Smaller subjects: neuromodulation in children and in animal models

IOM Panel Discussion

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Special considerations in pediatric neuromodulation

- Vulnerabilty and ethical considerations
- Head and brain growth
- Capacity to cooperate
- Developmental regulation of neuronal excitability

Risks and potential mechanisms for injury to the developing brain

- Enhanced excitabilty and vulnerability to seizure in early life
  - Risk for excitotoxicity
- Enhanced synaptic plasticity
  - Risk for interference with learning and memory
- Ongoing neurogenesis, synaptogenesis, myelination, etc.
  - Risk of use-dependent structural change

frontiers in
HUMAN NEUROSCIENCE

ORIGINAL RESEARCH ARTICLE
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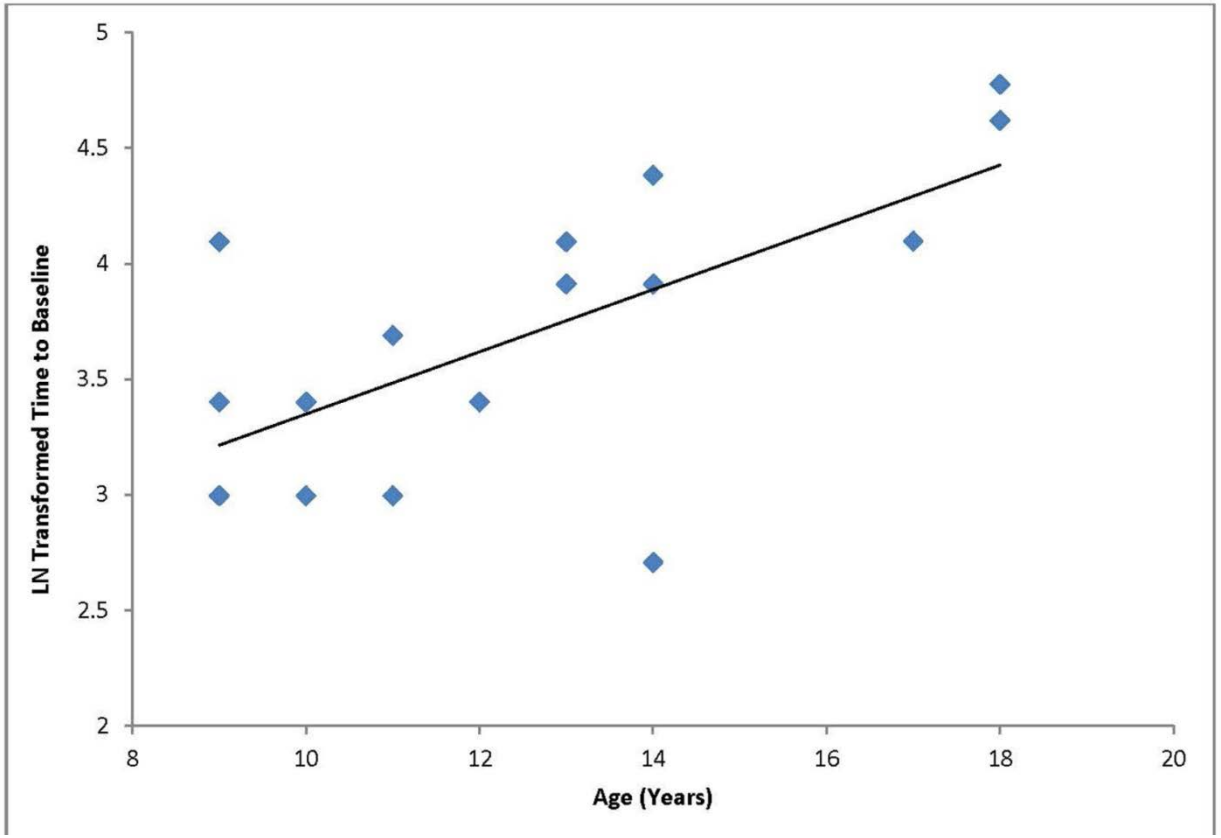
Modulation of corticospinal excitability by transcranial magnetic stimulation in children and adolescents with autism spectrum disorder

Lindsay M. Oberman[1,2,3,4], Alvaro Pascual-Leone[1] and Alexander Rotenberg[1,2]**

