ARCHIVAL REPORT

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

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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.

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.

Key Words: 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

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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