Exp Brain Res (1997) 115:541–545

RESEARCH NOTE

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Shortening of simple reaction time by peripheral electrical and submotor-threshold magnetic cortical stimulation

Received: 15 July 1996 / Accepted: 25 February 1997

Abstract Subthreshold transcranial magnetic stimulation (TMS) over the motor cortex can shorten the simple reaction time in contralateral arm muscles if the cortical shock is given at about the same time as the reaction stimulus. The present experiments were designed to investigate whether this phenomenon is due to a specific facilitatory effect on cortical circuitry. The simple visual reaction time was shortened by 20–50 ms when subthreshold TMS was given over the contralateral motor cortex. Reaction time was reduced to the same level whether the magnetic stimulus was given over the bilateral motor cortices or over other points on the scalp (Cz, Pz). Indeed, similar effects could be seen with conventional electrical stimulation over the neck, or even when the coil was discharged (giving a click sound) near the head. We conclude that much of the effect of TMS on simple reaction time is due to intersensory facilitation, although part of it may be ascribed to a specific effect on the excitability of motor cortex.

Key words Simple reaction time · Electrical stimulation · Transcranial magnetic stimulation · Intersensory facilitation · Motor cortex · Human

Introduction

Pascual-Leone et al. (1992, 1994a, b) reported that transcranial magnetic stimulation (TMS) delivered over the motor cortex below threshold for evoking a muscle twitch could shorten simple reaction time (SRT) to a visual "go" signal in normal subjects and also (to a greater extent) in patients with Parkinson's disease (PD). They suggested that TMS had a specific facilitatory influence on the motor cortex and further argued that chronic electrical stimulation of the motor cortex by implanted subdural electrodes would be therapeutic for akinesia in PD patients.

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On the other hand, it is well known that SRT can be shortened if the cue signal is accompanied by a second stimulus of various modalities. This phenomenon is known as intersensory facilitation (IF; for extensive review, see Nickerson 1973). The conjunction of the visual reaction stimulus and TMS given over the scalp (which produces local sensation as well as an auditory click in addition to an effect on the central nervous system) is typical of the type of combination usually used to evoke IF. However, Pascual-Leone et al. thought this was an unlikely explanation for their results, since experiments in which TMS was given over other parts of the scalp failed to show any effect on SRT. Although this result appeared to support the hypothesis of a specific effect on the motor cortex, it was surprising that there was such a complete lack of IF in the control studies: the SRT to a visual cue signal given alone was exactly the same as when the signal was paired with TMS over cortical regions other than the motor cortex. In the present paper, we have reinvestigated this phenomenon and found that such stimulus pairings usually give quite strong IF, and that SRT was reduced to a similar level regardless of the site where TMS was given.

Materials and methods

Experimental setup

The following experiments were done with the approval of the Ethics Committee of the University of Tokyo. Eight normal subjects participated in the study, and all gave their informed consent prior to the experiments. Each subject sat on a chair, with their forearms resting on padded supports, and made extension of the right wrist as quickly as possible in response to the illumination of a small red light-emitting diode (LED), 2.5 mm in diameter, placed 50 cm in front of the face. EMG recordings were made from surface electrodes placed over the belly and tendon of the wrist extensor extensor carpi radialis (ECR) and its antagonist flexor carpi ulnaris (FCU). The signals were amplified through filters set at 100 Hz and 3 kHz then full-wave rectified (DP-1200; NEC San-Ei, Japan). SRT was defined as the interval between the light signal and the onset of EMG in ECR. At least 20 practice trials were given prior to each session until SRT became stable.

First, we reinvestigated the effect of subthreshold TMS on SRT reported by Pascual-Leone et al. (1992, 1994a). Each session consist-

ed of three types of trials intermixed in a randomized order: trials with light signals alone (test trials), trials in which TMS was given in combination with the light signal at various delays (conditioned trials), and catch trials in which TMS was given alone. White noise was given through a headphone in order to mask the click sounds accompanying TMS. The delay was defined as the time of TMS relative to the time of the light signal. For negative values, TMS preceded the light signals, and for positive values they followed them. In catch trials, comprising 10–15% of the total trials, subjects were required *not* to respond, which ensured that they always responded to the light signals and not to TMS. If the subject inadvertently responded in a catch trial, all responses in that session were discarded. Three subjects performed the same task without masking sounds, but the results for these subjects will be presented in combination, because the amount of SRT shortening was almost identical whether the task was perfomed with or without masking sound.

