Brain Structural Effects of Psychopharmacological Treatment in Bipolar Disorder

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Abstract: Bipolar disorder is associated with subtle neuroanatomical deficits including lateral ventricular enlargement, grey matter deficits incorporating limbic system structures, and distributed white matter pathophysiology. Substantial heterogeneity has been identified by structural neuroimaging studies to date and differential psychotropic medication use is potentially a substantial contributor to this. This selective review of structural neuroimaging and diffusion tensor imaging studies considers evidence that lithium, mood stabilisers, antipsychotic medication and antidepressant medications are associated with neuroanatomical variation. Most studies are negative and suffer from methodological weaknesses in terms of directly assessing medication effects on neuroanatomy, since they commonly comprise posthoc assessments of medication associations with neuroimaging metrics in small heterogenous patient groups. However the studies which report positive findings tend to form a relatively consistent picture whereby lithium and antiepileptic mood stabiliser use is associated with increased regional grey matter volume, especially in limbic structures. These findings are further supported by the more methodologically robust studies which include large numbers of patients or repeated intra-individual scanning in longitudinal designs. Some similar findings of an apparently ameliorative effect of lithium on white matter microstructure are also emerging. There is less support for an effect of antipsychotic or antidepressant medication on brain structure in bipolar disorder, but these studies are further limited by methodological difficulties. In general the literature to date supports a normalising effect of lithium and mood stabilisers on brain structure in bipolar disorder, which is consistent with the neuroprotective characteristics of these medications identified by preclinical studies.

Keywords: Bipolar disorder, diffusion tensor imaging, lithium, magnetic resonance imaging, medication effects, neuroimaging.

INTRODUCTION

Although less extensively researched than schizophrenia, bipolar disorder has been linked to a range of neuro-anatomical abnormalities compared with healthy volunteers in cross-sectional imaging studies to date. One theme to emerge from these studies, which is highlighted in meta-analyses and systematic reviews, is the marked heterogeneity of findings. Potential sources of this heterogeneity include methodological variation in imaging acquisition and analysis, and clinical variation in illness presentation, risk factor exposure and the use of psychotropic medication. In this article I selectively review neuroanatomical imaging studies of bipolar disorder, with a focus upon the findings from meta-analyses, discuss evidence that psychotropic medications used in bipolar disorder are associated with variation in neuroanatomy from complimentary research areas such as animal studies, review in detail those individual studies assessing psychotropic medication effects and discuss the design of future studies which may serve to better elucidate the relationship between the use of psychotropic medication and brain structural variation in bipolar disorder.

Region of Interest MRI Studies

In the first meta-analysis of regional volumetric MRI studies performed on adult bipolar patients, McDonald [1] and colleagues reported that the only significant finding to emerge was enlargement of the right lateral ventricle in patients compared with controls, but that there was marked heterogeneity of several limbic system structures investigated. A further meta-analysis by Kempton *et al.,* [2], which included CT and qualitative MR studies, reported that bipolar disorder was associated with ventricular enlargement and increased rates of white matter hyperintensities, with significant heterogeneity across many regions. A meta-analysis of MR studies that included paediatric samples identified increased volume of the ventricles and globus pallidus, and subtle reduced cerebral volume and prefrontal volume in patients with bipolar disorder compared with controls [3]. Again there was significant heterogeneity across many structures. In a large mega-analysis of individual level patient data that controlled for certain potential confounds and examined associations with clinical variables, Hallahan and colleagues [4] identified increased right ventricular volumes and enlargement of the left temporal lobe and right putamen in adult patients with bipolar disorder.

Voxel Based Analysis MRI Studies

In a meta-analysis of voxel based morphometry studies of grey matter in schizophrenia and bipolar disorder

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employing anatomical likelihood estimation, Ellison-Wright and Bullmore [5] reported that bipolar disorder is associated with significant grey matter deficit in the paralimbic regions of the bilateral insula and anterior cingulate, and contrasted these circumscribed deficits with the substantially more widespread grey matter deficit found in schizophrenia. A further meta-analysis confined to adult patients and utilising another version of anatomical likelihood estimation similarly reported grey matter deficits in the right anterior cingulate and also bilateral ventrolateral and right dorsolateral prefrontal grey matter in bipolar disorder [6]. A meta-analysis using the technique of signed differential mapping identified grey matter deficits in the left rostral anterior cingulate cortex and right fronto-insular cortex in bipolar disorder [7]. Selvaraj and colleagues [8] employed a different technique of voxel wise meta-analysis by analysing original t-maps from contributing studies and reported evidence for consistent grey matter deficits in the right prefrontal cortex, anterior temporal cortex, insula, and claustrum in bipolar disorder, with widespread study heterogeneity elsewhere in the brain.

