Research paper

Coil orientation affects pain sensation during single-pulse transcranial magnetic stimulation over Broca's area

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ABSTRACT

Objective: Pain sensation at the site of stimulation is a side effect of transcranial magnetic stimulation (TMS). The purpose of this study was to investigate how or whether the coil orientation affected TMS-induced pain on Broca's area (BA) or primary motor cortex (M1).
Methods: In Experiment 1, we measured pain thresholds during single-pulse TMS delivered over BA or left M1 at seven coil orientation angles ($-90°$ to $90°$, in $30°$ increments) relative to the posterior-anterior (PA) orientation. In Experiment 2, we evaluated subjective pain intensity when delivering TMS at an intensity of 110% of the resting motor threshold, which is commonly used in conventional TMS studies.
Results: In Experiment 1, we found a significant relationship between coil orientation and pain thresholds during BA stimulation but not M1 stimulation. During BA stimulation, pain thresholds were significantly lower when the coil orientation was $30°$ upward ($-30°$ condition) relative to the PA orientation compared with $60°$ downward ($60°$ condition). In Experiment 2, pain sensations were significantly stronger in the $-30°$ condition compared with those in the $60°$ condition. We also confirmed that the averaged location of pain on the head in both conditions were more than 25 mm from the left lateral orbital rim.
Conclusions: The coil orientation of TMS over BA affects pain sensations. This might be attributable to the activation of nociceptors and nociceptive fibers in the muscle tissues above BA, rather than the orbicularis oculi muscle.
Significance: Although the influence of coil orientation on the TMS efficacy is unclear, this study suggests that manipulating the orientation of the TMS coil may be helpful in reducing pain when applying TMS to BA.
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1. Introduction

Transcranial magnetic stimulation (TMS) is a neuromodulatory technique that is widely used to explore brain functions in basic research (Valero-Cabré et al., 2017; Kobayashi and Pascual-Leone, 2003; Rossini et al., 2015; Tanaka et al., 2010). Although TMS is a safe tool, it has some minor side effects. One of these is the sensation of pain occurring on the scalp below and/or around the stimulation site (Rossi et al., 2009; Wassermann, 1998; Loo et al., 2008). TMS induces an electric field in the head by rapidly and strongly changing the magnetic field via current flowing through the coil in a non-invasive manner, which can activate brain neurons (Rossi et al., 2009). However, this also activates nociceptors and nociceptive fibers in the muscle and skin tissues, which leads to pain sensations (Rossi et al., 2009).

Recently, we quantitatively evaluated pain thresholds during the delivery of single-pulse TMS over Broca's area (BA) and the primary motor area (M1) and found that pain thresholds for both BA and M1 were significantly lower than the motor threshold (MT) as measured via motor evoked potentials (MEPs; Tani et al., 2020). Given that a stimulus intensity that is equivalent to or greater than the MT is often used in TMS experiments (Rossini et al., 2015), this result suggests that most experiments might evoke pain sensations at the site of stimulation. Because such pain interferes with the completion of experiments (Wassermann, 1998; Satow et al., 2002) and influences task performance (Abler et al., 2005; Meteyard and Holmes, 2018; Holmes and Meteyard, 2018), accurate evaluation of the relationship between brain and behavior using TMS relies on effective brain stimulation with as little pain as possible.

One possible solution to control TMS-induced pain involves manipulating the orientation of the TMS coil relative to the head. Because TMS-induced electric fields depend on coil orientation

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and position, coil orientation is likely to modulate the influence of TMS on the brain and other tissues, such as the skin and muscles (Gomez-Tames et al., 2018; Laakso et al., 2014; Janssen et al., 2015). Although a previous study revealed that coil orientation did not affect scalp-pain induced by single-pulse TMS (Meteyard and Holmes, 2018), this study had disadvantages, such as few coil orientation conditions and unclear stimulation cortical sites due to the use of 10–20 electrode placement. To address this issue, in the present study, we precisely identified BA and M1 using a navigation system and evaluated coil orientation dependency of pain thresholds during single-pulse TMS using seven coil directions (Experiment 1). We found coil orientation dependency only for BA, such that pain thresholds were significantly lower when the coil orientation was 30° upward relative to the posterior-anterior (PA) coil orientation versus 60° downward. In Experiment 2, we confirmed whether this coil orientation dependency was also present when subjective pain intensity was measured during BA stimulation with a stimulation intensity above the individual MTs, which is commonly used in TMS experiments.

