Brain Structural Signature of Familial Predisposition for Bipolar Disorder: Replicable Evidence For Involvement of the Right Inferior Frontal Gyrus

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Abstract

Background—To translate our knowledge about neuroanatomy of bipolar disorder (BD) into a diagnostic tool, it is necessary to identify the neural signature of predisposition for BD and separate it from effects of long-standing illness and treatment. Thus, we examined the associations among genetic risk, illness burden, lithium treatment, and brain structure in BD.

Methods—This is a two-center, replication-design, structural magnetic resonance imaging study. First, we investigated neuroanatomic markers of familial predisposition by comparing 50 unaffected and 36 affected relatives of BD probands as well as 49 control subjects using modulated voxel-based morphometry. Second, we investigated effects of long-standing illness and treatment on the identified markers in 19 young participants early in the course of BD, 29 subjects with substantial burden of long-lasting BD and either minimal lifetime ($n = 12$), or long-term ongoing ($n = 17$) lithium treatment.

Results—Five groups, including the unaffected and affected relatives of BD probands from each center as well as participants early in the course of BD showed larger right inferior frontal gyrus (rIFG) volumes than control subjects (corrected $p < .001$). The rIFG volume correlated negatively with illness duration (corrected $p < .01$) and, relative to the controls, was smaller among BD individuals with long-term illness burden and minimal lifetime lithium exposure (corrected $p < .001$). Li-treated subjects had normal rIFG volumes despite substantial illness burden.

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Conclusions—Brain structural changes in BD may result from interplay between illness burden and compensatory processes, which may be enhanced by lithium treatment. The rIFG volume could aid in identification of subjects at risk for BD even before any behavioral manifestations.

Keywords

Bipolar disorder; genetic risk; illness burden; inferior frontal gyrus; neuroimaging; lithium

Bipolar disorder (BD) is a severe, often chronic mental illness that ranks among the leading causes of disability worldwide (1). The diagnosis of BD is based on a description of behavioral manifestations. Despite the strong genetic underpinning of BD (2), no generally accepted biological markers of the illness have been identified. These issues contribute to the fact that in a third of the patient population, the correct diagnosis is made over 10 years after the onset of first symptoms, and 40% to 70% of patients with BD are misdiagnosed (3,4). In addition, although family history is the strongest risk factor for BD, most offspring of BD parents will not develop the illness (5). Thus, there is a great need to better understand the pathophysiology of BD and to translate this knowledge into a more refined and earlier diagnosis. Neuroimaging provides an excellent system-level tool for the study of biological processes underlying psychiatric disorders in general and BD in particular.

Whereas strong evidence supports the presence of structural variations in the brains of BD patients, the interpretation of these findings is difficult (6,7). Neuroanatomic abnormalities reported in BD patients may represent inherited risk factors or may emerge as secondary to the burden of illness, comorbid conditions, or medication exposure (6–8). Distinguishing between the neurobiological causes and consequences of the illness is necessary for heuristic and clinical reasons. Whereas the biological risk factors could aid in early diagnosis, the changes secondary to BD may be useful outcome measures for interventions.

One of the best ways to identify biological risk factors for BD is to study individuals at genetic risk for the illness, a so-called high-risk (HR) design. By focusing on unaffected relatives of BD patients, the HR design controls for the effects of burden of illness or medication. Previous neuroimaging HR studies in BD have been negative (9–16) or inconsistent with regard to the location and direction of findings (17–23). The heterogeneity of the results may be related to methodologic differences between the studies.

One important source of heterogeneity in the HR studies is the age of recruited individuals. The onset of BD typically falls into adolescence and early adulthood (24,25). This timing may be related to the continuing structural maturation of the brain during the transition period between childhood and adulthood (26). Using the HR design in individuals passing through the at-risk age range is a particularly powerful approach for studying the neurobiological underpinnings of BD. However, previous exploratory HR studies have investigated either children (22) or adults past the average age of illness onset (20,21,23).

In this series of cross-sectional studies, we first researched neuroanatomic markers of familial predisposition for BD by studying adolescent/young adult individuals with a genetic risk for the illness. Second, we explored the effects of long-standing illness and treatment on the identified markers in BD participants with substantial illness burden and varied exposure

to lithium (Li). We used modulated voxel-based morphometry (VBM) analyses to study gray matter (GM) in the cortical regions.

