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Brain lithium, *N*-acetyl aspartate and *myo*-inositol levels in older adults with bipolar disorder treated with lithium: a lithium-7 and proton magnetic resonance spectroscopy study

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Abstract

Objectives—We investigated the relationship between brain lithium levels and the metabolites *N*-acetyl aspartate (NAA) and *myo*-inositol (*myo*-Ino) in the anterior cingulate cortex of a group of older adults with bipolar disorder (BD).

Methods—This cross-sectional assessment included nine subjects (six males and three females) with bipolar I disorder and currently treated with lithium, who were examined at McLean Hospital's Geriatric Psychiatry Research Program and Brain Imaging Center. The subjects' ages ranged from 56 to 85 years (66.0 ± 9.7 years) and all subjects had measurements of serum and brain lithium levels. Brain lithium levels were assessed using lithium magnetic resonance spectroscopy. All subjects also had proton magnetic resonance spectroscopy to obtain measurements of NAA and *myo*-Ino.

Results—Brain lithium levels were associated with higher NAA levels [df = (1, 8), B = 12.53, $t = 4.09$, $p < 0.005$] and higher *myo*-Ino levels [df = (1, 7), $F = 16.81$, $p < 0.006$]. There were no significant effects of serum lithium levels on any of the metabolites.

Conclusion—Our findings of a relationship between higher brain lithium levels and elevated NAA levels in older adult subjects with BD may support previous evidence of lithium's neuroprotective, neurotrophic, and mitochondrial function-enhancing effects. Elevated *myo*-Ino related to elevated brain lithium levels may reflect increased inositol monophosphatase (IMPase) activity, which would lead to an increase in *myo*-Ino levels. This is the first study to demonstrate alterations in NAA and *myo*-Ino in a sample of older adults with BD treated with lithium.

Keywords

brain lithium; geriatric bipolar disorder; *myo*-inositol; *N*-acetyl aspartate; proton magnetic resonance spectroscopy

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Lithium has been used for over 35 years for the treatment of bipolar disorder (BD), yet the precise neurobiological mechanisms through which lithium exerts its clinical effects are not clear. Concerns regarding neurotoxic side effects of lithium in older adults, including a more prolonged recovery from lithium-induced delirium (1) and the risk of lithium-induced renal insufficiency, have led to both declining rates of lithium use in older adults (2) and questions about the most effective clinical approach to utilizing lithium safely in older adults with BD.

Lithium magnetic resonance spectroscopy (^{7}Li MRS) measures *in vivo* brain lithium levels. In a recent study at McLean Hospital's Geriatric Psychiatry Research Program and Brain Imaging Center, Belmont, MA, USA, we demonstrated that elevations in brain lithium levels were associated with frontal lobe dysfunction and higher Hamilton Depression Rating Scale (HDRS) (3) scores in older adults with BD (4). The higher HDRS scores were associated with somatic symptoms of depression, such as fatigue.

Proton magnetic resonance spectroscopy (^{1}H MRS) measures *in vivo* levels of brain metabolites, including *N*-acetyl aspartate (NAA), a putative marker of neuronal viability, and *myo*-inositol containing compounds (*myo*-Ino). More than half of the studies of adults with BD compared with healthy comparison subjects (HCS) (5–11) report decreased NAA in subjects with BD compared with HCS (5, 6, 10, 11). Lithium has been shown (after four weeks of treatment) to increase brain NAA levels acutely in subjects with BD and in healthy controls (12). Similarly, Silverstone et al. (13) measured increased NAA/Cr levels in the frontal and temporal lobes of BD subjects chronically treated with lithium compared with healthy controls. NAA, which is synthesized in mitochondria, also helps to maintain myelin and is involved with neuron-to-glia signaling (14, 15).

Proton magnetic resonance spectroscopy can also measure *myo*-Ino levels. The inositol depletion hypothesis suggests that lithium's efficacy in BD may be related to an inhibition of inositol monophosphatase (IMPase), leading to a reduction in brain *myo*-Ino and an increase in inositol-1-phosphate (I-1-P) (16).

Given our recent findings of frontal lobe dysfunction associated with higher brain lithium levels, the purpose of this study was to establish whether there was an association between brain lithium levels and NAA levels in the anterior cingulate cortex (ACC) of older adults with BD. Regional neuroanatomical abnormalities in the prefrontal cortex (PFC) and ACC have been consistently implicated in BD (17). We also wished to further explore the effects of lithium on *myo*-Ino in older adults with BD. We hypothesized that elevations in brain lithium would be associated with an increase in NAA and a decrease in *myo*-Ino, reflecting alterations in cellular signaling required for the therapeutic efficacy of lithium.

