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NEUROANATOMY IN PATIENTS WITH PERSISTENT DEPRESSIVE DISORDER AND IMMUNE CELL CHANGES

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RESUMO

Esse trabalho analisou estudos que combinaram métodos de neuroimagem estrutural e funcional em pacientes deprimidos em comparação com controles. Também procurei simplificar o Transtorno Depressivo Persistente (TDP) devido a dinâmica atual de leitura, já que o intuito é alertar para o transtorno em si. O estudo aprovado pelo comitê de ética local da Dresden University of Technology, sobre o TDP levar às alterações nas células imunes motivou-me a um aprofundamento sobre o transtorno, e as respectivas áreas do cérebro que sofrem alterações anatômicas. Assim como os neurotransmissores envolvidos.

Palavras-chave: TDP. HPA. Transtorno Depressivo. Neuroanatomia da Depressão

ABSTRACT

This work analyzed studies that combined structural and functional neuroimaging methods in depressed patients compared to controls. I also tried to simplify Persistent Depressive Disorder (PDD) due to the current dynamics of reading, since the intention is to alert to the disorder itself. The study approved by the Dresden University of Technology's local ethics committee on TDP leading to changes in immune cells motivated me to delve deeper into the disorder, and the respective areas of the brain that undergo anatomical changes. As well as the neurotransmitters involved.

Keywords: PDD. HPA. Depressive Disorder. Neuroanatomy of Depression.

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1 INTRODUCTION

Depression must be identified appropriately and in a timely manner to better understand, prevent, and treat cases such as the example of Persistent Depressive Disorder (PDD). Neuroimaging studies have revealed widespread abnormalities in brain structure and function in patients with depression, revealing the need to explore abnormalities in brain structure and function and altered metabolite levels to define better diagnostic and therapeutic applications. Many studies conclude the relationship of enhanced default mode network connectivity associated with reduced brain structural integrity.

The study approved by the local ethics committee at Dresden University of Technology found that depressive disorders can lead to alterations in immune cells, which draws attention to better prevention, diagnostics and treatments. This study not only aims to analyze the most consistent and salient physiological abnormalities in hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and chronic low-grade inflammation associated with elevated levels of cortisol and pro-inflammatory cytokines, respectively, but seeks to understand the nuances of this disorder in summary form.

Persistent Depressive Disorder (PDD)

Also known as Dysthymia, Persistent Depressive Disorder (PDD) is a mental disorder that affects people of all ages and triggers depression in the elderly. The condition has in its diagnosis the persistence of depressive symptoms for more than two years. PDT is mild or moderate depression that does not go away. A person with PDT has a sad, gloomy, or depressed mood and two or more other symptoms of depression. Its difference to depression is that PDT is less severe than major depressive disorder (MDD), but can trigger it.

It is depressive symptoms that persist for ≥ 2 years without remission in adults and at least one year in children and adolescents, a category that consolidates the disorders formerly called chronic major disorder and dysthymic disorder. Symptoms begin during adolescence and may persist for up to decades.

A depression that oscillates, above and below the linear of a major depression.

The behavior is of people who are usually melancholic, pessimistic, passive, lacking a sense of humor, introverted, lethargic, hypercritical of themselves and others, and complaining. With greater chances of having anxiety disorders, substance abuse, or dramatic personality disorders such as histrionic, borderline, and others.

Unlike major depression, in PDT some symptoms are characterized by extreme behaviors. For diagnosis, patients must have had depressed mood most of the day for a greater number of days than symptom-free days for ≥ 2 years, and ≥ 2 of the following:

- Low appetite or overeating;

- Feeling of hopelessness, worthlessness, and/or isolation;

- Insomnia, restlessness, or hypersomnia;

- Relationship problems;

- Trouble sleeping or oversleeping;

- Low energy, fatigue, or hyperactivity

- Low self-esteem;

- Anxiety with no apparent cause

- Lack of concentration or difficulty in making decisions;

- Feelings of hopelessness;

A study conducted by the Federal University of Juiz de Fora (UFJF), in Minas Gerais, reported an increase in emotional problems that can lead to persistent depressive disorder. Psychosocial factors are considered to be one of the main determinants for this condition, and it is common for the patient not to recognize the problem, confusing whether they are negative or just momentary thoughts.

