

Anatomical MRI Study of Subgenual Prefrontal Cortex in Bipolar and Unipolar Subjects

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This study attempted to replicate previous findings of decreased gray matter content in the subgenual prefrontal cortex (SGPFC) in mood disorder patients. Eighteen DSM-IV unipolar patients, 27 DSM-IV bipolar patients, and 38 healthy controls were studied. A 1.5T GE Signa Imaging System with Signa 5.4.3 software was used. The semi-automated software MedX (Sensor Systems, Sterling, VA) was utilized for the anatomical measures of SGPFC volumes. There were no significant differences in SGPFC volumes in

familial and non-familial unipolar and bipolar patients compared with healthy controls, nor between drug-free and lithium-treated bipolar patients (ANOVA, $p > .05$). In vivo abnormalities in the volumes of SGPFC were not identified in mildly depressed or euthymic unipolar or bipolar mood disorder outpatients, either familial or non-familial.

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The pathophysiology of mood disorders is still largely unknown. It has been hypothesized that the affective

dysregulation in mood disorder patients may be related to abnormalities in specific brain neuroanatomic pathways that modulate emotion (Soares and Mann 1997; Strakowski et al. 2000). Evidence from the neuroimaging literature suggests that the prefrontal cortex, including the subgenual prefrontal cortex (SGPFC), may play a key role in the pathophysiology of mood disorders (Drevets and Raichle 1992; Soares and Mann 1997). Abnormally decreased sizes in the prefrontal cortex of mood disorder patients have been reported in a few (Coffey et al. 1993; Krishnan et al. 1992; Sax et al. 1999), but not all controlled MRI studies (Coffman et al. 1990; Schlaepfer et al. 1994; Strakowski et al. 1999, 1993). A post-mortem study (Rajkowska et al. 1999) suggested reduced density and size of both neurons and glial cells in prefrontal cortex of patients with major depressive disorder.

The SGPFC is an important sub-region of the prefrontal cortex that corresponds to Brodmann area 24, and has been of particular interest, in recent years, as a potential site of abnormalities that could be implicated in the pathophysiology of mood disorders. It is situated ventrally to the genu of the corpus callosum, and shares

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reciprocal connections with important structures related to emotional processing, such as the hypothalamus, amygdala, and medial thalamic nuclei surrounding the third ventricle (Drevets 2000, 1997). There are reports demonstrating that adults with prior normal personalities, after damage to ventro-medial frontal cortices, developed defects in decision making and planning, manifested as abnormal social conduct (Damasio et al. 1990). Interestingly, two prior controlled MRI studies reported abnormally decreased left SGPFPC volumes in familial unipolar and bipolar mood disorder patients (Drevets et al. 1997; Hirayasu et al. 1999).

The present study attempted to replicate previous findings of anatomical abnormalities in SGPFPC in unipolar and bipolar mood disorder subjects. Based on prior findings, we expected abnormally decreased left SGPFPC in familial unipolar and bipolar patients, but not in non-familial ones. Moreover, we wanted to examine whether there would be any differences in SGPFPC volumes in drug-free compared with lithium-treated bipolar patients. We expected to find it to be decreased in drug-free, but not in lithium-treated, patients as it has been suggested that lithium treatment may have neuroprotective effects, which could be potentially mediated by putative effects in the expression of the cytoprotective protein bcl-2 (Chen and Chuang 1999; Manji et al. 2000).

MATERIALS AND METHODS

Subjects

This research study was approved by the local biomedical IRB. All subjects provided signed informed consent, after having understood all issues involved in participation in the study protocol. Eighteen unmedicated DSM-IV unipolar outpatients (mean age \pm SD = 42 \pm 10 years; 1 male, 17 females; 10 depressed, 8 euthymic; 7 familial, and 11 non-familial patients), 27 DSM-IV bipolar outpatients (mean age \pm SD = 35 \pm 11 years; 15 males, 12 females; 11 depressed, 1 hypomanic, 15 euthymic; 21 bipolar type I, 6 bipolar type II; 12 familial, and 15 non-familial patients), and 38 healthy controls (mean age \pm SD = 37 \pm 10 years; 24 males, 14 females) were studied. Part of the present subject sample was included in previous reports that focused on other brain structures (Brambilla et al. 2001a, 2001b, 2001c; Caetano et al. 2001; Sassi et al. 2001). At the time of participation in the study, all unipolar patients and 11 bipolar patients (mean age \pm SD = 38 \pm 11 years; 5 males, 6 females) were off all psychotropic drugs for at least two weeks; the bipolar patients were also off lithium for at least one month. The remaining 16 bipolar patients (mean age \pm SD = 33 \pm 11 years; 9 males, 7 females) were on lithium monotherapy (median duration = 28 weeks, range: 6–384 weeks). Unipolar patients, bipo-

