THE MACROSCOPICAL ANATOMY OF DEPRESSION HIGHLIGHTED BY NEUROIMAGING STUDIES. A REVIEW

Anca Sava[1,2], Ş. Turliuc[3,4*], C.I. Stan[1], Dana Mihaela Turliuc[5,6], A.I. Cucu[6], Nicoleta Dumitrescu[4*], A.D. Costache[7], Gabriela Florenţa Dumitrescu[2], Claudia Florida Costea[5,8]

"Grigore T. Popa" University of Medicine and Pharmacy, Iaşi, Romania

1. Morpho-Functional Sciences I

3. Department of Medical III

5. Department of Surgery II

7. Doctoral School

"Prof. dr. N. Oblu" Emergency Clinical Hospital, Iaşi, Romania

2. Department of Pathology

6. II[nd] Neurosurgery Clinic

8. II[nd] Ophthalmology Clinic

4. „Socola" Institute of Psychiatry, Iaşi, Romania

THE MACROSCOPICAL ANATOMY OF DEPRESSION HIGHLIGHTED BY NEUROIMAGING STUDIES. A REVIEW (Abstract) : Major depressive disorder is characterized by depressed mood, diminished interests, impaired cognitive function and vegetative symptoms, such as disturbed sleep or appetite. Its etiology is believed to be multifactorial, and no mechanism has been established to explain all aspects of the disease. In addition, the anatomical substrate is also still under debate, even though in the last four decades, due to advances in neuroimaging some, many attempts have been made to identify the anatomical structures involved in MDD. This article aims to review the knowledge on the macroscopical aspects of major depressive disease based on the up to date neuroimaging studies in order to be useful not only in identifying a possible mechanism of the disease development, but also in establishing an appropriate treatment of this disease. We can conclude that imaging investigations revealed brain structural abnormalities in depressed individuals. Anatomical changes of both grey matter and white matter were reported for major depressive disorder, being visible on MRI images as reduced volumes of the prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex (subgenual), medial temporal lobe (hippocampus and amygdala), and basal ganglia structures**,** but as enlargement of the lateral and third ventricles. Functional imaging studies (using single-photon emission tomography (SPET), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) performed on patients with major depressive disease have also shown abnormalities of cerebral blood flow (and/or metabolism) in the prefrontal cortex (orbitofrontal, dorsolateral and dorsomedial cortex), anterior cingulate cortex (especially subgenual region), amygdala, thalamus, and basal ganglia. **Key-words** : MAGNETIC RESONANCE IMAGING, THE PREFRONTAL CORTEX, HIPPOCAMPUS, AMYGDALA, BASAL GANGLIA**,** CEREBRAL VENTRICLES

INTRODUCTION

Major depressive disorder (MDD) is a disease characterized by persistent depressed mood, anhedonia, impaired cognitive function and vegetative symptoms, such as sleep or appetite disorders, and occasionally delusions or hallucinations (1, 2).

Epidemiological studies show that over the past 25 years, the prevalence of MDD increased especially among the American adolescents and young adults (3). MDD becomes highly prevalent in USA especially because some cases do not see a doctor or do not adhere to treatment (4).

The disease is diagnosed about twice as often in women than in men and affects one in six adults in their lifetime (1). The etiology of MDD is believed to be multifactorial, including genetic, biological, environmental, and psychosocial factors, to which may be also added abnormalities in neurotransmitters (5).

To date, no mechanism has been established to explain all aspects of the disease. In addition, the anatomical substrate is also still under debate. It is considered that the neuroanatomical areas relevant to the mood are the medial thalamus, the ventral striatum and pallidum, the amygdala and the hypothalamus. All these structures are widely connected to the medial prefrontal cortex (PFC). This system also binds to the relevant structures from the brainstem (e.g., the serotonergic nuclei of the dorsal raphe and the adrenergic nucleus coeruleus). It has been hypothesized that in case of an imbalance between these neuroanatomical structures a disruption of this neurocircuit could appear, primarily due to decreased activity in the prefrontal cortex, thus affecting its regulatory (inhibitory) action on limbic structures, which in turn become hyperactive. This disorder may be responsible for clinical depressive syndrome and autonomic, neuroendocrine disorders and other associated visceral functions (6).

This article aims to review the knowledge on the macroscopic aspects of MDD based on the up to date neuroimaging studies in order to be useful not only in identifying a possible mechanism of the disease development, but also in establishing an appropriate treatment of this disease.

A BRIEF HISTORY OF DEPRESSION

Depression has been a health problem about which has been written since antiquity, both in terms of its causes and manifestations, and in terms of its treatment.

It was described in ancient Mesopotamian texts in the second millennium B.C. and was considered to be caused by the demons. As such, it was treated by priests, considered a kind of "doctors" who did not treat physical illnesses, but only spiritual or mental illnesses.

It was also known in Greece in the 4th century B.C., and was originally called "*melancholia*" (from the Greek names : $melas_{Gr}$ = black and $chole_{gr}$ = bile) and was considered to be a medical condition. In that time, in Hippocratic writings its definition was as follows : "Fear or sadness that last a long time mean melancholia". It was considered that the disease was caused by an imbalance of the four humors, or fluid substances, i.e. blood, yellow bile, black bile and phlegm, which were believed to govern human well-being and disease. Melancholy was defined by Hippocrates as a state of "aversion to food, despondency, sleeplessness, irritability, restlessness" (7). In the second century C. E., Galen also stated that "melancholia" was due to an excess of black bile and described it as follows : „Although each melancholic patient acts quite differently than the others, all of them seem to be filled with fear or despondency. They find fault with life and hate people but not all want to die … Others again will appear to you quite bizarre because they dread death and desire to die at the same time" (8).

