EFFECTS OF RADIO ELECTRIC ASYMMETRIC CONVEYER (REAC) NEUROBIOLOGICAL TREATMENTS IN DIFFUSE AXONIAL INJURY: A RANDOMIZED, DOUBLE-BLIND CLINICAL TRIAL

Unique Protocol Id: 84791824.8.0000.0068

Date: October/15/2025

Abstract

Background: Severe traumatic brain injury, particularly diffuse axonal injury (DAI), often leads to lasting neurological issues. Cerebral dysfunction in DAI can be evaluated by monitoring cerebral electrical activity (CEA) through EEG. The radio electric asymmetric conveyer (REAC) is a noninvasive method designed to rebalance cellular polarity via endogenous bioelectric fields and modulate CEA. This technique may alter CEA, which can be detected using quantitative EEG (qEEG).

Objective: To assess qEEG changes following DAI and brain wave alterations after a REAC protocol in this group.

Methods: In this prospective, randomized, double-blind clinical trial, adult (≥18 y.o.) DAI patients will be assigned to active or sham groups for 19 sessions of either true or sham REAC following ICU discharge. Interventions include one Neuro Postural Optimization session and 18 NPPO-BWO-G sessions (up to four per day). The main outcome is to evaluate changes in qEEG patterns through population brain electrical mapping after REAC therapies. Additionally, voluntary adults (≥18 y.o.) with no history of neurological diseases will be submitted to the same protocol to further comparisons between qEEG patterns.

Keywords: cognitive dysfunction; diffuse axonal injury; radio electric asymmetric conveyer; rehabilitation; traumatic brain injury.

LIST OF ACRONYMS AND ABBREVIATIONS

ANOVA..... *analysis of variance*

ANP ..... neuropsychological assessment

BDNF..... *brain-derived neurotrophic factor*

Beta-APP.....Beta-*Amyloid-Precursor-Protein*

BVMT..... *Brief Visuospatial Memory Test*

CE ..... cortical excitability

CRT .....cognitive rehabilitation therapy

CONSORT ..... *Consolidated Standards of Reporting Trials*

cTBS..... *continuous theta burst stimulation*

DAI.....diffuse axonal injury

DWI ..... *diffusion weighted imaging*

EEG…….electroencephalogram

EMP .....motor evoked potential

FIC ..... intracortical facilitation

GABA ..... *gamma-aminobutyric-acid*

GRE.....*gradient echo*

HVLT ..... *Hopkins verbal learning test*

LAT ..... traumatic axonal injury

LED ..... *Light-Emitting Diode*

LLLT ..... *Low Level Light/Laser*

LM .....Resting Motor Threshold

LTD .....*Long-Term Depression*

LTP.....*Long-Term Potentiation*

M1.....primary motor area

MRI..... magnetic resonance imaging

MSC ..... minimum state of consciousness

NMDA.....N-Methyl-D-Aspartate

PDC..... prefrontal dorsolateral cortex

PET ..... *positron emission tomography*

PVS ..... persistent vegetative state

RCT ..... randomized clinical trial

STAITER..... state-trait anxiety inventory

SIII .....short interval intracortical inhibition

TC .....computed tomography

TBI .....traumatic brain injury

TD.....diffusion tensor

TF3D ..... three-dimensional fiber tractography

TMT .....*trail making test*

LIST OF UNITS

µA.....microAmpere

Cm ..... centimetre

Ms .....millisecond

ºC.....degree Celsius

T .....Tesla

Db..... decibel

Mv ..... miliVolt

Hz ..... Hertz

V ..... Volt

m ..... meter

LIST OF FIGURES

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability globally, significantly affecting the quality of life for patients and caregivers [1-3].

In the United States, traumatic brain injury is the leading cause of death for people aged 1 to 45 and a major risk factor for morbidity and mortality in polytrauma cases [4].

Although epidemiological data in Brazil are limited, studies indicate that TBI is a significant public health issue, primarily impacting the country's young and economically active population [5, 6].

Automobile accidents and falls are primary causes of traumatic brain injury, with incidence rates highest among young adults (20 to 29 years) and individuals over 80 years old [4-6].

TBI is a highly heterogeneous condition, with multiple classification systems that emphasize distinct aspects such as the underlying mechanism of injury, clinical severity, radiological characteristics, and pathophysiological processes. These classifications play an important role in standardizing data collection, identifying prognostic factors, and informing the selection of appropriate therapeutic approaches tailored to individual cases.

From a pathophysiological perspective, traumatic brain injury (TBI) causes damage through primary lesions—direct energy transfer to the brain at trauma—and secondary effects, which involve cellular and molecular changes occurring for hours to weeks post-injury [7, 8].

Diffuse axonal injury (DAI) is a type of lesion in TBI that leads to significant brain dysfunction and affects roughly 40% of patients, making it a leading cause of neurological problems in survivors [9-11].

Clinically, it is defined as a coma lasting more than 6 hours after TBI, excluding cases caused by ischemic brain injury or intracranial masses [10, 12]. Gennarelli et al.'s 1982 study described DAI in primates as a range of injuries mainly involving brain white matter

damage [9]. In 1989, Adams established objective criteria for classifying DAI from an anatomopathological perspective into three categories: mild, moderate, and severe [10]. In each case, the principal form of structural damage is axonotomy (axon injury), which may occur immediately at the time of trauma (primary) or subsequently (secondary), following a series of biomolecular events [13-15].

Detecting this condition during routine exams in TBI patients can be challenging, as DAI-related abnormalities are often missed by standard CT or MRI scans and may require advanced imaging techniques to identify structural changes in the central nervous system [16-23].

From a neurological perspective, TBI can result in a wide range of cognitive, behavioral, and sensory-motor changes that may affect the patient's quality of life. Cognition encompasses the processes involved in acquiring knowledge and includes factors such as thought, language, memory, reasoning, and task execution, which are considered important for intellectual development [24, 25].

