



e-ISSN: 2319-8753 | p-ISSN: 2347-6710

# IJRSET

International Journal of Innovative Research in  
**SCIENCE | ENGINEERING | TECHNOLOGY**

# INTERNATIONAL JOURNAL OF INNOVATIVE RESEARCH

IN SCIENCE | ENGINEERING | TECHNOLOGY

Volume 10, Special Issue 3, December 2021

**ISSN** INTERNATIONAL  
STANDARD  
SERIAL  
NUMBER  
INDIA

**Impact Factor: 7.569**

9940 572 462

6381 907 438

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# Optogenetic Stimulation of Gamma Wave to Cure Alzheimer's Disease

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**ABSTRACT:** Slow gamma oscillations (30–60Hz) correlate with retrieval of spatial memory. Altered slow gamma oscillations have been observed in Alzheimer's disease. Spatial memory loss as well as reduced slow gamma amplitude and phase-amplitude coupling to theta oscillations phase. To restore gamma oscillations in the hippocampus, we used optogenetics to activate medial septal parvalbumin neurons at different frequencies. We show that optogenetic stimulation of parvalbumin neurons at 40Hz (but not 80Hz) restores hippocampal slow gamma oscillations amplitude, and phase-amplitude. Restoration of slow gamma oscillations during retrieval rescued spatial memory in mice despite significant plaque de- position. These results support the role of slow gamma oscillations in memory and suggest that optogenetic stimulation of medial septal parvalbumin neurons at 40Hz could provide a novel strategy to cure Alzheimer's disease.

**KEYWORDS:** optogenetic stimulation, Alzheimer's disease, Wireless Optogenetic Nanonetwork

## I. INTRODUCTION

Brain waves have oscillating electromagnetic fields produced by neurons in the cerebral cortex firing electrical impulses as they process information. Much as people clapping their hands in synchrony generate thunderous rhythmic applause, the combined activity of thousands of neurons firing together produces brain waves. These waves come in various forms and in many different frequencies. Alpha waves, for example, oscillate at frequencies of 8 to 12 hertz. They surge when we close our eyes and shut out external stimulation that energizes higher frequency brain wave activity. Rapidly oscillating gamma waves, which reverberate at frequencies of 30 to 120 hertz, are of particular interest in Alzheimer's research, because their period of oscillation is well matched to the hundredth-of-a-second time frame of synaptic signaling in neural circuits. Brain waves are important in information processing because they can influence neuronal firing. Neurons fire an electrical impulse when the voltage difference between the inside and outside of the neuron reaches a certain trigger point. The peaks and troughs of voltage oscillations in brain waves nudge the neuron closer to the trigger point or farther away from it, thereby boosting or inhibiting its tendency to fire. The rhythmic voltage surging also groups neurons together, making them fire in synchrony as they "ride" on different frequencies of brain waves.

If you have Alzheimer's, your brain doesn't produce strong brain waves in that particular frequency. boosting the power of these weakened gamma waves would be helpful in treating this severe and irreversible dementia.

To increase gamma wave power, optogenetic stimulation, a novel technique that allows researchers to control how and when individual neurons fire by shining lasers directly into them, via fiber-optic cables implanted in the brain. stimulated neurons in the visual cortex of a patient with Alzheimer's, making them fire impulses at 40 hertz. Stimulation of neurons currently is possible through implantable electrodes but limited to a population of neurons. Secondly, a major hurdle lies in developing miniature devices that can last for a lifetime in the patient's brain. In parallel, Optogenetics has emerged proposing the stimulation of neurons using light by means of optical fibers inserted through the skull. Many challenges are thus introduced in terms of suitability to patient's lifestyle and biocompatibility. We have recently proposed the concept of wireless optogenetic nano net working devices (WiOptND), addressing these long-term deployment problems, and at the same time targeting single neuron stimulation

