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Cingulate gyrus volumetry in drug free bipolar patients and patients treated with valproate or valproate and quetiapine

Murad Atmaca [a,*], Huseyin Ozdemir [b], Sebnem Cetinkaya [b], Serap Parmaksiz [a], Hasan Belli [c], A. Kursad Poyraz [b], Ertan Tezcan [a], Erkin Ogur [b]

[a] Firat University, School of Medicine, Department of Psychiatry, Elazig, Turkey
[b] Firat University, School of Medicine, Department of Radiology, Elazig, Turkey
[c] Elazig Mental Health and Disorders Hospital, Elazig, Turkey

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Abstract

In patients with bipolar disorder, recent brain imaging studies have reported cingulate cortex volume change. We performed a volumetric magnetic resonance imaging (MRI) study to assess the subregions of the cingulate gyrus; left anterior cingulate (LAC), left posterior cingulate (LPC), right anterior cingulate (RAC), and right posterior cingulate (RPC). Our sample consisted of bipolar patients that are either unmedicated ($n = 10$), on valproate monotherapy ($n = 10$) or on valproate plus quetiapine ($n = 10$) versus healthy comparisons ($n = 10$). Thirty right-handed bipolar disordered patients were recruited. Of them, 10 were first-applying patients who never had taken any drug for this condition (medication-naive group), 10 were on valproate treatment (valproate group) and 10 were on valproate plus quetiapine treatment (valproate plus quetiapine group). Cingulate gyrus volumes included both cortex and white matter. Drug-free patients had significantly smaller LAC and LPC volumes compared with valproate and valproate plus quetiapine groups and healthy controls. In addition, in post hoc comparisons, a trend toward significant difference was found between valproate plus quetiapine group and valproate group in regard to only LAC. Our findings suggest that valproate and quetiapine may have neuroprotective effects.

Keywords: MRI; Cingulate cortex; Volumetric; Valproate; Bipolar disorder; Quetiapine

1. Introduction

Recent imaging studies have revealed important findings in bipolar disorder in addition to other psychiatric disorders (Soares and Mann, 1997; Strakowski et al., 2002).Three earlier investigations failed to demonstrate any differences in the volume of cingulate cortex between bipolar patients and control subjects (Coffman et al., 1990; Strakowski et al., 1993; Lopez-Larson et al., 2002). However, others found following cingulate abnormalities; a gray matter density decrease in the left anterior cingulate (Lyoo et al., 2004), reductions in gray matter density concentrated in the frontal and cingulate gyri, particularly in the right hemisphere (Doris et al., 2004), and reduced left anterior cingulate volumes (Sassi et al., 2004). The majority of published studies of functional neuroimaging in bipolar disorder have revealed hypermetabolism in striatal (Drevets et al., 1997; Blumberg et al., 2000) and pallidal areas (Mayberg, 2001; Allman et al., 2001; Cardinal et al., 2002; Phan et al., 2002). In their study, Bertolino et al. (2003) showed that patients with bipolar disorder had a regional reduction of NAA relative signals, suggesting neuronal damage or malfunction of the hippocampus. Benes et al. (2001) suggested that local circuit cells in layer II of anterior cingulate cortex might be decreased in bipolar disorder. The cingulate cortex is a functionally heterogeneous region, however, and in these previous studies the

* Corresponding author. Present Address: Firat (Euphrates) Universitesi, Firat Tip Merkezi, Psikiyatri Anabilim Dali, 23119 Elazig, Turkey, Tel.: +90 424 233 3555/2282; fax: +90 424 238 8096.
E-mail address: matmaca_p@yahoo.com (M. Atmaca).

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subgenual cingulate followed the activation of other limbic areas, such as the insula, whereas both anterior and posterior cingulate cortices behaved accordingly with other neocortical regions, such as other prefrontal and parietal areas (Mayberg et al., 1999).

