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Brain Lithium Levels and Effects on Cognition and Mood in Geriatric Bipolar Disorder: A Lithium-7 Magnetic Resonance Spectroscopy Study

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Abstract

Objectives—The authors investigated the relationship between brain lithium, serum lithium and age in adult subjects treated with lithium. In addition, the authors investigated the association between brain lithium and serum lithium with frontal lobe functioning and mood in a subgroup of older subjects.

Design—Cross-sectional assessment.

Setting—McLean Hospital's Geriatric Psychiatry Research Program and Brain Imaging Center; The Division of Psychiatry, Boston University School of Medicine.

Participants—Twenty-six subjects, 20 to 85 years, with Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition–TR bipolar disorder (BD), currently treated with lithium.

Measurements—All subjects had measurements of mood (Hamilton Depression Rating Scale [HDRS] and Young Mania Rating Scale) and serum and brain lithium levels. Brain lithium levels were assessed using lithium Magnetic Resonance Spectroscopy. Ten subjects older than 50 years also had assessments of frontal lobe functioning (Stroop, Trails A and B, Wis. Card Sorting Task).

Results—Brain lithium levels correlated with serum lithium levels for the group as a whole. However, this relationship was not present for the group of subjects older than 50. For these older subjects elevations in brain (but not serum) lithium levels were associated with frontal lobe dysfunction and higher HDRS scores. The higher HDRS were associated with increased somatic symptoms.

Conclusion—Frontal lobe dysfunction and elevated depression symptoms correlating with higher brain lithium levels supports conservative dosing recommendations in bipolar older adults.

The absence of a predictable relationship between serum and brain lithium makes specific individual predictions about the “ideal” lithium serum level in an older adult with BD difficult.

Keywords

Lithium; bipolar disorder; elderly; frontal lobe dysfunction; MR spectroscopy

Lithium remains one of the first-line treatments for acute mania in younger adults¹ and continues to be used as a treatment for mania in older adults despite the lack of randomized control trials.² Although older individuals with bipolar disorder (BD) experience low rates of sustained symptomatic recovery under conditions of standardized treatment with medications including lithium,³ retrospective analyses of older BD patients included in mixed-aged double-blind maintenance studies of bipolar depression have demonstrated both efficacy and tolerability of lithium.⁴ Concerns regarding neurotoxic side effects of lithium in older adults, including a more prolonged recovery from lithium-induced delirium,⁵ have led to questions about the most effective way to use lithium safely in older adults with BD. Lithium neurotoxicity, including adverse effects on memory and speed of cognitive and psychomotor performance,⁶ may be of particular concern in an older individual with BD as evidence suggests increased cognitive deficits in older compared with younger BD patients.^{7,8}

The clinical practice of monitoring serum lithium levels in patients with BD is based on the assumption that serum levels of lithium linearly correlate with the amount of lithium in the brain. However, in the elderly population this relationship may become more variable due to age-related changes in metabolism, body composition, and renal function that alter lithium pharmacokinetics. The effects of these age-related changes on serum lithium levels in the elderly have been well-documented and include an extended elimination half-life and higher serum lithium levels at lower doses.⁹ Few studies have investigated the relationship between age-related changes and brain lithium levels.¹⁰ Furthermore, previous studies have not examined the relationship between brain lithium levels and measures of neuropsychological function and mood in bipolar subjects of any age.

Using Lithium (Li) Magnetic Resonance Spectroscopy (MRS), we can obtain an in vivo measure of Li concentrations within the brain. Previous studies using this technique have demonstrated an age-associated change in the brain-to-serum ratio, in individuals from ages 7–52, in which the brain-to-serum Li ratio increases with age.¹⁰ High brain lithium levels have also been shown to correlate with side effects.¹¹ The primary aim of this study was to determine if the brain-to-serum lithium ratio increased with advancing age beyond midlife, reflecting persisting age-related alterations in the uptake of lithium into the brain. The secondary aim of this study was to examine the relationship between brain and serum lithium levels and effects on neuropsychological functioning and mood in a group of older bipolar subjects. We hypothesized that the brain to serum lithium ratio would continue to increase with advancing age beyond midlife, reflecting persisting age-related alterations in the uptake of lithium into the brain. We also hypothesized that higher brain lithium levels would adversely effect performance on tests of executive function, but not adversely impact mood symptoms.