White Matter Pathophysiology and Diffusion Tensor Imaging Studies

The high prevalence, albeit variable, of qualitatively rated white matter hyperintensities in patients with bipolar disorder (39%) compared with controls (18%) was highlighted in a meta-analysis by Beyer and colleagues [9]. Other meta-analyses have identified reduced area of the corpus callosum in bipolar disorder [10] and reduced global white matter volume in patients experiencing their first manic episode [11, 12]. This neuroimaging evidence combined with converging evidence from molecular genetics and neuropathology implicating genetic variants and altered gene expression linked to oligodendrocyte and myelination genes in the illness has fuelled interest in studying white matter pathophysiology in bipolar disorder [13].

Diffusion tensor imaging is the most widely employed method to investigate abnormalities of microstructural white matter *in vivo*. Fractional anisotropy, the commonest metric to be derived from such DTI studies to date, is a marker of axonal organisation with low values representing more disordered structure whilst higher values represent greater cohesion of fibre-bundles. A meta-analysis of whole brain DTI studies by Vederine *et al.,* [14] identified two right hemisphere clusters of significantly reduced fractional anisotropy in bipolar disorder, one in the anterior cingulate and another close to the parahippocampal gyrus. A further systematic review and meta-analysis employing the technique of effect-size signed differential mapping [15] reported that bipolar disorder was associated with widespread white matter tract involvement incorporating commissural, association and projection fibres, with the meta-analysis identifying significantly reduced fractional anisotropy in right posterior temporoparietal and left cingulate regions.

Taken together the structural neuroimaging literature to date confirms that brain abnormalities are present in bipolar disorder with the most consistent evidence for ventricular enlargement, focal grey matter deficit incorporating limbic regions known to have a key role in mood regulation, white matter abnormalities in anterior limbic regions and with more widespread extension to include longitudinal and interhemispheric tracts. There is also evidence for considerable heterogeneity among studies. Multiple sources of clinical heterogeneity are possible in addition to psychotropic medication use including mood state, diagnosis within the bipolar spectrum, severity of illness, progression from first episode through to sustained illness, lifestyle factors such as the use of alcohol and illicit substances, variation in genetic and environmental risk factors, impact of illness on neurodevelopmental trajectory - for example adolescent vs adult onset. Several individual studies provide some evidence supporting the relevance each of these factors which will not be reviewed in detail here. The evidence that psychotropic medication use in bipolar disorder is a significant driver of the heterogeneity identified in neuroanatomical studies will now be addressed in more detail.

Is there Evidence from Preclinical Studies that Psychotropic Medications used in Bipolar Disorder Affect Brain Structure?

There is now considerable preclinical literature from studies in rodents and human cell lines providing evidence of both neurotrophic and neuroprotective effects of lithium. The mechanisms whereby this occurs may be related to inhibiting proapoptotic pathways, such as glycogen synthase kinase-3β (GSK-3β), increasing levels of the neuroprotective B-cell lymphoma protein-2 (bcl-2), and regulating the neurotrophic intracellular signalling cascade involving brain-derived neurotrophic factor (BDNF) [16, 17]. Neuroprotective properties have also been attributed to valproate, possibly through its action on histone deacetylases and consequent enhancement of bcl-2 and of neurotrophic factors [18]. Although less extensively investigated, there is also evidence that the mood stabilisers carbamazepine and lamotrigine upregulate growth factors in frontal cortex of rodents [19-21].

Furthermore when lithium is given to humans without bipolar disorder, as in a study by Monkul and colleagues [22], who administered lithium at therapeutically relevant doses for 4 weeks to thirteen healthy volunteers with MR scanning before and after, participants displayed prefrontal grey matter increases as well as global white matter volume increase. The authors questioned whether this imaging effect was related to neurotrophic or osmotic effects. The latter interpretation is supported by another study on human volunteers administered lithium that included a placebo group [23]. An apparent increase in grey matter in those participants taking lithium detected by voxel based morphometry was not found with an alternative paired edge finding methodology and the authors interpret their findings as indicating that lithium causes alterations in the MR signal rather than actual volume increase of grey matter.

In contrast to the apparent neurotrophic effects of mood stabilizing treatment, there are a number of reports that antipsychotic medications, especially first generation agents, are associated with brain tissue loss. Macaque monkeys and rats who have been chronically administered antipsychotic medications such as haloperidol or olanzapine for several months display distributed reduced volume of grey and white matter [24, 25]. The grey matter deficits in rodents were

noted to resolve on withdrawal of the antipsychotic agent, in direct contrast to the effects of lithium which were associated with persistent increased volume of grey matter [26]. This preclinical evidence is reflected in the clinical literature on schizophrenia, where several longitudinal reports have identified an association with antipsychotic use and reduced grey matter over time [27, 28]. This effect is described for both first and second generation antipsychotics but may be more attenuated or even absent with the latter [29-31]. Indeed there is evidence from rodent studies that administration of second generation antipsychotic medication is associated with increased neuropil and synaptogenesis [32]. From this preclinical evidence, it is tempting to speculate that the contrasting findings between schizophrenia and bipolar disorder in structural neuroimaging studies may be related to the differential use of psychotropic medication in these disorders, with the neurotrophic mood stabilising agents responsible for attenuation or reversal of grey matter deficits in bipolar disorder, and the use of persistent antipsychotic medication in schizophrenia linked to the more substantial grey matter deficits associated with that syndrome [5, 33, 34].

