A Longitudinal Study of the Effects of Lithium Treatment on Prefrontal and Subgenual Prefrontal Gray Matter Volume in Treatment-Responsive Bipolar Disorder Patients

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Objective: Recent molecular, preclinical, and preliminary clinical studies suggest that the therapeutic effects of mood stabilizers may be mediated by modulating expression of potent neurotrophic and neuroprotective factors having the potential to reverse impairments of cellular resilience, reductions in brain volume, and cell death or atrophy. Our main goal was to investigate the potential clinical significance of these findings in relation to bipolar disorder.

Methods: The longitudinal effect of lithium on brain gray matter volume was investigated in well-characterized (DSM-IV criteria) bipolar depressed subjects (N = 28) at baseline (medication-free) and after lithium administration (4 weeks). Total brain gray matter, prefrontal gray matter, and left subgenual prefrontal gray matter volumes were determined using validated semiautomated segmentation and region of interest methodology. The study was conducted from November 1997 until April 2004 at Wayne State University School of Medicine, Detroit, Mich.

Results: Significant increases in total brain gray matter volume in bipolar subjects were observed after 4 weeks of lithium administration ($p = .0043$). Moreover, regional analyses in the bipolar subjects revealed significant differences between responders (> 50% decrease in Hamilton Depression Rating Scale total score) and nonresponders; only responders showed a significant increase in gray matter volume in the prefrontal cortex ($p = .003$) and an increase at trend level in the left subgenual prefrontal cortex volume ($p = .0786$).

Conclusions: The increase in gray matter volume in these areas, which various neuroimaging and postmortem neuropathology studies have implicated in the neuropathophysiology of bipolar disorder, suggests that the observed effects may be linked to clinical response. The findings also support the notion that future treatments that more directly target molecules in critical central nervous system pathways that regulate cellular plasticity hold promise as novel, improved, long-term treatments for mood disorders as well as some neurodegenerative conditions, such as Alzheimer's disease.

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Mood disorders have traditionally been conceptualized as neurochemical disorders, but there is now evidence from a variety of sources demonstrating regional reductions in central nervous system (CNS) volume,[1,2] as well as reductions in the numbers and/or sizes of glia and neurons in discrete brain areas.[3,4] Although the precise cellular mechanisms underlying these morphometric changes remain to be fully elucidated, the data suggest that severe mood disorders are associated with impairments of structural plasticity and cellular resilience.[5–8]

Lithium continues to be one of the mainstays in the treatment of bipolar disorder; it is effective not only in treating mania and depression but also in reducing the excessive mortality associated with this severe illness.[9–11] Lithium is also one of the most successful augmentations to antidepressant drugs in treatment-resistant unipolar depression.[12] Despite its role as one of psychiatry's most important treatments, the precise biochemical mechanisms associated with its therapeutic efficacy remain to be fully elucidated. It is noteworthy that recent preclinical studies

have demonstrated that lithium inhibits glycogen synthase kinase 3 (GSK-3), a major proapoptotic signaling molecule,[13–18] robustly increases the expression of the B-cell lymphoma/leukemia-2 gene (*bcl-2*), which encodes cytoprotective protein, in the CNS in vivo and in cells of human neuronal origin,[19,20] and exerts potent neurotrophic and neuroprotective effects in a variety of preclinical models.[4,18,20–22] Additionally, preliminary clinical studies by our laboratory have previously demonstrated a significant increase in total brain gray matter volume[23] as well as increased brain levels of the neurochemical N-acetylaspartate (NAA)—a putative marker of neuronal viability and function—after 4 weeks of lithium treatment in a small group of depressed bipolar patients.[24] This finding suggests that modulation of neurotrophic signaling cascades may be of relevance to humans.

In the current study, we describe a longitudinal investigation of a well-characterized, relatively large sample of medication-free subjects with bipolar disorder (N = 28). We observed the effects of 4 weeks of blinded lithium treatment on total brain gray matter volume utilizing high-resolution, morphometric magnetic resonance imaging (MRI). In addition, we investigated the potential clinical significance of these gray matter findings by correlating treatment responsiveness with changes in gray matter volume in the brain regions most consistently implicated in the neuropathophysiology of mood disorders.[1,2] Specifically, we performed selective subregional analyses of the morphometric MRI data, hypothesizing that the prefrontal cortex and subgenual prefrontal cortex would have a differential gray matter volume increase in those patients clinically responsive to lithium treatment when compared to nonresponders. We report increased total brain gray matter volume, as well as increased prefrontal cortex and subgenual prefrontal cortex gray matter volumes, in lithium responders. These results suggest that the observed lithium-induced increases in human brain gray matter volume have clinical relevance and occur within a time frame consistent with the known neurotrophic and neuroprotective effects of lithium via increased CNS expression of bcl-2 and GSK-3 inhibition. The findings may have implications not only for the treatment of mood disorders but also for certain neurodegenerative conditions.