2. Experiment 1

2.1. Material and methods

2.1.1. Participants

Fifteen healthy participants were recruited for each of the BA and M1 conditions (*BA*, 10 men and five women, 22.1 ± 2.9 years; *M1*, 11 men and four women, 22.0 ± 1.0 years). All participants provided written informed consent prior to the experiment. This study was approved by the ethical committee of Hamamatsu University School of Medicine and was conducted according to the Declaration of Helsinki. All participants in the present study had previously participated in our previous study (Tani et al., 2020). A part of the behavioral data reported here was used in our previous computational study (Gomez-Tames et al., 2021).

2.1.2. Identification of the stimulation site and coil orientation

We used a magnetic resonance imaging (MRI)-based navigation method to accurately deliver TMS over targeted cortical locations according to the TMS coil orientation. Prior to the TMS experiment, each participant underwent a T1-weighted MRI head scan with a 3T scanner (Discovery MR750 3.0T, GE Healthcare Japan, Japan). The parameters for the MRI scan were as follows: repetition time = 7.2 ms, echo time = 2.1 ms, flip angle = 15°, field of view = 256 mm × 256 mm, voxel size = 1 mm × 1 mm × 1 mm. Based on the obtained T1 image, we built a three-dimensional cortical surface model of individual participants using a frameless navigation system (Brainsight, Rogue Research Inc, Canada) and anatomically identified the stimulation sites (BA or left M1) on the constructed model.

The stimulation sites for BA and left M1 in this study were left Brodmann area 44 and the center of the hand knob (Yousry et al., 1997) area on Brodmann area 4, respectively. We used seven orientations for the magnetic coil on each stimulation site: −90°, −60°, −30°, 0°, 30°, 60°, and 90° relative to the reference coil orientations. The reference orientations were defined as the PA orientation for BA, and 45° inward relative to the PA orientation for M1, as shown in Fig. 1. This range of coil orientations is often used in basic and clinical TMS studies (Epstein et al., 1996; Naeser et al., 2005; Volz et al., 2015; Hamada et al., 2013).

2.1.3. TMS delivery

We delivered monophasic single-pulse TMS using a Magstim stimulator (Magstim 200, Magstim Co. Ltd, UK) with a figure-eight coil (60 mm diameter; Magstim Co. Ltd, UK). In this experimental setting, the current flow induced in the head was mainly travelling in an outward direction parallel to the midline between the two magnetic coils (Ueno et al., 1988). Using the navigation system, we monitored the position and orientation of the TMS coil relative to the participant's head by capturing the positions of reflection markers mounted on the head and coil with a camera. During stimulation, we ensured that the coil was accurately located and orientated by watching a PC display.

2.1.4. Procedure

We used a single-blind design, and participants were not informed of the study's objective or hypothesis. The procedure was based on our previous work (Tani et al., 2020). Participants sat in a reclining chair and were asked to relax. They were instructed to verbally report the presence or absence of scalp pain after each stimulation. No specific definition was given for the type of pain. To determine the pain threshold, we used an adaptive staircase method. Specifically, we lowered the intensity of the TMS when the participant reported pain and raised the intensity when they reported the absence of pain. The pain threshold was defined as the minimum stimulation intensity that induced pain in at least 5 of 10 trials. The starting TMS intensity for each participant was set at approximately 5% lower than the individual pain thresholds obtained in our previous study (Tani et al., 2020). After measuring the pain threshold for one coil orientation, we proceeded to the next condition.