This definition has been preserved for fourteen centuries, but in the XVIth century, the human body was seen as a temple and a simulacrum of God. Since the Supreme Architect built the microcosm, the dissection of the human body could reveal the Creator's plan, thus allowing man to see God through his Creation. As a result, anatomy became a very popular topic both among scientists and for the general public, who paid to attend dissections. Because the dissections had become public, there was a need for a permanent place that offered the opportunity for as many people as possible to participate in dissections that became real shows. As a result, the construction of anatomical theater began in Western Europe and anatomy and a great enthusiasm for knowing the human body through dissections followed.

Anatomical theaters appeared in some of the big cities of Western Europe as a materialization of doctors' desire to know as much as possible about the human body they had to treat in the event of illnesses. The first permanent anatomical theater was built in 1594 under the careful guidance of the professor of surgery and anatomy, Fabrizio d'Acquapendente (1537–1617), at the University of Padua. Three years later, another anatomical theater was established at the University of Leiden (9).

As such, a real revolution in the way of learning anatomy spread rapidly in Europe and new anatomical theaters were built. Their stated purpose was to find out the secrets of the human body. Anatomical theaters hosted public

dissections of the bodies of the executed criminals. The dissections took place just like a show, with stage, direction, actors and audience. The *Theatrum anatomicum* in Leiden soon became the place where the anatomical dissection gathered together almost all the important people in the city, but also great philosophers who wanted to capture the material nature of man in its decomposed, lifeless, amorphous form as the object of study. In the great anatomical theaters, man became only an object of macroscopic study of his organs (10). As a result, anatomists and natural philosophers began to be more attracted to the mechanical aspects of the functioning of the human body. In 1628, the English anatomist William Harvey published *De motu cordis* in Leiden, presenting the heart as a pump that ensured blood circulation. Between 1629 and 1633, the French philosopher René Descartes conceived his work *L'Homme*, in which he compares the human body with a complex biological machine, obeying the laws of mechanical physics because it operates with pumps and fluids (10).

But some of the man of learning became aware of the idea of a nature different from the human body. Once the mechanisms of functioning of the various human organs were known, as well as the diseases of the visible organs, such as the heart, lungs, etc., scholars began to wonder how diseases that affect human behavior can occur.

So, if in anatomical theaters the body was dissected with a scalpel and a knife, Richard Burton (1577-1640), an English writer, tried to dissect the human mind with the help of rigorous investigations of philosophical and medical books, seeking a remedy for both his own melancholy and that of others (11).

Burton published in 1621 *The Anatomy of Melancholy* (Figure 1), a three-part treatise on what we now call depression. The first part discussed about the nature, symptoms and various causes of melancholy, among which the author includes, under the influence of the age in which he lived, God, witches, devils, poverty, imprisonment, parents, "much study", "desire for revenge" or "excessive use of mulled wine". The second section presents remedies such as exercise and diet, purging, blood-letting and potions. The third part describes in detail two particular types of "melancholy" - melancholy of love and religious melancholy (11).

The book can be considered a medical textbook whose subject is melancholy, known at that time as "a mental distress characterized by the impairment of the patient's mental faculties (typically reason or imagination), combined with a tell-tale absence of fever and accompanied by the passions of fear and sorrow" (12).

But the true neuroanatomy of depression was established a hundred years ago when, in 1937, James Papez attempted "to allocate specific organic units to a larger organization dealing with a complex regulatory process" and described the "system of emotion", in fact a neural circuit of control of the expression of emotions, connecting a group of brain structures surrounding the brainstem: "The hypothalamus, the anterior thalamic nucleus, the cingulate gyrus, the hippocampus and their interconnections, constitute a harmonious mechanism which may elaborate the functions of central emotion as well as participate in the emotional expression" (13), as he wrote in his paper from 1937 (Figure 2). According to Papez, this circuit forms a functional way of communication between the above structures, allowing cortical control of emotion, as well as a role in memory storage.

In the 1980s, in the absence of modern neuroimaging, knowledge of the link between brain structures and human behavior was based on clinical observations of the effects of various localized neurological conditions, such as strokes, brain tumors, and craniocerebral trauma. The emergence of neuroimaging techniques, first computed tomography (CT) and positron emission tomography (PET), then magnetic resonance imaging (MRI) and functional MRI (fMRI), established the importance of the "emotion neurocircuit", which was expanded to include other important areas of the brain and especially the prefrontal cortex (PFC). These brain structures and their connections, which have been widely studied, are responsible for maintaining emotional stability, and certain deficiencies in them have a role in the pathophysiology of depression (14).

Over the past four decades, in vivo neuroimaging studies have brought significant data to the scientific community regarding dysfunctional brain regions in depression.

In the early 1980s, computer tomography (CT) seemed to be a promising tool in exploring psychiatric disorders because it was useful