METHOD

Subjects

Patients were recruited through advertisements in the local media and direct referral from physicians in the region. Adult patients who gave written informed consent, as approved by the Institutional Review Board at Wayne State University, were eligible for this study, which was conducted at the Department of Psychiatry and Behavioral Neurosciences, Wayne State University, Detroit, Mich., from November 1997 until April 2004. In addition, all eligible patients were required to meet *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[25] criteria for bipolar I disorder, most recent episode depressed or bipolar II disorder, depressed. The diagnosis was determined using the Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV).[26] Patients were excluded if they met diagnostic criteria for psychoactive substance abuse or dependence within 1 year preceding the index episode or for any other DSM-IV Axis I disorder during the $2^1/_2$ years preceding the index episode. Patients were also excluded from the study if they had any of the following medical conditions, which might have put them at greater risk for side effects from lithium: (1) renal disease; (2) hepatic disease; (3) hematologic disease; or from the MRI procedure: (1) a cardiac pacemaker; (2) brain surgery for an aneurysm; (3) recent major surgery; (4) the presence of ferromagnetic implanted devices, such as neurostimulators; or (5) metal fragments in or near the eye or brain.

The longitudinal effect of lithium on brain gray matter volume was investigated in a total of 28 patients, 10 of whom participated in our previous study,[24] who met the criteria outlined above (mean age = 33 years, SD = 11 years, range = 19–56 years; women, N = 13; men, N = 15). The addition of subjects in the present study was critical to achieve sufficient power to determine if the observed changes in gray matter volume in specific brain regions implicated in the neuropathophysiology of bipolar disorder were correlated with lithium-treatment responsiveness. Twenty-three of these patients had a diagnosis of bipolar I disorder (history of major depression plus mania) and 5 had a diagnosis of bipolar II disorder (history of major depression and hypomania, a milder form of mania). On admission to the inpatient research unit, all subjects were administered identical-appearing capsules 4 times per day. Subjects who were taking any psychotropic medications at time of admission to the research unit were tapered off these medications utilizing these identical-appearing capsules for a minimum 14-day drug washout period (depending on the half-life of the previous treatment medication). On completion of the washout period, the patients had their affective symptomatology reassessed with the Hamilton Rating Scale for Depression (HAM-D)[27] by trained blinded raters (intrarater reliability = 0.95). All patients were in the depressed or euthymic state after the washout period (HAM-D mean score = 17.6, SD = 8.3, range = 3–37). The patients then underwent a baseline MRI scan (see neuroimaging methods described below) prior to the initiation of lithium treatment. Lithium treatment was initiated and titrated in the form of identical-appearing capsules to obtain a target therapeutic plasma level (~0.8 meq/L) over the first week of treatment. Medication blinding was achieved given

that multiple research studies, investigating several different medications, including placebo, lithium, and others, were concurrent on the unit. All medications were individually prepared for each subject by the pharmacy in the form of identical-appearing capsules. The research subjects and the neuropsychiatric research unit staff, excluding the supervising physician, were blinded to the study medication. A quantitative morphometric MRI scan was utilized to measure brain gray and white matter volumes in the patients at baseline and after 4 weeks of blinded lithium administration.

MRI Protocol

The volumetric MRI studies were conducted on a 1.5-tesla Signa Horizon 5.7 scanner (GE Healthcare, Milwaukee, Wis.) utilizing a 3-dimensional spoiled gradient recalled echo pulse sequence (SPGR) that acquired 124 contiguous slices (1.5 mm thick) of anatomical data in the coronal plane (echo time = 5 ms, repetition time = 25 ms, acquisition matrix = 256 × 256, field of view = 24 cm, flip angle = 10°). Further details on the scanning protocol are described elsewhere.[24]