People more predisposed to mood disorders are usually in the risk group for PDT, more common in psychologically vulnerable people. Women are at greater risk for emotional impairment.

Treatment for PDT can vary according to the patient's profile and the level of severity of the condition and include:

- medications to control depression and anxiety;

- Psychotherapy combined with medication and brain stimulation;

- psychoeducation based on psychological counseling and alternative activities;

- cognitive-behavioral therapy combined with psychiatric medication

- neuropsychiatric follow-up;

- Selective serotonin reuptake inhibitors (SSRIs);

- Serotonin-norepinephrine reuptake inhibitors (SNRIs);

The patient may need to take medication for a month or more before feeling the difference.

PDT may be related to low serotonin levels, triggered by traumatic events or sequence of negatively impacting events. Most people with PDT also have an episode of major depression at least once at some point, which is sometimes called "double depression."

To prevent it and/or make it less severe:

- Eat a well-balanced diet of nutritious foods;

- Exercise several times a week;

- Limit alcohol and avoid recreational drugs;

- Take your prescribed medications correctly and discuss any possible side effects with your health care provider;

- Watch for any changes in PTO and talk to your doctor about them;

- Do something good for someone else;

- Control anxiety and stress;

- Get treatment early, at the first sign of a problem;

- Have some leisure time;

- Socialize with people who have positive attitudes;

- Paint or try some arts and crafts;

- Spend time away, travel;

- Spend time with friends, in person or on the phone;

- Walk with friends or family, do activities that relax;

Risk Factors

Certain factors may increase the risk of developing or triggering persistent depressive disorder, including:

- Having a first-degree relative with major depressive disorder or other depressive disorders;

- Traumatic or stressful life events, such as the loss of a loved one or financial problems;

- Personality traits that include negativity, such as low self-esteem and being very dependent, self-critical, or pessimistic;

- History of other mental health disorders, such as a personality disorder;

Risky personalities:

In principle, personality usually lasts a lifetime, while moods come and go. But dysthymia has to last longer than

any other psychiatric disorder in the textbook. This can make it difficult to distinguish from a personality disorder-especially the group that includes an avoidant, dependent, and obsessive-compulsive personality, with its symptoms of shyness, excessive worry, helplessness, and social withdrawal.
Some prefer to talk about a depressive personality disorder. This diagnosis was dropped from the official manual in 1980, but has been reintroduced as a possible topic of investigation. Proposed symptoms include a strong tendency to criticize oneself and others, pessimism, guilt, melancholy, and melancholy. Anhedonia and physical symptoms are not part of the definition, but this personality disorder has much in common with dysthymia.
Mood and personality are the emotional climate and mood of individuals, so the symptoms of mood and personality disorders naturally overlap. The thought schemas that cognitive therapists find at the roots of major depression and dysthymia - certain beliefs about the self, the world, and the future - are also the basis of depressive personality. Mood disorders can have effects on a person's emotional state and social life that resemble a personality disorder. And people are more easily demoralized and recover more slowly from any stress or misfortune if they are pessimistic and self-critical by nature-or emotionally unstable, impulsive, and hypersensitive to loss. (Harvard Newsletter)

Depressive disorders can lead to changes in immune cells

People who have suffered from persistent depressive disorder (PDD), to have their diagnosis marked by the persistence of depressive symptoms for more than two years, show increased cell deformability in monocytes and neutrophils (group of immune system cells that have the function of defending the body from foreign bodies such as viruses and bacteria), while erythrocytes (red blood cells or RBCs) and lymphocytes (white blood cells) were more deformable in the present persistent depressive disorder. Thus, associating PDT with increased deformability of blood cells.

HPA hyperactivity and chronic low-grade inflammation represent hallmarks of the pathophysiological model, the results further point to persistently activated immunity in depressive disorders. In combination with altered lipid metabolism and blood cell membrane assembly, cellular functional changes mediated by cytoskeletal adaptations are very likely to occur. Cellular functional changes can be detected disease-specifically by morphorreological measurements, potentially

leading to a co-diagnostic marker.

