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EEG source analysis in patients receiving 5-Hz transcranial magnetic stimulation as antidepressant treatment

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Original article

SUMMARY

Transcranial Magnetic Stimulation (rTMS) is a technique that allows noninvasive electrical stimulation of the cortex with few side effects. An antidepressant effect has been proposed when rTMS is delivered over prefrontal dorsolateral cortex (DLPFC) ≥5Hz. Quantitative EEG studies have shown increases in alpha and theta power bands as well as frontal interhemispheric asymmetries in most recordings from depressed patients. rTMS over left DLPFC at 5Hz involve a safer and more tolerable procedure, and its neurophysiological correlates has not been explored using EEG source analysis. The aim of this research was to study changes in EEG sources using VARTERA method in a group of patients with major depressive disorder (MDD) treated with 5Hz rTMS over left DLPFC as single or combined treatment with escitalopram.

Methods

18 patients with DSM-IV MDD diagnosis without treatment for the current episode were included. Subjects were randomly assigned to one of two groups: A) rTMS+escitalopram 10mg, n=9; B) rTMS+placebo, n=9. Subjects received 15 sessions of rTMS on a daily basis. In order to compare changes in EEG sources two recordings were obtained, prior and after treatment. HDRS, BDI and HARD were used for clinical assessments.

Results

All patients of group A and eight patients of group B showed response to treatment (considered as a reduction of 50% in HDRS score). An increase in absolute power at 9.37Hz and 10.17Hz in temporal and postcentral gyrus on the left hemisphere was found in group B. Absolute power in those frequencies was decreased in the same regions for group A. In addition, an increased power in beta band frequencies was observed in both hemispheres for group A.

Conclusion

Increases in alpha band could be the hallmark of the 5Hz rTMS, but it could be reduced by escitalopram. Besides, increases observed in beta band for group A could be related to escitalopram effect.

Key words: EEG, source analysis, major depressive disorder, rTMS.

RESUMEN

La estimulación magnética transcraneal repetitiva (EMTr) es una técnica que permite estimular eléctricamente la corteza cerebral de manera no invasiva y con pocos efectos secundarios. Se ha propuesto que la EMTr aplicada sobre la corteza prefrontal dorsolateral (CPFDL) izquierda con frecuencias ≥5Hz tiene efectos antidepresivos. Se ha encontrado que en el electroencefalograma cuantitativo (QEEG por sus siglas en inglés) la mayoría de pacientes deprimidos presentan incrementos en las bandas theta y alfa, así como asimetrías interhemisféricas en la actividad alfa en regiones anteriores. La EMTr sobre la CPFDL izquierda a 5Hz ofrece ventajas considerables en seguridad y tolerabilidad; sin embargo, sus correlatos neurofisiológicos no han sido explorados por el análisis de fuentes del EEG.

Objetivo

Estudiar los cambios en las fuentes del EEG según el método VARETA en un grupo de pacientes con trastorno depresivo mayor que recibieron EMTr a 5Hz sobre la corteza prefrontal dorsolateral izquierda como tratamiento único o en combinación con escitalopram.

Material y métodos

Se estudiaron 18 pacientes con diagnóstico de trastorno depresivo mayor de acuerdo con los criterios del DSM-IV sin tratamiento para el episodio en curso. Los sujetos habían sido aleatoriamente asignados a uno de los siguientes grupos de tratamiento: A) EMTr+escitalopram 10mg, n=9; B) EMTr+placebo, n=9. Se aplicó EMTr, a 5Hz en una sesión diaria durante 15 días. Se obtuvieron dos registros electroencefalográficos, uno basal y otro final, con el fin de comparar los cambios en las fuentes de actividad eléctrica cerebral, pretratamiento y post-tratamiento. Se realizaron evaluaciones clinimétricas con las escalas de Hamilton para Depresión y Ansiedad y el Inventario de Depresión de Beck.

Resultados

Todos los pacientes en el grupo A y ocho pacientes en el grupo B respondieron al tratamiento, con una reducción de 50% o más en la escala HDRS. En el análisis de fuentes se encontró un efecto en el grupo B caracterizado por incremento en la PA de 9.37 a 10.17Hz, en regiones temporales y giro poscentral izquierdos, mismo que se encontró disminuido en el grupo A, Además se encontró un incremento en fracuencias correspondientes a la banda beta en regiones frontales de ambos hemisferios en el grupo A.

Conclusiones

Podría considerarse que el incremento en la banda alfa es característico de la EMTr a 5Hz, mismo que se ve reducido por efecto del escitalopram. Por otro lado, se observó que el grupo A mostró incrementos en fuentes correspondientes a la banda beta como posible efecto relacionado del fármaco antidepresivo.

Palabras clave: EEG, análisis de fuentes, trastorno depresivo mayor, EMTr.

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INTRODUCTION

During the last decade, the research on the repetitive transcranial magnetic stimulation (rTMS) as a therapeutic intervention for the major depressive disorder (MDD) has shown sufficient evidence to consider it as a safe and efficient procedure.[1–3] Most of the recent researches have established administration forms and parameters of the rTMS under which the anti-depressive response is clearly higher than placebo.[3–5] The optimum stimulation parameters are still being one of the objectives of clinical research; among which the intensity and location of the stimulation place, the number of sessions and the stimulation frequency have been the most important aspects to be determined.[6] Most of the clinical trials have established that the application of frequencies above 1Hz on the left dorsolateral prefrontal cortex (DLPFC) has antidepressive effects.[7,8] Among the published studies, maybe the most commonly used frequency has been 10Hz. However, lower frequencies have proved anti-depressive effectiveness with the advantage that they generate less discomfort during application, offering a reduced risk of a seizure crisis induction pursuant to the published safety parameters.[9] The application of rTMS at 5Hz on this region has been described in numerous clinical trials with similar effects at other parameters.[10,11]

The quantitative electroencephalogram (QEEG) is a method to measure the spontaneous electrical activity of the brain at rest.[12] In addition, it has been proposed as a way to assess the electroencephalographic profiles from different psychiatric disorders,[13] as well as for the early identification of the response to the anti-depressive pharmacotherapy.[14,15] Various studies have described the distribution of the classical bands of the EEG spectral analysis. Likewise, various initial studies have mentioned that a high percentage of depressed patients shows a power increase in alpha and theta bands[16–18] (Monakhov and Perris, 1980; Nieber and Schlegel, 1992; Nyström, Matousek and Hällström, 1986).

A recent development in the QEEG analysis is the application of a mathematical algorithm allowing the estimate of the EEG generators registered from the scalp. This method has been called Variable resolution electromagnetic tomography (VARETA).[19] Ricardo-Garcell *et al*. (2009) studied, through VARETA, to 36 patients with MDD (27 women). All patients had unusual cerebral electrical activity sources (significant increase in the current density. The majority (35 out of 36) was located in both hemispheres but with the maximum inverse solution predominated in the right hemisphere (24 *vs*. 12). In 29 patients the topography of the sources corresponded to the frontal lobes, many located in the dorsolateral prefrontal cortex and in the frontal cingulate cortex. Increases in current density prevailed in alpha and theta bands, which matches with the results observed in the MEBAs[20] and in some studies with LORETA in depressed patients.[21] The purpose of this research was studying the changes in the EEG sources through the VARETA method in a group of patients with major depressive disorder treated with 5Hz rTMS over the left DLPFC as single or combined treatment with escitalopram, a selective inhibitor of serotonin capture.

MATERIALS AND METHODS

Participants

The patients were taken from a previous double blind clinical trial. Before their participation all subjects were informed about the protocol and gave their informed consent in writing. Such protocol was assessed and approved by the Institutional Research Ethics Committee. In order to confirm the diagnosis of patients the SCID-I[22] interview was used and for the clinical assessments the following scales were applied: The Hamilton Depression Rating Scale (HDRS),[23] the Hamilton Anxiety Rating Scale (HARS)[24] and the Beck Depression Inventory (BDI).[25] A translated version of the Security Questionnaire for Transcranial Magnetic Stimulation was applied to each subject.[26] 18 patients participated with a major depressive disorder (MDD) diagnosis with a level of severity assessed through the Hamilton Depression Rating Scale of 20 points or more, 25-55 years of age, with no main diagnosis of severe personality disorder on axis II, with no antidepressive pharmacological treatment during the episode that gave rise to the medical consultation in which they accepted to participate and to sign the informed consent form. Exclusion criteria: Patients with a history of seizure crisis or epilepsy, with pacemaker, metallic or magnetic or intracranial objects (splinters, plates, vascular clippings), carriers of chronic-degenerative conditions (for example, collagenopathies, nephropathies, serious metabolic disorders) or of any organic brain disease affecting the psychiatric illness, with any neurological or psychiatric pharmacological treatment, history or diagnosis of dependence or substance abuse.

Safety Measures: After dismissing the existence of any of the aforementioned risks, special emphasis was given to those questions related to the patients' safety in order to avoid overlooking any risk, mainly risks associated with the rTMS.[26]

Likewise, a comprehensive review of the baseline EEG was performed in order to detect any cortical hyperexcitability condition and thus minimize the convulsive risk when applying this treatment.

Pharmacological treatment: 10mg of escitalopram were administered on a daily basis, as a fixed dose, from the first day of treatment with rTMS. No other medications were jointly used in this study. The escitalopram was presented in a capsule in exactly the same manner as the placebo. During working days the medicine was administered in the Research Unit of the National Institute of Psychiatry "Ramón de la Fuente" (INPRF) a few minutes before the rTMS session. On non-working days, the corresponding doses were

given to each patient. The placebo was prepared in capsules having the same color of the medicine, but filled with sugar.

Repetitive Transcranial Magnetic Stimulation

The rTMS sessions were conducted at a specially designed area for this procedure. A Dantec Magpro Rapid stimulator was used, which has a figure-of-eight coil, MC-B70, 3.7-inch (95mm) external diameter. The coil is articulated with a steel arm mounted on the wall that allows its mobility in three planes and facilitates its placing and installation on a particular point over the head of patients while the treatment is applied. A comfortable office chair was used, so that patients could remain seated during session. The stimulation was applied according to the following parameters: 100% intensity of the motor threshold; left dorsolateral prefrontal cortex location in accordance with the 2-in (5cm) method at the front part of the maximum motor response in the short abductor of the contralateral thumb.[27] 30 trains of 10 seconds each were applied with intertrain intervals of 10 seconds. The recommended safety parameters were at all moments followed in previous studies,[9,28,29] both for estimating the stimulation intensity and for avoiding risks.

EEG Acquisition and Analysis

The digital capture of the EEG was made on a computer loaded with Windows 98 operative system and with an analogous-digital interface card for the Medicid IV digital electroencephalograph. A photostimulator was used to discard the photosensitive epileptiform activity. For the acquisition and obtaining of the EEG spectral measurements analysis, the following Neuronic S.A. software was used: Trackwalker 2.0 for recording, Neuronic EEG Cuantitativo Tomográfico 6.0 for the spectral measurements obtaining, Neuronic Visualizador Tomográfico 2.0 for visualizing the cerebral electrical activity sources. The EEG recording was conducted in the Psychophysiology Laboratory of the INPRF, which has a partially muffled room, with controlled lighting and electrically isolated. During the record obtaining a grounded stretcher couch was used for patients. 19 surface electrodes stick to a stretchy cap and distributed according to the 10-20 International System and four individual gold electrodes; two for the reference electrodes and two for the measuring of the eye movements. Conductive paste was used for the four individual electrodes and conducting gel for the 19 electrodes stick to the cap.

Spectral Analysis of the EEG Sources

VARETA was used in the frequency domain to calculate the sources distributed for each frequency. This method offers a discreet solution that has different amounts of spatial softener for the different types of generators. It also restricts the current sources to the grey matter through the imposition of a probabilistic mask that eliminates those sources where the mask solution equals zero, as happens in the cerebrospinal fluid or in the white matter.[19]

Statistical Analysis

The Neuronic Estadística software was used to conduct the Student's t-test for the comparisons of the different intra-group (t-test for dependent samples) and inter-group (t-test for independent samples) variables (clinical and electroencephalographic).

RESULTS

Final sample for this study: 18 patients, assigned to two groups: A (rTMS+escitalopram) n=9 and B (rTMS+placebo) n=9, number of previous episodes 2,3 (SD=1.6) and 3,1 (SD=1.7), age of onset 29.44 (SD=7.5) and 34.44 (SD=7.5), HDRS at the onset 27.11 (SD=3) and 28.44 (SD=5.3), BDI 24.6 (SD=5.2) and 28.44 (SD=7.2), HARS 25.11(SD=3) and 26.44 (SD=5.3) for groups A and B, respectively. There were no significant differences for the baseline variables, except for the age for group A of 36 (SD=8.7) and for group B of 48.3 (SD=7.4) ($T=-3.14$, 16 gl, $p<0.005$). The reduction in the HDRS scale was for group A of -18.78 (SD=3.60) (69.2%) and for B of -17.67 (SD=5.9) (62.1%); there were no significant differences among groups. All patients of group A covered the answer criterion for the treatment defined as a reduction of 50% or more in the HDRS scale score with regard to the baseline, while in group B eight out of nine patients did it. The remission criterion —defined as a punctuation ≤7 in the HDRS— in the third week was fulfilled by four patients of group A and four patients of group B. There were no significant differences between both groups in none of the clinical response criteria.

The baseline EEG recording for both groups was compared through a narrow band analysis (each 0.39Hz, from 0.78 through 19.14), in order to assess whether statistically significant differences existed before starting any treatment. Significant differences were detected between both groups at particular frequencies of each of the four EEG classical bands (delta, theta, alpha and beta) (Table 1). However, there was a set of frequencies in each of such bands, generally in consecutive frequencies where no significant differences were found; so that the activity of these frequencies can be regarded as common for both groups. Said frequencies ranged from 0.78Hz to 1.56Hz, 3.52Hz to 4.3Hz, 5.86 to 10.16, 13.6Hz to 10Hz, 14.86Hz to 16Hz and 18.8Hz to 19.14Hz. Therefore, the interpretation of the changes that occurred before and after the two treatment methods used was precisely focused on these frequencies in which the groups did not differ at the beginning (Table 2).

The group A (rTMS+escitalopram) showed decreases in frequencies 3.52, 7.42 in posterior regions and 10.16 in tem-

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Table 1. Frequencies that showed significant differences in the baseline EEG recording between both treatment groups

A Less than B Pre				B Less than A Pre			
	Laterality	Region	T		Laterality	Region	T
1.95				**1.95**	Right (bilat)	Middle frontal gyrus	
2.34	Left	Superior occipital gyrus	2.60	**2.34**			
2.73	Bilateral	Superior occipital gyrus	2.50	**2.73**			
3.12	Bilateral	Superior occipital gyrus	2.70	**3.12**			
4.69	Left (bilat)	Superior frontal gyrus	2.27	**4.69**			
5.08	Left (bilat)	Superior frontal gyrus	2.86	**5.08**			
5.47	Left (bilat)	Superior frontal gyrus	2.27	**5.47**			
10.55				**10.55**	Left	Superior frontal gyrus	-2.25
10.94				**10.94**	Left	Superior frontal gyrus	-2.70
11.33				**11.33**	Left	Superior frontal gyrus	-3.60
11.72				**11.72**	Left	Superior frontal gyrus	-2.50
12.11	Left	Cuneo	2.10	**12.11**	Right	Inferior frontal gyrus	-2.90
12.50				**12.50**	Right	Precentral gyrus	-2.80
12.89				**12.89**	Right	Precentral gyrus	-2.50
13.28				**13.28**	Right	Inferior frontal gyrus	-2.90
14.45				**14.47**	Left	Superior frontal gyrus	-2.38
16.42	Left	Left occipital gyrus	3.40	**16.41**			

$p < 0.025$.

poral medial gyrus, and increases in frequencies 6.64, 7.42, 7.81, within theta range, and 8.2, 8.59 within alpha range in frontal regions in both cases. Also, there were increases in consecutive frequencies going from 14.08 up to 16.8 within the beta frequency, even in frontal regions.

Group B (rTMS+placebo) showed decreases in frequencies 3.5, 3.91 at delta band, as well as in 4.30 and 6.64 in theta; both cases in posterior regions. However, there were increases in frequencies 9.3, 9.77 and 10.16 within the alpha range in regions close to the motor cortex and in the temporal lobe respectively (Table 2).

DISCUSSION

By analyzing significant changes occurred in group B (rTMS+placebo), the effect that may be considered more related to the rTMS was an increase of the activity from 9.37Hz

Table 2. Frequencies that having been homogeneous at the beginning of the study in both groups, showed differences in the pretreatment-postreatment comparison

Decrease				Increase			
Hz	Laterality	Region	T	Hz	Laterality	Region	T
Group A, rTMS + escitalopram							
3.52	Right (bilat)	Occipital pole	-3.13	**3.52**			
6.64				**6.64**	Right	Superior frontal gyrus	2.30
7.42	Right	Middle occipital gyrus	-2.50	**7.42**	Right	Superior frontal gyrus	2.24
7.81				**7.81**	Right	Middle frontal gyrus	2.80
8.20				**8.20**	Left	Inferior frontal gyrus	3.56
8.59				**8.59**	Left	Superior frontal gyrus	2.34
10.16	Left	Middle temporal gyrus	-2.30	**10.16**			
14.06				**14.08**	Left (bilat)	Middle frontal gyrus	5.80
15.23				**15.25**	Left	Superior frontal gyrus	2.80
15.62				**15.62**	Right	Middle frontal gyrus	3.40
16.02				**16.02**	Right	Lateral orbitofrontal	4.50
16.80				**16.80**	Right	Middle frontal gyrus	2.29
Group B, rTMS + placebo							
3.52	Left	Occipital pole	-2.45	**3.52**			
3.91	Left	Occipital pole	-2.30	**3.91**			
4.30	Right	Middle temporal gyrus	-2.44	**4.30**			
6.64	Left	Postcentral gyrus	-2.85	**6.64**			
9.37				**9.37**	Right (bilat)	Postcentral gyrus	3.50
9.77				**9.77**	Left	Precentral gyrus	3.07
10.16				**10.16**	Left	Superior temporal gyrus	2.50

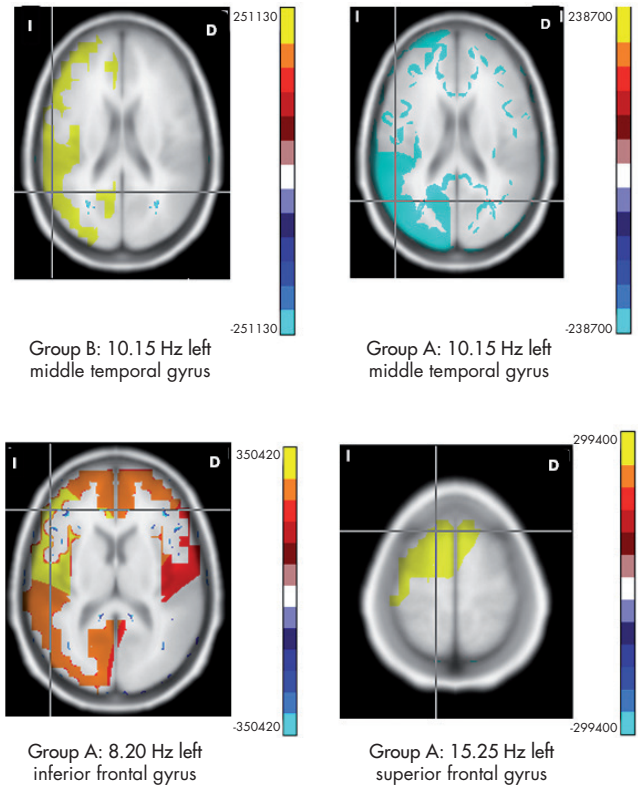

Figure 1. Representative images of the changes observed in the EEG pre-post treatment sources. a) An increase in the inverse solution in 10.15 Hz, corresponding to the alpha band range, can be observed in the group of patients who received only rTMS as active maneuver, while in b) a decrease may be observed in same regions. Increases in group A, c) in 8.20 in the alpha band range and d) increases in 15.25 Hz in the beta band.

to 10.16Hz; that is, an increase of absolute power in three frequencies neighboring the left hemisphere, which reduces the possibility of a spurious finding. Such increase of the activity in these frequencies of the alpha band was observed especially in regions neighboring the primary motor cortex ipsilateral to the stimulated hemisphere. This is interesting because in all patients the motor threshold was estimated on a daily basis with simple pulses on the primary motor cortex. This could lead to an effect on the neighboring regions, especially those found in frequencies 9.37Hz to 10.16Hz. Other authors have described similar acute changes in the alpha band, when applying rTMS on the motor cortex.[30,31]

In group A —where the effect of the rTMS and of the escitalopram combined— there were significant increases in beta band from 14.08Hz to 16.8Hz, in consecutive frequencies, in frontal regions of both hemispheres. This result could correspond to the effect induced by the escitalopram, since it has been similarly described for the effect of the racemic molecule, the citalopram, with increases in absolute power of the beta band and reductions of the alpha in frontal regions.[21]

The decrease of the alpha activity (10.16Hz) found in the left temporal medial gyrus could also be an effect attributable to the combination of escitalopram and rTMS, since the only application of the rTMS showed an increase in absolute power in this frequency (Figure 1). Considering the fact that the EEG recordings were performed immediately after finishing the treatment sessions, at this moment it is not possible to confirm whether at this moment the increase of absolute power in the beta band observed in group B after the rTMS was a temporal effect of the rTMS that subsequently was reduced due to the action of the selective inhibitor drug of serotonin recapture; therefore, if EEG recordings were performed longer after treatment has finished, the other excess of alpha activity that appeared in group A might disappear.

The existence of frequencies that were not modified with none of the two treatments called attention, particularly those corresponding to the low range of the delta band and the high range of the beta band (Table 2). The foregoing suggests that there are frequencies in the EEG that might be considered as feature variables while others could be status variables, that is, those that were modified under the treatments effects. Notwithstanding, this interpretation must be viewed with caution due to the small size of the sample used in this research.

CONCLUSIONS

The 5-Hz rTMS applied in isolation on depressed patients increases cerebral electrical activity in some frequencies at the low range of the alpha band in the stimulated hemisphere. The combined effect of the 5-Hz rTMS and escitalopram maintains the increase of the alpha activity in the low range in the left hemisphere, but probably it is a transitory effect of the rTMS, since a reduction of the activity was observed in one of the frequencies increased with the single rTMS.

The combined effect of the rTMS with the escitalopram produces an increase in the frontal regions in the beta band that seems to be related to the specific effect of the escitalopram.

The following limitations have to be stressed in this study: 1. the groups showed significant heterogeneity at the beginning of treatment, which made necessary to assess those frequencies with similar groups; 2. the size of the sample was small, thus a larger sample might have showed greater consistency as for the observed changes.

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