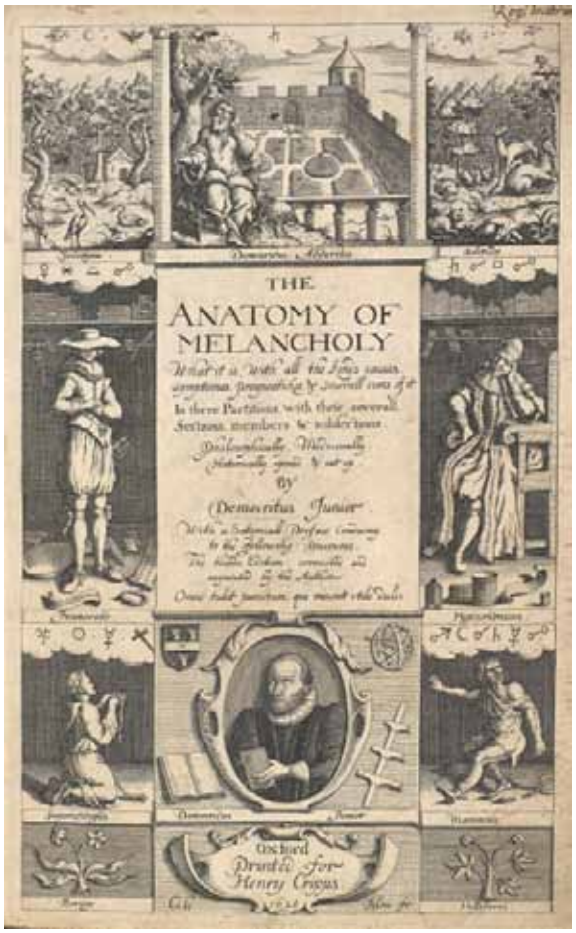

Fig. 1. The frontispiece of the book *The Anatomy of Melancholy*, written by Richard Burton (third edition, 1628) (11).

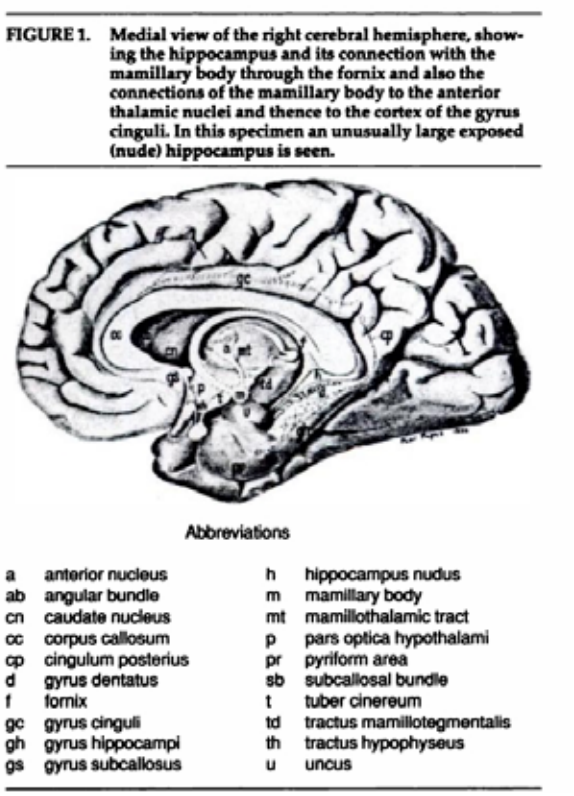

FIGURE 1. Medial view of the right cerebral hemisphere, showing the hippocampus and its connection with the mamillary body through the fornix and also the connections of the mamillary body to the anterior thalamic nuclei and thence to the cortex of the gyrus cinguli. In this specimen an unusually large exposed (nude) hippocampus is seen.

Abbreviations

a	anterior nucleus	h	hippocampus nudus
ab	angular bundle	m	mamillary body
cn	caudate nucleus	mt	mamillothalamic tract
cc	corpus callosum	p	pars optica hypothalami
cp	cingulum posterius	pr	pyriform area
d	gyrus dentatus	sb	subcallosal bundle
f	fornix	t	tuber cinereum
gc	gyrus cinguli	td	tractus mamillotegmentalis
gh	gyrus hippocampi	th	tractus hypophyseus
gs	gyrus subcallosus	u	uncus

Fig. 2. Medial view of the right cerebral hemisphere as it was showed in Papez's paper depicting the circuit that later will bear his name (13).

in the searching for organic or functional abnormalities of the nervous system (15).

Indeed, the studies that followed, performed on brain CT images, highlighted certain differences between psychiatric patients and controls.

It has been found that patients with major depressive disorder (MDD), especially the elderly, presented abnormal ventricular enlargement, cortical atrophy, and cerebellar atrophy, as well as differences in the density of different brain structures (16-18).

It was followed immediately by the use of positron emission tomography (PET) in various depressive states and the images obtained showed consistent abnormalities in some regions of the brains of depressed subjects in comparison to matched controls, such as the prefrontal, cingulate, and amygdala regions (19). But the identification of the anatomical areas involved in depression was done mainly due to the discovery of the structural and functional abnormalities visible on MRI scans in such patients (20).

However, in the last four decades, numerous advances have been made in identifying the anatomical structures involved in MDD. Based on imaging investigations, the researchers found that, anatomically, depression is currently associated with structural and functional abnormalities in the limbic-cortico-striato-pallido-thalamic. Brain structural anatomical abnormalities in depressed individuals have been described for both grey matter and white matter, being visible on MRI images as reduced volumes of the hippocampus, prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex (subgenual) and basal ganglia structures, medial temporal lobe (hippocampus and amygdala), striatum, but enlargement of the lateral ventricles (20, 21).

A decreased inhibitory control of the prefrontal cortex over limbic structures is thought to cause cognitive and behavioral signs of depression, as well as abnormalities in neuroendocrine function, pain modulation, and neurotransmitter activity because prefrontal cortex has connections with hypothalamus and midbrain, especially with the periaqueductal area (6).