In the field of neuroscience, optogenetics is gaining popularity as an alternative method for neural stimulation. In optogenetics, the neurons are engineered so that they are sensitive to light at specific wavelengths in order to have either excitatory or inhibitory effects .Optogenetics provides an advantage over the use of electrodes due to its higher

precision, less stress to the cells, and lower noises. These noises may disturb the neural activity recording process since the recorded signal does not merely come from the target neurons, but also from the stimulation electrodes. However, further improvements are still required to the current solutions. They include the degree of intrusion through the skull and alternative power supply compared to the use of batteries. These shortcomings limit the degree of practicality for the patients in their daily life. On neural networks, neurons communicate with each other through the process of action potentials and synapses. The neuron cell body (soma) connects to other cells using the dendrites and axons, which receives and transmits signals with neighboring cells. The problem arises when this physical transportation network is impaired due to various problems such as aging, disease, or the death of cells, among others. Even a single neuron failure may result in communication impairments along the cortical circuit. In this case, the implementation of a single neuron level stimulation implant can restore the neural circuit communication between the layers.

## II. MOTIVATION

Alzheimer's disease, which is characterized by progressive loss of memory and cognitive function, affects 15 million people worldwide. The incidence increases steadily from 1 percent per year at the age of 65 years to nearly 8 percent per year after the age of 85 years. Because survival for a decade is common, the prevalence increases from 3 percent at the age of 65 years to 47 percent after the age of 85 years.<sup>2</sup> Mutations in the gene for the amyloid precursor protein and the genes for presenilin 1 and 2 cause rare dominantly inherited forms of the disease occurring before the age of 60 years, and the e4 variant of apolipoprotein E is associated with the sporadic form and some familial forms with onset after the age of 60 years. Definite cases are those confirmed by the postmortem findings of dense plaques containing the amyloid peptide and elements of degenerating neurons, neurofibrillary tangles composed of abnormally phosphorylated tau protein, and loss of neurons and synapses in the brain. Degeneration in the basal forebrain profoundly reduces the content of acetylcholine and the activities of choline acetyltransferase. Although other neurotransmitters can be involved, the loss of acetylcholine occurs early and correlates with the impairment.

## III. LITERATURE REVIEW

Existing treatments for Alzheimer's disease (AD) have questionable efficacy with a need for research into new and more effective therapies to both treat and possibly prevent the condition. This review examines a novel therapeutic modality that shows promise for treating AD based on modulating neuronal activity in the gamma frequency band through external brain stimulation. The gamma frequency band is roughly defined as being between 30 Hz-100 Hz, with the 40 Hz point being of particular significance<sup>[1]</sup>. Ultrasonic neuromodulation is a rapidly growing field, in which low-intensity ultrasound (US) is delivered to nervous system tissue, resulting in transient modulation of neural activity. This review summarizes the findings in the central and peripheral nervous systems from mechanistic studies in cell culture to cognitive behavioural studies in humans<sup>[2]</sup>. In recent years, numerous research efforts have been dedicated towards developing efficient implantable devices for Deep Brain Stimulation (DBS). However, there are limitations and challenges with the current technologies. Firstly, the stimulation of neurons currently is only possible through implantable electrodes which target a population of neurons. This results in challenges in the event that stimulation at the single neuron level is required. Secondly, a major hurdle still lies in developing miniature devices that can last for a lifetime in the patient's brain. Recently, the concept of neural dust has been introduced as a way to achieve single neuron monitoring and potentially actuation. In parallel to this, the field of optogenetics has emerged where the aim is to stimulate neurons using light, usually by means of optical fibers inserted through the skull. Obviously, this introduces many challenges in terms of user friendliness and biocompatibility. We address this shortcoming by proposing the wireless optogenetic neural dust (wi-opt neural dust). The wi-opt neural dust is equipped with a miniature LED that is able to stimulate the genetically engineered neurons, and at the same time harvest energy from ultrasonic vibrations. The simulation results presented in the paper investigate the behaviour of the light propagation in the brain tissue, as well as the performance of designed circuitry for the energy harvesting process<sup>[3]</sup>. In the hippocampal regions of DG, CA3, and CA1, and jointly DG-CA3/CA1 and CA3-CA1, gamma induction resulted in a statistically significant improvement in terms of increased numbers of spikes, spikes per burst, and burst duration as compared with the model simulating Alzheimer's disease (AD). The positive maximal Lyapunov exponent was negative in both the control model and the one with gamma induction as opposed to the pathological model where it was positive within the DG-CA3-CA1 region<sup>[4]</sup>.



