Corticospinal excitability is modulated by temporal feedback gaps

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The integration of sensorimotor information is important for accurate goal-directed movement and affects corticospinal excitability (CE). This study investigated CE during the motor preparation period in a goal-directed movement task with temporal feedback gaps. Each trial began with a pair of first-informative and second-response beeps presented successively as cues. Trials with temporal feedback gaps showed that virtual hand movements lagged 400 ms behind actual performed movements. The participants were instructed to prepare for movement in accordance with the first beep, start the movement upon hearing the second beep, and perform movements that were both fast and accurate to the virtual target. We delivered a single-pulse of transcranial magnetic stimulation to the first dorsal interosseous muscle 250 ms before the presentation of the response beep. Motor-evoked potential amplitudes with temporal feedback gaps were significantly higher than those without temporal feedback gaps. Moreover, motor-evoked potential amplitudes with temporal feedback gaps gradually decreased over the course of the trials, whereas those without temporal feedback gaps did not change. In summary, CE during the motor preparation period was increased by temporal feedback gaps, and this excitation decreased in accordance with adaptation to temporal feedback gaps. *NeuroReport* 29:1558–1563 Copyright © 2018 The Author(s). Published by Wolters Kluwer Health, Inc.

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Introduction

Accurate human movement requires sensory information about the body and environment to be transformed into an appropriate motor command [1]. During goal-directed movements, sensory information is continuously integrated into the motor plan to ensure the accuracy of movement [2]. However, there are inherent gaps in proprioceptive and visual feedback because of neural transmission and integration time. Even if these gaps are relatively short, the control system faces a significant problem because of potentially destabilizing effects arising from bodily and environmental dynamics. Therefore, the effects of temporal feedback gaps are important to consider, because accurate goal-directed movements entail substantial gaps between the movement and feedback.

The primary motor cortex (M1) produces successive motor commands in accordance with the sensory feedback information to produce optimal movement during a preparatory phase just before movement initiation [3,4]. Therefore, M1 excitability by corticospinal output [i.e. corticospinal excitability (CE)] during this motor preparatory phase may be related to the temporal feedback gaps during goal-directed movement. Specifically, sensory feedback gaps, such as a mismatch between proprioceptive afferent and visual signals, lead to motor plan adaptation to modify the expected proprioceptive and visual signals [5].

The underlying neuronal mechanisms for sensorimotor integration have been investigated experimentally by controlled virtual reality (VR) manipulations of sensory feedback during movements [6]. Kitazawa *et al.* [7] estimated that a 50-ms delay of visual feedback results in a 50% reduction in adaptation rate. This study suggests that sensory gaps resulting from feedback delays attenuate motor adaptation [7]. However, whether M1 excitability changes are related to motor adaptation or the mismatch of sensory signals remains unresolved. Because previous studies have assessed CE at rest [8,9] or during movement [10], it has been challenging to resolve whether the CE changes during the motor preparation period (MPP) are due to sensory feedback gaps. Therefore, it remains unknown whether discrepancies between proprioceptive afferent and visual signals affect CE during goal-directed movement. Addressing these lacunae will elucidate the relationship between sensory information and M1 excitability changes during motor preparation in the context of sensory feedback gaps. Exploring how sensory feedback gaps affect CE may have important implications in motor analysis and neuroscience.

We hypothesized that if CE during the MPP and movement kinematics (MKs) reflect a mismatch of sensory signals, then excitability should be increased by sensory feedback gaps during goal-directed movement. Therefore, the purpose of

this study was to identify quantitative changes in CE and MK during the MPP with and without temporal feedback gaps.

Participants and methods

Participants

Participants were comprised of seven (three men and four women) healthy and neurologically intact right-handed volunteers aged 20–21 years (mean±SD age 20.7±0.5). The screening showed that none of the participants were at risk of adverse events from transcranial magnetic stimulation (TMS) [11], took medications, or had any psychiatric or neurological diseases. We carefully assessed intraindividual changes and then assessed group or interindividual changes. We confirmed right-handedness with the Edinburgh Handedness Inventory [12], recording a mean±SD laterality quotient score of 0.9±0.2 points. The experimental procedures were approved by the Ethics Committee of the Saitama Prefectural University and performed in accordance with the principles of the Declaration of Helsinki. All participants provided written informed consent.

