Research Report

Opposite effects of suicidality and lithium on gray matter volumes in bipolar depression

Francesco Benedetti [a,c,*], Daniele Radaelli [a,c], Sara Poletti [a,c,d], Clara Locatelli [a,c], Andrea Falini [b,c], Cristina Colombo [a], Enrico Smeraldi [a,c]

[a] Department of Clinical Neurosciences, Scientific Institute San Raffaele and University Vita-Salute, Milan, Italy
[b] Department of Neuroradiology, Scientific Institute San Raffaele and University Vita-Salute, Milan, Italy
[c] C.E.R.M.A.C. (Centro di Eccellenza Risonanza Magnetica ad Alto Campo), University Vita-Salute San Raffaele, Milan, Italy
[d] Dottorato in Neuroscienze e Disturbi del Comportamento, Dipartimento di Scienze Farmacologiche, Università degli Studi di Palermo, Italy

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ABSTRACT

Background: Mood disorders are associated with the highest increase of attempted and completed suicide. Suicidality in major depressive disorder and in schizophrenia has been associated with reduced gray matter volumes in orbitofrontal cortex. Lithium reduces the suicide risk of patients with bipolar disorder (BD) to the same levels of the general population, and can increase GM volumes. We studied the effect of a positive history of attempted suicide and ongoing lithium treatment on regional GM volumes of patients affected by bipolar depression.
Methods: With a correlational design, we studied 57 currently depressed inpatients with bipolar disorder: 19 with and 38 without a positive history of suicide attempts, 39 unmedicated and 18 with ongoing lithium treatment. Total and regional gray matter volumes were assessed using voxel-based morphometry.
Results: Total GM volume is inversely correlated with depression severity. A positive history of suicide attempts was associated with higher stress in early life. Suicide attempters showed reduced GM volumes in several brain areas including dorsolateral prefrontal cortex, orbitofrontal cortex, anterior cingulate, superior temporal cortex, parieto-occipital cortex, and basal ganglia. Long term lithium treatment was associated with increased GM volumes in the same areas where suicide was associated with decreased GM.
Conclusions: Reduced GM volumes in critical cortical areas of suicidal patients could be a biological correlate of an impaired ability to associate choices and outcomes and to plan goal-directed behaviors based on a lifetime historical perspective, which, coupled with mood-congruent depressive cognitive distortions, could lead to more hopelessness and suicide. Lithium could exert its specific therapeutic effect on suicide by acting in the same areas.

1. Introduction

Among factors affecting the probability to commit suicide, mood disorders are associated with the highest increase of attempted and completed suicide. About 30% of patients with bipolar disorder (BD) attempt suicide during their lifetime (Chen and Dilsaver, 1996; Leverich et al., 2003), and about 20% eventually die from suicide (Jamison, 1986; Osby et al., 2001).

Treatment of lifetime suicidality is a major issue for psychiatrists, but few clear-cut treatment options are available. Despite antidepressant interventions clearly reducing the suicide risk associated with acute mood episodes, large

* Corresponding author at: Istituto Scientifico Ospedale San Raffaele, Department of Clinical Neurosciences, San Raffaele Turro, Via Stamira d'Ancona 20, Milano, Italy. Tel.: +39 02 26433156; fax +39 02 26433265.
E-mail address: benedetti.francesco@hsr.it (F. Benedetti).

scale epidemiological studies do not support the usefulness of antidepressant drugs in reducing lifetime completed and attempted suicide (Tiihonen et al., 2006). On the other hand, the most compelling evidence affirms that lithium, the mainstay for the long-term treatment of BD, is able to reduce the suicide risk of patients with BD to the same levels of the general population (Baldessarini et al., 2003). This effect seems specific and independent of the therapeutic mood stabilizing effect: when comparing lithium with drugs of similar mood-stabilizing efficacy, such as valproate, half as many suicides are observed with lithium than with valproate (Goodwin et al., 2003).

Given the high burden of suicide and the uncertain therapeutic strategies, the search of individual factors associated with suicidality could allow to improve diagnosis and treatment by developing predictive models and thus enhancing suicide prevention efforts (Oquendo et al., 2006). Genetic studies suggested that suicide and attempted suicide are heritable independent of the associated diagnosis (Currier and Mann, 2008), and several biological abnormalities in brain neurotransmitter systems have been observed after completed suicide (Mann, 2003). More recently, brain imaging studies also suggested structural correlates of suicidality in patients affected by psychiatric disorders. Although there is little consensus of opinion on structural imaging of the suicidal brain (Desmyter et al., 2011), the systematic review of comparative imaging studies showed that changes in the structure and functions of the brain in association with suicidal behavior were mainly found in the orbitofrontal and dorsolateral parts of the prefrontal cortex (van Heeringen et al., 2011).

