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STRUCTURAL CHANGES OF THE CENTRAL NERVOUS SYSTEM IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER: A NARRATIVE REVIEW OF THE LITERATURE

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Abstract: Goal: To analyze and summarize the structural changes observed in the central nervous system in individuals diagnosed with Major Depressive Disorder. Literature Review: Major Depressive Disorder (MDD) is a complex condition characterized by persistently depressed mood and loss of interest in daily activities. Symptoms such as changes in sleep, appetite and suicidal thoughts are relevant in the diagnosis, according to the DSM-5. Neurobiology involves neurotransmitters, such as serotonin and dopamine, affecting mood and energy. Furthermore, neural circuits and brain plasticity influence emotional processing and mood regulation in depression, reflected in structural and functional changes in the prefrontal cortex and affected brain networks. Brain imaging highlights changes in brain volume and neural activity, revealing dysfunction in areas crucial to depression, while neuroplasticity shows impacts on neurogenesis and synapses, offering avenues for therapeutic interventions. Final considerations: Structural changes in the brain of patients with Major Depressive Disorder (MDD) are reflected in changes in volume and neural connectivity, associated with depressive symptoms. Neuroimaging identifies changes in the prefrontal cortex, anterior cingulate and hippocampus, related to emotional and cognitive regulation, highlighting the importance of understanding these changes for innovative and personalized therapies.

Keywords: Major Depressive Disorder, Depression, Nervous System Changes, Neuroplasticity.

INTRODUCTION

Major depressive disorder (MDD) is an affective disorder with a prevalence of development throughout life, which is present in 18% of Brazilians (BROMET E et. al., 2011). The etiology of MDD may be related to genetic factors, dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, deficit in monoaminergic neurotransmission, neurotrophism and neuroplasticity, inflammation, neuroanatomical and functional changes. Considered a heterogeneous and multifactorial disorder, it is important to understand the central pathophysiology to differentiate patients into homogeneous subgroups and guide treatment selection (KESSLER RC, 2003).

MDD is a heterogeneous condition with a variety of presentations and a broad constellation of associated symptoms. The Diagnostic and Statistical Manual of Mental Disorders, fifth edition, criteria for diagnosing and classifying the severity of major depressive disorder are that, over a period of two weeks or more, five or more of the following symptoms must be present, with at least one of them being depressed mood or loss of interest or pleasure in daily activities: depressed mood most of the day, almost every day, marked decrease in interest or pleasure in activities, significant changes in weight or appetite, insomnia or hypersomnia, agitation or psychomotor retardation, fatigue or loss of energy, excessive feelings of worthlessness or guilt, difficulty concentrating or making decisions, recurring thoughts of death, suicidal ideation or suicide attempt. The severity of depression can be mild, moderate or severe, depending on the number of symptoms, intensity and impact on social and occupational functioning. It is important to consider not only symptom counts but also the degree of functional impairment and disability when performing a comprehensive depression assessment (AMERICAN PSYCHIATRIC ASSOCIATION, 2014).

Dysregulation of the hypothalamic-pituitary-adrenal axis and the effects of stress hormones on the hippocampus have been associated with changes in memory. In the different phases of the memorization process, the main findings are: short-term memory, in which depressed patients report difficulties with concentration and memorization, but most studies have not found changes in this area. However, one study observed failures in associative learning in depressed elderly people. Long-term memory, recall and recognition of verbal and non-verbal information appear to be compromised in depressed patients, according to most studies. Furthermore, in semantic memory in depressed patients with psychosis, there is evidence of impairment in the recall of information organized by meaning in semantic categories, possibly related to symptoms such as delusions or delusional ideas (SILBERMAN EK, 1985).

In some studies, MDD presents an onset in two phases, with most patients manifesting symptoms in their 20s and a second peak in their 50s. Women are twice as likely to develop depression compared to men. Additionally, there are additional risk factors associated with this disorder, such as being divorced or separated, a prior history of depressive episodes, high levels of stress, past traumatic experiences, and a family history of major depressive disorder in first-degree relatives. In patients with major depressive disorder, the presence of anxiety, psychotic symptoms, substance abuse and borderline personality disorder is associated with an unfavorable prognosis, with longer episodes and more intense symptoms (BENAZZI F, 2004).

Structural magnetic resonance studies have sought to identify the brain regions involved in the pathogenesis of major depressive disorder (MDD). Voxel-based morphometry (VBM) is a method used to detect changes

in brain structure in patients with MDD. These studies reported reduced gray matter volume in regions such as the frontal cortex, cingulate cortex, hippocampus, amygdala, and putamen in depressed patients. The age at onset of depression has been suggested as an important factor in changing gray matter volume in different brain regions (ZHOU Y et. al., 2011).

