PRECLINICAL AND CLINICAL SPECTROSCOPY – Note

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Quantitative Lithium Magnetic Resonance Spectroscopy in the Normal Human Brain on a 3 T Clinical Scanner

Fiona E. Smith,[1]* David A. Cousins,[2] Peter E. Thelwall,[1] I. Nicol Ferrier,[3] and Andrew M. Blamire[1]

Lithium (Li) is a core for many neuropsychiatric conditions. The safe serum range of Li treatment is narrow, and regular monitoring by blood test is required, although serum levels are thought to be a poor indicator of Li concentration in the brain itself. Brain Li concentration can be measured by magnetic resonance spectroscopy. However, little data exist in the healthy human brain, and there are no studies of the relaxation properties of brain ^{7}Li at 3 T. Here, 11 healthy male subjects were prescribed Li over a period of 11 days. In seven subjects, the in vivo T_1 of ^{7}Li was measured to be 2.1 ± 0.7 s. In the remaining subjects, spectroscopic imaging (1D) yielded a mean brain ^{7}Li concentration of 0.71 ± 0.1 mM, with no significant difference between gray and white matter. Mean serum concentration was 0.9 ± 0.16 mM, giving a mean brain/serum ratio of 0.78 ± 0.26. Magn Reson Med 66:945–949, 2011.

Key words: lithium; magnetic resonance spectroscopy; spectroscopic imaging; in vivo measurement

Lithium (Li) is commonly prescribed to those with recurrent affective disorders, stabilizing mood through complex interactions in the brain. Regular monitoring of serum concentration is required, and although the range 0.5 to 1.0 mM is advised (1), response and safety are not guaranteed; serum levels may therefore be a poor indicator of the concentration of Li at its site of action (1,2). Magnetic resonance spectroscopy (MRS) techniques have enabled the detection of Li in vivo (3); however, little is known of its spatial distribution in the human brain. Increased grey matter but not white matter volume has been ascribed to Li (4), making the determination of its concentration in these different tissue classes important.

Li has two stable isotopes (^{6}Li and ^{7}Li), the most abundant of which (^{7}Li, 92.5%) has been studied by MRS in the rat (5,6) and human brain (7–9). Li-7 is a spin 3/2 nucleus with an NMR sensitivity of 0.294 relative to the proton which, when combined with a tissue concentration that arises entirely from therapeutic dosing, results in a low overall signal-to-noise ratio (SNR). Low SNR is a major limiting factor, with low resolution, multislice, and volume coil-based spectroscopic imaging (SI) protocols approaching an hour in duration (10), whereas more rapid sequences are possible at the expense of localization (11). The thick-slab localization strategy most commonly adopted typically covers the largest possible volume of the cerebrum using 1D Image Selected Invivo Spectroscopy (ISIS) (2,9,12–14), providing limited data on tissue-specific ^{7}Li concentration.

The T_1 relaxation time of ^{7}Li is central to the acquisition and quantitation of the Li signal; however, to date, in vivo estimates are all either at low field (11,12) or, in animal models, at ultra high field (6,11,12). There is little to guide data collection at 3 T (9), the field strength common to the now widely available multinuclear clinical scanners suited to ^{7}Li MRS (9,15,16). Human group data on ^{7}Li T_1 have been reported only for small samples of patients, with the measurements in healthy subjects restricted to studies of one or two individuals (17–19).

Here, we report measurement of ^{7}Li T_1 relaxation times in the brains of a group of healthy subjects using a clinical 3 T scanner. Through the development of a quantitative ^{7}Li SI protocol, we also investigated whether any differences exist in the distribution of Li between gray and white matter.

MATERIALS AND METHODS

Subjects

Eleven healthy male subjects were recruited from the local population by advertisement. All participants were in good health and not taking prescription medication. We excluded any volunteers with a history of psychiatric illness, drug and alcohol abuse, head injury, seizures, cerebrovascular disease, other neurological disorders, or general medical conditions that would preclude Li prescription, notably renal impairment, thyroid dysfunction, or psoriasis. At enrolment, we assessed all individuals with the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Non-Patient version (20), performed a physical examination, and tested their urine to detect any current illicit drug use. The study protocol was approved by the Newcastle upon Tyne Research Ethics Committee, and all subjects gave written informed consent.

