INBRAIN

Quantificação de metais no cérebro humano

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III ESCOLA DE INVERNO EM FÍSICA APLICADA À MEDICINA E BIOLOGIA

INBRAIN

Laboratory

Goal: Functional and structural study of the brain through non-invasive physics techniques application aiming basic knowledge and methods applicable in clinical practice.

Main lines of research:

- Neurovascular metabolic coupling (TMS, EEG, fMRI, NIRS, ASL, fMRS).
- Structural connectivity and functional networks in brain normal aging (DTI, fMRI, EEG, ASL, TMS).
- **Quantitative magnetic resonance imaging** techniques (Relaxometry, Magnetization Transfer, Diffusion, MRS, fMRI) to characterize central nervous system diseases (Epilepsy, Alzheimer Disease, Stroke, Multiple Sclerosis, Parkinson).
- **Assessment of paramagnetic ions content in the human brain.**
- Neurofeedback.

Current students: 1 MSc., 4 PhD., 5 UG.

Former students: 11 MSc., 3 PhD.

https://inbrainlab.wixsite.com/inbrainlab

Contrast mechanisms

$$M_\perp = f(\rho, T_1, T_2, T_{1\rho}, T_2^*, \delta, D, k, \chi)$$

- Relaxation (T_1, T_2) } Traditional images
- Nuclear density (ρ) } Traditional images / Spectroscopy
- Chemical shift (δ) } Spectroscopy
- Magnetization Transfer (k) — CEST
- Motion ($\vec{V}$, D) — Angiography, Diffusion, Perfusion
- Susceptibility (χ, T_2*) — fMRI, QSM

qMRI

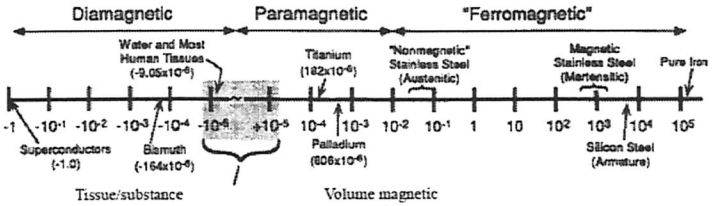
$$M_\perp = f(\rho, T_1, T_2^*, \delta, D, k, \chi)$$

- Absolute values
  - -Spatial scale: Morphology.
  - -Time scale: T_1, $T_{1\rho}$, T_2, T_2*
  - -Combination: Diffusion coefficient, Permeability, Velocity.
  - -Dimensionless: FA, pH, Tissue fractions
- Relative values
  - -Brain activation.
  - -Susceptibility. - Oxygenation.
  - -Functional connectivity.
  - -Temperature.
  - -Metabolite concentration.
  - -Pressure. -Strain.

Quantitative Susceptibility Mapping

Magnetic susceptibility ($\vec{\chi}$) describes the material's response to an externally applied magnetic field ($\vec{H}$).

$$\vec{M} = \vec{M}_0 + \vec{\chi} \cdot \vec{H}$$

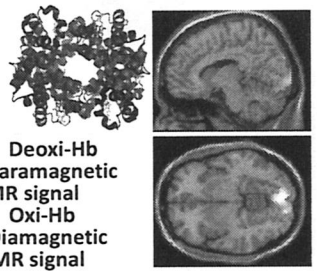


Tissue/substance	Volume magnetic susceptibility (χ)
Pure water (T = 37 °C)	-9.05×10^{-6}
Human tissue	$\sim(-11$ to $-7) \times 10^{-6}$
Myelin	-10×10^{-6}
Red blood cell (deoxygenated)	-6.52×10^{-6}
Red blood cell (oxygenated)	-9.19×10^{-6}
Red blood cell (methemoglobin)	-7.2×10^{-6}
Bovine rib bone powder	-11.3×10^{-6}
Ferritin (fully loaded with 4500 Fe^{3+} ions)	$+520 \times 10^{-6}$

Medical Physics 23, 815, **1996**.

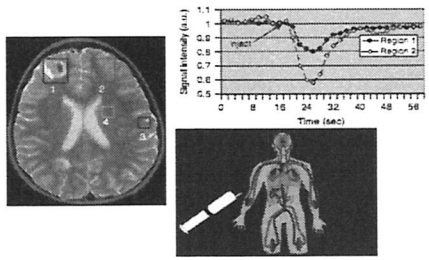
Susceptibility effects in MRI

BOLD/fMRI

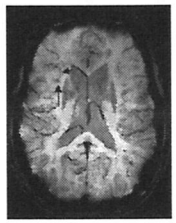


- **Deoxi-Hb**
- **-Paramagnetic**
- **MR signal**
- **Oxi-Hb**
- **-Diamagnetic**
- **MR signal**

Contrast agents/Perfusion



Susceptibility weighted imaging (SWI): Iron deposition/vascular studies.

