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ARTIGO DE REVISÃO

PATHOPHYSIOLOGICAL, NEUROCHEMICAL AND BRAIN IMAGING ANALYSIS AS PARAMETERS FOR THE EARLY DIAGNOSIS OF BIPOLAR DISORDER

Análise patofisiológica, neuroquímica e de imagem cerebral como parâmetros para o diagnóstico precoce do transtorno bipolar

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ABSTRACT

Introduction: Bipolar affective disorder is a complex psychiatric disorder. Its most striking feature is the alternation, sometimes sudden, of episodes of depression with those of euphoria (mania and hypomania) and asymptomatic periods in between. The crises can vary in intensity (mild, moderate and severe), frequency and duration. Objectives: The aim of this study was to identify the pathophysiology and neurochemistry of bipolar disorder, from diagnosis to treatment. Material and Methods: The methodology used was a literature review. The research was carried out through an electronic search for scientific articles published on the Scielo (Scientific Electronic Library Online) and Lilacs (Latin American Health Sciences Literature) and Pubmed websites. The health terminologies consulted in the Health Sciences descriptors (DeCS/BIREME) were used; the pathophysiology and neurochemistry of bipolar disorder, from diagnosis to treatment. Results: Structural neuroimaging studies have shown significant changes in brain volume, suggesting atrophy and/or neuronal loss, at least in a proportion of individuals with BD. Several studies have reported a significant decrease in gray matter in the prefrontal and temporal cortex, as well as an increase in the lateral ventricles. Bipolar patients tend to show reductions in gray matter in the frontal regions of the brain involved in self-control, while sensory and visual regions are normal. Conclusion: When struggling with a mental health disorder, the road to improvement usually begins with the long process of trying various treatments and approaches to find the one that best suits the patient.

Palavras-chave: Bipolar disorder; mania; hypomania; mental health.

RESUMO

Introdução: O transtorno afetivo bipolar é um transtorno psiquiátrico complexo. Sua característica mais marcante é a alternância, às vezes repentina, de episódios de depressão com episódios de euforia (mania e hipomania) e períodos assintomáticos intermediários. As crises podem variar em intensidade (leve, moderada e grave), frequência e duração. Objetivos: O objetivo deste estudo foi identificar a fisiopatologia e a neuroquímica do transtorno bipolar, desde o diagnóstico até o tratamento. Material e Métodos: A metodologia utilizada foi uma revisão de literatura. A pesquisa foi realizada por meio de busca eletrônica de artigos científicos publicados nos sites Scielo (Scientific Electronic Library Online) e Lilacs (Literatura Latino-Americana em Ciências da Saúde) e Pubmed. Foram utilizadas as terminologias em saúde consultadas nos descritores em Ciências da Saúde (DeCS/BIREME); a fisiopatologia e neuroquímica do transtorno bipolar, do diagnóstico ao tratamento. Resultados: Estudos de neuroimagem estrutural mostraram alterações significativas no volume cerebral, sugerindo atrofia e/ou perda neuronal, pelo menos em uma proporção de indivíduos com TB. Vários estudos relataram uma diminuição significativa da substância cinzenta no córtex pré-frontal e temporal, bem como um aumento nos ventrículos laterais. Pacientes bipolares tendem a apresentar reduções na massa cinzenta nas regiões frontais do cérebro envolvidas no autocontrole, enquanto as regiões sensoriais e visuais são normais. Conclusão: Ao lidar com um transtorno de saúde mental, o caminho para a melhora geralmente começa com o longo processo de tentativa de vários tratamentos e abordagens para encontrar aquele que melhor se adapta ao paciente.

Keywords: Transtorno bipolar; mania; hipomania; saúde mental.

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INTRODUCTION

A Personality refers to unique characteristics of adaptation to constantly changing internal and external environments [1].

Approximately 10 to 20% of the world's population has some kind of personality disorder (PD), i.e. they have extreme personality deviations from what is considered normal and, because it is something linked to the individual's functioning, it lasts for decades, so these disorders, as well as being common, are chronic [2].

It is possible to diagnose these disorders when the person has already formed their personality, which is usually from the age of 18, allowing diagnosis in adolescence and early adulthood [3].

