A new brain stimulation method: Noninvasive transcranial magneto–acoustical stimulation*

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We investigate transcranial magneto–acoustical stimulation (TMAS) for noninvasive brain neuromodulation *in vivo*. TMAS as a novel technique uses an ultrasound wave to induce an electric current in the brain tissue in the static magnetic field. It has the advantage of high spatial resolution and penetration depth. The mechanism of TMAS onto a neuron is analyzed by combining the TMAS principle and Hodgkin–Huxley neuron model. The anesthetized rats are stimulated by TMAS, resulting in the local field potentials which are recorded and analyzed. The simulation results show that TMAS can induce neuronal action potential. The experimental results indicate that TMAS can not only increase the amplitude of local field potentials but also enhance the effect of focused ultrasound stimulation on the neuromodulation. In summary, TMAS can accomplish brain neuromodulation, suggesting a potentially powerful noninvasive stimulation method to interfere with brain rhythms for diagnostic and therapeutic purposes.

Keywords: transcranial magneto–acoustical stimulation, brain neuromodulation, electric current, Hodgkin–Huxley neuron model

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1. Introduction

Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) as noninvasive brain stimulation tools have been used for treating and rehabilitating neurological and psychiatric disorders such as Parkinson's disease, Alzheimer's disease, autism, etc.[1–4] However, these techniques lack spatial resolution, which restricts the therapeutic applications in stimulating deep brain areas. In comparison with tDCS and TMS, focused ultrasound stimulation (FUS) can perform a deep stimulation with a spatial resolution of approximately 2 mm.[5] The effectiveness of FUS has been demonstrated in animals and humans.[6–8] In this paper, transcranial magneto–acoustical stimulation (TMAS) that was proposed by Norton in 2003 is developed for noninvasive brain neuromodulation.[9,10] FUS has the characteristics of noninvasive, high spatial resolution and high penetration depth. The mechanism of FUS is that the ultrasound-induced cavitation of these nanometric bilayer sonophores can induce a complex mechanoelectrical interplay that leads to excitation, primarily through the effect of currents induced by membrane capacitance change.[11] The mechanism of TMAS is that an electric current is generated by the static magnetic field and ultrasonic waves in tissues to modulate neuronal activity. Therefore, the physical fields and mechanisms of FUS and TMAS are different. Compared with tDCS and TMS, the TMAS has a high spatial resolution, which is determined by the size of the focused ultrasound. In addition, TMAS has a higher penetration depth since there is no interplay between the magnetostatic field and brain tissue.

Here, we study the TMAS with simulation and animal experiment. First, the neuronal action potentials are simulated with TMAS based on the Hodgkin–Huxley neuron model. Then, the electric current generated in rat brain tissue by ultrasound and magnetostatic field is detected. Finally, we stimulate the rat somatosensory cortex with TMAS, record local field potentials (LFPs) and analyze the amplitudes of LFPs at different stimulation statues that include control status (CTRL), static magnetic field status (SMF), TMAS and FUS.

2. Methods

2.1. Theory research

The schematic diagram of TMAS is shown in the lower-right of Fig. 1(a). The action of a focused ultrasonic wave moves charged ions in the nerve tissue. When a magnetostatic field is perpendicular to the movement direction of the charged ions, the Lorentz force on the ions can be induced in the tissue.[12] The Lorentz force separates the positive and negative ions to opposite directions, thereby forming electric

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current $I_{\rm ext}$ to stimulate neurons.

We assume that the pressure waves are longitudinal and propagate along the z axis and that the magnetostatic field is along the x axis, thereby placing the current density along the y axis in the standard Cartesian coordinate axes.