Patients and methods

The Institutional Review Board at McLean Hospital approved this study. Subjects were recruited through referrals from the McLean Hospital Geriatric Psychiatry Inpatient Service, Partial Hospital Program and Outpatient Clinic. Subjects were also recruited through flyers posted around McLean Hospital and advertisements in local newspapers and radio.

Inclusion criteria for this study included current treatment with lithium for DSM-IV-TR bipolar I disorder (18) and a first episode of mania before age 50 (early-onset BD). Subjects aged 50 to 90 years of both sexes were eligible. Exclusion criteria included a serious or unstable medical illness, including cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematologic disease; a first episode of mania after age 50 (late-onset BD); a history of seizure disorder; and a history or current diagnosis of any other DSM-IV-TR Axis I psychiatric illness. One subject had a comorbid diagnosis of alcohol dependence.

All subjects signed a written informed consent form. Subjects meeting inclusion/exclusion criteria continued taking lithium medication without change. All subjects were assessed with a psychiatric interview by a board-certified psychiatrist to establish a diagnosis of BD.

Proton and lithium MRS examinations for all subjects were scheduled to commence between 07:30 and 08:30. Immediately following the 4.0 T MRS examination, subjects had a blood draw to determine trough serum lithium levels. The ^{7}Li MRS examination was scheduled to occur within 8–12 h after the previous lithium dose to determine a trough brain 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.

MRI and spectroscopy acquisition

Diagnostic imaging was performed on a GE 1.5 T Signa (General Electric Medical Technologies, Milwaukee, WI, USA) with a volume head coil. Brain MRI data were acquired for purposes of ruling out clinically significant central nervous system (CNS) disorders. These MRI scans were reviewed by a board-certified neuroradiologist.

All MRS studies were performed on a 4.0 T Varian Unity/Inova whole body magnetic resonance scanner (Varian NMR Instruments, Palo Alto, CA, USA) equipped with a dual-tuned proton and lithium volumetric head coil (MR Instruments, Minneapolis, MN, USA). Proton spectra were acquired from a 2 cm × 2 cm × 2 cm voxel localized on the ACC using the point resolved spectroscopy sequence [repetition time (TR) = 2 s, echo time (TE) = 30 ms, and averages = 128]. The voxel was placed over the anterior cingulate gyrus, in a predominantly gray-matter area, superior to the orbits and inferior to the genu of the corpus collosum. Lithium spectra were acquired from a 60 mm slice centered on the superior edge of the corpus collosum using the Image Selective In Vivo Spectroscopy (ISIS) spectroscopy sequence (TR = 5 s and averages = 64) (19). The lithium spectrum included signal acquired from the *in vivo* brain lithium and a LiCl standard attached to the side of the coil. Once the subject had left the magnet, a lithium spectrum from a 6 mM LiCl phantom and the coil standard was acquired under identical conditions to the *in vivo* study.

MRS analysis

Following data acquisition, the proton spectra were fit using LCModel (Version 6.1-0) (20) and a simulated basis set. The Cramer-Rao spectral inclusion criteria for the spectra were NAA, Cho, Cr, and *myo*-Ino SD < 15%.

The lithium spectroscopy data were transferred from the 4 T Varian Unity/Inova to a Windows PC (Windows XP Service Pack 2 with a Pentium IV processor) to be processed

using FELIX (Accelrys, San Diego, CA, USA). FELIX is a proprietary multidimensional nuclear magnetic resonance processing package capable of peak fitting using a simulated annealing algorithm. Following a direct current offset correction and 10 Hz exponential filtering, the spectra were Fourier transformed to the frequency domain. The frequency spectra were phase corrected and baseline corrected (with a cubic spline) and fit using a Lorentzian fit. The *in vivo* brain lithium levels were calculated using the following equation:

$$[Li] = (Sbo)/(Spo) * (Vb/Vp) * [6\ mMLiCl] * Q$$

$$Sbo = Sb/[1 - EXP(-TR/T1b)]$$

$$Spo = Sp/[1 - EXP(-TR/T1p)]$$

Sb: Signal from brain.

Sp: Signal from phantom.

TR: repetition time of the ISIS sequence = 5 s.

T1b: T1 relaxation time of the lithium brain signal = 4.12 s.

