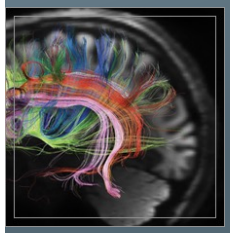



The Physics of Neuromodulation

Noninvasive Neuromodulation Unit (NNU)

Experimental Therapeutics & Pathophysiology Branch

NIMH

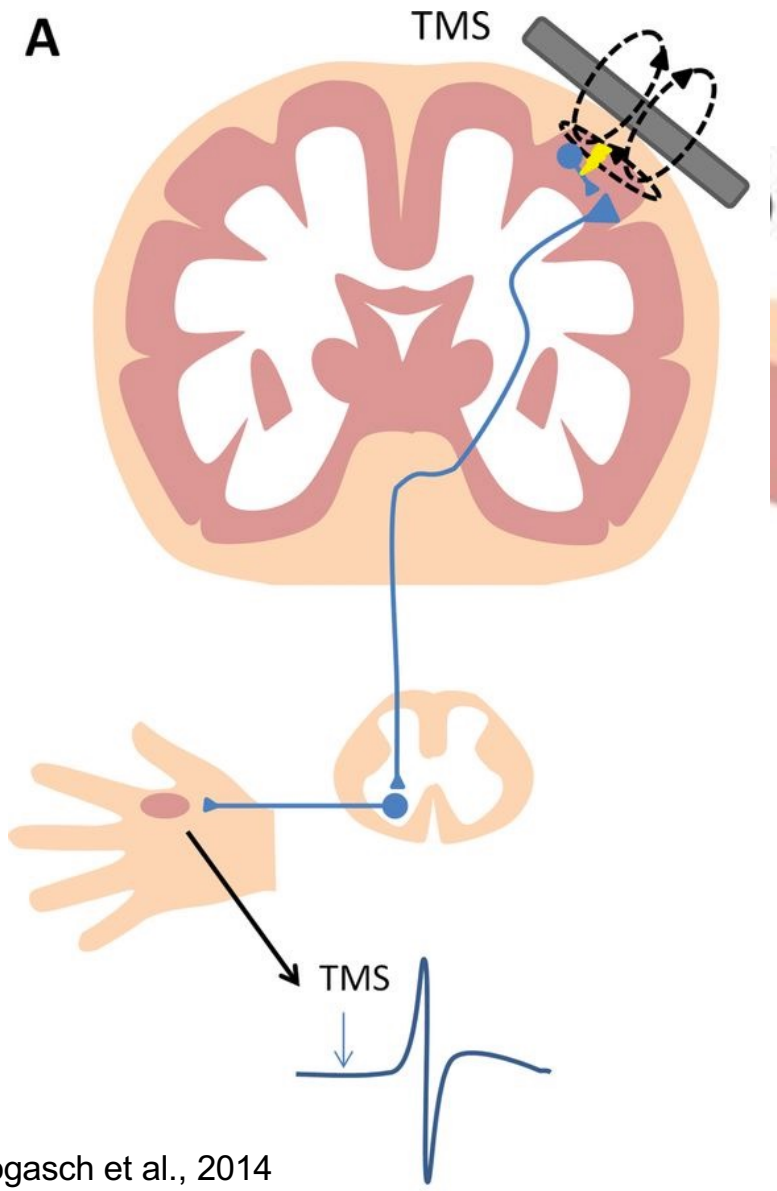
August 4, 2017

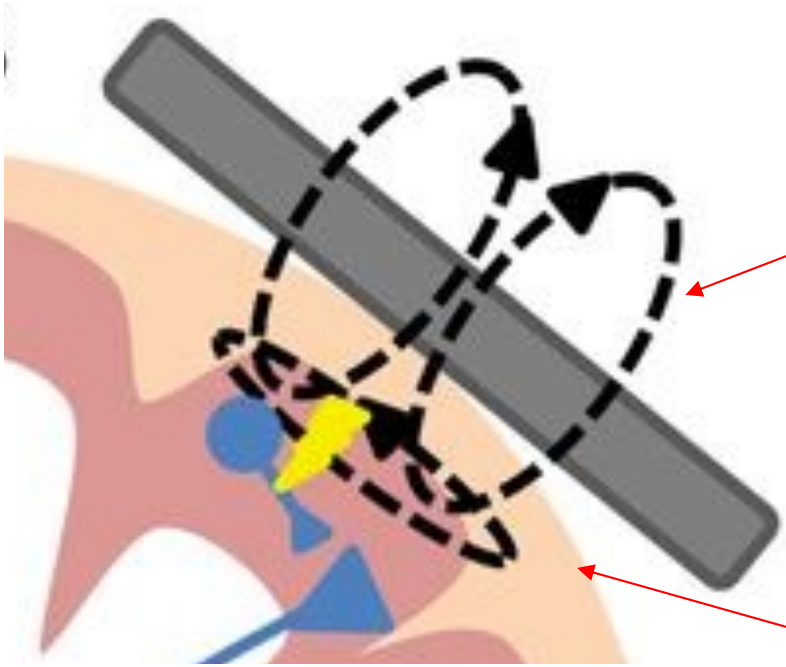
National Institute of Mental Health

A framework for understanding neuromodulation

1. Stimulating the brain non-invasively
2. The terminations and bends of axons are thought to be the elements stimulated by TMS
3. Cortical layer specificity: D and I-waves
4. Receptor-level specificity: TMS paired pulses

A framework for understanding TMS





Rogasch et al., 2014

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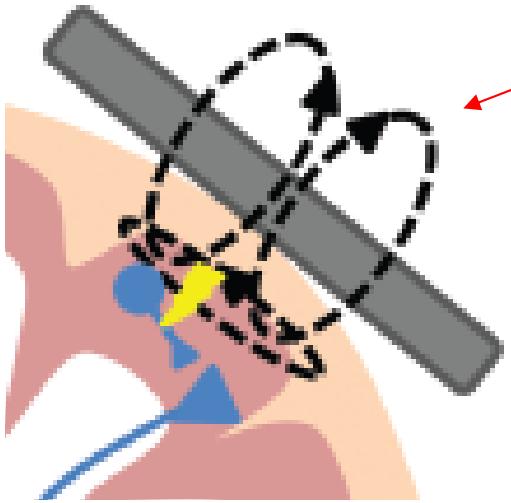
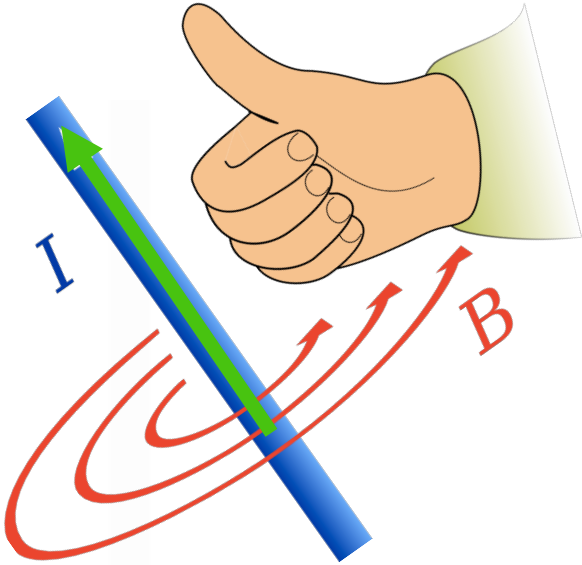
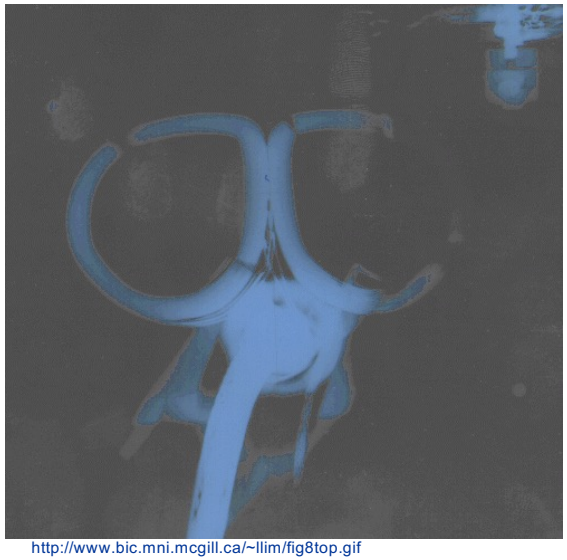
How is the magnetic field generated?



Magnetic Field



1.5 to 2T



http://www.bic.mni.mcgill.ca/~llim/fig8top.gif

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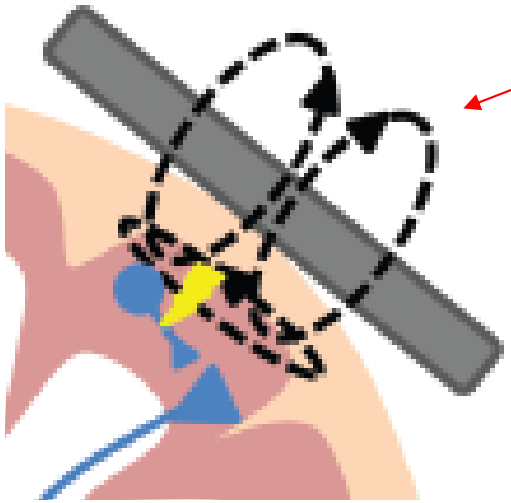
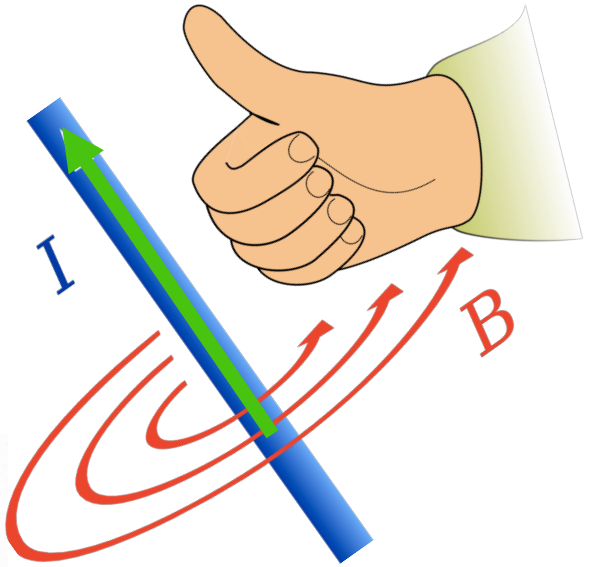
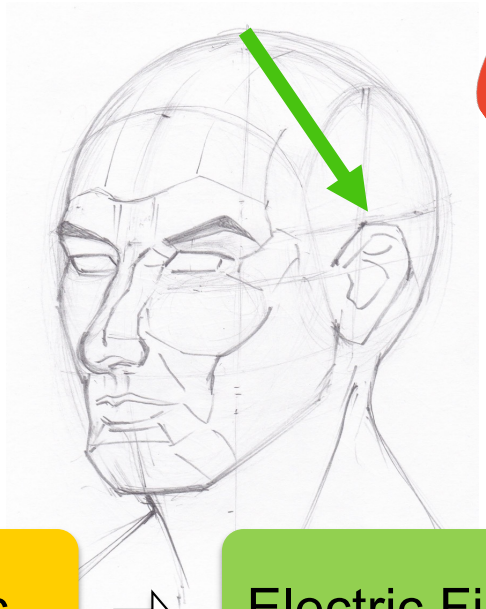
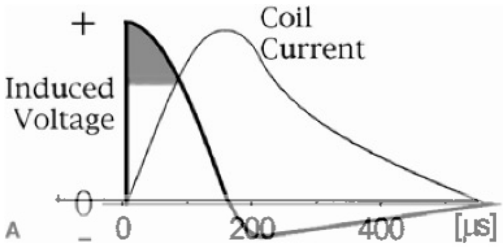




$$\mathcal{E} = -\frac{d\Phi_B}{dt},$$





Current in the coil → Magnetic Field → Electric Field in the Brain

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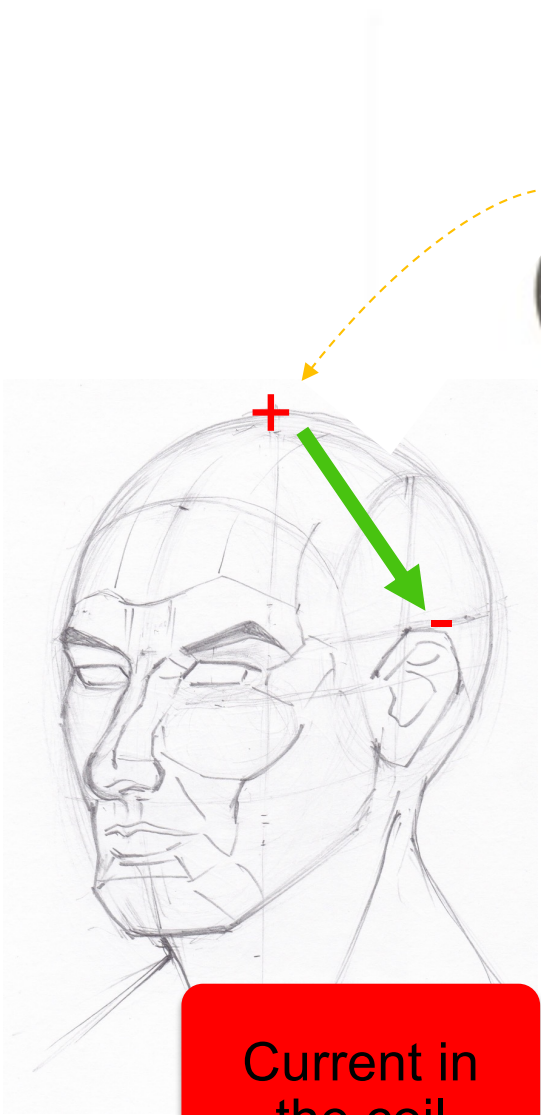
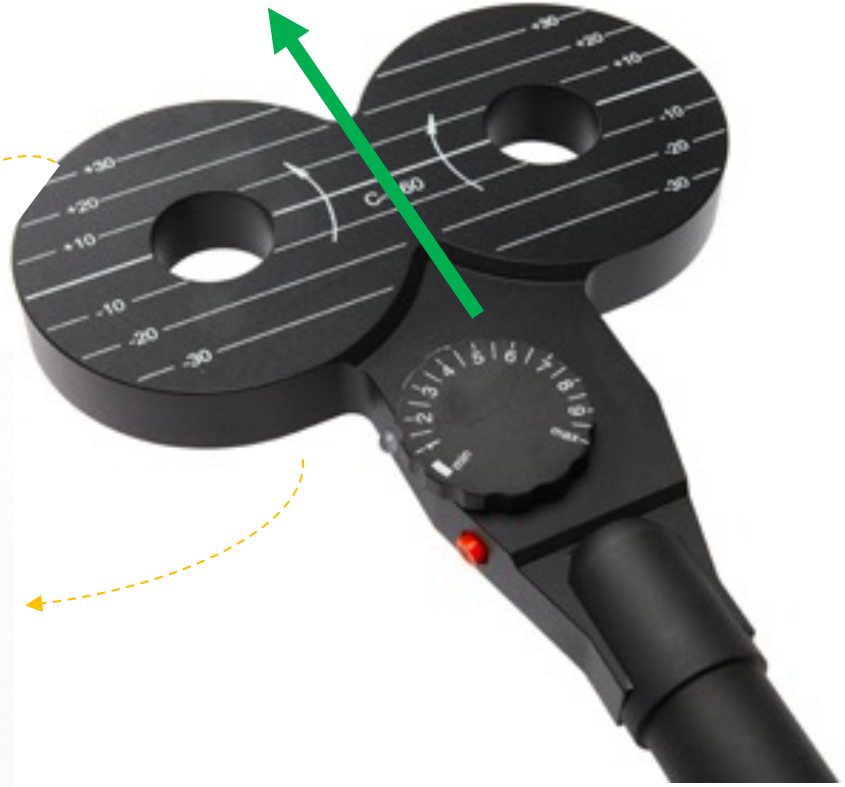
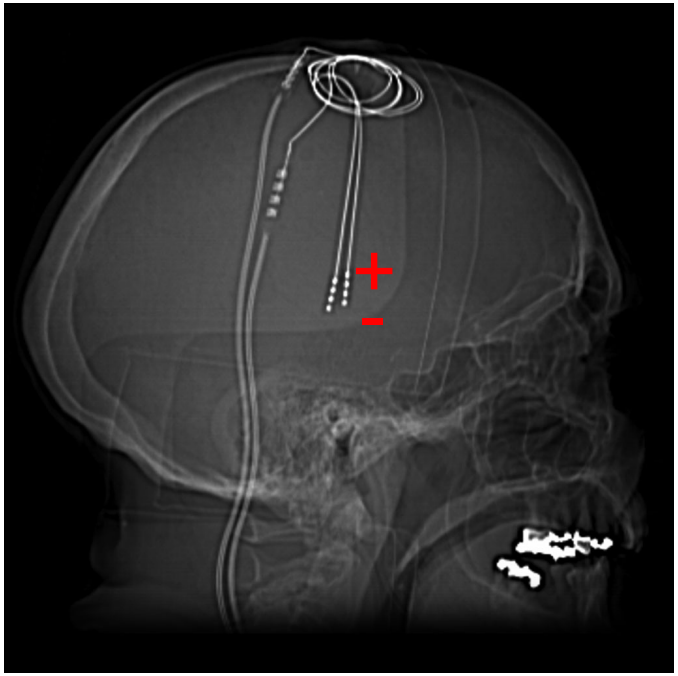
How is the magnetic field generated?







