Characterization and Modulation of Cognitive Functions using Transcranial Magnetic Stimulation-induced Electroencephalogram Oscillations

March 2020

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Acknowledgments

Firstly, I would like to express my sincere gratitude to my advisor Dr. Masahiro Kawasaki for the continuous support of my Ph.D. study and related research, for his patience, motivation, and immense knowledge. His guidance helped me in all the time of research and writing of this dissertation.

I would also like to thank the rest of my co-advisors: Dr. Masahiko Morita, Dr. Fumihide Tanaka, Dr. Keiichi Kitajo, and Dr. Hiroaki Kumano, for their insightful comments and encouragement. Their guidance incented me to widen my research from various perspectives.

I am also grateful to a number of people who in diverse and generous ways have supported me to finish writing this dissertation. I would like to thank my advisor for master's degree, Dr. Shinobu Nomura, of Waseda University. My learning and research experiences of clinical psychology and psychosomatic medicine helped me to expand my research from clinical perspectives. I would like to thank Dr. Taiga Hosokawa, and the colleagues at Stress Care Tokyo Ueno Clinic. I am grateful to Dr. Kazuo Hiraki and the members of Hiraki Laboratory of University of Tokyo. With their understanding and support, I was able to finish up my dissertation. Last but not the least, I would like to thank my family and friends for supporting me throughout writing this dissertation and my life in general.

Abstract

Efficacious cognitive function is essential for maintaining mental and physical health. Therefore, establishing effective methods to enhance cognitive functions is important. It is also crucial to understand the neural mechanisms underlying cognitive function since much uncertainty still exists. In this dissertation, we propose that a recent approach called TMS-EEG, which combines a neuroimaging technique called electroencephalography (EEG) with a non-invasive brain stimulation technique called transcranial magnetic stimulation (TMS), is useful for both understanding and enhancing cognitive function. TMS-EEG overcomes the limitations of both techniques and allows for more in-depth evaluations and effective neuromodulation. In particular, the evaluation of TMS-induced EEG oscillatory brain activity can provide a causal link between brain function and behaviour. The combination allows for the accurate modulation of task-specific oscillation with the aim of modulating its relevant cognitive function. Despite its recognised potential, there remains a lack of evidence on using the TMS-EEG approach for characteristic evaluation and cognitive enhancement.

This dissertation was designed to illustrate the utility of the TMS-EEG approach for characteristic evaluation and cognitive function modification. To achieve this, three experimental studies were conducted. In the first study, we examined whether TMS-induced EEG oscillatory information is capable of evaluating network properties of cognitive processes. This is essential for elucidating the neural mechanisms that underlie cognitive function. Cognitive enhancement is closely related to the treatment of mental health disorders. Therefore, in the second study, we examined whether TMS-induced EEG oscillatory information is useful for evaluating disease- and treatment-states in depression. The characteristics of cognitive impairments vary depending on the individual. Therefore, selective modification of a cognitive function according to a person's needs is key for cognitive enhancement. In the final study, we investigated whether modulating TMS-induced oscillatory activity can selectively change its relevant cognitive performance. The findings of this dissertation increase understanding of the TMS-EEG approach and evaluate its effectiveness in evaluating and modifying cognitive function.

Contributors and Funding Sources

The dissertation of Eri Miyauchi was reviewed and supported by the following advisors:

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Chapter 2 is presented in the form of an article, which was co-authored by Dr. Masahiro Kawasaki and Dr. Keiichi Kitajo and listed in the List of Published Articles. Co-authors provided the data and guidance on writing, formatting, and editing the paper. The data analyses were conducted with the supports of Yuji Mizuno, Yosuke Ushiku, Yohei Yamada, and Kenji Kobata of RIKEN Brain Science Institute. The research was supported by Grant-in-Aid for Scientific Research on Innovative areas15H01576, 21120005 and 25119512), Grant-in-Aid for Scientific Research (B) (26282169), JST PRESTO, and Program to Disseminate Tenure Tracking System MEXT.

Chapter 3 is presented in the form of an article, which was co-authored by Dr. Masahiro Kawasaki, Dr. Masayuki Ide, Dr. Hirokazu Tachikawa, Dr. Kiyotaka Nemoto, and Dr. Tetsuaki Arai of the Faculty of Medicine and listed in the List of Published Articles. Co-authors supported in part of the data acquisition, formatting, and editing the paper. The research was supported by a Grant-in-Aid for Scientific Research on Innovative areas (15H01576) and the Program to Disseminate Tenure Tracking System MEXT.

The research conducted in Chapter 4 was supported by a Grant-in-Aid for Scientific Research on Innovative areas (15H01576) and the Program to Disseminate Tenure Tracking System MEXT.

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CHAPTER 1: GENERAL INTRODUCTION

1 MOTIVATION FOR THIS WORK

Cognitive functioning is essential for mental and physical health. Therefore, the establishment of effective methods, approaches, or a system for cognitive enhancement is important in the fields of medicine, psychology, and cognitive neurosciences. To achieve this goal, it is also crucial to understand the neural mechanisms that underlie the various cognitive functions, since much uncertainty still exists.

In cognitive neuroscience, a growing body of literature recognises that regionally specific neural oscillations are linked to specific brain functions [1]. Much electroencephalography (EEG) research has focussed on studying the mechanism that underlies the cognitive processes related to the oscillatory activity.

Recently, a new approach that combines EEG with a non-invasive brain stimulation technique called transcranial magnetic stimulation (TMS) has received attention for evaluating cortical properties [2]. TMS is a technique that induces instantaneous or persistent changes in neural activity, depending on its application. Application of TMS pulses enables direct perturbation of cortical regions, and simultaneous EEG recordings allow for the immediate measurement of the electrophysiological responses of the stimulated neurons [3, 4]. For example, a single pulse of TMS is considered an event or a sensory stimulus for conventional event-related potential paradigms in EEG experiments [5]. Thus, unlike experiments with EEG alone, combining EEG with TMS allows changes in input parameters and/or stimulation to be precisely controlled, meaning that more accurate evaluations can be made.

Recent studies have suggested that when TMS is applied in a repetitive paradigm (repetitive TMS; rTMS), it can induce local entrainment of ongoing endogenous oscillatory activity during a task, impacting cognitive performance. The effect may depend on the function of the oscillation [6, 7]. In other words, modulation of the oscillatory activity associated with cognitive function may modify cognitive function. Thus, combining TMS with EEG could be beneficial for enhancing or decreasing cognitive function.

Taken together, TMS-EEG can be considered a useful approach for both understanding and modifying cognitive functions.

2 BACKGROUND AND RELATED WORK

2.1 COGNITIVE FUNCTIONING

2.1.1 Definition

Cognitive function can be referred to as the processes of organising information. For example, acquiring information (perception), selecting (attention), representing (understanding) and retaining (memory) information, and using it to guide behaviour (reasoning and coordination of motor outputs) [8]. In general, intact cognition is essential for mental and physical health. For example, cognitive impairment is a common condition in the elderly, and it has been suggested that the degree of cognitive decline is associated with poor physical performance and well-being [9].

Furthermore, cognitive functions are impaired in many mental and neurological disorders. For instance, Alzheimer's disease is characterized by memory dysfunction. In Alzheimer's, the range of cognitive impairment increases with time, as the disease progresses to include the neocortex [10]. Depression, a major contributor to global mental health issues [11], is characterised by the impairment of cognitive functions such as thinking, attention, decision making, formulating ideas, reasoning, and memory [12]. Therefore, the enhancement of cognitive function appears to be critical for mental health and well-being.

2.1.2 Methods for Cognitive Enhancement

Cognitive enhancement may be defined as any improvement or augmentation of core information processing systems in the brain, including the mechanisms underlying various cognitive processes [8, 13]. Bostron and Sandberg, in their review of methods for cognitive enhancement, [8] provided various examples of the methods being studied, including drugs, genetic modifications, education, mental training, brain-computer interface, and TMS. However, they also point out that most of the methods remain either highly experimental or have small effect sizes. Indeed, a recent study even suggested that after treating depression, there are only small improvements in cognitive function [14]. Moreover, many of the studies that aimed to treat mental health disorders have not focused on cognitive enhancement [10]. In brief, despite the importance of cognitive functioning to mental and physical health, reliable cognitive enhancement methods have not been established.

2.2 EEG OSCILLATORY ACTIVITY

2.2.1 Components to Evaluate Cortical Properties

Neural activity is known to oscillate at a wide spectrum of frequencies (0.05 to 600 Hz) [6, 15]. It can be recorded by EEG, a non-invasive electrophysiological recording technique, through

electrodes placed over the whole brain [6]. EEG oscillatory activity can be described by parameters such as the oscillation frequency, amplitude, and phase [16].

The oscillation's frequency is typically grouped into several frequency bands: gamma (30-200Hz), beta (13-30 Hz), alpha (8-12 Hz), and theta (4-7 Hz), which have been related to distinct cortical function [17]. For example, slow (lower) oscillatory activity is known to be associated with sleep, while faster (higher) oscillations are associated with the awake state [6].

The amplitude reflects the distance between the crest and trough of an oscillatory cycle for each frequency. Power is a measure that estimates the magnitude of oscillatory amplitude within a defined time window [18]. Therefore, we can evaluate the magnitude of neural activity during specific cognitive processes using amplitude information.

The phase determines the precise discharge times of neural assemblies and therefore indicates a particular timing within a single oscillatory cycle or period [18]. The focus is on the case when the phase is approximately constant over a limited time point (i.e., phase locking). Its relationship to events and brain regions is measured [19-21]. When oscillatory phases in distant regions (global) are synchronised, it suggests that these regions are functionally correlated and support neural communication and information transmission. These are known to be relevant for many cognitive processes [21, 22]. Therefore, we can evaluate functional neural connectivity during specific cognitive processes using oscillatory phase information.

EEG oscillatory information allows us to understand the local and global cortical properties of cognitive functions.

2.2.2 Limitations of EEG

Although evaluating EEG oscillatory activity is a great way to understand cortical properties, it can only identify correlational links between brain activity and behaviour [1] and not their causal relationship. Moreover, in the EEG experimental paradigm, precise control over changes in the input parameters and/or stimulation is difficult.

2.3 TMS

2.3.1 Single-pulse and Repetitive TMS

TMS is a non-invasive brain stimulation technique that delivers one or multiple magnetic impulses to the human head with an electromagnetic coil, creating a magnetic field that passes the skull, induces an electric current in a focal area underneath the coil, and interacts with ongoing neural activity [23]. TMS can induce behavioural responses along with instantaneous or persistent neural changes. This has led the technique to be used in both research and clinical settings. Although the mechanism of the neuromodulatory effects of TMS is still poorly understood, it has been used to investigate the brain-behaviour relationship and to treat several neurological and mental health disorders [24].

