REVIEW

RJME Romanian Journal of Morphology & Embryology http://www.rjme.ro/

Morphopathological changes in obsessive-compulsive disorder

ANA MIRUNA DRĂGOI[1)], LOREDANA-GEORGIANA PECIE[2)], BOGDAN-EDUARD PATRICHI[3)], MARIA LADEA[4)]

[1)]*Department of Psychiatry, Prof. Dr. Alexandru Obregia Clinical Hospital for Psychiatry, Bucharest, Romania*

[2)]*Faculty of Psychology and Educational Sciences, University of Bucharest, Romania*

[3)]*Discipline of Psychiatry and Psychology, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

[4)]*Department of Neurosciences, Carol Davila University of Medicine and Pharmacy, Bucharest, Romania*

Abstract

The pathophysiology of the obsessive-compulsive disorder (OCD) has been studied for many years using several structural magnetic resonance imaging, discovering that the anomalies of function and structure of the brain are widespread, they involve different areas, structures and circuits with a complex interconnectivity. More than that, these anomalies cover all the life of a patient, from early childhood, due to variations of developmental stages until adult life. The research is highly important also because OCD has a major hereditary factor, with the phenotype variance between 27–47% due to hereditary factors. Under this paper, that follows last 10 years studies in this area, we will find some relevant findings consisting on neuroanatomic changes, the morphology findings of *striatum*, *globus pallidus* and thalamus, the blood flow circuit changes in various regions of the brain, brain connectivity and various correlations of them. Not to forget that OCD must be understand as an emotional disorder but in the same time as a cognitive disorder too. This approach highlights the abnormalities that have been found in brain regions involved in the cognitive and emotional behavior, as for example: extended temporal, parietal, and occipital regions, anterior cingulate, frontal *gyrus*, amygdala.

Keywords: obsessive-compulsive disorder, deep brain stimulation, gray matter alterations, prefrontal-striatal disorder, anterior cingulate cortex, occipital cortical area.

Introduction

Obsessive-compulsive disorder (OCD) with onset in over 80% of cases in childhood or adolescence, by the patient's desire to obsessively repeat various actions or thoughts, actions and/or thoughts that cannot be kept under control and that are time consuming, it is considered a chronic anxiety disorder extremely present worldwide. The relatively high prevalence of 3% and the accompanying morbidity triggered numerous pathophysiological studies, but without clearly highlighting the pathophysiology of this tubing [1]. The chronicity of this mental disorder, sometimes because of an inefficient treatment, adversely affects the patient's life in all its plains: social, family, professional. The response rate to treatment of only 60% of patients in the case of OCD inevitably leads to a low quality of life, whether we are talking about pharmacological treatment, psychotherapy or a correlation between them. OCD frequently has dissociative symptoms having a direct correlation between the level of dissociation and the severity of OCD [2]. Thus, in some cases that are not responding to the medication or psychotherapy, even if it is not the first line of treatment for this disorder, electro-convulsive therapy or neurosurgical interventions are used, such as: anterior capsulotomy, subcaudate tractotomy, but extremely rarely used.

Our review aims to synthesize recent data and inter-disciplinary research about the morphopathological changes of the brain of patients diagnosed with OCD.

Gray matter (GM) modifications

There were identified GM modifications in both adolescents and adults with OCD.

Both age groups had a greater striatal volume and less gray matter volume (GMV) in the prefrontal area. Using magnetic resonance imaging (MRI) technique, researchers have analyzed the GMV with different field values, from 1.5 T to high-field 3 T having in this way different metanalytic findings. In younger population, a smaller GMV has been identified in the left middle occipital *gyrus* (MOG). In the same time, in adults, the GMV was increased in the dorsal part of the left cerebellum and in the same time, it was smaller in the bilateral anterior cingulate cortex (ACC). In the same time, if no drugs were involved, the GMV was greater in the parietal region and temporo-insular areas both in youths and adults.

Studies have shown that there are differences about the GMV in various brain regions in adults diagnosed with OCD. More specifically, the changes imply in the prefrontal cortex and ACC a smaller GMV. On the opposite side, the changes also imply greater striatal and cerebellar GMV. Abnormalities of the GMV in the prefrontal-striatal circuit have been clearly identified using the fully computerized technique voxel-based morphometry (VBM).

There are also reported GMV alterations in OCD-youths in the parietal and occipital cortex [3].

The prefrontal-striatal circuitry in pediatric and adult OCD patients

OCD is accepted to be seen as a prefrontal-striatal disorder. Ahmari *et al.* study main findings are consistent with this hypothesis, highlighting decreases of GMV in the prefrontal regions and an increased striatal volume. In studies performed on mice, the researchers have found a persistent behavior similar to OCD when they stimulated the prefrontal-striatal circuit repeatedly. In this way too, the prefrontal-striatal circuits are proved to have a main role in OCD [4]. Research that used positron emission tomography–computed tomography (PET–CT) [5] and task-based functional MRI (fMRI) [6] also supported this pathophysiological classical circuitry in OCD etiology. Studies analyzing the functional connectivity (FC) show evidence for the prefrontal-striatal model of the OCD evidencing aberrant FC between prefrontal and striatal regions [7]. These findings of an increased striatal volume are in congruence with previous VBM meta-analysis [3, 8].

Correlations of the occipital cortex pathology on OCD youths

The same study highlights that, in the case of young patients, mainly children, the GMV is reduced in the case of OCD with a preference for left MOG, a fact that remained unchanged in the subgroup of those who did not receive anti-obsessive medication. Through independent component analysis (ICA), frequently used in fMRI studies, is been highlighted a link between visual perception-procession deficits, associated to the parietal-temporal-occipital area and frontal-subcortical activation. The higher the social stimuli patient faces the higher seems to be the deactivation of occipital/parietal regions [9]. The interruption of the network that links the frontal eye fields with the occipital areas have been shown using the diffusion tensor imaging (DTI) techniques, proving in this way that the inferior frontal-occipital *fasciculus* have an abnormal fractional anisotropy. The implication of the visual network in the pathology of OCD seems to be compensated in the adolescence and adult life of the patient because there is no decrease of GMV in the MOG on the adults with OCD that have had an early onset of the pathology [3].

Correlations of ACC and cerebellum in OCD adults

The studies have identified a decrease of the GMV in ACC (bilaterally) that reaches up to the frontal cortex in adult patients with OCD. In the same time, the same pathology has not been identified in youths with OCD. It is well known the role of the ACC as a functionally heterogeneous region, in what concerns mood disorders, schizophrenia but also in cognitive, affective processes that are linked directly with goal-action behavior. In this way, the cognitive decisions are directly affected, as well as error monitoring behavior, all of them in direct connection with OCD pathology. A reduced FC between dorsal *striatum* and the rostral ACC has been identified in pediatric patients with OCD even though there were no structural alterations of the ACC. Multiple studies have been performed on patients with OCD compared to groups of healthy subjects or between different categories of patients with OCD, some with onset in adulthood, others with onset in childhood, being known in the literature that OCD has a high prevalence of onset at an early age (more common in boys); in them, the disorder persists even in adult life [10]. The reduction of GMV is achieved gradually over time, if those concerned do not receive anti-obsessive medication. They will have GMV reductions in ACC over time. Behind this morphopathological aspect is the neurophysiological aspect, namely the decrease of glutamate concentrations in ACC in subjects with OCD compared to the group of normal subjects. Changes in functionality and metabolism in ACC are prior to structural deficits [3].