lar patients, and healthy controls did not differ significantly regarding their educational level (13 unipolar patients, 15 bipolar patients, and 15 controls completed high school; 5 unipolar patients, 12 bipolar patients, and 23 controls completed college and/or a professional school; $\chi^2 = 5.47$, $df = 2$, $p = .07$).

Patients met the DSM-IV diagnostic criteria for unipolar or bipolar disorder, as determined by direct interview with the Structured Clinical Interview for DSM IV (SCID) (Spitzer et al. 1994), and had no comorbid psychiatric disorder, current medical problems, or alcohol or substance abuse within the six months preceding the study. The Bech-Rafaelsen Mania Scale (BRMS) (Bech et al. 1979) and the Hamilton Depression Rating Scales (HRDS) (Hamilton 1960) were used to rate the clinical symptoms, and were administered within a week of the MRI study. Patients' clinical information was retrieved from patients' psychiatric interviews and medical charts. The psychiatric family history information was retrieved by directly questioning patients and/or relatives, and by reviewing patients' charts. According to what was reported by the patients and/or relatives, and also based on information available in patients' charts, first-degree relatives were considered positive for mood disorders if there was a past history of ever having received a diagnosis of unipolar or bipolar disorder by a physician. Patients with at least one first-degree relative with a history of mood disorders were considered familial mood disorder patients.

Healthy controls had no DSM-IV axis I disorders, as determined by direct interview with the SCID-IV non-patient version (SCID-IV-NP). They had no current medical problems, and no history of psychiatric disorders among first-degree relatives. The psychiatric family history for the healthy controls was obtained by directly asking them about family history of mental illness, and reporting the data in the SCID-IV-NP interview. The SCID-IV interviews, for patients and controls, were completed by a trained social worker or a registered nurse at the Depression and Manic Prevention Program (directed by Dr. Ellen Frank). After completion of the SCID-IV interview, the psychiatric diagnoses were confirmed by a study psychiatrist.

MRI Procedure

MRI scans were acquired with a 1.5T GE Signa Imaging System running version Signa 5.4.3 software (General Electric Medical Systems, Milwaukee, WI). A sagittal scout series was first obtained to verify patient position, image quality, and locate a midline sagittal image. A T1-weighted sagittal scout image was obtained for graphic prescription of the coronal and axial images. 3D gradient echo imaging (Spoiled Gradient Recalled Acquisition, SPGR) was performed in the coronal plane

(TR = 25 ms, TE = 5 ms, nutation angle = 40°, FOV = 24 cm, slice thickness = 1.5 mm, NEX = 1, matrix size = 256 × 192) to obtain 124 images covering the entire brain. Additionally, a double echo-spin echo sequence was used to obtain T2 and proton density images in the axial plane, in order to screen for neuroradiological abnormalities.

Anatomical measurements were conducted on a Sun workstation (Sun Microsystems, Palo Alto, CA) using the semi-automated software MedX version 3.2 (Sensor Systems, Sterling, VA). Volumetric measurements of left and right SGPFC gray matter were obtained manually by a trained evaluator (M.A.N.) blind to group assignment and to subjects' identity, following the same tracing method used by Drevets et al. (1997). The volumes of these brain structures were expressed in mm³. The intra-class correlation coefficients (ICCs), estab-

lished by two independent raters (P.B., M.A.N.) tracing 10 training scans, were: $r = 0.931$ for right SGPFC gray matter, $r = 0.956$ for left SGPFC gray matter, and $r = 0.975$ for intra-cranial brain volume (ICV) measures.

Anatomical Landmarks

SGPFC All tracing was done manually in the coronal plane, after realigning the images along the anterior-posterior commissure line. The tracing of the right and left SGPFC (Figure 1) began at the most anterior slice in which the corpus callosum appeared. The gray matter of the first full gyrus below the corpus callosum was traced, and the tracing stopped at the slice anterior to the one where the internal capsule no longer divided the striatum.

