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**Functional-imaging and electrophysiological
correlates of obsessive-compulsive disorder
and their potential use in neurofeedback
intervention**

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Declaration

I declare that the work submitted here is my own and that it has been conducted under supervision of Prof. Jiří Horáček and Dr. Marco Congedo. I also declare that all the used information resources have been listed in the section References. No part of this dissertation has been submitted for any other degree.

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Jana Kopřivová

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SUMMARY

Background: Obsessive-compulsive disorder (OCD) is a common mental disorder that may seriously affect quality of life and even the ability to work. Despite advanced medical care there are still patients who do not respond or do not respond sufficiently to treatment. Recently proposed treatment strategies such as deep brain stimulation or repetitive transcranial magnetic stimulation have targeted several levels of fronto-striatal circuits which dysfunction underlies OCD pathophysiology. Likewise, neurofeedback (NFB) could target dysfunctional fronto-striatal networks by providing almost real-time feedback about their activity. As the success of these methods critically depends on good knowledge of dysfunctional loops in OCD, a more detailed investigation of neurobiological basis of this disorder is highly needed.

Aims: The aim of the first part of this dissertation was to provide an overview of the current literature related to OCD and NFB. The second section of the thesis is based on five original studies of the author that were conceived to 1) explore anatomical correlate of OCD in our patients, 2) to verify its functional relevance and specificity in electroencephalographic (EEG) studies, and 3) to test the utility of the findings in NFB treatment of OCD.

Methods: In our studies we included patients with clinical diagnosis of OCD, panic or generalized anxiety disorder, and healthy controls matched for age, sex, eventually education. We acquired demographic, clinical, anatomical, and EEG data. Anatomical and EEG data were analyzed on a voxel-wise level using voxel-based morphometry and standardized low-resolution electromagnetic tomography (sLORETA). In addition, EEG data were analyzed by means of normative independent component analysis. Across studies, we performed correlations with clinical variables, especially with symptom severity and treatment response. The effect of NFB was tested in a double-blind sham feedback controlled study where we compared also pre- to post- treatment EEG and clinical symptom severity.

Results: We found that: 1. OCD patients had reduced grey matter volume in the medial frontal cortex as well as in the right temporo-parieto-occipital, right precentral, left middle temporal region, in the left cerebellum, and in bilateral pons. 2. OCD patients had increased low-frequency (2 – 6 Hz) EEG activity in the medial frontal cortex. 3. OCD patients showed increased low-frequency (3 – 6 Hz) activity in one of the seven independent EEG components previously described in normal resting brain. 4. The elevated low-frequency activity was not present in patients with panic or generalized anxiety disorder. 5. The severity of obsessive-compulsive symptoms was positively related to the left orbitofrontal grey matter volume and negatively related to grey matter volume in supramarginal gyri. 6. Better treatment outcome was negatively related to pre-treatment low-frequency (2 – 6 Hz) activity in the medial frontal cortex, beta (18.5 – 21 Hz) activity in the medial frontal, left lateral orbitofrontal, and dorsolateral prefrontal cortex, and low alpha (8.5 – 10 Hz) activity especially in the left fusiform and parahippocampal gyrus. On the other hand, a better treatment outcome was positively related to the amount of pre-treatment high beta activity (21.5 – 32 Hz) in the independent EEG component differentiating between OCD patients and healthy subjects as well as in the subgenual and dorsal anterior and posterior cingulate extending up to the lateral surface of the frontal and parietal cortices. 6. Although there were no significant pre- to post-training differences, the trained component power fell below the 95th percentile of the normative database after NFB training. NFB group showed higher percentage improvement of the compulsion score compared to patients receiving sham feedback.

Conclusion: Our findings are in favour of the current opinion that the traditional orbitofronto-striatal loop is not sufficient to explain OCD pathogenesis and that abnormalities in this disorder include more widely distributed brain regions. Central role of the anterior cingulate across our studies as well as increased amount of low-frequency activity in OCD offer a new view of OCD as a salience network-related disorder. Given the negative relationship between the amount of the low-frequency activity in the medial frontal cortex and future treatment response, we suggested that by NFB we targeted a network related to treatment resistance rather than a correlate of symptom severity, possibly explaining why the immediate clinical effect was low.

SOUHRN

Úvod: Obsedantně-kompulzivní porucha (OCD) je časté psychické onemocnění, které může vážně narušit kvalitu života a dokonce pracovní schopnost. Navzdory moderní lékařské péči jsou stále pacienti, kteří na léčbu neodpovídají nebo neodpovídají dostatečně. Nejnovější terapeutické postupy jako hluboká mozková stimulace či repetitivní transkraniální magnetická stimulace se zaměřily na různé úrovně fronto-striálních okruhů, jejichž dysfunkce je podkladem OCD. Podobně také neurofeedback (NFB) by mohl zacílit na dysfunkční fronto-striální okruhy tím, že by téměř v reálném čase poskytoval zpětnou vazbu o jejich aktivitě. Vzhledem k tomu, že úspěch těchto metod kriticky závisí na dobré znalosti dysfunkčních okruhů u OCD, detailnější zkoumání neurobiologické podstaty této poruchy je velmi potřebné.

Cíle: Cílem první části práce bylo poskytnout přehled současných poznatků týkajících se OCD a NFB. Experimentální část práce je založena na souboru pěti vlastních originálních prací, jejichž cílem bylo 1) zjistit anatomický korelát OCD u našich pacientů, 2) ověřit jeho funkční relevanci a specifitu v elektroencefalografických (EEG) studiích, a následně 3) testovat využitelnost našich nálezů v léčbě OCD pomocí neurofeedbacku.

Metodika: Do studií byli zařazeni pacienti s klinickou diagnózou OCD, panická nebo generalizovaná úzkostná porucha a zdravé kontroly odpovídajícího věku, pohlaví, případně i vzdělání. Získávali jsme demografické a klinické údaje, anatomická data a EEG data. Anatomická i elektroencefalografická data jsme zpracovali na úrovni voxelů pomocí morfometrie založené na voxelech (voxel-based morphometry) a standardizované elektromagnetické tomografie s nízkým rozlišením (sLORETA). EEG data jsme navíc hodnotili pomocí normativní analýzy nezávislých komponent. Napříč studiemi jsme prováděli korelace s klinickými proměnnými, zejména se závažností symptomů a odpovědí na léčbu. Efekt neurofeedbacku byl testován ve dvojité slepé studii kontrolované placebo feedbackem, kde jsme srovnávali také EEG a klinické symptomy před a po léčbě.

Výsledky: Zjistili jsme, že: 1. Pacienti s OCD měli menší objem šedé hmoty v mediální frontální kůře, jakož i v pravé temporo-parieto-okcipitální oblasti, levém středním temporálním gyru, mozečku a Varolově mostu bilaterálně. 2. Pacienti s OCD vykazovali zvýšenou aktivitu v oblasti nízkých frekvencí EEG (2 – 6 Hz) v mediální frontální kůře. 3. Pacienti s OCD vykazovali zvýšenou nízkofrekvenční EEG aktivitu (3 – 6 Hz) v jedné ze sedmi nezávislých komponent EEG, které byly popsány v normálním mozku v klidovém stavu. 4. Zvýšené množství nízkofrekvenční EEG aktivity nebylo přítomno u pacientů s panickou nebo generalizovanou úzkostnou poruchou. 5. Závažnost obsedantně-kompulzivních symptomů souvisela pozitivně s objemem šedé hmoty v levé orbitofrontální kůře a negativně s objemem šedé hmoty v supramarginálních gyrech. 6. Odpověď na léčbu a EEG před léčbou korelovaly negativně v oblasti nízkých frekvencí (2 – 6 Hz) v mediální frontální kůře, v pásmu beta (18.5 – 21 Hz) aktivity v mediální frontální, levé laterální orbitofrontální a dorsolaterální prefrontální kůře a v pásmu alfa (8.5 – 10 Hz) aktivity zejména v levém fusiformním a parahipokampálním gyru. Na druhé straně, lepší odpověď na léčbu byla spojena s vyšším množstvím vysoké beta (21.5 – 32 Hz) aktivity před léčbou v nezávislé komponentě EEG diferencující mezi pacienty s OCD a zdravými subjekty, stejně jako v subgenuálním a dorzálním předním cingulu, zadním cingulu a laterálním povrchu frontálního a parietálního kortexu. 6. Přestože jsme nezjistili signifikantní rozdíly před a po tréninku, výkon trénované komponenty po NFB klesl pod 95. percentil normativní databáze. Ve skupině trénované pomocí NFB došlo k většímu procentuálnímu zlepšení kompulzí než ve skupině trénované pomocí placebo feedbacku.

Závěr: Naše závěry podporují současný názor, že tradičně zmiňovaný orbitofronto-striální okruh není dostatečný k vysvětlení patogeneze OCD a že abnormality u této poruchy zahrnují širší oblast mozku. Centrální úloha předního cingula napříč našimi studiemi, stejně jako zvýšené množství nízkofrekvenční EEG aktivity nabízejí nový pohled na OCD jakožto na poruchu sítě zpracovávající významnost podnětů, tzv. salience network. Vzhledem k negativní korelaci mezi množstvím nízkofrekvenční aktivity v mediální frontální kůře a odpovědí na budoucí terapii, se domníváme, že pomocí NFB jsme cílili na neurální síť vztahující se k rezistenci na léčbu, spíše než na korelát závažnosti symptomů. To možná vysvětluje, proč okamžitý klinický efekt NFB byl nízký.

ABBREVIATIONS

ACC	Anterior cingulate cortex
ADHD, ADD	Attention deficit disorders with or without hyperactivity
BA	Brodmann area
BSS	Blind source separation
CBT	Cognitive-behavioural therapy
CSF	Cerebrospinal fluid
DLPFC	Dorsolateral prefrontal cortex
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
DTI	Diffusion tensor imaging
EAAC/EAAT	Excitatory amino-acid carrier/transporter
EEG	Electroencephalogram, electroencephalography
ERN	Error-related negativity
FDR	False discovery rate
fMRI	Functional magnetic resonance
FWE	Family wise error
GABA	Gamma-aminobutyric acid
GAD	Generalized anxiety disorder
GM	Grey matter
ICA	Independent component analysis
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICoN	Independent component neurofeedback
MEG	Magnetoencephalography
MFC	Medial frontal cortex
NFB	Neurofeedback
NICA	Normative Independent component analysis
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
OFC	Orbitofrontal cortex
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PFC	Prefrontal cortex
rCBF	Regional cerebral blood flow
RCZ	Rostral cingulate zone
ROI(s)	Region(s) of interest
(s)LORETA	(standardized) low-resolution electromagnetic tomography
SCPs	Slow cortical potentials
SMR	Sensorimotor rhythm
SPECT	Single photon emission computed tomography
SSRIs	Selective serotonin reuptake inhibitors
VBM	Voxel-based morphometry
WM	White matter
Y-BOCS	Yale-Brown Obsessive Compulsive Scale

1 INTRODUCTION

Obsessive-compulsive disorder (OCD) is a relatively common neuropsychiatric disorder marked by recurrent intrusive thoughts (obsessions) and/or repetitive behaviours (compulsions). Obsessions are unwanted and often repugnant thoughts recognized as one's own that cause anxiety and distress. Compulsions (stereotyped behaviours or mental acts) are carried out to reduce or prevent this anxiety or distress and are perceived to avert dreaded events. They are not enjoyable and usually the person realizes their pointlessness and makes attempts, though unsuccessful, to resist them (World Health Organisation, 1992; American Psychiatric Association, 1994). Detailed diagnostic criteria according to the International Statistical Classification of Diseases and Related Health Problems, the ICD-10, are specified in Table 1.

A. Either obsessions or compulsions (or both) are present on most days for a period of at least 2 weeks.
B. Obsessions (thoughts, ideas, or images) and compulsions (acts) share the following features, all of which must be present: a) they are acknowledged as originating in the mind of the patient, and are not imposed by outside persons or influences b) they are repetitive and unpleasant, and at least one obsession or compulsion that is acknowledged as excessive or unreasonable must be present c) the patient tries to resist them (but resistance to very long-standing obsessions or compulsions may be minimal). At least one obsession or compulsion that is unsuccessfully resisted must be present d) (4) experiencing the obsessive thought or carrying out the compulsive act is not in itself pleasurable (this should be distinguished from the temporary relief of tensions or anxiety)
C. The obsessions or compulsions cause distress or interfere with the patient's social or individual functioning, usually by wasting time.
D. Obsessions and compulsions are not the result of other mental disorders such as for example schizophrenia or related disorders (F20-F29) or mood disorders (F30-F39).

Table 1: Obsessive-compulsive disorder diagnostic criteria according to ICD-10 (World Health Organisation, 1992).

OCD often occurs with comorbid diagnoses such as anxiety and mood disorders as well as impulse-control and substance use disorders (Ruscio et al., 2010). In the current Diagnostic and Statistical Manual of Mental Disorders, DSM-IV (American Psychiatric Association, 1994) OCD has been classified as an anxiety disorder.

However, the upcoming fifth revision of the Manual (DSM-V) lists OCD under Obsessive-Compulsive and Related Disorders together with body dysmorphic disorder, trichotillomania, skin picking or hoarding disorder (<http://www.dsm5.org>). Hoarding disorder is a new diagnostic category replacing the current hoarding OCD subtype that has repeatedly been reported to differ from other OCD variants (Lochner et al., 2005).

The disorder has a lifetime prevalence of more than 2% in general population (Ruscio et al., 2010) and more than 10% prevalence in first-degree relatives of OCD patients (Nestadt et al., 2000) suggesting a genetic component in OCD pathogenesis. So far, only the glutamate transporter gene *SLC1A1* has been associated with OCD and several genes involved in serotonergic and dopaminergic system have been reported as potential risk factors for OCD development (for a review see Fineberg et al., 2011).

The treatment of OCD consists mainly of pharmacotherapy, cognitive-behavioural therapy (CBT) or both. The first-line pharmacological treatment with serotonin reuptake inhibitors is effective only in about 40 to 60 percent of cases (Kaplan and Hollander, 2003). In patients refractory to these drugs, pharmacological augmentation with neuroleptics antagonizing the D2 dopamine receptor can be efficacious (Bloch et al., 2006). Cognitive-behavioural therapy has been reported to show similar and even more long-term treatment effect as serotonergic drugs in mild to moderate OCD cases (Abramowitz, 1997). Still, despite of advanced medical care, roughly one third of OCD patients do not achieve an adequate clinical response (Fineberg and Gale, 2005). As OCD is associated with a significant impairment in functioning and quality of life (Hollander et al., 2010), it is highly important to develop alternative treatment methods to help refractory patients. Promising results have been reported after neurosurgery (Bear et al., 2010) or deep brain stimulation that has recently been intensively studied (Greenberg et al., 2006). Less invasive repetitive transcranial magnetic stimulation has been applied with ambiguous outcome (Slotema et al., 2010) and non-invasive neurofeedback (NFB) approach described in case reports (Hammond, 2003) awaits closer examination.

Because the success of all the above mentioned methods largely depends on precise determination of parameters that should be targeted, it is necessary to better understand OCD-related neuroanatomical and functional characteristics. The aim of this dissertation was 1) to search for anatomical correlates of OCD, 2) to confirm their functional relevance in EEG source localization studies, the most prominent knowledge

gap in OCD literature, and 3) to test the utility of our findings in the treatment of OCD using multichannel neurofeedback based on advanced methods of EEG analysis.

This dissertation is divided into two main sections – the theoretical part reviewing current OCD and NFB literature, and the experimental part summarizing the main findings of five original papers of the author.

I. LITERATURE OVERVIEW

2 STRUCTURAL AND FUNCTIONAL ABNORMALITIES IN OCD

2.1 Anatomical studies

Anatomical studies in OCD provide support for widely distributed alterations in grey as well as in white matter. The most numerous anatomical in OCD studies focus on morphometric evaluation of the grey and white matter. Two main methodological approaches have been applied – the regions of interest (ROIs) analysis and the voxel-based morphometry (VBM). The first one includes only a limited number of *a priori* selected brain regions that have to be manually delineated. In contrast, the VBM (Ashburner and Friston, 2000), a relatively new and automated approach, allows to perform whole brain analysis and thus to reveal abnormalities in regions not *a priori* hypothesized. The disadvantages include potential bias due to normalizing anatomical different brains and (Crum et al., 2003) and in choosing smoothing kernel size (Jones et al., 2005).

In OCD, the ROIs studies reported most consistently reduced grey matter (GM) volume in orbitofrontal cortex and other limbic structures belonging to the orbitofronto-striatal loop (Menzies et al., 2008a). Moreover, VBM analyses extended the findings to dorsal brain areas, such as the dorsolateral prefrontal (Christian et al., 2008; Gilbert et al., 2008; van den Heuvel et al., 2009), temporal (Kim et al., 2001; Menzies et al., 2007; Yoo et al., 2008) and parietal (Kim et al., 2001; Valente et al., 2005; Menzies et al., 2007; van den Heuvel et al., 2009) cortex, insula and cerebellum (Kim et al., 2001; Pujol et al., 2004; Menzies et al., 2007;). Some of these regions were further and in more detail investigated by the ROIs approach. For example, the unbalanced volumetric characteristics were found in the insula indicating its enlarged anterior (Nishida et al., 2011; Song et al., 2011) and reduced posterior (Song et al., 2011) part. The most recent meta-analysis of VBM studies including 401 OCD subjects and 376 healthy controls concludes that OCD patients show increased GM volumes in bilateral lenticular nuclei extending to the caudate nuclei, as well as decreased volumes in bilateral dorsal medial frontal/anterior cingulate gyri (Radua et al., 2010).

Compared to GM, studies on white matter (WM) abnormalities in OCD are less common. However, WM may play a critical role in OCD pathophysiology as documented by the clinical effect of neurosurgery and deep brain stimulation often targeting white matter tracts (Nenadic, 2008; Haber and Brucker, 2009). In the last years, the interest in WM in OCD is growing and the attention is paid to the volumetric alterations as well as to the WM microstructure. Moreover, non-anatomical research, such as candidate genes studies (Zai et al., 2004; Stewart et al., 2007) or magnetic resonance spectroscopy (Kitamura et al., 2006), contributes to the understanding of the role of the WM in OCD pathophysiology. Morphometric studies of the WM in OCD did not yield entirely consistent results. Pujol et al. (2004) and Matsumoto et al. (2010) did not find any differences in WM volume between OCD and healthy control subjects, whereas others reported changes in the total WM volume (Atmaca et al., 2007; Duran et al., 2009; Koprivova et al., 2009a). However, if local WM abnormalities were found, they were always present in the frontal (Carmona et al., 2007; van den Heuvel et al., 2009; Macmaster et al., 2010; Togao et al., 2010;) or parietal lobe (Carmona et al., 2007; Lazaro et al., 2009).

Microstructure of the WM has been studied by diffusion tensor imaging, DTI (Le Bihan et al., 2001). The method is based on quantification of water diffusion in tissues. In GM, water diffusion is close to isotropic, however in WM the predominant direction of water diffusion is along the WM tracts. Fractional anisotropy is the most commonly reported measure of water diffusion. Lower fractional anisotropy indicating more isotropic diffusion has been reported in WM damage or disorganization (Beaulieu, 2002). The first DTI study in OCD was published in 2005 (Szeszko et al., 2005) and the number of publications has grown especially in the last year. In OCD, alterations of fractional anisotropy have mostly been reported in the medial frontal, especially anterior cingulate, WM (e.g. Szeszko et al., 2005; Menzies et al., 2008b; Ha et al., 2009), parietal WM (Szeszko et al., 2005; Menzies et al., 2008b), corpus callosum (e.g. Yoo et al., 2007; Garibotto et al., 2010; Nakamae et al., 2011), internal capsule (Cannistraro et al., 2007; Yoo et al., 2007), and long-distance fascicules (Garibotto et al., 2010; Fontenelle et al., 2011; Zarei et al., 2011). However, the results are inconsistent and a quantitative meta-analysis is lacking.

Several anatomical studies were conceived to address the hypothesis of neurodevelopmental origin of OCD and searched for markers of putative neurodevelopmental abnormalities. Shim et al. (2009) demonstrated that OCD compared to healthy controls were less likely to show a well-developed left paracingulate sulcus, Wobrock et al. (2010) described prefrontal hypogyrification in OCD patients, and finally Pujol et al. (2011) found frontobasal shape deformation in OCD that was related to the frontal sinus size. The coincidence of brain shape variations with morphological changes in the frontal sinus should indicate a potential association between OCD and late neurodevelopment disturbances, as the frontal sinus emerges during the transition between childhood and adulthood, similarly as many OCD cases.

A number of studies aimed to determine whether the morphometric alterations in OCD are related to symptom severity, whether they represent risk factors for OCD (endophenotypes) or whether they reduce or disappear together with clinical improvement. Symptom severity correlations yielded numerous results, though they are lacking consistency. However, the meta-analysis by Radua and Mataix-Cols (2009) revealed that studies that included individuals with more severe OCD were significantly more likely to report increased GM volumes in the basal ganglia. Current use of antidepressant medication had no effect on this result. OCD endophenotypes (objective, heritable, quantitative traits hypothesized to represent genetic risk for polygenic disorders) have been studied by Menzies and colleagues (Menzies et al., 2007; Menzies et al., 2008b). It has been shown that OCD patients and their unaffected first-degree relatives show similar abnormalities in GM, WM as well as behavioural performance at a response inhibition task. Some of the anatomical alterations in OCD have been reported to normalize following successful pharmacological treatment. For example, a decrease of the pre-treatment abnormally high volume in the thalamus (Rosenberg et al., 2000) or left amygdala (Szeszko et al., 2004) were observed after 12 - 16 weeks of paroxetine monotherapy, whereas no thalamic volume changes were found after successful cognitive-behavioural therapy (Rosenberg et al., 2000). Similarly, a randomized study by (Hoexter et al., 2012) reported a volume increase of the pre-treatment abnormally smaller left putamen after 12 weeks of fluoxetine pharmacotherapy but not after cognitive-behavioural therapy. The normalizing effect of SSRIs (selective serotonin reuptake inhibitors) on fractional anisotropy in the corpus callosum has also

been demonstrated in drug-naïve OCD patients (Yoo et al., 2007). Finally, Lazaro et al. (2009) demonstrated that children and adolescents with untreated OCD present grey and white matter decreases in lateral parietal cortices that were no longer present after clinical improvement.

