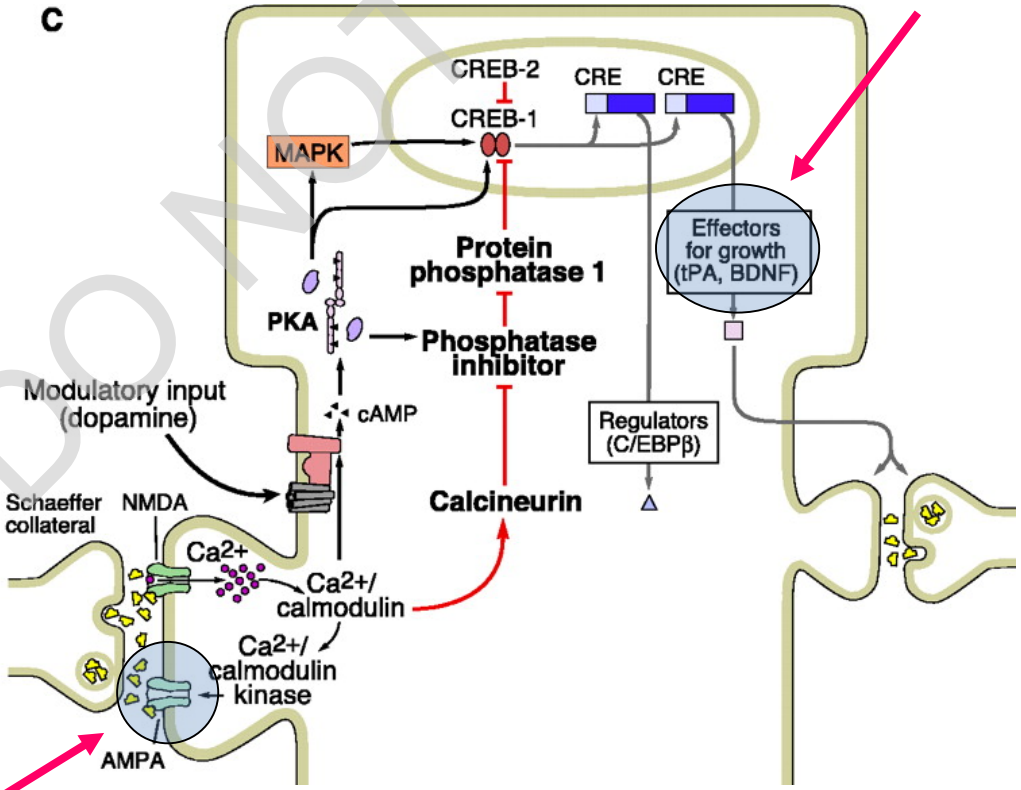
Transcranial magnetic stimulation for refractory focal status epilepticus in the intensive care unit

Anli Liu[a,b], Trudy Pang[c,e], Susan Herman[c,e], Alvaro Pascual-Leone[c,e], Alexander Rotenberg[d,e,*]



