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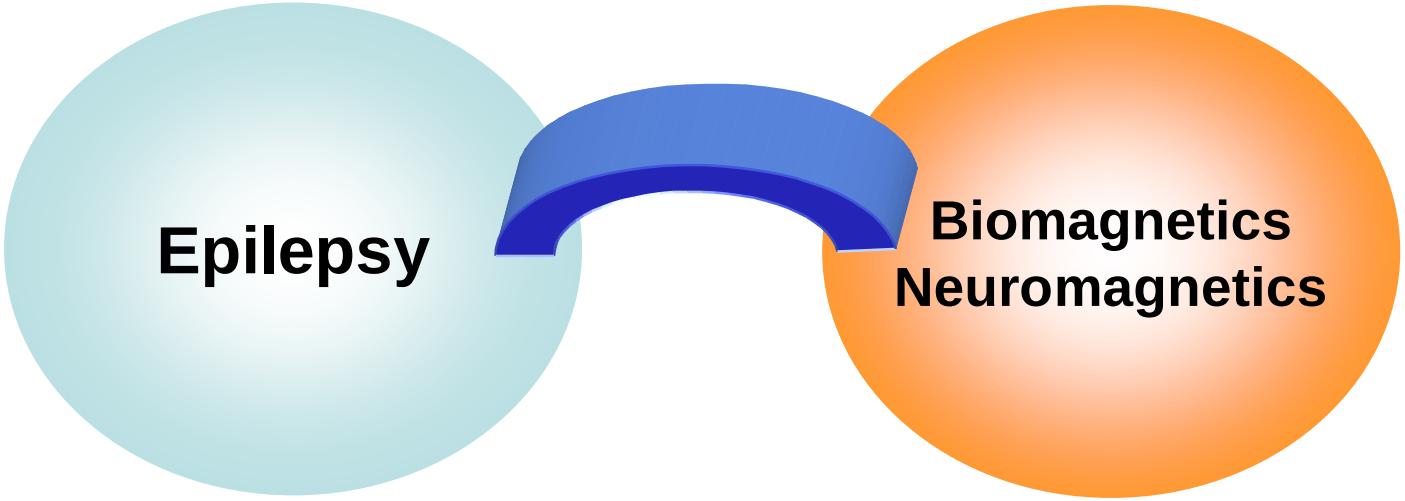
Biomagnetic and Neuromagnetic Approaches to the Study of Epilepsy

Shoogo Ueno

Professor Emeritus, University of Tokyo
Professor, Graduate School of Engineering, Kyushu University

1. Biomagnetics and Epilepsy
2. TMS (Transcranial Magnetic Stimulation)
3. MEG (Magnetoencephalography)
4. MRI (Magnetic Resonance Imaging)
5. Magnetic Control of Cell Orientation and Cell Growth
6. Iron and Epilepsy: RF Exposure and Oxidative Stress

Biomagnetics and Epilepsy



TMS
MEG
MRI
Magnetic Orientation
Magnetic Proteins
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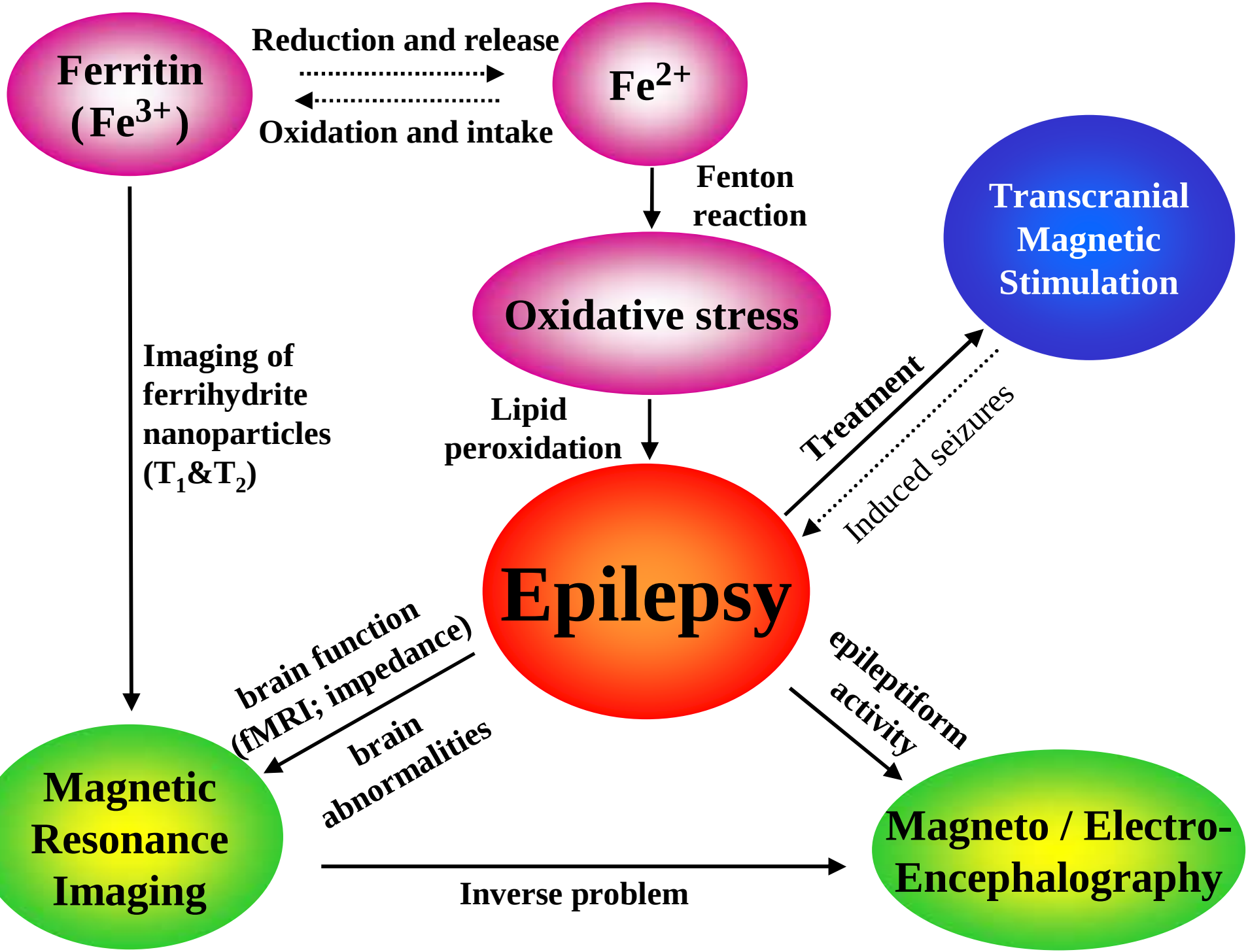
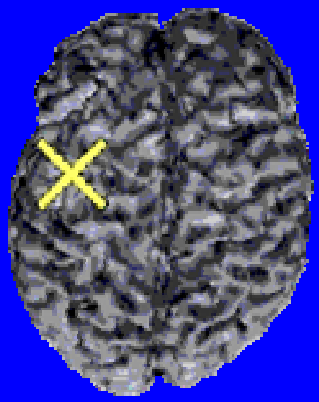
Epilepsy is one of the central nervous system diseases related to seizures caused by abnormally synchronized discharges of neuronal electrical activities in the brain. Biomagnetics may contribute to its diagnosis and treatment.

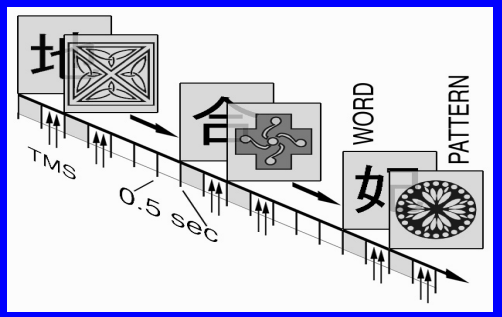

Ferritin
(Fe3+)
Reduction and release
Oxidation and intake
Fe2+
Fenton
reaction
Transcranial
Magnetic
Stimulation
Oxidative stress
Imaging of
ferrihydrite
nanoparticles
(T1&T2)
Lipid
peroxidation
Treatment
Induced seizures
Epilepsy
brain function
(fMRI; impedance)
brain
abnormalities
epileptiform
activity
Magnetic
Resonance
Imaging
Inverse problem
Magneto / Electro-
Encephalography

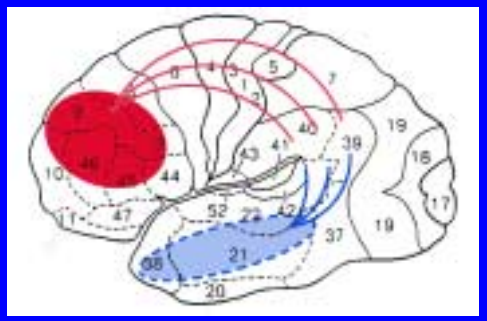
TMS and Brain Dynamics

TMS

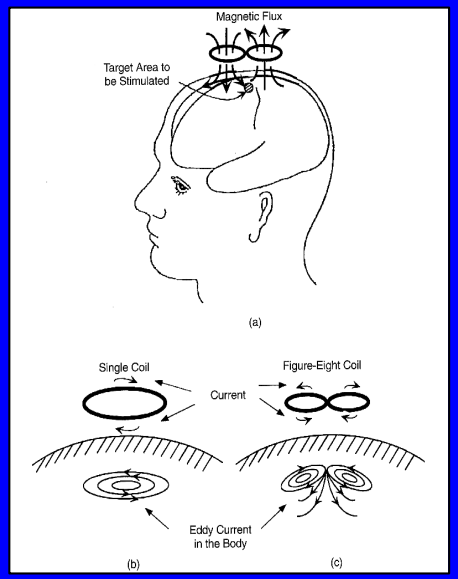


Brain Dynamics

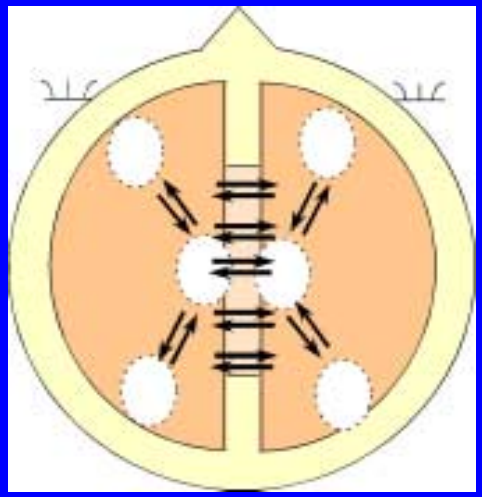




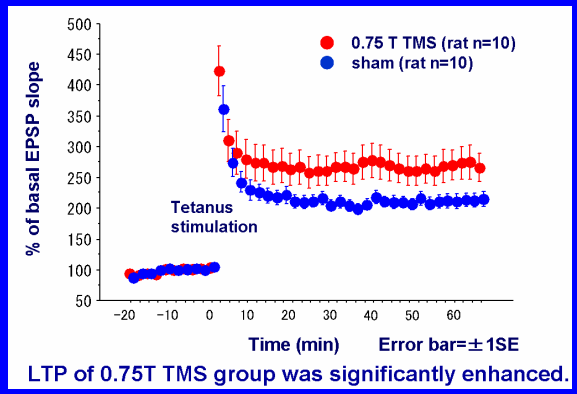
Working Memory Task



Principle of TMS



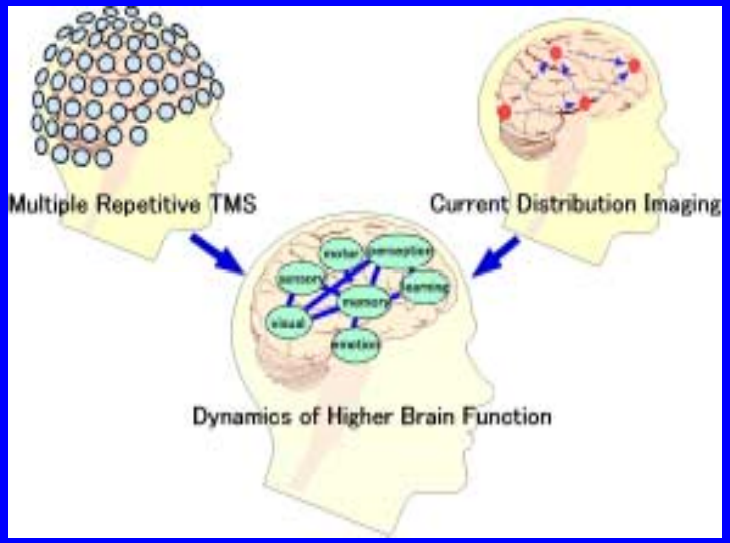
Neuronal Connectivity



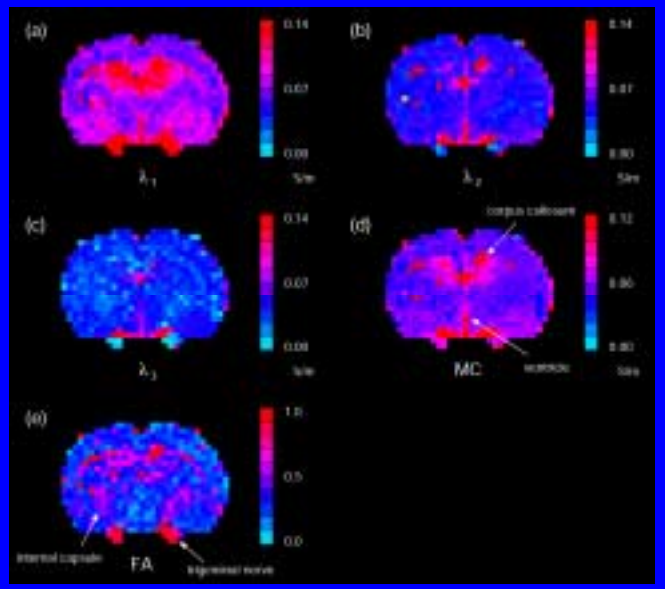
Long-Term Potentiation

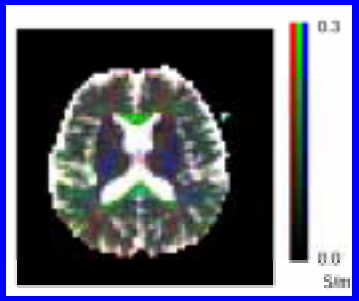
Therapeutic Application of TMS
Control of Neuronal Plasticity
Treatment of Depression

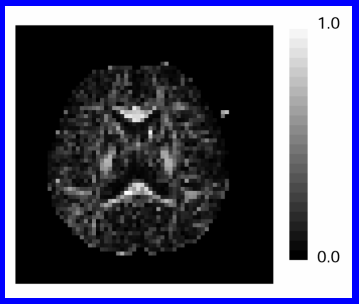
Biomagnetic Imaging and Brain Dynamics



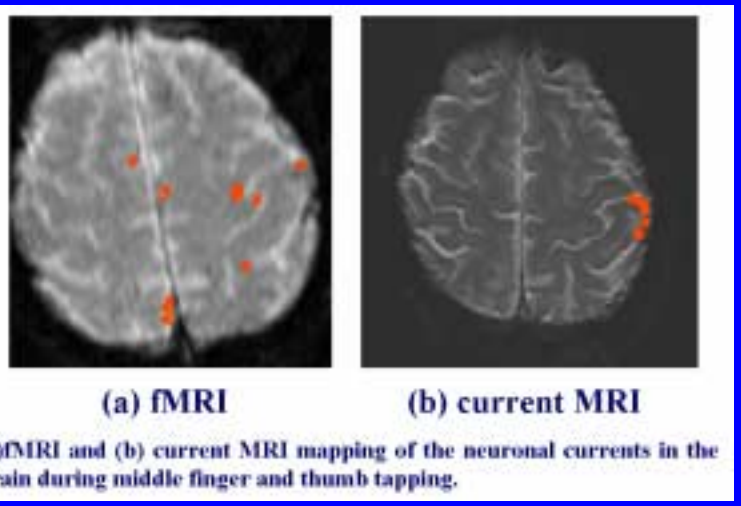
Study of Brain Dynamics by TMS, MRI, and EEG



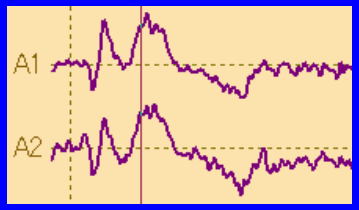


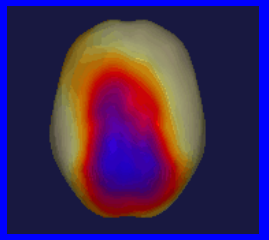


Conductivity Tensor MR Imaging



Current MR Imaging

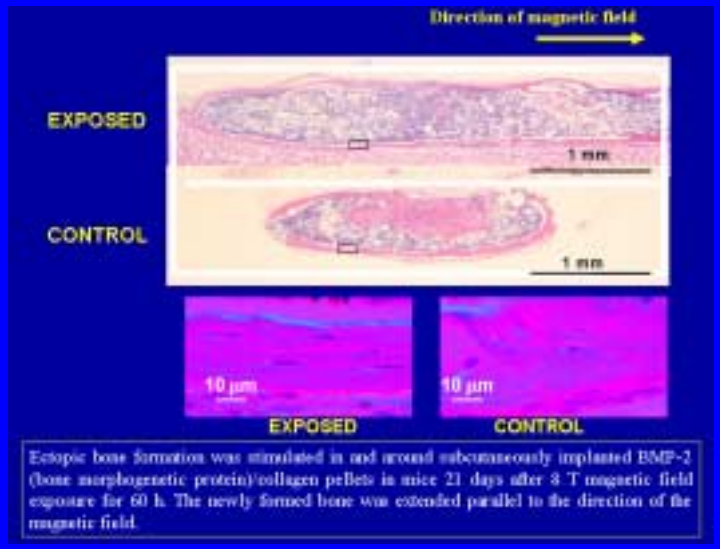




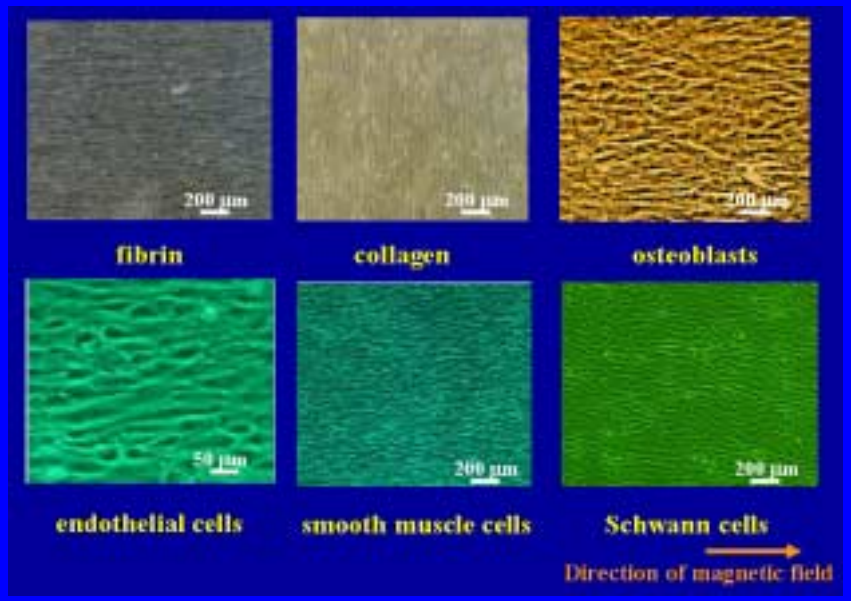
MEG and EEG

Parting of Water and Cell Orientation by Magnetic Fields

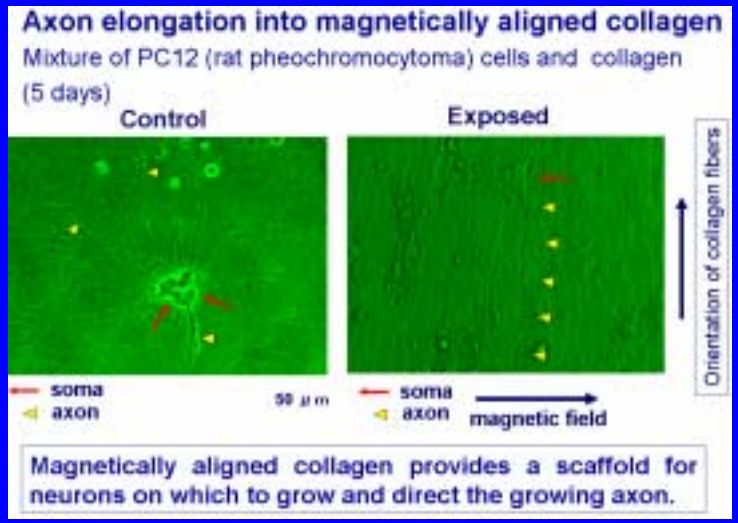
Parting of Water



Bone Growth by Magnetic Field

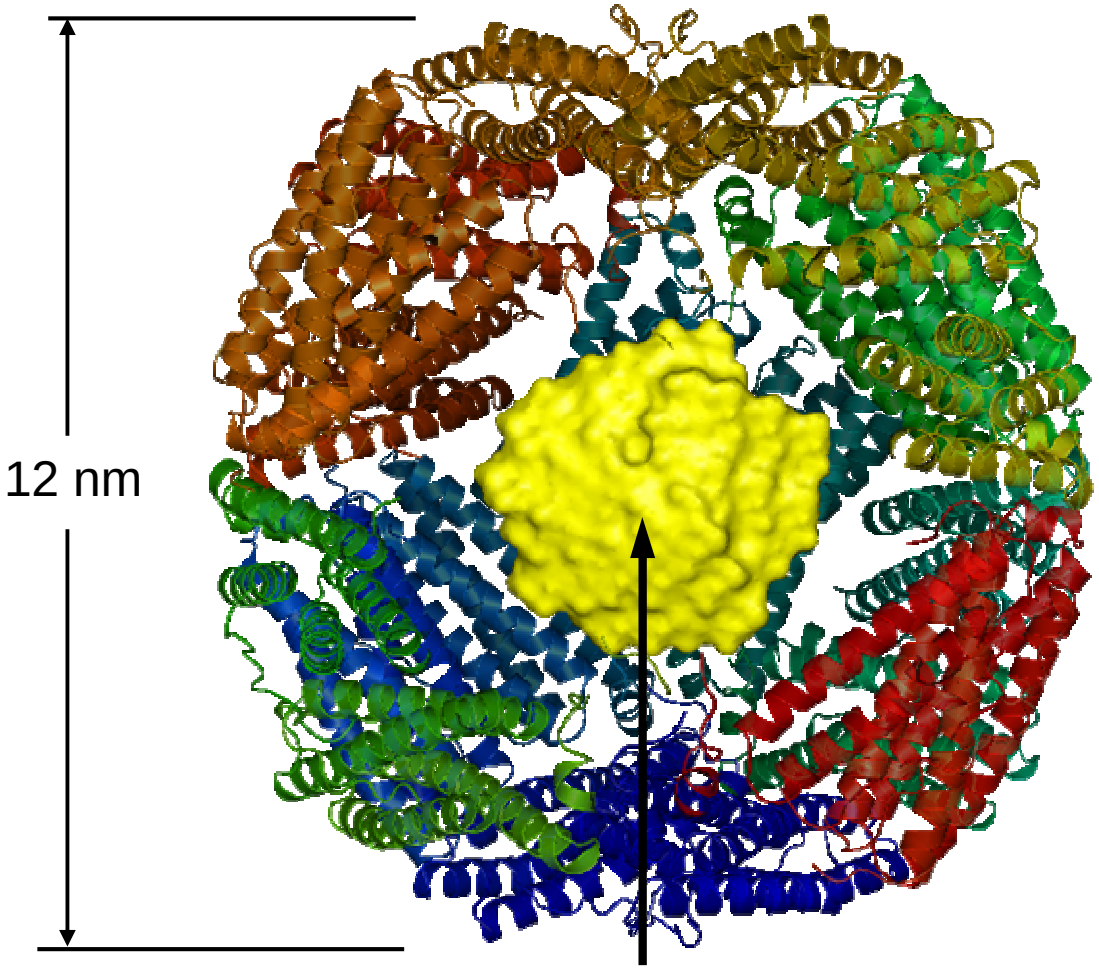


Magnetic Orientation of Adherent Cells



Axonal Growth by Magnetic Field

Ferritins: structure and properties



Apoferritin shell dissociation temperature ~ 80 º C;
pH stability range: 2-12

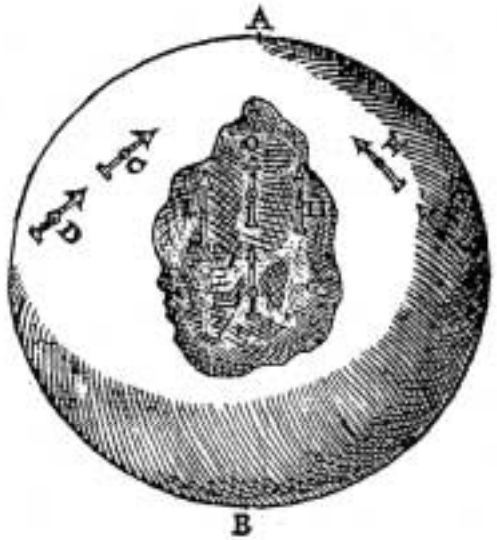
R.R. Crichton et al., Biochem. J. 133, pp. 289-299 (1973)

Lowest cohesion energy points:
3- and 4-fold symmetry axis

Ferrihydrite nanoparticle (Fe,O,H,P) of radius ≤4 nm (≤ 4500 Fe^{3+} ions)
Average magnetic moment of 500-1000 μ_B, J ~ 30-100 kJm^{-3}.

F. Brem, G. Stamm and A.M. Hirt, J. App. Phys. 99, 123906 (2006)

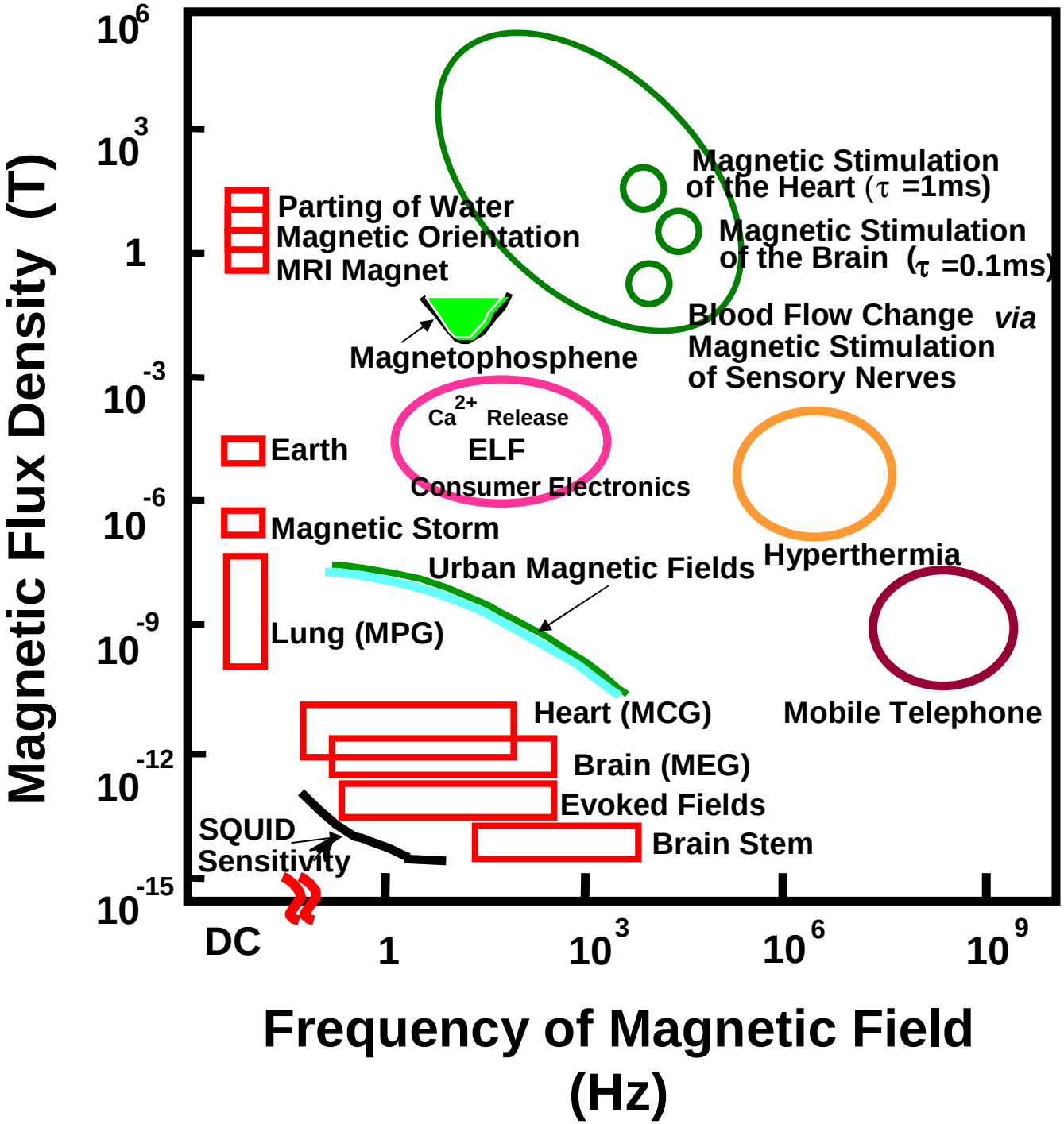
William Gilbert, Father of Magnetism
"The Earth is itself a huge magnet."



