Subgenual cingulate volumes in affected and unaffected offspring of bipolar parents

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Abstract

Background—Bipolar disorders (BD) have a strong genetic underpinning, yet no biological vulnerability markers for BD have been identified. Decreased volumes of subgenual cingulate (SGC) were replicated in familial bipolar patients. Presence of abnormality in unaffected subjects at genetic risk for an illness needs to be established before SGC volumes can be used as an endophenotype. This is the first study of SGC volumes in affected and unaffected subjects at familial risk for mood disorders.

Method—High-risk participants were recruited from families multiply affected with BD. The high-risk sample included 13 affected and 13 unaffected offspring of bipolar I parents, who were matched by age and sex with 31 controls without a personal or family history of psychiatric disorders. The expanded sample consisted of 24 unaffected, 19 affected subjects all with a first or second degree relative suffering from BD I or II. The age range for all subjects was 15–30 years. Subgenual cingulate volumes were measured on 1.5 T 3D anatomical MRI images using standard methods.

Results—We found comparable SGC volumes among unaffected, affected offspring of BD I parents and controls. Likewise no SGC abnormalities were found in the expanded sample of subjects with BD I or II relatives. Left SGC volumes in all groups were smaller than right SGC volumes without laterality by group interaction. The exclusion of 5 medicated subjects did not change the results.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

Limitations—Cross sectional design, inclusion of both bipolar I and bipolar II probands.

Conclusions—Subgenual cingulate volume abnormalities were absent in unaffected or affected relatives of bipolar patients and thus did not meet criteria for endophenotype.

Keywords

Bipolar disorders; MRI; Subgenual cingulate; High-risk

1. Introduction

Bipolar disorders are severe, highly recurrent, frequently chronic psychiatric conditions with marked genetic underpinning. No generally accepted biological markers of the vulnerability towards the illness have yet been identified. This hinders the diagnosis and leads in part to the fact that in a third of the patient population the correct diagnosis of the illness is done 10 and more years after the onset of first symptoms. Furthermore between 40% and 69% of patients with bipolar disorders are misdiagnosed (Hirschfeld et al., 2003; Ghaemi et al., 1999), which has detrimental effects on the course and outcome of illness. There is thus a great need for better biological diagnostic measures allowing for more precise and earlier diagnosis of bipolar disorders.

Neuroanatomical abnormalities could be potential candidates for biological markers or endophenotypes in bipolar disorders. Converging lines of evidence suggest that the ventromedial prefrontal cortex and anterior cingulate are implicated in mood regulation and pathophysiology of mood disorders (Hajek et al., 2005). Co-segregation of illness with a biological abnormality in families is one characteristic of endophenotype. Interestingly, a majority of studies in familial patients (Brambilla et al., 2002; Sharma et al., 2003; Hirayasu et al., 1999; Drevets et al., 1997; Sanches et al., 2005) and none of the studies in sporadic patients with mood disorders (Hirayasu et al., 1999; Brambilla et al., 2002; Sharma et al., 2003) reported significant subgenual cingulate (SGC) volume decrements in patients compared to controls. Furthermore SGC volumetric abnormalities have been observed already in first-episode familial patients (Hirayasu et al., 1999). In order for a particular biological change to be considered an endophenotype, presence among unaffected subjects at genetic risk for developing an illness needs to be demonstrated (Gottesman and Gould, 2003). No studies so far have assessed SGC volumes in unaffected relatives of bipolar patients, using a high-risk design.

We present the first study of SGC volumes in affected and unaffected subjects at familial risk for mood disorders. We expected smaller SGC volumes in both affected and unaffected high-risk subjects relative to controls.

