DE LA RECHERCHE À L'INDUSTRIE

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Ultra high-field MR

Imaging and Spectroscopy

Cyril Poupon & Fawzi Boumezbeur

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« Session 5 : Technologies émergentes »

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Outline

Introduction

I- Proton ultra-high field (UHF) MRI: a technical challenge *C. Poupon*

II- Metabolic Imaging using low gyromagnetic nuclei *F. Boumezbeur*

Conclusion

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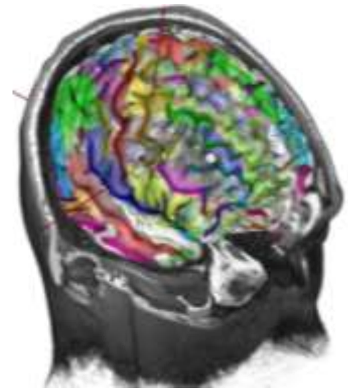
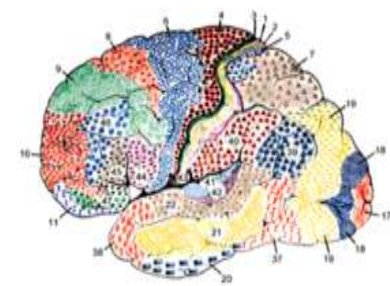
Imaging : the cornerstone to probe brain anatomy and function *in vivo*

MACRO 1mm

Yesterday and today : macroscopic functional architecture of the brain

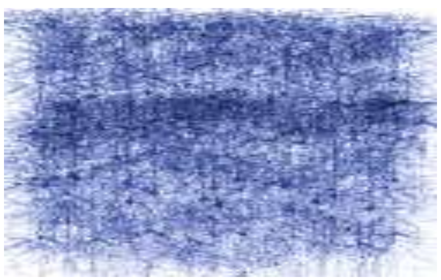
Today and tomorrow : genes and brain
25000 genes, 10^{11} neurons, 10^{15} synapses !
Brain development, plasticity





MESO 100µm

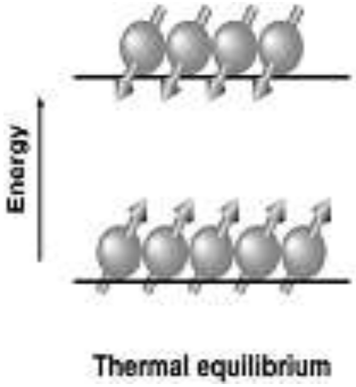
Tomorrow : the « neural code », challenge of the 21st century
Coupling between structure and function,
Multi-scale functional architecture



MICRO 1µm

Healthcare challenge :
- prevention, early diagnosis of pathologies (neurodegenerative, psychiatric)
- rehabilitation / reprogrammation (stroke, lesions)
- molecular therapies

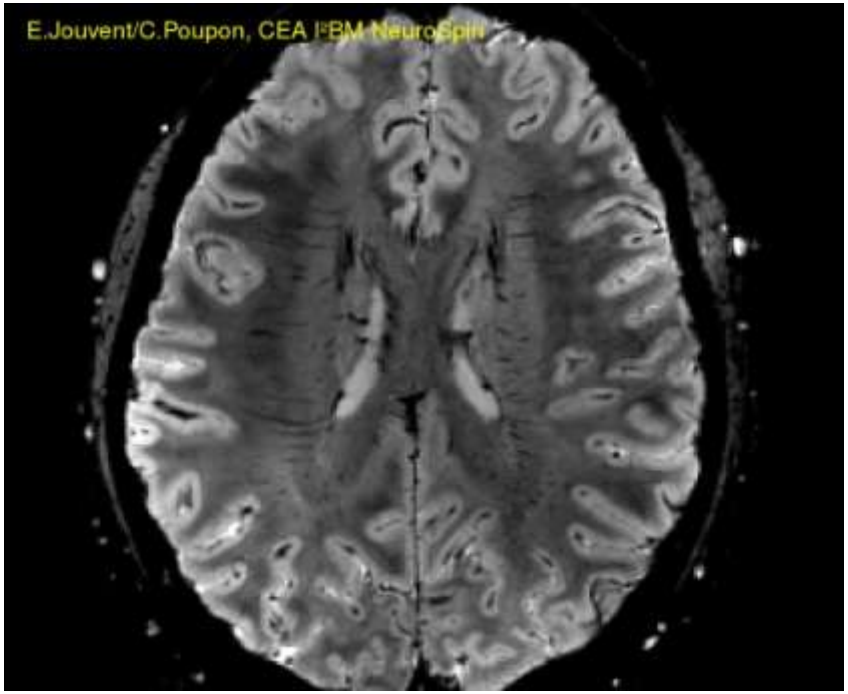
Need for imaging at the mesoscale (<100µm) : structure & function



Nuclear magnetization ∝ $\gamma B_0 / kT$ therefore **increasing the magnetic field** enhances the **observation of**:

- the **neurons** at work
- the **connections** between neurons
- the **genes** at work
- the **metabolism** of the brain
- the **developing** brain
- the brain **disorders**

Example of imaging at 7T :



in vivo

post-mortem

Jouvent, Poupon et al 2011

The NeuroSpin facility : dedicated to UHF MRI and Neurosciences

Head : Dr Denis Le Bihan

~170 people

4 laboratories :
- Clinical and Translational Lab (L. Hertz-Pannier)
- MR Physics and Spectroscopy Lab (C. Poupon)
- Image Processing and Analysis Lab (V. Frouin)
- Cognitive neuroscience Lab (S. Dehaene)

7 research programs :
- MRI unlimited
- Brain development and plasticity
- Genetics, neuroimaging, bioinformatics
- Multiscale brain architecture
- Translational research
- Higher order cognitive functions

Clinical 3T

“standard”

Clinical 7T

« advanced »

Clinical 11.7T

« world 1st ? »

Preclinical 7T

“standard”

Preclinical 11.7T

« advanced »

Preclinical 17T

« world 1st »

Introduction

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Since the 2000's, UHF MRI has been the standard for preclinical imaging

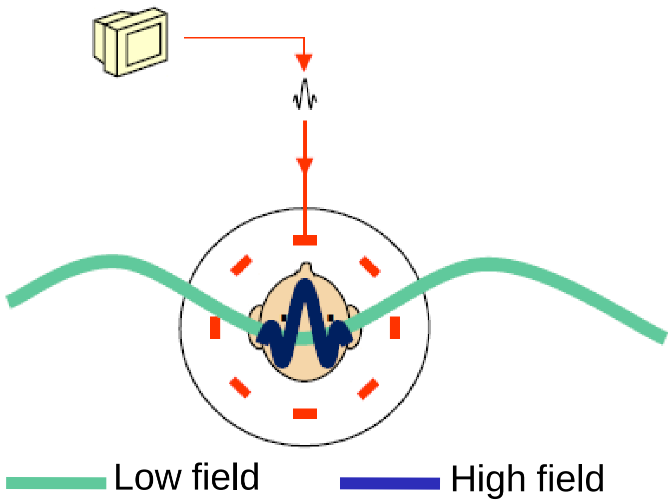
& was thought to be directly applicable to **clinical imaging**.

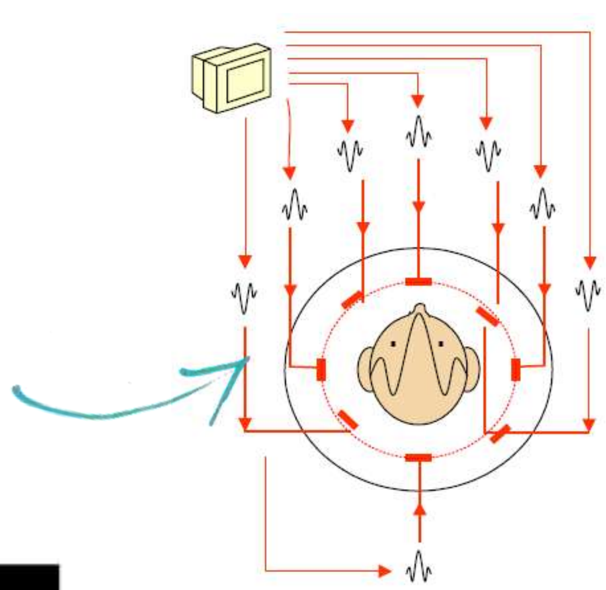
Yet several challenges have arisen that need to be alleviated :

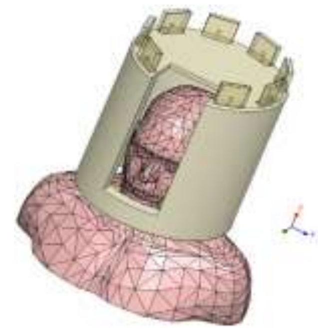
- **shorter wavelength**: increasing the magnetic field decreases the wavelength. When λ becomes smaller than the size of the sample, signal/contrast inhomogeneities are observed over the field-of-view;
- **shorter T_2 relaxation times**: stronger signal decay means less time to acquire the signal;
- **longer repetition times** are needed due to longer T_1 and higher energy deposition. This leads to longer acquisition times;
- **safety**: more practical constrains are to be followed for a safe use of UHF MRI.

As a consequence, the UHF MRI community has dedicated this past decade on the development of novel methods to address these pitfalls.

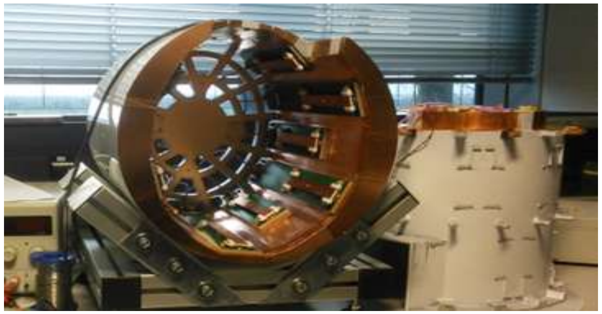
Solution to shorter wavelength: parallel transmission