De Magnete, William Gilbert (1600)

"Magnetic force is animate or imitates life; and in many things surpasses human life, while this is bound up in the organic body."

-William Gilbert, 1600


Magnetic Flux Density (T)
10^6
10^3
1
10^-3
10^-6
10^-9
10^-12
10^-15
Parting of Water
Magnetic Orientation
MRI Magnet
Magnetophosphene
Magnetic Stimulation of the Heart (τ =1ms)
Magnetic Stimulation of the Brain (τ =0.1ms)
Blood Flow Change via Magnetic Stimulation of Sensory Nerves
Ca2+ Release
ELF
Consumer Electronics
Earth
Magnetic Storm
Urban Magnetic Fields
Hyperthermia
Lung (MPG)
Heart (MCG)
Mobile Telephone
Brain (MEG)
Evoked Fields
Brain Stem
SQUID Sensitivity
DC
1
10^3
10^6
10^9
Frequency of Magnetic Field (Hz)

- Iron and Epilepsy: Oxidative stress
- MEG / EEG and Epilepsy
- TMS Treatment for Epilepsy
- MRI and Epilepsy
- Neuro-regeneration

Iron and Epilepsy: Oxidative stress

• Injecting ferrous or ferric chloride into the sensorimotor cortex results in chronic recurrent focal paroxysmal electroencephalographic discharges as well as behavioral convulsions and electrical seizures. Iron-filled macrophages, ferruginated neurons, and astroglial cells surrounded the focus of seizure discharge
Willmore LJ, et al. Ann Neurol 4:329-336, 1978

• Cerebral contusion causes extravasation of red blood cells associated with deposition of hemosiderin, gliosis, neuronal loss and occasionally the development of seizures. Free radical reactions initiated by iron may be a fundamental reaction associated with brain injury responses, and with posttraumatic epileptogenesis.
Willmore LJ, et al. Int. J. Devl. Neuroscience 9: 175-180, 1991

• Epileptic seizures are a common feature of mitochondrial dysfunction associated with mitochondrial encephalopathies. Recent work suggests that chronic mitochondrial oxidative stress and resultant dysfunction can render the brain more susceptible to epileptic seizures.
Patel M, Free Rad. Biol. & Med. 37: 1951–1962, 2004

MEG / EEG and Epilepsy

MEG combined with EEG can accurately identify the sources for spike patterns.
This makes of MEG a very useful tool for presurgical evaluation and the analysis of epileptiform activity without the need for other, more invasive methods such as intracranial encephalography.

Otsubo H, et al., Epilepsia 42: 1523-1530, 2001.
Minassian BA, et al., Ann. Neurol. 46: 627-633, 1999 (Otsubo).
Bast T, et al., NeuroImage 25: 1232-1241, 2005 (Scherg).
Ebersole JS, Epilepsia 38: S1-S5, 1997
Iwasaki M, et al., Epilepsia 43: 415-424, 2002 (Nakasato)
Nakasato N, et al., Electroenceph. Clin. Neurophys. 171: 171-178, 1994

TMS: Magnetic treatment for Epilepsy

Epileptic conditions are characterized by an altered balance between excitatory and inhibitory influences at the cortical level. Transcranial magnetic stimulation (TMS) provides a noninvasive evaluation of separate excitatory and inhibitory functions of the cerebral cortex. In addition, repetitive TMS (rTMS) can modulate the excitability of cortical networks.
Tassinari CA, et al., Clin. Neurophys. 114: 777-798, 2003.

Low-frequency rTMS reduced interictal spikes, but its effect on seizure outcome has been measured to be not significant. However, focal stimulation for a longer duration tends to further reduce seizure frequency.
Joo EY, et al., Clin Neurophys. 118: 702-708, 2007.

It has been speculated that the depressant effect is related to long-term depression (LTD) of cortical synapses.
Iyer MB, et al., J. Neurosc. 23: 10867-10872, 2003.

Magnetic Resonance Imaging of Epilepsy

MRI can be used as an effective tool for presurgical evaluation of epilepsy
Rosenow F, Luders H, Brain 124: 1683-1700, 2001.

EEG combined with fMRI could be an effective option in the study of epilepsy and could be used to limit the regions to analyse by electrode implantation
Gotman J., et al, J. Magn. Res. Im. 23: 906-920, 2006

In ultrafast functional MRI timed to epileptic discharges recorded while the patients were in the imager and compared with images not associated with discharges it is possible to image a focal increase despite EEG measurements of generalized discharges.
Warach S, et al., Neurology 47: 89-93, 1996

Neuro-regeneration

Strong static magnetic fields can be used to modulate the neural electric impulses.
Sekino M, et al., IEEE Trans. Magn. 42: 3584-3586, 2006

Fibrin, osteoblasts, endothelial cells, smooth muscle cells, and Schwann cells can be oriented in the direction parallel to a strong (8 T) magnetic field. Collagen is oriented in the direction perpendicular to the magnetic field.
Ueno S, et al., J. Magn. Magn. Mat. 304: 122–127, 2006

It is possible to use this effect in artificial nerve grafts to enhance and orient the growth of damaged axons via strong magnetic fields.

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3. MEG (Magnetoencephalography)
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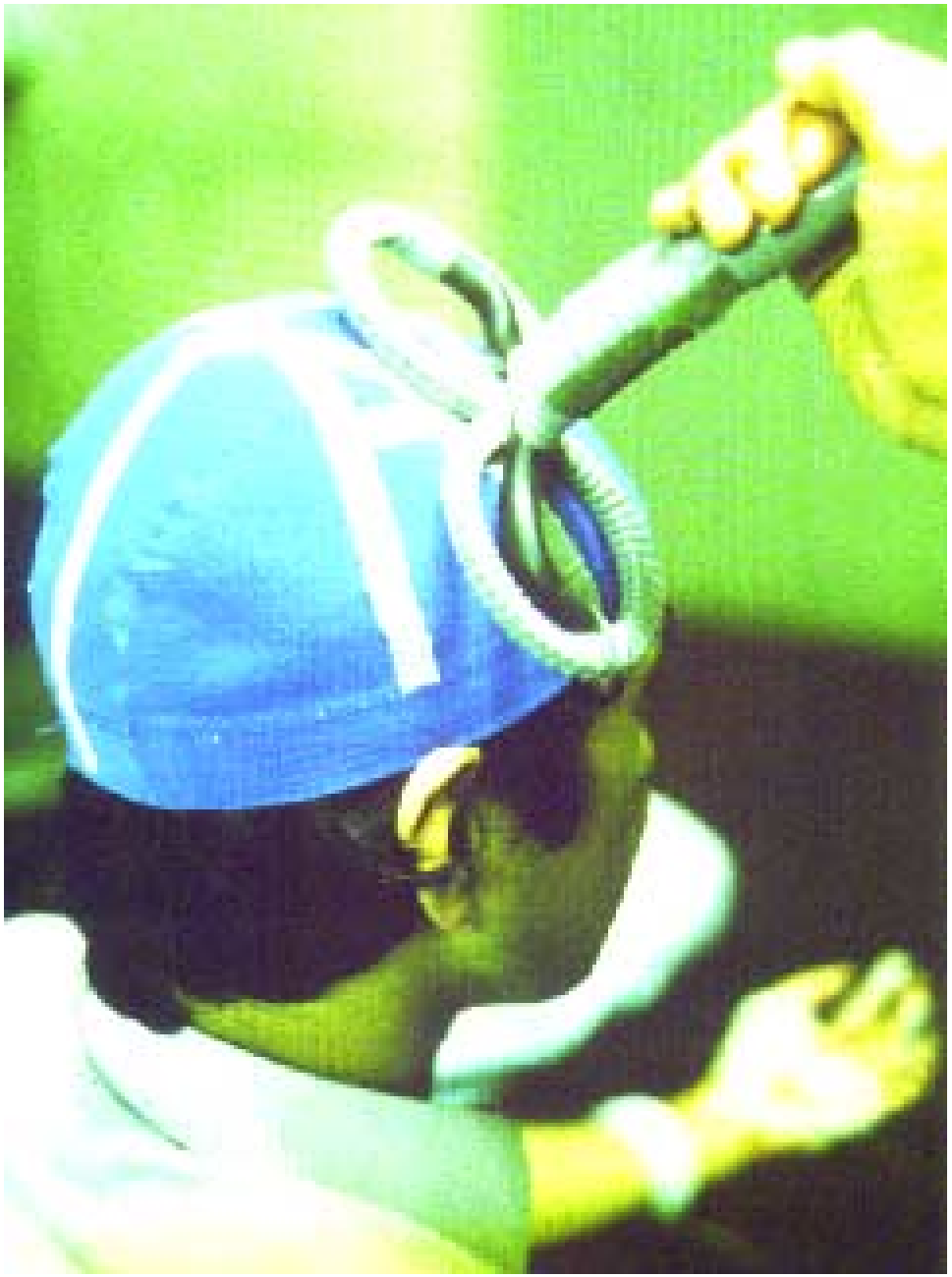
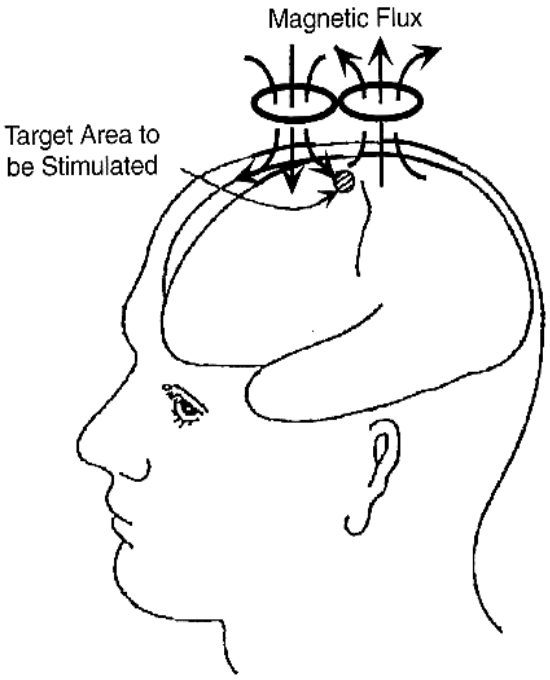
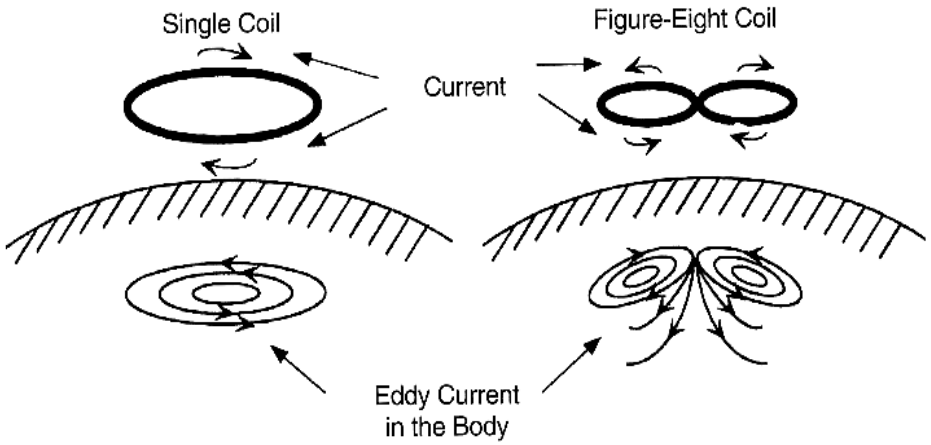
TMS（Transcranial Magnetic Stimulation)



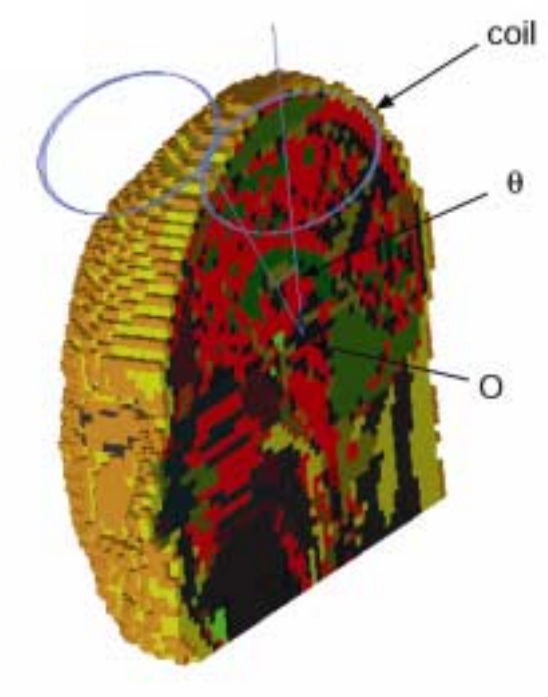


(a)

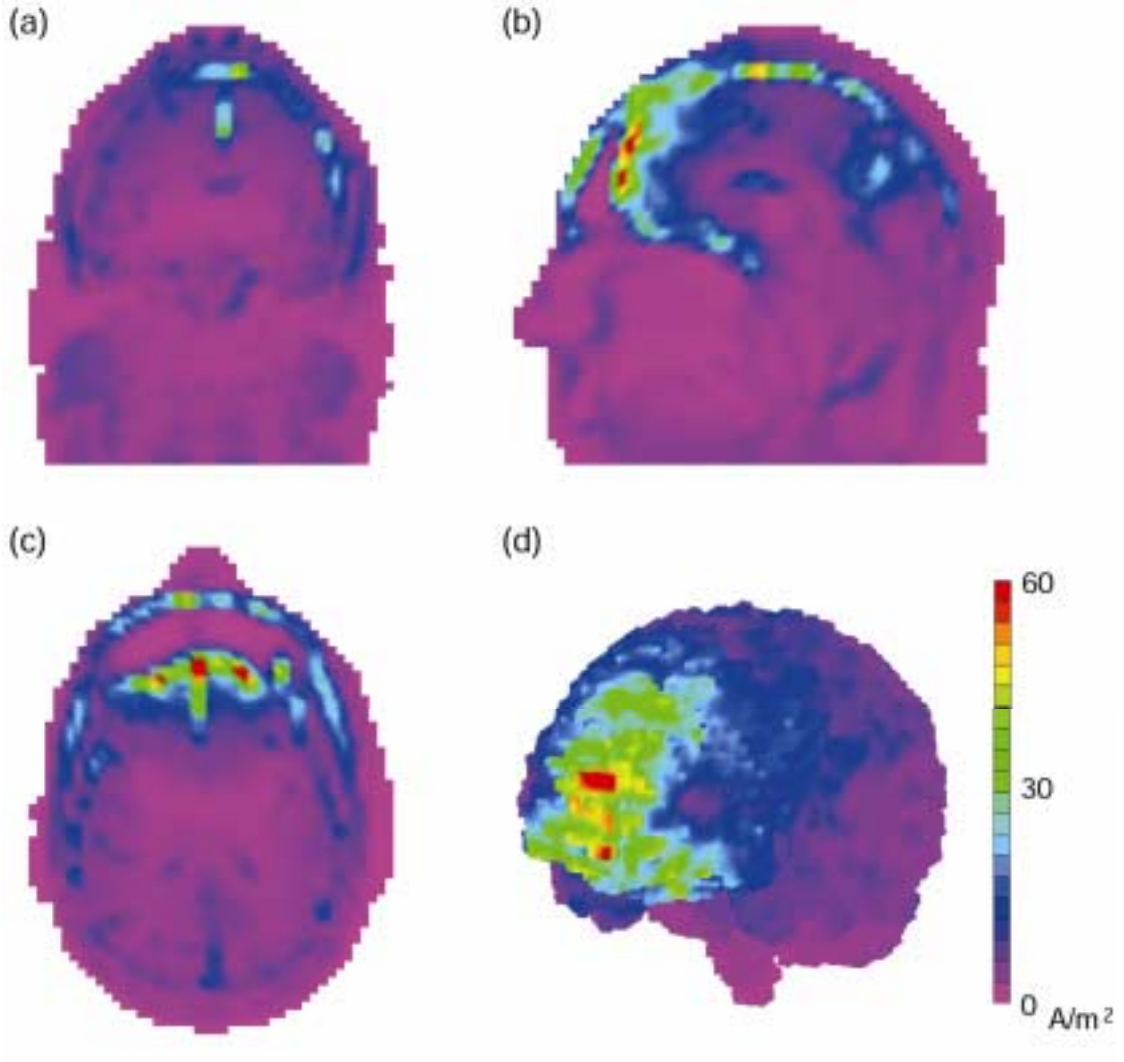


(b) (c)

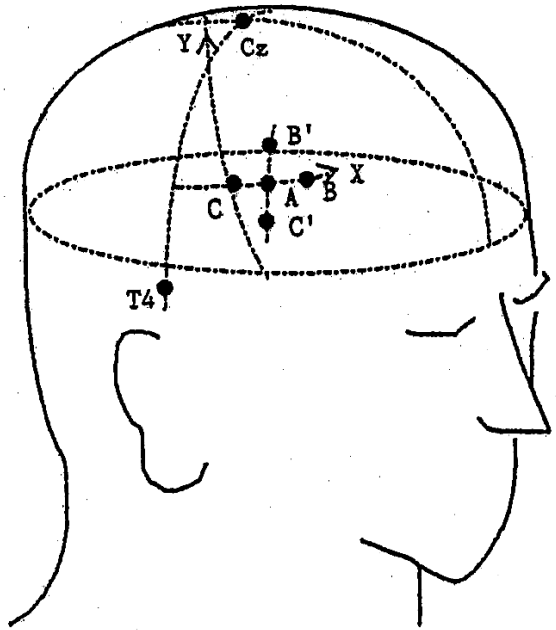
Current Distributions in TMS

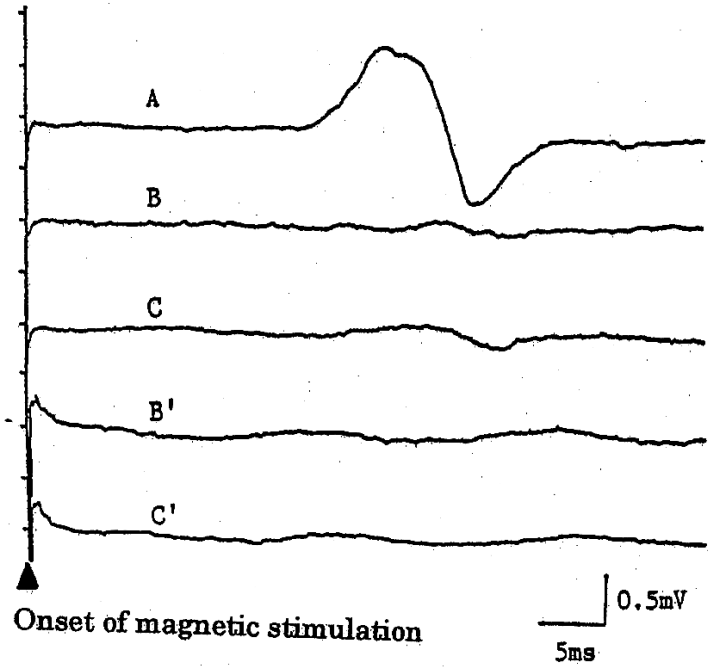


Numerical model of the human head

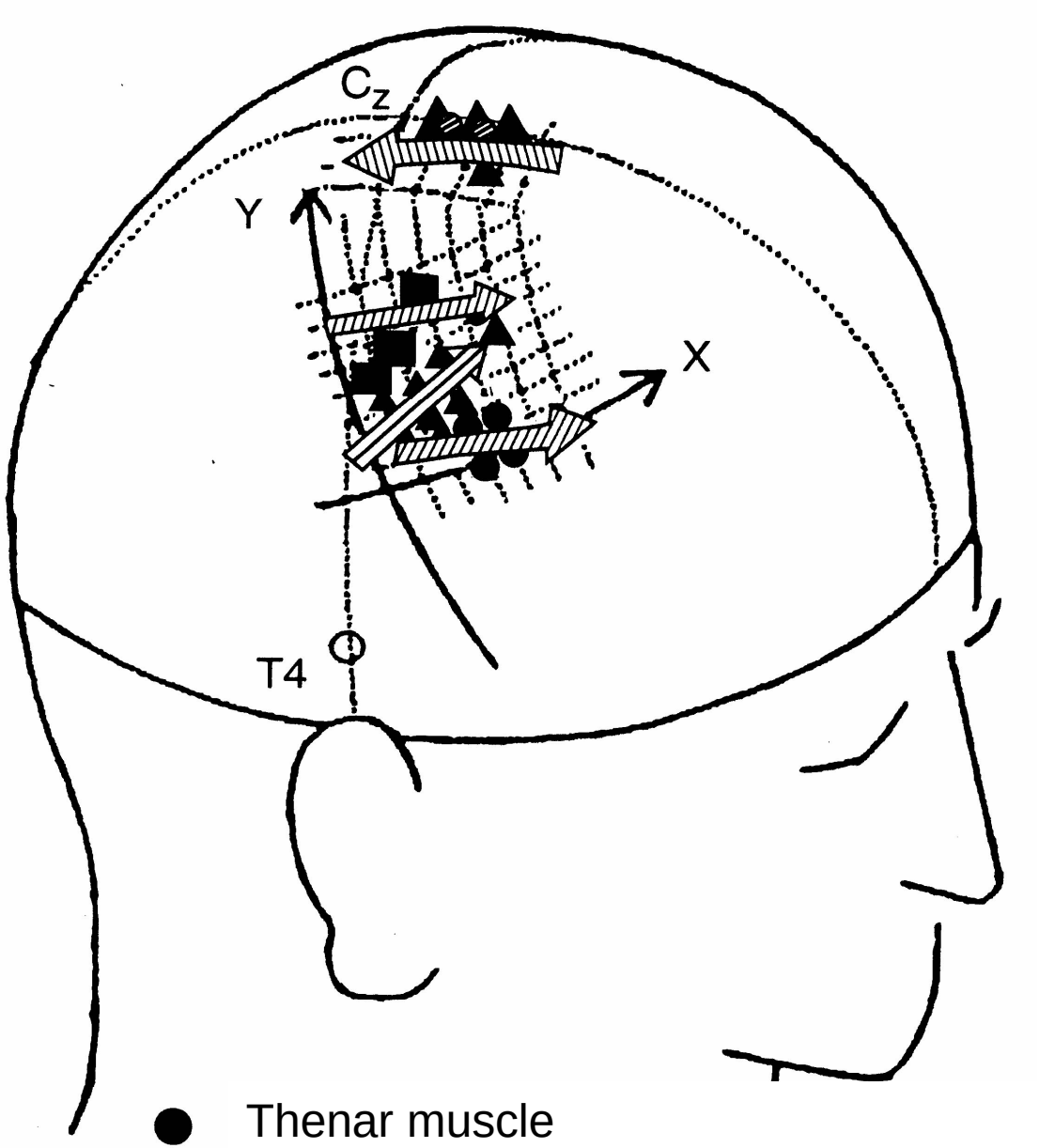


Current distributions in TMS represented in (a) coronal, (b) sagittal, and (c) transversal slices, and (d) the brain surface.