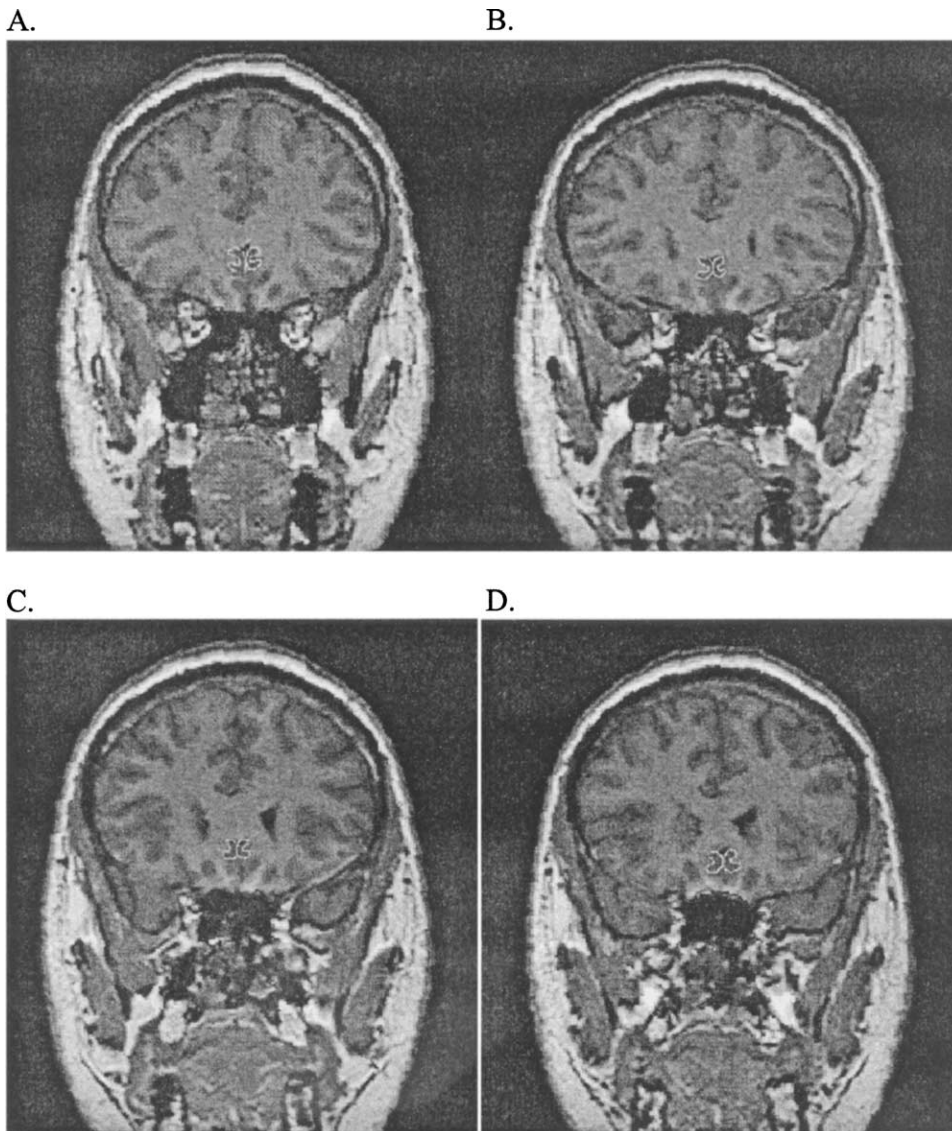


Figure 1. The tracing of right and left SGPFC started at the most anterior slice in which the corpus callosum appeared (A). The gray matter of the first full gyrus below the corpus callosum was traced (B and C), and the tracing stopped at the slice anterior to the one where the internal capsule no longer divided the striatum (D).

Intra-cranial Brain Volume

The first slice that contained brain matter was traced around the outside border of the brain, excluding everything other than total cerebral gray and white matter, CSF, dura mater, and sinuses. Temporal lobes, optic chiasma, pituitary, brainstem, and the cerebellar hemispheres were included. The inferior border did not extend below the base of the cerebellum. The tracing continued until no brain matter was visible.