METHODS

The Institutional Review Boards at McLean Hospital and Boston University School of Medicine approved this study. Subjects were recruited through a) the McLean Hospital Mood Disorders Division, Geriatric Psychiatry Research Program and through referrals from the McLean Hospital Geriatric Psychiatry Inpatient Service, Partial Hospital Program and Outpatient Clinic; and b) the Division of Psychiatry, Boston University School of Medicine. Subjects were also recruited through flyers posted around the McLean Hospital and Boston University Medical campus and newspaper and radio advertisements in the Boston metropolitan areas.

Inclusion criteria for this study included current treatment with lithium for BD (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR)* Bipolar I Disorder, Bipolar II Disorder, or Bipolar Disorder Not Otherwise Specified), and a first episode of mania before the age of 50. Subjects aged 18–90 years of both sexes were eligible although subjects younger than 50 were required to be euthymic, whereas subjects older than 50 did not have to meet this inclusion criterion. Past studies have reported decreased levels of red blood cell sodium to lithium (Na–Li) counter transport in Blacks of African descent; therefore, this study was confined to White Caucasian subjects.^{12–14} Women of childbearing potential needed to be practicing an acceptable birth control method to participate. Exclusion criteria included a serious or unstable medical illness, and a history or current diagnosis of the following Axis I *DSM-IV* psychiatric disorders: schizophrenia, schizoaffective disorder, delusional disorder, psychotic disorders not otherwise specified, major depressive disorder, or patients with mood congruent or mood incongruent psychotic features. Some subjects had posttraumatic stress disorder, alcohol dependence, or anxiety disorders.

All subjects signed a written informed consent form. Subjects deemed eligible continued taking lithium without change. All subjects were assessed with a psychiatric interview by a board-certified psychiatrist. *DSM-IV-TR* criteria were used to establish a current diagnosis of BD. Acute medical comorbidities precluding inclusion in the study were assessed by clinical interview and review of appropriate medical records.

Lithium MRS examinations for all subjects were scheduled to commence between 7:30 and 9:00 A.M. and the testing was finished by 10 A.M. Immediately after the 4.0 T MRS examination, subjects had a blood draw to determine serum lithium levels. The MRS examination was scheduled to occur within 8–12 hours after the previous lithium dose to determine a trough lithium level. All subjects also completed a 1.5 T diagnostic magnetic resonance imaging (MRI) scan to rule out intracranial pathology precluding participation in the study.

At a separate visit, within 2 weeks of the MRS examination, neurocognitive testing was performed on the subset of subjects aged 50 years and older, and a blood sample was obtained to determine serum lithium levels. The blood draw was scheduled to determine a serum trough lithium level.

Neurocognitive Testing and Mood Rating Scales

Neurocognitive assessments in the older group (N = 10) included the Stroop Color and Word Test,¹⁵ the Trails A and B,¹⁶ and the Wisconsin Card Sorting Task (WCST).^{17,18} The Wechsler Abbreviated Scale of Intelligence¹⁹ was also administered. Memory function was assessed using the Consortium to Establish a Registry for Alzheimer's Disease Clinical and Neuropsychological Assessment of Alzheimer's Disease^{18,20} testing battery. This battery included the Boston Naming Test (15 items),²¹ the Mini Mental Status Exam,²² a three trial word list memory task, and a test of constructional praxis. Semantic and phonemic verbal fluency were assessed using a letter and category fluency task (FAS and animals).²³ T Scores were calculated from normative data sets designed for older adults.^{15,17,20,23,24}

In addition, mood was assessed using the Hamilton Depression Rating Scale (HDRS²⁵) and Young Mania Rating Scale (YMRS²⁶) before the MRS examination. All younger subjects were questioned with 28 items from the HDRS. Nine of the older subjects were also questioned with 28 items from the HDRS. In addition, they answered three questions, whether they had feelings of helplessness, hopelessness, or worthlessness; giving them an HDRS-31 score. For a post hoc analysis in the older subjects, the HDRS-31 was divided into emotional items (depressed mood, guilt, anxiety (psychic), helplessness, etc.) and items addressing somatic symptoms (insomnia, hypersomnia, gastrointestinal complaints, weight change, etc.).

