Dynamic imaging of hyperpolarized ^{6}Li cerebral distribution at pharmacological concentration

Mor Mishkovsky[1], Andrea Capozzi[2], Najat Salameh[2], Jean-Noel Hyacinthe[3], Rolf Gruetter[1,4], and Arnaud Comment[2]

[1]*Laboratory of Functional and Metabolic Imaging, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland,* [2]*Institute of the Physics of Biological Systems, Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland,* [3]*Haute Ecole de Santé, University of Applied Sciences Western Switzerland, Geneva, Switzerland,* [4]*Center of biomedical imaging (CIBM), Ecole Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland*

Target audience: Scientists and radiologists who have an interest in *in vivo* imaging of hyperpolarized precursors

Purpose: Hyperpolarized magnetic resonance enables the real-time measurement of biochemical transformations and most *in vivo* applications have so far focused on metabolic studies following the injection of hyperpolarized ^{13}C-labeled precursors [1]. Hyperpolarization techniques can however also be used to enhance the signal of small molecules for use as contrast agents for angiography and perfusion MRI [2-4]. The long *in vivo* T_1 of ^{6}Li makes it an attractive hyperpolarized contrast agent [5]. As lithium salt is used for treating bipolar disorder, the aim of the present study was to monitor the cerebral distribution of hyperpolarized ^{6}Li at pharmacological concentration.

Methods: Samples were prepared by freezing droplets of d_8-glycerol: H_2O (1:1, v/v) containing 840 mM ^{6}LiCl and 66 mM TEMPOL radical and hyperpolarized in a 7 T custom-designed polarizer (197 GHz / 1.00±0.05 K) [6]. The liquid-state enhancement was measured in a phantom following dissolution in 5 mL of phosphate buffer (prepared with D_2O) and injection into a 10 mL plastic tube placed inside the MR scanner. Liquid-state as well as *in vivo* measurements were carried out in a 9.4 T/ 31 cm actively shielded animal scanner (Varian/Magnex) using a home-built ^{1}H/^{6}Li volume coil for *in vitro* acquisitions and a quadrature ^{1}H - single loop ^{6}Li surface coil for the animal studies. Animals were anesthetized using 1.5% isoflurane and their physiology was monitored during the entire length of the experiments. Field inhomogeneity was corrected using the FASTMAP protocol. For *in vivo* applications, 20 µL of sample were polarized for 2 h and cerebral ^{6}Li images were acquired after i.v. injection of a bolus of 500 µL / 3 mM hyperpolarized ^{6}Li aqueous solution in the tail vein of C57BL6/j female mice (31 g) [7]. Data acquisition using a ^{6}Li bSSFP sequence started at the time of the injection and an image (FOV = 30 x 30 mm^2, matrix size of 32 x 32 and one slice of 1 cm thickness) was recorded every 3 s.

Results and discussion: Hyperpolarized ^{6}Li signal and its thermal counterparts are presented in Fig. 1. A polarization of 8 % was measured in solution at room temperature. Higher polarization levels can be achieved by optimizing the formulation of the DNP sample. High-resolution ^{6}Li images superimposed onto ^{1}H anatomical images are shown in Fig. 2. These demonstrate that the ^{6}Li cerebral distribution can be measured in real time. Note that the plasma concentration of lithium was 0.62 mM, i.e. within its therapeutic window (0.6 – 1.2 mM) [8].

Conclusion: These results show that it is possible to monitor sub-millimolar concentrations of hyperpolarized ^{6}Li in the brain in real time. We observed that Li ions penetrate deeper into the brain tissue within the time span of the measurement. This study opens new opportunities to assess the effect of Li^+ on cerebral function.

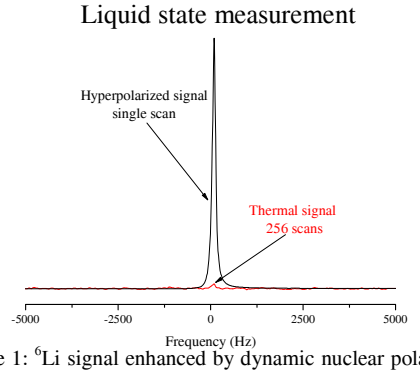

Figure 1: ^{6}Li signal enhanced by dynamic nuclear polarization (black) and its corresponding thermally polarized signal (red) of 200 µL sample polarized at 1 K in and 7 T polarizer and measured in aqueous solution at 300K in a 9.4 T scanner following sample dissolution.

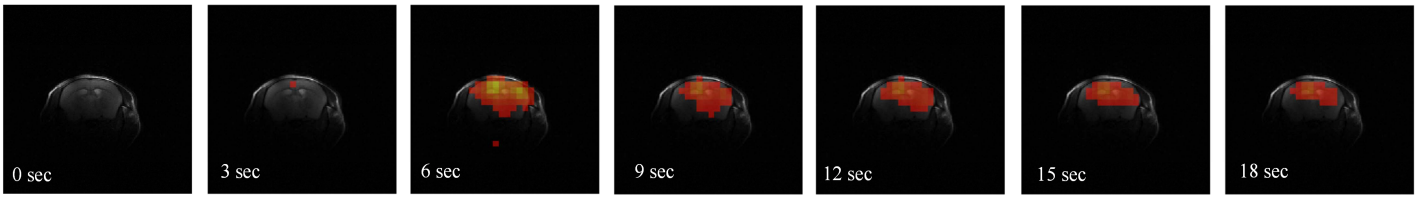

Figure 2: Real-time cerebral distribution of hyperpolarized ^{6}Li in intact mouse brain. Hyperpolarized ^{6}Li images (red) are superimposed onto anatomical ^{1}H images. The in-plane resolution of the ^{6}Li images is 0.9 x0.9 mm^2.

Reference: (1) Comment A. and Merritt M.E. Biochemistry 2014 (2) Golman K and Petersson S. Acad Radiol 2006 (3) Grant A. *et al*. Magn. Reson. Med. 2011 (4) Duhamel G. *et al.* Magn. Reson. Med. 2001 (5) van Heeswijk RB *et al*. Magn. Reson. Med. 2009 (6) Cheng T. *el al*. PCCP 2013 (7) Cheng T. *et al.* NMR in Biomed. 2013. (8) Thase M.E. *et al*. Annu Rev Clin Psychol. 2008. **Acknowledgments:** This work was supported by the Swiss National Science Foundation (PP00P2_133562), the Centre d'Imagerie BioMédicale (CIBM) of the UNIL, UNIGE, HUG, CHUV, EPFL, and the Leenards and Louis-Jeantet Foundations.