Manic episodes are related to changes in frontal cortex: a longitudinal neuroimaging study of bipolar disorder

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Higher numbers of manic episodes in bipolar patients has, in cross-sectional studies, been associated with less grey matter volume in prefrontal brain areas. Longitudinal studies are needed to determine if manic episodes set off progressive cortical changes, or if the association is better explained by premorbid brain conditions that increase risk for mania. We followed patients with bipolar disorder type 1 for 6 years. Structural brain magnetic resonance imaging scans were performed at baseline and follow-up. We compared patients who had at least one manic episode between baseline and follow-up (Mania group, n = 13) with those who had no manic episodes (No-Mania group, n = 18). We used measures of cortical volume, thickness, and area to assess grey matter changes between baseline and follow-up. We found significantly decreased frontal cortical volume (dorsolateral prefrontal and inferior frontal cortex) in the Mania group, but no volume changes in the No-Mania group. Our results indicate that volume decrease in frontal brain regions can be attributed to the incidence of manic episodes.

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Introduction

Bipolar disorder is a common and chronic psychiatric disorder characterized by mood disturbances with recurrent episodes of mania, hypomania, and depression interspersed by euthymic periods with none or subsyndromal mood symptoms (Merikangas et al., 2011). The disorder is not only associated with premature death, significant disability and impaired psychosocial functioning, but also confers significant societal costs that are mainly driven by poor work adjustment and lost productivity (Ekman et al., 2013). Euthymic bipolar disorder is known to be associated with cognitive impairment (Palsson et al., 2013; Sparding et al., 2015). Importantly, some studies suggest a progressive worsening of prefrontal cognitive functions such as executive functions (Altschuler et al., 2004; Frangou et al., 2005; Lim et al., 2013; Sparding et al., 2015). Cross-sectional studies have demonstrated that the number of
Manic episodes correlates with poor cognitive functioning (Lopez-Jaramillo et al., 2010) suggesting that manic episodes might be related to brain changes and worsening of cognitive functioning.

Brain imaging studies comparing patients with bipolar disorder with healthy controls consistently demonstrate smaller cortical volumes in insula, anterior cingulate cortex, and prefrontal cortex (McDonald et al., 2004; Kempton et al., 2008; Arnone et al., 2009; Bora et al., 2012; Selvaraj et al., 2012; Eker et al., 2014; Maller et al., 2014; Savitz et al., 2014). Moreover, studies consistently report disease-related progressive grey matter loss in primarily frontal regions such as prefrontal and anterior cingulate cortex (Lim et al., 2013), which is in line with the frequently observed impairments in executive function in bipolar disorder. Imaging studies also lend some support to the proposition that manic episodes are related to brain abnormalities. We found, for example, a significant inverse correlation between the number of lifetime manic episodes and grey matter volume in the dorsolateral prefrontal cortex (DLPFC) (Ekman et al., 2010). Similarly, Lyoo et al. (2004) found an inverse correlation between the number of previous manic episodes and grey matter volume in the inferior frontal cortex, adjacent to the DLPFC (Lyoo et al., 2004). Although these cross-sectional studies can be interpreted as manic episodes result in decreased grey matter volume (or vice versa), they are also compatible with the notion that less grey matter volume is a premorbid condition that increases the risk of mania. To determine if manic episodes are associated with actual cortical changes in frontal brain regions, a longitudinal study design is needed where grey matter changes and manic episodes are prospectively investigated over time.

The aim of the present study was to test the hypothesis that occurrence of manic episodes is associated with a longitudinal decrease of grey matter volume in frontal brain regions, where previous studies have reported a correlation between the number of manic episodes and grey matter volume: DLPFC (Ekman et al., 2010) and inferior frontal cortex (Lyoo et al., 2004). We scanned the brains of euthymic patients with bipolar disorder type 1 using MRI at baseline and followed them prospectively in a longitudinal study. The MRI scan was repeated after 6 years. We assessed individual change of three different cortical measures (volume, thickness, and area) in DLPFC and inferior frontal cortex, and compared patients who had no manic episode during the follow-up period (No-Mania group) with those who had at least one manic episode (Mania group).