When TMS is applied to one area at a precise time point into a trial (i.e., single-pulse TMS), the time course of functionally relevant activity in the stimulated area can be traced. In this manner, TMS can be used as an interventional technique to investigate causality in the brain-behaviour

relationship [1]. In particular, upon delivery of a TMS pulse, noise can be induced in the brain, which interferes with the various sensory, motor, and cognitive performances, and provides the proper timing and location of TMS pulse delivery [25-28]. For instance, Amassian et al. [29] reported the visual 'virtual lesion' effect of single-pulse TMS that when a single-pulse TMS is applied to the occipital pole at a certain delay from visual stimulus onset, temporal impairment of visual perception is induced. In clinical settings, physicians use electromyographic responses of the thumb during a single pulse of TMS for diagnosing brain lesions and specific diseases [30].

On the other hand, when TMS is delivered in several pulses in a rapid sequence (rTMS), neural excitability is transiently modulated, with the net effect depending on the stimulation frequency. For instance, stimulation at a low frequency (~1Hz) induces inhibition, whereas stimulation at a high frequency can result in excitatory changes in the stimulated area [6, 31]. Interestingly, the modulatory effect of rTMS outlasts the duration of the direct stimulation for several minutes, presuming that rTMS can induce neuroplastic changes that arise from metabolic changes at the synapses. This has become the premise for most therapeutic TMS effects [32]. Indeed, many studies have shown its efficacy for reducing symptoms of major depression, auditory hallucinations, tinnitus, and obsessive-compulsive disorder [32]. Although most studies have not focused on the neuromodulatory effects of rTMS on cognitive restoration or enhancement [10], recent studies suggest that when rTMS is applied over a central node of a brain network, which is hypothesised to be related to a targeted cognitive function, cognitive task performance can be modified [2]. Altogether, it can be stated that rTMS has great potential for cognitive enhancement.

2.3.2 Limitations of TMS

One major drawback of this approach is that we cannot evaluate how TMS affects neuronal and cognitive processing and how these influence behaviour. Consequently, it fails to explain individual differences in clinical responses or the TMS-induced effects observed in off-target sites [24]. Furthermore, a recent review pointed out that many of the cognitive enhancement effects reported in the research were unexpected [13].

The neuromodulatory effects (magnitude and direction) of rTMS depend on both extrinsic (e.g., stimulation numbers, intensity, and frequency) and intrinsic factors (e.g., the functional state of the target brain area) [33]. The influence of these factors on cognition and the extent of changes in cognitive performance remain unclear [34]. Therefore, understanding the relationship between TMS-induced neural and behavioural changes should increase the effectiveness of TMS.

2.4 TMS-EEG

2.4.1 Advantages of TMS-EEG

Combining the two different methods overcomes the limitations of both techniques. Application of TMS pulses enables direct perturbation of cortical regions, and simultaneous EEG recordings allow for the immediate electrophysiological responses of the stimulated neurons to be

measured [3, 4]. TMS is considered an event or a sensory stimulus for conventional event-related potential paradigms in EEG experiments [5]. Therefore, unlike in experiments with EEG alone, TMS-EEG allows changes in input parameters and/or stimulation to be closely controlled. This means that more in-depth evaluations and effective neuromodulation can be made. In particular, evaluation of TMS-induced oscillatory brain activity may provide a causal link between brain function and behaviour [1]. More specifically, when a set of neuronal groups can causally affect the firing of other neuronal groups within a system, their relationship can be explained by "effective connectivity" [23]. It was found that TMS-EEG can detect the effective cortical connectivity (directionality) of different cognitive states from functional connectivity by evaluating the propagation of time-locked TMS-induced responses between distant areas [24]. Moreover, the combination allows for the accurate modulation of task-specific oscillations to manipulate its relevant function and verify the neuromodulatory effects in the brain.

2.4.2 Findings of TMS-EEG Studies

Indeed, the TMS-EEG approach has advanced understanding of the potential mechanisms of TMS as well as influential factors for effective cognitive enhancement. For instance, it has been suggested that single-pulse TMS-induced oscillations reflect phase resetting of on-going cortical oscillations [32]. Recent TMS-EEG studies have suggested that single-pulse TMS can induce transient neural oscillations in several frequency bands in different cortical areas [6, 35-27]. Kawasaki et al. [32] demonstrated the effect of single-pulse TMS-induced phase resetting across the brain by calculating the phase-locking factor (PLF). This is an index of phase-locking of the oscillatory activity on an electrode across trials [19]. Their approach allowed us to define the intensity of information flow through a cortical network as well as the causal and directional flow of information.

On the other hand, recent TMS-EEG studies suggest that rTMS can induce local entrainment of ongoing endogenous oscillatory activity during a task, which impacts cognitive performance. The effect may depend on the function of the oscillation [2,6,7]. Phase-locking further illustrates the possible effectiveness of using stimulation frequency and target location that are relevant to cognitive function.

2.4.3 Points to Consider in Using TMS-EEG

Despite its recognised potential, there remains a lack of evidence on using TMS-EEG to modify cognitive function. Bergman et al. [38] discussed the hurdles of conducting experiments and interventions using TMS-EEG. TMS-induced oscillatory activity is strongly confounded by co-evoked auditory potentials caused by the TMS click sound. Therefore, the TMS-EEG paradigm needs to be elaborated accordingly (i.e., adding sham-condition). Moreover, there should be a considerable number of TMS-related artefacts (e.g., electrical, mechanical, and biological non-cortical artefacts), which requires extensive post-processing of the data for analysis [38].

3 PURPOSE OF THIS WORK

This dissertation aimed to illustrate the utility of the TMS-EEG approach for characteristic evaluation and modification of cognitive functions. TMS-EEG is defined as an approach that utilises the neuromodulatory effect of TMS and the evaluation of TMS-induced EEG oscillatory information. To achieve this, we first intend to investigate the network properties of cognitive functions using TMS-induced oscillatory activity. Next, we will further investigate the use of TMS-induced oscillatory activity to characterise the network properties and their changes with depression treatment. Finally, we will attempt to modify cognitive behaviours by modulating EEG oscillations and evaluate them using TMS-induced EEG oscillatory activity.

In this dissertation, Chapter 2 introduces the use of TMS-induced phase information to evaluate the directionality of information flow within a cortical network relevant to working memory. Chapter 3 shows the use of TMS-induced phase information to evaluate changes in the network characteristics of depressive states along with treatment. Chapter 4 demonstrates the use of EEG amplitude information and rTMS for the selective modulation of oscillatory activity, which consequently induces the modification of giving-up behaviour. Chapter 5 reviews the main findings and identifies the limitations of the study as well as recommendations for future work.

As described earlier, there is little published data around using the TMS-EEG approach for cognitive modifications due to methodological difficulties. Therefore, this research should make an important contribution to research on TMS-EEG by demonstrating analytical methods to dissociate meaningful information from empirical data. Furthermore, the findings of this dissertation should enhance understanding of the TMS-EEG approach, particularly regarding its efficacy for evaluating and modifying cognitive functions.

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CHAPTER 2: CHARACTERIZING PROPERTIES OF COGNITIVE FUNCTION USING TMS-EEG

1 INTRODUCTION

Neural substrates of working memory (WM) are thought to be separate systems; the prefrontal area for the executive system and posterior sensory areas for the maintenance system, including parietal areas for visual WM and temporal areas for auditory WM [1–3]. Recent human electroencephalography (EEG) studies have shown that a global network with large-scale phase synchronization has an important role in WM [4–6]. In particular, theta rhythms in distributed brain regions are considered to interact with each other [7, 8]. Moreover, it has been suggested that low-frequency synchronizations connect the frontal area with posterior sensory areas for the executive system [9–11]. However, network directionality of such interactions in WM is not clear; either top-down or bottom-up mechanisms which are defined as signals from sensory to frontal areas or signals from frontal to sensory areas, respectively in this study.

Previous studies based on transcranial magnetic stimulation (TMS) and EEG have suggested that single-pulse TMS can manipulate local synchronization in-targeted neural areas [12–14] and induce spatial propagation during a resting state [15]. It is plausible that this method could identify network directionality among WM relevant brain regions by focusing on TMS-induced changes in EEG rhythms during WM tasks. For example, if phase synchronization changes when TMS is delivered to the frontal cortex, directionality is likely to be top-down. In contrast, if phase synchronization changes when TMS is delivered to the sensory cortices, directionality is likely to be bottom-up.

This study aim to clarify WM network directionality. Two types of WM manipulation tasks [an auditory WM task (AWM) and a visual WM task (VWM)] were performed [10], and single-pulse TMS was delivered to three target areas (frontal area, visual area, auditory area). The tasks were also performed during sham-TMS and within a no-TMS condition.

2 MATERIALS AND METHODS

2.1 PARTICIPANTS

Ten patients Ten healthy right-handed volunteers (four females; mean to-normal visual acuity, normal hearing acuity, and normal motor age = 23.5 ± 1.1 years, range 20–33 years) with normal or corrected- performance took part in this EEG experiment. All participants gave written

informed consent, and the protocol was approved by the Ethical Committee of the RIKEN (in accordance with the Declaration of Helsinki), before the experiments were performed.

2.2 EXPERIMENT

2.2.1 Auditory working memory task

Participants, wearing earphones, faced a computer screen placed 60 cm away. At the beginning of each trial, participants were required to memorize a 1-digit number presented as an auditory stimulus through the earphones for 1 s (sample display, Fig. 2-1a). After a 2-s retention interval, another 1-digit number was presented as an auditory stimulus for 1 s, and participants were asked to add the presented number to the earlier memorized number. This mental addition ("manipulation phase") was repeated 3 times, and a probe number was presented as an auditory stimulus, after a white fixation point had turned gray (test display). Participants had to determine whether the probe number matched the mental calculation total within 2 s (while the fixation point was red) by pressing a button. An inter-trial interval (ITI) duration was set at 2 s. Stimuli were generated using Matlab2010 with the Psychophysics Toolbox extension.

2.2.2 Visual working memory task

At the beginning of each trial, 5 x 5 square grids (5◦ x 5◦) and a red circle (1◦ x 1◦) were presented on the computer screen for 1s (sample display, Fig. 2-1b). Participants were required to memorize the position of the red circle. After a 2-s retention interval, participants needed to mentally move the red circle in accordance with a white arrow presented at the center of the screen for 1 s ("manipulation phase"). The arrow was directed upward, down- ward, rightward, or leftward. Participants were asked to repeat this mental manipulation 3 times and then indicate whether the men- tally determined position of the red circle matched a visual probe (test display). Button presses, ITI duration, and stimulus creation were identical to the AWM task.

2.3 TMS

On each trial, three pulses of single-pulse TMS were applied to frontal (Fz), temporal (TP7), or parietal (Pz) areas during the manipulation phase of the task. Specifically, for each manipulation cue (a number with a note symbol in Fig. 2-1a for the AWM tasks or a white arrow in Fig. 2-1b for the VMM tasks), a single pulse of TMS was applied at one of three cue-TMS stimulus onset asynchronies (0, 500, and 1000 ms). We used a figure-eight coil, with a 70-mm wing diameter connected to a biphasic stimulator (Magstim Rapid, Magstim Company Ltd., UK) for TMS application. For maintaining the coil position and direction throughout each session, the flexible arm of a camera stand was used. Prior to performing the experiments, the TMS intensity of each participant was determined as the 95% motor threshold which was minimum intensity to make his/her index finger twitch. To test placebo effects of TMS, the sham- TMS condition was conducted by applying TMS pulses to 15 cm from the top of the head.

