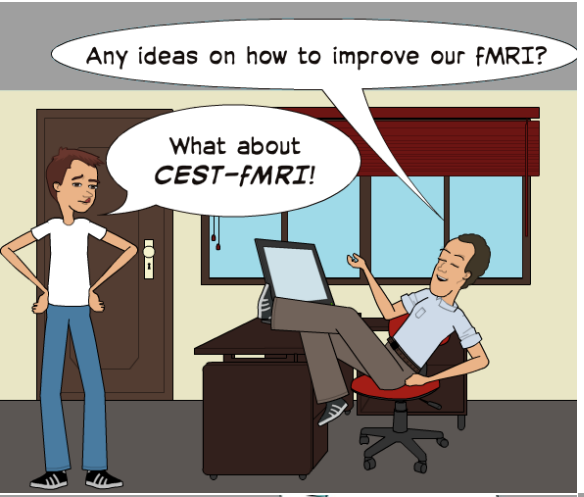
#247 - CEST fMRI at ultra-high magnetic field

Plasma screen n°11



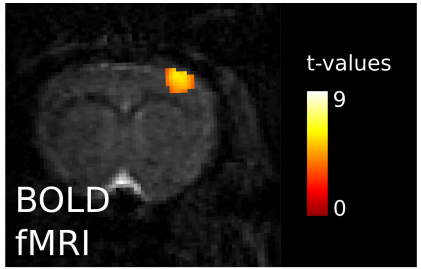
CEST = **C**hemical **E**xchange **S**aturation **T**ransfer

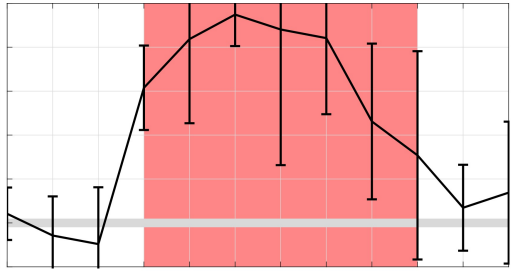
+

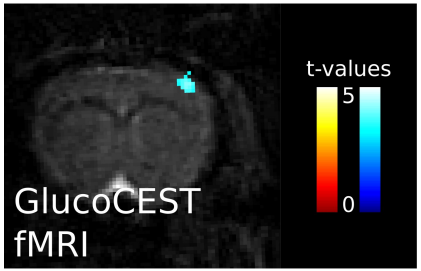
Functional MRI at **17.2T**

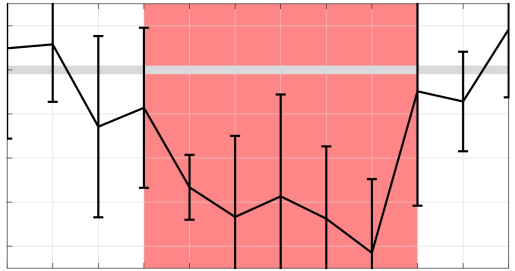
Novel fMRI contrast based on CEST!

→ GlucoCEST drop during activation









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CEST fMRI at ultra-high magnetic field

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Summary

- **Purpose**
- **CEST-fMRI method design**
- **CEST-fMRI methods**
- **CEST-weighted fMRI results**
- **Towards quantitative CEST-fMRI**
- **Discussion**

