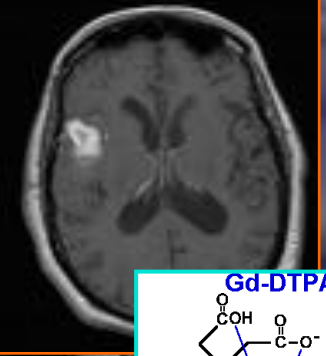
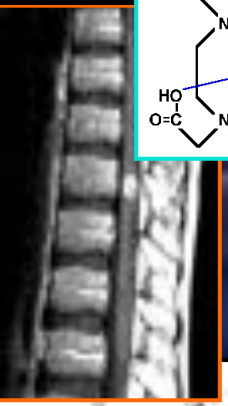
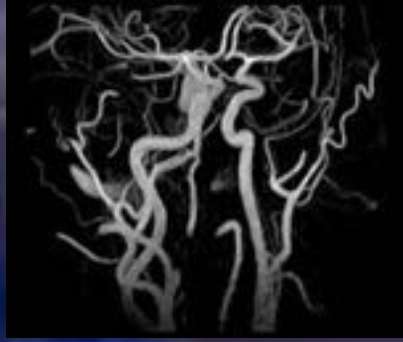
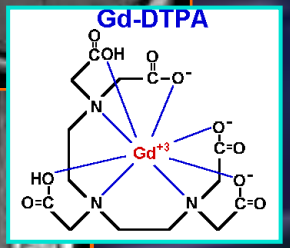
Contrast Agents

Rad 226





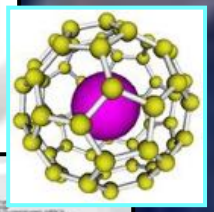


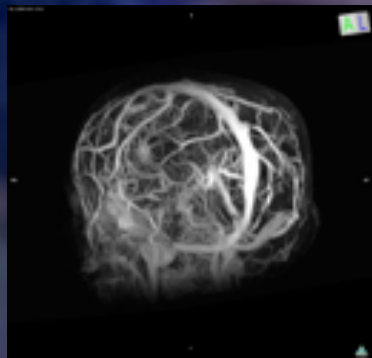


Mike Moseley, Ph.D.

Department of Radiology
Stanford University

May, 2019






MR Contrast
Review
Isn't Gadolinium the
alpha-dog of MR contrast?

Or…Is Chaos Approaching?

Mad Max - Warner Bros 2015


Lets Look at MR Contrast...
Challenges in contrast agents
T1 agents
T2 agents
Gradients
Novel ideas
Mad Max - Warner Bros 2015

Approaching the storm

Can Contrast Be a "Bad" Thing?

Recent reports of Gd accumulation and "NSF"

DOI:10.2214/AJR.06.1094
AJR 2007; 188:586-592

Original Research

Gadodiamide-Associated Nephrogenic Systemic Fibrosis: Why Radiologists Should Be Concerned

Dale R. Broome[1], Mark S. Girguis[1], Pedro W. Baron[2], Alfred C. Cottrell[3], Ingrid Kjellin[1] and Gerald A. Kirk[1]

Rare multisystemic fibrosing disorder, 12/575 pts.
All patients had renal insufficiency.
Developed NSF post-Gd (Omniscan) despite early dialysis…
Conclusion: NSF "strongly associated" with Gd administration.

symmetric skin thickening and edema in medial thighs

Nephrogenic Systemic Fibrosis

Gadolinium Attorneys

Philadelphia, Pennsylvania, New Jersey, Delaware and Natio

800-597-9585

Gadolinium-Based Contrast Agents Also Linked to Life-Threatening Skin Thickening

Among patients with severe kidney disease, the use of gadolinium-based contrast agents is linked to the development of Nephrogenic Systemic Fibrosis, or NSF. NSF was first identified in 1997 and while its cause is unknown, it's only been reported in those with kidney disease.

NSF causes skin thickening that can prevent bending and extending your joints. It can also develop in your diaphragm, thigh muscles, lung vessels, and lower abdomen. Along with causing decreased mobility of joints, NSF can be fatal.

Because of this connection, the US Food and Drug Administration (FDA) requested that the manufacturers of all five gadolinium-based contrast agents (Magnevist, MultiHance, Omniscan, OptiMARK, and ProHance) add a boxed warning and a new Warnings section to their labels to describe the risk of developing NSF.[3]

Gadolinium: The MRI Agent Linked to Brain Abnormalities

January 09, 2014 | 34,920 views

Gadolinium-Based Contrast Agents Linked to Brain Hypersensitivity

It revealed areas of high intensity, or hyperintensity, in two brain regions (the dentate nucleus (DN) and globus pallidus (GP)), which correlated with the number of gadolinium-based enhanced MRIs.

It's unknown at this time what the hyperintensity may mean, however hyperintensity in the DN is associated with multiple sclerosis. It's now being suggested that this hyperintensity may be the result of the large number of enhanced MRI scans often received by multiple sclerosis patients. Hyperintensity of the GP, meanwhile, is linked with liver dysfunction. The study's lead author noted:[2]

Tomonori Kanda M.D., Ph.D., Kazunari Ishii, M.D., Ph.D., Hiroki Kawaguchi, M.D., Kazuhiro Kitajima, M.D., Ph.D., and Daisuke Takenaka, M.D., Ph.D. **High Signal Intensity in the Dentate Nucleus and Globus Pallidus on Unenhanced T1-weighted MR Images: Relationship with Increasing Cumulative Dose of a Gadolinium-based Contrast Material**. *Radiology*, December 2013

Marching on the Castle Gad?

RSNA
Radiological Society of North America

820 Jorie Blvd
Oak Brook, IL 60523
TEL 1-630-571-2670
FAX 1-630-571-7837
RSNA.org

NEWS

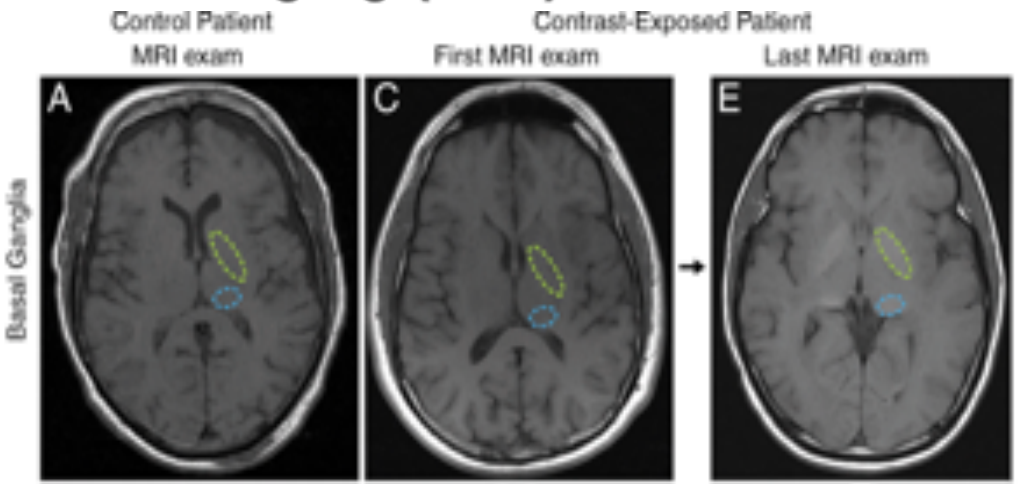
RSNA Press Release

Contrast Agent Linked with Brain Abnormalities on MRI

Released: December 17, 2013

U.S. Food and Drug Administration
Protecting and Promoting *Your* Health

FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI)



About one-third of the 20 million MRIs in the United States each year use one of nine gadolinium-based contrast agents.

Gadolinium-based Contrast Agent Accumulates in the Brain Even in Subjects without Severe Renal Dysfunction: Evaluation of Autopsy Brain Specimens with Inductively Coupled Plasma Mass Spectroscopy

Radiology July 2015
Volume 276, Issue 1

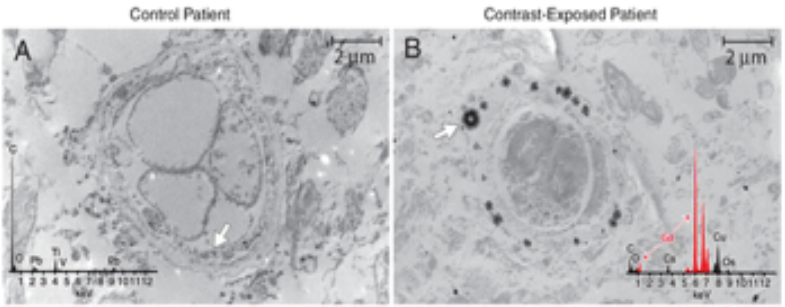
Tomonori Kanda, MD, PhD Toshio Fukusato, MD, PhD Megumi Matsuda, MD Keiko Toyoda, MD, PhD Hiroshi Oba, MD, PhD Jun'ichi Kotoku, PhD Takahiro Haruyama, MD, PhD Kazuhiro Kitajima, MD, PhD Shigeru Furui, MD, PhD

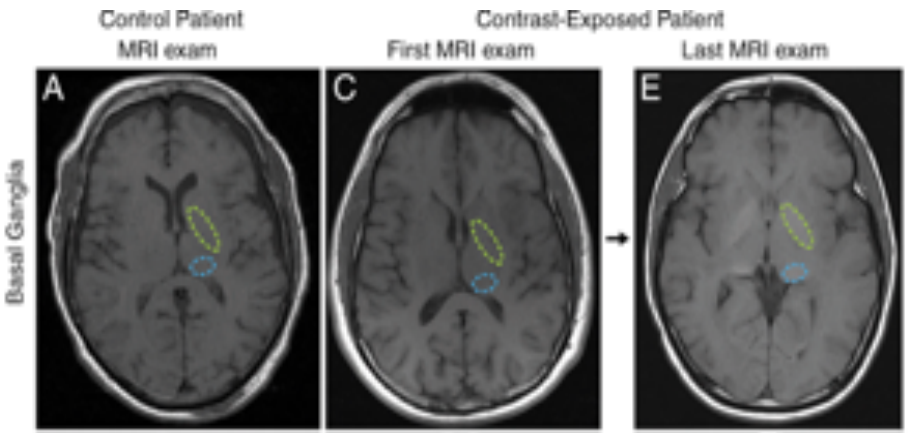
Intracranial Gadolinium Deposition after Contrast-enhanced MR Imaging

Radiology June 2015
Volume 275, Issue 3

Robert J. McDonald, MD, PhD Jennifer S. McDonald, PhD David F. Kallmes, MD Mark E. Jentoft, MD David L. Murray, MD, PhD Kent R. Thielen, MD Eric E. Williamson, MD Laurence J. Eckel, MD

From the Departments of Radiology (R.J.M., J.S.M., D.F.K., K.R.T., E.E.W., L.J.E.), Neurosurgery (D.F.K.), and Laboratory Medicine and Pathology (M.E.J., D.L.M.), College of Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905.





Environmental Science & Technology

Article

pubs.acs.org/est

Increases in Anthropogenic Gadolinium Anomalies and Rare Earth Element Concentrations in San Francisco Bay over a 20 Year Record

Vanessa Hatje,*[†] Kenneth W. Bruland,[†] and A. Russell Flegal[‡]

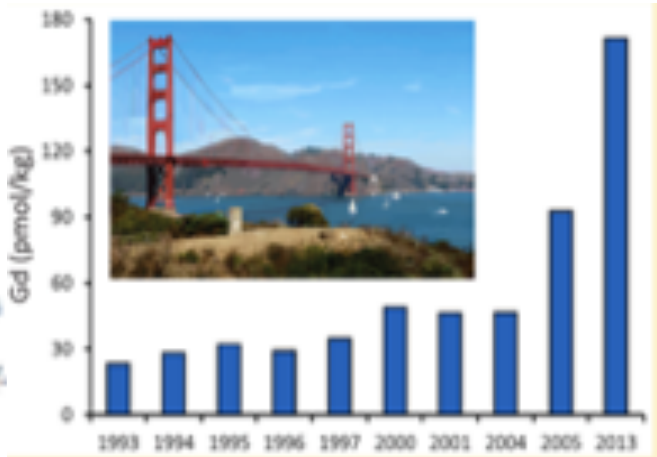
[†]Department of Ocean Sciences and [‡]WIGS, Institute of Marine Sciences, University of California Santa Cruz, California 95064, United States

MRI use causes gadolinium levels to rise in SF Bay

By Brian Casey, AuntMinnie.com staff writer

January 26, 2016 -- A new study has found that levels of gadolinium have been rising steadily in the waters of San Francisco Bay over the past two decades. The study attributes the rising levels to growing use of gadolinium for scientific and medical applications, in particular as a contrast agent for MRI scanning.

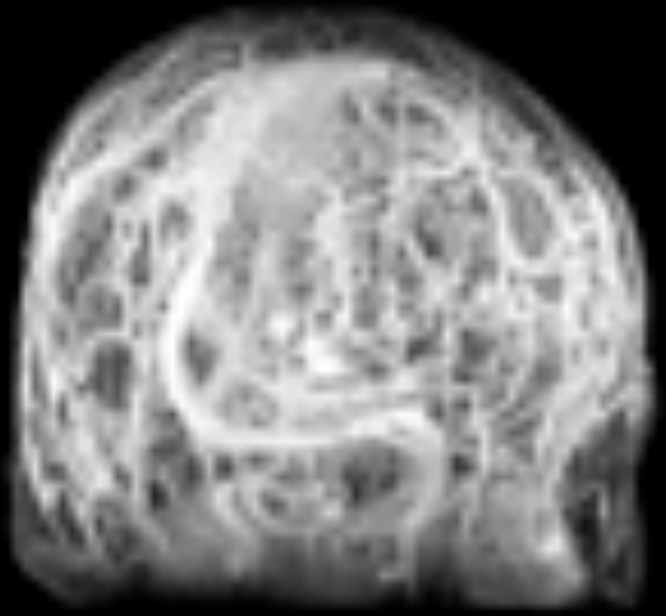
Levels of gadolinium in San Francisco Bay have risen sevenfold in the two decades since 1993, not long after the first MRI contrast agent was approved in the U.S., according to an article published January 7 in *Environmental Science & Technology*. What's more, gadolinium levels are much higher in the southern part of the bay, which is home to a number of scientific and medical institutions, than in the central and northern parts.



The Impact will be *loud...*

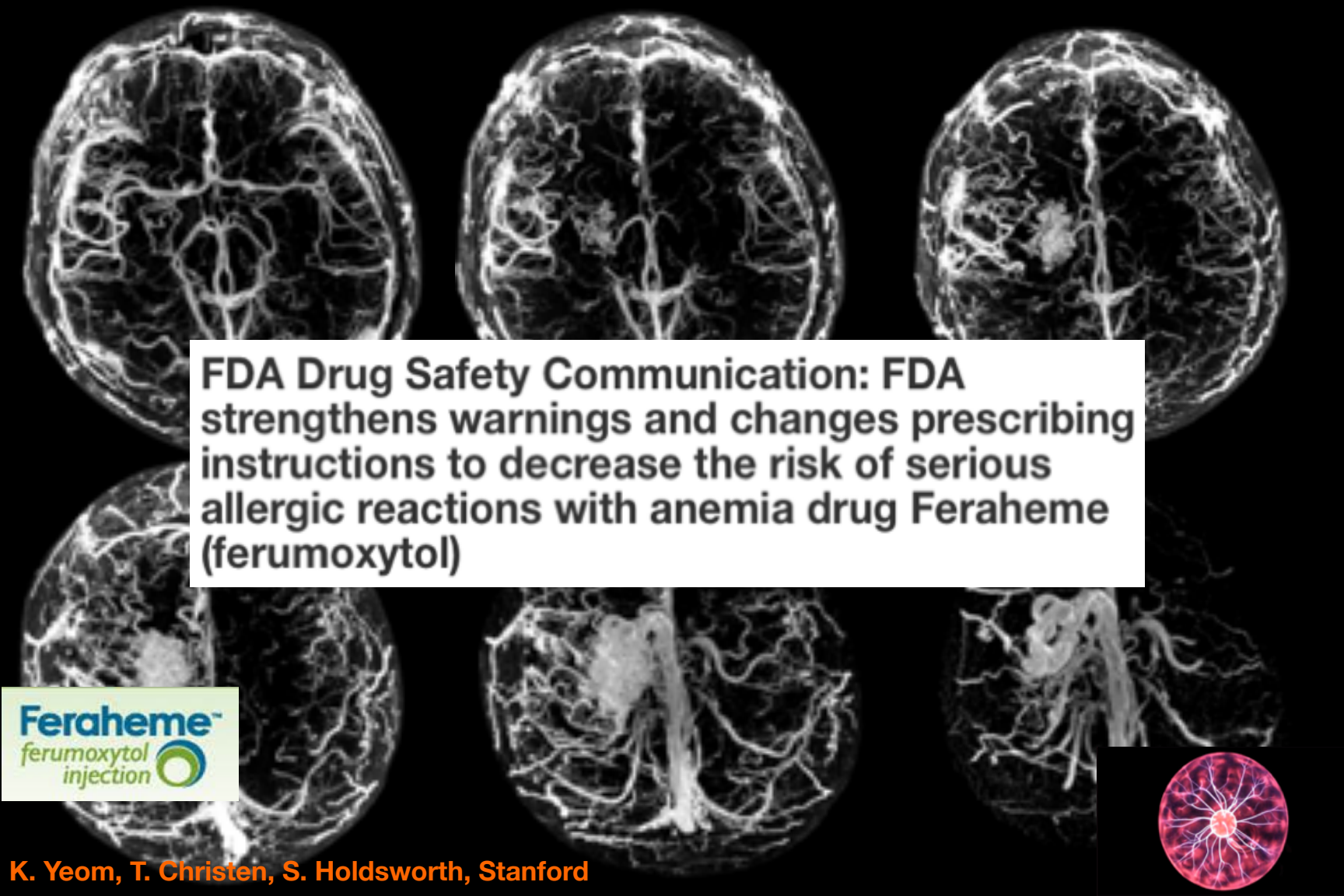
Mad Max - Warner Bros 2015

Ferumoxytol: *Gad-killer or just kille*



Feraheme™
ferumoxytol
injection

K. Yeom, T. Christen, S. Holdsworth, Stanford


FDA Drug Safety Communication: FDA strengthens warnings and changes prescribing instructions to decrease the risk of serious allergic reactions with anemia drug Feraheme (ferumoxytol)
Feraheme
ferumoxytol injection
K. Yeom, T. Christen, S. Holdsworth, Stanford

How Did It All Start?

Mad Max - Warner Bros 2015

Who Are the Front Runners?

Mad Max - Warner Bros 2015

Why Alter MR Tissue Contrast?

1. Proton Relaxation
1.5 Proton Density
1. Proton Exchange
2. Proton Frequency
3. Polarization
4. Chemical Shift metabolism
5. Magnetiztion transfer
6. Other nuclei, F19, C13, O17
7. Other nuclei exchange O17
8. Proton Diffusion
9. Magnetic Susceptibility
10. Tissue conductivity

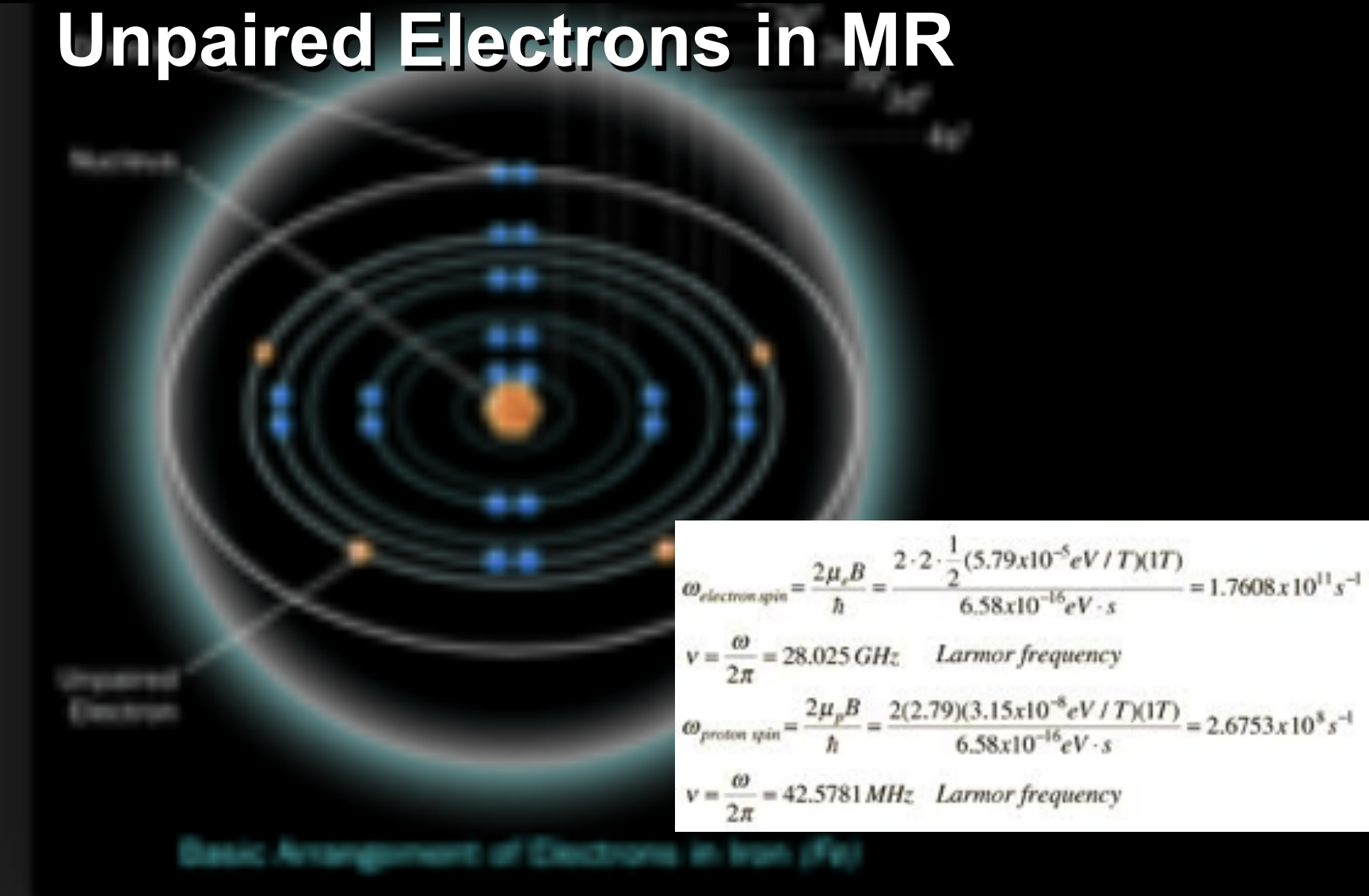
Why Alter MR Tissue Contrast?

1. Nuclei (proton) density - PD
2. Spin lattice Relaxation – T1
3. Susceptibility – T2, T2*

Are amenable for pharmacologic perturbation...

$$SI = PD\,[\,1 - e^{-TR/T1}\,]\,e^{-TE/T2}$$

Unpaired Electrons in MR



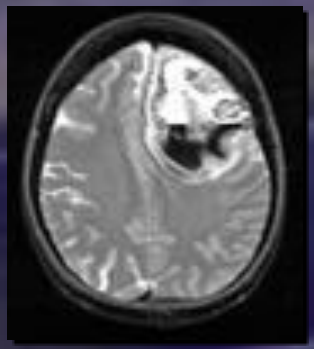
$$\omega_{electron\ spin} = \frac{2\mu_e B}{\hbar} = \frac{2 \cdot 2 \cdot \frac{1}{2}(5.79x10^{-5} eV/T)(1T)}{6.58x10^{-16} eV \cdot s} = 1.7608x10^{11} s^{-1}$$

$$\nu = \frac{\omega}{2\pi} = 28.025\,GHz \quad Larmor\ frequency$$

$$\omega_{proton\ spin} = \frac{2\mu_p B}{\hbar} = \frac{2(2.79)(3.15x10^{-8} eV/T)(1T)}{6.58x10^{-16} eV \cdot s} = 2.6753x10^{8} s^{-1}$$

$$\nu = \frac{\omega}{2\pi} = 42.5781\,MHz \quad Larmor\ frequency$$

Unpaired Electrons in MR

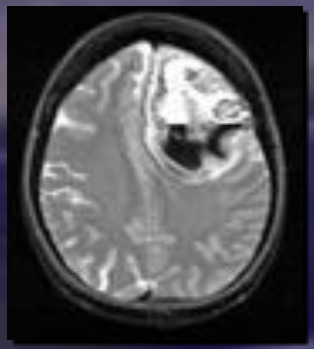


$$SI = N(H)\,[\,1 - e^{-TR/T1}\,]\,e^{-TE/T2}$$

1. T1-shortening on T1w images*.
   paramagnetic agents (Gd-DTPA).
   coated supermagnetic irons (iron particles).

2. T2 (or T2*) shortening on T2*w images.
   para-/superparamagnetic agents (iron particles).
   paramagnetic agents (Gd- or Dy-DTPA)

Unpaired Electrons in MR*



$$SI = N(H)\,[\,1 - e^{-TR/T1}\,]\,e^{-TE/T2}$$

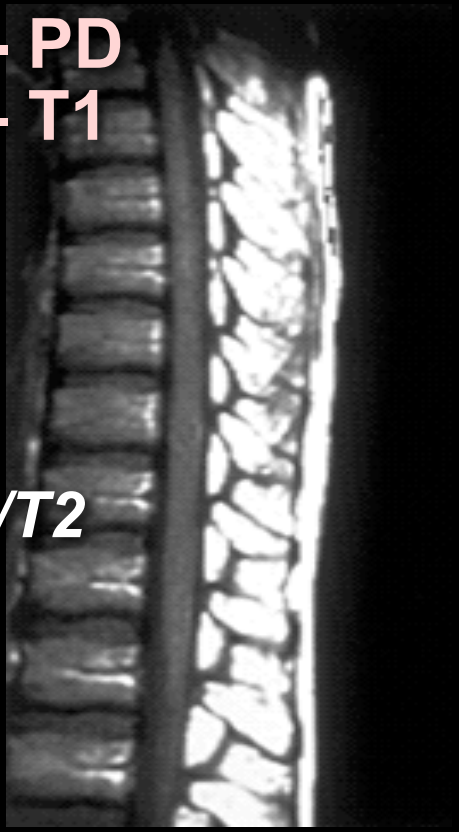
1. T1-shortening agents on T1w images.
   Paramagnetic agents (Gd is best).
   coated supermagnetic irons (iron particles).

2. Chemical-shifting on T2 or CEST images.
   Chemical shift (Pr, Eu, Tb, Dy, Tm, Yb).

Why Alter MR Tissue Contrast?