2.2 Functional neuroimaging studies (PET, SPECT, fMRI)

The aim of functional neuroimaging studies is to measure various aspects of brain functions in order to better understand how the brain works in normal and pathological conditions. The most common methods of functional neuroimaging include positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance (fMRI), multichannel electroencephalography (EEG), and magnetoencephalography (MEG).

Functional neuroimaging studies in OCD assessed brain activity in patients compared to healthy or clinical controls in resting state, during symptom provocation or during performance of tasks putatively related to the disorder. They also evaluated post-treatment changes and searched for predictors of treatment response. A number of PET and SPECT studies addressed the serotonergic or dopaminergic brain system, i.e. serotonin or dopamine transporters or receptors (e.g. Perani et al., 2008; Hesse et al., 2011).

2.2.1 *Resting state*

At rest, various cortical and subcortical regions of the orbitofronto-striatal as well as the dorsal fronto-striatal loop showed abnormalities in OCD in PET and SPECT studies. For example, Lucey et al. (1995) reported reduced rCBF (regional cerebral blood flow) in OCD within the right and left superior frontal cortex, right inferior frontal cortex, left temporal cortex, left parietal cortex, right caudate nucleus and right thalamus, Busatto et al. (2000) found reduced radiotracer uptake in the right lateral orbitofrontal cortex and in the left dorsal anterior cingulate cortex in OCD, and Kwon et al. (2003a) demonstrated increased metabolic activity in the right orbitofrontal cortex (OFC) and decreased metabolic activity in the left parieto-occipital junction in OCD

patients compared to healthy controls. A meta-analysis of PET and SPECT studies in OCD showed differences in radiotracer uptake between patients with OCD and healthy only in the orbital gyrus and the head of the caudate nucleus (Whiteside et al., 2004). A meta-analysis of fMRI studies in OCD provided support for abnormalities in orbitofronto-striatal regions and reported consistent finding also in the lateral frontal, anterior cingulate, middle occipital and parietal cortices and cerebellum (Menzies et al., 2008a).

Resting neuroimaging was also analyzed in search for predictors of treatment response. Buchsbaum et al. (2006) demonstrated that OCD nonresponders to SSRIs with low relative metabolic rates in the striatum and high relative metabolic rates in the anterior cingulate gyrus were more likely to show a clinical response to additive risperidone treatment. Rauch et al. (2002) found that lower rCBF values in OFC and higher rCBF values in posterior cingulate predicted a better response to fluvoxamine treatment. Similarly, Saxena et al. (1999) showed that lower pre-treatment metabolism in OFC predicted a better response to paroxetine medication. Interestingly, Brody et al. (1998) found that higher normalized metabolism in the left OFC before treatment was associated with greater improvement after behavioural therapy but with a worse treatment response to fluoxetine. Finally, Buchsbaum et al. (2006) showed that patients with low relative metabolic rates in the striatum and high relative metabolic rates in the anterior cingulate gyrus were more likely to show a clinical response to risperidone treatment.

It has been demonstrated that the abnormal resting state activation tends to normalize post-treatment. In a 18-fluoro-deoxyglucose PET study Hansen et al. (2002) found a reduction in regional cerebral glucose metabolic rate the right caudate nucleus after successful treatment with paroxetine (12-20 weeks). Similarly, Saxena et al. (2002) reported metabolic decreases after treatment with paroxetine in the right caudate nucleus together with metabolic decreases in other regions of the fronto-striatal networks (right ventrolateral prefrontal cortex, bilateral orbitofrontal cortex, and thalamus). Furthermore, a SPECT study by Diler et al. (2004) demonstrated rCBF reduction in the bilateral caudate, dorsolateral prefrontal cortex (DLPFC), cingulate, and right anteromedial temporal region after 12 weeks of treatment with paroxetine. These findings contrast with a study by Apostolova et al. (2010) that found post-treatment increase of local metabolic rate of glucose in the right caudate after successful therapy

(cognitive-behavioural or pharmacotherapy). Yamanishi et al. (2009) reported significantly lower rCBF after 12 weeks of behavioural therapy in the left medial prefrontal cortex and bilateral middle frontal gyri in treatment responders compared to nonresponders.

2.2.2 Symptom provocation

Voxel-based meta-analysis of obsessive-compulsive symptom provocation PET and fMRI studies reported an increased likelihood of activation of the orbitofrontal and anterior cingulate loops as well as of the dorsolateral frontoparietal network including prefrontal cortex, precuneus, and the left superior temporal gyrus (Rotge et al., 2008). Mataix-Cols et al. (2004) demonstrated a distinct pattern of symptom-related activation connected with different obsessive-compulsive symptom dimensions (washing, checking, and hoarding).

Hendler et al. (2003) found that lower brain perfusion in the dorsal-caudal anterior cingulate and higher brain perfusion in the right caudate during symptom provocation (but not at rest) predicted a better treatment response to sertraline medication. Nakao et al. (2005b) reported reduction of symptom provocation-related activation (i.e. in the orbitofrontal, dorsolateral prefrontal, and anterior cingulate cortices) after treatment with fluvoxamine or behaviour therapy.

2.2.3 Task-related activity

The research suggests that OCD patients show altered response inhibition, set shifting, planning, reward-processing and performance monitoring. Several other mental functions, such as memory and verbal fluency (Nabeyama et al., 2008), decision making (Cavedini et al., 2002) or implicit learning (Rauch et al., 2007) have been studied in OCD, however the findings are still inconclusive.

The response inhibition refers to the ability to exert executive control over pre-potent responses (Chamberlain et al., 2005). It has been studied in motor and cognitive domain using tasks such as Go/No-Go or Stroop test. In the Go/No-Go paradigm the task is to respond to target stimuli as fast as possible and to avoid the response when non-target stimuli are presented. In the Stroop test the subjects are required to name the

ink colour of printed words that have an interfering semantic content referring to another colour (e.g. the word “blue” is written in red ink).

The research suggests that response inhibition is impaired in OCD patients and, moreover, similar impairment has been reported also in unaffected first-degree relatives (Chamberlain et al., 2007). Furthermore, different pattern of brain activation during response inhibition tasks performed in an fMRI scanner has been reported in OCD. During a Go/No-Go task Roth et al. (2007) found more diffuse and bilateral pattern of activation in OCD compared to healthy controls activating predominantly the right hemisphere. In OCD, Page et al. (Page et al., 2009) showed underactivation in task-relevant orbitofrontal/dorsolateral prefrontal, striatal and thalamic regions and increased activation in cerebellum and predominantly posterior brain regions. In motor Stroop task they found underactivation in temporo-parietal areas and increased activation in cerebellum and predominantly posterior brain regions. In thy study by Nabeyama et al. (2008) OCD patients showed less activation in the anterior cingulate gyrus and cerebellum during Stroop task compared to healthy controls. However, after 12 weeks of behavioural therapy (without medication) associated with clinical improvement, the activation in the cerebellum and parietal lobe increased and the activation of OFC, middle frontal gyrus, and temporal regions decreased. Similarly, Nakao et al. (2005a) have also observed a post-treatment increase in Stroop task-related activation in the parietal cortex and cerebellum in OCD.

In ***set shifting***, two different forms have been investigated in OCD, the attentional and the affective set shifting (Menzie et al., 2008a). In *attentional set shifting* tasks, the subject must shift his attention from one stimulus or its aspect to another one, previously irrelevant. There is evidence that OCD patients show impaired performance on this task and set shifting deficits have been reported also in unaffected first-degree relatives (Chamberlain et al., 2007). Gu et al. (2008) found that OCD made more mistakes in task-switch trials and failed to show activation in various regions recruited in healthy controls during task performance (bilateral DLPFC, premotor area, cingulate cortex, parietal lobe, occipital cortex, temporal cortex and caudate nucleus during task switching). In the reversed contrast condition, the authors demonstrated an increased activation of OFC and ventromedial prefrontal cortex in OCD during task-repeat compared to task-switch. They proposed that impaired task-switching ability in OCD

patients might be associated with an imbalance in brain activation between dorsal and ventral frontal-striatal circuits. Page et al. (2009) showed underactivation in switch-task relevant orbitofrontal and dorsolateral prefrontal, striatal and thalamic regions and underactivation in temporo-parietal areas. Again, suggesting the importance of both, ventral and dorsal frontal-striatal circuits in set shifting deficit in OCD.

In the affective set shifting the stimulus value is changed (e.g. the rewarded stimulus is no longer rewarded). Remijne et al. (2006) used fMRI during a reversal learning task that is supposed to detect altered reward and punishment processing and requires behavioural modification according to new reinforcement contingencies (affective switching). Compared to healthy controls, patients showed less activation in the left posterior OFC, bilateral insular cortex, bilateral dorsolateral, and bilateral anterior prefrontal cortex to during affective switching. These results also confirm the orbitofronto-striatal and dorsal prefrontal dysfunction in OCD as well as the importance of the anterior insula in OCD. Later, Chamberlain et al. (2008) demonstrated the presence of the abnormal activation pattern during reversal learning task also in first-degree relatives of OCD patients. Han et al. (2011) reported persisting task switching-related activation deficit in dorsal frontoparietal regions in OCD after clinical improvement.

Reward processing has been studied in the reversal learning or in monetary incentive paradigm. Incentive studies demonstrated altered reward-related activity in ventral striatum (Jung et al., 2011) or nucleus accumbens (Figue et al., 2011) in OCD compared to healthy control subjects.

The **planning** aspect of executive functions has been analyzed using a Tower of London test where the task is to rearrange a set of balls in pockets on a computer screen to match the appearance of another set determined by the computer with minimum possible number of moves (Chamberlain et al., 2005). Behavioural impairment on this task as well as decreased responsiveness of dorsal prefrontal-striatal circuits has been demonstrated in OCD by van den Heuvel et al. (2005a). During planning, the patients showed lower task-related activation than controls in several regions previously found to be involved in planning, particularly dorsolateral prefrontal cortex, basal ganglia and parietal cortex. Moreover, the patients compared to controls showed also higher and

presumably compensatory task-related activation in the bilateral ventrolateral prefrontal, anterior cingulate, and parahippocampal cortices, left temporal cortex, and dorsal brainstem. Further support for reduced planning task-related activation of the dorsolateral prefrontal and parietal cortex in subjects with obsessive-compulsive symptoms compared to healthy controls has been provided by a twin study by den Braber et al. (2008). Similarly, Huyser et al. (2010) found reduced recruitment of frontal and parietal regions in paediatric OCD patients compared with controls during the planning versus control task. These differences were no more observed after cognitive behavioural treatment. Impairment on the Tower of London task has also been reported in unaffected first-degree relatives of OCD patients (Delorme et al., 2007) suggesting its genetic basis. However, the altered frontal-striatal and limbic activations during planning is not OCD specific. The same activation pattern has been found in patients with panic disorder and hypochondriasis - a putative OCD spectrum disorder (van den Heuvel et al., 2011).

Overactive ***performance monitoring*** appears to be one of the most prominent features of OCD. Performance monitoring hypothesis in OCD has been formulated by Pitman (1987) and suggested that OCD patients have a permanent feeling that something is wrong or “not just right” and experience a need to correct the problem. Pitman proposed that an excessive error signal generated by the anterior cingulate cortex (ACC) underlies this phenomenon. Performance monitoring has been studied by two complementary methodologies, functional magnetic resonance imaging (fMRI) and event-related potentials, during performance of a cognitive task.

There is a substantial support for an overactive performance monitoring or error detection in OCD (for a review, see Endrass et al., 2008). However, further evidence showed that the same region of the ACC is activated during correct trials in which competing responses are in conflict (e.g. Carter et al., 1998). This finding would also better correspond to the OCD nature because recurrent compulsive behaviour typically follows correct completion of a behavioural task, e.g. hand washing (Maltby et al., 2005). Thus, further research concentrated on testing the hypothesis that ACC plays the key role not only in error detection processes but also in error prevention. According to van Veen and Carter (2002a) the timing of events after error commission and during correct conflict trials is similar. Following error commission, stimulus processing

continues and the correct response is activated. The moment when the correct and incorrect responses are activated is the moment of the greatest conflict. During conflict trials, the wrong response is being prepared first but it is withheld and replaced by the correct one. Thus, the activation of ACC is expected prior to the response during correct conflict trials and following the response during error trials (van Veen and Carter, 2002b). The fMRI study by Ursu et al. (2003) provided evidence for both, the increased error-related activity as well as the elevated conflict-related activity in ACC during correct trials in OCD patients.

The study by Maltby et al. (2005) clearly shows that correctly rejected, high-conflict trials that require response inhibition provide a better model for OCD than do error trials. In a fMRI Go/No-Go paradigm the authors showed that in correctly rejected, high-conflict trials OCD patients as well as healthy controls activated brain regions related to performance monitoring (rostral and caudal ACC, lateral prefrontal cortex) whereas OCD patients exhibited hyperactivity also in posterior cingulate and fronto-striatal circuits (lateral OFC, caudate, and thalamus) associated with OCD across multiple neuroimaging paradigms. Yücel et al. (2008) also demonstrated hyperactivation of the medial frontal cortex during high- vs. low-conflict trials in patients with OCD. In addition, thanks to the combined fMRI and magnetic resonance spectroscopy methodology their study suggested that medial frontal hyperactivation might be a compensatory response to a neuronal abnormality in the same region.

2.3 Electroencephalographic studies

Current electroencephalographic (EEG) literature related to OCD includes two main approaches: the event-related approach in the performance monitoring paradigm, and spectral analysis of the resting state EEG in quantitative EEG studies. Both approaches are interested in source localization and thus provide complementary information about aberrant EEG sources in OCD.

2.3.1 Performance monitoring in EEG studies

In EEG studies, performance monitoring has been investigated using an event-related potential called error-related negativity (ERN). It is a negative deflection with

fronto-central distribution generated shortly (<100 ms) after commission of error (as originally proposed by Gehring et al., 1993) or during conflict monitoring (Endrass et al., 2008). Interestingly, with respect to altered reward processing in OCD, it has also been considered as a reinforcement learning signal originating from the midbrain dopamine system signalling “worse than expected” outcomes (Holroyd and Coles, 2002).

The source of the ERN has been localized in or near to dorsal ACC (as defined by Bush et al., 2000) in EEG source localization studies (van Veen and Carter, 2002a) as well as during simultaneous EEG and fMRI recording (Debener et al., 2005). Furthermore, a meta-analysis of midline foci of activation reported in fMRI studies investigating brain activity during pre-response conflict, decision uncertainty, response errors, and negative feedback demonstrated hyperactivation of the posterior medial frontal cortex with particular clustering in the rostral cingulate zone, the human homolog of the monkey’s rostral cingulate motor area, that cuts across various Brodmann areas beyond the traditionally reported ACC (Ridderinkhof et al., 2004a). Neurons within this area are sensitive to reward expectancy and reinforcement (Shidara and Richmond, 2002; Ito et al., 2003). It has been proposed that changes in dopamine activity indicating a negative and positive reward prediction error (see below) are associated with decreased and increased ERN amplitude, respectively (Holroyd et al., 2003). Although the main role in performance monitoring has been attributed to dorsal medial frontal cortex, it has been shown that other structures such as ventral ACC, lateral prefrontal cortex or insula make part of a performance monitoring network (Maltby et al., 2005). Research suggests that the activation of the particular component of the performance monitoring system may have a specific timing. Particularly, that caudal ACC may reflect the initial identification of response conflict, while rostral ACC activation may reflect subsequent affective evaluation of the response (van Veen and Carter, 2002b; Maltby et al., 2005).

Studies show that ERN arises at least in part from ongoing theta activity of 4 – 7 Hz (Luu and Tucker, 2001; Luu et al., 2003; Luu et al., 2004; Trujillo and Allen, 2007). According to current opinion, the ERN may reflect theta coordination of the broader activity of the action-regulation circuitry in the limbic system, rather than just reflecting the functions of a single ACC region (Luu et al., 2003). It has been suggested that the performance monitoring network communicates via transient synchronous oscillations

in the theta range (Cavanagh et al., 2009). Interestingly, already (Gevins et al., 1989) revealed that theta activity over the frontal midline sites was related to theta recorded at the left lateral frontal electrodes during error feedback signal.

First evidence for an enhanced task-related ERN in OCD and at the same time empirical support for the Pitman's hypothesis provided (Gehring et al., 2000). Further research confirmed the finding of increased ERN in OCD compared to healthy controls (Johannes et al., 2001; Ruchow et al., 2007; Hajcak et al., 2008) and suggested the same pattern in non-clinical children and adolescents with obsessive-compulsive symptoms (Hajcak and Simons, 2002; Santesso et al., 2006). Increased ERN in OCD has been reported irrespective to medication use (Stern et al., 2010). The relationship between the ERN and obsessive-compulsive symptom severity is less clear, however, positive correlation between the ERN amplitude and Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS, Goodman et al., 1989) score has been reported (Gehring et al., 2000; Ursu et al., 2003). On the other hand, Hajcak et al. (2008) did find no relationship between ERN amplitude and obsessive-compulsive symptoms and proposed that an enhanced ERN in OCD is a lasting trait marker rather than a marker of the actual state. These results together with the finding of an enhanced ERN in unaffected first-degree relatives of OCD patients (Riesel et al., 2011) support the notion that an increased ERN may be a neural endophenotype of OCD.

2.3.2 Resting state quantitative EEG studies

Quantitative electroencephalographic studies based on spectral analysis of the resting state EEG reported abnormalities registered at frontal or frontotemporal electrode sites in OCD (e.g. Prichep et al., 1993; Karadag et al., 2003; Pogarell et al., 2006), however, results are less consistent in terms of frequencies affected. Both, decreased or increased activity have been described at slow or fast frequencies (see Table 2).

This diversity is probably due to methodological differences such as inclusion of patients with comorbid depression or due to the heterogeneity of OCD population itself. At the beginning of the 1990s, Prichep and colleagues have described two distinct EEG profiles in OCD patients related to differential response to SSRIs medication (Prichep et al., 1993). About 80% of patients characterized by excess of relative power in the theta

band were SSRIs nonresponders, while the same amount of patients characterized by increased relative power in the alpha band responded to SSRIs (Prichep et al., 1993). These findings were further supported by Hansen et al. (2003) who described increased relative alpha power in almost 95% of SSRIs responders.

Authors	Year	Frequency Affected	Localization of the Findings
Perros et al.	1992	↑ theta	predominantly left frontotemporal
Kuskowski et al.	1993	↓ delta and ↓ beta	right hemisphere
Prichep et al.	1993	↑ theta OR ↑ alpha	frontal or frontotemporal
Locatelli et al.	1996	↑ delta and ↓ alpha	frontotemporal
Tot et al.	2002	↑ delta, ↑ theta and ↓ alpha	left frontotemporal
Karadag et al.	2003	↑ theta and ↓ beta	frontotemporal
Bucci et al.	2004	↓ alpha	predominantly frontal
Pogarell et al.	2006	↑ delta, ↓ alpha and ↓ beta	predominantly frontal

Table 2: Resting state EEG spectral analysis findings in OCD. The arrows signify increased (↑) and decreased (↓) activity in OCD compared to healthy controls.

At the time of the conception of this thesis, only limited attention has been paid to the localization of generators of the aberrant EEG activity in OCD. The first study by Sherlin and Congedo (2005) have shown an increased beta power in the cingulate gyrus (the lower frequency of the beta band, the more anterior its location within the cingulate gyrus). However, this study comprised only 8 obsessive-compulsive subjects selected on the basis of the psychopathology questionnaire SCL-90-R. The remaining two source localization studies were related to treatment response prediction (Fontenelle et al., 2006; Bolwig et al., 2007). Fontenelle et al. (Fontenelle et al., 2006) found lower beta activity in the rostral ACC (Brodmann area – BA 24 and 32) and in the medial frontal gyrus (BA 10) in treatment responders compared to nonresponders. Bolwig et al. (2007) described a post-treatment decrease of alpha activity in OCD patients who responded to SSRIs. Our study focusing on EEG source analysis in obsessive-compulsive disorder (Koprivova et al., 2011a) together with a recent study by Velikova et al. (2010) have largely increased the knowledge on abnormal EEG generators in OCD and provided a solid basis for neurofeedback intervention. Velikova et al. (2010) found increased delta band power in the right insula and increased beta power in frontal, parietal and limbic lobes in OCD patients. Our study (Koprivova et al., 2011a) reported increased low-

frequency activity (2 – 6 Hz) in OCD patients localized in the medial frontal cortex with highest *t*-values in the dorsal anterior cingulate.

2.4 The key structures related to OCD

2.4.1 *Basal ganglia*

The role of the basal ganglia in the pathophysiology of OCD is multifactorial as several fronto-striatal loops, each playing a special role, underlie OCD symptoms. In general, the role of basal ganglia is to integrate inputs from the cortex and to select a particular motor or cognitive program (Aouizerate et al., 2004). Dorsal striatum is involved in procedural learning of behavioural routines that may run in loops in OCD (Baxter et al., 1999), whereas ventral striatum integrates signals with emotional content, and given its dopaminergic input it is involved in reward-related behaviour and learning (Groenewegen and Trimble, 2007). In OCD, the main role is attributed to the ventral striatum, a part of the striatum that is connected with limbic structures, such as the amygdala, hippocampus, midline thalamus, and certain regions of the prefrontal cortex. In addition, the ventral striatum receives dopaminergic input from the ventral tegmental area and has the highest density of serotonergic inputs in the striatum (Groenewegen and Trimble, 2007). Nucleus accumbens, a part of the ventral striatum (Haber and McFarland, 1999), plays an important role in reward-related processes mediated by dopamine (Wacker et al., 2009).