MRI Analysis

The MRI scans were first visually inspected for quality and evidence of magnetic field inhomogeneities and/or motion artifacts. Imaging data were transferred to a computer workstation where image formatting and quantitative volumetric measurements were made using standard, widely available image-processing software packages (MEDx [Medical Numerics, Inc., Germantown, Md.]; and National Institutes of Health (NIH) Image software [NIH, Bethesda, Md.]) utilizing a semiautomated segmentation algorithm for obtaining reliable quantitative neuroanatomic measurements of regional gray and white matter and cerebrospinal fluid (CSF) that we have described elsewhere.[24,28] Morphometric analyses were performed by a trained investigator blinded to both subject information and treatment status. Total brain volume (TBV), prefrontal cortex (PFC), and subgenual prefrontal cortex (SGPFC) volumes were measured. Intrarater reliabilities for the regions measured in this study ranged from 0.92 for the subgenual prefrontal cortex region to 0.98 for the measure of total brain gray matter volume, consistent with previously published studies.[29,30] All brain regions were traced manually in accordance with previously published neuroanatomical definitions of regional boundaries.[29,31] Standard neuroanatomical atlases were also used as a guide during the tracing procedures.[32] Brain regions were traced as follows:

Total Brain Volume

The entire brain, excluding cerebellum and brainstem, was traced on every other slice, numbering approximately 62. Gray and white matter volumes, excluding CSF in the ventricles and sulcal spaces, were calculated separately and then added for a measure of TBV.

Prefrontal Cortex Volume

Cortex was traced on successive slices beginning with 2 slices anterior to the most anterior slice that contained genu of the corpus callosum (posterior end of prefrontal cortex) and ending with the most anterior slice that contained gray matter (frontal pole). Gray and white matter volumes were calculated separately and then added for total PFC volume.

Subgenual Prefrontal Cortex

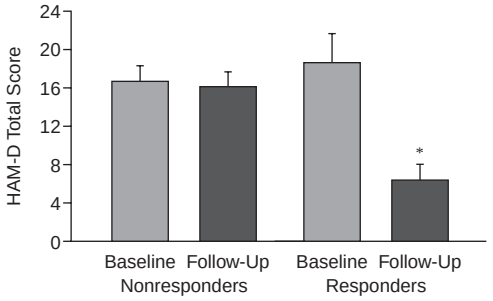
The region of interest for the SGPFC was defined as described in Botteron et al.[30] and Drevets et al.[29] Right and left SGPFC were defined as all gray matter in the first full gyrus inferior to the corpus callosum. The anterior boundary was defined by the first coronal plane, which intersects the anterior portion of the corpus callosum. The posterior boundary was defined as the last slice before the internal capsule is first visualized.

RESULTS

Four weeks of lithium treatment exerted an antidepressant effect in this population of well-characterized, medication-free, bipolar depressed patients (baseline HAM-D mean total score = 17.6, SD = 8.3, range = 3–37; follow-up HAM-D mean total score = 12.7, SD = 7.9, range = 0–36). A 1-tailed matched t test demonstrated that this decrease in HAM-D total score after lithium treatment was statistically significant (t = 3.005, df = 27, p = .003). The mean ± SD plasma lithium level for the entire group was in the therapeutic range (0.9 ± 0.2 meq/L; range = 0.5–1.4 meq/L). With a threshold for clinical response in these depressed bipolar subjects set at > 50% decrease in HAM-D total scores, a total of 11 subjects were categorized as lithium treatment responsive and the remaining 17 as nonresponders (Figure 1). Mean ± SD plasma lithium level for the responders and nonresponders (0.85 ± 0.16 meq/L, 0.88 ± 0.25 meq/L, respectively) was not significantly different (t = 0.364, df = 28; p = 72). These 2 groups also did not differ at baseline with respect to TBV or TBV gray matter. Additionally, the responders and nonresponders were similar with respect to age (responders = 29.7 ± 9.3 years, nonresponders = 34.5 ± 12.3 years; t = 1.1, df = 26, p = .28) and sex (responders; men = 6, women = 5;, nonresponders: men = 9, women = 8; $\chi^2 = 0.007$, p = .93) but did differ with respect to race (responders: African American = 4, white = 6, Hispanic = 1; nonresponders: African American = 2, white = 15; $\chi^2 = 4.04$, p = .04).