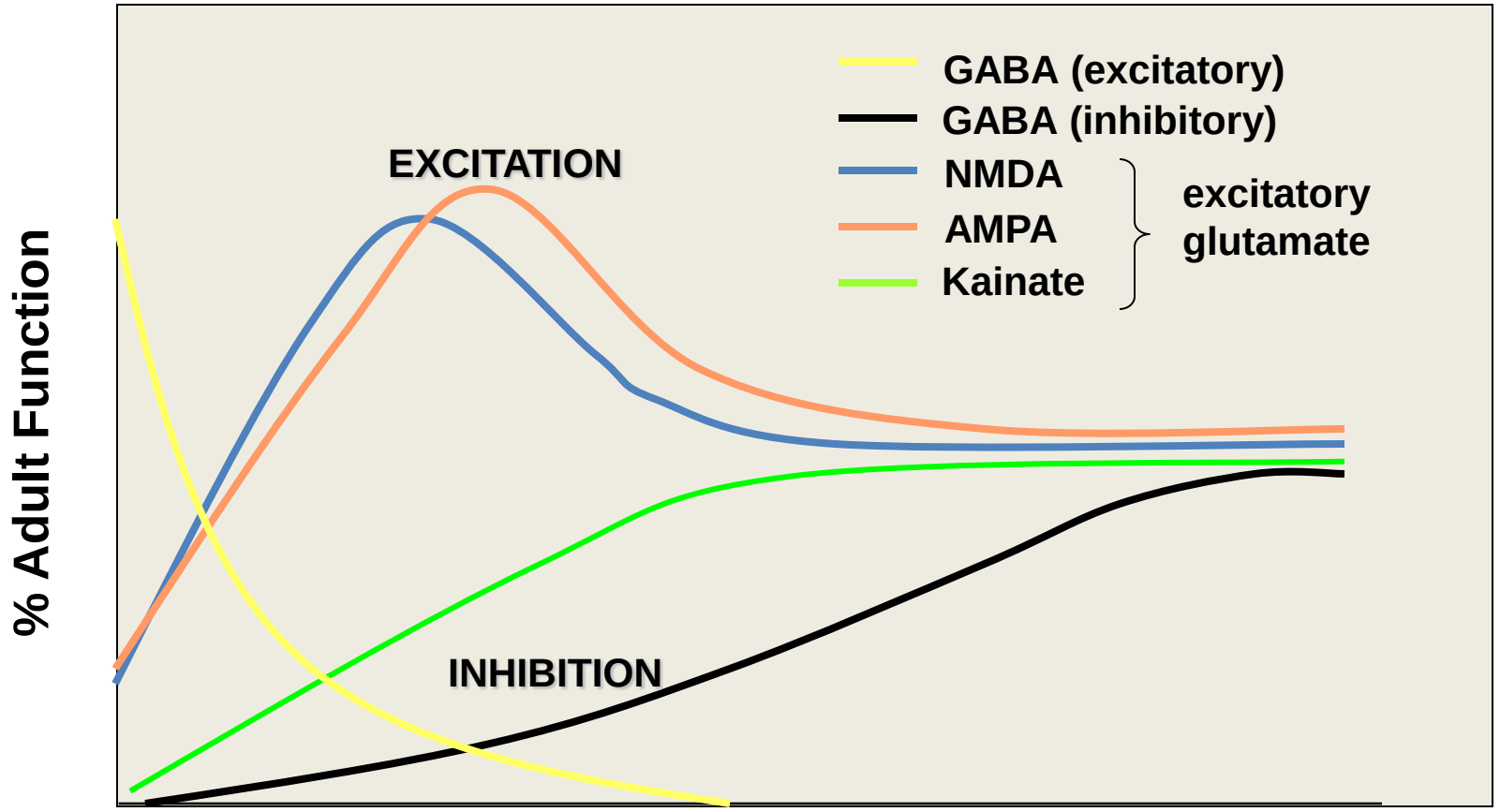
Maturation of motor plasticity



Developing brain is a moving target

- Vulnerability (or resistance) to injury likely varies with age
- Studies restricted to narrow age windows are lacking
  - Subdivision of the pediatric age group are necessary