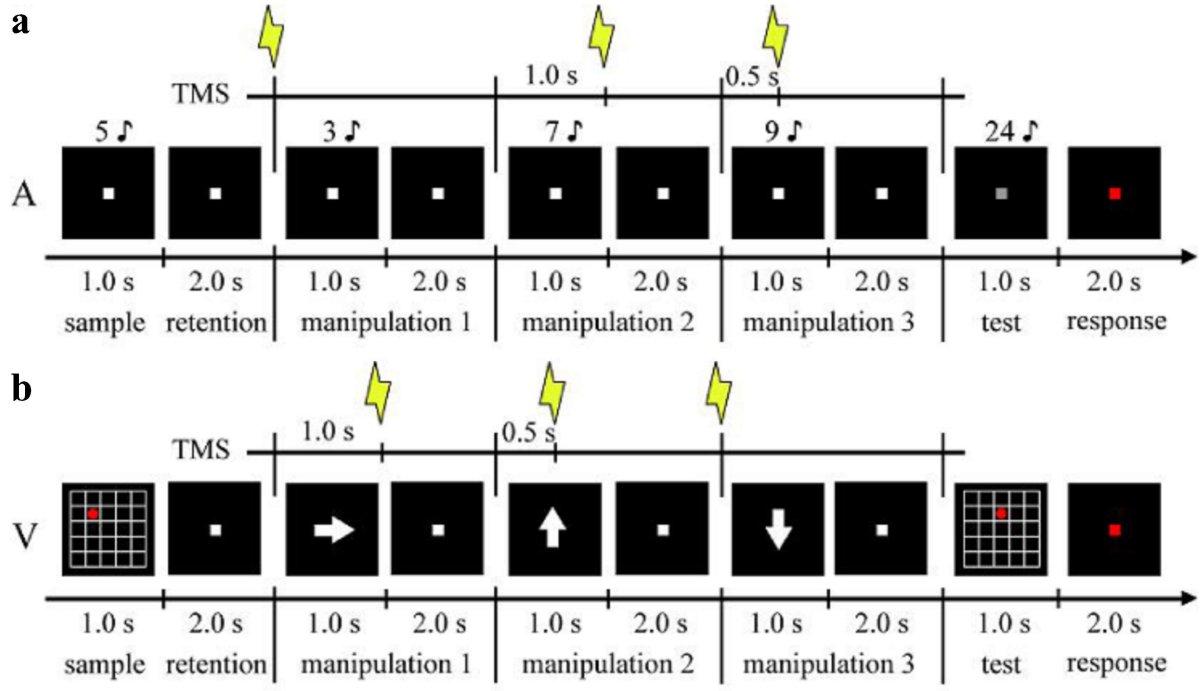

Figure 2-1. Schematic illustrations of 1 trial sequence for the auditory (A) and visual (V) working memory (WM) tasks. Yellow hexagons indicated the timing of TMS applications.

2.4 EXPERIMENTAL PROCEDURE

Each participant completed 10 separate sessions; 2 WM tasks (AWM and VWM tasks) X 5 TMS conditions (frontal, temporal, parietal, sham, and no-TMS) in a counterbalanced order. Each session consisted of 24 trials (72 TMS applications). All participants were well trained before the EEG-measurement sessions.

2.5 EEG RECORDINGS

EEG recordings were performed using 67 scalp electrodes (Ag/AgCl), embedded in a TMS-compatible electrode cap (Easy Cap; EASYCAP Gmbh, Germany), and in accordance with placement based on the international 10/10 system. The sampling rate was 1000 Hz. Reference electrodes were located on the right and left mastoids. Electrode impedance was kept below 10 k Ω. Electrooculography (EOG) was recorded from electrodes placed vertical and horizontal from the right and left eyes. The EEG and EOG signals were amplified using a BrainAmp MR+ apparatus (Brain Products, Germany).

2.6 EEG ANALYSES

We used MATLAB software (R2015b, Mathworks Inc., Natick, MA, USA) to perform all analyses.

2.6.1 Pre-processing

We only analyzed EEG data for correct trials. EEG data was segmented to 3-s epochs for the manipulation period from the instruction onset for manipulation. We removed EEG data points affected by TMS artifacts (from −1 to 7 ms post-TMS onset) using linear interpolation [16]. The EEG epochs were subjected to info- max independent components analysis (ICA). ICA components that were significantly correlated with the vertical or horizontal EOGs were eliminated as ocular artifacts. ICA-corrected data were recalculated using regression for the remaining components [9]. To eliminate volume conduction errors, we performed current source density analysis at each electrode position [17, 18] and applied the spherical Laplace operator to the voltage distribution on the scalp surface.

2.6.2 Wavelet analysis

We applied wavelet transforms using Morlet's wavelet function [19]. Six time points were selected for the analysis (0, 500, 1000, 1500, 2000, and 2500 ms). The phase for each time point at each TMS application was the arctangent of the original, convoluted EEG signal s(t) results with a complex Morlet's wavelet function w(*t, f*):

$$w(t,f) = (\sigma_t \sqrt{\pi})^{-\frac{1}{2}} \exp(-t^2 / 2\sigma_t^2) \exp(i2\pi ft)$$

where σ t is the standard deviation of the Gaussian window. The wavelet used was characterized by a constant ratio (f/ σ f = 7), with f ranging from 2 to 20 Hz (1-Hz steps).

2.6.3 PLV

To identify the phase relations between any 2 electrodes, we calculated phase locking values (PLV) at time point (t) and frequency (f) as follows:

$$\mathrm{PLV(t)} = \frac{1}{N}\left|\sum_{n=1}^{N} e^{i\Delta\theta_{jk}(t,f,n)}\right|$$

where Δθjk (t, f, n) is the phase difference between the jth and kth electrodes and the phase difference between the jth and kth electrodes and the number of trials N [20]. We first calculated the PLV for each subject and then compared the PLV on each time point for manipulation periods with the averaged PLV for baseline periods (i.e. ITI) by using the Wilcoxon sign rank test with Bonferroni correction. We made region-of-interest (ROI) analysis and selected Fz, TP7, and Pz as the representative frontal, temporal, and parietal electrodes in reference to our previous studies [9]. We evaluated the PLV between these three ROI electrodes and the other electrodes.

2.6.4 Statistical analysis

Within-group comparisons of MADRS scores (pre- vs. post-ECT) were performed using paired t-tests. Moreover, the relationships between the EEG results (i.e., PLV) and MADRS scores were analyzed using Pearson's correlation coefficient.

3 RESULTS

3.1 BEHAVIORAL RESULTS

Subject-averaged accuracy rates (± s.d.) during the AWM 96.5 ± 1.2% for no, frontal, temporal, parietal, and sham-TMS were as follows: 96.7 ± 1.3, 96.0 ± 0.8, 97.2 ± 0.6, 96.3 ± 1.0, and conditions, respectively. Subject-averaged accuracy rates (± s.d.) during the VWM were as follows: 96.9 ± 1.3, 95.6 ± 1.3, 96.0 ± 1.1, sham-TMS conditions, respectively. A 2-factor ANOVA revealed 96.3 ± 1.5, and 95.6 ± 0.9% for no, frontal, temporal, parietal, and no main effect of task ($F_{1,90} = 0.42$, $p = 0.52$), TMS conditions ($F_{4,90} = 0.26$, $p = 0.90$), and no significant interaction ($F_{4,90} = 0.14$, $p = 0.97$). These results indicated that EEG comparisons among the different conditions were not influenced by either task difficulty or TMS effects.

3.2 EEG RESULTS

We identified electrode pairs showing the PLV at each time point was significantly higher than the averaged PLV for the baseline period ($p < 0.05$; Bonferroni correction). Since the present study investigated theta synchronization modulation, we focused on the theta-range (e.g. 4 Hz) PLV between the frontal and other electrodes, between the temporal and other electrodes, and between the parietal and other electrodes. Fig. 2-2 shows the significant pairs between the ROI electrodes and the other electrodes at each time point during the no-TMS, frontal-TMS and temporal-TMS (parietal- TMS) conditions during the AWM (VWM) tasks. Fig. 2-2 showed the 1000ms-TMS results as the representative results. Fig. 2-3 shows the average counted number of electrode pairs showing significantly higher theta (4 Hz) PLV for manipulation periods than that for ITI periods ($p < 0.05$; Bonferroni correction) among the 6 latencies (0 ms, 500 ms, 1000 ms, 1500 ms, 2000 ms, and 2500 ms) and among the 3 TMS application timings (0 ms, 500 ms, and 1000 ms).

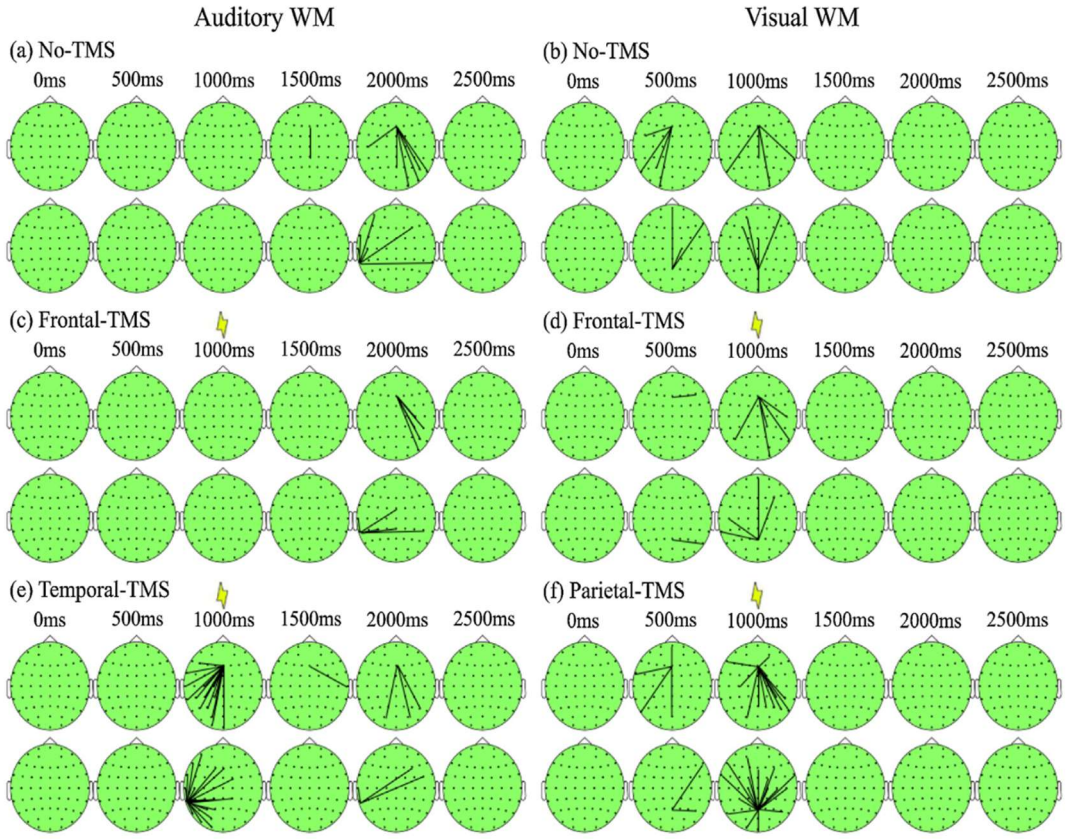

Figure 2-2. Electrode pairs between the ROI electrodes and the other electrodes showing significantly higher theta (4Hz) PLV for manipulation periods than that for ITI periods ($p < 0.05$; Bonferroni correction). Note that the onset of manipulation phase was 0ms.The significant PLV between the frontal and other electrodes (upper) and between the temporal and other electrodes (lower) under no-TMS (a), frontal-TMS (c), and temporal-TMS (e) conditions during AWM task. The significant PLV between frontal and other electrodes (upper) and between parietal and other electrodes (lower) under no-TMS (b), frontal-TMS (d), and parietal-TMS (f) conditions during VWM task. In figure (c), (d), (e), and (f), TMS was applied at 1000ms.

