Journal of Affective Disorders 225 (2018) 599–606

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Review article

Global grey matter volume in adult bipolar patients with and without lithium treatment: A meta-analysis

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ARTICLE INFO

Keywords:
Lithium
Neuroimaging
Bipolar disorder
Meta-analysis

ABSTRACT

Objective: The goal of this meta-analysis was to quantitatively summarize the evidence available on the differences in grey matter volume between lithium-treated and lithium-free bipolar patients.
Methods: A systematic search was conducted in Cochrane Central, Embase, MEDLINE, and PsycINFO databases for original peer-reviewed journal articles that reported on global grey matter volume in lithium-medicated and lithium-free bipolar patients. Standard mean difference and Hedges' g were used to calculate effect size in a random-effects model. Risk of publication bias was assessed using Egger's test and quality of evidence was assessed using standard criteria.
Results: There were 15 studies with a total of 854 patients (368 lithium-medicated, 486 lithium-free) included in the meta-analysis. Global grey matter volume was significantly larger in lithium-treated bipolar patients compared to lithium-free patients (SMD: 0.17, 95% CI: 0.01–0.33; $z = 2.11$, $p = 0.035$). Additionally, there was a difference in global grey matter volume between groups in studies that employed semi-automated segmentation methods (SMD: 0.66, 95% CI: 0.01–1.31; $z = 1.99$, $p = 0.047$), but no significant difference in studies that used fully-automated segmentation. No publication bias was detected (bias coefficient $= -0.65$, $p = 0.46$).
Limitations: Variability in imaging methods and lack of high-quality evidence limits the interpretation of the findings.
Conclusions: Results suggest that lithium-treated patients have a greater global grey matter volume than those who were lithium-free. Further study of the relationship between lithium and grey matter volume may elucidate the therapeutic potential of lithium in conditions characterized by abnormal changes in brain structure.

1. Introduction

Lithium has long been used as a mood stabilizer (Oruch et al., 2014) and remains a first-line drug for management of bipolar disorder (Yatham et al., 2013). Despite its widespread use, its mechanisms of action have yet to be fully elucidated. In the last twenty years, numerous studies have examined the putative neurotrophic and neuroprotective effects of lithium (Machado-Vieira et al., 2009). To see if these effects are present clinically, grey matter volume may be used as a proxy measure of neurotrophic activity. Indeed, emerging evidence suggests an increase in grey matter volume in bipolar patients following lithium therapy globally (Lyoo et al., 2010; Moore et al., 2009), and in specific regions of the brain (Selek et al., 2013; Yucel et al., 2008). However, other studies have shown no effect of lithium treatment on grey matter volume (Chen et al., 2007; Eker et al., 2014; Wijeratne et al., 2013). As a further complication, bipolar disorder itself is associated with structural brain changes (Arnone et al., 2009; Bora et al., 2010; Kempton et al., 2008; McDonald et al., 2004). While previous literature (Hajek et al., 2012b; Hallahan et al., 2011; Hibar et al., 2016) examined subcortical grey matter volumes in lithium-treated and lithium-free bipolar patients, global grey matter volume data have been studied (Germana et al., 2010; Lyoo et al., 2010; Sassi et al., 2002; Wijeratne et al., 2013) but not reviewed. Bipolar disorder has been associated with decreased global grey matter volumes (Arnone et al.,

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http://dx.doi.org/10.1016/j.jad.2017.08.078
Received 12 May 2017; Received in revised form 20 July 2017; Accepted 27 August 2017
Available online 30 August 2017

2009; Lim et al., 1999). Global grey matter volume is important as it has been shown to predict cognitive decline (Hensel et al., 2005; Risacher et al., 2009), which may be important for a bipolar population as this disorder is associated with cognitive dysfunction (Sole et al., 2017). The goal of this study was to provide a quantitative synthesis of available data on global grey matter volumes in those treated with lithium treatment compared with controls.

2. Methods

This meta-analysis followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A systematic search was conducted in Cochrane Central, Embase, MEDLINE, and PsycINFO databases for English-language literature published prior to June 3, 2016. We used search terms for "lithium," "bipolar disorder," and "grey matter volume." The search was limited to human studies where robust database limiters were available. Detailed search terms and sample search strategy can be found in Supplementary eFig. 1.

We excluded publications without authors, conference abstracts and review articles. Our inclusion criteria for original journal articles were: 1) measured global grey matter volume in adult bipolar patients and 2) distinguished between lithium-medicated and lithium-free (i.e. not taking lithium at time of scan) patients. Studies were not required to have a healthy control group. In cases where multiple studies examined the same population, the study with the larger sample size was included. Due to the limited number of longitudinal studies, we limited our analysis to cross-sectional studies.

Two independent raters assessed each article for eligibility; consensus was reached on all included studies. Global grey matter volumes (with standard deviation), demographic data and imaging parameters were extracted by two raters. Some studies that otherwise met inclusion criteria did not provide volumetric data, in which case missing data were requested from corresponding authors. Where volumetric data were reported by subgroup within lithium-treated and lithium-free cohorts, volumes were arithmetically aggregated.

