Limbic Paroxysmal Magnetoencephalographic Activity in 12 Obsessive-Compulsive Disorder Patients: A New Diagnostic Finding

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Background: We describe frontotemporal paroxysmal rhythmic activity recorded by magnetoencephalography (MEG) in patients with obsessive-compulsive disorder (OCD).

Method: Twelve patients with OCD (per ICD-10 and DSM-IV criteria), aged 18 to 65 years, were assessed using MEG. Patients' classification according to the Yale Brown OCD Scale was as follows: severe = 8, moderate = 3, and mild = 1. MEG findings were compared with those of 12 age- and sex-matched healthy subjects (control group) with no previous history of psychiatric or neurologic disorders. All study participants underwent neurologic and basic medical examinations, including magnetic resonance imaging, electrocardiograms (EEGs), and electrooculograms. The study was conducted between January 2001 and January 2002.

Results: Two types of MEG activity were observed in patients with OCD: (1) frontotemporal paroxysmal rhythmic activity with low-amplitude spikes (< 1 picoTesla) in 92% (11/12) of patients and (2) intermittent isolated spikes and sharp waves in all patients (12/12). The OCD group had paroxysmal rhythmic MEG activity in the cingulate cortex (12/12), insula (10/12), hippocampus (9/12), temporal superior gyrus and angular and supramarginal gyri (9/12), precentral and postcentral gyri (8/12), orbitofrontal cortex (5/12), and parietal lobes (5/12). MEG recordings were normal in the control group, and EEG findings were normal in both the OCD and control groups.

Conclusions: Frontotemporal paroxysmal rhythmic activity with a preferential limbic distribution is a sensitive MEG finding in patients with OCD. Although the pathophysiology of this abnormality remains unknown, a corticostriatal network dysfunction was hypothesized.

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Symptoms of obsessive-compulsive disorder (OCD) comprise obsessions, compulsions with rituals, and a constellation of comorbid pathology, such as sensory disturbances, doubts, overestimation, language problems, emotional abnormalities (depression, anxiety), alterations in recent memory, and minor neurologic signs.[1–3]

The few studies describing electroencephalographic (EEG) abnormalities in patients with OCD have produced controversial results due to a lack of homogeneous diagnostic inclusion criteria and the inclusion of patients with other associated illnesses such as epilepsy.[4] Several studies report nonspecific EEG background activity changes,[5–7] and a single report shows intermittent left temporal lobe sharp-wave activity of questionable significance in a patient who had experienced a single generalized seizure.[8] None of these studies, however, report paroxysmal rhythmic (epileptiform-like) activity or isolated spikes. The EEG abnormalities described in OCD are associated with a more severe clinical presentation and with a poorer therapeutic response.[9,10] The presence of epileptiform activity in patients with OCD might be important therapeutically, since a satisfactory response to anticonvulsants has been reported in patients with severe OCD, particularly in those patients who are resistant to conventional pharmacotherapy.[9,10] Therefore, an EEG should be part of the routine examination of patients with OCD.[9]

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Table 1. Clinical Data, YBOCS Scores, and MEG Findings for 12 Patients With Obsessive-Compulsive Disorder

Patient	Age, y	Sex	Current SSRI Treatment	Symptoms	YBOCS Score (severity)	MEG Result (dipoles/min)
1	44	Female	Fluoxetine	Checking obsessions, symmetry and touching rituals	30 (severe)	16.45
2	58	Male	Citalopram	Obsessional thoughts, simple phobias	17 (moderate)	4.85
3	26	Female	Paroxetine	Obsessional thoughts, depression, washing rituals	24 (severe)	9.76
4	23	Male	Paroxetine	Obsessional thoughts, anxiety	18 (moderate)	6.30
5	28	Male	Fluoxetine	Obsessional thoughts, simple phobias, ordering rituals	25 (severe)	31.95
6	35	Female	Citalopram	Obsessional thoughts, washing and ordering rituals	31 (severe)	21.10
7	28	Male	Paroxetine	Checking thoughts, washing rituals	15 (mild)	2.90
8	26	Female	Citalopram	Doubt and checking thoughts, obsessional thoughts, washing rituals	26 (severe)	51.10
9	36	Female	Sertraline	Obsessional thoughts, counting, touching and washing rituals	30 (severe)	5.75
10	21	Male	Paroxetine	Obsessional thoughts, washing rituals	16 (moderate)	5.70
11	29	Male	Sertraline	Obsessional and checking thoughts, symmetry and washing rituals	32 (severe)	21.20
12	40	Female	Citalopram	Obsessional thoughts, simple phobias, washing and cleaning rituals	30 (severe)	20.10