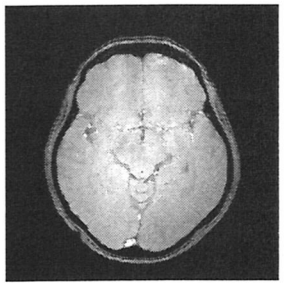


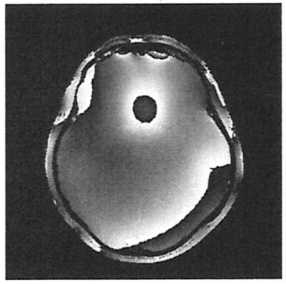
Magn. Reson. Med. 52, 612, **2004**.

Essential MRI behind QSM

$$S(\vec{r}) = M(\vec{r}) \cdot e^{i\phi(\vec{r})}$$

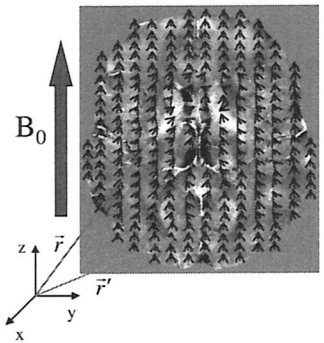
$$M(\vec{r}) = \sqrt{(Real(S))^2 + (Imag(S))^2} \qquad \phi(\vec{r}) = tan^{-1}\left(\frac{Imag(S)}{Real(S)}\right)$$





Previous applications of phase imaging:
-Temperature and pH monitoring.
-Fat mappping.
-Magnetic field mapping.

Essential physics behind QSM



Using a dipolar approximation:

$$\Delta B_z(\vec{r}) = \mu_0 \cdot M_z(\vec{r}) * G(\vec{r})$$

Where: $G(\vec{r}) = \frac{3 \cdot (\hat{r} \cdot \hat{z})^2 - 1}{4 \cdot \pi \cdot r^3}$ Point-dipole response

Using: $M_z(\vec{r}) = \frac{\chi(\vec{r})}{\mu_0} \cdot B_0$

$$\Delta B_z(\vec{r}) = B_0 \cdot FT\left[\chi(\vec{k}) \cdot G(\vec{k})\right] = \frac{\phi(\vec{r})}{\gamma \cdot TE}$$

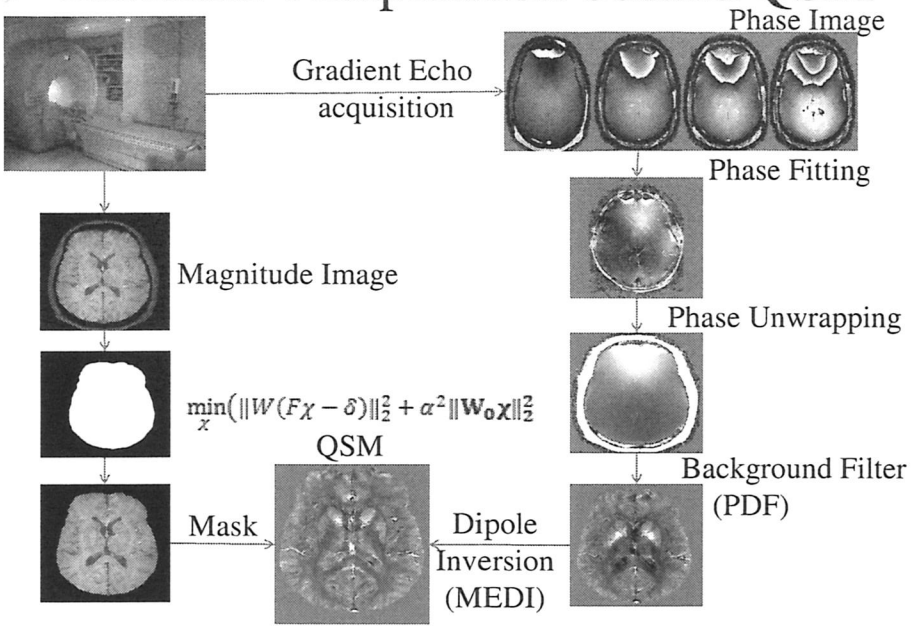
$$\chi(\vec{r}) = FT^{-1}\left\{\frac{FT\left[\phi(\vec{r}) / (\gamma \cdot TE)\right]}{FT[G(\vec{r})]}\right\} \cdot B_0$$

SM: Filter on the phase image in the reciprocal space

Concepts Magn. Reson. B, 19B, 26, **2003**.

Concepts Magn. Reson. B, 25B, 65, **2005**.

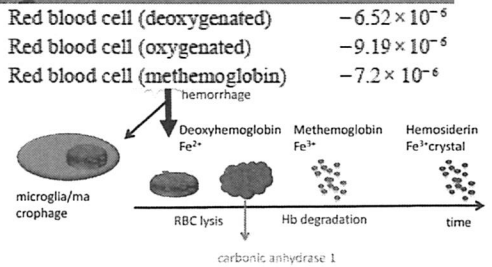
Essential computation behind QSM



QSM applications: O_2

- MR Venography and Oxygen Saturation.