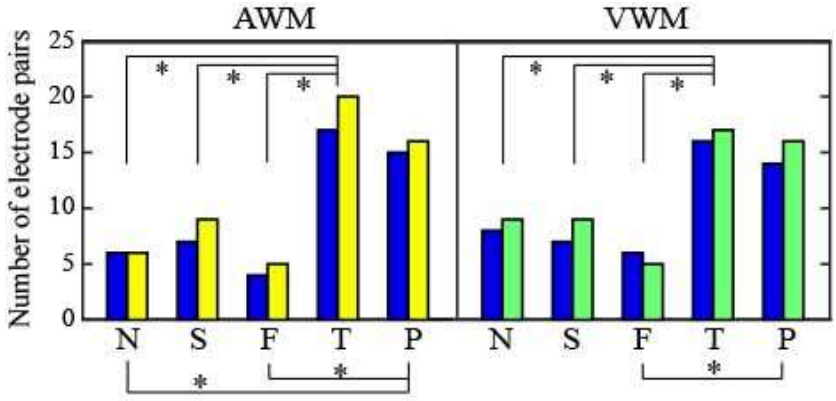

Figure 2-3. The average counted number of electrode pairs showing significantly higher theta (4Hz) PLV for manipulation periods than that for ITI periods ($p < 0.05$; Bonferroni correction) among the 6 latencies (0ms, 500ms, 1000ms, 1500ms, 2000ms, and 2500ms) and among the 3 TMS application timings (0ms, 500ms, and 1000ms). Significant pairs between the frontal and the other electrodes (blue), between the temporal and the other electrodes (yellow), and between the temporal and the other electrodes (green) under no-TMS (N), sham-TMS (S), frontal-TMS (F), temporal-TMS (T), and parietal-TMS (P) conditions. The differences between conditions were analyzed by Cui-squared test with Bonferroni-corrected multiple comparison (* : $p < 0.05$).

The no-TMS condition included several significant pairs: between the frontal and other electrodes and between the temporal (parietal) and other electrodes during the AWM (VWM) tasks. These results were similar to those from the frontal-TMS and sham- TMS conditions. Interestingly, sensory-TMS (i.e. temporal-TMS and parietal-TMS) conditions significantly increased the number of significant pairs between the frontal and other electrodes and between the TMS-targeted and other electrodes in comparison with the no- TMS, frontal-TMS, and sham-TMS conditions ($p < 0.05$; Chi-squared test with Bonferroni corrected multiple comparison). These tendencies (i.e the number of significant pairs) were almost the same among TMS application timing.

The above results for the analyses using the single time point of EEG data might be sensitive to noise or extreme points. Therefore, the analyses need to be redone averaging over longer windows than a single time point. We averaged the PLV data over 100 msec time cation and conducted the same statistical analyses under all the windows; −50 msec to 50 msec from the onset of the TMS application and conducted the same statistical analyses under all the conditions. As the results, the number of electrodes showing significant connectivity was 0 (from the frontal electrode) and 0 (from the temporal electrode) under no-TMS, 0 (from the frontal electrode) and 0 (from the temporal electrode) under frontal-TMS, and 7 (from the frontal electrode) and 8 (from the temporal electrode) under temporal-TMS, during auditory WM conditions; 3 (from the frontal electrode) and 3 (from the parietal electrode) under no-TMS, 4 (from the frontal electrode) and 3 (from the parietal electrode) under frontal-TMS, and 7 (from the frontal electrode) and 8 (from the parietal electrode) under temporal-TMS, during visual WM conditions. These results were almost same as the results for the analysis using the single time point data.

4 DISCUSSION

The present study elucidated a bottom-up network in WM through functional changes in theta phase synchronization induced by TMS. Consistent with earlier studies suggesting that theta phase synchronization reflects a global connection among relevant brain regions [5, 8, 9], theta phase synchronization was observed between WM task-relevant areas: between the frontal and parietal areas during a VWM task and between the frontal and temporal areas during an AWM task. As expected from a previous study, which suggested that single-pulse TMS modulates global phase synchronization and information flow among brain networks at rest [15], TMS manipulated brain activity with global theta phase synchronization during WM tasks. Our EEG data revealed a significant difference in the amount of TMS-induced changes in theta phase synchronization between TMS-targeted areas. Additionally, TMS- induced changes in theta phase synchronization indicated that network directionality was bottom-up rather than top-down. In the parietal-TMS condition during the VWM task, induced theta phase synchronization from both frontal and parietal areas increased. In the temporal-TMS condition during the AWM task, induced theta phase synchronization from both frontal and temporal areas increased. Although there were slight changes in theta phase synchronization in the parietal-TMS condition during the AWM task and in the temporal-TMS condition during the VWM task, these results are modality specific; therefore, it is possible that network directionality during the WM tasks was bottom-up. Note that in the frontal-TMS condition, results from both the VWM and AWM tasks were similar to the no-TMS condition. These results show that there was no increase in induced theta phase synchronization in the frontal-TMS condition; thus, these results indicate that network directionality during the WM tasks was not top-down. It should be noted results in the sham-TMS condition were similar to the no-TMS condition. These results suggest that our findings were not influenced by auditory evoked responses induced by the associated TMS "clicking" sound during the experiment.

Induced theta phase synchronization was increased only when TMS was delivered to the sensory areas, not the frontal areas. Thus, it could be argued the information network employed during the WM tasks were bottom-up rather than top-down. This proposal is supported by previous findings regarding the effects of TMS on EEG signals. Previous studies have shown that TMS manipulates brain activation not only in TMS-targeted areas [12–14] but also in rele- vant non-TMS targeted areas [21–23]. Furthermore, a single-pulse TMS to sensory areas, but not motor areas, increases theta phase synchronization among sensory and motor areas during a resting state. This reflects processing in the default mode network. The information theory (i.e. transfer entropy) clarified directionality to be bottom-up in the default mode network [15]. These findings lead to the hypothesis that when TMS is applied to incoming areas within a relevant brain network, the outgoing areas are modulated; however, the converse is not true. Although our study revealed the possibility that sensory areas could be candidate, incoming areas in WM, outgoing areas were not clarified. This was because we merely showed a phase synchronization expanse from TMS-targeted areas. To address these issues, future studies should identify detailed brain areas and networks using high spatial-resolution measurements.

Note is that the asymmetry in connectivity results could be due to a TMS threshold being higher in PFC than in temporal or parietal cortex. Unfortunately, this study could not identify whether or not the magnitudes of stimulation modulating the PFC and sensory areas are different. Future study should clarify the issues with the same analysis for the EEG data which is recorded during TMS into the frontal and sensory areas in the resting states.

Although our EEG data clearly showed that a bottom-up network is used in WM, our conclusions are limited by a lack of significant differences in our behavioral data. Moreover, our conclusions are limited because there remains an alternative explanation for our results using the top-down mechanisms from the frontal areas to the sensory areas. That is, our results merely reflect facilitated bottom-up processing of the cue stimulus, rather than reflecting manipulation-related activities. Previous studies have demonstrated the close relationships between the top-down processing and working memory performance; the diminished top- down modulation in the posterior regions from the prefrontal regions predicted the decrement of the working memory performance [11]. Thus, future studies need to include tasks designed to control for task difficulty, and relevant behavioral data should be compared.

5 CONCLUSION

In summary, we clarified the existence of a bottom-up network in WM based on the observance of increased TMS-induced theta oscillations in the frontal areas during WM tasks. Our approach to determine information flow by manipulating a global phase synchronization would enable to evaluate network directionality of the other cognitive processing.

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CHAPTER 3: ASSESSING CLINICAL CHANGE WITH NETWORK PROPERTIES USING TMS-EEG

1 INTRODUCTION

Neuromodulatory techniques, such as repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and electroconvulsive therapy (ECT) [1], have been used for the treatment of several neurological and psychiatric disorders, including Parkinson's disease [2], schizophrenia [3], and major depressive disorder (MDD) [4,5]. Although the exact mechanisms of these techniques are not yet fully understood, it is thought that neuromodulation regulates functional disturbances in relevant distributed neural circuits [6] by inducing electric currents that lead to plastic reorganisation of cortical circuits [7]. ECT has long been considered to be highly effective for treating depression [8, 9], which has been associated with abnormal functional connectivity [10]. Some studies have argued that ECT modulates the EEG complexity [11, 12] and the functional connectivity in functional magnetic resonance imaging [13,14]. However, the neural mechanisms of both ECT and depression remain unclear. It is thus important to evaluate the therapeutic effects of neuromodulation using precise methods that capture neuromodulation-induced functional changes.

In recent years, the combination of TMS with electroencephalography (EEG) (hereafter called TMS-EEG) has been used to evaluate the electrophysiological effects of neuromodulatory techniques. Application of TMS pulses enables direct perturbation of cortical regions, and simultaneous EEG recording allows the immediate electrophysiological responses of the stimulated neurons to be measured [15, 16]. In particular, TMS is considered as an event or a sensory stimulus for conventional event-related potential paradigms in EEG experiments [17]. Thus, unlike experiments with EEG alone, TMS-EEG allows changes in input parameters and/or stimulation to be closely controlled, which means that more accurate evaluations can be made.

TMS-EEG paradigms have been employed to measure the effect of neuromodulation on the cortex by quantifying changes in motor evoked potentials (MEPs) elicited from the motor cortex [17] and TMS-evoked potentials (TEPs) elicited from non-motor cortical regions [16]. For example, changes in MEP amplitudes in response to single-pulse TMS of controlled intensity are thought to provide an index of rTMS-induced neuroplasticity of the motor cortex [17-19]. Although MEPs can be easily recorded and analysed [20], these are influenced by non-cortical confounds such as spinal cord excitability [16]. Moreover, because the exact neural mechanism of neuromodulation is not yet fully understood, it is not clear whether MEP changes accurately monitor neuromodulation-induced neuroplasticity.

