# Theoretical and Experimental Studies of Transcranial Alternating Current Stimulation (tACS) Beating Signal in Phantoms and Mice Brains

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## Abstract

Brain simulation techniques have demonstrated undisputable therapeutic effects on neural diseases. Invasive stimulation techniques like deep brain stimulation (DBS) and noninvasive techniques like transcranial magnetic stimulation (TMS) have been approved by FDA as treatments for many drug resist neural disorders and diseases. Developing noninvasive, deep, and targeted brain stimulation techniques is currently one of the important tasks in brain researches. Transcranial direct current stimulation (tDCS) and transcranial alternative current stimulation (tACS) techniques have the advantages of low cost and portability. However, neither of them can produce targeted stimulation due to lacking of electrical field focusing mechanism. Recently, Grossman et al. reported using the down beating signals of two tACS signals to accomplish focused stimulation. By sending two sine waves running at slightly different high frequencies (~2kHz), they demonstrated that they can modulate a “localized” neuron group at the difference frequency of the two sine waves and at the same time avoid excitation of neurons at other locations. As a result, equivalent focusing effect was accomplished by such beating mechanism. In this work, we show neither theoretically nor experimentally the beating mechanism can produce “focusing effect” and the beating signal spread globally across the full brain. The localized modulation effect likely happened right at the electrode contact sites when the electrode contact area is small and the current is concentrated. We conclude that to accomplish noninvasive and focused stimulation at current stage the only available tool is the focused TMS system we recently demonstrated.

## Introduction and Background

In recent years, brain simulation techniques have demonstrated undisputable therapeutic effects on neural disorder or diseases. Deep brain stimulation (DBS) have been approved by FDA as treatment for Parkinson's disease (PD), essential tremor, dystonia, and obsessive-compulsive disorder (OCD) [1]; and transcranial magnetic stimulation (TMS) as treatment for drug resist major depression and migraine [2]. These led to widespread excitement about the possibility of developing new brain stimulation techniques that are noninvasive, portable and light weight. Transcranial direct current stimulation (tDCS) and transcranial alternative current stimulation (tACS) techniques have been utilized as such portable, do-it-yourself (DYI), people's technologies to treat many kinds of neural problems or enhance brain functions from attention to learning [3][4]. However, neither tDCS nor tACS were spatially specific for targeted stimulation due to lacking of electrical field focusing mechanism. Recently, Grossman et.al. proposed using the down beating signals of two tACS signals to accomplish focused stimulation [5]. As shown in Figure 1, by sending two sine waves running at slightly different high frequencies (~2kHz) he demonstrated that he can modulated "localized" neuron groups at the exact difference frequency and at the same time avoid excitation of other neurons along the two high-frequency sinewave paths. In his theoretical presentation the beating seemed to be only happened in the middle of the two high frequency signal source locations. As a result, equivalent focusing effect was accomplished by such beating mechanism. In this work, we show both theoretically and experimentally the beating mechanism cannot produce "focusing effect" and the beating signal spread globally across the full brain. The localized modulation effect likely happened right at the electrode contact sites when the electrode contact area is small and the current is concentrated. This was also further verified by direct AC modulation of mice motor cortex at low frequencies (<10 Hz) and observed neural modulation (limb movement) at the exact modulation frequency.

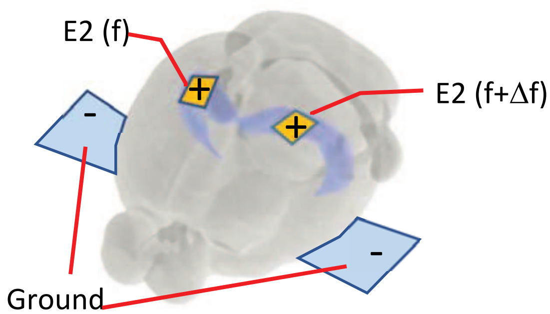
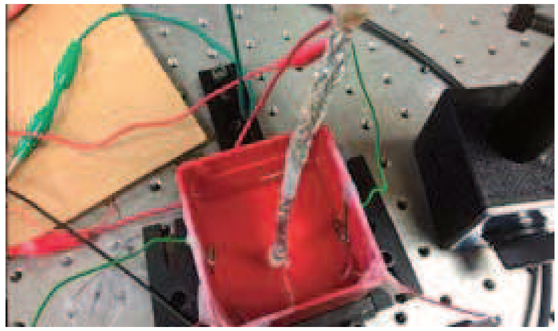


