Review of different modes of TES used in treatment of neurodegenerative disorders

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Abstract:

According to the Environmental Health Perspectives, over fifty-million people are effected by neurodegenerative disorders and the number of effected people is increasing rapidly. The most common neurodegenerative diseases include Parkinson's disease, Alzheimer's disease, Huntington's disease, Amyotrophic lateral sclerosis (ALS), and Motor neuron disease . These diseases reduce the ability for communication of cells in Central Nervous System(CNS) by killing or impairing the cells. Since the central nervous system is comprised of the brain and spine, overtime these diseases can limit movement, speech, memory, and other motor skills needed for day to day independent living. There is no cure for neurodegenerative diseases, but there are several treatments. One of the non-invasive treatments is called Transcranial Electrical Stimulation (TES). Transcranial Electrical Stimulation is a type of therapy that uses a low current passed to the brain to allow for restore, recover, and assist neurobiological function in targeted areas. The main three types of Transcranial Electrical Stimulation that include Transcranial Alternate Current Stimulation(tACS), Transcranial Direct Current(tDCS), and Transcranial pulsed current stimulation (tPCS) are the more commonly used types of TES . In this paper, the use of different types of TES methods in regards to treatment for neurodegenerative diseases will be discussed.

Introduction:

According to the World Health Organization(WHO), several neurodegenerative diseases are amongst the 10 most common reasons of death [6]. Neurodegenerative diseases occur when specific neurons in the Central or Peripheral nervous systems die [2] [6]. The Central nervous system is comprised of the brain and the spine. The CNS impacts the way our body processes information and translates the information to other parts of the body. The Peripheral nervous system is comprised of the Somatic nervous system(SNS) and the Autonomic nervous system(ANS). Together, the SNS and ANS control the conscious and unconscious movements one makes. Thus, when the CNS and PNS is damaged, the impact on one's motor skills, thought processes, involuntary and voluntary reactions, physical reflexes, and communication can hinder the ability to perform normal daily tasks [73]. As a result, a person may lose motor functionality, cognitive function and observe a decrease in quality of life as well as a decrease in life expectancy itself. Currently there is no cure and the most common treatments are through medications or deep brain stimulation Medications are more effective in the preliminary stages of neurodegenerative diseases and not as effective at later stages of neurodegenerative diseases, has many side effects [11].

Deep brain stimulation is a very invasive technique used in attempt to reestablish neuronal function or preserve neuronal function. This technique can possibly cause more harm as brain matter could degrade more due to the fragile state of brain tissue[16]. Current alternative treatments that are invasive are limited and are not ideal. Thus, there has been more interest in recent years to explore non-invasive techniques. One of the current experimental treatments that is used for non-invasive treatment of neurodegenerative diseases, is Transcranial Electrical Stimulation(TES)[7][11][15].

TES is the passing of a current to localized regions in the brain to reestablish and preserve communication between neurons in areas where there is neurodegeneration through the stimulation of neurons. The system of TES begins with using electrodes, a head cap, a stimulator, and cable connectors connected to the head to help modulate current flow through the cerebral cortex. A signal is generated by the simulator, passed through the wire connections to the electrodes that interface with the scalp. TES treatment can be defined by the type of current delivered[7][8][9][10][19].