Li Administration

Blood samples were taken for routine biochemical analysis of serum creatinine, and the result, together with the

[1]Newcastle Magnetic Resonance Centre, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom.

[2]Newcastle Magnetic Resonance Centre, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom.

[3]Academic Psychiatry, Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, United Kingdom.

*Correspondence to: Fiona E. Smith, PhD, Newcastle Magnetic Resonance Centre, Newcastle University, Campus for Ageing and Vitality, Newcastle upon Tyne, NE4 5PL, United Kingdom. E-mail: f.e.smith@ncl.ac.uk

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subject's age and weight, was used to calculate the dose of Li by the Cockcroft-Gault method (21), with a target serum concentration of 0.8 mM/L. Li was started at the individually calculated dose without an escalation phase, aiming for a duration of 11 days on Li (equating to an effective therapeutic dose for a full week after reaching steady state). Subjects received Li carbonate as multiple 200 mg standard release Priadel tablets (Sanofi Aventis, Paris) which they took as a single dose at night. Following the full course of administration, subjects returned for their scheduled investigations; MR imaging and spectroscopy were performed ~12 h after the last dose; and blood for serum Li concentration was taken immediately before the MR protocol and analyzed by atomic absorption spectroscopy.

Scanner and Radiofrequency Coil System

^{7}Li spectroscopy was performed using a 3 T Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands) equipped with a second broadband channel for non-proton nuclei. An 8-cm diameter circular surface coil (tuned to the ^{7}Li frequency of 49.6 MHz) was constructed in-house, which incorporated an internal reference marker at the coil center for calibration purposes. This marker comprised a hollow polyurethane sphere that contained 2 mL of an aqueous solution of 50 mM LiCl solution with 135 mM dysprosium chloride ($DyCl_3$) added as a shift reagent. $DyCl_3$ was found to be the most stable preparation for a concentration standard, yielding a reference sample with a T_1 of 17 s and a displaced ^{7}Li resonance of ~10 ppm downfield. This enabled the discrimination of signals acquired concurrently both from brain tissue and standard.

T_1 Measurement

T_1 measurements were made in the brains of seven subjects using a nonlocalized, steady-state saturation sequence with 90° adiabatic half-passage excitation and five repetition times ranging between 1 and 10 s (6 ms pulse duration, spectral width of 8 kHz and 2048 data points, and 40 averages per pulse repetition time [TR]). The coil placement was standardized to external anatomical reference points (the lower margin of the coil was sited midway on a line between the external auditory meatus and the outer canthus of the eye on the left-hand side of the subject's head), resulting in the typical sampling region illustrated in Fig. 1. To validate the results of these measurements, the theoretical spatial B_1 distribution of the surface coil was used (22) in a Bloch simulation of the complete adiabatic acquisition sequence to determine the reliability of the saturation with depth from the coil and hence estimate error in the calculated T_1 value. This was further confirmed using experimental measurements in an extended aqueous Li phantom of known T_1 relaxation time.

^{7}Li SI Protocol

Spatially localized ^{7}Li data were acquired in the remaining four subjects using a 1D-SI sequence with the spatial encoding plane positioned parallel to the coil plane (adiabatic half-passage excitation, pulse duration 6 ms, TR 6500 ms, 12 encode steps, 12 cm field of view, three averages, weighted *k*-space averaging, spectral width 8 kHz, 2048 data points, and total scan time ~4 min). For calibration purposes, the SI sequence was also applied in extended volume aqueous phantoms containing four concentrations of Li (0.1, 0.3, 1.0, and 3.0 mM/L) at two different saline strengths (150 and 300 mM) (23).

