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Challenges and opportunities of an emerging deep brain stimulation approach in research

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Abstract. With the continuous development of neuromodulation technology, non-invasive brain stimulation methods have received increasing attention in the treatment of neuropsychiatric disorders and the study of brain function. Among them, transcranial temporal interference (TI) stimulation technology has aroused great controversy because of its ability to precisely modulate deep brain regions. This article reviews the principles and applications of TI stimulation techniques and their potential in neuromodulation, aiming to summarize and analyze the current state trends and key issues in TI research. The article first introduces the technical principle of TI stimulation, elucidating that it realizes non-invasive and precise modulation of deep brain regions by introducing two high-frequency AC currents to form a low-frequency interference envelope in the brain. Subsequently, the article describes in detail the application of TI stimulation in different deep brain regions, emphasizing the key roles of electrode location selection and electric field modeling in optimizing the electric field distribution. Meanwhile, the article compares the similarities and differences between TI stimulation and other electrical stimulation methods (e.g., tDCS and tACS), pointing out the advantages and disadvantages of TI stimulation in the precise modulation of deep brain regions. Finally, the article also discusses the current challenges of TI stimulation technology, such as the limitations of simulation technology and the difficulties in precise targeting of deep brain regions. Comprehensive analysis provides an important reference for the future direction of TI stimulation technology in neuroscience research and clinical application.

Keywords: Temporal Interference Stimulation, Deep Brain Modulation, Non-invasive Neurostimulation, Electric Field Modeling.

1. Introduction

TI (Temporal Interference) stimulation is an innovative neuromodulation technique that utilizes two high-frequency alternating currents with slightly different frequencies to generate low-frequency interference signals in the brain, thus non-invasively and precisely modulating deeper regions of the

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brain. Since nerves are not sensitive to high-frequency stimulation and are only affected by low-frequency stimulation [1], the mechanism of TI stimulation is to generate low-frequency interfering signals at the intersection of two high-frequency currents by adjusting the difference in frequency between the two currents, so that the technique can precisely regulate neuronal activity in deep brain areas [2], thus realizing effective stimulation of specific brain areas such as the hippocampus [3] or the motor cortex [4], etc. TI stimulation, along with transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS), belongs to the category of neuromodulation techniques using electrical stimulation. However, unlike tDCS and tACS, which mainly affect superficial brain tissues [5], TI stimulation can focus on deeper structures and reduce side effects in non-targeted areas [6] and, therefore, has greater potential for research and therapeutic applications. TI stimulation has shown potential for cognitive enhancement, improvement of motor skills [4], and the treatment of neuropsychiatric disorders [7], and has particular promise for a wide range of targeting deeper brain regions for the treatment of Parkinson's disease [8], Alzheimer's disease [7], and depression. Despite the potential of TI stimulation, it still faces challenges in accurately targeting deep brain regions, and the accuracy of current simulation and modeling techniques still needs to be further improved [9]. In addition, the safety issue of current intensity is a huge test, while some studies suggest that tACS may also have the ability to stimulate deep brain regions, which questions the unique advantages of TI.

2. Mechanism of TI

2.1. The Technical Principle of TI

TI Stimulation technology utilizes two high-frequency alternating currents, usually in the kilohertz range, with only subtle frequency differences. These currents are introduced into the brain through scalp electrodes, creating intersecting electric fields in the brain [10]. Since these two currents have slightly different frequencies, their intersection produces a low-frequency interference envelope (e.g., 10 Hz)(Figure 1), a frequency that falls within the response range of neurons [10]. The high-frequency current itself is too high in frequency to directly activate the neuron, while the interference signal is concentrated in the region where the electric fields intersect, allowing effective stimulation of deep brain tissue. Therefore, TI stimulation can achieve non-invasive and precise modulation of deep brain regions without significantly affecting superficial tissues, which provides an important idea for the research and intervention of deep brain structures.