On the other hand, TEP-based measures are not influenced by non-cortical confounds [16] and can be used to analyse the whole brain effect of neuromodulation. For example, analysis of TEP amplitudes allows local responses to neuromodulation to be assessed [21], and calculations of coherence from TEPs allow global neuromodulation-induced changes to be assessed [22]. However, analysing amplitudes is not an ideal approach to assess the effects of neuromodulation therapies, because these are primarily used to treat psychiatric patients who already exhibit large individual differences in brain activity [10,23]; furthermore, this approach requires a baseline normalisation prior to analysis. Instead, phase, which is calculated by time-frequency analysis, does not require normalisation and can uniformly assess the temporal dynamics of TMS-induced brain activity. Therefore, this approach can be used to assess network connectivity of not only local synchronisation under a single electrode, but also global synchronisation between two distant electrodes, and with a high temporal resolution.

In recent years, it has been suggested that TMS-induced oscillations reflect phase resetting of on-going cortical oscillations [24]. Recent TMS-EEG studies have suggested that single-pulse TMS can induce transient neural oscillations in several frequency bands in different cortical areas of the human brain [25-28]. Kawasaki et al. [24] demonstrated the effect of single-pulse TMS-induced phase resetting across the brain by calculating the phase locking factor (PLF), which is an index of phase-locking of the oscillatory activity on an electrode across trials [29]. Their approach allowed the intensity of information flow through a cortical network to be defined, as well as the causal and directional flow of information, which was identified to flow from visual to motor areas [24]. In addition, Miyauchi et al. [30] found that phase locking value (PLV), a measure of the intensity of phase synchronies between two electrodes [31], can be used to evaluate the propagation effect of single-pulse TMS-induced phase resetting within a functional network relevant with working memory. In other words, PLF indicates the effective connectivity between two electrodes with a time lag, whereas PLV represents the coherent synchronization between two electrodes at one time point without a time lag.

The purpose of this study was to explore the relationship between the TMS-induced changes in PLV and PLF and clinical changes of depression induced by ECT in patients with MDD. This study has focused on the visuo-motor network as the stimulation target because the directionality of information flow in the network has been defined [24] and the visuo-motor connectivity has been reported to reflect the decrement in visuo-motor performance in depression [32]. Therefore, TMS was applied to visual and motor areas (i.e. targeting the visuo-motor network) to induce phase propagation before and after ECT. Functional changes were calculated using PLF and PLV measures, and ECT-induced clinical changes were measured using the Montgomery–Åsberg Depression Rating Scale (MADRS) [33].

2 MATERIALS AND METHODS

2.1 PARTICIPANTS

Ten patients (five men and five women aged 27–77 years; mean age: 54.5 years) with MDD completed all experiments. Diagnoses of major depressive disorder were established according to

the Diagnostic and Statistical Manual of Mental Disorders (5th edition) [34] criteria by experienced psychiatrists. Disease severity was evaluated using MADRS within 1 day prior to the first ECT session and 1 day after the ECT session. Psychiatrists interviewed each patient for scoring MADRS. Disease severity was evaluated using the MADRS within 1 day prior to the first ECT session and 1 day after the ECT session. Moreover, dementia was evaluated using the Mini-Mental State Examination (MMSE) [35]. Patients were being treated with antidepressants, antipsychotics, anticonvulsants, and/or benzodiazepines. During the experiments, antidepressant treatments were not altered, but anti-psychotic intake was altered in one patient and benzodiazepines were altered in two patients. Eight patients were ECT-naïve and two patients (Patients 3 and 8) were administered ECT for maintenance. All patients gave written informed consent before participation. The study was approved by the Faculty of Medicine and Medical Science, Research Ethics Committee of the University of Tsukuba and was in accordance with the Declaration of Helsinki.

2.2 ECT PROCEDURE

Brief pulse, constant current, square wave ECT (Thymatron System IV, Somatics Inc., Lake Bluff, IL, USA) was administrated two or three times a week with bilateral electrode placement. The half-age method [36] was used for determining energy intensity of the first session, and intensity was then increased by 10-20% in each subsequent session to elicit adequate seizures. Adequate seizures with 100% energy intensity could not be elicited in one patient (Patient 5), and so a sine-wave device (CS-1, SAKAI Medical Co., Ltd., Tokyo, Japan) was used for ECT (110-120 V, 7 seconds) from the 2nd to 6th sessions. Anaesthesia was induced by thiamylal, and succinylcholine was administrated for muscle relaxation. Nicardipine was administrated to prevent excessive hypertension. The number of ECT sessions varied among patients according to the severity of the disease or responses to ECT.

2.3 TMS PROCEDURE

TMS-EEG was measured within 1 day prior to the first ECT session and 1 day after the ECT session. Each participant completed two separate sessions (corresponding to visual-TMS and motor-TMS conditions) before and after ECT. The order of conditions was counterbalanced across participants. Each session consisted of 40 TMS applications. Single-pulse TMS was delivered to the respective brain area at jittered time intervals that ranged from 2.5 to 6.5 s (0.5 s steps) and each session lasted for 3 min. TMS sessions were conducted in a dimly lit electronic- and sound-shielded room. During sessions, participants sat in a chair, rested their chin on a chin-rest, and closed their eyes. Participants wore earplugs to help attenuate the effects of TMS-related noise.

TMS was delivered through a figure-of-eight coil with a 70-mm wing diameter that was connected to a biphasic stimulator (Magstim Rapid MRS1000/50, Magstim Company Ltd., UK). We used the flexible arm of a camera stand to fix the coil at the same position and direction for the duration of each session. TMS intensity was fixed to 0.79 Tesla. This intensity was close to

95% of the averaged motor threshold across participants found in our previous study [24]. When delivering TMS to the visual areas, we fixed the TMS coil over the occipital pole (over the Oz electrode) with the handle oriented upward. In contrast, when delivering TMS to the motor areas, we placed the TMS coil tangential to the scalp, with the handle pointing 45° posterolaterally over the central left area (over the C3 electrode)..

2.4 EEG RECORDING

Continuous EEG was recorded from 27 scalp electrodes (Ag/AgCl) embedded in a TMS-compatible electrode cap (EasyCap; EASYCAP GmbH, Herrsching, Germany) in accordance with the extended version of the International 10-20 system. EEG data were recorded and amplified using BrainAmp MR+ apparatus (Brain Products, Munich, Germany) at a sampling rate of 1000 Hz. Reference electrodes were placed on the left and the right mastoids and were virtually connected.

We focused on the C3 and Oz electrodes as the left motor and visual areas, because our previous study clearly showed transitions of the TMS-evoked PLF changes from the Oz to the C3 electrodes [24]. Moreover, we stimulated in the vicinity of these areas under the motor and visual TMS conditions. Therefore, this study only examined the synchronisation between motor and visual areas and the information transmission from motor to visual areas or from visual to motor areas.

2.5 EEG ANALYSES

We used MATLAB software (R2015b, Mathworks Inc., Natick, MA, USA) to perform all analyses.

2.5.1 Pre-processing

EEG data were segmented into 3-s epochs (from 1-s pre-TMS to 2-s post-TMS). To reduce TMS-related artifacts, we removed the EEG data from -1 to 7 ms from TMS onset using linear interpolation, according to previous studies [24, 37]. The EEG data were bandpass filtered (0.1–30 Hz). Electrode amplitudes exceeding ±100 μV during the 100 ms before stimulus onset and the 400 ms after onset were considered to indicate the presence of ocular artifacts (i.e. eye movements) and corresponding trials were removed from the analysis.

2.5.2 Time-frequency analysis

Time-frequency phases were calculated with wavelet transforms using Morlet's wavelets function w (t, f0) [15]. Morlet's wavelets w (t, f0) have a Gaussian shape both in the time domain (SD σt) and in the frequency domain (SD σf) around their central frequency f0. The following formula was used to calculate Morlet's wavelets:

$$w(t,f) = (\sigma_t \sqrt{\pi})^{-\frac{1}{2}} \exp(-t^2 / 2\sigma_t^2) \exp(i2\pi ft)$$

with $\sigma_f = 1/(2\pi\sigma_t)$

We used a wavelet that was characterised by a constant ratio (f ⁄ σf = 5), with f ranging from 1–20 Hz (1-Hz steps). The time-frequency phases were segmented into the three following frequency bands: theta (4–7 Hz), alpha (8–12 Hz), and beta (13–20 Hz).

2.5.3 PLV

We used the PLV to identify the TMS-evoked phase synchronisation between visual and motor electrodes. The PLV for an electrode pair (ei, ej), time point (t), and frequency (f) was calculated as follows:

$$PLV(t,f,e_i,e_j) = \frac{1}{N} \left| \sum_{n=1}^{N} \exp^{i(\phi(t,f,n,e_i) - \phi(t,f,n,e_j))} \right|$$

where ϕ is the instantaneous phase of EEG data and N is the total number of epochs included in the calculation.

2.5.4 PLF

In contrast, we used the PLF to identify the TMS-evoked phase resetting at each electrode. The PLF for an electrode (e_i) was calculated as follows:

$$PLF(t,f,e_i) = \frac{1}{N} \left| \sum_{n=1}^{N} \exp^{i\phi(t,f,n,e_i)} \right|$$

2.5.5 Statistical analysis

Within-group comparisons of MADRS scores (pre- vs. post-ECT) were performed using paired t-tests. Moreover, the relationships between the EEG results (i.e., PLV) and MADRS scores were analyzed using Pearson's correlation coefficient.

3 RESULTS

3.1 CLINICAL EFFECT OF ECT

The demographic information of patients is shown in Table 3-1. All patients had been diagnosed with MDD prior to experiments, and included those with partial and full remission. All patients showed higher MMSE scores than the cut-off point (23/24) for cognitive impairment, which suggests that any individual differences in TMS-EEG results were not due to the effects of cognitive impairment.

Pre-ECT, five patients (Patients 1-5) showed MADRS scores of over 20, which is cut-off point for moderate depression. Of these, Patient 1 had a score over 35, which is cut-off point for severe depression. In contrast, all patients had post-ECT MADRS scores under 20. Seven patients appeared to benefit from ECT, as indicated by a reduction of MADRS scores post-ECT compared to pre-ECT. While this difference in MADRS scores (pre-ECT vs. post-ECT) was not significant, we nonetheless observed a strong trend for lower MADRS scores after ECT (pre-ECT = (mean±s.e.m.) 19.50±4.51; post-ECT = 9.00 ± 2.06; paired t-tests, $t = 2.075$, $p < 0.053$).

Table 3-1. Individual patient demographics. d: antidepressants, p: antipsychotics, b: benzodiazepines, c: anticonvulsants.

ID	Age	Sex	Disease	MMSE	MADRS (pre-ECT)	MADRS (post-ECT)	Δ MADRS	No. ECT	Medication (dose alteration)
1	77	F	MDD	25	49	17	32	8	d
2	27	M	MDD	28	30	5	25	4	d,p,b
3	74	F	MDD	27	20	5	15	2	d,b
4	54	F	MDD	29	27	15	12	6	p,b
5	68	M	MDD	26	24	14	10	6	P (risperidone 1mg)
6	27	M	MDD	30	15	9	6	5	p,b (etizolam 0.5mg↓)
7	43	M	partial remission	30	6	0	6	6	d,p
8	69	F	full remission	30	0	0	0	2	d,p,b
9	42	M	MDD	30	16	17	-1	10	p,b,c (flunitrazepam 1mg↓)
10	64	F	MDD, OCD	29	6	8	-2	6	d,b

3.2 PLV IN VISUAL-TMS CONDITIONS

To measure global synchronisation of the visuo-motor network, we calculated the PLV between visual and motor areas. The individual time-frequency PLVs between motor and visual electrodes for pre-ECT and post-ECT sessions are shown in Figure 3-1A.