2. Methods

2.1. Subjects

2.1.1. Families—The HR offspring were recruited from families with multiple members affected with BD according to methods described elsewhere (Duffy et al., 2002). Briefly, suitable families were identified through adult probands with bipolar I or II disorder who

had participated in genetic studies and had been recruited from outpatient clinics at the Queen Elizabeth II Health Centre in Halifax. Each affected parent completed a SADS-L interview (Endicott and Spitzer, 1978) conducted by two research psychiatrists blind to the identity of the person. Final DSM-IV diagnoses were decided using all available clinical materials in a blind consensus fashion by an independent panel of senior clinical researchers. In order to control for clinical heterogeneity, primary analyses were done only in offspring of parents with a diagnosis of bipolar I disorder. Similar to previous studies (Duffy et al., 2002; Todd et al., 1996), we also expanded the sample by including subjects with family history of bipolar I disorders in second degree relatives or bipolar II disorders in first or second degree relatives. Bipolar II subjects were similar in their clinical presentation to the bipolar I participants in that they experienced a low prevalence of comorbid conditions and an episodic course of illness. Bipolar II probands differed from bipolar I participants only in severity of mania. Family studies using similarly narrow diagnoses generally found bipolar II to be a part of the same genetic spectrum as bipolar I (Gershon et al., 1982).

2.1.2. High-risk offspring—Depending on their age, the offspring were interviewed by a child/adolescent or adult psychiatrist using the KSADS-PL (Kaufman et al., 1997) or SADS-L format. Diagnoses were made based on DSM-IV, as well as Research Diagnostic Criteria in a blind consensus review, which included at least two additional research psychiatrists. As part of the high-risk study, offspring are re-assessed annually or at any time symptoms develop. The HR unaffected group was comprised of 24 offspring with no lifetime history of psychiatric disorder. High-risk affected subjects consisted of 19 offspring who met criteria for a lifetime diagnosis of mood disorder or in one case psychosis NOS, which may be considered an antecedent of BD. All HR affected subjects were in remission at the time of scanning, as determined by clinical interview and functioning at school or work. Exclusion criteria included: 1. history of closed head injury resulting in loss of consciousness; 2. untreated active medical illness (e.g., diabetes); 3. identified learning disability or diagnosis of ADHD; 4. substance-related disorder within the past 6 months; 5. lifetime history of substance dependence; 6. history of neurological disease.

2.1.3. Offspring of well parents (controls)—Controls consisted of 31 healthy offspring of well parents recruited from similar sociodemographic areas as the patients, who were interviewed by a child/adolescent or adult psychiatrist in accordance with the KSADS-PL or SADS-L format and deemed to be well upon blind consensus review. The control subjects were selected to closely match HR subjects by age and sex. Exclusion criteria were the same as in the HR groups with the addition of a personal or family history of psychiatric disorders.

Prior to conducting the assessments, all interviewers underwent extensive training consisting of participation in interviews, interviews under supervision, and blind consensus diagnostic reviews.

After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the Research Ethics Boards of IWK Health Center and Capital District Health Authority, Halifax, Nova Scotia.

2.2. MRI methods

2.2.1. MRI acquisition parameters—All MR acquisitions were performed with a 1.5 Tesla General Electric Signa scanner and a standard single-channel head coil. After a localizer scan, a T1-weighted SPGR (spoiled gradient) scan was prescribed with the following parameters: flip angle = 40°, TE = 5 ms, TR = 25 ms, FOV = 24 cm × 18 cm, matrix = 256 × 160 pixels, NEX=1, no inter-slice gap, 124 images 1.5 mm thick.

2.2.2. MRI volumetry—Anatomical measurements were conducted using the AFNI software for Linux (Cox, 1996), in a single batch, according to a well-established procedure (Drevets et al., 1997). Prior to volumetric measurements, all scans were reoriented perpendicular to the bicomissural line. Subsequently the gray matter of the first full gyrus beneath the corpus callosum was manually traced in all coronal slices between the anterior most point of the corpus callosum and the anterior most plane where the internal capsule no longer divided the striatum. In addition we used the sagittal plane to check for accuracy of the superior inferior landmarks and the axial plane to better delineate the left from the right subgenual cingulate. Segmentation was performed by one investigator (EG) blinded to the diagnosis and group assignment of subjects. Subsequently all scans were checked for consistency of landmarks and tracing by a second rater (TH) also blinded to the diagnosis and group assignment of subjects. The intra-class correlation coefficients established by tracing 10 scans by two independent raters (EG, TH) were $r=0.95$ for both the right and left SGC (inter-rater reliability). Intra-class correlation coefficient for 10 randomly selected SGCs of the study subjects measured twice by the same rater (EG) was $r=0.99$ and $r=0.98$ for the left and right SGC respectively (intra-rater reliability). Average difference between the two measurements of the same scan by the same rater was $-9.9 \pm 24.32 \text{ mm}^3$ for the left and $-2.24 \pm 18.18 \text{ mm}^3$ for the right SGC.