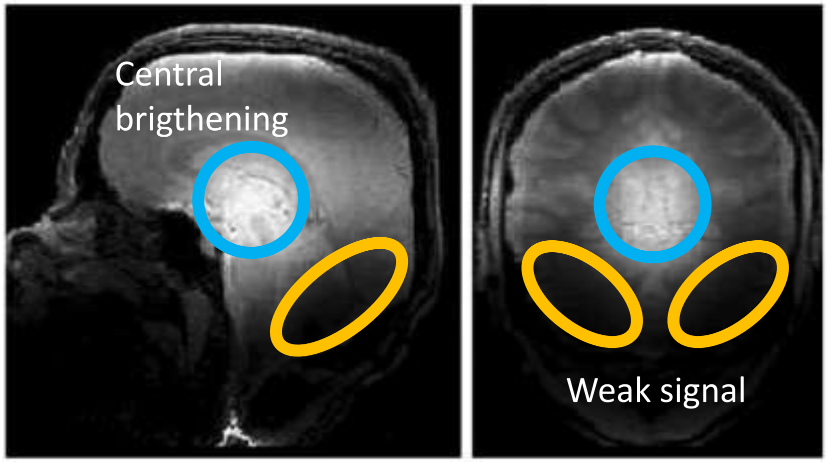


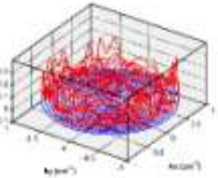


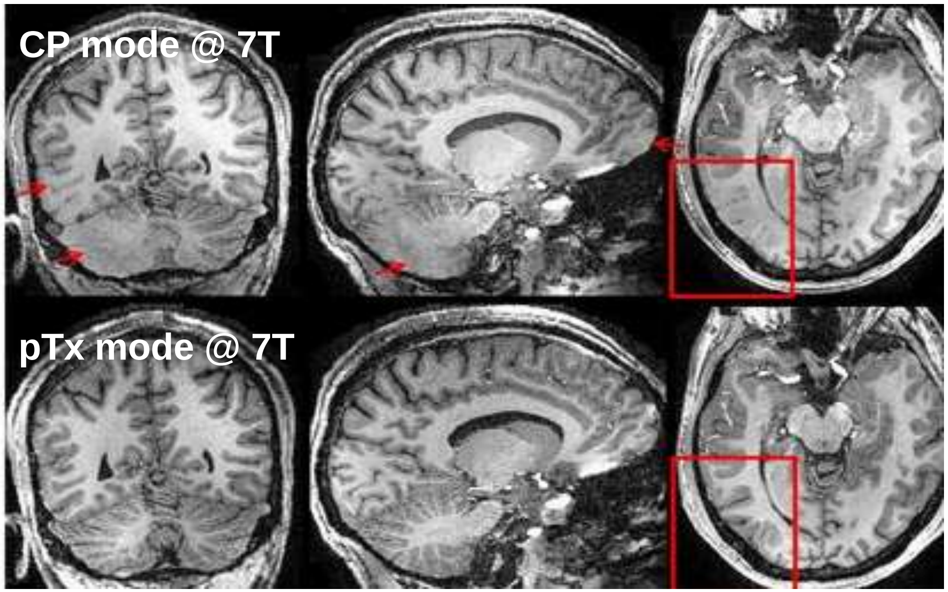


Courtesy of M Luong, E. Giacomini, E. Georget, M.F. Hang, E. Chazel









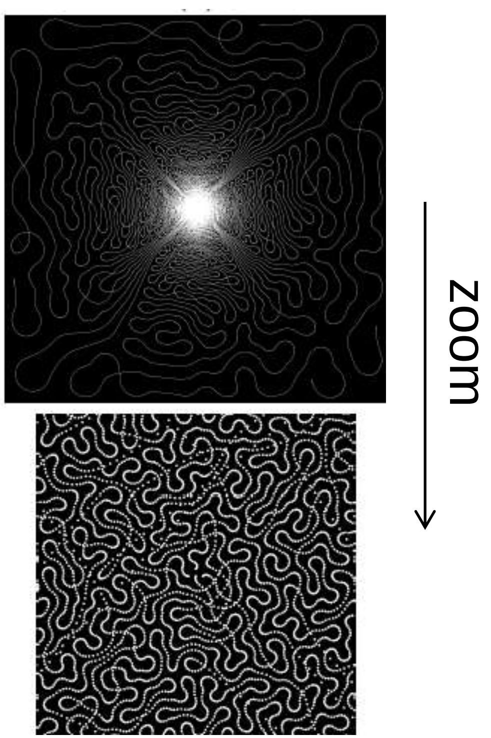
7 patents: EP15306569.3, US62053603, EP14165238.8, PCT/IB2011/051581, PCT/IB2010/001479, PCT/IB2009/005066, PCT/IB2007/004256.

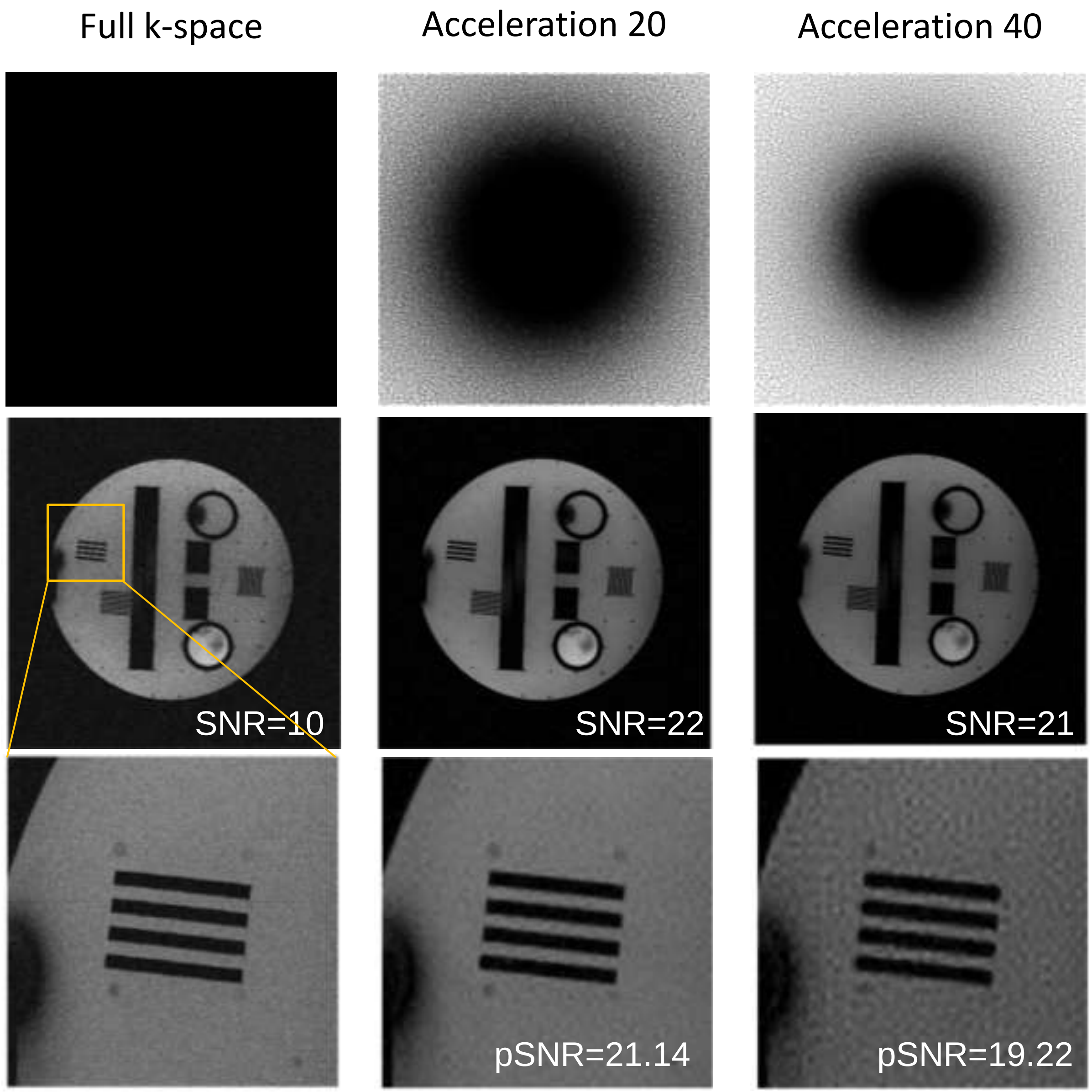
FP7/2013-2018 ERC Grant Agreement n°309674.

Courtesy of N. Boulant, A. Amadon

Solution to shorter T_2: compress sensing

- Design of parcimonious k-space trajectories embedding hardware constrains
- Only a few percents of full k-space data sampled

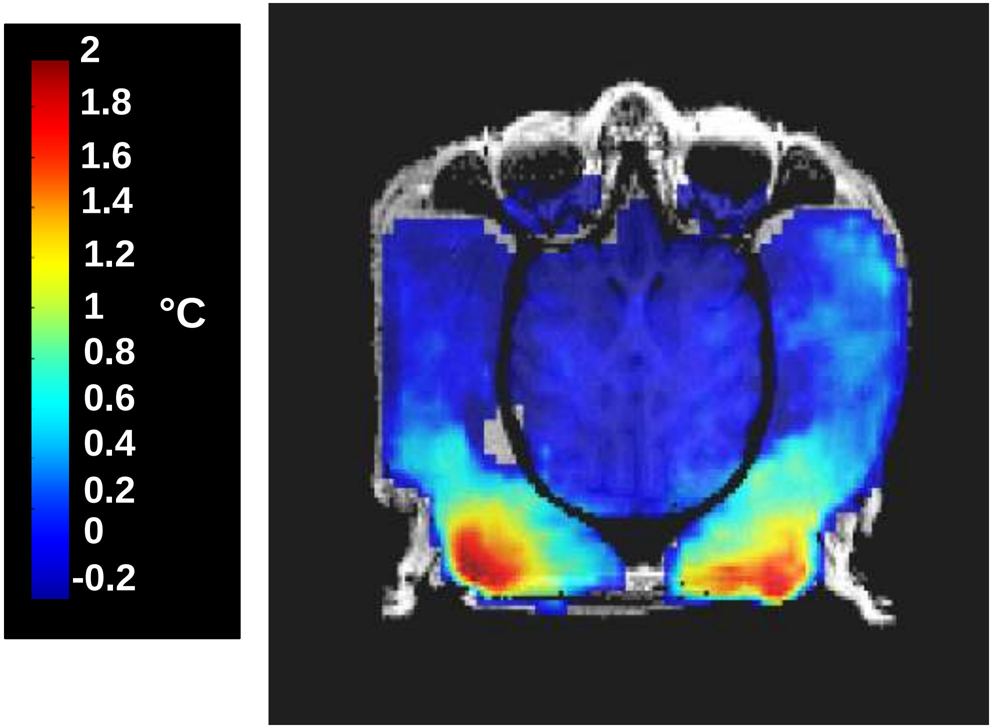


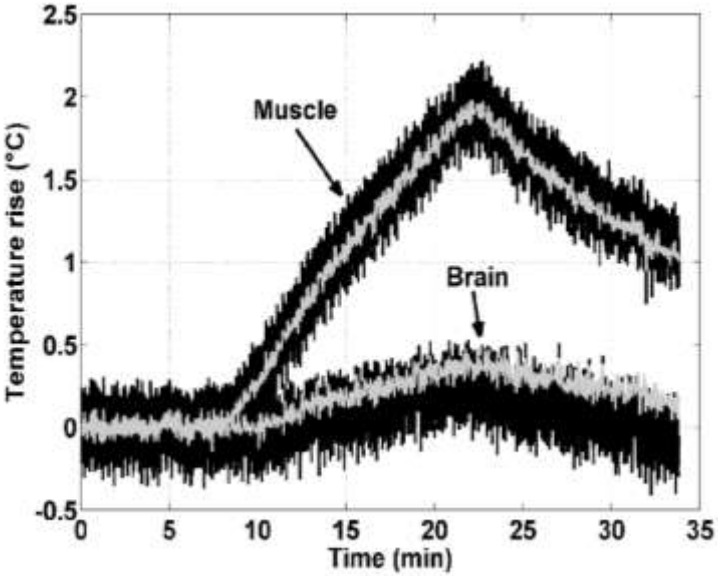


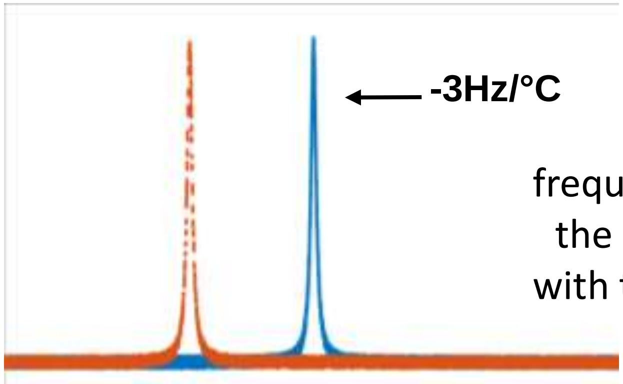
Courtesy of P. Ciuciu, C. Lazarus, A. Vignaud

Magnetic resonance thermometry measurements on the anesthetized baboon

Boulant et al. NMR in biomedicine 28:101-107 (2015).







frequency shift of the ^1H_2O signal with temperature

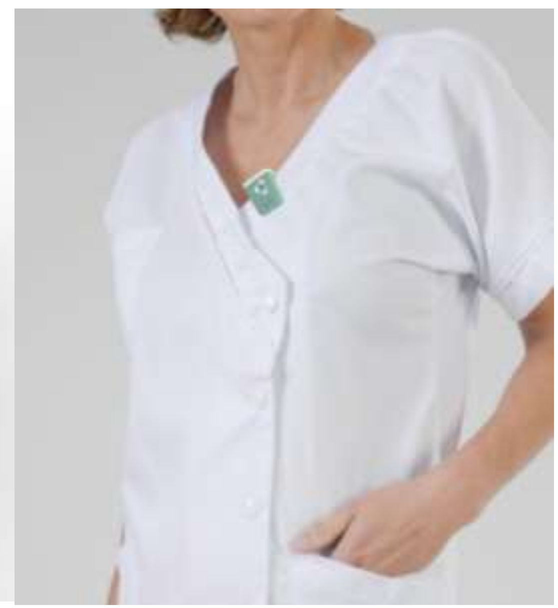
Safety : monitoring of workers, revisited contra-indications for patients/volunteers

workers

- Magnetic field monitoring of workers using a dedicated dosimeter (Healtis / INSERM IADI)
- Slow displacements around the magnet

