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## **Phosphorylated metabolite T<sub>1</sub> relaxation times measured in the macaque brain using <sup>31</sup>P MRS at 11.7T**

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**Title:**

Phosphorylated metabolite  $T_1$  relaxation times measured in the macaque brain using  $^{31}\text{P}$  MRS at 11.7T

**Authors:**

Alfredo L. Lopez Kolkovsky<sup>1</sup>, Marion Gay<sup>1</sup>, Maxime Roustan<sup>1</sup>, Thomas Lilin Froment<sup>1</sup>, Alexis Amadon<sup>1</sup>, Franck Mauconduit<sup>1</sup>, Fawzi Boumezbeur<sup>1</sup>

<sup>1</sup>*NeuroSpin, BAOBAB, CEA, CNRS, Paris-Saclay University, Gif-sur-Yvette, France*

**Synopsis:**

**Motivation:** Knowledge of phosphorylated metabolite  $T_1$  relaxation times is needed for optimal pulse sequence parameterization, magnetization transfer experiments and for partial  $T_1$  saturation correction during quantification.

**Goals:** To measure metabolite relaxation times in the macaque brain at 11.7T without muscle signal contamination.

**Approach:** Perform inversion-recovery acquisitions with semi-LASER and short-TE STEAM sequences.

**Results:**  $T_1$  relaxation times between 2.6 to 3.0 s were found for phosphodiesteres and  $\text{P}_i$ , ~2.4 s for PCr, 3.6 s for PE, while the  $T_1$  values for the ATP- $\gamma$  and ATP- $\alpha$  resonances were within the 0.8 to 1.0 s range.

**Impact:** Knowledge of the  $T_1$  relaxation times will play a key role in  $^{31}\text{P}$  metabolite quantification and in determining the optimal acquisition parameters for  $^{31}\text{P}$  MRSI measurements in the macaque brain at 11.7T.

## Main Text

### Introduction

$^{31}\text{P}$  MRS benefits from ultra-high magnetic fields (UHF) by an intrinsic increase in sensitivity and a shortening of  $T_1$  relaxation times, providing an additional boost in signal-to-noise ratio (SNR). Yet,  $T_1$  values remain elevated for typical acquisition parameters and are therefore needed to correct for partial saturation effects during metabolite quantification, and also for optimizing acquisition parameters.

There are important differences in phosphorylated metabolite concentrations (4 to 10-fold) between muscle and brain tissues. It is thus critical to avoid muscle signal contamination when acquiring cerebral  $^{31}\text{P}$  MR spectra, notably in macaques. Single voxel spectroscopy acquisitions can provide high SNR spectra within relatively short acquisition times while reducing extracranial signal contributions. In this pilot study, we performed semi-LASER acquisitions to quantify  $^{31}\text{P}$   $T_1$  relaxation times in the macaque brain at 11.7T. To reduce the impact of the short  $T_2$  times and scalar-coupling effects of the ATP resonances, short-TE STEAM measurements were also performed.

### Methods

**Animal Preparation.** 2 male rhesus macaques (10.2 and 12.5 kg, 12.5 and 13.5 years old, respectively) were scanned twice, at least two weeks apart. Animals were anesthetized initially with a ketamine and dexmedetomidine mix (3.0/0.015 mg/kg) and maintained under 2-4% sevoflurane during the MR experiment. They were ventilated, perfused and placed in sphinx position. Body temperature was kept constant using a heated water bed pad. Vital signals were continuously monitored (3885 Patient Monitor, IRADIMED). All experiments were conducted in accordance with European (EU Directive 86/609), French regulations (French Act Rural Code R 214-87 to 126) and the National Institutes of Health's Guide for the Care and Use of Laboratory Animals. Animal studies were approved by the institutional (CEA) Ethical Committee (CETEA protocol #A23\_067).

**Experimental setup.** Acquisitions were performed on the Iseult 11.7T whole-body scanner<sup>1</sup> using a dual-tune RF coil setup (RAPID Biomedical) consisting of a  $^{31}\text{P}$  1Tx/6Rx surface coil placed on the head of the animal and a  $^1\text{H}$  1Tx/8Rx volume coil enclosing the animal head and  $^{31}\text{P}$  coil.

**MRI acquisitions.**  $B_0$  maps were calculated off-line from multi-echo spoiled GRE images (TR/TE1/TE2/TE3=20/1/3/6 ms, 2.5 mm isotropic resolution) and used for  $B_0$ -shimming.