T1p: T1 relaxation time of the lithium phantom signal = 0.52 s.

Sb: integral of lithium signal from the brain measured using FELIX.

Sp: integral of lithium signal from a 6 mM LiCl phantom measured using FELIX.

Vb: sampled volume of the brain measured using NVM (see below). This volume includes only brain and excludes cerebrospinal fluid (CSF) and muscle.

Vp: sampled volume of the phantom measured using NVM.

Q: loading term = Sin[((Standard with phantom/standard with brain)*18) degrees].

Image segmentation and volume calculations

Structural 4.0 T MRI scans were segmented using open-source software, NVM (freely available from Neuromorphometrics, Inc., at http://neuromor-phometrics.org:8080/nvm/), to determine gray matter, white matter, and CSF contributions to the ACC voxel of interest, and to determine the volume of brain tissue (subtracting skull and CSF) contributing to the lithium spectroscopy slab.

Serum lithium

Serum lithium levels were determined by Quest Diagnostics®, Inc.

Statistical analysis

Linear regression with a backward elimination procedure for covariate selection was used as the primary analysis method. For hypothesis-driven tests, statistical significance was defined at an alpha level of 0.05 using two-tailed tests. SPSS 11.0 for Macintosh OSX was used for all computations.

Results

Nine subjects with DSM-IV-TR bipolar I disorder, currently treated with lithium, were examined. The subjects' ages ranged from 56 to 85 years (66.0 ± 9.7 years); there were six male subjects and three female subjects. 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. Serum lithium levels were acquired on two occasions: on the day of their initial assessment [serum lithium level = 0.65 ± 0.07 mEq/L (n = 9)], and on the day of the MRS examination [serum lithium level = 0.71 ± 0.18 mEq/L (n = 7)]. Serum lithium levels were not available for two of the subjects from the day of their MRS examination. For these two subjects, the serum lithium level acquired on the day of their initial assessment was used in the 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 (ICC) (absolute agreement) for the serum levels between Day 1 and Day 2 was = 0.80 (n = 8).

The mean metabolite levels (institutional units) and standard deviations for all the measured proton MRS metabolites are shown in Table 2. For comparison with other studies, we also include metabolite ratios to creatine. Structural 4.0 T MRI scans were segmented using open-source software to determine gray matter, white matter, and CSF contributions to the voxel of interest (see Table 2). The voxel gray matter content was used as a covariate in the statistical analysis. The brain lithium levels, serum lithium levels and the brain-to-serum ratio are also included in Table 2.

Linear regression with a backward elimination procedure for covariate selection was conducted to look at the effects of age, sex, voxel gray matter content, and brain lithium levels on the ACC NAA and *myo*-Ino levels. Brain lithium levels were associated with higher NAA levels [df = (1, 8), B = 12.53, $t = 4.09$, $p < 0.005$] (see Fig. 1) and higher *myo*-Ino levels [df = (1, 7), B = 4.75, $t = 4.10$, $p < 0.006$] (see Fig. 2).

There was no significant correlation between the other measured metabolites [creatine + phosphocreatine (Cr), choline-containing compounds (Cho), glutamate (Glu), and glutamine (Gln)] and the brain lithium levels. There were no significant effects of serum lithium levels on any of the metabolites.

Discussion

This is the first study to demonstrate alterations in NAA and *myo*-Ino in a sample of older adults with BD treated with lithium. Previous studies have focused on samples of children, adolescents, and younger adults with BD and found evidence of elevated NAA levels in bipolar patients treated with lithium (21) and mixed reports of lithium's effects on *myo*-Ino (22–24). Furthermore, unlike previous studies, we examined the relationship between brain lithium levels and the metabolites NAA and *myo*-Ino. Consistent with previous studies in adults and with our initial hypothesis, we demonstrated an association between brain lithium levels and higher NAA levels. However, contrary to our original hypothesis, we found an

association between brain lithium levels and elevated levels of *myo*-Ino-containing compounds.

NAA and *myo*-Ino in proton MRS studies in bipolar disorder

There have been over 20 studies that include a total of over 300 child, adolescent, and adult subjects with BD using proton MRS to study brain metabolites such as NAA, choline, glutamate/glutamine, and *myo*-Ino (21). NAA levels were generally found to be lower in the frontal lobe structures and hippocampus of euthymic bipolar individuals compared with healthy control subjects. Although lithium treatment in general seemed to be associated with an increase in NAA, some studies found a decrease in NAA with lithium treatment.