The input structure of basal ganglia is striatum receiving mostly excitatory projections from the cortex. The output structures are the globus pallidus interna and pars reticulata of the substantia nigra both sending inhibitory projections to the thalamus (Ruzicka, 2006). The pathway between the striatum and the output structures can be direct (dopamine acts via D1 receptor) or indirect (D2 receptors). The latter successively involves the globus pallidus externa and the subthalamic nucleus. Both pathways are connected with cortex via thalamus. Activation of the direct pathway leads to cortical activation because striatum sends inhibitory projections to globus pallidus interna and thus reduces its inhibitory influence on the thalamic relay. On the other

hand, the indirect loop blocks the thalamic relay thanks to an increased inhibitory activity of globus pallidus interna (Fig. 1).

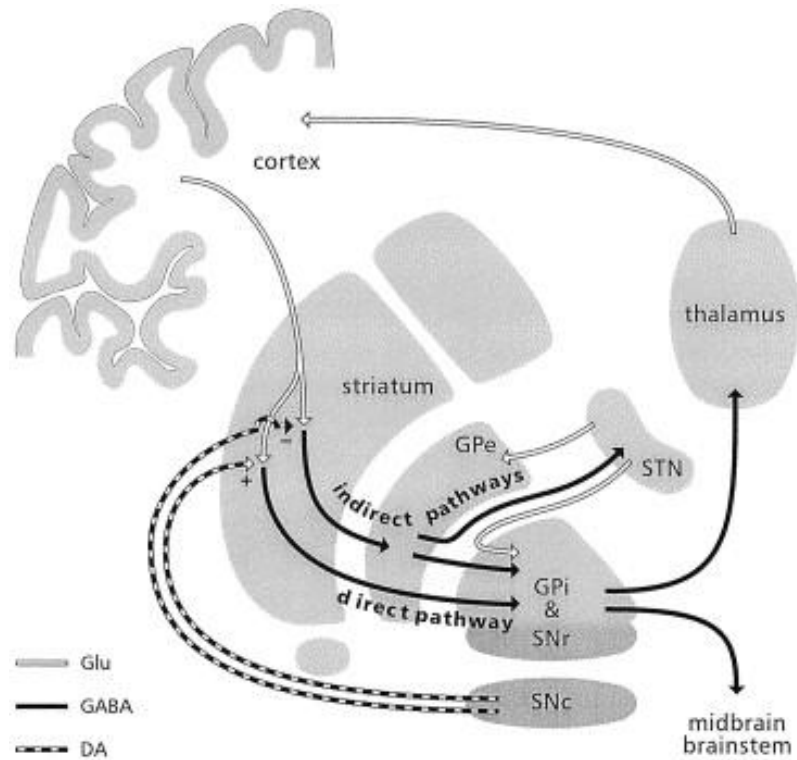


Fig. 1 (from Visser et al., 2000): Microcircuitry of the basal ganglia. Abbreviations: GPe, globus pallidus externa; GPi, globus pallidus interna; SNc, pars compacta of the substantia nigra; SNr, pars reticulata of the substantia nigra; STN, subthalamic nucleus.

2.4.2 Prefrontal cortex

Three main divisions have been distinguished within the prefrontal cortex (PFC) – lateral PFC, medial frontal cortex (MFC) and orbitofrontal cortex (OFC). All of them have been further segmented into smaller subregions – dorsolateral and ventrolateral prefrontal cortex (lateral PFC), anterior cingulate, pre-supplementary and supplementary motor area, frontal eye fields and dorsomedial prefrontal cortex (medial PFC), medial, ventral, lateral, and frontopolar OFC (for a review see (Ridderinkhof et al., 2004b)).

Lateral prefrontal cortex

Ventrolateral prefrontal cortex (BA 44 and BA 45, corresponding to the pars opercularis and pars triangularis of the inferior frontal gyrus, respectively) plays an important role in response inhibition (Aron et al., 2003) and in set-shifting (Hampshire and Owen, 2006), that both have been reported impaired in OCD (see above).

Dorsolateral prefrontal cortex encompassing Brodmann areas 9 and 46 is connected with extensive parts of the OFC, supplementary motor area, pre-supplementary motor area (medial BA 6), premotor cortex (lateral BA 6), frontal eye fields (Ridderinkhof et al., 2004b) and parietal cortex (Menzi et al., 2008a).

This region participates in the most complex cognitive functions such as planning, working memory, decision-making or set shifting that have also been reported impaired in OCD. Functional neuroimaging have showed decreased activity of DLPFC in OCD which may explain the difficulty to stop compulsive behaviours (Aouizerate et al., 2004).

Medial frontal cortex

The anterior cingulate cortex (ACC, Brodmann areas 24, 25, 32, 33) can be divided into two main parts – the ventral subdivision subserving affective functions and the dorsal part implicated in cognitive functioning (Bush et al., 2000). The cognitive subdivision belongs to attentional network and is connected with dorsolateral prefrontal, premotor and parietal cortex. The affective subregion has connections with amygdala, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and OFC (Aouizerate et al., 2004; Bush et al., 2000). A different subdivision of the cingulate cortex into subgenual and pregenual ACC, anterior and posterior midcingulate, and dorsal and ventral posterior cingulate has been proposed by Vogt (2005). The ACC as defined by Bush et al. (2000) includes in the Vogt's terminology also anterior midcingulate.

In OCD patients, ACC hyperactivation has been found at rest, during symptom provocation as well as after commission of errors in cognitive tasks (for a review see Ursu et al., 2003) and its normalization has been reported after treatment (Perani et al., 1995).

ACC subserves a variety of functions such as visceromotor control, vocalizations associated with the expression of internal states, emotional responses, movement execution, response selection and cognition, pain, memory, and social behaviour

(Devinsky et al., 1995). In the context of OCD, the main interest has been paid to its role in anxiety and especially in performance monitoring. Although the role of the posterior MFC incl. ACC in performance monitoring has been well established (see above), little is known about how it relates to behavioural adjustment. According to current view, monitoring-related posterior MFC activity engages control processes in the lateral PFC important for adaptive behaviour. The connections between the two structures are plausibly reciprocal and may be in part mediated by subcortical structures such as the basal ganglia and mesencephalic nuclei or by the supplementary or pre-supplementary motor area (Ridderinkhof et al., 2004a).

Orbitofrontal cortex

The orbitofrontal cortex (OFC) can be defined as the part of the prefrontal cortex that receives projections from the magnocellular, medial, nucleus of the mediodorsal thalamus. Brodmann areas occupied by the OFC are 10, 47, 11, 12, 13, 14 (Kringelbach and Rolls, 2004).

The orbitofrontal cortex receives inputs from all the sensory modalities and thus it is polymodal region implicated in multimodal stimulus-reinforcement association learning (for a review of OFC connections see (Kringelbach and Rolls, 2004). Sensory information to the OFC comes from insula (taste olfaction), inferior temporal cortex (object-related visual information), temporal pole and anterior part of the superior temporal sulcus (further visual information), superior temporal cortex (auditory information), somatosensory cortex, pericentral operculum and insula (somatosensory information) and ventrolateral posteromedial thalamic nucleus (visceral information). Moreover, the OFC receives projections from all part of the anterior cingulate, from posterior cingulate, motor cingulate area, premotor cortex, DLPFC (BA 9 and 46), hypothalamus and hippocampus. Moreover, the orbitofrontal cortex receives projections from the mediodorsal thalamus and cholinergic and aminergic inputs from subcortical areas. Most of the above mentioned connections are reciprocal. In addition, the OFC projects to striatum which is important in relation to OCD.

Orbitofrontal cortex is an intersection of cognitive, emotional and behavioural regulation. It consists of several functionally and anatomically distinct areas and can be divided into medial (and more posterior) and lateral part. Medial OFC is connected with

ventral tegmental area, nucleus accumbens and controls incentive motivation. The lateral OFC is connected with DLPFC, nucleus caudatus and regulates motor activity (Evans et al., 2004). Therefore, function of the OFC has been tested in tasks with monetary incentives, in reversal learning or response inhibition paradigm. As reported above, OCD patients show impaired performance and altered brain activity in these tasks.

2.4.3 Parietal cortex

Although reported already by early studies (Nordahl et al., 1989; Lucey et al., 1995), abnormalities of the parietal cortex in OCD have long been underestimated and emphasized only recently (Kitamura et al., 2006; Menzies et al., 2007). In the parietal regions of OCD patients a smaller (Valente et al., 2005) or greater (Menzies et al., 2007) grey matter volume have been described as well as reduced volume of the white matter (Carmona et al., 2007), lower fraction anisotropy (Szeszko et al., 2005; Menzies et al., 2008b), increased choline containing compounds (Kitamura et al., 2006), altered glucose metabolism (Nordahl et al., 1989) or task-related activation during fMRI (Henseler et al., 2008; Woolley et al., 2008; Jung et al., 2011).

Parietal cortex forms together with the dorsal ACC and dorsolateral PFC a superordinate cognitive control network in the brain subserving a wide variety of executive functions (Niendam et al., 2012) whose deficits have been reported in OCD (see above).

2.4.4 Temporal region

Except from mesial temporal structures, the temporal cortex has not been reported in models of OCD pathophysiology. However, several studies using different methodologies have suggested its potential role in this disorder. Specifically, the superior temporal gyrus that may be involved in OCD pathophysiology thanks to its rich interconnections with the orbitofrontal cortex and the amygdala have shown reduced grey matter volume (Choi et al., 2006), reduced cortical thickness in OCD (Shin et al., 2007) or reduced grey matter volume (Yoo et al., 2008). In a meta-analysis of functional neuroimaging studies, the superior temporal cortex was among the areas consistently activated during symptom provocation (Rotge et al., 2008). Also magnetoencephalographic studies have reported abnormal activity of the superior

temporal cortex in OCD (Amo et al., 2006; Maihofner et al., 2007). The function of the superior temporal cortex in humans is segregated between the left hemisphere and the right hemisphere. Whereas the left superior temporal cortex is specialized for language processing, its right-hemispheric homologue processes object- and space-related information in the environment (Karnath, 2001). The superior temporal cortex has been suggested to play a role in the perception of biological motion and showed an increased activation during this task in OCD (Kim et al., 2008). Interestingly, the rostral and middle parts of the superior temporal gyrus are connected with ventral portions of the caudate nucleus (Yeterian and Pandya, 1998) that is of special importance in OCD (see above).

An empirical hint for the involvement of the medial temporal gyrus in OCD pathophysiology comes from the link between OCD and temporal lobe epilepsy (Monaco et al., 2005; de Oliveira et al., 2010). This structure comprised of the parahippocampal, entorhinal and perirhinal cortices and the hippocampus is essential for memory functions (Squire et al., 2004). In OCD, Morein-Zamir et al. (2010) demonstrated a specific associative memory deficit suggesting abnormal medial temporal lobe involvement in this disorder. Structural and functional alterations of the parahippocampal gyrus (Valente et al., 2005; van den Heuvel et al., 2005a) have been reported in OCD. The hippocampus in OCD patients has been reported to show shape deformity (Hong et al., 2007), decreased volume (Kwon et al., 2003b; Atmaca et al., 2008), aberrant recruitment during implicit learning task (Rauch et al., 2007) and its size (Carmona et al., 2007; Atmaca et al., 2008) or function have been related to the severity of clinical symptoms (Kwon et al., 2003a; van Laere et al., 2006).

2.4.5 Amygdala

The amygdala has been linked to negative emotions such as fear and anxiety (Davis, 1992). However, recent evidence indicates that it is also involved in reward and motivational processing through reciprocal connections with the nucleus accumbens and the OFC (Aouizerate et al., 2004). In OCD, the hippocampus-amygdala complex has been associated with refractoriness to treatment (Atmaca, 2011).

2.4.6 *Insula*

Apart from insular projections of taste, olfactory, visceral, and somatosensory information into the orbitofrontal cortex (Kringelbach and Rolls, 2004), it appears that in relation to OCD direct reciprocal connections between the anterior insula and dorsal ACC are of special importance. These connections are via a special kind of neuronal cells, called von Economo neurons, that enable fast, highly integrated information exchange (for a review, see Craig, 2009). Recently, it has been suggested that the anterior insula and the von Economo neurons it contains play a fundamental role in awareness (Craig, 2009). It has been proposed that the anterior insular cortex and the ACC may be considered as input (anterior insula) and output (ACC) regions of a functional system, typically engaged across cognitive, affective, and behavioural contexts, suggesting that it is of fundamental importance for mental life (Medford and Critchley, 2010). In addition to the rostral cingulate zone (RCZ), the anterior insula has consistently been activated during errors and performance monitoring (Klein et al., 2007).

In OCD, recent studies reported morphometric as well as functional alterations of the anterior insula. Enlarged volume of the anterior insula (Nishida et al., 2011; Song et al., 2011), greater functional connectivity between the ventromedial PFC and regions of bilateral anterior insula/frontal operculum and right thalamus (Stern et al., 2011), insular hyperactivation during error trials or performance monitoring (Huyser et al., 2011; Stern et al., 2011), and increased EEG delta activity in the right insula (Velikova et al., 2010) have been reported in OCD.

2.4.7 *Thalamus*

The thalamus represents one of the key parts of the fronto-striatal circuits. It receives glutamatergic inputs from various cortical areas as well as GABAergic (GABA – gamma-aminobutyric acid), inputs from basal ganglia pathways and then sends glutamatergic projections back to the cortex (Aouizerate et al., 2004). It is divided into several functionally segregated nuclei. In their OCD model, Aouizerate et al. (2004) have proposed the involvement of three thalamic nuclei in OCD pathophysiology: the anterior nucleus implicated in emotional processing through its connections to the ACC via the mammillary bodies, the ventral anterior nucleus participating in cognitive functions based on the link with the dorsolateral PFC, and the medial dorsal nucleus

projecting to the orbitofrontal and dorsolateral prefrontal cortices. In addition, the role of the reticular thalamic nucleus and GABAergic projections to the other thalamic neurons in OCD has been proposed in the glutamatergic hypothesis (Rotge et al., 2010).

2.5 Alterations of brain neuromediator systems in OCD

Serotonin and dopamine, the two major modulatory inputs originating in the brain stem, play an important role in OCD pathophysiology. Their importance is well supported by clinical efficacy of serotonin inhibitors and antidopaminergic drugs in a substantial part of OCD patients (Kaplan and Hollander, 2003; Bloch et al., 2006). Recently, the role of glutamate in OCD has been documented (e.g. Carlsson, 2000; Rotge et al., 2010; Pittenger et al., 2011).

2.5.1 Serotonergic system

Serotonergic projections from nuclei raphe represent the largest and most complex neurochemical efferent system in the human brain (Aouizerate et al., 2004). It impacts on excitability and is involved in affective regulation, motivational processes, cognitive flexibility and impulse control and it also plays a role in performance monitoring by modulating (i) the emotional or motivational valence of feedback, (ii) cognitive flexibility or impulsivity, (iii) the impact of other neurotransmitters through modulation of cortical excitability (Jocham and Ullsperger, 2009).

The role of serotonin in OCD is not fully elucidated, however, recent review studies has suggested potential importance of the 5HT1D (Aouizerate et al., 2005) or 5-HT2A (Fineberg et al., 2011) receptor subtype. For reasons that remain unclear, therapeutic doses of selective serotonin reuptake inhibitors (SSRIs) in OCD often need to be higher than those in depression (Bloch et al., 2010).

2.5.2 Dopaminergic system

In OCD, the mesocorticolimbic dopaminergic system is of special interest. Its neurons originate in the mesencephalic ventral tegmental area and project to the nucleus accumbens and other limbic ventral striatal regions and cortical areas, especially the OFC and ACC (Aouizerate et al., 2005).

The mesocortical limbic system is essential for the learning and motivational processes, two critical aspects of behaviour oriented to reaching goals or obtaining rewards (Salamone and Correa, 2002). It has been shown that firing pattern of dopaminergic neurons reflects a prediction error. If the outcome is better than predicted, dopaminergic neurons increase their firing. Similarly, if the outcome is worse than predicted, the firing rate decreases (for review see Schultz, 2007). Based on the dopaminergic feedback information, the striatal neurons modify their activity to maximize future reward (Aouizerate et al., 2004). The reinforcement-learning theory of performance monitoring as proposed by Holroyd and Coles (2002) suggests that phasic changes in dopamine release directly affect activity of the apical dendrites of pyramidal cells in the RCZ, thereby inducing the ERN (Ullsperger, 2010). However, according to recent evidence the dopamine signal does probably not have sufficient temporal precision to drive a short-term electrophysiological event such as the ERN (Lapish et al., 2007). More likely, dopamine acts on the generation of ERN by setting the background of cortical excitability and thus modulating the effect of fast-acting neurotransmitters such as glutamate and GABA (Jocham and Ullsperger, 2009). The activity of the dopaminergic system itself is modulated by serotonin. In OCD, serotonergic hypofunction leads to the dopaminergic loops being overactive (Koo et al., 2010).

In OCD, lower levels of striatal dopaminergic D2 receptor binding in the basal ganglia (Denys et al., 2004) and increased dopamine transporter binding (Kim et al., 2003) have been reported. According to Aouizerate et al. (2005) the elevation in the dopamine transporter and down-regulation of the D2 receptor may result from a compensatory mechanism due to higher synaptic concentrations of dopamine in the striatum.

2.5.3 The role of glutamate

Accumulating recent evidence has suggested the role of the glutamate in OCD pathophysiology (e.g. Carlsson, 2000; Rotge et al., 2010; Pittenger et al., 2011). Interestingly, the most reliable result of genetic studies in OCD relates to the variability of the gene SLC1A1 for glutamate transporter EAAC-1/EAAT-3 (excitatory amino-acid carrier/transporter), for a summary, see Pauls (2008). An association between polymorphisms in the *N*-methyl-D-aspartate (NMDA) NR2B subunit and OCD risk has

also been reported (Arnold et al., 2004). Both, the EAAC-1/EAAT-3 glutamate transporter and the NMDA NR2B subunit are expressed predominantly on the post-synaptic and peri-synaptic membrane suggesting the post-synaptic dysfunction in glutamate signalling represents the most likely candidate mechanism at the molecular level in OCD (Wu et al., 2012).

In general, the role of glutamate transporters is to remove glutamate from the synaptic cleft and maintaining low extracellular level of this agent because glutamate excess is known for its excitotoxicity (Mark et al., 2001). It seems that functional alteration of the EAAC-1/EAAT-3 may represent a susceptibility factor mediating cortical neuroexcitotoxicity, however other factors such as infection with Borna disease virus, immunopathological reactions and alteration of the thalamo-cortical pathways are necessary (Rotge et al., 2010).

Together with GABA, glutamate is the primary neurotransmitter within the cortico-striatal circuits (Pittenger et al., 2011), the key components in OCD pathophysiology. Rotge et al. (2010) proposed thalamic neurons are protected against the neurotoxic effect of glutamate thanks to GABA-ergic innervations from basal ganglia and thalamic reticular nucleus. He suggested that Borna disease virus in the thalamus increases glutamatergic concentration in the synaptic cleft, therefore causing hyperactivity of glutamatergic neurons projecting into the cortex. He hypothesized that the expression of the SLC1A1 gene in the thalamus might be limited to the nucleus sending projections to the ACC and OFC. Alternatively, he suggested that the Borna disease virus might have a preferential neurotropism for this thalamic nucleus. This would be consistent with the notion that ACC and OFC in OCD show a smaller volume (Rotge et al., 2009b) and overactivity during the resting state (Menzies et al., 2008a; Rotge et al., 2008) and with recent finding of inverse relationship between the thalamic and orbitofrontal volumes in OCD (Rotge et al., 2009a).

Although interesting, many questions of the glutamatergic hypothesis remain unresolved. Of note, there are reciprocal modulations between glutamate and serotonin, and between glutamate and dopamine. For example, glutamatergic antagonists increase serotonergic transmission through 5-HT_{2A} receptor and, on the other hand, the stimulation of 5-HT_{2A} receptor leads to a decrease in glutamatergic transmission (for a summary, see Rotge et al., 2010)). Indeed, the use of glutamate-modulating agents in refractory OCD seems to be promising (for a review, see Pittenger et al., 2011), and,

moreover, a recent-case study in a refractory OCD patient (Rodriguez et al., 2011) reported substantial reduction of obsessions (cca 50%) after ketamine, a potent NMDA blocker known for its rapid antidepressant effect (Zarate et al., 2010).

2.6 Connectivity studies

The aim of connectivity studies is to explore the interactions between various brain structures. Functional connectivity can be defined as correlation of activity in different brain structures. It does not explain how the correlation is mediated (Nyberg and McIntosh, 2000). Brain networks can be characterized by nodes (regions they contain) and edges (connections) which dysfunctions may lead to aberrant signalling and functional deficits and over time also to structural changes even in distant brain regions (Menon, 2011).

Connectivity studies in OCD have been performed on PET (Horwitz et al., 1991; Mallet et al., 1998), EEG (Desarkar et al., 2007; Velikova et al., 2010) and most recently on task-related (Fitzgerald et al., 2010; Schlosser et al., 2010) or resting state fMRI data (Harrison et al., 2009; Jang et al., 2010; Sakai et al., 2011; Zhang et al., 2011). Their results are difficult to summarize because they are not fully comparable due to different methodologies. Two resting state fMRI connectivity studies analyzed correlations between several basal ganglia seed regions and the rest of the brain on a voxel-wise basis. They found increased functional connectivity between the ventral striatum/nucleus accumbens and the OFC (Harrison et al., 2009) or ventral medial cortex (Sakai et al., 2011). Harrison et al. (2009) found a positive correlation of functional connectivity between these regions and the severity of clinical symptoms. In another study, Zhang et al. (2011) assessed functional connectivity of 39 seed ROIs all over the brain. Compared to healthy controls, OCD patients showed abnormalities in functional connectivity of brain regions subserving control functions as well as higher local clustering in the control network, implying reduced signal propagation speed and synchronizability across distant regions.

