Dissociation Between MEG Alpha Modulation and Performance Accuracy on Visual Working Memory Task in Obsessive Compulsive Disorder

Kristina T. Ciesielski,^{1,2*} Matti S. Hämäläinen,¹ Daniel A. Geller,³
Sabine Wilhelm,³ Timothy E. Goldsmith,² and Seppo P. Ahlfors¹

¹MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts

²Department of Psychology, University of New Mexico, Albuquerque, New Mexico

³Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts

Abstract: Oscillatory brain activity in the alpha band (8–13 Hz) is modulated by cognitive events. Such modulation is reflected in a decrease of alpha (event-related desynchronization; ERD) with high cognitive load, or an increase (event-related synchronization) with low cognitive demand or with active inhibition of distractors. We used magnetoencephalography to investigate the pattern of prefrontal and parieto-occipital alpha modulation related to two variants of visual working memory task (delayed matching-to-sample) with and without a distractor. We tested nonmedicated, nondepressed patients suffering obsessive-compulsive disorder (OCD), and pair-matched healthy controls. The level of event-related alpha as a function of time was estimated using the temporal-spectral evolution technique. The results in OCD patients indicated: (1) a lower level of prestimulus (reference) alpha when compared to controls, (2) a task-phase specific reduction in event-related alpha ERD in particular for delayed matching-to-sample task with distractor, (3) no significant correlations between the pattern of modulation in prefrontal and parietal-occipital alpha oscillatory activity. Despite showing an abnormally low alpha modulation, the OCD patients' performance accuracy was normal. The results suggest a relationship of alpha oscillations and the underlying thalamocortical network to etiology of OCD and an involvement of a compensatory mechanism related to effortful inhibition of extrinsic and intrinsic interference. *Hum Brain Mapp* 28:1401–1414, 2007. © 2007 Wiley-Liss, Inc.

Key words: limited resources inhibitory control; visual-spatial working memory task; event-related alpha modulation; event-related desynchronization (ERD); event-related synchronization (ERS); temporal-spectral evolution technique (TSE); magnetoencephalography; obsessive-compulsive disorder (OCD)

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*Correspondence to: Kristina T. Ciesielski, Ph.D., MGH/MIT/HMS Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital, 149 13th Street, Charlestown, Massachusetts 02129, USA. E-mail: ktc@nmr.mgh.harvard.edu

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INTRODUCTION

Cognitive processes require a transient integration of multiple, broadly distributed, and continuously interacting functional networks. The development of such long-range dynamic communication networks is potentially achievable through the synchronization of oscillations at particular frequencies. The oscillations at the alpha band (8–13 Hz), generated in thalamocortical feedback loops and in corticocortical parietal networks [Lopes da Silva, 1991; Nunez et al., 2001; Pfurtscheller et al., 1996; Steriade et al., 1990], have gained particular attention, being related to neural

mechanisms of complex cognitive processes including attention, memory, and mental imagery [Bremer, 1958; Gevins and Schaffer, 1980; Kaufman et al., 1989; Klimesch, 1999; Lopes da Silva et al., 1980; Pfurtscheller, 1992; Tesche et al., 1995]. The alpha recorded by electroencephalography (EEG) [Nunez et al., 2001] or magnetoencephalography (MEG) [Hamalainen and Hari, 2002; Hari and Salmelin, 1997] is modulated by extrinsic or intrinsic events [Bremer, 1958; Contreras et al., 1996; Lopes da Silva and Pfurtscheller, 1999; Lopes da Silva et al., 1980; Pfurtscheller and Arnibar, 1977; Steriade and Llinas, 1988]. Such event-related modulation can be quantified by event-related desynchronization (ERD) or synchronization (ERS) [Pfurtscheller and Arnibar, 1978], defined, respectively, as the event-related decrease or increase in the power of the oscillations relative to baseline.

EEG studies have shown monotonic alpha attenuation corresponding to gradually increased working memory loads [Gevins and Smith, 2000; Kaufman et al., 1991; Neupper and Pfurtscheller, 2001; Pfurtscheller and Klimesch, 1992], and stronger coupling of occipital and frontal alpha in “seen” as opposed to “not seen” trials of working memory tasks [Babiloni et al., 2005; Buchel and Friston, 1997; Gevins et al., 1997]. Posterior alpha ERS was shown to increase with practice [Gevins et al., 1997; Smith et al., 1999]. This is consistent with studies describing ERS as part of an active inhibitory mechanism, important for predicting and suppressing distractor stimuli [Foxe et al., 1998; Fu et al., 2001; Neupper and Pfurtscheller, 2001; Worden et al., 2000]. Klimesch et al. [1999] show ERS of alpha during a semantic long-term memory task as related to an inhibition of task irrelevant cortical processes. Similarly, Jensen et al. [2002] have reported an ERS of alpha during the retention interval in a modified Sternberg working memory task, and have related it to the effort of controlling distractors. An increase of alpha has also been associated with the brain region related to the “to-be ignored function” [Foxe et al., 1998; Worden et al., 2000]. Furthermore, theoretical studies suggested that ERS surrounding the ERD may represent an active selective inhibition of task-irrelevant cortical regions [Suffczynski et al., 2001].

