Lithium, Gray Matter, and Magnetic Resonance Imaging Signal

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Background: Magnetic resonance imaging studies have reported that lithium can increase the volume of gray matter in the human brain, a finding that has been ascribed to the established neurotrophic or neuroprotective effects of the drug. Lithium, however, might directly influence the intensity of the magnetic resonance signal so it is possible that the volumetric findings are artifactual, essentially a consequence of altered image contrast.

Methods: Anatomical and quantitative magnetic resonance scans were acquired on 31 healthy young men before and after taking either lithium or placebo for 11 days. Brain volume change was derived with two established techniques: voxel-based morphometry (a statistical approach using signal intensity to segment images into tissue types), and Structural Image Evaluation, using Normalization, of Atrophy (a technique that operates by detecting changes in the position of the boundaries of the brain). In a subgroup ($n = 12$), tissue-specific magnetic resonance relaxation times were compared before and after lithium with quantitative T_1-mapping techniques.

Results: Voxel-based morphometry revealed that gray matter volume was increased by lithium but not placebo ($p = .001$), whereas Structural Image Evaluation, using Normalization, of Atrophy showed no difference between lithium and placebo ($p = .23$). Taking lithium reduced the T_1 relaxation of the gray matter only ($p = .008$).

Conclusion: Magnetic resonance images of the brain differ before and after lithium, but this difference might derive from a change in the characteristics of the signal rather than a tangible increase in volume.

Bipolar disorder is a common psychiatric condition in which there are marked alterations in mood and behavior, together with enduring abnormalities in cognition (1). It is recognized that neuronal damage might accrue as the illness progresses, apparent as structural brain changes in imaging and neuropathological studies (2). Lithium, a drug commonly prescribed for the illness, has well-established neuroprotective properties (3). Cross-sectional (4–6) and longitudinal (7–9) magnetic resonance imaging (MRI) studies of patients with bipolar disorder have reported that lithium increases the volume of gray matter in the brain, often interpreted in a neuroprotective framework (10). Gray matter volume increase has also been reported in healthy volunteers receiving lithium (11,12), although not all studies have shown this (13). In patient groups, a volume increase of between 2% and 10% is typical; plateauing after several weeks (9), it has been detected by global assessments and regional measurements, notably the in the hippocampus, amygdala, anterior cingulate, and prefrontal cortex. A positive association with therapeutic response has been observed (14), but no easily discernible relationship with dose has emerged (5). White matter volume is unchanged by lithium (9).

An alternative to the neuroprotective explanation—itself grounded in preclinical research—is that lithium affects cellular hydration, primarily increasing the water content of the gray matter (15). It has also been suggested that lithium might bring about a change in the MRI signal (7,12), essentially altering tissue contrast. This notion has yet to be explored in detail but warrants further attention. When segmenting a brain image into different tissue classes for volumetric analysis, automated techniques typically scrutinize the signal intensity profile of each voxel (16). Were signal intensity to change, tissue classification could be altered and with it the derived volumes. Because most anatomical MRI sequences derive signal intensity from the T_1 relaxation properties of water, it is likely salient that lithium shortens the T_1 time of water in aqueous solution (17) and in the brain (18).

We sought to test the hypothesis that the lithium-induced increase in gray matter volume on MRI could arise not from a physical change in the volume of the brain but from an alteration in the T_1 relaxation properties of the water in the tissues exposed to lithium. That is, the reported volume change might be an artifact of the signal acquisition and image analysis process. It was predicted that an increase in gray matter would be apparent with analysis techniques that are heavily dependent on image intensity but not with paired edge finding methods. A second prediction was that lithium administration would reduce the T_1 relaxation time of water in gray matter but not white matter.

Methods and Materials

Participants

Thirty-two healthy young men were recruited by advertisement from the population of the North East of England. Subjects chose to take part in one of two mutually exclusive studies running in parallel at the same research center. The research was approved by Gateshead and South Tyneside Local Regional Ethics Committee (06/Q0901/70), and all subjects provided written informed consent. The principal study was designed specifically to test the stated hypothesis. The second was a placebo-controlled functional magnetic resonance imaging (fMRI) study investigating the effects of lithium on dopaminergic systems, designed a priori in such a way that data pertinent to

our hypothesis was accrued. Quantitative T_1 images were not acquired from every subject given lithium in the fMRI study and in none of those taking placebo; the relaxometry sequences were added to the protocol midway (at the expense of one of the functional tasks) as the hypothesis presented in this article was prioritized. Paired anatomical imaging data were acquired from all subjects in both studies, pooled to increase the power of the analysis and to permit comparison of the effects of lithium against a placebo (the placebo group drawn exclusively from the fMRI study).

