Cortical Thickness and Subcortical Volumes in Schizophrenia and Bipolar Disorder

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Background: Schizophrenia and bipolar disorder are severe psychiatric diseases with overlapping symptomatology. Widespread brain morphologic abnormalities, including cortical thinning and subcortical volume reductions, have been demonstrated in schizophrenia but it is unclear whether similar abnormalities are present in bipolar disorder. The purpose of this study was to compare cortical thickness and subcortical volumes in schizophrenia and bipolar disorder, to assess differences and similarities in cortical and subcortical brain structure.

Methods: We analyzed magnetic resonance images from a sample of 173 patients with schizophrenia spectrum disorder, 139 patients with bipolar disorder, and 207 healthy control subjects. Cortical thickness was compared between the groups in multiple locations across the continuous cortical surface. Subcortical volumes were compared on a structure-by-structure basis.

Results: There was widespread cortical thinning in schizophrenia compared with control subjects, in frontal, temporal, occipital, and smaller parietal regions. There was no cortical thinning in bipolar disorder compared with control subjects or in schizophrenia compared with bipolar disorder. However, the subgroup of patients with bipolar disorder Type 1 showed cortical thinning, primarily in the frontal lobes and superior temporal and temporoparietal regions. Both patient groups showed substantial subcortical volume reductions bilaterally in the hippocampus, the left thalamus, the right nucleus accumbens, the left cerebellar cortex, and the brainstem, along with substantial ventricular enlargements.

Conclusions: We found substantial overlap in the underlying brain morphologic abnormalities in schizophrenia and bipolar disorder in subcortical structures, and between schizophrenia and bipolar disorder Type 1 in the cerebral cortex.

Key Words: Bipolar disorder, cerebral cortex, Freesurfer, MRI, schizophrenia, subcortical structures

Schizophrenia and bipolar disorder are two of the most severe psychiatric diseases, both in terms of suffering for patient and family and in terms of health care costs. The current diagnostic distinction between the two diseases stems from Kraepelin’s original division of psychotic disorders into dementia praecox and manic-depressive illness (1). However, in clinical practice, the distinction between the two disease categories is sometimes blurred, and it is unclear whether schizophrenia and bipolar disorder are separate disease entities, with separable genetic causes and distinct pathologic processes (2,3). If schizophrenia and bipolar disorder share a common underlying pathophysiology, it can be expected that brain structural changes in the two patient populations are similar. To test this hypothesis, we investigated cortical thickness and subcortical volumes in patients with schizophrenia and bipolar disorder, relative to healthy control subjects, to compare differences in brain morphology between the patient groups.

Subtle but widespread brain abnormalities in schizophrenia have consistently been demonstrated in magnetic resonance imaging (MRI)-based morphometry studies (4,5). The most consistent findings have been increased lateral ventricle size and volume reductions in the left medial temporal lobe, primarily the hippocampus (5), as well as gray matter reductions in the frontal lobe, including the anterior cingulate, and the lateral temporal lobe (4–9). Since the late 1990s, advances in neuroimaging data processing and analysis have made it possible to obtain automatic measurements of cortical thickness with submillimeter precision, in multiple locations across the cortical surface (10,11), as well as automatically segmented volumes of subcortical structures (12), thus covering the entire brain, while retaining maximal regional specificity. The first study to apply cortical surface reconstruction methods to investigate cortical thinning in schizophrenia reported differences between patients and healthy subjects primarily in frontal and temporal regions (13). Recently, these findings have been replicated in larger schizophrenia samples (14,15). However, because neither of these previous studies included a second clinical group, such as bipolar disorder, it is difficult to ascertain whether the observed effects are specific to schizophrenia or characteristic of severe mental illness in general.

