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INNOVATIVE APPROACHES AND THERAPIES IN RELATION TO NEUROPLASTICITY AND THE HEPATIC RELATIONSHIP IN NEUROPSYCHIATRIC DISORDERS

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Abstract: Neuroplasticity can be defined as the capacity of the developing brain to adapt in response to experience, and is a fundamental process that influences cognitive abilities throughout life. This dynamic phenomenon involves structural and functional changes in neural networks, which are crucial for acquiring, consolidating and refining cognitive abilities such as memory, attention, language and executive function. The aim of this original article is to present the efficacy of therapeutic methods in the treatment of neuropsychiatric disorders, their safety and related protocols. The work consists of a bibliographic review carried out through scientific databases such as LILACS, *Scientific Electronic Library Online* (Scielo), *National Library of Medicine* (NIH), Nature, Medline, using 31 articles out of 79 selected. It is understood that chronic psychological stress affects gastrointestinal physiology, which can cause changes in immune response and epithelial transport; both functions are partially regulated by the enteric nervous system, in this context, neuroplasticity induces the brain to compensate for damage or dysfunction in specific regions, allowing individuals to preserve cognitive function despite the decline related to brain damage, this adaptive process can be known as cortical remapping. There are several ways in which changes in the microbiota can influence brain plasticity. Some of the mechanisms include the regulation of gene expression, as well as the production of neuroactive molecules and the modulation of microglial activity, in addition to the fact that some bacteria synthesize a variety of molecules such as GABA, tryptophan and serotonin, which potentially influence brain production and relationship, and are therefore highly discussed in disorders such as Parkinson's disease (PD). Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique that promotes transient polarity-dependent

changes in spontaneous neuronal activity, promoting neuroplasticity in regions where it is applied. This effect is mediated by the application of constant low-amplitude electrical currents using electrodes positioned epicranially above a specific brain region of interest. In addition to this method, other techniques such as transcranial magnetic stimulation can be discussed. This neuromodulatory method induces a magnetic field that depolarizes superficial pyramidal neurons within the cortex. When delivered to the primary motor cortex (M1), it activates the corticospinal output neurons, evoking a descending corticospinal discharge that results in a motor response within the target muscle, representing improvements in PD and Alzheimer's disease (AD), among other diseases correlated with tremor and movement disorders. Meanwhile, deep brain stimulation (DBS) is a neurosurgical procedure that allows neuromodulation based on targeted circuits, used in PD, dystonia or movement disorders, also associated with neuroplasticity. In conclusion, the ECP method using low-frequency sound pulses is currently proving to be the safest and most effective method.
Keywords: Neuroplasticity; Transcranial Direct Current Stimulation; Transcranial Magnetic Stimulation; Deep Brain Stimulation;

INTRODUCTION

Neuroplasticity can be defined as the ability of the central nervous system (CNS) to respond to intrinsic or extrinsic stimuli by reorganizing its structure, function and connections. In a complementary way, neuroplasticity can be understood as the process of molecular brain changes following an injury, such as a stroke or traumatic brain injury, and can therefore be divided into two types of mechanisms: processes related to neuronal regeneration such as synaptic plasticity and neurogenesis, and functional reorganization associated with equipotentiality, vicariation and diaschisis. Meanwhile, the molecular events involved in neuroplasticity can be divided into structural ones called neurogenesis and associated with the formation of dendritic spines and functional ones such as changes in the release of neuronal transporters, receptor sensitivity and activation of postsynaptic mechanisms (SCHRANZ et al., 2022).

Neuroplasticity is dependent on morphological changes in synaptic connections that are constantly renewed or recreated, with the balance of these processes being strongly dependent on neuronal activity. In this context, various events that are considerable for cognitive preservation, such as memory consolidation, can be attributed to molecular processes that allow the neuron to alter its response to certain stimuli and corresponding events. Consequently, this phenomenon is directly related to greater synaptic efficacy through an electrophysiological alteration called long-term potentiation, capable of consolidating morphological and functional alterations in synapses over a long period, characterized by gene transcription and protein synthesis (CANO; CAMPRODON, 2023).