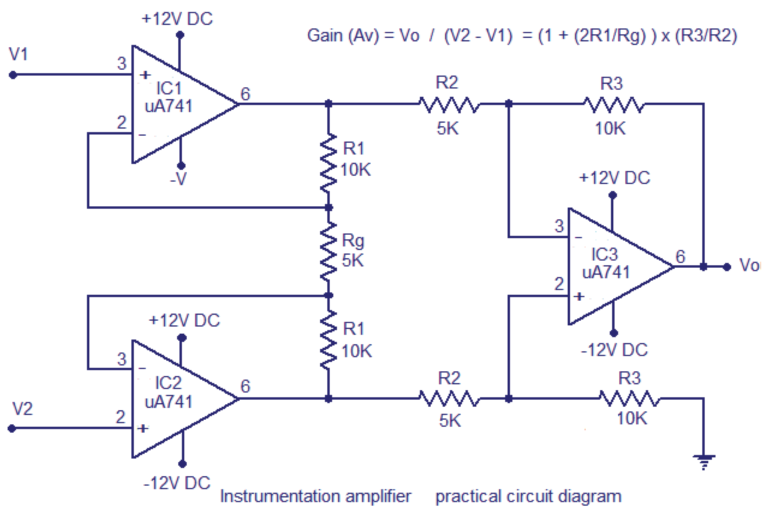

Figure 1 Schematics of electrode arrangement for transcranial alternating current stimulation using beating frequency.

## Method

In our phantom experiment, a brain phantom was built up with saline and electrodes submerged in the conductive liquid. In Figure 2(a), two electric field components Ex and Ey resulting from the two alternating currents simultaneously applied to a square shaped container filled with saline, a simplified simulation of brain. (XY plane was the horizontal plane which was in parallel with the liquid surface.) We made a dipole probe [6] which was used to map the local current density distributions. I1 and I2 are the currents from the two AC sources, and are respectively oscillating at the frequencies of f1 (1 kHz, higher than the range of frequencies of normal neural operation) and f2 (1.01 kHz, for example), producing a difference frequency of 10Hz so that neurons were driven only at the this beating frequency. High current gain amplifiers were used at each current path to supply stable currents to the phantom. The circuit diagram in Figure 2(b) indicates an amplifier of basic op amps. The gain is adjustable by changing the resistance values of components R1, R2, R3 and Rg.



(a)




(b)

Figure 2 (a). Brain phantom experimental setup, the container dimension was 7cm by 7cm; (b). Circuit diagram of the amplifier. We used two push pull amplifier using Darlington pair and instrumental amplifier to get the signals.

## Simulation and Experimental Results

Simulations were done using Matlab with 4 electrodes to the edge of a circular brain model (20 cm in diameter) as 2 pairs of independent current sources. The frequencies were 500Hz and 510Hz. The current density vectors (2D including Jx and Jy) distribution was calculated. Distributions of *vector components* Jx and Jy near the central region of phantom are presented in Figure 3. A vaguely focused "focal spot" of Jx component could be achieved by adjusting both the locations of the electrodes and the amplitude ratio of the two sources. However, along the Jy component direction, there was no focusing effect. When combining the fields using square of vector summation $|(\boldsymbol{J}1+\boldsymbol{J}2)|^2$ , where $\boldsymbol{J}1$ and $\boldsymbol{J}2$ are the vector current densities of the source 1 and 2, the intensity distribution at the center of the phantom as well as 2 other locations, 4cm and 8cm away from the center were plotted in Figure 3 as well. The envelop of the10Hz beating signals with KHz carrier was shown to be spread across a large region of the phantom and there was no obvious "focusing" of the amplitude of the 10Hz beating signal envelop.