Post-ECT, all patients showed transient enhancements of visuo-motor PLVs ranging from 1 to 20 Hz at around TMS onset. These enhancements were observed ahead of TMS onsets because of the wavelet time resolution. Low-frequency PLVs, especially alpha bands (9-12 Hz), increased from TMS onsets.

Pre-ECT, enhancements of PLVs ranging from 1 to 20 Hz were not observed in the five patients with high MADRS scores. In contrast, the five patients with low MADRS scores showed transient enhancements of low-frequency PLV (i.e. alpha PLV) at both pre-ECT and post-ECT.

Next, we calculated the maximum alpha PLVs within a latency window of -500 ms to 500 ms from TMS onset. These were significantly and negatively correlated with MADRS scores at pre-ECT ($r = -0.704$, $p < 0.024$), but not at post-ECT ($r = 0.182$, $p = 0.615$; Figure 3-2A). This correlation was still significant after excluding the three patients (ID:5, 6, 9) whose drugs were altered during the experiments (-0.757, $p < 0.048$). Moreover, the differences in alpha PLVs between pre- and post-ECT were significantly and negatively correlated with differences in MADRS scores between the pre- and post-ECT (Figure 3-2A; $r = -0.782$, $p < 0.007$). This correlation was still significant after excluding the three patients (ID:5, 6, 9) whose drugs were altered during the experiments ($r = -0.808$, $p < 0.028$).

3.3 PLF IN VISUAL-TMS CONDITIONS

We used the visual (TMS-targeted area) and motor (TMS-distant area) PLFs to measure local synchronisation ability and network-mediated local synchronisation ability (i.e., transmission intensity), respectively. The individual time-frequency PLFs on motor and visual electrodes at pre-ECT and post-ECT in visual-TMS conditions are shown in Figure 3-1B and 1C. All patients showed transient enhancements of PLFs of visual areas that ranged from 1 to 20 Hz, especially in alpha bands, at around the onset of the TMS at both pre- and post-ECT. These enhancements were particularly strong at post-ECT.

In contrast, the PLFs of motor areas showed no or small alpha transient enhancements in patients with high pre-ECT MADRS scores. However, patients with low pre-ECT MADRS scores showed high alpha PLF enhancements of motor areas. Post-ECT, most patients (all but Patient 5) showed alpha PLF enhancements of motor as well as visual areas.

The maximum values of the alpha PLF (within the latency window -500 ms to 500 ms from TMS onset) of motor areas were significantly and negatively correlated with MADRS scores at pre-ECT ($r = -0.907$, $p < 0.001$), but not at post-ECT ($r = 0.086$, $p = 0.813$). This correlation was still significant after excluding the three patients (ID:5, 6, 9) whose drugs were altered during the experiments ($r = -0.951$, $p < 0.001$). In contrast, the maximum values of alpha PLFs of visual areas were not correlated with MADRS scores at either pre-ECT ($r = -0.527$, $p = 0.118$) or post-ECT ($r = 0.549$, $p = 0.100$). Individual motor and visual PLF data are shown in Figure 3-2B and

2C. Moreover, the differences in alpha motor PLFs between the pre- and post-ECT were significantly and negatively correlated with differences in MADRS scores between pre- and post-ECT (Figure 3-2B; $r = -0.911$, $p < 0.001$). No such correlation was observed for alpha visual PLFs ($r = -0.427$, $p = 0.218$).

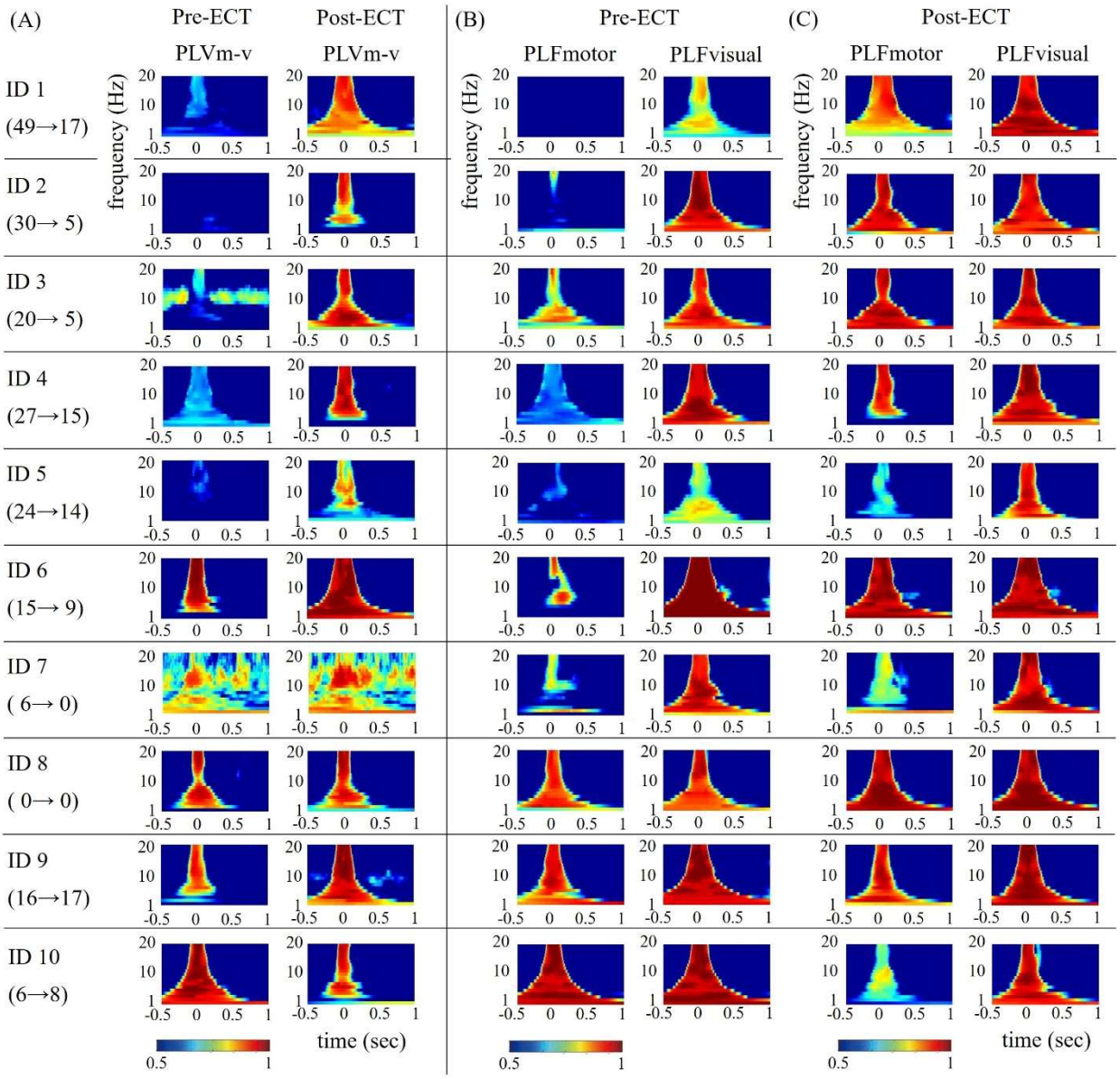

Figure 3-1. PLV and PLF in visual-TMS conditions. (A) Individual time-frequency PLV between motor and visual areas and (B, C) time-frequency PLF on motor and visual areas in pre-ECT and post-ECT sessions. The individual MADRS scores at pre-ECT and post-ECT are shown as the left and right numbers below the patient number, respectively.

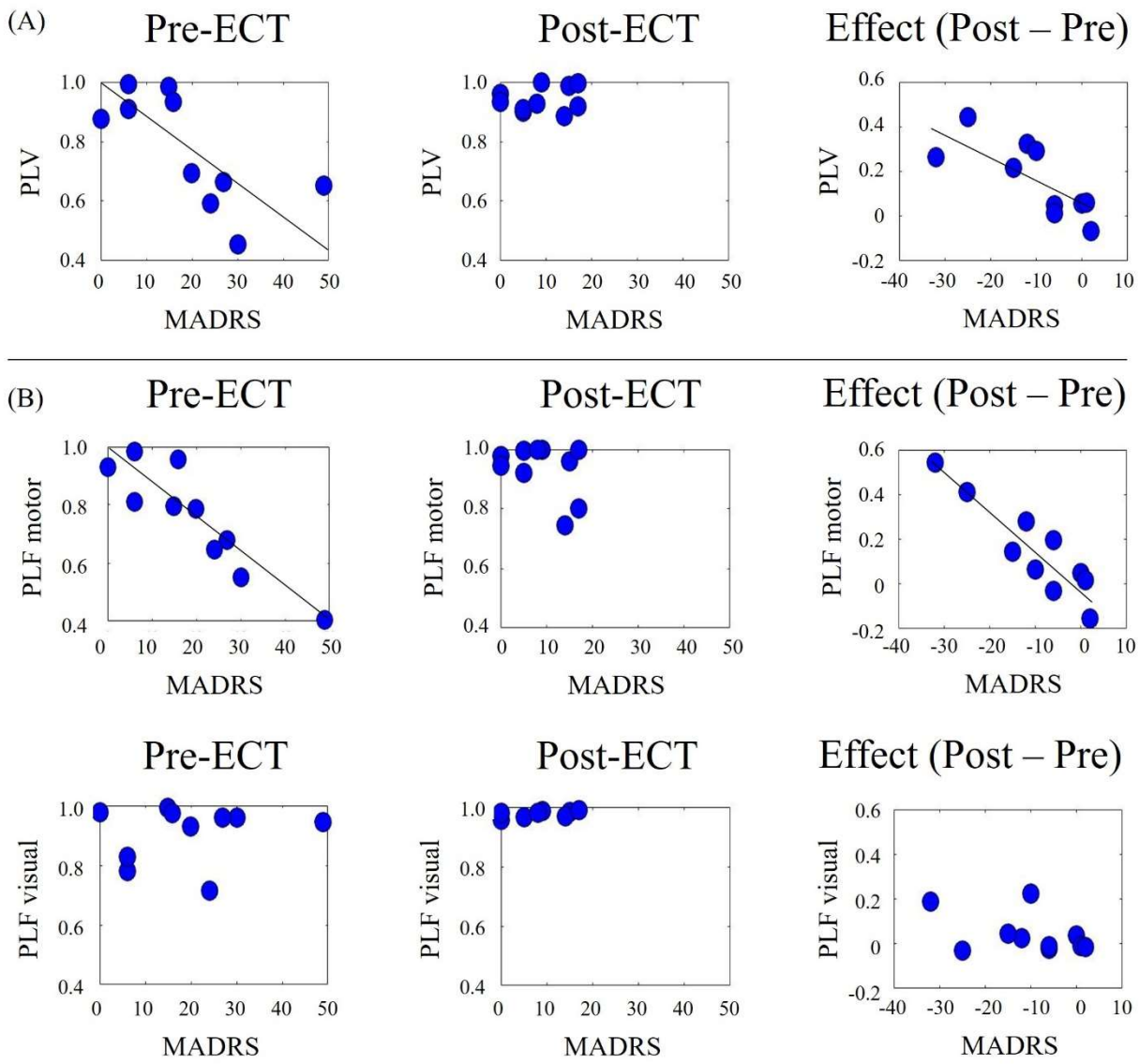

Figure 3-2. PLV and PLF in visual-TMS conditions. (A) Scatter plots between MADRS scores and (A) visual-motor alpha PLV, (B) alpha motor PLF, and (C) alpha visual PLF, in the pre-ECT (left) and post-ECT (centre) sessions. Scatter plots shown in panels on the right show the differences in MADRS scores and differences in PLV/PLF between pre- and post-ECT.