In this sense, hippocampal neurogenesis is an important process in the process of structural neuroplasticity, which is involved in diverse neuropsychiatric pathologies such as depression, Alzheimer's disease (AD), Parkinson's disease (PD), which is composed of four distinct phases: proliferation, migration, differentiation and maturation (TARTT et al., 2022). Therefore, the cell precursor found in the hippocampus, especially in the subgranular zone of the dentate gyrus is an astrocyte that expresses important markers of cell proliferation, such as glial fibrillary acidic protein, nuclear antigen of cell proliferation. Neurons that are newly generated mature in the granular region of the dentate gyrus and are excitatory glutamatergic neurons, so the neu-

rogenesis of these cells is regulated by neurotrophin levels, such as brain-derived neurotrophic factor (BDNF). Therefore, stimuli that interfere with the production and activity of BDNF, such as in bipolar affective disorder (BAD), also influence the neurogenesis of the adult hippocampus (CRAMER et al., 2011).

Neuroplasticity is the biological basis that enables the acquisition of new skills and the maintenance or recovery of cognitive and sensorimotor functions in neurological diseases, and the participation of BDNF in neuroplasticity is particularly important in both structural changes and synaptic function, where BDNF positively regulates the synthesis of proteins involved in synaptic changes, as well as influencing the process of neurogenesis in the dentate gyrus, which preferentially forms glutamatergic neurons (JOSHUA, 2022). Among human CNS injury syndromes, one area in which neuroplasticity has been extensively studied is motor recovery after stroke, as motor deficits are present in most of these patients, and the degree of motor recovery can greatly influence whether the stroke proves to be disabling or not. While brain plasticity related to neuropsychiatric disorders shows some similarities to that found in the setting of CNS injury, as a form of adaptation, however, they are mainly characterized by abnormalities in the distributed limbic, prefrontal and fronto--striatal neural circuits that underlie motivation, perception, cognition, behavior, social interactions and emotion regulation (TORICELLI et al., 2021).

According to the idea previously discussed, it is understood that after injuries or the development of neuropsychiatric illnesses, neuroplasticity is the basis for recovery and functional remodeling. By redirecting neuronal pathways, creating new connections and developing alternative regions to perform interrupted tasks, neuroplasticity allows the brain to compensate for damaged areas. According to Dietz and Ward(2015) ballistic movements performed in rehabilitation in patients after stroke, such as in affected limbs, can increase corticospinal excitability and interaction with the primary motor cortex, while transcranial magnetic stimulation stimulates long-term pontentiation, in conjunction with performing movements with the affected limb, associated with increased motor cortical plasticity. According to Liao *et al.*,(2022), pharmacotherapy is also an important therapy in the rehabilitation of these patients. The use of 100 mg per day of levodopa for 3 weeks combined with physiotherapy has been found to be an effective drug for motor recovery in these patients

Despite the presence of diverse innovations in medicine, there are still neuropsychiatric conditions that have no cure or due to certain medications still showing improvements in symptoms, but considerable long-term side effects. Patients with post-stroke motor impairment often do not respond fully to drug-based treatments, so these limitations highlight the need for new approaches that can complement or improve existing treatments. Non-invasive neuromodulation techniques such as transcranial magnetic stimulation, cranial direct current stimulation (tDCS) offer promising changes by targeting specific areas of the brain to promote recovery and neuroplasticity. Neuroplasticity is crucial for brain rehabilitation to recover and regain function after neurological insults such as stroke, traumatic brain injury (TBI) or neurodegenerative diseases. This in-depth narrative review explores cutting-edge methods and treatments that support neuroplasticity and encourage recovery in people with these neurological diseases. Such as tDCS, transcranial magnetic stimulation and other therapies.

METHODOLOGY

This original article is a bibliographical review of several original articles, which were looked at in scientific databases such as LILACS, *Scientific Electronic Library Online* (Scielo), *National Library of Medicine* (NIH), Nature and Medline. The terms used in this study referred to therapeutic and innovative methods on neuroplasticity and neuropsychiatric disorders.

