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Translational research of occupational therapy and neurorehabilitation

Edited by
Ryouhei Ishii, Scott Alan Smith, Ryoichiro Iwanaga, Jing Xiang, Leonides Canuet, HIdeki Miyaguchi and Hiroyuki Inadomi

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Translational research of occupational therapy and neurorehabilitation

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Editorial: Translational research of occupational therapy and neurorehabilitation

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Editorial on the Research Topic
Translational research of occupational therapy and neurorehabilitation

The American Occupational Therapy Association (AOTA) defines Occupational Therapy (OT) as "a health and rehabilitation profession that assists individuals of all ages who have an injury, illness, cognitive impairment, mental illness, developmental, learning, or physical disability to maximize their independence. OT is aimed at maximizing autonomy in all aspects of daily activities, assisting the person in all types of disabilities and giving meaning by means of organized and deliberate activity, known as 'occupation'. OT therapy sessions are focused on engaging patients with meaningful activities to achieve goals and achieve adequate levels of satisfaction, productivity and independence. Patients can thus experience increased competence, self-efficacy, independence, purpose and, above all, a greater sense of wholeness.

New research and emerging technologies are providing therapeutic strategies and new devices to the field of neurorehabilitation (NR) research and OT clinical practice. This Research Topic highlights some of the innovative research findings that these new technologies are bringing to OT and NR. The first section introduces new technological approaches in OT and NR for cognitive and psychiatric disorders. Next, the application of new technologies to the rehabilitation of motor function through motor imagery and neurofeedback is presented. Finally, studies of neuromodulation to assess and directly work with motor function are reported. All suggest that new technologies such as virtual reality (VR), non-invasive brain stimulation and robot-assisted training can increase the effectiveness of OT and NR strategies. Brain imaging techniques such as electroencephalography (EEG), event-related potentials (ERP), near-infrared spectroscopy (NIRS) and functional magnetic resonance imaging (fMRI) also provide non-invasive and objective outcome measures for OT and NR.

Tomori et al. (2012) introduced Aid for Decision-making in Occupation Choice (ADOC), a digital tool facilitating shared decision-making in occupational target planning, enhancing collaboration between therapists and patients. Tokuda et al. investigated the impact of self-choice of interesting occupations on cognitive processing and job-related satisfaction using ERP and ADOC, revealing a significant increase in P300 amplitude during self-selection of an interesting job, suggesting the importance of patient involvement in goal setting. Kubo et al. explored how prior knowledge of traffic signals influences behavioral responses and neural mechanisms using RT and ERP, uncovering Stroop-like interference between prior knowledge and actual signal meaning. Shiraiwa et al. studied the physiological mechanisms underlying the therapeutic effects of craft activities in occupational therapy, revealing increased parasympathetic and sympathetic activity during craft tasks, suggesting a correlation between cardiac autonomic function and frontal midline theta rhythm (Fmθ) activity. Tabira et al. investigated the relationship between attentional bias and psychological ratings in chronic low back pain (LBP) patients, highlighting associations between psychological factors, attentional bias, and pain-related outcomes, indicating the potential benefits of attentional bias modification training in LBP management.

Niki et al. conducted a pilot study investigating the efficacy of immersive virtual reality (iVR) reminiscence in alleviating anxiety in the elderly with cognitive decline. Their findings suggest that iVR reminiscence, particularly when using live-action pictures, may effectively reduce anxiety without causing serious side effects. Yamada and Sumiyoshi conducted a review on transcranial direct current stimulation (tDCS) and its potential in treating various psychiatric disorders. They discussed the neurobiological mechanisms underlying tDCS and its ability to modulate cortical excitability, neurotransmitter activity, and information processing efficiency in the brain. Koyanagi et al. investigated the utility of functional near-infrared spectroscopy (fNIRS) in diagnosing post-stroke depression (PSD). They found that depressed patients exhibited lower oxy-Hb integral values and reduced frontal lobe activation compared to non-depressed patients, suggesting fNIRS oxy-Hb as a useful diagnostic tool for PSD.

Moriuchi et al. explored the relationship between motor imagery (MI) ratings and neurophysiological ratings during combined MI and action observation (MI+AO) tasks. They found a significant positive correlation between MI quality and transcranial magnetic stimulation (TMS)-evoked motor evoked potentials (MEPs), suggesting that MI quality may reflect corticospinal tract excitability during MI+AO tasks. Iso et al. investigated the relationship between oxy-Hb concentration during a motor imagery (MI) task and the level of motor learning. They observed significant changes in oxy-Hb concentration in the supplementary motor area (SMA), suggesting that hemodynamic brain activity during MI tasks may correlate with the level of motor learning.

In their study, Aoyama et al. explored the efficacy of Kinesthetic Illusion induced by Visual Stimulation (KINVIS) as a standalone intervention for finger flexor spasticity in stroke patients. By conducting a single-session KINVIS intervention on 14 stroke patients, they observed significant improvements in Modified Ashworth Scale scores and active range of finger extension movements. Additional experimentation suggested potential neurophysiological changes underlying the reduction in spasticity, indicating the clinical significance of KINVIS in improving upper limb function post-stroke. Irie et al. investigated the neuroscientific basis of motor imagery (MI) intervention for children with developmental coordination disorder (DCD). Their review highlighted neural alterations associated with DCD, including decreased activity in the mirror neuron system and sensory integration regions. Additionally, they proposed MI methods involving action observation and visual-motor tasks to activate relevant brain regions, offering insights into effective intervention strategies for children with DCD.

Matsuda et al. examined whether the efficacy of mental practice (motor imagery training) could be enhanced by providing neurofeedback based on transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEP). Their study suggested that TMS-induced MEP-based neurofeedback might enhance the effect of mental practice, indicating a potential avenue for improving motor learning outcomes through combined interventions. Zhang and Fong investigated the modulatory effect of priming intermittent theta burst stimulation (iTBS) with continuous theta burst stimulation (cTBS) on sensorimotor oscillatory activities in healthy adults. Their findings suggested that priming iTBS with cTBS yielded similar effects to iTBS alone in enhancing sensorimotor event-related desynchronization induced by mirror visual feedback. However, priming iTBS demonstrated more pronounced enhancements in movement-related desynchronization, particularly in the high mu band, suggesting a potential advantage of this combined stimulation protocol for motor learning paradigms. Fong et al. investigated the immediate effects of mirror visual feedback (MVF) on motor execution in stroke patients and healthy individuals using EEG. They found significant suppression of high beta event-related desynchronization (ERD) over the contralateral motor area during unimanual arm movements with MVF, suggesting a shift in sensorimotor ERD toward the contralateral hemisphere induced by MVF.

Sagari et al. examined the effects of antagonistic tasks on prefrontal cortical cerebral hemodynamics in healthy adults. They found that complex antagonistic tasks led to a greater increase in prefrontal cortex oxygenated hemoglobin concentration compared to non-antagonistic tasks, highlighting the impact of task complexity on cerebral blood flow dynamics. Matsumoto A. et al. investigated the contribution of corticospinal excitability to anticipatory postural adjustments (APAs) in lower limb muscles during ballistic upper limb movements. They observed increased corticospinal excitability in the tibialis anterior muscle preceding the dart throwing movement, suggesting a role of the corticospinal pathway in APAs. Matsumoto T. et al. also explored the influence of goal-directed movement on ipsilateral primary motor cortex (ipsi-M1) excitability during unilateral finger tapping tasks. They found reduced short-interval intracortical inhibition (SICI) in the ipsi-M1 during visually guided finger movements, suggesting modulation of ipsi-M1 excitability during goal-directed tasks. Matsugi et al. investigated arterial pressure and heart rate responses to noisy galvanic vestibular stimulation (nGVS) during static supine and

whole-body tilt in healthy older adults. They found that nGVS did not significantly affect arterial pressure or heart rate, indicating the safety of nGVS application in this population.

Johnson et al. emphasized the importance of considering memory consolidation and reconsolidation in rehabilitation, highlighting the need for further research to explore their role in enhancing learning and memory between rehabilitation sessions. They suggested that understanding these processes could lead to the development of more effective and long-lasting rehabilitation interventions. Translational research in occupational therapy and neurorehabilitation holds immense significance in enhancing the quality of life for individuals facing various cognitive, physical, and psychiatric challenges. By bridging the gap between cutting-edge research findings and practical clinical applications, translational research empowers therapists to adopt innovative strategies and technologies, thereby maximizing the effectiveness of therapeutic interventions.

Through the integration of emerging technologies such as virtual reality, noninvasive brain stimulation, and robot-assisted training, occupational therapists can revolutionize neurorehabilitation approaches. These technologies offer promising avenues for enhancing cognitive function, motor skills, and emotional wellbeing in patients with neurological conditions. Moreover, the development of digital tools like Aid for Decision-making in Occupation Choice (ADOC) facilitates shared decision-making between therapists and patients, fostering a collaborative approach to goal setting and rehabilitation planning. By leveraging tools like ADOC, therapists can personalize interventions to align with each patient's unique preferences and priorities, ultimately promoting greater satisfaction and engagement in therapy sessions.

Furthermore, neurophysiological studies exploring phenomena such as attentional bias modification and motor imagery shed light on the underlying mechanisms of therapeutic interventions. By elucidating the neural correlates of cognitive processes and behavioral responses, researchers can refine existing interventions and develop targeted strategies to address specific impairments more effectively. Additionally, the utilization of advanced imaging techniques like functional near-infrared spectroscopy (fNIRS) offers valuable insights into the neurological changes associated with conditions such as post-stroke depression. By employing fNIRS as a diagnostic tool, therapists can accurately assess cerebral function and tailor interventions to address mood disturbances, thereby facilitating more comprehensive rehabilitation outcomes.

Overall, translational research in occupational therapy and neurorehabilitation holds tremendous promise for advancing clinical practice and improving the lives of individuals with neurological disorders. By embracing innovation, collaboration, and evidence-based practice, therapists can continue to enhance the efficacy and accessibility of rehabilitation services, ultimately empowering patients to achieve greater independence, functionality, and quality of life.

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Self-Selection of Interesting Occupation Facilitates Cognitive Response to the Task: An Event-Related Potential Study

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Introduction: In this study, we examined whether the self-selection of occupations of interest affects reaction times (RTs) and cognitive processing by using the Aid for Decision-making in Occupation Choice (ADOC) and event-related potentials (ERP). We also assessed the relationship of these with psychological indicators.

Method: We extracted 78 occupations from the ADOC in consideration of the subjects' age, and three conditions were set: (1) self-selection of an interesting occupation; (2) self-selection of a disliked occupation; and (3) forced selection. The RT task was executed under their conditions during which ERP was measured. We compared the P300 component of ERP in these conditions. Moreover, we examined the association of cognitive processing and degree of satisfaction and performance concerning occupation, with psychological indicators.

Results: P300 amplitude at Fz significantly increased in the self-selection of an interesting occupation. P300 amplitude at Pz was significantly positively correlated with the occupational satisfaction score.

Conclusion: Self-selection of interesting occupations in the ADOC resulted in increased attention resource allocation by increasing motivation. Further, there was a positive correlation between satisfaction concerning the occupation and attention of resource allocation. Therefore, occupational therapists should know which occupations the patients consider interesting and help them to select by themselves, thus enhancing their satisfaction after consultation. These interventions may contribute to promoting motivation and cognitive processing.

Keywords: self-selection, ADOC, attention, occupational therapy, ERP

INTRODUCTION

In recent years, a top-down approach grounded on occupation-based practice has been promoted in the clinical setting of occupational therapy (Nielsen et al., 2017; Nagayama et al., 2018; Maruta et al., 2020). The goal setting is considered a key component of these approaches, with the understanding that selected goals will drive the clinical decision-making process (Levack and Dean, 2012). The Aid for Decision-making in Occupation Choice (ADOC) is a tool to promote the implementation of shared decision-making in occupation-based goal setting (Tomori et al., 2012). Therapists adapt meaningful occupations to rehabilitations in consideration of the degree of satisfaction and performance for occupations after therapists and patients select them by using ADOC. The ADOC makes it possible to share decision making between therapists and patients in an occupation-based goal setting (Tomori et al., 2012, 2015). In this way, it is important for the therapist to share the goals with the patient and to help the patient select the occupations with intention. Moreover, motivational involvement in the occupations is essential for the self-selection of them.

The Self-determination theory provides a comprehensive framework for assessing motivation. Ryan and Deci (2000) classified motivation into three types: no motivation, extrinsic motivation, and intrinsic motivation. It has been reported that intrinsic motivation improves performance and sustainability more than extrinsic motivation (Patall et al., 2008; Areepattamannil et al., 2011). These motivations are positioned on a continuum according to the degree of self-determination. Extrinsic motivation approaches intrinsic motivation by internalizing the external environment and values and integrating them into the self (Ryan and Deci, 2000).

Brain networks have been identified in neuropsychological research on self-selection. Murayama et al. (2015) examined brain occupations using fMRI and compared self-determination (subjects selected the design of a stopwatch by themselves) with forced-determinations (the examiner made the selection). That study revealed that the ventral striatum and medial prefrontal cortex play important roles in the performance of self-selection (Murayama et al., 2015).

On the other hand, event-related potentials (ERP) represent the means to assess cognitive processing with a high temporal resolution (Helfrich and Knight, 2019). The P300 component, which is generated around 300 ms after stimulation in one of the ERP waveforms is triggered by tasks that require cognition and judgment. P300 latency reflects cognitive processing time (Kutas et al., 1977), and the amplitude reflects attention resource allocation (Schubert et al., 1998). Therefore, the study of ERP and P300 components in self-determination and motivation could contribute to the understanding of the cognitive processing and brain activities involved in the performance of self-selection. P300 amplitude was significantly higher in the most motivated participants than in the least motivated ones (Kleih et al., 2010). Further, using ERP, Tanaka et al. (2014) examined cognitive processing responses related to differences in preference. P300 amplitudes for the favorite and disliked animal pictures tended to increase more than the pictures were neither liked nor disliked. In short, P300 amplitudes might promote cognitive processing responses to likes and dislikes (Tanaka et al., 2014).

However, the findings from these studies are difficult to apply in clinical occupational therapy, in terms of meaningful occupations, because of fundamental studies on self-determination and simply comparing differences in preference. We hypothesized that the examination of the P300 component would be responded to during the selection of meaningful and interesting occupations using the ADOC. The result of cognitive processing responses may contribute to emphasizing the importance of goal setting in occupation-based practice.

Therefore, in this study, healthy subjects were asked to select meaningful or disliked occupations using ADOC, and ERP and reaction time (RT) were measured when the occupation images were presented. The aims of this study were: (1) to clarify whether self-selection of both meaningful and interesting occupations increased the cognitive processing of the tasks; and (2) to investigate the association of cognitive processing, degree of satisfaction, and performance with occupation and psychological indicators.

MATERIALS AND METHODS

Subjects

We put up a poster with details of this study on the bulletin board in the Kagoshima University, recruited the participants of the experiment, and used only the applicants as subjects. Twenty-three healthy subjects from Kagoshima University (mean age = 24.1, SD = 5.1, 11 males) participated in this study. All subjects had a normal or corrected-to-normal vision. None of them had a history of neurological or psychiatric disorders or took psychiatric medicine. They gave verbal and written informed consent to participate in the study, but they were not told the aim of the experiments to avoid the effect of information and intended bias on all data. This study was approved by the Ethics Committee on Epidemiological Studies, Kagoshima University (Ref No. 180157).

Assignments and Stimuli

We used a visual response task and extracted 78 types of occupations from all the 95 tasks of ADOC in consideration of the subjects' age. We presented visual stimuli and measured RT using an image stimulation system (Multi trigger system MTS0410, Medical Try System, Tokyo). The visual stimuli were presented for 500 ms each, with an interstimulus interval of 2,000 ms, a comprised target stimulus of 30%, and a non-target stimulus of 70%, following a visual oddball paradigm (Maruta et al., 2019). Each condition was finished after the target stimuli were presented 35 times.

Recording and Data Analysis

Electroencephalogram and evoked potentials, Neuro Pack X1 (NIHON KOHDEN, Tokyo) were monitored using an electromyography tester. EEG was recorded from three scalp sites (Fz, Cz, Pz) according to the 10-20 systems and the sampling rate was 1,000 Hz (Maruta et al., 2019). Ag/AgCl electrodes

were referenced to the earlobes and electrode impedance was kept below 5 kΩ. Eye movements were monitored using electrooculograms (EOGs) recorded from electrodes lateral to and below the left eye. For all ERPs, a bandpass filter was applied between 0.5–50 Hz. Remaining epochs were visually inspected, manually removing those containing blinks, eye movements, or other sources of transient noise from the analysis. The peak latency of the P300 components was measured at 250–500 ms. P300 amplitude was defined as the difference in μV from the baseline before the presentation of visual stimuli to the most positive trough between 250–500 ms. When measuring the peak amplitude and latency of the P300 component, some participants showed double peaks of P300. In this case, we selected the largest waveform peak. We also recorded horizontal and vertical electrooculograms to remove artifacts. The P300 component was detected after the ERP waveforms corresponding to the target stimuli were averaged.

Experimental Protocol

There were three experimental conditions for different visual stimuli. In the first condition, the subjects were asked to select an occupation they considered both meaningful and interesting from a list of 78 occupations using ADOC (self-selection meaningful condition: SSMC). In the second condition, they were asked to select an occupation they disliked (self-selection dislike condition: SSDC). In the third condition, we selected an occupation that was neither liked nor disliked for the subjects (forced-select condition: FSC). The three conditions were performed in random order. The subjects were introduced with the experimental method and asked to practice 10 times before starting the experiment. Subjects were instructed to push a handgrip button to target stimuli with their dominant thumb as accurately and quickly as possible while seated approximately 100 cm from a 19-inch LCD monitor, and ERP was measured during the tasks. Each condition was finished after the target stimuli were presented 35 times. A 3 min rest was provided between conditions (**Figure 1**). In the SSMC, we examined satisfaction and performance scores for self-selection of meaningful occupation. The participants were asked to provide a satisfaction score for their meaningful and interesting occupations ranging from 1, extremely unsatisfied, to 10, extremely satisfied. In the same way, they were asked to provide a performance score. A 10-point score meant that the participants were good at the selected occupation, and 1 point meant that they could not do it at all (**Figure 2**). Subjects were instructed to push the handgrip button to target the stimuli with their dominant thumb as accurately and quickly as possible, while seated approximately 100 cm from a 19-inch LCD monitor and viewing the ADOC images.

Psychological Indicators

The Japanese version of the Maudsley Personality Inventory (JMPI) was administered to the subjects to examine the association between introverted/extroverted personality types (E score) and cognitive processing. The JMPI consists of extroversion-introversion (E scale, 24 items), the neurotic tendency (N scale, 24 items), a false scale (L scale, 20 items), and 12 neutral items (Iwasaki et al., 1970). High scores are proportional to extroversion on the E scale (Arthur and Jensen, 1958).

Statistical Analysis

We conducted a Shapiro–Wilk test to test the normality of the P300 component among the three conditions, and normality was confirmed. We used repeated-measures-ANOVA to compare P300 amplitude, latency, and RT in the three conditions, followed by Bonferroni's *post hoc* comparisons at $P < 0.05$ of significance. Moreover, we used Spearman's rank correlation coefficient to investigate the association between P300 components as the dependent variable, and satisfaction/performance scores for occupation, E score as independent variables. Statistical analyses were performed with SPSS version 25.0.

RESULT

Summary of the Subjects of the Study

We investigated 22 subjects (mean age = 24.3, SD = 5.2, 11 males) because one subject had less than 20 waveforms without artifacts in each condition (Cohen and Polish, 1997). **Figure 3** shows the P300 average waveform obtained under each condition. All the errors (two subjects each made an error twice) during task performance were generated only when non-target visual stimuli were presented, so the results were not affected.

P300 Component and RT

The main difference between the three conditions was observed in the P300 amplitude at Fz ($F_{(2,42)} = 6.2$, $P = 0.004$). After examining each condition, the P300 amplitude at Fz ($F_{(2,42)} = 6.2$, $P = 0.004$) in the SSMC was more significantly increased than in the other two conditions (SSMC vs. SSDC; $P = 0.02$, SSMC vs. FSC; $P = 0.04$). There was no difference between SSDC and FSC (**Figure 4**). Moreover, there was no significant difference at Cz ($F_{(2,42)} = 2.1$, $P = 0.13$) or Pz ($F_{(2,42)} = 3.1$, $P = 0.06$). The difference in P300 latency and RT between the conditions was not significant (**Figures 5**, **6**).

Association Between P300 Component, RT, Satisfaction, Performance, and Psychological Index in the SSMC

P300 amplitude at Pz was significantly and positively correlated with occupational satisfaction score (**Figure 7**). The high score of the performance degree did not significantly increase. No significant correlation between the P300 component and extroversion-introversion (**Table 1**).

DISCUSSION

Self-Selection Interesting Condition and P300 Amplitude

We found that the P300 amplitude at Fz in SSMC was more significantly increased than in SSDC and FSC.

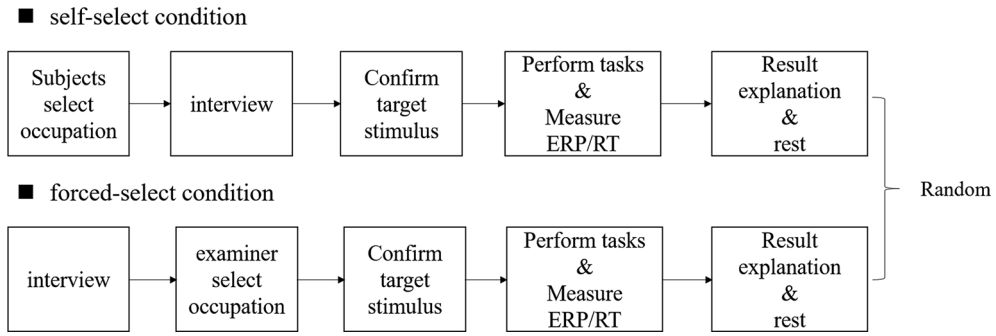

FIGURE 1 | Experimental procedure of the self-selection and the forced-selection conditions. The order of the conditions was randomized, and a 3-min break was provided between each condition.

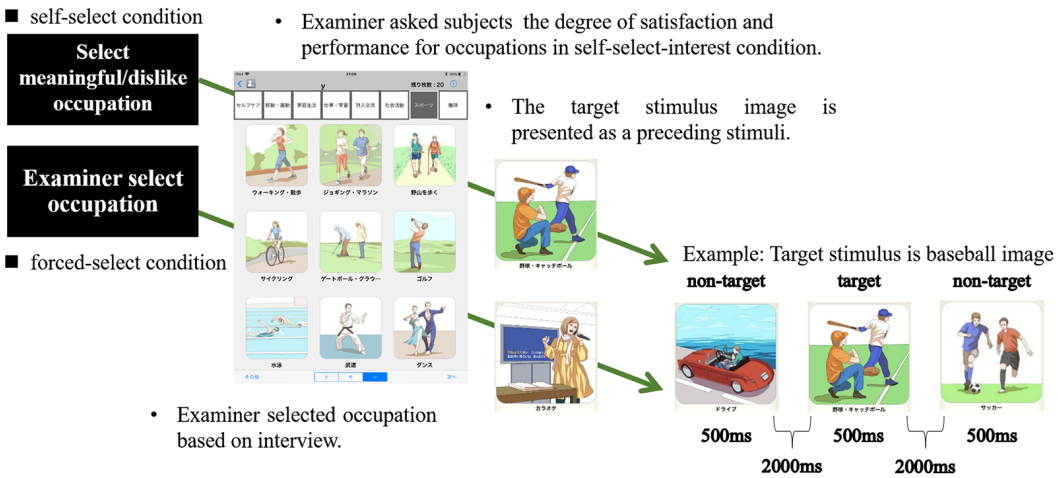

FIGURE 2 | Experimental procedure of the self-selection and forced-selection conditions. Subjects selected the target stimuli in the self-selection condition. Only in the self-selection interesting condition, subjects were asked to indicate their degree of satisfaction and performance for the occupation. We selected the target stimulus based on the interview in the forced-select condition. We conducted visual reaction tasks after the target stimuli were confirmed.

P300 amplitude reflects attention resource allocation to the task (Kaga et al., 1995) and is caused by factors such as task relevance, motivation, and alertness (Olofsson et al., 2008). P300 amplitude in the self-determination condition resulted in a more significant increase than in the forced-determination condition when the oddball task was conducted by using character images as visual stimuli (Maruta et al., 2019). Further, Suzuki et al. (2005) reported that P300 amplitude was significantly decreased while watching an interesting video than uninteresting videos in auditory stimuli task. Therefore, selecting an interesting and meaningful occupation in the ADOC suggests that attention resource allocation to the presented stimuli more increases than others' choices (SSDC and FSC).

The P300 source has not been accurately revealed various investigations on the subject. Mulert et al. (2004) suggested that the P300 source is involved in areas such as the inferior parietal lobule, temporal-parietal junction, supplementary motor cortex, anterior cingulate cortex, and superior temporal gyrus. Especially, it has been reported that the dorsal anterior cingulate cortex is activated, requiring continuous adjustment of attention distribution (Tops and Boskem, 2011). Moreover, the dorsal anterior cingulate cortex, supplementary motor area, and front insula were significantly more activated in the self-determination condition (subjects selected the design of the task tools) than in the forced-determination condition (in which the examiner made the selection; Murayama et al., 2015). These previous studies could suggest that the anterior cingulate cortex is part of the P300 origin and is activated during self-determination.

In this study, P300 amplitude might have increased significantly in SSMC because of the self-selection of interesting occupations enhances motivation and facilitates the allocation of attention resources to target stimuli. Moreover, the P300 amplitude at Fz increased, which was consistent with the results of Maruta et al. (2019). It is possible that the anterior cingulate cortex, which is activated in the SSMC, reflected P300 amplitude in this study. However, this hypothesis cannot be readily accepted because we did not analyze brain function images.

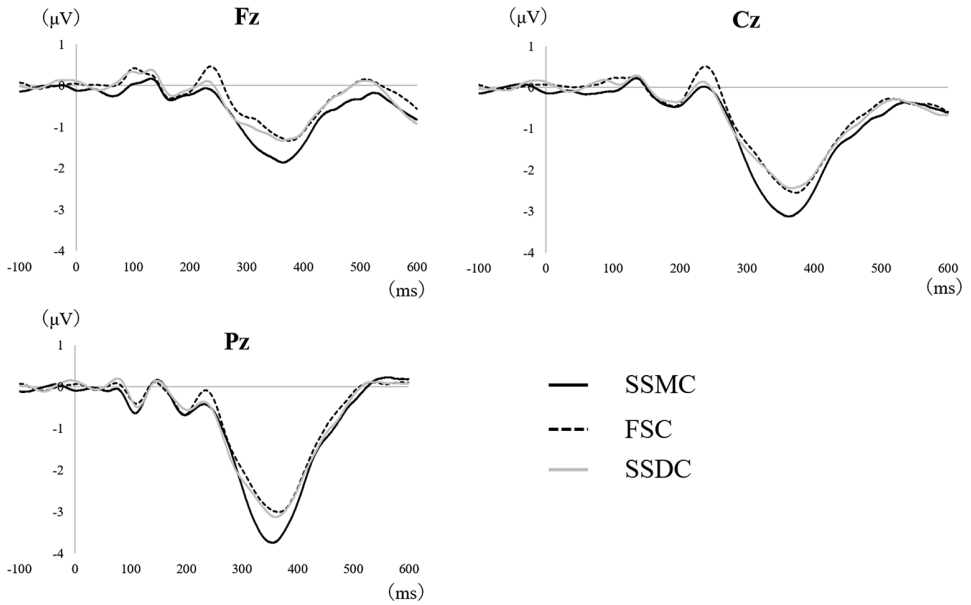

FIGURE 3 | Event-related potentials (ERP) averaging waveforms were obtained between the self-selection and forced-selection conditions (N = 22). The average waveforms of ERP obtained in all conditions were shown for three scalp sites. FSC, forced-selection condition; SSDC, self-selection dislike condition; SSMC, self-selection meaningful condition.

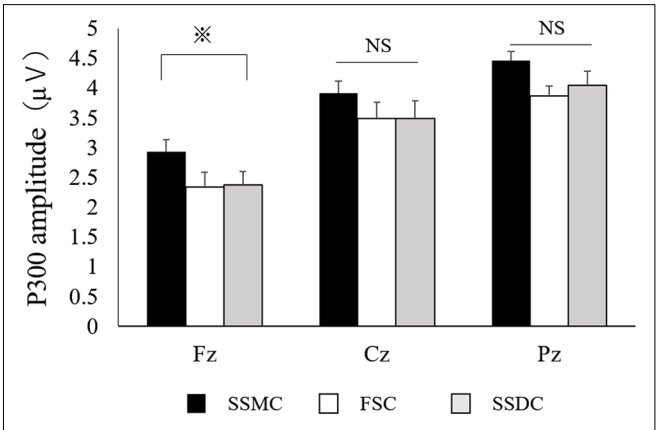

FIGURE 4 | Comparison of P300 amplitude between the self-selection and forced-selection conditions. The results of the P300 amplitude were analyzed using repeated-measures-ANOVA followed by Bonferroni *post hoc* tests. P300 amplitude at Fz significantly increased more in SSMC. FSC, forced-selection condition; SSDC, self-selection dislike condition; SSMC, self-select-meaningful condition; NS, not significant; ※$P < 0.05$.

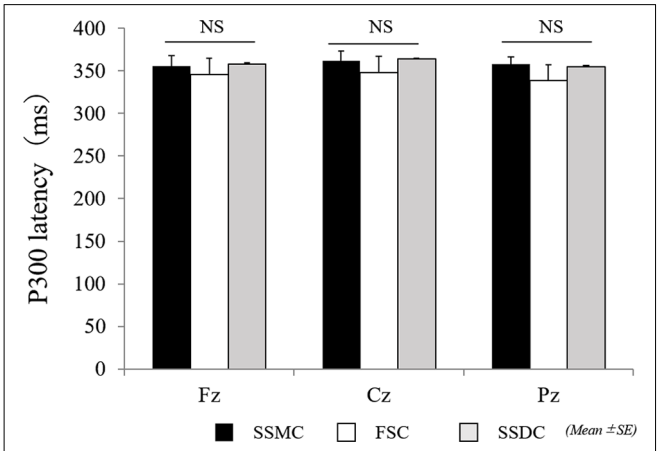

FIGURE 5 | Comparison of P300 latency between self-select and forced-select condition. The results of P300 latency were analyzed using repeated-measures-ANOVA. No significant effect was found. FSC, forced-selection condition; SSDC, self-selection dislike condition; SSMC, self-selection meaningful condition; NS, not significant.

Self-Selection Interesting Condition and P300 Latency and RT

We found that P300 latency and RT were not different between the conditions. According to previous studies, they are related to the perception processing time of stimuli (Kutas et al., 1977; Duncan-Johnson, 1981), and depend on age and task difficulty (McCarthy and Donchin, 1981; Takakura et al., 2016).

The results of the present study suggest that self-selection of interesting occupations had no significant effect on perceptual processing time because there is no significant difference in subject's age between groups and the same stimuli were presented in all conditions.

Association Between the Degree of Satisfaction for Interesting Occupations and P300

In the present study, the degree of satisfaction for the selected interesting occupation and the P300 amplitude at Pz showed a moderate positive correlation in the SSMC.

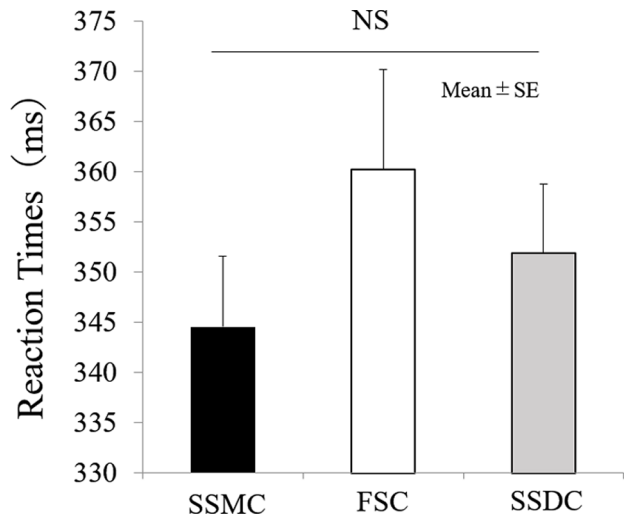

FIGURE 6 | Comparison of RT between self-select and forced-select condition. The results of RT were shown in repeated-measures-ANOVA. No main effect was found. FSC, forced-selection condition; RT, reaction time; SSDC, self-selection dislike condition; SSMC, self-selection meaningful condition; NS, not significant.

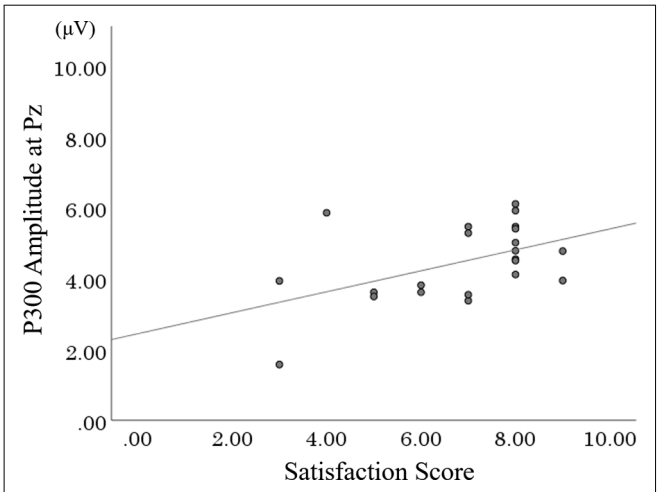

FIGURE 7 | Scatter plot of the correlation between P300 amplitude at Pz and satisfaction score in SSMC. SSMC, self-selection meaningful condition.

Meaningful activity (interesting occupation) affects the fulfillment of basic psychological needs (autonomy, relevance, and ability; Eakman, 2014). These are the basic needs on which self-determination theory is based. Meaningful occupations help to motivate by satisfying these needs. Moreover, the degree of satisfaction with daily occupations is relative to the self-evaluation of quality of life (Eklund and Leufstadius, 2007).

In this study, the self-selection of interesting and meaningful occupations increased motivation by fulfilling basic psychological needs, and their satisfaction could have promoted more cognitive processing than the other conditions (SSDC and FSC). In clinical practice, setting a goal that can enhance the satisfaction of a meaningful occupation may contribute to promoting cognitive processing responses, increasing motivation, and improving quality of life.

Association Between Psychological Characteristics and P300

The analysis of examining the association between the E score by the Maudsley personality test and the P300 component showed no association between the degree of satisfaction and performance for occupation and E score in the SSMC.

Cahill and Polish (1992) reported that extroverts tended to show a higher P300 amplitude than introverts did in an oddball task.

In contrast with the latter study, we used the participants' meaningful occupations as target stimuli instead of ranges, and so the stimuli properties and instructions were fundamentally different. Therefore, due to the differences in the methods used, our results from the experiments using visual stimuli suggest that P300 and psychological characteristics were not related.

Limitations and Issues of This Research

Regarding the limitations and issues of this research, the following points can be mentioned. The subjects of this study were young people, therefore it is necessary to investigate this phenomenon in a wide range of ages and clinical situations. Also, the ERP results in this study revealed only a tendency, and analysis of brain function images was not performed. This study was preliminarily conducted with only three basic brain sites as the first step to a bridge-setting goal and basic research in occupational therapy. Further research needs to explore the association between self-selection of interesting occupations and brain function.

CONCLUSION

The selection of an interesting and meaningful occupation in the ADOC promotes cognitive processing by increasing motivation

TABLE 1 | Association between P300 component, RT, satisfaction, performance, and E score in the self-selection interesting condition.

	SSMC P300 Amp			SSMC P300 Lat			RT
	Fz	Cz	Pz	Fz	Cz	Pz	
Satisfaction	0.371	0.418	0.457*	0.23	0.242	0.054	0.382
Performance	0.414	0.325	0.368	−0.026	−0.038	−0.029	0.235
E score	−0.274	−0.392	−0.381	0.292	0.152	0.261	−0.063

*SSMC, self-selection meaningful condition. Amp, Amplitude; Lat, Latency; RT, Reaction Time; E score, introverted/extroverted personalities types (JMPI); Spearman's rank correlation coefficient, Correlation coefficient, *P < 0.05.*

and attention resource allocation. Moreover, since we found a moderate correlation between the degree of satisfaction with occupation and attention resource allocation, we suggest that the degree of satisfaction reported for the occupations affects cognitive processing. Occupational therapists should know which occupations the patient considers interesting, and help them to select one by themselves, and, thus, may be enhancing their satisfaction after consultation. These interventions may contribute to promoting motivation and cognitive processing. Our main conclusion is that selecting an interesting and meaningful occupation promotes cognitive processing.

DATA AVAILABILITY STATEMENT

All datasets presented in this study are included in the article.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee on Epidemiological Studies, Kagoshima University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KTok conceived the concept of the manuscript. KTok wrote the first draft of the manuscript. MM, SS, GH, KTom and TT wrote the sections of the draft. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: KTok was employed by the company Department of Rehabilitation, Medical Corporation, Gyokusyoukai Takada Hospital.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
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The Vividness of Motor Imagery Is Correlated With Corticospinal Excitability During Combined Motor Imagery and Action Observation

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The present study aimed to investigate the relationship between motor imagery (MI) assessment (ability and quality) and neurophysiological assessment [transcranial magnetic stimulation (TMS)-induced motor-evoked potentials (MEPs)] during combined MI and action observation (AO; MI + AO). Sixteen subjects completed an MI task playing the piano with both hands, and neurophysiological assessment was performed during the MI task. The Movement Imagery Questionnaire-Revised was adopted to evaluate MI ability, while the visual analogue scale (VAS) was adopted to evaluate MI quality. A TMS pulse was delivered during the MI task, and MEPs were subsequently recorded in the abductor pollicis brevis (APB). We found a significant positive correlation between the VAS score and the TMS-induced MEPs ($\rho = 0.497$, $p < 0.001$). These findings suggest that the VAS score could potentially reflect the corticospinal excitability during MI + AO, particularly in complex MI tasks.

Keywords: motor imagery, neurophysiological assessment, corticospinal excitability, transcranial magnetic stimulation (TMS), movement imagery questionnaire-revised (MIQ-R), visual analogue scale (VAS)

INTRODUCTION

Motor imagery (MI) is defined as a "mental simulation" or "mental rehearsal" of movement without any actual body movement (Jeannerod, 1994; Jeannerod and Decety, 1995; Decety, 1996). Prior neuroimaging studies, an activation likelihood estimation meta-analysis, and some reviews revealed that there are similar brain areas that activated both MI and actual movements, such as the premotor area (PMA), supplementary motor area (SMA), inferior parietal lobule, superior parietal lobule, cerebellum, basal ganglia, and the prefrontal cortex (Hétu et al., 2013; Hardwick et al., 2018). Moreover, prior neurophysiological studies using transcranial magnetic stimulation (TMS) revealed that the corticospinal

excitability significantly increased during MI compared to rest (Kasai et al., 1997; Fadiga et al., 1999).

There have been several studies related to MI using neuroimaging technology and neurophysiological methods. In these studies, as supplementary data for accuracy of results, it is considered important to show the subject's MI ability to form and control accurate mental images of movement and the quality and vividness of their image of the motor act (Guillot and Collet, 2005; Sharma et al., 2006). In particular, the Movement Imagery Questionnaire (MIQ; Malouin et al., 2007), Vividness of MIQ (VMIQ; Isaac et al., 1986), and Kinesthetic and Visual Imagery Questionnaire (KVIQ; Malouin et al., 2007) are used to measure the subject's MI ability, whereas the visual analogue scale (VAS; Mateo et al., 2018) and Likert scale (Ruffino et al., 2017) describe the subjective perception of how clear and vivid the MI was. In the present study, we defined "MI ability assessment" as that which evaluates the subject's MI ability with a task that is different from the task to be learned in MI training. We defined "MI quality assessment" as that which evaluates how vividly the MI task learned during MI training was performed.

We investigated the relationship between the neurophysiological assessment and the subjective MI questionnaire used to confirm the results in the MI study. Concerning the relationship between the VAS value as an indicator of MI quality and neurophysiological assessment using TMS, the amplitude of TMS induced-motor evoked potentials (MEPs) during MI was greater at higher VAS scores (Ohno et al., 2011; Ikeda et al., 2012). Using near-infrared spectroscopy that measures concentration changes of oxygenated hemoglobin (oxy-Hb) as a neurophysiological assessment, it was found that oxy-Hb in the SMA and PMA are similarly activated during both MI and motor execution in subjects with a VAS of 80 mm or more. Moreover, the authors suggested that it might be possible to evaluate the vividness of MI from the degree of activation of the SMA and PMA (Iso et al., 2016). Other studies also found a significant correlation between MI quality assessment using a seven-point Likert scale and neurophysiological assessment using functional magnetic resonance imaging (fMRI; Lorey et al., 2011; Zabicki et al., 2019). Other studies investigated the relationship between MI ability assessment and neurophysiological assessment using TMS induced-MEP amplitude (Williams et al., 2012) and electroencephalography (EEG; Toriyama et al., 2018) and revealed a significant correlation between MI ability assessment and neurophysiological assessment.

The MI tasks used in these previous studies were relatively simple movement tasks, such as a reach movement or a single joint movement, and almost all subjects were able to image the task vividly. In the present study, we adopted a complex and task-oriented task, as these MI tasks are not readily imaged vividly. In the past, almost all TMS studies have recorded MEPs from the muscles of the hand or upper limb. The piano task had been adopted in many TMS studies (Houdayer et al., 2016; Rossi et al., 2019). In our opinion, playing the piano requires highly complex skills, such as orderly, sequential control of individual finger movements; therefore, the piano task was suitable for the TMS study, particularly the MEPs recording from finger muscles. A previous study of the relationship between cortical motor output maps evoked by TMS and the effect of MI training adopted the piano task as an MI task (Pascual-Leone et al., 1995). The piano task could be adjusted for the level of difficulty and reflects the difference in the vividness of MI among subjects. For these reasons, the piano task was adopted as the MI task in the present study. Moreover, the piano task would be suitable to be used as a motor learning task in our next study, because it has many indicators, such as velocity, duration, and precision.

Although prior studies have investigated the relationship between neurophysiological assessment and MI ability or quality assessment, few studies have investigated the relationship among these assessments simultaneously, and there is still uncertainty about which assessment can be used as ancillary data for neurophysiological assessment to reflect greater certainty. Also, in the aforementioned study using the piano task in MI training (Pascual-Leone et al., 1995), it was revealed that motor learning progresses by MI training, but there was as much performance improvement as there was physical practice alone. Moreover, MI training led to the same plastic changes in the cortical motor output maps as those shaped by physical training. Therefore, the present study aimed to clarify the relationship between the MI ability assessment, MI quality assessment, and neurophysiological assessment using TMS. Moreover, to reveal how neurophysiological assessment and MI assessment change over time, we also analyzed the change over time due to the MI session.

MATERIALS AND METHODS

Subjects

Sixteen healthy subjects (eight men and eight women, mean age 25.2 $\pm$ 5.0 years) were enrolled in the present study after providing written informed consent. All subjects are self-reported as right-handed.

The present study was based on the global guidelines for care in the use of TMS (Rossi et al., 2009). In the first stage of recruitment, all subjects filled out a questionnaire designed to exclude those with contraindications; however, none reported neurological impairment or contraindications to TMS. All experimental procedures were conducted following the Declaration of Helsinki. The study was approved by the local ethics committee at the Nagasaki University Graduate School of Biomedical and Health Sciences (No. 19061304).

Experimental MI Task

The MI task included playing the piano with both hands. The music used in the task was partially modified concerning the piano task used in a previous study (Houdayer et al., 2016), considering the difficulty of playing the piano with both hands. Subjects played the piano with a music score shown in **Figure 1** (**Figure 2** shows musical notes on a piano keyboard). **Figure 3** shows the five frames from the video clip used in this experiment. In the present study, to trigger stimulation at a specific time and match the timing of TMS and MI, a method of practicing the motor imagery while observing the video was adopted. To create the stimulus video, a model was filmed from a first-person

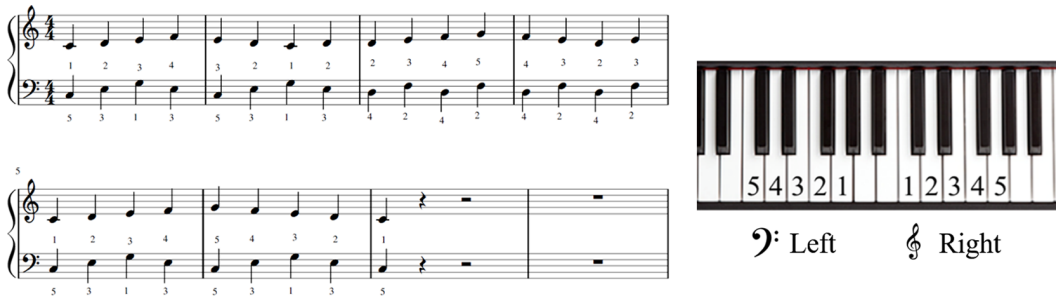

FIGURE 1 | The musical score used in this experiment.

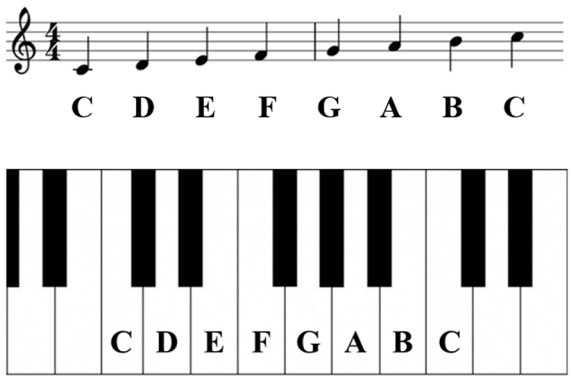

FIGURE 2 | Musical notes on a piano keyboard.

viewpoint playing the piano with both hands. The model has played the piano for over 10 years. The video was recorded using a web camera (c920r, Logicool; Lausanne, Switzerland) and had a duration of almost 33,000 ms (890 frames). We played the video by presenting a series of single frames, each lasting 33.3 ms (800 × 600 pixels, color depth 24 bits, frame rate 30 fps), which was sufficiently fast to produce an animation effect.

MI Assessment

Neurophysiological Assessment

The corticospinal excitability was assessed in each subject by recording the MEPs induced by TMS while the subject imaged the experimental task while observing the stimulus video. To trigger stimulation at specific times, WMV files were converted to JPEG files consisting of 890 individual frames, and the stimulus video was shown in succession to obtain the animation effect. The presentation time of each frame was twice the length of the refresh interval used by the PC monitor (refresh interval = 16.67 ms).

Before the MI task, corticospinal baseline excitability at rest was assessed in each subject by recording 10 MEPs while the subject observed a white cross on a black screen under controlled conditions. The interval between the TMS stimuli was 10 s in controlled conditions. Subsequently, the experimenter instructed the subject to imagine playing the piano with both hands as if doing it for real and started to assess the corticospinal excitability during combined MI and action observation (AO; MI + AO). TMS was delivered once for each video clip, randomly at the timing of striking a C or G note. In summary, 50 trials were conducted in all MI task conditions. We used a custom-made computerized pulse-generation system. To ensure that TMS was always delivered at the correct time and that the experimental design was correctly implemented, the order of TMS delivery times (C and G notes) was randomized by using the LabView system (LabView, National Instruments; Austin, TX, USA).

Surface electromyography (EMG) activity was recorded in the right abductor pollicis brevis (APB) and the right abductor digiti minimi (ADM) muscles, using pairs of 9-mm Ag–AgCl surface cup electrodes (SDC112, GE Healthcare; Chicago, IL, USA). Surface EMG signals were amplified and filtered at a bandwidth of 5–3,000 Hz using a digital signal processor (Neuropack Sigma MEB-5504, Nihon Kohden; Tokyo, Japan). Analog outputs from a single processor were digitized at a sampling rate of 10 kHz and saved onto a computer for off-line analysis using an A/D converter (PowerLab16/30, AD Instruments; Bella Vista, NSW, Australia).

At the beginning of the experiment, we identified the optimal TMS coil position for evoking the greatest MEPs in both the right APB and the right ADM (the hot spot). TMS was delivered to the left primary motor cortex hot spot, marked with a pen on a swimming cap covering the scalp of each subject. TMS was employed *via* a 70-mm figure-eight coil connected to a magnetic stimulator (Magstim200, Magstim; Whitland, UK). The coil was placed tangentially to the scalp with its handle pointing backward and rotated approximately 45° away from the mid-sagittal line. Care was taken to maintain the same coil position relative to the scalp throughout the experiment. The resting motor threshold (MT) was defined as the lowest stimulus intensity that evoked an MEP at least 50 μV in amplitude in the right APB and ADM in 5 out of 10 trials. The test stimulus intensity was set at 110–130% of the resting MT and the size of the test stimuli ranged from 33 to 85% (mean 60.9 ± 11.9%). The mean size of the control MEP for the APB and ADM was approximately 0.5–1.0 mV. Throughout the experiments, subjects were instructed to avoid inadvertent movements that could give rise to background EMG

FIGURE 3 | The sequence of stills from the video clip used in the motor imagery (MI) task. The frame in the dashed box is at the timing of striking a C note and the frame in the solid box is at the timing of striking a G note. During the first 150 frames, a white cross in the center of a black screen was presented. Following the action being displayed, a C note was struck at 155, 335, 635, and 880 frames (of 890 in total) after action onset (after the white cross disappears). After 506/890 frames of the action onset, a G note was struck. TMS was delivered at one of these five-time points. TMS, transcranial magnetic stimulation.

activity. For each muscle in each trial, the 20-ms period preceding TMS triggering was checked for background EMG activity. If background EMG data was found, data from both muscles in the trial were rejected. MEP amplitude (peak-to-peak) was measured over each muscle in every trial. MEP amplitude was analyzed using peak-to-peak values and expressed as a percentage of the mean amplitude under control conditions.

MI Quality Assessment

The VAS has been widely used for subjective assessment of pain (Bijur et al., 2001; Suso-Martí et al., 2019) where patients mark the degree of pain on a 100-mm horizontal line. Recently, the VAS has been used for assessing the vividness of MI (Mateo et al., 2018). In this study, subjects marked a location on a 100-mm horizontal line, the two ends of which were labeled "0 = none at all" and "100 = very highly vivid image," according to the vividness of the imagery they experienced.

MI Ability Assessment

All participants completed the Movement Imagery Questionnaire-Revised (MIQ-R; Hall and Martin, 1997) at the beginning of the experiment. The MIQ-R evaluates the subject's ability to see (visual imagery) and feel (kinesthetic imagery) different movements, such as jumping, knee raising, and trunk flexion. This assessment consisted of eight separate movement items (four visual and four kinesthetic conditions). First, subjects performed the movement item, imagined the movement, and then scored their imagery using a seven-point Likert scale (1 = very hard to see/feel; 4 = neutral (not easy/not hard); 7 = very easy to see/feel, and intermediate levels). The MI ability was evaluated based on the total score; the higher the total MIQ-R score, the higher the MI ability.

Experimental Procedure

We investigated which MI assessment (ability or quality) was strongly associated with the neurophysiological assessment.

First, to evaluate the subject's MI ability, subjects underwent the MIQ-R. Next, to eliminate cognitive elements as much as possible in the task of playing the piano with both hands, which is an experimental MI task, we gave the subjects time to learn the order in which the keys were struck. There was no time limit, and the test was performed until the subject learned the order in which to strike. After fully understanding and confirming the MI tasks such as the timing of striking the keys by self-reporting, the neurophysiological assessment was started. TMS was performed once for each trial, for 50 stimulations during 50 trials of the MI task. The MI quality was assessed using the VAS every 10 trials to evaluate how vivid the total of 10 instances of MI tasks was imaged. In the end, MI quality was assessed five times over 50 trials. The analysis was conducted multilaterally based on the data obtained in each evaluation.

Data and Statistical Analysis

If background EMG data was found, data from both muscles in the trial were rejected. The MEP amplitude (peak-to-peak) was measured over each muscle in every trial. MEP amplitude was analyzed using peak-to-peak values and expressed as a percentage of the mean amplitude under control conditions.

Confirmation of Muscle-Specific Activity During MI + AO

A previous study on MI using TMS revealed that MEPs recorded from muscles involved in the imagined movement are spatially and temporally modulated during imagined movement, as they are during actual movement (Stinear and Byblow, 2003). To confirm whether the MEPs were modulated in a muscle-specific manner during MI + AO in the present study, the data from 50 trials were statistically analyzed using two-way analysis of variance (ANOVA) comparing muscles (APB, ADM) and timing of key strikes (striking a C note with a thumb, striking a G note with a little finger). Planned *post hoc* multiple comparisons were conducted using Bonferroni's test.

Transition of Neurophysiological Assessment and MI Quality Assessment Among Each Set

To check whether the MEP (neurophysiological assessment) or VAS (MI quality assessment) results changed over time, the data were statistically analyzed using ANOVA according to sessions (first, second, third, fourth, fifth). Planned *post hoc* multiple comparisons were conducted using Dunnett's test.

Relationship Between Neurophysiological Assessment and MI Quality Assessment

Subjects were asked for an "MI quality assessment" (VAS) every 10 MI task trials and five VAS assessments were conducted over the 50 MI task trials. Neurophysiological assessment (TMS assessment) was conducted every MI task trial, and the average of the data obtained in every 10 trials (relative MEP amplitude) was calculated, and five MEP amplitudes were calculated in

50 trials. Spearman's correlation analysis was performed using the corresponding data of each assessment to investigate the relationship between TMS assessment and VAS assessment.

Relationship Between Neurophysiological Assessment and MI Ability Assessment

Subjects were asked for an "MI ability assessment" (MIQ-R) only once before starting the MI task trial. Neurophysiological assessment (TMS assessment) was conducted every MI task trial, and the average of the data obtained in 50 trials (relative MEP amplitude) was calculated. Spearman's correlation analysis was performed using the corresponding data of each assessment to investigate the relationship between the TMS assessment and the total MIQ-R score.

Relationship Between MI Quality Assessment and MI Ability Assessment

Subjects were asked for an "MI quality assessment" (VAS) every 10 MI task trials and five VAS assessments were conducted over the 50 MI task trials. On the other hand, subjects were asked for "MI ability assessment" (MIQ-R) only once before starting the MI task trial. Spearman's correlation analysis was performed using the corresponding data of each assessment to investigate the relationship between the VAS data assessed in each session and the total MIQ-R score.

RESULTS

MI Ability Assessment

The total average MIQ-R score was 47.6 ± 7.5, the total average kinesthetic score was 24.6 ± 3.6, and the total average visual score was 23.0 ± 5.1.

Muscle-Specific Modulation of MEP Amplitudes During MI

The mean MEP amplitudes as a percentage of control (± standard error) induced in the right APB and ADM in response to a single-pulse TMS are shown in **Figure 4**. Two-way ANOVA revealed a significant interaction between "Timing of TMS" and "muscle" ($F_{(1,15)} = 17.425$, $p < 0.01$).

Post hoc analysis revealed that MEPs recorded from the APB in the timing of "striking a C note with a thumb" significantly increased compared to the timing of "striking a G note with a little finger." Moreover, MEPs recorded from the ADM in the timing of "striking a G note with a little finger" significantly increased compared to the timing of "striking a C note with a thumb." From these results, the present study revealed the muscle-specific modulation of MEP amplitudes during MI + AO, in line with a previous study (Stinear and Byblow, 2003).

Progression of MEP and VAS Scores Over Time

The mean VAS scores in each session are shown in **Figure 5**. One-way ANOVA revealed a significant main effect of "session" ($F_{(4,60)} = 15.973$, $p < 0.001$). *Post hoc* multiple comparisons revealed that MEPs in the second, third, fourth, and fifth sessions were significantly greater than those observed in the first session

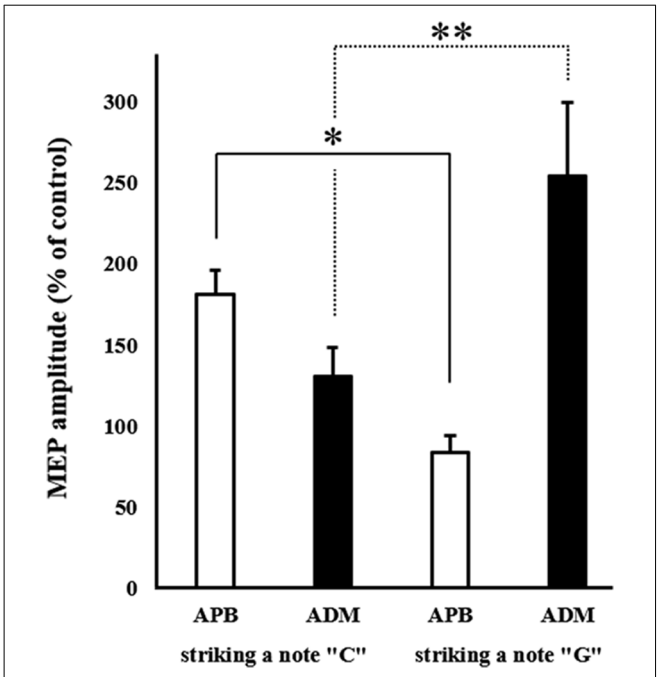

FIGURE 4 | Mean MEP amplitudes over the right APB and ADM at the two different timings of TMS during combined MI and action observation (AO). Values are expressed as a percentage of control condition amplitude ($n = 16$). Data are presented as mean ± SE. The asterisk (*) and double-asterisk (**) indicate differences between conditions. *$p < 0.001$, **$p < 0.05$. ADM, abductor digiti minimi; APB, abductor pollicis brevis; MEP, motor-evoked potential; TMS, transcranial magnetic stimulation.

(second session: $p < 0.01$, third, fourth, and fifth sessions: $p < 0.001$).

The mean MEP amplitudes recorded from the APB in each session are shown in **Figure 6**. One-way ANOVA revealed a significant main effect of "session" ($F_{(4,60)} = 3.910$, $p < 0.01$). *Post hoc* multiple comparisons revealed that MEPs in the fifth session were significantly greater than those observed in the first session ($p < 0.01$).

Relationship Between Neurophysiological Assessment and MI Quality Assessment

A significant positive correlation was detected between the VAS and MEP ($\rho = 0.497$, $p < 0.001$; **Figure 7**).

Relationship Between Neurophysiological Assessment and MI Ability Assessment

There was no significant correlation between the MIQ-R and MEP (*non-significant*; **Figure 8**).

Relationship Between MI Quality Assessment and MI Ability Assessment

There was no significant correlation between the VAS assessed in each session and the total MIQ-R score.

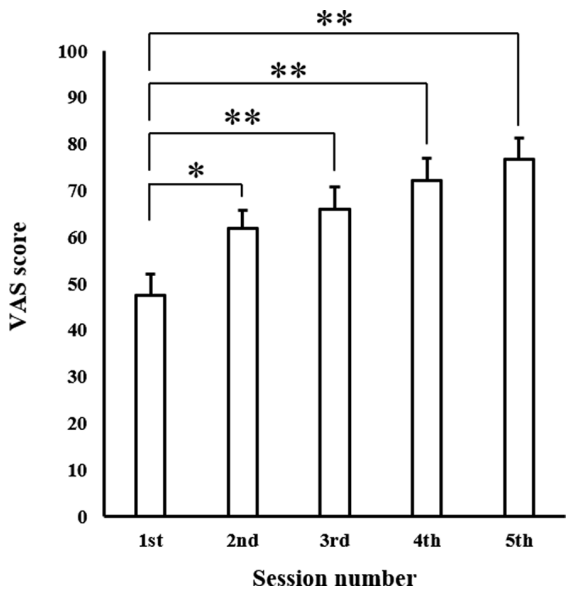

FIGURE 5 | Mean MI ability assessment results in each session. Values represent VAS score (n = 16). Data are presented as mean ± SE. The asterisk (*) represents $p < 0.01$, and the double-asterisk (**) represents $p < 0.001$. VAS, visual analogue scale.

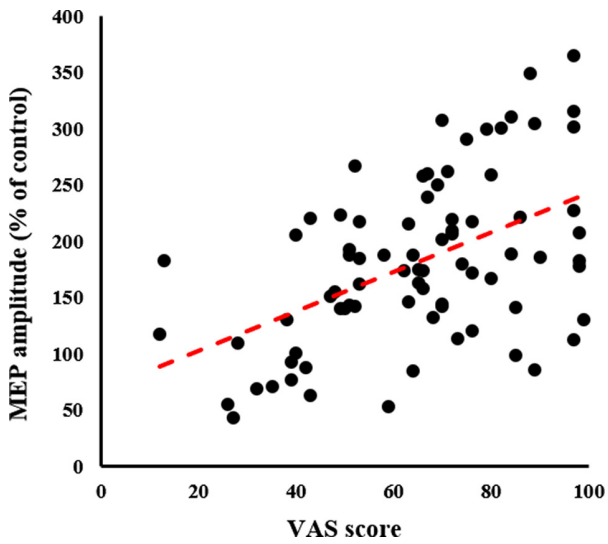

FIGURE 7 | Relationship between MI quality assessment and neurophysiological assessment. The X-axis represents the VAS score and the Y-axis represents MEP amplitude as a percentage of the control condition; significant Spearman's correlation (ρ = 0.465, $p < 0.001$) is noted. The higher the VAS score, the greater the MEP amplitude. MEP, motor-evoked potential; VAS, visual analogue scale.

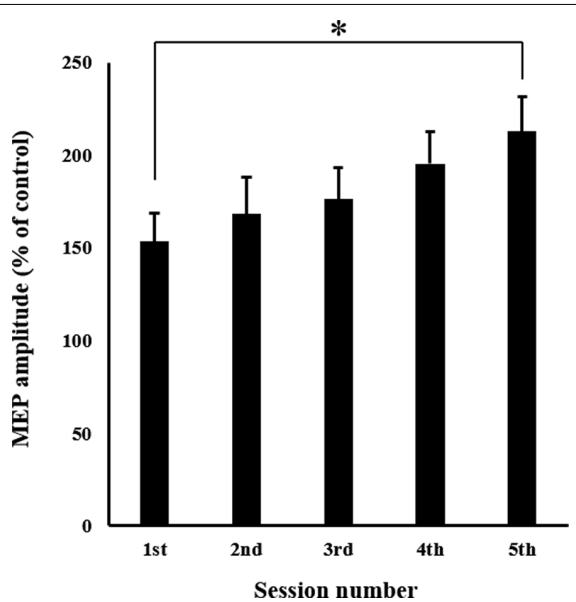

FIGURE 6 | Mean MEP amplitudes over the right APB in each session. Values are expressed as a percentage of control condition amplitude (n = 16). Data are presented as mean ± SE. The asterisk (*) represents $p < 0.01$. APB, abductor pollicis brevis; MEP, motor evoked potential.

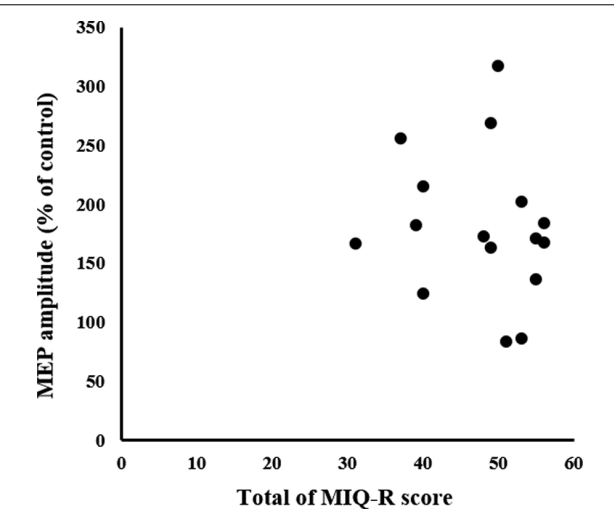

FIGURE 8 | Relationship between MI ability assessment and neurophysiological assessment. The X-axis represents the total MIQ-R score and the Y-axis represents MEP amplitude as a percentage of the control condition; no correlation is seen. MEP, motor-evoked potential; MIQ-R, Movement Imagery Questionnaire-Revised.

DISCUSSION

Previous studies on MI have investigated the relationship between neurophysiological assessment and MI ability assessment (Lebon et al., 2012; Wang et al., 2014; Toriyama et al., 2018) or MI quality assessment (Lorey et al., 2011). Only a few studies have investigated the multiple relationships between these assessments (Mizuguchi et al., 2019); therefore, there are still many uncertainties. To reveal which assessment reflects the outcome of the neurophysiological assessment, as supplementary data for accuracy of results, we investigated the various relationships among MI ability assessment, MI quality assessment, and neurophysiological assessment. As a result, we only found a positive correlation between the MI quality assessment, which evaluates the vividness of the tasks learned

in MI training, and neurophysiological assessment. Similar to previous studies on MI using TMS, we also found that the primary motor cortex corresponding to the muscle activity activated during actual movement was activated in a muscle-specific manner. Therefore, the task itself and the accuracy of the experiment are considered valid. Moreover, we found that the neurophysiological assessment (TMS-induced MEPs) and MI quality assessment (VAS) significantly changed over time during the MI + AO session.

There are many questionnaires for MI assessments, including the KVIQ, VIMQ, Likert scale, and VAS, but we used the MIQ-R for MI ability assessment and the VAS for MI quality assessment. The former assessed the subject's MI ability, while the latter assessed the degree of vividness for the task of imaging movement. As an analogy, we use the results of a "physical fitness test" (Henriques-Neto et al., 2020) which comprises grip strength, repeated side jumps, 50-m running, and other tests to evaluate individual motor skills. The physical fitness test is to comprehensively judge the subject's fundamental motor ability. If this score is high, it can be interpreted that the comprehensive fundamental motor ability is high. However, when looking at individual events, it is not always possible to say that any sport can be practiced well just because the results of a physical fitness test are good. It is the same with MI ability assessment in MI, and it is considered that a person with a high MI ability score does not necessarily vividly imagine all MI tasks. In the present study, we examined the relationship between neurophysiological assessment and each MI assessment using tasks that are incompatible with the tasks used during MI ability assessment. As a result, we found a positive correlation only between neurophysiological assessment, particularly corticospinal excitability, and MI quality assessment. In a previous study, there are significant positive correlations between the MI quality assessment [i.e., perceived vividness using seven-point scale rating from very high (7) to very low (1)] and neural activation in the left ventral premotor cortex and right inferior parietal lobule by fMRI (Zabicki et al., 2019). The authors argued that the activation state of the primary motor cortex is tuned by the activation state of the premotor cortex and can, therefore, be associated with subjective vividness. Although they could not suggest a detailed mechanism, our findings suggest that the difference of vividness affected the activation of the primary motor cortex due to changes in the premotor cortex activation. In MI tasks with object-related movement, the vividness of MI is parametrically associated with neural activity within sensorimotor areas (Lorey et al., 2011). In MI tasks with finger tapping, MI quality assessment by VAS correlated with the activity of the right orbitofrontal cortex (Houdayer et al., 2016). These results support our findings and it is suggested that brain activity during MI could change depending on MI quality assessment, which is the degree of vividness in the task of MI.

In the present study, we did not find a correlation between MI ability assessment and neurophysiological assessment. In a previous study examining the relationship between MI ability assessment and neurophysiological assessment in a tennis movement task used as an MI task, tennis players and novices were evaluated for MI ability assessment, and in a neurophysiological movement task, only tennis players had a significant correlation (Fourkas et al., 2008). Similar results were found in a study on badminton players (Wang et al., 2014). However, when simple movements such as thumb opposition movements and wrist movement are used as MI tasks, a significant correlation was found between MI ability assessment and neurophysiological assessment (using TMS and EEG; Williams et al., 2012; Toriyama et al., 2018). To summarize the results of these findings, in tasks involving proficiency when experts and novices were compared, a correlation was found only for experts, whereas for simple actions that were relatively easy and could be performed by anyone, there was a correlation. Considering these previous findings, it was suggested that whether there was a correlation between MI ability assessment and neurophysiological assessment could be determined by whether the task using MI was mastered or not.

We also found that neurophysiological assessment (TMS-induced MEPs) and MI quality assessment (VAS) significantly changed over time during the MI + AO session in the present study. A previous study showed that MI training led to the development of neuroplasticity (Avanzino et al., 2015). Moreover, another study showed that corticospinal activation during MI is positively related to the magnitude of imagery-dependent motor cortical plasticity following MI training (Yoxon and Welsh, 2020). In the present study, we observed the changes over time in a short period, only 50 times, but in the future, we will assess long-term changes. It is also necessary to investigate the relationship with the performance of actual motor learning.

A limitation of this study is the small sample size; there were 16 subjects, which might not be a sufficient sample size to collect relevant data. Furthermore, we did not perform sample size estimation and power analysis before the beginning of the study. The lack of significance in some statistical tests may be due to the small sample size.

CLINICAL IMPLICATION

Motor imagery training involves repeatedly performing motor imagery to improve the performance of exercise tasks, and has been applied in the fields of sports, rehabilitation, and music. Particularly, in the field of rehabilitation, motor imagery training has shown to be beneficial in the recovery of an affected upper limb and balance in some systematic reviews (García Carrasco and Aboitiz Cantalapiedra, 2016; Guerra et al., 2017). Moreover, a previous study in healthy subjects has found high vividness scores to be related to greater improvement (Ruffino et al., 2017). These findings suggest that it is important how vividly a subject can perform motor imagery in order to practice effective motor imagery training. We determined that motor imagery vividness is positively correlated with amplitudes of motor-evoked potentials, but there was no correlation between motor-evoked potentials and motor imagery ability. Our findings might be useful to evaluate how vividly a subject can perform motor imagery; however, there are many unclear points. To further explore the relationship between the effects of motor imagery training and motor imagery assessment, future studies should investigate the relationship from various aspects.

CONCLUSION

MI quality assessment can be performed regardless of the type of MI task or an individual's proficiency for the task. Therefore, MI quality assessment, which assesses the vividness of imagination, maybe a more useful assessment as supplementary data to guarantee the accuracy of results for MI studies.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Nagasaki University Graduate School of Biomedical and Health Sciences (No. 19061304). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TMo, NI, and THi conceived and designed the experiments. TMo, AN, KA, KN, and THa performed the experiments. TMo, NI, and THi analyzed the data. TMo and JN created the experimental program. TMo, KN, NI, and THi drafted the manuscript. All authors contributed to the article and approved the submitted version.

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Relationship Between Attention Bias and Psychological Index in Individuals With Chronic Low Back Pain: A Preliminary Event-Related Potential Study

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Introduction: Attention bias towards pain-related information exists in patients with chronic pain, and recently, attention bias modification (ABM) training has been administered to patients with chronic pain. In this study, we conducted an attention bias modification task in conjunction with event-related potential measurements for individuals with chronic low back pain (LBP) and investigated the relationship between attention bias and psychological assessment.

Methods: Eleven women and two men with chronic LBP participated in the study.

Results: The Japanese version of the STarT Back Screening Tool (J-SBST) total score was significantly correlated with the N1 amplitude of Cz. The J-SBST psychological score was significantly correlated with the N1 amplitude of Cz and with reaction time (RT). The Japanese version of the Pain Catastrophizing Scale (PCS) and Japanese version of the Beck Depression Inventory-Second Edition (BDI-II) scores were significantly correlated with the P2 amplitude at Fz (only PCS), Cz, and Pz.

Conclusions: Our findings suggest that J-SBST, which provides a comprehensive evaluation of psychological factors, PCN with measuring of catastrophizing in the context of actual or anticipated pain, and BDI-II, can likely help identify chronic LBP patients with attention bias. For chronic LBP patients who are classified according to J-SBST or PCN pain-related outcome improvement with ABM training can be expected.

Keywords: attention bias modification, chronic low back pain, event-related potentials (ERP), psychological index, individuals

INTRODUCTION

The role of attention processing in chronic pain is important (Pincus and Morley, 2001), and many studies have investigated the existence of attention bias towards pain-related stimuli. A meta-analysis investigating attention bias to pain-related information indicates that attention bias towards pain-related words or pictures exists in people with chronic pain (Schoth et al., 2012; Crombez et al., 2013). Attention bias is generally divided into avoidance and hypervigilance from the direction of the bias of attention, and Herbert et al. (2014) reported that pain hypervigilance is associated with pain intensity and clinical disability, as well as enhanced pain sensitivity. Attention bias to pain can lead to an increased disability, enhanced pain catastrophizing, and avoidance of activities. Psychological factors, including fear-avoidance beliefs or somatizing tendency, had a significant association with chronic low back pain (LBP) among care workers (Yoshimoto et al., 2019). The Subgrouping for Targeted Treatment Back (STarT Back) Screening Tool (SBST) to assess and stratify patients with LBP according to the risk of LBP chronicity as psychological factors has been globally used and indicated that stratification of risk groups by the Japanese version of the SBST (J-SBST) may help predict prognosis of LBP (Matsudaira et al., 2016, 2017).

In the literature related to anxiety, attention bias towards threat has been indicated (Bar-Haim et al., 2007; Bar-Haim, 2010). Attention bias modification (ABM) is a recently developed psychological intervention to modify attention bias towards negative stimuli for such anxiety disorders (Bar-Haim et al., 2007; Hakamata et al., 2010). Numerous reports confirm the effectiveness of ABM, particularly effective for reducing threat bias and anxiety symptoms in people with generalized anxiety and social phobia (Amir et al., 2009a,b; Schmidt et al., 2009). The dot-probe task is a widely used method for assessing attentional bias (MacLeod et al., 1986). In the dot-probe task, a randomized pair of stimuli, one which is neutral and the other, a threat-perception negative emotion, is presented on the upper and lower portions of a screen, respectively; the neutral stimulus is chosen over the stimulus that causes negative emotion. Repeating these tasks provides a way to desensitize negative emotions. MacLeod et al. (2002) developed a computerized task to train participants to attend away from a negative stimulus. ABM has been applied not only to anxiety (Hakamata et al., 2010; Tayama et al., 2018) but is also used for smokers (Attwood et al., 2008) and alcoholic patients (Schoenmakers et al., 2010), and the effects have been reported.

Recently, ABM training has also been administered to chronic pain patients (Dehghani et al., 2004; Sharpe et al., 2012; Schoth et al., 2013; Heathcote et al., 2017). For example, in a randomized controlled trial for 34 chronic pain patients, the ABM training group showed a significant reduction in pain-related outcomes, such as anxiety sensitivity and functional disability than did the placebo group (Sharpe et al., 2012). However, a randomized controlled trial for 66 adolescents with chronic pain reported that there was no evidence that ABM changed attentional bias or that pain-related outcomes differed between the ABM and placebo or no-training groups (Heathcote et al., 2017). In patients with chronic pain, the effectiveness of ABM training is not well established and further studies are required.

Reaction time (RT) is usually used as an index of attention bias in the dot-probe task, however, poor internal reliability is indicated (Kappenman et al., 2014). Therefore, in addition to the RT index of attention bias, recent studies measure event-related potentials (ERPs) of the electroencephalogram (EEG) in conjunction with the dot-probe task (Holmes et al., 2009; Kappenman et al., 2015; Gibb et al., 2016). The ERPs exhibit superior temporal resolution and can provide a more direct measure of attention allocation in attention bias in conjunction with the dot-probe task. In ERPs study of patients with anxiety, P140 amplitude was increased using a visual dot-probe task (Rossignol et al., 2013), and N200 amplitude was increased using emotion-word Stroop task (Sass et al., 2014), and initial shift in attention to threat stimuli has been identified. The parietal P100 component is an early visual ERP component whose amplitude and latency are affected by the neural processing of facial expressions (Kolassa et al., 2006). N1 reflects feature detection and sensory attention capture based on the salience of the stimulus from two visual-detection experiments (Wascher et al., 2009), and maybe attributed to increased efforts to divert attention away from visual threat stimuli (Dennis and Chen, 2007). The generator mechanisms are not fully understood, it is classically known that sensory regions are one of the generators of N1 (Picton et al., 1976). P2 has been associated with the processing of emotion in faces (Carretié et al., 2001), and was a neural response that is sensitive to threat-related stimuli using dot-probe task (O'Toole and Dennis, 2012). N2 component reflects attention control and inhibition mechanisms (Falkenstein et al., 1999; Flostein and Van Perren, 2008), and maybe attributed to increased efforts to divert attention away from visual threat stimuli (Dennis and Chen, 2007). P3 has been associated with the strategic orienting of attention (Friedman et al., 2001; Fichtenholtz et al., 2007). In the attention bias task in patients with anxiety, the discussion is divided such as slight appear (Eldar and Bar-Haim, 2010; O'Toole and Dennis, 2012) and not appear (Dennis-Tiwary et al., 2016; Tayama et al., 2018), and early components are receiving more attention. However, only a few studies on attention bias in patients with chronic pain have used ERP measurements.

In this study, we have conducted the ABM task in conjunction with ERP measurements for individuals with chronic low back pain (LBP), which has a high prevalence in Japan (Nakamura et al., 2011). This study aimed to clarify the relationship between attention bias and psychological assessments of individuals with chronic LBP, we examined the attentional component of the ERPs as well as the RT in the ABM to determine whether patients with chronic LBP who have higher socio-psychological factors such as fear-avoidance, catastrophizing and depression show more attentional bias to threat stimuli, therefore, this study can provide psychophysiological insight into how the psychological domains and its severity in individuals with chronic LBP relate to attention bias using ERP as well as RT. We contribute to the development of ABM training, occupational therapy, and management in individuals with LBP.

MATERIALS AND METHODS

Participants

A total of 11 women and two men with chronic LBP were recruited from the local community (mean age: 70.3 ± 8.3 years). Participants met the following inclusion criteria: (1) a minimum of a 6-month history of pain; (2) absence of neurological or psychiatric disorders; (3) absence of other chronic disorders. All participants had a normal or corrected-to-normal vision. The study was approved by the research ethics committee of Nishikyushu University and was conducted following the Declaration of Helsinki.

Attention Bias Modification Task

We used a personal computer (AT992; EPSON, Nagano, Japan), a 19-inch monitor (Pro-Lite E1980SD; Iiyama, Tokyo, Japan), and an image controller (MTS0410; Medical Try System, Tokyo, Japan) for the ABM task. The distance between the participant and the center of the monitor display was about 65 cm. We used facial images of eight different people from The Japanese Female Facial Expression database as visual stimuli. Neutral and threat (angry or fear) facial expression images were used for the task.

On each trial, a randomized pair of neutral and threat facial expressions were presented against a white background on the upper and lower portions of the screen, respectively. The ABM task consisted of three blocks. Following a 500-ms presentation of a fixation cross at the center of the screen, the target image pair was presented for 500 ms. Following the removal of the images, a symbol ("E") was presented at the bottom of the screen until the participant pressed the button (**Figure 1**). Participants were required to indicate the position of the neutral face as rapidly and accurately as possible by pressing one of two buttons on a button box using the middle or index finger of the dominant hand. RT was measured starting at probe presentation. Trial with RTs that were <200 ms or >1,000 ms and those with incorrect answers were excluded from the analysis (Dehghani et al., 2004). Each participant performed 128 trials.

EEG Recordings and Analysis

We used the Neuropack X1 MEB-2300 series electromyogram measuring system (Nihon Kohden Corporation, Tokyo, Japan) for EEG measurements and the EPLYZER2 (Kissei Comtec, Matsumoto, Japan) for waveform analysis. The EEGs were recorded with Ag/AgCl disk electrodes placed at the Fz, Cz, and Pz positions (Mühlberger et al., 2009; Tayama et al., 2018) according to the International 10-20 system. Each scalp electrode was referenced to linked earlobes. The ground electrode was placed at the Fpz position. To eliminate eye movements or blinks exceeding 100 μV, electrooculograms were also recorded. Also, subject muscle movements were monitored and recorded on video. Electrode impedance was maintained below 5 kΩ. The EEG was digitized at a sampling rate of 1,000 Hz. EEG data in the range of 200 ms pre-stimulus to 600 ms post-stimulus were epoched. The N1 and N2 peaks were measured as the voltage at the most negative peak in the latency window of 100–150 ms and 150–300 ms after stimulus onset at all electrode positions. The P1, P2, and P3 peaks were at the most positive peak in the latency window of 50–100 ms, 100–200 ms, and 250–500 ms at all electrode positions. The final ERP waveforms were obtained by removing electrooculograms and muscle movements from the only waveforms of correct in the ABM task.

Psychological Measurements

Japan Low Back Pain Evaluation Questionnaire (JLEQ)

The JLEQ is a 30-item, self-administered questionnaire including seven questions on LBP status in the previous few days (items 1–7), 17 questions on problems with activities of daily living due

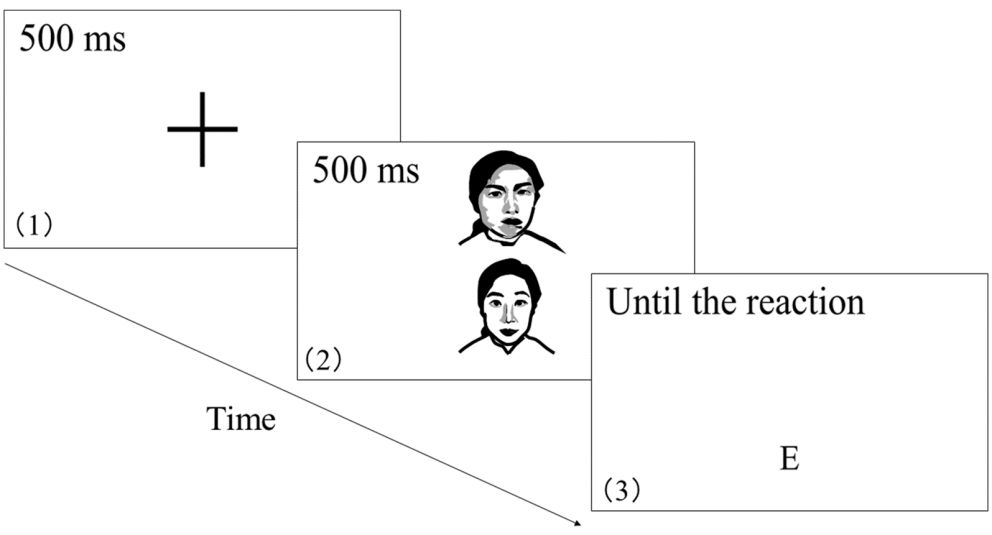

FIGURE 1 | The procedure of attention bias modification (ABM) task. The image presentation sequence and duration were as follows: (1) fixation cross was presented for 500 ms; (2) target image pair was presented for 500 ms; (3) symbol was presented at the bottom of the screen until the participant pressed the button. Participants were required to indicate the position of the neutral face as rapidly and accurately as possible by pressing one of two buttons on a button box.

to LBP (items 8–24), and six questions on general health and psychological status in the previous month (items 25–30). Each of the questions was scored on a 5-point scale. The JLEQ scores provide a measure of the level of impairment in activities of daily living of patients with chronic LBP and have shown adequate validity and reliability (Shirado et al., 2007).

Japanese Version of the Fear Avoidance-Beliefs Questionnaire (FABQ)

The FABQ is a 16-item measure of fear-avoidance beliefs in patients with LBP (Waddell et al., 1993). Items 2–5 evaluate fear-avoidance beliefs about physical activity, and items 6, 7, 9–12, and 15 evaluate fear-avoidance beliefs about work. Each question is scored on a scale of 0–6. We evaluated fear-avoidance beliefs about physical activity. Good psychometric properties have been reported in Japanese workers with LBP (Matsudaira et al., 2014).

Japanese Version of the STarT Back Screening Tool (J-SBST)

The STarT Back has been widely used to stratify patients with LBP according to the risk for chronicity. The STarT Back consists of nine items. Items 1–4 evaluate physical factors, and items 5–9 assess psychosocial factors, related to LBP (Hill et al., 2008). Response options for items 1–8 are "disagree" (0 points) or "agree" (1 point). Responses to item 9 are on a scale of 1–5: "not at all," "slightly," "moderately," "very much," or "extremely." The first three options ("not at all," "slightly," and "moderately") are scored as 0, and the remaining two options ("very much" and "extremely") are scored as 1. Good psychometric properties and validity have also been reported for the Japanese version of the STarT Back (J-SBST; Matsudaira et al., 2016).

Japanese Version of the Pain Catastrophizing Scale (PCS)

The PCS is a 13-item, self-administered questionnaire to measure pain catastrophizing and has shown high levels of reliability and validity (Sullivan et al., 1995). Each question is scored on a scale of 0–4. The total scores range from 0 to 52. Adequate reliability and validity have been also reported for the Japanese version (Matsuoka and Sakano, 2007).

Japanese Version of the Beck Depression Inventory-Second Edition (BDI-II)

The BDI-II, a widely-used, self-reporting instrument for measuring the severity of depression, consists of a 21-item questionnaire. Each question is scored on a scale of 0–3. The total scores range from 0 to 63. The Japanese version of the BDI-II has also been reported to exhibit adequate validity and reliability (Kojima et al., 2002).

Statistical Analysis

Statistical calculations were carried out using IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). The analysis of correlation was performed after checking data with a normal distribution using the Shapiro-Wilk test. If the normal distribution was confirmed, Pearson's correlation was calculated. If non-parametric data were found, Spearman's correlation was analyzed. We performed Pearson's correlation analysis to determine whether the N1 amplitude, P2 amplitude, and RT are related to the psychological index. The analysis was performed on all data obtained from 13 participants. $P < 0.05$ was statistically significant.

RESULTS

Latencies and Amplitudes of Each Component in ERP and RT in the ABM Task

The mean RT in the ABM task was 446.4 ± 137.5 ms. The number of correct in ABM tasks was more 99/128 in each participant, and the correct rate was 86.2 ± 7.4%. A total of 9.3 ± 5.5 contaminations of electrooculograms and muscle movements were removed from the ERP waveform of 110.3 ± 9.5 (86.2 ± 7.4%) correct answers in the ABM task. Finally, 101.0 ± 11.8 ERP waveforms were obtained.

The grand-average of webform in ERP at Fz, Cz, and Pz were showed in **Figure 2**, and latencies and amplitudes of each component in ERPs were showed in **Table 1**. N1 and P2 were all detected, but P1 was detected in only six to eight participants (Fz;6, Cz;8, Pz;8), N2 was detected in only six to eight participants (Fz;8, Cz;8, Pz;6), P3 was detected in only one to two participants (Fz;1, Cz;1, Pz;2).

Psychological and Pain-Related Assessment Score

Table 2 shows the psychological index score of each participant.

Association Between Psychological Index Score and N1 Amplitude, P2 Amplitude, and RT

The N1 amplitudes of Cz showed a significant negative correlation with the STarT Back total scores ($r = -0.646$, $p = 0.017$), STarT Back psychological scores ($r = -0.662$, $p = 0.014$). The P2 amplitudes of Fz, Cz and Pz showed a significant negative correlation with the PCS scores (Fz; $r = -0.634$, $p = 0.020$, Cz; $r = -0.705$, $p = 0.007$, Pz; $r = -0.615$, $p = 0.25$) and BDI-II score (Cz; $r = -0.743$, $p = 0.004$, Pz; $r = -0.604$, $p = 0.029$). There was no significant correlation between theN1 amplitudes of Fz and Pz with any of the psychological indexes. RT showed a significant positive correlation with the STarT Back psychological scores ($r = -0.605$, $p = 0.029$). **Table 3** shows the correlation coefficient between each psychological index and the N1 and P2 amplitudes, and RT.

DISCUSSION

In this study, attention bias measurement using the ABM task was performed for individuals with chronic LBP, and its relevance to the psychological index was investigated. Our results showed that higher J-SBST total and psychological scores were associated with larger N1 amplitudes of Cz, and higher PCS was associated with larger P2 amplitudes of Fz, Cz, and Pz. Higher BDI-II scores were associated with larger P2 amplitudes of Cz

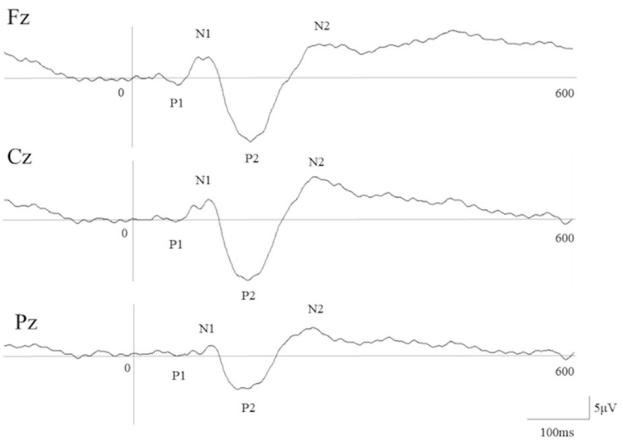

FIGURE 2 | Grand-average of event-related potentials (ERPs) waveform in attention bias modification (ABM) task. This grand-average of ERP waveform is from 200 ms before to 600 ms after stimulation in the ABM task.

TABLE 1 | Psychological index and pain-related score in each participant.

	JLEQ			FABQ	J-SBST		PCS	BDI-II
	Total score	LBP status score	Psychological score		Total score	Psychological score		
1	5	2	0	4	0	0	0	5
2	32	10	5	4	2	1	10	5
3	18	4	1	3	3	1	25	5
4	34	12	4	30	4	2	18	5
5	13	4	0	15	2	1	8	0
6	15	8	2	15	0	0	12	1
7	12	2	4	6	5	4	9	0
8	16	4	3	14	0	0	4	0
9	16	6	3	21	4	3	26	5
10	47	9	7	15	5	7	28	13
11	16	5	1	24	2	1	35	19
12	33	8	6	18	7	6	29	13
13	53	17	9	22	6	2	14	11
Average	21.9 ± 11.3	6.2 ± 3.0	3.4 ± 2.4	13.0 ± 8.7	3.1 ± 2.3	1.6 ± 1.5	16.6 ± 10.5	5.9 ± 5.8

The average is presented as mean ± SD. JLEQ, Japan Low Back Pain Evaluation Questionnaire; FABQ, Japanese version of the Fear Avoidance-Beliefs Questionnaire; J-SBST, Japanese version of the Keele STarT Back screening tool; PCS, Japanese version of the Pain Catastrophizing Scale; BDI-II, Japanese version of the Beck Depression Inventor-Second Edition; LBP, Low back pain.