The first structural study showed that patients with major depressive disorder (MDD) and a history of a suicide attempt demonstrated significantly more subcortical gray matter (GM) hyperintensities than non-suicidal MDD controls, thus suggesting GM pathology as a correlate of this psychopatological feature (Ahearn et al., 2001). In patients affected by MDD a history of suicide attempts was associated with reduced GM in bilateral orbitofrontal cortex (OFC) and with larger right amygdala volumes (Monkul et al., 2007a), and with reduced GM density in fronto-striatal structures including cingulate cortex and caudate nuclei (Wagner et al., 2011). A study in late-onset MD showed that compared with nonsuicidal counterpart, suicidal depression was associated with decreased GM and WM volume in the frontal, parietal, and temporal regions, and the insula, lentiform nucleus, midbrain, and the cerebellum, with marked regional volume reduction in dorsal medial prefrontal cortex (Hwang et al., 2010). Suicidal patients affected by schizophrenia showed reduced GM in superior temporal and OFC cortex (Aguilar et al., 2008), a region where increased white matter was also reported (Rusch et al., 2008). A functional study showed that MDD patients with a history of suicide attempt still had abnormal activation of OFC and anterior cingulate during emotional tasks in euthymic conditions (Jollant et al., 2008). These data supported the hypothesis that abnormalities in fronto-limbic circuitries might be a major underpinning of suicidality independent of the associated psychopathological conditions.

Patients with BD show reduced OFC activity and GM volumes (Haldane and Frangou, 2004; Konarski et al., 2008),

and OFC GM has been inversely correlated with depressive symptom intensity (Nery et al., 2009). One study associated suicidality with reduced volume of anterior corpus callosum in patients affected by BD, thus supporting a role for abnormal prefrontal function in this psychopathological dimension of BD (Matsuo et al., 2010). No study of suicidality and GM structure is however available.

The purpose of this study was to evaluate the effect of a positive history of attempted suicide and ongoing lithium treatment on regional GM volumes of patients affected by bipolar depression.

2. Methods

We studied 57 consecutively admitted inpatients affected by Bipolar Disorder, and referred to our hospital for a major depressive episode without psychotic features (DSM-IV criteria, SCID-I interview). Nineteen patients had a positive history of suicidality. Following the existing literature about structural correlates of suicidality (see Introduction), the criterion for suicidality was one or more documented suicide attempts (broadly defined as any behavior aimed at killing oneself) during the lifetime. Thirty-eight patients (2:1 ratio) matched for age and sex, and without a positive history of suicide attempts, served as controls.

Patients were included if they had been taking lithium salts during the last six months, or if they had not taken lithium during the previous five years. The information was assessed by the psychiatrist in charge and by an independent rater using best estimation procedure, taking into account available charts, case notes and information provided by at least one relative. Exclusion criteria were other diagnoses on Axis I; mental retardation on Axis II; pregnancy, history of epilepsy, major medical and neurological disorders; a history of drug or alcohol dependency or abuse within the last six months. After complete description of the study to the subjects, written informed consent was obtained. The study was approved by the local Ethical Committee.

Severity of current depression was rated on the 21-item Hamilton Depression Rating Scale (HDRS) by trained psychiatrists. Perceived depression was self-rated by the patients on the Beck Depression Inventory (BDI). Given the reported positive relationship between early life stress and suicide in patients with bipolar disorder (Leverich et al., 2003), early (between age 5 and 15) and recent (last 3 years) stressful life events were scored by trained raters on the Social Readjustment Rating Scale (SRRS)(Holmes and Rahe, 1967), which focuses on occurrences that lead to readjustment-requiring changes in usual activities and that frequently precede illness onsets (Dohrenwend, 2006).

3. Image acquisition and post-processing

Brain imaging volumetric T1-weighted sequences were acquired on a 3.0 Tesla scanner (Gyroscan Intera, Philips, Netherlands) using a 6 channels SENSE head coil using a T-1-weighted MPRAGE sequence (TR 2500 ms, TE 4.6 ms, field of view FOV = 230 mm, matrix = 256×256, in-plane resolution 0.9×0.9 mm, yielding 220 transversal slices with a thickness of 0.8 mm). Images were analyzed using Statistical Parametric Mapping software (SPM5, Wellcome Department of Imaging

Neuroscience, Institute of Neurology and the National Hospital for Neurology and Neurosurgery; London, England) and the voxel-based morphometry (VBM) toolbox (VBM 5.1; http://dbm.neuro.uni-jena.de/vbm/) implemented in SPM5 (http://www.fil.ion.ucl.ac.uk/spm/), which combines tissue segmentation, bias correction, and spatial normalization into a unified model. We used the optimized VBM procedure, which segments gray and white matter, and normalizes gray matter (GM) segmented images to a standard space by matching them to their template (Ashburner and Friston, 2005). The procedure yielded modulated GM normalized images: modulated parameters were used to test for voxelwise differences in the relative volume of GM by compensating for the effects of warping, to ensure that the total amount of GM in a region is the same before and after spatial normalization (Good et al., 2001). The voxel size for all images was resliced to $1 \times 1 \times 1$ mm. We realigned the scans to correct for head movement. Images were then normalized to the standard EPI template volume of the Montreal Neurological Institute (MNI) reference brain, and smoothed using a 8-mm full-width at half-maximum (FWHM) isotropic Gaussian kernel. Total intra-cranial volume was calculated as the sum of the volumes of gray matter, white matter, and cerebro-spinal fluid, as estimated by the MATLAB get_totals script implemented for SPM (http://www.cs.ucl.ac.uk/staff/g.ridgway/vbm/get_totals.m).

