

## 7Li-MRS shows a higher lithium brain absorption in remission of bipolar disorder

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**TARGET AUDIENCE:** Psychiatrists, neurologists, radiologists and MR spectroscopists will potentially benefit from this information.

**PURPOSE:** In vivo 7Li-MRS is a unique tool to measure the lithium concentration in the brain and as such it can aim in the understanding on how lithium therapy works in bipolar disorder (BD), and why some patients do not respond to this therapy. In this study we assessed by in vivo 7Li-MRS lithium brain concentration in a group of BD patients after 6 weeks of lithium therapy, in order to test the hypothesis that patients presenting remission of the disease have a different absorption of lithium in the brain than non-remitted patients.

**METHODS:** A total of 24 of patients with BD (type I and II) and a mean age of 28 ( $\pm 6$ ) years were included in the study. On the first day, patients were started on lithium 450mg/day, and subsequent dosage adjustments were allowed at a flexible fashion up to 900mg/day. Plasma lithium levels were obtained at days 7, 14, and at endpoint (6 weeks). As a primary outcome the clinical assessment with the 21-item Hamilton Depression Rating Scale (HAM-D) was used. Remission was defined as a HAM-D <8 at endpoint. After 6 weeks of lithium therapy patients were submitted to a 7Li-MRS exam with a 3T whole body Intera Achieva scanner (Philips Healthcare, Best, Netherlands) and a double tuned 7Li-1H head coil (RAPID Biomedical). The spectroscopy sequence used was a slice selective ISIS sequence (TE/TR= 95.6 $\mu$ s/5s) with an adiabatic rf pulse exciting a 60mm thick slab, covering most part of the brain from the level of the corpus callosum (Fig. 1 left). Afterwards the same 7Li-MRS sequence was applied on a 1.0 mmol LiCl water solution doped with gadolinium, to be used as a concentration reference. Axial high resolution 1mm<sup>3</sup> volumetric images were also obtained to be used for tissue segmentation into CSF, grey and white matter within the selected MRS slice. The integral of the single lithium peak was quantified after spectral apodization, zero filling and manual phase correction. After correcting for the different coil load and temperature in the phantom and patient, lithium brain concentration was calculated according to the method proposed by Soares et al.<sup>1</sup>

**RESULTS:** The mean HAM-D at baseline was 22 ( $\pm 3$ ), and at endpoint was 7 ( $\pm 6$ ), resulting in a mean HAM-D score change of 68% ( $\pm 26\%$ ). Patients were divided in two groups: patients presenting or not presenting remission after 6 weeks of treatment, and results for these two groups are listed in Table 1. HAM-D scores before initial of treatment were not different for these groups. Serum lithium concentration was also not different, but the brain lithium concentration showed a tendency to higher values for the remission group.

remission	n	HAM-D pre	HAM-D pos	serum [Li] in mEq/L	brain [Li] in mEq/L	brain/serum lithium ratio
yes	15	22.0 $\pm$ 3.1	4.2 $\pm$ 2.4	0.48 $\pm$ 0.23	0.30 $\pm$ 0.21	0.65 $\pm$ 0.42
no	9	23.5 $\pm$ 4.1	12.4 $\pm$ 6.5	0.52 $\pm$ 0.14	0.15 $\pm$ 0.07	0.35 $\pm$ 0.23
p		0.29	0.02*	0.62	0.06 <sup>S</sup>	0.03*

Table 1: Mean and standard values for the groups of remitted and non-remitted patients. \*statistical significance at the 0.05 level. <sup>S</sup>a tendency to significance, which would convert to a statistical significance if a one-tailed t-test would be considered.

When correlating the lithium brain concentration with the HAM-D score and the HAM-D score change after treatment, we found a tendency to a negative correlation ( $r=-0.353$ ,  $p=0.091$ ; and  $r=-0.375$ ,  $p=0.071$ , respectively), whereas when trying to correlate these outcome measures with the serum lithium concentration, no correlation at all was found ( $r=0.179$ ,  $p=0.352$ ; and  $r=0.086$ ,  $p=0.665$ , respectively). Finally, when we correlate the brain lithium concentration to the serum lithium concentration only for the remitted patients, we obtained a positive and significant correlation between both measures ( $r=0.67$ ;  $p=0.009$ ), while this correlation disappears when only non-remitted patients are considered ( $r=-0.38$ ;  $p=0.313$ ) (Fig. 1 right). As shown in Table 1, we also found a significantly higher brain to serum lithium ratio for remitted patients when compared to non-remitted patients.

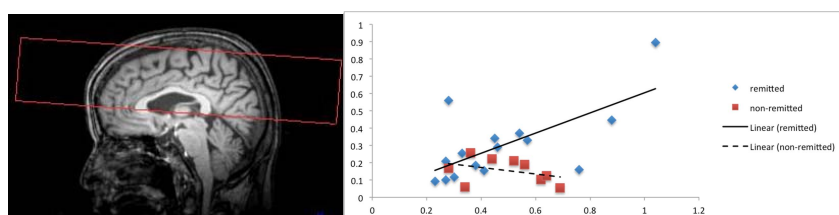


Figure 1. Left: Brain slice selected in the 7Li-MRS acquisition. Right: Brain versus serum lithium concentration (in mEq/L) for remitted and non-remitted patients.

**DISCUSSION:** Our results demonstrate that a high lithium serum concentration does not always result in a high lithium brain concentration. Only remitted patients showed a linear correlation between serum and brain lithium, indicating that something in non-remitted patients prevents them from absorbing more lithium in the brain. This finding supports a previous report, where it was suggested that serum to brain lithium ratio may vary with clinical status<sup>2</sup>. In our sample, at week 6, all remitted patients were euthymic, and non-remitted patients were depressive. None were in mania. Kato et al.<sup>3</sup> showed a positive correlation between brain lithium concentration and remission in manic patients, but no correlation with the serum lithium concentration. Our results show that this observation is also true for depressive patients. A 31P-MRS study demonstrated membrane alterations for the different clinical states: depressive, manic or euthymic<sup>4</sup>. It might be speculated that membrane properties influence lithium absorption in the brain. More 7Li-MRS studies need to be performed in order to elucidate what are the factors contributing to higher lithium brain absorption.

**CONCLUSION:** With 7Li-MRS it was possible to show that lithium brain absorption in patients presenting remission is higher than in patients that did not remit. 7Li-MRS might be used as an early marker of treatment response and can help to elucidate the mechanisms of lithium in the brain.

**REFERENCES:** 1. Soares JC, Boada F, Spencer S, Mallinger AG, Dippold CS, Wells KF, Frank E, Keshavan MS, Gershon S, Kupfer DJ. Brain lithium concentrations in bipolar disorder patients: preliminary (7)Li magnetic resonance studies at 3 T. *Biol Psychiatry*. 2001; 49(5): 437-43. 2. Kato T, Takahashi S, Inubushi T. Brain lithium concentration by 7Li- and 1H-magnetic resonance spectroscopy in bipolar disorder. *Psychiatry Res*. 1992; 45(1): 53-63. 3. Kato T, Inubushi T, Takahashi S. Relationship of lithium concentrations in the brain measured by lithium-7 magnetic resonance spectroscopy to treatment response in mania. *J Clin Psychopharmacol*, 1994; 14(5): 330-5. 4. Kato T, Takahashi S, Shioiri T, Inubushi T. Alterations in brain phosphorous metabolism in bipolar disorder detected by in vivo 31P and 7Li magnetic resonance spectroscopy. *J Affect Disord*. 1993; 27(1): 53-9.