1. Nuclei (proton) density - PD
2. Spin lattice Relaxation – T1
3. Susceptibility – T2, T2*

$$SI = PD\,[\,1 - e^{-TR/T1}\,]\,e^{-TE/T2}$$



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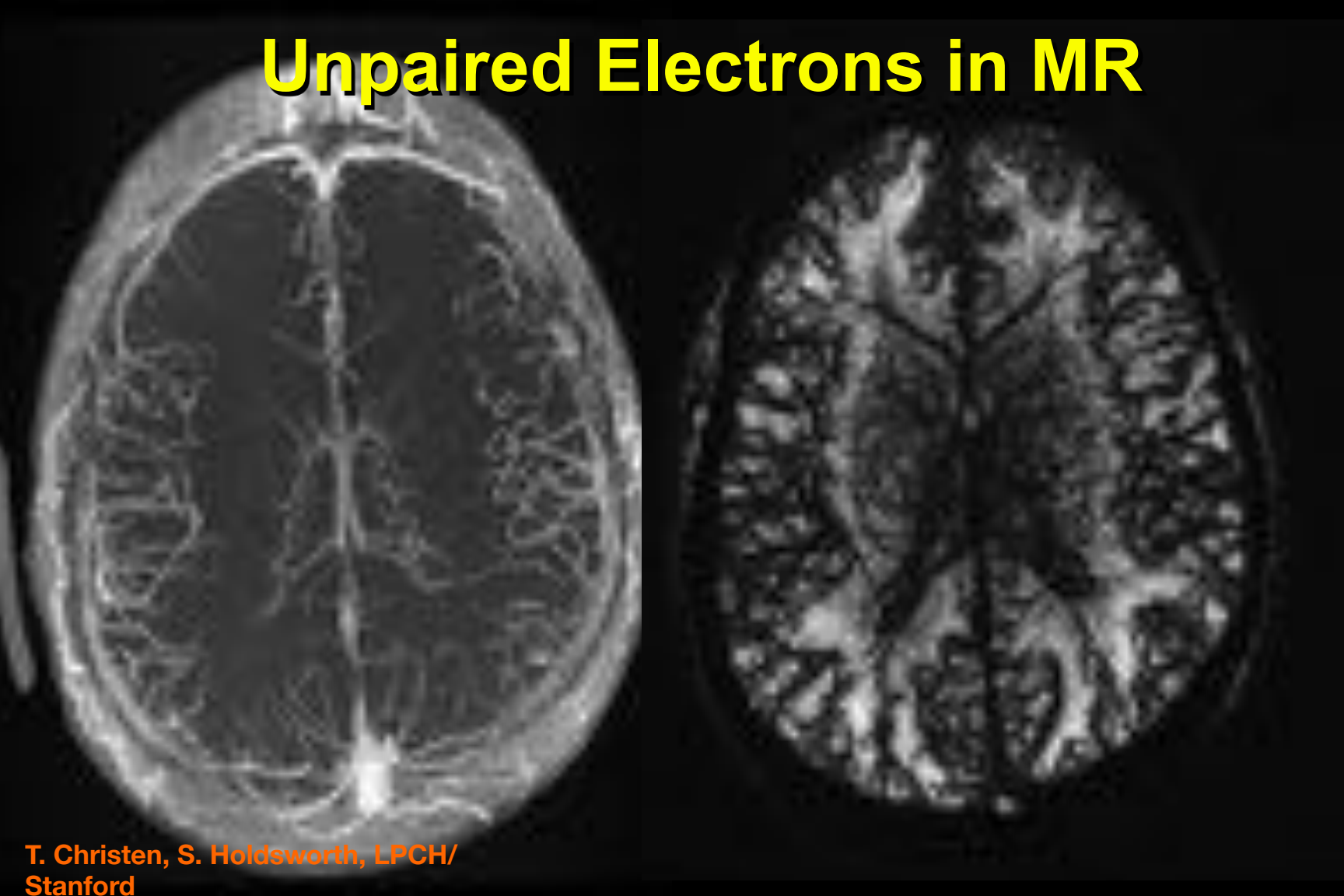
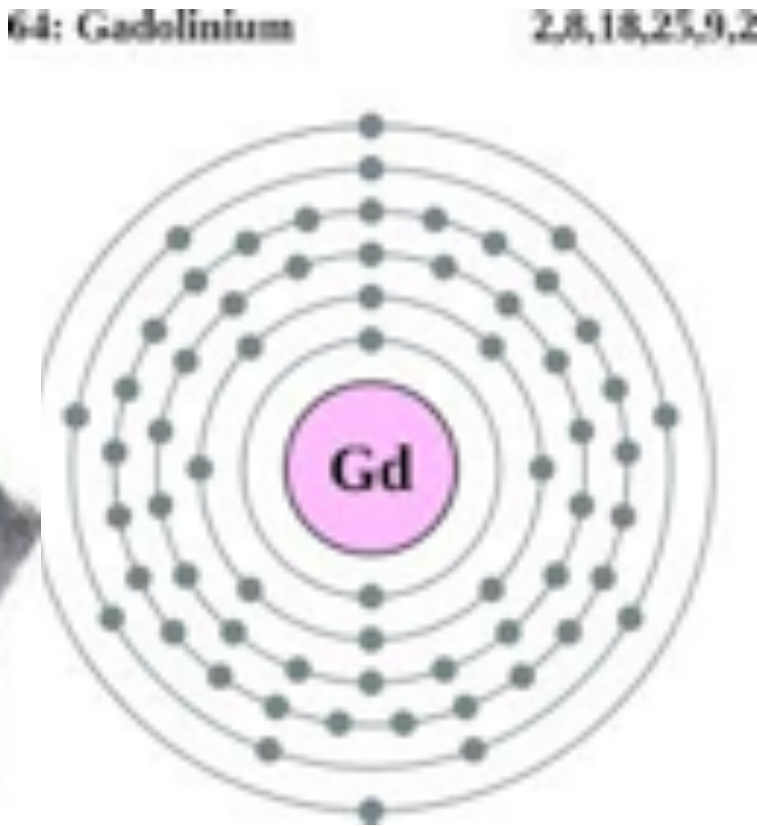
Unpaired Electrons in MR

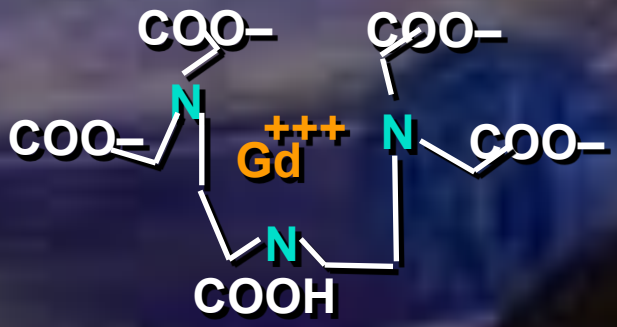


T. Christen, S. Holdsworth, LPCH/ Stanford

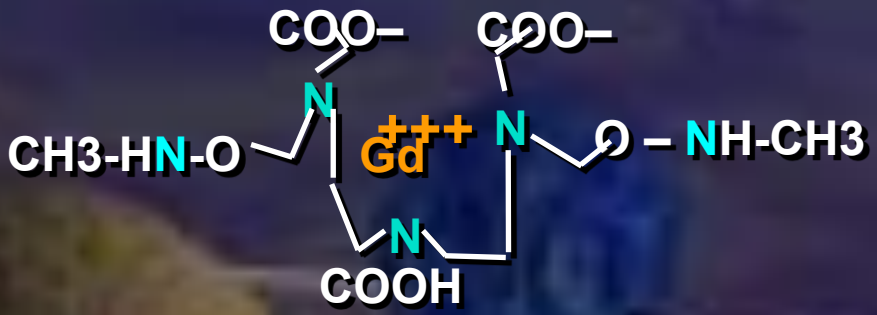
Why Gadolinium?



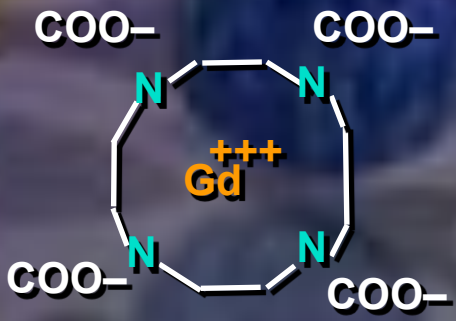
Gd-DTPA: Berlex – Magnevist™



Gd-DTPA-BMA: "Omniscan ™" Nycomed-Amersham-GEHealthcare



Gd-DOTA: Geurbet – DOTAREM™

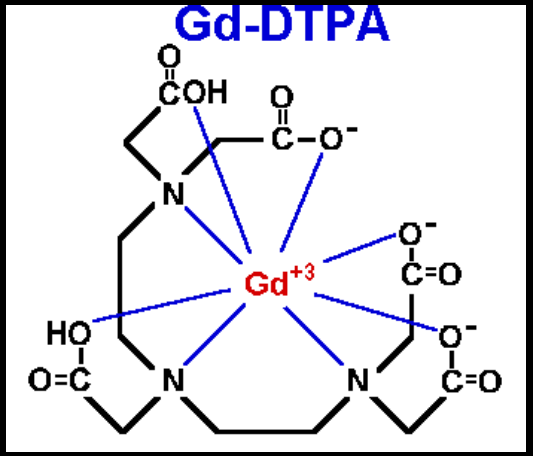


Gadolinium an MR Agent - *Why chelate a good thing?*

Gd-DTPA formation constant = 10^{29}

Half-life in urine = 21.0 min after intravenous injection
in blood = 19.6 min

Compound	LD 50 with intravenous dose in rats (mmol/kg body weight)
Gd-DTPA	10
Gd-EDTA	0.3
Gd-Cl3	0.4
Meglucamine diatrizoate (common X-ray contrast agent)	18



Gd-DTPA: Berlex – Magnevist™

The chelate binds the metal tightly…
Excreted renally (>99.9%).
Occupies space and coordination sites…
A necessary evil.

Contrast Agents

Topics:

- Contrast agent families
- T1 and T2 effects
- In vivo physiology
- Imaging with contrast agents

Reading References:

- On-line resource: www.emrf.org and stuff therein…
- On-line resource: Greg Brown, http://www.users.on.net/vision
- Bloembergen, Purcell, and Pound, "Relaxation Effects in NMR Absorption", *Phys. Rev.* 73:679-712, 1948.

Unpaired e^- and "T1 Relaxivity"

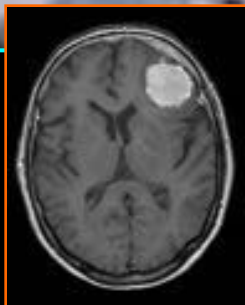
Unpaired electron clouds fluctuate around metal.
e^- create fluctuation in local B0 *- interactions with protons.*
Fluctuating B0 fields *– Acts as magnetization sink.*
Randomizes magnetization.
Result looks like T1 relaxation –
Fast relaxation = Shortened T1.

Apparent shortening of T1-
at a given B0 and temperature...

$$1/T1_{(observed)} = 1/T1_{(intrinsic)} + r1\,[Conc]$$

(200 msec = 1000 msec + 3.8*[0.1mmol/kg])

*$mmol^{-1}$ L sec^{-1}



Unpaired e^- and "T1 Relaxivity"

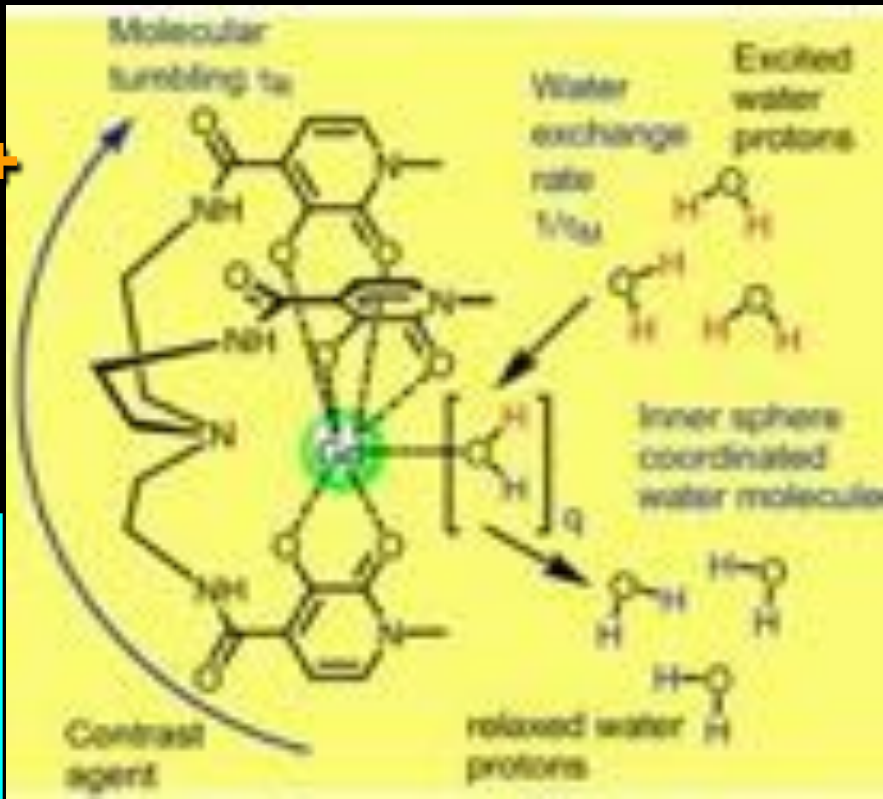
Proton spins near metal sees fluctuating B0 caused by the electron spins near proton frequency. ***637,000 x more effective!*** **Any proton magnetization is damped by the oscillations of the electron spins.** ***Result is "relaxed" protons.***

1/T1 (metal-proton) ~

1/ τs (correlation time of electrons) +

1/ τm (time protons are near) +

1/ τr (Rotational motion of complex)

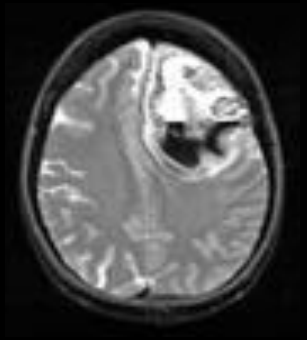


Magnetic Susceptibility

MR relaxation enhancement ("relaxivity") is a question of unpaired electrons...

Diamagnetic agents *no unpaired e-* *no effect on T1, T2. PD only*	10^{0}	T1 - T2*-	Oils, PFOB
Paramagnetic agents *unpaired e-* *noninteracting domains*	10^{-1}	T1↓↓ T2*↓	Gd^{+3}, Fe^{+3}
Superparamagnetic *unpaired e- pools* *noninteracting domains*	10^{+2}	T1↓ T2*↓↓↓	Fe particle
Ferromagnetic *unpaired e- oceans* *strongly interacting domains* *(>0.035μm) threshold...*	10^{+4} 10^{3} *cm / gauss	T1- T2↓↓↓	Metal Artifacts…

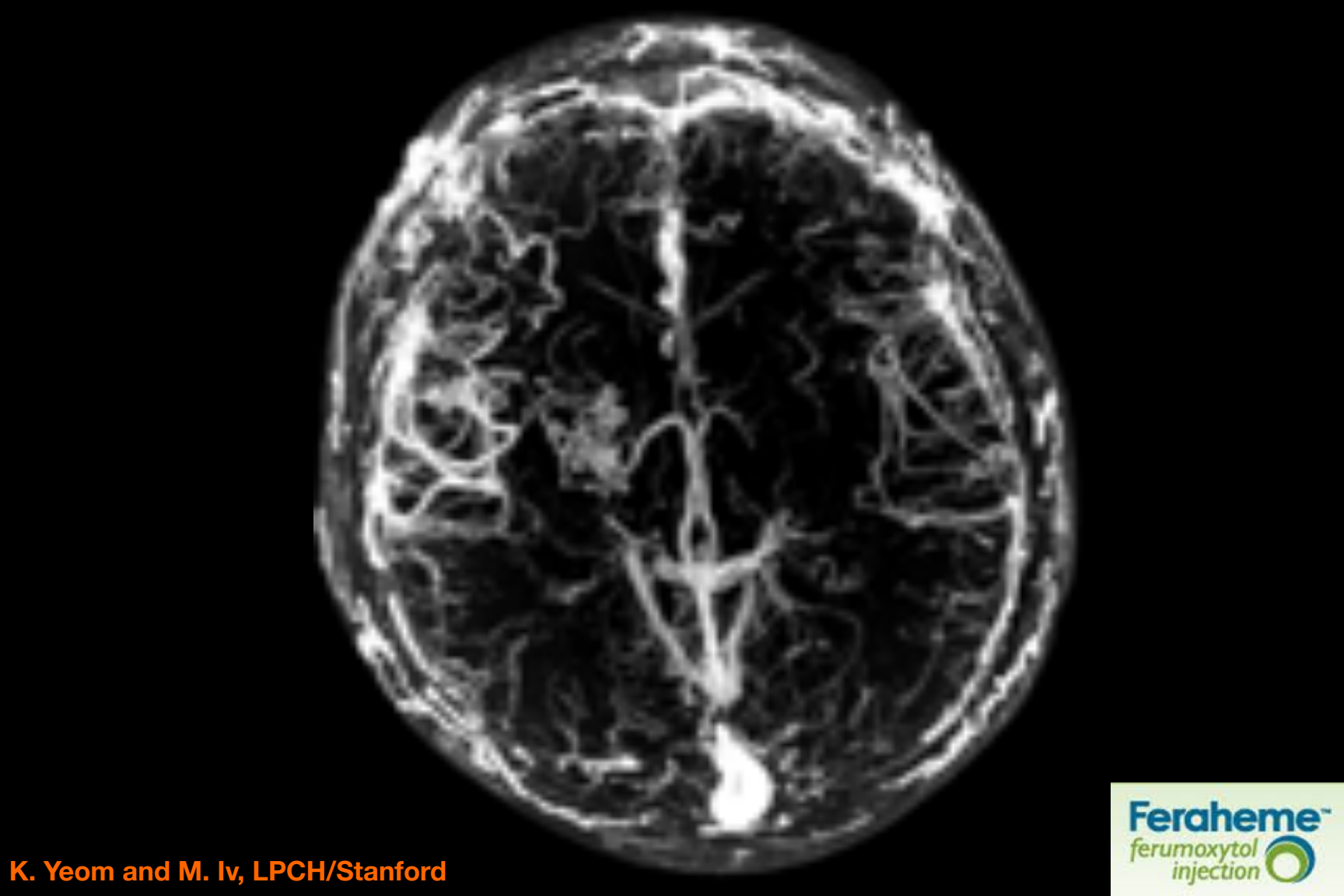
Altering Tissue Contrast



$$SI = N(H)\,[\,1 - e^{-TR/T1}\,]\,e^{-TE/T2}$$

1. T1-shortening on T1w images.
   paramagnetic agents (Gd-DTPA).
   coated supermagnetic irons (iron particles).

2. T2 (or T2*) shortening on T2*w images.
   para-/superparamagnetic agents (iron particles).
   paramagnetic agents (Gd- or Dy-DTPA)



K. Yeom and M. Iv, LPCH/Stanford

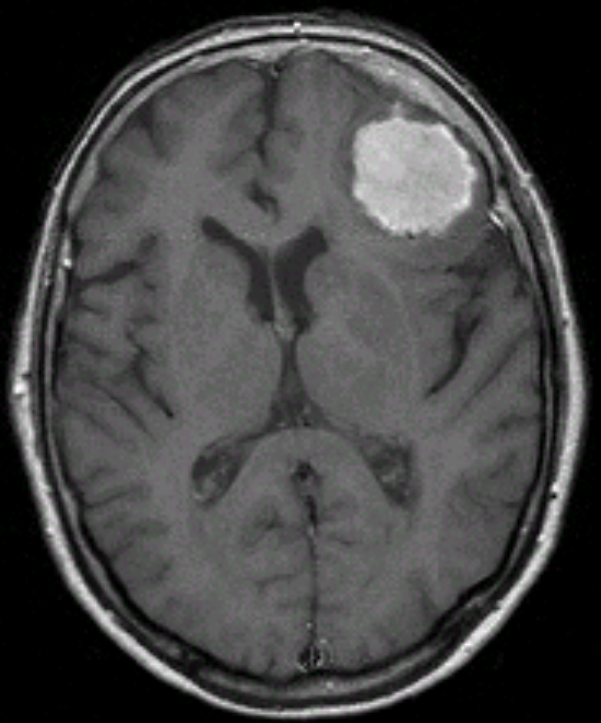
T1 Relaxivity –

Good Stuff:

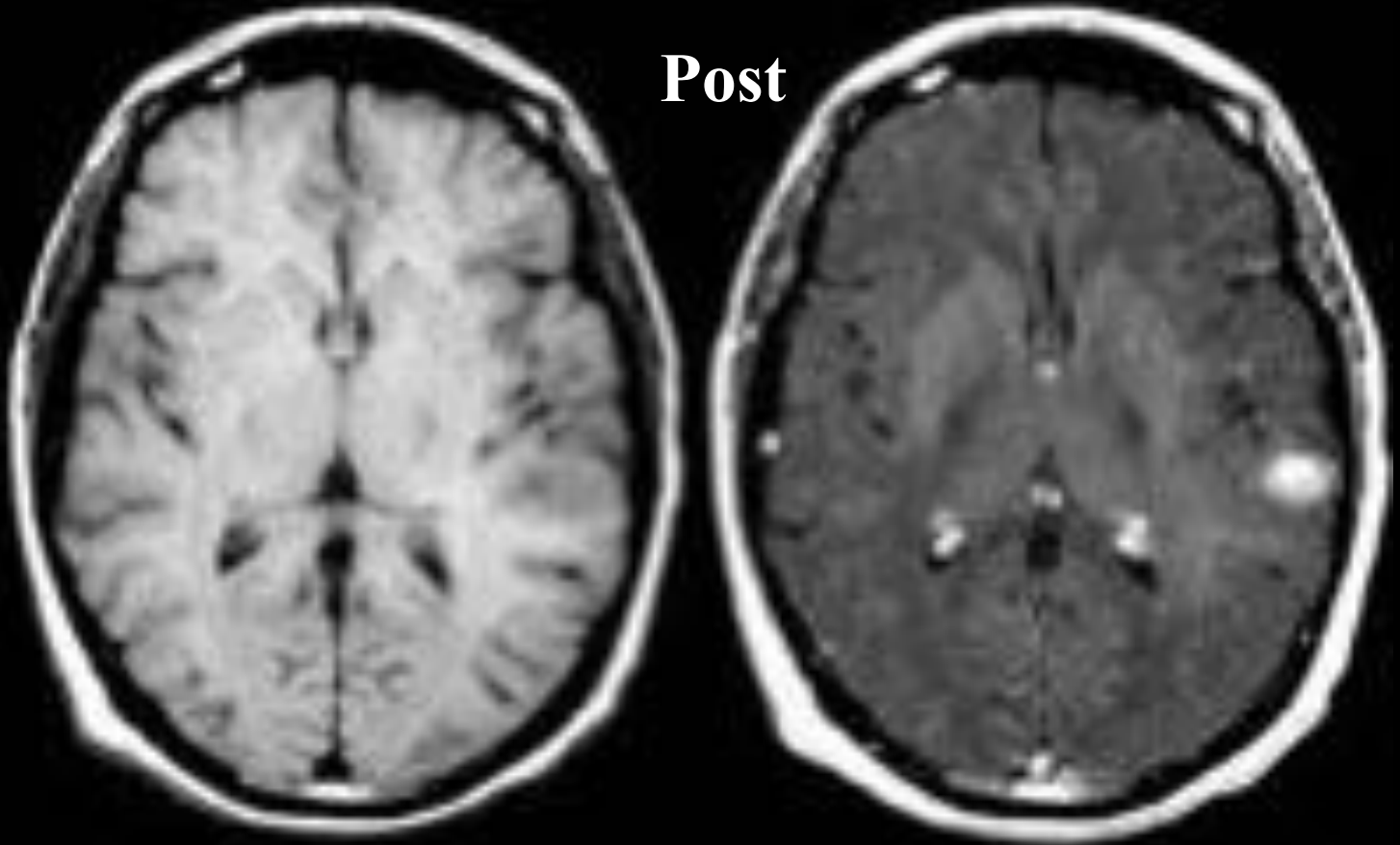
Positive effect on T1-weighted MRI.
T1w MRI typically rapid.
Doesn't cross intact BBB.
Relatively rapid, safe.
Patents nearing end…

However:

MW a bit small (MW~500au).
Extravasates too easily.
Clears with 17 min plasma $T_{1/2}$



Gd-DTPA Enhances BBB Breakdowns



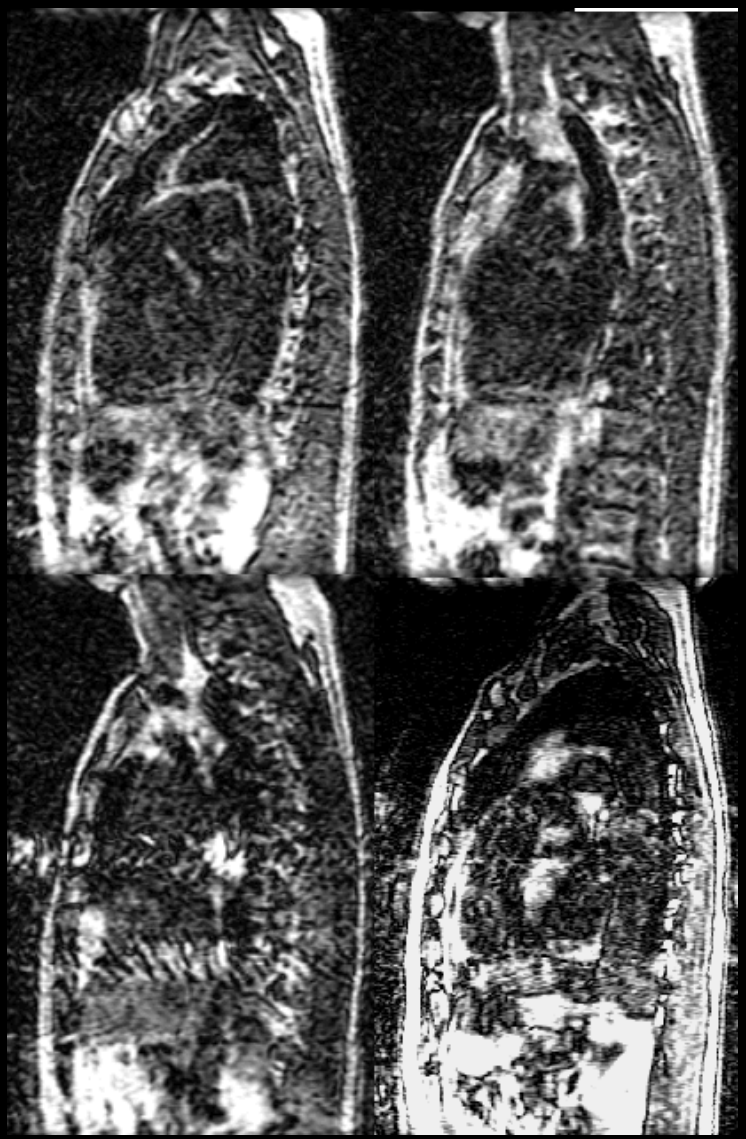
Use of an MT-prepped sequence
MEMP – Stanford -Pike, Glover

Advanced Options for MRA

In-plane (coronal) images saturate in-flow...

Poor SNR
Not used...

Fast SPGR
30 seconds/
16 slices
3DFT.

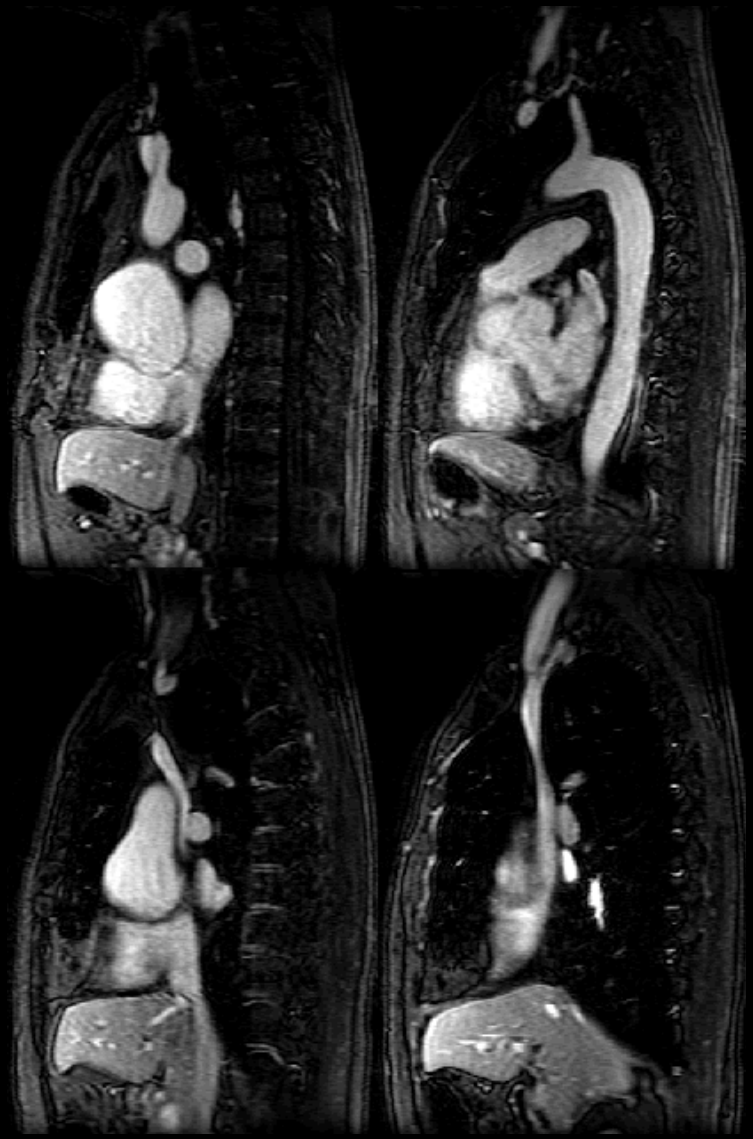


Advanced Options for MRA

Contrast shortens T1.

No saturation of vascular spins.
Not flow, but anatomy...

