Toward a better understanding of the pathophysiology of OCD SSRI responders: QEEG source localization

Bolwig TG, Hansen ES, Hansen A, Merkin H, Prichep LS. Toward a better understanding of the pathophysiology of ORD SSRI responders: QEEG source localization.

Objective: To demonstrate the utility of three-dimensional source localization of the scalp-recorded electroencephalogram (EEG) for the identification of the most probable underlying brain dysfunction in patients with obsessive–compulsive disorder (OCD).

Method: Eyes-closed resting EEG data was recorded from the scalp locations of the International 10/20 System. Variable resolution electromagnetic tomography (VARETA) was applied to artifact-free EEG data. This mathematical algorithm estimates the source generators of EEG recorded from the scalp.

Results: An excess in the alpha range was found with sources in the corpus striatum, in the orbito-frontal and temporo-frontal regions in untreated OCD patients. This abnormality was seen to decrease following successful treatment with paroxetine.

Conclusion: The VARETA findings of an activation/deactivation pattern in cortical and subcortical structures in paroxetine-responsive patients are in good accordance with data obtained in previously published positron emission tomography studies related to current hypotheses of a thalamo-striatal-frontal feedback loop being relevant for understanding the pathophysiology of OCD.

Significant outcomes

- QEEG/VARETA is useful in furthering the understanding of the pathophysiology of OCD SSRI responders.
- QEEG/VARETA data in OCD patients is consistent with that obtained with other neuroimaging techniques.

Limitations

- Data in the present study are limited to a highly selected group of patients.
- The number of patients studied is relatively small.
- Conclusions regarding the general applicability needs further studies in a wider range of neuropsychiatric disorders.

Introduction

Obsessive–compulsive disorder (OCD) is a non-psychotic disorder, the hallmark of which is recurrent intrusive thoughts (obsessions) and repetitive ritualistic behaviour (compulsions).

Traditional estimates of OCD in the general population were below 0.1%, but epidemiologic studies during the last 20 years have shown OCD to affect about 1% of the population worldwide (1).

Modern theories regarding the pathophysiology of OCD are based both on a wealth of
information about brain structures and pathways involved in the disease, and assumptions regarding the working action of effective drugs [selective-serotonin reuptake inhibitors (SSRIs)]. Most of the studies have focused on results from different types of neuroimaging, including: single photon emission tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (MRI) (2–5).

Although the data obtained with different imaging methodologies may vary, the majority of findings point to an involvement of the basal ganglia along with the related cortical and thalamic structures (2, 3, 6, 7). Most also agree on the involvement of the anterior cingulate gyrus. The accumulated data allow conceptualizing of OCD being a brain disorder dominated by a disturbance of the thalamo-striatal-orbital-frontal feedback loop (4, 6, 8, 9). During both resting state and symptom provocation (4, 5), neuroimaging studies have supported the importance of this model of a disturbed feedback loop in understanding the neuropathology of OCD.

The early observations that clomipramine was effective in obsessional disorder (10) and superior to tricyclics with little or no inhibition of serotonin reuptake (11) made way for the now widely accepted pharmacological first-line treatment of OCD with SSRIs. The described feedback-loop disturbance has been found influenced following treatment with serotonin blocking agents (12, 13) suggesting it is a state – rather than trait – phenomenon.

A recent PET study using the receptor ligand altanserin in untreated OCD patients showed an increased density of 5-HT2a receptors only in the caudate nucleus, which normalized following successful SSR1 treatment (14). Further, in a SPECT study using a 5-HT-transporter ligand the same research group found a decreased number of transporters in upper brain stem regions in untreated OCD patients (15). Such imaging techniques have helped elucidate structure and function underlying obsessions and ritualistic behavior, and also aided our understanding of the background for the efficacy of SSRIs in the therapy of OCD.

While the application of conventional electroencephalogram (EEG) has not contributed to an understanding of mechanisms underlying OCD previous studies using neurometric quantitative EEG (QEEG) methods (16–19) have identified two electrophysiological subtypes with differential responsiveness to SSR1 (20, 21).

**Aims of the study**

In the present report we wish to demonstrate the utility of using three-dimensional (3D) source localization of the scalp recorded EEG for the identification of cortical and subcortical brain structures involved in OCD.

**Material and methods**

**Subjects**

Study cases were selected from the 20 patients previously reported on (21) using QEEG subtyping. All 20 patients fulfilled DSM-III-R criteria for OCD, and at the time of the study with no comorbid symptomatology, especially depression. Eighteen of these patients (mean age 43 years, 11 males and seven females) showed significant clinical improvement indicated by a mean decrease of 55% in the Y-BOCS score. Further these 18 responders had a characteristic QEEG patterns of the ‘responder’ subtype, characterized by an excess of alpha-band activity in the frontal regions (21).

In this study, the QEEG data from these 18 responders were subjected to variable resolution electromagnetic tomography (VARETA) source localization.

**EEG acquisition**

Subjects were seated comfortably while 20 min of eyes closed resting EEG data were collected from the 19 monopolar electrode sites of the International 10/20 System, using silver/silver chloride electrodes referenced to linked earlobes. Data acquisition was performed on a Spectrum 32 (Cadwell Laboratories, Kennewick, WA, USA). A differential eye channel (diagonally placed above and below the eye orbit) was used for the detection of eye movement. All electrode impedances were below 5000 Ohms. The EEG amplifiers had a bandpass from 0.5 to 70 Hz (3 dB points), with a 60 Hz notch filter. Data were sampled at a rate of 200 Hz with 12-bit resolution.

**EEG data analysis**

**Frequency analysis**

Raw EEG data was reviewed for purpose of identifying and removal of artifact. This step was performed by visual inspection by a trained, experienced EEG technician and was aided by the use of a computerized artifact algorithm.