4. Data analysis

Data were analyzed within the context of the General Linear Model (GLM).

Clinical and demographic characteristics of participants divided according to the study groups were compared with ANOVA and Student's *t* test as appropriate.

To investigate factors affecting the severity of current depression, HDRS scores were analyzed with history of attempted suicide, total GM volume, and lithium treatment as factors, and including in the model sex and age as nuisance

covariates. The effect of the whole model (i.e., considering all independent factors together) on the dependent variable was tested. The statistical significance of the effect of the single independent factors on the dependent variable was then calculated (least squares method) by parametric estimates of predictor variables. Analyses were performed using a commercially available software (StatSoft Statistica 6.0, Tulsa, OK, USA) and following standard computational procedures (Hill and Lewicki, 2006).

To investigate the influence of a positive history of attempted suicide on regional GM volumes, modulated images were entered into an analysis of variance for the group comparison of GM volume, with suicidality (positive/negative history of suicidal acts) and lithium treatment as factors. This procedure allowed (1) to study the main effects of suicidality and lithium, and (2) to identify the regions where both factors significantly influenced GM volumes (conjunction analysis, as implemented in SPM5 statistical software package). We included as nuisance covariates age and sex as possible confounding factors, and total intra-cranial volume to adjust for global atrophy and identify regions with differences that cannot be explained by the total gray matter differences. Statistical threshold was $p < 0.05$ corrected for multiple comparisons with false discovery rate (FDR) error correction. Brain regions were identified with Wake Forest PickAtlas (www.fmri.wfubmc.edu).

5. Results

Clinical and demographic characteristics of the patients, and intracranial volumes of GM and WM, are shown in Table 1. Patients with a positive history of suicide attempts showed higher levels of early life stress (number of events: 20.31 ± 9.75 vs 13.76 ± 7.58, $t = 2.79$ $p = 0.007$; SRRS score: 443.42 ± 234.97 vs 316.54 ± 164.49, Student's $t = 2.37$, $p = 0.021$), but not of recent stress. Patients with lithium showed a lower severity of current depression than patients

Table 1
Clinical and demographic characteristics of the sample. * = significantly higher values in patients with a positive history of suicide attempts. ** = significantly lower values in lithium-treated patients.

	Negative history of attempted suicide		Positive history of attempted suicide		F (3,53)	p
	Lithium-free (n = 28)	Lithium-treated (n = 10)	Lithium-free (n = 11)	Lithium-treated (n = 8)		
Age	45.93 ± 10.48	46.20 ± 13.27	43.64 ± 10.36	45.63 ± 11.26	0.13	0.94
Sex (M/F)	8/20	3/8	3/7	5/3	3.58	0.31
Education (yrs)	11.00 ± 4.07	10.90 ± 3.31	12.55 ± 3.14	11.80 ± 4.71	0.50	0.68
Age at onset	30.75 ± 8.98	32.00 ± 7.24	27.82 ± 12.16	26.60 ± 4.19	0.83	0.49
Duration of illness (yrs)	14.04 ± 10.03	14.20 ± 8.66	15.82 ± 12.04	20.16 ± 10.57	0.78	0.51
Duration of current episode (wks)	21.38 ± 12.07	26.84 ± 29.11	19.57 ± 9.77	30.18 ± 51.38	0.43	0.73
Number of previous depressive episodes	4.21 ± 5.01	1.80 ± 1.32	4.00 ± 2.28	4.86 ± 2.76	1.20	0.32
Number of previous manic episodes	2.89 ± 4.65	2.40 ± 1.84	3.27 ± 2.33	4.26 ± 2.18	0.43	0.73
Early stressors (n) *	13.22 ± 7.94	15.28 ± 6.62	23.82 ± 8.67	15.50 ± 9.55	4.54	0.01
Early stressors (SRRS scores) *	303.64 ± 162.45	352.65 ± 173.52	518.00 ± 239.08	340.88 ± 198.89	3.54	0.02
Recent stressors (n)	16.96 ± 7.78	14.22 ± 5.06	20.91 ± 9.28	14.88 ± 5.14	1.71	0.18
Recent stressors (SRRS scores)	394.58 ± 139.27	378.23 ± 204.45	552.82 ± 309.94	402.50 ± 92.38	2.13	0.11
HDRS score **	24.32 ± 4.14	21.00 ± 3.43	23.27 ± 4.34	22.13 ± 3.00	2.00	0.12
BDI score **	16.66 ± 5.81	13.03 ± 4.97	18.64 ± 9.58	13.65 ± 6.45	1.67	0.19
Gray matter volume (ml)	758.91 ± 53.85	754.94 ± 61.82	735.24 ± 69.85	736.48 ± 43.06	0.64	0.59
White matter volume (ml)	597.77 ± 35.45	573.60 ± 29.49	579.31 ± 52.59	589.87 ± 51.33	1.12	0.35
Cerebrospinal fluid (ml)	412.28 ± 77.63	422.05 ± 63.57	458.17 ± 134.82	423.21 ± 67.54	0.72	0.55
Total intracranial volume	1768.96 ± 99.86	1750.58 ± 43.19	1772.71 ± 46.12	1749.56 ± 12.67	0.29	0.84