TABLE 2 | Latencies and amplitudes of each component in event-related potentials (ERPs).

	P1	N1	P2	N2
Latency (ms)				
Fz	73.3 ± 8.9	108.7 ± 15.7	161.8 ± 18.9	233.14 ± 15.1
Cz	76.2 ± 14.1	115.4 ± 19.4	161.7 ± 20.6	232.7 ± 15.2
Pz	76.7 ± 8.0	117.8 ± 17.9	160.8 ± 30.72	211.3 ± 7.9
Amplitude (μV)				
Fz	5.1 ± 5.6	−5.3 ± 7.2	14.5 ± 11.6	−7.4 ± 5.6
Cz	1.6 ± 3.3	−4.2 ± 4.3	15.7 ± 11.8	−7.3 ± 6.6
Pz	2.8 ± 6.2	−3.4 ± 3.2	8.3 ± 6.9	−5.8 ± 5.5

The average is presented as mean ± SD. N1 and P2 were all detected, but P1 was detected in only 6–8 participants (Fz;6, Cz;8, Pz;8), N2 was detected in only 6–8 participants (Fz;8, Cz;8, Pz;6), P3 was detected in only 1–2 participants (Fz;1, Cz;1, Pz;2).

and Pz. Also, it was observed that longer RTs corresponded to the higher Psychological score of J-SBST.

ERPs can enable the investigation of responses of individuals related to internal and external events (Fonaryova Key et al., 2005), and the visual cognitive process is said to consist of an early automatic stage representing exogenous aspects and the late strategic stage representing endogenous aspects (Luck, 2014). The early components of ERPs, P1, N1, and P2, are exogenous components caused by external events, and the late components, N2 and P3, are endogenous components caused by internal

TABLE 3 | Correlation coefficient between each psychological index and the N1, P2 amplitudes and RT.

		JLEQ		FABQ	J-SBST		PCS	BDI-II
		Total score	Psychological score		Total score	Psychological score		
N1	Fz	0.312	0.234	−0.311	0.004	−0.066	0.449	0.196
	Cz	−0.083	−0.160	−0.271	−0.646*	−0.662*	−0.035	0.137
	Pz	0.204	−0.166	−0.165	−0.288	−0.380	0.500	−0.501
P2	Fz	−0.324	−0.487	−0.413	−0.454	−0.587	−0.634*	−0.545
	Cz	−0.426	−0.382	−0.477	−0.215	−0.121	−0.705**	−0.743**
	Pz	−0.442	−0.372	−0.340	−0.101	0.029	−0.615**	−0.604*
RT		−0.563	0.084	−0.133	0.322	0.605*	−0.019	−0.177

*Pearson's correlation coefficient, *$p < 0.05$. **$p < 0.01$. JLEQ, Japan Low Back Pain Evaluation Questionnaire; FABQ, Japanese version of the Fear Avoidance-Beliefs Questionnaire; J-SBST, Japanese version of the STarT Back screening tool; PCS, Japanese version of the Pain Catastrophizing Scale; BDI-II, Japanese version of the Beck Depression Inventor-Second Edition; RT, Reaction time.*

events. The N1 and P2 components, which was associated with psychological indicators in the current study reflects exogenous automatic attention, and it is noted to be related to early emotion processing for N1 amplitude (Keil et al., 2001; Foti et al., 2009; Gable and Harmon-Jones, 2012), recognition processes for P2 amplitude (Halit et al., 2000). In an ERP study investigating emotional processing in social anxiety, the N1 amplitude to facial stimuli increased in the high social anxiety (HSA) group as compared with that in the low social anxiety group, which means that the HSA group showed an early attentional bias to facial expressions (Felmingham et al., 2016). The ERP study investigating attentional bias in obsessive-compulsive disorder (OCD) reported that the N1 and P2 amplitudes to OCD-related expression stimuli increased in the OCD group as compared with the healthy control group (Zhang et al., 2017). Since people with chronic pain also exhibit an attentional bias towards pain-related words or pictures (Schoth et al., 2012; Crombez et al., 2013), the N1 and P2 amplitudes to threat-related facial expression is considered to increase in people with chronic pain. Also, previous studies suggested that stimuli with negative emotionality elicited increased P2 amplitudes relative to a stimulus with positive emotionality (Carretié et al., 2001; Huang and Luo, 2006). Accordingly, participants with higher attention bias in this study should exhibit increased N1 and P2 amplitudes. In attention-bias measurement using the dot-probe task, the differences in RT to threat and neutral stimuli indicate attention bias (MacLeod et al., 1986), and people with attention bias toward negative information respond rapidly to a threat stimulus and the RT to a neutral stimulus is longer. Therefore, it can be interpreted that participants with longer RT in the current study exhibited an attention bias towards the threat stimuli.

In this study, participants with a higher total score of J-SBST showed increased N1 amplitudes of Cz and longer RTs. Also, participants with a higher psychological score of J-SBST showed increased N1 amplitudes of Cz. Furthermore, participants with a higher score of PCS and BDI-II showed increased P2 amplitudes of Cz and Pz. Our findings suggested that individuals with chronic LBP with high STarT Back or PCS or BDI-II had attention bias towards the threat stimulus.

In the Cz, N1 amplitude, which reflects feature detection and sensory attention capture was associated with J-SBST, which measures risk factors (especially, psychological factors) in individuals with chronic LBP. This suggests that higher psychological factors specific to individuals with chronic LBP may have generated sensory attention to threat stimuli, and N1 may have been enhanced by efforts to avoid threat stimuli. The P2 was also associated with PCS regardless of location. P2 has been associated with the processing of emotion in faces (Carretié et al., 2001) and attention disengagement (Bar-Haim et al., 2005), suggesting that P2 was more sensitive to discrimination of facial expression with the higher level of catastrophizing in chronic LBP, and P2 amplitudes may have been associated. The inclusion of Fz may be related to only discrimination of facial expression in near the parietal (O'Toole and Dennis, 2012), but also the prefrontal cortex, which contributes to cognition and emotion due to chronic pain (Price, 2000; Apkarian et al., 2004). In the relation between P2 and BDI-II, chronic pain patients have a higher incidence of depression (Sheng et al., 2017; Zis et al., 2017), and have attention bias toward the negative expressions (Kaiser et al., 2018), it may be a mechanism similar to PCS. Furthermore, the significant association between RT and the psychological score of J-SBST is consistent with previous studies on ABM in patients with chronic LBP (Dehghani et al., 2004; Sharpe et al., 2012; Schoth et al., 2013; Heathcote et al., 2017). It was suggested that individuals with more negative psychological states resulting from chronicity of LBP were more likely to pay attention to the threat stimuli, and took longer to select neutral stimuli.

STarT Back Screening Tool was originally developed as a screening tool to identify prognostic indicators of LBP to support primary care clinical decision-making in the UK and is widely used to stratify patients with LBP according to the risk for chronicity (Hill et al., 2008). STarT Back Screening Tool is an assessment tool that includes five carefully selected items, which are psychosocial risk factors. The Pain Catastrophizing Scale is a 13-item self-report measure of catastrophizing in the context of actual or anticipated pain (Sullivan et al., 1995). Attention bias is reported to be related to psychological factors such as anxiety (Bar-Haim et al., 2007), fear-avoidance (Hughes et al., 2017), catastrophizing (Michael and Burns, 2004; Heathcote et al., 2015) with negative mental set brought to bear on actual or anticipated pain, and thus, present results suggested that chronic LBP patients with attention bias towards the threat stimulus had a various influence on psychosocial aspects.

Also, Hill et al. (2011) administered treatment based on the results with the STarT Back Screening Tool and reported

that the outcome with the cognitive-behavioral therapy (CBT)-added protocol was better for the high-risk group, for which psychological factors are considered to be strongly involved. Chronic pain is particularly susceptible to cognitive and psychological aspects, and in recent years several effects of CBT on chronic pain have been reported (Hoffman et al., 2007; Williams et al., 2012; Knoerl et al., 2016). CBT is also recommended for social anxiety disorder (SAD; Pilling et al., 2013) and meta-analyses have reported the effect of CBT on SAD (Mayo-Wilson et al., 2014). Furthermore, Lazarov et al. (2017) have examined the effect of ABM for cognitive-behavioral group therapy (CBGT) using a randomized controlled trial for 50 patients with SAD. They reported that the CBGT with the ABM group had greatly reduced symptoms after treatment than did the CBGT with the placebo group, and the effects were maintained at a 3-month follow-up. Since the results of the current study are suggestive of an association of J-SBST, PCN, and BDI-II with attention bias, CBT combined with ABM may be effective for individuals with chronic LBP classified as high risk with J-SBST or PCN.

This study has several limitations. First, we could not recruit an adequate number of individuals with chronic LBP; therefore, we need to expand the sample size in future studies. Second, due to the lack of a control group, we could not compare attention bias in the patients with that in healthy controls. Finally, the medication and treatment status of the participants were not effectively considered in this study, which could affect the generalization of our findings. However, this study contributes to the possibility of the development of advanced treatment for individuals with chronic LBP and is an important finding for the management of chronic pain.

CONCLUSIONS

The findings suggest that the evaluations of pain-related psychological factors such as J-SBST or PCN or BDI-II scores are related to attention bias of individuals with chronic LBP identified by ERP and RT. In particular, the psychological scores of J-SBST and PCN related to attention bias for individuals with chronic LBP. In other words, chronic LBP patients with attention bias must assess psychosocial factors from various aspects. Furthermore, ABM may be effective in the treatment of chronic LBP older patients with attention bias, and early and middle components of ERP can also be used as one of the outcomes. Future intervention studies on treatment combined with ABM for them are necessary.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research ethics committee of Nishikyushu University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TT conceived the study and participated in its design, coordination, acquisition, analysis, and interpretation of data. KM and JT conceived the study and participated in its design and interpretation of data. MM, TM, TH, AS, GH, and HT participated in data acquisition and helped draft the manuscript. All authors contributed to the article and approved the submitted version.

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Cerebral Hemodynamics During a Cognitive-Motor Task Using the Limbs

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Background: Antagonistic tasks are cognitive-motor task trainings. Intervention programs involving antagonistic exercise tasks are being employed to help prevent falls and reduce the need for nursing care in older populations. Meanwhile, the effects of such tasks on blood flow in the brain remain obscure. This study aimed to clarify the effects of antagonistic tasks on prefrontal cortical cerebral hemodynamics.

Materials and Methods: We assessed 13 healthy adults (two men, 11 women; mean age, 21.4 ± 1.0 years). Participants imitated each of the antagonistic tasks presented on a PC monitor placed at a 120-mm viewing distance. All participants performed six tasks, consisting of upper-limb tasks (non-antagonism, simple antagonism, and complex antagonism) and upper- and lower-limb tasks (tasks combining lower-limb opening and closing movements with each upper-limb task). We used near-infrared spectroscopy (NIRS) to measure cerebral blood flow dynamics, with oxygenated hemoglobin (Oxy-Hb) concentration changes as the main outcome. A 10-channel probe was placed on the participants' forehead, focusing on the prefrontal cortex. We first obtained a baseline NIRS measurement for 10 s; the participants then imitated the task presented on the PC monitor for 90 s. We measured the number of errors and the subjective difficulty of each task.

Results: The increase in prefrontal cortex Oxy-Hb concentration was significantly higher in the complex antagonist conditions than in the non-antagonistic and simple antagonistic conditions. There were no significant prefrontal cortex Oxy-Hb differences between the upper limb and upper- and lower-limb conditions (increasing number of motor limbs).

Conclusions: The study findings support that an increase in finger-shaped complexity has a greater effect on cerebral blood flow dynamics in the prefrontal cortex than does an increase in the number of motor limbs involved in the task.

Keywords: near-infrared spectroscopy, oxygenated hemoglobin, antagonistic task, cerebral hemodynamics, visual analog scale

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INTRODUCTION

Over 28% of individuals in Japan are aged 65 years or older, and the number of adults over 75 years is increasing (Cabinet Office Government of Japan, 2019). For many years, several care prevention projects have been implemented in various settings to promote healthy lifestyles among older adults in Japan. Numerous interventions combine cognitive and exercise tasks in the context of care prevention programs for community-dwelling older adults (Shigematsu et al., 2008a,b; Suzuki et al., 2013). These interventions seek to prevent falls and activate cognitive functions, effectively reducing the need for nursing care (Pichierri et al., 2011; Kojima et al., 2017). These interventions are designed to impose a dual-task and cognitive load on the participants. Antagonistic exercise is a program frequently implemented by occupational therapists and care workers (Tabira et al., 2012). They consist of a task in which the patients perform opposing movements using their left and right upper limbs and their upper and lower limbs in a rhythmic manner. Antagonistic exercise helps improve attention and working memory. The purpose of this exercise focuses on maintaining and improving abilities in older adults such as attention and working memory. Despite its implementation in many medical and nursing facilities, the selection of tasks is based on empirical rules, for which the difficulty and effects of the antagonistic manipulation techniques remain unknown.

Previously, we implemented a program that included antagonistic exercises for older adults in the community and observed improvements in memory and attention functions for 6 months (Sagari et al., 2012). However, the effects of antagonistic exercise on cognitive function were difficult to assess due to the complexity of the intervention program. Recently, near-infrared spectroscopy (NIRS) has been frequently used as a means of capturing cerebral blood flow dynamics during exercise and cognitive tasks, allowing researchers to assess the effects of such tasks on humans. Numerous studies have examined cerebral hemodynamics using NIRS during a wide variety of motor activities, such as running or walking (Suzuki et al., 2004; Harada et al., 2009), cycling (Ide et al., 1999), and finger tapping (Holper et al., 2009). Moreover, researchers have reported cerebral hemodynamics during cognitive tasks, such as trail building (Ohsugi et al., 2013), rock-paper-scissors (Yamauchi et al., 2013), motor imagery (Iso et al., 2016), and sequential finger touching (Amemiya et al., 2010; Sagari et al., 2015). In a prior study, we used NIRS to examine the effects of antagonistic exercise tasks of varying degrees of difficulty on cerebral hemodynamics in the prefrontal cortex and observed an increase in oxygenated hemoglobin (Oxy-Hb) values in the bilateral prefrontal cortex (Tabira et al., 2012) as the task complexity increased. However, since the task consisted solely of hand movements, it did not reflect the antagonistic manipulation-based interventions performed in medical and nursing care facilities, which engages both the upper and lower limbs, with flexing and extending exercises of the elbow joints. In addition, in the previous study, we only examined the four asymmetrically located NIRS probes, and there was a methodological problem. Therefore, in this study, we analyzed all the NIRS probes that could measure our data. We originally planned to conduct this study on the elders; however, it was easier to target university students, therefore the subjects are younger adults. The objective of our study was to clarify the effects of several characteristics of antagonistic tasks on prefrontal cortical cerebral hemodynamics. According to our hypothesis, the prefrontal cortex is more activated in the upper and lower-limb motor tasks than in upper-limb tasks alone. In addition, we predicted that activation of the prefrontal cortex may also occur due to finger-shape complexity.

MATERIALS AND METHODS

Participants and Experimental Procedures

In this study, we assessed 13 healthy adults (two men, 11 women; mean ± standard deviation age, 21.4 ± 1.0 years) between September 2017 and March 2020. Participant eligibility included age >20 years and the ability to perform normal exercises. Individuals with a history of central nervous system disorders were excluded.

The participants imitated each of the antagonistic tasks presented on a PC monitor (510 × 210 mm) placed at a 120-mm viewing distance as they remained seated in a calm environment (**Figure 1**). They performed six tasks: tasks involving the upper limbs only (tasks involving non-antagonism, simple antagonism, and complex antagonism) and those involving both the upper and lower limbs (wherein lower-limb opening and closing movements were performed simultaneously with each upper-limb task; **Figure 2**). NIRS (WOT-100: HITACHI, Tokyo, Japan; Leaflets of WOT-100, 2020) was used to measure cerebral blood flow dynamics. The 10-channel probe was placed on the participants' forehead, focusing on the prefrontal cortex (Atsumori et al., 2009). Thirty seconds following an instruction to close their eyes, the participants were instructed to reopen them and look at the cross located at the center of the PC monitor for 10 s. This 10 s was used as the baseline for NIRS measurement. Subsequently, participants imitated the task presented on the PC monitor for 90 s. We previously prepared randomized task sheets and allocated them to the subjects. The task was recorded by a video camera (GZ-E242-S Everio, JVC, Yokohama, Kangawa, Japan) to determine the number of errors. This number was counted during the task and later confirmed by repeated observation of the recorded video by an inspector. An error was considered for clearly incorrect imitated movements. For evaluation of the subjective difficultly of each task, participants were given a visual analog scale (VAS; Wewers and Lowe, 1990) following completion of all tasks and instructed to rate the difficulty of the task using the scale.

This study was approved by the ethical review board of Shinshu University School of Medicine (Study No. 3818). All procedures were carried out in accordance with the ethical standards of the Declaration of Helsinki. All participants provided written informed consent.

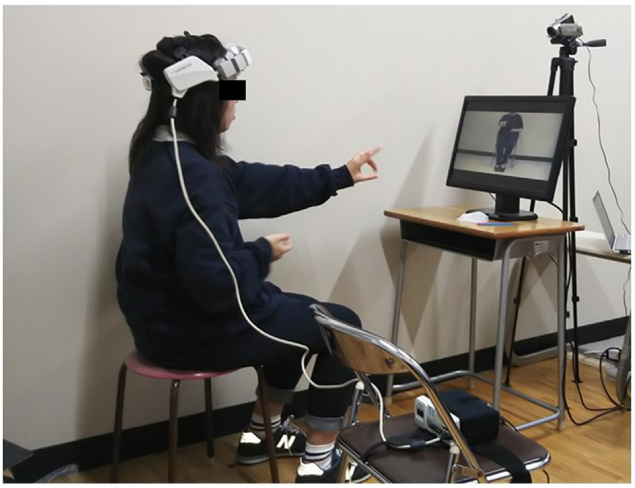

FIGURE 1 | Experimental setup of the antagonistic exercise tasks. The photograph shows a subject wearing a headset probe with the near-infrared spectroscopy (NIRS) device. The tasks being performed were recorded by the video camera. The participants had to imitate various tasks presented on a PC monitor placed in front of the subject at a viewing distance of 120 mm.

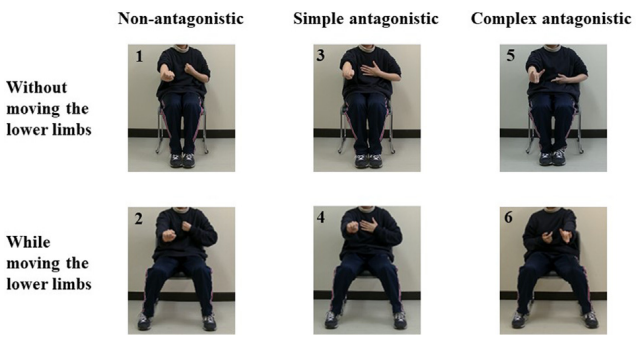

FIGURE 2 | Pictures depicting the antagonistic exercise tasks used in this study. Task 1: Non-antagonistic task using the upper limbs. Task 2: Non-antagonistic task using the upper and lower limbs. Task 3: Simple antagonistic task using the upper limbs. Task 4: Simple antagonistic task using the upper and lower limbs. Task 5: Complex antagonistic task using the upper limbs. Task 6: Complex antagonistic task using the upper and lower limbs.

NIRS Measurements

NIRS measurements were performed using a continuous-wave system equipped with 2 × 4 optode probe sets (eight incident light and 10 detector fibers), resulting in a total of 10 channels with an inter-optode distance of 30 mm. The probe unit covered an area of 30 × 105 mm^2 on the participants' foreheads, including both temples. This arrangement enabled the monitoring of cortical activation, mainly in the prefrontal cortex (Atsumori et al., 2009). The prefrontal cortex is responsible for attention and working memory (Carlen, 2017). The probe sets are shown in **Figure 3**. The continuous-wave NIRS system uses two different wavelengths (∼790 and 850 nm). Relative changes in the absorption of near-infrared light were sampled at 5 Hz, converting them into related concentration changes

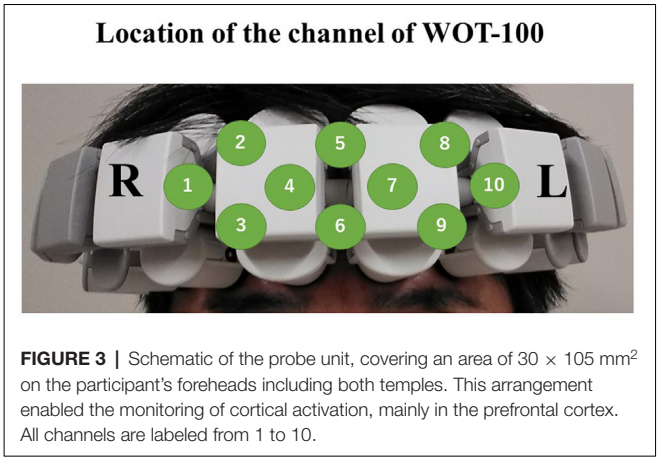

FIGURE 3 | Schematic of the probe unit, covering an area of 30 × 105 mm^2 on the participant's foreheads including both temples. This arrangement enabled the monitoring of cortical activation, mainly in the prefrontal cortex. All channels are labeled from 1 to 10.

for Oxy-Hb and deoxygenated hemoglobin based on the modified Beer–Lambert approach (Obrig and Villringer, 2003). The moving average method (with a 5 s window) was used to exclude any short-term motion artifacts in the analyzed data. Baseline was defined as the 10-s period prior to task onset. We also calculated the average value for each of the channel data during the 90-s task performance period, and then these values were averaged over 10 channels. Additionally, we used changes in Oxy-Hb concentration as an indicator of fluctuations in the regional cerebral blood volume, since an earlier NIRS signal study using a perfused rat brain model proposed that Oxy-Hb, rather than deoxygenated hemoglobin, is the most sensitive parameter for an activation study. Oxy-Hb is an indicator of local neural activity rather than an indicator of fluctuations in regional cerebral blood volume (Hoshi et al., 2001).

The Antagonistic Task

In Task 1 (non-antagonistic task using the upper limbs; NU), the elbows were alternately bent and stretched once every 2 s approximately, with all fingers of both hands fully flexed to form a fist. For Task 2 (non-antagonistic task using the upper and lower limbs; NUL), the lower limbs were alternately opened and closed once every 2 s approximately while performing Task 1. In Task 3 (simple antagonistic task using the upper limbs; SU), the left elbow was placed in a flexed position and the fingers of the left hand were in full flexion to form a fist, while the right elbow was placed in an extended position and the fingers of the right hand were in full extension (i.e., in the "paper" shape from rock-paper-scissors). The positions were alternated between the right and left hands according to the set rhythm. In Task 4 (simple antagonistic task using the upper and lower limbs; SUL), the lower limbs were alternately opened and closed approximately once every 2 s while performing Task 3. In Task 5 (complex antagonistic task using the upper limbs; CU), the right thumb and index finger were extended; the middle, ring, and little fingers were flexed ("gun" shape); and the elbow was flexed. On the left hand, the thumb, middle finger, and ring finger were flexed; the index finger and little finger were extended ("wolf head" shape); and the elbow was alternately extended

and bent. The positions were alternated between the right and left hands according to the set rhythm approximately once every 2 s. In Task 6 (complex antagonistic task using the upper and lower limbs; CUL), the lower limbs were alternately opened and closed approximately once every 2 s during Task 5.

Statistical Analysis

Normality assumption was verified using the Shapiro–Wilk test. We compared Oxy-Hb values across the six tasks using one-way repeated measures analysis of variance (ANOVA), with Bonferroni tests for multiple comparisons. We compared the subjective difficulty and number of errors across the six tasks using Friedman's test and Scheffe tests for multiple comparisons. Additionally, the number of errors, subjective difficulty, and Oxy-Hb values were divided according to the following factors: upper limbs/upper limbs and lower limbs (increasing number of motor limbs), and non-antagonism/simple antagonism/complex antagonism (increasing finger-shape complexity). For Oxy-Hb comparisons, a two-way repeated-measures ANOVA was employed with the significance level set at $p < 0.05$. For subjective difficulty and number of error comparisons, Friedman's test with Scheffe tests was used with the significance level set at $p < 0.05$. The correlation coefficients between Oxy-Hb and VAS were analyzed by calculating Spearman's rank correlation coefficients. The effect size was calculated for the test in Oxy-Hb only. Statistical analyses were performed using the BellCurve for Excel (Social Survey Research Information Co., Limited, Tokyo, Japan).

RESULTS

Oxy-Hb data followed a normal distribution, while VAS scores and number of errors did not. The results (numerical values) for VAS scores, number of errors, and Oxy-Hb concentration changes are presented in **Table 1**. With regard to subjective difficulty, Friedman's test revealed a significant main effect of subjective difficulty among tasks ($p < 0.001$). *Post hoc* tests showed a significant increase in subjective difficulty for SUL, CU, and CUL compared to the subjective difficulty of NU ($p = 0.037$, $p < 0.001$, $p < 0.001$). In addition, *post hoc* tests showed a significant increase in subjective difficulty for CU and CUL when compared to that of SU ($p = 0.024$, $p < 0.001$) and for NUL vs. CU ($p = 0.028$) and CUL vs. NUL ($p = 0.001$). Friedman's test revealed a main effect between the upper limb and upper- and lower-limb conditions (increasing number of motor limbs) in terms of subjective difficulty (VAS scores; $p < 0.001$). *Post hoc* tests showed a significant increase in subjective difficulty for tasks involving both the upper and lower limbs compared to tasks involving only the upper limbs ($p < 0.001$). The main effect of subjective difficulty was also observed between non-antagonistic, simple antagonistic, and complex antagonistic conditions (increasing finger-shape complexity; $p < 0.001$). *Post hoc* tests revealed that the complex antagonistic conditions were significantly more challenging than the non-antagonistic and simple antagonistic conditions ($p < 0.001$, $p < 0.001$).

Friedman's test showed a significant main effect of the number of errors in each task ($p < 0.001$). *Post hoc* tests revealed a significantly higher number of errors in CU than in NU ($p = 0.026$) and in CU than in SU ($p = 0.018$) or in NUL than in CU ($p = 0.018$). Friedman's test showed no main effect between the upper limb and upper- and lower-limb conditions (increasing number of motor limbs) in terms of error count. The main effect of the number of errors was observed among non-antagonistic, simple antagonistic, and complex antagonistic conditions (increasing finger-shape complexity; $p < 0.001$). *Post hoc* tests revealed that the number of errors was significantly higher in the complex antagonistic than in the non-antagonistic and simple antagonistic conditions ($p < 0.001$, $p = 0.007$).

Oxy-Hb concentration changes across tasks did not show a significant effect in a one-way repeated measures ANOVA, and a two-way repeated-measures ANOVA did not identify a significant effect between the upper limb and upper- and lower-limb conditions (increasing number of motor limbs). The main effect of Oxy-Hb concentration was observed among non-antagonistic, simple antagonistic, and complex antagonistic conditions (increasing finger-shape complexity; $p = 0.02$; $\eta^2 = 0.09$). The *post hoc* test revealed significantly higher values for the complex antagonistic condition than for the non-antagonistic and simple antagonistic conditions ($p = 0.017$, $p = 0.024$; $r = 0.40$, $r = 0.51$; **Figure 4**). There was a significant positive correlation between Oxy-Hb

TABLE 1 | Subjective difficulty VAS scores, number of errors, and Oxy-Hb concentration changes in the prefrontal cortex for each task.

	Non-antagonistic task using the upper limbs	Non-antagonistic task using the upper and lower limbs	Simple antagonistic task using the upper limbs	Simple antagonistic task using the upper and lower limbs	Complex antagonistic task using the upper limbs	Complex antagonistic task using the upper and lower limbs
VAS score, mm	4 (1–3)	15 8–20)	13 (2–27)	28 (10–38)	61 (47–68)	80 (51–86)
Number of errors	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–1)	3 (0–23)	1 (0–16)
Prefrontal cortex Oxy-Hb concentration changes, mMmm	0.02 ± 0.04	0.06 ± 0.06	0.01 ± 0.04	0.01 ± 0.05	0.18 ± 0.07	0.15 ± 0.08

Note. Data of VAS score and number of errors are presented as the median and interquartile range. Data of prefrontal cortex Oxy-Hb concentration changes are presented as the mean ± standard deviation. VAS, visual analog scale; Oxy-Hb, oxygenated hemoglobin.

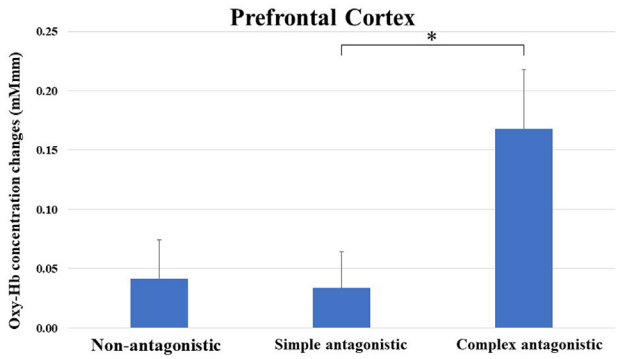

FIGURE 4 | Oxy-Hb concentration changes in the prefrontal cortex during non-antagonistic, simple antagonistic, and complex antagonistic tasks. Two-way repeated measures analysis of variance (ANOVA) and *post hoc* tests revealed a significant difference in Oxy-Hb levels between simple and complex antagonistic tasks. $^{*}p < 0.05$. Oxy-Hb, oxygenated hemeoglobin.

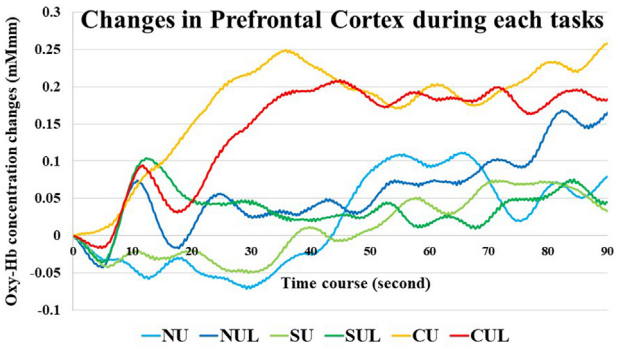

FIGURE 5 | Time courses of Oxy-Hb concentration changes in the prefrontal cortex during each task. NU, non-antagonistic task using the upper limbs; NUL, non-antagonistic task using the upper and lower limbs; SU, simple antagonistic task using the upper limbs; SUL, simple antagonistic task the upper and lower limbs; CU, complex antagonistic task using the upper limbs; CUL, complex antagonistic task using the upper and lower limbs.

and VAS (ρ = 0.344, p = 0.002). Time courses of Oxy-Hb concentration changes in the prefrontal cortex during each task are shown in **Figures 5**, **6**.

DISCUSSION

Subjective Difficulty and Errors in the Antagonistic Task

With regard to subjective difficulty (VAS score), NU was the least challenging, while CUL was the most difficult. The other tasks showed increasing difficulty in the following order: NUL, SU, SUL, and CU. Similarly, the tasks were associated with an increasing number of errors in the following order: NUL (minimum errors), SU, NU, SUL, CU, and CUL (maximum errors). Also, increasing finger-shape complexity increased both subjective difficulty and number of errors. This trend was particularly significant in the complex antagonistic task. A previous study using an antagonistic task (Tabira et al., 2012) demonstrated an increased number of errors as the hand shape became increasingly complex. Therefore, the results of the current study were similar to those of the previous study. Adding the lower-limb opening and closing motion to the upper-limb task increased the subjective difficulty, although it is insufficient to induce an error. Therefore, increasing finger-shape complexity and an increasing number of motor limbs could increase subjective difficulty in the antagonistic task.

Cerebral Blood Flow Dynamics During an Antagonistic Task

The prefrontal cortex Oxy-Hb did not significantly differ between the upper limb and upper- and lower-limb conditions (increasing number of motor limbs). However, a significant difference was found between the non-antagonistic, simple antagonistic, and complex antagonistic conditions (increasing finger-shape complexity). Additionally, the complex antagonistic condition increased the Oxy-Hb concentration in the prefrontal cortex, significantly more than did the non-antagonistic and simple antagonistic conditions. This phenomenon could result from subjective difficulty induced by the complex antagonistic condition. As a result, we speculated that errors would increase under the complex antagonistic condition. In a previous study (Tabira et al., 2012), the Oxy-Hb concentration in the prefrontal cortex increased with the difficulty of the antagonistic task in older adults. This finding suggested that the prefrontal cortex was activated by increasingly complex finger shapes. The results of the previous study are similar to our current results. However, the previous study did not include the lower-limb condition. In this study, we found that the prefrontal cortex was not activated by the increasing number of motor limbs, e.g., the inclusion of the lower limbs. However, the current study's subjects consisted of young adults. This highlights the differences in the prefrontal cortical hemodynamic response to the task between the young and old adults (Ohsugi et al., 2013; Beurskens et al., 2014). Therefore, the results of this study should be interpreted with caution. Previously, some studies investigated cerebral blood flow in the prefrontal cortex during cognitive-motor tasks (Holtzer et al., 2011, 2017; Mirelman et al., 2014). These studies reported that by adding a computational task to gait and adjusting difficulty, the prefrontal cortex was activated when the task became difficult. This task was a very rare one, and difficulty adjusted according to the complexity of the movement. Even in such a task, it became clear that the prefrontal cortex was activated as the task became more difficult. In addition, in the prefrontal cortex Oxy-Hb increased rapidly or slowly during the task and was maintained in the final stages as the test subjects had to concentrate on the task while doing it. However, if the participants become accustomed to the task, the changes in Oxy-Hb could decrease over time (Sagari et al., 2012; Alves Heinze et al., 2019).

Clinical Application

Antagonistic exercise is widely used in medical and nursing care facilities for cognitive function improvement and

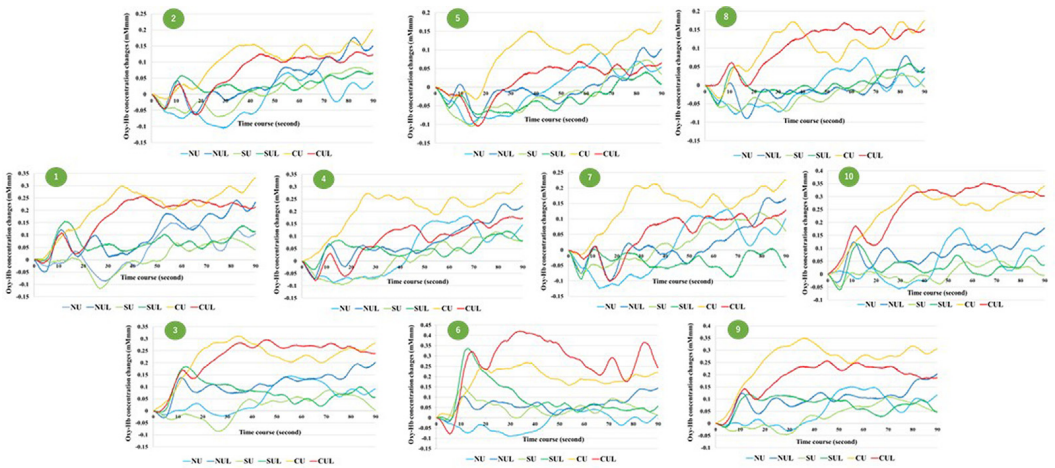

FIGURE 6 | Time courses of Oxy-Hb concentration changes in all channel. NU, non-antagonistic task using the upper limbs; NUL, non-antagonistic task using the upper and lower limbs; SU, simple antagonistic task using the upper limbs; SUL, simple antagonistic task using the upper and lower limbs; CU, complex antagonistic task using the upper limbs; CUL, complex antagonistic task using the upper and lower limbs.

maintenance (Nagasaki Prefectural Government, Community Support Activity, 2020; Tokushukai Medical Group Newspaper Digest, 2020). According to this study's results, the complex antagonistic task was effective in activating the prefrontal cortex. Half of the participants made several errors during the complex antagonistic task, suggesting that the tasks responsible for occasional incorrect movements are effective at stimulating brain activity. Additionally, the subjective difficulty experienced by participants during the complex antagonistic task was approximately 60–80 mm, which might help predict the related brain activity. Using NIRS, cognitive function improvement and maintenance programs can be enhanced while providing feedback on the prefrontal activation status (Mihara et al., 2013; Kinoshita et al., 2016). However, in actual medical and nursing care facilities, it is more realistic to select tasks based on the predicted activation status of the prefrontal cortex, which can be determined by referring to the VAS scores and error counts associated with a task.

Limitations

This study had several limitations. First, the number of errors was counted by an inspector. Since the data are subjective, the development of devices to record objective data, without user bias, is required. Second, the lower-limb task used in this study consisted of lower-limb opening and closing, and simple movements might not have made a difference in the cerebral hemodynamics when comparing the upper limb and the upper- and lower-limb conditions (increasing number of motor limbs). Further complexity of the lower-limb task may result in differences in the cerebral hemodynamics of the prefrontal cortex. Third, activation in the supplementary motor area, dorsal premotor cortex, and sensorimotor cortex, which are linked to the prefrontal cortex, could not be detected due to the technical limitations of the NIRS apparatus (WOT-100), which has a relatively small probe. Fourth, since the study participants were young adults, future studies with older adults are warranted. Using G power, assuming $\alpha = 0.05$ (1-β) = 0.8 and effect size = 0.25, 24 patients were required for our study. Unfortunately, we were unable to obtain this target number and the male–female ratio was greatly skewed. Finally, because of the differences in the male-to-female ratio in the cohort, future studies should include more male subjects.

CONCLUSION

The purpose of this study was to clarify the effects of antagonistic tasks on prefrontal cortical cerebral hemodynamics. Our study findings showed that the complex antagonistic condition increased Oxy-Hb in the prefrontal cortex, more than the non-antagonistic and simple antagonistic conditions. These findings indicate that areas of the subjects' prefrontal cortex were activated by increasingly complex finger shapes during the antagonistic task. These results support that an increase in the number of motor limbs involved in the task has fewer effects on the cerebral blood flow dynamics in the prefrontal cortex than does an increase in finger shaped complexity. This information could be helpful for occupational therapists when recommending antagonistic exercise.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethical review board of Shinshu University

School of Medicine (Study No. 3818). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Contributions were as follows: AS, HM, and MK: study concept and design. AS, HK, MS, and JI: data acquisition. AS, HK, and HM: data analysis and interpretation. AS and MK: manuscript writing. All authors contributed to the article and approved the submitted version.

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Changes in Electroencephalography and Cardiac Autonomic Function During Craft Activities: Experimental Evidence for the Effectiveness of Occupational Therapy

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Occupational therapy often uses craft activities as therapeutic tools, but their therapeutic effectiveness has not yet been adequately demonstrated. The aim of this study was to examine changes in frontal midline theta rhythm (Fmθ) and autonomic nervous responses during craft activities, and to explore the physiological mechanisms underlying the therapeutic effectiveness of occupational therapy. To achieve this, we employed a simple craft activity as a task to induce Fmθ and performed simultaneous EEG and ECG recordings. For participants in which Fmθ activities were provoked, parasympathetic and sympathetic activities were evaluated during the appearance of Fmθ and rest periods using the Lorenz plot analysis. Both parasympathetic and sympathetic indices increased with the appearance of Fmθ compared to during resting periods. This suggests that a relaxed-concentration state is achieved by concentrating on craft activities. Furthermore, the appearance of Fmθ positively correlated with parasympathetic activity, and theta band activity in the frontal area were associated with sympathetic activity. This suggests that there is a close relationship between cardiac autonomic function and Fmθ activity.

Keywords: occupational therapy, frontal midline theta rhythm, autonomic nervous system responses, cardiac sympathetic index, cardiac vagal index, craft activities

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INTRODUCTION

The central role of occupational therapy (OT) is to enhance health and well-being. The "occupation" term in occupational therapy refers to the everyday activities people do to occupy their time and bring meaning and purpose to their lives as individuals, families, and communities [World Federation of Occupational Therapists (WFOT), 2010]. Craft activities have been used as a means of intervention in occupational therapy since the beginning of the profession (Kleinman and Stalcup, 1991; Harris, 2008), especially by occupational therapists working with patients in psychiatric health care (Craik et al., 1998; Griffiths and Corr, 2007). However, previous research on the therapeutic effects of craft activities have primarily been qualitative.

Perruzza and Kinsella's literature review (2010) suggests that creative activities aid in perceptual control, construction of a sense of self, representation, illness experience transformation, acquisition of a sense of purpose, and building social support. Additionally, Leckey (2011) reported that creative activities can have healing and protective effects on mental well-being, which was confirmed by Preminger (2012).

The use of craft activities in occupational therapy has been shown to have some therapeutic effectiveness. Eklund (1999) reported the effectiveness of creative activities in occupational therapy. The OT intervention group had greater improvements in psychological and occupational functioning and global mental health compared to the control group. The randomized controlled trial (Buchain et al., 2003) explored the effects of OT combined with psychopharmacological treatment for clients with schizophrenia. The results showed that patients who received OT along with clozapine had greater improvements in work performance and interpersonal relationships than those who received clozapine alone. Foruzandeh and Parvin (2013) reported a significant improvement in positive and negative symptoms in patients with schizophrenia in the OT group compared to the control group. The results of these previous studies have proven that occupational therapy interventions using craft activities can reduce a variety of psychiatric symptoms and improve occupational functioning. However, there are several phenomena that cannot be studied in the experimental brain research arena due to the need to adapt strictly prescribed methods (Seitamaa-Hakkarainen et al., 2016), and there are few prior studies that provide neuroscientific evidence of therapeutic effects.

The effects of activity-based interventions are thought to originate from the subject's focus on the activity, which can be evaluated using the frontal midline theta rhythm (Fmθ) of an EEG. Fmθ is a 5–7 Hz theta wave that appears in the medial frontal region during extensive cognitive tasks requiring mental concentration (Ishihara and Yoshii, 1972; Ishii et al., 1999). For example, Fmθ reinforcement has reported in meditative states (Aftanas and Golocheikine, 2001), in the pre-fire phase of rifle shooting (Doppelmayr et al., 2008), and when completing implicit tasks (Ishii et al., 2014). During the appearance of Fmθ, more attention is allocated to work tasks and less to monitoring the environment, the self, and the passage of time, making it difficult to interrupt focus on work.

Fmθ is thought to originate in the anterior cingulate cortex (ACC), which is involved in regulation of attention behaviors such as spontaneous attentional functions and conflict resolution (Asada et al., 1999; Ishii et al., 1999, 2014). The ACC also contributes to cognitive control and decision making (Bush, 2009; Mars et al., 2011), and is thought to be responsible for learning the value of a task, selecting tasks based on the learned values, and motivating task execution (Holroyd and Yeung, 2012). Critchley et al. (2004) found that the ACC is involved in regulation of the autonomic nervous system (ANS), with patients containing ACC lesions exhibiting impaired autonomic responses (Critchley et al., 2003). According to studies of brain networks, the autonomic nervous system is regulated by the central autonomic network (CAN) (Verberne and Owens, 1998; Saper, 2002), which includes the ventral medial prefrontal cortex, the ACC, and the insula (Critchley et al., 2011). Representative brain networks include the default mode network (DMN) of the resting state, the executive network (EN) of the task executing state, and the salience network (SN), which examines internal and external information and is involved in switching between the DMN and EN (Damoiseaux et al., 2006; De Luca et al., 2006; Bressler and Menon, 2010; Deco and Corbetta, 2011; Doucet et al., 2011; Menon, 2011). The relationship between brain networks and autonomic activity has also been studied. Beissner et al. (2013) reported that sympathetic-related regions predominate in the EN and SN, while parasympathetic regions predominate in the DMN. Based on these findings, it can be hypothesized that task-related frontal theta rhythms, which reflect the activity of the attentional network (including the ACC), may relate to peripheral autonomic activities.

Frequency-domain analysis (spectral analysis) and time-domain analysis of electrocardiograms (ECG) are often used to evaluate ANS activity during task execution. However, it is difficult to assess sympathetic and parasympathetic nerves separately using frequency-domain analysis (Sawada, 1999; Lahiri et al., 2008: Dodo and Hashimoto, 2015, 2017), while Lorenz plot analysis, a type of time-domain analysis, can measure parasympathetic and sympathetic nervous system activity separately (Toichi et al., 1997). In Lorenz plot analysis, the cardiac sympathetic index (CSI) is used as a measure of sympathetic nervous system activity and the cardiac vagal index (CVI) is used as a measure of parasympathetic nervous system activity. Allen et al. (2007) used Lorenz plot analysis to study performance of a mental arithmetic task requiring active concentration, revealing that execution of this task increased CSI and did not change CVI compared to baseline conditions. In addition, during meditation, both CSI and CVI have been reported to significantly increase during the appearance of Fmθ compared to in the resting state (Kubota et al., 2001). Many studies on Fmθ have used mental tasks, such as a rote computation tasks, so it is not clear how autonomic activity changes during Fmθ-emergent craft activities. We hypothesized that a state of relaxation similar to that of meditation could be achieved in craft activities if a state of concentration of attention was present. Therefore, our study aimed to use Lorenz plot analysis to examine the effect of Fmθ-emergent craft activities on the ANS and evaluate the impact of our results on the potential for therapeutic effects from occupational therapy.

MATERIALS AND METHODS

Participants

Twenty-eight healthy volunteers participated in this study. No participants had cardiac, respiratory, and other diseases that would cause ANS dysfunction. Informed consent was obtained from all participants prior to the experiment. Patients were asked to refrain from eating and drinking (other than water) for 2 h before the experiment. Four participants were excluded based on the following criteria: one for EEG artifacts, one for ECG artifacts, and two for arrhythmias. Ultimately, 24 participants (10 males and 14 females; age range: 20–27 years; mean age: 23.2 ± 1.9 years) were included in the analysis.

Procedures

Task

The task chosen was a form of canvas craft. The task was to thread a thin piece of a single color of cotton yarn through a soft

polyethylene mesh (a 35 mm × 80 mm square containing 3 mm × 3 mm holes) using a special needle for metallic yarn in order to create a bookmark. Canvas crafts are widely used in Japan as they are easier than knitting. Before each experiment, we presented samples of canvas handicrafts and practiced making them while explaining the procedure. The experiment was then conducted after participants fully understood the preparation procedure and confirmed that there were no unclear steps.

Experiment

Participants experienced a 3-min resting condition (staring at an image of a solid cross), followed by a 7-min craft task (canvas craft), which was repeated for two trials. We selected one condition in which Fmθ was observed during the craft task and defined it as the "Fmθ condition."

EEG Recording and Data Acquisition

BIO-NVX36 (East Medic Co., Ltd., ISHIKAWA, JAPAN) was used for EEG and ECG recordings. EEG recording was done with 19 electrodes using the International 10–20 System and a sampling frequency of 1000 Hz. Electrode resistance was kept below 5 kΩ. Digitized EEG (sampling rate 1000 Hz, bandpass 1.5–100 Hz) was sampled at an epoch of 1.02 s. The criteria of Fmθ were; a train of rhythmic waves, observed at a frequency of 5–7 Hz, having a focal distribution with maximum around the frontal midline in the EEG (Ishihara and Yoshii, 1972; Inouye et al., 1994; Kubota et al., 2001). In this study, theta waves lasting more than 1 s were also selected. ATAMAP II (Kissei Comtec Co., Ltd., Matsumoto, Japan) was used for EEG mapping, and the appearance of Fmθ confirmed by inspecting and mapping the waveforms. The appearance of theta rhythm in the Fz electrode was quantitatively evaluated using spectral analysis software. For spectral analysis, the Fmθ power values were calculated using sampling of 1.02 s epochs, applying a Hanning window to each 1,024-point segment, and using a fast Fourier transform (FFT) to obtain the spectral density per 1.02 s epoch in units of amplitude (μV). Ten of the 24 participants exhibited Fmθ while performing the task. The 14 participants for whom Fmθ did not appear were excluded. In addition, one participant with Fmθ in both the resting and task conditions was ultimately excluded and data from nine participants (three males and six females; age range: 20–25 years; mean age: 22.4 ± 1.6 years) was analyzed. If Fmθ appeared in both trials, the trial in which Fmθ appeared more frequently was selected. An example of EEG and topographical map at the appearance of Fmθ are shown (**Figures 1A,B**).

Autonomic Nervous Response

The ECG signal (Lead 1) was fed into a microcomputer and the inter-beat interval (IBI) triggered by the R-wave measured at a sampling rate of 1 kHz. For the resting condition, a 3-min continuous IBI was used to assess autonomic function. For the Fmθ condition, a 3-min continuous IBI corresponding to the period of Fmθ appearance was selected for the assessment of autonomic function. Lorenz plot analysis was performed using a MaP1060 (NIHONSANTEKU Co., Ltd., Osaka, Japan) to evaluate HRV. The variability of R-R intervals (RRIs) was observed and transformed into an elliptic distribution using Lorenz plots (Toichi et al., 1997) then the

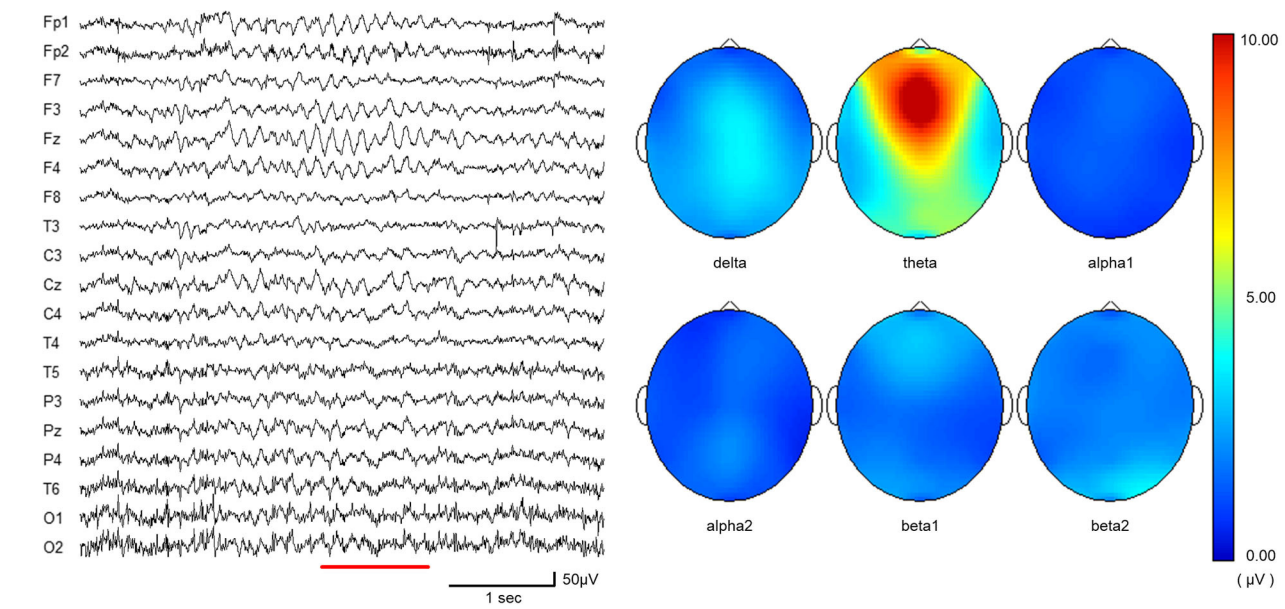

FIGURE 1 | (A) EEG sample taken from craft task period showing typical pattern of Fmθ. **(B)** EEG topographic map (from **A**) showing typical peak in theta band in Fz electrode. The spectral density of delta (2.0–4.0 Hz), theta (4.0–8.0 Hz) alpha1 (8.0–10.0 Hz), alpha2 (10.0–13.0 Hz), beta1 (13.0–20.0 Hz), and beta2 (20.0–30.0 Hz) waves for the period of 1.02 s were calculated in amplitude (micro V) using fast Fourier transform (FFT).

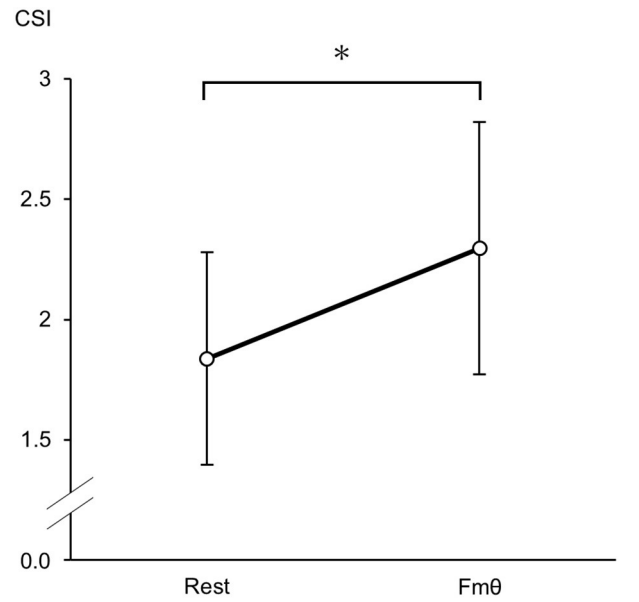

FIGURE 2 | Cardiac sympathetic index (CSI) changes during the rest condition and Fmθ condition. Values are expressed as means and SDs. *$p < 0.05$.

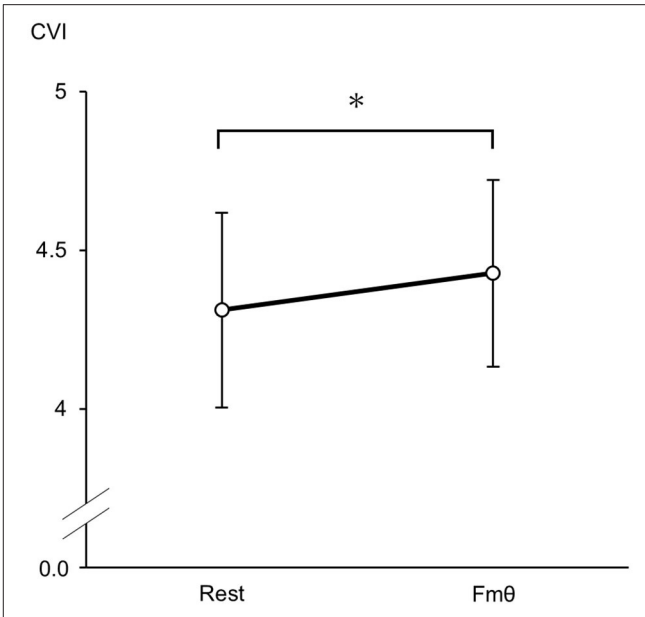

FIGURE 3 | Cardiac vagal index (CVI) changes during the rest condition and Fmθ condition. Values are expressed as means and SDs. *$p < 0.05$.

length of the longitudinal (L) and transverse (T) axes within the ellipsoid distribution calculated. The cardiac vagal index (CVI) was calculated as a log10 (L × T) transformation and the cardiac sympathetic index (CSI) was calculated as L/T (Toichi et al., 1997).

Statistical Analyses

The data were analyzed using IBM SPSS version 26. To compare CSI, CVI, and mean RRI values between rest conditions and Fmθ conditions, paired *t*-tests were performed. Cohen's *d* was calculated to determine effect size. In addition, correlation analyses of the number of Fmθ occurrences and power values for CSI, CVI, and changes in CSI and CVI for each period were performed using Pearson's correlation coefficient test.

RESULTS

Change of Cardiac Autonomic Activities

Both the cardiac sympathetic index (CSI) and cardiac vagal index (CVI) significantly increased when Fmθ was present compared to rest conditions [CSI: $t(8) = 2.578$, $p = 0.049$, $d = 0.95$; CVI: $t(8) = 2.323$, $p = 0.033$, $d = 0.39$, paired *t*-test]. CSI values during Fmθ conditions (M = 2.30 ± 0.52) were significantly higher than during rest conditions (M = 1.84 ± 0.44; **Figure 2**). Similarly, CVI values during the Fmθ condition (M = 4.43 ± 0.29) were significantly higher than in the rest condition (M = 4.31, SD = 0.31; **Figure 3**). In contrast, mean RRI was not significantly different in the Fmθ conditions (M = 877.2 ± 118.6) compared to during rest conditions (M = 897.4 ± 90.1) ($t(8) = 1.215$, $p = 0.259$, $d = 0.19$, paired *t*-test).

TABLE 1 | Correlations between serum Fmθ power, Fmθ number of appearance and cardiac autonomic activities.

	Fm θ power (micro V)		Fm θ number of appearance	
	r	***p* – *value***	***r***	***p* – *value***
CSI of rest condition	−0.624	0.073	0.041	0.917
CSI of Fmθ condition	0.361	0.339	−0.140	0.719
Change of CSI	0.782	0.013*	−0.154	0.693
CVI of rest condition	−0.216	0.576	0.764	0.016*
CVI of Fmθ condition	−0.279	0.468	0.821	0.007*
Change of CVI	−0.116	0.767	0.055	0.889

*Pearson's correlation coefficient test, *p < 0.05.*

The Correlation of Frontal Theta Activity With CSI and CVI

The mean value of theta power in the Fz electrode was 10.89 ± 1.2 μV, and the mean number of Fmθ appearances was 4.7 ± 3.0. Correlation analysis showed that the power value of Fmθ was positively correlated ($r = 0.782$) with changes in CSI (**Table 1**). The number of Fmθ appearances was positively correlated with resting CVI ($r = 0.764$) and the Fmθ appearance period ($r = 0.821$).

DISCUSSION

In this study, participants whose Fmθ states appeared during crafting had increased activity of both the sympathetic nervous system, as measured CSI, and the parasympathetic nervous system, as measured by CVI, during Fmθ appearances compared

to resting periods. Mental arithmetic tasks have been reported to increase CSI values (Allen et al., 2007; Dodo and Hashimoto, 2019), potentially due to sympathetic activation reflecting mental stress (Lucini et al., 1997). Although an increase in CSI has been associated with a decrease in mean RRI (Pagani et al., 1991), in this study there was no change in mean RRI. This result indicates that a state of relaxation is achieved during craft task completion that is comparable to the resting state. These results also suggest that an increase in CVI may have buffered the impact of the craft activity on CSI values, resulting in lower changes to heart rate. This indicates that crafting activities involve both active, arousal-promoting processes and relaxation processes.

Studies on the effects of meditation and mindfulness have also reported increases in both sympathetic and parasympathetic levels (Jevning et al., 1992; Ditto et al., 2006), suggesting that concentration on crafting tasks can create a similar state. Furthermore, Kubota et al. (2001) reported an increase in both CSI and CVI autonomic activity during the appearance of Fmθ during meditation tasks, which was attributed to a combined concentration-relaxation state. Our study suggests that a similar relaxed-concentration state can be achieved by crafting. The ability of crafting to create a state of relaxation has previously been reported (Reynolds, 2000; Collier, 2011; Preminger, 2012), with a systematic review of arts and crafts activities by Martin et al. (2018) suggesting that these activities contribute to stress reduction and relaxation, all of this were confirmed by our study.

We found that the number of Fmθ appearances was positively correlated with the CVI at rest and during Fmθ appearances. These results suggest that sustained concentration on a task is associated with a relaxed state. However, correlations between Fmθ appearances and resting CVI values indicate potential influence test participant personality traits. In support of this connection, previous research has shown that anxiety and personality traits affect the rate of Fmθ appearance (Inanaga, 1998), which may indicate that those who are more likely to exhibit Fmθ have higher parasympathetic activity. In fact, Tang et al. (2009) reported that Fmθ appearance is correlated with parasympathetic activity, further suggesting a close relationship between the two phenomena.

Also, in our study, the power value of Fmθ was positively correlated with the change in CSI. Moreover, the current proposed source of Fmθ is the region extending from the medial aspect of the prefrontal cortex to the ACC (Asada et al., 1999; Ishii et al., 1999, 2014), with the ACC found to regulate sympathetic activity (Critchley et al., 2003). Finally, overall, our study's results support these findings of previous studies.

Most previous studies on Fmθ have used memorization-, meditation-, and computer game-based tasks, with few reports on Fmθ appearance while performing craft activities. Unlike mental tasks, handicraft activities involve many physical tasks due to the use of tools and objects and associated coordination of eye and hand movements. Performing craft activities requires intimately intertwined, multi-purpose cognition and embodied processing (Huotilainen et al., 2018). In addition, attention is required to successfully complete sequences of performance processes, which likely partly underlies Fmθ induction. The uniqueness of occupational therapy is that the activity involved changes the patient's mental state using objects, freeing the patient from language-based aggression. This may be one mechanism that helps produce the therapeutic effectiveness of relaxed-concentration states in occupational therapy.

While our study confirms the therapeutic effectiveness of crafting activities for some patients, the patient number of Fmθ appearances in this study is about half. Some participants may also exhibit Fmθ states while performing other types of craft beyond our weaving activity, and different types of crafts may vary in their likelihood to induce relaxed concentration states. Based on these caveats, occupational therapists need to provide the most appropriate craft for a given patient.

LIMITATIONS

Multiple limitations were present in our study. First, our sample size was small and the age range was limited to 20–27, limiting our ability to generalize our findings. We chose this age range as this was the group in which Fmθ was most likely to appear. Second, the resting task consisted of looking at a solid cross, and while participants were given instructions to relax, this may not reflect their usual resting state. In fact, one participant exhibited Fmθ during this resting task, indicating that this was a task requiring constant attention. While our resting task was chosen to inhibit eye movement and prevent other artifacts, it apparently may not be a resting state for all participants. However, we recognized that this resting task was more restful than when crafting. These are issues to be considered in future research. This study did not determine the source of Fmθ, but previous studies have shown that ACC is the source of Fmθ. These reports are consistent with our hypothesis, given the role of the ACC in both cognitive function and autonomic control. However, these are only speculations, and there is a need to clarify the current source density and connectivity using the exact low-resolution brain electromagnetic tomography (eLORETA) method (Pascual-Marqui et al., 2011).

CONCLUSION

During craft activities in which Fmθ appeared, both parasympathetic and sympathetic indices were increased compared to the resting condition. This result suggests that a certain relaxed-concentration state is achieved by concentrating on craft activities. This can be interpreted as indicating that an appropriate level of concentration for task performance will also cause the same degree of physical relaxation as resting. The results of this study confirm that concentrating on craft activities without being self-conscious has a calming effect and creates a relaxed state, providing evidence for the effectiveness of craft-based occupational therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of Kyoto University Graduate School of Medicine (approval number: R1639). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KS, SY, and YN contributed to the design, implementation of the research, and the analysis of the results. KS wrote the manuscript with support from MT. All authors contributed to the article and approved the submitted version.

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Immersive Virtual Reality Reminiscence Reduces Anxiety in the Oldest-Old Without Causing Serious Side Effects: A Single-Center, Pilot, and Randomized Crossover Study

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Background: Dementia is one the major problems of aging societies, and, novel and effective non-drug therapies are required as interventions in the oldest-old to prevent cognitive decline.

Objective: This study aims to examine the efficacy and safety of reminiscence using immersive virtual reality (iVR reminiscence) focusing on anxiety that often appears with cognitive decline. The secondary objective is to reveal the preference for VR image types for reminiscence: live-action (LA) or computer graphics (CG).

Methods: This was a pilot, open-label, and randomized crossover study which was conducted on January 2020 at a single nursing home. The subjects were randomly divided into two groups (A or B) in equal numbers, and they alternately viewed two types of VR images (LA and CG) themed on the mid- to late Showa era (A.D. 1955–1980) in Japan. In group A, the CG images were viewed first, and then the LA images were viewed (CG→ LA). In group B, the images were viewed in the opposite order (LA→ CG). Before VR viewing, subjects responded to Mini-Mental State Examination (MMSE) Japanese version and State-Trait Anxiety Inventory (STAI) Japanese version. After viewing the first and second VR, subjects responded to STAI and the numerical rating scale (NRS) for satisfaction and side effects (nausea, dizziness, headache, and tiredness).

Results: Ten subjects participated in this study. The values of analyses are presented in the mean (SD). The age was 87.1 years (4.2), and the MMSE was 28.5 (1.8). The total STAI score before VR viewing was 36.1 (7.2), but it significantly decreased to 26.8 (4.9) after the first VR viewing ($P = 0.0010$), and further decreased to 23.4 (2.8) after the second VR viewing ($P < 0.001$). The NRS score for satisfaction tended to be higher after viewing LA in group A (CG→ LA) (CG vs. LA; 7.0 (2.3) vs. 8.6 (1.5), $P = 0.0993$), while in group B (LA→ CG), the score after CG was slightly lower than that after LA. There were no serious side effects.

Conclusions: This study suggests that iVR reminiscence can reduce anxiety in the oldest-old without causing serious side effects. Furthermore, the impacts might be better with LA images.

Keywords: virtual reality, reminiscence, anxiety, satisfaction, late elderly

INTRODUCTION

Dementia is one the major problems of aging societies, and various studies are being carried out around the world to address the issue. However, no curative drug therapy for dementia has yet been established. Furthermore, in 2018, four commercially available drugs for dementia (donepezil, galantamine, rivastigmine, and memantine) were excluded from national insurance coverage in France due to their high risk of side effects, rather than their efficacy (Krolak-Salmon et al., 2018). More recently, a series of phase 3 trials of new dementia drug candidates (Salloway et al., 2014; Honig et al., 2018; Wessels et al., 2019) ended in failure, highlighting the limitations of drug therapy for dementia. On the other hand, the FINGER study (Ngandu et al., 2015) recommended that interventions should be undertaken simultaneously to prevent cognitive decline because dementia is an interrelated multifactorial disorder. In addition, Livingston et al. (2017) identified nine factors that can prevent developing dementia through self-effort, specifically, dementia onset can be delayed if lifestyle (hypertension, obesity, smoking, depression, and diabetes) is improved, physical activity is increased, and coping with social isolation is begun at the early stage of suspected cognitive decline [i.e., mild cognitive impairment (MCI)]. In addition, Barnes and Yaffe (2011) suggest that decreased physical activity and depression are more risk factors for Alzheimer's disease than lifestyle-related diseases such as diabetes. Depression and anxiety are typical behavioral and psychological symptoms of dementia (BPSD), which often occur at the stage of MCI and bring a relatively heavy care burden (Black and Almeida, 2004). Therefore, although coping with these mental symptoms is important both in the elderly with MCI and their caregivers, it is rather difficult to respond with pharmacotherapy for mental symptoms (Yury and Fisher, 2007). In addition, since it is not possible to administer prophylactically antidementia drugs at the MCI stage, some novel non-drug therapies are urgently required.

Several approaches are reported to prevent cognitive decline, such as occupational therapy (Hermans et al., 2007; Gitlin et al., 2008), exercise therapy (Laurin et al., 2001; Thomas and Hageman, 2003; Rolland et al., 2007; Santana-Sosa et al., 2008; Hauer et al., 2012), and music therapy (Ueda et al., 2013). In addition, as a psychotherapy, there is reminiscence therapy advocated by Butler (1963), and further studies using this approach have shown to reduce cognitive decline, anxiety, and depressive symptoms (Goldwasser et al., 1987; Wang, 2007; Huang et al., 2015; Lok et al., 2019). In this context, there is a growing interest in digital therapeutics (DTx), a new non-drug approach that utilizes digital technologies such as the Internet of Things, artificial intelligence (AI), and virtual reality (VR). Because DTx is characterized by its extremely high affinity for telemedicine, the demand is skyrocketing globally at the moment with the coronavirus disease 2019 (COVID-19) raging all over the world (Guan et al., 2020; Li et al., 2020; Zhu et al., 2020). DTx is expected to prevent the spread of emerging and re-emerging infections without compromising the quality of healthcare (Humphreys et al., 2020; Ohannessian et al., 2020; Rockwell and Gilroy, 2020; Wang et al., 2020).

Recently, an approach using DTx was also considered for reminiscence; however, there are still few reports. For example, Subramaniam and Woods (2016) visualized memories heard from six dementia patients and compared the effects of life story videos with those of traditional album-style life story books, suggesting that life story videos had the more potential to improve patient quality of life. In addition, Moon and Park (2020) conducted twice-weekly reminiscence sessions with 25 dementia patients for 4 weeks, using tablets PC with an app installed that allowed the subjects to select and play back a collection of favorite images of their memories *via* the Internet. The comparison the results with those of 24 participants in the conventional reminiscence group without digital devices shows that depression were significantly reduced in the group that used the digital devices immediately after the initial reminiscence and 4 weeks later. In addition, we found for the first time that usage of immersive VR (iVR) to recall memorable places improved various physical and mental symptoms, such as pain, anxiety, and depression in terminally ill cancer patients (Niki et al., 2019). VR is a generic term for technology that works on human sensory organs to artificially create a three-dimensional (3D) environment that feels like reality. Because iVR has been commercially available since 2016 and has a very short history, there are no studies comparing the effects of 2D and 3D as a memory-recalling approach like reminiscence to the best of our knowledge. However, Schutte and Stilinovi (2017) compared the effects of iVR on empathy and engagement of "being there" with a 2D monitor. The results showed that both empathy and engagement were higher for iVR experiences than for 2D monitors, suggesting that iVR is more powerful in working with emotions. Therefore, we hypothesize that the iVR could be also more effective in a reminiscence. In this study, we first examined the efficacy and safety of iVR reminiscence as a pilot study, focusing on anxiety as one of the psychiatric symptoms that often appears with cognitive decline.

MATERIALS AND METHODS

Subjects

The inclusion criterion involves those 75 years of age or older who were using day services at a nursing home as of January 2020.

The exclusion criteria were set as follows: (1) poor recognition of VR images and (2) cognitive function was too low to answer the questionnaire. Poor recognition of VR images defined as "when the subjects complain of not being able to see the image clearly and the difficulty persists even after adjusting the mounting position of the VR headset." The too low cognitive function to answer the questionnaire defined as "when there was no coherent conversation between the questioners and subjects and the subjects were unable to answer the questions on the Likert scale of the State-Trait Anxiety Inventory (STAI) Japanese version (Iwata et al., 1998a,b) and the numerical rating scale (NRS)." Staff of the nursing home explained the study to the subjects in written form, and informed consent was obtained in writing.

Preparation of VR Images

Two types of VR images were prepared: live-action (LA) images and computer graphics (CG) images themed on the mid- to late Showa era (A.D. 1955–1980) in Japan. The LA images were shot using a 360° camera (Insta360 Pro 2X, Arashi Vision Inc., Shenzhen, China) at *Itsuka Kita Michi* in *Miroku no Sato* (https://www.mirokunosato.com/itsuka), a theme park in Fukuyama City, Hiroshima Prefecture. *Itsuka Kita Michi* is a facility that precisely recreates elements such as arcade, elementary schools, post-offices, shopping streets, and fields of the Showa era 30's (A.D. 1955–1965) in Japan, and we took many photos to document every scene in this facility. In addition, we purchased the "Showa 80's (A.D. 1970–1980) Japanese town model set vol. 3" (FUNSET; https://assetstore.unity.com/packages/3d/environments/urban/shouwa-80-s-japanese-town-model-set-vol-3-mall-127437) from Unity asset store and edited the CG images using Unity (Unity Technologies, San Francisco, USA), a game engine that creates VR content. Six situations were set up as familiar scenes to those aged 75 and over: arcades, cafeterias, sunken hearths, dagashi shops (old Japanese candy stores), downtown, and fields.

Operation of VR Images

A subject during iVR reminiscence and examples of LA and CG images are shown in **Figure 1**. Oculus Go (Facebook Technologies, California, USA) was used as the VR headset. The LA images were a slide show of 54 photographs, shown at 15-s intervals. The subjects simply had to wear the headset and watch. For the CG images, the researcher selected the scenes according to the subjects' wishes. The images in the VR headset were mirrored on the tablet PC. The researcher performed movement operations in VR space instead of subjects by using a controller while watching the mirrored images on the tablet PC, therefore, the subjects only had to wear the headset.

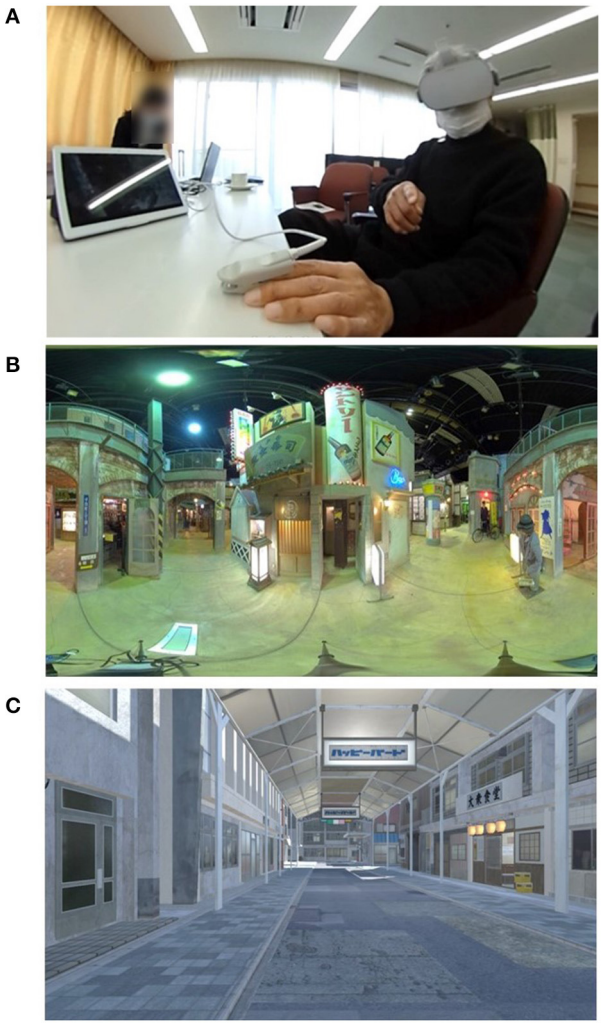

FIGURE 1 | A subject during immersive virtual reality reminiscence (iVR reminiscence) **(A)** and examples of live-action (LA) and computer graphics (CG) images **(B,C)**. Two types of VR images were prepared: live-action (LA) images and computer graphics (CG) images themed on the mid to late Showa era (A.D. 1955–1980) in Japan. Oculus Go (Facebook Technologies, California, USA) was used as the VR headset. The LA images were a slide show of 54 photographs shown at 15-s intervals. The researcher pressed a button to start the slideshow, and the subjects simply had to wear a headset. For the CG images, the researcher selected the scenes based on the wishes of the subjects. The researcher performed movement operations in VR space, and the subject only had to wear the headset. By mirroring the images from the VR headset to a tablet PC, the images that the subjects were watching inside the headset could be shared. While viewing VR, there were no restrictions on conversation among the researchers and the nursing home staff, so we had natural conversations with the subjects in response to what they said.

Study Design, Implementation, and Evaluation of the iVR Reminiscence

This is a single-center, pilot, open-label, randomized crossover study. The subjects were randomly divided into two groups in equal numbers, and alternately viewed two types of iVR images (LA and CG). In group A, the CG images were viewed first, and then the LA images were viewed. In group B, the images were viewed in the opposite order. The randomization was conducted by the permuted block method. The block size was set to four subjects per block, and the allocation of each block was predetermined (AABB, BAAB, and ABAB). Before the first viewing, subjects were assessed on their current cognitive function and anxiety by the Mini-Mental State Examination (MMSE) Japanese version (Sugishita et al., 2016) and the STAI Japanese version (Iwata et al., 1998a,b). The STAI is a globally

used tool for measuring adult emotions and consists of 20 questions that assess how the respondents are feeling right now. For each question of STAI, subjects responded on a 4-point Likert scale (1 = almost never, 2 = occasionally, 3 = most of the time, 4 = almost always). The total score for STAI ranges from 20 to 80, with higher scores indicating stronger anxiety. Then, subjects wore a VR headset and viewed the first VR images for 10 min. After the first viewing, subjects responded to STAI and the NRS for satisfaction and side effects (nausea, dizziness, headache, and tiredness). NRS is a tool that evaluates the degree of emotion or symptoms on a scale of 0 to 10. In this study, satisfaction was set to "0 = not at all to 10 = quite satisfied," and side effects were set to "0 = not at all to 10 = most severe." Then, after a 10-minbreak, the subjects viewed the second VR images for 10 min, and they received the same evaluations as the first time and answered the question, "Which images were better, the LA or the CG images?" While viewing VR, there were no restrictions on conversation among the researchers, nursing home staff, and subjects. To ensure that subjects were not nervous about their first experience of viewing iVR, the familiar nursing home staff were present throughout the experiment. In addition, if the subjects showed any unusual behavior such as excitement within 1 week of the study date, the nursing home staff would record the date, time, and condition and would contact the principal researcher.

Primary and Secondary Endpoints

The primary endpoint was the change in total STAI scores after the second VR viewing from before viewing. The secondary endpoints were the safety of the iVR reminiscence and the preference for LA or CG images.

Statistical Analyses

Data were collected through February 2020 and analyzed from March to April 2020. In the results, the values of analyses are presented in the mean and standard deviation (SD). Comparisons of STAI scores before and after the first VR viewing, and after second viewing were performed by a Dunnett's test with the STAI scores before the first VR viewing as control groups. A Student's *t*-test was performed to compare subjects' backgrounds and the amount of change in STAI scores between two groups. A paired *t*-test was performed for changes in satisfaction and side effects. BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for statistical analysis, with two-tailed $P < 0.05$ as statistically significant.

Ethical Considerations

The study was approved by the Research Ethics Review Committee of the Osaka Center for Cancer and Cardiovascular Disease Prevention (approval number; R1-RINRI-9) and was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000039762).

RESULTS

Twelve individuals were enrolled in the study, one was excluded due to poor recognition of VR images, and one was excluded from the analysis because she was unable to answer the questionnaire. The backgrounds of the 10 subjects who completed the study are shown in **Table 1**. The mean age was 87.1 years (4.2), the mean MMSE was 28.5 (1.8), and the lowest MMSE score was 24. Group B was significantly older than group A ($P = 0.0299$); however, there were no significant differences in other variables.

Figure 2 shows the change in STAI scores with VR viewing, and the amount of change in STAI scores is shown in **Figure 3**. Regarding the change in total STAI scores on the primary endpoint (**Figure 2A**), the mean score was 36.1 (7.2) before viewing, but it decreased to 26.8 (4.9) after the first viewing ($P = 0.0010$), and further decreased to 23.4 (2.8) after the second viewing ($P < 0.001$).

Comparing the amount of changes in total STAI scores between the groups (**Figure 3A**), after the first viewing, there was a 10.8-point (3.7) decrease in group A (CG→ LA) and a 7.8-point (2.0) decrease in group B (LA→ CG) compared with before viewing. After the second viewing, there was a further decrease of 5.4 points (3.3) in group A (CG→ LA) and 1.4 points (1.7) in

TABLE 1 | Subjects' backgrounds.

Variables	All subjects ($n = 10$)	Group A ($n = 5$)	Group B ($n = 5$)	*P*-value (groups A vs. B)
Age, years, mean [*SD* (range)]	87.1 [4.2 (82, 93)]	84.4 [2.3 (82, 88)]	89.8 [4.0 (83, 93)]	0.0299
Male [*n* (%)]	4 (40)	1 (20)	3 (60)	0.5238
Level of care needed [*n* (%)]				N/A
Requiring support 1	2 (20)	1 (20)	1 (20)	
Requiring support 2	4 (40)	2 (40)	2 (40)	
Requiring long-term care 1	2 (20)	1 (20)	1 (20)	
Requiring long-term care 2	2 (20)	1 (20)	1 (20)	
Requiring long-term care 3	0 (0)	0 (0)	0 (0)	
Requiring long-term care 4	0 (0)	0 (0)	0 (0)	
Requiring long-term care 5	0 (0)	0 (0)	0 (0)	
MMSE-J, mean [*SD* (range)]	28.5 [1.8 (24, 30)]	28.8 [0.8 (28, 30)]	28.2 [2.5 (24, 30)]	0.6233

Student's t-test.

SD, standard deviation; N/A, not available; MMSE-J, Mini-Mental State Examination Japanese version.

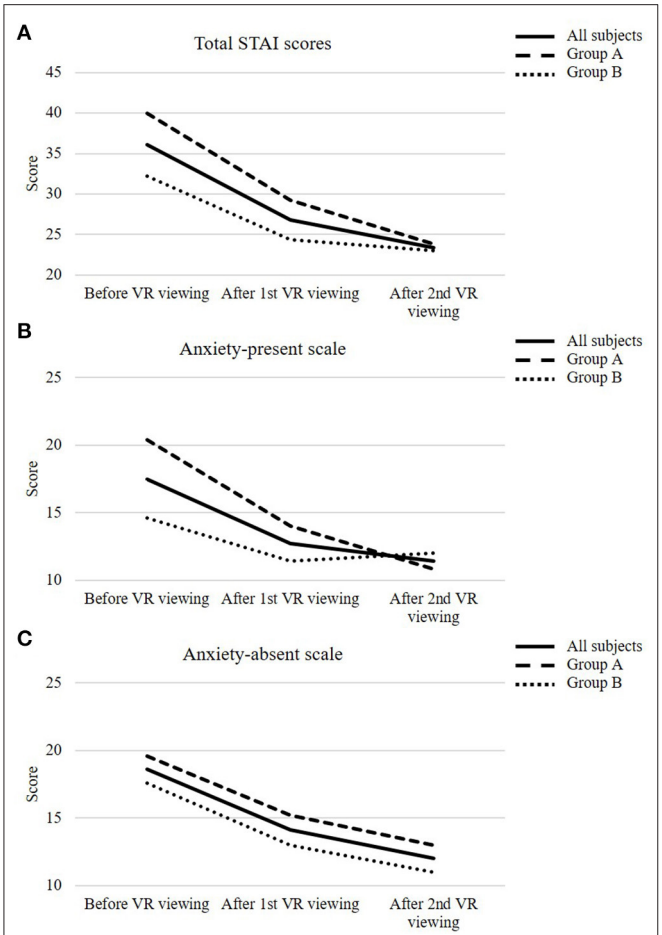

FIGURE 2 | The change in State-Trait Anxiety Inventory (STAI) scores before virtual reality (VR) viewing, after the first and second VR viewing in all subjects and each group. The change in total STAI scores **(A)**, anxiety-present scale **(B)**, and anxiety-absent scale **(C)**. All subjects are represented by solid lines, and groups A and B are represented by thick and thin dotted lines, respectively. Subjects were assessed on their anxiety by the STAI Japanese version before VR viewing. Then, subjects wore a VR headset and viewed the first VR images for 10 min. After the first VR viewing, subjects responded to STAI and the numerical rating scales for satisfaction and side effects (nausea, dizziness, headache, and tiredness). Then, after a 10-min break, the subjects viewed the VR images for 10 min, which were different from the first time, and after the second VR viewing, they received the same evaluations as the first time.

group B (LA→ CG), and the amount of change was significantly larger in group A than that in group B ($P = 0.0334$).

Since the STAI consists of the anxiety-present scale (P-scale), which consists of negative questions to detect the presence of anxiety, and the anxiety-absent scale (A-scale), which consists of positive questions to detect the absence of anxiety, we conducted analyses categorized by P-scale and A-scale (**Figures 2B,C** and **3B,C**). Regarding the change in P-scales between before and after the first viewing, there was a significant decrease from 20.4 (1.9) to 14.0 (1.9) in group A (CG→ LA) ($P < 0.001$), whereas in group B (LA→ CG), the decrease was from 14.6 (4.0) to 11.4 (2.6), although not significant ($P = 0.2481$). Regarding the change in the A-scale between before and after the first viewing, there was an insignificant decrease from 19.6 (5.7) to 15.2 (3.8) in group A (CG→ LA) ($P = 0.2049$) but a significant decrease from 17.6 (1.5) to 13.0 (3.0) in group B (LA→ CG) ($P = 0.0089$). The total STAI scores, A-scale, P-scale, and the results of Dunnett's test for the all subjects, groups A and B, respectively, are shown in **Supplementary Table 1**.

The results of the evaluation of satisfaction and side effects of VR viewing are shown in **Table 2**. The NRS score for satisfaction tended to be higher after the second viewing in group A (CG→ LA) than the first viewing [first (CG) vs. second (LA); 7.0 (2.3) vs. 8.6 (1.5), $P = 0.0993$], while in group B (LA→ CG), the NRS score after the second viewing was slightly lower than the first viewing [first (LA) vs. second (CG); 8.6 (2.2) vs. 8.2 (1.9), $P = 0.1778$]. No dizziness caused by VR viewing was observed. For nausea, one subject in group A (CG→ LA) reported NRS = 1 after viewing CG, but the score became 0 after viewing LA. For tiredness, in group A (CG→ LA), one subject reported NRS = 3 after viewing CG, but the score became 0 after viewing LA, while in group B (LA→ CG), one subject reported NRS = 1 after viewing LA, and the score did not change after viewing CG. Regarding headache, one subject in group A (CG→ LA) reported NRS = 1 after viewing CG and there was no change after viewing LA. None of the subjects reported any unusual behavior such as excitement within one week of the study date. Besides, for the question; "Which images were better, the LA or the CG images?," six subjects answered that they preferred LA images.

DISCUSSION

In this study, we explored efficacy and safety of iVR reminiscence for the oldest-old, focusing on anxiety as one of psychiatric symptoms that often appears with cognitive decline. Moreover, we also examined the preference for VR image types for reminiscence. We found that iVR reminiscence could transiently reduce anxiety without causing serious side effects, and the impact might be better with LA images than CG. This is the first medical report that examined not only the efficacy and safety of iVR reminiscence but also the preference for image types in the oldest-old.

Only one subject had a suspected MCI [MMSE ≤27 (Kaufer et al., 2008; Saxton et al., 2009)], so it was estimated that most subjects' cognitive functioning was relatively preserved.

In this study, the total STAI score decreased by a mean of 12.7 points after the second viewing. In terms of the minimum amount of change that can be interpreted as to how much the score changes would be clinically meaningful to the patient, i.e., the minimal clinically important difference (MCID), Corsaletti et al. (2014) reported that the MCID for STAI was 10 points. Belland et al. (2017) reported that for elderly people with a mean (*SD*) age of 73 years (6), the total STAI scores decreased by a mean (*SD*) of 10.00 points (12.29) after music therapy. Besides, Chirico et al. (2020) investigated three groups of breast cancer patients: a group viewing nature images in iVR, a music therapy group, and a nonintervention group, and reported that the total STAI score before and after each intervention was 6.85 and

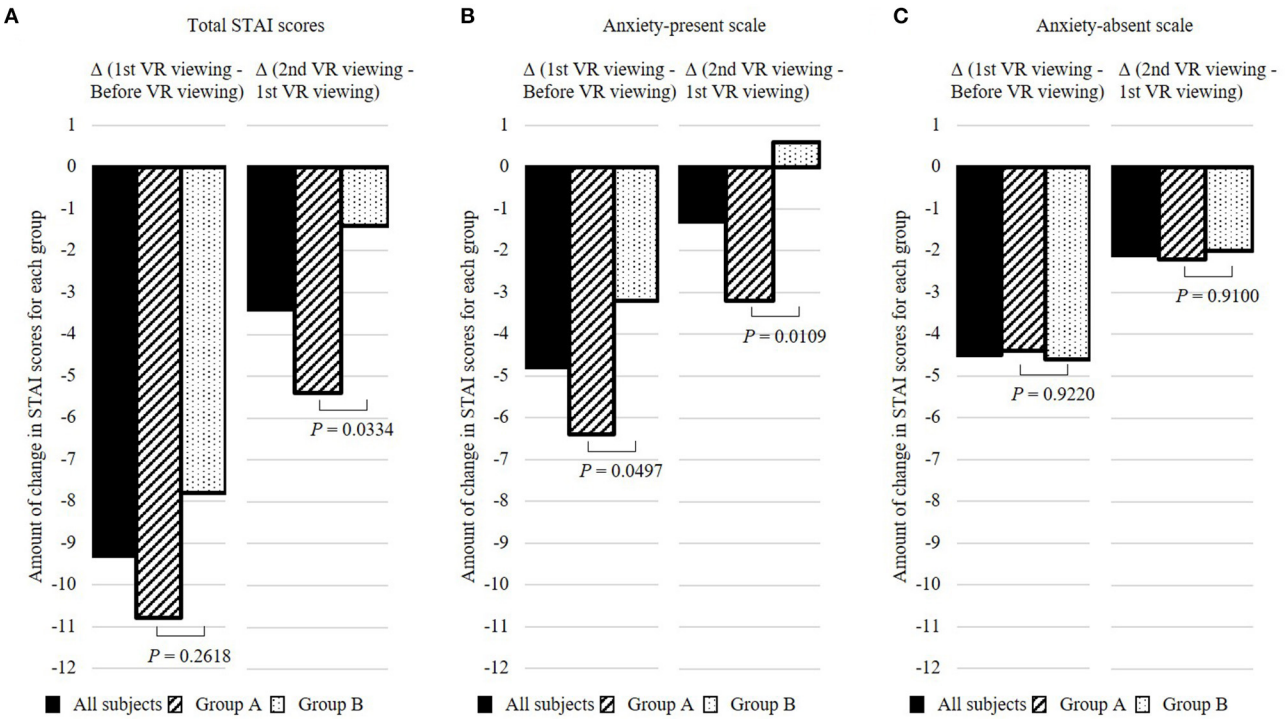

FIGURE 3 | The amount of change in State-Trait Anxiety Inventory (STAI) scores in total STAI scores **(A)**, anxiety-present scale **(B)**, and anxiety-absent scale **(C)**. All subjects are represented by black squares, and groups A and B are represented by slanted and dotted squares, respectively. Subjects were assessed on their anxiety by the State-Trait Anxiety Inventory (STAI) Japanese version before and after the first VR viewing, and after second VR viewing. The amount of change in STAI scores from before VR viewing to after the first VR viewing (before VR viewing—after the first VR viewing) and the amount of change in STAI scores from after the first VR viewing to after the second VR viewing (after the first VR viewing—after the second VR viewing) were calculated.

