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研究課題名（和文）Personalizing Brain Stimulation Dosage by New Neurostimulation Computational Model

研究課題名（英文）Personalizing Brain Stimulation Dosage by New Neurostimulation Computational Model

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研究成果の概要（和文）：医療用の刺激装置では、脳に電流が誘導される。本研究では、磁気刺激時の誘導電流と脳神経細胞との相互作用を推定している。そのため、電気生理学的特性頭部モデルの誘導電界の計算、物理的神経モデルの活性化を組み合わせた新しい計算モデルを開発できた。そして、このモデルにより、計測された運動反応を生み出すための刺激パラメータと脳内刺激領域を予測することに成功した。この結果から、異なる運動脳領域に対する刺激パラメータの最適化、選択性プロトコルの改善、国際安全ガイドラインのための安全限界の推定が可能となった。

研究成果の学術的意義や社会的意義
This research answered where and how much stimulation occurs at the cellular level during brain stimulation. This finding will directly apply to medical treatments through individualized stimulation protocols that will accelerate the development of brain stimulation protocols.

研究成果の概要（英文）：Electric currents are induced in the brain using stimulation devices for medical applications. This work estimated the interaction between the induced electric currents and brain neurons during magnetic stimulation. A novel computational model was developed that combined (1) computation of induced electric currents in the human head based on electrophysiological properties and anatomical data from magnetic resonance imaging and (2) cortical neuron activation based on microscopic biophysical modelling. The model successfully predicted the stimulation parameters and stimulation area in the brain for generating measured motor responses. This permitted optimization of stimulation parameters for different motor brain areas, improvement of selectivity protocols, and evaluation of limits for international safety guidelines/standards.

研究分野：Neural Engineering

キーワード：Brain Stimulation　Neuron　Biophysical Model　Electromagnetics

１．研究開始当初の背景

Electrostimulation has been reported to produce therapeutic potential without obvious side effects (Rossini et al., 2015). One electrostimulation approach is transcranial magnetic stimulation (TMS) which induces an electric current in the brain via a magnetic coil on the scalp near the brain area of interest (Fig. 1) (Barker et al., 1985). The delivery of the electric current using this non-invasive approach has attracted the attention of many researchers that have worked on TMS experiments aiming at medical diagnosis, therapy of various neurological disorders, and neuroscience applications. In order for high accuracy estimation of the induced electric current in the brain, computational physics is used to quantify the TMS-induced electric field distribution in the brain based on brain imaging that permits visualization of the induced electric currents in the brain (Windhoff et al., 2013). However, it is still unclear the interaction between the TMS-induced electric fields and brain neurons activation fundamental to associating the stimulation and physiological responses.

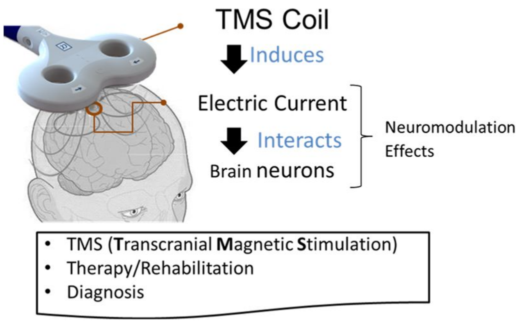

Fig. 1. Transcranial magnetic stimulation (TMS) induces an electric current in the brain the interacts with the brain neurons producing neuromodulation effects. This technique has been used for treatment of neurophysiological disorders.

２．研究の目的

The aim was to determine the electric current to stimulate specific brain targets at individual level, providing a deeper understanding of TMS mechanism. To achieve this, a new multiscale electrophysiological model was developed to describe physiological responses to TMS-induced electric currents. The multiscale model comprises two steps: (1) computation of the induced electric current in the brain and (2) estimation of the neurostimulation effects of the electric current in the neuronal circuitry. The ultimate goal is to achieve better clinical and therapeutic results through the developed computational techniques.

３．研究の方法

(a) Computational model

Volume conductor of the head models was constructed from MRI data. Then, electrophysiological neuronal circuitry of the motor cortex was implemented in the volume conductor based on anatomical and electrophysiological data available in the literature to estimate the interaction of TMS-induced electric current stimulation with neuronal elements and its relationship physiological responses (Figure 2).

(b) Experiments

TMS experiments were conducted to measure the relationship between stimulation parameters and physiological responses (i.e., motor evoked potentials). The proposed model was used to investigate and validate the physical quantities related to neuromodulation by reproducing the same experimental conditions in the computational simulation.

