

In Vivo 3D Lithium MRI of the Human Brain

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INTRODUCTION

Bipolar Disorder (BPD) is one of the most severe forms of mental illness. It affects an estimated 4.4% of the population in the United States and it is the 6th leading cause of disability for people between 15 and 44 years of age [1]. Lithium carbonate is an established treatment of first choice for different stages of the disorder [2]. Despite its exceptional mood-regulating properties, however, lithium has dangerous and life-threatening side effects. Managing such side effects requires a careful dose-escalating regimen that takes place over the span of several weeks to establish a serum lithium concentration (SLC) in the range of 0.5-1.0mM. Because neurological toxicity increases with lithium accumulation in the brain [3], it is well accepted that Brain Lithium Concentration (BLC) should be a safer prospective indicator of response to treatment than the standard of care SLC. Several groups have pursued the measurement of BLC [4,5,6], their findings indicate that BLC, as measured by Magnetic Resonance Spectroscopy (MRS), is a better prognostic indicator of treatment response than SLC. Due to the low BLC at therapeutic concentrations and the magnetic field strengths previously used, however, whole brain MRS protocols had to be used in order to obtain a measurable signal. Because of excessive partial-voluming effects, whole brain, MRS-based BLC is biased towards lower values and provides no information about spatial heterogeneity. A spatially resolved measure of BLC could overcome these limitations leading to a more sensitive probe for the brain uptake of the drug as well as providing a better understanding of lithium's preferred accumulation sites and how these relate to the neural systems underlying voluntary and automatic emotion regulation [7]. In this work we present the first demonstration of 3D lithium MRI in the in Vivo human Brain at 7 Tesla.

METHODS

Data were acquired *in vivo* using a whole body Magnetom TIM 7 Tesla scanner (Siemens AG, Erlangen, Germany). Data acquisition took place using a single-tuned, eight-channel RF coil (Stark Contrast, Erlangen, Germany) (Fig. 1, left) and an acquisition-weighted stack of spirals sequence (AWSOS) [8] (Fig. 1, right) and under approved Institutional Review Board (IRB) protocol. Standard Gradient recalled proton images were acquired for volumetric and co-registration purposes after a shimming procedure using an 8-channel transmit/receive proton coil. Phantom studies were also carried out for determining the sensitivity limits of the approach and to develop an empirical calibration curve.

RESULTS

Phantom studies demonstrated that the sensitivity of lithium MRI at 7T is at least 0.25mM. As this concentration is about half of the lower end of the therapeutic range (0.5-1.0mM), the sensitivity of the technique, as currently implemented, is sufficient to provide in vivo results. Proton images collected to ensure appropriate localization of the anatomy are presented in figure 2 (top). The field homogeneity obtained prior to the acquisition of these images was maintained by dialing in the same shim coefficients upon repositioning the subject at the same spatial position within the lithium RF coil. Lithium MRI images were obtained for this subject in a total acquisition time of 32 minutes. The images were obtained as the sum of squares from the eight independent channels. No uniformity correction was applied.

CONCLUSIONS

We have demonstrated the use of Ultra High Field MRI for the study of primary BPD. Our results indicate that it is practical to measure the 3D accumulation of lithium in the brain of BPD subjects with a SLC at the lower end of the therapeutic range using acceptable imaging times.

These results should pave the way for a comprehensive assessment of the pharmacodynamics and mechanisms of action of this widely used yet poorly understood drug.

REFERENCES: [1] Merikangas KR, et al., *Arch. Gen. Psychiatry*, **64**:543, 2007. [2] Price L, et al., *New Eng J Med*. **331**:591, 1994. [3] Newman PK, et al., *PostGrad. Med J*, **55**:701, 1979. [4] Gonzalez RG, et al., *AJNR*, **14**:1027, 1993. [5] Soares JC, et al., *Biol. Psychiatry*, **49**:437, 2001. [6] Forester BP, et al., *Bipolar Disord.*, **10**:691, 2008. [7] Phillips ML, et al., *Mol. Psych.*, **13**: 829, 2008. [8] Qian Y, et al., *MRM*, **60**:135, 2008.

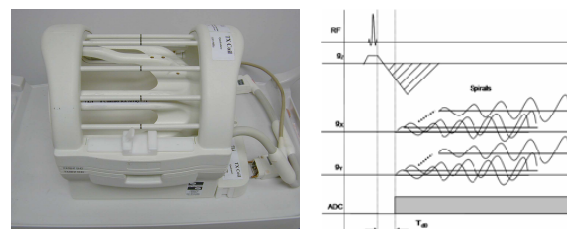


Figure 1: (left) *Eight-channel 7T Lithium RF Coil.* (right) *Timing diagram for the AWSOS sequence.*

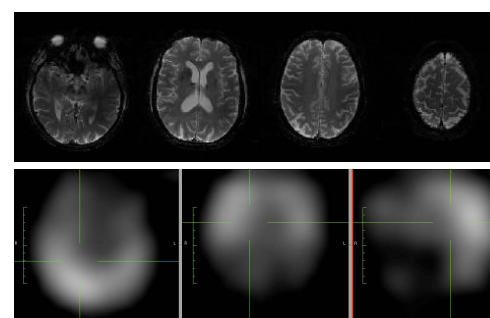


Figure 2: *3D Lithium MRI from a BPD subject with a SLC at the lower end of the therapeutic range. (Top) Gradient Echo images for anatomical co-registration. (Bottom) orthogonal projections of the 3D lithium data set (Voxel=4cc, 32 mins, TE=0.6ms, TR=1s, 7 Tesla).*