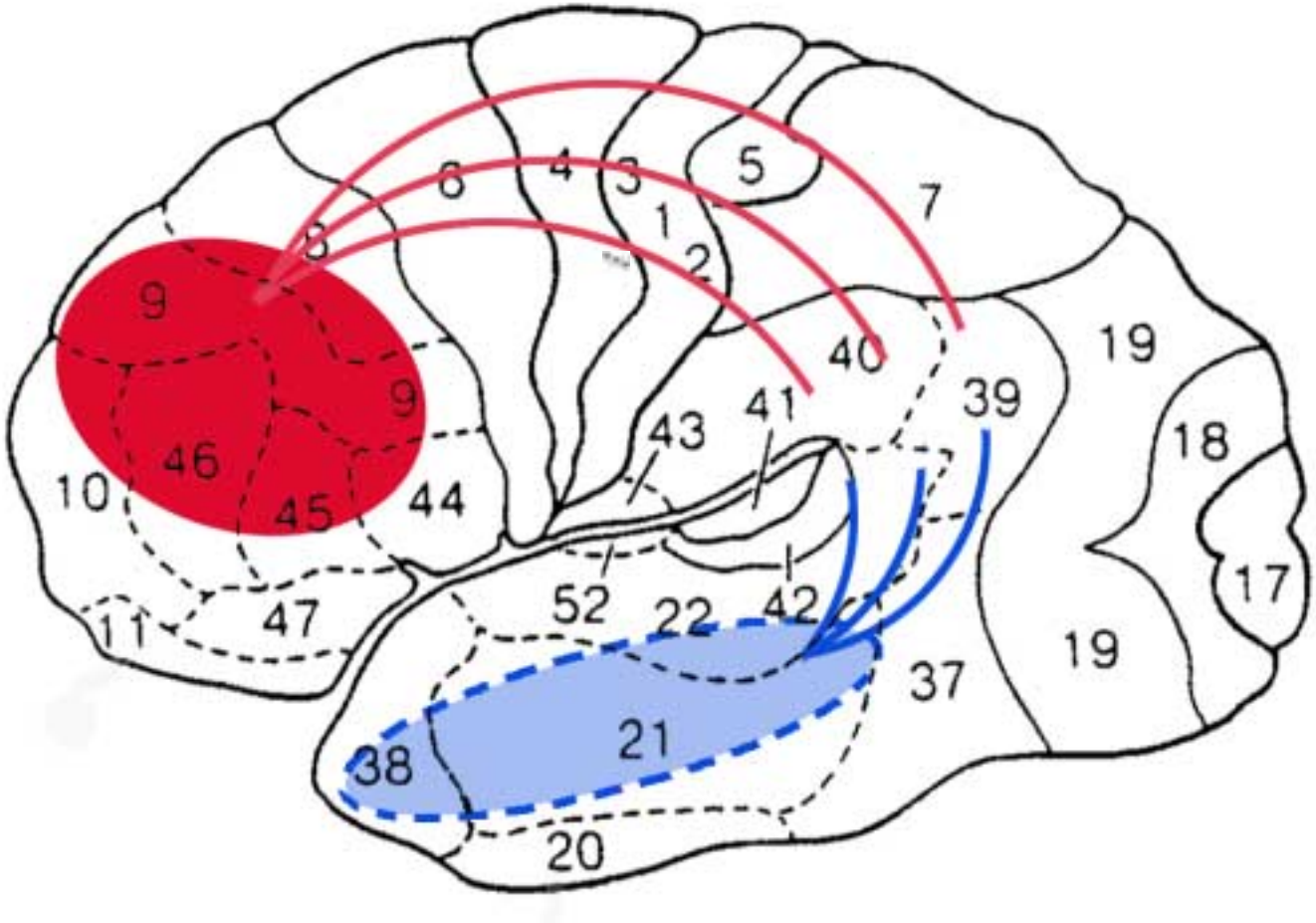
Onset of magnetic stimulation

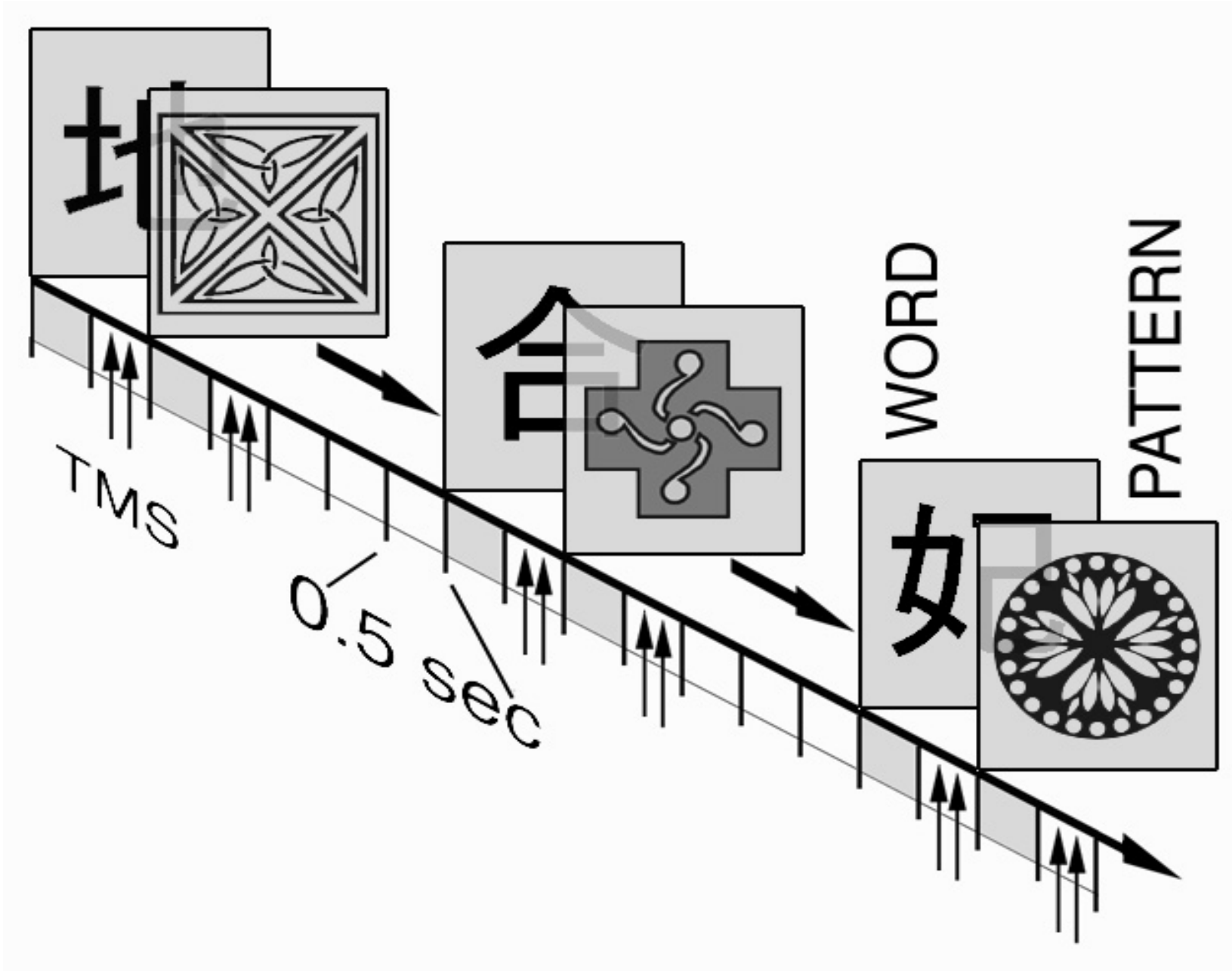

Cz
Y
X
T4
Thenar muscle
Hypothenar muscle
Bracioradial muscles
Abductor hallucis muscle
Abductor digiti minimi muscle

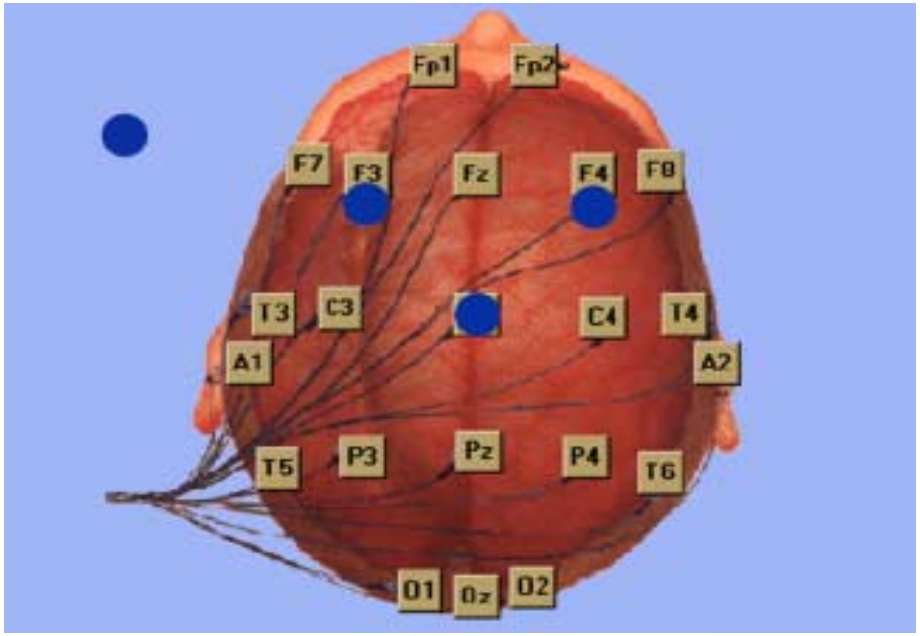
Medical Applications of Transcranial Magnetic Stimulation

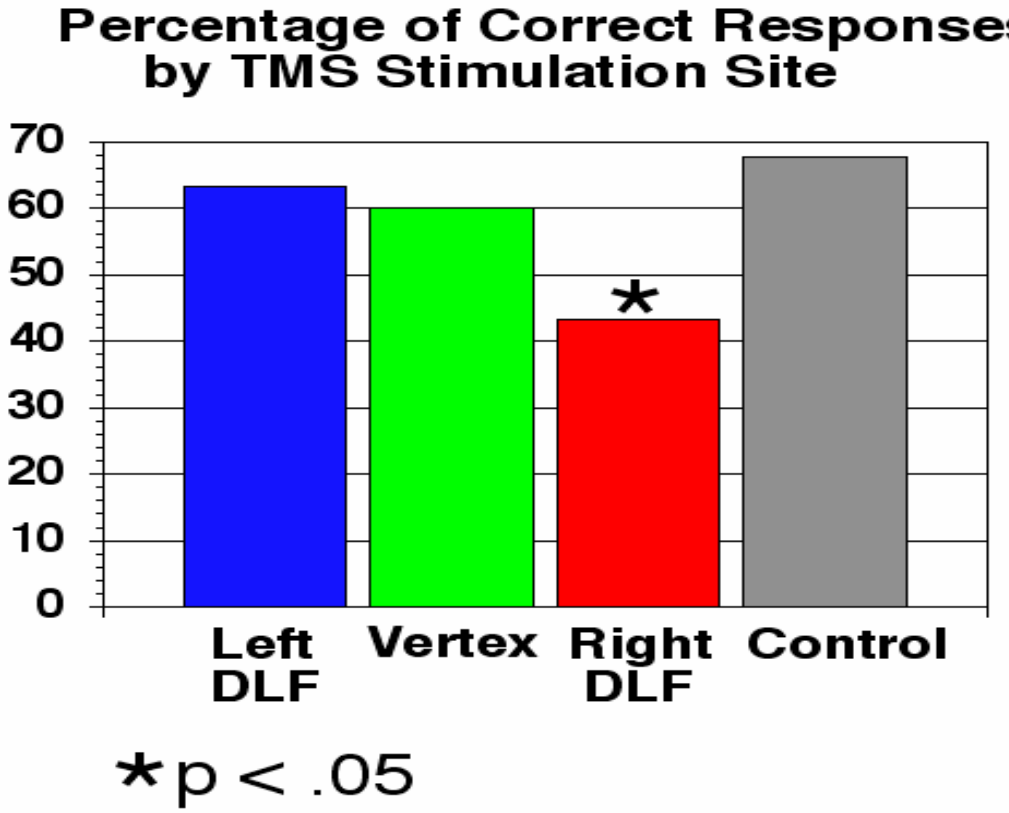
1. Estimation of localized brain function
2. Creating virtual lesions to disturb dynamic neuronal connectivities
3. Damage prevention and regeneration of neurons
4. Modulation of neuronal plasticity
5. Therapeutic and diagnostic applications for the treatment of CNS diseases and mental

- Working memory is dependent on prefrontal granular cortex.
- Associative memory is dependent on the hippocampus and




WORD
PATTERN
TMS
0.5 sec


Fp1
Fp2
F7
F3
Fz
F4
F8
T3
C3
C4
T4
A1
A2
T5
P3
Pz
P4
T6
O1
Oz
O2


Percentage of Correct Responses by TMS Stimulation Site
70
60
50
40
30
20
10
0
*
Left DLF
Vertex
Right DLF
Control

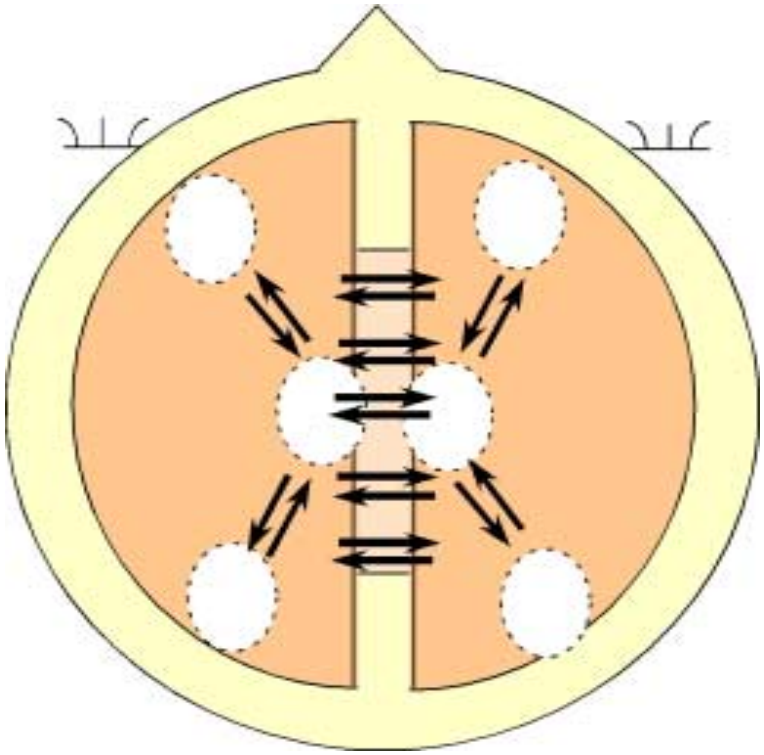
*p < .05

TMS and Brain Dynamics

1. TMS appears to disrupt associative learning for abstract patterns over the right dorsolateral prefrontal cortex.

2. Prefrontal working memory systems appear to play an important role in monitoring and learning paired associations, and may be lateralized in accordance with other hemispheric specializations.

Intra- and Interhemispheric Connectivity



Interhemispheric connectivity

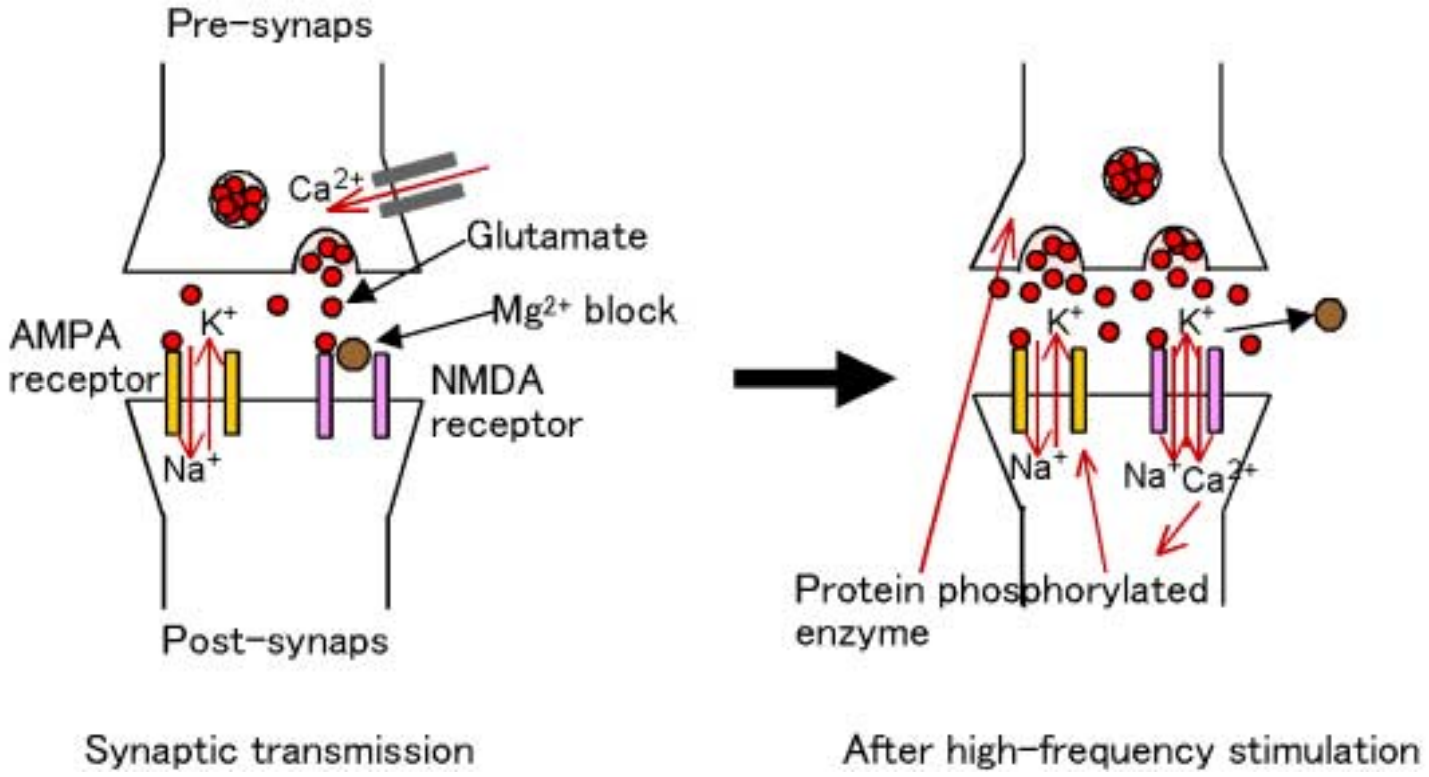
Commissural fibers

- corpus callosum
- anterior/posterior commissure
- hippocampal commissure

Long-term potentiation, LTP

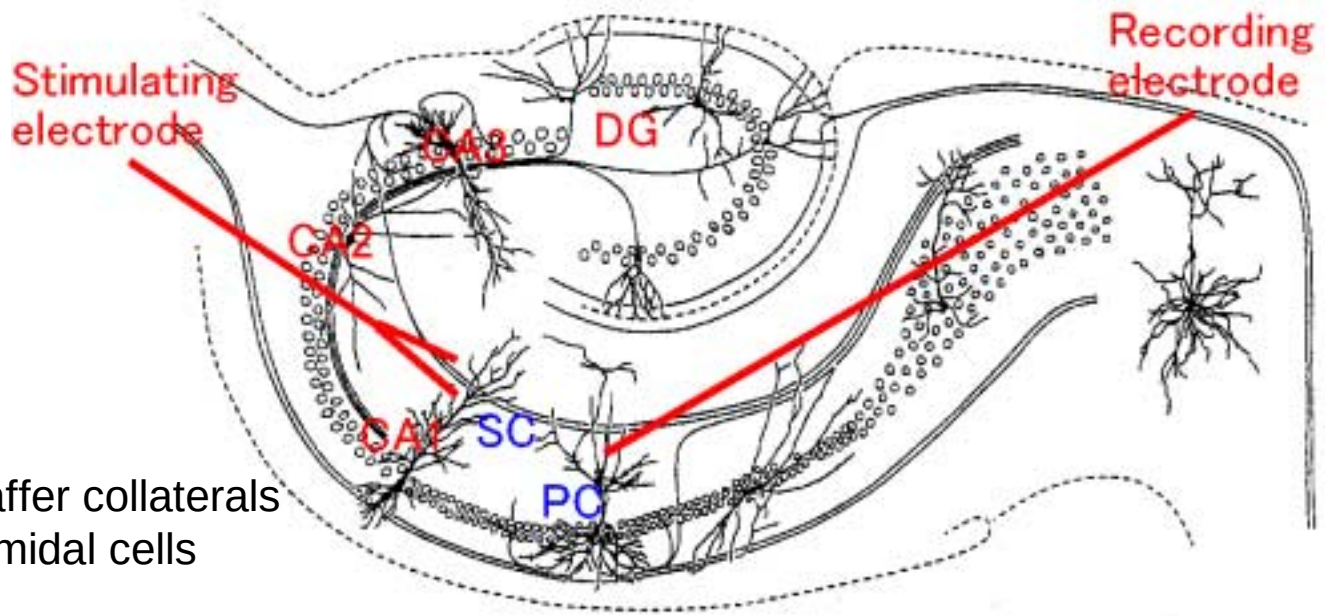
Long-lasting increase in synaptic efficacy resulting from high-frequency stimulation of afferent fibers.

LTP in the hippocampus = typical morel of synaptic plasticity related to learning and memory.



- Enhancement of transmitter release
- Activation of AMPA and NMDA receptors

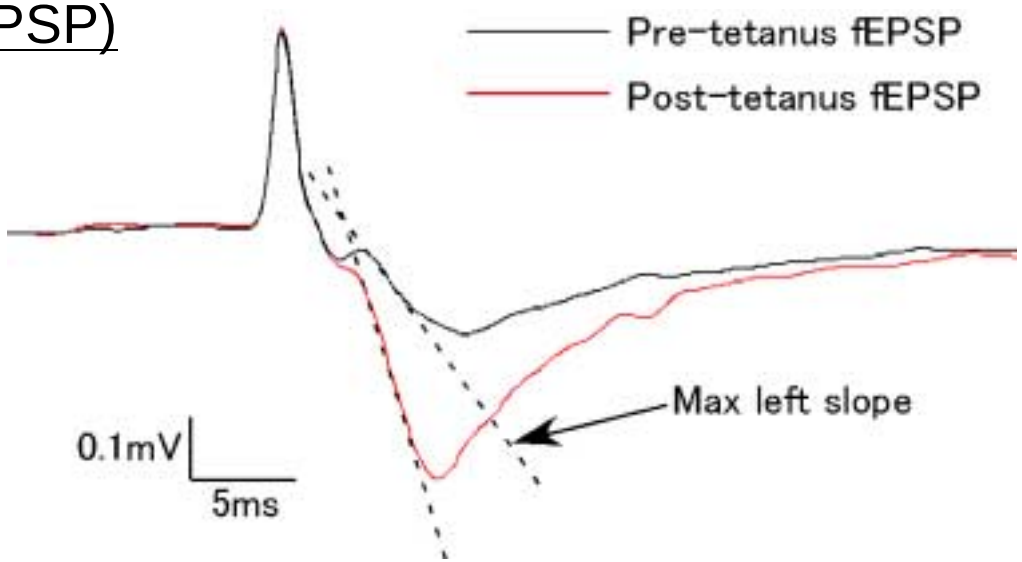
Measurement of fEPSP and LTP



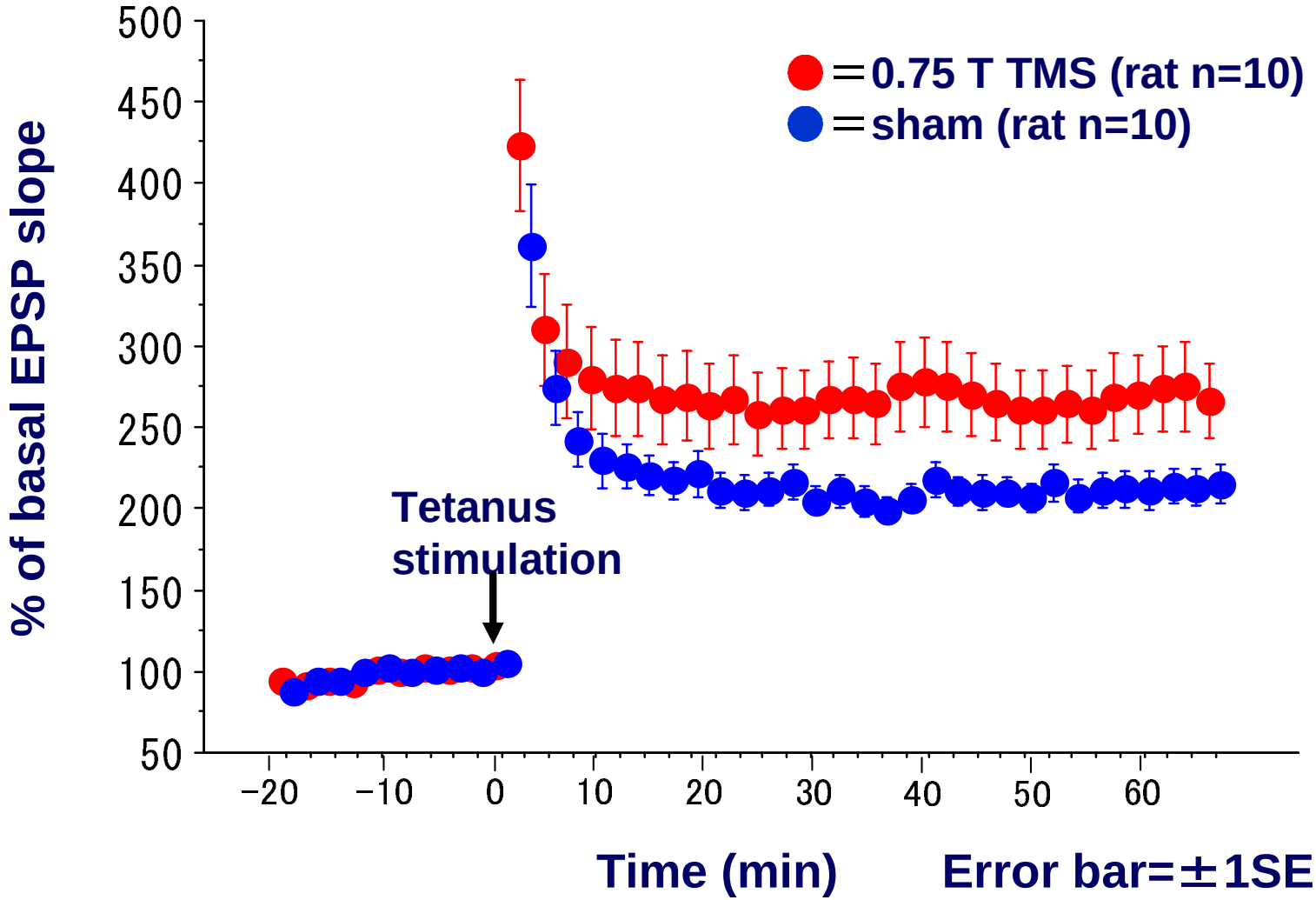
SC: Schaffer collaterals
PC: pyramidal cells

Excitatory postsynaptic potential (EPSP)

Tetanus stimulation (100 Hz for 1 sec) →Enhancement of EPSP
= Long-term potentiation (LTP)

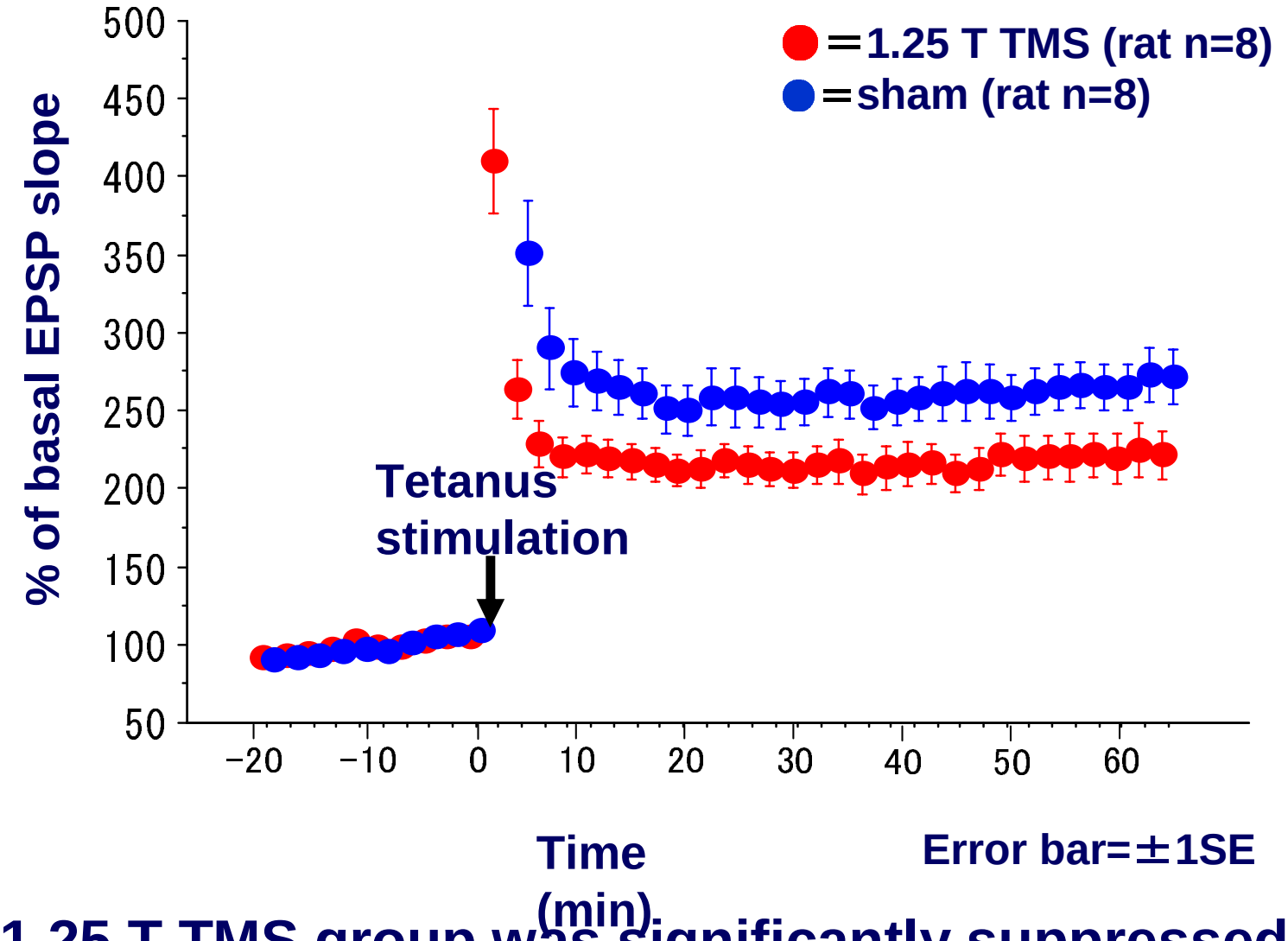


LTPs of 0.75 T TMS



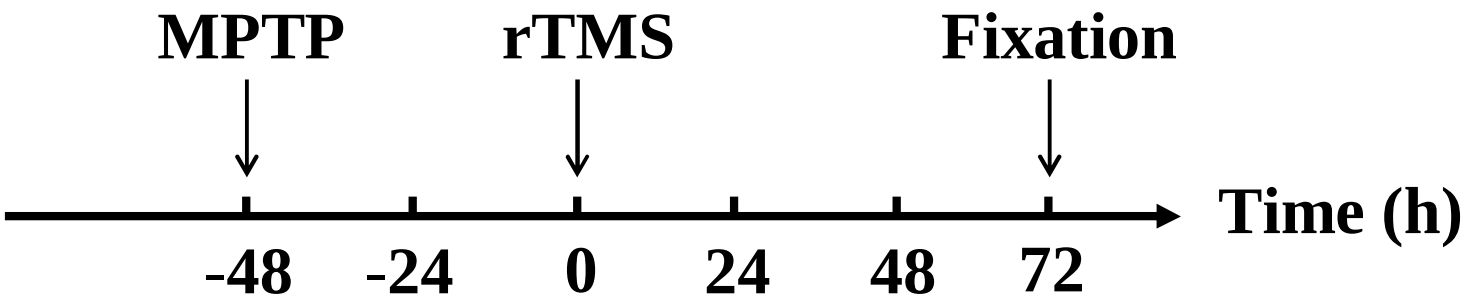
LTP of 0.75T TMS group was significantly enhanced (p=0.0408).