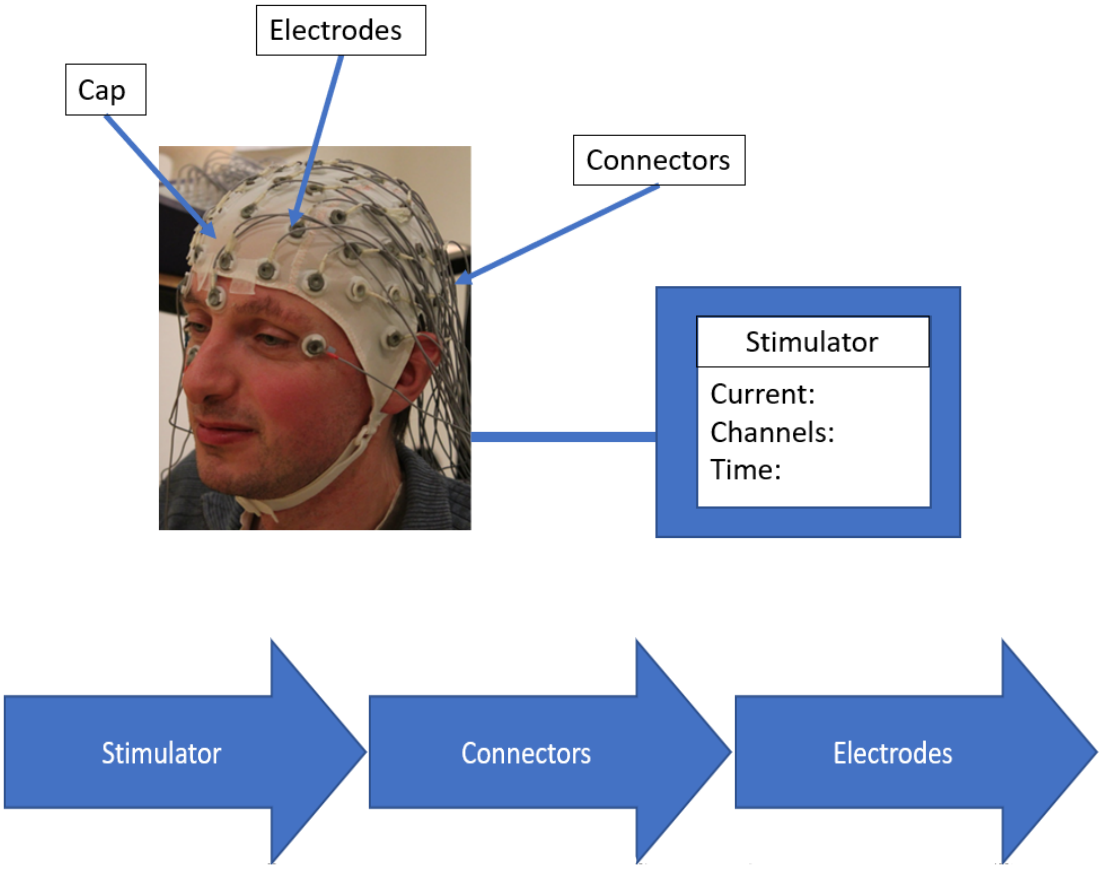

Figure 1: This is a diagram of the TES system set-up. One can control the amount and type current being passed, the channels that the stimulation is at, and the time.

There are three types of TES that are of interest and are currently being studied for treatment neurodegenerative diseases. The first is known as Transcranial Alternating Current Stimulation(tACS). The current in this treatment varies sinusoidally and in direction over time [4][7].

The second is known as Trascranial Pulse Current Stimulation (tPCS). This method sends pulses of electrical current at specific intervals at a time. The final and most well studied is the Transcranial Direct Current Stimulation (tDCS) [4]. This is a method that utilizes constant stimulation that only flows in one direction[7][10].

The objective of TES treatment is done with the aim to restore, repair, and recover or maintain current neurobiological function when a neurodegenerative disease is present [7]. In this paper we will go over the three TES methods tACS,tDCS, tPCS, their uses in current and past research, and the future of these treatments in regards to their use to treat neurodegenerative diseases [3].

Types of TES for Neurodegenerative Diseases:

In this section, we will cover three main types of Transcranial Electrical Stimulation (TES). The TES system is comprised of Electrodes, a head cap or stabilizer, a cable connector, and a stimulator are the key components that are enclosed in a TES system . The electrodes are carefully placed on the head and used to transfer the electrical current to the head. The stabilizer, which can be tape, a head cap, or another apparatus that stabilizes the electrodes securely on the head. The stimulator creates and modulates how the electrical signal is modulated through the electrodes and onto the scalp. The stimulator is the component that generates the electrical signal for stimulation.