Neuronal Receptor Expression vs Age

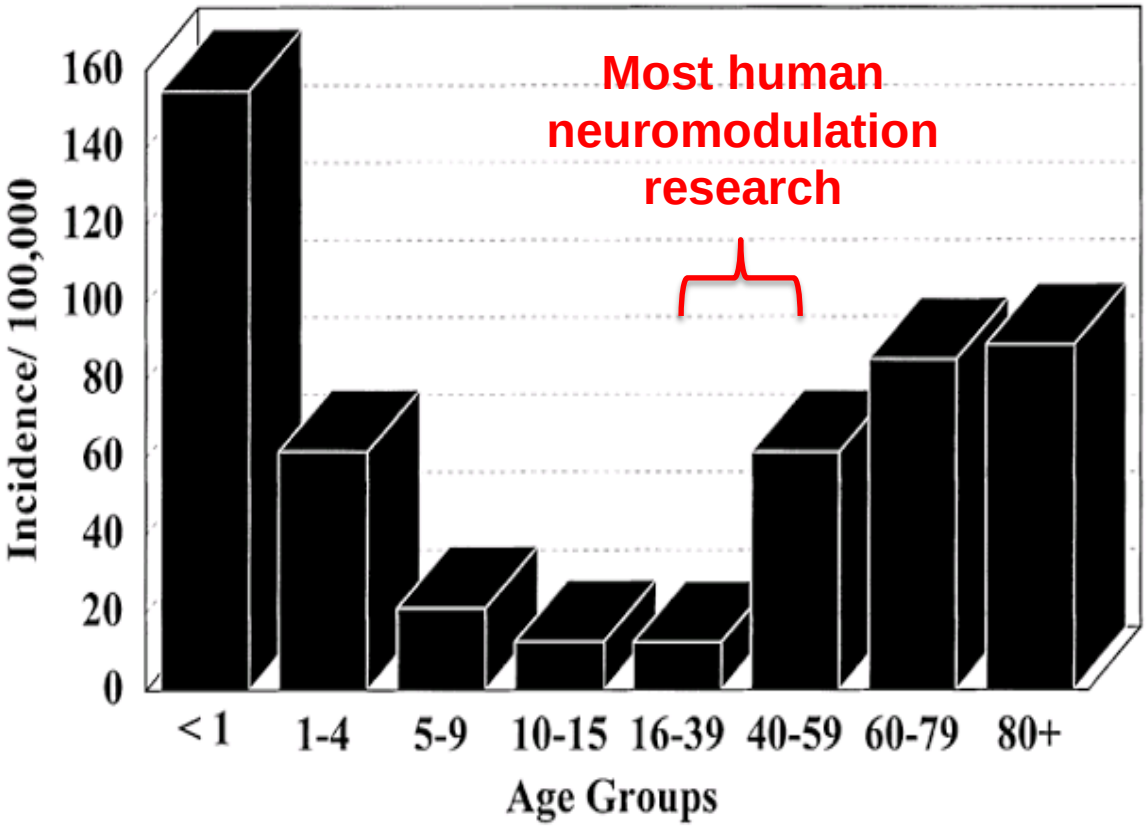


Rodent	P0	P5	P10	P15	P20	P25	P30	Adult
Human	preterm		term	1-2y	>10y			Adult

Silverstein and Jensen, *Ann Neurol*, 2007
Rakhade and Jensen, *Nature Rev.*, 2010