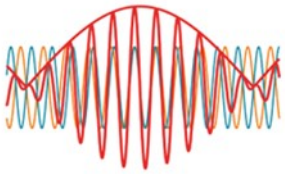


Figure 1. Low-Frequency Interference Envelope Generation[3]

2.2. The Neural Theory of TI

The neural mechanism of TI stimulation relies on the specific activation of deep neurons by low-frequency interference envelopes. When two high-frequency AC currents intersect in the brain, the resulting interference signal induces neuronal firing over a range of frequency differences, a phenomenon that occurs centrally within deep structures [2]. Since the nerves are not sensitive to high-frequency stimuli and are only affected by low-frequency stimuli, these high-frequency currents themselves do not directly activate the neurons, but the low-frequency interference envelope generated at the intersection effectively acts on the neurons [1]. The response of neurons to the interference envelope ensures precise stimulation within a specific frequency range, and by adjusting the frequency difference of the AC currents, the frequency of the interference can be precisely controlled, thereby modulating the neuronal activity pattern [2]. This mechanism allows effective activation of deep neurons

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without affecting superficial tissues, providing important support for functional research and clinical applications of deep brain structures.

3. Experiment Method

3.1. Brain Region Selection in TI

In TI stimulation studies, the selection of target brain regions is crucial, and current research focuses on several key deep brain regions. The hippocampus has been a major target for exploring cognitive enhancement and Alzheimer's disease treatment due to its central role in memory encoding and recall [3]; the prefrontal cortex (PFC) is closely related to higher cognitive functions and emotion regulation, and is particularly valuable for research in the neuromodulation of depression and anxiety disorders [11]; the striatum has been widely used in the study of movement disorders such as Parkinson's disease because of its key role in motor control and reward system [12]; in addition, The motor cortex (Motor Cortex) has been a major target for exploring motor function enhancement and rehabilitation due to its central role in controlling voluntary movements, and it is particularly valuable for research in treating movement disorders such as stroke recovery and cerebral palsy [4]. The study of these brain regions not only helps to understand the neural mechanisms of TI stimulation but also provides important theoretical support for the development of new treatments for neuropsychiatric disorders.

3.2. Electrode Selection

3.2.1 Electric Field Modeling in Reality

Electrode placement location selection in modern neurostimulation studies can be achieved by electric field techniques. This approach typically utilizes detailed human anatomical models that combine information on tissue conductivity and neuronal orientation, supplemented by diffusion tensor imaging (DTI), to predict the distribution of electric fields in the brain. This modelling approach allows precise localization of target brain regions and minimizes exposure of electric fields to non-targeted areas, resulting in accurate and effective neuromodulation [3]. The advantage of this approach is its high degree of precision and ability to personalize the design for specific stimulation of deep brain regions by non-invasive means. However, this method also suffers from the disadvantages of high computational complexity and dependence on model accuracy, while experimental validation is still required to ensure the reliability of the results. To ensure the accuracy of localization, further validation is often performed through experimental measurements, such as in human cadavers or other models, to confirm that the electric field is concentrated in the intended target region. This process provides fundamental support for neurostimulation research, enabling non-invasive deep brain area stimulation.

3.2.2 Electric Field Modeling in Calculation Software

TI stimulation simulations with simulation software have been widely used for the selection of electrode locations in neurostimulation studies. Researchers use computer simulation to model the distribution of electric fields in the brain for different stimulation methods to validate and optimize electrode configurations to ensure that the electric fields are accurately focused on specific target brain regions. This technique identifies the optimal electrode locations and parameter settings for an individual, thereby focusing the stimulation pattern precisely on the target area and maximizing the neuromodulation effect. The specific steps of the electric field simulation are as follows. First, the researchers used high-precision computational modelling techniques to simulate the distribution of electric fields in brain tissue under different parameter configurations, focusing on the characteristics of electric fields in complex deep brain regions [13]. Subsequently, the simulation technique was used to predict the neural responses that these parameter combinations might elicit in the target brain regions, thereby determining the optimal frequency and current intensity combinations. Next, the model predictions were validated using actual experiments to ensure the accuracy and reliability of the simulation results. The non-invasive nature of the simulations not only reduces the cost of the

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experiments but also increases their efficiency. However, although this technique plays a key role in optimizing non-invasive neurostimulation protocols, it still has some limitations. Currently, widely used simulation software focuses on DC electric fields (e.g., SimNIBS) [9], whereas TI stimulation involves AC electric fields. Although AC electric fields can be programmed to simulate AC electric fields, DC electric fields cannot effectively simulate the effects of stimulation in deeper regions of the brain due to the different capacitance and impedance properties of brain tissue. Although this technique has shown obvious advantages in specific applications, further research and validation are needed to accurately simulate the electric field distribution in the deep regions of the brain in order to improve its reliability and accuracy in practical applications.