**MRS acquisitions.**  $T_1$ -weighted  $^{31}\text{P}$  MRS spectra were acquired from a 30x12x30 mm<sup>3</sup> voxel with contributions from the superior frontal, precentral and postcentral gyri using semi-LASER (TR/TE=5000/34 ms, 96 averages, 90° flip angle, 4096 points, 8 kHz bandwidth, -1.2 ppm shift relative to PCr) and STEAM (TR/TM/TE= 3000/20/6 ms, 160 averages, 90° flip-angle, 4096 points, 8 kHz bandwidth, -1.2 ppm shift relative to PCr). Inversion times used for both sequences were: 15, 250, 500, 1000, 1500 and 2000 ms. An additional acquisition with TI = 3000 ms was performed with semi-LASER. An adiabatic full-passage pulse (HS modulation, N=4, R=40, 8 ms duration, -1.2 ppm shift relative to PCr) was used for inversion. For one exam, only the semi-LASER dataset was acquired.

**Data analysis.** Spectra were processed using jMRUI (v7.0)<sup>2,3</sup>. Processing consisted of zero-filling to 8192 points, apodization (5 Hz, Lorentzian filter) and manual zero-order phase correction. Quantification was performed with AMARES<sup>4</sup>. Two components were used for inorganic phosphate (Pi). Relaxation times were calculated assuming a mono-exponential recovery.

### Results and Discussion

Figure 1 shows the MRS voxel position for one animal. Typical spectra acquired with semi-LASER or STEAM are shown for the same animal and session in figures 2 and 3, respectively. Figure 4 shows the spectral fitting results for spectra without signal inversion. The phosphocholine (PCh) and the extracellular Pi resonances were not reliably detected. Table 1 summarizes our measured metabolite

T<sub>1</sub> relaxation times. T<sub>1</sub> relaxation times between 2.6 to 3 s were found for phosphodiester and Pi, ~2.4 s for PCr, 3.6 seconds for phosphoethanolamine and they were within 0.8 to 1.0 seconds for the ATP-γ and ATP-α resonances.

A strong variability was observed for Pi ( $2.8 \pm 1.4$  s), likely due to insufficient SNR in the spectra with intermediate inversion times. The resonances of Pi, PCh and nicotinamide adenine dinucleotide (NAD) are the most challenging to detect in the brain<sup>5</sup>. Multi-shot sequences such as ISIS and SPECIAL have been shown to provide higher temporal SNR than STEAM or semi-LASER at UHF<sup>5</sup>. Additionally, shifting the carrier frequency to +4 ppm could also boost the SNR of Pi, phosphomonoesters and phosphodiesters (data not shown). Future experiments will evaluate the SNR gains of these strategies for the reliable T<sub>1</sub> estimation of Pi, PCh and NAD.

## Conclusion

Our preliminary results provide a starting point for optimizing the acquisition parameters for <sup>31</sup>P MRSI applications in the macaque brain at 11.7T. Future work will focus on reliably estimating Pi, PCh and NAD T<sub>1</sub> values.