The cingulate cortex is believed to function as an interface between emotion and cognition (Bush et al., 2000), with interconnected subregions specialized in diverse cognitive functions, such as episodic memory retrieval, active attention processes, initiation and inhibition of motor behavior, working memory tasks, and reward-based behavior (Cardinal et al., 2002; Bush et al., 2002). Thus, the involvement of abnormalities in cingulate cortex in mood disorders, and most particularly the anterior cingulate, is supported by findings from several studies involving distinct methodologic approaches. The posterior cingulate cortex has also been examined in patients with mood disorders, although not as consistently as the anterior cingulate. There is strong evidence demonstrating that activation of the posterior cingulate is related to enhancement of memory retrieval after an emotion-laden stimuli (Maddock, 1999; Maddock et al., 2003), suggesting a role for the posterior cingulate in bridging emotion and memory. Anatomic abnormalities in cingulate cortex structures, which were reported to be abnormal in bipolar patients, could be possibly involved in the pathophysiology of bipolar disorder. Valproic acid is widely used for the treatment of bipolar disorder. The mechanisms underlying the therapeutic effects of it has not been well-established. It has been recently reported that at therapeutic levels valproic acid directly inhibits histone deacetylase (HDAC), an enzyme strongly implicated in the modulation of gene expression, causing histone hyperacetylation (Göttlicher et al., 2001). Valproic acid has been also shown to activate the cell survival factor, Akt, presumably through inhibition of HDAC (De Sarno et al., 2002). In rat cortical neurons, long-term valproic treatment blocks glutamate-induced excitotoxicity and prolongs survival of those (Jeong et al., 2003). To the best of our knowledge, no study on bipolar patients has compared first-episode drug-naive bipolar patients with medicated patients (mood stabilizers, antipsychotic medication) and controls. Therefore, we performed a volumetric MRI study in first-episode treatment-naive patients, those with bipolar disorder ongoing valproate treatment, those with valproate plus quetiapine and healthy controls focusing on subregions of cingulate gyrus.

2. Materials and methods

Thirty right-handed patients with bipolar disorder versus healthy control comparisons ($n = 10$) were consecutively recruited from Firat University School of Medicine Department of Psychiatry. Of them, 10 were first applying patients who never had taken any drug for this condition (medication-naive group), 10 were on valproate treatment (valproate group) and the rest were valproate plus quetiapine treatment (valproate plus quetiapine group). Medication-naive group patients were those applying for their 'first-episode' and so had no previous history of treatment, and all of them were in-patients. From valproate group, seven were out-patients and three were in-patients. Valproate plus quetiapine group had five in-patients and five out-patients. Valproate group subjects were selected among first applying bipolar patients who were treated with valproate alone ($\geqslant 75$ ml) for at least six months and demonstrated 50% or more reduction on the Young Mania Rating Scale (YMRS) (Young et al., 1978) according to baseline. Diagnoses were made according to the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV) and the Structured Clinical Interview for the Diagnostic Schedule for Mental Disorders – Fourth Edition (SCID) (First et al., 1997). Severity of manic symptoms was assessed with the YMRS and that of depressive symptoms was evaluated by Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960). Valproate plus quetiapine group subjects had been on monotherapy with valproate ($\geqslant 75$ μg/ml) for a minimum of 3 months prior to quetiapine initiation and demonstrated less than 30% reduction on the YMRS according to baseline and no better than "minimally improved" on the Clinical Global Impression improvement item. They were added quetiapine and demonstrated 50% or more reduction on the YMRS) according to baseline. The mean duration of illness was 3.5 ± 2.2 years in valproate group and 2.8 ± 1.4 years in valproate plus quetiapine group. Medication prior to the current treatment comprised different antipsychotics, lithium, carbamazepine and lorazepam; see Table 1 for details on the groups. A group of healthy controls ($n = 10$) were matched on age, sex, education, and handedness. Patients with any comorbid psychiatric disorder, current medical problems, or alcohol/substance abuse within the 6 months preceding the study were excluded.

Healthy control subjects and their first-degree relatives had no DSM-IV axis I disorder, as determined by the SCID (non-patient version), no current medical problems, and no history of neurologic or psychiatric disease.

Symptom severity was rated by using the YMRS for manic symptoms and Hamilton Depression Rating Scale for depressive symptoms. Written informed consent was obtained from the subjects, after full explanation of the entire procedure. The study protocol was approved by the Local Ethics Committee of the Fırat University School of Medicine.

Magnetic resonance imaging scans were acquired with a 1.5 T General Electric signa scanner. Spiral pulse sequences were employed because of insensitivity to subject motion. A high-resolution structural image of the entire brain was obtained using sagittally acquired 3D spiral fast spin echo high-resolution images (repetition time, TR = 2000 ms; echo time, TE = 15.6 ms; field of view, FOV = 240 mm; flip angle = 20^0, bandwidth = 20.8, slice thickness = 2.4 mm, echo spacing = 15.6 ms, eight echoes, resolution = $0.9375 \times 0.9375 \times 1.328$ mm).

