Psychological Medicine

cambridge.org/psm

Lithium prevents grey matter atrophy in patients with bipolar disorder: an international multicenter study

Franz Hozer[1,2,3,4], Samuel Sarrazin[3,4], Charles Laidi[3,4,5,6], Pauline Favre[3,4], Melissa Pauling[3,4,5,6], Dara Cannon[7], Colm McDonald[7], Louise Emsell[8,9], Jean-François Mangin[10], Edouard Duchesnay[10], Marcella Bellani[11], Paolo Brambilla[12], Michele Wessa[13], Julia Linke[13], Mircea Polosan[14], Amelia Versace[15], Mary L. Phillips[15], Marine Delavest[16,17], Frank Bellivier[16,17], Nora Hamdani[4,5,6], Marc-Antoine d'Albis[3,4,5,6], Marion Leboyer[4,5,6,18] and Josselin Houenou[3,4,5,6,18]

[1]Department of Psychiatry, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Corentin-Celton, Issy-les-Moulineaux, France; [2]Paris Descartes University, PRES Sorbonne Paris Cité, Paris, France; [3]UNIACT Lab, Psychiatry Team, NeuroSpin Neuroimaging Platform, CEA Saclay, Gif-sur-Yvette, France; [4]INSERM U955, Mondor Institute for Biomedical Research, Team 15, Translational Psychiatry, Créteil, France; [5]Department of Psychiatry, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpitaux Universitaires Mondor, Créteil, France; [6]Fondation FondaMental, Créteil, France; [7]Centre for Neuroimaging & Cognitive Genomics (NICOG), NCBES Galway Neuroscience Centre, National University of Ireland Galway, H91 TK33 Galway, Ireland; [8]Translational MRI, Department of Imaging & Pathology, KU Leuven, Leuven, Belgium; [9]Department of Old Age Psychiatry, University Psychiatry Centre, KU Leuven, Leuven, Belgium; [10]UNATI Lab, NeuroSpin Neuroimaging Platform, CEA Saclay, Gif-sur-Yvette, France; [11]UOC Psychiatry, Azienda Ospedaliera Universitaria Integrata Verona (AOUI), Verona, Italy; [12]Department of Neurosciences and Mental Health, Fondazione IRCCS Ca' Grand Ospedale Maggiore Policlinico, University of Milan, Milan, Italy; [13]Department of Clinical Psychology and Neuropsychology, Johannes Gutenberg-University Mainz, Mainz, Germany; [14]Grenoble Alpes University, Grenoble Institute of Neuroscience, INSERM U1216, Hôpital Grenoble Alpes, Grenoble, France; [15]Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh, Pittsburgh, Pennsylvania, USA; [16]Department of Psychiatry, Assistance Publique-Hôpitaux de Paris (AP-HP), Hôpital Lariboisière-Fernand Widal, INSERM U705 CNRS UMR 8206, Paris, France; [17]Paris Diderot University, Paris, France and [18]Faculté de Médecine de Créteil, Université Paris Est Créteil, Créteil, France

Original Article

Cite this article: Hozer F *et al* (2021). Lithium prevents grey matter atrophy in patients with bipolar disorder: an international multicenter study. *Psychological Medicine* **51**, 1201–1210. https://doi.org/10.1017/S0033291719004112

Received: 21 December 2018
Revised: 31 August 2019
Accepted: 23 December 2019
First published online: 27 January 2020

Key words:
Bipolar disorder; grey matter volume; lithium; MRI

Author for correspondence:
Franz Hozer, E-mail: franz.hozer@aphp.fr

Abstract

Background. Lithium (Li) is the gold standard treatment for bipolar disorder (BD). However, its mechanisms of action remain unknown but include neurotrophic effects. We here investigated the influence of Li on cortical and local grey matter (GM) volumes in a large international sample of patients with BD and healthy controls (HC).

Methods. We analyzed high-resolution T1-weighted structural magnetic resonance imaging scans of 271 patients with BD type I (120 undergoing Li) and 316 HC. Cortical and local GM volumes were compared using voxel-wise approaches with voxel-based morphometry and SIENAX using FSL. We used multiple linear regression models to test the influence of Li on cortical and local GM volumes, taking into account potential confounding factors such as a history of alcohol misuse.

Results. Patients taking Li had greater cortical GM volume than patients without. Patients undergoing Li had greater regional GM volumes in the right middle frontal gyrus, the right anterior cingulate gyrus, and the left fusiform gyrus in comparison with patients not taking Li.

Conclusions. Our results in a large multicentric sample support the hypothesis that Li could exert neurotrophic and neuroprotective effects limiting pathological GM atrophy in key brain regions associated with BD.

Introduction

Lithium (Li) salts have been used to treat bipolar disorder (BD) since the late 1940s (Shorter, 2009), and it remains the first-line mood stabilizing drug to treat patients with BD (Yatham et al., 2013). Despite mechanisms of action remaining incompletely elucidated, Li is hypothesized to exert robust neuroprotective and/or neurotrophic effects on a grey matter (GM) volume as reported both in rodent models (Vernon et al., 2012) and in samples of patients with BD (Benedetti et al., 2015; Giakoumatos et al., 2015; McDonald, 2015). Meta-analyses of cross-sectional structural magnetic resonance imaging (sMRI) studies (Bora, Fornito, Yücel, & Pantelis, 2010; Selvaraj et al., 2012) indeed highlighted smaller local GM throughout the entire cortex of patients with BD compared to healthy controls (HC). Although longitudinal studies

CAMBRIDGE UNIVERSITY PRESS

of GM changes among patients with BD remain scarce and unequivocal (Abé et al., 2015; Kozicky et al., 2016), recent hypotheses suggest an accelerated age-related GM atrophy among patients with BD, referred to 'neuroprogression' in BD (Schneider, DelBello, McNamara, Strakowski, & Adler, 2012). Through neuroprotective properties on the cortical and subcortical structures, Li is highly suspected to limit this pathological process in the brain of patients with BD, as highlighted by two meta-analyses showing greater total GM volume among Li-treated patients with BD (Kempton, Geddes, Ettinger, Williams, & Grasby, 2008; Sun et al., 2018). The two largest studies to date based on the same ENIGMA BD Working Group sample studied subcortical volumes (Hibar et al., 2016) and cortical thickness and surface area (Hibar et al., 2018) among respectively 4304 and 6503 participants, revealing larger thalamic volumes, and greater cortical thickness and surface area in left paracentral and right superior parietal gyri among Li-treated patients compared to Li-free patients. However, these mega-analyses did not analyze cortical volumes. If cortical thickness and surface area seem to be more sensitive than GM volumes for gene identification and hence should be preferred for imaging genetic studies (Eyler et al., 2012; Winkler et al., 2010), their changes due to age-related GM atrophy have been rarely studied longitudinally (Storsve et al., 2014), while volumetric decreases in aging have been strongly established (Fjell & Walhovd, 2010; Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012; Pfefferbaum et al., 2013). In addition, although harmonized analysis and quality-control protocols were used, data processing and analyses at different sites limited these studies; moreover, alcohol misuse was not included in the analyses, although it may influence cortical structure (Jernigan et al., 1991). The largest monocentric study analyzing cortical and subcortical GM volumes of 266 patients with BD (including 175 treated with Li) highlighted smaller total GM, thalamus, putamen, pallidum, hippocampus, and accumbens volumes among Li-free patients compared to Li-treated patients (Abramovic et al., 2016). However, the results did not survive correction for total brain volume; moreover, the impact of alcohol misuse was not explored.