TMS was given with a magnetic stimulator (Magstim 200; Magstim, UK) through a figure-eight-shaped coil (internal diameter 4.5 cm) for focal stimulation, with the coil current at the center flowing from anterior to posterior or from posterior to anterior. The intensity of subthreshold TMS was fixed at the highest intensity with which no MEPs were elicited in ECR during slight voluntary contraction (10% of maximal voluntary contraction) or during the experimental sessions when the stimuli were delivered over the forearm motor area contralateral to the responding hand. The intensity came within 30–50% of the maximal output of the stimulator. The center of coil was held over the forearm motor areas of both hemispheres, the vertex (Cz in the international 10–20 system), and the parietal area (Pz), respectively, in four separate sessions. In a separate session performed by three subjects, TMS was delivered randomly over the ipsi- or contralateral forearm motor areas by using two coils.

To investigate the effect of click sounds accompanying the magnetic pulse on SRT, three subjects performed another session while the magnetic coil was held *off* the scalp, 10 cm above Pz without masking.

Subsequently, the effect of peripheral electrical stimulation (ES) on SRT was investigated. The experimental paradigm was the same as above, except that ES was used instead of TMS. In preliminary studies, we tried stimuli on such parts of the skin as the neck, forearm, and leg. The neck was chosen because the most obvious effect was obtained with stimuli on the skin of the mantle area. The electrical stimulus, a single 0.2-ms-square pulse, was given by a peripheral nerve stimulator (Electronic stimulator 3F46, NEC San-Ei, Japan), the intensity being set at 1.5 to 2 times the sensory threshold.

Statistical analysis

We collected 15–20 test trials and ten conditioned trials for each delay, and the mean and standard deviation of SRT were calculated separately for control trials and conditioned trials at each delay. In each subject, the SRTs at various delays were compared statistically with the control SRT in the same session using Student's *t*-test. As a result, mean SRTs in conditioned trials were on the whole significantly shorter than or at the same level as those in control trials between delays –50 ms and 150 ms. Therefore the shortening of SRT (dSRT) was calculated by subtracting the mean SRT in conditioned trials from that of control trials in the same session. Thereafter a time course was constructed by plotting the dSRT (ordinate) against the delay (abscissa). For statistical analysis of dSRT in the sessions using TMS (with and without masking sounds), repeated-measures ANOVA was first performed with two factors, delay of TMS (0, 50, 100 ms) and site of stimulation (motor cortex, Cz and Pz). Since the time courses were almost identical among the three sites (see Results), we pooled the results for each site at each delay and proceeded to compare how the time courses of dSRT differed with various types of stimulation (TMS, ES, and click sounds when the coil was delivered *off* the scalp). ANOVA was again performed with factors of delay and type of stimulation. dSRTs at delay –50 ms were excluded from analysis because they were quite variable among trials and across subjects. This might be due to hesitant reactions induced by the stimulus preceding the light "go" signal (See Discussion).