Fast SPGR
30 seconds/
16 slices
3DFT.
0.1 mmol/kg Gd DTPA

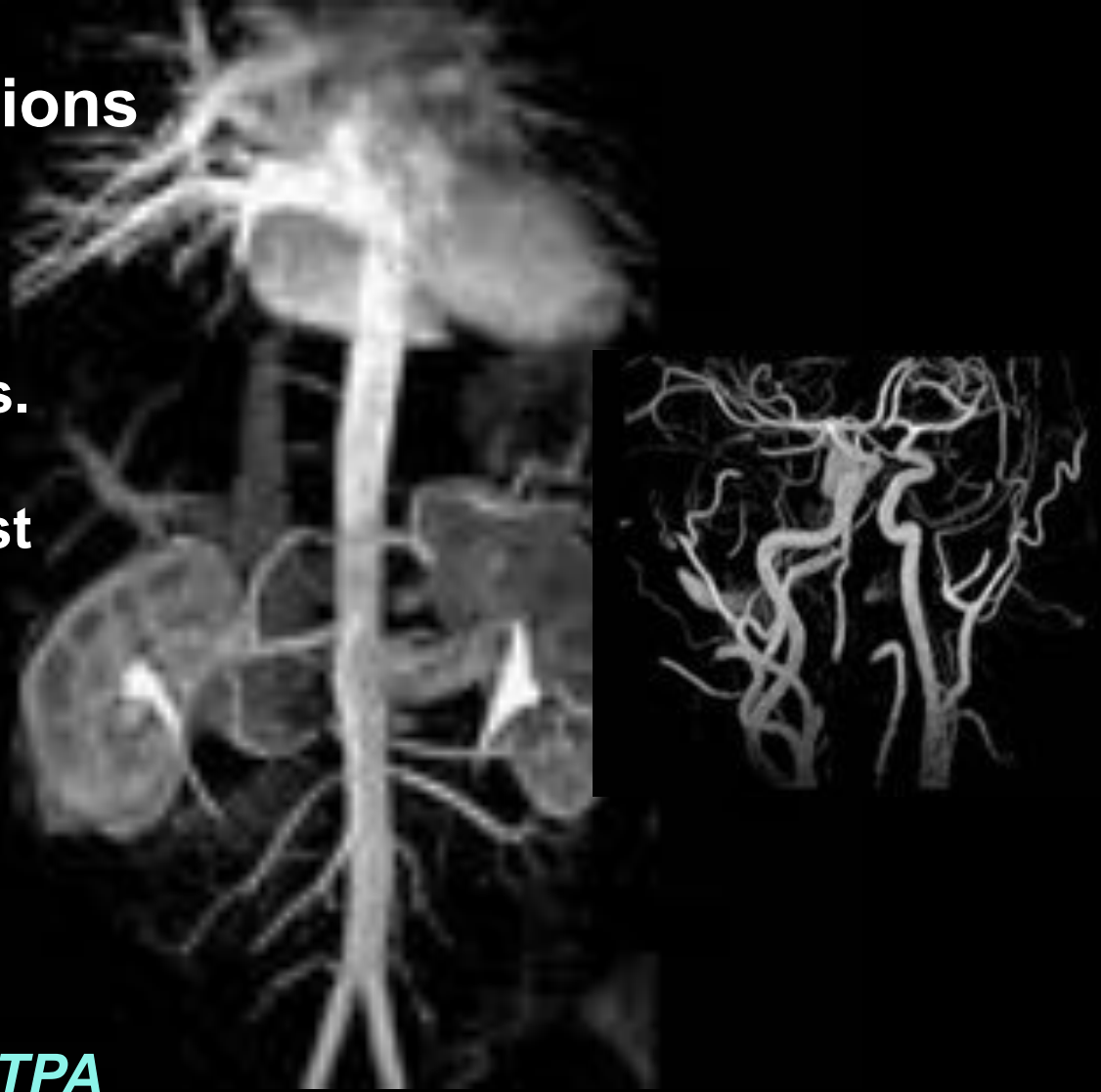


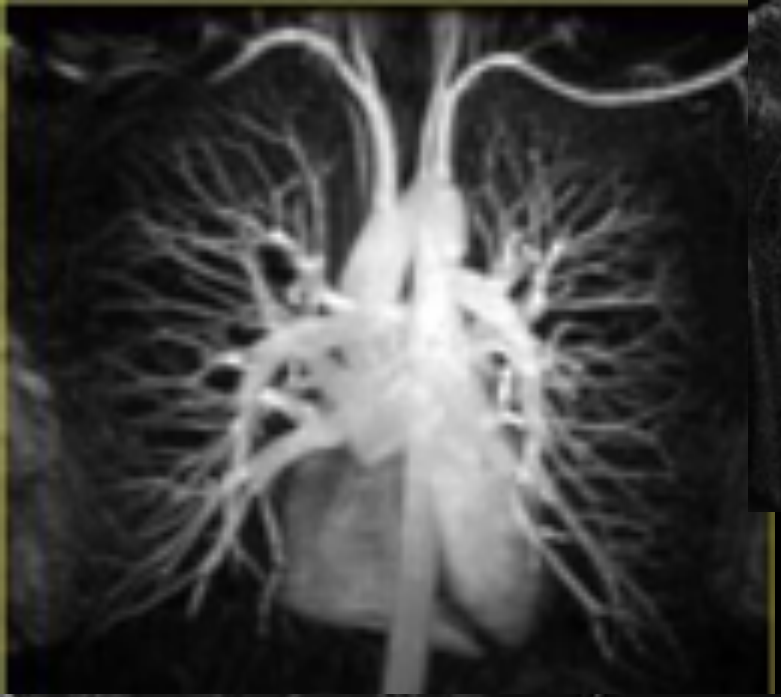
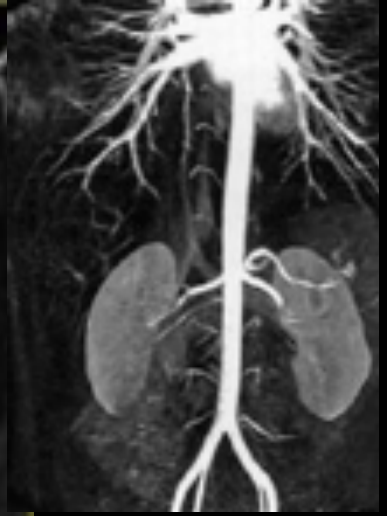
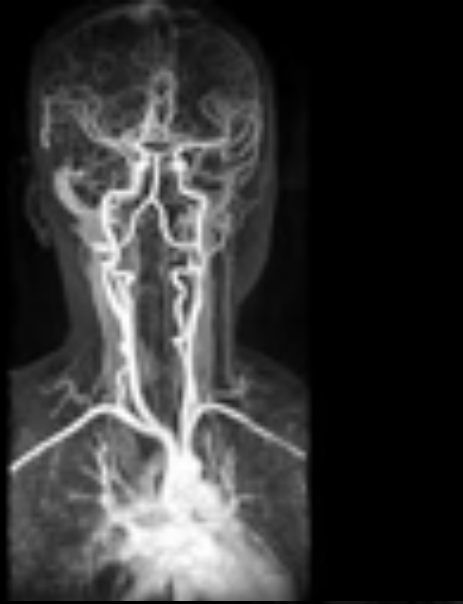
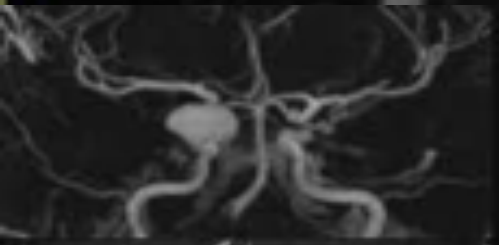
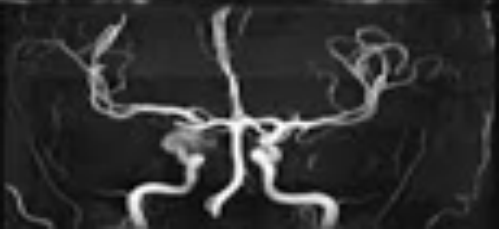
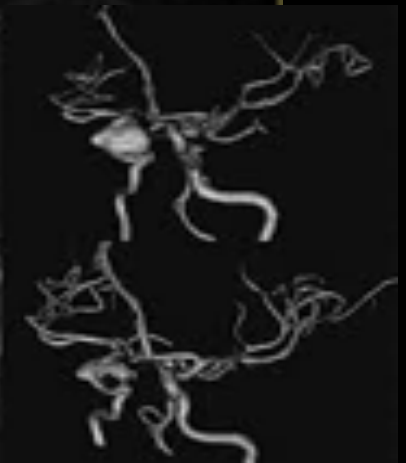
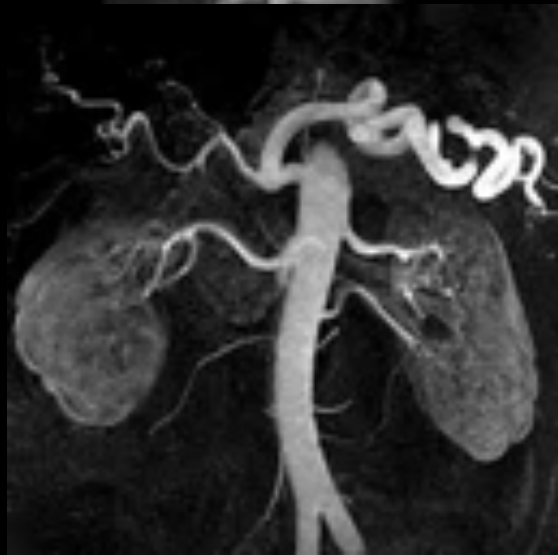
Advanced Options for MRA

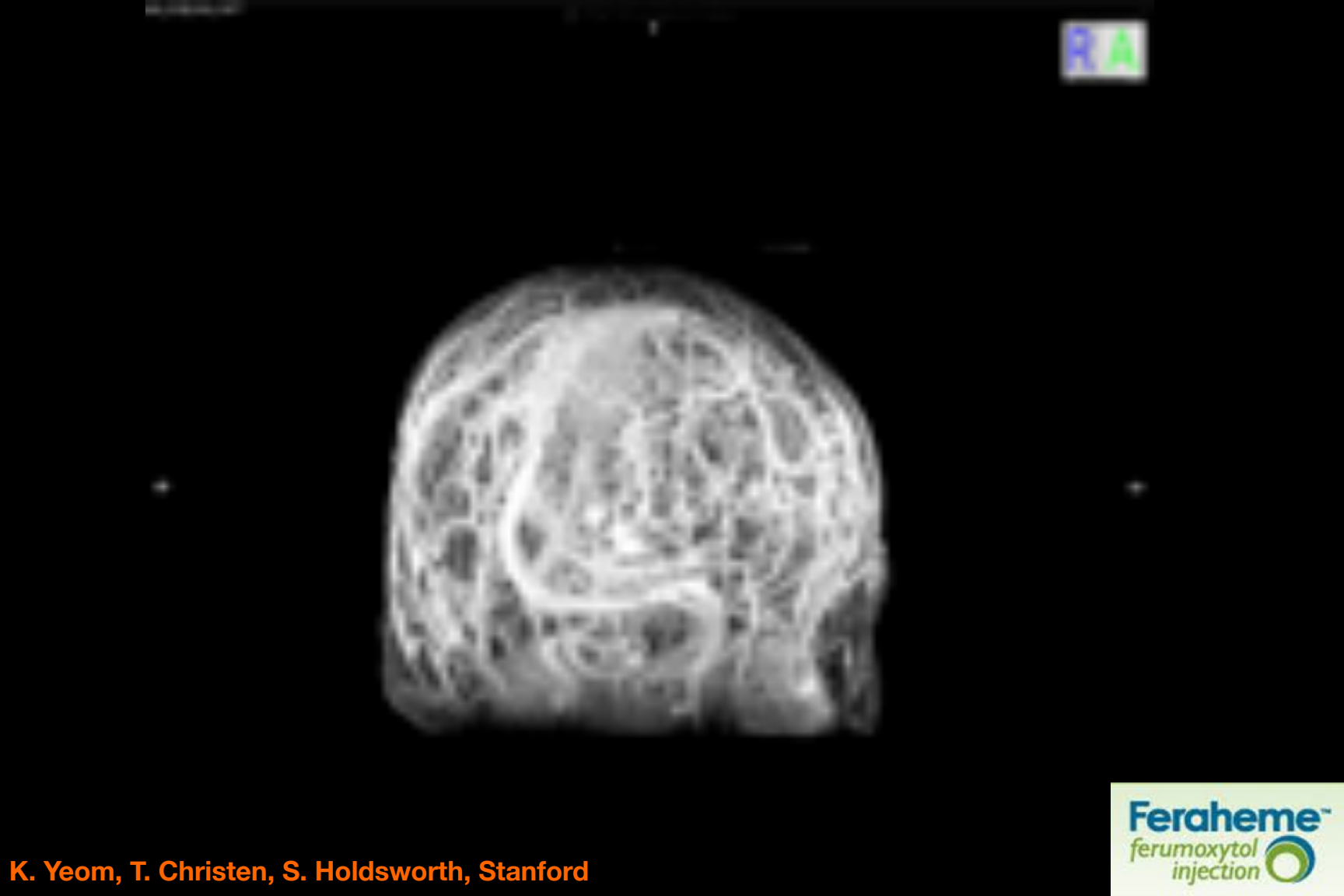
MIP'ping works.

New area of fast vascular MRI.

Fast SPGR
30 seconds/
16 slices
3DFT.
0.1 mmol/kg Gd DTPA





K. Yeom, T. Christen, S. Holdsworth, Stanford

Lanthanide Chelated Agents

CNS:

BBB leakage – tumors, etc.

T1-enhanced MRA.

Bolus dynamics.

Cardiac, Cardiovascular:

Delayed enhancement!

Wall actions, Bolus dynamics.

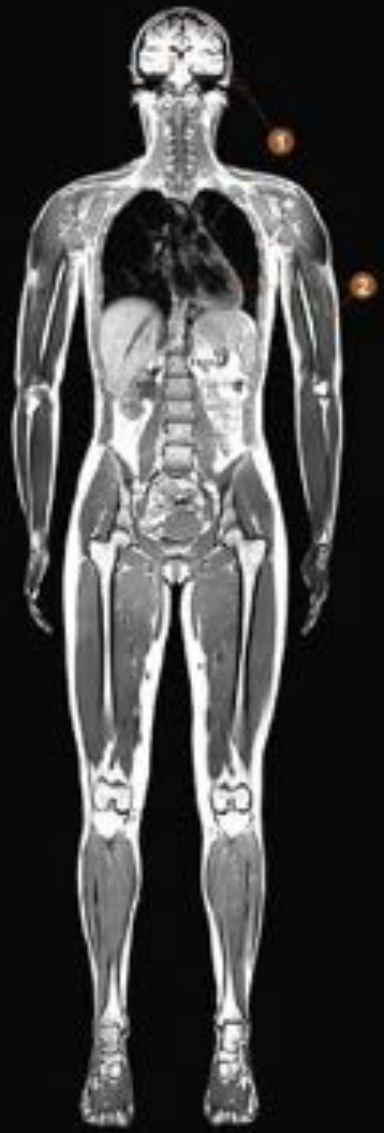
T1-enhanced MRA.

Non-neuro:

Tumor update and leakage.

MSK tears.

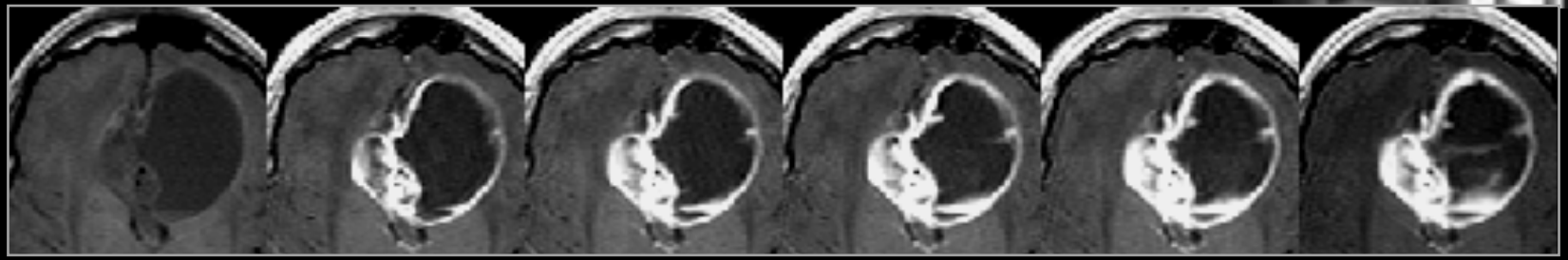
Blood pool issues.



Plasma Retention

Physiologic Parameters

BBB disruptions – “ECF” agent
Lack of BBB - tumors
Vascular permeability
Renal retention / collection



pre post 0 post 5 post 15 post 30 post 45

Lanthanide Chelated Agents

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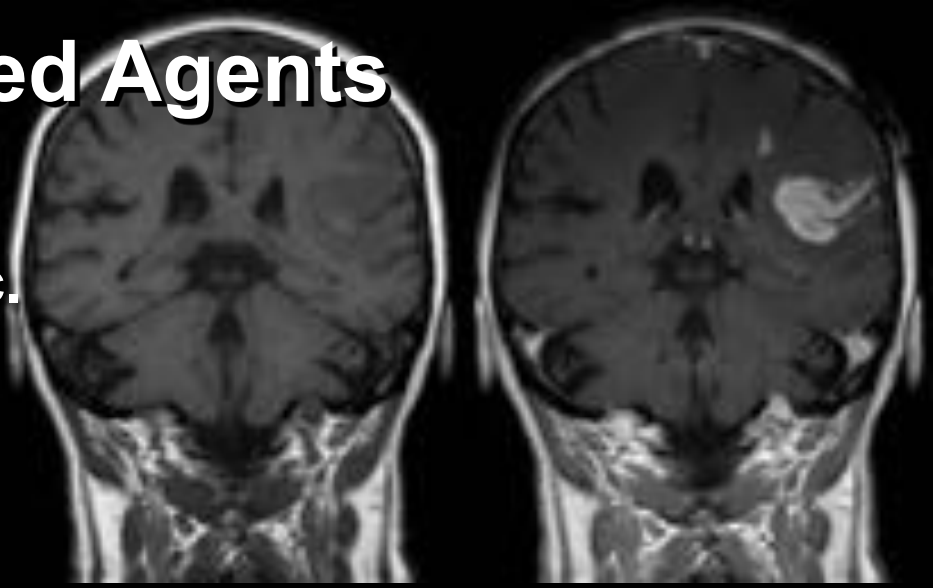

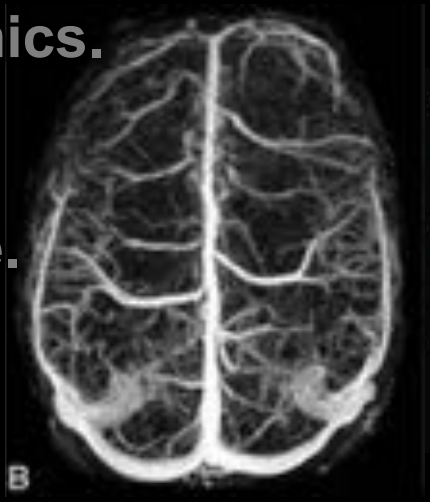

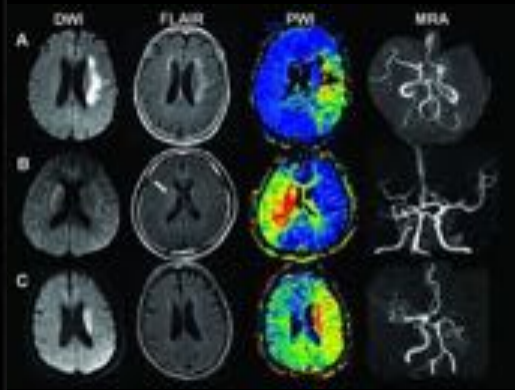

Lanthanide Chelated Agents

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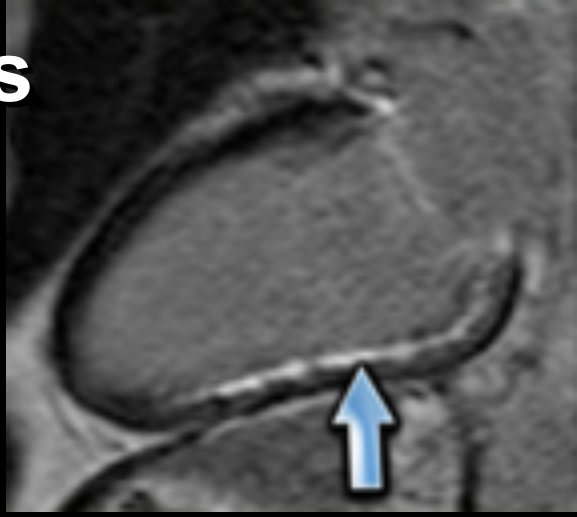
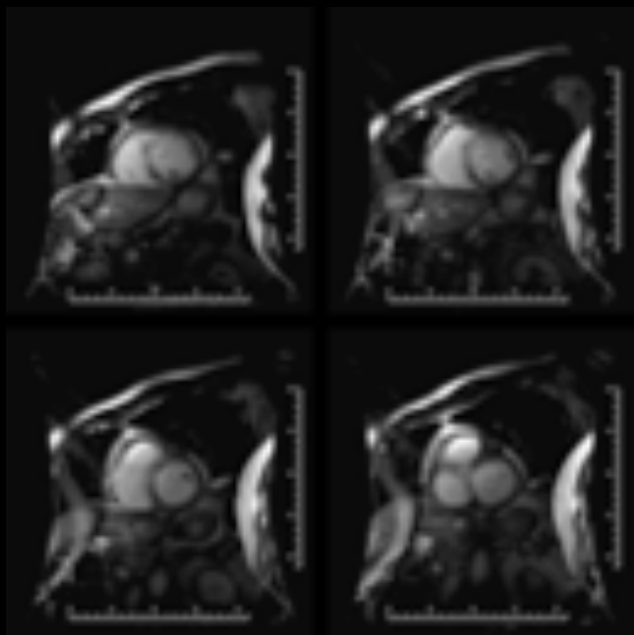
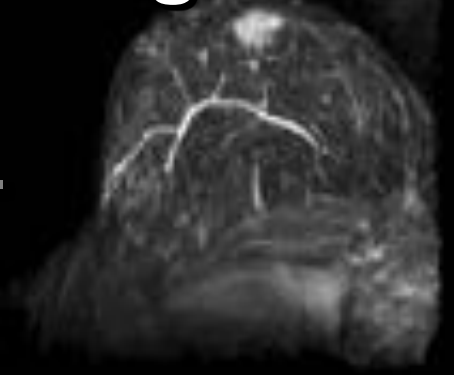
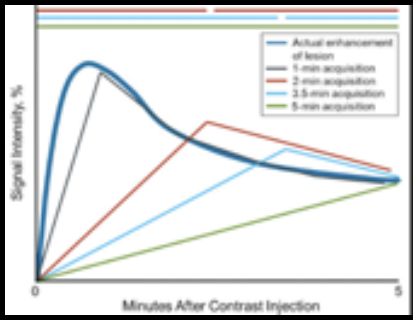


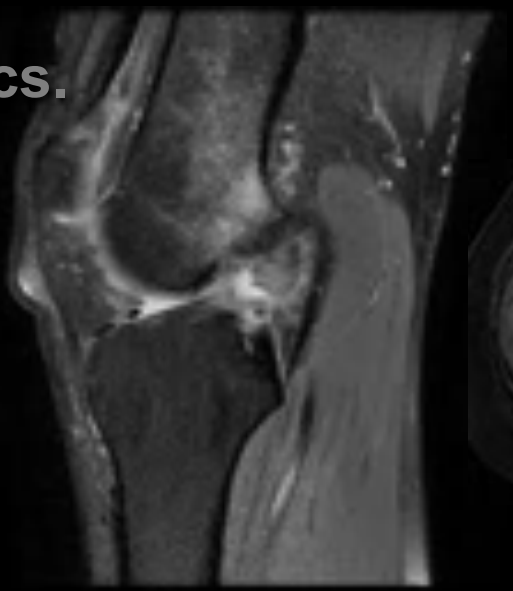


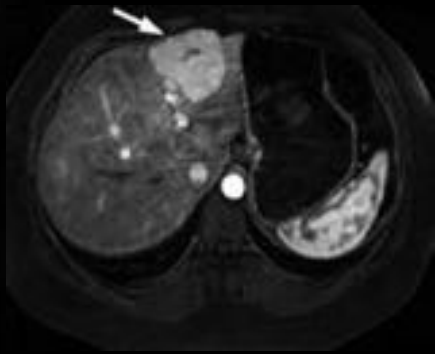
Lanthanide Chelated Agents

CNS:
BBB leakage – tumors, etc.
T1-enhanced MRA.
Bolus dynamics.
Cardiac, Cardiovascular:
Delayed enhancement!
Wall actions, Bolus dynamics.
T1-enhanced MRA.
Non-neuro:
Tumor update and leakage.
MSK tears.
Blood pool issues.
Liver…









Proton Relaxation by Paramagnetic Metal Ions.

Unpaired electrons relax protons
Much more efficient...

Number of unpaired electrons -

Gd, Dy = 7 unpaired electrons.
Fe, Mn = 5 unpaired electrons.
Fe domains create big magnetic moments.

Electron-spin (esr) relaxation times - ts

Gd - long esr T1 = good T1-shortening.
Dy - short esr T1 = poor T1-shortening.

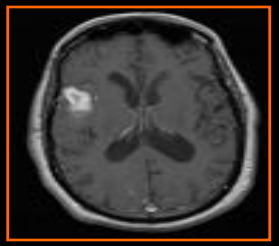
Proton near paramagnetic centers- tm

Coordination sites and placement critical.
DTPA occupies more than EDTA, unfortunately...

Paramagnetic correlation times - tr

Gd-DTPA-albumin increases T1 relaxivity 10 fold.

T1 Relaxivity – *Why Gd-DTPA?*



Magnetic moment (# unpaired electrons)

- Gd has 7 unpaired e^-
- OxyHb (Fe^{+2}) vs. DeOxyHb (Fe^{+3})

Electron relaxation rate (near that of protons?)

- Gd-DTPA vs. Dy-DTPA

Tumbling of the cloud (exposure time to protons)

- Gd-DTPA-binding

Approach of water to the unpaired electrons...

- MetHb

$$1/T1_{(observed)} = 1/T1_{(intrinsic)} + R1\,[Conc]$$

(200 msec = 1000 msec + 3.8[0.1mmol/kg])

T1 Relaxivity – *Better than Gd-DTPA?*

Magnetic moment (# unpaired electrons)

OxyHb vs. MetHb

Electron relaxation rate (near that of protons?)

Gd-DTPA vs. Dy-DTPA

Tumbling of the cloud (exposure time to protons)

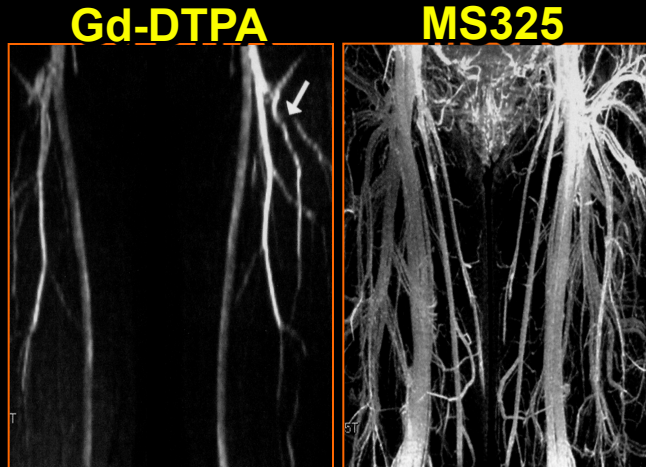
Gd-DTPA-binding

Approach of water to the unpaired electrons...

