Part 2. Neurobiology of the Bipolar Spectrum

Brain structural changes in bipolar disorders – interplay between illness burden and lithium treatment

Tomas Hajek MD, PhD
Department of Psychiatry, Dalhousie University, Halifax, Canada
Prague Psychiatric Centre, Department of Psychiatry and Medical Psychology, 3rd School of Medicine, Charles University, Prague, Czech Republic

Abstract

Structural imaging findings in psychiatric disorders, including the mood disorders, have been inconsistent, with rare replications and frequent contradictory findings. The argument that is presented here is that it is ultimately the clinical variables which will allow us to clarify the seemingly confusing neuroimaging findings. This can be demonstrated in the example of hippocampal volumes in bipolar disorders (BPD). Whereas cumulatively, bipolar patients show preserved hippocampal volumes, when studies are subdivided, based on exposure to lithium (Li), BPD subjects not exposed to Li show smaller hippocampal volumes than controls, who have smaller hippocampal volumes than Li-treated participants. In addition, hippocampal volumes in BPD seem to be negatively associated with the illness burden (duration of illness, numbers of episodes) but only among participants with limited exposure to Li. This neuroprogressive nature of illness translates into increased risk of neurodegenerative disorders in patients with BPD, a risk that may be alleviated by Li treatment.

Key words: bipolar, neuroprotection, neurodegenerative, hippocampus

The structural findings in patients with psychiatric disorders, including mood disorders, have generally been inconsistent. They have rarely been replicated and there are frequently contradictory results. Clinical variables, such as duration of illness, numbers of episodes, family history, the presence of comorbid conditions, as well as exposure to medication may all impact neuroimaging findings, sometimes in opposing directions (1-3). Considering the number of factors affecting the brain structure in bipolar disorders (BPD), it is not difficult to find neuroimaging abnormalities in these patients. What is more difficult is the interpretation of the findings. Neuroanatomical changes in BPD may either represent inherited risk factors for the illness or emerge as secondary to the burden of illness (duration of illness, numbers of episodes), comorbid conditions or medication exposure. I will make the argument that it is ultimately the clinical variables, which will allow us to clarify the seemingly confusing neuroimaging findings. Conversely, more careful consideration of clinical heterogeneity in research design of imaging studies might make neuroimaging more relevant for everyday clinical practice of psychiatry. These issues can be demonstrated in the example of hippocampal volumes in BPD.

Smaller hippocampal volumes relative to controls are among the most replicated neuroimaging findings in patients with major depressive disorder (4). In contrast, eight previously published meta-analyses found preserved hippocampal volumes in patients with BPD (5-12). The cumulative absence of hippocampal volume abnormalities among BPD subjects is unexpected, considering the clinical overlap between unipolar and bipolar depression. There is no clinical or laboratory feature of unipolar depression, which would not also be reported in patients with bipolar disorders. In addition, depression in BPD is typically the main manifestation of the illness (13), is more likely to recur (14), and may start earlier (15) than unipolar depression.

Patients with unipolar and bipolar depression, however, differ broadly in terms of medication exposure. Although Li shows antidepressant properties even in unipolar depression (16), it is predominantly used as a mood stabilizer in bipolar disorders (17). Neuroprotective effects of lithium

have been well documented in tissue cultures and animal models (18;19), with some suggestion of similar effects also in human subjects (20-24). Could it be that hippocampal volume changes in BPD are masked by exposure to the putative neuroprotective effects of Li (18;19)?

To test this hypothesis we performed a meta-analysis of studies, which subdivided patients based on the presence or absence of Li treatment. BPD subjects who were currently not treated with Li had significantly smaller bilateral hippocampal volumes relative to healthy controls who, in turn, had significantly smaller hippocampal volumes than Li-treated BPD participants (25). These findings explain the negative results of previous meta-analyses, where the substantially larger hippocampal volumes in the Li-treated subjects could have masked the smaller hippocampal volumes in the non-Li subgroups. However, the interpretation of results as an effect of Li is difficult. It was unclear, in a number of included studies, whether or not the patients were compliant, or whether they were treated with a sufficient dose of Li for a sufficient duration of time. In addition, none of the included studies controlled for the illness burden (duration of illness, numbers of episodes). This is important as hippocampal volume decrease is associated with illness burden (26;27) and is unlikely to be present in the early stages of illness. Investigating the effects of Li on hippocampal volumes thus requires maximizing the burden of illness.

To address these limitations, we studied bipolar patients with high burden of illness (10 years of illness and at least 5 episodes) and either no current or chronic, ongoing, regularly-monitored Li treatment for at least 2 years. Among BPD participants selected for substantial illness burden, only those not treated with lithium had lower hippocampal volumes than controls. BPD patients with similar illness burden and ongoing Li treatment had hippocampal volumes comparable to controls. Since the Li and non-Li groups in our study did not differ in relevant clinical variables, patient-related factors were unlikely to underlie the results. It seems more likely that the observed differences were related to differential exposure to Li (28). In addition, our previous studies showed preserved hippocampal volumes in unaffected subjects at genetic risk for BPD (29) or in Li-naïve bipolar patients early in the course of illness (28;29), suggesting that hippocampal volume changes in BPD are not pre-existing but rather develop only later in the course of the illness (see Figure 1). These results provide an indirect support for negative effects of illness burden on hippocampal volumes in bipolar disorders and for neuroprotective effects of lithium.