Physiology is reflected in disease …and perhaps in neurostimulation risks

Status Epilepticus by Age



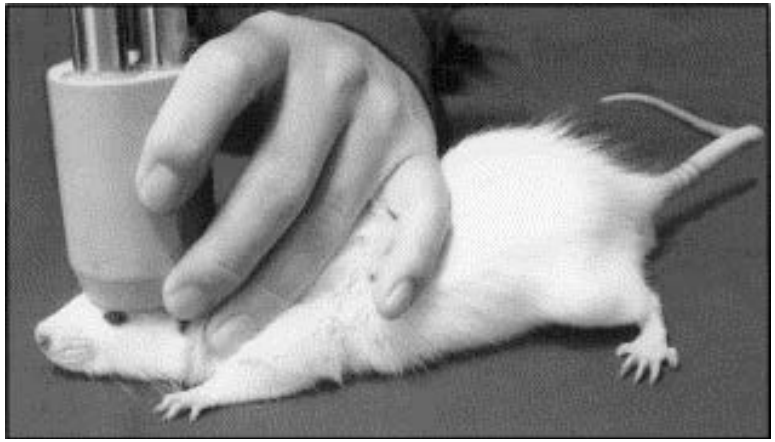
DeLorenzo et al., 1992

Clinical research limitations

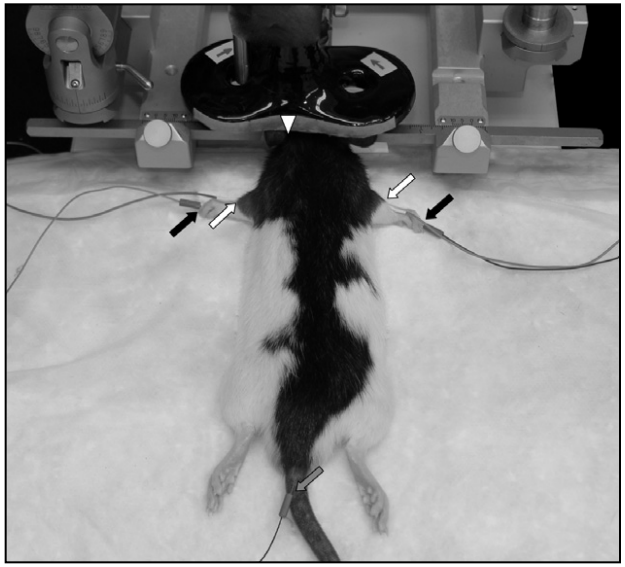
- Patient volume is limited
- Patient populations often inhomogeneous
- Interactions with drugs and other treatments uncertain
- Access to tissue is rare

Ongoing trial: 1 Hz rTMS for temproal lobe epilepsy (BCH)

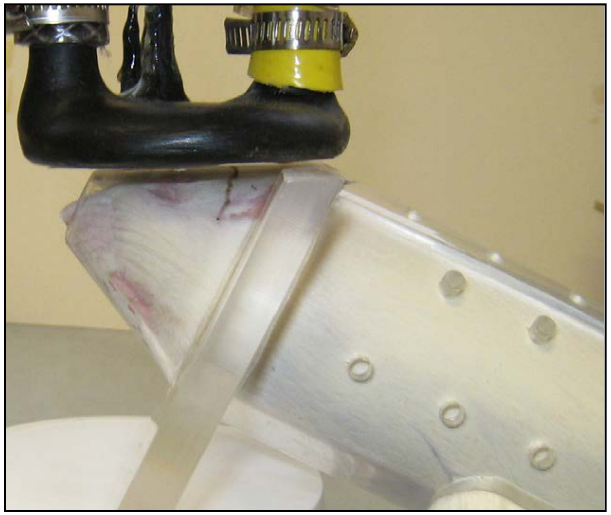
We can complement clinical research with with preclincal studies



