Neuroscience Letters 496 (2011) 181–185

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Prestimulus top-down reflection of obsessive-compulsive disorder in EEG frontal theta and occipital alpha oscillations

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ARTICLE INFO

Article history:
Received 11 December 2010
Received in revised form 23 March 2011
Accepted 9 April 2011

Keywords:
Alpha activity
Inhibition
Obsessive-compulsive disorder
Theta activity
Top-down processing

ABSTRACT

It has recently been reported that prestimulus electroencephalogram (EEG) frontal theta and occipital alpha oscillations of healthy controls were modulated by the type of upcoming tasks, reflecting prestimulus top-down preparation. The present study explored the differences in dynamics of frontal theta and occipital alpha activities between obsessive-compulsive disorder (OCD) patients and healthy participants in terms of reflection of prestimulus top-down regulation. EEGs were recorded from 16 OCD patients and 16 healthy controls using a color and a shape discrimination task. The power and time course of oscillatory activity were calculated by convolving the EEG signals with Morlet wavelets. Although OCD patients yielded significantly lower total alpha and total theta power results than the normal controls, they demonstrated that significantly higher total alpha and total theta power preceded the difficult task (shape-task) as compared to the easy task (color-task). Furthermore, the frontal region, where OCD patients usually revealed abnormalities, showed significant differences in the prestimulus total theta power between the normal and OCD groups. Taken together, frontal theta and occipital alpha oscillations seem to be potent electrophysiological correlates reflecting impairment in the prestimulus top-down processing of OCD patients.

Mental readiness is advantageous when accomplishing perceptual identification or preparing to perform upcoming tasks efficiently. Accordingly, a cognitive intention embedded in top-down processing may precede the occurrence of events or stimuli and then guide bottom-up sensory processing. It has recently been observed that prestimulus frontal theta and occipital alpha activities of normal participants were modulated by the type of upcoming color-shape discrimination tasks, and these findings were interpreted as reflecting preparatory top-down mental states prior to stimulus onset [20]. In this experimental paradigm, participants might have a task-oriented prestimulus mental state ready in order to perform a subsequent task.

Given these observations from normal controls, if the same experimental paradigm is applied to patients with psychiatric or neurological disorders (particularly with dysfunctions in attention and inhibitory control), the findings will provide more information for the functional significance of prestimulus frontal theta and occipital alpha activities in task-related modulation. It has been suggested that deficits in the ability to selectively attend to relevant information while concurrently suppressing competing irrelevant information is a central feature of obsessive-compulsive disorder (OCD) [6]. The impairment of inhibitory control in OCD patients might be reflected in abnormal cognitive functions [1], which seem to be due to reduced attentional selectivity between task-relevant and task-irrelevant details [10].

All of these points led us to investigate the functional significance of prestimulus frontal theta and occipital alpha activities of OCD in terms of top-down inhibitory control. We hypothesised that OCD patients' impaired inhibitory regulation of task-irrelevant information might be reflected in the abnormal modulation of prestimulus alpha and theta activities. To test this hypothesis, we replicated the color-shape discrimination task used in previous studies [19,20] on OCD patients and compared the results with those of controls.

Sixteen normal participants (9 females, mean age 23) and 16 OCD patients (4 females, mean age 24) participated in this study under the ethics guidelines established by the Institutional Review Board and the Declaration of Helsinki (World Medical Association, 1964). All participants had normal or corrected-to-normal vision, and none of them were color-blind (examined by the *Ishihara* color

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doi:10.1016/j.neulet.2011.04.018

test). All OCD patients met the Diagnostic and Statistical Manual (DSM-IV) criteria for OCD, as determined by the Structured Clinical Interview for the DSM-IV (SCID) [7]. Obsessive-compulsive symptoms and their severity were evaluated and scored by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) [8]. The severity of depressive and anxiety symptoms in OCD patients was scored by the Montgomery-Asperg Depression Rating Scale (MADRS) [21] and the Hamilton Anxiety Rating Scale (HARS) [9], respectively. In addition, we used the Wisconsin Card Sorting Test (WCST) to evaluate executive function [12]. Eleven OCD patients (68.75%) were taking only selective serotonin reuptake inhibitors (SSRIs), and the remaining five patients (31.25%) were taking a combination of SSRIs and low-dose benzodiazepines.

