Cortical folding in patients with bipolar disorder or unipolar depression

Jani Penttilä, MD, PhD; Marie-Laure Paillère-Martinot, MD, PhD; Jean-Luc Martinot, MD, PhD; Damien Ringuenet, MD; Michèle Wessa, PhD; Josselin Houenou, MD; Thierry Gallarda, MD; Frank Bellivier, MD, PhD; André Galinowski, MD, MSc; Pascale Bruguière, PhD; François Pinabel, MD; Marion Leboyer, MD, PhD; Jean-Pierre Olié, MD, PhD; Edouard Duchesnay, PhD; Eric Artiges, MD, PhD; Jean-François Mangin, PhD; Arnaud Cachia, PhD

Penttilä, Paillère-Martinot, Martinot, Ringuenet, Wessa, Houenou, Duchesnay, Artiges, Mangin, Cachia — INSERM, U797 Research Unit "Neuroimaging & Psychiatry," the CEA, "Neuroimaging & Psychiatry" U797 Unit, Hospital Department Frédéric Joliot & Neurospin, Paris Sud University, Orsay, and Rene Descartes University, Paris; Paillère-Martinot — Assistance Publique–Hôpitaux de Paris (AP-HP), Department of Adolescent Medicine, Maison de Solenn, Cochin Hospital, Paris; Ringuenet — AP-HP; Department of Psychiatry and Addictology, Paul Brousse Hospital, Villejuif, France; Wessa — Department of Cognitive and Clinical Neuroscience, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany; Houenou, Bellivier, Leboyer — AP-HP; Department of Psychiatry, Chenevier-Mondor Hospital, Créteil; Gallarda — SHU, Department of Psychiatry, Sainte Anne Hospital, Paris; Bellivier, Leboyer — INSERM, U 995, IMRB, Department of Genetics, Psychiatry Genetics, Creteil, F-94000, University Paris 12, Faculty of Medicine, IFR10, Creteil; Galinowski, Olié — INSERM, Pathophysiologie des Maladies Psychiatriques, U894-7, Université Paris Descartes, Faculté de Médecine Paris Descartes, SHU, Hôpital Sainte-Anne, Paris; Bruguière — INSERM, U731, Paris, F 75013, University Pierre & Marie Curie-Paris 6, UMR S 731, Paris, F 75013, AP-HP, Pitié-Salpêtrière Hospital, Department of Physical Medicine and Rehabilitation; Pinabel — AP-HP, Department of Adult Psychiatry, Kremlin-Bicêtre Hospital, France; Duchesnay, Mangin — LNAO, NeuroSpin I^{2}BM, Saclay, France

Background: Analysis of cortical folding may provide insight into neurodevelopment deviations, which, in turn, can predispose to depression that responds particularly poorly to medications. We hypothesized that patients with treatment-resistant depression would exhibit measurable alterations in cortical folding. **Methods:** We computed hemispheric global sulcal indices (g-SIs) in T_1-weighted magnetic resonance images obtained from 76 patients and 70 healthy controls. We separately searched for anatomic deviations in patients with bipolar disorder (16 patients with treatment-resistant depression, 25 with euthymia) and unipolar depression (35 patients with treatment-resistant depression). **Results:** Compared with healthy controls, both groups of patients with treatment-resistant depression exhibited reduced g-SIs: in the right hemisphere among patients with bipolar disorder and in both hemispheres among those with unipolar depression. Patients with euthymic bipolar disorder did not differ significantly from depressed patients or healthy controls. Among patients with bipolar disorder who were taking lithium, we found positive correlations between current lithium dose and g-SIs in both hemispheres. **Limitations:** We cannot estimate the extent to which the observed g-SI reductions are linked to treatment resistance and to what extent they are state-dependent. Furthermore, we cannot disentangle the impact of medications from that of the affective disorder. Finally, there is interindividual variation and overlap of g-SIs among patients and healthy controls that need to be considered when interpreting our results. **Conclusion:** Reduced global cortical folding surface appears to be characteristic of patients with treatment-resistant depression, either unipolar or bipolar. In patients with bipolar disorder, treatment with lithium may modify cortical folding surface.

Contexte : L'examen des plissements du cortex pourrait fournir un argument en faveur de déviations de son développement qui, en retour, prédisposeraient certains individus à la dépression réfractaire à la pharmacothérapie. Nous avons formulé l'hypothèse que les

Correspondence to: Dr. M.-L. Paillère-Martinot, Maison de Solenn, Hôpital Cochin, 97 boul. de Port-Royal, 75014 Paris, France; fax 33 1 6986 7810; ml.paillere@cch.aphp.fr

J Psychiatry Neurosci 2009;34(2):127-35.

Submitted Mar. 20, 2008; Revised May 22, Sep. 2, 2008; Accepted Sep. 3, 2008

patients ayant une dépression réfractaire au traitement présenteraient des anomalies mesurables des plissements corticaux. **Méthodes :** Nous avons calculé des indices hémisphériques globaux de sulcation (g-SI) à partir des images par résonance magnétique pondérées en T_1 obtenues chez 76 patients et de 70 témoins sains. Nous avons recherché des déviations anatomiques de manière séparée chez des patients atteints de trouble bipolaire (16 patients ayant une dépression réfractaire au traitement et 25 en état euthymique) et chez des patients ayant une dépression unipolaire (35 patients atteints de dépression réfractaire au traitement). **Résultats :** Comparativement aux témoins sains, les 2 groupes de patients atteints de dépression réfractaire au traitement présentaient une diminution des g-SI : dans l'hémisphère droit chez les patients atteints de trouble bipolaire et bilatéralement chez les patients atteints de dépression unipolaire. Les patients ayant un trouble bipolaire euthymique ne différaient pas significativement des patients déprimés ou des témoins sains. Parmi les patients ayant un trouble bipolaire qui prenaient du lithium, nous avons observé des corrélations positives entre la dose actuelle de lithium et les indices de sulcation dans les 2 hémisphères. **Limites :** Nous ne pouvons déterminer dans quelle mesure les réductions des indices observées sont liées à la résistance au traitement ou à l'état des patients. En outre, nous ne pouvons distinguer l'impact des médicaments de celui des troubles affectifs. Enfin, l'existance d'une variation inter-individuelle et d'un chevauchement des valeurs des g-SI entre patients et témoins doit être prise en compte dans l'interprétation des résultats. **Conclusion :** La réduction globale de la surface des plissements corticaux semble caractéristique des patients ayant une dépression réfractaire au traitement qu'elle soit unipolaire ou bipolaire. Chez les patients atteints de trouble bipolaire, le traitement au lithium pourrait modifier la surface des sillons corticaux.

