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Distributions of cortical depth of the index finger region in the M1: A representative depth parameter for transcranial ultrasound stimulation

Transcranial ultrasound stimulation (TUS) is an emerging neuromodulation technique that can noninvasively stimulate both cortical and subcortical regions in humans [1–4]. Like transcranial magnetic stimulation (TMS), the first dorsal interosseous (FDI) representation in the primary motor cortex (M1) is a standard target in various basic TUS experiments. Unlike TMS, however, the focus depth for the stimulation target must be set for TUS experiments. Ideally, the depth of the stimulation target should be determined based on subject-wise brain activation using functional magnetic resonance imaging (fMRI). Unfortunately, acquiring fMRI data may be a considerable burden for most TUS researchers due to limited accessibility to scanners. Here, we determined the FDI region in the M1 (FDI-M1) using fMRI in 50 subjects. The distribution of the brain activation along the cortical depth was biased toward the surface side, with a median of 2.7 mm from the cortical surface. We further propose an easy and practical solution for the focus length parameter in TUS experiments of the FDI-M1, consisting of setting the target to 2.7 mm (or approximately 3 mm) away from the cortical surface.

1. Methods

Details of the experimental procedures are described in Supplementary Methods.

2. Results

Brain activation during the motor task was confined to the region anterior to the central sulcus in the left hemisphere (Fig. 1A–C). There was variability in the depth from the cortical surface to the FDI-M1. Based on structural images, two types of distances were measured: (1) a distance between the scalp and cortical surface ($d_{\text{scalp–cortical surface}}$) and (2) a distance between the cortical surface and FDI-M1 ($d_{\text{cortical surface–FDI-M1}}$) (Fig. 1D). Fig. 1E shows the distribution of $d_{\text{cortical surface–FDI-M1}}$. The median was 2.7 mm and 80% of the population was located within 6 mm from the cortical surface. Fig. 1F and G shows the distributions of $d_{\text{scalp–cortical surface}}$ and the distance between the scalp and FDI-M1 ($d_{\text{scalp–FDI-M1}}$), respectively (median: 15.1 mm and 17.9 mm). A correlation between $d_{\text{scalp–cortical surface}}$ and $d_{\text{cortical surface–FDI-M1}}$ was not significant ($r = 0.15$, $p = 0.30$), which suggested that two distances were independent.

The FDI-M1 was targeted by TMS with the aid of an online navigator, and resting motor threshold (RMT) and active motor threshold (AMT) were measured [5]. RMT was 54.0 ± 9.4% (mean ± SD) and AMT was 42.8 ± 8.2%. A significant correlation was observed between RMT and AMT ($r = 0.95$, $p = 2.5 \times 10^{-26}$) (Fig. 1H). These motor thresholds were similar to those in the previous independent study using the same system, where the optimal site for eliciting motor-evoked potentials was determined by systematic stimulation [6] (RMT was 50.0–59.6% and AMT was 34.6–39.7%). Thus, the fMRI activation site can reasonably be regarded as the best site for TMS.

The motor threshold tends to be greater when $d_{\text{cortical surface–FDI-M1}}$ is greater. Thus, the correlation between the motor threshold and $d_{\text{cortical surface–FDI-M1}}$ suggests that the cortical depth of the hot spot for TMS corresponds with that of the FDI-M1 determined with fMRI. The regression analyses with the distances as explanatory variables (Supplementary Results; Figs. S1 and S2) indicate that motor thresholds depended on the cortical surface–FDI-M1 distance, as reported previously [7,8], and validate the FDI-M1 detected by fMRI.

Next, we examined to what extent TUS can stimulate the FDI-M1. When the ultrasound focus was targeted 2.7 mm below the cortical surface, estimation of ultrasound intensity revealed that the FDI-M1 was effectively stimulated (Fig. 1I). When the ultrasound focus was targeted to the FDI-M1 for individual subjects, the intensity at the FDI-M1 was slightly larger than that when the focus was targeted 2.7 mm below the cortical surface commonly across subjects, but the difference was not significant ($t(49) = 1.7$, $p = 0.09$, paired t-test) (Fig. 1J). This suggests the utility of the common 2.7 mm below the cortical surface for the focus length parameter.

3. Discussion

In this study, we provided the distribution of the depth of the FDI-M1 from the cortical surface with a median of 2.7 mm. A recent consensus paper described that the primary target of TMS is the crown top or lip regions of cortical gyri [9]. In the present study, most of the fMRI-detected FDI-M1 was located at the crown top or lip regions of cortical gyri, supporting our view that fMRI activation site is stimulated by TMS. The effective ultrasound stimulation to the FDI-M1 could be achieved when the focus is set to the median depth (approximately 3 mm). It is to be noted, however, that

Abbreviations: TUS, transcranial ultrasound stimulation; TMS, transcranial magnetic stimulation; fMRI, functional magnetic resonance imaging; M1, primary motor cortex; FDI, first dorsal interossous.