There has, to our knowledge, been only one whole-brain study of cortical thickness in bipolar disorder, which reported cortical thinning in circumscribed regions of the frontal lobes and primary sensory regions in the parietal and occipital lobes (16). In addition, two region of interest studies limited to the medial frontal lobe found cortical thinning in the left paracingulate region (17) and increased cortical thickness in the right anterior cingulate (18) in bipolar disorder Type 1. In general, morphometry studies of bipolar disorder have yielded inconsistent results, and a recent meta-analysis con-
cluded that the only consistent findings in volumetric studies of bipolar disorder are increased lateral ventricle size and deep white matter hyperintensities (19).

Direct comparisons between schizophrenia and bipolar disorder have been limited to single regions of interest (20–23), and these studies have generally used small samples (20,22,23). Hippocampal volume reductions in schizophrenia but not in bipolar disorder have been reported (20,21), although one study found reduced left hippocampus volume also in bipolar disorder (23). One voxel-based morphometry study compared patients with schizophrenia and bipolar disorder to their nonaffected relatives (24), reporting gray matter reduction in the left frontal lobe in schizophrenia, relative to nonaffected relatives, and no corresponding reduction in bipolar disorder. However, no direct statistical comparison was made between schizophrenia and bipolar disorder.

We used MRI scans optimized for gray–white matter contrast to obtain measurements of cortical thickness and subcortical volumes from a large sample of patients with schizophrenia, bipolar disorder, and healthy control subjects. To our knowledge, this study is the first to compare cortical thickness in schizophrenia and bipolar disorder directly and the first to investigate a comprehensive list of subcortical structures in these patient groups.

Methods and Materials

Subjects

All participants were recruited between 2003 and 2009 as part of an ongoing study of psychotic disorders (Thematically Organized Psychosis Research). All participants gave informed consent to participation, and the study has been approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate. Exclusion criteria for all participants were a history of moderate or severe head injury, neurological disorder, IQ < 65, and age outside the range 18–65 years. Control participants were excluded if they had abused cannabis within the last 3 months or had a dependency on the drug, if they or any of their first-degree relatives had a lifetime history of severe psychiatric disorder, or if they had a history of medical problems thought to interfere with brain function.

One hundred thirty-nine patients with bipolar disorder Type 1 (n = 87) or Type 2 (n = 52), 173 patients with a schizophrenia-spectrum disorder (i.e., schizophrenia, n = 132; schizoaffective disorder, n = 31; or schizoaffective disorder n = 10), and 207 healthy control subjects were included in the study. In the following we refer to schizophrenia spectrum as “schizophrenia”. Clinical assessment was carried out by trained psychiatrists and clinical psychologists. Diagnosis was based on the Structured Clinical Interview for DSM-IV Axis I disorders (25). Current positive and negative symptoms were rated using the Positive and Negative Symptom Scale (26). Psychosocial functioning in patients was assessed with the Global Assessment of Functioning scale, split version (27). For the bipolar disorder group, current depressive symptoms were rated using the Inventory of Depressive Symptomatology—Clinician Rating (28), and current manic symptoms were rated using the Young Mania Rating Scale (29). Demographic and clinical data are found in Table 1 (for more detailed information, see Section S1 in Supplement 1).

Brain Imaging

MR Image Acquisition. All participants underwent MRI scanning on a 1.5-T Siemens Magnetom Sonata scanner (Siemens Medical Solutions, Erlangen, Germany) equipped with a standard head coil. After a conventional three-plane localizer, two sagittal T1-weighted magnetization prepared rapid gradient echo volumes were acquired with the Siemens mIP3d1_ns pulse sequence (echo time = 3.93 msec, repetition time = 2730 msec, inversion time = 1000 ms, flip angle = 7°; field of view = 24 cm, voxel size = $1.33 \times 0.94 \times 1 \text{ mm}^3$, number of partitions = 160). Acquisition parameters were optimized for increased gray–white matter image contrast.

Patients and control subjects were scanned continuously throughout the 6-year period during which the data were collected, thus ensuring that there was no confounding effect of time. There was no scanner upgrade in this period.

