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José Carlos Lobo Espanhol

Effects of lithium use on the white matter of patients
with bipolar disorder – a systematic review

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Effects of lithium use on the white matter of patients with
bipolar disorder – a systematic review

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DESIGNAÇÃO DA ÁREA DO PROJECTO

3.2 Medicina clínica

TÍTULO DISSERTAÇÃO

Effects of lithium use on the white matter of patients with bipolar disorder – a systematic review

ORIENTADOR

Maria Augusta Vieira Coelho

COORDINADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTES TRABALHOS APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 11/01/2021

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Effects of lithium use on the white matter of patients with bipolar disorder – a systematic review

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Abstract

Background: Several studies revealed changes in the microstructure of white matter in bipolar disorder patients. Lithium has been reported as having neuroprotective effects. However, its effect on white matter remains unclear. This systematic review aims to identify the existing clinical evidence of lithium's effect on the white matter from bipolar disorder patients.

Methods: PRISMA guidelines were followed for a systematic literature review to assess the effect of lithium on the white matter of patients with bipolar disorder. From a total of 204 studies screened, 16 were included in the final systematic review. Quality assessment of the included records was assessed by the Newcastle-Ottawa scale.

Results: Most studies included (13 out of 16) evaluated diffusion tensor imaging measures to assess white matter integrity. Of these, eleven reported a positive effect of lithium on the integrity of white matter of bipolar disorder patients. Two reported no effect.

Two studies evaluated white matter volume. The first reported that lithium attenuates reduction of white matter volume over time, and the second reported significantly smaller white matter volume in non-lithium using patients.

The last evaluated ventricular brain ratio and reported that patients treated with lithium did not have a significantly greater ventricular size than their normal control counterparts.

Conclusions: Lithium appears to positively influence the evolution of the white matter abnormalities described in bipolar disorder patients. Should this information be confirmed in future research, and given its important mood stabilizer effect, it could further reinforce the use of lithium in the treatment of bipolar disorder.

Keywords: White Matter, Lithium, Bipolar Disorder, Bipolar Disease, Diffusion Tensor Imaging

Introduction

Bipolar disorder (BD) is a major mental illness affecting 1% of the world's population (Necus et al., 2019). Despite the availability of numerous treatments, lithium retains a key position in major treatment guidelines, notably for the prevention of manic episodes (Severus et al., 2014).

Diffusion tensor imaging (DTI) studies have shown changes in the microstructure of white matter (WM) in BD (Nortje et al., 2013). DTI is an MRI technique that allows in vivo noninvasive measurement of the translational motion of water, providing information about its anisotropy (or lack of it) in different tissues. DTI has been commonly used to quantitatively measure the integrity of tissues which may be compromised by neurological diseases, such as WM tracks of the brain, which normally impart significant anisotropy to water motion in healthy brains. However, this anisotropic effect is diminished when axonal or neuronal damage is present (Lope-Piedrafita, 2018). A systematic review by Nortje et al. showed that all major classes of WM tracts are implicated, and revealed three significant clusters of decreased fractional anisotropy (FA) in BD (a right posterior temporoparietal cluster and two left cingulate clusters) (Nortje et al., 2013).

There is emerging evidence for lithium contributing to measurable structural changes in BD patients (Lyo et al., 2010; Moore et al., 2009; Usher et al., 2010). However, whereas there is general consensus that lithium has a normalizing or preserving effect on brain volume, leading to attenuated differences between patients and controls (Abramovic et al., 2016; Bearden et al., 2007; Germaná et al., 2010; Hafeman et al., 2012; Hibar et al., 2018; Singh and Chang, 2012), such a role is much less clear for lithium in studies of WM microstructure (Abramovic et al., 2018). Given this fact, this review aims to answer the question, “Does the use of lithium influence the evolution of the white matter abnormalities described in bipolar disease patients?”.

Methods

This systematic review was conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2009).

Inclusion criteria

Studies were considered for inclusion if their target population consisted of patients diagnosed with BD.

Exclusion criteria

All non-investigational non-human studies were excluded (animal models, reviews, letters, notes). Studies where the effect of lithium was referenced, but not explored, were also excluded.

Search strategy

For the literature search strategy, see [Table A1](#) in the Appendix.

Results

204 results were identified through the database search. After removing duplicates, 168 records were left. All the records were screened and excluded based on abstract/title, with 21 full-text articles assessed for eligibility for inclusion. A PRISMA flow diagram in [figure 1](#) demonstrates the procedure followed to select the papers used in this systematic review.

Characteristics of the studies, based on PICOS (population, interventions, comparisons, outcomes, study design) criteria, are shown in [Table I](#) (Abramovic et al., 2016; Benedetti et al., 2011; Benedetti et al., 2013; Benedetti et al., 2018; Berk et al., 2017; Besson et al., 1987; Emsell et al., 2013; Foley et al., 2018; Furlan et al., 2019; Gildengers et al., 2015; Haarman et al., 2016; Kafantaris et al., 2017; Macritchie et al., 2010; Necus et al., 2019; Versace et al., 2008)

Quality of evidence was assessed using the Newcastle-Ottawa scale (NOS), which considers the selection and comparability of study participants, as well as ascertainment of outcomes (GA Wells, 2019)

The results of this quality assessment using the NOS are presented in [Table II](#) (Abramovic et al., 2016; Abramovic et al., 2018; Benedetti et al., 2011; Benedetti et al., 2013; Benedetti et al., 2018; Berk et al., 2017; Besson et al., 1987; Emsell et al., 2013; Foley et al., 2018; Furlan et al., 2019; Gildengers et al., 2015; Haarman et al., 2016; Kafantaris et al., 2017; Macritchie et

al., 2010; Necus et al., 2019; Versace et al., 2008). The 16 included studies scored between 5 and 8 points.