#### IV. PROPOSED SYSTEM

In recent years optogenetics has rapidly become an essential technique in neuroscience. Its temporal and spatial specificity, combined with efficacy in manipulating neuronal activity, are especially useful in studying the behaviour of awake behaving animals. Conventional optogenetics, however, requires the use of lasers and optic fibers, which can place considerable restrictions on behaviour. Here we combined a wirelessly controlled interface and small implantable light-emitting diode (LED) that allows flexible and precise placement of light source to illuminate any brain area. We tested this wireless LED system in vivo, in transgenic mice expressing channelrhodopsin-2 in striatonigral neurons expressing D1-like dopamine receptors. In all mice tested, we were able to elicit movements reliably. The frequency of twitches induced by high power stimulation is proportional to the frequency of stimulation. At lower power, contraversive turning was observed. Moreover, the implanted LED remains effective over 50 days after surgery, demonstrating the long-term stability of the light source. Our results show that the wireless LED system can be used to manipulate neural activity chronically in behaving mice without impeding natural movements.

Recent advances in optogenetics have provided a method to selectively manipulate neural activity. This method allows experimenters to excite or inhibit molecularly defined neuronal populations using genetically encoded light gated ion channels or pumps. To study the behaviour of awake behaving animals, the conventional method is to connect the chronic implant in the head to an external light source commonly a diode laser via fiber optic cables. Being physically connected to a laser, however, constrains natural movements.

It greatly restricts the distance that animals can move from the light source, introducing torque to the cranial implant that can perturb free movement. It also limits the number of animals that can interact with one another during stimulation: e.g., two behaving rodents will become tangled if they are both connected to lasers with optic cables.

As neuroscience rapidly moves toward the goal of studying brain function under natural and ethologically realistic conditions, the above limitations present a major technical challenge. There is a strong demand for effective optical stimulation that does not rely on optic fibers. This requires both a local light source as well as a compact and lightweight power source. We developed a convenient system for wireless optogenetic stimulation using compact LEDs, with a number of advantages over recently developed systems. This system can also be easily expanded to permit simultaneous wireless recording and stimulation.