Materials and methods

Participants

Euthymic subjects were recruited from the St. Göran project, which is a long-term follow-up program at the bipolar outpatient unit at the Northern Stockholm psychiatric clinic, Stockholm, Sweden. Details on exclusion and inclusion criteria, diagnostic tools and methods can be found in Ekman et al. (2010). In brief, patients at the unit were invited to participate in the study provided that they were diagnosed with bipolar disorder type I, II, not otherwise specified (NOS) or schizoaffective disorder manic type. The clinical diagnosis of bipolar disorder was established according to the structured interview instrument Affective Disorder Evaluation, which had previously been employed in the Systematic Treatment Enhancement Program for Bipolar Disorders project (Sachs et al., 2003). The Affective Disorder Evaluation includes a social amaness, medical history, and the affective module of the Structured Clinical Interview for DSM-IV. Education information were categorized into: (i) pre-high school (9 years); (ii) high school (12 years average); (iii) university (<3 years, 2 years average); and (iv) university (>3 years, 4 years average). The number of mood episodes, as well as information on comorbidity and medication was determined by at least two board certified clinical psychiatrists through a detailed interview with the participants at time points 1 and 2, under consideration of the patients’ electronic clinical records. Euthymia was defined by Montgomery Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) and Young Ziegler Mania Rating Scale (YMRS) (Young et al., 1978) scores of <14 at each time point. The subjects were not remunerated for participation.

Participants with bipolar disorder type 1 who had completed a baseline brain scan as well as a 6-year follow-up including brain scan and clinical assessment were included in this study (n = 31). The cohort was divided into those who had no manic episodes (the No-Mania group, n = 18) between baseline and follow-up, and those who had at least one manic episode (the Mania group, n = 13). All patients were in euthymic state on scan day, and were scanned in random order during each time point.

The study was approved by the Ethics committee of the Karolinska Institutet, Stockholm, Sweden. After complete description of the study to the subjects, written informed consent was obtained according to the Declaration of Helsinki.

MRI acquisition

MRI scans were acquired at the MR Research Center, Karolinska University Hospital, Stockholm. Coronal 3D T1-weighted images were acquired with a spoiled gradient echo recall sequence (3D-SPGR, repetition time = 21.0 ms, echo time = 6 ms, field of view = 18 cm, flip angle = 30°, acquisition matrix = 256 × 256 × 128, voxel size: 0.7 × 0.7 × 1.8 mm³) using a 1.5-Ta MRI medical scanner (General Electric Signa Excite 1.5T) equipped with an eight channel head coil. Additional axial fluid attenuation inversion recovery T2-weighted scans were acquired for examination by a senior radiologist to exclude clinically significant anatomical abnormalities and neuropathology.

Time point 1 MRI baseline data were acquired from January 2006 to September 2008. Six-year follow-up (Time point 2) MRI data were acquired from August 2012 to March 2014. All subjects were examined with the same MRI scanner and scan protocol at both time points. During time point 1 data acquisition, the calibration filter for the scanner was set from acq=150 to acq=150, the calibration filter for the scanner was set from acq=150 to acq=150.
Image processing

The same investigator manually reoriented all T1-weighted images to the anterior–posterior commissure line using Matlab version 8.1 (R2013a) and SPM8. Measures for cortical volume, cortical thickness, and cortical surface area were obtained using the semi-automated segmentation and cortical surface reconstruction methods provided by Freesurfer v5.1 (Dale et al., 1999; Fischl et al., 1999, 2004a, b; Fischl and Dale, 2000) for methodological details. In brief, the procedure includes intensity normalization, removal of non-brain tissue, segmentation of cortical grey, subcortical white, deep grey matter volumetric structures, as well as triangular tessellation of the grey/white matter interface and the pial surface (white matter/CSF boundary). Cortical thickness was calculated as the closest distance from the grey/white to the pial surface at each vertex on the reconstructed surfaces. All surface reconstructions were visually inspected and, where necessary, corrected manually by trained operators using editing tools provided by Freesurfer, including corrections of erroneous skull stripping, white matter and grey matter segmentations. Freesurfer also allows an automated parcellation of the cortical surfaces into 34 anatomical regions of interest (Desikan atlas) (see Fischl et al., 2004a, Desikan et al., 2006 for technical details). For each region of interest, measures were obtained from subjects’ native space. Although longitudinal image processing methods have improved during the last few years, to present results unaffected by any possible bias induced by longitudinal processing (Reuter and Fischl, 2011; Reuter et al., 2012), we present the findings obtained by individual image processing in the main body of the manuscript. Results obtained by performing additional longitudinal processing steps are presented in Supplementary Table 5. At this point, we preface that the results obtained with these two processing methods led to the same conclusions.