Introduction

Affective disorders have increasingly been associated with deviations in brain structure,[1–3] such as a widening of cortical sulci in bipolar disorder.[4] Some of these alterations may be neurodevelopmental,[5] whereas others appear to develop with repeated affective episodes.[3] In the human brain, the mature sulco-gyral pattern is thought to result from fetal and childhood processes that have shaped the cortical anatomy from a smooth lissencephalic structure to a highly convoluted surface.[6,7] This cortical folding process may be mediated in part by mechanical forces stemming from grey matter thickness and white matter connectivity.[8–10] Thus, the study of cortex gyrification and sulcation may provide insight into neurodevelopmental deviations, which, in turn, can predispose to depression that responds particularly poorly to treatment.[11]

We hypothesized that patients with treatment-resistant depression would exhibit measurable alterations in cortical folding. To test this hypothesis, we measured hemispheric sulcal folding surface in magnetic resonance images (MRIs) obtained from patients with treatment-resistant unipolar depression or bipolar disorder, patients with euthymic bipolar disorder and healthy controls. Since unipolar depression and bipolar disorder are considered to differ in their neurobiological basis,[12] we performed our analyses using a diagnosis-specific approach.

Methods

Participants

Between February 2001 and June 2006 we recruited patients from consecutive admissions at an outpatient clinic and 5 psychiatry wards of university hospitals in Paris, France. The 1.5 T General Electric MRI procedure described in the section that follows was stable during this time period. Experienced senior psychiatrists (D.R., J.H., T.G., F.B., A.G., P.B., F.P.) established the patients' diagnoses using the DSM-IV[13] and the Mini-International Neuropsychiatric Interview.[14] We enrolled the patients in 2 different brain imaging protocols. The present study describes sulcal analyses of pooled data separately for patients with bipolar disorder (Study 1) and unipolar depression (Study 2). We also recruited healthy controls by word of mouth, and we enrolled them in the study at the same time as the patients. They had no personal history of psychiatric or neurological disorders, as assessed by the Mini-International Neuropsychiatric Interview and a medical examination. We used the same group of healthy controls for comparison with participants in the Study 1 and Study 2 subgroups.

Our studies were carried out in accordance with the Declaration of Helsinki. The local ethics committees (AP-HP-Salpêtrière and Bicêtre hospitals) approved our protocol, and, after complete description of the studies, each participant provided written informed consent.

Study 1

The Study 1 subgroup included 16 patients with bipolar disorder who fulfilled the criteria of a current major depressive episode. We considered these patients' conditions to be treatment-resistant based on lack of response to at least 2 antidepressants from different pharmacologic classes taken for at least 1 month in adequate dosages.[15] These patients had been treated with minimal and stable doses for at least 2 weeks to be included in a transcranial magnetic stimulation protocol.[16] This subgroup also included 25 patients with euthymic bipolar disorder who scored 5 or lower on the 21-item Hamilton Depression Rating Scale (HAM-D)[17] and 8 or lower on the Young Mania Rating Scale.[18] We determined that these patients did not have a history of treatment-resistant depression based on their hospital admission records and interviews with experienced psychiatrists (M.L., J.H., M.L.P.M.). The patients in this group were originally recruited for a functional MRI study.[19]

Study 2

The Study 2 subgroup included 35 patients with treatment-resistant[15] unipolar depression with a current major depressive episode who were originally included in the same protocol as the depressed patients with bipolar disorder in the Study 1 subgroup. Similarly, these patients with unipolar

depression had been treated with minimal and stable medication doses for at least 2 weeks preceding the study.

Exclusion criteria for all groups were electroconvulsive therapy (ECT) during the 6 months preceding the study, alcohol or substance dependence, any serious medical condition or history of neurological disorders.

We recorded demographic and clinical data for each participant. We rated level of education as follows: 1 = no secondary education, 2 = a vocational training certificate or a professional studies certificate taken at a secondary education school, 3 = a high school diploma, 4 = 2 years of study after high school, 5 = more than 2 years of study after high school. We assessed handedness using the Annett questionnaire,[20] in which a score of 100 corresponds to maximal right-handedness and a score of –100 corresponds to maximal left-handedness.

We clinically evaluated patients using the HAM-D[17] and the Montgomery and Åsberg Depression Rating Scale.[21] We also evaluated the patients with euthymic bipolar disorder using the Young Mania Rating Scale.[18]

Magnetic resonance imaging and estimation of global sulcal indices

We acquired three-dimensional (3D) high-resolution anatomic images with a 1.5 T General Electric Signa System scanner (General Electric Medical Systems) and a 3D T_1-weighted fast spoiled gradient echo sequence, which provided a high contrast between grey and white matter (124 contiguous slices of 1.3-mm thickness, field of view 24×24 cm, matrix 256×256, voxel size $0.94 \times 0.94 \times 1.3$ mm; echo time = 2.2 ms, inversion time 600 ms, repetition time = 12.5 ms, 2 excitations). These high resolution images enabled reconstruction of the fine individual cortical folds required for sulcus segmentation.[22]

To assess cortex gyrification, we subjected the raw MRI data to automated estimation of sulcus areas[23] by means of a 3-step procedure[24] using BrainVISA software (http://brainvisa.info/). This method has recently been applied to the investigation of cortical folding abnormalities in patients with schizophrenia.[23,24] First, we segmented the brain tissues (cerebrospinal fluid [CSF], grey and white matter) from non-normalized raw MRI data using a fully automatic procedure.[22] For each participant's hemisphere, we estimated total intracranial volume as the sum of grey matter, white matter and CSF volumes. We also calculated corrected hemispheric brain tissue volumes (raw volumes divided by total intracranial volume) to control for intersubject global brain volume differences. Second, we automatically segmented the cortical folds throughout the cortex from the skeleton of the grey matter/CSF mask and created a graph-based representation of the cortex containing information related to morphology (area, depth and length) and spatial organization (relative position, relative orientation).[22] No spatial normalization was applied to the MRI data to overcome potential bias due to the sulcus shape deformations induced by the warping process. Third, we computed the area of each cortical fold as the sum of all the triangle areas defining the fold mesh. We measured the global sulcal index (g-SI) for each hemisphere as the ratio between the total sulcal area (i.e., the sum of the areas of all segmented cortical folds) and the outer cortex area. We defined the hemispheric outer cortex area as the area of a smooth envelope of the brain mask. The envelope was achieved with a morphologic closing of the brain mask;[22,25] we used an isotropic closing of 5 mm to ensure the boundary smoothness.