A longitudinal pressure wave propagating along the z axis obeys the classical wave equation

$$\frac{\partial^2 u}{\partial z^2} = \frac{1}{c_0^2}\frac{\partial^2 u}{\partial t^2}, \tag{1}$$

where u is the distance of the ion from its equilibrium position. In the case of a progressive sine wave, the instantaneous speed v_z of the ion can be expressed as

$$v_z = V_z \sin(\omega t - \phi), \tag{2}$$

where V_z is the magnitude of the speed of the ion, ω is the angular frequency and obeys the equation of

$$\omega = 2\pi f, \tag{3}$$

where f is the ultrasound frequency.

The relationship between the magnitude of the speed of a fluid element and the magnitude of the instantaneous pressure P can be expressed as

$$P = \rho c_0 V_z, \tag{4}$$

where ρ is the tissue density and c_0 is the ultrasound speed.

According to Montalibet's theory,[13] the current density J_y along the y axis, generated by ultrasound and magnetostatic fields in a biological medium can be expressed as

$$J_y = \sigma \frac{V_z B_x}{1+\tan^2\psi} \sin(\omega t - \psi), \tag{5}$$

where σ is the conductivity of the tissue with a typical value of the conductivity of tissue, 0.5 S/m;[10] B_x is the intensity of the magnetostatic field; Ψ is the phase angle and obeys the following equation:

$$\tan\psi = \omega\tau, \tag{6}$$

with τ being the time constant and of the order of femtoseconds for typical electrolytes. At the ultrasound frequencies (200 kHz–700 kHz) generally used in ultrasound stimulation,[14] the quantities of $\tan\Psi$ and Ψ are small and negligible with respect to unity. Therefore, equation (5) can be expressed as

$$J_y \approx \sigma V_z B_x \sin\omega t. \tag{7}$$

The relationship between the intensity of the ultrasonic power and the ultrasound pressure satisfies the following equation:

$$I = \frac{1}{2}\frac{P^2}{\rho c_0}, \tag{8}$$

where I is the intensity of the ultrasonic power.

Combining Eqs. (3), (7), and (8), we obtain the following equation:

$$J_y \approx \sigma B_x \sqrt{\frac{2I}{\rho c_0}} \sin(2\pi f t). \tag{9}$$

The electric current field $\boldsymbol{J}_y$ induced by Lorentz force can give rise to a secondary electric current field $\boldsymbol{J}_s$. The total electric current field $\boldsymbol{J}$ can be expressed as

$$\boldsymbol{J} = \boldsymbol{J}_y + \boldsymbol{J}_s. \tag{10}$$

Compared with the electric current density J_y, the secondary electric current density J_s can be ignored.[9] Therefore, the total electric current density can be expressed as

$$J \approx J_y. \tag{11}$$

The value of the total electric current density J, which corresponds to the electric current $I_{\rm ext}$, can be used to stimulate the neuron and is used for simulation in the Hodgkin–Huxley neuron model.

The Hodgkin–Huxley neuron model, which successfully describes the dynamic process of the generation of squid axon action potential,[15,16] is a representative model for studying electrophysiological characteristics of a neuron. The Hodgkin–Huxley neuron model includes the following differential equations[15]

$$\begin{aligned}
C_m\frac{{\rm d}V}{{\rm d}t} &= I_{\rm ext} - [\bar{g}_{\rm Na} m^3 h(V - V_{\rm Na}) + \bar{g}_{\rm K} n^4 (V - V_{\rm K}) \\
&\quad + g_{\rm L}(V - V_{\rm L})], \\
\frac{{\rm d}m}{{\rm d}t} &= \phi[\alpha_m(V)(1-m) - \beta_m(V)m], \\
\frac{{\rm d}h}{{\rm d}t} &= \phi[\alpha_h(V)(1-h) - \beta_h(V)h], \\
\frac{{\rm d}n}{{\rm d}t} &= \phi[\alpha_n(V)(1-n) - \beta_n(V)n],
\end{aligned} \tag{12}$$

