Imaging metabolic and structural vulnerability in brain diseases: Beyond proton MR

Wafaa Zaaraoui, PhD

CNRS Researcher

Centre de Résonance Magnétique Biologique et Médicale (CRMBM)

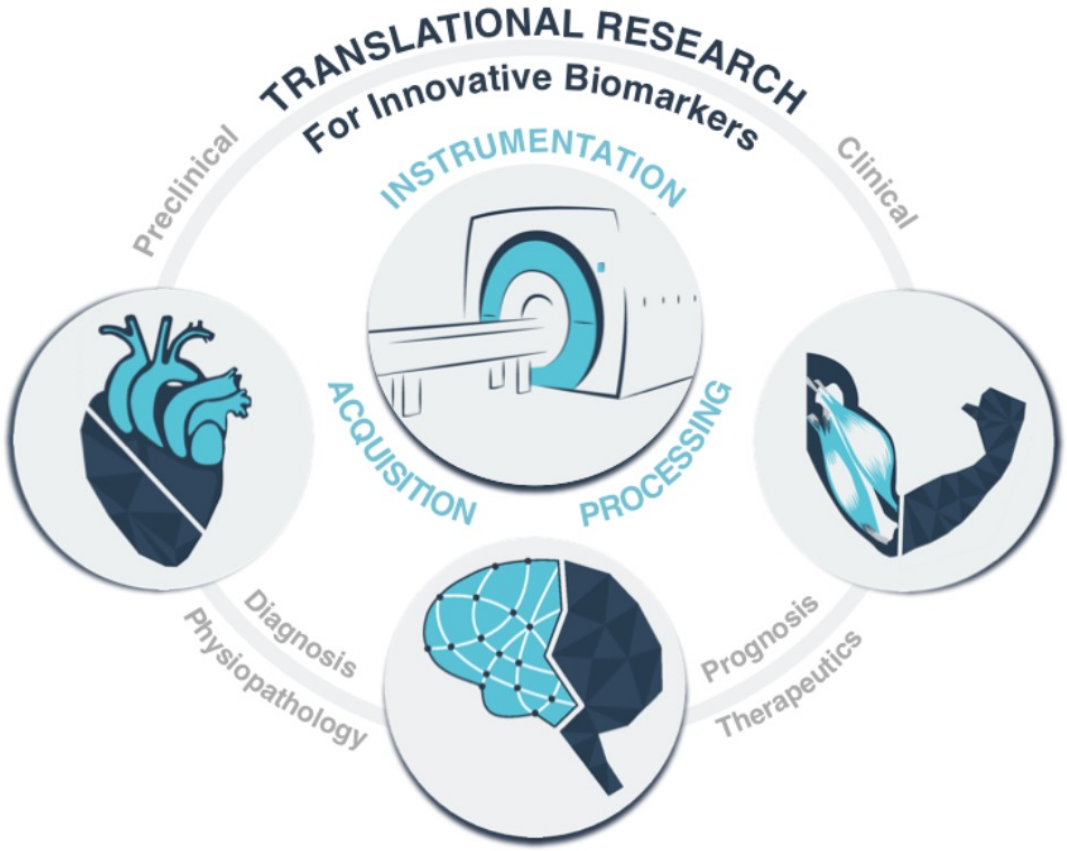
Aix-Marseille Université

Marseille, France

CENTER FOR MAGNETIC RESONANCE IN BIOLOGY AND MEDICINE

CRMBM-CEMEREM UMR 7339

Director: Dr Monique Bernard
Deputy director: Pr Maxime Guye



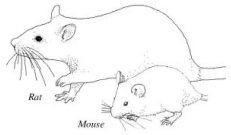
Innovative MRI methods for the exploration of cardiovascular, musculoskeletal, central nervous systems

Timone campus

CRMBM: pre-clinical facilities

Bruker Pharmascan® 70/16

Bruker 500WB Avance 11.75T



Multinuclear high field MRI/MRS systems for small animal *in vivo* imaging studies equipped with radiofrequency probes for body, brain, spinal cord, muscle and cardio-vascular studies.

Multinuclear high resolution MR spectrometers for perfused organs, biological fluids equipped with 5mm, 100mm and 20 mm multinuclear probes

Physiological Monitoring

MR-compatible rat and mouse monitoring and gating systems are avalaible for all MR experiments

Several home-built cradles were specifically designed for the strictively non invasive functional investigation of rat and mouse muscle with 1H/31P coils included

Animal Facility

The platform includes animal facilities with space to prepare the rats and mice for MR exams, an equipped surgery room and a wide assortment of ancillary equipment, i.e. anesthesia machines, infusion pumps, heating pads.

Biology and Biochemistry lab

CRMBM - CEMEREM: clinical facilities (100% research)

Clinical MRI

3T Vida Siemens

7T Terra Siemens
CE approved

Physiological Monitoring

For all MR scanners:

- MR-compatible physiology monitoring and gating systems
- MR-compatible automatic contrast agent injectors
- Dedicated MR compatible ergometers (home-built or commercial)

Clinical Department

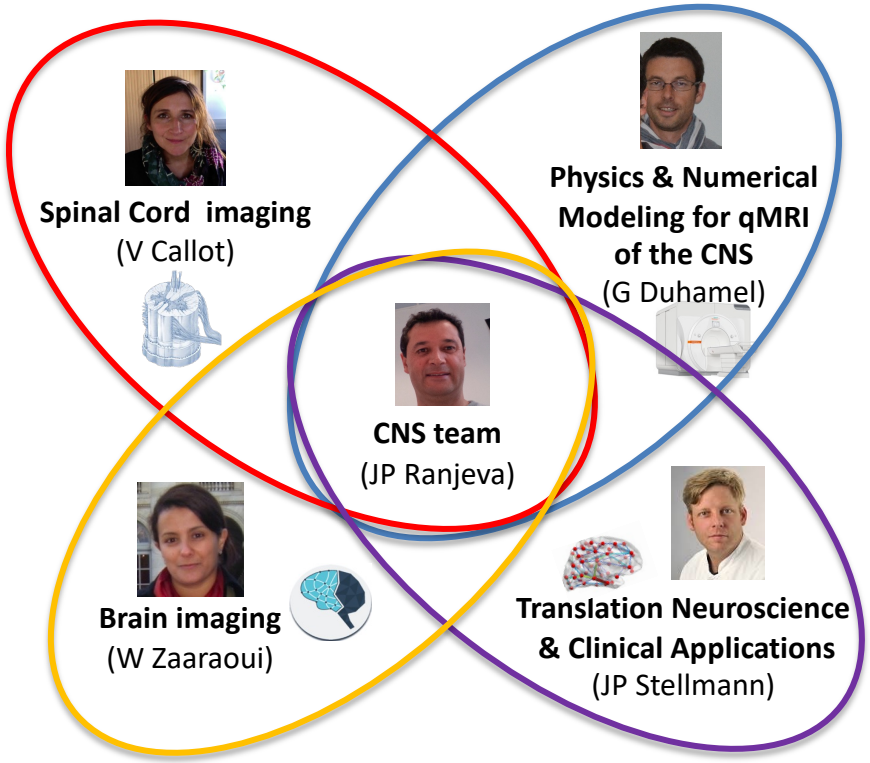
Accreditation of CEMEREM for human research by ARS (Agence Régionale de Santé)

CEMEREM under responsability of a medical doctor head of CEMEREM clinical department Timone Hospital

All protocols submitted to appropriate ethic committee agreements (CPP comité de protection des personnes)

The Central Nervous System team with 4 groups

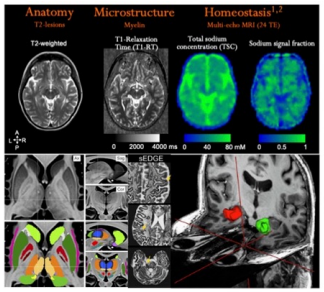
Development and application of advanced MRI/MRSI methods and contrasts to better understand, monitor and treat neurological/psychiatric diseases

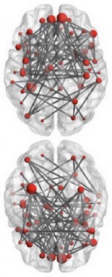


Increasing knowledge on multicontrast MRI and addressing methodological challenges at high (3T) and ultra high (7T) field strengths for clinical neuroscience

https://crmbm.univ-amu.fr/research/teams/central-nervous-system/

The Brain imaging group





https://crmbm.univ-amu.fr/topic/brain_imaging/

Research Works

PRINCIPAL INVESTIGATOR : WAFAA ZAARAOUI

The brain imaging group aims at developing new MR biomarkers at high (3T) and ultra-high (7T) fields to characterize the anatomy, the microstructure, the meso-scale network organization, the metabolism and the homeostasis of the brain. The objectives are to push forward the limits of brain imaging using the added value of UHF MRI and counteracting the pitfalls, focusing on improved spatial resolution to characterize anatomy and function of complex small size gray matter structures or cortical layers. We also contribute to the advances of multimodal UHF MRI to characterize brain connectivity, and we work at rendering UHF X-nuclei MRI/MRSI usable in clinical compatible protocols.

Group Members:

- Leader: Wafaa Zaaraoui (CR CNRS)
- Jean-Philippe Ranjeva (PR Neurosciences)
- Maxime Guye (PU-PH Biophysics, AMU/APHM)
- Adil Maarouf (MCU-PH, Neurology, AMU/APHM)
- Jan-Patrick Stellmann (MCU-PH, Radiology, AMU/APHM)
- Aude-Marie Grapperon (PH Neurology, APHM)
- Yann le Fur (IR CNRS)
- Hugo Dary (IR CNRS)

Post-Doctoral researchers :

- Penelope TILSLEY
- Tangi Roussel
- Mohamed Mounir El MENDILI
- Roy Haast

PhD students :

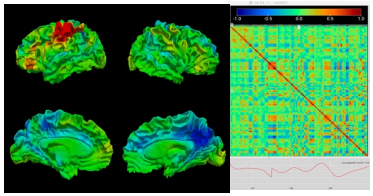
- Kushboo PENJABI
- Coleen ROGER
- Maëva Cotinat
- Lucas Gauer

Multimodal and multicontrast brain imaging @ 3T & 7T

Improvement of functional MRI for activation patterns and Functional Connectivity

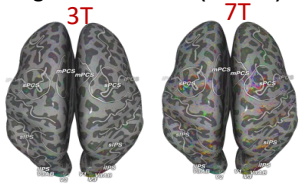
=> Better acquisition (PTx) higher temporal (MB) resolution and spatial (VASO) resolutions

Faster rs-fMRI for Dynamic FC

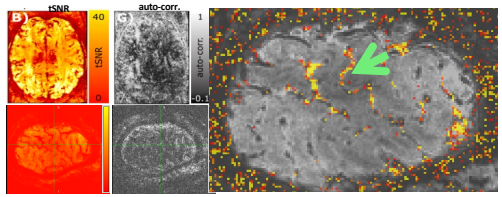


High res Task-fMRI (MB-EPI)

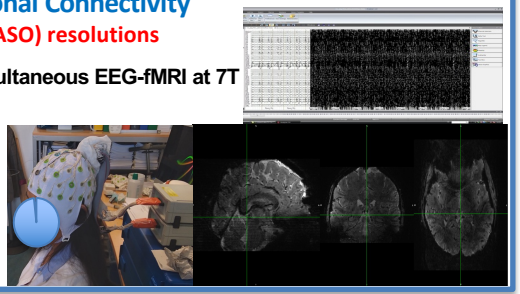
3T 7T



Layer resolved-fMRI (VASO)



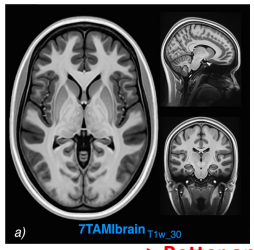
Simultaneous EEG-fMRI at 7T



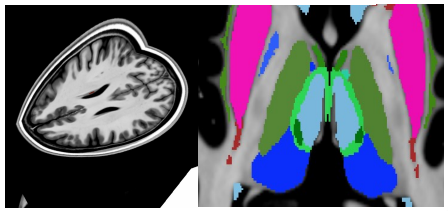
Improvement of brain morphometry and parcelation

=> Better (PTx) and Faster (CS) acquisitions

Brain template (3D-MP2RAGE)(0.6mm)^3



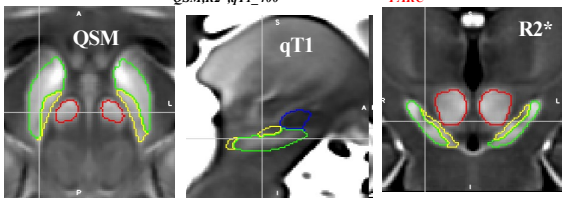
7T-AMI DGN atlas



=> Better and Faster post-processing pipelines (AI)

Fast multiparametric quantitative approaches

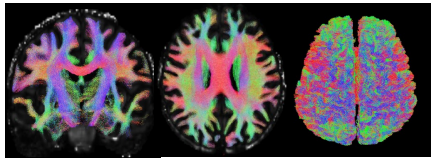
$7TAMIbrain_{QSM,R2*,qT1\_400}$ $7TAMIbrain_{PARC}$



Better brain network characterization for individual modeling (TVB, prognosis of individual trajectories)

Improvement of structural connectivity

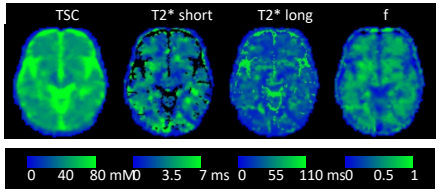
=> Better and faster HARDI



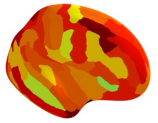
Improvement of ionic/homeostatic imaging and metabolic imaging

=> Faster ^{23}Na MRI , ^{31}P MRSI, and 3D ^{1}H-MRSI

^{23}Na MRI

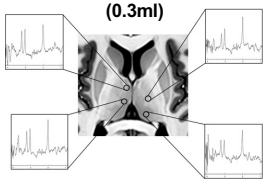


^{31}P MRSI

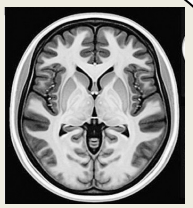


PCr map

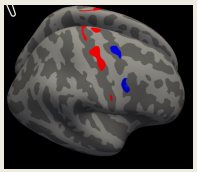
2D semi-laser ^{1}H PRESS CSI (0.3ml)



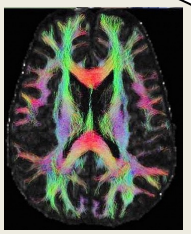
Multimodal MRI protocol @ CRMBM-CEMEREM



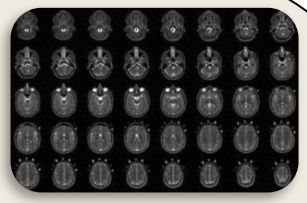
High-resolved anatomy



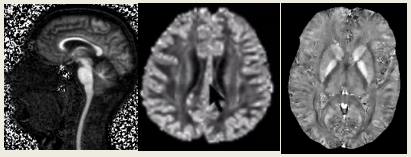
Morphometry



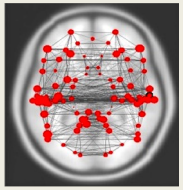
Structural Connectivity
DTI



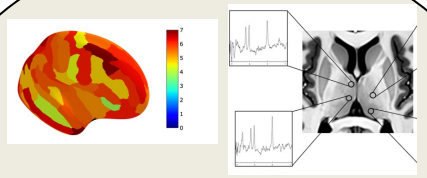
Sodium homeostasis
^{23}Na MRI



Tissue structure
Quantitative R1, R2*, QSM



Functional Connectivity
Rs-fMRI

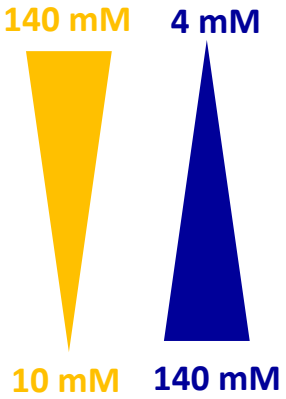


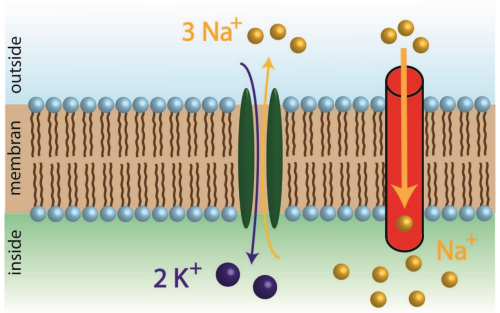
Metabolic assessment
^{31}P and ^{1}H MR spectroscopy

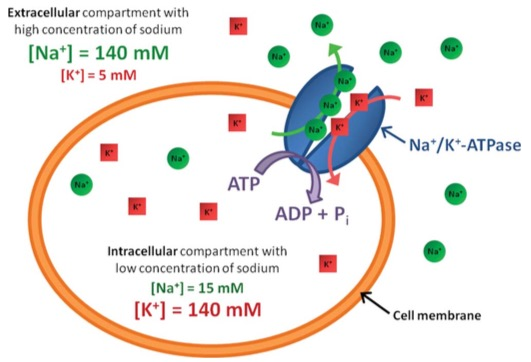
Sodium MRI: in vivo marker of sodium homeostasis

Sodium MRI provides information on:

- Function/viability of cells
- Excitability of cells
- Early marker in many brain disease processes







Reviews: Madelin et al, JMRI 2013; Shah et al, NMR Biomed 2016; Petracca et al, NMR in Biomed 2016; Thulborn, Neuroimage 2018

Sodium MRI in Multiple Sclerosis: Why?