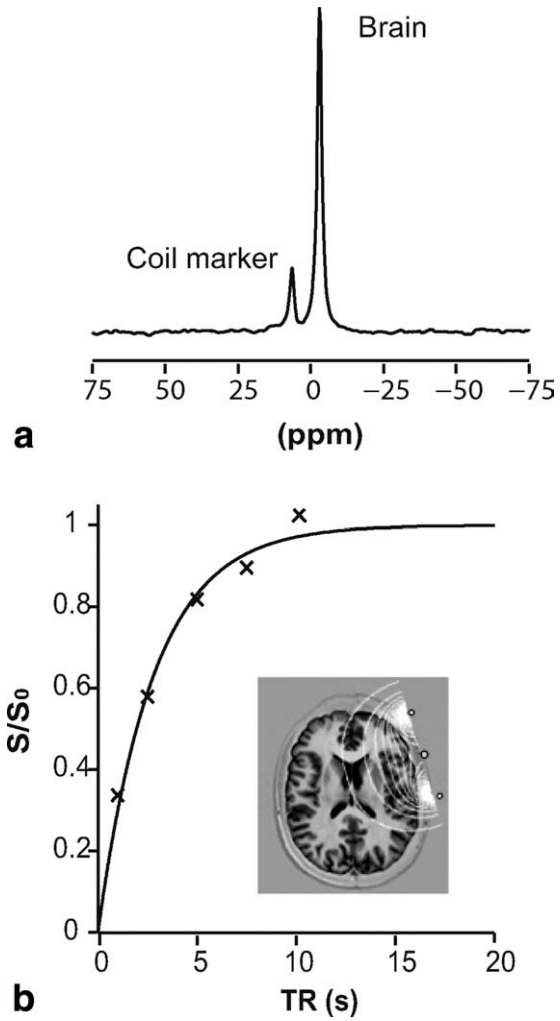

FIG. 1. Typical nonlocalized spectrum (**a**) and steady-state saturation curve (**b**) from which T_1 was calculated (T_1 for this subject = 2.8 s). Inset shows coil location and theoretical B_1 profile over the frontal–parietal region.

Variation in coil performance between subjects was assessed by measuring the pulse width for nonselective 90° excitation of the surface marker (fully relaxed TR = 60 s, hard pulse, four flip angles, and one average).

Finally, 3D T_1-weighted anatomical images were also collected using an eight-channel head coil in a separate scan session during the same visit (1-mm isotropic resolution, TR = 9.6 ms, TE = 4.6 ms). These images were used to determine the volume of brain tissue contributing to each spectral row beneath the coil.

Spectroscopic Analysis and Quantitation

Li spectra were processed using the AMARES algorithm within the jMRUI software package (24). Peak areas from the saturation recovery spectra were fit to a single exponential curve to determine the T_1 of ^{7}Li in vivo.

Table 1
Subject Data

Anthropometric data		
Sex	M:F	11:0
Age	Mean ± SD (years)	22 ± 4
Lithium administration		
Dose	Mean ± SD (mg)	942 ± 98
Duration	Mean ± SD (days)	11 ± 1
Serum concentration	Mean ± SD (mM/L)	0.7 ± 0.3

The calculation of ^{7}Li concentration in vivo was made relative to the extended volume calibration phantoms. From the phantoms, signal strength versus depth was determined for each concentration and loading and normalized to the signal from the surface marker to create calibration curves. In vivo spectra were normalized to the surface marker, and the results were compared with the calibration curves to determine the uncorrected ^{7}Li concentration. Tissue volume contributing to each spectral row was measured from the T_1-weighted anatomical scans that were submitted to a two-compartment segmentation (gray and white matter) in native space using SPM8 (25). This volume was then used to scale the MRS data to achieve the final corrected Li concentration in each SI row. Finally, following methodology previously used for Li brain quantification work by Gonzalez et al. (12), a correction was made for signal arising from blood using the serum levels measured from each subject. The volume of brain vasculature was estimated to be 5%.

Statistical Analysis

Correlation between the serum levels and the mean brain ^{7}Li concentration over all SI slices was assessed using bivariate analysis, taking a significance level of $P < 0.05$ (two tailed) with group data reported as mean ± SD for each variable. Statistical analysis was performed using Minitab (Minitab version 15; Minitab Inc., Pasadena, CA).