The descriptors used in this research were: "Transcranial Magnetic Stimulation", "Depression", "Neuroplasticity", "Cranial Direct Current Stimulation", "Deep Brain Stimulation", "Liver and Neuroplasticity". The data was collected between 2020 and 2024, over the last 4 years. The inclusion criteria were studies available in full and free of charge online, the articles used were original as literature reviews, randomized and double-blind studies, systematic reviews on different therapeutic methods, their technologies and the impact of their interventions, articles in Portuguese and English were used. While the exclusion criteria for this article were the exclusion of duplicate articles, incomplete works, paid-for works and articles that were not in English and Portuguese. 79 original articles were found, of which 31 were used to develop this article.

RESULTS AND DISCUSSION

THE RELATIONSHIP BETWEEN NEUROPSYCHIATRIC DISEASES AND THE DIGESTIVE SYSTEM

Among the most exciting and rapidly evolving fields of neuroscience is the microbiota-gut-brain axis, which explores the mutual influences and communications between the gut, its microbes and brain function. The vagus nerve, the tenth cranial nerve, is the main neural component of the brain-gut axis and the primary parasympathetic nerve that connects the brain to the viscera, this is composed 80% afferent fibers and 20% efferent, the vagal afferent endings can respond both to distension of the gastrointestinal tract through mechanosensors and to intestinal peptide hormones, neurotransmitters and microbial metabolites. Inflammation is associated with depression in a bidirectional manner, while chronic inflammatory diseases of the gut, liver and brain, such as inflammatory bowel disease (IBD), non-alcoholic fatty liver disease and multiple sclerosis are associated with higher rates of depression (GUO *et al*.., 2024)

Consequently, dysbiosis of the microbiome by diet or other means therefore has the potential to disrupt immune homeostasis. Given that up to 80% of human immune cells reside in the gastrointestinal tract, increased circulating pro-inflammatory cytokines induce or exacerbate chronic inflammatory diseases and psychiatric disorders. Clinical studies have shown that the presence of post-infarction hypoxic hepatitis or pre-infarction liver disease is associated with increased mortality and worse neurological recovery, according to McClung and Nestler(2008) there is an increase in tissue damage and CD45+ cells in brains with simultaneous liver ischemia.

The extrinsic neural control of gastrointestinal function, specifically the motility of the stomach and upper tract, originates parasympathetically via the efferent vagus nerve and is mainly made up of vagal reflexes. Therefore, vagal afferent neurons, whose cell bodies are located in the nodose ganglion, innervate the stomach and upper gastrointestinal tract and relay this sensory signal to the solitary tract, Consequently, this sensory signal is integrated with inputs from the brainstem and hypothalamus, which are involved in energy homeostasis and send GABAergic, glutamatergic and catecholaminergic projections to preganglionic motoneurons, while plasticity can be induced by diet within astroglial networks, with association to the nucleus accumbens, present in central reward circuits (SILVA; CARON, 2021).

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BDNF plays essential roles in synaptic plasticity, neurogenesis and resistance to neuronal stress, it also plays an important role in behavioral and neuronal network adaptations to intermittent metabolic exchange methods, because BDNF expression in cells in various regions is induced by running and tyrosine kinase in neural stem cells, In addition, insulin--like growth factor 1 (IGF1) signaling is also up-regulated in response to intermittent metabolic exchange methods such as intermittent fasting, as demonstrated in studies of the effects of ketogenic diets, exercise (MATTSON et al., 2018).

Meanwhile, according to Guo *et al*, (2024) reported that in their study there was a significant positive and negative regulation of genes in the frontal lobe in the presence of simultaneous hepatic ischemia, with 245 positively regulated genes and 350 negatively regulated genes being identified in the frontal lobe, which would be correlated with the metabolism of linoleic acid and arachidonic acid, which metabolically are crucial pathways for brain function, mainly in modulating synaptic transmission and neurotransmitter release, supporting neuronal survival under various pathological conditions, including ischemic lesions.