Abbreviations: MEG = magnetoencephalography, SSRI = selective serotonin reuptake inhibitor, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Magnetoencephalography (MEG) is a noninvasive technique that records brain magnetic activity without distortion and with a high spatial and temporal resolution (millimeters and milliseconds, respectively)[11] that is not matched by any other neuroimaging diagnostic tool.

The genesis of magnetic brain activity is intrinsically related to the genesis of brain electrical potentials, which are dependent upon alternating excitatory and inhibitory postsynaptic potentials impinging upon the dendrites and soma of the cortical pyramidal neurons.[12] An excitatory synaptic input arriving in the dendrites will produce a local depolarization with a correspondent electronegative field in the dendritic tree and an electropositive field in the soma, thus creating an electrical dipole that is recorded by EEG. Conventionally, electrical current flows from the positive to the negative pole of the dipole, and, according to the Biot-Savart law, current flow through a conducting media such as the brain generates a magnetic field that is perpendicular to the direction of current flow. This activity is recorded by MEG.[12] The magnetic field is not distorted by the nonhomogeneous brain constituents (gray and white matter, cerebrospinal fluid, blood vessels) and can be recorded outside the skull by coils (magnetometers) immersed in helium, which allow low temperature (–269º C [–452.2º F]) superconductivity.

Modern whole-head MEG systems facilitate recording of cortical brain activity and provide a much higher resolution than EEG in the localization of deeply placed sources (dipoles) in the brain, such as in the hippocampus and orbitofrontal and cingular regions.[13,14] MEG allows accurate localization of generators (dipoles) oriented tangentially in the cortex and mainly measures activity from convoluted cortical fissures, areas in which EEG resolution is known to be limited.[15] MEG has better spatial accuracy than EEG because electrical potentials measured on the scalp are often distorted by various inhomogeneous brain tissues, making accurate identification of the activated area difficult. The magnetic field, in contrast, is not influenced by the inhomogeneities of the intracranial space.[15]

MEG records background brain activity, as well as epileptiform and nonepileptiform potentials.[16] Due to the recent introduction of MEG as a diagnostic tool, there is no information available regarding MEG abnormalities in OCD.

The superimposition of MEG results on magnetic resonance imaging (MRI) allows precise anatomical localization of findings, enhancing the clinical usefulness of MEG.[15] The aim of this study was to describe MEG findings in patients with OCD and attempt to explain the physiopathogenesis of the disorder.

METHOD

We studied 12 patients (6 men, 6 women) (Table 1) with the clinical diagnosis of OCD (ICD-10 and DSM-IV criteria) based on symptoms present for at least a year prior to entering the study. All patients were diagnosed with OCD by a certified psychiatrist. Other study inclusion criteria included age of 18 to 65 years, a score > 7 on the Yale-Brown Obsessive Compulsive Scale (YBOCS),[17] no previous neurologic or psychiatric pathology (except for OCD symptoms), normal MRI results, and no history of alcohol or drug abuse. All 12 patients presented with obsessive symptoms and suffered from compulsive behavior; 3 had simple phobias. The study was conducted between January 2001 and January 2002.

The mean ± SD age of the OCD group was 32.8 ± 10.5 years (range: 21 to 58 years). We used the YBOCS to classify OCD severity in the 12 patients. Eight patients were identified as severe (score of 24 to 31), 3 as moderate (score of 16 to 23), and 1 as mild (score of 8 to 15) (Table 1). At the time of the study, all patients with OCD were taking selective serotonin reuptake inhibitors (SSRIs).

A control group of 12 healthy subjects with no previous history of psychiatric or neurologic disorders was recruited for this study and matched according to age and sex with the cohort of patients with OCD.