MetHb

T1 Relaxivities mmol^{-1} L sec^{-1}:

Gd-DTPA	~	*4*
Gd-dimers	~	*10*
Gd-Dextrans	~	*40*
MS-325-HSA	~	*45*
Iron oxides	~	*20*



Paramagnetics - Blood Pool Agents

Gd-phostriamine MS-325 -Epix - Schering

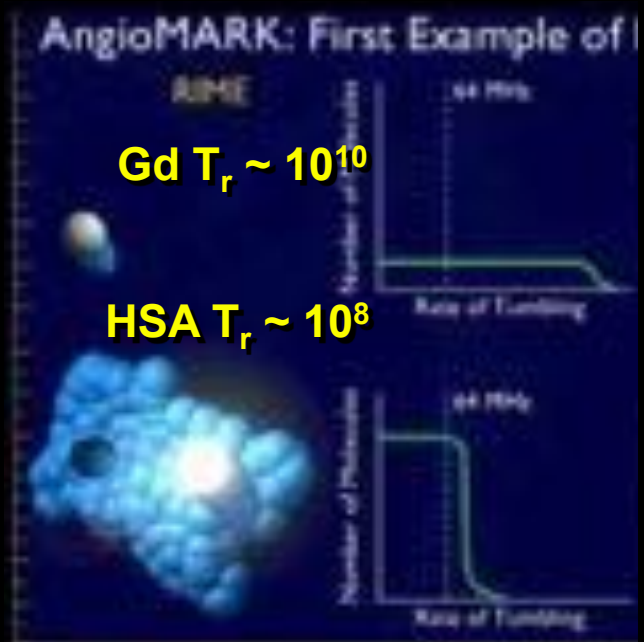
T1-shortening agents:

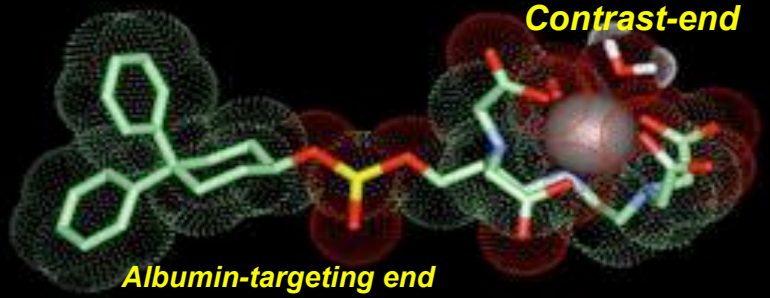
Affinity to HSA

80-90% labeled

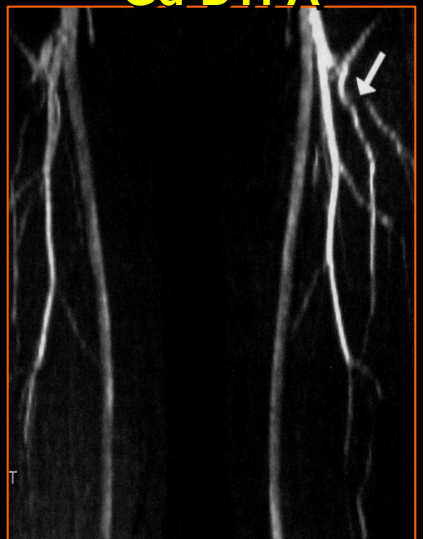
R1 ~ 40-50

$T_{1/2}$ ~ 60minutes

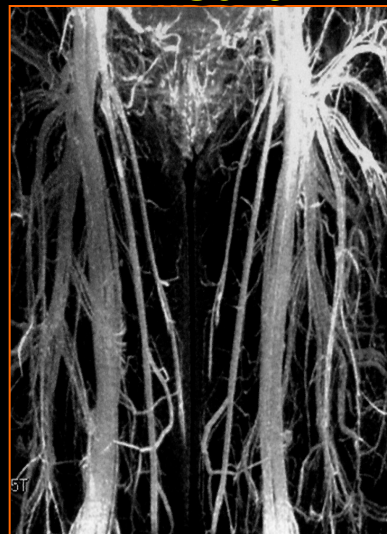




Gd-DTPA



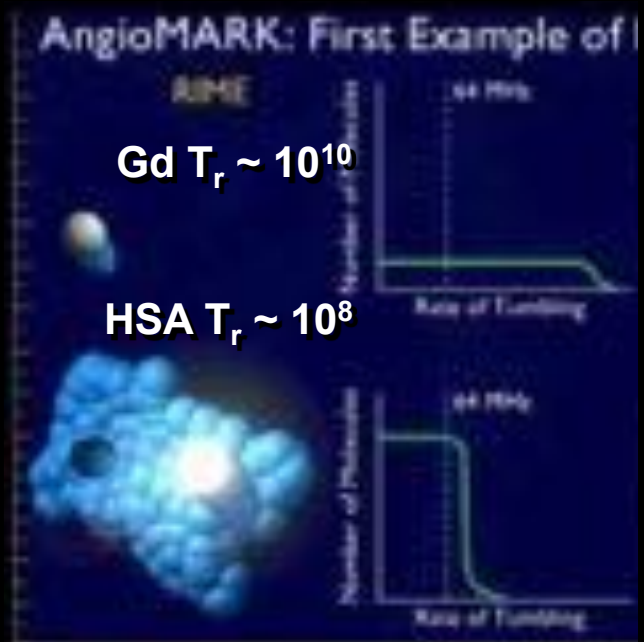
MS325



Paramagnetics - Blood Pool Agents

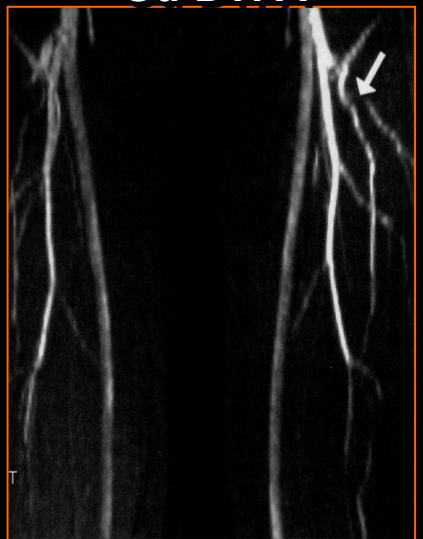
Gd-phostriamine MS-325 -Epix - Schering

T1-shortening agents:
- **Affinity to HSA**
  - **80-90% labeled**
  - **R1 ~ 40-50**
  - **$T_{1/2}$ ~ 60minutes**

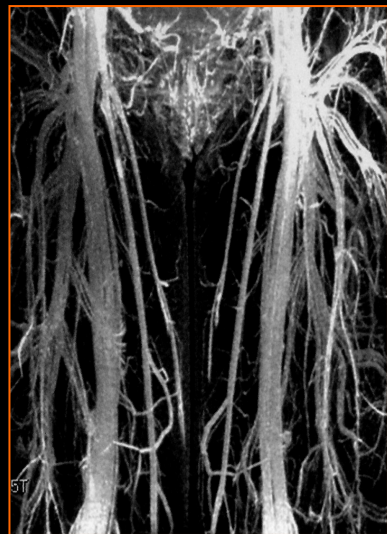


"Conventional" MRI Contrast-end

Gd-DTPA



MS325



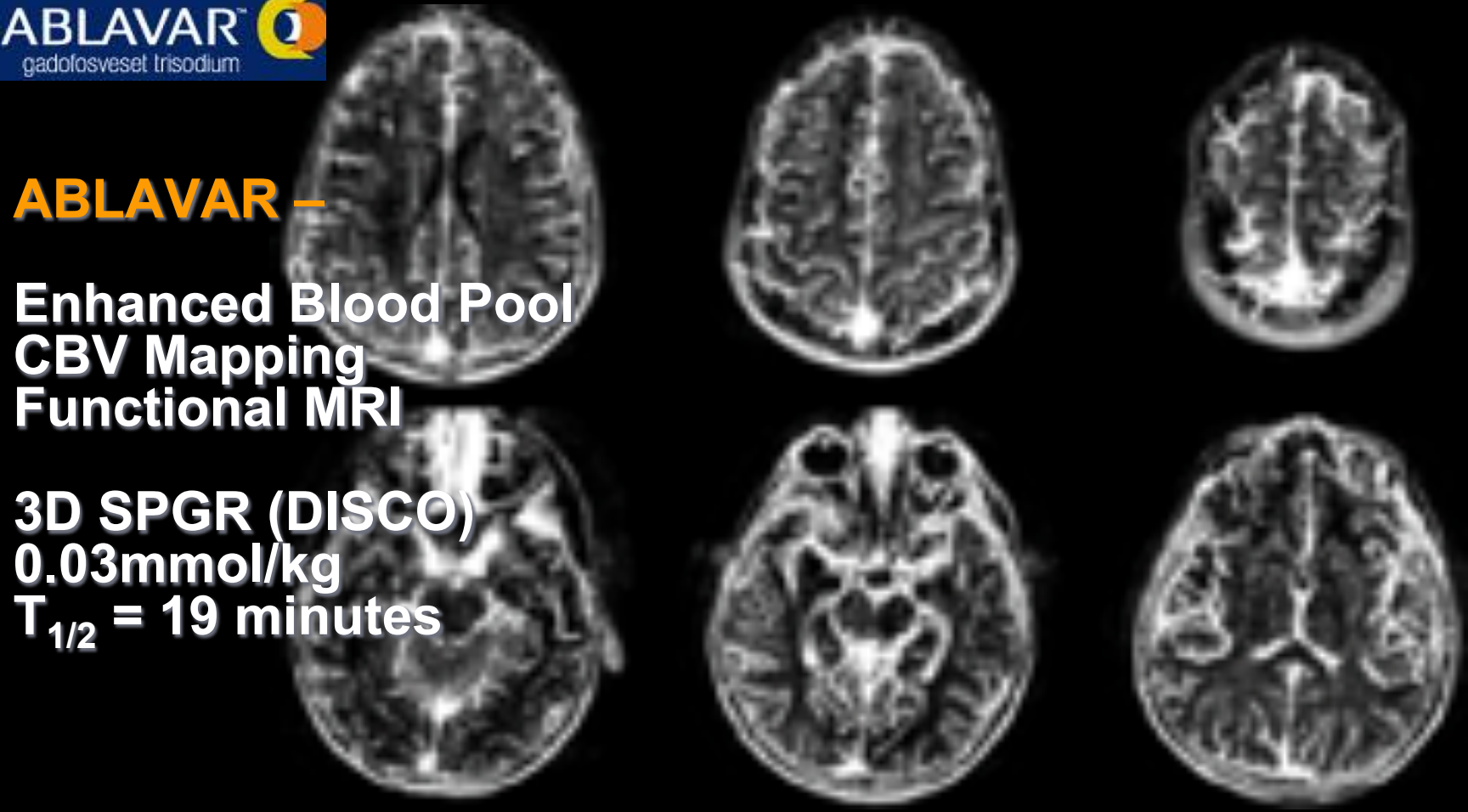
Blood Volume from T1-Contrast

ABLAVAR™
gadofosveset trisodium

ABLAVAR –

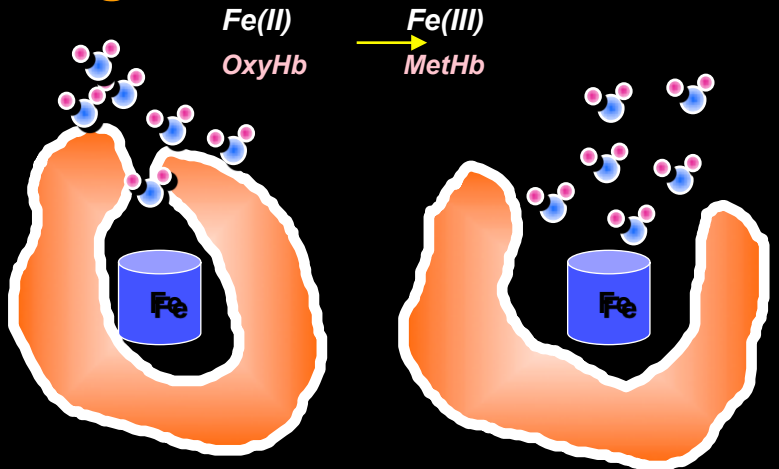
Enhanced Blood Pool
CBV Mapping
Functional MRI

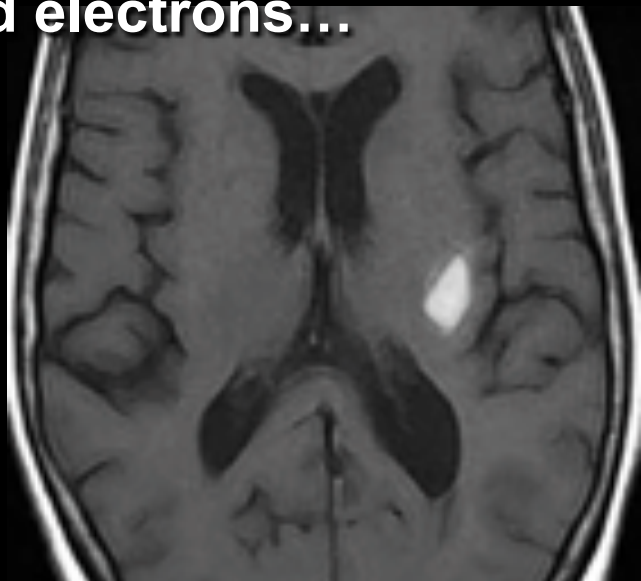
3D SPGR (DISCO)
0.03mmol/kg
$T_{1/2}$ = 19 minutes



T1 Relaxivity – *Not just Gd-DTPA…*

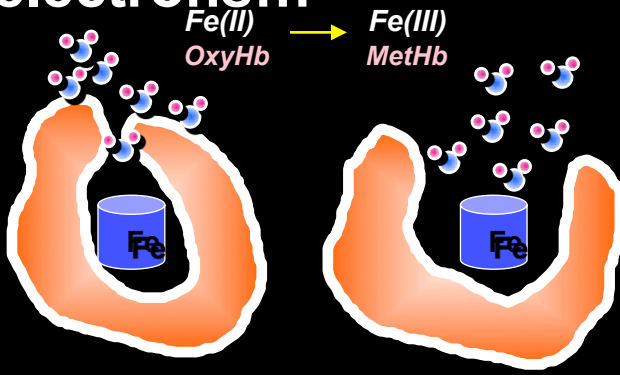
Magnetic moment (# unpaired electrons)
OxyHb vs. MetHb
Electron relaxation rate (near that of protons?)
Gd-DTPA vs. Dy-DTPA
Tumbling of the cloud (exposure time to protons)
Gd-DTPA-binding
Approach of water to the unpaired electrons…
Methemoglobin

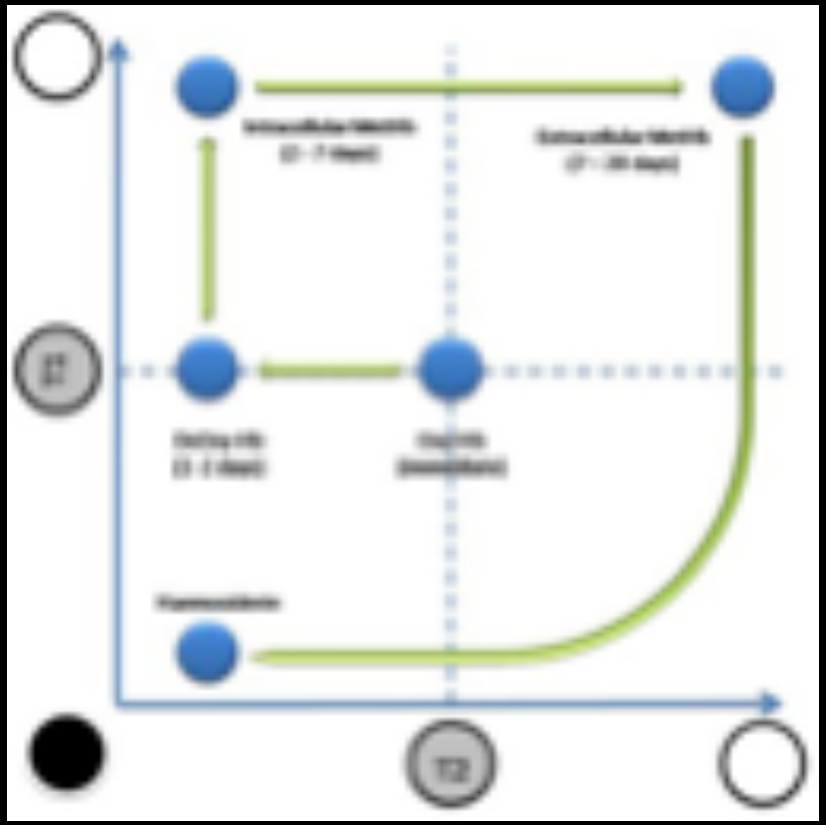


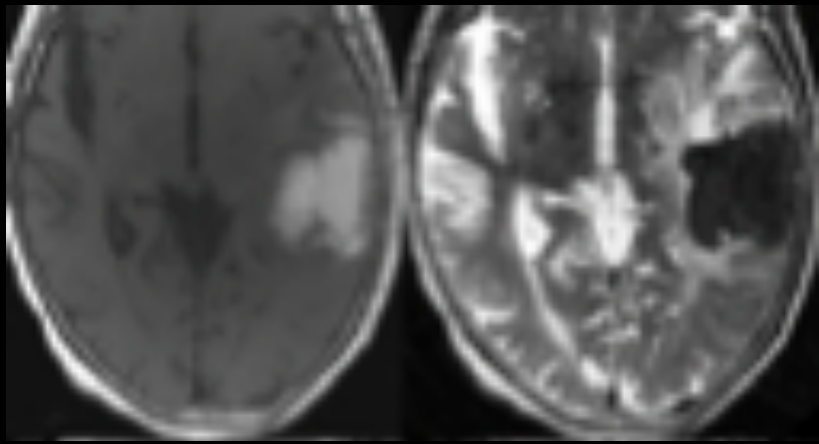


T1 Relaxivity – *Natural Iron Contrast*

Approach of water to the unpaired electrons…
Methemoglobin!

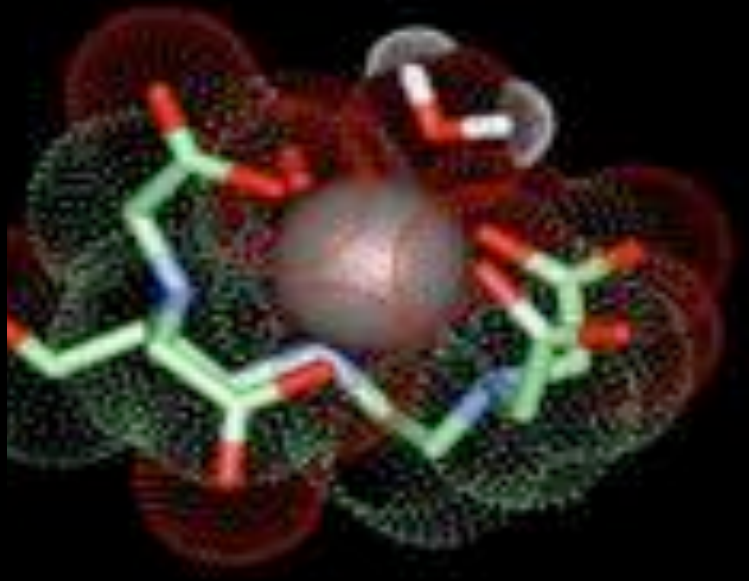




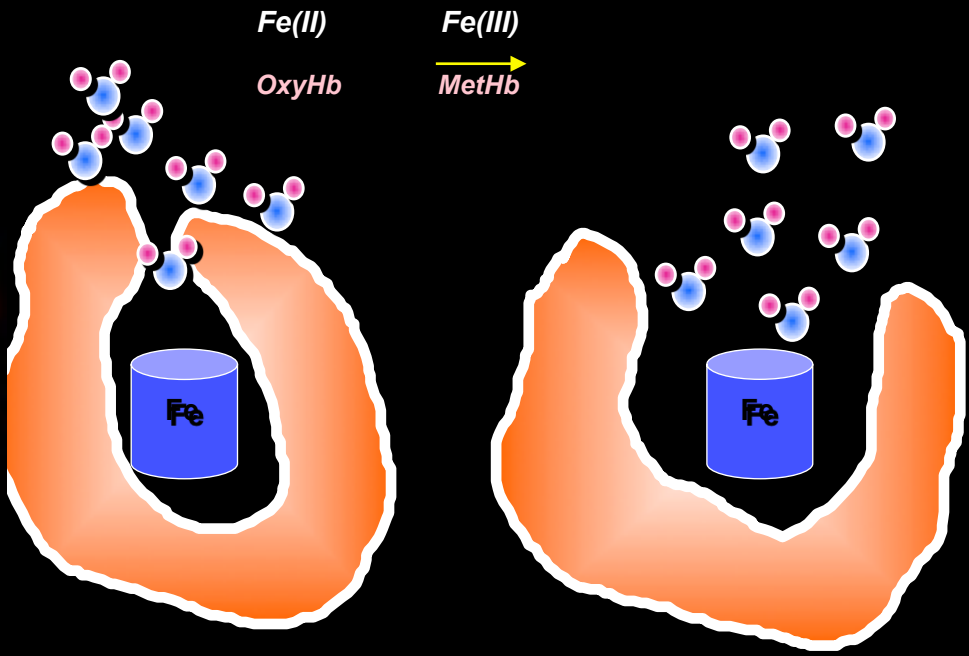


Molecular Imaging Using"Relaxivity”?

Hint 1



Hint 2

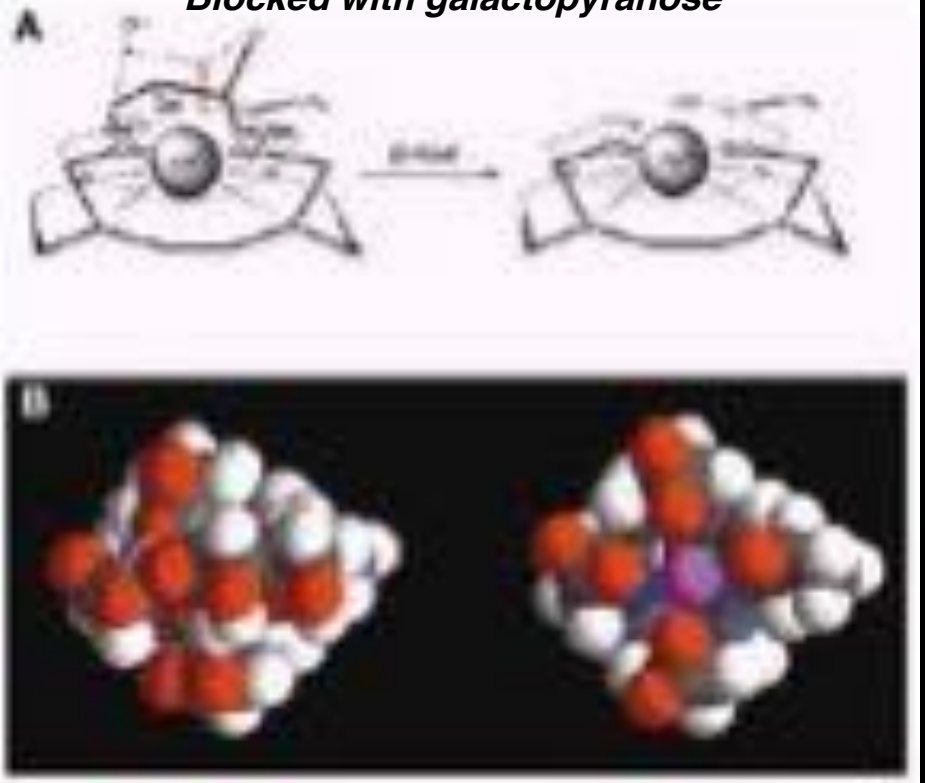


H1 T1 and "Relaxivity"

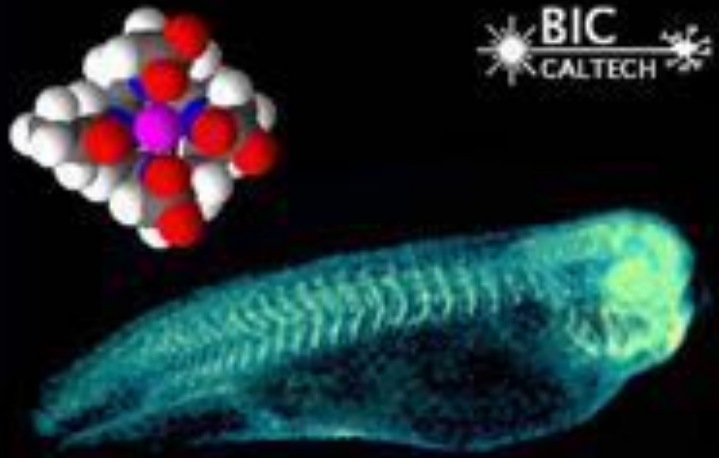
MR Functional Reporter agents for Enzym

"Egadme"

Blocked with galactopyranose



Cleavage of the Egadme by β-galactosidase
Creates increase in R1



Meade, et al. Nature 2000

Further “Hat” Designs in MRI

T1 Relaxivity – *Not just Gd-DTPA…*

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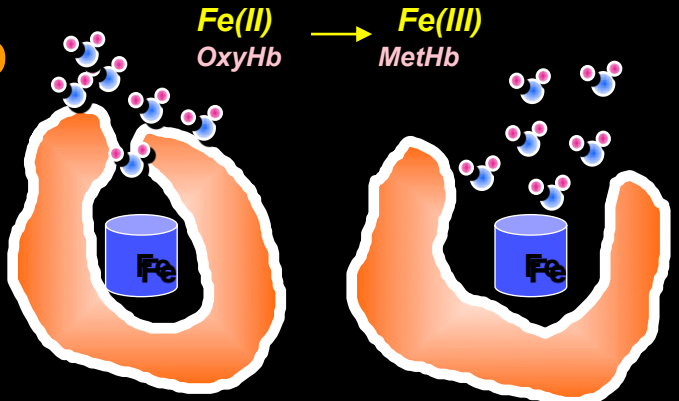
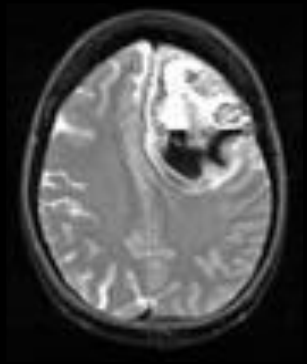


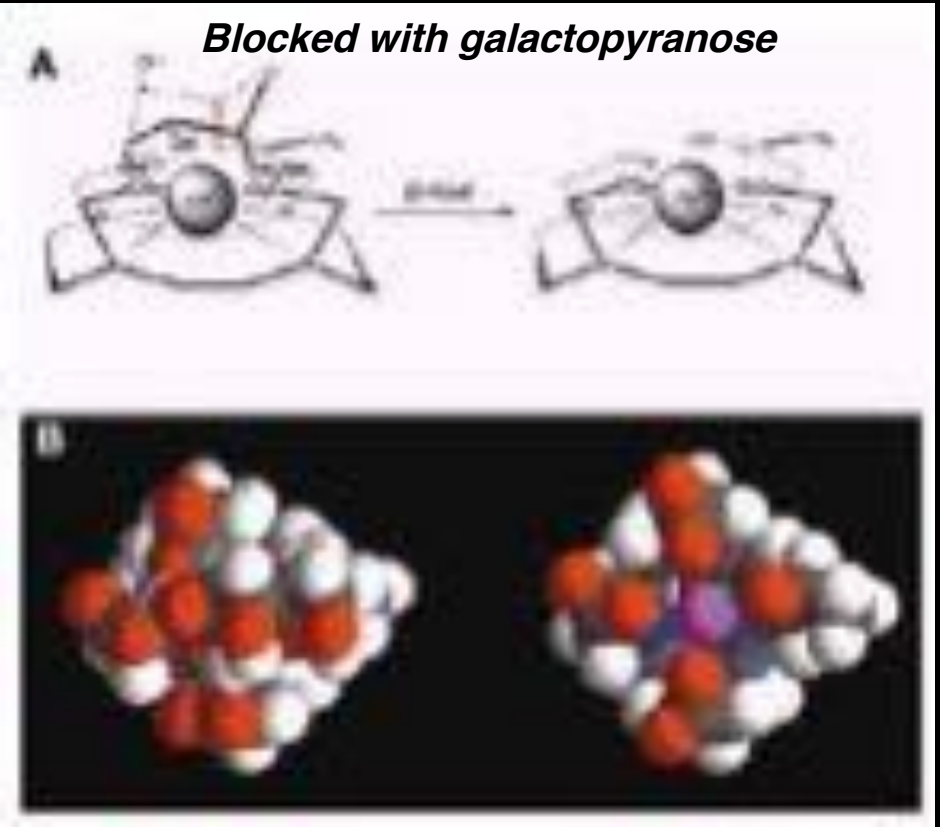


H1 T1 and "Relaxivity"

MR Functional Reporter agents for Enzyme activity

"Egadme"

Blocked with galactopyranose



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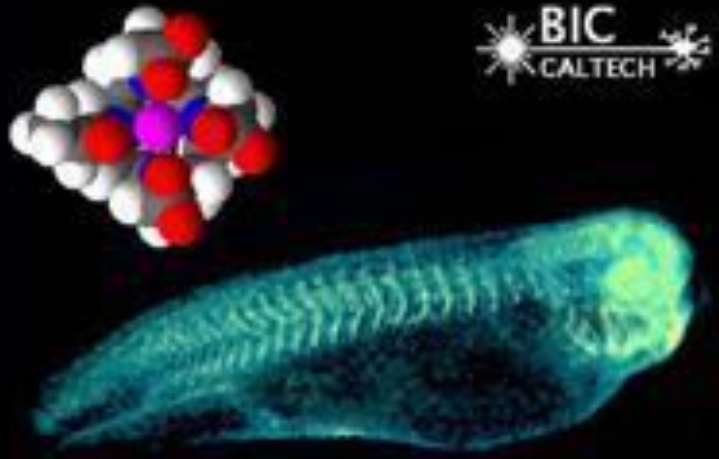
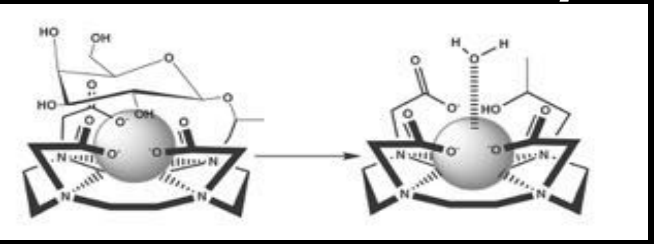


Meade, et al. Nature 2000

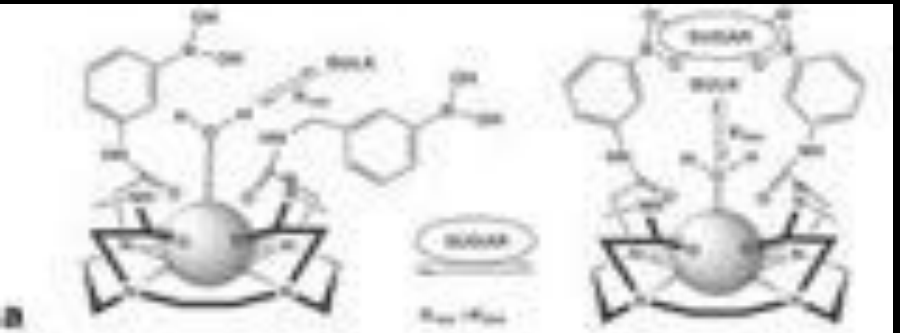
H1 T1 and "Relaxivity"

MR Functional Reporter agents for All Kinds of Stuff

Querol Bogdanov JMRI 2006



β-Gal sensitive



glucose-sensitive

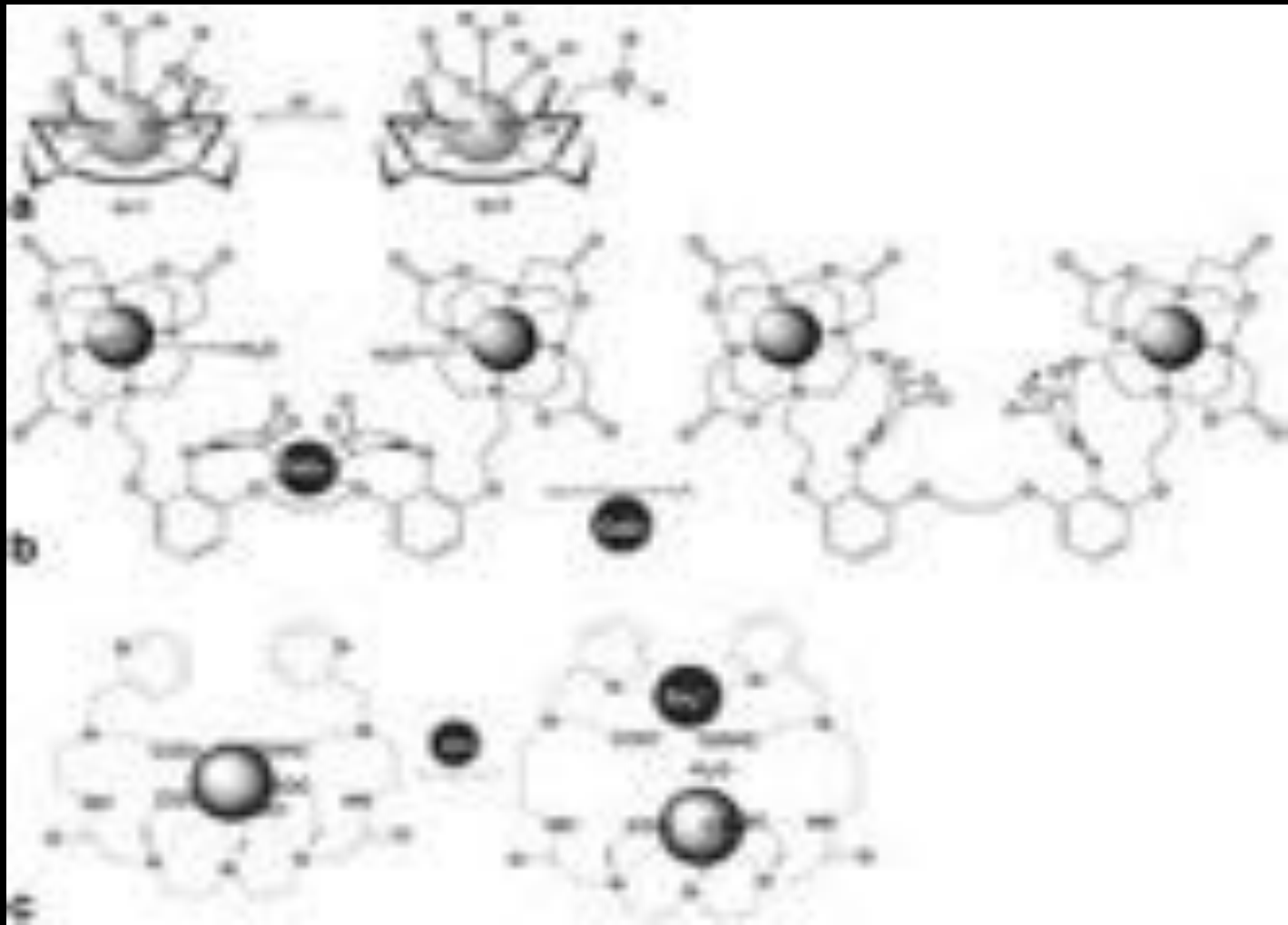
lactate-sensitive.