A cortex with extensive folding has a large g-SI, whereas a cortex with low degree of folding has a small g-SI (Fig. 1). At constant outer cortex area, the g-SI increases with the number and/or area of sulcal folds, and, on the contrary, the g-SI of a lissencephalic cortex is 0. The g-SI describes the burying of the cortex and is therefore slightly different from the standard two-dimensional (2D) gyrification index,[26–28] which embodies additional information related to the cortex thickness and the sulcal opening.

For each participant, we visually checked all the image-processing steps, and we detected no gross segmentation

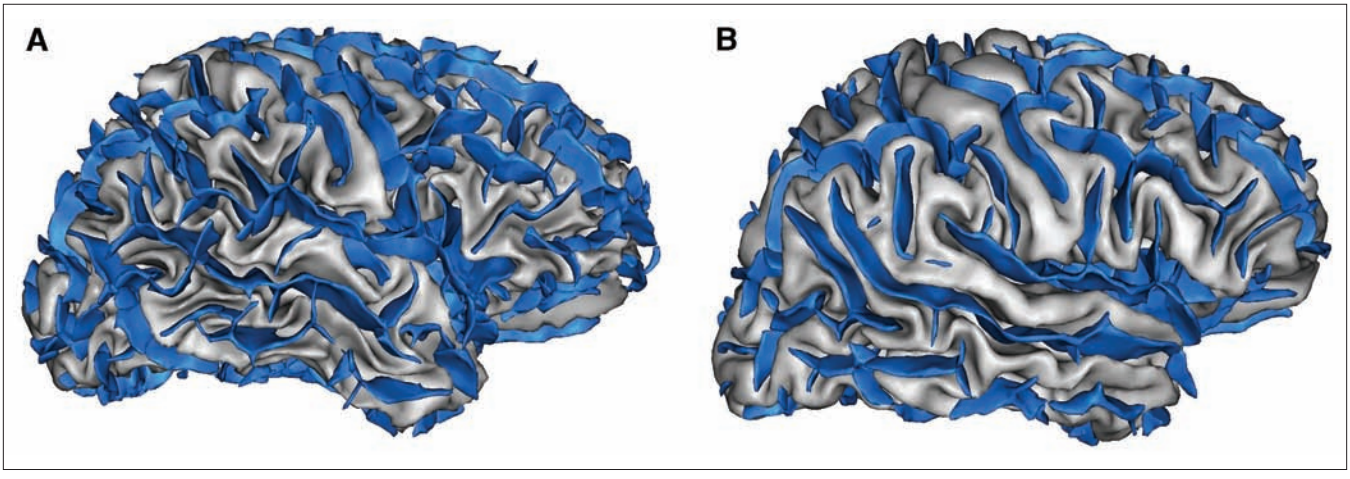

Fig. 1: Lateral views of the right hemispheres of 2 participants, illustrating (**A**) a high and (**B**) a low degree of overall sulcation. Reconstructed sulci are shown on a background of white matter mesh. (**A**) A 26-year-old healthy man; global sulcal index (g-SI) = 1.746. (**B**) A 56-year-old woman with treatment-resistant unipolar depression; g-SI = 1.221.

error (e.g., cortical ribbon thinning, gyrus or sulcus missing). We manually corrected minor segmentation errors, which most often occurred in the margin between the occipital lobes and the cerebellum. We computed g-SIs automatically with no manual intervention.

Statistical analysis

We performed our statistical analyses separately for Study 1 and Study 2, using the same principles. We assessed between-group differences in hemispheric g-SIs and grey and white matter volumes using univariate multiple regression analyses within the framework of the linear model, with group, sex and education as factors and age as a numeric covariate. To estimate the confounding effect of cortical grey matter volume on g-SI differences, we also performed statistical analyses using corrected grey matter volume as a covariate. When we detected a significant main effect of group, we continued our analysis with post hoc paired comparisons using a Tukey test with Bonferroni correction.

We probed statistical significance with F tests in the linear model and with t tests in the paired post hoc analyses. We considered a 2-sided $p < 0.05$ to be statistically significant. We performed all statistical analyses with R 2.5 software (www.r-project.org/), using dedicated libraries ("car," "effects" and "multtest") for the analysis of linear models.

We separately examined the possible effects of patients' current use of psychotropic drugs (mood-stabilizing agents, antidepressants, antipsychotics or benzodiazepines), number of manic or depressive episodes during the course of the illness, duration of illness/current episode and age at onset of illness by adding each as a covariate in the linear models, where we simultaneously used sex and education (and also patient group in Study 1) as factors and age as a numeric covariate. We further investigated the effect of lithium (Study 1) by calculating rank-based nonparametric Spearman correlation coefficients for the relations between g-SIs and the current dose of lithium and the duration of treatment.

Results

Participants

We included 76 patients and 70 healthy controls in our study. The Study 1 subgroup comprised 41 patients with bipolar disorder (16 with treatment-resistant depression and 25 with euthymia). The Study 2 subgroup comprised 35 patients with unipolar depression. We also included 70 healthy controls. Participant characteristics are provided in Table 1. In Study 2, the between-group difference in sex ratio reached statistical significance ($\chi^2 = 4.317$, $p = 0.037$), but apart from that the patient groups in Studies 1 and 2 did not differ significantly with respect to the presented demographic variables (assessed using χ^2 test or analysis of variance).