All study participants signed a consent form prior to the study. A complete clinical history (biographical and family data, previous psychiatric disorders, previous medical disorders, and current symptoms) was obtained from all subjects included in this study. Each study participant also underwent neurologic and basic medical examinations.

MEG was performed during wakefulness, with the study participant inside a magnetic shielded room, using a 148-channel whole-head MEG Magnes 2500 WH (4D NeuroImaging Technologies, Inc., San Diego, Calif.). A typical recording session requires that the patient's head be placed inside the magnetometer helmet, where it remains immobile. Each study participant received simultaneous EEG, using the International 10-20 System for electrode placement; electrocardiogram (ECG); and electrooculogram (EOG). ECGs and EOGs helped to detect artifacts.[18] A digitization of the subject's head previous to data acquisition allowed us to calculate the local curvature for each MEG channel group and to express it as a local sphere model. During the recordings, subjects remained awake with eyes closed, and no activation methods were employed. Each recording session lasted 20 minutes, and data were acquired using a 678.17-Hz sample rate and a 0.1 to 100 Hz band-pass filter. MEG and EEG data were digitized and filtered (1 to 70 Hz band-pass filter) for analysis. The signal analysis comprised visually selected segments of MEGs and EEGs, which contained abnormal activity with no artifact.

An equivalent current simple dipole model (ECD) was used to calculate the spatial location of the neuronal currents responsible for the genesis of the abnormal activity.[19] ECD localization was calculated with regard to the Cartesian coordinates defined by the fiducial anatomic markers (bilateral preauricular points and nasion). The precise fixation of the Cartesian coordinates in the subject's MRI was carried out with the aid of the Spatial Temporal Analysis/Review program (ETIAM, University of Rennes, France).[20]

In order to visualize MEG fiducial points in the subject's MRI, the digitized headshape was superimposed on the volumetric MRI images (chamfer volume). The brain areas responsible for the generation of magnetic activity can be localized as a result of a perfect adjustment between the MEG and MRI fiducial points. We also checked fitness between scalp digitized points and the MRI scalp contour. MRI T1-weight images were employed (TR = 13.6 ms, TE = 4.8 ms, recording matrix = 256 × 256 pixels, 1 excitation, 240-mm field of view, 1.4-mm slice thickness).

Dipole selection criteria for sharp waves and spikes comprised a correlation coefficient > 0.95, a root mean square of at least 400 fT, a magnetic dipole moment under 400 nAm, a goodness of fit > 0.95, and a confidence volume < 15 cm^3.[21] Equivalent current dipole was generally selected from a segment ranging from 20 ms before the spike or sharp wave onset to 20 ms after its maximum amplitude point. Usually, more than 1 dipolar moment per spike was selected. The location of the magnetic dipoles corresponding to sharp waves and spikes in the MEG recording was calculated. The method employed in the MEG recordings and data analysis is further detailed elsewhere.[22]

Parametric Spearman correlations were used to compare MEG results and YBOCS scores of OCD patients. MEG results are expressed in dipoles per minute, which indicates the number of selected dipoles from all MEG abnormalities for each patient in a unit of time. These data analyses were performed using the SPSS 8.0 statistical package (SPSS Inc., Chicago, Ill.).

RESULTS

MEG tracings were normal in the control group. EEG recordings were interpreted as normal in control subjects and in patients with OCD.