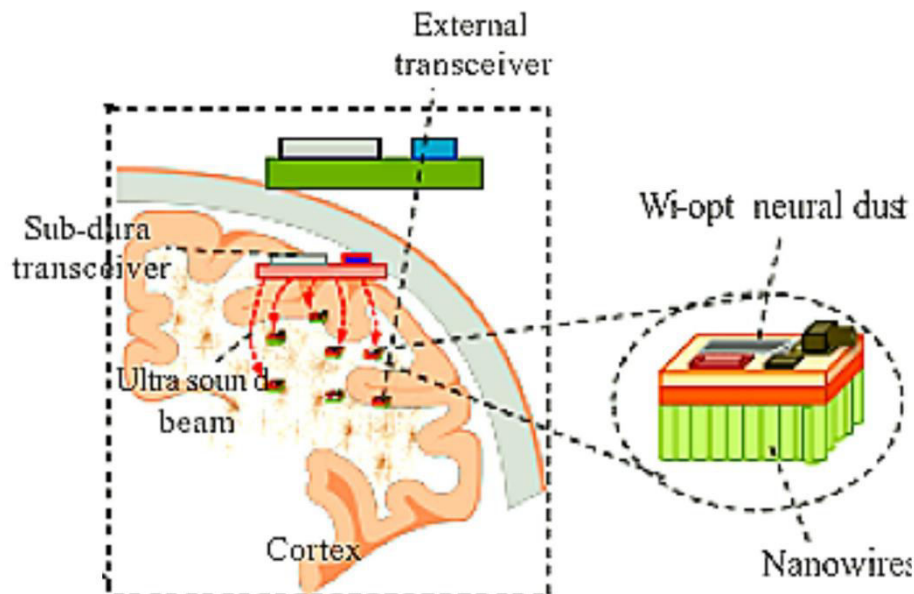


Figure 4.1: Illustration of the overall architecture of the Wireless Optogenetic Nanonetwork.

The WiOptND are in the various layers of the cortex, and is charged by the ultrasound signals emitted from the sub dura transceiver, which in turn is communicated from the external transceiver.

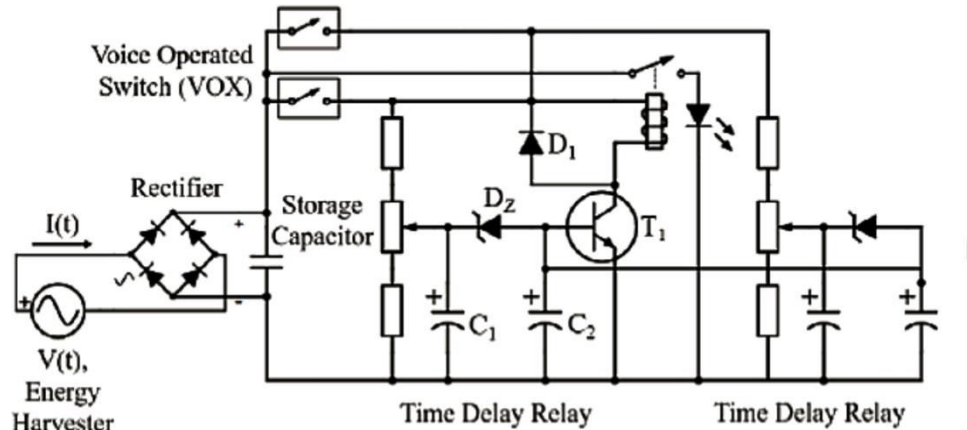


Figure 5.1: WiOptND circuit diagram with integrated time-delay relay.

## APPLICATIONS

The quantitative results of the study are encouraging and suggest that 40 Hz stimulation over time can lead to increased cognition. Further studies are needed to confirm this and to assess which if any of the groups (mild, moderate, severe) benefit the most from this treatment. Participants were more confused in the DVD sessions as to why they were d this could have added to their levels of anxiety/agitation. The DVD did not prove to be stimulating, but rather induced a more quiet and sleepy mood. Interestingly, the DVDs are designed to calm a person with AD, and while they did facilitate sleep and quieter states of being, they did not have an effect on reducing anxiety/agitation. 40 Hz treatment appeared to have the largest impact on persons having mild to moderate AD.

The premise of this study and the possible explanation for the findings are the effect of RSS on the power of the oscillatory coherence in gamma at 40 Hz. The scientific foundation for an oscillatory theory of AD is not well developed but the most applicable theory, thalamocortical dysrhythmia, suggests that AD is characterized by an increase in power in lower delta and theta frequencies and a decrease in power in the alpha, beta, and gamma frequencies. Research points to a relationship between coherent oscillation activity in the gamma band and cognitive functions that is organized by the thalamocorticothalamic system. Specifically, research shows that with AD there is a decrease in the power levels around 40 Hz although there also seems to be a general decrease in this level with cognitive decline and aging .