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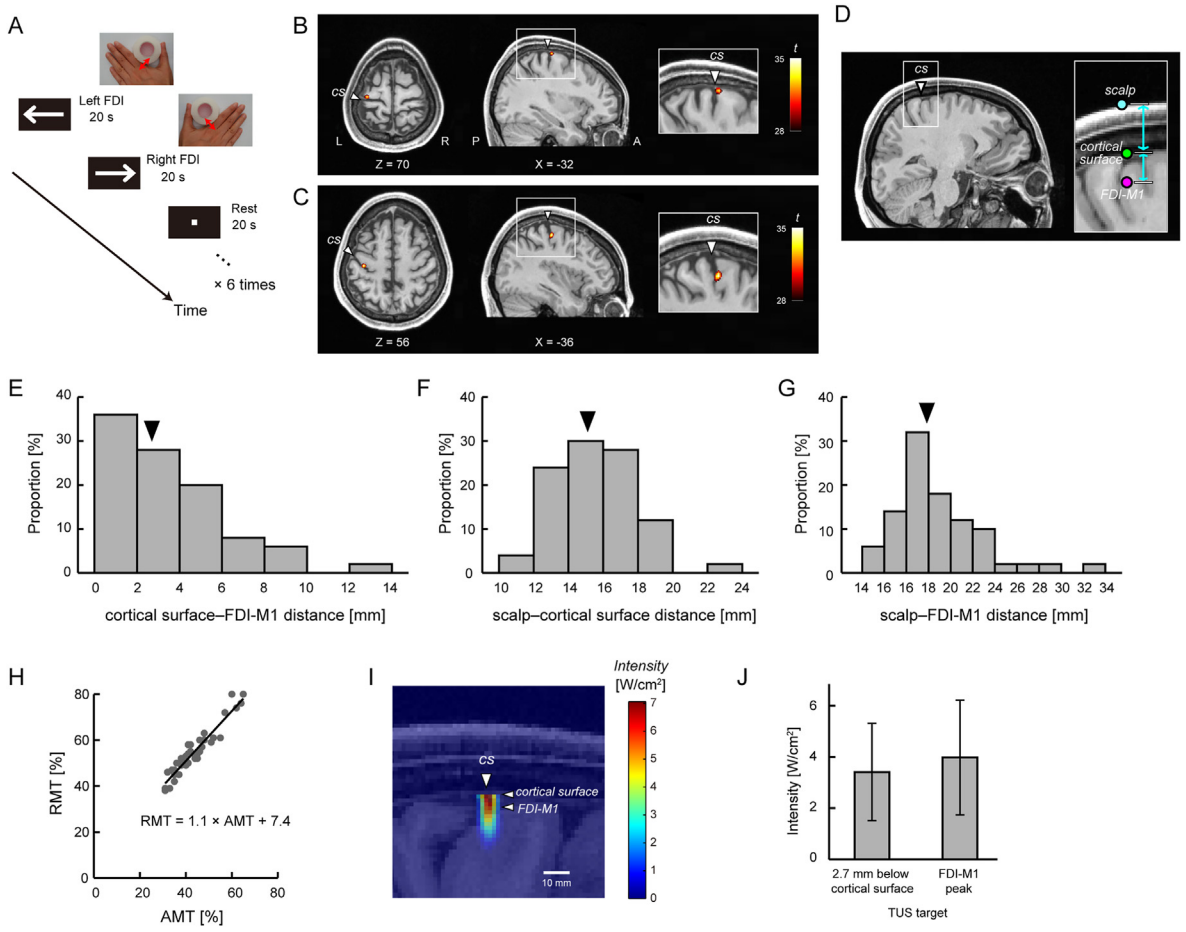

Fig. 1. FDI-M1 identification, distributions of distances, and ultrasound stimulation.
(A) A finger movement task to identify the first dorsal interosseous (FDI) representation in the primary motor cortex (M1). The subjects were instructed to move their left or right FDI at 2 Hz as the arrows blinked for 20 s each, followed by a 20-s rest. The left-right-rest cycle was repeated six times. (B, C) Brain activation maps during the motor task in representative subjects in the horizontal and parasagittal slices (moving right FDI vs. moving left FDI) in the normalized MNI space. The FDI-M1 was located at the cortical surface in B, whereas the FDI-M1 was located deeply in the central sulcus in C. The triangles indicate the central sulcus. L, left; R, right; A, anterior; P, posterior; cs, central sulcus. (D) Two types of distances measured for each subject: the distance between the scalp and the cortical surface and the distance between the cortical surface and the FDI-M1. (E, F, G) Distributions of the cortical surface–FDI-M1 (E), scalp–cortical surface (F), and scalp–FDI-M1 (G) distances. The black triangle indicates the median of the distribution. (H) A scatter plot of correlation between active motor threshold (AMT) and resting motor threshold (RMT). One dot represents data from one subject. (I) The simulated intracranial ultrasound intensity when the target location was set at 2.7 mm below the cortical surface in a representative subject. The intensity in the brain was shown for display purposes. (J) The estimated ultrasound intensity at the FDI-M1 when the TUS target location was set at 2.7 mm below the cortical surface commonly across subjects (left) and that when the TUS target location was set at the individually determined FDI-M1 (right). Error bars indicate the standard deviation.

even when the depth away from the FDI-M1 located 3 mm below the cortical surface was targeted, the FDI-M1 can be considered well stimulated [3], since the shape of the area affected by TUS is an ellipsoid in the depth direction. At the same time, in TUS experiments, the focus length must be set, and we propose an easy and practical solution for the focus length parameter.