In a clinical trial by Kafantaris et al., clinically referred lithium-naïve pediatric patients were administered clinical rating scales and DTI examinations at baseline and following 4 weeks of lithium treatment. Clinical ratings were repeated following 8 weeks of treatment. Patients with Clinical Global Impressions (CGI) ratings of 1 (“very much improved”) or 2 (“much improved”) were classified as responders. Ten healthy volunteers received baseline and follow-up DTI examinations. Using the ENIGMA pipeline, the relationship between changes in FA in the cingulum hippocampus (CGH) and clinical response to lithium was investigated (Kafantaris et al., 2017).

Patients demonstrated significantly lower FA compared to healthy volunteers in the left and right CGH WM at baseline. Following 4 weeks of lithium treatment, FA in the left CGH increased in patients, but no significant changes in FA were observed among the untreated healthy volunteers. Lithium responders had a significantly greater increase in FA compared to non-responders. Moreover, baseline (pretreatment) FA in the left CGH white matter significantly predicted week 8 overall CGI severity score, with post hoc analyses indicating that these effects were evident for both severity of depression and mania (Kafantaris et al., 2017).

Haarman et al. performed a study in which 21 euthymic BD-I patients and 22 healthy controls (HC) participants were included in psychiatric interviews and MRI image acquisition (diffusion-weighted (DW) and T1-weighted scans). FA, radial, mean, and axial diffusivity (RD, MD, AD) were estimated from the DW data, using DTI. These measures were then compared between groups using FSL Tract Based Spatial Statistics (TBSS) (Haarman et al., 2016).

A difference in FA, MD, RD, and AD between the whole sample of euthymic BD-I patients and HC could not be detected. Amongst others, lithium-using patients demonstrated a higher FA and lower RD when compared to non-lithium-using BD-I patients in the corpus callosum and left anterior corona radiata (Haarman et al., 2016).

The authors conclude that the differences in FA between patients using and not using lithium suggest a counteracting effect of lithium on white matter microstructural disturbances (Haarman et al., 2016).

Benedetti et al. studied the role of the Homer family of postsynaptic scaffolding proteins in bipolar depression and treatment response. Homer is a target for antidepressants and mood stabilizers. The AA risk genotype of the Homer rs7713917 A > G SNP has been associated with mood disorders and suicide, and in healthy humans with brain function. To do so, 199 inpatients, affected by a major depressive episode in course of BD, were studied. 147 patients were studied with structural MRI of grey matter (GM) and WM, and 50 with BOLD functional MRI of emotional processing. 158 patients were treated with combined total sleep deprivation and light therapy (Benedetti et al., 2018).

At neuroimaging, patients with the AA genotype showed lower GM volumes in medial prefrontal cortex, higher BOLD fMRI neural responses to emotional stimuli in anterior cingulate cortex, and lower FA in bilateral frontal WM tracts. Lithium treatment increased AD more in AA patients than in G*carriers. At clinical evaluation, the same AA homozygotes showed a worse antidepressant response to combined SD and LT (Benedetti et al., 2018).

In another study by Benedetti et al., they took a sample of 70 patients affected by a major depressive episode in course of BD and investigated the effect of ongoing long-term lithium treatment and GSK3- β promoter rs334558 polymorphism on WM microstructure, using DTI and tract-based spatial statistics with threshold-free cluster enhancement (Benedetti et al., 2013).

The authors reported that the less active GSK3 β rs334558*C gene-promoter variants, and the long-term administration of the GSK3- β inhibitor lithium, were associated with increases of DTI measures of AD in several WM fiber tracts, including corpus callosum, forceps major, anterior and posterior cingulum bundle (bilaterally including its hippocampal part), left superior and inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left posterior thalamic radiation, bilateral superior and posterior corona radiata, and bilateral corticospinal tract (Benedetti et al., 2013).

They suggest that GSK3- β inhibition and lithium could counteract the detrimental influences of BD on WM structure, with specific benefits resulting from effects on specific WM tracts contributing to the functional integrity of the brain and involving interhemispheric, limbic, and large frontal, parietal, and fronto-occipital connections (Benedetti et al., 2013).

Gildengers et al. examined cognitive and neuroimaging data in 58 individuals with BD mean (SD) age 64.5 (9.8) years and 21 mentally HC of similar age and education. Subjects received comprehensive neurocognitive assessment and structural brain imaging, examining total GM volume, overall WM integrity (FA), and total WM hyperintensity (WMH) burden (Gildengers et al., 2015).

In comparison to controls, subjects with BD had worse overall cognitive performance, lower total GM volume, and lower WM integrity. Among BD subjects, longer duration of lithium treatment was related to higher WM integrity after controlling for age and vascular disease burden, but not with better cognitive performance, thus suggesting that lithium treatment appears to be related to better brain integrity in older individuals with BD, in particular in those who take it long-term (Gildengers et al., 2015).