We investigated two specific frontal regions of interest, the DLPFC and the inferior frontal cortex. For each participant and for each time point, a left and right DLPFC region of interest was constructed by summing (cortical volume and cortical surface area), or averaging (cortical thickness) measures extracted from superior frontal, rostral, and caudal middle frontal subregions (as in Durazzo et al., 2013; Vijayakumar et al., 2014). The inferior frontal cortex region of interest was built by combining the pars opercularis, pars triangularis, and pars orbitals subregions. The total DLPFC and inferior frontal cortex was then created by combining the measures from left and right hemispheres. For each participant, we calculated the relative difference in DLPFC volume, thickness, and surface area by subtracting the measure at time point 1 from the corresponding measure obtained at time point 2. We then scaled the outcome to the participants’ outcome measure at time point 1 to obtain a measure reflecting an individual’s relative cortical change in per cent between time points 1 and 2. Negative values thus reflect a decrease and positive values an increase in grey matter volume, thickness or area between time points 1 and 2. Values close to zero indicate that no change occurred over time.

The regions (MNI coordinates of cluster peaks) reported in previous studies on which we based the DLPFC and inferior frontal cortex regions of interest are regionally close. They might be located between, and/or comprise parts of both, DLPFC and inferior frontal cortex. Therefore, we separately investigated the six adjacent individual regions from which the DLPFC and inferior frontal cortex regions of interest were built up in an explorative analysis.

Statistical analyses

To determine left/right hemisphere asymmetry, cortical volume, cortical thickness, and cortical surface area changes in left and right DLPFC and inferior frontal cortex were compared within each group using paired sample t-tests. Group differences in the change variables were tested in separate univariate analyses of covariance (ANCOVA) as implemented in SPSS v20, with the change variables as dependent variables and group as fixed factor. The MRI scanner calibration filter was set up as a binary covariate assigning 0 to subjects scanned with the SCIC and 1 to those scanned with the PURE filter setup. We also tested for effects of age, years of education, intracranial volume, time difference between time points 1 and 2, body mass index, number of lifetime manic episodes (before time point 1), and sex by entering those variables separately or simultaneously with MRI filter as covariates.

Significant ANCOVA findings (P < 0.05) in which the variable ‘group’ was a significant predictor were followed up with t-tests to further investigate the main effect of group. In the main analysis, alpha levels (P = 0.05) for group comparisons were corrected for multiple comparisons with an adjusted Bonferroni method using the average inter-correlation coefficient of all six investigated measures (cortical volume, cortical thickness, and cortical surface area for DLPFC and inferior frontal cortex, respectively; r = 0.51) (Sankoh et al., 1997). The corrected alpha level, reflecting the upper threshold for P-values that can be considered as significant after Bonferroni adjustment, was P = 0.021 for the main analysis. The inter-correlation coefficient of all individual regions (cortical volume, cortical thickness, and cortical surface area for superior, caudal and rostral middle frontal, pars opercularis, triangularis and orbitalis) was r = 0.43, rendering a corrected alpha of 0.010 for the explorative analysis. Effect sizes for group mean differences were calculated via Cohen’s d.

