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A novel transcranial magnetic stimulator for focal stimulation of rodent brain

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To the editor:

Transcranial magnetic stimulation (TMS) is emerging as a therapeutic tool for treating a number of neuropsychiatric disorders, however, its underlying mechanisms remain largely unknown. Due to potential safety and ethical concerns, studies to uncover the neurobiological mechanisms of TMS cannot be fully accomplished in humans, preclinical rodent studies are of great importance in this regard. Furthermore, which brain region and network are stimulated and how the stimulation is delivered temporally will likely affect TMS outcomes. In order to draw spatially translatable neurobiological conclusions, and ultimately to inform clinical interventions to improve efficacy, it is critical that animal studies mimic human TMS conditions. Unfortunately, there is no commercial rodent TMS coil that can mimic the spatial focality of human TMS. Even with the best rodent TMS coil currently available [1], a large volume of brain tissue would be stimulated, which prevents spatially relevant mechanistic understanding of preclinical models and their translation to human TMS studies [2–4].

Various methods have been proposed to enhance the focality of the TMS coils [5]. However, in general, conventional TMS coil designs are limited by coil to brain size ratio. Theoretical analysis from Cohen et al. suggests that an increase in electrical current by a factor of 25 is needed to scale a human TMS coil to rodent-size [6]. Since human TMS coils use pulsed currents at kiloampere (kA) level [7], producing a coil carrying 25kA currents would be extremely challenging due to heating and mechanical stress from electromagnetic forces, not to mention a TMS power source providing 25kA current.

We have developed an innovative concept to dramatically enhance the efficiency of TMS coil, a major challenge associated with small coil size; we have applied a new wire-wrapping method to break the circular symmetry of the field pattern, achieving focused electric field distribution. In vivo, experimentsdemonstrate reproducible contralateral single-limb activation and motor evoked potential (MEP).

A key strategy in our coil design is the usage of long sheets of silicon steel magnetic core. Silicon steel has high magnetic permeability and drastically enhances magnetic field strength, but also has a high magnetic saturation values (2 T). Individual sheets (0.35 mm × 4.2 mm × 150mm) were insulated to minimize eddy current. Fig. 1(a) shows the TMS coil. It is 15cm in length and has 60 turns of magnetic wires, each containing a bundle of 100 insulated litz wires (28 Gauge) in parallel. The coil outer diameter is about 2.5cm. The cylindrical shape of the coil produces a ring-shaped electric field distribution, which is not desirable in terms of the focality of the coil. COMSOL (finite element analysis software, COMSOL Inc) simulations indicate that tilting the wire-wrapping angle can break the symmetry and effectively accomplish a sharply focused electric field. As shown in Fig. 1(b) and (c), with 5° tilted wire-wrapping, an asymmetric electric field distribution is created, and the three-dimensional plot clearly shows the sharpness of the electric field distribution. The inductance of the coil was 47μH. An impedance-matched TMS circuit was developed to drive this coil (see Supplemental Materials). We mapped the induced electric field distribution using a three-dimensional vector field probe developed in the lab [8]. The measurement was performed at the plane 5mm below the coil surface. Fig. 1(d) shows the electrical field distribution, which matches well with the simulated results in Fig. 1(c).

In vivo, TMS experiments were perform on male C57BL/6J mice (n = 6). Animals were anesthetized with sodium pentobarbital intraperitoneally (50 mg/kg), MEP was recorded using a similar approach reported by Rotenberg et al. [9]. All procedures were approved by NIDA animal care and use committee. The coil was mounted to a customized three-axis micromanipulator. The focal electrical field point was carefully aligned to the targeted mouse motor cortex. Fine adjustments of the coil were made to induce limb twitch on the contralateral hindlimb, but not the ipsilateral hindlimb, any of the forelimbs or any other body part. (see Supplementary Materials for video recording). Fig. 1(e) shows a representative MEP signal. The delay from TMS pulse was about 9 ms, consistent with previous reports [9], suggesting multi-synaptic cortical origin.

Supplementary video related to this article can be found at https://doi.org/10.1016/j.brs.2018.02.018.

Our TMS coil has multiple advantages over existing ones. First, conventional TMS coils use air-core structure, and are limited to a thickness of 1–2cm (normal to coil plane). Our simulation suggests that, with air-core structure, the magnetic field quickly saturates when the coil thickness is bigger than 2cm. To further enhance the magnetic field strength, one has to accumulate more wirings along the coil's horizontal plane, but this is limited when the coil size has to match the rodent brain. By contrast, with the aid of long magnetic core, our simulations indicate that the magnetic field