rTMS mechanisms

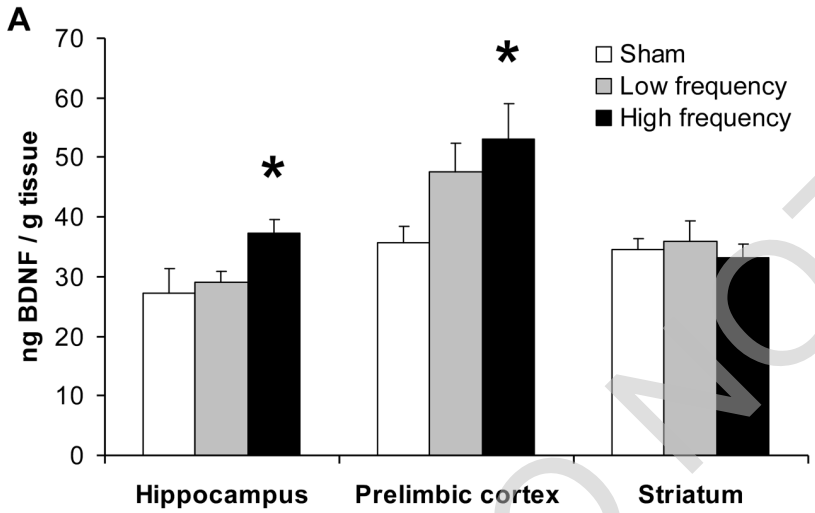




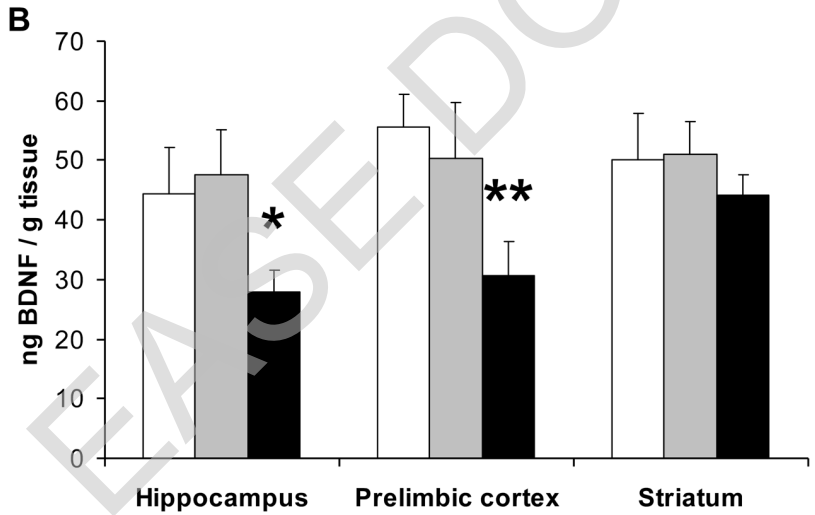
Kandel, 2001

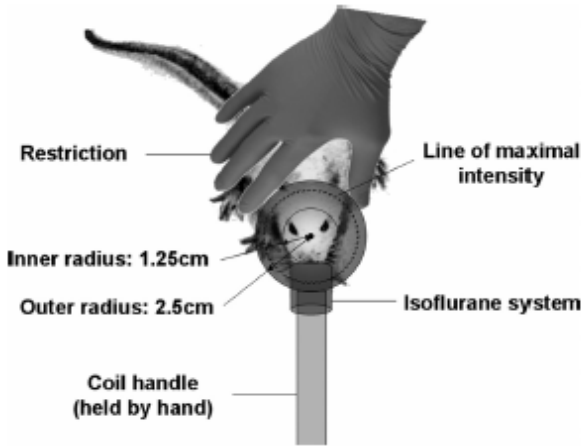
BDNF expression after rTMS