Experimental setup

Each participant sat comfortably with the right forearm, palm, and fingers, excluding the index finger, resting on the test equipment. After index finger abduction, the index finger automatically returned to the neutral starting position by an elastic band. The coordinate data of the index finger were recorded by the Leap Motion controller (Leap Motion, San Francisco, USA) on a table. The Leap Motion controller has three infrared irradiators, two infrared receivers, and spatial resolution of 1/100 mm without markers. These data were fed to a photorealistic virtual 3D hand model by a VR headset (HTC Vive; Halve, Washington, DC, USA) worn by the participant. Head motion was tracked by two infrared cameras. This system has been widely utilized as an instrument with VR software for motion analysis of the fingers and upper extremities [13]. Thus, real-time visual feedback of index finger motion was conveyed on the monitor as a moveable VR-rendered white-colored hand model by the participant in real time. The aimed target position was 15° index finger abduction, which was displayed as a flesh-colored index finger model on the VR monitor. Throughout the experimental runs, we also recorded participants' index finger positions using a lightweight potentiometer (FA-DL-263; 4Assist, Tokyo, Japan) mounted on the index finger and hand. A positive potentiometer value corresponded to finger abduction (0° indicates the starting position). The signals from the linear potentiometer were low-pass filtered (< 20 Hz) and digitized at 10 kHz (PowerLab; ADInstruments, Colorado Springs, Colorado, USA). The data were recorded and stored for offline analysis (LabChart 7.3; ADInstruments) on a personal computer.

Movement kinematic

Peak velocity was quantified by the maximum of the slope of the recorded index finger angle curve for movement duration, and reaction time was calculated as the time elapsed between

the response beep and the onset of movement. Total movement duration was considered the period from movement onset to offset. Movement onset was defined as the time point when the index finger velocity exceeded 5% of peak velocity. The final position was defined as the time point when the index finger velocity was less than 5% of peak velocity to ensure that the attained target position was truly the end of the intended movement and not simply a point in transit. Primary submovement duration was calculated as the time elapsed between movement onset and the time point of the second zero crossing of the acceleration profile.

Motor-evoked potential recordings

We recorded surface motor-evoked potentials (MEPs) from the first dorsal interosseous (FDI) muscle with double differential surface electrodes (FAD-DEMG1; 4Assist). Before MEP recording, the skin overlying the FDI muscle was cleaned with alcohol to reduce its electrical resistance. The recording and reference electrodes were placed over the muscle. The MEP signals were amplified ×100, bandpass-filtered at 5–2000 Hz, digitized at 10 kHz with a PowerLab system (ADInstruments, Dunedin, New Zealand), and stored on magnetic media.

Transcranial magnetic stimulation

TMS was delivered to the scalp through a figure-eight coil (internal diameter of each wing: 70 mm) using a Magstim 200^2 stimulator (Magstim, Whitland, UK). To induce a current from the posterolateral to anteromedial left brain, the coil was held tangentially to the scalp at ∼45° to the midline, and the handle was pointed dorsolaterally. At the start of the experiment, we elucidated the optimal coil position for eliciting maximal MEPs in the FDI (termed the 'hot spot') by moving the coil over the left M1 and marking it with a soft-tipped pen. The hot spot's resting motor threshold was defined as the minimum stimulus intensity required to elicit an MEP in the relaxed FDI of at least 50 µV in five out of 10 consecutive trials.

Goal-directed movement task

Each experiment was composed of four crossover blocks of 45 movements each. Blocks 1 and 3 (or blocks 2 and 4) included the delayed visual hand movement feedback, that is, the virtual hand's movements lagging 400 ms behind the actual performed movements. Time perception within the milliseconds-to-seconds range plays a fundamental role in adaptive behavior [11]. In previous time estimation tasks [12,14], a time interval of 400–2400 ms was used for the participant's time performance. Thus, in our study, the temporal feedback gap was 400 ms, which was clearly perceived as delayed finger motion by the participant. Blocks 2 and 4 (or blocks 1 and 3) included the no-delay visual hand movement feedback, that is, the virtual hand's movements were the same as the actual performed movements. In this task, a pair of identical-sounding beeps (first, informative; second, response) were presented successively to the participant (inter-trial interval, 6 s). The informative beep provided information