where C_m is the membrane capacitance; $I_{\rm ext}$ is the external electric current generated by TMAS in our study; V is the membrane potential and can be expressed as $V = V_{\rm intra} - V_{\rm extra}$, with $V_{\rm intra}$ and $V_{\rm extra}$ being the intracellular and extracellular membrane potential, respectively; $V_{\rm Na}$, $V_{\rm K}$, and $V_{\rm L}$ are the equilibrium potentials of sodium, potassium, and leak electric current, respectively; $g_{\rm Na}$, $g_{\rm K}$, and $g_{\rm L}$ are the maximal conductances of the corresponding ionic electric currents and are nonlinear functions of V, given by the following equations:

$$\begin{aligned}
&\alpha_m(V) = 0.1(25-V)/[\exp((25-V)/10) - 1], \\
&\beta_m(V) = 4\exp(-V/18), \\
&\alpha_h(V) = 0.07\exp(-V/20), \\
&\beta_h(V) = 1/[\exp((-V+30)/10) + 1], \\
&\alpha_n(V) = 0.01(10-V)/[\exp((10-V)/10) - 1], \\
&\beta_n(V) = 0.125\exp(-V/80).
\end{aligned} \tag{13}$$

The fixed parameters used for simulation are listed in Table 1.

Table 1. Fixed parameters for TMAS principle and Hodgkin–Huxley neurons model.

Parameters	Values	Units
σ	0.5	S/m
ρ	1120	Kg/m^3
c_0	1540	m/s
C_m	1.0	μF/cm^2
$\bar{g}_{\mathrm{Na}}$	120	mS/cm^2
$\bar{g}_K$	36	mS/cm^2
g_L	0.3	mS/cm^2
V_{Na}	115	mV
V_{K}	–12	mV
V_{L}	10.59	mV
T	6.3	°C

2.2. Experimental research

A total of fifteen Sprague-Dawley rats (male, 3-month-old) each with body weight of approximately 200 g were used in this electrophysiological study. All efforts were made to minimize animal suffering and the number of animals used. The rat was surgically anesthetized with sodium pentobarbital (3%, 5 mg/100 g, IP), and then fixed on a stereotaxic apparatus (ST-5ND-C, USA) with ear bars and a clamping device. The fur of the rat head was shaven, and the skin was cleaned with 0.9% sodium chloride physiological solution. The skin was cut along the midline of the skull, and the subcutaneous tissue and periosteum were cleaned. The skull was drilled, and the bone was chipped to expose an approximate brain tissue area of 2 mm×2 mm and formed a bone hole.

The scheme of the experimental setup is shown in Fig. 1(a) and the corresponding photograph is shown in Fig. 1(b). Ten permanent magnets (Nd–Fe–B, 100 mm (length) ×100 mm (width) ×20 mm (height)) were inserted in a homemade U-shaped device as shown in the lower-right corner of Fig. 1(b)). The rat head was placed in the middle of the U-shaped device and the rat mouth was fixed by a clamping device. The ultrasonic transducer with a center frequency of 500 kHz, a bandwidth of 50%, a focal length of 30 mm and a diameter of 20 mm (Daping, Hangzhou, China) was placed above the rat head. There was a plastic ultrasonic collimator filled with medical ultrasound gel between the transducer and the rat skull. A single tungsten electrode with a length of 15 cm and diameter of 1 mm (MicroProbes, USA) passed through the bone hole was inserted into the brain tissue below the ultrasonic transducer. The angle between the single electrode and the ultrasonic probe was ∼ 50. The grounded wire and the reference wire are fixed on the scalp by the surgical suture needle. The single tungsten electrode, grounded wire and the reference wire connected with a headstage that was fixed on a stereotaxic apparatus.

An ultrasonic transmitter and receiver card (USB-UT350T, Ultratek, USA) controlled by a computer was used to apply a pulse signal to the focused ultrasonic transducer. Local field potentials (LFPs) from the somatosensory cortex, captured by the single electrode (MicroProbes, USA), were amplified by a microelectrode AC amplifier (Model-1800, A-M system. Inc, USA). The analog signals from AC amplifier were converted into digital signals by a neural signal processor (Cerebus, Cyberknetics, USA) and transmitted to a computer.