without (HDRS scores: 21.50 ± 3.20 vs 24.03 ± 4.16, t = 2.28 p = 0.027; BDI scores: 17.22 ± 7.00 vs 13.31 ± 5.50, t = 2.09, p = 0.041). No other effect of these variables, nor their interaction, was significant.

To better characterize these effects, a GLM ANOVA with history of attempted suicide, total GM volume, and ongoing lithium treatment as factors, and sex and age as nuisance covariates, showed that the severity of current depressive symptomatology as rated on HDRS was not influenced by history of suicide, but was significantly lower in patients on lithium (F = 6.147; d.f. 1,47; p = 0.0164) and inversely proportional to total GM volume (higher volume, lower HDRS ratings: $\beta = -0.430$, t = 2.891, p = 0.0058). The whole model had a significant effect on severity of depression (multiple R = 0.548; adjusted R^2 = 0.167;

F = 2.245; d.f. 9,47; p = 0.0352). No other factor, nor their interactions, significantly affected current depression severity. No relationship was detected between depression severity and both white matter and cerebro-spinal fluid volumes.

The VBM analysis with history of suicide attempts as independent variable showed that patients with a positive history of suicide attempts had lower GM volumes in several brain areas (Table 2, Fig. 1), including DLPFC, OFC, anterior cingulate cortex (ACC), superior temporal cortex (STC), parietal and occipital cortex. Two clusters in bilateral STC showed an opposite direction of effect (higher GM volumes in suicidal patients.

The VBM conjunction analysis with ongoing lithium treatment and history of suicide attempts as factors showed

Table 2

Areas where a positive history of suicidal acts significantly influenced gray matter volumes, and levels of significance of the observed difference. Data are shown for all clusters surviving statistical threshold (p<0.05 FDR corrected): anatomy, Broadmann's area (BA), lateralization (L/R), MNI coordinates (x, y, z) of voxels with higher Z values (signal peaks); cluster size (mm³); level of significance corrected for multiple comparisons (False Discovery Rate). In all clusters, except those marked with (*), a positive history of suicide was associated with lower GM volumes.