LTPs of 1.25 T TMS



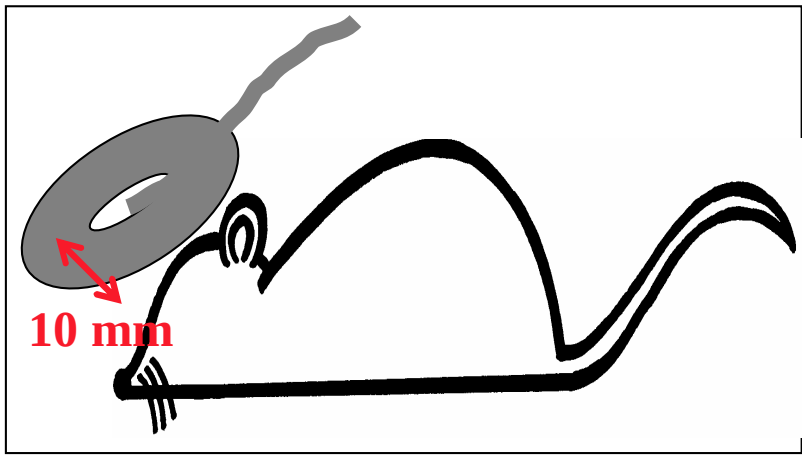
LTP of 1.25 T TMS group was significantly suppressed (p=0.0289).

Effect of rTMS (repetitive TMS) on injured neurons



Subjects: Wistar rats (♂)
5 weeks old

Neurotoxin: MPTP
(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) (20 mg/kg)



Injections: 4 subcutaneous injections per day, 2 hour interval between injections

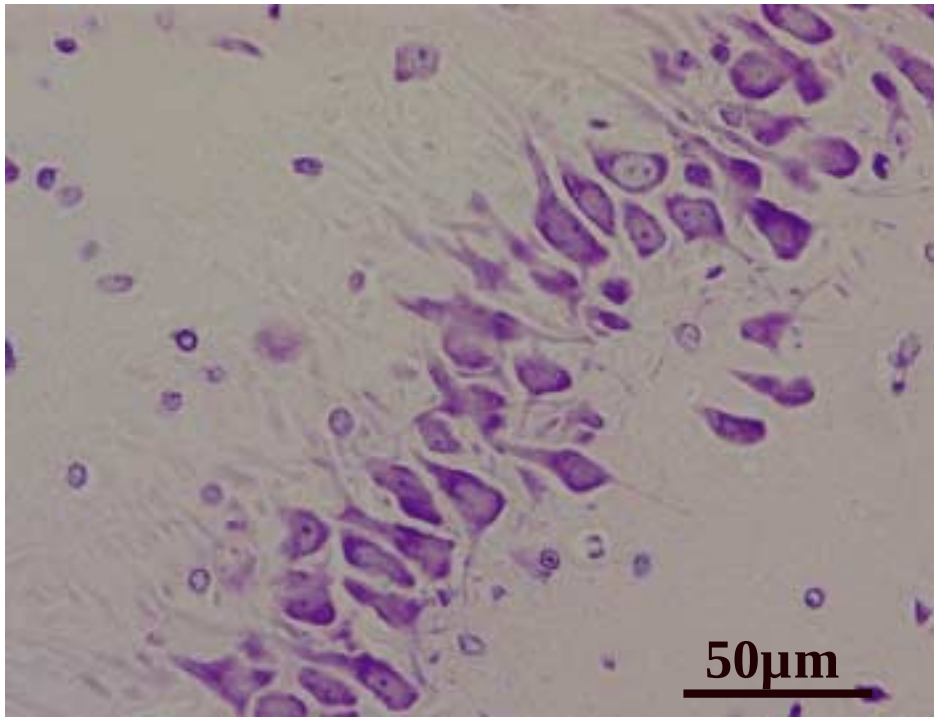
Magnetic field: 1.25 T at the center of coil

25 pulses/sec ×8 sec ×10 trains (= 2000 pulses) per day

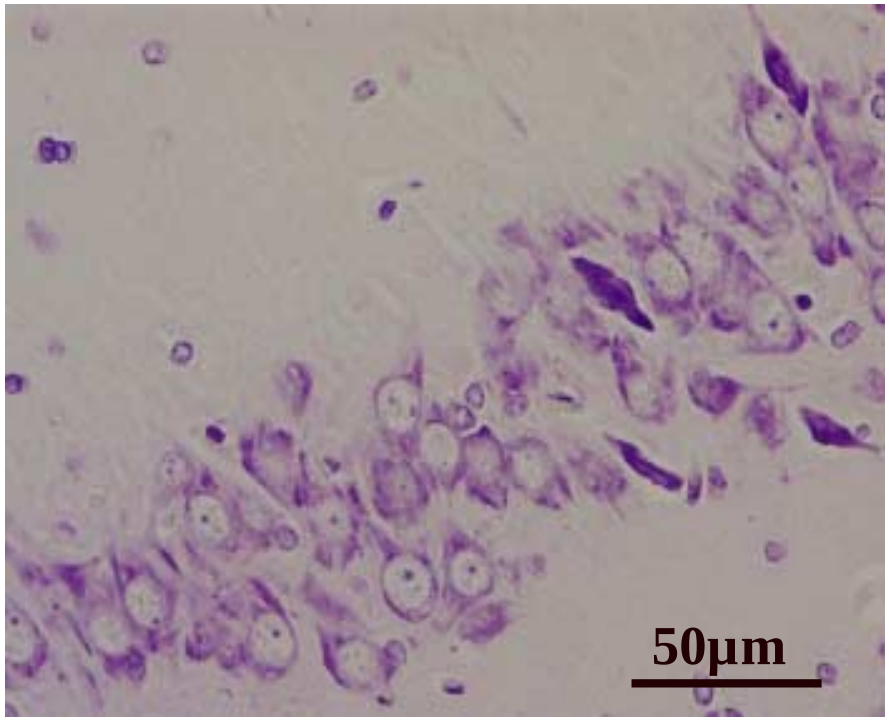
Interval between trains = 10～15 min

Effect of rTMS on the injured neurons in the hippocampal CA3

nissl stain



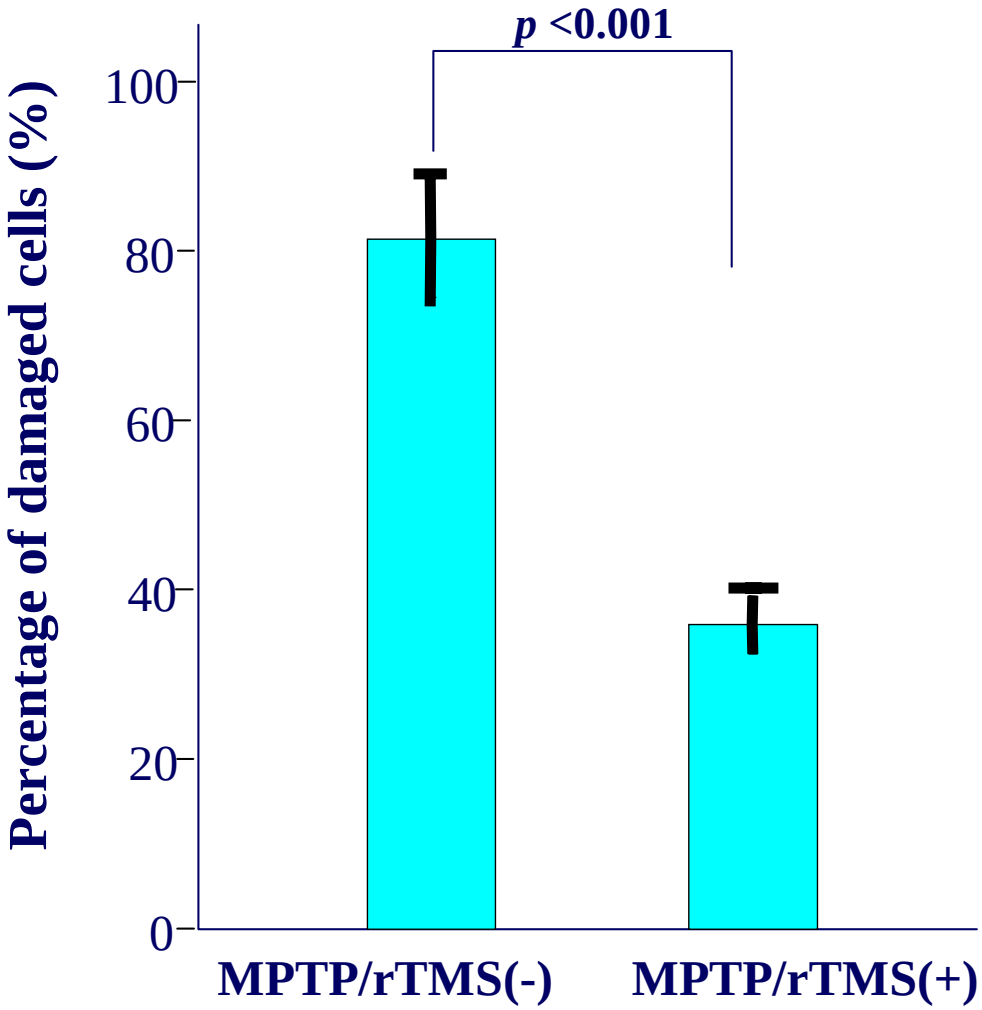
MPTP/rTMS(-)



MPTP/rTMS(+)

rTMS prevented damage to hippocampal CA3 pyramidal neurons.

Percentage of damaged cells in hippocampal CA3

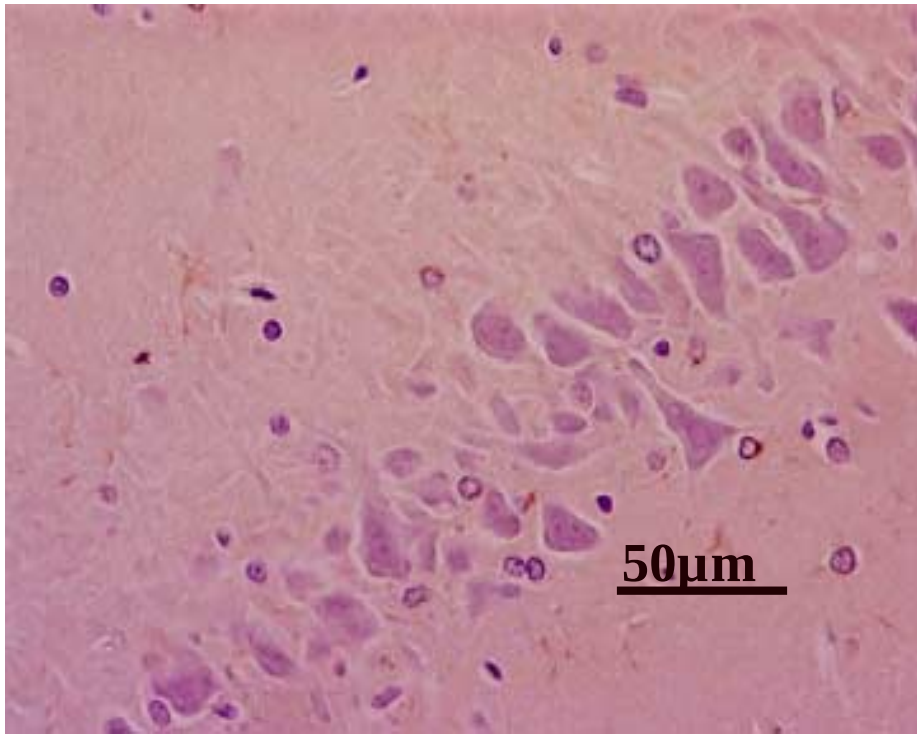


Rat n = 6, Sample n = 24 for each group.

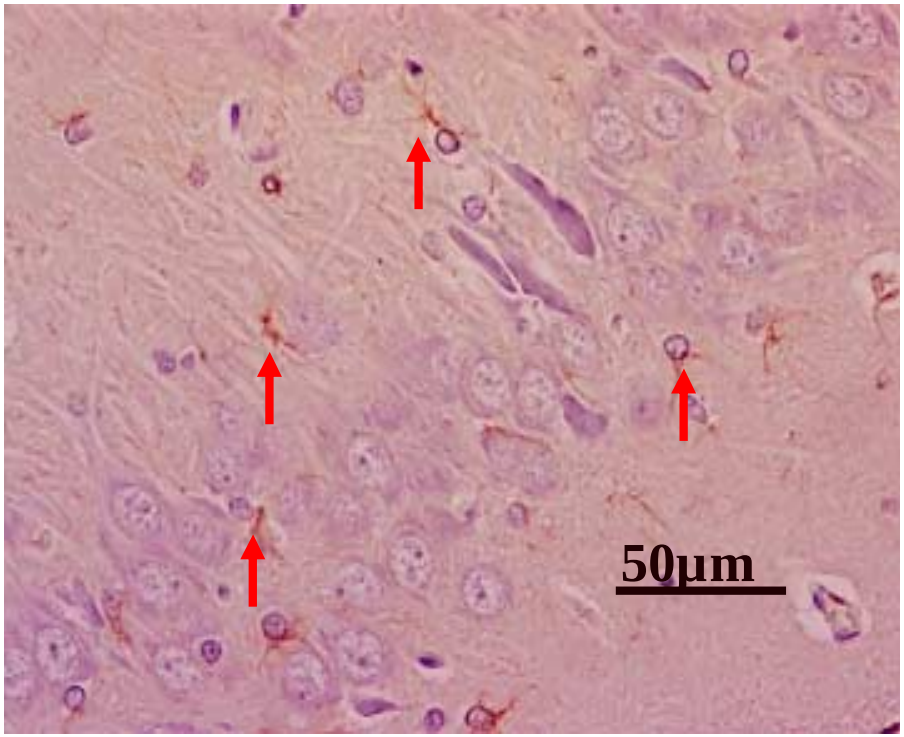
The percentage of damaged cells of the MPTP/rTMS(+) group was significantly lower than that of the MPTP/rTMS(-) group.

Activation of astrocytes in the hippocampal CA3

immunocytochemistry



MPTP/rTMS(-)



MPTP/rTMS(+)

Arrows indicate GFAP (glial fibrillary acidic protein) positive astrocytes. GFAP is a cell specific marker in astrocytes.

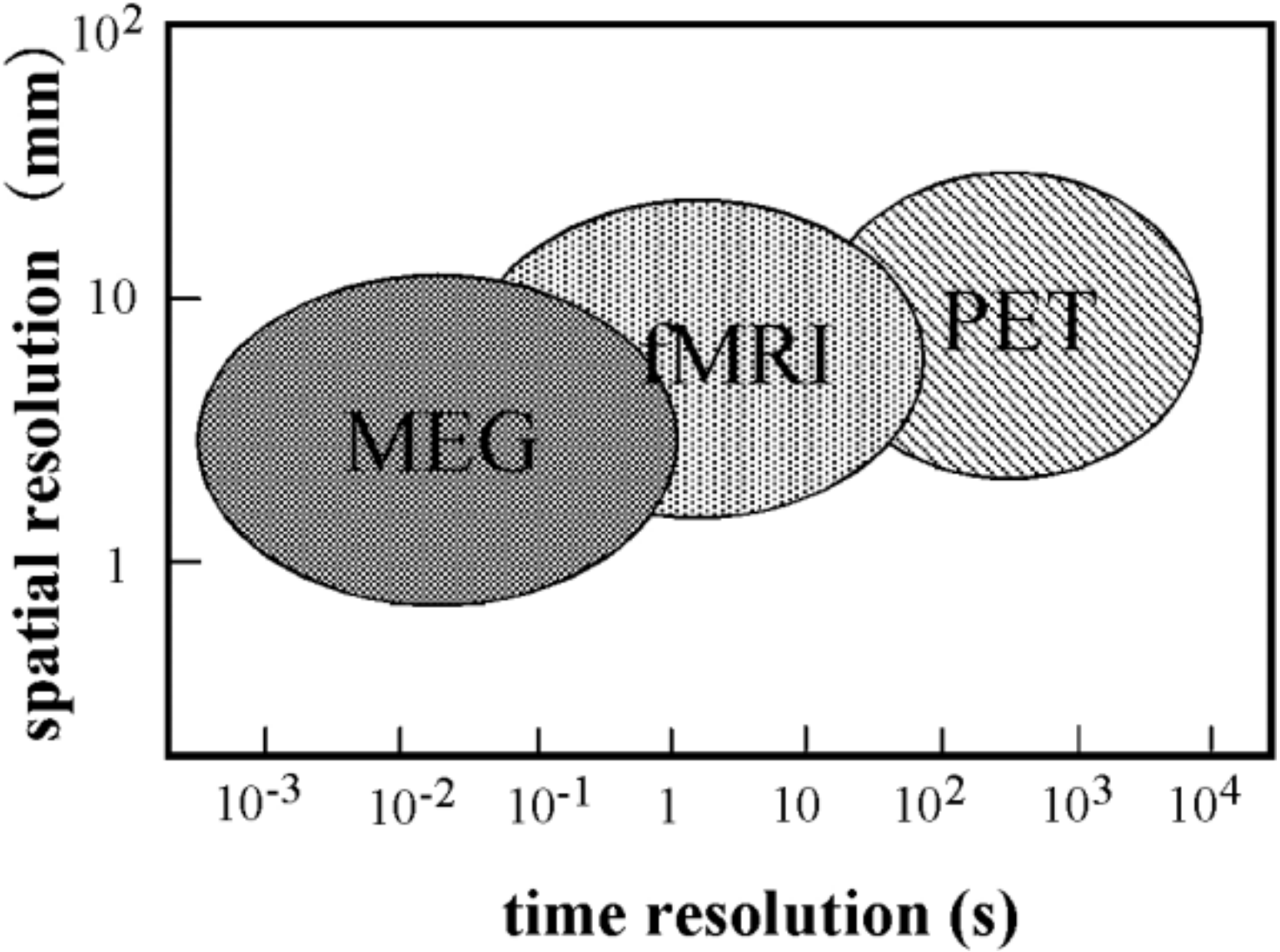
• rTMS **increased** the **GFAP immunoreactivity** in the hippocampal CA3.

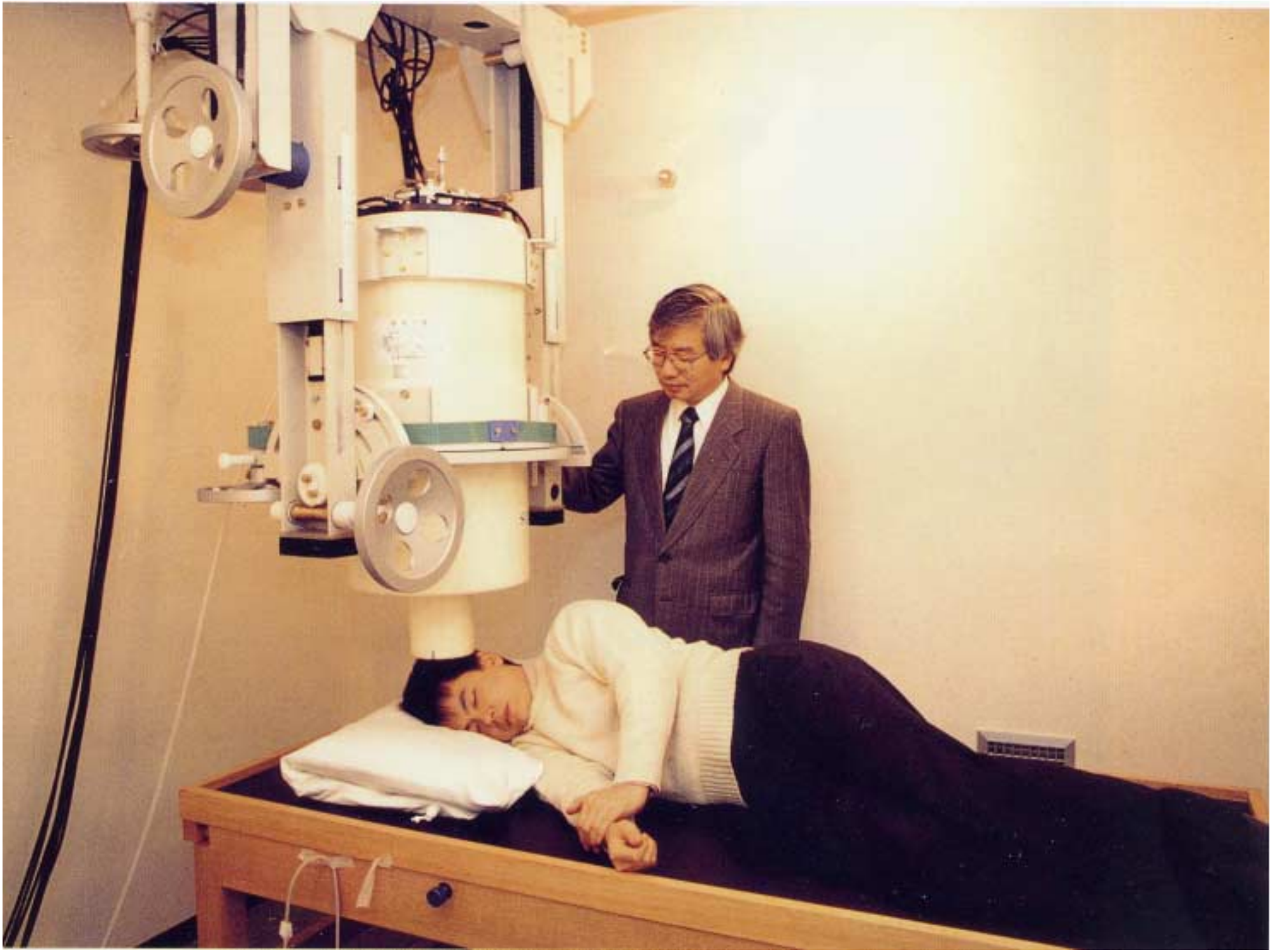
Effect of rTMS on injured neurons

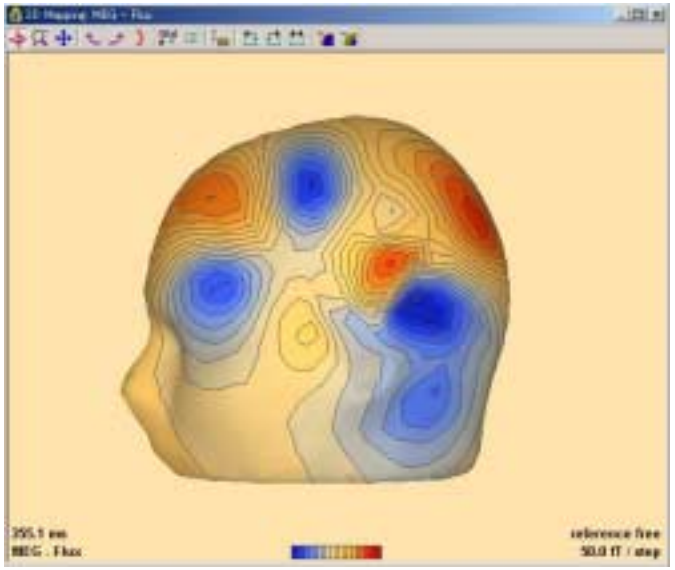
- **The activation of astrocytes and neurotrophic factors by rTMS possibly contributes to the recovery and protection of neurons.**

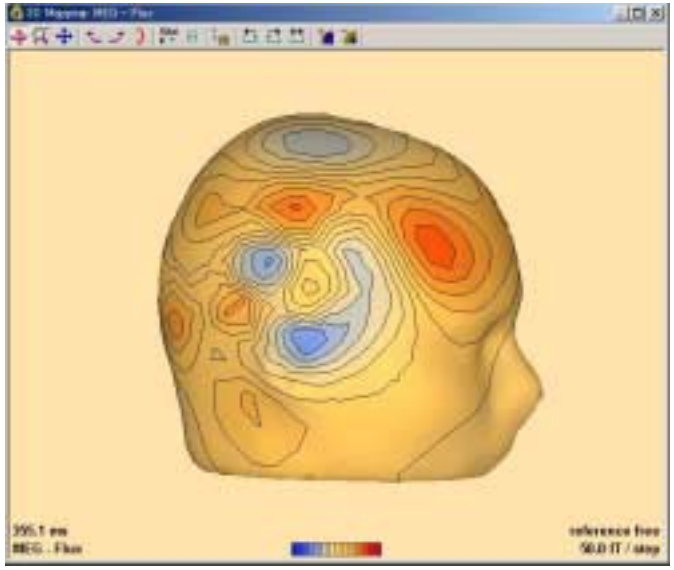
- **rTMS may aid in the recovery of injured neurons and protect neurons from injury.**

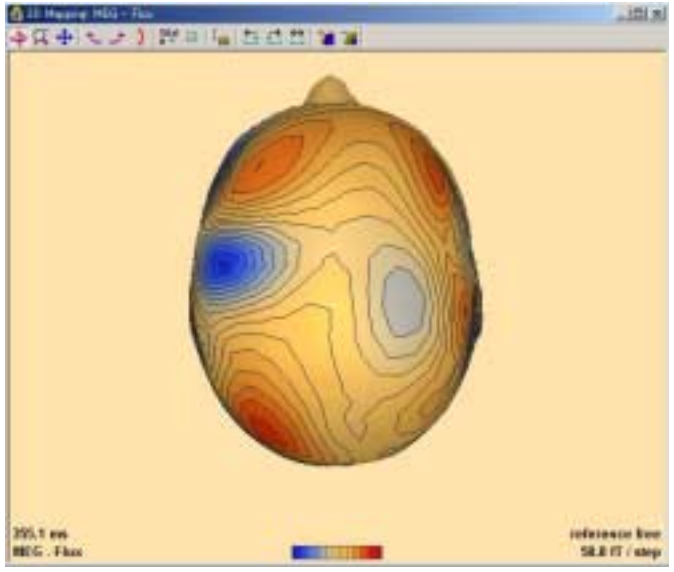
1. Biomagnetics and Epilepsy
2. TMS (Transcranial Magnetic Stimulation)
3. MEG (Magnetoencephalography)
4. MRI (Magnetic Resonance Imaging)
5. Magnetic Control of Cell Orientation and Cell Growth
6. Iron and Epilepsy: RF Exposure and Oxidative Stress


spatial resolution (mm)
10^2
10
1
MEG
fMRI
PET
10^{-3}
10^{-2}
10^{-1}
1
10
10^2
10^3
10^4
time resolution (s)