concerning the forthcoming movement performed immediately after the response beep. The interstimulus interval between the informative and response beeps was 1 s. The delay between the informative and response beeps corresponded to the MPP. Participants were instructed to 'prepare the movement in accordance with the first beep, start the movement as soon as you hear the second beep, and then make movements that are both fast and accurate.' In addition, they were asked to make the movements in a smooth, continuous motion and position the finger (white colored) in the virtual finger target (flesh colored) without overshooting or secondary adjustments (i.e. terminate finger movement in the target). This was to ensure that the goal-directed movement aiming for the target position was attained and was not simply a stopping movement. Notably, participants had to adjust their movements when the visual feedback changed again from delayed to synchronous. This experimental setup allowed for the successful observation of changes in MEP and kinematic parameters during short-term adaptation of a goal-directed aiming movement because the participants were naive to the experiment. Previous studies have reported that CE changes at the end of motor preparation between the informative signal and the response signal (250 ms prior to the response cue) [4]. Therefore, we delivered a single-pulse TMS at 120% of the FDI's resting motor threshold 750 ms after the presentation of the informative beep (250 ms before the response beep).

Data analysis

The MEP and kinematic data were normalized by linear transformation and expressed as Z scores because we investigated intraindividual variability during goal-directed movement tasks. A previous study noted that MEP amplitude [15] and kinematics [16] randomly fluctuate during tasks. We therefore constructed a state-changing model, which includes trend process with y-intercept and slope, and steady process with random variation for decomposing inherent random fluctuation of MEPs and kinematics as follows:

$$f(t) = \alpha + \beta t + \varepsilon_t, \qquad (1)$$

where α refers to the initial CE and kinematics reflecting the effect of changing conditions with and without a temporal feedback gap, β refers to the slope of CE and kinematics reflecting the effect of condition with or without a temporal feedback gap, ε_t is the steady process with random variation reflecting inherent fluctuation of MEPs and kinematics, and t is the number of trials during goal-directed movement. The data from each participant were fitted to the model using the least-squares method. We used the akaike information criterion (AIC) to assess the compatibility of the α and β values of the model. The AIC was calculated as follows:

$$AIC = n \log\left(\frac{SSR}{n}\right) + 2k, \qquad (2)$$

where n is the number of data, SSR is the sum of squared residuals between the model's predictions and actual data, and

k is the number of parameters. A lower AIC value indicates better α and β values of the model [17]. The efficiency of the ε_t value of the model was assessed by the Phillips–Perron unit root test to measure the steady-state with random variation of ε_t. Thus, the data eliminate inherent fluctuations of MEPs and kinematics in steady state, and α and β values of the models permit the evaluation of whether temporal feedback gaps affect CE and kinematics. We analyzed differences in MEP amplitudes and kinematics, eliminating inherent fluctuations with and without temporal feedback gaps by paired t-tests. We defined statistical significance as P value less than 0.05. All statistical analyses were performed with R 3.4.0 software (R Foundation for Statistical Computing, Vienna, Austria).

Results

All participants completed all experimental conditions. No adverse TMS-related effects occurred during the experiments. Table 1 shows the differences in α and β values with and without temporal feedback gaps. Based on ε_t value estimation of with the Phillips–Perron unit root test, in 26 of 28 data sets (92.9%), the series of ε_t of the model was steady-state with random variation (each dataset's mean value was 0.00). The y-intercept (α) of CE during the MPP, reaction time, movement time, and primary submovement time with temporal feedback gaps shifted upwards compared with that without temporal feedback gaps; contrarily, peak velocity with temporal feedback gaps shifted downward compared with that without temporal feedback gaps. The slope (β) of MEP amplitudes with temporal feedback gaps was negative. However, changes in MEP amplitudes without temporal feedback gaps, and peak velocity, reaction time, movement time, and primary submovement time with and without temporal feedback gaps were small and generally stable. Figure 1 shows the differences in MEPs and MK, eliminating inherent fluctuations (ε_t) with and without temporal feedback gaps. Paired t-tests revealed that MEPs, movement time, and primary submovement time with temporal feedback gaps were significantly higher than those without temporal feedback gaps ($P < 0.05$). Peak velocity with temporal feedback gaps was significantly lower than that without temporal feedback gaps ($P < 0.05$). However, reaction time differences between conditions were small and nonsignificant ($P = 0.386$).