Current in the coil → Magnetic Field → Electric Field in the Brain

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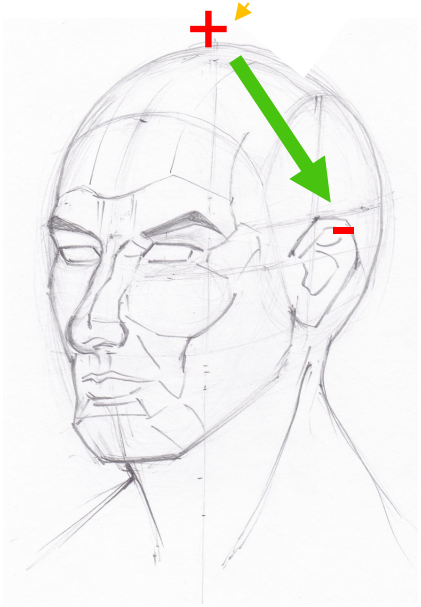
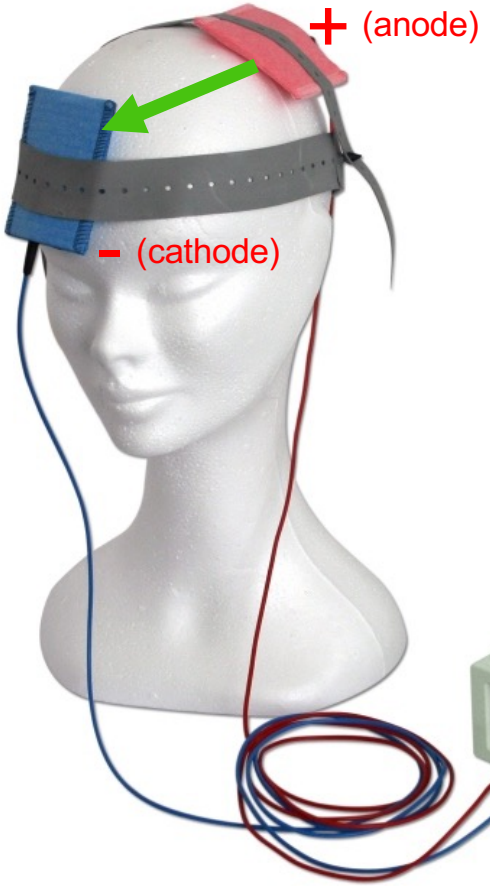
tDCS applies current directly to the scalp





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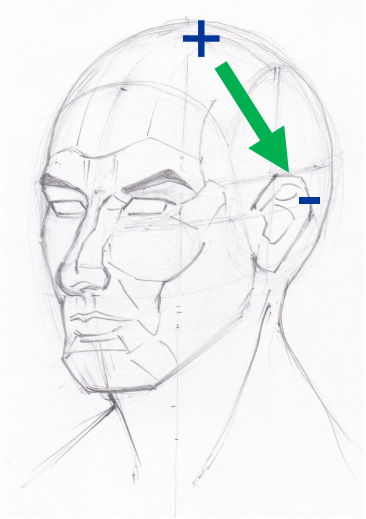
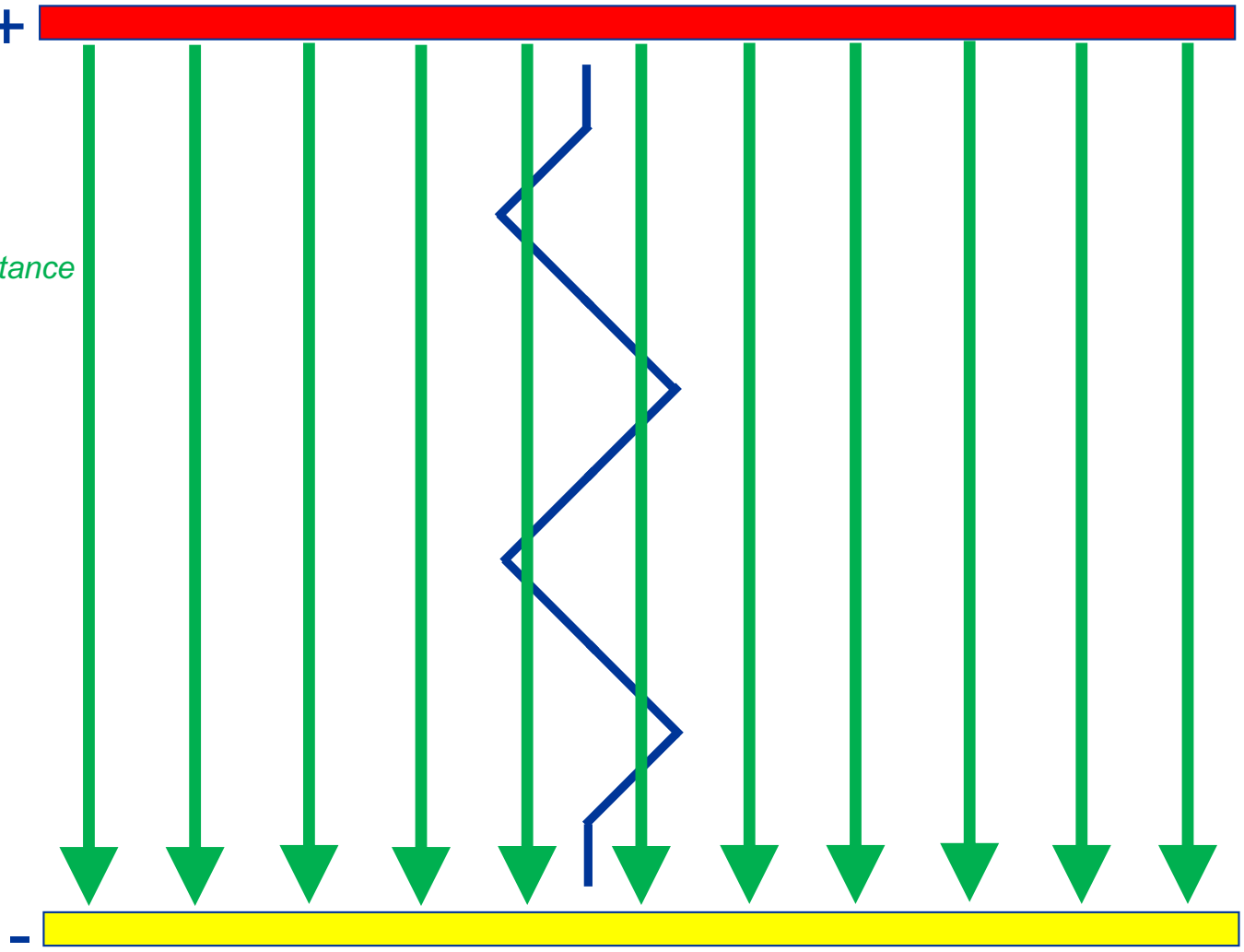
What is an electric field?

v=ir
*voltage = current * resistance*





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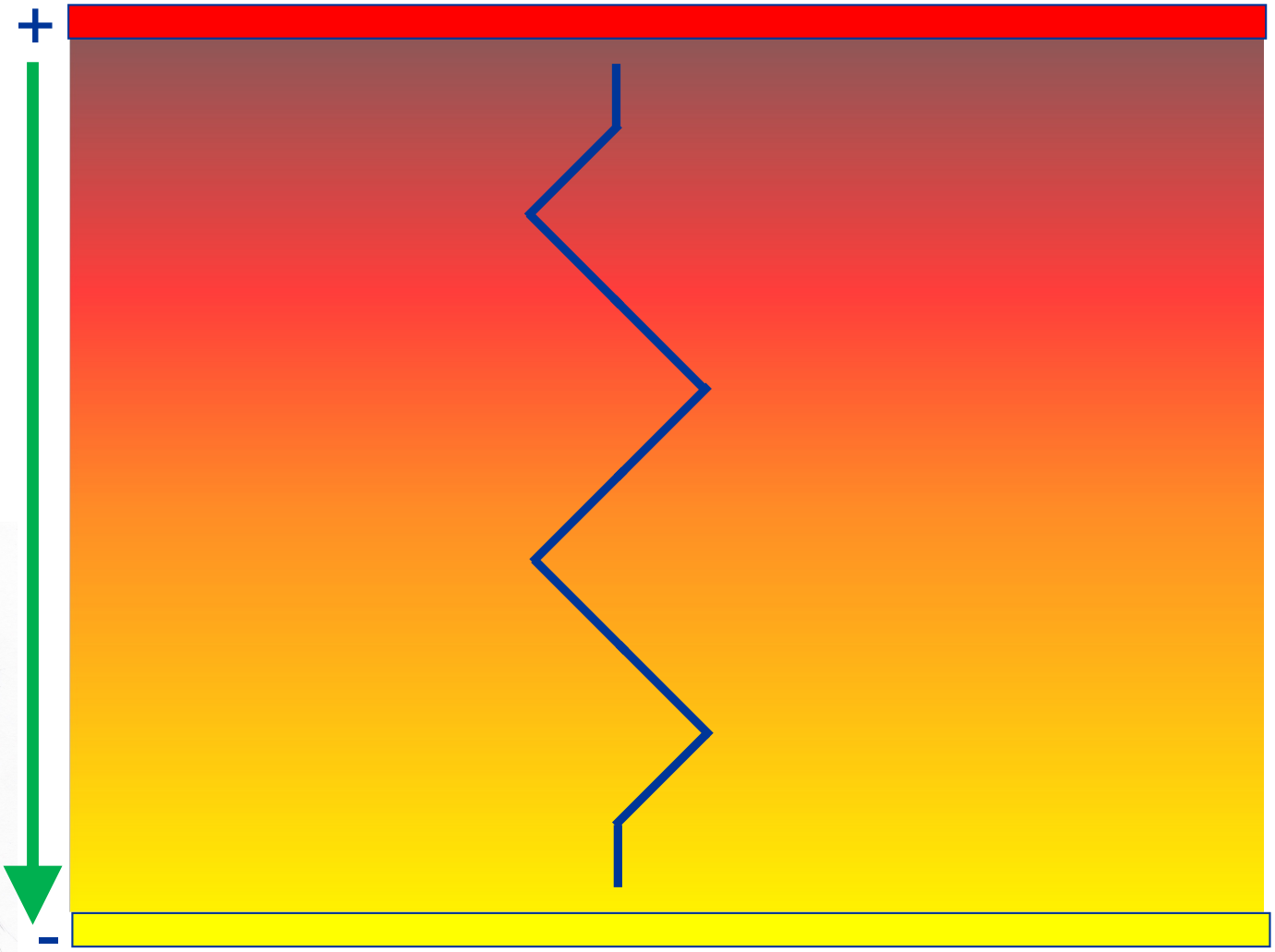
What is an electric field?



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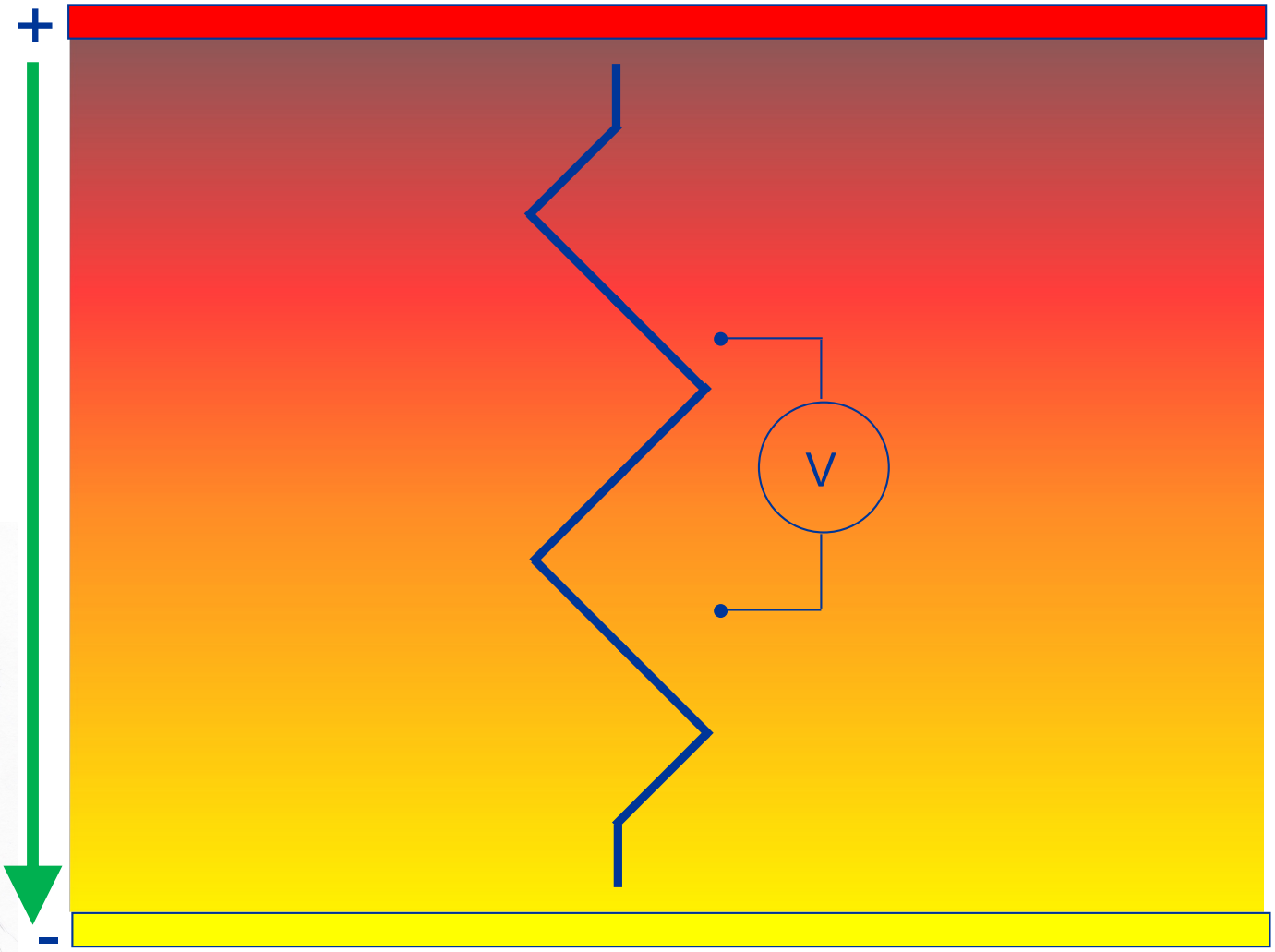
What is an electric field?



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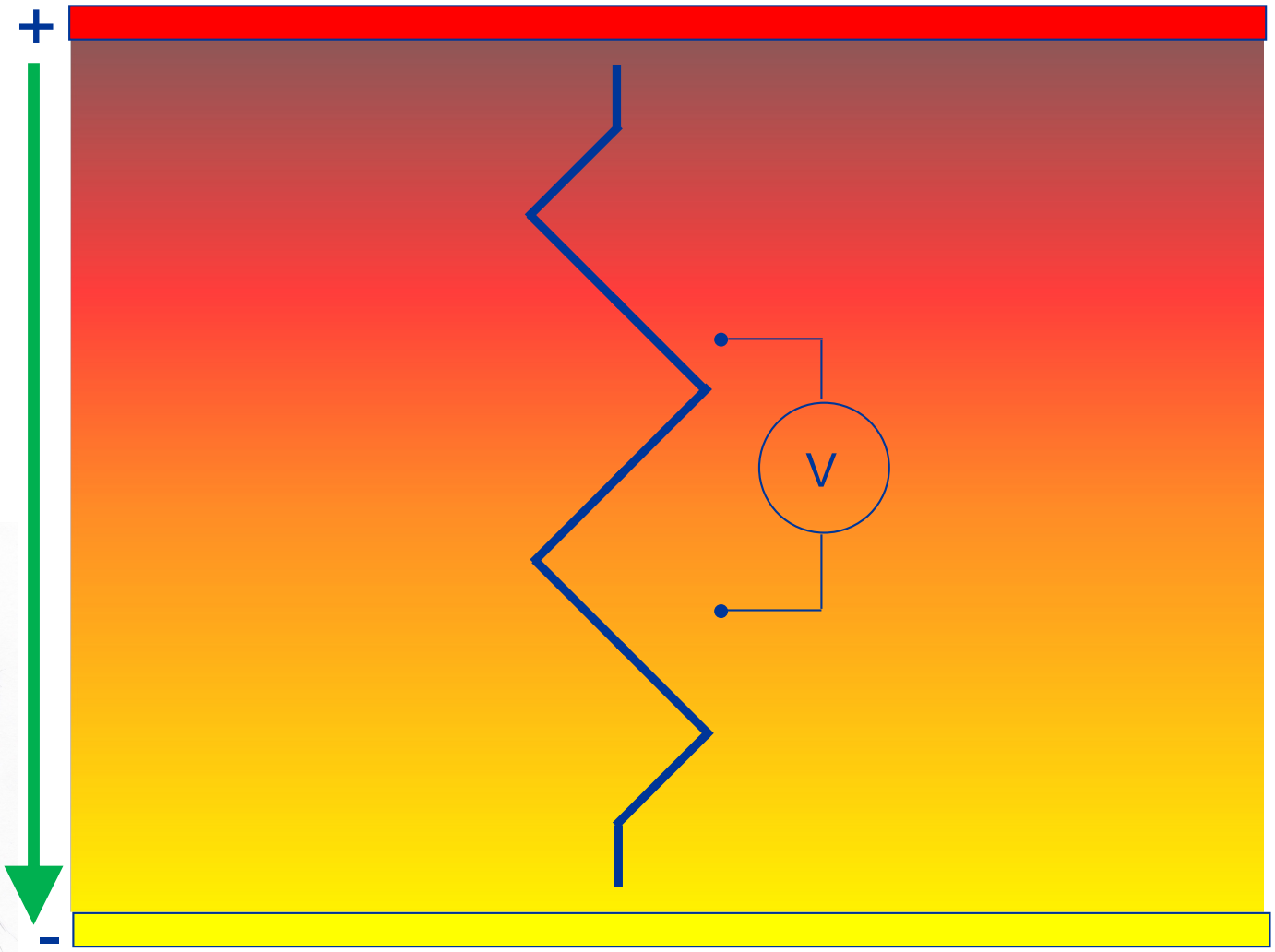
What is an electric field?