What Studies in Bipolar Disorder Patients can Assess the effects of Psychotropic Medication on Brain Structure?

Ideally the neuroanatomical deficits associated with bipolar disorder could be identified by imaging patients with active illness prior to the use of medication and then subsequently after the administration of various psychotropic medications. However structural neuroimaging studies performed in bipolar disorder have mostly been conducted on patients already receiving psychotropic medication. There are substantial challenges in recruiting for neuroimaging studies bipolar patients who have never received psychotropic medication. Many patients experiencing a first manic/hypomanic episode have previously suffered from depression for which they may have received medical treatment. Many patients presenting to services with manic symptoms are often acutely unwell, require rapid medical treatment and may lack insight or capacity to consent to engage in an imaging study. On a related point those medication naive patients presenting with a first hypo/manic episode who are able to participate in a neuroimaging assessment are likely to have a milder form of illness and thus less representative of the general population of bipolar disorder patients. These factors limit the ability of research groups to acquire neuroimaging from patients with bipolar disorder who are psychotropic medication naïve compared, for example, to schizophrenia where patients may have an insidious onset or present with prodromal symptoms which facilitates recruitment to neuroimaging research studies [35].

However there are a small number of cross-sectional structural neuroimaging studies on patients with first episode bipolar disorder who were medication naïve at the time of scanning. In a DTI study of 13 medication naïve patients with psychotic bipolar 1 disorder, Lu and colleagues [36] reported that patients had significantly reduced fractional anisotropy and increased radial diffusivity in distributed regions compared to controls and to unmediated patients with schizophrenia. Similarly in a larger number of 38 patients

with bipolar II/NOS disorder who were antipsychotic and mood stabiliser naïve at the time of scanning, Yip *et al.,* [37] reported that patients had widespread reductions in fractional anistropy and increased mean diffusivity compared to controls, whereas no grey matter deficits were detected using voxel based morphometry. These studies support developmental abnormalities of white matter as potentially core to the pathophysiology of bipolar disorder. Reduced area of the corpus callosum [38] and reduced volume of the cerebellar vermis [39] and cingulate gyrus [40] compared with controls have also been reported in small samples of medication naïve patients with bipolar disorder.

A larger number of studies included patients with first episode bipolar disorder who have been scanned shortly after the onset of illness. Meta-analysis of such studies on first episode bipolar patients demonstrate brain abormalities are detectable compared to healthy volunteers. They include reduced intracranial volume, reduced whole brain volume and reduced global white matter in patients with bipolar disorder compared with healthy volunteers [11, 12]. However, in contrast to schizophrenia, there was no significant reduction in global grey matter or in lateral ventricular volume in first episode bipolar disorder; instead significant heterogeneity between studies for left lateral ventricular volume was detected [12]. These first episode studies on patients at an early stage of their illness when they have experienced limited or no exposure to medication provide substantial evidence that neuroanatomical changes found in more chronic populations cannot be solely attributable to psychotropic medication usage.

A further study design which can identify neuro-anatomical abnormalities which cannnot be due to medication effects and therefore can probe the underlying biology of bipolar disorder, in this case related to genetic liability, is the asessment of unaffected relatives of patients. A number of such studies have now been completed and have reported neuroanatomical changes in the unaffected relatives of patients with bipolar disorder compared to controls, including grey matter deficit in the right anterior cingulate and ventral striatum [41] and in the left anterior insula [42], as well as ditributed white matter volume and fractional anisotropy reductions [41-46]. These neuroanatomical abormalities are interpreted as likely genetic or endophenotypic effects. However the literature in this field lacks consistency and there are several studies which do not detect abnormalities in the relatives of bipolar disorder patients [47-49]. The discrepancies in findings to date may be due to subtle differences in neuroanatomy being present in relatives, or variation in differences depending on the clinical presentation or subgroup of illness, for example whether samples are genetically enriched or the bipolar disorder phenotype is accompanied by psychotic symptoms. Further large prospective studies on homogenous samples will be required to clarify these issues [49, 50].

In relation to probing medication effects in already medicated bipolar patients, studies have mostly been cross-sectional with a posthoc analysis of variation in neuro-anatomical variables with the reported use of medication. A small number of longitudinal studies have also been

conducted. The analysis from cross-sectional studies of variation with medication usage carries with it a number of caveats. The manner in which subject groups are divided is likely more related to the availability of data on medication exposure than hypotheses about medication effects and makes assumptions that are not necessarily linked to the likely biological processes at play. For example studies examining lithium effects usually separate participants into subgroups of those taking lithium or not at the time of scanning, however this ignores whether lithium free patients have been exposed to lithium previously, how long they have taken lithium for, what dosage/serum level of lithium the patients are exposed to, whether the lithium tended to be prescribed for patients with a particular clinical presentation (such as more manic episodes), whether the non-lithium exposed group are receiving other mood stabilising/ antipsychotic medications that also may be acting through similar neurotrophic mechanisms as outlined above. Many structural neuroimaging studies using a region of interest approach also confine analyses to the regions chosen for investigation which may be limited and miss areas of the brain that could show regionally specific medication effects.