Increased metabolism in ACC, posterior cingulate cortex (PCC), middle temporal *gyrus* (MTG) and *insula* and decreased metabolism in the parietal-occipital and frontal regions

In OCD, the orbital *gyrus* is of considerable importance due to the hyperactivity of the neural circuits, as well as the patient's hypometabolism. Other regions involved are the middle frontal cortex and the occipital parietal lobe. MRI and PET–CT were performed showing decreased metabolism in supplementary motor area (SMA), as well as in the parietal-occipital areas 20 and 22 [11]. This is due to early changes in OCD and correlates with decreased metabolism in the lower middle frontal *gyrus*, as well as in the occipital lobe. In OCD, the connections between the cortical areas mentioned above and the striatal circuits are affected. This causes deficiencies in the cognitive functioning of these patients, deficiencies that are not dependent on the orbitofrontal-striatal circuits. There are functional neuroimaging studies that claim that patients with untreated OCD cause hypermetabolism in those cortical areas. Thus, there have been neurosurgical theories that have supported the appropriateness of ablative approaches.

Other psychiatric theories claim that regional metabolism can be decreased by medication. Psychological theories support the same effect of decreasing metabolism through behavioral-cognitive psychotherapy, as Gabbard stated that "psychotherapy changes the functioning of the brain". At the level of the bilateral thalamic capsule, we notice in OCD the decrease of the metabolism in ACC (Brodmann areas BA24/BA32) in orbitofrontal cortex (OFC), in the dorsomedial thalamus, as well as in the caudate *nucleus*, in the right cerebellar amygdala. On the other hand, there is an increase in metabolism in the cingulate area, thalamus and caudate *nucleus*, a metabolism that can be decreased under antioxidant medication. Thus, Sertraline from selective serotonin reuptake inhibitors (SSRIs) and Clomipramine from tricyclic antidepressants, used at higher doses than in depressive pathology, cause favorable clinical results after effective treatments (high doses, appropriate time). Instead, failure to treat OCD can cause damage caused by a high, bilateral metabolism in the precentral *gyrus* (BA6), as well as in the superior temporal and occipital. In the case of ablative neurosurgical approaches (bilateral capsulotomy), a clinical improvement is proven by the action on the metabolism of the frontal *gyrus* (both superior and inferior) in the dorsal ACC and in the

occipital lobe. The same effects are determined by the anterior cingulotomy [12]. In the study to which we refer, all the regions of the brain described above imply in OCD an abnormal metabolism, except for the orbitofrontal region of the cingulate *gyrus* and the caudate *nucleus*. Decreased metabolism occurs compensatively in OCD in the parietal-occipital and frontal regions.

Variations of regional cerebral blood flow (rCBF) in forebrain regions and in posterior brain regions

The pathophysiological mechanism of the disorder is connected with cerebral systems like the OFC, the ACC, the dorsolateral prefrontal cortex (DLPC), part of the caudate *nucleus* and thalamus. Another way of studying OCD is the imagistic scan of rCBF with the use of single-photon emission computed tomography (SPECT), as alterations of the blood flow result in dysfunctions of the brain. Imagistic studies showed modification of the blood flow (increasing and decreasing) in different cerebral regions of individuals diagnosed with OCD: in the basal ganglia, in the OFC, in the cingulate cortex. The scans also revealed modifications in the spontaneous activity of the neurons in the inferior parietal cortex, in the occipital lobe and in the cerebellum. In another study, Busatto *et al.* showed that the OCD patients have an increased blood flow in the cerebellum. Dysfunctions in the forebrain and/or posterior brain areas can lead to OCD symptomatology (the appearance of repetitive thoughts and behavior) [12]. Care must be taken considering that a continuous preoccupation of work productivity (leading to burnout), excluding personal pleasure or the work relations, is one of the symptoms of OCD [13].

OCD with anhedonia (OCD-AH) patients expressed a decline of the amplitude of low-frequency fluctuation (ALFF) in the area of the right superior temporal *gyrus* (STG). They also showed its elevation in the medial prefrontal cortex (MPFC).

OCD-AH patients and those without anhedonia (OCD-NH) showed cerebral modifications partly different. In the OCD-AH patients was reported a smaller ALFF and right STG and a greater ALFF in MPFC. ALFF levels in the right STG are negatively related with the intensity of the social anhedonia. ALFFs in the MPFC are positively linked with social and physical anhedonia [14].

OCD as a disorder, in addition to obsessive-compulsive symptoms, encompasses the less studied component of anhedonia. Anhedonia is related to motivation, emotionality, affective resonance, behavior and attitudes, based on the cortico-striatal-thalamo-cortical (CSTC) circuits. These neurofunctional circuits are the ones that underlie the processing of rewards during the performance of tasks, but they also act in rest states. Studies have shown that in patients with OCD there is altered regional activity and abnormal FC of these circuits [15]. It is important that all these circuits are also involved in OCD anhedonia. Neuroimaging studies show how the neural correlations of anhedonia are represented by the regulation of CSTC circuits in OCD. The anticoagulant cortico-striatal reward circuit (one of the CSTC circuits) involves the following brain regions: MPFC, DLPFC, ACC, OFC, *striatum* and thalamus [15–17]. Because there are significant differences between individuals with OCD in the ability of these circuits to function on a continuum between normality and marked dysconnectivity, and in terms of symptoms, patients with OCD may not have significant impairment of thymic function or may have severe anhedonia. The emphasis of current studies, compared to previous ones, should be on investigating affectivity and from a neurophysiological point of view on elucidating the neural connectivity that underlies anhedonia. For patients with OCD and anhedonia, a significant increase in ALFF was found from the medial frontal cortex and expanding anteriorly to the cingulate cortex, the bilateral OFC, and to the frontal *gyrus*, both on the right side and on the left side. For the same subgroup of patients, ALFF decreases in the posterior regions: the PCC, the bilateral thalamus, the right hippocampal *gyrus*, the right STG. Along the same lines, the study showed that subjects with OCD who do not associate anhedonia (compared to the subgroup of healthy people) have higher ALFF values in bilateral OFC, left superior frontal *gyrus* (SFG) and lower left frontal *gyrus*, and lower ALFF values in PCC [14].