Furlan et al. studied DTI measures of water diffusion, fMRI corticolimbic functional response and connectivity, and multi-parameter cytofluorometry analysis of NK (CD56+) subpopulations, in 30 inpatients with active BD type I. NK cells were also obtained in 36 HC (Furlan et al., 2019).

Patients had significantly higher circulating counts of CD56+GMCSF+, CD56+INF γ +, and CD56+IL17+. NK cell levels positively associated with FA measures. CD56+TNF α +, CD56+INF γ +, and CD56+GMCSF+ directly correlated with FA, and inversely with RD and MD. Duration of lithium treatment associated with higher CD56+TNF α +, CD56+IL2+, and CD56+IL4+, and positively associated with FA in tracts were NKs had significant effects. A mediation model suggested a partial mediation of CD56+TNF α + cells, higher in patients on lithium, on the effects of lithium on FA. Frequencies of the same cytokine-producing NK cells also influenced fMRI cortico-limbic functional connectivity during processing of both, emotional and non-emotional stimuli (Furlan et al., 2019).

This suggests that these cytokine-producing NK cells partially mediate the effect of lithium on WM (Furlan et al., 2019).

Berk et al. conducted a single-blinded equivalence randomized controlled maintenance trial in a prospective cohort of first episode mania (FEM) patients (n = 26) to longitudinally compare the putative protective effects of lithium and quetiapine on GM and WM volume. A HC sample was also collected (n = 20). Using structural MRI scans, voxel-wise GM and WM volumes at

baseline and changes over time in response to treatment were investigated. Patients were assessed at three time points (baseline, 3 and 12-month follow-up), whereas HC were assessed at two time points (baseline and 12-month follow-up). Patients were randomized to lithium (serum level 0.6 mmol l⁻¹, n = 20) or quetiapine (flexibly dosed up to 800 mg per day, n = 19) monotherapy (Berk et al., 2017).

At baseline, compared with HC subjects, patients with FEM showed reduced GM in the orbitofrontal cortex, anterior cingulate, inferior frontal gyrus, and cerebellum. In addition, patients had reduced internal capsule WM volume bilaterally ($t_{1,66} > 3.20$, $P < 0.01$). Longitudinally, there was a significant treatment $\times$ time effect only in the WM of the left internal capsule ($F_{2,112} = 8.54$, $P < 0.01$). Post hoc testing showed that, compared with baseline, lithium was more effective than quetiapine in slowing the progression of WM volume reduction after 12 months ($t_{1,24} = 3.76$, $P < 0.01$). This data supports the role of lithium, but not quetiapine therapy, in limiting WM reduction early in the illness course after FEM (Berk et al., 2017).

Besson et al. examined manic depressive patients on long-term prophylactic therapy with lithium carbonate using nuclear magnetic resonance imaging of the brain (Besson et al., 1987). Results showed that patients treated with lithium did not have a significantly greater ventricular size than their normal control counterparts, suggesting that the treatment with lithium favorably altered the progress of this condition (Besson et al., 1987).

In yet another study by Benedetti et al., conventional and DT MRI sequences of the brain were acquired from 15 adult patients with major depressive disorder (MDD), 15 with BD, and 21 age-matched HC. Using FSL software, diffusivity changes of the WM fiber bundles belonging to the emotional network were measured (Benedetti et al., 2011).

Compared to controls and MDD patients, BD patients had significantly decreased average FA, increased average MD, and increased average AD and RD values in the majority of the WM fiber bundles connecting structures of the anterior limbic network (p-values ranging from 0.002 to 0.040). Medication load did not influence the results, except for lithium, which was associated with normal diffusivity values in tracts connecting the amygdala with the subgenual cingulate cortex (Benedetti et al., 2011).

Emsell et al. obtained structural MRI (sMRI) for 60 patients with prospectively confirmed euthymic BD I and 60 individually age- and gender-matched HC. High angular resolution DTI scans were obtained for a subset of this sample comprising 35 patients and 43 controls. Voxel based analysis of both sMRI and DTI data sets was performed (Emsell et al., 2013).

BD patients displayed global reductions in WM volume and FA reductions in the corpus callosum, posterior cingulum, and prefrontal WM compared with controls. There were corresponding increases in RD in the callosal splenium in patients compared with controls. No significant group differences were detected in GM. In patients, lithium was associated with a bilateral increase in GM volume in the temporal lobes, but not with any DTI parameter (Emsell et al., 2013).

Abramovic et al. investigated the relation of WM microstructure with the main pharmacological treatments, as well as its relation with IQ. Patients with BD (N=257) and controls (N=167) underwent DTI and comprehensive clinical assessments including IQ estimates. DTI images were analyzed using tract-based spatial statistics. FA and MD were determined (Abramovic et al., 2018).

Patients had significantly lower FA and higher MD values throughout the WM skeleton compared to controls. Within the BD patients, lithium use was associated with higher FA and lower MD. Antipsychotic medication use in the BD patients was not associated with FA but, in contrast to lithium, was associated with higher MD. IQ was significantly positively correlated with FA and negatively with MD in patients as well as in controls (Abramovic et al., 2018).