Interestingly, in the Zhang's study, higher positive correlations in OCD were found in short-range connections, whereas lower correlations were associated with long-range connections. Altered connectivity between distant cortical sites (frontal and occipital) in OCD has also been reported by the EEG study by Desarkar et al. (2007)

who found increased correlations in the theta frequency band. Long-distance tracts in OCD have been reported to show reduced fractional anisotropy and its relationship to symptom severity and neuropsychological performance (Garibotto et al., 2010).

2.7 Fronto-striatal circuits

Although OCD pathophysiology is not fully understood, there is a wide-spread agreement on the key role of aberrant functioning or imbalanced interactions in fronto-striatal circuits in this disorder. Originally, five parallel segregated fronto-striatal circuits have been proposed by Alexander et al. (1986): the motor (originating in the supplementary motor area, premotor, motor, and somatosensory cortex), oculomotor (originating in the frontal eye field), dorsolateral prefrontal, orbitofrontal (medial and lateral), and anterior cingulate circuit. This segregation has been confirmed by a recent meta-analysis of PET and fMRI studies (Postuma and Dagher, 2006) and is now generally accepted. In addition to Alexander's loops, Middleton and Strick (2001) proposed a sixth circuit including inferior temporal and posterior parietal cortex. All circuits share the same structure (originating in the cortex and via direct and indirect pathway continuing to the thalamus and back to the cortex) but are anatomically segregated. They receive projections from noncircuit structures and also project to regions outside the five circuits and thus subserve functional connectivity of related areas (Bonelli and Cummings, 2007).

In OCD, the main role has traditionally been attributed to the orbitofronto-striatal loop including OFC, ventral striatum, ventral pallidum and mediodorsal thalamus (for a review see Menzies et al., 2008a). However, given the evidence from the above mentioned studies, it is now clear that the traditional orbitofronto-striatal model is not sufficient to explain the basis of OCD.

2.8 OCD models

Several hypotheses and models have been proposed to explain how a dysfunction within these circuits leads to clinical symptoms (Aouizerate et al., 2004; Menzies et al., 2008a). According to Modell et al. (1989), OCD symptoms arise from an aberrant

positive-feedback loop between the orbitofrontal cortex and mediodorsal thalamus caused by dysregulation of basal ganglia circuits resulting in reduced GABA-ergic input to the thalamus. Alternatively, Baxter (1999) suggested that OCD symptoms are due to imbalanced interaction between the direct (connected with OFC and ACC) and indirect (connected with DLPFC) striato-pallidal pathway leading to hyperactivity of the orbitofrontal and cingulate circuits and to dysfunction of the dorsolateral prefrontal loop. Alternatively, Schwartz et al. (1999, in Aouizerate et al., 2004) attributed the key role in OCD pathophysiology to cholinergic interneurons in the head of the caudate nucleus whose activity is modified by individually significant information and may influence the information processing in the striatum during learning. Alterations in this processing impact on the activity in the cortical structures implicated in performance monitoring leading to a feeling that something is wrong and a need to correct the problem. According to Aouizerate et al. (2004) a critical feature of OCD seems to be a dysfunction in error recognition and reward-related processes. OFC and ACC subserve the error detection process and through their large projections to the caudate nucleus they are also involved in behaviour planning based on reinforcement contingencies. The authors suggest that the overactivity of the mesocorticolimbic dopaminergic system may play a key role in the emergence of obsessions reflecting excessive computation about predictability of the event and it may also participate in the production of compulsive behaviours (compulsions may be viewed as a form of reward). Moreover, the expression of compulsive behaviours might be facilitated by decreased serotonergic activity because serotonergic projections exert a tonic inhibitory control over the activity of the dopaminergic system in the striatum and cortex. A recent review and meta-analysis by Menzies et al. (2008a) provides evidence that also parietal areas may be implicated in OCD pathophysiology. According to their model, there are two relatively segregated fronto-striatal loops implicated in OCD pathophysiology. One is the traditional orbitofronto-striatal circuit subserving affective functions and the other, called dorsolateral prefronto-striatal loop, participates in spatial and attentional processes. The dorsolateral prefrontal loop involves projections from the DLPFC and posterior parietal areas to the head of the caudate, then to the mediodorsal and ventral anterior thalamus via the globus pallidus and pars reticulata of the substantia nigra (Alexander et al., 1986).

2.9 OCD as a heterogeneous disorder

The heterogeneous nature of the obsessive is well accepted. It has been confirmed at the level of clinical symptoms as well as by structural and functional neuroimaging. By definition, OCD patients can suffer either from obsession, compulsions or from both symptom clusters (World Health Organisation, 1992) that can be of different quality (contamination/washing, symmetry/ordering, harm/checking, so called pure obsessions such as sexual or religious, hoarding). As mentioned above, the hoarding subtype seems to differ from the other clusters (Lochner et al., 2005), however also the other clinical subtypes have shown significant differences in morphometric (van den Heuvel et al., 2009) and functional (Mataix-Cols et al., 2004; van den Heuvel et al., 2005b) characteristics. It has also been demonstrated that early vs. late onset OCD patients show differences in neurobiological (Busatto et al., 2001; Hesse et al., 2011) and treatment response (Stewart et al., 2004; Langner et al., 2009) characteristics. EEG studies reported differential EEG pattern in treatment responders and non-responders (Prichep et al., 1993; Hansen et al., 2003; Fontenelle et al., 2006).

3 NEUROFEEDBACK

Neurofeedback (NFB) is a non-invasive method based on the learning principle. The technique consists of recording the brain activity and feeding it back to the individual with a little delay in the form of a dynamic sensorial object. For example, the estimated power in a specific frequency and scalp location may be traced as a line graph on a screen adding several points per second. Thanks to this feedback and to the reinforcement obtained when the desired criteria are met the individual may acquire a certain awareness or even control upon the brain activity generating the measurement (Congedo et al., 2004; Kotchoubey et al., 2002a). In turn, such control may be used to normalize abnormal features of brain activity (e.g. Beauregard and Levesque, 2006).

Over the years of its clinical application, neurofeedback proved effective in the treatment of attention disorders (Arns et al., 2009; Gevensleben et al., 2009b) and epilepsy (Kotchoubey et al., 2001; Stermann and Egner, 2006). In the case of other disorders, incl. anxiety disorders (Moore, 2000), some success has been reported but the data are still insufficient and research is in progress.

3.1 Historical overview

The history of neurofeedback, particularly EEG biofeedback, started in the late 1960s at two different research laboratories in the USA (Kamiya, 1968; Wyrwicka and Stermann, 1968). Whereas the Kamiya's approach aimed at the regulation of the alpha and theta activity, the Stermann's approach was based on the training of sensorimotor rhythm (SMR). Alpha-theta NFB was conceived to induce a relaxed or even meditative state and its anxiolytic effect was described (Hardt and Kamiya, 1978). However, further studies did not yield consistent results (e.g. Plotkin and Rice, 1981). Alpha-theta NFB also used to be connected with altered states of consciousness (Budzynski, 1999) and its popularity dropped soon. The interest in this NFB approach returned in the late 80s and in the 90s thanks to studies in alcoholism and post-traumatic stress disorder (e.g. Peniston and Kulkosky, 1989 and 1991).

The second NFB approach was launched by serendipitous finding of increased epileptogenic threshold in cats previously trained to increase their SMR brain waves

amplitudes (for a review see Stermán and Egner, 2006). The SMR training was then successfully tested in human patients with epilepsy (Stermán and Friar, 1972) and attention hyperactivity disorder (Lubar and Shouse, 1976).

In the Stermán's concept, NFB was considered an operant conditioning technique (Stermán, 1981). On the other hand, Kamiya and colleagues (Hardt and Kamiya, 1976) stressed the role of self-regulation. Although operant conditioning principle may be present in the NFB learning, there is evidence that NFB training leads to a certain awareness of one's own brain processes (Kotchoubey et al., 2002b) and that the trained brain activity can be shaped at will after NFB (Congedo et al., 2004).

Since the time of its invention, the scope of the NFB has been greatly enlarging together with technological development. Nowadays, it is possible not only to train the amplitude in a specific frequency band but coherence or amplitude asymmetry training is also available. Moreover, NFB based on inverse solution techniques such as low-resolution electromagnetic tomography neurofeedback – LORETA NFB (Congedo et al., 2004) or NFB based on blind source separation such as independent component neurofeedback – ICoN (Congedo, 2007) have largely improved spacial specificity, the major limitation of the traditional NFB. Spatial specificity has also been addressed by fMRI NFB (Yoo and Jolesz, 2002) that is currently on fashion (e.g. Hamilton et al., 2011; Ruiz et al., 2011; Zotev et al., 2011; Weiskopf, 2012). Importantly, technical progress in neuroimaging technology allows a more detailed exploration of pre- to post-NFB changes, thus providing a more powerful tool for the understanding of how NFB works.

3.2 Mechanism of NFB action

It is supposed that various training protocols may influence distinct neural networks, however, it has been suggested that they share the same basis by acting through neuromodulation and long-term potentiation (Abarbanel, 1995). Long-term potentiation includes anatomical changes at the level of neuronal membranes and is defined as a stable and relatively long-lasting increase of synaptic response to a constant afferent volley (Abarbanel, 1995). This explains ongoing remission of symptoms reported by follow-up studies conducted several months up to 2 years after the completion of NFB training (Tansey and Bruner, 1983; Saxby and Peniston, 1995;

Hammond, 2001; Weiler et al., 2002; Becerra et al., 2006; Strehl et al., 2006a; Leins et al., 2007; Gevensleben et al., 2010).

3.2.1 SMR

As summarized by Sterman and Egner (2006), SMR recorded on the scalp emanates as a result of the interaction between thalamocortical neurons of the ventrobasal nuclei of the thalamus, thalamic reticular nucleus and sensorimotor cortex. The hyperpolarized thalamocortical neurons become regularly depolarized due to slow calcium influx. This results in a rhythmic stimulation of the somatosensory cortex and thalamic reticular nucleus which in turn leads to a GABAergic inhibition of thalamocortical relay neurons of the ventrobasal thalamic nuclei resulting in their hyperpolarization followed by a new cycle of slow depolarization. Thalamocortical impulses end in the layer IV of the cortex, at the apical dendrites of pyramidal cells. The distal parts of the same neurons, located in the layer I of the cortex, also receive impulses from cortical areas subserving attention necessary to perform the SMR NFB. This coincidence makes ideal conditions for long-term potentiation (Sterman and Egner, 2006). During SMR production the input from the sensorimotor cortex to the putamen is reduced, thus leading to a greater inhibitory influence on the thalamic relay cells back to the cortex. The putative basis of the clinical effect in epilepsy includes an increased excitation threshold and improved control over the excitation in the sensorimotor systems (Sterman and Egner, 2006).

It has been shown that SMR production is associated with striatal activation (Birbaumer, 2005, in Sterman and Egner, 2006). Moreover, an increased activity of the striatum has been reported in children with ADHD (attention deficit hyperactivity disorder) after 40 sessions of SMR and low beta amplitude up-training (Levesque et al., 2006).

3.2.2 SCPs

Similarly to SMR training, the learned self-regulation of slow cortical potentials (SCPs) has also proven successful in the treatment of seizure and attention disorders. SCPs are slow direct-current shifts originating from the upper cortical layer (Birbaumer et al., 1990). They last from several hundred milliseconds up to several seconds. It has been shown that negative SCPs reflect increased cortical excitation (lowered excitation

thresholds in the apical dendrites of cortical pyramidal neurons) whereas positive SCPs indicate reduction of cortical excitation (raised excitation thresholds) (Birbaumer, 1997).

In patients with epilepsy large superficial negativities precede seizure activity (Kotchoubey et al., 1996). Therefore, the aim of SCPs training in epilepsy is to teach the patient to voluntarily shift the SCPs in a positive direction and thus interrupt seizure onset (Serman and Egner, 2006).

In children with ADHD reduced cortical negativity during anticipation of a task has been reported (Rockstroh et al., 1990). This suggests that children with attention disorders fail to engage specific cortical networks which contribute to the performance decrement (Strehl et al., 2006a). The SCPs training should enable the patients to voluntarily increase cortical excitability and thus improving attentional capacity.

It has been suggested that learned increases in positive SCPs are, similarly as the SMR pattern, associated with increased metabolic activity in the striatum (Serman and Egner, 2006) and that regulation of frontocentral negative SCPs affects the cholinergic-dopaminergic balance (Strehl et al., 2006a).

3.2.3 Alpha-theta

The third most widely used training protocol following the Kamiya's approach in NFB, is the alpha-theta training performed with eyes closed with the aim to rise the ratio of the theta over the alpha activity. This training protocol has been successfully used in alcoholics (Peniston and Kulkosky, 1989; Saxby and Peniston, 1995) as well as in enhancement of artistic performance (Egner and Gruzelier, 2003; Raymond et al., 2005a). Changes in personality measures and enhanced well-being have been described after this training (Raymond et al., 2005b). It has been proposed that alpha-theta training acts via limbic system and long distance circuitry in the brain (Gruzelier, 2009).

3.3 Neurobiological changes after NFB

The research has shown that NFB has a capacity to change electrophysiological and other functional imaging markers. The most frequently reported is an amplitude change within the trained band or an amplitude ratio of two targeted frequency bands

(Monastra et al., 2002; Fuchs et al., 2003; Leins et al., 2007; Gevensleben et al., 2009a), but changes of evoked potentials (Heinrich et al., 2004; Kropotov et al., 2005) or even fMRI changes have been reported following neurofeedback (Beauregard and Levesque, 2006). Several studies specifically addressed successful and unsuccessful NFB learners and demonstrated the presence of electrophysiological change only in those who were able to modulate their EEG activity during NFB in the desired direction (Lubar et al., 1995; Kropotov et al., 2005).

Despite of demonstrated changes in resting state EEG after NFB, there are studies reporting no or ambiguous (e.g. Egner et al., 2004) impact of NFB on resting state EEG. According to Arns et al. (2009), the NFB effect should be assessed by behavioural questionnaires and/or event related EEG rather than by resting state EEG examination.

3.4 Neurofeedback application

PubMed search for literature related to neurofeedback yielded more than 300 relevant studies concerning published in the years from 1971 to 2011. Figure 2 shows number of publications in five-year intervals. It demonstrates the initial boom, subsequent decrease and the renaissance of the neurofeedback research. Figure 3 shows the mean impact factor of the journals publishing NFB research in the years 1998 – 2011 (*Journal Citation Reports®*, Thomson Reuters). Figure 4 shows the main domains of the NFB research. As demonstrated in the Figure 5, epilepsy as the leading clinical diagnosis at the onset of the NFB era was later replaced by attention deficit disorders with or without hyperactivity (ADD/ADHD).

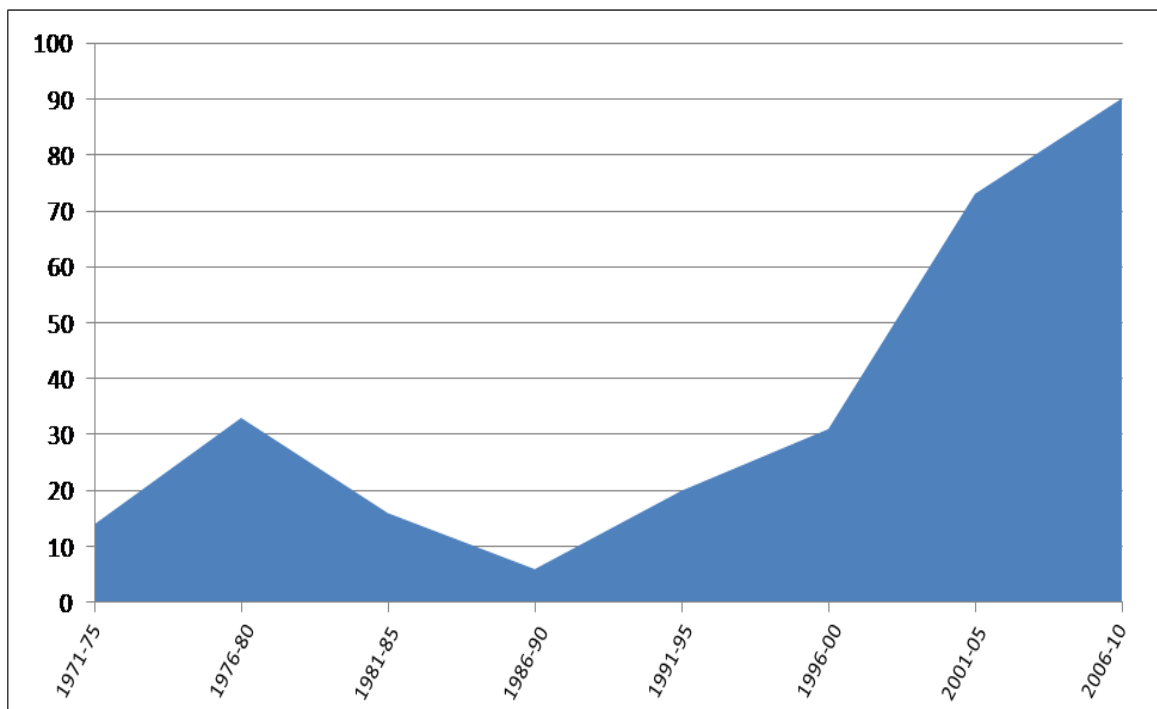


Fig. 2: NFB publications in PubMed (1971-2010).

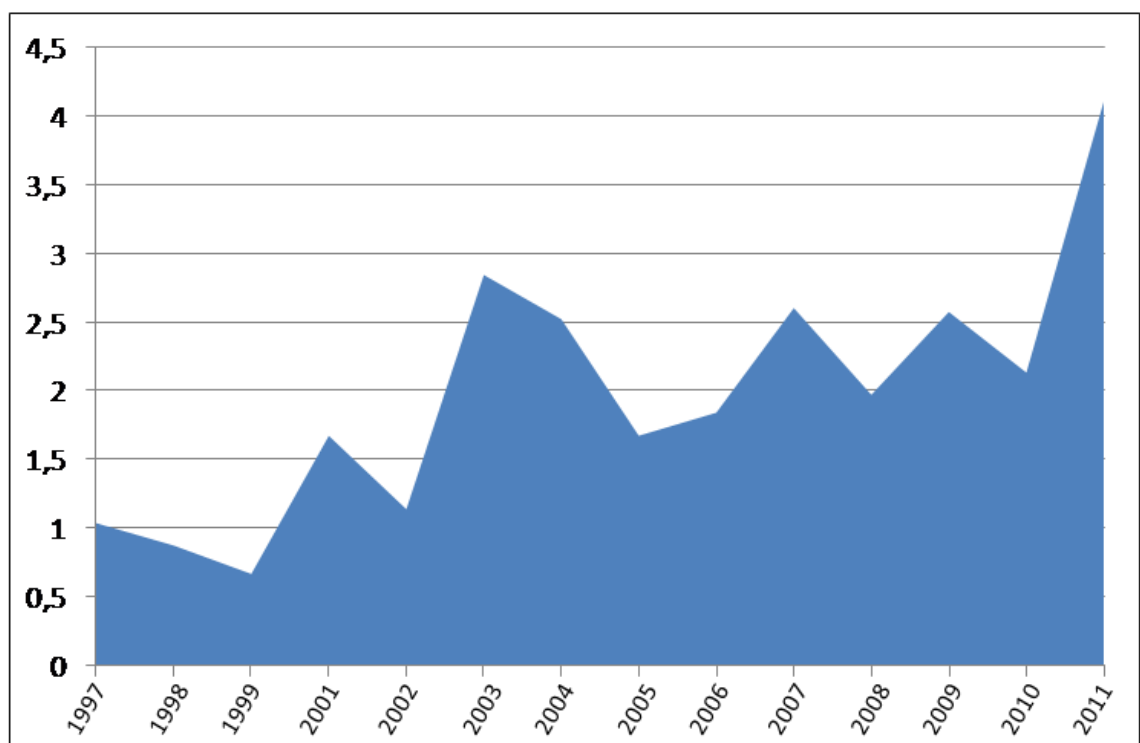


Fig. 3: Mean impact factor of journals publishing NFB studies (1998 – 2011).

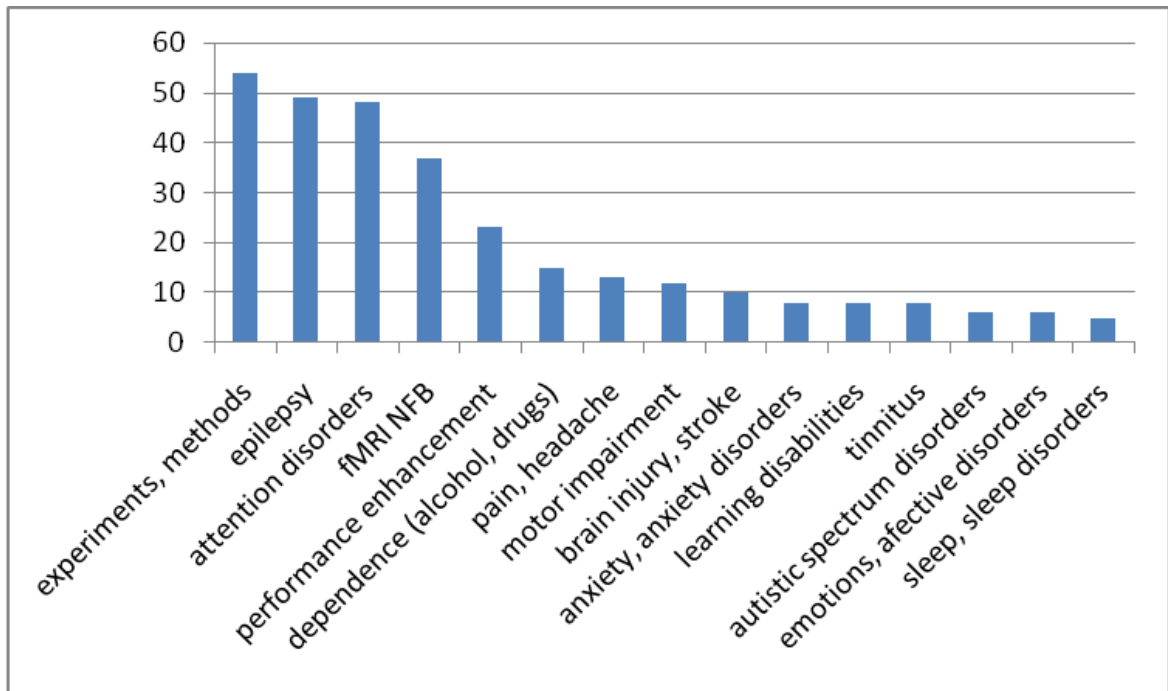


Fig. 4: Main domains of the NFB research.