TABLE 2 | Evaluation of satisfaction and side effects after virtual reality (VR) viewing.

	Group A ($n = 5$)			Group B ($n = 5$)		
	After 1st VR viewing (CG)	**After 2nd VR viewing (LA)**	***P*-value**	**After 1st VR viewing (LA)**	**After 2nd VR viewing (CG)**	***P*-value**
Satisfaction [mean (*SD* (range))]	7.0 [2.3 (5, 10)]	8.6 [1.5 (7, 10)]	0.0993	8.6 [2.2 (5, 10)]	8.2 [1.9 (5, 10)]	0.1778
Nausea [mean (*SD* (range))]	0.2 [0.4 (0, 1)]	0.0 [0.0 (0, 0)]	0.3739	0.0 [0.0 (0, 0)]	0.0 [0.0 (0, 0)]	N/A
Dizziness [mean (*SD* (range))]	0.0 [0.0 (0, 0)]	0.0 [0.0 (0, 0)]	N/A	0.0 [0.0 (0, 0)]	0.0 [0.0 (0, 0)]	N/A
Headache [mean (*SD* (range))]	0.2 [0.4 (0, 1)]	0.2 [0.4 (0, 1)]	N/A	0.0 [0.0 (0, 0)]	0.0 [0.0 (0, 0)]	N/A
Tiredness [mean (*SD* (range))]	0.8 [1.3 (0, 3)]	0.0 [0.0 (0, 0)]	0.2420	0.2 [0.4 (0, 1)]	0.2 [0.4 (0, 1)]	N/A

Paired t-test.
VR, virtual reality; CG, computer graphics; LA, live action; SD, standard deviation; N/A, not available.

3.33 points down in the VR group and music therapy group, respectively, indicating that iVR intervention was more effective than music therapy in reducing anxiety. Of course, it is necessary to directly compare iVR reminiscence with conventional one, but iVR reminiscence might be expected to have an anxiety-reducing effect comparable with conventional non-drug therapies.

Meanwhile, it is essential to share the images that the subjects are viewing together at the same time because many reminiscences are performed with several people. Ferguson et al. (2020) evaluated the effect in a study with 25 dementia patients in a hospice (mean age 85 years) who viewed 360° iVR images of a sandy beach and reported the limitations of this the study, which were that the researchers could not know what the subjects were watching in a VR headset and thus could not response to subjects. We devised a way to share the images which the subjects were watching by mirroring the images on the tablet PC so that the researchers and nursing home staff could communicate smoothly with the subjects. This may also have contributed to the reduction of STAI score larger than the MCID.

Furthermore, no serious side effects were observed in this study. This result supports previous reports that iVR did not cause serious side effects even in people older than 70 years. In the report by Ferguson et al. (2020), two of the 25 patients with dementia exhibited unusual behavior during 3–5 h after

viewing of iVR. In addition, our previous study with 20 terminal cancer patients (mean age 72.3 years) did not show any serious side effects associated with iVR viewing (Niki et al., 2019). Comparable studies are limited because there are few studies worldwide using iVR with subjects over 70 years old, but of the two studies above, Ferguson et al. (2020) used images of a beach and Niki et al. (2019) used 3D photos (still images) from Google earth VR, respectively. In other words, there was little movement of the images, and the risk of nausea (VR motion sickness), which is a side effect of most concern in VR, was considered to be small. Since more movement was found in CG used in this study, the nausea was of concern, but none of the subjects complained of nausea after viewing iVR.

In addition, we also take a guess whether LA or CG is more suitable for use in iVR reminiscence for future research in this pilot study. While LA has the advantage of being able to quickly, inexpensively, and easily create realistic VR contents, the disadvantage of being impossible to recreate nonexistent scenery. CG can create nonexistent scenery, but it takes a lot of time and cost to create realistic VR contents. The results of this study show that LA might have better effects than CG. This may be due to the result that LA images worked more on the positive emotions. One of the reasons for this result is that the NRS score for satisfaction tended to be higher after viewing LA in group A (CG→ LA). On the contrary, in group B (LA→ CG), the NRS score tended to decrease after viewing CG. In addition, tiredness was relieved after viewing LA in group A (CG→ LA), but not in group B (LA→ CG), and slightly more subjects (6/10) responded that they would prefer LA. For the second reason, the comparisons of STAI scores before and after the first viewing showed that the change in A-scales of STAI reflecting positive emotions significantly decreased in group B (LA→ CG), whereas that in group A (CG→ LA), was not significant. This may be due to the difference of personalities of the subjects between two groups. Namely, the mean (*SD*) of total STAI score before the first viewing in group A [40.0 (7.3)] tended to be higher than that in group B [32.2 (5.1)] ($P = 0.086$). There might be some subjects who felt nervous about their first VR experience in group A because some subjects told us, "I am feeling nervous because it is my first experience." Meanwhile, some subjects in group B said, "I will try anything." In this way, most subjects of group B tended to actively participate in this session. The decrease in P-scales of STAI reflecting negative emotions in group A after the first viewing may be due to the subjects' understanding what VR was, resulting in a less nervous state. Meanwhile, the subjects in group B did not show much nervousness even before viewing, so there was no significant change in the P-scales associated with first viewing. Therefore, the significant decrease in A-scale in group B (LA→ CG) could be purely due to the positive effect of iVR reminiscence. In fact, perhaps because group A (CG→ LA) had the mental capacity to enjoy the content of the iVR after the first viewing, there was a significant decrease in A-scale after the second viewing. In addition, in group B, P-scales increased after viewing CG compared with viewing LA, which was the exact opposite of the results in group A. For the third reason of the result that LA images worked more on the positive emotions may be due to the "uncanny valley phenomenon" (Mori et al., 2012) that the closer the animation is to the real world, the more uncanny it becomes. In fact, some subjects said, "It looks like a ghost town and it's creepy" while viewing the CG images. One method of reminiscence, which especially evokes pleasant memories of the past, is called mental time travel (MTT). Since MTT has been shown to cause activation of the hippocampus in the medial temporal lobe Milner et al. (1998), it is supposed to be important to show how VR images work on positive emotions.

There are some limitations to this study. First, because this study was a randomized crossover trial, there might have been a carryover effect from the first viewing and it cause time-dependent reduction of stress derived from familiarization with new iVR experience. Thus, consideration of appropriate washout time and comparison with traditional reminiscence will be necessary. Besides, the number of subjects was very small, thus, future studies in which the sample size is calculated based on the results of this study are needed. Second, we assessed only transient changes of anxiety. Third, some VR images were different from those of the subjects' own memories. Generic themes and scenes are usually used in reminiscence, so this is partly unavoidable. However, it has been shown that life review, which is a method to recall personal memories, can alleviate psychiatric symptoms in the elderly (Korte et al., 2012; Preschl et al., 2012). Therefore, whether it is possible to realize a tailor-made reminiscence by utilizing novel technologies such as AI will be a challenge for VR reminiscence. Fourth, the lack of side effects was predictable because of the static and short-time iVR expositions, thus, safety or tolerability of iVR might not be assessed truly. For example, the maximum amount of time that can be viewed without feeling nauseated remains unclear. Fifth, although there were no significant differences between the two groups, the degree of anxiety at baseline was different. We tried to alleviate some of the nervousness about meeting the researchers and viewing iVR for the first time by having familiar nursing home staff present with the subjects throughout the study, but we were unable to completely relieve the nervousness from some subjects. Thus, it is necessary to set up using the STAI score as a criterion at the time of recruitment and to divide the subjects into groups so that their backgrounds are as similar as possible. Finally, because the subjects were not limited to people with MCI, additional studies in people with MCI is needed in the future.

CONCLUSIONS

This study suggests that iVR reminiscence may be a novel method to reduce anxiety in the oldest-old. Since this study is a pilot study and includes important theoretical and methodological questions that should be solved, for example, it is necessary to enrich the content based on LA images and to examine the efficacy and safety of continued interventions from multiple perspectives in future studies. However, as one of the new forms of healthcare in the rapidly aging modern world and during and the current era coexist with the COVID-19, it is now increasingly important to promote DTx to enable remote healthcare. The rapid accumulation of the evidence on DTx for preventing cognitive decline is desired because DTx could contribute to a

global improvement in the quality of healthcare, as they have the potential to provide borderless, high-quality healthcare through the Internet.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethics Review Committee of the Osaka Center for Cancer and Cardiovascular Disease Prevention (approval number; R1-RINRI-9). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KN and TI: concept and design. KN, MY, MI, NT, and AW: acquisition, analysis, or interpretation of data. KN and MY: drafting of the manuscript. MU, DI, KS, and TI: critical revision of the manuscript for important intellectual content. KN: statistical analysis. TI: obtained funding and supervision. MI, AW, DI, KS, and TO: administrative, technical, or material support. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnhum.2020.598161/full#supplementary-material

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REVIEW
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Neural Basis and Motor Imagery Intervention Methodology Based on Neuroimaging Studies in Children With Developmental Coordination Disorders: A Review

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Although the neural bases of the brain associated with movement disorders in children with developmental coordination disorder (DCD) are becoming clearer, the information is not sufficient because of the lack of extensive brain function research. Therefore, it is controversial about effective intervention methods focusing on brain function. One of the rehabilitation techniques for movement disorders involves intervention using motor imagery (MI). MI is often used for movement disorders, but most studies involve adults and healthy children, and the MI method for children with DCD has not been studied in detail. Therefore, a review was conducted to clarify the neuroscientific basis of the methodology of intervention using MI for children with DCD. The neuroimaging review included 20 magnetic resonance imaging studies, and the neurorehabilitation review included four MI intervention studies. In addition to previously reported neural bases, our results indicate decreased activity of the bilateral thalamus, decreased connectivity of the sensory-motor cortex and the left posterior middle temporal gyrus, bilateral posterior cingulate cortex, precuneus, cerebellum, and basal ganglia, loss of connectivity superiority in the abovementioned areas. Furthermore, reduction of gray matter volume in the right superior frontal gyrus and middle frontal gyrus, lower fractional anisotropy, and axial diffusivity in regions of white matter pathways were found in DCD. As a result of the review, children with DCD had less activation of the left brain, especially those with mirror neurons system (MNS) and sensory integration functions. On the contrary, the area important for the visual space processing of the right brain was activated. Regarding of characteristic of the MI methods was that children observed a video related to motor skills before the intervention. Also, they performed visual-motor tasks before MI training sessions. Adding action observation during MI activates the MNS, and performing visual-motor tasks activates the basal ganglia. These methods may

improve the deactivated brain regions of children with DCD and may be useful as conditioning before starting training. Furthermore, we propose a process for sharing the contents of MI with the therapist in language and determining exercise strategies.

Keywords: developmental coordination disorder, neuroimaging, brain, motor imagery, methods

INTRODUCTION

Developmental coordination disorder (DCD) manifests as "clumsiness and slowness or inaccuracy of motor skills and defective acquisition and performance of coordination skills, which interfere with activities of daily living." The prevalence is 5–6% in children aged 5–11 years, and the sex ratio ranges from 2:1 to 7:1 (male:female; American Psychiatric Association, 2013). Various subtypes of motor problems have been reported and commonly include issues related to motor skills such as balance, coordination, and writing (Nakai et al., 2011; Vaivre-Douret et al., 2011). Underdeveloped motor skills make it difficult to perform the basic movements required for daily activities (Wilson et al., 2013; Adams et al., 2016a). Furthermore, problems associated with DCD extend to exercise-related activities as well as other aspects. For example, reduced participation in play and group sports causes physical problems such as weakness and obesity (Watkinson et al., 2001; Mandich et al., 2003; Cairney et al., 2005). Self-esteem and self-affirmation may be impaired, and secondary disorders such as depression and anxiety-related mental disorders have also been recognized (Poulsen et al., 2008; Lingam et al., 2012; Missiuna et al., 2014; Caçola, 2016; Cairney et al., 2016).

DCD can occur alone or with other diseases and disorders. In particular, its coexistence with attention-deficit/hyperactivity disorder (ADHD), termed "deficit of attention, motor control, and perception syndrome", is high (Fliers et al., 2008; Díaz-Lucero et al., 2011); moreover, it is reported that more than 80% of individuals with coexisting autism spectrum disorder (ASD) experience significant problems in daily life situations (Green et al., 2009; Van Waelvelde et al., 2010). Impaired spatial grasping ability and visual and motor perception may underlie these comorbidities, but the common neurological basis has not been clarified.

The exercise-related problems of children with DCD rarely resolve spontaneously with age. They often persist in adolescence and adulthood (Zwicker et al., 2012b; Bo and Lee, 2013), and may further promote secondary disabilities given the lack of proper intervention (Cantell et al., 1994). Therefore, some form of support becomes necessary. Various programs have been implemented for exercise support to children with DCD, and some short-term results have been reported (Yu et al., 2018). It is known that training that simply involving correcting inaccurate coordination is not always effective, and nowadays the usefulness of a task-oriented approach, in which the child finds multiple solutions and selects the most desirable one, has been suggested (Smits-Engelsman et al., 2018). However, a systematic review and meta-analyses published between 1996 and 2012, judged to be of low quality in a report, questioned the quality of the evidence in this regard and the effectiveness of such interventions (Miyahara et al., 2017, 2020). In other words, there are very few rigorously planned and verified studies and corresponding reviews regarding interventions for children with DCD, and there is currently no evidence to prove that these interventions improve outcomes. In recent years, attempts have been made to develop international guidelines for DCD (Blank et al., 2019), and interventions involving task-oriented approaches (Ward and Rodger, 2004), and neuromotor task training (Ferguson et al., 2013) are recommended, indicating that these are considered effective. Besides, from a novel perspective, interventions using motor imagery (MI) have also been reported. Since MI simulates in the brain without actually exercising, it is less likely to cause exercise errors and may be useful as a pre-training condition for children with DCD. A point to be noted while carrying out exercise image intervention is that the intervention method differs depending on factors such as the age and condition of the target individual and the type of exercise. To address this issue, Schuster et al. (2011) analyzed systematic MI training sessions (MITS) and reported the details of successful MI intervention techniques. However, most of the studies analyzed involved interventions for adults, and only two involved interventions for children up to 9 years of age. Furthermore, both studies involved interventions for healthy children. Therefore, it is necessary to investigate the methodology of MI intervention for children with DCD that is currently being conducted and integrate it with the results of brain imaging studies to derive effective intervention methods.

Various studies using brain functional imaging to study the pathophysiology of DCD have also been conducted. Based on functional MRI (fMRI) studies using hand movement tasks, compared to children with typical development (TD), children with DCD were found to have lower activation in the middle frontal gyrus (MFG), superior frontal gyrus (SFG), cerebellum, supramarginal gyrus (SMG), and inferior parietal lobules (IPLs; Fuelscher et al., 2018). A study focusing on the mirror neuron system (MNS), including the inferior frontal gyrus (IFG), premotor cortex (PMC), IPL, and superior temporal sulcus, has also been reported (Reynolds et al., 2015b; Lust et al., 2019). In 2016, a critical review of previous MRI studies was published and concluded that the neural bases in children with DCD included the frontal lobe, parietal lobe, basal ganglia, and cerebellum (Biotteau et al., 2016). As mentioned above, knowledge of DCD's neural basis and network abnormalities has been accumulated, but few studies have mentioned intervention methods based on these studies. Therefore, we focused on MI, which is one of the neurological rehabilitation, and aimed to derive an effective intervention

method for children with DCD based on the results of neuroimaging studies.

The purpose of this study was to examine MI interventions for children with DCD based on neuroimaging studies and to propose new methods. Therefore, we planned to carry out two reviews. One reviewed MRI articles up to 2020 and summarized the latest information on how the neural bases and networks of children with DCD differ from those of children with TD. The other was to summarize the MI intervention methods used for children with DCD.

MATERIALS AND METHODS

A comprehensive search was completed in the databases Medline, CINAHAL, AMED, and The Cochrane Library.

Neuroimaging Studies

The search strategy used MeSH terms and text words for ("child" or "child, preschool," or "pediatric") and ("motor skills disorders" or "developmental coordination disorder" or 'DCD') and ("Magnetic Resonance Imaging" or "functional connectivity" or "neural pathways") in August 2020. Brain function analyses using MRI for children with DCD involve the following: (1) fMRI; (2) diffusion tensor imaging (DTI); or (3) voxel-based morphometry (VBM). Exclusion criteria were: (1) adult studies or preterm children; (2) review and meta-analysis literature; (3) cerebral palsy; and (4) dysgraphia.

fMRI

Based on the blood-oxygenation-level-dependent effect (Kim and Ogawa, 2012), somatosensory sensations, such as visual, auditory, tactile, taste, and olfactory sensations, can be identified using an MR device by analyzing the increase in blood flow associated with brain activity and identifying the activation site. Similarly, it is possible to understand which part of the brain is active when exercise or cognitive stimulation is applied. It is also possible to investigate neural networks, language, memory, emotion, attention, and brain plasticity. Studies have also focused on resting-state MRI (Buzsákim and Draguhn, 2004) because neural activity in the brain fluctuates with a certain frequency band even in the resting state (Raichle, 2011). With this method, the subject is taught to be at rest by keeping their eyes closed or gazing at a fixed point. In many cases, the measured spontaneous volatility of the blood-oxygenation-level-dependent signal is used to assess the degree of correlation between the neural activities of distant regions. This synchronization between brain regions is called functional connectivity, and a functional index or a network index (the default mode network) based on it has been proposed as a new biological index (Mohan et al., 2016).

DTI

Diffusion-weighted images are used as the basis for calculations in DTI. This method has been used to evaluate the diffusivity of water molecules in the brain, where the direction of diffusion of water molecules is determined by the direction of nerve fiber conduction (Basser et al., 1994). Two types of indices are obtained from DTI: fractional anisotropy (FA), which represents the degree of diffusion anisotropy, and apparent diffusion coefficient, which represents the apparent magnitude of diffusion. It is also possible to observe the positional relationship between the nerve fibers in the body tract, sensory tract, visual axis, and lesion site.

VBM

After anatomical standardization/tissue fractionation (for demarcation into gray matter, white matter, and cerebrospinal fluid space), image analysis of brain morphology is performed pixel-by-pixel based on the image database of the normal brain and specific factors (sex, age, lifestyle habits, neuropsychiatric disorders; Ashburner and Friston, 2000).

Neurorehabilitation Studies (MI)

The search strategy used MeSH terms and text words for ("child" or "child, preschool," or "pediatric") and ("developmental disabilities" or "motor skills disorders" or "developmental coordination disorder" or 'DCD') and ("mental imagery" or "mental practice" or "mental training" or "mental rehearsal" or "mental movements" or "eidetic imagery" or "visual imagery" or "guided imagery" or "motor imagery"). The inclusion criteria were: (1) any design of quantitative intervention studies with a focus on imaging movements; (2) studies that included children with DCD; and (3) study intervention that focused on motor skill, performance, or strength improvement. Exclusion criteria were: (1) mental practice not related movements; and (2) mental practice without physical exercise. MITS was classified based on the 17 elements of the PETTLEP (physical, environment, timing, task, learning, emotion, and perspective; Holmes and Collins, 2001) approach-based MITS reported by Schuster et al. (2011; **Supplementary Table 2**). The Physiotherapy Evidence Database list was used to evaluate RCTs and assign a maximum score of 10 points; (Maher et al., 2003). An RCT is a study in which people are allocated at random (by chance alone) to receive one of several clinical interventions. One of these interventions is the standard of comparison or control. The control may be a standard practice, a placebo, or no intervention at all. For the case series experimental design, the 11-point Single Case Experimental Design scale was used (Tate et al., 2008). All studies were rated by the first author based on detailed rating guidelines. Studies received one point for each fulfilled methodological criterion on the respective rating list. The higher the achieved score, the better the study quality.

RESULTS OF NEUROIMAGING STUDIES

The neuroimaging review included 20 magnetic resonance imaging studies. In all studies, children with DCD experienced problems in their daily lives and were mostly assessed using the Movement Assessment Battery for Children (one study had unclear criteria and the other used the Bruininks-Oseretsky Test of Motor Proficiency). Most participants were 7–12 years old, but some studies included those up to 17 years of age. Participants performed various tasks during fMRI, such as go/no-go, tracking, fine-motor, trial-tracking, motor

response, finger sequencing, and hand clenching tasks and observing, executing, and imitating a finger sequence, finger tapping sequence, and finger adduction/abduction. Others were conducted in the resting state, or the tasks were not listed. MRI was conducted at a magnetic flux density of 1.5 T in only one study and of 3.0 T in others. The details of the results are summarized in **Supplementary Table 1**. We have also depicted the results in **Figure 1** to clearly show the differences in brain activation in DCD and TD. If brain activation were DCD > TD, the corresponding Brodmann area (BA) number is displayed in red. On the contrary, if brain activation were DCD < TD, it is displayed in blue. When reports were inconclusive (DCD > TD or DCD < TD), they are displayed in purple. Regions not mentioned are shown in white. BrainNet Viewer was used to creating the figure[1] (Xia et al., 2013).

fMRI Results

It was clear that the activation of the left brain was broadly reduced in children with DCD, while that in parts of the right brain was higher than in children with TD (**Figure 1**). The results are summarized below according to the sites and analysis types.

Frontal Lobe

The left medial frontal gyrus (BA6), SFG (BA8), bilateral SFG (BA9), right dorsolateral prefrontal cortex (BA9), IFG (BA9), MFG (BA9), and left IFG (BA47) had lower activation in children with DCD than in children with TD. Conversely, the right lateral orbitofrontal cortex (BA11) and MFG (BA46) are more active in children with DCD (Caeyenberghs et al., 2016). The right precentral gyrus and medial frontal gyrus (BA6) showed a decline in activation in two studies (Reynolds et al., 2015a, 2017), but in the study by Zwicker et al. (2010) high activation was reported. In the pars opercularis of the IFG (BA44), children with DCD had lower activation during imitation and higher activation during observation than those in children with TD (Licari et al., 2015; Reynolds et al., 2015a).

Parietal Lobe

In the left postcentral gyrus (BA2, 3), superior parietal lobe (BA7), bilateral precuneus (BA7), and left precuneus (BA39), children with DCD showed lower brain activation than children with TD. Conversely, the right postcentral gyrus (BA3) is activated to a greater extent in children with DCD. The bilateral IPL (BA40), SMG (BA40), and temporoparietal junction (BA40) are less activated those in children with DCD (Kashiwagi et al., 2009; Zwicker et al., 2011; Debrabant et al., 2013), while a study by Zwicker et al. (2010) reported high activation of the left IPL and right SMG.

Temporal Lobe

In the left fusiform gyrus (BA37), superior temporal gyrus (BA41), and transverse temporal gyrus (BA41), children with DCD have lower brain activation than children with TD (Zwicker et al., 2011; Debrabant et al., 2013). Conversely, the right superior temporal gyrus (BA41) is more active than in children with DCD (Zwicker et al., 2010).

Occipital Lobe

In the right lingual gyrus (BA18) and left middle temporal gyrus (MTG, BA19), children with DCD have lower brain activation than children with TD (Zwicker et al., 2011; Reynolds et al., 2015a). In the right lingual gyrus (BA19), activation was shown to be higher those in children with DCD (Zwicker et al., 2010).

Limbic System and Islands

In the limbic system and islands, the bilateral insula (BA13), left cingulate gyrus (BA23, 24), right posterior cingulate (BA29), left parahippocampal gyrus (BA30), posterior cingulate (BA30), and right precuneus (BA31), children with DCD were shown to have lower brain activation than children with TD (Reynolds et al., 2015a, 2019). Conversely, the right parahippocampal gyrus (BA30) was shown to be more active in some children with DCD (Zwicker et al., 2010).

Basal Ganglia and Cerebellum

In the basal ganglia, children with DCD have been shown to have lower brain activation in the bilateral thalamus and caudate than children with TD (Reynolds et al., 2019). In the cerebellum, bilateral cerebellar crus I, and left cerebellar lobules VI and IX, children with DCD have lower brain activation than children with TD (Zwicker et al., 2011; Debrabant et al., 2013). Conversely, the right cerebellar lobule VI has higher activation than in children with DCD (Zwicker et al., 2010).

Connectivity

The results were summarized in **Supplementary Table 1**. Querne et al. found that, compared to children with TD, children with DCD had weaker connections between the right middle frontal cortex (BA46) and anterior cingulate cortex (BA32) and the middle frontal cortex (BA46) and inferior parietal cortex (BA40). On the other hand, the connection between the bilateral anterior cingulate cortex (BA32) and inferior parietal cortex (BA40) and the left middle frontal cortex (BA46) and inferior parietal cortex (BA40) is stronger in children with DCD (Querne et al., 2008). Mcleod et al. used resting-state fMRI analysis to show that the connection between the left M1 and bilateral IFG, insular cortex, superior temporal gyrus and caudate, right FOC, SMG, nucleus accumbens, pallidum, and putamen was weaker in children with DCD (McLeod et al., 2014). Also, they investigated the association of the sensorimotor cortex (SM1) with the basal ganglia and cerebellum, and in TD, the right thalamus and left cerebellar lobe V were found to be more strongly associated with the right SM1 than the left. However, in children with DCD, the left thalamus and right cerebellar lobe V were more strongly associated with the left SM1 than with the right. The right putamen was more strongly associated with the right SM1 than with the left in the TD group. However, in children with DCD, no strong intrahemispheric connections with the motor cortex were found in the right putamen, which was equally well-connected to the left and right SM1 (McLeod et al., 2016). Also, Rinat et al. (2020) showed that the connection between bilateral SM1 and posterior cingulate cortex (PCC; BA23, BA31)

[1]https://www.nitrc.org/projects/bnv/

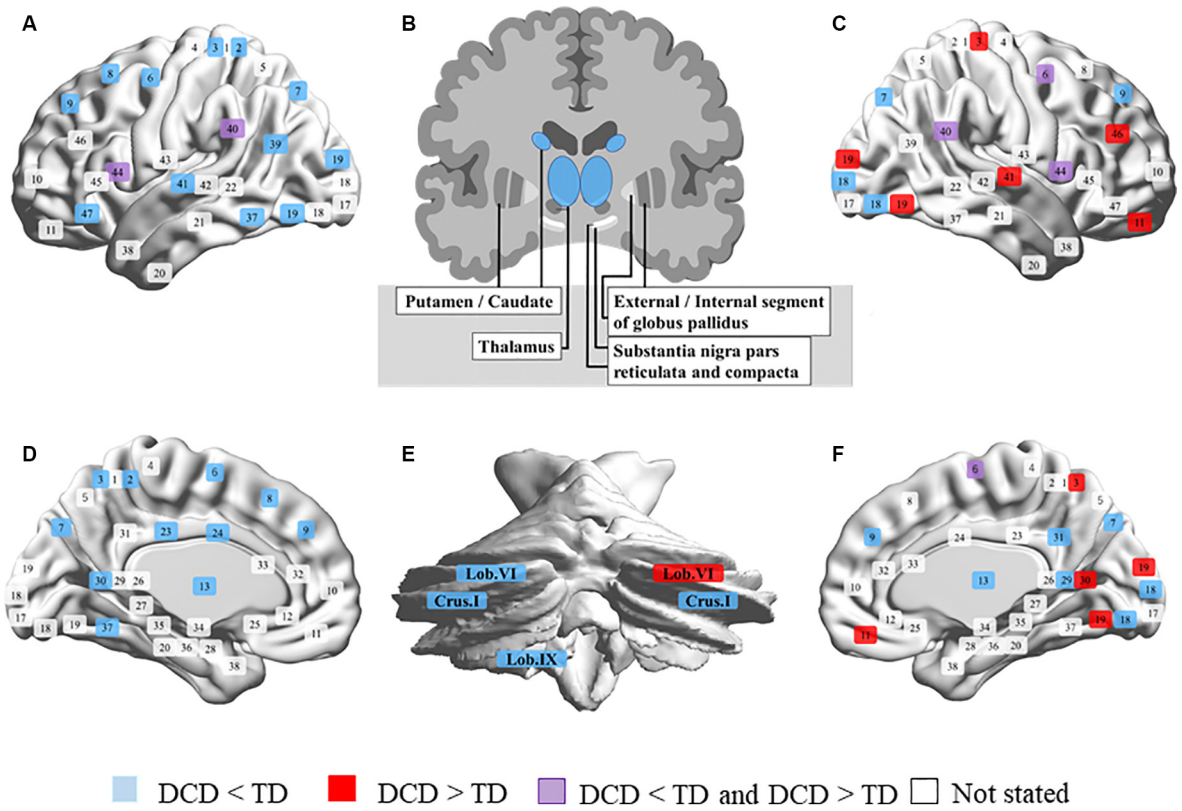

FIGURE 1 | Comparison of brain activity in developmental coordination disorder (DCD) and typical development (TD). **(A)** Left outside of the sagittal plane. **(B)** Coronal plane of the basal ganglia. **(C)** Right outside of the sagittal plane. **(D)** Left inside of the sagittal plane. **(E)** Coronal plane of the cerebellum. **(F)** Right inside of the sagittal plane. Brodmann area (BA) 1, 2, 3, postcentral gyrus; 4, precentral gyrus; 5, superior parietal lobule; 6, premotor cortex and supplementary motor cortex; 7, superior parietal lobule; 8, frontal eye fields; 9, dorsolateral prefrontal cortex; 10, anterior prefrontal cortex; 11, 12, superior frontal gyrus; 13, insular cortex; 17, primary visual cortex; 18, secondary visual cortex; 19, associative visual cortex; 20, inferior temporal gyrus; 21, middle temporal gyrus; 22, superior temporal gyrus; 23, 24, 28–33, cingulate cortex; 25, subgenual area; 26, ectosplenial portion of the retrosplenial region of the cerebral cortex; 27, piriform cortex; 34, dorsal entorhinal cortex; 35, 36, perirhinal cortex and ectorhinal area; 37, fusiform gyrus; 38, temporal pole; 39, angular gyrus; 40, supramarginal gyrus; 41, 42, primary auditory cortex; 43, primary gustatory cortex; 44, pars opercularis, part of the inferior frontal gyrus; 45, pars triangularis, part of the inferior frontal gyrus; 46, dorsolateral prefrontal cortex; 47, pars orbitalis, part of the inferior frontal gyrus.

and precuneus (BA7, BA31), SM1 and left posterior middle temporal gyrus (pMTG) was weaker in children with DCD than that in children with TD.

DTI Study Results

Zwicker et al. (2012a) showed that children with DCD had lower mean diffusivity in the corticospinal tract than children with TD. Furthermore, posterior thalamic radiation also decreased axial diffusivity. Langevin et al. (2014) reported that in the bilateral superior posterior parietal and left superior longitudinal fasciculus III, FA in children with DCD was lower than in those with TD. According to a report by Debrabant et al. (2016) the FA of the left retrolenticular limb of the internal capsule was lower in children with DCD compared to those with TD, while the radial diffusivity was increased; the same trend was observed on the right. They used a predictive statistical model to show that the cerebellum lobule VI and the right parietal superior gyrus are the most effective for distinguishing children with DCD from children with TD. Also, a study by Brown-Lum et al. (2020) which investigated the entire brain, showed a decrease in FA of the cerebral peduncle, superior cerebellar peduncle, external capsule, and splenium of the corpus callosum. In the corticospinal tract, cerebral peduncle, posterior thalamic radiation at the retrolenticular part of the internal capsule and external capsule, axial diffusivity was also reduced.

VBM Study Results

Reynolds et al. (2017) reported that, compared to children with TD, children with DCD had significantly greater gray matter volume, which decreased to the right in the right SFG (BA6) and right MFG (BA6, 8).

DISCUSSION (NEUROIMAGING STUDIES)

Regarding the neural bases of DCD, a review of fMRI studies published in 2016 referred to the frontal lobe, parietal lobe, basal ganglia, and cerebellum (Biotteau et al., 2016). Our review indicates decreased activity in the bilateral thalamus

decreased connectivity of the SM1 and left posterior middle temporal gyrus, bilateral posterior cingulate cortex, precuneus, cerebellum, and basal ganglia, loss of connectivity superiority in the above regions. Furthermore, reduction of gray matter volume in the right SFG and MFG and lower FA and axial diffusivity in regions of white matter pathways were found in DCD.

The thalamus plays an important role in relaying sensory information (visual, auditory, somatosensory, etc.) to the cerebral cortex. Somatosensory information is sent to the SM1 and the IPL *via* the thalamus, the efferent copies of exercise are integrated, and the exercise program is modified. Also, the thalamus is involved in selective visual spatial attention and relays attentional feedback to the visual cortex (Saalmann et al., 2012; Zhou et al., 2016). Hypothalamic inactivity leads to the inhibition of this sensory information, which may be related to the problems of motor planning and visuospatial cognition of children with DCD.

It has been suggested that the MTG is involved in the visual and auditory perception of tools and in tool movement in cooperation with the bilateral fusiform gyrus and the left parietal lobe (Assmus et al., 2007; Xu et al., 2016; Tomasello et al., 2017). Also, the MTG has been reported to play a role in the recognition of semantic actions, the expression of such actions, action monitoring during the performance, and comparison of sensory input and sensory prediction (Kalénine et al., 2010; Wallentin et al., 2011; Davey et al., 2015; Aue et al., 2019; van Kemenade et al., 2019); it is also thought to combine sensorimotor knowledge of meaningful behavior. When these observations are collectively interpreted, it is clear that MTG plays an important role in behavior-related knowledge and interpretation. The problem of gripping and using tools in children with DCD may be related to the inactivation of MTG. The PCC is involved in many cognitive functions, such as visual processing, motor performance (Field et al., 2015), visual space navigation (Bzdok et al., 2015), and decision-making (Heilbronner et al., 2011). The precuneus is involved in self-related processes such as retrieval of autobiographical and episodic memory, visual-spatial processing, and MI. Many studies have shown the involvement of the PCC and precuneus in various aspects of visual-spatial processing. Visuospatial abilities are associated with DCD, and decreased connectivity with the SM1 may be associated with diminished motor control that is dependent on visuospatial information (Tsai et al., 2009, 2012).

Strong functional connections in the thalamus on the ipsilateral side of the right brain and the cerebellum V on the contralateral side were observed in TD. On the other hand, children with DCD had strong functional connections to the thalamus in the left side of the brain and the contralateral cerebellum V. This observation was first reported by McLeod et al. (2016). One possibility is that children with TD have to mitigate the non-dominance of their left hand to perform tasks with both hands smoothly. Children with DCD have stronger functional connections to compensate for clumsiness due to sensory-motor disorder of the right hand. Besides, the children with TD and ADHD had a strong connection of the putamen on the ipsilateral side with the right SM1, whereas children with DCD strong connections on both the left and the right. In a previous study, children with DCD also showed a decrease in the diffusivity of the corticospinal tract (Zwicker et al., 2012a), suggesting that the unilateral significance of the dominant hand seen in TD is low.

Decreased gray matter volume in the right premotor and frontal lobes is associated with DCD-related dysfunctions, such as those related to working memory (Tsai et al., 2012), motor planning and performance, and attention (Tsai et al., 2009). The MTG is involved in motor control (Hanakawa et al., 2008) and contributes to decision-making and inhibitory control (Garavan et al., 1999; Talati and Hirsch, 2005); problems with these brain functions may be associated with motor control issues and behavioral consequences of poor accuracy or efficiency in children with DCD (Wilson et al., 2002; Adams et al., 2014; Reynolds et al., 2015b). Furthermore, the relationship between movement and brain function during motor control in children with DCD has been confirmed based on both cerebral blood flow in fMRI and event-related potential in electroencephalography (Zwicker et al., 2010, 2011; Pangelinan et al., 2013).

The corticospinal tract is an extensive network of projected white matter pathways that connect the primary motor cortex to the spinal cord *via* the corona radiata, internal capsule hind limbs, and cerebral peduncle. The posterior thalamic radiation at the retrolenticular part of the internal capsule and external capsule is another network of projected white matter tracts associated with sensory and motor processing. Previous studies have also shown that children with DCD have low FA in these areas (Zwicker et al., 2012a). Brown-Lum et al. (2020) found that children with DCD also had low FA in the cerebellum pathway by examining the entire brain. These pathways enter and exit the spinal cord, pons, and cerebral cortex, and cerebellum, helping to improve motor movements, learn new motor skills, and balance proprioceptive information into a posture (Keser et al., 2015). This finding complements the findings from functional MRI studies that showed inactivation of the cerebellar and mural regions in children with DCD compared to children with TD.

Focusing on the red and blue color in **Figure 1**, it is interesting that children with DCD have less extensive activation of the left brain than those in children with TD, and that activation in parts of the right brain (BA3, 11, 19, 30, 41, 46, cerebellar lobule VI) was enhanced. It has been pointed out that children with DCD often have problems with cross-modal information processing involving visual space recognition, kinesthetic perception, and matching of vision and proprioceptive sensation (Wilson and McKenzie, 1998; Schoemaker et al., 2001; Gomez and Sirigu, 2015). This activation may be a result of trying to compensate for the problem of sensory integration by visual space processing. It can also be interpreted that interhemispheric inhibition (IHI) occurs due to repeated high activity in the right hemisphere. However, since there are very few reports on activation at this time, careful discussion regarding this aspect is still needed. In rehabilitation interventions for children with DCD, it is necessary to aim at reconstructing brain function, and

MI is one of the intervention methods. MI is defined as mentally evoking a certain motion and is a method used in multiple fields, such as sports, education, psychology, and rehabilitation (Caeyenberghs et al., 2009; Cumming and Ramsey, 2009). Especially in the area of rehabilitation, randomized controlled trials (RCTs) have shown their effectiveness for neurorehabilitation after stroke (Page et al., 2001; Liu et al., 2004). With the recent development of brain science methods, the neural basis of MI is becoming clear. Previous studies have repeatedly reported that brain activity similar to that at the time of motor execution occurs during MI (Zabicki et al., 2017). It has been reported that MI activates the bilateral PMC, supplementary motor area, dorsal and ventral PMCs, superior and inferior parietal lobules, basal ganglia (putamen), cerebellum (lobule VI), and left cingulate gyrus (Hardwick et al., 2018). Some of the brain areas that are activated by MI overlap with the neural base of DCD. Also, studies using transcranial magnetic stimulation have shown plastic changes due to mental practice and an increase in the excitability of the M1 during MI (Kasai et al., 1997; Stinear et al., 2006; Avanzino et al., 2015).

RESULTS OF NEUROREHABILITATION STUDIES

In total, three studies by Australian and European groups published in Wilson et al. (2002, 2016), and Adams et al. (2017), and one protocol listed in Adams et al. (2016b) were included in the literature review. Concerning study design, two studies were RCTs, while one was a case series. Study quality was rated on a 10-point scale for RCTs and an 11-point scale for the case series. All interventions were for children with DCD between the ages of 7 and 12 years. The extracted information is summarized in detail in **Table 1**.

The MITS factors for all MI interventions are summarized in **Table 2**. MI was performed in individual sessions and added or embedded before, between, or after physical practice (PP). MI sessions were supervised by a research assistant or therapist. The position of the participants during MI was task-specific. Participants received acoustic and visual MI instructions, which were mainly standardized and pre-recorded. The perspective used during MI practice was chosen from both internal and external viewpoints. The MI used kinesthetic as well as visual modes, and MI interventions were mainly investigated with respect to motor-focused tasks. All interventions involved watching a video of the movement before initiating the MI intervention, and the two interventions included a visual imagery exercise, a relaxation protocol, and mental preparation. MI training was directed by stepwise guidance, and detailed instructions regarding the methods were given to the children. The MI training contents could be changed based on the participant's weaknesses or additional motor skills. Details regarding the task environment (location) were not reported. Each intervention involved a 60-min session conducted once a week for 5 weeks (total 300 min) in two studies; 45-min sessions were conducted per week for 9 weeks (total 405 min) in one study. One of the reports included the MI intervention

TABLE 1 | Overview of extracted descriptive previous studies.

References	Intervention duration (days)	Study design	Groups	Patients	Participants	Gender	Age	Training task	Measurement	Results	Quality rating
Wilson et al. (2002)	5	RCT	3	54	DCD	NSt	7–12	Catching a tennis ball, throwing a tennis ball, striking a softball, jumping to a target using a two-leg take-off, balancing a ball on a bat while walking, placing objects using a formboard.	MABC	↑	3/10
Wilson et al. (2016)	5	RCT	3	36	DCD	NSt	7–12	Catching a tennis ball, throwing a tennis ball, striking a softball, jumping to a target using a two-leg take-off, balancing a ball on a bat while walking, placing objects using a formboard.	MABC	↑	3/10
Adams et al. (2017)	9	CCS	2	8	DCD	Both	7–12	Running and playing tag, throwing and catching a ball, hopping and playing hopscotch, jumping (almost others rope skipping), bicycling, playing baseball, playing tennis, writing, eating with cutlery.	MABC-2	↑	5/11

NSt, not stated; M-ABC, movement assessment battery for children; M-ABC-2, movement assessment battery for children–second edition; ↑, positive change.

TABLE 2 | Overview of extracted motor imagery training sessions (MITS) elements.

MITS element	Wilson et al. (2002)	Wilson et al. (2016)	Adams et al. (2017)
Position	Task-specific	Task-specific	NSt
Location	NSt	NSt	NSt
Focus	Motor-focused	Motor-focused	Motor-focused
Order	MI before, between, and after PP	MI before, between, and after PP	MI before and after PP
Integration	Embedded	Embedded	Added
MI instructions medium	Acoustic and visual (CD-ROM, video)	Acoustic and visual (CD-ROM, video)	Acoustic and visual (video)
Instruction mode	Pre-recorded	Pre-recorded	Pre-recorded
Supervision	Supervised	Supervised	Supervised
Directedness	Directed with stepwise guidance	Directed with stepwise guidance	Directed
Instruction type	Detailed	Detailed	Detailed
Instruction individualization	Standardized	Standardized	Standardized
Familiarization	Received familiarization	Received familiarization	Received familiarization
Change	Changed	Changed	Changed
MI session	Individual	Individual	Individual
Eyes	Opened	Opened	Opened
Perspective	Internal and external	Internal and external	Internal and external
Mode	Kinesthetic and visual	Kinesthetic and visual	Kinesthetic and visual

time, which was 20 min, including video observation and actual practice.

DISCUSSION (NEUROREHABILITATION STUDY)

Our research question was aimed at examining how MI interventions are performed in children with DCD. The purpose of our literature review was to answer this question and explore the current approaches to MI intervention in children with DCD. Our literature search focused on identifying medical treatments based on the clinical diagnosis of DCD.

This is the first report to clarify the methodology of MI intervention for children with DCD. As a result of the investigation, we found that participants' attitudes during MI were task-specific. Participants received linguistically standardized explanations, and MI was performed from the kinesthetic and visual modes from the internal (first person) and external (third person) perspectives. Participants observed and prepared videos on motor skills before starting MI, which was performed before PP and alternately during or after PP. In some ways, it was confirmed that MI interventions for healthy children and adults and children with DCD differed in several ways.

Regarding the timing of implementing MI, Feltz and Landers (1983) recommend that it be implemented before PP. Schuster et al. (2011) on the other hand, recommend that it be performed after the PP. The timing of the MI depends on the purpose of the training, such as whether the content of the imagined exercise is new learning or preparation for an acquired motion. As MI intervention for children with DCD aims to enhance weak and unacquired movements, MI was performed before PP in all studies or added during or after the PP. In other words, the afferent information obtained from the actual movement is useful for movement expression during MI.

In all studies, children observed a video of the motions before the MI intervention. This is useful for learning the motor element of the imaged motion and enables participants to prepare for MI. In addition to the PMC and the parietal lobe, which are reported to be active in MI, the brain regions that are active in action observation (AO) include the occipital lobe and the IFG (Hardwick et al., 2018). Possibly the AO can activate a wide range of brain areas with reduced activity. Recent studies suggest that combining or simultaneously using AO and MI has a better effect on exercise outcomes than MI or AO alone (Eaves et al., 2016). It has also been verified that MI and AO are more effective than MI alone in interventions for children (Scott et al., 2019). It is also reported that MI intervention causes a temporary deterioration in motor performance due to mental fatigue caused by repeated MI (Rozand et al., 2016). These findings suggest that performing MI and AO simultaneously may reduce mental stress. Also, the speed of the video to be observed is added to the nominal, and the slow-motion is used for observation. It has been reported that AO in slow motion promotes greater activation of the M1 compared to that at normal speed (Moriuchi et al., 2014, 2017). It is believed that slow-motion makes it possible to decompose and better understand the elements of motion, which in turn better activates the AO network. So far, it is known that motor-related areas, which are important for motor activity, are activated more by kinesthetic images, and the visual cortex, which processes visual information, is activated more by visual images (Guillot et al., 2009). Therefore, for the acquisition of motor skills, MI intervention often uses a first-person and kinesthetic image (Ridderinkhof and Brass, 2015). However, even if the participants are instructed to perform only the kinesthetic motor image task, there is no guarantee that they will be able to recall the pure kinesthetic motor image as instructed. Therefore, it is considered useful to use the first-person and third-person actions observed in the video in advance for MI.

GENERAL DISCUSSION

Brain function in children with DCD can be plastically altered and need not remain constant throughout life. A report by Williams et al. suggests that aging changes the network of pathways important for motor planning, control, and cognition and that various experiences during growth can help to develop

compensatory pathways (Williams et al., 2017). A study of motor learning in healthy adults also confirmed a decrease in connectivity from the primary motor cortex (M1) to the basal ganglia and from the supplementary motor cortex (SMC) to the M1. On the contrary, changes in connectivity enhancement from the basal ganglia to the SMC and from the dorsal motor cortex to the SMC were also observed (Ma et al., 2010; Patel et al., 2013). The main purpose of our study is to derive an effective MI intervention method based on the neuroimaging studies of DCD. There are two characteristics of MI intervention for children with DCD: (1) AO is performed before MI and exercise to learn the elements of exercise that they are not good at; and (2) Perform a visual-motor task before MI or exercise to perform mental preparation and conditioning. As has been identified, areas of decline include areas important for exercise execution and sensory integration, such as SMC and IPL, and major areas of MNS, such as IFG. These areas are consistent with the main symptoms of DCD, including reduced ability to correct with motor commands and feedback, imitation, and difficulty in motor learning. It should be noted that the pars opercularis of the IFG (BA44), children with DCD had lower activation during imitation and higher activation during observation than children with TD (Licari et al., 2015; Reynolds et al., 2015a). These results suggest that observation is more effective than imitation in children with DCD, and it may be useful to perform AO before the start of training. A review of Neuroimaging studies showed that children with DCD had reduced thalamic activity and weaker connectivity to SMC. The thalamus plays an important role in relaying somatosensory and is also involved in the correction of undoing based on sensory information. It is difficult to activate the thalamus in simulations such as MI and AO that do not involve actual movements. The thalamus is also involved in selective visual spatial attention (Wilson et al., 2002, 2016), suggesting that the visual-motor task is useful in this regard. Also, children with DCD tend to use the right brain to handle more visuospatial information to compensate for their lack of somatosensory. Therefore, we think that it may be possible to activate the thalamic pathway and promote sensory-based correction of luck by combining visual information and movement. Furthermore, we focused on the cerebellum, which is important for planning and modifying exercise such as feedforward. Especially, the cerebellar-crus-I has been reported to be involved in linguistic working memory (Marvel and Desmond, 2010), it may be activated by expressing the elements of movement and perception in words. Verbalizing the elements of motion simulated by MI and AO corrects feedforward-level errors and enables motion under appropriate motor strategies. A method similar to this idea is the task-oriented approach CO-OP (cognitive orientation to daily occupational performance). CO-OP is a cognitive movement (behavioral) approach that supports children in the process of discovery and learning to specifically work on children's cognition and achieve the motor tasks they desire. It is characteristic that it assists in controlling behavior by verbalizing the flow of problem-solving such as goal setting, planning, execution, and self-reflection (Sangster et al., 2005). By sharing motor and sensory information obtained from AO and MI with the instructor *via* language, it may be possible to clarify the motor strategy and correct it before making an error. In some people with DCD, there was an imbalance in activity in the left and right hemispheres. IHI is believed to have spurred this situation. IHI from the contralateral to the ipsilateral motor cortex has been shown to increase during MI (Liang et al., 2014). Therefore, it may be possible to suppress the activity of the right hemisphere by increasing the activity of the left hemisphere with repeated MI. In our review, we could not find out the details of the report on task environment (location). As with the PETTLEP method, MI is recommended to be performed in a real environment, and ideally subsequent practices should be performed in a similar setting. Treatment of children with DCD has often done in hospitals and therapy rooms. We consider that children need to perform tasks in real-life situations, such as the home practice reported by Adams et al. (2017).

One of the problems in research on DCD was the coexistence of ASD and ADHD. It was found that the activity of the brain region was different when DCD alone and ADHD coexisted. To clarify the brain function specialized for the symptoms of DCD, it is necessary to establish exclusion criteria and proceed with research and review. DCD is also a more highly heterogeneous disorder than other developmental disorders. Therefore, it is necessary to study by dividing into several subtypes (classification by exercise/behavior level or brain imaging, et cetera). Also, few RCT treatises are using MI for children with DCD, and it is currently difficult to carry out a meta-analysis. MI intervention is easy to have variations and needs to be verified by a unified method by each researcher.

CONCLUSION

In this review, we investigated the brain activity that is the basis of clumsiness in children with DCD. Adding to what is known from previous reports, our results indicate: (1) decreased activity of the bilateral thalamus; (2) decreased connectivity of the SM1 and the left MTG and the SM1 and the bilateral PCC and precuneus; (3) loss of superiority of connectivity of the SM1 and the cerebellum and basal ganglia in children with DCD; and (4) reduction of gray matter volume in the right SFG and MFG and lower FA and axial diffusivity in regions of white matter pathways were found in DCD. Also, we investigated an intervention methodology using MI as a neurorehabilitative technique for children with DCD. Characteristically, MI intervention was performed before, during, or after PP. Then, the motor skills were learned by performing AO before MI. MI was performed from both internal and external points of view to focus on the child's weak motor skills and to facilitate motor learning. It was considered possible to activate the brain regions that form the neural base of DCD by using MI and AO together and performing a visual-motor task. Also, it is recommended that MI and physical practice be carried out in an environment where they operate, and the method includes self-practice at home. Furthermore, neuroimaging studies suggested that it may be useful to verbalize the exercise planning obtained by MI and AO, introspection accompanying actual movements, and the flow of problem-solving.

AUTHOR CONTRIBUTIONS

KI, AM, and NL reviewed the literature and discussed the contents. KI wrote the article, and SZ checked the text and created part of the figure. TK checked and revised the whole article. All authors contributed to the article and approved the submitted version.

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The Effects of Priming Intermittent Theta Burst Stimulation on Movement-Related and Mirror Visual Feedback-Induced Sensorimotor Desynchronization

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The potential benefits of priming intermittent theta burst stimulation (iTBS) with continuous theta burst stimulation (cTBS) have not been examined in regard to sensorimotor oscillatory activities recorded in electroencephalography (EEG). The objective of this study was to investigate the modulatory effect of priming iTBS (cTBS followed by iTBS) delivered to the motor cortex on movement-related and mirror visual feedback (MVF)-induced sensorimotor event-related desynchronization (ERD), compared with iTBS alone, on healthy adults. Twenty participants were randomly allocated into Group 1: priming iTBS—cTBS followed by iTBS, and Group 2: non-priming iTBS—sham cTBS followed by iTBS. The stimulation was delivered to the right primary motor cortex daily for 4 consecutive days. EEG was measured before and after 4 sessions of stimulation. Movement-related ERD was evaluated during left-index finger tapping and MVF-induced sensorimotor ERD was evaluated by comparing the difference between right-index finger tapping with and without MVF. After stimulation, both protocols increased movement-related ERD and MVF-induced sensorimotor ERD in high mu and low beta bands, indicated by significant time effects. A significant interaction effect favoring Group 1 in enhancing movement-related ERD was observed in the high mu band [$F_{(1,18)} = 4.47$, $p = 0.049$], compared with Group 2. Our experiment suggests that among healthy adults priming iTBS with cTBS delivered to the motor cortex yields similar effects with iTBS alone on enhancing ERD induced by MVF-based observation, while movement-related ERD was more enhanced in the priming iTBS condition, specifically in the high mu band.

Keywords: theta burst stimulation, event-related desynchronization, metaplasticity, motor cortex, mirror visual feedback, occupational therapy

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INTRODUCTION

Theta burst stimulation (TBS) is an accelerated form of repetitive transcranial magnetic stimulation (rTMS), which has been extensively employed in human studies after the first human experiment (Huang and Rothwell, 2004). Non-invasive brain stimulation, including rTMS, is getting common to be used an adjunct with conventional occupational therapy, particularly in hemiparetic arm

rehabilitation (Kakuda et al., 2012). Using repetitive short bursts of high frequency stimulation (e.g., 50 Hz), given five times per second, TBS is able to modulate corticomotor excitability, as measured by the amplitude of motor evoked potential (MEP) (Huang and Rothwell, 2004). TBS given in an intermittent manner—intermittent theta burst stimulation (iTBS)—can lead to a facilitatory effect on the stimulated cortex, while TBS given in a continuous manner—continuous theta burst stimulation (cTBS)—does the opposite (Huang et al., 2005). However, substantial response variability to TBS among humans has been noted in the previous literature (Karabanov et al., 2015). Although TBS is an accelerated form of excitatory rTMS that may lead to superior clinical outcomes, a recent experiment showed that the response rate to iTBS or cTBS (i.e., the percentage of participants who presented increased or decreased MEP upon completion of the stimulation) is around 60% (Mc Calley et al., 2019) and did not improve along with more delivered doses of the same stimulation, indicating that TBS has no effects on a substantial number of subjects. The inconsistency of the response to TBS may limit its utility in both research and clinical interventions (Schilberg et al., 2017).

Numerous biological factors that can influence the response to TBS have been reported; one of the adjustable factors is the history of neuronal activities (Karabanov et al., 2015). Synaptic plasticity is regulated by previous neuronal activities via metaplasticity. Metaplasticity is a neuroprotective mechanism that modulates the threshold of synaptic plasticity to ensure that the neural system cannot be predominated by long-term potentiation (LTP) or long-term depression (LTD) (Muller-Dahlhaus and Ziemann, 2015). Brain response to rTMS is likely to be influenced with the metaplastic mechanism. As an example, an excitatory rTMS protocol may fail to facilitate corticomotor excitability (i.e., LTP-like neuroplasticity) when the neuronal activities are already at a high level before the stimulation commences. Considering the mechanism of metaplasticity, several priming stimulation protocols, designed with a priming session followed by a stimulation session, have been investigated in healthy adults, with the aim to harness metaplastic mechanisms for potentiating the effects of rTMS (Hassanzahraee et al., 2018). Theoretically, an inhibitory priming session using cTBS is likely to make the brain-state more amenable to the facilitatory effects of iTBS, thereby delivering a stronger synergistic effect. In healthy individuals, this inhibitory priming session seems to amplify the facilitatory effect of iTBS, in contrast to iTBS alone, as reflected by the amplitude of MEP (Mastroeni et al., 2013; Opie et al., 2017). Utilizing the potential metaplasticity is likely to increase the effects of TBS, thus improving its clinical utility in populations with diseases (Cassidy et al., 2014).

The potentiating effect of priming iTBS has only been proven with lines of evidence of TMS-electromyography (EMG) based metrics, such as MEP and short-interval intracortical inhibition (SICI) (Murakami et al., 2012; Mastroeni et al., 2013; Opie et al., 2017). However, the magnitude of TMS-EMG based metrics is also contaminated by the neuronal responses at subcortical and spinal levels, as well as the peripheral MEP (Tremblay et al., 2019). Electroencephalography (EEG) is a non-invasive measure of the electric activity of cortical neurons (Cohen, 2017). Event-related desynchronization/synchronization (ERD/ERS) is a relative power decrease/increase of ongoing EEG activity in a specific frequency band, due to a decrease/increase in synchrony of the underlying neuronal populations (Neuper et al., 2006). Sensorimotor ERD is thought to be a neurophysiological marker of activation or excitation of sensorimotor areas elicited by a given stimulus or performing a task (Pfurtscheller and Lopes da Silva, 1999), and its magnitude is associated with sensorimotor excitability (Takemi et al., 2013). Sensorimotor ERD could be induced through either movement execution or movement observation (Neuper et al., 2006). Movement-related sensorimotor ERD in both mu (i.e., central alpha, 8–12 Hz) and beta (12–30 Hz) rhythms was first reported by Pfurtscheller and Lopes da Silva (1999). During unilateral hand movement, movement-related sensorimotor ERD was found to be prominent in the hemisphere contralateral to the moving hand when preparing to move, and it expands bilaterally when executing the movement (Neuper et al., 2006).

Sensorimotor ERD can also be viewed when observing the movement without overt movement execution, which is attributed to an assumed function of the human mirror neuron system (MNS) (Muthukumaraswamy et al., 2004; Frenkel-Toledo et al., 2014). MNS is a class of the neuronal population that discharges during movement observation and execution. MNS was first found in the premotor and parietal areas of macaque monkeys (Rizzolatti et al., 1996) and numerous neuroimaging studies in humans have reported consistent neural activation over frontal-parietal areas in response to movement observation, indicating that there exists a homological neural system in humans (i.e., human MNS) (Caspers et al., 2010). There is functional connectivity between the MNS and primary sensorimotor cortex (Pineda, 2008) and the downstream modulatory activity of the MNS on the primary sensorimotor cortex could be indexed by observation-induced sensorimotor ERD (Muthukumaraswamy et al., 2004). Mirror visual feedback (MVF) has been widely used in studies examining observation-induced sensorimotor ERD in healthy adults (Bartur et al., 2015; Lee et al., 2015; Rossiter et al., 2015) and has also been utilized as a therapeutic form of intervention for the rehabilitation of upper limb motor functions after stroke (i.e., mirror therapy) (Zhang et al., 2018). In the MVF paradigm, mirror apparatus is placed at the midsagittal plane of the participant. Participants are instructed to perform unilateral hand movements while simultaneously viewing the MVF of their moving hand from the mirror. It has been reported that MVF could lead to a shift of sensorimotor ERD from the hemisphere ipsilateral to the moving hand (Bartur et al., 2015; Lee et al., 2015; Rossiter et al., 2015). Therefore, MVF-induced sensorimotor ERD is a useful index to study observation-induced sensorimotor activation and the involvement of MNS, which is potentially correlated with the capacity of motor learning from movement observation. This paradigm also allows us to study the excitability of sensorimotor area when the corresponding upper extremity remains static, thus becoming potentially useful in studying the sensorimotor plasticity in patients with severe upper extremity disability such as stroke (Fong et al., 2019).

Sensorimotor ERD can be used to probe cortical oscillatory activities of large number of neurons in different rhythms, which would provide new insight on the sensorimotor plasticity induced by priming iTBS. A previous study comparing the effects of TBS on MEPs and movement-related rhythms showed that the modulatory effect of TBS was more reliable on movement-related ERD than that on MEPs (Dionisio et al., 2019). To date, no study has explored the differential effects of priming iTBS (i.e., cTBS followed by iTBS) and iTBS on sensorimotor ERD. Hence, our study aims to investigate the neuromodulatory effect of priming iTBS on movement-related and MVF-induced sensorimotor ERD, compared with non-priming iTBS, on healthy adults. We hypothesized that both protocols could enhance the sensorimotor ERD induced by either movement or MVF-induced observation, and priming iTBS with cTBS could yield a stronger facilitatory effect, comparing with iTBS alone.

MATERIALS AND METHODS

Participants

Potential participants were recruited from a local university. Twenty young healthy participants (Group 1: age = 27.40 ± 2.07, two women and eight men; Group 2: age = 27.10 ± 2.08, two women and eight men) were recruited. All of them were postgraduate and met all of the following criteria: (1) 18 to 30 years old; (2) right-handed, according to the Edinburgh handedness inventory (Oldfield, 1971); and (3) normal or corrected-to-normal vision. Participants were excluded if they met any of the following criteria: (1) any contraindication to TBS, such as a history of seizures, metal implants, and pregnancy. All participants were screened by a standard safety checklist before enrollment (Rossi et al., 2011); (2) previous history of any neurological or psychiatric diseases; (3) presence of upper limb injuries in the past 3 months; and (4) presence of congenital upper limb deformities. This study was approved by the Human Subjects Ethics Committee, The Hong Kong Polytechnic University (reference number: HSEARS20190326003). All participants voluntarily consented to participate in this study and their written informed consent was obtained before participation commenced.

Experimental Procedures

Participants were randomly allocated to one of the following two groups by drawing lots: Group 1: cTBS followed by iTBS; and Group 2: sham cTBS followed by iTBS. All participants had to attend four consecutive TBS sessions and two EEG assessments before and immediately after 4 daily sessions of stimulation.

Motor Threshold Assessment

The stimulation site for iTBS was the right primary motor cortex (M1). The optimal position was defined as the coil position eliciting the most stable and the largest MEP, with the coil rotated 45° from the sagittal plane. The stimulation position was maintained by a neuro-navigation system (Localite, Bonn, Germany). Resting motor threshold (RMT) is defined as the minimum intensity over the hot spot that elicits an MEP of no <50 μv in three out of six trials over the contralateral first dorsal interosseous (FDI) (Groppa et al., 2012). MEPs were visualized and measured through the MEP monitor (MagVenture, Denmark), with an inter-pulse interval of at least 5 s.

iTBS Session

Daily serial sessions of iTBS were delivered by MagPro X100 stimulator (MagVenture, Denmark) with a standard butterfly-shape coil (C-B60), over the right M1 for 4 consecutive days. iTBS can induce the changes in corticomotor excitability and such effects are likely to be solidified over multiple-day stimulation (Wassermann and Zimmermann, 2012). Therefore, we decided to use repeated sessions of stimulations in order to stabilize the modulatory effects and also to imitate the intervention design commonly used in clinical applications (Perellon-Alfonso et al., 2018). We followed previous studies, using four daily sessions of iTBS for healthy adults (Hamzei et al., 2012; Lappchen et al., 2015; Zhang and Fong, 2019). The post EEG measurement was arranged on the same day after the 4th session of iTBS intervention.

The standard 600-pulse TBS protocol was followed (Huang et al., 2005). The stimulation intensity of iTBS was set at a safety limit of 70% of the individual's RMT (Goldsworthy et al., 2012). We did not set the intensity based on the active motor threshold (AMT), because a previous study has shown that pre-stimulation muscle contraction during the measure of AMT could influence the after-effects of TBS (Goldsworthy et al., 2012). Participants in the priming group (Group 1) received 600-pulse cTBS at the intensity of 70% RMT, followed by 600-pulse iTBS at the intensity of 70% RMT. Participants in the non-priming group (Group 2) received 600-pulse cTBS at the intensity of 20% RMT (i.e., sham cTBS), followed by 600-pulse iTBS at the intensity of 70% RMT. Sham stimulation was delivered using the same coil that delivers only 20% of the individual RMT. The reduction of intensity is a simple way for sham stimulation which has been used in previous studies (Dieler et al., 2014; Zhang and Fong, 2019). A previous neurophysiological experiment confirmed that no effect on MEPs can be observed when the stimulation intensity of TBS was decreased to ∼62% (55–69%) of AMT. Therefore, we hypothesized that TBS at 20% of RMT could be served as a sham stimulation without causing significant modulatory effect to the stimulated cortex. All participants were told that TBS was a subthreshold stimulation that could not induce significant arm movements or somatosensory perception. The interval between priming and stimulation sessions was 10 min. We choose the 10 min interval based on a previous study about reversal of synaptic plasticity in response to TBS (Zhou et al., 2003), and followed a recent human neurophysiological study about priming iTBS (Opie et al., 2017). Participants were asked to complete a questionnaire regarding the side effects of iTBS they experienced upon the completion of each stimulation session. We assessed the treatment belief of each subject, upon the completion of the post EEG measurement. We asked the participants the question "did you believe that you have been applied brain stimulation in the past 4 sessions?" The treatment belief was assessed by a

10-point Likert scale, from fully disbelieve (rated as 0) to fully believe (rated as 10).

EEG Acquisition

EEG was captured with a 64-channel cap, using a Digital DC EEG Amplifier and Curry 7 (Compumedics Neuroscan, USA). Electrode impedance was kept below 10 kOhm and the signal was sampled at 1,000 Hz. Participants were seated upright in an electromagnetic shielded room and required to minimize any body movements during the recording. Movement-related and MVF-induced sensorimotor ERD were evaluated. Left index finger tapping and incongruent (i.e., mirrored) visual observation of the right index finger tapping were used to elicit the ERD over bilateral sensorimotor areas, with a possibly right dominant lateralization (Pfurtscheller and Neuper, 1994; Zhang and Fong, 2019). For movement-related ERD, participants were instructed to tap on a computer keyboard three times with their left index finger, in response to 60 auditory cues (i.e., 300 ms beep sounds) delivered at random intervals (from 7 to 10 s) and to relax the finger after the completion of the movement (reference to finger tapping tasks). Participants were asked to focus on a centrally located fixation cross in a computer monitor placed in front of them. For MVF-induced ERD, participants were asked to tap on a computer keyboard three times with their right index finger, in response to 60 auditory cues delivered at random intervals (from 7 to 10 s), and to relax the finger after completing the movement (reference to finger tapping tasks). Movements were performed under two conditions. (1) A mirror view of the movement: Participants performed right-index tapping while simultaneously looking at the MVF of their moving finger. The MVF was created using a physical mirror (406 × 432 mm) placed over their midsagittal plane, between both arms. A black curtain was used to block the view of their moving hand. (2) A direct view of the movement: Participants performed right-index tapping while looking at the direct visual feedback (DVF) of their moving finger. Their left hand was hidden by a non-transparent board (see **Figure 1** for the EEG set-up). The order of conditions was randomized by drawing lots. A total of 60 movements were collected for each condition, with 180 movements in total. To avoid the potential effects of ordering, we counterbalanced the order of these 3 conditions. The inter-trial interval was similar to previous studies about movement-related and MVF-induced ERD (Rossiter et al., 2015; Espenhahn et al., 2017; Fong et al., 2019), which allowed us to detect the ERD pattern elicited by movement execution or observation. The randomly given inter-trial interval was applied to avoid that the brain activity in

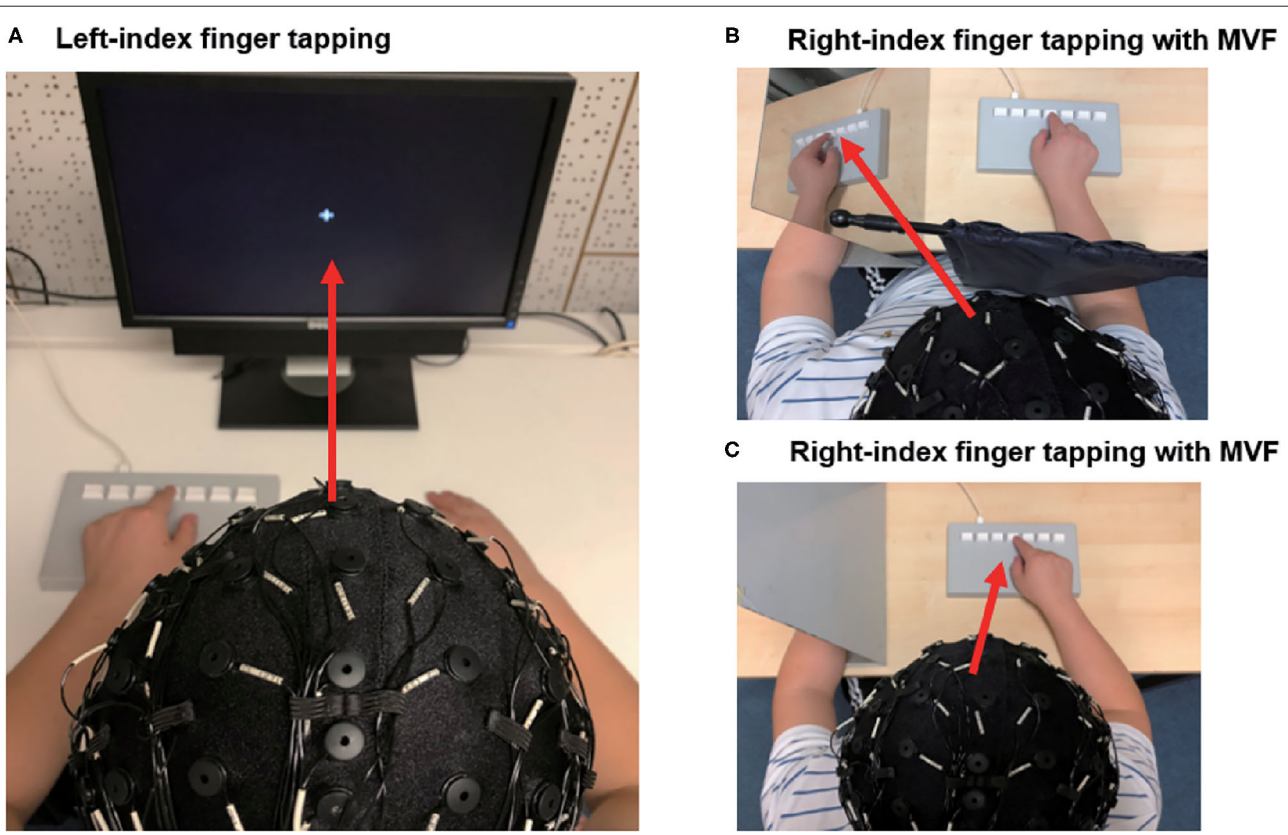

FIGURE 1 | Setup of the EEG experiment. **(A)** Participants performed left-index finger tapping in response to auditory cues. Participants were instructed to focus on a fixation cross. **(B)** Participants performed right-index finger tapping in response to auditory cues. Participants were instructed to observe the mirror visual feedback of their moving index finger. A black curtain was used to block the direct view of their moving hand **(C)** Participants performed right index tapping in response to auditory cues. Participants were instructed to observe their moving index finger. The red arrows represent the visual direction during the movement.

association with participants' anticipation to auditory cues was synchronized with the presentation of the given stimulus.

EEG Preprocessing

Signals captured were processed offline using EEGLab (Delorme and Makeig, 2004) and custommade Matlab scripts. Raw EEG signals were band-pass filtered between 1 and 80 Hz and then down-sampled at 250 Hz. Additionally, a 50 Hz notch filter was applied. Data were referenced to bilateral mastoid electrodes. Signals with significant movement artifacts and long-term eye closure were rejected during the visual inspection. Then EEG was segmented into 5,000 ms epochs (pre-stimulus −2,000 ms and post-stimulus 3,000 ms, with 0 as the 1st index finger tap to the keyboard). Eye movement artifacts were corrected using an independent component analysis algorithm (Delorme and Makeig, 2004). Typical components reflecting blinking and horizontal eye movement were rejected.

EEG Time-Frequency Analysis

Clean trials were analyzed in a time-frequency domain. The event-related spectral perturbation (ERSP) method was used to compute ERD power (Delorme and Makeig, 2004). For ERSP calculation, the power spectrum was calculated on each epoch and normalized each of them by its respective mean baseline spectra. We selected a baseline period from −1,500 to −1,000 ms for correction, to avoid the contamination of neural oscillations caused by auditory cues delivered prior to the execution of movement. Subsequently, the power was averaged across all included trials and converted to log power (see the following formula).

$$ERSP\,(f,\ t) = \frac{1}{n}\sum_{k=1}^{n}\left(F_k(f,\ t)^2\right)$$

where n is the number of trials, and $F_k(f,\ t)$ is the spectral estimation of the kth trial at frequency f and time t. ERD was further computed using the following formula (Makeig, 1993):

$$ERD\ power = \frac{1}{N}\sum_{f\in F}\sum_{t\in T}(ERSP\,(f,t))$$

where F represents the frequency band of interest. We defined four frequency bands of interest, including mu-1 (8–10 Hz), mu-2 (10–12 Hz), beta-1 (12–16 Hz), and beta-2 (16–30 Hz) based on our previous studies (Fong et al., 2019; Zhang and Fong, 2019). T represents the time interval of interest and a window from 0 to 1,000 ms was selected to reflect the movement stage. N is the number of time-frequency bins in a selected two-dimension rectangular matrix. Following previous literature (Bartur et al., 2015; Lee et al., 2015; Zhang and Fong, 2019), we extracted averaged ERD powers at two electrodes C3 and C4 to represent the left and right sensorimotor activation, respectively. In accordance with previous studies, an asymmetric index (i.e., no hemispheric effect) was calculated with the following formula and used in further statistical analyses (Fong et al., 2019). A more positive value indicates more activation of the right sensorimotor area.

$$\text{Asymmetric index} = \big(\text{C3 ERD power}\big) - \text{(C4 ERD power)}$$

Statistical Analysis

A statistical analysis was performed using SPSS version 23.0. GraphPad Prism version 7 and custom Matlab scripts were used for the figure visualization. Analysis of variance (ANOVA) was performed separately for each frequency band and the asymmetric index was used as the dependent variable. The level of significance was $p < 0.05$. Violation of sphericity was corrected by Green-Geisser. Potential between-group difference of the dependence variable at baseline was tested by independent t-tests. Two-way repeated measures analysis of variance (ANOVA) with time (pre vs. post) as a within-subject factor and group (Group 1 vs. Group 2) as a between-subject factor was used to analyze the movement-related ERD. Three-way repeated measures ANOVA with time (baseline vs. post-stimulation) and condition (mirror view vs. direct view) as within-subject factors and group (Group 1 vs. Group 2) as a between-subject factor was used to analyze the MVF-induced ERD. In case of any significant effect found, paired t-tests were used for the *post hoc* comparisons. If any of the dependent variable showed significant between-group difference at baseline, analysis of covariance (ANCOVA) with the baseline value as the covariance would be used instead. Missing data were imputed using a last observation carried forward (LOCF) method; that is, if a subject dropped out, the missing value was replaced by the last assessment results.

The current study used a small sample size and the Bayesian procedures may enhance the statistical information of our results (Quintela-del-Río et al., 2019). Thus, we included a Bayesian analysis to help highlight the relative strength of the evidence in support of either the null or alternative hypothesis (Biel and Friedrich, 2018) using JASP program (Wagenmakers et al., 2018). Bayesian repeated measures ANOVA and paired t-tests were performed. The Bayes Factors (BF) were reported, which evaluated the conditional probability between 2 competing hypotheses (null and alternative hypotheses) and quantify the support levels for each hypothesis. We reported the values as BF_{10}, with a value >1 indicating increased evidence in favor of the alternative hypothesis. The BF_{10} values for the main and interaction effects in ANOVA were computed using the BF inclusion values output with the "across matched models" option (Koen et al., 2018). BFs were interpreted using the categorical labels, with BF_{10} values between 1 and 3 correspond to anecdotal evidence, between 3 and 10 correspond to moderate evidence, 10 and 30 correspond to strong evidence, and > 100 correspond to decisive evidence.

RESULTS

Among the 20 included participants, one participant (age = 25 years, male) in Group 2 dropped out after the first session because he was afraid of the potential risks caused by TBS, although he did not report any side effects after his first session. No major side

effect (e.g., headache, seizure, insomnia, or fatigue) was reported among the participants.

The treatment belief rating for the 10 cases in Group 1 was 9.40±1.40, ranging from a score of 6 to 10, while the rating for the 9 cases in Group 2 was 7.89±3.55, ranging from a score of 0 to 10. Only 1 case in Group 2 strongly believed that he had not been applied any brain stimulation in the 4 day experiment. No statistical difference in the treatment belief between the 2 groups was detected ($t = 1.20$, $p = 0.26$).

We conducted a simulation head model about the TMS-induced electrical fields using SimNIBS (Thielscher et al., 2015; Saturnino et al., 2019) (**Figure 2**). The RMT was set at 47% maximal machine output which was the mean value of all included participants.

The peak value of electrical fields induced by active stimulation at 70% RMT (i.e., 33% maximal machine output) was 50.7 V/m, while the peak value of electrical fields induced by sham stimulation at 20% RMT (i.e., 9% maximal machine output) was 12.9 V/m. Thus, our simulation suggested that sham stimulation at 20% RMT induced a nearly 75% reduction in electrical fields in the brain compared with active stimulation at 70% RMT. The reduction of electrical fields of our sham rTMS method is comparable with another commonly used sham method by tilting the TMS coil 90 degrees off the scalp, with one or two wings of the coil touching the scalp (Lisanby et al., 2001).

A demonstration of movement-related ERD and MVF-induced ERD at baseline ($n = 20$) was depicted in **Figure 3**.

Movement-Related ERD

The results of an ANOVA examining movement-related ERD are shown in **Table 1** and the descriptive data are graphically depicted in **Figure 4A**. No baseline between-group difference was found in any of the frequency band (all $p > 0.05$). There were significant time effects noted in both the high mu [$F_{(1,18)} = 6.52$, $p = 0.020$, $\eta^2 = 0.27$, $BF_{10} = 3.01$] and low beta bands [$F_{(1,18)} = 6.00$, $p = 0.025$, $\eta^2 = 0.25$, $BF_{10} = 3.54$]. The Bayesian statistics showed anecdotal and moderate evidence in favor of the alterative hypothesis for the main effect of time. A significant interaction effect was noted in the high mu band [$F_{(1,18)} = 4.47$, $p = 0.049$, $\eta^2 = 0.20$, $BF_{10} = 1.96$] and the mean changes (±standard deviation) of asymmetric index in the high mu band were 0.65 ± 0.47 in Group 1 and 0.06 ± 0.75 in Group 2, indicating that a more obvious shift in sensorimotor high mu ERD toward the right hemisphere was noted in participants who received priming iTBS, compared with those who received iTBS alone. The Bayesian statistics showed anecdotal evidence for the alternative hypothesis for the interaction. **Figure 5** shows the topographical distributions of movement-related high mu ERD at baseline and post-stimulation. No other significant effects were found in the two-way ANOVA.

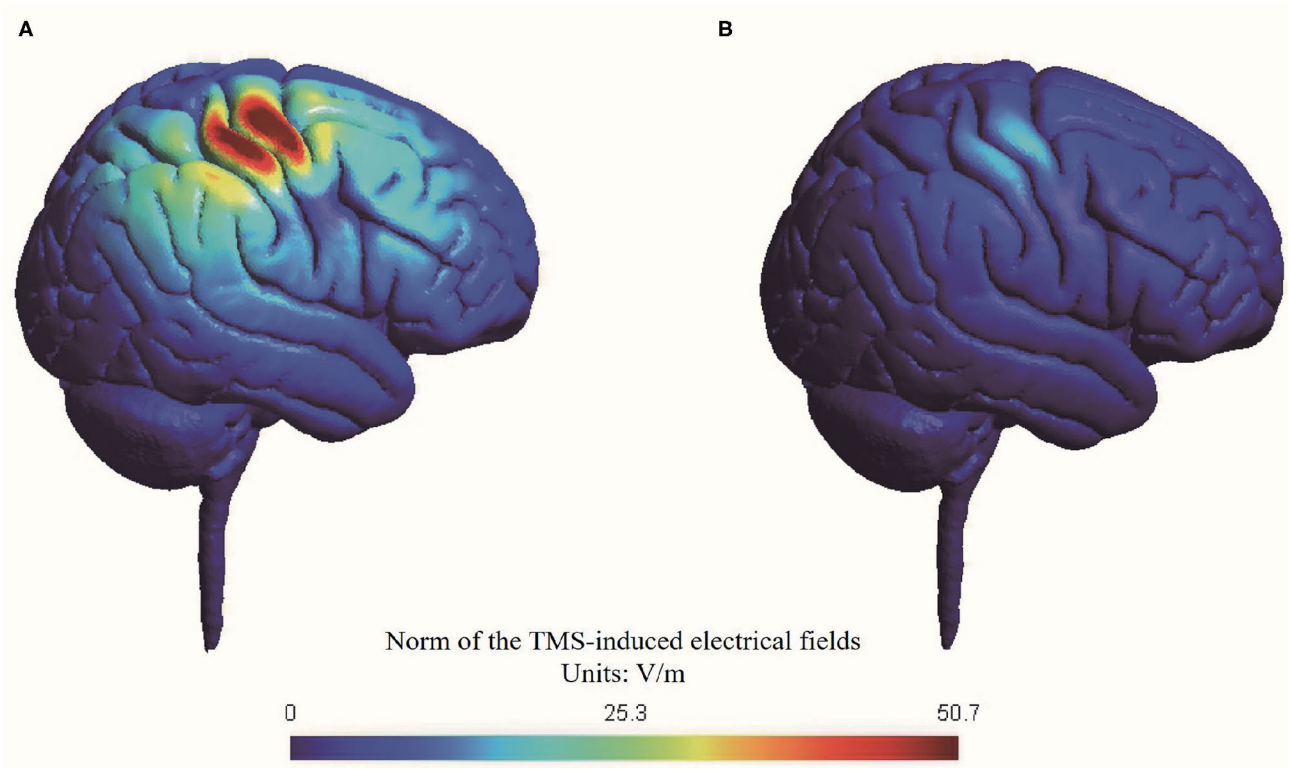

FIGURE 2 | Simulation of transcranial magnetic stimulation-induced electrical fields in head model. **(A)** Active stimulation at 70% RMT; **(B)** Sham stimulation at 20% RMT.

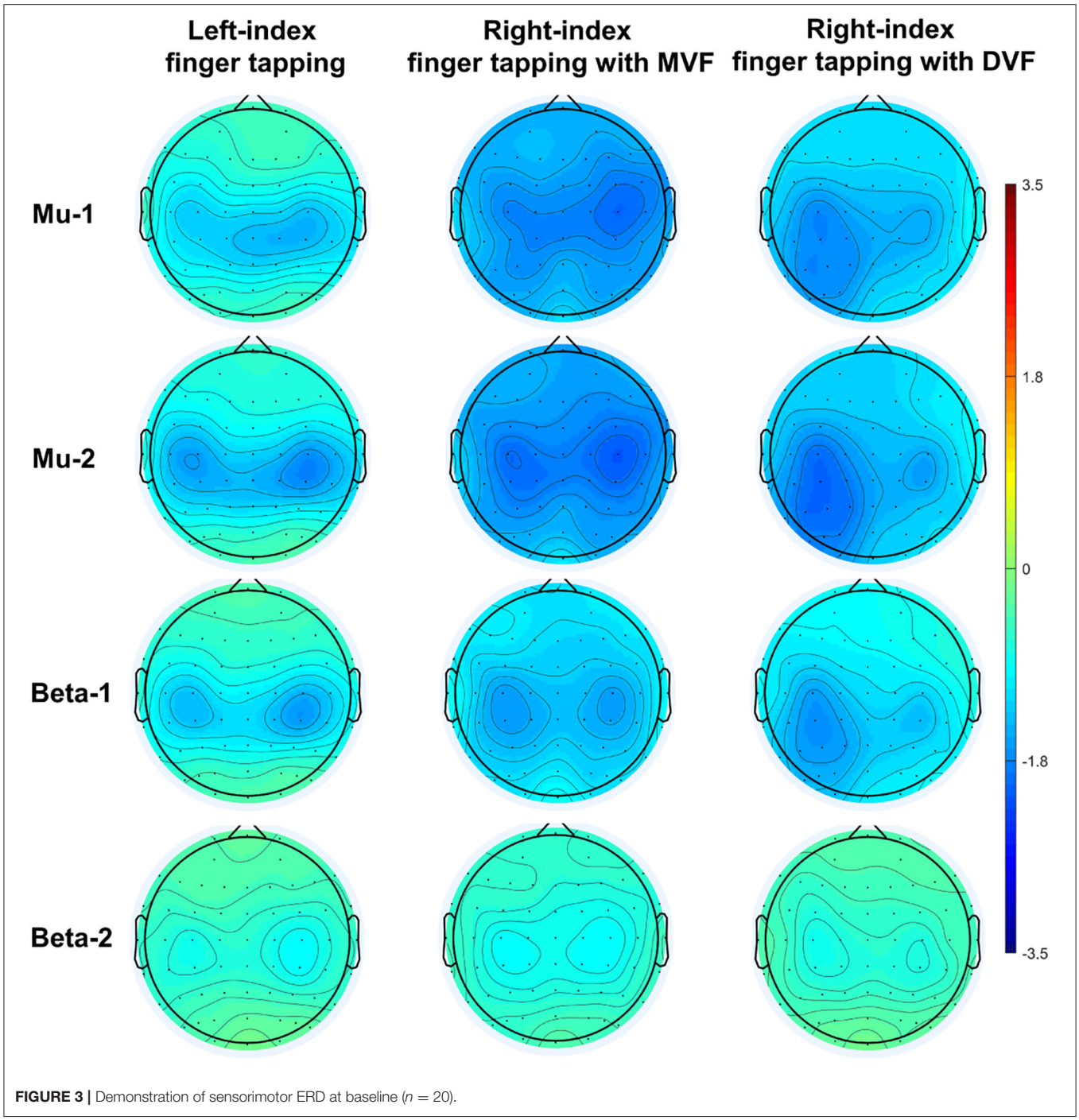

FIGURE 3 | Demonstration of sensorimotor ERD at baseline ($n = 20$).

MVF-Induced ERD

The results of the ANOVA examining MVF-induced ERD are shown in **Table 2** and the descriptive data are graphically depicted in **Figure 4B**. No baseline between-group difference was found in any of the frequency band (all $p > 0.05$). Significant time effects were observed in both the high mu [$F_{(1,18)} = 4.65$, $p = 0.045$, $\eta^2 = 0.21$, $BF_{10} = 1.55$] and low beta [$F_{(1,18)} = 6.10$, $p = 0.024$, $\eta^2 = 0.25$, $BF_{10} = 4.56$] bands, and significant condition effects were observed in the low mu [$F_{(1,18)} = 20.84$, $p < 0.001$, $\eta^2 = 0.54$, $BF_{10} = 3556.80$], high mu [$F_{(1,18)} = 16.12$, $p = 0.001$, $\eta^2 = 0.47$, $BF_{10} = 2603.50$], and low beta bands [$F_{(1,18)} = 11.72$, $p = 0.003$, $\eta^2 = 0.39$, $BF_{10} = 127.33$]. No other significant effects were found in the three-way ANOVA. Within-condition comparisons tested by paired t-tests showed that a dominant right-lateralized sensorimotor ERD was found in the low mu (baseline: $t = 2.78$, $p = 0.012$, $BF_{10} = 4.41$; post-stimulation: $t = 4.58$, $p < 0.001$, $BF_{10} = 145.93$), high mu (baseline: $t = 2.47$, $p = 0.023$ $BF_{10} = 2.58$; post-stimulation: $t = 4.35$, $p < 0.001$, $BF_{10} =$

TABLE 1 | Difference in movement-related event-related desynchronization between groups at baseline and post-stimulation.

	Group 1		Group 2		Time effect		Time by group interaction effect	
	Baseline	Post	Baseline	Post	F-value	*p*-value	F-value	*p*-value
Mu-1	0.22 (0.39)	0.58 (0.48)	0.08 (0.44)	0.14 (0.52)	1.67	0.212	0.83	0.375
Mu-2	0.06 (0.53)	0.71 (0.56)	0.16 (0.72)	0.22 (0.30)	6.52	0.020*	4.47	0.049*
Beta-1	0.03 (0.54)	0.52 (0.71)	0.17 (0.64)	0.41 (0.31)	6.00	0.025*	0.72	0.409
Beta-2	0.05 (0.33)	0.10 (0.58)	0.22 (0.44)	0.27 (0.49)	0.11	0.747	0.00	0.986

*Data are represented as mean (SD); *p < 0.05.*

91.95), and low beta bands (baseline: $t = 2.31$, $p = 0.032$, $BF_{10} = 1.978$; post-stimulation: $t = 3.40$, $p = 0.003$, $BF_{10} = 14.02$) under the MVF condition, in contrast to the DVF condition. Significant differences across time were only found in the high mu ($t = 2.35$, $p = 0.030$, $BF_{10} = 2.09$) and low beta bands ($t = 2.79$, $p = 0.012$, $BF_{10} = 4.47$) under the MVF condition, but not in other frequency bands under the DVF condition.

DISCUSSION

The present study aimed to elucidate the modulatory effect of priming iTBS on sensorimotor oscillation during voluntary movement and movement observation, in contrast to non-priming iTBS on healthy adults. Our study found that: (1) both stimulation protocols increased movement-related ERD in high mu and low beta bands, with a superior effect in regard to enhancing movement-related high mu ERD in participants who received priming iTBS; and (2) both protocols were equivalent in enhancing MVF-induced ERD in the high mu and low beta bands.

Movement-Related ERD

Voluntary hand movements could attenuate the activities of mu and beta rhythms, as reported by several human EEG experiments carried out by Pfurtscheller and his colleagues (Pfurtscheller and Neuper, 1994; Stancak and Pfurtscheller, 1995; Pfurtscheller et al., 2000). The power suppression of mu and beta bands over the central electrodes induced by voluntary movement has been confirmed to be correlated with the activation of the sensorimotor area (Pfurtscheller and Lopes da Silva, 1999). iTBS is a facilitator of cortical excitability (Huang and Rothwell, 2004). A priming session of cTBS has been shown to intensify the facilitatory effect of subsequent iTBS on the motor cortex, as suggested by an increased MEP amplitude (Murakami et al., 2012; Opie et al., 2017) and a reduction of SICI (Murakami et al., 2012), in contrast to iTBS without priming. In the present study, we found that both priming iTBS and non-priming iTBS enhanced movement-related ERD only in high mu and low beta, but not in low mu and high beta bands, which supported our hypothesis that an inhibitory priming stimulation could intensify the facilitatory effects of subsequent iTBS on sensorimotor areas. Sensorimotor mu ERD has been found to be correlated with both MEP and SICI (Takemi et al., 2013, 2015; Thies et al., 2018); however, the functional dissociation between low mu and high mu rhythms has been reported by a previous study (Frenkel-Toledo et al., 2013). The authors found that high mu ERD, but not low mu ERD, had a clear response to movement execution. Indeed, some early studies have demonstrated that movement-related high mu ERD was found to be topographically restricted to the sensorimotor area, while low mu ERD was relatively topographically widespread (Pfurtscheller et al., 2000). Movement-related high mu ERD is likely to be a more sensitive marker of the activation of sensorimotor activation caused by voluntary movement than low mu ERD (Pfurtscheller and Lopes da Silva, 1999; Frenkel-Toledo et al., 2013). This could explain why we could only observe the facilitatory effect of two motor cortex stimulations on high mu but not low mu ERD. Sensorimotor beta ERD during movement is also thought to be correlated with voluntary movement and motor control. In the present study, low beta ERD was increased by both stimulation protocols, while high beta ERD remained stable at pre- and post-stimulation. The impairment of beta oscillation during movement has been found in previous studies on healthy older adults (Schmiedt-Fehr et al., 2016) and patients with motor impairments due to a stroke (Rossiter et al., 2014). These studies analyzed beta rhythms from 15 to 30 Hz, thus neglecting the low beta band. Our findings showed that high beta ERD was stable during movement in healthy adults with intact motor functions, after repetitive excitatory motor cortex stimulation, while low beta ERD varied along with the stimulation. Low beta ERD is more likely to be correlated with low-level motor control related to corticomotor excitability, while high beta ERD may be correlated with high-order motor functions, such as cognitive-motor control (Adam et al., 2015). In future, the effects of TBS on high beta oscillation and its relationship with the level of motor deficits and the ability of an individual to relearn motor skills warrant investigation in older populations and with patients with neurological conditions, such as stroke.