The findings also raise a number of clinical questions. Does the putative neuroprogressive nature of BPD translate into increased rates of neurodegenerative disorders? Does Li alleviate this risk? Could it even be used to treat neurodegenerative disorders? Analyses of the Danish population databases showed increased rates of dementias in patients with mood disorders relative to general population or patients with other chronic conditions (diabetes, osteoarthritis) (30;31). Interestingly the risk of dementia further increased with numbers of episodes of mood disorders (32).

Two small, uncontrolled studies have looked at effects of Li on the risk for dementia. A study using general medical practice database suggested that a greater proportion of patients with the diagnosis of dementia were treated with Li relative to patients without the diagnosis of dementia (33). In this study prescription of Li could have been a marker for the presence of mood disorders, which increase the risk of dementias. This potential confounding factor would be better addressed by comparing mood disorders in patients with and without Li treatment. Such a study showed that Li-treated bipolar patients over 60 years of age had lower rates of dementia than bipolar patients not treated with Li, despite absence of differences between the groups in illness burden (34). An epidemiological study demonstrated that whereas patients with a single prescription of lithium had an elevated risk of dementias, repeated prescriptions of lithium brought the risk down to that of the general population level (35).

The above-mentioned studies are difficult to interpret as they do not control for patient-related or prescriber-related confounding factors. Physicians may be, for example, less likely to prescribe Li to patients showing cognitive impairment or such patients may be less likely to tolerate Li. This would artifactually decrease the rates of Li-treated patients with dementias. The best way to control these confounders and to demonstrate anti-dementia properties of Li would be to use a prospective,

randomized, blinded trial.

A single 10-week, multicentre, placebo-controlled, single-blind study of patients with mild Alzheimer disease (AD) reported no significant benefits of Li treatment on either cognitive performance or cerebrospinal fluid (CSF) concentrations of disease-related biomarkers (36). Interestingly, a single site analysis of data from this study did find increases of BDNF in Li-treated patients (37). The study was criticized, on the basis of the dosage and duration of treatment. Also the potency of any given medication to prevent AD and to treat a full-blown dementia would likely differ. Thus it may be preferable to test the effects of lithium in subjects who are at an increased risk for developing AD. Encouragingly, a single 12-month, double-blind, placebo-controlled trial in subjects with amnestic mild cognitive impairment showed slowing of cognitive decline, a significant decrease in CSF concentrations of phospho-tau, with a trend for decrease in beta amyloid (38).

To summarize, it seems that bipolar disorders negatively affect the structure of the brain. The neuroprogressive nature of illness translates into an increased risk of neurodegenerative disorders in patients with BPD, a risk that further increases with the numbers of episodes of mood dysregulation. Li-treated patients have mostly preserved brain structure, even in the presence of a marked burden of illness. These putative neuroprotective effects of Li seem to also alleviate the risk of neurodegenerative disorders on a population level, an effect that requires repeated prescriptions of Li. In contrast, controlled studies did not show persuasive effects of Li in treating patients with full-blown AD, although there are promising findings in subjects with mild cognitive impairment.

These findings also have broader implications. The notion that mood disorders have a neuroprogressive component and leave measurable "scars" in the brains of patients has marked consequences for our conceptualization and treatment of these conditions. Similarly, these results change our views about the pharmacodynamic properties of psychiatric medication. At least for lithium, it seems that the effects are not only about modulating the synaptic transmission/software of the brain, but rather about changing its very hardware or rather wetware.

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Figure 1: Effects of illness burden (duration of illness, numbers of episodes) and exposure to Li on hippocampal volumes. The yellow/orange cluster denotes a significant hippocampal volume decrease in non-Li relative to control participants (corrected $p < 0.05$). For details, please see reference (28).

GP Comment

What have I learned from this paper?

I have always conceptualised that the hippocampus stores the memories needed to co-ordinate an effective thinking response and is central to performance and wellbeing. Lithium also has an unequivocal antisuicidal effect (BMJ Editorial 2013 347: f 4449 by Ann Berghoffer). This paper helps me to re-evaluate the role of lithium in the treatment of BPD. Lithium has a valued role in the clinical treatment of BPD and is a first-line treatment where primary and secondary care need to work together, explaining the benefits, together with the need for careful monitoring and follow through. This paper helps me to explain the benefits.

Dr David Beales FRCP MRCGP DCH DRCOG Dip Psych, GP with a Special Interest in Behavioural Medicine, Ropley.

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