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Review article

Meta-analysis of regional white matter volume in bipolar disorder with replication in an independent sample using coordinates, T-maps, and individual MRI data

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ABSTRACT

Converging evidence suggests that bipolar disorder (BD) is associated with white matter (WM) abnormalities. Meta-analyses of voxel based morphometry (VBM) data is commonly performed using published coordinates, however this method is limited since it ignores non-significant data. Obtaining statistical maps from studies (T-maps) as well as raw MRI datasets increases accuracy and allows for a comprehensive analysis of clinical variables. We obtained coordinate data (7-studies), T-Maps (12-studies, including unpublished data) and raw MRI datasets (5-studies) and analysed the 24 studies using Seed-based d Mapping (SDM). A VBM analysis was conducted to verify the results in an independent sample. The meta-analysis revealed decreased WM volume in the posterior corpus callosum extending to WM in the posterior cingulate cortex. This region was significantly reduced in volume in BD patients in the independent dataset ($p = 0.003$) but there was no association with clinical variables. We identified a robust WM volume abnormality in BD patients that may represent a trait marker of the disease and used a novel methodology to validate the findings.

1. Introduction

Converging evidence from different MRI modalities suggests that bipolar disorder (BD) is associated with white matter abnormalities. Diffusion tensor imaging meta-analyses in BD have shown fractional anisotropy reduction in clusters located in both anterior and posterior white matter areas (Nortje et al., 2013; Vederine et al., 2011). In addition, meta-analyses of studies using T2 weighted images have confirmed increased rates of deep white matter hyperintensities (WMH) in this disorder (Beyer et al., 2009; Kempton et al., 2008). Meta-analytical

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data on white matter volume in BD are still limited. Overall, total white matter volume has been found to be preserved (Arnone et al., 2009; Kempton et al., 2008; McDonald et al., 2004b). In terms of regional change, two meta-analyses confirmed a reduction in cross-sectional area of the corpus callosum in BD (Arnone et al., 2008a; Kempton et al., 2008). These findings originate from region of interest (ROI) studies that are restricted to pre-defined areas and so may exclude other regions involved in the illness (Giuliani et al., 2005). Alternatively, voxel-based morphometry (VBM) studies survey the whole brain and examine regions not included in ROI studies (Giuliani et al., 2005; Mechelli et al., 2005). There have recently been a number of meta-analyses of grey matter VBM studies in BD (Bora et al., 2010; Ellison-Wright and Bullmore, 2010; Houenou et al., 2011; Selvaraj et al., 2012; Wise et al., 2016) many of which used published coordinate data (Bora et al., 2010; Ellison-Wright and Bullmore, 2010; Houenou et al., 2011) and one meta-analysis which examined white matter volume using coordinate data from 5 studies (Ganzola and Duchesne, 2017). Meta-analyses of coordinate data are limited because they take into account significant peak findings but ignore sub-threshold results. Two studies (Selvaraj et al., 2012; Wise et al., 2016) have performed a VBM meta-analysis of grey matter using statistical maps (T-maps) in BD. These three dimensional maps comprise statistical data of volume differences in thousands of voxels in the brain. A T-map meta-analysis is more accurate than a coordinate-based meta-analysis, although it requires T-maps to be obtained from the authors of each study (Radua et al., 2012).

We used the software Seed-based d Mapping (SDM) in our meta-analysis of white matter in BD, since it is possible to combine coordinate data, T-maps and even processed raw data (Radua et al., 2012). A growing controversy in scientific research is lack of reproducibility (Editorial, 2016) and this problem has been shown to apply to VBM studies (Boekel et al., 2015). To address this issue we investigated whether the volume reduction identified in our meta-analysis could be replicated in an independent sample. Finally we examined the association between clinical variables and white matter volume in 6 raw MRI datasets comprising 184 BD patients. To our knowledge, our meta-analysis includes the largest number of T-maps of any structural MRI meta-analysis in the bipolar disorder or schizophrenia literature.

2. Methods and materials

An overview of the methodology is shown in Fig. 1.

