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Review Article

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Transcranial Ultrasound Neuromodulation and Gamma Entrainment in Neurological Disorders

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Abstracts

In the last decade, there has been growing interest in the research of aberrant gamma wave restoration as a potential therapeutic intervention in various neurological disorders. Gamma is the fastest wave in the brain, which originates in the cortex and hippocampus. The slow and fast components of gamma waves in the brain are responsible for the retrieval of memory and storage of information. Aberrant gamma oscillations cause cognitive dysfunction and brain atrophy. As an emerging technique, ultrasound neuromodulation and gamma entrainment have recently been actively investigated to restore gamma oscillation in neurological disorders, mainly Alzheimer's disease (AD), in animal models and patients. The findings so far support the suitability of ultrasound for the neuromodulation of neurones in reducing or preventing the accumulation of beta-amyloid peptides in AD and improving cognitive function in some other neurological disorders. There is clear evidence that ultrasound gamma entrainment is an effective and safe intervention and could be a strong candidate as a potential therapeutic intervention in neurological disorders. Transcranial focused ultrasound, a non-invasive and safe neurostimulation technique, can directly act on bioelectrical neural activity. At present, the research into the use of transcranial ultrasound as a potential therapeutic intervention remains in its infancy. However, increasing evidence suggests that ultrasound neuromodulation and gamma entrainment have the potential to be a promising therapeutic intervention in neurological disorders and be translated into clinical application.

Keywords: Gamma entrainment; Neuromodulation; Neurological disorders; Transcranial ultrasoundand

Introduction

In the human brain there are 5 types of brain waves: alpha (8-12 Hz), beta (12-40 Hz), theta (4-8 Hz), delta (0-4 Hz) and gamma (25-100 Hz). Of the brain waves, gamma is the fastest. They are generated in the entorhinal cortex and the CA3 region of the hippocampus [1]. Gamma waves play a significant role in hippocampal functions. High frequency (30-70 Hz) gamma band oscillations in the human electroencephalogram (EEG) reflect perceptual and cognitive processes [2]. Due to the high oscillation of gamma waves, they are involved in higher cognitive functions that require significant neuronal coordination such as the selection of information to store and memory retrieval [3]. In various neurological disorders, aberrant gamma waves underly poor memory formation and cognitive function.

In recent years, restoration of gamma oscillations has been found to have the potential to alleviate symptoms of different neurological disorders in mice and improve their cognitive function [4]. A major focus of gamma entrainment studies is on Alzheimer's disease (AD), the most common form of dementia.

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This disease is characterised by the accumulation of beta-amyloid peptides (Aβ), the major component of amyloid plaques. A number of studies using non-invasive brain stimulation techniques such as light flicker stimulation at 20-80 Hz have been found to improve cognitive function and reduce the effect of AD pathology. Soluble and insoluble Aβ are the targets of gamma stimulation in models of AD in mice. Current research suggests gamma stimulation can reduce the accumulation of Aβ [5,6]. Despite these encouraging findings, there are still no clinically viable techniques and suitable approaches for the testing of gamma stimulation techniques on AD patients. A major limitation is the lack of appropriate brain stimulation tools suitable for use in human AD patients. A more recent technique using ultrasound has been shown to reversibly modulate the activity of neurons in vitro, suggesting a use of the technique for gamma entrainment that can potentially be translated into clinical use, particularly in terms of its non-invasive, non-radioactive, cost-efficient, and accessible nature. This review will focus on recent progress in ultrasound neuromodulation and particularly gamma entrainment as a potential therapeutic approach for neurological disorders.

Aberrant gamma waves in brain disorders and restoration of gamma oscillation

In various brain disorders, in particular dementia, the gamma waves become aberrant, characterised by memory impairment of the individual. Aberrant gamma waves underly cognitive decline in patients with dementia. For instance, in schizophrenic patients, a significant increase in gamma amplitudes was observed during positive symptoms such as hallucinations, while negative symptoms were found to be correlated with a decrease in gamma responses [7]. Patients with attention deficit hyperactivity disorder exhibited an increase in gamma amplitudes. An increase in gamma activity was seen in epileptic patients, while a reduction was observed in AD. In AD, the formation of Aβ increases with worsened gamma oscillation. The aberrant gamma waves are present before the accumulation of amyloid plaques, suggesting that abnormalities in gamma oscillations could be an early biomarker for AD [8,9]. Studies of mouse models consistently show reduced gamma wave activity in AD [10,11]. At present, it is not clear whether aberrant gamma oscillations are a result of AD pathology, or a cause of the cognitive symptoms associated with AD. Nevertheless, there is a consensus among researchers that the aberrant waves are an important target of treatment for reducing the symptoms of neurological disorders, and modulation of gamma activity is a promising method to meet the objective of improving cognitive function in patients with neurological disorders. For instance, restoring the levels of the interneuron-specific and parvalbumin cells' sodium channel proteins has beneficial effects on gamma brain activity and cognitive function. Reduction of slow gamma activity (25–50 Hz) in the hippocampal area CA1 can result in impaired memory function [12] and decreased gamma activity in mice models of AD can result in memory dysfunction [13].