Thus, modulation of alpha amplitude and its topography may potentially reflect the individual’s cognitive strategy and proficiency in encoding and retrieval by elucidating the interplay between excitatory and inhibitory processes [Neupper and Pfurtscheller, 2001; Schnitzler and Gross, 2005; Ward, 2003]. Functional coupling between the parietal-occipital and prefrontal alpha may provide an insight into the neural mechanisms of relevant working memory networks. Considering the above, alpha modulation appears to be a measure well suited for investigation of neurophysiological mechanisms that are failing in their inhibitory control of neuronal networks.

A problem in inhibitory control has been repeatedly implicated in patients suffering obsessive-compulsive disorder (OCD) [Greenberg et al., 2000; Rauch et al., 2001;

Rosenberg et al., 1997]. Clinical research on OCD has revealed elevated levels of activation in the prefrontal-striatal-thalamocortical pathways [Baxter et al., 1987, 1988; Jenike et al., 1991; Malloy, 1987; Perani et al., 1995; Rauch et al., 2001; Rosenberg et al., 1997], and slow performance and impairment in visual-spatial recognition and memory [Galderisi et al., 1995; Hartston and Swerdlow, 1999; Purcell et al., 1998], the latter mostly due to a reduced attentional selectivity between task-relevant and task-irrelevant details [Enright and Beech, 1990; Harston and Swerdlow, 1999]. Conceptually, both these leading OCD characteristics may derive from a fundamental deficit in the flexibility of inhibitory/excitatory control of the involved brain networks. Moreover, employing the alpha band for investigation of OCD appears particularly befitting, as the areas specific to generation of alpha oscillations are among those found deficient in OCD.

There are few quantitative EEG (QEEG) studies to date on alpha oscillations in OCD, and as far as we are aware none in MEG. Most reports on QEEG in OCD have focused on resting state alpha [Bucci et al., 2004; Karadag et al., 2003; Shin et al., 2004]. In a carefully selected population of OCD patients and controls, Bucci et al. [2004] measured QEEG in a resting state and reported a lower alpha power in the anterior and posterior brain regions in OCD patients. The authors interpret this result being due to an overactivation of the thalamocortical pathways subserving attention. Similar reductions in alpha power are reported as characteristic of OCD patients with more severe symptoms [Karadag et al., 2003]. In contrast, studies on subclusters of OCD patients, who are good responders to serotonin-reuptake inhibitors, showed an increased relative power of alpha [Mas et al., 1993; Prichep et al., 1993]. An OCD symptom provocation study [Simpson et al., 2000] reported elevated alpha over the posterior regions and a reduced power of alpha in the frontal regions. These results were considered to be supportive to the frontal brain hyperactivation reported from earlier neuroimaging findings in provocation studies [McGuire et al., 1994; Rauch et al., 1994]. To increase the consistency of alpha measures, the current study is focusing on event-related alpha modulation, as opposed to the more individually variable resting state alpha [Karadag et al., 2003; Shin et al., 2004]. The second effort in this study is a careful selection of nonmedicated and clinically nondepressed OCD patients and well matched healthy controls to reduce confound of depression and individual differences on data outcome.

The relationship of the prefrontal-striatal-thalamocortical pathways to neuropathology of OCD and to the generators of alpha oscillations provides a conceptual framework for the current study. This relationship suggests that a measure of task-related alpha modulation in patients with OCD may shed some light on the neurophysiological mechanisms underlying their impaired cognitive and neuronal inhibitory control. We employed a variant of the delayed matching-to-sample task (DMST) that taxes the visual-spatial capacity. We measured a reference alpha

(also called tonic alpha, [Klimesch et al., 2001]) and, consecutively, a task-related ERD of alpha for each of three task phases: encoding, retention interval, and retrieval. Since the frontal-parietal network has been firmly linked to visual-spatial working memory tasks [Cohen, 1999; D'Esposito et al., 1999; Garavan et al., 1999; Smith and Jonides, 1998], we examined the correlative relationship between parietal and prefrontal ERDs.

DMST involves the presentation of a template stimulus (encoding), followed by a delay of several seconds, during which the information is actively maintained in mind (retention phase), and then by presentation of similar retrieval stimuli. The task is to respond to one of the retrieval stimuli matching the encoding stimulus. Although the effective modulation of neural resources is relevant to all phases of the DMST (encoding, retention, retrieval), retrieval requires the most active suppression of the earlier irrelevant items in memory, and a shifting to new responses [Anderson and Bjork, 1994; Anderson and Spellman, 1995; Carr and Dagenbach, 1990; Keele and Neill, 1978; Konorski, 1967; Neill and Westberry, 1987; Norman and Shallice, 1980]. The prediction that oscillatory abnormalities in OCD may be prominent in the retrieval phase was foreshown in our earlier MEG source localization study [Ciesielski et al., 2005], in which enhanced evoked activity in OCD patients was prominent during the retrieval phase. Since this abnormally high activation was mostly within the anterior orbital region, anterior insula, and superior temporal sulcus, the question arose whether alpha oscillations, which are specific to parieto-occipital brain regions, will be able to capture some of these abnormalities. To further maximize the scrutiny of group differences, we used a second variant of the DMST task with a distractor presented very soon (200 ms) after the encoding stimulus (DMST-WD). The expectation was that introducing a distractor to OCD patients suffering from unselective processing of task-relevant and task-irrelevant stimuli may lead to a further increase in the task difficulty, lowering the response accuracy and increasing the reaction time (RT) [Purcell et al., 1998; van der Wee et al., 2003].