In this respect, we here conducted an international multicentric, cross-sectional, brain structural MRI analysis to investigate Li influence on cortical and local GM volumes among patients with BD, taking into account potential confounding factors such as a history of alcohol misuse. We expected a priori to find greater GM volumes in patients with BD treated with Li compared to patients not under Li therapy.

Material and methods

Participants

We obtained data on adult inpatients and outpatients with BD type I (BD-I) (by DSM-IV-R criteria) from six international participating university-affiliated psychiatry departments: Mondor University Hospitals (Creteil, France); University Hospital of Grenoble (Grenoble, France); the Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine (Pittsburgh, PA, USA); the Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University (Mannheim, Germany); the InterUniversity Center for Behavioral Neurosciences, University of Udine (Udine, Italy); and the Clinical Science Institute, National University of Ireland (Galway, Ireland) (Favre, Baciu, Pichat, Bougerol, & Polosan, 2014; Ferro et al., 2017; Sarrazin et al., 2015). Controls, recruited from media announcements and registry offices, had no personal or family history of Axis I mood disorder, schizophrenia or schizoaffective disorder and no personal history of alcohol misuse. Exclusion criteria for all participants comprised age <18, history of neurological disease or head trauma with loss of consciousness, and contraindications for MRI. Trained practitioners established the diagnosis using the Diagnosis Interview for Genetic Study (Creteil), the Structured Clinical Interview for DSM-IV (Grenoble, Galway, Mannheim and Pittsburgh), and the Schedules Clinical Assessment Neuropsychiatry (Udine). The local ethics committee of each center approved the study. All the subjects received a complete description of the study and gave their written informed consent.

Data acquisition

Each participant underwent high resolution 3-dimensional T1-weighted sMRI. All scanner and acquisition parameters are reported in online Supplementary Table S1. Raw images were assessed visually for movement, susceptibility, and noise artefacts by two operators (FH and SS); images with significant artefacts or movements were consensually dropped from the initial sample based on a blind polling procedure.

Data processing

Cortical grey matter volume

We estimated cortical GM volume, normalized for subject head size, with Structural Image Evaluation using Normalization of Atrophy for cross-sectional measurement (SIENAX), which is part of the FSL toolbox (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/SIENA) (Smith et al., 2004; 2002). Briefly, the SIENAX pipeline started by extracting brain and skull image from the single whole-head input data (Smith, 2002). The brain image was then affine-registered to MNI152 standard space (Jenkinson, Bannister, Brady, & Smith, 2002). We thus obtained a volumetric scaling factor, to be used later as normalization for head size. Then, tissue type segmentation with partial volume estimation was carried out (Zhang, Brady, & Smith, 2001) to calculate estimates of cortical GM volumes. These volumes were then scaled by the volumetric scaling factor, to obtain volumes, normalized for subject head size to limit head-size variability between subjects.

Local grey matter volumes

The same T1-weighted images were analyzed with the Voxel-based morphometry (VBM) using the FSL protocol (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM) (Douaud et al., 2007; Smith et al., 2004). After skull-stripping, the GM was segmented, followed by affine registration to the MNI152 standard space. The resulting images were averaged and flipped along the *x*-axis to create a left-right symmetric, study-specific GM template. Second, all native GM images were non-linearly registered to the study-specific template and were corrected for local expansion (or contraction) that could result from the non-linear component of the spatial transformation, using the Jacobian of the warp field. As the affine part was not included in the Jacobian, data remained thus normalized for subject brain size. The last pre-processing step was a smoothing with an isotropic Gaussian kernel with a sigma of 3 mm.

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

Statistical analyses

Demographic and clinical variables

Using Student's t tests and χ^2-tests as appropriate, we first compared patients taking and not taking Li at the time of scan on the following demographic and clinical variables: age, sex, euthymic mood state (defined as Hamilton Depression Rating Scale <14 or Montgomery-Asberg Depression Rating Scale <20 in one hand, and Young Mania Rating Scale or Bech-Rafaelsen Mania Scale <14 in the other hand), other current medication (i.e. antipsychotic, anticonvulsant, and antidepressant medication), illness duration (defined as duration since first mood episode), history of alcohol misuse, and lifetime duration of Li treatment; subjects were grouped according to the scanning site. We then compared patients with BD and HC on the same variables, if applicable.

Cortical grey matter volume

Above all, we harmonized our data using the ComBat algorithm scripted for R following the authors guidelines (Fortin et al., 2017), to control successfully for the site effect. Our first objective was to investigate Li influence on cortical GM volume. We used thus a multiple regression model to predict this volume (harmonized for site) among the subsample of patients with BD with the following independent variables: use of Li (i.e. patients taking or not taking Li at the time of scan), age, sex, history of alcohol misuse, and illness duration. Then, we used two successive multiple regression models predicting cortical GM volume (harmonized for site) among the whole sample. First, we used diagnosis (i.e. patients with BD or HC), age, sex, and history of alcohol misuse as independent variables, to quantify the possible GM volume changes in patients with BD in relation to controls; secondly, we used clinical status (i.e. patients with BD taking Li, not taking Li, and HC), age, sex, and history of alcohol misuse as independent variables to quantify the possible GM volume changes in the two subgroups of patients in relation to controls. To confirm objectively which were the best models to use, we used Akaike's information criterion (AIC) to retain models with the lowest AIC among possible models (online Supplementary Table S2). To test whether effects of Li use or BD diagnosis on GM volume were linked to age, sex, or illness duration, we introduced in *post-hoc* analyses 5 interaction terms in our models (i.e. Li use × age, Li use × sex, Li use × illness duration, diagnosis × age, and diagnosis × sex). Moreover, to test the influence of lifetime duration of Li treatment on the GM volume, we used this variable as a regressor in *post-hoc* analyses. We checked that the assumptions of these tests were valid: linearity, homoscedasticity, and normality (assessed by partial regression plots and a plot of studentized residuals against the predicted values, by visual inspection of a plot of studentized residuals *v.* unstandardized predicted values, and by the Q–Q plot, respectively), multicollinearity (assessed by tolerance values greater than 0.1), and high leverage and highly influential points (assessed by leverage values greater than 0.2 and values for Cook's distance above 1, respectively). All statistical tests were considered significant if p values adjusted for the false-discovery rate (FDR) were less than 0.05. All analyses were conducted using R statistics version 3.4.3 (https://www.r-project.org/).

Local GM volumes

We compared local GM volumes between patients taking and not taking Li including age, sex, history of alcohol misuse, illness duration, and scanning site as covariates. Further, we investigated local GM volume differences between BD patients and HC including age, sex, history of alcohol misuse and scanning site as covariates. Both analyses were conducted using randomize, FSL's tool for nonparametric permutation inference on neuroimaging data. We corrected for multiple comparisons across space (Winkler, Ridgway, Webster, Smith, & Nichols, 2014) with the threshold-free cluster enhancement method (10 000 permutations) (Smith & Nichols, 2009), applying a family-wise error corrected p value <0.05.