The overlying and different brain modifications of OCD patients – both with good and poor insight

The OCD–poor insight (OCD-PI) patients revealed decreased ALFF in MTG and STG and also greater ALFF in right MTG. The level of the insight of the OCD patients was negatively related with the ALFF level for left MTG and for the right STG. The spontaneous cerebral activity of those regions could be the neural basis of insight in the OCD. The characteristic of OCD consists in the patient's ability to recognize the absurdity of his symptoms in terms of the intrusive nature of obsessions, as well as the unjustified repetition of rituals. In other words, OCD pathology involves the presence of insight either higher or lower (compared to psychotic disorders, such as schizophrenia). Among patients with OCD, the subgroup of those with reduced insight, involves higher rates of abnormalities at the following levels: hippocampus sting, brainstem, interhemispheric commissures, ventricles, temporal lobe [18].

ALFF differences between OCD-GI and OCD-PI

The analysis of variance (ANOVA) of the ALFF maps in terms of comparison between the three groups of subjects [OCD-PI and OCD–good insight (OCD-GI) patients, normal subjects]) shows significant differences at the following levels: frontal cortex, temporal cortex, occipital cortex, cerebellar region, limbic area. Thus, low-frequency fluctuations (LFF) with a large amplitude variation were highlighted. This occurs in the right STG and motor area and in the bilateral *cuneus*. LFF have a small variation in amplitude in the left cerebellar hemisphere, in the left caudate *nucleus*/*pallidum* and in the left middle occipital *gyrus*. These differences were noted in the group of patients with OCD-GI compared to normal subjects. In the group of patients with OCD-PI, we notice higher values of ALFF in the right middle occipital *gyrus*, as well as smaller values in the left caudate *nucleus*, left

hippocampus, left cerebellum, left caudate *nucleus*, left angular *gyrus*, left middle occipital *gyrus*, left median *gyrus*) [18].

Correlations between ALFF values and insight level

The studies regarding ALFF, at the level of the temporal *gyrus*, compared the variation of the low-frequency amplitude in the middle region to its upper region. ALFF has low values in the same regions in both classes of patients (with good and poor insight): middle left occipital *gyrus*, left caudal *nucleus*/*pallidum*. The subgroup of patients with low insight OCD has elevated ALFF values in the right middle occipital *gyrus* and reduced ALFF values in the left MTG and right STG. These low values are still important modifications in the subgroup of patients with reduced insight even after symptoms were controlled with anti-obsessional medication. Fan *et al.* [18] research reveals the importance of temporal brain regions when studying the insight and also highlights when we try to understand the clinical heterogeneity of OCD, how relevant is the presence or the absence of the insight. Because right STG, as the major structure involved in emotional perception, correlates its involvement in the level of insight in patients with OCD. The presence of insight in psychiatry, both in the subgroup of patients with OCD-GI and in the case of schizophrenia (those patients who have insight on symptoms), reflects an excessive mental involvement for those concerned to self-monitor their abnormal experiences, to recognize them as unusual. In OCD-GI, the idea is taken into account from the moment they feel the intention and before the moment when the patients act. This ability to self-monitor permanently maintained at high levels among patients with OCD-GI means that they detect the reasons behind the obsessions or compulsions, to notice the moment of intentionality and triggering. Taking action in terms of compulsions or rituals is more about reducing anxiety and less about preventing or canceling the terrible event that the person in question is thinking about. The clear awareness of the intention with the excessive mental involvement of self-monitoring of the fact that the respective mental experience is abnormal, acts in time on the GM at the STG level. GM in the STG decreases as clinically, OCD patients lose insight. The same thing happens in schizophrenia [18].

Hyperactivity in the CSTC circuit in OCD

There are some neurobiological models of OCD that postulate how the typical clinical symptomatology of the disorder is linked to hyperactivity in the CSTC circuit. Smaller imaging researches concluded that the effective treatment for OCD is actually related with decreased activity of that circuit. Anxiety, repetitive behaviors, lack of modulation of the responses are symptoms that can be the result of an imbalance between the dorsal and ventral CSTC circuit [19].

Van der Straten *et al.* [19] findings also sustain the theory that the symptom's improvement is linked with a reduction of the glucose metabolism and of the rCBF in the circuit stated above. Other studies, using PET–CT showed an alteration of the glucose metabolism in the OFC, the caudate *nucleus* and the thalamus. SPECT researches reported an important reduction of the blood flow in the caudate *nucleus*. A meta-analysis concluded that when it comes to the caudate *nucleus*, this is not any difference between the outcome of medication or cognitive-behavioral therapy (CBT).

It is generally thought that an increased blood flow can be the result of an increasing of the glucose metabolism. In healthy population, the glucose metabolism in the brain and the rCBF were directly associated. Alterations of this correlation were found in major depressive disorder. In major depressive disorder, the researchers have identified altered coupling of cerebral glucose metabolism and rCBF. In OCD, the improvement seems to be related to a reduction in the activity of CSTC circuit [19].

The autogenous–reactive classification model for OCD

Autogenous-type OCD patients (OCD-AO) have a greater ALFF in the left anterior *insula* (AI) in comparison to healthy control individuals and with reactive-type OCD patients (OCD-RO). Also, compared with the same people, OCD-AO had an increase of regional homogeneity (ReHo) in the right AI and showed a hyperconnectivity between the ACC and the bilateral AI. When compared to the control group, OCD-AO and OCD-RO patients showed some common functional deficits in the prefrontal cortex and bigger FC between the location of major functions and the bilateral AIs.

When comparing OCD-RO patients with the OCD-AO ones, the latter subgroup reveals a reduced neuronal viability in the amygdala-hippocampal area and a decreased GMV in the right AI [20–22]. The amygdala-hippocampal region was involved in acquiring and reinforcement of anxiety response and conditioned fear in the OCD and also in maintaining the acquired aversive response associated with the intrusive thought [23]. It was concluded that dysfunctions of the amygdala-hippocampal region are relevant especially for OCD-AO patients (because the autogenous obsessions seem to be more ego-dystonic and result in more aversion and negative emotions than the OCD-RO ones) [24]. The *insula*/Rolandic *operculum* was linked with response inhibition and impulsivity [25].

When talking about OCD-AO patients, the inhibitory control is diminished and it can be correlated with the decreased volume in the *insula*/Rolandic *operculum* [26].