In this study, priming iTBS seems to be superior to iTBS in enhancing movement related ERD in the high mu band. Although the effect was only modest, we found that a priming session of cTBS did not abolish the excitatory effect of the

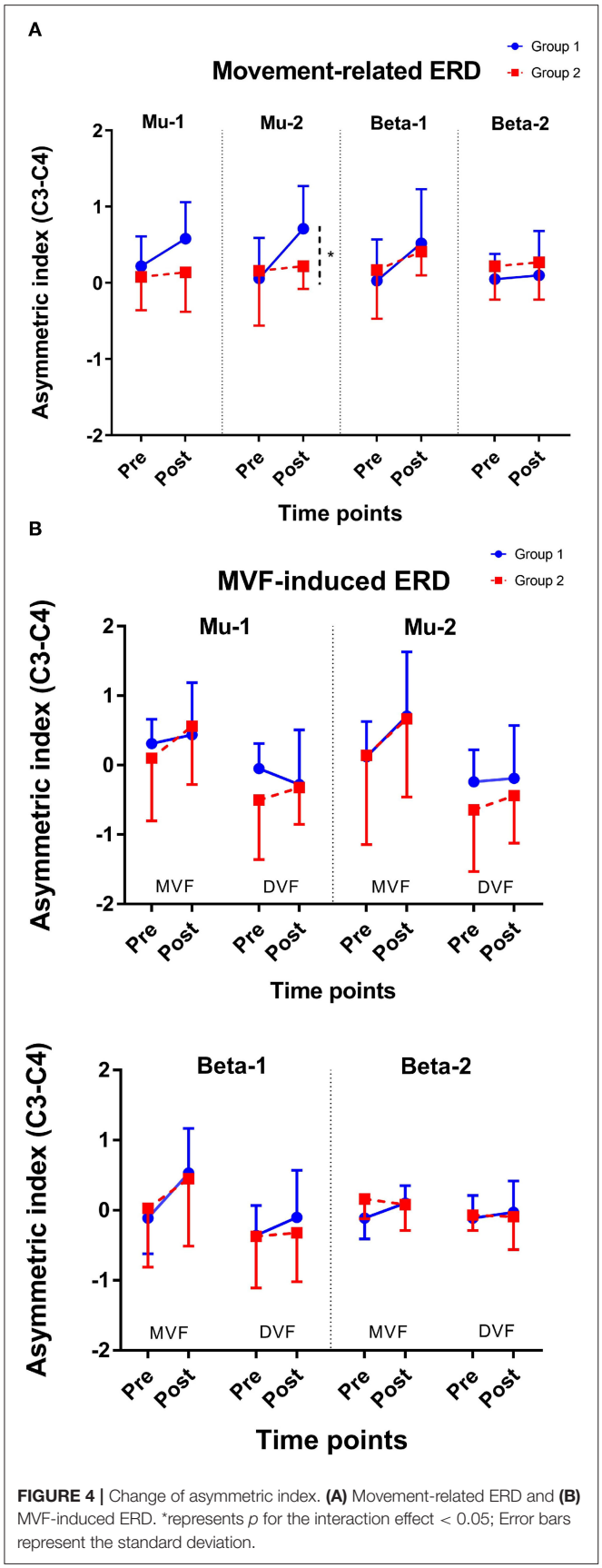

FIGURE 4 | Change of asymmetric index. **(A)** Movement-related ERD and **(B)** MVF-induced ERD. *represents p for the interaction effect < 0.05; Error bars represent the standard deviation.

subsequent iTBS session; it may even potentially boost the effects, found in high mu ERD. These findings support the potential role of metaplasticity in modulating the cortical response to excitatory motor cortex stimulation (Muller-Dahlhaus and Ziemann, 2015). However, the possibility of cortical inhibitory functions induced by the priming and non-priming iTBSs was not known, and further study may also explore the potential effect of priming protocol on cortical inhibitory functions, as measured by concurrent TMS-EEG.

MVF-Induced ERD

Previous experiments have found that MVF induced a shift in ERD toward the sensorimotor area ipsilateral to the moving hand, compared with DVF, in healthy adults (Bartur et al., 2015; Lee et al., 2015; Zhang and Fong, 2019). In the present study, the effects of MVF were found in low mu, high mu, and low beta bands, which is in line with previous investigations conducted among healthy adults (Bartur et al., 2015; Lee et al., 2015; Zhang and Fong, 2019). Moreover, we found that both protocols enhanced the MVF-induced ERD in the high mu and low beta bands, indicating that both TBS protocols delivered to the motor cortex could make the brain more receptive to MVF, which provide neurophysiological evidence to explain the behavioral benefits from excitatory motor cortex stimulation on the observation-based motor learning (Hoff et al., 2015; von Rein et al., 2015; Zhang and Fong, 2019). However, we did not find any significant difference between the two TBS protocols. MVF-induced ERD is thought to be a summation of the activation of the sensorimotor cortex, presumed MNS, and other neural networks related to attention and cognitive control (Deconinck et al., 2015; Zhang et al., 2018). The magnitude of MVF-induced ERD may also be influence with the level of perception of embodiment during the observation, thus resulting in greater variability in response (Alimardani et al., 2016). The small between-group differences in the motor area may not be clearly reflected on the MVF-induced ERD. The facilitatory effect of priming protocol on MVF-induced oscillation may become observable when it is in combination of observation-based behavioral training (e.g., mirror training) (Zhang and Fong, 2019). Moreover, for populations with reduced responses to MVF and a limited ability to relearn motor skills via observation—patients who have suffered a stroke, for example (Bartur et al., 2018)—the alteration of this marker also needs to be examined and correlated with the potential functional recovery caused by priming iTBS.

It should be recognized that our experiment along with previous studies did not systematically investigate the potential variation in the effects of the priming TBS caused by the parameter difference, such as the delay interval between the priming stimulus and the conditioning stimulus, and the stimulation intensity. An interval of 10 min between cTBS and subsequent iTBS was used in our experiment and Opie et al. (2017); however, an interval of 15-min was applied in Murakami et al. (2012) and a 30 min interval was applied in Mastroeni et al. (2013). Most studies used an identical intensity for both priming and stimulation sessions (Hassanzahraee et al., 2018).

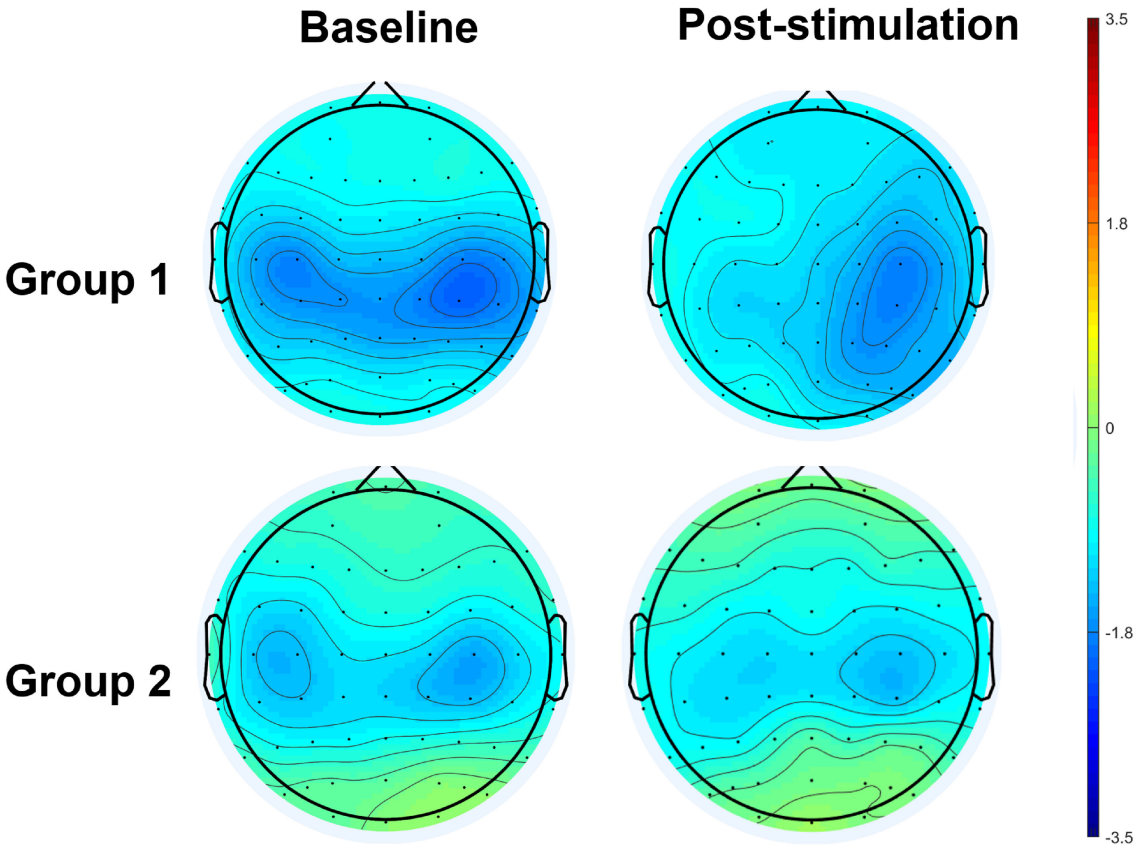

FIGURE 5 | Topographical distribution of movement-related high mu ERD at baseline and post-stimulation. A significant interaction effect favoring Group 1 was observed, in contrast to Group 2.

However, one experiment showed that a priming cTBS session at a lower intensity (AMT = 70%) followed by a conditioning iTBS session at a higher intensity (AMT = 80%) could also induce the metaplastic effects (Murakami et al., 2012). The optimal selection of the parameters in the priming protocol is still unknown which needs to be further investigated.

LIMITATIONS

Our experiment has some limitations. First, the sample size of this study was small, and replication of a larger sample is warranted. However, as an exploratory study, there is no similar existing study from which to calculate an appropriate sample size. We followed previous ERD research and simply used an empirically estimated sample size of 10 cases in each group (Hasegawa et al., 2017). Second, we did not include behavioral outcomes for evaluation in this study. According to a previous study conducted with healthy adults, the neurophysiological effects of iTBS are less likely to be generalized into real behavioral changes in participants with intact motor functions (Zhang and Fong, 2019). Further studies may include a kinematic measure of index finger movements or hand fine motor tasks, and explore the potential behavioral correlates of sensorimotor ERD in healthy adults. It would be more meaningful to explore the behavioral outcomes altered by different stimulation protocols in participants with motor deficits—for example, patients with stroke. Thirdly, only two groups (priming iTBS vs. non-priming iTBS) were employed in the present study, since our focus was to find potential differential effects of these two groups. Without a no iTBS control, we cannot rule out that the significant time effects might be attributed to spontaneous fluctuations in ERD across different sessions, although the test-retest reliability of sensorimotor ERD has been proven in a previous experiment (Espenhahn et al., 2017). However, it was still interesting to see an interaction effect in favor of priming iTBS in high mu band. In addition, the way of applying sham cTBS in the current experiment could be improved. Although there was not significant between-group difference in the treatment belief, sham TBS at a reduced intensity of 20% RMT was still associated with a higher risk of unblinding of subjects. A specialized sham TMS system which could mimic auditory and somatosensory perceptions would be preferable. In addition, we could not fully rule out the possibility that priming stimulation at a very weak intensity might still induce metaplasticity, by changing the state of readiness of synapses to generate LTP-like effects. Lastly, we investigated different frequency bands separately, since

TABLE 2 | Difference in mirror visual feedback-induced event-related desynchronization between groups at baseline and post-stimulation.

		Group 1		Group 2		Results[¶]
		Baseline	Post	Baseline	Post	
Mu-1	*MVF*	0.31 (0.35)	0.44 (0.75)	0.10 (0.90)	0.56 (0.84)	(a) $F = 0.99$, $p = 0.332$ (b) $F = 1.80$, $p = 0.196$ (c) $F = 20.84$, $p < 0.001$* (d) $F = 5.34$ $p = 0.474$
	DVF	−0.05 (0.36)	−0.28 (0.79)	−0.50 (0.86)	−0.32 (0.53)	(e) $F = 2.14$, $p = 0.160$ (f) $F = 0.03$, $p = 0.863$
Mu-2	*MVF*	0.12 (0.51)	0.71 (0.92)	0.14 (1.28)	0.67 (1.13)	(a) $F = 4.65$, $p = 0.045$* (b) $F = 0.17$, $p = 0.898$ (c) $F = 16.12$, $p = 0.001$* (d) $F = 0.64$, $p = 0.434$
	DVF	−0.24 (0.46)	−0.19 (0.76)	−0.64 (0.89)	−0.44 (0.68)	(e) $F = 2.74$, $p = 0.115$ (f) $F = 0.16$, $p = 0.692$
Beta-1	*MVF*	−0.11 (0.51)	0.53 (0.64)	0.03 (0.84)	0.45 (0.96)	(a) $F = 6.10$, $p = 0.024$* (b) $F = 0.60$, $p = 0.450$ (c) $F = 11.72$, $p = 0.003$* (d) $F = 0.25$, $p = 0.626$
	DVF	−0.36 (0.43)	−0.10 (0.67)	−0.37 (0.74)	−0.32 (0.70)	(e) $F = 3.63$, $p = 0.073$ (f) $F = 0.00$, $p = 0.996$
Beta-2	*MVF*	−0.11 (0.30)	0.10 (0.25)	0.16 (0.28)	0.08 (0.37)	(a) $F = 2.55$, $p = 0.626$ (b) $F = 0.96$, $p = 0.340$ (c) $F = 3.28$, $p = 0.087$ (d) $F = 0.78$, $p = 0.639$
	DVF	−0.11 (0.32)	−0.03 (0.45)	−0.07 (0.22)	−0.09 (0.47)	(e) $F = 0.40$, $p = 0.845$ (f) $F = 0.404$, $p = 0.533$

*[¶]Repeated measures ANOVA; data are represented as mean (SD); *$p < 0.05$.*
(a) Time effect; (b) Time by group interaction effect; (c) Condition effect; (d) Condition by group interaction effect; (e) Time by condition interaction effect; (f) Time by condition by group interaction effect.

the previous literature has suggested that functional differences exist between them (Frenkel-Toledo et al., 2013). Thus, we allowed multiple testing on each frequency band separately, without applying a Bonferroni method for a more stringent *p*-value. Together with our previous experiment (Zhang and Fong, 2019) and other studies (Pfurtscheller and Lopes da Silva, 1999; Frenkel-Toledo et al., 2013; Bartur et al., 2015), further investigations among healthy adults might focus on high mu and low beta ERD.

CONCLUSIONS

Both priming iTBS and standard iTBS delivered to motor cortex increases in relation to movement-related sensorimotor activation in the hemisphere contralateral to the moving hand and MVF-induced sensorimotor activation in the hemisphere ipsilateral to the moving hand. Priming iTBS seems to be only superior in inducing a shift of movement-related sensorimotor activation toward the hemisphere contralateral to the moving hand, as suggested by the increase in high mu ERD. Further studies may investigate the durability of the modulatory effects at follow-up, as well as the clinical application of the priming iTBS protocol in patients with stroke.

EQUIPMENT

a. SymAmps2 amplifier and Curry 7, Compumedics Neuroscan, Charlotte, NC, USA
b. MagPro X100 and MagOption rTMS stimulator with Coil C-B60 Butterfly, Standard, MagVenture, Denmark
c. Localite TMS Navigator, Localite, Germany.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Human Subjects Ethics Committee, The Hong Kong Polytechnic University (reference number: HSEARS20190326003). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JZ and KF were involved in the conception and design of the study and approved the submission of the final version of the manuscript. JZ conducted the experiment and wrote up the first draft of the study. KF supervised the progress made and reviewed and edited the manuscript. All authors contributed to the article and approved the submitted version.

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frontiers in Human Neuroscience

REVIEW
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Neurobiological Mechanisms of Transcranial Direct Current Stimulation for Psychiatric Disorders; Neurophysiological, Chemical, and Anatomical Considerations

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Backgrounds: Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation technique for the treatment of several psychiatric disorders, e.g., mood disorders and schizophrenia. Therapeutic effects of tDCS are suggested to be produced by bi-directional changes in cortical activities, i.e., increased/decreased cortical excitability via anodal/cathodal stimulation. Although tDCS provides a promising approach for the treatment of psychiatric disorders, its neurobiological mechanisms remain to be explored.

Objectives: To review recent findings from neurophysiological, chemical, and brain-network studies, and consider how tDCS ameliorates psychiatric conditions.

Findings: Enhancement of excitatory synaptic transmissions through anodal tDCS stimulation is likely to facilitate glutamate transmission and suppress gamma-aminobutyric acid transmission in the cortex. On the other hand, it positively or negatively modulates the activities of dopamine, serotonin, and acetylcholine transmissions in the central nervous system. These neural events by tDCS may change the balance between excitatory and inhibitory inputs. Specifically, multi-session tDCS is thought to promote/regulate information processing efficiency in the cerebral cortical circuit, which induces long-term potentiation (LTP) by synthesizing various proteins.

Conclusions: This review will help understand putative mechanisms underlying the clinical benefits of tDCS from the perspective of neurotransmitters, network dynamics, intracellular events, and related modalities of the brain function.

Keywords: transcranial direct current stimulation, non-invasive brain stimulation, neurotransmitter, LTP, neuromodulation, neural network

INTRODUCTION

Transcranial direct current stimulation (tDCS) is a non-invasive method that modulates neural activities in the brain by delivering low-amplitude (usually no more than 2 mA) over a short period (no more than 30 min) between electrodes (anode and cathode). At least, one of the electrodes is placed on the scalp, through which electronic currents penetrate the skull to enter the brain and facilitate or inhibit spontaneous neural activities in the vicinity of electrodes (Yokoi et al., 2018; **Figure 1**).

Effectiveness of tDCS in the treatment of major depressive disorder (MDD) has been reported (Yokoi et al., 2018). Thus, a meta-analysis has shown a moderate effect of tDCS on depressive symptoms in patients with acute depression (Hedges'g = 0.37) (Shiozawa et al., 2014). Also, there has been a series of reports showing the ability of tDCS to ameliorate positive/negative symptoms of schizophrenia (Kim et al., 2019). For example, hallucinations (positive symptoms) (Hedges'g = 0.86) and negative symptoms (0.41) have been found to be improved by multi-session tDCS on the frontal or frontotemporal lobe (see montages in **Table 1**) twice daily for 5 days (Kim et al., 2019). Moreover, meta-analysis for cognitive function in patients with schizophrenia indicates the ability of multi-session tDCS on the prefrontal cortex (see montage in **Table 1**) to improve working memory (Hedges'g = 0.49), an important cognitive domain (Narita et al., 2020; **Table 1**).

In spite of accumulated evidence for the efficacy of tDCS in treating psychiatric disorders, particularly schizophrenia and mood disorders, its mechanism of action has not been fully elucidated (Stagg and Nitsche, 2011). Therefore, the current review aimed to provide an overview of the actions of tDCS, especially anodal stimulation, on neurotransmission and neural networks in the brain, to help understand the mechanisms underlying its therapeutic effects.

The effect of tDCS on psychiatric symptoms has been mainly reported in studies using anodal stimulation over the frontal cortex. On the other hand, where the cathodal electrode is placed has not been uniform, indicating anodal stimulation has attracted interests to consider the mechanism of tDCS (Fregni et al., 2020). As the clinical benefits of tDCS have been found when multi-sessions are applied (Shiozawa et al., 2014; Kim et al., 2019; Narita et al., 2020), emphasis was placed on long-term changes of neural events produced by tDCS.

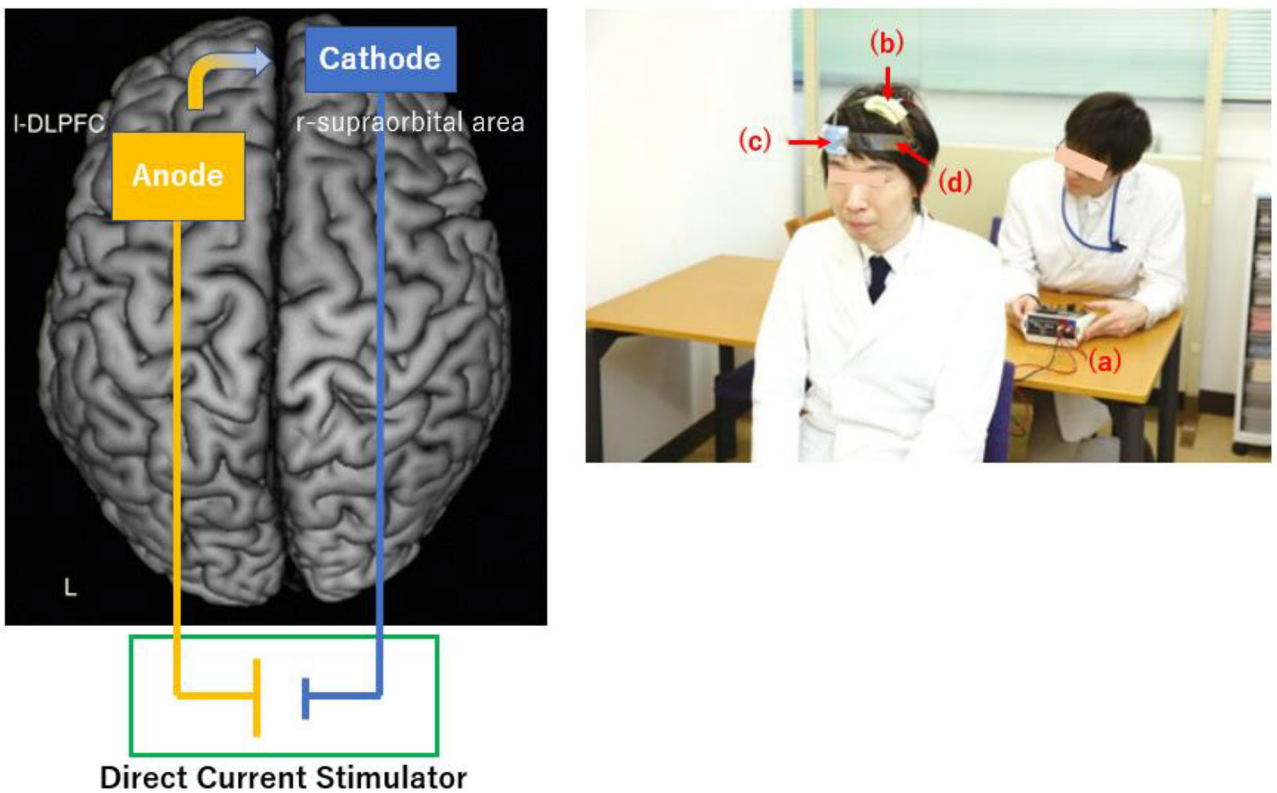

FIGURE 1 | Schematic diagram **(Left)** and experimental setup **(Right)** for tDCS. **(Left)** The anode and cathode electrodes are positioned over the left dorsolateral prefrontal cortex and over right supraorbital region, respectively. The direction of current flow is from the anode to cathode. **(Right)** An administrator controls the stimulator (a). Anodal (b) and cathodal (c) electrodes of 35-cm^2 in size are placed on F3 and right supraorbital region, respectively. A head strap (d) is used as needed to increase reproducibility.

TABLE 1 | Meta-analyses of the effects of tDCS.

Study	Target disease	No. of RCT (*n*)	Montage (anode/cathode)	Intensity (mA)	Duration (min)	No. of sessions	Outcomes	Effect size (Hedges'g)
Shiozawa et al. (2014)	MDD	7 RCTs (259)	F3/RSO, F3/F4, F3/F8	1–2	20–30	5–15	HAMD MADRS	0.37
Kim et al. (2019)	Schizophrenia (positive symptoms)	5 RCTs (186)	Between F3 and FP1/Between T3 and P3	2	20	10–15	AHRS PANSS PSYRATS	0.86
Kim et al. (2019)	Schizophrenia (negative symptoms)	7 RCTs (257)	Between F3 and FP1/Between T3 and P3, F3/F4	2	20–30	10–15	PANSS SANS	0.41
Narita et al. (2020)	Schizophrenia (cognitive functions)	9 RCTs (270)	Between F3 and FP1/Between T3 and P3, F3/F4, F3/FP2	1–2	20–30	2–40	Digit span MCCB, SOPT N-back task 2-back task	0.49 (working memory)

MDD, major depressive disorder; RCT, randomized controlled trial; HAMD, Hamilton Rating Scale for Depression; MADRS, Montgomery-Åsberg Depression Rating Scale; AHRS, Auditory Hallucination Rating Scale; PANSS, Positive and Negative Syndrome Scale; PSYRATS, Psychotic Symptom Rating Scales; SANS, Scale for the Assessment of Negative Symptoms; MCCB, MATRICS Consensus Cognitive Battery; SOPT, Self-Ordered Pointing Task.

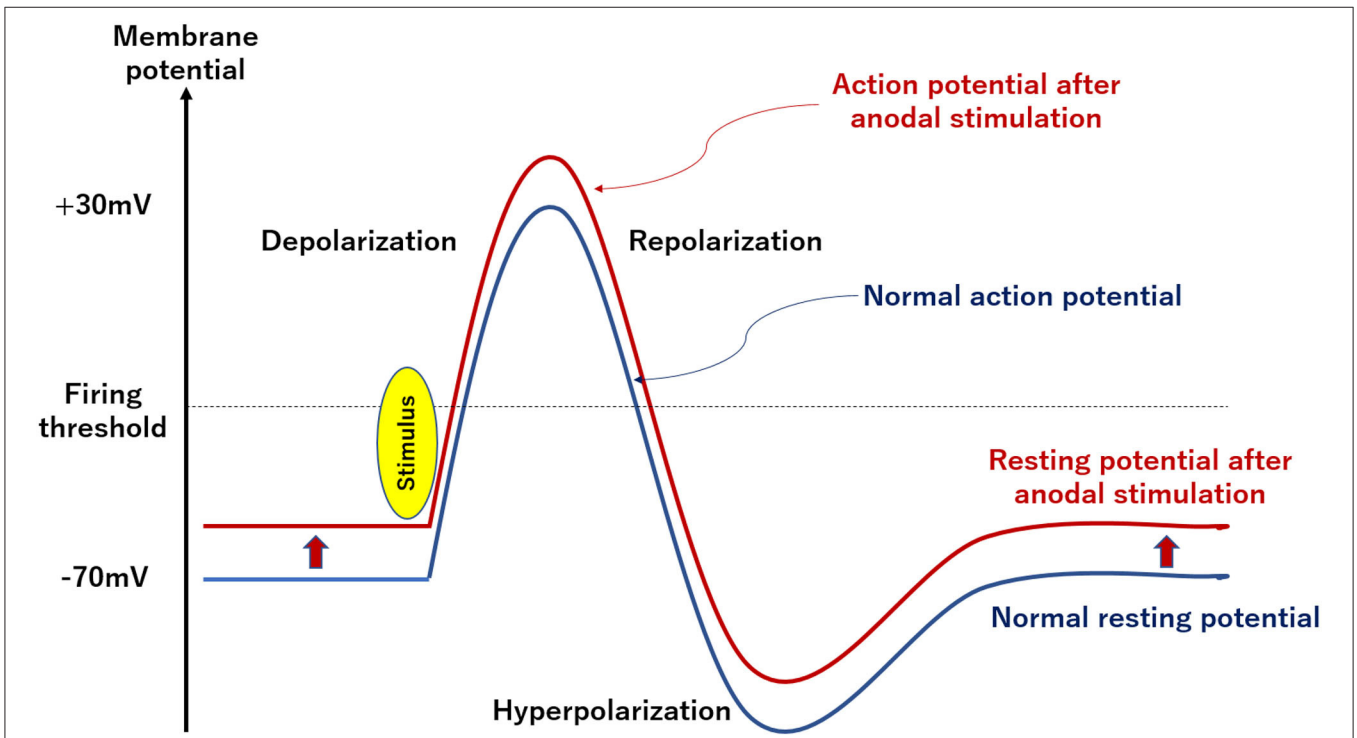

FIGURE 2 | Schematic diagram of changes in neuron potential by tDCS. Anodal stimulation with tDCS (1–2 mA) is not strong enough to depolarize the membrane potential of neurons to the firing threshold. Conversely, cathodal stimulation is thought to deepen the resting membrane potential and make it difficult for neurons to depolarize.

NEUROPHYSIOLOGICAL UNDERSTANDING OF tDCS

Anodal stimulation with tDCS (1–2 mA) by itself is not strong enough to depolarize the membrane potential of neurons to the firing threshold, and only increases the rate of spontaneous combustion and their excitability (Nitsche and Paulus, 2000; Philip et al., 2017; **Figure 2**). Conversely, cathodal stimulation is thought to deepen the resting membrane potential, making it difficult for neurons to depolarize, which reduces spontaneous combustion rates and excitability of neurons (Nitsche and Paulus, 2000; Philip et al., 2017; **Figure 2**). Importantly, these effects of tDCS depend on the intensity and duration of stimulation (Nitsche and Paulus, 2000), and radial electric field (Seo and Jun, 2019).

Electrophysiological understanding of tDCS may be facilitated by the stimulation-dependent model (Fertonani et al., 2011). In this model, anodal stimulation is considered to

TABLE 2 | Effects of concomitant medication on anodal tDCS on the motor cortex of healthy subjects (adapted from Medeiros et al., 2012).

Study	*N*	Stimulation intensity (mA)	Stimulation duration (min)	Stimulation site	Pharmacological intervention	Effects
Liebetanz et al. (2002)	11	1	5	Left M1	Carbamazepine (CBZ) Dextromethorphan (DMO)	Both drugs suppressed the effect of tDCS.
Nitsche et al. (2003)	11–14	1	11∼13	Left M1	CBZ, DMO Flunarizine (FLU)	All suppressed the effect of tDCS.
Nitsche et al. (2004a)	6–12	1	11	Left M1	Lorazepam (LOR)	Delayed the effect of tDCS.
Nitsche et al. (2004b)	12	1	13	Left M1	d-cycloserine (d-CYC)	Prolonged the effect of tDCS.
Nitsche et al. (2004c)	5–12	1	13	–	Amfetaminil (AMP) Propranolol (PRO)	AMP enhanced and prolonged the effect of tDCS while PRO shortened it.
Nitsche et al. (2006)	4–12	1	13	Left M1	Sulpiride	Suppressed and delayed the effect of tDCS.
Kuo et al. (2007)	10–12	1	13	Left M1	Rivastigmine (RIVA)	Suppressed the effect of tDCS.
Kuo et al. (2008)	7–11	1	13	Left M1	Levodopa (L-dopa)	Suppressed the non-specific effects of tDCS while enhanced local effects on synapses of specific neurons.
Rango et al. (2008)	10	1.5	15	Right M1	None	Increased the myo-inositol content under the anode electrode.
Nitsche et al. (2009)	12	1	13	–	Citalopram (CIT)	Enhanced and prolonged the effect of tDCS.
Stagg et al. (2009)	7–11	1	10	–	None	Locally decreased GABA in the cortex. Glutamic acid decreased in correlation with the decrease in GABA due to cathodal stimulation.
Monte-Silva et al. (2010)	12	1	13	Left M1	L-dopa	Suppressed the effect of tDCS.
Stagg et al. (2011)	12	1	10	Left M1	None	Decreased GABA. Positive correlation was found between motor learning and changes in the fMRI signal on the left M1.
Thirugnanasambandam et al. (2011)	48	1	13	Left M1	Nicotine	Suppressed the effect of tDCS.
Chaieb et al. (2012)	8	1	5	Left M1	d-CYC	Suppressed the effect of tDCS.

tDCS, transcranial direct current stimulation; M1, primary motor cortex.

promote depolarization of neurons, and cathodal one causes hyperpolarization to suppress it. Moreover, electrical stimulation affects multiple neurons and increases their membrane potentials to induce depolarization. These events in the vicinity of neural membranes has been proposed to explain the ability of tDCS to improve brain functions (Silvanto et al., 2008).

Increased excitability of local neurons by anodal stimulation is thought to increase blood flow around the stimulation site, and induce subsequent metabolic changes. Specifically, blood-flow changes through tDCS on the prefrontal cortex have been measured by functional near-infrared spectroscopy (fNIRS) (Merzagora et al., 2010). In this study, the increase of oxygenated hemoglobin concentrations under the anodal electrode was significantly larger than those for the cathode. This is thought to reflect the ability of anodal stimulation to induce metabolic changes among neurons (Merzagora et al., 2010).

TABLE 3 | Pharmacological actions.

Drug	Pharmacological action
Carbamazepine (CBZ)	Sodium channel inhibitor
Dextromethorphan (DMO)	NMDA receptor inhibitor
Flunarizine (FLU)	Calcium channel inhibitor
Lorazepam (LOR)	GABA receptor agonist
d-cycloserine (d -CYC)	NMDA receptor partial agonist
Amfetaminil (AMP)	Adrenergic receptor agonist
Propranolol (PRO)	Adrenergic receptor inhibitor
Sulpiride (SUL)	Dopamine receptor inhibitor
Pergolide (PGL)	Dopamine receptor agonist
Rivastigmine (RIVA)	Cholinesterase inhibitor
Levodopa (L-dopa)	Dopamine precursor
Citalopram (CIT)	Serotonin reuptake inhibitor
Nicotine	Nicotinic acetylcholine receptor agonist

BIOCHEMICAL EFFECTS OF tDCS

Changes in neurotransmissions by anodal stimulation have been reported in relation to metabolic changes in the brain. Here, we review the accumulated evidence for the effect of stimulation of the motor cortex in patients with chronic pain and those receiving post-stroke motor rehabilitation (Medeiros et al., 2012; **Tables 2**, **3**). For example, the effect of anodal stimulation is suppressed by carbamazepine (sodium channel inhibitor) (Liebetanz et al., 2002), indicating that inhibition of intracellular influx of extracellular sodium ion suppresses anode-induced depolarization of neurons, and subsequent excitements.

Glutamate receptor subtypes governing excitatory synaptic transmissions include AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartate) receptors, both of which are coupled with ion-channels. The AMPA receptor is involved in the intracellular influx of sodium ion during neuronal depolarization, causes transient action potentials, and accounts for most of the excitatory synaptic transmissions. On the other hand, the NMDA receptor is involved in the intracellular influx of calcium ion during depolarization, produces prolonged action potentials, and mediates neural circuits governing memory and learning. Therefore, actions on NMDA receptors, inducing plasticity of neurons, play a dominant role in improving symptoms of psychiatric disorders. Accordingly, dextromethorphan (NMDA receptor inhibitor) suppresses the effect of anodal stimulation (Liebetanz et al., 2002; Nitsche et al., 2003, 2004a), while d-cycloserine (partial NMDA receptor agonist) prolongs it (Nitsche et al., 2004b). This is in line with the observations that NMDA receptor agonists enhance excitatory synaptic transmissions, while NMDA receptor inhibitors suppress it (Liebetanz et al., 2002; Nitsche et al., 2003, 2004a,b). Also, GABA (gamma-aminobutyric acid: γ-aminobutyric acid), a neurotransmitter that inhibits synaptic transmissions, may play a role. Thus, lorazepam, a GABA receptor agonist, delays the effect of anodal stimulation

TABLE 4 | Changes in the brain networks by anodal tDCS.

Study	Subject (*n*)	Stimulation intensity (mA)	Stimulation duration (min)	Stimulation site	Pharmacological intervention	Results
Clark et al. (2011)	Healthy subjects (7)	2	30	Right parietal lobe	None	Increased glutamic acid concentrations under anode electrodes.
Polanía et al. (2011)	Healthy subjects (13)	1	10	Left primary motor cortex	None	Reduced direct functional connectivity to gray matter away from the left somatomotor cortex (SM1). Enhanced functional connectivity between the premotor area and the parietal lobe via the left SM1. Enhanced functional connectivity between the left posterior cingulate cortex and the right DLPFC.
Stagg et al. (2014)	Healthy subjects (10)	1	10	Left primary motor cortex	None	Negative correlation between GABA concentrations and functional connectivity of the resting motor network. Decreased GABA concentrations. Enhanced the functional connectivity of the resting motor network.
Hunter et al. (2015)	Healthy subjects (9)	2	30	Right parietal lobe	None	Increased glutamic acid concentrations under anode electrodes. Enhanced the functional connectivity of the superior parietal-inferior parietal-left frontal parietal-cerebellum. Suppressed the functional connectivity of the anterior cingulate-basal ganglia.
Bachtiar et al. (2015)	Healthy subjects (12)	1	20	Left primary motor cortex	None	Decreased GABA concentrations. Enhanced the functional connectivity of the resting motor network. Decreased GABA concentrations and enhanced functional connectivity of motor networks by different mechanisms.
Fonteneau et al. (2018)	Healthy subjects (32)	2	20	Both dorsolateral prefrontal cortex (DLPFC)	None	Increased dopamine release in the striatum.
Wörsching et al. (2018)	Healthy subjects (28)	2	20	Right DLPFC	None	Decreased resting-state fMRI connectivity in a medial part of the left prefrontal cortex. Decreased regional brain activity during a delayed-response working-memory (DWM) retrieval. Faster responses to the DWM task.
Fukai et al. (2019)	Healthy subjects (20)	2	26	Left DLPFC	None	Increased dopamine release in the right ventral striatum.
Bulubas et al. (2019)	Patients with major depression (52)	2	30 (22 sessions)	Left DLPFC	Escitalopram 20 mg/day	Association between larger gray matter volumes and depression improvement assessed over a treatment period of 10 weeks.

(Nitsche et al., 2004c). On the other hand, the anodal stimulus itself causes a local decrease in GABA concentrations in the cortex (Stagg et al., 2009, 2011).

Monoamine neurotransmitters, such as dopamine, serotonin, and acetylcholine have been reported to mediate the effect of tDCS (Nitsche et al., 2006, 2009; Kuo et al., 2007, 2008; Monte-Silva et al., 2010; Thirugnanasambandam et al., 2011). For example, sulpiride, a dopamine receptor blocker (Nitsche et al., 2006), suppresses the effects of anodal stimuli, while levodopa, a dopamine precursor (Kuo et al., 2008; Monte-Silva et al., 2010), locally enhances excitement of certain synaptic transmissions (Kuo et al., 2008). These findings suggest that the action of tDCS may include regulation of dopamine transmissions. Also, citalopram, a serotonin reuptake inhibitor, enhances anodal stimulation (Nitsche et al., 2009). Regarding acetylcholine transmissions, rivastigmine, a cholinesterase inhibitor, suppresses the effect of tDCS (Kuo et al., 2007). In sum, the direction of influence on actions of anodal stimulation varies depending on monoamine neurotransmitters.

The above considerations overall lead to the concept that anodal stimulation enhances excitatory synaptic transmissions by stimulating glutamate transmissions and suppressing GABA transmissions in the cortex. On the other hand, it modulates the dopamine system, enhances and suppresses serotonin and acetylcholine transmissions, respectively. These effects of tDCS on monoamine transmissions are considered to be associated with change of the balance between excitatory and inhibitory inputs in the brain (Okun and Lampl, 2008).

NEUROANATOMICAL UNDERSTANDING OF THE EFFECT OF tDCS

Impaired functional connectivity between brain regions has been reported in patients with psychiatric disorders, such as schizophrenia and bipolar disorder (Yamada et al., 2020). In schizophrenia patients, a study using resting functional magnetic resonance imaging (fMRI) found a separation between the medial prefrontal cortex and the dorsolateral prefrontal cortex (Chai et al., 2011). Another study found changes of dynamic functional connectivity mainly in the thalamus and cerebellum, as well as frontal, temporal, occipital, fusiform, post-central, cuneus, supramarginal, and calcarine cortices in patients with schizophrenia or bipolar disorder. Specifically, functional connectivities involving the post-central, frontal, and cerebellar cortices are weakened across schizophrenia and bipolar disorder, while those involving the insular, temporal, frontal, fusiform, lingual, occipital, supramarginal cortices, as well as thalamus and cerebellum, are strengthened (Du et al., 2017). Kunze et al. systematically applied tDCS to a large-scale network model consisting of 74 brain regions to investigate the functional connectivity of dynamic states. They found alterations of the competitive interrelationship of functional networks by tDCS (Kunze et al., 2016).

Based on these findings, the mechanism of action of tDCS on neural circuits are summarized in **Table 4**. Anodal tDCS may enhance excitatory synaptic transmissions by changing the balance between glutamate and GABA activities (Clark et al.,

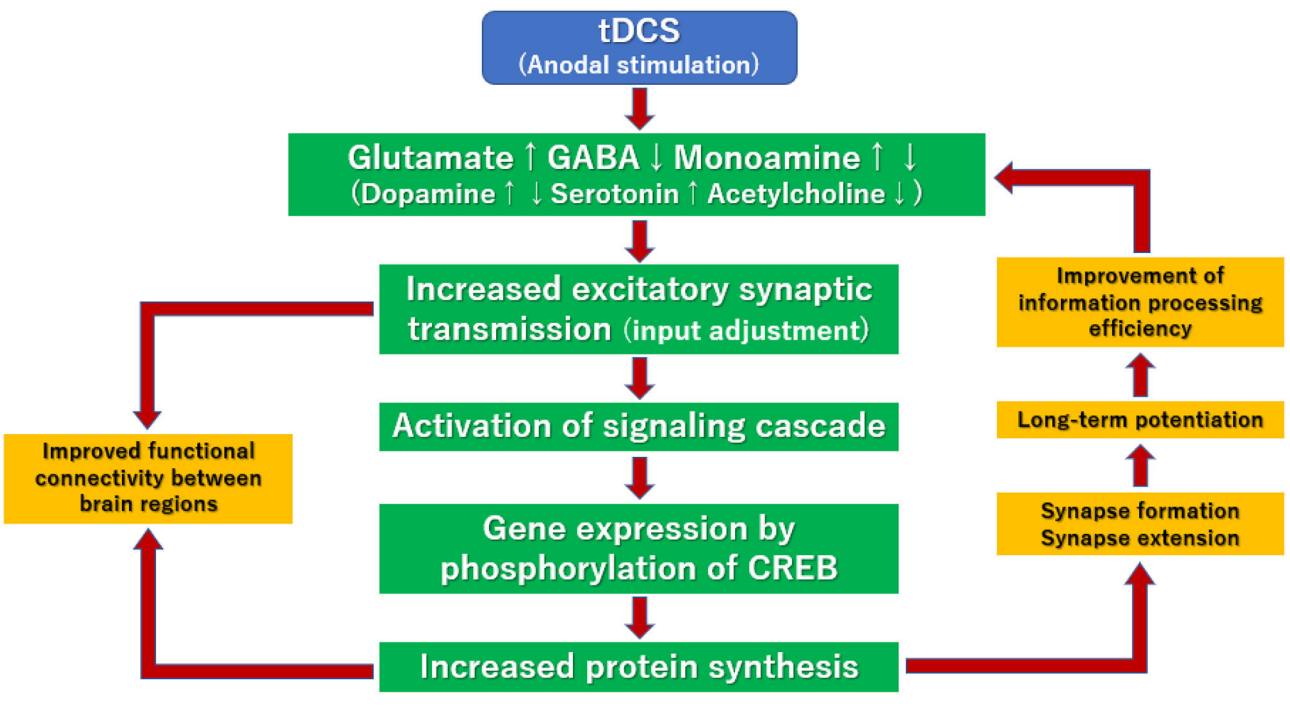

FIGURE 3 | Putative mechanisms for the enhancement of long-term potentiation by tDCS. Various neurotransmitters activate/inhibit transduction cascades bound to G-proteins or ion-channels, leading to phosphorylation of cAMP-responsive element binding protein (CREB) and activation of genes in the nucleus of neurons. These signal transduction cascades enhance the synthesis of various proteins, such as neurotransmitter synthases, receptors, ion channels, and intracellular signal proteins. Facilitative actions of these proteins that regulate efficiency of neurotransmissions in the cerebral cortex circuit may explain the ability of tDCS to induce LTP.

2011; Stagg et al., 2014; Bachtiar et al., 2015; Hunter et al., 2015), leading to modification of functional connectivity between brain regions, including the stimulation site (Polanía et al., 2011; Stagg et al., 2014; Bachtiar et al., 2015; Hunter et al., 2015). Furthermore, the effects of tDCS may be extended in the brain, through an increased/decreased release of monoamine transmitters, such as dopamine, on neural circuits that do not necessarily involve the anodal stimulation site (Polanía et al., 2011; Hunter et al., 2015; Fonteneau et al., 2018). These neural events are thought to improve psychiatric symptoms and cognitive function (Fukai et al., 2019). In summary, anodal stimulation is likely to modify activity levels of both specific brain regions and multiple network systems (Luft et al., 2014).

MECHANISM OF ACTION OF tDCS VIA LONG-TERM POTENTIATION AND GLIAL CELLS

Long-term potentiation (LTP), continuous enhancement of signal transduction between neurons, is thought to mediate the effect of tDCS (**Figure 3**). First, action potentials in presynaptic neurons are converted into chemical signals at the presynaptic membrane. Subsequently, neurotransmitters (glutamate, GABA, dopamine, serotonin, acetylcholine, etc.) are released into the synaptic gap. The process by which this neurotransmitter is transmitted to post-synaptic neurons is called the signal transduction cascade. In this cascade, various neurotransmitters activate/inhibit transduction cascades bound to G-proteins or ion-channels, leading to phosphorylation of cAMP-responsive element binding protein (CREB) and activation of genes in the nucleus of neurons. Also, the neurotrophic factor-bound transduction cascade may play a role by activating various kinase enzymes (Stephen, 2013). These signal transduction cascades enhance the synthesis of various proteins, such as neurotransmitter synthases, receptors, ion channels, and intracellular signal proteins. Facilitative actions of these proteins that regulate efficiency of neurotransmissions in the cerebral cortex circuit may explain the ability of tDCS to induce LTP (**Figure 3**).

Brain-derived neurotrophic factor (BDNF) may also mediate the development of LTP (Cocco et al., 2018). So far, multi-session anodal simulations on the left dorsolateral prefrontal cortex (DLPFC) has been shown to improve mood symptoms *without* significant change in BDNF concentrations in the blood of patients with major depressive disorder (Brunoni et al., 2015). Further study is warranted to see if tDCS affects BDNF levels in other psychiatric disorders.

TABLE 5 | Animal studies on the mechanism of long-term potentiation (LTP) by anodal tDCS.

Study	Age or weight, species	Stimulation intensity, duration	Stimulation site	Results
Hattori et al. (1990)	190–240 g Wistar rats	0.3, 3, or 30 μA 30–240 min, 3–5 times per day for several days	Sensory-motor cortex	Increased cAMP accumulation in the polarized cortex in 3 μA. Decreased cAMP accumulation in the polarized cortex in 0.3 μA.
Fritsch et al. (2010)	Male 6–8 weeks old mice	10 μA	Motor cortex (M1) slices	Induced synaptic plasticity *in vitro* by DCS, which was dependent on enhanced BDNF-secretion and TrkB-activation.
Jiang et al. (2012)	Adult, Sprague-Dawley rats, model of middle cerebral artery occlusion	mA, 30 min 3, 7, or 14 sessions	Primary motor cortex	Enhanced density of dendritic spines after stroke. No change in the up-regulated PX1 mRNA expression after stroke. Improved post-stroke motor function on days 7 and 14.
Ranieri et al. (2012)	150–200 g Wistar rats	200–250 μA, 20 min	Hippocampal slices	Modulated LTP at rat hippocampal CA3-CA1 synapses.
Podda et al. (2016)	Male 30–45 days old mice	350 μA, 20 min	Left hippocampus	Exhibited 1-week lasting enhancement in hippocampal LTP, learning, and memory, which were associated with enhanced acetylation of BDNF promoter I, expression of BDNF exons I and IX, and BDNF protein levels. Enhanced CREB phosphorylation, pCREB binding to BDNF promoter I, and recruitment of CREB-binding protein.
Monai et al. (2016)	8–12 weeks old mice	0.1 mA, 10 min	Primary visual cortex	Induced surges of Ca^{2+} influx into astrocytes across the entire cortex by using a transgenic mouse expressing G-CaMP7 in astrocytes. Changed the meta-plasticity of the cortex through astrocytic Ca^{2+}/IP3 signaling.
Yu et al. (2019)	8 weeks old male Sprague-Dawley rats	250 μA, 30 min	Hippocampal CA1 slices	Enhanced LTP in hippocampal CA1 slices from rats. Exhibited high levels of BDNF in the hippocampal CA1 region.

Glial cells, including astrocytes, have been reported to be activated by tDCS (Ruohonen and Karhu, 2012). As these cells regulate the concentrations of chemical substances and neurotransmitters in the outer space of neurons, the mechanisms by which tDCS ameliorate psychiatric symptoms may involve some modalities other than direct actions on neuronal cells. For example, findings from animal studies suggest involvement of LTP and glial cells (see **Table 5**). In rats, anodal tDCS stimulation on hippocampal CA3-CA1 synapses has been reported to induce LTP (Ranieri et al., 2012). Also, tDCS increases cAMP accumulation in the polarized cortex (Hattori et al., 1990), and changes mRNA expressions, leading to the increase in the density of dendritic spines in subjects with strokes (Jiang et al., 2012).

Monai et al. reported that tDCS augments noradrenaline levels by increasing intracellular calcium ion concentrations through stimulation of α1 adrenergic receptors on astrocytes in genetically modified mice (Monai et al., 2016). Also, an increase in intracellular concentrations of calcium ions by tDCS has been found in human cells (Dubé et al., 2012), suggesting the involvement of astrocytes in the ability of tDCS to induce LTP.

BDNF binds to TrkB receptors that regulate the growth and synaptic activity of neurons, and are thought to be involved in the formation of LTP (Stephen, 2013). For example, anodal tDCS induces synaptic plasticity *in vitro*, which is dependent on enhanced BDNF-secretion and TrkB-activations (Fritsch et al., 2010). Moreover, Podda et al. (2016) reported that mice subjected to anodal tDCS exhibited hippocampal LTP and improvement of learning and memory. These effects have been reported to be associated with enhancement of acetylation of BDNF promoter I, expression of BDNF exons I and IX, and BDNF protein levels (Podda et al., 2016). The hippocampi of mice receiving tDCS also exhibit enhanced CREB phosphorylation, and phosphorylated CREB at Ser133 ($pCREB^{133}$) binds to BDNF promoter I, and recruits of CREB-binding proteins. These findings suggest that anodal tDCS increases hippocampal LTP and memory via mechanisms related to BDNF genes (Podda et al., 2016; Yu et al., 2019).

CONCLUSIONS

In this review, we discussed the electrophysiological understanding of tDCS on the basis of the stimulation-dependent model. Biochemically, enhancement of excitatory synaptic transmissions through anodal stimulation is likely to facilitate glutamate transmission and suppress gamma-aminobutyric acid transmission in the cortex. Accordingly, tDCS may positively or negatively regulate dopamine, serotonin, and acetylcholine transmissions. These neural events may change the balance between excitatory and inhibitory inputs. In this way, anodal stimulation may modulate activity levels of multiple network systems.

LTP may also provide putative mechanisms underlying the ability of tDCS to treat psychiatric disorders. Future studies should consider other domains of symptoms of psychiatric conditions of schizophrenia and mood disorders, e.g., social cognition and meta-cognition (Nishida et al., 2018; Yamada et al., 2019), as a target of treatment with tDCS. Also, identifications of predictors for its therapeutic benefits in clinical settings deserve further endeavors (Bulubas et al., 2019).

LIMITATIONS

The current review is narrative and the articles were not systematically searched. Moreover, many of the papers presented in this review targeted healthy individuals rather than those with psychiatric disorders. It should be noted that patients with mental illnesses might respond differently to tDCS from healthy people. Furthermore, some articles included in this review were on the effect of tDCS over motor cortex. Further study is warranted to examine evidence for stimulation on prefrontal cortex that has been the main target of psychiatric disorders, such as depression and schizophrenia (Mezger et al., 2020).

AUTHOR CONTRIBUTIONS

YY and TS planned and designed the review, made substantial contributions, and approved the final manuscript. YY collected the data and drafted the first manuscript. TS critically reviewed the draft and revised it. All authors contributed to the article and approved the submitted version.

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A Study on the Effect of Mental Practice Using Motor Evoked Potential-Based Neurofeedback

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This study aimed to investigate whether the effect of mental practice (motor imagery training) can be enhanced by providing neurofeedback based on transcranial magnetic stimulation (TMS)-induced motor evoked potentials (MEP). Twenty-four healthy, right-handed subjects were enrolled in this study. The subjects were randomly allocated into two groups: a group that was given correct TMS feedback (Real-FB group) and a group that was given randomized false TMS feedback (Sham-FB group). The subjects imagined pushing the switch with just timing, when the target circle overlapped a cross at the center of the computer monitor. In the Real-FB group, feedback was provided to the subjects based on the MEP amplitude measured in the trial immediately preceding motor imagery. In contrast, the subjects of the Sham-FB group were provided with a feedback value that was independent of the MEP amplitude. TMS was applied when the target, moving from right to left, overlapped the cross at the center of the screen, and the MEP amplitude was measured. The MEP was recorded in the right first dorsal interosseous muscle. We evaluated the pre-mental practice and post-mental practice motor performance in both groups. As a result, a significant difference was observed in the percentage change of error values between the Real-FB group and the Sham-FB group. Furthermore, the MEP was significantly different between the groups in the 4th and 5th sets. Therefore, it was suggested that TMS-induced MEP-based neurofeedback might enhance the effect of mental practice.

Keywords: mental practice, motor evoked potential, neurofeedback, transcranial magnetic stimulation, motor imagery training

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INTRODUCTION

With the progress in brain imaging technology in recent years, mechanisms in the brain that have been treated as black boxes are gradually being clarified. In particular, even when the brain is damaged, such as in cerebrovascular disorders, it has been proven that plastic brain changes, as a consequence of training, do occur. In recent years, attention has been focused on rehabilitation based on knowledge of the mechanisms in the brain. Under such circumstances, mental practice (i.e., motor imagery training) is one of the means of rehabilitation acting in complement to movement therapy; mental practice is a method of repeatedly reproducing motor imagery.

Motor imagery is the execution of a mental action in a state where there is no clear movement or muscle activation (Mizuguchi et al., 2014). It has been reported that in motor imagery, activation in the brain is recognized to be almost similar to the actual action, without the accompanying movement. Specifically, studies using positron emission tomography (PET) and magnetic resonance imaging (fMRI) have reported that the premotor area, supplementary motor area, cingulate, and parietal cortex are activated during these mental exercises (Porro et al., 1996, 2000; Deiber et al., 1998; Lotze et al., 1999; Gerardin et al., 2000; Ehrsson et al., 2003; Hanakawa et al., 2003; Jackson et al., 2003; Kuhtz-Buschbeck et al., 2003; Dechent et al., 2004; Meister et al., 2004). In addition, activation of the primary motor cortex (M1) has been reported by studies using electroencephalography (EEG) and transcranial magnetic stimulation (TMS) (Pfurtscheller and Neuper, 1997; Hollinger et al., 1999; Caldara et al., 2004; Mattia et al., 2004). Mental practice does not require special machines or devices, and subjects can easily work on it without any time or space restrictions. Furthermore, since it can be carried out without actual movement, it can be applied to patients who do not have the capacity to perform voluntary exercise and minimize dangers such as risk of falling (Dietrich, 2008). In fact, there is also a report, using randomized controlled trials, that demonstrates the effect of mental practice on the improvement of upper limb paralysis in stroke patients (Page et al., 2009; Nilsen et al., 2012; Park and Lee, 2015). Furthermore, a systemic review showed that mental practice is an effective intervention for upper limb dysfunction in stroke patients (Langhorne et al., 2009).

However, although evidence has been shown for the effect of mental practice, it is not widely used in clinical settings. The reason for this is that since motor imagery is processed in the brain, it is difficult to objectively evaluate how clearly the subject undertakes motor imagery as a task, from the viewpoint of the therapist. Therefore, it is difficult to give accurate feedback during practice. To address this problem, attempts to evaluate brain activity in motor imagery using brain imaging technology and provide feedback to the subject in real-time, have been reported (Broetz et al., 2010; Ang et al., 2011; Pichiorri et al., 2015; Mehler et al., 2019). For example, a previous study measured the change in cerebral blood flow rate in a motor-related region (right dorsal region of the premotor cortex), as a blood oxygenation level-dependent signal using fMRI. Through feedback to participants, it was possible to perform mental practice while maintaining increased motor imagery ability; as a result, the study reported an improvement in performance (Hui et al., 2014). In addition, oxygenated hemoglobin signals in the premotor area, on the opposite side, were recorded with motor imagery using near-infrared spectroscopy (NIRS); we performed the measurements by dividing participants in to the real-FB group (feedback of the correct amount of cerebral blood flow change to the subject) and the sham-feedback group (feedback of a false cerebral blood flow change). The real-FB group showed that the self-assessment scale scores for kinesthetic motor imagery were higher than those of the Sham-feedback group (Mihara et al., 2012). However, the abovementioned neuroimaging equipment is expensive, highly restrictive, and possibly difficult to widely use in the clinic. Conversely, TMS is a method that can evaluate brain activity during motor imagery, like to be using fMRI and NIRS. The motor evoked potential (MEP) is widely used as an evaluation of M1 excitability, and the MEP amplitude (peak-to-peak) has been reported to be significantly higher during motor imagery than in control conditions in several previous studies (Fadiga et al., 1998; Facchini et al., 2002; Munzert et al., 2009).

It has been reported that a greater MEP amplitude is associated with greater motor imagery (Williams et al., 2012) and more vivid kinesthetic motor imagery (Ohno et al., 2011; Ikeda et al., 2012; Moriuchi et al., 2020). Based on the above, it is possible that results similar to the results of feedback performed by fMRI and NIRS can be obtained even when feedback using TMS is performed. Compared to fMRI and NIRS, TMS equipment is relatively inexpensive and easy to move, so there are few restrictions; as such, we thought that it would be useful for increasing opportunities for neurofeedback in clinical situations.

Therefore, the purpose of this study was to verify whether M1 excitability can be promoted by feedback to the subject with the MEP amplitude (peak-to-peak) induced by TMS as an index.

MATERIALS AND METHODS

Subjects

A power analysis using G-power revealed a requisite sample size of 22 (with an effect size of 0.4 and significance level of $p < 0.05$, power of 0.8). A total of 24 healthy subjects (14 men and 10 women; mean age, 22.4 $\pm$ 3.4 years) were enrolled in the study. All participants provided written informed consent, and all were right-handed (as indicated by self-report). None of the subjects reported neurological impairment or contraindications to TMS. The study was approved by the local ethics committee of Nagasaki University Graduate School of Biomedical Sciences. All experimental procedures were conducted in accordance with the Declaration of Helsinki (World Medical Association, 2013).

To reveal the effect of TMS feedback, all participants were randomly allocated to either the real-feedback group (Real-FB) ($n = 12$; a group given a right MEP amplitude) or the sham-feedback group (Sham-FB) ($n = 12$; a group given a non-related value of MEP amplitude).

Experimental Set-Up

Subjects were seated on a reclining chair 80 cm away from a computer monitor (19-inch, resolution 1,024 $\times$ 768 pixels, refresh frequency 60 Hz) and were instructed to keep both hands in a pronated position on a horizontal board attached to the chair's armrest. They were instructed to keep the right forearm as still and relaxed as possible while paying attention to the visual stimuli presented on the monitor. The position of the right index finger was adjusted, as shown in **Figure 1**, so that the switch could be pressed by the abduction movement.

Experimental Task

The motor imagery task was conducted as shown in **Figure 1**. The timing of the TMS trigger needs to stimulate at the same point as the action, during motor imagery. Therefore, in the present study,

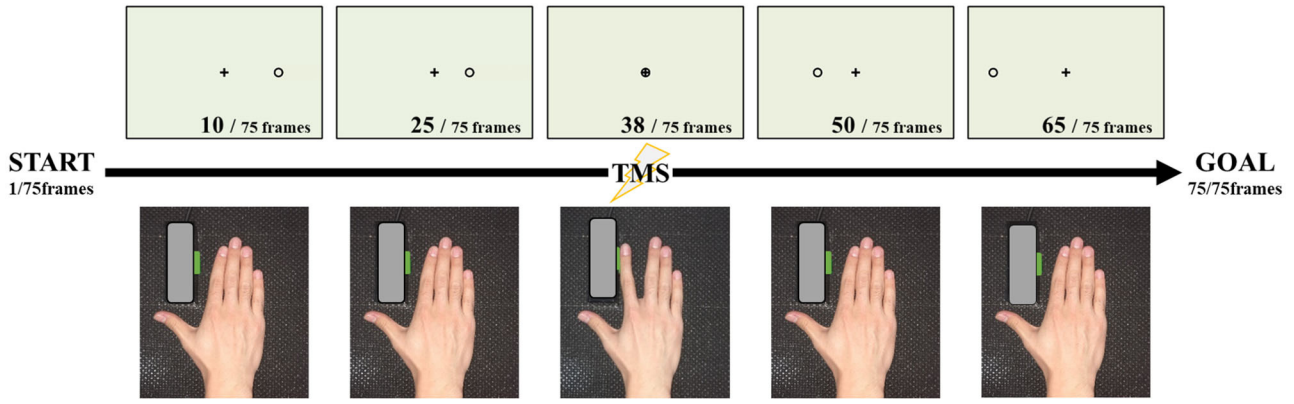

FIGURE 1 | Experimental set-up and task. Seventy-five images were continuously reproduced, and magnetic stimulation was applied at the time of the 38th frame at which the cursor overlapped with the target point. At the time when the cursor overlapped with the target point, we instructed the participant to press the button by index finger abduction.

we adopted the coincidence timing task, which involved pressing the button through index finger abduction, coinciding with the arrival of a cursor, running on a straight forward line from the start point. In the performance evaluation of this experiment, the abduction switch was pressed with the index finger touching the button, such that the abduction angle was very small. The starting point was to the right of the monitor and the target point was in the middle of the screen.

The experimental video was made from 75 individual JPEG files, from the starting point to the end point, and shown in succession to obtain the animation effect, which was presented at a speed of 33.3 ms/frame. The timing of the coincidence with the arrival of the cursor to the target point was the 38th file. Based on the above, the circle reached the target in 1.27 s, and the distance from the start position to the target was 12.5 cm on the monitor. One set (20 trials) was used for performance evaluation.

An experimental movie was played where a black cross in the center of a white screen was presented. After the warning signal (beeping sound), the cursor ran on a straight line at a constant speed from the starting point, to the target point. Subjects were required to pay attention to the movement of the cursor on the monitor and to press the button with index finger abduction, when the cursor arrived at the target point. The experimental program used in the present study was a custom-made program by LabVIEW systems (LabVIEW, National Instruments, USA).

Mental Practice

Mental practice with motor imagery was conducted for five sets with 20 trials per set. Therefore, the total number of trials was 100. Subjects were instructed to kinesthetically imagine the coincidence timing task as if they were actually performing the movement, and subsequently recall the sense of the fingertip, muscle strength, and the sound when they pressed the button.

TMS Feedback

We used MEP induced by TMS during motor imagery for neurofeedback. The TMS trigger was set at the timing of the arrival of a cursor to the target point. Subjects obtained feedback of the obtained MEP amplitude values. **Figure 2A** shows the monitor of the neuro-feedback system used in the present study. We set the level meter, at the bottom of the monitor, which could reflect the corticospinal excitability during motor imagery. A value of 100% indicated corticospinal excitability in the resting condition. This level meter was represented by a scale from 0 to 200%, where every 10% indicated the relative change in corticospinal excitability during motor imagery (**Figure 2B**). A previous study reported that the difference in vividness for motor imagery affected corticospinal excitability (Moriuchi et al., 2020). Therefore, if subjects can imagine something vividly, the value of the level meter reaches over 100%. On the other hand, if subjects cannot imagine vividly, the value of the level meter will be equal to or <100%.

Corticospinal excitability was assessed in the program and immediately displayed on the level meter. For the Real-FB group, the level meter provided the real value of each trial. However, for the Sham-FB group, the level meter randomly provided a non-related value of the actual corticospinal excitability. The bar displayed by the program is set to vary randomly between 0 and 200%. Therefore, it is considered that it was displayed nearly evenly for the Sham-FB group. The subjects were provided with sufficient prior explanation by the experimenter about the mechanism of the level meter used for feedback. In addition, we explained that the closer to Good, the better the motor imagery, and the closer to Poor, the worse the motor imagery.

TMS and MEP Recording

Surface EMG signals were amplified and filtered at a bandwidth of 5–3,000 Hz using a digital signal processor (Neuropack Sigma MEB-5504, Nihon Kohden; Tokyo, Japan). Analog outputs from a single processor were digitized at a sampling rate of 2,000 Hz and saved to a computer for offline analysis using an A/D converter (PowerLab16/30, AD Instruments, Sydney, Australia).

At the beginning of the experiment, we identified the optimal TMS coil position for evoking MEPs in the right FDI (the

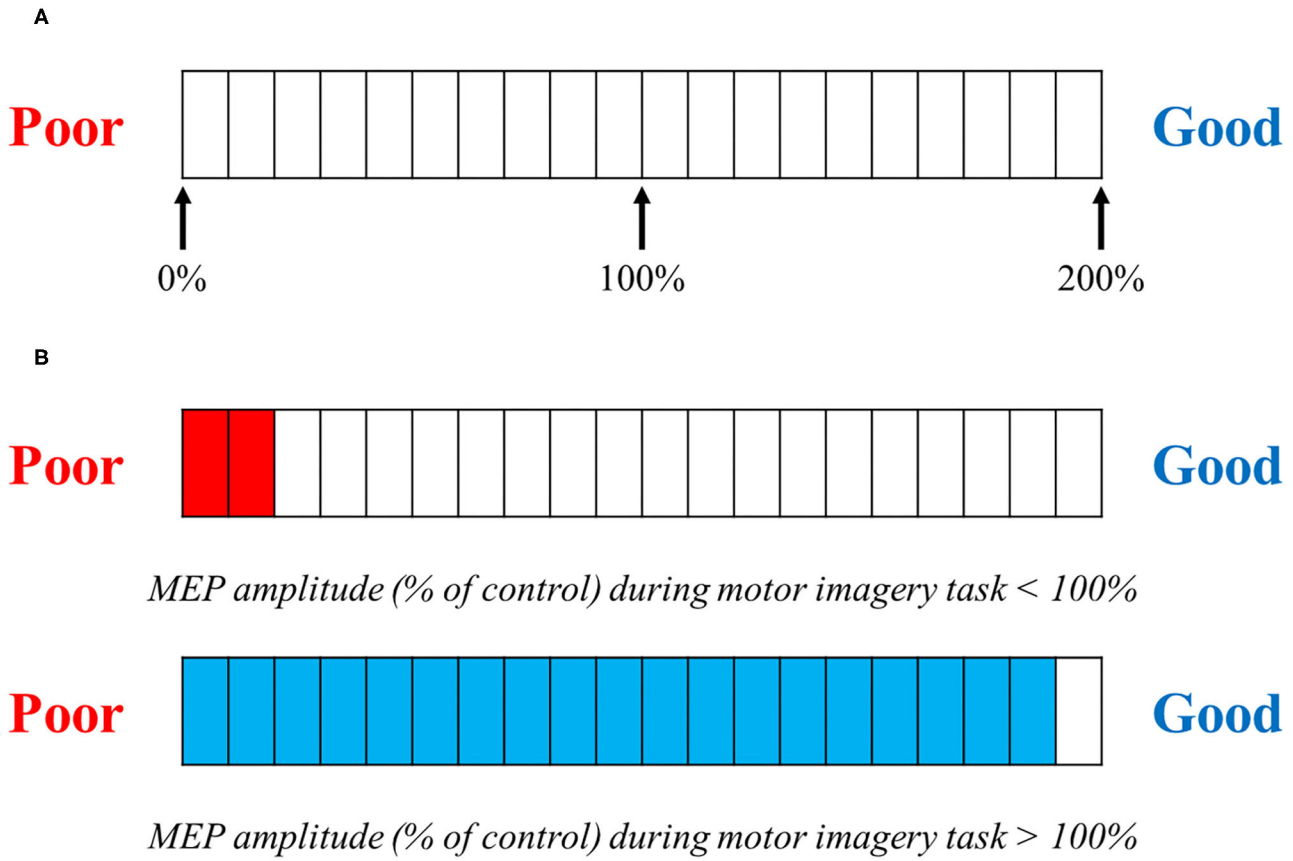

FIGURE 2 | TMS feedback. **(A)** Motor evoked potential (MEP) amplitudes compared with baseline were feedback visually on each trial. **(A)** shows the level meter displayed to the subject when providing feedback. This is represented by a graduation that ranges from 0 to 200%, in 10% increments. The value in the motor imagery task, compared with the MEP at rest, is displayed. **(B)** If the MEP amplitude size during the motor imagery task is <100% compared with that in the control (at rest) MEP amplitude size, the level meter is displayed in red; if the MEP amplitude is over 100%, the level meter is displayed in blue.

hotspot). TMS was delivered to the left M1 hotspot, marked with a pen on a swimming cap covering the scalp of each subject. TMS employed a 70 mm figure-eight coil connected to a magnetic stimulator (Magstim 200, Magstim, UK). The coil was placed tangentially to the scalp with its handle pointing backward and rotated ∼45° away from the mid-sagittal line. Care was taken to maintain the same coil position relative to the scalp throughout the experiment. The resting motor threshold (MT) was defined as the lowest stimulus intensity that evoked a MEP of at least 50 μV in amplitude, in the right FDI, in five out of 10 trials. The test stimulus intensity was set at 110–130% of the resting MT. The mean amplitude of the control MEP for the FDI was 0.5∼1.0 mV. Throughout the experiments, subjects were instructed to avoid inadvertent movements that could give rise to background EMG activity. For each muscle in each trial, the 20 ms period preceding TMS triggering was checked for background EMG activity.

Evaluation

An assessment of performance and vividness for motor imagery was conducted before and after the intervention of mental practice using TMS feedback. Performance assessment was based on how far the target point and the cursor deviated, when the subjects pressed the switch button in the coincidence timing task. Subjects were given 20 trials and we evaluated how many images were displaced with respect to where the target point and the cursor coincided. Calculation of the number of errors was incorporated into the program and could be performed automatically. The maximum value of the error was 37, which was calculated from the target point.

To rate the vividness of the subjects' motor imagery, the subjects were asked to complete a self-evaluation test on a visual analog scale (VAS). Subjects marked a location on a 100-mm horizontal line, the two ends of which were labeled "0 = None at all" and "100 = Very vivid image," according to the vividness of the imagery they imagined (Martin and Ulrike, 2006; Ikeda et al., 2012).

Experimental Procedure

We conducted 20 trials of performance evaluation of actual movement in both groups (pre-evaluation). We then measured the MEP amplitude at rest. Subsequently, motor imagery training of pressing the switch, was carried out to ensure vividness of

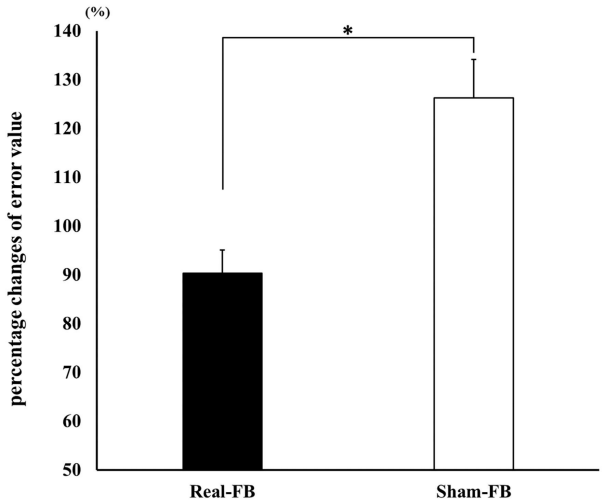

FIGURE 3 | Change in motor performance. Percentage change in the error values (mean ± SE) in each feedback group. *$p < 0.05$.

TABLE 1 | Error value and percentage change of error values for each group.

		Pre	Post
Real-FB group	Error value	42.3 ± 15.9	38.9 ± 16.9
	Percentage changes of error value	90.4 ± 16.6	
Sham-FB group	Error value	35.2 ± 11.8	43.8 ± 15.2
	Percentage changes of error value	126.3 ± 27.6	

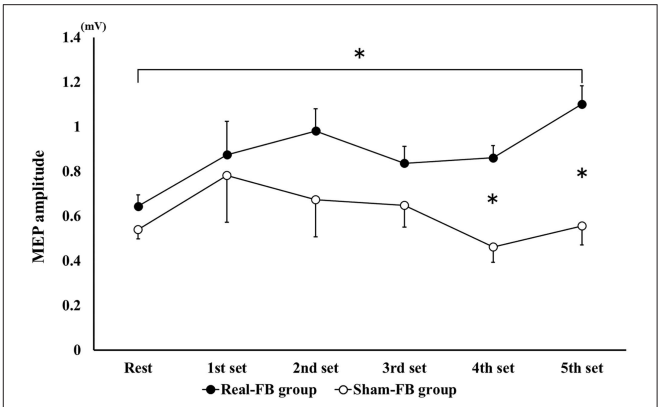

FIGURE 4 | MEP amplitude change in each set during the motor imagery task. Changes in MEP amplitude (mean ± SE) for each feedback group. *$p < 0.05$.

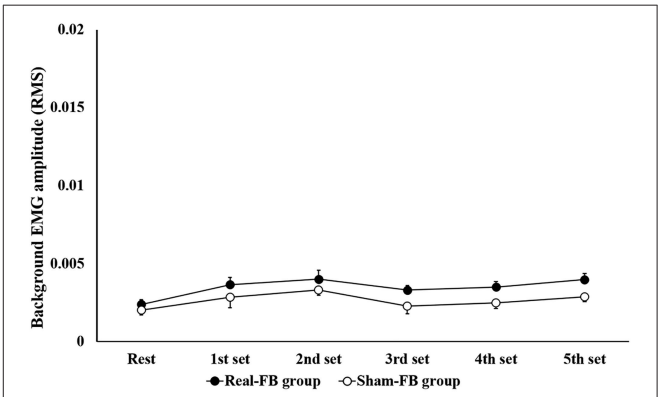

FIGURE 5 | Background EMG amplitude in each set during the motor imagery task. Changes in root mean square of the background EMG amplitude (mean ± SE) for each feedback group.

the motor imagery of the subject, and the VAS was used to evaluate the vividness of the subjective motor imagery (pre-evaluation). We then performed a motor imagery task as a mental practice using TMS feedback across five sets (total 100 trials), with 20 trials being one set. After the experimental task, both groups were again evaluated by VAS (post-evaluation), and the performance evaluation of actual movement was conducted for 20 trials (post-evaluation). The two groups were compared and analyzed.

Data and Statistical Analysis

We compared performance improvement (percentage change of error values), MEP, and changing vividness of motor imagery (percentage change of VAS scores) between the Real-FB group and Sham-FB group. The error value and VAS score were calculated using the following equation: [(the error value of 20 trial or VAS score of the post-test—the error value of 20 trial or VAS score of the pre-test)/the error value of 20 trial or VAS score of the pre-test × 100+100]. An independent *t*-test was used to examine group differences in performance improvement. Furthermore, if a background EMG was found, the data of the trial were rejected. The MEP amplitude (peak-to-peak) was measured in every trial. The data were analyzed statistically using two-way analysis of variance (ANOVA), with the factors "group" (Real-FB vs. Sham-FB), and "trial sets" (rest, 1st−5th sets). The background EMG activities (with each TMS trial data represented as the root-mean-square (RMS) amplitude of the 20 ms prior to the TMS trigger) of right FDI muscles were analyzed using two-way repeated-measure ANOVA, with the factors "group" (Real-FB vs. Sham-FB), and "trial sets" (rest, 1st−5th sets). When a main or interaction effect was found in "trial sets," a *post-hoc* analysis was conducted using Dunnett's test. On the other hand, if the main or interaction effects was found in "group," an independent *t*-test was performed to examine group differences for each set.

In all analyses, a *p*-value of < 0.05 was considered statistically significant. All analyses were performed using statistical analysis software (SPSS version 22.0, IBM, USA).

RESULTS

Change in Motor Performance

First, a two-way ANOVA was performed in a total of 20 trials using the error value for each trial. The results of the two-way

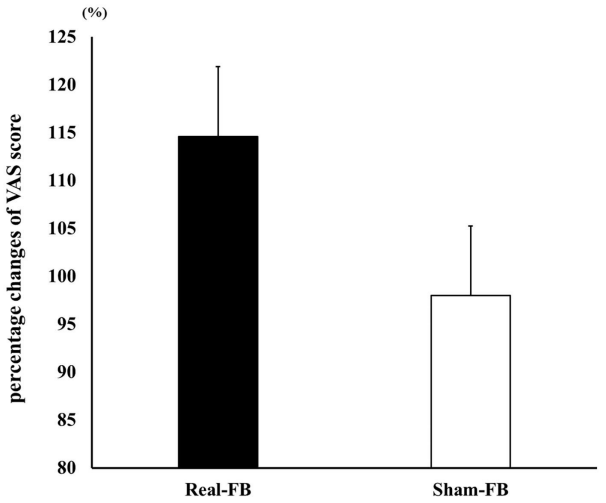

FIGURE 6 | Percentage change in VAS score. Percentage change in the VAS score (mean ± SE) in each feedback group.

ANOVA for "group" (Real-FB vs. Sham-FB) and "evaluation point" (pre-evaluation vs. post-evaluation) showed that there were significant main effects for "group" and "evaluation point" and a significant interaction. A Box's M test confirmed that p = 0.556; the observed covariance matrix of the dependent variable was equal between the two groups.

Figure 3 shows the motor performance (± standard error) change in both groups. A significant difference was observed in the percentage change of the error values between the Real-FB group and the Sham-FB group. The motor performance uses the errors in 20 trials, thus, a lower value means a better performance. The percentage change in error values was 100% or less in the Real-FB group and 100% or more in the Sham-FB group. In other words, this shows that the timing error decreased in the Real-FB group and increased in the Sham-FB group. **Table 1** shows the error value and percentage change of error values, in each group.

Change in MEP Amplitude During Mental Practice

Subjects in the Real-FB group had a >100% MEP compared to rest MEP, with the 1st set corresponding to 116/240 trials, 2nd set corresponding to 142/240 trials, 3rd set corresponding to 125/240 trials, 4th set corresponding to 136/240 trials, and 5th set corresponding to 164/240 trials. Among individuals, individuals achieved more than 100% of MEP compared to rest MEP in about 30/100–80/100 trials. **Figure 4** shows the change in the mean MEP amplitude (± standard error) in both groups. The two-way ANOVA showed a significant main effect for "trial sets" and "group." Dunnett's *post-hoc* test revealed that there was a significant difference between the rest set and the 5th set of MEPs. Moreover, an unpaired *t*-test between groups of Real-FB group and Sham-FB group found no significant difference in the MEP amplitude at rest, but a significant difference was observed in MEP amplitudes in the 4th and 5th sets ($p < 0.01$). A Box's M test confirmed that $p = 0.458$; the observed covariance matrix of the dependent variable was equal between the two groups. **Figure 5** shows the changes in the RMS background EMG amplitude (in both groups. The two-way ANOVA showed no significant main effect and interaction for "trial sets" and "group" of the background EMG.

Change in the Vividness (VAS) of Subjective Motor Imagery

Figure 6 shows the change in VAS (± standard error) in both groups. The results of the two-way ANOVA showed no significant interaction between groups and trials. A Box's M test confirmed that $p = 0.736$; the observed covariance matrix of the dependent variable was equal between the two groups. Furthermore, there was no significant difference in the percentage change in VAS scores; however, there was a tendency for improvement in the Real-FB group's VAS score in the "evaluation point" ($p = 0.059$). **Table 2** shows the VAS score and percentage change of VAS values of each groups.

DISCUSSION

The purpose of this study was to clarify whether the effect of mental practice is enhanced when providing neurofeedback based on TMS-induced MEP as an index. In order to clarify the effect of TMS feedback, we divided the subjects into two groups; the Real-FB group which received a feedback MEP amplitude as an index and the Sham-FB group which received feedback values not related to MEP amplitude. The two groups were then compared, and a significant difference was observed in the percentage change of error values between the Real-FB group and the Sham-FB group. Furthermore, the MEP was significantly different between the groups in the 4th and 5th sets. On the other hand, there were no significant differences found in VAS scores. However, there was an improvement tendency between pre- and post-mental practice in the Real-FB group.

Change in Motor Performance

In this study, we used the coincidence timing task, which involved pressing a button by index finger abduction. As a result, there were significant differences in the percentage change of error values. Shenghong et al. (2020) reported that the effect of neurofeedback training during simple motor imagery was only significant in the real-feedback group but not in the sham group. Moreover, the previous study used real-time fMRI neurofeedback-guided motor imagery based on contralateral M1 hand area blood oxygen level dependent (BOLD) signals in healthy subjects and found positive correlations between contralateral M1 activation and performance changes in the motor imagery task as an isometric force precision grip task (Blefari et al., 2015). In other words, subjects with stronger contralateral M1 activation during motor imagery may benefit more from mental practice. These findings support the result of the present study that performance was improved by using MEP amplitude and reflected the excitability of the

TABLE 2 | VAS score and percentage change of VAS values of each groups.

		Pre	Post
Real-FB group	Score (mm)	70.2 ± 12.3	80.4 ± 17.8
	Percentage changes of VAS value (%)	114.6 ± 25.2	
Sham-FB group	Score (mm)	71.3 ± 11.0	70.0 ± 14.6
	Percentage changes of VAS value (%)	98.0 ± 25.2	

corticospinal tract including the M1. However, we examined the short-term performance change in only 100 trials. In previous studies on the effectiveness of mental practice, researchers examined the effect of mental practice on short-term performance change with the hand sequence task, most of which examined the effects within weeks to months (Yasushi et al., 2010; Frenkel et al., 2014; Avanzino et al., 2015; Di Rienzo et al., 2015). Therefore, we think it is necessary to verify the long-term intervention effects of feedback using TMS.

Change in MEP Amplitude During Mental Practice

In this study, there were significant main effects in "trial sets" and "group"; there was a significant difference between rest and the 5th set of MEPs in the Real-FB group. Moreover, a significant difference was observed in MEP amplitudes at the 4th and 5th sets ($p < 0.01$).

Therefore, it was suggested that M1 excitability during mental practice is kept higher in the Real-FB group than in the Sham-FB group. Such a result may have been obtained potentially because in the Real-FB group, true feedback of M1 excitability in motor imagery is accurate feedback. As in the present study, Mihara et al. used NIRS to assess brain activity feedback near the contralateral premotor cortex during motor imagery in a real-FB group. They reported that cerebral cortex activity was increased centered on the contralateral premotor cortex but decreased near the dorsolateral parietal association cortex. Furthermore, operant conditioning, which provides the size of MEP feedback, shows that participants can self-modulate their own brain state (for example, by providing feedback according to the MEP size, MEP could be increased for UP training sessions and conversely decreased for DOWN training sessions) (Kathy et al., 2018). In this study, we thought that the MEP during MI in the Real-FB group could be maintained at a high value by feedback of the MEP as a bar.

In contrast, in the Sham-FB group, it is thought that confusion occurred because it was difficult to judge the correctness of the motor imagery itself through introspection of the motor imagery and the gap of the feedback result. Mihara et al. (2012) reported that under sham conditions, subjects could feel uncertain and lose confidence in kinesthetic imagery with incorrect feedback, which could mislead the subjects. In this study, it is possible that the feedback was not stable, such as in the form of Good or Poor feedback, even though the motor imagery was performed in the Sham-FB group. In addition, there is a possibility that the timing of the motor imagery may be questionable, or anxiety may have been caused whereby the motor imagery may not have been created; it is thought that MEP decreased due to confusion.

Based on the above observations, it was suggested that the MEP amplitude-based feedback used in this study could maintain high MEP during MI and may enhance the effect of mental practice.

Change in Vividness of Subjective Motor Imagery

In this study, subjective motor imagery vividness was evaluated using the VAS. As a result, there was no significant difference in the percentage change in VAS score. However, there was an improvement tendency between pre- and post-mental practice in the Real-FB group.

A feedback study using NIRS reported by Mihara et al. (2012) showed that subjective motor imagery vividness was significantly higher in the Real-FB group than in the Sham-FB group. Unfortunately, although there was a tendency, we could not show a statistically significant difference in this study. However, as mentioned above, there was a significant difference between the two groups in the MEP amplitude in the motor imagery task. In the Real-FB group, a high MEP was maintained in the 5th set, and it was reported that MEP is highly related to the vividness of subjective motor imagery (Moriuchi et al., 2020). Therefore, we considered that a tendency to improve in the Real-FB group VAS score was observed. Moving forward, we think that it is necessary to examine long-term intervention effects as well as performance changes.

Limitations

Referring to the study of Mihara et al. (2012), we compared two groups, the Real-FB group that received feedback on the MEP amplitude as an index and the Sham-FB group that received feedback values that were not related to the MEP amplitude. However, this study design does not show the difference in effect from the case where feedback is not given. Searching for studies that verified the effects of other neurofeedback, we found that studies that set groups that do not provide feedback, as a control group (deCharms et al., 2005), or those that adopted a region other than the target region, or a signal from a third party for feedback of the sham-FB group (Subramanian et al., 2011; Sitaram et al., 2012; Young et al., 2014), have also been reported. Taking these reports into consideration, setting a group to not receive feedback as a control group, could have shown an effect of feedback using TMS on mental practice. In addition, as mentioned above, this study merely examined the effect of short-term mental practice on healthy subjects. In the future, to clarify effective methods of mental practice in rehabilitation, it is necessary to investigate the change in performance by long-term intervention settings and examinations for stroke patients, for example.

Clinical Implications

Mental practice using fMRI and NIRS is considered to be difficult to perform in clinical terms from the viewpoint of constraint and mobility. We hypothesized that performing mental practice using TMS would be more feasible to use in clinical settings. As a result of this study, a significant difference was observed in the percentage change of error values between the Real-FB group and the Sham-FB group. Furthermore, there was a significant difference between the rest set and the 5th set of MEPs. Recent studies on mental practice using neurofeedback have reported that accurate feedback of brain status can maintain high vividness of motor imagery and performance improvement was observed. Similar to these findings, in this study, maintenance of increased MEP amplitude was observed in the Real-FB group compared with the resting amplitude. It seems that mental practice could be performed while maintaining the vividness of the high motor imagery corrected by feedback of M1 excitability; mental practice using TMS seems to be effective. In this study, we examined only the short-term effects; however, we will consider that a similar performance improvement as in fMRI and NIRS studies would be observed by verifying the long-term effects.

In addition, changes in M1 excitability are also being evaluated in various TMS-based studies at all stages from the acute phase to the chronic stage, after stroke (Cicinelli and Traversa, 1997; Escudero et al., 1998; Delvaux et al., 2003; van Kuijk et al., 2008; McDonnell and Stinear, 2017; Mooney et al., 2020). In other words, although there are restrictions such as consciousness level, since the MEP amplitude can be derived at any stage after stroke, we consider that neurofeedback using MEP amplitude can be used at any stage of stroke. Regarding the use of this method in a clinical setting, we couldn't verify the effect of giving feedback in patients only with the results of this study, so we considered that this method is inadequate for use in a clinical setting. However, it was suggested that giving real feedback could maintain the increased MEP amplitude, compared with the resting amplitude in healthy subjects; therefore, with mental practice while giving real feedback using TMS, mental practice can be carried out while maintaining higher motor imagery vividness, which may be recognized as an improvement in function.

CONCLUSION

Feedback using MEP amplitude, induced by TMS as an index, suggested the possibility of enhancing the effect of mental practice because enhanced M1 excitability during mental practice was observed. Thus, in future studies, it is necessary to verify the comparison with the control group and long-term effects of intervention.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The local ethics committee of Nagasaki University Graduate School of Biomedical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

DM, TH, and KS conceived and designed the experiments. TM, DM, YI, KF, and WM performed the experiments. TM, MM, and TH analyzed the data. TS and JN created the experimental program. DM, TM, and TH drafted the manuscript. All authors contributed to the article and approved the finalized submitted version.

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No Impact of Stochastic Galvanic Vestibular Stimulation on Arterial Pressure and Heart Rate Variability in the Elderly Population

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Objective: Noisy galvanic vestibular stimulation (nGVS) is often used to improve postural stability in disorders, such as neurorehabilitation montage. For the safe use of nGVS, we investigated whether arterial pressure (AP) and heart rate vary during static supine and slow whole-body tilt with random nGVS (0.4 mA, 0.1–640 Hz, gaussian distribution) in a healthy elderly population.

Methods: This study was conducted with a double-blind, sham-controlled, cross-over design. Seventeen healthy older adults were recruited. They were asked to maintain a static supine position on a bed for 10 min, and the bed was tilted up (TU) to 70 degrees within 30 s. After maintaining this position for 3 min, the bed was passively tilted down (TD) within 30 s. Real-nGVS or sham-nGVS was applied from 4 to 15 min. The time course of mean arterial pressure (MAP) and RR interval variability (RRIV) were analyzed to estimate the autonomic nervous activity.