To test if the observed change variables in each group differed from zero, i.e. if a change occurred or not, the change variables were analysed within each group separately using one-sample t-tests. The same adjusted Bonferroni approach was used to correct alpha levels in one-sample t-tests. Adjusted alpha for the main analysis was 0.020 (r = 0.48) in the No-Mania and 0.019 (r = 0.46) in the Mania group. Adjusted alpha for all 18 individual tests in the explorative analysis was 0.009 (r = 0.39) in the No-Mania and 0.008 (r = 0.38) in the Mania group. Distributions of all investigated variables were tested for normality using the one-sample Kolmogorov-Smirnov test. Correlations among demographic measures were calculated with Spearman’s Rho.

Results

Patient characteristics

Table 1 displays the clinical characteristics of the groups. The Mania and No-Mania groups were similar with respect to age, years of education, body mass index (BMI), age of
onset, duration of the disease, the number of manic and depressive episodes at baseline (time point 1), number of patients who had depressive episodes between time points 1 and 2, and the number of depressive episodes between time points. BMI did not change significantly over time in any of the groups. The groups did not differ in the time elapsed between time points 1 and 2. Despite that the Chi$^2$ for sex was not significant, possible effects of sex were considered and tested in the statistical analyses below. The Mania group had on average two manic episodes between the time points 1 and 2 (nine participants with one manic episode, two with two, one with three, and one participant with 10 manic episodes). The No-Mania group had per definition no manic episode between time points 1 and 2.

Table 2 outlines drug use and psychiatric comorbidities. In each group and at both time points, about 80% of participants used lithium. Other mood stabilizers were used by 38% of the Mania group and 20% of the No-Mania group at each time point. At each time point, antipsychotic medication was used by ~50% of the Mania group and ~30% of No-Mania group. Antidepressants were used by 40% in the Mania group at both time points, whereas in the No-Mania group 60% of used antidepressants at time point 1 and 30% at time point 2: seven participants in the No-Mania group discontinued and one participants started antidepressant medication between the two time points. Fischer’s exact $\chi^2$ tests indicated a significant difference in antidepressant use between time points 1 and 2 in the No-Mania group, which was not significant in Mania. Hence, the drug use was comparable among groups and time points except for antidepressant use. We compared the MRI outcome measures between No-Mania patients who changed antidepressant use over time and those who did not. No differences in any of the investigated outcome measures were observed. Table 2 also displays psychiatric comorbidities and the prevalence of patients with a history of psychosis. The numbers of participants with psychiatric comorbidities were balanced in both groups at each time points. Thus, neither psychiatric comorbidities nor pharmacological treatment are likely to confound the group comparison (see also Phillips et al., 2008; Hafeman et al., 2012) and was not corrected for in the main statistical analyses. However, because some medications, especially lithium, were associated with cortical changes (Hafeman et al., 2012), we conducted analyses where we controlled for medication used at time points 1 and 2, respectively. The results of those follow-up tests can be found in the Supplementary Tables 2 and 3. Here we want to note that interpreting the results controlled for medication is not trivial. Symptoms and use of a specific medication might be related to the patients’ brain morphology, which in turn might be related to the incidence of mania. Hence, controlling for medication use might in fact disguise effects the authors are interested in to detect.

### Cortical measures

As no bilateral differences were observed, all measures of left and right hemisphere were combined to a total measure. The Mania and No-Mania groups differed significantly in cortical volume change between time points 1 and 2 (Table 3 and Fig. 1): whereas the DLPFC (and inferior...
frontal cortex) volume decreased over time in the Mania group, no change was observed in the No-Mania group. The Mania and No-Mania groups also differed in the change of cortical thickness that occurred between time points 1 and 2; whereas the DLPFC thickness increased in the No-Mania group, it tended to decrease in the Mania group \((P = 0.140)\) (indicated as not significant in Table 3). The same trend was observed for inferior frontal cortex, although this finding did not survive multiple comparison correction. The cortical thinning observed in the Mania group was significant after longitudinal image processing, however, the increase in cortical thickness in No-Mania was not observed, and therefore should be treated with caution (Supplementary Table 5). The Mania and No-Mania groups did not differ in the per cent change of cortical area between time points. However, one-sample t-tests for each group separately indicated that DLPFC and inferior frontal cortex surface area decreased 3.0–4.5% in both groups.