Although TBI is strongly linked to cognitive dysfunction, effective treatment remains difficult. While cognitive rehabilitation therapies have shown benefits in some studies, results are inconsistent [26-29].

Drug therapies for post-TBI cognitive disorders have proven ineffective [30]. The limited effectiveness of conventional cognitive rehabilitation in DAI patients has led to the exploration of new therapies. Neuromodulation techniques, both invasive and noninvasive, offer promising options by targeting specific brain regions to alter activity and support recovery.

Radio electric asymmetric conveyer (REAC) technology is a noninvasive technique that was first described by Rinaldi and Fontani [31, 32]. REAC neurobiological modulation with specific protocols such as neuro-postural-optimization (NPO) and neuro-psycho-physical-optimization – brain wave optimization-G (NPPO-BWO-G) is a safe, established technique with proven therapeutic benefits for various neurological and psychiatric disorders [33-40].

Given the significant brain damage and multiple disabling neurological sequelae, in severe TBI patients, combined with the limited efficacy of conventional pharmacological and cognitive rehabilitation interventions, REAC may be a promising therapeutic approach for affected patients. We will conduct a randomized clinical trial to assess REAC's effects in patients with DAI.

GOALS

Primary Endpoint

- To evaluate the qEEG changes in patients with subacute/chronic DAI, following REAC neuromodulation.

Secondary Endpoint

- To evaluate the qEEG changes in adults free of neurological conditions, following REAC neuromodulation.
- To evaluate cognitive and humor changes in adults free of neurological conditions, following REAC neuromodulation.

LITERATURE REVIEW

TBI Classifications

TBI is typically a heterogeneous condition being classified by clinical severity, mechanism of injury and pathophysiology, all of which are relevant to properly determine treatment and prognosis.

From a clinical point of view, TBI is classified as mild, moderate and severe depending on the duration of the loss of consciousness, level of consciousness on the Glasgow Coma scale and the presence or absence of post-traumatic amnesia, as well as its duration. However, knowledge of other information, such as history of exogenous intoxication, use of sedatives and neuromuscular blockers, as well as orotracheal intubation, is essential to avoid misclassification of TBI [41, 42].

Gennarelli *et al*. (1982) classified the injuries caused by TBI into 5 major groups: skull fractures, focal lesions, diffuse lesions, penetrating injuries and explosion injuries. Diffuse lesions differ from focal lesions in that they usually do not present macroscopic structural damage. This type of injury causes diffuse brain dysfunction and affects about 40% of patients with severe TBI [9, 43]. Basically, this type of injury is the result of two basic mechanisms: by contact and inertial (acceleration). Contact injuries require the occurrence of direct trauma of the skull against another object. On the other hand, inertia injuries, commonly called acceleration injuries, are due to sudden and intense movement of the skull, regardless of the occurrence of impact of the skull against external structures. It is worth mentioning that, of the 3 possible types of acceleration (translational, rotational and angular), the angular type is the one that is most associated with DAI because in this mechanism there is a combination of translational and, mainly, rotational movements, causing diffuse brain injury [44, 45].

From the histopathological point of view, the 3 main tissues involved in TBI (bone, vessels and cerebral parenchyma) differ considerably with regard to their tolerances to compression, tension and shear. Because of these different inertia properties of the affected tissues, the brain is susceptible to abrupt rotational forces. In this way, when the skull undergoes a sudden rotation, the superficial layers of the brain (closest to the skull) are accelerated (or braked) before the deep ones, producing a shear

stress. As a consequence, this mechanism can cause the rupture of axons and vessels in various regions of the brain, notably in the white fibers of projection, cortico-subcortical transition, dorsolateral rostral regions of the brainstem, corpus callosum, hippocampus and cerebellum [46-48].

Regarding the pathophysiology, the brain lesions observed in TBI can be divided into two broad categories that are distinct, but closely related to each other: primary and secondary lesion. This classification guides most of the treatments in current clinical practice. For example, surgical treatment of primary brain lesions, such as the removal of an intracranial hematoma, is one of the main measures instituted in the treatment of these patients in the acute phase. Likewise, the identification, treatment and prevention of secondary brain lesions is the main focus of therapy instituted within neurological intensive care centers in patients with severe TBI.

The deleterious effects observed in TBI are the result of the primary injury, that is, of the immediate trauma in the brain tissue and dependent on physical phenomena, added to the secondary lesions, which are those that follow the aggression that occurred at the first moment, being dependent on biomolecular and pathophysiological processes [7].

Although the mechanisms of primary injury are numerous and heterogeneous, they are all the result of external mechanical forces transferred to the intracranial structures. The severity of the primary injury depends on the intensity and temporal and spatial distribution of the insult. More intense, long-lasting and therefore more severe aggressions usually cause neuronal necrosis while mild injuries result in apoptosis[8].

On the other hand, secondary injuries involve complex biological processes and include all the cascading molecular mechanisms that follow the moment of trauma and that can last for hours or even days. These mechanisms include neurotransmitter-mediated excitotoxicity, electrolyte disturbances, mitochondrial dysfunction, inflammatory response, and cell death (necrosis and apoptosis).

At first, the excess release of glutamate, the main excitatory neurotransmitter of the central nervous system, leads to the phenomenon of glutamatergic excitotoxicity mediated by NMDA (N-Methyl-D-Aspartate), culminating in processes of neuronal dysfunction and death [49-52]. This process induces the accumulation of calcium ion in

the neuronal intracellular compartment, promoting inflammation, mitochondrial dysfunction and apoptosis, and may even trigger and potentiate oxidative stress through the phenomenon of spreading cortical depression [7, 53-56].