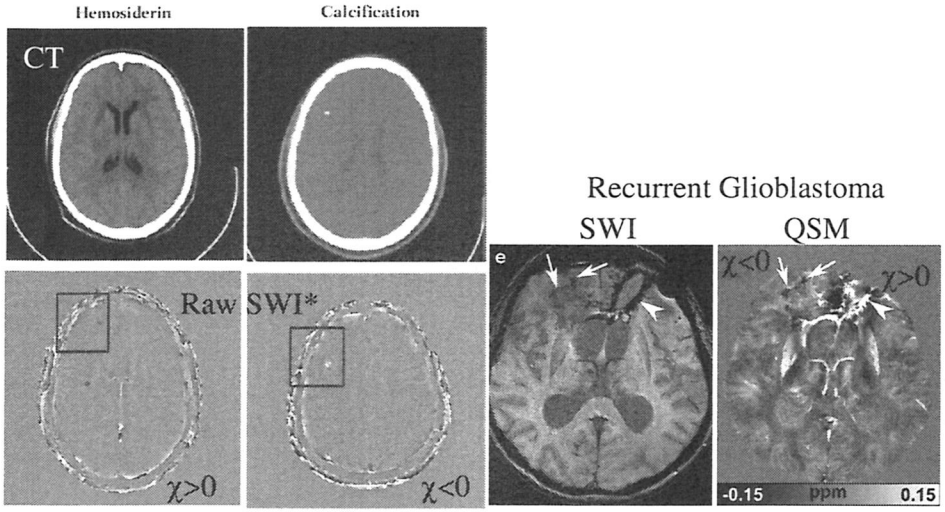
- Micro-hemorrhages.



Clin Neuroradiol (2015) (Suppl) 25:225–230

QSM applications: Blood deposits

- Paramagnetic and diamagnetic blood deposits.

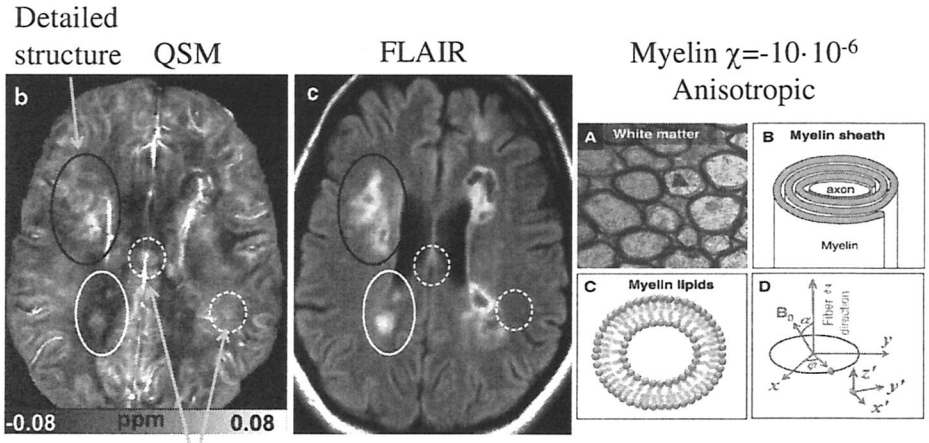


Radiol. Bras. 48, 93, **2015.**

Clin Neuroradiol (Suppl) 25, 225, **2015.**

QSM applications: Myelin

- Multiple sclerosis.



Clin Neuroradiol (Suppl) 25, 225, **2015.**

NeuroImage 59, 2088, **2012.**

QSM applications: Iron

- Neurodegenerative diseases.

PARKINSON'S DISEASE

JOURNAL OF MAGNETIC RESONANCE IMAGING 35:48–55 (2012)

Original Research

High Resolution Magnetic Susceptibility Mapping of the Substantia Nigra in Parkinson's Disease

J.M.D. Barbosa et al. / Magnetic Resonance Imaging 33 (2015) 559–565

Quantifying brain iron deposition in patients with Parkinson's disease using quantitative susceptibility mapping, R2 and R2*

Usefulness of Quantitative Susceptibility Mapping for the Diagnosis of Parkinson Disease

AJNR Am J Neuroradiol ●● ● 2015

Movement Disorders, Vol. 31, No. 3, 2016

Quantitative Susceptibility Mapping of the Midbrain in Parkinson's Disease

PLOS ONE | DOI:10.1371/journal.pone.0162460 September 6, 2016 RESEARCH ARTICLE

Quantitative Susceptibility Mapping in Parkinson's Disease

Regionally progressive accumulation of iron in Parkinson's disease as measured by quantitative susceptibility mapping NMR Biomed. (2016)

