Complete title: **Standardized low-resolution electromagnetic tomography in obsessive-compulsive disorder - a replication study**

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**Abstract**

Previous EEG source localization studies in obsessive-compulsive disorder (OCD) reported ambiguous results. The reason probably lies in different OCD samples included in the studies – obsessive-compulsive subjects selected based on a psychopathology questionnaire (the Symptom Checklist – Revised), drug-naïve OCD cases or patients with a long-term disorder. This study was conceived as a replication of our previous research on OCD population coming to treatment in Prague Psychiatric Centre (Koprivova et al., 2011). We included 50 OCD patients (8 drug-free and 42 medicated with SSRIs) and 50 healthy controls. All subjects were different from those enrolled in the previous study. Resting state EEG was analyzed in 8 frequency bands as well as with 1 Hz frequency resolution using the standardized low-resolution electromagnetic tomography (sLORETA). In OCD, sLORETA indicated low-frequency power excess at 2 and 3 Hz in the cingulate gyrus with maximal \(t\)-values in Brodmann area 24. The low-frequency activity was unrelated to the severity of clinical symptoms and illness duration but delta power in the right orbitofrontal cortex positively correlated with age of OCD onset. Our results confirm previous finding of the low-frequency excess in the cingulate gyrus in OCD and document the essential role of delta frequencies. Delta activity in the cingulate gyrus is negatively associated with reward-signalling...
dopamine release in the ventral striatum and increases in states connected with a need for reinforcement. Thus, delta activity could reflect a repetitive need to perform compulsive behaviour in OCD patients.

**Keywords**

Obsessive-compulsive disorder (OCD) – electroencephalography (EEG) – standardized low-resolution electromagnetic tomography (sLORETA) – age of onset – illness duration – symptom severity
Introduction

Obsessive-compulsive disorder (OCD) is a relatively common neuropsychiatric condition a lifetime prevalence of more than 2% in general population [16] marked by recurrent intrusive thoughts (obsessions) and/or repetitive behaviours (compulsions). Although OCD pathophysiology is not fully understood, there is a widespread agreement on the key role of aberrant functioning or imbalanced interactions in fronto-striatal circuits [2]. The traditional orbitofronto-striatal model including orbitofrontal cortex, ventral striatum, ventral pallidum and mediodorsal thalamus has recently been challenged by a two-network model including orbitofronto-striatal as well as dorsolateral prefronto-striatal loop [12]. However, evidence from performance monitoring [5] and resting state EEG source localization studies [9,18,20] stressed the role of the cingulate gyrus in this disorder. Inverse solution techniques such as low-resolution electromagnetic tomography – LORETA [13,14] demonstrated increased low-frequency as well as beta EEG activity in OCD subjects at rest in this structure. Sherlin and Congedo [18] reported increased amount of beta activity in the cingulate gyrus in obsessive-compulsive subjects (the lower frequency of the beta band, the more anterior its location within the cingulate gyrus). Elevated resting-state beta activity in the cingulate gyrus was later reported also by Velikova et al. [20]. On the other hand, the largest study in this area found increased low-frequency activity (2 – 6 Hz) in the medial frontal cortex, especially anterior cingulate gyrus in OCD [9]. Higher pre-treatment delta in anterior cingulate and/or similarly localized pre-treatment beta were related to a worse treatment response to SSRIs [6] and/or cognitive behavioural therapy [10]. On the other hand, pre-treatment high beta in middle to posterior cingulate gyrus and adjacent areas was positively related to a better response to cognitive-behavioural therapy [10].

Thus, the results of EEG source localization studies are only partially overlapping. They consistently support the role of the cingulate gyrus in OCD but they report abnormalities at low as well as at high frequencies. As discussed in [9] the reason could be due to heterogeneity of OCD, especially to a different obsessive-compulsive population included in EEG studies. Sherlin and Congedo [18] included eight obsessive-compulsive subjects based on a psychopathology questionnaire (the Symptom Checklist – Revised), Velikova et al. [20] included 37 drug-naïve OCD cases and the largest previous study [9] comprised 50 OCD patients who had been suffering from OCD in average for 12.5 years usually were previously treated.

The aim of this replication study was to compare EEG sources in a different sample of OCD patients from Prague Psychiatric Centre and a different sample of healthy controls. We tested the difference between EEG
sources in OCD patients and healthy controls as well as the relationship between EEG activity and clinical variables (age of OCD onset, illness duration and symptom severity).

