

QEEG changes during switch from depression to hypomania/mania: A case report

Miloslav KOPECEK^{1,2,3}, Barbora TISLEROVA^{1,2}, Peter SOS^{1,2}, Martin BARES^{1,2},
Tomas NOVAK^{1,2}, Vladimir KRAJCA⁴, and Martin BRUNOVSKY^{1,2,4}

1. Prague Psychiatric Centre, Ustavni 91, Prague 8 – Bohnice, 181 03, Czech Republic.
2. The Department of Psychiatry and Medical Psychology, 3rd Faculty of Medicine, Charles University, Ruska 87, Prague 10, 100 00, Czech Republic.
3. Center of Excellence for Research & Treatment of Bipolar Disorder, Department of Psychiatry, University of North Carolina at Chapel Hill, NC, USA.
4. Department of Neurology, Faculty Hospital Bulovka, Prague, Czech Republic.

Correspondence to: Miloslav Kopecek, M.D., Ph.D.
Center of Excellence for Research & Treatment of Bipolar Disorder
Department of Psychiatry, University of North Carolina at Chapel Hill
Campus Box 7160, Chapel Hill, NC, 27599-7160, USA.
PHONE: +1-919- 966-5069
E-MAIL: kopecek@pcp.lf3.cuni.cz

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Abstract

BACKGROUND: QEEG cordance and low-resolution electromagnetic tomography (LORETA) are relatively new applications of QEEG. Four small-scale studies have shown that decreases of QEEG prefrontal theta cordance after the first week on new antidepressants predict clinical response to treatment in patients with unipolar depression.

METHODS: We calculated prefrontal theta cordance and changes in 3D distribution of brain electrical activity using LORETA in the case of a 54-year old man experiencing his third depressive episode.

RESULTS: We did not detect a decrease of prefrontal theta cordance after one week of new treatment and the patient did not respond to this therapy after four weeks. However, we observed a decrease of prefrontal theta cordance after the first week of clomipramine therapy. Manic symptoms emerged after two weeks of clomipramine treatment. A decrease of prefrontal theta cordance preceded the clomipramine induced switch to hypomania during the next episode of depression also. LORETA before and during clomipramine therapies detected a significant increase of theta in the right postcentralis gyrus in the parietal lobe, and a borderline increase of alfa2 in the right middle frontal gyrus.

DISCUSSION: In a patient with bipolar spectrum disorder we found that a treifold change in theta prefrontal cordance preceded mood changes in a similar way as in patients with unipolar depression. We speculate that the changes detected by LORETA can be attributed to the anticholinergic activity of clomipramine and the specific effects of a mood switch. Our data suggest that the new applications of QEEG can be sensitive to mood changes and have potential in bipolar disorder research.

Abbreviations and units:

BA	– Brodmann area
BD	– Bipolar disorder
BDI-SF	– Short Form of Beck Depression Inventory
CGI	– Clinical Global Impression
EEG	– electroencephalography
fMRI	– functional Magnetic Resonance Imaging
LORETA	– Low Resolution Electromagnetic Tomography
MADRS	– Montgomery-Åsberg Depression Rating Scale
mg	– milligram
mlU/l	– milli-International Units per liter
mmol/l	– millimol/liter
PET	– Positron Emission Tomography
QEEG	– Quantitative Electroencephalography
rTMS	– repetitive Transcranial Magnetic Stimulation
SPECT	– Single Photon Emission Tomography
SSRI	– Selective Serotonin Reuptake Inhibitor
TCA	– tricyclic antidepressant
YMRS	– Young Mania Rating Scale

INTRODUCTION

The switch to hypomania/mania during treatment of unipolar depressive disorder with antidepressants was described with frequencies occurring between 0–22.4% [30,45]. Using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), these patients are diagnosed with a manic or hypomanic episode associated with antidepressants. Some authors have proposed that these patients should be classified in the bipolar spectrum [1,30], while others do not [7]. Antidepressant induced switch to hypomania/mania are estimated to occur in 0–84.2% patients with bipolar disorder (BD) [4,24]. Switch phenomena have been described during treatment with almost every antidepressant modality even nonpharmacological ones [5,16,61,63].

The neurobiologic basis of a drug induced switch is unknown, as is a spontaneous switch to mania. Antidepressant-related switches could be considered a subtype of switches [14], occurring in predisposed individuals because of the eliciting action of antidepressants [57]. The switch to mania after specific antidepressant treatment could reflect an endophenotype which could be composed of a more homogenous group of patients than the phenotype of bipolar disorder.

In this study, we present a case series of antidepressant induced switches together with detected electrophysiological changes. We used two types of new EEG analyses (theta QEEG cordance and Low Resolution Electromagnetic Tomography – LORETA) to describe EEG changes before the switch to mania.

QEEG cordance is a new EEG method, that combines complementary information from the absolute (the amount of power in a frequency band at a given electrode) and relative power (the percentage of power contained in a frequency band relative to the total spectrum) of EEG spectra. Cordance combines these parameters to achieve a stronger association with cerebral perfusion than either measure alone. Of the three

QEEG measures (absolute power, relative power, and cordance) examined, cordance had the strongest relationship with perfusion [40].

LORETA is a neurophysiological method, that allows truly three-dimensional tomography of brain electrical activity [51].

QEEG techniques

Nineteen surface electrodes were placed according to the international 10/20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1 and O2), with all electrode impedances kept below 5 k Ω . We used the BrainScope amplifier system (unimedis, Prague), with the Cz as a reference electrode. The EEG was recorded with the patient in a semi recumbent position, with eyes closed in a maximally alert state in a sound-attenuated room with subdued lighting. The data, 30 minutes in duration, were collected with an on-line computer system. All signals were sampled with a frequency of 250 Hz with 0.5–70 Hz filters, and the data were stored for further computer off-line analysis. Before analysis of the data, artifact detection was performed visually with the exclusion of all EEG segments which contained obvious eye and head movements, muscle artifacts or decrease of alertness. After re-computation to average reference, spectral analysis was performed for at least 30s of artifact-free data. The cross-spectra for LORETA analysis were averaged across the overlapping windows which yielded into seven frequency bands delta (1.5–6 Hz), theta (6.5–8 Hz), alpha-1 (8.5–10 Hz), alpha-2 (10.5–12 Hz), beta-1 (12.5–18 Hz), beta-2 (18.5–21 Hz) and beta-3 (21.5–30 Hz) [37].

Theta prefrontal cordance and LORETA analysis

According to previous studies [8–10,17,39], average cordance values from three frontal electrodes (Fp1, Fp2 and Fz) in theta frequency band (4–8 Hz) were subjected to statistical analysis.

Subsequently, LORETA was used to estimate changes in 3D intracerebral current density distribution. LORETA 3D images were compared with voxel-by-voxel t tests, resulting in t statistic 3D images. In these images, cortical voxels of statistically significant differences were identified by a nonparametric approach using a randomization strategy that determined the critical probability threshold values for the actually observed statistic with corrections for multiple testing of single voxels. Only the voxels with t-values, that exceeded the critical threshold for $p = 0.05$ were taken into account. Statistical analysis of LORETA data was made by the comparison (by paired t-tests of log-transformed LORETA power spectra) of two EEG recordings in the clomipramine treatment (after 1st week of 1st and 2nd clomipramine therapy, before switch to mania) with two EEG recordings in the depressive episode, before clomipramine therapy.

Table 1. Clinical characteristics and EEG cordance before and after switch to 1st episode of mania. * marks how change in theta frontal cordance after one week on new medication predict mood change.

Scales	Treatment and scores in scales					
	Baseline scores	Ven 1 st week	Ven 4 th week	Clo 1 st week	Clo 2 nd week	Li+Ris 4 th week
MADRS	24	30	25	25	4	0
CGI-D/CGI-M	4/1	5/1	4/1	4/1	1/3	1/5
BDI-SF	16	20	16	16	2	0
YMRS	X	X	X	X	12	24
cordance value	0.63	0.66 (↑)*	0.83 (↑)	0.77 (↓)*	X	X

MADRS, CGI-D – Depressive - Clinical Global Impression scale, CGI-M - Mania - Clinical Global Impression Scale, BDI-SF - Beck Depression Inventory – Short Form [11], YMRS - Young Mania Rating Scale [64], Clo – clomipramine, Li – lithium, Ris – risperidone, Ven – venlafaxine ER, X – No observed. ↓ - decrease, ↑ - increase

Table 2. Clinical characteristics and EEG cordance before and after switch to 2nd hypomania episode. * marks how change in theta frontal cordance after one week on new medication predict mood change.

Scales	Treatment and scores in scales				
	baseline scores Ser+Li+Ris	1 st week Clo+Li+Ris	2 nd week Clo+Li+Ris	3 rd week ↓Clo+Li+Ris	4 th week Ola+Li
MADRS	24	24	8	2	2
CGI-D /CGI-M	4/1	3/1	2/3	1/4	1/2
BDI-SF	19	19	11	1	1
YMRS	0	0	14	16	8
cordance value	0.827	0.727 (↓)*	0.687 (↓)	0.727(↑)	0.757(↑)

MADRS – Montgomery-Åsberg Depression Rating Scale, CGI-D – Depressive - Clinical Global Impression scale, CGI-M - Mania - Clinical Global Impression Scale, BDI-SF - Beck Depression Inventory – Short Form [11], YMRS - Young Mania Rating Scale [64], Clo – clomipramine, Li – lithium, Ola – olanzapin, Ris – risperidone, Ser – sertraline, X – No observed, ↓ - decrease, ↑ - increase.

Case report and the change of theta prefrontal cordance

A 54-year old man experiencing his third depressive episode was admitted to The Prague Psychiatric Centre (PPC). His brother suffered from BD I and his sister was healthy. No parent had suffered from mental illness. He was married, had one son and worked as a teacher in the high school. He used tamsulosin (an α 1a-selective alpha blocker) for treatment of benign prostatic hyperplasia. His first depressive episode occurred when he was 52 years old, and for which he took citalopram followed by escitalopram, bupropion and underwent psychotherapy. He did not reach full remission and was not able to go back to his work. He had no history of manic or hypomanic episodes. During his second depressive episode at age 54, he was treated with mirtazapine 45 mg/d and amisulpride 50 mg/d. With treatment his mood improved, but he still did not reach full remission. After six months of treatment with mirtazapine and amisulpride he experienced two months of full recovery, but then suddenly experienced his third depressive episode for which he was hospitalized at the PPC. After admis-

sion to the PPC he consented to participate in a clinical study. At The PPC the diagnosis of recurrent major depressive disorder was evaluated according to DSM IV criteria and confirmed using The Mini – International Neuropsychiatric Interview – M.I. N. I., Czech version 5.0.0. [58]. The patient suffered from depressive mood, abulia, mental slowing, decreased appetite, weight loss, insomnia, working incapacity and tiredness. He underwent an EEG examination, baseline mood evaluation (Table 1) and then started a four week monotherapy course of venlafaxine ER up to 225 mg/d. No decrease in theta prefrontal cordance value occurred after one week of venlafaxine therapy (Table 1), and he did not reach a significant antidepressant response after four weeks of therapy (reduction of $\geq 50\%$ in total MADRS – Montgomery-Åsberg Depression Rating Scale [46]). Subsequently, the therapy was changed to clomipramine given up to 100 mg/d by the intravenous route given along with oxazepam 30 mg/d and nitrazepam 5 mg/d. After the first week of the clomipramine therapy was started, prefrontal cordance decreased (Table 1). The mood switched to mania in the second week

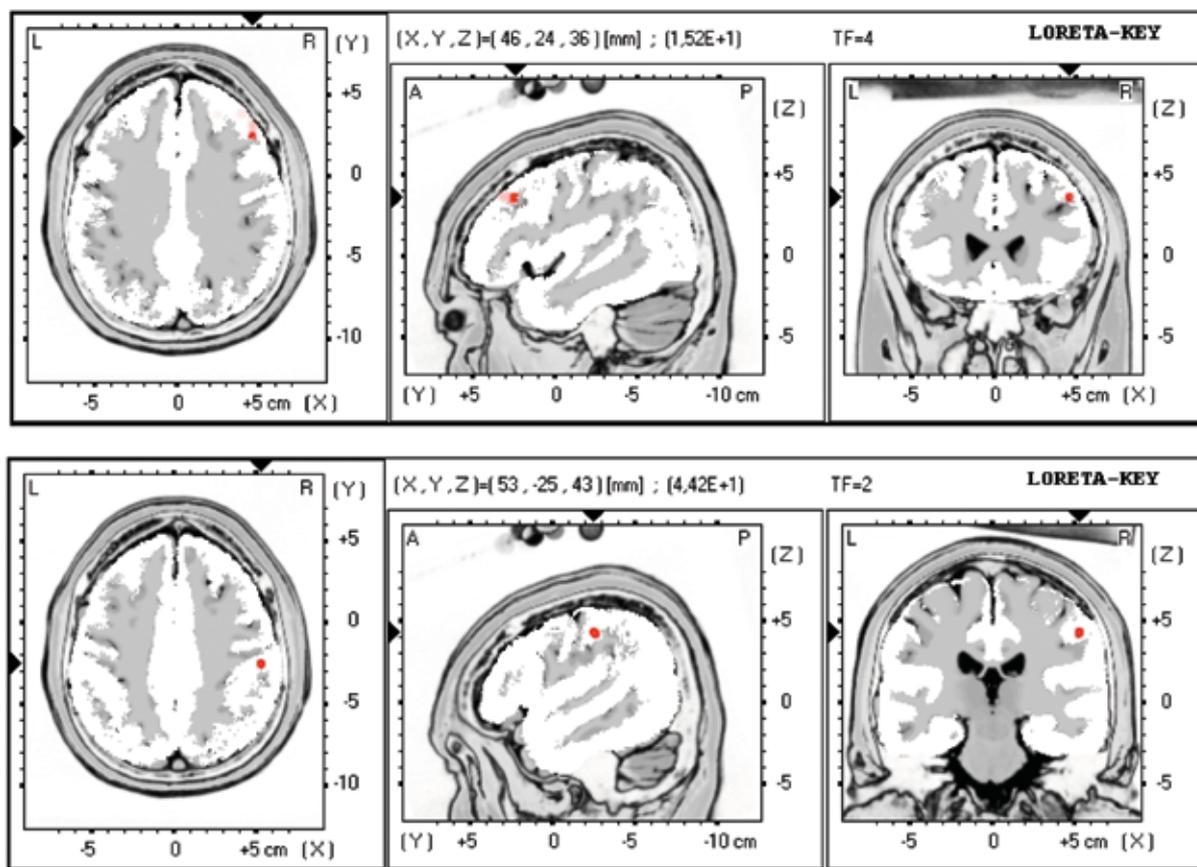


Figure 1. Images of voxel-by-voxel t-statistic of brain regional electrical activity using LORETA, comparing before-after one week clomipramine power density in patient in theta and alfa 2 band. An increase of current density after clomipramine is indicated by red. Upper figure shows a voxel with maximal tmax increase of current density in the alfa2 band in the Middle Frontal Gyrus, Brodmann area 9 ($X=46, Y=24, Z=36$), lower figure shows a voxel with maximal increase of current density in the theta band tmax in the Postcentral Gyrus, Parietal Lobe, Brodmann area 2, ($X=53, Y=-25, Z=43$). Structural anatomy is shown in gray scale (white-to-black). Left: axial slices, seen from above, nose up; center: sagittal slices, seen from the left; right: coronal slices, seen from the rear. The extreme t-values are given as (X,Y,Z) coordinates in Talairach space, and are graphically indicated by black triangles on the coordinate axes. Talairach coordinates: X from left (L) to right (R); Y from posterior (P) to anterior (A); Z from inferior to superior.

of clomipramine treatment. The patient was euphoric, hyperactive and talkative. He had a decreased need for sleep, described racing thoughts and his behavior was deliberate and inappropriate (he wore women's clothes as he walked around the hospital). He was transferred to a locked psychiatric unit, tapered off clomipramine and started antimanic treatment. Manic symptoms disappeared after six weeks of lithium (900 mg/d) and risperidone (5 mg/d) therapy. The patient was in full remission for the next four months after which the next depressive episode started. His psychiatrist added sertraline 200 mg/d to lithium (900 mg/d) and risperidone (2 mg/d). Six-weeks of outpatient sertraline therapy had no effect and the patient was rehospitalized in PPC. The symptoms were same as in the previous depressive episodes (Table 2). His lithium plasma level was within the therapeutic range (0.69 mmol/l) and elevation of plasma prolactin (675 mIU/l) was consistent with low dose risperidone therapy [34]. After unsuccessful treatment of the depression with sertraline, it was decided use an

oral form of clomipramine. The patient was informed that during clomipramine therapy, he was at risk of the induction of hypomania/mania but that use of lithium and risperidone could reduce this risk [12,48]. The patient agreed to have clomipramine therapy and further EEG assessments. Thus oral clomipramin 100 mg/d was added to lithium (900 mg/d) and risperidone (2 mg/d). After one week of clomipramine therapy, we observed a decrease of theta prefrontal cordance and further decreased two weeks later (Table 2). During the second week of this clomipramine therapy, morning tiredness promptly disappeared and the first signs of the switch to hypomania occurred (the patient was hyperactive, cheerful and talkative). In the third week clomipramine was decreased to 50 mg/d and the theta prefrontal cordance increased. Due to continuing mood elevation, we tapered the patient off clomipramine and switched the risperidone to olanzapine. A week after this new treatment, theta prefrontal cordance increased again and mood was euthymic during next eight weeks.

Table 3. Receptors' affinity of antidepressants used in the case

	NE	5-HT	DA	Alfa-1	H1	M
escitalopram	+/-	+++++	0	+/-	+/-	+/-
citalopram	+/-	++++	0	+	+	+/-
bupropion	0	+/-	+	+/-	+/-	0
sertraline	+	+++++	+++	++	0	+
venlafaxine	+	++++	+/-	0	0	0
mirtazapine	+/-	0	0	+	+++++	+
clomipramine	+++	+++++	+/-	+++	+++	+++

NE= norepinephrine; 5-HT= serotonin; DA= dopamine, Alfa-1 = alpha adrenergic, H1 = histaminic, M = muscarinic; +++++=most potent; +/-=weak effect; 0 = no effect. Adapted from [50,55]

LORETA changes

We also used LORETA analysis changes before and after the first week of the first and second clomipramine treatment phases to elucidate electrophysiological changes that preceded the switch to mania/hypomania. We combined data from both trials to increase power. We found significant increases in the theta band ($p=0.002$) in the right parietal lobe (postcentral gyrus, Brodmann area – BA 2) and borderline increases of alfa2 in the right middle frontal gyrus (BA 9) $p= 0.056$ (Figure 1).

DISCUSSION

To the best of our knowledge, this is the first description of the application of theta prefrontal cordance to the study of patients with bipolar disorder. The absence of a prefrontal theta cordance decrease after venlafaxine therapy in our patient predicted non-response, in agreement to previous studies in patients with unipolar depression [8–10,17,18]. Further therapy with intravenous clomipramine was associated with a decrease of theta prefrontal cordance and a switch to mania which occurred a week later. Previous reports have described that decreases in prefrontal theta cordance predict antidepressive responses to drugs [8–10,17,18] and rTMS [36]. Increase of prefrontal theta cordance was associated with placebo response [39] and or dissimulation [35]. However, no reference to a switch to mania was mentioned. The patient was treated with lithium and risperidone as antimanic therapy and later as mood stabilizing therapy, but this combination did not prevent a further depressive episode. We were not sure that the switch was due to clomipramine induced mania, a spontaneous switch to mania with random co-occurrence, or a switch after benzodiazepine medication [19,26].

A second trial with oral clomipramine treatment induced hypomania despite the possibility that lithium and risperidone might be effective in the prevention of mania, because it has been effective as an antimanic

ic treatment before. The lithium plasma level was stable, and the patient treated with 2 mg/d of risperidone, a lower dose than used during the acute treatment of mania. In our opinion, the second occurrence of hypomania during clomipramine therapy excluded the possibility of a spontaneous switch to hypomania or a benzodiazepine induced mania, and made clomipramine more probable as a causal agent of the switch. Also after the first and second depressive episodes, no spontaneous switch occurred during treatment with antidepressants. For both manic episodes, the switch was preceded by a decrease of prefrontal theta cordance (Table 1 and 2). Rather than measurement of absolute value previous studies have used a decrease in theta prefrontal cordance after treatment with a new drug to predict response, and a non-decrease to predict non-response [8–10,17,18].

It is not clear which brain processes underlie decreases of theta prefrontal cordance. Previous human studies suggest that theta band reflects the activity of anterior cingulate gyrus [6,54], that support recent EEG and default mode fMRI study [59]. Abnormality in anterior cingulate gyrus in patients with mood disorders were detected using structural MRI [28] and PET [20]. Responders and nonresponders to antidepressants treatment had different frontal theta activity using EEG [47,53], glucose metabolism [44] and blood flow using fMRI [27,29] or SPECT [38] in anterior cingulate gyrus. Based on this data, we suppose that the change of theta prefrontal cordance might be the main correlate of early activity changes in the anterior cingulate.

The patient did not experience manic symptoms after receiving escitalopram, citalopram or bupropion, which act as serotonin reuptake inhibitors and a norepinephrine-dopamine reuptake inhibitor (Table 3). We did not observe a switch to mania after sertraline or venlafaxine which act as a serotonin and a weak dopamine reuptake inhibitor and serotonin-norepinephrine reuptake inhibitor respectively, and which have no antihistaminic or significant anticholinergic activity [55]. The switch to mania did not occur after mirtazapine therapy which increases serotonin via ac-

Table 4. Theta prefrontal cordance and EEG findings in patients with unipolar depression after 1 week of antidepressant, in patient with clomipramine induced mania/hypomania and in healthy controls after acute intravenous application of scopolamine and during drug induced euphoria

	Theta prefrontal cordance	LORETA	EEG
Patients with unipolar depression	Reduction predicts later response. [8–10,17,18] Absence of reduction predicts non-response. [8–10,17,18]	Decrease of theta band in BA 8, 9 [13]	
Patient with switch after clomipramine	Reduction preceded twice early switch to mania/hypomania. Absence of reduction preceded once no antidepressant effect.	1) marginal increase of the alpha-2 band in BA 9 2) an increase in the theta band in the right parietal lobe	
healthy volunteers after scopolamine intake [33]			1) a decrease of the alpha-2 band, mainly over frontal regions 2) increased delta and theta activity in central and parieto-occipital regions

tivity on presynaptic α 2-noradrenergic receptors and blocks 5-HT_{2A} and histamine receptors [55] or after the addition of low doses of amisulpride, a drug that increases dopamine in prefrontal cortex [60].

Clomipramine has a high affinity for serotonin reuptake inhibition, high antagonistic activity on histamine H₁ and muscarinic acetylcholine receptors, and medium affinity for norepinephrine reuptake inhibition [55]. The antihistaminic activity is not related to an antidepressive effect but blockade of muscarinic receptors may be related to an antidepressant effect [22,31,32].

We speculate that the anticholinergic activity of clomipramine played a role in the switches to hypomania/mania in our patient. A recent study demonstrated antidepressant activity for an anticholinergic drug – scopolamine in depressive patients [22] and another showed reduced muscarinic type 2 receptor binding in the anterior cingulate in patients with bipolar disorders [15]. These studies have caused renewed interest in the acetylcholine hypothesis in affective disorder [31,32]. Anticholinergic drugs such as scopolamine have been recently studied in healthy volunteers, mainly to evaluate cholinergic hypothesis of Alzheimer diseases using QEEG. These studies detected increased delta and theta activity in central and parieto-occipital regions [33,56] that agree with our observation of an increase in the theta band in the right parietal lobe using LORETA. This change seems more related to an anticholinergic effect of clomipramine.

Of course we could not rule out synergic effect between anticholinergic activity and norepinephrine and/or serotonin reuptake inhibition during clomipramine use. This is a typical receptor profile of tricyclic antidepressants (TCA). TCA are associated with an increased risk of switch to mania during treatment of bipolar depression than treatment with other antidepressants

[25,52]. TCA is also probably associated with induction of rapid cycling in patients with bipolar disorder [3,62].

A decrease of the alpha-2 band, mainly over frontal regions, was detected in healthy volunteers after scopolamine administration [21,33]. We observed a marginal increase of the alpha-2 band, using LORETA, that indicated a reaction to the clomipramine treatment in our patient or a prospective sign of a pending manic/hypomanic state. However, we interpreted these changes carefully, due to a marginal statistical effect. Nevertheless, we did not detect similar changes in patients with unipolar depression after one week of antidepressant treatment using LORETA [13]. This lack of change suggests that this effect is not connected to an antidepressant response in patients with unipolar depression, and could be potentially connected with clomipramine induced mania/hypomania (table 4). Increased frontal alpha activity were detected in alcohol, cocaine and mariuhana induced euphoria [41–43] that indicate possible association between increased frontal alpha and switch to mania. Moreover, abnormalities in the right frontal cortex were described during secondary [23,49] and primary mania [2] and recently were observed changes in glucose metabolism in the frontal cortex during a switch to mania after subthalamic deep brain stimulation [61].

We are aware of the difficulty generalizing from a case report and the necessity to confirm our findings in large controlled study. Nevertheless, the data from our case report should indicate more extensive research for this new application of QEEG as cordance or LORETA in patients with bipolar disorder. Our data suggest that the new application of QEEG can be sensitive to mood changes and have potential in the research of bipolar disorder. The advantage of QEEG, being that it uses a

conventional EEG recorder and so has a larger potential for application in clinical practice than functional MRI, PET or SPECT.

Anticholinergic mechanisms could play a role in some patients with TCA-induced switches and this information could be used to find a more homogenous population for genetic studies in patients with BD. In our case, we did not see a prophylactic effect of lithium on the switch, which is in agreement with other studies that did not find a prophylactic effect of lithium in TCA-induced switches and for that lithium is less effective in the case of the rapid cycling that can also be induced by TCA.

CONCLUSION

This case report is interesting from four points of view: i) It presents repeated switches to mania/hypomania after clomipramine therapy in which antimuscarinic activity could play a role, ii) it shows that theta prefrontal cordance can precede changes in mood not only in unipolar depression but in bipolar depression too iii) it shows that changes detected by LORETA in the parietal cortex seems to reflect antimuscarinic activity and iv) it allows speculation that changes in activity in the right frontal cortex indicate an area responsible for switches to hypomania/mania.

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QEEG changes during switch from depression to hypomania/mania

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