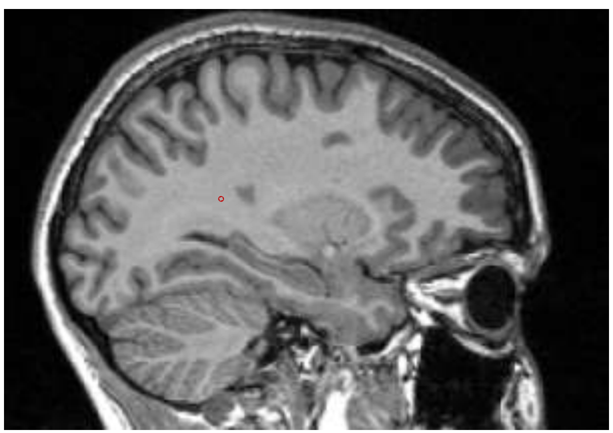
patients

- Patients & volunteers wearing clinical items of clothing to prevent any risk
- Enhanced contra-indications and specific care for implants (few of them are more than 3T proof)

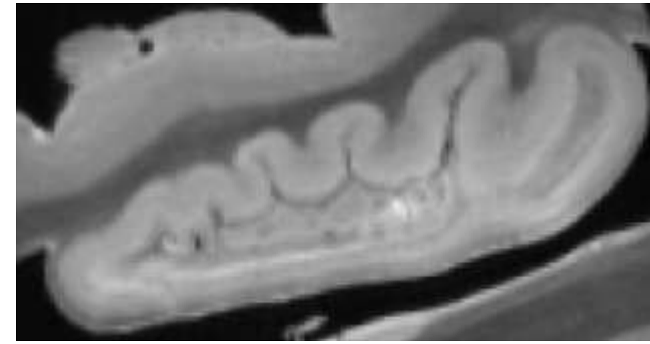
Courtesy of Felblinger & Pasquier

^{1}H UHF MRI = improved resolution

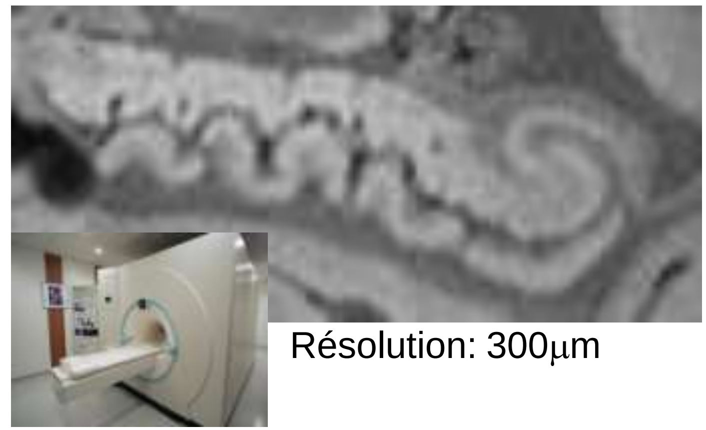


Beaujoin et al, 2016

11.7T

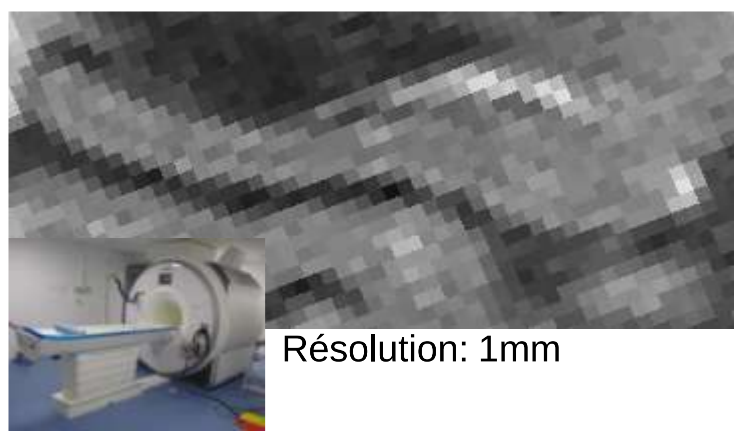


Résolution: 200µm



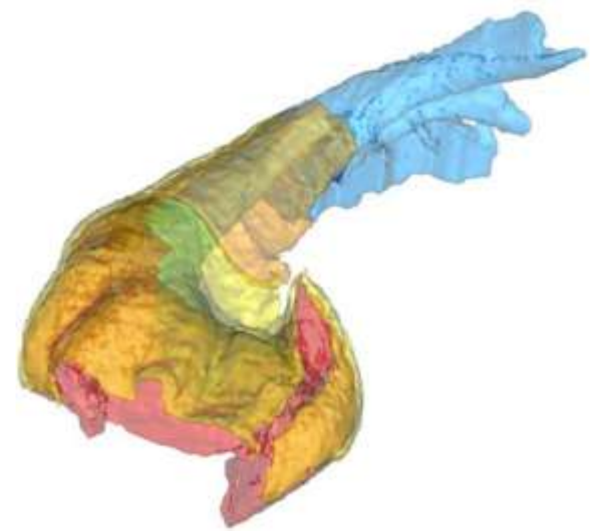
Résolution: 300µm

7.0T



Résolution: 1mm

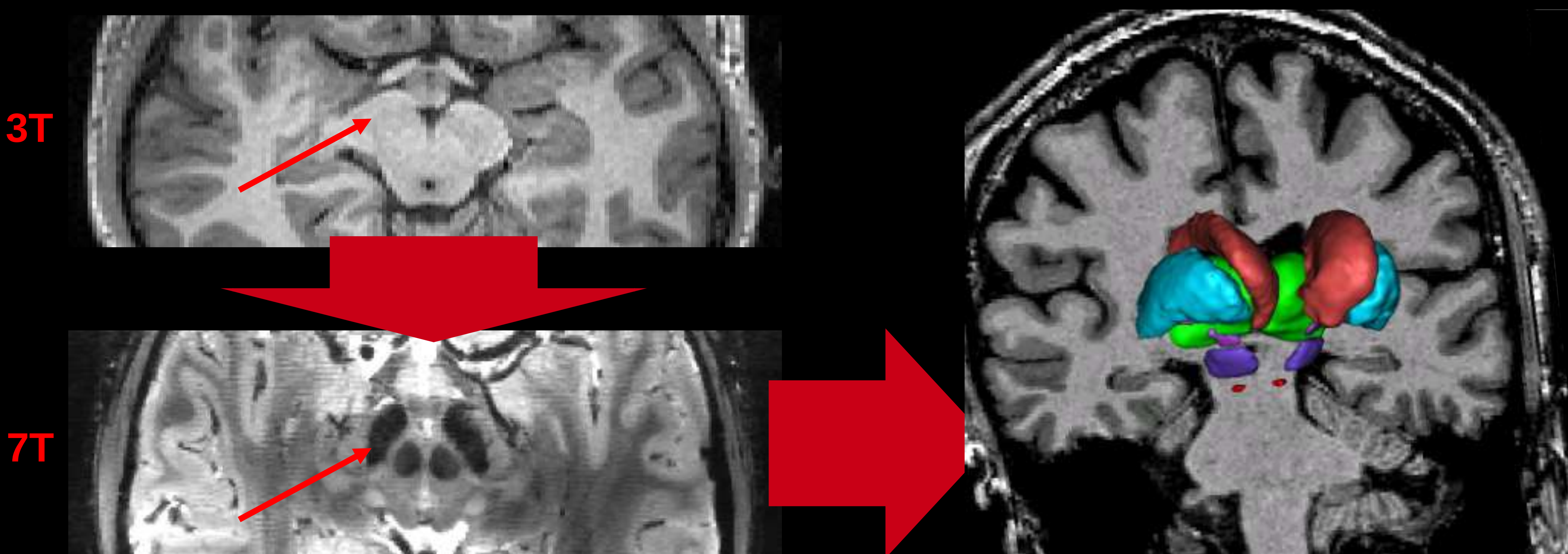
3.0T



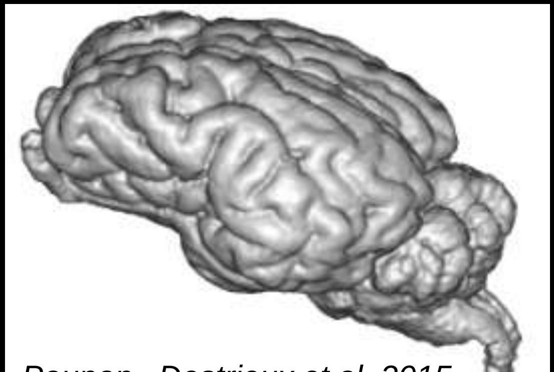
^{1}H UHF MRI = novel contrast mechanisms

UHF MRI also provides **novel sources of contrat** due to the presence of iron at various concentrations in brain structures.

Impact of 7T MRI on the study of Parkinsonian syndromes : brainstem nuclei are much better delineated at 7T in comparison with 3T using T2* contrast