Around 50% of psychiatric patients often have PT as a comorbidity of other clinical syndromes, so that PT is a predisposing factor for psychiatric disorders such as substance abuse, suicide, eating disorders, anxiety disorders, affective disorders and impulse control disorders, which interferes with treatment results and increases the morbidity and mortality of these patients [4].

The clinical assessment by the psychiatrist should take place over time, in more than one consultation, so that it is possible to note the stability of the personality traits, as well as their presence in various situations in the individual's life and not only in stressful situations, for example, in order to characterize a disorder [1].

People with personality disorders often refuse psychiatric help, often denying their problems. Their behavior doesn't cause them anxiety, because they don't identify suffering from what others see in their symptoms [5].

It's worth noting that when we talk about PT, we're not referring to personality traits, but rather rigid and maladaptive behaviors that cause functional impairment or suffering for the patient. The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-V) defines personality disorders based on the following criteria A set of experiences and behaviors that deviate significantly from the individual's cultural norms and persist. This can be observed in two or more areas, such as cognition, affectivity, interpersonal functioning, impulse control; B. The pattern is inflexible; C. It is persistent, causes significant suffering and functional impairment in various areas of life; D. It is stable and long-lasting, and its onset occurs at least from adolescence or early adulthood; E. The persistent pattern is not better explained as a manifestation or consequence of another mental disorder; F. It is not associated with the physiological effects of a substance (e.g., drug of abuse, medication) or another medical condition (e.g., traumatic brain injury) [5-7].

Based on these criteria, the DSM-V classifies three subgroups of PD: group A, which includes disorders with odd or withdrawal characteristics, such as: paranoid, schizoid and schizotypal; group B, which are those disorders

with dramatic or impulsive characteristics such as: borderline, antisocial, narcissistic and histrionic; and group C, which includes disorders with anxiety and fear characteristics such as: avoidant, dependent and obsessive-compulsive [6].

In bipolar disorder (formerly known as manic-depressive disorder), episodes of depression alternate with episodes of mania (or a less severe form of mania called hypomania). Mania is characterized by excessive feelings of euphoria and self-confidence or physical activity that are out of proportion to any situation, and many people engage in risky behaviour [7].

The name bipolar disorder is based on the change in mood between two extremes, or poles, of mood disorders / depression and mania. It affects around 4% of the US population to some degree. Bipolar disorder affects men and women equally, and usually begins in adolescence, in the 20s or 30s, and is rare in children [8].

Most bipolar disorders can be classified as Bipolar I: The person has had at least one complete manic episode (which has prevented them from performing their normal duties or includes delusions) and has usually also had depressive episodes; Bipolar II: The person has had severe depressive episodes and at least one milder manic episode (hypomanic), but no complete manic episodes [9].

However, some people have episodes that are reminiscent of bipolar disorder, but which are milder and do not meet the specific criteria for bipolar I or II disorder. These episodes can be classified as non-specific bipolar disorder or cyclothymic disorder [5].

What is currently being sought is an understanding of the main pathophysiological and neurochemical etiologies of BD, since early diagnosis can help in the early treatment of the patient.

OBJECTIVES

The aim of this study was to identify the pathophysiology and neurochemistry of bipolar disorder, from diagnosis to treatment.

MATERIAL AND METHODS

The methodology used was a literature review. The research was carried out by means of an electronic search for scientific articles published on the Scielo (Scientific Electronic Library Online) and Lilacs (Latin American Health Sciences Literature) and Pubmed websites. The health terminologies consulted in the Health Sciences descriptors (DeCS/ BIREME) were used; the pathophysiology and neurochemistry of bipolar disorder, from diagnosis to treatment.

The inclusion criteria were: original article, published in Portuguese and English, freely accessible, in full, on the subject, in electronic format and published in the last five years (2020 to 2024) totaling 25 articles.

RESULTS AND DISCUSSION

The exact cause of bipolar disorder is unknown. It is believed that heredity is not linked to the development of this disorder. In addition, it is possible that certain substances produced by the body, such as the neurotransmitters noradrenaline or serotonin, are not normally regulated in people with bipolar disorder [8].

Bipolar disorder sometimes begins after a stressful event, or this event initiates another episode. However, no cause and effect relationship has ever been proven [9].