The authors found evidence for marked differences in FA and MD particularly in (but not restricted to) corpus callosum, between BD patients and controls. This effect was most pronounced in lithium-free patients, implicating that lithium affects WM microstructure and attenuates differences associated with BD. Effects of antipsychotic medication intake were absent in FA and only subtle in MD relative to those of lithium (Abramovic et al., 2018).

Macritchie et al. measured diffusion parameters at several regions in the corpus callosum and in deep/periventricular white matter in 28 currently euthymic patients with BD and controls. WM hyperintensity loads were assessed (Macritchie et al., 2010).

Comparing the whole data-sets using the sign test, in the group with BD, MD was greater at all 15 sites ($P < 0.001$), and FA was reduced at 13 ($P < 0.01$). The effect of diagnosis was

significant for callosal MD and FA and for deep/periventricular MD (MANCOVA). Comparing individual regions (Mann–Whitney U-test), prefrontal and periventricular MD were significantly increased; callosal and occipital FA were significantly reduced. Former substance use and lithium were possible confounding factors. Periventricular WM hyperintensities were associated with significantly increased periventricular MD in individuals with BD (Macritchie et al., 2010).

The authors conclude that generalized WM microstructural abnormalities may exist in BD, possibly exacerbated by past substance use and ameliorated by lithium (Macritchie et al., 2010).

Necus et al. studied the relationship between the spatial distribution of brain lithium and WM integrity. Euthymic patients with BD receiving lithium ($n = 12$) and those on other medications but naïve to lithium ($n = 17$) underwent diffusion imaging alongside matched HC ($n = 16$). Generalized FA (gFA) within WM was compared between groups using a standard space WM atlas. Lithium-treated patients underwent novel multinuclear lithium magnetic resonance imaging (^7Li -MRI) to determine the relative lithium concentration across the brain. The relationship between ^7Li -MRI signal intensity and gFA was investigated at the resolution of the ^7Li -MRI sequence in native space (Necus et al., 2019).

Lithium-treated BD and HC groups had higher mean WM gFA than the BD group treated with other medications ($t = 2.5$, $p < 0.05$; $t = 2.7$, $p < 0.03$, respectively). No differences in gFA were found between patients taking lithium and HC ($t = 0.02$, $p = 1$). These effects were seen consistently across most regions in the WM atlas. In the lithium-treated group, a significant effect of the ^7Li -MRI signal in predicting the gFA ($p < 0.01$) was identified in voxels containing over 50% WM (Necus et al., 2019).

The authors concluded that the higher gFA values observed in the lithium-treated BD group suggests that long term lithium is associated with greater WM integrity, and that their novel analysis supports this further, showing a positive association between WM gFA and the spatial distribution of lithium (Necus et al., 2019).

Abramovic et al. aimed to disentangle disease-specific brain deviations from those induced by antipsychotic medication and lithium intake using a large homogeneous sample of patients with BD type I. MRI brain scans were obtained from 266 patients and 171 control subjects.

Subcortical volumes and global and focal cortical measures (volume, thickness, and surface area) were compared between patients and controls. In patients, the association between lithium and antipsychotic medication intake and global, subcortical and cortical measures was investigated (Abramovic et al., 2016).

Patients showed significantly larger lateral and third ventricles, smaller total brain, caudate nucleus, and pallidum volumes, and thinner cortex in some small clusters in frontal, parietal and cingulate regions as compared with controls. Lithium-free patients had significantly smaller total brain, thalamus, putamen, pallidum, hippocampus and accumbens volumes compared to patients on lithium. In patients, use of antipsychotic medication was related to larger third ventricle and smaller hippocampus and supramarginal cortex volume. Patients with BD showed abnormalities in total brain, subcortical, and ventricle volume, particularly in the nucleus caudate and pallidum. Abnormalities in cortical thickness were scattered and clusters were relatively small. Lithium-free patients showed more pronounced abnormalities as compared with those on lithium (Abramovic et al., 2016).

Versace et al. used tract-based spatial statistics (TBSS) to examine WM skeleton in subjects with BD vs HC subjects. They studied 56 individuals, 31 having a DSM-IV diagnosis of BD type I (mean age, 35.9 years; age range: 24-52 years) and 25 controls (mean age, 29.5 years; age range: 19-52 years). The main outcomes measured were FA, LD and RD (Versace et al., 2008). They found a significant negative correlation between FA and psychotropic medication load among subjects with BD in a cluster in the left optic radiation, as well as significantly decreased FA among subjects with BD taking mood stabilizers in the same left optic radiation cluster and in the right anterothalamic radiation. Together, these findings suggest an ameliorative effect of psychotropic medication and particularly mood stabilizers in reducing abnormally increased FA among subjects with BD (Versace et al., 2008).

The authors found no significant difference in FA between subjects with BD taking vs not taking lithium, suggesting that mood stabilizers other than lithium may contribute to changes in FA among subjects with BD (Versace et al., 2008).

Foley et al. compared FA measures from the uncinate fasciculus, cingulum body and parahippocampal cingulum with tractography methods in 40 HC, 32 patients with BD-I, 34

patients with BD-II, 17 siblings of patients with BD-I and 14 siblings of patients with BD-II (Foley et al., 2018).