Study 1

Of the 16 patients with treatment-resistant depression, 4 patients were taking mood-stabilizing agents (2 lithium), 2 were taking antipsychotics, 5 were taking antidepressants and 8 were taking benzodiazepines. Three patients had received ECT. Of the 25 patients with euthymia, 19 were taking mood-stabilizers (11 lithium), 7 were taking antipsychotic drugs,

Table 1: Demographic and clinical characteristics of patients and controls

	Group; mean (SD)*			
	Bipolar disorder			
Characteristic	Depression Study 1 (n = 16)	Euthymia Study 1 (n = 25)	Unipolar depression Study 2 (n = 35)	Control† (n = 70)
Sex, male:female	7:9	14:11	11:24	37:33
Age, yr	46.4 (6.6)	46.6 (12.5)	47.2 (8.8)	42.8 (11.5)
Weight, kg	70.8 (14.1)	73.1 (14.8)	72.7 (14.5)	69.9 (11.4)
Height, cm	168.1 (8.4)	171.7 (11.0)	166.9 (8.0)	169.6 (9.4)
Education‡	3, 0, 1, 1, 10	1, 1, 2, 7, 13	12, 5, 3, 3, 12	13, 10, 7, 7, 32
Handedness, Annett score§	83.4 (49.4)	63.1 (60.1)	85.6 (45.1)	82.5 (32.5)
Age at onset of illness, yr	25.6 (8.0)	23.3 (9.7)	30.2 (10.8)	—
Duration of illness, yr	20.8 (8.8)	23.3 (12.5)	16.9 (9.6)	—
No. of major depressive episodes	4.5 (1.9)	3.1 (2.2)	3.6 (1.7)	—
No. of manic episodes	1.2 (1.2)	2.7 (2.6)	0.0 (0.0)	—
Treatment responsiveness	Treatment-resistant	Treatment-responsive	Treatment-resistant	—
Current state	Major depressive episode	Euthymia	Major depressive episode	—
Duration of current state, yr	2.8 (2.8)	4.7 (6.1)	2.4 (1.8)	—
HAM-D score	24.1 (4.3)	1.7 (1.6)	27.4 (6.9)	—
MADRS score	33.6 (7.2)	1.9 (1.9)	32.9 (7.6)	—
YMRS score	—	1.0 (2.0)	—	—

HAMD = Hamilton Depression Rating Scale;[17] MADRS = Montgomery and Åsberg Depression Rating Scale;[21] SD = standard deviation; YMRS = Young Mania Rating Scale.[18]
*Unless otherwise indicated.
†The same control group was used for comparison with patients in Studies 1 and 2.
‡Number of participants at levels 1, 2, 3, 4 and 5 of education, respectively, where 1 = no secondary education, 2 = a vocational training certificate or a professional studies certificate taken at a secondary education school, 3 = a high school diploma, 4 = 2 years of study after high school and 5 = more than 2 years of study after high school.
§The scale is from –100 (maximal left-handedness) to 100 (maximal right-handedness).

8 were taking antidepressants and 6 were taking benzodiazepines. Two patients had previously received ECT.

There were no between-group differences in hemispheric grey matter volumes (Table 2) or white matter volumes (data not shown; $F_2 \leq 1.0$, $p > 0.30$). The g-SI analyses revealed a statistically significant between-group difference: compared with healthy controls, patients with bipolar disorder and treatment-resistant depression had, on average, 4% smaller g-SIs in the right hemisphere ($p = 0.040$) (Table 2 and Fig. 2A). We observed a significant main effect of corrected grey matter volume on g-SIs in both hemispheres ($F_1 > 11$, $p < 0.001$). When we added corrected grey matter volume as a

Table 2: Main results of global sulcal index and grey matter volume analyses in Study 1

	Group; mean (SD)*			Group difference		
				Main effect		
Brain hemisphere; measure	Bipolar disorder and depression ($n = 16$)	Euthymic bipolar disorder ($n = 25$)	Control ($n = 70$)	F_2	p value	Paired post hoc comparisons
Left hemisphere						
g-SI	1.409 (0.102)	1.451 (0.103)	1.466 (0.099)	2.1	0.13	
Grey matter volume, cm^3	238.7 (23.9)	252.8 (24.1)	246.9 (23.5)	1.7	0.19	
Corrected grey matter volume, %	40.0 (3.0)	41.7 (3.1)	41.5 (3.0)	1.9	0.16	
Right hemisphere						
g-SI	1.434 (0.095)	1.453 (0.097)	1.499 (0.093)	4.1†	0.020	Bipolar disorder and depression v. control: $t_1 = -2.5$, $p = 0.040$ [$t_1 = -2.0$, $p = 0.11$]† Euthymic bipolar disorder v. control: $t_1 = -2.0$, $p = 0.12$ Bipolar disorder and depression v. euthymic bipolar disorder: $t_1 = -0.6$, $p = 0.79$
Grey matter volume, cm^3	237.0 (24.0)	251.5 (24.3)	245.9 (23.6)	1.8	0.18	
Corrected grey matter volume, %	40.0 (3.0)	41.3 (3.1)	41.4 (3.0)	1.5	0.23	

g-SI = global sulcal index; SD = standard deviation.
*Data are linearly adjusted for age, sex and level of education.
†The result of g-SI analysis performed with corrected grey matter volume (raw grey matter volume divided by total intracranial volume) as an additional confounding covariate in linear models.