Results

Clinical sample

The initial sample comprised 606 subjects; 16 were excluded due to motion artefacts in their scans. Further, three controls were excluded because of reported past alcohol misuse. Our final sample included 271 patients and 316 controls. Among patients with BD, 120 were treated with Li (including 28 with Li monotherapy); information about the use of Li was missing for two patients (0.7%) who were consequently not included in the Li analysis. Among patients taking Li, average lifetime duration of Li treatment was 7.1 years. Patients taking and not taking Li did not differ in age, sex, history of alcohol misuse, illness duration, euthymic mood state, and antipsychotic medication (Table 1). The use of antidepressants and anticonvulsants was significantly lower among patients taking Li. Detailed demographic and clinical characteristics of the study participants can be found in Table 1. Detailed characteristics of treatments among patients with BD can be found in online Supplementary Table S3.

Lithium and brain volumes among patients

Cortical grey matter volume

The multiple regression models (including Li use, age, sex, history of alcohol misuse, and duration of illness) statistically significantly predicted cortical GM volume ($F_{(5, 260)} = 31.2$, $p < 0.0005$, adjusted $R^2 = 0.36$) (Table 2).

Li use (i.e. patients taking or not taking Li at the time of scan) was significantly associated with the cortical GM volume ($B = 10\,253.9$, $t = 2.51$, $p = 0.01$, FDR-corrected $p = 0.02$). This means that given all other variables equal, an average patient treated with Li would be expected to have a cortical GM volume of 10 254 mm^3 (i.e. 1.6%) greater than patients not taking Li. There was no interaction between Li use and age, Li use and sex, and Li use and illness duration in predicting cortical GM volume (online Supplementary Tables S4–S6). The lifetime duration of Li treatment was not associated with GM volume among patients currently treated with Li (online Supplementary Table S7) and among all patients with BD (online Supplementary Table S8).

Voxel-wise analysis of local grey matter volumes

Patients taking Li had greater GM volumes in three clusters compared to patients not taking Li. We identified one large cluster (1144 voxels) in the right middle frontal gyrus, and two smaller clusters in the right anterior cingulate and the left fusiform gyrus (411 and 11 voxels, respectively). There were no areas with significant smaller GM volumes in patients taking Li compared to patients not taking Li. These findings are shown in Fig. 1*a*, and the locations of the clusters are listed in Table 3.

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

Table 1. Demographic and clinical characteristics of patients with bipolar disorder and healthy controls

	Patients with bipolar disorder			p^*	
	Li+[a] ($n = 120$)	Li-[a] ($n = 149$)	Healthy controls ($n = 316$)	Li + *v.* Li-	BD *v.* HC
Categorical variables[b]					
Female sex	62 (51.7)	93 (62.4)	173 (54.7)	0.08	0.55
Euthymic mood state[c]	99 (85.3)	118 (78.8)	NA	0.17	NA
History of OH misuse[d]	16 (13.3)	19 (13.0)	NA	0.94	NA
Other current medication			NA		NA
Anticonvulsant[a]	38 (31.7)	88 (59.1)		<0.0005	
Antipsychotic[e]	60 (50.0)	68 (45.6)		0.51	
Antidepressant[a]	38 (31.7)	65 (43.6)		0.045	
Site				<0.0005	<0.0005
Creteil, France	18 (15.0)	16 (10.7)	54 (17.1)		
Galway, Ireland	44 (36.7)	14 (9.4)	59 (18.7)		
Grenoble 1, France	5 (4.2)	7 (4.7)	12 (3.8)		
Grenoble 2, France	10 (8.3)	6 (4.0)	11 (3.5)		
Mannheim, Germany	12 (10.0)	29 (19.5)	38 (12.0)		
Pittsburgh, USA	21 (17.5)	44 (29.5)	28 (8.9)		
Udine 1, Italy	5 (4.2)	14 (9.4)	83 (26.3)		
Udine 2, Italy	5 (4.2)	19 (12.8)	31 (9.8)		
Numerical variables[f]					
Age at MRI, y	39.2 (11.1)	40.8 (11.6)	36.9 (11.1)	0.26	0.001
Illness duration[a], y	13.9 (9.7)	15.4 (9.7)	NA	0.20	NA
Lifetime Li Treatment duration[g], y	7.1 (7.2)	1.4 (4.5)	NA	<0.0005	NA

BD, bipolar disorder; HC, healthy controls; Li, lithium; MRI, magnetic resonance imaging; NA, not applicable; OH, alcohol; USA, United States of America; y, years.
*Student's *t* test or χ^2 test.
[a]Information missing for 2 (0.7%).
[b]Calculated as number (percentage) of participants. Percentages have been rounded and may not total 100.
[c]9 (3.3%).
[d]5 (1.8%).
[e]3 (1.1%).
[f]Calculated as mean (S.D.).
[g]126 (46.8%) patients.

Table 2. Prediction of cortical grey matter volume among patients with bipolar disorder

	Cortical grey matter volume			
Variable	B[a]	S.E.[b]	t[c]	p
Use of Li (Y minus N)	10 253.9	4084.6	2.51	0.013
Sex (F minus M)	18 165.2	4132.5	4.40	<0.0005
History of OH misuse (Y minus N)	−14 042.5	6045.5	−2.32	0.021
Age	−2021.3	222.7	−9.08	<0.0005
Illness duration	12.9	261.5	0.05	0.961

F, female; Li, lithium; M, male; N, no; OH, alcohol; Y, yes.
[a]Unstandardized regression coefficient.
[b]Standard error of the coefficient.
[c]*t* value.

Bipolar disorder and brain volumes

Cortical grey matter volume

Analyzing the whole sample (patients and controls), the multiple regression model (including diagnosis, age, sex, and history of alcohol misuse) significantly predicted cortical GM volume ($F_{(4,\ 579)} = 106.9$, $p < 0.0005$, adjusted $R^2 = 0.42$) (Table 4).

Diagnosis (i.e. patients with BD or HC) was significantly associated with cortical GM volume ($B = -14\,288.8$, $t = -4.67$, $p < 0.0005$, FDR-corrected $p < 0.0005$). This means that given all other variables equal, an average patient with BD would be expected to have a cortical GM volume of 14 289 mm^3 (i.e. 2.2%) smaller than controls. There was no interaction between diagnosis and age, and diagnosis and sex in predicting cortical GM volume (online Supplementary Tables S9 and S10).