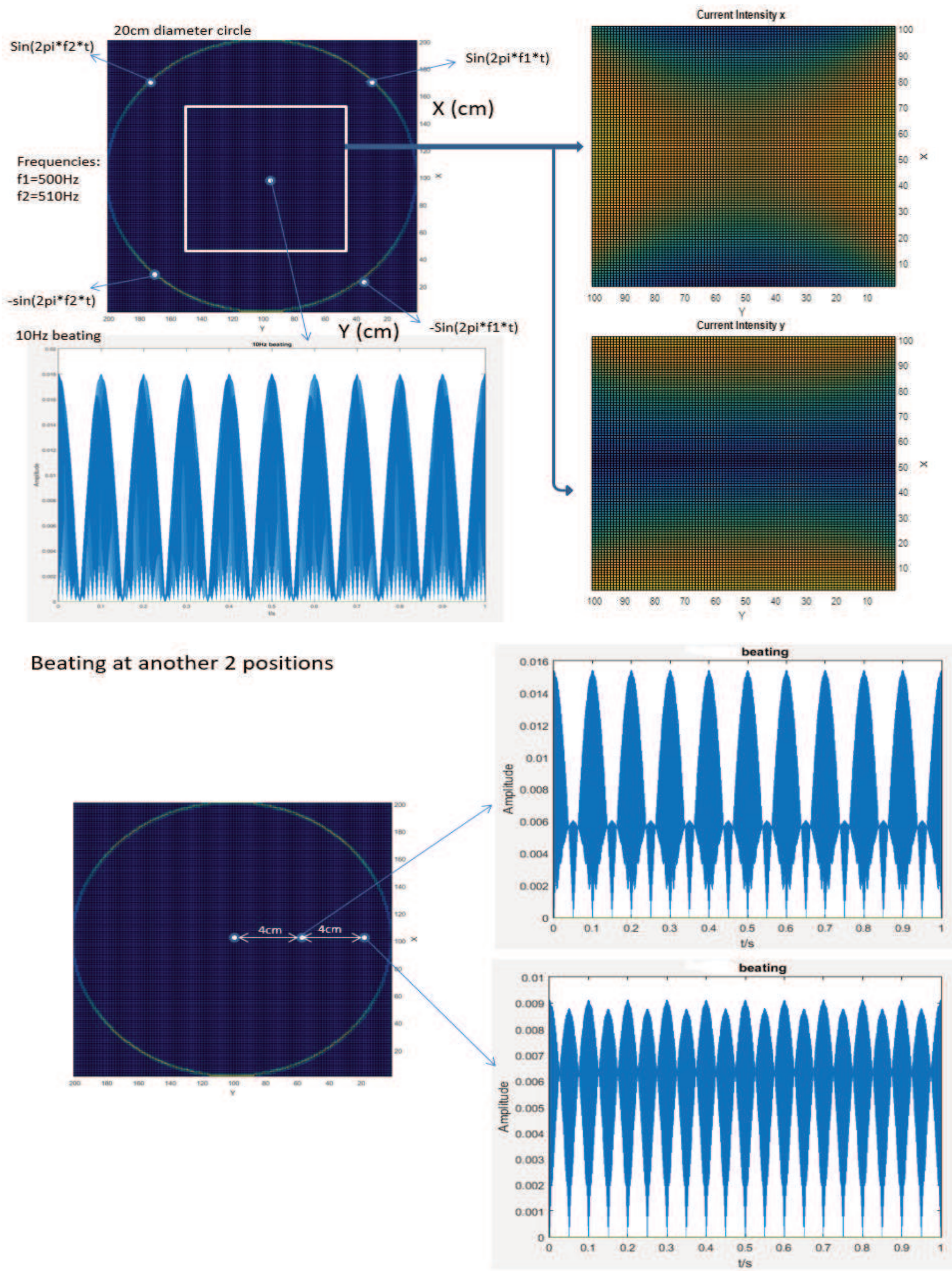
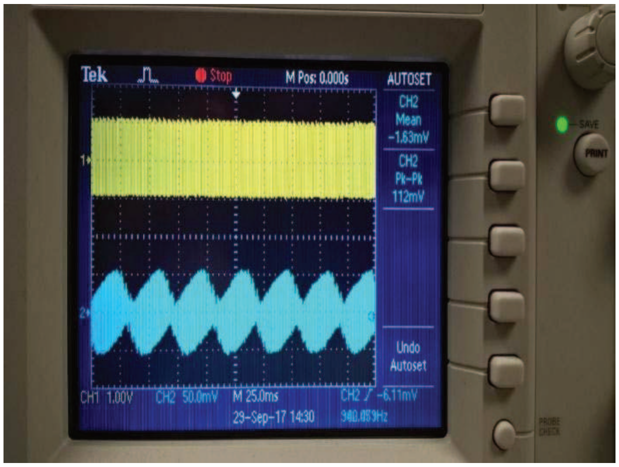
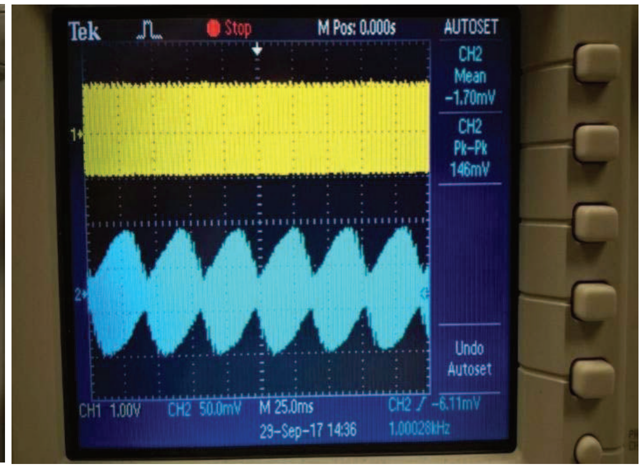