The frontal area has been identified as important in depression, due to clinical changes related to attention, psychomotor skills, executive capacity and decision making (ALEXOPOULOS GS et. al., 2002). Anatomical and neuroimaging studies have shown changes in frontal areas in patients with unipolar and bipolar depression, including reduced size of the bilateral orbital cortex and decreased blood flow and metabolism in the prefrontal cortex. The reduced metabolism in the prefrontal cortex appears to be related to an anatomical change in this region.

The subgenual prefrontal cortical region also showed a reduction in volume in depressed patients and presented hyperactivity during manic or depressive phases, returning to baseline functioning when the mood normalized. This region is involved in the generation of sad thoughts and may be overactive in depressed patients, associated with incessant negative thoughts. The origin of the reduction in the size of this region observed in PET scans is still controversial and may be related to tissue damage caused by chronic hyperfunction of these brain areas (ROZENTHAL M. et. al., 2004).

Major depression is associated with the suppression of the neural system responsible for processing external information and maintaining wakefulness, favoring systems involved in internal processing, such as thoughts and emotions (DREVETS WC, 2003). Anatomical studies revealed changes in the subcortical white matter, basal ganglia, and thalamus. These changes appear to reflect neurodegenerative effects resulting from recurrent mood episodes. Furthermore, ventricular enlargement, cortical atrophy and accentuation of sulci have been observed in patients with mood disorders. Blood flow and metabolism in the dopaminergic tracts of the mesocortical and mesolimbic system are also reduced in depression, but there is evidence that antidepressants can partially normalize these changes (BOTTERON KN, 2002).

Functional studies have revealed changes in the frontostriatal system in patients with unipolar and bipolar depression, including reduced blood flow and metabolism in the basal ganglia. In unipolar patients, there is an increase in the rate of white matter, especially in the periventricular area, and a reduction in the caudate and putamen nuclei (SOARES J and MANN JJ., 1997).

Therefore, the following review aims to analyze and synthesize the structural changes observed in the central nervous system in individuals diagnosed with Major Depressive Disorder, exploring the scientific findings available in current literature, with the aim of offering a more comprehensive understanding of the associated neuroanatomical changes to this psychiatric condition.

LITERATURE REVIEW

NEUROANATOMY AND NEUROBIOLOGY OF MAJOR DEPRESSIVE DISORDER (MDD)

Major Depressive Disorder (MDD) is a complex mental condition that affects countless people globally. Characterized by a persistently depressed mood, loss of interest in everyday activities, and a variety of physical and mental symptoms, its diagnosis is determined by specific criteria established in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (ZHANG J, et al., 2023).

To diagnose major depression, it is necessary to observe the presence of at least five of the following symptoms for a minimum period of two weeks. Among them, one must be depressed mood or loss of interest or pleasure in previously enjoyed activities. These symptoms include changes in weight or appetite, sleep disturbances, agitation or psychomotor retardation, fatigue, feelings of worthlessness or guilt, difficulty concentrating, and recurrent thoughts about death or suicide (AMERICAN PSYCHIATRIC ASSOCIATION, 2014).

The neurobiology of depression is a complex and evolving field, with genetic, environmental, and neurochemical factors playing a role. Neurotransmitters such as serotonin, norepinephrine and dopamine have been closely associated with depressive symptoms, with reduced levels of these neurotransmitters associated with disturbances in mood, energy and motivation (RANA T et. al,2021). The role of these neurotransmitters in depression is supported by research into the effects of antidepressant medications, which often target these systems (RAJENDRAM R et. al., 2021). Furthermore, other factors such as neurogenesis, neuroinflammation and oxidative damage have also been implicated in the pathophysiology of depression (FARIOLI-VECCHIOLI S. and CUTULI, D. 2023). Overall, understanding the neurobiology of depression is still developing, and more research is needed to fully elucidate the complex mechanisms involved.

Additionally, neural circuits play a significant role in depression. Anomalies in the prefrontal cortex, the area responsible for emotional control and information processing, and a reduction in the hippocampus, essential for memory and emotional processing, are correlated with the manifestation of depression (KUNICKI A., 2012). Neurotoxic factors such as chronic stress and inflammation also play an important role. Prolonged stress can lead to neuronal atrophy and reduced brain plasticity, affecting areas crucial for emotional processing. Furthermore, the interaction between inflammatory processes and depression is evident, where inflammatory substances can influence the manifestation and severity of depressive symptoms (FARIA R, 2014).