Discussion

Using a VR-based hand-target task with temporal feedback gaps between proprioceptive and visual information, we hypothesized that mismatched sensory signals should produce changes in MEP amplitudes and MK. We measured changes in CE and MK related to temporal feedback gaps during a goal-directed movement task. Our results showed that (a) CE, movement time, and primary submovement time with temporal feedback gaps were larger than those without temporal feedback gaps, whereas peak velocity with temporal feedback gaps was smaller than those without temporal feedback gaps, and (b) CE during the MPP with temporal feedback gaps gradually decreased over the course of the adaptation

Table 1 Differences in motor-evoked potential amplitudes and kinematics with or without temporal feedback delay

	α		β	
	With temporal gap	Without temporal gap	With temporal gap	Without temporal gap
MEP amplitudes	0.28 ± 0.18	−0.16 ± 0.20	−0.010 ± 0.006	0.004 ± 0.008
Peak velocity	−0.16 ± 0.26	0.33 ± 0.28	0.001 ± 0.009	−0.008 ± 0.012
Reaction time	0.12 ± 0.16	−0.15 ± 0.23	−0.005 ± 0.006	0.006 ± 0.009
Movement time	0.15 ± 0.18	−0.24 ± 0.18	0.002 ± 0.007	0.003 ± 0.008
Primary submovement time	−0.02 ± 0.15	−0.15 ± 0.14	0.006 ± 0.005	0.002 ± 0.005

Values are mean ± SEM.
MEP, motor-evoked potential.

Fig. 1
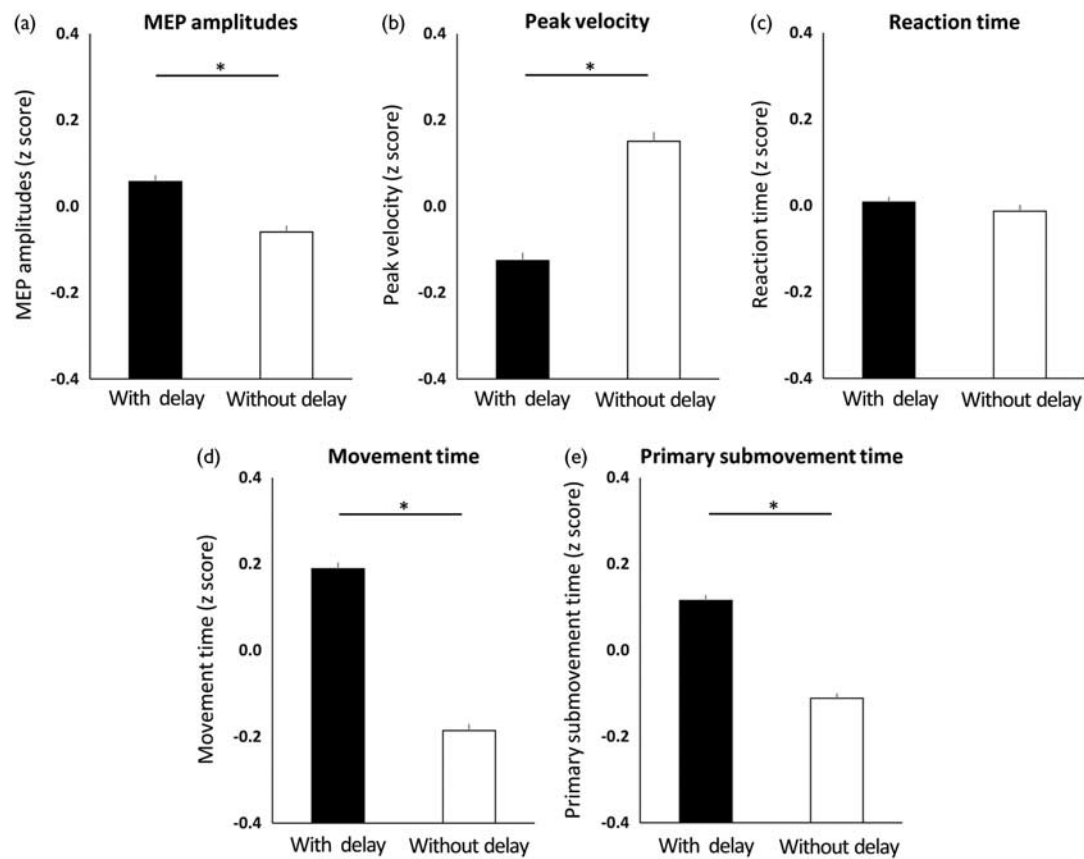
Bar graphs of motor-evoked potentials (MEPs) and movement kinematic with (filled column) and without (open column) temporal feedback delay. MEPs, peak velocity, movement time, and primary submovement time were significantly different with and without temporal feedback delay (*$P < 0.05$). However, reaction time differences between conditions with and without temporal feedback delay were small and nonsignificant ($P = 0.386$).