Recent studies have shown that stimulating the brain to induce gamma oscillations through gamma entrainment can have significant beneficial effects in animal models of AD. Gamma rhythms can recruit both neuronal and glial responses to attenuate AD-associated pathology [4]. Slow gamma oscillations (30-60 Hz) correlate with the retrieval of spatial memory. Altered slow gamma oscillations have been observed in AD. To restore gamma oscillations in the hippocampus, [14] used optogenetics to activate medial septal parvalbumin neurons at different frequencies in an AD mouse model. They found that optogenetic stimulation of parvalbumin neurons at 40 Hz (but not 80 Hz) restores hippocampal slow gamma oscillations amplitude and phase-amplitude coupling. Restoration of slow gamma oscillations during retrieval rescued spatial memory. Thus, restoring gamma oscillations may be a useful therapeutic approach. Nevertheless, translating this experimental intervention to patients is limited by a lack of appropriate brain stimulation tools. Recently, [15] have found that ultrasound can reversibly modulate the activity of neurons in vitro.

Transcranial ultrasound neuromodulation

Ultrasound is a non-invasive technique and can penetrate human tissue and the skull. Ultrasound applies mechanical forces on cell membranes that can cause cavitations in the brain and soft tissues at high intensities [16]. During the last decade, transcranial ultrasound, focused or unfocused, has been used for studying neuromodulation in both animal models and patients with neurological disorders.

[17] first described human transcranial application of unfocused ultrasounds for neuromodulation in the posterior frontal cortex, in patients suffering from chronic pain. They found that transcranial unfocused ultrasound (tUS) was successful in reducing the pain felt and improving patients' moods. Later, [18] described the first human application of transcranial focused ultrasound (tFUS) technique targeting the primary somatosensory cortex of healthy volunteers. The tFUS and tUS neuromodulation techniques share the same basic mechanisms of action. However, when applied to the same target the two techniques can lead to quite different results, which is related to the intrinsic differences between them. The most important difference between the tFUS and tUS is the volume of the brain involved in the ultrasound field. The volume of the brain involved in the focused or unfocused neuromodulation and the underlying neural circuits are essential for the determination of the output of the tFUS or tUS neuromodulation. In experiments where tFUS and tUS targeted the same primary motor cortex, tFUS induced a motor evoked potential inhibition [19], whereas tUS increased motor evoked potential amplitude [20]. Besides, in tFUS the sonication delivered is pulsed, characterized by pauses

between the sonications, whereas in tUS the sonication delivered during the stimulus duration period is generally continuous. Through the guidance of MRI, ultrasound can be focused on one region in the brain. MRI-guided high-intensity transcranial ultrasound has already been used to ameliorate pathological symptoms of movement disorders like Parkinson's disease by targeting the motor cortex [21]. tFUS can stimulate an area of a few millimetres of tissue when the ultrasound is applied through the human skull, although it can cause thermal lesions in the range of 55-60 °C [22]. This technique did not cause any haemorrhages or other harmful reactions in the tissues of Parkinson's patients. tFUS has been shown to be an important potential neuromodulatory technique for improving motor behaviour in Parkinson's patients. Further research to increase the understanding of the mechanism of ultrasound neuromodulation on Parkinson's disease will be beneficial for future applications of the technique in patients [23]. Focused ultrasound technique has also been used to facilitate drug deliveries to specific regions of the brain via the blood-brain barrier [24]. This method of drug delivery could be applied for neuromodulation purposes in neurological diseases [25]. The effect of ultrasound on ion channels enables this technique to target specific regions of the brain (cortex and hippocampus) to entrain aberrant gamma waves.