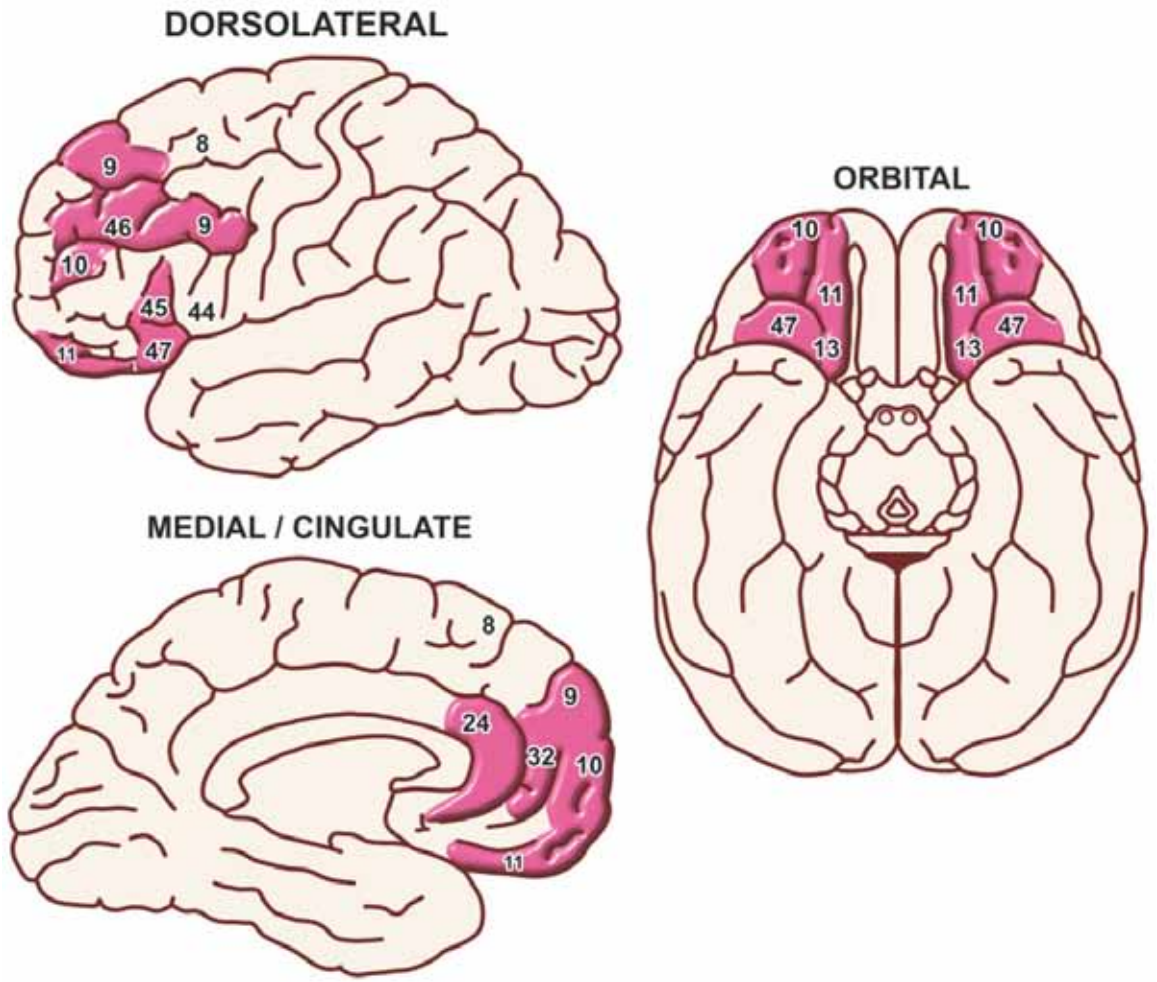

Fig 3. Brodmann's areas from prefrontal cortex involved in major depressive disorder.

MORPHOLOGICAL AND FUNCTIONAL ABNORMALITIES OF BRAIN STRUCTURES IN MAJOR DEPRESSIVE DISORDER

1. Volumetric analysis of the frontal lobes in depressed patients

The prefrontal cortex can be divided into several sections, i.e. dorsolateral, dorsomedial, ventrolateral, ventromedial, and orbitofrontal regions (Figures 3 and 4). Ventromedial (Brodmann's areas 10, 11, 32) and dorsolateral regions (Brodmann's areas 9, 10, 46, and 47) play a role in generating emotions, and regulate autonomous and neuroendocrine responses, pain modulation, aggression and sexual and eating behaviors. Orbital PFC (Brodmann's areas 10, 11, 47) plays an important role in correcting behavioral or emotional responses (partially generated by the amygdala). The anterior cingulate cortex (ACC) is the frontal part of the cingulate cortex and consists of Brodmann's areas 24, 32, and 33 (14).

In depressed patients, functional abnormalities have been identified in these areas, especially in the form of decreased glucose metabolism in PET using studies (22).

The orbitofrontal cortex (OFC) has been implicated in the pathophysiology of major depression disorder through evidence obtained using neuroimaging and neuropathological techniques. However, there is a regional specificity at this level, an important role being played by the posterior lateral and medial parts of OFC. Depressed patients show at this level volumetric reduction of the grey matter and histopathological abnormalities of the constituent cells, but in the anteromedial OFC situated in the ventromedial frontal polar cortex there is an increase in physiological activity during the depressive phases of major depressive disorder (MDD) (23).

Structural neuroimaging studies conducted by Lacerda et al. also showed reductions in grey matter volumes in the right medial and left lateral OFC among people with major depression (24).

Kaya et al. stated that the lateral orbitofrontal cortex (OFC), which projects to the anterior cingulate cortex (ACC), has an increased sensitivity in depression, while the medial OF is underactive in depression (25).

There are some authors that take into consideration a possible role in MDD for the subcallosal cingulate gyrus, which consists of Brodmann's area 25, as well as parts of Brodmann's area 24 and Brodmann's area 32 (26).

Bremner et al. measured by MRI scans the volume of the orbitofrontal cortex (OFC) and other frontal cortical regions in patients with MDD in remission and control subjects. Patients with depression had a reduced volume of medial orbitofrontal cortical cortex (girus rectus) with more than 30% compared with normal brain, but there were very small reduction, even though there were not statistically significant, of the volumes of other frontal regions, including the anterior cingulate cortex of the Brodmann Area 24 - subgenual gyrus, the anterior cingulate cortex of the Brodmann Area 32 (27).