This study employed the same experimental paradigm as the previous studies by Min et al. [19,20]. Pairs of colored figures randomly drawn from a set of red or green circles or squares were used as stimuli. Stimuli were presented for 500 ms. Two colored figures consisting of a stimulus set were presented side-by-side on a light-gray background at an eccentricity of a 3° visual angle, and each colored figure of a stimulus set spanned a 4° visual angle. All types of stimuli appeared pseudo-randomly with equal probability. Each stimulus presentation was followed by variable inter-stimulus intervals randomly ranging from 1500 to 2500 ms. Participants were asked to remain centrally fixated and instructed to press a button with the index finger of one hand if the target feature of the task ('color' in the color task and 'shape' in the shape task) was the same and to press a button with the other hand if it was not. Participants were asked to press the button as quickly as possible. Response hands and the order of tasks were counterbalanced across participants. The experiment consisted of 384 trials for each task. Only trials with correct responses were further analyzed.

The EEG was recorded using a GRASS 15A54 amplifier (Grass Technologies, USA) with 21 sintered Au/Ag-electrodes. The electrodes are located according to the international 10-20 system. We also placed an electrode on each mastoid for linked reference and a ground electrode at the nasion. Eye movement activity was monitored with two additional electrodes placed supra-orbitally to both eyes and was referenced to the linked mastoids. Electrode impedances were kept below 10 kΩ prior to data acquisition. The EEG was sampled at 1000 Hz. Data were epoched from 1000 ms prestimulus to 1000 ms poststimulus. Data epochs containing eye-movements or other artifacts (maximum amplitude ±70 μV or electrode drifts) were rejected. One participant from the control group and three from the OCD group had to be excluded from further analyses because of poor data quality.

The power of oscillatory activity was investigated by convolving the EEG signals with Morlet wavelets [13]. The wavelet transform was performed for each individual trial, and the absolute values of the resulting transforms were averaged. This measure of signal amplitude in single trials reflects the *total activity* for a certain frequency range. However, to compute the *evoked activity*, which is, by definition, phase-locked to the stimulus, the wavelet transform was applied to the averaged evoked potential. In the present study, we computed the power (μV^2) of oscillatory activity.

Since the neural network around the frontal lobe is crucial to the cognitive processes of OCD patients [18], and in the present study the prestimulus occipital alpha and frontal theta power were most pronounced in normal controls, we selected two electrodes representing frontal and occipital brain areas (i.e. Fz and Oz, respectively) for further analysis. In the present study, we confined alpha activity to the frequency range from 8 to 13 Hz and theta activity to the frequency range from 4 to 7 Hz. For the evoked alpha and theta power, we measured the maximum power at the two electrodes in the time window from 150 to 350 ms poststimulus for alpha and from 200 to 400 ms poststimulus for theta. All of these time windows were selected on the basis of their grand-averages and individual variations. We performed a baseline correction from 250 to 50 ms prestimulus on the evoked activity. For the prestimulus total power of these activities, we computed mean power in the time window from 300 to 50 ms prior to stimulus onset in each frequency range. No baseline correction was applied to the total power since the total alpha power in a prestimulus period would vanish after baseline correction.

Reaction times and accuracy (error rates) of task-performance were also measured for the behavioral analysis. Reaction times were collected within their individual 95% confidence interval. These behavioral measures as well as the electrophysiological activity were analyzed with a repeated-measures analysis of variance (ANOVA) comprising a within-subjects factor labeled as 'task' ('color-task' versus 'shape-task') and a between-subjects factor labeled as 'group' ('control' versus 'OCD'). In addition to these factors, we employed an additional within-subjects factor labeled as 'electrode' ('Fz' versus 'Oz') to compare the electrophysiological activity between the frontal and occipital brain areas. The Greenhouse-Geisser correction was used where appropriate. The *post hoc* comparison within each condition was evaluated by a one-way ANOVA with a 'group' factor ('control' versus 'OCD').

