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# Noninvasive Deep Brain Stimulation

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A deep brain stimulation (DBS) system delivers waves as electrical impulses to key brain structures, to modulate neural activity, to restore the balance of circuits that are disrupted, overcoming abnormal activity in brain deep regions. In 2002, invasive DBS (I-DBS) for the treatment of Parkinson's disease (PD) was approved by the US Food and Drug Administration (FDA).[1] In clinical study, implementing the I-DBS electrodes in the brain is an only way to deliver constant electrical stimulation to areas within the brain. DBS is used for treatment of patients with PD, dystonia, tremor, Tourette syndrome, intractable pain, epilepsy, major depression, bipolar disorder, obsessive–compulsive disorder, anorexia nervosa, Alzheimer disease. Studies verify that application of DBS therapy is expanding rapidly as the worldwide use of DBS is more than 160 000 cases.[2] DBS is a generally safe procedure but, it is very expensive, potentially a dangerous surgical procedure and like any surgical procedure comes with some risks as complications.[3] In addition, despite the success of DBS in patients' treatment some key questions remained unanswered such as which areas of the brain should be stimulated for each patient.[2] This letter aims to highlight the merits of new DBS technology to create patient-specific solutions for treatment of various neurological and psychiatric conditions, and this generated great interest in the development of new technologies and new education. In addition, neurosurgeons, neuroscientist, spine surgeons, and researchers are appearing on the letter.

Up to now, three noninvasive DBS technologies have been used in animal studies[4,5]: (1) Grossman et alintroduced a noninvasive DBS method that called temporal interference (TI) stimulation. In TI, two low-frequency waves with a small difference (e.g., 2.0 kHz and 2.01 kHz), are inserted transcranially, and the brain rectifies the differential signal of very low frequency and gets stimulated (Figure 1).[4] They represented activation of deep neurons in the mice hippocampus while the cells placed in the path between stimuli and target was not stimulated.[4] (2) Zhou et al reported noninvasive ultrasound DBS (U-DBS) for the treatment of PD in a mice model. They showed that the U-DBS stimulation of the subthalamic nucleus (STN) or the globus pallidus (GP) could improve the motor behavior of a PD mice model.[5] In this study the nucleus stimulation was performed with spatial resolution up to millimeter, the safety of ultrasound stimulation was distinguished and no hemorrhage or tissue damage was detected.[5] In addition, a wearable head-mounted ultrasound array transducer was designed to precisely focus on the deep nucleus of mouse brain (Figure 2).[5] (3) Additionally, Chen et al have developed an approach to non-invasively manipulate optogenetically the modified nerve cells in deep structures inside the brain in live mouse models. In this work a near-infrared (NIR) light was placed above the skull. It is known that NIR rays can simply pass through the brain tissue with a negligible scattering and reach the deep within the brain. Optogenetical activation of the modified neurons was performed by embedding the up-conversion nano-particles (UCNPs; blue) in the brain to absorb the NIR light and emit a visible light of specific wave length (Figure 3).[6]

Let's look closer and find out why noninvasive DBS technology is needed. It is believed that, in noninvasive DBS technologies, multiple deep brain targets can be stimulated simultaneously,[4,6] to optimize the treatment of patients with CNS disorders. Nevertheless, recent (failed) clinical trials of I-DBS in depression, and modest treatment results in dementia and epilepsy, encourage their further development.[1] Although, understanding of how I-DBS works has progressed over the past two decades, however there is still much to be learned. For the time being, noninvasive DBS technology is needed for a variety of reasons, such as to assess the best DBS target, to identify brain circuits involved in CNS disorders, growing understanding of the mechanisms involved, better performance evaluation DBS systems, find new therapeutic targets, increasing accuracy in treatment, optimal patient selection and the appropriate target location according to the patient age and cognitive status,

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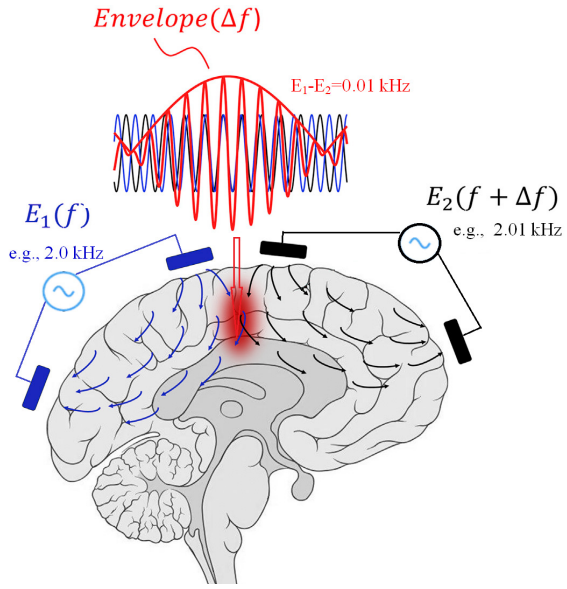


**Figure 1.** Noninvasive DBS method that called temporal interference (TI) stimulation. Figure reproduced with the permission of Grossman et al.[4]

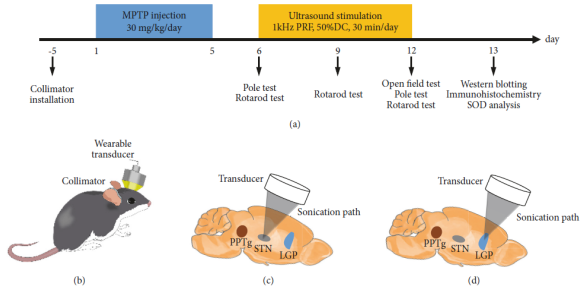


**Figure 2**. Noninvasive Ultrasound Deep Brain Stimulation. (a) Timeline of the experiment; 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine was administrated from day 1 to 5 and U-DBS stimulation was delivered from day 6 to 12. Rotarod test was assessed on day 6, 9, and 12. Pole test was done on day 6 and 12, and the open field test was conducted on day 12. (b)The wearable ultrasound for deep brain stimulation of the STN (c) or GP (d). Figure reprinted with the permission of Zhou et al.[5]

and reduce the research costs. Now, the crucial question is: which of the three noninvasive DBS technologies is a selected candidate for achieving the listed goals and it works well in the clinical practice? as it will answer in the future. Overall, we suppose that further practicing the noninvasive DBS in treatment of neurological and psychiatric disorders could provide new treatment options and expand current knowledge.

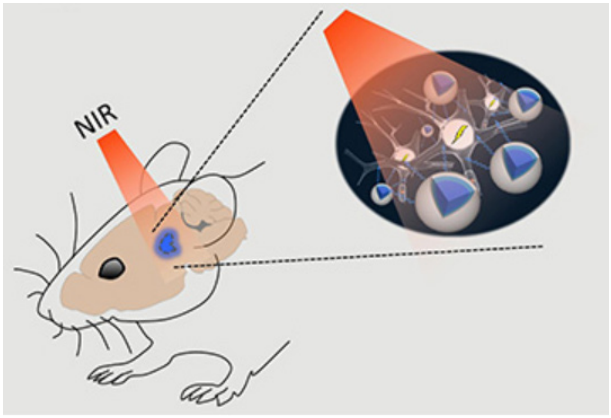


**Figure 3.** Noninvasive deep brain stimulation with Optogenetics. Figure reproduced with the permission of Chen et al.[6]

### Conflict of Interest

The authors declare that they have no conflict of interests.

### Ethical Statement

Not applicable.

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