Each AP accompanied by ↑ **sodium influx**

Elevated Na channel expression
(especially $Na_v1.6$)
↑ **persistent currents**

Demyelination
Impaired AP conduction

Energy Imbalance
Higher demand to maintain resting potential and transmembrane concentrations

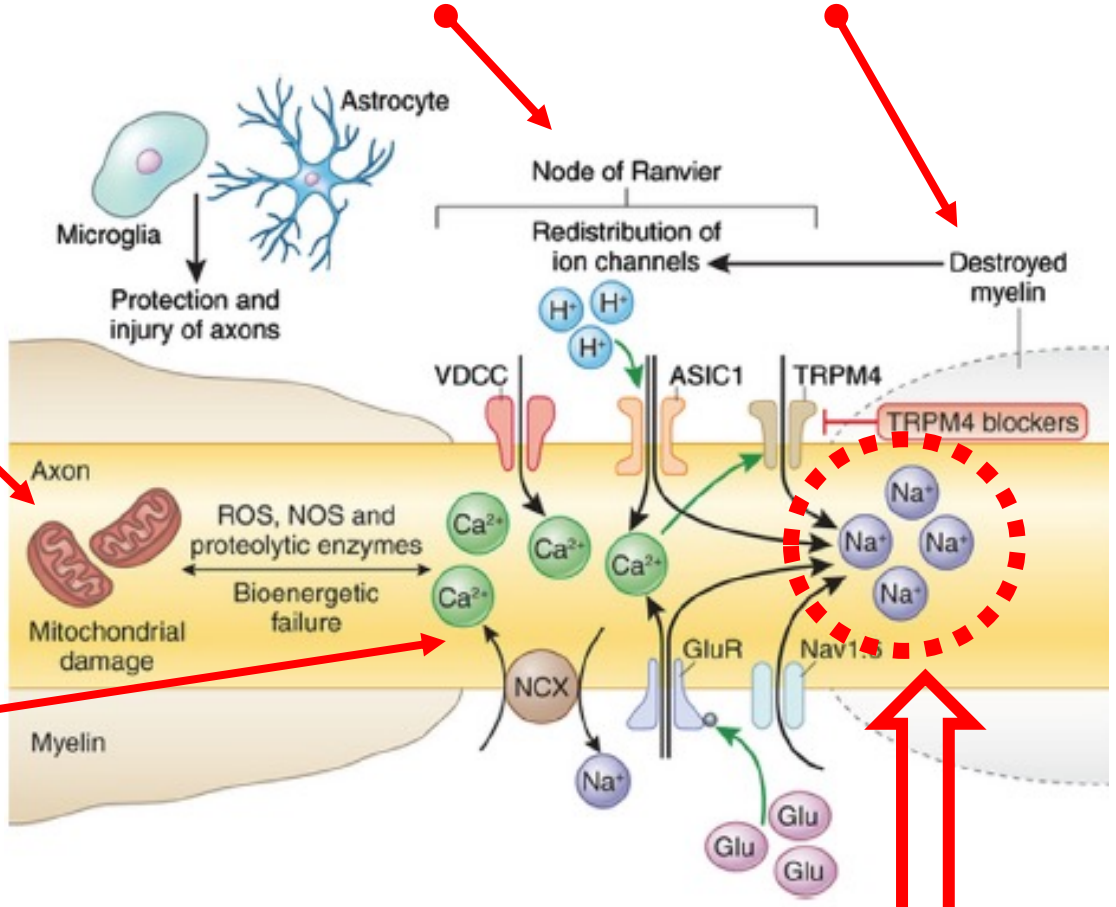
Mitochondrial dysfunction

Nitric Oxide (inflammation)
interferes with ATP production

Energy failure
Na/K-ATPase failure
↑$[Na]_{intracellular}$

Calcium Elevation
Response to elevated $[Na]_I$
Na/Ca ATPase reversal

Neuro-Degeneration
toxic effects of calcium-dependent enzymes



Inglese et al, MS & Rel. Dis. 2013

Increase of $[Na]_{intracellular}$ involved in processes leading to neurodegeneration

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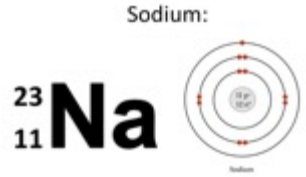
Magnetic properties of ^{23}Na

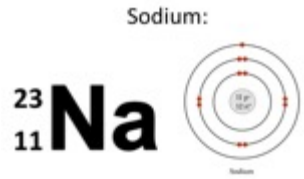


^{23}Na has the most favorable properties for MRI after ^{1}H

	^{1}H	^{23}Na
Spin quantum number	1/2	3/2
Gyromagnetic ratio γ (MHz/T)	42.58	11.26
Sensitivity at constant field per nucleus $\alpha \quad \nu^3.I\ (I+1)$	1	0.0925
In vivo concentration of nucleus (mol/kg)	85.6	0.05
SNR relative to ^{1}H of tissue water	1	$2x10^{-4}$

Adapted from Bottomley, Encyclopedia of MR 2012

Magnetic properties of ^{23}Na



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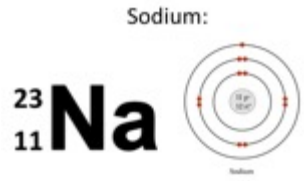
Challenges

=> Very low sensitivity of ^{23}Na MRI signal (=1/20 000 signal ^{1}H)

=> Very fast transverse relaxation time (T_2 ^{23}Na < 2ms)

Magnetic properties of ^{23}Na



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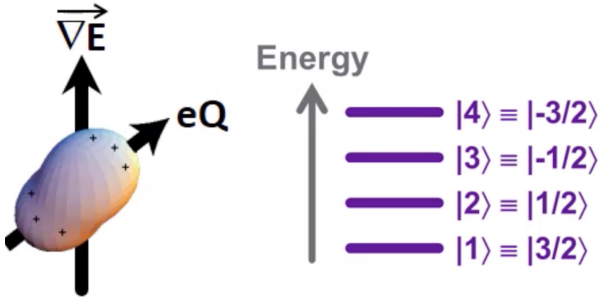
NMR properties of spin 3/2

- **Electric quadrupolar moment** (eQ)
- Strong interaction with surrounding **electric field gradients** (EFG)
- **Residual quadrupolar interaction** = main process of relaxation
- **Biexponential T2** depending on *motional regime* and *anisotropy*

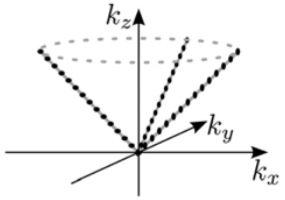


Sodium MRI: what strategies?

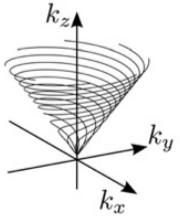
Sodium: $^{23}_{11}Na$

- High or ultra-high field MR system
- RF capabilities for **X-nuclei** (multinuclear option)
- Strong gradient strengths and high slew rates
- MRI sequence dedicated for ultra-short echo-time (**UTE**) => not commercial
- Adapted coils for ^{23}Na
- Increase voxel size (lower spatial resolution (3-5mm)^3) to increase SNR

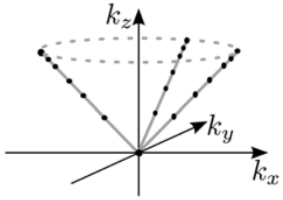
3D Radial



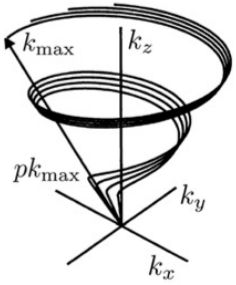
Cones



DA 3D Radial

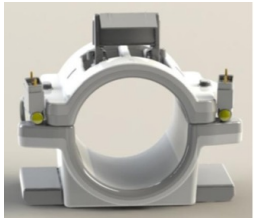


TPI



Shah et al, NMR Biomed 2016 (review)

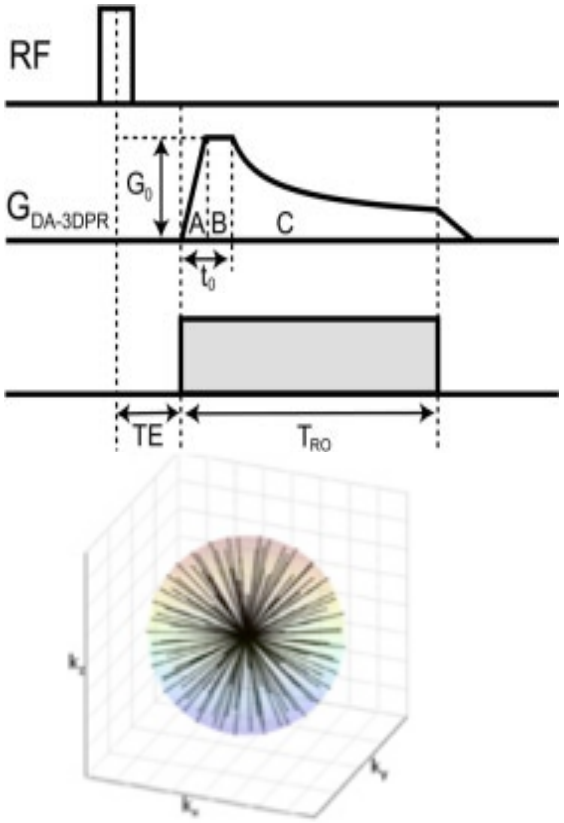
7T ^{23}Na-^{1}H volume head coil (QED)

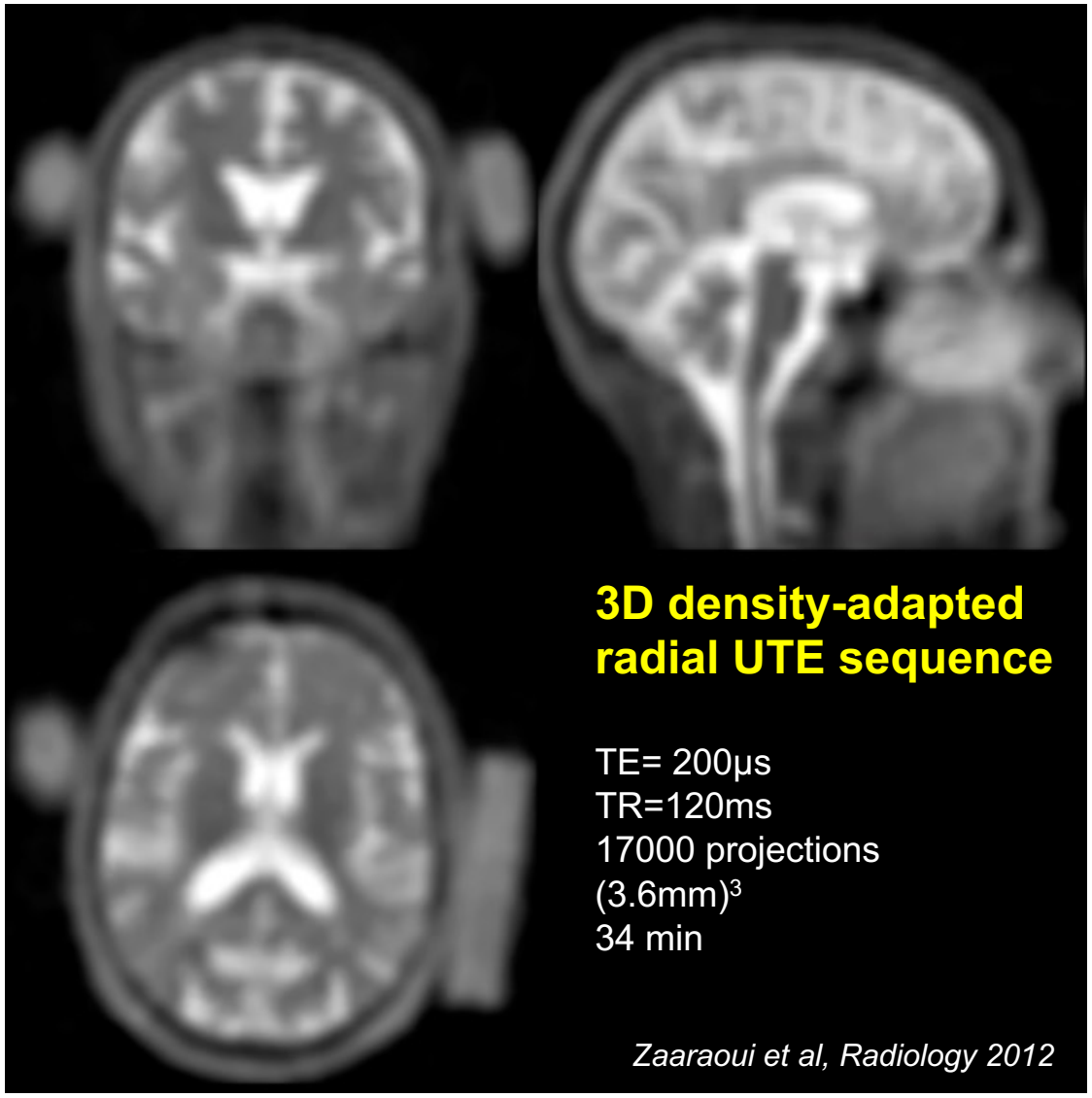


@ CRMBM

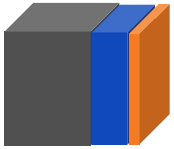
3T ^{23}Na-^{1}H volume head coil (RapidBiomed)

Sodium MRI: Methods development





Total Sodium Concentration (TSC)



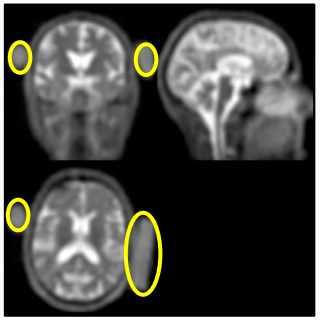
Intra-cellular (85% vol / [Na] ≈ 15mM)

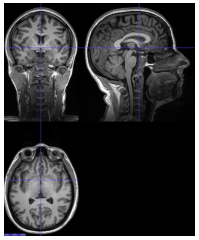
Extra-cellular (12% vol / [Na] ≈ 140mM)

Vascular (3% vol / [Na] ≈ 140mM)

Sodium MRI: Image processing pipeline

Quantitative total ^{23}Na MRI
- Gridding method
- Hanning filter
- Rician denoising filter
- Check for B_0, B_1, T_1 and T_2
- External quantitative references





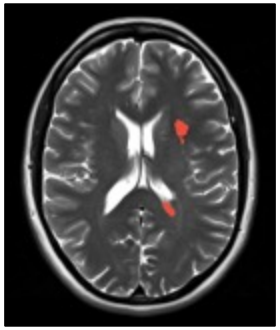
Coregistration to ^{1}H 3D MPRAGE (SPM8/12)

Segmentation (SPM8/12)
- White matter compartment
- Grey matter compartment
- Cerebrospinal fluid compartment

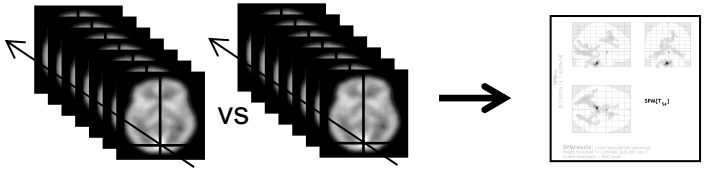
Normalisation MNI (SPM8/12)

Smooth (SPM8/12)

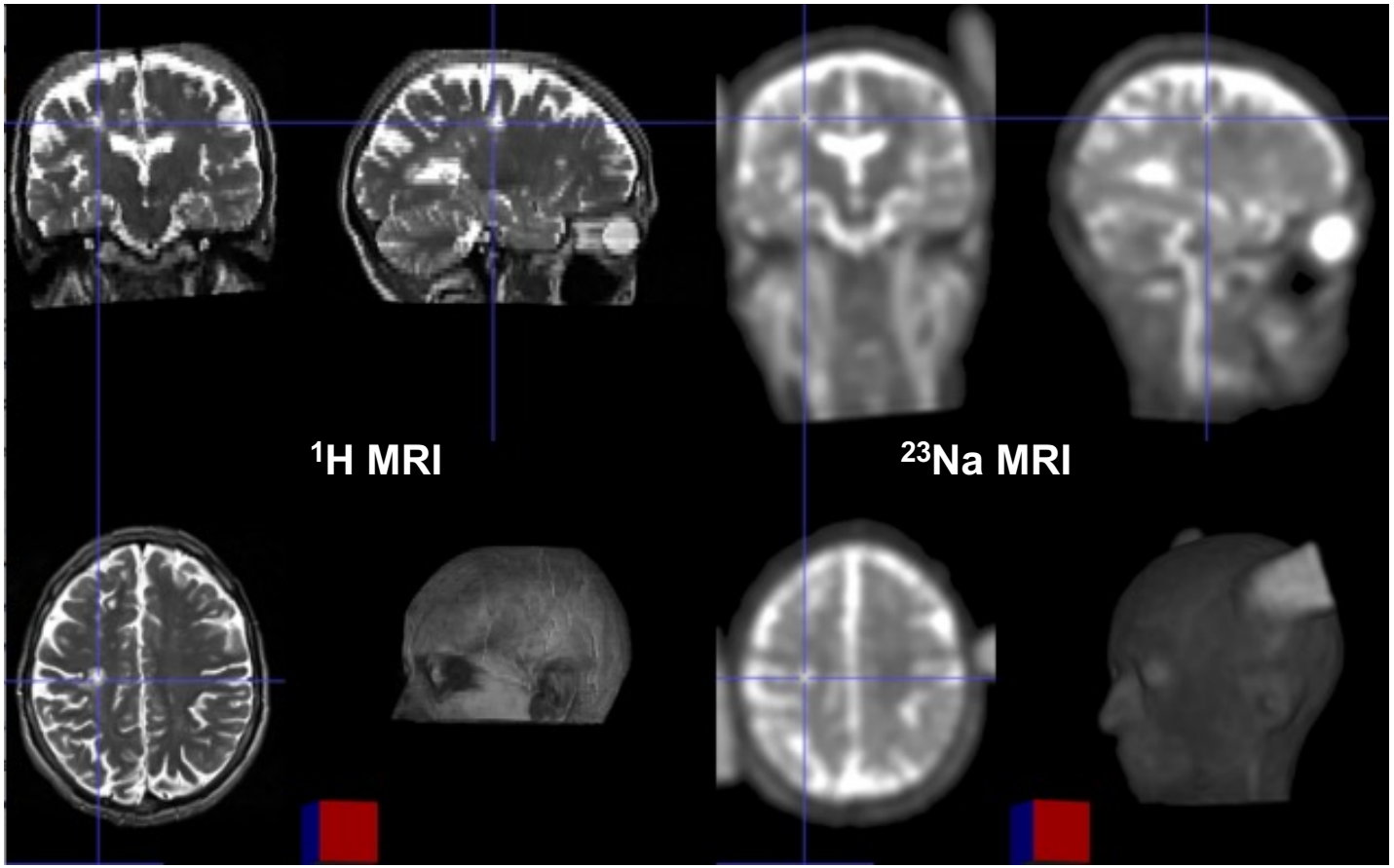
T2 lesions mask (multiple sclerosis)
Manual delineation in 1H T2w



Voxel based analyses (SPM8/12)
Quantitative sodium accumulation maps in patients compared to controls



Sodium MRI in Multiple Sclerosis



Zaaraoui et al, Radiology 2012; Maarouf et al, MAGMA 2014; Maarouf et al, Neurology 2017; Donadieu et al, MSJ 2019; Maarouf et al, MSJ 2022

Sodium MRI in Multiple Sclerosis

Radiology

2012

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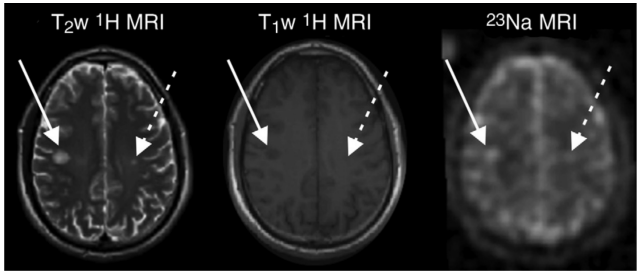