Forty-eight artifact-free EEG segments, each 2.5 s in duration were subjected to very narrow-
band spectral analysis (0.39 Hz increments from 0.39 to 19 Hz). As in the neurometric analysis of the EEG, transforms of the spectral power were applied to achieve Gaussian distributions. Using norms for narrow-band spectral power (19), regression equations for each frequency were calculated to correct for age-dependent sources of variance in the source log spectra.

Source localization

The most significant point in the narrow band frequency analysis was selected as input for the source localization. VARETA source localization method was used (22). VARETA is a mathematical algorithm for estimating the source generators of EEG recorded from the scalp. Sources are restricted to gray matter by the use of a probabilistic mask that prohibits solutions where the mask is zero. The definitions of regional probability for source localization are derived from a Probabilistic Brain Atlas (PBA) developed at the Montreal Neurological Institute (23). A three concentric sphere model was fitted to the Montreal Neurological Institute (MNI) mean head by a least square procedure. When 19 electrodes have been used to record the EEG as in this study, the brain volume is divided by VARETA into 3500 voxels.

Three-dimensional color-coded tomographic images are generated for the very narrow band point selected, with source generator distributions superimposed upon transaxial, coronal and sagittal slices of the PBA which correspond to the loci of the inverse solutions. In each case, the frequency at which the maximum significance was found is taken as the frequency of the main source. This must be carried out taking into consideration the large number of measurements and their correlation. In this work, the approach introduced by Worsley et al. (24, 25) is taken, and the color coding indicates excess or deficit of spectral activity above the selected probability level.

Results

Before treatment, the QEEG/VARETA data was characterized by a pattern of activation/deactivation in cortical and subcortical structures in the 18 OCD patients responding to the SSRI paroxetine. Figure 1 illustrates the VARETA results from the baseline (drug-free) EEG recording in two of these patients. Figure 2 shows the group average VARETA for the 18 treatment responsive patients, imaged at the most significant peak of deviation in the very narrow-band frequency spectra, 10.61 Hz. The most significant activation can clearly be seen in the thalamus, the corpus striatum (including the caudate nucleus), the orbito-frontal and temporoparietal regions. Abnormalities were greater on the right hemisphere than on the left. It is noted that

Fig. 1. Images in this figure follow radiological convention, with the right side of the head depicted on the left side of the slice. Each image depicts the Z-score of the sources in every voxel depicted in a transaxial slice, superimposed upon slices taken from the probabilistic magnetic resonance imaging Atlas constructed at Montreal Neurological Institute (23) from two subjects selected from the selective-serotonin reuptake inhibitors responder population from Copenhagen University Hospital. Images are shown as successive slices separated by 7 mm for the axial view (top two rows), sagittal view (middle two rows) and coronal views (bottom two rows). These sources were identified using variable resolution electromagnetic tomography as the most probable generators of the most excessive narrow-band alpha-peak in the quantitative electroencephalogram (top panel at 10.92 Hz, bottom panel at 10.14 Hz). Images are color coded in standard deviation units with excesses shown as increasing from red to yellow and deficits ranging from blue to turquoise, across the range indicated as the number of standard deviations ± as indicated on the figure.
the individuals shown in Fig. 1 demonstrate that
the group average shown in Fig. 2 is representative
of the individuals in the group.

Figure 3 is the image of the difference between
the baseline and treatment conditions, where
decreases on medication are shown in blue/greens
on the color scale. Following remission there was a
significant decrease in the alpha band excess,
especially prominent in the orbito-frontal regions,
the caudate nucleus, and the thalamus.

Discussion

We have demonstrated the utility of a 3D statistical
parametric mapping of EEG source spectra using
VARETA in a selected group of OCD patients.
The approach to 3D visual inspection of brain
structure is relatively new and has been demon-
strated to correspond to conventional imaging
results in studies of cerebrovascular disease and
tumors (26, 27). Likewise, results in the present
study are in good accordance with previous observations using PET (2–8) as well as with deoxyglucose PET data derived from the present group of patients (13).

Quantitative EEG offers strong advantages when compared with other imaging methods as it is inexpensive, has been shown to be valid with high test–retest reliability (28), and most important, it is a non-invasive method. A disadvantage at the present time is that a drug-free condition is required for maximum sensitivity. A limitation of the present study is that the number of patients is small, and further that we have limited the study to comprising only one group of individuals, namely OCD patients responding to SSRI.

Previous QEEG studies of OCD (20, 21) have shown a characteristic pattern of frequency band distribution in two-dimensional studies with a clear picture of alpha excess especially in the frontal

*Fig. 3. Images displayed as in Fig. 1, however, in this figure variable resolution electromagnetic tomography (VARETA) are computed for the difference between baseline and treatment response for the group average of selective-serotonin reuptake inhibitors responders (n = 18). Color-coding as in Fig. 1 is in standard deviation units, indicating the significance of the change from baseline when on medication for the sources identified using VARETA computed at the point of maximum change in the narrow-band frequency spectra for the group (10.14 Hz). In this figure, blue/green colors represent decreases in activity from the baseline. Confidence levels of change are computed as noted in Fig. 2 above.*
region. The VARETA findings described in this study of the same patients as in Hansen et al. (21) replicate the observation of ‘hyperfrontality’, but they also allow a depiction of activation and deactivation in the thalamo-striatal-frontal feedback loop assumed to be crucial for the pathophysiology of OCD (5–8). More studies are warranted to fully exploit the potential of QEEG and VARETA in subtyping, not only in relation to OCD but most likely also in other neuropsychiatric disorders and to explore the relationship with the clinical profiles.

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Declaration of interest
None.

References
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