Cell deformability was altered in a disease-specific manner. The results suggest that depressive disorders are associated with a general increase in blood cell deformability, while for cell size no difference was observed. The most consistent differences were found in lymphocytes, monocytes and neutrophils, highlighting the impact of depressive disorders on the mechanical properties of primary immune cells. Correction for multiple testing highlights differences in cell deformability in the granule-monocyte and neutrophil cell fraction in individuals with PDT across the lifespan compared to healthy controls to be more pronounced.

Increased levels of glucocorticoids and catecholamines result in increased white blood cell counts as the cells demarginalize from vessel walls. Interestingly, these observations have recently been associated with cell softening. In this study, elevated levels of circulating white blood cells in individuals suffering from depressive disorders could not be confirmed, presumably due to the smaller sample size and the resulting lower power to detect the relatively small differences in immune cell counts. On the other hand, increased erythrocyte deformability was found in individuals with PDT. The tight control of homeostatic erythrocyte deformability is arguably of great importance in providing passage through narrow capillaries and tissue oxygen supply, critical for various organs, including the central nervous system.

About the hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis responds to acute stressors, including stress and excessive anxiety, by releasing a series of hormones and neuro-steroids that allow the individual to react with an appropriate physiological response. When acute stress occurs, the hypothalamus releases corticotrophin-releasing factor (CRF), in the anterior pituitary, releasing corticotrophin or ACTH, which acts on the adrenal glands and causes the release of cortisol. Cortisol acts on glucocorticoid receptors (GC) in the hippocampus and hypothalamus to suppress HPA axis activity regulated by a negative feedback loop, preventing a chronic and damaging activation of the HPA axis. GABA receptors located in the hypothalamus exert an inhibitory effect that shuts down HPA axis activity by preventing CRF release. The

neuroesteroid allopregnanolone (3α,5α-THP), the metabolite of progesterone, acts as a positive allosteric modulator (reverse agonist on a target protein) of GABA receptors. The binding of allopregnanolone, to GABA receptors increases its binding to receptors and acts in silencing the HPA axis.

Psychiatric disorders among them PDT and MDT have been linked to dysfunction of the HPA axis and may be caused by genetic or epigenetic factors affecting glucocorticoid or GABA receptor function. The activity of the HPA axis in depressed people is increased or downregulated

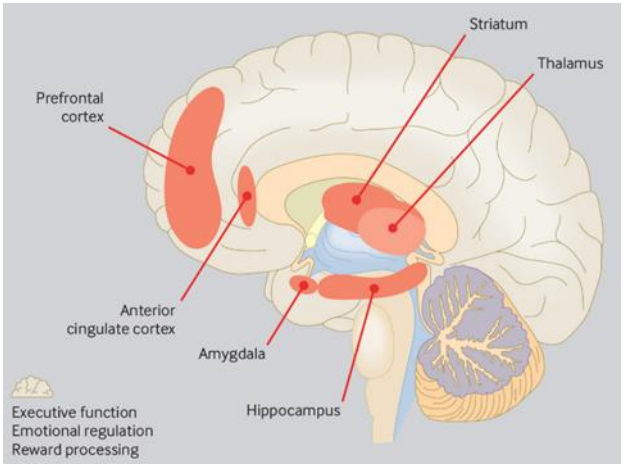
> The anti-inflammatory and immunosuppressive effects of glucocorticoids are evident at pharmacological doses, while physiologically these hormones play an important regulatory role in the immune system. Several studies have demonstrated that RG function is impaired in depression resulting in reduced RG-mediated negative feedback in the HPA axis and increased CRH production and secretion in several brain regions possibly involved in the etiology of depression. The concept of impaired RG signaling is a key mechanism in the pathogenesis of depression. Data indicate that antidepressants have direct effects on the RG, leading to intensified function and increased RG expression. The mechanism of alteration of these receptors also involves non-steroidal components, such as cytokines and neurotransmitters. (VILELA et all, 2014)