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No. of women	11	10
Disease duration (mo)	14 (8–48)	156 (60–360)

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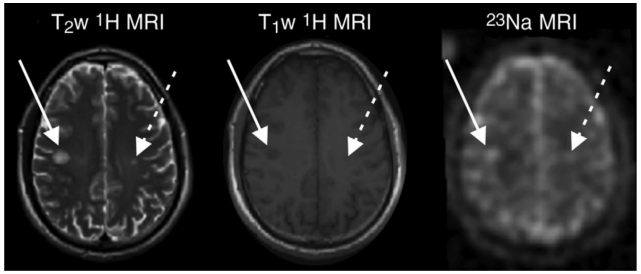

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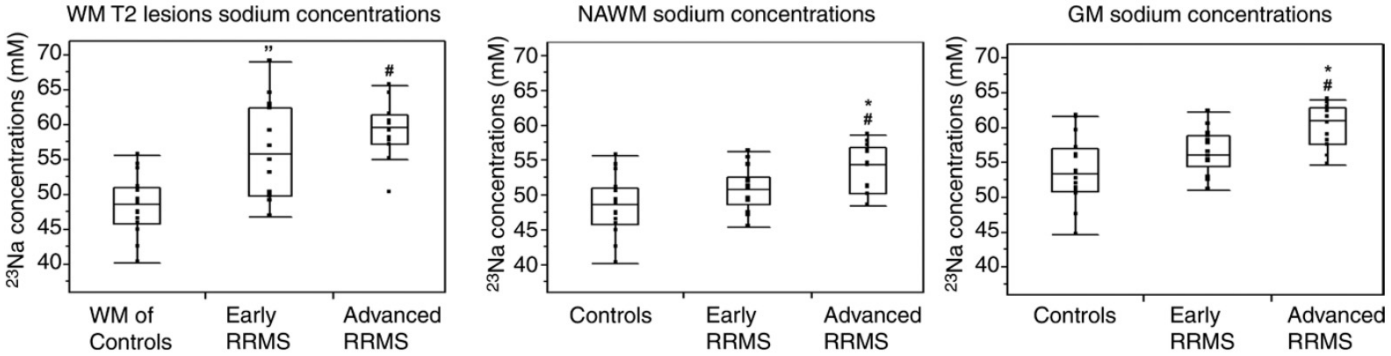

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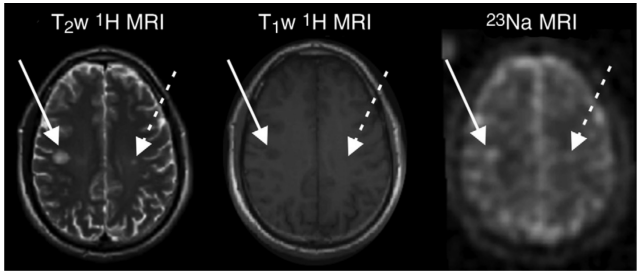

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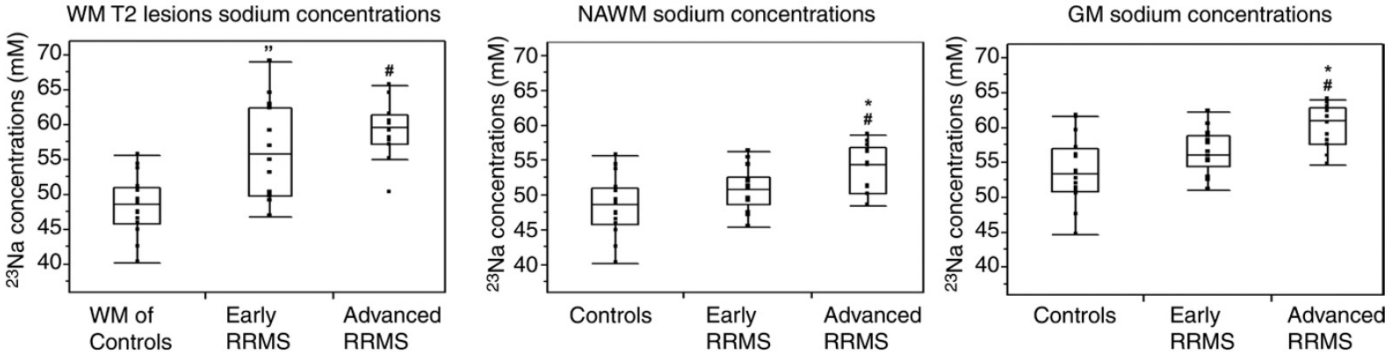

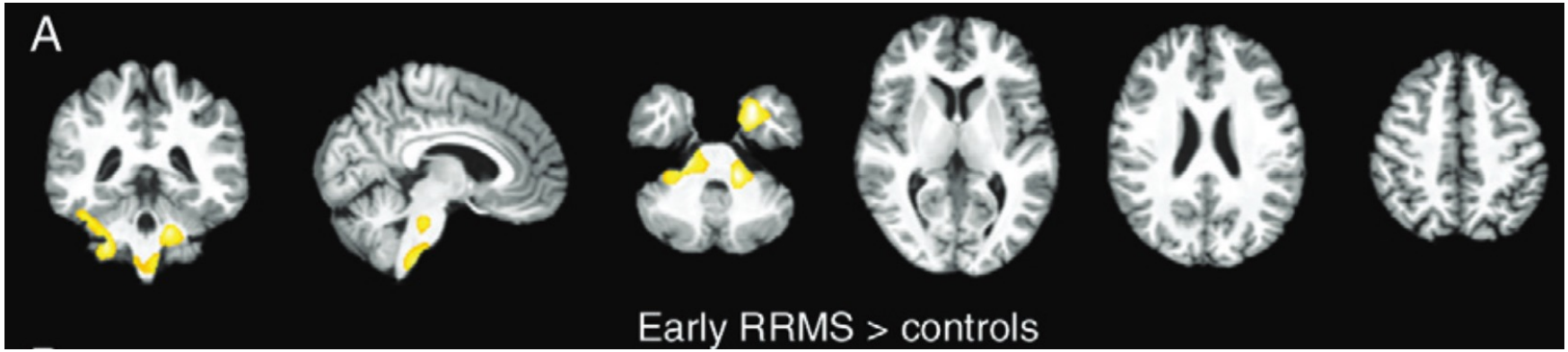

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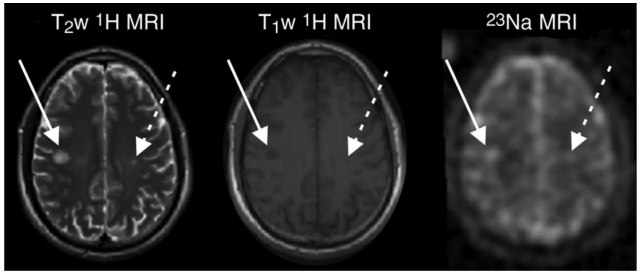

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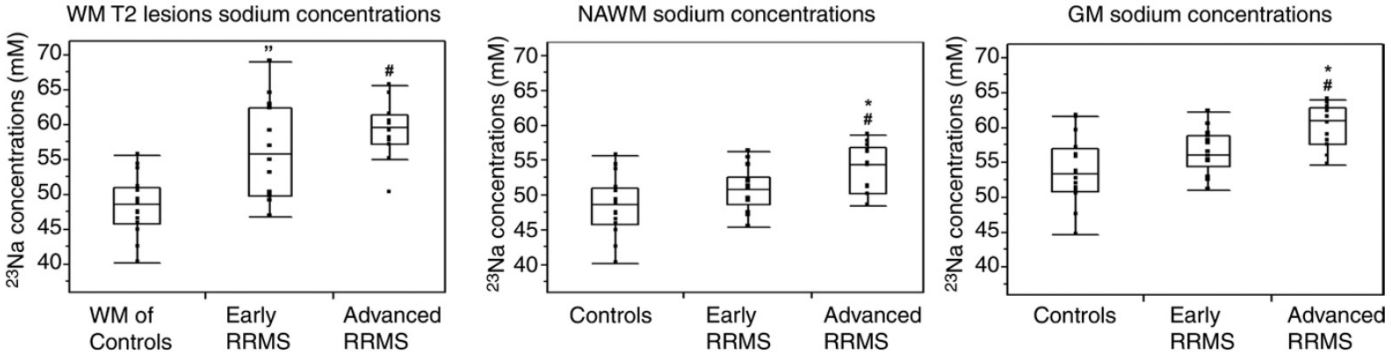

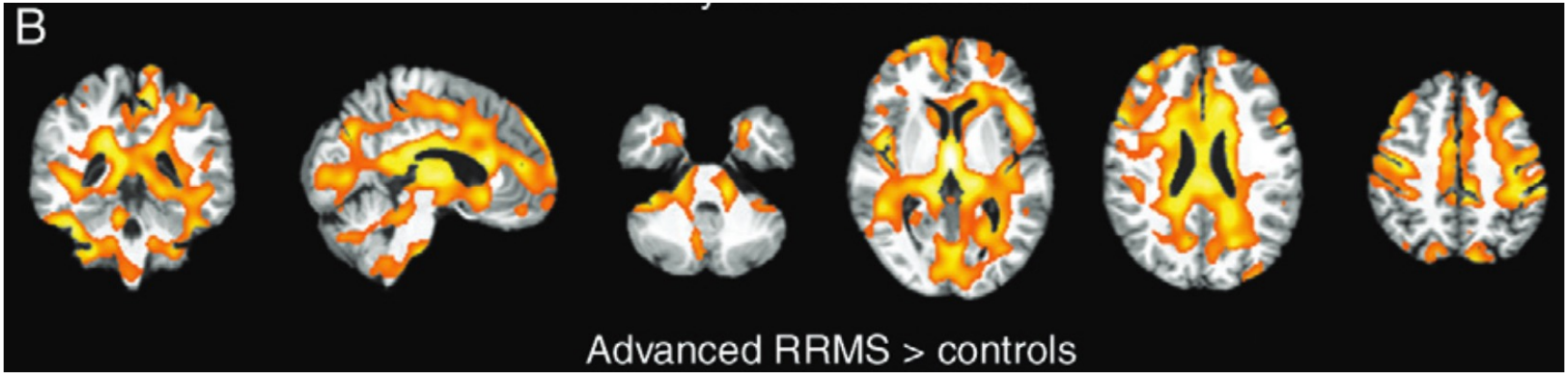

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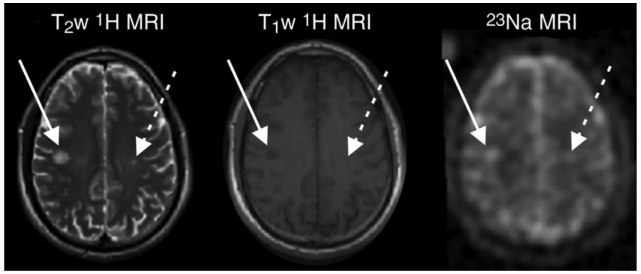

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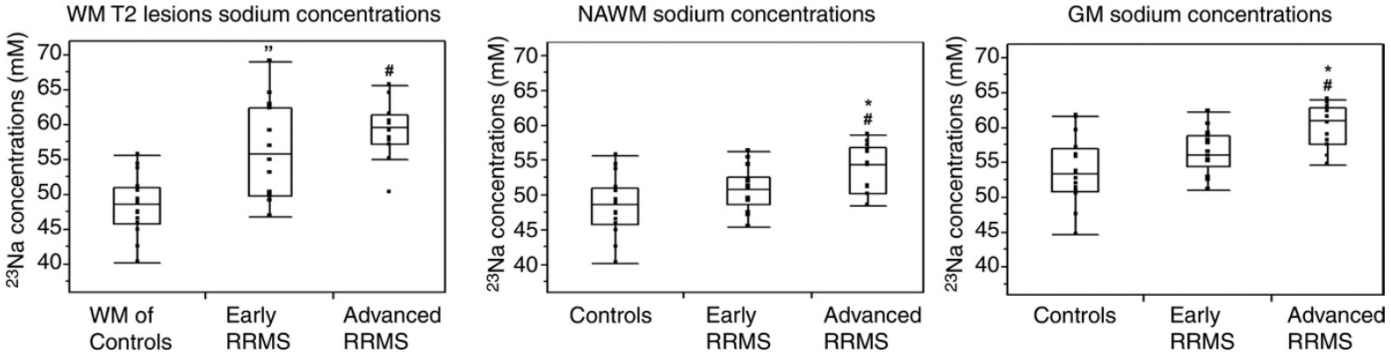
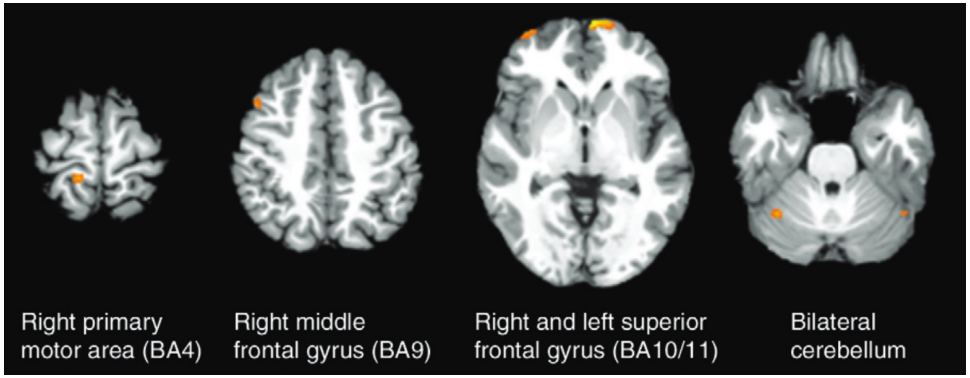


Correlations with EDSS



Sodium MRI in progressive Multiple Sclerosis

Magn Reson Mater Phy
DOI 10.1007/s10334-013-0396-1

RESEARCH ARTICLE

2013

Topography of brain sodium accumulation in progressive multiple sclerosis

Adil Maarouf · Bertrand Audoin · Simon Konstandin · Audrey Rico · Elisabeth Soulier · Françoise Reuter · Arnaud Le Troter · Sylviane Confort-Gouny · Patrick J. Cozzone · Maxime Guye · Lothar R. Schad · Jean Pelletier · Jean-Philippe Ranjeva · Wafaa Zaaraoui

	All patients (n = 20)	PPMS (n = 11)	SPMS (n = 9)
Age (years) Median [range]	47.5 [33–70]	48 [38–70]	47 [33–67]
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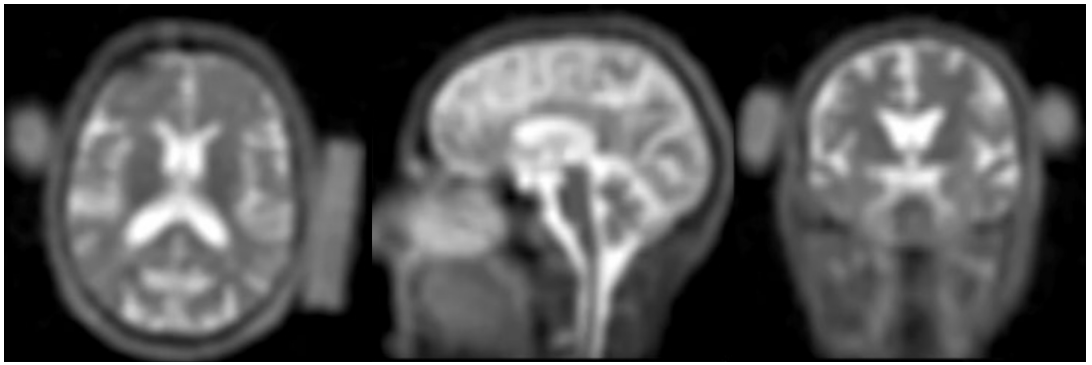

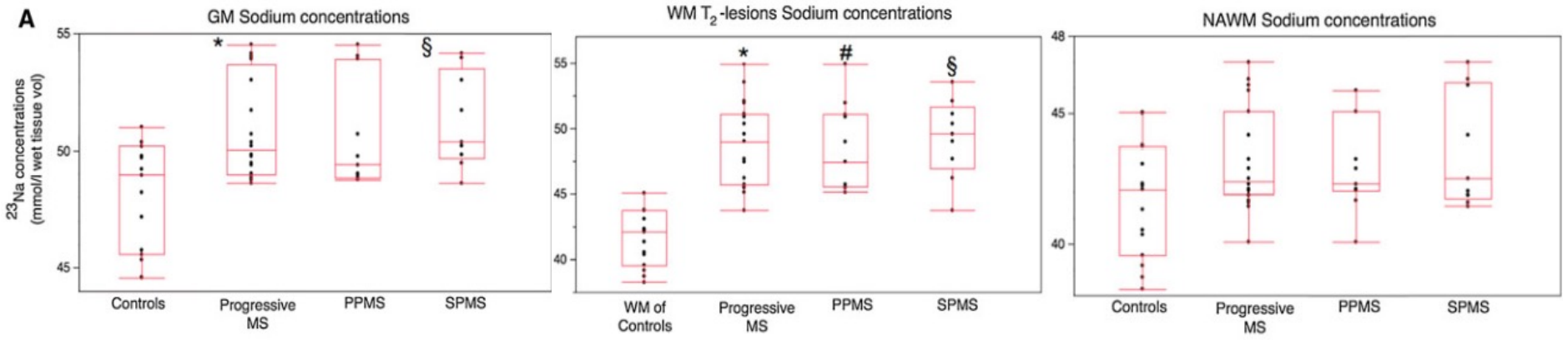

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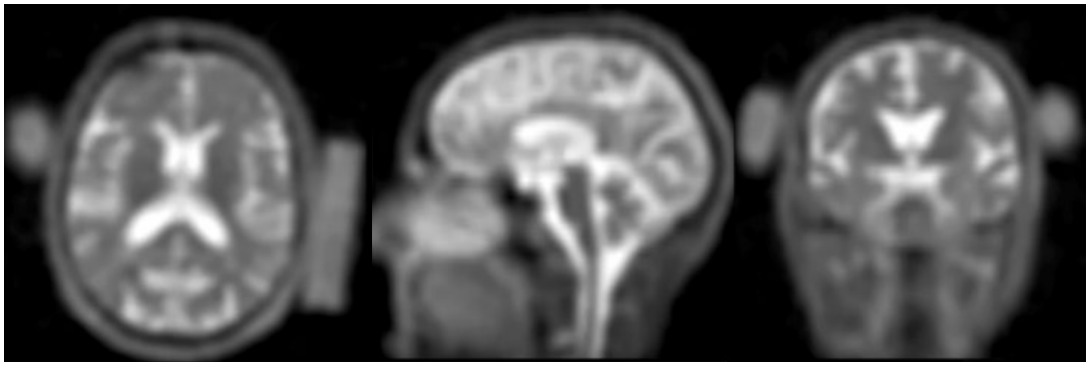