The type of current that is passed to the scalp is controlled by the stimulator. The three types of current that can be passed through the electrodes are alternating, direct, or pulsed. The type of stimulation is the differentiator between tACS, tDCS, and tPCS as different types of current create different types of excitations [7][20]. This current is passed from the stimulator, through the cables, to the scalp, to create neuronal excitation. Neuronal excitation is important as it elicits activity from the neuron[8][9][10][20]. Any issues in neurodegenerative diseases where a neuron does not activate, or only partially activates, can hinder neuron response and communication. The excitation of the neuron can be assisted through TES to either try to recover or maintain the current functionality of the brain[11]. It also allows observations of how electrical pathways in the brain. Through this observation, a better understanding of neuronal function can be established to notice and prevent neuronal degradation at an earlier stage and build models of action potentials of the neurons. Outside of understanding neuronal pathways when TES is performed, the frequency at which TES is performed at is also important. Specific frequency ranges are labeled with a frequency band based on the state the brain is at. In **Table 1.** below, each frequency band implicates and has been connected to a frequency range. Relative to TES, the main frequency bands that are evaluated in studies for TES are the Gamma and Alpha bands [27].

Frequency band	Frequency	Brain states
Gamma (γ)	>35 Hz	Concentration
Beta (β)	12–35 Hz	Anxiety dominant, active, external attention, relaxed
Alpha (α)	8–12 Hz	Very relaxed, passive attention
Theta (θ)	4–8 Hz	Deeply relaxed, inward focused
Delta (δ)	0.5–4 Hz	Sleep

Figure 2 shows the different frequency bands and frequencies associated with different brain states [36].

This section of the paper will evaluate how each of these stimulation therapies work, and the therapy's impact on treating patients with neurodegenerative diseases. [26] [27]

tACS

Transcranial Alternating Current Stimulation occurs by stimulating the brain with current that varies sinusoidally and direction over time between electrodes. This technique has mainly been used to study to evaluate how gamma-tACS effects patients who are affected by mild cognitive deficiencies from Alzheimer's would improve one's memories. Gamma-tACS is when the frequency of the signal is set above 35 Hz. When gamma waves are observed in the brain, the brain is in a state of concentration. This is the state when someone is most alert. Thus, with stimulation of the brain at these frequencies should elicit improved concentration and attention. Also, if gamma waves seem to be diminished when performing an EEG on either the prefrontal or cerebral cortex, this is indicative of a mental or neurodegenerative disorder. If the brain was stimulated to function at these frequencies, testing for short-term, long-term, and working memory cognitive skills before and after stimulation could be evaluated to determine if gamma-tACS stimulation is effective. [21][22][24][26][30]

One study by Benussi et. al took 20 patients with mild cognitive deficiencies from Alzheimer's. The patients were assessed based on the short story, clock-drawing, Rey complex figure, and several other assessments to establish a baseline of their mental state. In the treatment, Patients were given gamma-tACS 40 Hz stimulation for 60 minutes over the medial parietal cortex, Pz area, and the precuneus of the brain. This part of the brain is known to control memory, spatial function, and navigation. To compare function before and after the subject was given the treatment, patients were tested on words through free-recall and interference trial to determine improvement in memory based cognitive skills. This was done to test the episodic memory, which focuses on amount and content of their memory. Statistical data showed a p-value of 0.001 as a P value below 0.05 shows that the hypothesis of gamma-tACS over the Pz area improving would show improvement of memory performances. Thus, they proved that the stimulation did work in patients who had mild cognitive effects from Alzheimer's [65].

Another study done for patients who had mild cognitive impairments and received tACS. In this experiment, gamma-tACS was given for one week with a current of 2 mA for 30 minutes over the dorsolateral prefrontal cortex (DLPFC). The tACS was shown to also impact the beta activity in the brain and having a positive impact on the cognition of the patient. In the same study, patients were given tDCS to compare. However, their cognitive test scores did not show any improvement with the tDCS treatment [75].

Thus, if tACS is explored more and optimized, it could be a better treatment as it is shown to be effective in improving cognitive function in patients based on the treatment studies discussed relative to tACS experiments. As gamma-tACS has been linked to improving beta activity and cognition in the brain relative to patients who have MCIs in Alzheimer's, it would be interesting to observe it being applied to patients who have MCIs, but other neurodegenerative diseases.

tDCS

During Transcranial Direct Current Stimulation(tDCS), current flows in one direction from anode to cathode [32][37]. tDCS has been studied for Alzheimer Disease, Frontotemporal dementia, Parkinson's, and when having Mild Cognitive impairment. [10][32][33][34][35][36][14].