Tissue type segmentation was performed automatically using 3dAnhist command in AFNI software (Cox, 1996). This command uses cut-off values to separate tissue types, CSF and vasculature appearing in black, gray matter, and white matter. The volumes of each tissue type were calculated according to the criteria previously published (Gispert et al., 2004).

3. Statistical analyses

All statistical analyses were done using the BMDP statistical software. We performed repeated measures analyses of variance (ANOVAs) with subgenual cingulate volumes as the dependent variable, laterality as the repeated measure and status (affected, unaffected, control subjects) and sex as the grouping variables. To compare intracranial and gray matter volumes between affected, unaffected high-risk subjects and controls, we used one-way analysis of variance. Categorical demographic variables (sex, handedness) were compared using the Pearson χ^2 test. To look for association between age and subgenual cingulate volumes and to compare equality of regression lines across groups, we used least square linear regression, (module 1R in BMDP statistical software). We report nominal, two tailed p values.

We carried out a power analysis for one-way ANOVA with 3 groups and an average of 23 subjects (71/3) in each group.

4. Results

4.1. Demographics

We recruited 13 unaffected, 13 affected offspring of bipolar I parents and 31 controls. The expanded sample consisted of subjects with family history of bipolar I disorders in second degree relatives ($N=4$ unaffected, $N=1$ affected), subjects with bipolar II disorders in first ($N=7$ unaffected, $N=3$ affected) or second degree relatives ($N=1$ affected). The overall sample thus consisted of 24 unaffected familial, 19 affected familial and 31 controls. For details see Table 1.

4.2. Subgenual cingulate volumes in offspring of bipolar I parents

There were no differences in the proportion of women, age, ICV, GM between the 13 affected, 13 unaffected offspring of bipolar I parents and 31 controls. There was a trend for more left handed subjects in the unaffected offspring group ($\chi^2=5.97$, $DF=2$, $p=0.05$). The volumes of subgenual cingulate were comparable among groups ($F=1.05$, $DF=2$; 54, $p=0.36$), (see Table 1). The left subgenual cingulate in all groups was significantly smaller than the right SGC ($F=7.09$, $DF=1$; 54, $p=0.01$), however with no significant laterality by status interaction. There were no differences in SGC volumes between male and female subjects nor was there any sex by group interaction.

4.3. Subgenual cingulate volumes in expanded sample

There were no differences in proportion of women, age, laterality, ICV, GM between the 19 affected, 24 unaffected offspring of bipolar I parents and 31 controls. The volumes of subgenual cingulate were comparable among groups ($F=1.52$, $DF=2$; 71, $p=0.22$), (see Table 1). The left subgenual cingulate in all groups was significantly smaller than the right SGC ($F=8.23$, $DF=1$, 71, $p=0.005$), however with no significant laterality by status interaction. There were no differences in SGC volumes between male and female subjects nor was there any sex by group interaction.

4.4. Exploratory analyses

There were no differences between subjects from families containing bipolar I vs. families containing only bipolar II subjects, neither was there any family type by laterality interaction. There were no differences between left and right handed subjects in SGC volumes, neither was there a group by handedness interaction.

There was no association between gray matter and SGC volumes. There was a significant positive association between ICV and left subgenual cingulate volumes ($F_{Ratio}=9.18$, $DF=1$; 71 $p=0.003$). Covarying for intracranial volume did not change the results. There was no correlation between age and left or right subgenual cingulate volume for any of the groups. Excluding 5 medicated subjects did not change the results. Likewise the results remained similar after exclusion of 1 subject with psychosis NOS.

With 74 subjects in 3 groups, we have 86% power to detect effect size of 0.5.

5. Discussion

We found comparable volumes of subgenual cingulate among the affected, unaffected at risk subjects and controls. With the total of 74 scanned subjects, this is the second largest study of SGC volumes in mood disorders. The largest and also negative investigation looked at 83 subjects with bipolar and unipolar disorders (Brambilla et al., 2002). With 74 subjects in 3 groups, we have 86% power to detect effect size of 0.5, which is sufficient as previous positive studies showed effect sizes between 0.8 and 1.3. Expanding the sample would be unlikely to change these results, as there was not even a trend for difference and the SGC volume distributions in the three groups markedly overlapped. It is thus unlikely that our results were false negative.