Ferritin (fully loaded with 4500 Fe^{3+} ions) $+520 \times 10^{-6}$

MULTIPLE SCLEROSIS

Radiology

Radiology: Volume 267: Number 2—May 2013

Quantitative Susceptibility Mapping in Multiple Sclerosis

MUTATIONS

Movement Disorders

CLINICAL PRACTICE RESEARCH ARTICLE

7-Tesla Magnetic Resonance Imaging for Brain Iron Quantification in Homozygous and Heterozygous *PANK2* Mutation Carriers

AMYOTROPHIC LATERAL SCLEROSIS

AJR:204, May 2015

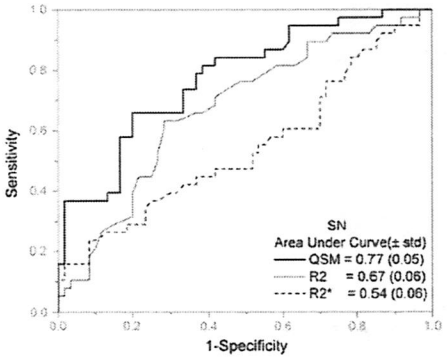
Quantitative Susceptibility Mapping of the Motor Cortex in Amyotrophic Lateral Sclerosis and Primary Lateral Sclerosis

QSM applications: Iron

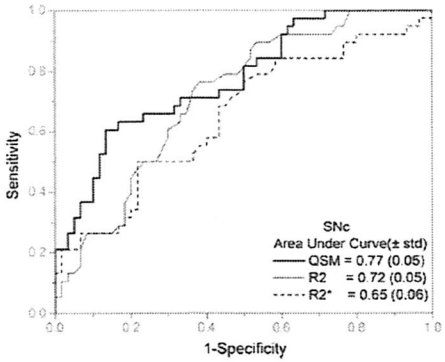
Ferritin (fully loaded with 4500 Fe^{3+} ions) $+520 \times 10^{-6}$

Parkinson's Disease: QSM, R2 or R2*?

Substantia nigra



Substantia nigra pars compacta



Magn, Reson. Imag.: 33, 559, **2015**.

Iron & Neurodegeneration

Observations:

-Abnormally high iron levels in brain areas which take part in several neurodegenerative disorders.

-The disruption expression of iron metabolism proteins, induced by genetic or non-genetic factors, is the cause of the increased brain iron.

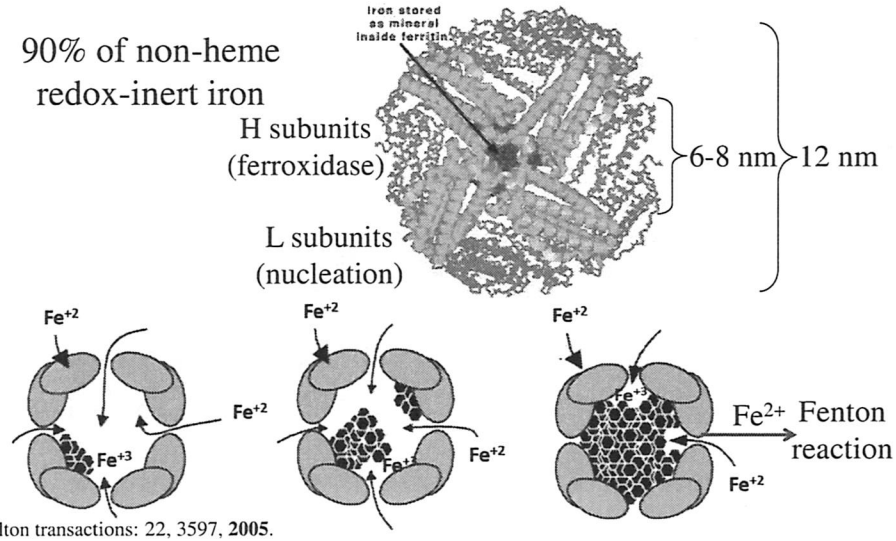
Hypothesis: Some mishandling of the iron metabolism in human brain can be involved in the onset of some neurological disease.

It is important iron quantification in vivo!

Iron metabolism & Ferritine

Heme: Hb (Fe^{2+})+MetHb (Fe^{+3}) Non-heme: Ferritine, Transferrin,...

90% of non-heme redox-inert iron



Dalton transactions: 22, 3597, **2005**.

Metal measurements

Iron/Susceptibility quantification techniques applied to biological samples

In vitro (Iron)

- Perls' Stain (Fe^{3+}, Fe^{2+}).
- NAA • MAS. • XRF.
- ICP-(Mass/AE Spectroscopy).
- EPR (Fe^{3+}).

In vivo (Susceptibility)

- SQUID (digestive system).
- Magnetic Resonance (brain).

How the susceptibility values are related to the metal content in the brain?

Validation studies are necessary!