Methods and Materials

We report on two related studies. Study 1 was a two-center genetic HR design study aimed at identifying biological risk factors for BD. We recruited offspring from families of well-characterized adult probands with BD and divided them on the basis of the presence or absence of personal history of mood disorders. Including both affected and unaffected offspring is necessary to establish the presence of neurobiological changes in families and their association with the illness. We performed VBM of GM and considered only changes replicated in both centers as true positives (replication design). We further checked for association of these changes with BD in an unrelated sample of young BD participants. In Study 2, we recruited subjects with substantial illness burden (duration of illness, numbers of episodes) and either limited lifetime or long-term ongoing Li treatment, to explore the effects of illness burden and Li treatment on brain regions identified in Study 1. Interviews in all participants from both studies were done by psychiatrists according to Schedule for Affective Disorders and Schizophrenia—Lifetime version (SADS-L) (27) or Schedule for Affective Disorders and Schizophrenia for School-Age Children (KSADS-PL) (28) in participants under 18 years of age. Diagnoses were made based on DSM-IV, as well as Research Diagnostic Criteria.

Study 1

To isolate biological risk factors for BD, we recruited offspring from families of well-characterized adult BD probands in two centers: Halifax, Canada, and Prague, Czech Republic. The unaffected offspring of BD parents represent a heterogeneous group that contains individuals who are resilient, those who did not inherit a significant degree of the genetic liability, and those who will become ill in the future. The average genetic liability among unaffected offspring of BD probands decreases with age as those with higher liability become affected. Therefore, it is important to include individuals around the typical age of onset, who remain at a substantial risk of future conversion to BD (24,25). Thus, the inclusion criterion for all groups in both centers was age between 15 and 30 years. Common exclusion criteria for all groups in both centers were personal history of 1) any serious medical or neurologic disorders, 2) substance abuse/dependence during the previous 6 months, or 3) magnetic resonance imaging (MRI) exclusion criteria. In addition to these, controls from both centers were excluded if they had any personal or family history of DSM-IV Axis I psychiatric disorders.

High-Risk Offspring—Families were identified through adult probands with BD, who had participated in 1) previous genetic and high-risk studies (29,30) for the Halifax sample and 2) the Czech Bipolar Disorder Case Registry (31) for the Prague sample. Only the offspring from these families, not the probands, were a part of the MRI study. The offspring from BD parents were divided into two subgroups: 1) the Unaffected HR group, which consisted of 50 offspring with no lifetime history of psychiatric disorders. These individuals were at an increased risk for BD because they had one parent affected with a primary mood

disorder. 2) The Affected Familial group, which consisted of 36 offspring who met criteria for a lifetime Axis I diagnosis of mood disorders (i.e., a personal history of at least one episode of depression, hypomania, or mania meeting full DSM-IV criteria). When available, we recruited more than one offspring per family.

Young BD Participants—To check whether any of the changes identified among the offspring would generalize to an unrelated clinical sample of BD participants early in the course of illness, we also recruited 19 subjects with personal history of BD and age between 15 and 30 years from the patient databases at the Prague Psychiatric Center. None of these Young BD subjects was related to any other study participant or had any first-degree relative with BD.

Control Subjects—Forty-nine healthy control subjects were recruited by word of mouth in Halifax and by an advertisement in Prague. They were interviewed by a psychiatrist and determined to be free of personal or family history of psychiatric illness.

Study 2

To investigate the effects of illness burden and Li treatment on neural correlates of disposition to BD identified in Study 1, we recruited 3 groups of unrelated participants: 1) BD patients with long-term ongoing Li exposure and a substantial illness burden (Li group), 2) BD patients with minimal or no lifetime Li exposure and a substantial illness burden (non-Li group), and 3) age- and sex-matched control subjects with no personal or family history of psychiatric disorders.

All patients had regular follow-ups at a specialized mood disorders program at Dalhousie University, Halifax, Canada, including monitoring of Li levels at least twice per year. The prospective monitoring prevented subtherapeutic Li levels, which could be insufficient to elicit GM volume changes, or supratherapeutic Li levels, which could be neurotoxic. We also recruited control subjects among hospital employees and matched them to the BD patients by age and sex. Control subjects were interviewed by a psychiatrist and determined to be free of personal or family history of psychiatric illness.

Inclusion Criteria—The BD patients (both Li and Non-Li groups) were required to have 1) diagnosis of BD I or II disorder made by a psychiatrist, 2) at least 10 years of illness since the first mania or depression meeting full DSM-IV criteria, 3) at least 5 episodes of illness (including manic, depressive, or mixed episodes); 4) current Hamilton Depression Rating Scale (17-item version) less than 7, 5) current Young Mania Rating Scale less than 5, and 6) euthymia for at least 4 months.