BRAIN IMAGING AND FUNCTIONAL NEUROIMAGING

In structural neuroimaging, magnetic resonance imaging (MRI) studies have revealed significant findings in patients with MDD. Through structural MRI and brain volumetry, changes were observed in specific regions of the brain. For example, evidence suggests a reduction in the volume of some areas, such as the hippocampus and prefrontal cortex, associated with depression. These findings reinforce the link between brain structure and the manifestation of MDD, highlighting crucial regions in emotional processing and mood regulation that may be compromised in this condition (DURAN F, 2008).

On the other hand, functional neuroimaging provides a dynamic view of brain activity in individuals with MDD. Studies using techniques such as functional magnetic resonance imaging (fMRI) have examined brain activity, neural connectivity, and areas affected during depressive episodes. Dysfunction is observed in brain networks involved in emotional processing, such as the limbic circuit and the anterior cingulate cortex. Furthermore, changes in connectivity between different brain regions, such as a decrease in communication between the prefrontal cortex and the hippocampus, have also been identified (ALMEIDA J, 2009).

PREFRONTAL CORTEX AND CINGULUM

The prefrontal cortex and anterior cingulate are essential brain areas that play key roles in emotional regulation, decision-making and cognitive processing, directly influencing symptoms associated with Major Depressive Disorder (MDD). Structural neuroimaging studies, including techniques such as magnetic resonance imaging (MRI) and brain volumetry, have investigated possible changes in these regions in individuals with MDD. A relationship is observed between structural changes, such as reduced volume or neuronal density, in the prefrontal cortex and anterior cingulate and the manifestation of depressive symptoms. These structural changes can contribute to the dysfunction of these areas, affecting their ability to regulate emotions and make decisions (RUSHWORTH M. et al.2004).

The prefrontal cortex plays a crucial role in emotional regulation, evaluating consequences, and making decisions. Its dysfunction can result in difficulties in emotional control, a tendency to negatively evaluate neutral or positive situations, and an inability to adjust behaviors in response to environmental changes. In turn, the anterior cingulate is involved in emotional regulation, error processing and attributing emotional relevance to stimuli. Changes in this area can lead to an exacerbated emotional response to negative stimuli and difficulties in regulating emotions (PIZZAGALLI DA and ROBERTS AC, 2022).

NEUROPLASTICITY AND DEPRESSION

Neuroplasticity refers to the brain's dynamic ability to adapt and reorganize structurally and functionally in response to experiences, environmental stimuli, and injuries. In the context of Major Depressive Disorder (MDD), the study of neuroplasticity reveals important aspects about the brain changes underlying the depressive condition and possible paths for therapeutic interventions. Depressed patients often present changes in neuroplasticity, affecting processes such as neurogenesis (production of new neurons) and synaptic plasticity (changes in the strength and structure of connections between neurons). Neurogenesis, especially in the hippocampus, has been the subject of study in the context of depression.

Findings suggest that depressed patients may have a decrease in hippocampal neurogenesis, which may contribute to reduced volume in this brain region and impairments in memory and emotional processing (CARRILLO-MARQUEZ JR and CARRILLO-RUIZ JD, 2022).

Furthermore, synaptic plasticity, fundamental for communication between neurons, is also affected in depression. Changes in the density and efficiency of synapses have been observed in areas such as the prefrontal cortex and hippocampus, negatively influencing emotional regulation, learning and memory. Studies suggest that treatments for depression, such as antidepressant therapy and psychotherapy, can work by promoting changes in neuroplasticity. For example, antidepressants can stimulate neurogenesis and synaptic plasticity, restoring brain function compromised in depression. Understanding changes in neuroplasticity in depressed patients is crucial for developing new therapeutic approaches. Strategies that aim to restore neurogenesis and synaptic

plasticity may be promising prospects for the treatment of MDD, offering new possibilities to help modulate depressive symptoms and promote recovery in affected individuals (CHIANG HS et al., 2022).

FINAL CONSIDERATIONS

The structural changes observed in the brains of individuals with Major Depressive Disorder (MDD) offer a complex insight into the effects of this condition on brain anatomy. These changes, such as volume reduction in specific areas and changes in neural connectivity, are closely associated with the clinical symptoms of depression. Structural neuroimaging, particularly through magnetic resonance imaging, has revealed regions such as the prefrontal cortex, anterior cingulate and hippocampus showing structural changes related to emotional regulation, decision making, memory and cognition. These findings point to the multifaceted complexity of depression, highlighting not only biochemical imbalances but also physical changes in the brain. Understanding these changes is crucial for more comprehensive therapeutic approaches, such as therapies aimed at restoring affected brain function and stimulating neuroplasticity, representing promising areas of investigation for the development of more effective and personalized treatments for those suffering from the challenge of MDD.

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