Introduction

Obsessive–compulsive disorder (OCD) is considered as a manifestation of recurrent cortico-subcortical processing deficit. Among the described five functional cortico-striato-thalamo-cortical loops (Affifi and Bergman, 2005), imaging studies in OCD showed abnormalities in related structures such as orbito-frontal (OF), limbic and dorso-lateral prefrontal (DLPF) loop pathways (Saxena et al., 1999; Alptekin et al., 2001; van den Heuvel et al., 2005; Russell et al., 2003; Valente et al., 2005; Fitzgerald et al., 2000; Cannistraro et al., 2004).

The integrity of thalamo-cortical and cortico-cortical circuits may be investigated by means of the analysis of EEG oscillatory activity, mainly EEG power and coherence.

Several studies have investigated EEG power in OCD (John and Prichep, 2006), with conflicting results, reporting excess alpha and beta activity in the central channels (Prichep et al., 1993), increased delta and decreased alpha (Locatelli et al., 1996; Bucci et al., 2004) or decrease of both delta and beta (Kuskowski et al., 1993). Recent functional imaging techniques based on quantitative EEG allow 3-D presentation of EEG current source densities (low-resolution electromagnetic tomography—LORETA, Variable resolution electromagnetic tomography—VARETA). Using these methods, increased beta in the region of cingulate gyrus was found in OCD compared with controls (Sherlin and Congedo, 2005). Increased alpha activity in the thalamus, corpus striatum, orbito-frontal and temporoparietal regions has been reported in OCD patients responders to SSRI (Bolwig et al., 2007), while a lower frontal beta activity was associated with a better treatment response (Fontenelle et al., 2006). One of the main confounding factors when interpreting resting EEG analysis in neuropsychiatric disorders is the effect of psychoactive drug treatment on EEG. In fact, one study was not restricted to drug-free patients (Sherlin and Congedo, 2005) and the other only included patients responders to SSRI (Bolwig et al., 2007).

Whether changes in EEG power are mainly a result of changes in cortical arousal or linked also with changes in deeper structures is still a matter of debate. Some authors have suggested that slow (delta and theta) oscillations are EEG correlates of processes influenced by subcortical activity, whereas fast (alpha and beta) oscillations are generated within cortical networks (Robinson, 1999; Knyazev and Slodobskaya, 2003; Neuper and Pfurtscheller, 2001, View Record in Scopus). In accordance with this view, it has

Dysfunctional brain circuitry in obsessive–compulsive disorder: Source and coherence analysis of EEG rhythms

Svetla Velikova a, Marco Locatelli b, Chiara Insacco b, Enrico Smeraldi b, Giancarlo Comi a, Letizia Leocani a,⁎

a Department of Neurology, Clinical Neurophysiology, Neuroperehabilitation, Institute of Experimental Neurology, IRCCS University Hospital San Raffaele, Via Olgettina 60, 20132 Milan, Italy
b Department of Neuropsychiatric Sciences, IRCCS University Hospital San Raffaele, San Raffaele Turro, Via Stamira d’Ancona 20, Milan, Italy

⁎ Corresponding author. Department of Clinical Neurophysiology, Hosp. San Raffaele, Via Olgettina 60, 20132 Milan, Fax: +39 2 2643 3085.
E-mail address: letizia.leocani@hsr.it (L. Leocani).

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been suggested that coupling between slow and fast frequencies could provide information about subcortical–cortical communication (Knyazev and Slobodskaya, 2003). This hypothesis might be supported by the findings of a link between brain oscillations and behaviour, as well as between brain oscillations and biochemical changes. Moreover, substances known to change cortico-subcortical communication lead also to changes in the coupling of EEG bands (Schutter and van Honk, 2004; van Peer et al., 2008).

EEG coherence is a measure for phase consistency (as a function of frequency) between two EEG signals. It has been considered as an indicator of functional cortico-cortical connections (Thatcher et al., 1986) and reflects the competition between functional segregation and integration between specific brain regions (Nunez et al., 1999). A previous study on EEG coherence in OCD reported increased fronto-occipital theta coherence in the right hemisphere (Desarkar et al., 2007).