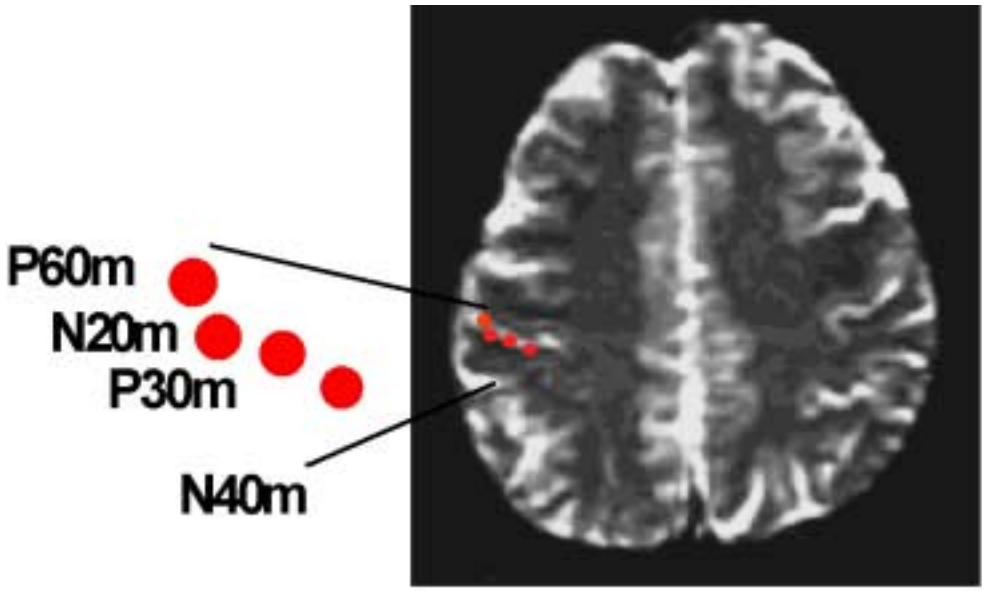
Inverse Problem

I. Estimation of Current Dipoles

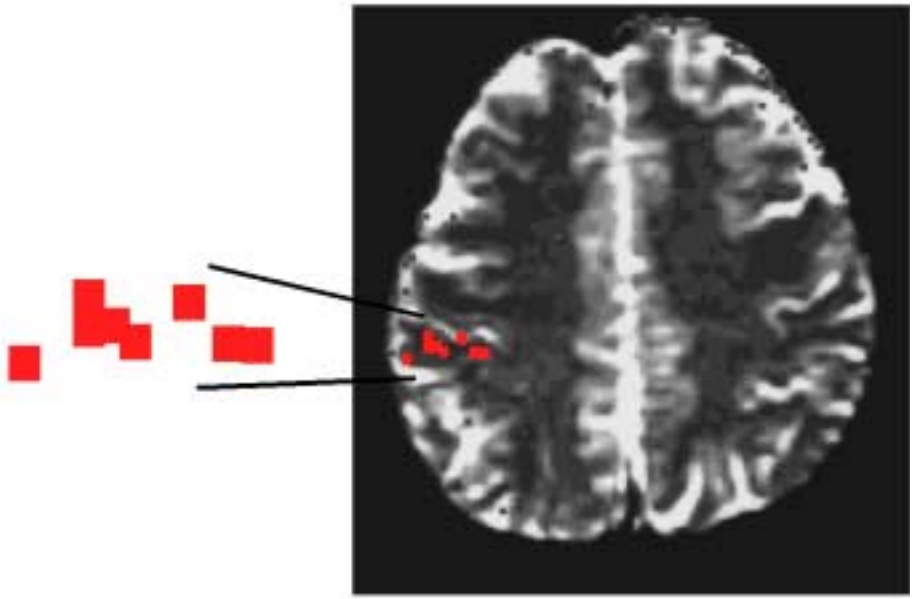
* Newton Iteration Method
* Marquardt's Method
* Simulated Annealing Method
* Genetic Algorithm

II. Estimation of Current Distribution

* Fourier's Transformation Method
* Pattern Matching Method
* Minimum Norm Estimation
* MUSIC (Multiple Signal Classification) Algorithm
* Sub-Optimal Least-Squares Subspace Scanning Method
* Spatial Filtering Method
* LORETA (Low Resolution Brain Electromagnetic Tomography)

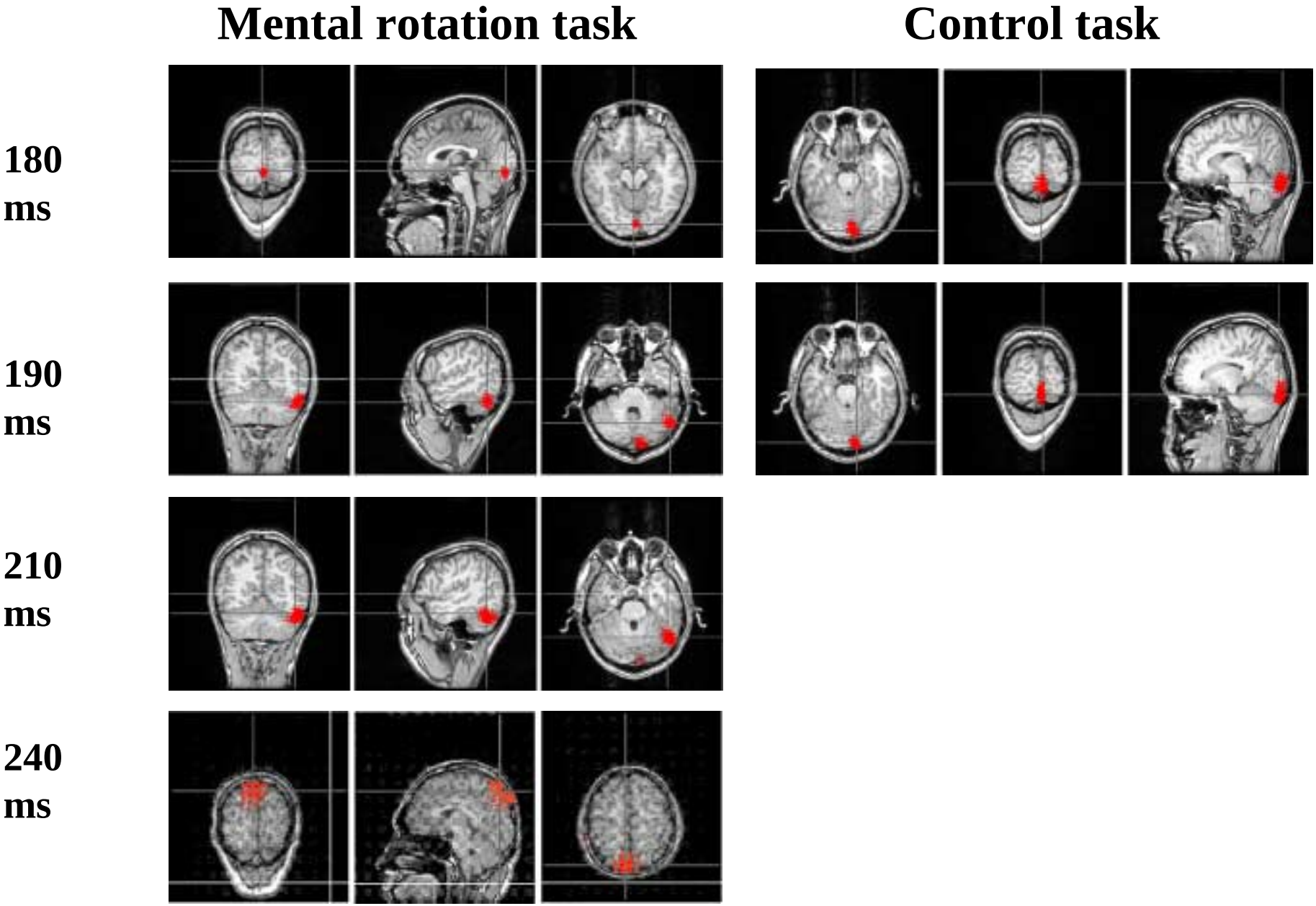


(a) MEG

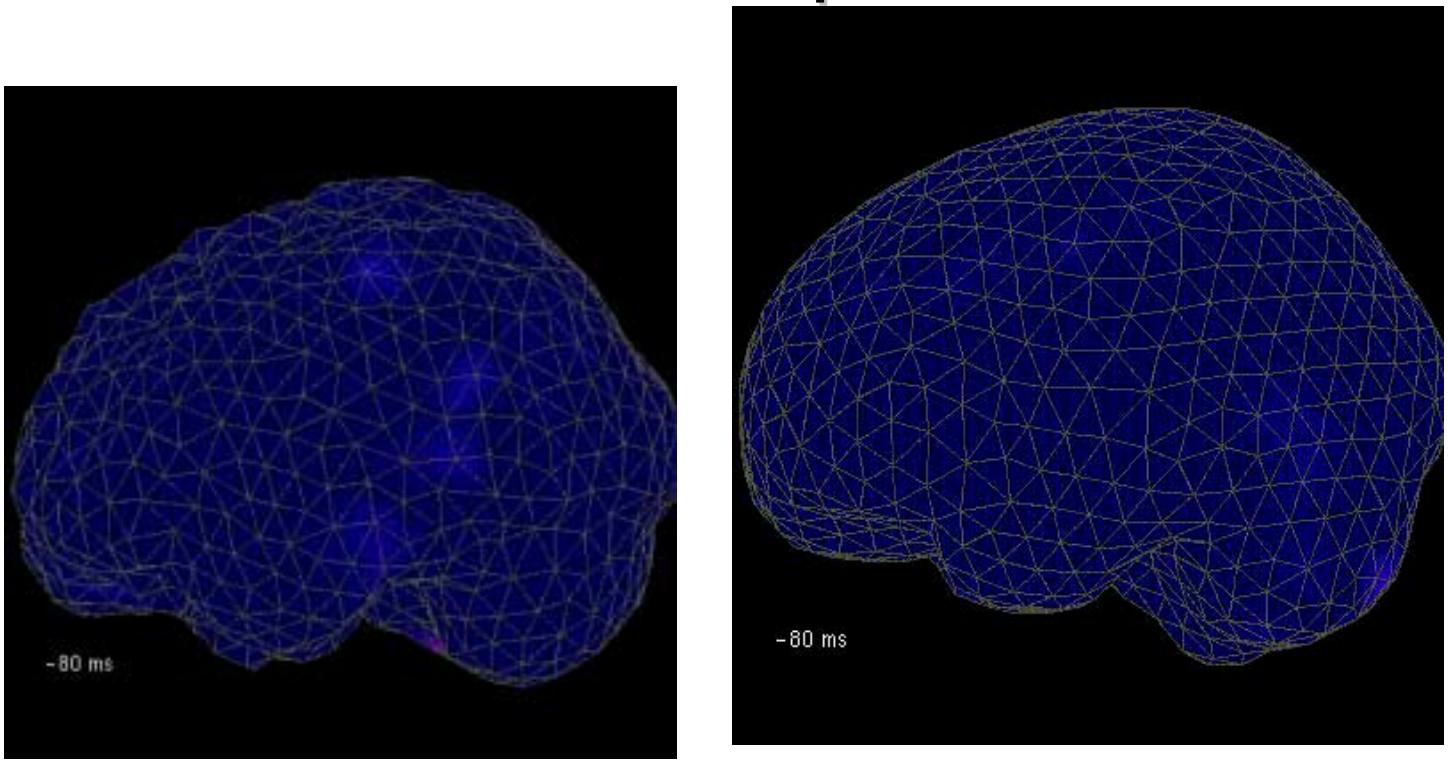


(b) fMRI

Estimated source distributions (mental rotation)



Reading of Kanji and Kana words: A comparative study between native and non-native speakers



Kanji Reading

Left (Native), Right (Non-native)

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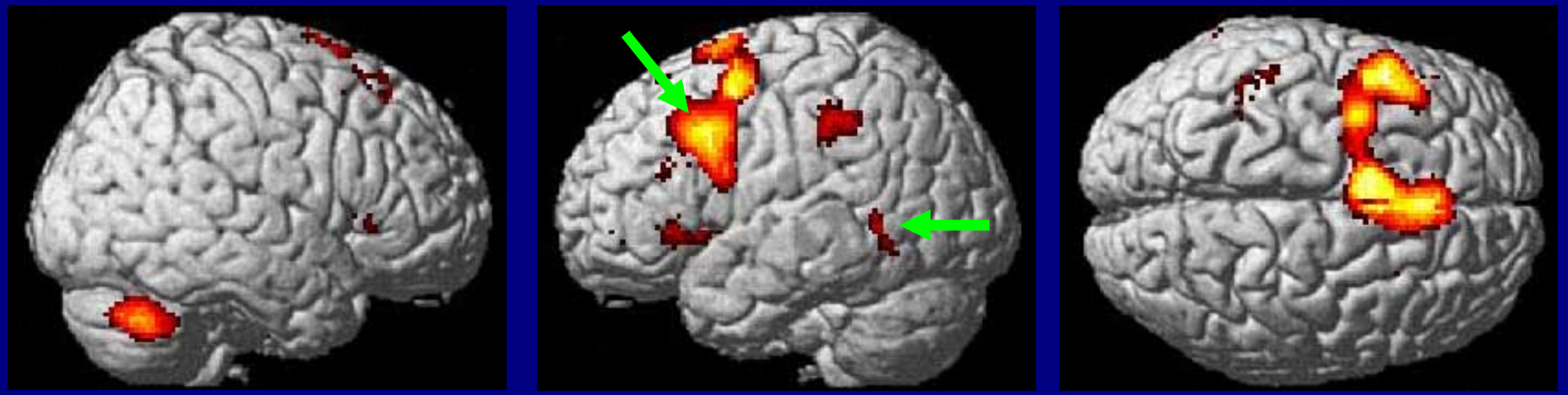
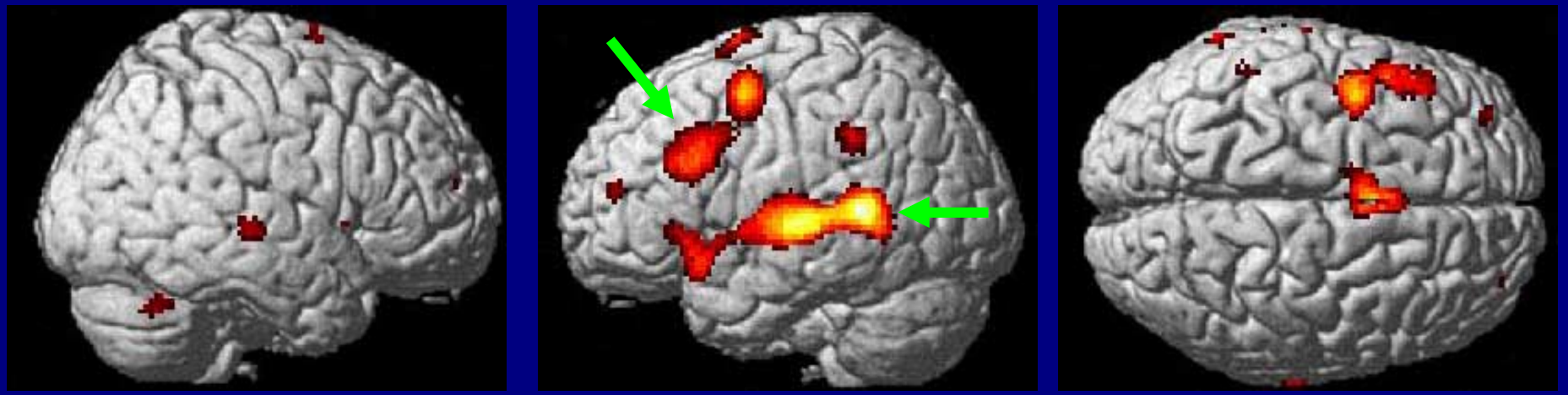
Functional MRI: Mapping of Language Areas by fMRI

Word generation – Speech for words starting with “A”

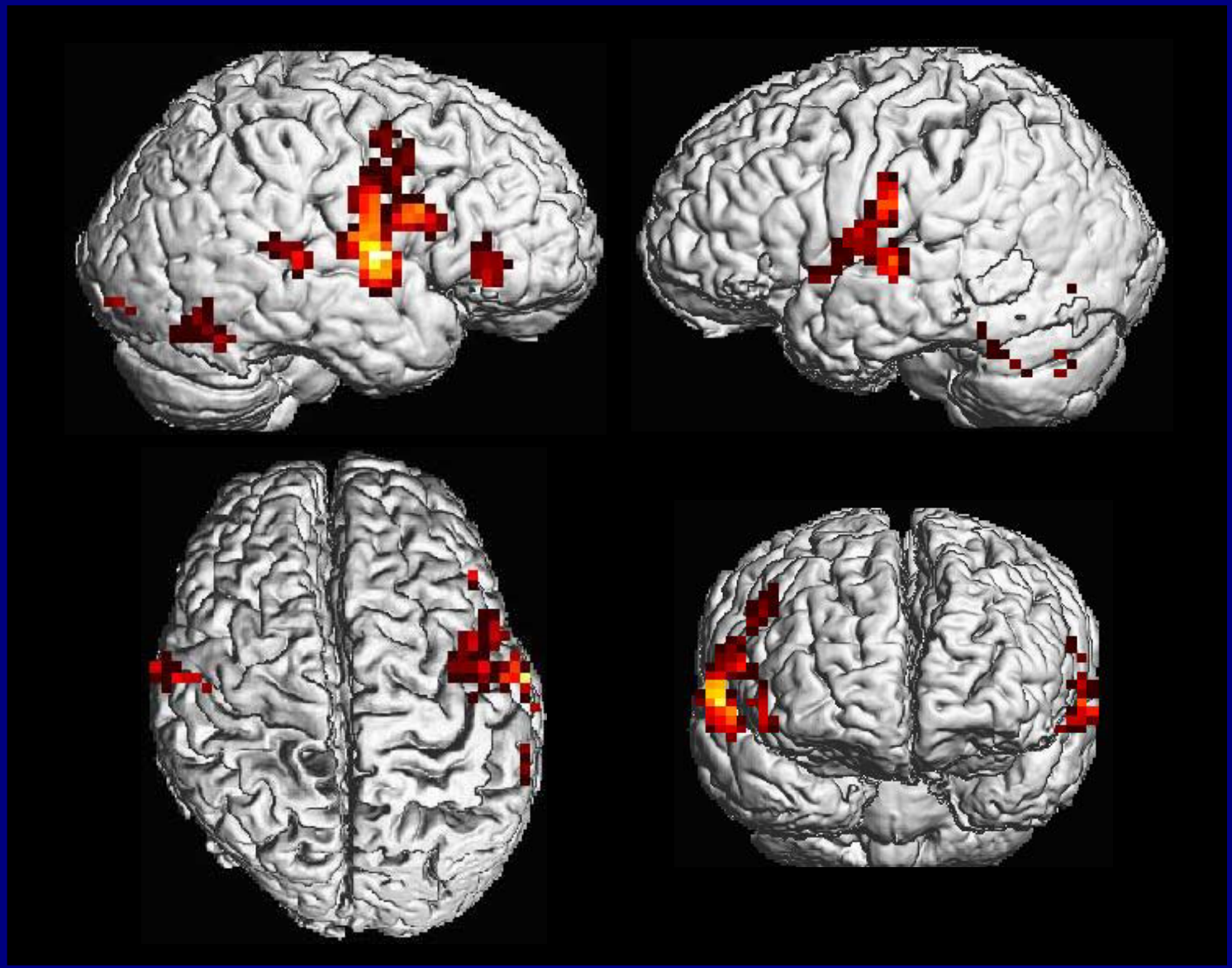


Verb generation – Conceptualization (door → open; chair → sit down)



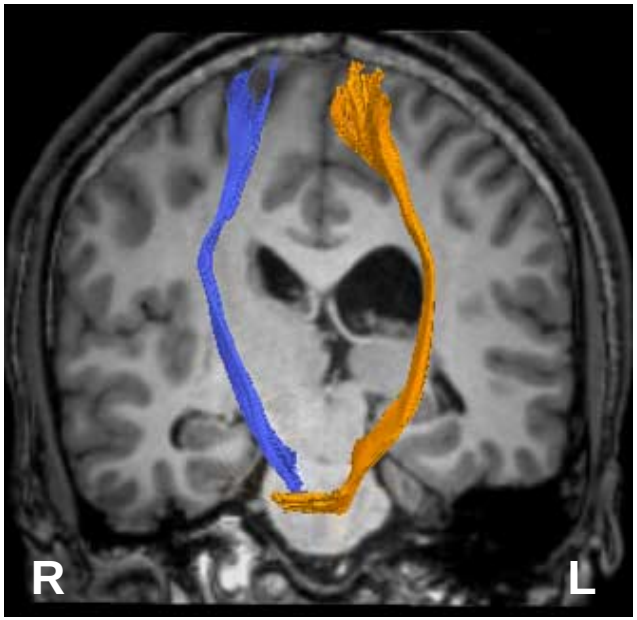
Courtesy of Dr. T. Yoshiura (Kyushu University)

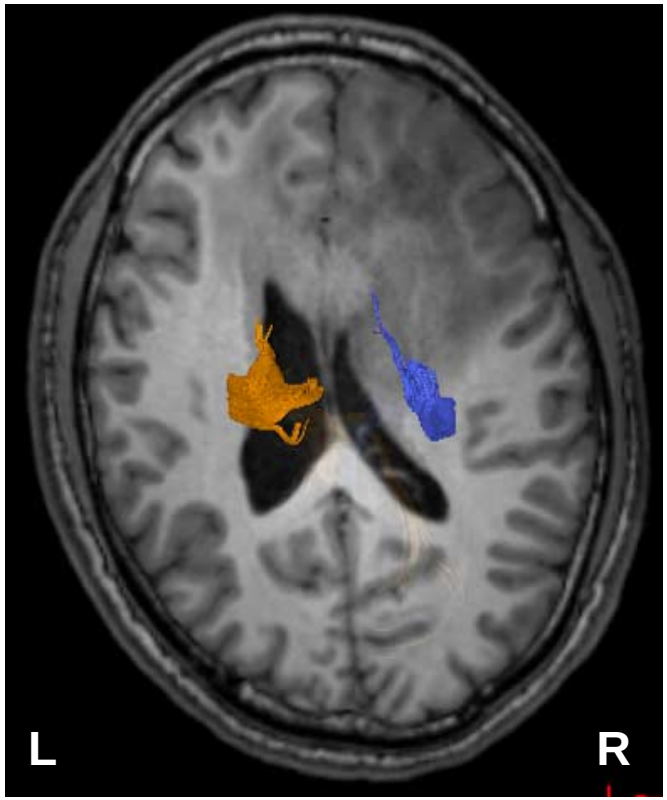
Mapping of language areas by fMRI for pre-surgical monitoring of a patient with temporal epilepsy

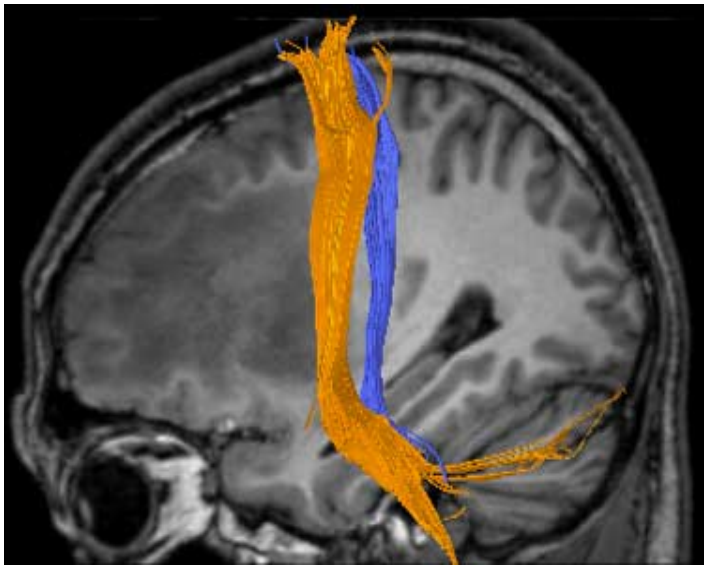


Courtesy of Dr. T. Yoshiura (Kyushu University)

Fibertractography of pyramidal tracts in a patient with a brain tumor

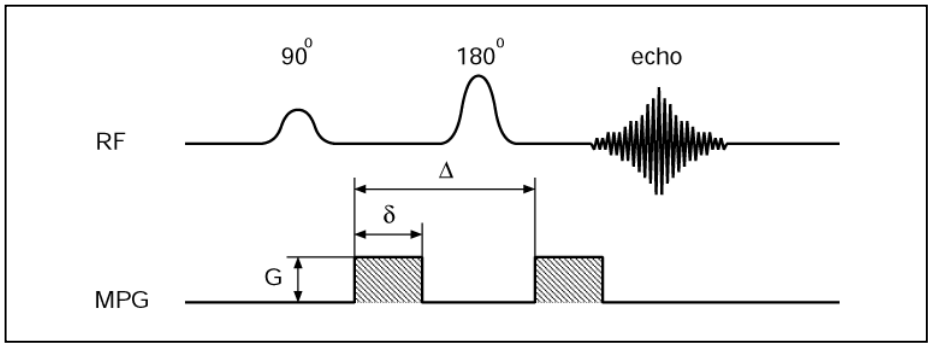






Courtesy of Dr. T. Yoshiura (Kyushu University)

Diffusion MRI



b factor

$$b = \gamma^2 G^2 \delta^2 \left(\Delta - \frac{\delta}{3} \right)$$

γ : gyromagnetic ratio
G : gradient intensity
δ : duration of MPG(s)
Δ : Interval between MPG(s)

Theoretical signal attenuation

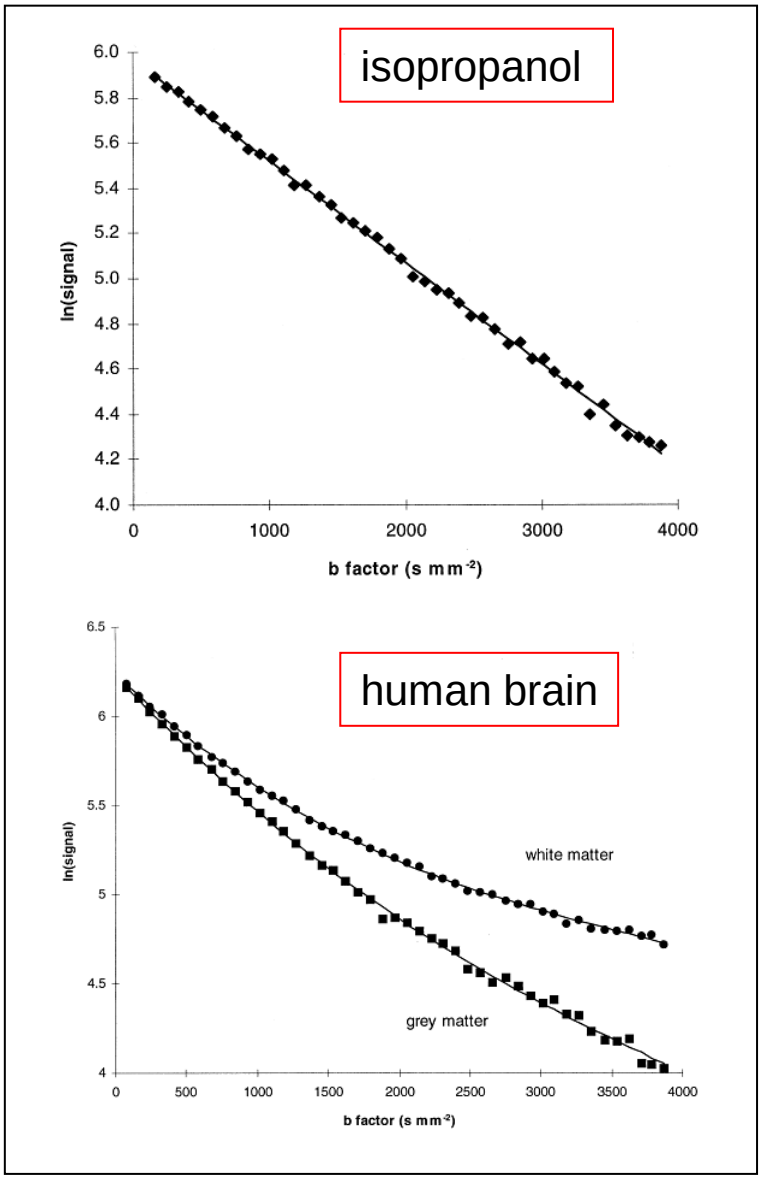
$$\frac{S(b)}{S(0)} = \exp(-bD)$$

S(b) : signal intensity
D : apparent diffusion coefficient (ADC)

Biexponential signal attenuation in biological tissues

$$\frac{S(b)}{S(0)} = f_{\text{fast}} \exp(-b \cdot D_{\text{fast}}) + (1 - f_{\text{fast}}) \exp(-b \cdot D_{\text{slow}})$$

D_{fast} : fast component (extracellular space)
D_{slow} : slow component (intracellular space)
f_{fast} : fraction of fast component



Clark CA, Le Bihan D. Magn Reson Med 2000;44:852-859.