Complementarily, patients with chronic liver disease or liver failure often develop neurological complications, suggesting the presence of toxins not effectively removed or restricted normal peripheral liver metabolic by-products with direct effects on the nervous system or liver-dependent dysregulation of the immune system affecting neurological outcome. Specifically, dysregulated bile acid metabolism and levels are associated with rapid deterioration of neurological function in various neurological diseases. It can be seen that the brain consumes around 120 grams of glucose daily, accounting for almost 60% of glucose utilization by the whole body in the resting state, in this sense the net effect of activating these defense mechanisms against hypoglycemia is an increase in the availability of metabolic substrates, such as increased hepatic glucose production and lipolysis (SILVA; CARON, 2021).

In addition, circadian rhythms participate in physiological and homeostatic processes, are important rhythms that involve the nervous system and the gastrointestinal tract, and are controlled by transcriptional feedback by the hypothalamus (CROUSE *et al*., 2021). Abnormalities in circadian rhythms are reported in adults with depressive disorder and have been associated with key clinical features, including unstable mood, daytime fatigue, reduced motor activity, somatic symptoms and weight changes (LANE *et al)*.., 2023)

TRANSCRANIAL MAGNETIC STIMULATION, TRANSCRANIAL DIRECT CURRENT STIMULATION AND NEUROREHABILITATION

In stroke rehabilitation, non-invasive brain stimulation techniques such as transcranial magnetic stimulation and transcranial direct current stimulation are used to modulate neuroplasticity. These techniques are based on the use of magnetic pulses applied to the scalp, while transcranial magnetic stimulation can selectively activate or inhibit neuronal circuits in the brain, transcranial direct current stimulation modifies the excitability of neurons by administering a weak electric current through electrodes positioned on the scalp (EINSTEIN et al., 2022).

The tDCS method can be understood as the administration of a weak electric current via electrodes through the scalp, resulting in a subliminal modulation of resting membrane potentials, which causes a change in excitability and cortical activity: depolarization increases excitability and spontaneous neuronal activity, while the anodic method stimulates

increased activity in the desired area, such as the induction of plasticity by long-term potentiation, the cathodic method decreases excitability in certain areas similar to depression. However, Farnad *et al.*,(2021) report that tDCS depends on glutamatergic mechanisms, involving (N-methyl-D-aspartate) NMDA receptors, which are also calcium-dependent.

Transcranial direct current stimulation (tDCS) modulates cortical excitability and synaptic plasticity, while in healthy patients and chronic stroke patients, anodic tDCS promotes neuroplasticity involving activities such as motor learning, improved upper limb function and increased gray matter volume. The underlying cellular effects that contribute to behavioral improvements are well understood and include enhanced BDNF signaling and improved synaptic transmission. In this context, the application of tDCS in conjunction with early neurorehabilitation may maximize the use of the early plastic window after stroke, especially in patients with limited physical abilities (FRITSCH et al., 2024).

In a complementary way, studies have shown that visual functions can be transiently altered with tDCS applied to the visual cortex in patients with schizophrenia, according to Jashan *et al*.,(2020)though there are no reports of tDCS applied to visual cortex in SZ. In a within-subject, crossover design, we evaluated the effects of tDCS on visual processing in 27 SZ. All patients received anodal, cathodal, or sham stimulation over the central occipital region in 3 visits separated by 1 week. In each visit, a backward masking task and an electroencephalography measure of visual neuroplasticity were administered after tDCS. Neuroplasticity was assessed with visual evoked potentials before and after tetanizing visual high-frequency stimulation. Masking performance was significantly poorer in the anodal and cathodal conditions compared with sham. Both anodal and cathodal stimulation increased the amplitude of P1 but did not change the plasticity index. We found significant plasticity effects of tDCS for only one waveform for one stimulation condition (P2 for anodal tDCS the results obtained suggest that does influence an electrophysiological component initial visual processing, but further studies are needed.