Electric Field = Volts per meter (1st spatial derivative of V)

A framework for understanding TMS

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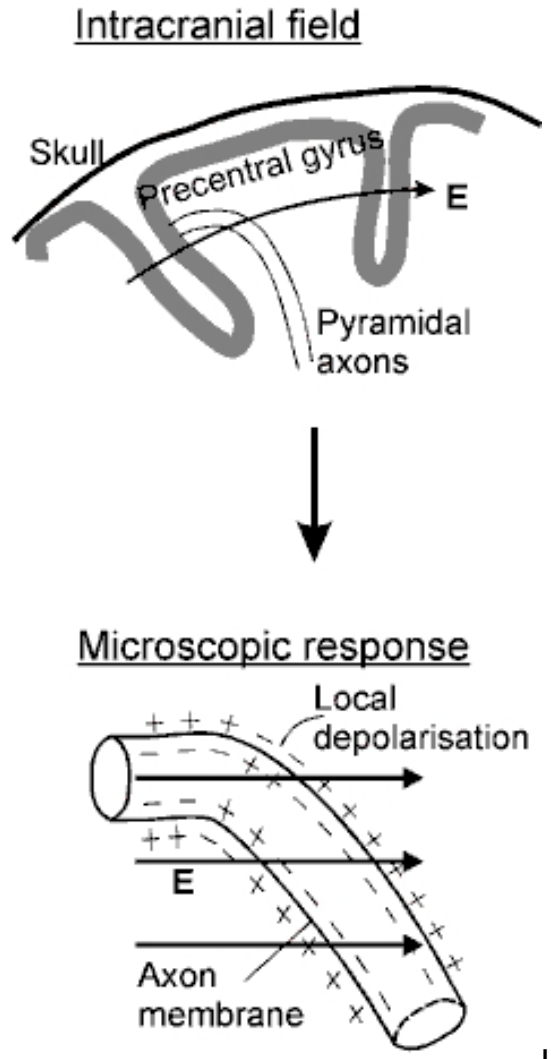
4. Receptor-level specificity: TMS paired pulses

What matters is the 2nd spatial derivative – Introducing the *activating function*

Electric Field = 1st spatial derivative of Voltage
in units of V/m

Activating Function = 2nd spatial derivative of Voltage
1st spatial derivative of Electric Field
in units of V/m^2



Hallett 2007

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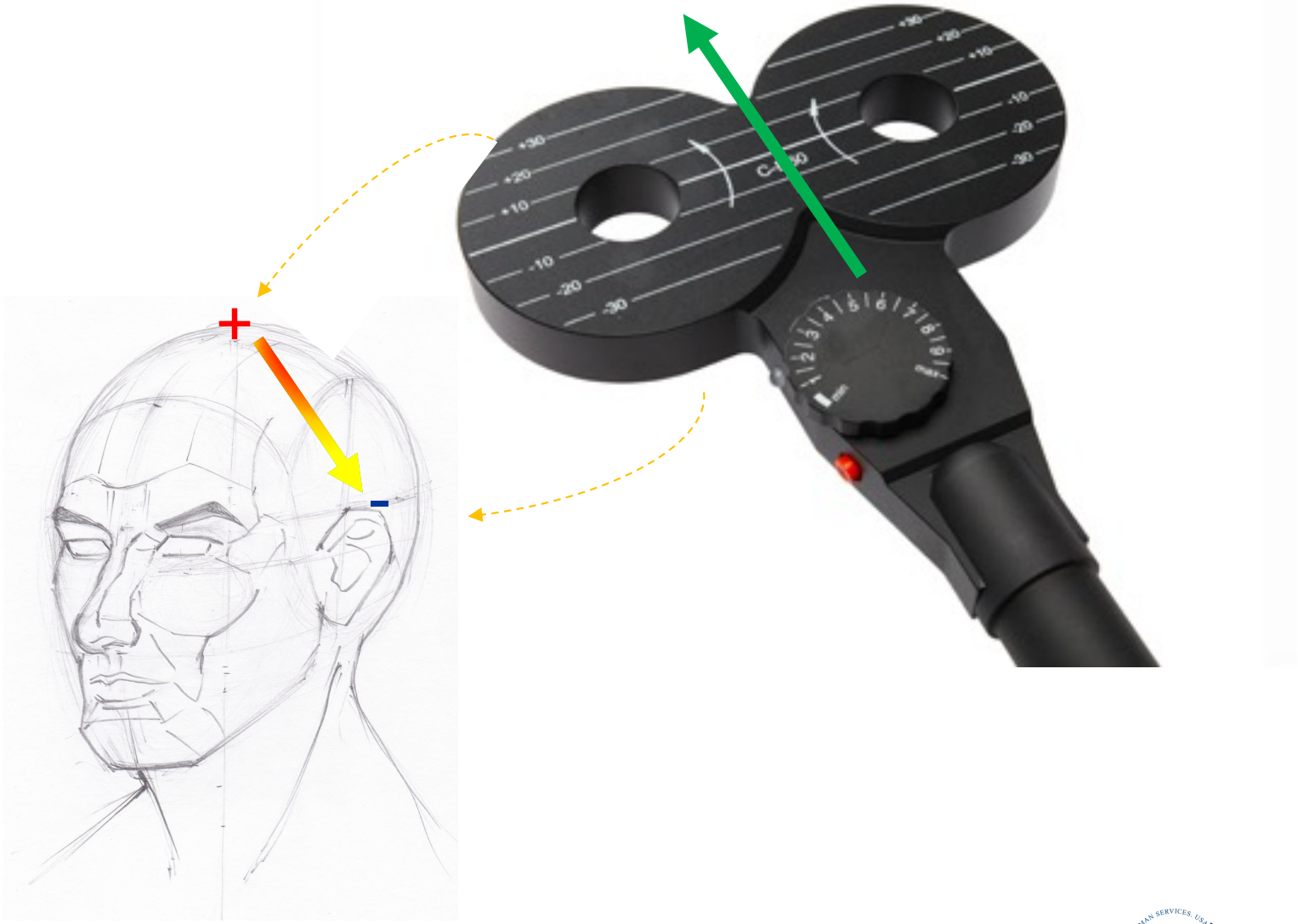
What matters is the 2nd spatial derivative – Introducing the *activating function*



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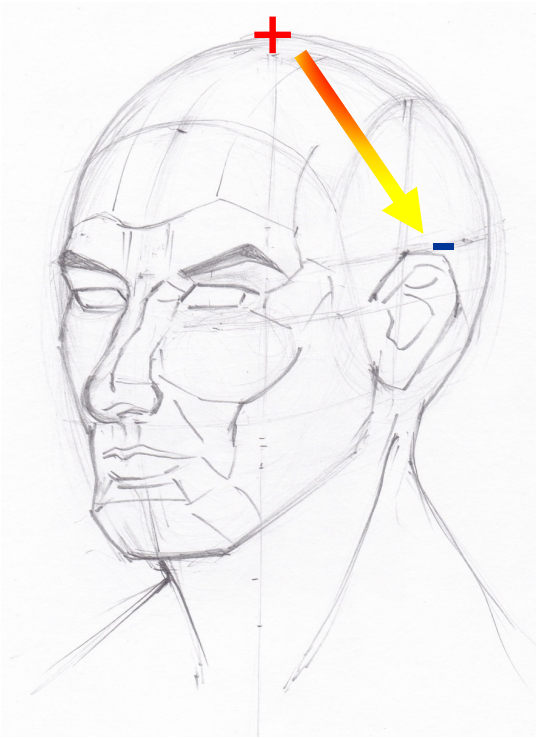
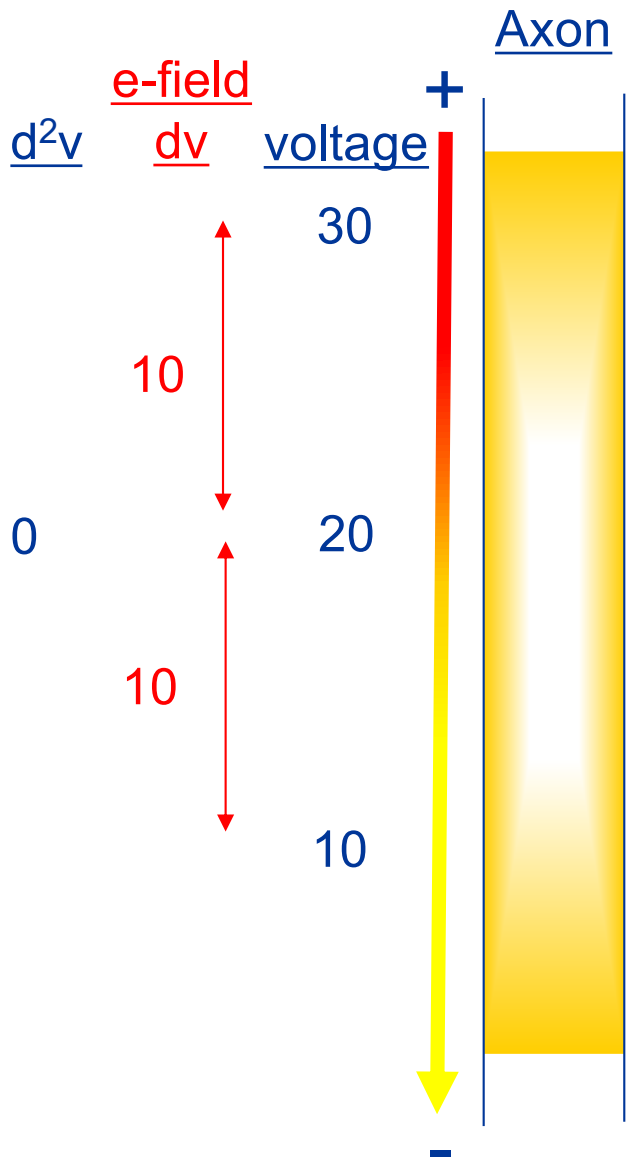
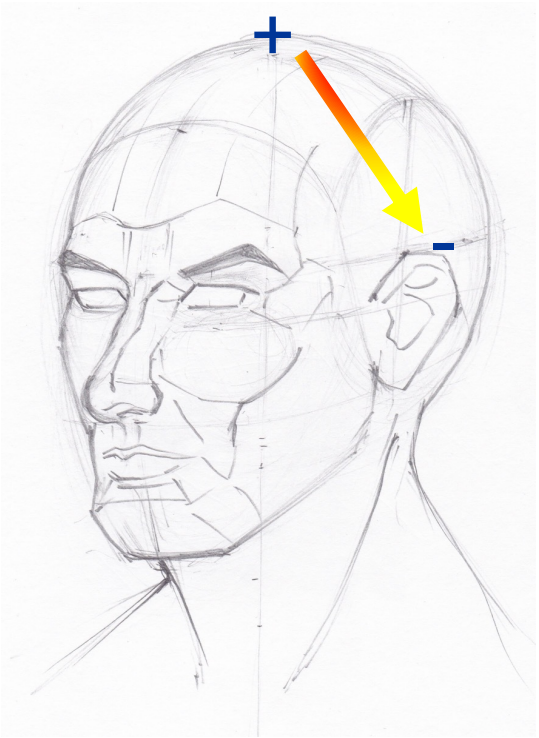
What matters is the 2nd spatial derivative – Introducing the *activating function*





What matters is the 2nd spatial derivative – Introducing the *activating function*



Axon

e-field

d^2v dv voltage

+

30

10

0 20

10

10

-

Kirchoff's Current Law

voltage

30

R2

v=ir

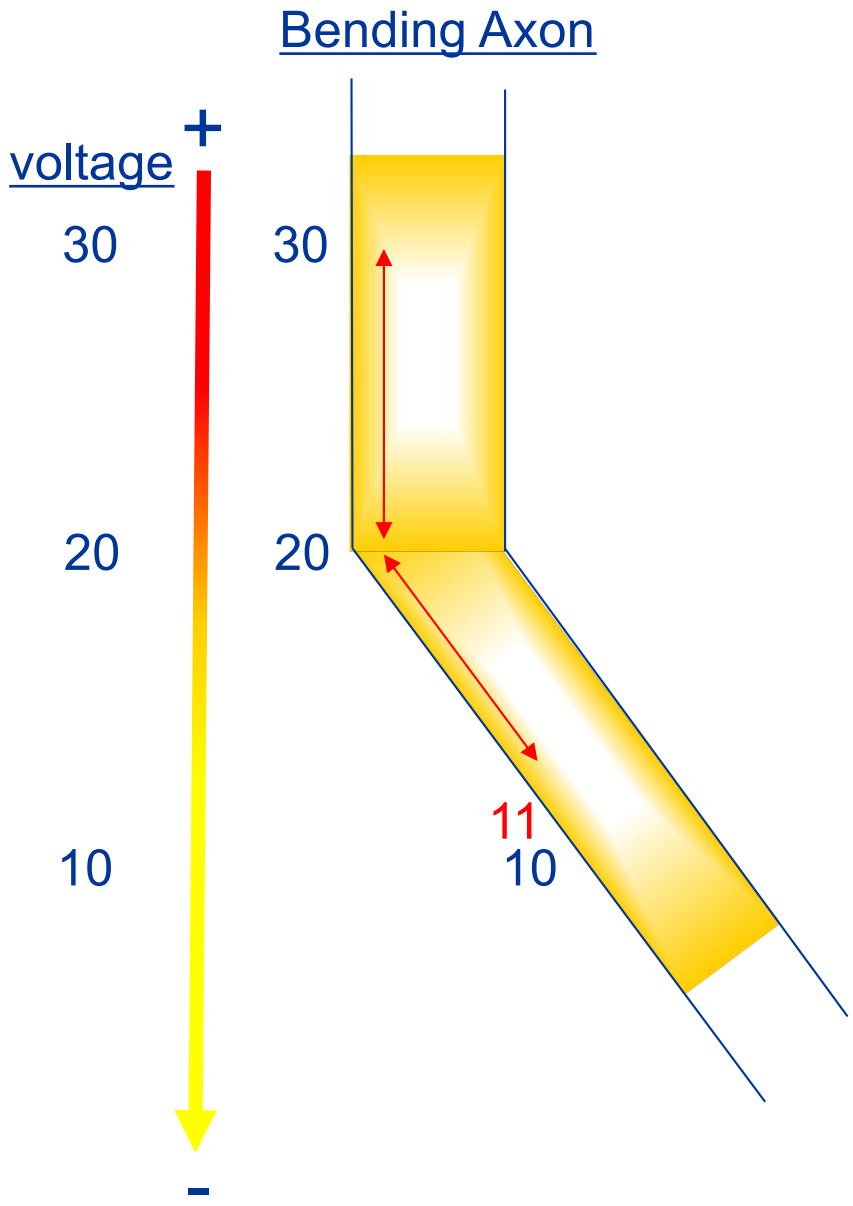
R3

20 B X

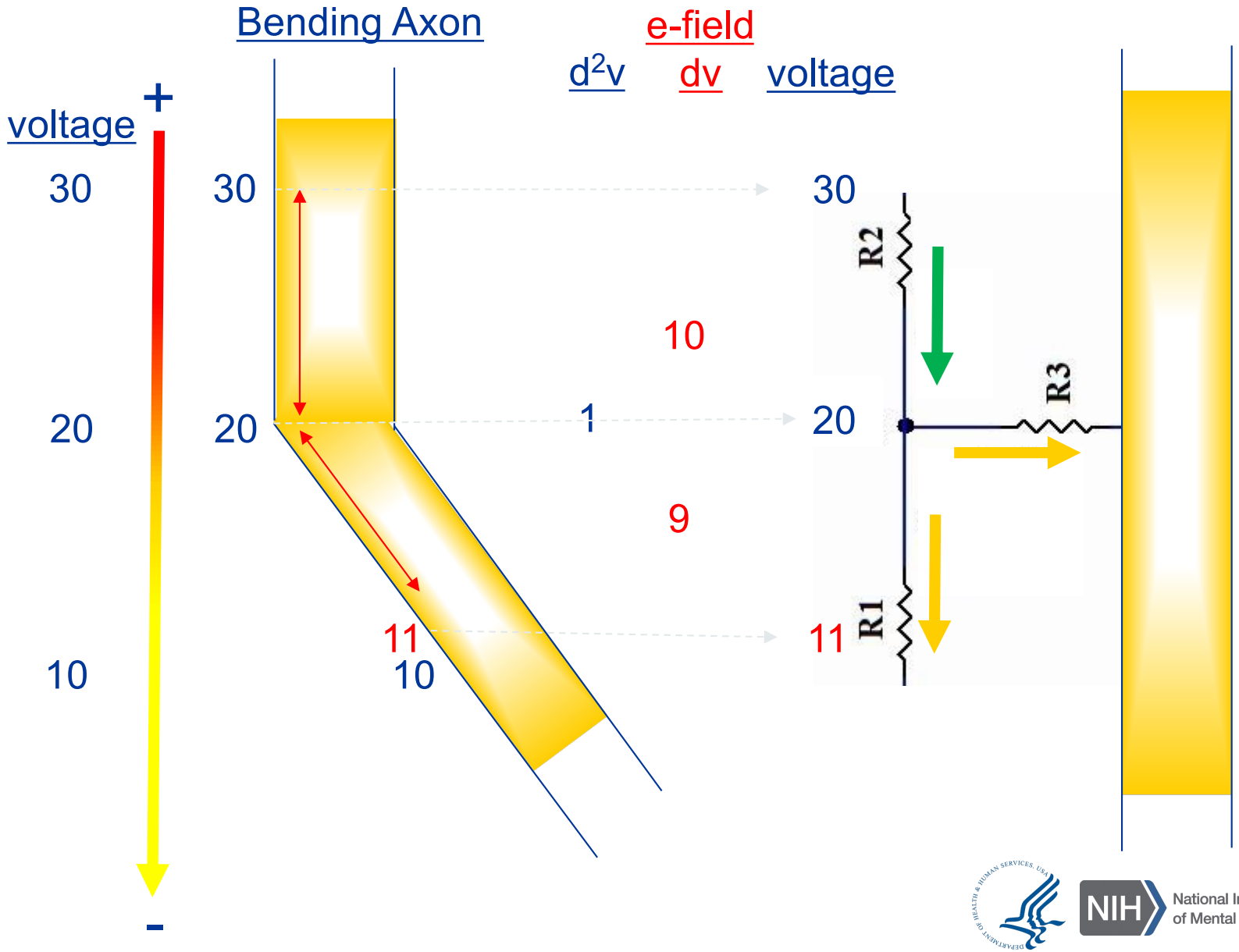
R1

10

What matters is the 2nd spatial derivative – Introducing the *activating function*