FA in the uncinate fasciculus showed a significant positive association between lithium status and FA in the left uncinate fasciculus ($r = 0.37$, $P = 0.004$). There were trends between lithium status and FA in the right uncinate fasciculus ($r = 0.24$, $P = 0.055$). Regression analyses were then run to ascertain whether clinical group allocation (i.e. BD-I versus BD-II) still explained a significant amount of variance after accounting for FA variance explained by those medication variables. Clinical group allocation (BD-I versus BD-II) still explained a significant amount of FA in the left uncinate fasciculus after accounting for variance explained by lithium status, and the same was found for the right uncinate fasciculus (Foley et al., 2018).

Discussion

To our knowledge, this is the first systematic review assessing the effect of lithium on the WM abnormalities described in BD patients.

Most of the studies included in this review (13 out of the 16 included) evaluated DTI measures to assess WM integrity. Of these, ten reported a positive effect of lithium on the integrity of the WM of BD patients, in a variety of locations ([Table III](#)), and one related longer duration of lithium treatment with higher overall WM integrity (Gildengers et al., 2015). Only 2 reported no effect. The first reported no significant associations between lithium status and any DTI measure (Emsell et al., 2013). The second reported no significant difference in FA between subjects with BD taking vs not taking lithium (Versace et al., 2008).

Two other studies evaluated WM volume. One reported significantly smaller WM volume in non-lithium using patients, as compared with lithium using patients (Abramovic et al., 2016). The other reported that the lithium group showed an attenuated reduction of WM volume over time, compared with the quetiapine group at 12 months of follow-up, but only on the left internal capsule (Berk et al., 2017).

The last study evaluated ventricular brain ratio and reported that patients treated with Li did not have a significantly greater ventricular size than their normal control counterparts (Besson et al., 1987).

Quality of evidence and limitations

Several limitations stand out among the studies included in this systematic review.

Multiple studies included reported low sample sizes (Benedetti et al., 2011; Benedetti et al., 2013; Gildengers et al., 2015; Haarman et al., 2016; Kafantaris et al., 2017; Necus et al., 2019), which is a major limitation.

Another limitation is the cross-sectional nature of some studies (Abramovic et al., 2018; Gildengers et al., 2015; Necus et al., 2019; Versace et al., 2008).

The previous use of lithium by patients in the non-lithium groups (Abramovic et al., 2016; Abramovic et al., 2018) is also a limitation, since it can lead to an underestimation of the effect of lithium, as the effect of lithium on the brain is not reversible in rodents (Vernon and Hajek, 2013)

Some studies did not use a medication naïve group of patients (Abramovic et al., 2016; Abramovic et al., 2018; Benedetti et al., 2013; Benedetti et al., 2018; Furlan et al., 2019; Haarman et al., 2016), which would have helped to better assess the effects of lithium.

Some studies also reported having differing psychotropic regimens (intra or inter-group regimens, duration of medication use, or doses administered) or concomitant medications, which could have influenced the results obtained (Abramovic et al., 2016; Benedetti et al., 2013; Benedetti et al., 2018; Berk et al., 2017; Foley et al., 2018; Furlan et al., 2019).

DTI's own limitations and data analysis strategy chosen are also reported by some studies as a limitation (Benedetti et al., 2011; Benedetti et al., 2013; Furlan et al., 2019; Haarman et al., 2016; Macritchie et al., 2010).

Differences in past alcohol and illicit substance abuse were also reported in some studies (Macritchie et al., 2010; Versace et al., 2008), which could be a confounding factor.

Benedetti et al. reported retrospective determination of lithium use (Benedetti et al., 2013), thus making it biased by the impossibility to assess compliance.

Macritchie et al. also some variation of disease duration and severity (Macritchie et al., 2010), which could influence the results obtained.

Some studies report a lack of HC group (Benedetti et al., 2018; Furlan et al., 2019) or a small HC group (Kafantaris et al., 2017), limits generalizability to the general population.

Another limitation reported was the recruitment from a single location and/or single ethnic group (Benedetti et al., 2013; Benedetti et al., 2018; Furlan et al., 2019), thus raising the possibility of population stratification.

Gildengers et al. also reported, as a limitation, the generalizability of findings derived from patients treated in an academic medical center that prioritizes lithium as a first-line agent, as well as survivorship bias (Gildengers et al., 2015).

Differences in groups' characteristics, namely IQ level, was also reported by Abramovic et al. (Abramovic et al., 2018).

One study reported most patients as having psychotic symptoms at baseline, which limits extrapolation to non-psychotic patients (Berk et al., 2017).

Emsell et al. reported as limitations the fact that it only studied BD I patients, and that VBM results are highly dependent on several parameter settings and it is possible to generate different outcomes even with the same data set (Emsell et al., 2013).

Regarding the limitations of the present systematic review, the number of articles included was not ideal. However, the number of studies on the effects of lithium on the WM of BD patients are very limited.

Future research and studies

Further research into this topic is needed, as the mechanism by which lithium changes WM in the brain is yet unknown. It is also important to consider other factors, including duration of lithium use, previous medications used, type of BD, starting age of administration, concomitant use of other medications, alcohol or drugs and concomitant diseases that can affect brain structure.

The studies should be undertaken in patients at the same disease stage and undergoing the same treatment regimen, ideally medication naïve patients with similar characteristics. The inclusion of a medication naïve patient group using a placebo would be ideal; however, this would be unacceptable for obvious ethical reasons.