MR Image Processing. The FreeSurfer 3.0.2 software package (http://surfer.nmr.mgh.harvard.edu) was used to create a three-dimensional model of the cortical surface for cortical thickness measurements (for a more complete description, see Section S2 in Supplement 1). Surface maps were smoothed with a full-width-half-maximum Gaussian kernel of 30 mm (662 iterations) and averaged across participants using a nonrigid high-dimensional spherical averaging method to align cortical folding patterns (30,31). Subcortical volumes were obtained from the automated procedure for volumetric measures of brain structures implemented in Freesurfer (12). Twenty-seven volumetric measures were investigated, including 10 subcortical structures from each hemisphere, left and right cerebellar gray and white matter segmentations, the third and fourth ventricles, and the brain stem. For simplicity, we refer to these collectively as “subcortical structures” although, strictly speaking, hippocampus and cerebellum are not subcortical.

Statistical Analysis

Cortical Thickness Analysis. A general linear model (GLM) was estimated at each vertex across the cortical surface, with cortical thickness as dependent variable, diagnosis (schizophrenia, bipolar disorder, control subjects) and sex as categorical predictors, and with age as continuous predictor. This procedure allows for generation of statistical parametric maps which can be thresholded. The left and right hemisphere cortical surfaces were analyzed separately. The maps show the distribution of p values for pairwise comparisons between the diagnostic categories, as defined by the following contrasts: 1) healthy control subjects versus schizophrenia, (2) bipolar disorder versus schizophrenia, and (3) healthy control subjects versus bipolar disorder. To correct for multiple comparisons, p-maps were thresholded to yield an expected FDR of 5% (32).

Subcortical Analyses. The 27 subcortical structure volumes and intracranial volume (ICV), were imported into the SPS816.0 software (http://www.spss.com) for statistical analyses. For each structure, a GLM was fit with volume as dependent variable, diagnosis (schizophrenia, bipolar disorder, control subjects), and sex as categorical predictors, and age and ICV as continuous predictors. First, an Ftest for main effect of diagnosis (omnibus test) was done. Subsequently, contrast analyses were done comparing the diagnostic groups pairwise, as described above for cortical thickness. To correct for multiple comparisons, the Bonferroni–Holm procedure, which corrects for the family-wise error rate, was applied in two steps. First, the omnibus tests were corrected. Second, within each subcortical structure that survived the first round of corrections, the correction procedure was applied to the pairwise contrasts. Only results that survived this two-step multiple correction procedure were considered significant.

Follow-Up Analyses of Subgroups. The main analyses were followed up with an analysis on patients with bipolar disorder Type 1, using the same model as described above. Finally, we
Cortical Findings

Schizophrenia Versus Healthy Control Subjects. Cortical thickness was significantly reduced in schizophrenia compared with healthy control subjects in large regions across the cerebral cortex (Figure 1A). The most widespread thinning was seen in the lateral and medial frontal lobes, including the left anterior cingulate, and in the temporal lobes, but the lateral and medial occipital lobe and some smaller parietal regions were also affected. This pattern was mostly bilateral but with some differences between the hemispheres. Most of the frontal lobe was affected in both hemispheres, but the medial orbitofrontal cortex was mainly affected on the right. In the left temporal lobe, the superior temporal gyrus (STG), to some extent the middle temporal gyrus (MTG), and the parahippocampal and fusiform gyri showed cortical thinning. The entire right temporal lobe showed cortical thinning both laterally, ventrally and medially, with the most significant findings in the middle and inferior temporal gyrus laterally, and the parahippocampal, entorhinal, and fusiform gyri medially and ventrally. In addition, in the left hemisphere, there was cortical thinning in the inferior parietal lobe, the lateral occipital lobe, and the precuneus and lingual gyrus. In the right hemisphere, there was cortical thinning in the supramarginal, inferior parietal, and lateral occipital gyri, the