ERD relationship to the reference (tonic) alpha oscillations during the prestimulus period has been postulated in regulation of cortical activation and inhibition [Klimesch et al., 1996, 2006; Neupper and Pfurtscheller, 2001]. It has been reported that subjects who have difficulty in inhibiting distractors have a lower reference alpha [Crawford et al., 1995; Klimesch et al., 2001]. Considering the high level of intrinsic interference, obsessive thoughts, mental rituals, and a consistent preoccupation with irrelevant details in OCD, we hypothesized that reference alpha may be reduced in OCD patients, and their modulation of ERD will be attenuated. Klimesch [1999] described this as "worst case" in the tonic vs. phasic (i.e., reference vs. task) alpha relationship.

We present below MEG data from OCD patients and healthy pair-matched controls performing a visual-spatial DMST task. We examined event-related changes in the

level of alpha oscillations as a function of time using the temporal spectral evolution (TSE) technique [Salmelin and Hari, 1994]. The participating patients were unmedicated and clinically nondepressed individuals suffering moderate-to-severe OCD. Thus, we are set to answer three major questions: Is the task-related alpha modulation, ERD, abnormal in OCD, and if yes, is this abnormality task-phase specific? What is the relationship of the reference (tonic) alpha to the pattern of ERD of alpha in OCD patients? Is a desynchronization of alpha over the anterior brain regions associated with a concomitant desynchronization over the posterior regions, and if yes, does this pattern of networking hold in OCD?

MATERIALS AND METHODS

Participants

Eight unmedicated and clinically nondepressed OCD patients from the OCD Clinic at Massachusetts General Hospital, Boston, and Health Sciences Center, University of New Mexico provided data for this study. According to the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition (DMS-IV) [First et al., 1995], the patients had no other psychiatric, medical, or neurological illnesses except OCD. The patients were either never medicated or had been at least six month free of any medication. All patients were tested with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) [Goodman et al., 1989] to assess the presence and severity of obsessions and compulsions. Y-BOCS total score for groups indicated a moderate degree of OCD symptoms: 25.6 (2.8). Depression severity, as measured using Beck depression inventory, was clinically nonsignificant: 8.4 (2.1). Among intrusive thoughts and mental rituals were symmetry, exactness, religious anxiety, harm, counting, sexual acts, and guilt. Among compulsions were hand washing, ordering, compulsive buying, dressing rituals, cleaning, and touching. Most patients reported difficulty in decision making and in initiating novel actions. The medical and developmental history of the control group was unremarkable. The patients were matched by control subjects for age, gender, years of education, handedness, and performance on several neuropsychological tests [see also Ciesielski et al., 2005]. There were no significant group differences on neuropsychological tests including FAS Verbal Fluency Test, and on Stroop Word-Color Test. The differences in age (C: 32.6, OCD: 33.4; age span: 15–39 both groups), gender (five males in each group), handedness (all right handed), or years of education (C: 12.9, OCD: 14.0) were not significant. Patient-control pair matching subjects were tested within close time proximity, within a similar time of the day (late morning-early afternoon), and on the same equipment.

All participants signed an informed consent form; the procedures were approved by The Institutional Review Boards for Human Research at the VA Medical Center in

Albuquerque, UNM School of Medicine and at Massachusetts General Hospital in Boston.

Visual-Spatial DMST

Two variants of a modified DMST were used (Fig. 1): without distractor (DMST-ND) and with distractor (DMST-WD). In terms of the major cognitive process involved, DMST could be classified as a “delayed recognition” task. The DMST-ND task involved: (1) An encoding phase with presentation of a black and white checkerboard pattern of 200 ms duration and $1.3^\circ \times 1.3^\circ$ visual angle, (2) Retention phase of 2,950 ms, and (3) A Retrieval phase with presentation of two similar patterns (200 ms) to be compared to the Encoding template. The subject was to indicate which of the two patterns matched the template by pressing a button with the left or right index finger, corresponding to the stimuli, as accurately and as fast as possible. The response was counted, if the subject pressed the button before the beginning of the next trial. The DMST-WD task was identical to the DMST-ND, except that a Distractor pattern (200 ms duration) was presented during the Retention phase, 1000 ms after the offset of the Encoding stimulus; the total duration of the Retention phase in DMST-WD was 3150 ms. The DMST-ND and DMST-WD were administered in separate sessions, with DMST-ND always presented first.

To reduce the contingent negative variation component, associated with a regular target presentation, we randomly added trials (12–15%) with different timing between encoding and retrieval (2500–3500 ms). These trials were not included in the analysis. The subjects participated in two runs of 164 trials each, with a short break in-between. Each trial lasted ~6 s; the recording time was about 30 min.

MEG Data Acquisition

MEG signals were recorded using a Neuromag-122™ (Elekta Neuromag Oy, Finland) system with 122 planar gradiometers covering the whole scalp in four patients and four controls. Another four pairs of our OCD-control subjects were studied with a Vectorview™ (Elekta Neuromag Oy) system, which comprises 306 sensors arranged in trip-lets of two planar gradiometers and one magnetometer; for consistency and comparability with the other subjects, only 204 gradiometers were used in the analysis. Both MEG systems were calibrated with identical current-dipole phantoms provided by the manufacturer, allowing us to confirm the consistency of data collected with the two systems. The measurements were carried out in a magnetically shielded room (Imedco AG, Switzerland) comprising two (Neuromag-122) or three (Vectorview) layers of mu-metal and aluminum as well as an active compensation system to enhance the shielding at low frequencies. Head movements were controlled using a chinstrap. The precise location of the head with respect to the sensors was determined with three or four head-position indica-

Figure 1.