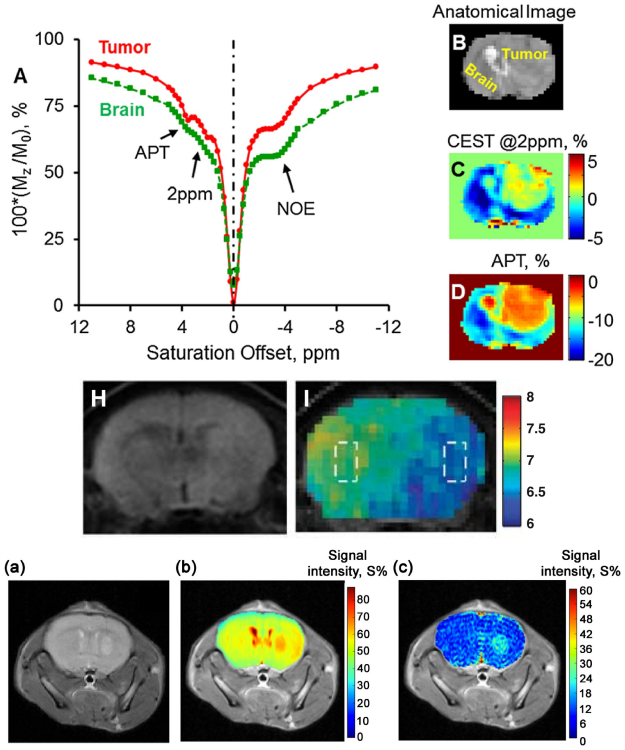
Purpose

- BOLD indirectly measures **neurovascular coupling**
  - naturally poor in spatial and temporal resolutions
- Some emerging methods to study brain activation:
  - spectroscopy (fMRS) suggests **metabolic changes**[1]
  - diffusion fMRI suggests **structural modifications**[2]
- **Chemical Exchange Saturation Transfer** (CEST) is sensitive to such metabolic and morphological changes

1. Mangia S et al. J Cereb Blood Flow Metab 2009;29:441-463
2. Le Bihan D. Proc Natl Acad Sci U S A. 2006;103:8263-8268

CEST-fMRI method design
→ What is CEST-MRI?

- **Indirect detection of low-concentrated metabolites**/proteins/macromolecules by:
  - Irradiating over small chemical shift ranges
  - Measuring the water signal changes
- Endogenous CEST contrast depends on:
  - Molecule abundance
  - Exchange rates (which can depend on tissue micro-structure and -environment)
  - T1 (which depends on tissue time relaxation properties and B0)
- Applied to brain tumor and stroke imaging

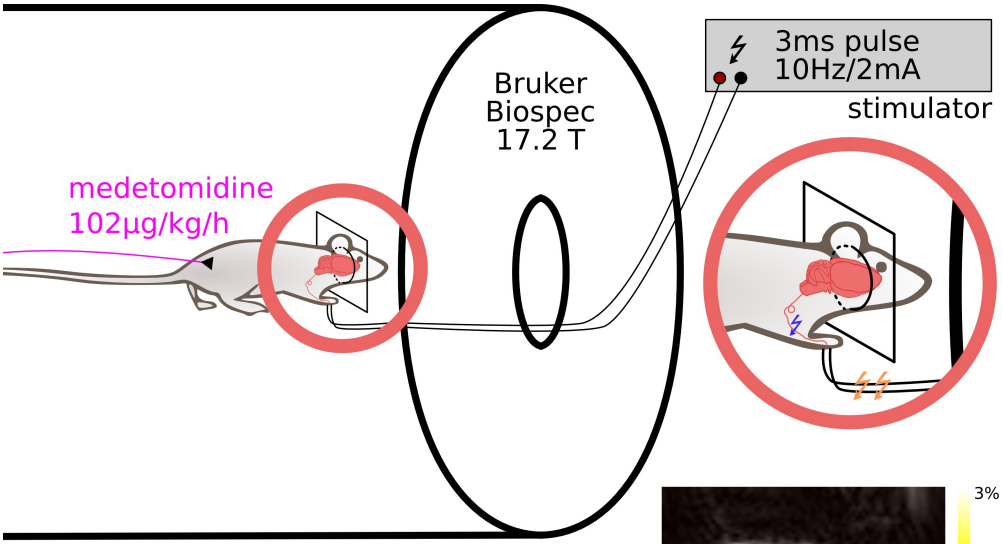


CEST imaging of a 9L glioma in a rat at 9.4T.
Cai K et al. NMR Biomed 2014;28:1-8

CEST pH imaging of a stroke in a rat at 9.4T.
McVicar, N et al. J Cereb Blood Flow Metab 2014;34:690-698

GlucoCEST imaging of a human glioma in a mouse at 11.7T.
Xu X et al. Magn Reson Med 2015;74:1556-1563