Voxel-wise analysis of local grey matter volumes

In the voxel-wise analysis, patients with BD had smaller GM volumes in multiple areas compared to controls. We identified

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

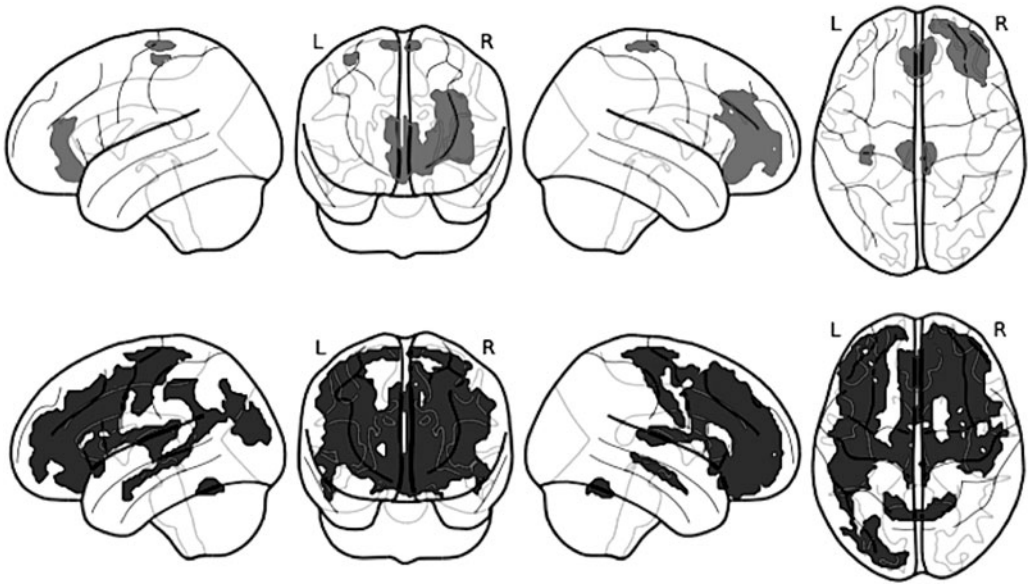

Fig. 1. (*a*) (Upper Panel): Areas of significantly greater GM in patients with BD taking Li compared to patients not taking Li; (*b*) (Lower Panel): Areas of significantly smaller GM in patients with BD compared to HC (1-*p* value map, threshold-free cluster enhancement method, 10 000 permutations, *p* value family-wise corrected <0.05).

Table 3. Local grey matter volume differences between patients taking and not taking Li, and patients and healthy controls

		Coordinates[b]					
Contrast	Cluster size[a]	*x*	*y*	*z*	Regions	*T*[c]	*p*
Patients taking Li > not taking Li	1144	26	88	39	Right middle frontal gyrus	3.47	0.003
	411	44	86	37	Right anterior cingulate	3.37	0.02
	11	67	38	29	Left fusiform gyrus	5.1	0.04
Patients taking Li < not taking Li	–	–	–	–	–	–	–
Patients with BD < HC	8387	27	89	37	Right middle frontal gyrus	6.68	<0.0005
	5346	59	74	31	Left inferior frontal gyrus	5.82	<0.0005
	1032	70	47	33	Left middle temporal gyrus	5.44	<0.0005
	665	59	19	44	Left middle occipital gyrus	4.77	<0.0005
	233	30	75	34	Right insula	4.68	0.002
	218	28	57	43	Right insula	4.09	0.01
	198	19	55	29	Right middle temporal gyrus	5.81	<0.0005
	18	20	48	43	Right superior temporal gyrus	3.72	0.04
	11	59	80	30	Left middle frontal gyrus	4.06	0.04
	4	55	79	28	Left inferior frontal gyrus	4.14	0.04
Patients with BD > HC	–	–	–	–	–	–	–

BD, bipolar disorder; HC, healthy controls; Li, lithium; MNI, Montreal-Neurological Institute.
[a]Number of voxels within each cluster.
[b]MNI coordinates of the voxel of maximal statistical significance within each cluster.
[c]*T* value for the voxel of maximal statistical significance within each cluster.

thus two widespread clusters (>5000 voxels) in right middle frontal gyrus and the left inferior frontal gyrus; five intermediate clusters (between 198 and 1032 voxels) in the left middle temporal gyrus, the left middle occipital gyrus, the right insula, and the right middle temporal gyrus; and three smaller clusters (<50 voxels) in the right superior temporal gyrus, the left middle frontal gyrus, and the left inferior frontal gyrus. There were no areas with significant greater GM volumes in patients compared to controls. These findings are shown in Fig. 1*b*, and the locations of the clusters are listed in Table 3.

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

Table 4. Prediction of cortical grey matter volume among the whole sample with diagnosis as a regressor

	Cortical grey matter volume			
Variable	B^a	S.E.[b]	t^c	p
Diagnosis (BD minus HC)	−14 288.8	3057.9	−4.67	<0.0005
Sex (F minus M)	17 541.7	2918.3	6.01	<0.0005
History of OH misuse (Y minus N)	−11 044.3	6357.2	−1.74	0.083
Age	−2323.9	129.9	−17.89	<0.0005

BD, bipolar disorder; F, female; HC, healthy controls; M, male; N, no; OH, alcohol; Y, yes.
[a]Unstandardized regression coefficient.
[b]Standard error of the coefficient.
[c]t value.

Table 5. Prediction of cortical grey matter volume among the whole sample with clinical status as a regressor

	Cortical grey matter volume			
Variable	B^a	S.E.[b]	t^c	p
Clinical status (minus HC)				
BD with Li	−6055.6	3819.7	−1.59	0.113
BD without Li	−20 715.4	3645.7	−5.68	<0.0005
Sex (F minus M)	17 899.4	2914.0	6.14	<0.0005
History of OH misuse (Y minus N)	−11 597.7	6294.3	−1.84	0.066
Age	−2310.7	129.3	−17.87	<0.0005

BD, bipolar disorder; F, female; HC, healthy controls; Li, lithium; M, male; N, no; OH, alcohol; Y, yes.
[a]Unstandardized regression coefficient.
[b]Standard error of the coefficient.
[c]t value.

Lithium and cortical grey matter volume among the whole sample

Analyzing the whole sample (patients and controls), the multiple regression models (including clinical status, age, sex, and history of alcohol misuse) significantly predicted cortical GM volume ($F_{(4,\ 572)} = 88.3$, $p < 0.0005$, adjusted $R^2 = 0.43$) (Table 5).

Clinical status (i.e. patients with BD taking Li and not taking Li minus HC, respectively) was significantly associated with cortical GM volume for patients without Li ($B = -\ 20\,715.4$, $t = -5.68$, $p < 0.0005$, FDR-corrected $p < 0.0005$) but not for patients with Li ($B = -6055.6$, $t = -1.59$, $p = 0.11$, FDR-corrected $p = 0.11$). This means that given all other variables equal, an average patient with BD not treated with Li would be expected to have a cortical GM volume of 20 715 mm^3 (i.e. 3.3%) smaller than controls, whereas cortical GM volume of an average patient with BD treated with Li would not significantly differ from cortical GM volume of HC.

Discussion

In one of the largest samples of patients with BD and controls, we confirmed the positive association between Li and cortical as well as regional GM volumes in patients with BD, potentially reflecting a beneficial effect of this compound on GM. More specifically, greater local GM volumes were found in the right middle frontal gyrus, the right anterior cingulate gyrus, and the left fusiform gyrus in patients with BD treated with Li. In contrast, we observed smaller cortical and regional GM volumes in patients with BD compared to HC, mainly in the middle frontal gyrus, inferior frontal gyrus, middle temporal gyrus, middle occipital gyrus, and insula. This reinforces the view of BD being associated with smaller frontal and cingulate GM volumes, with differences depending on Li prescription.