Patients with bipolar disorder are commonly administered treatment with multiple psychotropic medications [51]. When patients are taking several medications, they may have interactive effects on brain structure compared to monotherapy, however studies are unlikely to have sufficient statistical power to parse such effects. Some studies have attempted to model the amount of psychotropic medication used by contructing a single variable to reflect dose, such as chloropromazine equivalents for antipsychotic medication, number of medications given, or a medication load variable such as that described by Versace and colleagues [52], which combines the dosage and number of medications used. Although such a quantitative variable could improve statistical power to detect medication-neuroanatomy associations, it collapses different medications which may be having separate neurobiological effects into single variable. Furthermore any observational studies carry the caveat that patients are likely to be prescribed higher doses and multiple medications if they are experiencing a more severe and unstable illness. The optimal study design to separate out medication effects from potentially confounding clinical indications is to include neuroanatomical imaging as an assessment tool in prospective double blind randomised controlled trials of monotherapy medication for bipolar disorder, either against placebo or another active compound. Such a study in schizophrenia, where patients were sequentially scanned over a two year period, reported that haloperidol treated patients displayed significantly reduced global grey matter whereas patients randomised to olanzapine did not [30]. One small structural neuroimaging study utilsing this design in established bipolar disorder has been published to date, where patients were randomised to receive lithium or valproate (vide infra) [53]. I will now consider in more detail the results of cross-sectional and longitudinal studies of psychotropic medication effects on neuroanatomy in bipolar disorder as assessed though structural neuroimaging and diffusion tensor imaging studies and divided by tissue class and medication subtype.

GREY MATTER

Lithium

The majority of individual cross sectional studies that have compared brain structures in patients taking lithium to those not taking this medication in fact have not reported any significant differences in regional brain volume [54]. However many studies were small and likely to have had limited statistical power to detect effects as well as suffering from other methodological shortcomings in terms of detecting medication related effects as discussed above.

Thus some individual cross sectional studies have reported increased global grey matter volume in patients with bipolar disorder taking lithium compared to medication free patients [55, 56], whereas other studies have failed to identify any effect [57, 58]. However, when the results of multiple studies are combined, an overall association between taking lithium and increased global grey matter volume emerges: a metaregression analysis to explore sources of heterogeneity in the meta-analysis by Kempton and colleagues [2] found that lithium use was associated with increased volume of grey matter in patients.

Interestingly the increased statistical power associated with tracking intra-individual variation in longitudinal studies tends to support this finding. Hence ten bipolar patients treated with lithium for only 4 weeks were noted to have increased grey matter volumes of about 3% after repeat scanning by Moore and colleagues [59]. In a later study on a larger group of 28 patients with bipolar depression, the same group replicated this finding of increased total grey matter volume after 4 weeks of lithium treatment [60]. Furthermore the grey matter volume increase associated with lithium administration was confined to treatment responders in this study. In another longitudinal study with serial scanning of 22 bipolar disorder patients who were medication free at first scanning and subsequently treated with lithium (n=13) or valproate (n=9), Lyoo *et al.,* [53] reported that lithium treatment was associated with increased grey matter volume which was maintained at 16 weeks of treatment and again associated with positive clinical response. The authors concluded that lithium use in bipolar disorder is associated with sustained increases in cerebral grey matter and that these neuroanatomcial changes are likely related to the therapeutic efficacy of lithium.

More consistent findings from individual studies emerge when certain regional structures are investigated. Many region of interest studies have measured volume of the hippocampus and amygdala in bipolar disorder given the key role these limbic system structures play in memory and emotional processing. The hippocampus is also a site of potential neurogenesis and susceptible to the effects of mood related stress, such as through glucocorticoid mediated toxicity [61]. The hippocampus and amygdala show no overall volume difference in adult patients with bipolar disorder compared to controls in meta-analyses, but are regions of significant between study heterogeneity [1, 2]. Individual study results indicate that variable lithium use is a likely contributor to this heterogeneity. Hence in longitudinal

studies, Yucel and colleagues [62] reported that patients with bipolar disorder treated with lithium for short term periods of up to 8 weeks had bilateral increased volume of the hippocampus and hippocampal head compared to unmedicated patients or controls. The same authors report that patients with bipolar disorder who experienced long term treatment with lithium for 2 to 4 years displayed increased hippocampal volume (and improved verbal memory performance) over time [63]. In their metaregression analyses, Kempton and colleagues [2] also report a trend level effect (p=0.051) for increased hippocampal volume in patients with bipolar disorder compared with controls as the proportion of patients taking lithium in the study increased and Arnone *et al.,* [3] report an association of mood stabiliser use with increased volume of the amygdala.

