Quantification of brain proton longitudinal relaxation ($T_1$) in lithium-treated and lithium-naïve patients with bipolar disorder in comparison to healthy controls

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Abstract

Background: Proton longitudinal relaxation ($T_1$) is a quantitative MRI-derived tissue parameter sensitive to myelin, macromolecular, iron and water content. There is some evidence to suggest that cortical $T_1$ is elevated in bipolar disorder and that lithium administration reduces cortical $T_1$. However, $T_1$ has not yet been quantified in separate groups containing lithium-treated patients, lithium-naïve patients, and matched healthy controls.

Methods: Euthymic patients with bipolar disorder receiving lithium ($n = 18$, BDL) and those on other medications but naïve to lithium ($n = 20$, BDC) underwent quantitative $T_1$ mapping alongside healthy controls ($n = 18$, HC). $T_1$ was compared between groups within the cortex, white matter and subcortical structures using regions of interest (ROI) derived from the Desikan-Killiany atlas. Effect sizes for each ROI were computed for BDC vs BDL groups and Bipolar Disorder vs HC groups.

Results: No significant differences in $T_1$ were identified between BDL and BDC groups when corrected for multiple comparisons. Patients with bipolar disorder had significantly higher mean $T_1$ in a range of ROIs compared to healthy controls, including bilateral motor, somatosensory and superior temporal regions, subcortical structures and white matter.

Conclusions: The higher $T_1$ values observed in the patients with bipolar disorder may reflect abnormal tissue microstructure. Whilst the precise mechanism remains unknown, these findings may have a basis in differences in myelination, macromolecular content, iron and water content between patients and controls.

KEYWORDS
bipolar disorder, lithium, quantitative MRI, $T_1$ relaxometry

1 | INTRODUCTION

Bipolar disorder is a complex mental illness associated with multiple, potentially distinct brain structural features. Structural neuroimaging techniques have identified a number of abnormalities in bipolar disorder that have contributed towards a greater understanding of the aetiology and symptomatology of this disorder. The most common magnetic resonance imaging (MRI) techniques used...
to quantify structural brain changes in vivo include the use of T1 and T2 contrast-weighted sequences, which provide high-resolution structural information and can be used to detect volumetric changes. However, signals acquired during contrast-weighted imaging are relative measurements, meaning that comparison of signal intensity between individuals, sites, protocols, scanners and different time points is challenging. Quantitative imaging techniques such as relaxometry enable acquisition of absolute T1 relaxation times. Such T1 measurements serve as a quantitative MRI parameter that is sensitive to myelin, macromolecular, iron and water content, more readily comparable between sites and over multiple time points.

Evidence from studies employing relaxometry suggests that patients with bipolar disorder exhibit differences in proton relaxation times within the brain. For example, longitudinal relaxation (T1) within the frontal and temporal lobes has been shown to be higher in patients with bipolar disorder. Higher T1 is also associated with lower myelin content and other microstructural changes pertinent to bipolar disorder. For instance, reductions in white matter integrity have been found to occur in bipolar disorder so the elevated T1 may be driven by demyelination as a feature of this disorder. Lithium, a first line treatment for bipolar disorder, is associated with greater white matter integrity but its effects on proton relaxation in bipolar disorder remains unclear. Lithium administration in healthy individuals has been shown to reduce T1 times in grey matter, but this may be a biophysical effect as this phenomenon is also known to occur in vitro when lithium is added to aqueous solution.

Recent studies employing a related quantitative T1 mapping technique have found that T1 is higher within cerebral white matter and cerebellum in patients with bipolar disorder compared to controls. When patients were subdivided according to medication use, it was found that those prescribed lithium exhibited lower T1 values than patients taking other medications; however, this finding was not replicated in a later study.

Studies have yet to quantify T1 across the brain of lithium-treated and lithium-naïve patients using high-resolution quantitative T1 mapping. In this study, we use a rapid acquisition technique (DESPOT1) to quantify T1 within the brain of lithium-treated and lithium-naïve patients with bipolar disorder, together with healthy controls. We hypothesised that patients taking lithium would have lower T1 than those naïve to lithium and that T1 would be higher in patients compared to controls.