The manic symptoms of bipolar disorder can occur for other reasons, such as illness caused by high levels of thyroid hormone (hyperthyroidism) [8].

In addition, manic episodes can be caused or triggered by medication (such as corticosteroids) or narcotics (such as cocaine and amphetamines) [5-8].

In bipolar disorder, episodes of symptoms alternate with periods of virtually no symptoms (remissions). Episodes last from a few weeks to three to six months. Cycles of time elapse from the start of one episode to the next, and vary in duration [9].

Some people don't have frequent episodes, possibly only a few times in their lives, while others have four or more episodes every year (called a rapid cycle). Despite this wide variation, the length of the cycle for each person is relatively consistent [10].

Episodes consist of depression, mania or less severe mania (hypomania). Only a few people alternate between mania and depression during each cycle. In the majority, one or the other predominates to a certain extent [11].

A person with bipolar disorder may attempt to commit or consummate suicide. This person is at least 15 times more likely to commit suicide than the general population [10].

Depression in bipolar disorder resembles depression that occurs on its own. The person with depression feels excessively sad and loses interest in their activities. They think and move slowly and may sleep more than usual. They may have an increased or decreased appetite or lose or gain weight. They may feel overwhelmed by feelings of hopelessness and guilt. They may not be able to concentrate or make decisions [12].

Psychotic symptoms (such as hallucinations and delusions) are more common in depression occurring in bipolar disorder than in depression occurring on its own [13].

Untreated episodes of mania end more abruptly than episodes of depression and are usually shorter, lasting from a few weeks to several months [14].

The person with mania feels exuberant, remarkably full of energy and euphoric or angry. They may also feel excessively self-confident, act or dress extravagantly, sleep only a few hours and talk more than usual. Thoughts become accelerated. The person is easily distracted and constantly switches from one subject or goal

to another. They engage in activities (such as business activities, gambling or risky sexual behavior) one after the other, without thinking about the consequences (such as loss of money or injury). However, the person usually thinks they are in their best mental state [14].

The person with mania loses track of their situation. This impairment, combined with their high capacity for activity, can make them impatient, intrusive, nosy and aggressively angry when contradicted. Consequently, the person may have problems in social relationships and may believe that they are being treated unfairly or persecuted [15].Some people hallucinate, hear and see things that don't really exist [15].

Manic psychosis is an extreme form of mania. The person has psychotic symptoms similar to those present in schizophrenia. They may have extremely grandiose delusions. Other people may believe they are being chased. The level of activity increases significantly. The person may run around and shout, swear or sing. Mental and physical activity can become so exacerbated that there is a complete loss of coherent thought and behavior (delusional mania), causing extreme exhaustion. The person with this disorder needs immediate treatment[16].

Hypomania is not as serious as mania. The person feels cheerful, needs little sleep and is mentally and physically active[16].

Hypomania is a productive period for some people. The person has a lot of energy, feels creative and confident and generally performs well in social situations. They may not want to leave this pleasant state. However, other people with hypomania are easily distracted and irritable, which sometimes results in nervous outbursts. They often make commitments they can't keep or start projects they don't finish. They change their mood quickly. They may recognize these effects and feel bothered by them, as do the people they live with[16].

When depression and mania or hypomania occur in a single episode, the person may feel momentarily sad in the midst of euphoria, or thoughts may start to speed up in the midst of depression. Often, the person feels depressed, wakes up early the next day and feels euphoric and full of energy [17].

The diagnosis of bipolar disorder is based on specific lists of symptoms (criteria). However, it's possible that the person with mania doesn't describe their symptoms accurately, because they think there's nothing wrong with them. So the doctor often seeks information from family members. The person and their family members can use a short questionnaire to help them assess their risk of bipolar disorder (see Questionnaire on mood disorders) [18].

The doctor checks the medications being taken to see if any may have contributed to the symptoms. The doctor also looks for signs of other general health problems that may be contributing to the symptoms. For example, they may carry out blood tests for hyperthyroidism and blood and urine tests to detect the use of narcotics [15].

The doctor determines whether the person is experiencing an episode of mania or depression in order to prescribe the appropriate treatment [15].