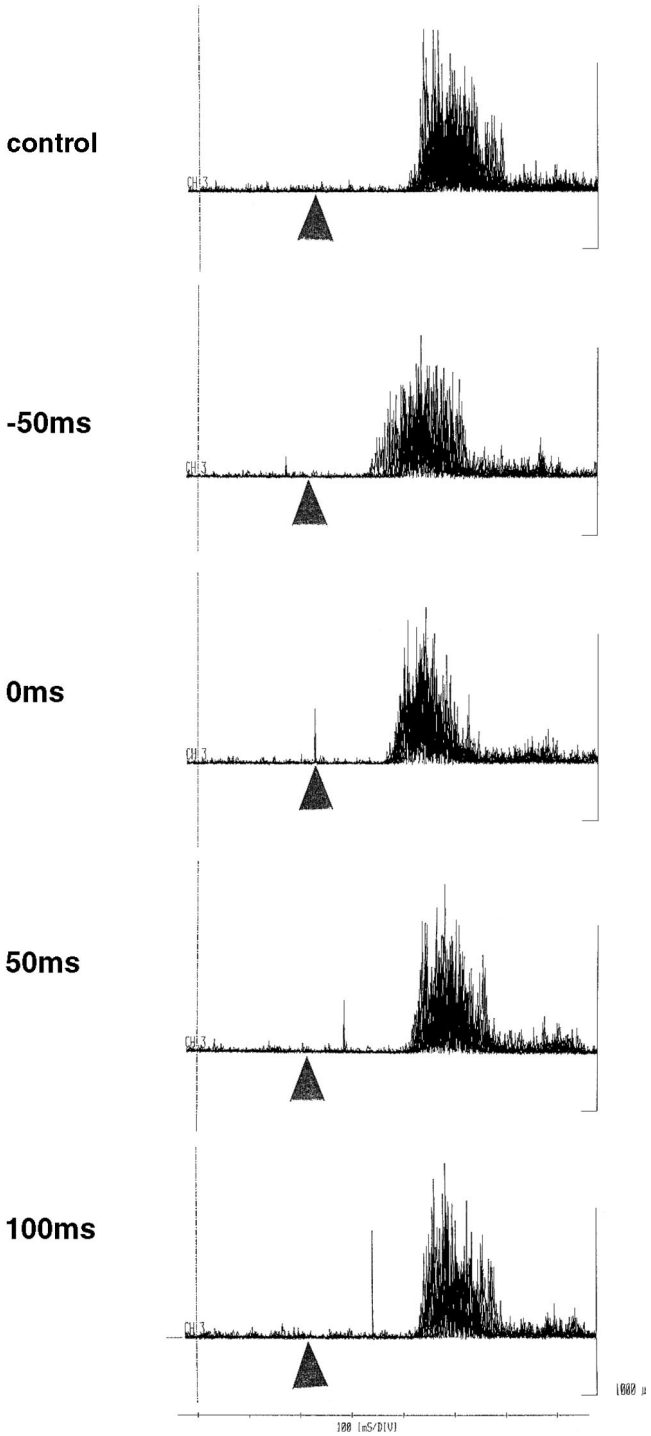

Fig. 1 Changes in EMG onset caused by subthreshold transcranial magnetic stimulation (TMS) in a subject. The coil was placed over the motor cortex contralateral to the responding hand, with the coil current flowing from anterior to posterior. The *top trace* shows the superimposition of 15 trials in response to light signals alone (control trials). In the other traces, light signals were given in combination with TMS, each at the delay shown on the *left* (superimposition of ten trials). *Triangles* indicate the time of the light signal, and the spiky artifacts give the time of TMS. The greatest shortening (about 50 ms) occurred at a delay between –50 and 0 ms

Results

Figure 1 shows the changes in EMG onset in a subject when TMS was given over the motor cortex contralateral to the responding hand at various delays (coil current at the center flowing from anterior to posterior). As compared to control trials (top trace), EMG onset was earlier at delays of –50 ms and 0 ms. SRT was almost equal to the control level at delays of 50 ms and 100 ms, while it was slightly longer at delay –100 ms (data not shown). When dSRT was plotted against the delay, maximum reduction occurred at a delay between –50 and 0 ms (Fig. 2A, unfilled squares), where it became 40–60 ms shorter than control level. SRT gradually approached control level by a delay of 200 ms. Since the time course of shortening was identical also when we used a coil current flowing from posterior to anterior, we will combine the results for both current directions.