Table 1. Demographics and Clinical Dataa

<table>
<thead>
<tr>
<th></th>
<th>Schizophrenia (n = 173)</th>
<th>Bipolar Disorder (n = 139)</th>
<th>Healthy Control Subjects (n = 207)</th>
<th>ANOVAχ²/t tests</th>
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<tr>
<td>Age, yearsb</td>
<td>32.3 (9.0)</td>
<td>35.4 (11.3)</td>
<td>36.2 (9.7)</td>
<td>F = 7.7, p = .001, 1 &lt; 2, 3</td>
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<td>104 (60.1)</td>
<td>54 (38.8)</td>
<td>108 (52.2)</td>
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<td>Handedness, n (% right)</td>
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<td>98 (86.7)</td>
<td>190 (91.8)</td>
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<td>Ethnicity, n (% Caucasian)</td>
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<td>128 (92.1)</td>
<td>205 (99.0)</td>
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<td>Education, yearsc</td>
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<td>14.2 (3.0)</td>
<td>14.1 (2.3)</td>
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<td>WASI (IQ)</td>
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<td>109.3 (11.8)</td>
<td>114.6 (9.4)</td>
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<td>Age at Onset of Illness, yearsc</td>
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<td>28.9 (11.0)</td>
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<td>Duration of Illness, yearsc</td>
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<td>6.5 (6.5)</td>
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<td>60 (43)</td>
<td>9 (5)</td>
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<td>Lithium</td>
<td>3 (2)</td>
<td>19 (14)</td>
<td>1.0 (3)</td>
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<tr>
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<td>51 (37)</td>
<td>.7 (4)</td>
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<td>Antidepressants</td>
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<td>48 (35)</td>
<td>1.4 (8)</td>
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</tr>
<tr>
<td>Sedatives</td>
<td>17 (10)</td>
<td>13 (9)</td>
<td>.9 (1.1)</td>
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At the time of investigation 206 patients (146 with schizophrenia and 60 with bipolar disorder) received antipsychotic medication. Among these, 9 patients with schizophrenia and 4 patients with bipolar disorder received typical antipsychotic medication, and 126 patients with schizophrenia and 55 patients with bipolar disorder received atypical antipsychotic medication. Sixteen patients with schizophrenia and 18 patients with bipolar disorder received no psychopharmacologic medication at the time of investigation.

Number of cases with missing data: handedness—schizophrenia: 21; handedness—bipolar disorder: 26; education—schizophrenia: 1; WASI IQ—schizophrenia: 23; WASI IQ—bipolar disorder: 28; age of onset and illness duration—schizophrenia: 1; age of onset and illness duration—bipolar disorder: 7; PANSS positive and negative scores—schizophrenia: 9; PANSS positive and negative scores—bipolar disorder: 2; PANSS general and total scores—schizophrenia: 11; PANSS general and total scores—bipolar disorder: 2.

ANOVA, univariate analysis of variance; DDD, defined daily doses; in accordance with guidelines from the World Health Organization Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcdd); GAF, global assessment of functioning; PANSS, Positive and Negative Symptom Scale; WASI, Wechsler Abbreviated Scale of Intelligence.

aMean and SD are reported unless otherwise specified. Analyses of demographics and clinical data were performed in SPSS (http://www.spss.com). All tests were two-tailed.

bA positive t value indicates schizophrenia > bipolar disorder; a negative t value indicates bipolar disorder > schizophrenia.

cTukey post hoc tests.

dAge was defined as age at the time of magnetic resonance imaging scanning.

*Years of education refers to the total number of years of completed education as reported by the participant.

fAge at onset was defined as age at first contact with the mental health service due to a primary symptom.

gDuration of illness was defined as number of years between age at onset and age at MRI scanning.

also performed an analysis where the 31 patients with schizoaffective disorder were excluded from the schizophrenia spectrum group, to determine if that affected the results for schizophrenia.