Study One

A longitudinal open-label investigation of the effects of lithium on proton relaxation times and brain MRI volumetric analysis was undertaken. All subjects ($n = 8$) were men 18–45 years of age and in good health. Potential subjects were excluded if they had a history of psychiatric illness, drug and/or alcohol abuse, head injury, seizures, cerebrovascular disease, other neurological disorders, or general medical conditions that would preclude lithium prescription (specifically renal impairment, thyroid dysfunction, psoriasis, and ailments necessitating the prescription of drugs with known interactions). At enrolment, individuals were assessed with the Structured Clinical Interview for the DSM-IV Non-Patient Version (19), underwent a physical examination, and provided urine for testing to exclude current illicit drug use. Anatomical and quantitative T_1 images were acquired in all subjects at baseline and after lithium administration. Subjects were randomized to either high- or low-dose regimes after baseline imaging, but all were aware that they would be assigned to take lithium.

Study Two

This study was a longitudinal fMRI study investigating the effects of lithium on a stimulant model of mania. Screening, inclusion, and exclusion criteria matched the first study but with the additional requirement that subjects be right handed and naïve to stimulants, illicit or otherwise. Scan sessions were performed at baseline and after a course of high-dose lithium ($n = 9$), low-dose lithium ($n = 9$), or placebo ($n = 6$); group allocation was determined by block-randomization (block size $= 3$), and tablet administration was single-blind. Each subject received an intravenous dose of methamphetamine (.15 mg/kg) during each scan session. In all instances, anatomical and quantitative scan data were acquired before the methamphetamine was given, and a minimum period of 2 weeks separated the scan sessions.

Lithium/Placebo Administration

Lithium carbonate was prescribed as a single dose at night for 11 days (multiples of 200 mg Priadel tablets [Sanofi-Synthelabo, Paris, France]), equating to an effective therapeutic dose for a full week after allowing 4 days to reach steady-state. The dose was calculated for each subject with the Cockcroft-Gault method (20) and initiated without titration. All subjects were randomly allocated to either high- or low-dose schedules, aiming for blood lithium concentrations of .9 mmol/L and .5 mmol/L, respectively. Those in the placebo group received blank lactose tablets for 11 days, masked and packaged to match the appearance of the medication given to the lithium groups. Scans were acquired before and after the period in which subjects took their tablets, with the second MRI performed close to 12 hours after the last dose of the regime. A blood sample was taken from all subjects just before the scan commenced and used to determine the serum lithium concentration in those taking the drug.

Neuroimaging

Data Acquisition. All scans were performed on the same 3 Tesla Achieva whole-body scanner (Philips Medical Systems, Best, The Netherlands) with an 8-channel SENSE head coil. The protocol comprised: 1) high-resolution three-dimensional (3D) T_1-weighted anatomical (repetition time [TR] = 9.6 msec; echo time [TE] = 4.6 msec; flip angle = 8°; field of view = 240 × 240 mm; contiguous); 2) fast quantitative T_1 measurement with a custom inversion recovery prepared echo-planar imaging sequence (TR = 15 sec; TE = 24 msec; inversion time = .25–2.5 sec in 12 uniform steps; matrix 128 × 128, 72 slices, isotropic 2-mm resolution); and 3) low-resolution B_o field-map with a dual echo 3D gradient-echo (TR = 27 msec, TE = 2.6, 6.1 msec).

Data Analysis and Subject Attrition. Image analysis was performed by a single researcher (D.A.C.) on a Linux platform (Ubuntu 8.04 LTS) with various proprietary, open-source, and locally developed software packages (MATLAB, MathWorks, Natick, Massachusetts; SPM8, Wellcome Trust Centre for Neuroimaging, University College London, United Kingdom; MRICRO, McCausland Center for Brain Imaging, Columbia, South Carolina; FSL, Oxford Centre for Functional MRI of the Brain, University of Oxford, United Kingdom). Before automated analysis, anatomical images were scrutinized for quality; a subject in Study One had a poor quality scan and was excluded from all analyses, leaving a total of 25 lithium-treated and 6 placebo-treated subjects with images suitable for structural analysis. Quantitative T_1 data were acquired in 12 subjects taking lithium (high-dose $n = 6$, low-dose $n = 6$), 7 enrolled in Study One, and 5 from Study Two.