To investigate whether any differences could be detected between gray matter and white matter Li concentrations, the 3D T_1-weighted anatomical scans were segmented to create images of white and gray matter within each plane of the SI data. The percentage gray matter contribution to each spectrum was then determined. Regression analysis was performed between tissue ^{7}Li concentration and gray matter fraction with the hypothesis that a slope significantly different from zero would indicate a gray matter to white matter concentration difference.

RESULTS

As detailed in Table 1, subjects received doses of Li typical of standard treatment regimes (mean serum concentration, 0.7 ± 0.3 mM) over the specified period (mean duration 11 ± 1 days).

A typical in vivo ^{7}Li saturation recovery (S-R) series for one subject is given in Fig. 1. Direct fitting of the S-R data gave a mean T_1 of ^{7}Li in vivo of 2.1 ± 0.7 s ($n = 7$, range = 1.5–3.4 s). The simulated flip-angle distribution and phantom validation studies suggested that the maximum error in T_1 from assuming uniform 90° excitation was an underestimation of T_1 by a maximum of 5%.

An example of SI data obtained for one subject is shown in Fig. 2. By using this fully relaxed data acquisition (TR = 6.5 s versus measured T_1 of 2.1 s) with a total examination time of 4 min, the spectral SNR was determined to be 20 (at 3–4 cm depth), and data were quantifiable to a maximum depth of 8 cm. The mean ^{7}Li concentrations by depth, including the mean of all subjects, are presented in Fig. 3a, from which we calculated brain ^{7}Li concentration (averaged over all SI slices) of 0.71 ± 0.19 mM. For the subjects who underwent SI, the serum concentration of Li was 0.9 ± 0.16 mM, giving a mean brain/serum ratio of 0.78 ± 0.26. There was no significant correlation between serum levels and mean ^{7}Li concentration in brain. For the 1D-SI data, the total Li concentration tended to be lower in the outer brain slices that are expected to contain the larger proportion of gray matter. Regression between tissue Li concentration and gray matter fraction, determined from imaging, gave a slope that was not significantly different from zero, indicating that there was no gray matter to white matter concentration difference although accuracy was limited by the small range of values ($r = 0.01$, $P = 0.9$).

DISCUSSION

Li MRS has been conducted by several groups over the past 20 years, with a wide range of quantitative methods applied (3,7,10–12,14,15,17,19,26–29). The wider availability of high-field-strength clinical scanners (with their potential for better SNR and potentially reduced scan times) has rekindled interest in advancing techniques for measuring ^{7}Li in vivo.

With a few exceptions (17–19), there have been clinical MRS studies of patients taking Li as treatment for bipolar disorder (2–4,7–14,29), in which the relationship between response, brain, and serum concentrations is of some importance. Initial reports of a correlation between

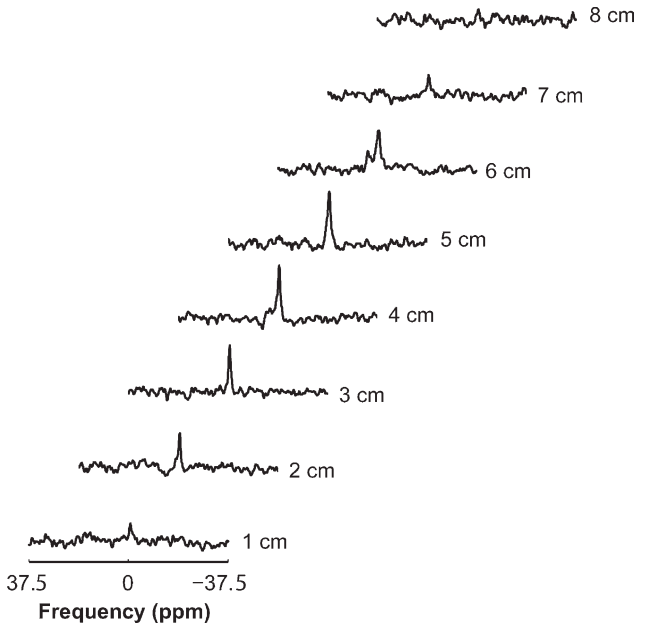

FIG. 2. Example of a 1D-SI dataset for one subject over eight slices (1 cm thickness) to a maximum depth of 8 cm in brain tissue.