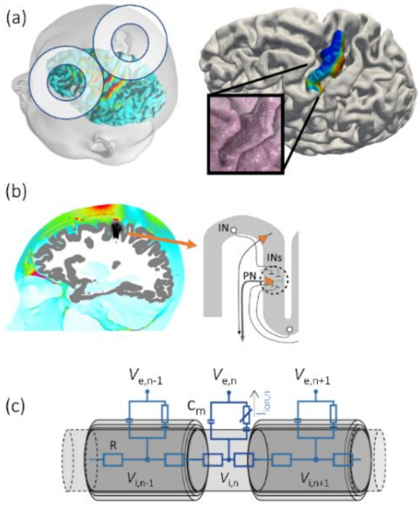

Fig. 2. Implemented multiscale electrophysiological model. (a) Transcranial magnetic stimulation (TMS)-induced electric field drives neural activation; (b) Neurons are arranged in horizontal layers with different cell types and neural connections that can project to other areas of the brain regions (c) Cable equation represents a myelinated axon and coupled with the TMS-induced electric field.

４．研究成果

(1) Multiscale model for cortical stimulation

The induced electric field (EF) was computed using subject-specific head models and experimental-specific TMS coil configuration during suprathreshold stimulation for relaxed muscles. The experimentally-derived EFs were used to calculate the activation of pyramidal tract model embedded in the head models to derive the activation site on the brain surface at the macroscopic level. The TMS activation site was located at the anterior wall of the central sulcus, which agreed with a concurrent TMS/fMRI study. By combining subject-specific multiscale modelling with experimental TMS measurements, we showed that this method could serve as a TMS imaging technique.

Figure 3 shows individualized activation maps (Gomez-Tames et al., 2020). They are obtained from direct activation of the pyramidal axon using TMS experimentally-derived EFs targeting finger muscle. The computational locations of the minimum stimulus intensity and center of gravity (CoG) spots are projected to the standard brain for comparison due to the inter-individual difference of the cortical anatomy, as shown in Figs 3B and 3C. The results showed that the computed activation locations are distributed consistently at the anterior wall of the central sulcus towards the gyral lip. The CoG location derived from the activation map is the most accurate metric with respect to experimental TMS/fMRI. Also, the relationship between computed thresholds of different hotspots and measured stimulation thresholds presents a significant correlation ($R^2 = 0.60$, $p = 0.02$). The results showed that the metric of the normal component of the electric field distribution is suitable for estimating stimulation at cellular level.

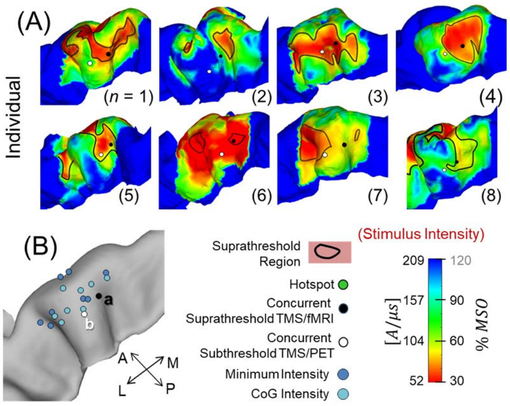

Fig. 3. Activation maps. (A) Individualized activation maps (n = 8) in the motor cortex. (B) Averaged activation map in the standard brain template.

(2) Brain Cortical Motor Mapping

No study has evaluated the relationship between the induced electric field and motor responses in TMS focusing on lower limb muscles. We investigated the dependency on coil orientation of the threshold of MEPs based on experimental measurements of TMS targeting the lower limb together with computational modelling.

The experimental results showed that TMS with medial-lateral direction more readily generates cortical activation of leg muscle (TA muscle). The latency of MEPs was shortest with medial-lateral induced currents. The normal component of the computed electric field indicates that it may be acting on neurons that are preferentially oriented at the optimal orientation. We also observed that the EF distribution of the field strength is less focused in deeper parts which makes them less appropriate as metric in terms of the internal electric fields thresholds (Hayashi et al., 2021).