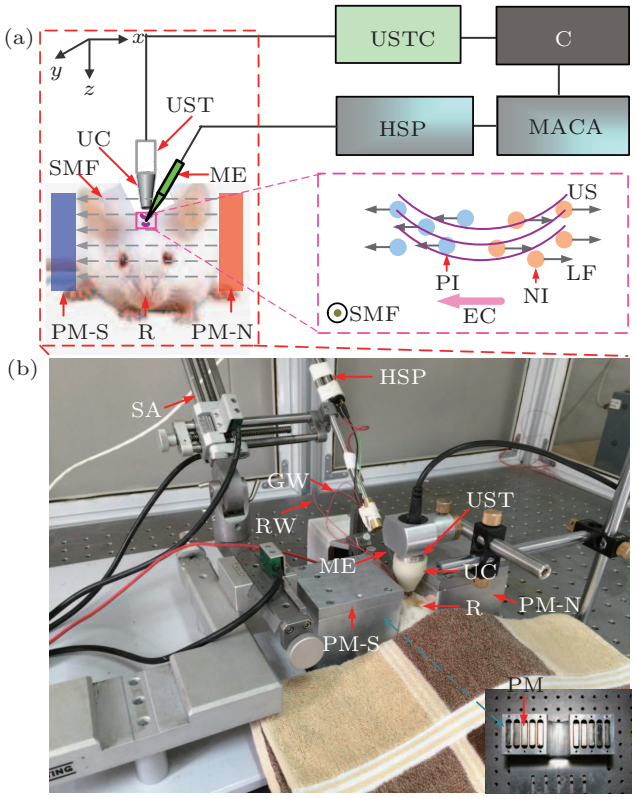


Fig. 1. (color online) (a) Schematic diagram of the experiment setup. (C: computer, HSP: headstage probe, MACA: microelectrode AC amplifer, USTC: ultrasonic transmitter card, SMF: static magnetic field, ME: microelectrode, US: ultrasound, UST: ultrasound transducer, PM-N: permanent magnet-N pole, PM-S: permanent magnet-S pole, R: rat, PI: positive ion, NI: negative ion, LF: Lorenz force, and EC: electric current). (b) The photography of the experiment setup (SA: stereotaxic apparatus, GW: ground wire, RW: reference wire, UC: ultrasonic collimator, and PM: permanent magnet).

The magnetic field intensity measured by Gaussmeter (WT20D, WeiTe, China) at the rat head was approximately 0.35 T. In the experiment, the center frequency, stimulus frequency, and the single stimulus pulse duration were 500 kHz and 100 Hz, 32 μs respectively. The spatial-peak pulse-average intensity (I_{SPPA}) measured by the ultrasound energy density instrument (YP0511F, Hangzhou, China) was 21.1 W/cm^2 and the corresponding spatial-peak temporal-average intensity (I_{SPTA}) was 135.04 mW/cm^2. The ultrasound intensity was below 190 W/cm^2, the maximum recommended limit for diagnostic imaging applications.[7] The LFPs were collected and digitized at a sample rate of 2 kHz, and with a low-pass filter at 125 Hz in the Cerebus system.

First, the LFPs without any stimulation were recorded as a control status (status abbreviation: CTRL). Second, we inserted the permanent magnets on both sides of shaped-U de-

vice and recorded the LFPs in the presence of a static magnetic field (status abbreviation: SMF). Third, an ultrasonic wave was transmitted to the rat head and the stimulation lasted 10 min. We recorded the LFPs after stimulation (status abbreviation: TMAS). Finally, the permanent magnets were removed and the rat was only stimulated by ultrasound for 10 min. After FUS, the LFPs were recorded (status abbreviation: FUS).