2 METHODS

2.1 Participants

Thirty-eight euthymic subjects with a diagnosis of bipolar disorder (I or II) and 18 healthy control subjects recruited to the Bipolar Lithium Imaging and Spectroscopy Study (BLISS) were studied. Of those with bipolar disorder, 18 were taking lithium as a long-term treatment (Bipolar Disorder Lithium, BDL) and 20 were taking other maintenance treatments but were naïve to lithium (Bipolar Disorder Control, BDC). The healthy control subjects (HC) had no history of psychiatric illness and were not taking any psychotropic medications. Subjects attended a screening visit to confirm eligibility and underwent a structured clinical interview using the NetSCID diagnostic tool (a validated online version of the Structured Clinical Interview for DSM-5 Criteria; Telesage, Inc). Interviews and objective ratings were conducted by a trained clinical research assistant (CJF) and discussed with a senior psychiatrist (DAC). All subjects were 18 to 65 years of age and between 50 and 150 Kg in weight (upper limit determined by MRI scanner bed restrictions). Across all groups, subjects were excluded if they had a contraindication to magnetic resonance examination (including claustrophobia), a current or past medical condition deemed likely to tangibly affect brain structure, a substance use disorder (current or to a significant degree in the past; NetSCID Module E), a recent alcohol intake exceeding 21 units (self reported), a learning disability or an impairment of capacity. Patients were excluded if they were currently liable to detention under the Mental Health Act 1983 (amended 2007). Comorbid psychiatric diagnosis in the patients, assessed using the NetSCID, was permissible (excluding neurodevelopmental, substance use as previously described and neurocognitive disorders) so long as their primary diagnosis was bipolar disorder, confirmed by a senior psychiatrist (DAC) reviewing case notes as required. Euthymic mood state was confirmed at entry to the study, defined as scores of less than seven on both the 21-item Hamilton Depression Rating Scale (HAM-D) and the Young Mania Rating Scale (YMRS). BDL subjects were required to have been taking lithium carbonate regularly for at least 1 year at the time of recruitment (target therapeutic range 0.6-1.0 mmol/L) and all were taking at least one concomitant medication. BDL subjects completed the Lithium Side Effects Rating Scale (LISERS), a self-administered scale rating the common side effects of lithium, each on a four-point severity scale and expressed as a summed score. All scans were performed at 9 AM and the BDL subjects were instructed to take their lithium as usual the night before and submitted to a blood test immediately prior to scanning to measure their serum lithium concentration. All subjects provided written informed consent and the study was granted a favourable ethical opinion by a United Kingdom National Research Ethics Committee (14/NE/1135).

2.2 MRI acquisition

MR scans were performed using a 3 Tesla Philips Achieva MRI scanner (Philips Medical System) using an 8-channel head coil. The scan protocol included:

2.2.1 T1-weighted imaging acquisition

3D T1-weighted images (T1w) of brain anatomy, acquired in all subjects using the 8-channel SENSE head coil, were obtained with a 1H gradient echo sequence (TR = 9.6 ms, TE = 4.6 ms,
FOV = 240 × 240 × 180 mm³, acquisition matrix = 240 × 208 × 180, acquisition voxel size = 1 × 1.15 × 1 mm³, reconstructed into a matrix size of 256 × 256 × 180, 1 average).

2.2.2 | T₁ parameter map acquisition

The Driven Equilibrium Single Pulse Observation of T₁ (DESPOT1) method¹⁰ using two Spoiled Gradient Recalled-Echo images (SPGR) acquired with flips angles (FA) of 4° and 15° was used to generate T₁ parameter maps. Other image parameters were identical for each image (TR = 11.7 ms, TE = 2.4 ms, FOV = 250 × 140 × 250 mm³, acquisition voxel size = 0.99 × 1.0 × 2.0, reconstruction voxel size = 0.87 × 0.87 × 1.0, acquisition matrix = 252 × 250 × 140 (slices) reconstructed into 288 × 288 × 140). A B₁ map was also acquired using a dual TR method with a conventional 3D spoiled gradient echo pulse sequence with the following parameters (nominal TR = 30ms, TR extension = 120 ms, Flip Angle = 60 degrees, FOV = 250 × 130 × 250 mm³).