Relationship between conductivity and the diffusion coefficient

1. Conductivity depends on the viscosity because the balance between the electrostatic force and viscous resistance governs the drift velocity of an ion.
2. The diffusion coefficient of water is also related to its viscosity.

$F = qE$ Electrostatic Force

$F = 6\pi r_i \eta v$ Viscous Resistance

$$qE = 6\pi r_i \eta v \quad ①$$

$j = qNv$ Current Density and Migration Velocity ②

$$D = \frac{kT}{6\pi r_w \eta}$$ Stokes-Einstein Equation ③

$$\sigma = \frac{j}{E} = \frac{q^2 N}{6\pi r_i \eta} = \frac{r_w q^2 N}{r_i kT} D$$

Ohm's Law ①② ③

$$\therefore \sigma = \frac{r_w q^2 N}{r_i kT} D$$

q : Charge of Ion

r_i : Stokes Radius of Ion

r_w : Radius of Water Molecule

η : Viscosity of Solution

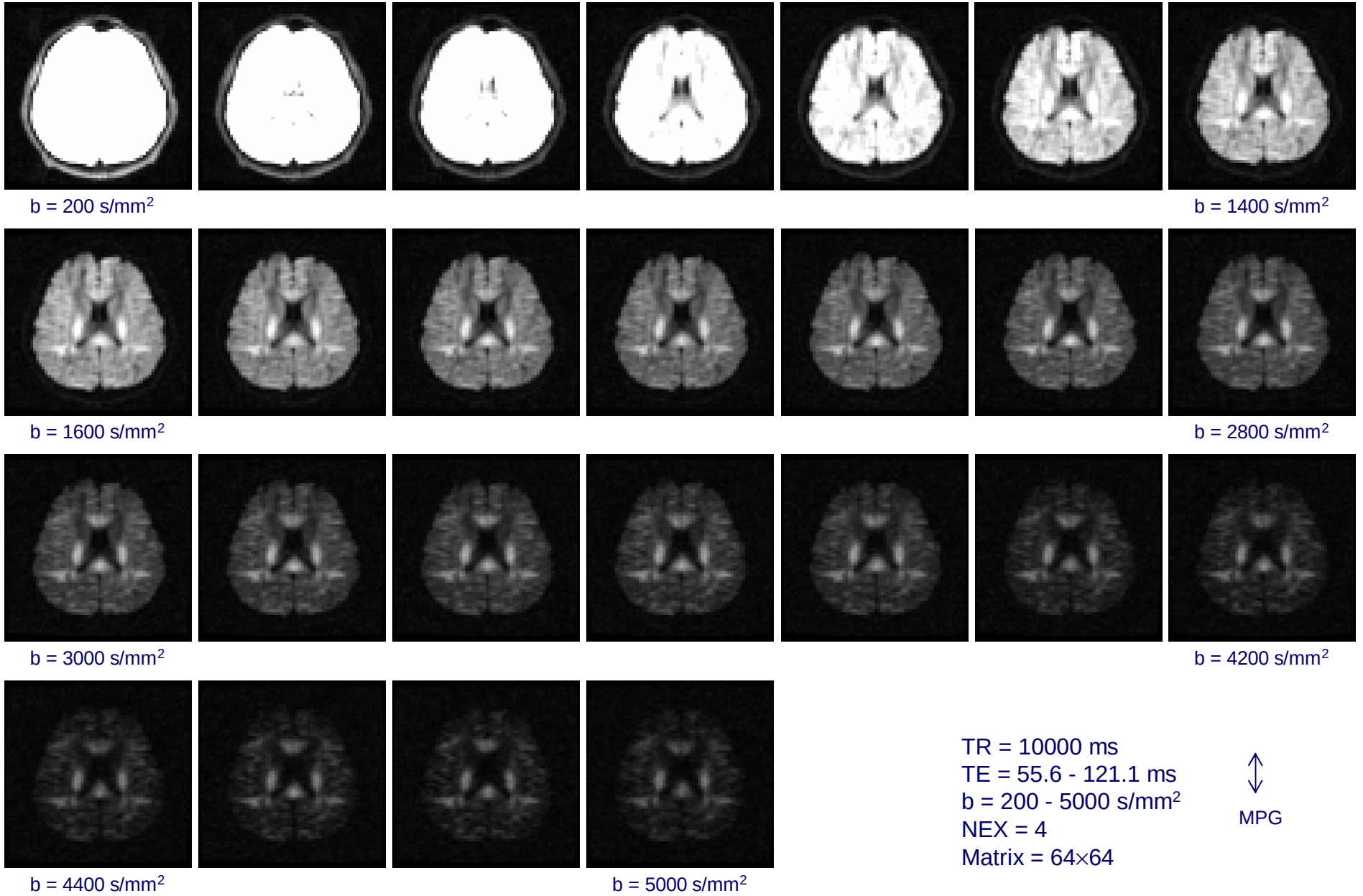
v : Migration Velocity of Ion

N : Ion Density

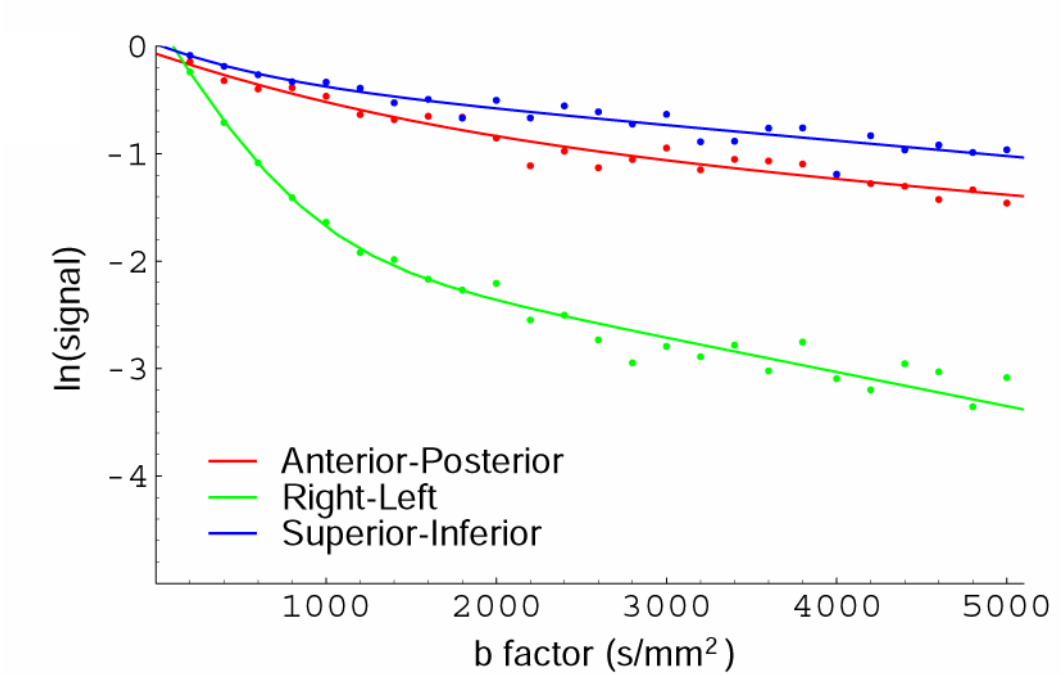
k : Boltzmann Constant

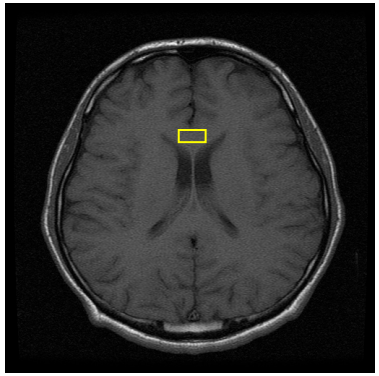
T : Temperature

Signal attenuation in the human brain



Relationships between the b-factor and the logarithm of the signal intensity in the corpus callosum



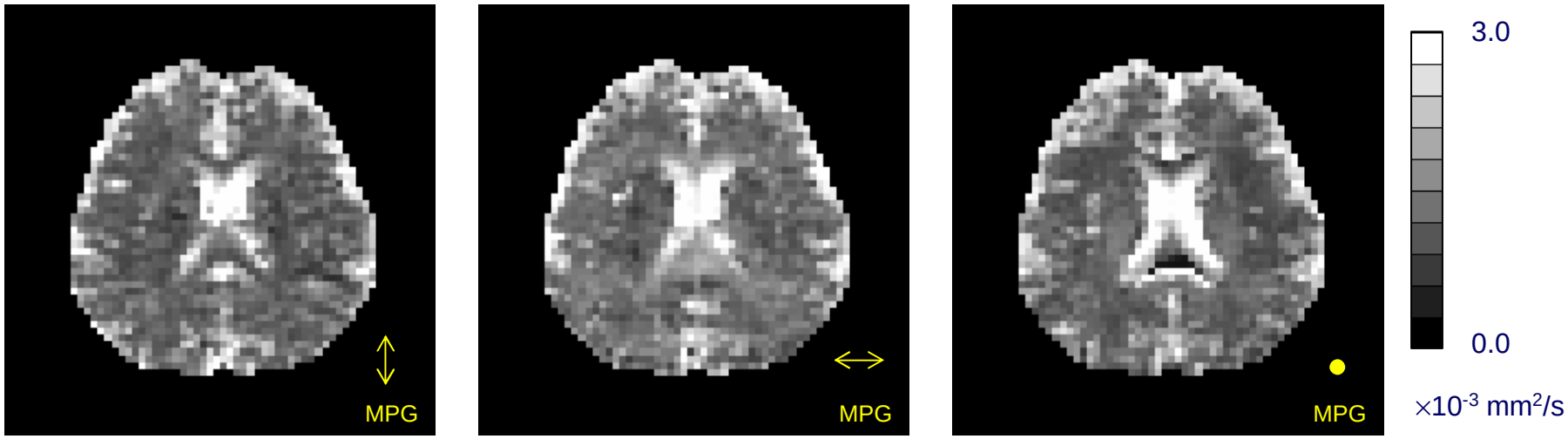


	Annerior-Posterior	Right-Left	Superior-Inferior
D_{fast} ($\times 10^{-3}$ mm^2/s)	2.09 ± 0.45	2.46 ± 0.55	2.32 ± 0.71
f_{fast}	0.58 ± 0.04	0.54 ± 0.07	0.56 ± 0.05
D_{slow} ($\times 10^{-3}$ mm^2/s)	0.50 ± 0.11	0.42 ± 0.07	0.44 ± 0.09
f_{slow}	0.42 ± 0.04	0.46 ± 0.07	0.44 ± 0.05

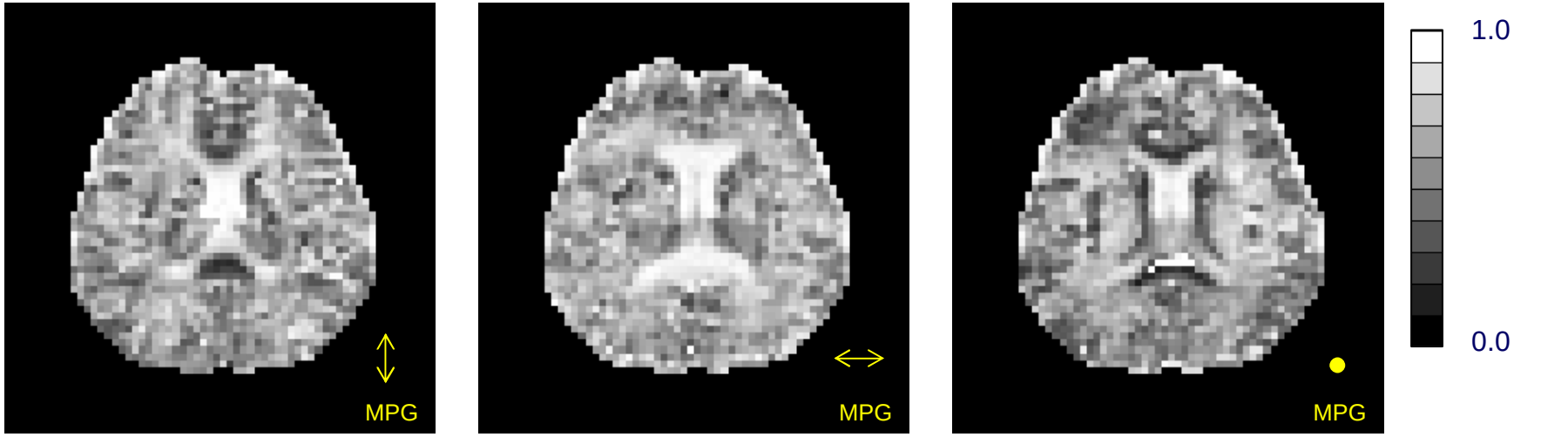
An application of the MPG in the right-left direction caused the most rapid signal attenuation.

Images of the fast component (D_{fast}, f_{fast})

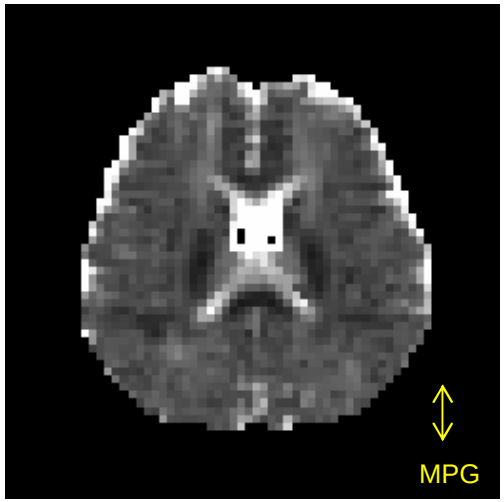
D_{fast} map

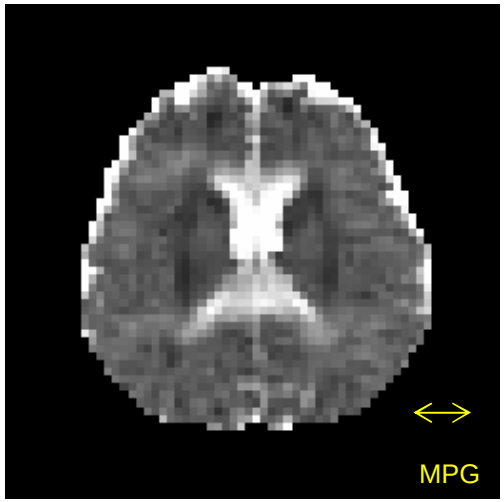


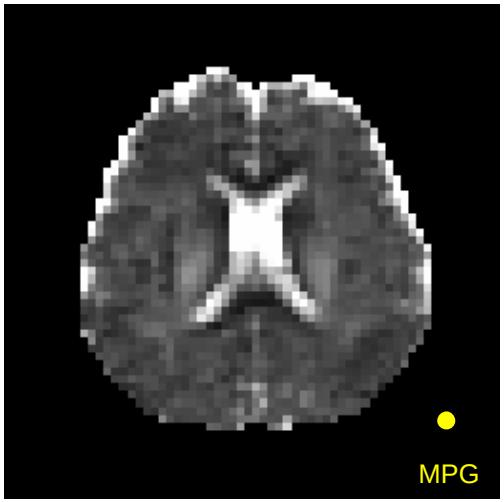
f_{fast} map

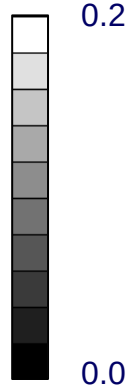


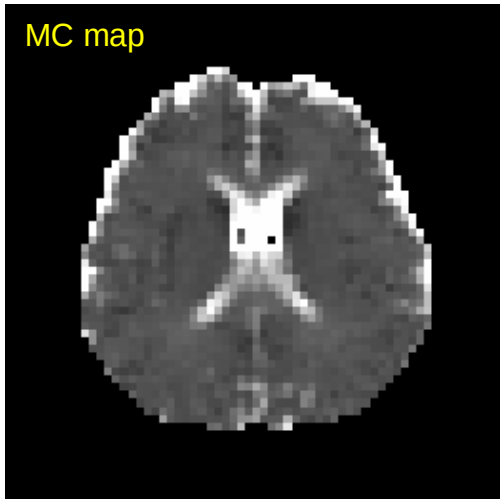
Conductivity images

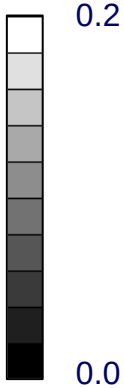


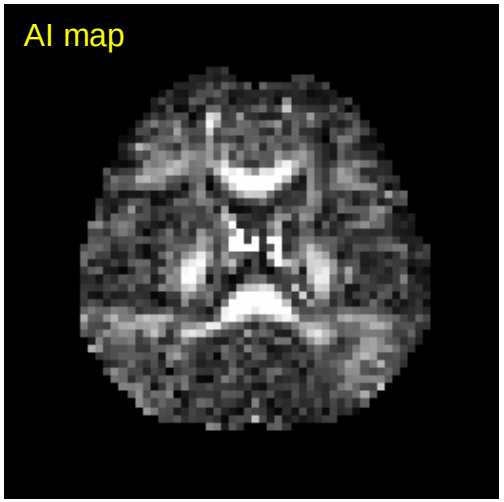


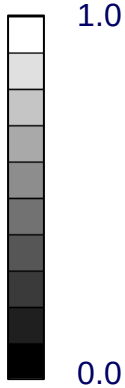




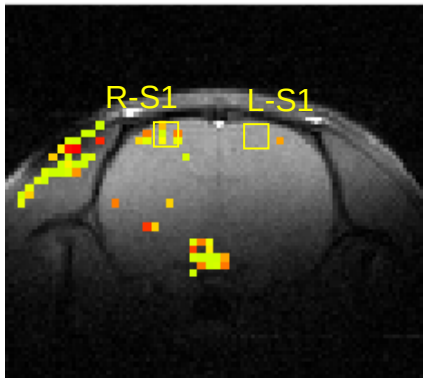




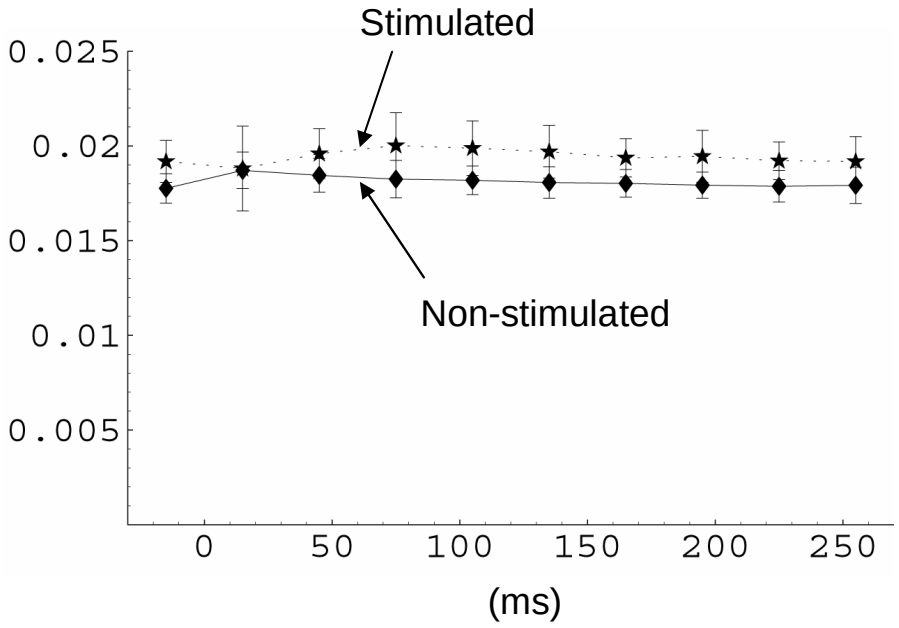




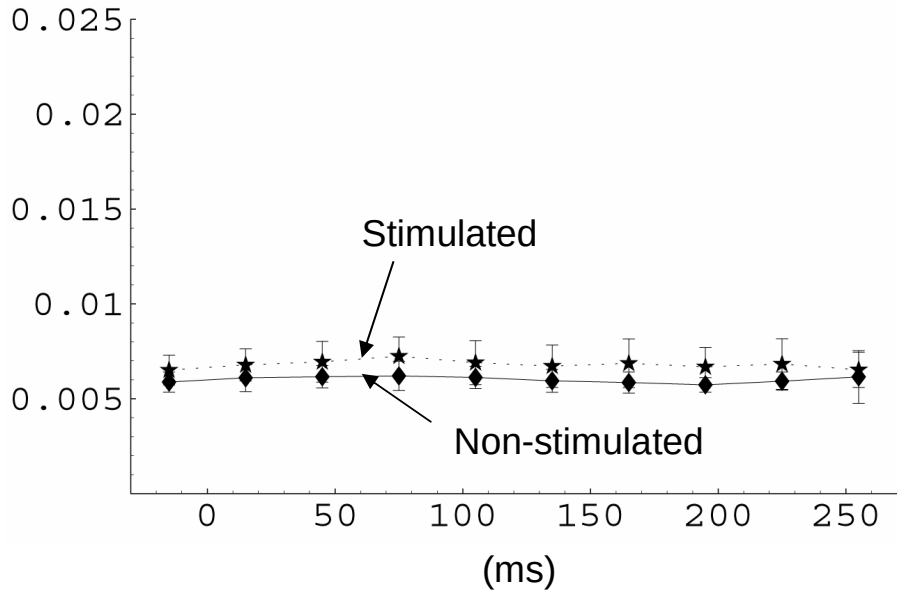
Detection of change of magnetic fields related to neuronal electrical currents by MRI



BOLD-fMRI of the somatosensory area activated by electrical stimulation of the left hindpaw of a rat.

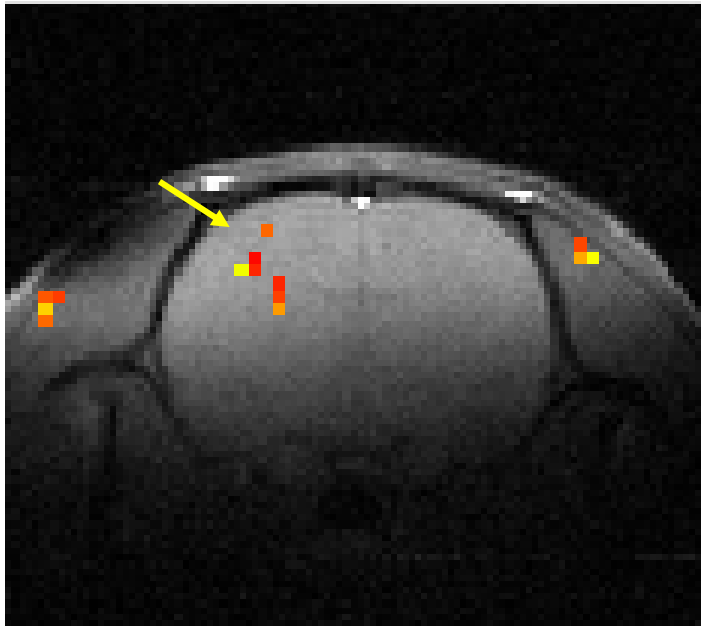


Right somatosensory area



Left somatosensory area

Current MR Imaging: Imaging of magnetic fields caused by neuronal electrical activities in the brain



Subtraction image of signals at 30 – 60 ms from signals at 60 – 90 ms.

Pulse Sequence : gradient echo
Spatial Resolution : 500 μm
Slice Thickness: 2 mm

Theoretical limit of the detection of magnetic field by MRI

Magnetic field generated by neuronal electrical current

5 pT = 5.0×10^{-12} T on the surface of the human head (30 mm away from the source)

4.5×10^{-9} T at the vicinity of neurons 1 mm away from the neurons

Limit of sensitivity after a times averaged.

$$\sigma_B = \frac{N}{S\gamma T_E\sqrt{a}}$$

$$R_s = 1.17(\Omega)$$

$$N = n\sqrt{4kT_S\Delta f R_S}$$

$$= 1.11\times10^{-5}(\mathrm{V})$$

Limit of sensitivity at the gray matter

$\sigma_B = 2.61\times10^{-8}$ T

a = 20 → 5.8×10^{-9} T

	Human	Rat
Repetition time (T_R)	400 ms	333 ms
Echo time (T_E)	5 ms	30 ms
Static field (B_0)	1.5 T	4.7 T
RF field (B_1)	2×10^{-6} T	3.5×10^{-5} T
Field of view (L)	220 mm	32 mm
Slice thickness (h)	6 mm	2 mm
Flip angle (θ)	90°	20°
Number of pixels (n)	256	64
Resistance (R)	1.17 Ω	0.08 Ω
Number of averages (a)	20	20
Limit of sensitivity (σ_B)	5.8×10^{-9} T	4.3×10^{-11} T

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Mechanisms of biological effects of electromagnetic fields

1) Time-varying magnetic field

eddy currents $J = -\sigma \frac{\partial B}{\partial t}$ — **nerve stimulation**

heat $SAR = \sigma \frac{E^2}{\rho}$ — **thermal effects**

2) Static magnetic fields

i) homogenous magnetic field

magnetic torque

$$T = -\frac{1}{2\mu_0} B^2 \Delta\chi \sin 2\theta$$

magnetic orientation of biological cells

ii) inhomogeneous magnetic field

magnetic force

$$F = \frac{\chi}{\mu_0} (\text{grad } B) B$$

parting of water by magnetic fields (Moses effect)

3) Multiplication of magnetic fields and other energy

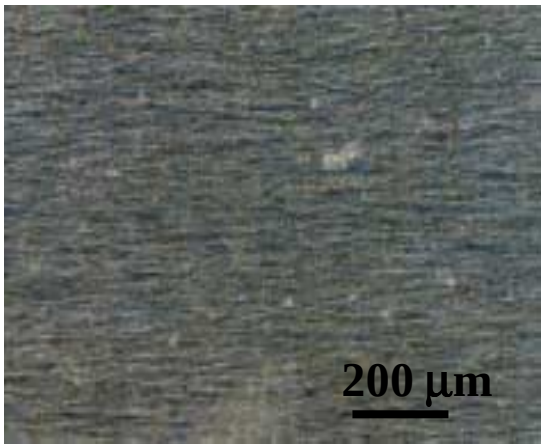
photochemical reactions with radical pairs

singlet-triplet intersystem crossing

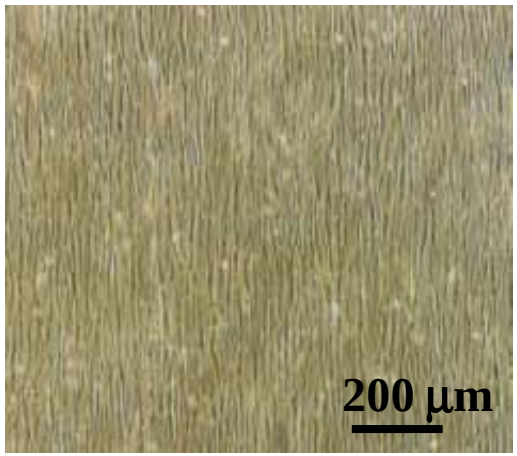
yield effect of cage -product and escape -product