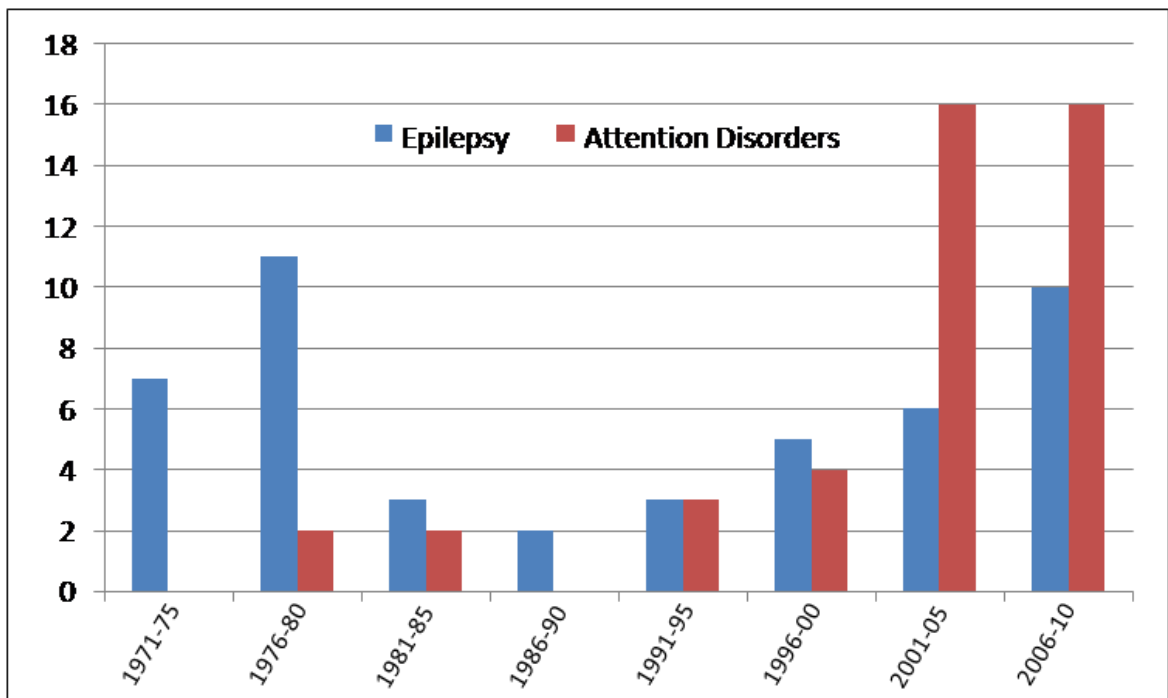


Fig. 5: Number of NFB studies in epilepsy and attention deficit disorders (1971 – 2010).

3.4.1 Neurofeedback in epilepsy

Two different NFB approaches have been described in epilepsy – the SMR training and the regulation of slow cortical potentials (SCPs). In controlled studies both methods proved successful in relieving clinical symptoms (Lantz and Serman, 1988; Kotchoubey et al., 2001). Nowadays the main research interest lies in the SCPs regulation (e.g. Kotchoubey et al., 1996; Kotchoubey et al., 1997; Kotchoubey et al., 1999a; Kotchoubey et al., 1999b; Strehl et al., 2005), however, the SMR training has recently been explored as well (Walker, 2008; Zhao et al., 2005). Although the role of unspecific factors in the treatment outcome has been admitted (Kotchoubey et al., 1999b; Strehl et al., 2006a), there is evidence that SCPs shifts towards positive or negative values are connected with changes of brain activity as detected by fMRI (Strehl et al., 2006b). Moreover, using implanted electrodes in patients with resistant epilepsy it was found that hippocampal slow potentials correlate with slow potentials recorded on the scalp (Fell et al., 2007).

Current state-of-the-art of NFB in epilepsy has been summarized in the meta-analysis by Tan et al. (2009) and the review by Nagai (2011). Both studies concluded that NFB may be useful in patients with pharmaco-resistant epilepsy.

3.4.2 Neurofeedback in attention disorders

The idea to apply SMR up-training in attention deficit hyperactivity disorder (ADHD) resulted from the notion that the SMR is produced in a wakeful state without motor activity (Serman and Egner, 2006). The first study in a hyperactive child was published in 1976 (Lubar and Shouse, 1976) and thanks to its positive impact on attention the method was then used in attention deficit disorders with or without hyperactivity (AD/HD). A second NFB approach in AD/HD based on the SCPs training was launched by Heinrich et al. (2004). Clinical efficacy of the two training protocols seems to be equal (Leins et al., 2007). Following encouraging results a number of controlled studies has been conceived and a variety of control conditions have been defined – from a waiting list, via standard pharmacotherapy, attention training, other kind of biofeedback, group therapy, to sham (or placebo) feedback where the feedback signal is only randomly related to the patient's EEG. The methods and the results of controlled studies in AD/HD are described in the Table 2.

Authors/ Year	Subjects	Sessions	Methods	Results
Linden et al., 1996	18 children	40	NFB (beta/theta) vs. no intervention	NFB led to better results at the measures of intelligence, attention and behaviour
Monastra et al., 2002	100 children	34 - 50	Pharmacotherapy and education, one group received also NFB (beta/theta)	Clinical symptoms improved in both groups, however after drug discontinuation the improvement persisted only in the NFB group. EEG changes were present only after NFB.
Fuchs et al., 2003	34 children	36	NFB (SMR and beta1) vs. pharmacotherapy	The improvement in both groups was comparable.
Heywood and Beale, 2003	7 children	80	Alternating NFB (SMR/theta) and sham NFB	NFB was not better than sham NFB when two drops-out were included in the statistical assessment.
Heinrich et al., 2004	22 children	25	NFB (SCPs) vs. no intervention	After NFB clinical symptoms and attention improved and EEG changed.
Rossiter, 2004	62 children and adults	40 or 60	NFB (beta/theta) vs. pharmacotherapy	Both groups improved in attention, behaviour was improved only after NFB.
Levesque et al., 2006	20 children	40	NFB (SMR/theta and beta/theta) vs. no intervention	At the beginning of the study fMRI during a cognitive task showed the same activation in both groups. After NFB an additional activation was found in anterior cingulate.
Drechsler et al., 2007	30 children	30	NFB (SCPs) vs. group training based on CBT	The results indicated that NFB had a specific effect that was connected with an improved control over the brain activity. Unspecific factors contributed to behavioural improvement.
Leins et al., 2007	38 children	30	NFB (beta/theta) vs. NFB (SCPs)	Both training protocols led to the improvement at behaviour, attention and intelligence measures. Clinical effect persisted six months later.
Doehnert et al., 2008	26 children	30	NFB (SCPs) vs. group therapy based on CBT	The results showed that the effect of NFB is mediated by specific and unspecific factors. After NFB, there was a tendency for the improvement of those EEG parameters that were related to the improvement at behavioural scales.
Gevensleben et al., 2009a; Gevensleben et al., 2009b; Gevensleben et al., 2010	102 children	36	NFB (1 block of beta/theta a 1 block of SCPs) vs. attention training	Symptoms improvement was higher after NFB and only after NFB there was a reduction of theta activity in EEG. The effect persisted six months later.
Bakhshayesh et al., 2011	35 children	30	NFB (beta/theta) vs. electromyographic BFB (frontal muscle relaxation)	After NFB, there was a greater improvement of clinical symptoms and improvement in tests of attention and reaction time. The improvement of hyperactivity and impulsivity was in part also due to unspecific factors.
Bakhtadze et al., 2011	93 children	30	NFB (SMR/theta and beta/theta) vs. no intervention	NFB improved the P3component of the evoked potentials reflecting the speed of information processing and decision making – the processes that are impaired in attention disorders.
Lansbergen et al., 2011	14 children	30	NFB (based on EEG, mostly SMR/theta) vs. sham NFB, a double blind study	All children and parents cooperated well and mostly did not recognize if they were receiving NFB or sham NFB. Clinical symptoms improved in both groups.
Steiner et al., 2011	41 children	cca 23	NFB (beta/theta) vs. attention training	Clinical symptoms improved in both groups.
Abbreviations: EEG - electroencephalogram; fMRI – functional magnetic resonance; CBT – cognitive-behavioural therapy; NFB - neurofeedback; SCPs – slow cortical potentials; SMR – sensorimotor rhythm				

Table 3: Controlled studies in NFB in AD/HD.

Current state-of-the-art of NFB in AD/HD has been summarized in a meta-analysis by Arns et al. (2009) showing that NFB is superior to a passive or semi-active control condition (such as waiting list, EMG biofeedback or cognitive training) in the three core symptoms of ADHD (hyperactivity, inattention, impulsivity) and that it is as effective as stimulant medication in the reduction of impulsivity (data for hyperactivity and inattention were insufficient). NFB had a high effect size for inattention and impulsivity and a medium effect size for hyperactivity. Based on The Guidelines for Evaluation of Clinical Efficacy of Psychophysiological Interventions (LaVaque et al., 2002) accepted by the International Society for Neurofeedback and Research (ISNR) and the Association for Applied Psychophysiology and Biofeedback (AAPB) and similar to those from the American Psychological Association (APA) the authors concluded that NFB can be considered efficacious and specific for the treatment of AD/HD.

3.4.3 Neurofeedback in OCD

Neurofeedback in OCD has not been systematically studied so far, however encouraging case studies have been published (Hammond, 2003). Based on its biological basis, OCD is a promising target for neurofeedback therapeutic intervention. We hypothesized that learning aimed at normalizing abnormal EEG activity (Koprivova et al., 2011a) activity would improve OCD symptoms.

However, NFB is traditionally based on the signal of one or two scalp electrodes and its major limitation is the poor spatial specificity of the trained region due to the volume conduction of electric fields in the brain (Nunez and Srinivasan, 2006). Also, scalp EEG signal suffers from poor signal-to-noise ratio and is contaminated by biological artefacts such as hearth, ocular and facial muscle electric fields. Moreover, the orbitofrontal and anterior cingulate cortices are hard to access because their contribution to the scalp signal is low. These shortcomings can be tackled by multichannel neurofeedback based on new methods of EEG analysis (Congedo et al., 2004; Cannon et al., 2007). As a promising approach it appears the derivation of feedback signal by means of blind source separation methods, BSS (Jutten and Herault, 1991), for example by independent component analysis, ICA. Using BSS, it is possible to decompose the recorded signal from the scalp into independent signals (components) pointing to intracranial generators of the registered activity. It is assumed that these

components represent the activity of simple and spatially delimited neuronal populations which is separated from other brain activity, biological artefacts and noise. Thus, they become promising candidates for the feedback signal used in the learning process to regulate the selected activity in the desired direction. This form of neurofeedback has been tested in OCD as a part of this thesis (Koprivova et al., submitted).

3.4.4 Neurofeedback in other clinical diagnoses

Among other clinical diagnoses where NFB was tested are depression (controlled study by Choi et al., 2011, reviews by Hammond, 2005; Dias and van Deusen, 2011), fibromyalgia (controlled study by Kayiran et al., 2010), migraines (controlled studies by Siniatchkin et al., 2000; Walker, 2011), motor impairment – especially in relation to brain-computer interface (e.g. Prasad et al., 2010), insomnia (controlled studies by Cortoos et al., 2010; Hammer et al., 2011), autistic spectrum disorders (reviews by Coben et al., 2010; Thompson et al., 2010; Holtmann et al., 2011), learning disabilities (controlled studies by Fernandez et al., 2003; Becerra et al., 2006; Fernandez et al., 2007; Breteler et al., 2010), tinnitus (Gosepath et al., 2001; Schenk et al., 2005; Dohrmann et al., 2007), traumatic brain injury (review by Thornton and Carmody, 2009), anxiety disorders (controlled study by Rice et al., 1993, review by Moore, 2000), dependence (controlled studies by Scott et al., 2005; Arani et al., 2010, reviews by Trudeau, 2005; Sokhadze et al., 2008) and other (see Koprivova et al., 2008).

3.4.5 Neurofeedback in performance enhancement

Performance enhancement is the most widespread NFB application in healthy subjects. NFB has been used with the aim to improve cognitive performance (Vernon et al., 2003), cognitive performance in elderly (Angelakis et al., 2007; Becerra et al., 2012), artistic performance (Raymond et al., 2005a; Gruzelier et al., 2010), sport performance (Landers et al., 1991) and professional skills in microsurgeons (Ros et al., 2009).

II. EXPERIMENTAL PART

4 AIMS AND HYPOTHESES

The primary objective of this thesis was to better understand the neurobiological background of OCD, especially its structural and electrophysiological correlates, and to identify parameters that could be trained by neurofeedback. Additionally, NFB training of one proposed EEG component has been tested in OCD.

The first study we conceived was a voxel-based morphometry study to test if there are structural alterations in OCD compared to healthy controls (Koprivova et al., 2009a). Based on the previous research (Menzies et al., 2008a), we hypothesized that OCD would show volumetric abnormalities within the orbitofrontal as well as the dorsolateral prefrontal fronto-striatal circuits.

The second and the key study of this thesis (Koprivova et al., 2011a) compared EEG sources in OCD patients and healthy controls using the standardized low-resolution electromagnetic tomography (sLORETA, Pascual-Marqui et al., 2002) and normative independent component analysis (NICA, Congedo et al., 2010). We hypothesized that OCD patients would show aberrant EEG activity in cortical regions related to OCD, especially in the medial frontal cortex as indicated by our previous morphometry study (Koprivova et al., 2009a).

In subsequent two studies, we tested if the EEG abnormality we found in OCD is a common marker of OCD and anxiety disorders (panic disorder and generalized anxiety disorder) or whether it is restricted to OCD (Koprivova et al., 2009b; Koprivova et al., 2011b).

Finally, based on the results of the above mentioned studies, we tested the use of independent component NFB training in OCD patients (Koprivova et al., submitted). We hypothesized that NFB would lead to the improvement of OCD symptoms and to a change in EEG parameters towards normal values. Moreover, in this study, we searched for EEG correlates of symptom severity and for predictors of the treatment response.

5 SUMMARY OF THE METHODS

This section provides a summary of the key methods applied in original papers that form the basis of this dissertation and where all the methodological details can be found (Koprivova et al., 2009a; Koprivova et al., 2009b; Koprivova et al., 2011a; Koprivova et al., 2011b; Koprivova et al., submitted). We used the voxel-based morphometry for MRI anatomical data, and the sLORETA and NICA for EEG data.

5.1 Subjects

Patients included in the studies were diagnosed with OCD, panic or generalized anxiety disorder based at least on ICD-10 diagnostic criteria (World Health Organisation, 1992). All patients were right-handed. The exclusion criteria involved concurrent severe or chronic medical disease, substance abuse, mental retardation, organic mental disorder, lifetime history of psychosis, mood disorders, severe head injury and neurosurgery. In addition, healthy controls were required to have no history of any mental disorder.

5.1.1 Medial frontal and dorsal cortical morphometric abnormalities are related to obsessive-compulsive disorder (Koprivova et al., 2009a)

This study enrolled 15 patients diagnosed with OCD and 15 healthy controls. One patient had to be excluded due to accidental finding of glioma. For details see Table 4.

Characteristics	OCD patients (n = 14)		Control subjects (n = 15)		Analysis	
	Mean	SD	Mean	SD	Test statistics	p
<i>Demographic</i>						
Age (years)	28.6	6.1	28.7	6.5	$t = -0.04$, d.f. = 27	0.969
Sex (men:women)	5:9	NA	6:9	NA	$\chi^2 = 0.06$, d.f. = 2	0.812
Education (3 levels)	2:10:2	NA	0:6:9	NA	$\chi^2 = 7.43$, d.f. = 3	0.024
<i>Clinical</i>						
Y-BOCS score	16.4	7.0	NA	NA	NA	NA
obsession subscore	8.1	2.9	NA	NA	NA	NA
compulsion subscore	8.2	4.5	NA	NA	NA	NA
age of OCD onset (years)	13.9	6.6	NA	NA	NA	NA
duration of illness (years)	15.6	8.3	NA	NA	NA	NA

Abbreviations: SD - standard deviation, NA - not applicable/not applied, d.f. - degrees of freedom

Table 4: Demographic and clinical characteristics of the sample published in Koprivova et al., 2009a.

At the time of study, four patients were drug-free, eight were using SSRIs medication, one patient was treated with a combination of SSRIs and mirtazapine and one with venlafaxine. Medication status was stable for at least one month. Clinical symptoms were assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS).

5.1.2 EEG source analysis using standardized electromagnetic tomography (sLORETA) in panic disorder (Koprivova et al., 2009b)

This study included 14 drug-free patients diagnosed with agoraphobia with panic disorder (F40.01, 7 patients) or with panic disorder (F41.0, 7 patients) and 14 healthy control subjects matched for age, sex and handedness (Table 5).

Characteristics	OCD patients (n = 14)		Control subjects (n = 14)	
	Mean	SD	Mean	SD
Demographic				
Age (years)	33.3	10.4	33.3	10.0
Sex (men:women)	5:9	NA	5:9	NA
Handedness (right:left)	14:0	NA	14:0	NA

Abbreviations: SD - standard deviation, NA - not applicable

Table 5: Demographic and clinical characteristics of the sample published in Koprivova et al., 2009b.

5.1.3 EEG source analysis in obsessive-compulsive disorder (Koprivova et al., 2011a)

Our key study enrolled 50 in-patients diagnosed with OCD and 50 healthy controls matched for age, sex and handedness (Table 6). At the time of EEG recording, 20 patients were drug-free and 30 were using SSRIs medication. The medication status was stable for at least 4 weeks prior to the study. Clinical data in the patient group included age of OCD onset, illness duration and symptom severity as assessed using the Y-BOCS and the Hamilton Anxiety Rating Scale (HAMA, Hamilton, 1959).

	OCD (N = 50)		controls (N = 50)		OCD - DF (N = 20)		OCD - SSRIs (N = 30)			OCD vs. controls	OCD - DF vs. controls	OCD - SSRIs vs. controls	OCD-DF vs. OCD- SSRIs
Sample characteristics	mean	SD	mean	SD	mean	SD	mean	SD	stat. test	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>
Demographic													
age (years)	29.2	5.0	28.4	5.6	28.4	4.7	29.1	5.3	Wilcoxon	0.319	0.303	0.533	0.781
sex (M:F)	20:30	NA	23:27	NA	7:13	NA	13:17	NA	chi-sq.	0.545	0.401	0.816	0.556
handedness (right:left)	48:2	NA	48:2	NA	19:1	NA	29:1	NA	chi-sq.	1.000	0.852	0.879	0.768
Clinical													
Y-BOCS (<i>n</i> = 38)	19.4	8.0	NA	NA	16.4	7.6	21.0	7.9	<i>t</i> -test	NA	NA	NA	0.092
obsessions	9.8	3.4	NA	NA	9.4	3.6	10.0	3.3	<i>t</i> -test	NA	NA	NA	0.576
compulsions	9.8	5.0	NA	NA	7.5	4.4	11.0	5.0	<i>t</i> -test	NA	NA	NA	0.040
HAMA (<i>n</i> = 35)	12.7	6.0	NA	NA	12.7	5.0	12.7	6.5	<i>t</i> -test	NA	NA	NA	0.979
age of onset (years)	16.9	7.2	NA	NA	18.1	6.9	16.1	7.4	<i>t</i> -test	NA	NA	NA	0.406
illness duration (years)	12.5	7.9	NA	NA	11.2	8.8	13.3	7.4	<i>t</i> -test	NA	NA	NA	0.402

Abbreviations: M:F – male:female, Y-BOCS - Yale-Brown Obsessive-Compulsive scale, SD - standard deviation, DF - drug-free, SSRIs – selective serotonin reuptake inhibitors, NA - not applied/not applicable

Table 6: Demographic and clinical characteristics of the groups of subjects published in Koprivova et al., 2011a.

5.1.4 EEG source analysis in patients with anxiety disorders and obsessive-compulsive disorder (Koprivova et al., 2011b)

In the next research projects we included 17 patients with generalized anxiety disorder (F41.1), 17 patients with panic disorder (F40.01 – agoraphobia with panic disorder, 10 patients, F41.0 – panic disorder, 7 patients), 17 patients with obsessive-compulsive disorder (F42) a 53 healthy controls (Table 7).

	GAD (N = 17)		PD (N = 17)		OCD (N = 17)		CONTROLS (N = 53)	
Sample characteristics	mean	SD	mean	SD	mean	SD	mean	SD
age (years)	32,9	6,05	33,6	7,48	31,9	5,13	29,6	7,61
sex (men:women)	1:16	NA	1:16	NA	2:15	NA	23:30	NA
handedness (rigt:left)	17:0	NA	17:0	NA	17:0	NA	53:0	NA
medication (no:SSRIs)	6:11	NA	6:11	NA	6:11	NA	51:2	NA

Abbreviations: GAD – generalised anxiety disorder, PD – panic disorder, OCD – obsessive-compulsive disorder, SD – standard deviation, NA – not applicable, SSRIs – selective serotonin reuptake inhibitors

Table 7: Demographic and clinical characteristics of the sample published in Koprivova et al., 2011b.