3. Results

3.1. Simulation of TMAS

To test whether TMAS is able to excite action potential of a neuron, the Hodgkin–Huxley neuron model is used to perform CTRL, SMF, TMAS status. In the simulation, the ultrasonic power is 21.1 W/cm^2 that is lower than that used to stimulate primary somatosensory cortex of human in FUS, and the stimulus frequency is 100 Hz. According to the formula $I = p_0^2/2\rho c_0$, where p_0 is the maximum amplitude of the sound pressure P, ρ is the brain tissue density and c_0 is the speed of ultrasound wave in soft tissue. When I is 21.2 W/cm^2, the sound pressure p_0 is 0.85 MPa. The intensity of the static magnet is 0.35 T. According to formula (9), the maximum electric current density is 7.9 μA/cm^2.

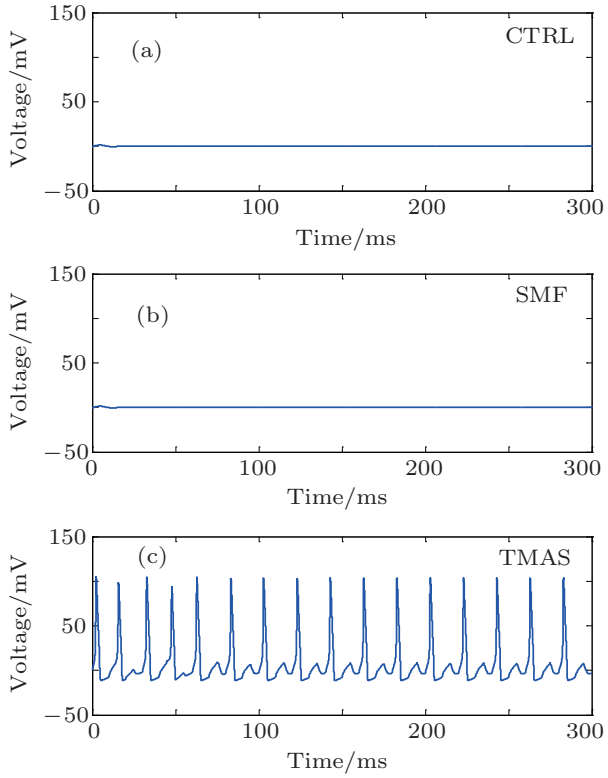


Fig. 2. (color online) Simulation results by using Hodgkin–Huxley neuron model with an electric current density of 7.9 μA/cm^2 and a stimulus frequency of 100 Hz for (a) CTRL status, (b) SMF status, and (c) TMAS status.

The simulation results shown in Fig. 2 indicate that there is no action potential with the statuses of CTRL and SMF (Figs. 2(a) and 2(b)), due to lack of the excitation current when the neuron is not stimulated, or only in the static magnetic field. Figure 2(c) shows that the action potential is generated under TMAS with a current density of 7.9 μA/cm^2. The above results show that the TMAS can stimulate a neuron and excite action potential in the Hodgkin–Huxley neuron model.

3.2. Detecting electric current generated by TMAS in brain tissue

In order to detect electric current generated by TMAS in brain tissue, an experimental setup is build. The scheme and photograph of the setup are shown in Appendix A: Supplementary Materials (Fig. S1). The rat head moving part of the skull is placed in the middle of the U-shaped device. We use the ionized water to wash the blood to exclude the influence of foreign ions. A sinusoidal signal with a frequency of 500 kHz is generated by arbitrary function generator (33220A, Agilent, USA) and then is separated into two parts by T-type BNC connector. One part is then amplified by a linear power amplifier (240L, ENI Inc., Rochester, NY) to generate ultrasound. The other part is input to the oscilloscope (Two channels, MSO7052B, Agilent, USA). The electric current generated in brain tissue by ultrasound and magnetic field is detected by the custom-designed copper electrodes. The electrodes are linked through two electrical wires to a 1-MV/A current amplifier (HCA-2M-1M, Laser Components, Olching, Germany). The current signal is amplified by the current amplifier and then observed by the oscilloscope (Two channels, MSO7052B, Agilent, USA) with 50-Ω input impedance. The experimental results are shown in Fig. 3. The yellow line represents the electric signal from the function generator, and the green line is for the electric current signal from brain tissue. Both of them have the same frequency (Their numbers of peaks are the same in the same time interval). According to formula (9), the electric current signal has the same frequency as the electric signal (ultrasound signal), therefore, the result is corresponding to formula (9). The above result demonstrates that the ultrasound and magnetic field can induce electric current in brain tissue.