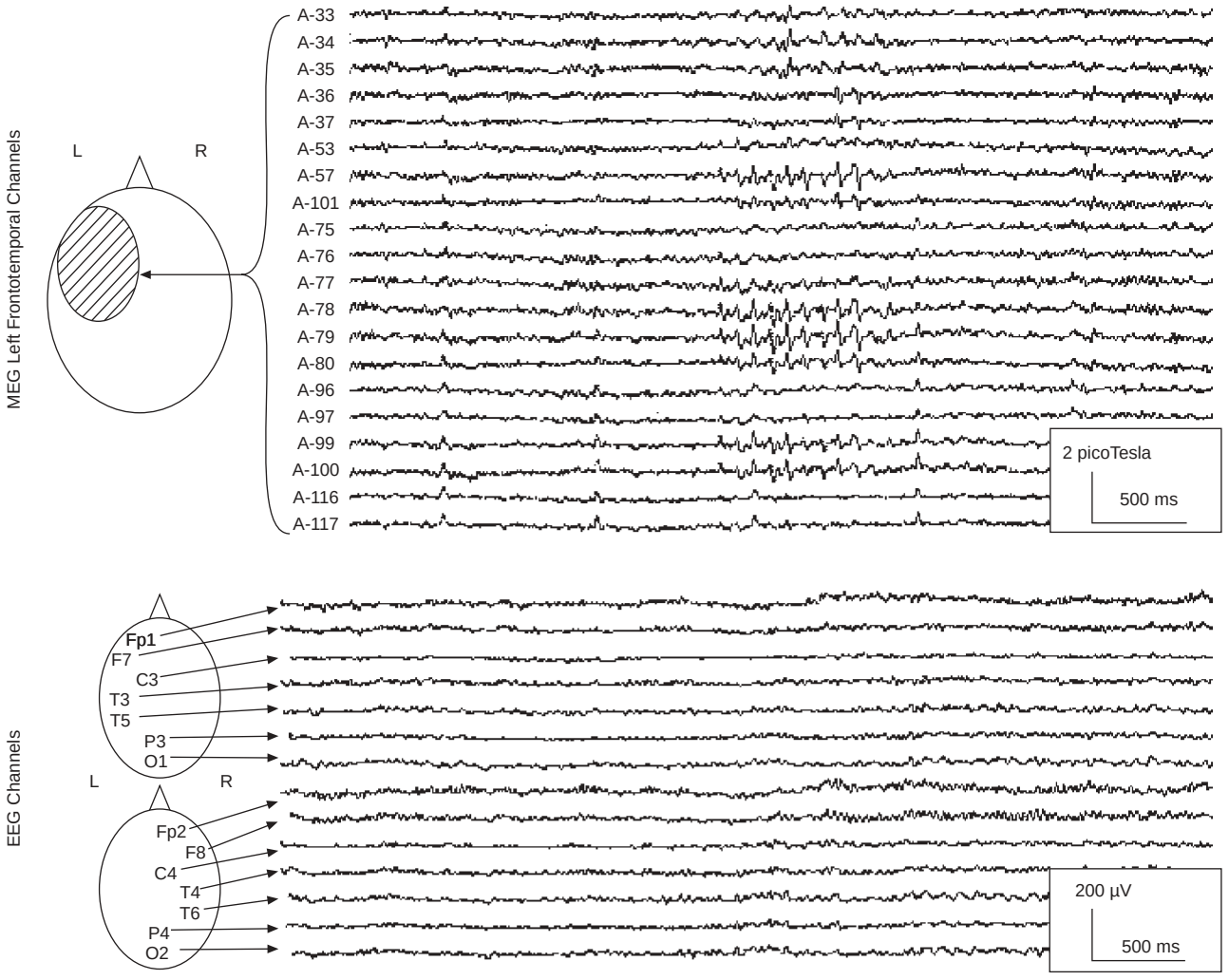
From a morphological standpoint, 2 types of MEG abnormalities were recorded in patients with OCD during wakefulness. (1) Low-amplitude (< 1 picoTesla) monophasic or biphasic spikes, 10 to 70 ms, called "peaks" were seen in 11 of 12 patients. The spikes appeared in the form of short bursts (3 to 6 spikes) called "peak fields," lasting approximately 1 second and resembling paroxysmal rhythmic activity at 9 to 10 Hz (Figure 1). (2) Isolated monophasic or biphasic spikes (10–70 ms) and sharp waves (70–200 ms) with an amplitude of 1 to 2 picoTesla and resembling epileptic spikes were seen in all patients (12/12).

The incidence of paroxysmal rhythmic activity and isolated spikes correlated with the severity of OCD. The parametric Spearman correlation of dipoles per minute and YBOCS scores (Table 1) was positive (r = 0.822) and reached statistical significance (p = .001).