SCA - “Sensing Contrast Agents”

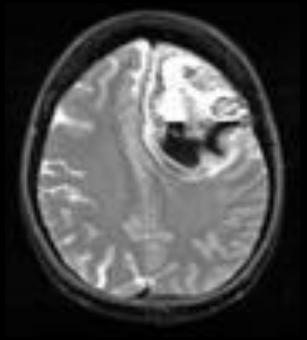
(a) pH

(b) Ca

(c) Zn



Altering Tissue Contrast



$$SI = N(H)\,[\,1 - e^{-TR/T1}\,]\,e^{-TE/T2}$$

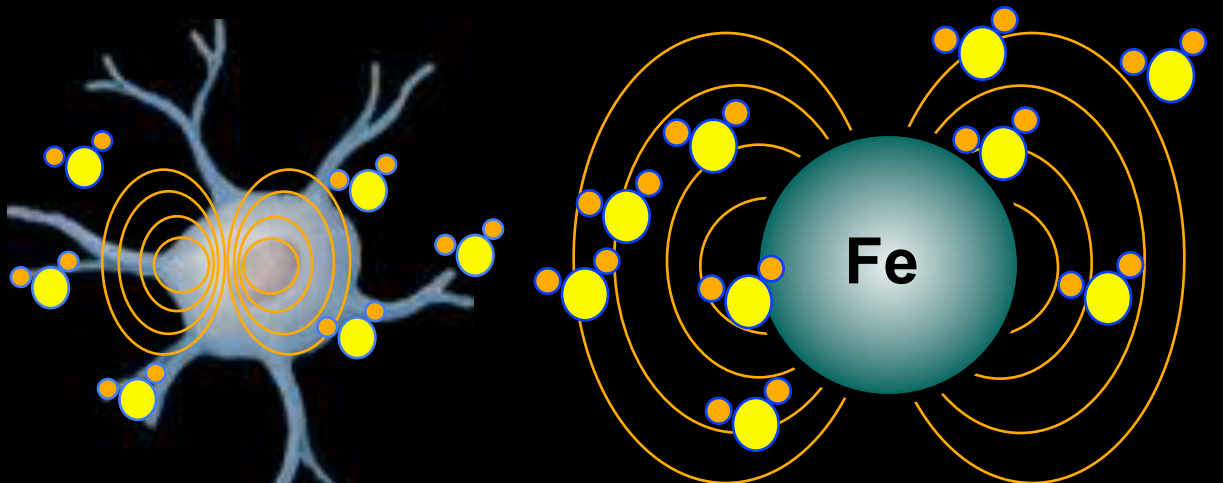
1. T1-shortening on T1w images.
   - paramagnetic agents (Gd-DTPA).
   - coated supermagnetic irons (iron particles).

2. T2 (or T2*) shortening on T2*w images.
   - para-/superparamagnetic agents (iron particles).
   - paramagnetic agents (Gd- or Dy-DTPA)

What is Magnetic Susceptibility?

The magnetic susceptibility is the difference of the magnetic field across a sample. *Each substance in a magnetic field alters that field.*

Iron has a larger MS effect than water, e.g...



$B_{eff} = B_0 (1 - {}^2X)$

Bone - water

Air - water

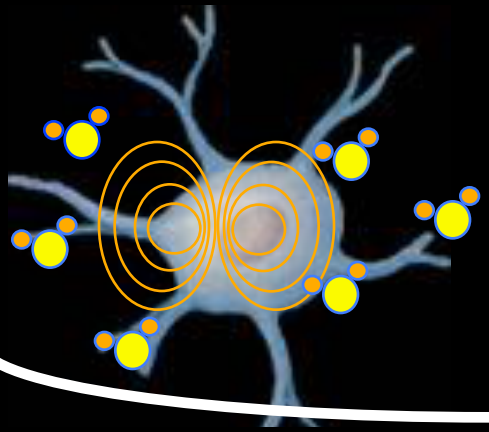
Iron - water

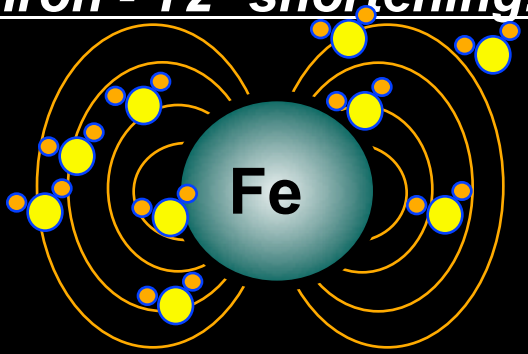
small gradient across sample

large gradient across sample

WM

GM Iron - T2* shortening...





SI

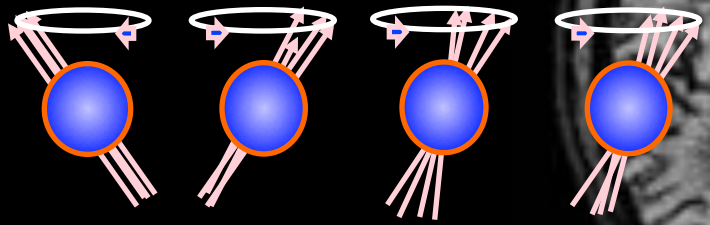
Observed T2*

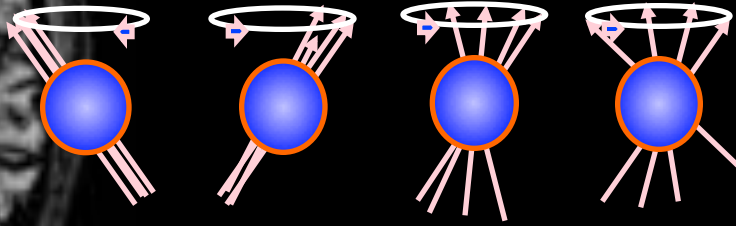
Time

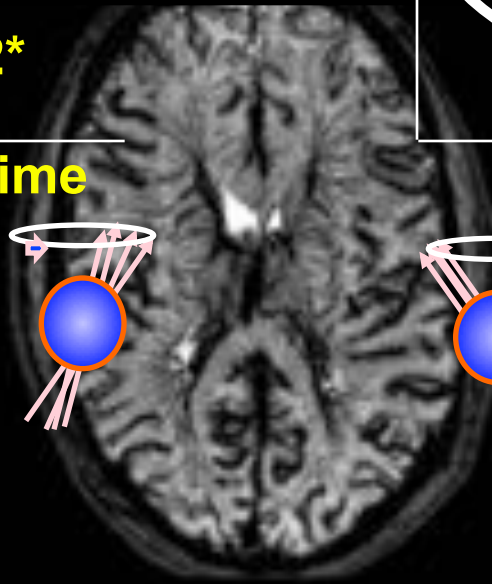
SI

Observed T2*

Time



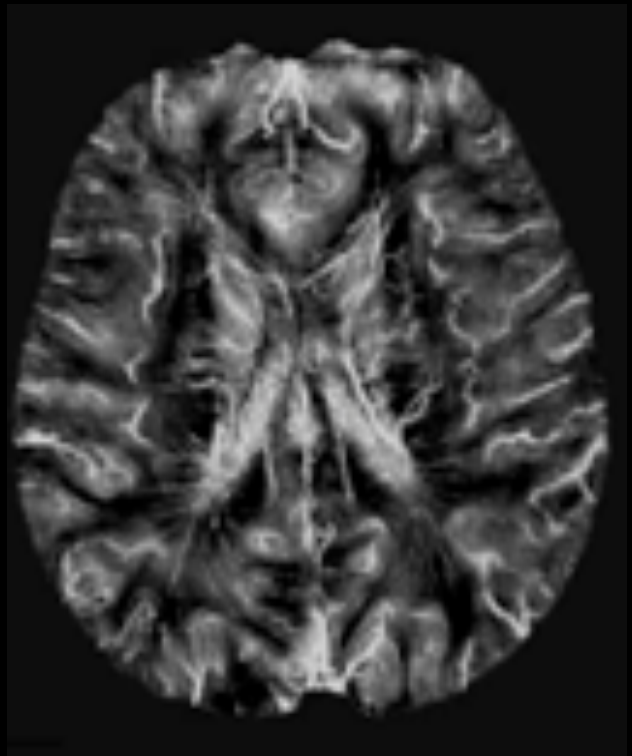




Quantitative Susceptibility Mapping

What and Why?

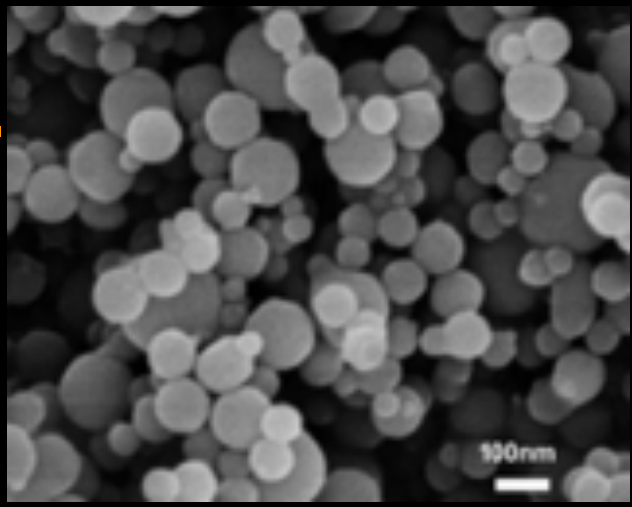
- **QSM natural extension of GRE and is both bleed/WM sensitive.**

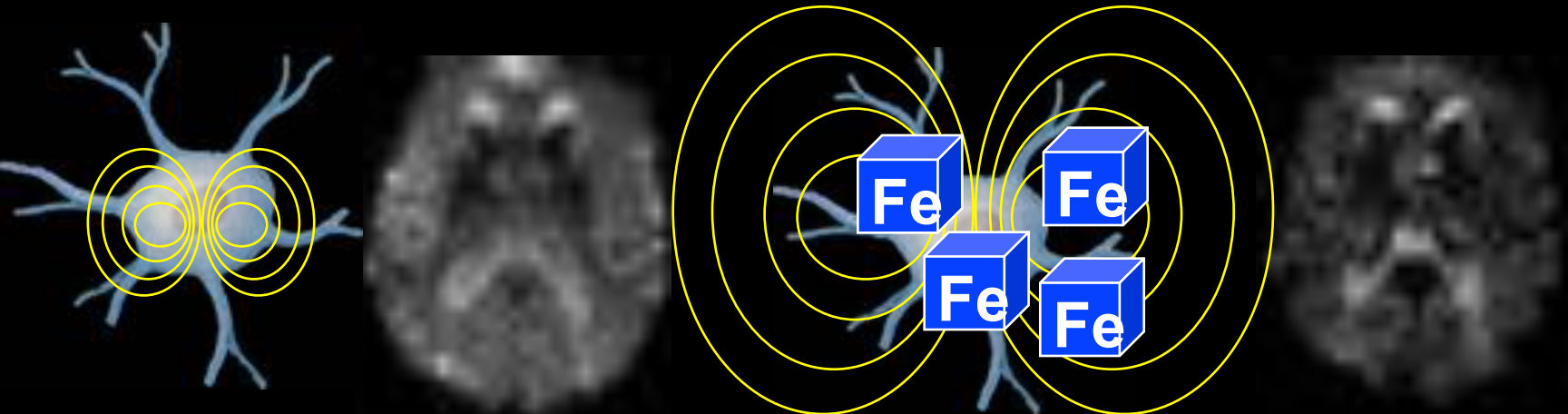


MR T2 Molecular Imaging

Magnetic susceptibility

Local gradients (unpaired e^-).
Magnetic Susceptibility =
T2 decreased.

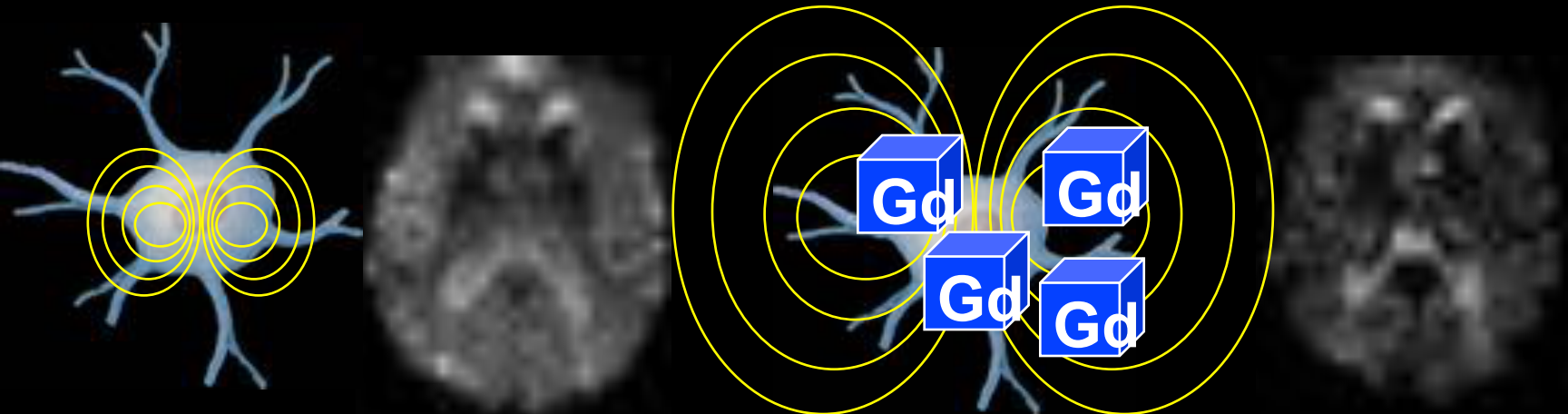




Unpaired e^- and "T2* Relaxivity"

*Magnetic susceptibility reduces T2**

Local gradients (unpaired e^-).
Local environment (clots, packed RBC).
Enhanced by proton diffusion.
Increased spin dephasing =
T2 decreased.*



Unpaired e^- and "T2* Relaxivity"

Magnetic susceptibility factors

Magnetic moment (# unpaired electrons) – $Fe^{+3} > Fe^{+2}$

Size of "domains" – Fe-oxide > FeCl

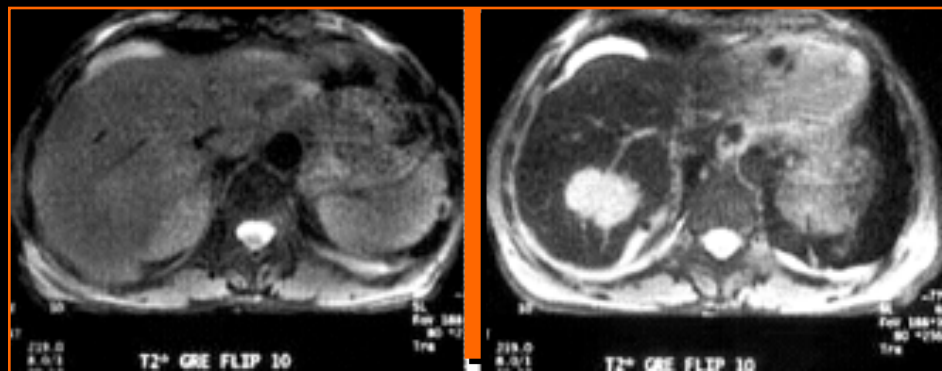
Size and concentration of particle –

SPIO (RES capture) > USPIO (blood pool)

T2* Effects (in order):

- Iron oxides (SPIO)
- Iron oxides (USPIO)
- FeCl
- DyDTPA
- GdDTPA
- DeOxyHb
- OxyHb

Feridex-enhanced MR "USPIO"



Superparamagnetics

Alterations of T1 and T2

Particulates (superparamagnetic irons):

Possesses mild T1-shortening at low [Fe].

Large T2* effect at higher [Fe].

Biodistribution vary depending on size:

>20 nm size	***Liver (RES) uptake agents***
20	***Oral (gut) agents***
10-20	***Lymph nodes, blood pool***
4-6	***Hepatocytes, targets***

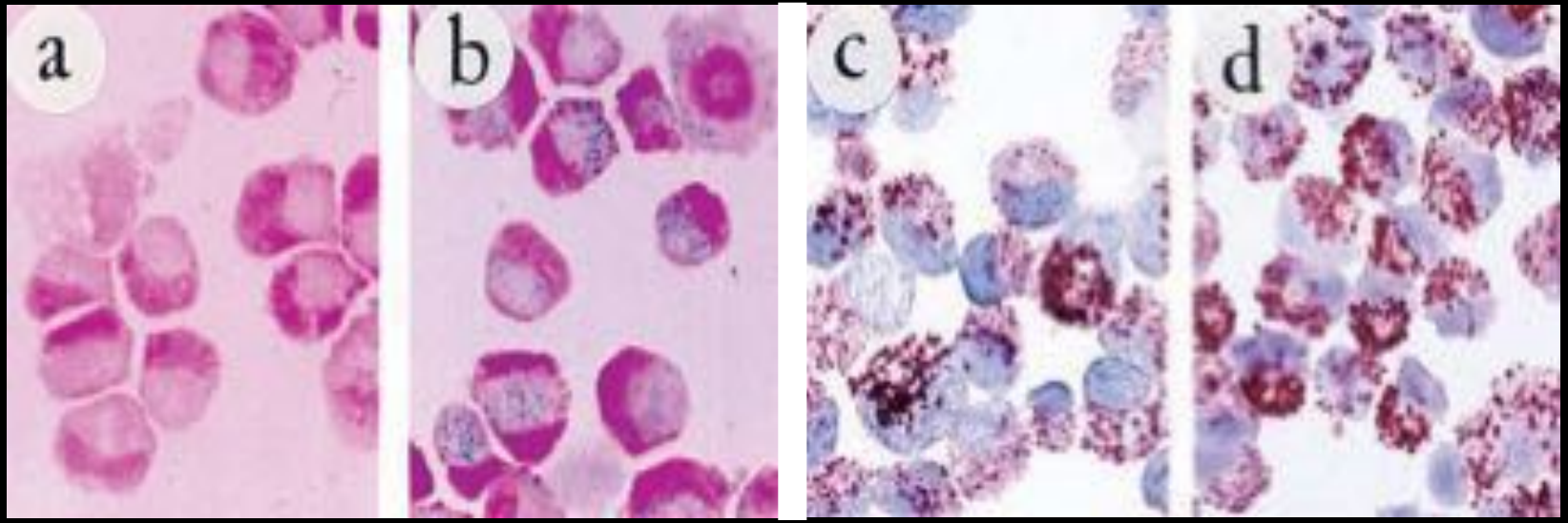
ze is the most important aspect of biodistribution.

l particles must be < 5 µm to avoid entrapment in lung.

Neurotransplantation of magnetically labeled oligodendrocyte progenitors: MR tracking of cell migration and myelination

J. W. M. Bulte†‡, S.-C. Zhang§, P. van Gelderen¶, V. Heryneki, E. K. Jordan†, I. D. Duncan§**, and J. A. Frank

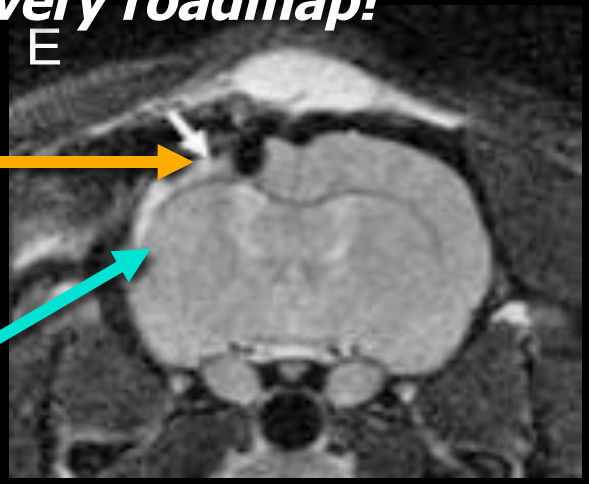
PNAS, 96, 1999



50 mg MION-46L-OX-26
Cell Density 2.5–3.0 3 10^5 per 15 cm^2 surface area

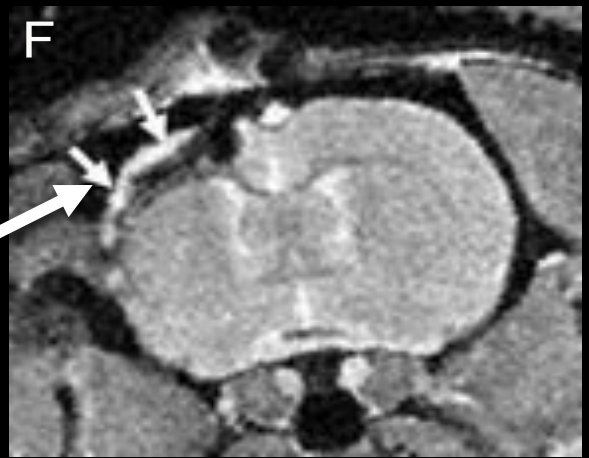
Mapping the Brain Neural Fiber Pathways

Inject MR-iron labeled stem cells
Stem cells migrate to injury via white matter tracts
Use DTI as delivery roadmap!



Stem cell implant colony

Stroke in brain



Migration of colony along white matter to repair stroke

Guzman, Bammer, Moseley, Steinberg
Stanford

Superparamagnetics

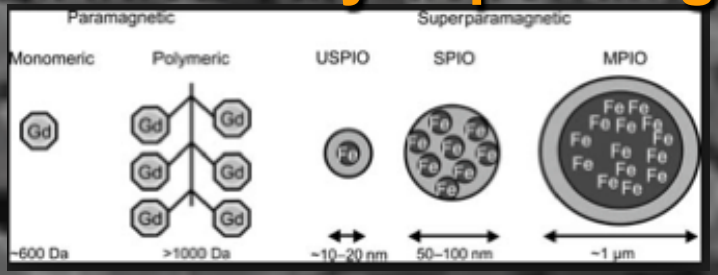
Alterations of T1 and T2

Particulates (superparamagnetic irons):

Possesses mild T1-shortening at low [Fe].

Large T2* effect at higher [Fe].

Biodistribution vary depending on size:



>20 nm size	*Liver (RES) uptake agents*
20	*Oral (gut) agents*
10-20	*Lymph nodes, blood pool*
4-6	*Hepatocytes, targets*

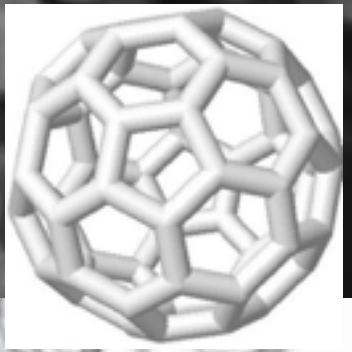
Size is the most important aspect of biodistribution.
All particles must be < 5 µm to avoid entrapment in lung.

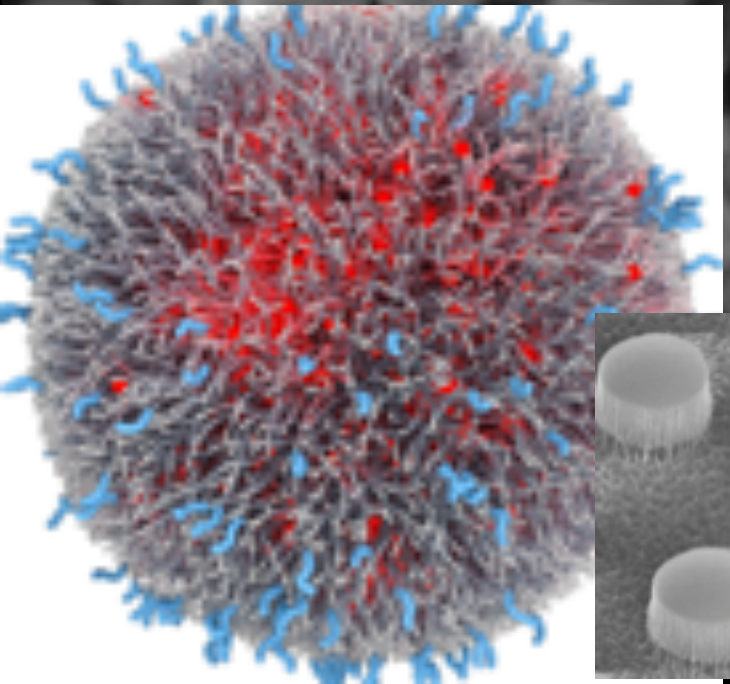
Nanoparticles!