Within the data for OCD patients, we conducted additional correlation analyses between electrophysiological measures and psychiatric indices, including OC, depression, anxiety symptoms and executive functions. The paper-and-pencil YBOCS yielded 'obsessions (YBOCS-OBS)', 'compulsions (YBOCS-CMP)' and 'total (YBOCS)' scores. Three variables were also employed from the WCST: 'category', 'perseverative response' and 'perseverative error'. For correlation analyses, we used a two-tailed Pearson's correlation.

We observed shorter reaction times for the OCD patients than normal controls ($F(1,26) = 6.336$, $p < 0.05$; control: 506.9 ms, OCD: 428.2 ms). Although there was no significant main effect of 'task' ($F(1,26) = 0.001$, *n.s.*), there was a significant interaction in the reaction times ('task' × 'group': $F(1,26) = 6.725$, $p < 0.05$). Subsequent tests revealed that this effect was significant in the shape task ($F(1,26) = 9.026$, $p < 0.01$; control: 527.7 ms, OCD: 408.0 ms) but not in the color task ($F(1,26) = 1.645$, *n.s.*). We found that the color task performance resulted in a significantly higher accuracy than the shape task performance ($F(1,26) = 30.028$, $p < 0.001$; color-task: 93.4%, shape-task: 71.2%). However, there was no significant main effect of 'group' ($F(1,26) = 2.679$, *n.s.*) and no significant interaction in accuracy ('task' × 'group': $F(1,26) = 0.003$, *n.s.*).

The evoked alpha power at the electrode Oz correlated negatively with the obsession subscale (YBOCS-OBS) during the shape task ($r = -0.58$, $p < 0.05$; cf. Fig. 1A) and correlated positively with the 'perseverative response' of the WCST during the color task ($r = 0.68$, $p < 0.05$). In addition, the evoked theta power at the electrode Oz during both tasks showed strong positive correlations with the 'perseverative response' of the WCST (color-task: $r = 0.71$, $p < 0.05$, shape-task: $r = 0.62$, $p < 0.05$; cf. Fig. 1B) and correlated negatively with the 'category' score of the WCST during the color task ($r = -0.63$, $p < 0.05$).

We observed a marginal significance that the color task led to stronger evoked alpha power than the shape task ($F(1,26) = 3.661$, $p = 0.067$; color-task: 2.1 μV^2, shape-task: 1.8 μV^2). We found that the electrode Fz yielded significantly higher evoked theta activity than the electrode Oz ($F(1,26) = 6.599$, $p < 0.05$; Fz: 4.4 μV^2, Oz: 1.8 μV^2).

OCD patients had significantly lower prestimulus total alpha power than healthy controls ($F(1,26) = 9.096$, $p < 0.01$; control: 19.9 μV^2, OCD: 4.6 μV^2). We also observed a significant main effect of 'task' ($F(1,26) = 4.914$, $p < 0.05$) with a higher prestimulus alpha power for the shape task (color-task: 9.5 μV^2, shape-task: 16.1 μV^2). The prestimulus alpha power was most pronounced around the occipital region in the control group, whereas the pres-