In a study by Moore and Galloway (25), lithium (mean levels of 0.8 mEq/L) was shown to increase NAA levels acutely after four weeks of treatment in the brains of 14 subjects with BD and 9 HCS. There was no correlation between serum lithium levels and NAA levels. However, this result is inconsistent with a number of other MRS studies of patients with BD, pre- and post-lithium treatment, including a previous study by the same group (22, 26–28); and a study by Brambilla et al. of HCS pre- and post-lithium treatment (29). None of these studies found significant effects of lithium on NAA.

A number of studies of BD subjects who had been medicated with lithium for at least six months have shown that NAA or NAA/Cr levels were equivalent to or higher than the levels in HCS. In four studies of lithium-treated BD subjects, no significant differences were found in NAA/Cr levels compared with HCS (23, 30–32). In another study, Silverstone et al. (13) found higher NAA/Cr levels in the frontal and temporal lobes among lithium-treated BD subjects compared with HCS. More recently, Brambilla et al. (33) measured increased NAA/Cr in the left dorsolateral prefrontal cortex of lithium-treated subjects compared with subjects who were not treated with lithium, and Frye et al. (34) found decreased NAA in the ACC of 16 BD subjects compared with HCS, but only 5 were treated with lithium. Interestingly, Winsberg et al. (11) and Ohara et al. (31) both report decreased NAA/Cr associated with illness duration.

The findings from proton MRS studies investigating *myo*-Ino in child, adolescent, and adult BD subjects and healthy controls are less clear. Silverstone et al. (35) failed to find changes in *myo*-Ino/Cr in the temporal lobes of healthy adults following chronic lithium administration. However, Davanzo et al. (26) looked at the effect of lithium on *myo*-Ino/Cr in the ACC of youths with BD (manic phase) and found *myo*-Ino/Cr to be increased at baseline compared with one week of lithium therapy and compared with HCS. These results are similar to those of Moore et al. (28), who observed decreased *myo*-Ino levels in the frontal lobes of depressed adults with BD following acute lithium treatment. Davanzo et al. (26) also noted that the *myo*-Ino/Cr decreases were greater in lithium responders than non-responders. These studies lend weight to the inositol depletion hypothesis of lithium's efficacy in BD.

Support for lithium's neuroprotective, neurotrophic, and mitochondrial function-enhancing properties

Our findings of a relationship between higher brain lithium levels and elevated NAA levels in older adult subjects with BD support evidence of lithium 's neuroprotective, neurotrophic and mitochondrial function-enhancing effects. We believe these results fit into a model wherein lithium inhibits GSK-3 (36), increases B-cell lymphoma/leukemia-2 gene (bcl-2) (37), which appears to inhibit necrotic and apoptotic cell death (36), and increases brain-derived neurotrophic factor (BDNF) (38) and hence NAA. Lang et al. (39) found a direct correlation between serum levels of BDNF and ACC NAA in healthy subjects. Therefore, NAA, in addition to being a marker of neuronal viability, may also be a marker for BDNF activity.

Increased gray matter volume has been demonstrated with chronic lithium treatment in patients with BD (23). Elevations in brain NAA levels, therefore, may reflect increased neuronal viability and function in bipolar subjects treated with lithium (23). Elevations in brain NAA associated with brain lithium levels suggest that lithium may also be exerting a neurotrophic effect.

In addition to a neurotrophic and neuroprotective role, lithium may also exert beneficial effects through its ability to enhance mitochondrial function. Recent work has demonstrated that lithium increases mitochondrial mass and adenosine triphosphate (ATP) production (40). NAA is synthesized in mitochondria by the membrane-bound enzyme l-aspartate *N*-acetyl-transferase, a catalyst that is found only in brain tissue (41). Research suggests that decreased levels of NAA may imply impaired mitochondrial energy production (42, 43) and that NAA levels are closely related to mitochondrial energy metabolism, and thus may serve as a measure of mitochondrial function (41, 44–47).

Lithium has also been shown to increase both bcl-2, an anti-apoptotic protein (37), and NAA (23). Both of these properties suggest that lithium stimulates neurogenesis (the synthesis of proteins, lipoproteins, and enzymes in the brain), which requires significant energy consumption (48). Therefore, although lithium is associated with ATP production, treatment with lithium may also paradoxically lead to decreases in ATP levels as a result of enhancing processes requiring high energy. Finally, although it is difficult to interpret cause and effect in this cross-sectional study, it is possible that the bipolar individuals studied may actually have increased mitochondrial metabolism, and hence greater NAA, and may retain more brain lithium due to enhanced transport into the cell.