The first study took 12 individuals and had them receive stimulation treatments for 6 months. They assessed the improvement based on testing participants on trained and untrained items. The patients were shown to have shown improvement through more activity in the parietal, frontal, and Sham even 2 months after the final tDCS treatment [25][26][29][30][33][34][35][36]. This can be shown in **Figure 3 below [36]**

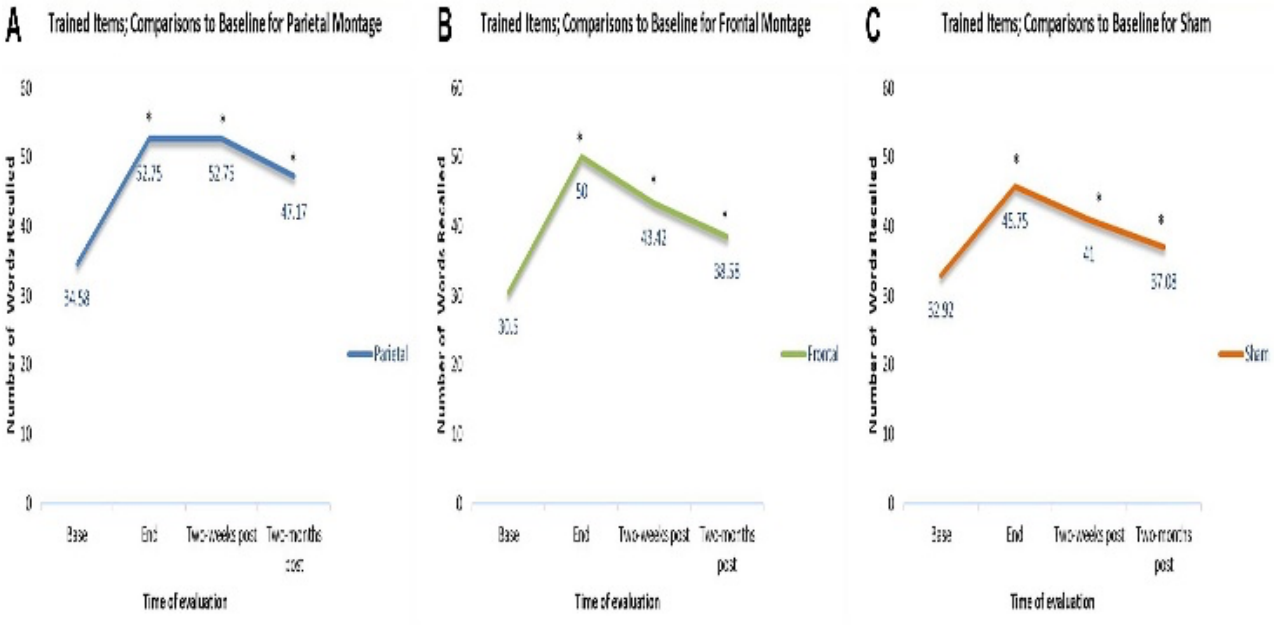

Figure 3 shows that tDCS can make minor improvements as a therapy of TES [36].

Transcranial Direct Current Stimulation was also used in another study to see if it was effective in memory recognition. 10 patients were given anodal tDCS, cathodal tDCS, and Sham individually over the temporoparietal areas. After, the patients were given several different types of memory and visual tasks to determine the effect of each tDCS. It was found that anodal tDCS had increased memory, while cathodal tDC had the opposite effect and sham had no effect. Thus, showing that stimulation of the neuron through anodal tDCS, rather than inhibition in brain stimulation of the neurons in cathodal tDCS was effective in increasing the memory of the Alzheimer's patients. This study shows that tDCS can be helpful in memory recognition of Alzheimer's patients.

Another study focused on the tDCS on gait in patients with Parkinson's disease. In this study, the motor cortex was targeted. When repeated several times for at least 10 minutes, there was improvement in function of the motor cortex without any discomfort. As time progressed, there were complaints of a burning sensation or tingling. Thus, Parkinson's can be minorly

treated with tDCS, but needs to be monitored carefully as if the current is too high or given for a long time, it can give the patient discomfort [36][14].

Even though tDCS is shown to have minor improvement, it has shown to be more effective with other types of TES treatments. Another study on Parkinson's disease with tDCS in combination with physical therapy showed to be effective. This study split a group of 20 patients and had half use tDCS and physical therapy and another had placebo tDCS and physical therapy. There was only improvement in cognitive function, motor function, and less depressive symptoms in the tDCS group with physical therapy. Thus, showing that tDCS in combination with other therapies, can be effective [76].