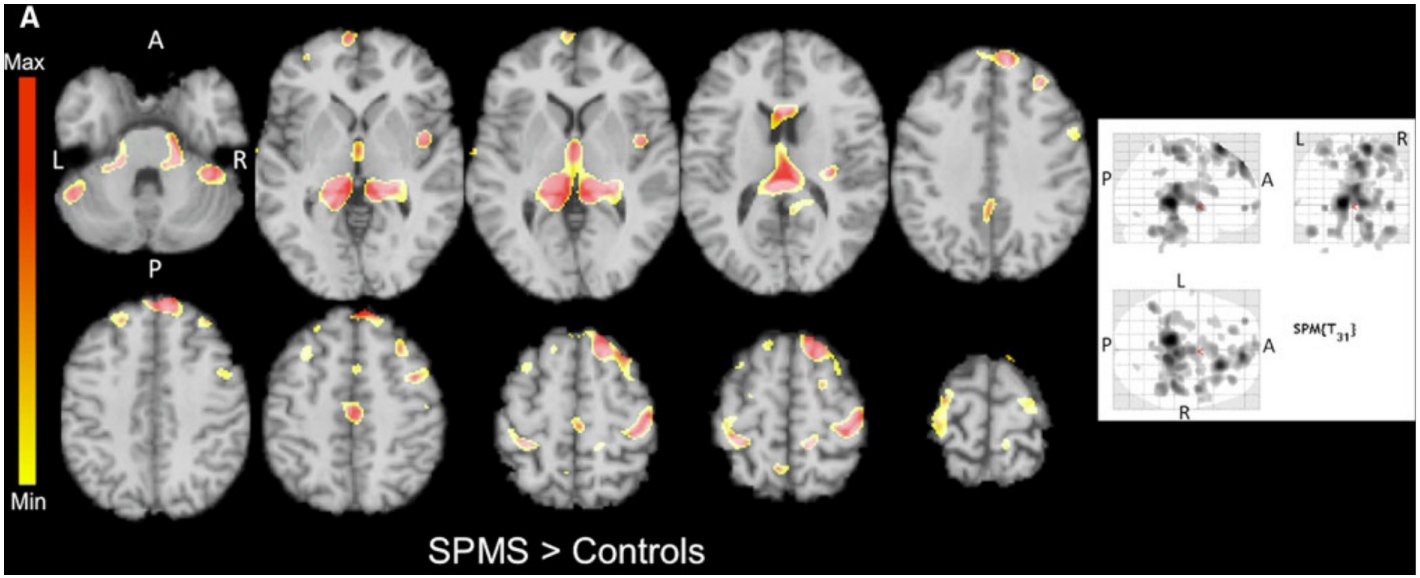

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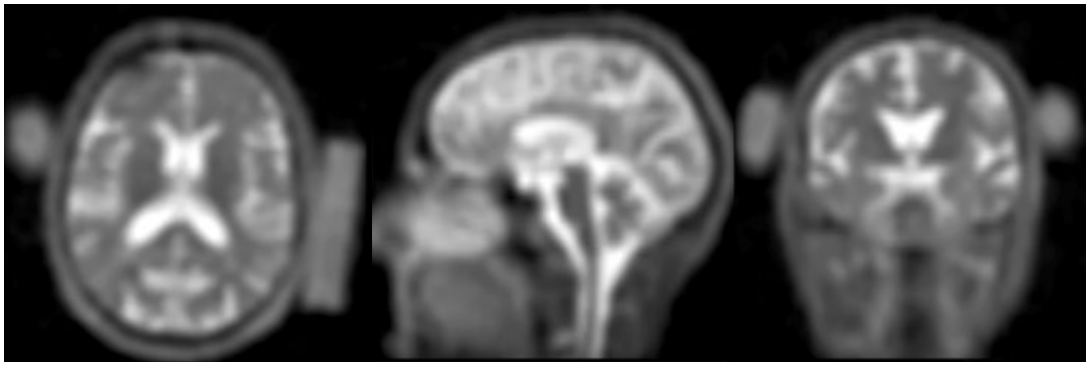

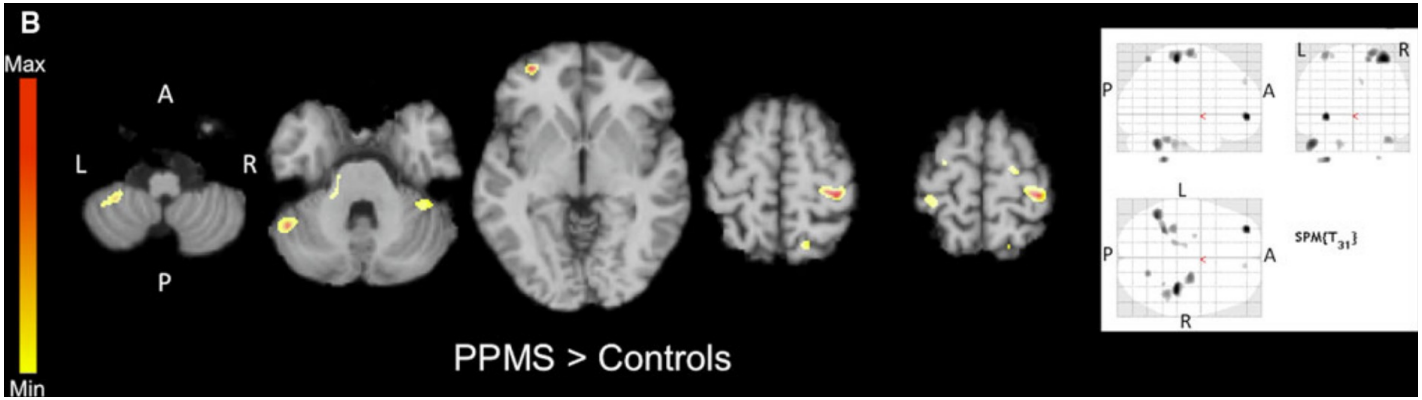

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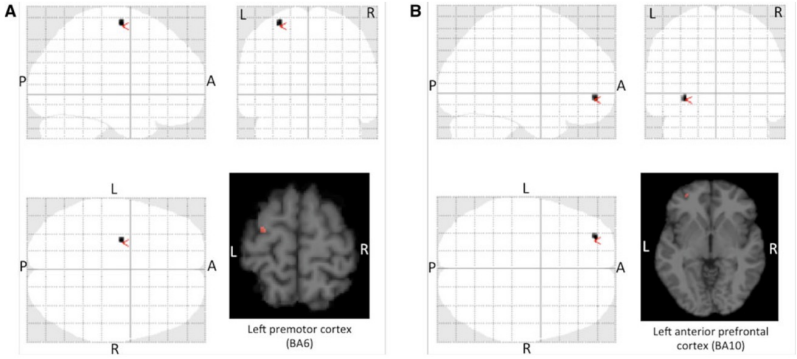
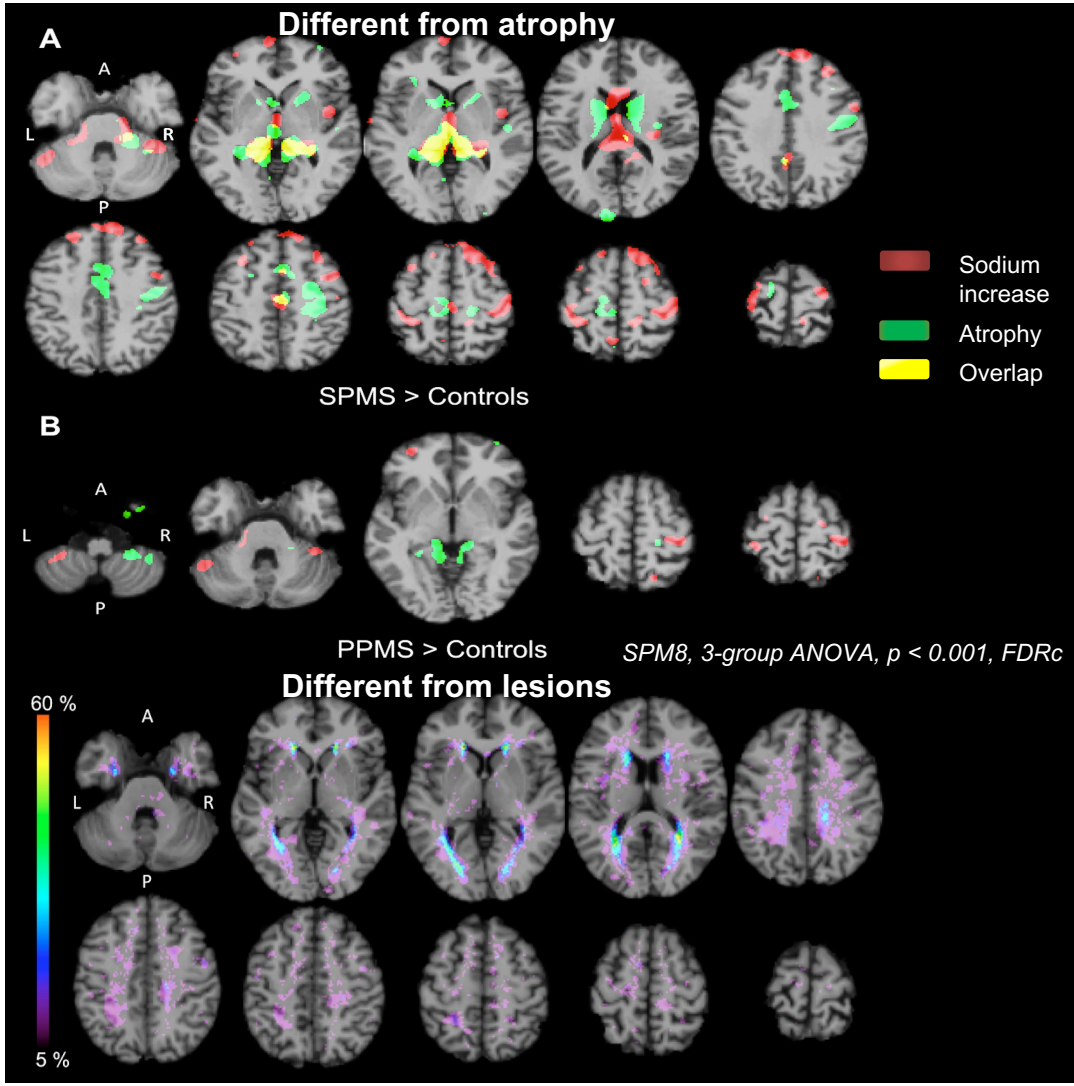


Clinical correlations



Sodium MRI and cognition in Multiple Sclerosis

Increased total sodium concentration in gray matter better explains cognition than atrophy in MS

2016

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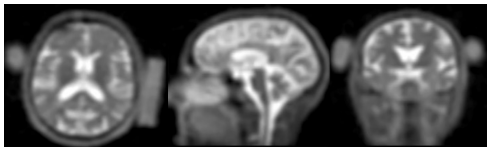

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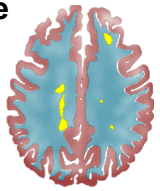
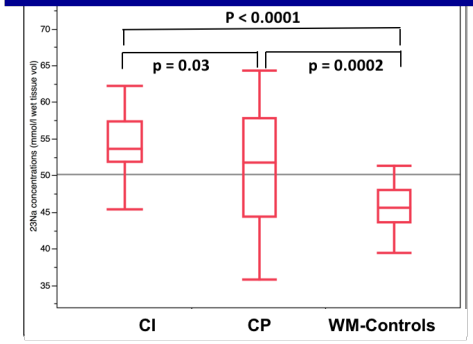
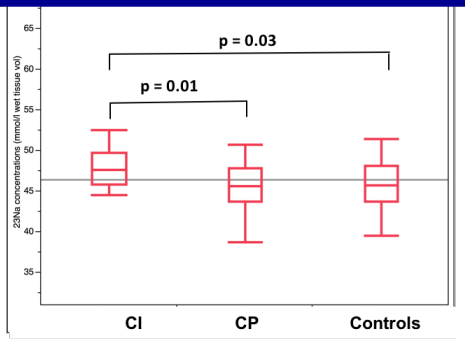


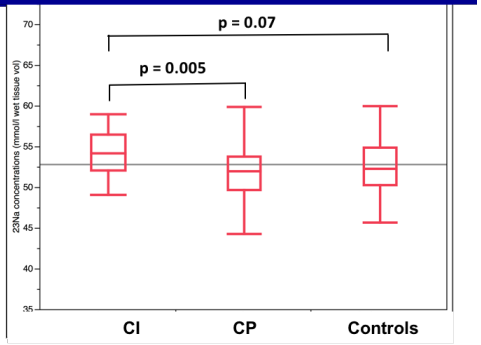
T2-lesions Sodium concentrations



NAWM Sodium concentrations



GM Sodium concentrations



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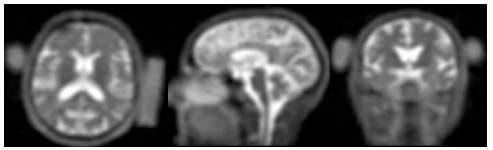

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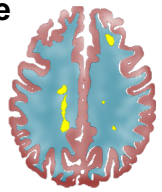

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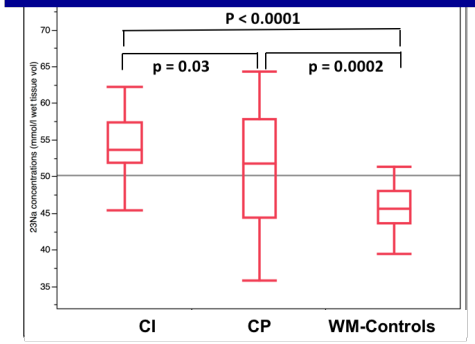

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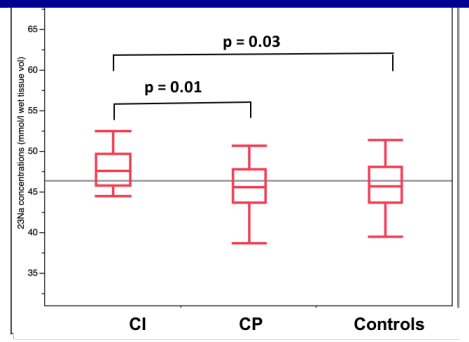

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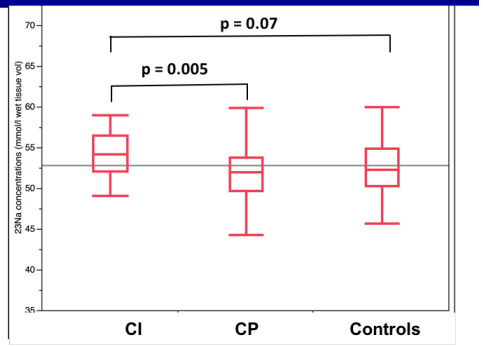

Stepwise regression model

- age
- disease duration
- GM sodium concentration
- NAWM sodium concentration
- GM fraction
- Brain parenchymal fraction

Sodium MRI and cognition in Multiple Sclerosis

CRMBM-CEMEREM UMR 7339

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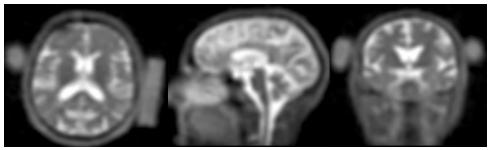

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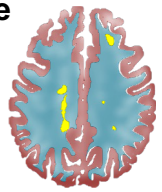
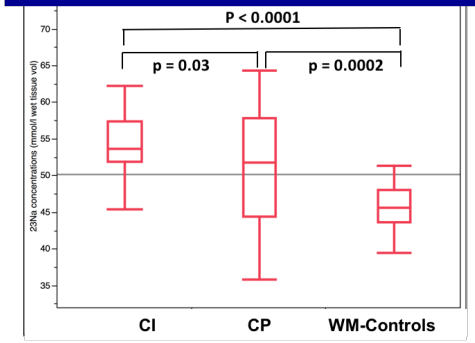
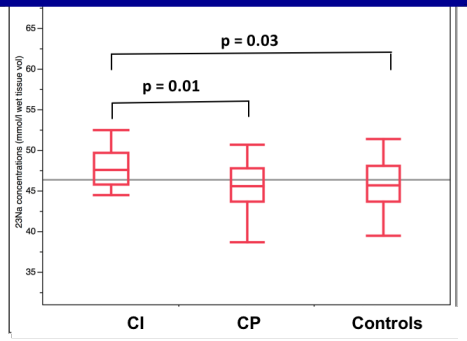


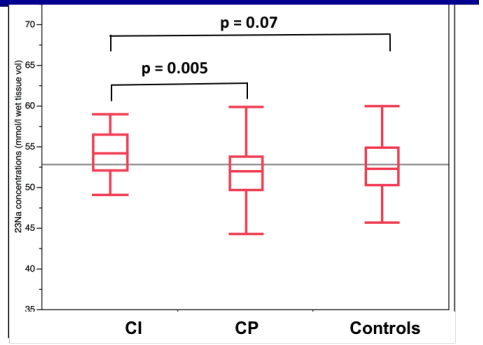
T2-lesions Sodium concentrations



NAWM Sodium concentrations



GM Sodium concentrations

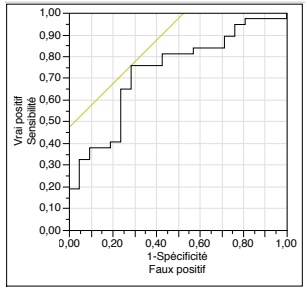


Stepwise regression model

- **age**
- ~~disease duration~~
- **GM sodium concentration**
- ~~NAWM sodium concentration~~
- ~~GM fraction~~
- ~~Brain parenchymal fraction~~