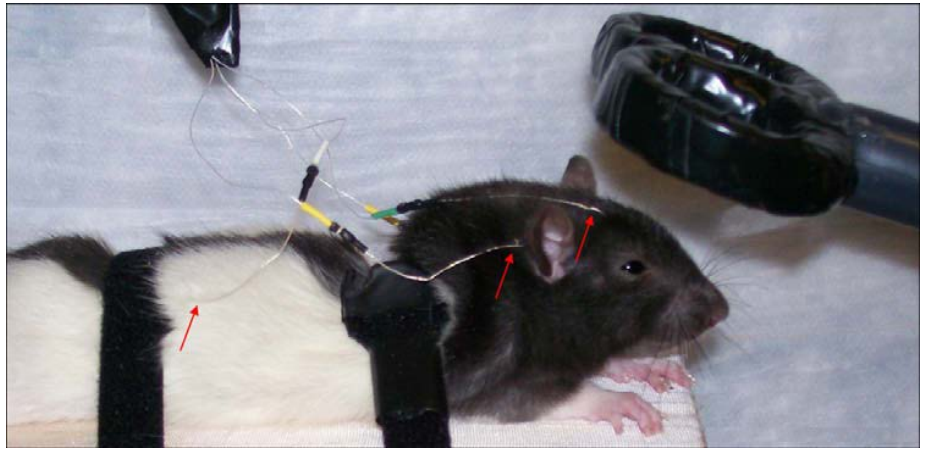
Liebetanz et al., J Psychiatr Res 2003



Rotenberg et al., Clin Neurophys 2009



Charlet de Sauvage et al. Clin Neurophys 2007



Rotenberg et al., Clin Neurophys 2008

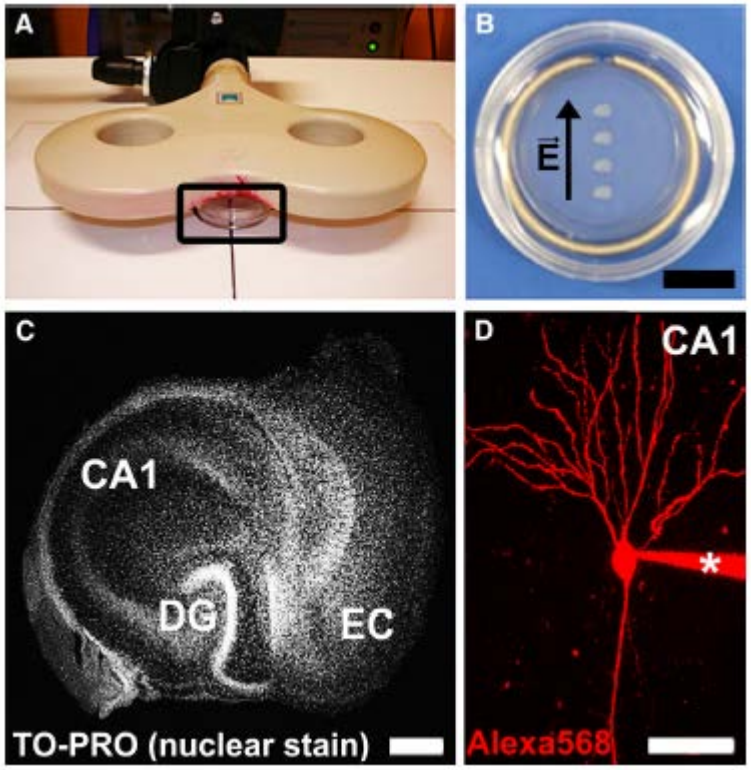
Mechanisms are more accessible in preclincal models

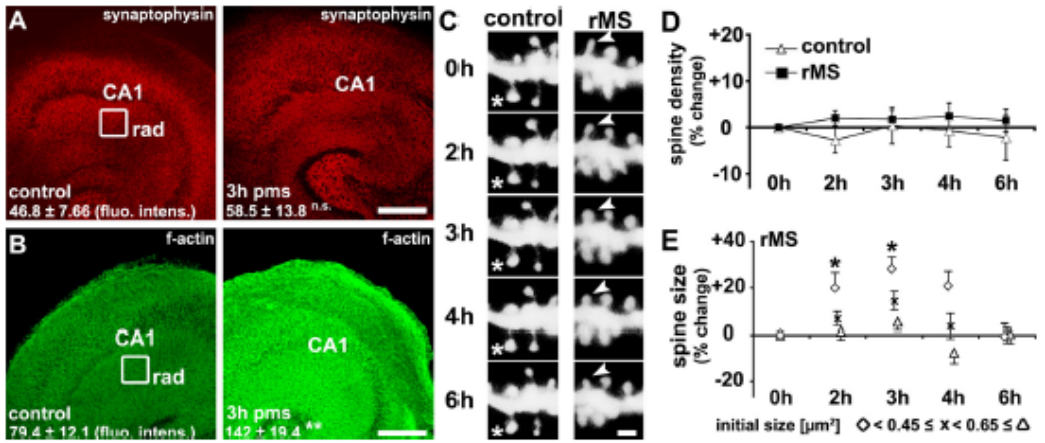
17514 • The Journal of Neuroscience, November 28, 2012 • 32(48):17514–17523

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]†





Preclinical tests of therapeutic protocols

Clinical Neurophysiology 119 (2008) 2697–2702

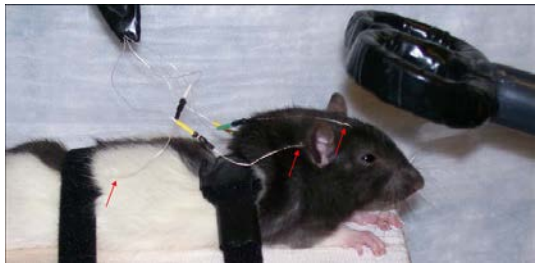
Contents lists available at ScienceDirect