The above results suggested that information transfers from the visual to motor areas post-ECT, but not pre-ECT. Therefore, we calculated the differences in maximum PLF values and their peak latencies from TMS onset between visual and motor areas. We considered the differences in peak latencies of maximum TMS-induced PLF appearances between visual and motor areas to reflect the speed of information transmission within the network. Differences in maximum PLF values were not correlated with MADRS scores (Figure 3-3A; $r = 0.035$, $p = 0.925$). However, the time differences of PLF peak latencies were significantly and positively correlated with MADRS scores (Figure 3-3B; $r = 0.778$, $p < 0.008$).

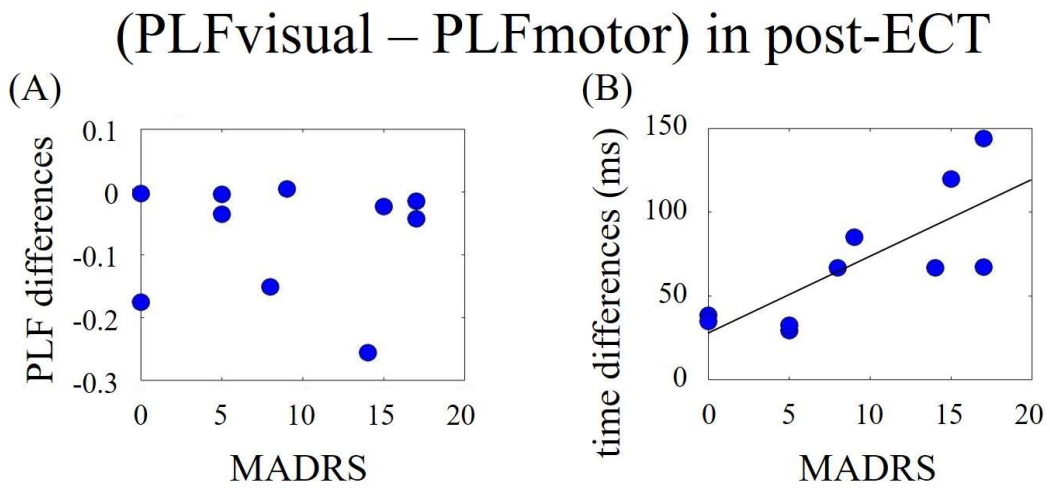

Figure 3-3. Visual-TMS conditions. (A) Scatter plots between MADRS scores and PLF values between visual and motor areas post-ECT. (B) Scatter plots between MADRS scores and differences in PLF peak latencies between visual and motor areas post-ECT.

3.4 PLV AND PLF IN MOTOR-TMS CONDITIONS

We conducted the same PLV and PLF analyses for the motor-TMS condition to investigate their relationship with MADRS scores. Most patients showed no transient enhancements of visuo-motor PLVs ranging from 1 to 20 Hz at around the onset of TMS for either pre- or post-ECT time points. Moreover, there were no correlations between the maximum values of alpha PLV and MADRS scores at either pre-ECT ($r = -0.331$, $p = 0.351$) or post-ECT sessions ($r = 0.287$, $p = 0.422$; Figure 3-4A).

For PLFs of the motor areas (i.e. the TMS-targeted areas), most patients showed transient enhancements ranging from 1 to 20 Hz, especially in alpha bands, at around the onset of TMS at both pre- and post-ECT. However, these enhancements were not correlated with MADRS scores at either pre-ECT ($r = 0.397$, $p = 0.255$) or post-ECT ($r = -0.291$, $p = 0.415$; Figure 3-4B). The PLF of visual areas showed no transient enhancements and no correlation with MADRS scores at either pre-ECT ($r = -0.216$, $p = 0.550$) or post-ECT ($r = 0.099$, $p = 0.786$; Figure 3-4C).

The differences of alpha PLVs and PLFs between pre- and post-ECT also showed no correlation with the differences in MADRS scores between the pre- and post-ECT (PLV: $r = -0.222$, $p = 0.539$; PLF on motor: $r = 0.172$, $p = 0.634$; PLF on visual: $r = 0.183$, $p = 0.612$).

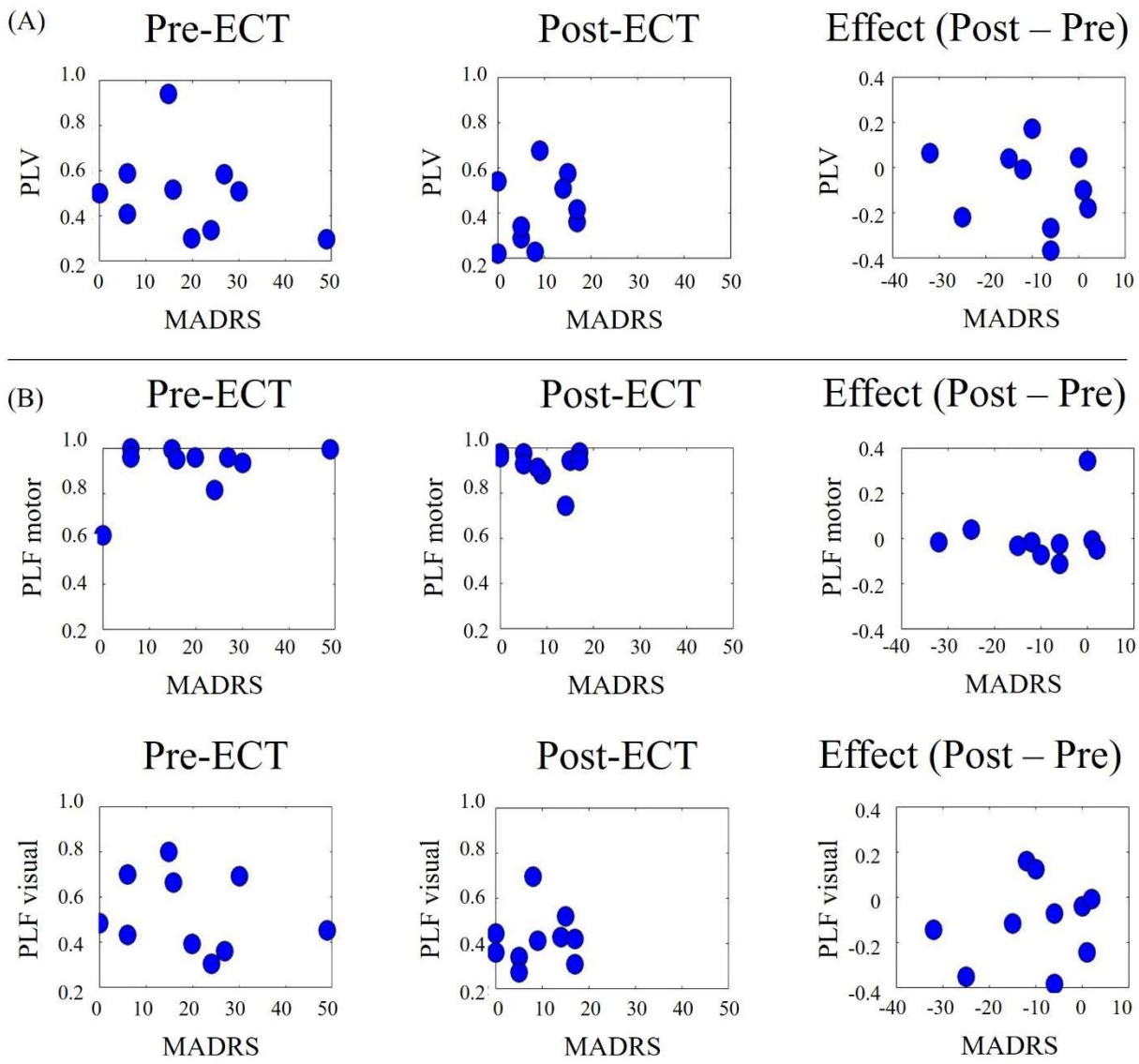

Figure 3-4. Motor-TMS conditions. (A) Scatter plots between MADRS scores and (A) visual-motor alpha PLV, (B) alpha motor PLF, and (C) alpha visual PLF, in the pre-ECT (left) and post-ECT (centre) sessions. Scatter plots shown in panels on the right show the differences in MADRS and differences in PLV/PLF between pre- and post-ECT.

4 DISCUSSION

In this study, we aimed to investigate whether PLV and PLF can be used to assess depression severity and the ECT-induced functional changes in MDD. The intensity of phase synchronies/propagation within the network was evaluated using PLV, and the intensity and direction of information flow was evaluated using PLF. To this end, we computed the following parameters: (1) TMS-induced PLVs between visual and motor areas, (2) TMS-induced PLF at visual and motor areas, (3) differences in transmission intensities of TMS-induced PLF between visual and motor areas, and (4) differences in TMS-induced PLF peak latencies between visual and motor areas. We then analysed whether those parameters differed before and after ECT, and how these changes were associated with the ECT-induced changes in depression severity.

4.1 PLV FOR ECT/DEPRESSION ASSESSMENT AND MECHANISM

The most interesting finding was that pre-ECT TMS-induced PLV was negatively correlated with depression severity, and that pre-post changes in TMS-induced PLV were positively correlated with the reduction in depression severity. This indicates that the pre-post change in TMS-induced PLV can be used to assess the antidepressant effects of ECT, and, more generally, that TMS-induced PLV can be used to evaluate depressive states. Moreover, these correlations were strongest in the alpha band frequency, which suggests that the inter-areal alpha synchrony of the visuo-motor network is decreased during MDD, and increased by ECT. These results agree with previous findings that the larger increase in cortical excitability induced by 10-Hz rTMS predicts a greater reduction in depressive symptoms after therapeutic neuromodulation [38]. Furthermore, our results further support the idea that depression is associated with a decrease in functional network connectivity at resting state [10]. However, it is somewhat surprising that the results were not best described at the theta frequency band, as was found by previous related studies [24, 30]. This may be due to the small number of trials and a consequently limited statistical power. Interestingly, the PLV changes were smaller when the severity of depression was moderate to high, which suggests that ECT-induced alterations of the network only occur in more severe cases of depression.

