Neurofeedback and its applications: a literature review leaves its effectiveness in autism spectrum disorder (ASD)

Neurofeedback e suas aplicações: uma revisão da literatura deixa sua eficácia no transtorno do espectro do autismo (TEA)

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ABSTRACT
This study aimed to understand how the innovative neurofeedback technique has effectiveness in improving specific parameters in autism spectrum disorder (ASD). Searches were performed on Scielo, Scopus, Scirus, Pubmed, Medline, Lilacs, Bireme, BDTD, Redalyc with the following descriptors "neurofeedback", "ASD", "treatment" and the combination of these terms. The findings were compiled in a narrative way with the articles published between 2016 and 2021.

Keywords: neurofeedback, TEA, treatment.
RESUMO
O presente objetivou compreender como a técnica inovadora do neurofeedback possui efetivação na melhoria de parâmetros específicos no transtorno do espectro autismo (TEA). Foram realizadas Buscas no Scielo, Scopus, Scirus, Pubmed, Medline, Lilacs, Bireme, BDTD, Redalyc com os seguintes descritores “neurofeedback”, “TEA”, “tratamento” e a combinação desses termos. Os achados foram compilados de forma narrativa com os artigos publicados entre os anos de 2016 a 2021.

Palavras-Chave: neurofeedback, TEA, tratamento.

1 INTRODUCTION

The present work is a literary review with the intitude of understanding how the innovative neurofeedback technique has effectiveness in improving specific parameters in autism spectrum disorder (ASD). ASD has grown a lot in the population, as well as studies and research in the area.

In view of the above, the present study has as research problem: what is neurofeedback? What are your applications? And more specifically in ASD, what are the advances listed in the literature? Searches were performed on Scielo, Scopus, Scirus, Pubmed, Medline, Lilacs, Bireme, BDTD, Redalyc with the following descriptors "neurofeedback", "ASD", "treatment" and the combination of these terms. The findings were compiled in a narrative way with the articles published between 2016 and 2021.

They will be used as basic authors: Au, Breitling, Bystad, Castro, Fernandes, Lee, Palm, Pedapati, Steenburgh. The present research is justified by the need for a greater interpretation of the data already listed in the literature with the objective of collecting evidence, synthesizing and critically describing the available literature related to the applicability and efficacy of ETCC in people with ASD.

2 THEORETICAL FOUNDATION

Autism Spectrum Disorder (ASD)

Autism Spectrum Disorder is a Neurodevelopmental Disorder, characterized by deficits and difficulties in communication and social interaction, associated with restricted and circumscribed interests and activities, constituted a range of challenges for the national and international medical community. According to the Center for Diseases Control and Prevention of the United States of America, the prevalence of Autism Spectrum Disorder is currently estimated at 1:58 cases, being four times more common in boys than girls (AU et al., 2016).
The earlier the Diagnosis and the beginning of treatment, the more expressive the results will be, so that the quality of life of children and adults can be significantly improved by an early diagnosis and by the performance of a responsible and monitored treatment. In fact, the speed of brain connection formation and neuroplasticity are in the phase of greater brain development in the first years of life (BECKER; RIESGO, 2016). For children diagnosed with neurodevelopmental disorders, early stimulation is essential to aid brain development in the healthiest possible way, optimizing the results of its functioning in the long term (BIKSON et al., 2016).

The diagnosis of ASD is made clinically by direct observation of the presence of behavioral symptoms that characterize the core of the disorder and interviews with patients responsible (American Psychiatric Association, 2013). Some batteries are used to perform the clinical diagnosis, such as the Childhood Autism Rating Scale (CARS), the Autism Assessment Evaluation Checklist (ATEC), the Children's Global Assessment Scale (CGAS), and the Aber Behaviorrant Checklist (ABC). CARS is a battery with 15 items related to social behavior, emotional response, use of objects, body language, adaptation to changes, visual responses, perceptual responses, fear and anxiety (BROWN; PARIKH; PATEL, 2019).