awake



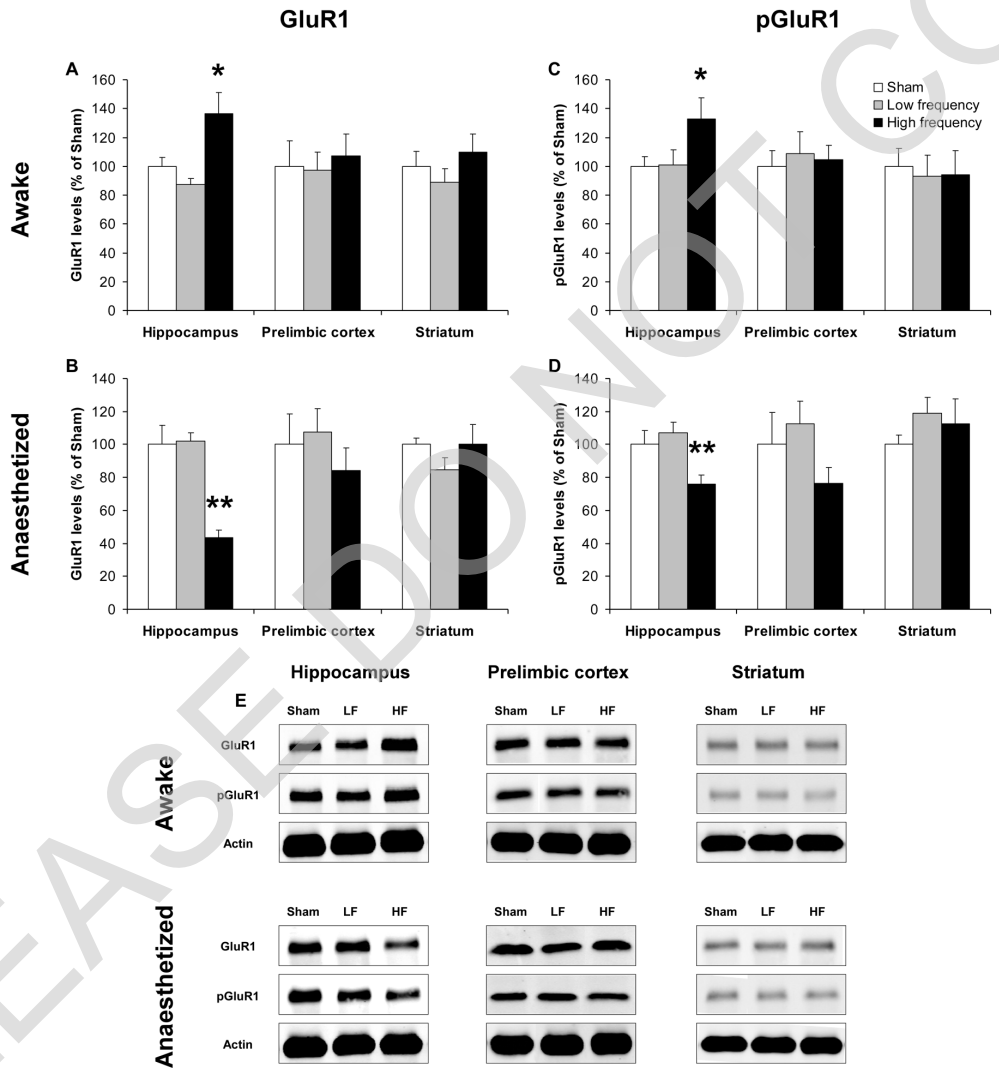
anesthetized





Gersner et al., J. Neursci 2011

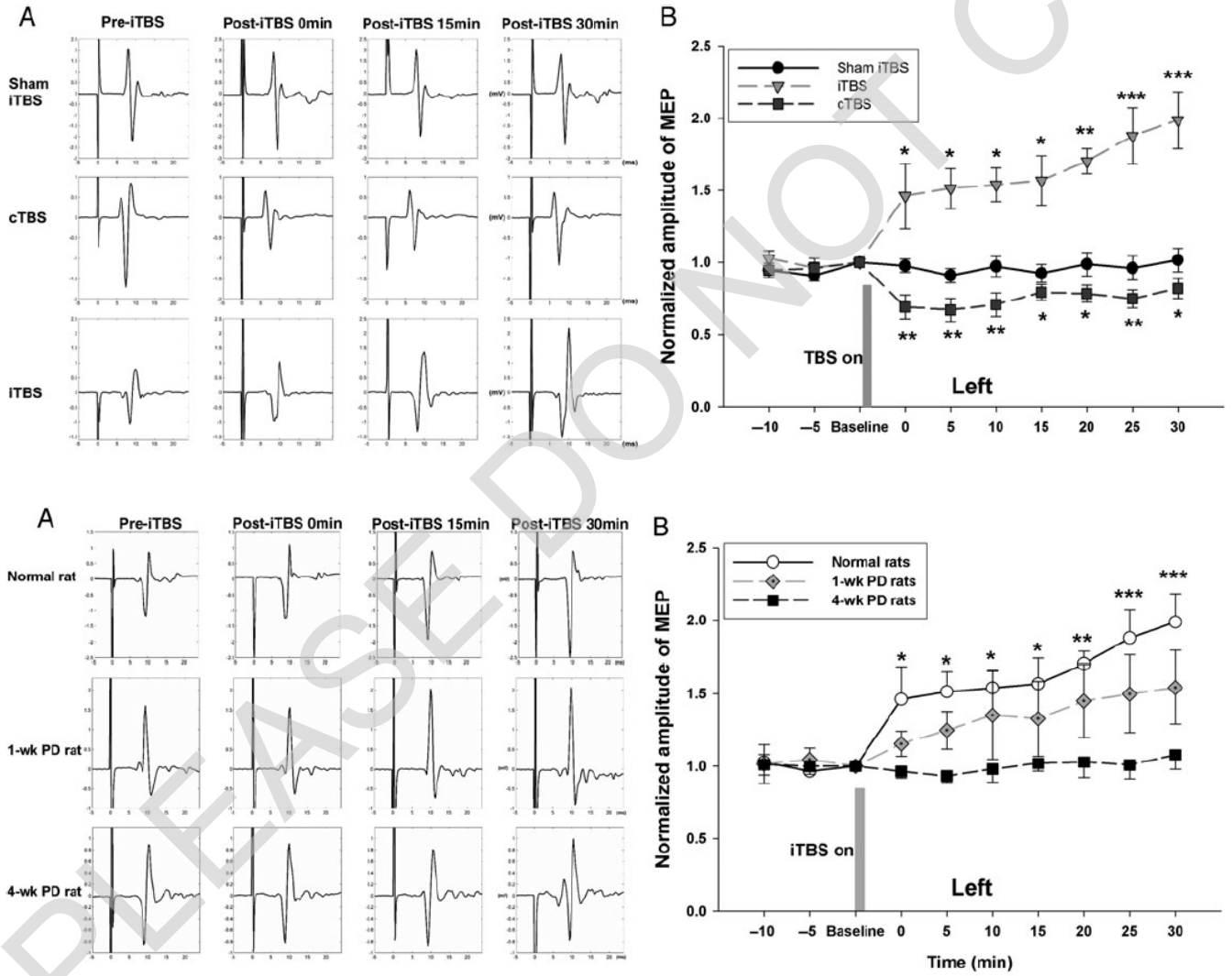
GluR1 expression and phosphorylation after rTMS