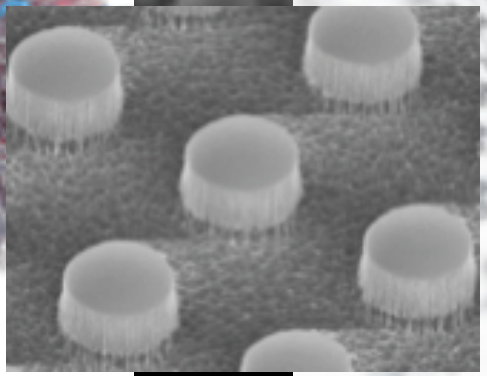
Magnetic susceptibility factors

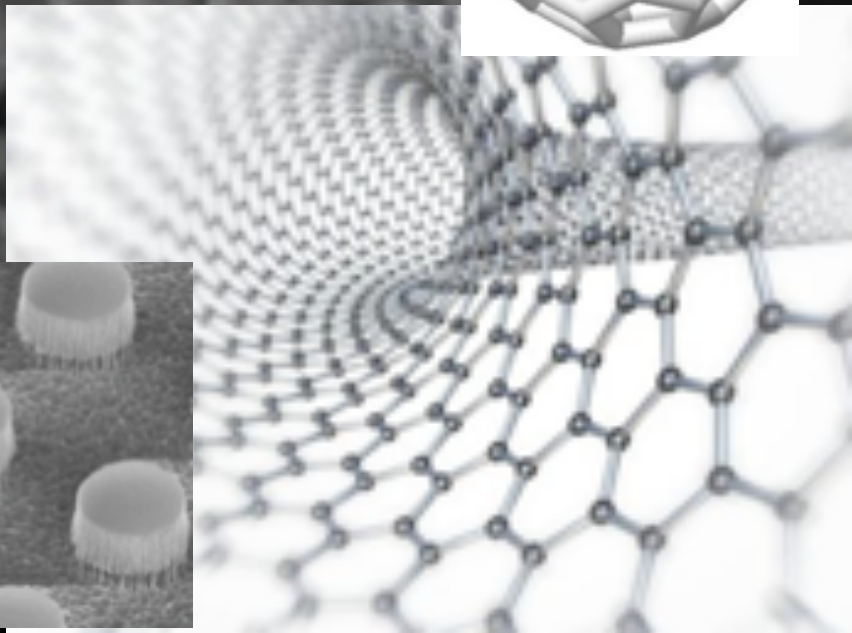
Particulates (superparamagnetic irons):

- **Possesses mild T1-shortening at low [Fe].**
- **Large T2* effect at higher [Fe].**
- **Biodistribution vary depending on size:**



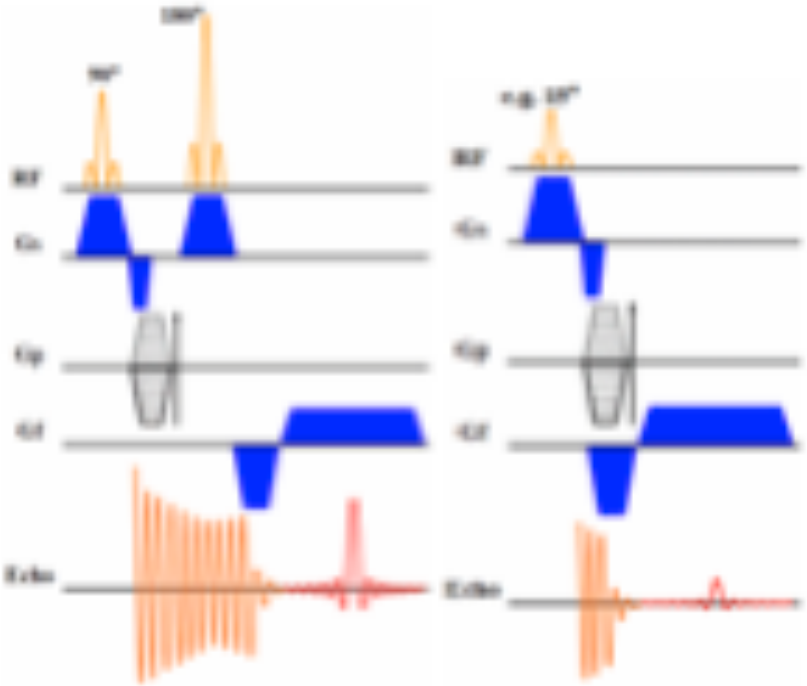


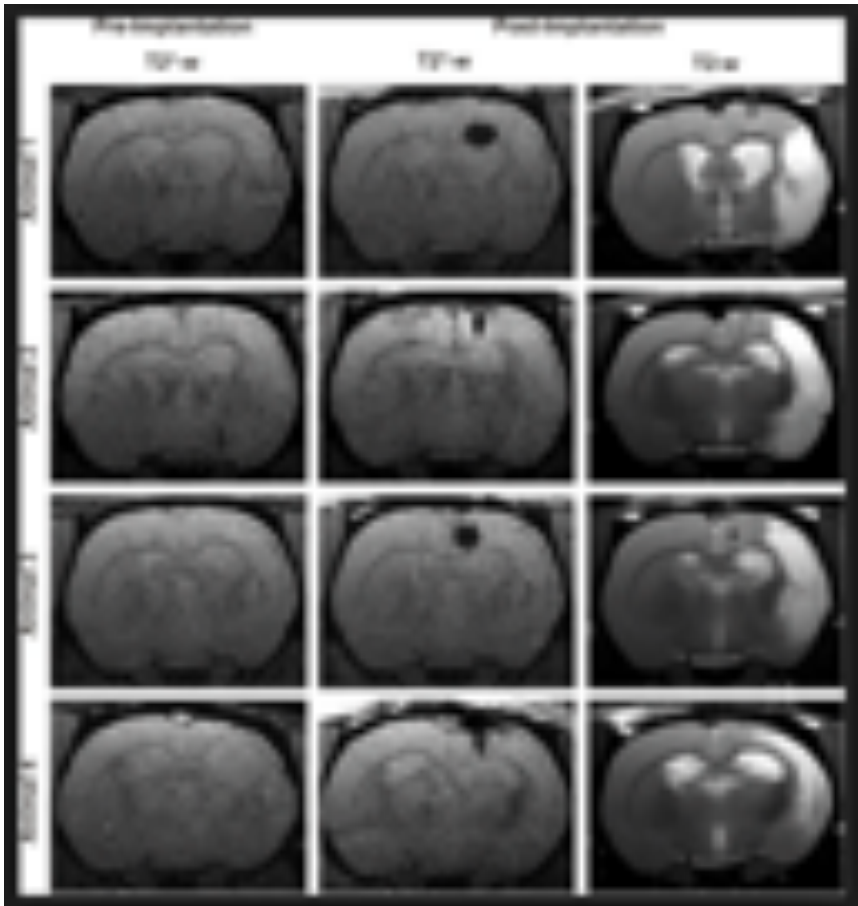




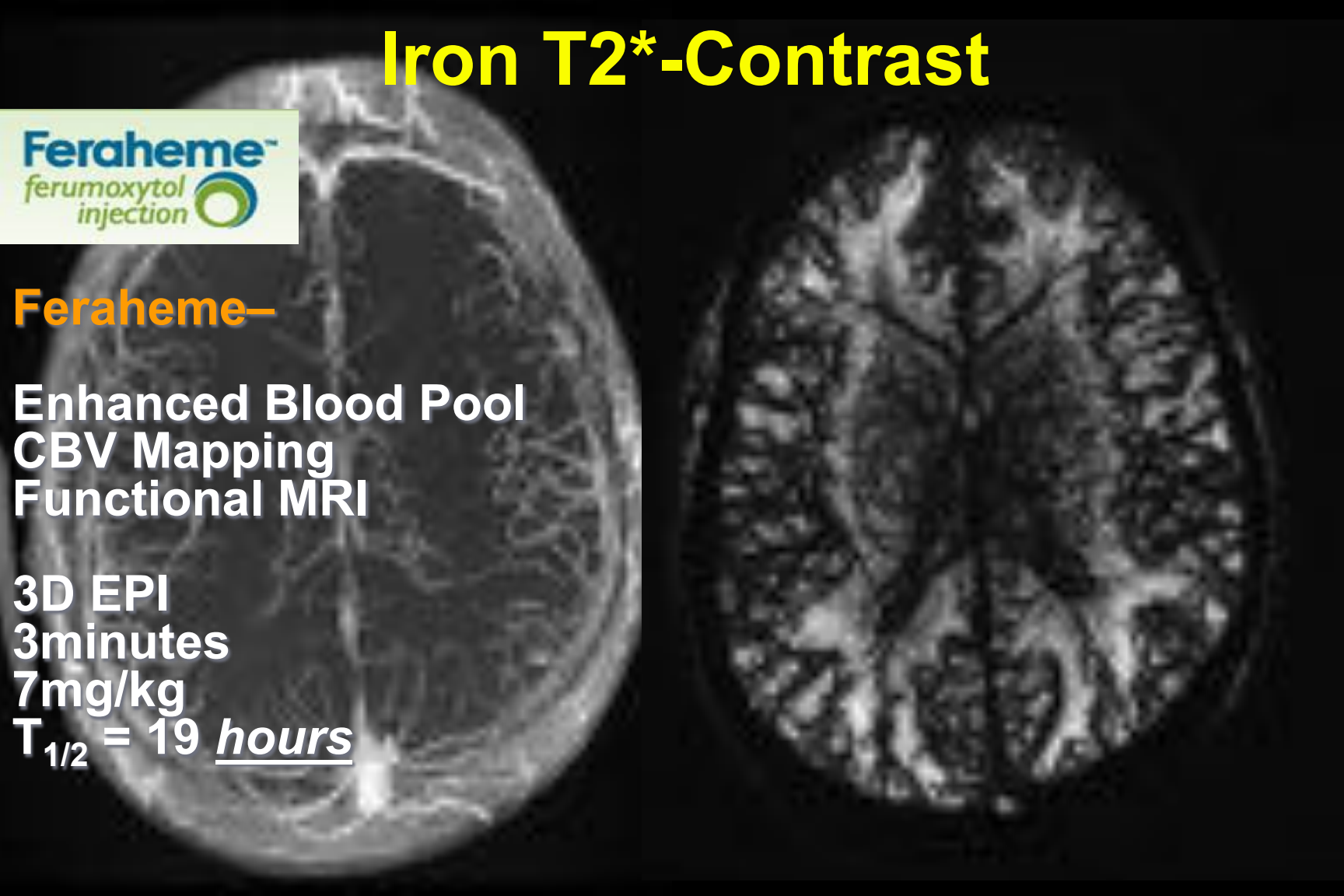
Nanoparticles!

Effect of field on signal creation. SE vs. GRE





Iron T2*-Contrast



Feraheme–

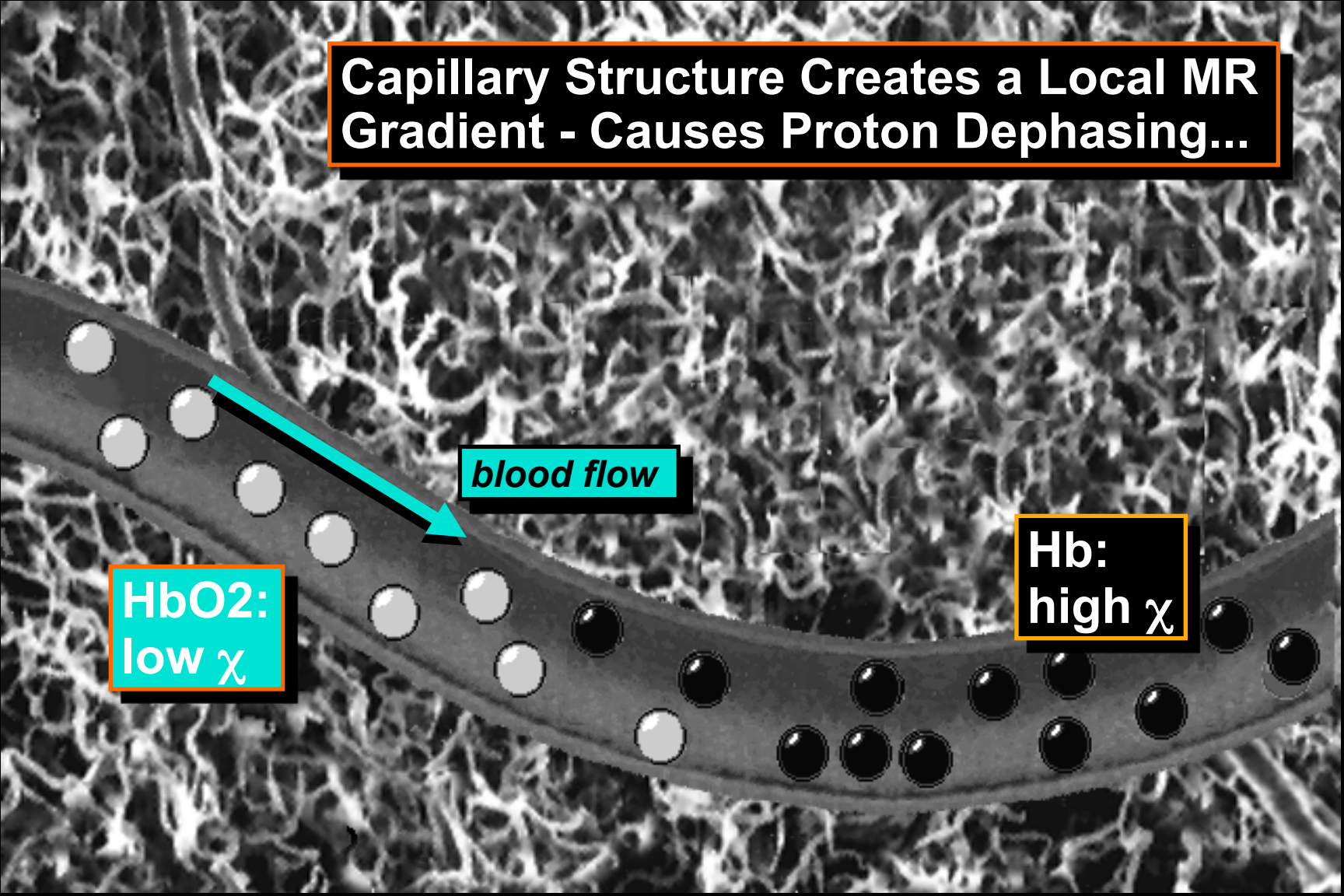
Enhanced Blood Pool
CBV Mapping
Functional MRI

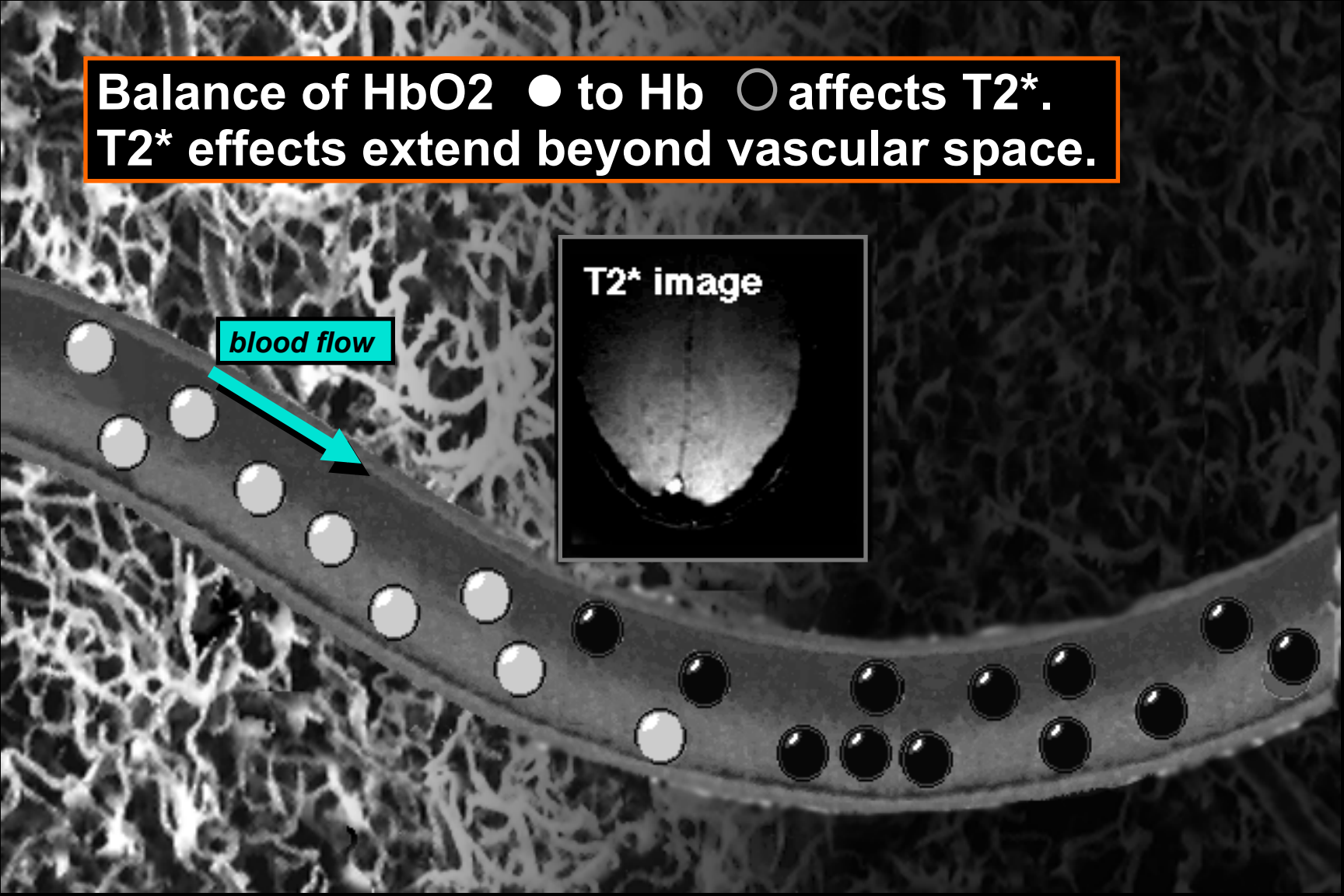
3D EPI
3minutes
7mg/kg
$T_{1/2}$ = 19 ***hours***

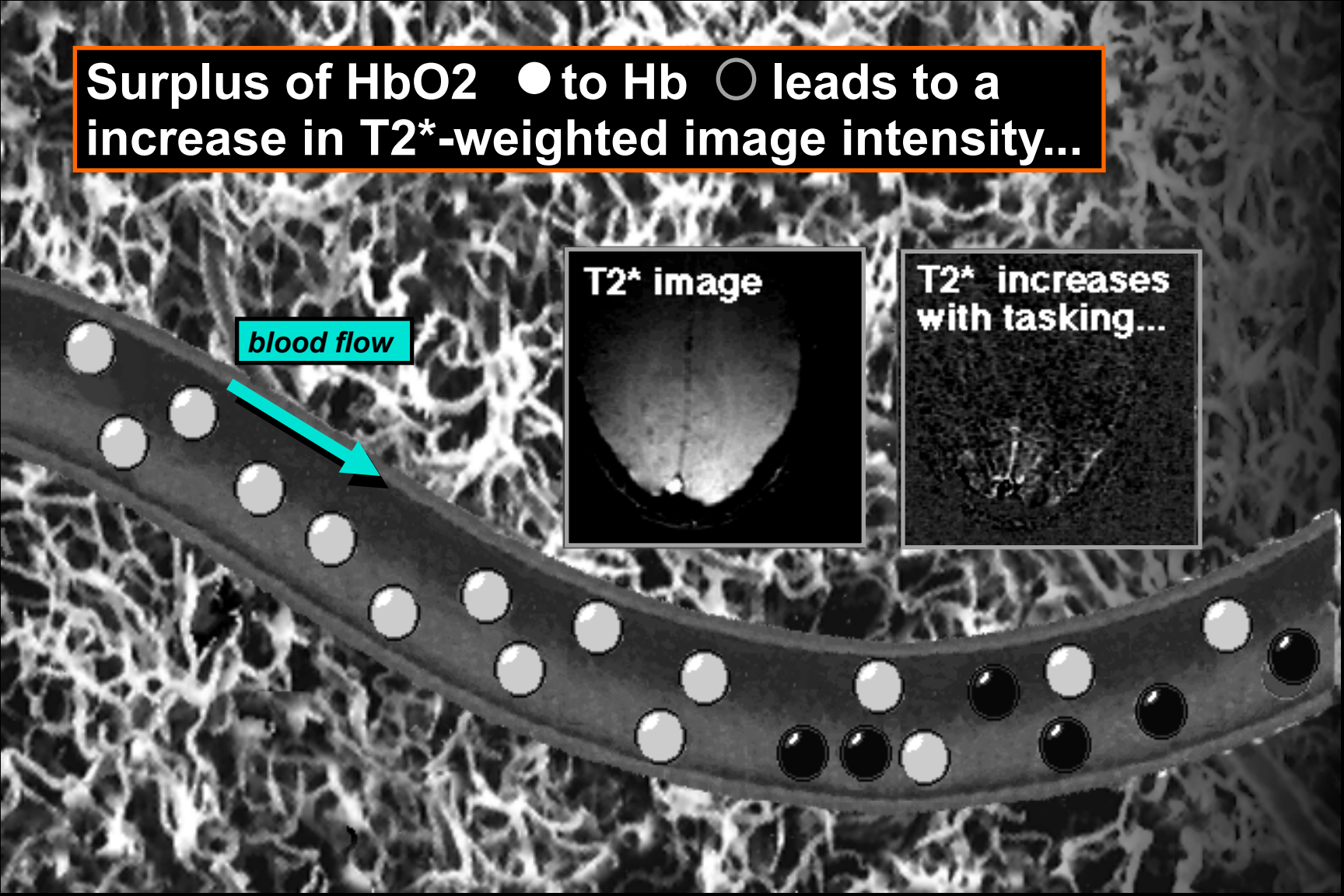
Blood = Ideal MR Contrast Agent?

HbO2
diamagnetic
Low $^2\chi$

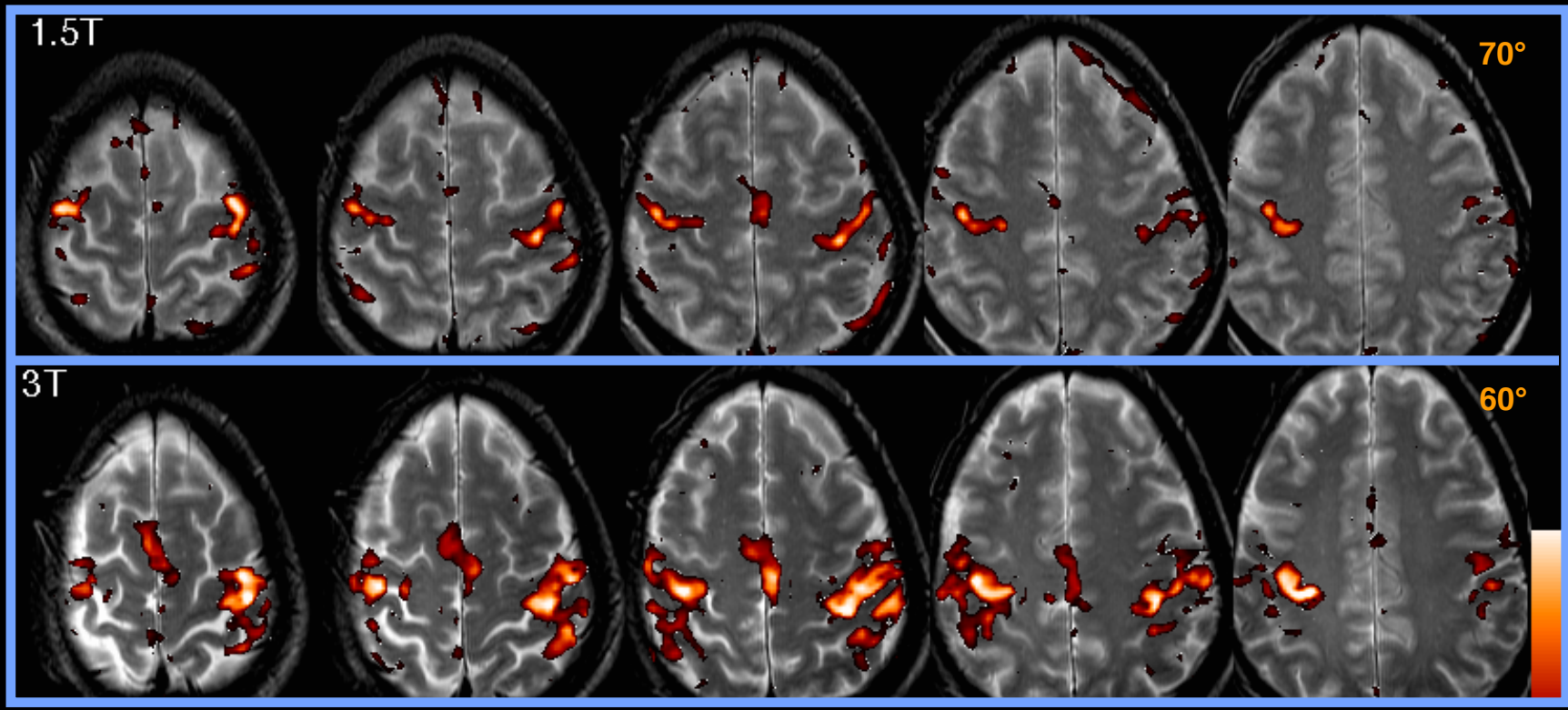
Hb
4 unpaired electrons - paramagnetic
High $^2\chi$


Capillary Structure Creates a Local MR Gradient - Causes Proton Dephasing...
blood flow
HbO2: low χ
Hb: high χ


Balance of HbO2 ● to Hb ○ affects T2*.
T2* effects extend beyond vascular space.
T2* image
blood flow


Surplus of HbO2 ● to Hb ○ leads to a increase in T2*-weighted image intensity...
blood flow
T2* image
T2* increases with tasking...

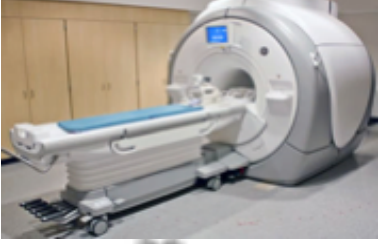
1.5T vs. 3.0T Motor Task Finger Apposition



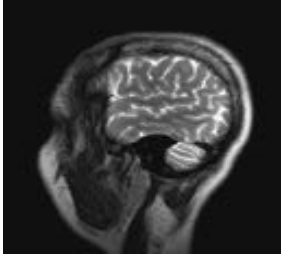
Spiral 2D single shot, 200 frames, TR 1000ms, TE 40ms
3T 60°; 1.5T 70° *(T1› @ 3T: T1@1.5T~900ms; T1@3.0T~1400ms)*
20cm FOV, 5mm/skip 0, 90x90, 6 slices

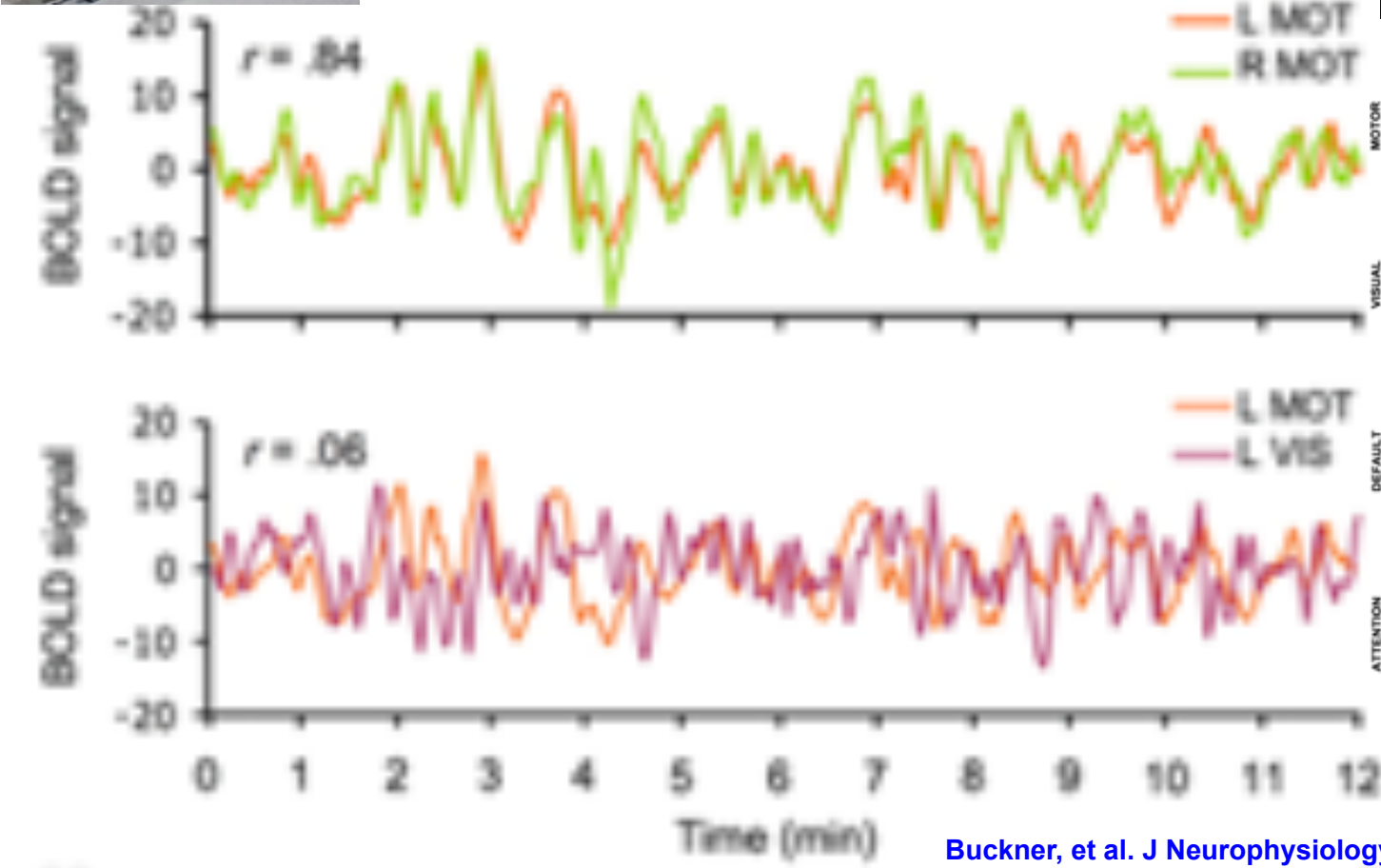
G. Glover, Dept. of Radiology

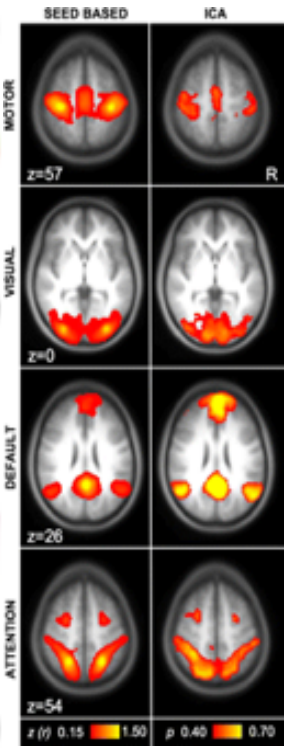
fMRI "*Resting State*"- Brains at Rest



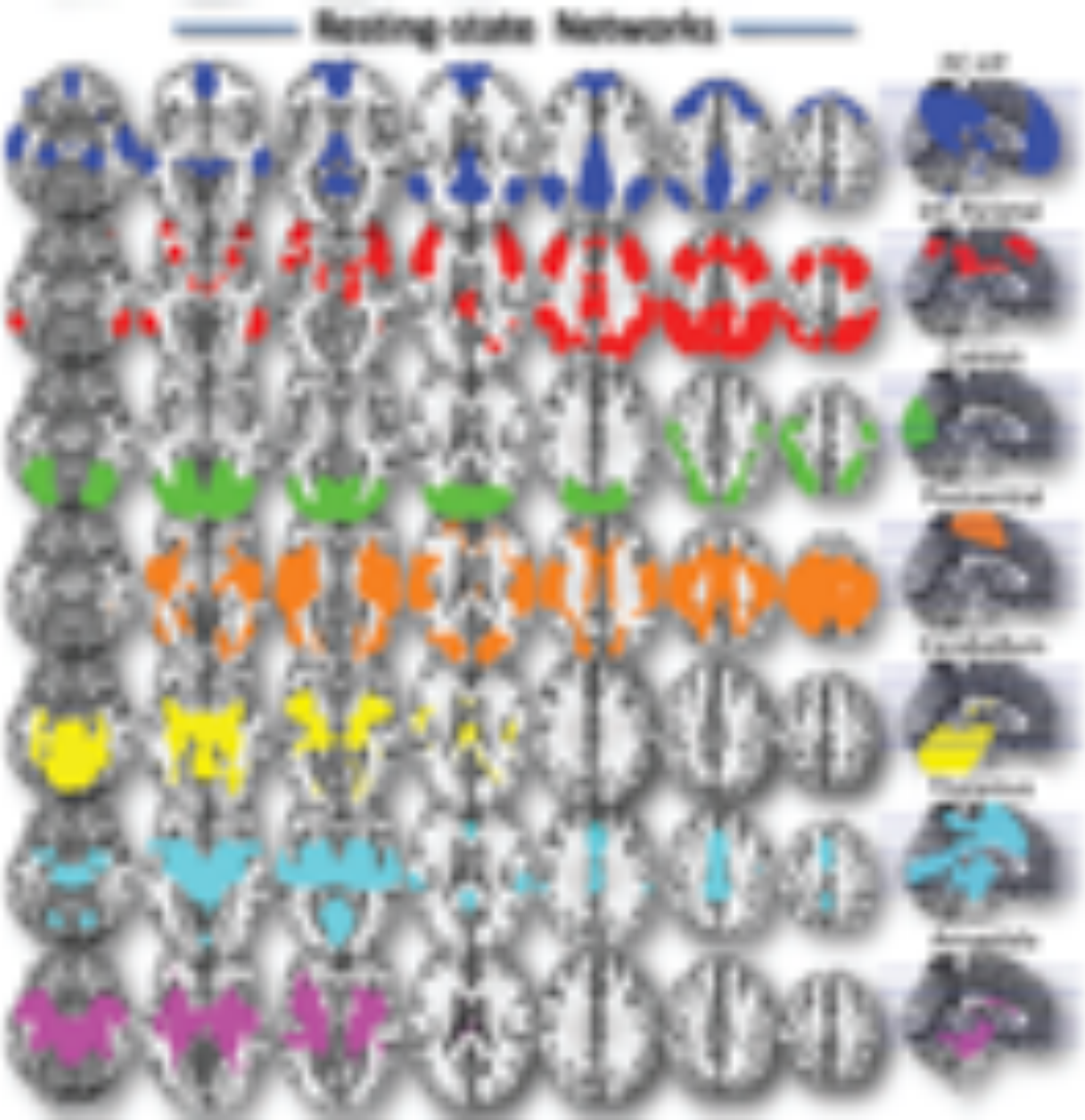
fMRI "*Resting State*"