[1]H UHF MRI = histological-like anatomical imaging

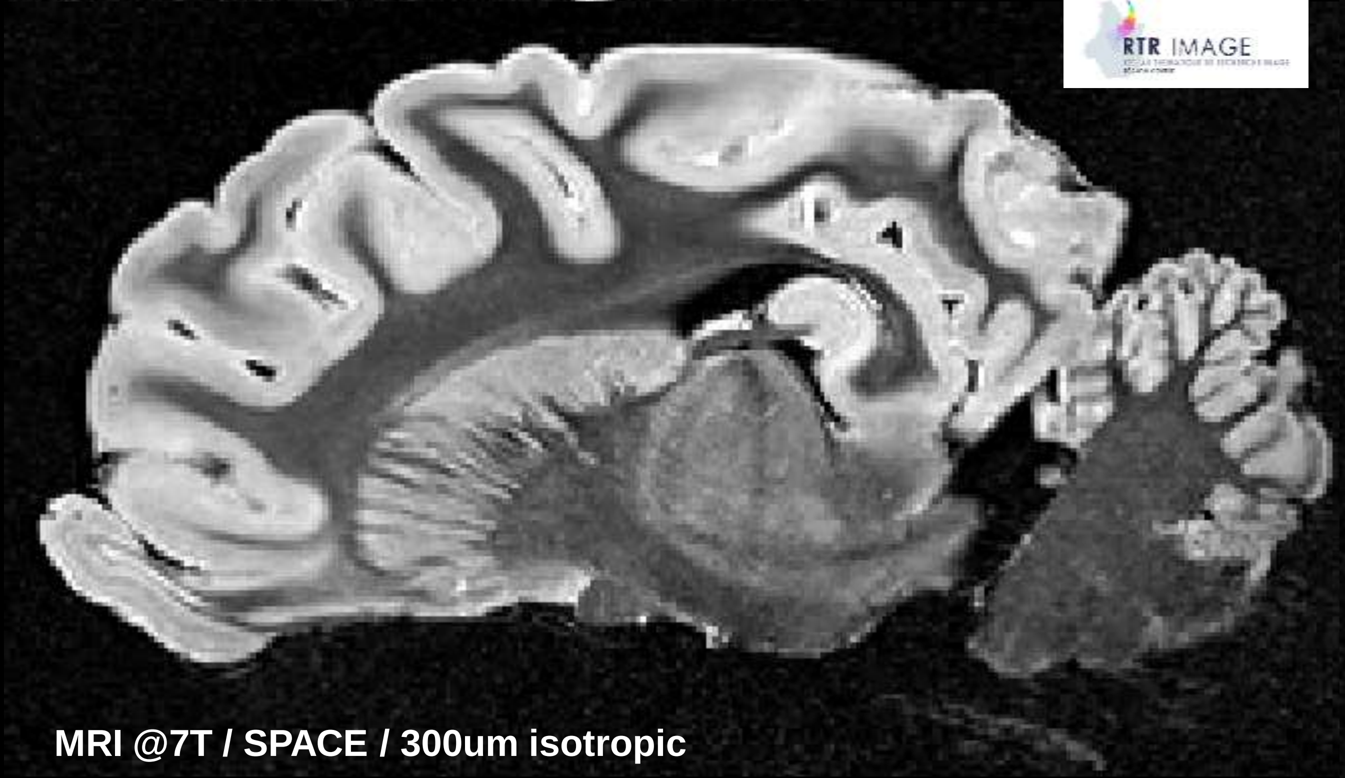


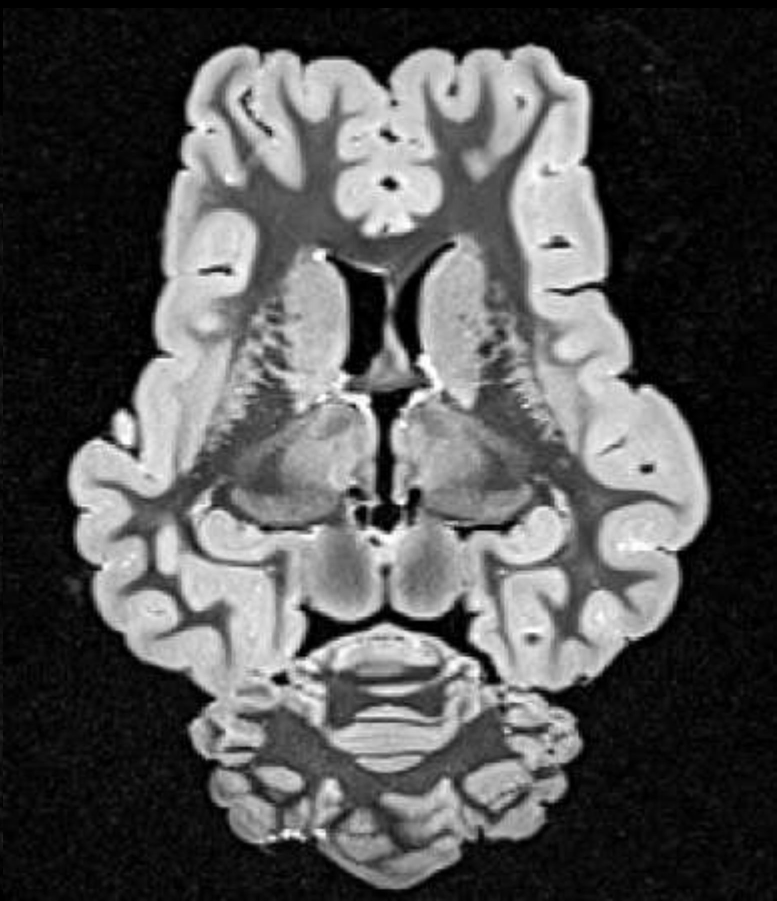
. Poupon, Destrieux et al. 2015

INRA SCIENCE & IMPACT

Région Centre

RTR IMAGE





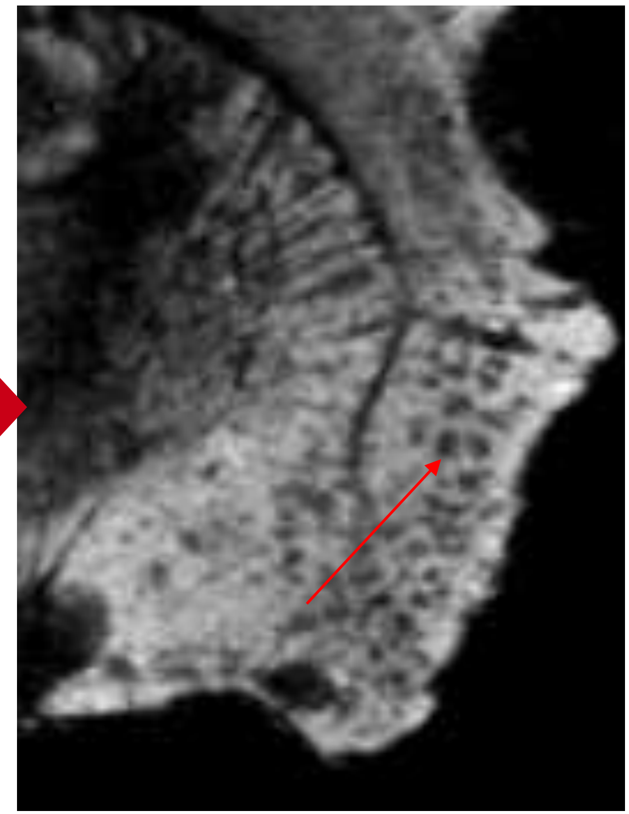
^{1}H UHF MRI = amyloid plaques in a rodent model of Alzheimer's disease

Comparison of preclinical imaging at 7T versus 17T

7T

23µm x 23µm x 90µm

17T



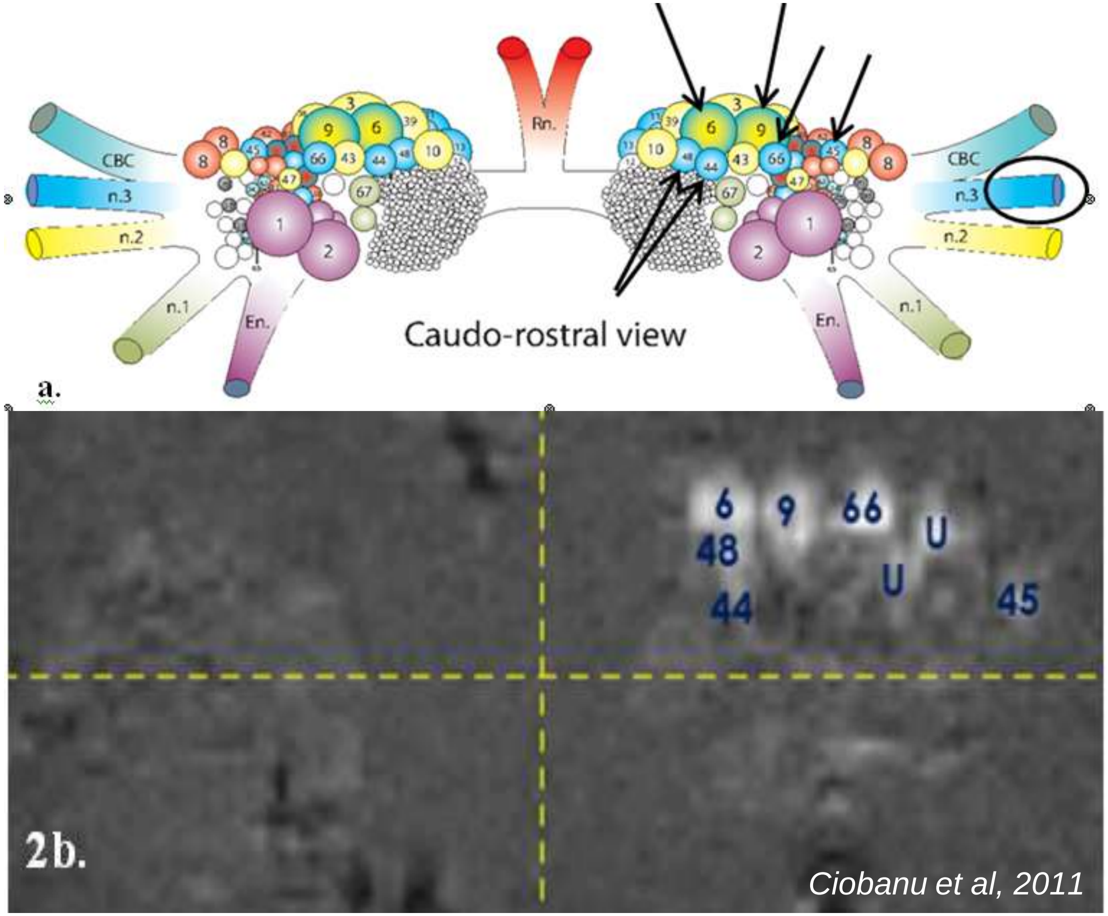
30µm x 30µm x 30µm

Ciobanu et al, 2011
Dhenain et al, 2011

Amyloid plaques are much better delineated at 17T than at 7T!

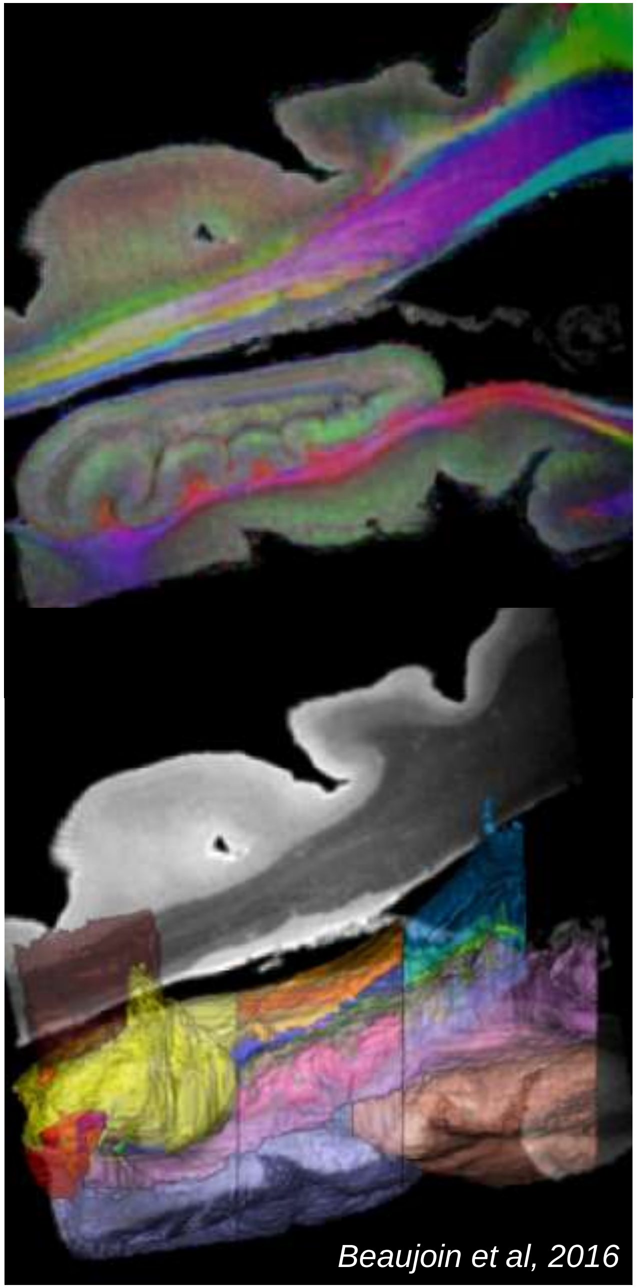
2010 : NeuroSpin was equiped with the 1st horizontal magnet at 17T in the world dedicated to preclinical studies in rondents capable of imaging single networks !

Manganese-enhanced MRI of the bucal ganglia of aplysia californica:

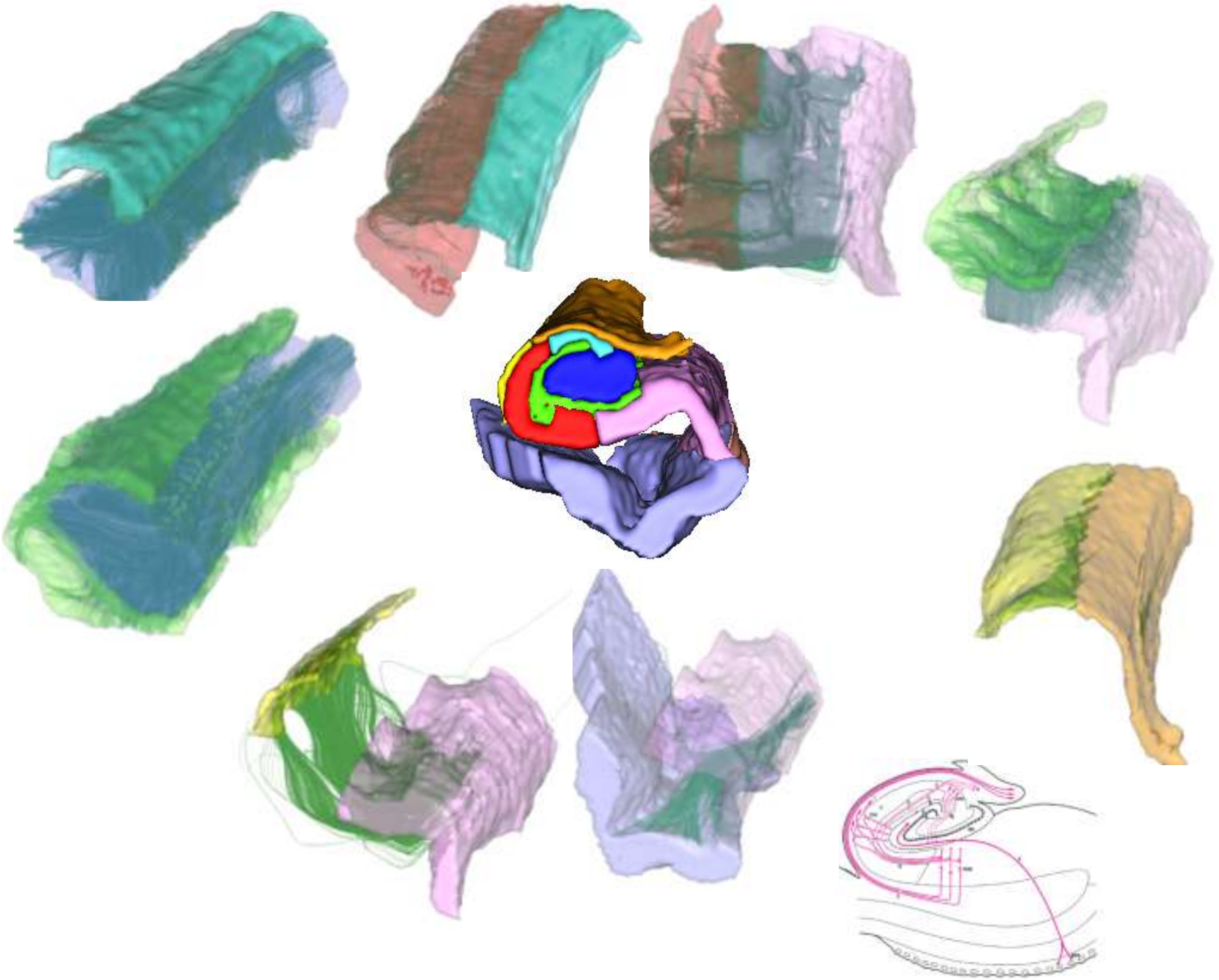


Ciobanu et al, 2011

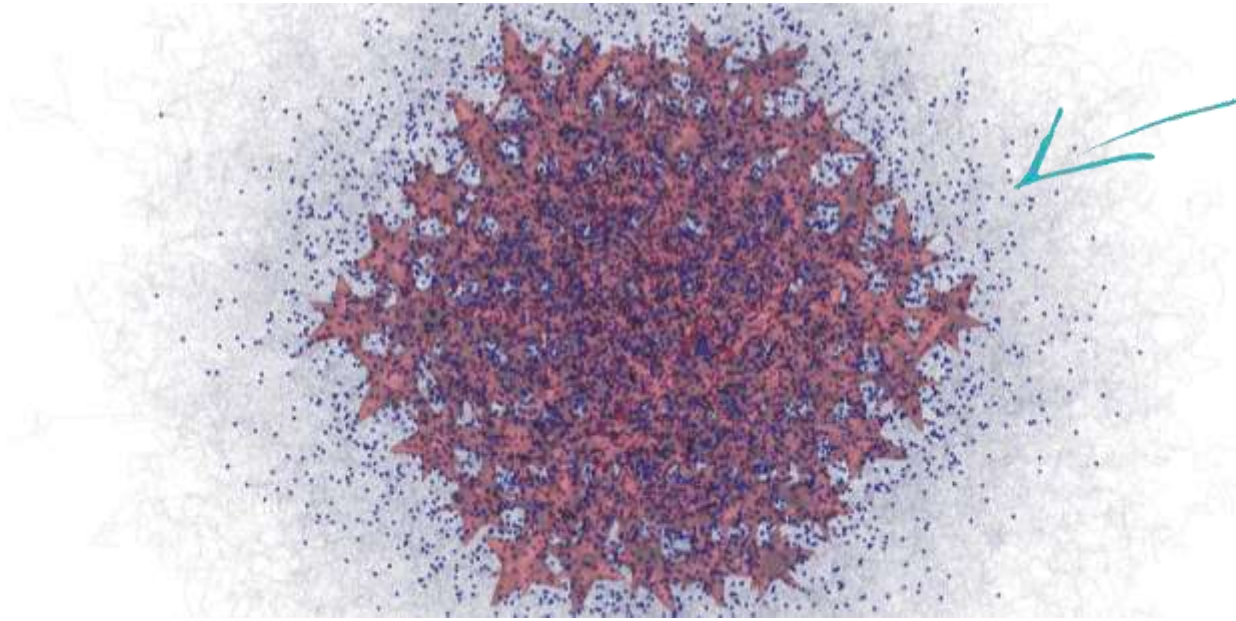
- individual neurons (300µm)
- study of the axonal transport of a small neural network

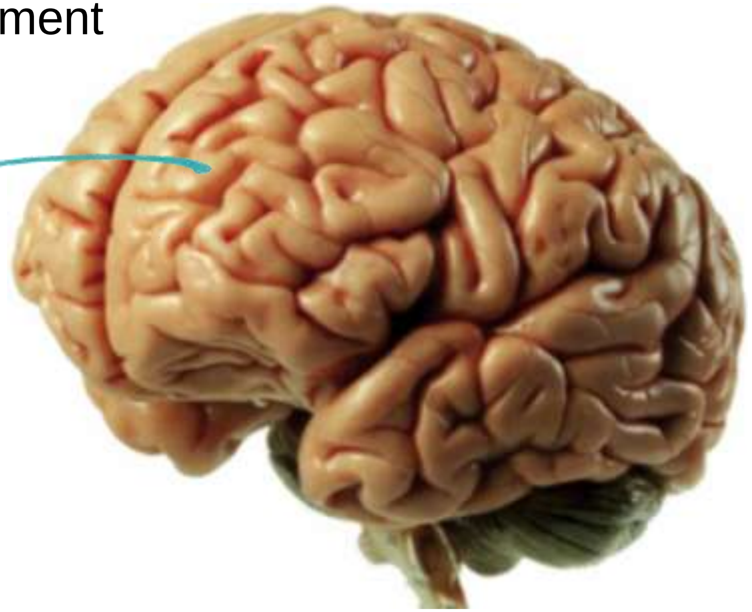


Tractography of the polysynaptic circuit of a human brain hippocampus at 11.7T

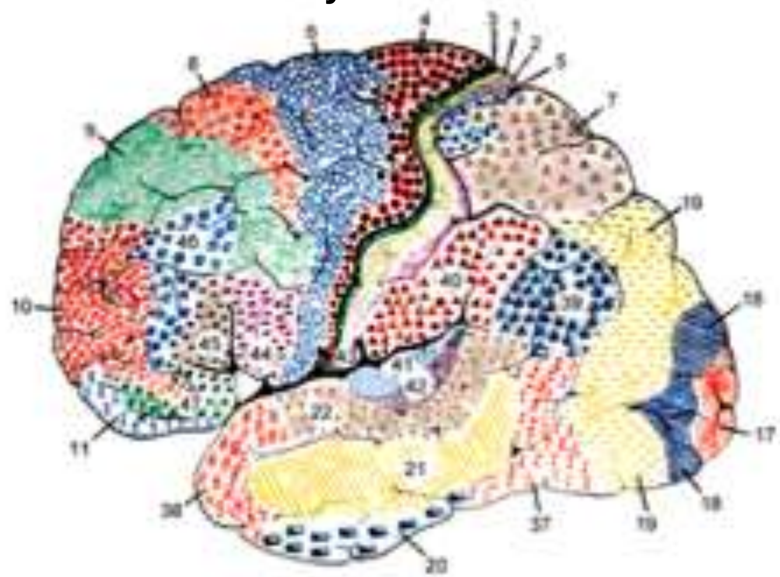


Diffusion process providing signatures of the cellular environment

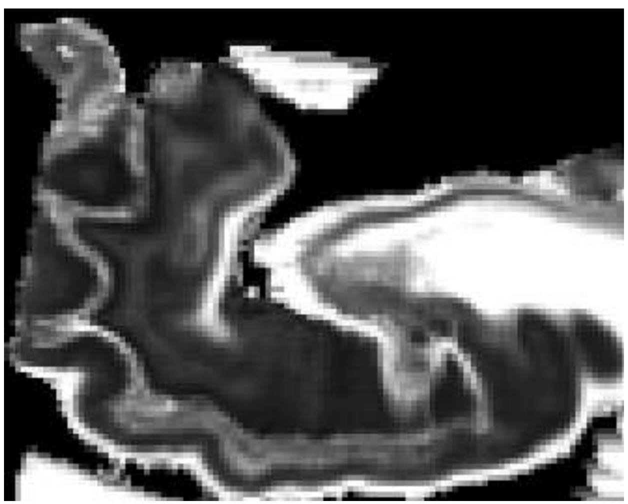


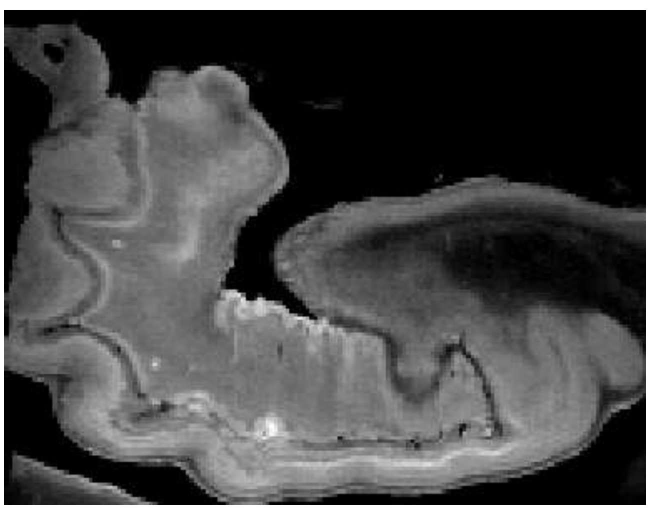


Individual cytoarchitecture



Dendrite density map at 11.7T revealing layers of the hippocampus





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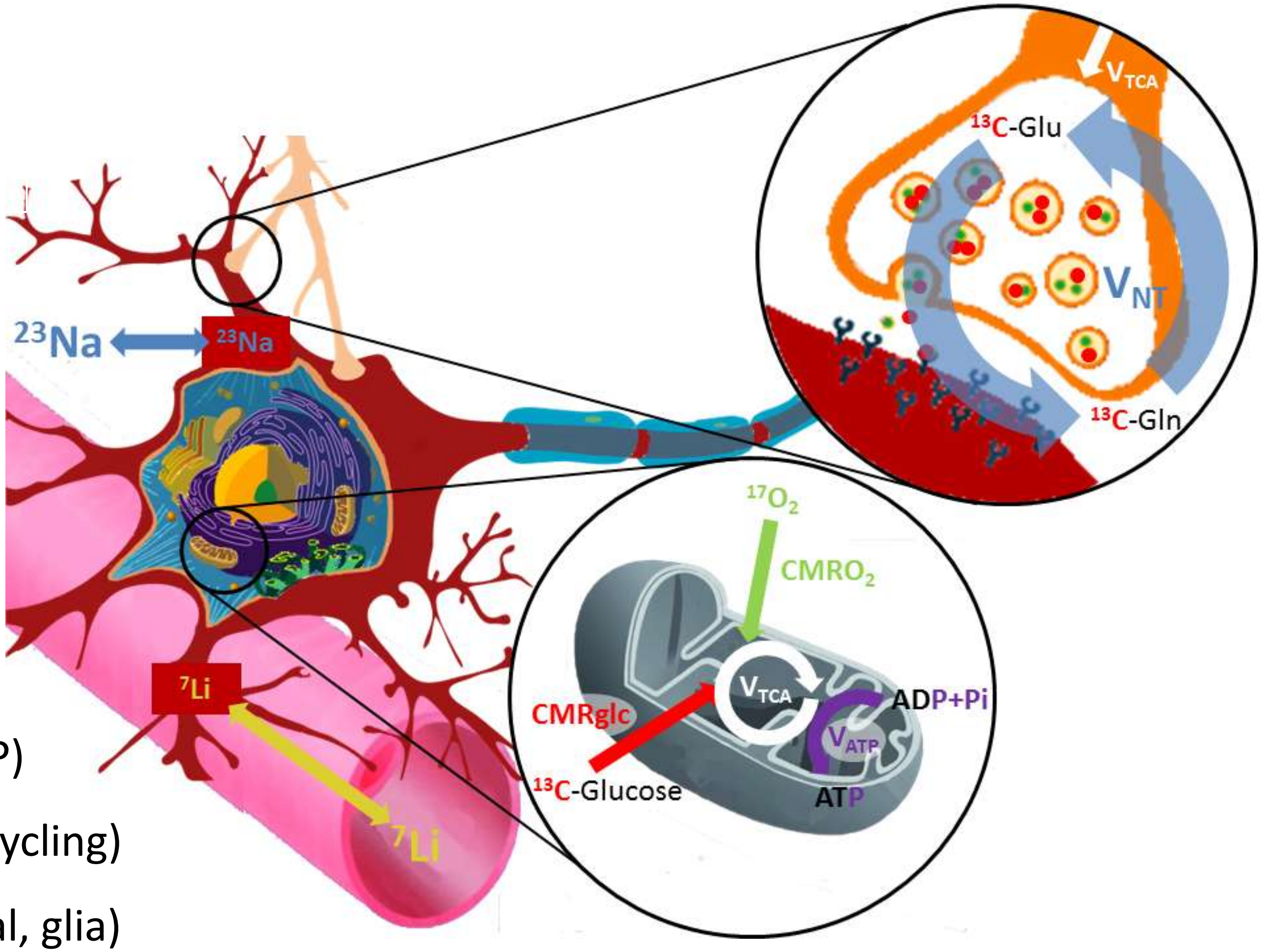
Non-proton (X) MR Imaging and Spectroscopy

aims at studying nuclei (other than ^{1}H) of biological relevance such as...