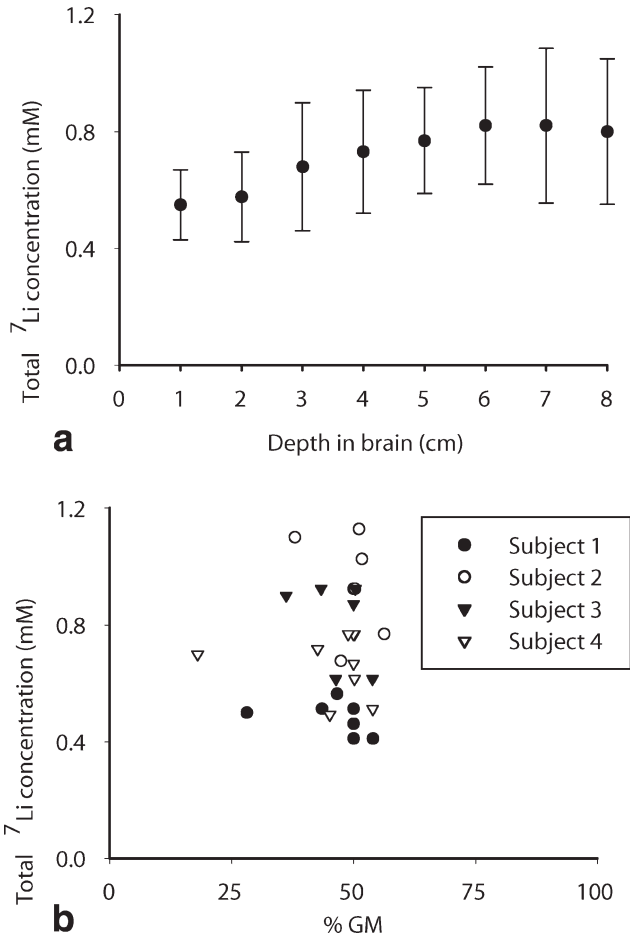

FIG. 3. Mean Li concentration versus depth into brain over all subjects (**a**) and total ^{7}Li concentration versus percentage gray matter for each slice and all subjects (**b**).

the brain and serum Li levels have not been invariably upheld (8,12), perhaps as a consequence of diverse group characteristics, for example, the brain to serum ratio appears to correlate with age, but not consistently in older groups (14). Separation of the effects of age from illness is difficult because of the paucity of data from a range of healthy subjects. The current study has addressed this by investigating healthy young men receiving Li for a period consistent with its acute clinical effects (30) and to a serum level comparable with therapeutic dosing. The brain to serum ratio of 0.78 ± 0.26 was consistent with estimates from similarly aged patients with bipolar disorder (13). No correlation between brain and serum Li concentration was observed, possibly a consequence of the narrow range of serum levels. However, in rats under tightly controlled conditions, a strong correlation of brain and serum Li has been reported (28).

Most commonly, Li quantitation has been attempted using fully relaxed acquisition conditions, eliminating the need for T_1 relaxation correction. This approach is consistent with the use of signal differencing-based localization schemes such as ISIS (2,9,12–14) as well as simple adiabatic 90° excitation. The gauging of T_1 permits the determination of the minimum TR, enabling maximal sensitivity to be achieved. However, there is little available data of the T_1 of Li in vivo at 3 T. The T_1 value of 2.1 s obtained in this study is relatively low when compared with other reported human studies, although a similar value of 2.2 s has been reported in rat brain at 7.0 T (6) and similar levels of variation exist across studies in rats (2.2 s at 7.0 T, and 3.3 s and 4.1 s at 4.7 T) (6). The majority of studies of healthy humans were performed in only one or two subjects who did not allow a measure of the intersubject variability in T_1 to be determined. Our study is the most comprehensive study currently available ($n = 7$), and this has enabled a range of T_1 values of 1.5–3.4 s to be determined in a healthy group for the first time. The ^{7}Li T_1 in vivo varies substantially among subjects, a finding previously observed in other published studies but as yet unexplained (11). Our T_1 data may have been contaminated by signal from tissues other than the brain (e.g., muscle), potentially explaining its lower value. Previous estimates of the Li T_1 in muscle actually indicate that it is longer than in brain, making this assertion unlikely (18). Coil placement over the frontal regions rather than the occipital region also minimized the potential contamination from Li in skeletal muscle (5), the data from the SI-encoding sequence showing no discernable signal from the slices closest to the coil. The largest potential source of error in our method is nonexcitation at 90° leading to lower saturation than expected. We therefore validated our method both using simulation of the radiofrequency coil performance and experimentally in an aqueous phantom using a small point source sample at coil isocenter where adiabatic excitation was verified to give uniform 90° excitation. These studies suggested that the maximum error in calculated T_1 was 5%, suggesting a maximum value of 2.2 s in vivo.