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Table 1
Clinical and demographic characteristics of normal control subjects and patients with bipolar disorder

	First-applying ($n = 10$)	Valproate ($n = 10$)	Valproate plus quetiapine ($n = 10$)	Controls ($n = 10$)	p
Age	23.4 ± 5.6	25.8 ± 6.4	24.9 ± 5.1	24.3 ± 4.3	>0.05
Gender (F/M)	6/4	5/5	6/4	5/5	>0.05
Age at onset (years)	23.0 ± 5.2	22.3 ± 4.4	22.1 ± 4.0	–	>0.05
Education (high school)	7	6	6	8	>0.05
Handedness (right)	10	10	10	10	>0.05
Length of illness (years)	0.2 ± 0.3	3.5 ± 2.2	2.8 ± 1.4	–	<0.01
Treatment duration (years)	–	2.8 ± 1.3	2.5 ± 1.7	–	>0.05
Prior treatments					
Classical antipsychotics	–	7	8		
Depot antipsychotic	–	1	–		
Lithium	–	7	8		
Carbamazepine	–	3	2		
Lorazepam	–	2	3		
Number of patients who were manic	10	2	2	–	
Number of patients who were depressive	–	3	2	–	
Number of patients who were mixed episode	–	1	2	–	
Number of patients who were euthymic	–	4	4	–	
YMRS scores	21.9 ± 5.3	14.0 ± 2.1	15.5 ± 1.8	–	<0.01
HDRS scores	6.4 ± 2.3	18.8 ± 0.9	17.8 ± 1.1	–	<0.01
Length of treatment with valproate (month)	–	8.3 ± 4.4	5.8 ± 3.1	–	<0.05
Length of treatment with quetiapine (month)	–	–	4.9 ± 2.8	–	
Dose of valproate (mg/day)	–	1225.0 ± 226.8	950.0 ± 120.5	–	
Dose of quetiapine (mg/day)	–	–	705.0 ± 95.2	–	

No significant differences exist between groups in age, handedness and gender composition. HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.

Anatomic measurements were conducted on a computer workstation with the GE Volume Viewer voxtool 3.0 64q program. A trained evaluator blind to group assignment and to subjects' identity obtained volumetric measurements of the regions studied. The cingulate gyrus was divided into four subregions: left anterior cingulate (LAC), left posterior cingulate (LPC), right anterior cingulate (RAC), and right posterior cingulate (RPC). All volumes are reported in cubic centimeters. All measurements were made by a single well-trained and reliable rater (HO). Interrater reliability as measured by the intraclass correlation coefficient was equal or above 0.80 for the cingulate subregions and 0.84 for intracranial volume (ICV), whole brain, gray and white matter volumes.

A coronal tracing procedure based on anatomic atlases (Jackson and Duncan, 1996; Patel and Friedman, 1997) and adapted from Noga et al. (1995) and Sassi et al. (2002) was used. The tracing was started with the anterior cingulate at two slices anterior to the most anterior slice where the genu of the corpus callosum was visible, with the cingulate sulcus as the upper limit and the callosal sulcus as the lower limit defining the cingulate gyrus. The tracing was maintained caudally on all slices until the slice where the anterior commissure was most apparent was reached. The anterior commissure indicated the posterior limit of the anterior cingulate. The subsequent slice marked the anterior border of the posterior cingulate, and the cingulate gyrus was traced in the same manner. The last slice measured in the posterior cingulate occurred when the cerebral aqueduct appeared within the pons. The tracings at left and right side were done separately, but the same slices defining the anterior and posterior boundaries were used on both sides (Fig. 1).

All analyses were carried out using the SPSS for Windows software, version 10.0 (SPSS, Chicago, IL). All the MRI volumetric measures were ICV corrected and were found to be normally distributed as determined by the Shapiro-Wilks test. We performed ANCOVA with age, gender, and ICV as covariates to compare the anterior cingulate volumes among the groups. Post hoc comparisons were carried out using Scheffe test. Spearman's rank correlation test was used to examine the effects of age and specific clinical variables on the anatomical volumes. Categorical variables were analyzed by χ^2 test. Statistical significance level was set at $p < 0.05$.