The comparable SGC volumes among affected, unaffected high-risk subjects and healthy controls are contrary to our a priori hypothesis. Since no other high-risk MRI studies of subgenual cingulate volumes exist, we can only make indirect comparisons with volumetric MRI studies of patients with mood disorders. Previous investigations have shown smaller SGC volumes in some (Sharma et al., 2003; Hirayasu et al., 1999; Drevets et al., 1997), but not all (Brambilla et al., 2002; Sanches et al., 2005), studies of familial mood disorders patients, whereas none of the three studies in patients without family history of mood disorders found significant differences between the groups (Hirayasu et al., 1999; Brambilla et al., 2002; Sharma et al., 2003). There are however also positive as well as negative studies lacking information about family history (Botteron et al., 2002; Hastings et al., 2004; Coryell et al., 2005; Bremner et al., 2002; Zimmerman et al., 2006). Differences in methods, clinical or demographic factors could underlie the inconsistent findings.

Two of the previously reported positive studies did not provide information about blinding of raters for MRI volumetry of subgenual cingulate (Sharma et al., 2003; Hastings et al., 2004). Manual tracing of region of interest requires subjective input. Blinding is thus crucial, to prevent experimenter bias. Both volumetrists in our study were completely blinded to subject status. Furthermore, unlike in other studies, all tracings were double checked by a second rater. Some of the positive studies failed to provide information about inter-rater reliability (Sharma et al., 2003) or showed low reliability for SGC tracing ($r=0.6-0.7$ as opposed to $r=0.95$ in our study) (Hastings et al., 2004). In terms of clinical assessments we directly interviewed all affected parents, as well as multiple other family members. All diagnoses were established in a blind consensus fashion by an independent panel of senior clinical researchers. Furthermore the high-risk subjects are followed up prospectively. No other study of subgenual cingulate used such rigorous clinical assessments.

Our affected group, which consisted of outpatients, was similar to familial subjects from studies by Soares and colleagues (Brambilla et al., 2002; Sanches et al., 2005), which also found comparable SGC volumes between patients and controls. It is contrary to a positive study in currently hospitalized bipolar I subjects (Hirayasu et al., 1999). The differences between studies cannot however readily be attributed to the severity of illness, as there is also one positive study in never hospitalized outpatients (Botteron et al., 2002) and one negative study in currently hospitalized patients (Zimmerman et al., 2006). Medication status appears unlikely to play a role, as significant changes in SGC volumes between

patients and controls were previously found in unmedicated as well as medicated subjects. Both medicated and unmedicated patients were also present in previous negative studies.

Other clinical sources of heterogeneity between studies include the diagnosis of subjects and criteria for family history. This is the only study using high-risk design, that is recruiting subjects primarily based on their family history. Our affected offspring group thus consisted of 7 subjects with bipolar disorders, 10 patients with previous episodes of unipolar depression, one subject with dysthymia and 1 subject with psychosis NOS, all recruited from families with multiple members affected with bipolar disorders. Exclusion of subject with psychosis NOS did not change the results. Furthermore smaller subgenual cingulate volumes have been found both in unipolar and bipolar subjects, with similar findings in unipolar and bipolar subjects in both studies allowing for direct comparison between these diagnostic categories (Drevets et al., 1997; Brambilla et al., 2002). Diagnostic status of subjects was thus unlikely to confound the findings.