The experimental paradigm. Two variants of a modified DMST were used, DMST With No-Distractor (DMST-ND, **A**) and With Distractor (DMST-WD, **B**), to examine cortical activation during three processing phases: encoding, retention, and retrieval. DMST is a working memory task that targets visual-spatial functions reported to be deficient in OCD. The intervals used in the calculation of event-related changes and oscillations are indicated by shading (Ref., reference period; E., encoding; Re., retention; Rt., retrieval).

tor coils attached to the scalp. A head-based MEG coordinate frame was established by locating fiducial landmarks (nasion and preauricular points) with a Polhemus Fasttrak 3D digitizer. The data were digitized at 300 Hz (Neuromag 122) or 600 Hz (Vectorview), with an antialiasing low-pass filter set at 100 and 200 Hz, respectively. The stimulus presentation set-up was similar in both Laboratories. The visual stimuli were presented using a liquid crystal display projector onto a back-projection screen placed 1.7 m in front of the subject. Eye movements and blinks were monitored with vertical and horizontal EOG. The subjects were trained not to blink during the trial until the button-press response was made; this provided, in most cases, blink-free epochs.

TSE Analysis of Alpha Oscillations

Trials contaminated by eye blinks in the period of 0.0–4.0 s were excluded from the analysis. The rejection criterion was adjusted individually for each subject, the most

common value being EOG amplitude range exceeding 100 μ V or the MEG gradiometer amplitude exceeding 1,000 fT/cm. Trials with both correct and incorrect responses were included; however, the number of incorrect responses was minute (see *Behavior* under “Results” section) and unlikely to affect the analysis outcome. The level of event-related α -activity as a function of time was estimated using the TSE technique [Salmelin and Hari, 1994]. TSE waveforms were computed by band pass filtering (8–13 Hz, FFT-based finite impulse response, zero phase, cosine squared tapers) the individual stimulus-locked epochs and then rectifying and averaging them. The root-mean-square values over 10 occipital/parietal sensors were computed for each subject in the two conditions (DMST-ND and DMST-WD), and the mean value was obtained for four 400 ms time windows (see Fig. 1). For the DMST-WD, the time windows were as follows: (1) –500...–100 ms before the encoding stimulus (reference); (2) 200...600 ms after the onset of encoding stimulus (encoding); (3) 1,400...1,800 ms after the onset of the encoding stimulus, that is 200...600 ms after the distractor stimulus onset (retention), and (4) 3,550...3,950 ms after the onset of the encoding stimulus, that is 200...600 ms after the retrieval stimulus onset (retrieval). For the DMST-ND, the time windows were as above, except for the retrieval the window was 3,350...3,750 ms (always, 200...600 ms after the stimulus onset for Retrieval).

For the purpose of statistical analysis, the normalized alpha measures for the encoding (E), retention (Re), and retrieval (Rt) windows were obtained by dividing the values with the reference value of alpha: e.g., $[(E - \text{Reference})/\text{Reference}] \times 100\%$. The proportion of power of alpha is expected to be a more reliable measure of task related change than the absolute power, which has a relatively poor test-retest reliability [John et al., 1980] and it is a highly individual feature. The event-related alpha modulation is a short lasting, regional amplitude attenuation in the alpha oscillations that occurs in direct relation to an event [Pfurtscheller and Aranibar, 1977]. This phenomenon has been termed an ERD [Pfurtscheller, 1992; Pfurtscheller and Aranibar, 1977], in contrast to ERS (event-related synchronization), which is described as a phasic, regional increase of alpha activity in relation to an internal or external event, and dependent on the state of the brain [Pfurtscheller, 1992].

Statistical Analysis

To examine the direction and magnitude of ERD in OCD patients and controls, an “indicator of variability” (V) was calculated. V illustrates the general variability of the ERD measures across the three DMST phases (encoding, retention, and retrieval). The following formula was used: $V = (|E - M| + |Re - M| + |Rt - M|)/3$, where mean (M) = $(E + Re + Rt)/3$; and E, Re, Rt represent the normalized alpha measures during encoding, retention, and retrieval, respectively. If the V indicator was

significantly different in the control and OCD group (larger numerical value for V indicated higher general variability of alpha across task conditions) we investigated which of the task phase (E, Re, Rt) contributed to this general group difference in modulation of alpha. Thus, we investigated the direction and the magnitude of changes using ERD measures in each pair of (OCD and control) subjects using the Wilcoxon Signed Ranks Test for matched pairs [Siegel and Castellan, 1988]. Since the published studies emphasize a parietal-prefrontal coupling of alpha oscillatory activity during working memory task, two within-group (OCD patients and controls) sets of correlations between brain regions (parieto-occipital vs. prefrontal) were performed on ERD measures for Retrieval using a non-parametric Spearman’s correlation coefficient (two-tailed).