ROC analyses GM TSC

- Se = 76%
- Sp = 71%
- AUC = 0.73

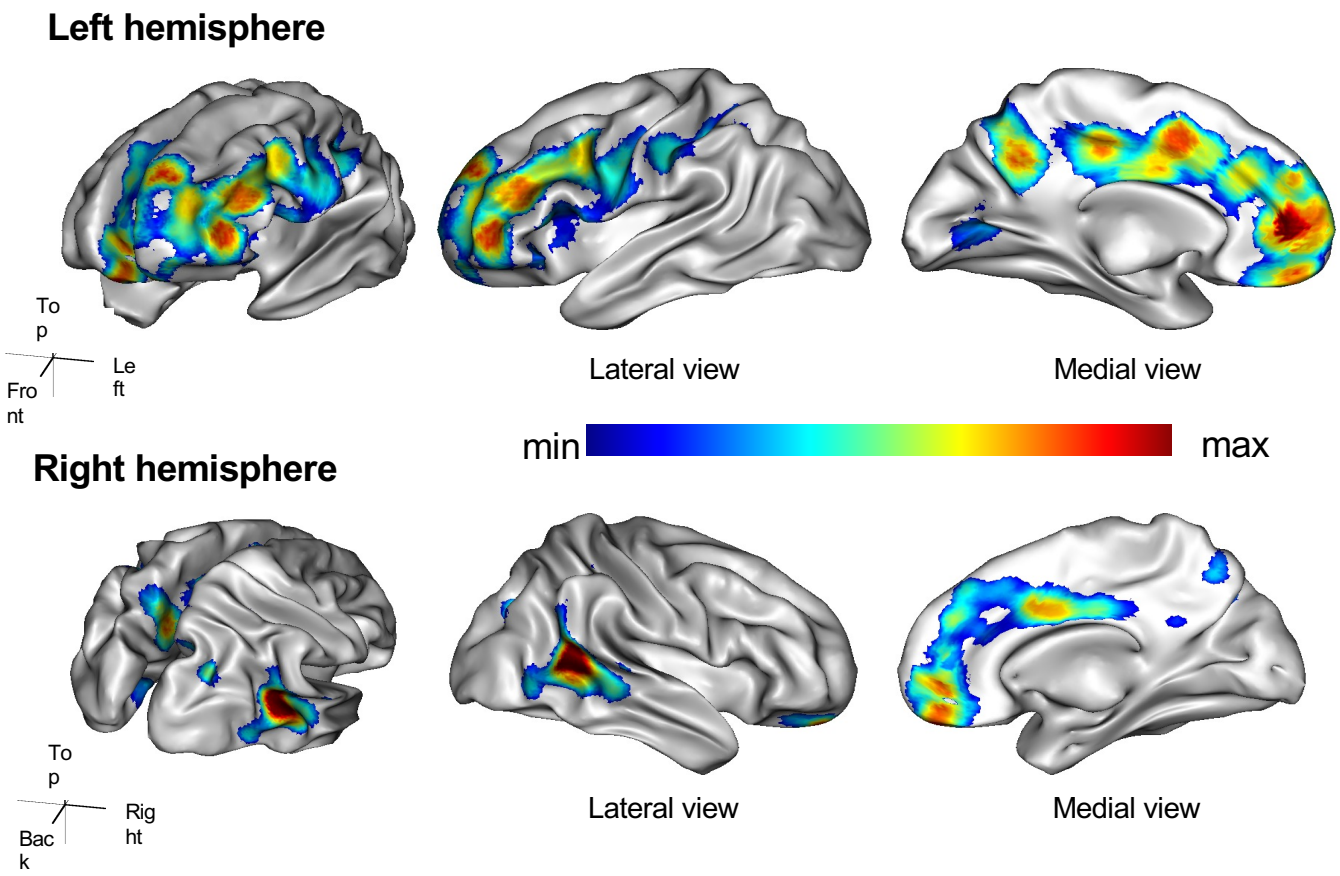


Sodium MRI and cognition in Multiple Sclerosis

Increased total sodium concentration in gray matter better explains cognition than atrophy in MS

2016

Adil Maarouf, MD
Bertrand Audoin, MD, PhD
Fanelly Pariollaud, PhD
Soraya Gherib, MSc
Audrey Rico, MD, PhD
Elisabeth Soulier
Sylviane Confort-Gouny, PhD
Maxime Guye, MD, PhD
Lothar Schad, PhD
Jean Pelletier, MD, PhD
Jean-Philippe Ranjeva, PhD
Wafaa Zaaraoui, PhD



Sodium MRI map at the individual level

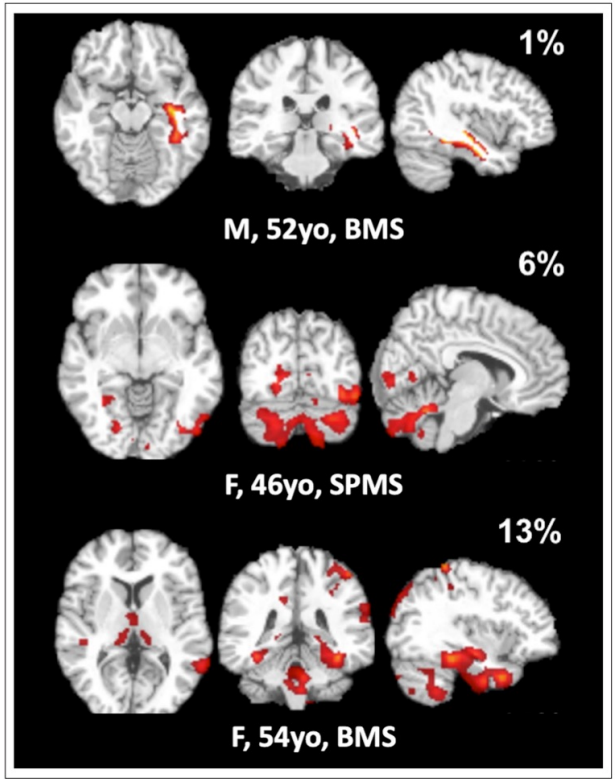
MULTIPLE SCLEROSIS JOURNAL MSJ 2022

Original Research Paper

Grey-matter sodium concentration as an individual marker of multiple sclerosis severity

Adil Maarouf, Bertrand Audoin, Soraya Gherib, Mohamed Mounir El Mendili, Patrick Viout, Fanelly Pariollaud, Clémence Boutière, Audrey Rico, Maxime Guye, Jean-Philippe Ranjeva, Wafaa Zaaraoui and Jean Pelletier

	BMS (n=21)	NBMS (n=25)	Healthy controls (n=56)	p-value (BMS vs NBMS)	p-value (BMS vs HC)	p-value (NBMS vs HC)
Age (years)	47.5 ± 8.1	46.7 ± 9.3	41.9 ± 12.9	0.86	0.22	0.21
Sex (F/M)	16/5	18/7	33/23	1	0.19	0.32
Clinical phenotype (Lublin and Reingold 1996)	21 BMS	16 RRMS 9 SPMS	n/a	n/a	n/a	n/a
Disease duration (years)	19.2 ± 5.6	18.3 ± 5.7	n/a	0.69	n/a	n/a
DMT	0	25	n/a	n/a	n/a	n/a



10 of 21 BMS (48%) and 19 of 25 NBMS (76%) patients showed GMSA (p = 0.05) affecting, respectively, 4.4 ± 9.6% of GM volume versus 5.4 ± 9.3%

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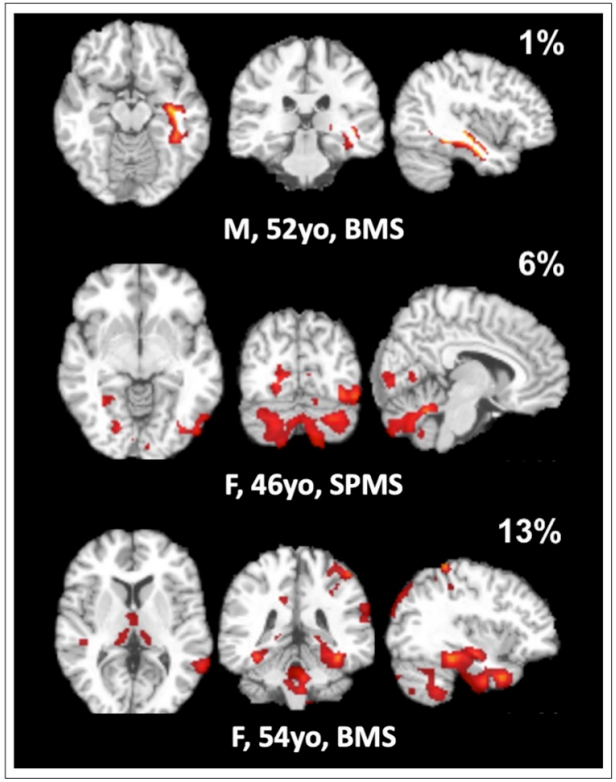

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	With GMSA (n=10)	Without GMSA (n=11)	p^a
Age (years)	46.2 ± 10.6	48.8 ± 5.0	0.75
Sex (F/M)	8/2	8/3	1
Cognitive impairment (Y/N)	5/5	2/9	0.14
Disease duration (years)	20.5 ± 7.5	18.1 ± 3.0	0.89
EDSS	1.6 ± 0.8	1.1 ± 0.5	**0.04**
MSFC	−0.09 ± 0.46	0.40 ± 0.23	**0.01**
T2LL (cm^3)	7.0 ± 2.8	3.6 ± 3.9	**0.01**
Cortical GM volume (cm^3)	579 ± 45	598 ± 26	0.17
Thalamic volume (cm^3)	13.6 ± 1.7	14.8 ± 0.9	**0.02**

	Odds ratio	Lower 95%	Upper 95%	p-value
(1) Parameters associated with BMS status, after stepwise regression				
Model				0.01
Thalamic volume	0.64	0.44	0.95	0.03
(2) Parameters associated with 'truly' BMS status, after stepwise regression				
Model				0.008
GMSA (no)	4.6	1.14	18.8	0.03
Thalamic volume	1.01	0.99	1.03	0.07

^{1}H MRSI & ^{23}Na MRI in MS

MULTIPLE SCLEROSIS JOURNAL | MSJ — 2017

Original Research Paper

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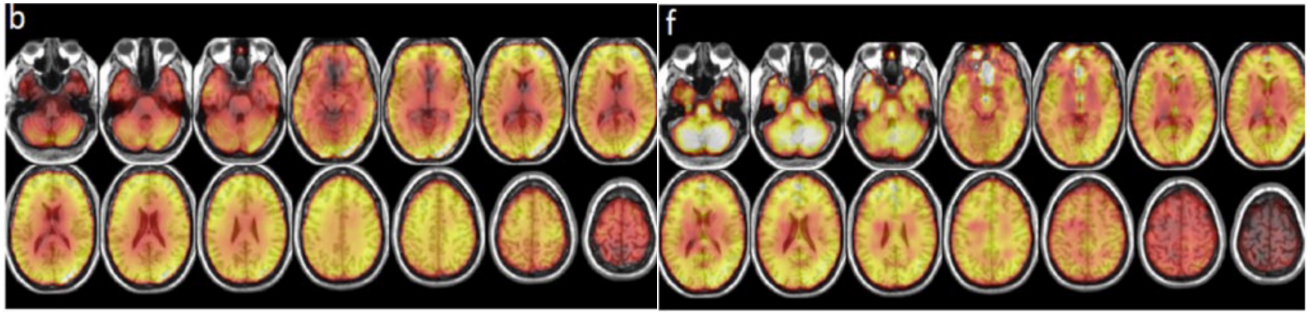

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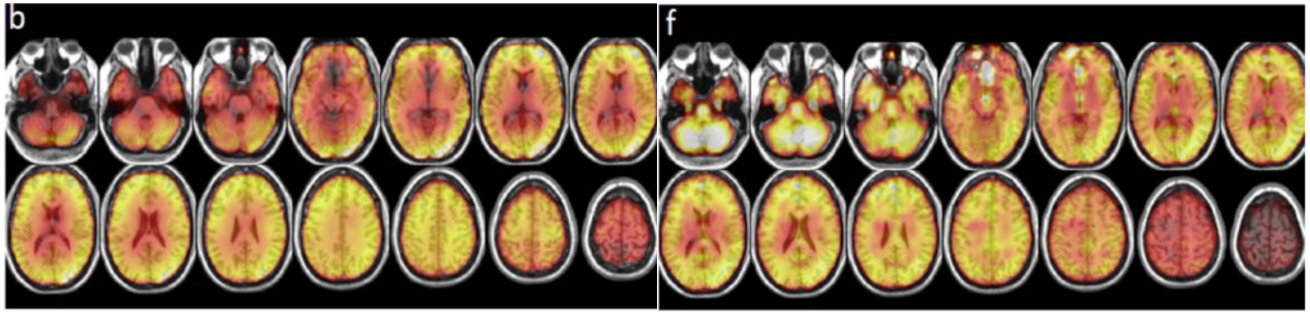

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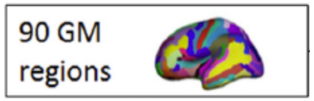

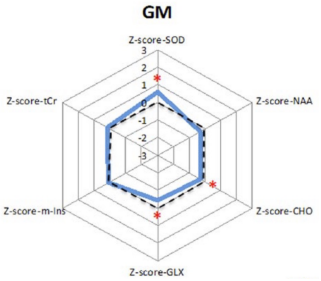

GM TSC and NAA
($\beta = -0.831$; adjusted r2 = 0.341, $p < 0.0032$)

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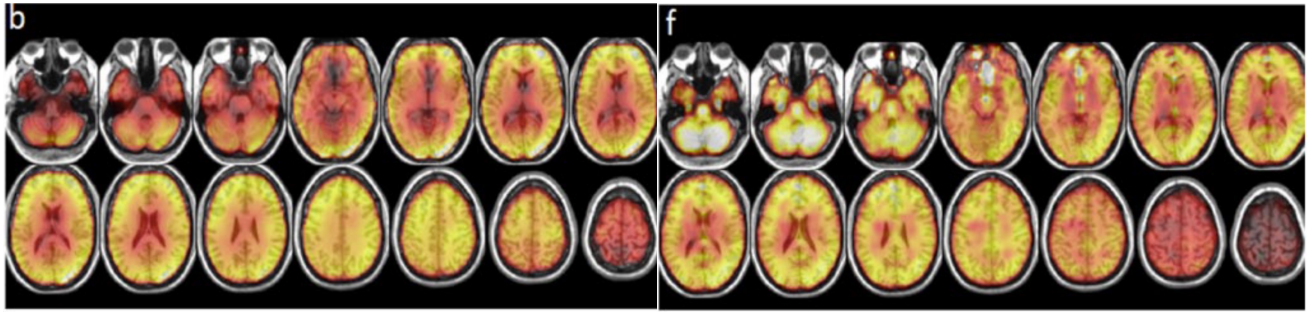

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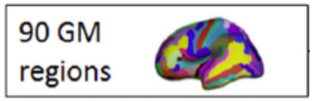

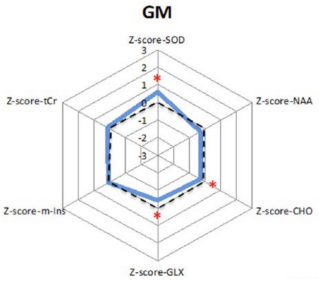

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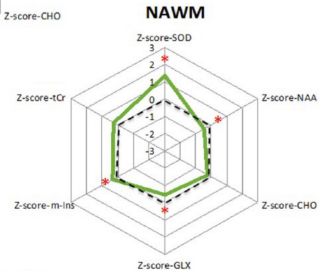

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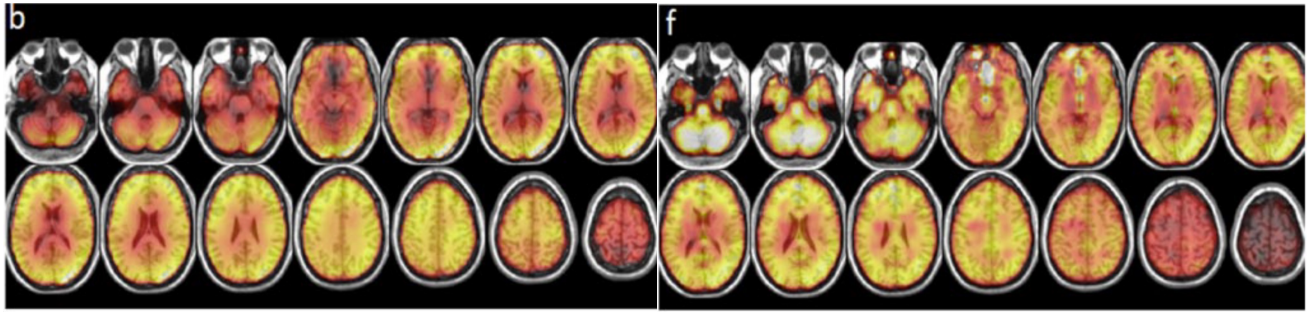

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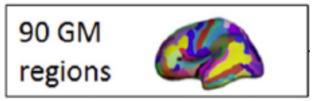
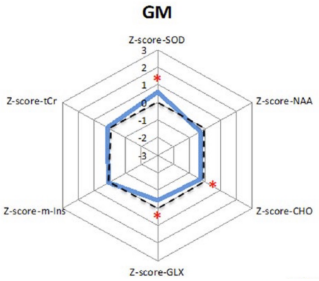
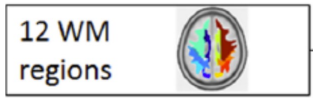
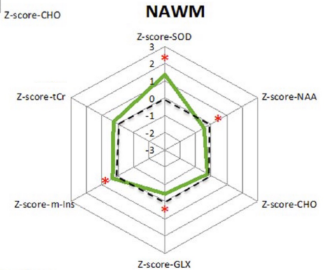




GM TSC and NAA
(β = −0.831; adjusted r2 = 0.341, p < 0.0032)





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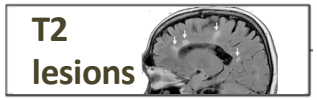
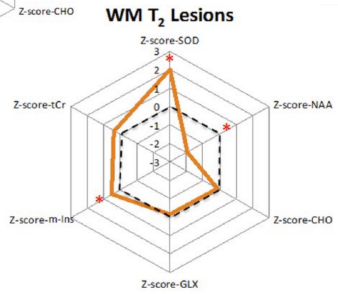




Lesions TSC and NAA (β = −1.261; p < 0.000)
Lesions TSC and m-Ins (β = −2.693; p = 0.0030)
Lesions TSC and tCr (β = 2.822; p = 0.0017)
adjusted r^2 = 0.574, p = 0.0005

Intracellular sodium MRI?

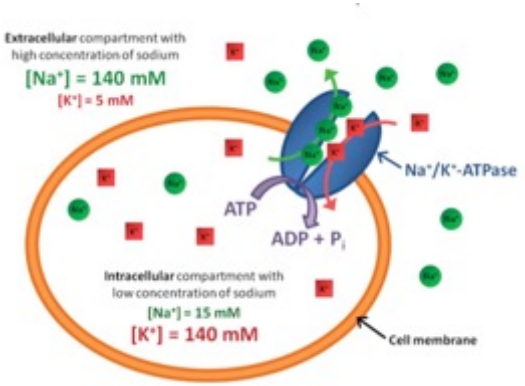
Total Sodium Concentration (TSC)

Intra-cellular (85% vol / [Na] ≈ 15mM)

Extra-cellular (12% vol / [Na] ≈ 140mM)

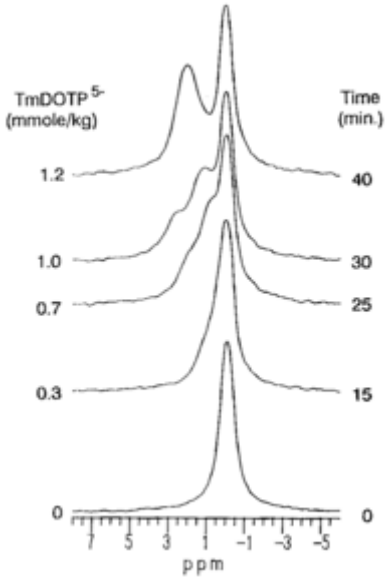
Vascular (3% vol / [Na] ≈ 140mM)

Thulborn et al, Radiology 1999



Intracellular sodium MRI?