What matters is the 2nd spatial derivative – Introducing the *activating function*



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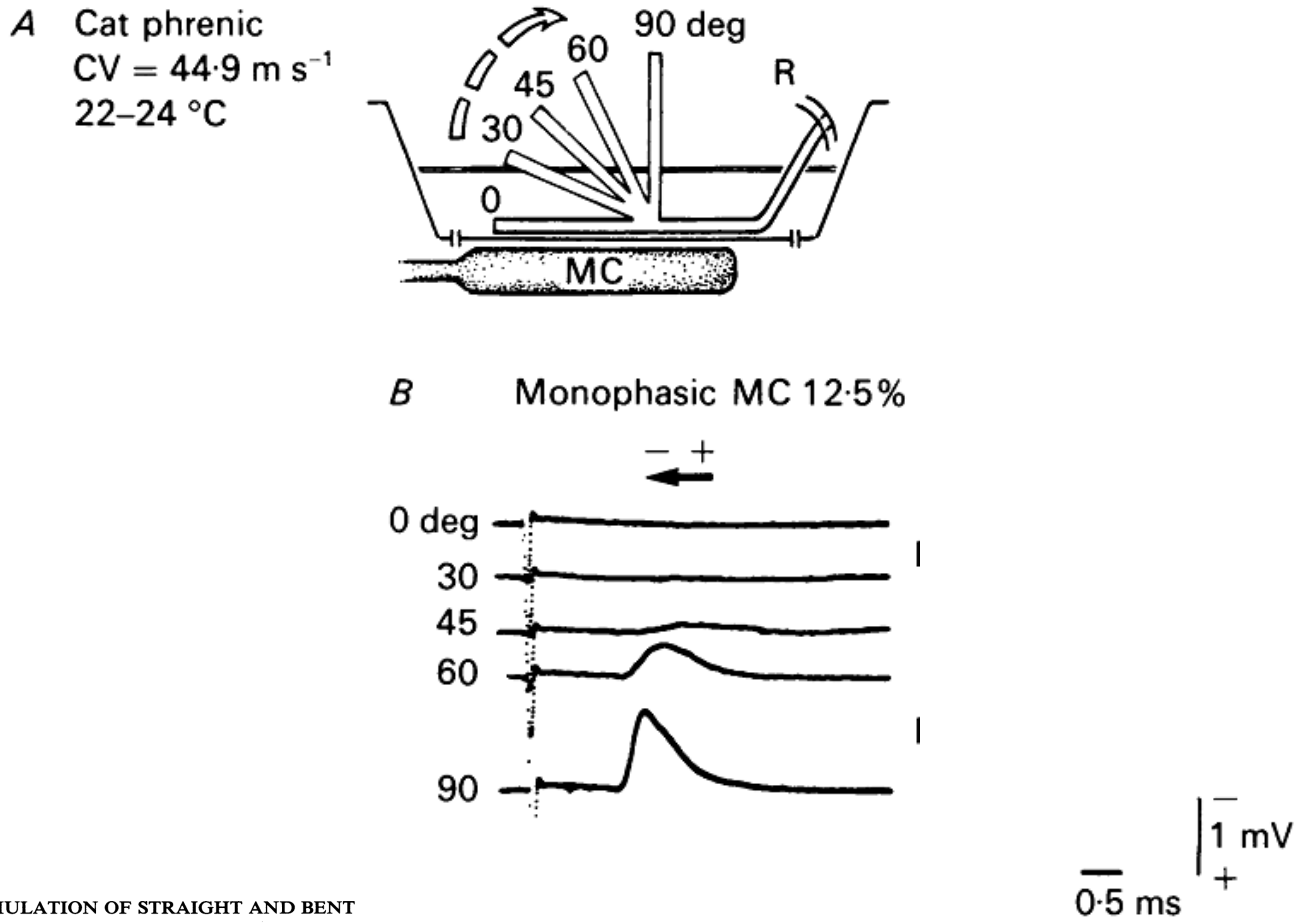
What matters is the 2nd spatial derivative – Introducing the *activating function*



MAGNETIC COIL STIMULATION OF STRAIGHT AND BENT AMPHIBIAN AND MAMMALIAN PERIPHERAL NERVE *IN VITRO*: LOCUS OF EXCITATION

By P. J. MACCABEE, V. E. AMASSIAN*, L. P. EBERLE* and R. Q. CRACCO

*From the Departments of Neurology and *Physiology, SUNY Health Science Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA*

Journal of Physiology (1993), **460**, *pp.* 201–219

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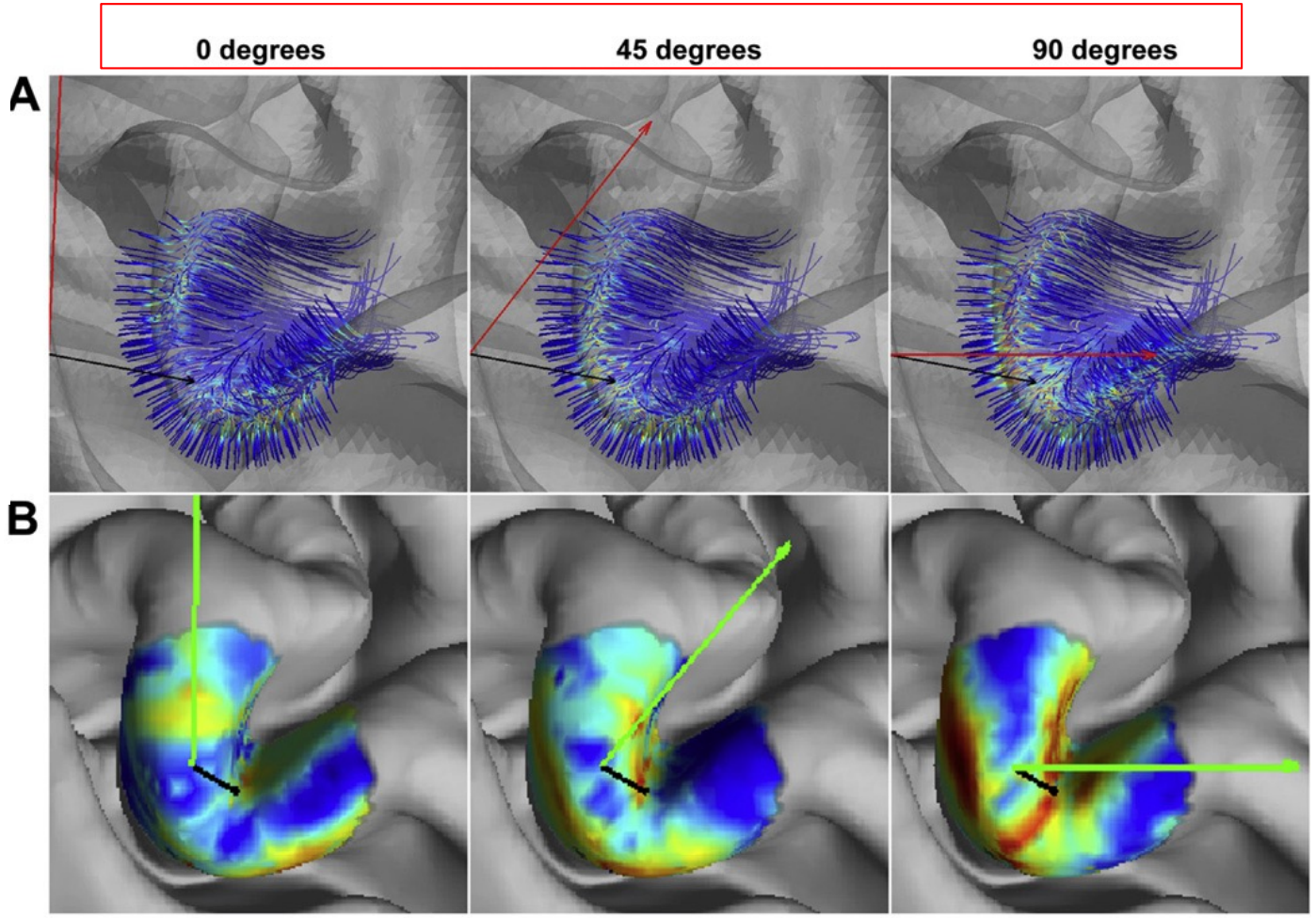
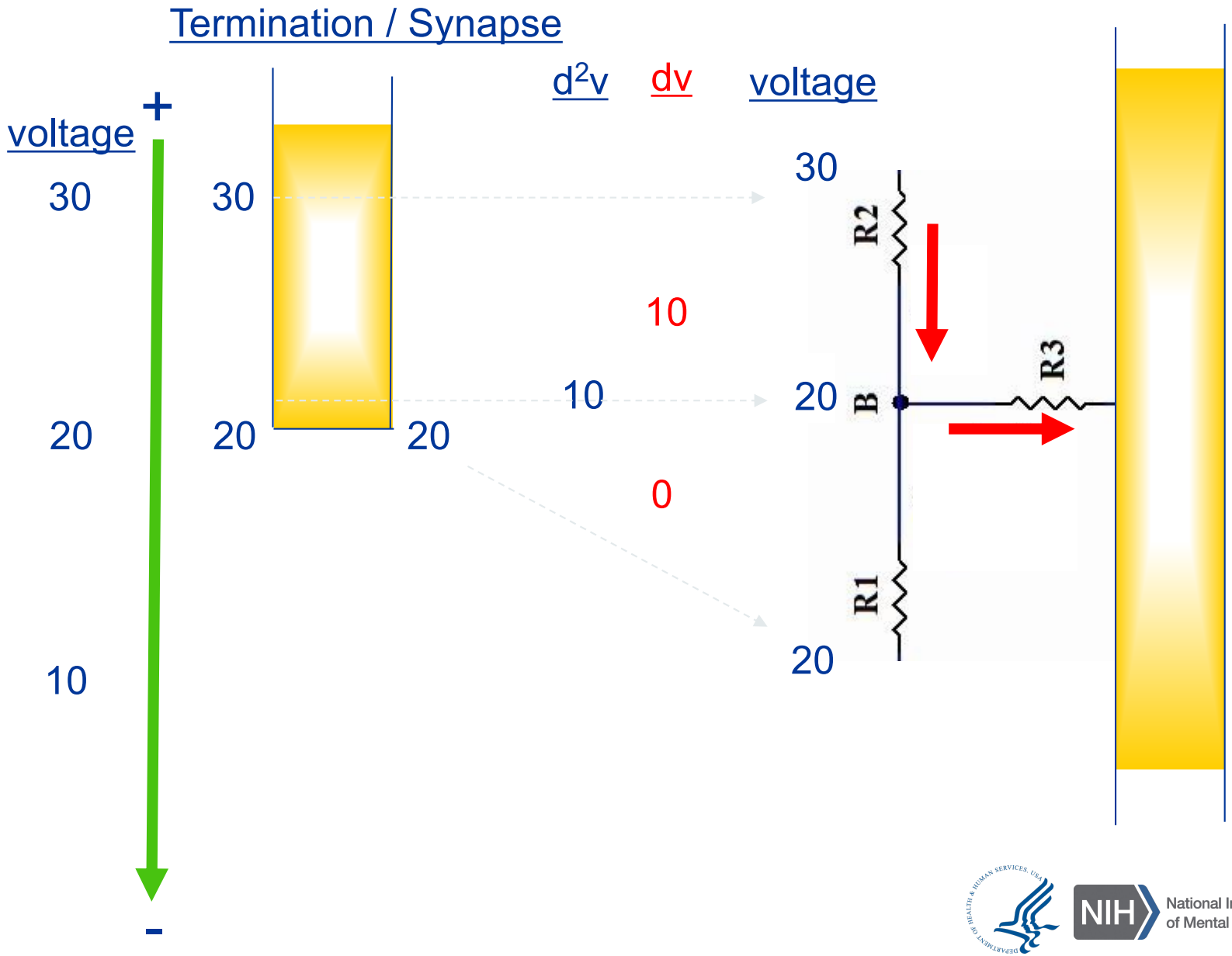
What matters is the 2nd spatial derivative – Introducing the *activating function*

So….coil orientation matters



Nummenmaa et al., 2014

What matters is the 2nd spatial derivative – Introducing the *activating function*



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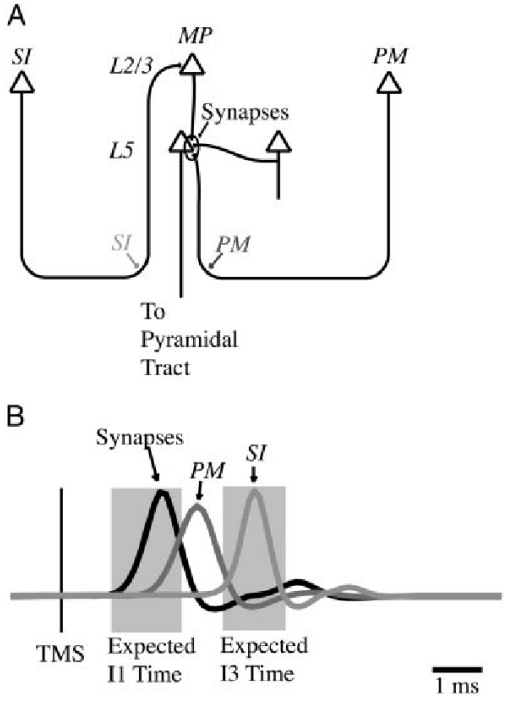

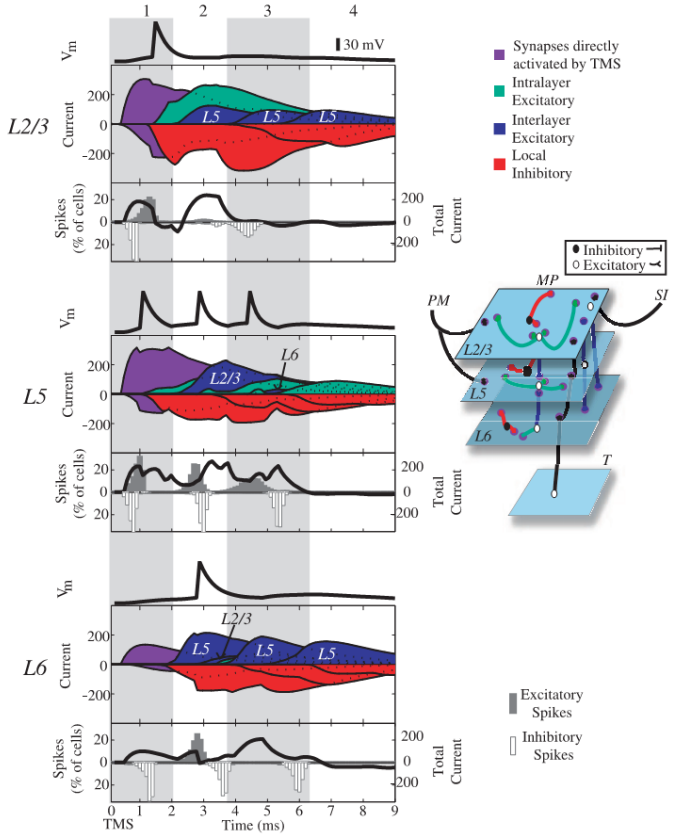

Steve K. Esser, Sean L. Hill and Giulio Tononi
J Neurophysiol 94:622-639, 2005. First published Mar 23, 2005; doi:10.1152/jn.01230.2004

A framework for understanding TMS

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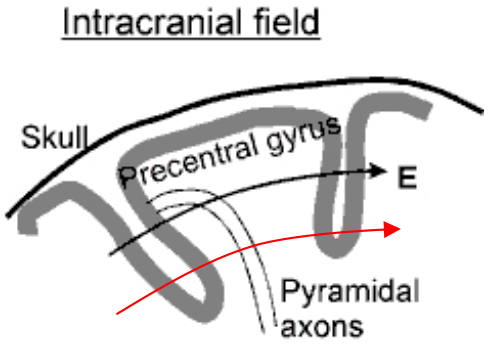
4. Receptor-level specificity: TMS paired pulses