Magnetic orientation of adherent cells

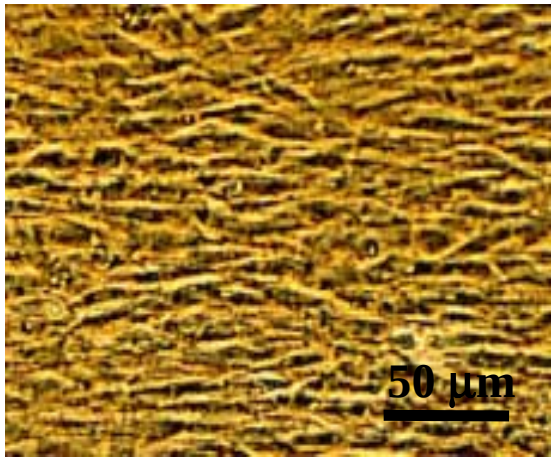
Direction of magnetic field



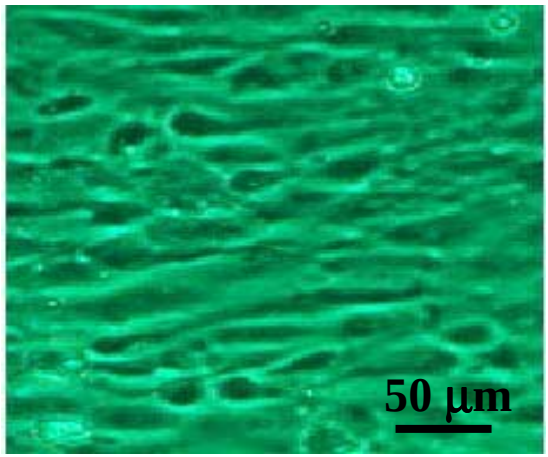
fibrin



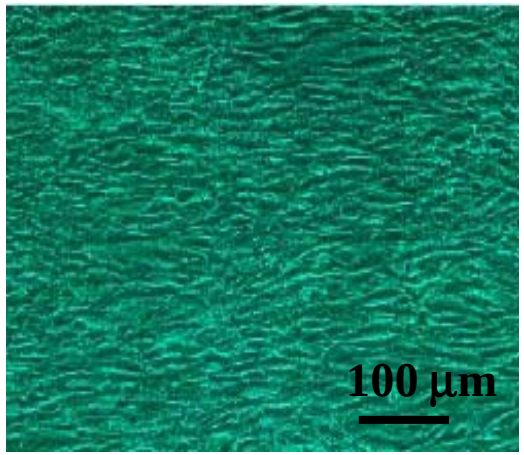
collagen



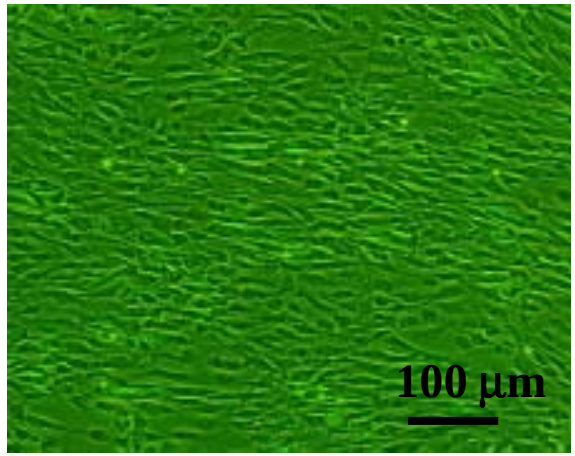
osteoblasts



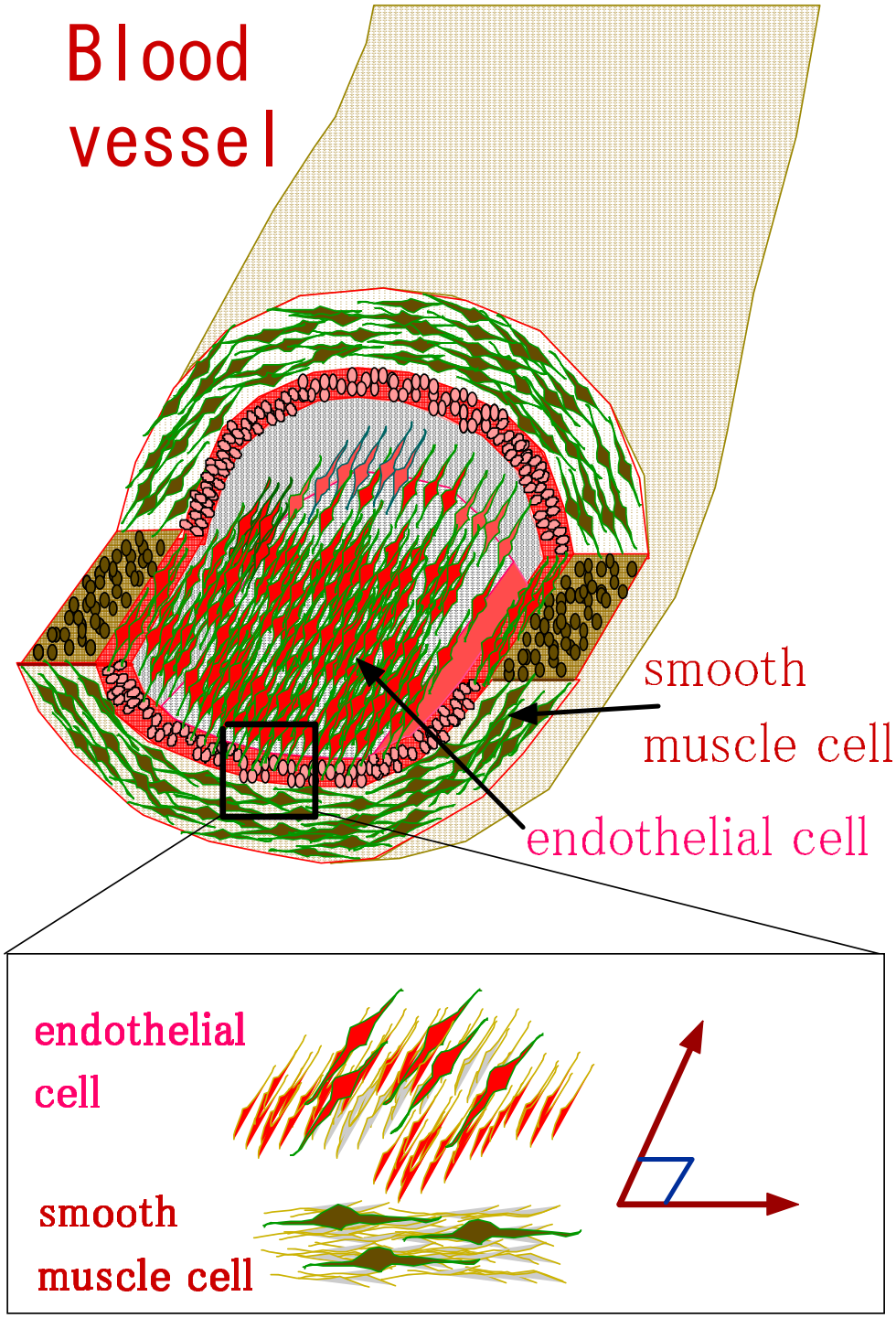
endothelial cells



smooth muscle cells



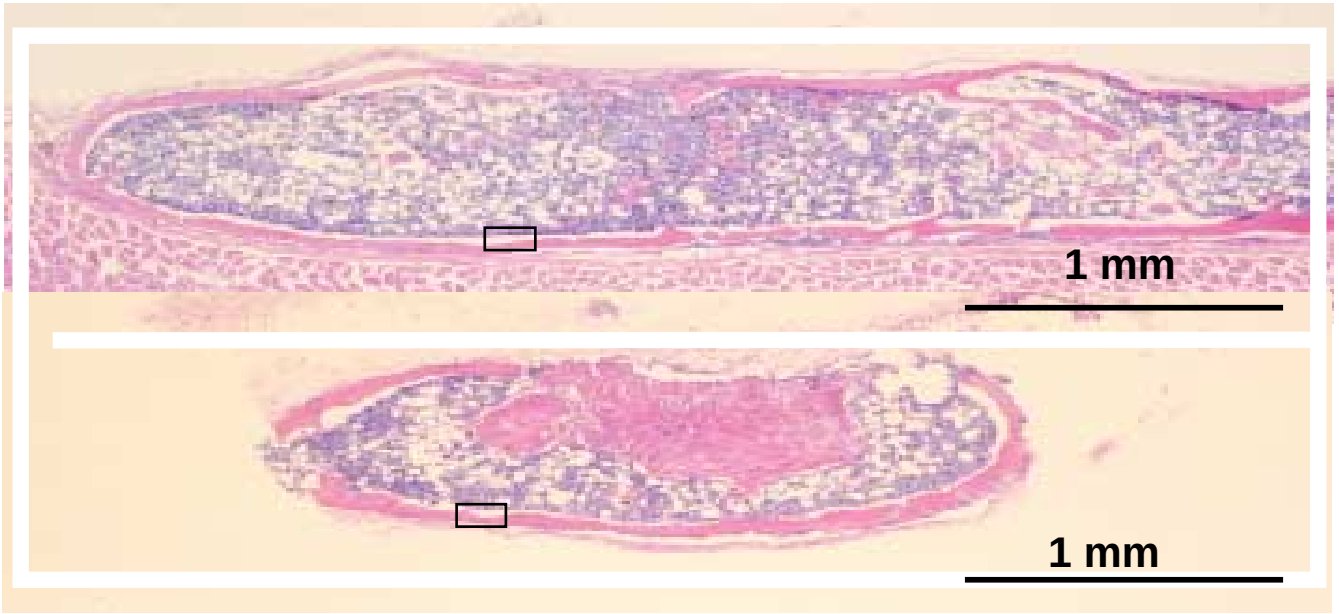
Schwann cells

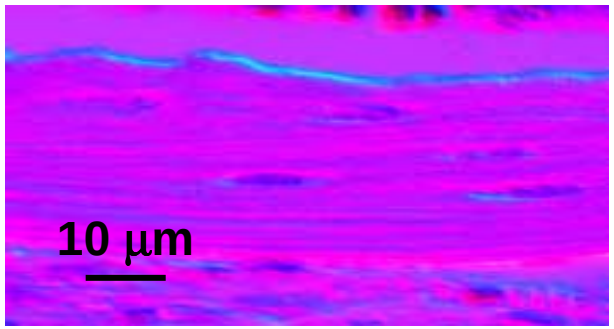

Blood
vessel
smooth
muscle cell
endothelial cell
endothelial
cell
smooth
muscle cell

Direction of magnetic field

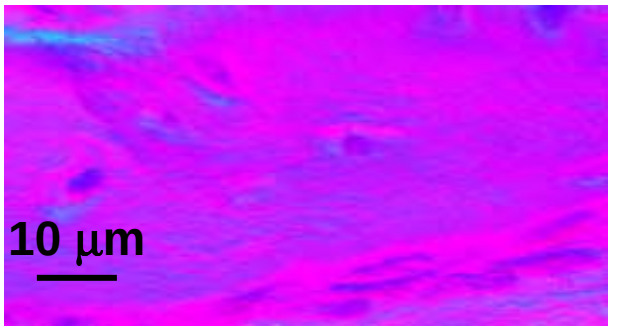
EXPOSED

CONTROL





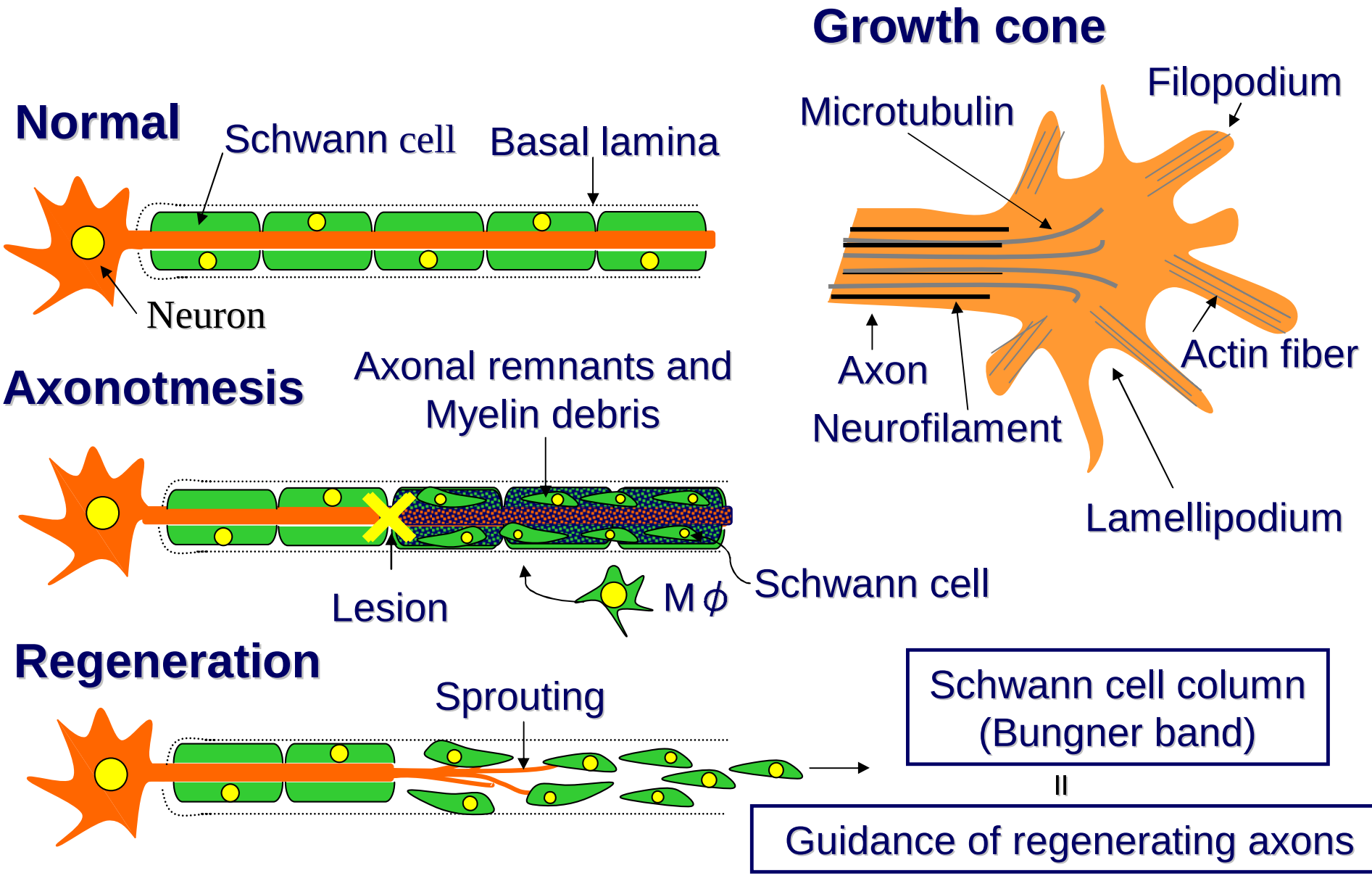
EXPOSED



CONTROL

Ectopic bone formation was stimulated in and around subcutaneously implanted BMP-2 (bone morphogenetic protein)/collagen pellets in mice 21 days after 8 T magnetic field exposure for 60 h. The newly formed bone was extended parallel to the direction of the magnetic field.

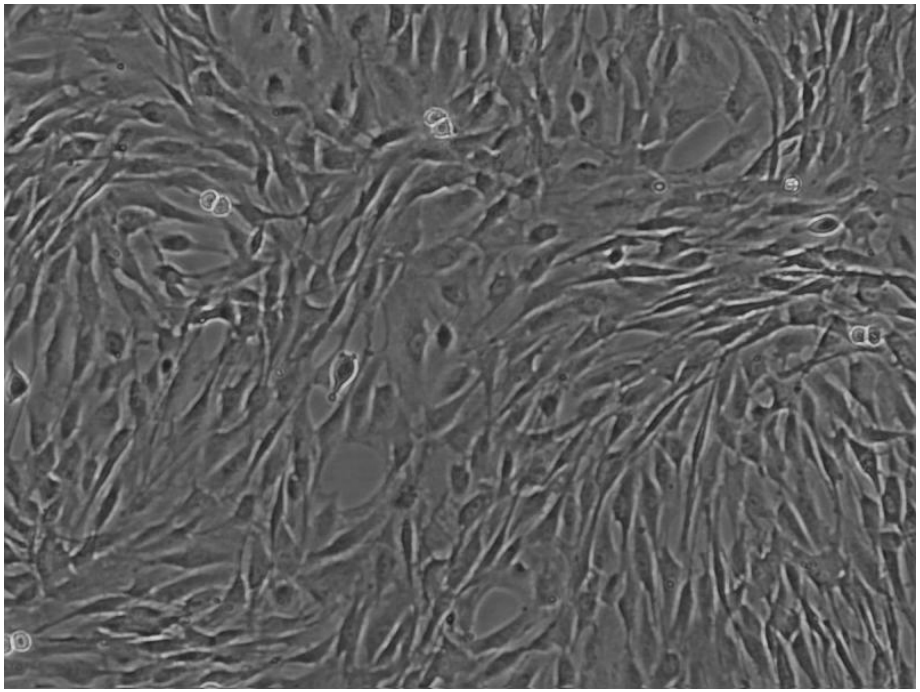
Wallerian degeneration & sprouting



Magnetic orientation of Schwann cells

Control

Exposed



100 μm

8 T magnetic field

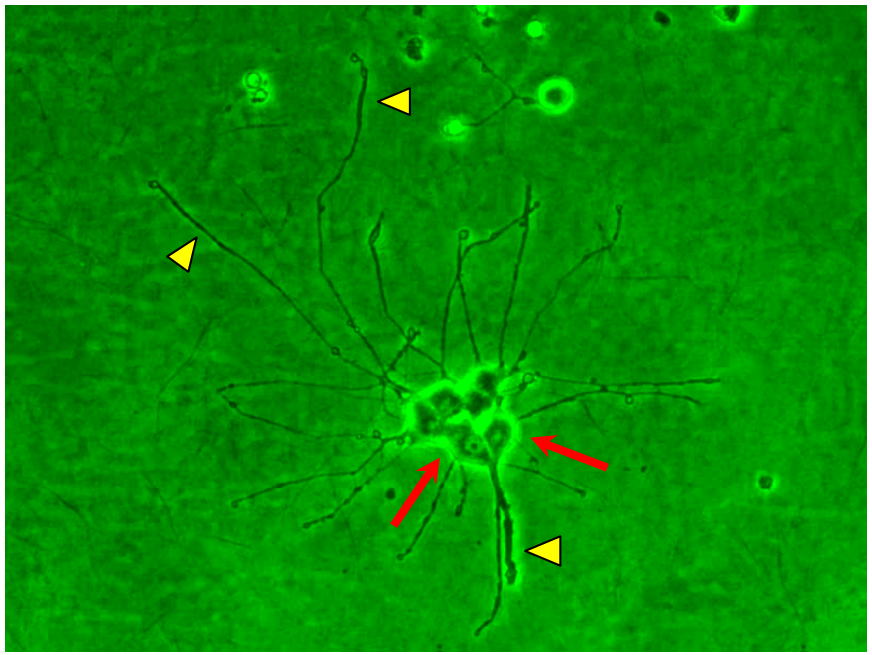
100 μm

Schwann cells oriented parallel to the direction of the magnetic field after 8 T exposure for 60 h in the confluent condition.

Axon elongation into magnetically aligned collagen

Mixture of PC12 (rat pheochromocytoma) cells and collagen (5 days)

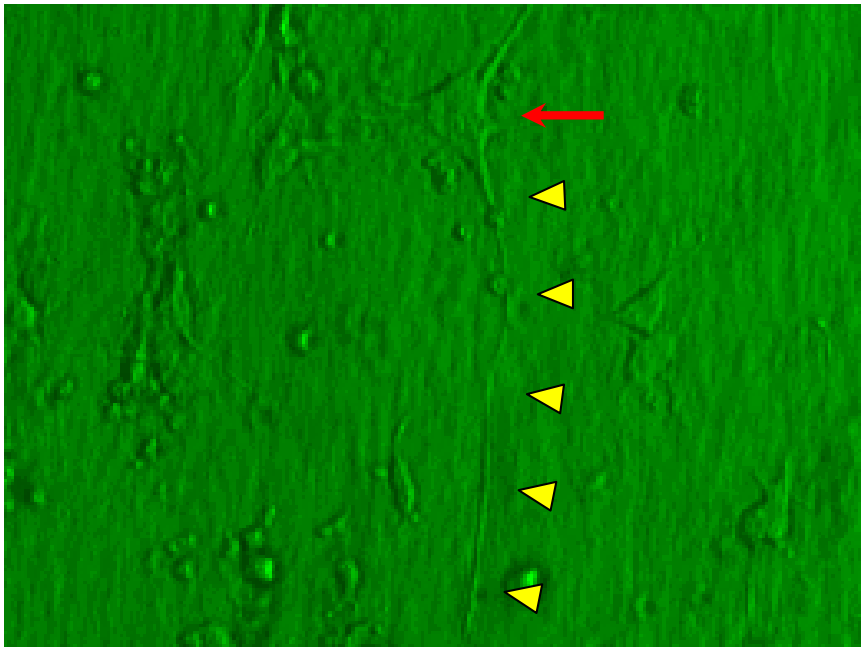
Control



←: soma
◁: axon

50 μm

Exposed



←: soma
◁: axon

magnetic field

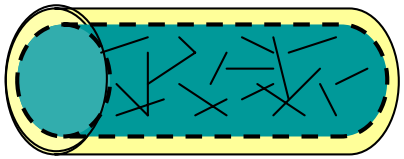
50 μm

Orientation of collagen fibers

Magnetically aligned collagen provides a scaffold for neurons on which to grow and direct the growing axon.

Medical application for artificial nerve graft

Silicone tube
(length : 15.0 mm
inter diameter : 1.5mm)

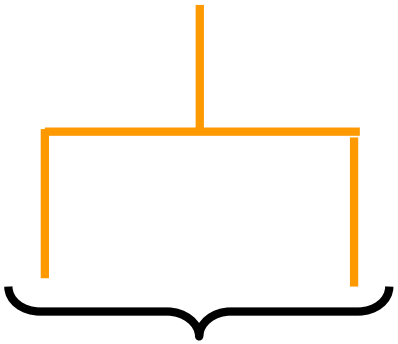


Type Ⅰ collagen solution

〈 Control 〉

Incubation for 2 h

(37 ℃)



〈 Exposure 〉

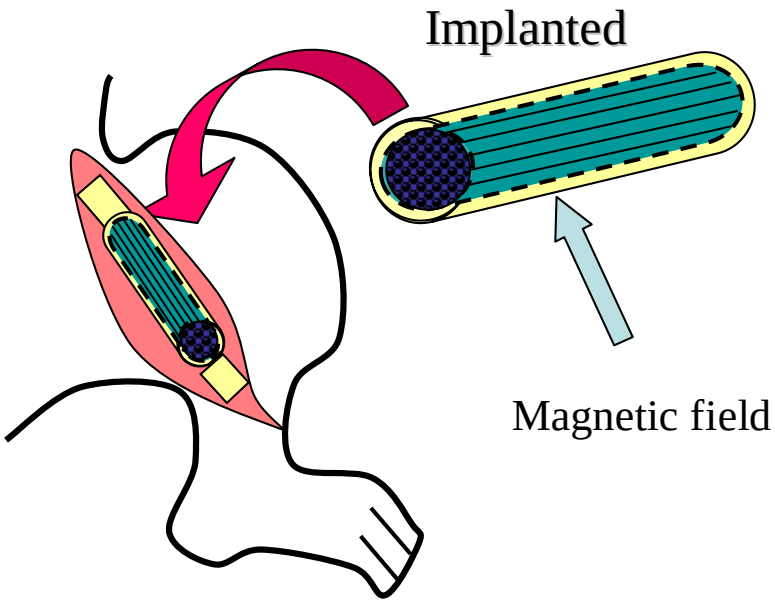
8-T exposure for 2 h (37 ℃)

Experimental groups

1) Control (0T)
2) Exposed (8T)

Examinations (po.12W)

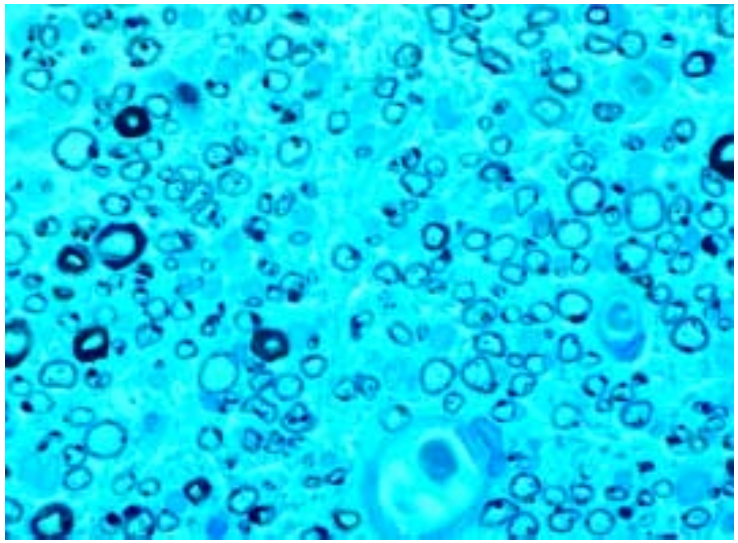
1) % occupied neural tissue
2) Morphological examination
3) Nerve functional examination



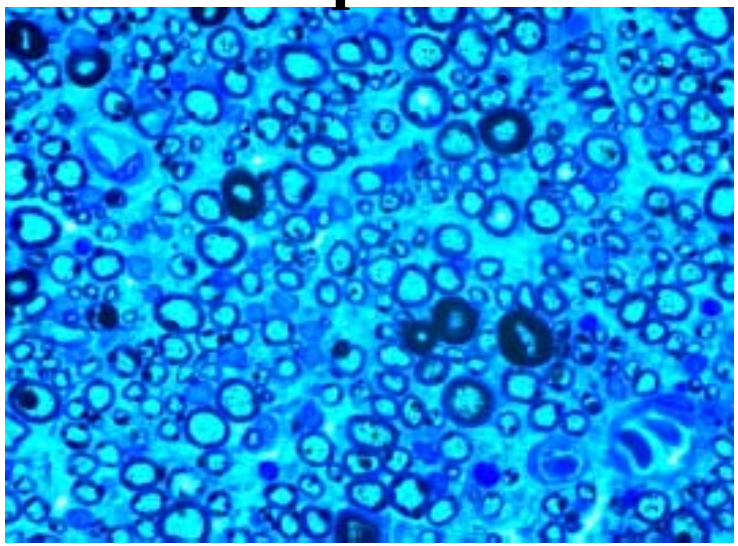
Wistar rat
Sciatic nerve defect

Morphological examination（12 W)

Control



Exposed



20 μm

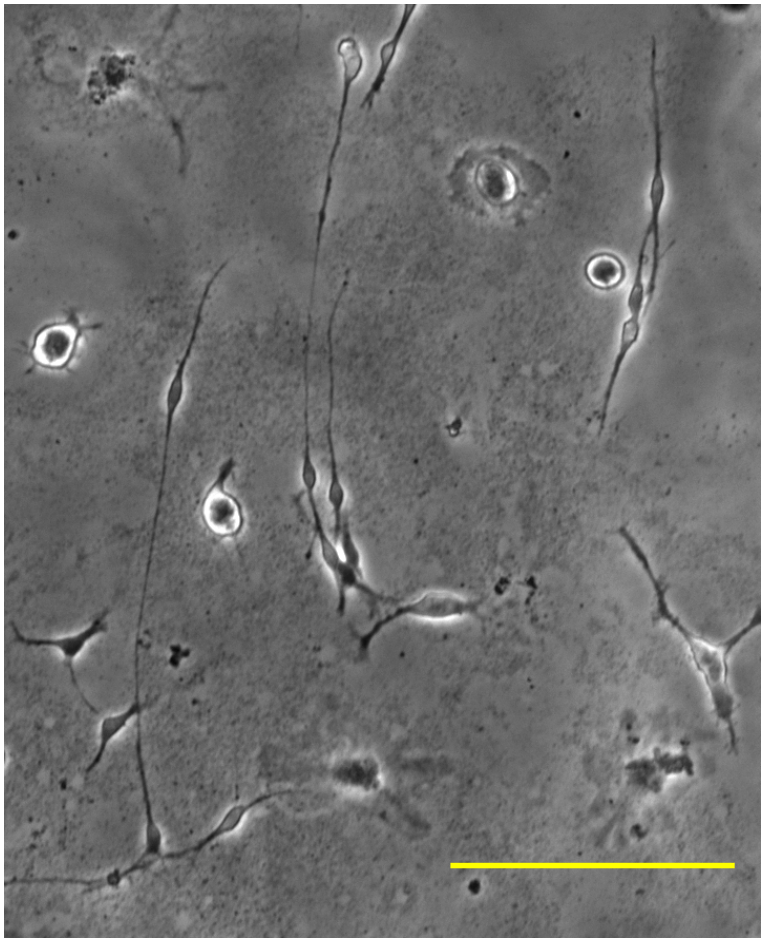
Numbers and diameters of myelinated fibers (po.12W)

	Control	**Exposed**
Numbers	274.0±11.7	373.4±27.6**
Diameters (μm)	5.53±0.064	5.81±0.087*

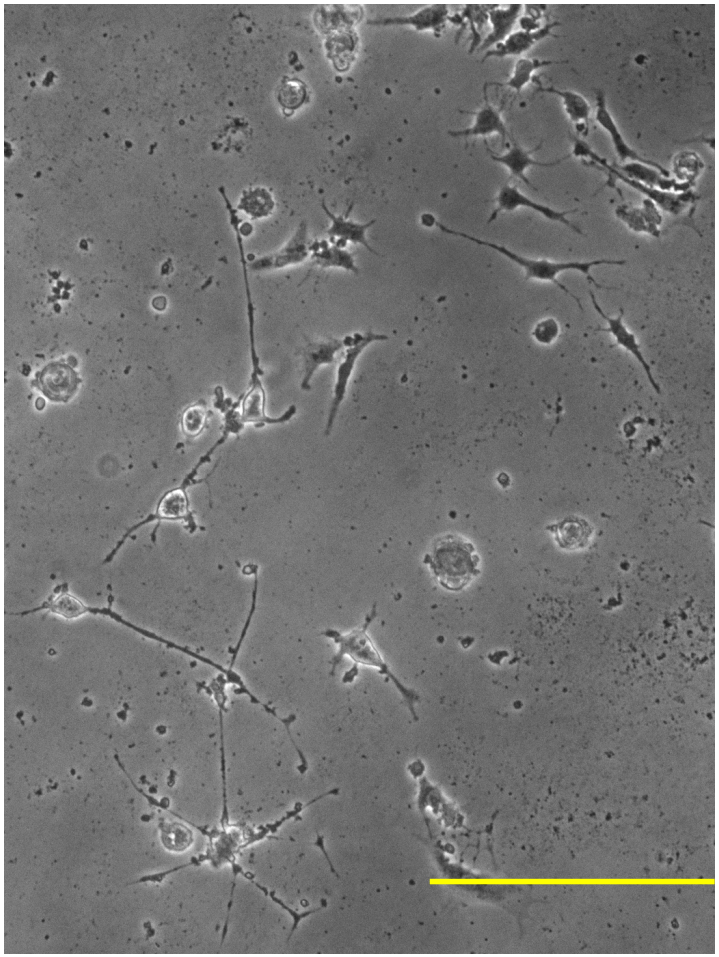
*p<0.05, **p<0.01

1. Biomagnetics and Epilepsy
2. TMS (Transcranial Magnetic Stimulation)
3. MEG (Magnetoencephalography)
4. MRI (Magnetic Resonance Imaging)
5. Magnetic Control of Cell Orientation and Cell Growth
6. Iron and Epilepsy: RF Exposure and Oxidative Stress

Epileptic seizures can be related to neuronal damage induced by lipid peroxidation. Iron plays a fundamental role in oxidative stress because it is a catalyst in the Fenton reaction. The good functioning of ferritin, the protein responsible of oxidizing and storing Fe (II) is therefore essential to avoid epileptic onsets.