The Li group had to have a current Li treatment lasting a minimum of 24 months. The Non-Li group had to have less than 3 months of lifetime Li treatment and no Li exposure within 2 years prior to scanning.

Exclusion Criteria—The participants from any of the three groups were excluded if they met any of the MRI exclusion criteria or had any serious medical or neurologic illness. Patients with BD (both Li and Non-Li groups) were excluded for any of the following

reasons: 1) more than one lifetime course of electroconvulsive therapy (ECT) or ECT in the previous 12 months, 2) active substance abuse in the previous 12 months, 3) lifetime history of other comorbid psychiatric disorders, 4) personality disorders, 5) changes in psychiatric medication in the previous 3 months, or 6) current psychotic features or acute suicidality. The healthy control subjects were excluded if they had a personal or family history of psychiatric disorders.

After receiving a complete description of the study, written informed consent was obtained from every individual. The studies were approved by the Research Ethics Boards of the Izaak Walton Killam (IWK) Health Center and the Capital District Health Authority, Halifax, Nova Scotia and by the Prague Psychiatric Center Institutional Review Board.

MRI Procedures Common to Both Studies

MRI Acquisition Parameters—The participants were scanned at two sites, Halifax and Prague. All magnetic resonance acquisitions were performed with a 1.5-Tesla General Electric Signa scanner and a standard single-channel head coil located at the IWK Health Centre, Halifax, Canada and the Military University Hospital Prague, Czech Republic. We acquired T1-weighted spoiled gradient recalled scans: flip angle = 40°, echo time = 5 msec, repetition time = 25 msec, field of view = 24 cm × 18 cm, matrix = 256 × 160 pixels, number of excitations = 1, no interslice gap, 124 coronal 1.5-mm thick slices.

Voxel-Based Morphometry—The data were processed with the SPM8 software (<http://www.fil.ion.ucl.ac.uk/spm>). We used VBM implemented in the VBM8 toolbox (<http://dbm.neuro.uni-jena.de/vbm.html>) with default parameters, following methods previously published (32) and used by members of our group (21). The images were bias-corrected, tissue classified, and registered using linear (12-parameter affine) and nonlinear transformations (warping), within a unified model (33). The resulting images were visually inspected for quality by expert raters blinded to group assignment, guided by boxplots and covariance matrices from the VBM8 toolbox. There were no excessive motion artifacts in the data. Subsequently, the analyses were performed on GM and white matter (WM) masks, which were multiplied by the nonlinear components derived from the normalization matrix to locally preserve the actual GM and WM values (so-called modulated volumes). In effect, an analysis of the modulated data tests for regional differences in the absolute amount (volume) of GM or WM, corrected for individual brain size (34). Finally, the modulated volumes were smoothed with a Gaussian kernel of 8-mm full width at half maximum.

Statistical Analyses

When comparing the clinical and demographic variables, we used a one-way analysis of variance or a t test for continuous and χ^2 test for categorical variables.

Because we had uniformly acquired data from two independent sites and because replication is the best test of true versus false-positive findings, we decided to use the replication design. To ascertain the pairwise pattern and direction of changes between HR offspring and control subjects, we used independent sample t tests in SPM8. We first performed exploratory whole-brain analyses in the Halifax sample (Unaffected HR vs. Control groups, Affected

Familial vs. Control groups) to generate hypotheses, which we then tested for replication in the Prague sample (Unaffected HR vs. Control groups, Affected Familial vs. Control groups). We tested for an overlap between the group differences using anatomic labels, combined masks, and signed differential mapping (SDM, <http://sdmproject.com/>; see Supplement 1). Abnormal GM volumes, particularly those found among both the Unaffected HR and Affected Familial participants could indicate a biological risk factor. Larger GM volumes or changes specifically found among Unaffected HR but not Affected Familial subjects could be considered resilience factors.

We applied a nominal statistical threshold of $p < .001$ with an extent threshold of 10 voxels. The nominal p values in the Prague study were corrected for the number of specific hypotheses tested (replication corrected p).

Subsequently, we tested whether any of the replicated abnormalities identified in the earlier-mentioned comparisons would also be found in the Young BD participants, the Li, or Non-Li groups relative to the Control groups. We used age as a nuisance variable in all analyses. We calculated the effect size (Cohen's d) for differences between the groups from cluster maxima.

To test the relationship between the duration of illness, age, and GM volume, we fitted simple regression models in SPM8. For these post hoc analyses, we applied a threshold of $p < .05$ corrected for multiple comparisons using the family-wise error (FWE) rate with an extent threshold of 10 voxels.