In addition to the events involving glutamate, there is evidence that GABA (*gamma-aminobutyric acid*), the main inhibitory neurotransmitter of the cerebral cortex, is also involved in the process of secondary injury related to TBI. Studies in rats have demonstrated the recovery of sensory and motor functions, as well as better cognitive performance and increased survival, in animals undergoing GABAergic neuron transplantation [57, 58]. Demirtas-Tatlidede *et al.* [25] described the occurrence of excess GABA-mediated inhibition in the subacute phase of TBI, which could explain the arousal alterations seen in this population.

Diffuse axonal injury

General aspects and terminology

DAI accounts for almost one-third of deaths due to TBI. DAI is considered the main risk factor for morbidity and mortality of TBI victims, being the main cause of coma, neurological sequelae and chronic disorders of the level of consciousness (vegetative state and minimal state of consciousness) after TBI [10-12].

The spectrum of DAI ranges from its mildest form (concussion), when there are only changes in neuronal function but without damage to the cellular structure, to the most severe cases, when diffuse axonal damage occurs at the microscopic level in addition to macroscopic findings[12].

The terminology of the DAI was clarified by Geddes *et al*. [59]. The definitions suggested by the author are:

- Traumatic Axonal Injury (TAI): axon injury caused by trauma. The extent can vary greatly and may affect only small foci up to extensive lesions of the cerebral parenchyma.
- Diffuse Traumatic Axonal Injury (DTAI): originally called "DAI"", this represents the most severe form of this spectrum.
- Diffuse Axonal Injury (DAI): initially described as a syndrome clinicopathological of patients unconscious from the moment of TBI, without expansive intracranial

lesions and with diffuse lesion of the axons in the brain, including the brainstem [60]. Ideally, the traumatic etiology of axonal damage should always be cited when the term is used to describe a neuropathological diagnosis.

For didactic purposes and considering the consecration of the term DAI in clinical practice, we will use this term to describe the extensive diffuse axonal brain lesion resulting from TBI.

Generally, these lesions result from the involvement of the white matter when subjected to rotational forces, as well as through the effect of acceleration and deceleration on the brain parenchyma, exerting shear stress on the fibers and, consequently, axonal injury [43, 46, 47, 61].

Pathology

The diagnosis of DAI can only be confirmed through anatomopathological examination (APE). Adams et al. [10] developed a classification to assess the severity of DAI based on macroscopic and microscopic findings of silver-impregnated brain tissue (Table 1):

Table 1 - Adams classification (1989) according to anatomopathological criteria

DAI Grade I (light)	Microscopic changes in the white matter of the cerebral hemispheres, corpus callosum, brainstem, and occasionally cerebellum.
DAI grade II (moderate)	Grossly evident lesions on the corpus callosum, usually as punctate hemorrhages
DAI grade III (severe)	In addition to the findings present in grade II, additional focal lesions in the dorsolateral regions of the rostral portion of the brainstem, with involvement of the superior cerebellar peduncle.

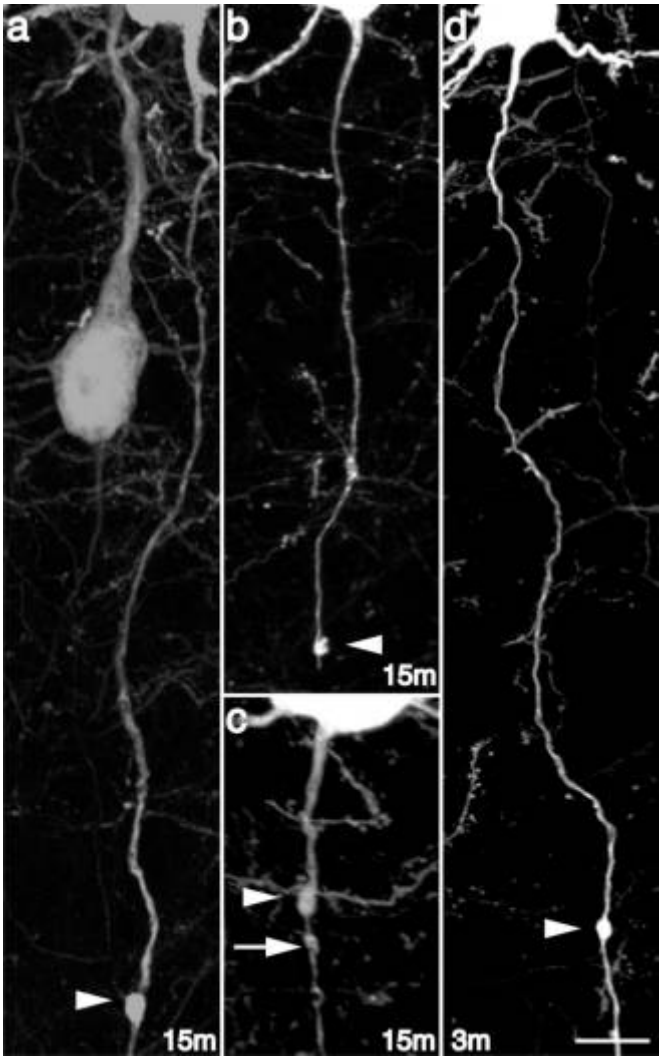
DAI – Diffuse Axonal Injury

At first, the microscopic changes of DAI are imperceptible in conventional APE. In 1993, Gentleman *et al*. [62] described a robust immunoreactivity method, capable of identifying changes present in the axonal lesion within only a few hours of the trauma. Through immunohistochemistry, it was possible to detect focal accumulations of beta-

amyloid precursor protein (beta-APP - *beta-amyloid precursor protein*) two hours after TBI, while axon varicose veins and axonal swelling could be seen after 12 to 24 hours. When compared to preparations impregnated by silver, the immunohistochemistry technique proved to be superior and able to identify more exuberantly the lesions in the axons, becoming considered the gold standard technique for detection of DAI [11, 62]. Subsequently, some studies demonstrated that immunoreactivity to beta-APP was not exclusive to DAI but was also described in other forms of brain injury, such as hypoxic-ischemic lesions [63, 64].