Effects of Medication, Duration of Illness, and Symptom Severity. Four types of medication (typical and atypical antipsychotics, antidepressants, and lithium), duration of illness, and symptom severity were tested for an effect on cortical thickness or subcortical volumes. Sex by diagnosis interactions were also tested for (Section S3 in Supplement 1).
isthmus of the posterior cingulate, the precuneus and, to some
extent, in the lingual gyrus. There was also cortical thinning in
the most inferior portion of the precentral gyrus in both hemi-
spheres. (Effect size maps are found in Figure 2A. Means and
effect sizes for selected regions of interest are found in Table 2,
and the corresponding percentages are found in Table S1 in
Supplement 1.)

**Schizophrenia Versus Bipolar Disorder.** There were no sig-
nificant findings for this contrast.

**Bipolar Disorder Versus Healthy Control Subjects.** There
were no significant findings for this contrast.

**Cortical Findings: Follow-Up Analyses**

**Bipolar Disorder Type 1 Versus Healthy Control Subjects.**
There was widespread significant cortical thinning in the lateral
and medial frontal lobes in patients with bipolar disorder Type 1
compared with control subjects (Figure 1B). These findings were
more significant in the right hemisphere but somewhat more
widespread in the left hemisphere. The lateral orbitofrontal
cortex was exclusively affected in the left hemisphere, and in the
right frontal lobe, it was primarily the superior frontal gyrus
(SFG) that was affected. There was also cortical thinning in the
left posterior STG and in a small region in the inferior parietal
gyrus, and there was cortical thinning in the right supramarginal
gyrus, as well as small scattered regions in the right inferior and
superior parietal gyrus, inferior temporal gyrus and parahip-
pocampal gyrus. (Effect size maps are found in Figure 2B, and
means and effect sizes for selected regions of interest are found
in Table 3.)

**Bipolar Disorder Type 1 Versus Schizophrenia.** There were
no significant findings for this contrast.

**Schizophrenia Without Schizoaffective Patients Versus
Healthy Control Subjects.** The results for this contrast were
similar to the results for the full schizophrenia group (Figure S1
in Supplement 1).

Figure 1. Statistical maps showing significant differences
between (A) schizophrenia and healthy control subjects,
and (B) bipolar disorder Type 1 and healthy control sub-
jects. The exact false discovery rate threshold depends on
the data and is therefore not necessarily identical for left
and right hemisphere. We have chosen the lowest thresh-
old across the hemispheres for each figure. The differ-
ences in threshold between the left and right hemisphere
maps within these two figures were negligible. (The
schizophrenia category consists of all schizophrenia spec-
trum diagnoses included in this study, i.e., schizophrenia,
schizophreniform disorder, and schizoaffective disorder.)
Subcortical Findings

There were significant bilateral volume reductions in the hippocampus in schizophrenia relative to healthy control subjects (Table 4); specifically, 4.1% in the left and 5.1% in the right hippocampus. There were also significant volume reductions in the left thalamus (2.9%) and left amygdala (4.3%). In the bipolar disorder group, there were significant bilateral reductions of hippocampal volume (2.8% and 3.2%) and a left thalamus volume reduction (2.3%). In both schizophrenia and bipolar disorder, there was substantial bilateral enlargement of the lateral and inferior lateral ventricles (schizophrenia: 16.5%–24.1%; bipolar disorder: 12.5%–17.5%), and the third ventricle (schizophrenia: 22%; bipolar disorder: 19.2%). Both schizophrenia and bipolar disorder also showed significant volume reductions in the brainstem and the right nucleus accumbens, and reductions in cerebellar cortical volume, on the order 2% to 4%. Finally, patients with schizophrenia had significantly larger volumes in the right putamen, relative to patients with bipolar disorder (2.7%) and healthy control subjects (3.2%).

Follow-Up Analyses of Subgroups

The analyses with the bipolar Type 1 disorder subgroup produced approximately the same results as the analyses with the whole bipolar disorder group (Table S2 in Supplement 1). The analyses where patients with schizoaffective disorder were excluded from the schizophrenia spectrum group produced approximately the same results as for the full schizophrenia group.