Result: nGVS and/or time, including pre-/post-event (nGVS-start, TU, and TD), had no impact on MAP and RRIV-related parameters. Further, there was no evidence supporting the argument that nGVS induces pain, vertigo/dizziness, and uncomfortable feeling.

Conclusion: nGVS may not affect the AP and RRIV during static position and whole-body tilting or cause pain, vertigo/dizziness, and discomfort in the elderly.

Keywords: stochastic resonance, galvanic vestibular stimulation, arterial pressure, heart rate variability, RR interval variability, whole-body tilting

INTRODUCTION

Non-invasive brain and cranial nerve stimulations are useful treatment modalities for disorders, such as neurorehabilitation montage (Adair et al., 2020). Galvanic vestibular stimulation (GVS) (Fitzpatrick and Day, 2004) is often used both to test vestibular function and as a treatment (Lopez, 2016; Sluydts et al., 2020). It has recently been reported that transcranial stochastic galvanic stimulation of the vestibular nerve improves the stability of posture in elderly people (Fujimoto et al., 2016) and patients with a vestibular disorder (Fujimoto et al., 2018). Noisy GVS (nGVS) (Wuehr et al., 2017) supposedly improves body balance by modulating the threshold of motor response through vestibular input (Fujimoto et al., 2016, 2018; Inukai et al., 2018b). The vestibular system contributes to autonomic regulation (Yates et al., 2014; McCall et al., 2017), and sinusoidal GVS can impact the blood pressure (BP) (Tanaka et al., 2012) and heart rate (HR) variability (Tanaka et al., 2014). A ballistic head-up tilt in the spine capable of activating the vestibular complex system can induce BP and HR variability, and this effect is further facilitated by sinusoidal GVS (Tanaka et al., 2014), indicating that sinusoidal GVS facilitates the vestibular autonomic reflex (Radtke et al., 2003). A strong square wave pulse GVS given to a conscious rat was observed to obscure the arterial pressure (AP) response (Abe et al., 2008). Furthermore, electrical stimulation over and around the ear might stimulate the vagus nerve (Adair et al., 2020) and induce changes in BP and HR-variability (Balasubramanian et al., 2017). However, there is no concrete evidence to prove that nGVS, which is used to improve body balance in the elderly population, can affect BP, HR, and HR variability in the elderly population. Therefore, in this study, we investigated the effect of nGVS on BP and HR, including HR variability, in a healthy elderly population in a static supine position to obtain evidence for ensuring safety when using nGVS.

The ability of nGVS to improve stability and body balance depends on the instability in the upright standing posture before the stimulation (Inukai et al., 2018b), indicating that the effect of nGVS may change depending on the position of the head or/and whole-body movement. The modulation of BP and HR-variability during whole-body movement, including the change in the head direction in response to gravity, by nGVS should be probed (Tanaka et al., 2014). However, both BP and HR are modulated during/after a voluntary movement (Lawrence et al., 2015). Therefore, we used a moving bed, which can change the angle of the whole-body passively, to investigate the effect of nGVS on BP and HR-variability during whole-body movement while preventing voluntary movement.

The primary vestibular nerve projects to the rostral ventrolateral medulla in the brain stem, and the activation of the vestibular nerve by head movement induces the vestibular autonomic reflex, which majorly includes modulation of BP and HR (Yates et al., 1995). A previous study in cats revealed that whole-body tilting up (from a horizontal level to 60°) induces a 30% change in blood flow volume in the leg about 20 s after the tilt-up (TU) (Yavorcik et al., 2009). This finding indicates that BP and HR modulation may occur 20 s after stimulating positional change for the whole-body. Therefore, in this study, we measured and analyzed BP and HR for 20 s or more before/after the event (TU, tilt-down (TD), and GVS-onset).

BP is modulated by autonomic nerve activity (Guyenet, 2006). Autonomic nerve activity can be estimated by measuring the variation in RR-intervals available from electrocardiography (ECG) (Kon et al., 2006; Kuwahata et al., 2011). The coefficient of variation of RR intervals (CVRR) is determined by dividing the standard deviation of RR intervals by the mean RR interval (Kon et al., 2006), and it is considered to reflect the activity of the sympathetic nerve (Kuwahata et al., 2011). A previous study performed a power spectral analysis of the RR-interval (Pagani et al., 1986) to elucidate the effect of head-up tilting on autonomic nerve activity (Tanaka et al., 2014). The high frequency (HF) component was considered to reflect the activity of the parasympathetic nerve; the low frequency (LF) component reflected the activity of both sympathetic and parasympathetic, and the LF/HF ratio reflected the activity of the sympathetic nerve (Pagani et al., 1986). Based on these findings, the CVRR, LF, HF, and LF/HF ratio were calculated to estimate the activity of the sympathetic and/or parasympathetic nerve in nGVS, TU, and TD.

Bilateral bipolar square wave direct current GVS may induce slight pain at the site of electrode placement after stimulation with 1.5 mA intensity in healthy and stroke patients (Utz et al., 2011; Dlugaiczyk et al., 2019). Further, GVS may induce a sensation of vertigo/dizziness (Dlugaiczyk et al., 2019) and nausea (Quinn et al., 2015), and these sensations might appear in a patient with a vestibular disorder (Chen et al., 2020). Therefore, data on the degree of pain, vertigo/dizziness, and uncomfortable feeling were collected from all participants after examination using the nGVS montage.

Based on the above background knowledge, we aimed to probe the hypothesis that nGVS does not modulate AP and HR variability in elderly people during static and dynamic postural change without pain, vertigo/dizziness, and discomfort. We analyzed the time course of the mean arterial pressure (MAP), HR, CVRR, LF, HF, and LF/HF in Sham-/Real-nGVS, TU, and TD in a healthy elderly population. Further, the degree of pain, vertigo/dizziness, and level of discomfort were analyzed for each stimulation condition.

MATERIALS AND METHODS

Participants

Before conducting the experiments, the appropriate sample size was estimated by power analysis using software G*power (Version 3.1.9.4) (Faul et al., 2007) for a two-way analysis of variance (ANOVA). The effect size f was set to 0.4, alpha error probability to 0.05, beta error probability to 0.95, number of groups to 2, and number of measurements to 6. The calculated total sample size was 12; therefore, 18 subjects were recruited with an anticipation of a 30% dropout. One subject was precluded from the experimental analysis because the MAP could not be measured.

All participants were recruited through the Daito silver human resource center in Daito city. The inclusion criteria were: (1) age > 65 years, (2) no history of cardiovascular or

otolaryngological disease, (3) no history of neurological disease, including epilepsy, and (4) ability to understand and agree to the contents of this experiment. Seventeen healthy elderly people (13 males, mean age: 74.5 ± 6.0 years, mean height: 160.7 ± 6.5 cm, mean weight: 58.8 ± 8.3 kg) participated in the study. During registration, the participants did not report any history of epilepsy or other neurological diseases, which are especially related to the vestibular system. The Ethics Committee of Shijonawate Gakuen University approved the experimental procedures (Approval Code: 19-5), and the study was conducted according to the principles and guidelines of the Declaration of Helsinki (World Medical, 2013). All participants provided written informed consent.

Experimental Procedure

This was a double-blinded, sham-controlled, cross-over design study. The participants and assessors were blinded to the nGVS condition, both before and after the experiment. The participants joined a Real-nGVS condition trial and a Sham-nGVS condition trial with an interval of more than 3 weeks between the two. The stimulation condition was selected randomly.

Figure 1A shows the experimental setup. The participant was in a supine position on a flatbed in a head-up tilting position (UA-790/795, OGwellness, Japan). The head, pelvis, and both lower limbs of the participants were fixed to the bed using belts. Both feet were in contact with the footplate. A sensor and transmitter for electrocardiography (ECG) were set around the center of the chest. A cuff for measuring the AP was set to the left index finger. The electrode for GVS was set to the bilateral mastoid process.

Figure 1B shows the experimental procedure. The participant was asked to relax with eyes closed during the experiment and was held in a supine position for 10 min. After 10 min, the bed was tilted up from the flat (horizontal) level to 70° in 30 s (TU) (Theodorakis et al., 2003) without announcing the start of TU. This semi-standing position was held for 3 min. After a 3 min hold in this semi-standing position, the bed was tilted down to a flat (horizontal) level within 30 s (TD). The Real-nGVS or Sham-nGVS was delivered from the 4th min to the 15th min. The AP and ECG were recorded during the experiment.

After experimenting in both nGVS conditions, the degree of pain, vertigo/dizziness, and discomfort around the ear were measured with a Visual Analog Scale (VAS) (Heller et al., 2016). In case of no sensation, the participant was asked to report 0 mm. For maximum sensation, the participant was asked to report 100 mm. For a middle-grade sensation between no sensation and the maximum, the participant was asked to report 50 mm.

AP Measurement

AP was continuously measured using Finometer MIDI (Finapress Medical Systems B.V., Netherlands) and BeatScope Easy (v02.10 build 004, Finapress Medical Systems B.V., Netherlands) connected to a personal computer. This medical device and software are used to diagnose orthostatic dysregulation (Romero-Ortuno et al., 2013) in Japan.

Figure 1A shows the setup for AP measurement. The upper limbs were held on the side of the body, and the cuff and sensor were attached to the distal phalanx of the left index finger (Jagomagi et al., 2010). The sampling rate was set to 0.5 Hz. The MAP was calculated using a built-in-formula as follows: MAP = (systolic AP + 2*diastolic AP)/3. For the time-course analysis of MAP (Leonetti et al., 2004), the mean of MAPs for 10 s was calculated from the start of the event (GVS, TU, and TD) to −20, −10, 10, 20, 30, 40, 50, and 60 s.

ECG and RR Interval Analysis

We used a real-time heart rate (HR) variability analysis program MemCalc/Bonaly Light (GMS Co., Ltd., Tokyo) and a wireless biometric sensor and transmitter (RF-ECG, transmit frequency: 2.4 GHz, MemCalc, GMS Co., Ltd., Tokyo) to measure the ECG. Two Ag/AgCl electrodes (Blue Sensor EKG Snap Electrode, overall dimensions: 48 × 57 mm, Ambu, Baltorpbakken, Denmark) were attached to the left anterior portion of each subject's chest, and the ECG signals were wirelessly transmitted to a personal computer.

Based on the ECG data obtained, beat-to-beat RR intervals were linearly interpolated depending on the subjects' HR followed by resampling at 1.2 Hz to obtain an equidistant time series using the MemCalc/Bonaly Light (GMS Co. Ltd., Tokyo) analysis program. The HR (number of heartbeats in 1 min) was calculated from the RR intervals in each sample. A power spectral analysis was performed within a 30 s time window using the same analysis program, and the power of LF component (0.04–0.15 Hz, LF, s^2) and HF component (0.15–0.4 Hz, HF, s^2) was calculated (Pagani et al., 1986). A moving average of the power was calculated and updated every 2 s, and as a representative value, the mean LF power and HF power was calculated for 10 s from the start of the event (GVS, TU and TD) to −20, −10, 10, 20, 30, 40, 50, and 60 s, similar to the MAP for time-course analysis.

The changes in LF and HF were used to measure the changes in sympathetic and parasympathetic nerve activity, respectively. The changes in HF were considered a reflection of the modulation in the sympathetic nerve activity, based on a report that LF/HF reflects the modulation in sympathetic nerve activity (Pagani et al., 1986). A previous study performed a beat-by-beat time-course analysis of LF, HF, and LF/HF and the significant modulation of these parameters at approximately 10 beats and 10 s before and after the intervention (Chouchou et al., 2019). Therefore, a 10 s time window can be considered appropriate for this study to analyze the RR interval.

nGVS

nGVS was performed as previously reported (Matsugi et al., 2020a,b). nGVS was delivered via Ag/AgCl surface electrodes (Blue Sensor EKG Snap Electrode, overall dimensions: 48 × 57 mm, Ambu, Baltorpbakken, Denmark) affixed to the right and left mastoid processes. A DC-STIMULATOR PLUS (Eldith, NeuroConn GmbH, Ilmenau, Germany) was used to deliver random nGVS to the primary vestibular nerve. For nGVS in the stimulation mode, a random level of current was generated for every sample to be used as "noise" (sample rate, 1280 samples/s) (Moliadze et al., 2012; Inukai et al., 2018b), and the intensity was set at 0.4 mA, which was previously reported as an effective intensity for the elderly (Inukai et al., 2018a). Statistically, the random numbers were normally distributed

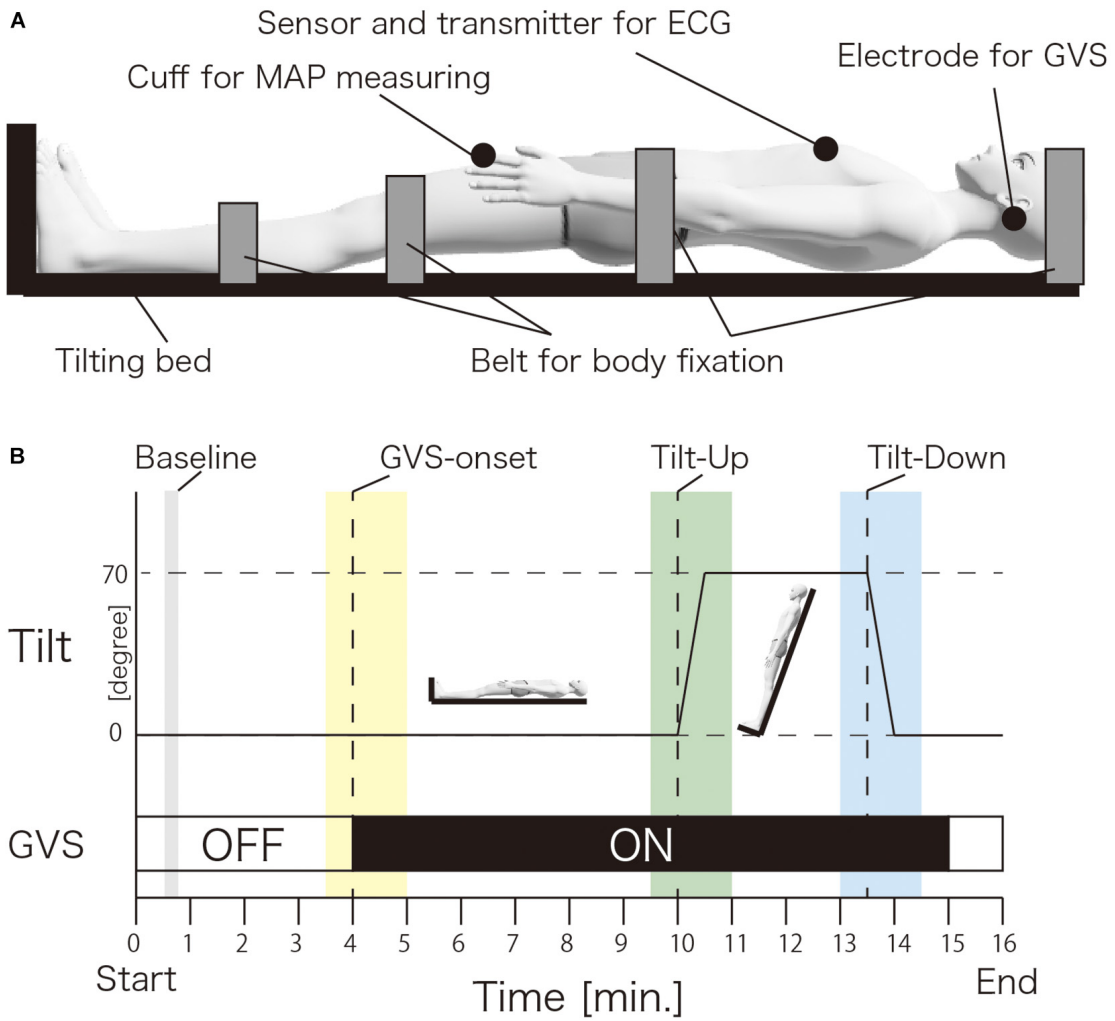

FIGURE 1 | Experimental setup **(A)** and procedure **(B)**. **(A)** The participant was in a supine position on a flatbed. The head, pelvis and both lower limbs were fixed by belts. The electrode for galvanic vestibular stimulation was set to bilateral mastoid processes. The sensor and transmitter for the electrocardiography were set around the center of the chest. A cuff for measuring the arterial pressure was set to the left index finger. **(B)** The left vertical line indicates the degree of tilt. The bottom horizontal line indicates the time. The dotted vertical lines indicate the GVS-onset, Tilt-up start and Tilt-down start. The gray, yellow, green, and blue vertical lines indicate the baseline, GVS-onset, Tilt-up, and Tilt-down measurement time window. The horizontal white line indicates GVS-off and black line indicates GVS-on. MAP; mean arterial pressure, ECG; electrocardiography, GVS; galvanic vestibular stimulation.

over time, the probability density followed a Gaussian bell curve, and all coefficients featured a similar size for the frequency spectrum in this mode. A waveform was applied with 99% of the values between −0.5 and + 0.5 mA, with only 1% of the current level within ± 0.51 mA. The stimulation time was set to 660 s without being ramped up and down. For the sham stimulation, direct current stimulation was applied at an intensity of 0 mA (sham-nGVS).

Statistical Analysis

The MAP/baseline, HR/baseline, CVRR/baseline, LF/baseline, HF/baseline, and LF/HF/baseline were calculated. Next, we discarded the outlier data-points with mean ± 5 times of standard deviation (SD) in MAP, HR, CVRR, LF, HF, and LF/HF in GVS-on, TU, TD in sham and real-nGVS condition.

Bayesian hypothesis test can assist in the interpretation of null results, and this method was used in the standalone analyses (Dienes et al., 2018; Hoekstra et al., 2018; Matsugi et al., 2019; van Ravenzwaaij et al., 2019; Keysers et al., 2020). Bayesian Wilcoxon signed-rank was used to estimate the evidence supporting the hypothesis that the VAS score for pain, vertigo/dizziness, and discomfort is not significantly different. To test the hypothesis that stimulation and time does not affect MAP, HR, CVRR, LF, HF, and LF/HF, a Bayesian Two-way Repeated Measures analysis of variance (ANOVA) (Stimulation * Time) was performed while assuming equal distribution, based on a previous study (Matsugi et al., 2019). In case equal distribution was not assumed, we used Bayesian One-way Repeated Measures ANOVA. If parametric one-way ANOVA was used after assumption check for using one-way ANOVA, Kruskal-Wallis test, as a non-parametric test, was

applied to test the difference. The alpha level was set to 5% for the assumption test and Kruskal-Wallis test.

For the Bayesian test, posterior odds were corrected for multiple testing by fixing a prior probability that the null hypothesis holds good across all comparisons at 0.5 (Westfall et al., 1997). Statistical analyses were performed using the JASP software (version 0.12.2; University of Amsterdam, Amsterdam, Netherlands) (Team, 2019; Keysers et al., 2020). The most common prior model that was default in the software was selected, based on the methods reported previously (Hoekstra et al., 2018; Matsugi et al., 2019), and r scale fixed effects = 0.5, r scale random effects = 1, and r scale covariates = 0.354 were used.

We estimated the predictive performance of two competing hypotheses: the null hypothesis, wherein stimulation and time had no effect, and the alternative hypothesis wherein stimulation and time had an effect (Hoekstra et al., 2018). The Bayes factor (BF) (Hobbs and Carlin, 2008) allows researchers to quantify the evidence in favor of the null hypothesis (Zaslavsky, 2013; Hoekstra et al., 2018). If BF_{10} is > 3, it is considered that there is more than substantial evidence for accepting the alternative hypothesis (Hoekstra et al., 2018). In contrast, if BF_{10} is < 1, it is believed that there is no evidence for accepting the alternative hypothesis (Hoekstra et al., 2018). Further, if $3 < BF_{10} < 1$, it is considered that there exists mixed evidence supporting null and alternative hypotheses.

RESULTS

Seventeen elderly participants completed all the experiments, and their data were used for the analysis. Before the examination, data from one participant was not included because the MAP could not be measured (see section "Materials and Methods"). No adverse effects necessitating the stoppage of the study were observed during or after all the trials.

Table 1 shows the result of VAS for pain, vertigo/dizziness, and discomfort. Only 1 participant reported very slight vertigo/dizziness (Sham: 7 mm, Real: 2 mm) and discomfort (Sham: 3 mm, Real: 3 mm). The participant reported that these sensations occurred at the start of TU for some seconds in both Sham and Real-nGVS conditions. The BF_{10} for vertigo/dizziness and discomfort were 0.34 and 0.36, respectively. In contrast, a Bayesian Wilcoxon test could not be conducted for pain because all the values were 0 in Sham- and Real-nGVS conditions. This indicates that nGVS was conducted in the subthreshold of sensation.

Figures 2A–L shows the time-course of MAP, HR, CVRR, LF, HF, and LF/HF. The assumption test for two-way ANOVA revealed that all conditions were not distributed equally between the two groups. Bayesian one-way ANOVA could not be applied to LF in TU in Sham condition, HF in TU in sham and real condition, and LF/HF in GVS-on, TU, and TD in sham condition, and TD in real nGVS condition. For these parameters, the Kruskal-Wallis test was applied, and no significant difference was observed between the time. In another condition, Bayesian one-way ANOVA was applied, and BF_{10} was observed to be > 1. These results indicate that there was no change in all parameters between both sham- and real-nGVS conditions. All data and results of the analyses along with code in JASP are available online in data storage[1].

[1]http://dx.doi.org/10.17632/8gx48tmvjr.2

TABLE 1 | Visual Analog Scale for pain, vertigo/dizziness, and uncomfortable feeling.

	Sham			Real		
Subject	**Pain**	**Vertigo/ dizziness**	**Uncomfortable feeling**	**Pain**	**Vertigo/ dizziness**	**Uncomfortable feeling**
1	0	0	0	0	0	0
2	0	0	0	0	0	0
3	0	0	0	0	0	0
4	0	0	0	0	0	0
5	0	0	0	0	0	0
6	0	7	3	0	2	3
7	0	0	0	0	0	0
8	0	0	0	0	0	0
9	0	0	0	0	0	0
10	0	0	0	0	0	0
11	0	0	0	0	0	0
12	0	0	0	0	0	0
13	0	0	0	0	0	0
14	0	0	0	0	0	0
15	0	0	0	0	0	0
16	0	0	0	0	0	0
17	0	0	0	0	0	0

The unit is in mm.

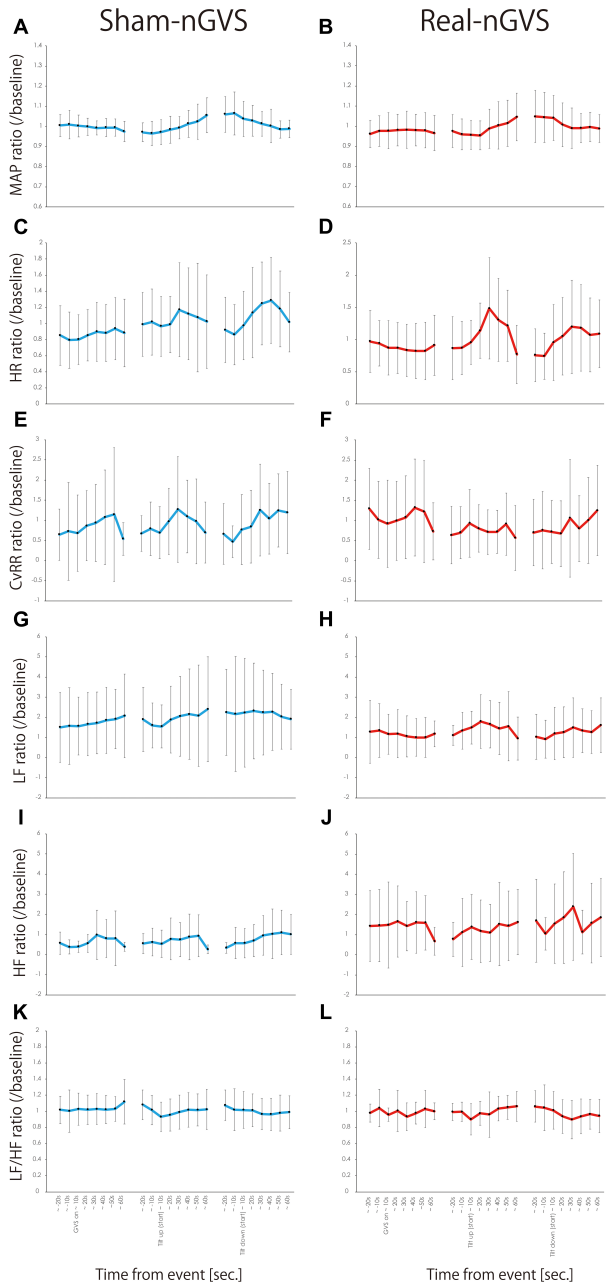

FIGURE 2 | MAP **(A,B)**, HR **(C,D)**, CVRR **(E,F)**, LF **(G,H)**, HF **(I,J)**, and LF/HF **(K,L)** in Sham-nGVS (left line) and Real-nGVS (right line). The circles indicate the mean values per baseline, and error bar indicate standard deviation. MAP, mean arterial pressure; HR, heart rate; CVRR, coefficient of variation in RRI; LF, low-frequency component; HF, high-frequency component.

DISCUSSION

To probe the hypothesis that nGVS does not modulate AP and HR variability without harmful sensation in a static position and/or dynamic postural change, we analyzed the time-course of MAP, HR, CVRR, LF, HF, and LF/HF immediately before/after GVS-onset, TU, and TD in 17 healthy elderly people. The result of the Bayesian one-way ANOVA and Kruskal-Wallis test showed no evidence supporting the hypothesis that nGVS could change MAP and RR-related parameters in GVS-onset, TU, and TD. Further, the Bayesian Wilcoxon test result showed no evidence supporting the hypothesis that nGVS induces pain, vertigo/dizziness, and discomfort. These findings indicate that stochastic noisy electrical stimulation to the vestibular nerve may not impact the AP, HR, and HR variability without pain, vertigo/dizziness, and a sensation of discomfort.

The potential effects of nGVS has been explored through basic research on noise stimulation. The stochastic resonance phenomenon of enhanced non-linear response to an input signal has been reported to be involved in the effects of nGVS (Douglass et al., 1993). In the vestibular system, a particular level of mechanical noise on the semicircular canals can improve the performance of the vestibular system in peripheral sensory processing (Flores et al., 2016). nGVS-induced modulation of the threshold of the vestibulospinal response (Matsugi et al., 2020a) is thought to contribute to body sway changes (Matsugi et al., 2020b; Sprenger et al., 2020). The vestibular system contributes to autonomic regulation (Yates et al., 2014; McCall et al., 2017); therefore, nGVS might modulate AP and HR variability. However, our study results indicate nGVS has no effect on AP and HR variability during the static and dynamic postural change in older adults.

We observed that nGVS with 0.4 mA intensity has no effect on AP and HR variability without pain, vertigo/dizziness, and uncomfortable feeling in elderly people. A previous study reported that nGVS with 0.4 mA intensity can improve postural stability of community-dwelling elderly people without serious harm (Inukai et al., 2018a). Both of these findings are consistent with each other, supporting the fact that nGVS exerts no harmful effect. Sinusoidal GVS reportedly alters the RR interval variability in young adults and modulates the vestibular autonomic response of AP (Tanaka et al., 2012, 2014). Further, previous studies have reported that GVS may induce a sensation of vertigo/dizziness (Dlugaiczyk et al., 2019) and nausea (Quinn et al., 2015). One possible reason for the difference in AP response and harmful sensation may originate from the stimulation type, which is an electrical stimulation with a noisy and sinusoidal waveform. Another possible reason is the difference in intensity (that is 2 and 0.4 mA). Non-invasive brain stimulation effect depends on the electrical stimulation pattern (Finisguerra et al., 2019). The nGVS effect on AP and HR variability may depend on the stimulation pattern.

In this study, the pain was not induced by nGVS in any participant. A previous study reported that the pain threshold for direct current electrical stimulation is approximately 4 mA in humans (Lobel et al., 1998). A square-wave pulse GVS of 3 mA for 200 ms with an electrode over the bilateral mastoid process, similar to that in this study, did not induce pain (Matsugi et al., 2017; Okada et al., 2018), and continuous direct current GVS of 1 mA induced a slight sensation in about 25% of young adult participants (Nakamura et al., 2020). On the contrary, nGVS of 1 mA intensity using the same stimulator as in our study did not induce pain in 30 young adults in a static prone position (Matsugi et al., 2020a) and 17 young adults in a static standing

position (Matsugi et al., 2020b). Therefore, an intensity of 0.4 mA for nGVS might be below the threshold of sensation, and based on these findings, we believe that nGVS at 0.4 mA cannot induce pain in the elderly population. However, one female participant suffered from slight vertigo/dizziness and discomfort. However, this participant reported that this sensation was felt in both examinations and only a few seconds after the TU started. Therefore, vertigo/dizziness and a sensation of discomfort may not be associated with stimulation and are possibly caused by the head movement accompanying the TU. In vertigo/dizziness induced by the change in head position, the rate of occurrence in women is about 2 times more than that in men, and the prevalence of this condition in the elderly population is about 10% (von Brevern et al., 2007). Perhaps this female participant had an undiagnosed, mild Benign Positional Paroxysmal Vertigo (Mandala et al., 2019).

There were some limitations in this study. We observed no change in all parameters immediately before/after the event; however, we cannot deny the possibility that there was modulation at other times, such as the time from 60 s after the GVS to just before the TU. Next, the effect of nGVS on the balance depends on the postural instability before stimulation (Inukai et al., 2018b). However, we did not examine the effect of nGVS on postural stability in these participants. Therefore, we cannot exclude the possibility that not all participants responded to nGVS. Further studies are needed to correlate the degree of effect of nGVS on postural stability, AP, and HR. Moreover, there was no change in MAP in the sham-nGVS condition in TU in our results; therefore, we cannot reject the possibility that nGVS modulates AP and HR variability in elderly people with cardiocirculatory disorders, such as orthostatic hypotension, arrhythmia, and heart failure. In line with the results, we believe that our findings are limited to a healthy elderly population. Another limitation is that our TU method is acceptable to test for orthostatic hypotension; however, the speed of TU may weakly induce the modulation of AP in healthy elderly people. There is a possibility that the effect of nGVS on AP and HR variability may manifest with faster TU and TD.

Regarding the clinical significance of this study, our result provides evidence for the safety of using nGVS in elderly people. While previous studies report the effectiveness of nGVS (Fujimoto et al., 2016, 2018, 2019; Inukai et al., 2018a,b), they provide no evidence on its impact on AP and HR variability. In future studies, the effect of nGVS on AP and HR variability in patients with cardiocirculatory disorders, such as orthostatic hypotension, arrhythmia, and heart failure, should be tested further to ensure safety.

In conclusion, we observed that stochastic electrical stimulation of the vestibular nerve does not affect AP and HR variability in healthy elderly population during static position and dynamic passive postural change, without any harmful sensation. These findings may provide evidence for the safety of nGVS use in elderly people to improve postural stability.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: http://dx.doi.org/10.17632/8gx48tmvjr.2.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the Shijonawate Gakuen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM, KN, and TS: conceptualization. AM, TS, YO, NM, JN, SD, KO, and YT: data curation. AM and KN: formal analysis and methodology. AM, KN, TS, YO, and KN: funding acquisition. KN: resources, software, and supervision. AM, TS, NM, JN, SD, KO, and YT: validation. AM: visualization and writing—original draft. AM, KN, TS, YO, NM, JN, SD, KO, and YT: writing—review and editing. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Excitability of the Ipsilateral Primary Motor Cortex During Unilateral Goal-Directed Movement

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Introduction: Previous transcranial magnetic stimulation (TMS) studies have revealed that the activity of the primary motor cortex ipsilateral to an active hand (ipsi-M1) plays an important role in motor control. The aim of this study was to investigate whether the ipsi-M1 excitability would be influenced by goal-directed movement and laterality during unilateral finger movements.

Method: Ten healthy right-handed subjects performed four finger tapping tasks with the index finger: (1) simple tapping (Tap) task, (2) Real-word task, (3) Pseudoword task, and (4) Visually guided tapping (VT) task. In the Tap task, the subject performed self-paced simple tapping on a touch screen. In the real-word task, the subject tapped letters displayed on the screen one by one to create a Real-word (e.g., apple). Because the action had a specific purpose (i.e., creating a word), this task was considered to be goal-directed as compared to the Tap task. In the Pseudoword task, the subject tapped the letters to create a pseudoword (e.g., gdiok) in the same manner as in the Real-word task; however, the word was less meaningful. In the VT task, the subject was required to touch a series of illuminated buttons. This task was considered to be less goal-directed than the Pseudoword task. The tasks were performed with the right and left hand, and a rest condition was added as control. Single- and paired-pulse TMS were applied to the ipsi-M1 to measure corticospinal excitability and short- and long-interval intracortical inhibition (SICI and LICI) in the resting first dorsal interosseous (FDI) muscle.

Results: We found the smaller SICI in the ipsi-M1 during the VT task compared with the resting condition. Further, both SICI and LICI were smaller in the right than in the left M1, regardless of the task conditions.

Discussion: We found that SICI in the ipsi-M1 is smaller during visual illumination-guided finger movement than during the resting condition. Our finding provides basic data for designing a rehabilitation program that modulates the M1 ipsilateral to the moving limb, for example, for post-stroke patients with severe hemiparesis.

Keywords: transcranial magnetic stimulation, intracortical inhibition, ipsilateral primary motor cortex, laterality, goal-directed movement

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INTRODUCTION

Transcranial magnetic stimulation (TMS) is one of the tools for the non-invasive examination of the excitability of human primary motor cortex (M1). Previous TMS studies have revealed that the activity of the ipsilateral to the active hand (ipsi-M1) plays an important role in motor control (Tinazzi and Zanette, 1998; Buetefisch et al., 2014; Reid and Serrien, 2014). For example, when TMS is applied over the ipsi-M1 to elicit motor evoked potentials (MEPs) in a resting hand, their amplitudes are larger during complex than during simple movements (Tinazzi and Zanette, 1998; Morishita et al., 2011, 2012). Meanwhile, MEP amplitude was found to be larger during the observation of grasping than during the observation of simple arm movement (Fadiga et al., 1995). Furthermore, observation of actual grasp was demonstrated to induce larger MEPs than observation of pantomimed (or meaningless) grasp, which was defined as an intransitive movement not associated with a particular goal (Enticott et al., 2010). Despite these findings indicating that the corticospinal excitability can be modulated by the goal-directedness of a movement, its effect on the ipsi-M1 excitability has not been elucidated fully.

In addition, laterality has also been shown to affect the excitability of M1. For instance, in right-handed individuals, the threshold for muscle activation was lower in the right arm compared with the left arm (Triggs et al., 1994). Also, intracortical inhibition has been found to be stronger in the left than in the right M1 during a resting state (Civardi et al., 2000; Hammond et al., 2004; Hammond and Garvey, 2006). Furthermore, the excitability of the ipsi-M1 was larger for the tasks performed with the non-dominant left hand than for those executed with the dominant right hand (Ziemann and Hallett, 2001; Ghacibeh et al., 2007; Morishita et al., 2011; Reid and Serrien, 2014). Therefore, it is necessary to examine whether laterality influences the effect of goal-directedness on ipsi-M1 activity.

Accordingly, in this study we tested the hypothesis that ipsi-M1 excitability and intracortical inhibitory circuits would be influenced by goal-directedness and laterality during unilateral finger movements. If goal-directed movements can enhance the activity of the ipsi-M1, these movements may be applicable to stroke rehabilitation, since increased activity of the ipsilesional M1 is crucial for successful rehabilitation in hemiparetic post-stroke patients (Carey et al., 2005; Yamada et al., 2013).

MATERIALS AND METHODS

Subjects

Ten healthy volunteers (7 males and 3 females, 21.4 ± 1.26 years, mean ± SD) participated in this study. All participants provided written informed consent prior to the experiment, which was conducted in accordance with the principles of the Declaration of Helsinki. All participants were right-hand dominant (Laterality Quotient 99.0 ± 3.16, mean ± SD) according to the Edinburgh Handedness Inventory (Oldfield, 1971). The protocol was approved by the Ethics Committee of Niigata University of Health and Welfare.

Experimental Procedure

The subject was seated with their arms resting comfortably on a table and was asked to perform four finger tapping tasks with the dominant and non-dominant index fingers using a touch screen (FDX10001T, EIZO, Japan), which was placed on the table.

Unilateral Finger Tapping Task

(1) Simple tapping (Tap) task: The subject performed self-paced simple tapping (five taps) on a touch screen.

(2) Real-word task: A real five-letter word (e.g., apple) and nine letters arranged in a 3 × 3 matrix were displayed on the touch screen, and the subject tapped the letters on the screen one by one to create the displayed word. We selected simple English words of five letters (taught in junior high school in Japan) to exclude possible differences in letter search time and tapping speed. Because there was a movement goal (i.e., creating a word), this task was considered to be goal-directed, as compared to the Tap task (Gordon et al., 1998).

(3) Pseudoword task: The subject tapped the letters to create a pseudoword (e.g., gdiok) in the same manner as in the Real-word task, i.e., the subject tapped the letters on the screen to create the displayed pseudoword (not on a whim). Although creating a word (Real-word task) was considered to be more goal-directed than simple tapping (Tap task), the number of muscles involved in these tapping tasks was different as the Real-word task involved wrist movements. In addition, visual stimuli were used in the Real-word task. To control these factors, the Pseudoword task was included: the subject produced approximately the same amount of movement as in the Real-word task; however, the word was less goal-directed.

(4) Visually guided finger tapping (VT) task: Nine buttons (3 × 3 matrix) on the touch screen turned yellow one by one, and the subject was required to touch the illuminated button. This task to simply follow the illumination was considered to be less goal-directed than the Pseudoword task. **Figure 1** and **Table 1** show the experimental settings and the characteristics of each task, respectively. Before starting the experimental session, we explained the procedure of the finger tapping tasks to the subject and asked her/him to practice the tasks. The subject practiced each motor task for approximately 5 min, respectively. The examiner confirmed that the subject was able to perform the word creation task and the visually guided finger tapping task without missing a tap. During the tapping tasks, except for the Tap task, the keys to be tapped (target keys) were randomly presented on the screen. Experimental tasks with the dominant and non-dominant hands were tested in separate sessions on different days, and the order of these tasks were randomized among the subjects. The tasks were spaced by resting periods of at least 1 min.

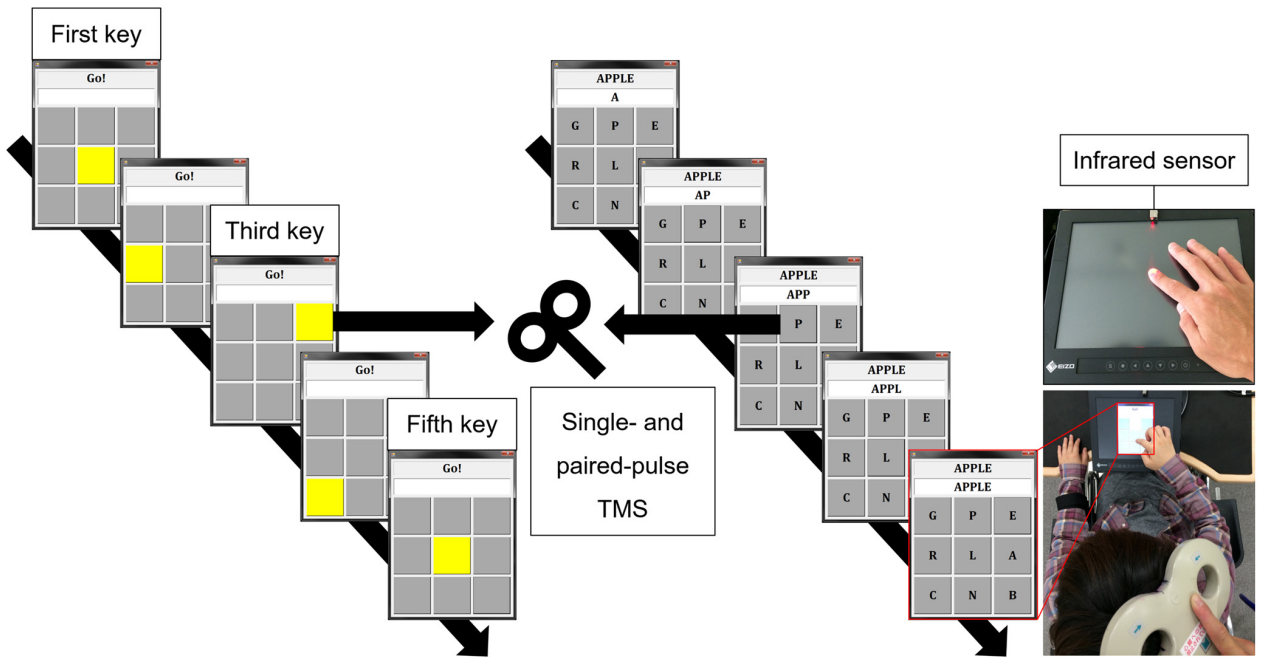

FIGURE 1 | Experimental setting. Tap task **(upper right)**: self-paced finger tapping on a touch screen. VT task **(left)**: pressing the illuminated button (yellow key) one by one. Real-word task **(middle)**: creating a real word (e.g., apple) by tapping letters one by one. Infrared sensor and touch on screen (third key) were used as TMS trigger for the Tap task and the other tasks, respectively. TMS: transcranial magnetic stimulation, VT: visually guided finger tapping task.

Electromyography Recording

Surface electromyography (EMG) was recorded from the first dorsal interosseous (FDI) muscles of the dominant right hand and the non-dominant left hand using disposable silver-silver chloride surface electrodes. The recording and reference electrodes were placed over the muscle belly and tendon, respectively. The EMG signals were amplified (×100; DL-140, 4 assist, Japan), band-pass filtered between 5 and 1,000 Hz, digitized at 4k Hz using an analog-to-digital converter (PowerLab, AD Instruments, Australia), and stored in a personal computer for off-line analysis (LabChart 7, AD Instruments, Australia). Prior to the experimental sessions, we examined the maximal voluntary contraction (MVC) of the FDI muscle. The subject was asked to gradually increase the force from zero to maximum over 3 s and to maintain maximal force for 3 s by abducting the index finger. The subjects received visual feedback and verbal encouragement during MVC. The subject performed three trials with resting for at least 90 s between trials (Maluf et al., 2005; Kirimoto et al., 2014).

TABLE 1 | Characteristics of unilateral finger tapping tasks.

	Finger movement	Wrist movement	Goal-directedness
Resting condition	−	−	−
Tap task	+	−	±
VT task	+	+	+
Pseudoword task	+	+	++
Real-word task	+	+	+++

Transcranial Magnetic Stimulation Measurement

Transcranial Magnetic Stimulation was delivered using a figure-of-eight coil (external loop diameter of 95 mm) connected to two stimulators (Magstim 200, Magstim, United Kingdom). The coil was manually fixed tangentially to the sculp with the handle pointing in a posterolateral direction at an angle of 45° from the midsagittal line. The subject wore a swimming cap, and the outer edge of the coil was marked with a pen so that the position of the coil would not change during the experiment. The site where weak TMS consistently evoked the largest MEP in the FDI muscle was determined as the motor hotspot. The resting motor threshold (rMT) was defined according to international guidelines (Rossini et al., 2015). RMT was defined as the lowest stimulus intensity was required to elicit MEP amplitude (>50 μV) in about 50% of 10 consecutive stimuli. During the experimental tasks (four finger tapping tasks) and a rest control condition, single- and paired-pulse TMS were applied to the M1 ipsilateral to the hand performing the task to measure corticospinal excitability and intracortical inhibition in the resting FDI muscle. Specifically, when the subject performed the tapping task with the dominant right hand (*active*), TMS was applied to the right (ipsilateral) M1 and MEPs were recorded from the left (*resting*) FDI muscle, and when the subject performed the tapping task with the non-dominant left hand (*active*), TMS was applied to the left (ipsilateral) M1 and MEPs were recorded from the right (*resting*) FDI muscle. The intensity of single-pulse TMS to measure corticospinal excitability was set to elicit MEP with a peak-to-peak amplitude of about 1

mV during resting condition and fixed across conditions in each subject. Paired-pulse TMS is widely used to evaluate non-invasively human M1 excitability. Application of a subthreshold conditioning stimulus (CS) followed by a suprathreshold test stimulus (TS) after short interstimulus interval (ISI) of 1–5 ms reduces the test MEP amplitude (Kujirai et al., 1993; Hanajima et al., 1998). Moreover, a suprathreshold CS with a long ISI of 50–150 ms similarly reduces amplitude of test MEP (Valls-Sole et al., 1992; Wassermann et al., 1996). Due to difference in ISI, these inhibitory phenomena are known as short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI), respectively. SICI is likely mediated by γ-aminobutyric acid (GABA) type A ($GABA_A$) receptors, and LICI by GABA type B ($GABA_B$) receptors (Ziemann et al., 1996a; Nakamura et al., 1997; McDonnell et al., 2006). Further, they are thought to be of cortical origin (Nakamura et al., 1997). For both the SICI and LICI, the intensity of CS was adjusted to obtain a conditioned MEP amplitude of about 50% of the unconditioned MEP at rest to avoid a floor effect (Cirillo et al., 2011; Uehara et al., 2013b). The intensity of TS was set to elicit MEP with a peak-to-peak amplitude of about 1 mV during resting condition and motor tasks, respectively. The detail of TMS intensity is summarized in **Table 2**. ISI between CS and TS was 3 and 100 ms for SICI and LICI, respectively (Hanajima et al., 1998; Sanger et al., 2001). Single- and paired-pulse TMS were delivered randomly in the same session using a pulse stimulator (Random double-pulse system, 4 assist, Japan). The infrared sensor (FS-N11MN, Keyence Corporation, Japan) and the touch screen (third key press) were used as TMS trigger for the Tap task and the other tasks (**Figure 1**). TMS was applied once every five taps, and the subject tapped a total of 180 times until 36 MEPs (12 for each) were recorded in the *resting* FDI. Each task was divided into two sessions (90 taps for each) to avoid fatigue. Letter searching time may differ when the subject taps first or second key press, and tapping speed may vary when the subject executes the fourth and fifth key presses. Therefore, we used the third key press as TMS trigger to avoid these factors.

Data and Statistical Analysis

Electromyography from the *active* FDI muscle (tapping hand) was rectified and normalized to the MVC value (% MVC). We then calculated the mean EMG activity in *active* and *resting* FDI muscles during a period of 100 ms just prior to the TMS pulse. In paired-pulse TMS, the mean EMG activity in both FDI muscles was calculated during a period of 100 ms just prior to the CS. We also calculated the peak-to-peak amplitude of MEP. SICI and LICI were expressed as the ratio of the conditioned MEP amplitude to the unconditioned MEP amplitude. A MEP ratio less than 1 indicated inhibition, whereas a MEP ratio greater than 1 indicated facilitation. All data were expressed as mean ± SEM. Two-way repeated-measures analysis of variance (ANOVA) was performed to examine the effects of laterality (dominant and non-dominant hands) and to evaluate the impact of the different conditions (Resting condition, Tap task, VT task, Pseudoword task, and Real-word task). The sphericity of the data was tested by the Mauchly's test, and the Greenhouse-Geisser corrected significance values were tested when sphericity was not met. Bonferroni's correction for multiple comparisons was used for post hoc analysis. A value of $p < 0.05$ was considered statically significant for all analyses. The effect size for each ANOVA was calculated using eta squared (η^2) (Cohen, 1988).

RESULTS

Table 3 shows the amplitude of EMG activity in the *active* FDI muscle during the unilateral finger tapping tasks. The EMG activity was around 20% MVC for all the tasks, and there was no significant difference between them. **Table 4** shows the amplitude of EMG activity in the *resting* FDI muscle during the resting condition and the motor tasks. Two-way repeated-measures ANOVA on the amplitude of EMG activity in the *resting* FDI muscle for SICI showed a significant main effect of laterality (Laterality; F (1,90) = 9.66, p = 0.003, η^2 = 0.090, condition; F (4,90) = 1.70, p = 0.35, η^2 = 0.042, interaction; F (4,90) = 2.06, p = 0.11, η^2 = 0.031). Similarly, LICI showed significant main effect of laterality (Laterality; F (1,90) = 13.36, p = 0.001, η^2 = 0.117, condition; F (4,90) = 0.98, p = 0.42, η^2 = 0.034, interaction; F (4,90) = 1.77, p = 0.14, η^2 = 0.062).

Figure 2 shows the representative MEPs. **Figure 3A** shows MEP amplitude in the *resting* FDI muscle following single-pulse TMS. Two-way repeated-measures ANOVA on single-pulse MEP amplitude revealed no main effect or interaction between laterality and condition (laterality; F (1,90) = 0.71, p = 0.40, η^2 = 0.007, condition; F (4,90) = 0.74, p = 0.57, η^2 = 0.031, interaction; F (4,90) = 0.30, p = 0.88, η^2 = 0.013).

Figures 3B,C show MEP ratio for SICI and LICI. Unconditioned MEP amplitude in the *resting* FDI muscle following single-pulse TS during unilateral finger tapping tasks performed with the dominant and non-dominant hands were comparable (non-dominant hand: Tap task 0.81 ± 0.16 mV; VT task 0.96 ± 0.13 mV; Pseudoword task 1.06 ± 0.11 mV; Real-word task 1.10 ± 0.15 mV. Dominant hand: Tap task 1.20 ± 0.23 mV; VT task 0.97 ± 0.23 mV; Pseudoword task 1.07 ± 0.28 mV; Real-word task 1.09 ± 0.21 mV). Two-way repeated-measures ANOVA on MEP ratio for SICI showed significant main effects of laterality (F (1,90) = 8.94, p = 0.004, η^2 = 0.078) and condition (F (4,90) = 2.68, p = 0.04, η^2 = 0.092). The laterality effect indicated that SICI was smaller in the right than in the left M1. Post hoc analysis revealed a significantly smaller SICI during the VT task than during the resting condition ($p < 0.05$). No interaction between laterality and condition was found (F (4,90) = 1.46, p = 0.22, η^2 = 0.051). Two-way repeated-measures ANOVA on MEP ratio for LICI showed a significant main effect of laterality (F (1,90) = 7.89, p = 0.01, η^2 = 0.066), but there was no main effect of condition (F (4,90) = 0.68, p = 0.61, η^2 = 0.026) or interaction (F (4,90) = 0.78, p = 0.54, η^2 = 0.033). The main effect of laterality indicated that LICI was smaller in the right than in the left M1.

DISCUSSION

We investigated whether excitability of the M1 ipsilateral to the active hand would be influenced by the goal-directedness of

TABLE 2 | Summary of the TMS intensity in each condition (mean ± SD, % of maximal stimulator output: %MSO).

	Single-pulse TMS		CS				TS	
	Non-dominant M1	Dominant M1	Non-dominant M1		Dominant M1		Non-dominant M1	Dominant M1
			SICI	LICI	SICI	LICI	TS	TS
Resting condition							56.8 ± 8.83	52.2 ± 7.38
Tap task							55.2 ± 9.31	52.3 ± 7.30
VT task	56.8 ± 8.83	52.2 ± 7.38	34.6 ± 5.15	53.7 ± 8.53	31.8 ± 6.14	49.7 ± 6.90	55.4 ± 8.25	52.2 ± 7.38
Pseudoword task							55.4 ± 8.25	51.7 ± 7.39
Real-word task							55.6 ± 8.40	52.0 ± 7.56

TABLE 3 | Amplitude of EMG activity in the *active* FDI muscle (tapping hand) during unilateral finger tapping tasks (mean ± SEM, %MVC).

	Non-dominant hand				Dominant hand			
	Tap task	VT task	Pseudoword task	Real-word task	Tap task	VT task	Pseudoword task	Real-word task
Single-pulse TMS	29.8 ± 5.75	19.8 ± 2.58	21.4 ± 2.98	15.7 ± 2.75	21.9 ± 3.60	21.7 ± 3.79	20.1 ± 3.75	18.8 ± 3.51
SICI	24.3 ± 4.73	18.8 ± 3.35	19.2 ± 2.14	15.3 ± 2.21	24.7 ± 3.83	19.2 ± 2.83	20.8 ± 3.48	21.1 ± 4.24
LICI	27.2 ± 5.67	23.3 ± 3.36	16.5 ± 2.67	17.4 ± 3.15	23.0 ± 4.24	22.0 ± 3.46	18.0 ± 3.44	18.1 ± 3.59

TABLE 4 | Amplitude of EMG activity in the *resting* FDI muscle during rest condition and unilateral finger tapping tasks (mean ± SEM, μV).

	Non-dominant hand					Dominant hand				
	Resting condition	Tap task	VT task	Pseudoword task	Real-word task	Resting condition	Tap task	VT task	Pseudoword task	Real-word task
Single-pulse TMS	4.56 ± 0.32	5.16 ± 0.66	4.64 ± 0.34	5.57 ± 0.88	5.24 ± 0.59	3.35 ± 0.26	4.71 ± 0.51	4.69 ± 0.59	4.23 ± 0.44	4.30 ± 0.66
SICI	4.49 ± 0.34	4.88 ± 0.45	4.78 ± 0.29	5.59 ± 0.51	4.52 ± 0.43	3.67 ± 0.42	4.52 ± 0.36	4.21 ± 0.37	3.98 ± 0.25	4.05 ± 0.41
LICI	4.76 ± 0.33	4.81 ± 0.54	4.64 ± 0.41	6.10 ± 0.80	4.46 ± 0.30	3.48 ± 0.31	4.22 ± 0.39	3.85 ± 0.34	3.76 ± 0.34	4.31 ± 0.45

the movement and laterality during unilateral finger movements using motor tasks whose goal-directedness was systematically adjusted. As a result, our findings indicated that (1) unexpectedly performing a goal-directed movement does not necessarily result in a greater reduction of intracortical inhibitory circuits in the ipsi-M1, (2) SICI in the ipsi-M1 can be smaller during visual illumination-guided finger movement as compared to the resting condition, and (3) intracortical inhibitory circuits in the ipsi-M1 is smaller in the right than in the left M1.

Effect of Goal-Directed Movement on the Ipsi-M1 Activity

Tinazzi and Zanette (1998) examined the ipsi-M1 excitability in different finger opposition tasks and found greater ipsi-M1 excitability during sequential finger opposition than during simple opposition with the third finger and thumb. In addition, Morishita et al. (2011) compared the excitability of the ipsi-M1 between fine motor (chopsticks manipulation) and pseudo-fine motor (repetitive grasping with the thumb and index and middle fingers) tasks, and revealed that the excitability of the ipsi-M1 was larger during the fine motor task. These results indicate that the excitability of the ipsi-M1 is larger during complex movements than during simple movements. Meanwhile, the corticospinal excitability was found to be larger during the observation of the goal-directed movement than during the observation of meaningless movements (Enticott et al., 2010). From this evidence, we assumed that the ipsi-M1 excitability would increase as the task becomes more goal-directed (i.e., tapping letters on a screen one by one to create a word). However, the corticospinal excitability and intracortical inhibition were not influenced by the goal-directed task in this study, and alternatively we found a smaller SICI in the ipsi-M1 during the visually guided finger tapping task compared with the resting condition. These results suggest that simple visual guidance rather than goal-directed movement is key to the modulation of SICI in the ipsi-M1.

Several studies have examined M1 excitability and SICI during cognitive tasks. For instance, in Stop Signal and Go/No-Go tasks, SICI in the contralateral M1 was demonstrated to be greater during the stop and No-Go trials than during the go trial (Sohn et al., 2002; Coxon et al., 2006; Lindberg et al., 2016). These results indicate that SICI is involved in the selection and inhibition of voluntary movements. In the present study, subjects were requested to select letters in order to create a word in the Real-word and Pseudoword tasks, and this selection requirement seemed to be much lower in the visually guided motor task. We speculate that this characteristic of the VT task affected SICI in the ipsi-M1.

Besides those cognitive task studies, several studies have examined the modulation of SICI using triple-pulse TMS. For instance, CS applied over the premotor area before the

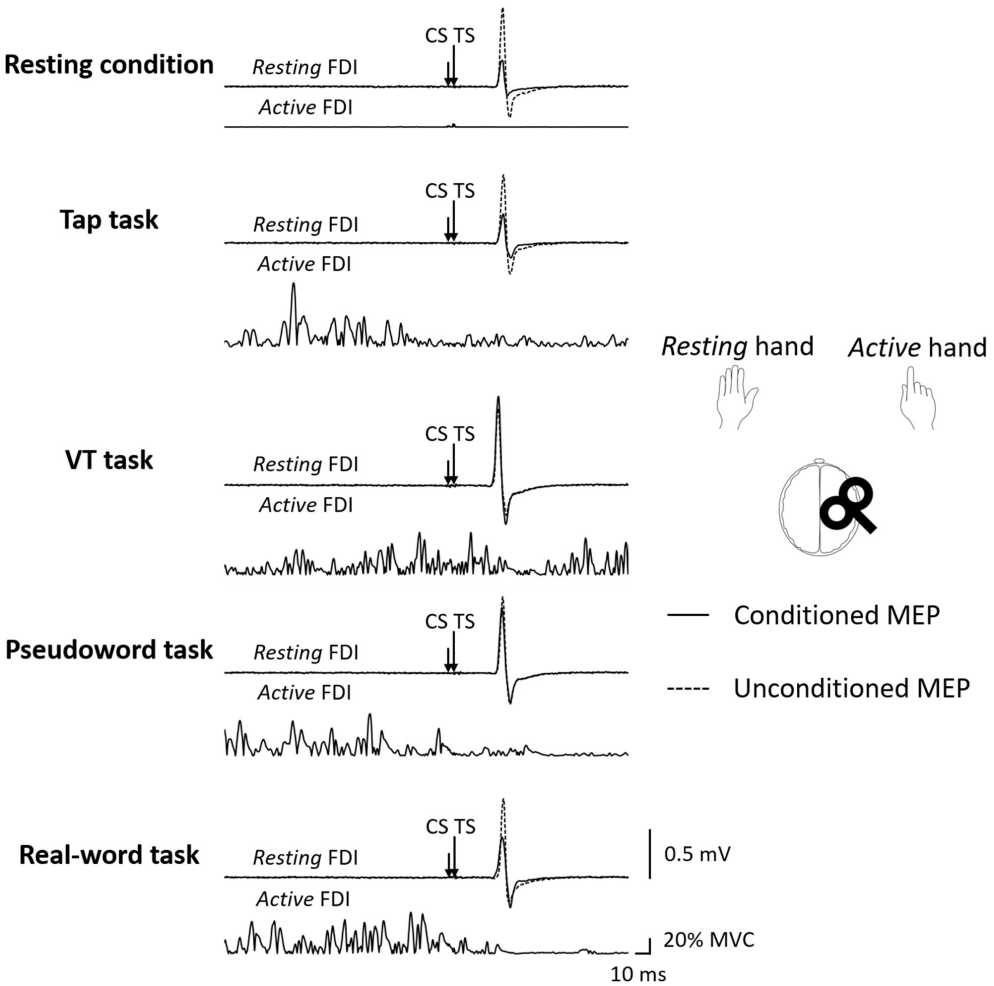

FIGURE 2 | The representative MEP waveforms evoked by paired-pulse TMS (ISI 3 ms) during each condition. The subject performed the unilateral finger tapping tasks with the dominant right hand (*active*), TMS was delivered to the ipsilateral (right) M1, and MEPs were recorded from left (*resting*) FDI muscle. CS: conditioning stimulus, FDI: first dorsal interosseous, ISI: interstimulus interval, MEP: motor evoked potential, TMS: transcranial magnetic stimulation, TS: test stimulus, VT: visually guided tapping task.

CS for SICI was found to reduce the test MEP amplitude (Mochizuki et al., 2004). Moreover, SICI was found to be reduced by the interhemispheric inhibition (IHI) that occurs between the bilateral M1s and also by the cerebellar inhibitory input (Daskalakis et al., 2002, 2004). Since the cerebellar-cortical circuit including premotor area can play an important role in externally triggered movements (Taniwaki et al., 2006), activities of the cerebellar or premotor areas may have been involved in the reduction of SICI in the ipsi-M1 during the VT task.

One possible explanation for the insignificant effect of goal-directed task could be that the influence was more evident in brain areas and networks that cannot be evaluated by single- or paired-pulse TMS. Previous brain imaging studies demonstrated that the supplementary motor area (Shibasaki et al., 1993) and the premotor area (Kawashima et al., 1998; Verstynen and Ivry, 2011) play important roles in the execution of complex finger movements. In addition, the interhemispheric connection between the bilateral somatosensory cortices and the corticocortical connections between the sensorimotor and premotor areas are involved in the control of limb movements (Bundy and Leuthardt, 2019). Thus, the connectivity between the M1 and high-order cortical regions possibly involved in goal-directed movements (Iacoboni et al., 2005) should be investigated using functional brain imaging and electroencephalography in future studies.

Laterality of Intracortical Inhibitory Circuits Within the Ipsi-M1

We found that SICI and LICI in the ipsi-M1 were smaller in the right than in the left M1. It has been reported that SICI and LICI are stronger in the left than in the right M1 during the resting state in right-handed individuals (Civardi et al., 2000; Hammond et al., 2004; Hammond and Garvey, 2006). On the other hand, results regarding the SICI in the ipsi-M1 during movements in terms of laterality have been inconsistent. Some

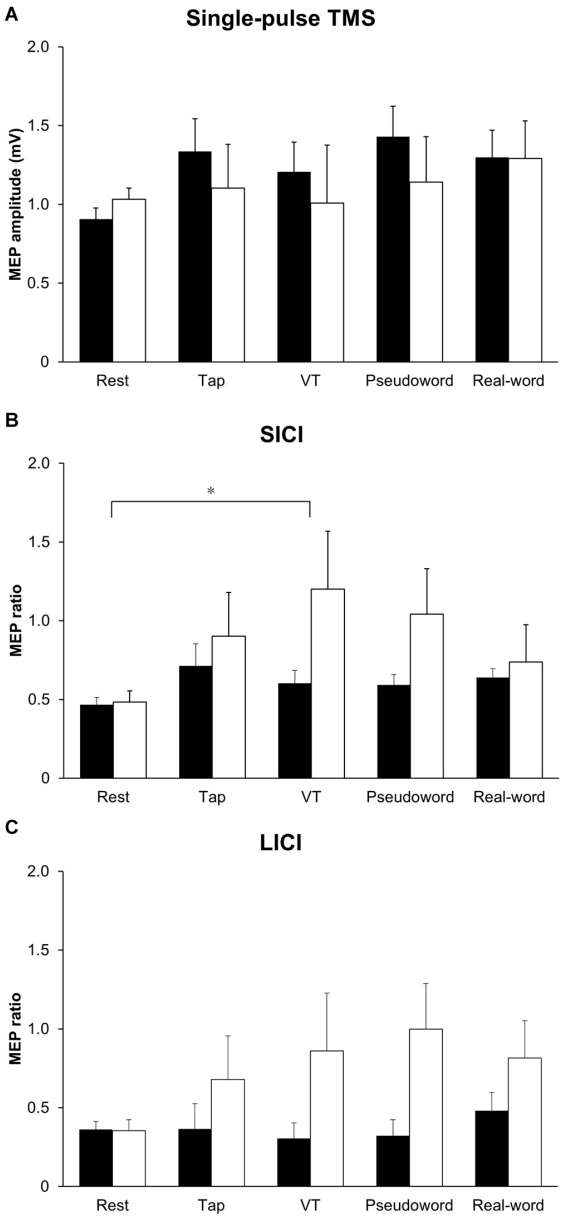

FIGURE 3 | Group data (n = 10) of **(A)** MEP amplitude in the *resting* FDI muscle following single-pulse TMS, **(B)** MEP ratio for SICI, and **(C)** MEP ratio for LICI in each condition. A MEP ratio less than 1 indicates inhibition, and a MEP ratio greater than 1 indicates facilitation. The closed bars represent the results of the non-dominant hand performance and the corresponding resting condition, and the opened bars represent the results of the dominant hand performance and the corresponding resting condition. SICI was significantly smaller in the VT task than in the resting condition (*$p < 0.05$) **(B)**. FDI: first dorsal interosseous, LICI: long-interval intracortical-inhibition, MEP: motor evoked potential, SICI: short-interval intracortical inhibition, TMS: transcranial magnetic stimulation. VT: visually guided tapping task.

studies showed reduced SICI only in the right M1 (Hinder et al., 2010; van den Berg et al., 2011), while the others showed reduced SICI only in the left M1 (Morishita et al., 2011). Since not enough research has been conducted on LICI, cross-study comparisons cannot be made in this regard. Nevertheless, our results seem to support the previous findings that intracortical inhibitory circuits are stronger in the left than in the right M1. We speculate that more complex intracortical connections in the left than in the right M1 (Amunts et al., 1996), greater dexterity in dominant than non-dominant hand (Hammond et al., 2004), and stronger IHI from left to right M1 (Netz et al., 1995) contributed to the laterality of intracortical inhibitory circuits observed in the present study.

Corticospinal Excitability

There was no difference in MEP amplitude elicited by single-pulse TMS between tasks. This indicates that corticospinal excitability was not influenced by goal-directed movement, and that the corticospinal excitability did not change in the VT task despite the finding of reduction in SICI. Corticospinal excitability depends on the balance between excitatory and inhibitory neural systems within the M1, which are distinct from the corticospinal pathway. These neural systems are thought to not only modulate corticospinal excitability but also interact with each other within the M1 (Sanger et al., 2001; Reis et al., 2008; Ni et al., 2011). Di Lazzaro et al. (2002) and Fierro et al. (2010) used repetitive TMS to examine corticospinal excitability and intracortical inhibitory circuits at rest. Meanwhile, Smyth et al. (2010) and Quinn et al. (2018) used motor tasks to measure effect of motor learning on corticospinal excitability and intracortical inhibitory circuits. In this relation, some studies have shown a decrease in SICI and no change in corticospinal excitability (Di Lazzaro et al., 2002; Smyth et al., 2010), while the others showed a decrease in both SICI and corticospinal excitability (Fierro et al., 2010; Quinn et al., 2018). Quinn et al. (2018) investigated corticospinal excitability and SICI in the forearm flexor and extensor muscles during a visuomotor task, and found that the corticospinal excitability was reduced in both the forearm flexor and extensor muscles, while SICI was reduced only in the forearm extensor muscle. It is known that inhibitory and excitatory circuits can act independently in M1 (Ziemann et al., 1996b; Liepert et al., 1998); thus, changes in SICI may not be directly related to changes in corticospinal excitability. Our findings are in line with these observations. Additionally, the effect of motor task on the ipsi-M1 activity may depend on the type of motor task. While we used a phasic tapping task, previous TMS studies that demonstrated an increase in the ipsi-M1 excitability and a decrease in SICI used a static contraction task (Muellbacher et al., 2000; Liang et al., 2008, 2014). Furthermore, Liepert et al. (2001) revealed that the ipsi-M1 excitability was larger during static contraction than phasic contraction. Therefore, the discrepancy with previous studies may be due to differences in the task/contraction type.

Long-Interval Intracortical Inhibition

Similar to the corticospinal excitability, LICI was not different between the tasks. The only study that has investigated LICI in the ipsi-M1 during unilateral finger movement was the research conducted by Uehara et al. (2013b). They reported reduced LICI in the ipsi-M1 during repetitive finger abduction paced according to auditory cues (Uehara et al., 2013b). In addition, LICI in the M1 contralateral to active hand was found to be

smaller during precision grip than during index finger abduction, and the synergic movement of the thumb and index finger along with their afferent inputs are thought to contribute to the reduction of LICI (Kouchtir-Devanne et al., 2012; Caux-Dedeystere et al., 2014). These findings possibly suggest that LICI is involved in movements requiring force control rather than in goal-directed movements.

There is a confounding factor that could affect the result of LICI. Specifically, the timing of TS for LICI was different from that of SICI. TS for single-pulse TMS and SICI was delivered immediately after the key tap, whereas TS for LICI was delivered 100 ms after the key tap. Therefore, it is possible that SICI and LICI were assessed during different cognitive and motor processes. In a study by Uehara et al. (2013a), TMS was delivered over the ipsi-M1 using a different interval from EMG onset to TMS (0–500 ms), and ipsi-M1 excitability was found to be independent of this interval when low intensity contraction (30% MVC) was used. Because the motor tasks used in this study were performed at a low intensity (approximately 20% MVC) and timing of TS was within 500 ms, it is unlikely that the timing of TS affected the excitability of the ipsi-M1.

Potential Application to Rehabilitation

Although patients with mild to moderate hemiparesis can perform exercises with the affected arm to some degree and hence have a relatively favorable clinical prognosis (Kwakkel et al., 2003), those with severe hemiparesis have poorer prognosis because of limited voluntary control (Kwakkel et al., 2003). As increased activity of the ipsilesional M1 is a key to successful rehabilitation in hemiparetic post-stroke patients (Carey et al., 2005; Yamada et al., 2013), motor exercise of the unaffected limb to enhance ipsilesional M1 activity may become one of the means to facilitate motor recovery in post-stroke patients with severe symptoms. From this perspective, our findings suggest a potential use of visual guidance to enhance the ipsilesional M1 activity. More thorough investigations will be necessary, however, to confirm this interesting possibility.

LIMITATIONS

This study has some limitations. First, there was a significant difference in EMG activity in the *resting* FDI muscle between the dominant and non-dominant hands (**Table 4**). However, these EMG activities were very small (less than 10 μV) and Cavanagh and Komi (1979) defined muscle activity as above 30 μV. Hence, background EMG was not a confounding factor for MEP results. Second, we recorded EMG activity only from the FDI muscle. The motor tasks, except for the Tap task, involved the movement of multiple joints, including the fingers and wrist. Nevertheless, MEP amplitude did not differ between the Tap task and the other motor tasks. Hence, it is unlikely that the multiple joints movement affected MEP amplitude. Third, we did not assess IHI between hemispheres. As the interhemispheric interaction can be modulated by goal-directed movements, it should be examined in a future study. Fourth, we measured SICI only with ISI of 3 ms and did not assess short-interval intracortical facilitation. A thorough examination of SICI with an ISI of 1–4 ms and short-interval intracortical facilitation may provide more detailed mechanisms. Finally, our sample size was small, and although we consider that the effect size was medium (Cohen, 1988), increasing the number of subjects may allow for a better understanding of the differences found in this study.

CONCLUSION

In conclusion, unexpectedly we found that SICI in the ipsi-M1 is smaller during visual illumination-guided finger movement than during the resting condition. Less selection requirements during the visually guided movements could be the underlying reason. The laterality of intracortical inhibitory circuits in the ipsi-M1 could be associated with hemispheric asymmetry. Our findings provide basic data for the development of a rehabilitation program that modulates the M1 ipsilateral to the moving limb, which could be used, for example, for post-stroke patients with severe hemiparesis.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of Niigata University of Health and Welfare. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

HK and TM designed the study. TM and TK performed the experiment. TM analyzed the data and wrote the initial draft of the manuscript. KY, XC, and NK assisted in the preparation of the manuscript. HK and TW edited and revised the manuscript. All authors approved the final version of the manuscript, and agreed to be accountable for all aspect of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Hemodynamic Signal Changes During Motor Imagery Task Performance Are Associated With the Degree of Motor Task Learning

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Purpose: This study aimed to investigate whether oxygenated hemoglobin (oxy-Hb) generated during a motor imagery (MI) task is associated with the motor learning level of the task.

Methods: We included 16 right-handed healthy participants who were trained to perform a ball rotation (BR) task. Hemodynamic brain activity was measured using near-infrared spectroscopy to monitor changes in oxy-Hb concentration during the BR MI task. The experimental protocol used a block design, and measurements were performed three times before and after the initial training of the BR task as well as after the final training. The BR count during training was also measured. Furthermore, subjective vividness of MI was evaluated three times after NIRS measurement using the Visual Analog Scale (VAS).

Results: The results showed that the number of BRs increased significantly with training ($P < 0.001$). VAS scores also improved with training ($P < 0.001$). Furthermore, oxy-Hb concentration and the region of interest (ROI) showed a main effect ($P = 0.001$). An interaction was confirmed ($P < 0.001$), and it was ascertained that the change in oxy-Hb concentrations due to training was different for each ROI. The most significant predictor of subjective MI vividness was supplementary motor area (SMA) oxy-Hb concentration (coefficient = 0.365).

Discussion: Hemodynamic brain activity during MI tasks may be correlated with task motor learning levels, since significant changes in oxy-Hb concentrations were observed following initial and final training in the SMA. In particular, hemodynamic brain activity in the SMA was suggested to reflect the MI vividness of participants.

Keywords: motor imagery, motor learning, oxygenated hemoglobin, ball rotation task, motor area

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Abbreviations: ANOVA, analysis of variance; BCI, brain computer interface; BR, ball rotation; deoxy-Hb, deoxygenated hemoglobin; fMRI, functional magnetic resonance imaging; KVIQ, Kinesthetic and Visual Imagery Questionnaire; MI, motor imagery; NIRS, near-infrared spectroscopy; oxy-Hb, oxygenated hemoglobin; PET, positron emission tomography; Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; ROI, region of interest; SMA, supplementary motor area; SMC, somatosensory motor cortex; TMS, transcranial magnetic stimulation; VAS, visual analog scale.

INTRODUCTION

To effectively perform motor imagery (MI), it is important to ensure the vividness of participants' MI in objective terms. MI is defined as mental rehearsal in which an individual simulates an objective action within the brain without performing actual motions, and similar brain activation caused by performing motions is observed (Jeannerod, 2001; Kimberley et al., 2006). MI allows rehearsal without performing the actual motions and has been used as a tool for practicing in the sports field (Guillot and Collet, 2008; MacIntyre et al., 2018). Performing MI repeatedly, which is called mental practice, has been used not only in the sports field, but also in the field of rehabilitation in recent years. MI can also be executed in patients who have difficulty performing motions, particularly in those with cerebrovascular disease, and it has been reported as an effective method for improving motor function (Page et al., 2001, 2011; Liu et al., 2004; Sharma et al., 2006; Riccio et al., 2010). As a treatment strategy, MI is regarded as a method for complementing motion performances due to the exhibition of similar brain activation to that caused by performing motions, which has been reported to change brain plasticity (Ruffino et al., 2017; Li et al., 2018; Yoxon and Welsh, 2019).

It is important to evaluate the effectiveness of MI to induce similar brain activation to that caused by performing motions. Participants' MI ability, clarity, means, and experience in MI tasks are factors that have been shown to affect effectiveness (Mulder et al., 2004; Mulder, 2007; Schuster et al., 2011). To assess the MI ability, questionnaires such as the Kinesthetic and Visual Imagery Questionnaire (KVIQ) (Malouin et al., 2007) and the Revised Movement Imagery Questionnaire (Gregg et al., 2010) have been developed and used in the clinical setting. The Visual Analog Scale (VAS) has been used for the assessment of the subjective clarity of MI, and it has an advantage in that the clarity can be assessed for each task of MI used in mental practice (Lotze and Halsband, 2006; Ikeda et al., 2012). However, these assessments of MI ability and MI clarity are subjective and the clarity with which the participants can perform MI cannot be objectively assessed.

Therefore, we consider that neurophysiological assessment is necessary for directing brain activation during MI similar to that during motion. There have been reports of studies on brain activity during MI using brain imaging devices such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) (Stephan et al., 1995; Ruby and Decety, 2003; Solodkin et al., 2004; Hanakawa et al., 2008). Studies using fMRI and PET showed deactivation of the primary motor cortex, and activation of the premotor cortex (PMA) and the supplementary motor area (SMA) (Hanakawa et al., 2003; Lotze et al., 2003; Cunnington et al., 2005). Previous neurophysiological studies using transcranial magnetic stimulation (TMS) have also reported excitatory changes in the primary motor cortex during MI (Kasai et al., 1997; Stinear and Byblow, 2003; Pelgrims et al., 2011). The results regarding the activation sites in the brain vary depending on the device. In addition, some devices are highly restrictive; thus, it is not easy to use such devices for assessment in actual rehabilitation settings. Although spatial resolution is inferior to PET and fMRI, near-infrared spectroscopy (NIRS) can monitor brain activation in the region of interest by devising probe placement. Therefore, we have been studying whether NIRS can be used as a neurophysiological assessment method. NIRS is highly portable and widely applicable, which allows its use during bedside care and treatment since it is less restrictive and non-invasive. Thus, it could be easily used in the field of rehabilitation. Several studies have examined brain activation during MI using NIRS and cerebral hemodynamics during MI of a tapping task (Iso et al., 2016), swallowing (Kober and Wood, 2014), and eating have been shown (Matsuo et al., 2020). In addition, several studies have aimed to increase the effect of MI by feeding the cerebral hemodynamics measured by NIRS back to patients to enhance brain activation (Mihara et al., 2012; Kober et al., 2014, 2018; Ota et al., 2020).

However, although the experience in tasks and the degree of learning have been shown to affect MI (Mulder et al., 2004; Mulder, 2007; Schuster et al., 2011), no studies have examined how much they affect the changes in cerebral hemodynamics during MI. We previously examined the performance of motions and cerebral hemodynamics during MI (Iso et al., 2016), and the effects of the dominant/non-dominant hand (Matsuo et al., 2020). The results showed an increase in cerebral hemodynamic change in the PMA and SMA, comparable to that observed during exercise. While TMS or fMRI studies have already reported the effects of experience and competence in MI tasks on the excitability of the primary motor cortex (Szameitat et al., 2007; Tsukazaki et al., 2012; Wriessnegger et al., 2014), no NIRS studies have determined such effects. Moreover, there are no NIRS studies that have examined the association between task competence and activity in the SMA involved in motor learning. To develop future neurophysiological assessment methods using NIRS, it is necessary to determine the cerebral hemodynamics of each region associated with MI by considering the effects of the experience in tasks and the degree of learning.

The objective of the present study was to examine the relationship between changes in cerebral hemodynamics during MI and the degree of task learning. The degree of task learning was examined using a ball rotation (BR) task, which has been used in many studies (Nojima et al., 2012; Suzuki et al., 2013; Horiba et al., 2019). We examined motor-related areas that exhibit the equivalent level of activation to that during the performance of motions using NIRS.

MATERIALS AND METHODS

Participants

The target sample size of this study was based on 80% statistical power to detect changes in task learning with a 0.40 effect size and a two-sided α-level of 0.05. A sample size of 10 was calculated by G*Power (Faul et al., 2007, 2009). The participants were 16 neurologically healthy right-handed adults (age: 31.6 ± 4.0, male: 13, female: 3). Hand dominance was determined using the Edinburgh Handedness Inventory (Oldfield, 1971). None of the participants had switched handedness. The MI abilities of the participants were evaluated using the KVIQ (77.8 ± 2.24 points). The present study was approved by the ethics committee of the

medical corporation Toujinkai and conducted after we obtained consent for participation in writing from all the participants.

Experimental Procedure

The participants sat on a comfortable chair and placed their hands on the table. The experimental task was a BR in the palm, in which the learning of the motion can be expected to be achieved by short-term practice of the actual motion (Kawashima et al., 1998). The BR is a task of rotating two iron balls in the palm counterclockwise, which has been used in many studies (Nojima et al., 2012; Suzuki et al., 2013; Horiba et al., 2019). We explained the BR task to the participants, showed them how it worked, and made them actually perform the task in order to understand it. However, we avoided participants learning the BR task and only aimed to get them to understand the content of the task in a short period of time. The protocol of the entire experiment is shown in **Figure 1**. First, cerebral hemodynamics during the BR-MI task was measured. A block design was used for the measurements, in line with previous research (Wriessnegger et al., 2008; Amemiya et al., 2010; Iso et al., 2016; Matsuo et al., 2020). The participants were instructed to perform the BR-MI task for 30 s and then maintain a resting condition for 40 s. NIRS measurement takes about 5 min depending on the block design. We instructed the participants to perform MI while feeling the muscles as if they were actually performing the motions. We also instructed them to maintain the same posture as that taken during the MI task while they rested and relaxed without thinking of anything. They were instructed to execute the MI task with their eyes closed during MI, as well as during rest, and not to move. In addition, after we fully explained the experimental protocol to the participants, the flow of the task was guided with beeping sounds during the experiment. The measurement of cerebral hemodynamics was performed a total of three times: before and after the initial training of the BR task and after the final training.

Thus, to determine the relationship between cerebral hemodynamics and task competence, participants completed five 1-min sessions of BR tasks involving real movements as the initial training, and the number of BR task completions was measured at each session. The rest period between sessions was about 3 min. Further, participants were asked to self-practice as the final training for improving task competence before completing the sixth 1-min session of BR tasks. The physical training (final) was performed until the subject was satisfied, and the number of BR task completions was measured at the sixth session. The final training was designed for participants to reach the level of competence sufficient to carry out BR tasks. They were asked to self-practice at their own pace, avoiding effects from muscle or mental fatigue. About an hour was given for self-practice. Furthermore, subjective vividness of MI was evaluated three times after NIRS measurement using the VAS (Lotze and Halsband, 2006; Ikeda et al., 2012). The subjects marked a location on a 100-mm horizontal line, the two ends of which were labeled "0 = None at all" and "100 = Very vivid image," according to the vividness of the imagery they experienced.

NIRS Measurement and Analysis

For NIRS measurements, we used a 24-channel system (ETG-4000; Hitachi Medical Co., Tokyo, Japan) equipped with 4 × 4 optode probe sets (eight incident lights and eight detector fibers), resulting in a total of 24 channels at an inter-optode distance of 3.0 cm. The NIRS channels were placed according to the international 10–20 system, and the Cz position was used as a marker to ensure replicable placement of the optodes (Okamoto et al., 2004; Tsuzuki et al., 2007). A total of eight regions of interest (ROIs) were selected based on previous studies (Hatakenaka et al., 2007; Amemiya et al., 2010; Sagari et al., 2015). The optodes were positioned using a custom-made cap that covered the right and left dorsolateral prefrontal cortex (PFC), pre-SMA, SMA, dorsal PMA, and somatosensory motor cortex (SMC). The areas and optodes covering them were as follows: left SMC, channels 18 and 22; right SMC, channels 21 and 24; SMA, channels 9, 12, 13, and 16; pre-SMA, channels 2, 5, and 6; left PMA, channels 8, 11, and 15; right PMA, channels, 10, 14, and 17; left PFC, channels 1 and 4; and right PFC, channels 3 and 7 (**Figure 2**). Channels 19, 20, and 23 were not further analyzed.

The continuous-wave NIRS system uses two different wavelengths (625 and 830 nm), which were both used in this study. Relative changes in the absorption of near-infrared light were sampled at 10 Hz, and these values were converted to changes in the concentration of oxy-Hb and deoxygenated hemoglobin (deoxy-Hb) based on the modified Beer-Lambert approach (Cope and Delpy, 1988; Obrig and Villringer, 2003). We used changes in the oxy-Hb concentration as an indicator of fluctuations in the regional cerebral blood volume, as an earlier NIRS signal study using a perfused rat brain model proposed that oxy-Hb and not deoxygenated hemoglobin, is the most sensitive parameter for an activation study (Hoshi et al., 2001). Oxy-Hb is an indicator of local neural activity, rather than of fluctuations

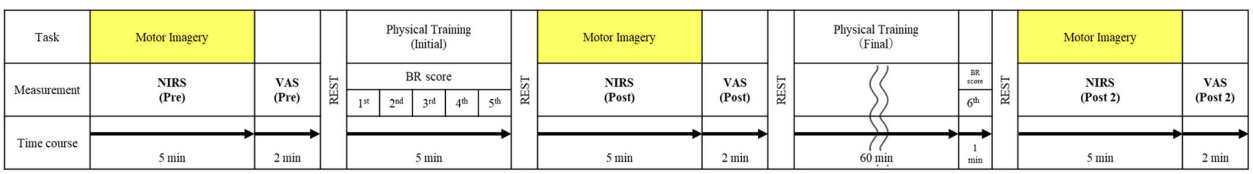

FIGURE 1 | The experimental protocol. The physical practice (initial and final training) was performed in three phases classified as pre, post, and post 2. The training was performed in six sessions. The black arrow shows the timeline of this protocol. The horizontal row of task represents the MI of ball rotation or physical practice in each item. The initial training consisted of five sessions of 1 min each. The final training consisted of 60 min of self-training and 1 min of one session. MI, motor imagery; BR, ball rotation task; NIRS, near-infrared spectroscopy; VAS, visual analog scale.

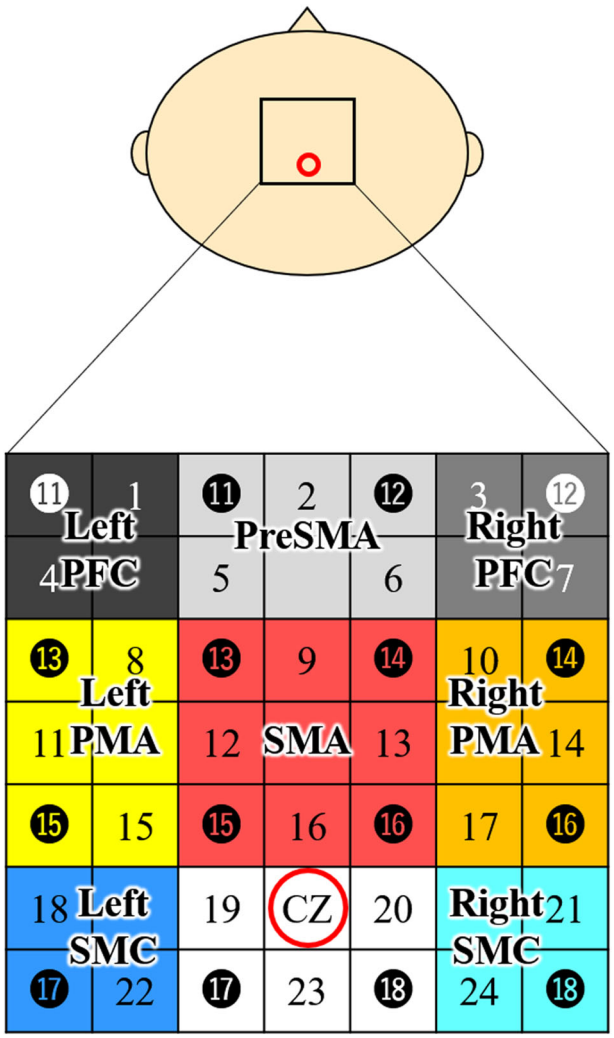

FIGURE 2 | Channel configuration of the 4 × 4 optode probe set. The 24-channel NIRS probe set was positioned over the motor areas. Black circles indicate the positions of NIRS emitters and detectors. The black numbers represent the channels, and the colored boxes show the regions of interest. According to the international 10–20 placement system, Cz was used as a marker position to ensure replicable placement of the optodes. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; Pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; NIRS, near-infrared spectroscopy.

in the regional cerebral blood volume (Hoshi et al., 2001). We determined the pre-task baseline as the mean over the 5 s prior to the task period, and the post-task baseline as the mean over the last 5 s of the post-task period (**Figure 3**). We applied linear fitting to the data between these two baselines (Marumo et al., 2009; Pu et al., 2012). The data were converted into Z-scores using values at 0–5 s from the onset of resting as baselines. We used the average measured 5–30 s after the task had started, considering the time required for changes in oxy-Hb. The average was calculated for each of the eight ROIs. Channels with high noise levels were marked using a 3.0 Hz high-pass filter, and noise components were separated and analyzed using wave analysis. Channels whose standard deviation exceeded 0.08 were assumed to be influenced by excessive noise and were thus excluded (Iso et al., 2016; Matsuo et al., 2020). In addition, during NIRS measurement, the contraction of participants' thenar muscles was monitored using electromyography (MYOTRACE400 EM-501, Sakai Medico, Japan). Electromyography is a technique that provides biofeedback of muscle activity. During NIRS measurements, motion was monitored by electromyography, which was set to sound when an EMG of 50 μV or higher appeared. Subjects with clear muscle activity during NIRS measurements were excluded, but there were no subjects excluded in this study. For statistical analyses, one-way repeated measures analysis of variance (ANOVA) was performed for the number of BR task completions and the VAS score, followed by a Bonferroni *post hoc* test. To measure oxy-Hb changes, two-way ANOVA was performed, with training and ROI as factors, followed by the Bonferroni *post hoc* test. Five hundred pieces of bootstrap oxy-Hb data were generated for each ROI and VAS in before, initial, and final trainings by randomly drawing a series of actual sample data from the oxy-Hb and VAS score to elicit the difference of variable data between before, initial, and final trainings due to the limited actual sample size. This bootstrap resampling method is widely used in demographic studies (Suzuki et al., 2020). Then, differences in the bootstrap oxy-Hb data between eight ROIs and three training phases (i.e., before, initial, and final trainings) were compared by two-way ANOVA. In addition, a generalized linear model with a gaussian distribution was used to estimate the relationship between the bootstrapping oxy-Hb and VAS scores (Kawanabe et al., 2018). The significance level was set at 5%. The statistical software used was IBM SPSS statistics 26 for one-way ANOVA and two-way ANOVA, Python language for bootstrapping, and R 3.5.2 software (R Foundation for Statistical Computing, Vienna, Wien, Austria) for generalized linear model analysis.

RESULTS

The number of BRs in each session, VAS scores before and after the initial training, and after the final training (pre, post, and post 2), and the oxy-Hb in each brain area are shown in **Figures 4–13**. **Figure 4** shows the time course of oxy-Hb and deoxy-Hb in each ROI (Z-score). The results of the generalized linear model analysis for predictors of VAS scores are shown in **Table 1**.

There was a significant effect of training on the number of BRs [$F_{(5,90)} = 8.245$, $P < 0.001$; **Figure 5**]. The number of BRs increased with training, and there was a significant difference observed between the sessions six ($P < 0.05$) compared to those in the initial training session. After the final training session, the average number of BRs was 86.1, which was larger than that observed in the five initial training sessions.