In a post hoc sensitivity analysis, we compared the No-Mania group with those Mania patients who only had one single manic episode between time points 1 and 2, thus excluding four participants. The results did not change (Supplementary Table 1). This is also the case when removing one participant with eating disorder from the analysis. Age, sex, the interscan interval, BMI, the number of lifetime manic and depressive episodes at baseline, the number of depressive episodes between time points 1 and 2, intracranial volume, cortical volume/area/thickness at baseline, age of disease onset, history of psychosis, or number of years ill, respectively, were either not significant predictors in the statistical model and/or using them as covariates in group comparisons did not change the reported results in a significant manner. The same applied for medication use (Supplementary Table 2 and 3). Comparing cortical change measures in the combined cohort correcting for group assignment revealed no differences between sexes. Groups were also equivalent on cortical volume, thickness, and area at baseline. In the combined cohort, as well as in Mania, there was no correlation between the number of manic episodes at baseline and the number of life time manic episodes between time points. The number of manic episodes between time points did not correlate with the time difference between scans. The same applied for depressive episodes. The number of depressive episodes did not correlate with the number of manic episodes between time points.

**Discussion**

Frontal abnormalities are frequently reported in bipolar disorder and consistent with observed deficits in executive functioning, which mainly involve prefrontal brain regions. We prospectively investigated prefrontal cortical changes in thickness, volume, and surface area over a 6-year period in patients with bipolar disorder type 1. We compared patients who had at least one manic episode between baseline and follow-up (Mania group) with those who had no manic episode (No-Mania group) during the same time period. The main finding is that progressive frontal cortical abnormalities were strongly related to manic episodes.

In the Mania group, we found that cortical volume and area decreased in both DLPFC and inferior frontal cortex. The cortical thickness in DLPFC and inferior frontal cortex showed a tendency to decrease (not statistically significant). Hence, the decreased cortical volume could be explained by a combination of decreased cortical area and cortical thinning, which is further supported by results shown in Supplementary Table 5. Our explorative analysis of smaller regions of interest revealed that the mania-associated volume decrease might be spread over a wider area of frontal regions, but with largest effect sizes in the rostral middle frontal region (Table 4). It is worth mentioning that a decreased cortical volume was observed also when we excluded patients with more than one manic episode. This indicates that a significant decrease of cortical volume in frontal regions can be attributed to one single manic episode, further emphasizing potential severe consequences of a single manic episode.

By contrast, we found no detectable change in DLPFC and inferior frontal cortex cortical volume in the No-Mania group. Although the surface area decreased, this effect might have been countered by increased cortical thickness resulting in unaltered cortical volume in the No-Mania group. Hence, our findings suggest that incident manic episodes are associated with actual cortical volume changes in frontal brain regions.
Our results agree with previous cross-sectional studies revealing negative correlations between the number of manic episodes and grey matter volume in DLPFC (Ekman et al., 2010) and inferior frontal brain regions (Lyoo et al., 2004). Whereas those cross-sectional studies could not determine whether prefrontal abnormalities were premorbid characteristics of patients susceptible to mania or whether they had developed in relation to the manic episodes, the present study suggest that manic episodes are strongly associated with actual changes in prefrontal structures. Moorhead et al. (2007) also reported a correlation between the number of manic episodes and decreased cortical volume in a 4-year follow-up study of 20 patients. Although they limited their investigation to a temporal...
cortical region (fusiform gyrus), their study nevertheless concords with the notion that manic episodes in bipolar disorder are related to progressive grey matter changes (see Supplementary Table 4 for a further exploration of mania-associated cortical changes in the fusiform). However, even though the fact that we did not observe any DLPFC volume changes in the No-Mania groups over 6 years argues against that, we cannot completely rule out that some grey matter volume loss might have preceded the manic episodes and increased the risk for mania in the Mania group.