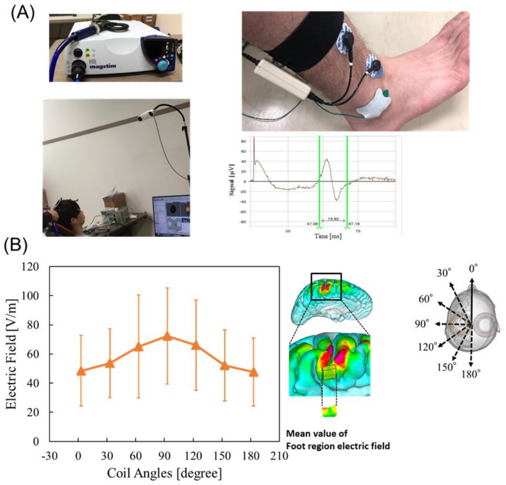

Fig. 4. Characterization of TMS parameters. (A) TMS stimulation experiment to determine the motor evoked response on the right foot. (B) The mean values of the electric field threshold are based on normal component corresponding to the foot region.

In addition, we explored potential high-resolution mapping of two hand muscles considering that they are represented next to each other on the brain cortex. Figure 5 shows the mapping results of the two muscles in the hand motor cortex. It can be seen that the FDI location is lateral to the ADM, which is consistent with a previous study (Bungert et al., 2017). The Euclidean distance between CoGs of FDI and ADM was 2.7 mm. In the case of the ADM map for the normal component, the region was more extended, including FDI area. Future studies will facilitate the understanding of the neural circuits involved by TMS stimulation and increase the detail of multiple mapping regions (Hikita et al., 2022).

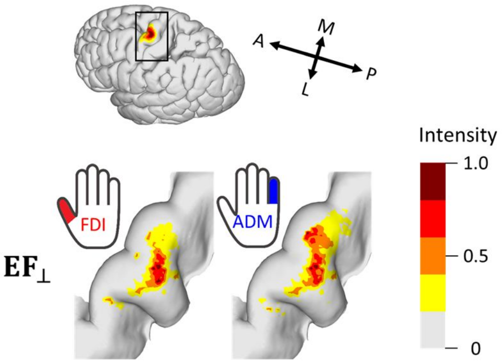

Fig. 5. Group activation map (n = 6) of two finger muscles (FDI and ADM).

(3) Human Safety

We also estimated the activation of cortical axons by the induced internal electric field to derive and discuss conservativeness of permissible field strengths in the international guidelines/standards (i.e., reference levels) for IF frequencies defined between 1 kHz to 10 MHz. Threshold-frequency curves were derived from uniform exposure of the axon nerves and compared with permissible exposure levels prescribed in ICNIRP and IEEE standard/guidelines. Fig. 6 shows that permissible external magnetic field strength and internal electric field are conservative over the frequency range. Specifically, the IEEE reference level is smaller by a factor of 10–145 and 20–75 for the internal electric field and external magnetic field, respectively in a controlled environment. ICNIRP occupational basic restriction and reference level are also smaller by a factor of 30–160 and 140–630, respectively (Gomez-Tames et al., 2019).

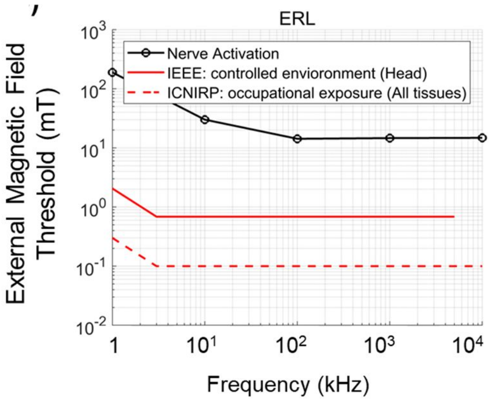

Fig. 6. Excitation thresholds for uniform exposure compared with ICNIRP guidelines and IEEE safety

In conclusion, the multiscale model permitted clarifying physical quantities of stimulation based on neural stimulation that enabled investigating stimulation protocols with high accuracy and safety.

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１．著者名 Gomez-Tames Jose、Laakso Ilkka、Murakami Takenobu、Ugawa Yoshikazu、Hirata Akimasa	４．巻 17
２．論文標題 TMS activation site estimation using multiscale realistic head models	５．発行年 2020年
３．雑誌名 Journal of Neural Engineering	６．最初と最後の頁 036004～036004
掲載論文のDOI（デジタルオブジェクト識別子） 10.1088/1741-2552/ab8ccf	査読の有無 有
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〔図書〕　計0件

〔産業財産権〕

〔その他〕

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６．研究組織

	氏名 （ローマ字氏名） （研究者番号）	所属研究機関・部局・職 （機関番号）	備考

７．科研費を使用して開催した国際研究集会

〔国際研究集会〕　計0件

８．本研究に関連して実施した国際共同研究の実施状況

共同研究相手国	相手方研究機関