From an anatomical perspective, the distribution of paroxysmal rhythmic MEG activity involves multiple brain regions, most in the territory of the limbic system. The OCD group had paroxysmal rhythmic MEG activity in the cingulate cortex (12/12), insula (10/12), hippocampus (9/12), temporal superior gyrus and angular and supramarginal gyri (9/12), precentral and postcentral gyri (8/12), orbitofrontal cortex (5/12), and parietal lobes (5/12) (Table 2).

Patients with the most severe OCD clinical status typically showed paroxysmal rhythmic activity in the following anatomical regions: orbitofrontal cortex (medial predominance, Figure 2A), cingulate cortex (bilateral anterior and posterior regions, Figure 2B), right superior temporal gyrus-angular-supramarginal gyri (Figure 2C), hippocampus bilaterally (often associated with activity in other temporal gyri, Figures 2A and 2D), and the insular

Figure 1. MEG-EEG Recording of Paroxysmal Rhythmic Activity at 9 Hz Seen Exclusively in the MEG Tracing (left frontotemporal channels)[a,b]



[a]EEG shows occipital alpha activity, which is not synchronous with the paroxysmal rhythmic MEG activity.
[b]Monopolar montage with Cz as reference.
Abbreviations: EEG = electroencephalogram, MEG = magnetoencephalogram.

region. Other areas showing paroxysmal rhythmic activity were prefrontal gyrus bilaterally, precentral and postcentral gyri bilaterally, parietal areas, and left temporal superior gyrus and adjacent areas (angular and supramarginal gyrus).

DISCUSSION

Paroxysmal rhythmic activity as a sensitive MEG finding was documented in 92% (11/12) of patients with OCD and occurred in the presence of normal EEGs. Furthermore, all patients with OCD showed MEG isolated spikes and sharp waves intermittently.

Comparatively, the rate of epileptiform abnormality in a nonepileptic psychiatric inpatient population is 2.6%[23] and reaches 2.2% in a nonepileptic neurologic cohort.[24] In patients with psychogenic nonepileptic seizures, however, epileptiform abnormality can be as high as 12.3%.[25] Studies performed in healthy young subjects indicate an incidence of epileptiform potentials ranging from 0.5% to 2.4%.[26] Although our findings confirm the sensitivity of MEG to document paroxysmal discharges in OCD, the specificity of these MEG findings remain unknown. Future studies searching for paroxysmal MEG activity in other psychiatric disorders, such as anxiety or unipolar disorders, might clarify this issue. In addition, subsequent studies in patients with a milder expression of OCD will help to better define the sensitivity of MEG in OCD. Our data indicate that MEG abnormalities are more prominent in patients with a greater clinical compromise.

Table 2. Dipole Localization of Paroxysmal Rhythmic Activity in MRIs of 12 Patients With Obsessive-Compulsive Disorder

	MEG Dipole Localization							
Patient	Parietal Areas	TSG, Angular and Supramarginal Gyri	Orbitofrontal Cortex	Prefrontal Cortex	Cingulum	Insula	Hippocampus	Precentral and Postcentral Gyri
1	Right, left	Right, left	Med left		Ant right/ post left	Left	Right, left	Med left/lat right, left
2	Left	Right, left		Lat left	Post left	Right, left	Right, left	Lat left
3	Right, left				Post right, left			Right, left
4			Lat left	Lat right	Post right	Right	Right, left	
5		Right	Med right, left	Med left/lat right, left	Ant left/post right, left	Right	Right, left	Lat left
6		Right	Med left/ lat left	Lat right, left	Post right	Right, left	Right, left	
7					Ant right/ post right	Right	Right	Med right/ lat right
8		Right			Post right, left	Right, left	Right, left	
9		Left	Med right	Lat right	Post right	Right	Right	
10		Left			Post right, left	Right, left		Lat right, left
11	Right	Right			Ant right/post right, left		Left	Lat right
12	Right, left	Right, left		Lat right	Ant right/post right, left	Right, left		Med right, left/ lat right, left

Abbreviations: ant = anterior, lat = lateral, med = medial, MEG = magnetoencephalography, MRI = magnetic resonance imaging, post = posterior, TSG = temporal superior gyrus.