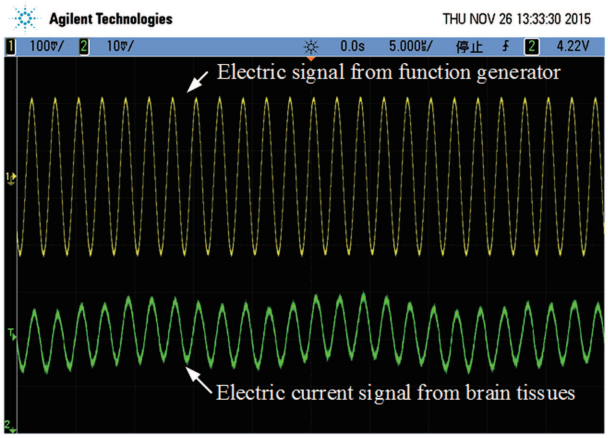


Fig. 3. (color online) Electric signal from function generator, and electric signal from brain tissue.

3.3. Experiment of TMAS on LFPs of rat cortex

To quantitatively evaluate the effect of TMAS on brain neuromodulation, the LFPs for four different statuses are recorded and their corresponding mean amplitudes are computed. The LFP signals in CTRL, SMF, TMAS and FUS statuses are shown in Figs. 4(a)–4(d). There is no action potential in CTRL and SMF statuses shown in Figs. 4(a) and 4(b) respectively. When the cortex is stimulated by TMAS and FUS separately, there appear action potentials in LFPs pointed by red arrows shown in Figs. 4(c) and 4(d) respectively. We can also clearly observe that the amplitude of the LFPs with TMAS is higher than those of CTRL, SMF and FUS statuses.

The mean amplitudes of the LFPs shown in Fig. 4(e) were 0.1095±0.038 mV (CTRL), 0.1103±0.035 mV (SMF), 0.3768±0.075 mV (TMAS), 0.3768±0.075 mV (FUS), respectively ($n = 15$, mean±s.d., $^*p < 0.05$, paired t-test). The ratio of the mean amplitude between the SMF and CTRL statuses is 1.01 that is close to 1. The results indicate that there is no significant interaction between the static magnetic field and brain tissue. For the TMAS status, the ratios of the mean amplitude between tFUMS and CTRL, and between tFUMS and SMF are 3.44 and 3.42, suggesting that the neuronal activity can be enhanced by TMAS. Meanwhile, the ratios of the mean amplitude between FUS and CTRL, and between FUS SMF are 2.38 and 2.36, which indicate that FUS can also modulate the oscillatory activities of brain, which is consistent with the result of previous FUS study.[10] To compare mean absolute amplitude between the TMAS and FUS and the increase in the amplitude of LFP is 1.45. Furthermore, the oscillatory activities of brain are significantly increased with TMAS, demonstrating that the TMAS can enhance the effect of FUS on the brain neuron modulation.