Patients with obsessive-compulsive disorder were selected from previously published sample (Koprivova et al., 2011a) based on their demographic characteristics. Drug-free patients with panic disorder were also recruited from previously published sample (Koprivova et al., 2009b).

5.1.5 Randomized, double-blind, and parallel study of clinical effect of independent component neurofeedback in obsessive-compulsive disorder (Koprivova et al., submitted)

The neurofeedback study included 20 in-patients diagnosed with OCD. Two patients dropped out for motivation or family reasons after completing two and three sessions, respectively. Five patients were drug-free and 15 were medicated with SSRIs. The medication was stable four weeks before the study and remained unchanged until its end. The demographic and clinical characteristics are shown in Table 8.

	All patients (pre-tr.) (N = 18)	NFB 1 (pre- treatment) (N = 8)	SFB 1 (pre- treatment) (N = 10)	All patients (post-tr.) (N = 18)	NFB 1 vs. SFB 1 <i>p</i>	NFB 2 vs. SFB 2 <i>p</i>	NFB 1 vs. NFB 2 <i>p</i>	SFB 1 vs. SFB 2 <i>p</i>
Sample characteristics	number	number	number	number	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>
Medication				5:13				
(none:SSRIs)	5:13	2:6	3:7		0.814	0.814	NA	NA
Demographic								
sex (men:women)	4:14	1:7	3:7	4:14	0.375	0.375	NA	NA
Education (secondary:higher)	9:9	3:5	6:4	9:9	0.343	0.343	NA	NA
	Median (range)	Median (range)	Median (range)	Median (range)				
age (years)	26.5 (19-42)	24.5 (19-42)	28 (20-38)	NA	0.396	NA	NA	NA
Clinical symptoms								
Y-BOCS	24 (5-33)	25.5 (5-33)	21.5 (16-28)	12 (2-33)	0.324	0.788	0.018	0.028
Obsession subscore	12 (3-17)	12.5 (3-17)	10.5 (8-14)	6.5 (2-18)	0.417	0.893	0.036	0.021
Compulsion subscore	12 (2-16)	12.5 (2-16)	11 (7-14)	6 (0-15)	0.367	0.440	0.012	0.041
BAI	20 (4-42)	18 (6-29)	29.5 (4-42)	10.5 (2-44)	0.142	0.350	0.262	0.044
BDI	19 (0-39)	16.5 (0-39)	23.5 (0-39)	8.5 (0-36)	0.449	0.721	0.128	0.021

Abbreviations: NFB – neurofeedback, SFB – sham feedback, NFB 1 (NFB 2) – neurofeedback group before (after) treatment, SFB 1 (SFB 2) – sham feedback group before (after) treatment, Y-BOCS - Yale-Brown Obsessive-Compulsive scale, BAI – Beck Anxiety Inventory, BDI – Beck Depression Inventory, NA - not applied/not applicable

Table 8: Demographic and clinical characteristics of the groups of subjects in the study by Koprivova et al. (submitted). The Mann-Whitney U-test was used to compare NFB and SFB group, the Wilcoxon signed-rank test was applied to explore post-treatment changes and the chi-square test was used for categorical variables.

5.2 Designs of the studies

The following Table 9 summarizes the study design of the five above mentioned studies. Moreover, in the NFB study (Koprivova et al., submitted) we performed not only pre-to post-treatment comparison but we also compared NFB and sham feedback groups before as well as after NFB treatment. This study was double blind and controlled by sham feedback that was exactly the same as NFB except that the feedback screen was not guided by real-time brain activity but by EEG signal previously recorded during NFB training of another patient.

	patients vs. healthy controls	patients vs. clinical controls	correlations with clinical variables	pre- to post-treatment comparison
<i>Koprivova et al., 2009a</i>	yes	no	yes	no
<i>Koprivova et al., 2009b</i>	yes	no	no	no
<i>Koprivova et al., 2011a</i>	yes	no	yes	no
<i>Koprivova et al., 2011b</i>	yes	yes	no	no
<i>Koprivova et al., submitted</i>	no	no	yes	yes

Table 9: Summary of the study designs.

5.3 Data acquisition

5.3.1 Anatomical data

Anatomical data were acquired on a 3 T Siemens Trio scanner with a standard 12-channel head coil using the following protocol: T1-weighted 3Dmagnetization prepared rapid acquisition gradient echo (MPRAGE) with voxel size of 1mm×1mm×1mm, 160 sagittal slices, echo time (TE) of 4.63 ms, repetition time (TR) of 2300 ms, flip angle of 10°, and field of view (FOV) of 256 mm.

5.3.2 EEG data

EEG was recorded during eyes-closed resting state on a BrainScope differential amplifier (Unimedis Ltd., Czech Republic) against the AFz, FCz or Cz reference. The signal was obtained from 19 scalp locations according to the international 10–20 system using an ECI electro-cap (Electro-Cap International, Inc., Eaton, USA). The data were sampled at a rate of 250 or 256 Hz and filtered with a 0.15–70 Hz band-pass filter.

5.4 Data analysis

5.4.1 *Voxel-based morphometry (VBM)*

Voxel-based morphometry is an automated method allowing whole brain analysis without a priori hypotheses. Although VBM has been criticized for its basic principle of brain normalization, inaccurate localization due to image registration and smoothing or for statistical approaches assuming normal distribution of the data, VBM has proven useful in characterizing subtle changes in brain structure in a variety of diseases associated with neurological and psychiatric dysfunction (Mechelli et al., 2005). In VBM, T1-weighted images are segmented into GM, WM and cerebrospinal fluid (CSF) and normalized to a brain template. Spatial normalization expands and contracts some brain regions. Therefore, a modulation step (i.e. multiplying voxel values by the Jacobian determinants derived from the spatial normalization) is often used to restore the original volume information. The results of modulated VBM are usually interpreted as markers of volume changes and in most recent publications are simply labeled as volumes (Mechelli et al., 2005).

In our study we used an optimized VBM protocol where each 3D volume of T1-weighted images was segmented into GM, WM and CSF. The normalization parameters estimated by matching GM tissue with the standard GM template provided by the analyzing software SPM5 (<http://www.fil.ion.ucl.ac.uk/spm/software/spm5>) were applied to the original T1-weighted images. Optimally normalized T1-weighted images were then segmented into GM, WM, and CSF segments, modulated by Jacobian determinants and smoothed by a Gaussian kernel of 10 mm full width at half maximum. Between-group comparisons of GM, WM and CSF volume were performed by independent sample t-tests (Koprivova et al., 2009a). Regression analysis was used to investigate the relationship between GM and WM volume and age of OCD onset, duration of illness and Y-BOCS score.

5.4.2 *Standardized low-resolution electromagnetic tomography (sLORETA)*

Low-resolution electromagnetic tomography (LORETA, Pascual-Marqui, 1999) is a widely used inverse solution technique that estimates the intracranial distribution of electrical activity (current density) in the cortex based on a three shell spherical head

model co-registered with Talairach coordinates (Talairach and Tournoux, 1988). In other words, the LORETA enables to localize intracranial generators of the EEG activity recorded on the scalp. The scope of LORETA as well as the scope EEG recorded on the scalp is almost exclusively limited to cortical grey matter because subcortical structures such as basal ganglia or brain stem nuclei are closed dipoles and their electrical potentials cannot be recorded on the scalp.

The standardized version of the method, the sLORETA, achieves zero localization error in simulations (Pascual-Marqui, 2002). However, the LORETA/sLORETA source localization is susceptible to errors and it is less accurate than direct measurements from anatomical regions. The spatial resolution of the method is low and a confounding effect comes also from the use of a standard head model that is usually applied and that was used also in our study as individual MRI anatomical data were not available for all subjects. On the other hand, the LORETA and sLORETA are fully non-invasive and relatively cheap, making them widely accessible. So far, their use has been restricted only for research purposes.

For EEG analyses in our studies we used the Eureka software (NovaTechEEG, Inc., Mesa, Arizona, USA) linked to the LORETA-Key software (Key Institute for Brain-Mind Research, Zurich, Switzerland) and we implemented the sLORETA transformation matrix. We obtained sLORETA current density estimates in 2394 cortical voxels of 7x7x7 mm labeled with Talairach coordinates (Talairach and Tournoux, 1988). The between-group and within-group comparisons of log-transformed and smoothed data were performed by means of randomization-permutation statistics in MHyT software (NovaTechEEG, Inc.).

5.4.3 Normative independent component analysis (NICA)

As opposed to sLORETA, the independent component analysis (ICA) is a data-driven (i.e. model-free) technique widely used to decompose the multivariate EEG signal into sources as independent as possible (Onton et al., 2006; Congedo et al., 2008). The assumption of EEG source independence is consistent with the fact that the cortex is organized into functionally distinct areas and that neighbouring and highly connected regions (e.g. via corpus callosum) are likely to fire in synchrony (Onton et al., 2006). Physical and statistical principles supporting the use of decomposition methods based on second-order statistics for EEG data have been reviewed in Congedo

et al. (2008). The ICA separates the signal based on its intrinsic relationships. On the other hand ICA would group correlated sources into the same components, even if they are distant in space from each other (Koprivova et al., 2011a). The normative ICA (NICA) method has recently been introduced by Congedo et al. (2010) who demonstrated that there are replicable group independent components in the resting brain of healthy individuals.

In our study (Koprivova et al., 2011a) we employed the method by Congedo et al. (2010) and used the ICoN software (<http://sites.google.com/site/marcocongedo/software/nica>) to estimate Fourier cospectral matrices for each subject in the control group and each frequency. Group ICA was performed as the approximate joint diagonalization of the grand-average Fourier cospectral matrices. We diagonalized cospectra in the range of 2–26 Hz and based on the previous study by Congedo et al. (2010) we extracted the seven most energetic components. The resulting demixing matrix was then used to extract the power of the same components from the OCD group as well as to compute the mixing matrix which contains in columns scalp spatial pattern associated with each component and thus can serve as an input for sLORETA to estimate their cortical location. For each component, absolute, relative and normal power were computed and compared to normative data obtained from the control group using the randomization-permutation approach as in sLORETA.

6 SUMMARY OF THE RESULTS

This section summarizes the main findings of our studies conceived to address the hypotheses of this thesis and published (or submitted) in peer-reviewed or impacted journals (Koprivova et al., 2009a; Koprivova et al., 2009b; Koprivova et al., 2011a; Koprivova et al., 2011b; Koprivova et al., submitted). All detailed results are described in original papers attached to this thesis.

6.1 Reduced grey matter volume in OCD

Our voxel-based morphometry study (Koprivova et al., 2009a) found significant grey matter reduction in OCD patients localized in the medial frontal cortex as well as in the right temporo-parieto-occipital, right precentral, left middle temporal region, in the left cerebellum, and in bilateral pons and mesencephalon ($p \leq 0.05$, FDR corrected, extent threshold 100 voxels, Table 10, Fig. 6).

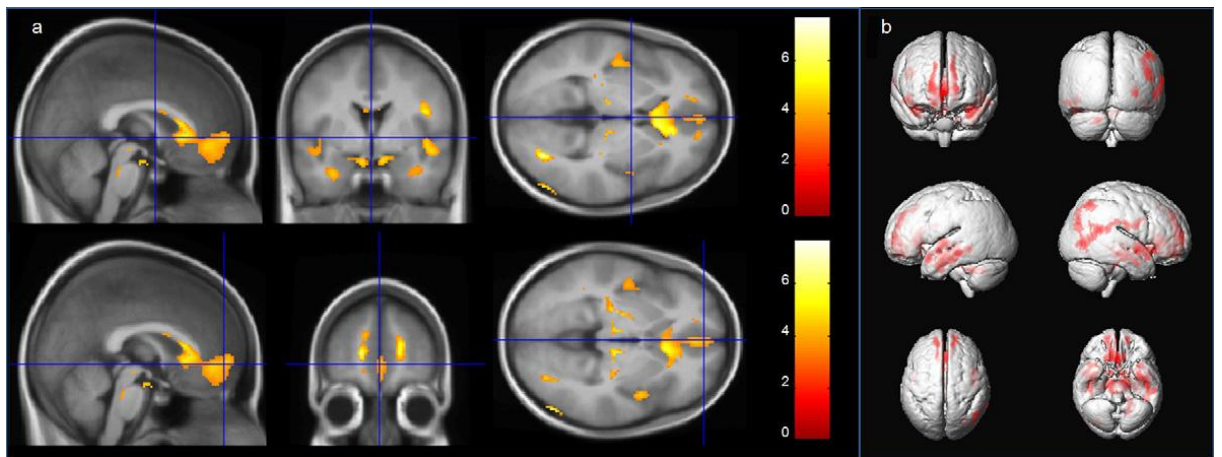


Fig. 6 (Koprivova et al., 2009a): GM volume changes in OCD patients compared to controls. Figure displays regions reduced in GM in OCD ($p \leq 0.05$, FDR corrected, extent threshold 100 voxels). Images are sliced according to the following coordinates_{xyz} in the standard stereotactic space (Talairach and Tournoux, 1988): 1a: 0, 0, 0; 1b: 7, 54, 4 (a). For the three-dimensional display a study-specific template was used (b).

Cluster-level			Voxel-level					Coordinates	Localization
p(cor)	No. of voxels	p(unc)	p(FWE-cor)	p(FDR-cor)	t-value	equiv.Z	p(unc)	x,y,z {mm}	
0.287	108	0.025	0.003	0.006	7.65	5.44	0.000	32 -72 2	R Lingual Gyrus (BA 19)
0.009	303	0.001	0.027	0.009	6.61	4.98	0.000	-10 46 32	L Medial and Superior Frontal Gyrus
			0.046	0.009	6.35	4.85	0.000	-16 54 6	- medial part (BA 9, 10)
			0.445	0.010	5.11	4.19	0.000	-14 50 22	
0.000	1486	0.000	0.031	0.009	6.55	4.95	0.000	12 34 4	Anterior Cingulate (BA 24)
			0.080	0.009	6.07	4.71	0.000	6 24 0	
			0.342	0.010	5.27	4.28	0.000	-4 22 2	
0.001	467	0.000	0.035	0.009	6.49	4.92	0.000	50 -80 30	R Superior Occipital Gyrus (BA 19)
			0.048	0.009	6.32	4.84	0.000	50 -64 52	R Inferior Parietal Lobule (BA 40)
			0.088	0.009	6.02	4.69	0.000	68 -54 16	R Superior Temporal Gyrus (BA 22)
0.000	692	0.000	0.045	0.009	6.35	4.85	0.000	-48 -18 -20	L Middle Temporal Gyrus (BA 21)
			0.531	0.011	4.98	4.11	0.000	-58 -28 -14	
			0.543	0.011	4.96	4.10	0.000	-40 -40 -8	
0.006	329	0.000	0.123	0.009	5.84	4.60	0.000	16 54 8	R Medial and Superior Frontal Gyrus
			0.608	0.011	4.87	4.05	0.000	12 46 34	- medial part (BA 8, 9, 10)
			0.957	0.017	4.26	3.66	0.000	14 50 24	
0.104	161	0.008	0.195	0.009	5.59	4.46	0.000	46 -2 22	R Precentral Gyrus (BA 6)
			0.739	0.013	4.69	3.94	0.000	48 -16 26	
0.000	1488	0.000	0.209	0.009	5.56	4.44	0.000	14 -16 -10	Pons and Mesencephalon
			0.219	0.009	5.53	4.43	0.000	-12 -14 -10	
			0.246	0.009	5.46	4.39	0.000	8 -22 -6	
0.014	273	0.001	0.361	0.010	5.24	4.26	0.000	42 -26 -14	R Fusiform Gyrus (BA 20)
			0.667	0.012	4.79	4.00	0.000	48 -20 -20	
			0.987	0.019	4.09	3.54	0.000	42 -6 -24	
0.118	154	0.009	0.410	0.010	5.16	4.22	0.000	-18 -58 -38	L Cerebellum
			0.525	0.011	4.99	4.12	0.000	-18 -48 -36	
			0.999	0.024	3.81	3.35	0.000	-26 -52 -40	
0.005	342	0.000	0.709	0.012	4.74	3.96	0.000	46 2 -8	R Superior Temporal Gyrus (BA 38)
			0.870	0.014	4.48	3.80	0.000	46 16 -8	
			0.938	0.016	4.32	3.70	0.000	40 12 -18	

Abbreviations: FWE – family-wise error, FDR – false discovery rate, BA – Brodmann area, L – left, R – right, GM – grey matter, p – p-value, Z – z-score

Table 10 (Koprivova et al., 2009a): GM volume reduction in OCD patients compared to controls. The table shows up to 3 local maxima more than 8.0 mm apart and reports only clusters containing more than 100 voxels ($p \leq 0.05$, FDR corrected). Voxels significant after FWE correction are in bold. Coordinates refer to standard stereotactic space (Talairach and Tournoux, 1988).

6.2 Increased low-frequency EEG activity in OCD

Our main study (Koprivova et al., 2011a) filling the gap in OCD literature comparing EEG sources in 50 patients with OCD (20 drug-free and 30 medicated with SSRIs) and 50 healthy control subjects confirmed the functional relevance of the medial frontal cortex in OCD. Using sLORETA, we found that OCD patients had increased normalized absolute power at low frequencies (2 – 6 Hz) in the medial frontal cortex as well as increased normalized absolute power at 2 and 3 Hz in the left parahippocampal gyrus and uncus (Table 11). The highest t-values were localized in the dorsal anterior cingulate ($t_{\max} = 4.24$, $p < 0.05$, FWE corrected, Fig. 7).

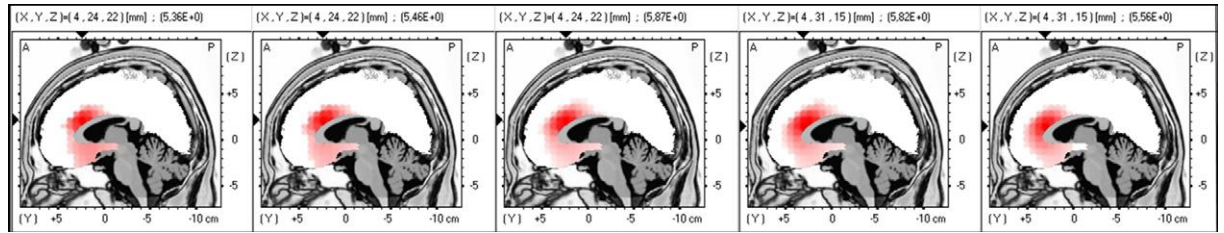


Figure 7 (Koprivova et al., 2011a): Sagittal view (left of the picture is front of the head) of absolute current density increase in OCD patients compared with controls at 2 – 6 Hz. Each figure is sliced to its own t -value maximum ($t_{\max 2\text{Hz}} = 5.36$, $t_{\max 3\text{Hz}} = 5.46$, $t_{\max 4\text{Hz}} = 5.87$, $t_{\max 5\text{Hz}} = 5.82$, $t_{\max 6\text{Hz}} = 5.56$). Figures show only the most significant voxels (the darker the red colour, the higher the t -value). For all significant voxels see Table 11.

	2 Hz		3 Hz		4 Hz		5 Hz		6 Hz	
Brain structure and Brodmann area	mean t	voxels	mean t	voxels	mean t	voxels	mean t	voxels	mean t	voxels
Anterior cingulate (BA 24, 25, 32, 33)	4.86	45	4.91	49	5.26	55	5.26	58	5.04	55
Cingulate gyrus (BA 24, 32)	4.65	21	4.76	27	4.82	38	4.83	31	4.60	17
Subcallosal gyrus (BA 25, 34)	4.70	15	4.65	14	4.77	14	4.78	10	4.62	8
Medial frontal gyrus (BA 9, 10, 11, 25)	4.58	22	4.55	29	4.71	45	4.79	51	4.62	47
Rectal gyrus (BA 11)	4.57	14	4.59	14	4.62	15	4.57	17	4.40	12
Left parahippocampal gyrus (BA 28, 34, 35, 37)	4.48	16	4.39	9	4.42	5	4.71	1	n.s.	0
Inferior frontal gyrus (BA 47)	4.42	8	4.40	5	4.38	6	4.34	3	n.s.	0
Left uncus (BA 28, 36)	4.40	10	4.33	3	n.s.	0	n.s.	0	n.s.	0
<i>total</i>		151		150		178		171		139

Table 11 (Koprivova et al., 2011a): 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.

In the NICA analysis, only one component differentiated between OCD patients and healthy controls ($p < 0.05$, corrected). The main results were significant at low frequencies, similar to the sLORETA findings. The local maxima of this component were localized in subgenual anterior cingulate (BA 25), subcallosal gyrus (BA 34), rectal gyrus (BA 11), insula (BA 13), superior temporal and parahippocampal gyrus (BA 38), midcingulate (BA 24) and marginally in lateral frontal lobe (BA 6, 8, 9) – Fig. 8, i.e. in regions partially overlapping with reduced grey matter in the previous voxel-based morphometry study in OCD (Koprivova et al., 2009a).