In severe mania or depression, hospitalization is usually necessary. Even when the mania is less severe, it may be necessary to admit the person to hospital if they engage in suicidal behavior, try to harm themselves or others, are unable to take care of themselves or have other serious problems (for example, alcohol use disorder or other substance use disorders). Most people with hypomania can be treated without hospitalization. It is more difficult to treat people with a rapid cycle. Without treatment, bipolar disorder recurs in almost everyone [1].

Treatment can include medications to stabilize mood (mood stabilizers), such as lithium, and some anticonvulsant medications; antipsychotic medications; certain antidepressants; psychotherapy; training and support; electroconvulsive therapy, which is sometimes used when mood stabilizers don't relieve depression; phototherapy, which can help treat seasonal bipolar disorder (which has some characteristics in common with seasonal affective disorder)[11].

Lithium can reduce the symptoms of mania and depression. Lithium helps prevent mood swings in many people with bipolar disorder. Since lithium takes between four and ten days to take effect, a faster-acting medication such as an anticonvulsant or a more modern (second-generation) antipsychotic drug is often administered to control agitated thoughts and activities. People with a family history of typical bipolar disorders are more likely to respond to lithium[13].

Lithium can have side effects. It can cause drowsiness, confusion, involuntary tremors, muscle spasms, nausea, vomiting, diarrhea, thirst, excessive urination and weight gain. In general, it worsens a person's acne or psoriasis. However, these side effects are usually temporary and the doctor can often reduce or alleviate them by adjusting the doses. Sometimes lithium has to be stopped because of side effects, which then disappear[13].

The doctor monitors the level of lithium in the blood through regular blood tests, because if the level is too high, side effects are more likely. Prolonged use of lithium can cause low levels of thyroid hormone (hypothyroidism) and can impair kidney function. Therefore, thyroid and kidney function should be monitored through regular blood tests and the lowest effective dose should be used[13].

The anticonvulsant drugs valproate and carbamazepine act as mood stabilizers. They can be used to treat mania when it first occurs or to treat mania and depression when they occur together (mixed state). Unlike lithium, these drugs do not damage the kidneys. However, carbamazepine can greatly reduce the number of red and white blood cells. Rarely, valproate damages the liver (especially in children), or severely damages the

pancreas. With close monitoring by the doctor, these problems can be detected in good time. Valproate is not usually prescribed for women with bipolar disorder if they are pregnant or of childbearing age, because the drug appears to increase the risk of the fetus having congenital brain or spinal cord defects (neural tube defects), attention deficit hyperactivity disorder and autism. Valproate and carbamazepine can be useful, especially when people don't respond to other treatments [19].

Lamotrigine is sometimes used to help control mood swings and treat depression. Lamotrigine can cause a serious rash. Rarely, the rash causes life-threatening Stevens-Johnson syndrome. People taking lamotrigine should watch out for new rashes (especially in the area around the rectum and genitals), fever, swollen glands, blistered sores in the mouth or eyes and swelling of the lips or tongue. They should report these symptoms to their doctor. To reduce the risk of developing these symptoms, the doctor should carefully follow the recommended dosage increase schedule. The drug is started at a relatively low dose, which is increased very slowly (over a period of weeks) to the recommended maintenance dose. If doses are interrupted for three days or more, the gradual dose increase schedule should begin again [20].

In fact, pharmacological studies have been consistent with these findings, with antidepressants and mood stabilizers having been shown to act on various intracellular mechanisms involving the regulation of gene expression and cellular plasticity [20].

Sudden episodes of mania are increasingly treated with second-generation antipsychotics because they act more quickly and the risk of serious side effects is lower than with other drugs used to treat bipolar disorder. These drugs include aripiprazole, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone, cariprazine and lumateperone[21].

In the case of bipolar depression, some antipsychotic drugs may be the best choice. Some are administered together with an antidepressant[2-5].

Long-term side effects of antipsychotic drugs include weight gain and metabolic syndrome. Metabolic syndrome is excess fat in the abdomen with reduced sensitivity to the effects of insulin (insulin resistance), high blood sugar levels, altered cholesterol levels and high blood pressure. The risk of this syndrome may decrease with aripiprazole and ziprasidone. First and second generation antipsychotics are sometimes prescribed during pregnancy, with the exception of risperidone, which has been associated with a small increase in the risk of birth defects [2].

Sometimes, certain antidepressants are used to treat severe depression in people with severe depression.