| Region	L/R	BA	Signal peak	Cluster size (mm³)	Z value	p (FDR)
Prefrontal cortex						
Superior and medial frontal gyrus	L	9	−12 55 33	1568	5.28	0.011
Superior and medial frontal gyrus	L	6–8	−4 8 53	420	3.89	0.027
Superior frontal gyrus	L	10	−8 65 20	200	3.79	0.030
	L	6	−16 19 63	170	4.25	0.019
	L	8–6	−30 19 54	239	3.86	0.028
Middle frontal gyrus	L	10	−49 51 −4	278	4.25	0.019
	L	10	−33 59 8	219	3.83	0.029
	L	11	−24 34 −12	56	3.37	0.044
Rectal and inferior frontal gyrus	L	11–47	−11 35 −28	200	3.82	0.030
Inferior frontal gyrus	L	47	−35 31 −20	337	3.67	0.034
Medial frontal gyrus	L	6	−9 −30 56	227	3.90	0.027
Superior frontal gyrus	R	8–9	23 42 41	689	4.16	0.020
	R	6	4 17 59	12	3.27	0.049
Middle frontal gyrus	R	6–8	27 17 59	720	4.32	0.019
Medial frontal gyrus	R	6	6 50 41	223	3.87	0.028
Insula	L		−43 −4 18	593	5.33	0.011
Temporal cortex						
Superior temporal gyrus*	L	41	−45 −33 6	121	4.04	0.023
Superior, middle temporal gyrus	R	42–22	70 −22 7	106	3.78	0.030
Superior temporal gyrus*	R	13	50 −43 16	16	3.39	0.043
Inferior temporal gyrus	R	20	50 −55 −18	68	3.74	0.032
Limbic lobe						
Anterior cingulate	L	32	−4 44 7	284	3.63	0.035
Anterior cingulate	L	33	−3 19 24	234	3.49	0.039
Anterior cingulate	R	32	4 43 10	52	3.31	0.047
Cingulate gyrus	R	32	5 26 34	350	3.99	0.024
Parietal cortex						
Superior parietal lobule	L	7	−38 −60 51	476	4.78	0.014
Postcentral gyrus	L	7	−6 −53 65	195	4.52	0.016
Inferior parietal lobule	L	39	−52 −66 37	154	3.63	0.035
Paracentral lobule	L	5	−2 −32 54	76	3.38	0.044
Paracentral lobule	L	31	−2 −19 50	87	3.36	0.045
Postcentral gyrus, inferior lobule	R	40	50 −34 54	322	3.27	0.049
Inferior parietal lobule	R	40	55 −61 40	104	3.54	0.038
Occipital cortex						
Lyngual Gyrus	L	18, 19	−7 −71 −9	4550	4.65	0.015
Middle occipital gyrus	L	37	−52 −72 0	920	4.58	0.016
Cuneus	L	19	−2 −82 31	343	4.28	0.019
Precuneus	L	7	−3 −44 45	750	3.88	0.027
Fusiform gyrus	L	18	−28 −94 −20	14	3.60	0.036
Angular gyrus	R	39	41 −78 31	384	4.42	0.017
Fusiform gyrus	R	37	36 −44 −13	131	3.60	0.036
Basal ganglia						
Thalamus		Pulvinar	8 −30 8	836	4.64	0.015
Caudate		Head	−16 18 6	24	3.37	0.044
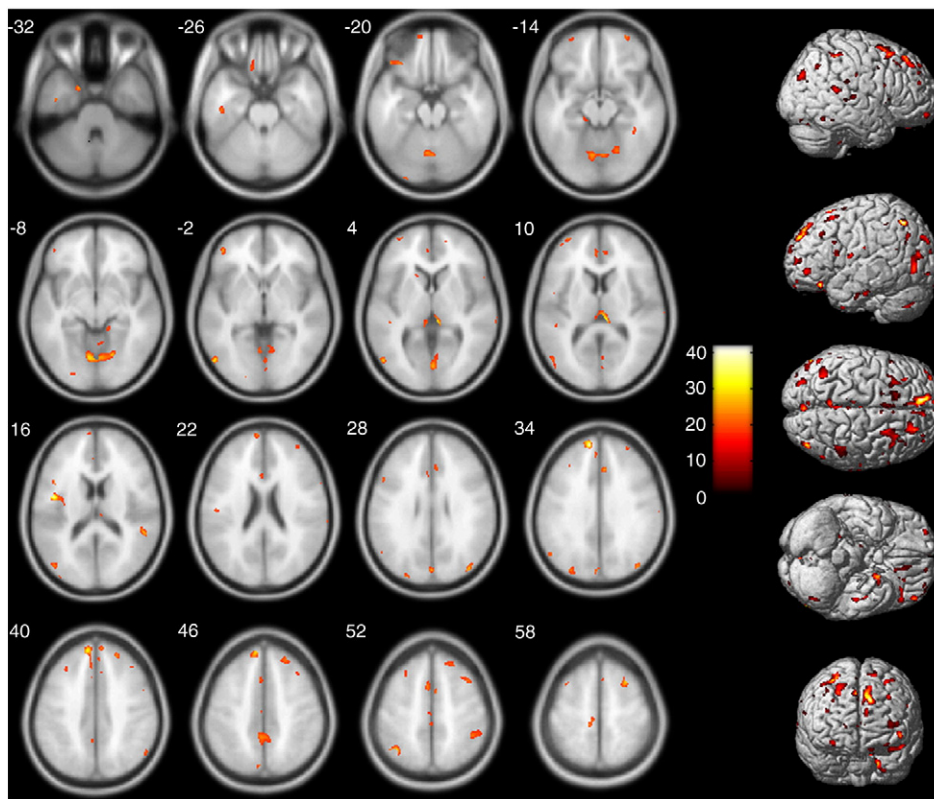
Fig. 1. Areas where a positive history of suicidal acts significantly influenced gray matter volumes. Threshold for visualization is p<0.001 uncorrected, see Table 1 to localize clusters surviving statistical threshold (p<0.05 FDR corrected).

that lithium-treated patients had higher GM volumes in the same cortical areas where suicide was associated with decreased GM (Table 3, Fig. 2). Thus, suicidal participants off-lithium had the lower GM volumes, non-suicidal on-lithium had the higher GM volumes, and the other two groups showed a variable degree of intermediate GM volumes depending on the specific brain area (see example in Fig. 3). Again, these areas included DLPFC, OFC, ACC, STC, parietal and occipital cortex; and again, one temporal cluster showed an opposite direction of effect.

6. Discussion

This is the first study of the effects of suicidality and lithium on GM volumes in patients affected by bipolar depression. We observed (1) that a positive history of suicide attempts is associated with reduced GM volumes in several brain areas, including DLPFC, OFC, ACC, STC, and (2) that lithium treatment is associated with higher GM volumes in the same regions.