Post-mortem studies

Quantitative MR Imaging of Brain Iron: A Postmortem Validation Study

Radiology: Volume 257: Number 2—November 2010

Quantitative susceptibility mapping (QSM) as a means to measure brain iron? A post mortem validation study

C. Langkammer et al. / NeuroImage 62 (2012) 1593–1599

In situ/small samples

Measuring iron in the brain using quantitative susceptibility mapping and X-ray fluorescence imaging

W. Zheng et al. / NeuroImage 78 (2013) 68–74

In vitro/imaging

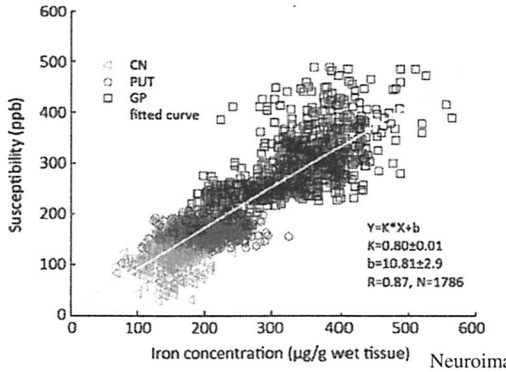
Validation of quantitative susceptibility mapping with Perls' iron staining for subcortical gray matter

H. Sun et al. / NeuroImage 105 (2015) 486–492

In situ/In vivo

Post-mortem validation

Linear relationship between total iron and susceptibility.



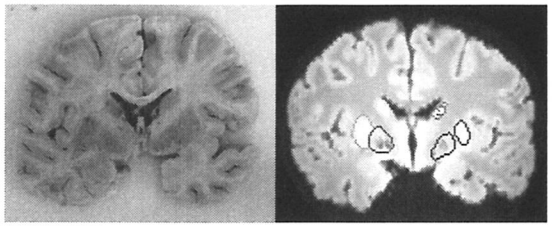
0.8 ppb per µg/g

Neuroimage: 78, 68, **2013**.

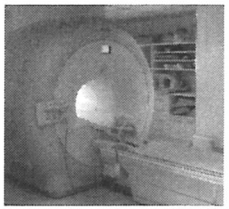
- Other metals? Cu is paramagnetic.
- Where is that iron? dHb is paramagnetic.
- Does QSM has additional specificity? …

Some measurements

- 3 postmortem human brains (<15 hours, In situ image).
- Formalin-fixed brains (>100 days, Ex situ image).
- 10 samples for each brain (GP, PUT, CN, THA, GM).

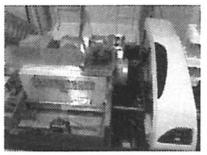


J.H.O.Barbosa, 2017.



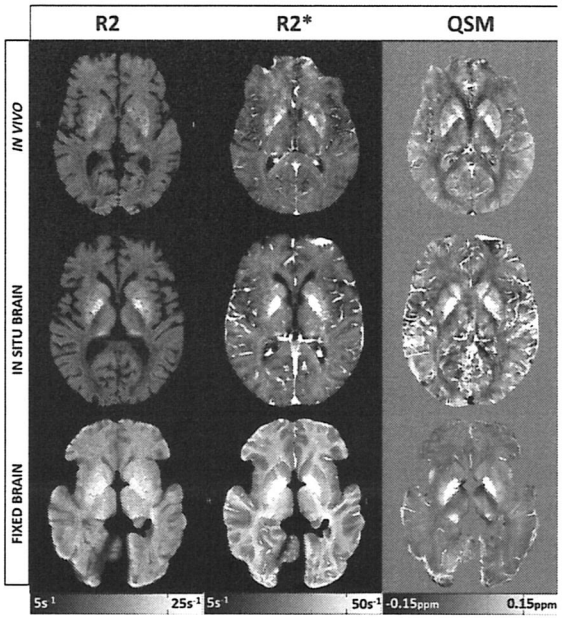
MRI, 3T

EPR, X-Band

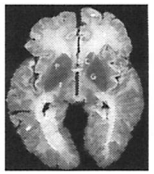


ICP-MS (Fe, Cu, Al, Zn)