It may be hypothesized that the combined rather than separate use of power and coherence analyses might allow a more complex exploration of structures and oscillatory networks playing a role in the pathophysiology of OCD. Moreover, it is also important to exclude that some EEG changes are related to drug treatment and not to the presence of OCD per se. The aim of the present study was to search for neurophysiological correlates of cortico-subcortical processing, using analysis of coherence and power (current source density and coupling between frequency bands) in drug naïve OCD patients. The novel elements of the present work in comparison with previous LORETA studies concern: (i) the selection of patients (a relatively large group without co-morbid diseases and never medicated for OCD symptoms); (ii) combination of LORETA method with two other QEEG approaches (EEG coherence analysis and coupling of EEG rhythms).

Methods

Subjects

Data from 37 patients with OCD (male 15, mean age 31 ± 10.5) were analyzed and compared with data from 37 age and sex matched control healthy subjects (mean age 31.5 ± 10.5). The diagnosis of OCD was made by a certified psychiatrist, according to DSM IV (American Psychiatric Association, 1994). The selection of participated patients was made following next steps:

The Structured Clinical Interview for DSM IV was used to determine axis I diagnosis. Including criteria was primary diagnosis of OCD according DSM IV. Excluding criteria were: (i) co-morbid DSM IV axis I disorders; (ii) specific medical or neurological conditions that would interfere with evaluation the results of the study (Tourette syndrome, hyperactivity, organic mental diseases, mental retardation, history of psychosurgery, history of epilepsy); (iii) previous or current psychoactive medication. Therefore, all patients were naive to medications and underwent EEG recording before starting any psychiatric treatment. Their scoring on the Yale-Brown Obsessive Compulsive Scale (Goodman et al., 1989) was: mean total score = 27.8, SD = 4.7, range = 20–40; mean obsessions subscale score = 14.4, SD = 2.2, range = 9–20; and mean compulsions subscale score = 13.2 SD = 3.7, range = 2–20). After complete description of the study to the subjects, written informed consent was obtained to participate in the study, which was approved by the local ethics committee.

EEG recording

Twenty-nine channel EEG with binaural reference was recorded with scalp electrodes mounted on an elastic cap (Electro-cap International, Eaton, OH) according to the 10–20 international system of electrode placement, with additional electrodes placed along the longitudinal axis. The EEG signal was amplified (Synamps Amplifiers, Neuroscan Inc., Herndon, VA), filtered (DC to 50 Hz), and digitized (250 Hz sampling frequency). Bipolar recordings of the electrooculogram and of the EMG from the extensor pollicis brevis (EPB) muscle were obtained to detect eye movement or failure to relax. The data were obtained from a period of 5 min at rest, with the eyes closed.

EEG analysis

During off-line analysis, EEG segments with artifacts were removed by visual inspection of the raw data. At least 70 artifact-free (after rejection of epochs with eye movement, other artifacts or failure in muscle relaxation in the EMG) 2-s epochs were obtained for each subject. The average absolute power and coherence with steps of 1 Hz for each of the 29 monopolar derivations was computed. Then, power and coherence values were averaged for the classical frequency bands: delta (1–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta 1 (13–18 Hz), beta 2 (19–21 Hz) and beta 3 (22–30 Hz) according to previous EEG studies using LORETA (Iotani et al., 2001; Gianotti et al., 2007), since each band provides information on different cortico-cortical and cortico-subcortical circuits (Robinson, 1999; Knyazev and Slobodskaya, 2003; Teipel et al., 2009).

LORETA analysis

Power data from each frequency band were used for calculation of current source density using standard LORETA procedure (Pascual-Marqui et al., 1994). Results were computed for the cortical areas of the Talairach probability atlas (Talairach and Tournoux, 1988), with a spatial resolution of 7 mm (2394 voxels). According to LORETA method, statistical group comparison was performed using non-parametric statistical analysis (unpaired t-test).

Coherence analysis

For each band, inter-hemispheric and intra-hemispheric coherence were computed from a total of 16 selected electrode pairs. Intra-hemispheric coherence was calculated from 8 electrode pairs, distributed in 4 regions: frontal (left: FP1-F3; right: FP2-F4), centro-parietal (left: C3-P3; right: C4-P4), temporal (left: T3-T5; right: T4-T6) and occipital (left: F3-O1; right: F4-O2). For calculation of inter-hemispheric coherence, other 8 electrode pairs, distributed also in frontal (FP1–FP2, F3–F4, F7–F8), centro-parietal (C3–C4, P3–P4), temporal (T3–T4, T5–T6) and occipital (O1–O2) regions were used. For coherence data, mixed Factorial ANOVA designed for repeated measures (1st level—two factors: intra-hemispheric/inter-hemispheric; 2nd level—4 regions and 3rd level—6 bands) was applied for detection of group effects, with post-hoc comparisons using unpaired t-test.