In general, this scale observes the severity of autism. ATEC is a battery with four subscales: 1. speech/language/communication (14 items; maximum score of 20); 2. social (20 items; maximum score of 40); 3. sensory and cognitive awareness (18 items; maximum score of 36); and 4. physical and behavioral health (25 items; maximum score of 75). In principle, the higher the score, the lower the patient's performance. The CGAS evaluates the psychosocial functioning of the child, scoring from 1 to 100, and the lower the result, the more severe the disorder in the child. Finally, the ABC is composed of 57 items that function as screening for unadaptive behaviors. Until then, there is no definitive treatment for autism (BREITLING et al., 2016).

Most treatments for central SYMPTOMS of ASD are based on behavioral and cognitive interventions. However, the results do not satisfy severe cases with catatonia, attention deficit and hyperactivity or high aggressiveness. Furthermore, pharmacological treatment, through antipsychotics or antidepressants, plays an adjunct role, but does not effectively reduce the central symptoms of the disorder. In many cases, adverse symptoms such as drowsiness, dry mouth, agitation, insomnia and increased behavioral impairment are observed (BYSTAD et al., 2016).
Therefore, it is necessary to develop or invest in innovative and more effective treatment options. In order to understand the pathophysiology of ASD, neuroimaging studies have been conducted over time. The findings indicated the existence of cerebral asymmetry, involving reduced activity in the left hemisphere – where there are structures related to language, memory and social functioning. This reduction in activity also originates from a differentiated sinaptic maturation, caused by microstructural abnormalities, especially in the left region of the dorsolateral prefrontal cortex (HRCFD) (CASTRO et al., 2016). The cerebral asymmetry present in ASD brought to light the discussion that the lateralization of neural functions in these circuitry may explain the origin of the damage in social interaction, communication, aggressiveness and language, some symptoms present in ASD (CAO et al., 2018).

Thus, in addition to therapies such as behavioral and pharmacological interventions, the advent of new procedures that use noninvasive brain stimulation techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (ETCC), can bring good results in the behavioral and cognitive improvement of ASD, as well as has been signaled in the treatment of other disorders such as schizophrenia, Alzheimer's disease, depression, among others. (CONCERTO et al., 2016). In addition, the use of ETCC in children and adolescents with attention deficit hyperactivity disorder showed behavioral improvement in aggressiveness and information processing, such as detection of environmental stimuli and ability to easily exchange between activities (CASTRO, 2016).

**Neurofeedback**

Neurofeedback is a promising treatment for autism spectrum disorders. Neurofeedback involves teaching an individual to control their brain activity consciously. This treatment is not widely available (because it is expensive) and researchers bet heamuch on its effectiveness in the treatment of autism spectrum disorder, Asperger's syndrome and other invasive developmental disorders (CRESPI et al., 2016).

It is important to educate yourself about the procedure, its effectiveness and the research behind it before considering it an option. Given the above, we have the following research question: What happens during neurofeedback therapy? During a typical neurofeedback session, the doctor connects the electrodes on the patient's face and head, as in a typical electroencephalographic test (EEG) (CRIPPA et al., 2016).
These electrodes transmit EEG activity, which is displayed on a screen to the patient and the doctor to see or hear. Typically, EEG activity is converted into something easier for the patient to understand, such as sounds or images (WARRIER et al., 2019). In a format somewhat similar to a computer game, the patient can then try to modify their brainwave activity to move an object on the screen or produce a certain routine procedure (CRAIG et al., 2018).

Each time the patient reaches the desired or routine movement, he receives a reward, often in the form of points. In theory, this process will help patients better learn to control their behavior (STEENBURGH et al., 2016). The goals of treatment, in general of neurofeedback therapy is to help a person with ASD to learn how to control their brainwaves and modify behaviors (FERNÁNDEZ; MOLLINEDO-GAJATE; PEÑAGARIKANO, 2018).

According to the literature, there are significant differences in brains and brainwave patterns in people on the autism spectrum compared to neurotypic individuals (SANTOS; MÉLO, 2018). Specific brainwave frequency targeting in Neurofeedback are designed to attack these specific brainwave frequencies that may present a problem for people with autism spectrum disorder (ASD): Delta waves (0.5-3 hertz): People with learning disabilities, social disabilities, and brain damage usually have high delta waves, resulting in zoning out. Theta waves (3-7 hertz): patients with autism typically have high theta waves, resulting without unusual drowsiness and difficulty concentrating on things outside of them selves (FERNANDES; ALVES, IALVES, SANTOS, 2017).