Contrast between conditions

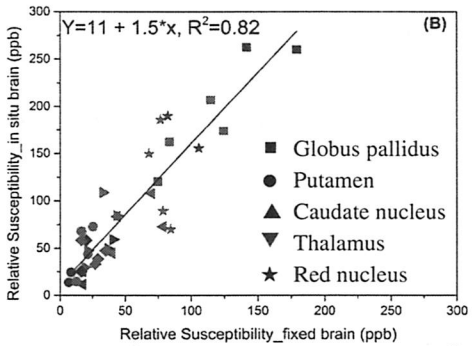


Perls' stain

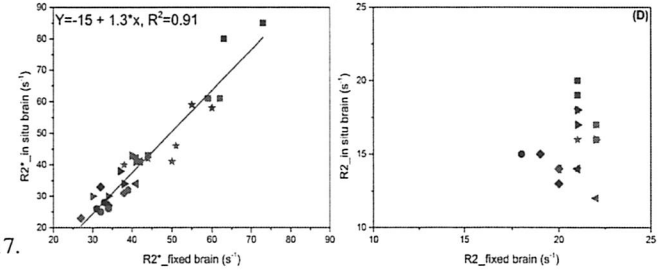


Am.J.R.: 147, 103, **1986**

Equivalence between conditions

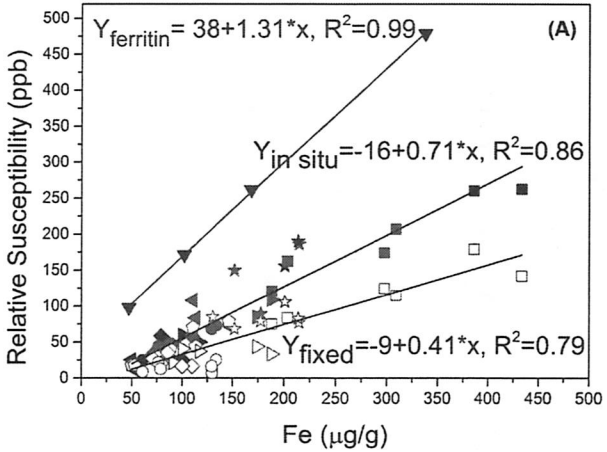


Extrapolation between conditions is possible for our susceptibility measurements!



J.H.O.Barbosa, 2017.

QSM vs Total iron



Ferritin slope: Theor.≈Experim.

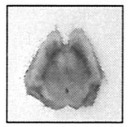
Med. Phys.: 23,815, **1996.**

Sensitivity reduction in vitro.

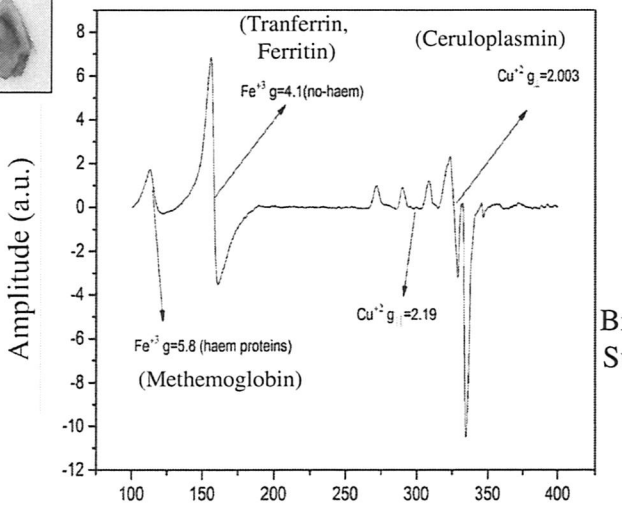
No correlations with other metals (Cu, Zn, Al)

J.H.O.Barbosa, 2017.

EPR measurements



EPR (X-Band) of brain tissues (77 K).



g≈2

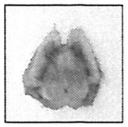
Broad line removed

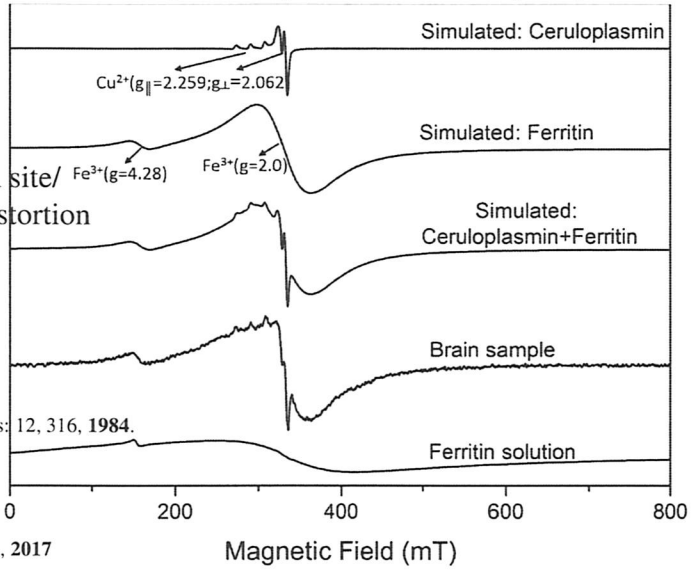
Superparamagnetic

Residual oxygen is a problem!