There has been growing interest in tFUS neuromodulation. In order to translate ultrasound into clinical application, the main parameters of the technique must be effectively used. The carrier frequency, peak intensity, duration, pulse repetition frequency and duty cycle can all influence the effectiveness of the gamma stimulation produced by ultrasound. Recent studies show that ultrasound stimulation modifies membrane gating kinetics by acting on mechanosensitive voltage-gated ion channels [26,27]. Low intensity pulsed ultrasound improves overall cognitive function in dementia [28]. In both animal experiments and human studies, low-intensity pulsed tFUS is the most effective ultrasound technique for neuromodulation [29,30,31]. Therefore, low intensity tFUS would be suitable for neuromodulation in neurological disorders. In contrast, high intensity continuous focused ultrasound can be used for the therapeutic treatment of tremours in neurological disorders such as Parkinson's disease through irreversible thermal lesioning [32,33]. One challenge of tFUS stimulation is the high acoustic impedance of the skull, preventing ultrasound from accurately targeting specific brain regions. To resolve this issue and prevent ultrasound stimulation from being widespread, ultrasound transducers can be arranged into multi-dimensional arrays to produce a more precise focus of ultrasound energy in the brain [34,35].

Ultrasound gamma entrainment in neurological disorders

Very recently, there are increased interest in using ultrasound gamma entrainment as a potential therapeutic intervention in AD animal models and patients, although there remain only limited reports available in the literature. The research so far has shown that ultrasound gamma entrainment is an effective and safe intervention and could be a strong candidate as a potential therapeutic treatment for neurodegenerative disorders, or more broadly neurological disorders.

Ultrasound gamma entrainment has been effectively used to reduce Aβ burden in rat models of AD in both the cortex and hippocampus [36]. [37] were the first who reported using ultrasound stimulation to examine brain morphology in AD patients. Their results suggest that ultrasound stimulation improves memory and reduces brain atrophy in human AD patients. Using high frequency ultrasound stimulation, [15] have recently found sustained neuronal excitation for around 8 hours after 40 seconds of ultrasound stimulation on primary rat cortical neurones. In the investigation of the effect of transcranial ultrasound pulsed at 40 Hz on the pathology of AD, [36] and colleagues used MRI guided ultrasound technique to accurately stimulate gamma waves in the hippocampal region of the rat brain. After 14 days of the ultrasound treatment on AD mouse brain, the research group observed a reduction in insoluble Aβ in the pre- and infra-limbic cortex and the hippocampus, compared with the sham group. However, a slight increase in soluble Aβ was also observed, suggesting a potential risk in using transcranial ultrasound to treat AD. The authors noted an overall improvement in spontaneous gamma oscillations and an increase in the power of gamma waves, compared with the sham group. These results were consistent with another earlier study by [38] who found a near 50% reduction in overall Aβ burden in mouse models of AD after just 5 days of tUS treatment. A near 30% reduction of Aβ burden was seen in just the CA1 region of the hippocampus. However, towards the end of the 5 days of treatment, the percentage of activated microglia colocalised with Aβ plaque reduced to the level of the sham group, suggesting a limitation in prolonged use of ultrasound. The authors' in vivo investigation of ultrasound neuromodulation showed that the application of transcranial ultrasound at 40 Hz and of low intensity permits targeted stimulation of brain regions. The stimulation does not have a generalized effect on the brain.

Current evidence supports the suitability of ultrasound for the neuromodulation of neurones in reducing or preventing the accumulation of Aβ in AD and improving cognitive function in

some other neurological disorders. As an emerging technique, transcranial focused ultrasound is a non-invasive and safe neural stimulation. It can directly act on bioelectrical neural activity and could be used for targeted drug delivery. With a higher spatial resolution, tFUS can reach deep structures and can target different sites of the nervous system, compared to magnetic or electric non-invasive brain stimulation. Clearly, ultrasound neuromodulation and gamma entrainment have the potential to be a promising therapeutic intervention in neurological disorders. There is growing interest in translating this technique into clinical application.

Conclusions

Ultrasound is a non-invasive, non-radioactive, cost-efficient, and readily accessible technology in most hospitals. It operates at 40 Hz which falls within the oscillatory band of gamma waves. A particular advantage for ultrasound as a potential neuromodulatory tool is the high accessibility of the device which is routinely used in most hospitals and other health care settings. As a novel therapeutic concept, transcranial ultrasound techniques such as high intensity focused ultrasound are already in clinical use for non-invasive focal surgery and clinical feasibility studies. The findings of recent research have provided strong impetus for further studies of tFUS and tUS as non-invasive neuromodulatory techniques in humans. The high spatial resolution of tFUS and the possibility of stimulating cortical and deep brain regions encourage the technique for many potential applications, such as cortical and subcortical mapping, functional connectivity analysis, and neuromodulation. At present, the research into the use of transcranial ultrasound as a potential therapeutic remains in its infancy. Further studies are warranted to determine how transcranial ultrasound can be used to entrain neuronal gamma oscillations, including characterising stimulation parameters for gamma entrainment, examining how entrainment modulates neurotrophic signalling, and exploring how ultrasound gamma entrainment affects neurological pathology and cognitive impairment in neurological disorders such as AD.

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Conflict of Interest

No conflict of interest.

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