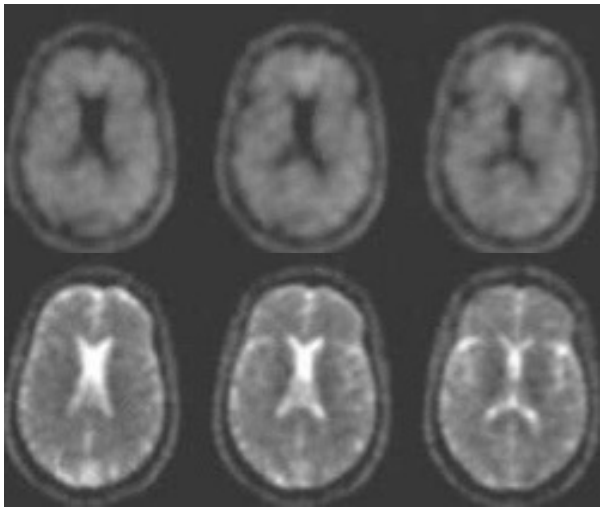
Toxic shift reagents



Bansal et al, JMRI 1992

Do not penetrate cell membrane
frequency offset in extracellular space

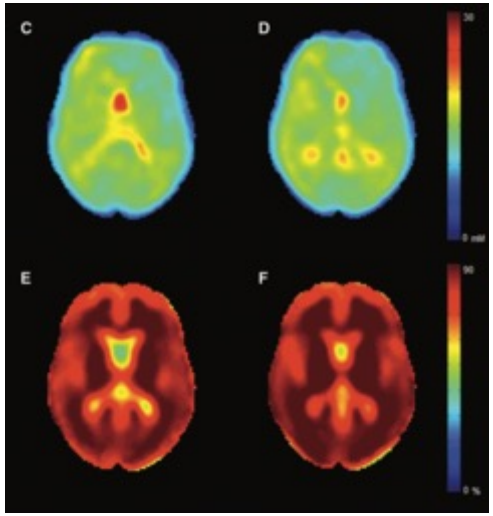
Inversion Recovery



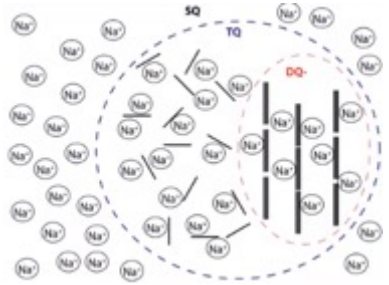
Stobbe, Beaulieu, MRM 2005

Suppression of ^{23}Na signal from CSF

Triple Quantum Filtering



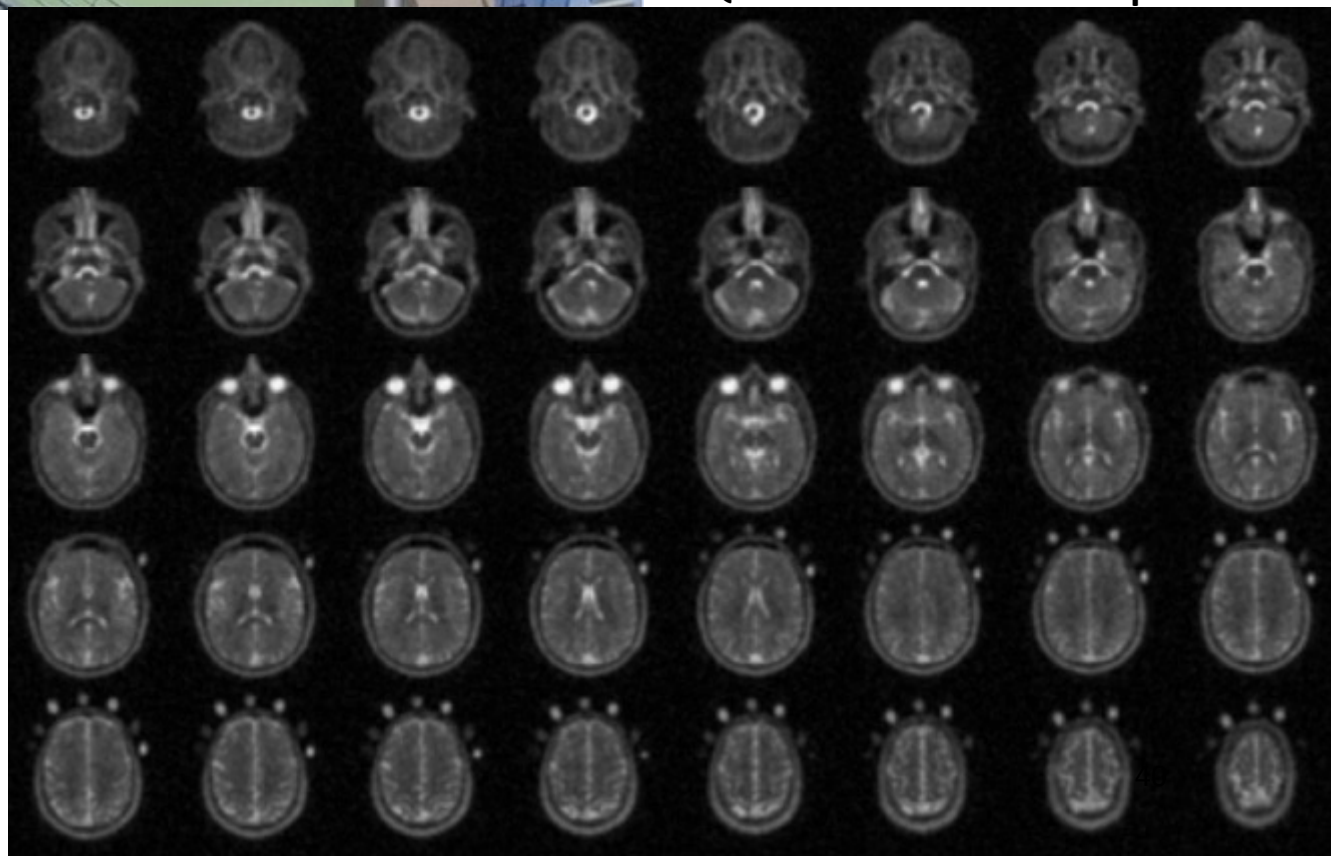
Petracca et al, Brain 2016



Intracellular sodium MRI: multi-echo approach

7T MRI in Marseille Hospital
CRMBM-CEMEREM

Quantitative sodium maps at 7T



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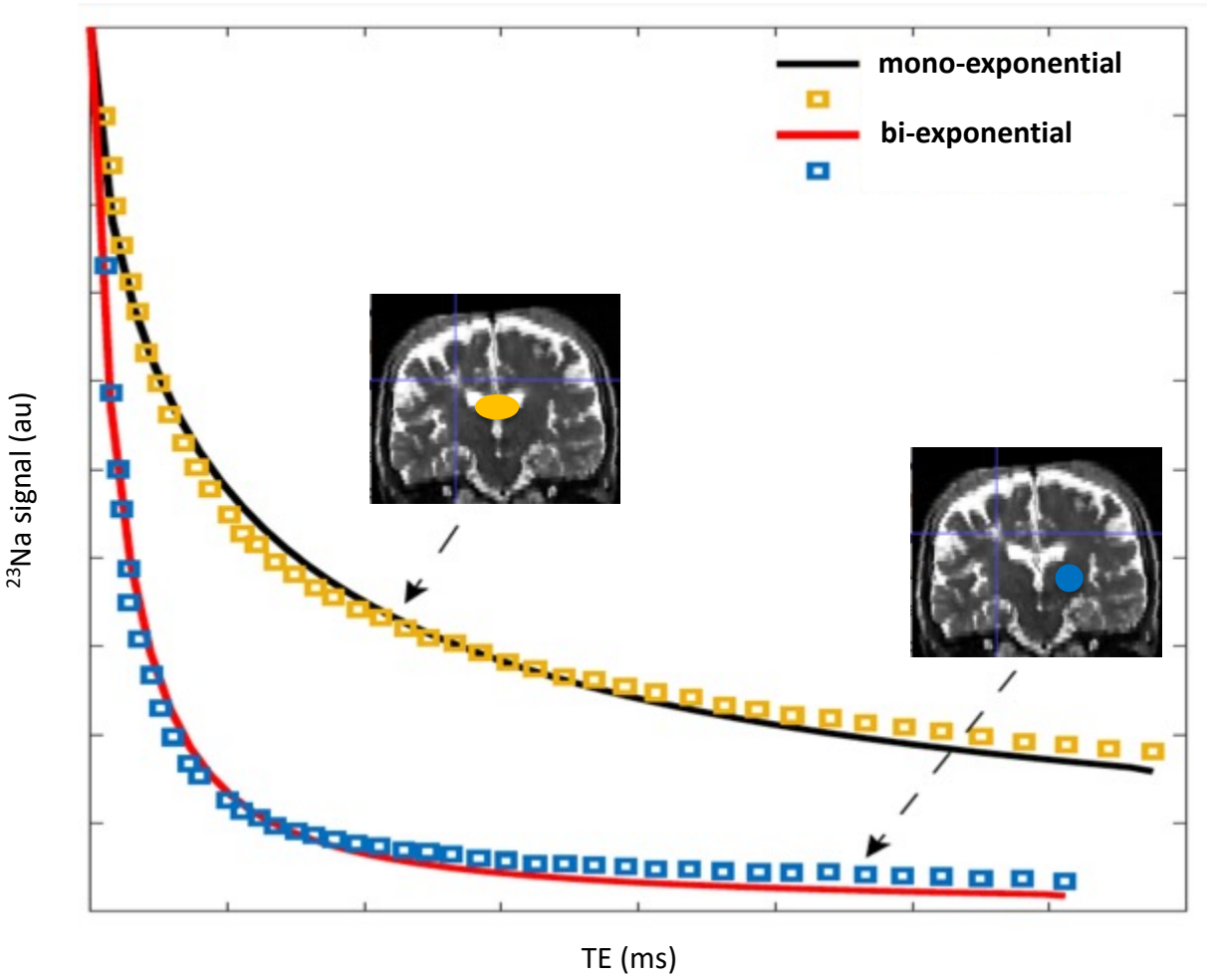
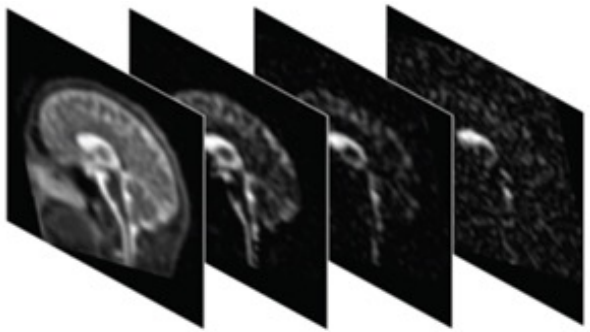
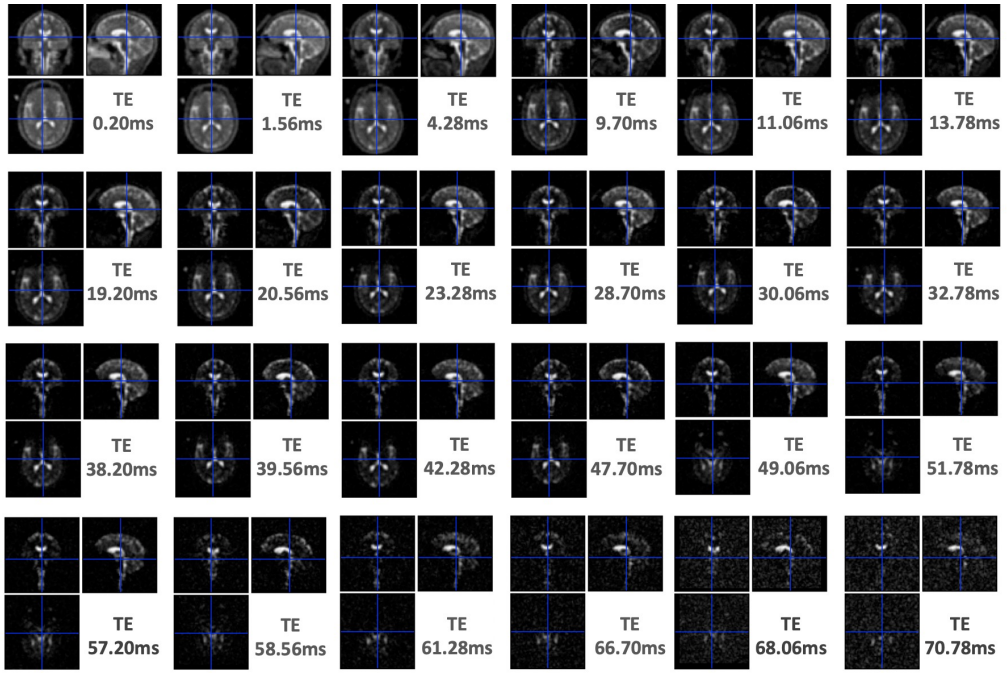


Multi-echoes quantitative sodium MRI at 7T

Acquisition of 3D DA radial ^{23}Na MRI at 24 TE (0.2 - 71 ms)



TR=100ms
resolution $(3mm)^3$
8 TE per run (3 runs)
TA= 3 x 10 min



Ridley et al, Sci Reports 2018; El Mendili et al, ISMRM 2022

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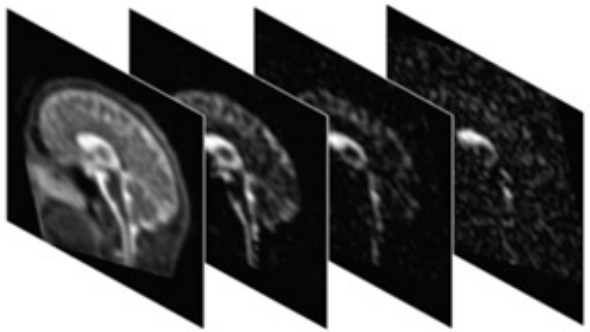
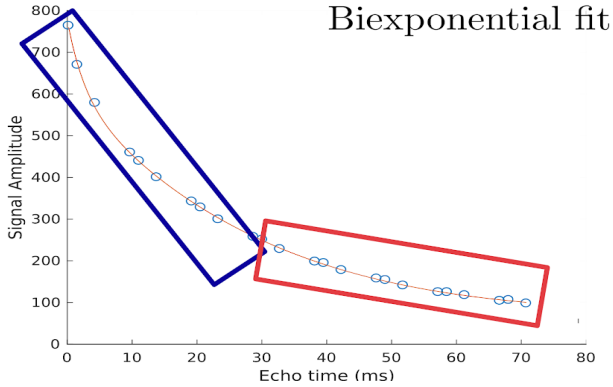


Realignment

Biexponential fit

$$Signal = \sqrt{\left[A^2\left(f \cdot e^{\frac{-TE}{T2^*_{short}}} + (1-f)\cdot e^{\frac{-TE}{T2^*_{long}}}\right)^2 + Ric^2\right]}$$

Biexponential fit



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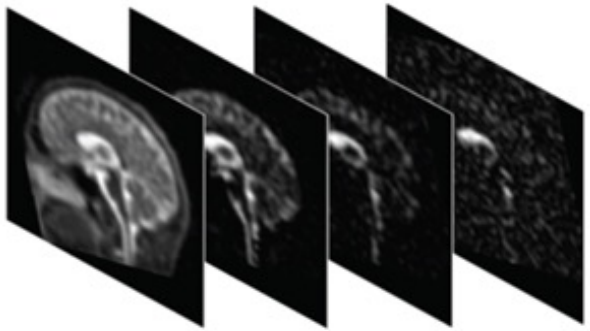

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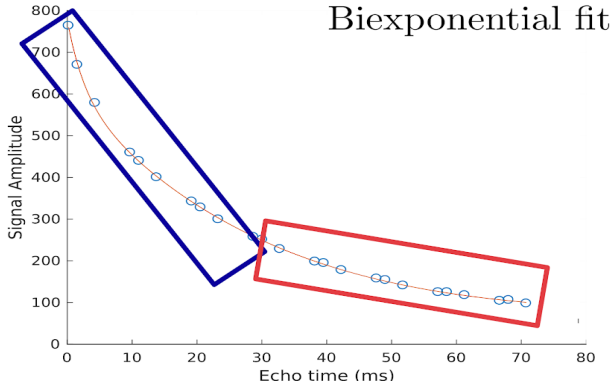

$T_2^*_{short}$ $T_2^*_{long}$

$M_{0\ short}$ $M_{0\ long}$

Fraction f = $\frac{\blacksquare}{\blacksquare + \blacksquare}$

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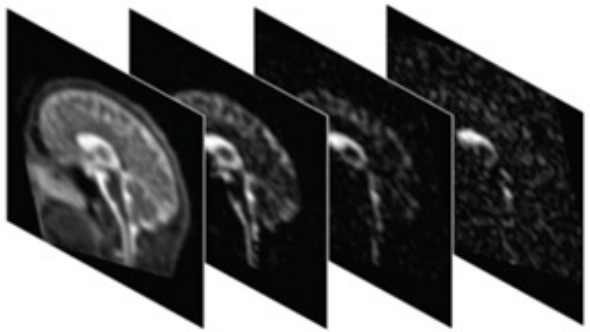
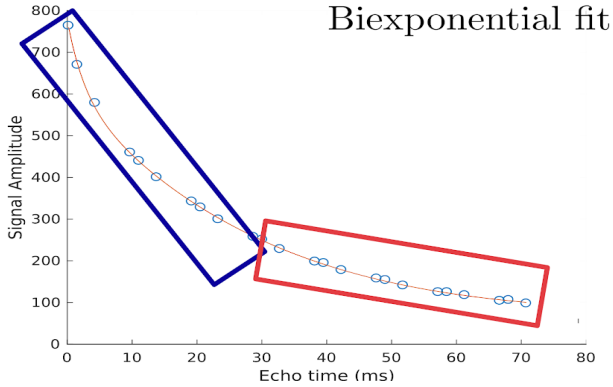


Realignment

Biexponential fit

$$Signal = \sqrt{\left[A^2\left(f \cdot e^{\frac{-TE}{T2^*_{short}}} + (1-f)\cdot e^{\frac{-TE}{T2^*_{long}}}\right)^2 + Ric^2\right]}$$