Coupling between slow and fast rhythms

In order to reduce the number of variables, power in beta frequencies was averaged within the 13–30 Hz interval. Coupling between slow (delta and theta) and fast (beta) frequencies was calculated for each group using the following parameters:

- delta/beta and theta/beta power ratio on Fz
- ratio values were used for intergroup comparison (independent samples t-test, two-tailed)
- power values in low (delta, theta) and high (beta) frequencies, measured on Fz were tested for within-group correlation between them (Spearman's correlation test) according to previously reported methods (Schutter and van Honk, 2004).

Results

Source analysis—LORETA

At source analysis of brain rhythms using LORETA, OCD showed significant increase of current source density compared with
normal control group for the delta in Insula (BA 13), and for the beta 1, beta 2 and beta 3 frequency bands in supplementary motor area (BA 6), dorsolateral prefrontal cortex (BA 9), frontopolar cortex (BA 10), anterior cingulated cortex (BA 24), frontal eye field (BA 8) (Fig. 1, Table 1).

EEG-coherence

Comparison between OCD and controls using repeated measures ANOVA showed a significant group effect ($F(5;68) = 5.534; p = 0.000$); this effect was present for inter-hemispheric ($F(15;58) = 22.262;$

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**Fig. 1.** LORETA images from non-parametric $T$-statistic, shown in 3 orthogonal brain slices (horizontal, sagittal, coronal). Red color represents significant ($p<0.05$) increased current density in patients with OCD ($n=37$), compared with control subjects ($n=37$). Increased current density was found in: delta-BA 13 (R); beta 1 -BA 6 (BL), BA 9 (L), BA 10 (R); beta 2: BA9 (L), BA 24 (BL); beta 3: BA9 (L), BA 6 (R), BA 8 (R), BA 24 (BL). Legend: BA—Brodmann area, L—left, R—right, BL—bilateral.
Several subcortical structures including brain-stem (Saper, 1982; Bioelectrical landmarks of anxiety. Increased beta oscillations have been observed in normal subjects during states of induced anxiety as compared with relaxation (Isotani et al., 2001), as well as in anxiety disorders (Sachs et al., 2004). The origin of spontaneous resting beta rhythm is not well understood, although it appears to be modulated by the GABA-ergic system (Jensen et al., 2005).

Several brain regions identified as dysfunctional in the present study have been previously indicated in other studies on OCD.

**Coupling between slow and fast rhythms**

Compared with healthy controls, OCD had a significantly reduced delta/beta \((r = 2.274; \text{p}=0.026)\) and theta/beta \((r = 2.477; \text{p}=0.016)\) ratio.

In control subjects there was a correlation between power in the low (delta and theta) and high (beta) frequencies: delta/beta \((r_1 = 0.350; p = 0.034); \) theta/beta \((r_2 = 0.500; p = 0.002)\); Spearman rank correlation. In OCD, no significant delta/beta and theta/beta correlation was found.

**Discussion**

**Source analysis—LORETA**

In the present study, comparison of resting EEG activity using e/ sLORETA between OCD, controls and showed significant increase of current source density for delta and beta band. The results are consistent with findings from Locatelli et al. (1996) on delta and with other EEG studies (Prichep et al., 1993; Sherlin and Congedo, 2005) reporting beta increase in OCD patients. A lower frontal beta activity has also been associated with a better future response to SSRI treatment (Fontenelle et al., 2006). The decision-making deficit in OCD has been emphasized as one of its fundamental feature (Cavedini et al., 2006). A functional study on pediatric OCD reported dysfunction in the left DLPFC (Russell et al., 2003).

**Brodmann area 10 (frontopolar area) plays a role in episodic memory retrieval and working memory. Disturbance in working memory has been found to be a trait deficit in OCD (Bannon et al., 2006).** Frontopolar cortex has been identified in a PET study as one of the regions with dysfunctional changes in drug-naive OCD (Perani et al., 2008). In healthy subjects increased current source density in BA 10 (in beta 2 band) has been established when states of anxiety and relaxation were compared (Isotani et al., 2001). On the basis of these findings we could hypothesize that increased current source density in the frontopolar area in OCD patients is linked with their higher level of anxiety, compared with control subjects. Involvement of the BA 10 was described in a pharmaco-LORETA study in OCD, where a lower activity in BA 10 was identified as one of the factors predicting response to antidepressant treatment (Fontenelle et al., 2006).