**Material and methods**

**Subjects**

Fifty right-handed patients diagnosed with OCD according to ICD-10 [22] and DSM-IV [1] criteria were included in the study. Eleven patients had comorbid diagnosis based on ICD-10 (social phobia – 3, mixed anxiety and depressive disorder – 3, panic disorder – 1, generalized anxiety disorder – 1, mental anorexia – 1, dysmorphophobia – 1, personality disorder – 1). Eight patients were drug-free, forty-two patients were medicated with SSRIs. In our previous study we also included drug-free and SSRIs medicated patients and demonstrated that the increased level of low-frequency activity found in OCD was not due to medication use [9]. Medication status was stable for at least one month prior to study. All patients participated in the 6-weeks cognitive-behavioural therapy programme, however, EEG was recorded at the beginning of the treatment, in the first week after admission. Therefore cognitive-behavioural therapy did not affect the results of this study. The demographic and clinical data are summarized in Table 1. The study was approved by the local Ethical committee and all subjects signed informed consent.

**EEG recording and analysis**

EEG was recorded during eyes-closed resting state on a Brainscope differential amplifier (Unimedis Ltd., Czech Republic) against the AFz reference. The signal was obtained from 19 scalp locations according to the international 10\(\times\)20 system using an ECI electro-cap (Electro-Cap International, Inc., Eaton, USA) with a sampling rate of 250 Hz. For more details see [9]. Artefacts were removed in EureKa software (NovaTechEEG, Inc., Mesa, Arizona, USA) and if necessary, continuous muscle artefacts were removed as independent components using ICoN software (http://sites.google.com/site/marcocongedo/software/nica). Before analysis, all data were filtered between 1 and 45 Hz, re-referenced against the average reference montage and re-sampled at 128 Hz for comparability with our older data.
Data analysis was performed by the standardized low-resolution electromagnetic tomography – sLORETA [14], an inverse solution technique estimating the intracranial distribution of electrical activity (current density) in the cortex based on a three shell spherical head model co-registered with Talairach coordinates [19]. In our study we used the LORETA-Key software (Key Institute for Brain-Mind Research, Zurich, Switzerland) and the sLORETA transformation matrix. We obtained current density estimates in 2394 cortical voxels of 7x7x7 mm. Absolute and relative current density was computed in 8 frequency bands delta (2 – 3.5 Hz), theta (4 – 7.5 Hz), alpha1 (8 – 10 Hz), alpha2 (10.5 – 12 Hz), beta1 (12.5 – 18 Hz), beta2 (18.5 – 21 Hz), beta3 (21.5 – 32 Hz) and gamma (32.5 – 44 Hz) as well as in 1 Hz frequency bins (2 – 44 Hz). Data were log-transformed, smoothed with a 14 mm spatial moving average filter and the absolute current density power was normalized. Groups comparisons and correlations with clinical variables were performed on a voxel-wise basis in the MHyT software (NovaTechEEG, Inc.) by means of randomization-permutation statistics. All bands were treated simultaneously in the t-test between two-sided max-statistics test guaranteeing that the family-wise type I error did not exceed the nominal level (0.05).

Results

Demographic and clinical data

The two groups did not differ in age, sex, handedness and education level (Table 1). Clinical data (age of OCD onset, illness duration and score at the Yale-Brown Obsessive-Compulsive Scale - Y-BOCS) were available in 40 patients. The mean Y-BOCS score was 21.4 indicating marked psychopathology. Mean age of OCD onset was 20 years and patients had been suffering from OCD for almost 11 years on average.

EEG sources in OCD patients and healthy controls

In OCD patients compared with healthy controls we found an increased amount of normalized absolute delta power in the anterior and middle cingulate (Fig. 1). The highest t-values were located in Brodmann area (BA) 24. In 1 Hz resolution analysis the difference between OCD patients and healthy controls was found at 2 and 3 Hz (Table 2). T-values at 4, 5 and 6 Hz in the same region were higher in OCD than in controls, however, statistical significance was not reached even in one-sided test or in single-bands testing.
Medication, gender and comorbid anxiety disorders

Drug-free and medicated patients did not show differences in the mean normalized absolute delta power in the region with significantly increased delta activity in OCD compared to healthy controls (t = 0.09, p = 0.932). Moreover, medication dosage (the imipramine equivalent of SSRI according to [3]) was not related to the amount of delta activity in this region (p = 0.029, p = 0.854).

EEG source comparison of subjects with and without comorbid anxiety disorder as well as comparison of male and female patients did not yield significant results (p > 0.05).