Previous studies used various criteria for family history. The most restrictive definition, similar to our primary group, was used by Sharma et al. (2003), who recruited only patients with first-degree relatives suffering from bipolar I disorder. Their study, with the above mentioned methodological limitations, revealed right subgenual cingulate abnormalities which have not been replicated in any other study. Drevets et al. (1997) in their positive study included patients with family history of bipolar disorder in first-degree relatives, without specifying whether these had been bipolar I or bipolar II patients. This is similar to our expanded sample. Two negative studies recruited subjects with family history of either unipolar or bipolar disorders (Sanches et al., 2005; Brambilla et al., 2002). This is contrary to our methods, where all subjects had multiple relatives affected with bipolar disorders. The least restrictive definition was used in a positive study by Hirayasu et al. (1999), who recruited subjects with family history of both unipolar and bipolar disorders in up to third degree relatives. Overall there does not seem to be a pattern of preferential transmission of subgenual cingulate abnormalities in particular type of families. Our definition of family history in the primary group (subjects with bipolar I parents) is the most restrictive and should achieve the most homogeneous sample. It is thus unlikely that our findings were confounded by heterogeneous genetic liabilities.

With regards to demographic factors, sex distribution and age might be potential sources of heterogeneity. Two previous, partly overlapping positive studies were done only in familial female patients with unipolar depression (Botteron et al., 2002; Drevets et al., 1997). Another study however found abnormalities only in men, but not in women (Hastings et al., 2004), while a single study found a trend for reduced right SGC in females, but increased right SGC volumes in males (Sharma et al., 2003). We recruited both men and women, which is similar to other positive as well as negative studies. The mean age in our affected population was 19.8 years. The only other study in familial subjects, with mean age of affected group of less than 20 years was also negative (Sanches et al., 2005). Our findings in affected subjects are contrary to another study, which reported SGC abnormalities already in first-episode familial subjects slightly older than our group—mean age 23.7 years (Hirayasu et al., 1999). It is possible that SGC abnormalities are unmasked by putative neurodevelopmental changes happening only in the mid twenties. Indeed maturation and

pruning of frontal cortical regions extends into early twenties (Gogtay et al., 2004). However in keeping with other studies (Botteron et al., 2002) we did not find any correlation between age and SGC volumes.

Absence of subgenual cingulate abnormalities among unaffected relatives of bipolar patients suggests that smaller subgenual cingulate is not a primary biological vulnerability marker for bipolar disorders. The fact that no SGC abnormalities were found even in already affected relatives of bipolar patients at the early stages of the illness further supports this claim. There is a growing body of evidence showing, that some of the volumetric abnormalities in mood disorders, such as hippocampal atrophy, are in fact secondary to burden of the illness (MacQueen et al., 2003; Sheline et al., 1999). Indeed the previous findings of reduced subgenual cingulate volumes in affected subjects with family history of mood disorders come mostly from studies in older subjects (Drevets et al., 1997; Hirayasu et al., 1999; Sharma et al., 2003) and subjects with longer history of mood disorders (Drevets et al., 1997; Sharma et al., 2003). Subgenual cingulate volume reduction thus might represent sequelae of the illness. This hypothesis is not supported by evidence for smaller subgenual cingulate volumes already in the first-episode subjects (Hirayasu et al., 1999). On the other hand no study has yet evaluated subgenual cingulate volumes prospectively in different stages of bipolar or unipolar disorders.

There are several limitations of this study, including the cross sectional design. A prospective design would better allow us to capture changes in neuroanatomy related to neurodevelopment or burden of illness. Some of the affected subjects suffered from unipolar depression. Depression is most typically the first manifestation of an illness even in patients, who later develop BD (Hillegers et al., 2005; Duffy et al., 2002), and about 70% of depressed first-degree relatives of bipolar probands are in fact bipolar (Blacker and Tsuang, 1993). If we want to study the early manifestations of bipolar disorders, inclusion of unipolar subjects with the family history of bipolar disorders is thus warranted and necessary. There was a trend for lower proportion of right handed subjects in the unaffected offspring of bipolar I subjects. This difference was unlikely to bias results as no group by handedness interaction was observed. Furthermore, there were no differences in laterality in the expanded sample. In some cases more than one subject per family was recruited. Typically, this would produce bias towards false positive rather than false negative results due to spuriously lower variance estimates. Since none of the findings were positive, we did not control for this.

In summary, this study found no evidence for subgenual cingulate volume changes in either affected or unaffected offspring of bipolar I parents or in affected or unaffected relatives of bipolar I or bipolar II subjects. Subgenual cingulate volumes in this study thus did not meet criteria for an endophenotype. The fact that subgenual cingulate volumes are spared early in the course of mood disorders is optimistic from a clinical point of view, as the previously reported SGC abnormalities may not represent vulnerability traits, but rather may be related to burden of illness and as such might be potentially preventable.