Functional and structural abnormalities of all the above structures have been widely described in mood disorders (Mayberg, 2003; Price and Drevets, 2010), and changes in their neural responses have been correlated with clinical response in bipolar depression (Benedetti et al., 2007). The present finding of abnormal GM volumes in suicidal patients is consistent with existing knowledge on the role of these structures in cognition and affect, and with brain imaging studies which associated suicidal behavior with changes in the structure and functions of DLPFC and OFC (van Heeringen et al., 2011).

The DLPFC is essential for the representation of goals and the means to achieve them, to plan task-appropriate responses in the face of competition with potentially stronger alternatives, to control affect-guided planning and anticipation that involves the experience of emotion associated with an anticipated choice, and DLPFC left regions have been associated with approach-related appetitive goals (Davidson et al., 2002).

The OFC is crucial for changing behavior when facing unexpected outcomes, when subjects must change an established behavioral response in order to adapt to new contingencies. It can exert this role by signaling outcome expectancies (Schoenbaum et al., 2009), thus disambiguating the relationship between multiple choices and their outcomes (Seo and Lee, 2010). The role of OFC is crucial in guiding contingent learning, the process by which the credit for an outcome becomes assigned to the appropriate previous choice, and is linked to the time frame of the associations between stimuli and responses: when OFC is lesioned, primates cannot shape behavior on the history of precise conjoint relationships between particular choices and particular rewards, but can still approximate choice-outcome associations using the recent history of choices and rewards (Walton et al., 2010).

The ACC is widely implicated in the detection of unfavorable outcomes, response errors, response conflict, and decision uncertainty (Ridderinkhof et al., 2004), and can be seen as a point of integration for visceral, attentional, and affective information that is critical for self-regulation and adaptability

Table 3

Areas where both a positive history of suicidal acts, and ongoing long-term treatment with lithium, significantly influenced gray matter volumes, and levels of significance of the observed difference. Data are shown for all clusters surviving statistical threshold (p<0.05 FDR corrected): anatomy, Broadmann's area (BA), lateralization (L/R), MNI coordinates (x, y, z) of voxels with higher Z values (signal peaks); cluster size (mm^3); level of significance corrected for multiple comparisons (False Discovery Rate). In all clusters, except that marked with (*), a positive history of suicide was associated with lower GM volumes, and lithium was associated with greater GM volumes.

Region	L/R	BA	Signal peak	Cluster size (mm^3)	Z value	p (FDR)
Prefrontal cortex						
Medial frontal gyrus	L	6	−5 13 50	293	4.06	0.025
Medial frontal gyrus	L	6	−5 40 40	39	3.58	0.048
Orbital and medial frontal gyrus	L	47	−12 23 −27	484	4.11	0.023
Superior and middle frontal gyrus	R	8, 6	32 18 53	547	4.70	0.009
Superior frontal gyrus	R	8	15 34 52	141	4.21	0.019
Superior frontal gyrus	R	6	4 4 53	137	3.90	0.031
Superior frontal gyrus	R	11	31 58 −14	213	4.52	0.012
Temporal cortex						
Medial temporal gyrus	L	19	−27 −85 26	102	3.71	0.041
Superior temporal gyrus (*)	R	13	55 −44 17	739	4.83	0.007
Superior temporal gyrus	R	22	66 −42 18	91	3.80	0.036
Inferior temporal gyrus	R	20	50 −52 −20	118	3.94	0.030
Limbic lobe						
Anterior cingulate	L	32	−4 29 25	303	4.02	0.027
Cingulate gyrus	L	32	−4 18 44	293	3.64	0.045
Cingulate gyrus	R	24	3 6 34	553	3.76	0.038
Parietal cortex						
Paracentral lobule	L	31	−3 −19 49	648	4.61	0.010
Precuneus	L	19	−32 −82 34	401	5.12	0.003
Precuneus	L	7	−7 −81 42	482	3.98	0.029
Precuneus and paracentral lobule	L	5	−2 −33 53	957	3.67	0.043
Inferior parietal lobule	R	40	45 −34 37	79	4.07	0.025
Inferior parietal lobule	R	40	68 −26 24	34	3.69	0.042
Occipital cortex						
Cuneus	L	18	−10 −77 18	286	4.46	0.013
Cuneus	R	19	7 −87 23	482	3.77	0.037

(Thayer and Lane, 2000). Regarding the role of ACC in mood disorders, it has been suggested (1) that ACC activation may be present when effortful emotional regulation is required in situations in which behavior is failing to achieve a desired outcome, or when affect is elicited in contexts that are not normative, and (2) that in depressed patients ACC dysfunction may be associated both with abnormal conscious experience of affect, and with impaired modulation of attention or executive functions and impaired monitoring of competition among various response options (Davidson et al., 2002).