3. Results

Drug-free group, valproate group, valproate plus quetiapine group and healthy control subjects did not differ in regard to age ($F = 2.02$; df = 3; $p > 0.05$), gender ($\chi^2 = 0.8$; $p > 0.05$), ICV ($1427.2 \pm 141.3\ cm^3$ for drug-free group, $1481.6 \pm 157.3\ cm^3$ for valproate group, $1455.9 \pm 149.7\ cm^3$ for valproate plus quetiapine group, and $1439.2 \pm 154.4\ cm^3$ for healthy controls; $F = 1.88$; df = 3; $p > 0.05$), or handedness (all subjects were right-handed) ($p > 0.05$). No gender differences were seen for age, ICV and handedness in all groups. Demographic and clinical variables of the groups are presented in Table 1. Whole brain volume ($F = 2.28$; df = 3; $p > 0.05$), gray ($F = 0.78$; df = 3; $p > 0.05$), and white matter volumes ($F = 1.60$; df = 3; $p > 0.05$), did not differ among groups.

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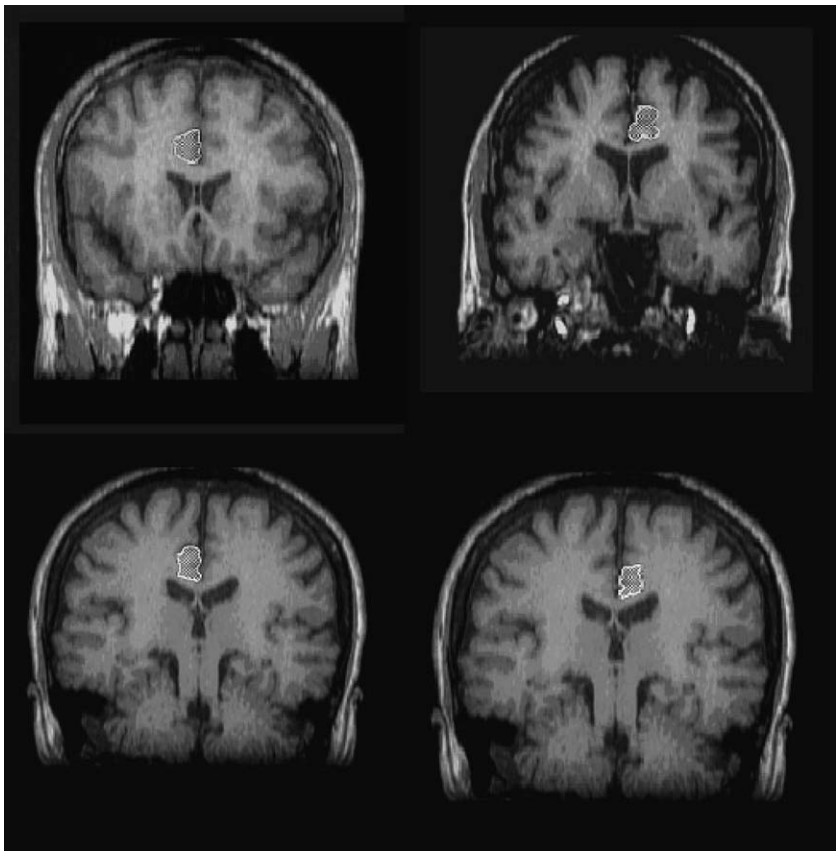

Fig. 1. Anatomic landmarks for the tracing of the cingulate sub-regions.

After collapsing all groups, no gender differences were for whole brain volume, total grey and white matter. Table 2 presents the mean volumes of structures measured for all subjects.

When ANCOVA using with age, gender, ICV, and disease duration as covariates, showed that drug-free patients had significantly smaller LAC ($F = 9.15$, df $= 3$; $p < 0.01$) and LPC ($F = 9.84$, df $= 3$; $p < 0.01$) volumes compared with valproate and valproate plus quetiapine groups and healthy controls. Post hoc comparisons between the two treatment groups showed a significant difference for the LAC ($F = 5.84$; df $= 1$; $p = 0.09$), whereas no significant difference was found between the two treatment groups and controls for both LAC and LPC. In regard to the LAC and LPC volumes, no other differences were determined among groups. On the other hand, the RAC and RPC volumes were not significantly different among groups using age, gender, ICV, and disease duration as

Table 2
Volumetric measurements of the bipolar patients and healthy control subjects