Voxel-Based Morphometry. T_1-weighted anatomical images were normalized and segmented with a three-compartment model in SPM8, with modulation of the segmented images so that the intensity of each voxel represented a volume measure (16). Images were smoothed with a Gaussian kernel of 12 mm full width half maximum before being submitted to voxel-wise comparison by paired t test, in keeping with the method of others (12,13). An initial height threshold of $p < .001$ was used, with a subsequent family-wise error (FWE) corrected cluster-level threshold of $p < .05$ to identify clusters passing correction for multiple comparisons. Global volumes for gray matter, white matter, and cerebrospinal fluid (CSF) were calculated by summing the voxel intensity values over each segmented image ("get totals" function in SPM8), akin to other studies (9,12).

Structural Image Evaluation, Using Normalization, of Atrophy. The percentage brain volume change between the two anatomical scans of each subject was estimated with Structural Image Evaluation, using Normalization, of Atrophy (SIENA) (21). This package is fully automated and in essence relies on segmentation only in so much as to detect the edges of tissue classes (in this study differentiating brain from CSF to determine whether the volume of the brain increased after lithium treatment). Volume change is estimated by finding the brain/non-brain edge points and then gauging the perpendicular edge displacement between the images from the two scan sessions for each subject. The mean edge displacement is then converted into a global estimate of percentage brain volume change.

Quantitative T_1 Analysis. Anatomical and 4D-acquired quantitative T_1 images were submitted to BET, the brain extraction tool in FSL (22). Next, 3D quantitative T_1 maps were calculated by pixel-wise fitting to the T_1 inversion recovery curve with a three parameter fit (M_o, flip angle, and T_1), after which the spatial distortion in 3D quantitative T_1 images were corrected with the phase map image (23). Regional analysis of tissue T1 was

achieved with an automated method that divided the whole brain into 16 regions of interest (ROI) for each tissue type (gray matter, white matter, and CSF; 48 in total). These regions were the pairs of right and left inferior frontal lobe, superior frontal lobe, temporal lobe, temporal-occipital lobe, occipital lobe, temporal-parietal lobe, parietal lobe, and the cerebellum. The analysis method operated in native-space, this strategy reducing partial volume errors compared with the similar analyses in standard-space (24). In brief, the method parcellates the entire brain with a set of standard-space ROI, which are transformed into native-space based with a multi-step registration with the high-resolution T_1-weighted anatomical scan of the individual patient. Next, the same anatomical scan is segmented into white matter, gray matter, and CSF masks (25) and combined with the brain region template to generate tissue-specific anatomical ROI, which are applied to the quantitative images under analysis. Regional histograms and mean T_1 values were then extracted from all regions except the cerebellum, whose mixed tissue properties produce a bimodal distribution.

Statistical Procedures

Data were analyzed with the Statistical Package for Social Sciences (SPSS for Windows Package 18, Chicago, Illinois). Before comparison of groups, continuous variables were tested for normality of distribution with the Shapiro-Wilk test and by examining Q-Q plots and histogram profiles. Subject characteristics and volumetric measures for the groups were compared with independent t tests (or nonparametric equivalents as indicated), with paired versions applied to examine differences related to lithium or placebo. Pearson's correlation coefficient was used to examine the relationship between serum lithium concentrations and volumetric estimates. All statistical tests were regarded as significant at $p < .05$, with the results expressed as mean values $\pm$ SD unless otherwise stated. Where appropriate, statistical tests were repeated after excluding outlying data points, defined as values in excess of three SDs around the mean.

Results

Anatomical imaging data were analyzable in 25 subjects who took lithium (mean age 22.4 $\pm$ 4.0 years) and 6 who received placebo (mean age 25.4 $\pm$ 4.0 years). The mean serum lithium levels were: high-dose group .82 $\pm$ .3 mmol/L ($n = 12$), low-dose group .47 $\pm$ .16 mmol/L ($n = 13$), whole group .64 $\pm$ .29 mmol/L ($n = 25$).

Voxel-Based Morphometry (VBM) Volumes

Lithium Group. Analysis of the volumes derived with VBM showed that gray matter volume increased with lithium (before 749.6 $\pm$ 80.8 cm^3, after 758.0 $\pm$ 88.3 cm^3; $t = -3.63$, $p = .001$). This is equated to an increase in gray matter volume of 1.1% when all those taking lithium were analyzed. White matter volume was unchanged, whereas the CSF volume decreased (before 273.1 $\pm$ 40.2 cm^3, after 264.7 $\pm$ 41.5 cm^3; $t = 3.24$, $p = .003$).