Major abnormalities of the HPA axis in major depression, for example, include increased cortisol secretion and reactivity, elevated basal levels of CRH in the cerebrospinal fluid, as well as increased pituitary and adrenal gland volumes and activity. glucocorticoid resistance where elevated cortisol levels are resistant to feedback regulation by the HPA axis that is related to a dysfunction of glucocorticoid receptors. Glucocorticoid resistance develops as a consequence of subclinical inflammation. Subclinical inflammation also appears in patients with a history of childhood trauma, which leads one to believe in an association between early stress and inflammation in all types of depression. There is an association between the gut microbiota and the HPA axis in depression, and the available evidence is based on studies in animal models. Various stressors can affect the abundance of Lactobacilli, Bacteroides and Clostridium in animal models, as well

as gut integrity. Lactobacillus- and Bifidobacterium-based probiotics have been found to restore stress-induced HPA axis dysfunction and help improve learning, memory, as well as symptoms of depression and anxiety.

Neuroanatomy of PDT

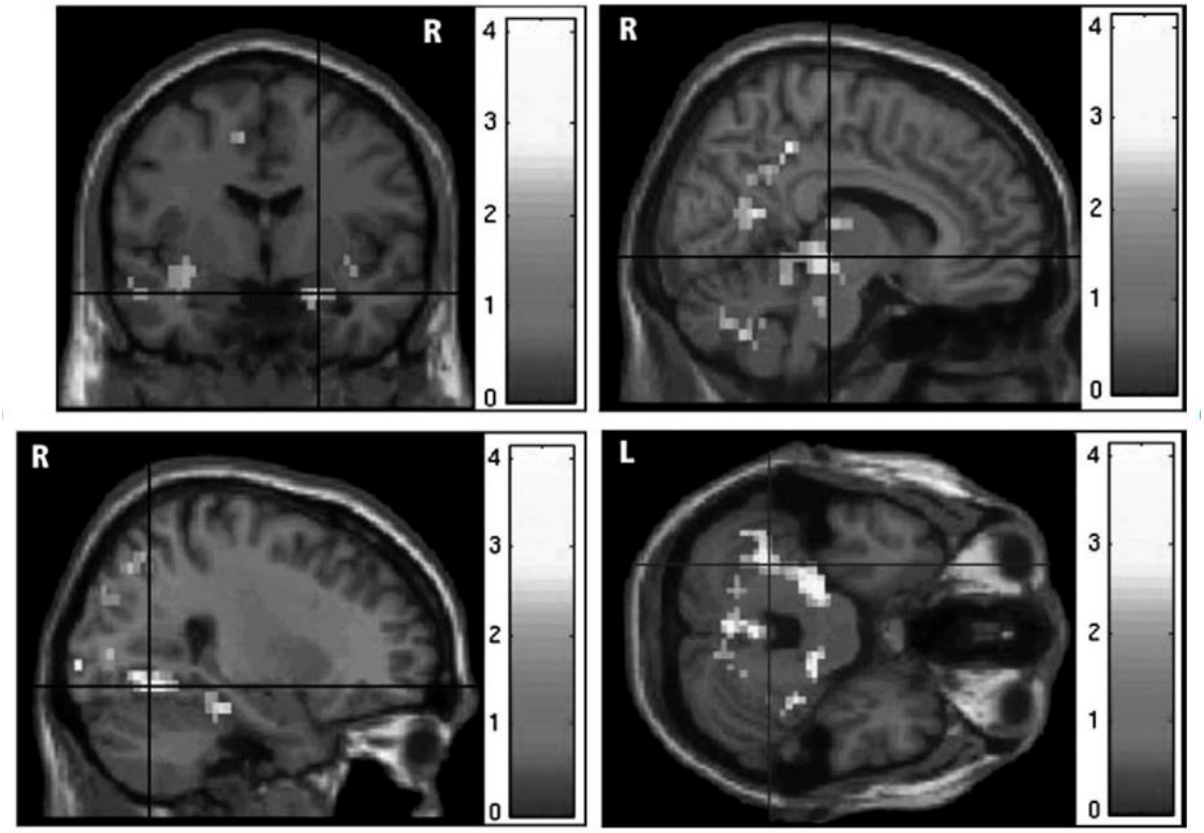
Figure 1



Significantly reduced activation in dorsolateral prefrontal cortex, hyperactivity in amygdala, anterior cingulate and insula. Findings suggest involvement of the prefrontal cortex, anterior cingulate, amygdala and insula in the neural circuits underlying PDT.