Figure 3 Matlab Simulation of beating signals and current focusing from two independent alternating current sources with different frequencies.




(a)

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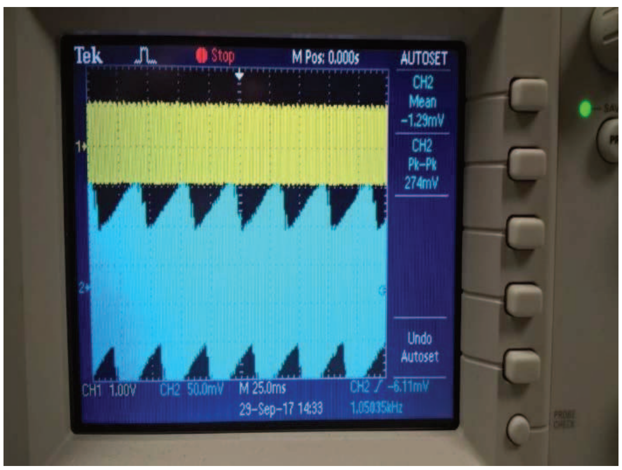
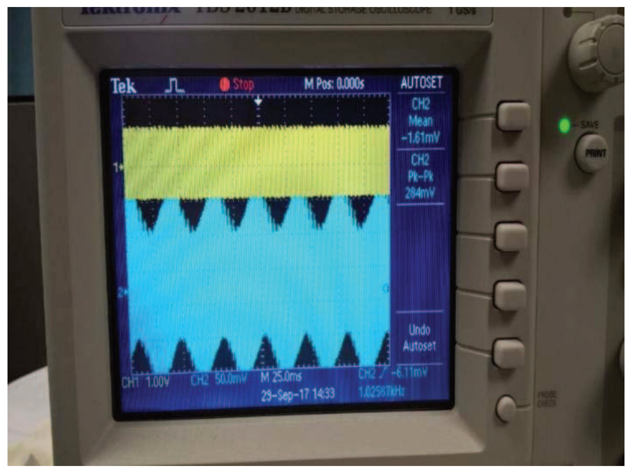



(c)




(d)

Figure 4 Electrical signals of the current in the brain phantom detected by the dipole probe at different locations and probe orientations (yellow traces are the input signals on the electrodes; blue traces are the signals detected by dipole probe.): (a). Dipole probe was placed in the middle line of the cup but is more north side from the line connecting the two positive electrodes; (b). Dipole probe in the middle of the cup aligned with the positive electrode; (c). Dipole probe placed left side of the cup aligned with the positive electrode; (d). Dipole probe placed right side of the cup aligned with the positive electrode.