Relationship of brain lithium and *myo*-inositol

Contrary to our original hypothesis, we found a positive association between brain lithium levels and *myo*-Ino. The proton MRS peak at 3.6 ppm, *myo*-Ino, represents inositol-containing compounds, which includes *myo*-Ino and I-1-P (49). However, I-1-P contributes about 1 mM, and *myo*-Ino contributes about 5 mM to the total peak area (50). This provides support that an increase in this resonance can be primarily attributed to an increase in *myo*-Ino.

Lithium was first shown to reduce cerebral concentrations of *myo*-Ino in the rat cerebral cortex in 1977, leading to the *myo*-inositol depletion hypothesis for lithium's mechanism of action in BD (51). The inositol depletion hypothesis suggests that lithium's efficacy in BD may be related to an inhibition of IMPase, leading to a reduction in brain *myo*-inositol and an increase in I-1-P (52). However, recent studies have shown that chronic lithium treatment increases IMPase activity, which would lead to an increase in *myo*-Ino levels (52, 53).

Another study, by Patel et al. (54), demonstrated increased *myo*-Ino at 42 days of lithium treatment compared with seven days of lithium treatment in depressed adolescents with BD. If lithium increased IMPase activity, the downstream consequence would be inhibition of protein kinase C (PKC) (55). Indeed, it has been shown that PKC is inhibited by lithium (56). Furthermore, PKC inhibits GSK-3 (57, 58) which may be the mechanism by which lithium upregulates BDNF and inhibits GSK-3 (38). Therefore, lithium activation of IMPase would lead to increased *myo*-Ino levels and an increase in BDNF, reflected by the measurement of NAA by proton MRS. Our results of higher *myo*-Ino levels correlating with elevated brain lithium in subjects receiving chronic lithium therapy are consistent with an increase in IMPase activity and an elevation of NAA.

Complicating the issue of the relationship between lithium and *myo*-Ino are conflicting findings regarding the relationship of inositol use to treatment response in bipolar adults. Although previous studies have reported a modest effect of inositol therapy for patients with treatment-resistant bipolar depression (59, 60), other studies have paradoxically shown that an inositol-deficient diet may augment the efficacy of lithium in BD (61). Our sample of older bipolar subjects had a mean 28-item HDRS score of 8.5, suggesting a mild degree of depression in this sample. The findings of a positive correlation between *myo*-Ino and brain lithium levels may be related to a trait marker of disease severity and may differ in euthymic bipolar adults.

Brain lithium levels in older adults with bipolar disorder

Importantly, our findings were limited to a relationship between the metabolites, NAA and *myo*-Ino, and brain lithium levels. We did not find a significant relationship between any of the brain metabolites measured by proton MRS and serum lithium in the periphery. Although clinicians rely on serum lithium measurements to serve as proxy indicators of brain lithium levels, there is evidence to suggest that a linear relationship between the brain and serum lithium breaks down in adults with BD beyond middle age (4). In the elderly population, the relationship between the brain and serum lithium 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 include an extended elimination half-life and higher serum lithium levels at lower doses (62).

Furthermore, intracellular neuronal accumulation of lithium may account for lithium-related CNS toxicity even with relatively low serum lithium levels. Lithium, a naturally occurring ion handled similarly to sodium ions (Na^+) in the human body (63), crosses the blood-brain barrier with a mean ratio of serum to CSF lithium of 3.6:1. In brain tissue, lithium entry is mainly through the voltage-sensitive Na^+ channel (64), while the major route of lithium

efflux is through the Na^+– Li^+ counter exchange system (64). Red blood cells (RBCs), neurons, and glia all transport lithium against an electrochemical gradient by means of Na^+–Li^+ counter-transport system (65, 66). There appears to be an inhibition of RBC Na^+–Li^+ counter-transport with long-term lithium treatment (67), leading to an increased intra- to extracellular lithium ratio. Dorus et al. (in an unpublished manuscript) considered that age-related CNS activity in the elderly might be in part related to higher intracellular lithium concentrations in RBCs (68). Thus, lithium neurotoxicity at normally nontoxic serum lithium levels may be due to excessive intracellular lithium accumulation. This effect may be exacerbated by long-term lithium treatment and age.