Each participant completed the experiment on two separate days. On each day, pain thresholds for the seven coil-orientation conditions were measured in a randomized order. The order of the coil-orientation conditions on the first and second days was set in reverse. We averaged the pain thresholds from the two days for each coil-orientation condition and used these as representative values for each participant. This procedure eliminated the strong influence of the order of the coil-orientation conditions on pain thresholds due to sensory adaptation or fatigue.

2.1.5. Data analysis

We assessed the pain thresholds for each coil-orientation condition. Because pain thresholds in one coil-orientation (−30°) condition for BA were not normally distributed across participants (Shapiro-Wilk tests, $p > 0.05$), we used Friedman tests to compare the pain thresholds between coil-orientation conditions. The significance level was set at $p < 0.05$.

2.2. Results

None of the participants complained of headache or mood swings during or after the experiment.

Fig. 2 shows the pain thresholds for each coil-orientation condition in BA and M1. Comparing the pain thresholds between BA and M1 revealed that BA pain thresholds were significantly lower than M1 pain thresholds (Mann-Whitney U test, $z = 3.4$, $p < 0.001$).

Friedman tests revealed a significant difference between coil-orientation conditions for BA ($\chi_6^2 = 26.28$, $p < 0.001$), but not for M1 ($\chi_6^2 = 4.78$, $p = 0.57$). This indicates that the coil orientation dependency of pain thresholds was observed only in BA. Post-hoc Schéffe tests for BA showed that pain thresholds for the −30° condition were lower than those for the 60° condition (two-tailed $p < 0.05$). In 14 of the participants (i.e., 93%), BA pain thresholds were lower in the −30° condition than in the 60° condition.

3. Experiment 2

In this experiment, we examined whether the coil orientation dependency was observed when BA stimulation was conducted at an intensity above the MT.
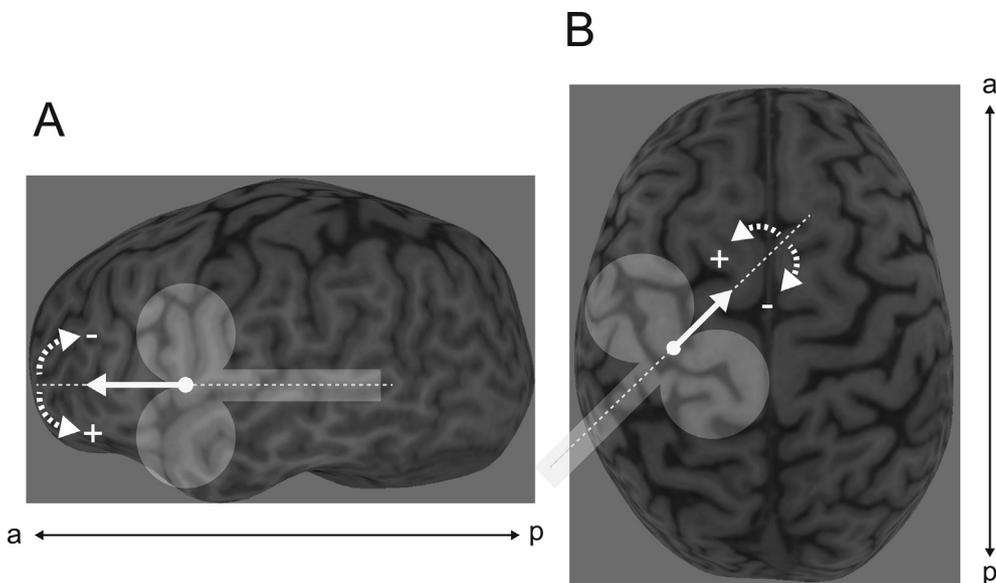
Fig. 1. Illustration of coil-orientation condition in BA (A) and left M1 (B). The reference coil orientations in BA and left M1 were shown on a 3D cortical surface model of a single participant constructed using navigation software. The characters "a" and "p" represent the anterior and posterior orientation of the head, respectively. Solid arrows denote the dominant direction of electric currents induced by monophasic, single-pulse TMS. Each coil orientation was determined by rotation angles relative to these reference orientations, as represented by dotted arrows.
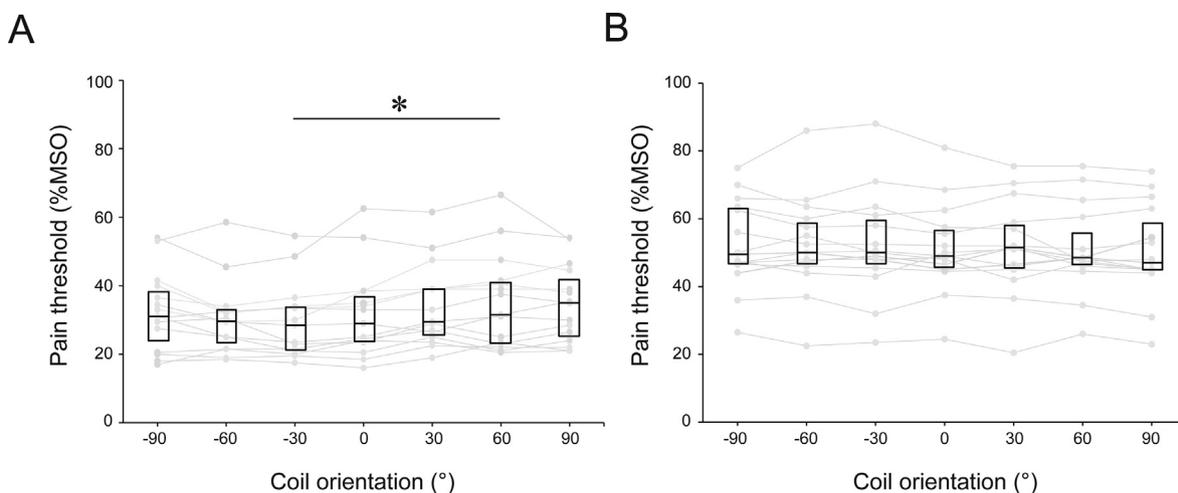