In the experiment, the current density measurement was done using a dipole probe [6] with the setup shown in Figure 2. We measured the interference patterns of the two 1mA AC sources at any location inside the phantom. Figure 4 shows the patterns at only a few fixed points. Figure 4(a) shows the measured pattern at the middle line of the cup but is more north side from the line connecting the two positive electrodes; 4(b) shows the pattern in the middle of the cup aligned with the positive electrode; 4(c) shows the pattern at left side of the cup aligned with the positive electrode; 4(d) shows pattern at right side of the cup aligned with the positive electrode. The triangular shape of the beating envelop is caused by phase and amplitude differences from the two AC sources. In the middle, the beating modulation depth was deep and complete but the envelop amplitude was smaller due to current density spread. Near the two sides of the phantom the overall amplitudes were bigger due to closer to one of the source but the modulation depth was shallow and incomplete. In any case when we moved the probe around continuously we didn't observe any focusing effect even near the middle of the phantom. In fact, the amplitude was weaker in the middle line and stronger when probe was closer to the electrode sources.

### Animal Experiment

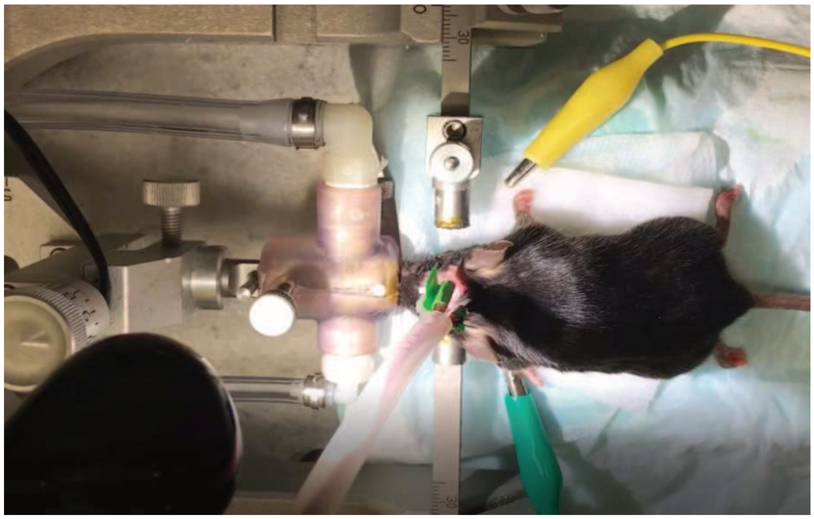


Figure 5 Mice stimulation experiment setup.

The animal experiment was done at University of Maryland School of Medicine to observe tACS stimulation effect on mice limb movements. The same circuit in Figure 2(b) was used to drive the electrodes which were located on the top of the mouse head as shown in Figure 1. For one of the AC source, the frequency was kept constant at 1kHz and for the other AC source the frequency varied from 1.001kHz to 1.020kHz. The current amplitude was kept <5 mA during stimulations. The bottom side of the mouse head was kept touching a piece of wet cloth which was soaked into saline before the experiments, and this piece of cloth was connected to the ground. In the first round of experiment, we removed only the skin of on top of its head and the electrodes directly touched the skull. However, the current failed to penetrate the skull to get into the deep brain region due to the extremely low conductivity of the skull itself. The measured impedance with skull was over 6 to 9 Mohms, which required kV level voltage source to reach mA level current. So, the current source was not able to follow the set values even at maximum voltage from the power supply at 28V. No movements of limb could be detected.

In the $2^{nd}$ round stimulation experiment, we followed Grossman's approach to thin down the skull of the mouse to further reduce its resistance down to kohm level. Movements of ear and other muscles were observed at beating frequencies ranging (1-12Hz). The muscle or limb movement was electrode location dependent in a way that different electrode location arrangement could cause different part of muscle to move. So, we further conducted direct modulation experiment by using single source modulation and reducing the source frequency to 1-12 Hz. The same phenomenon was observed as both channels were applied to form a beating frequency. This clearly indicated that the limb movement was caused by motor cortex evoked activation at the electrode site due to the fact that higher concentration of current density was flowing through the electrode. Either a low frequency AC signal or a low frequency beating signal can modulate the limb movement even though the beating signal modulation depth may not be optimized when it is closer to one of the electrode.