2.1. Meta-analysis of white matter VBM studies and creation of ROI

2.1.1. Data source and inclusion criteria of the studies

Articles were obtained from a literature search using the PubMed database. The keywords used were “VBM”, “voxel-based”, “morphometry”, “bipolar”, “mania” and “manic”. An additional manual search within the references section of the articles obtained was also conducted. The studies included were published up to September 2017. Studies were considered if they reported a VBM analysis of white or grey matter volume or density comparing BD patients to healthy controls. A flow chart regarding the selection of the included studies is shown in Fig. s1. Authors of VBM studies were contacted by e-mail asking for their T-map contrast of white matter volume in BD patients compared to controls, and if required, additional information about the associated design matrix to clarify the number of covariates used. To increase the number of studies included in our meta-analysis, authors of studies that only reported grey matter data were contacted to determine whether they had conducted an unpublished white matter analysis. VBM studies were excluded if the study did not report coordinates of white matter changes and if the authors were unable to provide a T-map image or raw MRI data. In studies where separate subgroups of patients were reported, the largest subgroup was used. To ensure that there was no bias to a priori small volume corrections, only studies including whole brain analyses have been considered.

2.1.2. Selection of studies

The initial search retrieved 142 studies of which 81 were eligible. Of the 81, 62 studies reported a grey matter VBM analysis only, and 19 conducted a white matter VBM analysis between BD and controls (Fig. s1). After contacting all of the authors, T-maps of white matter differences between BD patients and controls were obtained from 12 studies including 4 unpublished white matter analyses (Castro-Fornieles et al., 2017; Dukart et al., 2014; Ivleva et al., 2012; Matsubara et al., 2016). In addition a further 5 research groups which published grey matter analyses but did not include VBM white matter analyses, (Emsell et al., 2013; Haller et al., 2011; James et al., 2011; Kempton et al., 2009; Yip et al., 2013) agreed to send us the anonymised individual MRI scans. We subsequently conducted a white matter VBM analysis on these 5 datasets resulting in 5 new T-maps. Therefore, the present meta-analysis included a total of 17 T-maps (Fig. s1). In addition to the T-maps, this meta-analysis included 7 studies for which the peak coordinates were reported (Alonso-Lana et al., 2016; Bond et al., 2014; Farrow et al., 2005; Ishida et al., 2017; McDonald et al., 2005; Stanfield et al., 2009; Watson et al., 2012). The location of each study and the listed authors were compared to determine if there was any possible sample overlap between the studies, and no overlap was identified. Thus the meta-analysis included a total of 24 studies comprising 765 BD patients and 1055 healthy controls.

2.1.3. Creation of T-maps from voxel-based morphometry analysis of 5 raw datasets

Anonymised MRI scans from 5 research groups were processed using SPM8 assessing white matter differences. The VBM pre-processing performed is described below in Section 2 of the methods. Following pre-processing and voxel-wise statistical analysis, a T-map was created from each dataset from the contrast ‘BD patients > controls’ for regional white matter volume. As T-maps include T-scores for every white matter voxel in the brain no threshold was required before including them in the meta-analysis.

2.1.4. Seed-based d mapping analysis

The meta-analysis was performed using the software Seed-based d Mapping (SDM v5.141; available online at http://www.sdmproject.com/) which allows for the combination of statistical maps (T-maps) and peak coordinates (Radua et al., 2012) (Fig. 1). This method has been described in detail by Radua et al. (2012) and the meta-analysis was performed following the instructions available online at www.sdmproject.com/manual/. After receiving T-map images from study authors we verified that the degrees of freedom in each T-map file matched the design matrix reported in the corresponding paper. The T-maps were converted to an unbiased effect size and variance map using the SDM software (Radua et al., 2012). For the studies where only peak coordinates were available, SDM recreated an effect-size signed map (with both positive and negative effect sizes) of the differences in white matter. For each study reporting coordinates, the effect size was exactly calculated within the peaks and was estimated for the other voxels (Radua and Mataix-Cols, 2009; Radua et al., 2012). In order to avoid potential bias from more liberal thresholds applied to particular regions of the brain (e.g. small volume correction), the same threshold was used throughout the entire brain within each study, while different studies were permitted to use different thresholds (Radua, 2015). A z-score map of the pooled effect size was subsequently created by meta-analytically combining each study map, weighted by the inverse variance of each study with between study heterogeneity taken into account (Lansley et al., 2013; Radua et al., 2012; Radua et al., 2011). Thus studies with a larger sample size or less variability contribute more to the pooled effect size (Radua et al., 2012). Statistical significance was determined using a permutation test by means of Monte Carlo randomizations, applying 100 permutations (Radua and Mataix-Cols, 2009; Radua et al., 2011). We used the three thresholds suggested by Radua et al. (2012). The main threshold applied was an uncorrected p value of