A newer study where patients had Neurodegenerative Anomia was conducted with 12 patients. These patients were given stimulation over the left inferior parietotemporal region (P3), the left dorsolateral prefrontal cortex (F3) for 10 sessions of 30 minutes [58]. This did show minor improvement in all patients in their memory, but no improvement in neurophysiological tasks [58]. As Neurodegenerative Anomia is found in patients with varying levels and types of neurodegenerative diseases, this treatment could be studied and expanded to patients with other neurodegenerative diseases.

Overall, tDCS has been linked to improving memory when anodal tDCS is performed, but the limited positive impact, control, and negative impact it may have is reason to explore other types treatment, combined treatment with other therapies, or the newer tPCS treatment.

tPCS

Transcranial Pulsed Current Stimulation occurs by stimulating the brain with current that is repeated pulses that are sent with a dedicated time interval over a certain amount of time [26].

Unlike tDCS and tACS being used individually, tPCS is a relatively newer method. This is due to make sure that studies are done with proper efficacy. However, there are several clinical trials that are currently open or will be open for new patients. [25][26] [27][28][29][30]

However, computational models have been designed and shown to be effective in stimulation for modulation of cortical plasticity. This model was created and exhibited anodal excitation similar to other types of TES. The potential for this method is to be more effective than tDCS and tACS. It may also be a more controlled method of delivering electrical stimulation that does not cause suppression or damage to the brain like the tDCS and tACS methods [77].

Discussion:

Transcranial Electrical stimulation has been studied for years but has only been in clinical trials for the past few decades. This section will discuss current and future research perspectives for neurodegenerative diseases.

Future of TES in different Neurodegenerative diseases

One of the deadliest neurodegenerative diseases is Alzheimer's. It deteriorates the brain and is known to be the leading cause of dementia. Thus, basic skills, cognition, and motor skills that

impact a person's independence are stripped from them. [2]While several studies utilizing tDCS has been shown to be to be helpful in patients with neurodegenerative diseases to have minor cognitive improvements.

The NIH is currently assisting in funding three trials using tDCS to understand the improvements based on prior showing of improvement from tDCS on Alzheimer's patients [63][64]. Outside of these trials, there are other fields that use tDCS for other medical issues that could be translated to treatment for patients with neurodegenerative diseases. Aphasia is not uncommon with patients that neurodegenerative diseases. While tDCS has not been used in studies to treat aphasia related to neurodegenerative diseases, it has been shown to have positive effects on brain function and recovery for stroke victims. In the future similar treatments could also be tested to see if it improves aphasia in patients with neurodegenerative diseases. Also, studies using anodal tDCS have shown to have some improvement in patients with early stages of neurodegenerative diseases. It shows that neuronal activity that excites rather than suppression in areas such as the parietal and frontal lobes as well as tDCS should be used in combination with other methods of TES or therapy to improve, sustain and delay the effect neurodegenerative diseases have on memory and basic cognitive function.

A tACS trial is also currently underway. The first trial intends to see if there is a relationship between the use of tACS and the treatment of Aphasia. While this trial is not directly intended for patients of neurodegenerative diseases, Aphasia treatments can be utilized for patients who present with aphasia due to their neurogenerative disease [79]. The second trial is to see if amyloid-β (Aβ) plaque buildup and phosphorylated tau (p-tau) burden in the brain can be relieved [66]. This trial could be a paradigm altering technique that treats Alzheimer's as many current treatments for this are only pharmacological. It would also be interesting to explore gamma tACS in the main neurodegenerative diseases as it has shown to be helpful with MCI. [66]

Huntington's disease is also a genetic neurodegenerative disease that leads to disabilities and cognitive disorders. Currently, tDCS on it's own has been inconclusive, but there are studies that show promising preliminary studies that combine tDCS with other methods of TES. [32].There are also clinical trials for tPCS in relation to Huntington's disease. The aim of this trial is to see if there is any improvement in motor function and cognitive function with Huntington's patients [71]. There are also trials surrounding similar aims with Alzheimer's and Parkinson's [70][72]. tPCS is a more controlled and possibly more effective way of delivering electrical stimulation that would improve cognitive and physical disabilities as well as replace current pharmacological treatments.

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