Increasing stimulator output increases magnetic field depth and breadth



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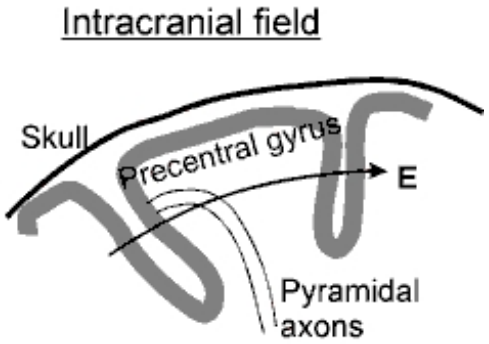
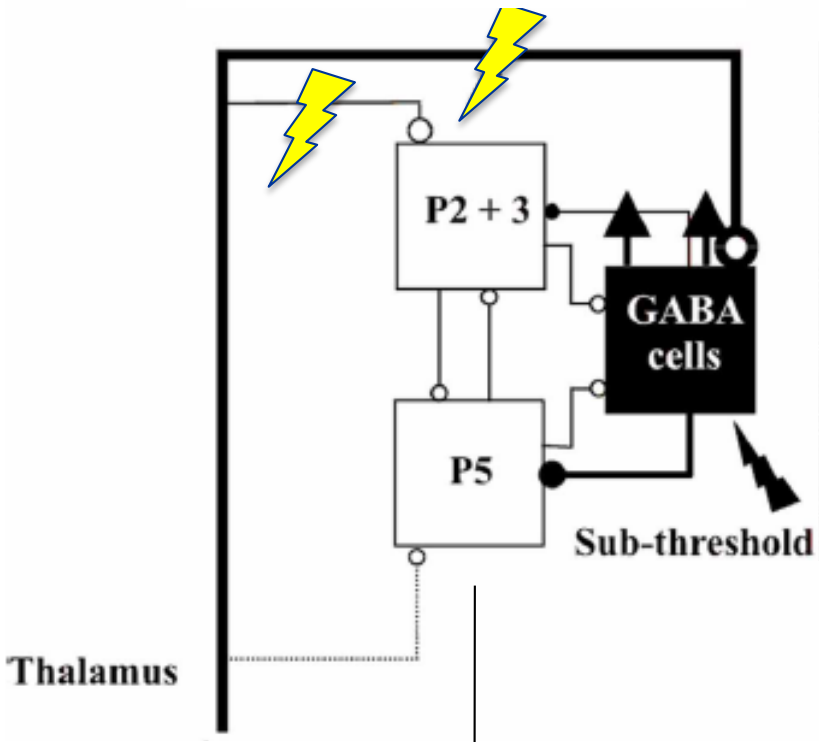
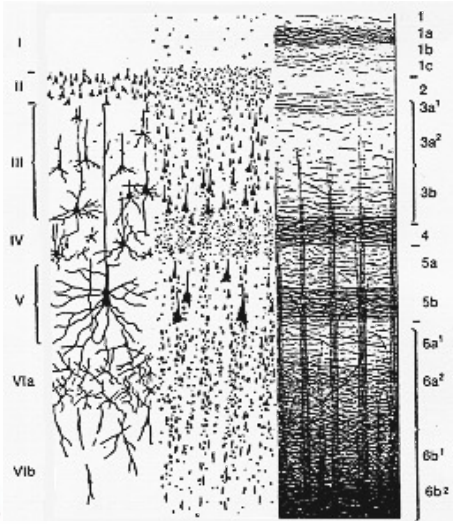
Direct (D) and Indirect (I) waves with MC TMS



Low Intensity TMS





To corticospinal tract

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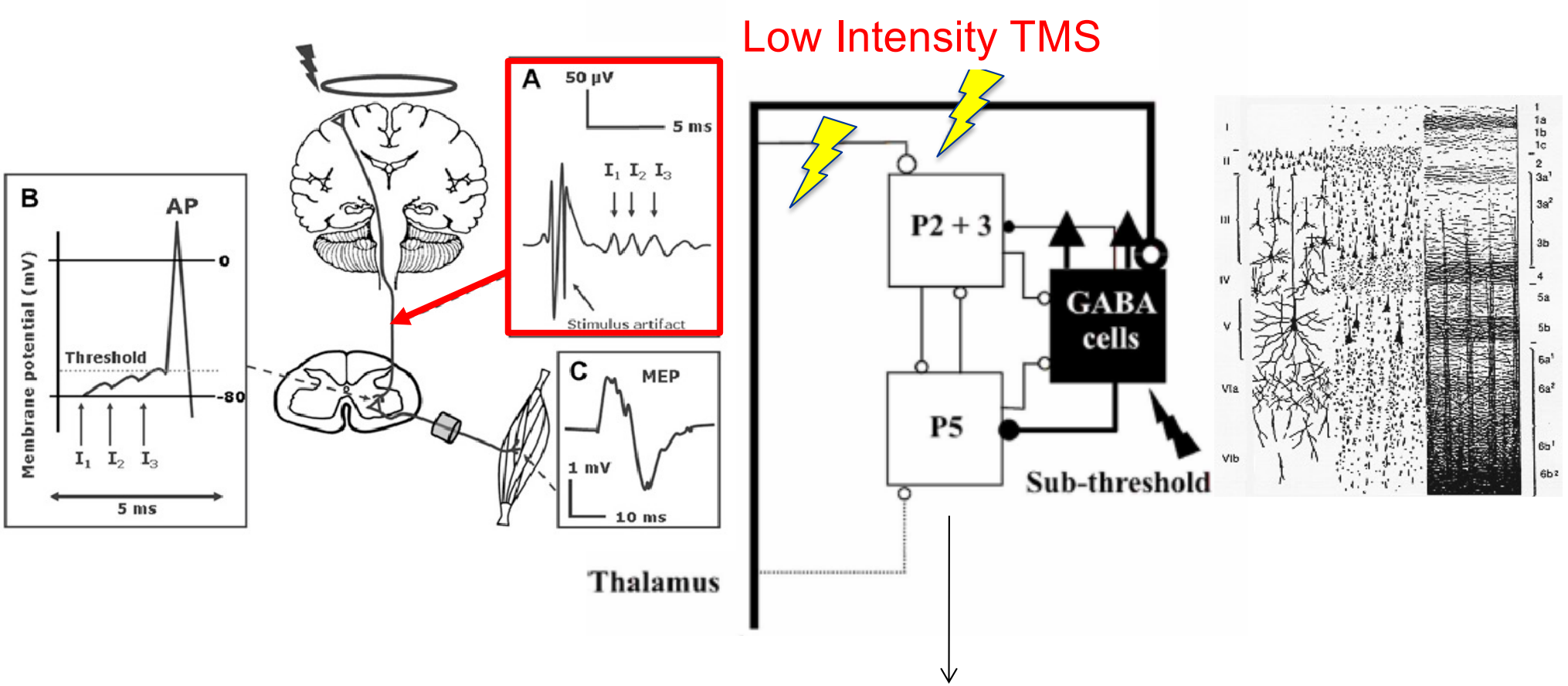
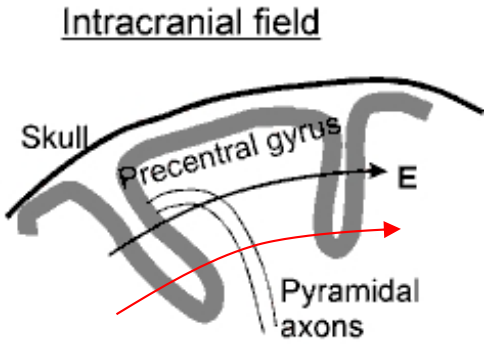
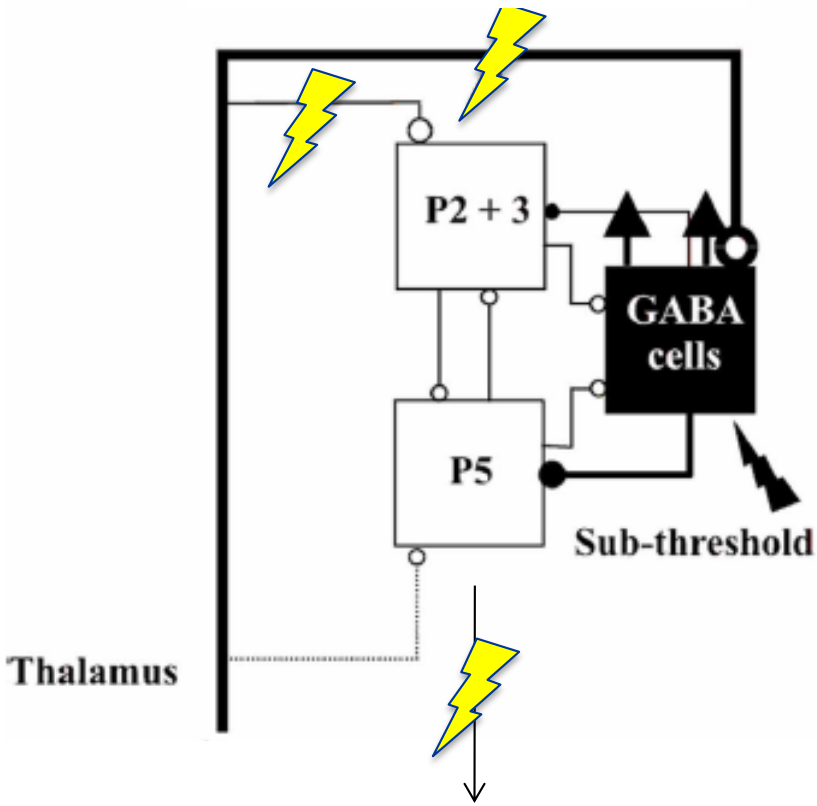
Direct (D) and Indirect (I) waves with MC TMS

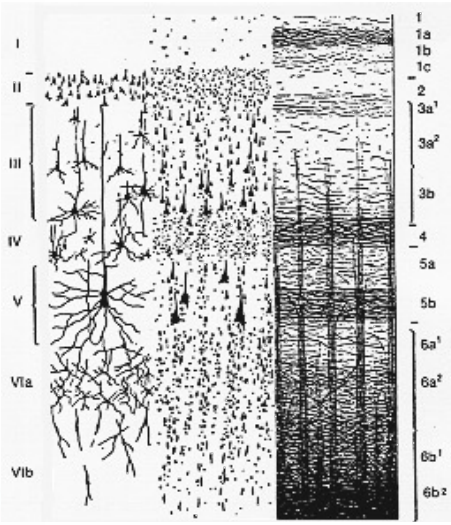


Direct (D) and Indirect (I) waves with MC TMS



High Intensity TMS





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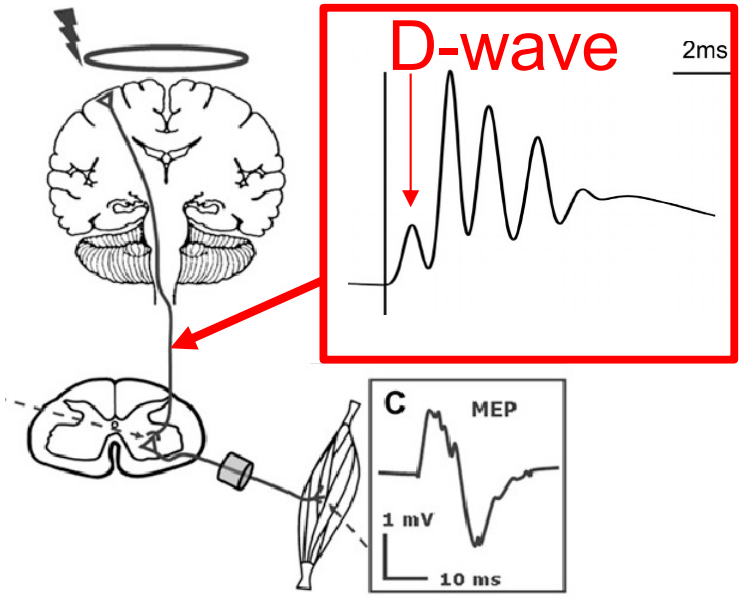
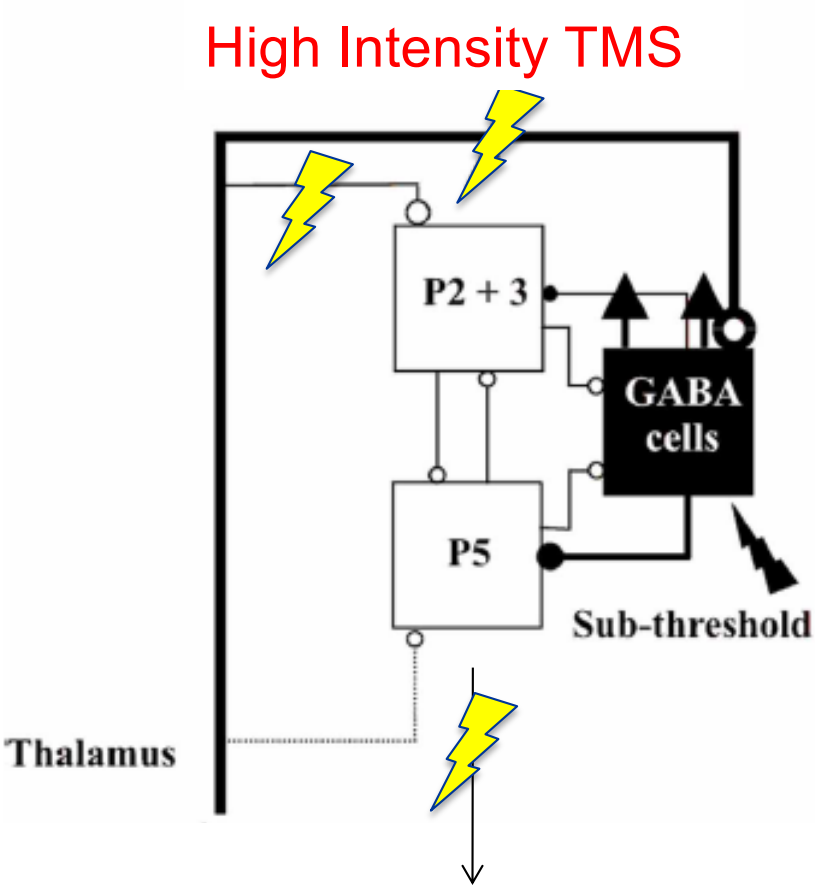
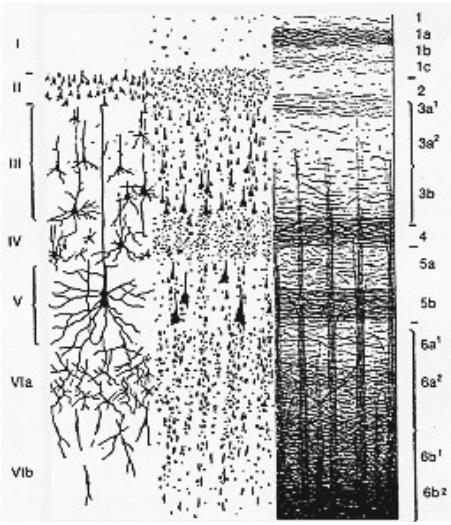
Direct (D) and Indirect (I) waves with MC TMS







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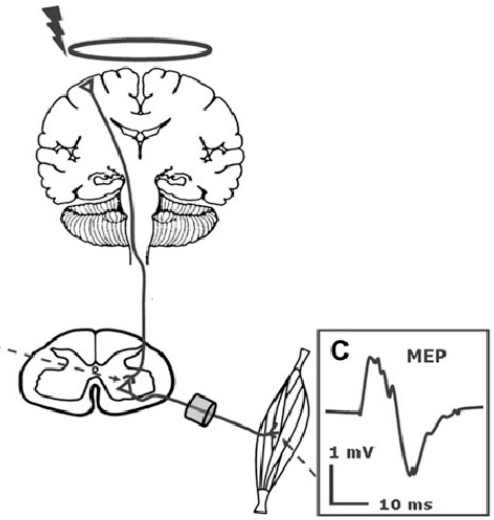
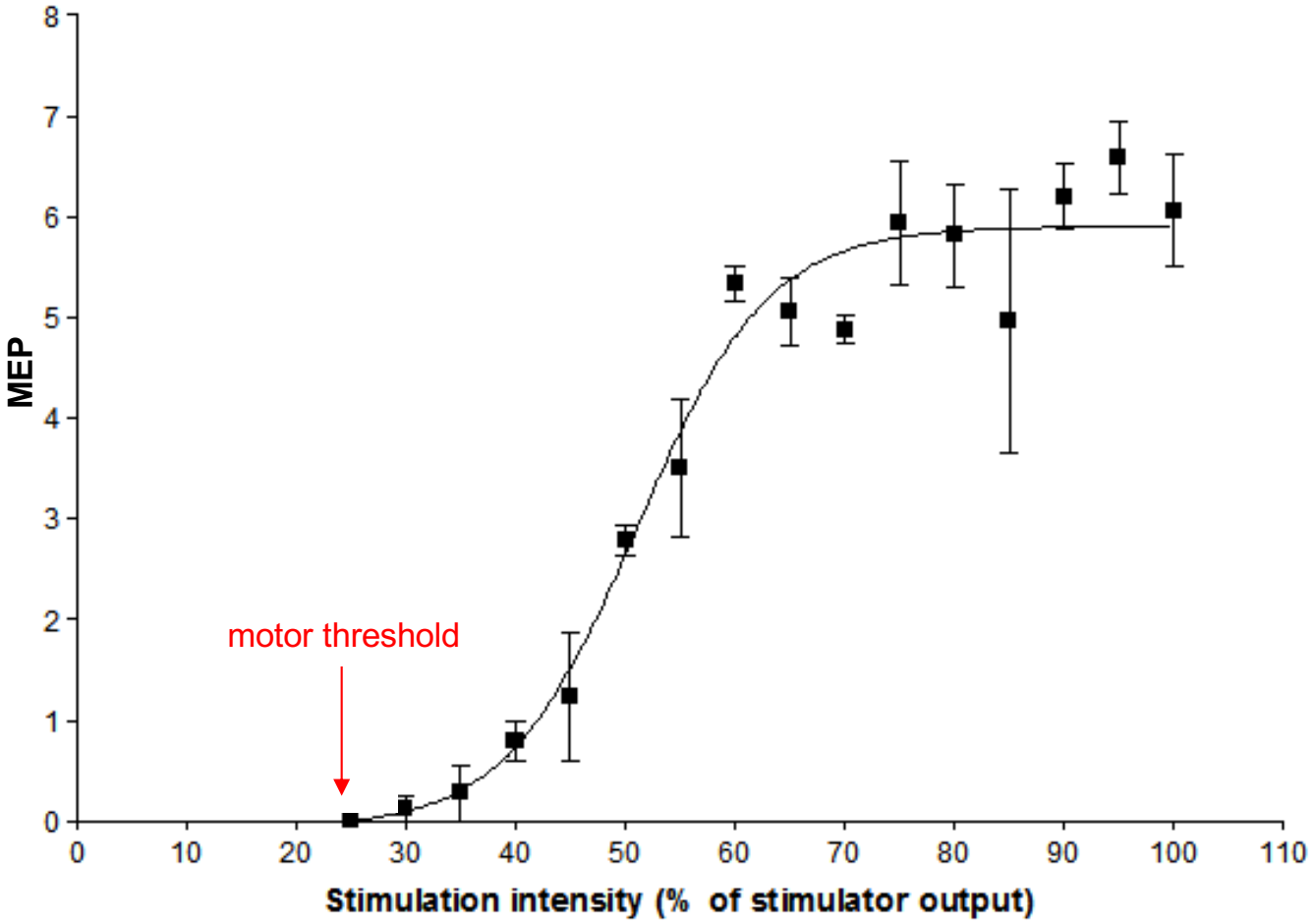
TMS Input-Output Recruitment Curves