Xia *et al.* [27] compared the differences in brain function both regionally and in terms of the integrity of the neural network, between OCD-AO and OCD-RO patients, respectively, using a control group of healthy subjects. The technique used was resting-state fMRI (rs-fMRI). Compared to healthy subjects, both those with OCD-AO and those with OCD-RO showed an increase in ALFF in left OFC and MPFC. ReHo is better in left MFG and right MFG. FC is stronger in the bilateral AI region. We are talking about a default connectivity (default mode network), which is also found in MPFC, PCC/*precuneus* and the angular *gyrus*. Patients with OCD autonomy had increased ALFF at the anterior left sting. ReHo is increased at the right AI level with high bilateral AI connectivity and in ACC. These neuroimaging changes

do not differ significantly from the subgroup of patients with OCD-RO and from the subgroup of healthy ones. Those with OCD-AO show increased FC between the bilateral AI and ACC, to patients with OCD-RO and to healthy subjects. The bilateral AI region and ACC are basic regions in the salience network (SN) of the brain, which aims to highlight, highlight in relief certain aspects of cognition. The present findings suggest that abnormal functioning of the salivary network occurs in patients with OCD-AO. SN is a pivot in the detection, processing and integration of both internal and external stimuli [27, 28]. Within the OCD-AO, the SN has a dysfunction, an excessive adherence to mental events which are being generated internally and represent the core of OCD's symptomatology (like thoughts with sexual thematic, violent impulses). Contextual stimuli can amplify the mechanism in terms of irrational generation of obsessions, a mechanism sustained from within. The anatomo-pathological correspondent is the volume changes at *insula* level, significant in patients with OCD who have aggressive impulses or excessive control [29]. They have difficulty in controlling the inhibitory type related to *insula* function compared to OCD-RO patients [26]. In addition, Harrison *et al.* [30], examining the same deviations in OCD connectivity, shows that sexual and religious thoughts – named here autogenous obsessions are linked with better connectivity between the striated *nucleus* and the insular region [27].

The *insula* area and SN-related abnormalities at this level have a fundamental role in developing and maintaining autogenous obsessions. However, in both OCD-AO and OCD-RO patients, there are deficient regional functionals, superimposed on several levels, both cortical and subcortical (ALFF increase in left OFC and MPFC, prefrontal cortex). Frontal-striatal dysfunction is conventional in OCD, ReHo is increased in bilateral MFG and straight SFG compared to the subgroup of healthy subjects.

Frontal-striatal model of OCD and altered brain connectivity

fMRI studies have been performed in which patients with OCD have had symptoms. Because throughout these studies there has been a decrease or increase in activity in the prefrontal regions, it has been concluded that pathophysiological functional changes are those that must be considered, globally, in all areas of the brain. In other words, neurophysiological studies should focus on the degradation of a certain area during a pregnancy, regardless of whether this degradation involves hypo- or hyperactivity at that level [31].

Yang *et al.* [31] demonstrated in his study of patients with OCD, a hyperactivation in the right *putamen* and upper frontal *gyrus* regions. In fact, we are talking about changes in the deeper circuits, of the frontal-striatal-thalamic type, which also involve the temporary lobe and SMA. These circuits are those known as conventional in OCD pathology and have as a clinical correspondent the impairment of the integrity of the brain control system if we look at it from an integralist perspective. The frontal-striatal circuit was first claimed to belong to the pathophysiological mechanism of OCD. Increased activity was found in SFG. It has been hypothesized that SFG has an important role in a multitude of higher cognitive functions but also in control motor functions [32], those that are affected in OCD. In SFG in patients with OSD, there was a decrease in the volume of both white matter and GM and an increase in fractional anisotropy values [33]. It should be noted, however, that Yang *et al.* study did not reveal abnormal activity in the OFC, as evidenced by other MRI–fMRI studies [34]. The OFC is considered to have an essential role in affectivity, motivation and behavior.

The clinical correspondent of the above discussion could be misleading about the lower involvement of emotions in OCD. Yang highlights the putative hyperactivity in OCD, the same hyperactivity being suggested by a meta-analysis of a neuroimaging study on emotional processing [35].

It was confirmed in multiple rows FC disturbance in the frontal-striatal-thalamic circuits, being confirmed the increase of FC in the limbic-striatal circuit and the decrease of FC in the frontal-temporal and frontal-striatal-thalamic networks. The latter are involved in cognitive as well as motor and emotional processes. The dysfunction of the connectivity described above disrupts the affectivity, thinking and activity of patients with OCD, this being the ethiopathogenic factor of the disease [31]. In OCD, the anomalies are found even at the level of the *striatum*–thalamic junction, the junction being involved in the expression of symptoms. FC decreases significantly between *putamen* and temporal spread. GM is altered in the upper temporal *gyrus* and MTG. FC decreases in rs-fMRI studies at these levels [31].

The relation between the possible pathogenesis of OCD and the intensified dopaminergic activity in certain brain regions

The brain of patient diagnosed with OCD showed also alterations in the metabolism of dopamine – it was increased in the left frontal premotor cortex and showed signs of escalation also in the left *cuneus* and right *precuneus* and *cuneus*, the left posterior cingulate *gyrus*, the left lingual *gyrus*, the right MTG and the cerebellum [36].

Hsieh *et al.* [36] imply that the greater function of the dopaminergic neurons in these areas is related to the emergence of OCD. The researchers used L-3,4-dihydroxy-6-[^{18}F]fluorophenylalanine ([^{18}F]-FDOPA) PET to evidence the presumed dysfunction in the dopaminergic system of the OCD brains. The study concluded that there are areas where the dopamine metabolism is increased – mostly outside the *striatum* (where the largest amount of [^{18}F]-FDOPA accumulates). Dopamine in the PFC has a significant role in reward conditioned-learning, in work-memory and in the adaptability related to changes in the environment. The papers found also other modifications relevant for OCD pathogenesis: an increase in the dopamine metabolism in both hemispheres of the cerebellum, in the bilateral *cuneus*, in the right *precuneus*, in the left posterior cingulate *gyrus* and in the bilateral lingual *gyri*, as well as abnormalities in the *cuneus* cortex.

CBT induces changes in cerebral metabolism in OCD

CBT was proved to be effective in treating OCD. Imagistic studies showed that this kind of therapy produces changes in the brain metabolism, but the exact response and the correlation with a clinical improvement of the symptomatology could not be identified, in the absence of some specific biomarkers.

Morgiève *et al.* [37] reported that a hemodynamic feedback to the given task was identified in the ACC the OFC one. This response was more intense when the persons were exposed to personalized images known to induce obsessions. When there was a clinical improvement, the anxiety scores and the hemodynamic response in the above-mentioned regions of the brain, also decreased, with the hemodynamic response going down even after the clinical presentation of the symptoms had reached a stable level.

According to the anatomic and functional models for OCD, the cognitive section of aforementioned therapy should correct the maladaptive cognitive patterns, which basically generate the obsessions. The target should be represented by the cortical processes originated in the ACC and in the OFC one – as these area areas are associated with the control of emotions through cognition [38]. The behavioral component of the aforementioned therapy is defined by two steps: first the exposure, second is the prevention of the response. The OCD associated behaviors, dysfunctional by definition, are stored in the basal ganglia. The aim is to regain cortical control over these dysfunctional behaviors [37].