Gersner et al., J. Neursci 2011

Functional Dopaminergic Neurons in Substantia Nigra are Required for Transcranial Magnetic Stimulation-Induced Motor Plasticity

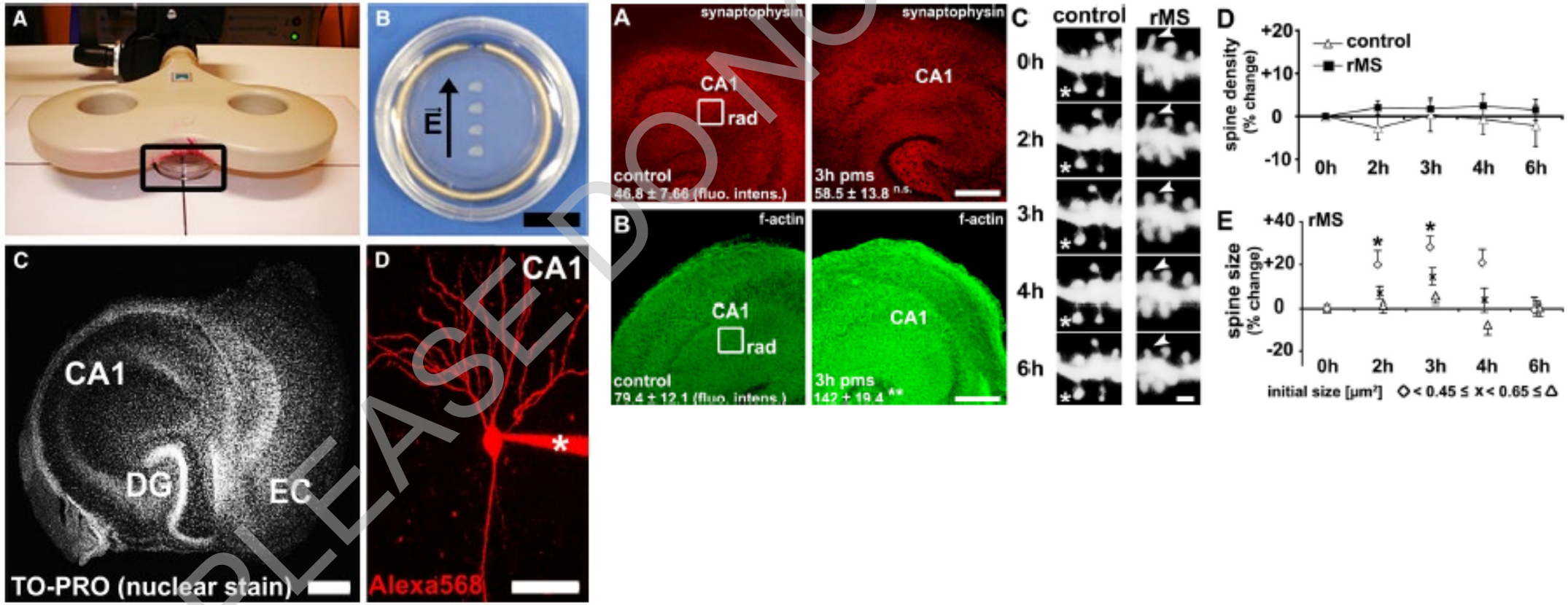
Tsung-Hsun Hsieh[1,2,4,†], Ying-Zu Huang[6,†], Alexander Rotenberg[7], Alvaro Pascual-Leone[8], Yung-Hsiao Chiang[1,2,9], Jia-Yi Wang[3] and Jia-Jin J. Chen[4,5]