The relationship between lithium dose and VBM-derived volumetric findings was explored. The higher-dose lithium group showed a numerically greater increase in mean percentage gray matter volume change than the low-dose group, but this did not reach statistical significance (higher-dose group 1.64 $\pm$ 1.71%, lower-dose group .634 $\pm$ 1.28%; $t = -1.68$, $p = .11$). Discrete correlation suggested a relationship between lithium dose and percentage gray matter volume increase but only at a trend level

(all subjects taking lithium: $r = .337$; $p = .099$); likewise for the decrease in CSF volume ($r = .341$; $p = .096$). The sample was divided post hoc into high- and low-serum concentration groups, determined as above or below the whole group median value of .6 mmol/L (higher-concentration group $n = 12$, mean lithium level .88 $\pm$ .19 mmol/L; lower-dose group $n = 13$, mean lithium level .41 $\pm$ .14 mmol/L). By this division, a gray matter volume increase was seen in the high-concentration group (before lithium 749.5 $\pm$ 74.3 cm^3, after lithium 762.5 $\pm$ 78.3 cm^3; $t = -3.55$, $p = .005$) but not the low-concentration group (before lithium 749.6 $\pm$ 89.4 cm^3, after lithium 753.8 $\pm$ 90.6 cm^3; $t = -1.67$, $p = .12$). A direct between-group comparison showed a trend for the percentage change in VBM-derived gray matter volume to be greater in the high-concentration group (post hoc sample division: high-concentration group 1.71 $\pm$ 1.65%, low-concentration group .57 $\pm$ 1.30%; $t = 1.93$, $p = .066$).

Placebo Group. The placebo group had no change in gray matter volume but did show an increase in white matter volume (543.6 $\pm$ 77.6 cm^3 vs. 550.3 $\pm$ 80.1 cm^3; $t = 4.14$, $p < .01$). The CSF volume was unchanged in the placebo group as a whole, but the percentage volume change value of one subject was outlying. Excluding this subject, the within-group analysis showed a reduction in CSF comparable to the white matter increase.

Between Group: Lithium Versus Placebo. Percentage change in tissue volumes were analyzed group-wise, all those receiving lithium compared with subjects taking placebo (Figure 1A). Percentage gray matter volume change differed between the two groups (lithium vs. placebo; $t = 2.67$, $p = .012$), but white matter (lithium vs. placebo; $t = -.76$, $p = .455$) and CSF did not (lithium vs. placebo; $t = -1.10$, $p = .279$).

Submitting data from all subjects who received lithium to a voxel-wise comparison (before and after medication) revealed no clusters representing volume increase at the FWE correction threshold of $p < .05$. Specifying a factorial design by dose, a comparable analysis was performed for the higher- and lower-dose lithium groups (Figure 2). With subtraction of the pre-lithium from the post-lithium images in the higher-dose group at the FWE correction threshold of $p < .05$, gray matter volume increase was seen in a solitary cluster (Montreal Neurological Institute $-6 \times 0 \times 20$; voxels = 31, $t = 5.41$, $p = .015$). Those taking a lower dose of lithium also demonstrated a regional increase in gray matter volume with VBM, a single small cluster passing the threshold for significance ($-14 \times -22 \times 4$; voxels = 10, $t = 5.31$, $p = .028$).

Volume Change with the SIENA Algorithm

The SIENA-derived mean percentage brain volume changes were small with no significant difference between the groups (placebo $-.01 \pm .17$%, lithium .24 $\pm$ .48%; $t = -1.23$, $p = .23$). A direct, within-group, head-to-head analysis of the SIENA and VBM data was performed (total brain volume according to VBM determined by combining gray and white matter values) (Figure 1B). In the lithium group, mean percentage brain volume change was greater with VBM than with SIENA (VBM = .79 $\pm$ .96%, SIENA .24 $\pm$ .48%; $t = -2.75$, $p = .01$). In the placebo group, the two techniques did not differ (VBM $-.10 \pm 1.49$%, SIENA $-.01 \pm .17$%; $t = .14$, $p = .90$).