Moreover, the ERD effect may depend on the power of alpha during the reference period (i.e., period precipitating the encoding phase). We investigated, therefore, whether there is a difference in the power of the reference alpha between the OCD and control groups at the prestimulus period. Significant differences were defined at $P < 0.05$ for a two-tailed test. Differences in the behavioral performance (accuracy, RTs) were examined with the Wilcoxon Signed Ranks Test for matched pairs.

RESULTS

Behavior

The accuracy level was high and comparable between the control and OCD group (Fig. 2A). The percent of correct responses for DMST-ND was as follows: controls 92.2 (SD = 5.3), OCD 94.5 (4.5), and for DMST-WD: controls 93.4 (7.3), OCD 95.3 (4.9). In both tasks, the RTs were considerably longer for OCD patients than for the control subjects (Fig. 2B). For DMST-ND the values were: OCD: 765 ms (213.7), controls: 563 ms (129.0) ($z = 0.674$, $P = 0.500$). For DMST-WD the values were: OCD: 772 (171.5), controls: 620 (205.8); ($z = 1.52$, $P = 0.128$), but the group differences on RT did not reach statistical significance.

ERD of Alpha

TSE waveforms in Figure 3A illustrate the alpha amplitude as a function of time for one matched pair of subjects over the parieto-occipital and frontal brain regions. The largest changes in the TSE are seen in parieto-occipital sensors. Figure 3B shows the root-mean-square value of the TSE waveforms over 10 parieto-occipital and 10 prefrontal sensors, for both the DMST-ND and DMST-WD conditions.

Table I shows results of group comparison between the variability indicator V , which describes general modulation across the three task phases (encoding, retention, and retrieval). For DMST-ND, neither parieto-occipital nor prefrontal group differences in the V factor reached statistical

Figure 2.

Behavioral performance during MEG sessions: accuracy of response (A) and RTs (B) in the DMST task without (ND) and with (WD) distractors. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

significance. However, for DMST-WD, the V factor over the parieto-occipital region was significantly lower in OCD patients ($z = 1.99$, $P = 0.046$).

The mean group ERD measures are presented in Table II. We investigated to which task phase (encoding, retention, or retrieval) the group differences are primarily related. Over the parieto-occipital sites the magnitude of the alpha modulation was not statistically different for the OCD and control subjects in neither of the task phases of the DMST-ND. The modulation of alpha was significantly smaller in OCD patients than in controls only in DMST-WD during the retrieval phase ($z = -2.380$, $P = 0.017$). Interestingly, although the prefrontal ERD alpha were generally of lower values than those over the parieto-occipital sites, the significant group differences persisted for prefrontal ERDs in the Retrieval phase in DMST-WD; controls showing lower levels of ERD, and, therefore, more modulation of alpha ($z = -2.19$, $P = 0.028$). Statistically significant group differences emerged for prefrontal ERD alpha measured during the retention period with distractor; controls showing more modulation of alpha than OCD patients, and therefore more processing resources assigned to the distractor ($z = -2.03$, $P = 0.043$). Figure 4 illustrates the within-group modulation of ERD of alpha in the different phases (encoding, retention, and retrieval) of the DMST-ND and DMST-WD.

Reference Alpha

The ERD effects vary with the power of alpha during the reference (prestimulus) latency window [Klimesch et al., 2001], i.e., the time window preceding the onset of an encoding stimulus. Table III presents the group values for measures of reference alpha, sometime also referred to as tonic power of alpha [Klimesch, 1999], for DMST-ND and DMST-WD. Amplitude of alpha generated over the parieto-occipital regions during the retention time window, before the onset of the task, was on average about 20% higher in control subjects than in OCD, but this difference

did not reach statistical significance. Although we expected that the reference alpha will stay at a stable level for the same group of subjects, and across task conditions. Surprisingly, the results showed statistically significantly different levels of reference alpha in OCD and controls for DMST-WD ($z = 2.24$; $P = 0.025$), with about 30% higher reference (baseline) alpha amplitude in controls.

Correlations Between Parieto-Occipital ERD and Prefrontal ERD

Within-group Spearman correlation coefficient was calculated for the ERD of alpha recorded over the parieto-occipital and prefrontal regions during the retrieval phase only. In controls significant correlations emerged between the prefrontal and parieto-occipital measures of ERD of alpha for DMST-WD ($sp = 0.792$, $P < 0.05$) and for ERD of alpha for DMST-ND ($sp = 0.857$, $P < 0.05$). No correlations between the prefrontal and occipito-parietal regions proved significant in the OCD patients.

DISCUSSION

Reduced Alpha Modulation in OCD Is Related to Suppressed Reference Alpha

The task-related ERD of alpha in parieto-occipital region was significantly reduced in patients with OCD and showed significantly less task-related modulation for the DMST-WD task, DMST-ND. The common observation is that cognitively demanding tasks are associated with larger ERD of alpha, in contrast to simple tasks, which require less investment of excitatory and inhibitory resources [Neuper and Pfurtscheller, 2001]. Current data suggests that OCD patients may have less flexibility in the mechanism of adjusting the neural resources to higher task demands. One possible explanation of such inflexibility in the neural networks is that alpha generators including thalamocortical and cortical-cortical loops [Lopes da Silva, 1991; Nunez et al., 2001; Pfurtscheller et al., 1996; Steriade et al., 1990] may be steadily running at a high level of their functional capacity and when the challenge of a more difficult task emerges, there are no spare resources to draw from. The clinical characteristics of a hypercontrolled OCD system [Bucci et al., 2004; van der Wee et al., 2003] involving an ongoing stream of obsessions and mental rituals, fits such an explanation. If this is feasible, the amplitude of reference alpha in OCD, preceding the onset of our DMST tasks, should already show desynchronization due to the intrinsic events, and therefore, show a lower amplitude than in controls. This was indeed what we found. The group differences in reference alpha were significant exclusively for the more difficult task, DMST-WD. Furthermore, the difference between groups resulted from the increased alpha amplitude in controls in preparation for higher task difficulty, whereas the OCD patients' level of reference alpha remained at par (uniform) across tasks. This result

Figure 3.