		Spin	Gyromagnetic ratio ($10^7 rad.T^{-1}.s^{-1}$)	Frequency @ 7.0T (MHz)	Natural abundance	Relative sensitivity	$[\ ]_{in\ vivo}$ (mol/L)
High abundance Nuclei	^{1}H	1/2	26.752	298.04	99.98	1.00	80 (H_2O)
	^{31}P	1/2	10.841	120.58	100.00	$6.65\ 10^{-2}$	$1\text{-}20\ 10^{-3}$
	^{23}Na	3/2	7.080	78.88	100.00	$9.27\ 10^{-2}$	~ 15.10^{-3} ~ 140.10^{-3}
	^{35}Cl	3/2	2.626	29.26	75.78	$3.58\ 10^{-3}$	~ 45.10^{-3}
	^{39}K	3/2	1,250	13.93	93.26	$4.75\ 10^{-4}$	~ 145.10^{-3} ~ 4.10^{-3}
Low abundance Nuclei	^{13}C	1/2	6.728	74.96	1.11	$1.76\ 10^{-4}$	$1\text{-}20\ 10^{-3}$
	^{15}N	1/2	-2.712	30.21	0.37	$3.86\ 10^{-6}$	$1\text{-}20\ 10^{-3}$
	^{17}O	5/2	-3.628	40.42	0.04	$1.08\ 10^{-5}$	40 (H_2O)
Absent in vivo	^{3}He	1/2	-20.380	227.05	$1.4\ 10^{-4}$	$5.75\ 10^{-7}$	–
	^{7}Li	3/2	10.398	115.84	92,58	0.272	~ 10^{-3}
	^{19}F	1/2	25.181	280.54	100.00	0.834	–
	^{129}Xe	1/2	-7.452	83.02	26,44	$5.71\ 10^{-3}$	–

Basic NMR properties of most nuclei of interest for biomedical research

X-NMR allows to probe non-invasively cellular homeostasis, metabolism and physiology.



Research and Clinical applications

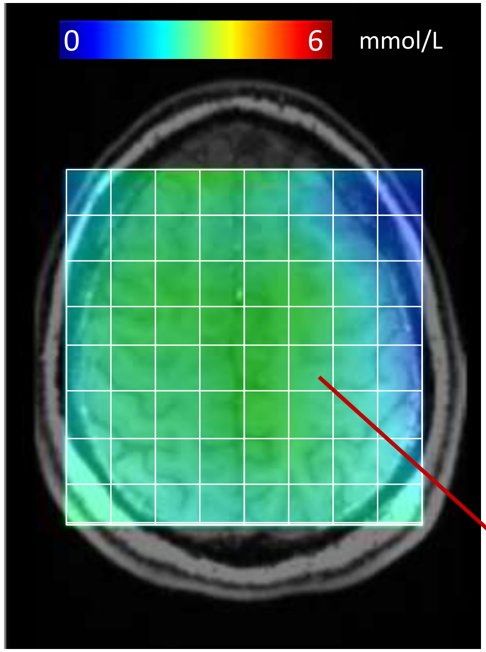
- Energy Metabolism (ex: $CMRO_2$, ATP)
- Neurotransmission (ex: Glu, GABA cycling)
- Cellular compartments (ex: neuronal, glia)
- Disease and Physiology monitoring
- MR-based molecular imaging
- Drug development

The challenge of *in vivo* X-MRI

For X-nuclei and their relatively low frequencies, the signal-to-noise ratio (SNR) increase almost quadratically with B_0 :

$$SNR \propto \gamma^2 B_0^{7/4}.(T_2^*/T_1)^{1/2}.[nucleus].V_{oxel}.(T_{acq})^{1/2}$$

From [Hoult & Richards, J Magn Reson 1976]

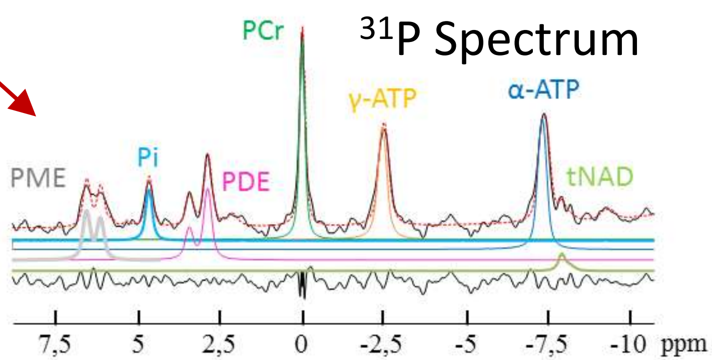


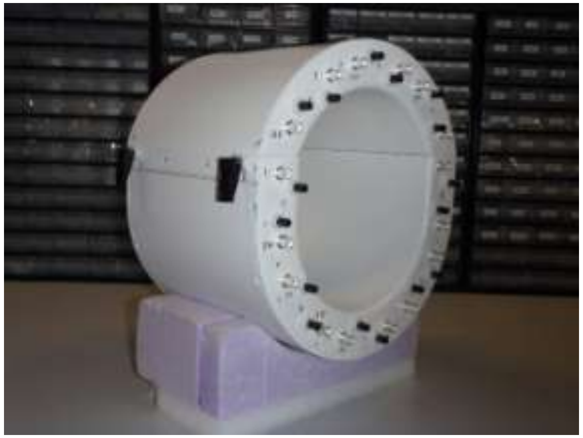
2D ATP concentration map in a healthy volunteer at 7T.

Courtesy A. Lopez-Kolkovsky

Yet, the intrinsically lower sensitivities and *in vivo* concentrations require a compromise in spatial and temporal resolution of X-MRI.

X-MRI requires specific hardware in particular dedicated dual-resonance $^1H/X$ radiofrequency coils.

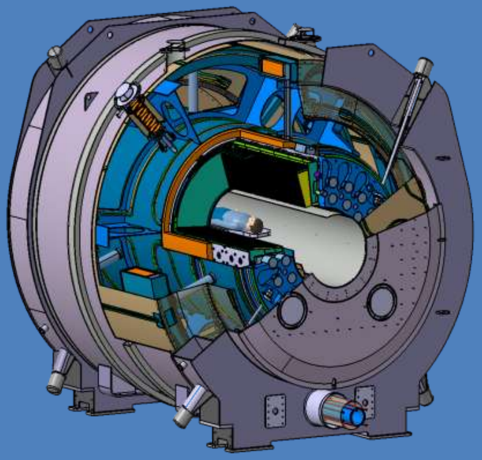




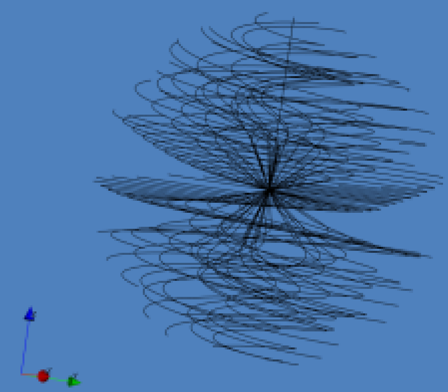
Dual-resonance $^1H/^{31}P$ RF coil (from Resonance Research Inc)

Technological solutions

Ultra High Magnetic Field



Optimized detection/imaging methods

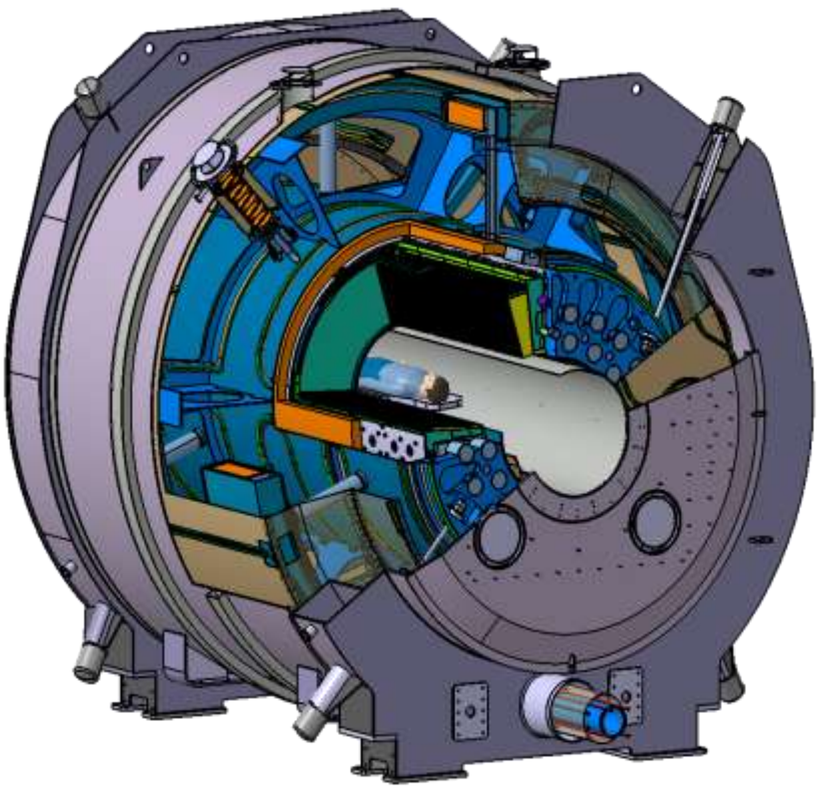


Hyperpolarization

Cryogenic RF coils

NeuroSpin will receive in 2016 the world-first clinical 11.7T MRI system with the objective to map the human brain at the mesoscopic scale.

NeuroSpin will be in charge of :
- managing the 11,7T MRI in collaboration with our colleagues from the Irfu
- converting the increased magnetic field into a gain in spatio-temporal resolution and contrast.