Electroconvulsive therapy (ECT, sometimes called "shock therapy") is sometimes used to treat treatment-resistant depression and mania [5] .

Light therapy, in which a person looks at bright lights that simulate sunlight, may be helpful in treating seasonal bipolar disorder (with fall/winter depression and spring/summer hypomania) or other types of non-seasonal bipolar disorder type I or II. It is probably most useful when used in addition to other treatments [9].

Transcranial magnetic stimulation, in which a device applies a harmless magnetic field to the head, used to treat severe and resistant depression, has also been shown to be effective in treating bipolar depression [8].

Psychotherapy is often recommended for people taking mood-stabilizing medications, especially to help them adhere to treatment. Group therapy often helps people, their partners, or family members understand bipolar disorder and its effects. Individual psychotherapy can help people learn to cope better with everyday problems [8].

Structural neuroimaging studies have demonstrated significant changes in brain volume, suggesting atrophy and/or neuronal loss, at least in a proportion of individuals with BD. Several studies have reported a significant decrease in gray matter in the prefrontal and temporal cortex, in addition to an increase in the lateral ventricles (FIGURES 1 and 2) [23].

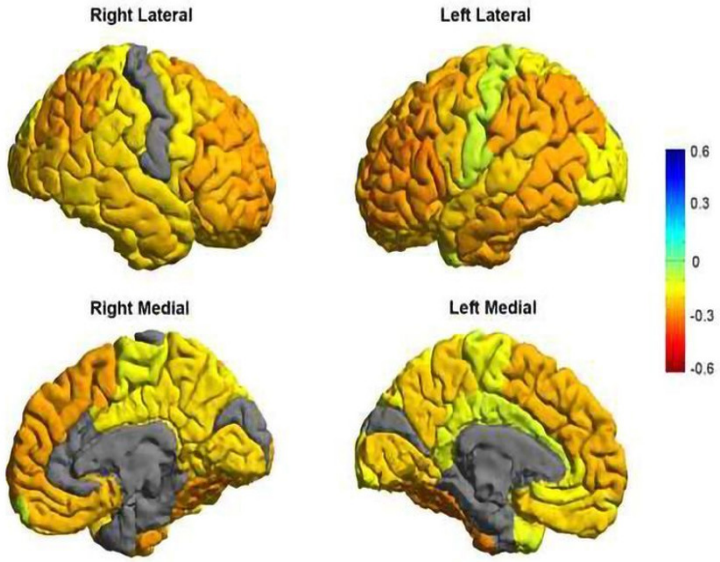

Figure 1. Bipolar patients tend to have reductions in gray matter in the frontal regions of the brain involved in self-control (orange colors), while sensory and visual regions are normal (gray colors). Source: [23].

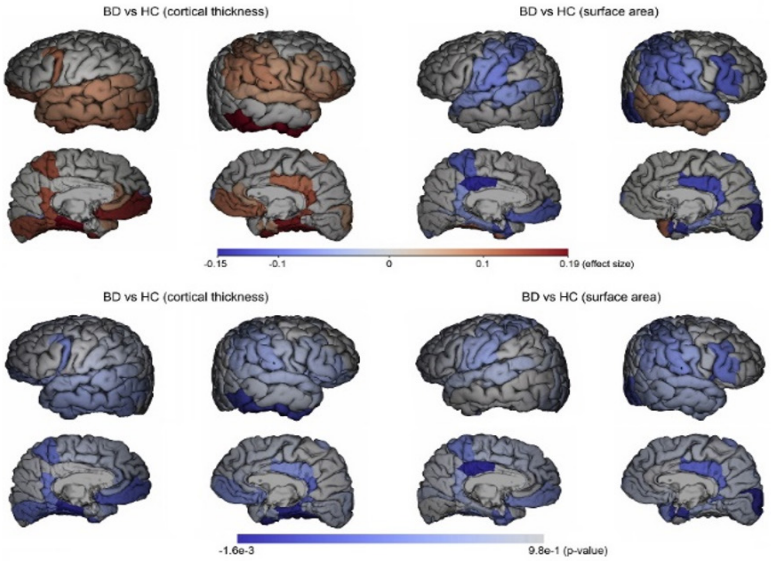

Figure 2. Effect sizes (Cohen's d) (top) and significance of group differences (p-value) (bottom) between patients with bipolar disorder (BD) and healthy control (HC) subjects mapped onto brain space. Cortical thickness findings (left) and surface area findings (right) are shown. The figure displays the overall pattern in the uncorrected raw results. Source: [23].