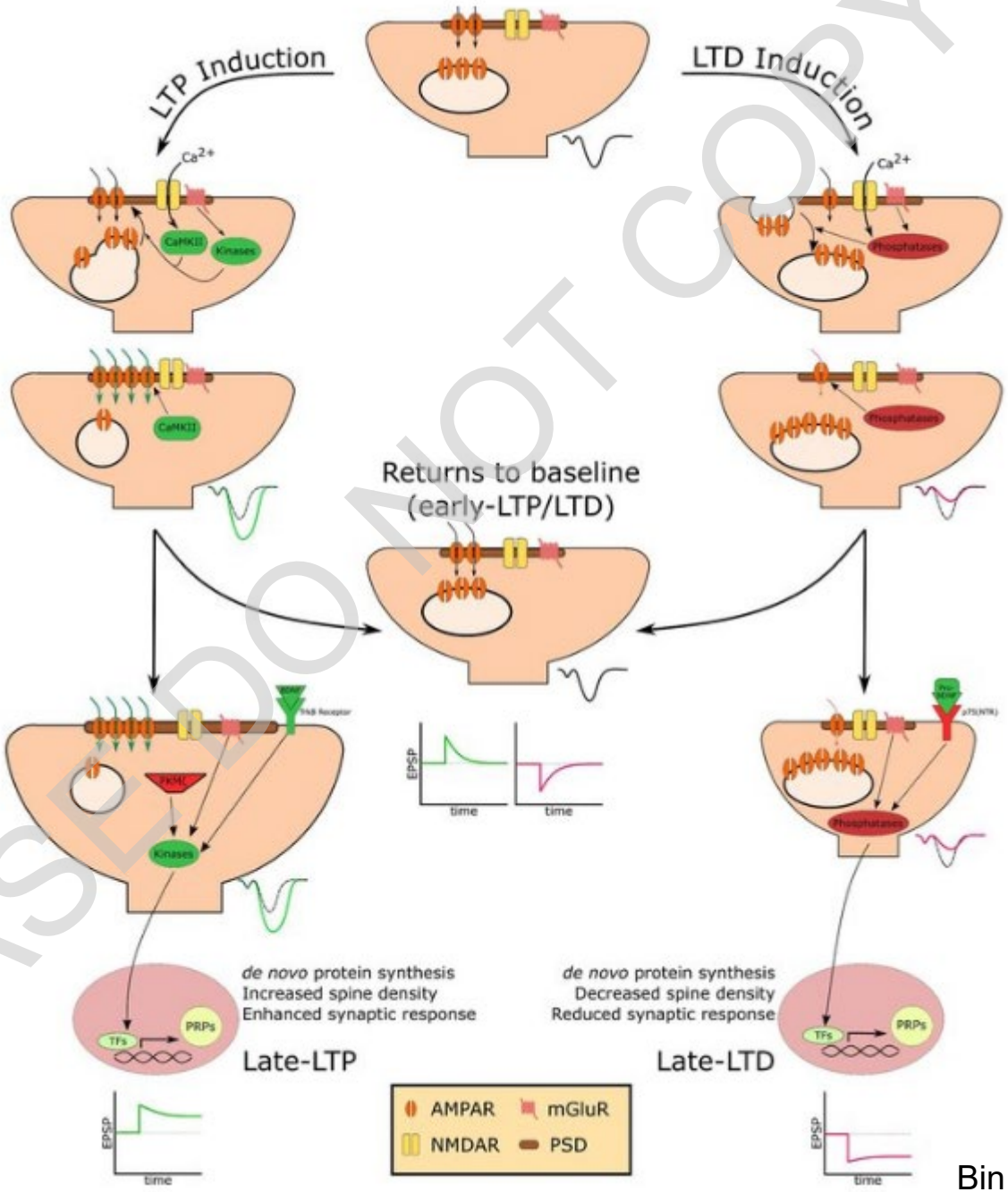
Development/Plasticity/Repair

Repetitive Magnetic Stimulation Induces Functional and Structural Plasticity of Excitatory Postsynapses in Mouse Organotypic Hippocampal Slice Cultures

Andreas Vlachos,[1]* Florian Müller-Dahlhaus,[1,2]* Johannes Rosskopp,[1,2] Maximilian Lenz,[1] Ulf Ziemann,[2,3]† and Thomas Deller[1]†