Courtesy P. Védrine, T. Schild & F. Lethimonnier

The aim of Hyperpolarization is to increase temporarily but dramatically the amount of signal. Typically a ~30000-fold SNR gain can be achieved *only for as long as the T_1.*

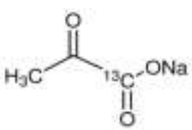
Different techniques are available:

Optical Pumping (mostly for ^{3}He & ^{129}Xe)

Para-hydrogen-induced Polarization

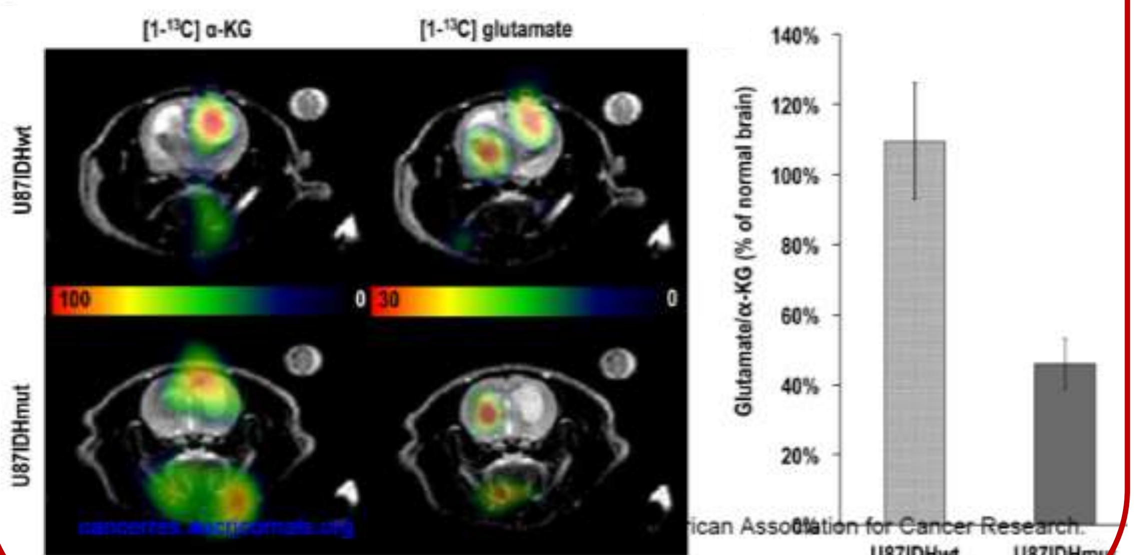
Dynamic Nuclear Polarization

most popular method especially to image tumors using ^{13}C-labeled substrates
[Gutte et al., Am J Nucl Med Mol Imaging 2015]

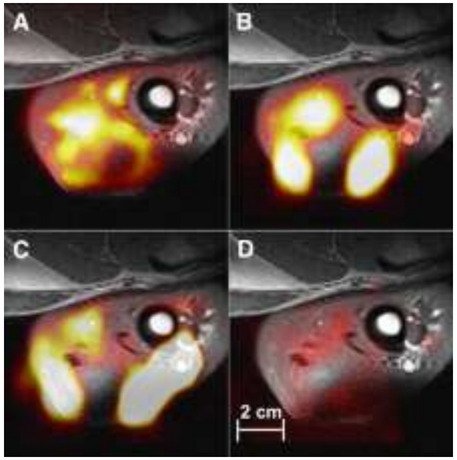


[^{13}C]Pyruvate

- Mutant IDH1 glioma can be detected using ^{13}C MRSI (low Glu/αKG ratio) and [1-^{13}C]Glutamate.



[Chaumeil et al., Cancer Res. 2014]



Multimodal ^{13}C-pyruvate & [^{18}F]FDG (HyperPET) sarcoma imaging

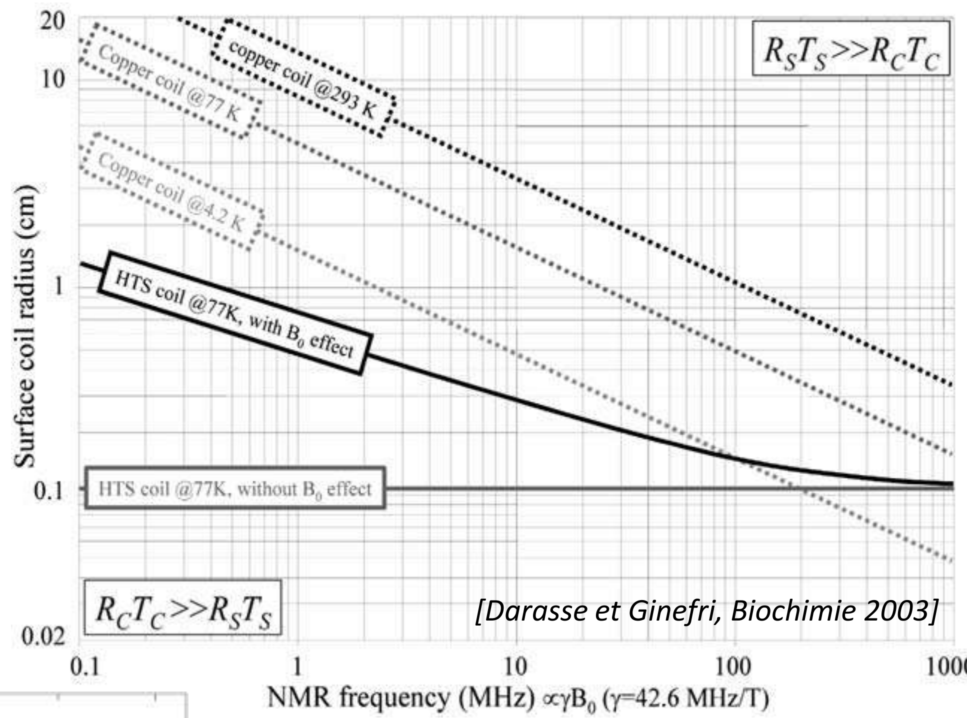
[Gutte et al., JNM 2015]

Objective: to cool the RF detection electronic so as to reduce the thermal noise.

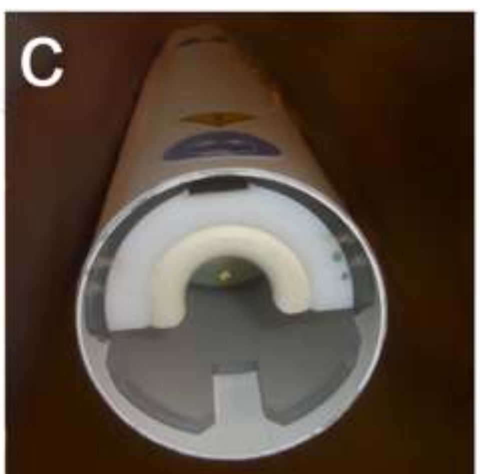
The gain in SNR depends on the operating frequency, the coil materials (copper or high temperature superconductors) and sample volume.

$$\mathrm{SNR}_{gain} = \frac{\mathrm{SNR}_{cryo}}{\mathrm{SNR}_{RT}} = \frac{\sqrt{R_S T_S + R_{C,RT} T_{C,RT}}}{\sqrt{R_S T_S + R_{C,cryo} T_{C,cryo}}}$$

RT=room temperature coil; cryo= cryogenic coil

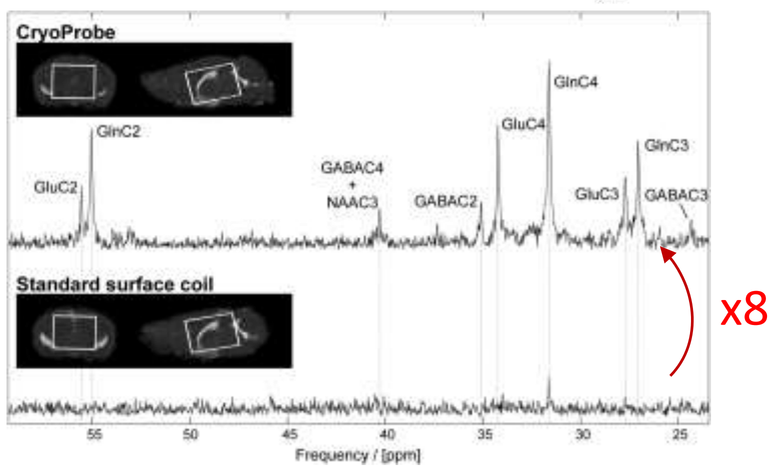


[Darasse et Ginefri, Biochimie 2003]



[Sack et al., NMRBiomed 2014]

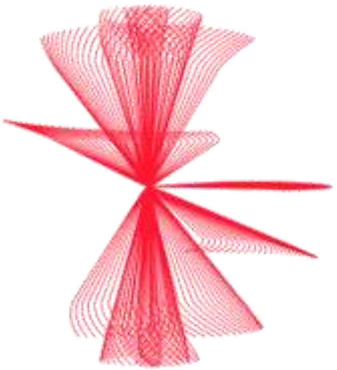
^{13}C CryoProbe (Bruker) with an additional ^{1}H saddle coil for mouse brain ^{13}C spectroscopy



Despite its limitation at UHF to preclinical MRI, cryogenic RF coils holds the promise of a large increase in NMR sensitivity for X-MRI.

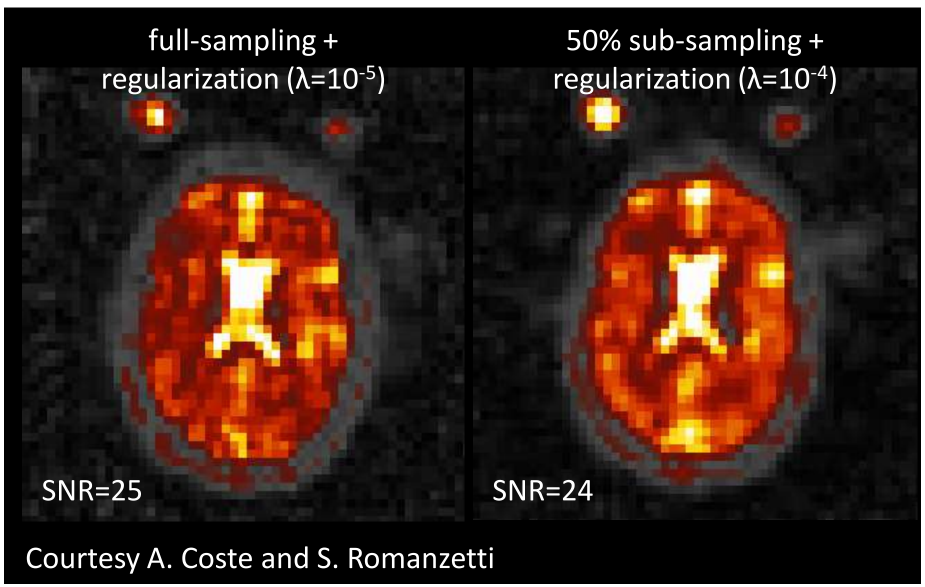
Optimized X-MRI Acquisition and Reconstruction

- Sequences such as the Twisted Projection Ultra-short TE Imaging (TPI) sequence are particularly relevant for imaging nuclei such as ^{23}Na, ^{17}O or ^{31}P with short T_2^*.

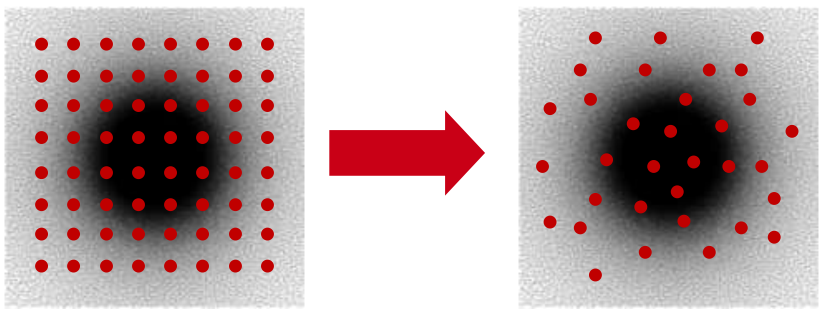


TPI Non-Cartesian sampling sequence from [Boada *et al.,* MRM 1997].

^{23}Na UTE MRI @ 3T

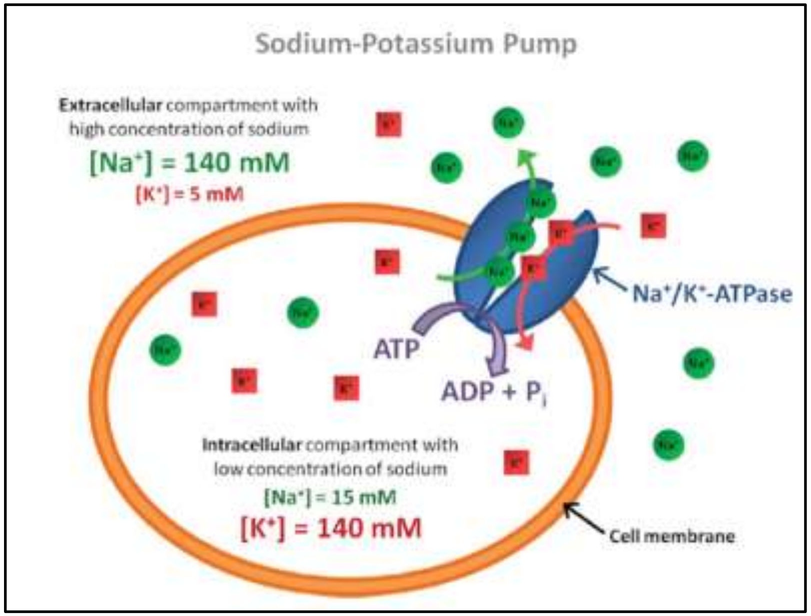


cartesian sampling « random » sampling



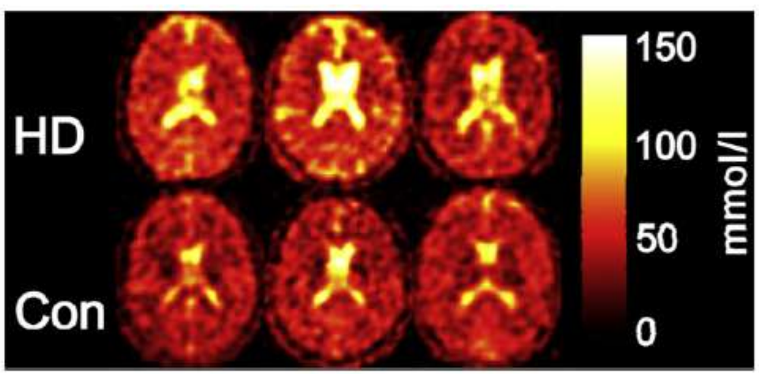
- Similarly to HR MRI, non-linear reconstruction algorithms (ex: FISTA[1], NUFFT[2]) can be combined with sparse sampling (Compressed Sensing) to reduce acquisition times while preserving sensitivity.