## Acknowledgements

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## Figures

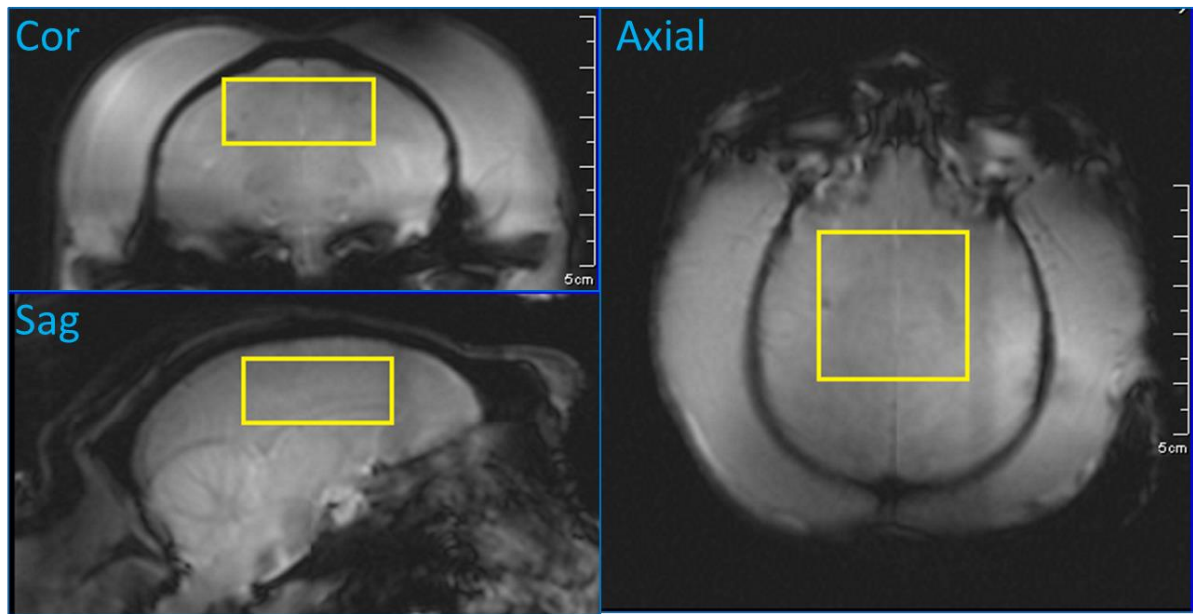


Figure 1. MRS acquisition volume overlaid to orthogonal images (spoiled GRE,  $0.5 \times 0.5 \text{ mm}^2$  resolution, 5 mm thickness).

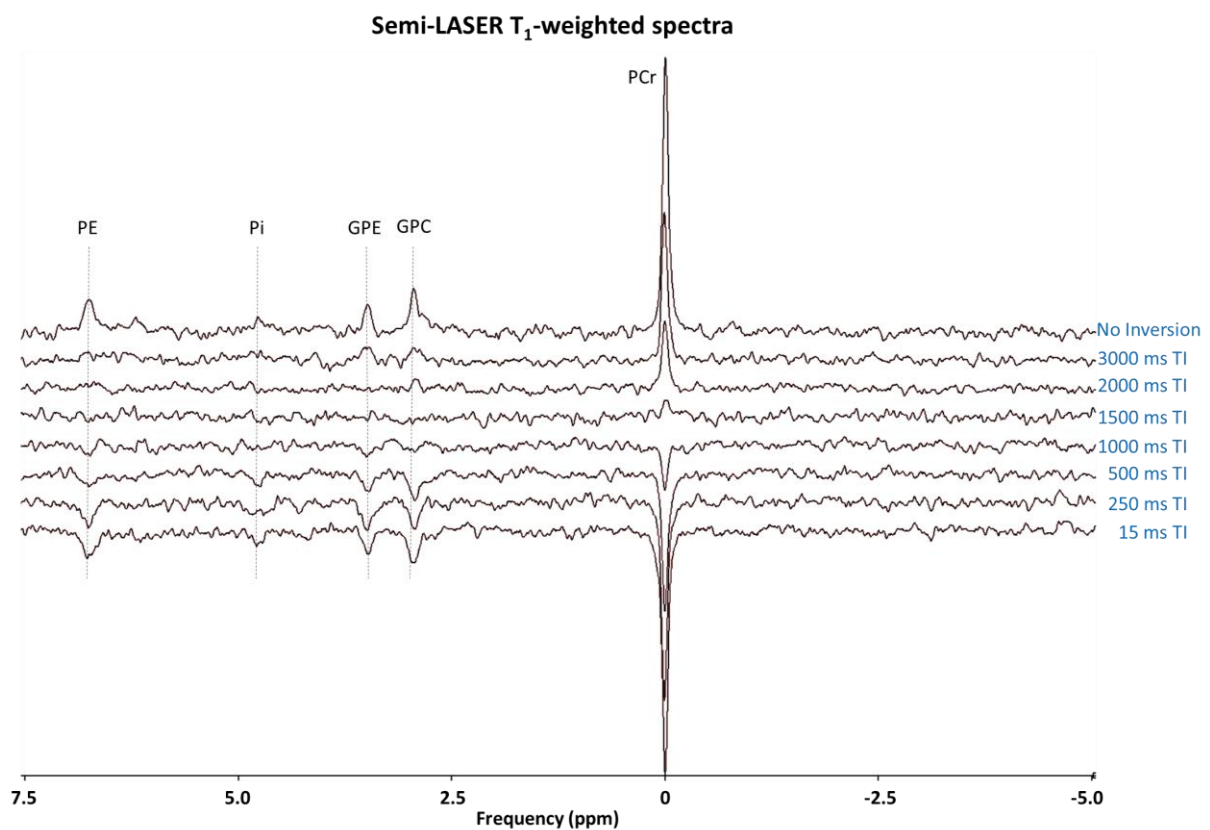


Figure 2.