source: 1 https://www.bmj.com/content/371/bmj.m3618

Figure 2



Os pacientes distímicos mostraram significativamente mais atividade da amígdala direita (superior esquerdo), talâmico direito (superior direito), giro fusiforme direito (inferior esquerdo) e atividade cerebelar esquerda do que os controles para o contraste negativo-neutro. Os controles não mostraram significativamente mais atividade do que os pacientes para este contraste.

source: 2 https://www.researchgate.net/figure/Dysthymic-patients-showed-significantly-more-right-amygdala-top-left-right-thalamic_fig1_24262516

It is hypothesized that reduced neurotransmission in the mesolimbic dopamine (DA) system may underpin some of the symptoms of depressive conditions. Mesolimbic DA plays a crucial role in incentive control, motivation and reward. There is also reduced DA activity in the limbic system, reversed by chronic antidepressant treatment.

Disruption of the neurotransmitters serotonin, epinephrine, norepinephrine and glutamate plays a role in PDT. The neurotransmitters serotonin, dopamine and norepinephrine travel through the gray matter. When the amount of gray matter is reduced, it disrupts the passage of these neurotransmitters, leading to the symptoms of the disorder.

The hypothesis that survives until today is that of "monoamine depression", that is, depression as a disorder is caused by the deficiency of a monoamine, either serotonin (5-hydroxytryptamine - 5-HT) (mild to moderate intensity anxiety) or the noradrenergic type (apatabolic coloring, endogenous expression). There are studies that highlight changes in the concentrations of serotonin and norepinephrine metabolites (norepinephrine - NA), decreased values, showing that the neuroendocrine responses to stimulation of serotoninergic and noradrenergic receptors were not successful, with recurrence of depressive symptoms.

Post-mortem studies performed on TDM patients showed both a low number of glial cells and an alteration of their morphology, which is mainly found in the CPF compared to other brain regions. Exposure to stress, according to recent studies, induces pathologies in glial cells, a fact demonstrated by a decrease in their density in the hippocampus and a decrease in the density of astrocytes in the CPF in studies performed in animals exposed to chronic stress. The results suggest that glial function is impaired or even compromised in the CPF and represents the anatomical substrate of depressive symptoms. We are talking here about a junctional intercellular communication that involves a gap between the sections, a gap that is noticeable in astrocytes and that in turn leads to changes in neural function in the CPF.

In depression, we find hyperactivity in limbic areas, which are known to be associated with emotion processing. They are inhibited by prefrontal areas if they become inappropriate. A well-established circuit that includes the lateral CPF, medial CPF, OFC, ACC, hippocampus, thalamus, and amygdala. The cortical-striatal model highlights those subcortical structures are important in information processing. There are overlapping cortical-striatal-palate-thalamic loops located in parallel, and any striatal dysfunction causes symptoms of psychomotor retardation. Reaction time is dependent on the level of blood oxygenation, which in turn regulates the concentration, stability and selectivity of attention (dependent on the level of blood oxygenation - BOLD). Increased activity is found in the above areas when the subject performs goal-directed actions, which involves both emotion and cognition at the decision-making level. We found an impairment of BOLD as well as hypoactivity in the cortical areas described in clinically depressed people compared to control groups. The CPF has a significant inhibitory regulatory effect on limbic

structures. When the CPF is compromised in depression, the balance between neurocircuit structures is disturbed due to decreased activity in the CPF. This dysfunction produces clinical symptoms in terms of behavior and intellect, and the neurophysiopathology is based on neuroendocrine disturbances, neurotransmitter disturbances, autonomic system disturbances, and immune dysfunction, all of which are characteristic of TDM. Antidepressants increase monoaminergic neurotransmitter concentrations and may reverse structural changes leading to beneficial modulations in the limbic neurocircuitry of the disrupted PFC.

Having parents diagnosed with depression increases three times the risk of the offspring developing a depressive episode. Research states that family history is not exclusively related to symptoms, but even associated with structural neuroanatomical alterations

It is known that childhood trauma leads to alterations in brain structure, presenting a diminished insular cortex, the region of the brain responsible for emotions. Not only this region, but also the hippocampus, amygdala, and medial prefrontal cortex are altered.