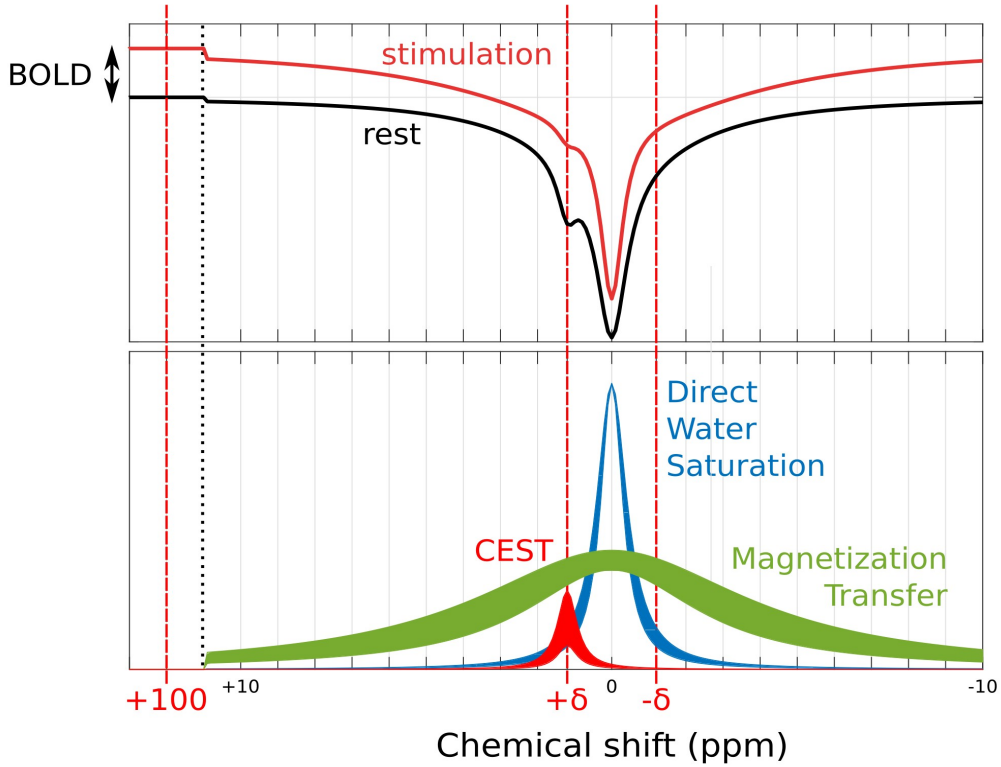
CEST-fMRI method design
→ What is fMRI at 17.2T?



- **B**lood-**O**xygen-**L**evel **D**ependent imaging
- Sprague Dawley rats anesthetized with **medetomidine** (102µg/kg/h)
- Left/right **fore-paw electrical stimulation** (10Hz/2mA)
- **Block-design paradigm** of 10 blocks (30s rest, 30s activation)
- **GE-EPI** (2x2cm FOV, 85x85 matrix, 1.2mm-thick slice, TE/TR=9/2500ms)
- **17.2T** Bruker Biospin, 30-mm diameter surface coil

CEST-fMRI method design → Optimization

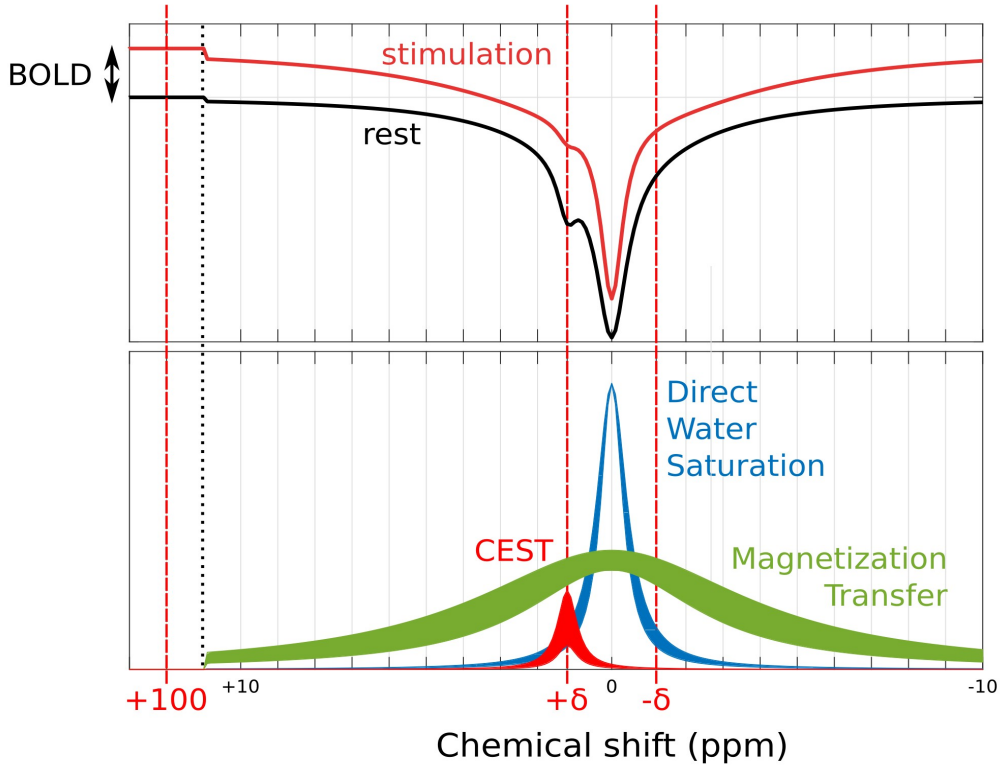
- General idea: **replace each EPI acquisition by a CEST-EPI scan**
- Problems:
  - **It is CEST!** we need long TRs to perform efficient RF saturation
  - **It is fMRI!** we need short TRs to collect time-domain data and increase sensitivity
  - **BOLD effect!** How to cancel it out?
  - **Magnetization Transfer (MT) effect!**[1] How to cancel it out?