MR Imaging and Spectroscopy Acquisition

Diagnostic imaging was performed on a GE 1.5 T Signa (GE Health Care Technologies, Milwaukee) with a volume head coil. These MRI scans were reviewed by a board-certified neuroradiologist.

The spectroscopy studies were performed on a 4.0 T Varian Unity/Inova whole body MR scanner (Varian NMR Instruments, Palo Alto, CA) equipped with a dual-tuned proton and lithium volumetric head coil (MR Instruments, Minneapolis, MN). Images were acquired using the proton channel localizers, and then shimming and lithium MRS were performed.

Lithium spectra were acquired from a 60-mm slice centered on the superior edge of the corpus collosum (Fig. 1A) using the image-selected in vivo spectroscopy (ISIS) sequence.²⁷ A two-step phase cycling (on/off) was used to achieve the slice localization. The ISIS parameters included TR = 5 s and 64 averages, for a total scan time of less than 5 minutes. The lithium spectrum included signal acquired from the in vivo brain lithium and a LiCl standard attached to the side of the coil (Fig. 1B). Once the subject has left the magnet a lithium spectrum from a 6 mM LiCl phantom and the coil standard were acquired under identical conditions to the in vivo study. The LiCl phantom has gadolinium added to shorten the T1 time and dysprosium to distinguish it from the LiCl coil standard.²⁸ The LiCl phantom is placed in a "loader shell" to provide equivalent dielectric loading to that of a human head. The T1 of the brain lithium signal (T1b) and the phantom lithium signal (T1p), at 4.0 T, had been determined previously at this site using an inversion recovery sequence.²⁹

MR Spectroscopy Analysis

The lithium spectroscopic data were processed using FELIX (Accelrys, San Diego, CA). Following a DC offset correction and 10 Hz exponential filtering the spectra were Fourier transformed to the frequency domain. The frequency domain spectra were then phase corrected and baseline corrected (with a cubic spline), and fit using a Lorentzian fit. In vivo brain lithium levels were calculated using the following equation:

$$[Li] = (S_{bo}) / (S_{po}) \times (V_b / V_p) \times [6 \text{ mM LiCl}] \times Q$$

$$s_{bo} = S_b / (1 - \text{EXP}(-TR/T1b))$$

$$s_{po} = S_p / (1 - \text{EXP}(-TR/T1p))$$

where S_b is the signal from the brain; S_p is the signal from the phantom; TR is the repetition time of the ISIS sequence (5 s); $T1b$ is the $T1$ relaxation time of the lithium brain signal (4.12 s); $T1p$ is the $T1$ relaxation time of the lithium phantom signal (0.52 s); S_{bo} is the integral of lithium signal from the brain measured using FELIX; S_{po} is the integral of lithium signal from a 6 mM LiCl phantom measured using FELIX; V_b is the sampled volume of the brain measured using NVM; V_p is the sampled volume of the phantom measured using NVM; and Q is the loading term = $\text{Sin}[(\text{Standard with phantom/standard with brain}) \times 18^\circ]$.

Image Segmentation and Volume Calculations

Structural 4.0 T MRI scans were segmented using open source software, “NVM” (<http://neuromorphometrics.org:8080/nvm/>), to determine the volume of brain tissue (subtracting out skull and CSF) contributing to the lithium spectroscopy slab.

Serum Lithium

Serum lithium levels were determined by Quest Diagnostics® Incorporated.

Statistical Analysis

The relationship between serum lithium, brain lithium, the ratio of serum/brain lithium, and age were initially explored with Pearson correlation. A significant result triggered a further test of both the younger group (20–49 years) replicating previous findings,¹⁰ and the older group (50–85 years). One-way analysis of variance was used to test the influence of sex on the above variables. To test the impact on cognitive performance of serum and brain lithium levels, two multiple regression models were constructed using FAS, animals, Trails A, WCST perseverative and nonperseverative errors as factors and brain or serum lithium levels as dependent variables. Trails B was tested against brain and serum lithium using Spearman correlation because of significant nonlinearity in the Trails B scores. Finally, Spearman correlations were used to determine the relatedness of brain and serum lithium to HDRS-31 and YMRS scores. A significant correlation triggered post hoc analysis of the HDRS-31 subscales as previously described.