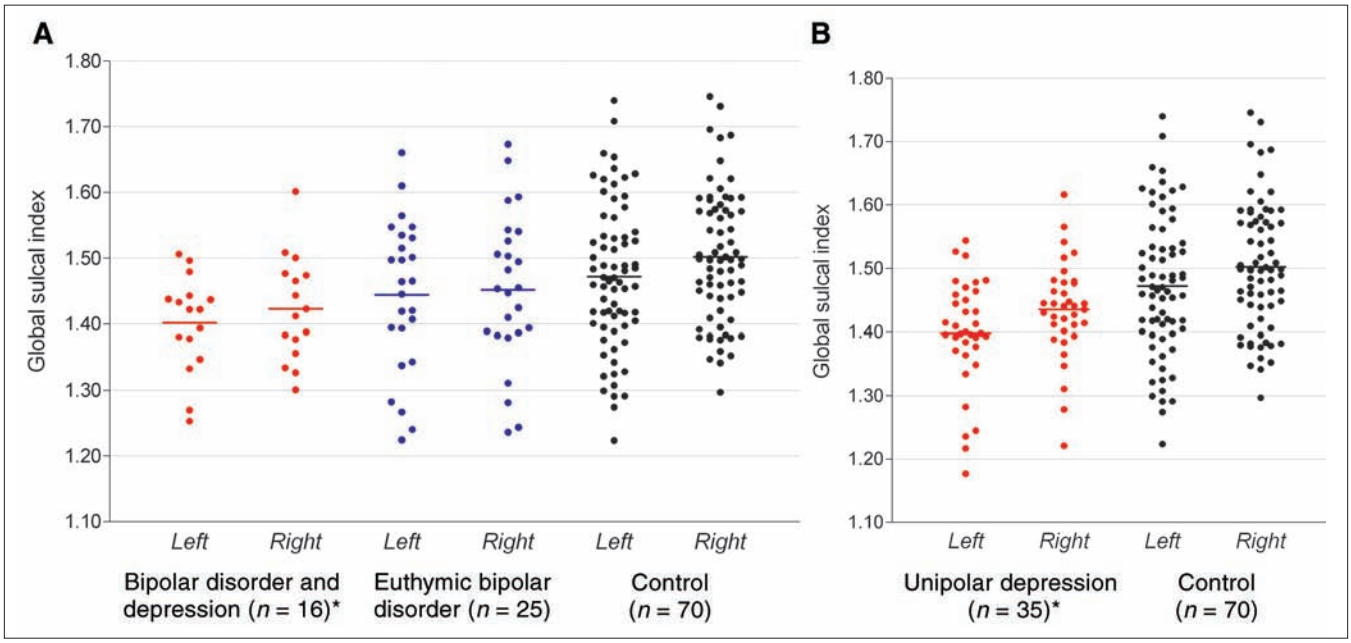

Fig. 2: (**A**) Hemispheric global sulcal indices (g-SIs) in patients with bipolar disorder and treatment-resistant depression, patients with euthymic bipolar disorder, and healthy controls (Study 1). Circles indicate individual values, horizontal lines the averages of these raw g-SI values in each group. *Statistically significant g-SI reduction in the right hemisphere compared with healthy controls ($p = 0.040$). (**B**) Hemispheric g-SIs in patients with treatment-resistant unipolar depression and healthy controls (Study 2). Circles indicate individual values, horizontal lines the averages of these raw g-SI values in each group. *Statistically significant g-SI reductions in both hemispheres compared with healthy controls ($p \leq 0.010$).

confounding covariate in the analyses, the g-SI difference between depressed patients with bipolar disorder and healthy controls no longer reached statistical significance (–3%, $p = 0.11$).

Although there were no statistically significant differences between healthy controls and patients with euthymic bipolar disorder who responded to treatment, the g-SIs of responsive patients were roughly at the midpoint between those of controls and those of patients with treatment-resistant depression (Fig. 2A). Thus, we searched for a linear trend between the 3 subgroups (i.e., bipolar disorder and depression < euthymic bipolar disorder < healthy controls). In the regression analysis, we therefore replaced the 3-level categorical group factor by a group-coded numeric covariate (depression: 1, euthymia: 2, healthy: 3). This analysis statistically confirmed the visual linear trend in g-SI values (left hemisphere: $F_1 = 3.9$, $p = 0.052$; right: $F_1 = 7.9$, $p = 0.006$).

We found that g-SI (and grey matter volume) in both hemispheres decreased with age (significant main effect of age: $F_1 > 22$, $p < 0.001$). In the right hemisphere, there was also a significant group-by-age interaction effect ($F_2 = 3.4$, $p = 0.038$). When we studied the 3 groups separately, we found that g-SI in the right hemisphere decreased with age among healthy controls ($F_1 = 9.3$, $p = 0.003$) and patients with euthymic bipolar disorder ($F_1 = 19.1$, $p < 0.001$), but not among the patients with bipolar disorder and depression ($F_1 = 0.5$, $p = 0.49$). Sex and education had no statistically significant effects on g-SIs, and there was no significant sex-by-age interaction effect.

Thirteen patients were taking a mean dose of 877 (standard deviation (SD) 335, range 400–1600) mg/d of litium. We found that patients who took lithium had 6% lower g-SIs in the right hemisphere (1.379, SD 0.088 v. 1.469, SD 0.083; adjusted for patient group, age, sex and level of education; $F_1 = 8.8$, $p = 0.006$) and 8% lower raw grey matter volume in the right hemisphere ($F_1 = 7.1$, $p = 0.012$) than patients who were not taking lithium. The g-SI in the right-hemisphere among patients taking lithium was also significantly lower than in healthy controls (–5%, $F_1 = 8.4$, $p = 0.005$). Furthermore, we found significant correlations between current lithium dose and g-SIs (left hemisphere, $r = 0.70$, $p = 0.007$; right hemisphere, $r = 0.58$, $p = 0.037$). The duration of treatment with lithium had no effect on g-SIs.

We found no statistically significant association between g-SIs and other clinical variables, including medication type and the number of affective episodes.

Study 2

Of the 35 patients with unipolar depression, 4 were taking mood-stabilizing agents (none with lithium), 3 were taking antipsychotics, 13 were taking antidepressants and 21 were taking benzodiazepines. Eleven patients had previously received ECT.

Patients in this subgroup had lower corrected grey matter volumes in both hemispheres than healthy controls (Table 3), whereas there were no between-group differences in white matter volumes (data not shown; $F_1 \leq 1.0$, $p > 0.31$). Compared with healthy controls, patients with unipolar depression had 3%–4% smaller g-SIs in both hemispheres ($p \leq 0.010$; Table 3 and Fig. 2B). We found that g-SIs were strongly dependent on hemispheric grey matter volumes ($F_1 > 9.9$, $p \leq 0.002$). When we performed g-SI analyses with corrected grey matter volume as a numeric covariate, the between-group difference in g-SIs almost reached statistical significance on the left side ($p = 0.053$). The g-SIs decreased with age ($F_1 > 12$, $p < 0.001$), irrespective of group ($F_1 < 0.03$, $p > 0.80$ for the group-by-age interaction effect) or sex ($F_1 < 0.13$, $p > 0.70$ for the sex-by-age interaction effect). Similar to the results of our analyses of the Study 1 subgroup, the main effects of sex ($F_1 < 2.0$, $p > 0.16$) and level of education ($F_4 \leq 1.0$, $p = 0.40$) on g-SIs in the Study 2 subgroup were nonsignificant.

We found no statistically significant main effect of other medications, the duration of illness/current episode or age at onset of illness on g-SI.