Limitations to this study include its small sample size, cross-sectional design, and the lack of an age-matched healthy control group or a group with BD treated with other specific therapies, such as divalproex, that would allow for comparisons of treatment-specific mechanisms of action, including the ability to adequately test the hypothesis of lithium's effects on *myo*-Ino and NAA. Although likely that there is a brain lithium-level threshold above which lithium treatment is neurotoxic and below which lithium is not clinically effective, the small sample size and lack of a control group of patients with BD taking specific alternative treatments did not allow for an analysis of such a question. In addition, some of our subjects were treated with concomitant psychotropic medications in a non-systematic fashion that may have limited our ability to interpret the relationship between brain metabolite changes and brain lithium levels (See Table 2 for concomitant psychotropic medications used).

Our interpretation of the relationship between brain *myo*-Ino and brain lithium levels may also be compromised by the clustered distribution of measured brain lithium values (0.00–0.20 and 0.40–0.80 mEq/L; see Fig. 2). Although the absence of brain lithium data between 0.20–0.40 mEq/L limits the interpretation of our findings, we did find that linear and logarithmic curve estimations for *myo*-Ino versus brain lithium levels significantly fitted the data ($F = 16.81$, $p < 0.006$ and $F = 34.56$, $p < 0.001$, respectively), with both curves demonstrating *myo*-Ino increasing with increasing brain lithium levels.

A further limitation to this study is the lack of younger subjects with BD who also received proton MRS to examine age-related effects on brain metabolites that reflect mitochondrial function and membrane synthesis. Previous studies using phosphorus (^{31}P) MRS have detected age-associated effects that may be related to changes in mitochondrial functioning, including elevated levels of phosphocreatine (PCr) and decreased brain pH (69, 70). Age-associated changes in brain chemistry have also been described in studies using ^1H MRS (71–74), including specific findings of decreased NAA possibly reflecting impaired mitochondrial energy function (42, 43).

Future prospective controlled studies of lithium compared with alternative treatments, including divalproex or atypical antipsychotics, utilizing MRS in older and younger adults with BD, may help to clarify more specifically age-related changes in brain metabolites and mechanisms of treatment response.

In summary, we found evidence of elevated NAA and increased *myo*-Ino levels associated with higher brain lithium levels in the ACC of a sample of older adults with BD. This study is the first to examine the association of brain lithium levels with *in vivo* brain metabolites using proton MRS. It is also the first to exclusively examine an older sample of BD subjects, a group that is likely to expand with the aging of the population and about which there has been little evidence-based treatment intervention research. Furthermore, the fact that older individuals with BD are subject to age-associated cerebral atrophy and mitochondrial dysfunction makes lithium's potential neuroprotective, neurotrophic, and mitochondrial function-enhancing effects potentially clinically appealing.