Positive effects of Li on cortical GM volumes in patients with BD are clearly parallel to results from two meta-analyses showing greater total GM volume (Kempton et al., 2008; Sun et al., 2018) in Li-treated patients with BD and three longitudinal studies relating Li to increased total GM volume after 4 and 16 weeks of treatment (Lyoo et al., 2010; Moore et al., 2000, 2009). Considering particular regional structures, we found only greater regional GM volumes associated with Li, in the right middle frontal gyrus, the right anterior cingulate gyrus, and the left fusiform gyrus. If positive effects of Li in the anterior cingulate cortex have been previously reported (Bora et al., 2010), effects of Li on frontal and fusiform gyrus have not been reported so far, whereas our local analyses of GM using VBM did not detect specific effects of Li in subcortical regions which have been studied extensively in the literature, such as hippocampus, amygdala (Hajek et al., 2014; Hallahan et al., 2011; López-Jaramillo et al., 2017) or thalamus (Hibar et al., 2016; López-Jaramillo et al., 2017). More generally, smaller GM volumes have been reported in middle frontal, anterior cingulate, and fusiform gyri among patients with BD compared to HC in previous meta- and mega-analyses (Bora et al., 2010; Hibar et al., 2018; Wise et al., 2017) that were not focused on medication. Furthermore, the largest cluster of greater GM volume among Li-treated patients we highlighted was located in the right middle frontal gyrus. Interestingly, the largest cluster of smaller GM volume among patients with BD in comparison with HC was also located in this gyrus. Finally, there was no statistically significant difference between cortical GM volume of Li-treated patients and controls. Overall, these results tend to support the hypothesis that Li could limit, perhaps normalize GM atrophy related to pathological processes in the brain of patients with BD.

It has been suggested that structural and functional abnormalities particularly in frontal, cingular, and fusiform gyri might be involved in mood dysregulation, suicide attempts, impulsivity as well as cognitive performance, rapid cycling or circadian abnormalities among patients with BD (Benedetti et al., 2015; Hozer & Houenou, 2016; Phillips & Swartz, 2014). Greater GM volumes in these regions among patients treated with Li could be correlates of mood stabilization, clinical or functional improvement related to Li. However, the mechanisms whereby this occurs remain unclear. One hypothesis is that Li could exert neurotrophic and/or neuroprotective effects. These mechanisms could be related to inhibition of pro-apoptotic pathways, such as glycogen synthase kinase-3β, increasing levels of the neuroprotective B-cell lymphoma protein-2 and thus regulating the neurotrophic intracellular signaling cascade involving the brain-derived neurotrophic factor (McDonald, 2015). The microstructural underpinning of Li-induced GM volume increases remains underexplored, but this is beyond the scope of the present study.

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

Aside from the effects of Li, we reported significantly lower cortical GM volumes among patients with BD compared to controls. So far, the literature has yielded inconsistent results with some studies showing more pronounced total GM atrophy among patients with BD (Brambilla et al., 2001; Gildengers et al., 2014; Lim, Rosenbloom, Faustman, Sullivan, & Pfefferbaum, 1999), which was also confirmed in a large meta-analysis (Arnone et al., 2009), whereas other studies (Beyer et al., 2009; Rej et al., 2014; Sarnicola et al., 2009; Wijeratne et al., 2013) and meta-analyses (Hallahan et al., 2011; Kempton et al., 2008; McDonald et al., 2004) failed to detect such differences. However, our finding of widespread bilateral patterns of reduced GM volume in patients with BD in frontal, temporal, and occipital gyri, and the insula fits well with previous reports of reduced local GM volume, thickness, and surface area in BD (Abramovic et al., 2016; Bora et al., 2010; Hibar et al., 2018; Selvaraj et al., 2012; Wise et al., 2017). Interestingly, most of these regions are preferentially affected by normal age-related GM atrophy (Hedman et al., 2012). One speculative hypothesis could be that Li might limit accelerated age-related GM atrophy in BD. However, this hypothesis is not supported by results of our *post-hoc* exploratory investigations, since we did not highlight interactions between BD diagnosis or Li use and age in predicting GM volumes. Of note, only 163 (28%) subjects were older than 45 years, probably leading to the lack of such significant interactions in our analyses. Future studies specifically designed to include elderly patients with or without Li are thus needed to elucidate this point.

Several strengths providing novelty to our study should be emphasized. To date, our study is to our knowledge the largest cross-sectional study specifically investigating brain tissue volume differences between patients taking and not taking Li. Moreover, conducting a multicenter investigation, we reduced biases related to recruitment from a single center and increased the external validity of our results. Using the ComBat algorithm to harmonize our data for site allowed to improve the control of the site effect. The processing and analyzing of our data in one site prevented variability related to multiple imaging methods, which represents a significant confound in previous meta- and mega-analyses of imaging data. Moreover, the use of SIENAX for our analyses is another strength. A majority of sMRI studies control brain tissue volumes for intra-cranial volume, to reduce head-size-related variability between subjects. This might be a problem in T1-weighted images, as it is hard to accurately separate skull and cerebrospinal fluid around brain. This is not required using SIENAX since brain volumes are scaled by a scaling factor to obtain volumes normalized for subject head size. Finally, we controlled for many variables potentially influencing brain tissue volumes such as age (Hedman et al., 2012), sex (Gur et al., 1999), history of alcohol misuse (Jernigan et al., 1991), and illness duration (Gildengers et al., 2014; Hallahan et al., 2011; Hibar et al., 2018).

However, there are some limitations that must be considered, when interpreting these results. Our analyses ignored compliance among Li-treated patients, as well as previous Li exposure among Li-free patients, as it is difficult to judge reliability of such data due to recall biases. Although previous studies suggested positive relationship between duration of Li treatment and GM volumes (Benedetti et al., 2015; Sani et al., 2018), we did not highlight such effects, probably because lifetime duration of Li treatment was available for only 143 patients with BD (53.2%), leading to a significant loss of statistical power when we used this variable as a regressor in our analyses. As serum Li levels were not available, we did not examine possible dose-effect relationship between Li and GM volumes. Furthermore, Li medication might be confounded with specific clinical phenotypes (such as predominantly manic episodes) that may have an influence on brain volumes; it could thus have been relevant to test for the influence of predominant mood polarity. However, more manic episodes are usually associated with smaller volumes (Abé et al., 2015). Patients on Li could otherwise have been preselected by being more responsive to the first-line treatment Li, or have greater cognitive reserve associated with being able to engage with a complex and demanding treatment plan; these clinical features may be associated with relatively greater GM volumes, without having to invoke the Li effect on GM. Only a longitudinal design could allow us to disentangle the different possibilities. Another source of bias is the impact of exposure to other medications, namely anticonvulsant, antipsychotic, and antidepressant drugs. The use of anticonvulsants and antidepressants was significantly higher among patients not taking than taking Li. It could be thus hypothesized that greater GM volumes among patients treated with Li might be actually due to deleterious effects of these drugs among patients not taking Li, rather than neuroprotective effects of Li. We did not consider the use of antidepressants as a covariate in our analyses, since there is little evidence for an effect of these drugs on GM volumes (Hafeman, Chang, Garrett, Sanders, & Phillips, 2012; McDonald, 2015). Concerning the use of anticonvulsants, we did not use it as a covariate to avoid multicollinearity biases, as patients taking Li were also those who were not taking anticonvulsants, and vice versa. Moreover, if some analyses highlighted associations between anticonvulsants use and smaller GM volumes in patients with BD (Hibar et al., 2018; 2016), most studies failed to highlight such a negative effect of anticonvulsants on GM volumes in patients with BD (Hafeman et al., 2012), whereas preclinical literature supports evidence of a tangible change in GM volume related to Li (Vernon et al., 2012). Finally, as most (76.7%) Li-treated patients were taking concomitant medication, it is not possible to rule out the effect of these drugs on Li-related greater GM volumes, although this association seems to occur regardless of associated medications (Hajek & Weiner, 2016; Sun et al., 2018). To control for impact of illness severity, we chose to use illness duration as a covariate in our models, since it seemed to be least likely affected by recall biases. Other clinical variables could have been however more relevant to highlight in particular differences between patients taking and not taking Li, such as a number or duration of episodes, cumulative time spent ill, or score at specific scales (Global Assessment of Functioning, or the Clinical Global Impression scales, for example). We did not take into account effects of the current mood state in our analyses. The rationale behind this decision was that 83.5% of patients in our sample were euthymic, without any significant difference of the mood state between patients taking and not taking Li; in addition, association between Li treatment and GM volume as well as association between BD diagnosis and brain structure do not seem to be affected by the mood state (Hajek & Weiner, 2016; Hibar et al., 2018; Sun et al., 2018). We did not investigate overall severity of illness (with Global Assessment of Functioning, or the Clinical Global Impression scales, for example). Such data could have added interesting information about the characteristics of possible differences between both bipolar patient groups. Due to missing data, we did not include potential relevant variables in our analyses, in particular history of psychosis, or other drug misuse history,