Longitudinal volumetric changes after lithium administration were first assessed using repeated-measures analysis of variance. Reported p values for the matched t tests are 1 tailed based on the large amount of preclinical

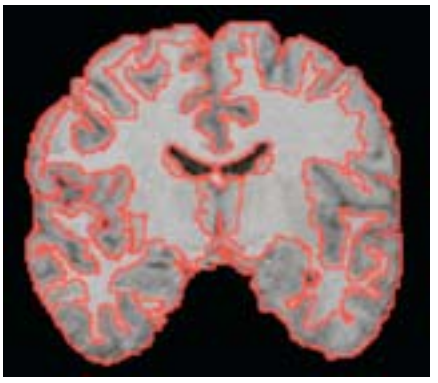
Figure 1. Comparison of Hamilton Rating Scale for Depression (HAM-D) Total Score at Baseline and After 4 Weeks of Lithium Treatment in Nonresponders and Responders to Lithium Treatment[a,b]



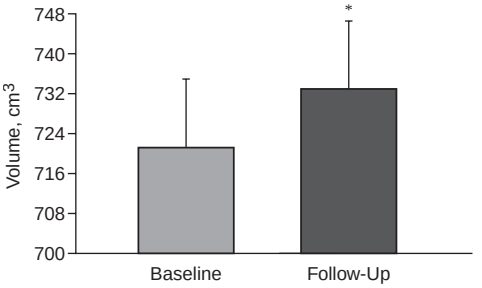
[a]Error bars represent ± SEM.
[b]Response was defined, according to convention, as a > 50% decrease in HAM-D total score. Higher score indicates greater depression.
*1-tailed t test, significant at $p < .05$.

Figure 2. Total Brain Volume

A. Slice From T1-Weighted Volumetric MRI Data Set Illustrating Segmentation of Total Brain Volume



B. The Total Brain Volume of Gray Matter at Baseline and After 4 Weeks of Lithium Treatment[a]



[a]Error bars represent ± SEM.
*1-tailed t test, significant at $p < .05$.
Abbreviation: MRI = magnetic resonance imaging.

evidence demonstrating the neurotrophic and neuroprotective effects of lithium,[4,18,20–22] in addition to several recent cross-sectional studies suggesting lithium-induced increases in gray matter volume in bipolar subjects.[33,34] One data point was excluded from the volumetric analyses because of MRI artifacts from dental braces and motion, so a total of 27 paired data sets were available for the analyses. Lithium treatment effects were first assessed for an overall effect on TBV gray and white matter (i.e., tissue type).

Although a main effect of lithium treatment on TBV was not found ($F = 2.03$, $df = 1,52$; $p = .16$), there was a lithium-treatment-by-tissue-type interaction ($F = 4.02$, $df = 1,52$; $p = .05$). Further analysis revealed a significant increase in TBV gray matter after 4 weeks of lithium treatment ($t = 2.838$, $df = 26$, $p = .0043$) (Figure 2), replicating the results of the previous preliminary study.[24] No significant change was observed in mean ± SD TBV white matter (baseline = 487.5 cm^3 [± 66.4 cm^3], follow-up = 487.7 cm^3 [± 71.8 cm^3]; $t = 0.364$, $df = 26$, $p = .72$). A total of 20 of 27 subjects had an increase (measurable positive change versus baseline volume) in TBV gray matter with 4 weeks of lithium treatment (9/10 in the lithium responsive group versus 11/17 in the treatment nonresponders).

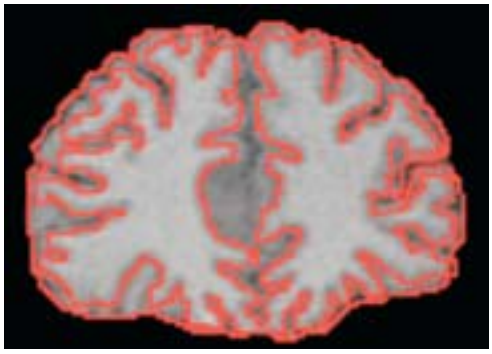
There was no relationship between lithium blood levels and anatomical change for the entire group (N = 27) or for the treatment responders alone (N = 10). Within the entire group, but not within the relatively small sample size of the responders alone, there was a trend for a correlation between clinical improvement (i.e., change in HAM-D total scores) and change in intracranial volume gray matter ($r = 0.35$, $F = 3.45$, $df = 26$, $p = .075$).

Because lithium had no perceived effect on TBV white matter, we focused subregional analyses exclusively on gray matter, assessing the entire bipolar group and also comparing responders and nonresponders (Figures 3 and 4). There was both a main effect of lithium treatment on PFC gray matter volume ($F = 4.79$, $df = 1,25$; $p = .04$) and a treatment-by-response interaction that reached a trend level of significance ($F = 3.57$, $df = 1,52$; $p = .07$). Specifically, the PFC gray matter volume was significantly increased after 4 weeks of lithium treatment ($t = 1.68$, $df = 26$, $p = .05$) in the overall patient group, whereas the responders showed a statistically significant increase in PFC gray matter volume ($t = 3.579$, $df = 9$, $p = .003$), and the nonresponders showed no change ($t = 0.217$; $df = 16$, $p = .415$).