Quantitative Proton T_1 Relaxation Time

With lithium treatment, there was a small but highly significant reduction in mean gray matter proton T_1 relaxation time when mean values derived from the histograms of all brain
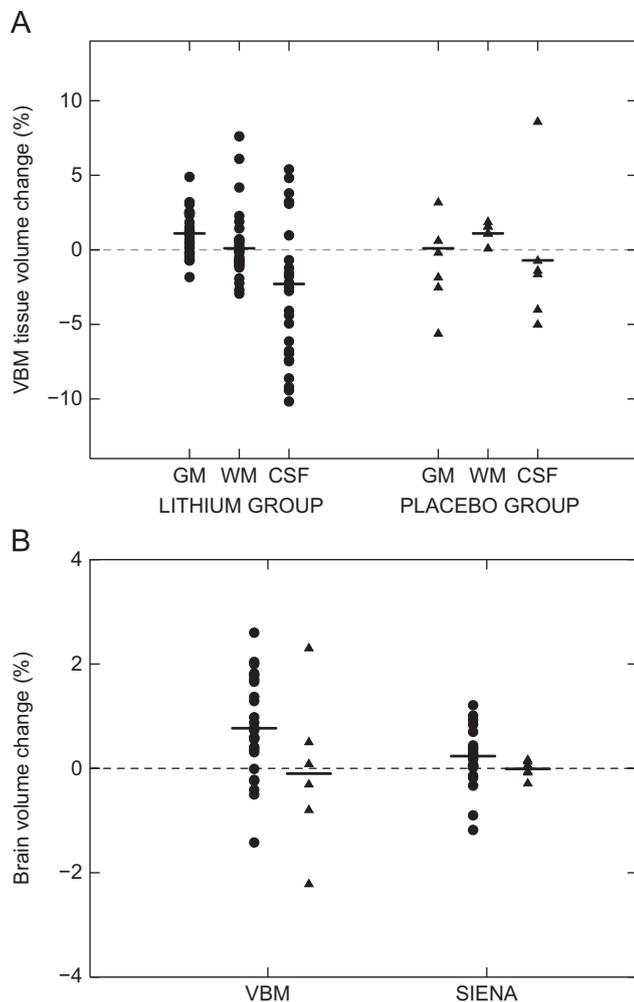
Figure 1. (A) Percentage change in tissue volume determined with voxel-based morphometry (VBM) for the lithium ($n = 25$) and placebo ($n = 6$) groups. **(B)** Percentage change in brain volume determined with VBM and Structural Image Evaluation, using Normalization, of Atrophy (SIENA) for the lithium (solid circle, $n = 25$) and placebo (solid triangle, $n = 6$) groups. CSF, cerebrospinal fluid; GM, gray matter; WM, white matter.

Figure 2. Regional gray matter change by voxel-based morphometry for the groups randomized to receive higher ($n = 12$) **(A)** and lower ($n = 13$) **(B)** doses of lithium (height threshold T = 4.95, extent threshold $k = 0$ voxels, $p < .05$ family-wise error correction). The scale represents the *t* score for the rendered voxels.

regions were compared (1474 ± 98 msec vs. 1466 ± 94 msec; $Z = -2.65$, $p = .008$). With consideration of each lobar region in turn, before and after lithium, trend-level reductions in the mean gray matter proton T_1 were found in the temporal-occipital region on the left (1501 ± 56 msec vs. 1482 ± 51 msec; $Z = -1.83$, $p = .060$) and the occipital region on the right (1520 ± 69 msec vs. 1503 ± 70 msec; $Z = -1.73$, $p = .084$). White matter proton T_1 values were unchanged after lithium.

At a trend-level, the change in gray matter T_1 values correlated negatively with percentage gray matter volume change ($r = -.50$; $p = .098$) and with serum lithium concentration ($r = -.517$; $p = .085$). Upon submission of the gray and white matter T_1-maps separately to a voxel-wise paired *t* test analysis, no significant regional differences emerged for either tissue class.