period, whereas those without temporal feedback gaps did not change. These results imply that CE during the MPP reflects mismatched sensory signals and sensorimotor adaptation.

Previous studies [10,18] have measured CE changes after various forms of intervention with respect to motor output, including sensorimotor adaptation. Recently, Bagce *et al.* [10] reported that a perturbation with different spatial gain did not lead to changes in CE during movement. They noted that the lack of an effect of visual-to-motor errors on

excitability is reasonable given the lack of direct visual inputs to M1 [10]. We found increases in excitability with temporal compared with without temporal feedback gaps, contrasting the previous study which assessed CE during movement. Our experimental setup allowed for the successful observation of changes in CE during the MPP because we delivered a single-pulse TMS over M1 250 ms before movement onset. Sensorimotor adaptation generally involves updating a motor plan that estimates sensory consequences of motor commands [19,20]. Studies on

nonhuman primates have demonstrated that the parietal cortex is anatomically linked to the premotor and supplementary motor cortical regions by the first branch of the superior longitudinal fasciculus [21]; thus, parietal input is provided from visual and proprioceptive regions to the premotor cortex, which in turn connects to M1. Moreover, the second branch of the superior longitudinal fasciculus from the parietal cortex is linked to the premotor cortex, providing visual and proprioceptive input to the premotor cortex [21,22]. Human studies investigating temporal feedback gap processing have found that the M1 is functionally influenced by many brain regions, including the parietal, premotor, and supplementary motor cortical areas [6,23]. In our study, although we did not identify the exact mechanism, we predict that M1 excitability during the MPP could have been heightened by temporal feedback gaps in terms of proprioceptive and visual information mismatches. One possibility is that output from many brain regions, including the parietal, premotor, and supplementary motor cortical areas may influence M1 excitability with different 'gains' according to the final movement to be performed. This is presumably regulated by the horizontal intracortical projections that connect anatomically and functionally related neuronal clusters within the M1 and sensory processing regions. This could explain why in our study, the MEP amplitudes with temporal feedback gaps were larger than those without temporal feedback gaps, but these amplitudes gradually decreased over the course of the adaptation period. This may imply that corticospinal excitation for mismatched sensory signals decreases in accordance with adaptation to sensory gaps. To clarify this, future studies should consider the time course in changes of M1 excitability and MK in relation to the various sensory feedback gaps during goal-directed movement.

Previous studies have suggested that goal-directed movements induce a long-lasting increase in synaptic strength in M1 horizontal connections, proposing an association with long-term potentiation like plasticity [24]. Corticospinal changes induced by goal-directed movements have generally been in the form of increased excitability [8,9,25]. However, CE during the MPP without temporal feedback gaps did not change in our study. Therefore, further studies using goal-directed movement tasks with a larger number of trials may be needed to elucidate changes in kinematic-related parameters during sensory adaptation and in CE without temporal feedback gaps.

Conclusion
We observed that CE during the MPP with temporal feedback gaps was larger than those without temporal feedback gaps, but this gradually decreased over the course of the adaptation period. These results imply that CE can be altered by mismatched sensory signals. These findings have implications for sensorimotor adaptation during goal-directed movement tasks, both of which

partly rely on CE, including the M1, and on adaptation to mismatched sensory signals. This study also provides evidence that TMS is a useful way to monitor corticospinal activity during sensorimotor adaptation.

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