RESULTS

Table 1 gives a description of the subjects' demographics, mean lithium dose, use of extended release lithium, and the number of other psychotropic medications they were receiving. Table 2 shows the subjects' age, duration of illness, and daily dose of lithium. For the older subjects (50–85 years), serum lithium levels were acquired on two occasions, on the day of the neurocognitive testing (serum lithium level = 0.68 ± 0.15 meq/L [N = 10]), and on the day of the MRS examination (serum lithium level = 0.64 ± 0.14 meq/L [N = 8]). Serum lithium levels were not available for two of the older subjects from the day of their MRS examination. For these two subjects the serum lithium level acquired on the day of their neurocognitive examinations was used in this analysis. All lithium levels were obtained as trough levels with subjects on stable lithium dosages, allowing levels across time points to be compared. The intraclass correlation coefficient (absolute agreement) for the serum levels between days 1 and 2 was 0.80 (N = 8).

Serum Lithium, Brain Lithium, Brain to Serum Ratio, and Age

With all subjects classed together, there was an association between the serum lithium levels and brain lithium levels ($r_p = 0.46$, $p < 0.02$, N = 26) (Fig. 2a). There was no correlation between serum lithium levels and age ($r_p = -0.03$, $p = 0.9$, N = 26), brain lithium levels and age ($r_p = -0.15$, $p = 0.5$, N = 26), or the brain to serum lithium ratio ($r_p = -0.11$, $p = 0.6$, N = 26) and age.

Post hoc division of subjects into younger and older groups to test the brain lithium and serum lithium association reaffirmed the presence of a correlation between serum lithium levels and brain lithium levels ($r_p = 0.65$, $p < 0.006$, N = 16) in the younger subjects.¹⁰ However, we could not detect that this relationship was present in the older subjects ($r_p = 0.11$, $p < 0.76$, N = 10) (Fig. 2b). We used multiple regression to test the difference in the slopes (Fig. 2b), which was not significant ($t_{[1,24]} = 1.19$, $p = 0.25$, N = 26).

An analysis of variance model with all subjects included showed no sex effect on any of either serum ($F_{[1,24]} = 0.00$, $p = 1.0$), brain ($F_{[1,24]} = 0.04$, $p = 0.9$), or ratio of serum to brain lithium parameters ($F_{[1,24]} = 0.26$, $p = 0.6$).

Neurocognitive Assessments

Neurocognitive assessments were performed on 10 subjects aged 57 to 85 (65.3 ± 9.6 years), four were women. The mean age and education corrected *T* scores are presented in Table 3. We examined those cognitive factors that relate directly to our hypothesis of effects of brain lithium on measures of executive functioning, including phonemic and semantic verbal fluency, psychomotor skills (Trails A), Stroop and WCST. We then created a single, multiple regression model from these factors in which brain lithium levels had a significant overall effect on these measurements ($F_{[6,9]} = 10.20$, $p = 0.04$). In particular, brain lithium levels had a significant effect on the Stroop Test ($t_{[3]} = -3.77$, $p < 0.01$), and the perseverative errors on the WCST ($t_{[3]} = -3.64$, $p < 0.03$). Trails A and the nonperseverative errors on the WCST did not achieve significance.

Brain and Serum Lithium Levels and Mood—Exploratory Analysis

The HDRS-31 and the YMRS were administered to the older subjects before their MRS examination. The mean HDRS-31 was 9.78 ± 7.17 ($N = 9$) and the mean YMRS was 3.00 ± 3.67 ($N = 9$). Brain lithium levels correlated positively with the HDRS-31 ($r_s = 0.92$, $p < 0.001$, $N = 9$) (Fig. 3). There was no association between serum lithium levels and the HDRS-31; or between brain lithium levels or serum lithium levels and the YMRS. In a post hoc analysis, the HDRS-31 was divided into emotional items (depressed mood, guilt, anxiety (psychic), helplessness, etc.) and items addressing somatic symptoms (insomnia, hypersomnia, gastrointestinal complaints, weight change, etc.) and these scores were compared with brain lithium levels. Using the Spearman correlation, we found a significant correlation between brain lithium levels and somatic symptoms ($r_s = 0.80$, $p < 0.01$, $N = 9$). There was less evidence for an association between brain lithium levels and the emotional symptoms ($r_s = 0.63$, $p < 0.07$, $N = 9$).