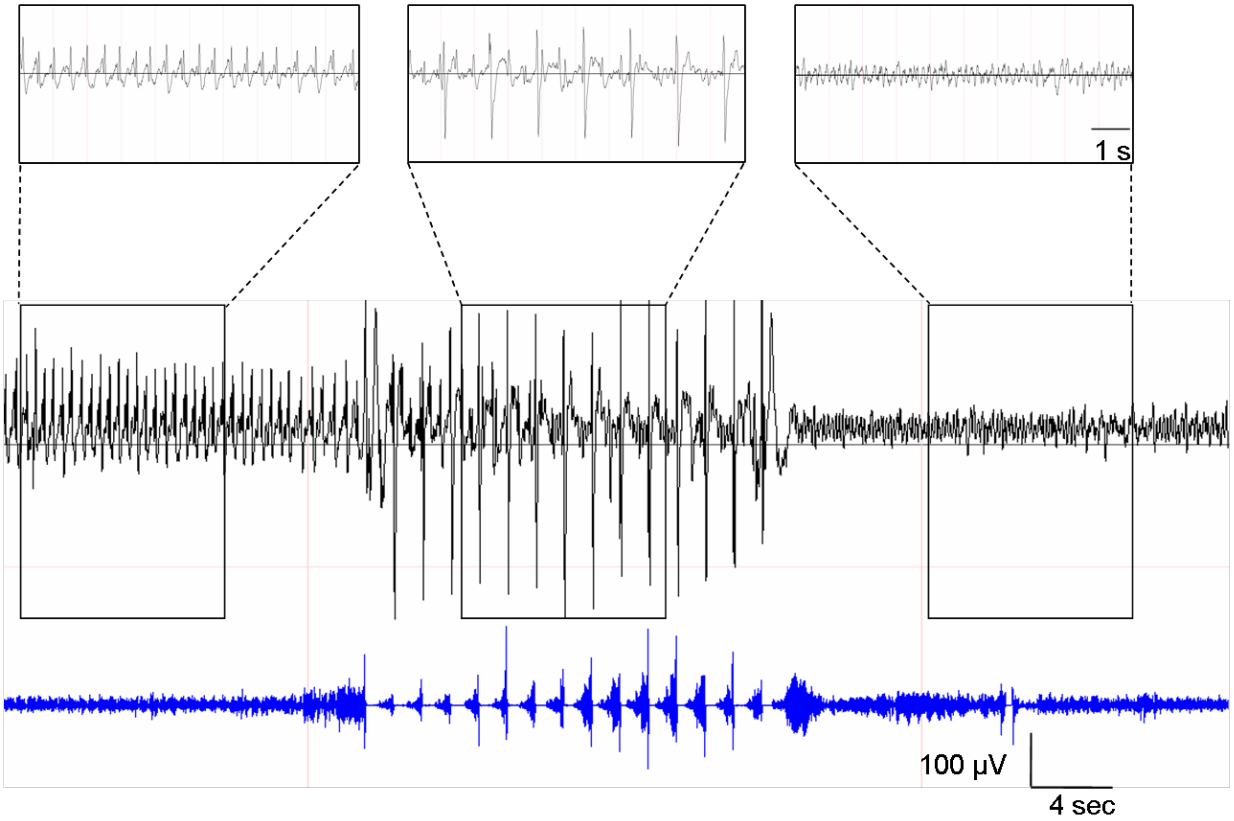
Clinical Neurophysiology

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

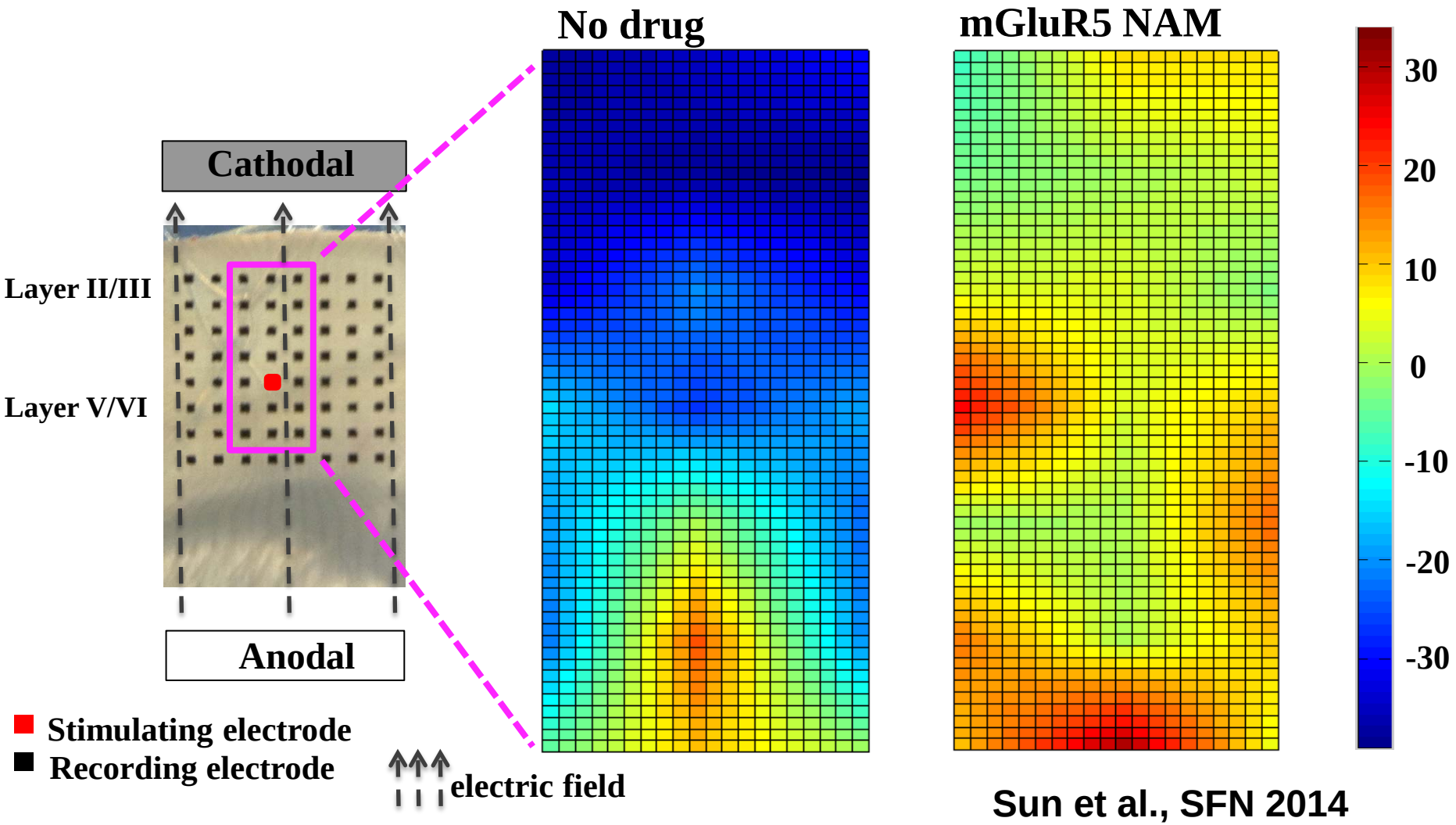
Seizure suppression by EEG-guided repetitive transcranial magnetic stimulation in the rat

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]