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

such as cannabis misuse. If some data support an association between a history of psychosis and GM atrophy in patients with BD (Hibar et al., 2018), cannabis misuse seems however to have limited brain effects in patients with BD (Hartberg et al., 2018). Finally, it has been suggested that Li could influence the intensity of the T1 magnetic resonance signal, leading to altered image contrast (Cousins, Aribisala, Nicol Ferrier, & Blamire, 2013). Differences between GM volumes of patients with and without Li we highlighted might thus derive from a change in the characteristics of the signal rather than a physical increase in volume, as the two methods we used (VBM and SIENAX using FSL) fully depend on grey and white matter border which could be confounded by Li use. However, effects of Li on GM volume are supported by preclinical literature highlighting strong evidence of a physical change in GM volume related to Li (Vernon et al., 2012).

In conclusion, we confirmed that Li is associated with a positive effect on cortical and local GM volumes in patients with BD. These effects were mainly localized in the right middle frontal gyrus and the right anterior cingulate. These results provide further clear evidence that Li could partly attenuate the more pronounced age-related GM atrophy in patients with BD. Longitudinal studies are now warranted to investigate the temporal dynamics of the neuroprotective and neurotrophic effects of Li among patients with BD.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291719004112

Acknowledgements. We are grateful to the participating subjects.

Financial support. The authors declare no competing interests. This work was supported by public funding from the Agence Nationale pour la Recherche (ANR MNP VIP 2008, ANR-11-IDEX-0004 Labex BioPsy, and ANR-DFG ANR-14-CE35-0035 FUNDO), the Fondation de l'Avenir (Recherche Médicale Appliquée 2014), the Fondation pour la Recherche Médicale (Appel d'offres analyse bioinformatique pour la recherche en biologie 2014), the Deutsche Forschungsgemeinschaft (SFB636/C6 and We3638/3-1), the NIMH R01 MH076971, the American Psychiatric Institute for Research and Education (APIRE Young Minds in Psychiatry Award), from the Italian Ministry for Education, University and Research (PRIN n. 2005068874), from Veneto StartCup 2007 to Dr Brambilla, and from the Regione Veneto, Italy (159/03, DGRV n. 4087), the Grenoble University Hospital, the French University Institute, the Grenoble Cognition Center, and the Health and Society Research Network of the Pierre Mendes-France University (Grenoble), the Grenoble MRI facility IRMaGE was partly funded by the French program Investissements d'avenir run by the Agence Nationale pour la Recherche; grant Infrastructure d'avenir en Biologie Sante–ANR-11-INBS-0006. S. Sarrazin has been supported by grants from the Labex Bio-Psy & APHP and Oeuvre Falret.

References

Abé, C., Ekman, C.-J., Sellgren, C., Petrovic, P., Ingvar, M., & Landén, M. (2015). Manic episodes are related to changes in frontal cortex: A longitudinal neuroimaging study of bipolar disorder 1. *Brain: A Journal of Neurology*, *138*(Pt 11), 3440–3448. doi: 10.1093/brain/awv266

Abramovic, L., Boks, M. P. M., Vreeker, A., Bouter, D. C., Kruiper, C., Verkooijen, S., … van Haren, N. E. M. (2016). The association of antipsychotic medication and lithium with brain measures in patients with bipolar disorder. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *26*(11), 1741–1751. doi: 10.1016/j.euroneuro.2016.09.371

Arnone, D., Cavanagh, J., Gerber, D., Lawrie, S. M., Ebmeier, K. P., & McIntosh, A. M. (2009). Magnetic resonance imaging studies in bipolar disorder and schizophrenia: Meta-analysis. *The British Journal of Psychiatry: The Journal of Mental Science*, *195*(3), 194–201. doi: 10.1192/bjp.bp.108.059717

Benedetti, F., Poletti, S., Radaelli, D., Locatelli, C., Pirovano, A., Lorenzi, C., … Colombo, C. (2015). Lithium and GSK-3β promoter gene variants influence cortical gray matter volumes in bipolar disorder. *Psychopharmacology*, *232*(7), 1325–1336. doi: 10.1007/s00213-014-3770-4

Beyer, J. L., Kuchibhatla, M., Payne, M. E., Macfall, J., Cassidy, F., & Krishnan, K. R. R. (2009). Gray and white matter brain volumes in older adults with bipolar disorder. *International Journal of Geriatric Psychiatry*, *24*(12), 1445–1452. doi: 10.1002/gps.2285

Bora, E., Fornito, A., Yücel, M., & Pantelis, C. (2010). Voxelwise meta-analysis of gray matter abnormalities in bipolar disorder. *Biological Psychiatry*, *67*(11), 1097–1105. doi: 10.1016/j.biopsych.2010.01.020

Brambilla, P., Harenski, K., Nicoletti, M., Mallinger, A. G., Frank, E., Kupfer, D. J., … Soares, J. C. (2001). Differential effects of age on brain gray matter in bipolar patients and healthy individuals. *Neuropsychobiology*, *43*(4), 242–247. doi: 54897.

Cousins, D. A., Aribisala, B., Nicol Ferrier, I., & Blamire, A. M. (2013). Lithium, gray matter, and magnetic resonance imaging signal. *Biological Psychiatry*, *73*(7), 652–657. doi: 10.1016/j.biopsych.2012.09.029

Douaud, G., Smith, S., Jenkinson, M., Behrens, T., Johansen-Berg, H., Vickers, J., … James, A. (2007). Anatomically related grey and white matter abnormalities in adolescent-onset schizophrenia. *Brain: A Journal of Neurology*, *130*(Pt 9), 2375–2386. doi: 10.1093/brain/awm184

Eyler, L. T., Chen, C.-H., Panizzon, M. S., Fennema-Notestine, C., Neale, M. C., Jak, A., … Kremen, W. S. (2012). A comparison of heritability maps of cortical surface area and thickness and the influence of adjustment for whole brain measures: A magnetic resonance imaging twin study. *Twin Research and Human Genetics: The Official Journal of the International Society for Twin Studies*, *15*(3), 304–314. doi: 10.1017/thg.2012.3

Favre, P., Baciu, M., Pichat, C., Bougerol, T., & Polosan, M. (2014). FMRI evidence for abnormal resting-state functional connectivity in euthymic bipolar patients. *Journal of Affective Disorders*, *165*, 182–189. doi: 10.1016/j.jad.2014.04.054

Ferro, A., Bonivento, C., Delvecchio, G., Bellani, M., Perlini, C., Dusi, N., … Brambilla, P. (2017). Longitudinal investigation of the parietal lobe anatomy in bipolar disorder and its association with general functioning. *Psychiatry Research*, *267*, 22–31. doi: 10.1016/j.pscychresns.2017.06.010

Fjell, A. M., & Walhovd, K. B. (2010). Structural brain changes in aging: Courses, causes and cognitive consequences. *Reviews in the Neurosciences*, *21*(3), 187–221.