Conclusions

Lithium appears to positively influence the evolution of the WM abnormalities described in BD patients. Should this information be confirmed in future research, and given its important mood stabilizer effect, it could further reinforce the use of lithium in the treatment of bipolar disorder.

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Attachments

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Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both	Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3, 1 st to 3 rd paragraphs
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3, 3 rd paragraph
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Not available
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4, 1 st and 2 nd paragraphs
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 4, 3 rd paragraph
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 4, 3 rd paragraph
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4, 4 th paragraph
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4, 5 th and 6 th paragraphs
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 4, 5 th paragraph

Risk of bias in individual studies/Risk of bias across studies	12/15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	Page 4, 7 th paragraph
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Non applicable, since this review does not include a meta-analysis
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Non applicable, since this review does not include a meta-analysis
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Non applicable, since this review does not include a meta-analysis
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 28, figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Pages 29 to 32, Table I
Risk of bias within and across studies	19/22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Pages 33 and 34, Table II
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Non applicable, since this review does not include a meta-analysis
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Non applicable, since this review does not include a meta-analysis
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Non applicable, since this review does not include a meta-analysis
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 12, 3 rd to 5 th paragraphs
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Pages 13 and 14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 1

Appendix

Table A1. Systematic electronic database search strategy ^a

#	Search terms
1	Bipolar disorder [tw]
2	Bipolar disease [tw]
3	BD [tw]
4	#1 OR #2 OR #3
5	White matter [tw]
6	Lithium [tw]
7	#4 AND #5 AND #6

a. Databases searched were PubMed and Scopus. The search was most recently performed on the 28th of September.

Figure 1. Flow diagram of the literature search process.

Table I – Characteristics of the studies included in the systematic review, identifying PICOS criteria (population, intervention, comparison, outcome, and study type)

Study	Study design	Population	Comparisons and sample size	Time	Intervention	Assessed outcomes	Lithium's effect
Kafantaris, Spritzer et al. 2017 (Kafantaris et al., 2017)	Clinical Trial	Li-naïve pediatric patients with DSM-IV criteria for BD I or BD not otherwise specified	Total n = 28; 18 patients; 10 healthy volunteers	8 weeks	4 weeks of Li treatment	Severity of mood symptoms (using CGI-S item, CDRS-R and YMRS) and FA in the cingulum hippocampus (using DTI)	Within the BD patients, Li use was associated with higher FA and lower MD in the cingulum hippocampus
Haarman, Riemersma-Van der Lek et al. 2016 (Haarman et al., 2016)	Observational study	Euthymic BD I patients, subsequently divided into Li-users and non-Li-users	Total n = 43; 21 euthymic BD I patients (12 Li-users and 9 non-Li-users); 22 healthy control patients	NA	NA	FA, RD, MD, and AD (estimated from the diffusion-weighted MRI scans, using DTI).	Within the corpus callosum and the left anterior corona radiata, FA was found to be significantly lower in non-Li-using BD-I patients compared to Li-using BD-I patients, as well as healthy controls
Benedetti, Poletti et al. 2018 (Benedetti et al., 2018)	Clinical Trial	Caucasian inpatients of Italian descent affected by a major depressive episode, without psychotic features, in course of BD type I (DSM IV-TR criteria)	Total n = 158; 91 AA homozygotes; 108 *G carriers	NA	5 days of total sleep deprivation and light therapy	GM volume (using T1-weighted MRI scans); DTI measures of WM microstructure (FA, MD, AD and RD)	Li treatment showed a significant interaction with rs7713917 in increasing AD in left anterior limb of internal capsule and right posterior corona radiata
Benedetti, Bollettini et al. 2013 (Benedetti et al., 2013)	Observational study	Inpatients affected by a major depressive episode, without psychotic features, with a diagnosis of BD type I (structured clinical interview for DSM disorders)	Total n = 70; 50 drug-free patients; 20 patients on Li treatment	NA	NA	WM microstructure (FA, MD, AD and RD; using DTI and tract-based spatial statistics with threshold-free cluster enhancement)	Duration of Li treatment positively correlated with AD and MD in several WM tracts (mainly in the left hemisphere), including corpus callosum, forceps major, anterior and posterior cingulum bundle, left superior and inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left posterior thalamic radiation, bilateral superior and posterior corona radiata, and bilateral corticospinal tract
Gildengers, Butters et al. 2015 (Gildengers et al., 2015)	Observational study	Individuals with BD I or II diagnosed by the SCID-IV	Total n = 79; 58 patients with BD; 21 controls	NA	NA	Neurocognitive assessment; total GM volume, overall WM integrity (FA), and total WM hyperintensity burden (using MRI scans)	Among BD subjects, longer duration of Li treatment was related to higher WM integrity

