

## 4T $^7\text{Li}$ MRSI in the brains of bipolar disorder subjects

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**Introduction:** Although lithium is a widely used first-line treatment for bipolar disorder, its mechanism of action is largely unknown<sup>1</sup>. Furthermore, therapeutic response is quite variable, and it remains impossible for clinicians to accurately predict which patients will respond prior to a lengthy lithium trial. Better understanding of the spatial distribution of lithium and the role that lithium neuropharmacokinetics play in clinical response may allow development of imaging-based biomarkers to better identify potential treatment responders and maximize treatment efficacy. This work is to develop  $^7\text{Li}$  MRSI methodology to measure regional brain lithium concentrations. We will validate two methods of measuring lithium concentration.

**Methods:** All MR studies were performed on a Varian INOVA 4T MRI system using a  $^1\text{H}/^7\text{Li}$  dual-tuned RF head coil. Ten bipolar subjects (3M/7F age  $29.7 \pm 10.7$ ) in depressed or mixed mood states who were on lithium treatment for between one and eight weeks (serum lithium average is  $0.51 \pm 0.18$  mM at the time of MRSI scan) were consented for the study. Each patient had blood drawn to measure their blood serum lithium to compare with the MRSI results. All patients had a 3D  $^1\text{H}$  MDEFT anatomical image acquired and a one-pulse 3D  $^7\text{Li}$  MRSI acquired using a three-dimensional spherical sampling scheme. The MRSI matrix was  $13 \times 13 \times 13$  with a  $24 \times 24 \times 24$  cm FOV. Each FID has 512 complex points and a 2 KHz spectral width. After point spread function correction, the nominal voxel resolution is approximately 12 ml.

The 3D MRSI matrix was zero-padded to  $16 \times 16 \times 16$  prior to processing. Two methods were used to analyze the data. Method I (1D-3D) applied a 1D FFT on each FID and then integrated the lithium map by applying a 3D FFT on the  $^7\text{Li}$  spectrum point by point along a specified range of points that covered the entire lithium peak. Method II (3D-1D) applied a 3D FFT on the data matrix point by point along the entire time-domain data in k-space. A 1D FFT was then applied on the FID data in each location. The matrices from the desired peak interval were then summed to create the lithium map. The interval used in Method I and Method II is the same and determined using the  $^7\text{Li}$  spectra from the center of k-space. To improve the quality of each spectrum and reduce overall noise a 10Hz exponential filter was applied prior to the 1D FFT. The spectrum was also phased and DC corrected. To determine the  $^7\text{Li}$  concentration of the maps we used phantom (with 5 mM lithium salt) data sets as a reference, acquired using the same settings as the patient data sets and corrected for  $T_1$  and  $T_2^*$  differences. The scaled lithium maps were then exported to and analyzed in AFNI. In AFNI the maps and anatomical images were normalized to the ICBM 452 T1 Atlas to make a group analysis.

**Results:** Fig. 1 shows the maps of a phantom generated from Method I (Fig. 1a), Method II (Fig. 1b), and the difference (Fig. 1c) between the two approaches. The result demonstrates that the difference between these two methods is negligible. Similar results were also seen in human brain data (not shown). The group maps of human data exhibited in three different orientations (Fig. 2) show uneven distribution through the entire brain, which was not observed in the phantom data. All these data have also been verified by using single voxel reconstruction method.

**Discussion:** Method II is traditionally chosen for MRSI data analysis since concentrations are ideally represented by areas under the peak, particularly when considering local inhomogeneity in 3D data sets. However, this data processing approach is extremely time consuming due to involving multi-voxel processing. Method I, in theory, is equivalent to Method II and is much easier to process practically, but this concept has not been verified experimentally. This work demonstrates and verifies that the result obtained from Method I and II is effectively the same. However, Method I requires much less computational effort since there are far fewer 3D FFTs that need to be performed compared to Method II.

Figure 2 illustrates brain lithium distribution maps from an average of 10 bipolar patients. The averaged brain lithium concentration map ( $n = 10$ ) shows that the maximum concentration observed is about 0.2 mM and the average is  $0.16 \pm 0.04$  mM, which is much smaller than that measured in serum ( $0.51 \pm 0.18$  mM). The finding of the brain/serum lithium ratio is lower than most previous  $^7\text{Li}$  MRS work in humans<sup>2</sup>. The lithium distribution in the brain in these subjects is not uniform, even though one might predict it would be since lithium is a cation and should diffuse freely in solution. This finding suggests that lithium may target specific brain tissues and/or certain enzymatic and macromolecular sites that are worthy of further investigation. To the best of our knowledge, this is the first demonstration of  $^7\text{Li}$  whole brain mapping in bipolar patients who are on lithium treatment.

1. RH Lenox, CG Hahn. J Clin Psychiatry 2000; 61: 5-15. 2. RA Komoroski. NMR Biomed 2005; 18: 67-73.

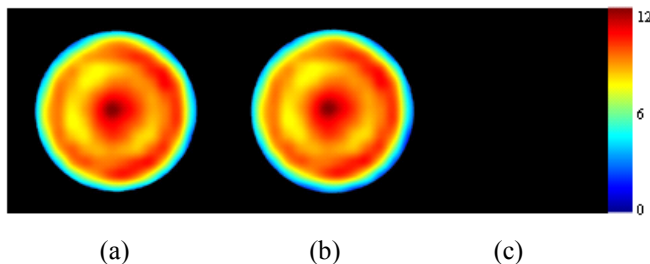


Figure 1(a) Method I (b) Method II (c) the difference between (a) and (b)

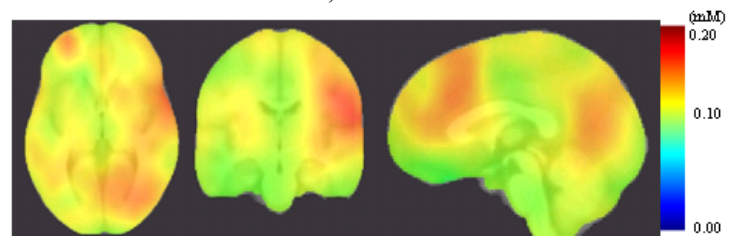


Figure 2 Lithium distribution in the brain of bipolar patients.