While in bipolar depression, there are some biomarkers, or combinations of biomarkers that are distinct between the different phases of bipolar mood. For example, elevated hs-CRP/IL-6 is observed in euthymia, decreased BDNF and increased TNF-alpha during the bipolar depressive phase, and sTNFR1 and TNF-alpha, along with decreased BDNF levels, are distinct to episodes of mania. According to Liao *et al*,(2022) the tDCS method helps with inflammatory levels in bipolar depression, the results of their studies suggested that IL-6 is a potential predictor of response to tDCS and that IL-8 may decrease after tDCS. Regarding interleukins, the literature shows that astrocytes can secrete many cytokines and chemokines, such as interleukin 1 (IL-1), IL-6, IL-8, nuclear factor-kappa B, interferon-γ-induced protein 10, tumor necrosis factor-α, macrophage inflammatory protein 1 alpha, macrophage migration inhibitory factor and granulocyte--macrophage colony-stimulating factor, causing infiltration of circulating leukocytes in the brain and leading to a chronic inflammatory process, which can be caused by microglia activity, thereforeastrocytes clearly contribute to neuroprotection, as they keep extrasynaptic glutamate levels low to avoid excitotoxicity (TORICELLI *et al*., 2021b).

According to the studies carried out by Jog *et al*.,(2023), it was found that by periodically applying transcranial magnetic stimulation to certain areas in the primary motor cortex (M1), while using the tDCS method to the cerebellum simultaneously, the inhibitory influence of the cerebellum on the M1 area was demonstrated, via the cerebello-thalamo-cor-

tical pathway, as the application of cathodic tDCS interrupted the neuroplasticity effects of transcranial magnetic stimulation on corticospinal and intracortical excitability. In this sense, it can also be observed that cathodal tDCS reduced the excitability of Purkinje cells, resulting in the disinhibition of dento-thalamo-cortical projections to M1 and a subsequent change in local excitability that influenced the response to transcranial magnetic stimulation.

Therefore, associated with neuroplasticity, dopamine plays an important role in a variety of cognitive processes, is related to its modulatory impact on neuroplasticity, including long-term potentiation and depression, Ghanavati *et al*, (2022) developed a study that observed the mechanisms associated with NMDA receptor activity and dopaminergic modulation associated with neuromodulation and plasticity induced by tDCS, administering drugs such as L-Dopa with a dose of 100mg and 10mg of D2 receptor agonist bromocriptine, it was found through the results of the study that the administration of these drugs and tDCS stimulation showed a similar mechanism, D2 activation decreases the excitatory effect associated with the NMDA receptor in the prefrontal pyramidal neuron, reversing the long-term potentiation and depression activity in the striatum, and there was also an important influence of calcium ion in the involvement of plasticity in NMDA receptors. In this context, bromocriptine favored the excitatory plasticity induced by anodic tDCS, restoring neuroplasticity to the application site. Therefore, the application of neuromodulatory methods in association with drugs can increase the therapeutic effect for these patients.

According to Ko(2021), the main mechanisms responsible for the therapeutic effect of transcranial magnetic stimulation are long--term potentiation and long-term depression, with pulses greater than 5 Hz. In this sense, together the induction of depolarization of the presynaptic neuron and depolarization of the dendrites of postsynaptic neurons results in the release of glutamate and the opening of voltage-dependent calcium channels, which would stimulate the accumulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in postsynaptic neurons.

Transcranial magnetic stimulation is a non-invasive brain stimulation technique that induces changes in cortical excitability through changes in force and generates functional and structural neuroplasticity in the brain, being effective for depression, schizophrenia, dementia and stroke. The theta burst method (TBS), is a repetitive induction protocol, according to Jung and Lambon Ralph(2021) TBS modulates gamma-aminobutyric acid (GABA) synthesizing enzymes, presynaptic GABA transporters and cortical inhibitory interneurons, changes have been observed in the gray and white matter, while Allendorfer *et al*. (2012) administered 10 days of TBS treatments to aphasic patients and found increased white matter integrity near the prefrontal gyri and in the anterior corpus callosum.