The literature is divided as to whether a second fast decaying component is observed in the Li spectrum, as a nonmonoexponential decay is expected for 3/2 spins. However, Li is only weakly quadrupolar and a biexponential decay has not been consistently identified, and the human data adequately fitted to a single exponential decay without additional benefit gained by application of a biexponential model. Although reduced visibility has been reported in rodents, biexponential decay for T_2 has been attributed to differential rates of relaxation for Li in intracellular and extracellular compartments rather than multicomponent relaxation of a given spin. We have assessed the influence of quadrupolar interactions on T_2 decay by measuring signal intensity with long (6 ms) and short (1 ms) duration of radiofrequency excitation pulses in phantom studies. No differences in signal intensity attributable to a fast-relaxing T_2 component were observed. In addition, the lineshape of our spectral peaks in the in vivo measurements did not show any detectable broad component. Therefore, even if a fast signal decay can occur with lithium it was not observed in our data.

The imaging studies in patients with bipolar disorder have examined the effect of Li on brain structure through segmentation and statistical parametric mapping approaches (4). The results indicate regional increases in gray matter, particularly localized to frontal and hippocampal regions and interpreted as arising from an effect of Li on neuroplasticity (4). Spatial information on Li distribution would allow improved understanding of

these imaging changes. The spatial distribution of Li in the rat brain appears to be uneven after short-term administration, at least when assessed using 2D SI at high field strength (6). As with all nonproton MRS investigations, the protocol design must balance achieving localization, spatial resolution, and adequate SNR with a clinically acceptable examination length. Acquisition of spatial information in clinical studies has varied from simple surface coil localization (8,11) to slab-localized one-dimensional ISIS (9,12–14), with the examination times ranging from minutes to almost 1 h with 2D SI. We applied a combination of surface coil localization with a 1D-SI approach to separate spectra from 10-mm-thick planes parallel to the surface coil (near sagittal orientation). Data were collected in 4 min, and the spatial resolution was sufficient to examine Li concentration by depth and tissue class. Li concentration tended to be lower in the outer brain slices. The superficial slices would be expected to contain larger proportions of gray matter (Fig. 3a), but regression of local concentration against percentage gray matter contribution showed no difference in ^{7}Li concentration between gray and white matter (Fig. 3b). This may be a consequence of the low resolution of our 1D-SI measurement, insufficient in itself for complete separation of signal from purely white and gray matter tissue regions. Future work should aim for greater localization allowing more accurate measurements of Li concentration in different brain regions including areas of predominantly white and gray mater.

CONCLUSION

Spatially localized measurements of ^{7}Li concentration were made in the brains of healthy volunteers in an examination time lasting below 20 min. The mean brain ^{7}Li T_1 in healthy subjects was 2.1 s, which is comparable with recent measurements at high field in rats (6) but lower than previous human data at 1.5 T (10). Brain Li concentration was ~80% of serum levels in healthy subjects. Although our 1D-SI measurements did not provide full localization, the resolution was sufficient to partially separate gray and white matter. However, linear regression between gray to white matter ratio and Li concentration did not reveal any statistically significant differences in Li concentration between different brain regions.

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