Results

Description of the Participants

For Study 1, we recruited 50 Unaffected HR (30 in Halifax, 20 in Prague), 36 Affected Familial (21 in Halifax, 15 in Prague), 19 Young BD (all in Prague), and 49 Control (31 in Halifax, 18 in Prague) participants. At each center, the groups were comparable in age, sex, handedness, and global brain volumes, with the exception of the Young BD participants, who were older than the respective Controls (Tables 1, 2).

For Study 2, we recruited 17 Li, 12 Non-Li, and 11 Control individuals. The three groups were comparable in age, sex, and brain volumes (Table 3). Both patient groups (i.e., Li and Non-Li) had a substantial and comparable burden of illness (Table 3).

VBM Results

Analysis of the Halifax sample showed significant differences between Unaffected HR and Control subjects in 10 regions and between Affected Familial and Control subjects in 6 regions (Table S1 in Supplement 1). Among these, only the larger GM volume in the right inferior frontal gyrus (rIFG) was replicated in both the Unaffected HR and the Affected Familial individuals from the Prague cohort (probability of spatial overlap in all four contrasts $SDM = .86$, $p = .0000001$, replication corrected $p < .00006$, Table 4, Table S2 in Supplement 1, and Figures 1 and 2).

The larger rIFG volume relative to the Controls was also replicated among the Young BD subjects, who were early in the course of their illness (replication corrected $p < .001$). In a combined group of Young BD subjects and Affected Familial participants, the rIFG volumes were negatively associated with the duration of illness (FWE corrected $p = .01$), but not with age. In keeping with this negative association, the patients with long-term illness burden and minimal Li exposure (Non-Li group) showed smaller rIFG volumes than the Controls (replication corrected $p < .001$). Li-treated patients with comparable illness burden showed no rIFG differences (increases or decreases) relative to the Controls, even when we relaxed the threshold to $p = .01$ (Table 4, Figure 2). Whereas the rIFG volumes negatively correlated with the duration of illness among BD subjects with no current and limited lifetime history of Li treatment (FWE corrected $p < .01$), there was no such association among the Li-treated BD subjects (Figure 3, Table 4).

The group differences in GM mentioned earlier were mostly constrained to the rIFG (Brodmann area 47), with a small contribution from the right middle frontal gyrus (Brodmann area 10). In addition, the clusters of differences between the groups directly overlapped within each acquisition site and were closely adjacent between the sites (Table 4, Figure 1). See Supplement 1 for additional exploratory analyses.

Discussion

We present replicated evidence for dynamic structural changes of rIFG in the course of BD. The larger rIFG met criteria for biological risk factor of BD, because it was present among both the Unaffected HR and Affected Familial subjects from both centers and was associated with the early stages of illness in an unrelated clinical sample of Young BD participants. Interestingly, the same region was negatively correlated with the duration of illness. As a result, patients with BD who had a substantial burden of illness and minimal lifetime exposure to Li showed smaller rIFG volumes than the control subjects. Perhaps neuroanatomic markers of vulnerability for BD are dynamically affected by illness-related variables. The negative association of rIFG with illness burden was not manifested in Li-treated BD patients, who had comparable rIFG volumes to the controls despite their substantial illness burden. Thus, Li treatment might prevent or correct these brain structural changes.

This is the first study to demonstrate a larger rIFG in individuals at genetic risk for BD. Our findings are consistent with previous reports in which BD subjects at the early stages of illness demonstrated larger rIFG volumes (35) and BD participants with a greater illness burden had smaller rIFG volumes (21,36–39) than control subjects. Several previous studies have also noted a negative association between the measures of illness burden and rIFG volumes among BD patients (21,37,38,40). Other brain regions, such as the amygdala, also show structural changes during the course of BD (7,41), albeit in the opposite direction to those of rIFG.

Larger regional brain volumes are usually considered to be a resilience marker (22), a consequence of delayed maturation (42), a preapoptotic edema (35), or an effect of medication (43). Medications did not play a role in our HR sample because the largest

differences were found in the unaffected, medication-naïve individuals, and most of the Affected Familial participants were not medicated. The larger rIFG volume does not seem to be a marker of resilience because the rIFG volumes were also larger among affected subjects. In addition, resilience could be more likely among unaffected offspring of BD parents who are past the average age of illness onset. We included Unaffected HR participants around the typical age of onset, who remain at a substantial risk of future conversion to BD (24,25). Delayed maturation is possible but would be difficult to infer from cross-sectional data (44,45). In addition, the IFG volumes did not show a significant decline with age in previous studies of healthy adolescents (45) or in our data set. Our previous proton magnetic resonance spectroscopy study from a partially overlapping sample showed comparable metabolite concentrations in a closely adjacent region among HR and control subjects (46), which argues against an underlying preapoptotic edema.