To establish a possible modification in the structures that are thought to be involved in depression, Coffey et al. measured their reconstructed volumes from serial MRI sections in the control group and in the group of patients with MDD. Thus, the volumes of the cerebral hemispheres, frontal lobes, temporal lobes amygdala-hippocampal complex, lateral ventricles, and third ventricle were measured (18).

This study showed that MRI identified several structural changes in patients with major depression, namely: cortical atrophy, especially due to a reduced frontal lobe volume with 7% in patients with severe depression than in normal control subjects, lateral ventricular enlargement, and subcortical hyperintensity (18).

Coffey et al. highlighted statistically insignificant volume reductions of the temporal lobe and amygdala-hippocampus complex, ranging from 7% to 10% in patients with MDD compared to the control group. They find enlargement of the lateral ventricles, too, but not of the 3rd ventricle (17).

Also, Coffey et al. found subcortical hyperintensity more frequently in deep white matter, periventricular white matter, basal ganglia, thalamus, and pons in elderly patients with depression. The mechanism of the subcortical hyperintensities identified on MRI images may be the hypoperfusion of the nervous tissue in those areas due to cardiovascular or cerebrovascular diseases that lead to subclinical cerebral ischemia.

Coffey et al. also believe that areas of subcortical hyperintensity can also occur from other causes, such as: malnutrition, weight loss, persistent hypercortisolism, alcohol and drug use, neglect of physical health, reduced compliance with treatment regimens, including antihypertensive drugs (18).

Coffey hypothesizes that diffuse subcortical lesions may disrupt or distort the transmission pathways of neurotransmitters, which connect the frontal lobes to subcortical structures leading to regional neurochemical alterations that can cause various disorders of affect, thought, or cognition (18).

Now it is well established that the anterior cingulate cortex (ACC) (Figure 4) plays a major role in mood disorders because this anatomical structure is located in a region that represents the interface of emotions, cognition, and motor control (28). Hirayasu et al. (29) found on MRI scans that a specific part of the left anterior cingulated gyrus called the subgenual prefrontal precortex has a reduced volume in patients with affective disorder who had a family history of affective disorder compared with normal subjects and with patients with affective disorder but with no family history of the illness.

Searching for the existence of structural changes in MDD, Kandrilova et al. (30) used a 3T MRI system in order to apply a voxel-based morphometry on brain of such patients. These researchers found out that MDD was associated with significant decreases in grey matter volume of some parts of the frontal and temporal lobes, i.e. medial frontal and anterior cingulate cortex on the left side and middle frontal gyrus, medial orbital gyrus, inferior frontal gyrus (triangular and orbital parts), and middle temporal gyrus (extending to the superior temporal gyrus) on the right side.

2. The contribution of hippocampus in major depression

The hippocampal formation (dentate gyrus, Ammon's horn, subiculum and parahippocam-