According to our findings, MEG dipoles corresponding to the paroxysmal rhythmic activity are localized in brain regions, which other neuroimaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), and MRI also identify as functionally impaired. Our findings also correlate with the results of neuropsychological examination, which indicates dysfunction of the brain regions where MEG finds paroxysmal activity.[27–32]

The amplitude of MEG paroxysmal rhythmic activity is small, generally less than 1 picoTesla (for comparative purposes, the amplitude of a MEG epileptic spike ranges from 1 to 5 picoTesla[15]). Since magnetic fields are not distorted by the resistive properties of the skull,[16] small potentials like this paroxysmal activity can be recorded. Small-amplitude EEG signals, however, are easily attenuated by the inhomogeneous boundaries of the brain and skull, often escaping detection.

Currently, we use simple dipole source analysis. The use of multiple dipole analysis would be helpful, since it measures information originating simultaneously in different constituents of brain networks, allowing visualization of functional coupling at millisecond intervals.[16]

We do not believe MEG paroxysmal rhythmic activity is the result of SSRI therapy, since, to our knowledge, there is no solid evidence that these drugs produce similar EEG changes.[33–35] Although there are no studies addressing the issue of SSRI therapy resulting in MEG paroxysmal rhythmic activity, the possibility seems unlikely, since our results indicate that the amount of paroxysmal MEG activity correlates with clinical severity of OCD, according to the YBOCS. Since paroxysmal MEG activity was observed only in patients with OCD undergoing SSRI treatment, and not in the control group, we cannot exclude a role of SSRI treatment in its genesis. Future studies using drug-naive treated OCD patients may shed some light on this problem.

One could postulate that the limbic paroxysmal rhythmic activity described in patients with OCD could be related to alpha rhythm because the frequency of these 2 types of activity is similar. This explanation is, however, not feasible, since MEG paroxysmal rhythmic activity could be seen independently from alpha rhythm, was never recorded from occipital regions, and was recorded even with the eyes open, which normally blocks alpha activity.

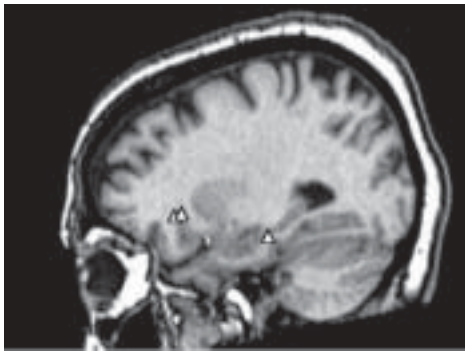
Functional neuroimaging studies performed either at rest or during sensorial or cognitive stimulation have consistently implicated the orbitofrontal cortex as a neurobiological substrate in the pathophysiology of OCD.[36] The most convincing evidence resides in the detection of higher metabolic rates in the orbitofrontal cortex and in the head of the caudate nucleus in patients with OCD.[37,38] Furthermore, recent PET and SPECT studies have found a relationship between emotional changes and enhanced metabolism in the cingular cortex.[23] The studies also showed normalization of these findings after pharmacologic treatment or psychotherapy.[23]

PET findings show an increased metabolism in the corpus striatum in patients with obsession. Similar changes have also been reported in the orbitofrontal, dorsolateral, prefrontal, and cingular cortices.[25]

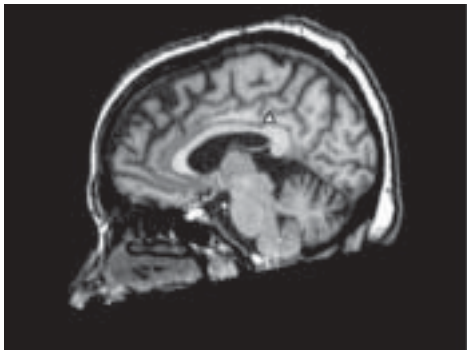
Functional magnetic resonance imaging has shown a significant increase in frontal lobe perfusion that correlates with symptom severity, as evaluated by the YBOCS.[26] This is in agreement with clinical and neuro-

Figure 2. Representation of MEG Dipoles on MRI of a Patient With OCD Classified as Severe (YBOCS score = 30)[a]