Biexponential fit

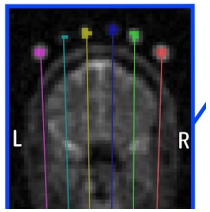


$T_2^*_{short}$ $T_2^*_{long}$

$M_{0\ short}$ $M_{0\ long}$

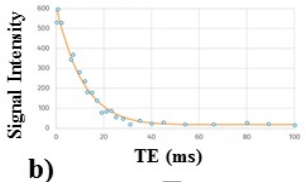
External tubes for quantification

6 tubes of known ^{23}Na mM included in ^{23}Na acquisition



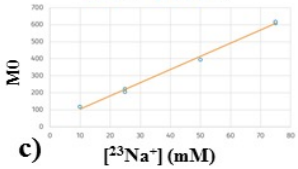
Calculation of M0 and T2* values for each tube

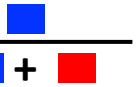
$\sqrt{[(M0 * e^{-x/T2})^2 + R^2]}$



Calculation of Na concentrations via their M0 value

$M0 = a * [Na^+] + b$

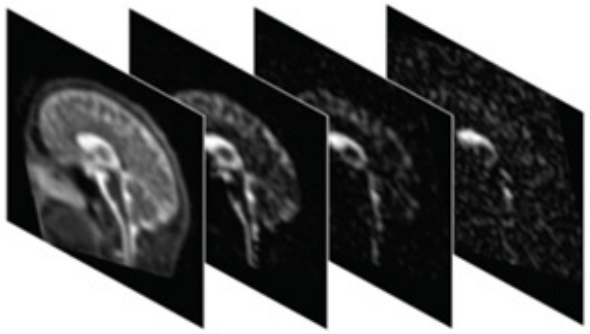


Fraction f = 

Ridley et al, Sci Reports 2018; El Mendili et al, ISMRM 2022

Multi-echoes quantitative sodium MRI at 7T

Acquisition of 3D DA radial ^{23}Na MRI at 24 TE (0.2 - 71 ms)

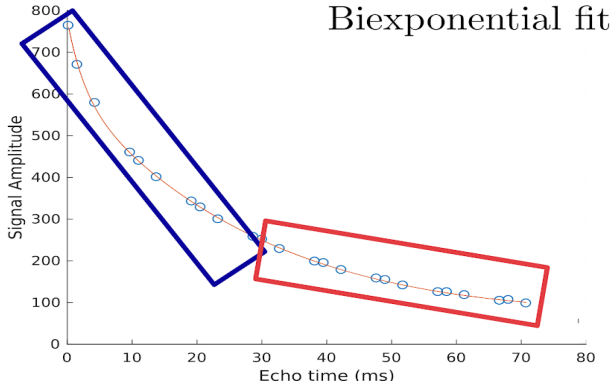


Realignment

Biexponential fit

$$Signal = \sqrt{\left[A^2\left(f\cdot e^{\frac{-TE}{T2^*_{short}}} + (1-f)\cdot e^{\frac{-TE}{T2^*_{long}}}\right)^2 + Ric^2\right]}$$

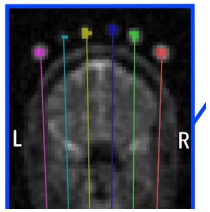
Biexponential fit



$T_2^*_{short}$ $T_2^*_{long}$

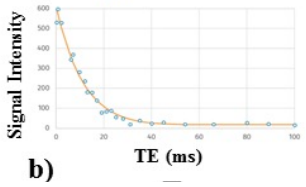
External tubes for quantification

6 tubes of known ^{23}Na mM included in ^{23}Na acquisition



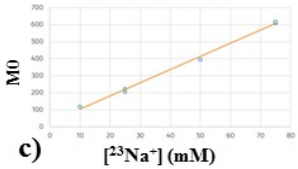
Calculation of M0 and T2* values for each tube

$\sqrt{[(M0*e^{-x/T2})^2 + R^2]}$



Calculation of Na concentrations via their M0 value

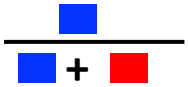
$M0=a*[Na^+]+b$



Signal Calibration

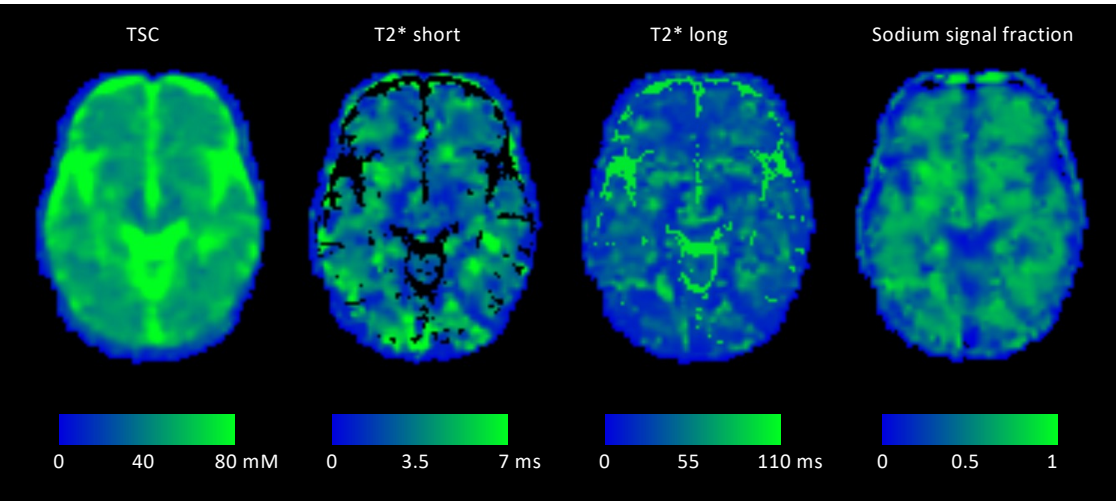
$M_{0\ short}$ + $M_{0\ long}$

TSC map

Fraction f = 

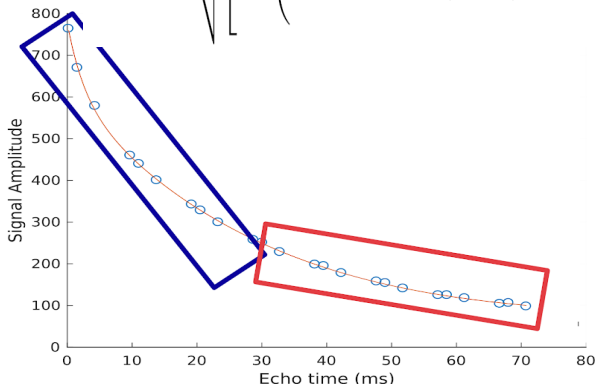
Ridley et al, Sci Reports 2018; El Mendili et al, ISMRM 2022

Multi-echoes quantitative sodium MRI at 7T



Biexponential fit

$$Signal = \sqrt{\left[A^2\left(f \cdot e^{\frac{-TE}{T2^*_{short}}} + (1-f) \cdot e^{\frac{-TE}{T2^*_{long}}}\right)^2 + Ric^2\right]}$$



$T_2^*_{short}$ $T_2^*_{long}$

TSC map

Fraction f = $\frac{\blacksquare}{\blacksquare + \blacksquare}$

Ridley et al, Sci Reports 2018; El Mendili et al, ISMRM 2022

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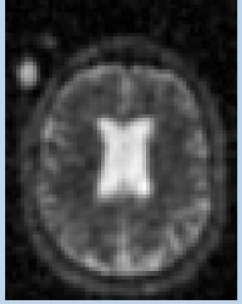
Preprocessing



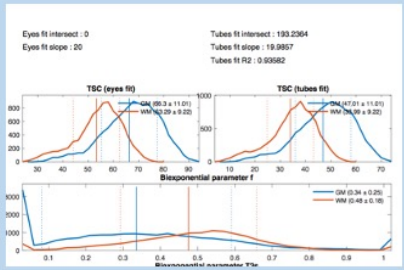
raw sodium data

- Dicom to nifti conversion
- Denoising
- Coregistration to TE1
- Coregistration to Template

Outcomes

ID	Region	TSC_mean	TSC_std	TSC_Echo1_mean	TSC_Echo1_std	f_mean
fk-p78-sla	GM	58.00267	14.10713	63.57450	15.37838	0.39702
fk-p78-sla	WM	46.01339	8.81320	50.62871	9.62027	0.56955
bp-p76-sla	GM	55.36221	18.31782	62.18944	19.23889	0.37968
bp-p76-sla	WM	42.67240	11.77428	48.92050	12.33854	0.53100
mb-p82-sla	GM	51.99299	12.70317	53.96410	13.18521	0.45714
mb-p82-sla	WM	40.92307	7.85973	42.44132	7.91537	0.60189
rc-p30-sla	GM	70.64067	24.78451	76.22250	25.87252	0.42340
rc-p30-sla	WM	60.11698	15.82429	65.32271	16.38711	0.48156
md-p07-sla	GM	55.13308	14.94600	55.57896	14.55260	0.47525
md-p07-sla	WM	42.20480	8.75285	42.86222	8.26481	0.64170
jq-p68-sla	GM	59.98918	17.73103	61.65391	17.64236	0.39829
jq-p68-sla	WM	46.51482	9.55035	48.17487	9.46149	0.59663
cm-p69-sla	GM	94.36528	24.09385	91.68832	22.20940	0.40306
cm-p69-sla	WM	74.74247	16.50211	71.55482	12.73405	0.48245
sc-p88-sla	GM	116.82806	26.78796	1004.91420	260.69494	0.44247
sc-p88-sla	WM	108.43985	22.38084	935.95042	223.51966	0.55269
mz-p75-sla	GM	90.96900	15.41616	79.54412	14.58266	0.39340
mz-p75-sla	WM	76.80956	9.81481	66.16410	9.21659	0.59084

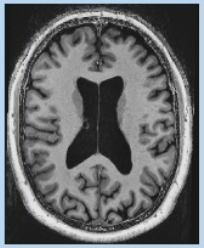
csv table



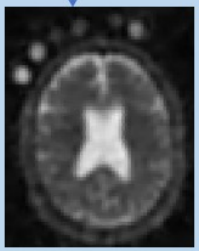
pdf quality control

- data extraction
- quality controls

Segmentation



preprocessed T1



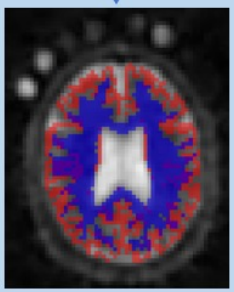
rdNa01-24

whole brain extraction

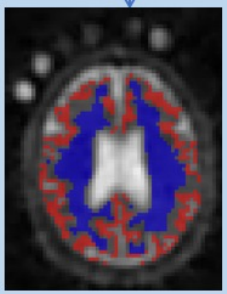
GM & WM segmentation

registration

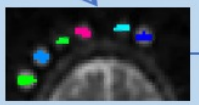
manual or automated segmentation



GM & WM (T1)

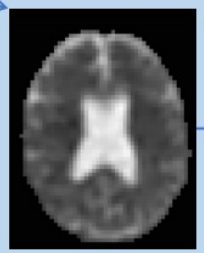


GM & WM (Na)



tubes mask

eyeballs mask

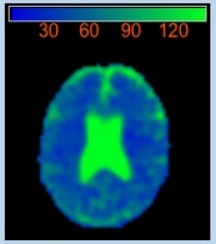


mrdNa01-24

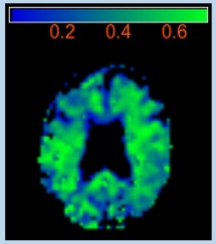
biexponential fit

monoexponential & linear fit

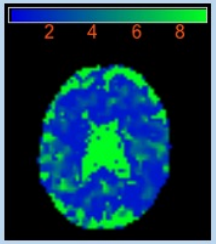
exponential fitting & maps generation



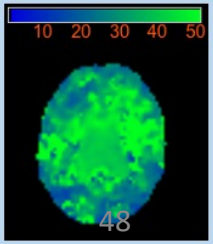
TSC map



f map



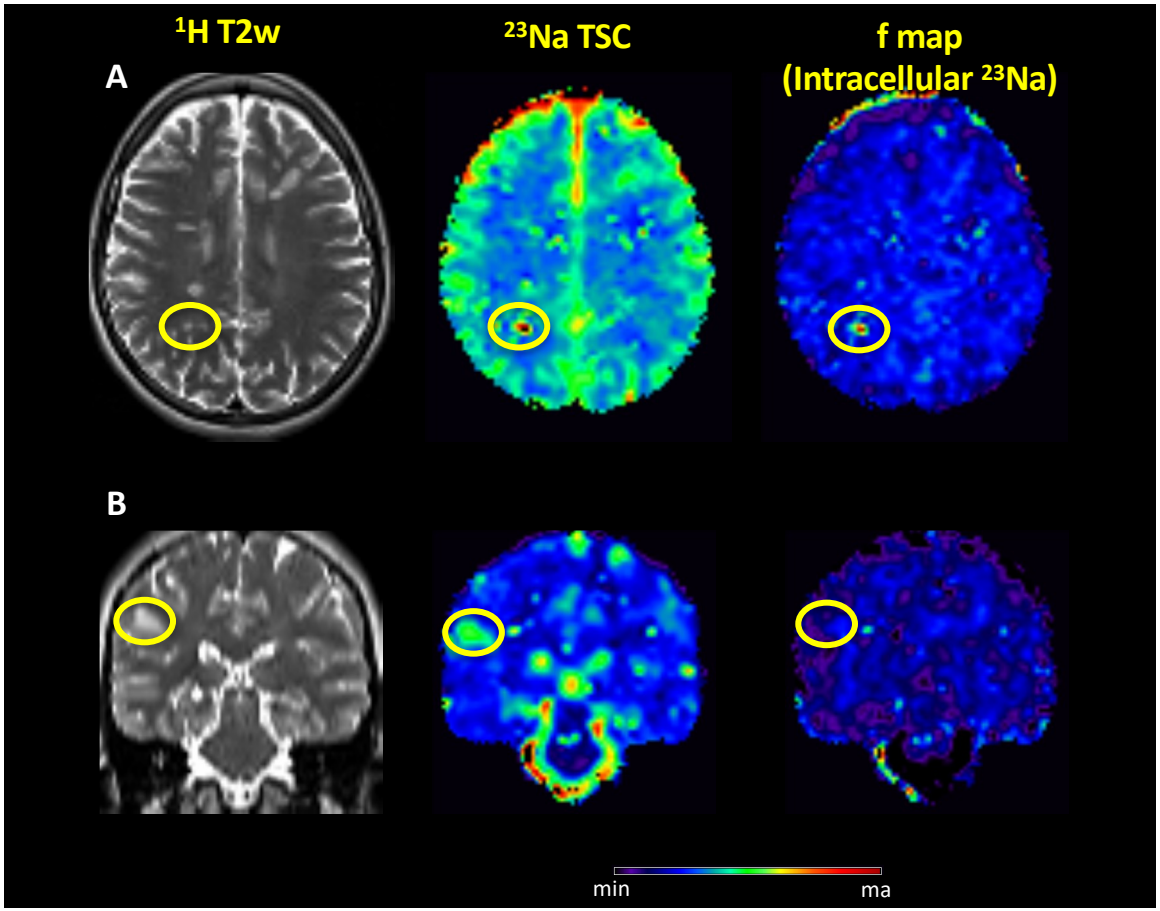
T2s map



T2l map

Multi-echoes ^{23}Na MRI at 7T: preliminary results in MS

	MS-CR Complete Recovery: EDSS=0	MS-PR Partial recovery: EDSS>0	HC
Number	19	14	25
Age (years)	31.68 ± 8.14	27.79 ± 6.44	31.92 ± 9.08
Gender	15F/4M	13F/1M	17F/8M
DD (years)	1.32 ± 1.32	1.55 ± 1.50	-
EDSS median [range]	0	1 [1-3]	-
T2-LL (ml)	1.91 ± 2.38	4.71 ± 4.88	-



El Mendili et al, ISMRM 2022
El Mendili et al, in preparation

Multi-echoes ^{23}Na MRI at 7T: preliminary results in MS

Expected Benefits in MS

Assessing lesion activity and neurodegeneration

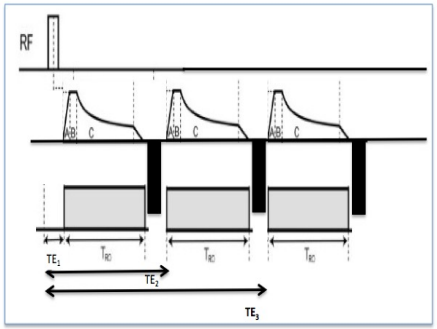
				p-value		
	Complete Recovery (CR)	Partial Recovery (PR)	Healthy Controls (HC)	CR vs PR	CR vs HC	PR vs HC
TSC (mM)						
GM	51.09 ± 4.80	49.73 ± 5.21	50.07 ± 4.15	0.460	0.460	0.832
NAWM	42.78 ± 5.92	41.48 ± 6.30	41.37 ± 3.69	0.563	0.342	0.944
T2-lesions	50.70 ± 7.78	51.17 ± 7.23	"	0.650	**<0.001**	**< 0.001**
Signal fraction						
GM	0.471 ± 0.021	0.468 ± 0.047	0.464 ± 0.028	0.851	0.408	0.726
NAWM	0.579 ± 0.010	0.563 ± 0.019	0.574 ± 0.011	**0.006**	0.154	**0.030**
T2-lesions	0.571 ± 0.091	0.497 ± 0.085	"	**0.042**	0.860	**< 0.001**
T1-RT (ms)						
GM	1899.1 ± 31.7	1870.5 ± 137.0	1887.3 ± 43.5	0.398	0.333	0.577
NAWM	1304.0 ± 32.3	1341.4 ± 88.8	1277.7 ± 30.9	0.111	**0.010**	**0.003**
T2-lesions	1663.4 ± 146.9	1747.4 ± 160.3	"	0.150	**<0.001**	**<0.001**
FA						
NAWM	0.419 ± 0.024	0.426 ± 0.022	0.437 ± 0.012	0.432	**0.002**	**0.037**
T2-lesions	0.354 ± 0.031	0.334 ± 0.029	"	0.092	**<0.001**	**<0.001**
MD[#]						
NAWM	5.315 ± 0.271	5.411 ± 0.225	5.178 ± 0.124	0.315	**0.032**	**<0.001**
T2-lesions	6.652 ± 0.677	7.201 ± 0.699	"	**0.043**	**<0.001**	**<0.001**

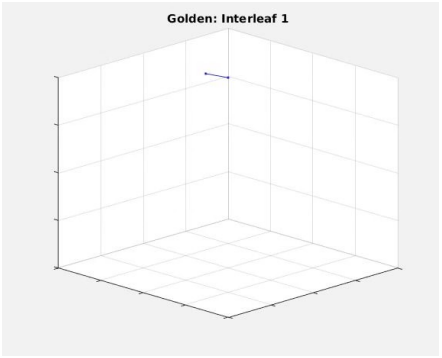
Values are expressed in mean ± SD. FA, fractional anisotropy; GM, grey matter; NAWM, normal appearing white matter; MD, mean diffusivity, TSC, total sodium concentration.
[+]General linear model. " T2-lesions in MS patients were compared with NAWM in HC. [#] $\times 10^{-4}$ mm^2/s.