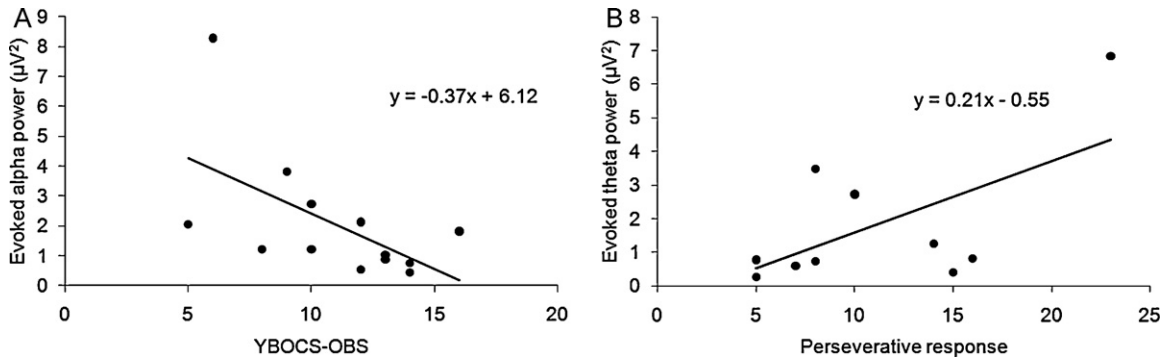

Fig. 1. Correlations of alpha and theta power with psychiatric indices. Relationship (A) between the evoked alpha power at the electrode Oz and the obsession subscale (YBOCS-OBS) and (B) between the evoked theta power at the electrode Oz and the 'perseverative response' of the WCST during the shape task in OCD patients. The *x*-axis indicates YBOCS-OBS scores in (A) and the perseverative response of the WCST in (B), and the *y*-axis indicates evoked alpha power (μV^2) in (A) and evoked theta power (μV^2) in (B). Linear fitting lines are also displayed with linear regression equations.

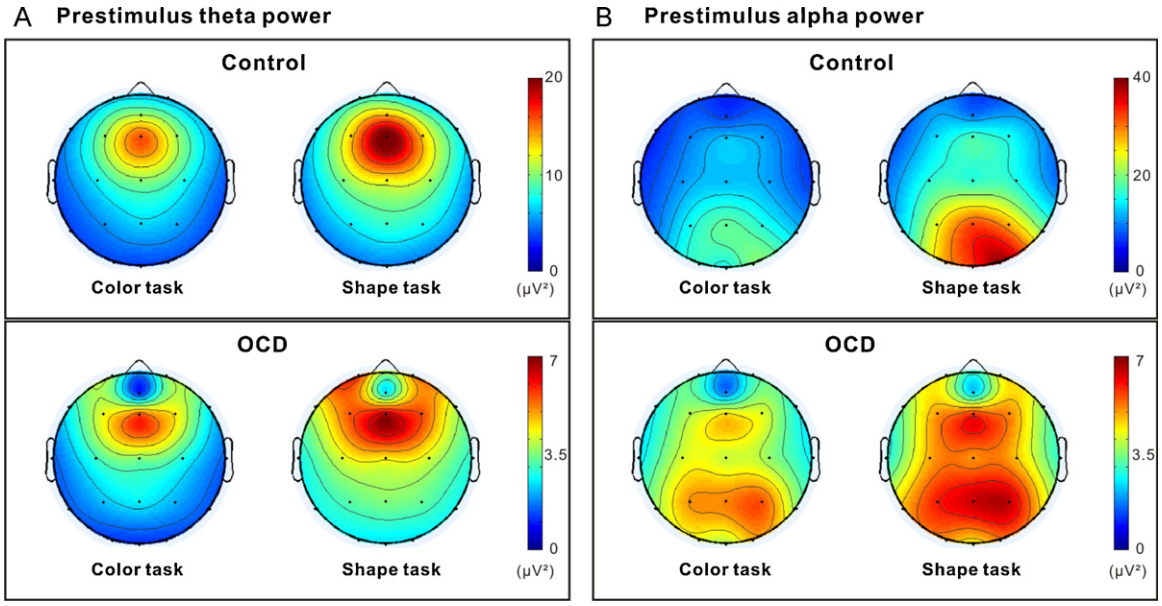

Fig. 2. Grand-averaged topographies. (A) Prestimulus theta and (B) prestimulus alpha power of both tasks in both groups. These topographical distributions were computed by averaging the mean power at participants' individual alpha and theta frequencies over the time window from 300 to 50 ms prestimulus. Within this time window, individual alpha and theta frequencies were obtained from the frequencies showing the maximal power of each task in the alpha band on the electrode Oz and in the theta band on the electrode Fz, respectively. All views are from the vertex, and the upside is nasal. Color bars indicate scales of the power (μV^2) of oscillatory activity.

timulus alpha power seemed to be shifted to the parietal region in OCD patients (cf. Fig. 2).