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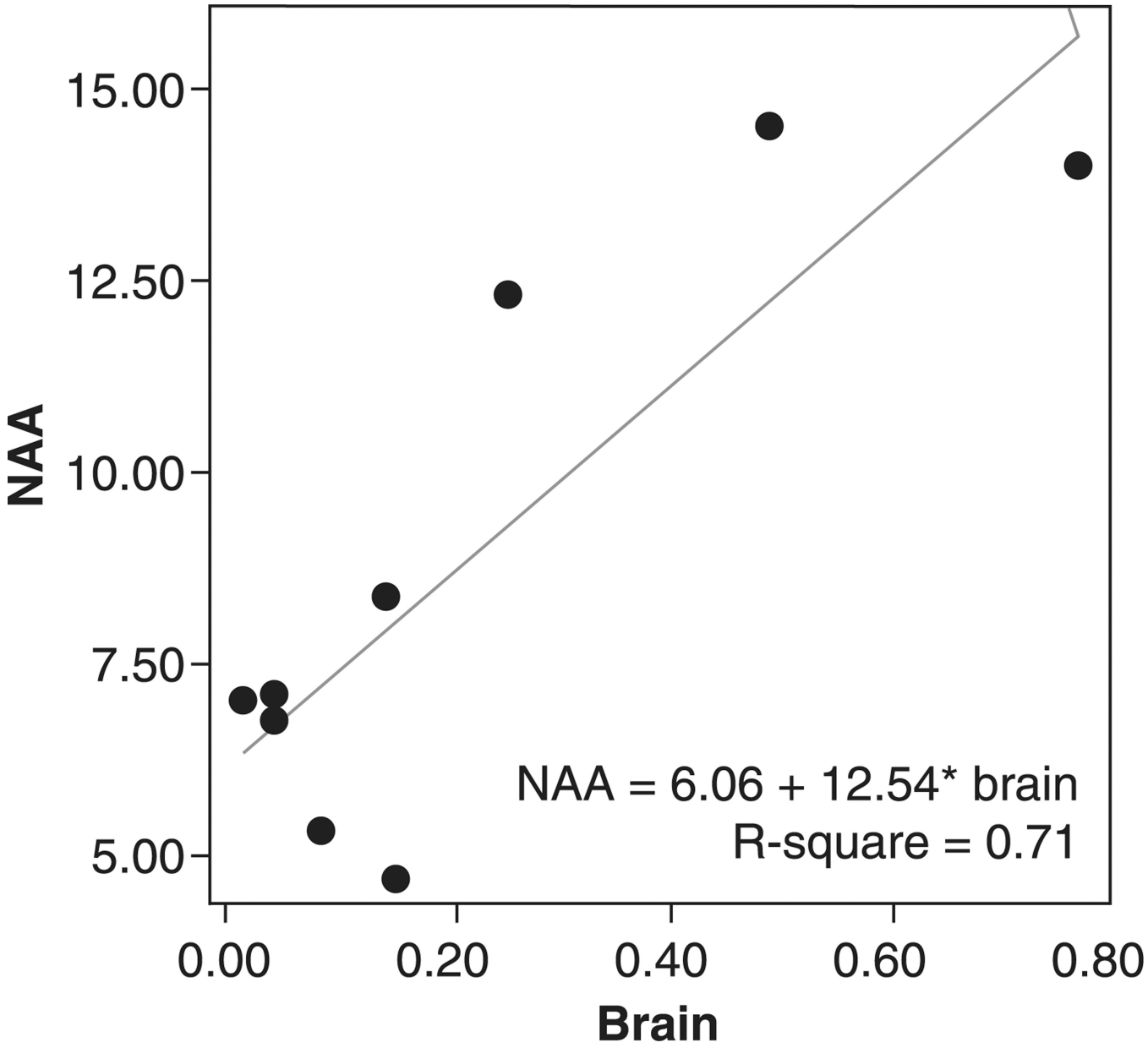

Fig. 1.

Brain lithium levels (mEq/L) versus anterior cingulate cortex *N*-acetyl aspartate (NAA) in older adults with bipolar disorder.