A significant effect on the VAS score was also seen, with the VAS score improved by training [$F_{(2,45)} = 17.287$, $P < 0.001$; **Figure 6**]. There was a significant improvement from 40.1 mm (before the initial training) to 65.0 mm ($P < 0.001$) (after

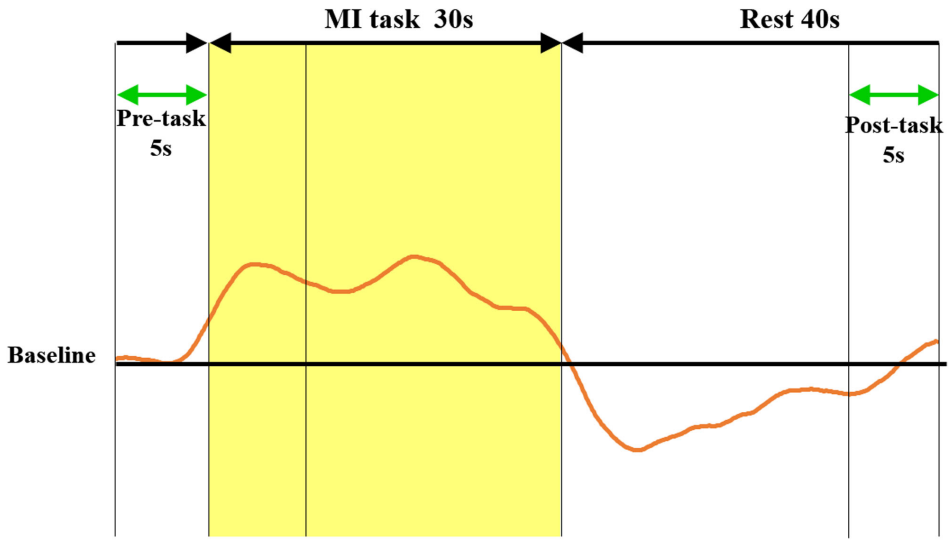

FIGURE 3 | Methods of calculating oxy-Hb change and Z score. The red curve represents the NIRS waveform in the sham case. This waveform was created by averaging the data measured over three cycles in a block design. Linear fitting was applied to the data between the pre-task (5 s) and post-task (5 s) periods (green arrows). The shaded yellow frame indicates the task period, and the non-shaded frame shows the rest period. The vertical axis represents oxy-Hb concentration (mMmm), and the horizontal axis represents the time course. Z-scores of oxy-Hb measured between 0 and 5 s during the pre-task were calculated. The mean value score measured between 5 and 30 s during the task was calculated. oxy-Hb, oxygenated hemoglobin; NIRS, near-infrared spectroscopy.

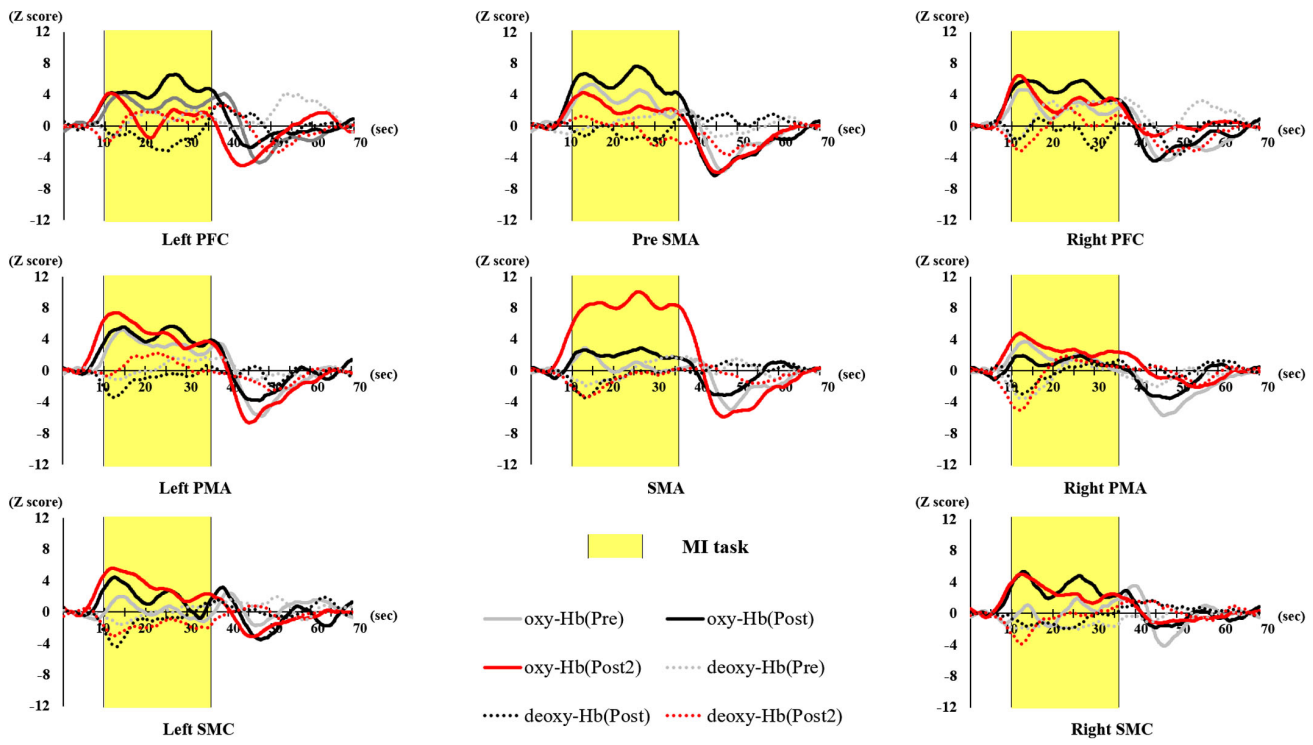

FIGURE 4 | Time course of hemodynamic signal changes for pre- and post- training (initial and final) in each ROI. The vertical axis represents Z score of oxy-Hb and deoxy-Hb, and the horizontal axis represents the time course. The blue line represents deoxy-Hb through all training. The figure shows changes in oxy-Hb and deoxy-Hb during the task in the Left PFC, Right PFC, Pre-SMA, Left PMA, Right PMA, SMA, and Left SMC. Shaded yellow frame indicates the task period. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; deoxy-Hb, deoxygenated hemoglobin; ROI, region of interest.

TABLE 1 | The results of the generalized linear model analysis for predictors of VAS score.

ROI	Coefficient	Standard error	*t* value	*P* value	
Left PFC	0.0374	0.037	1.021	0.307	
Right PFC	0.1454	0.05	2.908	0.001	**
Pre-SMA	0.1866	0.046	4.069	0	***
Left PMA	0.2129	0.038	5.553	0	***
Right PMA	0.1649	0.06	2.77	0.001	**
SMA	0.3654	0.05	7.321	0	***
Left SMC	0.3398	0.059	5.763	0	***
Right SMC	0.2203	0.073	3.025	0.001	**

*The coefficients across seven ROIs ranged between 0.15 and 0.36. *P < 0.05, **P < 0.01, and ***P < 0.001.*

Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; ROI, region of interest; VAS, visual analog scale.

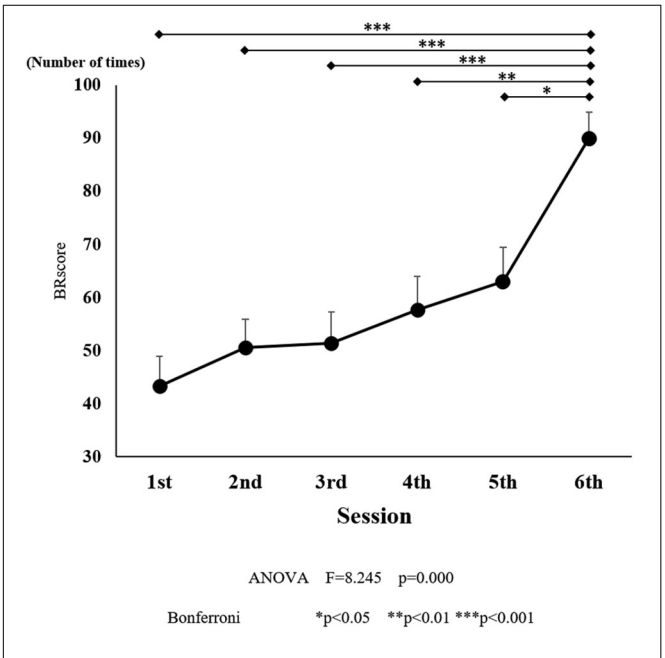

FIGURE 5 | Ball rotation score for each session. The line connecting the dots indicates that there was a significant difference in the *post hoc* analysis. Vertical bars represent the standard error. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$.

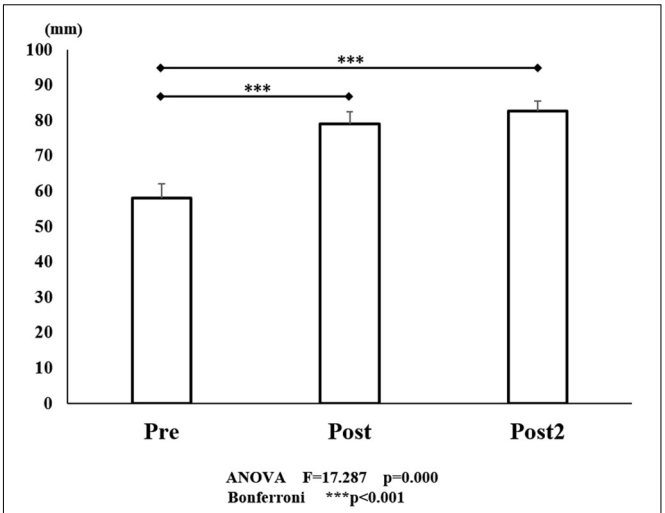

FIGURE 6 | VAS scores for pre- and post- training (initial and final). The line connecting the dots indicates that there was a significant difference on performing identified in the *post hoc* analysis. Vertical bars represent the standard error. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$. VAS, visual analog scale.

the initial training). However, although the score improved to 73.3 mm after the final training ($P < 0.001$), there was no significant difference between the VAS score after the initial training and that after the final training ($P = 1.000$).

With regard to oxy-Hb levels, a main effect of training [$F_{(2,11976)} = 305.422$, $P < 0.001$] was noted, with significant oxy-Hb changes observed in the pre- and post-initial and post final training (**Figure 7**). The oxy-Hb changes were highest after the post initial training and slightly decreased after the post final training. Further, a main effect of ROI was noted [$F_{(7,11976)} = 16.798$, $P < 0.001$], indicating that oxy-Hb changes did vary between different regions (**Figure 8**). *Post hoc* tests also showed a significant difference between ROIs, indicating large oxy-Hb changes in the left PMA. There was an interaction between training and ROI [$F_{(14,11976)} = 39.597$, $P < 0.001$], and oxy-Hb levels in the eight ROIs changed in differing directions pre- and post-training (**Figure 9**). *Post hoc* tests showed a significant increase in oxy-Hb changes in the post initial training, and maintenance or a decrease oxy-Hb changes in post final training (**Figure 10**). In the SMA, oxy-Hb changes increased with each training. There was no significant difference in oxy-Hb changes in many ROIs in the pre initial training, and the overall oxy-Hb changes were not observed (**Figure 11**). In the pre-initial training, the pre-SMA showed significant oxy-Hb changes when compared to the left SMC and Left PMA ($P < 0.05$), the right SMA showed significant oxy-Hb changes when compared to the left PMA ($P < 0.05$), and the left PFC showed significant oxy-Hb changes when compared to the left SMC ($P < 0.05$) (**Figure 11**). In the post initial training, increase of oxy-Hb changes were observed in the overall ROIs. The left PFC showed oxy-Hb changes, and significant differences were observed compared to the right PFC ($P < 0.01$), right PMA, SMA, and bilateral SMC ($P < 0.001$) (**Figure 12**). Additionally, left PMA and pre-SMA showed significant oxy-Hb changes compared to right PMA ($P < 0.01$), SMA, and bilateral SMC ($P < 0.001$) (**Figure 12**); compared with other regions, the SMA had significantly lower oxy-Hb changes, which was significantly different from all, except for left SMC ($P < 0.01$, $P < 0.001$) (**Figure 12**). In the post final training, the SMA showed highest oxy-Hb changes which was significantly different from all other ROIs ($P < 0.01$, $P < 0.001$), and followed by the left PMA (**Figure 13**). The left PFC showed significantly lower oxy-Hb changes than all other regions ($P < 0.01$, $P < 0.001$) (**Figure 13**).

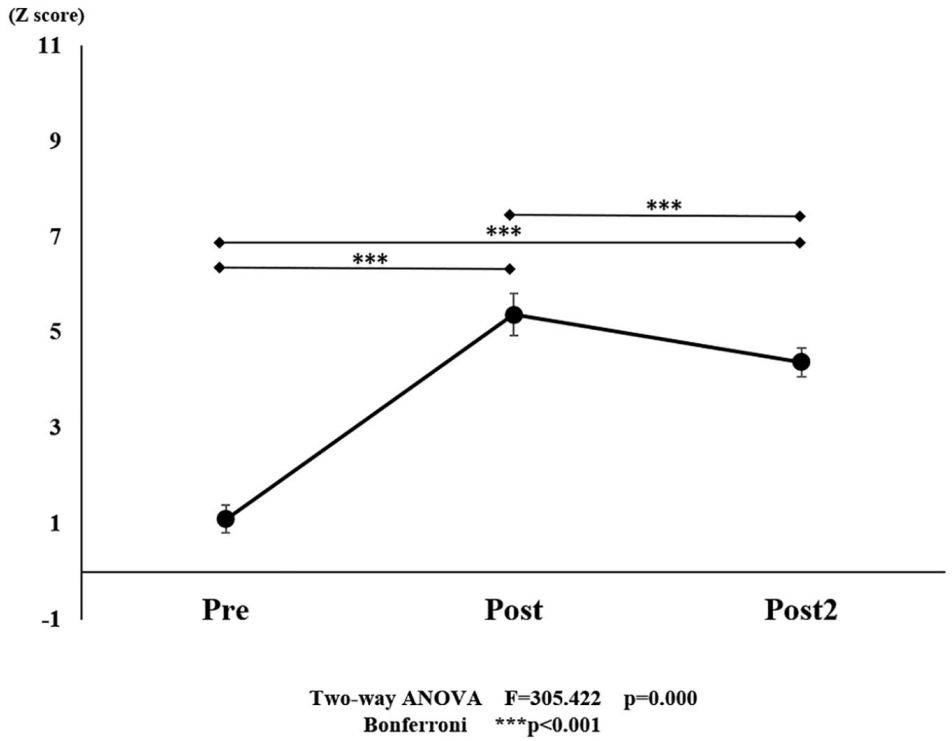

FIGURE 7 | Changes in oxy-Hb pre- and post-training (initial and final) for all ROI. The line connecting the dots indicates that there was a significant difference in the *post hoc* analysis. Vertical bars represent the standard error. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. oxy-Hb, oxygenated hemoglobin; ROI, region of interest.

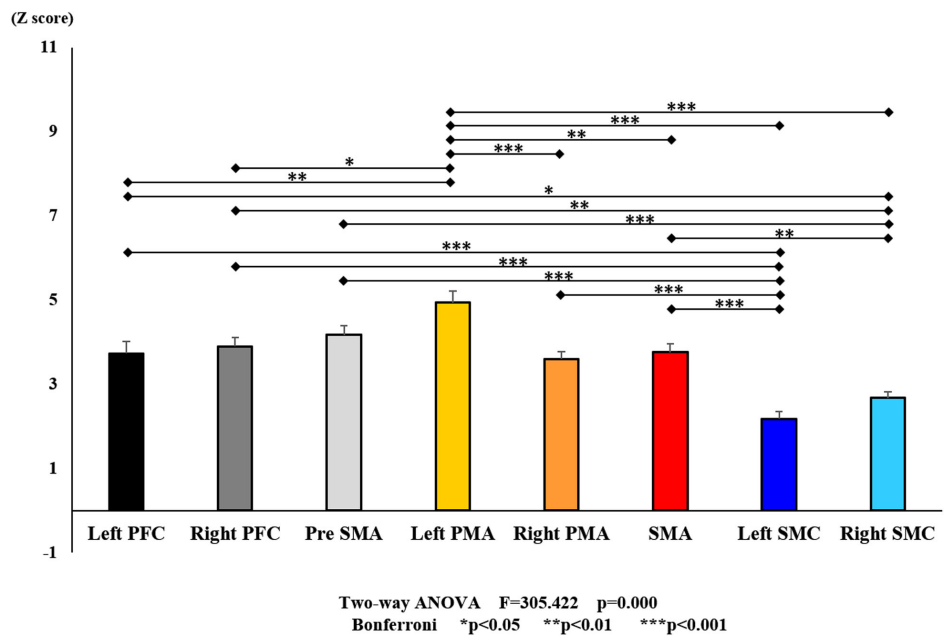

FIGURE 8 | Changes in all stages of oxy-Hb pre- and post-training (initial and final) for each ROI. The line connecting the dots indicates that there was a significant difference in the *post hoc* analysis. Vertical bars represent the standard error. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; ROI, region of interest.

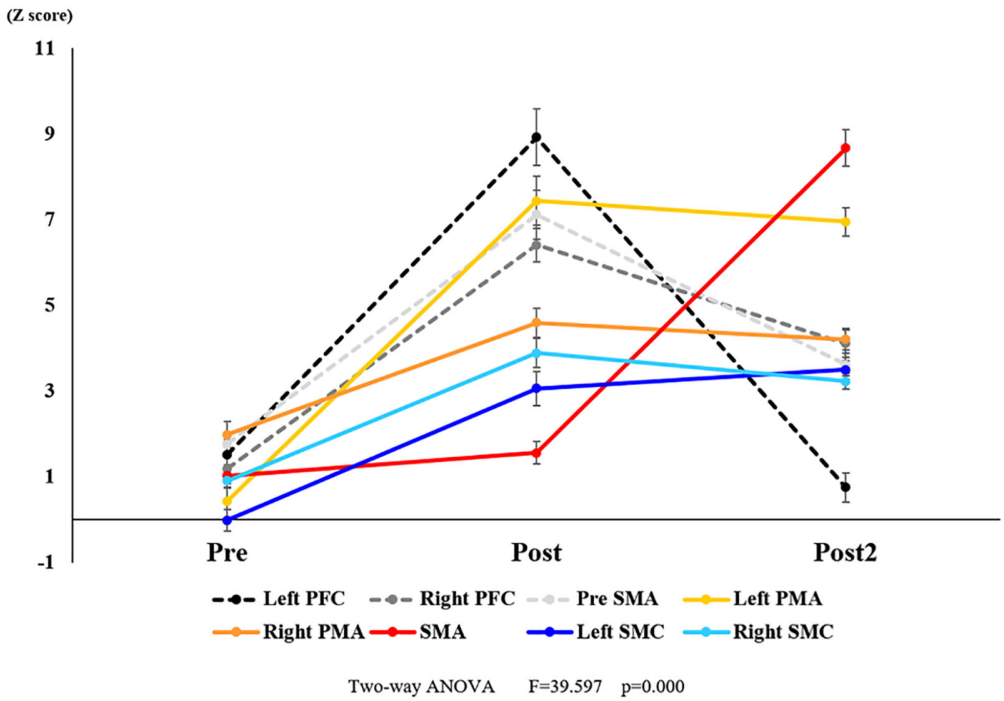

FIGURE 9 | Changes in oxy-Hb for each ROI pre- and post-training (initial and final). The Z score of oxy-Hb changes showed a significant interaction. Black dotted line represents the Left PFC. Dark gray dotted line represents the Right PFC. Light gray dotted line represents the pre-SMA. Yellow line represents the Left PMA. Orange line represents the Right PMA. Red line represents the SMA. Blue line represents the Left SMC. Light blue line represents the Right SMC. Vertical bars represent the standard error. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; ROI, region of interest.

The generalized linear model indicated that the oxy-Hb changes for seven ROIs were significant predictors of VAS score. The coefficients across seven ROIs ranged between 0.15 and 0.36 (**Table 1**).

DISCUSSION

Changes in the Number of BRs After Training

The number of BRs increased in every successive session, i.e., compared to the first session, it significantly increased in the second session and so on. Despite short-term training, the number increased significantly; thus, we consider that there was task learning to a certain extent. Compared to the previous study by Kawashima et al. (1998), the participants were not considered to have reached the level of complete learning based on the number of sessions and performance and reached the equivalent degree of learning after the final training. In the final training, instead of repeating the session, BR tasks were performed over time until the subjects were satisfied. Since a significant difference was found between Session 6 and the other sessions after the final training, it is considered that Session 6 was the stage where the tasks were learned considerably.

Changes in Subjective MI Vividness Before and After Training

There was a significant improvement in the VAS score after training, and the MI clarity improved. A previous study has shown that MI clarity improves with learning of tasks (Robin et al., 2007; Lawrence et al., 2013). The present study also showed learning of the task by training, which is considered to have affected the improvement in subjective MI clarity. However, since there was no significant difference between after the initial training and after the final training, compared to the degree of learning, the changes in the MI clarity are not considered to be completely related proportionally. At a stage where a certain degree of learning is obtained, the stage of the MI clarity is considered high; thus, in the case of a high degree of learning, further analysis may be necessary. As MI vividness improved noticeably through the initial training, no significant difference was observed in the final training. Thus, although there was a positive relationship between MI vividness and task competence, the subjective vividness of MI was relatively high from the early round of training due to exposure to tasks.

Changes in the Oxy-Hb Levels Before and After Training

The main effect of training was noted, and significant oxy-Hb changes were observed after the initial and final training,

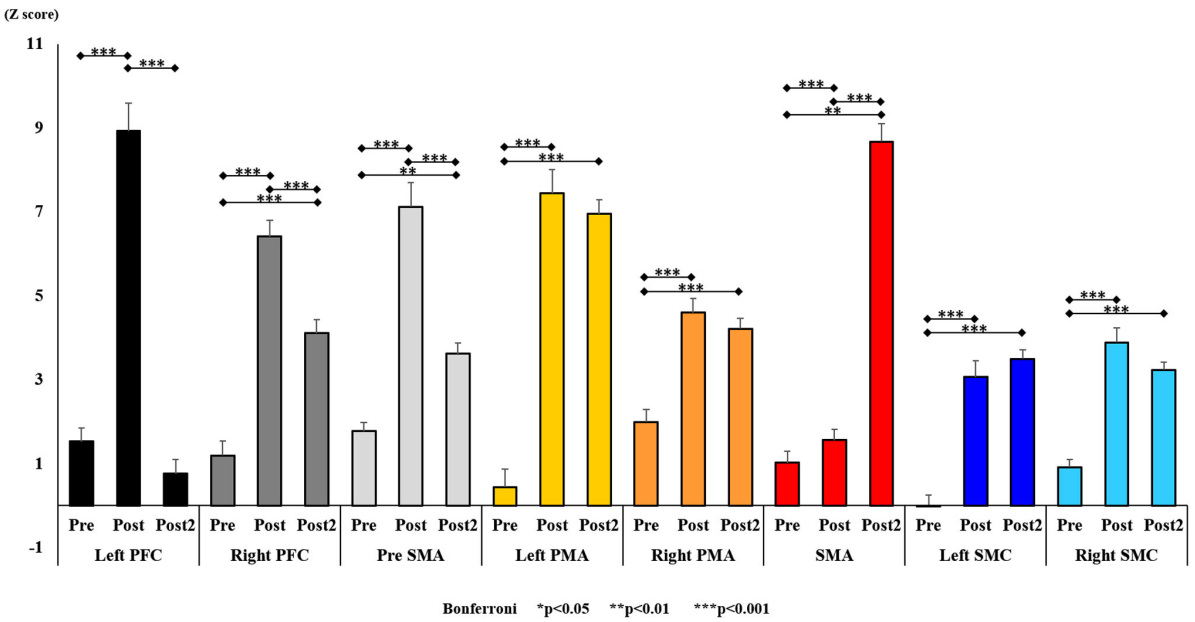

FIGURE 10 | Changes in oxy-Hb for each ROI pre- and post-training (initial and final). The line connecting the dots indicates that there was a significant difference identified in the *post hoc* analysis. Vertical bars represent the standard error. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; ROI, region of interest.

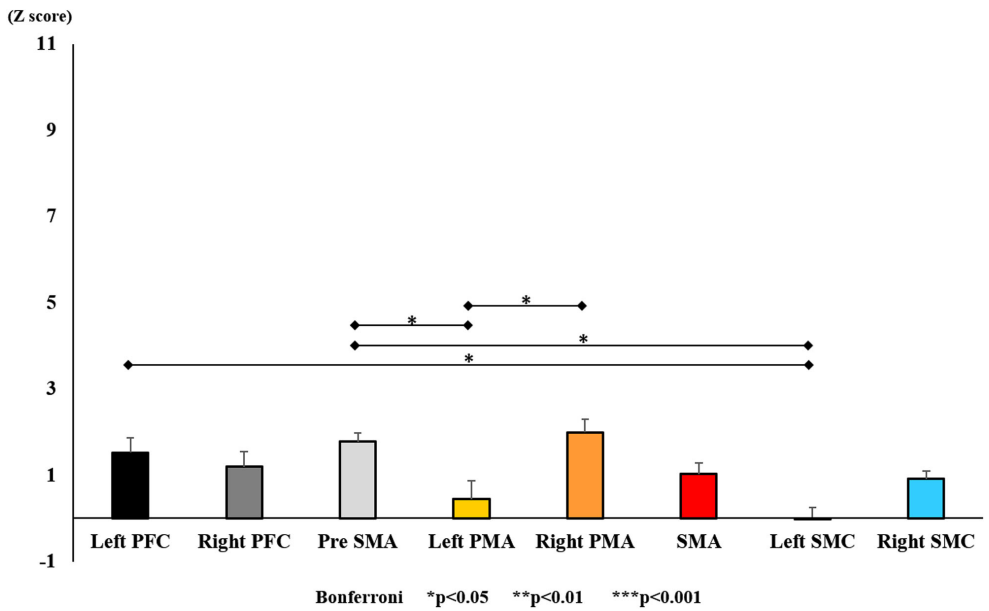

FIGURE 11 | Changes in oxy-Hb for each ROI pre-training (initial round). The line connecting the dots indicates that there was a significant difference in the *post hoc* analysis. Vertical bars represent the standard error. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; VAS, visual analog scale; ROI, region of interest.

compared to before the initial training. The results of this study matched those of previous studies in which oxy-Hb changes in the motor-related areas increased as the MI vividness increased (Mihara et al., 2012; Kober et al., 2014, 2018). The training facilitated learning of the MI task and enabled participants to form MI more vividly, increasing the oxy-Hb levels.

However, in this study, the oxy-Hb changes decreased in the motor-related area after the final training in which the learning of

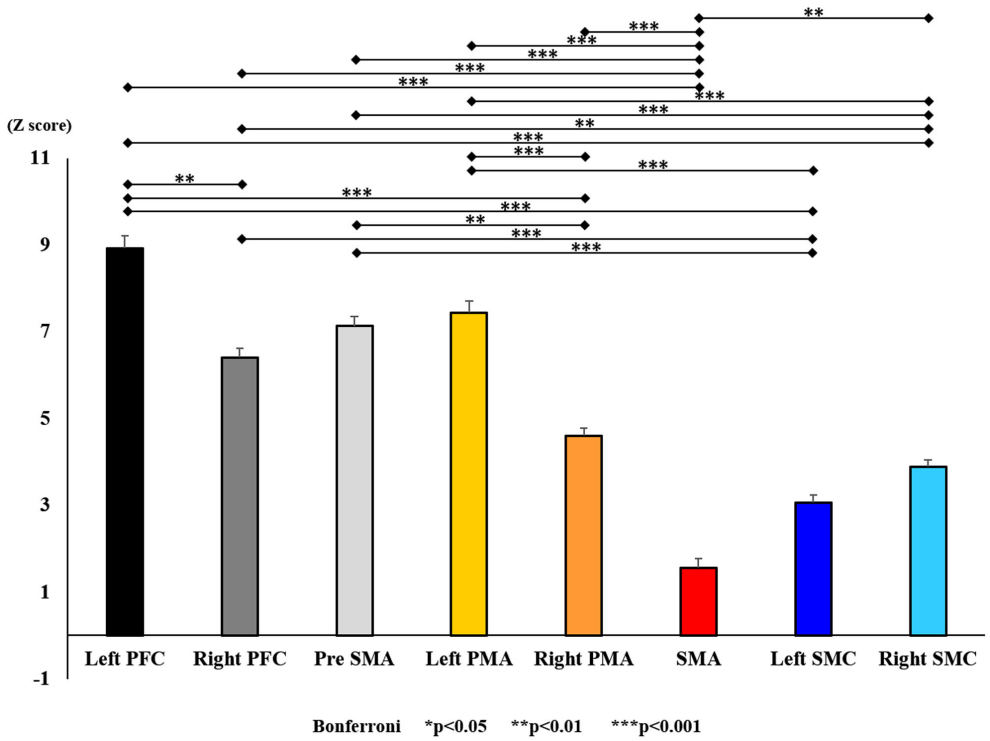

FIGURE 12 | Changes in oxy-Hb for each ROI post-training (initial round). The line connecting the dots indicates that there was a significant difference in the *post hoc* analysis. Vertical bars represent the standard error. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; ROI, region of interest.

MI tasks was promoted. The difference between this and previous research is that this research was conducted by adopting the tasks used for motor learning (Mihara et al., 2012; Kober et al., 2014, 2018). Previous studies have stated that brain activation is high when the task is difficult, and not activated enough when the task is low in difficulty (Hatakenaka et al., 2007; Amemiya et al., 2010; Sagari et al., 2015). Considering that the tasks were being learned after the final training, it is considered that the MI performed after the final training was relatively easy to carry out. Therefore, it is considered that the difficulty level of the task is at the stage where subjects performed MI easily, and the hemodynamic signal changes during MI are also considered to have decreased as an overall change in the motor-related area.

However, it has also been reported that hemodynamic signal changes during MI differ depending on the ROI (Wriessnegger et al., 2014; Iso et al., 2016; Matsuo et al., 2020), and this study also confirmed the main effect of ROI. The hemodynamic signal changes in the left PMA showed significantly high activation. The PMA has been reported to be deeply involved in motor learning, and activation of the PMA was consistent with previous studies (Tyszka et al., 1994; Hikosaka et al., 1996; Nakamura et al., 1998; Sakai et al., 1998; Kasess et al., 2008; Guillot et al., 2012). In addition, other ROIs showed higher activity compared to the bilateral SMC. The PFC and pre-SMA are also areas involved in early learning of exercise (Nakamura et al., 1998; Sagari et al., 2015), and SMA has been reported to activate during MI (Amemiya et al., 2010; Iso et al., 2016). Similarly, in this study, significantly higher activity was observed in the bilateral PFC, bilateral PMA, pre-SMA, and SMA. In addition, the bilateral SMC showed low activation in this study. Previous imaging studies have shown that SMC activity directly relates to movement output (Obrig et al., 1996; Christensen et al., 2000), while other studies showed increased activation of the primary motor cortex during MI with TMS (Lotze et al., 1999). Furthermore, some studies using NIRS during MI have shown activation of the primary motor cortex. Although the SMC is activated during MI, its role is in movement output, and it is possible that for this reason the hemodynamic signal changes were lower than for other ROIs.

However, in addition to the main effects of training and ROI, interactions were observed, and it was clarified that the hemodynamic signal changes differ depending on the ROI. In particular, the SMA showed an increase in the hemodynamic signal changes as training progressed compared to other ROIs. The SMA is activated in the late stage, suggesting its activation when habituation of movements, including motor planning and preparation, has already been established (Tyszka et al., 1994; Hikosaka et al., 1996; Nakamura et al., 1998; Sakai et al., 1998; Kasess et al., 2008; Guillot et al., 2012). It is an area responsible for performing MI-related activity, including motor preparation (Mihara and Miyai, 2016). With progression of learning the MI task, participants were able to evoke MI more vividly, leading to a

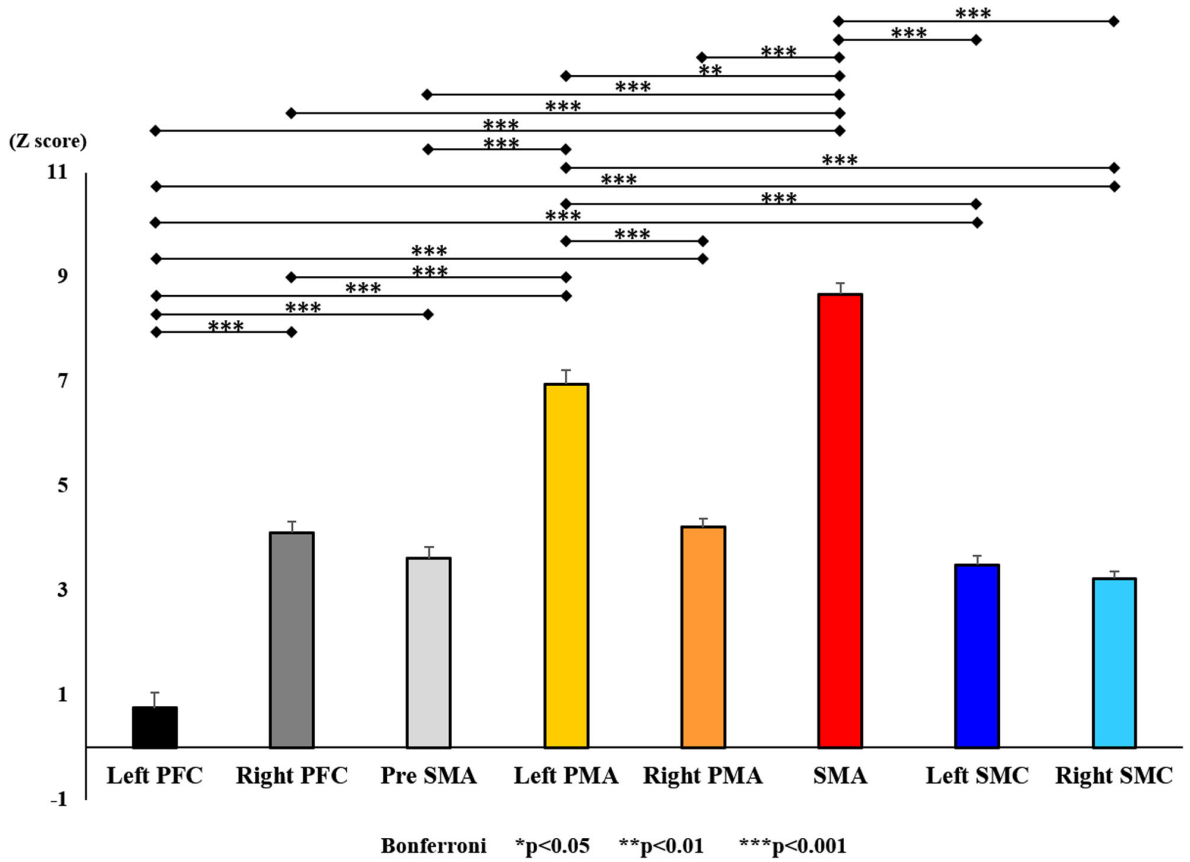

FIGURE 13 | Changes in oxy-Hb for each ROI post-training (final). The line connecting the dots indicates that there was a significant difference in the *post hoc* analysis. Vertical bars represent the standard error. $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$. Left PFC, left prefrontal cortex; Right PFC, right prefrontal cortex; pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; Left PMA, left pre-motor area; Right PMA, right pre-motor area; Left SMC, left somatosensory motor cortex; Right SMC, right somatosensory motor cortex; oxy-Hb, oxygenated hemoglobin; ROI, region of interest.

gradual increase in changes in cerebral blood flow in the SMA, which was one of the ROIs in this study. However, the SMA did not show high activation until the learning stage was quite advanced. The results of this study were consistent with those of previous studies regarding motor learning (Tyszka et al., 1994; Hikosaka et al., 1996; Nakamura et al., 1998; Sakai et al., 1998; Kasess et al., 2008; Guillot et al., 2012).

Therefore, our results show that training increased the hemodynamic signal changes in all ROIs, with the greatest increase observed in the PMA. However, only SMA the showed an increase in the hemodynamic signal with training compared to other ROIs.

Relationship Between Oxy-Hb Changes and Subjective Vividness of MI

A generalized linear model showed that oxy-Hb changes in seven ROIs, other than the left PFC, were significant predictors of VAS score. In particular, the SMA coefficient was the highest, which was a significant predictor for estimating VAS scores, and was shown to be most associated with VAS. Since the change in VAS and the change in oxy-Hb of the SMA due to training are also similar, the oxy-Hb change in the SMA best represents the vividness of MI. The SMA was reported to be activated in previous NIRS studies during MI (Mihara et al., 2012; Kober et al., 2014, 2018; Matsuo et al., 2020). Our present results showed that the selection of these areas was adequate for examining the MI vividness in terms of changes in cerebral hemodynamics using NIRS as an objective index for these changes. Our results were also consistent with the findings of a previous study (Mihara and Miyai, 2016), which reported that these areas are responsible for MI. An important aspect in mental practice is how vividly an individual can perform MI; if MI vividness can be evaluated neurophysiologically, MI can be used effectively in rehabilitation. MI is already used in neurofeedback systems such as Brain Computer Interface (BCI) and Functional electrical stimulation therapy (Khan et al., 2015; Koo et al., 2016; Likitlersuang et al., 2018). Our results demonstrate that hemodynamic signal changes in the SMA are associated with MI vividness, which can be used not only for mental practice but also for other techniques such as BCI.

Therefore, the hemodynamic signal changes in motor related areas centered on the SMA using NIRS might be used as a neurophysiological assessment for MI vividness.

Limitations

In the present study, we used BR as the learning task, which primarily relies on fingers dexterity; therefore, the relationship between MI vividness and cerebral hemodynamic changes obtained in this study might be limited to MI of the upper extremities.

In addition, this study was conducted on healthy subjects; when using MI vividness as an evaluation tool in patients with stroke it is necessary to consider the injured area.

Conclusion

The BR task used in the present study showed a clear motion learning from practicing the actual motions, thereby causing significant improvement in subjective MI vividness. In terms of hemodynamic signal changes, a main effect of training and ROIs were observed.

Moreover, the coefficients for estimating relationships are highest in the SMA, a key predictor for estimating VAS scores, which suggests that it is the best region for detecting MI vividness. Thus, our findings suggest that future studies should examine neurophysiological indices for MI vividness based on the hemodynamic signal changes of SMA.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the Medical Corporation Toujinkai. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NI, TM, KF, and THi conceived and designed the experiments. NI, TM, KF, WM, THa, FI, and THi performed the experiments. NI, MM, KF, WM, and THi analyzed the data. TM, THa, KC, MS, and THi created the experimental program. NI, TM, FI, and THi wrote the article. All authors discussed the results and contributed to the final manuscript.

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OPINION
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The Intersection of Offline Learning and Rehabilitation

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INTRODUCTION

Learning is fundamental to rehabilitation (Krakauer, 2006). The learning of cognitive and motor tasks similar to those in rehabilitative services (i.e., occupational therapy, physical therapy, speech language pathology, recreational therapy, music therapy, etc.) involve the creation (or modification) of neural representations associated with task performance (Dayan and Cohen, 2011). Later accessing these representations allows for performance with greater skill. These neural representations can therefore be referred to as memory traces, and rehabilitation can be thought of as involving the creation and/or modification of memories that can be stored for use in other contexts in the future.

The process of learning is comprised of practice-dependent (i.e., online) and practice-independent (i.e., offline) processes. Skill acquisition during initial practice is typically exhibited by fast improvements in performance (Dayan and Cohen, 2011). After encoding a memory and halting practice, a memory can then undergo consolidation, leading to slower improvements over a period of seconds, days, weeks, or months. The purpose of this paper is two-fold: to identify the currently known mechanisms of consolidation and reconsolidation that impact learning, and to discuss how these findings could impact the design and optimization of interventions and strategies for rehabilitation services. The concepts discussed in this paper are applicable to various forms of learning (e.g., cognitive, motor, visual perceptual) but for simplicity, many of the studies highlighted in this paper involve motor learning.

Consolidation

Consolidation involves the stabilization (Brashers-Krug et al., 1996; Yotsumoto et al., 2009; Censor et al., 2010; Cohen and Robertson, 2011) or enhancement (Karni et al., 1994; Stickgold et al., 2000; Walker et al., 2002; Fischer et al., 2005; Korman et al., 2007; Nishida and Walker, 2007) of performance across a period of wakeful rest or sleep. The time period for consolidation to occur is typically over hours or perhaps longer based on the complexity of the task, which is referred to here as slow consolidation. More recently though, evidence of rapid within-session consolidation has been identified during the seconds of rest between trials of motor practice (Bönstrup et al., 2019, 2020).

Both implicit and explicit learning involve consolidation. While time alone (i.e., regardless of being awake or asleep) is sufficient for implicit aspects of memory, a period of sleep is necessary for slow consolidation of explicit aspects of memory (Robertson et al., 2004; Albouy et al., 2013, 2015).

The degree of consolidation over a sleep period has been associated with the number of occurrences of sleep spindles and slow wave electroencephalographic waveforms, which predominantly occur during non-rapid eye movement sleep over task-related brain regions (Nishida and Walker, 2007; Barakat et al., 2013; Tamaki et al., 2013). However, the number of sleep spindles and slow waves experienced during sleep decreases with age, which may explain the

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decrease in sleep-based consolidation found in older adults (Brown et al., 2009; Wilson et al., 2012; Fogel et al., 2014; Roig et al., 2014) and in individuals with sleep apnea (Djonlagic et al., 2012, 2015; Landry et al., 2014; Johnson et al., 2019b).

Reconsolidation

When later recalling (or performing) a memory that has been consolidated through slow consolidation, online and offline processes can occur again to further fine tune recall (or performance) of the memory, known as reconsolidation (Nader et al., 2000; Walker et al., 2003; Forcato et al., 2007; Lee, 2008; Sandrini et al., 2015; Amar-Halpert et al., 2017; Herszage and Censor, 2018) but see Hardwicke et al. (2016). Gradual session-by-session improvements of a previously acquired and consolidated task may be promoted by reconsolidation between sessions, which is triggered by practice-induced memory reactivation during the session (Censor et al., 2010) or even the presentation of a task-associated sensory cue without active practice (Bavassi et al., 2019). The process of fine-tuning a memory through reconsolidation necessitates the integration of new task information obtained during reactivation so that memories can remain relevant and effective. Such new information may be in the form of sensorimotor calibrations, contextual cues, or additional declarative information. Less is known about rapid reconsolidation during early skill learning (Bönstrup et al., 2019, 2020).

Interference of Consolidation and Reconsolidation

Memories are unstable while undergoing consolidation and reconsolidation and are thus susceptible to interference (**Figure 1**), making subsequent behavior and sleep between sessions crucial to learning (Walker et al., 2003; Forcato et al., 2007; Lee, 2008; Censor et al., 2010). When motor task A is acquired and the consolidation process has begun, the subsequent learning of a different task, task B, can impair consolidation of task A such that later recall performance of task A is impaired. This is known as retroactive interference (Shadmehr and Brashers-Krug, 1997; Ghilardi et al., 2009). For example, learning two different motor tasks within 5 min, 30 min, or 2.5 h was found to induce forgetting of the first motor task learned relative to a gap of 5.5 or 24 h (Shadmehr and Brashers-Krug, 1997). Alternatively, proactive interference can occur when the consolidation process of an initial task can temporarily impair learning of a different task (Ghilardi et al., 2009; Cantarero et al., 2013). For example, Cantarero et al. (2013) found that transiently increased cortical excitability induced through learning an initial motor skill interfered with immediate learning of a second motor skill. However, no retroactive or proactive interference was found if cortical excitability was allowed to return to baseline over time (Cantarero et al., 2013). It should be noted that interference can occur between different task types (i.e., cognitive and motor) (Brown and Robertson, 2007; Mutanen et al., 2020). The topic of memory modification during instability extends to reconsolidation as well. For example, implementing reward during memory reactivation (wherein no reward was present during initial learning) has been found to disrupt reconsolidation, possibly by creating a competing memory trace (Dayan et al., 2016). Whether interference of skill occurs relates to the degree of memory stability when beginning to learn the subsequent task, as well as the similarity of the tasks.

Preventing Interference Effects

An unstable memory can be modulated (and generalized) more easily, whereas a stable memory is harder to modulate. There are two primary factors that have been found to enable memories to stabilize. The first factor is the amount/duration of practice. Increasing the number of repetitions of task A helps to stabilize a memory trace, thereby reducing retroactive interference. However, increased repetitions of Task A can also transiently increase proactive interference to a subsequently learned task (i.e., Task B) as Task A is being consolidated (Krakauer et al., 2005; Shibata et al., 2017). This retroactive protective effect of increased practice duration extends to reconsolidation as well, as increasing the length of time during which the memory is reactivated decreases retroactive interference (de Beukelaar et al., 2014).

Second, the duration between sessions of learning helps to stabilize memories via consolidation. Allowing for several hours between task practice has been shown to decrease both retroactive and proactive interference compared to a period of several minutes between tasks (Walker et al., 2003; Krakauer et al., 2005; Ghilardi et al., 2009). Including a period of sleep between task practice sessions also reduces the proactive and retroactive interference between two tasks and lessens the amount of time required for consolidation compared to waking hours (Ellenbogen et al., 2006, 2009; Abel and Bäuml, 2014), but see Bailes et al. (2020). For reconsolidation, Gabitov et al. (2017) found that learning of a new motor task caused retroactive interference immediately after memory reactivation, but not if an 8-h interval was afforded following memory reactivation. Others have reported that the role of retroactive interference is greatest immediately after memory reactivation (i.e., 0 s) and fades in magnitude over a short period of time (i.e., 20, 40, and 60 s) as the memory is being reconsolidated (de Beukelaar et al., 2016).

DISCUSSION

Consolidation and Reconsolidation During Rehabilitation

While consolidation and reconsolidation are relevant to psychotherapy treatments such as the extinction of fear memories (Monfils et al., 2009; Schiller et al., 2010), it remains to be seen whether rehabilitation services trigger consolidation and reconsolidation. There are long held principles that may make the consolidation and reconsolidation of memories during and after rehabilitation likely. For example, the notion of the "just right challenge," holds that tasks performed during rehabilitation should be meaningful and difficult (Ayres, 1983; Csikszentmihalyi and LeFevre, 1989; Moneta and Csikszentmihalyi, 1996; Csikszentmihalyi, 2000), and should incorporate learning principles (e.g., practice structure, repetition, feedback, reward) (Poole, 1991; Jarus, 1994). Motor

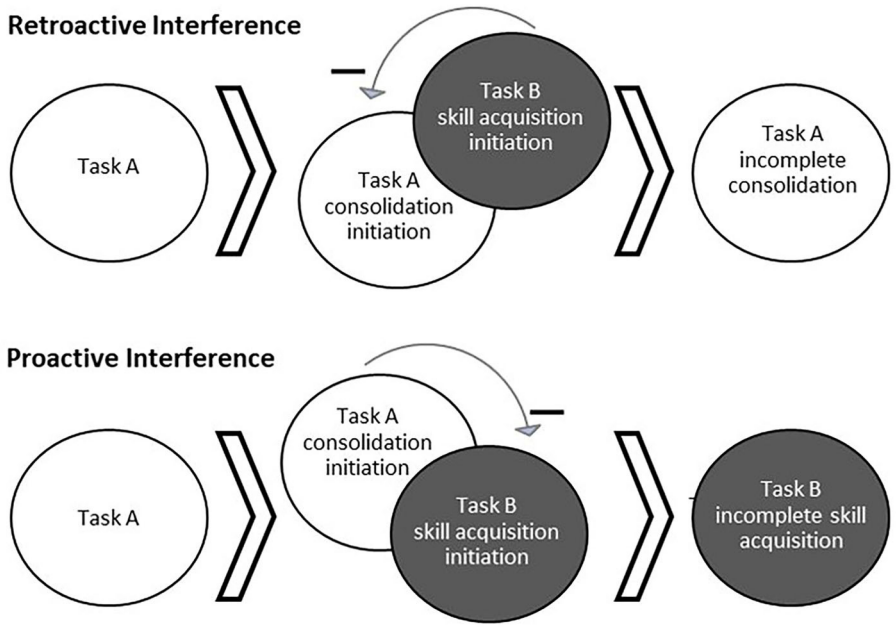

FIGURE 1 | Behaviorally-induced retroactive and proactive interference. Interference occurs when the processes for learning multiple tasks interact and cause a detriment to the consolidation or acquisition of one of the tasks. Top: Acquisition of a second task (Task B) while a first task (Task A) is still undergoing consolidation can result in interference of Task A consolidation, known as retroactive interference. Bottom: Alternatively, ongoing consolidation of a first task (Task A) can interfere with the acquisition of a second task (Task B), known as proactive interference.

learning concepts such as goal-oriented training or task-specific training are important for skill acquisition during sessions, but interference between-sessions may occur and requires further investigation. That is, individuals receiving goal-oriented training or task-specific training in multiple rehabilitation services (e.g., occupational and physical therapy) may benefit from coordination of scheduling and therapy content. For example, occupational and physical therapies could be scheduled on alternating days, or with several hours of time between the two therapy sessions on a single day.

We propose that future research investigate consolidation and reconsolidation between rehabilitation sessions. Given the overwhelming evidence for the process of memory reconsolidation in declarative and procedural memories, it might be expected that individuals undergoing rehabilitation would also experience reconsolidation between sessions of therapy. For example, regaining independence in performing activities of daily living involves learning processes (Bayona et al., 2005). Importantly, older adults have been shown to benefit from reconsolidation (Corbin, 2017; Tassone et al., 2020) despite the known declines in consolidation related to healthy aging (Brown et al., 2009; Wilson et al., 2012; Fogel et al., 2014; Roig et al., 2014). However, one study found that reconsolidation was impaired in older adults with stroke relative to age-matched subjects without stroke (Censor et al., 2016), while other research has found that individuals with stroke, but not age-matched healthy controls, benefit from sleep-based consolidation of a motor task (Siengsukon and Boyd, 2008, 2009). Thus, further investigation into consolidation and reconsolidation among patient populations is warranted.

Recipients of rehabilitation would also benefit from the continued development of clinical protocols using non-invasive brain stimulation as an adjunct to enhance therapy-related memory consolidation and reconsolidation. Indeed, several studies regarding stroke rehabilitation have found benefits of pairing non-invasive brain stimulation with participation in rehabilitation (Khedr et al., 2005; Chang et al., 2010; Ilić et al., 2016; Rocha et al., 2016). In addition, transcranial direct current stimulation during wake (Reis et al., 2009, 2015; Sandrini et al., 2014) and during post-encoding sleep (Marshall et al., 2004, 2006; Göder et al., 2013; Westerberg et al., 2015), as well as repetitive transcranial magnetic stimulation during wake (Turriziani, 2012; Sandrini et al., 2013), have previously been shown to enhance memory consolidation and reconsolidation. Other sensory stimulation techniques such as targeted memory reactivation (Rasch et al., 2007; Oudiette and Paller, 2013; Shimizu et al., 2018; Johnson et al., 2019a, 2020; Hu et al., 2020) and rhythmic auditory stimulation (Ngo et al., 2013; Ong et al., 2016) have been used during post-encoding sleep to enhance consolidation.

In addition to task-specific memory modulation, future research should also focus on how to best induce generalization of skill between therapies in relation to the degree of memory stability and task similarity. For example, Mosha and Robertson (2016) had participants learn a word list and a motor skill,

with overlapping rules to task elements, in quick succession and showed that generalization could be induced between the tasks (regardless of learning order) when the first memory was unstable. However, generalization did not occur when the memory for the first task was stabilized through the inclusion of a 2-h consolidation period. That is, generalization can occur to a Task B during instability of Task A, but such generalization can also come at the cost of retroactive interference to Task A (Robertson, 2018; Mutanen et al., 2020).

CONCLUSIONS

Rehabilitation often involves learning. We first describe why clinicians should consider memory consolidation and reconsolidation. Secondly, we encourage future research to investigate how consolidation and reconsolidation relate to rehabilitation and translate previous work to decrease interference effects and enhance memory consolidation between rehabilitation sessions. Doing so may aid in the development of efficient and long-lasting interventions that are generalizable to clinically meaningful activities.

AUTHOR CONTRIBUTIONS

BJ: conceptualization, literature review, and manuscript writing. LC and KW: conceptualization and manuscript writing. All authors contributed to the article and approved the submitted version.

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Event-Related Desynchronization During Mirror Visual Feedback: A Comparison of Older Adults and People After Stroke

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Event-related desynchronization (ERD), as a proxy for mirror neuron activity, has been used as a neurophysiological marker for motor execution after mirror visual feedback (MVF). Using EEG, this study investigated ERD upon the immediate effects of single-session MVF in unimanual arm movements compared with the ERD effects occurring without a mirror, in two groups: stroke patients with left hemiplegia and their healthy counterparts. During EEG recordings, each group performed one session of mirror therapy training in three task conditions: with a mirror, with no mirror, and with a covered mirror. An asymmetry index was calculated from the subtraction of the event-related spectrum perturbations between the C3 and C4 electrodes located over the sensorimotor cortices contralateral and ipsilateral to the moved arm. Results of the effect of task versus group in contralateral and ipsilateral motor areas showed that there was a significant effect of task condition at the contralateral motor area in the high beta band (17–35 Hz) at C3. High beta ERD showed that the suppression was greater over the contralateral hemisphere than it was over the ipsilateral hemisphere in both study groups. The magnitude of low beta (12–16 Hz) ERD in patients with stroke was more suppressed in contralesional C3 under the no mirror compared to that of the covered mirror and similarly more suppressed in ipsilesional C4 ERD under the no mirror compared to that of the mirror condition. The correlation analysis revealed that the magnitude of ERSP power correlated significantly with arm severity in the low and high beta bands in patients with stroke, and a higher asymmetry index in the low beta band was associated with higher arm functioning under the no-mirror condition. There was a shift in sensorimotor ERD toward the contralateral hemisphere as induced by MVF accompanying unimanual movement in both stroke patients and healthy controls. The use of ERD in the low beta band as a neurophysiological marker to indicate the relationships between the amount of MVF-induced ERD attenuation and motor severity, and the outcome indicator for improving stroke patients' neuroplasticity in clinical trials using MVF are warranted to be explored in the future.

Keywords: mirror visual feedback, occupational therapy, mirror neuron, event-related desynchronization, stroke

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INTRODUCTION

Hemiparetic upper limb impairment is a leading cause of long-term physical disability after stroke. Among stroke survivors, 70% experience permanent upper extremity hemiplegia (Jørgense et al., 2000), and 33–60% will continue to have no function at 6 months post-stroke (Kwakkel and Kollen, 2013). Often, arms recover slowly, and partial to full non-use of an arm is common even when stroke survivors can walk independently. Facilitation of motor relearning in order to elicit positive neuroplasticity of the damaged brain area during the rehabilitation of a hemiparetic arm has always been a challenging task for occupational therapy (Stoykov and Madhavan, 2015). Mirror therapy has been used by occupational therapists as an effective and cost-effective intervention for arm hemiparesis following stroke. Evidence shows that it can benefit stroke patients in their arm recovery at the subacute stage (Toh and Fong, 2012). One of the possible explanations is that the parietal–frontal area encompasses the so-called human mirror neuron system (MNS), which can be activated during both the observation and execution of movements (Rizzolatti and Craighero, 2004).

Mirror neurons were first discovered in a monkey experiment when the monkey do or observe an action (Rizzolatti and Craighero, 2004). Event-related desynchronization (ERD) – that is, by power suppression over frequency bands on an electroencephalogram (EEG) – has been indicated traditionally by a decrease in the amplitude of mu rhythms over the sensorimotor cortex, as recorded by electroencephalography. ERD can be interpreted as an electrophysiological correlate of an increased cortical excitability or an activated cortical area (Neuper and Pfurtscheller, 2001). Therefore, this phenomenon has been used as a neurophysiological marker for the activation of mirror neurons, owing to its previously defined physiological properties (Pineda et al., 2000; Muthukumaraswamy et al., 2004; Oberman et al., 2005). Such oscillations are based on neural substrates during the observation and execution of a motor act and are also associated with other human functions, such as imitation, language, and the like (Rizzolatti and Craighero, 2004; Binder et al., 2017; Perry et al., 2017). The core mirror neuron system (MNS) serves as a neural substrate to achieve the transformation of visual information into cortical areas for motor execution (Rizzolatti and Sinigaglia, 2010). The MNS is thought to be found in the frontal and parietal lobes – in the primary motor cortex (M1), the premotor cortex (PMC), the inferior frontal gyrus (IFG), and the inferior parietal lobe (IPL) – and to involve interactions between vision, motor commands, and proprioception for motor learning (Deconinck et al., 2015).

According to our recent review, the MNS is thought to be activated by the optical illusion of movement, such as during mirror visual feedback (MVF) or action observation (AO) (Zhang et al., 2018). A review of the literature on the long-term effects of action observation and MVF in stroke also concluded that with MVF, both action observation and action execution could enhance the magnitude of ERD in the sensorimotor cortex as recorded by an EEG and also could enhance the motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) (Kang et al., 2011, 2012; Liepert et al., 2014; Marangon et al., 2014). The ERD over the sensorimotor cortex could also be suppressed during action observation (Frenkel-Toledo et al., 2014, 2016; Perry et al., 2017). Therefore, ERD can serve as a neurophysiological marker of sensorimotor activation or a measure of visuomotor transformation, which could be induced through either a movement execution or a movement observation in occupational therapy treatment such as MVF (Zhang et al., 2018).

Mirror visual feedback also causes instant neuromodulatory effects of increased activation of the ipsilateral superior temporal gyrus (STG) (Matthys et al., 2009) and the PMC (Ramachandran and Altschuler, 2009) during training. The STG and the PMC serve as a network for the imitation of biological motion and the acquisition of motor skills (Deconinck et al., 2015). Previous studies have been conducted on ERD, focusing on action observation (Pineda et al., 2000) and an object-oriented action (Muthukumaraswamy et al., 2004) among healthy participants. In a previous experiment, we found that MVF induced a shift in ERD toward the sensorimotor area ipsilateral to the moving hand in healthy adults, when comparing direct view feedback in the low mu, high mu, and low beta bands (Zhang and Fong, 2019). However, to the best of our knowledge, the effects of ERD on mirror illusions in stroke patients receiving mirror therapy have not been investigated before. Thus, the aim of this study was to use EEG to compare the immediate effects of a single session of MVF and evaluating ERD in the motor cortex of both hemispheres that occurred with a mirror, no mirror, and those with a covered mirror in response to unimanual arm movement in patients with chronic stroke and in their healthy counterparts. We hypothesized that ERD is associated with the subject's observation of the mirror illusion and arm severity in patients with stroke and provides a selective index of movement-related activity that can be exclusively attributed to the discharge of mirror neurons in the motor cortex (Gallese et al., 1996).

MATERIALS AND METHODS

Participants

The participants in this study were 11 patients with chronic stroke whom we recruited by convenience sampling from community self-help groups in Hong Kong. The study's inclusion criteria were patients who had: (1) a neurological condition with unilateral left hemiparesis; (2) a score between levels 2 and 6 on the Functional Test of Hemiplegic Upper Extremity (FTHUE) (Fong et al., 2004), and higher scores represent a higher level of arm functioning; (3) chronic stroke, with the onset of the neurological condition having occurred more than 6 months previously; (4) the ability to understand and follow simple verbal instructions; (5) the ability to participate in a therapy session lasting at least 30 min; (6) the ability to be community ambulant, with or without aids; (7) normal or corrected-to-normal vision; and (8) right dominance before the stroke. Individuals with severe neglect and severe spasticity (Modified Ashworth Scale >3) (Bohannon and Smith, 1987) were excluded. Twenty age-matched healthy

right-handed controls with normal or corrected-to-normal vision (mean age = 61.3 years; 12 males, 8 females) were also recruited by convenience sampling from social networks in the community.

The study was performed in accordance with the principles of the Declaration of Helsinki, and ethical approval was sought from the Human Subjects Ethics Committee of The Hong Kong Polytechnic University (Ref. no.: HSEARS20121012008). Only participants who had given informed written consent were included.

Procedures

Participants performed one session of mirror therapy training for the EEG recording. The dimension of the mirror box apparatus was 16 × 17 inches, and the box was placed at the midsagittal plane of the participant. During the EEG experiment, each participant was asked to sit in a comfortable chair in front of a table, on which he/she was asked to place both arms. EEG was recorded during the three task conditions: tasks carried out in front of a mirror, tasks done with no mirror, and tasks performed in front of a covered mirror. The mirror task involved viewing a reflected image of the unaffected arm, with the affected arm at rest; the no mirror task was with the affected arm at rest while the unaffected arm was moving; and the covered-mirror task was to view a covered mirror while the affected arm was at rest and the unaffected arm was moving actively.

Each task condition consisted of two identical blocks, and each block consisted of 40 trials, with a 15-s break between the two blocks. The software E-Prime 2.0 (Psychology Software Tools, Inc., V2.0, Sharpsburg, PA, United States) was used to present the stimulus (the "ting" tone prompts). The software drove the loudspeaker, which presented one prompt every 5 s. The subject performed one "consecutive wrist flexion and extension movement" naturally, with the fullest range of motion possible, upon the onset of each prompt, until the entire task of one condition was completely finished. The brief break between each block was given to avoid possible fatigue. Between the task conditions, the investigators also allowed approximately 3 min of rest time, and they would explain to the participants the next task condition clearly during the rest times before the next task condition began.

We tested two groups: patients with stroke and age-matched healthy controls. In the control group, the participants were asked to use their dominant hands (with all being right-handed) as their active hand for movement (which was reflected into the mirror). Therefore, only stroke patients with left hemiplegia were recruited for comparison with their healthy counterparts. All participants were randomly assigned to different combinations of the three task conditions in different orders. The procedures were the same for both groups. Patients with stroke practiced the movements with the unaffected hand while watching the reflection of that unaffected hand in the mirror, whereas the controls moved their dominant hand while watching its reflection in the mirror. In the no-mirror tasks, patients with stroke were allowed to view their unaffected hand directly, and the controls viewed their dominant hand directly.

Measurements

Electroencephalograms (EEG) were recorded with a 64-channel electrode cap, according to the International 10–20 System of Electrode Placement, connected to a SymAmps2 amplifier (Compumedics Neuroscan, Charlotte, NC, United States). During the recording, all electrodes were referenced to the left mastoid and were re-referenced to linked mastoid offline. An electrooculogram (EOG) was recorded to monitor eye blinking and movement. Both the EEG and EOG electrode impedances were kept below 5 kOhm, and the signals were sampled at 1,000 Hz. Head movement and eye fixation were well controlled.

Data Preprocessing and Statistical Analysis

Electroencephalograms were processed offline using Scan 4.5 and CURRY 7 (Compumedics Neuroscan, Charlotte, NC, United States). Eye blink artifacts were first corrected by the regression method. Append recording was performed to append the three conditions of EEG raw data segments together as one data file. The bad channels were removed, and epochs with large muscle or otherwise strange events were also rejected. EEG data were then low-pass-filtered at 80 Hz and high-pass-filtered at 1 Hz, and downsampled to 200 Hz. Epochs from 1,000 ms before to 1,500 ms after the onset of the auditory prompts were extracted. Then eye movement artifacts were corrected using an independent component analysis algorithm (Delorme and Makeig, 2004). The artifact trials (epochs) were rejected based on higher-order statistical measures of the independent components (Delorme et al., 2001). Surface electromyography (EMG) was used to detect each wrist flexion and extension movement onset precisely.

Clean epochs were analyzed in the time–frequency domain. The event-related spectral perturbation (ERSP) method using the *newtimef* function of EEGLAB (Makeig, 1993) was used to compute the ERD power. ERSP was calculated relative to the baseline prior to each task trial. The subjects' brain responses during each movement task were measured by the averaged ERSPs at the ipsilateral motor cortex (electrode C4 for stroke patients with left hemiplegia, i.e., ipsilesional hemisphere and ipsilateral to the moving hand) and by the contralateral motor cortex (electrodes C3 for stroke patients with left hemiplegia, i.e., contralesional hemisphere and contralateral to the moving hand but ipsilateral to the hand behind the mirror) in the participants. Then, ERSPs from 400 to 1,100 ms were averaged in the alpha-1 band (8–10 Hz), the alpha-2 band (10–12 Hz), the low beta band defined at 12–16 Hz, and the new beta band (high beta) defined as 17–35 Hz in this study for each participant and in the three task conditions. The ERSPs were computed separately in the three task conditions. An asymmetric index was calculated from the subtraction of the ERSPs between C3 and C4 (the ipsilateral motor area) to account for the difference in activity in the contralateral and ipsilateral motor areas.

A three-way repeated-measure ANOVA was performed to test the significance of the effects of groups (stroke patients vs. healthy peers) and the three task conditions (mirror vs. no mirror vs. covered mirror). *Post hoc* analysis was conducted for testing

differences across time with the three task conditions. Then, a three-way ANOVA was performed with the within-subject factor for the three task conditions (real mirror vs. no mirror vs. covered mirror), hemisphere (contralateral vs. ipsilateral, here contralateral or ipsilateral to the trained hand), and the between-subjects factor for the groups (stroke patients vs. healthy peers) in the alpha-1, alpha-2, low beta, and high beta bands separately. Spearman's correlation coefficient was used to investigate the correlation between arm severity measured by the FTHUE and ERSP values of C3 and C4 in the three task conditions in each frequency band.

RESULTS

After preprocessing the data for the original 11 stroke patients and 20 healthy adults, we excluded the data for seven of the healthy participants and for one stroke participant with left hemiplegia who did not present with enough clean epochs for further analysis. Ultimately, data for 10 stroke participants with left hemiplegia and 13 normal healthy right-handed counterparts were used for further analysis, and their demographics are shown in **Table 1**. The majority of the variables passed the Shapiro–Wilk test of normality, except that four variables violated the normality, which were in the alpha-1 and alpha-2 bands only.

Figure 1 shows the topography of the alpha and beta band rhythms in the unimanual hand movement task during the three task conditions (with a mirror vs. with no mirror vs. with a covered mirror) in the group of stroke patients and in the age-matched controls. **Table 2** summarizes the means and standard deviations of the asymmetric index and ERSP power in alpha-1, alpha-2, low beta, and high beta in the three task conditions.

In the alpha-1 and alpha-2 bands, there was neither a significant main effect nor an interaction effect of *tasks* × *group* × *hemisphere* (**Figure 2**). The results of ANOVA revealed a significant effect from task in the low beta band (12–16 Hz) [$F(1,21) = 3.775$, $p = 0.031$]. Moreover, in the high beta band (17–35 Hz), the three-way ANOVA showed a significant interaction effect from *hemisphere* × *group* [$F(1,21) = 7.698$, $p = 0.011$], a significant main effect from hemisphere [$F(1,21) = 24.299$, $p < 0.0001$], and a significant main effect from the task [$F(2,42) = 3.216$, $p = 0.050$]. There was a marginal interaction effect from *task* × *hemisphere* in the high beta band, with an F ratio of $F(2,42) = 3.187$, $p = 0.051$.

Further examination of the effect of *task* × *hemisphere* showed that in the contralateral hemisphere, C3 (contralateral motor area) had more suppression in the no-mirror and covered-mirror conditions than they did in the mirror condition in the high beta band (17–35 Hz), with an F ratio of $F(2,42) = 6.003$, $p = 0.005$.

An ANOVA was carried out to explore the effects of the task condition and the group on the asymmetry index in the alpha-1, alpha-2, low beta, and high beta bands. Significant main effects of the group on the asymmetry index were found in the high beta band [$F(1,21) = 7.698$, $p = 0.011$], with the stroke patients showing greater asymmetry than the healthy controls did (**Figure 2**).

TABLE 1 | Baseline characteristics of the study population.

Variable	Stroke patients (n = 10)	Healthy controls (n = 13)	p
Age, mean ± SD	56.10 ± 14.35	55.54 ± 5.68	0.909[a]
Gender, *n* (%)			0.593[b]
Male	5 (50.00%)	7 (53.80%)	
Female	5 (50.00%)	6 (46.20%)	
Duration from stroke onset, *months* (mean ± SD)	35.80 ± 22.93	NA	NA
Hemiplegic side, *n* (%)			
Right	0 (0.00%)	NA	NA
Left	10 (100.0%)	NA	NA
Recruitment site, *n* (%)			
Hospital	0 (0.00%)	NA	NA
Self-help groups	10 (100.00%)	NA	NA
Arm functioning, *n* (%)			
Higher	4 (40.00%)	NA	NA
Lower	6 (60.00%)	NA	NA
FTHUE, mean ± SD	4.00 ± 1.33	NA	NA
FMA, mean ± SD			
UL subscore	19.60 ± 8.61	NA	NA
Hand subscore	9.30 ± 6.91	NA	NA
Total score	28.90 ± 14.91	NA	NA
ARAT, mean ± SD			
Grasp subscore	6.60 ± 6.36	NA	NA
Grip subscore	5.10 ± 4.73	NA	NA
Pinch subscore	5.10 ± 4.73	NA	NA
Gross subscore	4.60 ± 3.17	NA	NA
Total score	21.40 ± 19.54	NA	NA
WMFT, mean ± SD			
FAS subscore	27.40 ± 19.54	NA	NA
Grip subscore	6.94 ± 4.28	NA	NA

[a]*Independent t-test;* [b]*Chi-square test; ARAT, Action Research Arm Test; FMA, Fugl-Meyer Assessment; UL, Upper Extremity Score; FTHUE-HK, Functional Test for Hemiplegic Upper Extremity-Hong Kong version; WMFT, Wolf Motor Function Test; FAS, Functional ability score.*

Figure 3 shows the ERSP values of C3 and C4 in 3 task conditions in each frequency band in the two groups. *Post hoc* pairwise comparison was performed in the two bands – C3 and C4, and the asymmetric index (i.e., C3–C4). Regarding the high beta band in patients with stroke, we found a significant difference in C3 ERD between the no-mirror and mirror conditions, i.e., more suppression under the no-mirror condition in C3 compared to that of the mirror condition ($p = 0.022$) (**Figure 3D**). Regarding the low beta band in patients with stroke, we found a significant difference in C3 ERD between the no-mirror and covered-mirror conditions, i.e., more suppression in C3 under the no-mirror condition compared to that of the covered-mirror condition ($p = 0.014$), as well as a significant difference in C4 ERD between the no-mirror and mirror conditions, i.e., more suppression in C4 under the no-mirror condition compared to that under the mirror condition ($p = 0.032$) (**Figure 3C**). However, only a significant difference in the asymmetric index was found between the no-mirror and mirror conditions in healthy controls, i.e., more asymmetric

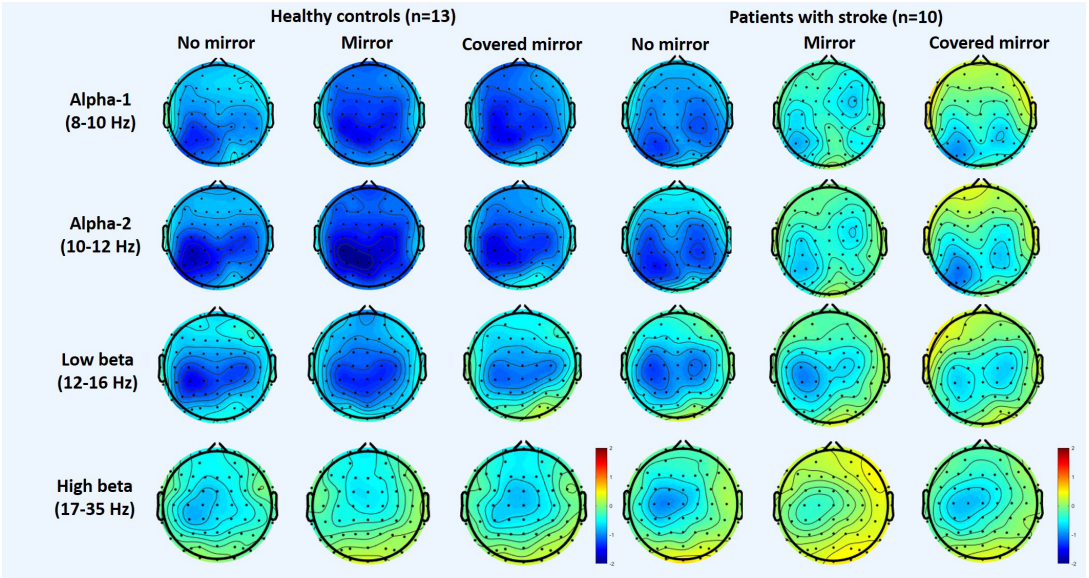

FIGURE 1 | Topography of the alpha and beta rhythms in three unimanual hand movement task conditions: with mirror, with no mirror, and with covered mirror, in two groups: stroke patients and healthy controls.

TABLE 2 | The means and standard deviations of asymmetric index and ERSP power in each of the three task conditions in patients with stroke and health controls.

Population	Stroke patients			Healthy controls		
Condition	**No mirror**	**Mirror**	**Covered mirror**	**No mirror**	**Mirror**	**Covered mirror**
Alpha-1						
C3	−1.08 (1.13)	−0.61 (1.05)	−0.41 (1.20)	−1.07 (1.61)	−1.36 (1.23)	−1.48 (1.35)
C4	−1.15 (1.39)	−0.62 (1.01)	−0.33 (1.20)	−0.97 (1.60)	−1.35 (1.32)	−1.18 (1.54)
Asymmetric index	0.07 (0.64)	0.01 (0.42)	−0.09 (0.94)	−0.11 (0.59)	−0.01 (0.52)	−0.30 (0.64)
Alpha-2						
C3	−1.29 (0.85)	−0.68 (1.27)	−0.54 (1.00)	−1.38 (1.42)	−1.56 (1.31)	−1.53 (1.11)
C4	−1.21 (1.12)	−0.58 (1.18)	−0.54 (1.03)	−1.34 (1.30)	−1.55 (1.40)	−1.30 (1.34)
Asymmetric index	−0.08 (0.55)	−0.10 (0.54)	0.00 (0.49)	−0.05 (0.61)	−0.01 (0.54)	−0.24 (0.59)
Low beta						
C3	−1.29 (1.01)	−0.96 (1.25)	−0.58 (0.82)	−1.33 (0.93)	−1.24 (1.10)	−1.06 (0.90)
C4	−1.02 (1.22)	−0.56 (1.20)	−0.67 (0.90)	−1.24 (0.76)	−1.24 (1.05)	−1.07 (1.00)
Asymmetric index	−0.27 (0.66)	−0.40 (0.66)	0.09 (0.67)	−0.09 (0.51)	0.00 (0.40)	0.01 (0.58)
High beta						
C3	−0.93 (0.99)	−0.33 (0.87)	−0.74 (0.87)	−0.76 (0.90)	−0.41 (0.65)	−0.62 (0.99)
C4	−0.18 (1.16)	0.10 (0.91)	−0.24 (0.76)	−0.51 (0.75)	−0.36 (0.82)	−0.45 (1.04)
Asymmetric index	−0.76 (0.85)	−0.43 (0.29)	−0.50 (0.28)	−0.25 (0.40)	−0.05 (0.38)	−0.17 (0.32)

under the no-mirror condition compared to the mirror condition ($p = 0.039$).

Table 3 shows the correlation between the levels of arm severity with ERSP power in the three task conditions in patients with stroke. Regarding the low beta band, there was a significant moderate correlation between the levels of arm severity measured by the FTHUE with the ERSP power in the no-mirror condition in C4 ($r = -0.731$) and the asymmetric index ($r = 0.675$). The levels of arm severity were found to correlate strongly with ERSP power in the mirror condition in C4 ($r = -0.700$). In contrast, the levels of arm severity correlated strongly with ERSP power in C3 in the no-mirror ($r = -0.706$) and mirror ($r = -0.737$) conditions as well as in C4 in the mirror ($r = -0.712$) and covered-mirror ($r = -0.700$) conditions.

DISCUSSION

This study used EEGs to investigate the immediate effects of a single session of MVF in the motor cortex compared with the effects occurring without a mirror during unimanual arm movements in patients with chronic stroke and in their healthy

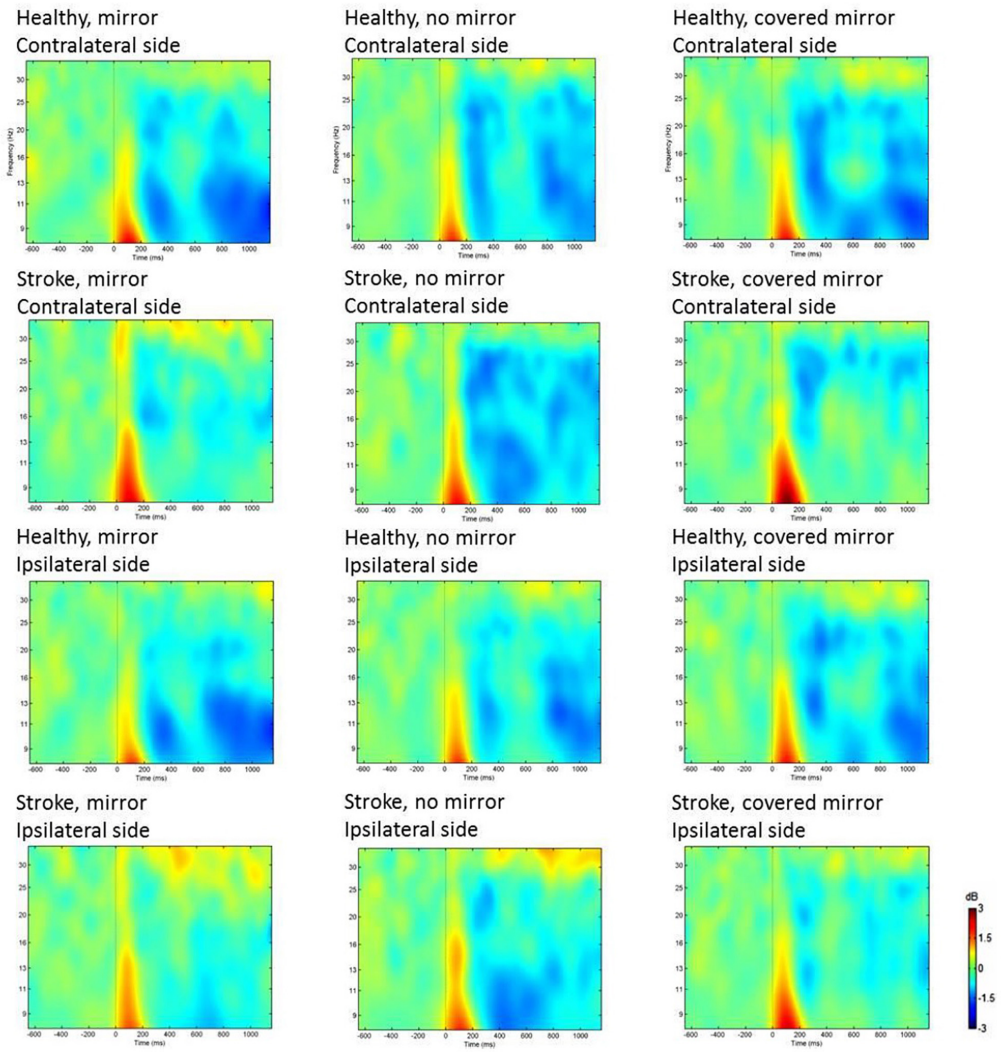

FIGURE 2 | Comparison of ERSPs at electrodes C3 (contralateral motor area) and C4 (ipsilateral motor area) in three unimanual hand movement task conditions: with mirror, with no mirror, and with covered mirror, in two groups: stroke patients and healthy controls, with ERD presented in color blue.

peers. EEG showed similar ERD to MVF in the alpha bands in patients with stroke compared to those found in healthy controls, although the ERSP power in patients with stroke was much lower, and that the attenuation of the low beta ERD was greater over the contralateral hemisphere than it was over the ipsilateral hemisphere in both no-mirror and mirror conditions in patients with stroke.

A reduction of the hemispheric asymmetry was found in patients with stroke in the high beta band during unimanual movement of the non-affected arm. In this study, the magnitude of MVF-induced low beta attenuation in contralesional hemisphere is similar to the finding in patients with right hemispheric stroke (Bartur et al., 2018) except that we also found more suppression in C4 over the ipsilesional hemisphere under the no-mirror condition compared to that under MVF. This finding was consistent with our review that MVF resulted in a shifted activation toward the ipsilesional hemispheres in patients who have had strokes; hence, a more symmetrical state between the two hemispheres may be achieved (Zhang et al., 2018). Stroke is a chronic and disabling disease that is common among the adult population. Recent studies have found that brain recovery can still take place long after the original event, if the patient is undergoing active rehabilitation. Mirror therapy emerged 10 years ago as an intervention for upper limb hemiparesis following stroke and has the advantage of being very inexpensive as well as simpler and less labor-intensive than other types of intervention. In stroke patients, one possible explanation for paralysis being unlearned after watching the mirror illusion during movement is that a residue of mirror neurons has survived the stroke, but it is either dormant or its activity is inhibited and does not reach the threshold. Another possibility is that the motor areas may have become temporarily inactive because the patient's visual feedback loop has closed, and the mirror image might

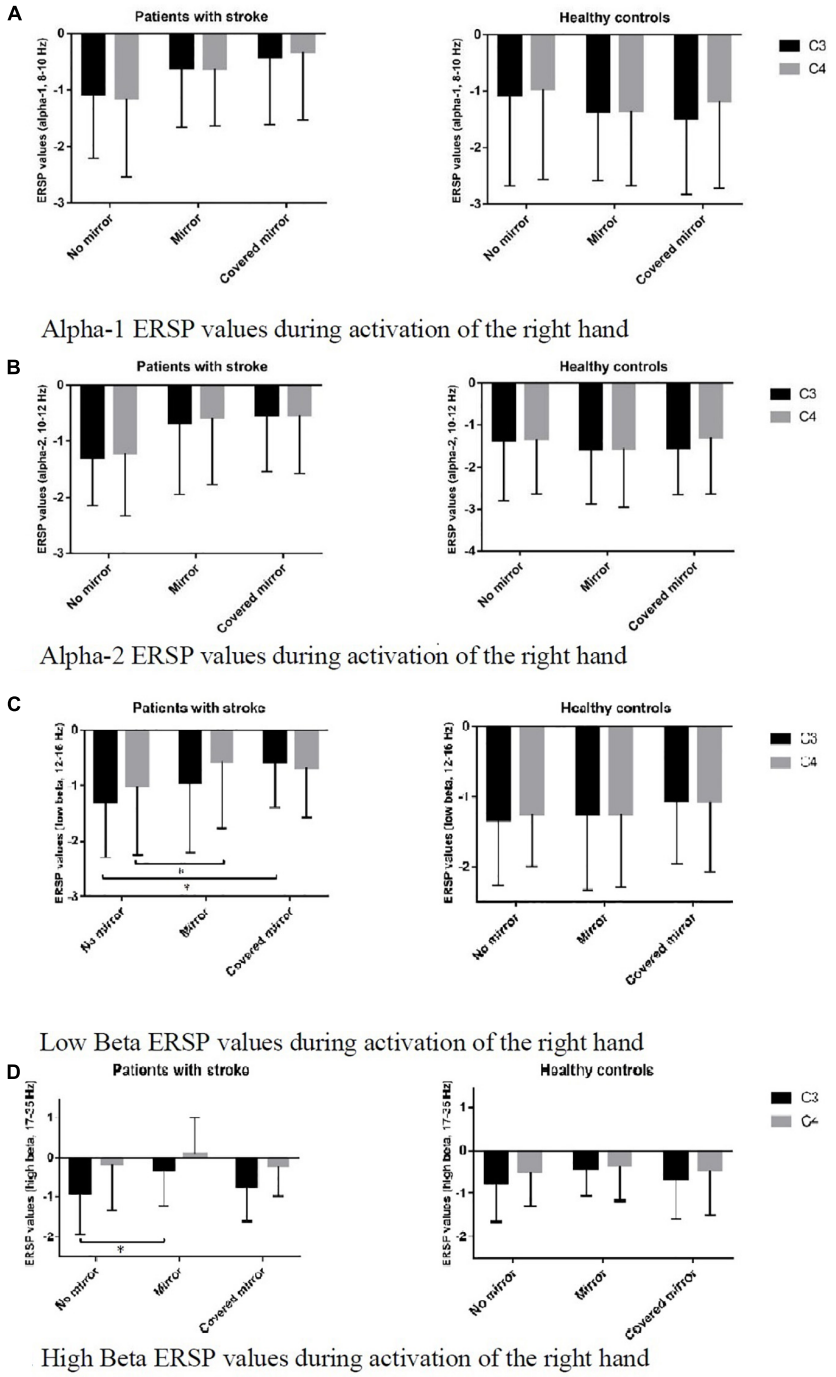

FIGURE 3 | ERSP values of C3 and C4 in three task conditions in each frequency band, in two groups: stroke patients and healthy controls. **(A)** Alpha-1 ERSP values during activation of the right hand. **(B)** Alpha-2 ERSP values during activation of the right hand. **(C)** Low Beta ERSP values during activation of the right hand. $^*p < 0.05$. **(D)** High Beta ERSP values during activation of the right hand. $^*p < 0.05$.

provide sufficient visual input to revive those motor neurons (Ertelt et al., 2007).

We know that M1 excitability is modulated simultaneously both by hemiplegic limb movement and by observation of the movement of the non-affected limb as reflected in the mirror during MVF, with the ipsilateral M1 becoming more active (Garry et al., 2005), as MVF decreases the motor threshold through a reduction in interhemispheric inhibition (Carson and Ruddy, 2012) and a reduction of intracortical inhibition (Lappchen et al., 2012). A key mechanism

TABLE 3 | Correlation between levels of arm severity with ERSP power in three task conditions in patients with stroke.

Condition	No mirror			Mirror			Covered mirror		
Position	**C3**	**C4**	**AI**	**C3**	**C4**	**AI**	**C3**	**C4**	**AI**
Alpha-1									
FTHUE	−0.056	−0.099	0.353	−0.074	−0.359	0.489	0.074	0.068	0.006
Alpha-2									
FTHUE	−0.248	−0.050	0.198	−0.384	−0.570	0.279	0.161	−0.223	0.440
Low beta									
FTHUE	−0.396	−0.731*	0.675*	−0.601	−0.700*	0.365	−0.155	−0.539	0.458
High beta									
FTHUE	−0.706*	−0.570	−0.204	−0.737*	−0.712*	0.229	−0.576	−0.700*	0.012

$p < 0.05$; FTHUE, levels of arm severity measured by the Functional Test of the Hemiplegic Upper Extremity; AI, asymmetric index.

hypothesized to explain these beneficial effects is that the mirror illusion transiently decreases the asymmetric activities of movement-related desynchronization in the beta frequency range (Rossiter et al., 2015).

In this study, it was interesting to find that there was a significant main effect of groups in both the contralateral and ipsilateral motor areas, and particularly in the contralateral motor area C3, in the age-matched controls and stroke participants' groups in the high beta band. Traditionally, we have believed in bilateral mu suppression during movement execution (Frenkel-Toledo et al., 2013). Previous studies also showed that MVF operates in a different manner – in different frequency bands and involving either or both hemispheres (Bartur et al., 2018).

We also found overall reduced ERD in both hemispheres in patients with stroke in various frequency bands compared to that of their healthy peers. This is consistent with other studies that the ERD induced by observation is very limited in stroke patients, in both ipsilesional and contralesional hemispheres. It is unclear why ERD does not occur in stroke patients partly because of the lower functional recovery of the affected arm. Our correlation analysis revealed that the magnitude of ERSP power correlated significantly with arm severity in the low and high beta bands in patients with stroke. The minus sign indicated that it was a negative relationship. Results revealed that higher levels of the FTHUE and higher functioning of the upper extremity (or less severe arm impairment) were associated with lower values of the ERSP power in the no-mirror and mirror conditions at the ipsilesional C4, i.e., stronger suppression at the low beta. The positive relationship of the levels of arm severity with the asymmetric index (a lower value showing more symmetry between the hemispheres and a shifted activation toward the ipsilesional hemisphere) in the low beta in the no-mirror condition revealed a higher asymmetry between the hemispheres, i.e., the ERSP values at the contralesional C3 was higher than that at the ipsilesional C4, in patients with higher arm functioning. At the high beta, similar findings were noted in the mirror and covered-mirror conditions in C4, but a significant negative correlation was also found in the contralesional C3 in the no-mirror and mirror conditions, which reflects likely the motor execution of the moving hand. Even though the underlying neural network cannot be fully understood at this stage, the reduced ERD in both hemispheres in patients who have had strokes might cause problems in action observation and movement preparation for execution in their motor learning, hence affecting their motor recovery. Furthermore, when patients suffer damage to their inferior parietal lobe or inferior frontal gyrus, the MNS as indicated by the ERD induced over their contralesional sensorimotor cortex through observation is attenuated too (Frenkel-Toledo et al., 2014, 2016; Perry et al., 2017). As a single MVF session was found to reduce the magnitude of ERD bilaterally in stroke patients in the current study, further investigation of the neurophysiological effects of MVF application in randomized controlled studies is warranted.

The results of this study show that there was an MVF-induced ERD attenuation in the high and low beta bands, and that the rhythm suppression was greater over the contralateral hemisphere (i.e., contralesional in stroke) than it was over the ipsilateral hemisphere in the low beta in stroke participants. This finding is consistent with the results of another study using magnetoencephalography (MEG) that the ERD in M1 beta decreased more in the bilateral mirror condition than in the bilateral no-mirror and unimanual mirror conditions (Tai et al., 2020), and that the ERD areas in both the alpha and beta were larger under the reciprocal mirror condition, followed by bilateral and no-mirror conditions (Chang et al., 2019). In a recent MEG study (Rossiter et al., 2015), similar results of movement-related beta desynchronization were found in patients and their healthy controls, but those observations differed from the results of another study (Frenkel-Toledo et al., 2013) that found in an EEG analysis a more pronounced suppression over the right hemisphere than over the left hemisphere sites during observation of action, regardless of the hand that moved (right or left hand). Our previous study demonstrated that a shift in sensorimotor asymmetry toward the contralateral hemisphere was induced by MVF immediately, in alpha-1, alpha-2, and beta-1 bands in healthy right-handed adults (Zhang and Fong, 2019). Another study showed that the hemispheric symmetry was reduced during non-affected arm movement in the mirror condition after a single session of MVF in patients with subacute stroke (Bartur et al., 2018). These indicated that MVF might contribute to stroke recovery by revising the interhemispheric

imbalance caused by stroke due to the activation of the MNS, hence promoting motor relearning in stroke patients (Zhang et al., 2018). Our findings concur with a previous study that the low beta ERD in both hemispheres has the potential to be used as a neurophysiological marker for the MVF treatment outcome for improving stroke patients' recovery in future studies (Bartur et al., 2018).