This trend was common to all subjects investigated. The mean control SRT for these subjects was 198.7 ± 26.8 ms (mean ± standard error) and significant reduction of SRT was noted at delays 0, 50, and 100 ms in all these subjects (Student's *t*-test, $P<0.05$). Thus dSRT at each delay was averaged across the subjects and was plotted against the delay (Fig. 2B). Again, with TMS delivered over the motor area contralateral to the reacting hand, the maximal shortening was about 40 ms, occurring at a delay of around 0 ms. SRT increased both before and after this delay, approaching control level by a delay of 100–200 ms (at delay –50 ms, 36.5 ± 14.7 ms; at 0 ms, 43.4 ± 21.4 ms; at 50 ms, 20.7 ± 12.4 ms; at 100 ms, 4.9 ± 10.8 ms). The shortening effect was similarly observed also when the magnetic coil was held over Pz or Cz (at a delay of –50 ms, dSRT = 39.1 ± 6.2 ms, 5.9 ± 16.5 ms; at 0 ms, dSRT = 48.4 ± 9.7 ms, 41.6 ± 7.5 ms; at 50 ms, dSRT = 15.3 ± 1.80 ms, 23.5 ± 10.9 ms; at 100 ms, dSRT = 9.5 ± 3.5 ms, 7.2 ± 4.7 ms; over Pz and Cz, respectively). ANOVA performed with 2 factors, delay and site of TMS, showed that the effect of delay was significant ($F = 26.479$, $P<0.001$), but there was no interaction between factors delay and site (delay × site: $F = 0.418$, $P = 0.7929$). This implied that the time course of dSRT did not differ statistically among the three sites. In three of the subjects, a similar shortening was observed also when the coil was placed over the motor cortices ipsi- and contralateral to the responding hand (at delay –50 ms, dSRT = –0.8 ± 13.1 ms, 8.1 ± 3.1 ms; at delay –20 ms, dSRT = 36.7 ± 5.4 ms, 24.6 ± 5.1 ms; at delay 0 ms, dSRT = 15.7 ± 4.8 ms, 7.9 ± 5.3 ms; over the ipsi- and contralateral motor cortex). There was no difference between the time courses for the bilateral motor cortices (effect of delay: $F = 7.632$, $P = 0.018$, delay × site; ipsi- and contralateral: $F = 1.054$, $P = 0.3597$)

A similar shortening was also noted when the coil was held *off* the scalp. The time courses of dSRT did not differ statistically from that for TMS delivered *on* the scalp (at delay –50 ms, dSRT = 26.1 ± 7.0 ms; at 0 ms, dSRT = 39.5 ± 6.7 ms; at 50 ms, dSRT = 18.0 ± 4.3 ms; at 100 ms, dSRT = 8.4 ± 3.5 ms, effect of delay: $F = 13.195$, $P<0.0001$, delay × type of stimulation: $F = 2.317$, $P = 0.0981$). This suggests that the click sound of TMS could serve as an additional cue for the reaction.

A similar shortening of SRT was noted when ES was given to the neck skin. SRT became shortest at a delay between –50 and 0 ms, and increased before and after this delay. Here again, the time course of dSRT was quite similar to that shown in Fig. 2 in one subject (Fig. 3A) and in five