Fig. 2. Pain thresholds for each coil orientation in BA (A) and M1 (B) in Experiment 1. Gray lines represent the mean values for each participant. The horizontal line within the black box and the lower and upper ends of boxes represent the median, first quartile, and third quartile of each threshold, respectively. *$p < 0.05$.

3.1. Material and methods

3.1.1. Participants

We recruited 10 healthy participants (four women, age 24.0 ± 3.8 years) for this experiment. The sample size was calculated for the Wilcoxon signed-rank test according to the following assumption: $dz = 0.94$, $p = 0.05$ (one-tailed), $1 - \beta = 0.8$, based on BA pain thresholds in the $-30°$ and $60°$ conditions in Experiment 1 (mean ± standard deviation [SD], 29.7 ± 10.8 and 35.1 ± 13.8 for the $-30°$ and $60°$ conditions, respectively; correlation, $r = 0.93$).

3.1.2. Assessment of subjective pain intensity and painful location

The experimental set-up for assessing subjective pain intensity was the same as that in Experiment 1.

For stimulation of BA, the TMS intensity was determined based on individual resting MTs (rMTs). We measured MEPs from the right first dorsal interosseous muscle (FDI) using an electromyography (EMG) unit during single-pulse TMS applied to the left pri-

mary motor cortex (M1). The stimulation site was anatomically determined as the center of the hand knob (Yousry et al., 1997). The rMT was determined as the minimum intensity that elicited MEPs with a peak-to-peak amplitude of 50 µV or greater in at least 5 of 10 trials.

Subsequently, we assessed subjective pain intensity during BA stimulation with a coil angle of $-30°$ or $60°$ relative to the PA orientation. After each stimulation, participants verbally reported the subjective pain intensity using an 11-point numerical rating scale (NRS) ranging from 0 (no pain) to 10 (maximum pain). The TMS intensity was set at 110% of the rMT. Each participant completed 10 trials for each coil-orientation condition ($-30°$ or $60°$), i.e., 20 trials in total. The order of coil-orientation conditions was randomized for each participant.