2.3 | Image processing and analysis

All images were exported in DICOM format and converted to NIFTI format data using the Matlab (Mathworks® Inc) toolbox "DICOM to NIFTI".¹³ Data pre-processing and analysis were performed using Nipype, a Python based platform that provides a uniform interface to existing neuroimaging software and facilitates interaction between these packages within a single workflow.¹⁴

2.3.3.1 | T₁w image processing

Brain tissue was sub-divided into a series of regions of interest (ROI), or parcels, for each individual subject for analysis of regional variation in T₁ by processing their T₁w structural images using the FreeSurfer recon-all pipeline (https://surfer.nmr.mgh.harvard.edu/, Version 6). Quality control of surface reconstruction was performed by visual inspection. Additional to the standard Desikan-Killiany atlas,¹⁵ we also analysed results from the Destrieux¹⁶ atlas to demonstrate consistency in the spatial pattern of results (Supplementary Material A, Figure A1 and Table A2). Cerbellar ROI were excluded from the final analysis in order to avoid partial volume effects owing to the difficulty in accurately parcellating the cerebellar cortex. T₁ within white matter was also compared in Montreal Neurological Institute (MNI) space using the John Hopkins University (JHU) White-Matter Tractography ROI atlas (Supplementary Material A, Figure A3 and Table A4).¹⁷

2.3.2 | T₁ map processing

Maps of brain proton T₁ were generated using the DESPOT1 method.¹⁰ In short, by holding TR constant and acquiring two images at fixed flip angles (4° and 15°) a voxel-wise estimation of T₁ can be acquired based upon the relationship between signal intensity between the two images. B₁ maps were used to correct this calculation for regional flip angle inhomogeneity. All images were visually inspected to ensure that there were no artefacts. Full details of the processing and calculation of T₁ values are provided in Supplementary Material B.

SPGR images (FA = 4°) were linearly registered to T₁w structural images using FMRIB’s Linear Image Registration Tool to address potential movement of subjects between sequences and to derive a transformation matrix.¹⁸ This transformation matrix was then used to project T₁ maps to T₁w images in native space.

2.4 | Statistical ROI analysis

Mean T₁ values for each subject were calculated for voxels classified as cortical, subcortical and white matter by Freesurfer for the analysis across the different tissue types. The effects of age and sex were detrended for each group individually to quantify differences between groups (BDC, BDL and HC). This was achieved by regressing out the effects of age and sex, and adding the residuals to the mean values of the group. We chose to report detrended values rather than residuals, as the T₁ values are in absolute units of time and should be comparable across studies. Normality of the distributions was tested between patients and controls were re-calculated using erosion iterations ranging from zero to four in order to determine the extent to which varying degrees of ROI erosion affected the final results. The results from this, including a representative example of ROI erosion, are included in Supplementary Material C (Supplementary Figure C1). To determine tissue-wide effects (eg, whole cortical grey matter), the corresponding ROIs were first combined and then eroded as a whole structure to then extract average tissue T₁ values.
using the Lillefors test, which revealed that a number of regions exhibited non-normal distributions. Consequently, Wilcoxon signed-rank tests were performed for each ROI, correcting for multiple comparisons across ROIs using the Benjamini-Hochberg method.19

3 | RESULTS

3.1 | Group characteristics

Eighteen BDL subjects (10 women; mean age: 50 ± 12 SD years), 20 BDC subjects (13 women; mean age: 44 ± 12 SD years) and 18 HC subjects (11 women; mean age: 49 ± 11 SD years) were included in the analysis. The groups did not differ in mean age (P = .19) or sex distribution (P = .84) but there was a difference in years of education (P < .01) (Table 1). Post-hoc testing revealed that the HC group had remained in education for longer than the BDL group (P = .004) and the BDC group (P = .006), but the bipolar disorder groups themselves did not differ in years of education (P = .9). Regarding illness characteristics, the BDL and BDC groups differed in terms of duration of illness (P = .03), but not in terms of subtype (BD I vs II, P = .11) or presence of co-morbid psychiatric diagnosis (P = 1). There were no group differences in YMRS scores (P = .06) but the groups differed in HAM-D scores (P = .01), the HC group having lower scores than the BDL group (P = .008) and BDC group (P = .001), but the BDL and BDC groups did not differ from each other (and all were considered euthymic). Barring lithium, no significant differences were found between the bipolar disorder groups across all major medication classes. Medication usage information for each group, and their corresponding P values, are provided in Table 2.