Furthermore, independent studies that evaluated specific regions of the temporal lobe showed both decreased and increased amygdala volume in bipolar individuals [24].

Whole-brain analysis showed that classification was possible across the occipital lobe and posterior areas of the temporal and parietal lobes in schizophrenia, bipolar disorder, and control groups [24].

Figure 3 shows a map of mean classification accuracies for each group.

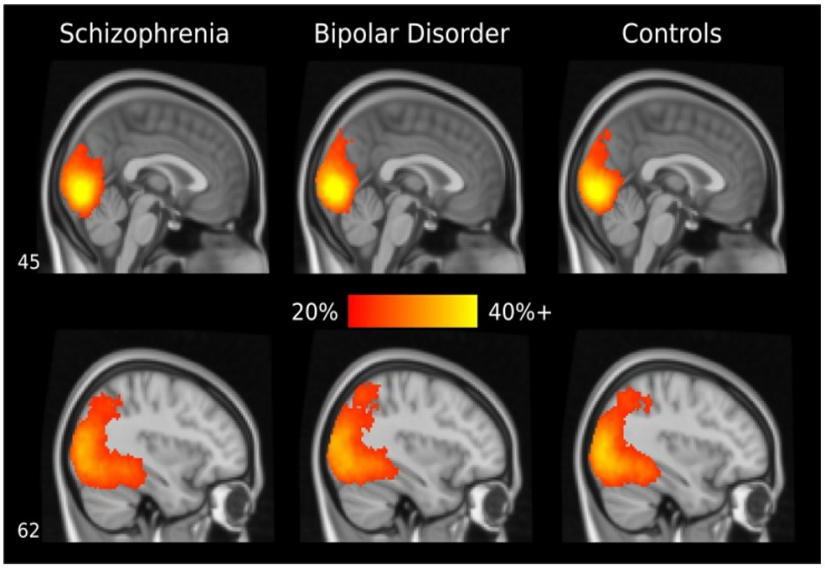

Figure 3. The map shows the classification of brain activation across the visual cortex in each group, with classification accuracies ranging from just above 20% to >40%. Source: [25]

A consistent finding in BD studies is a higher frequency of subcortical white matter hyperintensities. These diffuse white matter lesions may indicate disruptions in circuits involved in mood regulation [25].

Although less consistently, alterations in the basal ganglia and cerebellum have also been observed in bipolar patients. Taken together, these findings point to a possible dysfunction in the cortico-limbic circuit as an anatomical substrate of BD [25].

Functional neuroimaging studies provide additional evidence of alterations in glucose metabolism and decreased regional blood flow and cellular energy phosphates in cortical and subcortical regions in BD [25].

However, the resolution of current neuroimaging techniques is limited to millimeters, so postmortem studies that allow direct study of cellular and molecular resolution are essential [25].

CONCLUSION

When struggling with a mental health disorder, the road to improvement often begins with the long process of trying various treatments and approaches to find the one that works best for the patient.

Learning about the effects of medications used to treat the disorder can help a person take them as prescribed. A person may resist taking medications because they believe that they make them less alert and creative. However, decreased creativity is relatively uncommon because mood stabilizers often help a person function better at work, school, and in relationships and artistic pursuits.

A person should learn to recognize symptoms as they appear, and also learn ways to help prevent symptoms. For example, avoiding stimulants (such as caffeine and nicotine) and alcohol can help, as can getting enough sleep.

A doctor or therapist can talk to the person about the consequences of his or her actions. For example, if a person is prone to sexual excesses, he or she can be educated about how his or her actions can affect relationships and about the health risks of promiscuity, particularly AIDS. If the person tends to be financially extravagant, he or she may be advised to leave his or her finances in the hands of a trusted relative.

It is important for family members to understand bipolar disorder, be involved in the treatment, and offer support.

Support groups can help by providing a forum in which people can share common experiences and feelings.

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Observação: os/(as) autores/(as) declaram não existir conflitos de interesses de qualquer natureza.