A: TSE waveforms of α -band oscillations in 122 MEG sensors for one pair of OCD and control subjects. Note the modulation of alpha signals in the occipital and parietal sensors in controls, and the paucity of alpha in central and frontal sensors. **B:** Root-mean-square (RMS) waveforms over the 10 selected occipital sensors for DMST-ND (top) and DMST-WD (bottom). Both the baseline level and the magnitude of event-related modulation are lower in the OCD patient than in the control subject. The latency windows for reference (Ref), encoding (E), retention (Re), and retrieval (Rt) indicated in gray. **C:** Normalized alpha measure waveforms, obtained by dividing the waveforms in (B) by the mean value of the prestimulus baseline.

TABLE I. General variability (V) of the ERD across encoding, retention, and retrieval for OCD patients and control subjects over the parieto-occipital and the prefrontal regions

	DMST-ND				DMST-WD			
	Control	OCD	z	P	Control	OCD	z	P
Prefrontal	2.3 (1.0)	3.1 (1.7)	1.15	0.249	3.9 (4.2)	2.4 (1.8)	2.80	0.779
Parieto-occipital	9.0 (6.7)	4.0 (2.7)	1.82	0.069	11.4 (5.1)	6.5 (3.6)	1.99	0.046*

* $P < 0.05$.

TABLE II. Mean group ERD (event-related alpha desynchronization) measures for the two tasks (DMST-ND and DMST-WD) over prefrontal and parieto-occipital and brain regions

	Control	OCD	<i>z</i>	<i>P</i>
Prefrontal				
DSMT (no distractor)				
Encoding	-2.2 (5.2)	-0.02 (0.03)	0.841	0.400
Retention ND	1.5 (7.3)	-0.04 (2.9)	1.120	0.263
Retrieval	-3.2 (6.6)	-0.07 (6.0)	1.214	0.225
DSMT (with distractor)				
Encoding	-2.4 (5.0)	-0.09 (2.0)	1.82	0.069
Retention WD	-5.7 (4.4)	-0.03 (0.03)	2.03	0.043*
Retrieval	-8.6 (6.4)	-1.9 (5.9)	2.19	0.028*
Parieto-occipital				
DSMT (no distractor)				
Encoding	-19.8 (19.0)	-9.3 (6.7)	841	0.400
Retention ND	-4.7 (7.3)	0.8 (8.9)	0.105	0.917
Retrieval	-32.1(16.6)	-14.1 (5.8)	1.75	0.080
DSMT (with distractor)				
Encoding	-19.44 (16.0)	-10.2 (7.3)	1.12	0.263
Retention WD	-17.8 (23.0)	-9.8 (9.6)	0.70	0.483
Retrieval	-36.3(12.3)	-18.5 (4.7)	2.38	0.017*

*Significant at 0.05 level as in Wilcoxon Signed Ranks Test.

suggests that alpha immediately preceding the onset of a stimulus represents an active status of preparation within relevant networks to process sensory or cognitive information [Angelakis et al., 2003; Foxe et al., 1998; Pfurtscheller, 1992]. Prestimulus alpha, therefore, may serve the role of an indicator of “cognitive readiness,” an ability to prepare

for a task of a particular difficulty [Tolman, 1949]. OCD patients appear to be missing such differential preparatory capacity, as their prestimulus alpha is uniformly suppressed, indicating a persistently desynchronized system, with reduced sensitivity to the subtle requirements of selective modulation.

Figure 4.

A: Variability of the event-related changes in the normalized alpha measure across all three phases, encoding (E), retention (Re), and retrieval (Rt), for DMST-ND (top) and **B:** DMST-WD (bottom) conditions. Note the weak modulation of alpha levels between different task phases in the OCD group.

Reduced Modulation of ERD of Alpha in OCD Is Task-Phase Specific

The high temporal resolution of the MEG technique offered an opportunity to investigate the ERDs within the time frame of independent task phases (encoding, retention, and retrieval). We found that abnormally low parieto-occipital alpha modulation in OCD was specific to the retrieval phase. This may suggest a deficit in the allocation of inhibitory resources during the retrieval phase, which is most demanding for cognitive control. The parieto-occipital alpha did not show group differences in alpha modulation during the encoding and retention phases. The prefrontal alpha, despite low power in general, showed much stronger modulation in controls than in OCD patients in both the retention and the retrieval phases of the DMST-WD. Such abnormal allocation of cognitive resources in OCD has been implicated earlier by neuropsychological studies of episodic memory [Boone et al., 1991; Christensen et al., 1992; Zielinski et al., 1991]. In line with the latter, the first event-related potential (ERP) studies of OCD reported abnormalities that tended to increase with task complexity [Ciesielski et al., 1981; Towey et al., 1994].