Analyses were conducted in Stata 14 (StataCorp, College Station, TX) using the meta-analysis suite. Standard mean difference and Hedges' g were used to calculate effect size between lithium-medicated and lithium-free groups; Hedges' g was chosen for its consideration of small study bias. We evaluated between-study heterogeneity using Cochran's Q and I-squared indices, and used a random-effects model. We assessed publication bias visually using a funnel plot, as well as statistically using Egger's test. Comparisons using these methods were also made between healthy control groups and both lithium-medicated and lithium-free groups where data were available.

We conducted subgroup analyses by dichotomous characteristics (mood state, imaging methods) and meta-regressions with continuous variables (e.g. age, sex, age of onset of disease, duration of illness, length of lithium treatment, dose of lithium treatment, date of publication). As mood state may be associated with changes in grey matter volume (Brooks et al., 2009), we divided the studies based on mood state (e.g. euthymic, depressed, hypomanic) of the study population. Studies with patients in various mood states were classified as "mixed;" studies that did not report mood state of patients were classified as "unspecified." It has been postulated that the presence of lithium can alter the signal intensities of different tissue types in MRI images, leading to misclassification during automated segmentation processes and artificially generating a change in grey matter volume measures (Cousins et al., 2013). Given this, studies were grouped based on the type of image-processing technique used. Specifically, we conducted a sub-analysis dividing studies based on whether they employed semi-automated or fully-automated processes. In addition, since there were multiple studies using some iteration of statistical parametric mapping, we further sub-divided studies that used fully-automated processing into "SPM2," "SPM5," "SPM8" and "automated (other)."

Post-hoc analyses were conducted where potential confounds were thought to be present. Quality of evidence was evaluated using criteria adapted from the Newcastle Ottawa Scale and the Cochrane Collaboration's risk of bias assessment tool. Sensitivity analyses were conducted to elucidate the impact of potential outliers and data sets that were suspected to overlap with one another.

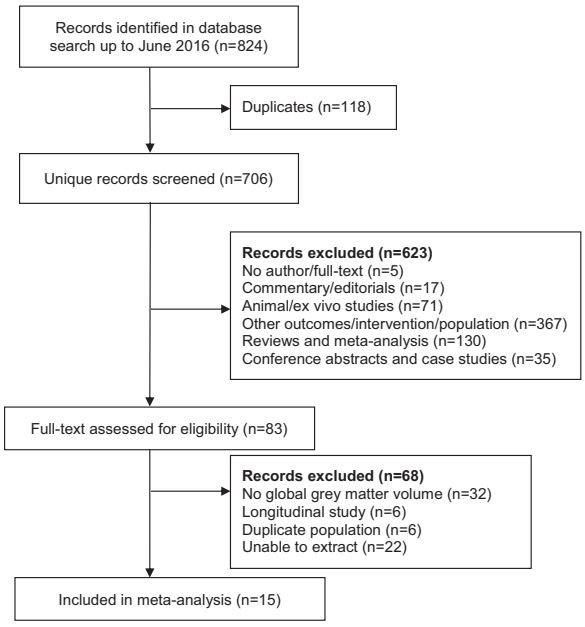

Fig. 1. PRISMA flow diagram for search strategy.

3. Results

3.1. Literature search

Our literature search identified 706 unique records, of which 83 full-text articles were reviewed for inclusion. Two independent raters identified 38 studies for inclusion, of which 15 studies reported data on grey matter volumes in lithium treated versus controls. Of those 15 studies, volumetric data were extracted directly from the publication for nine studies (Bearden et al., 2007; Benedetti et al., 2015; Benedetti et al., 2011; Chen et al., 2007; Germana et al., 2010; Hajek et al., 2014, 2012a; Radenbach et al., 2010; Sassi et al., 2002), and received from corresponding authors for 6 studies (Eker et al., 2014; Ha et al., 2009; Ivleva et al., 2013; Takahashi et al., 2010; van der Schot et al., 2009; Wijeratne et al., 2013). Our review process is illustrated in Fig. 1.

3.2. Patient characteristics

From the 15 included studies, a total of 854 patients (368 lithium-medicated, 486 lithium-free) were included in our meta-analysis. Basic patient demographic data were available for all but two studies (Ivleva et al., 2013; van der Schot et al., 2009). From the remaining studies, 40.4% (249/617) of patients were male and the average (SD) age of patients was 41.2 ± 12.4. Type of bipolar disorder was specified in 14 out of 15 studies, and mood state was reported in 11 out of 15 studies. Of the studies that reported type of bipolar disorder, 705 patients were diagnosed as Bipolar I (82.6%). Of the studies that reported mood state, 231 patients (39.6%) were depressed and 351 patients (60.1%) were euthymic; two patients (0.3%) were noted as hypomanic at the time of scan. Age of onset was reported in nine studies, and duration of illness was reported in 12 studies. Of those studies, the average age of onset was 27.2 ± 9.6 and duration of illness is 16.9 ± 10.9 years. Length of lithium treatment was reported in six studies, and average dose of lithium reported in 5 studies. Of those, average length of lithium treatment was 289.5 ± 297.1 weeks and average dose of lithium was