It is reasonably acceptable to use 15 mm as the representative scalp–cortical surface distance (Fig. 1F) and, as a result, to use 18 mm as the representative scalp–FDI-M1 distance (Fig. 1G). However, the thickness of the skull may vary depending on the races [10] and individuals. Since TUS experiments require simulation of intracranial intensity and thermal effects based on structural MRI or CT images, structural MRI or CT images for each individual might be available. In such cases, it would be more appropriate to measure the scalp–cortical surface distance for each individual based on structural MRI or CT images and, as a result, to use 3 mm + individually determined scalp–cortical surface distance as the scalp–FDI-M1 distance. Ideally, the cortical surface–FDI-M1 distance for each individual can be determined with fMRI. However, fMRI may not be easily accessible to most TUS researchers. We would therefore propose setting the stimulation target to 3 mm below the cortical surface commonly across subjects or to 18 mm below the scalp commonly across subjects.

Contributors

T.O. and S.K. designed the study. T.O., K.N., A.O., S.O., K.K., S.A, Y.O., S.T., and S.K. conducted experiments. T.O. and S.K. analyzed the data. T.O. and S.K. wrote the manuscript, with comments from all authors.

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Declaration of competing interest

The authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2022.09.012.

References

[1] Legon W, Sato TF, Opitz A, Mueller J, Barbour A, Williams A, Tyler WJ. Transcranial focused ultrasound modulates the activity of primary somatosensory cortex in humans. Nat Neurosci 2014;17:322–9.
[2] Verhagen L, Gallea C, Folloni D, Constans C, Jensen DE, Ahnine H, Roumazeilles L, Santin M, Ahmed B, Lehericy S, Klein-Flügge MC, Krug K, Mars RB, Rushworth MF, Pouget P, Aubry JF, Sallet J. Offline impact of transcranial focused ultrasound on cortical activation in primates. Elife 2019;8:e40541.
[3] Zeng K, Darmani G, Fomenko A, Xia X, Tran S, Nankoo JF, Shamli Oghli Y, Wang Y, Lozano AM, Chen R. Induction of human motor cortex plasticity by theta burst transcranial ultrasound stimulation. Ann Neurol 2022;91:238–52.
[4] Nakajima K, Osada T, Ogawa A, Tanaka M, Oka S, Kamagata K, Aoki S, Oshima Y, Tanaka S, Konishi S. A causal role of anterior prefrontal-putamen circuit for reponse inhibiton revealed by transcranial ultrasound stimulation in humans. Cell Rep 2022;40:111197.
[5] Osada T, Ogawa A, Suda A, Nakajima K, Tanaka M, Oka S, Kamagata K, Aoki S, Oshima Y, Tanaka S, Hattori N, Konishi S. Parallel cognitive processing streams in human prefrontal cortex: parsing areal-level brain network for response inhibition. Cell Rep 2021;36:109732.
[6] Hamada M, Terao Y, Hanajima R, Shirota Y, Nakatani-Enomoto S, Furubayashi T, Matsumoto H, Ugawa Y. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation. J Physiol 2008;586:3927–47.
[7] Stokes MG, Chambers CD, Gould IC, Henderson TR, Janko NE, Allen NB, Mattingley JB. Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. J Neurophysiol 2005;94:4520–7.
[8] Cai W, George JS, Chambers CD, Stokes MG, Verbruggen F, Aron AR. Stimulating deep cortical structures with the batwing coil: how to determine the intensity for transcranial magnetic stimulation using coil-cortex distance. J Neurosci Methods 2012;204:238–41.
[9] Siebner HR, Funke K, Aberra AS, Antal A, Bestmann S, Chen R, Classen J, Davare M, Di Lazzaro V, Fox PT, Hallett M, Karabanov AN, Kesselheim J, Beck MM, Koch G, Liebetanz D, Meunier S, Miniussi C, Paulus W, Peterchev AV, Popa T, Ridding MC, Thielscher A, Ziemann U, Rothwell JC, Ugawa Y. Transcranial magnetic stimulation of the brain: what is stimulated? - a consensus and critical position paper. Clin Neurophysiol 2022;140:59–97.
[10] Adeloye A, Kattan KR, Silverman FN. Thickness of the normal skull in the American blacks and whites. Am J Phys Anthropol 1975;43:23–30.

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