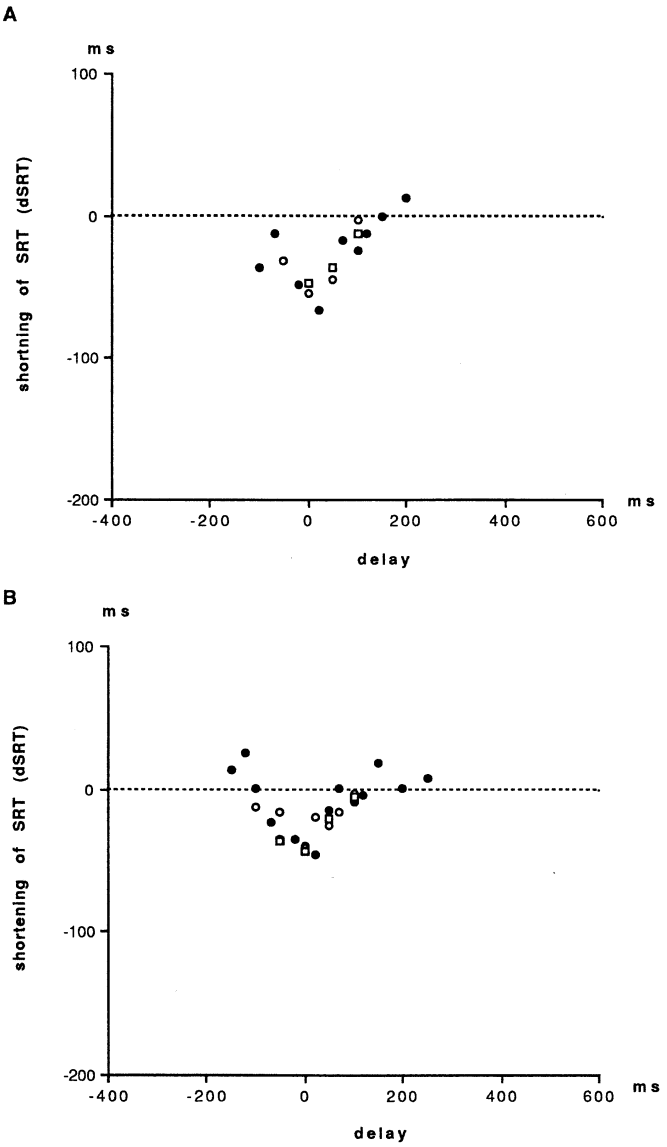

Fig. 2A, B Shortening of the simple reaction time (SRT) by subthreshold TMS. **A** dSRT was plotted as a function of the delay in a subject. The *circles*, *filled circles*, and *unfilled squares* each stand for the session in which the coil was placed over Pz, Cz, or over the motor cortex contralateral to the responding hand. SRT was shortest at around delay 0 ms, becoming shorter than control level by 40–60 ms. **B** dSRT averaged across five subjects was plotted against the delay. The time course was identical whether the coil was held over Cz, Pz, or over the motor areas or contralateral to the responding hand

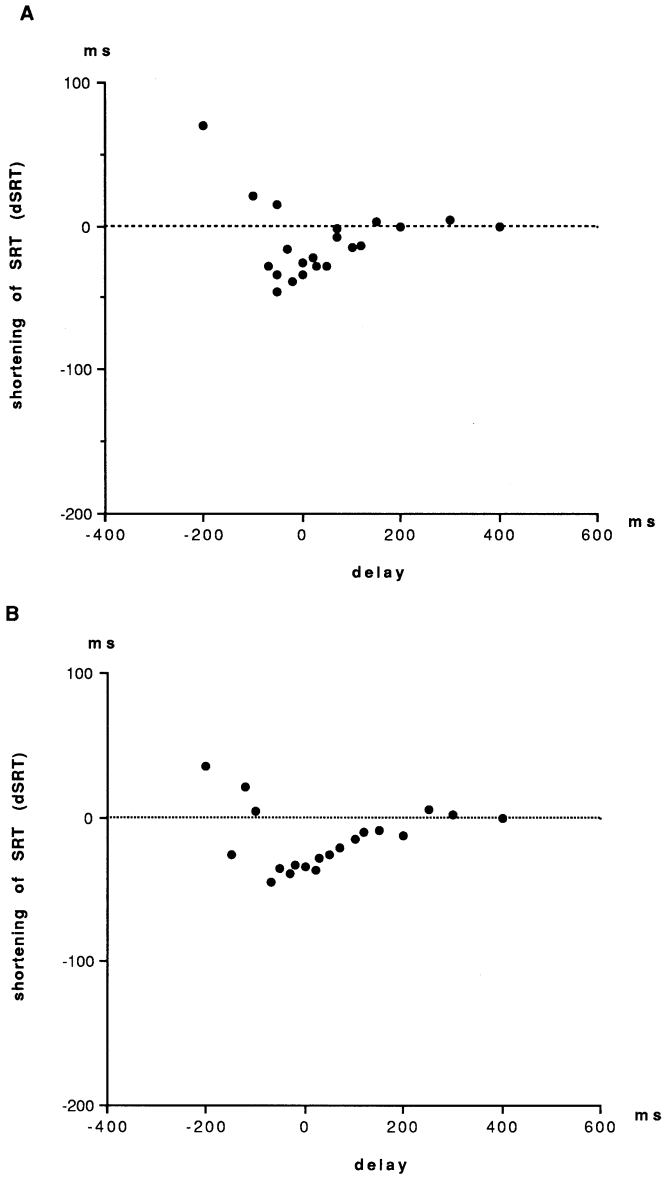

Fig. 3A, B Shortening of the SRT by electrical stimulation over the neck. **A** For one subject, dSRT was plotted as a function of the delay of electrical stimulation. The shortest SRT was noted at a delay between –50 and 0 ms; SRT became longer both before and after this delay, reaching control level by a delay of 150 ms. **B** Averaged dSRT across five subjects was plotted against delay. The SRT bottomed between delays –50 and 0 ms, while it approached control level after a delay of 100–150 ms. This curve shows an almost identical time course to that obtained for TMS

subjects (Fig. 3B; at delay –50 ms, dSRT = 35.6 ± 7.6 ms; at delay 0 ms, dSRT = 33.4 ± 8.0 ms; at delay 50 ms, dSRT = 25.9 ± 5.4 ms; at delay 100 ms, dSRT = 14.4 ± 10.8 ms). The effect of delay was again significant ($F = 28.621$, $P<0.002$), though the time course was not statistically different from that for TMS (delay × type of stimulation: $F = 2.220$, $P = 0.2617$).