Discussion

We observed significant reductions of hemispheric cortical folding surface (g-SI) in patients with unipolar depression

Table 3: Main results of global sulcal index and grey matter volume analyses in Study 2

	Group; mean (SD)*		Group difference main effect	
Brain hemisphere; measure	Unipolar depression ($n = 35$)	Control ($n = 70$)	F_1	p value
Left hemisphere				
g-SI	1.408 (0.099)	1.465 (0.098)	7.6 [3.8]†	0.007 [0.053]†
Grey matter volume, cm^3	239.9 (22.4)	245.2 (22.4)	1.2	0.27
Corrected grey matter volume, %	40.1 (3.1)	41.7 (3.1)	5.9	0.017
Right hemisphere				
g-SI	1.447 (0.087)	1.495 (0.087)	6.9 [3.4]†	0.010 [0.070]†
Grey matter volume, cm^3	239.7 (22.5)	244.2 (22.6)	0.9	0.35
Corrected grey matter volume, %	39.9 (3.1)	41.6 (3.1)	6.7	0.011

g-SI = global sulcal index; SD = standard deviation.
*Data are linearly adjusted for age, sex and level of education.
†The result of g-SI analysis performed with corrected grey matter volume (raw grey matter volume divided by total intracranial volume) as an additional confounding covariate in linear models.

and in patients with bipolar disorder and long-lasting treatment-resistant depression compared with healthy controls. Even though statistical analyses revealed only a right-side reduction of g-SI in depressed patients with bipolar disorder, their g-SIs in the left hemisphere were also very similar to what we observed in patients with unipolar depression (Table 2 and Table 3). In fact, if we had excluded patients with euthymia from our analyses and compared only patients with bipolar depression and healthy controls (equivalent to Study 2), the g-SI difference would have also reached statistical significance in the left hemisphere ($t = –2.079$, $p = 0.041$). Instead of indicating lateralized g-SI reduction in bipolar depression, our results suggest that long-lasting depression may involve generally altered cortical folding, in both unipolar depression and bipolar disorder.

Visual inspection and statistical analysis of the linear trend in g-SI data among the 3 subgroups implied that the g-SIs of treatment-responsive patients with bipolar disorder were roughly at the midpoint between those of controls and those of treatment-resistant patients with bipolar disorder. Thus, bipolar disorder may involve a certain degree of g-SI reduction (see Coyle and colleagues[4]), which is increased in patients with treatment-resistant depression.

We found an association between g-SI and hemispheric grey matter volume. This is consistent with the mechanic model[8–10] that cortical folding process is constrained by grey matter thickness, and also with the view that g-SI may be altered by neurodegenerative processes that cause reductions in grey matter volume. When grey matter volume was taken into account in the analyses, we could still observe trend-level group differences in g-SIs. In addition, in the Study 1 subgroup we detected a significant between-group difference in the right-hemisphere g-SI, but no difference in grey matter volumes. Thus, g-SI cannot be considered merely an estimate of grey matter volume; it presumably also carries information on other forces that influence the folding process (e.g., white matter connectivity).[8–10]

The 3%–4% reduction of g-SI in patients with treatment-resistant depression is almost comparable to the 4%–5% decrease of g-SI that we recently detected in patients with adult-onset[23] and early-onset[24] schizophrenia using the same sulcal morphometry method. In the context of schizophrenia, the alterations in cortical folding have been interpreted to reflect a neurodevelopmental abnormality.[29,30] Similarly, our current findings are in line with the assumption that vulnerability to depression that responds particularly poorly to treatment might involve neurodevelopmental factors.[11,31]

Alternatively, the g-SI reduction in patients with treatment-resistant depression could be seen as the result of a neurodegenerative process.[3,4,31] Coyle and colleagues[4] have demonstrated a general widening of cortical sulci in patients with bipolar disorder; they considered this finding to reflect cortical grey and white matter atrophy. It has been proposed that a chronic depressive state causes damage to the cortex structure, mediated by glucocorticoid neurotoxicity, reduction in neurotrophic factors and neurogenesis, and neuronal and glial cell loss.[2] On the other hand, neurologic illnesses that involve cortical atrophy have been associated with exceptionally high rates of depression,[32] which suggests a reverse causal relation: pathologic brain structure could also predispose to depression.

The observation that g-SIs generally decreased with age is in line with earlier findings that over time, cortical thickness decreases and the cortical sulci become more flattened and less curved.[33,34] As an exception to this, the right-hemisphere g-SI in patients with bipolar disorder and treatment-resistant depression did not show significant dependency on age; rather, these patients expressed low right-hemisphere g-SIs at a rather young age. These findings give rise to speculation that treatment-resistant bipolar disorder might involve a premature reduction of g-SI in the right hemisphere, similar to what is normally observed at a later age. Nevertheless, it is also quite possible that the lack of statistically significant age dependency is explained by the small number of patients ($n = 16$) in that group in our study. Even though cortical thinning has been demonstrated to progress more rapidly in men than women,[34] we found no sex differences in age effects (i.e., no significant sex-by-age interaction) in our study.

Cortical folding patterns show distinct sex differences, which may even be used for individual recognition of the participant's sex.[35,36] However, in our study and in that of Cachia and colleagues,[23] no significant effect of sex on hemispheric g-SIs was detected. Apparently the greater local folding surfaces in some cortical regions in men are compensated by smaller surfaces in other regions,[35,36] so that there is not necessarily a marked sex difference in global folding surface that is buried in the sulci, as estimated by g-SI.

In the between-group comparisons, we took into account the effects of sex[35,36] and age[33,34] on sulcal anatomy by using these factors as covariates in the statistical analyses. Therefore, it is assumed that age and sex should not have any marked influences on the main findings in our study.

The patients taking lithium had a lower g-SI in the right hemisphere compared with patients not taking lithium; however, we observed positive correlations between lithium dose and hemispheric g-SIs. This dose-dependent enlargement of cortical folding surface could be seen in perspective with the earlier notions that lithium can increase grey matter volume and density in patients with bipolar disorder,[37–39] thus counteracting illness-related cortical atrophy. In addition, lithium can increase the water content in brain tissue,[40] which may also have an impact on neuroimaging findings.[41] The reason why patients taking lithium had lower (instead of higher) g-SIs compared with patients not taking lithium is not clear. We speculate that the structural lithium-induced effect[37–40] might have been blurred in patients with a more severe form of bipolar disorder or that patients who required treatment with lithium formed a subgroup with specific neuroanatomic properties.