Temporal structures interact with limbic structures and prefrontal cortex in the generation and experience of emotion and mood (Price and Drevets, 2010). Superior temporal cortex GM density has been correlated with emotional intelligence, the ability to monitor and use information about own and others' emotions to guide thinking and action (Takeuchi et al., 2010). In patients with schizophrenia, abnormal STC GM has been correlated both with theory of mind and empathy deficits (Benedetti et al., 2009) and with suicide (Aguilar et al., 2008). Both thinning and thickening in different portions of lateral and superior temporal cortex have been described in bipolar disorder (Rimol et al., 2010), but not yet correlated with symptom dimensions.

In the light of the above, it is then tempting to speculate that reduced GM volumes in critical cortical areas of suicidal patients could be a biological correlate of an impaired ability to process emotions, and to associate choices and outcomes and to plan goal-directed behaviors based on a lifetime historical perspective. This, coupled with mood-congruent depressive

cognitive distortions, could lead to more hopelessness and then suicidal acts. Cognitive distortions during bipolar depression include pessimism, self-deprecatory and self-accusatory thoughts, and lead to mood-congruent biases in information processing that influence evaluative processes, social judgements, decision-making, attention, and memory (Clark et al., 2009) with a peculiar failure to anticipate positive incentives and to direct behavior toward the acquisition of appetitive goals (Davidson et al., 2002). These mood-congruent cognitive biases challenge contingent learning and decision making of patients, and functional MRI studies suggested a critical role of medial, orbitofrontal, dorsolateral PFC, and ACC in mediating them (Benedetti et al., 2007; Elliott et al., 2002; Price and Drevets, 2010). This perspective is in agreement with current views about the role of emotional processing in quickly developing suicidal ideation and resorting to painful self-harming behaviors while experiencing negative affective states (Anestis and Joiner, 2011), and with a pivotal functional MRI study of autobiographical scripts of a recent episode of attempted suicide suggesting that goal-directed suicidal behavior is associated with a reduction of mental pain (Reisch et al., 2010).

Lithium has been suggested to have neurotrophic and neuroprotective properties that ameliorate the proposed impairments of cellular plasticity and resilience that might underlie the pathophysiology of mood disorders (Bachmann et al., 2005). A meta-analysis of MRI studies in patients affected by BD associated ongoing lithium treatment with higher GM volumes (Bora et al., 2010). Lithium increases GM volumes in humans (Monkul et al., 2007b), and two
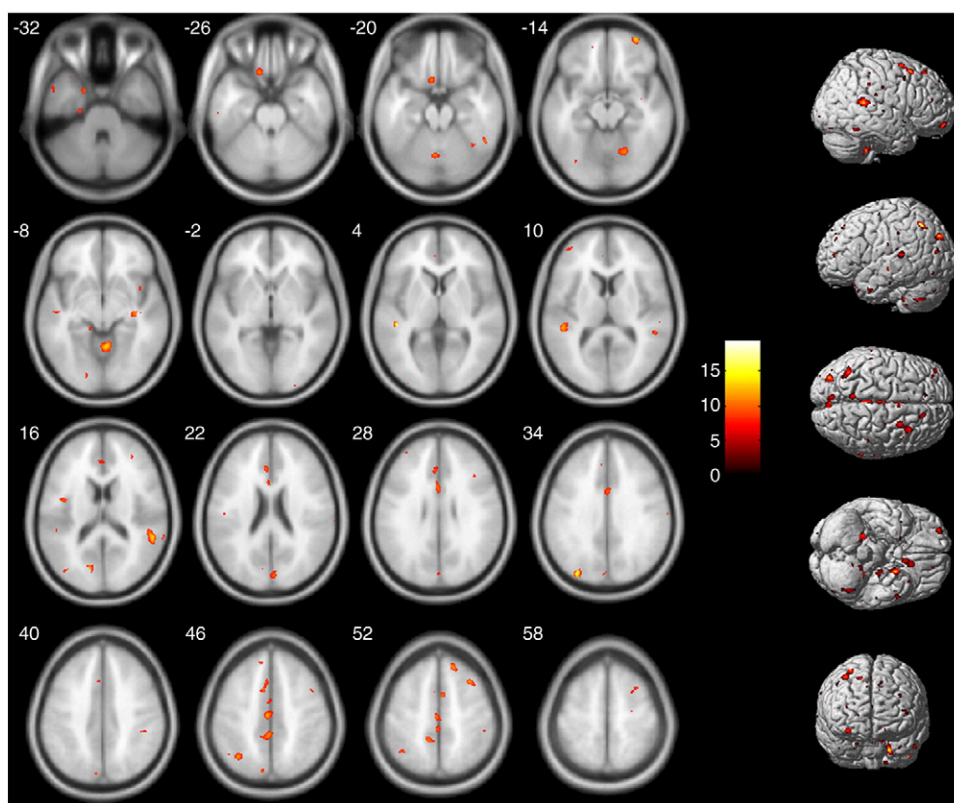
Fig. 2. Areas where both a positive history of suicidal acts, and ongoing long-term treatment with lithium, significantly influenced gray matter volumes. Threshold for visualization is p<0.001 uncorrected, see Table 2 to localize clusters surviving statistical threshold (p<0.05 FDR corrected).

longitudinal studies have recently associated the lithium-induced GM volume increase with treatment response in BD (Lyoo et al., 2010; Moore et al., 2009).