Neuromodulation Techniques are classified as; 1) Noninvasive techniques, including Transcranial Magnetic Stimulation (TMS); "Transcranial Direct Current Stimulation " ('TDCS') and "Trigeminal Nerve Stimulation " (Trigeminal Nerve Stimulation – 'TNS); 2) Minimally Invasive Techniques, i.e., Electroconvulsive Therapy (ECT); and 3) Invasive Techniques, including Deep Brain Stimulation (DBS) and Vagal Neuro Stimulation (VNS). The "ETCC" "Transcranial Stimulation by Direct Current") constitutes a noninvasive, painless technique, which, although it cannot produce directly evoked potentials, can influence the excitability of individual neurons, and can be used in such a way to specifically stimulate the brain area affects language (FERNANDES; DAYS; SANTOS, 2017).

ETCC has been widely studied and is one of the most promising techniques for the treatment of numerous conditions (RIZZUTTI, 2017). Etcc's base is to employ a battery-driven stimulator that emits low intensity continuous electrical currents (0.5 – 2.0
mA) by two electrodes (cameo and anode), ranging in size from 25cm² to 35cm², which are in contact with the scalp (FINISGUERRA; BORGATTI; URGESI, 2016).

The flow of this current is capable of modulating neuronal excitability, altering the resting potential of neurons and producing effects such as changes in prolonged neuronal excitability, which can be driven by synaptic plasticity. Thus, stimulation of only one area can improve adjacent areas (GORDON, 2017). Depending on the polarity of the stimulation, the anode will have a depolarizing effect, and the detonator will have a hyperpolarizing effect (GUSMAN, 2017). Due to its ability to induce cortical changes in the long term, ETCC has been considered as a treatment tool for numerous neurological and psychiatric conditions such as depression (HADDERS-ALGRA, 2018), schizophrenia (GRECCO et al., 2016) and Alzheimer's (GUSMAN, 2017), for example.

In general, ETCC can have acute or long-lasting effects on cortical functions, depending only on the parameters used in stimulation (such as location, frequency intensity or repetition of stimulation) (ROBLEDO; DONELLAN, 2016). In this context, the present study is justified as ETCC presents itself as a modulating tool of neuronal plasticity, and may have positive effects on the clinical improvement of patients with ASD (HORDER et al., 2018).

**Neurofeedback on autism spectrum disorder**

The aim of this review was to seek evidence and evaluate the efficacy of the use of ETCC in the treatment of cognitive and behavioral symptoms associated with ASD. The results of the Articles showed improvement in assay symptoms, such as improvements in language acquisition, decreased hyperactivity, decreased aggressiveness, increased activity (in the case of catatonia) (HUPFELD; KETCHAM, 2018).

The improvement in symptoms and in some behaviors occurred even in the face of stimulation protocols and different behavioral indicators, according to the objective of each article evaluated. In addition, the effects were relatively long-lasting, so that some studies report continued improvements after the follow-up period of three and six months of stimulations (KANG et al., 2018).

Few adverse reactions were observed, such as mild irritation of the scalp or applied area, and ETCC was well tolerated even after six months of consecutive daily applications (ROBERTSON; BARON-COHEN, 2017). The standard stimulation configuration consisted of the positioning of the electrode in the left DLPFC and the
reference configuration outside the scalp, in the contralateral deltoide. This configuration is based on neuroimaging findings and results of mt sme trials that observed irregular current flow between the left DLPFC, medial prefrontal cortex, supplementary motor area and parietal cortex (KHALEGHI et al., 2020).

This irregular flow corroborates the premise that there are dysfunctions between cortical functioning in certain regions of patients with ASD. In this sense, computational models pointed out that, with the commonly used ETCC configurations, the current also reaches deep brain structures involved in the pathophysiology of ASD (LATTARI et al., 2017).