Discussion

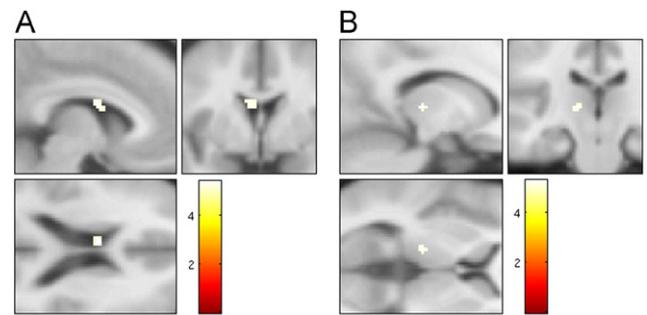The manner by which lithium increases MRI-based estimates of gray matter volume is inadequately explained by contemporary theories. Neuroprotective explanations are supported by strong preclinical data (26) but fail to account for the volume change in healthy subjects. Although a recent longitudinal rodent MRI and stereology investigation supports a volume increase with lithium (27), other studies have shown no effects on rat brain volumes or neuronal numbers even after several months of administration (28,29). With regard to hydration theories, rats given lithium acquire a 3% greater water content in the gray matter compared with those given placebo, but the difference is restricted to frontal regions (15) and, by extrapolation, probably insufficient to account for the larger global findings in humans. However, neuroprotective and hydration theories are potentially inseparable. Lithium has been shown to increase brain N-acetylaspartate (NAA)—a putative marker of neuronal integrity—but the value of this observation is uncertain because the spectroscopic assessment of NAA concentration was normalized to brain water (10). Furthermore, because NAA is an osmotic regulator (30), changes in its concentration could be a cause or consequence of altered hydration. The primacy of the hydration theory is undermined by the simple assertion that cells undergoing growth might expand their water content.

Our findings cast doubt on the assumption that the size of the brain changes with lithium. The hastening of gray matter T_1 relaxation might account for the disparity between VBM and SIENA volumetric estimates, for which we advance a biophysical explanation.

Contrast between tissues on T_1-weighted images is relative and inversely proportional to the T_1 relaxation time: CSF is dark because of its long T_1; the short T_1 of white matter renders it bright; gray matter is intermediate. Every voxel has an intensity profile that can be interpreted as a tissue type, but there is substantial overlap in the voxel intensity histograms from gray and white matter. Precise image segmentation is difficult in the presence of partial volume effects, wherein a single voxel contains a mixture of tissue types. Partial volume effects arise in genuinely mixed tissues (e.g., the thalamus) or when a voxel spans distinct tissues (susceptible areas include periventricular regions, cortical sulci, and temporal horns) (31). Automated analyses either exclude such voxels or allocate them to a tissue type on the basis of probability. Allocation might be guided by prior knowledge of the usual tissue distributions (16), but segmentation might go awry in the presence of unrecognized changes in voxel intensity profiles, and spurious volumetric findings could result.

In a longitudinal study of 20 patients with bipolar disorder, lithium shortened the T_1 of the brain in all cases (18). Our study using quantitative mapping localized the change in T_1 to the gray

matter. Crudely interpreted, hastening the T_1 relaxation of gray matter should increase its intensity on T_1-weighted images, making it appear more like white matter. Why then is it not the white matter volume that seems to increase with VBM? The boundary of the cortex with the CSF is highly convoluted, and tissue misclassification is especially common in deep sulci with closely approximated banks of gray matter (31). In marginal voxels with a near equal chance of being allocated to gray matter or CSF, an increase in the signal intensity of the tissue component might swing the final allocation toward gray matter, but because the classification is categorical, the entire voxel would be counted as gray matter during volumetric calculations. This process could account for the localization of our findings, the parallel reductions in CSF volume, and the very large changes reported by others when the cortex is the primary focus of investigation (5).

In aqueous solution, proton T_1 relaxation time is inversely proportional to lithium concentration (17), probably because the cation brings order to the structure of bulk water (32). Extrapolation to therapeutic concentrations suggests that this action alone would be insufficient to account for our findings. Whether the atomic-level interaction of lithium with water is amplified in the more structured environment of the cell, in particular around charged lipid bilayer membranes (33), is put forward for debate. The proposed "purely" biological effects of lithium might also reduce the T_1, and in this respect the discussion comes full circle. The T_1 profile of the adult brain responding to a neuroplastic stimulus is unknown, but it could deviate from the norm. Altering the water content of the brain does change its T_1 profile—this being an established method to detect edema (34)—but modeling this effect is challenging, because the direction of the T_1 change depends on the cause of disturbed hydration (35).