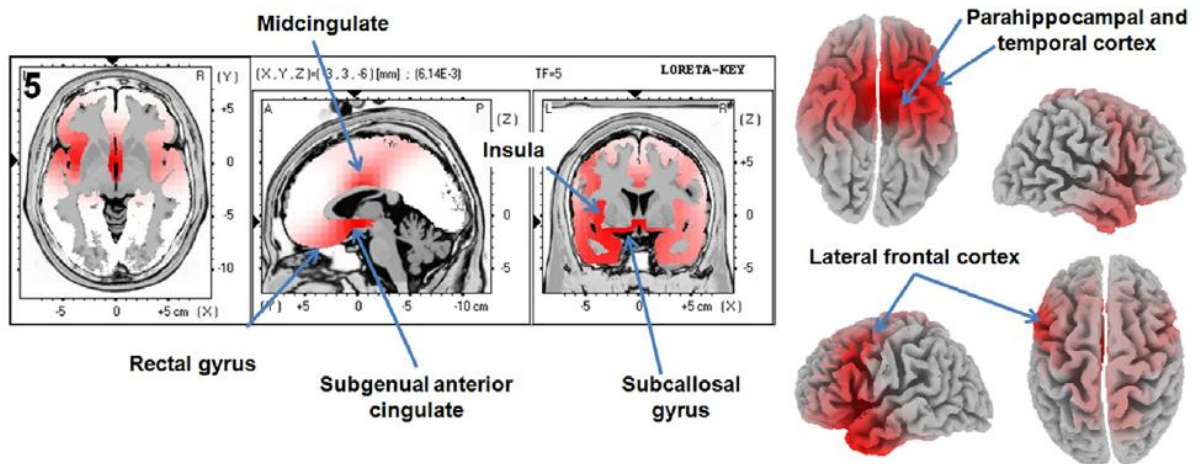


Figure 8 (Koprivova et al., 2011a): Seven independent components separated in the control group. The components are sorted according to explained variance and the images are sliced to their own maxima. From left to right, the inserts 1 to 7 show the axial (top of the picture is front of the head), sagittal (left of the picture is front of the head) and coronal (top of the picture is top of the head) view. The intensity of the red colour indicates the intensity of the signal contributing to the component (arbitrary unit and scaled to its own maximum for each component). Component 5 is also displayed on a three-dimensional cortical template.

The comparison of drug-free and SSRIs medicated patients showed that the results could not be attributed to the effect of medication.

6.3 A different EEG pattern in OCD vs. panic and generalized anxiety disorders

The low-frequency excess reported in OCD was not found in patients with panic (Koprivova et al., 2009b; Koprivova et al., 2011b) or generalized anxiety disorder – GAD (Koprivova et al., 2011b). Moreover, in Koprivova et al. (2011b) patients with panic disorder and GAD showed the same pattern of difference from healthy controls as well as from OCD patients (Fig. 9).

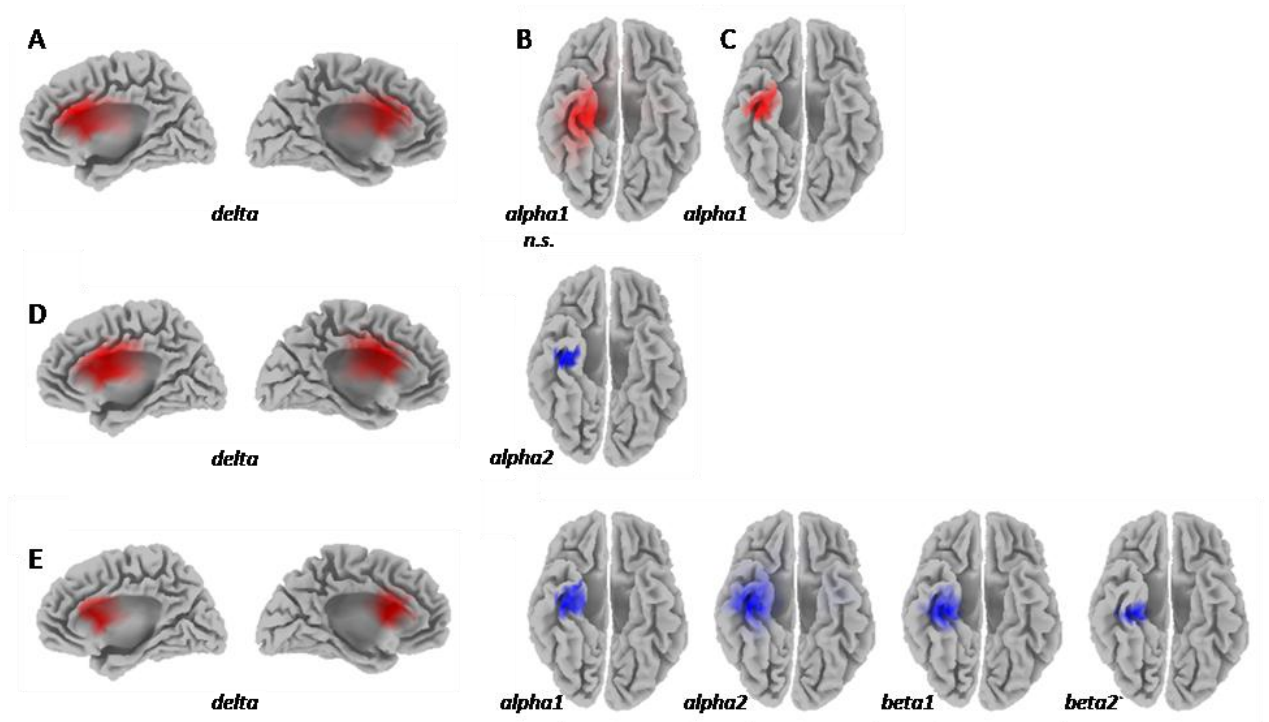


Figure 9 (after Koprivova et al., 2011b): sLORETA comparison of healthy controls ($n = 17$) with (A) OCD patients ($n = 17$), (B) generalized anxiety patients ($n = 17$), and (C) panic patients ($n = 17$), (D) sLORETA comparison of patients with OCD and generalized anxiety disorder, and (E) patients with OCD and panic disorder. Red and blue colour respectively signify higher and lower power in the comparison group mentioned first in this figure legend (i.e. controls vs. patients). The darker the colour, the higher the t -value. The results are significant at $p < 0.05$, corrected) except from those in (B) that did not reach significance and are reported for illustration.

6.4 Correlations with clinical variables

Across several studies, we searched for relationships between anatomical or electrophysiological features and clinical variables. Whereas in our largest EEG study (Koprivova et al., 2011a) we did not reveal any relationship between the increased low frequency activity on one hand and symptom severity on the other, in the morphometric study (Koprivova et al., 2009a) we found a positive relationship between left orbitofrontal grey matter volume and severity of obsessive-compulsive symptoms and a negative relationship between symptom severity and grey matter volume in supramarginal gyri. Moreover, earlier age of OCD onset and longer illness duration were associated with smaller left occipital grey matter and right parietal white matter and with greater left medial frontal grey matter and left frontal white matter ($p \leq 0.001$, uncorrected, extent threshold 50 voxels).

6.5 Predictors of treatment response

As hypothesized in Koprivova et al. (2011a), our later study (Koprivova et al., submitted) revealed a positive correlation between the amount of low-frequency activity (2 – 6 Hz) in the medial frontal cortex (esp. anterior cingulate) and the severity of obsessive-compulsive symptoms after treatment ($r \geq 0.660$, $p < 0.05$, corrected, Fig. 10), suggesting that the increased amount of the low-frequency activity is related to treatment non-responsiveness. In addition, the results indicated a trend towards a positive relationship between low-frequency component power (5 – 6 Hz) before treatment and the severity of obsessions post-treatment ($r \geq 0.701$, $p < 0.1$, two-sided). This result would be significant in a one-sided test that could actually be applied given the previous finding of increased low-frequency power in this component in OCD compared to healthy controls (Koprivova et al., 2011a).

Moreover, in the same patient group, pre-treatment absolute beta activity (18.5 – 21 Hz) in the bilateral medial orbitofrontal (more on the left side) cortex and the left pregenual anterior cingulate, lateral orbitofrontal, medial frontal and dorsolateral prefrontal cortex was positively related to the severity of obsessive-compulsive symptoms post-treatment (Fig. 11). On the other hand, a positive relationship was found between relative beta3 (21.5 – 32 Hz) before treatment and the improvement of the Y-BOCS score post-treatment. This beta3 activity showed highest t-values in the posterior cingulate extending up to the lateral surface of the frontal and parietal cortices encompassing motor and sensory areas, and furthermore in the subgenual and anterior cingulate (labeled also as anterior midcingulate), Fig. 12. Also the amount of high beta power in the independent component differentiating between OCD patients and healthy subjects (Koprivova et al., 2011a) was positively related to treatment response (Koprivova et al., submitted).

Furthermore, pre-treatment absolute low alpha (8.5 – 10 Hz) in the left fusiform and parahippocampal gyrus before treatment was negatively related ($r \leq -0.738$, $p < 0.01$) to the percentage improvement of the Y-BOCS score. Similarly, absolute low alpha power in a more widespread region with maximal correlation values in the left fusiform and left inferior temporal gyrus was positively related with obsessive-compulsive symptom severity post-treatment in the low-frequency subgroup ($r \leq 0.766$, $p < 0.01$), Fig. 13.

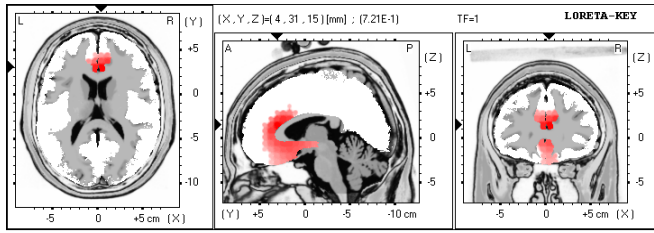


Fig. 10 (after Koprivova et al., submitted): Pre-treatment absolute delta power correlation with the Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS) score post-treatment ($r \geq 0.660$, $p < 0.05$) in subjects ($n = 15$) with pre-treatment low-frequency excess in the component 1 by Congedo et al. (2010). Voxels correlating at $r \geq 0.660$ are in red – darker colour signifies stronger correlation. The result is corrected for multiple comparisons. The image is sliced at its own maximum.

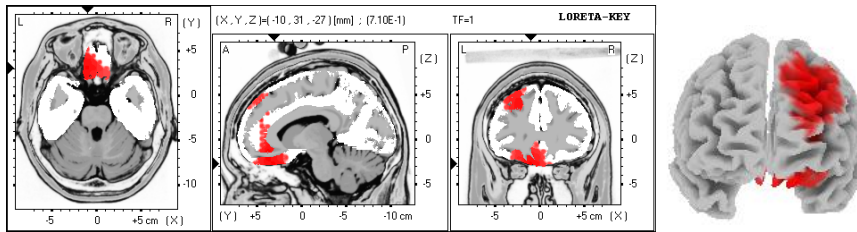


Fig. 11 (after Koprivova et al., submitted): Pre-treatment absolute beta2 (18.5 – 21 Hz) power correlation with the Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS) score post-treatment ($r \geq 0.695$, $p < 0.05$) in subjects ($n = 15$) with pre-treatment low-frequency excess in the component 1 by Congedo et al. (2010). Voxels correlating at $r \geq 0.695$ are in red – darker colour signifies stronger correlation. The result is corrected for multiple comparisons. The image is sliced at its own maximum.

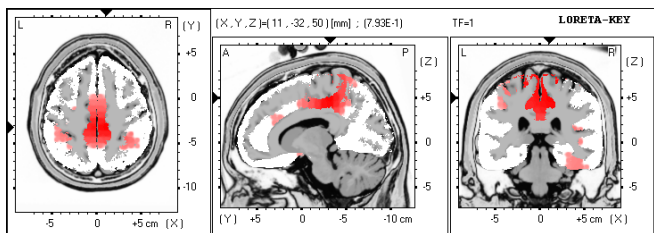


Fig. 12 (after Koprivova et al., submitted): Pre-treatment relative beta3 (21.5 – 32 Hz) power correlation with the percentage improvement at the Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS) score post-treatment ($r \geq 0.706$, $p < 0.05$) in subjects ($n = 15$) with pre-treatment low-frequency excess in the component 1 by Congedo et al. (2010). Voxels correlating at $r \geq 0.706$ are in red – darker colour signifies stronger correlation. The result is corrected for multiple comparisons. The image is sliced at its own maximum.

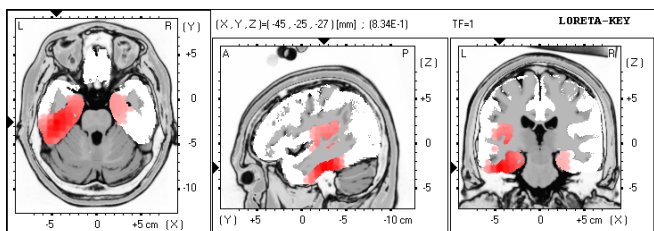


Fig. 13 (after Koprivova et al., submitted): Pre-treatment absolute low alpha (8.5 – 10 Hz) power correlation with the Yale-Brown Obsessive-Compulsive Rating Scale (Y-BOCS) score post-treatment ($r \geq 0.766$, $p < 0.01$) in subjects ($n = 15$) with pre-treatment low-frequency excess in the component 1 by Congedo et al. (2010). Voxels correlating at $r \geq 0.766$ are in red – darker colour signifies stronger correlation. The result is corrected for multiple comparisons. The image is sliced at its own maximum.

6.6 NFB results

Individually adjusted neurofeedback training aimed at down-training the abnormally high power in the EEG component 1 (Congedo et al., 2010) differentiating between OCD patients and healthy controls (Koprivova et al., 2011a) was associated with greater percentage reduction of the compulsion score after treatment ($p = 0.015$) and with a small and not significant decrease of the down-trained power in the NFB group post-treatment (Fig 14 and 15). In an additional analysis of the patient subgroup showing elevated low-frequency power before treatment ($n=15$), the difference in clinical outcome was no longer significant, however post-treatment reduction of relative low alpha power in posterior cingulate was revealed by sLORETA (Fig. 14).

Post-treatment, the relative beta band and a part of the theta band in the NFB group fell below the 95. percentile of the normative database. In the SFB group, relative theta power values remained above the 95. percentile (Fig. 15). Statistical comparisons of pre-treatment and post-treatment component relative power performed by a paired t-test showed a trend towards a decrease within the individually defined frequency band selected for the training only in the NFB group ($p = 0.147$, one-sided). No such trend was observed in the SFB group ($p = 0.817$, one-sided). The results of ANOVA with a within factor pre-post and between factor active-sham were not significant for the whole group ($F = 1.00$, $p \leq 0.331$) nor for the low-frequency subgroup ($F = 1.73$, $p \leq 0.212$, Fig. 16).

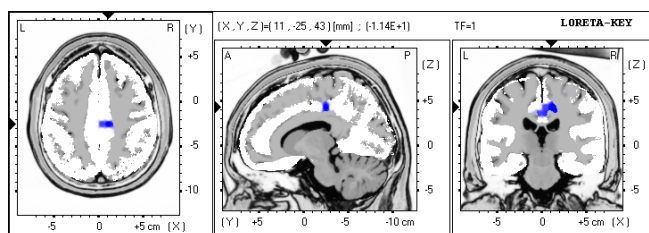


Fig. 14 (after Koprivova et al., submitted): Post-treatment relative low alpha (8.5 – 10 Hz) power reduction in the NFB subgroup ($p < 0.05$, corrected) in patients ($n = 6$) with pre-treatment low-frequency excess in the component 1 by Congedo et al. (2010). Significant voxels are in blue. The darker the colour, the higher the t-value. The image is sliced at its own maximum.

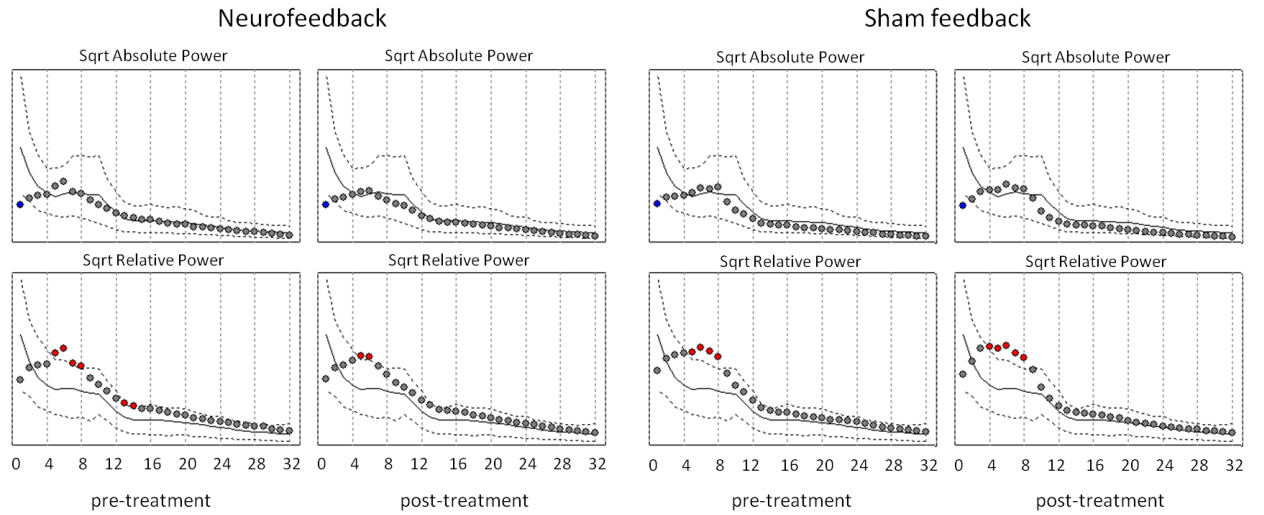


Fig. 15 (Koprivova et al., submitted): Absolute and relative power of the selected component before and after neurofeedback and sham feedback. The disks above the upper dotted line signify values exceeding the 95. percentile of the normative database.

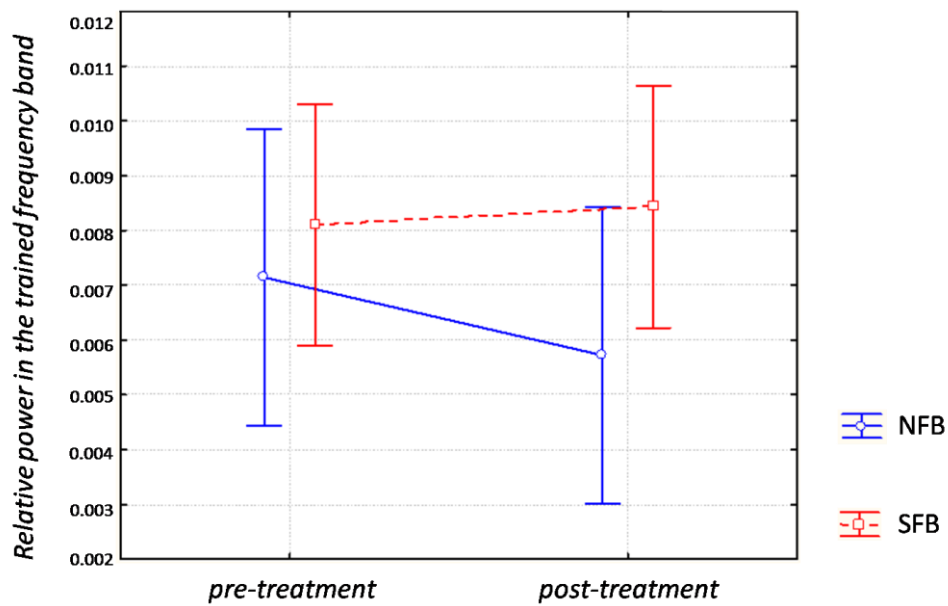


Fig. 16 (Koprivova et al., submitted): ANOVA results for the relative power of the component 1 (Congedo et al., 2010) in individually defined frequency bands selected for the training ($F = 1.73$, $p \leq 0.212$) in subjects ($n = 15$) with pre-treatment low-frequency excess in this component. The results of the neurofeedback (NFB) and sham feedback (SFB) group are in blue and red, respectively.

7 DISCUSSION AND IMPLICATION OF OUR FINDINGS

Although in the literature the main role in OCD has traditionally been ascribed to the orbitofronto-striatal loop, our findings emphasize the importance of the medial frontal cortex, especially anterior cingulate, and suggest that its role in OCD might have been underestimated. These findings are not in contradiction. The orbitofronto-striatal model has been based primarily on neuroimaging findings from PET, SPECT and MRI studies, whereas our research focused mainly on EEG source localization. It might be that abnormal activity in ACC is more easily to be captured by EEG than by neuroimaging methods. Indeed, a substantial body of evidence for the involvement of medial frontal cortex in OCD initially came from performance monitoring evoked-potential studies (e.g. Gehring et al., 1993) and their results were later confirmed in fMRI experiments (e.g. Maltby et al., 2005).

Given 1) the local maxima of increased low-frequency activity in dorsal ACC as defined by (Bush et al., 2000) or in rostral cingulate zone (RCZ) as referred to in performance monitoring studies (Ridderinkhof et al., 2004a) and 2) the most significant findings at 4 and 5 Hz, we interpreted the results in the context of performance monitoring and frontal midline theta (for details, see Koprivova et al., 2011a). Additionally, our findings can be viewed from the perspective of 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 (Knyazev, 2007). Recently Wacker et al. (2009) found a robust negative correlation between delta current density in the rostral ACC 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 signalized to the ventral striatum by an increased dopamine release (Schultz, 2007), delta activity should be negatively related with dopaminergic input. Indeed, animal studies demonstrated the association between dopamine release in the NAcc and decreased delta activity (for a review, see Wacker et al., 2009). 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 (Knyazev, 2011). It is

generated within the brain reward system (ventral tegmental area, nucleus accumbens, medial PFC, thalamic reticular nucleus). Thus, it could be hypothesized that our finding of increased delta in the medial frontal cortex in OCD reflects abnormal activity of the reward-related system signaling 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. It is possible that the explanation lies in the decreased responsiveness of the reward-related system in OCD. In healthy volunteers, Wacker et al. (2009) reported a positive association between anhedonia and resting state EEG delta activity in rostral ACC (similar but weaker correlation was found also for theta activity) and negative association between the anhedonia score and volume of nucleus accumbens and its responsiveness to reward feedback. It has been suggested that anhedonia is a vulnerability factor for various psychiatric disorders including OCD (Loas, 1996).