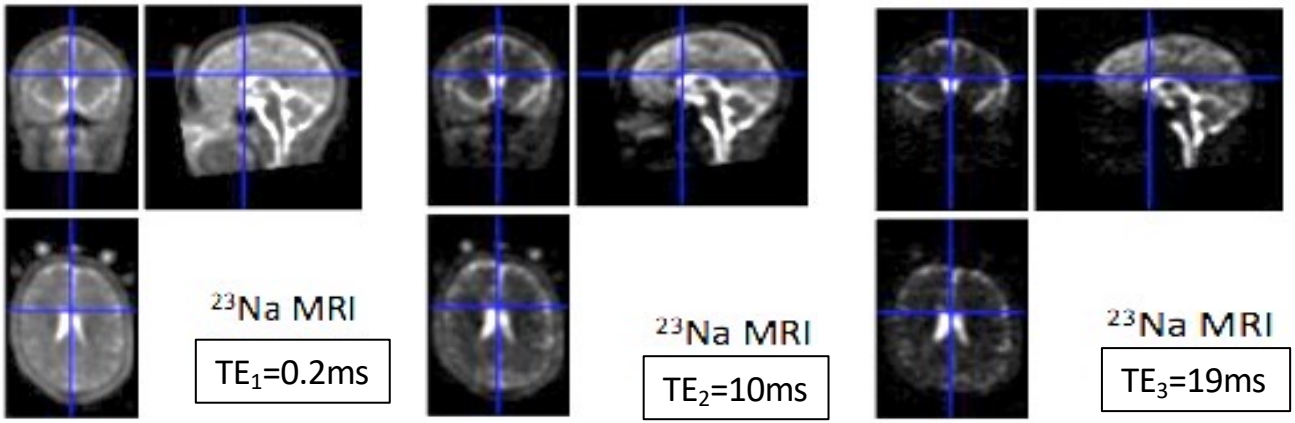
Better discrimination between Complete Recovery and Partial Recovery patients using **f**

El Mendili et al, ISMRM 2022
El Mendili et al, in preparation

Dynamic multi-echoes sodium MRI





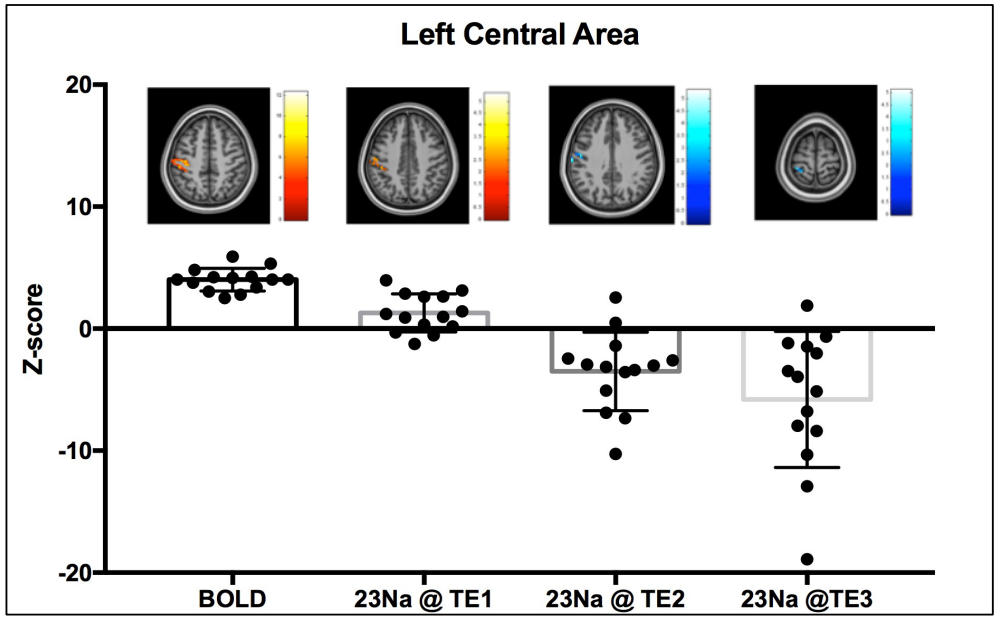


Bydder et al, Neuroimage 2018

Dynamic multi-echoes sodium MRI

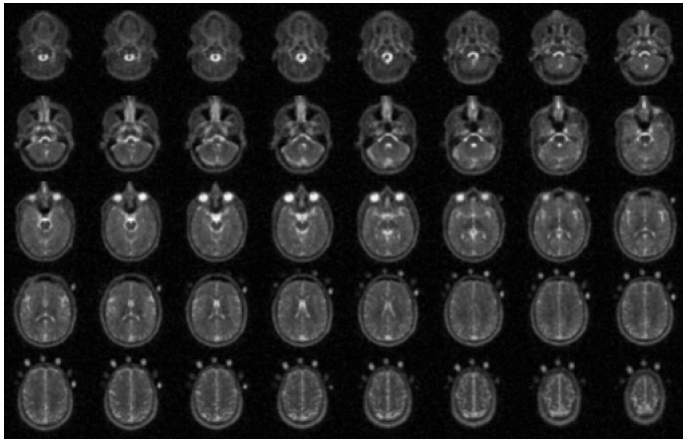
Sodium signal variations in regions with positive BOLD response

Activation of the controlateral motor areas (right-hand motor task)



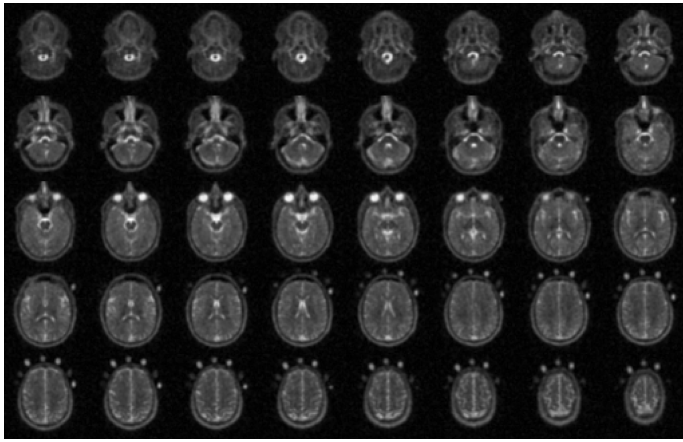
Bydder et al, Neuroimage 2018

Conclusions



- **^{23}Na MRI is feasible to study clinical brain applications**
- It benefits from high and **ultra-high magnetic field**
- ^{23}Na MRI provides **onic/metabolic information: direct window into on cells functionality**

Conclusions



- **^{23}Na MRI is feasible to study clinical brain applications**
- It benefits from high and **ultra-high magnetic field**
- ^{23}Na MRI provides **onic/metabolic information: direct window into on cells functionality**

- Increased TSC in the brain is consistently found in patients with multiple sclerosis
- Multiple phenomena involved in the increase of TSC
  - Different in different compartments
    - Acute lesions: inflammation, oedematous accumulation of interstitial fluid and swelling
    - Chronic lesions: microglial inflammation ? virtual axonal hypoxia and loss, other
    - Normal-appearing brain tissue: virtual axonal hypoxia and loss, small increases in extracellular space, excito-toxicity?
  - Variable over time
    - Present at onset of disease
    - Increase with duration of disease and disability
    - Less pronounced but more compartmentalised in patients with progression

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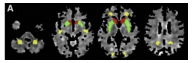
Conclusions

Multiple Sclerosis 

Maarouf et al. MSJ 2022, Collorone et al. Brain 2021, Weber et al. MSRD 2021, Eisele et al. MSRD 2019, Grist et al. JNS 2018, Donadieu et al. MS 2019, Huhn et al. JNS 2017, Eisele et al. J Neuroimag 2017, Maarouf et al. Neurology 2017, Petracca et al. Brain 2016, Eisele et al. MS 2016,Petracca et al. NMR Biomed 2016, Gnahm et al NI 2015, Maarouf et al. Magma 2014, Inglese et al. MSRD 2013, Paling et al. Brain 2013, Zaaraoui et al. Radiology 2012, Paling et al J Neurol 2011, Inglese et al Brain 2010

Amyotrophic Lateral Sclerosis 

El Mendili et al, AJNR 2022, Grapperon et al. Radiology 2019

Huntington 

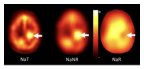
Reetz et al. Neuroimage 2012

Parkinson 

Grimaldi et al. Front Neurol 2021

Alzheimer 

Haeger et al. AD 2021, Mohamed et al. In vivo 2021, Mellon et al. AJNR 2009

Brain tumors 

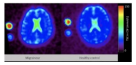
Mohamed et al. J Neuroimaging 2021, Regnery et al. Neuroimage Clin 2020, Shymanskaya et al. Mol Imag Biol 2020, Haneder et al. Neuroradiology 2015, Laymon et al. MRI 2012, Weber et al. Invest Radiol 2010, Bartha et al AJNR 2008, Boada et al. IEEE 2004, Ouwerkerk et al. Radiology 2003, Thulborn et al. MRM 1999,

Stroke & CVD 

Adlung et al. Cerebrovascular disease 2021, Neumaieer-Probst et al. Int J Stroke 2015, Shimizu et al. Neuroradiology 1993

TBI 

Grover et al. AJNR 2018,

Migraine 

Meyer et al. Eur Radiol 2019,

Epilepsy 

Azilinon et al, HBM 2023, Ridley et al. NI 2017

Conclusions

Sodium MRI in Neurodegenerative diseases

Amyotrophic lateral sclerosis

Radiology

ORIGINAL RESEARCH • NEURORADIOLOGY

Quantitative Brain Sodium MRI Depicts Corticospinal Impairment in Amyotrophic Lateral Sclerosis

Aude-Marie Grapperon, MD • Ben Ridley, PhD • Annie Verschueren, MD • Adil Maarouf, MD, PhD • Sylviane Confort-Gouny, PhD • Etienne Fortanier, MD • Lothar Schad, PhD • Maxime Guye, MD, PhD • Jean-Philippe Ranjeva, PhD • Shahram Attarian MD, PhD • Wafaa Zaaraoui, PhD

From the Aix Marseille University, CRMBM, UMR CNRS 7339, 27 Boulevard Jean Moulin, 13005 Marseille, France (A.M.G., B.R., A.V., A.M., S.C., E.F., M.G., J.P.R., W.Z.); APHM, Hôpital de la Timone, Referral Centre for Neuromuscular Diseases and ALS, Marseille, France (A.M.G., A.V., E.F., S.A.); APHM, Hôpital de la Timone, CEMEREM, Marseille, France (B.R., A.M., S.C., M.G., J.P.R., W.Z.); Computer Assisted Clinical Medicine, Heidelberg University, Mannheim, Germany (L.S.); and Aix Marseille University, INSERM, GMGF, Marseille, France (S.A.). Received October 3, 2018; revision requested December 10; revision received April 19, 2019; accepted April 29. **Address correspondence to** W.Z. (e-mail: *wafaa.zaaraoui@univ-amu.fr*).

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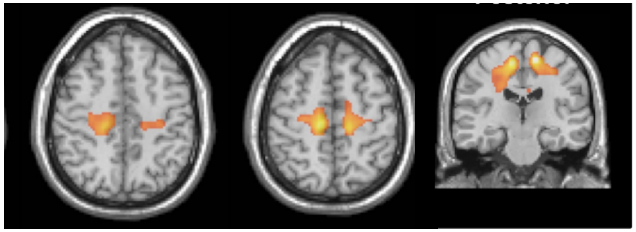

Grapperon et al, Radiology 2019

Parkinson's disease

frontiers in Neurology

ORIGINAL RESEARCH
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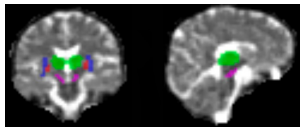
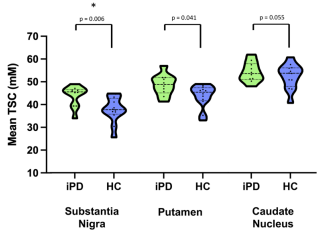
Increased Sodium Concentration in Substantia Nigra in Early Parkinson's Disease: A Preliminary Study With Ultra-High Field (7T) MRI

Stephan Grimaldi[1,2,3], Mohamed Mounir El Mendili[2,3], Wafaa Zaaraoui[2,3], Jean-Philippe Ranjeva[2,3], Jean-Philippe Azulay[1], Alexandre Eusebio[1,4] and Maxime Guye[2,3]*

[1] APHM, Hôpital Universitaire Timone, Department of Neurology and Movement Disorders, Marseille, France, [2] APHM, Hôpital Universitaire Timone, CEMEREM, Marseille, France, [3] Aix Marseille Univ, CRMBM, CNRS, Marseille, France, [4] Aix Marseille Univ, CNRS, Institut de Neurosciences de la Timone, Marseille, France





Grimaldi et al, Front Neurol 2021

=> TSC increase in clinically relevant brain regions

Conclusions

Sodium MRI in Epilepsy

NeuroImage 157 (2017) 173–183

Contents lists available at ScienceDirect

NeuroImage

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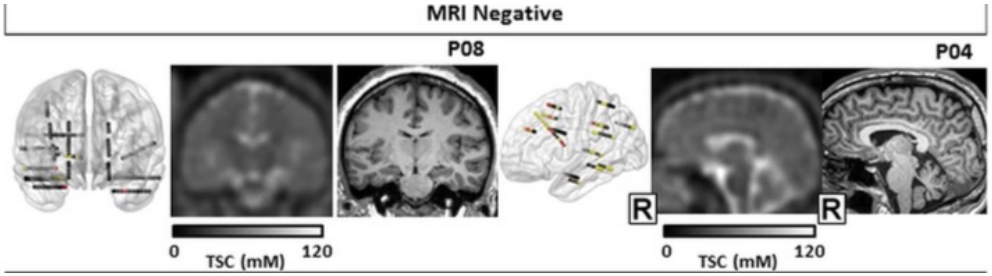
Brain sodium MRI in human epilepsy: Disturbances of ionic homeostasis reflect the organization of pathological regions

Ben Ridley[a,b], Angela Marchi[c,d], Jonathan Wirsich[a,b,d], Elisabeth Soulier[a,b], Sylviane Confort-Gouny[a,b], Lothar Schad[e], Fabrice Bartolomei[d,f], Jean-Philippe Ranjeva[a,b], Maxime Guye[a,b,*], Wafaa Zaaraoui[a,b]



Ridley et al, Neuroimage 2017

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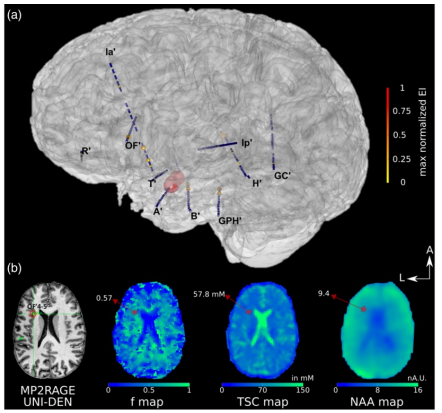
RESEARCH ARTICLE

WILEY

Combining sodium MRI, proton MR spectroscopic imaging, and intracerebral EEG in epilepsy

Mikhael Azilinon[1,2,3] | Julia Makhalova[3,4] | Wafaa Zaaraoui[1,3] | Samuel Medina Villalon[2,4] | Patrick Viout[1,3] | Tangi Roussel[1,3] | Mohamed M. El Mendili[1,3] | Ben Ridley[5] | Jean-Philippe Ranjeva[1,3] | Fabrice Bartolomei[2,4] | Viktor Jirsa[2] | Maxime Guye[1,3]

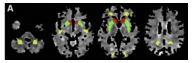
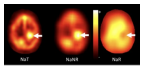
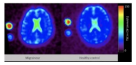


Azilinon et al, HBM 2023

=> Chronic increase of TSC in epileptogenic regions during the interictal period in human epilepsy

Conclusions

Upcoming guideline paper on ^{23}Na MRI & multicenter studies

Multiple Sclerosis		**Maarouf et al. MSJ 2022,** Collorone et al. Brain 2021, Weber et al. MSRD 2021, Eisele et al. MSRD 2019, Grist et al. JNS 2018, **Donadieu et al. MS 2019**, Huhn et al. JNS 2017, Eisele et al. J Neuroimag 2017, **Maarouf et al. Neurology 2017**, Petracca et al. Brain 2016, Eisele et al. MS 2016,Petracca et al. NMR Biomed 2016, Gnahm et al NI 2015, **Maarouf et al. Magma 2014**, **Inglese et al. MSRD 2013**, Paling et al. Brain 2013, **Zaaraoui et al. Radiology 2012**, Paling et al J Neurol 2011, Inglese et al Brain 2010
Amyotrophic Lateral Sclerosis		**El Mendili et al, AJNR 2022, Grapperon et al. Radiology 2019**
Huntington		Reetz et al. Neuroimage 2012
Parkinson		**Grimaldi et al. Front Neurol 2021**
Alzheimer		Haeger et al. AD 2021, Mohamed et al. In vivo 2021, Mellon et al. AJNR 2009
Brain tumors		Mohamed et al. J Neuroimaging 2021, Regnery et al. Neuroimage Clin 2020, Shymanskaya et al. Mol Imag Biol 2020, Haneder et al. Neuroradiology 2015, Laymon et al. MRI 2012, Weber et al. Invest Radiol 2010, Bartha et al AJNR 2008, Boada et al. IEEE 2004, Ouwerkerk et al. Radiology 2003, Thulborn et al. MRM 1999,
Stroke & CVD		Adlung et al. Cerebrovascular disease 2021, Neumaieer-Probst et al. Int J Stroke 2015, Shimizu et al. Neuroradiology 1993
TBI		Grover et al. AJNR 2018,
Migraine		Meyer et al. Eur Radiol 2019,
Epilepsy		**Azilinon et al, HBM 2023, Ridley et al. NI 2017**

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CRMBM, CNRS, Aix-Marseille Université, Marseille, France

W Zaaraoui
M El Mendili
A Maarouf
AM Grapperon
B Ridley
JP Ranjeva
S Gherib
M Bydder
R Dintrich
M Donadieu
M Azilinon
T Roussel
S Grimaldi
B Audoin

M Guye
S Confort-Gouny
L Pini
C Coste
P Viout
S Corella
V Gimenez
MP Ranjeva
A Le Troter
H Dary
JP Stellmann
F Pariollaud
F Reuter
J Pelletier

wafaa.zaaraoui@univ-amu.fr

A Nagel
Erlangen University, Germany

L Schad
Heidelberg University, Germany