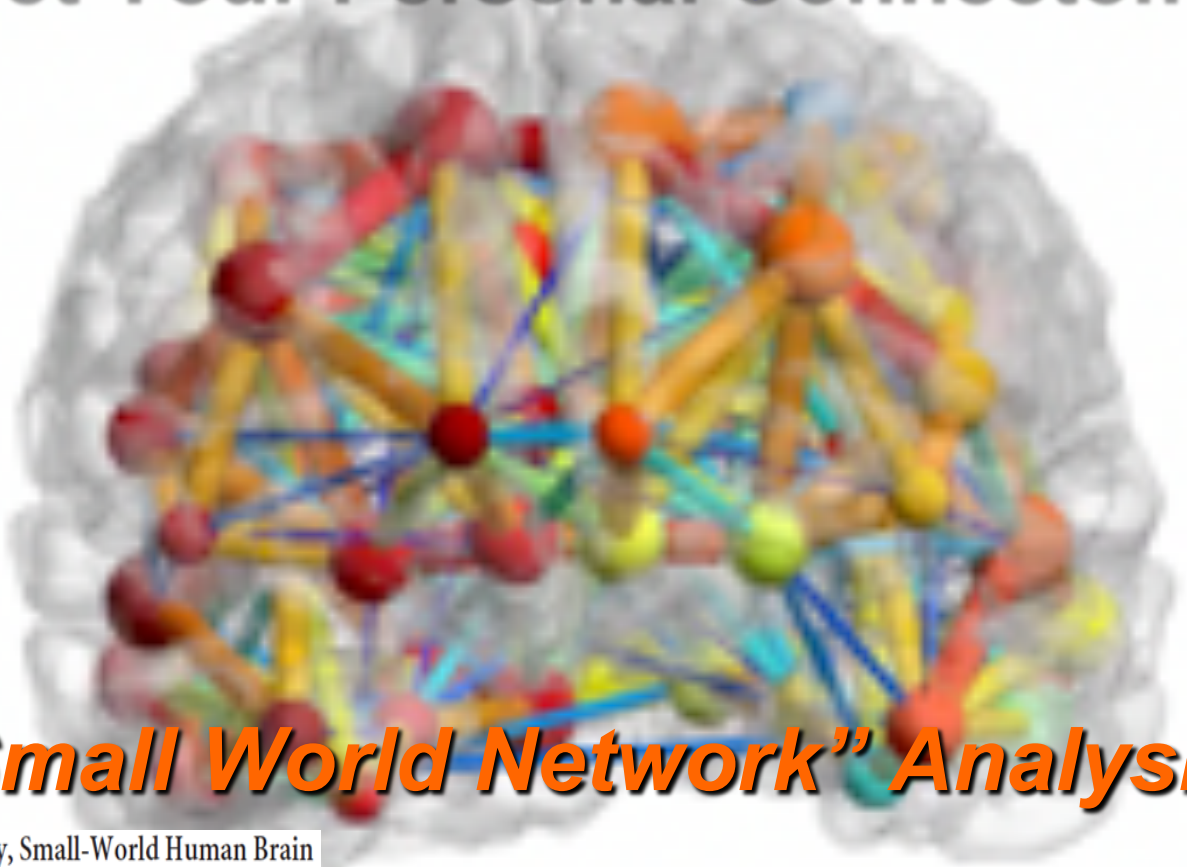


Buckner, et al. J Neurophysiology 103 (2010), 297.



Volkow and
Tomasi, NIDA

“Meet Your Personal Connectome”



“Small World Network” Analysis

A Resilient, Low-Frequency, Small-World Human Brain Functional Network with Highly Connected Association Cortical Hubs

J NeuroSci, 26, 2006

Sophie Achard,[1] Raymond Salvador,[1,2] Brandon Whitcher,[3] John Suckling,[1] and Ed Bullmore[1,3]

Salil Soman, CAFN, Stanford

What Does MR Offer?

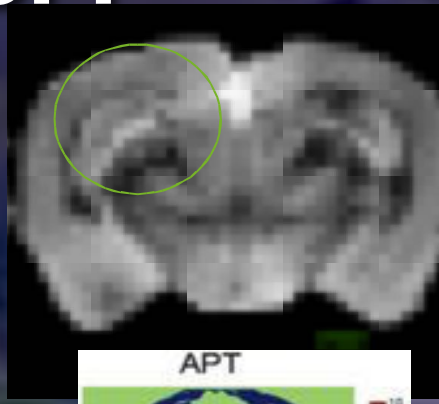
It is a major “clinical endpoint”.

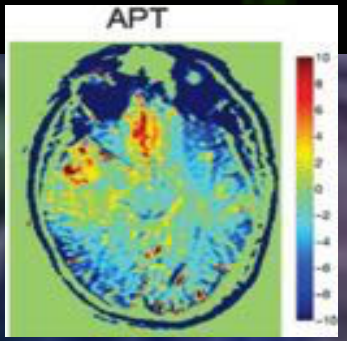
Near-ideal “translational” tool.

DWI, FLAIR, SWI

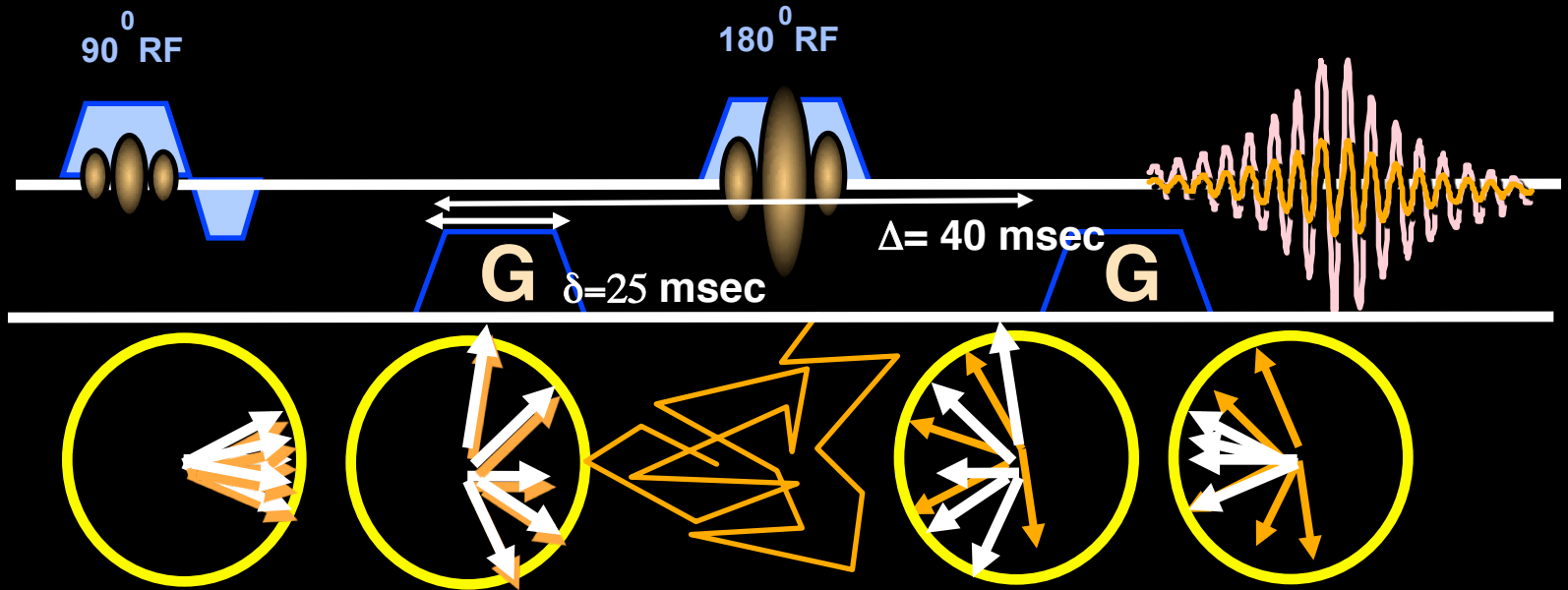
Nex-Gen MR Ideas for MI:

- High-field – SNR and T2* (BOLD)
- New contrast agents –ParaCEST
- New add-ons – MR/PET
- Multi-nuclear – *Hyper…!*



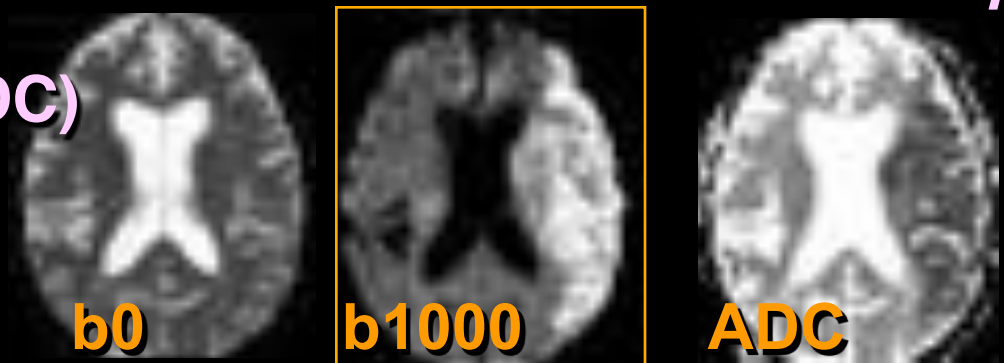


Proton Diffusion can be Measured as the "ADC"



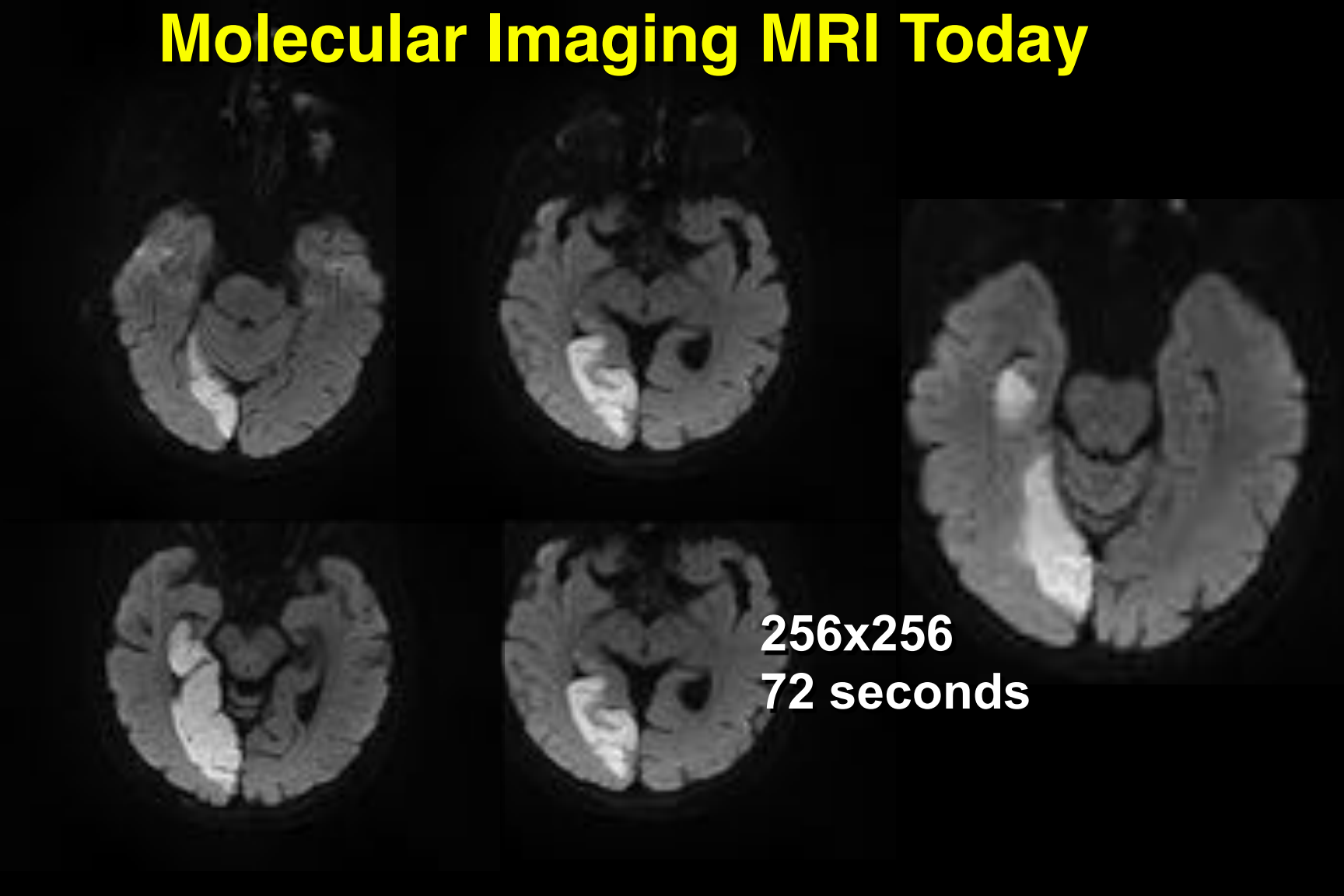
$$SI = ke(-\gamma^2 \delta^2 G^2 [\Delta - \delta/3] ADC)$$
$$= ke(-b\ ADC)$$

where b=0-1000 sec/mm²



ADC map

Molecular Imaging MRI Today



CLINICAL IMPLICATIONS OF NEUROSCIENCE RESEARCH

Section Editor
Eduardo E. Benarroch, MD

Aquaporin-4, homeostasis, and neurologic disease

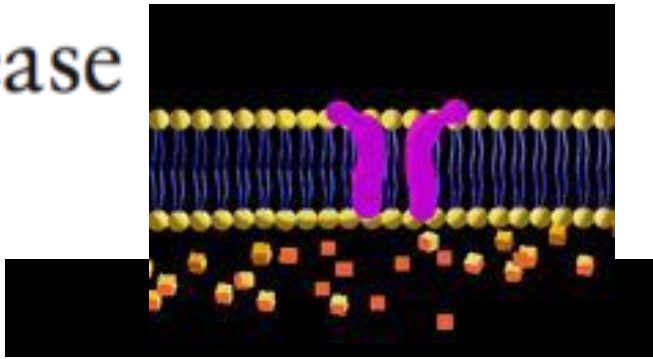
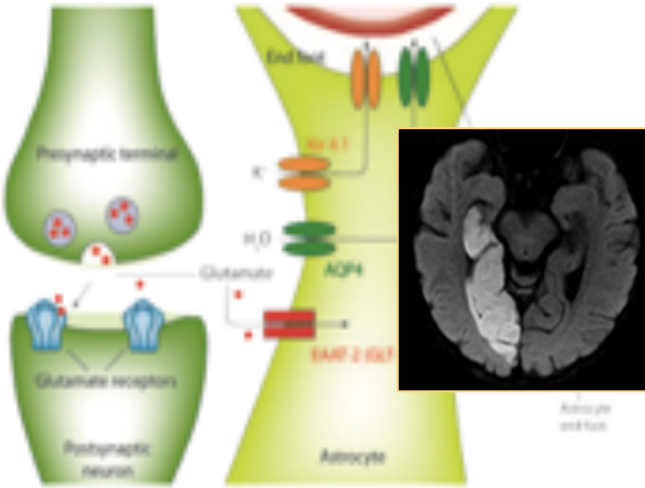


Figure 1 Role of AQP4 in water and K^+ homeostasis



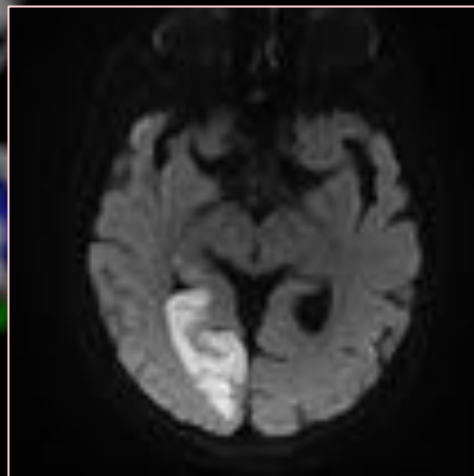
AQUAPORIN-4 AND NEUROLOGIC DISEASE

Cerebral edema. Perivascular AQP4 allows a bi-directional water flow between the blood and the brain and has been implicated in the pathogenesis of cerebral edema.[7] For example, AQP4 is upregulated in astrocytes in the setting of hypoxia, ischemia, traumatic brain injury, inflammatory disorders, exposure to interleukin-1β or ammonium, high-grade astrocytoma, and around metastatic adenocarcinoma. AQP4-null mice, which

AQP MRI

2019

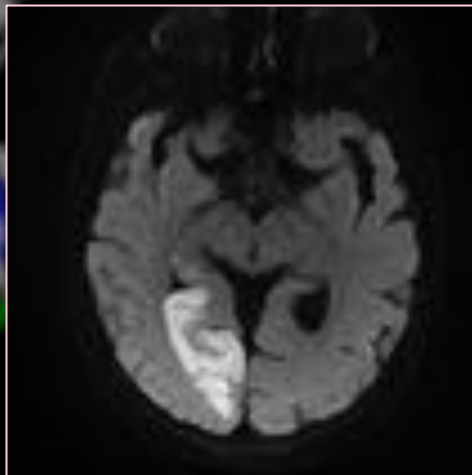
AQP abundant in brain.
Fast, easy, clinical DWI.
Proton transport.
Membrane sensitive.
Metabolic biomarker.



AQP MRI

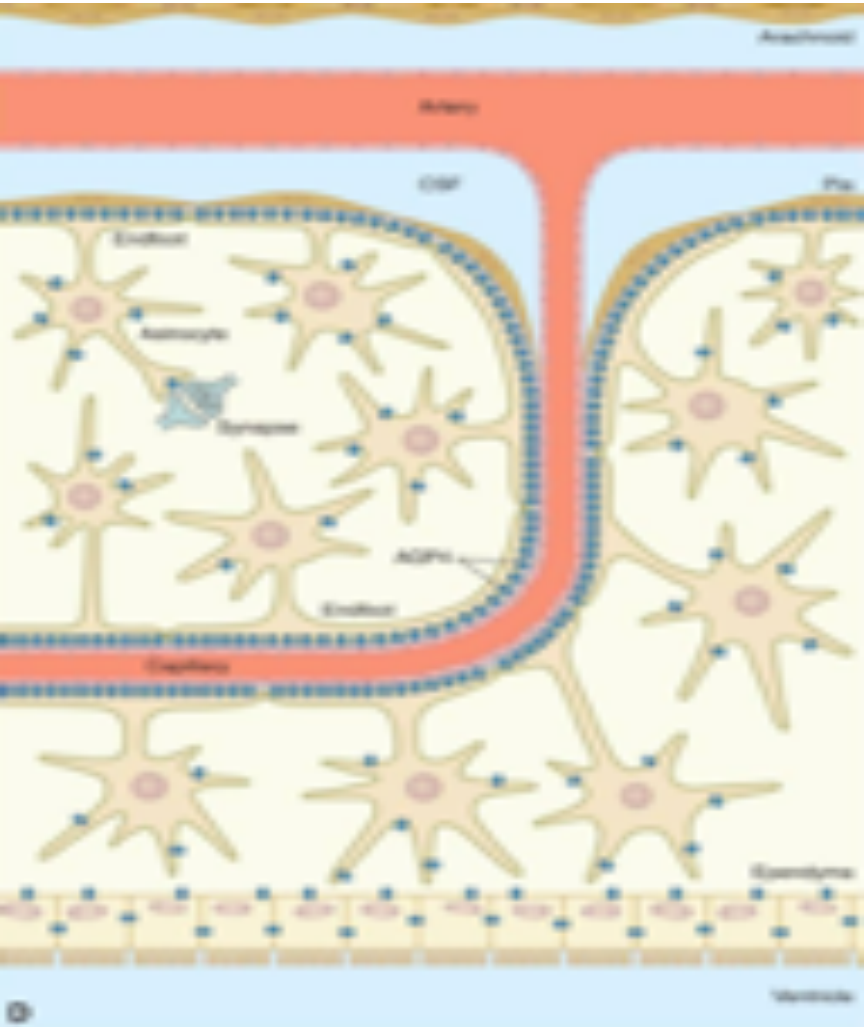
New Ideas?

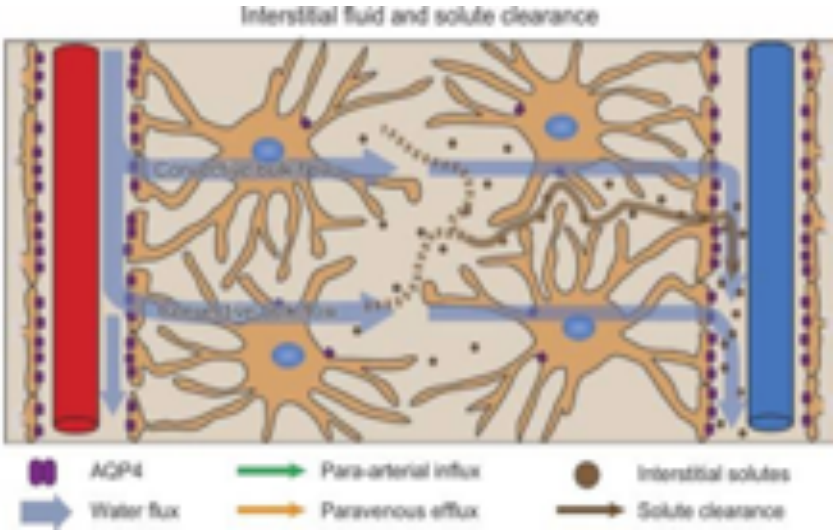
Tumor dynamics.
Response to therapy.
AQP ‘stress test’.
Glymphatics?
AD connection?



Physiological Roles of Aquaporin-4 in Brain

Erlend A. Nagelhus and Ole P. Ottersen[2]





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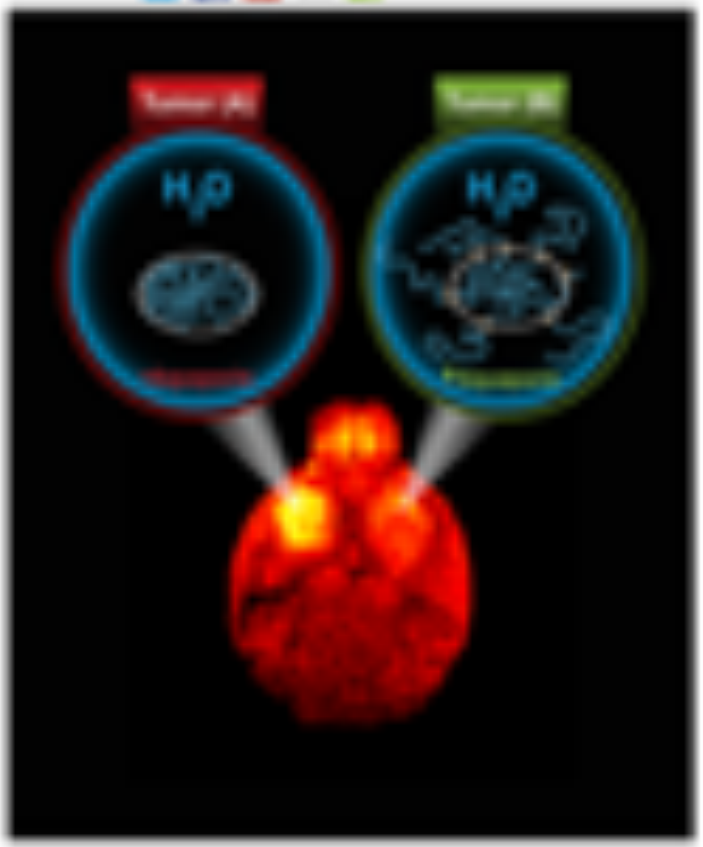
12/19/2013

Visualizing Gene Expression with MRI

Genes tell cells what to do—for example, when to repair DNA mistakes or when to die—and can be turned on or off like a light switch. Knowing which genes are switched on, or expressed, is important for the treatment and monitoring of diseases. Now, for the first time, Caltech scientists have developed a simple way to visualize gene expression in cells deep inside the body using a common imaging technology.

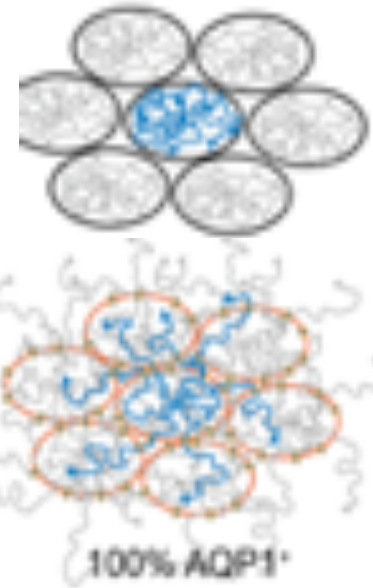
Researchers in the laboratory of Mikhail Shapiro, assistant professor of chemical engineering and Heritage Medical Research Institute investigator, have invented a new method to link magnetic resonance imaging (MRI) signals to gene expression in cells—including tumor cells—in living tissues. The technique, which eventually could be used in humans, would allow gene expression to be monitored non-invasively, requiring no surgical procedures such as biopsies.

The work appears in the December 19 online edition of the journal Nature Communications.



An illustration of engineered cells in cells

A Genetically Encoded Reporter for Diffusion Weighted Magnetic Resonance Imaging



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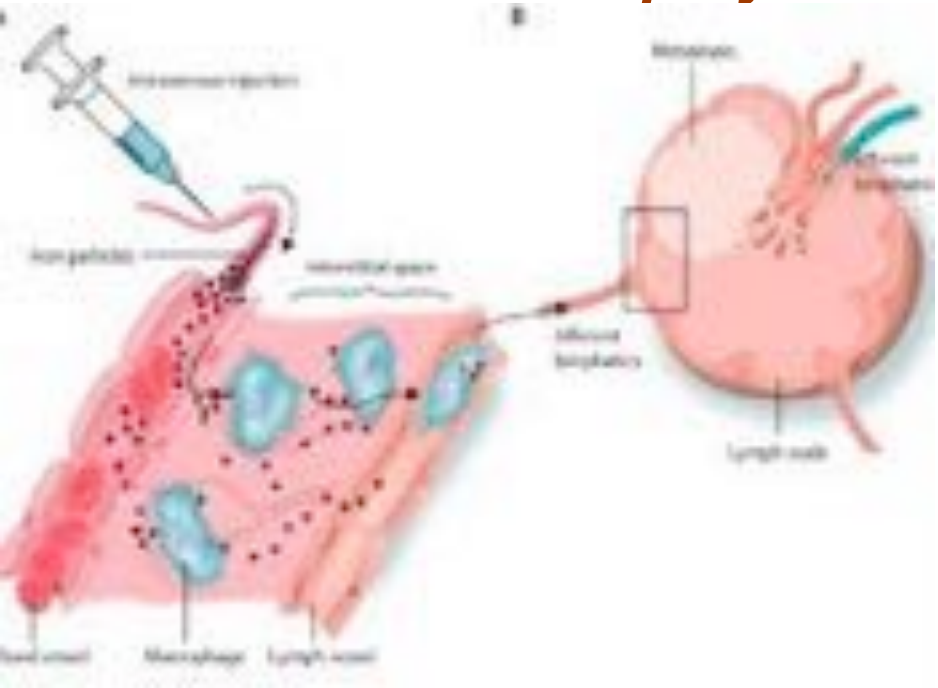
ABSTRACT

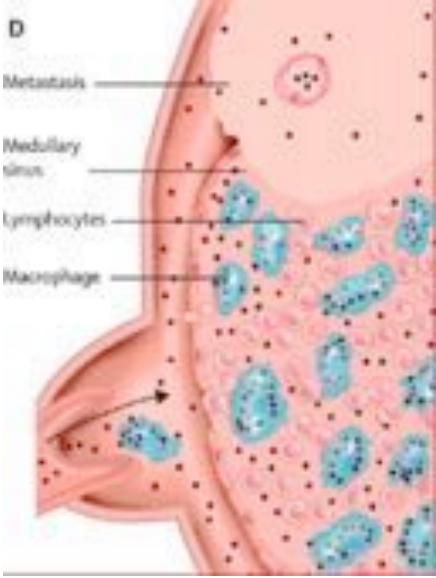
The ability to monitor gene expression in intact, optically opaque animals is important for a multitude of applications including longitudinal imaging of transgene expression and long term tracking of cell based therapeutics. Magnetic resonance imaging (MRI) could enable such monitoring with high spatial and temporal resolution. However, existing MRI reporter genes, based primarily on metal-binding proteins or chemical exchange saturation transfer probes, are limited by their reliance on metal ions or relatively low sensitivity. In this work, we introduce a new class of genetically encoded reporters for MRI that work by altering water diffusivity. We show that overexpression of the human water channel aquaporin 1 (AQP1) produces robust contrast in diffusion weighted MRI by increasing effective water diffusivity in tissues by over 100% without affecting cell viability or morphology. Low levels of AQP1 expression (~1 pM), or mixed populations containing as few as 10% AQP1-expressing cells, produce sufficient contrast to be observed by MRI. We demonstrate the utility of AQP1 in vivo by imaging gene expression in intracranial tumor xenografts. Overall, our results establish AQP1 as a new, metal-free, nontoxic and sensitive genetically encoded reporter for diffusion weighted MRI.