[1] A. Beck et al., SIAM J. Imaging Science 2009
[2] J.A. Fessler et al., J Magn Reson 2007



Na^+/K^+-ATPase transmembrane Pump.
From [Madelin et al. JMRI 2013].

▼TSC is higher in the brain of HD patients compared to healthy controls in particular in the striatum.



[Reetz et al., NeuroImage 2012]

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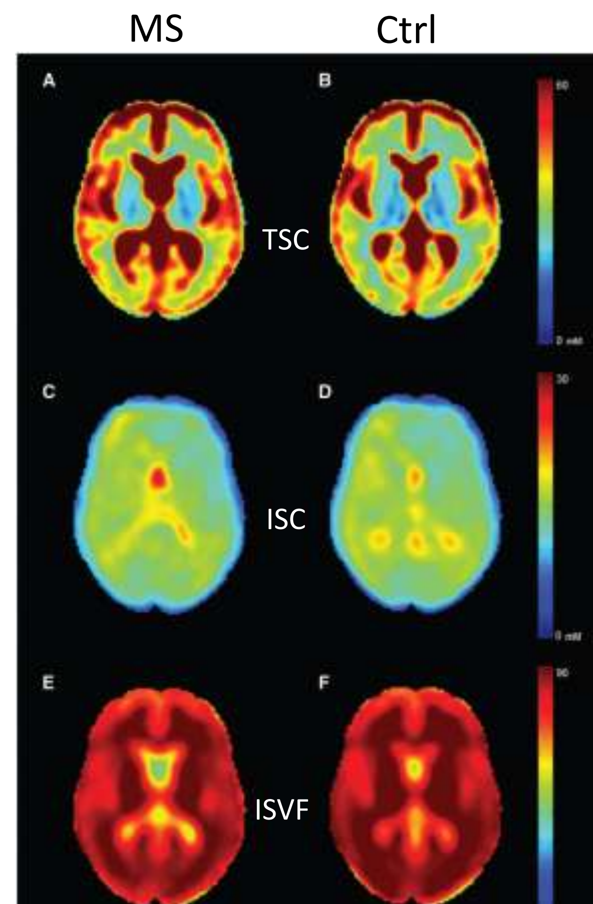
- Imaging sodium (^{23}Na) brain distribution in patients suffering from neurodegenerative diseases such as MS or HD allows to probe cellular homeostasis.

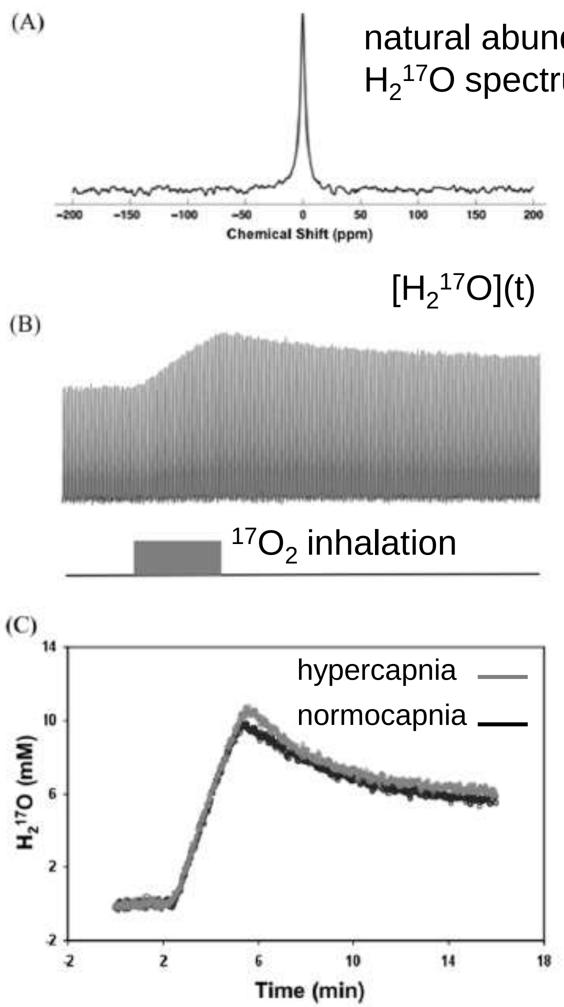
► In MS, the intracellular sodium volume fraction (ISVF) measured at 7T using TQF ^{23}Na MRI correlates with ^{1}H MR-visible lesions and Expanded Disability Status Scale.



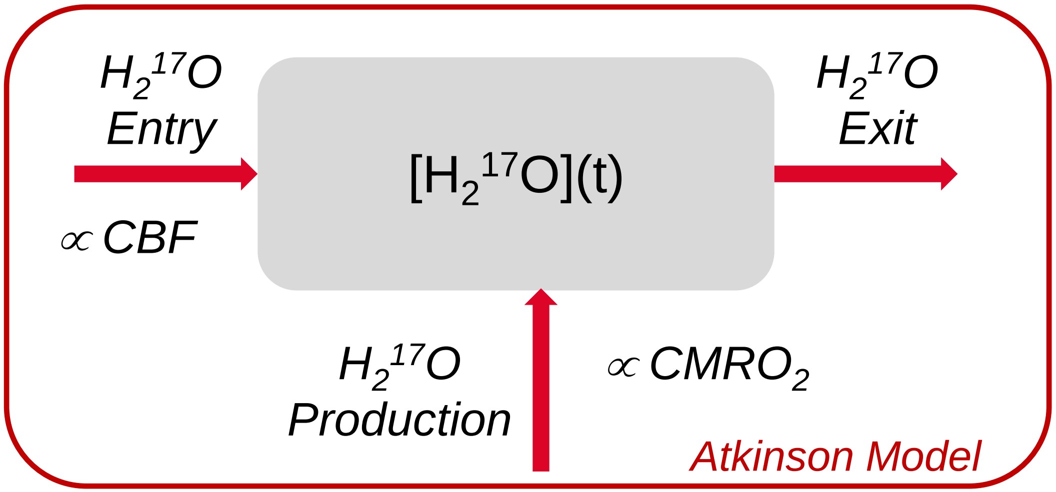
From [Petracca *et al.* Brain 2016]

More info tomorrow:
IRM du sodium : vers un biomarqueur de la neurodégénérescence ?
by Bertrand AUDOIN
(CRMBM, Marseille)

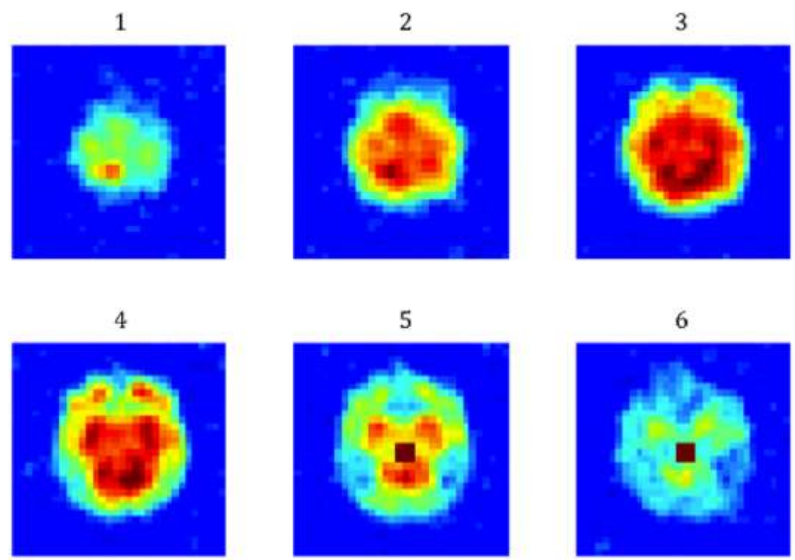
- Despite its low natural abundance (0,04%), ^{17}O offers the unique possibility to directly probe tissular perfusion, oxygenation and cellular respiration following the inhalation of $^{17}O_2$ or the administration of labeled water ($H_2^{17}O$).



^{17}O MRS in the rat brain.
From [Zhu et al.. MRM 2013]



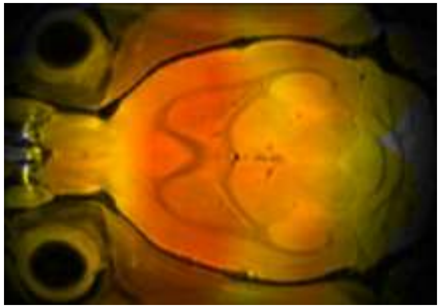
[Atkinson & Thulborn, NeuroImage 2010]



Courtesy C. Najac and J. Valette (DRF/I2BM/MIRCen)

◄ ^{17}O 3D CSI of the monkey brain at 7T.

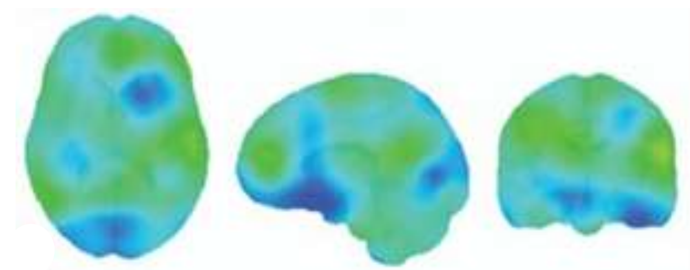
^{7}Li MRI



ex vivo ^{7}Li MRI of a Li-treated rat brain @ 17T

- Lithium is the leading treatment for relapse prevention.
- However, its mechanism of action remains poorly understood.
- Intracerebral Li concentration as a predicting biomarker of response to Lithium could improve patient outcome.

- Recently, a non-localized ^{7}Li MRS study at 3T (Machado-Vieira et al., Acta Psychiatr Scand 2015) has already validated our hypothesis.



▲^{7}Li 3D CSI of the human brain at 4T. From [Lee et al., MRM 2012]

Dual-resonance ^{1}H/^{7}Li RF coil (from Rapid Biomedical GmbH)

- In Spring, a 7T ^{7}Li MRI study will start at NeuroSpin in collaboration with Frank Bellivier (Inserm UMR-S1144) to explore the brain distribution of Li in good and bad responders

Outline

Introduction

I- Proton ultra-high field (UHF) MRI: a technical challenge *C. Poupon*

II- Metabolic Imaging using low gyromagnetic nuclei *F. Boumezbeur*

Conclusion

Conclusion

Proton & heteronuclear UHF MRI is a promising tool to investigate the brain structure, function and metabolism *in vivo* at unprecedented resolutions.

After a decade of methodological developments to alleviate the pitfalls of UHF MRI, UHF MRI has reached the level of maturity required for its application to clinical research and soon for clinical routine (as demonstrated by the announced CE and FDA 7T MRI systems available on the market).

Thanks you for your attention !

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Brain metabolism and X nuclei imaging team :	**Fawzi Boumezbeur** Boucif Djemaï
Coil Antenna team :	**Michel Luong** Matthieu Baudrier Edouard Chazel Guillaume Ferrand Elodie Georget Eric Giacomini
Electronics & Mechanics shop :	**Laurent Laribière** Jérémy Bernard Marie-France Hang

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