Before therapy, the exposure task activates regions known to be highly activated in OCD (ACC, OFC). Indeed, some imaging studies have shown differences in these regions, sometimes correlated with symptoms, and corrected after successful therapy. A few exposure experiments have activated the same circuit. The hyperactivity decreased over time, meanwhile CBT, confirming that personalized obsession-inducing images task makes an adequate probe of the OCD network.

The ACC and the OFC have inputs to both basal and ventral ganglia, so they are very important areas when talking about control of actions and behavior. They become hyperactive during an acute manifestation of OCD and this could reveal a trial, one without success, to replace the compulsive rituals with a goal-oriented action plan [39].

The CBT is less used in these circumstances. When used obsession-inducing stimuli it was seen a reduction in ACC activation. This might be reflected by the simultaneous alteration in the emotional response (like anxiety scores for example) and/or an improved regulation of emotions thanks to the completion of CBT. The activity in the left OFC and ACC continuingly decreased through therapy. This could reflect some modifications due to the therapeutic intervention. Anyway, this continued disappearance of symptoms keeps in place the neural plasticity, which has a goal in re-establishment of a 'normal' profile. Unfortunately, the right OFC hyperactivity was not reduced by CBT, in comparison to the left OFC and ACC and despite the clinical efficacy. Morgiève *et al.* postulates that the right OFC works in a manner that can make one more prone to develop OCD symptomatology. He also suggests that the left OFC and the ACC function in a network that is able to modulate the intensity of the symptoms. A full recovery would then mean a vanishing of the activity of the right OFC – which works as a "trait" network. This type of network can be related to some previous studies, which reported functional modifications in the OFC of OCD. These modifications and considered to be due to phenotypes of the disorder and due to the increased vulnerability to develop the disorder. There are some hemodynamic modifications in these brain regions (ACC and OFC), which can give a positive outcome (seen in the different clinical presentations). On the other hand, right OFC deviations stay the same even by a successful CBT. This finding suggests the impact of the earliest steps of CBT for a good prognosis and result [37].

Reductions in *N*-acetylaspartate (NAA) levels occur in many brain disorders even in OCD

In another study, the NAA/creatine (Cr) ratio is lower in the patient with OCD compared to the control group in the ACC and caudate *nucleus*. In the same group of patients, after 12 weeks of SSRI antidepressant medication (Sertraline) this ratio increases significantly. The research claims that decreased NAA can be successfully treated with SSRIs, with results occurring after 12 weeks.

On the other hand, NAA is a marker for neuronal integrity and is not specific to major depression or OCD. Decreased NAA levels are found in several brain disorders in which there are losses of neurons or axons. We bring in this sense Aoki *et al*. meta-analysis [40] also performed on comparative groups of patients with OCD *versus* normal subjects, Aoki *et al*. highlighting that at the cortical level (such as the frontal cortex) significantly decreases the level of NAA compared to the areas of the cortex where there are no significant differences (like basal ganglia or thalamus). Aoki *et al*. research also shows an important relation between decreased NAA in the MPFC and the intensity of OCD symptoms. It is worth mentioning the differences between schizophrenia and OCD in the prefrontal cortex, namely in OCD the importance of the medial region while in schizophrenia the importance of the dorsolateral region. According to the same study, NAA is low in OCD and the anterior cingulate region, as well as in the caudate *nucleus*. Even at this level (subcortical), after 12 weeks of Sertraline treatment, the increase in the NAA/Cr ratio is proven [41].

Tükel *et al*. study [41] reports low NAA levels and NAA/Cr ratio at striatal level. Compared to Aoki *et al*. study using Sertraline, Tükel *et al*. study uses Citalopram to demonstrate an increase in the NAA/Cr ratio at the cortical level (prefrontal cortex), as well as at the frontal white matter and at the cingulate level. The fact claims that the morphopathological regions explained above are those involved in OCD. Timely SSRI intervention in OCD normalizes low NAA levels by claiming that these

abnormalities are potentially reversible. Consequently, pharmacological intervention is necessary at the right time so that the disorder does not cause permanent neuronal loss. The first morphopathological regions that can be affected are the anterior cingulate *gyrus* and the caudate *nucleus*. After 12 weeks of SSRI treatment, there was a tendency to increase the NAA/Cr ratio in the *putamen*. From the point of view of scoring the clinical symptomatology, significant correlations were found between the decrease of the scores on the Yale–Brown Obsessive Compulsive (Y-BOCS) Scale and the increase of the NAA/Cr ratio at the level of the caudate *nucleus*. SSRIs thus become a necessary tool to ensure neural integrity, which in turn is determined by the metabolic state of neurons.

Bilateral deep brain stimulation (DBS) of the *nucleus accumbens* as a treatment for treatment-refractory OCD

DBS involves the placement of electrodes that send electrical impulses to certain areas of the brain, depending of the symptomatology that has to be treated. The best results appeared when the DBS aimed the ventral *striatum*, the subthalamic *nucleus*, the *nucleus accumbens* (as OCD is associated with abnormalities of the reward system). In a small clinical trial, three out of four patients showed an important clinical improvement after the *nucleus accumbens* was stimulated [42].

DBS-related transient adverse effect

The most notable transient adverse effect of this kind of stimulation was hypomania. This appeared quite fast after the switch of the contact points was moved from 0 or 1 to 2 or 3. The elevated mood was mild and did not necessitate treatment with a mood stabilizer as it remitted after an average of two days. This side effect was usually present when the stimulation was reactivated after some time. There were also reported some adverse effects which remained permanent during stimulation. Seven patients reported an increase of the libido, five patients reported mild recent memory loss and three patients reported having problems with finding their words [42].

DBS efficacy

In this study, all patients had electrode implanted in the same area with the same setting of the devices. They were observed for 21 months. A decrease in symptoms of 52% was found. Also, nine out of 16 patients had a good response – mean improvement of 72%. Depressive symptoms and anxiety improved with 50%. The procedure (the surgical implantation and the stimulation) were well tolerated.

A rapid escalation of the symptoms was observed in the patients whose devices were turned off in the first two weeks. The improvement was also rapid when the devices were turned on again without their knowledge. Also, the patients whose devices were not turned off during the first two weeks had a mild escalation of their obsessive-compulsive symptoms. This was attributed to their fears regarding the blinded phase. All patients obtained a significant improvement of the mood and there was no person requesting discontinuation of the treatment, even if some of them did not experience improvement in the obsessive-compulsive area of symptomatology. Symptoms were remitted in a specific order: the mood improved first, then the anxiety decrease, followed by obsession and lastly the compulsions – and in a specific time – depressive symptoms improved in seconds, anxiety took minutes, obsession days and compulsions weeks or months. Avoidance tendencies did not respond and they needed CBT, which proved to be very effective in treating compulsions and avoidance after electrode implantation [42].