Statistical Analyses

All analyses were conducted using the SPSS for Windows software, version 10.0 (SPSS Inc., Chicago), and 2-tailed statistical significance level was set at $p < .05$. All MRI volumetric measures were found to be normally distributed, as determined by the Shapiro-Wilks test. ANOVA, partial correlation coefficient, and Spearman's correlation coefficient were performed.

RESULTS

Unipolar patients, bipolar patients, and healthy controls did not differ significantly in measures of right or left SGPFC volumes (ANOVA, age, gender, and ICV as covariates, $p > .05$) (Table 1; Figure 2, panels A and B). Furthermore, after including educational level as a covariate, there were still no significant differences among the three groups for volumes of right or left SGPFC (ANOVA, age, gender, ICV, and educational level as covariates, $p > .05$). Right SGPFC and left SGPFC volumes did not differ significantly among female unipolar patients (mean \pm SD = 292.7 \pm 62.9 and 301.5 \pm 84.7 mm³, respectively), female bipolar patients (mean \pm SD = 316.2 \pm 68.9 and 295.2 \pm 76.0 mm³, respectively), and female healthy individuals (mean \pm SD = 311.2 \pm 72.3 and 289.1 \pm 55.8 mm³, respectively) (ANOVA, age and ICV as covariates: $F = 0.47$, $df = 2/38$, $p = .62$; $F = 0.11$, $df = 2/38$, $p = .89$, respectively).

No significant differences for right SGPFC or left SGPFC volumes were found among familial unipolar and non-familial unipolar patients, familial bipolar and non-familial bipolar patients, and healthy controls (ANOVA, age, gender, and ICV as covariates, $p > .05$) (Table 2; Figure 2, panels C and D).

Right and left SGPFC volumes did not differ significantly among drug-free bipolar patients (mean \pm SD = 330.9 \pm 105.2 and 303.7 \pm 61.0 mm³, respectively), lithium-treated bipolar patients (mean \pm SD = 315.4 \pm 61.2 and 311.1 \pm 68.8 mm³, respectively), and healthy controls (ANOVA, age and ICV as covariates: $F = 0.54$, $df = 2/60$, $p = .59$; $F = 0.39$, $df = 2/60$, $p = .68$, respectively).

There was no statistically significant correlation be-

tween length of illness or HRDS scores and right or left SGPFC volumes in unipolar (length of illness: median = 9 years, range = 1–33 years; $\rho = 0.46$, $p = .06$; $\rho = 0.37$, $p = .14$, respectively; HRDS scores: median = 14, range = 0–27; $\rho = 0.26$, $p = .30$; $\rho = 0.00$, $p = .99$, respectively) or bipolar patients (length of illness: median = 15 years, range = 1–38 years; $\rho = 0.15$, $p = .47$; $\rho = 0.25$, $p = .21$, respectively; HRDS scores: median = 6, range = 0–37; $\rho = -0.15$, $p = .51$; $\rho = -0.34$, $p = .11$, respectively) (Spearman's correlation coefficients). Among the lithium-treated bipolar patients (median = 900 mg/day, range: 675–2100 mg/day), the lithium dose at the time of the MRI scan did not correlate significantly with right or left SGPFC volumes (Spearman's correlation coefficients; $\rho = -0.16$, $p = .55$; $\rho = -0.29$, $p = .28$, respectively).

No statistically significant correlation was found between age and right or left SGPFC volumes in unipolar patients (correlation coefficient = 0.04, $df = 15$, $p = .89$; correlation coefficient = 0.19, $df = 15$, $p = .47$, respectively), bipolar patients (correlation coefficient = 0.33, $df = 24$, $p = .10$; correlation coefficient = 0.36, $df = 24$, $p = .07$, respectively), or healthy controls (correlation coefficient = 0.17, $df = 35$, $p = .32$; correlation coefficient = 0.17, $df = 35$, $p = .33$, respectively) (partial correlation analyses, controlled for ICV).