1. Kim T et al. Magn Reson Med. 2008;60:1518-1523

CEST-fMRI method design → Optimization

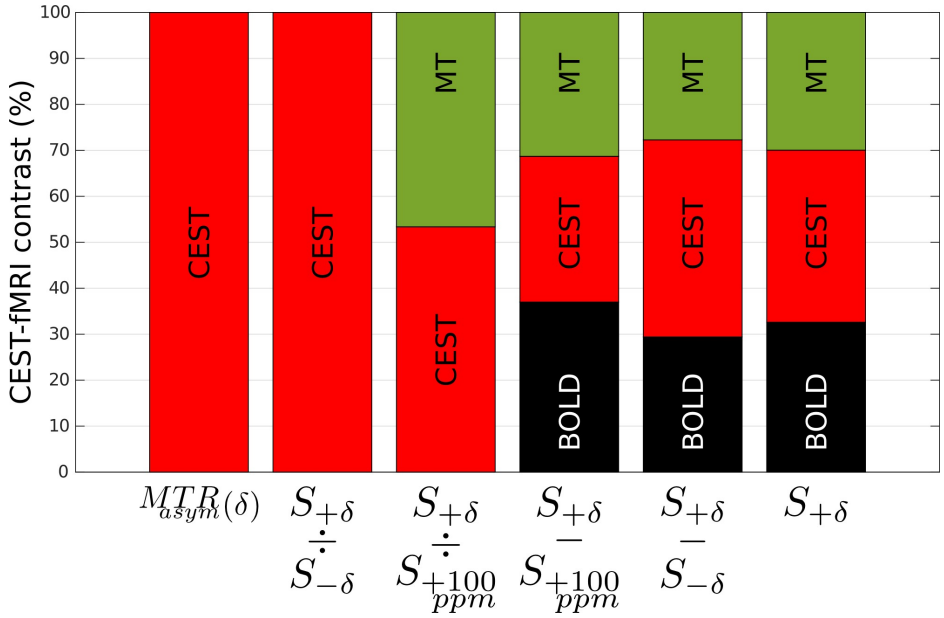
- Question: **How many and which chemical shifts should we irradiate in order to observe a CEST-fMRI contrast free of BOLD and MT effects?**
- Monte Carlo study using simulations of CEST-fMRI signals. Activation consisted in:
  - BOLD effect
    - +1 to +3% broadband intensity change
    - T2* changes reflected on the water linewidth
  - ± 1% wide-band symmetric MT effect
  - **± 0.5% local CEST effect at +δ ppm**
- CEST signals were “acquired” for saturation frequencies **+δ, -δ and +100 ppm** and mathematically combined



CEST-fMRI experimental design → Optimization

Two strategies were selected from the Monte Carlo results:

- **CEST-weighted fMRI strategy**
  - Qualitative CEST measurement
  - 2 saturation freqs: **+δ and -δ ppm**
  - Processing: ratio of images **S(+δ)/S(-δ)**
- **Quantitative CEST-fMRI strategy**
  - Based on conventional CEST-MRI
  - 3 saturation freqs: **+δ, -δ, 100 ppm**
  - Processing: MTR_{asym} map calculation



$$MTR_{asym}(\delta) = \frac{S(-\delta) - S(+\delta)}{S(+100ppm)}$$

CEST-fMRI methods

Those two strategies were implemented:

1. CEST-weighted fMRI

(+) 6 images per block, acceptable time resolution and sensitivity

(+) Minimum scan time of 2mins

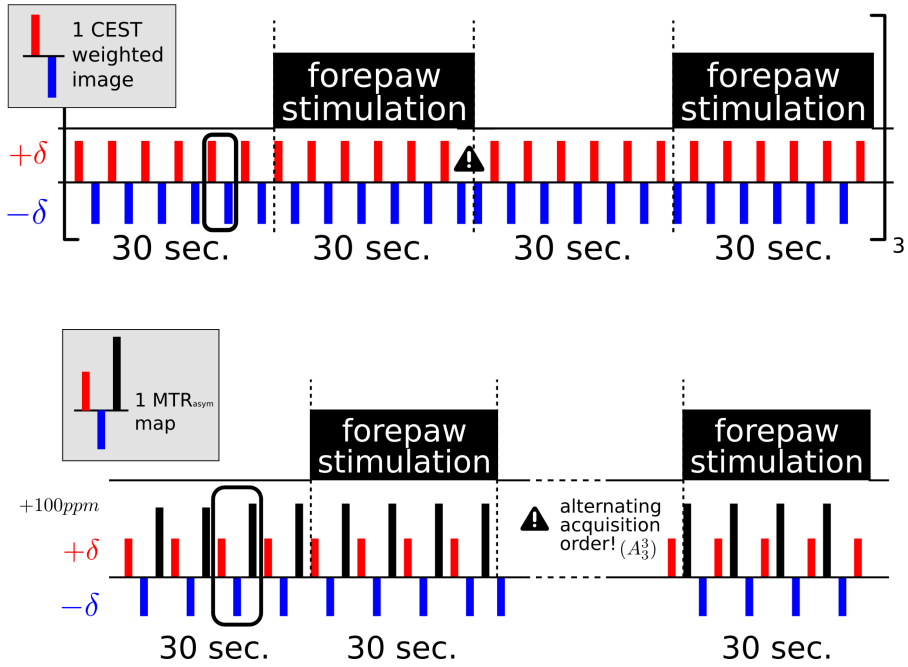
(−) Qualitative CEST measurement

2. Quantitative CEST-fMRI

(+) Quantitative CEST measurement

(−) Minimum scan time of 6mins

(−) 4 images per block, low time resolution and sensitivity



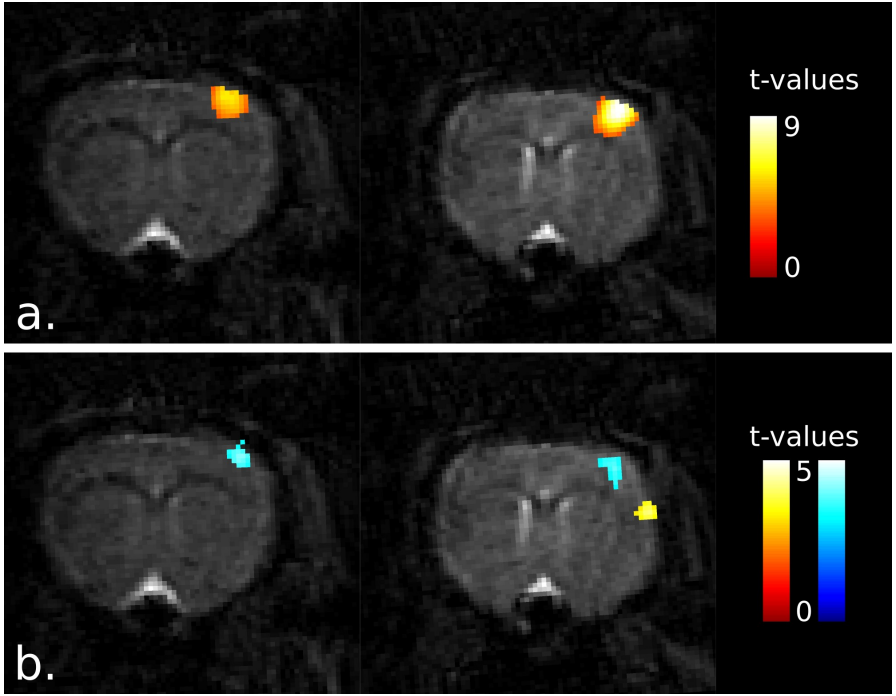
Results: CEST-weighted fMR images

a. BOLD GE-EPI images

b. **CEST-weighted fMR images** acquired with **δ=1.2ppm** (glucose exchange chemical shift).