Limitations of the Study

This was a cross-sectional study, the change of the amount of MVF-induced ERD attenuation across time had not been investigated, and that its relationships with motor severity and functional prognosis had not been revealed. The results of this study were based on a small sample from the chronic stroke population, so a bias was possible in the subject recruitment, which was based on convenience sampling. Since the participants with stroke were recruited through self-help organizations in the community, we did not know the detailed lesion site from the participants. Our results were based on a group of stroke patients with right hemispheric damage and had not compared their performance with that of patients with left hemispheric brain damage. This study only considered the ERD phenomena on the primary motor areas; other brain regions such as the parietal areas in the MNS had not been investigated. The hemispheric asymmetry in the low beta under MVF was particularly more salient following right hemispheric damage (Bartur et al., 2018). Although the MVF leading to an instant ERD might have been associated with facilitation of M1 (ipsilateral to the moving hand that was mirrored), our findings must be interpreted with care, and we caution that the variance in the movement task conditions, which was unimanual and without involvement of the affected hand, as well as the levels of stroke impairment, may have complicated the overall interpretation of the results. Moreover, the demographics of the older adult control participants did not closely match with those in the stroke group.

CONCLUSION

Our study shows that the laterality of bilateral sensorimotor ERD during unimanual arm movement could be mediated by the recognition of MVF in both stroke patients with right hemispheric damage and healthy controls. The findings of this study shed light for neurophysiological investigations during motor training in stroke rehabilitation. Further study should investigate the effects of training, both by MVF and bimanual arm training, with the goals of reestablishing the hemispheric balance that has been disrupted by an insult in the motor cortex and consequently of improving patient readiness in lateralized potential for motor recovery. The use of ERD in the low beta band in the motor cortex as a neurophysiological marker to indicate the relationships between the amount of MVF-induced ERD attenuation and motor severity and functional prognosis in patients with stroke, and an outcome indicator for improving patients' neuroplasticity in clinical trials is warranted to be explored in the future.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Human Subjects Ethics Committee of The Hong Kong Polytechnic University (Ref. No.: HSEARS20121012008). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KNKF and KHT were involved in the conception and design of the study and conducted the experiment. KNKF and CSFY collected the data. KNKF and JJQZ wrote up and edited the manuscript. All authors approved the submission of the final version of the manuscript.

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ORIGINAL RESEARCH
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The Effect of Prior Knowledge of Color on Behavioral Responses and Event-Related Potentials During Go/No-go Task

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In daily life, the meaning of color plays an important role in execution and inhibition of a motor response. For example, the symbolism of traffic light can help pedestrians and drivers to control their behavior, with the color green/blue meaning go and red meaning stop. However, we don't always stop with a red light and sometimes start a movement with it in such a situation as drivers start pressing the brake pedal when a traffic light turns red. In this regard, we investigated how the prior knowledge of traffic light signals impacts reaction times (RTs) and event-related potentials (ERPs) in a Go/No-go task. We set up Blue Go/Red No-go and Red Go/Blue No-go tasks with three different go signal (Go) probabilities (30, 50, and 70%), resulting in six different conditions. The participants were told which color to respond (Blue or Red) just before each condition session but didn't know the Go probability. Neural responses to Go and No-go signals were recorded at Fz, Cz, and Oz (international 10–20 system). We computed RTs for Go signal and N2 and P3 amplitudes from the ERP data. We found that RT was faster when responding to blue than red light signal and also was slower with lower Go probability. Overall, N2 amplitude was larger in Red Go than Blue Go trial and in Red No-go than Blue No-go trial. Furthermore, P3 amplitude was larger in Red No-go than Blue No-go trial. Our findings of RT and N2 amplitude for Go ERPs could indicate the presence of Stroop-like interference, that is a conflict between prior knowledge about traffic light signals and the meaning of presented signal. Meanwhile, the larger N2 and P3 amplitudes in Red No-go trial as compared to Blue No-go trial may be due to years of experience in stopping an action in response to a red signal and/or attention. This study provides the better understanding of the effect of prior knowledge of color on behavioral responses and its underlying neural mechanisms.

Keywords: N2, P3, Go/No-go task, reaction time, prior knowledge of color, event-related potential, Stroop

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INTRODUCTION

Execution and inhibition of voluntary movements are often influenced by the meaning of colors in contextually relevant situations. For instance, the color green/blue means go while the color red means stop in the traffic control system, which guides our behavior during walking and driving. According to Peschke et al. (2013), color of the traffic lights influences pedestrian's behavior

more than the object shape. However, it is currently unclear how individuals make responses to a signal when the meanings of colors are opposite to those in the traffic control system (i.e., the color green/blue means stop while the color red means go). As drivers need to *start* pressing the brake pedal when a traffic light turns red to avoid traffic accidents, it is important to understand how the prior knowledge of traffic light color impacts behavioral responses and the underlying neural mechanisms.

There are several studies that examined the effect of color on reaction times (RTs). For example, Eason et al. (1967) showed comparable reaction times for blue or red lights in a simple RT task. Also, Anllo-Vento et al. (1998) investigated attention to red-and-gray and blue-and-gray checkerboards using a task in which participants pressed a button when a dimmer target of attended color was detected, and found that RTs were similar for red and blue checkboards. On the other hand, in a visual search task, stimulus discrimination time was revealed to be faster for red than blue and yellow stimuli (Pomerleau et al., 2014). In addition, Hochman et al. (2018) investigated the effect of color on RTs using a stop-signal task, in which participants were required to respond to a traffic light picture (green and red) and had to stop the initiated response when an auditory stop signal was presented in some trials. They found that RTs in trials without the stop signal were faster with green than red traffic light picture, whereas stop-signal RTs were faster with red than green traffic light picture. Collectively, these studies indicate that there is the effect of color on behavioral responses in a relatively difficult tasks, especially when the task requires the ability to stop an ongoing action; however, there is no study investigating the effect of color on the ability to inhibit a response proactively.

One of the tasks that examine proactive response inhibition is a Go/No-go task. In the task, participants are required to respond when a target signal is presented but have to refrain from responding when a non-target signal is presented. To understand the neural mechanisms underlying the behavioral responses, brain activity is often recorded by means of event-related potentials (ERPs), which are well used to investigate the processing of exogenous and endogenous events due to the high temporal resolution. The first major ERP component observed mainly at the occipital site around 50–100 ms is commonly called C1 and originates in the primary visual cortex (Clark and Hillyard, 1996). The C1 has been considered to be unaffected by attention (Clark and Hillyard, 1996; Anllo-Vento et al., 1998), but by exogenous factors such as stimulus color (Anllo-Vento et al., 1998).

Following the C1, there are two major ERP components that are associated with cognitive processes. The first one is called N2, a negative component observed around 200 ms after the stimulus presentation. The N2 has been thought to be related to response inhibition because it is typically larger for a non-target than target signal at front-central sites (Folstein and Van Petten, 2008). Meanwhile, there is an argument that the N2 reflects conflict control process rather than response inhibition (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004; Enriquez-Geppert et al., 2010). In any case, the main source of N2 is estimated to be at the anterior cingulate cortex (ACC) (Nieuwenhuis et al., 2003).

The second one is called P3, which occurs following the N2 around 300 ms after the stimulus presentation. Although P3 has been reported to reflect a number of different cognitive mechanisms, such as confidence (Addante, 2015), novelty processing (Knight and Scabini, 1998), metacognition (Muller et al., 2021), and decision making (Boldt et al., 2019), here we focus on ones related to Go/No-go task. Specifically, Enriquez-Geppert et al. (2010) investigated the influence of conflict and inhibition on N2 and P3 using a combined Go/No-go and stop-signal task, during which the degree of conflict was manipulated by varying probability of go signal (75 vs. 25%) while inhibition was evaluated by three signals, Go, No-go and stop. They reported the larger P3 amplitude in stop than Go trial and found a minor effect of go-signal probability on the P3 amplitude compared to N2 amplitude. These results may indicate that the P3 reflects inhibition rather than conflict monitoring. Additionally, they estimated the main source of P3 as the inferior frontal cortex (IFC), which is considered to play an important role in response inhibition, as evidenced by a vast amount of previous literature (e.g., Meffert et al., 2016; Cunillera et al., 2016; Wessel and Aron, 2017). Thus, although disagreement remains over the interpretation of the N2 and P3, they seem to reflect response inhibition and/or conflict.

In relation to RTs and ERP components examined in the Go/No-go task, considerable works reported that they can be influenced by probability of target signals. Generally, RT slows down as the probability of target signals decreases (Bruin and Wijers, 2002; Nieuwenhuis et al., 2003; Hsieh et al., 2016). Also, it has been reported that N2 (Nieuwenhuis et al., 2003; Donkers and Van Boxtel, 2004) as well as P3 (Hsieh et al., 2016) amplitudes can be larger with lower target signal probability. Given these findings, the effect of color on the proactive response inhibition may be affected by the target signal probability. That is, the stronger influence of the color can be predicted with lower probability of target signals.

Accordingly, the purpose of this study was to investigate whether incongruency between prior knowledge of color (traffic lights) and the meaning of presented color would be a cognitive load in the Go/No-go task. To this end, we set up a Blue Go/Red No-go task (i.e., a blue light means to respond while a red light means to refrain) and a Red Go/Blue No-go task with three different target signal probabilities (Go probabilities). In previous literature, reaction time for naming a color is known to be slower when there is a conflict between color name and the color of ink (Stroop effect). Moreover, N2 and P3 amplitudes can be larger with incongruent than congruent stimulus (Pan et al., 2016; Wang et al., 2021). Consequently, we hypothesized that: (1) RTs would be faster when responding to Blue Go than Red Go signal; (2) N2 and P3 amplitudes would be larger in Red Go/Blue No-go than Blue Go/Red No-go task; (3) RTs and N2 and P3 amplitudes would be influenced by the incongruency between prior knowledge of color and the meaning of presented color more strongly in lower Go probability condition.

MATERIALS AND METHODS

Participants

Thirteen healthy participants (4 female, mean age = 28.2 years, SD = 8.5 years) took part in this study, following a previous study (Pomerleau et al., 2014). All participants were strongly right-handed as evaluated by the Edinburg Handedness Inventory scores of 0.9–1.0 (Oldfield, 1971), and had normal or corrected-to-normal vision. Written informed consent was obtained from all participants before beginning the experiment, which was conducted to principles of the Declaration of Helsinki. The study was approved by the Ethics Committee for Clinical Research of Hiroshima University (No. C-242).

Design and Procedure

A custom-made light-emitting diode (LED) device (4 Assist, Tokyo, Japan) was used to present blue and red lights (Watanabe et al., 2021). Although the illuminances of blue and red lights were different (7.71 lx for blue light and 4.93 lx for red light), we confirmed that simple RTs to these lights were statistically similar prior to the experiment. The participants faced the LED device set 1 m in front of them at the height of eye (**Figure 1A**) and performed a Go/No-go task. Blue and red lights were randomly presented for 100 ms at a random interval of 3,000 ± 300 ms (**Figures 1B,C**) and served as both target (Go) and non-target (No-go) signals. The participants were instructed to press a button held in the right hand as fast as possible when a target (Go) signal appeared and to withhold the response when a non-target (No-go) signal appeared.

The experiment had a 2 × 3 design with the following factors: Color (Blue Go/Red No-go and Red Go/Blue No-go) and Go probability (30, 50, and 70%), resulting in six different conditions. The participants were told which color to respond (Blue or Red) just before each condition session but didn't know the Go probability. Prior to the sessions, they practiced 30 trials. The condition order was randomized among the participants. Each condition consisted of 100 trials, and sufficient breaks were provided between the condition sessions. RT was calculated as the time from the appearance of Go signal to the pressing of the button. Similar to previous studies (Watanabe et al., 2015; Watanabe et al., 2016a; Rey-Mermet et al., 2019), trials exceeding 3SD from the mean RT of the condition were excluded from statistical analysis.

EEG Recording and Analysis

Electroencephalogram (EEG) was recorded using three Ag/AgCl active electrodes at Fz, Cz, and Oz according to the International 10–20 system. Eye blinks and movements were monitored via electrooculogram (EOG) using bipolar electrodes attached to the outer side of the right canthus and below the left eye (Watanabe et al., 2016b). All channels were referenced to the linked earlobes. The ground electrode was attached to the left forearm using the disposable gel electrode (GE Health Care Japan, Tokyo, Japan). The EEG and EOG were amplified (BA1008; Nihon Sankeku, Osaka, Japan), filtered between 0.1 and 100 Hz, and digitized at sampling rate of 1 kHz. Impedance was kept below 10 kΩ. The custom-made LED device was programmed to send a pulse trigger for synchronization with EEG (4 Assist, Tokyo, Japan). Continuous EEG data were segmented into 1,000 ms epochs starting 100 ms prior to the stimulus onset. Epochs exceeding ±100 μV were automatically discarded. Furthermore, we visually inspected and discarded epochs still contaminated by artifacts (Ozubko et al., 2021). The average number of discarded epochs was 14 ± 12, and the average number of retained epochs was

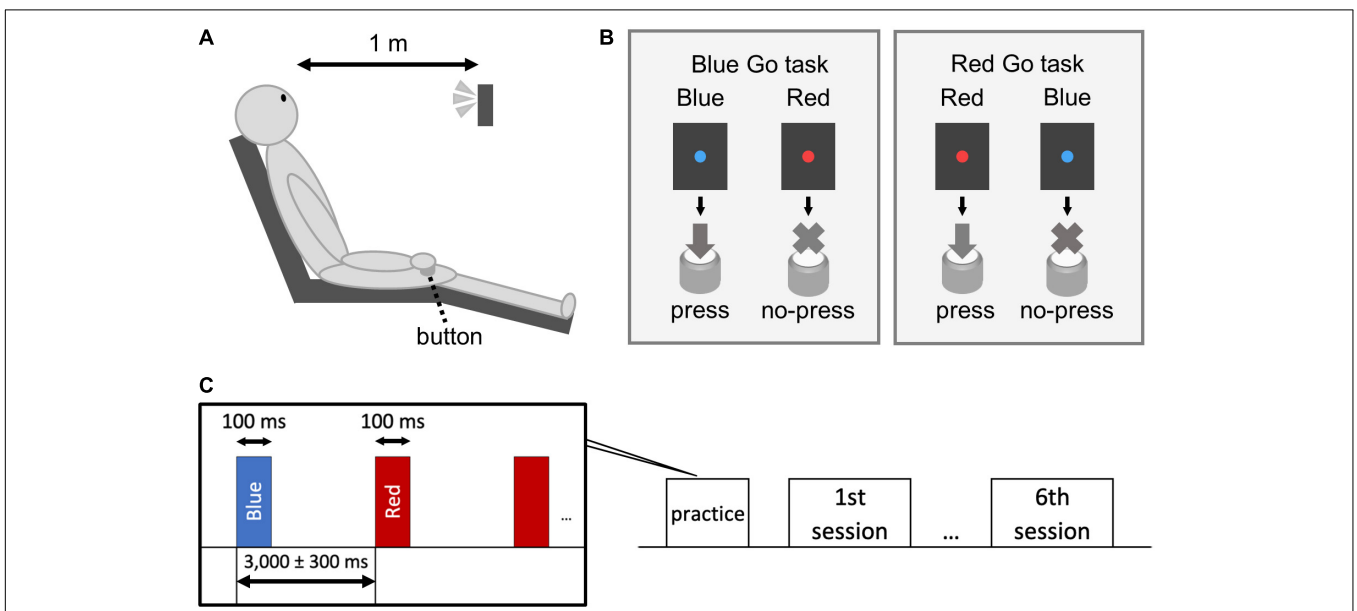

FIGURE 1 | Schematic illustration of the experiment. The subject sat on a chair and performed a Go/No-go task with the right hand **(A)**. We set up a Blue Go/Red No-go task and a Red Go/Blue No-go task **(B)**. The target/non-target signal was presented for 100 ms with an interstimulus interval of 3,000 ± 300 ms **(C)**.

36 ± 17. Following previous studies (Schoenberg et al., 2014; Nguyen et al., 2016), a threshold to exclude subjects from the analysis was set as five. The artifact-free epochs were then averaged separately for Go and No-go trials in each condition in order to obtain ERP components. Subsequently, we identified the following peaks: P1 from 100 to 170 ms, N2 from 130 to 300 ms, and P3 from 250 to 500 ms for the front-central site (Fz and Cz), and C1 from 50 to 110 ms, P2 from 180 to 250 ms, N2 from 200 to 300 ms, and P3 from 250 to 500 ms for the occipital site (Oz). Using these peaks, we finally calculated the C1, N2, and P3 amplitudes and latencies. The C1 amplitude was defined as the difference between C1 peak and a baseline (–100 to 0 ms), the N2 amplitude was defined as the difference between the P1 (Fz and Cz) or P2 (Oz) and N2 peaks, and the P3 amplitude was defined as the difference between the N2 and P3 peaks (peak-to-peak measurements). As the minimum number of artifact-free epochs accepted into condition averages in this study was seven (range 7–70), all conditions from all participants were included in the statistical analysis.

Statistical Analysis

SPSS Statistics software version 21 (SPSS; IBM Corp., Armonk, NY, United States) was used for statistical analysis. A two-way repeated-measures analysis of variance (ANOVA) was used to determine the effect of Color (Blue Go and Red Go) and Go probability (30, 50, and 70%) on the mean RT and ERP amplitude and latency. Furthermore, Pearson's correlation coefficients were calculated between the RT and ERP amplitude or latency. *Post hoc* test was conducted with Bonferroni adjustment. Significant level was set at $p < 0.05$. The effect size for each ANOVA was calculated using partial eta squared (partial η^2).

RESULTS

Behavioral Results

The average number of trials in which the participants did not respond to Go signals (Go omission errors) and that in which the participants responded to No-go signals (No-go commission errors) are presented in **Table 1**. These trials were not included in RT or ERP analysis.

Mean RTs are depicted in **Figure 2**. A two-way repeated-measures ANOVA indicated significant main effects of Color [$F(1, 12) = 22.933$, $p < 0.001$, partial $\eta^2 = 0.656$] and Go probability [$F(2, 24) = 25.373$, $p < 0.001$, partial $\eta^2 = 0.679$], but there was no significant interaction between them [$F(2, 24) = 0.911$, $p = 0.384$, partial $\eta^2 = 0.071$]. *Post hoc* analyses revealed that the higher Go probability, the faster RT ($p < 0.05$).

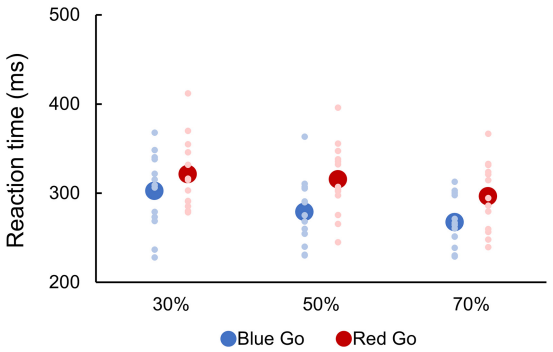

FIGURE 2 | Reaction time to go signal. There were six conditions created by crossing two target colors (Blue Go/Red No-go and Red Go/Blue No-go) and three target probabilities (30, 50, and 70%). Individual data (light color) and their mean (dark color) were presented for each condition.

ERP Results

Figure 3 shows grand average ERP waveforms for six conditions.

Early Component

A two-way repeated-measures ANOVA showed a main effect of Color [$F(1, 12) = 5.747$, $p = 0.020$, partial $\eta^2 = 0.485$] and an interaction between Color and Go probability [$F(2, 24) = 4.317$, $p = 0.018$, partial $\eta^2 = 0.329$] on C1 amplitude for Go ERPs. A *post hoc* analysis revealed that C1 amplitude was larger in Blue Go than Red Go trial in 30% Go probability. Regarding the C1 latency, there was no significant main effect or interaction for Go ERPs.

N2 and P3 Amplitudes

For both Go and No-go ERPs, a two-way repeated-measures ANOVA showed a main effect of Color on N2 amplitude, which was larger when responding to Red Go than Blue Go and when withholding a response to Red No-go than Blue No-go at Fz [Go: $F(1, 12) = 5.961$, $p = 0.018$, partial $\eta^2 = 0.337$; No-go: $F(1,12) = 33.525$, $p < 0.001$, partial $\eta^2 = 0.837$], Cz [Go: $F(1, 12) = 6.120$, $p = 0.016$, partial $\eta^2 = 0.303$; No-go: $F(1, 12) = 6.620$, $p = 0.013$, partial $\eta^2 = 0.431$], and Oz [Go: $F(1,12) = 7.444$, $p = 0.009$, partial $\eta^2 = 0.090$; No-go: $F(1, 12) = 7.770$, $p = 0.007$, partial $\eta^2 = 0.218$]. There was also a main effect of Go probability on N2 amplitude for No-go ERPs at Cz [$F(2, 24) = 3.185$, $p = 0.048$, partial $\eta^2 = 0.199$], and a *post hoc* analysis revealed that the N2 amplitude was larger in 30% than 70% No-go probability ($p = 0.043$, **Figure 4A**).

With respect to P3 amplitude, for both Go and No-go ERPs, a two-way repeated-measures ANOVA showed a main effect of Color at Cz [Go: $F(1, 12) = 7.739$, $p = 0.007$, partial $\eta^2 = 0.250$;

TABLE 1 | Go omission and No-go commission errors (mean ± SD).

	Blue Go 30%/Red No-go 70%	Blue Go 50%/Red No-go 50%	Blue Go 70%/Red No-go 30%	Red Go 30%/Blue No-go 70%	Red Go 50%/Blue No-go 50%	Red Go 70%/Blue No-go 30%
Go omission errors	0.77 ± 1.77	1.08 ± 1.75	1.08 ± 1.50	0.46 ± 0.97	0.54 ± 1.20	1.23 ± 3.85
No-go commission errors	0.31 ± 0.63	0.31 ± 0.63	0.46 ± 0.52	0.23 ± 0.44	0.69 ± 0.75	0.77 ± 1.24

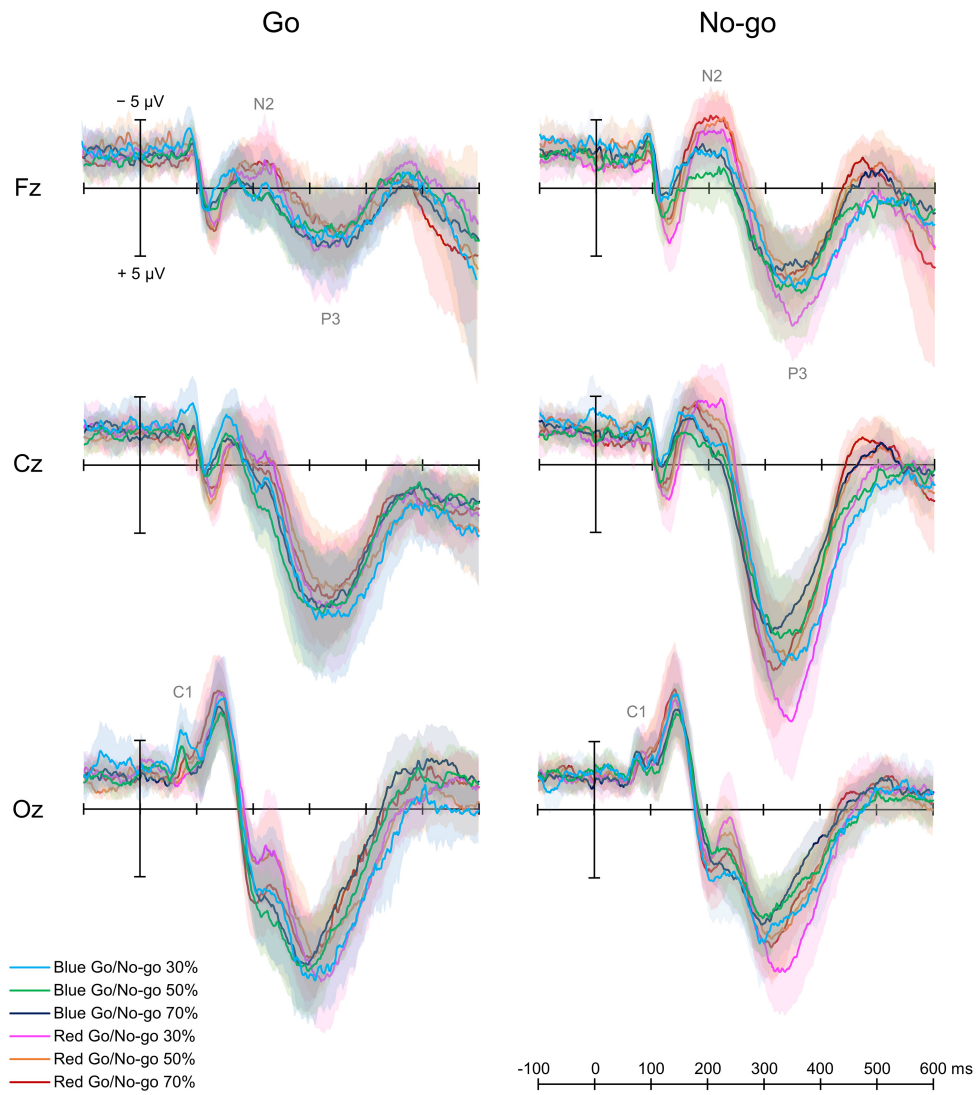

FIGURE 3 | Grand average event-related potential waveforms. There were six conditions created by crossing two target colors (Blue Go/Red No-go and Red Go/Blue No-go) and three target probabilities (30, 50, and 70%).

No-go: $F(1, 12) = 4.362$, $p = 0.041$, partial $\eta^2 = 0.124$] and Oz [Go: $F(1, 12) = 6.069$, $p = 0.018$, partial $\eta^2 = 0.247$; No-go: $F(1, 12) = 45.808$, $p < 0.001$, partial $\eta^2 = 0.774$]. Also, there was a main effect of Go probability on P3 amplitude for Go ERPs at Fz [$F(2, 24) = 5.137$, $p = 0.009$, partial $\eta^2 = 0.316$] and Cz [$F(2, 24) = 11.559$, $p < 0.001$, partial $\eta^2 = 0.597$], and for No-go ERPs at Fz [$F(2, 24) = 6.863$, $p = 0.002$, partial $\eta^2 = 0.462$], Cz [$F(2, 24) = 11.388$, $p < 0.001$, partial $\eta^2 = 0.609$], and Oz [$F(2, 24) = 15.296$, $p < 0.001$, partial $\eta^2 = 0.693$]. We further found an interaction between Color and Go probability on P3 amplitude for No-go ERPs at Oz [$F(2, 24) = 5.536$, $p = 0.006$, partial $\eta^2 = 0.283$]. *Post hoc* analyses demonstrated that the P3 amplitude for Go ERPs was larger in 30% than 70% Go probability at both Fz and Cz ($p < 0.01$), and that the P3 amplitude for No-go ERPs was larger in 30% than 50 and 70% No-go probability at Fz and Cz ($p < 0.05$). For No-go ERPs at Oz, *post hoc* analyses revealed that the P3 amplitude was larger in Red No-go than Blue No-go trial in 30% No-go probability ($p = 0.007$), and that it was larger in 30% than 50% ($p = 0.004$) and 70% ($p < 0.001$) No-go probability in Red No-go trial (**Figure 4B**).

N2 and P3 Latencies

For both Go and No-go ERPs, a two-way repeated-measures ANOVA showed a main effect of Color on N2 latency, which was faster when responding to Blue Go than Red Go and when withholding a response to Blue No-go than Red No-go at Fz [Go: $F(1, 12) = 7.041$, $p = 0.010$, partial $\eta^2 = 0.426$; No-go: $F(1, 12) = 7.533$, $p = 0.008$, partial $\eta^2 = 0.236$] and Cz [Go: $F(1, 12) = 9.504$, $p = 0.003$, partial $\eta^2 = 0.451$; No-go: $F(1, 12) = 8.678$, $p = 0.005$, partial $\eta^2 = 0.306$; **Figure 5A**].

A two-way repeated-measures ANOVA revealed a main effect of Color on P3 latency for Go ERPs at Cz [$F(1, 12) = 6.376$,

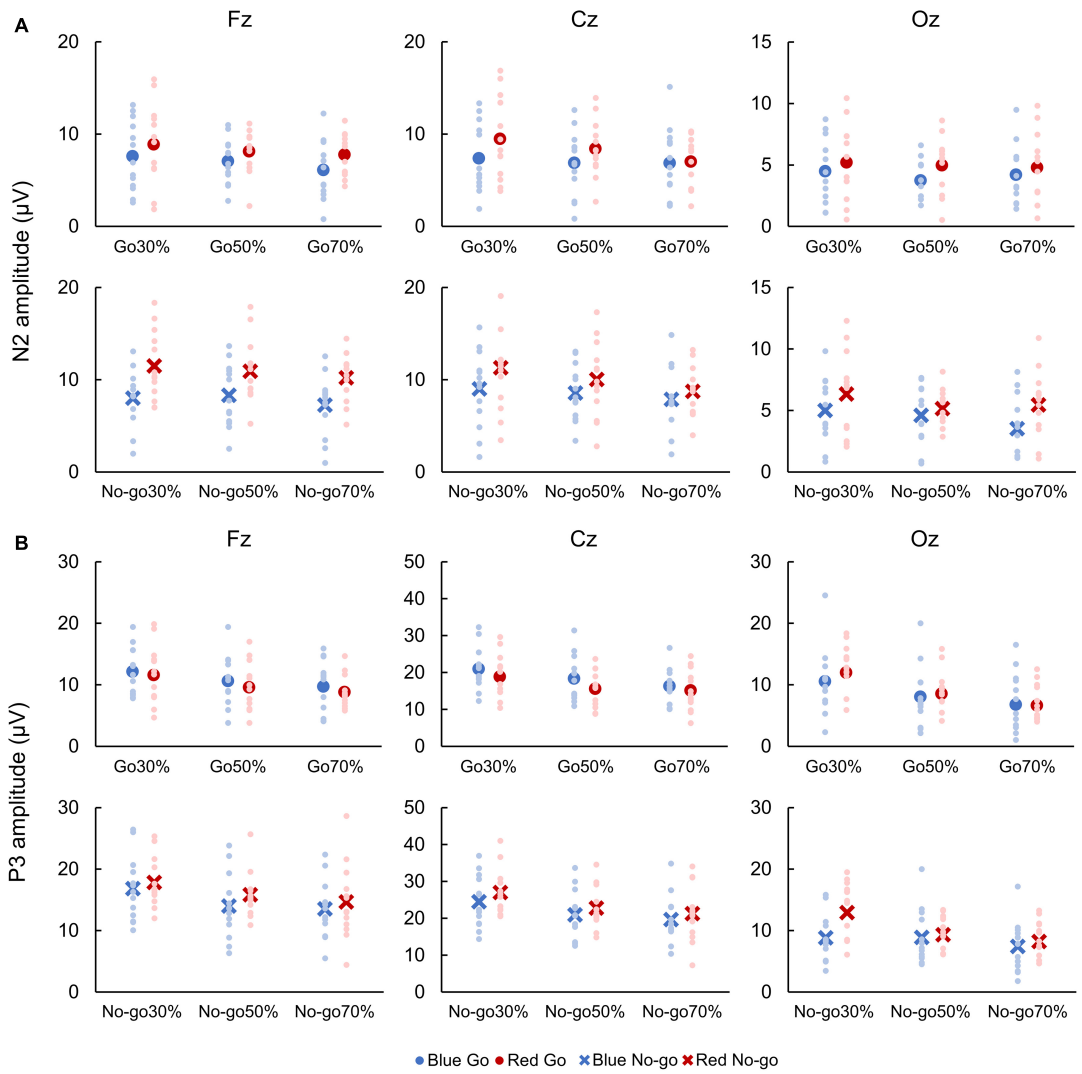

FIGURE 4 | Amplitudes of N2 **(A)** and P3 **(B)**. Blue color indicates responses to a blue light (Blue Go and Blue No-go), and red color indicates responses to a red light (Red Go and Red No-go). Individual data (light color) and their mean (dark color) were presented for each condition.

$p = 0.014$, partial $\eta^2 = 0.210$]. Also, there was a main effect of Go probability on P3 latency for Go ERPs at Oz [$F(2, 24) = 6.110$, $p = 0.004$, partial $\eta^2 = 0.363$] and for No-go ERPs at Cz [$F(2, 24) = 5.305$, $p = 0.008$, partial $\eta^2 = 0.318$]. *Post hoc* analyses revealed that the P3 latency for Go ERPs was faster in 70% than 30 and 50% Go probability at Oz. Conversely, P3 latency for No-go ERPs was faster in 70% than 30 and 50% No-go probability at Cz ($p < 0.05$; **Figure 5B**).

Correlations Between RT and ERP Amplitude/Latency

Table 2 shows correlations between the RT and N2 or P3 amplitude. Significant positive correlations were obtained between the RT and N2 amplitude at Fz for Go ERPs, and at Oz for No-go ERPs. There was a significant negative correlation between the RT and P3 amplitude at Cz for Go ERPs.

Table 3 shows correlations between the RT and N2 or P3 latency. We found significant positive correlations between the RT and P3 latency at Cz and Oz for Go ERPs.

DISCUSSION

The present study aimed to elucidate the effect of prior knowledge of color on RTs and ERPs during a Go/No-go task. For that purpose, we set up Blue Go/Red No-go and Red Go/Blue No-go tasks with three different Go probabilities (30, 50, and 70%). Overall, we found the slower RTs in Red Go than Blue Go trial, and also with lower Go probability. Furthermore, in general, amplitudes of N2 and P3 components of ERPs were larger in Red Go/Red No-go than Blue Go/Blue No-go trial and were larger with lower Go/No-go probability.

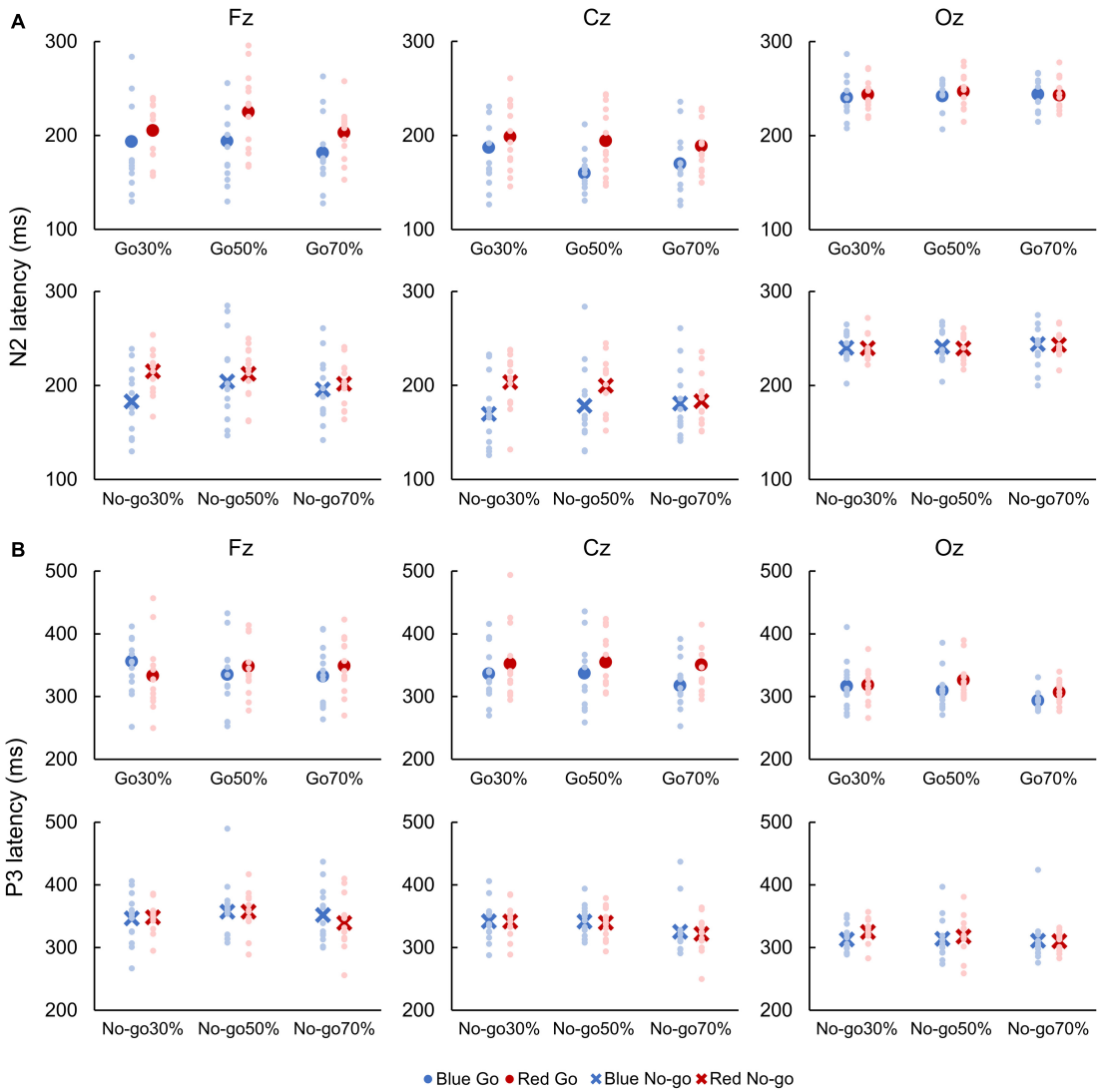

FIGURE 5 | Latencies of N2 **(A)** and P3 **(B)**. Blue color indicates responses to a blue light (Blue Go and Blue No-go), and red color indicates responses to a red light (Red Go and Red No-go). Individual data (light color) and their mean (dark color) were presented for each condition.

We found that the RT was faster in Blue Go than Red Go trial, and this result may be related to the Stroop effect (Stroop, 1935), in which the naming of written color words is impeded by the occurrence of different ink color. In a typical Stoop task with the conflict between a word name and its ink color, for instance, participants can respond faster to a letter "Red" printed in red than the one printed in blue. In addition, the Stroop-like effect has been reported using a conflict between color and shape of pedestrian traffic sign (e.g., walking sign in red color) (Peschke et al., 2013). On the other hand, in a simple RT task using written color words printed in congruent or incongruent color as target stimuli (e.g., a letter "Blue" printed in blue ink vs. a letter "Green" printed in yellow ink), RTs to congruent and incongruent words were found to be similar (Gonzalez-Rosa et al., 2013).

Moreover, in a previous study using a color-object verification task, surface color of an object was found to activate relevant semantic knowledge about the object, which impacted RTs (Bramão et al., 2012). Specifically, when asked to judge whether object's color was typical or atypical, RTs to objects with typical color were faster than ones with atypical color. Meanwhile, when asked to judge whether the surface color of an object (typical or atypical) was matched or unmatched with the color name presented beforehand while ignoring the prototypical color of the object, there was no significant difference in the RT

TABLE 2 | Correlation between RT and ERP amplitude.

	Go N2	No-go N2	Go P3	No-go P3
Fz	0.369	0.196	–0.134	–0.125
Cz	0.315	0.220	–0.338	–0.173
Oz	0.320	0.403	–0.054	0.228

TABLE 3 | Correlation between RT and ERP latency.

	Go N2	No-go N2	Go P3	No-go P3
Fz	0.289	–0.034	0.157	0.033
Cz	0.292	0.095	0.350	0.232
Oz	0.159	0.274	0.541	0.314

between typical and atypical colors. Collectively, these findings indicate that RTs can be influenced selectively by conflict between prior knowledge about objects' color and the presented color of the objects.

In the present study, therefore, the Stroop-like interference caused by information conflict between prior knowledge about traffic light signals and the meaning of presented color likely delayed the response to a signal in Red Go trials. Considering this finding in the context of real-world car driving, drivers need to recognize that responding to a red signal can be slower than responding to a green/blue signal and thus must not start pressing the brake pedal after the traffic signal turns red; they should start pressing the brake pedal when the traffic light turns yellow (to prevent a delayed response). Extending this study further by using driving simulators would provide more detailed information in the future.

With respect to Go probability, the RTs became slower as Go probability decreased, which is consistent with previous studies (Braver et al., 2001; Bruin and Wijers, 2002; Nieuwenhuis et al., 2003; Hsieh et al., 2016; Meffert et al., 2016). This result indicates that lower target-signal probability conditions are more difficult as there is a bias toward the high probability No-go response (refraining from responding) (Braver et al., 2001; Meffert et al., 2016). Contrarily, response preparation is enhanced in higher target-signal probability conditions (Low and Miller, 1999), allowing a faster response. Taken as a whole, our findings of RTs being slower in Red Go than Blue Go trials and also with lower Go probability agree with well-known notion that RTs can be influenced by conflicts and/or cognitive load (Peschke et al., 2013; Nieuwenhuis et al., 2003). This study adds to the current literature by demonstrating that prior knowledge of color can be a conflict when proactive response inhibitory function is required during a Go/No-go task. We suppose that experiment design used in this study can be a simple and effective way to manipulate cognitive load of Go/No-go task.

In regard to the ERP components, the C1 amplitude was larger in Blue Go than Red Go trial in 30% Go probability. In a previous study by Eason et al. (1967), amplitude of occipital ERP component around 50–100 ms was found to be larger with higher luminous intensity and when responding to a red than blue light in a simple RT task. Thus, the difference in C1 amplitude found in this study may be due to the difference in the luminous intensity of LED between blue and red lights. Meanwhile, simple RTs were revealed to be unaffected by light color (Eason et al., 1967), and we preliminarily found that they were unaffected by the luminous intensity of LEDs used in this study. Therefore, the C1 amplitude difference observed here likely did not contribute to the changes in RTs (in Go/No-go task). Indeed, the C1 originates in the primary visual cortex (Clark and Hillyard, 1996), and we found insignificant difference in the C1 latency. It appears that the visual stimulus was similarly processed at least to the primary visual cortex. Accordingly, the difference in task performance between Blue Go and Red Go trials can be attributed to changes in the higher-order processing shown in N2 and P3 amplitudes, as discussed below.

First, we demonstrated that the N2 amplitude was larger when responding to red than blue light in Go trials. This result can be attributed to a conflict between prior knowledge of color and the meaning of presented color, as N2 amplitude has been shown to be larger in incongruent than congruent trial in the Stroop task (Boenke et al., 2009; Pan et al., 2016). In a recent review by Heidlmayr et al. (2020), the cortical origin of N2 was considered to be the ACC, IFC, and/or prefrontal cortex. It has been reported that the ACC detects the presence of conflict (Botvinick et al., 2001), subsequently engaging the dorsolateral prefrontal cortex to impose cognitive control to resolve the conflict (Parris et al., 2019), whereas the IFC is responsible for processing of both response and semantic conflicts (Parris et al., 2019). Therefore, our finding of the larger N2 amplitude in Red Go than Blue Go trial may be due to the stronger activation of these brain regions. In addition to the amplitude, the N2 latency for Go ERPs was found to be faster in Blue Go than Red Go trial, which seems to be in line with a view that N2 latency reflects processing time of response selection (Gajewski et al., 2008).

In contrast to our expectation, N2 amplitude for Red No-go trials was larger than that for Blue No-go trials. Although hard to interpret, this result may be attributed to greater experience of inhibition with red light signals, as N2 amplitude for No-go trials is suggested to be related to attention and modulated by physical training (Yamashiro et al., 2015). For example, N2 amplitude for No-go trials was larger in fencers (Di Russo et al., 2006) and baseball players (Yamashiro et al., 2015) compared with controls. Even though the participants of the present study have not undergone any special training like top athletes, they have a great amount of experience to choose right actions according to the color of traffic lights. Thus, this experience might have enhanced the N2 amplitude for Red No-go trials. In addition, several studies have reported that N2 amplitude for No-go trials negatively correlates with RT, meaning that the shorter RTs are associated with the larger N2 amplitude for No-go trials (Yamashiro et al., 2015). The stronger inhibitory function reflected by the larger N2 amplitude is thought to result in the shorter RT (Band et al., 2003; Yamashiro et al., 2015). In the present study, the RT was faster and the N2 amplitude for No-go trials was larger in Blue Go/Red No-go than Red Go/Blue No-go task, although no significant correlation was found between the RT and N2 amplitude for No-go trials at front-central sites. Thus, we suppose that a stronger inhibitory function was recruited in Red No-go than Blue No-go trial, and this inhibitory function may have partially influenced the RTs.

Next, we would like to discuss about P3 amplitude, which is associated with a number of different cognitive mechanisms. Similar to previous studies (e.g., Hsieh et al., 2016), the P3 amplitude was influenced by Go probability in both Go and No-go trials. Also, it was larger in Red No-go than Blue No-go trial at Cz and Oz in some cases. Given that P3 reflects the

amount of allocated attention (Luck and Kappenman, 2011), the larger P3 amplitude in Red No-go trial may indicate that it was easier to pay attention to Red No-go than Blue No-go signal because of participants' familiarity with traffic light signals. With regard to RTs, a shorter RT has been reported to be associated with a larger P3 amplitude for No-go trials (Yamashiro et al., 2015), similar to the N2, and Nakata et al. (2012) suggested that a faster response to Go signal can occur as a result of a larger No-go related neural activity. Therefore, considering that P3 can reflect response inhibition (Enriquez-Geppert et al., 2010), the larger P3 amplitude for No-go trial in Blue Go/Red No-go than Red Go/Blue No-go task may have led to the faster response to Go signal in this study. On the other hand, although the neurophysiological mechanisms underlying P3 have been explored in a number of studies, no clear consensus has been reached on this matter, making the interpretation of P3 complicated and difficult (for reviews, Gupta et al., 2019; see also, Luck, 2014). In a review by Polich (2007), they showed that P3 is made up of several subcomponents including the frontal maximal P3a and temporal-parietal maximal P3b. The P3a may originate from the dorsolateral prefrontal cortex, IFC, and cingulate cortex, and can be influenced by stimulus probability, while the P3b may originate from the ventrolateral prefrontal cortex, superior temporal sulcus, and intraparietal sulcus and index a response to a target signal (Halgren et al., 1998). Yet, we could not detect these two subcomponents in this study, warranting future studies to better understand the functional role of P3 and its subcomponents in response inhibition as well as color conflict.

Finally, we would like to consider how our findings can be translated to clinical application. One possible way is an assessment of driving function of individuals with potential mild cognitive impairment (MCI), as their cognitive processing speed is highly associated with driving functions (Wadley et al., 2020; Toepper et al., 2021). During driving license renewal for the elderly, questionnaires and driving simulations are typically used to assess their driving function, and no neurophysiological assessments are performed. Meanwhile, recent studies have reported that abnormal ERPs can be a biomarker for detecting cognitive decline, particularly of verbal memory, in elderly individuals with preclinical Alzheimer's disease (Olichney et al., 2013) and MCI (Xia et al., 2020). In addition, ERPs associated with a Go/No-go task were found to be compromised in individuals with MCI (López Zunini et al., 2016). Therefore, the task and ERP measurements used in the present study could be a simple and efficient method to manipulate the cognitive load to detect a subtle cognitive decline that may cause bewilderment and delay in responses during driving. Further studies and technological advances are required to promote this field of research.

There are limitations that should be acknowledged in this study. First, the sample size was small; thus, future studies with larger sample sizes may be warranted to test our findings. Second, the minimum number of trials used to create the averaged waveform was seven. Although the threshold was set according to previous ERP studies (Schoenberg et al., 2014; Nguyen et al., 2016), it is recommended to include approximately 20 trials in another study (Cohen and Polich, 1997). Also, a recent study suggests that the number of trials for averaging should be increased especially when the sample size is small (Boudewyn et al., 2018). Therefore, caution may be needed when interpreting our ERP results. Due to the issues of sample size and minimum trials used for conditions, results of this study should be taken as preliminary and used to motivate future studies until they are able to be independently reproduced or replicated in a much larger sample size of participants and using a larger sample of valid trials for inclusion in ERP analyses.

In summary, we found that RT was slower and N2 amplitude was larger when making a response to red than blue light in a Go/No-go task, and these findings was interpreted as a Stroop-like interference, that is, a conflict between prior knowledge about traffic light signals and the meaning of presented signal. In addition, N2 and P3 amplitudes were larger in Red No-go than Blue No-go trial, which might have been induced by years of experience in stopping an action in response to a red signal and/or attention. This study provides the better understanding of the effect of prior knowledge of color on behavioral responses and its underlying neural mechanisms.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary materials, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee for Clinical Research of Hiroshima University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

NK, TW, and HK designed the study, edited, and revised the manuscript. NK and XC performed the experiment. NK analyzed the data and wrote the original draft of the manuscript. XC, TM, KY, and TK assisted the data analysis and the preparation of the manuscript. TW and HK supervised the study. All authors approved the final version of the manuscript.

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Influence of Visual Stimulation-Induced Passive Reproduction of Motor Images in the Brain on Motor Paralysis After Stroke

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Finger flexor spasticity, which is commonly observed among patients with stroke, disrupts finger extension movement, consequently influencing not only upper limb function in daily life but also the outcomes of upper limb therapeutic exercise. Kinesthetic illusion induced by visual stimulation (KINVIS) has been proposed as a potential treatment for spasticity in patients with stroke. However, it remains unclear whether KINVIS intervention alone could improve finger flexor spasticity and finger extension movements without other intervention modalities. Therefore, the current study investigated the effects of a single KINVIS session on finger flexor spasticity, including its underlying neurophysiological mechanisms, and finger extension movements. To this end, 14 patients who experienced their first episode of stroke participated in this study. A computer screen placed over the patient's forearm displayed a pre-recorded mirror image video of the patient's non-paretic hand performing flexion–extension movements during KINVIS. The position and size of the artificial hand were adjusted appropriately to create a perception that the artificial hand was the patient's own. Before and after the 20-min intervention, Modified Ashworth Scale (MAS) scores and active range of finger extension movements of the paretic hand were determined. Accordingly, MAS scores and active metacarpophalangeal joint extension range of motion improved significantly after the intervention. Moreover, additional experimentation was performed using F-waves on eight patients whose spasticity was reduced by KINVIS to determine whether the same intervention also decreased spinal excitability. Our results showed no change in F-wave amplitude and persistence after the intervention. These results demonstrate the potential clinical significance of KINVIS as a novel intervention for improving finger flexor spasticity and extension movements, one of the most significant impairments among patients with stroke. The decrease in finger flexor spasticity

following KINVIS may be attributed to neurophysiological changes not detectable by the F-wave, such as changes in presynaptic inhibition of Ia afferents. Further studies are certainly needed to determine the long-term effects of KINVIS on finger spasticity, as well as the neurophysiological mechanisms explaining the reduction in spasticity.

Keywords: kinesthetic illusion, visual stimulation, stroke, spasticity, body ownership, mirror therapy

INTRODUCTION

Stroke, one of the most prevalent neurological diseases worldwide, causes long-term motor impairment. In general, the upper extremities experience greater functional impairment after a stroke compared to the lower extremities, with limited recovery of motor function, especially in the fingers (Langhorne et al., 2009; Houwink et al., 2013). One factor strongly associated with finger motor function is spasticity of the finger flexor muscles (Pundik et al., 2019), which promotes impaired finger extension movements and has a direct negative impact on activities of daily living (ADLs), including eating, grooming, and dressing (Watkins et al., 2002; Sommerfeld et al., 2004). Furthermore, impaired finger extension movement due to spasticity has been assumed to potentially interfere with motor function improvement by increasing the difficultly of therapeutic exercise. Therefore, developing new rehabilitation techniques to reduce finger flexor spasticity may increase the efficiency of therapeutic exercise by improving finger extension movements, thereby contributing to improved performance of ADLs.

Mirror therapy has been one of the proposed treatments for upper limb paralysis after stroke (Altschuler et al., 1999). One feature of mirror therapy is the induction of kinesthetic sensation in the paretic hand by observing the reflected movements of the non-paretic hand in a mirror. A systematic review by Thieme et al. (2018) presented moderate quality evidence showing that mirror therapy promoted better improvement in motor function and motor impairment compared to other interventions. On the other hand, kinesthetic illusion induced by visual stimulation (KINVIS) is a rehabilitation system that can induce a vivid kinesthetic illusion (Kaneko et al., 2007) and can be used together with other intervention modalities (e.g., neuromuscular electrical stimulation) (Kaneko et al., 2019). Given that KINVIS does not require non-paretic hand movement during treatment, the potential for KINVIS to enhance abnormal interhemispheric inhibition associated with non-paretic hand movements is of no concern (Murase et al., 2004; Nowak et al., 2009). Studies in healthy volunteers have shown that motor-related cortical area activation and corticomotor excitability increase during and after KINVIS (Kaneko et al., 2007, 2015, 2016b, 2019; Aoyama et al., 2012; Shibata and Kaneko, 2019). A preliminary study examining the effects of KINVIS among post-stroke patients reported that the single intervention session increased beta band event-related desynchronization obtained from sensorimotor cortex during motor imagery (Okawada et al., 2020), as well as improved paretic upper limb motor function (Kaneko et al., 2016a). Moreover, a study of 11 stroke patients who underwent 10 days of rehabilitation that included KINVIS reported a significant reduction in the spasticity of the finger and wrist flexor muscles and improved upper limb motor function after the intervention (Kaneko et al., 2019). Thus, although KINVIS is expected to be effective in reducing spasticity, it remains unclear whether KINVIS alone is responsible for such an outcome considering that the aforementioned study utilized conventional rehabilitation together with KINVIS. Furthermore, the mechanisms through which KINVIS reduces spasticity have remained unknown. Therefore, Experiment 1 of the current study aimed to determine whether a single session of KINVIS alone could reduce finger flexor spasticity and improve the active range of finger extension in patients with stroke. Moreover, we herein investigated the relationship between changes in spasticity and active range of finger extension, as well as whether subjective illusory sensation and body ownership of the virtual hand presented in the video affected changes in spasticity and active range of finger extension.

Several previous studies using H-reflex and F-wave have shown that patients with stroke exhibiting spasticity have increased spinal reflex excitability (Milanov, 1992a,b; Pisano et al., 2000; Bakheit et al., 2003; Wupuer et al., 2013). In addition, previous studies have shown that F-wave and H-reflex decreases as spasticity is reduced by several interventions (Lo et al., 2009; Kondo et al., 2015; Miyara et al., 2018; Dos Santos et al., 2019). Given the physiological differences between H-reflex and F-wave, both of them assess different aspects of spinal reflex excitability (i.e., the former as a gross measure of alpha motoneuron pool excitability and transmission from the Ia afferent terminals to the alpha motoneurons and the latter as a measure of solely alpha motoneuron excitability) (Milanov, 1992a). However, no study using H-reflex or F-wave has yet investigated whether KINVIS reduces spinal reflex excitability in patients with spasticity. In general, F-wave could be more reliably obtained from the finger muscles compared with H-reflex. Therefore, we determined that F-wave was more suitable than H-reflex for this study, which aimed to identify changes in finger muscle spasticity. Thus, Experiment 2 aimed to elucidate neurophysiological mechanisms explaining the decrease in finger flexor muscle spasticity by recording F-waves from finger muscles to assess the excitability of the alpha motoneuron pool before and after KINVIS.

MATERIALS AND METHODS

Experiment 1

Patients

We estimated the sample size by conducting a power analysis using G**Power with a power of 0.8, an alpha of 0.05, and an effect size of d = 1.0, referring to the effect size obtained in

a previous study (Kaneko et al., 2019). A total of 14 (9 men and 5 women; mean age of 61.5 ± 13.4 years) patients who experienced stroke and exhibited spasticity in their paretic finger flexor muscles participated in this experiment, the characteristics of whom are summarized in **Table 1**. The duration since stroke onset was 16.3 ± 47.1 weeks. The inclusion criterion was patients with stroke over 20 years old who demonstrated finger flexor spasticity [Modified Ashworth Scale (MAS) ≥1]. In addition, previous studies have shown that the presence or absence of kinesthetic sensation has important effects on neurophysiological changes (Kaneko et al., 2007, 2015). Therefore, to investigate the effect of kinesthetic illusion on finger flexor spasticity, rather than just the effect of action observation, patients with subjective illusory sensation or sense of body ownership of ≥1 point on a 7-point Likert scale (see below) were included in this study. Exclusion criteria were as follows: (1) patients with recurrent stroke, (2) with neurological diseases other than stroke, and (3) who did not understand the purpose and task of this study. None of the patients who participated in the study had undergone surgical treatment. One patient (patient no. 7) was taking an anxiolytic drug, alprazolam. Alprazolam also has a muscle relaxant effect; however, this effect is generally weak (Evans, 1981). Patients provided written informed consent prior to study participation in accordance with the Declaration of Helsinki. The present study was approved by the local ethics committee of the Ibaraki Prefectural University of Health Sciences (approval No. e202).

Intervention

All patients underwent a single 20-min session of KINVIS (Aoyama et al., 2020; Okawada et al., 2020). The patients were seated in a comfortable chair with their paretic forearm on the table. Prior to the intervention, the patients were filmed executing the finger flexion–extension movement (3-s flexion and 3-s extension) with the non-paretic hand (Aoyama et al., 2020). During KINVIS intervention (KiNvis Therapy System^{TM}; Inter Reha, Tokyo, Japan), the patients were instructed to remain completely relaxed while observing a computer screen projecting a mirror image of the patient's non-paretic hand placed over their paretic hand (**Figure 1**). They were instructed to simply observe the movement on the screen, and to not perform motor imagery. The position and size of the artificial hand were adjusted appropriately to create a feeling that the artificial hand belonged to the patient's own body. KINVIS was performed for 20 min by repeatedly showing the 6-s video of the hand flexion–extension movement.

Assessment of Spasticity

Spasticity was assessed using the MAS (Li et al., 2014), which is an ordinal scale with scores of 0, 1, 1+, 2, 3, and 4, and has good or very good intra-rater reliability (Gregson et al., 1999; Ansari et al., 2008). The MAS score for flexor muscles of the index finger was measured during sitting with the forearm in neutral position (Hara et al., 2006) by a single physical therapist with extensive clinical experience with patients with stroke and no conflicts of interest. For statistical analysis, a score of 1 + was transformed to 2, while a score of 2, 3, and 4 was transformed to 3, 4, and 5, respectively (Kaneko et al., 2019).

Motor Task and Kinematic Analysis

The patients placed their paretic hand in a neutral position and performed as much finger extension movement as possible

TABLE 1 | Patient characteristics.

Patient no.	Age	Gender	Lesion side	Diagnosis	FMA upper limb	ARAT	MAS finger flexor muscles	Body ownership	Illusory sensation	Experiment
1	72	W	Lt	Thalamus hemorrhage	7	0	3	2	1	1, 2
2	85	M	Rt	Subcortical infarction	47	41	2	3	2	1
3	73	W	Rt	Putamen and corona radiata infarction	13	0	1	1	2	1, 2
4	51	M	Rt	Putaminal hemorrhage	43	26	2	1	2	1, 2
5	48	M	Rt	Putaminal hemorrhage	26	21	1	1	1	1
6	65	M	Rt	Basal ganglia and corona radiata infarction	41	33	1	3	2	1, 2
7	71	W	Lt	Putaminal hemorrhage	32	16	1	3	0	1, 2
8	72	M	Rt	Pontine infarction	40	20	1	1	1	1
9	44	W	Lt	Pontine hemorrhage	46	35	1	2	2	1, 2
10	55	W	Lt	Subcortical hemorrhage	20	4	1	2	3	1, 2
11	46	M	Lt	Putaminal hemorrhage	40	36	1	2	2	1
12	75	M	Lt	Basal ganglia and corona radiata infarction	9	3	3	3	−1	1
13	45	M	Lt	Putaminal hemorrhage	46	8	3	1	1	1, 2
14	59	M	Lt	Thalamus hemorrhage	29	20	1	2	2	1

FMA, Fugl-Meyer Assessment; ARAT, Action Research Arm Test; MAS, Modified Ashworth Scale.

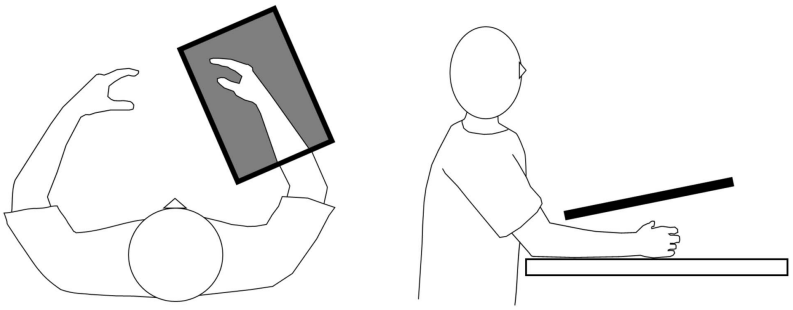

FIGURE 1 | Schematic diagram of the kinesthetic illusion induced by visual stimulation intervention.

from the maximum finger flexion angle for over three times. To focus on finger movements during kinematic analysis, the experimenter fixed the patient's distal forearm during the motor task. Reflective markers were placed on the landmarks of the radial side of the index finger [distal interphalangeal (DIP), proximal interphalangeal (PIP), and metacarpophalangeal (MP) joints axis] and radial styloid process (**Figure 2A**). Finger extension movements were captured from above using a digital video camera (EX-100F, 60 frames/s; Casio, Tokyo, Japan). The recorded images were digitized to obtain coordinates for the four reflective markers using a motion analysis system (Frame DIAS V; DKH, Tokyo, Japan). Two-dimensional (2D) coordinates for each marker were run through a fourth-order zero-lag low-pass Butterworth filter (cut-off frequency: 6 Hz). Changes in flexion angle of the PIP and MP joints were calculated from the trajectories of the reflective markers (**Figure 2B**). For each extension movement, the active range of PIP and MP joint extension from the maximum finger flexion angle was calculated and averaged over three times. PIP joint data in one patient could not be calculated given that the reflective marker of the DIP joint was masked by thumb movement. Such data were therefore excluded from subsequent analysis.

Questionnaire Regarding Body Ownership and Illusory Sensation

After KINVIS intervention, patients were asked to rate the sense of body ownership and illusory sensation during intervention using a 7-point Likert scale (–3, strongly disagree; 0, neither agree nor disagree; + 3, strongly agree) (Kaneko et al., 2019; Aoyama et al., 2020).

Analysis of Experiment 1

As the obtained data did not show a normal distribution by the Shapiro–Wilk test, the Wilcoxon signed-rank test was performed to determine whether KINVIS promoted changes in hand flexor muscle spasticity and active range of PIP and MP joints extension. The effect size (r) was also calculated by dividing the Z-score derived from each test by the square root of the sample size. Accordingly, effect size was interpreted as small (>0.1), moderate (>0.3), or large (>0.5) based on the guidelines of Cohen (1988). Spearman's correlation analysis was conducted to determine the relationship between changes in the degree of improvement in finger flexor muscle spasticity (Pre - Post MAS scores, where positive values indicated a decrease in spasticity), the degree of improvement in the active range of finger extension movement (Post - Pre, where positive values indicated an increase in finger extension range of motion), body ownership, and illusory sensation.

Experiment 2

Patients

In order to explore the neurophysiological mechanisms underlying reduced spasticity using KINVIS, the inclusion criteria for Experiment 2 were patients who participated in Experiment 1 and whose MAS scores decreased by at least 1 point after KINVIS intervention. Of the ten participants who met these criteria, two did not agree to participate in the experiment; thus, eight patients (three men and five women; mean age, 59.5 ± 12.2 years) participated in experiment 2. The patients provided written informed consent prior to participation in the experiment in accordance with the Declaration of Helsinki. This experiment was approved by the local ethics committee of the Ibaraki Prefectural University of Health Sciences (approval No. e202).

Electromyography

The skin area of the electrode attachment was swabbed with alcohol and prepared using an abrasive skin-prepping gel, after which surface Ag–AgCl electrodes were placed over the bilateral first dorsal interosseous (FDI). Electromyography (EMG) signals were amplified (Neuropack MEB2300; Nihon Kohden, Saitama, Japan) at a gain of 0.2–0.5 mV per division and band-pass filtered at 5–5 kHz. All signals were stored on a computer for offline analysis. The sampling frequency was set at 10 kHz.

F-wave

The patient's arm was placed on a table, and the elbow was flexed to approximately 90°, with the forearm in a supinated position. F-waves were recorded from the affected and non-affected FDI muscle, which is involved in index finger flexion. In addition, the F-wave amplitude and persistence of the paretic FDI muscle in patients with stroke with spasticity have been shown to be significantly increased as compared with those of the FDI muscle in healthy subjects (Wupuer et al., 2013). For these reasons, we

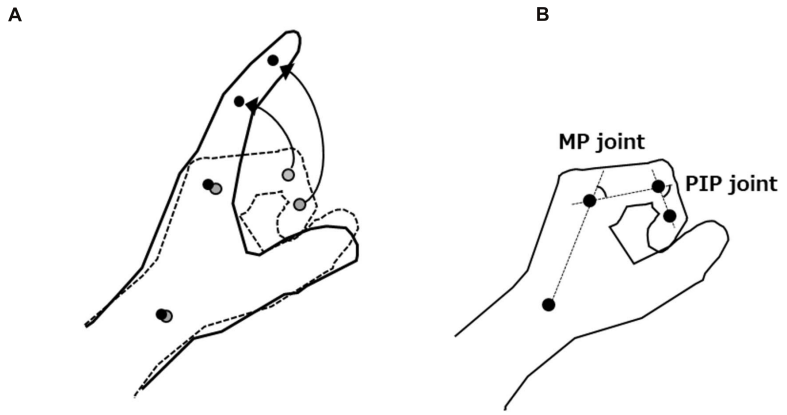

FIGURE 2 | (A) Motor task and trajectories of the reflective markers. **(B)** Measurement of flexion angle of the proximal interphalangeal (PIP) and metacarpophalangeal (MP) joints. We defined the active range of PIP and MP joint extension as the difference between each joint's maximum finger flexion and extension angles.

chose FDI as the target muscle for the F-wave. Supramaximal electrical stimulation was applied to the ulnar nerve at the wrist using a 0.2-ms rectangular electrical pulse (Aoyama et al., 2019). At least 30 F-waves were recorded under resting conditions. When a visually evident involuntary contraction of the FDI muscle was observed, the trial was rejected and another trial was recorded. F-wave persistence was defined as the ratio of trials in which F-wave amplitudes greater than 50 μV were obtained to the total number of trials. The F/M amplitude was defined as the ratio of the F-wave amplitude to the maximum M-wave amplitude.

Analysis of Experiment 2

One patient (patient no. 13) was having difficulty in holding the test arm position due to the strong spasticity of the forearm flexor and pronator muscles. Owing to this, we had difficulty fixing the stimulating electrode to the ulnar nerve for this patient. As a result, stable M-waves could not be obtained. Therefore, this patient's data were excluded from further analysis. To test the normality of the data, we performed the Shapiro–Wilk test. Since F/M amplitudes showed strongly positive skewed distributions and normality could not be obtained, logarithmic transformation was performed (Osborne, 2002; Bland et al., 2013). After the logarithmic transformation, kurtosis and skewness approached zero, and the Shapiro–Wilk test showed a normal distribution. The effects of time (pre- and post-intervention) and hand (paretic and non-paretic hands) factors on M-wave amplitude, F-wave persistence, and F/M amplitude were determined using two-way repeated measures analysis of variance. Partial η^2 was calculated as a measure of effect size (small: 0.01; medium: 0.06; large: 0.14) (Huck, 2011).

RESULTS

Experiment 1

Spasticity

Spasticity assessed via MAS was significantly reduced after a single session of KINVIS (Z = 2.972, n = 14, p = 0.003, effect size r = 0.794; **Table 2**). Among the 14 patients included herein, 10 showed at least a 1-point decrease in the MAS score, whereas none of the patients showed worsening symptoms.

Active Range of Proximal Interphalangeal and Metacarpophalangeal Joint Extension

No significant difference in the active range of PIP joint extension was observed before and after the intervention (Z = 0.664, n = 13, p = 0.507, effect size r = 0.184; **Table 2**). However, the active range of MP extension was significantly increased after KINVIS (Z = 1.977, n = 14, p = 0.048, effect size r = 0.528).

Relationship Between Finger Flexor Spasticity, Active Range of Finger Extension, Body Ownership, and Illusory Sensation

Spearman's rank correlation test showed no significant correlation between improvement in MAS score of the finger flexor muscle, improvement in active range of PIP and MP joint extension, body ownership, and illusory sensation in the artificial hand (improvement in MAS score vs. improvement in active range of PIP extension: rs = 0.178, n = 13, p = 0.543; improvement in MAS score vs. improvement in active range of MP extension: rs = –0.366, n = 14, p = 0.199; improvement in MAS score vs. body ownership: rs = 0.395, n = 14, p = 0.162; improvement in MAS score vs. illusory sensation: rs = –0.222, n = 14, p = 0.446, improvement in active range of PIP extension vs. body ownership: rs = –0.096, n = 13, p = 0.745; improvement in active range of PIP extension vs. illusory sensation: rs = 0.188, n = 13, p = 0.520; improvement in active range of MP extension vs. body ownership: rs = –0.464, n = 14, p = 0.095; improvement in active range of MP extension vs. illusory sensation: rs = –0.069, n = 14, p = 0.815).

Experiment 2

The raw waveforms of M and F waves obtained from the paretic and non-paretic hands of a representative subject before and after the intervention are shown in **Figure 3**. No significant interaction was observed between time and hand factors in the M-wave amplitude (F1, 6 = 0.324, n = 7, p = 0.590, effect size partial

TABLE 2 | Results of finger spasticity and active range of finger extension.

	Pre-intervention	Post-intervention	*p* value
Finger flexor spasticity:			
MAS score (0–5): Median (first quartile, third quartile)	1 (1, 3)	1 (0, 1)	0.003*
MAS score 0: Number of subjects	0	5	
MAS score 1: Number of subjects	9	8	
MAS score 2: Number of subjects	2	1	
MAS score 3: Number of subjects	3	0	
Active range of finger extension:			
MP joint: Median (first quartile, third quartile)	23.6 (7.8, 51.5)	27.8 (10.7, 47.9)	0.048*
PIP joint: Median (first quartile, third quartile)	68.2 (24.1, 89.6)	64.6 (33.5, 82.8)	0.507

*MAS, Modified Ashworth Scale; MP, metacarpophalangeal; PIP, proximal interphalangeal. For statistical analysis, MAS scores of 1 + and 2 are presented as 2 and 3, respectively. * indicates significant difference ($p < 0.05$).*

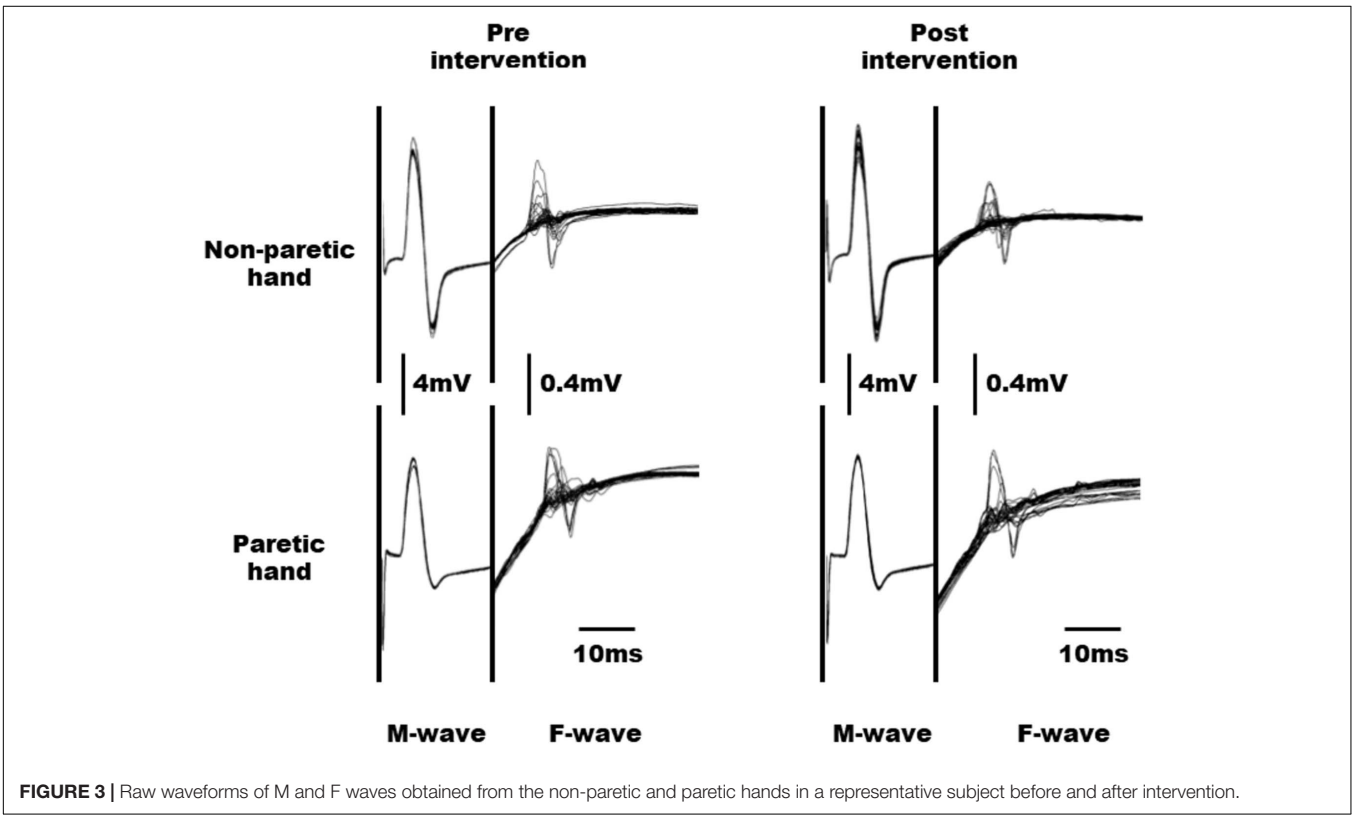

FIGURE 3 | Raw waveforms of M and F waves obtained from the non-paretic and paretic hands in a representative subject before and after intervention.

$\eta^2 = 0.051$; **Table 3**). Moreover, both time (F1, 6 = 0.482, $n = 7$, $p = 0.514$, effect size partial $\eta^2 = 0.074$) and hand factors (F1, 6 = 3.441, $n = 7$, $p = 0.113$, effect size partial $\eta^2 = 0.365$) showed no significant main effect on the M-wave amplitude. For the F/M amplitude, no significant interaction was obtained between time and hand factors (F1, 6 = 0.356, $n = 7$, $p = 0.572$, effect size partial $\eta^2 = 0.056$). The paretic hand had a significantly larger F/M amplitude than the non-paretic hand (F1, 6 = 10.704, $n = 7$, $p = 0.017$, effect size partial $\eta^2 = 0.641$). The time factor had no significant main effect on the F/M amplitude (F1, 6 = 0.115, $n = 7$, $p = 0.747$, effect size partial $\eta^2 = 0.019$). No significant interaction was observed between the time and hand factors on F-wave persistence (F1, 6 = 1.723, $n = 7$, $p = 0.237$, effect size partial $\eta^2 = 0.223$). Although the p value for the hand factor did not reach significance, the paretic hand tended to have higher F-wave persistence than the non-paretic hand (F1, 6 = 4.200, $n = 7$, $p = 0.086$, effect size partial $\eta^2 = 0.412$). The time factor showed no significant main effect on F-wave persistence (F1, 6 = 0.003, $n = 7$, $p = 0.957$, effect size partial $\eta^2 = 0.001$).

DISCUSSION

The current study showed that a single 20-min session of KINVIS immediately reduced MAS score and increased the active range of MP joint extension, suggesting its potential utility in improving finger flexor spasticity and finger extension movements in patients with stroke for whom effective treatments are limited.

TABLE 3 | Results of M-wave, F-wave persistence and F/M amplitude.

		Pre-intervention	Post-intervention	*p* value		
				Interaction	Main effect	
					Hand factor	Time factor
M-wave amplitude (mV)	Non-paretic hand	11.7 (4.1)	11.1 (3.4)	0.590	0.113	0.514
	Paretic hand	8.0 (4.6)	7.9 (4.3)			
F-wave persistence (%)	Non-paretic hand	69.1 (24.4)	63.3 (20.5)	0.236	0.086	0.957
	Paretic hand	86.0 (16.7)	91.4 (10.2)			
F/M amplitude (%)	Non-paretic hand	1.31 (1.15)	1.18 (1.09)	0.572	0.017*	0.747
	Paretic hand	2.61 (1.87)	2.61 (1.48)			

*Data are presented as mean (standard deviation). * indicates significant difference ($p < 0.05$).*

After 1 session of 20-min KINVIS intervention, MAS score decreased significantly with a large effect size, while 71.4% of the patients exhibited a 1 point and greater decrease in MAS score. Chen et al. (2019) reported that the minimal clinically important difference (MCID) in upper limb spasticity using MAS scores in patients with stroke was either 0.48 (medium effect size) or 0.76 (large effect size). This indicates that KINVIS promoted an improvement even greater than the MCID in over 70% of the patients, suggesting that KINVIS may be one of the clinically meaningful interventions for finger flexor spasticity in patients with stroke. On the other hand, mirror therapy, a technique that induces a kinesthetic illusion similar to KINVIS, has long been used to treat paretic upper limb in patients with stroke (Perez-Cruzado et al., 2017). However, mirror therapy has generally been considered to have no effect on upper limb spasticity (Yavuzer et al., 2008; Samuelkamaleshkumar et al., 2014; Perez-Cruzado et al., 2017). Although our results cannot elucidate why KINVIS and mirror therapy have different effects on spasticity, we surmise that differences in the nature of both interventions are involved. In particular, the crucial difference between both interventions is presence of non-paretic hand movement. The subjective kinesthetic sensation induced during mirror illusion is markedly affected by proprioceptive afferent input from the non-paretic hand (Chancel et al., 2016). Furthermore, the non-paretic hand movements may reinforce abnormal interhemispheric inhibition (Murase et al., 2004; Nowak et al., 2009). Conversely, the aforementioned effects caused by non-paretic hand movements certainly do not occur during KINVIS because of the use of a pre-recorded mirror image video. Indeed, Kaneko et al. (2019) reported that a 10-day intervention, including KINVIS, significantly reduced upper limb spasticity. However, given that their study concurrently applied KINVIS and NMES while also including conventional therapeutic exercise in the overall intervention protocol, whether KINVIS directly contributed to the reduction in upper limb spasticity remains unclear. Other effective treatments for spasticity include botulinum toxin injection (Brashear et al., 2002; Ro et al., 2020) and acupuncture (Tavakol et al., 2020). However, because these treatments are invasive, KINVIS is expected to be beneficial as a non-invasive treatment for spasticity. Further studies are needed to compare the efficacy and cost of KINVIS with those of other therapies for clinical application.

Our results showed that KINVIS intervention acutely increased the active range of MP joint extension. Studies have shown that decreased finger extension is one of the most common deficits in patients with stroke (Kamper and Rymer, 2001; Raghavan, 2007). The ability to extend the fingers by at least 10° has been one of the general inclusion criteria for constraint-induced movement therapy, which has been proven highly effective in treating motor dysfunction among patients with upper limb paralysis (Lin et al., 2019). Moreover, reports have shown that the ability to voluntarily extend the fingers was closely associated with the effects of constraint-induced movement therapy (Fritz et al., 2005). Therefore, the present results showing improved range of finger extension after the intervention suggests the potential utility of KINVIS in improving finger extension function to an extent where task-oriented upper limb training can be performed or as a conditioning intervention that aids in the effective performance of such training.

No significant correlation had been noted between the degree of improvement in spasticity and the degree of increase in active finger extension range of MP and PIP joint motion. This result implies that changes in these variables were independent of each other. A case report of a patient with stroke showed increased extensor digitorum activity after a single session of KINVIS (Aoyama et al., 2020). Therefore, change in hand extensor muscle activity may be a candidate factor affecting the improvement in active range of finger extension apart from hand flexor muscle spasticity. Excessive muscle contraction of the finger flexor muscle during active finger extension movement may be another factor contributing to improved range of finger extension (Kamper et al., 2003). As such, clarifying the factors that contribute to improved active range of finger extension by examining the changes in finger extensor and flexor activities during active finger extension movement is certainly necessary. The sense of body ownership and illusory sensation was not significantly correlated with the degree of improvement in spasticity and active range of finger extension. Notably, a previous study showed that the intensity of illusory sensation positively correlated with changes in corticomotor excitability, but it was not statistically significant (Aoyama et al., 2012). Therefore, the degree of illusory sensation and body ownership may not necessarily exert a strong influence on the improvement of spasticity and motor function. However, because this study

did not include patients who did not experience any illusory sensation and sense of body ownership, we cannot rule out that these are not related to symptom improvement.

Our finding showed that the paretic FDI muscle had a significantly higher F/M amplitude compared to the non-paretic FDI muscle. Moreover, the paretic FDI muscle tended had higher F-wave persistence than the non-paretic FDI muscle. These results are consistent with those presented in a previous study that examined F-waves in patients with stroke showing spasticity (Milanov, 1992a,b; Wupuer et al., 2013). Thus, the subjects included herein had increased spinal excitability before the intervention, supporting the presence of spasticity. On the other hand, despite the significant decrease in MAS score after KINVIS, no significant changes in F-wave amplitude and persistence were noted. Given that F-waves are generated by the backfiring of antidromically activated motoneurons (Mcneil et al., 2013), they are solely affected by alpha motoneuron excitability. Conversely, F-waves are not affected by the presynaptic inhibition of Ia afferent terminals, unlike H-waves, which are produced by Ia afferent firing (Pierrot-Deseilligny, 1997). Therefore, the absence of changes in the F-wave after KINVIS, despite the reduction in spasticity, may be due to the physiological changes that could not be detected by the F-wave, such as changes in presynaptic inhibition of Ia afferent input or reciprocal Ia inhibition. The Ia reciprocal and Ia presynaptic inhibitory interneurons receive descending drive (Jankowska and Tanaka, 1974; Cowan et al., 1986; Rothwell et al., 1991; Meunier and Pierrot-Deseilligny, 1998). Furthermore, the excitability of these inhibitory interneurons has been shown to be modulated before the onset of EMG activity of the antagonist muscle (Tanaka, 1976; Nielsen and Kagamihara, 1993). We speculate that KINVIS may selectively modulate the excitability of these inhibitory interneurons, without producing muscle activity. Supporting this hypothesis, Kawakami et al. (2018) reported that motor imagery enhanced the presynaptic inhibition of Ia afferent input and disynaptic reciprocal Ia inhibition of antagonists in patients with stroke. One study suggested that KINVIS should be interpreted as implicit motor imagery (Hanakawa, 2016) wherein the movement observed by the subjects in the video during KINVIS is passively imagined. In support of this notion, functional magnetic resonance imaging studies have shown that brain network activity detected during KINVIS was similar to that during motor imagery (Kaneko et al., 2015). Therefore, the findings of Kawakami et al. support our aforementioned assumptions. Future studies will need to examine the neurophysiological mechanisms of spasticity reduction following KINVIS using H-reflex and H-reflex conditioning-test paradigm. Moreover, there is a need to examine differences in neurophysiological changes between patients whose MAS scores decreased, or did not.

One of the most important limitations of this study is the absence of control groups or conditions. Therefore, we cannot deny the possibility that the results obtained in this study were due to the maintenance of rest or action observation. It is necessary to compare the effects of the KINVIS intervention with control tasks, such as rest or action observation, and with control patients who do not experience a sense of body ownership or illusory sensation. Furthermore, in the present study, patients who subjectively experienced a certain level of kinesthetic illusory sensation or a sense of body ownership were included to investigate the effects of kinesthetic illusions rather than the effects of mere action observation. Therefore, whether patients who do not experience kinesthetic illusory sensations or a sense of body ownership would experience improvements in the finger flexor spasticity and finger extension movement remains unclear. This issue should be examined in the future study.

In conclusion, the present study investigated the effects of a single KINVIS session on finger flexor spasticity, including its underlying neurophysiological mechanisms, and finger extension movements. Accordingly, our results showed that KINVIS significantly improved the MAS score and active range of MP joint extension. Moreover, no changes in F-wave persistence and amplitude had been noted after the intervention. The aforementioned results suggest that KINVIS may have clinical significance as a novel intervention for improving finger flexor spasticity and finger extension movements even when applied without NMES in patients with stroke. Given that the F-wave used herein could not identify the mechanism through which KINVIS reduces spasticity, future studies using H-reflex and/or H-reflex conditioning-test paradigm are warranted.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Local Ethics Committee of the Ibaraki Prefectural University of Health Sciences. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

TA and FK designed the study. YK and SW contributed to the clinical assessment. TA, AK, YK, KT, and FK collected the kinematic and neurophysiological data. TA, AK, and FK contributed to data analysis and interpretation. All authors contributed to wrote the manuscript, read, and approved the final manuscript.

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Conflict of Interest: FK is the founding scientist of INTEP Inc., a commercial company for the development of rehabilitation devices since July 2019. This company does not have any relationship with the device or setup used in the present study. FK received license fees from Inter Reha Co., Ltd.

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The Usefulness of Functional Near-Infrared Spectroscopy for the Assessment of Post-Stroke Depression

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Background: Post-stroke depression (PSD) is the most common mood disorder following stroke and is also the main factor that limits the recovery and rehabilitation of patients with stroke. The prevalence of PSD is ∼30%. Since there is no gold standard for the diagnosis and evaluation of PSD, it is important to raise awareness of PSD and to establish methods for its evaluation, early diagnosis, and treatment. In the field of psychiatry, functional near-infrared spectroscopy (fNIRS) has been used as a diagnostic tool for the measurement of oxygenated hemoglobin (oxy-Hb). This study aimed to assess whether fNIRS could be applied in the diagnosis and evaluation of PSD.

Methods: We recruited 45 patients with stroke, who were admitted to Nagasaki Kita Hospital between May 2015 and April 2019. The 17-item Hamilton Rating Scale for Depression (HAMD17), which is considered to be a useful screening and evaluation tool for PSD, was used for the assessment of patients after stroke; moreover, oxy-Hb was measured in the pre-frontal cortex. The subjects were divided into two groups: the depressed group ($n = 13$) and the non-depressed group ($n = 32$). We evaluated the correlation between the oxy-Hb integral values and HAMD17 scores.

Results: We investigated the relationship between the oxy-Hb integral values and HAMD17 total scores, and found a negative correlation between them ($\rho = -0.331$, $P < 0.005$). There was a significant difference in the oxy-Hb integral values during the activation task period between the depressed and non-depressed groups (3.16 ± 2.7 and 1.71 ± 2.4, respectively; $P = 0.040$). The results indicated that the patients of the depressed group showed lower oxy-Hb integral values and lower activation in the frontal lobe in comparison with the patients of the non-depressed group.

Conclusion: The present study highlights that the measurement of oxy-Hb by using fNIRS is a useful methodology for the diagnosis of PSD in patients after stroke.

Keywords: post-stroke depression, verbal fluency task, pre-frontal cortex, functional near-infrared spectroscopy, assessment

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INTRODUCTION

Post-stroke depression (PSD) is the most frequent psychiatric problem and is strongly associated with a further worsening of physical and cognitive recoveries, functional outcomes, and quality of life (Paolucci, 2017; Shi et al., 2017). In addition, PSD is a serious problem for both stroke survivors and healthcare professionals, as it negatively affects the ability of the patient to engage in rehabilitation (Zhao et al., 2018). Recent meta-analyses and reviews have shown that the incidence of PSD ranges from 18 to 33%, and the prevalence of the post-stroke depressive disorder is 33.5% (Mitchell et al., 2017; Medeiros et al., 2020). Risk factors for PSD include genetic factors, age, sex, medical history, psychological history, type and severity of the stroke, location of lesions, degree of disability, and influence of social support (Ayerbe et al., 2013; Robinson and Jorge, 2016; Shi et al., 2017). However, there is currently no "gold standard" for the diagnosis and assessment of PSD due to differences in the timing of assessments, the use of different rating scales for depressive symptoms, and the associated signs and symptoms (e.g., aphasia and cognitive impairment) make the diagnosis and evaluation of PSD difficult (Laures-Gore et al., 2017; Zhao et al., 2018). The early recognition, prevention, and treatment of PSD are vital for the recovery and prognosis of stroke survivors.

Functional near-infrared spectroscopy (fNIRS) is a well-established, non-invasive tool that can be used to continuously assess regional tissue oxygenation at the bedside (Hong and Naseer, 2016). It has been used in different clinical settings, especially in the field of neuroscience (Obrig, 2014; Hong and Yaqub, 2019; Chen et al., 2020). The purpose of this study was to investigate whether fNIRS is useful for the assessment of PSD in patients with stroke.

MATERIALS AND METHODS

Subjects

We recruited 45 patients with stroke (male, $n = 32$; female, $n = 13$; mean age, 67.8 $\pm$ 12.9 years), who were admitted to Nagasaki Kita Hospital from May 2015 to April 2019 (**Table 1**). Of the 45 patients, 26 had cerebral infarction and 19 had cerebral hemorrhage. The subjects were divided into two groups: the depressed group ($n = 13$) and the non-depressed group ($n = 32$) (**Supplementary Table 1**).

The inclusion criteria were as follows:

(1) Unilateral lesions of the cerebral hemispheres without involving the infratentorial region.

(2) More than 1 month after the onset of stroke.

(3) A Mini-Mental State Examination (MMSE) score of $\geqq$ 24.

(4) Antipsychotic drug dose below the recommendation of the WHO.

(5) No complicating neurodegenerative diseases.

(6) No history of mental illness.

(7) Being able to sit for at least 30 min.