Correlations with clinical variables

As clinical data were available in 40 OCD patients, correlations with clinical variables were performed only in this OCD subgroup. Normalized absolute delta activity in the right orbitofrontal cortex (BA 11 and 47) was positively related with age of OCD onset (r ≥ 0.51, p < 0.05, Fig. 2). However, no relationship was found between EEG activity and illness duration and severity of obsessive-compulsive symptoms.

Discussion

The main result of our study confirms previous finding [9] of increased low-frequency activity in the cingulate gyrus in OCD patients. Contrary to our previous study maximal t-values were not found in the dorsal anterior cingulate but more posteriorly, in the midcingulate. However, in both studies maximal t-values fell within the Brodmann area 24. Similarly, in both studies significant t-values were found also in subgenual anterior cingulate (BA 25), medial frontal and parahippocampal gyrus. Whereas in the previous research the difference between OCD patients and healthy controls was found at 2, 3, 4, 5 and 6 Hz and peaked at 4 and 5 Hz, this study revealed increased low-frequency activity only at 2 a 3 Hz. In the previous study, we discussed the results in the context of performance monitoring and frontal midline theta activity [9]. However, with respect to a specific increase of delta activity in this new data set of OCD patients, it seems to be reasonable to consider the findings in relation to the reward-related system.

It has been suggested that delta and theta oscillations reflect the activity of brain circuits that regulate behaviour on the basis of motivational drives and emotional appraisal [7]. Recently Wacker et al. [21] found a robust negative correlation between delta (2 – 6 Hz) current density in the rostral anterior cingulate and the
nucleus accumbens response to reward and thus provided further evidence for the hypothesis that the EEG delta rhythm is associated with reward processing in the ventral striatum. As reward is signaled to the ventral striatum by an increased dopamine release [17], delta activity should be negatively related to dopaminergic input. Indeed, animal studies demonstrated the association between dopamine release in the nucleus accumbens and decreased delta activity (for a review, see [21]). The review of relevant studies indicates that delta activity increases in states associated with a need for reinforcement and decreases when this reinforcement is obtained [8]. Thus, it could be hypothesized that our finding of increased delta activity in the cingulate gyrus in OCD reflects abnormal activity of the reward-related system signalizing an increased need of reward. This would be consistent with the urge to perform subjectively rewarding or relieving compulsive behaviours which is one of the most prominent clinical features of OCD.

Two other previous LORETA studies comparing obsessive-compulsive subjects and healthy controls reported increased activity at beta frequencies in patients groups [18,20]. This abnormality also encompassed the cingulate gyrus. These finding are rather complementary than contradictory because low-frequency oscillations and beta activity are functionally related. Knyazev et al. [8] showed that in aversive situations when no reinforcement or negative reinforcement is expected, correlation between delta (1 – 4 Hz, similar results were found also for theta) and beta frequencies appears or at least significantly increases in EEG, together with the amount of delta power. The delta network includes primarily the orbitofrontal and anterior cingulate region and, depending on situation demands, it may extend into temporal, parietal and occipital brain areas. It has been suggested that the delta network drives local beta oscillations in the same regions and coordinates the timing of neuronal activities between the areas through delta–beta coupling.

Similarly as in our previous study, no relationship was found between the amount of the low-frequency activity and severity of clinical symptoms. Possible reasons are discussed in [9]. However, positive correlation with age of OCD onset and delta activity as well as no relationship between delta power and illness duration reported in this study suggest that the increased delta activity in the right orbitofrontal cortex could be related to the early-onset OCD subtype. Previously, OCD has been described as a heterogeneous disorder in several aspects. For example, differences in neurobiology and treatment response were demonstrated between early- vs. late-onset OCD patients [4,11]. EEG studies reported a negative relationship between treatment response and pre-treatment low-frequency EEG power registered at frontal and temporal electrodes [15] or generated in anterior cingulate [10].
The limitations of the used methods include restricted scope of scalp recorded EEG almost exclusively to cortical structures as well as lower accuracy of sLORETA source localization compared to direct measurements from anatomical regions. Moreover, as our EEG research focused on power analysis of resting state EEG sources, only their abnormalities could have been detected in OCD. However, other EEG measures, task- or symptom provocation-related EEG alterations, or abnormalities in parameters undetectable by EEG may have remained unrevealed in our research. Finally, this paper was conceived as a replication study and did not focus on more specific issues such as potential EEG differences between OCD treatment responders and non-responders, between early- vs. late-onset OCD cases or different OCD subtypes that could maybe bring more light on EEG source abnormalities reported in OCD patients.