Normal controls showed significantly higher prestimulus total theta power than OCD patients ($F(1,26) = 8.846$, $p < 0.01$; control: 11.3 μV^2, OCD: 3.9 μV^2). We also found that the shape task was preceded by significantly higher prestimulus total theta power than the color task ($F(1,26) = 4.550$, $p < 0.05$; color-task: 6.7 μV^2, shape-task: 9.0 μV^2). Moreover, we found that 'electrode' had a significant effect ($F(1,26) = 19.108$, $p < 0.001$), indicating that the electrode Fz showed significantly higher prestimulus total theta power than the electrode Oz (Fz: 12.7 μV^2, Oz: 3.0 μV^2). In addition, we identified a significant interaction in the prestimulus total theta power ('electrode' × 'group'; $F(1,26) = 5.468$, $p < 0.05$). The *post hoc* tests demonstrated that normal participants showed more prominent prestimulus total theta power than OCD patients, particularly in the electrode Fz ($F(1,26) = 7.392$, $p < 0.05$; control: 18.5 μV^2, OCD: 6.1 μV^2) when compared to the electrode Oz ($F(1,26) = 7.943$, $p < 0.01$; control: 4.1 μV^2, OCD: 1.7 μV^2). As shown in Fig. 2, OCD patients showed different frontal topographies of the prestimulus theta power from normal controls, and a tentative frontal source dipole seemed to be rotated as compared to that of normal controls.

We observed a significantly lower prestimulus total alpha power in OCD patients. Since the prestimulus alpha in OCD also remained uniformly suppressed irrespective of tasks in the present study, OCD patients seem to characteristically show a persistent desynchronization of alpha activity before stimulus onset. A magnetoencephalography (MEG) study of OCD patients consistently showed reduced prestimulus alpha activity during visual working memory tasks [3].

A lower prestimulus alpha was observed in participants that have difficulty in suppressing distracters [5]. The prestimulus alpha may serve the role of an indicator of 'mental readiness' when preparing for an upcoming task [19]. Event-related synchronization in the alpha band has been observed during task-performance either under such conditions where participants have to withhold task-relevant information or over the brain regions that are task-irrelevant [15]. It has subsequently been proposed that alpha synchronization might reflect the active suppression of task-irrelevant cortical processing [17]. Since OCD patients are habitually preoccupied with task-irrelevant details and have an intrinsic deficit in their ability to control an ongoing stream of obsessions and mental rituals [2], their mental capacity to involve

ongoing processing seems to be limited when their mental load is highly imposed upon [3]. Taken together, such an impaired top-down inhibitory control of OCD patients may be reflected in abnormally reduced prestimulus alpha activity.

As compared to the healthy control group, the OCD patients also yielded significantly lower prestimulus total theta power, which was most pronounced at the electrode Fz (cf. Fig. 2). Since it has been reported that females demonstrate higher theta power than males [16], one might possibly suspect that the effects of significant reduction in the prestimulus frontal theta power of the OCD group come from come from the presence of less number of OCD female patients as compared to healthy female participants. To validate the present effect, we performed an additional analysis to clarify the group effect within each gender separately. The results show that the same tendency was consistently obtained although we reanalyzed the data independent of gender differences (Min et al., unpublished observations). Therefore, one can exclude a possibility that prestimulus effects in the frontal theta power are confounded by the portion of gender differences.

In spite of many unknowns, frontal theta activity has been generally reported to increase in tasks requiring attention or working memory [27] and has been thought to reflect inhibitory functions [30]. Wang et al. [30] suggested that theta activity, particularly from the anterior cingulate cortex, may reflect active inhibition. They observed transient phase locking of theta activity in relation to active inhibition in superficial cingulated layers. Since OCD patients usually have deficits in inhibitory regulation [25] and show frontal dysfunction [24], it seems conceivable that OCD patients would have abnormally low frontal theta power. In the present study, participants had to keep in mind throughout the whole experiment which feature (i.e. color or shape) of the stimuli was task-relevant and should be processed while simultaneously screening out the remaining task-irrelevant feature. Therefore, frontal dysfunction of OCD patients in such selective and controlled mental alertness for subsequent task-performance might be reflected in significantly reduced prestimulus frontal theta power, irrespective of whether it would be interpreted in terms of either enhanced attention to task-relevant processing or increased suppression of task-irrelevant processing.