Structure volumes (cm^3)	Drug-free group (I) ($n = 10$)	Valproate group (II) ($n = 10$)	Valproate plus quetiapine group (III) ($n = 10$)	Healthy control group (IV) ($n = 10$)	P
ICV[a]	1427.2 ± 141.3	1481.6 ± 157.3	1455.9 ± 149.7	1439.2 ± 154.4	$p > 0.05$
Whole brain volume	1119.4 ± 111.7	1160.1 ± 144.5	1141.2 ± 133.6	1130.6 ± 133.2	$p > 0.05$
Gray matter volume	334.1 ± 80.3	353.8 ± 41.7	350.5 ± 37.8	335.2 ± 26.9	$p > 0.05$
White matter volume	785.3 ± 83.1	806.3 ± 94.1	790.7 ± 80.8	795.4 ± 90.3	$p > 0.05$
Left anterior cingulate	2.33 ± 0.50	2.64 ± 0.59	2.83 ± 0.85	2.73 ± 0.77	$p < 0.01$ $^{*}p < 0.05$ (I–II) $^{**}p < 0.01$ (I–III, IV) $^{***}p = 0.09$ (II–III)
Right anterior cingulate	2.69 ± 0.72	2.77 ± 0.62	2.70 ± 0.57	2.80 ± 0.76	$p > 0.05$
Left posterior cingulate	2.36 ± 0.52	2.61 ± 0.46	2.70 ± 0.67	2.65 ± 0.58	$p < 0.01$ $^{*}p < 0.01$ (I–II, III, IV)
Right posterior cingulate	2.64 ± 0.41	2.70 ± 0.48	2.81 ± 0.71	2.72 ± 0.62	$p > 0.05$

Data are presented as means ± SD.
[a] ICV, intracranial volume.

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covariates ($F = 0.97$, df = 1; $p > 0.05$, for RAC and $F = 1.61$, df = 1; $p > 0.05$). In addition, in all groups, no significant difference was found between two genders in regard to the volumes of all of LAC, LPC, RAC and RPC.

A significant inverse correlation was found between length of illness and the LAC in only drug-free group ($r = -0.46$, $p < 0.05$). There was a trend toward inverse correlation between YMRS scores and the LAC ($r = -0.30$, $p = 0.07$) and LPC ($r = -0.36$, $p = 0.08$) volumes in drug-free group and was a significant negative correlation in valproate plus quetiapine group ($r = -0.47$, $p < 0.05$). No significant correlation was found between the parameters studied and the volumes of the structures investigated in healthy controls.

4. Discussion

This is the first study comparing cingulate volumes between untreated, first presenting patients and patients treated with valproate or a valproate/quetiapine combination. We demonstrated that drug-free patients had significantly smaller LAC and LPC volumes compared with valproate and valproate plus quetiapine groups and healthy controls even after correcting for age, whole brain volume and disease duration, whereas both treated groups did not differ from the controls. In addition, the LAC volume showed a trend for larger values in the group with combined valproate–quetiapine treatment compared with the group treated with valproate only.

To the best of our knowledge, only four previous studies have measured the cingulate cortex in patients suffering from bipolar disorder and presented conflicting results. Of them, three failed to demonstrate any differences in the volume of cingulate cortex between bipolar patients and control subjects (Coffman et al., 1990; Strakowski et al., 1993; Lopez-Larson et al., 2002). In their study, Sassi et al. (2004) found that using analysis of covariance with age and intracranial volume as covariates, untreated bipolar patients had decreased left anterior cingulate volumes compared with healthy control subjects and compared with lithium-treated patients. On the other hand, unadjusted left posterior cingulate cortex volumes were found reduced in their study. We suggest that these findings are partially in consistent with ours. Major methodologic differences, both on image acquisition and analysis and sample selection, might explain the discrepancies among these studies.

Moreover, our results also suggest some degree of laterality, because both the LAC and LPC were reduced in first applying bipolar patients. This is also in accordance with the left-lateralized structural changes reported by Bouras et al. (2001) and Hirayasu et al. (1999)at the subgenual cortex.