In vitro studies may provide insight into how rTMS modifies synapses

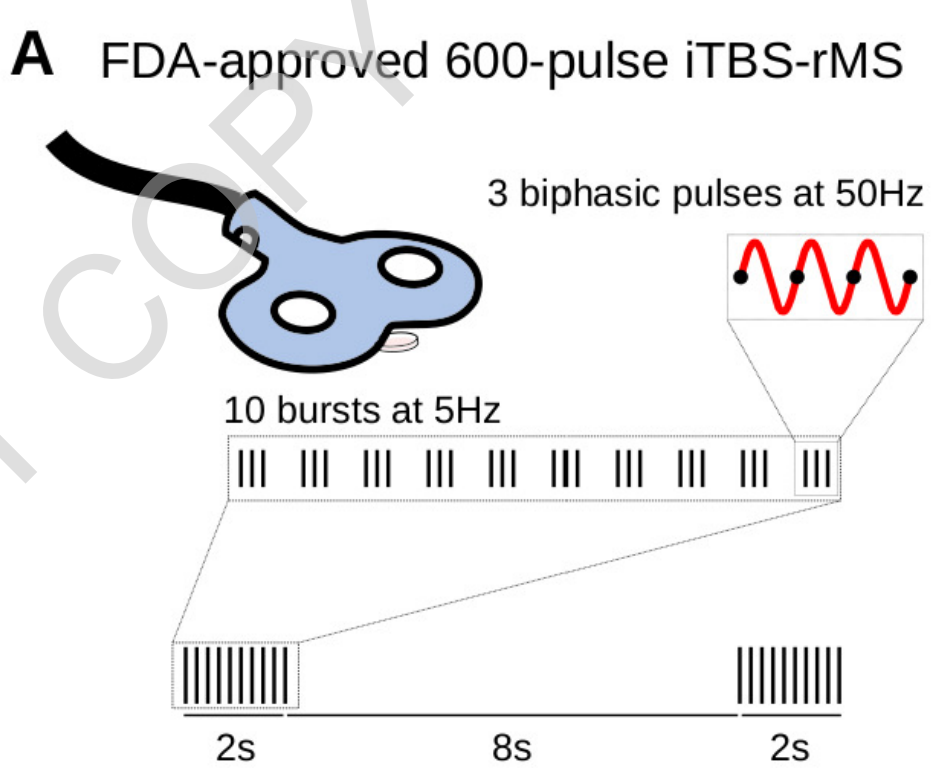


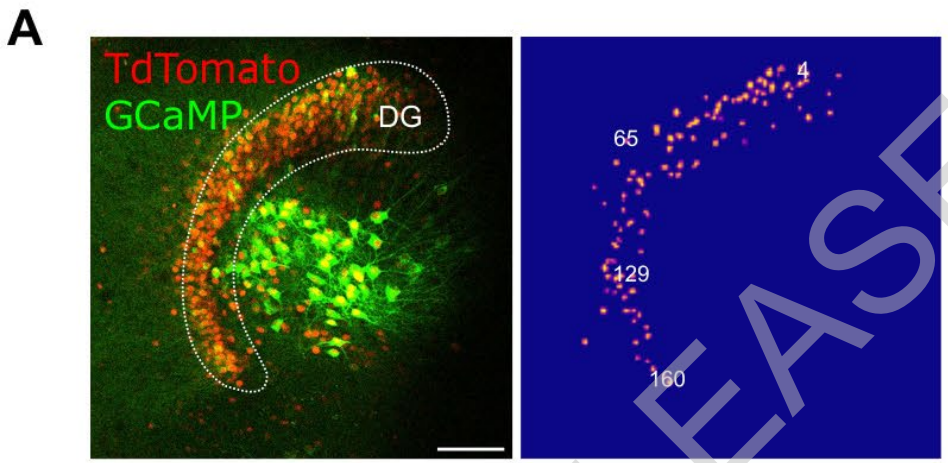
Bin Ibrahim et al., FEBS J., 2021

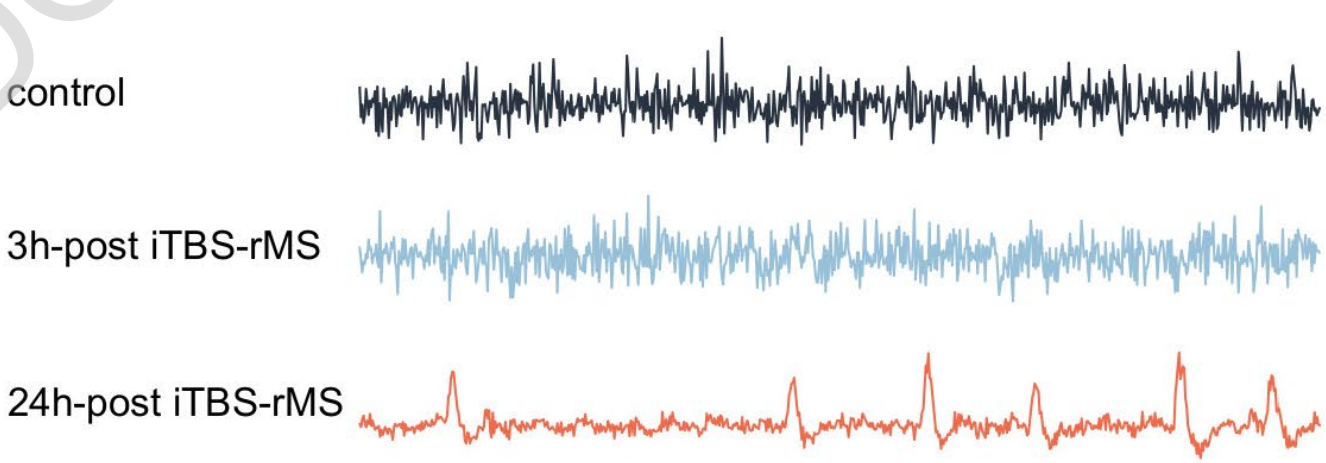
Repetitive magnetic stimulation with iTBS600 induces persistent structural and functional plasticity in mouse organotypic slice cultures