Pathogenesis of DAI

In DAI, the basic structural damage is axonotomy. Two basic mechanisms are implicated in this process: primary and secondary axonotomy. Primary axonotomy occurs immediately after tissue trauma and causes the influx of calcium into neurons and activation of proteases. Human studies have detected histological lesions between 4 to 6 hours after trauma [13]. Secondary axonotomy, on the other hand, begins hours after tissue injury and can last for years [14, 15, 46]. The failure of cell repair mechanisms, or the subsequent occurrence of ischemic lesions, results in disconnection of the distal axonal segment. Axoplasmic transport continues and this blockage due to axonal disconnection results in accumulation of material at the proximal end to the axon breaking point, causing localized axonal edema, also referred to as axonal bulb [65]. Although the magnitude of the trauma is apparently directly correlated with the severity of the axonal damage, secondary axonotomy seems to have greater relevance in TBI-related axonopathy [66].



Source: Greer JE *et al*., 2013[67]

Figure 2 – DAI rapidly induces secondary axonotomy

In a model of fluid percussion in rats, after the impact on the brain there was the formation of axonal dilatations (bulbs) (arrowheads) early as 15 minutes after the injury (a – c). Several injured fibers showed clear evidence of disconnection (b), although many demonstrated some degree of axonal continuity (a,c). In addition, the formation of the bulbs can be seen at various locations along the axon, both distal (a,b) and proximal (c) relative to the cell body. Range: 10 μm.

Clinical Aspects

DAI is defined from a clinical point of view as a state of coma after TBI that lasts for more than 6 hours, excluding cases related to ischemic brain lesions or intracranial

expansive lesions [10, 12]. Typically, patients with DAI are unconscious from the moment of impact, do not present a lucid interval and remain with severe impairment of the level of consciousness for a variable period of hours. Even those patients with less severe brain injury can regain the level of consciousness with definitive sequelae.

Gennarelli *et al.* classified diffuse traumatic brain injuries into 4 groups: mild, moderate (or classical), severe concussion, and DAI [10]. DAI can also be classified as mild, moderate or severe, and mild DAI occurs in 8% of severe TBI. In this type, the coma lasts from 6 to 24 h and after the trauma and the victims may evolve with psychological or neurological deficits. The evolution is variable: 78% of the cases evolve favorably, 2% have severe sequelae, 1% evolve with persistent vegetative state (PVS) and death occurs in about 15% of the patients. Moderate DAI, present in 20% of severe TBIs, is characterized by coma for more than 24 hours and recovery is often incomplete. The evolution is favorable in 59% of the victims, with severe sequelae in 12%, PVS in 5% and fatal evolution in up to 24% of the cases. Finally, severe DAI occurs in 16% of severe TBI and is characterized by a coma lasting days or weeks. These patients have frequent signs of brainstem dysfunction and dysautonomia (systemic arterial hypertension, hyperhidrosis, and hyperthermia). The evolution is favorable in only 28% of cases; 14% have severe sequelae, 7% progress to PVS and 57% die.

Radiological Aspects

Although patients with DAI usually present exuberant clinical alterations, the abnormal findings in a considerable part of the cases are not identified by the techniques of computed tomography (CT) or conventional magnetic resonance imaging (MRI) of the brain.

Despite the limitations of conventional routine imaging techniques, some macroscopic changes may suggest the presence of DAI:

- Focal lesions of the corpus callosum, seen as hemorrhagic foci. Occasionally these hemorrhages can rupture the interventricular septum, causing ventricle hemorrhage.

- Focal lesions in the dorsolateral quadrants of the rostral portions of the brainstem. Small hemorrhagic lesions can also be seen near the superior cerebellar peduncles.
- "*Gliding Contusions*": punctate hemorrhagic lesions affecting the parasagittal white matter in the upper portion of the cerebral hemispheres, usually in the transition zone between the white and gray matter. They are often bilateral and asymmetrical.

T2/FLAIR-weighted brain MRIs (*Fluid Attenuated Inversion Recovery*), particularly in the coronal and sagittal sections, are useful in the detection of DAI involving the corpus callosum and the fornix, two areas difficult to be analyzed in routine examinations obtained in the axial plane [16].

Focal lesions of the corpus callosum and dorsolateral rostral portions of the brainstem present in grade II and III DAI's may be visible in conventional neuroimaging studies. However, in patients with grade I DAI, these techniques may not show any abnormalities.

Diffusion sequence-weighted MRI (*DWI - diffusion weighted imaging*) measures the random motion, also known as Brownian motion, of water molecules in brain tissue. Because of its sensitivity for detecting acute stretch injuries, diffusion has been particularly useful in detecting DAI [17, 19-21]. Diffusion is able to detect more DAI-related lesions than T2-weighted images *fast spin echo* and/or T2 *gradient echo* (GRE) T2* within the first 48 hours after injury.

Diffusion tensor (DT) MRI has shown utility in assessing white matter integrity. This technique allows the determination of fractional anisotropy (FA), which measures the preferential movement of water molecules within the axons present in the white matter, with respect to their degree and direction (axis) of the diffusion of the water molecule. PA values range from 0 to 1, with 0 referring to completely isotropic diffusion (*e.g.* Water) and the value 1 related to diffusion only in a single direction, i.e., maximum anisotropy [22, 23]. In addition to PA, the integrity of white matter fibers can be measured with the use of three-dimensional tractography of white fibers (TF3D). However, few studies have sought to correlate the findings of 3D TF in patients with DAI

and more research is needed so that this technique can be incorporated into the clinical routine of investigation of these patients [18, 68-72].