DBS *vs.* lesions

The great advantage of DBS *vs.* lesions is the possibility to modulate the brain in a focal and adjustable manner. In Denys *et al.* study, the decrease of the OCD symptoms was mainly obtained when stimulating the *nucleus accumbens* core and the *nucleus* of the *stria terminalis* with dorsal electrode contacts 2 and 3, more than the shell of the *nucleus accumbens* as previous studies stated [42].

DBS reactivation on symptoms and neuroendocrine parameters

A transient elevated mood often precedes the symptomatology improvement after DBS. A precedent paper reported that the mood improvement after DBS is related to an activity decrease of the hypothalamic–pituitary–adrenal (HPA) axis.

de Koning *et al.* [43] evaluated the effects of DBS device reactivation with visual analog scales and by using neuroendocrine measurements after 30 minutes, two hours and six hours.

After one week with the stimulation device turned off, the obsessions and compulsions, the anxiety and the depressive symptoms escalated significantly, but they improved to the same extent in only two hours after the stimulation was reactivated. The levels of plasma prolactin and thyroid stimulating hormone (TSH) were reduced during the non-stimulation period (prolactin decreased with 41%, p=0.003; TSH decreased with 39%, p=0.003). Thirty minutes after the stimulation was reactivated, the values of these hormones also increased markedly. The fast and concurrent rise of prolactin and TSH is probably a result of thyrotropin-releasing hormone (TRH) stimulation – this being related to the elevated mood observed after DBS.

Research showed that mood improvement following long-term stimulation of the accumbal area is linked with a drop in the activity of the HPA axis, demonstrated by the lowered levels of free cortisol in urine. de Koning *et al.* results show that after DBS was discontinued for one week, reactivating it leads to a fast and concurrent improvement. The symptoms improved with approximately 50% in eight out of 10 responders (regarding anxiety, mood, obsessions and compulsions). The active DBS is correlated with a fast rise of the neuroendocrine hormones' levels when compared to the no stimulation period; however,

the study shows no correlation between the clinical outcome and these hormonal changes. Three out of five individuals from the study, who did not experience a good response after one year of DBS, reported a 50% improvement in their symptoms during the first two hours after the stimulation was reactivated. One patient used to turn off the stimulator every night, only to turn it on every morning seeking the transient alleviation of his mood, which lowered his OCD symptomatology during the day.

These results demonstrate that DBS could involve a fast switch of the psychiatric symptoms, through a mechanism not fully known.

de Koning *et al.* hypothesis is that the rapid changes seen in DBS are connected to the hypothalamus, at least partially. The TSH and prolactin are produced after stimulation of the TRH. The dopamine produced by neuroendocrine neurons to the median eminence of the hypothalamus inhibits the TSH and prolactin secretion. The negative correlation between homovanillic acid (HVA) and the levels of prolactin imply the role of dopamine in those changes. TRH induces elevation of mood and start of DBS for OCD is also linked with hypomanic symptoms.

Irritable bowel syndrome (IBS) and OCD

IBS is a disorder that implies an alteration of the brain–bowel axis. Stasi *et al.* (2017) wanted to assess the neuroendocrine activity associated with this disorder. The most common psychiatric related symptoms present in patients with IBS are: social maladjustment (60%), trait anxiety (40%), OCD (23%), depressive symptoms (23%), and state anxiety (17%) [44].

Neuroendocrine markers and obsessive disorders

There were relevant correlation of neuropeptide Y with "maladjustment". Endothelin had a marked correlation with "fears of repellent animals" and "fears of natural disasters". The cortisol measured in plasma was importantly linked to "obsessive disorders", maladjustment and "fear of repellent animals". Plasma levels of 5-hydroxytryptamine (5-HT; serotonin) were associated with "state anxiety", "trait anxiety", and "psychophysical disorders". Notice that 5-HT plays also an important role in depression pathogenesis [45]. 5-Hydroxyindoleacetic acid was related to "doubts and ruminations" and cortisol measured in urine was related to "trait anxiety" [44].

Conclusions

There is a large variety of abnormalities significantly associated in structural and functionality of the brain of the patients with OCD. Based on MRI and functional imaging studies, the thalamus, OFC, cingulate cortex, the *striatum* parietal, occipital and cerebellar regions are the major areas involved in OCD based on several theories widely conceptualized.

Conflict of interests

The authors declare that they have no conflict of interests.

References

[1] Krebs G, Heyman I. Obsessive-compulsive disorder in children and adolescents. Arch Dis Child, 2015, 100(5):495–499. https://doi.org/10.1136/archdischild-2014-306934 PMID: 25398447 PMCID: PMC4413836

[2] Trifu S. Dissociative identity disorder. Psychotic functioning and impairment of growing-up processes. J Educ Sci Psychol, 2019, 9(2):102–108.

[3] Hu X, Du M, Chen L, Li L, Zhou M, Zhang L, Liu Q, Lu L, Mreedha K, Huang X, Gong Q. Meta-analytic investigations of common and distinct grey matter alterations in youths and adults with obsessive-compulsive disorder. Neurosci Biobehav Rev, 2017, 78:91–103. https://doi.org/10.1016/j.neubiorev.2017.04.012 PMID: 28442404

[4] Ahmari SE, Spellman T, Douglass NL, Kheirbek MA, Simpson HB, Deisseroth K, Gordon JA, Hen R. Repeated cortico-striatal stimulation generates persistent OCD-like behavior. Science, 2013, 340(6137):1234–1239. https://doi.org/10.1126/science.1234733 PMID: 23744948 PMCID: PMC3954809

[5] Akkus F, Terbeck S, Ametamey SM, Rufer M, Treyer V, Burger C, Johayem A, Mancilla BG, Sovago J, Buck A, Hasler G. Metabotropic glutamate receptor 5 binding in patients with obsessive-compulsive disorder. Int J Neuropsychopharmacol, 2014, 17(12):1915–1922. https://doi.org/10.1017/S1461145714000716 PMID: 24833114

[6] Marsh R, Horga G, Parashar N, Wang Z, Peterson BS, Simpson HB. Altered activation in fronto-striatal circuits during sequential processing of conflict in unmedicated adults with obsessive-compulsive disorder. Biol Psychiatry, 2014, 75(8):615–622. https://doi.org/10.1016/j.biopsych.2013.02.004 PMID: 23489416 PMCID: PMC3722261

[7] Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S, Repovs G, Cole MW, Bednarski S, Krystal JH, Bloch MH, Li CS, Pittenger C. Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. Biol Psychiatry, 2014, 75(8):595–605. https://doi.org/10.1016/j.biopsych.2013.10.021 PMID: 24314349 PMCID: PMC3969771

[8] Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. Br J Psychiatry, 2009, 195(5):393–402. https://doi.org/10.1192/bjp.bp.108.055046 PMID: 19880927