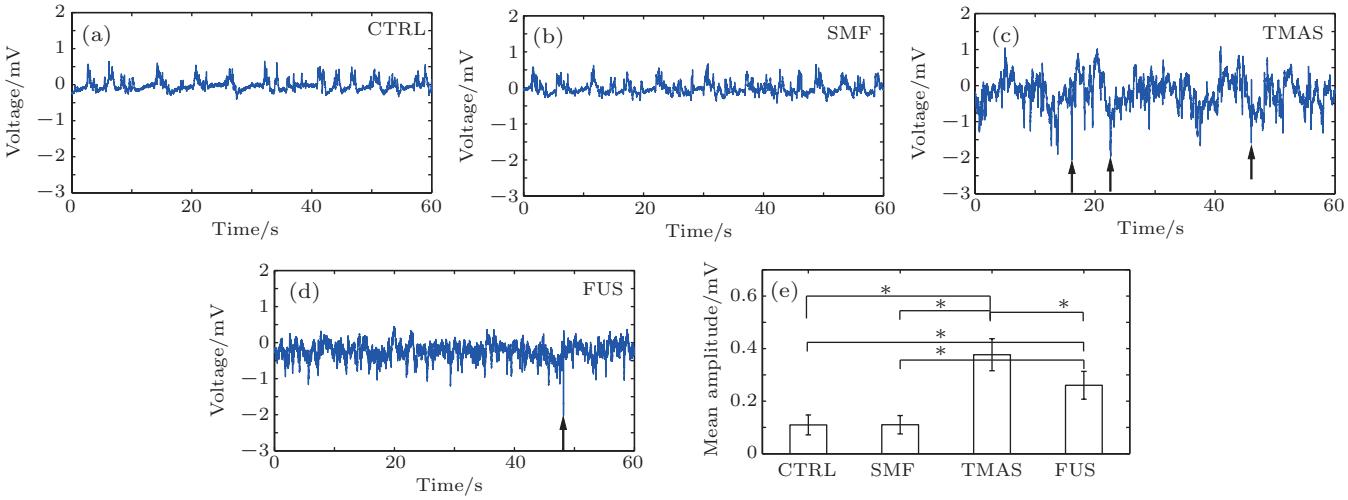


Fig. 4. (color online) LFPs in (a) CTRL status, (b) SMF status, (c) TMAS status, and (d) FUS status. (e) The mean amplitudes of the LFPs ($n = 15$, mean±s.d., $^*p < 0.05$, paired t-test).

4. Discussion and conclusion

The previous studies, in which the Maxwell equation combining the ultrasound and magnetic field was established and the distribution of electric field was obtained, predicted that TMAS can stimulate the nerve tissue,[10] in which, however, the action potentials in neuron models were not stimulated, nor the conclusion was verified experimentally. In our study, we combine the TMAS principle with the Hodgkin–Huxley neuron model to simulate action potential. Furthermore, we use TMAS to stimulate rat somatosensory cortex. The results show that the TMAS can generate electric current in brain tissue and the electric current can change the neural oscillation activities for brain neuromodulation. These results supply the basis for TMAS in the treatment of neurological and psychiatric diseases in clinic.

Appendix A: Supplementary materials

The scheme and photograph of the experimental setup are shown below.

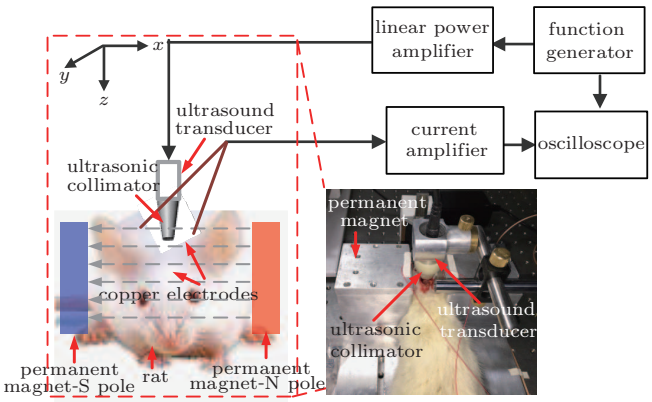


Fig. S1. (color online) The scheme and photograph of the setup.

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