DISCUSSION

In the present study, we did not find any evidence of volumetric reduction in left SGPFC volumes in familial mood disorder patients, contrary to our hypothesis and to reports from two previous controlled MRI studies (Drevets et al. 1997; Hirayasu et al. 1999). On the other hand, non-familial unipolar or bipolar mood disorder patients did not differ significantly in measures of left SGPFC volumes from healthy controls, which is consistent with findings reported in these two prior studies (Drevets et al. 1997; Hirayasu et al. 1999). Therefore, we have been unable to replicate the prior findings of reduced left SGPFC gray matter in familial mood disorder patients.

Drevets et al. (1997) found decreased gray matter content in left SGPFC in familial depressed, manic, or euthymic bipolar patients ($n = 21$; mean age \pm SD = 35 \pm 8 years; 8 males, 13 females) and in depressed unipolar subjects ($n = 17$; mean age \pm SD = 35 \pm 9 years; 7 males, 10 females) compared with healthy controls ($n = 21$; mean age \pm SD = 34 \pm 8 years; 10 males, 11 females). In the same study, by also utilizing the methodology of positron emission tomography (PET), they suggested that the anatomical abnormalities in SGPFC could possibly account for abnormally decreased regional metabolic activity in this brain region in familial

Table 1. Anatomical Measures of SGPFC in Bipolar Patients, Unipolar Patients, and Healthy Controls

Volume (mm ³)	BP (n= 27)	UP (n= 18)	HC (n= 38)	F	df	p
Right SGPFC	321.7 ± 80.5	295.4 ± 62.1	313.7 ± 76.2	0.43	2/77	.65
Left SGPFC	308.1 ± 64.6	300.2 ± 82.3	290.0 ± 77.0	0.21	2/77	.81

Anatomical measurements are reported as mean ± S.D. HC = healthy controls, UP = unipolar patients, BP = bipolar patients. SGPFC = subgenual prefrontal cortex. df = degrees of freedom. ANOVA analyses were performed with age, gender, and ICV as covariates.

depressed bipolar (n = 7) and unipolar subjects (n = 10). In a small group of familial bipolar patients in the manic state (n = 4), the metabolism in this brain region was abnormally increased. Subsequently, a post-mortem study by the same group (Ongur et al. 1998) demonstrated that the anatomical reduction of SGPFC gray matter was associated with a reduction in glia, but not

neuronal density or number, in a small group of familial unipolar (n = 6) and bipolar (n = 4) patients compared with healthy controls (n = 11). These findings suggested that anatomical abnormalities in left SGPFC, if present, would be specific to familial mood disorder patients. The second controlled MRI study (Hirayasu et al. 1999) evaluated the SGPFC in first-episode psychotic