Cognitive changes due to TBI and treatment

Cognitive impairment resulting from TBI is considered one of the most severe and debilitating neurological sequelae in this population, and may occur even in patients with mild TBI [24].

Cognitive sequelae are those in which there is impairment of attention, concentration, memory, verbal fluency, planning, decision-making, reasoning and problem solving, which may assume a persistent character and prevent the individual from reestablishing their independence or returning to their usual activities before the TBI [73, 74]. Although DAI can cause motor or sensory deficits, cognitive sequelae are more related to the individual's dependence, occurring in up to 65% of victims of severe TBI [75]. Of these, about 43% of patients have cognitive dysfunctions for more than 6 months and in more severe cases, even basic activities of daily living, such as preparing a meal and driving, are compromised [76].

Among the cognitive alterations observed in patients with TBI, the impairment of executive functions draws a lot of attention. This term refers to the set of higher-order cognitive skills capable of planning, executing and monitoring a series of actions aimed at achieving a goal. This cognitive domain depends fundamentally on the prefrontal cortex and its circuitry, being extremely important for the quality of life of the individual, since it directly influences everyday acts, such as performance at work or in interpersonal relationships [77]. Given the high prevalence of such cognitive disorders, it is not surprising that the frontal lobe, or the connections to this brain region, are particularly vulnerable to TBI [78]. For example, disturbances in working or planning memory may be seen in patients with focal lesions in the dorsolateral prefrontal cortex or in projections (white matter) between the lateral frontal region and posterior regions [21].

Memory disorders after DAI also deserve to be highlighted, since they are highly prevalent in this population, affecting up to 40 to 60% of victims of severe TBI. In fact,

TBI broadly affects the most diverse aspects of memory and presents a striking characteristic: the pattern of memory impairment is much more similar to that found in patients with frontal injury than individuals with amnesia [79]. In 2005, Mathias and Mansfield [80] compared 25 TBI victims with 25 healthy individuals matched for age and sex and found that the patients had worse performance in explicit memory. These same findings have been demonstrated in other studies, indicating memory disorders to be highly prevalent after DAI, affecting up to 40 to 60% of victims of severe TBI. In fact, TBI broadly affects the most diverse aspects of memory and presents a striking characteristic: the pattern of memory impairment is much more similar to that found in patients with frontal injury than individuals with amnesia [79].

Although the pathophysiological mechanism is not well understood, the cognitive changes found in these patients seem to be related to the impairment of circuits involving several neurotransmitters, such as serotonin, glutamate, dopamine, norepinephrine and acetylcholine [81]. In the acute phase of TBI there is a massive production and release of acetylcholine in combination with other neurotransmitters such as glutamate, catecholamines and serotonin, which contributes to the clinical disorders observed at this stage (changes in the level of consciousness, executive dysfunctions and memory impairment) [82, 83]. However, in chronic disorders affecting these cognitive domains, acetylcholine seems to be the most relevant neurotransmitter involved [81, 84]. After experimental studies demonstrated the impairment of cholinergic pathways after TBI in the 1990s, Dewar and Graham and Murdoch *et al*. [85, 86] conducted seminal studies *postmortem* in humans and demonstrated the pathophysiology of cholinergic dysfunctions observed in TBI victims. Despite the relative normalization of most neurotransmitters, cholinergic function remained chronically reduced, which was apparently directly related to the cognitive disorders observed [84-86].

The spontaneous cognitive recovery of DAI victims is well documented in the literature. Despite memory impairment after TBI, many patients have spontaneous recovery of cognitive functions. This is a well-known and reported phenomenon in the medical literature. Zaninotto *et al*., [87] followed 18 patients with DAI for 12 months after trauma and documented a significant improvement in verbal fluency at the 12th

month, compared to the performance obtained at the 6th month. Three years later, the same authors reported data from 40 patients with DAI and observed spontaneous improvement in visuospatial memory as a function of time at the end of the 1st year after TBI [88]. In addition to the spontaneous cognitive gain observed, many studies have demonstrated improvement in additional cognitive performance when submitted to cognitive rehabilitation therapies (CRT) [89-91]. In 2009, Rohling et al. [89] published a review showing improvement of memory in TBI and stroke patients who underwent CRT, being this benefit markedly in the domains of attention training, visuospatial memory and language. CRT is a term that describes treatments developed to improve cognitive performance, either by restoring lost cognitive functions or learning compensatory strategies. Specific CRTs have been developed for resolution of disorders of memory, attention, communication, and executive functions. In addition, a committee to evaluate CRTs for TBI patients was created by the *Institute of Medicine* in the United States [92]. This same committee evaluated the studies on specific CRT for executive functions and described a wide variety of different strategies employed, predominantly compensatory and applied in victims of moderate to severe TBI, and concluded that there is evidence that goal-guided training *Goal Management Training*, using previously planned tasks as guides for the planning and execution of new tasks, promotes positive effects on the performance of this domain cognitivo.Com relation to CRT for memory, Rohling *et al*. [89] questioned the benefit of this therapeutic strategy, since it did not find significant changes. However, few studies that were part of this meta-analysis specifically evaluated the memory domain, making it difficult to reach a definitive conclusion on this topic. In 2014, Elliott and Parente [93] published a meta-analysis evaluating the efficacy of CRT for the treatment of memory deficit in patients with TBI and stroke, including new studies, and revisited the data published by Rohling *et al*. in 2009 [89]. This time, the results indicated moderate and significant memory improvement with CRT, especially in the working memory component. Regarding the techniques used, it was demonstrated that the most recently described strategies, using digital resources such as the internet, were not superior to the protocols traditionally used [29].