Abbreviations: PSD, post-stroke depression; VFT, verbal fluency task; fNIRS, functional near-infrared spectroscopy; HAMD17, 17-item Hamilton Rating Scale for Depression; oxy-Hb, oxygenated hemoglobin; FIM, functional independence measure; FMA, Fugl-Meyer Assessment; BRS, Bruunstrom Recovery Stage; MDD, major depressive disorder.

This study was approved by the Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences (approval number: 17071374) and the Ethics Committee of Nagasaki Kita Hospital (approval number: 14–003). Written informed consent was obtained from all subjects in accordance with the Declaration of Helsinki.

Assessment of PSD

The 17-item Hamilton Rating Scale for Depression (HAMD17), which is a comprehensive and quantitative measure of clinical symptoms of depression, was used to evaluate PSD (Hamilton, 1960; Meader et al., 2014). The severity of each item was scored on a scale of 0–2 or 0–4. The subjects who showed a severity score of ≤ 7 were classified into the non-depressive group. The patients of the depressed group were further classified according to their HAMD17 score, as follows: mild, 8–16 points; moderate, 17–23 points; and severe, $\geq$ 24 points. The HAMD17 was performed within 1 week of fNIRS measurement.

Clinical Assessment of PSD

The following items that could affect the onset of PSD were examined:

- General information: age, sex, type of stroke, damaged hemisphere, date from the onset of stroke to the evaluation date, and medications.
- Cognitive function: MMSE.
- Activities of daily living: the sum of the functional independence measure (FIM) total score and exercise/cognitive items.
- Severity of paralysis after stroke: the upper limb function items of the Fugl-Meyer Assessment (FMA) and the upper limb, lower limb, and finger items of the Bruunstrom recovery stage (BRS).

Measurement of fNIRS

Probe Positioning and Measurement Points

We used a 46-channel fNIRS instrument (OMM-3000/16, Shimadzu Corporation, Japan) to measure changes in the concentrations of oxygenated hemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) at three wavelengths (780, 805, and 830 nm) of infrared light based on the modified Beer-Lambert law (Maki et al., 1995; Yamashita et al., 1996).

The probes of the fNIRS machines were placed on the frontal and bilateral temporal regions of the subject. The frontal probes measured the hemoglobin concentration changes at 19 measurement points with the lowest probes positioned along the Fp1–Fp2 line according to the international 10/20 system used in electroencephalography (Okamoto et al., 2004; Zhu et al., 2018).

The distance between a detector probe and injector probe pair was set at 3 cm, and the area between the detector probe and injector probe pair was defined as a "channel" (**Figure 1**).

Activation Task

Participants sat on a comfortable chair and were instructed to minimize any major body movements to avoid imaging artifacts, and the verbal fluency task (VFT) was used as an activation task (Takizawa et al., 2008, 2014). The VFT was a block design task and consisted of a 30-s pre-task baseline, a 60-s VFT task, and a

TABLE 1 | Demographic and clinical data of the patients.

	All patients	Depression group	Non-depression group	Group difference
	(*n* = 45)	(*n* = 13)	(*n* = 32)	*p*-value
Age[a]	67.8 ± 12.9	67.2 ± 9.6	67.8 ± 12.9	0.670
Gender, male/female[b]	32/13	9/4	23/9	0.859
Types of strokes[b]				
Infarction/hemorrhage	26/19	6/7	20/12	0.321
Right hemisphere stroke/left hemisphere stroke	26/19	6/7	20/12	0.094
Time from onset to fNIRS (months)[a]	2.8 ± 1.3	3.0 ± 1.5	2.7 ± 1.2	0.548
MMSE (point)[a]	28 ± 2.2	28.2 ± 1.5	28.0 ± 2.4	0.678
FIM (score)[a]				
Total	114.6 ± 11.0	108.4 ± 14.1	117.2 ±8.2	0.027*
Motor	82.8 ± 9.9	77.2 ± 13.1	85.0 ± 7.2	0.011*
Cognition	31.9 ± 3.7	31.2 ± 3.1	32.2 ± 3.8	0.122
FMA (point)[a]	50.2 ± 21.0	34.1 ± 23.9	56.7 ± 15.5	0.001**
BRS (stage)[a]				
Upper limb	4.8 ± 1.3	3.7 ± 1.2	5.3 ± 0.9	<0.001***
Lower limb	5.0 ± 1.2	4.3 ± 1.2	5.3 ± 1.0	0.005*
Finger	4.9± 1.2	4.0 ± 1.2	5.3 ± 1.0	0.001**
HAMD17 (point)[a]	4.7 ± 3.9	9.8 ± 2.7	2.6 ± 1.9	<0.001***
oxy-Hb Integrated value[a]	2.7 ± 2.7	1.7 ± 2.4	3.2 ± 2.7	0.040*

*Values are mean ± SD. *P < 0.05, **P < 0.01, ***P < 0.001. [a]Mann–Whitney U-test. [b]chi-squared test The Mann–Whitney U-test or Spearman rank correlation coefficient was used for comparing (these variables) each item between patients and controls. MMSE, Mini-Mental State Examinaton; FIM, Functional Independence Measure; FMA, Fugl-Meyer Assessment; BRS, Bruunstrom Recevery Stage; HAMD 17, The 17-item Hamilton Rating Scale for Depression.*

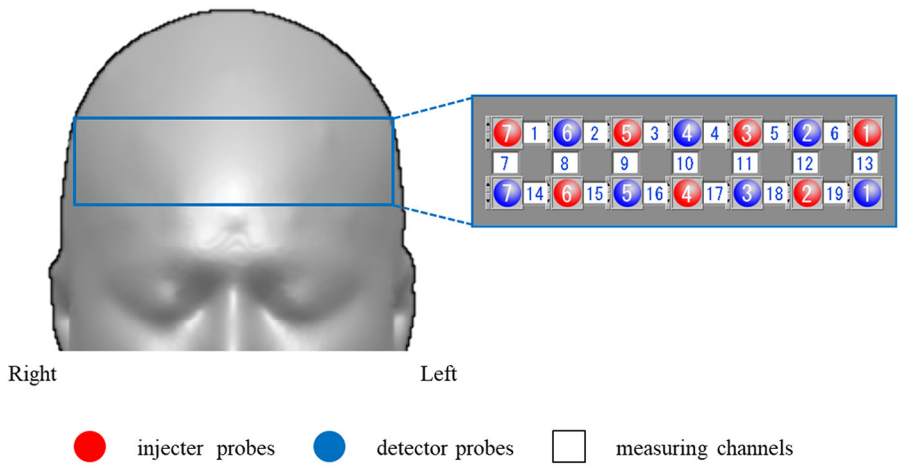

FIGURE 1 | Functional near-infrared spectroscopy (fNIRS) measurement points. We used a 19-channel system with 14 optodes, seven injector probes, and seven detector probes solid white numbers denote the channels of measurement.

70-s post-task baseline. The subjects were instructed to generate as many words as possible where the initial syllable was /a/, /ki/, or /ha/. The three initial syllables changed every 20-s during the 60-s task. The subjects were also instructed to utter the Japanese syllables (/a /, / i /, / u /, / e /, and / o /) during the pre- and post-task baseline periods, which were used for baseline correction (**Figure 2**).

Data Analysis of fNIRS

As no standardized method has been established for the analysis of fNIRS data, various approaches have been reported (Obrig and Villringer, 2003). In this study, after removing artifacts, the last 10 s of the 30-s pre-task period was used as the pre-task baseline and the first 55-s of the 70-s post-task period was used as the post-task baseline. Baseline correction was performed using the

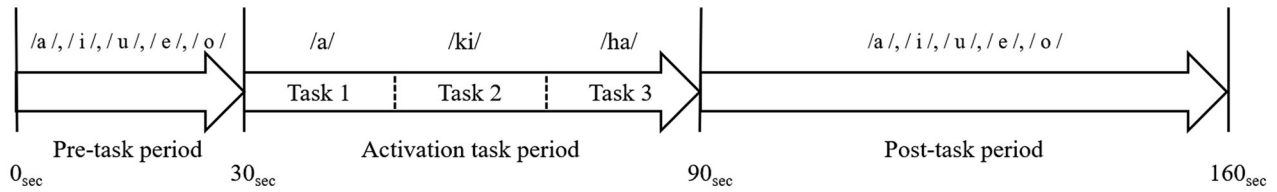

FIGURE 2 | The verbal fluency task (VFT) protocol. The cognitive activation task had a block design and consisted of a 30-s pre-task baseline period, a 60-s VFT activation task period (three initial syllables, 20-s each), and a 70-s post-task baseline period.

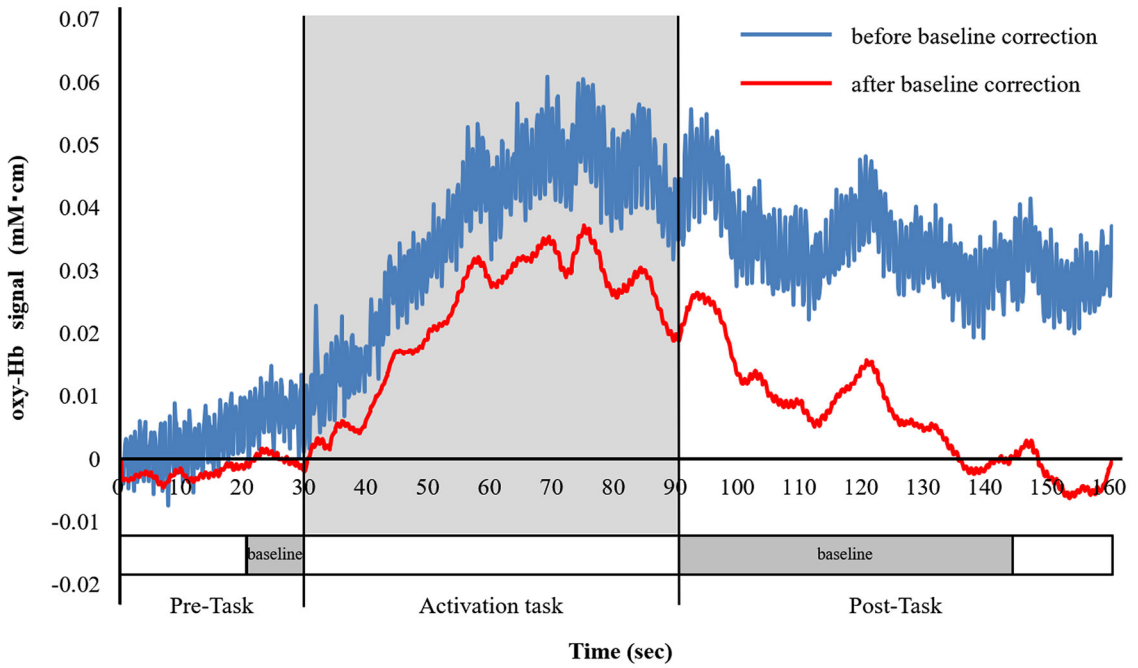

FIGURE 3 | Analysis of the fNIRS data. The blue line indicates oxygenated hemoglobin (oxy-Hb) before the baseline correction, and the red line indicates oxy-Hb after the baseline correction. Baseline correction was performed in the last 10-s of the pre-task period and the first 55-s of the post-task period, which is shown by the dotted line on the time axis. Baseline correction was performed using the moving average method. We, then, averaged the oxy-Hb data of 19 channels and calculated the integral value of the task periods.

moving average method (Suto et al., 2004; Kameyama et al., 2006; Takizawa et al., 2008, 2014).

We obtained the integral value by averaging the data of the 19 channels, showed the size of the hemodynamic response during the activation task period (**Figure 3**).

Regarding the index of brain activity in fNIRS, oxy-Hb has been demonstrated to have a strong positive correlation with regional cerebral blood flow (Hoshi et al., 2001), and an increase in regional cerebral blood flow has been found to reflect an increase in neural activity (Jueptner and Weiller, 1995). Total hemoglobin roughly corresponds to blood flow variability but when the variability is small, it is unreliable (Hoshi et al., 2001; Miyai et al., 2001), and there are individual differences regarding changes in deoxy-Hb (Hesselmann et al., 2001). In this study, we only on focused oxy-Hb and analyzed the data (Takizawa et al., 2008, 2014).

Experimental Environment and Position

The room was light- and sound-proofed to the best of authors' abilities. The instruments as well as the examiner were located behind the patient, where the examiner could examine the body movements of the patient without interfering with their visual field (Kondo et al., 2018). To prevent artifacts caused by visual stimuli, the personal computer screen was placed in front of the patient. In order to avoid physical movement artifacts and reduce the burden of fatigue and pain, the patient sat on a chair or wheelchair with a backrest, placed their hands on the desk, and placed their feet on the floor (Noda et al., 2012). fNIRS was performed after confirming general information.

Statistical Analysis

Statistical analyses were performed using IBM SPSS for Macintosh, and statistical significance was set at $P < 0.05$. The relationship between the oxy-Hb integral value and the total score of HAMD17 was analyzed using Spearman's rank correlation coefficient. The Mann–Whitney U test was used to analyze age, time from onset to evaluation, MMSE, FIM, FMA, BRS, HAMD17, and oxy-Hb integral values. Sex and stroke types were examined using the chi-squared test. Spearman's rank correlation coefficient was used to analyze the correlation between the FIM, FMA, BRS, and HAMD17 total scores.

In statistical analysis, the Shapiro–Wilk test confirmed that all variables did not show a normal distribution.

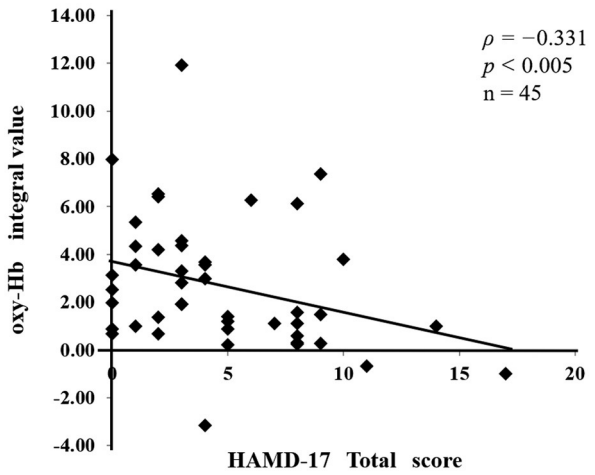

FIGURE 4 | The relationship between the assessment of post-stroke depression (PSD) and the severity of paralysis. A negative correlation ($\rho = -0.331$, $P < 0.005$) was found between the oxy-Hb integral values and the total 17-item Hamilton Rating Scale for Depression (HAMD17) scores.

RESULTS

Clinical Data

Table 1 shows the demographic characteristics of the 45 patients with stroke, who were divided into two groups: 32 patients without depression (the non-depressed group) and 13 patients with depression (the depressed group). We investigated the relationship between oxy-Hb integral values and HAMD17 total scores and found a negative correlation between them ($\rho = -0.331$, $P < 0.005$; **Figure 4**). Significant differences in the following items were observed between the non-depressed and depressed groups: FIM total score, $P = 0.027$; FIM motor items, $P = 0.011$; FMA, $P = 0.001$; BRS upper limb, $P < 0.001$; BRS lower limb, $P = 0.005$; BRS hand, $P = 0.001$; and HAMD17, $P < 0.001$. The following items did not differ between the two groups: age, sex, type of stroke, hemisphere, time from onset to assessment, and FIM cognitive items. The prevalence of PSD in the present study was 29%.

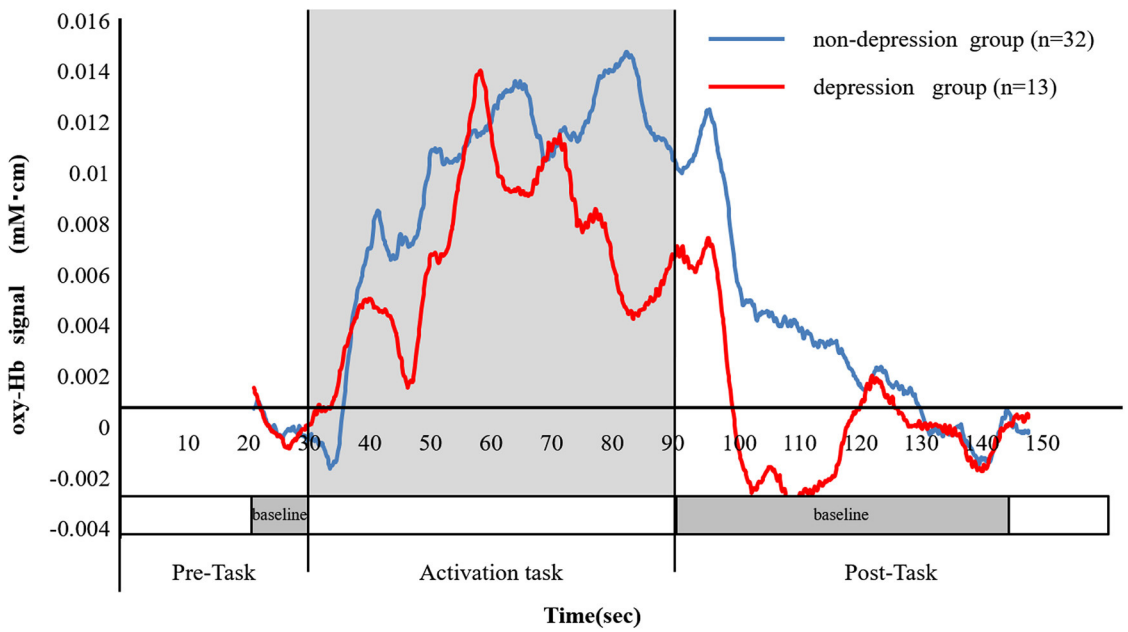

FIGURE 5 | The change in the ratio of the oxy-Hb between the depressed and non-depressed groups. The blue line shows the mean oxy-Hb values in the non-depressed group ($n = 32$), while the red line shows the mean oxy-Hb values in the depressed group ($n = 13$). The mean of the oxy-Hb integral values in the non-depressed group was significantly higher than those of the depressed group (3.16 ± 2.7 and 1.71 ± 2.4, respectively, $P = 0.040$).

Correlation Between the oxy-Hb Integral Value and the Severity of Paralysis

There was a significant difference between the depressed and non-depressed groups in the oxy-Hb integral value during the activation task period (3.16 ± 2.7 and 1.71 ± 2.4, respectively; $P = 0.040$). This result indicates that PSD may be induced by decreased oxy-Hb integral values and decreased activation in the frontal lobe (**Figure 5**). A negative correlation was found between the total scores of the HAMD17 and the FMA and BRS values (HAMD17: FMA, $\rho = -0.580$, $P < 0.005$; HAMD17: BRS upper limb, $\rho = -0.606$, $P < 0.005$; HAMD17: BRS lower limb, $\rho = -0.416$, $P < 0.005$; and HAMD17: BRS hand, $\rho = -0.559$, $P < 0.005$; **Figure 6**).

DISCUSSION

In this study, the subjects were classified into depressed and non-depressed groups based on the results of the HAMD17. A negative correlation was found between the oxy-Hb integral value and the HAMD17 total score ($\rho = -0.331$, $P < 0.005$). In addition, a significant difference was observed in the oxy-Hb integral values of the two groups ($P = 0.040$). The average value of the oxy-Hb integrated value during the activation task period was 1.71 ± 2.4 in the depressed group and 3.16 ± 2.7 in the non-depressed group, indicating that the depressed group had a lower oxy-Hb integral value and lower frontal lobe activation in comparison with the non-depressed group.

Functional Near-Infrared Spectroscopy Study Using a VFT in PSD

There are no established diagnostic criteria or specific methods for the evaluation of PSD, and the pathophysiology of PSD has not yet been clarified (Ayerbe et al., 2013; Villa et al., 2018; Zhao et al., 2018). fNIRS is a well-established non-invasive tool that can be used to continuously assess regional tissue oxygenation at the bedside.

In this study, we investigated the frontal lobe functions in patients with PSD after stroke by using fNIRS, with a VFT as an activation task. We found a negative correlation between the fNIRS oxy-Hb integral value and the HAMD17 total score. We also found a significant difference in the oxy-Hb integral values of the non-depressed and depressed groups. Makizako et al. (2013) reported that oxygen-Hb values

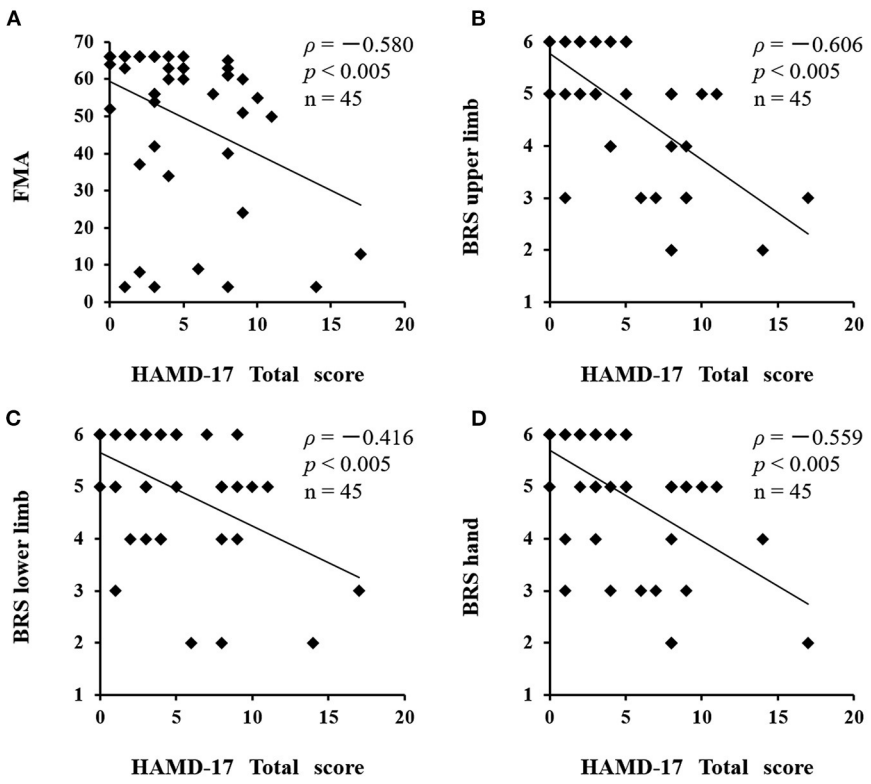

FIGURE 6 | Correlation between HAMD17 total scores and severity of paralysis after stroke. A negative correlation was found between the total scores of the HAMD17 and the FMA and BRS values. **(A)** HAMD17: FMA, $\rho = -0.580$, $P < 0.005$; **(B)** HAMD17: BRS upper limb, $\rho = -0.606$, $P < 0.005$; **(C)** HAMD17: BRS lower limb, $\rho = -0.416$, $P < 0.005$; **(D)** HAMD17: BRS hand, $\rho = -0.559$, $P < 0.005$). HAMD17, The 17-item Hamilton Rating Scale for Depression; FMA, Fugl-Meyer Assessment; BRS, Bruunstrom Recovery Stage.

in the pre-frontal cortices of aged people (mean age, 76.1–6.7 years) were increased in comparison with baseline values: however, the effect of aging was not clarified. Although the non-depressed group showed a higher oxy-Hb integral value than the depressed group, we could not examine the effects of aging as healthy subjects were not included in this study.

To date, several papers have investigated major depression using fNIRS during activation tasks.

Noda (Noda et al., 2012) reported that the oxy-Hb increase in the frontal and right temporal cortex during a VFT was attenuated in patients with major depressive disorder (MDD) in comparison with healthy controls. The relationship between the severity of depression symptoms and the change in oxy-Hb was studied in 30 patients with MDD and 30 controls who were matched for age, sex, and intelligence quotient. The oxy-Hb increase during the task in patients was significantly smaller in comparison with controls. The mean increase in oxy-Hb, during the task, showed a significant negative correlation with the total score of the Hamilton Rating Scale for Depression 21-item version.

Zhang et al. (2015) reported similar results to those of Noda et al. (2012), where patients with MDD had significantly lower pre-frontal activation during cognitive tasks in comparison with healthy subjects.

Kawano (Kawano et al., 2016; Takamiya et al., 2017) investigated the relationship between oxy-Hb integral values and the severity of depression, as assessed using the Hamilton Depression Scale in patients with various psychiatric disorders, such as MDD, and found that the severity of depression was negatively correlated with the integral value in the frontal lobe, irrespective of psychiatric disorders.

In a situation where the pathophysiology of PSD is still unknown, we believe that the decrease in the integral value of oxy-Hb and the increase in HAMD17 in the frontal lobe of the depressed group show significant results, as they represent similar findings to previous studies in the field of psychiatry.

Effects of Cerebral Lesions on PSD

Robinson et al. (1984) found that lesions involving the left frontal region of the brain were associated with a significantly higher frequency of depression during the first 2 months following acute stroke than comparable lesions of the right hemisphere or posterior lesions of the left hemisphere. Subsequently, the work of other investigators (Starkstein et al., 1987; Morris et al., 1996) identified that left-lateral frontal lobe, caudate, and putamen lesions were significantly more likely to produce depression during the acute stroke period than comparable lesions in the right hemisphere.

Nickel and Thomalla (2017) reviewed whether there is an association between PSD and stroke lesion characteristics, such as lesion size and lesion location. Available studies are hampered by methodological limitations, including the drawbacks of lesion analysis methods, small sample sizes, and the issue of patient selection. These limitations, together with differences in approaches to assess PSD and methods of image analysis, limit the comparability of results from different studies. Overall, the results are controversial, and no clear pattern of stroke lesions associated with PSD has emerged, although findings suggest that frontal stroke lesions are more so associated with a higher incidence of PSD. In the present study, the brain lesions in individual cases were diverse; thus, the relationship between the lesion and PSD could not be examined.

Effects of Antipsychotic Drugs on fNIRS Signals

Anti-psychotropic medications have been reported to affect fNIRS signals. Among these medications (Schecklmann et al., 2008), high doses of antidepressants showed significant effects on NIRS signals in comparison with low doses. Three patients in this study took small amounts of antidepressants or antipsychotics; thus, we considered that the drugs had no effect on their fNIRS signals (**Supplementary Table 1**).

Limitations

The NIRS methodology has several shortcomings. NIRS enables the measurement of hemoglobin concentration changes only as relative values, not as absolute values. Furthermore, NIRS has a relatively low spatial resolution in comparison with MRI, low cerebral penetration depth, and the contributions from extracerebral tissue, such as the skin and skull, may contaminate the NIRS signal. Due to a lack of standard quantification, the acquired hemoglobin data from various NIRS instruments are provided as relative values and are measured in different units (i.e., mmol mm, mmol/L, or arbitrary units). In this study, we obtained the integral value by averaging all the data of all channels, which showed the size of the hemodynamic response during the 60-s activation task period.

Regarding the NIRS reproducibility of NIRS data, the analysis of NIRS data requires careful interpretation analysis at the single subject and single-channel level is carefully interpreted (Schecklmann et al., 2008). In this study, we evaluated the analysis that was performed using the average values of multiple channels.

In recent years, some studies have been conducted using new analysis methods such as machine learning, and it is necessary to further study the methods of analysis (Kang and Cho, 2020).

Further studies, with larger study populations, are necessary to investigate the relationship between the lesion and PSD.

Conclusions

We investigated the frontal lobe functions in patients with PSD after stroke by using fNIRS with VFT as an activation task. We found a negative correlation between the fNIRS oxy-Hb integral value and the HAMD17 total score, as well as a significant difference in the oxy-Hb integral value between the non-depressed and depressed groups. Currently, there is no "gold standard" for the diagnosis and assessment of PSD. The present study indicates that the measurement of oxy-Hb using fNIRS is a useful diagnostic method for PSD in patients after stroke.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article **Supplementary Material**, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Nagasaki University Graduate School of Biomedical Sciences. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MK and MY are occupational therapists who were involved in PSD rehabilitation treatment and performed the experiments. MK, MY, WM, TM, and TH analyzed the data. MT was involved as a specialist from the Department of Neurology. MT, MY, and TH contributed to the preparation of the manuscript. All authors agreed with the items listed in the submission manual.

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Corticospinal Excitability of the Lower Limb Muscles During the Anticipatory Postural Adjustments: A TMS Study During Dart Throwing

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Objective: To investigate whether the changes in the corticospinal excitability contribute to the anticipatory postural adjustments (APAs) in the lower limb muscles when performing the ballistic upper limb movement of the dart throwing.

Methods: We examined the primary motor cortex (M1) excitability of the lower limb muscles [tibialis anterior (TA) and soleus (SOL) muscles] during the APA phase by using transcranial magnetic stimulation (TMS) in the healthy volunteers. The surface electromyography (EMG) of anterior deltoid, triceps brachii, biceps brachii, TA, and SOL muscles was recorded and the motor evoked potential (MEP) to TMS was recorded in the TA muscle along with the SOL muscle. TMS at the hotspot of the TA muscle was applied at the timings immediately prior to the TA onset. The kinematic parameters including the three-dimensional motion analysis and center of pressure (COP) during the dart throwing were also assessed.

Results: The changes in COP and EMG of the TA muscle occurred preceding the dart throwing, which involved a slight elbow flexion followed by an extension. The correlation analysis revealed that the onset of the TA muscle was related to the COP change and the elbow joint flexion. The MEP amplitude in the TA muscle, but not that in the SOL muscle, significantly increased immediately prior to the EMG burst (100, 50, and 0 ms prior to the TA onset).

Conclusion: Our findings demonstrate that the corticospinal excitability of the TA muscle increases prior to the ballistic upper limb movement of the dart throwing, suggesting that the corticospinal pathway contributes to the APA in the lower limb in a muscle-specific manner.

Keywords: postural control, center of pressure (COP), transcranial magnetic stimulation, motor evoked potential (MEP), central command, three-dimensional motion analysis, motor imagery ability

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INTRODUCTION

Perturbations from voluntary movements such as the reaching or unloading of the upper limb cause the shift of the center of gravity (COG) and impair the postural equilibrium in humans (Aruin and Latash, 1995a). The activities of the postural muscles in the trunk and lower limb occur prior to a voluntary upper limb movement (Kasai and Taga, 1992; Kawanishi et al., 1999; Chiou et al., 2018),

which is known as the anticipatory postural adjustments (APAs). The APA is thought to contribute to the postural control, which minimizes the postural displacement from an expected perturbation in advance and plays an important role in maintaining balance and preventing falls (Horak, 2006; Kanekar and Aruin, 2014a). The abnormal APA has been shown in elderly people (Kanekar and Aruin, 2014a,b) and in the patients with stroke (Palmer et al., 1996; Garland et al., 1997; Slijper et al., 2002; Bourke et al., 2015), cerebral palsy (Bigongiari et al., 2011; Girolami et al., 2011), Parkinson's disease (Viallet et al., 1987; Latash et al., 1995), multiple sclerosis (Krishnan et al., 2012; Aruin et al., 2015), and chronic low back pain (Hodges and Richardson, 1996; Massé-Alarie et al., 2012).

It has been reported that the preceding activity of the postural muscles in association with the APA was affected by the velocity of the intended movements (Lee et al., 1987). This is explained as a rapid shoulder movement causes a perturbation and the preceding activities of the postural muscles allow to minimize the postural instability in advance, while a slow shoulder movement causes minimum perturbation and needs no postural control in advance. The preceding postural control is observed approximately 100 ms before the initiation of the intended movement (Aruin and Latash, 1995b). Because the time window of the APA is too fast as a result of the afferent inputs from the upper limb movement, it is thought to be preprogrammed by the central nervous system (CNS) (Friedli et al., 1984; Massion, 1992).

Although the several cortical and subcortical mechanisms, involving the primary motor cortex (M1), supplementary motor area (SMA), basal ganglia, thalamus, brainstem, vestibule, and spinal cord, are thought to contribute to the APA (Viallet et al., 1992; Jacobs et al., 2009; Ng et al., 2011, 2013), the cortical contribution rather than the subcortical contribution might have a greater role (Massion, 1992; Chiou et al., 2018). To investigate cortical or corticospinal excitability, transcranial magnetic stimulation (TMS) has been widely utilized to date (Barker et al., 1985). The advantage of TMS is not only capable of stimulating the cerebral cortex non-invasively, but also of targeting the area in the M1 responsible for the control of a specific muscle. By using TMS, it has been shown that the corticospinal excitability increased in the lower limb and trunk muscles in the preparation of the rapid shoulder and elbow movements (Petersen et al., 2009; Chiou et al., 2016, 2018; Massé-Alarie et al., 2018).

The previous studies suggest that M1 may contribute to the APA, while the central mechanisms of the APA are not fully understood. Particularly, it remains unclear whether the corticospinal tract for the tibialis anterior (TA) muscle in the lower limb is involved in the APA when performing a ballistic movement of the upper limb. Because it has been shown that the motoneurons of the TA muscle receive a greater excitatory influence from the M1 compared to the antigravity muscle of the triceps surae muscle within the lower limb (Brouwer and Ashby, 1992; Bawa et al., 2002), it is expected that the excitability of the corticospinal projections to the TA muscle increases in the APA phase as well as that observed in the triceps surae muscle. We also believed that it would be of great interest to investigate a ballistic multijoint movement with more intended and goal-directed action, e.g., dart throwing. It is considered that the APA operates for the throwing movement involving a slight flexion of the elbow joint followed by an extension, which is poorly understood. Furthermore, whether the changes in the corticospinal excitability, if any, correlate to the outcome of the cognitive characteristics, namely, the changes in the kinematic parameters in association with the voluntary movement or the individual motor imagery ability, are considered in the scope of this study. It has been shown that the motor imagery accompanies increments of the cortical excitability including the M1 (Yahagi et al., 1996; Kasai et al., 1997). If the corticospinal tract contributes to the APA as we hypothesized, the corticospinal excitability may be modulated depending on the optimal attentional strategy of an individual, which is related to the modality dominance of the motor imagery (Sakurada et al., 2016).

We, therefore, hypothesized that the corticospinal pathway contributes to the APA in the lower limb preceding the ballistic upper limb movement. To test this hypothesis, we used TMS to examine the changes in the excitability of the corticospinal projections to the TA muscle in the time window of the APA phase during the dart throwing. Also, we assessed the kinematic parameters by means of the three-dimensional motion analysis, center of pressure (COP), and the individual visual and kinesthetic motor imagery abilities (Malouin et al., 2007).

MATERIALS AND METHODS

Participants

A total of 17 right-handed [the Flinders Handedness survey (FLANDERS) questionnaire, 8.8 ± 2.7 points] (Nicholls et al., 2013; Okubo et al., 2014) healthy volunteers, who did not suffer from any known neurological or orthopedic disorders and did not have any prescribed medication or CNS active drugs, participated in this study. Fifteen (six men and nine women; mean age 24 ± 4 years) of the participants were recruited in protocol 1, of which nine participants were additionally assessed by the three-dimensional motion analysis. Thirteen (five men and eight women; mean age 24 ± 4 years) of 15 participants who participated in protocol 1 were also in protocol 2. Seven (two men and five women; mean age 25 ± 4 years) of the participants were recruited in protocol 3, of which five participants participated in both protocols 1 and 2. All the participants, who were non-professional dart players, gave their informed written consent before the experiments. The experimental procedures and protocols were performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine.

Experimental Procedures

The participants were asked to stand upright on the throwing line (on a force plate) with their feet closed and face the dart board straight. A plastic competition dart board (diameter: 39.4 cm) was set in front of the participant, 220 cm from the throwing line and 173 cm off the ground. In the preparative position, the

participants were asked to hold a plastic tip dart (18 g) with the right dominant hand when keeping the right shoulder and elbow joint flexed and then to throw the dart after a visual go signal [light-emitting diode (LED) light], which was set beneath the dart board. The Participants were instructed to "keep standing in an upright position without moving as much as possible when holding the dart, then aim the center of the board (bulls-eye) and throw the dart as forcefully as possible by means of right elbow extension movement after the visual cue." The non-dominant arm and hand were relaxed throughout the experiment. About 5 to 10 familiarization trials were performed prior to the data recordings to familiarize the participants with the task.

Measurements of the Motor Performance

The kinematic assessments by the three-dimensional motion analysis were performed by using the KinemaTracer system (Motion Recorder, KISSEI COMTEC Corporation Ltd., Japan) of which the four cameras were set in an equidistant manner on the right side of the participant (sampling rate 50 Hz). Eight reflective markers were placed on the right acromion, lateral epicondyle approximating elbow joint axis, ulnar styloid, fifth metacarpal head, greater trochanter, lateral epicondyle of the knee, lateral malleolus, and fifth metatarsal head according to the Plug-in-Gait marker placement. The real-time angle changes in the shoulder, elbow, and wrist joints in the right upper limb and those in the hip, knee, and ankle joints in the right lower limb were recorded. COP was recorded throughout the experiment by a force plate (90 cm × 60 cm, TF-6090, Tec Gihan Corporation Ltd., Japan) set under the feet of the participant.

Electromyography Recordings

Surface EMG was recorded from the right anterior deltoid (AD), long head of triceps brachii (TB), TA, and soleus (SOL) muscles by using a pair of the silver-bar electrodes (10 mm in length, 1 mm in diameter, and 10 mm in distance, Bagnoli-4 EMG System, Delsys, Boston, Massachusetts, USA) attached on the muscle belly closely to the predicted neuromuscular junction of each muscle. The reference electrode was attached to the right olecranon. The AD and TB muscles are thought to contribute to dart throwing, while the TA and SOL muscles are thought to contribute to postural control. To confirm the contribution of the biceps brachii (BB) muscle to the APA, we recorded EMG activity of the BB muscle instead of the AD muscle in protocol 3. The EMG signals were amplified (1,000X) and passed through a bandpass filter between 20 and 2,000 Hz.

Transcranial Magnetic Stimulation

A double cone coil (13 cm external diameter of wings) connected to a magnetic stimulator (Magstim 200 square, The Magstim Company Ltd., Whitland, UK) was placed around the vertex (**Figure 1A**). The coil current was applied in an anterior-posterior direction with the coil loops lateral to the midline and, therefore, a monophasic current with a posterior-anterior direction was applied in the M1. The center of the junction of the coil was systematically adjusted to find the optimum location for the activation of the right TA muscle, which was 1 cm lateral and 1 cm anterior to the vertex. We determined the optimal position (motor hotspot) where stimulation of the slight suprathreshold intensity consistently produced the largest motor evoked potential (MEP) in the right TA muscle by moving the coil in 0.5 cm and the motor hotspot was marked with a pen on the swimming cap covered scalp. The resting motor threshold (rMT) was defined as the lowest stimulus intensity of TMS evoking MEP of above 50 μV in amplitude in more than half of the trials. The stimulus intensity was set at 1.1–1.2 times rMT (55 ± 8, 39–68% of the maximum stimulator output) for inducing a definitely identifiable MEP (approximately 0.2–0.4 mV in the resting state) in the experiments. TMS pulse was delivered by a three-channel electronic stimulator (SEN-7203, Nihon Kohden, Tokyo, Japan) by which the visual cue (LED light) was triggered synchronously.

Experimental Protocols

Three experimental protocols were carried out in this study. In protocol 1, participants performed the dart throwing with a visual cue triggered reaction time paradigm without TMS. The timing of visual cues was randomized, and the interval between the cues was approximately 15–30 s. One session included five trials and the time interval between the sessions was approximately 3–5 min. Participants performed 10 trials (two sessions) along with the recordings of the motor performance of the distances from the thrown darts to the bull's-eye, the three-dimensional motion analysis focused on the right upper and lower limb movements, and the COP. The EMG onset timing (interval from the visual cue to the EMG onset) of all four muscles was calculated.

In protocol 2, TMS was given at several time points, which were predetermined by the analysis in protocol 1. Because the EMG of the TA muscle was clearly observed prior to the EMG onset of the TB muscle (agonist muscle), TMS was applied at the timings of the visual cue, 0, 50, and 100 ms prior to the EMG onset of the TA muscle (TA onset, −50 ms, and −100 ms, respectively) and also the EMG onset of the TB muscle (TB onset, **Figure 1B**). Because of the difference in the timing of the movement initiation following the visual cue among the participants, the trigger timing of TMS was determined in each participant (total of 13 participants). It has been shown that the corticospinal excitability of the muscles involved in a motor task increased from about 100 ms prior to the EMG onset (Chen and Hallett, 1999). With respect to the APA, a previous study also reported that the corticospinal excitability increased 75 ms prior to the EMG onset of the postural muscle in the lower limb (Petersen et al., 2009). In this study, therefore, we aimed to explore the changes in the corticospinal excitability in the APA time window during the dart throwing and chose the timings immediately before the TA muscle bursts. The timing of the TB onset was chosen to explore the extent to the increment of the MEP amplitude at the moment of the agonist EMG onset, while the timing of the visual cue was chosen to confirm whether the changes in MEP were task-dependent. At least five trials (5–10 trials) were conducted at each time point. The EMG activity of the SOL muscle as an antigravity muscle and that of the AD muscle as an adjunctive muscle were frequently presented before the dart throwing because the participants held a dart with their right shoulder and elbow flexed in a standing position as mentioned above. Focusing on the TA muscle in this study, we carefully

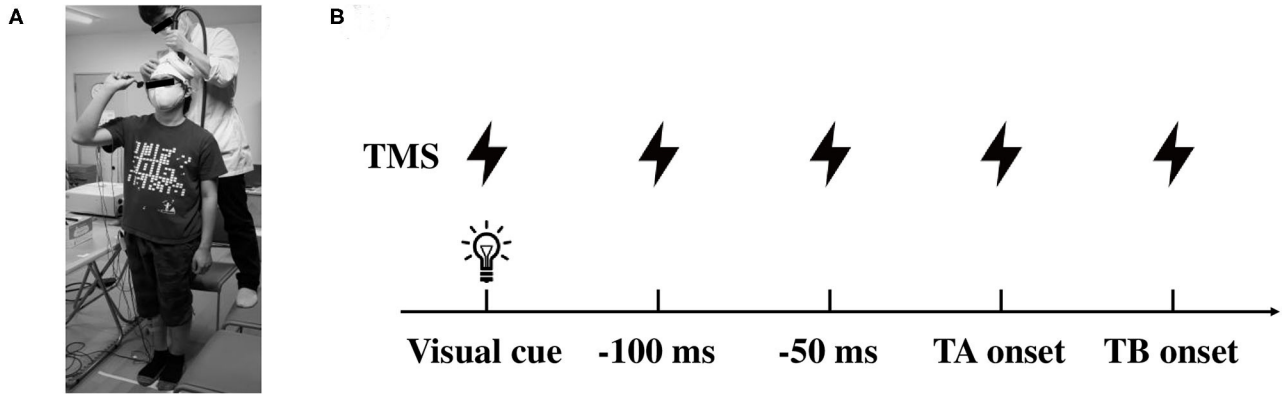

FIGURE 1 | Illustrations of the experimental setup. **(A)** Data collection of the motor evoked potential (MEP) in the lower limb muscles during dart throwing. **(B)** The timing of TMS application in protocol 2. TMS was applied at the visual cue, 100, 50, 0 ms prior to the TA onset and the TB onset. TMS, transcranial magnetic stimulation; TA, tibialis anterior; TB, triceps brachii.

confirmed, throughout the experiments and the offline analysis, that no EMG activity in the TA muscle at the time points TMS applied, except the time point of the TB onset. In the control condition, TMS was applied while the participants were standing upright in the resting state without holding a dart.

In protocol 3, we additionally recorded the EMG activity of the BB muscle instead of the AD muscle because the movement of the elbow flexion might play a role at the early stage of the APA according to the kinematic data. The experimental procedures were the same as in protocol 1.

Apart from the main protocols, the motor imagery abilities were assessed by using the Kinesthetic and Visual Imagery Questionnaire (KVIQ), which was developed to determine the individual visual imagery (VI) and kinesthetic imagery (KI) abilities, respectively (Malouin et al., 2007). Because it has been shown in the previous study that the motor performance outcome can be affected by the optimal attentional strategy of an individual, which is related to the modality dominance of the motor imagery (Sakurada et al., 2016), we aimed to explore the difference in the VI and KI in our participant group and, if any, the influence on the resulting motor performance or the corticospinal excitability.

Data Acquisition and Analysis

The linear distances from the bull's-eye to the thrown darts were measured as the results of the motor performance.

During the dart throwing task, the changes in the angle and angular velocity of the shoulder, elbow, and wrist joints in the right upper limb and those in the hip, knee, and ankle joints in the right lower limb were calculated (3D Calculator, KISSEI COMTEC Corporation Ltd., Japan). The force plate signal (force and its vectors in the axial directions of the x, y, and z-axes) was sampled at 50 Hz (Vital Recorder 2, KISSEI COMTEC Corporation Ltd., Japan) and the data were stored in a computer for the offline analysis (Kine Analyzer, KISSEI COMTEC Corporation Ltd., Japan). The total length of COP and rectangle area for 3 s from the visual cue were calculated.

The EMG activities were recorded and analyzed by using the data acquisition software (LabChart, ADInstruments, Sydney, Australia) for the PowerLab analog-to-digital convertor (PowerLab 8/30, AD Instruments, Sydney, Australia) at a 4-kHz sampling rate. EMG signals were rectified and analyzed with a moving average of 50 ms without TMS. The interval from the visual cue to the EMG onset of each muscle and the kinematic parameters was calculated, respectively. All the time course data were also realigned to the TB muscle onset (defined as 0 ms). The EMG activity before the visual cue (with a 100 ms window) was calculated and the value of mean $\pm$ 2 SD in each participant was used as a cutoff value to determine the onset and end of the EMG activities followed by the visual inspection of the experimenters. EMG activity with the maximum voluntary contraction (MVC) of each muscle was recorded at the beginning of the experiments. Participants were asked to maximally perform the shoulder flexion, elbow flexion and extension, and dorsal and plantar flexion for 2–3 s, and the MVC per second was calculated for each muscle. MVC for plantar flexion was measured in a standing position, while that for others in a sitting position. The integrated EMG (iEMG) activities were calculated and the averaged values per second during the motor tasks were presented as a percentage of MVC (%MVC).

The MEP amplitude was measured as the peak-to-peak values and normalized as a percentage of MEP at the control condition (%control). The background EMG (bEMG) activities prior to the TMS trigger (with a 100 ms window) were calculated in all the trials. The trials including significant bEMG activity in the TA muscle were excluded, except at the time point of the TB muscle in which almost all the trials contained bEMG activity (these data were all included in the analysis). After omitting the trials involving significant bEMG activity in the TA muscle (time points of visual cue, $-$100 ms, $-$50 ms, and the TA onset), the number for the control condition involved in the analysis was 8.7 $\pm$ 1.2 trials, while that for the time points during the motor task was 4.9 $\pm$ 2.3 trials.

The motor performance and kinematic data with TMS (protocol 2) were not utilized in the analysis because they would

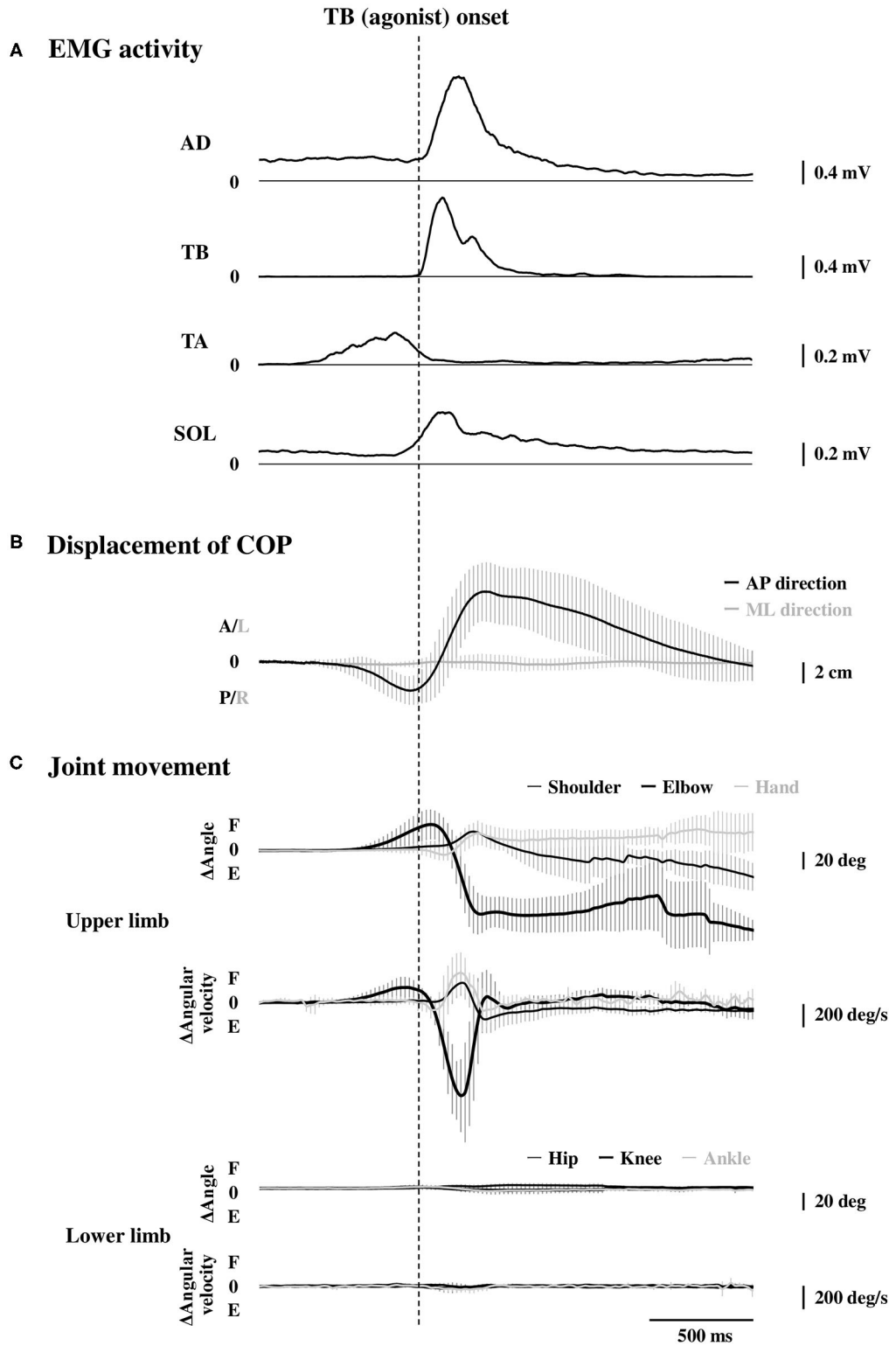

FIGURE 2 | Rectified and averaged EMG activities of the AD, TB, TA, and SOL muscles (**A**, $n = 15$), displacement of the COP (**B**, $n = 15$), and the joint movements in the upper and lower limbs (**C**, $n = 9$) in the time course. All the data were aligned to the EMG onset of the TB muscle. Error bar indicates the SD. EMG, electromyography; AD, anterior deltoid; TB, triceps brachii; TA, tibialis anterior; SOL, soleus; COP, the center of pressure.

be markedly influenced by the preceding TMS of which the stimulation would spread in the M1 and induce muscle activation not only in the TA and the SOL muscles but also in the other muscles (e.g., upper limb and trunk muscles).

Statistical Analysis

Data were analyzed by using the JMP Pro 15 software (SAS Institute Incorporation, Cary, North Carolina, USA). In protocols 1 and 3, the one-way ANOVA with repeated measures (factor: muscle) was used to determine the difference in the EMG onset timing followed by the Dunnett's *post-hoc* test. The timing between EMG onset and the onset of the COP displacement or elbow joint movement was analyzed with a paired *t*-test. The KVIQ score was analyzed with the Wilcoxon signed-rank test. The correlation analysis between the EMG onsets or kinematic data was performed by using Pearson's correlation coefficient analysis. In protocol 2, the MEPs in the TA and SOL muscles were normalized as a ratio of the control size (resting standing), and then grand mean ratios with SD from the pooled data were calculated. These data were analyzed by using the one-way ANOVA with the repeated measures (factor: time point) followed by a paired *t*-test with the Holm's Sequential Bonferroni Correction (Holm, 1979). The MEP amplitude at the TB onset and at the control was compared with a paired *t*-test. The correlation analysis of the changes in the MEP of the TA or SOL muscle with the KVIQ scores was performed by using Spearman's rank correlation. The level of the statistical significance was defined as $p < 0.05$. Results are presented as mean ± SD. The effect size for the ANOVA was calculated by using eta squared (η^2) (Cohen, 1988).

RESULTS

Electromyography Activity

Averaged data of the EMG activity, which is aligned to the TB onset in the time course, are shown in **Figure 2A** ($n = 15$). The iEMG of the AD, TB, TA, and SOL muscles during the dart throwing was 55.8 ± 32.0%, 52.7 ± 22.8%, 12.7 ± 7.0%, and 29.5 ± 26.6% MVC, respectively. The EMG onset timing was obviously different among the muscles [$F_{(3.42)} = 76.74$, $p < 0.0001$, $\eta^2 = 0.80$]; the EMG activity of the TA muscle significantly preceded the agonist TB muscle onset ($p < 0.0001$, **Table 1**), while the onset of the AD muscle was significantly delayed ($p < 0.001$). The EMG of the SOL muscle occurred slightly earlier (but not significant) compared to the TB muscle ($p = 0.13$). In addition, the onset of the BB muscle was significantly different compared to the other muscles [$F_{(3.18)} = 37.89$, $p < 0.0001$, $\eta^2 = 0.83$; *post-hoc* test, $p < 0.05$, respectively, **Table 1** and **Figure 4A**, $n = 7$] and the time intervals between the BB muscle and the TB, TA, and SOL muscles were 284.1 ± 98.6 ms, −42.4 ± 13.4 ms, and 283.7 ± 78.5 ms, respectively (realigned to the onset of the BB muscle).

Motor Performance

The errors calculated by the distances from the bull's-eye to the thrown darts were 9.8 ± 3.0 cm without TMS. The average changes in the displacement of the COP in the time course are shown in **Figure 2B** ($n = 15$). Although the COP showed a minimum change in the left-right direction, it moved slightly in the posterior direction initially (**Table 1**) and then switched to the anterior direction, significantly preceding the TB onset ($p < 0.0001$, respectively). The TA muscle was activated simultaneously with the posterior shift of the COP followed by the anterior shift of the COP. The total length of the COP was 32.0 ± 9.0 cm and the rectangle area of the COP was 39.9 ± 19.6 cm^2 during the dart throwing.

The maximum changes in the angle and angular velocity of all the joint movements are summarized in **Table 2** and the average changes in these parameters in the time course are shown in **Figure 2C** ($n = 9$). In this study, the flexion movements in the upper limb joints were approximately 30°, while the extension movement in the elbow joint achieved the full range of 90° along with the highest angular velocity. In the time course, the elbow flexion initiated prior to the TB muscle onset ($p < 0.0001$, **Table 1**) followed by an extension movement along with the

TABLE 1 | EMG and the onset of the kinematic parameters are aligned to the TB onset.

	Time [ms]
EMG	
BB	−284.1 ± 98.6
AD	50.1 ± 44.3
TA	−323.3 ± 127.9
SOL	−26.2 ± 62.5
Displacement of COP	
COP-posterior	−319.5 ± 126.5
COP-anterior	−96.8 ± 90.6
Elbow joint movements	
Elbow flexion	−284.4 ± 111.1
Elbow extension	17.3 ± 33.4

Values are mean ± SD.
EMG, electromyography; TB, triceps brachii; BB, biceps brachii; AD, anterior deltoid; TA, tibialis anterior; SOL, soleus; COP, the center of pressure.

TABLE 2 | Kinematic information during the dart throwing.

Joint	Movement	ΔAngle [deg]	ΔAngular velocity [deg/s]
Shoulder	Flexion	26.6 ± 9.7	317.0 ± 98.7
	Extension	1.4 ± 2.0	211.9 ± 114.3
Elbow	Flexion	33.8 ± 17.0	160.7 ± 80.2
	Extension	90.4 ± 18.6	1204.6 ± 220.7
Hand	Palmar flexion	28.9 ± 11.8	504.1 ± 142.2
	Dorsal flexion	12.2 ± 7.0	390.6 ± 104.3
Hip	Flexion	4.3 ± 2.5	38.4 ± 14.2
	Extension	0.8 ± 0.7	23.7 ± 9.3
Knee	Flexion	2.9 ± 2.9	34.8 ± 13.8
	Extension	4.0 ± 3.2	52.2 ± 35.6
Ankle	Dorsal flexion	2.6 ± 1.5	50.5 ± 22.8
	Plantar flexion	4.9 ± 3.9	86.5 ± 53.2

Values are mean ± SD.

TB muscle onset ($p = 0.16$). In the lower limb, on the other hand, the changes in the hip, knee, and ankle joints, which were always detected after the TB onset, were minimal, if any ($<5^\circ$ in average). We confirmed by these data that no obvious movement of the lower limb or trunk throughout the motor task, especially prior to the TB onset.

The COP or elbow movement onset timing against the TA onset was assessed, respectively (**Figure 3**). There was a significant positive correlation between the onset of the TA and the onset of the COP posterior or anterior shift. On the other hand, the TA onset was positively correlated to the onset of the elbow flexion, but not in the case of the elbow extension. The results were in line with those in protocol 3 that the onset of the BB muscle, but not the TB muscle, showed a significant positive correlation to the onset of the TA muscle (**Figure 4B**).

Motor Evoked Potential to TMS

Representative EMG activities and MEP recordings in the TA muscle are shown in **Figures 5A,B**, respectively. There was a significant difference in the MEP of the TA muscle between the time points [$F_{(4.48)} = 8.28$, $p < 0.0001$, $\eta^2 = 0.36$, **Figure 5C**]. A *post-hoc* analysis revealed that the MEP in the TA muscle significantly increased at −100 ms, −50 ms, and the TA onset, but not at the visual cue, compared to the control (0.28 ± 0.23 mV, $p < 0.01$, respectively). The MEP prior to the TA onset (−100 ms, −50 ms, and the TA onset) was also significantly larger compared to the visual cue ($p < 0.01$, respectively). The MEP at the TB onset compared to the control also showed a significant increase ($p < 0.01$), in which the MEPs with bEMG activities were included.

Although the MEP was recorded by TMS over the hotspot of the TA muscle, the MEP in the SOL muscle was also obtained simultaneously in 12 out of 13 participants. At these time points relative to the TA muscle onset, we found no changes in the MEP of the SOL muscle at the visual cue ($124.8 \pm 59.5\%$ control), −100 ms ($108.1 \pm 45.1\%$ control), −50 ms ($98.6 \pm 42.9\%$ control), and the TA onset ($87.1 \pm 45.5\%$ control) compared to the control size (0.23 ± 0.18 mV) [the one-way ANOVA, $F_{(4.44)} = 1.24$, $p = 0.31$, $\eta^2 = 0.08$], while the MEP significantly increased at the TB onset ($284.3 \pm 205.8\%$ control, $p < 0.05$).

Kinesthetic and Visual Imagery Questionnaire and Motor Evoked Potential

With respect to the motor imagery ability, the VI score (42.9 ± 7.2) was significantly higher compared to the KI score (36.5 ± 10.1) ($p < 0.01$). To explore whether the visual or kinesthetic imagery ability has relation to the MEP enhancement of the TA and SOL muscles, the MEP data at and immediately prior to the TA onset (0 ms, −50 ms, and −100 ms) were pooled and that correlation with the VI or the KI score was analyzed (**Figure 6**). The VI score, but not the KI score, was significantly correlated to the MEP enhancement in the TA muscle, while a significant correlation was observed neither with the VI score nor the KI score in the SOL muscle.

DISCUSSION

The major finding from this study was that the corticospinal excitability was significantly increased prior to the EMG activity of the TA muscle during the dart throwing. The ballistic movement of the dart throwing involved a slight elbow flexion followed by a full extension in association with the posterior and anterior movement of the COP. The preceding EMG activity of the TA muscle counteracted the COP changes operating for the incoming elbow flexion and extension, suggesting the contribution of the corticospinal tract of the TA muscle to the APA. Further, the visual, but not kinesthetic, motor imagery ability positively correlated to the MEP enhancement in the TA muscle. To the best of our knowledge, this study provides the first evidence that the corticospinal pathway may play a crucial role for the APA in the lower limb during the ballistic and repetitive throwing movement involving the elbow flexion and extension.

Kinematic Profiles and Electromyography Activity During the Dart Throwing

Previous studies reported that the APA in the rapid shoulder movements was typically observed from about 100 ms prior to the initiation of the intended movement (Aruin and Latash, 1995b). Rapid shoulder flexion caused the shift of the COG to the anterior direction due to forward shift in the arm placement whereas the COP shifted in a posterior direction in reaction to the movement of the upper limb and the EMG of the postural muscles such as erector spinae, biceps femoris, and the SOL muscles were activated before the initiation of the shoulder flexion. In contrast, the rapid shoulder extension caused the shift of the COG to the posterior direction due to backward shift in the arm placement whereas the COP shifted in an anterior direction in reaction to the movement of the upper limb and the EMG of the postural muscles such as rectus abdominis, rectus femoris, and the TA muscles were activated before the initiation of the shoulder extension. In this study, the dart throwing involved more complex elbow movement, namely, initiated with a slight elbow flexion followed by a full extension (**Figure 2**) and the COP data also involved both the posterior and anterior shifts. The rapid elbow extension made an anterior shift of the COP drastically, which indicated the posture fell forward eventually. Preceding the elbow movements, therefore, a posterior shift of the COP in advance was most likely to counteract and minimize the incoming anterior shift of the COP accompanied with the rapid elbow extension (**Figure 2**; **Table 1**). We could not exclude the possibility that the posterior shift of the COP might play a role in accelerating the whole body in the anterior direction during the elbow extension (Stamenkovic and Stapley, 2016). Nevertheless, by considering the temporal changes in the COP along with the elbow movements, the posterior shift of the COP would accompany the elbow flexion and the following anterior shift of the COP would accompany the elbow extension.

The results of the EMG activity revealed an early onset of the TA muscle and the posterior shift of the COP, i.e., approximately 320 ms prior to that of the agonist TB muscle (**Figure 2**; **Table 1**). The APA time calculated from the onset of the EMG or COP was somewhat longer compared to the previous studies by using the

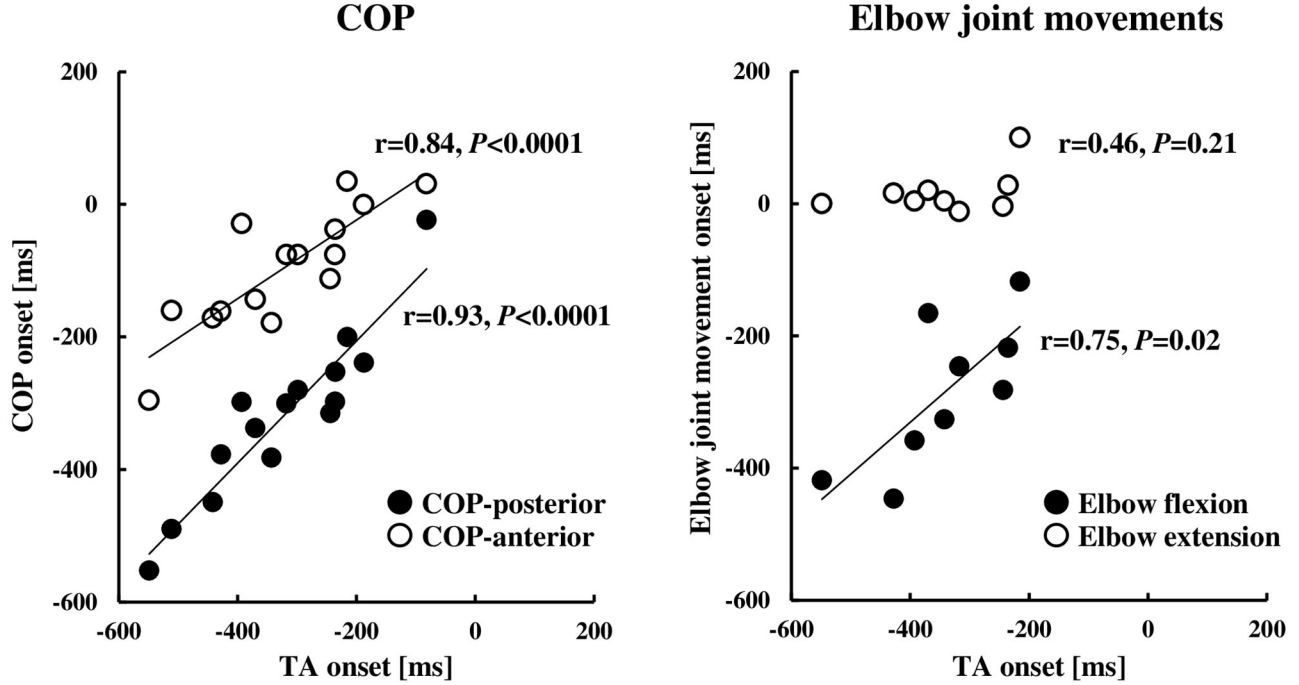

FIGURE 3 | Relationships between the onset of the TA muscle and COP ($n = 15$) or elbow joint movement ($n = 9$). The onset timings were calculated by the onset of the TB muscle (0 ms, the TB onset). COP, the center of pressure; TA, tibialis anterior; TB, triceps brachii.

traditional simple motor task (Aruin and Latash, 1995b; Petersen et al., 2009), but was similar to a previous study by using the dart throwing task in which the APA time was calculated by the ground reaction force (Juras and Słomka, 2013). The differential APA time among the studies might be attributed to the difference in the task difficulty. In this study, if the TA muscle activity in association with the posterior shift of the COP contributed to the anticipatory postural reactions preceding the ballistic elbow joint movement, one would expect that the timing of the TA onset correlated to that of the COP shift or elbow joint movement. TB muscle is the agonist muscle during the dart throwing, while the BB muscle is considered as the "first muscle activated." The TA muscle was activated approximately 40 ms prior to the EMG onset of the BB muscle (**Figure 4A**; **Table 1**). Interestingly, our results showed that the TA onset correlated to both the onsets of the posterior and anterior shift of the COP and the TA onset correlated to only the onset of the elbow flexion (BB muscle), but not the elbow extension (TB muscle) (**Figures 3**, **4B**). It suggested that the TA muscle activity contributed to the shifts of the COP preceding the elbow extension, while the onset timing varied depending on the elbow flexion. Because the mere rapid elbow flexion involves a shift of the COG in the posterior direction, the COP would have an anterior shift by the APA, if any. Therefore, the posterior shift of the COP associated with the TA muscle activity preceding the dart throwing could not be explained by the APA for the elbow flexion and would be an APA for the incoming anterior shift of the COP along with the elbow extension. In the complex movement of the upper limb such as dart throwing, a series of motions involving a slight elbow flexion followed by an extension might be considered as a preprogrammed "set of motions," and the TA muscle activity accompanied the posterior shift of the COP might contribute to the APA during the dart throwing, which was probably triggered by the initial slight elbow flexion.

On the other hand, the activation of the SOL muscle might also play a role in the APA for the anterior shift of the COG in association with the ballistic elbow extension (Petersen et al., 2009). In this study, however, the SOL muscle initiated almost simultaneously to the TB muscle, after the onset of the anterior shift of the COP (**Figure 2**; **Table 1**), suggesting a compensatory but not anticipatory postural reaction of the SOL muscle. Through this study, it seemed that the SOL muscle was no longer operative for the APA, possibly due to the earlier onset of the TA muscle, which was operating for the posterior shift of the COP and counteracting the incoming anterior shift of the COP associated with the ballistic elbow extension in the dart throwing.

Corticospinal Excitability During the Anticipatory Postural Adjustment

The results of the MEP in the TA muscle were in line compared to the results mentioned above (**Figure 5B**). It was no surprise that the MEP was enhanced in both the TA and SOL muscles at the time point of the TB onset because it is known that the EMG activity and increased excitability of the spinal motoneurons contribute to the MEP responses to TMS (Di Lazzaro et al., 1998). On the other hand, the MEPs in the TA muscle significantly increased immediately prior to the onset of the TA muscle, while those in the SOL muscle had no change. The MEP amplitude at

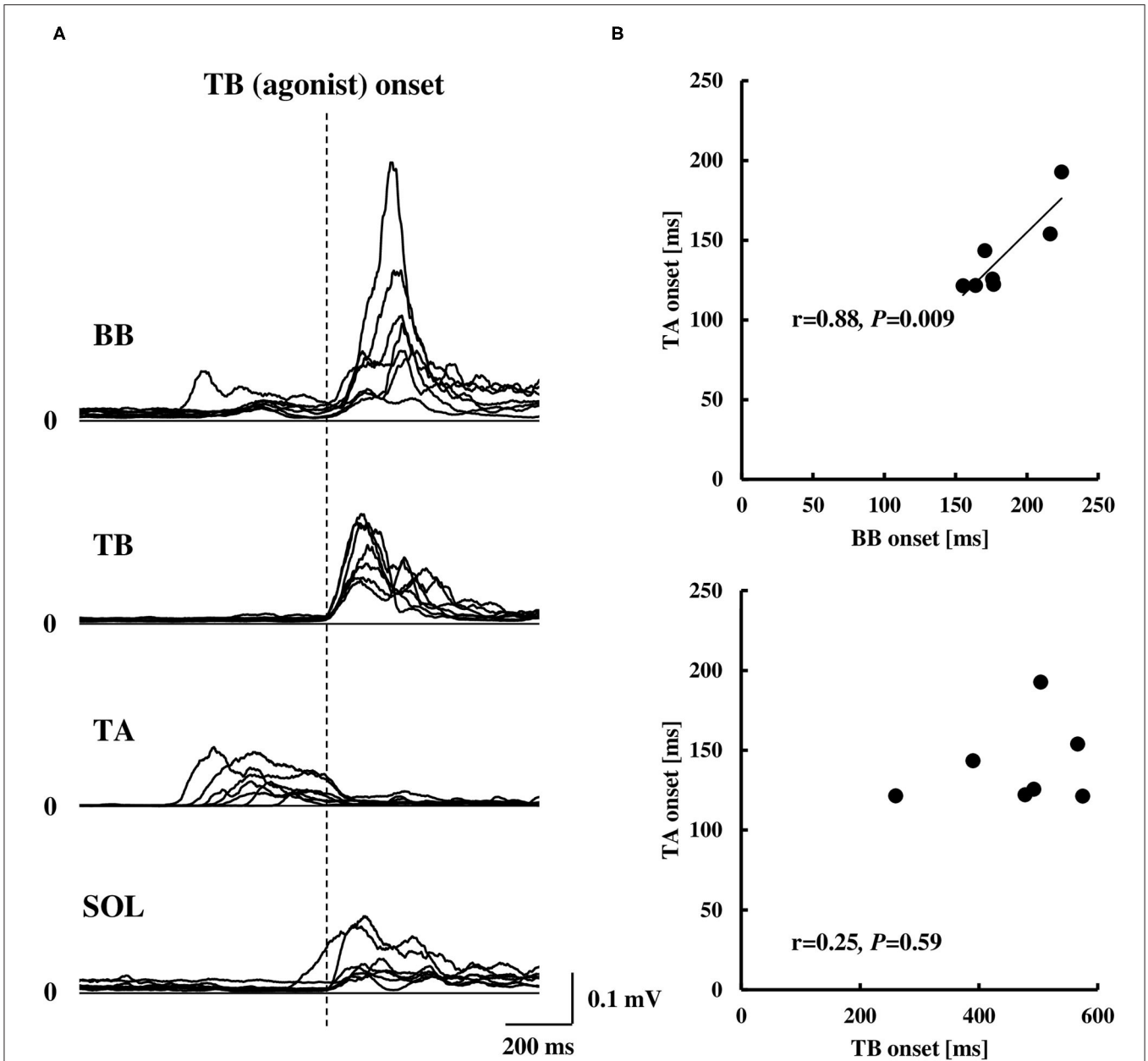

FIGURE 4 | Rectified EMG activities of the BB, TB, TA, and SOL muscles aligned to the EMG onset of the TB muscle (**A**, $n = 7$) and correlation of the EMG onset of the TA muscle compared to the BB or TB muscle (**B**, $n = 7$). Note that the EMG onset in **(B)** was calculated by the duration from visual cue to the EMG onset of each muscle. BB, biceps brachii; TB, triceps brachii; TA, tibialis anterior; SOL, soleus.

−100 ms, −50 ms, and the TA onset, which involved no bEMG activity, exhibited almost the same size compared to the TB onset, which involved bEMG activity, suggesting that it is unlikely that the increased excitability of the spinal motoneuron of the TA muscle contributes mainly to the MEP enhancement prior to the TA onset and it also might be attributed to the increased excitability at a supraspinal level.

Previous studies by using TMS reported that the M1 excitability was modulated before the voluntary movements (Tomberg and Caramia, 1991; Pascual-Leone et al., 1992; Hoshiyama et al., 1996; Chen et al., 1998). The corticospinal excitability of the muscles, which was directly involved in the tasks, increased from about 80–100 ms prior to the EMG onset for the simple reaction time and self-paced movement, respectively (Chen and Hallett, 1999). The postural muscles were not directly involved in the task but activated to minimize the postural displacement from an expected perturbation in advance (Bouisset and Zattara, 1987). In this study, the MEP in the

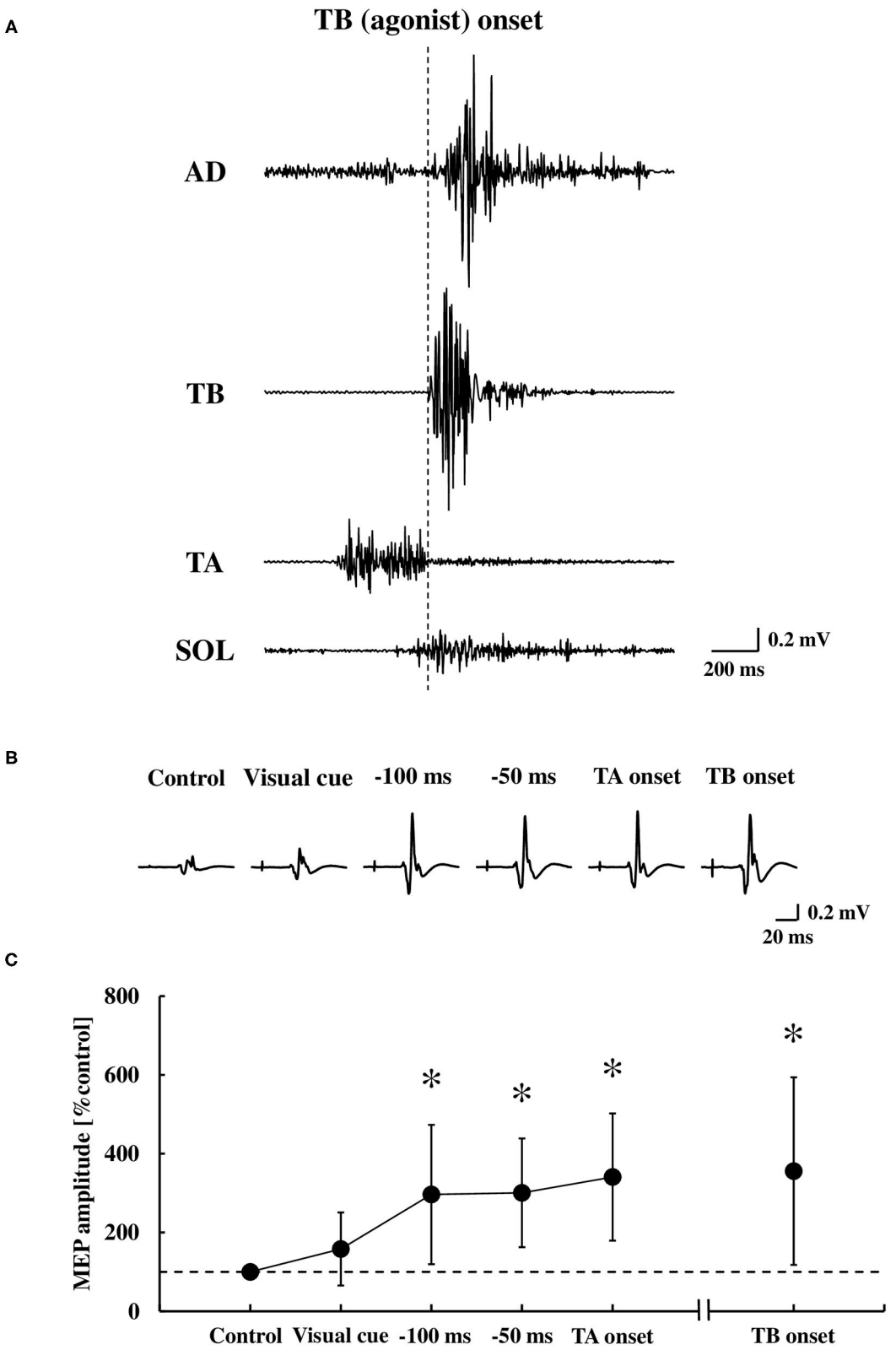

FIGURE 5 | Original tracings demonstrating the AD, TB, TA, and SOL muscle in the EMG activities during the dart throwing **(A)**, representative recordings of the MEP in the TA muscle (averaged five trials, respectively) **(B)**, and the average changes at the time points tested **(C)** ($n = 13$). Error bar indicates the SD. *$p < 0.01$ significant difference from the control or visual cue. AD, anterior deltoid; TB, triceps brachii; TA, tibialis anterior; SOL, soleus; MEP, motor evoked potential.

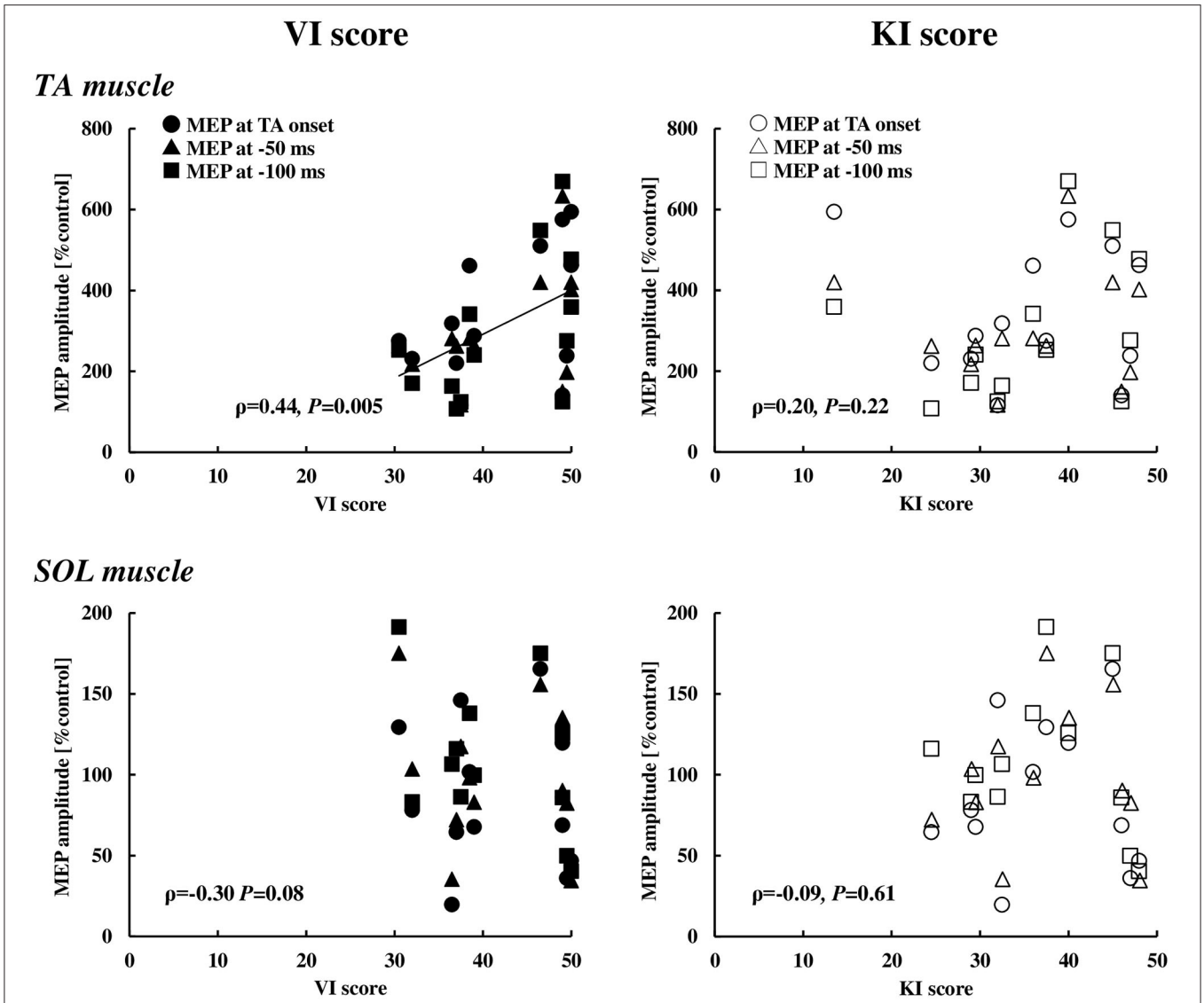

FIGURE 6 | Relationships between the VI or KI score and the MEP in the TA ($n = 13$) and SOL ($n = 12$) muscles at the timings of 0, 50, and 100 ms prior to the EMG onset of the TA muscle. VI, visual imagery; KI, kinesthetic imagery; TA, tibialis anterior; SOL, soleus, MEP, motor evoked potential.

TA muscle at −100 ms, −50 ms, and the TA onset significantly increased compared to the control, suggesting that the MEP in the TA muscle increased from at least 100 ms before the EMG onset of the TA muscle. This is consistent with the results of the previous studies which demonstrated that the corticospinal excitability of the muscles directly involved in the tasks increased from about 80–100 ms before the voluntary movements.

By using TMS combined with H-reflex, Petersen et al. (2009) investigated the modulation of the corticospinal excitability of the SOL muscle during a voluntary heel-raise or handle-pull task and concluded that M1 might be involved in the APA control of the lower limb muscle. Chiou et al. (2016, 2018) by using TMS demonstrated that, when performing the rapid shoulder flexion, the cortical excitability of the erector spinae muscle increased along with the reduced short-interval intracortical inhibition during the APA before receiving any afferent input from the periphery. Massé-Alarie et al. (2018) also examined the corticospinal excitability of the superficial multifidus and rectus abdominis muscles in the preparation of rapid shoulder movements. They concluded that there were two possible mechanisms underlying the motor preparation for the APA: a nonspecific inhibitory mechanism for the superficial multifidus muscle before the Go signal and a task-specific modulation of the corticospinal excitability of the superficial multifidus and rectus abdominis muscles after the Go signal. From the previous studies, the present findings suggested that the corticospinal excitability of the TA muscle increased immediately before the EMG burst (−100 ms–0 ms) at a time window of the APA. It has been suggested that the motoneurons of the TA muscle receive a greater excitatory influence from the M1 compared to the SOL

muscle (Brouwer and Ashby, 1992; Bawa et al., 2002), which is known as an antigravity muscle. If it is the case that the stronger the strength of the central control of the muscle, the larger the voluntary drive downstream from the higher brain center (Liang et al., 2011), our result of the longer APA duration of the TA muscle compared with the previous studies might reflect an early modulation by the central command for the postural control.

Taking into account the previous and present results, it suggested that the M1 plays a crucial role in the APA, although several candidates in the cortical and subcortical areas, e.g., SMA, basal ganglia, thalamus, brainstem, vestibule, and spinal cord are also thought to contribute to the APA (Viallet et al., 1992; Jacobs et al., 2009; Ng et al., 2011, 2013). In particular, it has been shown that the APA was impaired in the patients with the lesion of the SMA, while the APA was intact in a patient with a corpus callosum section (Viallet et al., 1992). A 1-Hz repetitive TMS (rTMS), which transiently disrupted SMA, but not in the case of the dorsolateral premotor cortex, resulted in a decreased duration of the APA in both the healthy humans and the patients with Parkinson's disease (Jacobs et al., 2009). A plausible mechanism for the APA is that the enhanced M1 excitability may be attributed to the projections from the SMA, by which the neural circuits responsible for the APA are predecided.

Cognitive Characteristics and Corticospinal Excitability

Previous studies have reported that the modality dominance of the motor imagery is related to the individual optimal attentional strategy, which was defined by the motor performance outcome under the different focus of the attention conditions (Sakurada et al., 2016, 2017, 2019), namely VI score with the external focus of attention, while the KI score with the internal focus of attention. It is known that the external focus of attention which concentrated on the movement outcome leads to better performance and efficient motor output rather than the internal focus of attention which concentrated on one's body movement (Wulf, 2013). In this study, the VI score was significantly higher compared to the KI score, and there was a significant positive correlation between the MEP in the TA muscle and the VI score, whereas no correlations were found between the MEP in the TA muscle and the KI score or the MEP in the SOL muscle and the VI or KI score (**Figure 6**). Without any instructions of attentional focus in the present study, although it was unable to identify whether the external or internal focus of attention the participants adopted if any, the results at least suggested that the motor imagery ability for visualizing the imagined movement might refer to the modulation of the corticospinal excitability of the TA muscle and reflect the central motor command during the APA phase.

Limitations

There are several potential limitations to this study. First, by using the double cone coil, the TMS would spread in the M1 and induce muscle activation not only in the TA and SOL muscles but also in the other muscles (e.g., upper limb and trunk muscles). Therefore, the motor performance of the dart throwing was measured in a separated protocol without TMS (protocol 1), which made it difficult to simultaneously analyze the kinematic and the MEP data in the time course in an identical trial. Second, although 5–10 MEPs were collected at each time point, the number of the MEPs in the final dataset was sometimes less than five at some time points during the motor task (4.9 ± 2.3 on average). Because the trials involving significant bEMG activity in the TA muscle were omitted from the analysis, the relatively small number of trials in these time points and the individuals might increase the variability of the results. Third, the MEP enhancements prior to the TA muscle onset revealed increased excitability of the corticospinal projections to the muscle, but whether the same population of the corticospinal neurons is used for conveying the signal for the APA and that for a voluntary movement involving the TA muscle is unclear. The previous study has referred to the possibility of similar behavior of the MEP between the APA and voluntary movement conditions (Petersen et al., 2009). Finally, because we have not measured the H-reflex or F-wave which reflects the spinal excitability, or the intracortical inhibition or facilitation by means of the paired-pulse TMS which reflects the cortical excitability, we could not assert the underlying mechanisms in the CNS. Taking into account the previous and present results, it is most likely that the increased corticospinal excitability during the APA is attributed to the excitability changes at the supraspinal level such as M1.

Clinical Applications

Postural instability and impairment of the APA have been shown in the elderly people (Kanekar and Aruin, 2014a,b) and in the patients with CNS disorders, such as stroke (Palmer et al., 1996; Garland et al., 1997; Slijper et al., 2002; Bourke et al., 2015), cerebral palsy (Bigongiari et al., 2011; Girolami et al., 2011), Parkinson's disease (Viallet et al., 1987; Latash et al., 1995), multiple sclerosis (Krishnan et al., 2012; Aruin et al., 2015), and chronic low back pain (Hodges and Richardson, 1996; Massé-Alarie et al., 2012). Therefore, effective rehabilitation interventions, which focus on the APA and for improving postural stability, are needed.

Dart throwing is a coordinated movement of the multi joints and contains the complex elements of the upper limb movements. With such a ballistic movement aiming the dart to the bull's-eye, which involves the slight elbow flexion and almost full extension, is a more intended and goal-directed action. Thus, our findings suggested that a multijoint movement and an intended and goal-directed ballistic movement can induce the longer time of the APA and, therefore, improve the posture control in an efficient way (Aloraini et al., 2019, 2020). In the rehabilitation for the elderly people or the patients with CNS disorders, the great APA might be induced by performing the multi joints movement and more intended and goal-directed action, but not just performing the ballistic upper limb movement. On the other hand, our findings with respect to the individual cognitive characteristics of the KVIQ showed us a possibility that instruction of utilizing the visual motor imagery might lead to further enhancement of the corticospinal excitability for the APA during the ballistic movements.

CONCLUSION

This study demonstrates that the corticospinal excitability of the TA muscle increases preceding the ballistic upper limb movement of the dart throwing, suggesting that the corticospinal pathway contributes to the APA in the lower limb in a muscle-specific manner. The extent toward the enhancement of the corticospinal excitability may be related to the visual motor imagery ability of an individual.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Kyoto University Graduate School and Faculty of Medicine. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM and NL designed the study. AM, NL, and HU performed the experiment. AM analyzed the data and drafted the first version of the manuscript. AM, NL, and KI interpreted the results. NL and KI edited and revised the manuscript. AM, NL, HU, and KI approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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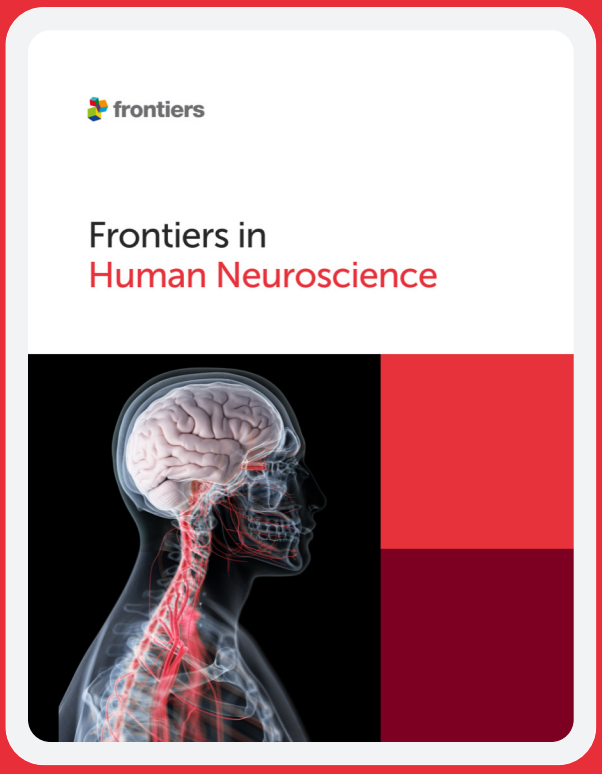

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