CONCLUSIONS

This study supported previous reports,^{10,28,30} of the presence of a correlation between serum lithium levels and brain lithium levels in younger adults. Our findings did not, however, find evidence to support the hypothesis that advancing age beyond midlife is associated with an elevation in the brain to serum lithium ratio. Furthermore, we found evidence that elevations in brain, but not serum, lithium levels were associated with executive dysfunction and higher depression rating scores in a sample of older adults with BD.

In our older sample, we found mean scores on measures of executive functioning slightly lower than age-adjusted population norms. Furthermore, our study demonstrated that elevations in brain lithium were associated with impairments in executive functioning as measured by the Stroop Interference tests and perseverative errors on the WCST. However, serum lithium levels did not correlate with findings of executive dysfunction in this subpopulation, suggesting that clinical monitoring of serum lithium alone without a clinical assessment of cognitive functioning may not be an adequate predictor of lithium neurotoxicity in older adults with BD. These findings also suggest that elevated brain lithium levels may exacerbate symptoms of cognitive dysfunction already associated with BD (see below). Furthermore, this supports earlier suggestions that serum lithium levels should be maintained at lower levels ($0.4\text{--}0.8$ meq/L)³¹ in older adults to minimize neurotoxic side effects.

Clinicians are often concerned about potential neurotoxicity associated with lithium treatment.³² Subtle signs of lithium neurotoxicity may be overlooked in an elderly population due to nonspecific signs such as fatigue, tremor, and unsteady gait that are more frequent in an older population. In addition, BD is characterized by persistent cognitive impairments³³ frequently involving executive functions mediated by the prefrontal cortex³⁴ and/or the anterior cingulate cortex.^{35,36} Moderate to severe cognitive impairment and memory loss are associated with the manic state in BD.^{37,38} Euthymic subjects also have some degree of cognitive dysfunction and impairment of executive function that becomes increasingly severe in patients with a chronic course of illness characterized by multiple manic and/or depressive episodes.³⁹

Differentiating the effects of medication from the effects of illness, particularly chronic illness, may be a difficult task. Two meta-analyses looking at the effects of lithium only showed that increasing lithium impairs verbal fluency and psychomotor task speeds,³² as well as memory, vigilance, reaction time, and tracking.⁴⁰ However, in our sample, neuropsychological tests in these domains, such as the Consortium to Establish a Registry for Alzheimer's Disease Verbal Fluency FAS, Trails A and B, and Boston Naming Test did not correlate significantly with brain lithium levels. Some tests of executive function, namely the Stroop Interference tests and perseverative errors on the WCST, showed significant correlation to brain lithium levels despite previous findings that deficits in executive function are usually attributed to the effects of chronic illness rather than medication.³³

Two possible explanations for these results then emerge. The first is that higher brain levels of lithium may contribute to the executive dysfunction seen in older subjects with BD. These deficits may be additive to the executive impairment effects related to chronic bipolar illness that has been observed in prior studies.³³ A second explanation is that these deficits in executive function may be attributable to the severity or chronicity of illness in the individual subjects. In this interpretation, the increased brain lithium levels may reflect an upward titration of dosage to achieve appropriate symptomatic control in those patients with more severe or chronic illness.