Moreover, the effects of medication on cingulate volumes have not been fully assessed yet. Previously, the neurotrophic effects of lithium have been demonstrated (Manji et al., 2000; Sassi et al., 2002; Brambilla et al., 2005). Similar to the effect of another mood stabilizing drug, lithium, valproic acid protects mature rat cerebellar granule cells in cultures from NMDA receptor-mediated excitotoxicity and this action is mimicked by other histone HDAC inhibitors such as butyrate and trichostatin A (Kanai et al., 2002). An increasing body of reports also demonstrate that valproic acid is neuroprotective against a variety of other insults (Bown et al., 2000; Wang et al., 2003). It has been demonstrated that the atypical antipsychotic drugs clozapine, olanzapine, and quetiapine can protect PC12 cells from death induced by hydrogen peroxide, and β-amyloid peptide (Qing et al., 2003). Recent morphometric analyses of the cingulate cortex and hippocampus reveal significant reductions in the density of non-pyramidal neurons in layer II of the anterior cingulate cortex (Benes et al., 2001) and in the CA2 region of the hippocampus (Benes et al., 1998) in bipolar disorder. It has been indicated that apoptosis may be involved in the neuronal atrophy in these disorders (Catts and Catts, 2000; Jarskog et al., 2000). PC12 cells have been widely used in studies of neuronal cell survival and death (Greene, 1978; Batistatou and Greene, 1991). Bai et al. (2002) provided evidence that the atypical antipsychotics clozapine, quetiapine, and risperidone protected PC12 cells from death after serum withdrawal, potentially mediated by up-regulating SOD1 and down-regulating p75NTR expression. This finding indicated that the atypical antipsychotics might play a neuroprotective role following treatment and might also contribute to their increased efficacy for schizophrenia or bipolar disorder as an adjuvant therapy, as seen in the present study. Actually, in the present study, in post hoc comparisons, a trend toward significant difference was found between valproate plus quetiapine group and valproate group in regard to only LAC volumes, but was not found between valproate group and healthy controls, or valproate plus quetiapine group and healthy controls for LAC and LPC volumes. These results may indicate that by treatment with valproate or valproate/quetiapine neurotrophic effects are triggered that prevent ongoing degenerative processes or reinstall formerly decreased volumes. Meanwhile one may consider that our finding that significant difference was found between valproate plus quetiapine group and valproate group in regard to LAC volumes could have reflected treatment responsivity in general since it seems the valproate plus quetiapine group responded less to pharmacotherapy. However, the finding of non-significant differences in LAC between treated patients and controls could indicate that neurotrophic effects are triggered by medication which lead to a volume increase of in the formerly smaller LAC.

The strengths of the present study include a well-characterized clinical sample and the use of well-established morphometric MRI methods. Nonetheless, some particular limitations in our present findings should be considered. The number of subjects was small (10 per group), limiting the strength of statistical comparisons and challenging the validity of parametric statistical methods. Given the intrinsic limitations of the morphometric MRI methods used, such studies are subject to both false-negative and false-

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positive results. The number of subjects studied was small and the statistical thresholds applied were modest, thereby accentuating these risks and underscoring the importance of replication. As this is a cross-sectional analysis we can not exclude that the volumetric results in the treated groups reflects premorbid or pre-treatment changes. Alternatively, prior treatment with "lithium (in seven patients from valproate and eight patients from valproate plus quetiapine groups)" makes it very hard to conclude that the larger cingulates in valproate only and valproate + quetiapine groups were due to valproate or quetiapine, it may as well be the result of long-term lithium therapy, knowing the clearly demonstrated neurotrophic effects of lithium (Manji et al., 2000; Brambilla et al., 2005; Sassi et al., 2002). On the other hand, the treated groups were not a random sample of patients receiving valproate or valproate plus quetiapine, but were selected on the basis of treatment response, so different volumes could also be associated to different treatment response patterns. Another limitation of the study is that we cannot exclude effects in other brain regions that are involved in bipolar disease, as the medial prefrontal cortex or the temporal cortices.

In summary, our study reports that drug-free patients has significantly smaller LAC and LPC volumes compared with valproate and valproate plus quetiapine groups and healthy controls. In post hoc comparisons, a trend toward significant difference was found between valproate plus quetiapine group and valproate group in regard to only LAC, but was not found between valproate group and healthy controls, or valproate plus quetiapine group and healthy controls for LAC and LPC, without any differences in the RAC and RPC volumes. These findings suggest that while valproate may have neuroprotective effects it seems valproate plus quetiapine to have stronger neuroprotective features on especially LAC which is demonstrated reduced in studies apart from the present study. Future prospective, controlled intervention and randomized neuroimaging and neuropsychological studies with larger patient samples are warranted in order to confirm these preliminary findings to better characterize.

References

Allman JM, Hakeem A, Erwin JM, Nimchinsky E, Hof P. The anterior cingulate cortex. The evolution of an interface between emotion and cognition. Annals of the New York Academy of Sciences 2001;935:107–17.

Bai O, Wei Z, Lu W, Bowen R, Keegan D, Li XM. Protective effects of atypical antipsychotic drugs on PC12 cells after serum withdrawal. Journal of Neuroscience Research 2002;69:278–83.

Batistatou A, Greene LA. Aurintricarboxylic acid rescues PC12 cells and sympathetic neurons from cell death caused by nerve growth factor deprivation: correlation with suppression of endonuclease activity. Journal of Cell Biology 1991;115:461–71.

Benes FM, Kwok EW, Vincent SL, Todtenkopf MS. A reduction of nonpyramidal cells in sector CA2 of schizophrenics and manic depressives. Biological Psychiatry 1998;44:88–97.

Benes FM, Vincent SL, Todtenkopf MS. The density of pyramidal and nonpyramidal neurons in anterior cingulate cortex of schizophrenic and bipolar subjects. Biological Psychiatry 2001;50:395–406.

Bertolino A, Frye M, Callicott JH, Mattay VS, Rakow R, Shelton-Repella J, et al. Neuronal pathology in the hippocampal area of patients with bipolar disorder: a study with proton magnetic resonance spectroscopic imaging. Biological Psychiatry 2003;53:906–13.

Blumberg HP, Stern E, Martinez D, Ricketts S, Assis J, White T, et al. Increased anterior cingulate and caudate activity in bipolar mania. Biological Psychiatry 2000;48:1045–52.

Bouras C, Kovari E, Hof PR, Riederer BM, Giannakopoulos P. Anterior cingulate cortex pathology in schizophrenia and bipolar disorder. Acta Neuropathologica (Berlin) 2001;102:373–9.

Bown CD, Wang JF, Young LT. Increased expression of endoplasmic reticulum stress proteins following chronic valproate treatment of rat C6 glioma cells. Neuropharmacology 2000;39:2162–9.

Brambilla P, Stanley JA, Nicoletti MA, Sassi RB, Mallinger AG, Frank E, et al. 1H magnetic resonance spectroscopy investigation of the dorsolateral prefrontal cortex in bipolar disorder patients. Journal of Affective Disorders 2005;86:61–7.

Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. Trends in Cognitive Sciences 2000;4:215–22.

Bush G, Vogt BA, Holmes J, Dale AM, Greve D, Jenike MA, et al. Dorsal anterior cingulate cortex: a role in reward-based decision making. Proceedings of the National Academy of Sciences of the United States of America 2002;99:523–8.

Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neuroscience and Biobehavioral Reviews 2002;26:321–52.

Catts VS, Catts SV. Apoptosis and schizophrenia: is the tumor suppressor gene, p53, a candidate susceptibility gene? Schizophrenia Research 2000;41:405–15.

Coffman JA, Bornstein RA, Olson SC, Schwarzkopf SB, Nasrallah HA. Cognitive impairment and cerebral structure by MRI in bipolar disorder. Biological Psychiatry 1990;27:1188–96.

De Sarno P, Li X, Jope RS. Regulation of Akt and glycogen synthase kinase-3 beta phosphorylation by sodium valproate and lithium. Neuropharmacology 2002;43:1158–64.

Doris A, Belton E, Ebmeier KP, Glabus MF, Marshall I. Reduction of cingulate gray matter density in poor outcome bipolar illness. Psychiatry Research 2004;130:153–9.

Drevets WC, Price JL, Simpson JR, Todd RD, Reich T, Vannier M, et al. Subgenual prefrontal cortex abnormalities in mood disorders. Nature 1997;386:824–7.

First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York: New York State Psychiatric Institute, Biometrics Research; 1997.

Göttlicher M, Minucci S, Zhu P, Kramer OH, Schimpf A, Giavara S, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO Journal 2001;20: 6969–78.

Greene LA. Nerve growth factor prevents the death and stimulates the neuronal differentiation of clonal PC12 pheochromocytoma cells in serum-free medium. Journal of Cell Biology 1978;78:747–55.

Hamilton M. A rating scale for depression. Journal of Neurology Neurosurgery and Psychiatry 1960;23:56–62.

Hirayasu Y, Shenton ME, Salisbury DF, Kwon JS, Wibble CG, Fischer LA, et al. Subgenual cingulate cortex volume in first-episode psychosis. American Journal of Psychiatry 1999;156:1091–3.