In a cross sectional study comparing 12 lithium treated patients with 37 lithium free patients, Foland *et al.,* [64] reported that lithium use was associated with increased volume of hippocampus and amygdala. Beyer and colleagues [65] in a study of older bipolar disorder patients reported that patients had larger left hippocampal volume than controls and this enlargement was associated with exposure to lithium. Bearden *et al.,* [66] reported that 21 adolescent bipolar disorder patients taking lithium for at least two weeks had larger total hippocampal volume than 12 unmediated patients and 62 matched healthy controls. Savitz *et al.,* [67] using high resolution imaging reported that depressed bipolar disorder patients who were medication naïve or unmedicated at time of scanning had significantly reduced amygdala volume compared to medicated patients, most of whom were taking lithium. Germana *et al.,* [58] reported that remitted patients with bipolar disorder taking lithium had increased volume of the hippocampus and amygdala compared to patients taking other psychotropic medications. Van Erp *et al.,* [68] reported that twins with bipolar disorder taking lithium had increased hippocampal volume compared to unaffected co-twins and control twins, whereas those bipolar patients not taking lithium did not differ from their well co-twins or controls. Usher *et al.,* [69] reported that euthymic patients with bipolar disorder taking lithium had larger amygdala volume compared with patients not taking lithium and healthy controls. Hajek *et al.,* [70] studied 37 bipolar patients treated with lithium for at least 2 years, 19 bipolar patients with minimal lithium exposure and 52 healthy controls and reported that lithium treated patients had similar hippocampal volume to controls, but significantly increased hippocampal volume compared to non-lithium treated patients.

Some other cross-sectional studies have failed to find lithium effects on the hippocampus or amygdala [71-74]. However, in a large mega-analysis of individual level patient data Hallahan and colleagues [4] assessed regional volumetric variation with lithium usage and included data on hippocampal volume from 174 bipolar disorder patients and 298 controls, and amygdala volume from 230 patients and 255 controls. Those patients taking lithium were found to have significantly enlarged hippocampal and amygdala volumes bilaterally compared with controls, whereas patients not taking lithium were found to have significantly smaller hippocampal and amygdala volumes compared with controls, providing strong evidence in the light of the many other previous positive studies for a volume increasing effect of lithium use in the medial temporal lobe. Interestingly the hippocampus is a particularly plastic brain region [75], and is one of the few areas to produce neurons post-natally [76]; therefore it may be more likely than other brain regions to be affected by medication induced neurogenesis [77]. The hippocampus and amygdala are closely interconnected within the anterior limbic system, which demonstrates task related hyperactivity in functional neuroimaging studies of bipolar disorder, possibly related to impaired prefrontal modulation of these regions within a network subserving mood regulation [78, 79].

Other components of this network, which underpins emotional processing and emotional regulation, comprise the anterior cingulate, striatum, orbitofrontal cortex, medial prefrontal cortex, ventrolateral prefrontal cortex and dorsolateral prefrontal cortex [79, 80]. These structures have also been a focus of investigation for medication effects in structural neuroimaging studies of bipolar disorder. Sassi *et al.,* [81] found reduced left anterior cingulate volume in untreated bipolar disorder patients whereas those taking lithium monotherapy had significantly larger anterior cingulate which did not differ from healthy controls. Bearden *et al.,* [82] reported increased grey matter density in the right anterior cingulate in bipolar patients taking lithium compared with those not taking lithium. In the study by Germana *et al.,* [58] of remitted bipolar disorder patients, those treated with lithium had increased grey matter in the subgenual anterior cingulate cortex, insula and postcentral gyrus, as well as medial temporal lobe, when compared with patients taking other mood stabilisers or antipsychotic medication. Wang *et al.,* [83] reported that adolescent patients with bipolar disorder taking lithium had larger orbitofrontal cortex volume compared to lithium negative patients. Mitsunga *et al.,* [84] reported that paediatric bipolar patients with a previous exposure to mood stabilisers, including lithium, had larger subgenual cingulate volume than bipolar patients without such exposure and controls. In a large sample of patients with bipolar 1 depressive phase, Benedetti *et al.,* [85] reported that lithium treatment was associated with increased grey matter volume in the right subgenual and orbitofrontal cortex and acted synergistically with a genotypic variant resulting in less active GSK-3 (which is inhibited by lithium) to produce this apparent neurotrophic effect in brain regions involved in affect regulation. The meta-analysis of voxel based morphometry studies by Bora *et al.,* [7] included an associated metaregression analysis which found that lithium treatment was associated with increased volume of the anterior cingulate cortex. In a longitudinal study of bipolar patients treated with lithium over a 4 week period, Selek and colleagues [86] reported that patients who responded to lithium treatment displayed increased volume of the left prefrontal cortex. Again a number of studies fail to identify volume variation in limbic system structures with lithium treatment [4, 42, 72, 87-89]. Taken together, whilst not as solid as the medial temporal lobe findings, substantial evidence has been accumulated that at least some patients on lithium have increased grey matter in other limbic structures.