Alternatively, rIFG volumes in BD might be determined by the interplay between two opposing processes: a putative toxic process followed by a reactive increase in neurotrophic mechanisms. There is evidence for structural plasticity of rIFG in response to capsulotomy (47) or medication exposure (48–50). Initially, the up-regulation of neurotrophic mechanisms may overcompensate and yield increased rIFG volumes, as was found among the Unaffected HR and affected subjects at the early stages of the illness. As the disease progresses, the compensatory mechanisms may become exhausted, resulting in GM loss, as demonstrated by the negative association of rIFG volumes with illness burden and the decreased rIFG volumes among the subjects selected for a substantial illness burden. Interestingly, Li seems to act in the same direction as the putative compensatory mechanisms. This is in keeping with potential neuroprotective/neurotrophic effects of Li (43,51–53).

Our findings were mostly constrained to the rIFG. Two other hypotheses might be congruent with this anatomic selectivity. There is evidence for functional reorganization of rIFG following damage to the left hemisphere (54–57). In addition, activity-dependent selective changes in gray matter have been demonstrated even in human adults (58). We can speculate that BD patients need to “overexercise” the rIFG to compensate for some cognitive or executive deficits or to maintain euthymia (the functional plasticity hypothesis). The increased functional demands on this region may render it more vulnerable to structural damage associated with illness burden. The rIFG is involved in a number of tasks potentially relevant to BD, including response inhibition, task set switching, blocking of memory retrieval (59), sustained attention (60), and possibly even empathy (61). Interestingly, previous studies have suggested that an impaired response inhibition is the most likely candidate for a neurocognitive endophenotype for BD (62–64). However, contrary to the functional plasticity hypothesis, both children and adults with BD showed deficits in their ability to engage the right inferior frontal cortex during a variety of tasks (65–67).

Alternatively, perhaps the increased rIFG volume compensates for structural damage in the interconnected GM nodes or in the WM connections of the IFG. Interestingly, BD patients exhibit microstructural changes within the uncinate fasciculus, which links the temporal lobe with the IFG (68–70). There is also replicated evidence in BD for volumetric decreases

within GM connections of the IFG, including the amygdala (7), the hippocampus (71), and the anterior cingulate (6).

This study has several limitations. A prospective design would have allowed us to track the trajectories of rIFG volume changes over time. Some of the Affected Familial participants suffered from unipolar depression. Depression is typically the first manifestation of an illness in patients who later develop BD (30,72), and approximately 70% of the depressed first-degree relatives of BD probands in fact suffer from BD (73). If we want to study the early manifestations of BD, inclusion of these likely pseudo-unipolar subjects with a family history of BD is inevitable. As in previous studies, we included individuals who had a personal or family history of bipolar II disorders (30,74). Similar to participants with BD I, these individuals had a low prevalence of comorbid conditions and an episodic course of illness. Family studies using similarly narrow diagnoses generally found BD II to be a part of the same genetic spectrum as BD I (75). Furthermore, neuroimaging studies have generally shown a lack of differences between patients with BD I and BD II (76–81). In some cases, more than one individual per family was recruited. Because of presumably lower variance within a family, this might lead to false-positive findings. However, when we repeated the analyses with only a single subject per family, the results remained essentially unchanged (see Supplement 1). Additionally, we also found abnormal rIFG volumes in two other groups of unrelated patients. Not all offspring of bipolar parents inherit the biological susceptibility and the penetrance of genetic predisposition, and any related brain structural changes into the behavioral phenotype is incomplete. Thus, not all of the Unaffected HR subjects are in a prodromal stage of the illness. At present, we do not know whether larger rIFG predicts conversion to BD, but we started following our sample to prospectively validate the prognostic value of abnormal rIFG.

The current study provides several key benefits over prior investigations. With 194 uniformly assessed participants, this is one of the largest neuroimaging investigations in BD. The study was specifically designed to investigate biological risk factors as well as the effects of illness burden and medication exposure on GM volumes. To this end, we used strict inclusion and exclusion criteria to ensure homogeneity within the groups and a large separation between the groups in relevant variables affecting brain structure. To our knowledge, this is the first study of subjects with a genetic risk for BD who were transitioning through the period of the highest risk for developing BD (adolescence/young adulthood). This approach maximizes the chances of identifying biological risk factors. Additionally, it is the only neuroimaging study to use the replication design. The replication of our findings in five groups of subjects from two independent centers provides a strong control against false-positive results.