Acknowledgments

Role of funding source

Supported by the NARSAD Young Investigator Award to Dr. Hajek, grants from the Department of Psychiatry, Dalhousie University, Capital District Health Authority, and from the Canadian Institutes of Health Research. None of these agencies had any further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

References

- Blacker D, Tsuang MT. Unipolar relatives of bipolar pedigrees: are they bipolar? *Psychol Gen*. 1993;5–16.
- Botteron KN, Raichle ME, Drevets WC, Heath AC, Todd RD. Volumetric reduction in left subgenual prefrontal cortex in early onset depression. *Biol Psychiatry*. 2002; 51:342–344. [PubMed: 11958786]
- Brambilla P, Nicoletti MA, Harenski K, Sassi RB, Mallinger AG, Frank E, et al. Anatomical MRI study of subgenual prefrontal cortex in bipolar and unipolar subjects. *Neuropsychopharmacology*. 2002; 27:792–799. [PubMed: 12431853]
- Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, et al. Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry*. 2002; 51:273–279. [PubMed: 11958777]
- Coryell W, Nopoulos P, Drevets W, Wilson T, Andreasen NC. Subgenual prefrontal cortex volumes in major depressive disorder and schizophrenia: diagnostic specificity and prognostic implications. *Am J Psychiatry*. 2005; 162:1706–1712. [PubMed: 16135631]
- Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res*. 1996; 29:162–173. [PubMed: 8812068]
- Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. *Nature*. 1997; 386:824–827. [PubMed: 9126739]
- Duffy A, Alda M, Kutcher S, Cavazzoni P, Robertson C, Grof E, et al. A prospective study of the offspring of bipolar parents responsive and nonresponsive to lithium treatment. *J Clin Psychiatry*. 2002; 63:1171–1178. [PubMed: 12523878]
- Endicott J, Spitzer RL. A diagnostic interview: the schedule for affective disorders and schizophrenia. *Arch Gen Psychiatry*. 1978; 35:837–844. [PubMed: 678037]
- Gershon ES, Hamovit J, Guroff JJ, Dibble E, Leckman JF, Sceery W, et al. A family study of schizoaffective, bipolar I, bipolar II, unipolar, and normal control probands. *Arch Gen Psychiatry*. 1982; 39:1157–1167. [PubMed: 7125846]
- Ghaemi SN, Sachs GS, Chiou AM, Pandurangi AK, Goodwin K. Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? *J Affect Disord*. 1999; 52:135–144. [PubMed: 10357026]
- Gispert JD, Reig S, Pascau J, Vaquero JJ, Garcia-Barreno P, Desco M. Method for bias field correction of brain T1-weighted magnetic resonance images minimizing segmentation error. *Hum Brain Mapp*. 2004; 22:133–144. [PubMed: 15108301]
- Gogtay N, Giedd JN, Lusk L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A*. 2004; 101:8174–8179. [PubMed: 15148381]
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160:636–645. [PubMed: 12668349]
- Hajek T, Carrey N, Alda M. Neuroanatomical abnormalities as risk factors for bipolar disorder. *Bipolar Disord*. 2005; 7:393–403. [PubMed: 16176432]
- Hastings RS, Parsey RV, Oquendo MA, Arango V, Mann JJ. Volumetric analysis of the prefrontal cortex, amygdala, and hippocampus in major depression. *Neuropsychopharmacology*. 2004; 29:952–959. [PubMed: 14997169]
- Hillegers MH, Reichart CG, Wals M, Verhulst FC, Ormel J, Nolen WA. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. *Bipolar Disord*. 2005; 7:344–350. [PubMed: 16026487]

- Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wible CG, Fischer IA, et al. Subgenual cingulate cortex volume in first-episode psychosis. *Am J Psychiatry*. 1999; 156:1091–1093. [PubMed: 10401458]
- Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the National Depressive and Manic-depressive Association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry*. 2003; 64:161–174. [PubMed: 12633125]
- Kaufman J, Birmaher B, Brent D, Rao U, Flynn C, Moreci P, et al. Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psych*. 1997; 36:980–988.
- MacQueen GM, Campbell S, McEwen BS, Macdonald K, Amano S, Joffe RT, et al. Course of illness, hippocampal function, and hippocampal volume in major depression. *Proc Natl Acad Sci U S A*. 2003; 100:1387–1392. [PubMed: 12552118]
- Sanches M, Sassi RB, Axelson D, Nicoletti M, Brambilla P, Hatch JP, et al. Subgenual prefrontal cortex of child and adolescent bipolar patients: a morphometric magnetic resonance imaging study. *Psychiatry Res*. 2005; 138:43–49. [PubMed: 15708300]
- Sharma V, Menon R, Carr TJ, Densmore M, Mazmanian D, Williamson PC. An MRI study of subgenual prefrontal cortex in patients with familial and non-familial bipolar I disorder. *J Affect Disord*. 2003; 77:167–171. [PubMed: 14607394]
- Sheline YI, Sanghavi M, Mintun MA, Gado MH. Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci*. 1999; 19:5034–5043. [PubMed: 10366636]
- Todd RD, Reich W, Petti TA, Joshi P, DePaulo JR Jr, Nurnberger J Jr, et al. Psychiatric diagnoses in the child and adolescent members of extended families identified through adult bipolar affective disorder probands. *J Am Acad Child Adolesc Psych*. 1996; 35:664–671.
- Zimmerman ME, DelBello MP, Getz GE, Shear PK, Strakowski SM. Anterior cingulate subregion volumes and executive function in bipolar disorder. *Bipolar Disord*. 2006; 8:281–288. [PubMed: 16696831]

Table 1

Demographics and subgenual cingulate volumes for offspring of bipolar I subjects and for the expanded sample of subjects with first or second degree relatives with bipolar disorders

	Primary group of subjects with bipolar I parents		Expanded group of subjects with family history of bipolar disorders in first or second degree relatives		Control	<i>p</i> (unaffected vs. affected vs. control subjects) primary group	<i>p</i> (unaffected vs. affected vs. control subjects) expanded group
	Unaffected	Affected	Unaffected	Affected			
<i>N</i>	13	13	24	19	31	N/A	N/A
Sex <i>N</i> (%) female	9 (69.2)	9 (69.2)	15 (62.5)	14 (73.7)	20 (64.5)	NS	NS
Age mean (SD)	19.7 (3.3)	21.90 (4.0)	19.8 (3.2)	21.3 (3.5)	20.6 (3.3)	NS	NS
Age range	15.9–25.6	15.1–30.4	15.0–25.6	15.1–30.4	15.8–30.2	N/A	N/A
Diagnosis of offspring	N/A	7MD, 2BDI, 2BDII, 1 dysthymia, 1 psych. NOS	N/A	10MD, 3BDI, 1BDNOS, 3BDII, 1dysthymia, 1Psych. NOS	N/A	N/A	N/A
Family history (bipolar 2nd degree relatives, bipolar I parent, bipolar II 1st degree relatives.)	0, 13, 0	0, 13, 0	4, 13, 7	2, 13, 4	0, 0, 0	N/A	N/A
Treatment at the time of scanning	N/A	2Li, 1AP	N/A	2Li, 1AD, 1AP, 1LA, 14 No treatment	N/A	N/A	N/A
Percent right handed	58	83	70	89	90	<i>p</i> =0.05	NS
ICV mean (SD) cm ³	1433.5 (188.1)	1438.3 (142.4)	1451.4 (183.8)	1428.9 (139.6)	1415.5 (126.3)	NS	NS
GM mean (SD) cm ³	848.5 (111.8)	899.5 (206.5)	876.9 (109.4)	898.7 (174.3)	864.6 (121.9)	NS	NS
LSGC mean (SD) mm ³	413.26 (155.72)	381.48 (112.98)	447.26 (162.36)	387.52 (106.08)	399.40 (132.30)	NS	NS
RSGC mean (SD) mm ³	382.80 (99.07)	303.50 (102.08)	393.03 (135.67)	342.85 (107.70)	362.53 (106.37)	NS	NS

Abbreviations: AD—antidepressants, AP—antipsychotics, BD—bipolar disorder, LA—lamotrigine, Li—lithium, MD—major depression, N/A—not applicable, NOS—not otherwise specified, NS—not significant.