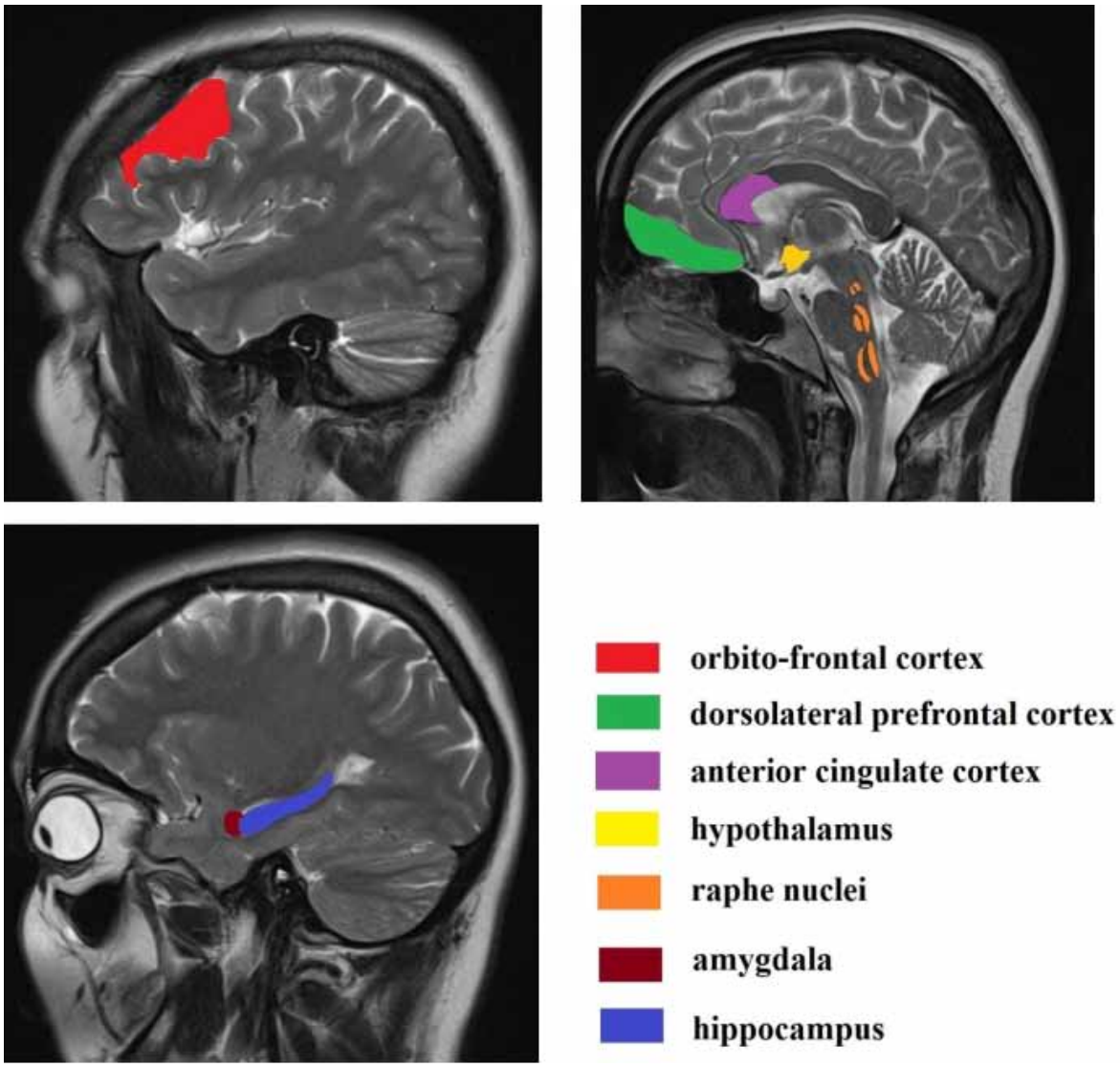

Fig. 4. Brain MRI scans – sagittal views. Region highlighted represented approximate location of the important areas involved in MDD (personal collection)

pal cortex) (Figure 4) is involved in mood disorders for two main reasons. First, several MRI studies found lower hippocampal volumes in major depression, especially in the first episode. This finding allows researchers to hypothesize that repeated episodes will lead to the cognitive decline observed in MDD during the course of the disease probably due to a more decreasing hippocampal volume (31).

Second, there is a well-studied model that links depression to the atrophic effects of glucocorticoids and stress on the pyramidal neurons of the hippocampus and their dendrites. The model is based on the role of the hippocampus in regulating the hypothalamic-pituitary-adrenal (HPA) axis, thus correlating it with hypercortisolemia and other signs of HPA axis dysfunction that occur in mood disorders and may be a risk factor for them (20).

In a well-documented review, Nolan et al. (32) emphasize the fact that the hippocampus was consistently smaller than the amygdala in all studies they have analyzed. The left and right hippocampi accounted each for about 90% of the volumes identified in the control subjects, and the left and right amygdalae accounted for 94.8% and 92.6% of the volumes of the same anatomical structures measured at control subjects. The authors conclude that in major depressive disorder, the role of stress in reducing the volume of the temporal lobe can be taken into consideration.

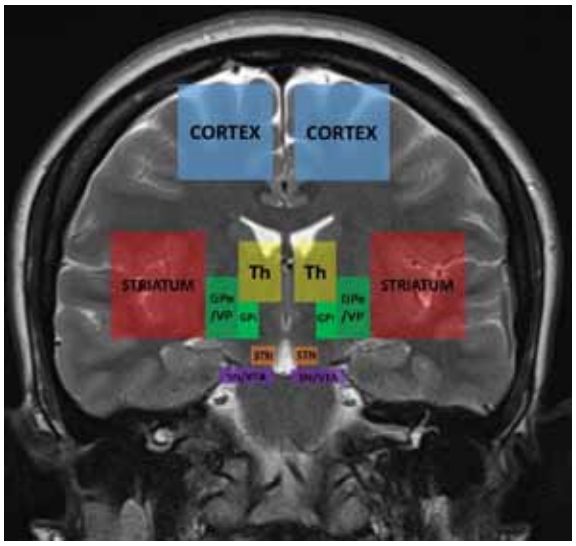

Fig. 5. Brain MRI scan – coronal views. Region highlighted represented approximate location of the important areas involved in MDD (personal collection).

Abbreviations: Th – thalamus; GP/ VP - globus pallidus/ventral pallidum; STN - subthalamic nucleus; SN/VTA - substantia nigra/ventral tegmental area.

3. Structural abnormalities of thalamus in major depression

Lu et al. used automated volumetric and shape analyses in order to evaluate the volume and shape changes of the subcortical grey matter structures, i.e. thalamus, and putamen (Figure 5), in untreated depressed patients and healthy subjects, respectively. These authors found out that the depressed patients, compared to healthy patients, presented significantly volume reductions in the bilateral putamen and left thalamus along with regionally contracted areas on the dorsolateral and ventromedial aspects of bilateral putamen, and on the dorsal and ventral aspects of left thalamus. Tractography also proved the fact that the areas of shape deformation of the bilateral putamen and left thalamus have connections with the frontal and temporal lobes, which are already known to be related to MDD.

These neuroimaging aspects provide clear evidence that the thalamus along with putamen and frontal and temporal lobes play important roles in the mechanism of MDD (33).

Batail et al. (34) searched for the role of thalamus in the prognosis of MDD. Using a voxel based-morphometry analysis, these authors performed a brain grey matter volume analysis on two groups of patients with MDD: a group was considered to be the "responder" group and the second one the "non-responder" group. The data they obtained proved that "non-responder" group had significantly smaller grey matter volume in the bilateral thalami, in precentral gyrus, middle temporal gyrus, precuneus and middle cingulum compared to "responder" group.

4. Anatomical study of basal ganglia in major depressive disorder

The basal ganglia (Figure 5) are anatomical structures with a role in controlling motor, cognitive and affective functions. Consequently, basal ganglia dysfunction is associated with motor, psychiatric and cognitive disorders. Due to the fact that basal ganglia roles were already known in Parkinson's disease and Huntington's disease, in recent years researchers have focused on basal ganglia roles in psychiatric conditions (2), especially on their involvement in the pathophysiology of major depressive disorder (MDD). It was found that there are alterations in functional connectivity of dorsal "cognitive" corticostriatal loops in MDD diagnosed in young patients. Kerestes et al. (35) found out that young depressed patients showed increased connectivity between the dorsal caudate nucleus and ventrolateral prefrontal cortex, bilaterally. When depression increases, the connectivity between the dorsal caudate and the right dorsolateral prefrontal cortex will also show an increase. These results demonstrate that increased connectivity between the dorsal caudate, which is usually associated with cognitive processes, and the ventrolateral prefrontal cortex, associated with affections, may reflect a compensatory mechanism for dysfunctional cognitive-emotional processing in young people's depression (35).