This interpretation seems in accordance with the viewpoint of a 'default mode network' that is commonly deactivated in goal-oriented cognitive tasks [23]. Perseveration, impulsivity, distractibility, obsessive visualization and mental rituals are typically observed in OCD [26,29], and OCD patients demonstrate less functional connectivity within the default mode network in the anterior cingulate cortex and middle frontal gyrus, as compared with healthy individuals [14]. In addition, the brain's ongoing intrinsic activity is principally involved in the retention of information needed for responding to environmental demands [23], and the activity of the default mode network may be progressively suppressed as a task increases the mental load (e.g. demands more task-relevant attention) [28]. During a mental loading task such as a Sternberg working memory task, the enhancement of frontal theta activity was observed in the default mode areas [27]. Presumably, the abnormal reduction of the frontal theta power of OCD patients can be expected to some extent, in the sense of general impairment of self-referenced or internally generated thoughts in OCD patients, owing to their abnormal default mode networks.

Since we found a negative correlation between the evoked alpha activity and the obsession subscale (YBOCS-OBS) at the electrode Oz (cf. Fig. 1A), it is likely that the posterior brain region is engaged in obsessive behavior. This negative correlation is understandable in the sense that severing an obsessive symptom may be associated with strengthened abnormal inhibitory control and thus a greater persistence against event-related changes, which may gradually hinder evoked alpha activity from flexible modulation. We also observed significant correlations of the WCST variables with evoked alpha and theta activities of OCD patients at the electrode Oz (cf. Fig. 1B). Although the WCST is principally administered to assess dorsolateral prefrontal functioning [11], a variety of brain areas, including the occipital lobes, are also involved in the performance of the card sorting test [22]. Since it has been proposed that alpha activity reflects inhibitory function [17], the positive correlation between the 'perseverative response' of the WCST and occipital alpha activity might indicate a significant role of the occipital lobe during executive inhibitory processing.

A lack of performance-accuracy differences between OCD patients and healthy controls was observed. Furthermore, as compared to the color task (easy task), the OCD patients yielded shorter reaction times in the shape task (difficult task) than the normal participants without a significant difference in accuracy. The OCD patients' higher performance provided challengeable evidence against their particular deficiency in attentional inhibitory control. Presumably, they utilize other neural resources applicable to control in various contexts in spite of their psychiatric impairment. We also found a significant interaction between the 'group' and 'electrode' factors in the total theta power. This finding indicates that the difference between frontal and occipital theta power was dependent on whether the participants were psychiatrically normal. As supposed from the topographical distributions, it seems that there may be modified dynamics in the neural networks of OCD patients to accomplish higher task-performance. Presumably, since OCD patients show hyperactivation of the frontal lobe [24], they may employ an adaptive compensatory frontal neural network. This view is in line with the interpretations of recent observations that the anterior N200 component elicited by correct responses increased abnormally during the Stroop task in OCD patients [4].

We observed that the shape task yielded significantly higher prestimulus alpha and theta power than the color task, irrespective of whether participants were healthy controls or OCD patients. Therefore, task-related prestimulus modulations of frontal theta and occipital alpha activities are still embodied in OCD patients. This is conceivable in the sense that although OCD individuals have deficits in inhibitory control, they still have the ability to prepare a mentally prepared state for upcoming tasks, possibly using the aforementioned modified neural networks. Such prestimulus active 'mental-readiness (or redirection of attention)' may efficiently influence and improve upcoming task-performance even in OCD patients. However, since the sample size of the present study was not considerably large enough, we are reluctant to generalize such interpretations based only on the present observations. In line with our observations, further developments and refinements of some cognitive tasks that can effectively evaluate central features of OCD symptoms, along with their simultaneous electrophysiological correlations that can parametrically reflect any spectral differences in OCD features, these will ultimately enable us to increase diagnosis-accuracy of OCD symptoms by cooperating with other established diagnostic methods. It may also contribute to our ability to detect a high risk of developing symptoms in advance of their full manifestation.

Acknowledgements

This research was supported by the Original Technology Research Program for Brain Science through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (MEST) (No. 20100018839) to HJP.

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