3.2 | Group comparison of T1 times across tissue types

A summary of T1 values subdivided according to tissue type and subject group are given in Table 3 below. Across subjects, mean T1 was higher in both patient groups relative to healthy controls in each tissue type.

One-way ANOVA revealed significant differences in mean T1 between the groups for each tissue type (Cortical F (2,52) = 3.2, P < .05; Subcortical F (2,52) = 3.5, P < .05; White matter F (2,52) = 5.7, P < .01). Post hoc t-tests (applying Tukey’s correction for multiple comparisons) revealed significant differences (P < .05) between both patient groups and healthy controls in white matter (Figure 1). Trend differences (P ≤ .1) were observed in mean cortical and subcortical T1 times. No differences in mean T1 values were observed between the two patient subgroups (BDL vs. BDC) in either tissue type (P = 1). Figure 1 shows mean detrended T1 per subject, subdivided by tissue type and group.

3.3 | Investigation of regional effects

3.3.1 | BDL vs BDC comparison

In order to investigate whether there were any regional differences in T1 times between BDL and BDC groups, effect sizes were

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**TABLE 1** Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>Bipolar disorder lithium (n = 18)</th>
<th>Bipolar disorder control (n = 20)</th>
<th>Healthy control (n = 18)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>8/10</td>
<td>7/13</td>
<td>7/11</td>
<td>X^2 (1) = 0.36, P = 0.84^a</td>
</tr>
<tr>
<td>Age (y)</td>
<td>50 (12)</td>
<td>44 (12)</td>
<td>49 (11)</td>
<td>X^2 (2) = 3.38, P = 0.19^b</td>
</tr>
<tr>
<td>Educational level (y)</td>
<td>14 (3)</td>
<td>14 (2)</td>
<td>17 (3)</td>
<td>X^2 (2) = 10.54, P &lt; 0.01^c,e</td>
</tr>
<tr>
<td>YMRS score</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>0.2 (0.5)</td>
<td>X^2 (2) = 14.41, P = 0.06^c,e</td>
</tr>
<tr>
<td>HAM-D score</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>1 (1)</td>
<td>X^2 (2) = 14.41, P &lt; 0.01^c,e</td>
</tr>
<tr>
<td>Bipolar disorder subtype (I/II)</td>
<td>9/9</td>
<td>5/15</td>
<td>n/a</td>
<td>X^2 (2) = 2.55, P = .11</td>
</tr>
<tr>
<td>Secondary diagnosis present</td>
<td>78%</td>
<td>80%</td>
<td>n/a</td>
<td>P = 1.00^d</td>
</tr>
<tr>
<td>Duration of illness (y)</td>
<td>14.0 (10.6)</td>
<td>6.4 (5.3)</td>
<td>n/a</td>
<td>U = 91, P = 0.03^e</td>
</tr>
<tr>
<td>Duration of lithium treatment (y)</td>
<td>10 (7)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Priadel™ dose (mg)</td>
<td>828 (256)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Serum lithium concentration (mmol/L)</td>
<td>0.7 (0.2)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>LISERS score</td>
<td>20 (15)</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Note: Values reported as mean (standard deviation).

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; LISERS, Lithium Side Effects Rating Scale; YMRS, Young Mania Rating Scale.

^aChi Square test.
^bKruskall-Wallis test.
^cMann Whitney U test between groups.
^dFisher’s Exact Test.
^eEducation; BDL vs HC P = .004; BDC vs HC P = .006; BDL vs BDC P = .6.
^fHAM-D; BDL vs HC P = .008; BDC vs HC P = .001; BDL vs BDC P = .95.
computed for each ROI in the Desikan-Killiany atlas. Effect sizes ranged from −0.61 to 0.45 (Figure 2), with a mean of 0.01. No ROI was significantly different between BDL and BDC groups following false discovery rate (FDR) correction.