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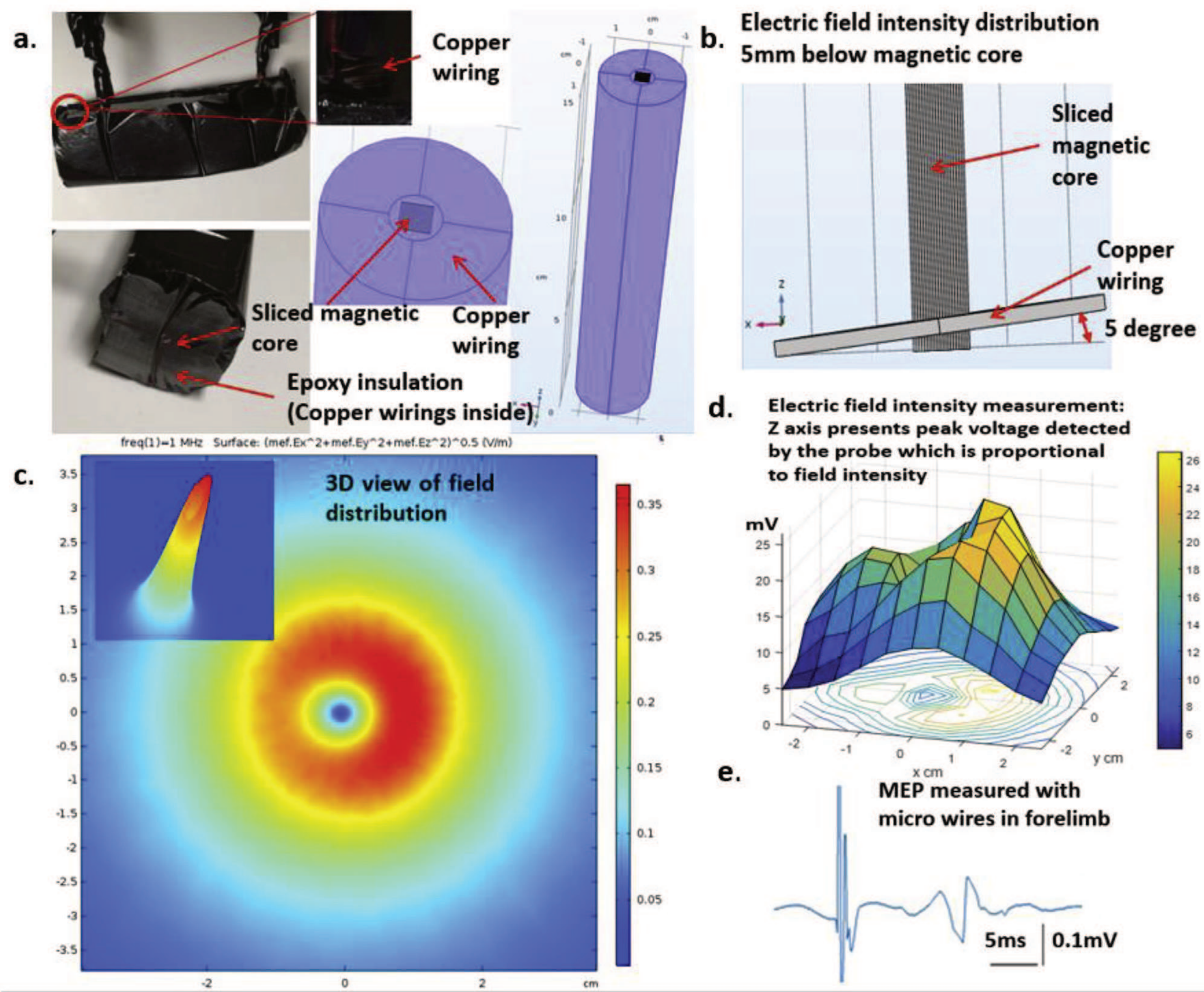

Fig. 1. a. TMS coil after fixation with epoxy (25mm in outer diameter, 6mm in inner diameter and 150mm in length); b. Modeling of wiring with an inclined angle; c. Simulated electric field distribution at the depth of 5mm; The inset shows asymmetric and sharp 3D field distribution; d. Measured electric field distribution at the depth of 5mm; e. Example of recorded EMG signal from a mouse limb. The large signal at the beginning was artifact from TMS pulse. EMG signal was about 0.12 mV peak-peak, lasting about 6 ms.

strength will increase with the coil length (and thus the number of turns) at a superlinear rate. The field strength therefore can be enhanced by increasing coil length without extending coil diameter. Second, commercial TMS systems require high voltage in the driver circuit to reach the motor threshold. Using Magstim Rapid2 and its 25mm figure-of-eight coil for brain stimulation, we found that it required a minimum of 80% of power output (1600V) to reach the threshold. The threshold voltage for our TMS coil was about 500V, due to the high permeability of the magnetic core. The estimated maximum current (I) in the coil is about 1.5kA, considering that the energy stored in capacitor C ($0.5 \times C \times V^2$, $C = 450\mu F$, $V = 500V$) is equal to the energy transferred to the coil ($0.5 \times L \times I^2$, $L = 47\mu H$). Importantly, even with the smallest commercial animal coil, the stimulation always induces other undesired trunk movements, indicating stimulations are not tightly focused. Our TMS stimulator induces brief twitch of a single contralateral hindlimb. According to the mouse motor cortex map by Tennant et al. [10], mouse hindlimb representation is about 1mm anteroposteriorly, and is in close proximity to the forelimb and trunk motor cortex, suggesting the focality of our TMS is about 1mm. Our coil design principles may provide guidelines for the development of the next generation TMS tools that target more focused areas in the human brain.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brs.2018.02.018.

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