Image ratios **S(-δ)/S(+δ)** were processed in SPM: intensity drift correction, image registration, SPM fMRI processing and p thresholding (0.001)

- The S(-δ)/S(+δ) fMR images show a **spatially localized decrease (blue), matching the BOLD activation area**
- No significant changes were successfully imaged for **δ=2ppm** or **δ=3.5ppm** (APT[1])



1. APT=Amide Proton Transfer, commonly-used CEST-MRI method

Results: CEST-weighted fMRI time courses

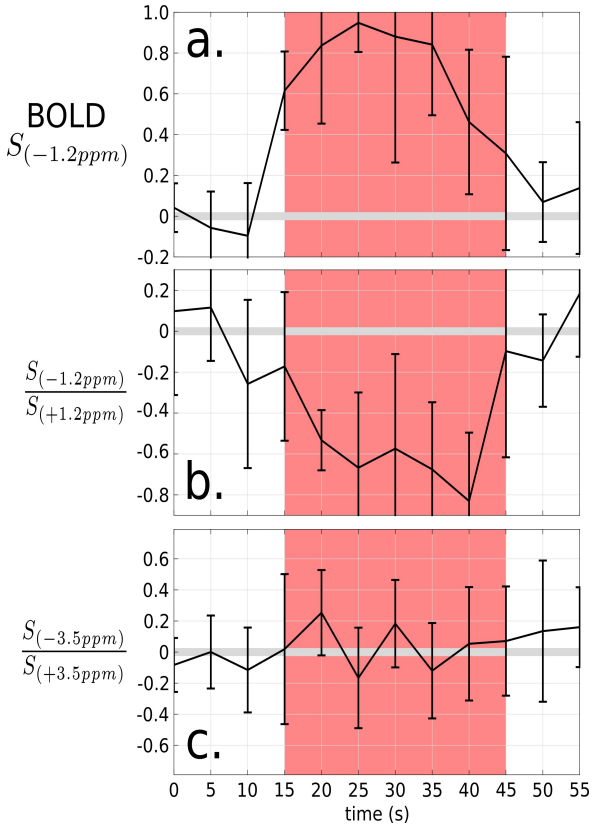
a. **BOLD** time evolution signal

b. **CEST-weighted** time evolution
S(-δ)/S(+δ) with **δ=1.2ppm** (glucose)

c. **CEST-weighted** time evolution
S(-δ)/S(+δ) with **δ=3.5ppm** (APT)

Signals were extracted from the BOLD activation ROI

- **δ=1.2ppm**: S(-δ)/S(+δ) decreases in average of -0.6% during stimulation (n=5 animals, BOLD<0.5% rejected)
- **δ=3.5ppm:** No significant changes were observed (n=4 animals, BOLD<0.5% rejected)

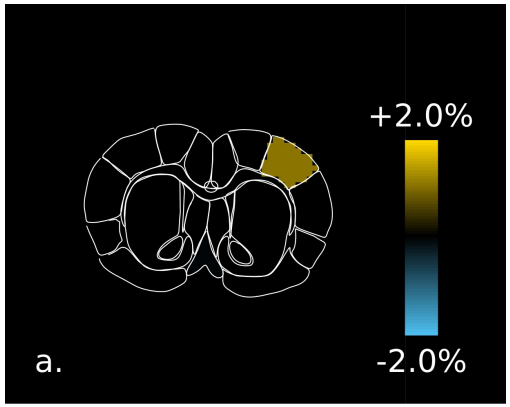


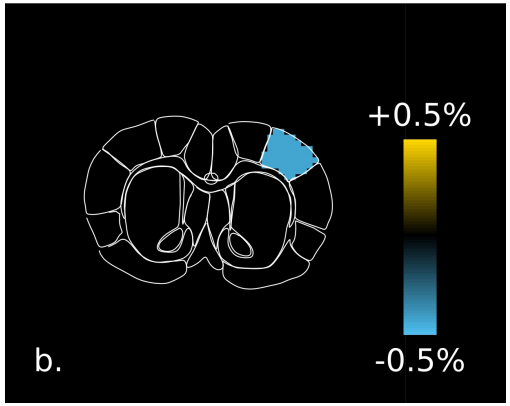
Results: CEST-weighted atlas brain analysis

a. **BOLD** segmented brain atlas (p<0.05)

b. **CEST-weighted** segmented brain image S(-δ)/S(+δ) with **δ=1.2ppm** (p<0.05)