4. Applications and Effects of TI

4.1. TI Stimulation in Primary Motor Cortex

In order to understand how TI stimulation impacts brain tissue and behaviours in practical applications, more and more studies are beginning to figure out the influence of TI stimulation. Due to its easier detection by instruments, most studies concentrate on the primary motor cortex. Research also compares transcranial temporal interference stimulation (tTIS) with other stimulation methods like transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation(tACS) to find out whether tTIS is effective on brain tissue and to identify the difference between tTIS and other electrical stimulation methods.

Some research has used tTIS to stimulate the primary motor cortex (M1) to investigate how TI stimulation affects human motor ability. A related study that used motor tasks as evaluation criteria had shown that tTIS could effectively enhance human motor performance [4]. This experiment compared two different tTIS frequencies: one with an envelope of 20 Hz and the other with 70 Hz. These two frequencies represented High Gamma and Beta Oscillations. The stimulation lasts 20 minutes, and they have the same current intensity. Behavioural data, including a random reaction time task (RRTT) a serial reaction time task (SRTT) and Motor Evoked Potential (MEP) amplitude to measure the differences before and after TI stimulation. In that experiment, significant differences were shown in both 20Hz frequency and 70Hz frequency in the reaction task. The significant difference was also shown on the MEP in the frequency of 20Hz. The results of significant differences in reaction tasks revealed that TI stimulation can effectively influence the primary motor to enhance human motor function.

In order to explore more deeply how TI stimulation affects the primary motor cortex and whether TI stimulation has a potential impact on deep brain regions, Zheng et al. investigated how repeated TI stimulation influences the lower limb motor control area [14]. This study used baseline assessments of lower limb motor abilities to evaluate the change after TI stimulation. The experiment used 20Hz frequency envelope. One pair of electrodes was set to 2 kHz, while the other pair was set to 2.02 kHz. Each stimulation lasted 20 minutes, and the peak value of the current was 2mA. The evaluation criteria, including countermovement jump (CMJ), squat jump (SJ), and continuous jump (CJ), all showed significant differences before and after the stimulation, which showed that repeated TI stimulation in the lower limb motor control area effectively improved healthy adult males' vertical jump performance.

There was another research aimed to examine changes in the functional connectivity of the brain by using TI stimulation in the primary motor cortex [15]. This experiment included two different types of stimulation, one TI stimulation and the other tDCS. Both types of stimulation lasted for 20 minutes. The evaluation criteria were the differences in resting-state functional connectivity before and after the experiment. Subjects had two functional imagining scans. One was before the stimulation, and the other was during the stimulation. They also had a structural imagining scan after stimulation. Comparing the sequence of stimuli of functional magnetic resonance imaging, all of them had significant differences in motor control, sensory processing, higher cognitive functions, and emotion and pain perception. However, there wasn't a significant difference between TI and tDCS. The experiment showed that TI can effectively change the blood oxygen level in the primary and secondary motor cortex, which means that TI may have the same stimulating effect as tDCS in the primary motor cortex.

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The experiments using TI stimulation to stimulate the primary motor cortex may affect people's motor ability by repeating stimulation or a period of stimulation.

4.2. TI Stimulation Modulates Brain α-power

Some research focuses on modulating brain α-power to explore the potential impact of TI stimulation.

An experiment investigated the potential influence of TI stimulation in the posterior areas [16]. This experiment used mental rotation tasks and measured Electroencephalography (EEG) values to calculate Event-Related Desynchronization (ERD) as the evaluation indicator. To ensure that both types of stimulation can stimulate the same brain area, two electrodes were used for tACS and simulation was conducted in software before the experiment to verify the placement of the four electrodes for TI stimulation. The electrical stimulation lasted for 20 minutes, and the TI stimulation envelope and tACS frequency were chosen by the Individual Alpha Frequency (IAF). The mental rotation tasks were performed before, during and after the stimulation. The experiment showed that the ERD in both TI stimulation and tACS had significant differences compared with sham stimulation, but the changes in mental rotation tasks were not obvious. This indicates that the TI stimulation might have little effect in assessing spatial cognitive abilities.

Another research focused on whether TI stimulation in the parieto-occipital brain area will change alpha oscillations [9]. This experiment used Magnetoencephalography (MEG) as the evaluating criteria. The experiment included both tACS and TI stimulation, each of them lasting for 20 minutes with the envelope of TI stimulation set to IAF frequency. Using Dynamic Imaging of Coherent Sources (DICS) analysis to calculate the alpha power in a specific region chosen by a clustering algorithm. The evaluation metrics of alpha power did show significant differences among tACS, TI stimulation and control stimulation. TI stimulation in the parieto-occipital area can't effectively change the alpha power.