Fortin, J.-P., Parker, D., Tunç, B., Watanabe, T., Elliott, M. A., Ruparel, K., … Shinohara, R. T. (2017). Harmonization of multi-site diffusion tensor imaging data. *NeuroImage*, *161*, 149–170. doi: 10.1016/j.neuroimage.2017.08.047

Giakoumatos, C. I., Nanda, P., Mathew, I. T., Tandon, N., Shah, J., Bishop, J. R., … Keshavan, M. S. (2015). Effects of lithium on cortical thickness and hippocampal subfield volumes in psychotic bipolar disorder. *Journal of Psychiatric Research*, *61*, 180–187. doi: 10.1016/j.jpsychires.2014.12.008

Gildengers, A. G., Chung, K.-H., Huang, S.-H., Begley, A., Aizenstein, H. J., & Tsai, S.-Y. (2014). Neuroprogressive effects of lifetime illness duration in older adults with bipolar disorder. *Bipolar Disorders*, *16*(6), 617–623. doi: 10.1111/bdi.12204

Gur, R. C., Turetsky, B. I., Matsui, M., Yan, M., Bilker, W., Hughett, P., & Gur, R. E. (1999). Sex differences in brain gray and white matter in healthy young adults: Correlations with cognitive performance. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *19*(10), 4065–4072.

Hafeman, D. M., Chang, K. D., Garrett, A. S., Sanders, E. M., & Phillips, M. L. (2012). Effects of medication on neuroimaging findings in bipolar disorder: An updated review. *Bipolar Disorders*, *14*(4), 375–410. doi: 10.1111/j.1399-5618.2012.01023.x

Hajek, T., Bauer, M., Simhandl, C., Rybakowski, J., O'Donovan, C., Pfennig, A., … Alda, M. (2014). Neuroprotective effect of lithium on hippocampal volumes in bipolar disorder independent of long-term treatment response. *Psychological Medicine*, *44*(3), 507–517. doi: 10.1017/S0033291713001165

Hajek, T., & Weiner, M. W. (2016). Neuroprotective effects of lithium in human brain? Food for thought. *Current Alzheimer Research*, *13*(8), 862–872.

Hallahan, B., Newell, J., Soares, J. C., Brambilla, P., Strakowski, S. M., Fleck, D. E., … McDonald, C. (2011). Structural magnetic resonance imaging in bipolar disorder: An international collaborative mega-analysis of individual adult patient data. *Biological Psychiatry*, *69*(4), 326–335. doi: 10.1016/j.biopsych.2010.08.029

Hartberg, C. B., Lange, E. H., Lagerberg, T. V., Haukvik, U. K., Andreassen, O. A., Melle, I., & Agartz, I. (2018). Cortical thickness, cortical surface area and subcortical volumes in schizophrenia and bipolar disorder patients with cannabis use. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *28*(1), 37–47. doi: 10.1016/j.euroneuro.2017.11.019

Hedman, A. M., van Haren, N. E. M., Schnack, H. G., Kahn, R. S., & Hulshoff Pol, H. E. (2012). Human brain changes across the life span: A review of 56 longitudinal magnetic resonance imaging studies. *Human Brain Mapping*, *33*(8), 1987–2002. doi: 10.1002/hbm.21334

Hibar, D. P., Westlye, L. T., Doan, N. T., Jahanshad, N., Cheung, J. W., Ching, C. R. K., … Andreassen, O. A. (2018). Cortical abnormalities in bipolar disorder: An MRI analysis of 6503 individuals from the ENIGMA Bipolar Disorder Working Group. *Molecular Psychiatry*, *23*(4), 932–942. doi: 10.1038/mp.2017.73

Hibar, D. P., Westlye, L. T., van Erp, T. G. M., Rasmussen, J., Leonardo, C. D., Faskowitz, J., … Andreassen, O. A. (2016). Subcortical volumetric abnormalities in bipolar disorder. *Molecular Psychiatry*, *21*(12), 1710–1716. doi: 10.1038/mp.2015.227

Hozer, F., & Houenou, J. (2016). Can neuroimaging disentangle bipolar disorder? *Journal of Affective Disorders*, *195*, 199–214. doi: 10.1016/j.jad.2016.01.039

Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *NeuroImage*, *17*(2), 825–841.

Jernigan, T. L., Butters, N., DiTraglia, G., Schafer, K., Smith, T., Irwin, M., … Cermak, L. S. (1991). Reduced cerebral grey matter observed in alcoholics using magnetic resonance imaging. *Alcoholism, Clinical and Experimental Research*, *15*(3), 418–427.

Kempton, M. J., Geddes, J. R., Ettinger, U., Williams, S. C. R., & Grasby, P. M. (2008). Meta-analysis, database, and meta-regression of 98 structural imaging studies in bipolar disorder. *Archives of General Psychiatry*, *65*(9), 1017–1032. doi: 10.1001/archpsyc.65.9.1017

Kozicky, J.-M., McGirr, A., Bond, D. J., Gonzalez, M., Silveira, L. E., Keramatian, K., … Yatham, L. N. (2016). Neuroprogression and episode recurrence in bipolar I disorder: A study of gray matter volume changes in first-episode mania and association with clinical outcome. *Bipolar Disorders*, *18*(6), 511–519. doi: 10.1111/bdi.12437

Lim, K. O., Rosenbloom, M. J., Faustman, W. O., Sullivan, E. V., & Pfefferbaum, A. (1999). Cortical gray matter deficit in patients with bipolar disorder. *Schizophrenia Research*, *40*(3), 219–227.

López-Jaramillo, C., Vargas, C., Díaz-Zuluaga, A. M., Palacio, J. D., Castrillón, G., Bearden, C., & Vieta, E. (2017). Increased hippocampal, thalamus and amygdala volume in long-term lithium-treated bipolar I disorder patients compared with unmedicated patients and healthy subjects. *Bipolar Disorders*, *19*(1), 41–49. doi: 10.1111/bdi.12467

Lyoo, I. K., Dager, S. R., Kim, J. E., Yoon, S. J., Friedman, S. D., Dunner, D. L., & Renshaw, P. F. (2010). Lithium-induced gray matter volume increase as a neural correlate of treatment response in bipolar disorder: A longitudinal brain imaging study. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *35*(8), 1743–1750. doi: 10.1038/npp.2010.41

McDonald, C. (2015). Brain structural effects of psychopharmacological treatment in bipolar disorder. *Current Neuropharmacology*, *13*(4), 445–457.