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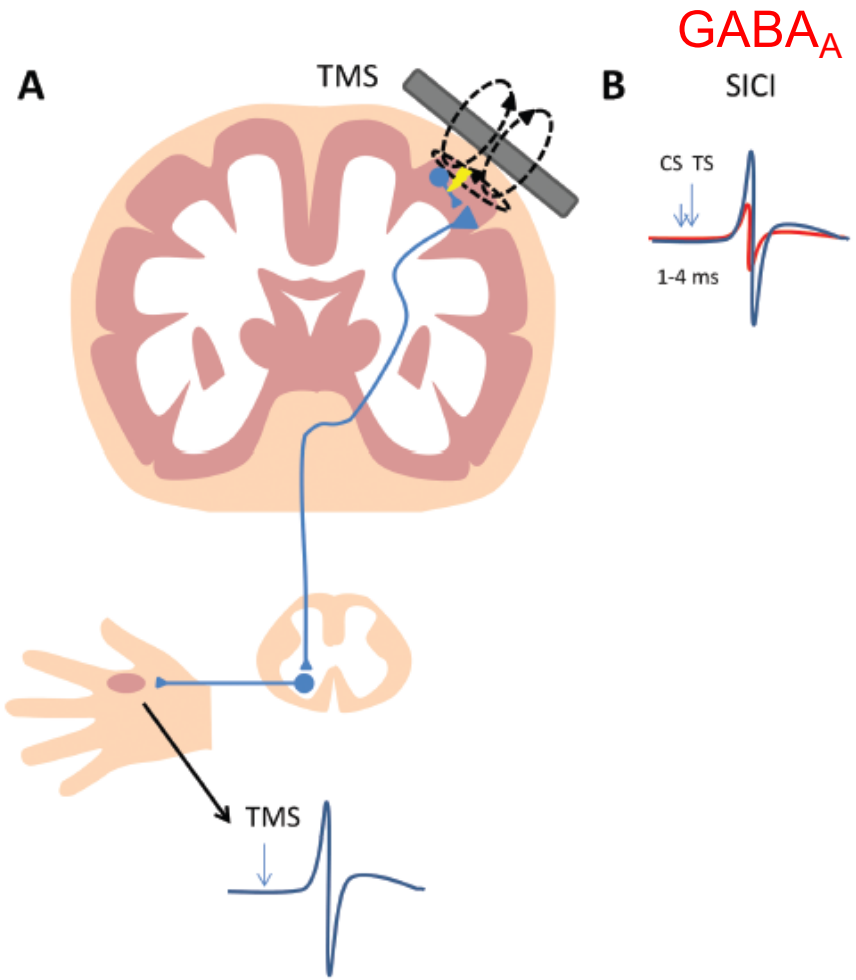
Paired pulses: Receptor-level specificity



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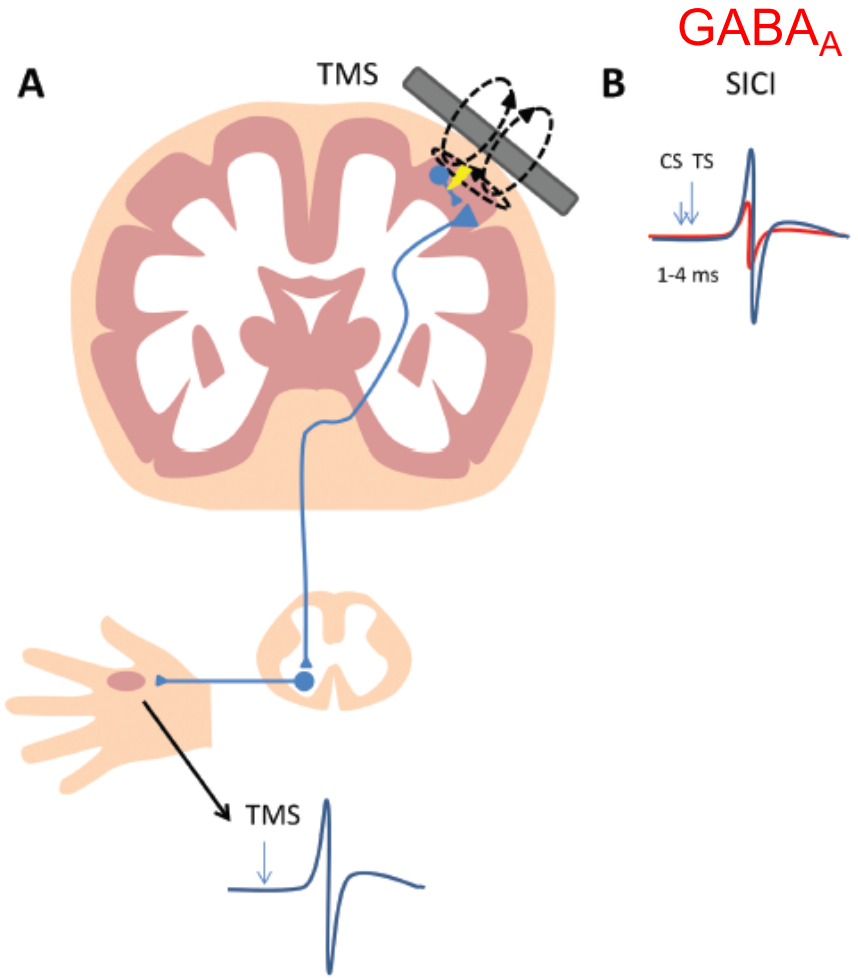
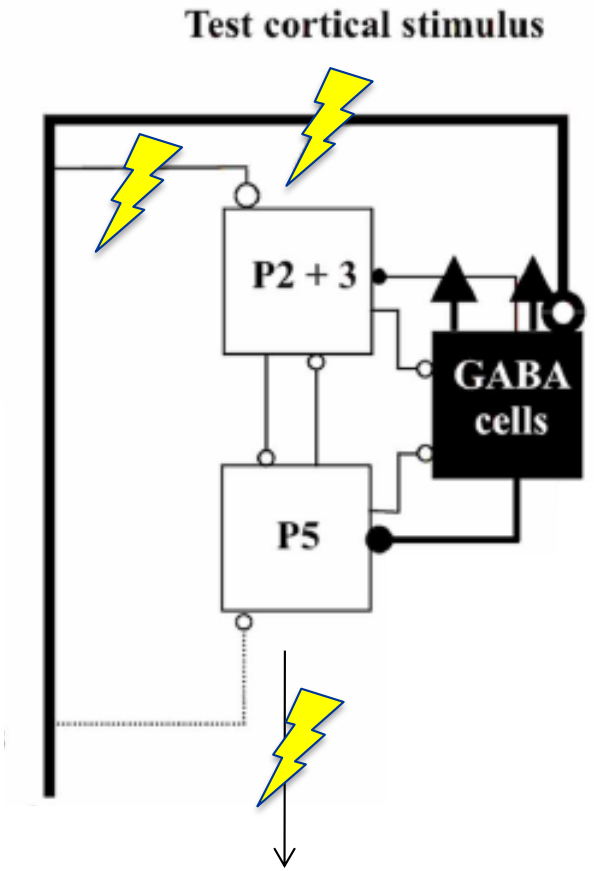
Paired pulses: Receptor-level specificity





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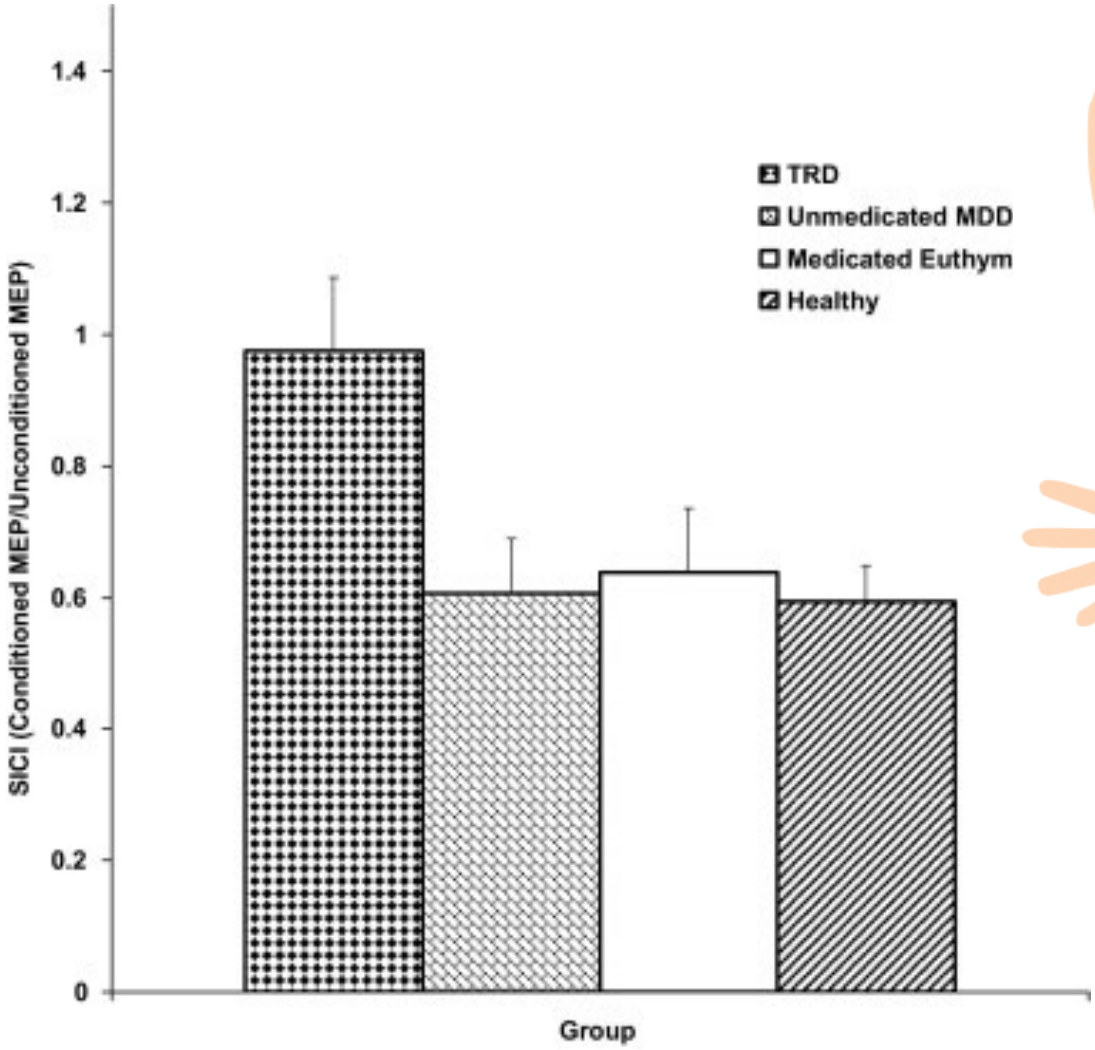
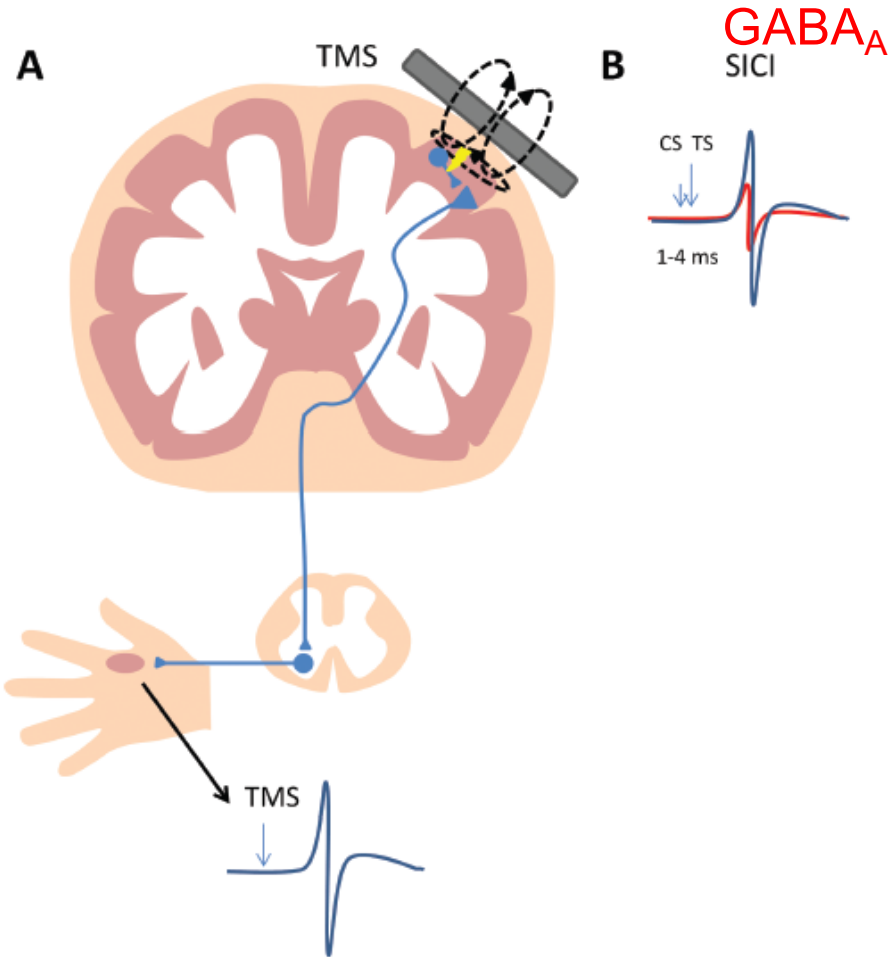
Short-interval cortical inhibition (SICI) deficits in treatment-resistant depression