Recent research on TI stimulation targeting to modulate brain α-power didn't have such an effective conclusion as stimulating the primary motor area.

4.3. TI Stimulation in Deep Brain Tissue

The further research directions of TI stimulation are to stimulate on the deep brain area. Some studies have already investigated the validity of TI stimulation inside the brain.

Two research explored the influence of TI stimulation on the striatum area. Both of the experiments stimulate the striatum area but with different envelope frequencies. One only research for the envelope frequency was 10 Hz [17], and the other experiment compared two different envelope frequencies [18]. One was 20Hz, and the other was 80Hz, using fMRI to compare the BOLD level during and, before, after the stimulation. These two studies all showed that stimulation in the striatum area could influence motor learning skills, and in the second experiment, 20hz stimulation reduced motor ability; meanwhile, 80hz stimulation can adjust blood oxygen levels, suggesting that different frequencies may have opposite effects.

In order to explore the effects of using TI stimulation to target the hippocampal area, an experiment used two different current magnitude rates in TI stimulation to compare their effects [3]. Using MRI and scores from memory tasks to evaluate the effect of TI stimulation showed that TI stimulation can affect memory, and different current magnitudes can change the stimulation position.

There was an experiment that only chose several patients who had motor disorders [19]. TI stimulation focused on the substantia nigra region, and the experiment used scores related to resting tremor to evaluate its effects. After 10- or 20-minute TI stimulation, each patient's scores were reduced, indicating that TI stimulation has the potential effects to help patients with motor disorders recover.

Experiments that stimulate the deep brain have already proved TI stimulation can effectively influence brain activity in some places. However, the effects of TI stimulation in the other deep regions still need to be explored.

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5. Advantages and Limitations of TI

5.1. Advantages

TI stimulation is a promising technology because, in principle, it can precisely stimulate deep brain regions. Compared to other stimulation methods which commonly been used these days, it can more easily and conveniently reach deep brain areas.

Unlike traditional deep brain stimulation [20], which is widely used for stimulating deep brain areas, it needs to implant electrodes into the interior of the brain. That will cause the risk of brain damage. TI stimulation can achieve similar effects by using non-invasive electrodes, which makes it a lower-risk treatment protocol and makes it easier to stimulate specific brain regions.

TI stimulation has already been proved it have a potential influence on certain brain regions and can help people to improve motor ability or memory ability and so on. In the future, this technology might be able to be used to help people with motor disability improve their quality of life. Additionally, this technology holds promise for enhancing cognitive functions to help people who want to improve their memory and so on.

5.2. Limitations

Although TI technology might become an effective method for stimulation treatment to TI stimulation in current applications, it still has lots of limitations and potential risks.

The effect of TI stimulation in deep brain regions is still being explored, as t achieving precise targeting within the brain is challenging. The common method is to use simulation to calculate an area which has not been verified in practice. Theoretically speaking, TI stimulation can arrive at the place the experiment wanted, but the actual effectiveness and accuracy of stimulation still need to be investigated. Current studies just used simulations to estimate the stimulation places, but this hasn't been thoroughly validated in clinical settings.

Moreover, some research has shown that other stimulation methods, such as tACS, also have potential effects to stimulate deep brain regions, so the difference between tACS and TI stimulation in the deep brain is unknown. Further studies need to find out the differentiation of these two stimulation methods to prove that in the deep brain tissue, TI stimulation is more effective and precise compared to tACS.

Safety is one of the most critical limitations as the stimulation using four electrodes to reach deep inside the brain still carries safety risks. The current intensity must be carefully controlled and kept within safe limits to avoid potential harm. Therefore, avoiding safety risks and improving the precision of TI stimulation are the important steps during the TI research.

6. Conclusion

As an emerging technology, the principle of TI stimulation has been proven to regulate neural response and precisely stimulate the specific tissues inside the brain. These days, instead of exploring the mechanism of action in animals, more and more studies have focused on showing how TI stimulation is applied to humans. The experiments of TI stimulation have demonstrated that it may have a positive effect not only in the primary cortex but also in the deep brain tissue. Although we can find that compared with commonly used stimulation methods, TI stimulation in the deep brain region is more convenient and precise, TI stimulation still has limitations, and its effectiveness and safety need further exploration.

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