The distinction between the role of delta frequencies in reward processing and the role of theta frequencies in performance monitoring may be smaller than it seems at first sight. The definition of EEG frequency bands is arbitrary and does not necessarily correspond to the underlying neurophysiological processes. For example, the often used cut off between the delta and theta frequency band is 4 Hz. However, based on factor analysis, a broader low frequency band ranging from 1.5 to 7 Hz has been proposed (Pascual-Marqui et al., 2007). Interestingly, the frequency band (2 – 6 Hz) affected in OCD in our sLORETA and NICA study has been reported to show highest correlation with cerebral perfusion as measured by positron emission tomography (Leuchter et al., 1999). This inconsistency not only makes it more difficult to integrate findings from various studies but it also has an impact on the upcoming research. For example, most performance monitoring event-related potential studies a priori excluded frequencies below 4 Hz (e.g. Luu and Tucker, 2001; Luu et al., 2003; Luu et al., 2004). Nevertheless, the delta band in the study by Wacker et al. (2009) confirming the significance of delta activity in reward processing was defined between 2 – 6 Hz and thus the results are fully relevant to our findings in OCD. Both, delta and theta oscillations, correlate with behavioural disinhibition and are negatively related to the amount of alpha activity, a putative electrophysiological correlate of inhibitory processes mediated by the prefrontal cortex (Knyazev, 2007). They have been linked

with brain systems regulating behaviour on the basis of motivational drives (especially delta oscillations) and emotional appraisal (theta oscillations).

It is now believed that the reward system does not deal only with rewards and it has been suggested that its main function is salience detection (Knyazev, 2007). Interestingly, normative ICA revealed that OCD patients showed abnormal activity in the group independent component supposed to relate to the salience network (Congedo et al., 2010). The salience network is built around paralimbic structures, most prominently the dACC and frontoinsula cortices, includes subcortical sites for emotion, homeostatic regulation, and reward. It is probably bound by the dorsomedial thalamus (Seeley et al., 2007). In Congedo et al. (2010) this component forms a network consisting of the subgenual and dorsal anterior cingulate (BA 23/24/32/33/25), insula (BA 13), middle/superior frontal gyrus and paracentral lobule (BA 4/5/6), and parahippocampal gyrus (BA 28/34/35/36). Our study (Koprivova et al., 2011a) showed similar spatial distribution. The highest contribution to the component activity originated in the subgenual ACC (BA 25) that is anatomically (Ghashghaei et al., 2007) and functionally connected to the dorsal ACC (Margulies et al., 2007), the key part of the salience network. In normal subjects, this component is characterized by a prominent normal theta and low normal alpha activity signifying its contribution to the total theta and alpha power generated all over the brain (Congedo et al., 2010). This is consistent with the notion that salience detection is subserved by slow EEG frequencies that are negatively related to the amount of alpha oscillations (Knyazev, 2007). The increased normal and relative low-frequency power of this component in OCD suggests the importance of the salience detection in this disorder.

Two other source localization studies reported increased amount of beta activity in obsessive-compulsive subjects compared to healthy controls (Sherlin and Congedo, 2005; Velikova et al., 2010). In contrast to Velikova et al. (2010) who analyzed drug-naïve OCD patients, our study (Koprivova et al., 2011a) included patients (drug-free and medicated with SSRIs) who had been suffering from OCD in average for more than twelve years and most of these patients had a history of several years of unsuccessful treatment. This suggests that our sample included a high percentage of treatment nonresponders. In line with the results by Prichep et al. (1993) we hypothesized that low-frequency excess may be related to treatment non-responsiveness. Indeed, in a

subsequent study, we demonstrated that delta oscillations (1 – 6 Hz) in the medial frontal cortex were positively related to the Y-BOCS score after treatment and thus predicted worse treatment outcome (Koprivova et al., submitted). Interestingly, we also found that similarly localized pre-treatment beta activity (18.5 – 21 Hz) was positively related with obsession severity post-treatment. Consistently, increased pre-treatment beta power in the rostral ACC and medial frontal gyrus has previously been linked to a worse treatment response in OCD (Fontenelle et al., 2006).

Low-frequency oscillations and beta activity are functionally related. Knyazev et al. (2011) 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 OFC–ACC 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. In the light of this research, the findings of increased low-frequency activity in OCD (Velikova et al., 2010; Koprivova et al., 2011a) and reports of beta power excess and its localization (Sherlin and Congedo, 2005; Velikova et al., 2010) seem be complementary, rather than contradictory.

Another view on our findings provides the concept of thalamocortical dysrhythmia proposed by Llinas et al. (1999). In thalamocortical dysrhythmia, a disrupted dynamic between the thalamus and the cortex arising due to changes in the behaviour of thalamic cells leads to recurrent generation of delta and theta oscillations and thus causes dysfunction of the affected thalamocortical circuits. At the cortical level, thalamocortical dysrhythmia is characterized by a core region oscillating at low frequency, surrounded by an abnormal zone of beta or gamma band activity (Llinas et al., 2005). Zhang et al. (2009) found that cells of the thalamic reticular nucleus can be hyperpolarized by an antagonist of the N-methyl-D-aspartate-type glutamate receptor (NMDAR). This hyperpolarization is sufficient to deinactivate T-type calcium channels and trigger rhythmic bursting at delta frequency. Moreover, it has been shown that NMDAR antagonist/NMDAR hypofunction and dopamine work synergistically on the

GABAergic cells of the thalamic reticular nucleus to generate the delta frequency EEG oscillations producing thalamocortical dysrhythmia (Zhang et al., 2009). In a MEG study, Schulman et al. (2011) demonstrated that psychiatric patients with schizophrenia, major depressive disorder or OCD showed a shift of the normal alpha frequency peak to the theta range (4 – 7.9 Hz, delta was not analyzed in that study) together with higher power in the beta range (12 – 30 Hz).

The alpha frequency band has also been of scientific interest in OCD. Increased alpha activity has previously been associated with SSRIs responsiveness in OCD (Prichep et al., 1993; Hansen et al., 2003) and its sources has been localized in the thalamus, corpus striatum (including the caudate nucleus), orbitofrontal and temporo-parietal regions. The abnormality had very narrow-band frequency spectra, was more pronounced in the right hemisphere and decreased following successful treatment with paroxetine (Bolwig et al., 2007). In contrast, in our study, we found that alpha power predicted a worse treatment outcome. However, the frequency spectrum of this alpha band was lower (8.5 – 10 Hz) suggesting its different physiological meaning. Also, whereas previous studies addressed response to pharmacotherapy, in our study the treatment consisted in cognitive-behavioural therapy and neurofeedback/sham feedback (in addition to a long-term stable SSRIs medication in some patients). Nevertheless, the localization of the alpha activity predictive for the treatment response is interesting. Its maxima were found in the left fusiform gyrus. In a MEG study by Ciesielski et al. (2011) this region (together with posterior cingulate) showed reduced activity during anticipation. Anticipation of unwanted and disturbing events can be regarded as an epitome of obsessions, the core symptom of OCD (Ciesielski et al., 2011).

It is now well established that many neuropsychiatric disorders, including OCD (Menzies et al., 2007), are associated with functional and structural abnormalities in multiple distant brain regions (Menon, 2011). The involvement of widely distributed brain regions in OCD has also been confirmed in our voxel-based morphometry study (Koprivova et al., 2009a). An emerging explanatory concept suggests that these disorders are mediated by deficits in access, engagement and disengagement of three core large-scale neurocognitive networks: the default-mode network anchored in the posterior cingulate cortex and medial PFC and typically most active during rest and deactivated during cognitive effort, the central executive network anchored in

dorsolateral PFC and the lateral posterior parietal cortex, and the above mentioned salience network anchored in the dorsal ACC and anterior insula and including also two key subcortical nodes particularly relevant for psychopathology: the amygdala and the substantia nigra/ventral tegmental area (Menon, 2011). The salience network strongly overlaps with activity patterns found in performance monitoring studies (Ullsperger et al., 2010). The salience network serves as an integral hub mediating network switching, engaging the central executive network and the disengaging the default-mode network. Thus, its alterations are reflected also in the other large-scale brain networks and may result in various mental disorders (Menon, 2011). Importantly, the networks overlap in several node structures that mediate their communication. Particularly, small regions in the anterior insula and the medial prefrontal cortex have been reported to belong to the salience as well as executive control network (Seeley et al., 2007). Moreover, the medial prefrontal cortex is also the essential part of the default mode network (Raichle and Snyder, 2007). Thus, our findings of medial frontal abnormalities in OCD suggest the alteration of the key node structure common to all large-scale networks and support the Menon's view on neuropsychiatric disorders.

Posterior cingulate (PCC), the pivotal element of the default mode network, including Brodmann areas 23 and 31 (Vogt and Laureys, 2005) is another important cortical hub. Recently it has been shown that it is comprised of several overlapping subregions that are functionally connected to distinct brain networks. Thus, the PCC integrates information from various sources and is implicated in signalling environmental changes and needs to alter behaviour (Leech et al., 2012). PCC is anatomically and functionally linked to the essential structures of the OCD circuit (e.g., anterior cingulate cortex, OFC, and striatum) and thus it is ideally positioned to modulate their activity (Rauch et al., 2002). Although this structure has not been emphasized in OCD models, several neuroimaging and EEG studies pointed to its role in this disorder (McGuire et al., 1994; Busatto et al., 2000; Rauch et al., 2001; Rauch et al., 2002; Maltby et al., 2005; Sherlin and Congedo, 2005; Szeszko et al., 2005; Fitzgerald et al., 2010; Ciesielski et al., 2011; Kocak et al., 2011) as well as did also our latest study (Koprivova et al., submitted) indicating a predictive value of PCC activity for the treatment outcome and a change of PCC activity after NFB training.

In OCD, higher pre-treatment regional cerebral blood flow in the PCC has been associated with a better treatment response to anterior cingulotomy (Rauch et al., 2001)

and fluvoxamine (Rauch et al., 2002). These data correspond to our finding of a positive association between high beta in the PCC and percentage improvement of the Y-BOCS score post-treatment, suggesting that higher PCC activity predicts a better treatment outcome irrespective of treatment modality. In our neurofeedback study, we observed post-treatment relative low alpha power reduction in the PCC in the NFB group (Koprivova et al., submitted). As alpha oscillations have been associated with inhibitory processes (Knyazev, 2007) and with lower EEG alpha-BOLD signal correlation (Laufs et al., 2003), it could be hypothesized that the PCC activity increased after NFB. Given the link between higher pre-treatment PCC activity and better treatment outcome, this would indicate that NFB training led to a shift toward a better treatment responsiveness. Indeed, correlation analyses revealed that the trained component was not related to OCD symptom severity (Koprivova et al., 2011a; Koprivova et al., submitted), but it was predictive for a worse treatment outcome (Koprivova et al., submitted). Therefore, it is possible that the primary target of the used NFB protocol was treatment nonresponsiveness that could secondary impact on clinical symptoms. However, because the EEG change outside the trained component was unexpected and the interpretation is only speculative as well as due to a small number of subjects in the NFB group, these results should be replicated and further explored before drawing a firm conclusion.

With respect to a priori hypotheses, NFB led to a greater percentage improvement of the Y-BOCS compulsion subscore and to a small and non-significant decrease of the down-trained EEG power. The details and possible reasons for non-significant findings such as sample size, number of sessions, reward threshold adjustment, implementation of active learning strategies, and sensitivity of the resting state EEG are discussed in Koprivova et al. (submitted). The independent component neurofeedback in OCD used in our study is, of course, not the only possible neurofeedback approach in OCD. For example, in the context of accumulating findings of high beta in OCD (Sherlin and Congedo, 2005; Velikova et al., 2010, Koprivova et al., submitted), it would be interesting to use LORETA NFB targeting at high beta in the mid- to posterior cingulate and adjacent areas. However, in the light of the emerging large-scale network paradigm, the independent component neurofeedback seem to be very meaningful. Rather than searching for other training options, we suggest that refining of training parameters and training conditions would be a more viable pursuit. For example, some patients in our

study spontaneously reported that NFB was boring for them. Although we used monetary incentive to motivate the subjects, it seems that it was not sufficient. The NFB screen was very simple consisting of a line and squares representing the instantaneous brain activity. This feedback has previously been successfully applied in healthy subjects (Congedo et al., 2004). However, our study included clinical patients, potentially having troubles with attention and motivation, who underwent much more training sessions (25 compared to 6 sessions in the previous study). Although one of the NFB inventors, prof. Sterman holds the view that the feedback signal should be rather simple (Sterman and Egner, 2006), other studies suggest that better results can be achieved by more immersive, virtual reality NFB (Cho et al., 2004; Gruzelier et al., 2010).

In NFB studies there are at least two approaches how to define training parameters. One is based on the correlation between EEG and clinical symptoms, the other aims at normalizing aberrant EEG features hypothesizing that this could help to restore normal balance of the brain and thus improve clinical symptoms. In our study, we adopted the second approach, as correlation between clinical symptoms and EEG was not found. However, this does not necessarily mean that no such correlation exists. The reasons of negative findings such as the use of clinical rating scales, different level of clinical symptoms during EEG examination, heterogeneity of OCD, and EEG trait markers are discussed in Koprivova et al. (2011a). Possibly, a solution could be brought by extraction of EEG training parameters from EEG recorded during individually tailored symptom provocation. Then, the training could be performed as usual or the patient could receive feedback about his brain activity during experiencing clinical symptoms.

Several limitations of our above mentioned studies should be noted. First, our morphometry study was limited by a small sample size, differences in education level and use of psychotropic medication. Second, all the EEG studies were based on scalp EEG examination limiting the scope of exploration almost exclusively to cortical structures. Third, sLORETA source localization is susceptible to errors and is less accurate than direct measurements from anatomical regions. Fourth, 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, such

as time or phase relationships between EEG signals, task- or symptom provocation-related EEG, or abnormalities in parameters undetectable by EEG may be altered in OCD and remained unrevealed in our research. Our neurofeedback study was limited by a small sample size and number of training sessions. Moreover, because the abnormal power spectrum in the first component was an inclusion criterion, the results are limited only to this OCD subgroup.

8 SUMMARY AND CONCLUSION

In summary, our results indicate the importance of the medial frontal cortex, especially anterior cingulate that has shown abnormalities in OCD compared to healthy and clinical control subjects in all performed studies using both structural imaging and EEG source localization. At the same time, they are in favour of the current opinion that the traditional orbitofronto-striatal loop is not sufficient to explain OCD pathogenesis and that more widely distributed abnormalities are present in this disorder.

Central role of the ACC across our studies as well as the enhanced low-frequency activity in OCD offer a new view of OCD as a salience network-related disorder: 1) ACC is the key element of the salience network (Seeley et al., 2007), 2) salience detection is subserved by slow EEG frequencies (Knyazev, 2007), 3) the independent EEG component abnormal in OCD has been proposed to overlap with salience network (Congedo et al., 2010), and 4) the phenomenology of OCD corresponds with aberrant processing of salience (e.g. performance monitoring hypothesis by Pitman, 1987).

NFB aimed at normalizing EEG power of the abnormal independent component in OCD led, compared to sham feedback, to a greater percentage improvement of compulsions and to a non-significant EEG change in the direction of the training. Given the negative relationship between the amount of the low-frequency activity in the medial frontal cortex and future treatment response, we suggested that by NFB we targeted a network related to treatment resistance rather than a correlate of symptom severity, possibly explaining why the immediate clinical effect was low. Although the results did not confirm direct applicability and usefulness of the independent component neurofeedback in the treatment of OCD, this approach seems to be interesting in the light of the emerging large-scale brain network paradigm. We suggest that refining training parameters or training conditions could provide more clinically relevant results.

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PUBLICATIONS OF THE GRADUANT

9.1 Publications underlying this dissertation

Publications in English:

Koprivova, J., Horacek, J., Tintera, J., Prasko, J., Raszka, M., Ibrahim, I., Hoschl, C., 2009. Medial frontal and dorsal cortical morphometric abnormalities are related to obsessive-compulsive disorder. *Neurosci Lett.* 464, 62-66. **IF 1.925**

Koprivova, J., Congedo, M., Horacek, J., Prasko, J., Raszka, M., Brunovsky, M., Kohutova, B., Hoschl, C., 2011. EEG source analysis in obsessive-compulsive disorder. *Clin Neurophysiol.* 122, 1735-1743. **IF 3.406**

Koprivova J., Congedo, M., Raszka, M., Prasko, J., Brunovsky, M., Horacek, J., submitted. Prediction of treatment response and the effect of independent component neurofeedback in obsessive-compulsive disorder: a randomized, sham-controlled, and double-blind study. *Neuropsychobiology*, under review. **IF 2.675**

Publications in Czech:

Koprivova, J., Sos, P., Prasko, J., 2009. [EEG source analysis using standardized electromagnetic tomography (sLORETA) in panic disorder]. *Psychiatrie.* 13, 165-168.

Koprivova, J., Raszka, M., Sos, P., Prasko, J., Brunovsky, M., Horacek, J., 2011. [EEG source analysis in patients with anxiety disorders and obsessive-compulsive disorder]. *Psychiatrie.* 15(Suppl.2), 49-53.

9.2 Further publications related to OCD or NFB

Publications in English:

Prasko, J., Raszka, M., Adamcova, K., Grambal, A., **Koprivova, J.**, Kudrnovska, H., Latalova, K., Vyskocilova J., 2009. Predicting the therapeutic response to cognitive behavioural therapy in patients with pharmacoresistant obsessive-compulsive disorder. *Neuro Endocrinol Lett.* 30, 615-623. **IF 1.047**

Raszka, M., Prasko, J., **Koprivova, J.**, Novak, T., Adamcova, K., 2009. Psychological dissociation in obsessive-compulsive disorder is associated with anxiety level but not with severity of obsessive-compulsive symptoms. *Neuro Endocrinol Lett.* 30, 624-628. **IF 1.047**

Prasko, J., Raszka, M., Diveky, T., Grambal, A., Kamaradova, D., **Koprivova, J.**, Latalova, K., Pastucha, P., Sigmundova, Z., 2010. Obsessive compulsive disorder and

dissociation - comparison with healthy controls. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 154, 179-183.

Publications in Czech:

Koprivova, J., Prasko, J., Brunovsky, M., Raszka, M., Novak, T., Horacek, J., 2007. [Functional connectivity in obsessive-compulsive disorder: correlation analysis of electromagnetic tomography (LORETA)]. Psychiatrie. 11(Suppl.3), 99-104.

Koprivova, J., Prasko, J., Brunovsky, M., Horacek, J., 2007. [Application of independent component analysis of EEG signal in an obsessive-compulsive patient]. Psychiatrie. 11, 240-243.

Koprivova, J., Brunovsky, M., Prasko, J., Horacek, J., 2008. [EEG biofeedback and its use in clinical practice]. Psychiatrie. 12, 10-16.

Prasko, J., Praskova, H., Raszka, M., **Koprivova J.**, 2008. [Obsessive-compulsive disorder and its treatment]. Medicina pro praxi. 5, 543-547.

Prasko, J., Raszka, M., Adamcova, K., **Koprivova, J.**, Kudrnovska, H., Vyskocilova J., 2008. [Cognitive-behavioural therapy response prediction in obsessive-compulsive patients who do not respond to pharmacological treatment]. Psychiatrie. 12(Suppl 3), 55-62.

Raszka, M., Prasko, J., Adamcova, K., **Koprivova, J.**, Vyskocilova, J., 2008. [Dissociation and cognitive functions in obsessive-compulsive disorder – a cross-sectional study]. Ceska a slovenska psychiatrie. 104, 289-296.

Raszka, M., Prasko, J., **Koprivova, J.**, Horacek, J., 2010. [Electrophysiological correlate of dissociations in obsessive-compulsive disorder – a pilot study]. Psychiatrie. 14(Suppl. 2): 70-72.

Raszka, M., **Koprivova, J.**, Novak, T., Prasko, J., 2011. [Dissociation was not asociated with worse treatment outcome to cognitive behavioural therapy in patients with obsessive-compulsive disorder]. Psychiatrie. 15, 4-8.

Raszka, M., **Koprivova, J.**, Novak, T., Prasko, J., 2011. [Theta activity of anterior cingulate cortex is associated with the relative change of anxiety level and severity of obsessive-compulsive symptoms in patients with obsessive-compulsive disorder – a pilot study]. Psychiatrie. 15(Suppl.2), 54-59.

Book chapters:

Prasko, J., **Koprivova, J.**, Raszka, M., 2007. [Obsessive-compulsive disorder]. In: Herman, E., Prasko, J., Seifertova, D. (Eds.), [Consultation Psychiatry]. Galen, Prague.

Prasko, J., Slepecky, M., **Koprivova, J.**, Papalova, S., Raszka, M., 2007. [Relaxation and biofeedback]. In: Herman, E., Prasko, J., Seifertova, D., (Eds.), [Consultation Psychiatry]. Galen, Prague.

9.3 Other publications

Publications in English:

Horacek, J., Brunovsky, M., Novak, T., Tislerova, B., Palenicek, T., Bubenikova-Valesova, V., Spaniel, F., **Koprivova, J.**, Mohr, P., Balikova, M., Hoschl, C., 2010. Subanesthetic dose of ketamine decreases prefrontal theta cordance in healthy volunteers: implications for antidepressant effect. Psychol Med. 40, 1443-1451. **IF 5.200**

APPENDIXES - The five original papers underlying this dissertation

APPENDIX 1

Koprivova, J., Horacek, J., Tintera, J., Prasko, J., Raszka, M., Ibrahim, I., Hoschl, C.,
2009. Medial frontal and dorsal cortical morphometric abnormalities are related to
obsessive-compulsive disorder. *Neurosci Lett.* 464, 62-66.

APPENDIX 2

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APPENDIX 5

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