ISMRM Meeting, **2015** – Toronto CA

EPR measurements



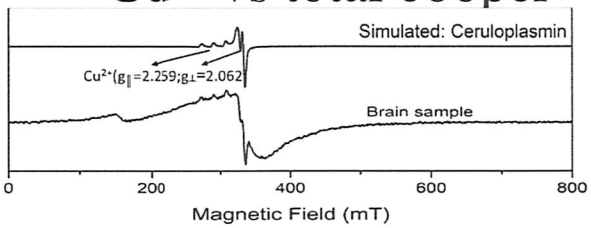


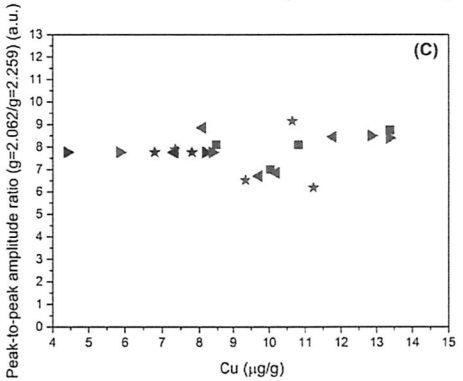
Tetrahedral site/
rhombic distortion

Biochem. Soc. Trans: 12, 316, **1984**.
JMR: 153,69, **2001.**

ISMRM Meeting, **2017**

Cu^{2+} vs total cooper



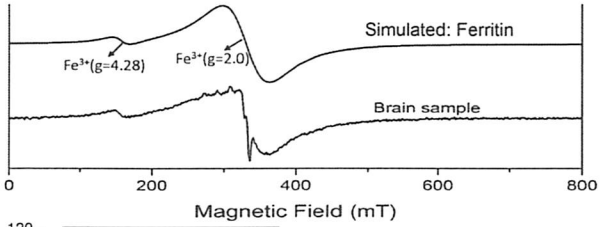


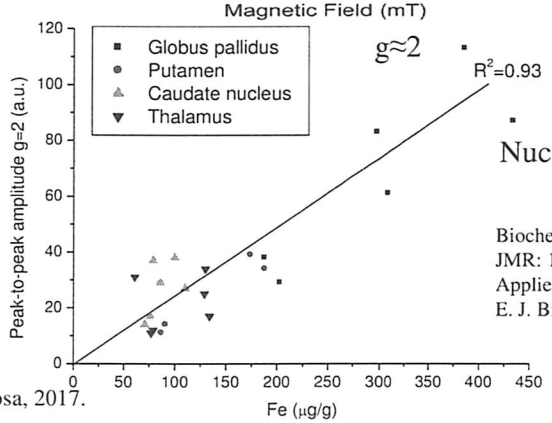
J. Mol. Biol.:2, 118, **1960.**

Same copper for any
concentration/region

J.H.O.Barbosa, 2017.

Fe^{3+} vs total iron



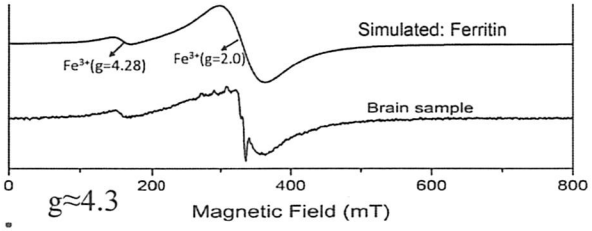


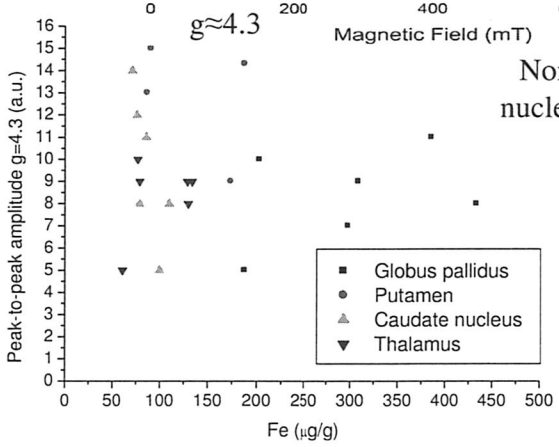
Nucleated Ferrihydrite/
FeO(OH) cores

Biochem. Soc. Trans: 12, 316, **1984**.
JMR: 153,69, **2001.**
Applied Clay Science: 53, 42, **2011**.
E. J. Biotechnology: 7, **2004**.

J.H.O.Barbosa, 2017.

Fe^{3+} vs total iron





Non aggregated Fe^{3+} bound/
nucleation sites of core growth/

Biochem. Soc. Trans: 12, 316, **1984**.

JMR: 153,69, **2001.**

or

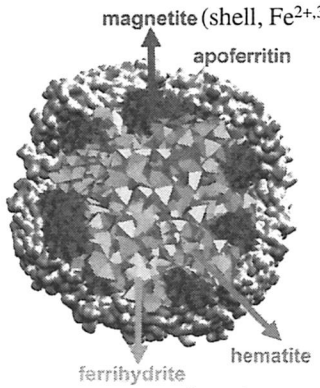
Hematite

Applied Clay Science: 53, 42, **2011**.
E. J. Biotechnology: 7, **2004**.