[9] Gruner P, Vo A, Argyelan M, Ikuta T, Degnan AJ, John M, Peters BD, Malhotra AK, Uluğ AM, Szeszko PR. Independent component analysis of resting state activity in pediatric obsessive-compulsive disorder. Hum Brain Mapp, 2014, 35(10):5306–5315. https://doi.org/10.1002/hbm.22551 PMID: 24867148 PMCID: PMC4169329

[10] Walitza S, Melfsen S, Jans T, Zellmann H, Wewetzer C, Warnke A. Obsessive-compulsive disorder in children and adolescents. Dtsch Arztebl Int, 2011, 108(11):173–179. https://doi.org/10.3238/arztebl.2011.0173 PMID: 21475565 PMCID: PMC3071953

[11] Zuo CT, Ma Y, Sun BM, Peng S, Zhang HW, Eidelberg D, Guan YH. Metabolic imaging of bilateral anterior capsulotomy in refractory obsessive compulsive disorder: an FDG PET study. J Cereb Blood Flow Metab, 2013, 33(6):880–887. https://doi.org/10.1038/jcbfm.2013.23 PMID: 23443174 PMCID: PMC3677106

[12] Wen SL, Cheng MH, Cheng MF, Yue JH, Wang H. Pharmacotherapy response and regional cerebral blood flow characteristics in patients with obsessive-compulsive disorder. Behav Brain Funct, 2013, 9:31. https://doi.org/10.1186/1744-9081-9-31 PMID: 23898909 PMCID: PMC3733897

[13] Trifu S. Neuroendocrine insights into burnout syndrome. Acta Endocrinol (Bucharest), 2019, 15(3):404–405. https://doi.org/10.4183/aeb.2019.404 PMID: 32010363 PMCID: PMC6992409

[14] Xia J, Fan J, Du H, Liu W, Li S, Zhu J, Yi J, Tan C, Zhu X. Abnormal spontaneous neural activity in the medial prefrontal cortex and right superior temporal *gyrus* correlates with anhedonia severity in obsessive-compulsive disorder. J Affect Disord, 2019, 259:47–55. https://doi.org/10.1016/j.jad.2019.08.019 PMID: 31437701

[15] Figee M, Vink M, de Geus F, Vulink N, Veltman DJ, Westenberg H, Denys D. Dysfunctional reward circuitry in obsessive-compulsive disorder. Biol Psychiatry, 2011, 69(9):867–874. https://doi.org/10.1016/j.biopsych.2010.12.003 PMID: 21272861

[16] Piras F, Piras F, Chiapponi C, Girardi P, Caltagirone C, Spalletta G. Widespread structural brain changes in OCD: a systematic review of voxel-based morphometry studies. Cortex, 2015, 62:89–108. https://doi.org/10.1016/j.cortex.2013.01.016 PMID: 23582297

[17] Jung WH, Kang DH, Kim E, Shin KS, Jang JH, Kwon JS. Abnormal corticostriatal-limbic functional connectivity in obsessive-compulsive disorder during reward processing and resting-state. Neuroimage Clin, 2013, 3:27–38. https://doi.org/10.1016/j.nicl.2013.06.013 PMID: 24179846 PMCID: PMC3791288

[18] Fan J, Zhong M, Gan J, Liu W, Niu C, Liao H, Zhang H, Tan C, Yi J, Zhu X. Spontaneous neural activity in the right superior temporal *gyrus* and left middle temporal *gyrus* is associated with insight level in obsessive-compulsive disorder. J Affect Disord, 2017, 207:203–211. https://doi.org/10.1016/j.jad.2016.08.027 PMID: 27723545

[19] Van der Straten AL, Denys D, van Wingen GA. Impact of treatment on resting cerebral blood flow and metabolism in obsessive compulsive disorder: a meta-analysis. Sci Rep, 2017, 7(1):17464. https://doi.org/10.1038/s41598-017-17593-7 PMID: 29234089 PMCID: PMC5727319

[20] Besiroglu L, Uguz F, Ozbebit O, Guler O, Cilli AS, Askin R. Longitudinal assessment of symptom and subtype categories in obsessive-compulsive disorder. Depress Anxiety, 2007, 24(7):461–466. https://doi.org/10.1002/da.20240 PMID: 17131352

[21] Subirà M, Alonso P, Segalàs C, Real E, López-Solà C, Pujol J, Martínez-Zalacaín I, Harrison BJ, Menchón JM, Cardoner N, Soriano-Mas C. Brain structural alterations in obsessive-compulsive disorder patients with autogenous and reactive obsessions. PLoS One, 2013, 8(9):e75273. https://doi.org/10.1371/journal.pone.0075273 PMID: 24098688 PMCID: PMC3787080

[22] Trifu S, Gutt A. Interpretative process – from utilization of predominant to psychotic decompensation. Procedia Soc Behav Sci, 2014, 187:429–433. https://doi.org/10.1016/j.sbspro.2015.03.080

[23] Via E, Cardoner N, Pujol J, Alonso P, López-Solà M, Real E, Contreras-Rodríguez O, Deus J, Segalàs C, Menchón JM, Soriano-Mas C, Harrison BJ. Amygdala activation and symptom dimensions in obsessive-compulsive disorder. Br J Psychiatry, 2014, 204(1):61–68. https://doi.org/10.1192/bjp.bp.112.123364 PMID: 24262816

[24] Seo JW, Kwon SM. Autogenous/reactive obsessions and their relationship with negative self-inferences. J Obsessive Compuls Relat Disord, 2013, 2(3):316–321. https://doi.org/10.1016/j.jocrd.2013.06.004

[25] Hsu JS, Wang PW, Ko CH, Hsieh TJ, Chen CY, Yen JY. Altered brain correlates of response inhibition and error processing in females with obesity and sweet food addiction: a functional magnetic imaging study. Obes Res Clin Pract, 2017, 11(6):677–686. https://doi.org/10.1016/j.orcp.2017.04.011 PMID: 28552670

[26] Fan J, Zhong MT, Gan J, Liu W, Niu C, Liao H, Zhang H, Yi J, Chan RCK, Tan C, Zhu X. Altered connectivity within and between the default mode, central executive, and salience networks in obsessive-compulsive disorder. J Affect Disord, 2017, 223:106–114. https://doi.org/10.1016/j.jad.2017.07.041 PMID: 28743059

[27] Xia J, Fan J, Liu W, Du H, Zhu J, Yi J, Tan C, Zhu X. Functional connectivity within the salience network differentiates autogenous-from reactive-type obsessive-compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry, 2020, 98:109813. https://doi.org/10.1016/j.pnpbp.2019.109813 PMID: 31785320

[28] Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct, 2010, 214(5–6):655–667. https://doi.org/10.1007/s00429-010-0262-0 PMID: 20512370 PMCID: PMC2899886