Medication, Duration of Illness, and Symptom Severity

There was no significant effect of medication, duration of illness, or symptom severity on cortical thickness or subcortical volumes. There was no significant sex–diagnosis interaction in any cortical or subcortical test.

Discussion

This is, to our knowledge, the first time cortical thickness has been compared directly in patients with schizophrenia, patients with bipolar disorder, and healthy control subjects. We report widespread bilateral reductions in cortical thickness in schizophrenia, relative to healthy control subjects, primarily in the frontal and temporal lobes but also in parietal and occipital regions (Figure 1A). There was no significant cortical thinning in the bipolar disorder group as a whole relative to healthy control subjects. However, comparing the subgroup of bipolar disorder Type 1 with healthy control subjects, we observed widespread cortical thinning bilaterally in the frontal lobes, as well as in more
circumscribed posterior temporal and temporoparietal regions (Figure 1B).

Three previous studies reported frontal and temporal cortical thinning in schizophrenia compared with healthy control subjects (13–15) but because neither study had a clinical control group, it was not possible to ascertain whether these reductions were specific to schizophrenia. The cortical thinning observed in schizophrenia in the previous studies is largely consistent with our findings. However, our findings suggest that the cortical thinning observed in the frontal lobes, the left posterior STG and right supramarginal gyrus is common to schizophrenia and bipolar Type 1 disorder. Because there was no cortical region that was significantly thinner in schizophrenia than bipolar disorder, or the subgroup of bipolar Type 1 disorder, we cannot conclude that cortical thinning in any region is specific to schizophrenia.

Average cortical thinning in schizophrenia was between 1.7% and 3.1% in regions with significant group differences (Table S1 in Supplement 1). This difference is smaller than in previous studies of cortical thickness in schizophrenia, which reported thinning in the 2.2% to 5.3% (13) and 3.2% to 8.7% (15) range. Duration of illness was 4 to 5 times shorter in our study, which may partly explain the smaller effect sizes assuming there is progressive atrophy after disease onset. There is some evidence for this, albeit limited to the early stages of the disease (33,34). There was no significant effect of duration of illness in our analyses, but the range of durations in our study is likely to be too narrow to detect such a correlation if it exists.

Lieberman et al. (35) reported reduction of cortical gray matter in patients receiving typical, but not atypical, antipsychotics, suggesting that typical antipsychotics may have neurotoxic effects or that atypical antipsychotics may have a neuroprotective or neurotrophic effect. Consistent with previous cortical thickness studies (13,15), we did not find any significant effect of antipsychotic or antidepressant medication. In fact, most of our patients received atypical antipsychotic medication and yet showed widespread cortical thinning, albeit with moderate effect sizes. However, the small number of patients receiving typical antipsychotics limits our power to detect possible effects.

Our findings are, at least partly, consistent with recent meta-analyses of voxel-based morphometry studies of schizophrenia, which reported gray matter volume reductions in left inferior frontal gyrus (IFG) (4,7,9), right IFG (7,9), left medial front gyrus (4,8), the anterior cingulate (7,9), and left STG (4,9). In addition, one study (7) reported right IFG reductions only in first-episode patients, and right MTG/STG reductions only in patients with chronic schizophrenia. However, our frontal findings are more widespread and symmetrical and include the orbitofrontal cortex, which is less commonly reported in the voxel-based morphometry literature. Our frontal findings for bipolar disorder Type 1 accord well with a recent meta-analysis (6), which found consistent gray matter density reductions in the prefrontal cortex (PFC) in bipolar disorder, together with total brain volume reduction and ventricular enlargements. If the cortical effect is mainly present in bipolar disorder Type 1, as our results suggest, the proportion of Type 1 and Type 2 is an important factor to consider when interpreting findings from morphometry studies of bipolar disorder.