$T_1$ -weighted  $^{31}\text{P}$  MR spectra measured with semi-LASER. Reference spectrum with no inversion (top) and spectra with decreasing inversion times (TIs) are shown. PE = phosphoethanolamine, Pi = inorganic phosphate, GPE = glicerophosphoethanolamine, GPC = glicerophosphocholine, PCr = phosphocreatine.

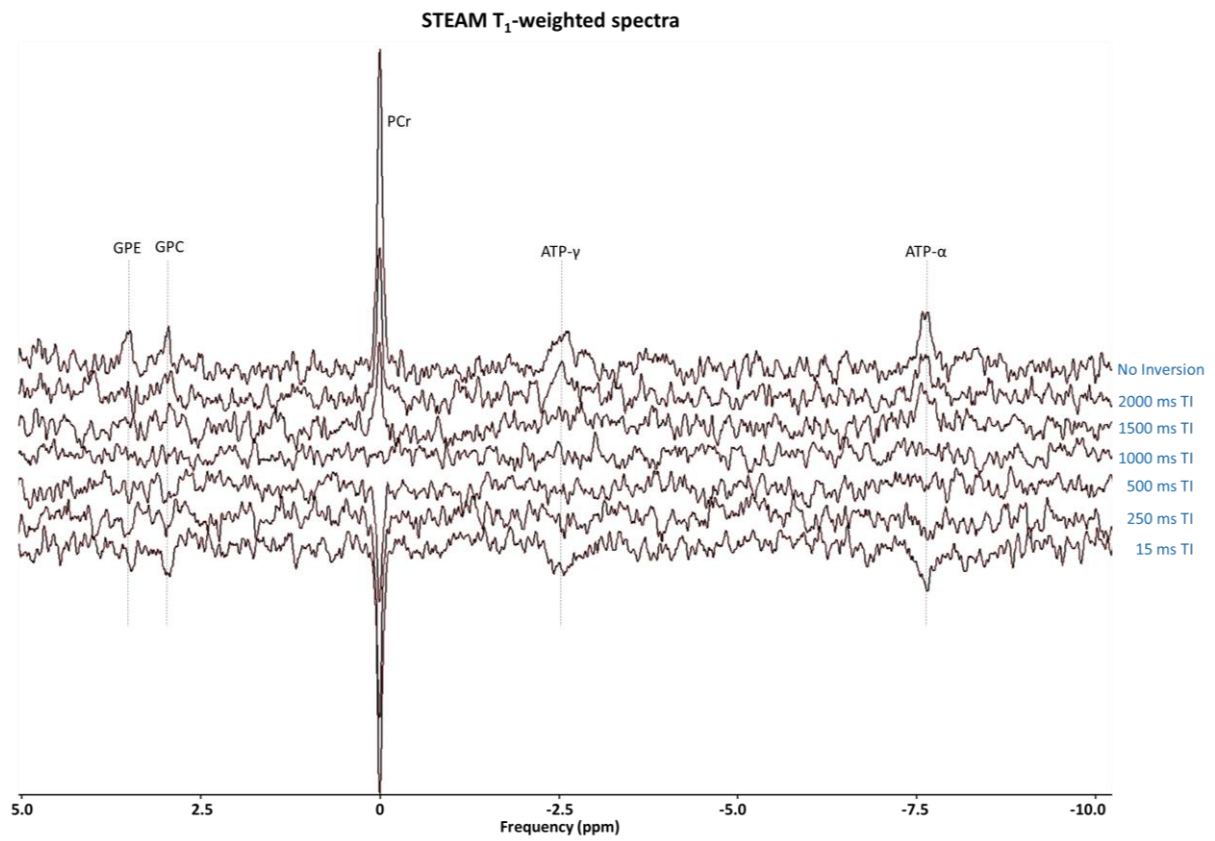


Figure 3.

$T_1$ -weighted  $^{31}\text{P}$  MR spectra measured with STEAM. Reference spectrum with no inversion (top) and spectra with decreasing inversion times (TIs) are shown. GPE = glycerophosphoethanolamine, GPC = glycerophosphocholine, PCr = phosphocreatine, ATP = adenosine triphosphate.