Both transcranial magnetic stimulation and TBS techniques are known to modulate the activity and influence the release of neurotransmitter systems and intracellular signaling pathways, mainly GABA and glutamate, which play critical roles in inhibitory and excitatory synaptic transmission, respectively. The literature shows that transcranial magnetic stimulation and TBS alter the function of their associated receptors, such as NMDA and AMPA receptors, and also modulate the expression of various proteins involved in synaptic structure and function. In addition, both techniques influence the expression of BDNF (CHENG *et al*.., 2023)

According to the aforementioned author, TBS-related techniques can generally be intermittent or continuous stimulation, administered in 3 stimuli at 50 Hz, every 2 seconds up to 20 to 40 seconds, from 300 to 600 stimuli. When stimulation is carried out intermittently, it lasts up to 190 seconds, resulting in cortical excitability that persists beyond the stimulation period, and also increases enzymatic and non-enzymatic components. Although intermittent TBS is reported to be an attractive technique for modulating cortical plasticity for clinical or therapeutic applications, recent studies have observed that the effect varies greatly between individuals. Therefore, TBS evidently reduces oxidative stress in these patients and aids in the modulation of inflammation important for patients with Autism Spectrum Disorder (ASD), or Epilepsy due to increased neuroinflammation. In AD, the intermittent method has been especially beneficial, as it reduces oxidative stress, lowers beta-amyloid levels and decreases reactive astrogliosis, and may be an excellent therapy for slowing down the progression of AD.

DEEP BRAIN STIMULATION (DBST) AND NEUROPLASTICITY

Deep brain stimulation (DBS) is a neurosurgical procedure that allows neuromodulation based on targeted circuits (KRAUSS *et al*., 2021). The therapeutic potential of DBS depends largely on the optimal positioning of the electrode within the target nucleus, it is a partially reversible and titratable treatment modality that has been widely used in the treatment of movement disorders, and PD. Local effects at the target stimulation site may involve neurotransmitter modulation, leading to generalized changes (VETKAS *et al*., 2022). The subthalamic nucleus (STN), a center in the motor circuit, is the most common target in ECP in the treatment of PD (BOUTET *et al*., 2021). AD and PD are common neurodegenerative disorders characterized by a progressive decline in cognitive and motor functions, both are associated with neuronal loss in various brain regions such as the hippocampus and the substantia nigra associated with motor dysfunction in PD (YUAN *et al*.., 2020)

As a promising therapeutic approach for patients with treatment-resistant obsessive--compulsive disorder (OCD), a condition linked to abnormalities in corticobasal ganglia networks, the ECP method can be performed on prefrontal cortex, anterior cingulate and basal ganglia connected to the limbic system (HABER; YENDIKI; JBABDI, 2021).

According to Fallowski *et al*,(2011) CTS may have efficiently induced behavioral changes and morphological changes in apical and basilar dendrites, thus inducing dendritic neuroplasticity in the prefrontal cortex in animals with depressive disorder, since neuronal adaptation is disrupted in mood disorders and treatments for depression would need to increase neuroplasticity.

ECP therapy using low-frequency sound pulses (TPS) induces stimulation of the neuronal chain, through neurogenesis due to tissue regeneration, also promoting neoangiogenesis and consequently stimulating the production of vascular endothelial growth factor (VEGF). This method consists of extracorporeal shocks, associated with the technique of brain tactography by neuronavigation and neuroimaging by magnetic resonance imaging (MRI), in a different way to the methods previously discussed such as ECP and transcranial magnetic stimulation, TBS shows no risk of seizures, without generating sound waves or inductive magnetic fields, and also penetration occurs in deeper areas of the brain (SANDLER; SHINZATO; BATTISTELLA, 2023).

FINAL CONSIDERATIONS

The evidence reviewed in this article leads to several general conclusions about therapeutic techniques and neuroplasticity, there are still many gaps in relation to metabolic and molecular factors involved or that can cause disturbances in the development of neuroplasticity. It is concluded that among the techniques discussed, the one that showed the best consistent results was TPS, due to its low incidence in seizures and long-term complications, however, other techniques such as ECP, tDCS, TBS, and transcranial magnetic stimulation have been used for longer and even after neurosurgical methods, and in patients with epilepsy, which has been found to be effective.

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