Anodic stimulation on the left DLPFC, aiming at cortical balance of this area, due to its extensive connection with other networks distributed in the brain, was the most used configuration in ASD, but not the only one (PEDAPATI et al., 2018). Thus, the DLPFC seems to be a site of potential interest to study the neuroplasticity of ASD, since it can promote the balance between excitation and inhibition resulting in the improvement of neuronal communication (LEE; LEE, KIM, 2016).

Changes in this balance can improve the functioning of cognition, mainly attention and working memory, and processing of information visual. In fact, the excitability of the prefrontal cortex improves symptoms, corroborating studies that showed decreased activity in the prefrontal cortex in people with TAs (MAROTTA et al., 2020).

Another line of evidence of stimulation in the DLPFC region comes from clinical trials from cathodic stimulations, rather than anodic, in the left DLPFC that reversed unadaptive behaviors, such as catatonia or hyperactivity (PALM et al., 2018). The therapeutic effects observed in the studies of this review were more related to the reduction of cortical excitability in the HRCFD and the possible cascade resulting from inhibitory effects on all neuronal networks interconnected with this region (MANOR et al., 2016).

The positive effects of stimulations had a impact on dysphoria, irritability, agitation, crying and behavioral symptoms evaluated by scales such as ABC, CARS, CGAS and ATEC (PAQUET et al., 2017). Neuroimaging studies indicate that the medial prefrontal cortex and medial temporal lobe are also critical in the pathophysiology of ASD due to the aspect of social retractionm related to individuals with ASD that cause dopaminergic reduction in this area, or areas interconnected with The HRD (MANOR et al., 2018).
Possible mechanisms of action of ETCC in ASD. A summary of the possible mechanisms of action by which the use of ETCC seems to provide benefits in the treatment of ASD is being provided by this review, although research is still specific and restricted within a complex universe involving the very pathophysiology of the disorder (OLDRATI et al., 2016). Of course, many discoveries will remain unknown, as will the main mechanisms of action that need to be tested, generalized and understood by further research. However, the effects of ETCC seem determined by neuronal polarity and probably by extension to neural circuitry (MOURA et al., 2019).

Stimulation protocols used: Anodic stimulation was responsible for increasing neuronal excitability, and cathodic stimulation triggers the reverse. This change in polarization is probably due to the displacement of resting potential, at least within a current conception related to the mechanism underlying the short-term effects of ETCC (MORAES et al., 2017).

The long-term effects of ETCC are proposed as due to changes in the sinatic regions, specifically by changes in activity in N-Methyl-D-aspartate (NMDA) and GABA receptors, which can then lead to permanent changes in areas that presented reduced activity, for example (PANIKRATOVA et al., 2020). In addition, ETCC may result in modulations of neuroplasticity by brain-derived neurotrophic factor (BDNF) dependent mechanism, since bndf hyperactivity plays a key role in the etiology of autism in the early stage of life. With these findings, it was possible to observe that the effects of ETCC are not limited to sites of application, having an effect even in other areas (MILLER et al., 2019).

3 FINAL CONSIDERATIONS

The results suggest that ETCC is a promising tool for the treatment of ASD. This occurred even in studies using different designs, objectives and conditions. This reinforces the use of ETCC as a promising clinical tool in the study and follow-up of ASD, especially considering symptomatic improvement when specific or conventional treatments have no effects.

Protocols aimed at stimulating regions such as DLPFC, for example, can lead to improved behavioral and cognitive impairments, besides serving as an investigative and therapeutic tool. Thus, it was clear that stimulation in this area causes improvements. Investigative studies do not clearly provide what are the altered physiological mechanisms or whether these changes can be generalized to the entire population with
ASD. Still, it is not clear which region is most affected and which region should be most stimulated. However, according to the neuroimaging studies and the findings presented, stimulation of THEHRD is the best choice per hour.

The need for further studies evaluating the efficacy of ETCC in ASD is one of the points to be considered. Due to the potentiality of the use of ETCC for ASD, it can be known which symptoms are best treated and when stimulation should be used as a therapeutic agent. The refinement of the technique should be performed so that professionals can know the exact moment of stimulation application. Understanding this is crucial, from the pathophysiology point of view, since it can provide new directions for the treatment of refractory or recurrent conditions.
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