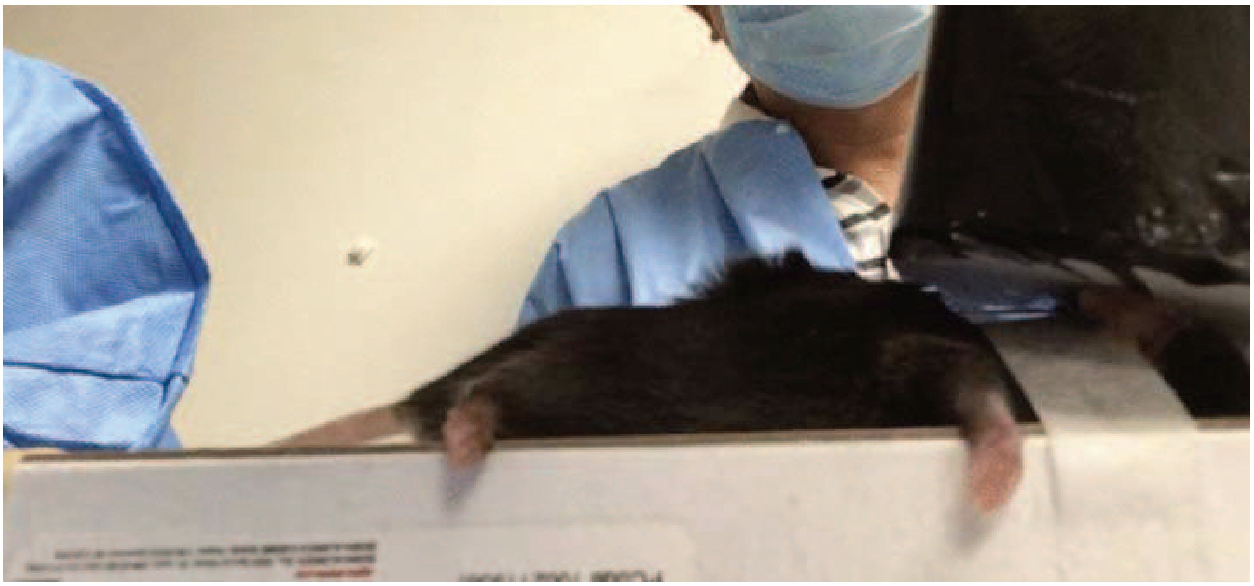


Figure 6 Focused TMS on mouse to induce repeatable unilateral movements

We have recently demonstrated using focused TMS to activate mice single limb movement which requires a focused spot size of <1mm diameter [7]. In our experiment in Figure 6, no surgery for removing animal scalp and skull is required. The process is completely noninvasive. We conclude that currently the only available noninvasive brain stimulation technique that target any desired location in a mouse brain with high spatial resolution is the focused TMS method demonstrated in our group [7].

## Summary

In this study, we theoretically and experimentally verified that the method of achieving focused deep brain stimulation using temporally interfering electric field failed to deliver targeted stimulation as claimed in previous research. There is no available focusing mechanism to accomplish spatial focusing. The demonstrated limb movement is likely due to the high current density at the electrode setting site not by adjust beating condition. Focused TMS is currently the only available method to accomplish noninvasive targeted stimulation.

## References

[1] Lyons MK. Deep brain stimulation: current and future clinical applications. InMayo Clinic Proceedings 2011 Jul 1 (Vol. 86, No. 7, pp. 662-672). Elsevier.

[2] Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. Journal of affective disorders. 2005 Nov 1;88(3):255-67.

[3] Brunoni AR, Nitsche MA, Bolognini N, Bikson M, Wagner T, Merabet L, Edwards DJ, Valero-Cabre A, Rotenberg A, Pascual-Leone A, Ferrucci R. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. Brain Stimulation: Basic, Translational, and Clinical Research in Neuromodulation. 2012 Jul 1;5(3):175-95.

[4] Antal A, Paulus W. Transcranial alternating current stimulation (tACS). Frontiers in human neuroscience. 2013 Jun 28;7:317.

[5] Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk HJ, Cassara AM, Neufeld E, Kuster N, Tsai LH, Pascual-Leone A. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017 Jun 1;169(6):1029-41.

[6] Qinglei Meng; Prashil Patel; Sudhir Trivedi; Xiaoming Du; Elliot Hong; Fow-Sen Choa,“ Sensor probes and phantoms for advanced transcranial magnetic stimulation system developments, “ SPIE DSS 9487, doi: 10.1117/12.2177014, May 2015.

[7] Meng Q, Jing L, Badjo JP, Du X, Hong E, Yang Y, Lu H, Choa FS. A novel transcranial magnetic stimulator for focal stimulation of rodent brain. Brain Stimulation. 2018 Mar 1, doi: 10.1016/j.brs.2018.02.018