Limitations

The major limitations of our investigation arise from the cross-sectional design and from sample selection: in Study 1,

the 2 patient groups differed from each other with respect to treatment-responsiveness and current state, and in Study 2, we did not have a corresponding group of treatment-responsive patients with unipolar depression. Therefore, we cannot actually estimate the extent to which the observed g-SI reductions are linked to treatment-resistance and the extent to which they are linked to the depressive state. Since the patients with euthymic bipolar disorder in Study 1 did not have a history of previous treatment-resistant depression, we cannot assess the difference between current and former treatment-resistant bipolar disorder. Owing to the study design, the g-SI changes observed in patients with treatment-resistant depression cannot be ascribed specifically to developmental factors or to tissue loss. A prospective study of treatment response in patients with a first episode of depression would be needed to explore this issue.

Furthermore, we cannot disentangle the impact of medications, current and previous, from that of the affective disorder. In addition to lithium, other psychotropic agents have also been reported to influence brain structure. For example, antidepressants and anticonvulsants can increase hippocampus volumes, presumably by promoting neurogenesis.[42,43] Antidepressants have also been suggested to improve structural plasticity and neural cellular resilience in depressive disorder.[44] Antipsychotic medications have been associated with decreased grey matter volumes in certain cortical regions (e.g., in the frontal lobe and left superior temporal gyrus).[45] The history of ECT among some of our patients is not supposed to have influenced the anatomy of their brains.[46,47]

Also, as Figure 2 clearly demonstrates, there is noteworthy interindividual variation and overlap of g-SIs among patients and healthy controls that need to be considered when interpreting the results of sulcal analyses.

Methodological considerations

To our knowledge, this is the first 3D whole-brain imaging study that describes global gyrification in patients with an affective disorder. The sulcal morphometry method that we used in this investigation and in our previous schizophrenia studies[23,24] can capture the complex 3D shapes of the cortical folds, which are much more difficult to characterize using a 2D approach (Fig. 1 and Fig. 2).[26–28] The g-SI estimates the cortical folding surface that is buried in the folds in each hemisphere; it is not dependent on sulcus opening or thickness. Our method is original in using the skeleton of the grey matter/CSF mask, with the cortical folds corresponding to the crevasse bottoms of the "landscape," the altitude of which is defined by intensity on MRI.[22] This skeleton-based definition is supposed to provide a stable sulcus localization that is hardly affected by variation in the grey matter/white matter contrast due to, for example, age-related changes in regional vascularisation or intracortical myelination.[48,49] Sulcus-based morphometry can provide information on brain surface anatomy in psychiatric disorders, which complements the measurements of local brain tissue volumes, cortical thickness and white matter connectivity.

Conclusion

Reduced cortical folding surface appeared to be a feature of both unipolar depression and bipolar disorder with treatment-resistant depression. Longitudinal MRI studies are needed to clarify whether such a g-SI reduction is state-dependent or, alternatively, a permanent feature (possibly of neurodevelopmental origin) predisposing to depression that responds poorly to medications, or whether it is the result of a long-lasting depression process or its treatment.

Acknowledgements: This study was supported in part by a grant from the "Programme Hospitalier de Recherche Clinique, Délégation à la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris" (given to M.L.P.M.) and the Health Ministry of France (PHRC/AOM-98099, given to M.L.P.M.), by an INSERM–PROGRESS grant (given to M.L.P.M.) and by a grant from the French National Agency for Research (PSYMARKER/APV051137LSA). M.L.P.M. was also supported by an APHP–INSERM interface grant. J.P. received personal grants from the Finnish Cultural Foundation and the Sigrid Jusélius Foundation, Finland. A.C. received post-doc grants from INSERM. D.R. was supported by the "Fondation pour la Recherche Médicale" and by the Atomic Energy Commission of France. M.W. was supported by a grant from the Deutsche Forschungsgemeinschaft, Germany (We3638/1-1) and J.H. by a grant from the French National Academy of Medicine. We would like to thank D. Rivière and Y. Cointepas for their fruitful support with the BrainVISA and Anatomist software.

Competing interests: None declared for Drs. Paillère-Martinot, Martinot, Ringuenet, Wessa, Houenou, Bellivier, Galinowski, Bruguière, Leboyer, Olié, Duchesnay, Artiges, Mangin and Cachia. Dr. Penttilä has received speaker fees from Servier Finland. Drs. Gallarda and Pinabel have received travel assistance from Lilly.

Contributors: Drs. Penttilä, Paillère-Martinot, Martinot and Cachia designed the study. Drs. Paillère-Martinot, Martinot, Ringuenet, Wessa, Houenou, Gallarda, Bellivier, Galinowski, Bruguière, Pinabel, Leboyer, Olié, Artiges acquired the data. Drs. Penttilä, Paillère-Martinot, Cachia, Duchesnay and Mangin analyzed the data. Drs. Penttilä, Paillère-Martinot and Cachia wrote the article. Drs. Penttilä, Paillère-Martinot, Martinot, Ringuenet, Wessa, Houenou, Gallarda, Bellivier, Galinowski, Bruguière, Pinabel, Leboyer, Olié, Duchesnay, Artiges, Mangin and Cachia reviewed the article. All authors gave final approval for publication.

References

1. Harrison PJ. The neuropathology of primary mood disorder. *Brain* 2002;125:1428-49.
2. Sheline YI. Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 2003;54:338-52.
3. Strakowski SM, Delbello MP, Adler CM. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. *Mol Psychiatry* 2005;10:105-16.
4. Coyle TR, Kochunov P, Patel RD, et al. Cortical sulci and bipolar disorder. *Neuroreport* 2006;17:1739-42.
5. Fornito A, Malhi GS, Lagopoulos J, et al. In vivo evidence for early neurodevelopmental anomaly of the anterior cingulate cortex in bipolar disorder. *Acta Psychiatr Scand* 2007;116:467-72.
6. Welker W. Why does cerebral cortex fissure and fold? In: Jones EG, Peters A, editors. *Cereb cortex*. Vol. 8B. New York (NY): Plenum Press; 1988. p. 3-135.
7. Dubois J, Benders M, Cachia A, et al. Mapping the early cortical folding process in the preterm newborn brain. *Cereb Cortex* 2008; 18:1444-54.
8. Hilgetag CC, Barbas H. Role of mechanical factors in the morphology

of the primate cerebral cortex. *PLOS Comput Biol* 2006;2:e22.