Lithium use was also associated with increased grey matter in other structures in various studies including superior temporal gyrus and planum polare [90], lateral temporal cortex [91], left temporal lobe volume [4], right thalamic volume [92], cerebellar vermis [39]. Taken together, and despite a number of negative studies in this methodologically complex area, the overwhelming evidence from the cross-sectional and in particular longitudinal studies conducted to date in bipolar disorder is that lithium treatment affects grey matter by increasing volume or normalising deficits in distributed regions that strongly include but also extend beyond those key limbic regions subserving emotion processing. These effects detected through *in vivo* structural neuroimaging in diverse patient cohorts may be related to the neurotrophic effects of lithium identified in preclinical studies.

Anti-epileptic Mood Stabilisers

Most studies that examined the association of psychotropic medication use with grey matter metrics in bipolar disorder have focussed on lithium administration, but some studies have also reported significant associations with the use of other antiepileptic mood stabilisers employing similar study methodology. Atmaca *et al.,* [40] compared grey matter volumes of cingulate subregions in 10 patients with bipolar disorder who were unmedicated, 10 on valproate monotherapy and 10 on valproate plus quetiapine, and demonstrated left-sided reductions of the anterior cingulate in the medication-naive patients when compared with the medicated patients, suggesting a neuroprotective or neurotrophic role for these medications. Chang *et al.,* [93] reported that paediatric bipolar patients who had been medicated with valproate or lithium had greater amygdala volume than patients without such exposure. In the study by Savitz *et al.,* [67] identifying reduced amygdala volume in medication free depressed bipolar disorder patients compared to medicated patients, amygdala volume was similarly normal in the valproate treated patients as the lithium treated patients. The study by Mitsunga *et al.,* [84] reporting larger subgenual cingulate volume in paediatric bipolar patients with a previous exposure to mood stabilisers than bipolar patients without such exposure and controls, found similar effects for patients on lithium and valproate. Baloch *et al.,* [94] reported that paediatric bipolar disorder patients taking mood stabilisers had larger volume of the right subgenual prefrontal cortex than those who were not. Wang *et al.,* [83] reported that bipolar disorder patients taking anticonvulsant mood stabilisers had larger orbitofrontal cortex than those who were not. A longitudinal study by Lisy *et al.,* [95] of 57 bipolar disorder patients unmedicated at baseline and rescanned over periods up to 34 months found that patients with bipolar disorder demonstrated increased grey matter in prefrontal cortex, limbic and subcortical regions over time, and that patients treated with antiepilipeptic mood stabilising drugs had increased grey matter in medial frontal cortex and right cerebellum, whereas no effect was detectable for those patients treated with lithium.

However most studies found no association between the use of antiepileptic mood stabilisers and grey matter volumes, including studies which did find such an effect for lithium treatment (see Hafeman *et al.,* [54] for a description of positive and negative studies in tabular form). For example Yucel and colleagues [62] in their longitudinal study of psychotropic treatment for up to 8 weeks found an apparent effect of lithium only on hippocampal volume and not valproate or lamotrigine. In the study by Lyoo *et al.,* [53] where bipolar patients were randomised to receive lithium or valproate, those patients with valproate treatment did not have significant grey matter increases, despite clinical improvement, in contrast to the effect detected for lithium. However, since the majority of medicated patients in studies to date tend to be taking lithium rather than other psychotropic medications, it is likely that these studies had even less power to detect positive effects that those examining an association with lithium use.

Antipsychotic and Antidepressant Medication

In the longitudinal study by Lisy *et al.,* [95], bipolar disorder patients receiving atypical antipsychotic medication (n=27) displayed increased grey matter in the left medial frontal gyrus. The meta-analysis by Arnone *et al.,* [3] included a meta-regression analysis to assess medication effects and identified an association between antipsychotic use and reduced volume of grey matter and of the right amygdala. The authors postulate that the use of antipsychotic medication may be a proxy for more severe bipolar illness. These authors also identified an association between antidepressant use and reduced volume of the right amygdala [3]. DelBello *et al.,* [96] also reported that bipolar adolescents exposed to antidepressants had smaller amygdala volumes, although there were only 4 subjects on antidepressant medication in this sample.

Several other studies assessed potential associations of taking various antipsychotic medications with volumes of a range of brain structures including global grey matter, striatal, medial temporal lobe and associated limbic structures, and categorising antipsychotic usage as a class of medication [97], subtypes of medications [98] or converted to chlorpromazine equivalents [99]. In contrast to the significant findings for grey matter excess with lithium and antiepileptic mood stabilisers, and to the reports of grey matter deficits in association with antipsychotic usage reported in schizophrenia, no other significant associations between grey matter variation and use of antipsychotic medications have been reported in bipolar disorder [4, 54]. Nor have the fewer number of individual studies assessing an association between grey matter volume variation and use of antidepressant medications in bipolar disorder found any significant effects [54].