To date, studies evaluating pharmacological treatments for cognitive changes resulting from TBI have failed to demonstrate a clear benefit of this therapeutic modality [94]. Extrapolating the findings of studies in patients with mild cognitive impairment, a known risk factor for Alzheimer's disease, that evaluated possible drug treatments for dementia, it was seen that the strategies studied failed to demonstrate this benefit. Still, no medication for this purpose has been approved for clinical use by the *United States Food and Drug Administration (FDA) [95-97]*. In contrast to most published studies, donepezil (an acetylcholinesterase inhibitor) can be used as an attempt to control symptoms in patients with severe and debilitating cognitive conditions, although its efficacy is still questionable [98].

Neuromodulation Methods in TBI

The International Neuromodulation Society (www.neuromodulation.com) defines therapeutic neuromodulation as: "*Alteration of nerve activity through targeted delivery of stimulus, such as electrical stimulation or chemical agents, to specific neurological sites of the body*". The limited results with conventional cognitive rehabilitation techniques motivated studies evaluating invasive and non-invasive neuromodulation strategies, as follows: Transcranial Magnetic Stimulation (TMS), Transcranial Direct Current Stimulation (tDCS), Low Intensity Laser Therapy and Light Emitting Diode (*LLLT - Low-Level Light/Laser and LED - Light-Emitting Diode*) Transcranial and Deep Brain Stimulation, the latter of which is an invasive technique. Among these, tDCS is the intervention currently with the largest number of clinical studies published on the subject [99]. However, most of the current evidence is case reports or case series, and the few randomized and covert clinical trials have a small sample size, allowing for limited analyses.

Given the various neuromodulation techniques described, an important question still to be answered is which of the strategies offers the best results. In fact, there is no data available that answers this question. Many topics still need to be explored: 1) effectiveness of these techniques when compared to each other; 2) the peculiarity of each of the methods that may be advantageous for the treatment in TBI; 3) safety and

tolerability; 4) consider the various biological processes that occur in the different phases of TBI, identifying favorable moments ("therapeutic windows") for the institution of a certain technique and 5) combining different modalities can optimize the final product.

Radio electric asymmetric conveyer

The REAC technology is a noninvasive, personalized approach to neuromodulation that has been investigated as a possible treatment for various neurological and psychiatric conditions.

REAC technology, in contrast to traditional neuromodulation methods that generally target specific neural pathways, operates by using very low-intensity asymmetrically conveyed radio electric fields to modulate the endogenous bioelectric field. This field includes the electrical activity of all body cells. The process is carried out with a REAC device, which produces an asymmetric radioelectric field, while the asymmetric conveyor probe interacts with the body's bioelectric field.

The main function of REAC technology is to affect endogenous bioelectric activity and cellular polarity. Cells maintain an internal and membrane charge imbalance, creating an electrical gradient that supports various cellular processes. The asymmetric radioelectric field generated by REAC can interact with this charge imbalance, which may result in changes to endogenous bioelectric activity and cellular polarity, potentially influencing neural communication.

REAC technology has demonstrated therapeutic promise for neurological and psychiatric conditions, and ongoing research suggests it may play a growing role in neuromodulation.

Clinical protocols

REAC technology provides several therapeutic protocols for neuro modulation and bio modulation. These protocols are used to address mood, behavior, motor control, and pain disorders, as well as in reparative and regenerative medicine.

Safety and Recommendations

The obtained certifications (CE and ANVISA) and existing studies confirm that the treatments of REAC technology are safe and effective when used as intended and by qualified professionals.

General considerations

REAC is a noninvasive technology that utilizes low-intensity radio electric (RE) emissions to interact with biological tissues.

Physical aspects

The physical aspects of Radio Electric Asymmetric Conveyer (REAC) treatments involve a noninvasive interaction of low intensity RE emissions with the patient's body. The device features a unique ACP that convey the RE field to the target area.
REAC treatments are non-invasive and painless. Patients typically lie or sit comfortably while the ACP is placed on specific areas of the body based on the treatment protocol. The treatment sessions duration can vary depending on the targeted condition and treatment plan. Overall, the physical aspects of REAC treatments involve the application of low power RE energy through a specialized probe to potentially influence cellular processes.

Adverse effects

No adverse effects have been reported to date. However, transient expected side effects that are part of the therapeutic response may occur, such as mild axial instability, asthenia, and mood swings.

Contraindications

At present, no specific contraindications to REAC neuromodulation treatments have been identified. However, it is recommended to avoid application in patients with pacemakers and pregnant women.

Ethical Aspects related to the use of REAC technology treatments.

Widespread axonal damage currently has no effective therapy. REAC neuromodulation treatments are safe and non-invasive and have been shown to

produce improvements in other neurodegenerative diseases. Based on these premises, there are no apparent ethical concerns.

Regulation

The devices used in this study are the BENE Model 110 devices, which have obtained both CE and ANVISA (Brazilian regulatory agency) certification.

Table 3 – Possible therapeutic applications for REAC in TBI

Therapeutics
Neuro postural optimization NPO and Neuro Psycho Physical Optimization – Brain Wave Optimization-G (NPPO-BWO-G) treatments Enhance: • Motor recovery • Cognitive rehabilitation (memory, language, executive functions) • Treatment of post-concussion syndrome • Reduction of depression, anxiety, and post-traumatic stress symptoms • Treatment of chronic disorders of the level of consciousness • Painful syndromes

REAC in cognitive, mood, behavior, and motor disorders.

Radio Electric Asymmetric Conveyer (REAC) technology is a relatively new approach to neuromodulation, aiming to influence the nervous system through the application of radio electric fields asymmetrically conveyed, using precise administration procedures. These specific treatments have proven useful and effective in numerous mood, behavior and movement control disorders [33-40, 100-134].

MATERIAL AND METHODS

Series

Participants will be prospectively included of both genders, between 18 and 60 years of age. Eligibility criteria is described in Tables 4 and 5.