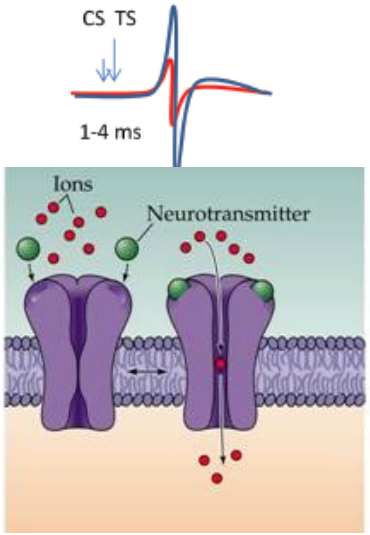
Levinson et al., 2010

National Institute of Mental Health

Translating Intracellular Recordings to TMS

$GABA_A$

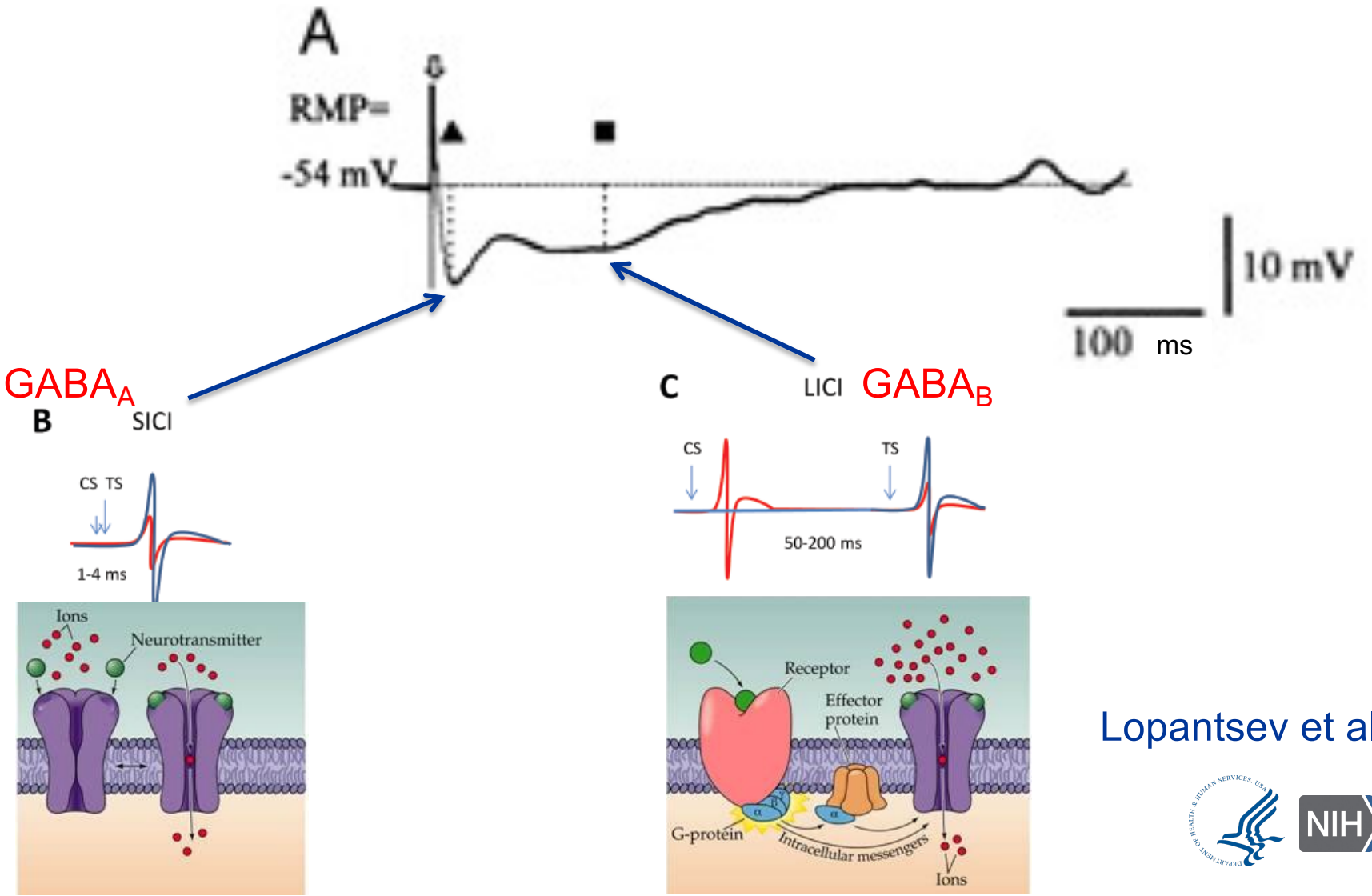
B SICI



Lopantsev et al., 1999

National Institute of Mental Health

Translating Intracellular Recordings to TMS



Lopantsev et al., 1999

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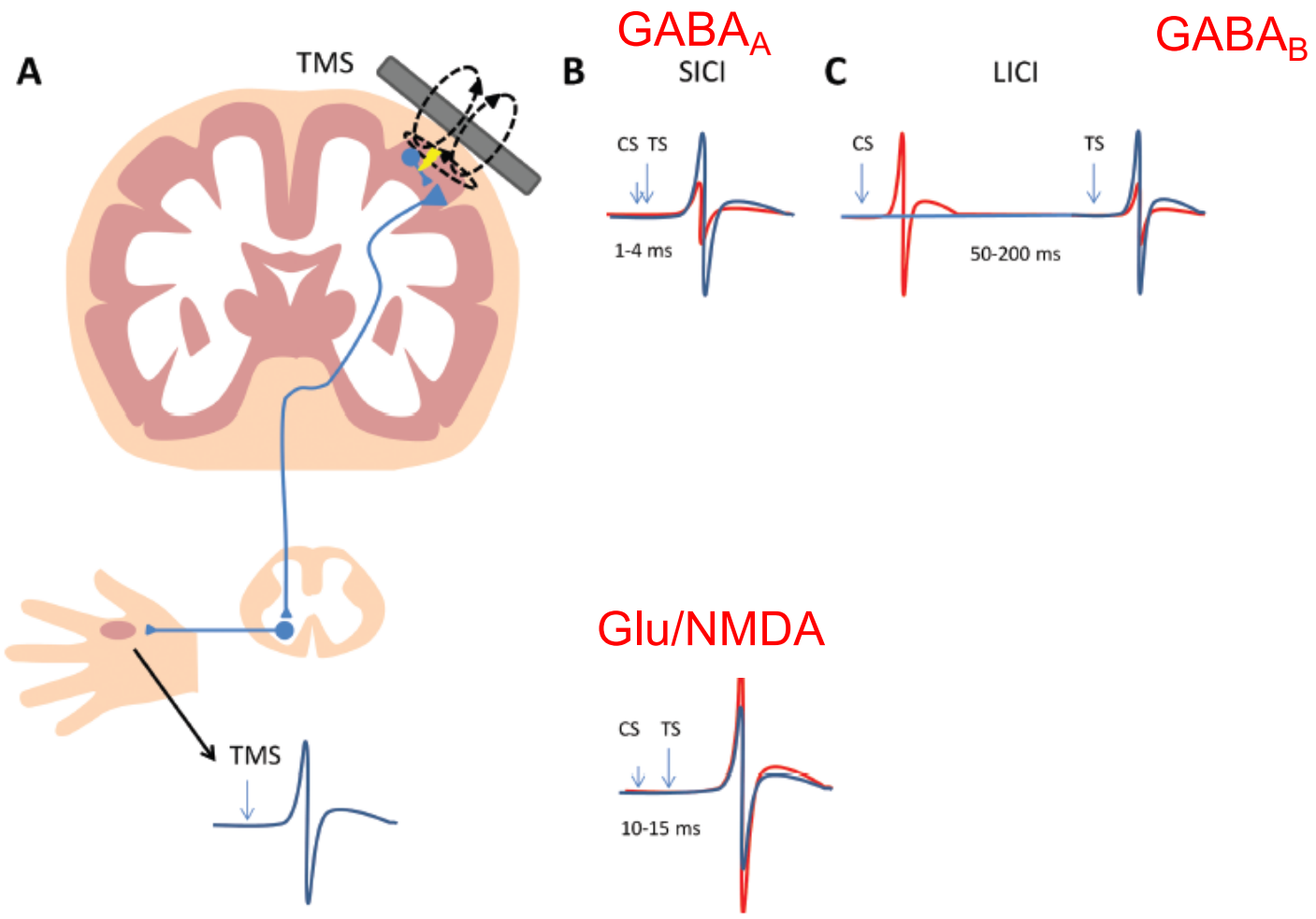
Paired pulses: Receptor-level specificity



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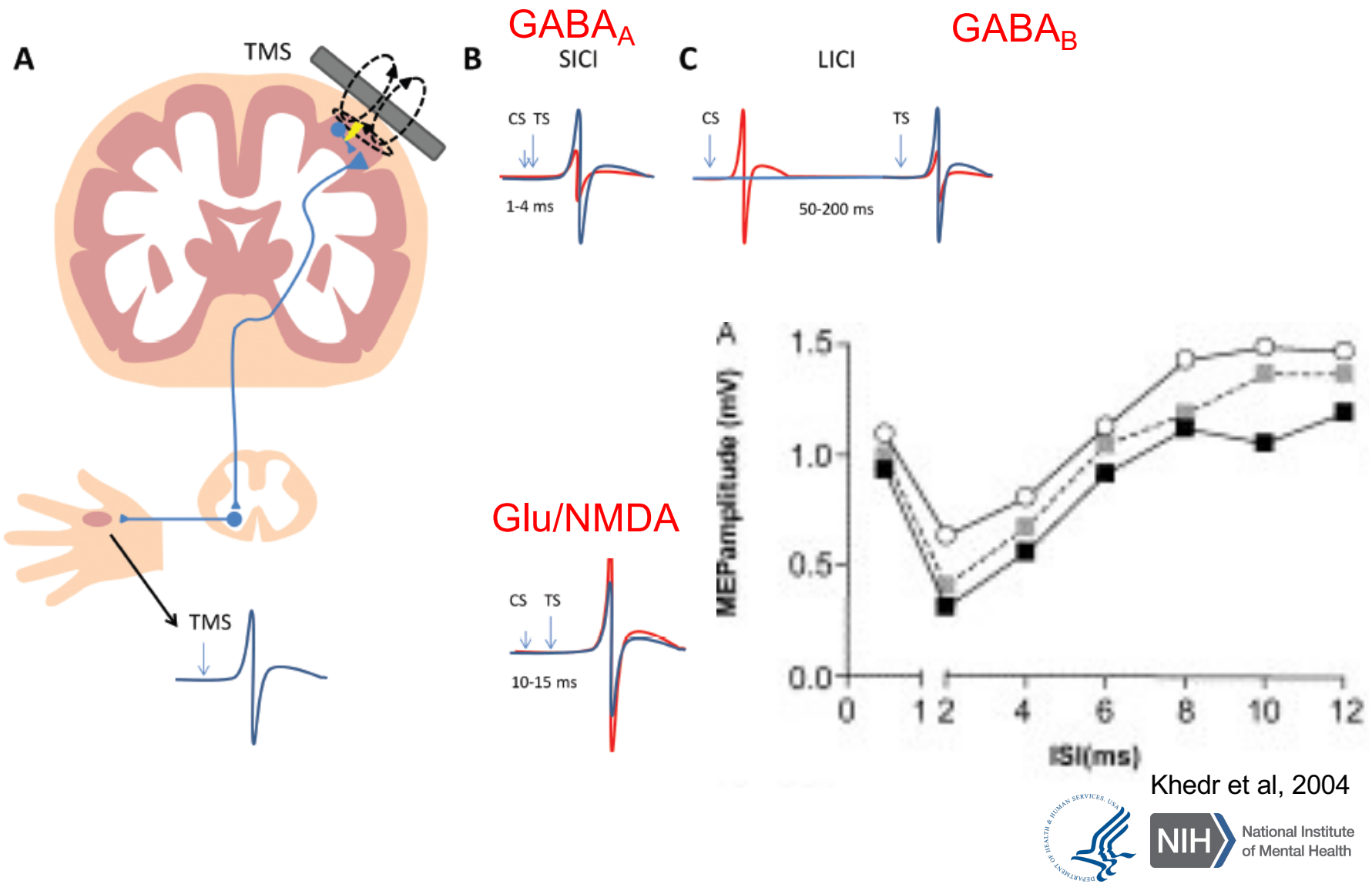
Paired pulses: Receptor-level specificity



Khedr et al, 2004

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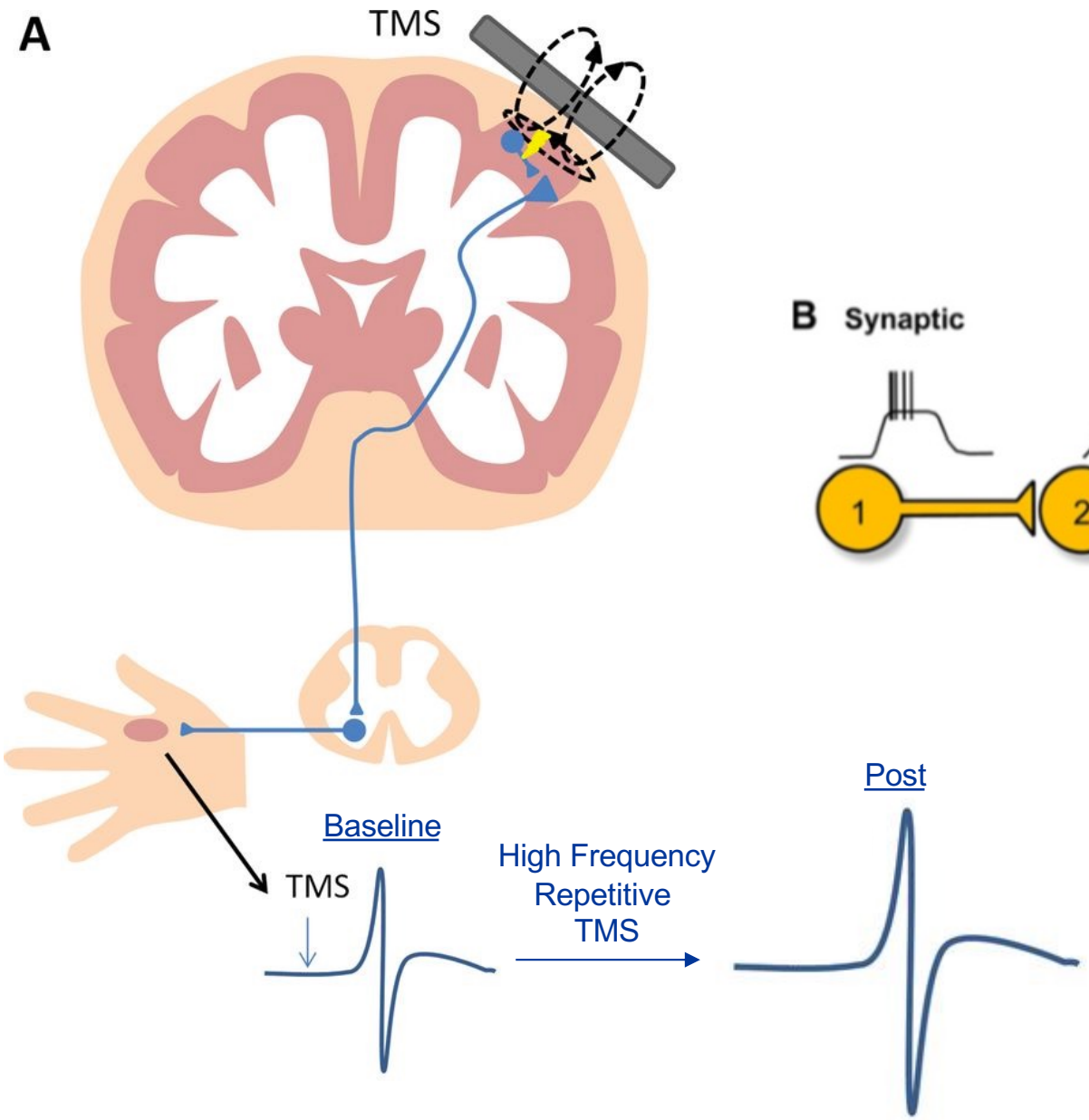
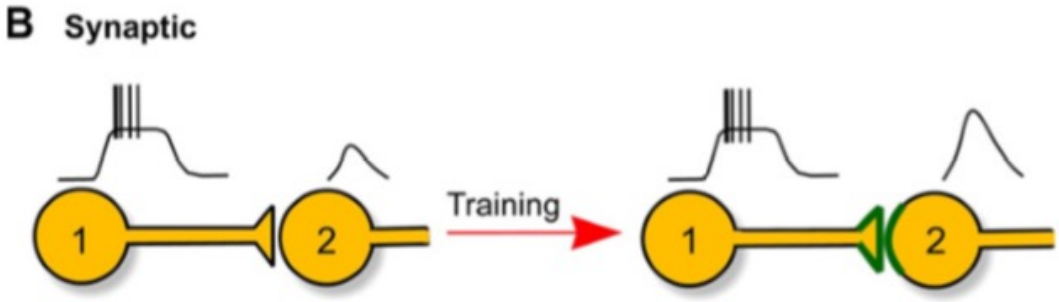
A framework for understanding TMS

1. Stimulating the brain non-invasively
2. The terminations and bends of axons are thought to be the elements stimulated by TMS
3. Cortical layer specificity: D and I-waves
4. Receptor-level specificity: TMS paired pulses
5. 1 more slide: repetitive TMS

Repetitive TMS is FDA cleared for depression





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Some contributions of *in vitro* / modelling studies towards understanding of electric fields

Electric field induced polarization

Elelctric fields induce hyperpolarization closest to the anode, and depolarization closest to the cathode

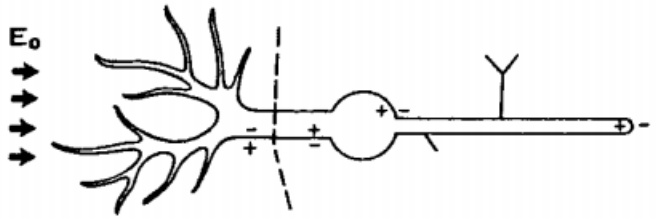

Fig. 1. Neuron structural model; dendrites to the left of the broken line. The arrows indicate the direction of the applied electric field $\bar{E}$, which gives the transmembrane potential polarities shown.

A Mathematical Model for Transmembrane Potentials Secondary to Extracellular Fields*

* This section was contributed by Dr. Lawrence Hause, Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin.

Article Author: Sances, Anthony,; Larson, Sanford J., joint author.

Journal Title: Electroanesthesia ; biomedical and biophysical studies /

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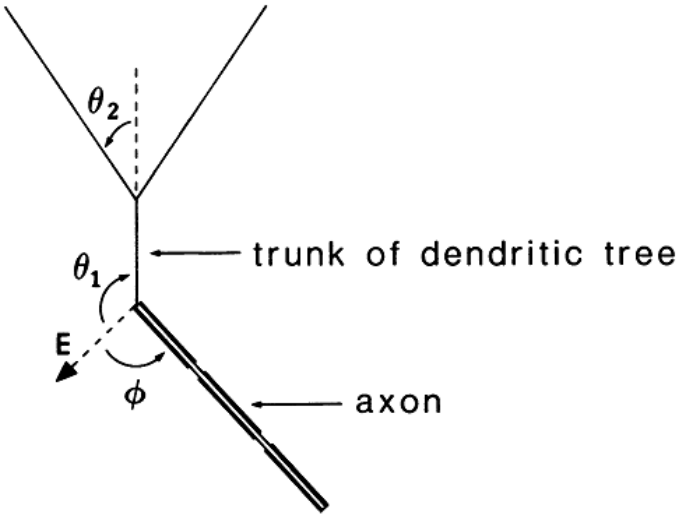
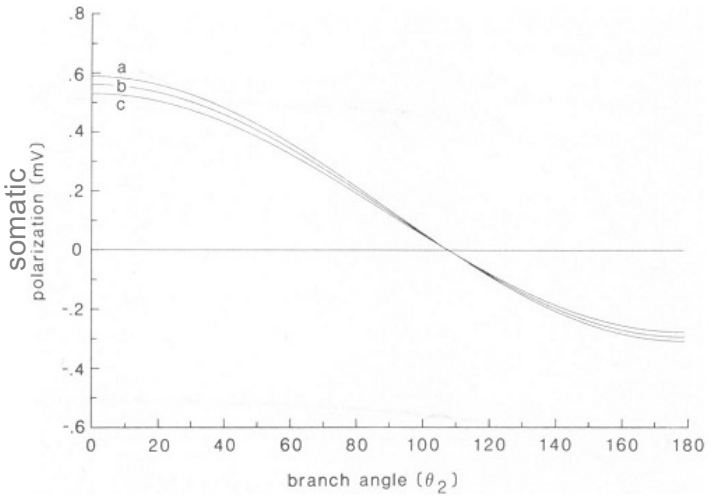
Some contributions of *in vitro* / modelling studies towards understanding of electric fields interactions with neurons

Degree of induced polarization and space constant (λ) governs intracellular distribution of polarization

Electric field induced polarization

Elelctric fields induce polarization at neuronal branch bends, terminations, and points of intracellular impedance change.