A number of limitations to this study need to be recognized. Percentage brain volume change by SIENA approximated to the .2% error margin of the technique (21), consistent with there being no tangible volume change with lithium. Voxel-based morphometry returned a greater volume change, but the magnitude was small, and it could be argued that this simply reflected the limitations of the statistical model. In defense, our findings were not driven by outlying values, and the VBM-derived volume change is comparable to previous studies of healthy subjects (11,12), albeit at the lower end. This was probably a consequence of the comparatively short treatment period, because gray matter volume change by VBM reaches a plateau after several weeks (9). It is also possible that healthy subjects respond differently to lithium, the literature consistently supporting a greater volume change in those with bipolar disorder in whom neuroprotective drug effects might be invoked. Scanner performance was controlled for by the block randomization design, which ensured subjects allocated to lithium/placebo were evenly distributed over the course of the study. Crucially, our placebo group was small, presumably contributing to the wide distribution of the data in that group and, in turn, the unexpected finding of an increase in white matter volume on VBM. There is no obvious biological reason why placebo should increase white matter volume, and this finding probably reflects the limitations of the statistical model in this small sample. Comparisons against the placebo group in this study must therefore be interpreted with caution. Finally, quantitative T_1 maps were acquired in a subsample of those taking lithium and in none of those randomized to placebo, likely lessening the power of the analysis. Although not here reported, even in this small subsample a significant increase in gray matter volume according to VBM was observed in the absence of a percentage brain volume change with SIENA.

In summary, there is a genuine difference in anatomical MRI data acquired before and after lithium, but we argue that the change is one of signal intensity (rooted in proton T_1 hastening) and that this has previously been misinterpreted as a volume increase in the gray matter. It seems likely that atomic-level interactions combined with the classical biological effects of lithium contribute to the signal change. Thus, the VBM findings might be better considered as a localization of the influence and action of lithium rather than a physical change in the volume of the brain. Replication or refutation of our findings will be carried out by interrogating extant data with VBM and SIENA, quantitative T_1 mapping being recommended for future MRI studies.

1. Robinson LJ, Thompson JM, Gallagher P, Goswami U, Young AH, Ferrier IN, et al. (2006): A meta-analysis of cognitive deficits in euthymic patients with bipolar disorder. *J Affect Disord* 93:105–115.
2. Machado-Vieira R, Manji HK, Zarate CA (2009): The role of lithium in the treatment of bipolar disorder: Convergent evidence for neurotrophic effects as a unifying hypothesis. *Bipolar Disord* 11:92–109.
3. Beaulieu J-M, Caron MG (2008): Looking at lithium: Molecular moods and complex behaviour. *Mol Interv* 8:230–241.
4. Sassi RB, Nicoletti M, Brambilla P, Mallinger AG, Frank E, Kupfer DJ, et al. (2002): Increased gray matter volume in lithium-treated bipolar disorder patients. *Neurosci Lett* 329:243–245.
5. Bearden CE, Thompson PM, Dalwani M, Hayashi KM, Lee AD, Nicoletti M, et al. (2007): Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biol Psychiatry* 62:7–16.
6. Yucel K, Taylor VH, McKinnon MC, MacDonald K, Alda M, Young LT, et al. (2008): Bilateral hippocampal volume increase in patients with bipolar disorder and short-term lithium treatment. *Neuropsychopharmacology* 33:361–367.
7. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000): Lithium-induced increase in human brain grey matter. *Lancet* 356:1241–1242.
8. Moore GJ, Cortese BM, Glitz DA, Zajac-Benitez C, Quiroz JA, Uhde TW, et al. (2005): Lithium increases gray matter in the prefrontal and subgenual prefrontal cortices in treatment responsive bipolar disorder patients. *Neuropsychopharmacology* 30:S179–S180.
9. Lyoo IK, Dager SR, Kim JE, Yoon SJ, Friedman SD, Dunner DL, et al. (2010): Lithium-induced gray matter volume increase as a neural correlate of treatment response in bipolar disorder: A longitudinal brain imaging study. *Neuropsychopharmacology* 35:1743–1750.
10. Moore GJ, Bebchuk JM, Hasanat K, Chen G, Seraji-Bozorgzad N, Wilds IB, et al. (2000): Lithium increases N-acetyl-aspartate in the human

brain: In vivo evidence in support of bcl-2's neurotrophic effects? *Biol Psychiatry* 48:1–8.

11. Leow AD, Thompson PM, Hayashi KM, Bearden C, Nicoletti MA, Monkul SE, et al. (2005): Effects of lithium treatment on human brain structure mapped using longitudinal MRI. *Neuropsychopharmacology* 30; S227–S227.

12. Monkul ES, Matsuo K, Nicoletti MA, Dierschke N, Hatch JP, Dalwani M, et al. (2007): Prefrontal gray matter increases in healthy individuals after lithium treatment: A voxel-based morphometry study. *Neurosci Lett* 429:7–11.

13. Scherk H, Kemmer C, Usher J, Reith W, Falkai P, Gruber O (2008): No change to grey and white matter volumes in bipolar I disorder patients. *Eur Arch Psychiatry Clin Neurosci* 258:345–349.