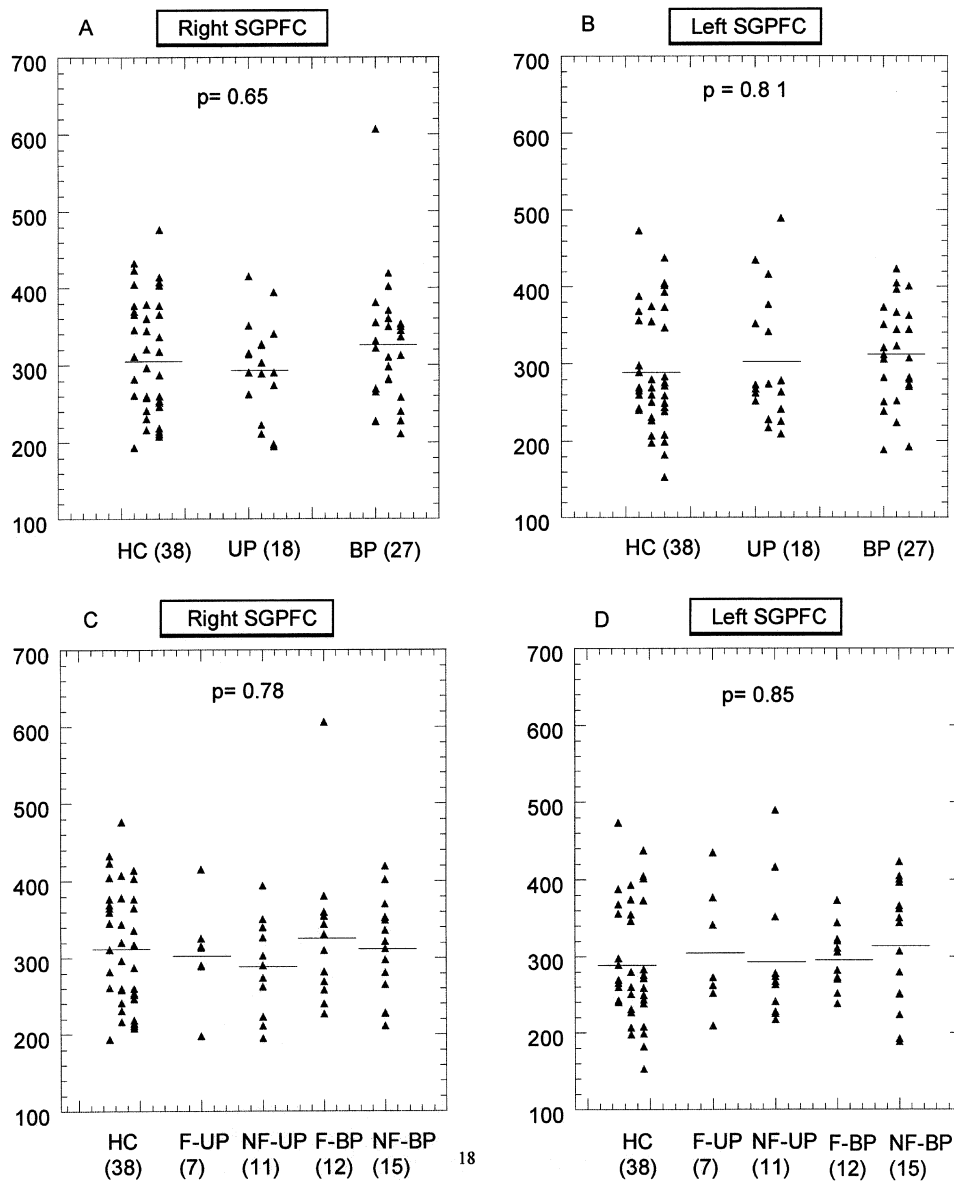


Figure 2. Bipolar patients, unipolar patients, and healthy controls did not differ significantly in measures of right (F = 0.43, df = 2/77, p = .65) (A) or left SGPFC volumes (F = 0.21, df = 2/77, p = .81) (B). Familial and non-familial unipolar patients, familial and non-familial bipolar patients, and healthy controls did not differ significantly in measures of right (F = 0.44, df = 4/75, p = .78) (C) or left SGPFC volumes (F = 0.35, df = 4/75, p = .85) (D).

HC = healthy controls; UP = unipolar patients; BP = bipolar patients; F-UP = familial unipolar patients; NF-UP = non-familial unipolar patients; F-BP = familial bipolar patients; NF-BP = non-familial bipolar patients.

Table 2. Anatomical Measures of SGPFC in Familial and Non-familial Bipolar and Unipolar Patients and Healthy Controls

Volume (mm ³)	F-BP (n = 12)	NF-BP (n = 15)	F-UP (n = 7)	NF-UP (n = 11)	HC (n = 38)	F	df	p
Right SGPFC	330.2 ± 100.4	314.9 ± 63.2	306.6 ± 64.2	288.2 ± 62.7	313.7 ± 76.2	0.44	4/75	.78
Left SGPFC	298.0 ± 39.0	316.2 ± 80.0	307.2 ± 79.8	295.8 ± 87.5	290.0 ± 77.0	0.35	4/75	.85

Anatomical measurements are reported as mean ± S.D. HC = healthy controls, F-UP = familial unipolar patients, NF-UP = non-familial unipolar patients, F-BP = familial bipolar patients, NF-BP = non-familial bipolar patients. SGPFC = subgenual prefrontal cortex. df = degrees of freedom.

ANOVA analyses were performed with age, gender, and ICV as covariates.

affective patients (n = 24; mean age ± SD = 24 ± 5 years; 18 males, 6 females; 21 bipolar, 3 unipolar patients). They found abnormally reduced gray matter volume in left SGPFC in familial (n = 14) compared with non-familial mood disorder patients (n = 10) and healthy controls (n = 20). This study provided an independent replication for the findings by Drevets et al. (1997) in the bipolar population, and gave additional support for the hypothesis that anatomical abnormalities in the left SGPFC are present in familial mood disorders. The meaning of potential abnormalities in left SGPFC for the pathophysiology of mood disorders is unclear, but such abnormalities, if present, could reflect a genetic vulnerability to develop mood disorders that occurs in the familial cases.