MEG recordings from several of the patients and control subjects participating in the present study were included in the earlier report on spatiotemporal patterns of evoked

TABLE III. Mean group measures of reference alpha across two task conditions: DMST-ND and DMST-WD

	DMST-ND				DMST-WD			
	Control	OCD	<i>z</i>	<i>P</i>	Control	OCD	<i>z</i>	<i>P</i>
Prefrontal	33.8 (6.8)	29.7 (4.9)	1.71	0.086	31.9 (5.6)	29.8 (4.4)	1.18	0.237
Parieto-occipital	73.1 (18.8)	54.7 (18.0)	1.57	0.116	87.4 (32.2)	57.7 (18.3)	2.24	0.025*

* $P < 0.05$.

MEG signals [Ciesielski et al., 2005]. The time windows for encoding, retention, and retrieval were identical in both studies, thus the same sample of data was processed in two different ways: the evoked MEG activation in the earlier study and the alpha oscillatory activity in the present one. A distributed MEG source analysis suggested that evoked activity in frontal orbital, insular, and superior temporal sulcus regions was abnormally enhanced in OCD patients, particularly during the retrieval phase [Ciesielski et al., 2005]. It is the same retrieval phase during which the present study showed in the parieto-occipital regions a significant reduction of the power of alpha and the modulation of alpha. It has been suggested that the reduction of alpha power may be inversely proportional to the increased population of cortical neurons recruited into functional networks subserving a task performance [Gevins and Shaffer, 1980; Pfurtscheller and Klimesch, 1992]; the increased evoked MEG activation may derive from the same mechanism of enlarged neural involvement. The task-imposed difficulty for patients with OCD may be a possible explanation. DMST stimuli compete for processing resources with OCD-related obsessions and mental rituals and, therefore, may require engagement of a dynamic compensatory mechanism for effortful inhibitory control. Higher task difficulty has indeed been reported to relate to a monotonic alpha attenuation, and an increase in skill for task performance to alpha enhancement [Gevins et al., 1997].

Three alternative perspectives on the mechanism of ERD reduction could be also considered. First, the mechanism of inhibition has been suggested to be limited in capacity [Bjorklund and Harnishfeger, 1995], and therefore, there are only limited inhibitory resources, which can be allocated to encoding, retention, and retrieval. Some portion of these resources is employed to inhibit intrusive thoughts or other task-irrelevant processing, clinically associated with OCD. This may limit the allocation of inhibitory resources to the final phase of the working memory task, the retrieval phase. Paraphrasing Lavie's theory of attention [de Fockert et al. 2001; Rees et al., 1997], the extent to which our subjects exhaust available inhibitory resources to inhibit the intrusive thoughts determines the extent to which the task-relevant inhibitory control will be employed.

A second perspective relates to inhibition on the neuronal level, which plays a specific role in working memory tasks. Physiological [Funahashi et al., 1989, 1990] and theoretical modeling studies [Dehaene and Changeux, 1997]

have shown that discrete populations of neurons are activated in sequence during the stimulus encoding, retention, and retrieval. Single unit electrophysiological studies suggest that inhibition may be involved in shaping the temporal pattern of activation seen in these neuronal populations and that the temporal profile of activation of prefrontal neurons is organized by inhibitory interactions between cells activated at different phases of the working memory task [Constantinidis et al., 2002; Cohen et al., 1997]. These authors suggest that the feed-forward and feed-back inhibition may be the operational mechanism for sequencing neuronal activity and evoking the transient activation state that occurs during discrete phases of cognitive operations involved in working memory. In such a case the reduced alpha involvement in the retrieval phase of the DMST-WD in OCD patients is a consequence of poor flexibility in switching between feed-forward and feed-back inhibition.

According to the third perspective, the reduced modulation of ERD of alpha in OCD may be related to primary deficits in alpha generation. Alpha, one of the large-scale systemic, rhythmic oscillations in the brain, is generated in the process of interactions between thalamocortical neurons and GABAergic (γ -aminobutyric acid) cells in the thalamic reticular nucleus [Lopes da Silva, 1991; Neupper and Pfurtscheller, 2001; Rinzel et al., 1998]. Deficient GABAergic inhibition may lead to increased glutamate-mediated excitatory activity and to abnormally high cortical activation. Thus, our data supports the view that an abnormal mechanism of alpha generation and modulation, linked to the GABA system, may be among the basic physiological abnormalities underlying disorders with deficits in inhibitory control such as OCD. In line with the above, the pharmacological agents that influence the balance of GABA and glutamate can mitigate the severity of OCD symptoms [Greenberg et al., 2000]. Furthermore, abnormalities in thalamocortical activation have been shown in neuroimaging studies of OCD [Rauch and Baxter, 1998; Rauch et al., 1995; Swedo et al., 1992] and in alpha oscillations in EEG studies [Flor-Henry et al., 1979; Simpson et al., 2000]. Flor-Henry et al. [1979] showed abnormal variability in brain oscillatory activity in temporal and parietal areas of OCD patients and related it to deficits in behavioral inhibitory processes. Abnormal alpha oscillations have also been reported within parietal and frontal regions in patients with phobias [Davidson et al., 2000], and diminished α -band activity has been reported in patients with schizophrenia [Sponheim et al., 2000]. The latter is consistent

with the abnormal morphology [Andreasen et al., 1994] and metabolism [Buchsbaum et al., 1996] of thalamus in schizophrenia. The abnormal pattern of alpha oscillations in schizophrenia and OCD attunes to a hypothesis of commonality between the abnormal biological mechanisms of inhibition in both disorders [Aoyama et al., 2000; Attiullah et al., 2000; Flor-Henry et al., 1979; Matsunaga et al., 2002; Tibbo et al., 2000]. Task-related modulation of alpha oscillations appear a useful measure of normal and disordered attentional and inhibitory mechanisms, and warrants further studies on brain mechanisms in psychopathological disorders, including OCD.