5. Amygdala volumetric studies in major depressive disorder

Amygdala (Figure 4 and 6) is an anatomical structure of the central nervous system that is known only for a short period of time and therefore the data obtained about it, both in anatomical, microscopic, physiological and pathophysiological terms, are constantly changing. The amygdala is an anatomical structure involved in coordinating cortical arousal and neuroendocrine response to indeterminate stimuli, as well as in emotional learning and mem-

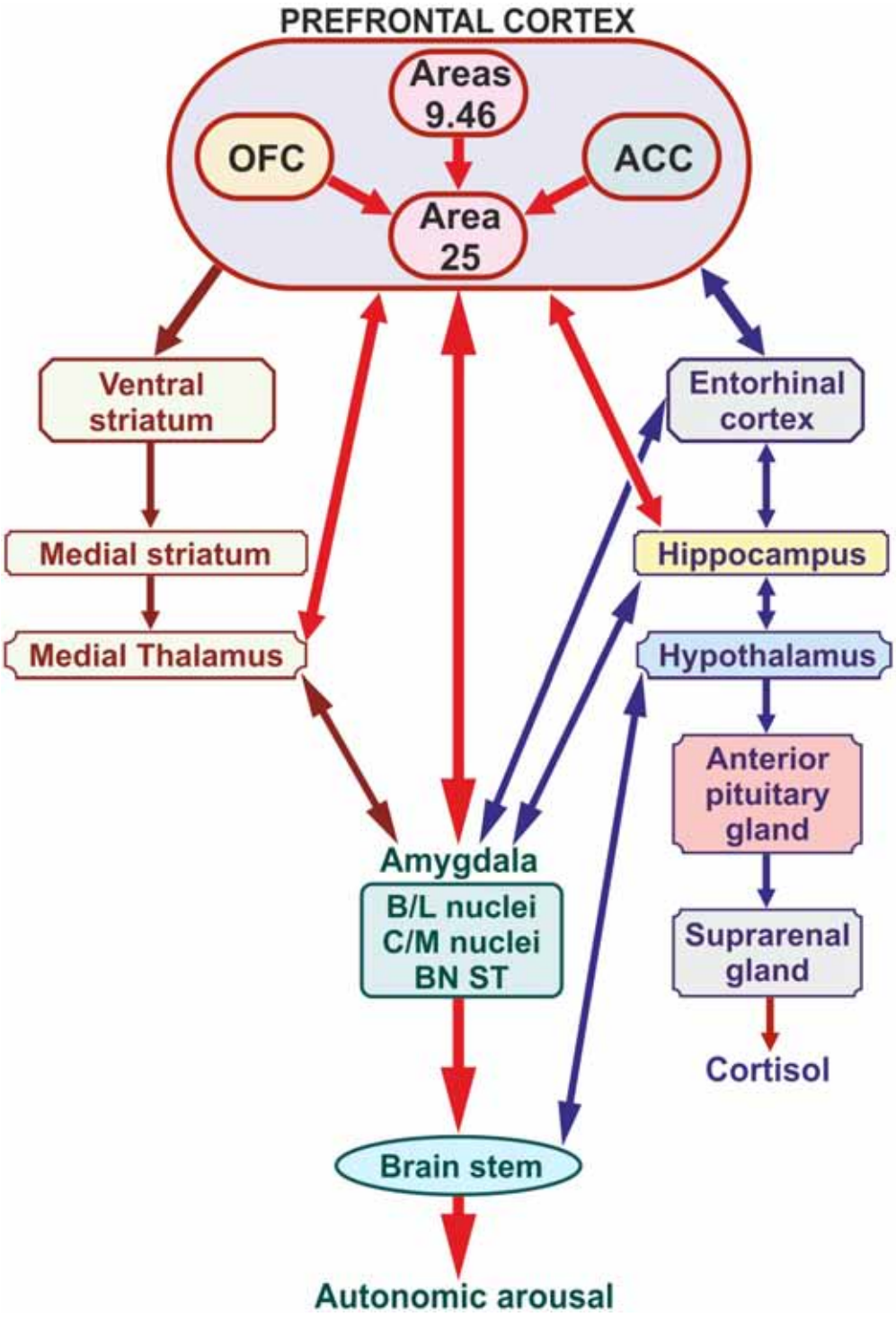

Fig. 6. Schematic connections between the pre-frontal cortex and limbic structures within the limbic-cortico-striato-pallido-thalamic circuits implicated in major depressive disorder.

ory. Amygdala impairment is associated with a wide range of psychiatric disorders, such as borderline personality disorder, depression, autism, post-traumatic stress disorder, phobias, temporal lobe epilepsy, inability to recognize facial expressions, and other psychiatric disorders (36).

The evidence regarding the volume of the amygdala in depression is quite poor, but it seems that abnormal activation of the amygdala correlates with the severity of depression and proved that this anatomic structure plays an important role in the mechanism of depression. There functional neuroimaging studies that

demonstrated a hyperactive amygdala in depressed adults (37), but also in depressed adolescents (38).