Abbreviated title: iTBS600 induces structural and functional plasticity

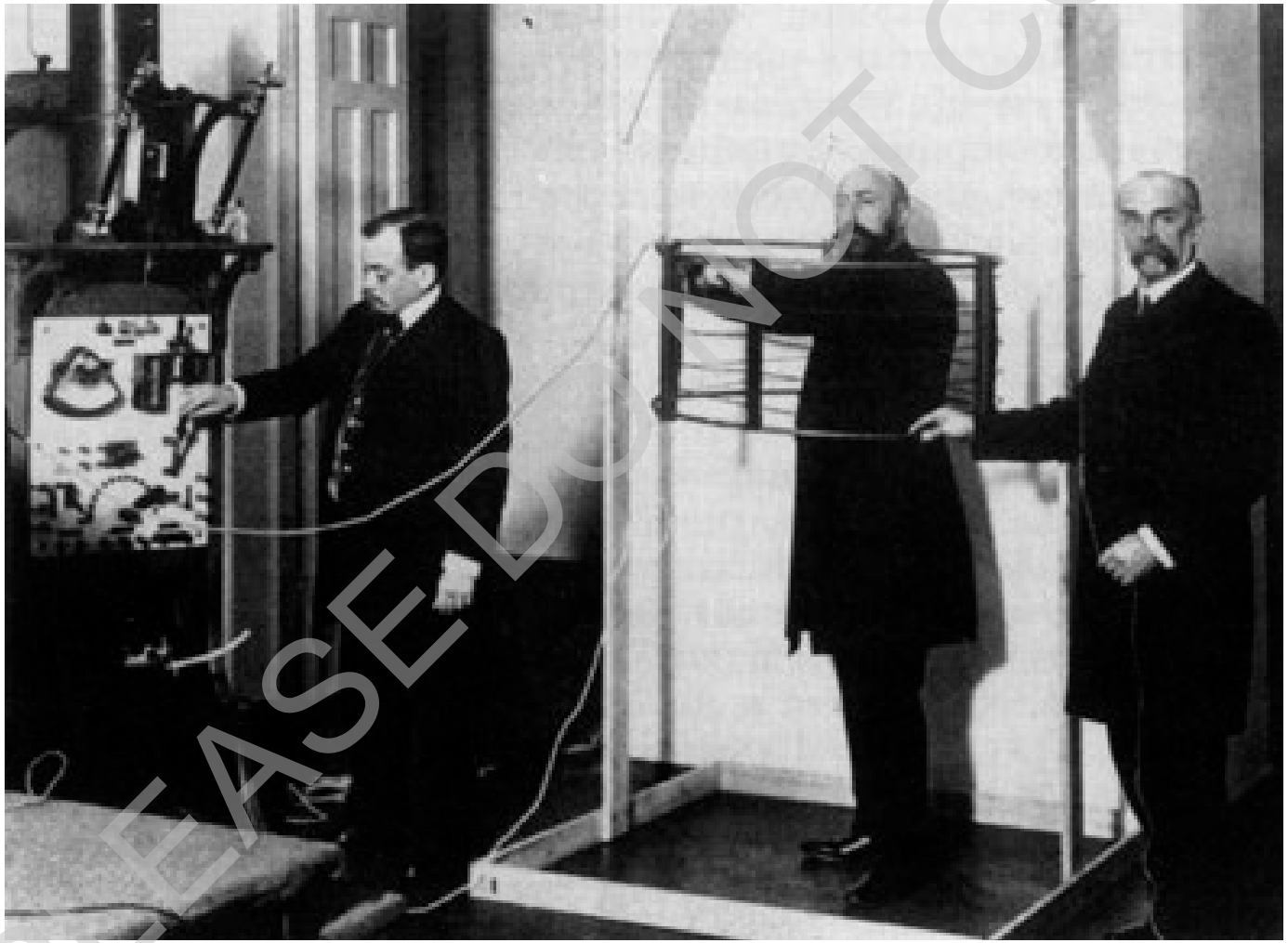
Han Lu[1,2,3,*], Shreyash Garg[1,4], Maximilian Lenz[1,5], Andreas Vlachos[1,2,6,*]







Who’s doing the heavy lifting?



Thanks!!!