- n=5 animals, BOLD<0.5% rejected, 1.08mm Bregma rat brain atlas
- An increase in BOLD and a decrease of the ratio S(-δ)/S(+δ) is observable in the primary somatosensory cortex (S1F)





Towards quantitative CEST-fMRI

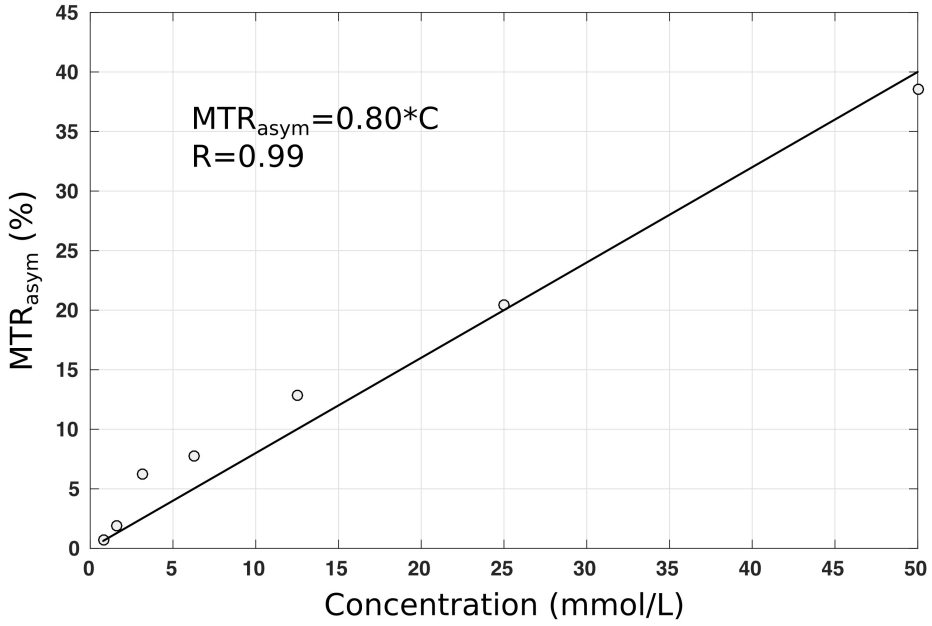
- **Method**

  In order to **quantify our observations at δ=1.2ppm** using the CEST-weighted method, we performed:

  - Careful *in vitro* calibrations on glucose samples with 0 to 50 mmol/L concentrations (pH=7.2)
  - *In vivo* measurements using the quantitative CEST-fMRI method based on MTR_{asym}

- **Results**

  - An **average MTR_{asym} decrease of -0.052%** was observed during stimulation
  - According to the *in vitro* calibration, this would correspond to a **glucose concentration decrease of -65 µmol/kg** during brain activation



Discussion

- Previous studies using fMRS,[1,2,3] PET[4] and PET-MRI[5] showed an **increased consumption** during brain activation
  - causing a temporary **drop of the glucose concentration**[6]
- Further investigations are needed to estimate the cerebral metabolic rate of glucose (**CMR_{glc}**) using CEST-fMRI data
- A drop in GlucoCEST signal could also originate from a decrease of the **glucose exchange rates** (changes in the micro-environment and/or micro-structure of neurons?)

1. Chen W et al. Proc Natl Acad Sci U S A 1993;90:9896-9900
2. Hyder F et al. J Cereb Blood Flow Metab 1997;17:1040-1047
3. Shestov AA et al. Am J Physiol Endocrinol Metab 2011;301:E1040-1049
4. Fox PT et al. Science 1988;241:462-464
5. Wehrl HF et al. Nat Med 2013;19:1184-1189
6. Giove F et al. Magn Reson Imaging 2003;21:1283-1293

Conclusions

- Some limitations of CEST-fMRI methods:
  - Sensitivity!
  - BOLD and MT effects contamination
  - Sensitive to dynamic water resonance frequency shift (susceptibility)

- Promising results!
- Not limited to glucose: lactate, glutamate, creatine and various proteins involved in the metabolism and the micro-structure of neurones have exchanging properties
- **Potentially a new contrast mechanism for fMRI**
- **Imaging of real-time metabolic changes upon neuronal activation**

Thanks for your attention

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