Discussion

Our study confirmed the finding of Pascual-Leone et al. that TMS over the motor cortex at an intensity below threshold shortens the visual SRT in the contralateral arm muscles if it is given in close temporal proximity to the visual go signal. The maximal shortening they obtained was 20–80 ms, which is close to the range of shortening in the present study (20–50 ms).

However, our results differed from theirs in that we obtained a similar shortening whether the coil was placed over Cz, Pz or over the bilateral motor cortices. As far as the accuracy of the present study goes, subthreshold stimulation over the motor cortex did not produce any site-specific effect in a reaction task that was statistically significant. A quite similar effect was also obtained by peripheral ES applied to the skin or by the click sound of the stimulator itself when the coil was held *off* the scalp. These facts taken together suggest that much of the shortening can reasonably be explained by IF. When TMS of weak intensity is delivered over the scalp, this can evoke current in the skin and contraction of musculature in the scalp, and a slight percussion to the head as well as a click sound, while little current is induced in cerebral structures including the motor cortex. Any combination of these factors can lead to shortening of SRT due to IF.

Pascual-Leone used white noise to mask the click sound of TMS, thereby excluding the possibility of IF due to this associated sound. However, the auditory masking could have been incomplete. In addition, the large magnetic field might have produced a small click through the headphones owing to induced current in the headphone coil. Another possibility is that the contraction of the scalp musculature or the sensory inputs from sensory receptors in the scalp could have accelerated the reaction. Indeed, in the present experiments, peripheral ES to the scalp shortened the visual SRT to the same level. Finally, Pascual-Leone et al. provided only one control reaction time for comparison with the reaction times when TMS was applied to many different sites on the head. It may well be that it did not apply equally well to all stimulation sites, being longer or shorter at some sites because repeated performance of the same task would inevitably influence the reaction time.

At intervals of –100 ms or earlier, the SRT tended to be slightly longer than the control level. This could be due to some hesitant reaction in which the subjects were made to respond to the preceding accessory stimuli but immediately became aware of having broken away and had to stop the premature response. Upon appearance of the light signal, the subjects had to make a second response, which would have occurred later than when there was no premature reaction. In fact, some of the subjects interviewed after the experiment reported on this hesitation.

The facilitatory effect on the motor cortex, if it exists, could be quite small (e.g., ~10 ms), especially in comparison with IF. If we assume that SRT is determined by the combination of IF and the central effect of TMS on the motor cortex itself, then it should be sometimes very

difficult to judge how the cortical processing is influenced on the basis of SRT. Consider a situation in which the stimulus intensity is strong enough to elicit current in the motor cortex and to delay the cortical processing of information, but the shortening effect induced by IF is greater. In this case, SRT may be slightly shortened, while the processing in the motor cortex is actually disrupted by TMS. Therefore this study will have an important implication in experiments in which TMS is used in combination with the simple reaction paradigm (FitzGibbon et al. 1993; Priori et al. 1993; Palmer et al. 1994). Lack of proper knowledge about IF can lead to a total misunderstanding of brain function studied by TMS, especially in terms of changes in SRT. To exclude the possibility of IF and to be sure that the shortening occurred due to the central stimulating effect of TMS, the experimenter should perform control trials in which these "additional cues" are given alone or in combination with TMS at various delays. Further study would be necessary before we can conclude on the therapeutic possibility of chronic motor cortex stimulation in PD patients.

Acknowledgements The authors are grateful to Dr. J. C. Rothwell for his invaluable suggestions to this paper. Part of this work was supported by grants from the Research Committee for Ataxic Diseases, the Ministry of Health and Welfare of Japan; from a grant-in-aid for Dystonia Research, the Ministry of Health and Welfare of Japan; from the Nakabayashi Trust for ALS Research; from the Brain Science Foundation; and from a research project grant-in-aid for Scientific Research (C) 08670696 from the Ministry of Education, Science, Sports, and Culture of Japan.

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