Dissociation Between the Prefrontal and Parieto-Occipital Networks in OCD

Most neuroimaging and lesion studies of working memory networks in healthy human and primates have suggested interactive involvement of the prefrontal orbital, dorsal, inferior parietal, and striatal networks [Bunge et al., 2002; Cohen, 1999; Desimone, 1998; Petrides, 2000]. Consistently, in our control subjects, the attenuation of ERD of prefrontal alpha was found to be concomitant with the attenuation in ERD of parieto-occipital alpha for retrieval phase in both tasks, with and without distractor. These results are consistent with other works suggesting a working memory task-related modulation of posterior alpha and its correlative relationship with prefrontal regions [Foxe et al., 1998; Jensen et al., 2002; Klimesch et al., 1999; Worden et al., 2000]. The lack of such prefrontal-parietal correlations in OCD patients, found in the present study, emphasizes an important role of both cortical regions in the symptomatology of OCD. Future studies on mechanisms underlying abnormal function in the prefrontal-parietal brain networks in OCD may elucidate the increased brain activation in OCD discussed above.

Dissociation Between Abnormal Modulation of ERD of Alpha and Normal Performance in OCD

A general rule is that the larger the prestimulus alpha power, the greater its power reduction (ERD) during stimulus processing and the better the cognitive performance [Gevins and Smith, 2000; Klimesch, 1999; Neubauer and Freudenthaler, 1995]. Furthermore, the progressive increase in working memory task-imposed load should result in steady alpha attenuation [Gevins et al., 1997, 1998]. These rules, based on experiments with healthy adults, do not hold for brains afflicted with OCD. Their prestimulus reference alpha is of low power, the event-related power reduction is small and yet, the cognitive performance of the OCD patients is excellent. In fact in some cases the individual with severe OCD performed better, particularly on the DMST-WD task, than a healthy control.

We did not employ a systematic measure of intrusive thoughts during the MEG session, as such a control may increase the symptom frequency; however, these were

present on and off throughout the testing sessions, as patients reported after testing. A compensatory mechanism may, therefore, be in operation to control for the intrinsic distractors and to secure high performance accuracy, despite the increased demand for inhibitory control in a task with increased task complexity. The normal performance on the visual-spatial DMST is consistent with a normal (or near normal) performance on the Wisconsin Card Sorting test, Word-Color Stroop test, and Verbal Fluency test in line with some studies [Abbruzzese et al., 1995; Boone et al., 1991; Gross-Isseroff et al., 1996; Martin et al., 1995; Zielinski et al., 1991], but not others, which show deficits in shifting sets, perseverations and visual-spatial organization [Head et al., 1989; Malloy 1987; Savage et al., 1999]. Purcell et al. [1998] observed that difficulties may be mitigated by clear external cues and may be increased if task performance is guided mostly by internal representations. The present task with clear external guidance evoked good performance, but little ERD of alpha in all patients. A similar dissociation between high performance and abnormal ERPs has been reported in a study of selective auditory attention in OCD [Towey et al., 1994]. A lack of behavioral differences between OCD and controls (both groups performed close to 100% accuracy) was accompanied in OCD by an abnormally enlarged amplitude of frontal processing negativity [negative deflection 200 ms post stimulus, associated with directed attention; Näätänen and Picton, 1987] and by the reduced parietal P300 component [related to stimulus significance; Donchin and Coles, 1988]. P300 was abnormally enhanced to task-irrelevant stimuli. The authors replicated these findings in yet another study with more difficult tasks [Towey et al., 1990], and suggested that a compensatory mechanism may be in operation in OCD patients performing attentional tasks [Towey et al., 1994]. This is one possible interpretation for our findings.

The current three major findings of processing abnormality in OCD patients, including the suppressed prestimulus alpha, weak event-related alpha desynchronization, and no evidence of normal interactive communications between the prefrontal and parieto-occipital networks, are in sharp contrast to their high and normal accuracy of performance. Consistent with an assumption of involvement of an additional compensatory network is the trend to longer response times (RTs) in OCD patients. On the neuronal level, the prolonged RTs may be related to effortful additional processing to overcome inhibitory failures. On the other hand, it may converge with a global decrease in white matter volumes reported in patients with OCD [Jenike et al., 1996; Rosenberg and Keshavan, 1998], and be considered as a biological signature of OCD. These hypotheses remain to be tested. In conclusion, the findings of studies on biological mechanisms of OCD, including the current one, bring to mind, more than any other disorder, the philosophical view offered by one of the advanced thinkers of the 20th century, neurologist Kurt Goldstein [1925], that clinical symptoms are the attempted solutions for the organism, not the signs of failure.

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