Table 4 - Inclusion criteria

1.	Clinical-radiological diagnosis of diffuse axonal lesion
2.	Traumatic brain injury suffered for at least one (1) week
3.	Be hospitalized at the neurotraumatology section at the Hospital das Clínicas Complex of the Medical School of the University of São Paulo (HCFMUSP)

Table 5- Exclusion criteria

1.	History of addictive behavior and/or serious psychiatric illnesses
2.	Presence of bone defects in the skullcap
3.	Uncontrolled epilepsy
4.	Carriers of implanted metallic or electronic devices: cardiac pacemaker, *stents*, epidural or deep brain electrodes, cochlear implants, drug infusion systems or intracranial clips
5.	Next of kin refusal to participate in any of the stages of the study, as well as to be randomly allocated to one of the groups
6.	Next of kin refusal to provide the free and informed consent for participation
7.	Gestation
8.	Severe, uncontrolled systemic disease

9.	Magnetic resonance imaging of the brain with findings not compatible with DAI or demonstrating the presence of expansive intracranial lesion.

The clinical diagnosis of DAI is defined as a state of coma after TBI, lasting at least 6 hours, after exclusion on imaging of intracranial lesions with mass effect or significant ischemic brain lesions. At hospital admission, all patients underwent head CT as a standardized routine of hospital care for patients with moderate and severe TBI. In addition, all patients underwent magnetic resonance imaging of the brain to identify injuries suggestive of DAI, as well as to rule out other causes of brain injury that could justify the patient's clinical picture.

Recruitment and adherence strategies

The participants will be recruited when hospitalized at the Neurotraumatology Clinic of the Hospital das Clínicas Complex of the Medical School of the University of São Paulo (HCFMUSP). Overall admission and in-hospital records will be collected of each patient who meet the inclusion criteria. Patients will complete the minimum period of 6 months of TBI of follow-up.

In this study, REAC will be performed a single session of Neuro Postural Optimization (NPO), and 18 Neuro Psycho Physical Optimization – Brain Wave Optimization-G (NPPO-BWO-G) treatment sessions for 4 daily sessions. Each next of kin will receive written instructions with the date and time of the next sessions in order to avoid misunderstandings.

Search locations

The study will be conducted within the HCFMUSP, in São Paulo - SP, which has 2400 beds distributed among its 8 specialized institutes and 2 auxiliary hospitals (www.hc.fm.usp.br). The research locations in the various stages of the study are described in Table 6:

Table 6 - Stages of the study and the respective places where they will be carried out

Stage of the study	Location	Purpose
Patient selection	ICU - Neurotraumatology	
Electroencephalogram	ICU - Neurotraumatology	Brain waves mapping
Brain MRI	Central Institute	DAI diagnostic
REAC	ICU - Neurotraumatology	Intervention

DAI: diffuse axonal injury, ICU: intensive care unit, MRI: magnetic resonance imaging, REAC: radio-electric asymmetric conveyer.

Study design

This is a prospective, randomized, double-blind, placebo-controlled clinical trial. According to the hypotheses of the present study, the sample size calculation was made considering an alpha error of 5% and based on other studies with similar design [135-140]. We estimate that 30 patients should complete the follow-up and be included in the statistical analyses. However, lack of adherence could be a problem. Thus, we estimate losses at 20% and calculated a final sample size of 36 participants. Subjects with no history of chronic neurological disorders will also be included and separated of DAI patients but submitted to the same protocols. After meeting the eligibility criteria, the participants will follow the steps of the study as described in Table 7.

Table 7 - The study steps

Patient selection	Medical record, radiology, participation consent
Step 1 (pre-intervention)	qEEG, TCD and brain4care up to 3 days before the start of REAC sessions
Step 2 (intervention)	NPO (single session)
Step 3 (intervention)	NPPO-GW (18 sessions)
Step 4 (post-intervention)	qEEG up to 3 days after the end of REAC sessions

Follow-up discharge, 3m and 6m	mRankin, GOSE, DASS 21

qEEG: quantitative electroencephalogram, TCD: transcranial Doppler, REAC: radio-electric asymmetric conveyer, NPO: neuro-postural optimization, NPPO-GW: gamma-waves neuro psycho physical optimization.

Randomization

A participant will select patients according to DAI criteria and obtain consent for participation with the next of kin for each eligible patient. Following, qEEG examinations will be performed. Up to three days after finishing NPPO-BWO sessions, a second acquisition of qEEG will be performed. All participants will be blinded between active and sham until the study is finished.

Participants will be randomly divided in a 1:1 ratio into two groups:

1. Active
2. *Sham*

The randomization process will be done in blocks interchanged, with the size of each block equal to four. The computerized system available in www.randomization.com will be used. For the persistence of allocation concealment, all evaluations will be performed using a database containing the group with a label "A" and "B". Consequently, all analyses were made without possible presumptions as to the allocation of the group.

Masking of Groups

In order to maintain masking in the study, the REAC device has a very similar shape, size, color, weight and emits very similar sounds. The participants and their families will not know which group the patient has been included up to the conclusion of the study. The entire process of selection, interview, neuropsychological evaluation and intervention with REAC will be similar in the groups, differing only the type of device used. The neuropsychologist responsible for the application of the neuropsychological tests will be unaware of the allocation of the intervention group.

Ethics

The project will be submitted to the Research Ethics Committee of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.

All responsibles for the patients will have full knowledge of the objectives and methods of the experiment and consented through written signature of the informed consent form. They will be informed about the experimental character of the proposed intervention, expected risks and benefits, as well as their random inclusion in one of the treatment groups (active and *Sham*). They will be aware that they could request their exclusion from the research at any time, without this interfering on the care that this patient receives in the institution.