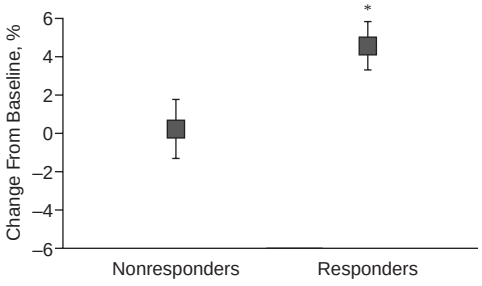
Effects of brain hemisphere, as well as treatment response, were examined for gray matter changes in the SGPFC. There were no main effects of brain hemisphere ($F = 0.64$, $df = 1,25$; $p = .43$) and treatment response ($F = 0.09$, $df = 1,25$; $p = .77$) or brain-hemisphere-by-response interaction ($F = 2.33$, $df = 1,25$; $p = .14$). Nevertheless, reduced PFC volume, especially left SGPFC volume, is a highly replicated finding in depressed patients with bipolar disorder or major depressive disorder.[29,30,35] On the basis of this evidence, a planned comparison of left SGPFC volume at baseline and follow-up was assessed in the lithium treatment responders. A 1-tailed paired t test

Figure 3. Prefrontal Cortex Gray Matter

A. Slice From T1-Weighted Volumetric MRI Data Set Illustrating Segmentation of Prefrontal Cortex Gray Matter



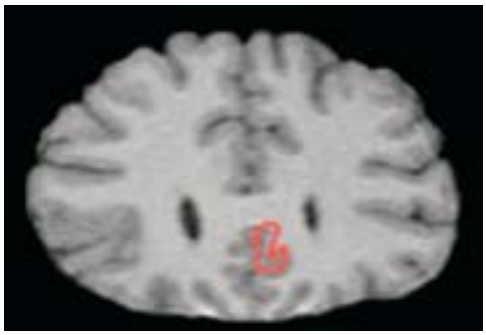
B. Comparison of Prefrontal Cortex Gray Matter Volume Increase in Treatment Nonresponders and Responders[a,b]



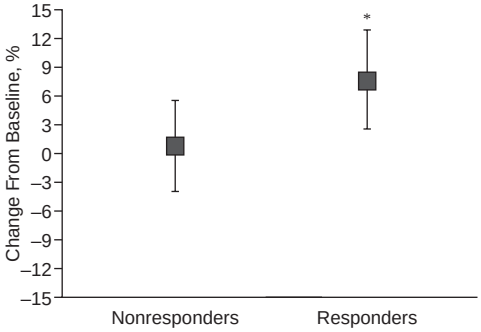
[a]Results are graphed as mean percentage change vs. baseline volume.
[b]Error bars represent ± SEM.
*1-tailed t test, significant at $p < .05$.
Abbreviation: MRI = magnetic resonance imaging.

Figure 4. Left Subgenual Prefrontal Cortex Gray Matter

A. Slice From T1-Weighted Volumetric MRI Data Set Illustrating Segmentation of the Left Subgenual Prefrontal Cortex Gray Matter



B. Comparison of Left Subgenual Prefrontal Cortex Gray Matter Volume Increase in Treatment Nonresponders and Responders[a,b]



[a]Results are graphed as mean percentage change vs. baseline volume.
[b]Error bars represent ± SEM.
*1-tailed t test, trend at $p < .079$.
Abbreviation: MRI = magnetic resonance imaging.

revealed an approximately 8% increase in the left SGPFC volume that was statistically at the level of a trend ($t = 1.530$, $df = 10$, $p = .0786$). There were no significant effects in any of the above correlations between clinical and brain volume measures when diagnostic (bipolar I vs. bipolar II), age, sex, or race variables were included in the analyses, a finding that is very likely reflective of our modest sample size.