Our findings also demonstrate that elevated brain lithium levels are associated with higher scores on the HDRS-31. In addition to emotional symptoms of depression, the HDRS-31 includes several somatic symptoms of depression such as fatigue or gastric distress that could overlap with symptoms of lithium toxicity. In a post hoc analysis, these somatic symptoms demonstrated a correlation with brain lithium levels in the older group, suggesting that the somatic complaints associated with lithium toxicity are important factors contributing to the association of high HDRS-31 scores and high brain lithium. We were unable to detect a similar relationship for the emotional symptoms (e.g., anhedonia, depressed mood, guilty rumination) of depression. This suggests that HDRS-31 scores in older adults with BD could be due to physical side effects caused by excess brain lithium rather than a recurrence of the emotional symptoms of depression. Clinicians should, therefore, consider the possibility of lithium toxicity when confronted with a depressive syndrome in older adults with BD on lithium. Rather than adding an antidepressant in such situations, the appropriate clinical management strategy would be to lower the lithium dose to minimize the toxic side effects of lithium and reduce the apparent somatic symptoms of depression.

Brain lithium levels measured using lithium MRS have shown that with aging, the amount of lithium in brain tissue increases in relation to the amount of serum lithium.¹⁰ In contrast to this earlier study looking at children and adults, our study did not find evidence of an increase in the brain to serum lithium ratio with advancing age beyond midlife. This may be due to the inclusion of children and adolescents in the earlier study. Also, the mean serum lithium level in the earlier study was 0.36 meq/L compared with 0.66 meq/L in this study. It should also be noted that serum lithium levels were not available for two of the older subjects from the day of their MRS examination. For these two subjects the serum lithium

level acquired on the day of their neurocognitive examinations was used in this analysis. However, there was no correlation between the brain to serum ratio and age for the 24 remaining subjects for whom we had serum and brain lithium levels acquired on the same day.

Consistent with previous studies,^{10,28,30} the brain lithium ratio correlated with the serum lithium ratio for the group as a whole. However, the relationship between brain lithium levels and serum lithium levels was not present for the group of subjects older than 50. It is possible that the greater level of depression in the older age group due to the relaxed inclusion criterion for euthymic condition could be one factor in the breakdown in the brain-serum lithium relationship. However, this explanation seems unlikely due to previous studies in younger age groups where similar inclusion criteria to the older subjects in this study were used and the serum-brain relationship was maintained.¹⁰ Therefore, why this relationship between serum and brain lithium seemed to specifically break down in those older than 50 raises questions about changes in lithium transport into brain that may be affected by factors associated with aging. Lithium ions are water-soluble and distribute throughout all of the water in the body in a manner that is similar to the distribution of sodium ions (Na⁺).⁴¹ Lithium crosses the blood-brain barrier (BBB) with a mean ratio of serum to CSF lithium of 3.6:1.⁴² However, the BBB becomes compromised with age.⁴³ In addition to changes in the BBB with age that may alter lithium uptake into the brain, clinical response to lithium can also be affected by age-related physiological changes, medical comorbidity, and concomitant medications that influence the pharmacokinetics of lithium in an older adult.⁴¹ For years it has been noted that a lower dose of lithium is required in an older individual to achieve the same serum concentration compared with a younger adult due to age-related decreases in both volume of distribution and renal clearance.⁴⁴

Limitations to our current study include a small sample size, cross-sectional design, neuropsychological testing on a subpopulation of older subjects only, and the lack of a healthy control comparison group on lithium to compare alterations in the brain and serum lithium levels and clinical effects on neuropsychological functioning and depressive symptoms in healthy older adults. Furthermore, given our small sample size (N = 10) of adults older than 50, definitive conclusions about our finding of no relationship between brain and serum lithium levels over the age of 50 must be understood as preliminary, requiring a larger subject population to understand this relationship more definitively. Additionally, differences in inclusion criteria for the younger and older subject groups (with regards to level of baseline mood symptoms) and the absence of neuropsychological measures for the group of younger subjects limited our ability to compare the relationship of brain and serum lithium levels to these relevant clinical effects across the age spectrum. We view our study results as preliminary and future studies should clearly address this limitation and include consistent clinical measures across the sample population.

Finally, a limitation of our imaging protocol includes the use of a 2-step ISIS sequence to achieve spatial localization. This introduces an error whereby some signal from outside the region of interest may contaminate the region of interest, leading to uncertainty as from exactly where the lithium signal measured is originating.⁴⁵

Our findings of executive dysfunction and elevated depression symptoms (related to somatic, not mood symptoms) correlating with higher brain lithium levels supports conservative dosing recommendations and maintaining lower serum lithium levels in older individuals with BD. Furthermore, the lack of a predictable relationship between serum and brain lithium, related perhaps to variability of aging effects on lithium transport and other mechanisms, make specific individual predictions about the “ideal” lithium serum level in an older adult with BD difficult.