**Brodmann area 8 includes frontal eye fields and plays a role in the control of saccadic eye movements—one of the often-reported abnormalities in OCD patients (van der Wee et al., 2006).**

Among other features on complex motor control, the *supplementary motor area (BA 6)* is involved in response inhibition (Picton et al., 2007), in which insufficiency is considered as one of the basic characteristic of OCD (Leocani et al., 2001; Kim et al., 2007).

**Anterior cingular cortex—ACC (BA 24)** takes part in a variety of cognitive processes, including problem solving, action planning, conflict monitoring, whose distortions in OCD are well established (Devinsky et al., 1995; Maltby et al., 2005; Soriano-Mas et al., 2007; Perani et al., 2008). Anterior cingulotomy have been used successfully for refractory OCD (Kim et al., 2003; Jung et al., 2006). Hyperactivity in ACC for beta oscillatory networks identified with LORETA has been previously reported in OCD (Sherlin and Congedo, 2005), moreover, lower activity in this region was found to correlate with better response to antidepressant treatment (Fontenelle et al., 2006).

Involvement of Brodmann area13 (insular cortex) has been reported in previous structural (Soriano-Mas et al., 2007) and functional studies on OCD (Shapira et al., 2003; Perani et al., 2008). The dysfunctions of this area have been identified as responsible for

\(p < 0.001\), but not for intra-hemispheric coherence. Post-hoc contrasts showed that OCD had decreased alpha inter-hemispheric coherence \((p = 0.019)\) in frontal, central and temporal regions \((p < 0.001)\).

<table>
<thead>
<tr>
<th>Lobe</th>
<th>Region</th>
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<th>Side</th>
<th>X</th>
<th>Y</th>
<th>Z</th>
<th>Band</th>
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<tr>
<td>Temporal</td>
<td>Insula</td>
<td>Brodmann area 13</td>
<td>R</td>
<td>39</td>
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<td>8</td>
<td>δ</td>
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<td>Middle frontal gyrus</td>
<td>Brodmann area 8</td>
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<td>43</td>
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<td></td>
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<td>Brodmann area 9</td>
<td>L</td>
<td>−38</td>
<td>31</td>
<td>36</td>
<td>δ/β</td>
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<tr>
<td></td>
<td>Superior frontal gyrus</td>
<td>Brodmann area 10</td>
<td>R</td>
<td>25</td>
<td>59</td>
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<td>δ</td>
</tr>
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<td></td>
<td>Prefrontal gyrus</td>
<td>Brodmann area 6</td>
<td>L</td>
<td>−24</td>
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<td>Limbic</td>
<td>Cingulate gyrus</td>
<td>Brodmann area 24</td>
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All significant values \((p < 0.05)\) correspond to a positive \(r\) value (i.e. increased current density in OCD vs. controls). Significant regions are indicated with the name of Brodmann area (BA) and Talairach-co-ordinates (Talairach and Tournoux, 1988). X = left (−) to right (+); Y = posterior (−) to anterior (+); Z = inferior (−) to superior (+). R = right; L = left; BL = bilateral.

**Table 1**

Summary of significant results from whole-brain LORETA comparison (non parametric unpaired t-test) between OCD patients \((n = 37)\) vs. control subjects \((n = 37)\).
Coupling between slow and fast rhythms

In the present study, increased delta and beta current source density in OCD has been found in parallel with middle frontal decoupling between them. Some authors proposed a positive correlation between delta/beta coupling and behavioural inhibition (Schutter and van Honk, 2004, 2005). This hypothesis might be supported by the evidence that cortisol leads to increased behavioural inhibition and delta/beta coupling (Schutter and van Honk, 2005; van Peer et al., 2008), while testosterone administration is associated to both rhythm decoupling and behavioural disinhibition (Schutter and van Honk, 2004). Studies on cortisol levels in OCD found increased values in comparison with controls (Catapano et al., 1992; Gustafsson et al., 2008). As in healthy subjects increased cortisol is linked with increased coupling between low and higher frequencies, it might be expected that in OCD coupling of delta/beta oscillations would be increased in comparison with controls. Indeed in the present study a decoupling between delta or theta and beta in OCD was found, suggesting that such changes could not be explained (or at least not only) with cortisol level. Decoupling between slow and fast EEG rhythms in OCD might be related not only to increased beta activity, but also to a dysfunction of a more complex cortical–subcortical system, as increased power in delta also was found. Therefore, it may be suggested that OCD is related not only to increased activation in frontal networks, but also to a frontal–subcortical functional disconnection.