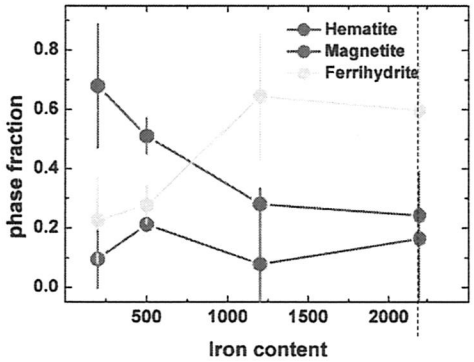
J.H.O.Barbosa, 2017.

Ferritine iron core

Polyphasic structure (ferrihydrite, magnetite, hematite)



Horse spleen ferritine



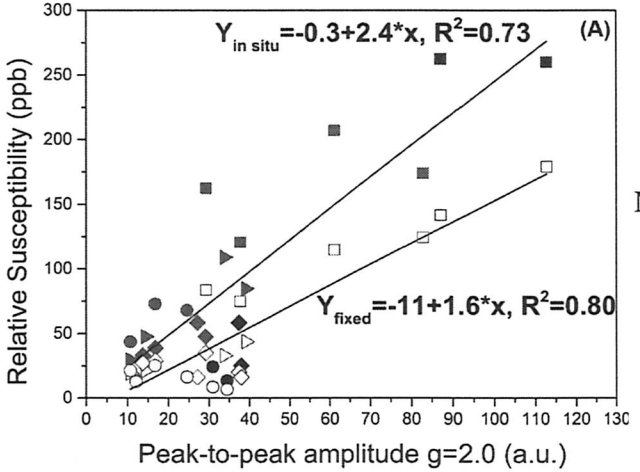
TEM, SAXS, and XANES

J. Struct. Biol.: 147, 166, **2004**.

Ferrithydrite phase is more labile to chemical reduction and mobilization.

J. AM. CHEM. SOC.: 130, 8062, **2008**.

QSM vs Fe^{3+}

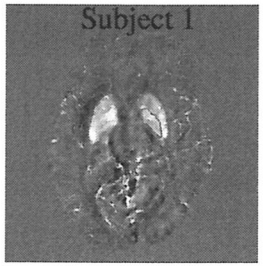


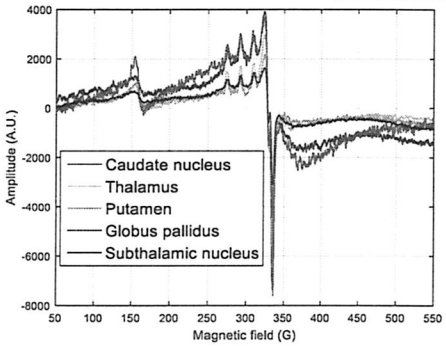
No correlations with other peaks (Fe^{3+} g≈4.3 or Cu^{2+})

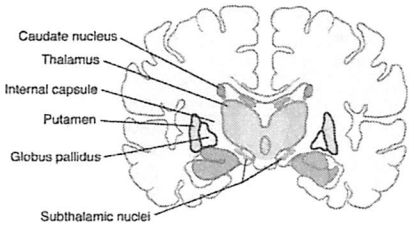
J.H.O.Barbosa, 2017.

Iron in ferrihydrite allows a rapid release, increasing free intracellular iron.
Studies in more subjects and patients are necessary!

New measurements







Key points

- QSM is a powerful in vivo technique for susceptibility mapping in the brain based on the MR phase images.
- Map computation demands several steps, some artifacts are present and a friendly program is not available yet.
- Clinical applications of QSM are being developed to probe neurodegenerative and inflammatory diseases, to assess hemorrhage, to characterize myelin, to measure metabolic consumption of oxygen, and to measure iron distribution.
- Nucleated ferrihydrite in ferritine, more labil iron, is the main susceptibility contrast in gray matter.

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Thank you for your attention!

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Opportunities

•Metabolic response in the presence of short term visual stimuli.
•Assessment of channel combination techniques for spectroscopy dynamic studies.
•Intelligence prediction from structural and functional brain connectivity.
•Study of the brain metabolic and electric response in the presence of visual stimuli in oxygen depletion.
•Evaluation of paramagnetic ions in the brain and their relationship with quantitative imaging techniques.
•Study of the haemodynamic response function in epilepsy patients.
•Tractography as *a priori* information in the evaluation of EEG data of epilepsy patients.
•Implementation of neurofeedback in EEG/fMRI experiments applied to the control of anxiety disorders.
•Fetal tractography.
•Evaluation of the use of magnetic resonance images in radiotherapy planning.
•Study of acoustic noise as sensitivity element of auditory tasks in fMRI.
•Definition of neuronal area recruited during electric stimulation of upper limbs.
•Implementation and application of ultra-short TE sequence in the study of the musculoskeletal system.
•Implementation and acquisition of phosphor spectra in bone tissue for the functional evaluation in view of glucose overload.

https://inbrainlab.wixsite.com/inbrainlab