Despite our lithium-treated patients not being full responders to long-term prophylaxis, because they developed a depressive episode during treatment, we observed that ongoing lithium was associated both with lower severity of current depression, and with higher GM volumes in the same OFC, DLPFC, and ACC areas where suicide was associated with

Fig. 3. Direction and size effect of the observed differences in gray matter volumes, for the conjuncted effect of positive history of suicide attempts and ongoing lithium treatment (Table 3), in the left orbital and medial frontal gyrus cluster surviving whole-brain FDR-correction for multiple comparisons at p<0.05. Results are shown for the voxel with the highest Z value (signal peak: left BA 47, MNI coordinates −12 23–27).

lower GM. Moreover, we observed that total GM volume inversely correlated with depression severity. These findings confirm previous reports that lithium has antidepressant effects also in patients non responding to long-term prophylaxis (Benedetti et al., 1999; Benedetti et al., 2008), and that GM volumes are inversely correlated with depressive symptomatology in bipolar patients (Nery et al., 2009). It is conceivable that the effects on GM could then provide a basis for the well known effect of lithium in reducing suicidal rates in BD (Muller-Oerlinghausen and Lewitzka, 2010). These hypotheses can however be tested only with prospective studies in suicidal patients.

Several mechanisms could contribute to the possible effect of lithium on regional GM volumes of suicidal patients. Inhibition of glycogen synthase kinase-3beta (GSK3β) protects against cell death, and an excessive activation promotes apoptosis (Benedetti et al., 2010; Gould et al., 2004): lithium inhibits GSK3β (Benedetti et al., 2005; Gould and Manji, 2005), which is abnormally active in the ventral prefrontal cortex of suicide victims (Karege et al., 2007). In bipolar depression, lithium overcomes the detrimental effects of the short form of the serotonin promoter (Benedetti et al., 2008), which has also been associated with impaired structural coupling between cortico-limbic structures (Pezawas et al., 2005). Lithium increases the activity of glutamine synthetase (Marcus et al., 1986), which is abnormally low in the brain of suicide victims (Klempan et al., 2009) thus possibly leading to prolonged alterations in glutamate and GABA function (Kalkman, 2011).
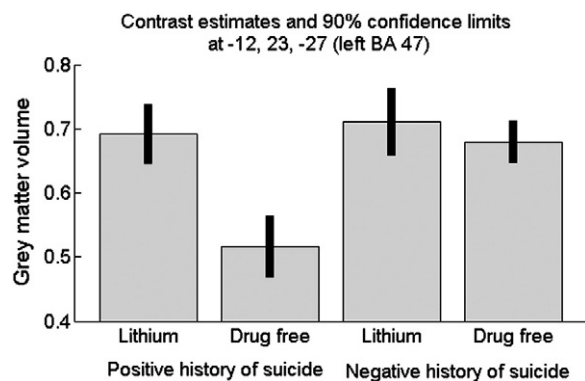
Finally, in agreement with previous reports (Leverich et al., 2003) we observed more early life stress in suicidal patients. Early life stress has been associated with persistent functional and structural brain changes in adult life, thus influencing cortico-limbic circuitries (Benedetti et al., 2011; Taylor et al., 2006). Several genetic factors modulate the relationship between stress and suicide (Caspi et al., 2003) and influence resilience to stress in patients with depression (Southwick et al., 2005). It can be hypothesized that these variables may interact in shaping the individual risk of committing suicide by influencing brain structure. Larger samples are needed to investigate this hypothesis, which exceeds the aims of the present study.

In conclusion, we confirmed in patients affected by BD previous findings in other diagnostic categories that associated suicidality with regional deficits in GM of prefrontal cortex (see Introduction), thus suggesting that reduced GM in PFC is a correlate of suicidality which is independent of the psychiatric diagnosis of the patients. Moreover, we extended these findings to other cortico-limbic brain areas including ACC and temporal cortex.

Limitations of the present study, which is retrospective and correlational in nature, also include issues such as generalizability, possible population stratification, medications over the lifetime and their effects on the observed differences, non drug-naive, no placebo control, no evaluation for compliance, varying treatment periods, without consideration of gene-environment interactions, no evaluation for family history of suicide and for lethality of suicide attempts, and technical issues related to the specific methods for the statistical analysis of brain imaging data. Moreover, the retrospective assessment of life events could have been biased by a more negative cognitive style in suicide attempters, but it has also been shown to be able to detect the structural and functional brain correlates of adverse childhood experiences in adult life (Benedetti et al., 2011; Taylor et al., 2006) and to assess the relationship between early stress and the occurrence of adult medical illnesses (Felitti et al., 1998).

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