The amygdala and hippocampus regulate the HPA system and the stress response in a coordinated manner, both with the hyperactivity of the amygdala, related to unconscious memories established by anxiety conditioning mechanisms, and with the decreased activity of the hippocampus, which participates in the storage of conscious memories during a traumatic learning situation. The GABA receptor brain complex shows decreased density of benzodiazepine and non-benzodiazepine receptors in peripheral blood cells. At least two critical receptors, especially serotonin 1A, corticotrophin-releasing factor receptor and some GABA receptor subtypes seem to be responsible for some of the anxiety circuits.

In depression, hyperactivity of the amygdala can cause it to release excessive amounts of stress hormone, which increases anxiety resulting in a greater release of more hormones resulting in an enlargement of the amygdala, like the hippocampus, this change in size can be reversed, it tends to decrease, especially in women, with chronicity.

Conclusion

In the field of neuroscience there have been questions about the changes that depressive disorders can cause in immune cells. A pertinent topic nowadays, in which depressive conditions are very present.

The most recent studies in this field have shown that people who suffer from depressive disorder (PDD), having their diagnosis marked by the persistence of depressive symptoms for more than two years, show increased cellular deformability in monocytes and neutrophils (group of immune system cells that has the function of defending the body from foreign bodies, such as viruses and bacteria).

It is also important to mention that erythrocytes (red blood cells or RBCs) and lymphocytes (white blood cells) were more deformable in the present persistent depressive disorder, so the association between PDT and increased deformability of blood cells can be made.

My research in this field is initially supported by this study, which was approved by the local ethics committee of the Dresden University of Technology. Thus, supported by the Martin Dockweiler University Hospital with whom I recently entered into a partnership, I hope to obtain more details in a study I am conducting that has as its theme the most consistent and salient physiological abnormalities in hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis and chronic low-grade inflammation associated with elevated levels of cortisol and pro-inflammatory cytokines, respectively.

Neuroanatomically, the data support the notion that TDM/TDP involve pathological alterations of limbic and cortical structures, and that they are generally more apparent in patients with more severe or persistent forms of the disease.

The main subcortical limbic regions of the brain implicated in depression are the amygdala, hippocampus, and dorsomedial thalamus. Structural and functional abnormalities in these areas have been found in depression. Decreased hippocampal volumes have been observed in individuals with depression.

Altered levels of metabolites are found in patients with depression, demonstrating the involvement of cell signaling metabolites, cell membrane components, neurotransmitters, inflammatory and immune mediators, hormone activators and precursors, and sleep controllers. The investigation of molecules through metabolomic analysis could aid in the discovery of biomarkers potentially

related to the predisposition, development, and prognosis of depression disorders and other mental illnesses.

For those on medications, caution should be exercised with supplementation that may increase the level of substances that are already controlled via medication. PDT may be related to low serotonin levels, triggered by traumatic events or a sequence of negatively impacting events. Most people with PDT also have an episode of major depression at least once at some point, which is sometimes called "double depression." Childhood trauma leads to changes in brain structure, presenting a diminished insular cortex, the region of the brain responsible for emotions. Not only this region, but also the hippocampus, amygdala, and medial prefrontal cortex are altered.

Also analyzed are changes in the gut microbiota; there is an association between the gut microbiota and the HPA axis in depression where stressors can affect the abundance of Lactobacilli, Bacteroides and Clostridium, as well as gut integrity. Lactobacillus- and Bifidobacterium-based probiotics help restore stress-induced HPA axis dysfunction and improve learning, memory, as well as symptoms of depression and anxiety.

PDT has been linked to dysfunction in the HPA axis that can be caused by genetic or epigenetic factors; they affect glucocorticoid or GABA receptor function. The activity of the HPA axis in depressed people is increased or dysregulated.

HPA axis hyperactivity, chronic low-grade inflammation and disturbed lipid composition combined, resulting in increased blood cell deformability, potentially lead to reduced overall integrity and altered blood cell functionality.

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