WHITE MATTER

Lithium

In relation to lithium effects upon white matter pathophysiology, less consistent findings emerge than for grey matter, but some studies report significant findings. Walterfrang *et al.,* [100] report that bipolar disorder patients have reduced thickness of the corpus callosum and anterior body of the corpus callosum, but that those patients taking

lithium have thicker anterior mid-body of the corpus callosum than those taking other psychotropic medications. Macritchie *et al.,* [101], in a DTI study identifying reduced fractional anisotropy in the corpus callosum and deep white matter in euthymic bipolar disorder, reported that patients treated with lithium had increased fractional anisotropy compared to those who were not; and increased diffusivity compared to controls was only found in the patients who were not treated with lithium. In a study by Sussman *et al.,* [102] identifying reduced fractional anisotropy in the anterior limb of the internal capsule, anterior thalamic radiation and uncinate fasciculus in patients with bipolar disorder compared with controls, the authors report a positive association between lithium use and fractional anisotropy in the anterior limb of the internal capsule at non-significant trend level. Benedetti *et al.,* [103] reported that bipolar disorder patients taking lithium had normal fractional anisotropy in tracts connecting the amygdala and subgenual cingulate, whereas lithium free patients had reduced fractional anisotropy compared with controls. Furthermore in a sample of 70 depressed bipolar patients, Benedetti *et al.,* [104] found that duration of lithium treatment was positively correlated with axial diffusivity in multiple white matter tracts including the corpus callosum and left superior longitudinal fasciculus. The authors concluded that lithium may be counteracting the detrimental effects of bipolar disorder on white matter structure, possibly mediated through GSK-3 inhibition. In a study of 58 older patients with bipolar disorder, Gildengers *et al.,* [105] identified that patients with a longer duration of treatment with lithium had less white matter microstructural abnormality as indicated by a significant correlation with mean whole brain fractional anisotropy, and less white matter hyperintensity burden. There was no association between fractional anisotropy and antipsychotic exposure.

Anti-epileptic Mood Stabilisers

The study by Atmaca *et al.,* [40] examining cingulate gyrus volume included measurement of white matter as well as cortex and reported that valproate medicated patients had larger cingulate volume that unmediated bipolar disorder patients. In a study by Versace and colleagues [52] using tract based spatial statistics in patients with bipolar disorder and healthy volunteers, a summary variable of medication load was negatively correlated with fractional anisotropy in the left optic radiation; furthermore reduced fractional anisotropy was reported in the left optic radiation and right anterothalamic radiation in those patients taking mood stabilisers compared to those who were not, whereas there was no difference in fractional anisotropy when comparing those patients taking lithium to those who were not. The authors interpreted these results as demonstrating an ameliorative effect of medication and especially mood stabilisers on fractional anisotropy abnormalities in bipolar disorder.

There are several other cross sectional DTI studies of bipolar disorder that examined associations between fractional anisotropy or diffusivity measurements and use of lithium, mood stabilisers, antipsychotic medications and antidepressant medications and failed to identify any significant differences [13, 54]. It is of interest however that those DTI studies which do report a medication effect for lithium and mood stabilisers all support a normalising effect, similar to the more numerous positive studies on medication effects in grey matter structures.

SUMMARY AND FUTURE DIRECTIONS

The vast majority of reports assessing the impact of psychotropic medications on brain anatomy *in vivo* are from neuroimaging studies which were not specifically designed to address this question, and most studies are unsurprisingly negative in terms of not detecting statistically significant results since they comprise small, cross-sectional samples, commonly heterogenous in both clinical features and medication exposure. That said, there is arguably considerable consistency in the positive studies to date in terms of the directionality of findings, whereby almost all studies which report significant neuroanatomical differences find an apparent ameliorative effect for the use of psychotropic medications in bipolar disorder. A summary of the significant neuroanatomical changes reported is provided in Table **1**.

The most substantial evidence is for the most frequently investigated compound and with the most statistical power, i.e. an effect of lithium use on grey matter volume, whereby lithium use in bipolar disorder patients is repeatedly associated with increased grey matter volume globally and in the medial temporal lobe, limbic and prefrontal regions. The likelihood that this is a true effect is enhanced by its support beyond small cross-sectional studies into those more methodologically robust designs which carry substantial statistical power such as meta-regression analyses, which include large numbers of patients, and prospective studies, which include intra-individual rescanning. The potentially important role that white matter pathophysiology plays in the aetiopathogenesis of bipolar disorder is underpinned by multiple recent diffusion tensor imaging studies with some evidence that genetic liability contributes to white matter microstructural abnormalities. Nevertheless there is also evidence that lithium treatment may have ameliorative effects on diffusion tensor imaging metrics.