[29] Alvarenga PG, do Rosário MC, Batistuzzo MC, Diniz JB, Shavitt RG, Duran FLS, Dougherty DD, Bressan RA, Míguel EC, Hoexter MQ. Obsessive-compulsive symptom dimensions correlate to specific gray matter volumes in treatment-naïve patients. J Psychiatr Res, 2012, 46(12):1635–1642. https://doi.org/10.1016/j.jpsychires.2012.09.002 PMID: 23040160

[30] Harrison BJ, Pujol J, Cardoner N, Deus J, Alonso P, López-Solà M, Contreras-Rodríguez O, Real E, Segalàs C, Blanco-Hinojo L, Menchon JM, Soriano-Mas C. Brain corticostriatal systems and the major clinical symptom dimensions of obsessive-compulsive disorder. Biol Psychiatry, 2013, 73(4):321–328. https://doi.org/10.1016/j.biopsych.2012.10.006 PMID: 23200527

[31] Yang X, Hu X, Tang W, Li B, Yang Y, Gong Q, Huang X. Intrinsic brain abnormalities in drug-naïve patients with obsessive-compulsive disorder: a resting-state functional MRI study. J Affect Disord, 2019, 245:861–868. https://doi.org/10.1016/j.jad.2018.11.080 PMID: 30699871

[32] Li W, Qin W, Liu H, Fan L, Wang J, Jiang T, Yu C. Subregions of the human superior frontal *gyrus* and their connections. Neuroimage, 2013, 78:46–58. https://doi.org/10.1016/j.neuroimage.2013.04.011 PMID: 23587692

[33] Li F, Huang X, Yang Y, Li B, Wu Q, Zhang T, Lui S, Kemp GJ, Gong Q. Microstructural brain abnormalities in patients with obsessive-compulsive disorder: diffusion-tensor MR imaging study at 3.0 T. Radiology, 2011, 260(1):216–223. https://doi.org/10.1148/radiol.11101971 PMID: 21474704

[34] Giménez M, Guinea-Izquierdo A, Villalta-Gil V, Martínez-Zalacaín I, Segalàs C, Subirà M, Real E, Pujol J, Harrison BJ, Haro JM, Sato JR, Hoexter MQ, Cardoner N, Alonso P, Menchón JM, Soriano-Mas C. Brain alterations in low-frequency fluctuations across multiple bands in obsessive compulsive disorder. Brain Imaging Behav, 2017, 11(6):1690–1706. https://doi.org/10.1007/s11682-016-9601-y PMID: 27771857

[35] Thorsen AL, Hagland P, Radua J, Mataix-Cols D, Kvale G, Hansen B, van den Heuvel OA. Emotional processing in obsessive-compulsive disorder: a systematic review and meta-analysis of 25 functional neuroimaging studies. Biol Psychiatry Cogn Neurosci Neuroimaging, 2018, 3(6):563–571. https://doi.org/10.1016/j.bpsc.2018.01.009 PMID: 29550459 PMCID: PMC5994188

[36] Hsieh HJ, Lue KH, Tsai HC, Lee CC, Chen SY, Kao PF. L-3,4-Dihydroxy-6-[F-18]fluorophenylalanine positron emission tomography demonstrating dopaminergic system abnormality in the brains of obsessive-compulsive disorder patients. Psychiatry Clin Neurosci, 2014, 68(4):292–298. https://doi.org/10.1111/pcn.12139 PMID: 24405478

[37] Morgiève M, N'Diaye K, Haynes WIA, Granger B, Clair AH, Pelissolo A, Mallet L. Dynamics of psychotherapy-related cerebral haemodynamic changes in obsessive compulsive disorder using a personalized exposure task in functional magnetic resonance imaging. Psychol Med, 2014, 44(7):1461–1473. https://doi.org/10.1017/S0033291713002237 PMID: 24001313

[38] Clark DA, Beck AT. Cognitive theory and therapy of anxiety and depression: convergence with neurobiological findings. Trends Cogn Sci, 2010, 14(9):418–424. https://doi.org/10.1016/j.tics.2010.06.007 PMID: 20655801

[39] Gillan CM, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW, de Wit S. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. Am J Psychiatry, 2011, 168(7):718–726. https://doi.org/10.1176/appi.ajp.2011.10071062 PMID: 21572165 PMCID: PMC3533260

[40] Aoki Y, Aoki A, Suwa H. Reduction of *N*-acetylaspartate in the medial prefrontal cortex correlated with symptom severity in obsessive–compulsive disorder: meta-analyses of ^{1}H-MRS studies. Transl Psychiatry, 2012, 2(8):e153. https://doi.org/10.1038/tp.2012.78 PMID: 22892718 PMCID: PMC3432192

[41] Tükel R, Aydın K, Ertekin E, Özyıldırım SŞ, Barburoğlu M. ^{1}H-magnetic resonance spectroscopy in obsessive-compulsive disorder: effects of 12 weeks of sertraline treatment on brain metabolites. Eur Arch Psychiatry Clin Neurosci, 2015, 265(3):219–226. https://doi.org/10.1007/s00406-014-0545-1 PMID: 25256264

[42] Denys D, Mantione M, Figee M, van den Munckhof P, Koerselman F, Westenberg H, Bosch A, Schuurman R. Deep brain stimulation of the *nucleus accumbens* for treatment-refractory obsessive-compulsive disorder. Arch Gen Psychiatry, 2010, 67(10):1061–1068. https://doi.org/10.1001/archgenpsychiatry.2010.122 PMID: 20921122

[43] de Koning PP, Figee M, Endert E, van den Munckhof P, Schuurman PR, Storosum JG, Denys D, Fliers E. Rapid effects of deep brain stimulation reactivation on symptoms and

neuroendocrine parameters in obsessive-compulsive disorder. Transl Psychiatry, 2016, 6(1):e722. https://doi.org/10.1038/tp.2015.222 PMID: 26812043 PMCID: PMC5068888

[44] Stasi C, Bellini M, Gambaccini D, Duranti E, de Bortoli N, Fani B, Albano E, Russo S, Sudano I, Laffi G, Taddei S, Marchi S, Bruno RM. Neuroendocrine dysregulation in irritable bowel syndrome patients: a pilot study. J Neurogastroenterol Motil, 2017, 23(3):428–434. https://doi.org/10.5056/jnm16155 PMID: 28460516 PMCID: PMC5503293

[45] Trifu S, Vladuti A, Popescu A. Neuroendocrine aspects of pregnancy and postpartum depression. Acta Endocrinol (Bucharest), 2019, 15(3):410–415. https://doi.org/10.4183/aeb.2019.410 PMID: 32010366 PMCID: PMC6992410

Corresponding author

Ana Miruna Drăgoi, Department of Psychiatry, Prof. Dr. Alexandru Obregia Clinical Hospital for Psychiatry, 10 Berceni Highroad, Sector 4, 041914 Bucharest, Romania; Phone +40770–420 108, e-mail: anamirunadragoi@gmail.com

Received: March 8, 2020

Accepted: July 19, 2020