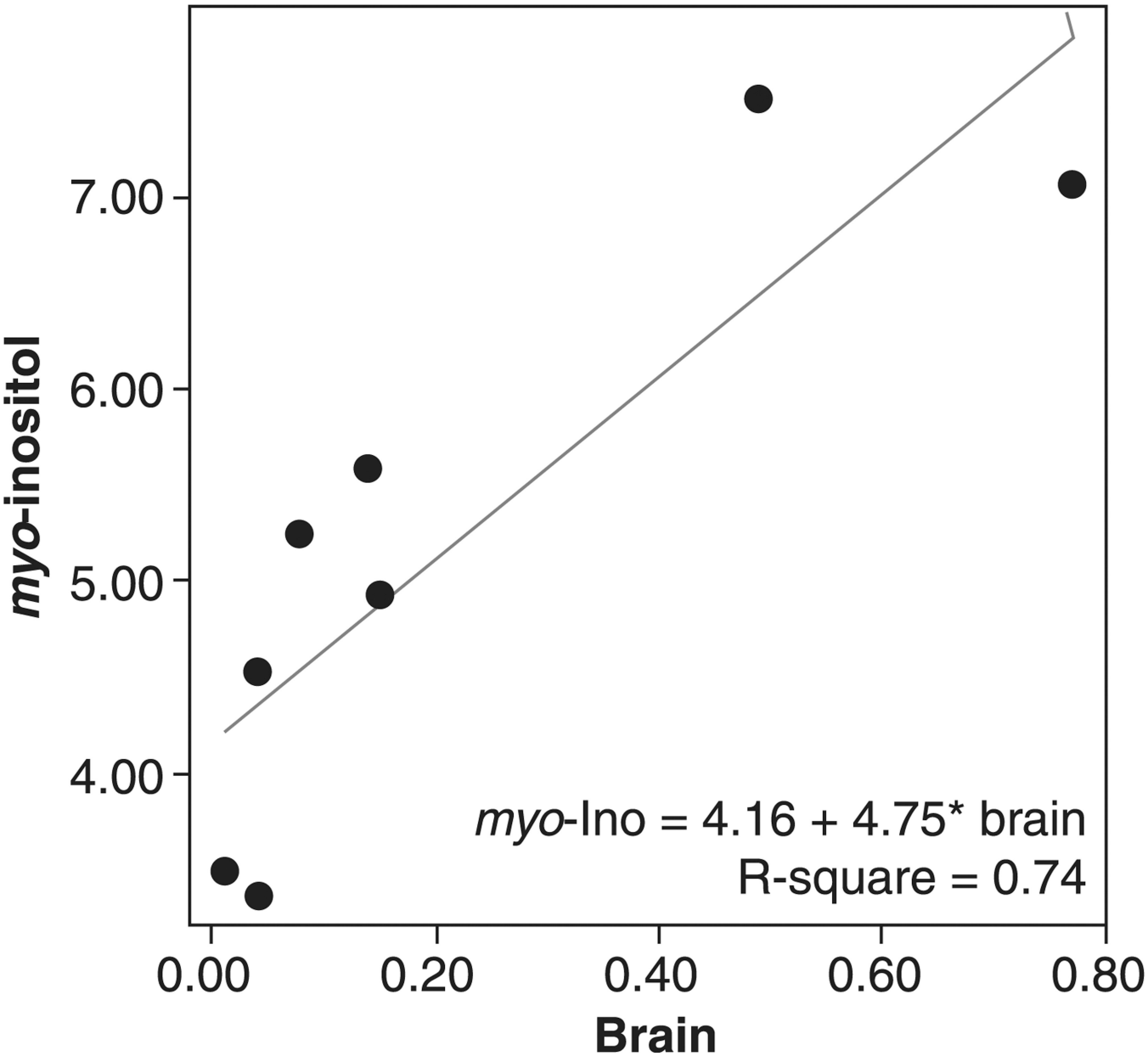

Fig. 2.
Brain lithium levels (mEq/L) versus *myo*-inositol (*myo*-Ino) in older adults with bipolar disorder.

Table 1

Age, sex, DSM-IV-TR diagnosis, lithium preparation, lithium dose per day (mg), duration of lithium treatment and other medications for the subjects who participated in this study

Age	Sex	DSM-IV-TR	Lithium preparation	Lithium dose per day (mg)	Duration of lithium treatment (years)	Other medications
56	Male	Bipolar I	Lithium carbonate	1,350	35	None
57	Male	Bipolar I	Lithium carbonate	1,200	14	Trazadone Clonazepam
60	Male	Bipolar I	Lithium carbonate	1,200	>20	Clorazepate Quinapril Atorvastatin Ropinirole
60	Male	Bipolar I	Lithium carbonate	600	>30	Lamotrigine Lisinopril Atorvastatin Quetiapine Lorazepam
63	Female	Bipolar I	Lithium carbonate	600	>20	Prednisone Donepezil Metoprolol Nicotine patch Olanzapine Aspirin Azathioprine Nexium Albuterol
67	Female	Bipolar I	Lithium carbonate	600	22	Haloperidol Insulin Chlorpromazine Carbamazepine Paroxetine Clonazepam
67	Female	Bipolar I	Eskalith	450	>30	Venlafaxine Olanzapine Zolpidem Bupropion Ranitidine Lisinopril Alendronate Mirtazapine
79	Male	Bipolar I	Lithium carbonate	300	9	Propranolol Allopurinol
85	Male	Bipolar I	Lithobid	450	33	Citalopram Pramipexol

Table 2

Mean and standard deviation for the voxel tissue content, metabolite absolute values, metabolite ratio to creatine, and the lithium measurements

Voxel tissue content	**Mean (%)**	**Standard deviation (%)**
White matter	14.37	2.97
Gray matter	71.31	5.79
Cerebrospinal fluid	14.31	6.72
Metabolite absolute values	**Mean (IU)**	**Standard deviation (IU)**
N-acetyl aspartate (NAA)	8.81	3.79
myo-Ino (n = 8)	5.18	1.50
Metabolite ratio to creatine	**Mean**	**Standard deviation**
NAA/Cr	1.11	0.18
myo-Ino/Cr (n = 8)	0.72	0.20
Lithium measurements	**Mean (mEq/L)**	**Standard deviation (mEq/L)**
Serum	0.67	0.19
Brain	0.22	0.25
	Mean	**Standard deviation**
Brain-to-serum ratio	0.33	0.38

IU = Institutional Units.