In summary, we provide replicated evidence that larger rIFG may represent a neuroanatomic signature of familial predisposition for BD. The study also illustrates how brain structural changes in BD may result from a dynamic interplay between illness burden and compensatory processes, which may be enhanced by pharmacologic treatment. Measuring the rIFG volume could aid in early identification of subjects at risk for BD even before any behavioral manifestations and could serve as an outcome measure for treatment of BD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Clusters of larger right inferior frontal gyrus (rIFG) volumes in the Halifax and Prague samples. Orange, larger rIFG among the Affected Familial relative to Control subjects; red, larger rIFG among the Unaffected subjects at genetic risk for bipolar disorder relative to Controls; yellow, overlapping rIFG increases between the Affected Familial and Unaffected subjects at genetic risk for bipolar disorder.

Figure 2.

Effect size, 95% confidence interval for differences in the right inferior frontal gyrus (rIFG) volumes between the clinical groups and control participants. HR, high risk; Li, lithium.

Figure 3.

Association between the duration of illness and the right inferior frontal gyrus volumes (rIFG) among the lithium-treated subjects and participants with no current and limited lifetime exposure to lithium.

Table 1

Description of the Halifax Sample (Study 1)

Halifax	Unaffected HR Participants	Affected Familial Participants	Control Participants	<i>p</i> Value
<i>N</i>	30	21	31	NA
Sex, <i>n</i> (%) Female	20 (66.7)	15 (71.4)	20 (64.5)	ns
Age, Mean (SD)—Years	19.5 (3.1)	21.0 (3.6)	20.6 (3.3)	ns
Age Range—Years	15.0–25.6	15.1–30.4	15.8–30.2	NA
Related to Another Study Participant, ^a <i>n</i> (%)	24 (80.0)	16 (76.2)	13 (41.9)	.004
Diagnosis	NA	13 MD, 3 BD I, 2 BD NOS, ^b 3 BD II	NA	NA
Comorbid Conditions	NA	1 ADO, 1 bulimia, 1 ADHD	NA	NA
Treatment at the Time of Scanning, <i>n</i> (%)	NA	6 (28.6)	NA	NA
Medication Type at the Time of Scanning	NA	AC = 1, AD = 2, AP = 1, Li = 2	NA	NA
Illness Duration—Years, Mean (SD)	NA	4.22 (2.14)	NA	NA
No. of Episodes, Mean (SD)	NA	2.3 (2.3)	NA	NA
No. of Hospitalizations, Mean (SD)	NA	.05 (.22)	NA	NA
GM Volume—cm ³ , Mean (SD)	668.5 (69.9)	653.0 (59.4)	633.6 (64.0)	ns
Total Brain Volume—cm ³ , Mean (SD)	1417.7 (160.4)	1399.1 (122.4)	1374.7 (115.9)	ns

AC, anticonvulsants; AD, antidepressants; ADHD, attention-deficit/hyperactivity disorder; ADO, anxiety disorder; AP, antipsychotics; BD, bipolar disorder; GM, gray matter; HR, high risk; Li, lithium; MD, major depression; NA, not applicable; NOS, not otherwise specified; ns, nonsignificant.

^aSiblings in all cases.

^bBoth BD NOS participants met criteria for major depressive episodes and had subsyndromal hypomanic symptoms.

Description of the Prague Sample (Study 1)