Some research argues that there is an increase in gamma band power with AD. However, this research did not filter 40 Hz but looked at the full 30–100 Hz band. Also, it looked primarily at evoked response levels rather than at spontaneous activity. In general there is support for the potential that altered theta and gamma rhythms may be a functional early biomarker for AD. Brain stimulation for AD is at the beginning exploratory stage. Deep brain stimulation is being used with the basic high frequency 130 Hz. Studies in repetitive transcranial magnetic stimulation are using 20 Hz . In terms of low frequency sound and vibrotactile stimulation, there is evidence that gamma-band oscillation can be modulated with sensory stimulation . It has also been shown that stimulating a particular frequency results in multiples and partials of that frequency also being stimulated . Stimulation of 40 Hz can be expected to produce a response at 80 Hz and 120 Hz as well as at 20 Hz. Since 40 Hz.

## ADVANTAGES

Optogenetic therapeutical treatment offers many advantages compared to pharmacological and electrical treatments, which are commonly used to treat neurological disorders. In contrast to the unselective treatment on the activity of different cell types of pharmacological and electrical approaches, optogenetics allows the targeted regulation of a specific cell population or circuit. Optogenetics displays a fast response compared to pharmacological treatments. Optical stimulation can affect neuronal activity in a millisecond timescale temporal resolution, whereas drug treatments take several minutes before inducing an effect.

Optogenetics could also be safer. While deep brain stimulation requires a risky surgical operation to implant the electrodes in the brain and neurostimulators under the skin to trigger current pulses, the optogenetic treatment requires

gene therapy and the implementation of a light device (externally wearable as described for retinitis pigmentosa) but no oscillating electric field that will be pulsed through the body.

## V. ISSUES AND CHALLENGES

As with any invasive neuromodulation technology, the most urgent issue requiring consideration is safety. Almost all available treatments for neurological or psychiatric disorders entail some risks and side effects. For an intervention to be authorized for general use, the benefits must outweigh the potential risks. However, predicting the adverse consequences of various technologies is not always easy. A tragic example of a poorly predicted outcome of medical intervention is the case of Jesse Gelsinger, an 18-year-old who died due to multi-organ system failure in the aftermath of clinical trial testing for gene therapy, which, similar to optogenetics, involved the injection of corrective genes inserted into a weakened flu virus that was supposed to evoke only transient, flu-like symptoms. However, since this incident, gene therapy based interventions have been significantly improved and apparently no similar accidents have occurred. Despite some inherent risks associated with the infusion of viruses into the human brain, recent studies have demonstrated that the types of vectors used for optogenetic stimulation (i.e., lentiviruses (LVs) or adeno-associated viruses (AAVs)) are generally safe and well tolerated by patients.

Another challenge that optogenetics will have to face concerns the duration and consequences of the expression of light-sensitive proteins in the human brain. For any gene therapy based intervention to be successful, the expression of key proteins must persist in neural tissue either for the patient's expected lifespan, or at least long enough to deliver the expected treatment outcome. Although we know that induced expression of non-native proteins remains high in a primate brain for as long as 15 years following the injection of an AAV, still more research is needed to determine its exact duration. In addition, there is a need to test the consequences of long-term expression of exogenous proteins in the mammalian brain, which have been studied very little to date.

Another issue that may pose a challenge is the need for rescaling. Present optogenetic studies use mouse brains as a proxy for studying the functioning of the human brain. However, a mouse brain is several times smaller than a human brain, and optogenetic tools will arguably need some adjustments. In particular, vector delivery systems, aimed at producing protein expression in areas large enough to induce observable effects in the human brain, will presumably need to be developed. Furthermore, to stimulate a targeted brain region efficiently, an implantable optogenetic device requires a sufficient light spread and intensity range and must be able to generate diverse illumination patterns (e.g., continuous illumination or short light pulses of changeable frequencies) and wavelengths suitable for activation of the targeted photosensory proteins of interest. Until recently, neuronal illumination and recording of a neuron's evoked electrical signal required the insertion of two relatively large devices into the brain: fiber optic probes and so-called "optrodes" (fiber optics combined with electrodes). This procedure was highly invasive and characterized by increased tissue damage and declining optical output over time. In order to overcome these limitations, several labs have worked on the development of alternative methods of optogenetic stimulation. Not surprisingly, given the rapid advancement of optogenetic related technology, they have already proposed several ultra-miniaturized (20 mg, 10 mm<sup>3</sup>), fully implantable, battery-free, wireless illumination devices suitable for brain and spinal cord.