9. Van Essen DC. A tension-based theory of morphogenesis and compact wiring in the central nervous system. *Nature* 1997;385:313-8.
10. Regis J, Mangin JF, Ochiai T, et al. "Sulcal root" generic model: a hypothesis to overcome the variability of the human cortex folding patterns. *Neurol Med Chir (Tokyo)* 2005;45:1-17.
11. Ansorge MS, Hen R, Gingrich JA. Neurodevelopmental origins of depressive disorders. *Curr Opin Pharmacol* 2007;7:8-17.
12. Cuellar AK, Johnson SL, Winters R. Distinctions between bipolar and unipolar depression. *Clin Psychol Rev* 2005;25:307-39.
13. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington: The Association; 1994.
14. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998;20 (Suppl 59):22-33; quiz 34-57
15. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry* 2007;52:46-54.
16. Paillère-Martinot ML, Galinowski A, Ringuenet D, et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: a [^{18}F]-fluorodeoxyglucose-PET and MRI study. *International Journal of Neuropsychopharmacology*. In press.
17. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;23:56-62.
18. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. *Br J Psychiatry* 1978;133:429-35.
19. Wessa M, Houenou J, Paillere-Martinot ML, et al. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry* 2007;164:638-46.
20. Annett M. The binomial distribution of right, mixed and left handedness. *Q J Exp Psychol* 1967;19:327-33.
21. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry* 1979;134:382-9.
22. Mangin JF, Riviere D, Cachia A, et al. A framework to study the cortical folding patterns. *Neuroimage* 2004;23(Suppl 1):S129-38.
23. Cachia A, Paillère-Martinot M-L, Galinowski A, et al. Cortical folding abnormalities in schizophrenia patients with resistant auditory hallucinations. *Neuroimage* 2008;39:927-35.
24. Penttilä J, Paillère-Martinot ML, Martinot JL, et al. Global and temporal cortical folding in patients with early-onset schizophrenia. *J Am Acad Child Adolesc Psychiatry* 2008;47:1125-32.
25. Mangin JF, Frouin V, Bloch I, et al. From 3D magnetic resonance images to structural representations of the cortex topography using topology preserving deformations. *J Math Imaging Vis* 1995;5:297-318.
26. Armstrong E, Schleicher A, Omran H, et al. The ontogeny of human gyrification. *Cereb Cortex* 1995;5:56-63.
27. Moorhead TW, Harris JM, Stanfield AC, et al. Automated computation of the Gyrification Index in prefrontal lobes: methods and comparison with manual implementation. *Neuroimage* 2006;31:1560-6.
28. Zilles K, Armstrong E, Schleicher A, et al. The human pattern of gyrification in the cerebral cortex. *Anat Embryol (Berl)* 1988;179:173-9.
29. Kulynych JJ, Luevano LF, Jones DW, et al. Cortical abnormality in schizophrenia: an in vivo application of the gyrification index. *Biol Psychiatry* 1997;41:995-9.
30. Sallet PC, Elkis H, Alves TM, et al. Reduced cortical folding in schizophrenia: an MRI morphometric study. *Am J Psychiatry* 2003; 160:1606-13.
31. Monkul ES, Malhi GS, Soares JC. Anatomical MRI abnormalities in bipolar disorder: Do they exist and do they progress? *Aust N Z J Psychiatry* 2005;39:222-6.
32. Starkstein SE, Robinson RG. Affective disorders and cerebral vascular disease. *Br J Psychiatry* 1989;154:170-82.
33. Kochunov P, Mangin JF, Coyle T, et al. Age-related morphology trends of cortical sulci. *Hum Brain Mapp* 2005;26:210-20.
34. Magnotta VA, Andreasen NC, Schultz SK, et al. Quantitative in vivo measurement of gyrification in the human brain: changes associated with aging. *Cereb Cortex* 1999;9:151-60.
35. Duchesnay E, Cachia A, Roche A, et al. Classification based on cortical folding patterns. *IEEE Trans Med Imaging* 2007;26:553-65.
36. Lao Z, Shen D, Xue Z, et al. Morphological classification of brains via high-dimensional shape transformations and machine learning methods. *Neuroimage* 2004;21:46-57.
37. Sassi RB, Nicoletti M, Brambilla P, et al. Increased gray matter volume in lithium-treated bipolar disorder patients. *Neurosci Lett* 2002;329:243-5.
38. Moore GJ, Bebchuk JM, Wilds IB, et al. Lithium-induced increase in human brain grey matter. *Lancet* 2000;356:1241-2.
39. Bearden CE, Thompson PM, Dalwani M, et al. Greater cortical gray matter density in lithium-treated patients with bipolar disorder. *Biol Psychiatry* 2007;62:7-16.
40. Phatak P, Shaldivin A, King LS, et al. Lithium and inositol: effects on brain water homeostasis in the rat. *Psychopharmacology (Berl)* 2006;186:41-7.
41. Regenold WT. Lithium and increased cortical gray matter — more tissue or more water? *Biol Psychiatry* 2008;63:e17; author reply e9. Epub 2007 Jul 9. Comment on: *Biol Psychiatry* 2007;62:7-16.
42. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. *Science* 2003;301:805-9.
43. Bremner JD. Stress and brain atrophy. *CNS Neurol Disord Drug Targets* 2006;5:503-12.
44. Fuchs E, Czeh B, Kole MH, et al. Alterations of neuroplasticity in depression: the hippocampus and beyond. *Eur Neuropsychopharmacol* 2004;14:S481-90.
45. Vita A, De Peri L. The effects of antipsychotic treatment on cerebral structure and function in schizophrenia. *Int Rev Psychiatry* 2007;19:429-36.
46. Coffey CE, Weiner RD, Djang WT, et al. Brain anatomic effects of electroconvulsive therapy. A prospective magnetic resonance imaging study. *Arch Gen Psychiatry* 1991;48:1013-21.
47. Nobler MS, Teneback CC, Nahas Z, et al. Structural and functional neuroimaging of electroconvulsive therapy and transcranial magnetic stimulation. *Depress Anxiety* 2000;12:144-56.
48. Paus T. Mapping brain maturation and cognitive development during adolescence. *Trends Cogn Sci* 2005;9:60-8.
49. Gogtay N, Giedd JN, Lusk L, et al. Dynamic mapping of human cortical development during childhood through early adulthood. *Proc Natl Acad Sci U S A* 2004;101:8174-9.