DISCUSSION

A growing body of preclinical literature has found that lithium exerts neurotrophic/neuroprotective effects in vitro and in animal models. Thus, lithium has been found to protect neuronal cell cultures against a variety of insults, including excessive glutamate, amyloid-β protein, serum deprivation, colchicine, low potassium, and prion related protein, among many others (see Chuang et al.[21] and Manji et al.[36] for reviews). Supporting the notion that these cell culture observations have true physiologic relevance, lithium is neuroprotective in many animal models including ischemia, Huntington's disease, human immunodeficiency virus (HIV) glycoprotein 120 envelope protein injection (a model of HIV-associated dementia), and radiation (see Chuang et al.[21] and Manji et al.[36] for reviews). The functional and morphometric findings in mood disorders (including imaging studies and postmortem pathology studies) have been extensively reviewed elsewhere.[1–3,37]

In brief, the brains of patients with mood disorders show both macroscopic and microscopic changes that separate them from healthy individuals. Structural imaging studies report a decrease in the gray matter volume of multiple areas of the orbital, medial, and dorsolateral PFC, with the most prominent reduction reported in the left (but not right) SGPFC. An increase in ventricular size also has been consistently reported in patients with bipolar disorder.[1] Many studies also report a decrease in the size of other neuronal structures.[1,3] Functional imaging has also revealed multiple abnormalities of regional cerebral blood flow and glucose metabolism in the same

prefrontal cortical structures.[1,2] Recent postmortem studies using unbiased stereology techniques and additional improved technologies[38] have identified a number of changes, including a decreased size and/or density of neurons and decreased number and density of glial cells in regions of the anterior cingulate cortex, SGPFC, and dorsolateral PFC (see Rajkowska[3] for a complete review of these findings). Extensive literature also suggests that it is very likely that lithium may exert some, if not most, of its neuroprotective effects through increased expression of bcl-2 and inhibition of GSK-3 (see Jope and Bijur,[18] Chuang et al.,[21] and Manji et al.[36] for reviews). Thus, both neuroimaging and postmortem investigations suggest that the pathology of mood disorders may involve cell- and structure-based impairments in function and plasticity, consequences that perhaps could be modified by the neurotrophic effects of medications.[37]

The main limitations of the present study include small sample sizes and previous pharmacologic treatment of the participants. Although a minimum 14-day washout period was used in this study, prior treatment of the bipolar patients with mood stabilizers could reduce the sensitivity of the lithium-induced anatomical changes. Additional limitations include the lack of comparison therapy and the possibility that gray matter increases are epiphenomena of symptom reduction as opposed to lithium treatment. Symptom resolution, however, has been previously shown not to be associated with gray matter increases in studies of depression. For example, depressed patients who improved during antidepressant drug treatment (mean duration = 4 months) showed no change in the SGPFC volume between the pretreatment and posttreatment scans.[29]

A final limitation of the study, common to all of those using current morphometric MRI techniques, is that the noninvasive MRI measurement of gray matter volume utilizes the inherent tissue contrast properties to differentiate gray matter from surrounding CNS tissues (white matter and CSF). Thus, a lithium-induced osmotic shift of water could conceivably cause an apparent increase in brain volume (e.g., swelling). However, the longitudinal increases in brain volume observed in this study were limited to gray matter only, with no change observed in the white matter (see Results), making this possibility less likely. Furthermore, this lithium-induced increase was not shown in a group of healthy volunteers, who demonstrated less than a 0.5% change in TBV gray matter after 4 weeks of lithium administration (G.J.M., B.M.C., D.A.G., et al., unpublished data, 1997–2004).

Despite these limitations, however, our finding of an increase in prefrontal gray matter structures in clinical responders to mood stabilizer treatment is of particular interest. Specifically, the data from our longitudinal study suggest a regionally specific, pharmacologically induced increase in human gray matter but not white matter volume after 4 weeks of treatment with lithium in bipolar depressed patients who clinically respond to treatment. This observation provides the first direct in vivo human evidence that medications with neurotrophic effects are capable of increasing gray matter volumes in the adult human brain in regions implicated in the neuropathophysiology of bipolar disorder. The observed differential regional gray matter change between lithium responders and nonresponders is very likely governed by a complex process involving multiple factors, including environment, duration/severity of illness, and genes related to the intracellular signaling pathways that control neuronal plasticity and cellular resilience.[39]

These results are in agreement with those of preclinical studies suggesting that lithium-induced changes in gray matter volume most likely reflect an expansion of neuropil.[40] In addition, these observed changes occur on a time scale associated with increased bcl-2 expression and GSK-3 inhibition,[18,21] suggesting that these neurotrophic signaling cascades may be responsible for at least some of lithium's therapeutic effects. The findings also support the notion that future development of treatments that more directly target molecules in critical CNS pathways that regulate cellular plasticity and resilience hold promise as novel, improved long-term treatments for mood disorders and certain neurodegenerative conditions, including Alzheimer's disease.[15,16]

Drug name: lithium (Eskalith, Lithobid, and others).

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