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Study	Study design	Population	Comparisons and sample size	Time	Intervention	Assessed outcomes	Lithium's effect
Furlan, Melloni et al. 2019 (Furlan et al., 2019)	Observational study	Inpatients with BD type I, currently in an active phase of the illness	Total n = 30	NA	NA	FA, MD, AD and RD (using DTI), fMRI corticolimbic functional response and connectivity, and multi-parameter cytofluorometry analysis of NK (CD56+) subpopulations	Duration of Li treatment associated with higher CD56+TNF α +, CD56+IL2+, and CD56+IL4+, and positively associated with FA in tracts were NK cells had significant effects (left inferior longitudinal fasciculus, left anterior thalamic radiation and left cingulum)
Berk, Dandash et al. 2017 (Berk et al., 2017)	Single blinded equivalence randomized controlled maintenance trial	First episode mania patients meeting DSM-IV-TR criteria for a manic episode on the SCID-I/P	Total n = 69; 30 controls; 39 patients	52 weeks	Li or quetiapine monotherapy	GM and WM volumes (using structural MRI scans);	Li group showed an attenuated reduction of WM volume over time compared with the quetiapine group at 12 months of follow-up, but only on the left internal capsule
Besson, Henderson et al. 1987 (Besson et al., 1987)	Observational study	Manic depressive patients, all complying with DSM 3 diagnostic categories for BD or major depression, on Li therapy alone	Total n = 20; 10 patients; 10 healthy controls	NA	NA	VBR (using NMR), memory tests (using the Weschler Memory Scale) and mood (measured by the Hamilton Rating Scale and the Manic Rating Scale).	Patients treated with Li did not have a significantly greater ventricular size than their normal control counterparts
Benedetti, Absinta et al. 2011 (Benedetti et al., 2011)	Observational study	Inpatients affected by mood disorder screened with the DSM-IV	Total n = 51; 30 patients affected by mood disorder (15 with major depressive disorder and 15 with BD I); 21 age-matched healthy controls	NA	NA	Average MD, AD, RD, and FA (using conventional and DTI MRI)	Patients treated with Li showed significantly higher FA values in the amygdala-BA25 connection than those who did not. Li-treated patients had values not significantly different than those of healthy controls, and Li-free patients had significantly lower values than those of healthy controls. A protective effect of ongoing Li treatment was observed in terms of relatively preserved FA values in the WM tracts connecting amygdala with subgenual cingulate cortex

Table I – Characteristics of the studies included in the systematic review, identifying PICOS criteria (population, intervention, comparison, outcome, and study type)

Study	Study design	Population	Comparisons and sample size	Time	Intervention	Assessed outcomes	Lithium's effect
Emsell, Langan et al. 2013 (Emsell et al., 2013)	Observational study	Patients with BD type I	Total n = 120; 60 patients with BD I; 60 individually age- and gender-matched healthy volunteers	NA	NA	GM, WM, cerebrospinal fluid, and total brain volumes (using structural MRI)	There were no significant associations between Li status and any DTI measure
Abramovic, Boks et al. 2018 (Abramovic et al., 2018)	Observational study	Patients with BD type I	Total n = 431; 262 patients with BD type I; 169 control subjects	NA	NA	FA and MD (using DTI)	Li- patients showed significant lower FA values than Li+ patients in the corpus callosum, fornix, and the major and minor forceps. MD showed an opposite, although less pronounced effect in similar areas, where MD was higher in Li- than in Li+ patients
Macritchie, Lloyd et al. 2010 (Macritchie et al., 2010)	Observational study	Right-handed individuals with BD (I or II)	Total n = 56; 28 right-handed individuals with BD (I or II); 28 right-handed controls, individually matched for age, gender and performance on the National Adult Reading Test	NA	NA	MD, FA, and WM hyperintensities (using DTI scans)	MD in the non-Li treated group was higher than in the Li group at 12 of the 15 sites. FA was lower at 10 of the 15 sites. In the non-Li-treated bipolar group compared with their controls, the pattern of increased prefrontal, periventricular and callosal MD previously observed in the main-group comparison persisted. This pattern was not seen in the Li-treated group compared with their control group.
Necus, Sinha et al. 2019 (Necus et al., 2019)	Observational study	Euthymic patients with BD, sub-divided in those receiving Li and those on other medications but naïve to Li	Total n = 45; 29 patients (12 receiving Li; 17 on other medications but naïve to Li); 16 matched healthy controls	NA	NA	Generalized FA (using T1-weighted and DTI acquisitions on MRI scans) Relative Li concentration across the brain (only in patients receiving Li; using multinuclear Li MRI scans)	Patients treated with Li had WM generalized FA values comparable to healthy controls and greater than patients receiving other medications in 44 out of 48 regions of interest, with eight regions exhibiting an effect size of greater than 0.8 (both cerebral peduncles, left hippocampus, left inferior

Table I – Characteristics of the studies included in the systematic review, identifying PICOS criteria (population, intervention, comparison, outcome, and study type)

Study	Study design	Population	Comparisons and sample size	Time	Intervention	Assessed outcomes	Lithium's effect
							cerebellar peduncle, both middle cerebellar peduncles, pontine crossing tract and both stria terminalis)
Abramovic, Boks et al. 2016 (Abramovic et al., 2016)	Observational study	Patients with BD type I according to DMS-IV criteria	Total n = 437; 266 patients (175 on Li; 91 on other medications); 171 control subjects	NA	NA	Subcortical volumes and global and focal cortical measures (volume, thickness, and surface area), using MRI scans	Significantly smaller volume of the total brain, GM, and WM volume, and larger third ventricle volume was found in Li- as compared with Li+ patients
Versace, Almeida et al. 2008 (Versace et al., 2008)	Cross-sectional, case-control	Patients with a DSM-IV diagnosis of BD type I	Total n= 56; 31 patients; 25 controls	NA	NA	FA, LD, and RD	Did not find a significant difference in FA between subjects with BD taking vs not taking Li
Foley, Bracher-Smith et al. 2018 (Foley et al., 2018)	Observational study	Patients with BD type I and type II, as well as siblings of these patients	Total n = 137; 40 healthy controls; 32 patients with BD-I; 34 patients with BD-II; 17 siblings of patients with BD-I; 14 siblings of patients with BD-II	NA	NA	FA measures from the uncinate fasciculus, cingulum body and parahippocampal cingulum	FA in the uncinate fasciculus showed a significant positive association between Li status and FA in the left uncinate fasciculus. There were trends between Li status and FA in the right uncinate fasciculus. Clinical group allocation (BD-I versus BD-II) still explained a significant amount of FA in the left uncinate fasciculus after accounting for variance explained by Li status, and the same was found for the right uncinate fasciculus