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FIGURE 1.

ISIS Localization and in Vivo Brain Lithium Spectrum

Notes: [a] Lithium spectra are acquired from a 60-mm slice centered on the superior aspect of the corpus callosum. This image shows the ISIS localization on an older male with bipolar disorder. [b] In vivo brain lithium spectrum acquired from an older male with bipolar disorder.

FIGURE 2.

Linear Regression of Brain Versus Serum Lithium Levels

Notes: [a] Brain and serum lithium levels in adults (age 20 – 85 years). Brain lithium levels correlated with serum levels in an overall analysis ($r_p = 0.46$, $p < 0.02$, $n = 26$). [b] Brain and serum lithium levels in adults (age 20 – 85 years). Brain lithium levels correlated with serum levels in the young subjects (<50 years) ($r_p = 0.65$, $p < 0.006$, $n = 16$), but was not present for the older subjects (50 – 85 years) ($r_p = 0.11$, $p < 0.76$, $n = 10$). The difference in the slopes shown is not significant ($t_{[22]} = 1.19$, $p = 0.25$, $n = 26$).

FIGURE 3.
Brain Lithium Levels and Hamilton Depression Rating Scale (HDRS) Scores in Older Adults with Bipolar Disorder ($r_s = 0.924$, $p < 0.001$, $n = 9$)

TABLE 1
Subject Demographics, Mean Lithium Dose, Use of Extended Release Lithium and Use of Other Psychotropic Medications

Age Group	N	Age Mean (SD)	Sex N (%) Female	Lithium Dose (mg) Mean (SD)	Extended Release (%)	Other Psychotropics M (SD)	YMRS Mean (SD)	HDRS-28 Mean (SD)
Younger (<50 yrs)	16	29.3 (7.8)	4 (25)	1106 (319)	9 (56)	2 (1.3)	0.37 (1.74)	2.3 (2.3)
Older (>50 yrs)	10	65.3 (9.6)	4 (40)	735 (370)	3 (30)	1.3 (1.3)	3.0 (3.67) (n = 9)	8.5 (5.9) (n = 9) ^a

^a HDRS-28 score is shown for older subjects.

TABLE 2

Age, Duration of Illness, and Daily Dose of Lithium

Age (yrs)	Duration of Illness (yrs)	Li Daily Dose (mg)
20	2	1,800
21	3	1,200
22	1	1,500
23	7	1,200
24	1	900
24	3	1,200
27	1	900
28	8	1,350
28	9	600
28	9	1,200
29	5	1,500
31	13	900
40	17	900
36	7	900
42	17	600
46	25	1,200
56	18	1,200
56	39	1,500
59	34	600
59	40	600
60	38	1,200
63	30+	600
67	30+	600
67	46	450
78	30+	300
84	58	450

TABLE 3

Mean Scores (Adjusted for Age, Education, Sex) for the Neurocognitive Tests

	N	Mean	<i>t</i> -Ratio	
			Serum	Brain
Phonemic verbal fluency	10	31.20 ± 16.10	2.97	0.59
Semantic verbal fluency	10	42.40 ± 11.27	1.87	2.16
Stroop Interference	10	47.33 ± 6.73	-3.13	-3.77*
Trails A	10	37.80 ± 18.04	-3.55	-0.15
WCST nonperseverative errors	10	45.10 ± 11.04	1.88	1.99
WCST perseverative errors	10	42.60 ± 11.06	-1.53	-3.64*

Notes: Multiple regression model employing neurocognitive tests as factors and 1) serum lithium levels or 2) brain lithium levels as the dependent variable. Overall model for brain lithium was significant ($F[6,9] = 10.20$; $p = 0.04$). Overall model for serum lithium was not significant ($F[6,9] = 2.89$; $p = 0.21$).

* $t[3]$: $p < 0.05$.

WCST: Wisconsin Card Sorting Task.