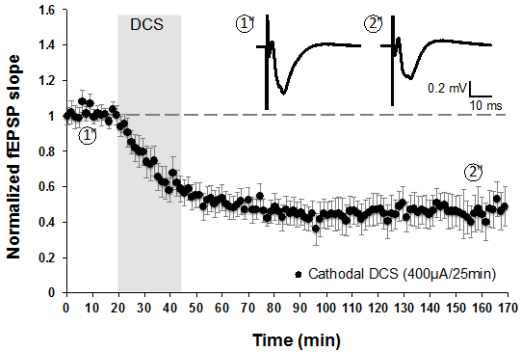
High resolution of cortical effects



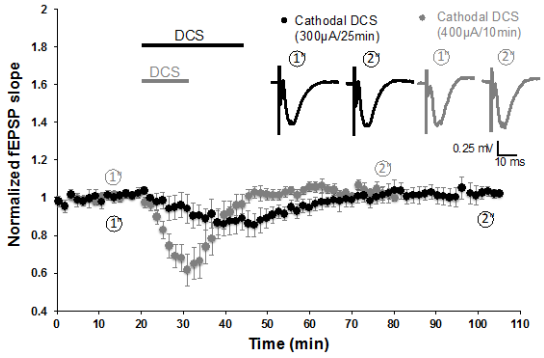
Sun et al., SFN 2014

Preclincal studies may enable logical coupling between brain stimulation protocols and drugs

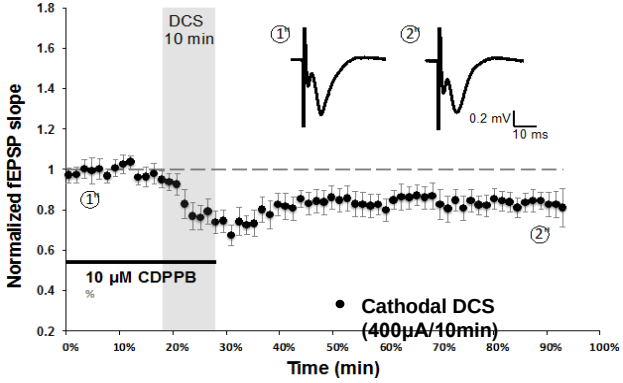
Effective DCS



Sub-effective DCS
(either low current or low duration)