## VI. FUTURE SCOPE

Optogenetics has been safely and effectively applied to awake non-human primate rhesus macaques. Clinical trials in phases I and II using adeno-associated virus injection have successfully demonstrated its safety in patients. Another remarkable translational effort was the first patient dosed with optogenetics for retinitis pigmentosa in a clinical trial conducted by RetroSense Therapeutics, which was reported in 2016. Similar to retinitis pigmentosa, there are many other diseases which do not have effective treatments or have treatments that are intolerable. Optogenetics has not only helped us discover the pathophysiology of many neurological diseases, but has also opened the door to use this novel strategy for future challenges too.

## VII. CONCLUSION

The increased attention towards brain stimulation has attracted researchers to search for innovative solutions that can enable long-term deployment as well as design of miniaturized devices that can self-generate power. At the same time, the emergence of optogenetics has provided a new approach for precise stimulation at the single neuron level. Here pro-



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pose the WiOptND that is constructed from nanoscale components and can be embedded into the cortex of the brain to stimulate neurons using light. A thorough description of the circuitry, as well as the components, are presented, including mechanisms of generating power through ultrasonic wave vibrations. The paper presented simulation results on the behaviour of optical light transmission and its effect on the brain tissue, as well as the energy performance of the device based on variations of ultrasonic frequencies and circuitry devices (e.g. capacitors and piezoelectric nanowire area). A number of charging protocols have also been evaluated ranging from the simple Charge and Fire to the Predictive Sliding Detection Window, and its variant the Markov-Chain Time Delay Patterns. The Predictive Sliding Detection Window utilizes predicted patterns of ultrasound frequencies to match to the neural spike patterns. The difference between the protocols is to improve energy efficiency by lowering the number of ultrasound emissions from the subdura transceiver while ensuring that neural spike misfiring ratio is low. In particular, the Markov-Chain Time Delay Patterns extension protocol resulted in the best performance. However, when the efficiency ratio is considered, the protocol highly depends on the neural spike rate and number of applied predicted patterns. The results from our simulation study have demonstrated the feasibility of using the WiOptND nanonetworks for long term deployments in the brain in order to stimulate neurons and provide new approach for treating alzheimer's disease.

**REFERENCES**

1. L. E. Hebert, J. Weuve, P. A. Scherr, and D. A. Evans. Alzheimer disease in the United States (2010–2050) estimated using the 2010 census. *Neurology*, 80(19):1778–1783,2013.
2. E. Dorsey, R. Constantinescu, J. Thompson, K. Biglan, R. Holloway, K. Kieburtz,
3. F. Marshall, B. Ravina, G. Schifitto, A. Siderowf, et al. Projected number of people with parkinson disease in the most populous nations, 2005 through 2030. *Neurology*, 68(5):384–386, 2007.
4. D. M. Huse, K. Schulman, L. Orsini, J. Castelli-Haley, S. Kennedy, and G. Lenhart. Burden of illness in parkinson's disease. *Movement Disorders*, 20(11):1449–1454, 2005. [4] A. Gustavsson, M. Svensson, F. Jacobi, C. Allgulander, J. Alonso, E. Beghi,
5. R. Dodel, M. Ekman, C. Faravelli, L. Fratiglioni, et al. Cost of disorders of the brain in Europe 2010. *European Neuropsychopharmacology*, 21(10):718–779, 2011.
6. R. Strother, J. Mrva, and G. Thrope. Implantable pulse generator for providing functional and/or therapeutic stimulation of muscles and/or nerves and/or central nervous system tissue, Oct. 12 2010. US Patent7,813,809.
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