A MODEL FOR THE POLARIZATION OF NEURONS BY EXTRINSICALLY APPLIED ELECTRIC FIELDS

DANIEL TRANCHINA* AND CHARLES NICHOLSON‡

*Department of Biology, and Courant Institute of Mathematical Sciences, New York University, New York, New York 10003; and ‡Department of Physiology and Biophysics, New York University Medical Center, New York, New York 10016

BIOPHYS. J. © Biophysical Society

Volume 50 December 1986 1139–1156

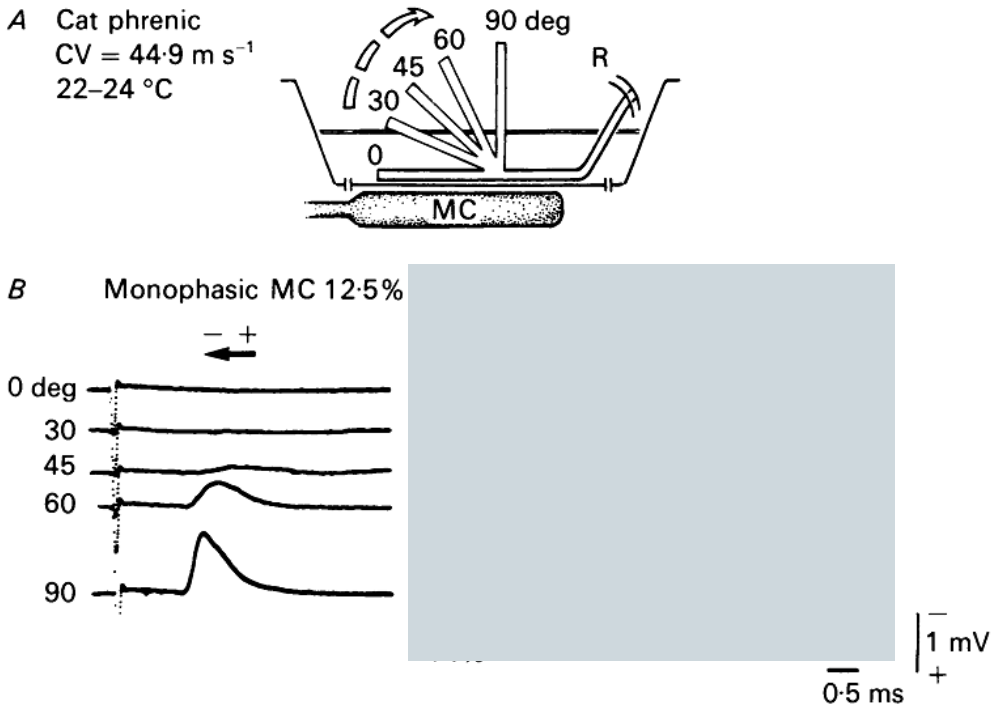
Some contributions of *in vitro* / modelling studies towards understanding resulting fields

Bends create a point of changing electric field

The derivative of the electric field, or 2nd derivative of induced membrane voltage, dictates points of greatest excitation (activating function)

Electric field induced polarization

Electric field along the activating function and induced



MAGNETIC COIL STIMULATION OF STRAIGHT AND BENT AMPHIBIAN AND MAMMALIAN PERIPHERAL NERVE *IN VITRO*: LOCUS OF EXCITATION

By P. J. MACCABEE, V. E. AMASSIAN*, L. P. EBERLE* and R. Q. CRACCO

*From the Departments of Neurology and *Physiology, SUNY Health Science Center, 450 Clarkson Avenue, Brooklyn, NY 11203, USA*

Journal of Physiology (1993), **460**, *pp.* 201–219

Some contributions of *in vitro* / modelling studies towards understanding of electric fields

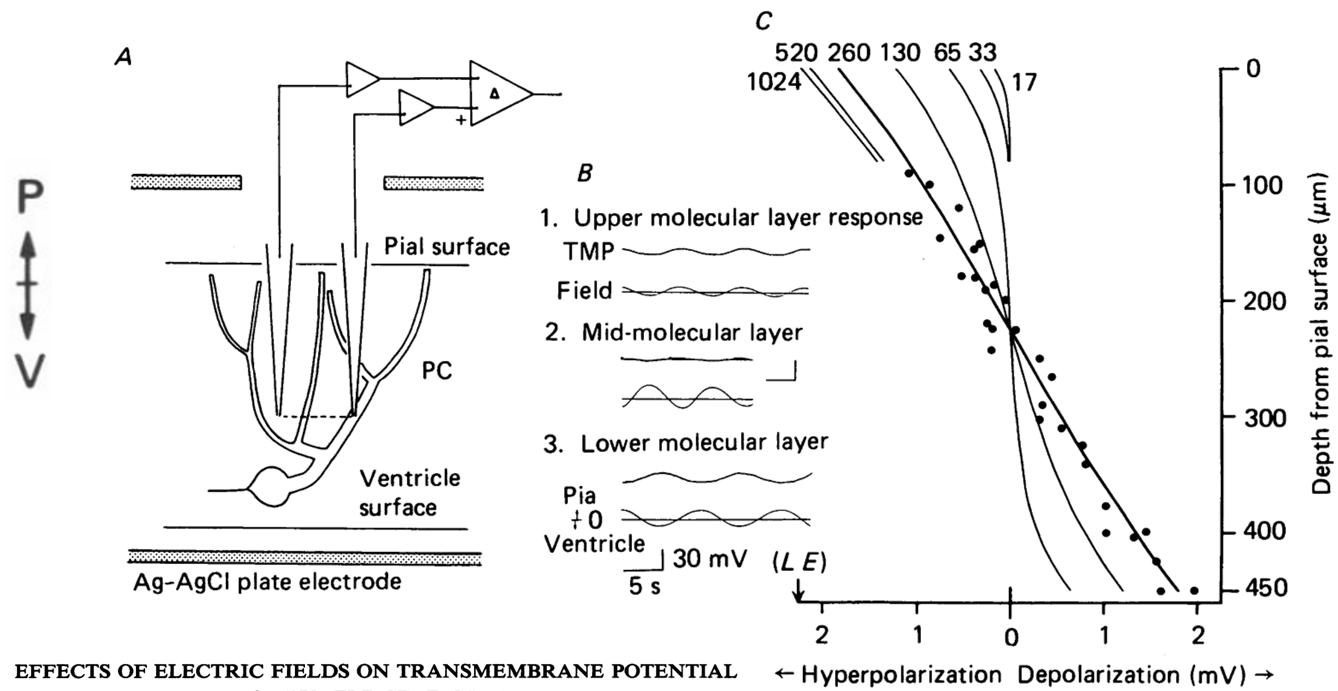
Electric field induced polarization

HRP Staining of individually recorded Purkinje and stellate cells during electric field stimulation

Electric fields induce polarization at neuronal branch bends, terminations and points of intracellular impedance change

Space constant (λ) proposed in a model to govern maximal polarization of a simple cable segment termination

simulation show the effects of neuronal morphology on induced polarization



EFFECTS OF ELECTRIC FIELDS ON TRANSMEMBRANE POTENTIAL AND EXCITABILITY OF TURTLE CEREBELLAR PURKINJE CELLS *IN VITRO*

By C. Y. CHAN*‡, J. HOUNSGAARD† and C. NICHOLSON*

*From the *Department of Physiology and Biophysics, New York University Medical Center, 550 First Avenue, New York, NY 10016 and †Institute of Neurophysiology, University of Copenhagen, Blegdamsvej 3C, DK-2200 Copenhagen N., Denmark*

Journal of Physiology (1988), **402**, *pp*. 751–771

J. Physiol. (1986), **371**, *pp*. 89–114

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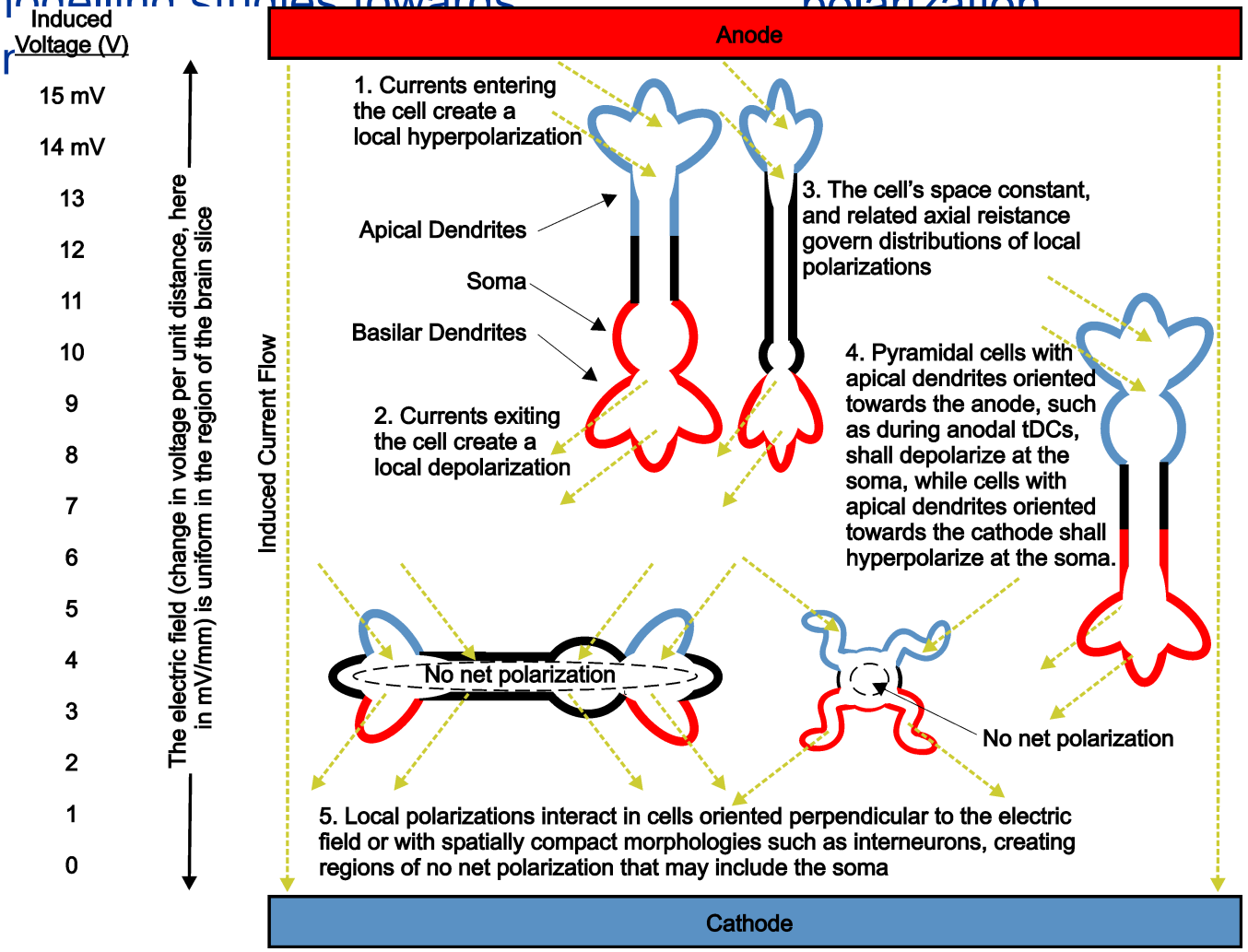
Some contributions of *in vitro* / modelling studies towards ur

Electric field induced polarization



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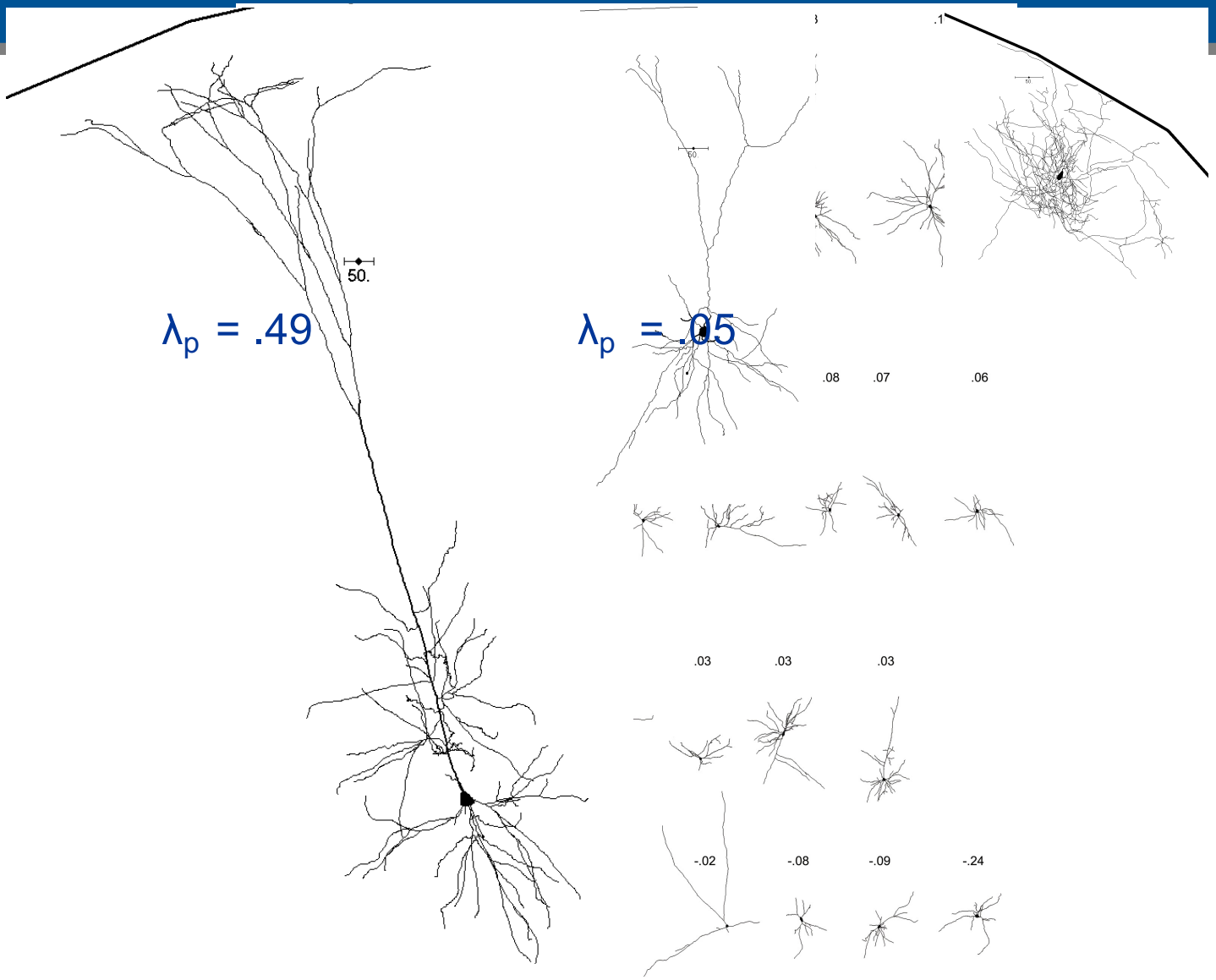

λ_p = .49

λ_p = .05

λ_p = .14

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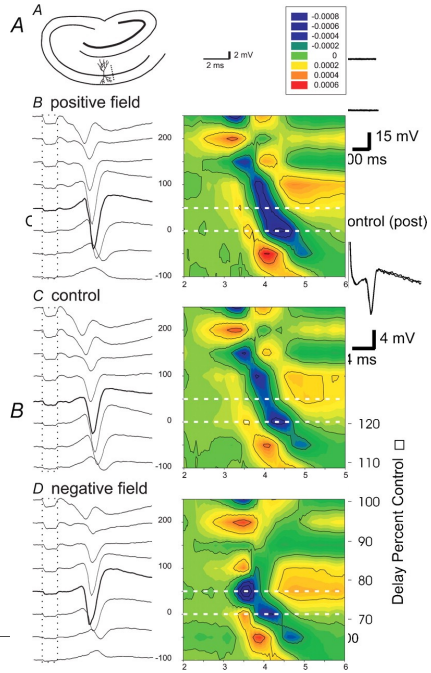
Some contributions of *in vitro* / modelling studies towards understanding of the mechanisms

Effects of Small/Endogenous Electric Fields

Electric fields shift the timing and amplitude of population spikes in a (quasi) linear manner



J Physiol Volume 557, Number 1, 175-190, May 15, 2004 DOI: 10.1113/jphysiol.2003.055772

Effects of uniform extracellular DC electric fields on excitability in rat hippocampal slices *in vitro*

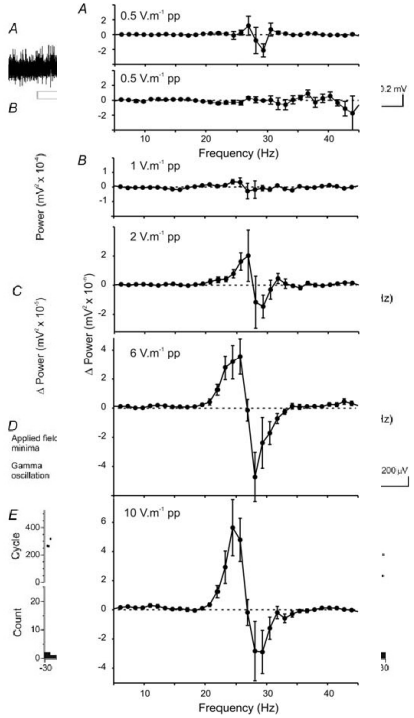
Marom Bikson[1], Masashi Inoue[2], Hiroki Akiyama[2], Jackie K. Deans[1], John E. Fox[1], Hiroyoshi Miyakawa[2] and John G. R. Jefferys[1]

[1] *Department of Neurophysiology, University of Birmingham, Birmingham, UK* [2] *Department of Life Science, Tokyo University of Pharmacy and Life Science, Tokyo, Japan*

Some contributions of *in vitro* / modelling studies towards understanding of electric fields

Effects of Small/Endogenous Electric Fields

A low amplitude oscillating electric field has been shown to entrain ongoing oscillations.



J Physiol 583.2 (2007) pp 555–565

Sensitivity of coherent oscillations in rat hippocampus to AC electric fields

Jacqueline K. Deans, Andrew D. Powell and John G. R. Jefferys

Department of Neurophysiology, Division of Neuroscience, Medical School, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK