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BRIEF REPORT

Low-resolution electromagnetic tomography and treatment response in obsessive–compulsive disorder

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Abstract

We investigated whether findings from pretreatment low-resolution electromagnetic tomography (LORETA) predicted response to drug treatment in patients with obsessive–compulsive disorder (OCD). The 3D intra-cerebral distribution of neuronal electrical activity from the scalp-recorded potential distribution of 17 drug-free patients with OCD was assessed with LORETA. They were treated with antidepressants in the maximum tolerated doses for at least 12 wk. Individuals were considered to be treatment responders if they displayed a reduction of at least 35% on the initial YBOCS scores and had a final CGI score of 1 or 2. The SPM-99 *t* test for independent samples was employed to compare, voxel-by-voxel, the brain electrical activities of responders ($n=10$) and non-responders ($n=7$). Responders exhibited significantly lower activities in beta band in the rostral anterior cingulate [Brodmann's area (BA) 24 and 32] ($p=0.002$) and the medial frontal gyrus (BA 10) ($p=0.002$), suggesting that a distinctive pattern of activity within the medial surface of the frontal lobe predicts therapeutic response in OCD.

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Key words: antidepressants, LORETA, obsessive–compulsive disorder, topographic brain mapping, treatment outcome.

Introduction

Despite the proven effectiveness of serotonin reuptake inhibitors (SRIs) in the treatment of obsessive–compulsive disorder (OCD), as many as 40–60% of patients do not respond to adequate trials with these drugs (Hollander et al., 2003). Identification of reliable predictors of responsiveness to pharmacological treatment may save patients lengthy trials with drugs that are unlikely to be effective and steer treatment towards modalities that have higher probabilities of succeeding (Saxena et al., 2003). Markers of treatment responsiveness might also provide further clues on the pathophysiology of OCD (Saxena et al., 2003).

Several neuroimaging techniques have been employed to investigate neurobiological predictors of response to medications in OCD. Studies with positron emission tomography (PET) suggest that lower activity within the right and/or the left orbitofrontal cortices (Rauch et al., 2002; Saxena et al., 1999) and higher activity in the posterior cingulate cortex (Rauch et al., 2002) and the right caudate nucleus (Saxena et al., 2003) predict a better therapeutic response to SRIs in patients with OCD. In contrast, Swedo et al. (1989) found that decreased metabolism in the anterior cingulate cortex was associated with a better short-term therapeutic response among adult patients with childhood-onset OCD.

Neuroscientific research using functional brain-imaging techniques characterized by high spatial and low temporal resolution, such as PET, may be complemented by eletroencephalography (EEG)-based methods, with their low spatial and high temporal resolution. Low-resolution electromagnetic tomography (LORETA) is a functional tomography that computes the 3D distribution of electrical neuronal activity from EEG and/or magnetoencephalography (MEG)

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measurements (Pascual-Marqui et al., 2002). Although extracranial electric and magnetic information are not considered enough to provide a unique determination of the sources of neuronal activity, they are sufficient for a low spatial resolution estimate (Pascual-Marqui et al., 2002).

LORETA is a useful, versatile, and cost-effective alternative to more complex and costly research tools. Our goal in this study was to investigate whether pre-treatment LORETA patterns of findings could be used to predict a positive response to pharmacological treatment in OCD. We hypothesize, based on the findings of the PET studies reported above, that distinctive patterns of electrical activity within the structures connected by the cortico-striato-thalamo-cortical circuitry – in particular, those involving the more superficially located ones, such as the frontal and the cingulate cortex – would be associated with different treatment outcomes.

Methods

Patients

Individuals with OCD were consecutively recruited among those seeking treatment in the Anxiety and Depression Research Programme of the Federal University of Rio de Janeiro. The inclusion criteria comprised: (1) age between 17 and 65 yr, (2) having OCD as the most significant current psychiatric diagnosis, and (3) being capable of reading and filling out forms. Exclusion criteria included: (1) the use of any drug that significantly affects the central nervous system in the 2 wk preceding the initial interview (5 wk in the case of fluoxetine), (2) significant medical, endocrine and neurological disorders (with the exception of tics), (3) current alcohol and drug abuse, (4) psychosis, and (5) severe personality disorder. Seventeen patients were selected and had their diagnosis confirmed by an experienced psychiatrist (L.F.F.) using the Structured Clinical Interview for DSM-IV (First et al., 1997). The volunteers were also assessed with the following instruments: the Clinical Global Impression (CGI; Guy, 1976), the Yale–Brown Obsessive–Compulsive Scale (YBOCS; Goodman et al., 1989), the Hamilton Depression Rating Scale-21 ($HAMD_{21}$; Hamilton, 1967), the Beck Depression Inventory (BDI; Beck, 1978) and the Global Assessment of Functioning (GAF) scale (APA, 1994). All the procedures involved in this work were in accord with the ethical standards of the Institutional Review Board (IRB) of the Institute of Psychiatry of the Federal University of Rio de Janeiro.

Functional images of neuronal electrical activity

A detailed account of our methods for acquisition and processing of EEG data can be found in Veiga et al. (2003). The 3D intra-cerebral distribution of neuronal electrical activity (current density) from the scalp-recorded potential distribution was assessed with LORETA (Pascual-Marqui et al., 2002). LORETA computes current density at each voxel in the brain as the linear, weighted sum of the scalp electric potentials (Pascual-Marqui et al., 2002). The 3D solution space was restricted to the cortical grey matter and hippocampus in the Talairach Atlas (available from the Brain Imaging Center, Montreal Neurological Institute, Canada).

A voxel was labelled as grey matter if its probability of being grey matter was: (1) higher than that of being white matter, (2) higher than that of being cerebrospinal fluid, and (3) greater than 33% (Pascual-Marqui et al., 2002). Only those grey-matter voxels that belonged to cortical and hippocampal regions according to the Talairach Atlas were used for the analysis. A total of 2394 voxels at 7 mm spatial resolution were produced under these neuroanatomical constraints. LORETA represents the electrical activity at each voxel as squared magnitude (power) of the computed current density.

The scalp-recorded potential distribution for each subject and for each classical frequency band (delta, theta, alpha and beta) was transformed into LORETA functional images. Next, each LORETA functional image was transformed to SPM-99 format (Statistical Parametric Mapping; Friston et al., 1996), and subsequently normalized with a spatial resolution of 1 mm for statistical analysis.

Pharmacological treatment

Patients were openly treated with several different drugs employed in maximum tolerated doses, including SRIs (clomipramine, fluoxetine, sertraline, and paroxetine), non-SRI tricyclic antidepressants (imipramine and nortriptyline) and other medications (venlafaxine and mirtazapine). The choice of a particular drug took into account the patient's current clinical profile, response to previous therapies (if there was any) and financial situation. Off-label medications (i.e. drugs that, although not currently recommended for the treatment of OCD, have their use supported by anecdotal reports) were prescribed in two clinical scenarios: (1) as therapeutic alternatives [venlafaxine (Hollander et al., 2003) or mirtazapine (Koran et al., 2001)] in patients with a past history of resistance to treatment with conventional drugs and (2) as

low-cost alternatives [imipramine and nortriptyline (Mavissakalian, 2000)] in cases in which severe personal financial restraints precluded patients from buying more expensive medications.

Patients who did not meet response criteria during the first drug trial [a reduction of at least 35 % in the initial total scores on YBOCS and a CGI of 1 (much better) or 2 (better) at the end of week 12] or turned out to be drug intolerant underwent a flexible treatment pathway that involved sequential administration of up to four different drugs employed in maximum tolerated doses. Patients were followed for up to 3 yr. At each visit, the volunteers were re-evaluated using the YBOCS, CGI, $HAMD_{21}$, BDI and GAF.

Statistical analysis

The Mann–Whitney test was employed to analyse continuous data and Pearson's goodness-of-fit χ^2 test was used to analyse categorical data; Fisher's exact test was employed when indicated.

The SPM-99 *t* test for two independent samples was used to analyse the differences in the brain electrical activity between groups (OCD non-responders vs. responders) voxel-by-voxel. The final result was a statistical map with the *t* test value for each voxel and its location in the brain, using the Talairach Atlas coordinates.

Results

The socio-demographic and clinical characteristics of the sample are shown in Table 1. Six patients had current major depressive disorder (MDD) (35.3%), four patients tic disorders (23.5%), three patients social anxiety disorder (17.6%), two patients dysthymic disorder (11.8%), two patients specific phobia (11.8%), and two patients panic disorder and agoraphobia (11.8%).

During the follow-up [mean duration 46.38 (±42.3) wk], the patients were treated with up to four different drugs employed in a sequential manner, as detailed above (mean of 1.82 different drugs per patient). Eight patients were treated with clomipramine [mean dose 131.2 (±78.7) mg], six with sertraline [mean dose 175.0 (±27.4) mg], five with fluoxetine [mean dose 72.0 (±17.9) mg], three with paroxetine [mean dose 46.6 (±23.1) mg], four with imipramine [mean dose 168.7 (±62.5) mg], two with nortriptyline [mean dose 55.0 (±63.6) mg], two with venlafaxine [mean dose 262.5 (±53.0) mg] and one with mirtazapine (dose of 15.0 mg).

Ten patients (58.8% of the sample) met the criteria for treatment response at the time the last observation was made. Responders and non-responders did not differ in most socio-demographic and clinical characteristics, such as age ($Z=-1.27$, $p=0.23$), age at OCD onset ($Z=-0.83$, $p=0.41$), duration of illness ($Z=-0.19$, $p=0.88$), number of significant obsessions ($Z=-1.43$, $p=0.19$) and compulsions ($Z=-0.66$, $p=0.53$), YBOCS ($Z=-0.58$, $p=0.60$), CGI ($Z=-0.61$, $p=0.60$), $HAMD_{21}$ ($Z=-0.40$, $p=0.74$), BDI ($Z=-0.60$, $p=0.60$), and GAF scores ($Z=-0.55$, $p=0.60$), and the prevalence of associated psychiatric disorders [including MDD ($\chi^2=1.63$, d.f. = 1, $p=0.33$)]. A significantly higher proportion of female patients was found among the responders ($\chi^2=6.80$, d.f. = 1, $p=0.009$).

The therapeutic approach [encompassing duration of the follow-up period ($Z=-0.05$, $p=1.00$), number of therapeutic trials ($Z=-1.20$, $p=0.27$) and use of off-label drugs ($\chi^2=0.001$, d.f. = 1, $p=0.64$)] was found not to be significantly different between the groups. The improvement in obsessive–compulsive symptoms

Table 1. Selected socio-demographic and clinical characteristics of the OCD sample

Age (yr)	33.29 (11.09)
Number of females	11 (64.7%)
Age of OCD onset (yr)	19.35 (10.14)
Duration of illness (yr)	14.06 (10.54)
Number of obsessions	2.35 (1.17)
Number of compulsions	2.35 (1.32)
YBOCS	23.64 (6.36)
CGI	5.05 (1.08)
BDI	17.35 (6.91)
HAMD	21.58 (7.03)
GAF	48.41 (5.93)

	Responders	Non-responders	Z score	*p* value
Initial scores				
YBOCS	22.70 (7.79)	25.00 (3.65)	−0.11	n.s.
CGI	4.90 (1.10)	5.28 (1.11)	−0.68	n.s.
BDI	22.00 (8.45)	20.42 (4.54)	−0.63	n.s.
HAMD	17.70 (6.73)	16.85 (7.66)	−0.36	n.s.
GAF	46.70 (6.18)	50.85 (4.98)	−0.66	n.s.
Final scores				
YBOCS	6.70 (5.96)	21.14 (4.91)	−0.301	0.003
CGI	2.08 (0.83)	4.42 (1.27)	−3.18	0.001
BDI	8.50 (6.86)	12.57 (0.78)	−0.79	n.s.
HAMD	6.90 (4.30)	8.00 (1.73)	−0.37	n.s.
GAF	73.67 (10.40)	63.18 (8.19)	−1.51	n.s.

OCD, Obsessive–compulsive disorder; YBOCS, Yale–Brown Obsessive–Compulsive Scale; CGI, Clinical Global Impression; BDI, Beck Depression Inventory; HAMD, Hamilton Depression Rating Scale; GAF, Global Assessment of Functioning.

Table 2. Single cluster summary (p value corrected for entire volume)

Voxel-level					
p corrected	t	Z	p uncorrected	x, y, z (mm)	Region
0.024	4.34	3.44	0.000	6, 46, 9	Rostral anterior cingulate
0.026	4.30	3.42	0.000	5, 52, 9	Right medial frontal gyrus

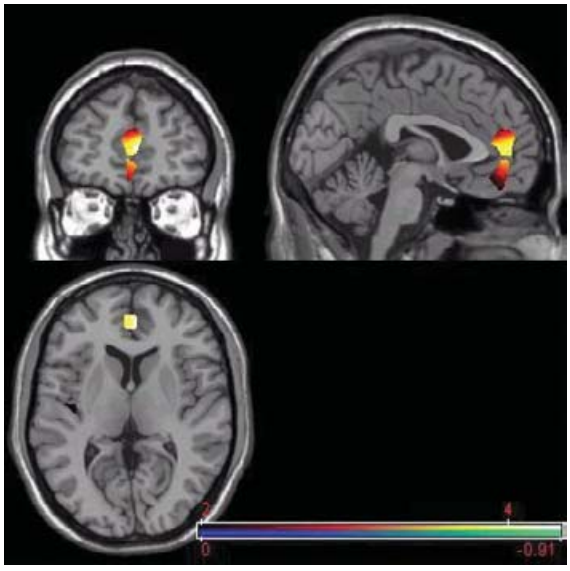

Figure 1. SPM t statistics images of brain regional electric activity for beta band (coronal, sagittal, and axial slices): OCD responders vs. non-responders (the coloured scale represents t values).

[the ΔYBOCS (calculated as the difference between YBOCS scores before and after treatment, considering the last observation made)] did not correlate with the improvement in depressive symptoms [according to the ΔHAMD ($\rho = 0.31$, $p = 0.10$) and the ΔBDI ($\rho = 0.27$, $p = 0.16$)].

The inter-group comparisons of LORETA findings showed that responders were characterized by significantly lower activities in the beta band in the rostral anterior cingulate (RAC) [Brodmann's area (BA) 24, 32, and 35] ($p = 0.02$) and the medial frontal gyrus (BA 10) ($p = 0.02$) (Table 2, Figure 1).

Discussion

To the best of our knowledge, our study was the first to employ LORETA as a tool for predicting therapeutic response to long-term pharmacological treatment in patients with OCD. We found that lower pretreatment activity in the beta band within the RAC (BA 24, 32 and 25) and the medial frontal gyrus (BA 10) was associated with a better therapeutic response.

The RAC, the affective/visceral functional subdivision of the cingulate cortex regulates the activity of the autonomic and endocrine systems and is involved in the modulation of high-order functions, such as conditioned emotional learning, assessment of motivational content and the assignment of emotional valence to external and internal stimuli (Yücel et al., 2003).

There is substantial evidence that the level of metabolic activity within RAC may predict therapeutic response in mood disorders. For instance, studies employing PET (Mayberg et al., 1997) and LORETA (Pizzagalli et al., 2001) showed that hypermetabolism and increased theta activity (a surrogate for increased activity) in the RAC correlated with a better therapeutic response in adult patients suffering from MDD.

In individuals with OCD, the RAC and/or the nearby structures were found to be hyperactive at rest (Swedo et al., 1989), during symptoms provocation (Breiter et al., 1996), and after commission of errors in cognitive tasks (Ursu et al., 2003). However, several PET studies reported that short-term clinical response in OCD correlated with the levels of glucose consumption in the orbito-frontal cortex, right caudate nucleus, and the posterior cingulate, but not in the RAC (Rauch et al., 2002; Saxena et al., 1999, 2003). Only Swedo et al. (1989) found that decreased metabolism in the latter region was associated with a better therapeutic response among adult patients with childhood-onset OCD.

Decreased beta activity in fronto-temporal regions of patients with OCD was reported in a number of studies (Karadag et al., 2003; Tot et al., 2002). Recently, Tot et al. (2002) found that treatment responders with OCD exhibited decreased left frontal beta activity during hyperventilation. The implications of these findings are not clear, since there is controversy on the significance of the neurophysiological role of beta activity: while some authors consider it a correlate of decreased activity, others associate it with increased metabolism (Gamma et al., 2004). Nevertheless, considering Swedo and co-workers' (1989) findings reported above, we hypothesize that the decreased beta activity we have found may reflect decreased metabolism in the RAC.

It is important to analyse why our results were different from those of some previous studies, in particular from the one in which Saxena et al. (2003)

observed that the metabolic predictors of response to paroxetine were significantly different in patients with MDD and with OCD. Using PET, these authors found that the improvement of symptoms in patients with MDD correlated with higher metabolic levels in the medial frontal cortex and in the RAC and with lower metabolic levels in the amygdala and in the thalamus. In contrast, the symptomatic improvement in patients with OCD was associated exclusively with higher metabolic activity in the right caudate nucleus. One important difference between this study and ours lies in fact that our patients were followed for longer periods. Admittedly, the neuroanatomical substrates involved in short- and long-term treatment response in OCD may differ. Since neuropharmacological treatment response involves relatively slow neuronal adaptative changes, it is possible that antidepressant drugs may exert their anti-obsessional effects by acting earlier in the basal ganglia and only later in the anterior cerebral regions (Baxter, quoted by Swedo et al., 1992). We suggest that while the activity within the right caudate nucleus may be linked more to an early response to antidepressants, the level of activity within the RAC may be a predictor of a more sustained therapeutic response in OCD.

The present data should be tempered by some methodological limitations. First, the sample size is relatively small. Second, given that 35.3% of our patients suffered from comorbid MDD, one cannot fully exclude the possibility that we may have identified the predictors of response of comorbid depressive symptoms rather than those specific to OCD. Nevertheless, neither did the improvement in obsessive–compulsive symptoms (the ΔYBOCS) correlate with the amelioration of the depressive symptoms (according to the ΔHAMD and the ΔBDI) nor was the response status associated with the presence of MDD. Third, there is still a certain degree of uncertainty regarding the correspondences between PET and LORETA (Gamma et al., 2004).

Finally, we found a significantly higher proportion of female patients among treatment responders. It could be argued that it was the female gender, rather than LORETA findings, that predicted the positive treatment response in our patients with OCD. Although we could not rule out this possibility because of the small number of volunteers enlisted in our research, several studies have demonstrated that treatment outcome in OCD is not related to gender (Fontenelle et al., 2002).

Despite these limitations, our study has replicated earlier findings regarding the role that abnormal activity in the RAC play in the pathophysiology of OCD. It demonstrated that EEG findings that reflect these disturbed patterns may predict a positive therapeutic response of obsessive–compulsive symptoms to antidepressants. It further highlighted the usefulness of LORETA as a relatively inexpensive and sensitive research tool. Additional studies employing larger samples are needed to confirm these findings and to expand them into the clinical practice.

Acknowledgements

None.

Statement of Interest

None.

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