In general, our cortical findings demonstrate abnormalities in brain regions that are known to be functionally associated with schizophrenia and bipolar disorder. The PFC is associated with “executive” functions that are typically disturbed in schizophrenia and bipolar disorder, such as monitoring the contents of working memory, response inhibition, and goal-directed behavior (36,37). Morphological changes in the frontal lobes have been linked with negative symptoms in schizophrenia (38,39), although links with positive symptoms have also been reported (40). However, it is also possible that the observed morphological changes are related to cognitive deficits. A recent study demonstrated similarities in neurocognitive deficits between schizophrenia and bipolar disorder, and showed that history of psychosis, not diagnostic category, was the determining factor (41). Post mortem studies of schizophrenia have fairly consistently found reduced neuronal size, and some findings suggest increased neuronal density and reduced neuropil, in the PFC and the hippocampus (42). Similar findings, albeit less consistent, have been made in the PFC in bipolar disorder (43), suggesting that the observed cortical thinning in the frontal lobe may represent pathophysiologically relevant changes on the cellular level in both disorders.

The anterior cingulate (AC) connects limbic structures with the PFC and plays an important role in frontolimbic networks regulating emotional and cognitive functions (44), and has therefore been implicated in schizophrenia (45) and bipolar disorder (16). It has been suggested that lithium may increase gray matter density in the AC region (46) but the present lack of significant findings in bipolar disorder probably cannot be explained as an effect of lithium, since the medication analyses failed to show any such effect in this region. However, it should be noted that the effect size in the right AC for bipolar disorder Type 1 vs. control subjects was comparatively high, i.e., relative to schizophrenia vs. control subjects (Tables 2 and 3), and it is possible that this trend could reach significance in a larger sample of patients with bipolar disorder Type 1.

There was bilateral cortical thinning in the lateral temporal lobe in schizophrenia, and in the left posterior STG and right supramarginal gyrus in bipolar disorder Type 1. The lateral temporal lobe contains several structures believed to be important for auditory processing, speech perception, and semantic processing, and, e.g., the planum temporale in the STG has been implicated in psychotic symptoms such as auditory hallucinations and thought disorder (40,47). Gray matter volume reductions in the STG and its subregions have been demonstrated in schizophrenia relative to healthy control subjects in a number of studies (47,48), and STG volume has been shown to correlate negatively with auditory hallucinations and thought disorder (49–52, but see 53,54). Several studies of bipolar disorder have also shown reductions in the left posterior STG, consistent with the present findings (55–57), although negative findings and increased volume have also been reported (58,59), and a recent study showed both thinning and thickening in different portions of the planum temporale (60).

Our findings in the lateral occipital lobes are somewhat unusual in context of the schizophrenia literature (4), although Kuperberg (13) reported cortical thinning in the temporoparietal junction, which overlaps our findings. Although the symptomatology of schizophrenia per se does not suggest visual deficits, behavioral studies have shown defects in various aspects of visual processing, including the ventral “what stream” (61), which corresponds well with our lateral temporo-occipital findings. The effect sizes were smaller in this region than in the frontal and temporal lobes, indicating that these are subtle effects that may require large samples to be reliably detected.
Subcortical Findings

Subcortically, the volume reductions were remarkably similar between schizophrenia and bipolar disorder. As in the cortex, the effect sizes were consistently higher in schizophrenia vs. control subjects than bipolar disorder vs. control subjects (with the exception of cerebellar cortex and brainstem) (Table 4). Excluding bipolar disorder Type 2 from the analyses did not change any of the results. The results could not be explained by the influence of lithium, antipsychotics or antidepressant medication.

There were bilateral hippocampal volume reductions in schizophrenia and bipolar disorder, relative to control subjects. Hippocampal reductions are frequently reported in the schizophrenia literature (5). A meta-analysis of 18 studies reported a 4% bilateral reduction on average (62), which is roughly in line with significant group differences in the cortical significance maps (only left hemisphere). Mean thickness was obtained from Freesurfer, and a general linear model was fitted in the SPSS software, yielding age-adjusted means that were used to obtain Cohen’s d for difference between two means.