Our current findings and the previously reported ones (Drevets et al. 1997; Hirayasu et al. 1999) are in agreement that SGPFC volumes are unaltered in non-familial mood disorder patients, either unipolar or bipolar. Nonetheless, we were not able to replicate the prior findings of abnormalities in the volume of left SGPFC in familial unipolar or bipolar patients (Drevets et al. 1997; Hirayasu et al. 1999). The discrepancy among these findings may be explainable by differences in the patient samples studied. Our sample was primarily composed of mildly depressed or euthymic outpatients, whereas the patients recruited in the two prior MRI studies were, respectively, moderate-to-severely depressed (Drevets et al. 1997), or hospitalized first-episode patients (Hirayasu et al. 1999). Thus, the milder illness severity of our sample could possibly have accounted for the discrepancy in our findings. In regard to the tracing methodology, the three studies utilized very similar procedures to trace the SGPFC region, as reported in Drevets et al. (1997).

Our study has a few limitations that need to be considered. First, we were not able to utilize structured diagnostic interviews with first-degree relatives to ascertain the psychiatric family history. The information on family history was obtained by directly questioning the patients and/or their relatives, whenever available, as well as by chart reviews. For this reason, it is possible that some family members may have had episodes of mood disorders that went undiagnosed, or that the family did not find out about, which would not have been identified. Therefore, it is possible that some of the

patients classified as non-familial cases could represent familial cases of the illness. Nonetheless, this does not constitute a distinction between the methodology utilized in our study and the two previously reported studies (Drevets et al. 1997; Hirayasu et al. 1999), where no direct structured interviews were utilized to confirm or exclude psychiatric diagnoses among the first-degree relatives. Future studies should include direct assessments of all first-degree relatives with structured interviews, as a way to accurately ascertain family psychiatric history. Another potential limitation of our findings is the gender composition of the unipolar group, in which the majority of the patients were females. Nonetheless, we accounted for this potential bias in our analyses by using gender as a covariate, and also by separately comparing female individuals across the three subject groups (unipolar patients, bipolar patients, and healthy controls).

Furthermore, in our present study no anatomical differences in SGPFC were present among drug-free bipolar patients, lithium-treated bipolar patients, and healthy controls. There was no significant relationship between lithium dose at the time of the MRI and anatomical measures of SGPFC among the lithium-treated bipolar patients. Differences in the SGPFC measures between drug-free and lithium-treated patients would have been of potential relevance because chronic lithium administration has been suggested to have possible neuroprotective effects in the brain (Chen et al. 2000; Manji et al. 2000). Nonetheless, in order to provide a conclusive test to the hypothesis of lithium having potential effects on volumes of SGPFC, a longitudinal study involving patients before and after treatment will be required. In the work by Drevets et al. (1997), abnormalities in left SGPFC persisted after antidepressant treatment in unipolar disorder patients, and in the study by Hirayasu et al. (1999), medication doses (i.e., neuroleptics) did not correlate with SGPFC volumes.

In conclusion, our findings do not support the hypothesis of abnormalities in the volumes of left SGPFC in familial unipolar and bipolar mood disorder patients. A possible explanation for the discrepancy between our findings and two prior reports that found abnormalities in this brain region may be related to peculiarities in our patient sample, where all subjects

were outpatients, and where a substantial part of the patients were euthymic at the time of the study. The two previous studies involved more severely depressed, and some psychotic patients. These conflicting findings may suggest that a volumetric reduction in left SGPF, if present, may be a trait abnormality in a sub-type of familial patients with a more severe phenotype of mood disorders, but not in familial or non-familial patients with less severe clinical manifestations of these illnesses. We also reported that SGPF volumes in drug-free and lithium-treated bipolar patients were similar, suggesting that lithium treatment does not seem to affect volumetric measures of this brain region. Future studies attempting to clarify the role of putative SGPF anatomical abnormalities in the pathophysiology of familial and non-familial mood disorders should involve larger patient samples, more severe cases, and also include direct interviews with all first-degree relatives to accurately ascertain psychiatric diagnoses in the family members.

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