McDonald, C., Zanelli, J., Rabe-Hesketh, S., Ellison-Wright, I., Sham, P., Kalidindi, S., … Kennedy, N. (2004). Meta-analysis of magnetic resonance imaging brain morphometry studies in bipolar disorder. *Biological Psychiatry*, *56*(6), 411–417. doi: 10.1016/j.biopsych.2004.06.021

Moore, G. J., Bebchuk, J. M., Wilds, I. B., Chen, G., Manji, H. K., & Menji, H. K. (2000). Lithium-induced increase in human brain grey matter. *Lancet*, *356*(9237), 1241–1242.

Moore, G. J., Cortese, B. M., Glitz, D. A., Zajac-Benitez, C., Quiroz, J. A., Uhde, T. W., … Manji, H. K. (2009). A longitudinal study of the effects of lithium treatment on prefrontal and subgenual prefrontal gray matter volume in treatment-responsive bipolar disorder patients. *The Journal of Clinical Psychiatry*, *70*(5), 699–705. doi: 10.4088/JCP.07m03745

Pfefferbaum, A., Rohlfing, T., Rosenbloom, M. J., Chu, W., Colrain, I. M., & Sullivan, E. V. (2013). Variation in longitudinal trajectories of regional brain volumes of healthy men and women (ages 10 to 85 years) measured with atlas-based parcellation of MRI. *NeuroImage*, *65*, 176–193. doi: 10.1016/j.neuroimage.2012.10.008

Phillips, M. L., & Swartz, H. A. (2014). A critical appraisal of neuroimaging studies of bipolar disorder: Toward a new conceptualization of underlying neural circuitry and roadmap for future research. *The American journal of psychiatry*, *171*(8), 829–843. doi: 10.1176/appi.ajp.2014.13081008

Rej, S., Butters, M. A., Aizenstein, H. J., Begley, A., Tsay, J., Reynolds, C. F., … Gildengers, A. (2014). Neuroimaging and neurocognitive abnormalities associated with bipolar disorder in old age. *International Journal of Geriatric Psychiatry*, *29*(4), 421–427. doi: 10.1002/gps.4021

Sani, G., Simonetti, A., Janiri, D., Banaj, N., Ambrosi, E., De Rossi, P., … Spalletta, G. (2018). Association between duration of lithium exposure and hippocampus/amygdala volumes in type I bipolar disorder. *Journal of Affective Disorders*, *232*, 341–348. doi: 10.1016/j.jad.2018.02.042

Sarnicola, A., Kempton, M., Germanà, C., Haldane, M., Hadjulis, M., Christodoulou, T., … Frangou, S. (2009). No differential effect of age on brain matter volume and cognition in bipolar patients and healthy individuals. *Bipolar Disorders*, *11*(3), 316–322. doi: 10.1111/j.1399-5618.2009.00670.x

Sarrazin, S., d'Albis, M.-A., McDonald, C., Linke, J., Wessa, M., Phillips, M., … Houenou, J. (2015). Corpus callosum area in patients with bipolar disorder with and without psychotic features: An international multicentre study. *Journal of Psychiatry & Neuroscience : JPN*, *40*(5), 352–359. doi: 10.1503/jpn.140262

Schneider, M. R., DelBello, M. P., McNamara, R. K., Strakowski, S. M., & Adler, C. M. (2012). Neuroprogression in bipolar disorder. *Bipolar Disorders*, *14*(4), 356–374. doi: 10.1111/j.1399-5618.2012.01024.x

Selvaraj, S., Arnone, D., Job, D., Stanfield, A., Farrow, T. F., Nugent, A. C., … McIntosh, A. M. (2012). Grey matter differences in bipolar disorder: A meta-analysis of voxel-based morphometry studies. *Bipolar Disorders*, *14*(2), 135–145. doi: 10.1111/j.1399-5618.2012.01000.x

Shorter, E. (2009). The history of lithium therapy. *Bipolar Disorders*, *11*(02), 4–9. doi: 10.1111/j.1399-5618.2009.00706.x

Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, *17*(3), 143–155. doi: 10.1002/hbm.10062

Smith, S. M., Jenkinson, M., Woolrich, M. W., Beckmann, C. F., Behrens, T. E. J., Johansen-Berg, H., … Matthews, P. M. (2004). Advances in functional and structural MR image analysis and implementation as FSL. *NeuroImage*, *23* (Suppl 1), S208–S219. doi:10.1016/j.neuroimage.2004.07.051

Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *NeuroImage*, *44*(1), 83–98. doi: 10.1016/j.neuroimage.2008.03.061

Smith, S. M., Zhang, Y., Jenkinson, M., Chen, J., Matthews, P. M., Federico, A., & De Stefano, N. (2002). Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *NeuroImage*, *17*(1), 479–489.

Storsve, A. B., Fjell, A. M., Tamnes, C. K., Westlye, L. T., Overbye, K., Aasland, H. W., & Walhovd, K. B. (2014). Differential longitudinal changes in cortical thickness, surface area and volume across the adult life span: Regions of accelerating and decelerating change. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *34*(25), 8488–8498. doi: 10.1523/JNEUROSCI.0391-14.2014

Sun, Y. R., Herrmann, N., Scott, C. J. M., Black, S. E., Khan, M. M., & Lanctôt, K. L. (2018). Global grey matter volume in adult bipolar patients with and without lithium treatment : A meta-analysis. *Journal of Affective Disorders*, *225*, 599–606. doi: 10.1016/j.jad.2017.08.078

Vernon, A. C., Natesan, S., Crum, W. R., Cooper, J. D., Modo, M., Williams, S. C. R., & Kapur, S. (2012). Contrasting effects of haloperidol and lithium on rodent brain structure : A magnetic resonance imaging study with postmortem confirmation. *Biological Psychiatry*, *71*(10), 855–863. doi: 10.1016/j.biopsych.2011.12.004

https://doi.org/10.1017/S0033291719004112 Published online by Cambridge University Press

Wijeratne, C., Sachdev, S., Wen, W., Piguet, O., Lipnicki, D. M., Malhi, G. S., … Sachdev, P. S. (2013). Hippocampal and amygdala volumes in an older bipolar disorder sample. *International Psychogeriatrics*, *25*(1), 54–60. doi: 10.1017/S1041610212001469

Winkler, A. M., Kochunov, P., Blangero, J., Almasy, L., Zilles, K., Fox, P. T., & … Glahn, D. C. (2010). Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. *NeuroImage*, *53*(3), 1135–1146. doi: 10.1016/j.neuroimage.2009.12.028

Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *NeuroImage*, *92*, 381–397. doi: 10.1016/j.neuroimage.2014.01.060

Wise, T., Radua, J., Via, E., Cardoner, N., Abe, O., Adams, T. M., … Arnone, D. (2017). Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder : Evidence from voxel-based meta-analysis. *Molecular Psychiatry*, *22*(10), 1455–1463. doi: 10.1038/mp.2016.72

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Beaulieu, S., Alda, M., … Berk, M. (2013). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder : Update 2013. *Bipolar Disorders*, *15*(1), 1–44. doi: 10.1111/bdi.12025

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 Transactions on Medical Imaging*, *20*(1), 45–57. doi: 10.1109/42.906424