Regarding the volume of amygdala in depressed patients, the literature shows inconsistent results. In several structural neuroimaging studies, some reported that depressed patients were characterized by a reduced volume of grey matter in the right and left amygdala volume than healthy subjects (39), but some others found a greater amygdala volume in depressed patients compared with nondepressed individuals (40), especially in patients with first-episode depression (41), and others found no difference in amygdala volume between depressed and nondepressed persons (32). In a meta-analysis, Hamilton et al. reported that unmedicated depression is associated with decreased amygdala volume, being correlated with decreased hippocampal volume due to stress-induced glucocorticoid excitotoxicity, as amygdala, like hippocampus, is dense with glucocorticoid receptors. On the other hand, it seems that amygdala volume is significantly increased in samples of medicated depressed participants due to the fact that antidepressant treatment facilitates growth of new neurons and glia (42).

6. Subcortical white matter lesions and major depressive disorder

In addition to the mentioned regional brain abnormalities, other neuroimaging studies have shown a strong association between MDD and the number and severity of white matter abnormalities seen on MRI scans as focal signal hyperintensities on T2 weighted images.

These white matter hyperintensities (WMHs) occur mainly in the deep subcortical white matter and to a lesser extent in the basal and periventricular ganglia.

In MDD, WMHs are particularly common in elderly subjects, in whom they are located periventricular and in the depth of the white matter, being associated with risk factors and the presence of vascular disease (43).

However, there are also neuroimaging morphometry studies performed in young depressive patients that reported similar results. Kieseppä et al. investigated patients with MDD using diffusion tensor imaging. The authors found that, compared to controls, patients with MDD showed decreased fractional anisotropy (FA) in the right cingulate cortex and posterior body of corpus callosum (44).

7. The role of the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients

The role of the hypothalamus (Figure 6) is extremely important for maintaining neuroendocrine circadian rhythms and managing affective processes. The hypothalamus has neural connections within the brain, but at the same time controls a variety of neuroendocrine processes that can influence target tissues throughout the body. Dysregulation of the hypothalamic-pituitary-adrenal axis and hyperactivity of the subgenual cortex are frequently observed in depression.

In order to understand the mechanism by which the hypothalamus, the hypothalamic-pituitary-adrenal axis and the subgenual cingulate cortex interact with each other, Sudheimer et al. (45) analysed the resting-state functional magnetic resonance imaging (fMRI) scans in order to identify low-frequency resting-state functional connectivity patterns of the hypothalamus in three groups: healthy subjects, patients with major depression, and patients with major depression with psychotic symptoms.

Healthy subjects presented strong hypothalamic functional connectivity with the subgenual cortex, but there was a reduced connectivity in the third group of patients with major depression with psychotic symptoms, the latter being also associated with increased cortisol secretion during the circadian nadir. These authors concluded that there is a altered communication between the hypothalamus and the subgenual cortex in patients with major depression with psychotic features.

8. Brain stem alterations in depressed patients

Structural imaging studies of major depression have also shown anomalies in the infratentorial structures (Figure 4 and 6). MRI study performed by Supprian et al. **(46)** focused on the pontomesencephalic area including the region of the raphe nuclei, at the level of which is the origin of major serotonergic projections from this region with a role in the pathophysiology of depression. These authors found a difference between patients with major depression and control subjects for T (2) -relaxation times in a region located along the midline of the pons.

Using Diffusion Tensor Imaging, Song et al. (47) investigated major brainstem white matter tracts in order to identify a difference between MDD patients and healthy subjects. Their results showed an altered structural connectivity between the brainstem and the amygdala in MDD patients group. These authors concluded that altered white matter integrity in the solitary tract of the patients with MDD proved the fact that dysfunctional brainstem-amygdala connectivity could be one of the mechanisms involved in pathophysiology of MDD.

9. The significance of volumetric assessment of intracerebral ventricles in major depressive disorder

Compared to the structure of a healthy brain, major depressive disorder has been associated with lateral ventricular enlargement, higher volume of cerebrospinal fluid, and smaller volumes of basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex and girus rectus.

Patients with MDD had a significantly lower hippocampal volume during depressive episodes compared whith the volume identified during remission. Compared with patients with BD, those with MDD had low rates of deep white hyperintensity, increased cross-section of the corpus callosum and hippocampus and smaller basal ganglia. Both disorders were associated with increased lateral ventricular volume and increased rates of subcortical grey matter hyperintensity compared to healthy subjects from the control group (48).

Recently, a group of researchers published the results of a CT scans study realized on young adult male patients with major depressive disorder and healthy subjects, which was oriented toward the assessment of the volume of the third ventricle. These authors showed that their patients presented an enlargement of the third ventricle due to changes of structures around this ventricle (49).

CONCLUSION

Neuroimaging studies have shown that major depressive disorder affects several regions of the brain. The disease occurs in the situation of a dysfunctional connectivity at the level of the circuit composed of the following structures : amygdala-striatal-pallidial-thalamic-prefrontal cortex.

Magnetic resonance imaging revealed brain structural abnormalities in depressed individuals that have been described for both grey matter and white matter, being visible as reduced volumes of the prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex (subgenual), medial temporal lobe (hippocampus and amygdala), and basal ganglia structures**,** but as enlargement of the lateral and third ventricles.

Functional imaging studies (using single-photon emission tomography (SPET), positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) performed on patients with major depressive disease have also shown abnormalities of cerebral blood flow (and/or metabolism) in the prefrontal cortex (orbitofrontal, dorsolateral and dorsomedial cortex), anterior cingulate cortex (especially subgenual region), amygdala, thalamus, and basal ganglia.

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**** Corresponding authors***

Şerban Turliuc, Associate Professor, MD, PhD „Socola" Institute of Psychiatry, Şoseaua Bucium, No. 36, 700282, Iaşi, Romania
Phone +40745.203002
e-mail: serban_turliuc@yahoo.com

Nicoleta Dumitrescu, resident physician, „Socola" Institute of Psychiatry, Şoseaua Bucium, No. 36, 700282, Iaşi, Romania
Phone +40755192787
e-mail : nina.dumitrescu000@yahoo.com