Table 2. Mean Cortical Thickness (mm) and Effect Size (d) Within Regions of Interest

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<th>Region</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
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</tbody>
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Ant Cing, anterior cingulate gyrus; BD, bipolar disorder; CTRL, control subjects; IFG, inferior frontal gyrus; Lat Occip, lateral occipital gyrus; MFG, medial frontal gyrus; MTG, middle temporal gyrus; SCZ, schizophrenia spectrum (schizophrenia, schizophreniform disorder, and schizoaffective disorder); SFG, superior frontal gyrus; STG, superior temporal gyrus; SPG, superior parietal gyrus.

The Desikan–Killiany atlas (78) was used to define cortical regions of interest. The regions chosen here overlap reasonably well, albeit not perfectly, with the cortical regions displaying the most significant group differences in the significance maps (only left hemisphere). Mean thickness was obtained from Freesurfer, and a general linear model was fitted in the SPSS software, yielding age-adjusted means that were used to obtain Cohen’s d for difference between two means.

Table 3. Mean Cortical Thickness (mm) and Effect Size (d) for Bipolar Disorder Type 1 and Percent Difference Relative to Schizophrenia and Healthy Control Subjects

<table>
<thead>
<tr>
<th>Region</th>
<th>Left Hemisphere</th>
<th>Right Hemisphere</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BD 1</td>
<td>BD 1-SCZ</td>
</tr>
<tr>
<td></td>
<td>Means</td>
<td>d (%)</td>
</tr>
<tr>
<td>IFG</td>
<td>2.23</td>
<td>.05</td>
</tr>
<tr>
<td>MFG</td>
<td>2.13</td>
<td>.07</td>
</tr>
<tr>
<td>SFG</td>
<td>2.49</td>
<td>−.04</td>
</tr>
<tr>
<td>Ant Cing</td>
<td>2.59</td>
<td>.15</td>
</tr>
<tr>
<td>MTG</td>
<td>2.57</td>
<td>−.01</td>
</tr>
<tr>
<td>STG</td>
<td>2.55</td>
<td>.11</td>
</tr>
<tr>
<td>Lat Occip</td>
<td>1.96</td>
<td>.18</td>
</tr>
<tr>
<td>SPG</td>
<td>1.84</td>
<td>−.10</td>
</tr>
</tbody>
</table>

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The thalamus has been considered central to the pathophysiology of schizophrenia due to its many connections with the PFC and limbic structures such as the hippocampus and the anterior cingulate. A deficit in circuitry connecting the thalamus with limbic and cortical structures, as well as the basal ganglia, could explain a wide range of schizophrenia symptoms (64). The observed hippocampal volume reductions in schizophrenia may be related to cognitive impairment, including memory deficits (65,66), and may also be linked with deficits in the PFC (67–69).

Functional abnormalities in the hippocampus (70), as well as hippocampal volume reductions in schizophrenia may be explained by several neurodevelopmental and neuroplastic mechanisms. In common with many other brain regions, the hippocampus has a high number of glutamatergic dendrites and dendritic spines, as well as a high density of glutamate receptors, which are highly susceptible to the dopaminergic and cholinergic neurotransmitter systems. Furthermore, the hippocampus is involved in the regulation of the release of dopamine and glutamate, which are important for the normal functioning of the limbic system. Finally, the hippocampus is involved in the regulation of the release of dopamine and glutamate, which are important for the normal functioning of the limbic system. This work was supported by the South-Eastern Norway Regional Health Authority (Grant Nos. 2004-123, 2008-011, and 2009-037) and the Research Council of Norway (Grant Nos. 190311/V 50, 167153/V 50). The funding sources had no further role in the design of the study; in the collection, analysis, and interpretation of the data; in writing the manuscript; or in the decision to submit the paper for publication. We thank the study...
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L.M. Rimol et al.

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