The study will be conducted according to the requirements of the institution's ethics committee and also based on the recommendations established in the Declaration of Helsinki (1964), as amended in Tokyo (1975), Venice (1983) and Hong Kong (1989).

The therapeutic application of REAC will be carried out according to the ethical principles established in the aforementioned declarations and in the ethics standards of the Ministry of Health (C.N.S. Resolution no. 196 10/10/96). The ethical foundations and guidelines for the clinical application of REAC followed the basic precepts of treatment with this technique according to the International Conference on REAC Safety Consensus, held in March 2008 in Siena, Italy.

This study will be registered in ClinicalTrials.Gov (www.clinicaltrials.gov), one of the most reliable sources of consultation on clinical studies in the world. This is the U.S. government agency responsible for centralizing and updating information about studies that have been registered on this platform and that are underway around the world.

Procedures

Quantitative Electroencephalogram

Purpose: Documenting brain waves patterns pre and post interventions.

Patients will be submitted qEEG testing before starting the REAC protocols and then after finishing the last session. For data collection, EEG examinations were performed using an international 10-20 electrode placement system. The examination will last 30 minutes, 15 minutes with eyes open and 15 minutes with eyes closed (relaxed wakefulness. The digital 19-channel Nihon Kohden® EEG 1200 version 01.71 (Nihon Kohden, Tokyo, Japan) will be used., The channels follow the 10-20 system: seven located in the frontal lobe (Fz, Fp1, Fp2, F3, F4, F7 and F8), three in the center (Cz, C3 and C4), four in the temporal lobe (T3, T4, T5 and T6), three in the parietal lobe (Pz, P3 and P4) and two in the occipital lobe (O1 and O2). For quantitative analysis, the data were converted using the Neuromap of the Neuroworkbench software, transferred to Matlab vR2002b and treated with the EEGlab v2023.0116 software. After being imported into EEGLAB, the spatial coordinates of each electrode will be inserted according to the 10-20 system. The signals were referenced using the average between the channels. The baseline was automatically removed using a 0.5Hz 117 high-pass filter. Artifacts are automatically rejected and incorrect data periods removed. Finally, the Independent Component Analysis is performed.

Processing

Using EEGlab's Darbeliai tool, the power spectral density of each channel is calculated for four bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-32 Hz), in which the absolute power will be determined. The relative power analysis will be performed using the Fast Fourier Transform FFT.

OUTCOMES

Primary:

Observe if there are significant changes in the electroencephalographic pattern, compared between the groups.

Secondary:

Observe if there are:

Significant clinical improvement determined by the mRankin and GOSE scales between the groups.

Statistical analysis

Categorical variables will be presented in absolute values and relative frequencies, while continuous variables will be described in measures of central tendency and dispersion. All analyses will be performed under the intention to treat.

The Kolmogorov-Smirnov test will be used to verify the parametric nature of the quantitative values observed in the battery of neuropsychological tests. The repeated measures related to the items neuropsychological assessment and cortical excitability will be compared through ANOVA-type analyses (*analysis of variance*) of two factors for repeated measures and the interaction test between the groups considered to test the null hypothesis[141, 142].

To compare the delta (Δ) values between the intervention groups, the Mann-Whitney test will be used. The comparison of the frequency of adverse effects according to the intervention groups will be performed using Pearson's chi-square. The Wilcoxon Rank-Sum test will be performed in the intra-group comparison regarding pre-intervention (E1) and post-early intervention (E2) performance in the neuropsychological assessment.

Statistically significant findings are those with a p-value or probability of type I error lower than 5%. The control of blinding will be done with the analysis of agreement with Cohen's kappa. The sample size is based on the TMT part B scores obtained after the intervention (E2). The analyses were performed using *Microsoft Excel* 2010 and *IBM SPSS* (*Statistical Package for Social Sciences*) v.21.0.

Funding

The present study will receive no funding. Device/software manufacturers will support the project providing their methods to be used in the study.

Chronogram

June 2024- Protocol submission.

Recruitment: One year.

Data analysis: Three months.

Publishing results: Manuscript submission to publication one month later.

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APPENDIX

Extended Glasgow Recovery Scale (GOS-e)

The Glasgow Recovery Scale (GOS) is a global scale for the functional evolution of TBI patients. The Extended GOS provides more detailed categorization into eight categories: Use of the structured interview is recommended to facilitate consistency in classification.

(8) Total recovery: this category includes individuals who resumed normal life without any alteration or complaint consequent to the trauma. Return to productivity is not a basic parameter for inclusion in this category.

(**7) Good recovery**: refers to individuals who have resumed normal life with the presence of mild physical or mental disabilities. As in the previous category, the return to productivity is not a basic parameter for inclusion in the category.

(6) Moderate disability: "independent but incapable". They can perform the basic activities of self-care and other essential activities to maintain independence without help, by themselves, with or without difficulties in the execution. The basic point of differentiation for good recovery is that individuals who are included in these categories are not able to resume all activities performed prior to the trauma.

(5) Marked moderate disability: "independent but incapable". It can perform the basic activities of self-care and the essential activities to maintain independence, with the help of devices or in an environment in which there are modifications to enable its realization.

(4) Severe-moderate disability: "conscious but dependent." Is able to maintain the basic activities of self-care, but to perform one or more, essential activities to maintain independence, needs the help of another person.

(3) Severe disability: "Conscious but dependent." You can't maintain the basic activities of self-care without the help of someone else. You need help with at least one of these activities.

(2) Persistent vegetative state (PVS): does not demonstrate evidence of significant responsiveness. He does not obey simple commands or utter any words. Differentiate from other conditions in which there is extreme reduction in responsiveness.

(1) Death: death as a result of trauma.

(a) Basic self-care activities: bathing, feeding, moving within the room/place where one is, taking care of one's excretory function, dressing, shaving, brushing teeth, combing.