Table 2

Prague	Unaffected HR Participants	Affected Familial Participants	Control Participants	Young BD Participants	p Value ^d	p Value ^b
N	20	15	18	19	NA	NA
Sex, n (%) Female	11 (55.0)	11 (73.3)	11 (61.1)	12 (63.2)	ns	ns
Age, Mean (SD)—Years	20.2 (4.2)	22.1 (4.8)	23.0 (3.5)	26.5 (3.4)	ns	.004
Age Range—Years	15.0–30.0	15.0–30.0	16.0–29.0	17.0–30.0	NA	NA
Related to Another Study Participant, ^c n (%)	4 (20)	2 (13.3)	2 (11.1)	0 (0)	ns	ns
Diagnosis	NA	6 MD, 5 BD I, 4 BD II	NA	16 BD I, 3 BD II	NA	NA
Comorbid Conditions	NA	3 ADO, 3 SA ^d	NA	3 ADO, 1 SA ^c	NA	NA
Treatment at the Time of Scanning, n (%)	NA	11 (73.3)	NA	18 (94.7)	NA	NA
Medication Type at the Time of Scanning	NA	AC = 3, AD = 5, AP = 6, Li = 1	NA	AC = 8, AD = 2, AP = 11, Li = 8	NA	NA
Illness Duration—Years, Mean (SD)	NA	3.2 (3.5)	NA	6.3 (4.0)	NA	NA
No. of Episodes, Mean (SD)	NA	2.8 (3.0)	NA	4.8 (3.4)	NA	NA
No. of Hospitalizations, Mean (SD)	NA	1.8 (1.7)	NA	2.3 (2.0)	NA	NA
GM Volume—cm ³ , Mean (SD)	645.9 (83.0)	620.8 (65.6)	622.7 (75.6)	615.6 (61.1)	ns	ns
Total Brain Volume—cm ³ , Mean (SD)	1403.3 (165.7)	1376.2 (141.9)	1396.8 (197.4)	1388.4 (115.6)	ns	ns

AC, anticonvulsants; AD, antidepressants; ADO, anxiety disorder; AP, antipsychotics; BD, bipolar disorder; GM, gray matter; HR, high risk; Li, lithium; MD, major depression; NA, not applicable; ns, nonsignificant; SA, substance abuse.

^a p value for Unaffected HR, Affected Familial, Control participants.

^b p value for Young BD, Control participants.

^c Siblings in all cases.

^d In remission for at least 1 year.

Table 3

Description of the Subjects in the Halifax Lithium Study (Study 2)

Halifax Lithium Study	Non-Li Participants	Li-Treated Participants	Control Participants	<i>p</i> Value ^a
<i>N</i>	12	17	11	NA
Sex, Females— <i>n</i> (%)	6 (50)	12 (70.6)	8 (72.7)	ns
Age, Mean (SD) Years	45.6 (8.9)	47.8 (10.1)	46.0 (8.6)	ns
Bipolar I/Bipolar II Disorder, <i>n</i> (%)	9 (75.0)/3 (25)	11 (64.7)/6 (35.3)	NA	ns
Duration of Follow-Up, Mean (SD)—Years	4.4 (4.3)	6.7 (2.8)	NA	ns
Years Since Diagnosis of Depression, Mean (SD)	25.3 (8.9)	26.3 (8.9)	NA	ns
Lifetime Episodes of Depression, <i>n</i> (%)	8.3 (5.8)	7.1 (5.0)	NA	ns
Cumulative Duration of Depressions, Mean (SD)—Months	21.0 (11.9)	19.6 (15.5)	NA	ns
Years Since Diagnosis of Mania, Mean (SD)	20.9 (11.4)	19.9 (7.3)	NA	ns
Lifetime Episodes of Mania, <i>n</i> (%)	2.3 (1.4)	3.9 (3.3)	NA	ns
Cumulative Duration of Manias, Mean (SD)—Months	6.2 (8.0)	7.8 (6.6)	NA	ns
Total Duration of Illness, Mean (SD)—Years	25.6 (9.8)	27.1 (8.2)	NA	ns
YMRS Total, Mean (SD)	1.1 (1.4)	1.1 (1.4)	NA	ns
HAMD-17 Total, Mean (SD)	2.6 (2.9)	2.3 (1.6)	NA	ns
Clinical Course Chronic, <i>n</i> (%)	2 (16.7)	4 (23.5)	NA	ns
Li-Naive Participants, <i>n</i> (%)	10 (83.3) ^b	NA	NA	NA
Li Duration at the Time of Scanning, Mean (SD)—Years	NA	10.6 (6.3)	NA	NA
Li Level at the Time of Scanning, Mean (SD) mmol/L	NA	.73 (.16)	NA	NA
Anticonvulsants at the Time of Scanning, <i>n</i> (%)	9 (75.0)	4 (23.5)	NA	.006
Anticonvulsant Duration at the Time of Scanning, Mean (SD)—Years	7.1 (4.2)	8.3 (6.2)	NA	ns
Antidepressants at the Time of Scanning, <i>n</i> (%)	6 (50.0)	7 (41.2)	NA	ns
Antidepressant Duration at the Time of Scanning, Mean (SD)—Years	7.2 (6.0)	4.8 (6.3)	NA	ns
Antipsychotics at the Time of Scanning, <i>n</i> (%)	4 (33.3)	2 (11.8)	NA	ns
Antipsychotics Duration at the Time of Scanning, Mean (SD)—Years	7.0 (1.5)	4.3 (1.3)	NA	ns
Family History of Mood Disorders Among First-Degree Relatives, <i>n</i> (%)	2 (16.7)	6 (35.3)	NA	ns
GM Volume, Mean (SD)—cm ³	580.7 (63.8)	590.4 (54.6)	573.0 (53.1)	ns
Total Brain Volume, Mean (SD) cm ³	1380.7 (164.5)	1369.2 (133.4)	1331.7 (129.0)	ns