It remains unclear at present whether these apparently ameliorative effects of lithium on the neuroanatomy of grey and white matter are related to its therapeutic effect or reflect epiphenomena unrelated to the clinical efficacy of lithium. The possibility of the former is supported by the extensive preclinical literature identifying neurotrophic and neuro-protective effects associated with lithium use [17]. However the clinical literature provides only sparse support for this hypothesis since the studies are overwhelmingly cross-sectional in design and thus cannot relate symptomatic or functional improvement to neuroanatomical change over time. Furthermore some longitudinal studies do not include analyses of symptomatic improvement with neuroanatomical variation [59, 62, 63, 95]. However it is notable that the longitudinal studies to date which have included such analyses reported that clinical responders to treatment with lithium have the greatest volume increases in grey matter and prefrontal grey matter [53, 60, 86]. These studies do suggest

Table 1. **Summary of the anatomical regions reported to significantly vary with psychotropic medication use in bipolar disorder***

Medication	Brain Region Variation Associated with Medication use
Lithium - longitudinal studies	↑ global grey matter ++ ↑ hippocampus ++ ↑ prefrontal cortex ++
- cross-sectional studies	↑ global grey matter ++ ↑ hippocampus ++ ↑ amygdala ++ ↑ anterior cingulate ++ ↑ orbitofrontal cortex ++ ↑ insula + ↑ postcentral gyrus + ↑ temporal lobe + ↑ prefrontal cortex + ↑ superior temporal cortex + ↑ thalamus + ↑ cerebellar vermis + ↑ corpus callosum area ++ ↑ microstructural organization in distributed white matter areas +
Antiepileptic mood stabilizing medication	↑ anterior cingulate ++ ↑ amydala + ↑ orbitofrontal cortex + ↑ prefrontal cortex + ↑ microstructural organization in distributed white matter areas ~
Antipsychotic medication	↑ medial prefrontal cortex + ↓ grey matter ~ ↓ amygdala ~
Antidepressant medication	↓ amygdala ~

* Footnote:
The majority of studies to date have examined the effect of lithium. Studies are cited and described in more detail in the manuscript text.
++ strong evidence for an effect, supported by more than one study or meta-analysis
+ some evidence for an effect
~ weak or equivocal evidence for an effect

that the clinical efficacy of lithium is mediated through neurotrophic effects in regions of affect regulation detectable through structural neuroimaging.

An apparently weaker effect on grey matter is reported for the antiepileptic mood stabilisers, with some studies finding more prominent grey matter increases for lithium compared with valproate including one study which used a randomised design [53]. However there is also consistent directionality of the findings, with most studies which had significant findings for mood stabilisers reporting that patients taking these medications have less substantial grey matter deficits than those who do not, again including limbic regions.

The literature is much more sparse for the effects of antiepileptic mood stabilisers on white matter microstructure and for the effects of antipsychotic and antidepressant medications on brain grey and white matter structure. However these studies have even more methodological difficulties than the studies on lithium, with different medications often grouped into a single class, polypharmacy with concomitant mood stabilisers, intermittent use of such medications, and lack of studies employing large patient numbers and prospective designs. It is nevertheless reassuring that the few studies reporting statistically significant findings with the use of these medications were again in the same direction as mood stabilisers towards an ameliorative effect.

The generally normalising effect of psychotropic medications upon brain neuroanatomy is mirrored by similar findings from the functional neuroimaging literature and consistent with the results of preclinical studies which indicate that medications such as lithium have neuroprotective properties [13, 54, 106].

As further structural and diffusion tensor imaging studies emerge on bipolar disorder, they are likely to be accompanied by many more posthoc analyses to assess for the potential impact of psychotropic medications upon the authors' findings. This will incrementally move the field forward and add to the literature. However to make more substantial progress and lead to more robust findings, structural neuroimaging research needs to move beyond the small scale cross-sectional studies which have characterised the field to date towards designs that will have enough statistical power to more emphatically address questions regarding the drivers of neuroanatomical variation in bipolar disorder. On the one hand this can be progressed by large scale collaborations between research groups where the processed or raw imaging data across many hundreds or thousands of patients with accompanying detailed information on clinical features and medication usage can be analysed using multivariate approaches to assess the impact of medication use when controlling as much as possible for clinical confounds. However there is also a need for large scale longitudinal studies ideally commencing with medication naïve individuals and with repeated multimodal imaging over time to chart the probable dynamic changes of brain structure in the course of bipolar disorder in order to tease apart the effects of clinical course variation and of psychotropic treatment. Ideally more clinically homogenous samples should be employed including monotherapy treatment to simplify the design and analyses. The effects of clinical confounding however can only be optimally removed by including repeated scanning in prospective studies that also include randomized use of psychotropic medications, which could potentially isolate the effect of particular medications upon brain anatomy in bipolar disorder. Firmly pinning down the effects of psychotropic medication upon neuroanatomy in bipolar disorder will boost other aspects of neuroimaging research into the illness by facilitating the parsing out of medication effects from those of illness course and risk factors, such as genotypic variation or exposure to environmental precipitants, and enhance the prospects of identifying reliable neuroimaging biomarkers in the illness.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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