Mice fetus' neuron cultures without (left) and with 1 μM ferritin (right). Note the aggregates (microglia) around the neural axons. Bars are 100 μm.



Background

The only proven form of interaction between radio frequency magnetic fields and biological systems is heating. This heating amounts to some 1-2 ℃ for frequencies around 1 GHz with amplitude of 1-10 μT, and it is negligible for fields or frequencies below these.

There is no proven mechanism for the interaction of radio frequency magnetic fields below 100 MHz and biological systems. Neither there is a proven effect of alternating magnetic fields on biomolecules.

No measurements of magnetic field effects on iron cage proteins (or indeed in single proteins) have ever been done.

Mobile Manufacterers forum; URSI forum, etc.

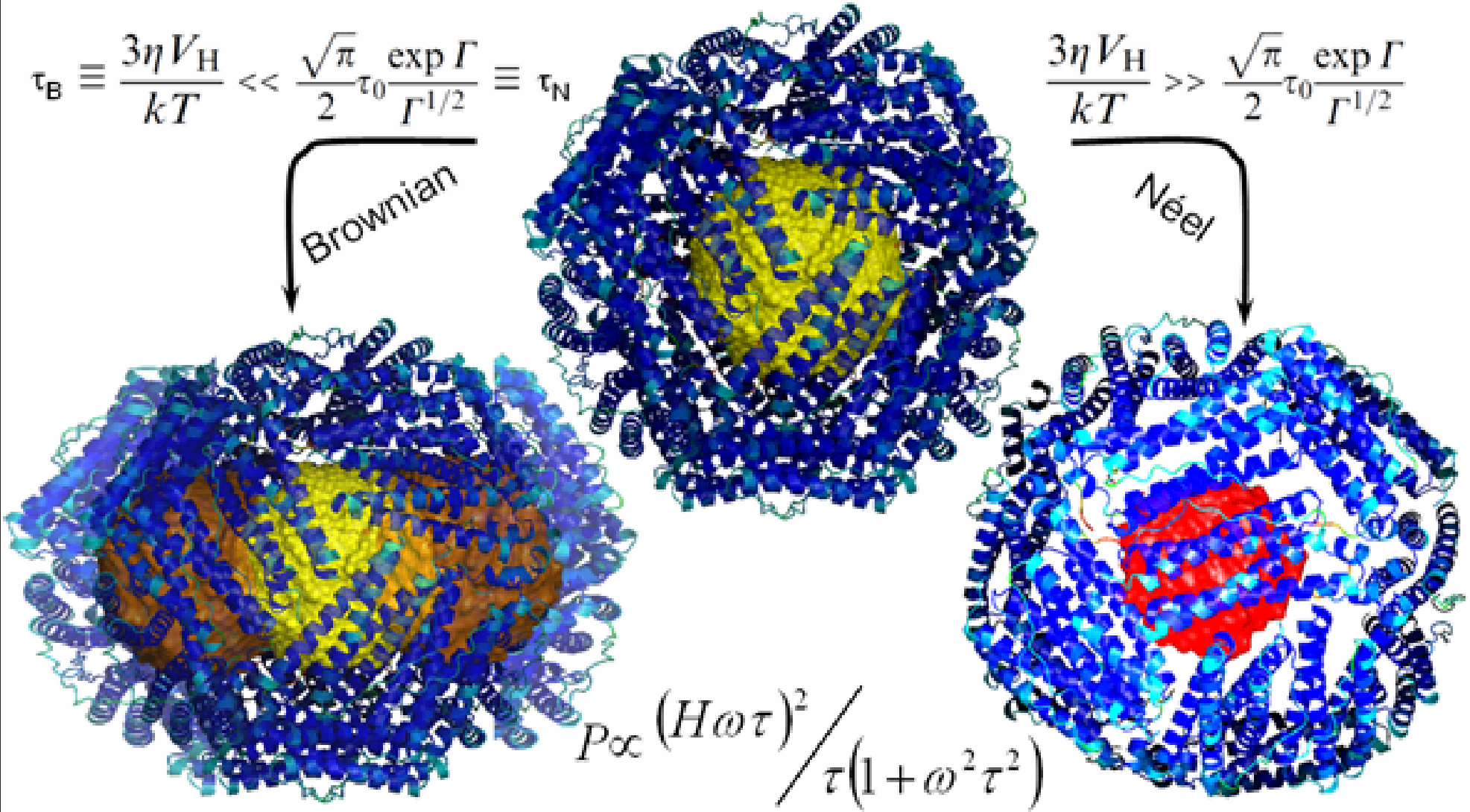
Effects of alternate fields on ferritin: time characteristic

$$\tau_B \equiv \frac{3\eta V_H}{kT} << \frac{\sqrt{\pi}}{2}\tau_0 \frac{\exp \Gamma}{\Gamma^{1/2}} \equiv \tau_N$$

$$\frac{3\eta V_H}{kT} >> \frac{\sqrt{\pi}}{2}\tau_0 \frac{\exp \Gamma}{\Gamma^{1/2}}$$

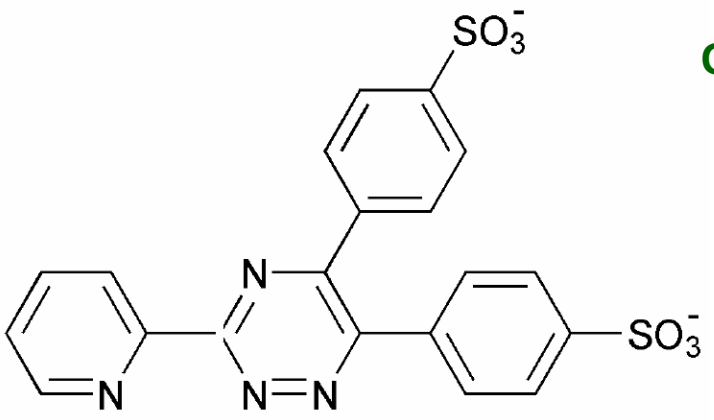
Brownian

Néel

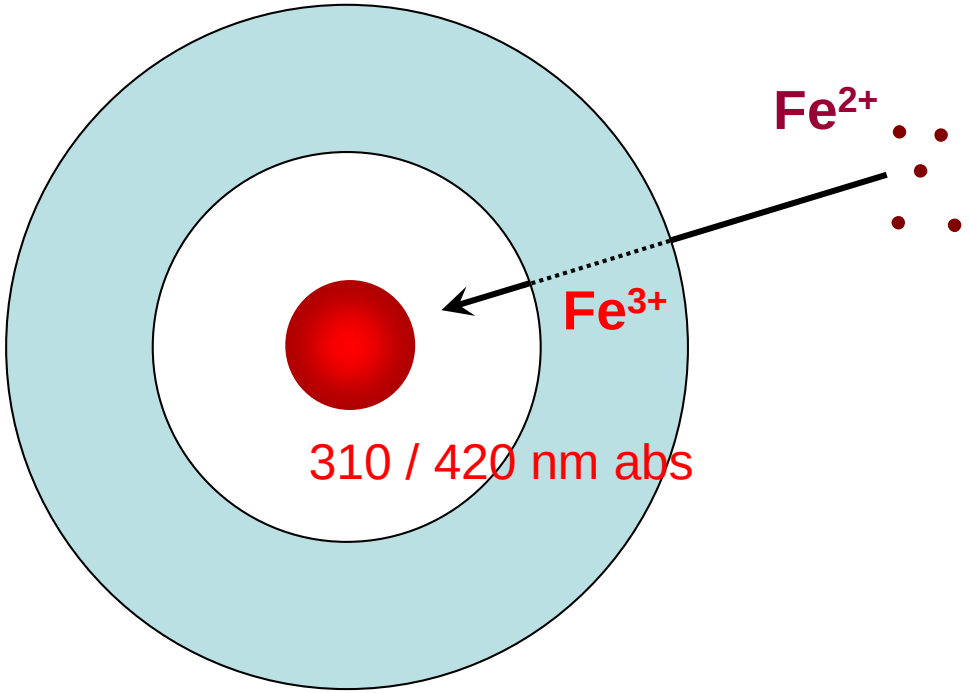


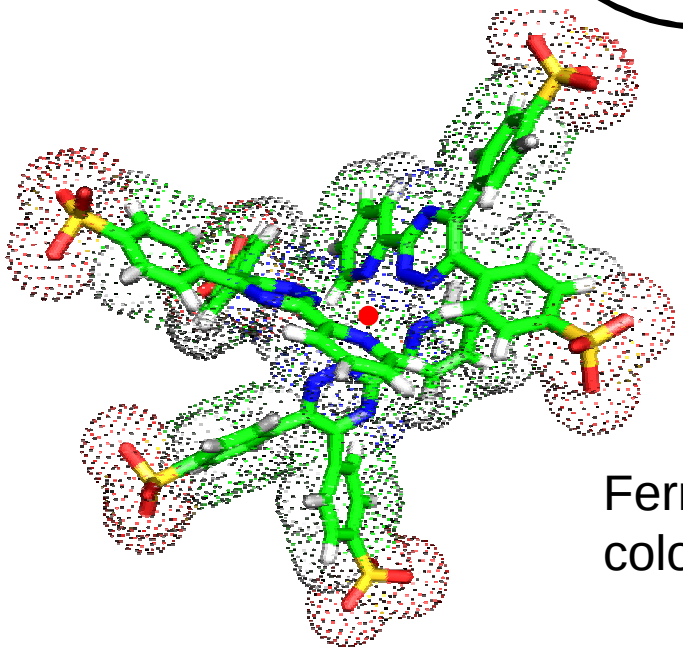
$$P \propto (H\omega\tau)^2 \Big/ \tau\left(1+\omega^2\tau^2\right)$$

Protein functions: Iron absorption and release



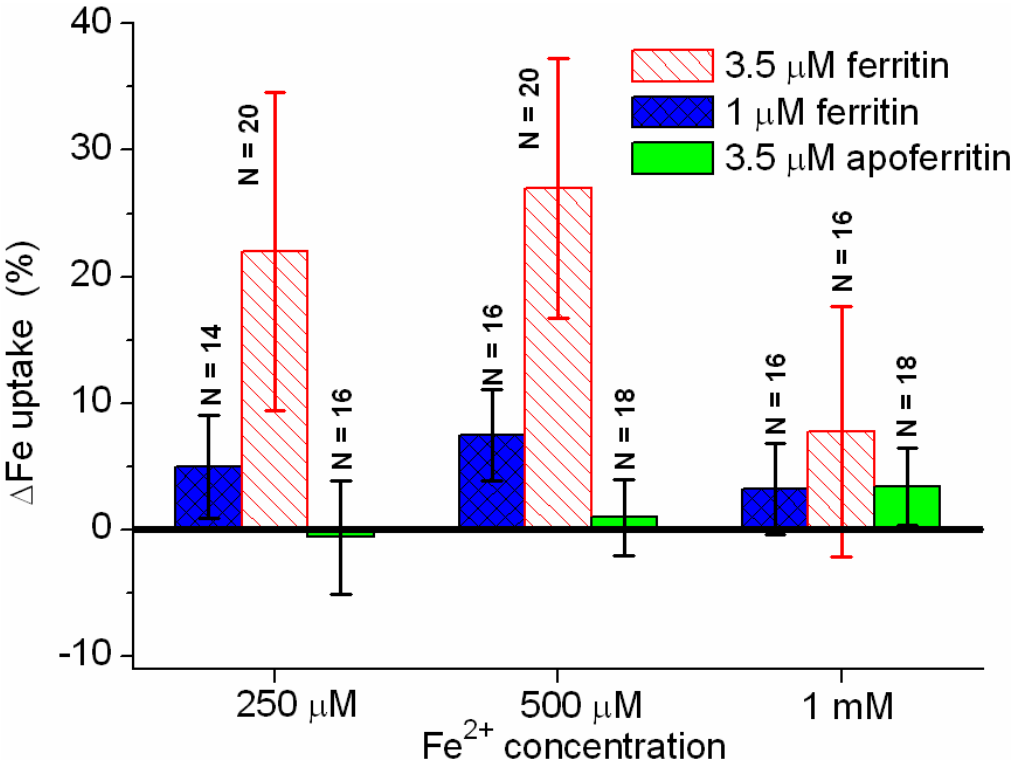
Guy N.L. Jameson et al., Org. Biomol. Chem. 2, 2346 (2004)

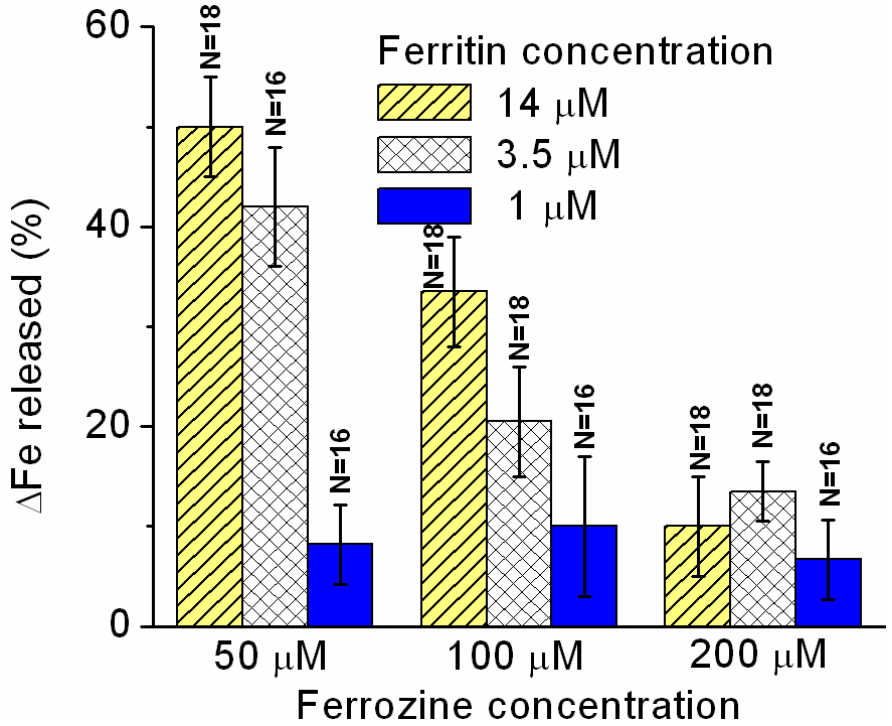




Ferrozine; iron chelator and colorimetric probe (562 nm; ε = 29700 $M^{-1}cm^{-1}$)

Effects of RF magnetic fields on iron uptake and release vs. concentrations

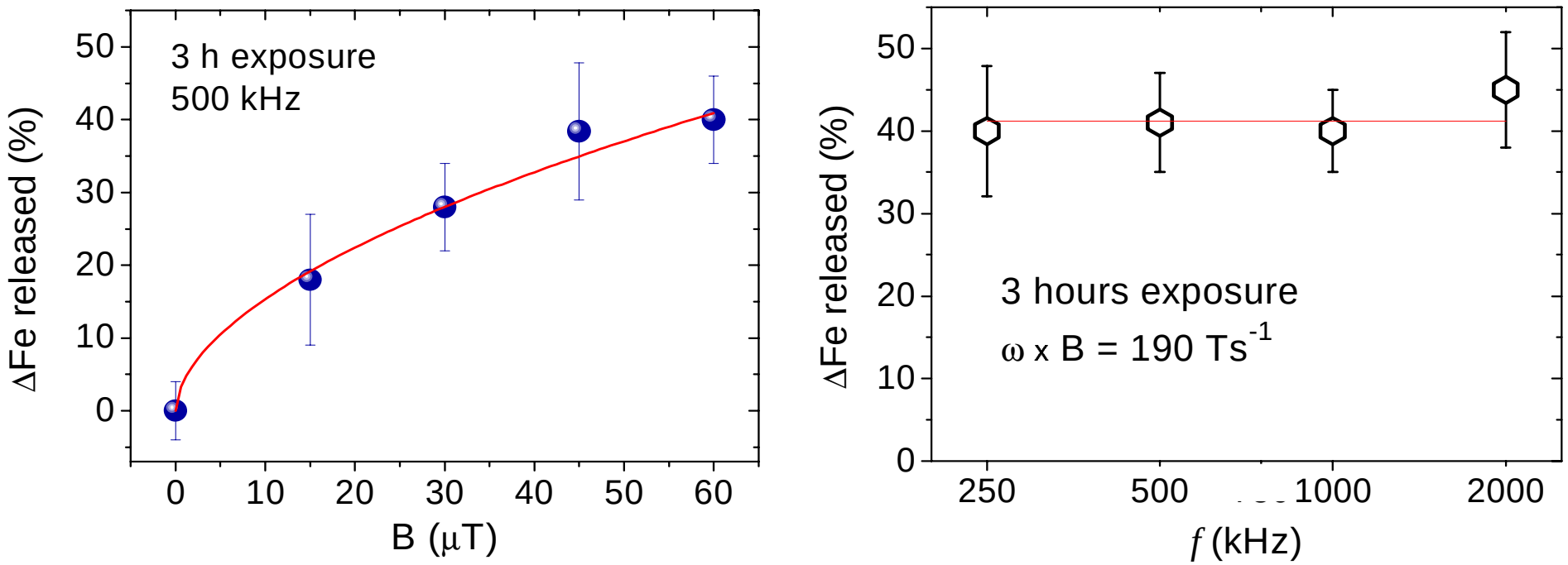




After a 5 hours exposure to fields of 1 MHz and 30 μT, the iron uptake and release is reduced. ΔFe uptake/released = (Fe $|_{control}$-Fe $|_{exposed}$) / Fe $|_{control}$, with Fe $|_{control}$ and Fe $|_{exposed}$ the iron chelated/uptaked after 1 hour in control and exposed samples, respectively.

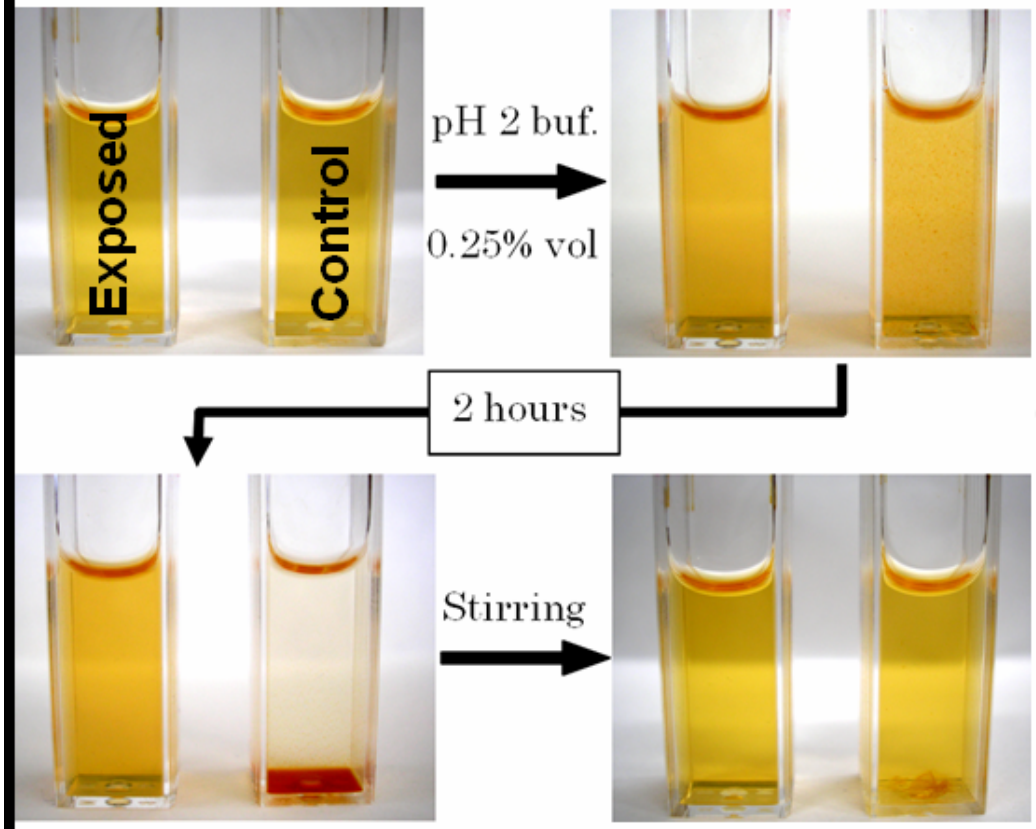
O. Céspedes and S. Ueno, Bioelectromagnetics (TBP April 2009)

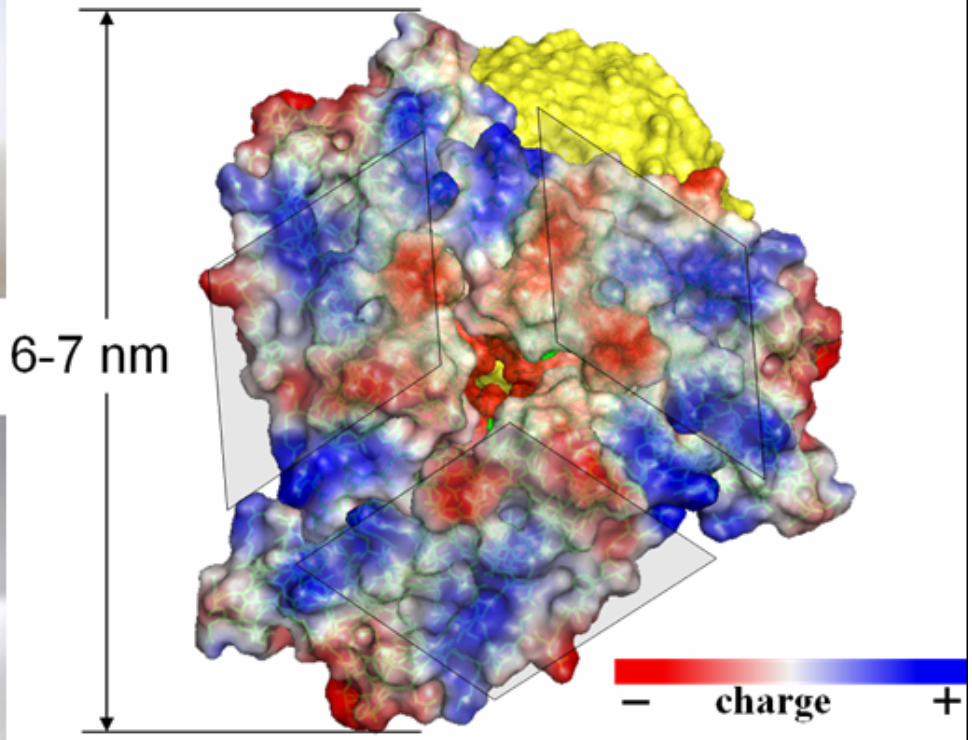
RF magnetic fields effects on iron release and uptake: ΔFe vs. B



The effect is dependent on the amplitude of the applied magnetic field but remains invariant at constant $\omega \cdot B$ product. 3.5 μM ferritin with 50 μM ferrozine (release). Line is a phenomenological fit to a power dependence ($\Delta Fe \propto B^q$ with $q \sim 0.5$; N = 111).

Magnetic field effect in iron release: precipitation i





The 3-fold points act as hydrophilic terminals essential to protein solubility. A sudden release of iron via reducing agents leads to blocking of the terminals and protein aggregation, followed by precipitation. The effect is quenched in protein solutions exposed to magnetic fields

Conclusions in Ferritin

A new mechanism of interaction, between RF magnetic fields and iron cage proteins is demonstrated, with effects on molecular dynamics and protein function.

The mechanism is based on the energy irradiated by the inner superparamagnetic nanoparticle, and it is dependent on the $\omega \cdot B$ product.

This effect may have consequences on iron biochemistry and oxidative stress.

1. TMS (Transcranial Magnetic Stimulation)
   T. Tashiro, M. Fujiki, T. Matsuda, C. M. Epstein, M. Sekino, T. Maeno, H. Funamizu, M. Ogiue-Ikeda, K. Iramina, and S. Ueno

2. MEG (Magnetoencephalography)
   K. Iramina, S. Iwaki, K. Gjini, T. R. Barbosa, and S. Ueno

3. Conductivity MRI and Current MRI
   M. Sekino, T. Matsumoto, T. Hatada, N. Iriguchi, and S. Ueno

4. Magnetic Control of Cell Orientation and Cell Growth
   M. Iwasaka, H. Kotani, Y. Eguchi, M. Ogiue-Ikeda, and S. Ueno

5. Iron and Epilepsy
   O. Céspedes and S. Ueno