Abbreviations used: NA – Non-Applicable; DTI – Diffusion Tensor Imaging; BD – Bipolar Disorder; FA – Fractional Anisotropy; MD – Mean Diffusivity; AD – Axial Diffusivity; RD – Radial Diffusivity; LD – Longitudinal Diffusivity; WM – White Matter; GM – Grey Matter; NMR – Nuclear Magnetic Resonance; Li – Lithium; CGI-S – Clinical Global Impressions Severity; CDRS-R – Children's Depression Rating Scale; YMRS – Young Mania Rating Scale; SCID-IV – Structured Clinical Interview for Axis I DSM-IV Disorders; NK – Natural Killer; SCID-I/P – Structured Clinical Interview for DSM-IV-TR—Patient Edition; VBR – Ventricular-Brain Ratio

Table II – Quality assessment of included trials using the Newcastle-Ottawa Quality Assessment Scale

Study	Selection				Comparability	Exposure			Total Quality Score (max. 9)
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Kafantaris, Spritzer et al. 2017 (Kafantaris et al., 2017)	1	1	0	1	2	0	1	0	6
Haarman, Riemersma-Van der Lek et al. 2016 (Haarman et al., 2016)	1	0	0	1	2	1	1	0	6
Benedetti, Poletti et al. 2018 (Benedetti et al., 2018)	1	1	0	0	1	1	1	0	5
Benedetti, Bollettini et al. 2013 (Benedetti et al., 2013)	1	1	0	0	2	0	1	0	5
Gildengers, Butters et al. 2015 (Gildengers et al., 2015)	1	0	1	1	2	1	1	0	7
Furlan, Melloni et al. 2019 (Furlan et al., 2019)	0	1	0	1	2	1	0	0	5
Berk, Dandash et al. 2017 (Berk et al., 2017)	1	1	0	1	1	1	0	0	5
Besson, Henderson et al. 1987 (Besson et al., 1987)	1	0	0	1	1	1	1	0	5
Benedetti, Absinta et al. 2011 (Benedetti et al., 2011)	1	1	0	1	1	1	1	0	6
Emsell, Langan et al. 2013 (Emsell et al., 2013)	1	0	1	1	2	1	1	0	7
Abramovic, Boks et al. 2018 (Abramovic et al., 2018)	1	1	1	1	2	1	1	0	8

Macritchie, Lloyd et al. 2010 (Macritchie et al., 2010)	1	0	0	1	2	1	1	0	6
Necus, Sinha et al. 2019 (Necus et al., 2019)	1	0	0	1	2	1	1	0	6
Abramovic, Boks et al. 2016 (Abramovic et al., 2016)	1	0	0	1	2	0	1	0	5
Versace, Almeida et al. 2008 (Versace et al., 2008)	1	0	0	1	2	1	1	0	6
Foley, Bracher-Smith et al. 2018 (Foley et al., 2018)	0	1	1	1	2	1	1	0	7

Table III. Locations targeted by lithium

Study	Location
Kafantaris et al., 2017 (Kafantaris et al., 2017)	Cingulum hippocampus
Haarman et al., 2016 (Haarman et al., 2016)	Corpus callosum and left anterior corona radiata
Benedetti et al., 2018 (Benedetti et al., 2018)	Left anterior limb of internal capsule and right posterior corona radiata
Benedetti et al., 2013 (Benedetti et al., 2013)	Corpus callosum, forceps major, anterior and posterior cingulum bundle, left superior and inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, left posterior thalamic radiation, bilateral superior and posterior corona radiata, and bilateral corticospinal tract
Furlan et al., 2019 (Furlan et al., 2019)	Left inferior longitudinal fasciculus, left anterior thalamic radiation, and left cingulum
Benedetti et al., 2011 (Benedetti et al., 2011)	Amygdala-BA25 connection
Abramovic et al., 2018 (Abramovic et al., 2018)	Corpus callosum, fornix, and the major and minor forceps
Macritchie et al., 2010 (Macritchie et al., 2010)	MD in the non-Li treated group was higher than in the Li group at 12 of the 15 sites. FA was lower at 10 of the 15 sites*
Necus et al., 2019 (Necus et al., 2019)	Both cerebral peduncles, left hippocampus, left inferior cerebellar peduncle, both middle cerebellar peduncles, pontine crossing tract and both stria terminalis
Foley et al., 2018 (Foley et al., 2018)	Uncinate fasciculus

* - Study does not specify locations