GM, gray matter; HAMD-17, Hamilton Depression Rating Scale; Li, lithium; NA, not applicable; ns, nonsignificant; YMRS, Young Mania Rating Scale.

^a Analysis of variance for age, *t* test for continuous and χ^2 test for categorical variables.

^b Two patients had a brief exposure to Li 9 and 13 years before scanning.

Results of the Voxel-Based Morphometry Analyses

Table 4

Individual Contrasts	Direction of Finding	Coordinates of the Maximum Difference (x, y, z)	No. of Voxels in Cluster	t	p	Cluster Composition—Gyri
Halifax Affected Familial vs. Control Participants (contrast 1)	↑	48, 34, −3	119	4.26	<.001	rIFG 62 voxels, rMFG 57 voxels
Halifax Unaffected HR vs. Control Participants (contrast 2)	↑	48, 36, −5	247	4.41	<.001	rIFG 60 voxels, rMFG 178
Prague Affected Familial vs. Control Participants (contrast 3)	↑	45, 27, −11	18	3.81	<.01 (RC)	All rIFG
Prague Unaffected HR vs. Control Participants (contrast 4)	↑	44, 27, −11	23	3.83	<.006 (RC) ^a	All rIFG
Prague Young BD vs. Control Participants (contrast 5)	↑	42, 30, −11	173	4.17	<.001 (RC)	rIFG 141 voxels, rMFG 32 voxels
Non-Li Group vs. Control Participants (contrast 6)	↓	45, 56, 4	142	−4.71	<.001 (RC)	rIFG 75 voxels, rMFG 67 voxels
Li group vs. Control Participants (contrast 7)	No difference	NA	NA	NA	ns	NA
Association Between Duration Of Illness, but not Age and GM Volumes (Affected Familial Participants in Prague, Halifax, Young BD Participants)	Negative association	50, 38, −3	10	5.37	<.01 (FWE C)	rIFG 2, rMFG 8
Association Between Duration Of Illness and GM Volumes Among Subjects With No Current, Limited Lifetime History of Li Treatment	Negative association	51, 30, −15	119	5.85	<.01 (FWE C)	rIFG 119
Association Between Duration Of Illness and GM Volumes Among Li Treated Subjects	No association	NA	NA	NA	ns	NA
Overlaps	Direction of Finding	Range of Coordinates for Overlaps (x, y, z)	No. Overlapping Voxels	Cluster Composition—gyri		
Overlap Unaffected HR and Affected Familial Subjects, Halifax (Contrasts 1 and 2)	↑	42; 52.5, 31.5; 37.5, −1.5; −7.5	66	rIFG 37 voxels, rMFG 28 voxels, GM not localized 1 voxel		
Overlap Unaffected HR and Affected Familial Subjects, Prague (Contrasts 3 and 4)	↑	42; 46.5, 25.5; 28.5, −9; −12	14	All rIFG		
Overlap Unaffected HR and Affected Familial and Young BD participants, Prague (Contrasts 3, 4, 5)	↑	42; 45, 25.5; 28.5, −9; −12	14	All rIFG		
Overlap Affected Familial and Non-Li group, Halifax (Contrasts 1 and 6)	↑/↓	45; 46.5, 52.5; 54, 0, −3	9	rIFG 3 voxels, rMFG 6 voxels		
BD, bipolar disorder; FWE C, family-wise error rate corrected; GM, gray matter; HR, high risk; Li, lithium; NA, not applicable; ns, nonsignificant; RC, replication corrected; rIFG, right inferior frontal gyrus; rMFG, right middle frontal gyrus.						

BD, bipolar disorder; FWE C, family-wise error rate corrected; GM, gray matter; HR, high risk; Li, lithium; NA, not applicable; ns, nonsignificant; RC, replication corrected; rIFG, right inferior frontal gyrus; rMFG, right middle frontal gyrus.

^aThe probability of replication of the Halifax findings in both the Unaffected HR and Affected Familial Participants in the Prague sample was $p < .00006$.