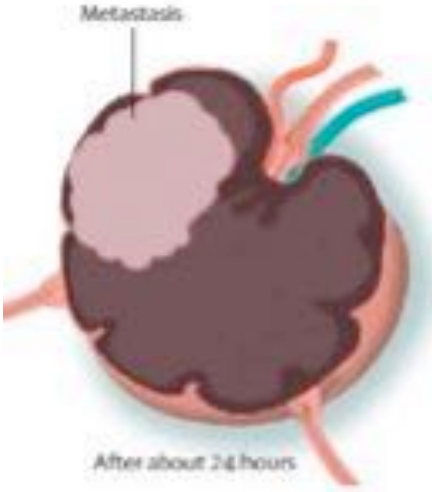
MR can haz more?

Iron nanoparticles in MRI

- Blood pool T2*
- Long retention times
- *Iron is taken up by macrophages!*







Radiology

Science to Practice

Science to Practice: Can Macrophage Infiltration Serve as a Surrogate Marker for Stem Cell Viability?

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Summary

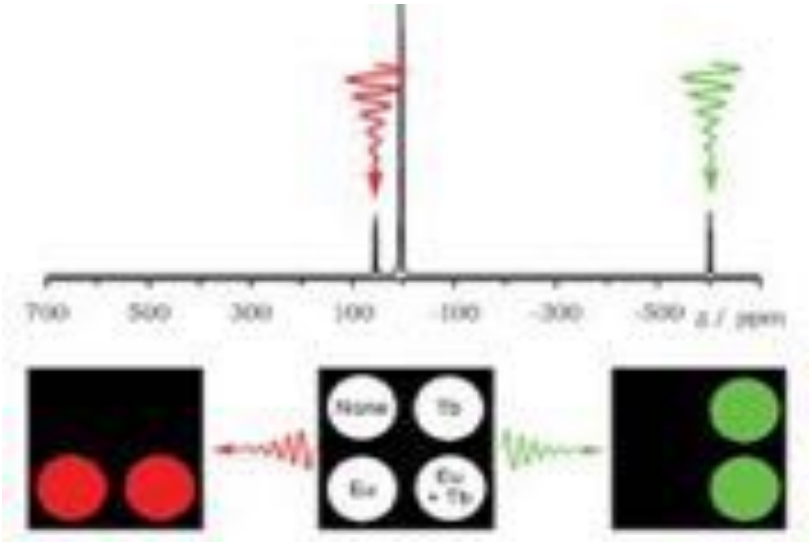
Following in vivo preloading of host macrophages with ultrasmall superparamagnetic iron oxide (USPIO) nanoparticles, it was shown that their magnetic resonance (MR) imaging–visible migration into knee implants of scaffolded adipose-derived stem cells (ADSCs) undergoing apoptosis can serve as a surrogate marker of stem cell death.

MR Agents in Disguise…

Paramagnetic Lanthanide Complexes as "PARACEST" Agents

- Lanthanide metals either:
  - shorten proton T1 (Gd does this…) *or*
  - shift their Larmor frequency (+ or -)

- Shift agents very old idea
- New novel applications
- T^0C, pH sensitive



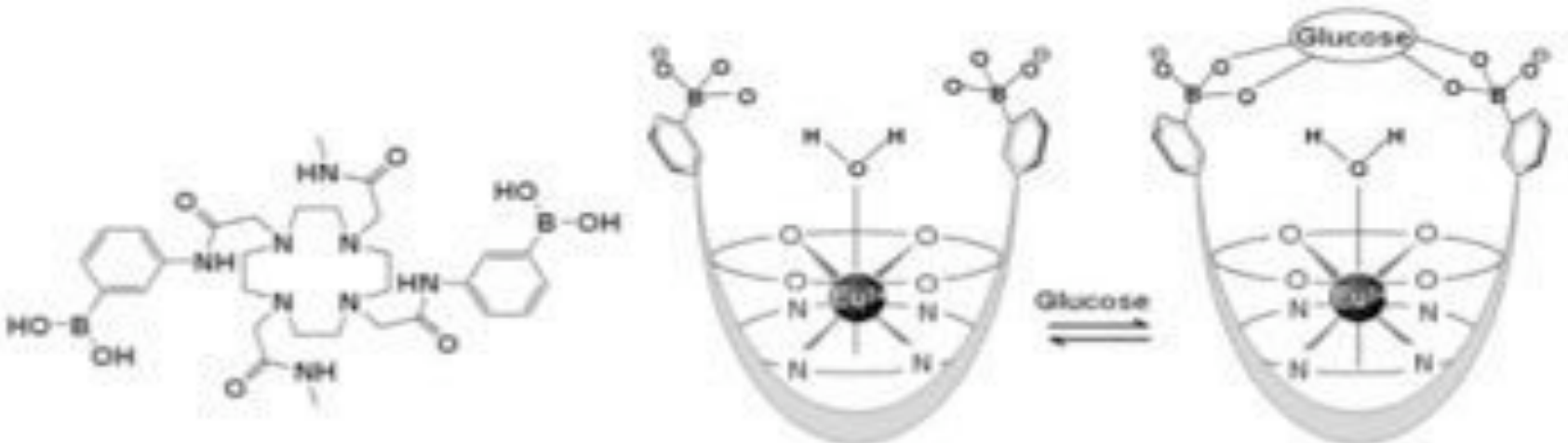
Sherry, et al. *Chem. Soc. Rev.*, 2006, 35, (6), 500-511

In Vivo Demonstration of "PARACEST" Agents

Magnetic Resonance in Medicine 60:1047–1055 (2008)

Imaging the Tissue Distribution of Glucose in Livers Using A PARACEST Sensor

Jimin Ren,[1] Robert Trokowski,[2] Shanrong Zhang,[1] Craig R. Malloy,[1,3] and A. Dean Sherry[1,2*]



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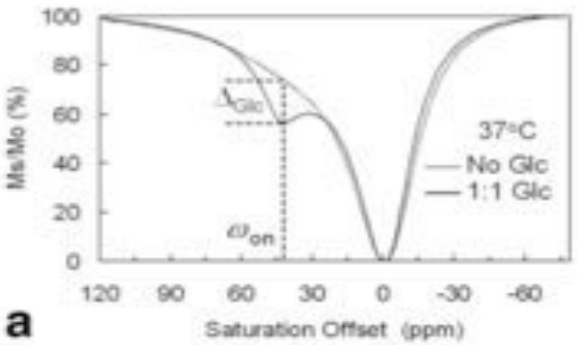
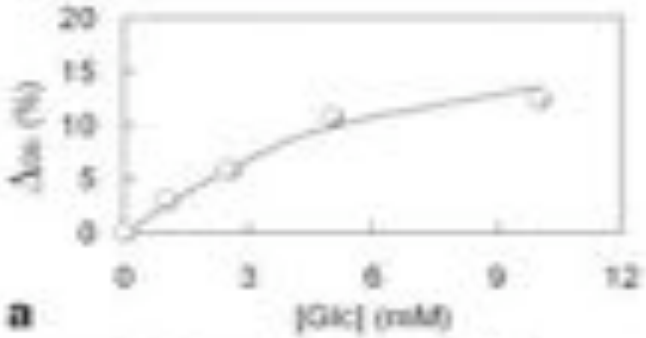
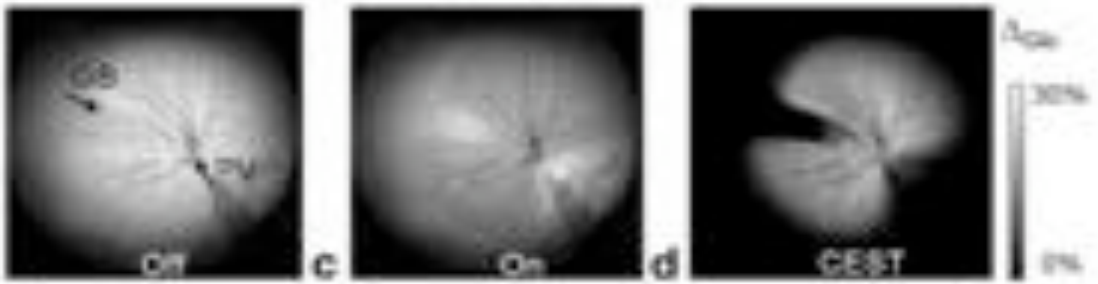






What Does MR Offer?

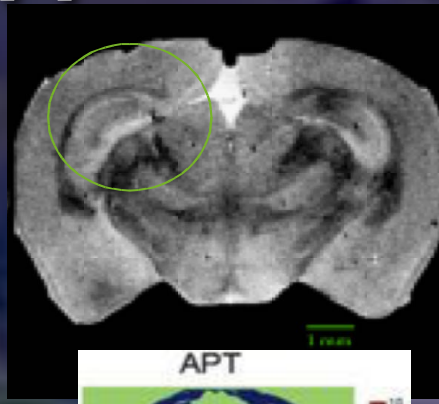
It is a major “clinical endpoint”.

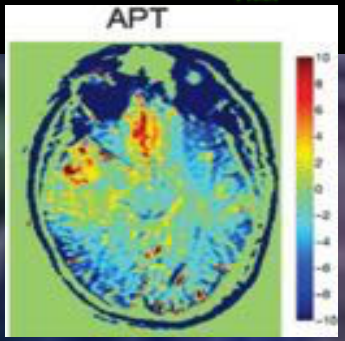
Near-ideal “translational” tool.

DWI, FLAIR, SWI

Nex-Gen MR Ideas for MI:

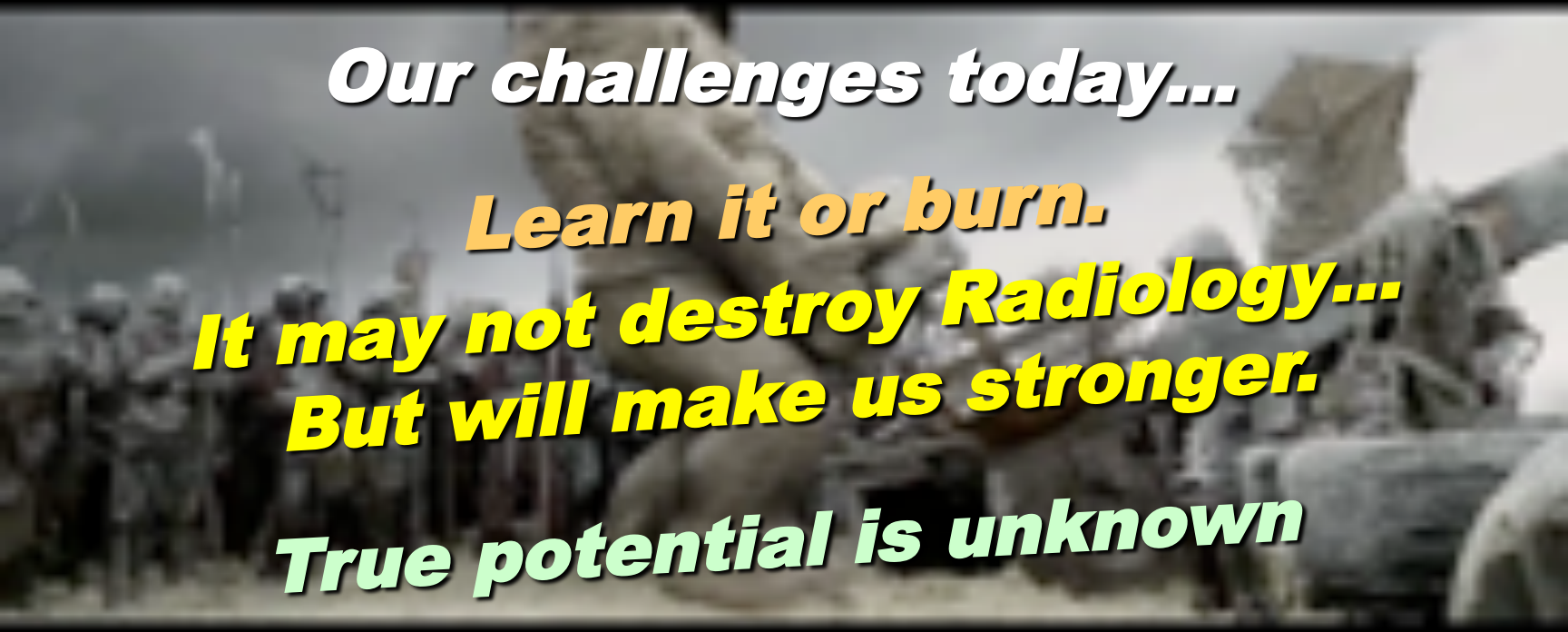
- High-field – SNR and T2* (BOLD)
- New contrast agents –ParaCEST
- New add-ons – MR/PET
- Multi-nuclear – *Hyper…!*






My # 4
"We Are in the Golden Age of Radiology"

The Attack of Deep Learning and AI



Our challenges today…

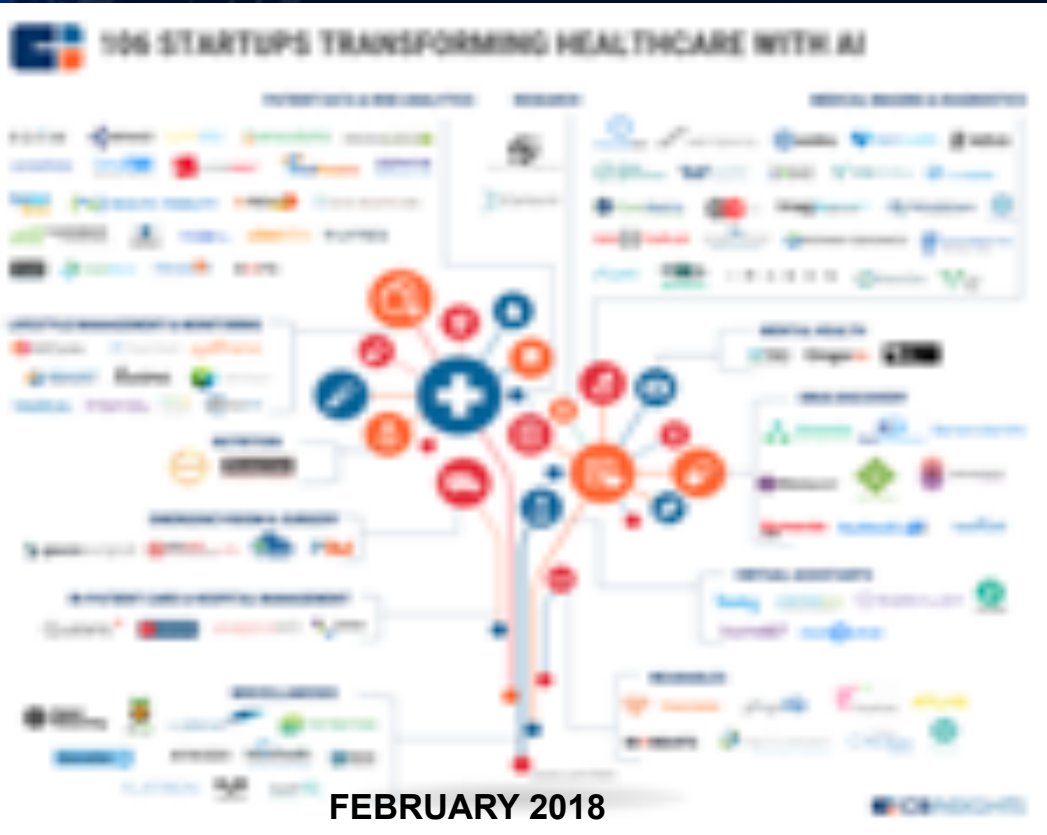
Learn it or burn.

It may not destroy Radiology…
But will make us stronger.

True potential is unknown

Lord of the Rings, New Line Cinema

Deep Learning:
Intelligence from Big Data



FEBRUARY 2018

TECH

Facebook is doing research to help speed up medical imaging — here's why

PUBLISHED TUE, AUG 21 2018 • 8:22 AM EDT | UPDATED TUE, AUG 21 2018 • 11:54 AM EDT

The Future of Radiology and Artificial Intelligence

Radiologists who use AI will replace those who don't

AuntMinnie.com

Attending radiologists need to bone up on AI

By Erik L. Ridley, AuntMinnie staff writer

January 28, 2019 -- To help ensure that medical students will still find radiology appealing, attending radiologists in academic departments need to stay informed about artificial intelligence (AI) technology and the exciting potential it offers for the specialty, according to an editorial published online January 24 in *Academic Radiology*.

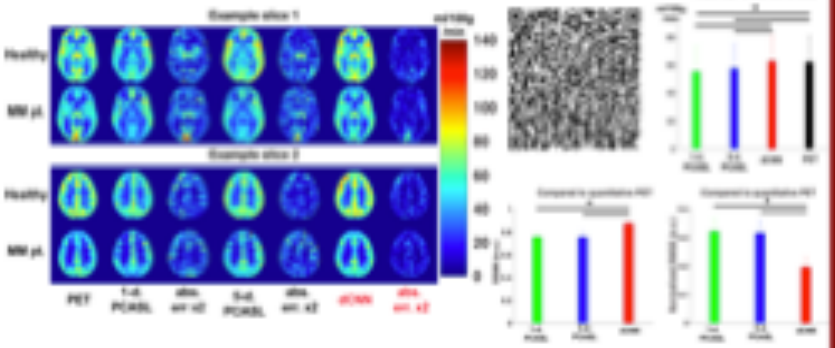
Radiology should be the medical specialty most primed to incorporate AI into its workflow, but, unfortunately, many attending radiologists aren't sure exactly how that will happen, wrote Dr. Allison Grayev of the University of Wisconsin School of Medicine and Public Health in Madison, WI.

Stanford MEDICINE Center for Advanced Functional Neuroimaging

Greg Zaharchuk and Mike Moseley

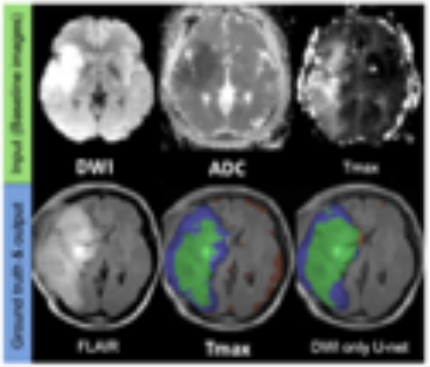
We develop new MRI and PET techniques to better understand human brain function and neurovascular diseases. Ask us about diffusion, perfusion, PET/MR, oxygenation imaging and deep learning applications!

Improved ASL using Deep Learning and Multi-contrast MRI



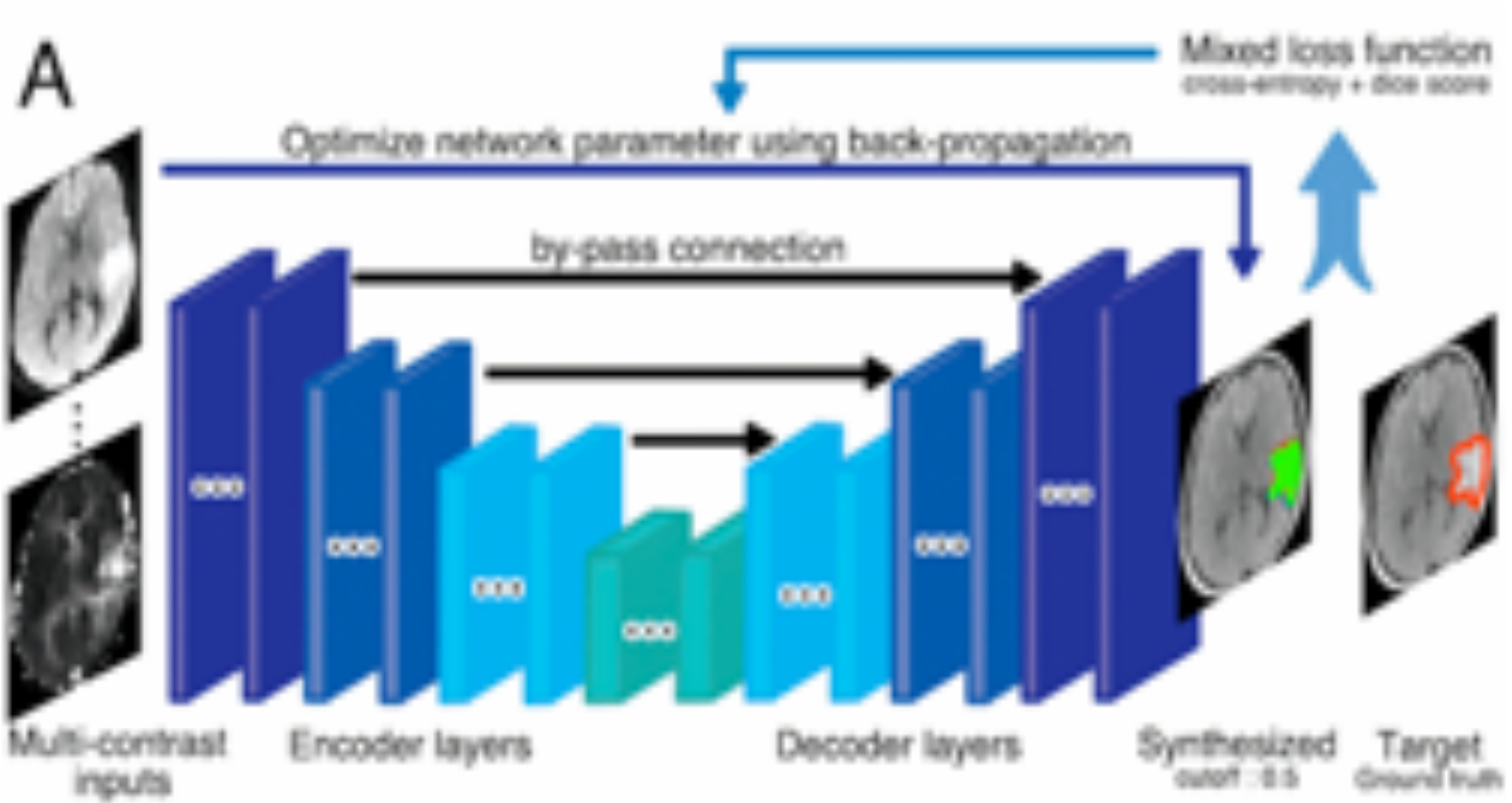
[15O] PET/MRI + DL

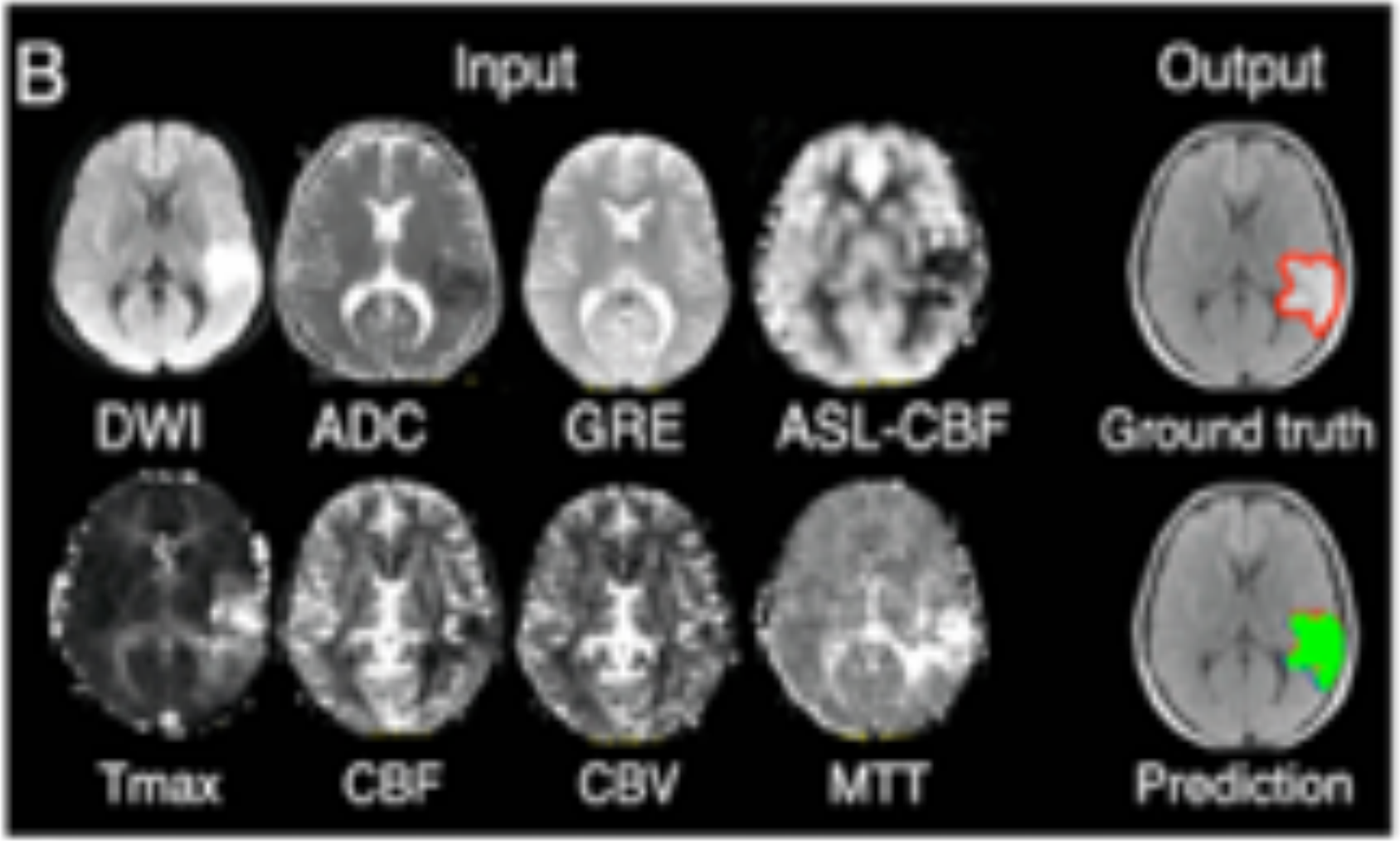
deepStroke: Predicting Stroke Lesion Outcome from Acute MRI



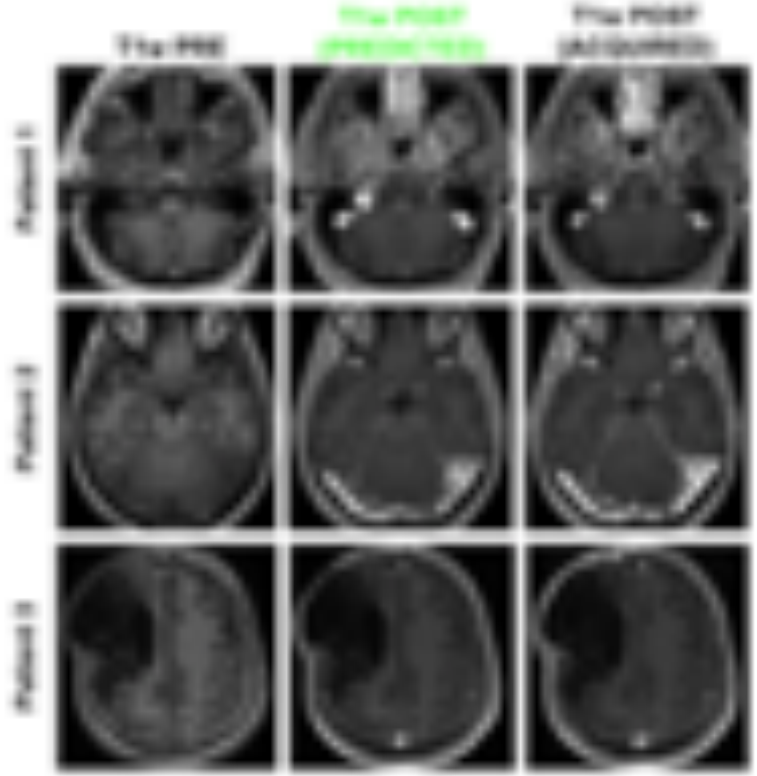
Stroke Outcome + DL

Predicting infarct development in acute ischemic stroke with baseline multimodal MRI and convolutional neural networks




B
Input
Output
DWI
ADC
GRE
ASL-CBF
Ground truth
Tmax
CBF
CBV
MTT
Prediction

Predicting Contrast Agent Enhancement with Deep Convolutional Networks



We tested whether deep convolutional neural networks (CNNs) could predict what an image would look like if a contrast agent was injected in the body. Great similarities were found between the predicted and the actual images acquired after contrast agent injection. If further validated, this approach could have great clinical utility in patients who cannot receive contrast.

My view of AI