EEG-coherence

Inter-hemispheric alpha coherence has been found decreased in OCD compared with normal subjects. The present results appear different from a previous report of increased fronto-occipital coherence in the right hemisphere in 20 medicated OCD patients (Desarkar et al., 2007). A direct comparison with the present study cannot be performed since discrepancies may also be linked to a different selection of patients and of the electrodes used for coherence calculation. Changes in inter-hemispheric coherence have been reported in different pathological and physiological conditions (Leocani and Comi, 1999). Decreased coherence in the drug-free OCD patients in the present study might be interpreted as linked with higher level of anxiety, as the relaxation induced by meditation (Murata et al., 2004) or benzodiazepines (Fingelkurts et al., 2004; Sampaio et al., 2007) leads to its increase. Changes after administration of benzodiazepines in the mentioned studies have been seen in line with a neurotransmitter hypothesis, assuming the possibility of excitatory action (not only inhibitory) of GABA, leading to a coherence increase. The investigation of anatomical correlates of the inter-hemispheric EEG coherence has indicated a contribution of corpus callosum, thalamus, midbrain, pons and cerebellum (Teipel et al., 2009). A significantly larger corpus callosum has been reported in treatment-naïve pediatric OCD (Rosenberg et al., 1997), while, in adults, increased signal intensity in the genu region has been found at MRI (Mac Master et al., 1999). On the other hand, some studies lacked to find significant differences in corpus callosum area between adult OCD patients and controls (Breiter et al., 1994; Jenike et al., 1996).

On the other hand, EEG coherence seems to reflect not only direct cortico-cortical functions, but also the influence of thalamus on functional communications between regions. According to the model of thalamo-cortical dysrhythmia (TCD), proposed by Llinas et al. (1999) and referred to a set of neuro-psychiatric disorders including OCD, thalamus seems to play a crucial role not only in cortico-subcortical circuits, but also in cortico-cortical communications, as shown by Guillery (1995) and Sherman and Guillery (1998, 2002). Within this model, cortico-cortical communication could be realised by both direct and, more importantly, trans-thalamic cortico-cortical pathways. They also suggested the possibility of testing thalamic function by analysing cortico-cortical communication and not thalamic activity itself. Moreover thalamic dysfunction in OCD has been previously reported (Maltby et al., 2005).

Taken together, several cortico-subcortical networks, including the thalamus, might be considered as linked with the present finding of decreased alpha inter-hemispheric coherence in OCD.

Conclusions

In the present study, source analysis of brain rhythms revealed involvement of cortical sources for slow and fast rhythm and their coupling. Moreover, cortico-cortical and cortico-subcortical dysfunction has been found as indicated by local coupling and coherence of brain oscillations. Both neurotransmitter and brain network abnormalities may be considered in explaining these findings. The crucial role of thalamus in generating alpha frequencies is well known (Buzsáki, 2006). On the other hand, changes in GABA have been reported mainly linked with beta oscillations (Jensen et al., 2005). The importance of thalamus and other subcortical structures in the pathophysiology of OCD has been pointed out by successful neurosurgical interventions, including pallidal and medial thalamic lesions in OCD patients resistant to drug treatment (Jeanmonod et al., 2003). Moreover, as a part of TCD model, a cortical activation of high-frequency (beta and gamma) bands has been described in relation to asymmetrical cortico-cortical GABA-ergic collateral inhibition (Llinas et al., 1999; Jeanmonod et al., 2003), which may also be responsible for clinical symptoms. It might be hypothesized that increased beta current source density in the present study is linked with this mechanism.

Through the combination of power and coherence analysis, different levels of cortico-subcortical processing deficit in OCD were distinguished. These abnormalities, which in our patients cannot be ascribed to changes induced by psychoactive drugs, may provide a tool for investigating the physiopathology of OCD and, if validated, allow objective measurement of the severity of involvement and of the efficacy of therapeutic interventions. Finally, simultaneous analysis of power (including source) and coherence of brain rhythms may provide an advantage in investigating the complex functional relationships between cortical and subcortical structures playing a role in the physiopathology of neuropsychiatric disorders.

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This article has not been submitted elsewhere. All co-authors have seen and agree with the contents of the manuscript.