Sub-effective DC + mGluR5 PAM



Sun et al., SFN 2014

DEVELOPMENTAL BIOLOGY **203**, 412–423 (1998)
ARTICLE NO. DB989039

The Direction of Neurite Growth in a Weak DC Electric Field Depends on the Substratum: Contributions of Adhesivity and Net Surface Charge

Ann M. Rajnicek,*,[1] Kenneth R. Robinson,† and Colin D. McCaig*
**Department of Biomedical Sciences, Institute of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, United Kingdom; and †Department of Biological Sciences, Purdue University, West Lafayette, Indiana 47907*

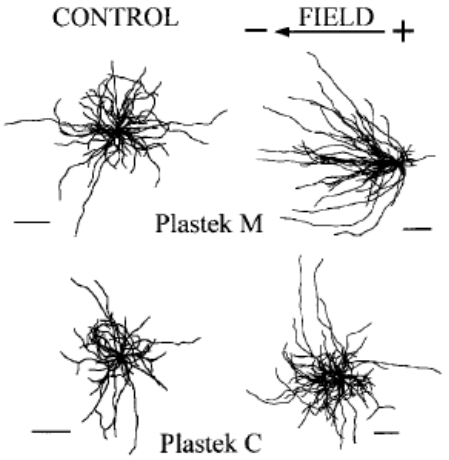


FIG. 3. Neurons in which cell bodies have been superimposed. Neurons were grown on Plastek M (negatively charged) or Plastek

European Cells and Materials Vol. 4. Suppl. 2, 2002 (pages 30-31) ISSN 1473-22

DIRECTING CELL SHAPE AND MIGRATION BY TOPOGRAPHIC AND ELECTRICAL SIGNALS

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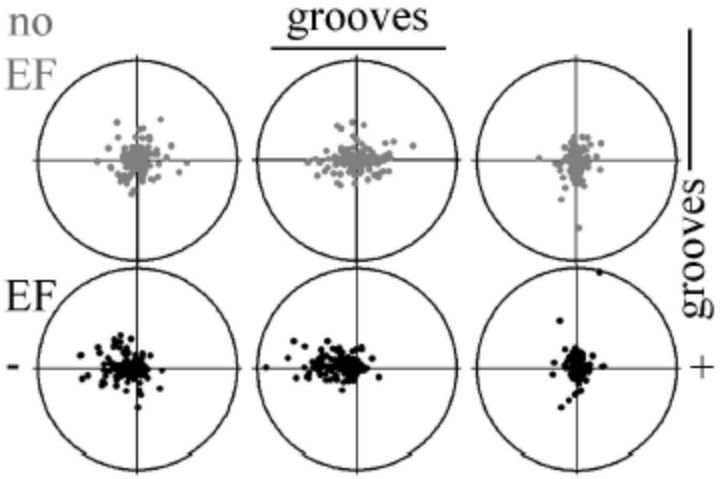

Fig. 2: Bovine corneal epithelial cell migration on flat or grooved quartz. Top row: cells in the absence of an EF. Bottom row: cells in an EF of 150 mV/mm, cathode at left. Left column: flat

Galvanotropism and gavanotaxis (relevant to tDCS?)

Current and recent lab members

Nicolas Chiriboga
Sameer Dhamne
Roman Gersner
Mustafa Hameed
Tsung-Hsun Hsieh
Henry Lee
Richard Manfready
Michaela Meyer
Paul Muller
Carmen Paredes
Maria Sanchez
Yan Sun
Andrew Vahabzadeh
Jingpu Zhao
Hongyang Zhao
Zhihong Zhou

Boston Children's Hospital

Until every child is well℠

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Children's Hospital Department of Neurology
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Colleagues and mentors

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Paradee Auvichayapat - Khon Kaen U., Thailand
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Joseph Madsen - BCH
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Phil Pearl - BCH
Ann Poduri - BCH
James Riviello - Columbia
Paul Rosenberg – BCH
Mustafa Sahin - BCH
Steve Schachter – CIMIT / BIDMC
Don Schomer – BIDMC
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Masanori Takeoka - BCH
Abraham Zangen – BGU, Israel