**Conclusions**

In conclusion, our results confirm the previous finding of the increased low-frequency activity in the cingulate gyrus in OCD as well as the absence of its relationship with the severity of clinical symptoms. Delta activity in the cingulate gyrus is negatively associated with reward-signalling dopamine release in the ventral striatum, one of the key structures in OCD pathophysiology.

**Acknowledgement**

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**References**


[18] L. Sherlin, M. Congedo, Obsessive-compulsive dimension localized using low-resolution brain electromagnetic


Table legends:

Tab. 1: Demographic and clinical characteristics of OCD patients and healthy controls.

Table 2: Number and localization of voxels with excessive absolute current density in OCD compared with controls ($p < 0.05$). The structures are reported in their mean t-value order.

Figure captions:

Fig. 1: Increased delta (2 – 3.5 Hz) normalized absolute power in OCD compared to healthy controls. Significant voxels ($p < 0.05$, corrected) are displayed – the darker the colour, the higher the t-value. The image is sliced at its own maximum.

Fig. 2: Normalized absolute delta (2 – 3.5 Hz) power correlation with age of OCD onset. Significant voxels ($p < 0.05$, corrected) are displayed – the darker the colour, the higher the r-value. The image is sliced at its own maximum.
Tab. 1: Demographic and clinical characteristics of OCD patients and healthy controls.

<table>
<thead>
<tr>
<th>Sample characteristics</th>
<th>OCD (N = 50)</th>
<th>controls (N = 50)</th>
<th>OCD vs. controls</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
<td>mean</td>
</tr>
<tr>
<td><strong>Demographic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>age (years)</td>
<td>31.14</td>
<td>9.35</td>
<td>31.48</td>
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<tr>
<td>sex (men:women)</td>
<td>17:33</td>
<td>NA</td>
<td>17:33</td>
</tr>
<tr>
<td>education (3 levels)</td>
<td>1:29:20</td>
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<td>2:27:21</td>
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<tr>
<td>handedness (right:left)</td>
<td>50:0</td>
<td>NA</td>
<td>50:0</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medication (none:SSRIs)</td>
<td>8:42</td>
<td>NA</td>
<td>50:0</td>
</tr>
<tr>
<td>Y-BOCS (n = 40)</td>
<td>21.35</td>
<td>7.89</td>
<td>NA</td>
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<tr>
<td>obsessions</td>
<td>10.63</td>
<td>4.12</td>
<td>NA</td>
</tr>
<tr>
<td>compulsions</td>
<td>10.60</td>
<td>4.19</td>
<td>NA</td>
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<tr>
<td>age of OCD onset (n = 40)</td>
<td>20.03</td>
<td>8.80</td>
<td>NA</td>
</tr>
<tr>
<td>illness duration (n = 40)</td>
<td>10.73</td>
<td>7.11</td>
<td>NA</td>
</tr>
</tbody>
</table>

(Abbreviations: SD – standard deviation, NA – not applied/not applicable, education levels – primary, secondary (incl. leaving examination), university, SSRIs – selective serotonin reuptake inhibitors, Y-BOCS - Yale Brown obsessive-compulsive scale, OCD – obsessive-compulsive disorder.)
Table 2: Number and localization of voxels with excessive absolute current density in OCD compared with controls ($p < 0.05$). The structures are reported in their mean $t$-value order.

<table>
<thead>
<tr>
<th>Brain structure and Brodmann area</th>
<th>$2 \text{ Hz}$</th>
<th></th>
<th>$3 \text{ Hz}$</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingulate gyrus (BA 23, 24, 31, 32)</td>
<td>4.61</td>
<td>59</td>
<td>4.21</td>
<td>8</td>
</tr>
<tr>
<td>Anterior cingulate (BA 25, 33)</td>
<td>4.42</td>
<td>4</td>
<td>n.s.</td>
<td>0</td>
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<tr>
<td>Medial and superior frontal gyrus (BA 6)</td>
<td>4.33</td>
<td>7</td>
<td>n.s.</td>
<td>0</td>
</tr>
<tr>
<td>Parahippocampal gyrus (BA 28, 34, 37)</td>
<td>4.24</td>
<td>4</td>
<td>n.s.</td>
<td>0</td>
</tr>
<tr>
<td>total</td>
<td></td>
<td>74</td>
<td>8</td>
<td></td>
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</table>
Highlights

- We compared resting state EEG in 50 obsessive-compulsive patients and 50 controls.

- In patients, increased delta activity was found in the cingulate gyrus.

- Delta is related to dopamine release and reward processing in the ventral striatum.