Jackson GD, Duncan JS. MRI anatomy: a new angle on the brain. New York: Churchill Livingstone; 1996.

Jarskog LF, Gilmore JH, Selinger ES, Lieberman JA. Cortical Bcl-2 protein expression and apoptosic regulation in schizophrenia. Biological Psychiatry 2000;48:641–50.

Jeong MR, Hashimoto R, Senatorov VV, Fujimaki K, Ren M, Lee MS, et al. Valproic acid, a mood stabilizer and anticonvulsant, protects rat cerebral cortical neurons from spontaneous cell death: a role of histone deacetylase inhibition. FEBS Letter 2003;542:74–8.

Kanai H, Sawa A, Chuang DM. Possible involvement of histone deacetylase inhibition in the neuroprotective and neurotoxic effects

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of valproate in cultured cerebellar granule cells. In: 32nd Annual meeting. Society for Neuroscience; 2002.

Lopez-Larson MP, DelBello MP, Zimmerman ME, Schwiers ML, Strakowski SM. Regional prefrontal gray and white matter abnormalities in bipolar disorder. Biological Psychiatry 2002;52:903–10.

Lyoo IK, Kim MJ, Stoll AL, Demopulos CM, Parow AM, Dager SR, Friedman SD, Dunner DL, Renshaw PF. Frontal lobe gray matter density decreases in bipolar I disorder. Biological Psychiatry 2004;55:648–51.

Maddock RJ, Garrett AS, Buonocore MH. Posterior cingulate cortex activation by emotional words: FMRI evidence from a valence decision task. Human Brain Mapping 2003;18:30–41.

Maddock RJ. The retrosplenial cortex and emotion: New insights from functional neuroimaging of the human brain. Trends in Neuroscience 1999;22:310–6.

Manji HK, Moore GJ, Chen G. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biological Psychiatry 2000;48:740–54.

Mayberg H. Depression and frontal–subcortical circuits: focus on prefrontal–limbic interactions. In: Lichter DG, Cummings JL, editors. Frontal–subcortical circuits in psychiatric and neurological disorders. New York: Guilford Press; 2001. p. 177–206.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, et al. Reciprocal limbic–cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 1999;15:675–82.

Noga JT, Aylward E, Barta PE, Pearlson GD. Cingulate gyrus in schizophrenic patients and normal volunteers. Psychiatry Research 1995;61:201–8.

Patel VH, Friedman L. MRI of the brain: normal anatomy and normal variants. Philadelphia: W.B. Saunders; 1997.

Phan KL, Wager T, Taylor SF, Liberzon I. Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI. Neuroimage 2002;16:331–48.

Qing H, Xu H, Wei Z, Gibson K, Li XM. The ability of atypical antipsychotic drugs vs. haloperidol to protect PC12 cells against MPP+-induced apoptosis. European Journal of Neuroscience 2003;17:1563–70.

Sassi RB, Nicoletti M, Brambilla P, Mallinger G, Fran E, Kupfer DJ, et al. Increased gray matter volume in lithium-treated bipolar disorder patients. Neuroscience Letter 2002;329:243–5.

Sassi RB, Brambilla P, Hatch MA, Mallinger AG, Frank E, Kupfer DJ, et al. Reduced left anterior cingulate volumes in untreated bipolar patients. Biological Psychiatry 2004;56:467–75.

Soares JC, Mann JJ. The anatomy of mood disorders—Review of structural neuroimaging studies. Biological Psychiatry 1997;4:86–106.

Strakowski SM, Wilson DR, Tohen M, Woods BT, Douglass AW, Stoll AL. Structural brain abnormalities in first-episode mania. Biological Psychiatry 1993;33:602–9.

Strakowski SM, DelBello MP, Zimmerman ME, Getz GE, Mills NP, Ret J, et al. Ventricular and periventricular structural volumes in first- versus multiple episode bipolar disorder. American Journal of Psychiatry 2002;159:1841–7.

Wang JF, Azzam JE, Young LT. Valproate inhibits oxidative damage to lipid and protein in primary cultured rat cerebrocortical cells. Neuroscience 2003;116:485–9.

Young RC, Biggs JT, Ziegler VE. A rating scale for mania: reliability, validity and sensitivity. British Journal of Psychiatry 1978;133:429–35.

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