The mechanisms underlying progressive structural brain changes in the Mania group are unknown. However, processes involving altered secretion of neurotrophic factors could play a role: a recent study found lower levels of secretogranin II—a neuroprotective compound that reflects secretion of neurotrophins—in CSF from patients with bipolar disorder type 1 (but not type 2) compared to controls (Jakobsson et al., 2013). Mania is also associated with stress-induced elevation of cortisol and adrenocorticotropic hormone (Schneider et al., 1995) that could contribute to small vessel disease. Indeed, one study found higher CSF levels of neurofilament light chain that is indicative of axonal damage (Jakobsson et al., 2014). Neuroinflammatory activation during mania involving proinflammatory cytokines has also been suggested to play a role in neuroprogression (Barbosa et al., 2014). In line with this, we found higher CSF levels of interleukin 8 (Isgren et al., 2015) and interleukin-1beta (Soderlund et al., 2011) in CSF from patients with bipolar disorder compared with controls. Thus, stress-induced neuronal degeneration and/or dendritic remodelling, as well as prefrontal hypometabolism (Brooks and Vizueta, 2014; Savitz et al., 2014) associated with mania are possible explanations for the observed grey matter loss in the Mania group, and agrees with the idea that mania precedes the grey matter loss.

Another notable finding is that the cortical thickness in the DLPFC increased from baseline to follow-up in the No-Mania group. Increased cortical thickness is commonly interpreted as better cortical/neuronal integrity and has been positively related to cognitive function (Walhovd et al., 2006; Makris et al., 2007; Choi et al., 2008, Karama et al., 2009; Engvig et al., 2010; Durazzo et al., 2013). Given that all subjects at baseline had endured some manic episodes, which are associated with grey matter loss, it is tempting to speculate that the observed cortical thickening at follow-up reflects a healing process that might occur if manic episodes are avoided. Whether this is the case, however, requires further investigation. The observed increase in cortical thickness could also be an effect of medication not coupled to cognitive improvements. Moreover, the increase of cortical thickness was not significant when longitudinal processing was performed (Supplementary material) and therefore should be treated with caution.

**Strengths and limitations**

The main strength of this study is the prospective and longitudinal nature, where we were able to follow patients...
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over a 6-year period during which the course of illness was meticulously documented. Both patient groups were randomly scanned during the same time periods at each time point. Moreover, the same scanner was used for baseline and follow-up investigation, which was checked for signal stability and geometry consistency four times per year. Thus, possible scanner drifts over time are unlikely to have influenced the observed group differences. We investigated three distinct cortical measures rather than merely assessing grey matter volume alone. This gives more insight into underlying biological mechanisms of cortical changes, which might be distinguishable by disease symptomatology. It is noteworthy that we detected significant changes without reducing variability by using additional longitudinal processing steps provided by Freesurfer. In addition, the reported results were not affected by bias from longitudinal processing methods as described in Reuter and Fischl (2011) and Reuter et al. (2012).

There are also some limitations to consider. First, even though our study is one of the largest long-term follow-up MRI studies of bipolar disorder to date, the sample size was limited to 31 subjects. Second, we assessed relatively large cortical regions defined by the Desikan’s atlas. Whole brain analyses with higher regional resolution, including the investigation of subcortical volumes, in larger study groups would give more detailed information on the effects of manic episodes on structural brain changes. Third, although the here observed cortical decline in the Mania group is higher than normal age-related changes reported by previous studies (Lemaître et al., 2012), the inclusion of control data can help in identifying to what extent. Moreover, while our main conclusion that mania is associated with cortical grey matter loss was consistent across both processing methods, it remains undecided if cortical thickness increases in the No-Mania group, warranting further investigation. Last, there might be confounding factors that may have influenced the findings, for example differences in diet and exercise, undocumented drug use, as well as genetic, social and environmental factors. As the groups were balanced in medication use and psychiatric comorbidities, it is unlikely that those factors significantly influenced the observed group differences. However, larger study samples, the consideration of medication dosage, and ideally placebo controlled clinical trials, would be needed to identify the degree to which those factors play out. Finally, as in all longitudinal studies over long time periods, high attrition rates are a common problem (in our case ~35%). Thus, it is unknown if cortical changes are of same nature in unmedicated patients, or patients who were lost to follow-up investigations.

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Supplementary material

Supplementary material is available at Brain online.

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