Additionally, to confirm whether TMS-induced pain could be attributed to the tissues in the temporal area or around the eyes, we asked five of the participants to indicate the specific location on their head where they had experienced pain. They pointed to
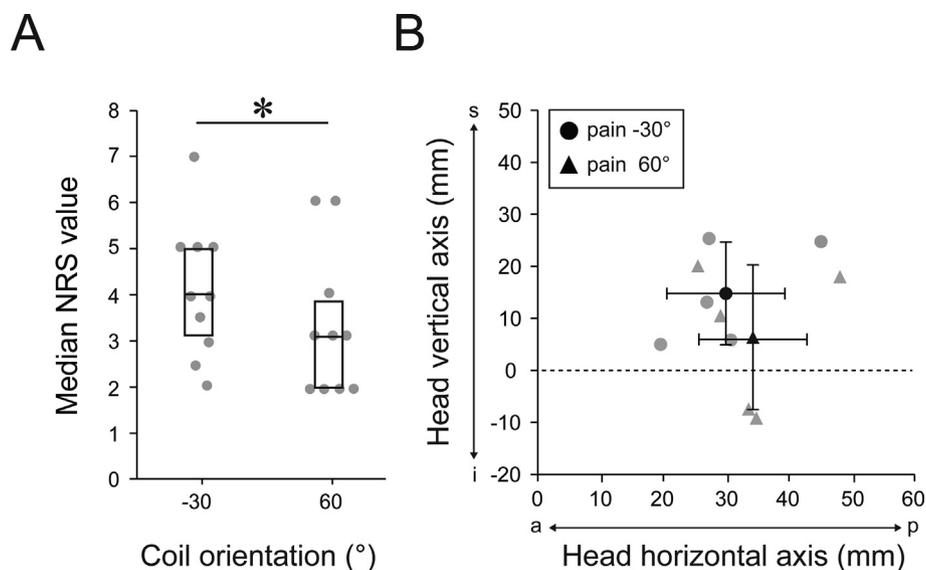
Fig. 3. Subjective pain intensity (A) and painful location (B) in Experiment 2. (A) NRS values in the −30° and 60° conditions. Gray-colored dots represent the median values for each participant. Horizontal lines within the black boxes and the lower and upper ends of the boxes represent the median, first quartile, and third quartile, respectively, of pain intensity across all participants. *: $p < 0.05$ (B) The coordinates of the painful locations in the −30° (*circle*) and 60° conditions (*triangle*) seen from the left side of the participant's head. The origin coincides with the left lateral orbital rim. Grey and black symbols represent mean values for each participant and across participants, respectively. Error bars represent standard deviations across participants.

the location with their index finger after reporting their subjective pain intensity. The spatial coordinates of each painful location were recorded using the Brainsight navigation system.

3.1.3. Data analysis

For subjective pain intensity, the median NRS score for each of the 10 trials was calculated as a representative value for each coil-orientation condition in each participant. We compared the NRS scores between the −30° and 60° conditions using a Wilcoxson signed rank test.

The coordinates of the painful locations in each trial were transformed into a coordinate system with the origin at the left lateral orbital rim. Then, the individual mean coordinates for the 10 trials were calculated for the −30° and 60° conditions and averaged across participants.

3.2. Results

Median (first and third quartiles) NRS values were 4.0 (3.1 and 5.0) and 3.0 (2.0 and 3.8) for the −30° and 60° conditions, respectively (Fig. 3A). A Wilcoxon signed rank test revealed that the NRS values were significantly higher in the −30° condition compared with those in the 60° condition ($z = 1.68$, one-tailed, $p < 0.05$). At the individual level, seven participants showed a higher NRS value for the −30° condition than for the 60° condition, and two participants showed equivalent values for both conditions in 10 participants. The difference in NRS values between the two conditions (−30° condition minus the 60° condition) ranged from −2.5 to 3.0.