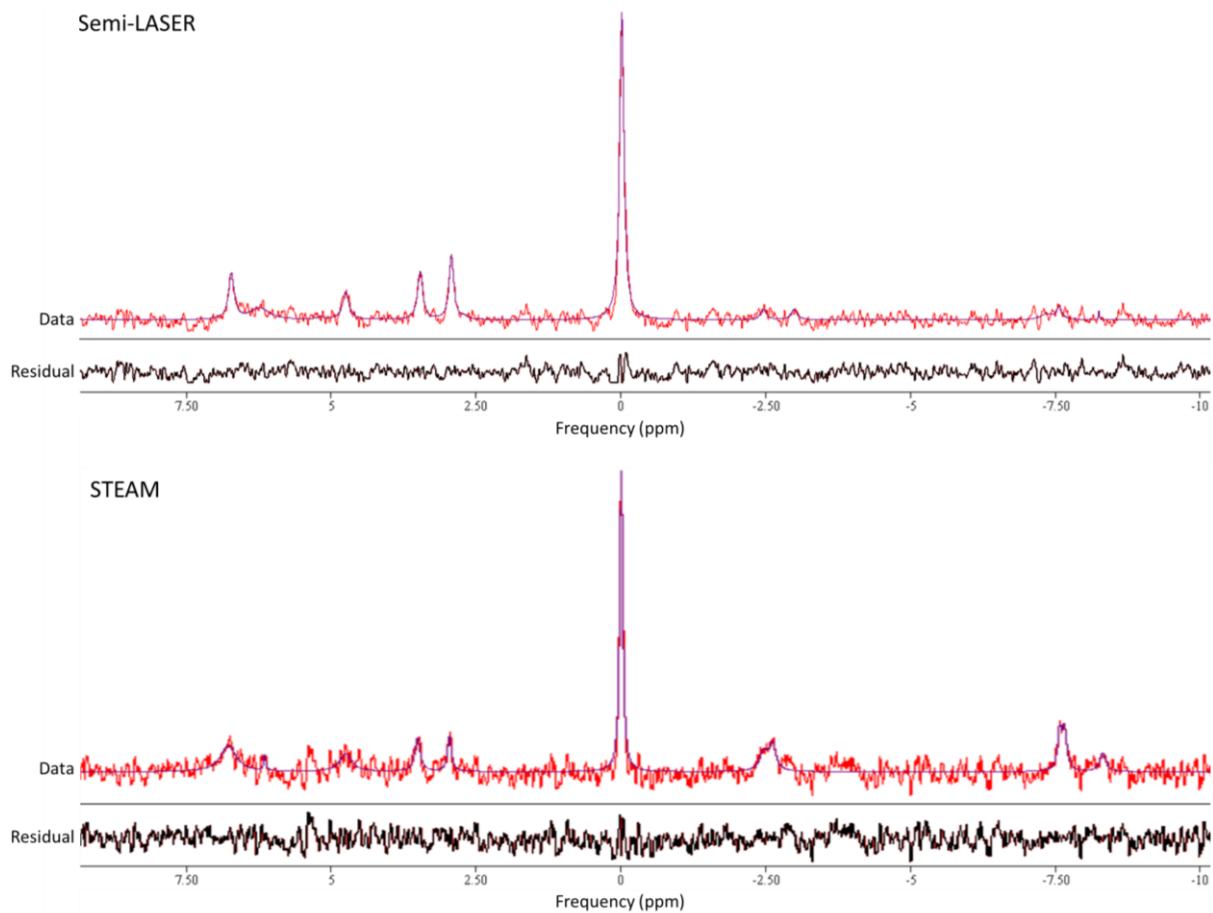


Figure 4.

AMARES fitting results of  $^{31}\text{P}$  MRS spectra acquired with semi-LASER (top) and STEAM (bottom) with without signal inversion preparation. Spectra (red) are overlaid with the AMARES fit (blue) and the residual signal (black) is shown below.

	$T_1$ relaxation time (ms)			Sequence
	Mean	$\pm$	Std	
ATP- $\alpha$	824	$\pm$	180	STEAM
ATP- $\gamma$	1046	$\pm$	188	STEAM
PCr	2344	$\pm$	621	STEAM
PCr	2532	$\pm$	527	semi-LASER
GPC	2962	$\pm$	602	semi-LASER
GPE	2663	$\pm$	390	semi-LASER
Pi	2788	$\pm$	1418	semi-LASER
PE	3654	$\pm$	571	semi-LASER

Table 1

Average  $T_1$  relaxation times of phosphorylated metabolites measured with STEAM (3 datasets) and semi-LASER (4 datasets).