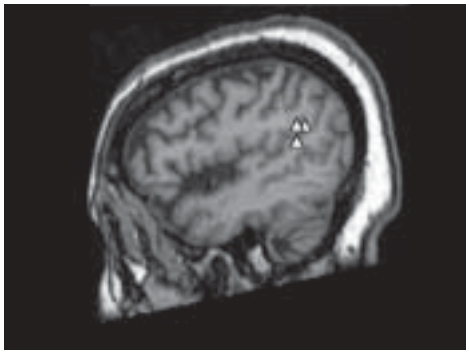
A. Medial Orbitofrontal Cortex and Left Hippocampus



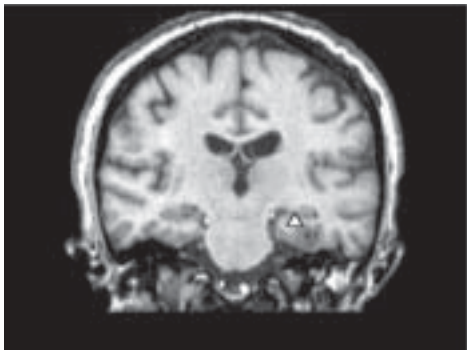
B. Left Posterior Cingulate Cortex



C. Angular and Supramarginal Gyri



D. Left Hippocampus



[a]Triangles represent paroxysmal rhythmic activity dipoles.
Abbreviations: MEG = magnetoencephalography, MRI = magnetic resonance imaging, OCD = obsessive-compulsive disorder, YBOCS = Yale-Brown Obsessive Compulsive Scale.

psychological data linking OCD symptoms with a frontal lobe dysfunction.[24]

We propose that the frontotemporal limbic paroxysmal activity recorded by MEG in patients with OCD behaves as an alien noise interfering with the normal functioning of the corticostriatal network linking the cingular and orbitofrontal cortex with basal gangliae structures, such as the caudate nucleus. The subcortical constituents of the corticostriatal network comprise the caudate nucleus, the putamen, and the accumbens or ventral striatus nucleus. The cortical constituents of the network include the anterior orbitofrontal cortex, posteromedial orbitofrontal cortex, cingular cortex, parahippocampus, anterior temporal cortex, and insula. The sensory, motor, and dorsolateral prefrontal cortex are also part of this network.

Electrical stimulation of the putamen and caudate nucleus in cats can produce a recruiting-like EEG response in both ectosylvian gyri, particularly at frequencies of 8 to 10 Hz. Shortly after intramuscular administration of penicillin, which in cats induces a transient experimental model of generalized epilepsy, the EEG response elicited by putamen or caudate nucleus stimulation resembles the frontotemporal paroxysmal rhythm recorded by MEG in patients with OCD.[39] Conceptually, a corticostriatal network dysfunction implies functional changes at cortical and subcortical levels. MEG is a helpful diagnostic tool in detecting the cortical component of the corticostriatal network dysfunction. This is a preliminary report, and our findings need to be further confirmed by studying additional patients.

CONCLUSIONS

Frontotemporal paroxysmal rhythmic activity with a preferential limbic distribution was a sensitive MEG finding in 11 of 12 patients with OCD. This abnormality was not seen in EEG recordings, and, therefore, MEG may play a crucial role in the diagnosis of OCD.

Several reports in the literature strongly suggest that the orbitofrontal cortex and the caudate nucleus are functionally and anatomically connected as part of a corticostriatal network. We propose that the frontotemporal paroxysmal rhythmic activity acts as an alien noise interfering with the normal functioning of the corticostriatal

network. Further confirmation of this hypothesis will require MEG and PET or SPECT co-registration in order to correlate the cortical areas of dysfunction identified by MEG with the cortical and subcortical areas of abnormal metabolism or blood flow detected by PET and SPECT.

It is anticipated that further studies will be required to better define the extent and dynamics of the corticostriatal network dysfunction in OCD. This information might be helpful in the formulation of a more meaningful classification of OCD.

Drug names: citalopram (Celexa), fluoxetine (Prozac and others), paroxetine (Paxil and others), sertraline (Zoloft).

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