14. Moore GJ, Cortese BM, Glitz DA, Zajac-Benitez C, Quiroz JA, Uhde TW, et al. (2009): A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. *J Clin Psychiatry* 70: 699–705.

15. Phatak P, Shaldivin A, King LS, Shapiro P, Regenold WT (2006): Lithium and inositol: Effects on brain water homeostasis in the rat. *Psychopharmacology* 186:41–47.

16. Ashburner J, Friston KJ (2000): Voxel-based morphometry—the methods. *Neuroimage* 11:805–821.

17. Fabricand B, Goldberg S (1967): Proton relaxation times in 7LiCl and 6LiCl solutions. *Mol Phys* 13:323–330.

18. Rangelguerra RA, Perezpayan H, Minkoff L, Todd LE (1983): Nuclear magnetic-resonance in bipolar affective-disorders. *AJNR Am J Neuroradiol* 4:229–331.

19. First MB, Spitzer R, Gibbon M, Williams JBW (2002): *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Non-Patient Edition. (SCID-I/NP)*. New York: Biometrics Research, New York State Psychiatric Institute.

20. Chiu CC, Shen WW, Chen KP, Lu ML (2007): Application of the Cockcroft-Gault method to estimate lithium dosage requirement. *Psychiatry Clin Neurosci* 61:269–274.

21. Smith SM, Zhang Y, Jenkinson M, Chen J, Matthews PM, Federico A, et al. (2002): Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 17:479–489.

22. Smith SM (2002): Fast robust automated brain extraction. *Hum Brain Mapp* 17:143–155.

23. Jenkinson M (2001): Improved unwarping of EPI images using regularised B0 maps. *Neuroimage* 13(suppl 1):165.

24. Aribisala BS, He J, Blamire AM (2011): Comparative study of standard space and real space analysis of quantitative MR brain data. *J Magn Reson Imaging* 33:1503–1509.

25. Zhang Y, Brady M, Smith S (2001): Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging* 20:45–57.

26. Wada A (2009): Lithium and neuropsychiatric therapeutics: Neuroplasticity via glycogen synthase kinase-3beta, beta-catenin, and neurotrophin cascades. *J Pharmacol Sci* 110:14–28.

27. Vernon AC, Natesan S, Crum WR, Cooper JD, Modo M, Williams SC, Kapur S (2012): Contrasting effects of haloperidol and lithium on rodent brain structure: A magnetic resonance imaging study with postmortem confirmation. *Biol Psychiatry* 71:855–863.

28. Licht RW, Larsen JO, Smith D, Braendgaard H (1994): Effect of chronic lithium treatment with or without haloperidol on number and size of neurons in the rat neocortex. *Psychopharmacology* 115:371–374.

29. Licht RW, Larsen JO, Smith D, Braendgaard H (2003): Chronic lithium treatment with or without haloperidol fails to affect the morphology of the rat cerebellum. *Euro Neuropsychopharmacol* 13:173–176.

30. Moffett JR, Ross B, Arun P, Madhavarao CN, Namboodiri AM (2007): N-Acetylaspartate in the CNS: From neurodiagnostics to neurobiology. *Prog Neurobiol* 81:89–131.

31. Rueda A, Acosta O, Couprie M, Bourgeat P, Fripp J, Dowson N, et al. (2010): Topology-corrected segmentation and local intensity estimates for improved partial volume classification of brain cortex in MRI. *J Neurosci Methods* 188:305–315.

32. Marcus Y (2009): Effect of ions on the structure of water: Structure making and breaking. *Chem Rev* 109:1346–1370.

33. López Cascales JJ, García de la Torre J (1997): Effect of lithium and sodium ions on a charged membrane of dipalmitoylphosphatidylserine: A study by molecular dynamics simulation. *Biochim Biophys Acta* 1330:145–156.

34. Kato H, Kogure K, Ohtomo H, Izumiyama M, Tobita M, Matsui S, et al. (1986): Characterization of experimental ischemic brain edema utilizing proton nuclear magnetic resonance imaging. *J Cereb Blood Flow Metab* 6:212–221.

35. Yun TJ, Na DG, Kwon BJ, Rho HG, Park S-H, Suh Y-L, et al. (2008): A T1 hyperintense perilesional signal aids in the differentiation of a cavernous angioma from other hemorrhagic masses. *Am J Neuroradiol* 29:494–500.