Fig. 3B shows the mean coordinates of the painful locations in the −30° and 60° conditions for each participant and across the five participants. The group-mean (±SD) painful locations were 29.9 ± 9.4 mm (horizontal) and 14.8 ± 9.9 mm (vertical) in the −30° condition and 34.2 ± 8.6 mm (horizontal) and 6.39 ± 13.9 mm (vertical) in the 60° condition.

4. Discussion

In the present study, we evaluated the coil orientation dependency of pain sensation induced by single-pulse TMS. In Experiment 1, we found that the coil orientation significantly affected

pain thresholds during BA stimulation, but not M1 stimulation. During BA stimulation, pain thresholds were significantly lower when the coil orientation was −30° relative to the PA orientation than when it was 60°. In Experiment 2, we confirmed that pain sensations were significantly stronger in the −30° condition than in the 60° condition when TMS over BA was applied at 110% of the rMTs, which is commonly used in TMS studies.

Although some degree of inter-participant variability in pain thresholds was observed, pain thresholds were lower in the −30° condition than in the 60° condition for 93% of participants. The results of Experiment 2 showed a similar trend in terms of subjective pain intensity (i.e., a stronger pain sensation in the −30° condition). These results indicate that the effect of coil orientation on pain sensation in BA is a relatively robust phenomenon.

Which tissues are responsible for the coil orientation dependency of pain sensations in BA? To determine whether TMS-induced pain was derived from the tissues in the temporal area or those around the eyes, we asked the participants in Experiment 2 to identify the location on their head where they felt the maximum levels of pain during BA stimulation. We found that the averaged location of pain in both the −30° and 60° conditions was approximately 30 mm away from the left lateral orbital rim (Fig. 3B). Given that the orbicularis oculi muscle is distributed within 25 mm of the left lateral orbital rim (Costin et al., 2014), our results suggest that the observed coil orientation dependency in BA is attributed to the tissues in the temporal area, and not those around the eyes.

Among the tissues in the temporal area, the temporalis muscle is thickly distributed above BA (Netter, 2014), and is therefore likely to be a main source of TMS-induced pain. We speculate that TMS at a coil angle of 30° upward relative to the PA orientation might more readily activate the nociceptors and nociceptive fibers within the temporalis muscle, which would lead to a stronger pain sensation. However, other thin muscle tissues, such as the temporoparietal and auricular muscles (Netter, 2014) might also contribute to the pain sensation. To identify the specific muscle tissues involved in pain sensations during TMS over BA, future experiments could measure the activation of the head muscles using EMG or inhibit local pain with an analgesic.

The findings of the present study are significant in two ways. First, as shown in Fig. 3A, several participants reported relatively

strong pain sensations during TMS. For such participants and those who value avoidance of side-effects, the present finding provides an additional option to experience reduced pain sensations during TMS. Second, previous studies have reported that single-pulse TMS-induced pain influences task performance as measured by accuracy and reaction time (Abler et al., 2005; Meteyard and Holmes, 2018; Holmes and Meteyard, 2018). Thus, manipulation of coil orientation during single-pulse TMS may attenuate undesirable effects, which enables more precise evaluation of BA function in basic research. Although coil orientation during rTMS was not tested in the present study, we speculate that similar coil orientation dependency of pain would be observed for rTMS because both single-pulse TMS and rTMS activate nociceptive fibers in the same muscle tissues on the head.

Two limitations must be noted. First, the experimenter was not blinded to coil orientation during the experiments. Therefore, experimenter bias may have influenced the present results to some extent. Second, the effect of coil orientation on TMS efficacy was not assessed. It has been shown that coil orientation influences the effect of BA-TMS on language function (Sollmann et al., 2018). Therefore, future studies that quantitatively evaluate both pain and TMS efficacy are needed to determine the optimal coil orientation for BA stimulation.

5. Conclusion

Coil orientation dependency was identified for TMS-induced pain sensations over BA. Although the influence of coil orientation on the TMS efficacy is unclear, this finding suggests that the manipulation of coil orientation may be effective for reducing pain sensations at the site of stimulation when targeting BA.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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