3.3.2 | HC vs BD comparison using Desikan-Killiany atlas

We investigated the individual regional effects considering the two patient groups as a whole bipolar group (BD) in order to determine whether there are regions in which the patient group exhibits significantly higher T1 than healthy controls. The results from this comparison (BD > HC) revealed that all effect sizes were greater than zero (mean: 0.6 range: 0–0.97, Figure 3). Forty-eight out of 90 ROIs survived correction for multiple comparison at a significance threshold of $P < .05$ (Figure 4). There was considerable hemispheric symmetry in terms of which regions exhibited significance, with most such cortical regions falling within the bilateral primary motor/sensory cortex and superior and middle temporal lobes (Figure 4C). A full list of effect sizes and $P$ values for all ROIs is provided in Supplementary Material C (Table C1).

The effect of ROI erosion on the effect size distribution was also investigated by plotting the distribution of effect sizes across a range of ROI erosion levels (see Supplementary Material C, Supplementary Figure C2). These data suggest that partial volume effects do not significantly alter this distribution.

TABLE 2 Medication use by class

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Bipolar disorder lithium (n = 18)</th>
<th>Bipolar disorder controls (n = 20)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>13 (72%)</td>
<td>15 (75%)</td>
<td>OR = 1.2, $P = .85$</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>11 (61%)</td>
<td>12 (61%)</td>
<td>OR = 1.0, $P = .94$</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>5 (28%)</td>
<td>11 (55%)</td>
<td>OR = 3.2, $P = .09$</td>
</tr>
<tr>
<td>Anxiolytics</td>
<td>4 (22%)</td>
<td>6 (30%)</td>
<td>OR = 1.5, $P = .72^a$</td>
</tr>
<tr>
<td>Hypnotic</td>
<td>5 (28%)</td>
<td>2 (10%)</td>
<td>OR = 0.3, $P = .22^a$</td>
</tr>
<tr>
<td>Antihistamine</td>
<td>0</td>
<td>1 (5%)</td>
<td>OR = 0, $P = 1.00^a$</td>
</tr>
<tr>
<td>Over the counter</td>
<td>0</td>
<td>1 (5%)</td>
<td>OR = 0, $P = 1.00^a$</td>
</tr>
<tr>
<td>Mood stabilisers/mania</td>
<td>18 (lithium, 100%)</td>
<td>0</td>
<td>n/a</td>
</tr>
</tbody>
</table>

Note: Values represent number of subjects and percentage of group. Chi Square tests found no differences in medication class between diagnostic groups other than lithium (OR: Odds Ratio) with $^a$Fisher’s exact test reported when one or more cells contained an expected count lower than five.

4 | DISCUSSION

We report that patients with bipolar disorder have higher proton longitudinal relaxation times throughout the brain, particularly in bilateral motor, somatosensory and superior temporal regions, compared to healthy controls. Contrary to our initial hypothesis, we found no significant difference in T1 between patients receiving lithium and those on other medications but naïve to lithium.

This study was initially motivated by the finding that lithium administration has previously been associated with lower T1 in grey matter in patients and healthy controls. It was hypothesised that patients receiving lithium treatment would exhibit shorter T1 compared with lithium-naïve patients. Our results identified greater T1 relaxation times throughout the brain in patients with bipolar disorder relative to healthy controls, but did not find a significant difference in T1 between lithium-treated and lithium-naïve sub groups. Patients with bipolar disorder have previously been found to have elevated T1 values and recent work has shown that patients with first episode psychosis (but not exclusively bipolar disorder) exhibit elevated T1 in white matter compared with healthy controls; this effect was found to be associated with symptom severity. The elevation of T1 in bipolar disorder could be explained by alterations in tissue microstructure such as integrity of myelination, macromolecular content, iron and/or water content. However, due to the complexity of factors that underpin longitudinal relaxation, in vivo it is difficult to predict which factors may drive T1 upwards and which will cause T1 to decrease.

Results from our region of interest analysis show a bilaterally distributed pattern of elevated T1 in patients relative to controls spanning primary somatosensory, motor and superior temporal cortex. Quantitative imaging has been used to study changes associated with brain maturation during development, revealing a pattern of development beginning in primary sensory areas and moving later to the respective association cortex. Divergence from this pattern of development has been linked to various psychiatric disorders.

High resolution quantitative T1 mapping has also been used to characterise patterns of cortical myelination across the healthy human brain in vivo. Notably, this has revealed shorter
T₁ within primary motor, somatosensory and temporal cortices relative to the respective association cortices, indicating greater cortical myelination across these regions. This spatial pattern of cortical myelination resembles the pattern of elevated T₁ times in our bipolar disorder subjects relative to controls. Large differences between patients and controls were seen in primary cortical regions, which likely have higher baseline levels of cortical myelination and so greater scope for change. Disruption of myelination may also prove consistent with the emerging literature demonstrating lower white matter integrity in patients with bipolar disorder.5,26 Cortical thinning is observed in patients with bipolar disorder,27 and is often held to represent a reduction in grey matter volume and/or density. Apparent cortical thinning may also be explained by increased myelination, which can reduce regional T₁ values and alter the contrast between grey and white matter, as shown in a recent combined diffusion MRI and quantitative T₁ relaxometry study of the visual cortex in childhood.28 In the largest combined analysis of bipolar disorder to date, cortical thinning was most marked in frontal regions with relative sparing of primary sensorimotor areas, and whilst comparisons must be made with caution, this could arguably be the reciprocal of the distribution of elevated T₁ values in our study. Future studies combining quantitative T₁, dMRI and T₁w imaging would be of great value in dissecting out the nature of cortical morphological changes in bipolar disorder.

Whilst relatively few studies have investigated brain T₁ during bipolar disorder, a related parameter "T₁ρ" (T₁-rho)—which is sensitive to changes in T₁ yet has different sensitivities to tissue microstructural properties—has been investigated in bipolar disorder during different mood states.8,9 T₁ρ was found to be elevated in euthymic patients with bipolar disorder across cerebral white matter and the cerebellum.8 Interestingly, that study also found reduced cerebellar T₁ρ values in patients receiving lithium treatment. In a follow-up study, a reduction in T₁ρ was found in the basal ganglia during mania and depression relative to euthymia9 but the previous association between lithium treatment and lower T₁ρ was not replicated. In our study we found significant elevations in T₁ throughout the basal ganglia in euthymic bipolar patients relative to controls and it would be of interest to quantify T₁ in non-euthymic states in future work.

4.1 | Strengths

To our knowledge, this is the first study to quantify regional T₁ throughout the brain in a cohort of lithium-treated vs lithium-naïve patients with bipolar disorder in comparison to healthy controls. All analyses were performed on quantitative T₁ data in subject native space, thereby avoiding non-linear warping of the quantitative T₁ data which tends to increase partial volume errors.29 In order to further minimise partial volume effects we chose to erode our subject specific regions of interest to varying degrees and compare the impact that this had upon effect size distributions. The results from this comparison indicate that our main findings were

**FIGURE 1** Detrended T₁ values by group and tissue class. Swarm plot in which each point represents the mean detrended T₁ for each subject in milliseconds, arranged by group and tissue class. P-values represent post-hoc (Tukey’s) corrected significance.

**FIGURE 2** Distribution of effect sizes (BDL < BDC) for all Desikan-Killiany regions of interest (ROI), segregated by tissue type.
unaffected by partial volume effects. Our $T_1$ values are also consistent with other quantitative studies at the same field strength\(^{28}\) and so add to the reference ranges in health and psychiatric illness.

### 4.2 | Weaknesses

Our previous report demonstrating that lithium administration reduced the $T_1$ of grey matter was longitudinal\(^6\) whilst the current study is cross-sectional and so vulnerable to selection bias and group differences, such as the greater duration of illness in the BDL group compared to the BDC group. Previous studies have demonstrated a relationship between duration of lithium treatment and various MRI measures, but we eschewed such an analysis as we lacked comparable data on the duration of treatment in the BDC group. A future longitudinal study in which $T_1$ is quantified before and after lithium administration would be desirable.

### 4.3 | Implications

We have identified a significant difference in brain proton $T_1$ between bipolar patients and healthy controls. As $T_1$ can readily be measured using a clinical MRI scanner, future work might explore
the capacity of the technique to serve as a diagnostic biomarker, discriminating between bipolar disorder and healthy populations. Further investigation into the underlying tissue changes which give rise to elevated $\text{T}_1$ may also provide insights into the pathophysiology of bipolar disorder. It is likely that treatment effects will best be explored in studies with a prospective design.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.