4.2 PLF (TRANSMISSION INTENSITY) FOR DEPRESSION ASSESSMENT

We found a negative correlation between pre-ECT TMS-induced PLF at the motor area and the severity of depression, which disappeared after ECT. The pre-post difference in the correlation is likely to be related to the change in the severity of depression over the course of the study. The severity of depression improved remarkably in all subjects after ECT; the severity of depression pre-ECT ranged from “symptom-free” to “severe”, whereas post-ECT severities ranged from “symptom-free” to “mild”. Consistent with our PLV results, it can thus be suggested that ECT-induced network alterations are more prominent in patients with moderate or severe symptoms of

depression. In addition, the transmission intensities of TMS-induced PLF within target networks is useful to assess moderate or higher depressive states.

4.3 PLF (TIME DIFFERENCE) FOR DEPRESSION ASSESSMENT

Interestingly, we found that peak differences of post-ECT TMS-induced PLFs between visual and motor areas were positively correlated with the severity of depression (Figure 3-3B). Such peak differences in PLFs were not detected at pre-ECT, i.e., no propagation effect was found. Our analysis of differences in PLF peak latencies is a new approach, and these findings are therefore only preliminary; however, presuming that differences in PLF peak latencies between the two areas indicate the time of propagation in the network, these results suggest that an alteration of the network is associated with a decrease in the speed of information transmission within the network, and that ECT increases this transmission speed. A note of caution is due here since the relationship was appeared only at post-ECT and not in pre-post differences, the relationship between pre-ECT depression severity and the transmission speed is not clear. However, this method could be used to evaluate depressive states when there is sufficient propagation within the network.

4.4 PLF CHANGE (LOCAL) FOR MECHANISM OF DEPRESSION

The TMS-induced PLF at the TMS-targeted areas showed no correlation with depression severity, either before or after ECT. This implies that local activities of the visual and motor areas are not relevant to depressive states, and that depression is associated with a global rather than local dysfunction. These conclusions are consistent with previous findings that a dysfunctional network underlies depression rather than a single brain area [10, 39].

4.5 VISUO-MOTOR NETWORK

There was no significant increase in TMS-induced PLV and in TMS-induced PLF at the visual area when TMS was targeted to the motor area. Consistent with previous studies [24, 30], these results indicate that information flows from visual to motor areas. Although the present study was not designed to provide new insights about the relationship between visuo-motor functional connectivity and depression, the observed dysfunction in visual-motor connectivity is potentially relevant to findings of impairments of sensory and motor processes that are reflected by slowed performance in depression [32]. We used the visuo-motor network as the stimulation target because this is the only network in which the directionality of information flow has been defined [24]. Future investigations could target different networks that have a more evident relationship with depression, such as the subgenual cingulate [40]. For this, it would be necessary to identify the flow directionality of the functional network associated with this area before conducting TMS-EEG to target the network.

4.6 LIMITATIONS AND FUTURE WORK

Firstly, the small sample size and small number of trials meant that it was not possible to validate the current results. For example, changes in network propagation may be limited to those of whom showed a significant reduction in depression severity. Therefore, future, larger-scale studies will be required for this. Secondly, the present study did not employ a control group for comparison, and so interpretations are limited to patients with MDD. That said, our results are consistent with studies with healthy subjects, which have reported an increase of TMS-induced PLF values at rest [24] and increased TMS-induced PLV [30]. Furthermore, it is difficult to implement invasive techniques such as ECT in healthy individuals. However, future studies could compare resting data between patients and healthy controls or use non-invasive therapeutic neuromodulations. Finally, we did not use a neuronavigation system or individual motor thresholds for target selection. Thus, it is possible that TMS-targeted locations were not identical across pre-ECT and post-ECT sessions. Some researchers have recommended the use of a navigated TMS to accurately compute the location of coil based on individual cortical surface anatomy [41], and future studies could consider this. To build an evaluation system using TMS-EEG based PLV and PLF for the therapeutic effects of neuromodulations, future studies should address the above limitations.

5 CONCLUSION

According to our results, pre-post differences in TMS-induced PLV can be used to assess the antidepressant effects of ECT, and TMS-induced PLV can be used to evaluate depressive states. Moreover, our results suggest that transmission intensities and speed of information transmission calculated from TMS-induced PLF can be used to evaluate moderate or higher states of depression. The present findings therefore have a number of important clinical implications. Namely, our results suggest that the TMS-induced PLV and PLF approaches can be used to assess the therapeutic effects of not only ECT, but also other neuromodulation techniques and medications that are used to improve cortical network function. Furthermore, our findings imply that our proposed approach can be used to assess depressive states, not only in patients with MDD, but also those with other neuropsychiatric disorders or any clinical condition involving impaired cortical networks. Future research using these TMS-induced PLV and PLF approaches will therefore help us to better understand the mechanisms underlying neuropsychiatric disorders.

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CHAPTER 4: MODULATION OF COGNITIVE FUNCTION USING TMS-EEG

1 INTRODUCTION

The characteristic symptoms of neurological and psychiatric disorders are distinctive, yet numerous neurological and neuropsychiatric disorders exhibit common cognitive impairment [1]. Because the degree of impairment in higher cognitive functions is a critical factor that impacts people's quality of life and disorder-related disability [1], establishing effective methods to enhance cognitive functions is important to improve and maintain mental health and well-being. Accordingly, it is also crucial to cultivate a better understanding of neural mechanisms underlying the cognitive functions related to those disorders since much uncertainty still exists about those.

A growing body of literature recognises that specific frequency bands are linked to specific brain functions [2], which has led to electroencephalography (EEG) research that investigates relationships between human oscillatory brain activity and cognitive functions. Meanwhile, there has been an increasing interest in non-invasive neuromodulation techniques, such as transcranial magnetic stimulation (TMS), which can induce alterations in neural activity underlying cognitive operations, and thus, may provide a means for cognitive restoration and enhancement [1]. Particularly, when TMS is applied in a repetitive paradigm (rTMS) over a central node of a brain network, which is hypothesised to support a targeted cognitive function, performance on the cognitive task can be modified [3]. Nevertheless, current data present no conclusive evidence regarding the efficacy of restoring cognitive deficits [1].

A recent meta-analytic review concluded that many of the modulatory effects reported in the research were not intentional, suggesting the difficulty in inducing modification selectively [3]. Nonetheless, if we comprehend "cognitive enhancement" as to induce an adaptive cognitive change for each individual, being able to selectively induce cognitive modification is critical since the goal of cognitive modification would depend on each individual. That is, one individual may need to promote a cognitive operation, but another individual may need to suppress it. This capacity is also critical for therapeutic use of rTMS in order to demonstrate consistent efficacy.

One of the reasons behind this may be because the neuromodulatory effects of rTMS depend heavily on various stimulation conditions, such as coil geometry, target location, stimulation intensity, and stimulation frequency [3]. Although it is suggested that stimulation frequency is a dominant factor for selective stimulation [4], little is known about the effects of frequency, especially when using an online rTMS paradigm [3]. Recent studies suggest that online rTMS can induce local entrainment of ongoing endogenous oscillatory activity during a task, which impacts cognitive performance, and the effect may depend on the function of the oscillation [3, 5, 6].This further illustrates the possible effectiveness of using stimulation frequency and target location that

are relevant with concerned cognitive function. Taken together, it seems reasonable to presume that an identification of task-specific neural activity (i.e. areas and frequencies) of cognitive function with EEG, and rTMS application on the identified areas/frequencies would be beneficial for selective modulation of cognitive performance.

Giving-up is an adaptive behavior that is associated with both mental and physical health [7], yet little is currently known in the field of cognitive and clinical neuroscience. Wrosch et al. [7] found that tendencies in failure in goal disengagement is associated with depressive states. Furthermore, van Randenborgh et al. [8] demonstrated that rumination, a well-known risk factor for the onset and maintenance of depressive states [9], plays a role in hindering adaptive giving-up behaviors. Therefore, cognitive enhancement of giving-up could lead to treatment of rumination and depressive states.

Giving-up refers to behaviors such as quitting on solving a problem [10], or disengaging from goals which are too difficult to attain [8]. In giving-up process, an individual tries to solve a problem, sets a goal to find a solution, but ultimately decides to disengage from the goal and quits solving the problem after goal-related and conflict thinking. Therefore, in the cognitive domain, giving-up is a process of making a decision for such behaviors, presuming to involve cognitive functions such as decision making, problem solving, and cognitive control.

Although there has been no detailed investigation of neural oscillates in the giving-up process, an existing body of research on related cognitive functions suggested that the frontal theta rhythm is the key mechanism underlying the giving-up process. For example, prefrontal theta oscillations have been associated with the implementation of cognitive control, action monitoring, and flexible behaviour [11-13]. Specifically, theta amplitude increase in the anterior cingulate cortex (ACC) is associated with conflict resolution during cognitive tasks [14] and ACC, which underlies central electrodes, is related with the decision-making process according to a functional imaging study [15].

In the present study, we aimed to selectively modulate giving-up behaviours and their cognitive functions using TMS-EEG. In order to achieve this, we investigated oscillatory correlates of the cognitive processes of giving-up by measuring changes in EEG activity during a problem-solving task in experiment 1. It was hypothesised that the frontal theta rhythm would be associated with the giving-up process and that the frontal alpha rhythm would be associated with the problem-solving behaviour according to previous study [16]. Then we explored the frequency-dependent stimulation effects of rTMS on performance of the problem-solving task and oscillatory activity by online rTMS with EEG recording in experiment 2. According to the results of experiment 1, we hypothesized that rTMS at theta frequency would induce endogenous theta activity and accelerate the giving-up behaviour; and rTMS at alpha frequency would induce endogenous alpha activity and slow down the giving-up behaviour.

2 MATERIALS AND METHODS

2.1 EXPERIMENT 1

2.1.1 Participants

Twenty-two healthy participants (nine women and 13 men, aged 18-26 years; mean age 21.5 ± 2.6 years) completed the experiment. Data obtained from four participants were excluded from the analysis because of significant background EEG artefacts, leaving 18 for the final sample (eight women, 10 men, aged 18-26 years; mean age 21.4 ± 2.6 years). All participants gave written informed consent before participation. This study was approved by the Research Ethics Committee of the University of Tsukuba and conducted in accordance with the Declaration of Helsinki.

2.1.2 Experimental design

The experiment procedure was designed to capture the moment when participants gave up on problem solving. In a sound-proofed, electric-shielded room, participants sat on a chair, placed their chin on a chinrest, and wore earphones throughout the sessions. During each trial, participants were instructed to solve Japanese riddles presented on a computer display and to press keyboard buttons (keypress response) to indicate when they gave up on solving the riddles (giving-up) or when they solved the riddle (problem-solving). The interval between the keypress and presentation of next riddle was 1.5 second. The riddles were selected from a royalty-free question bank on the Internet, and the difficulty of the problems was randomized. All participants completed three sessions (5 minutes per session) and were allowed to work at their own pace. The inter-session intervals were at least 1 minute long. Up to 30 riddles were prepared and distributed over three sessions.

2.1.3 EEG recording

Brain activity was measured using 27 active scalp electrodes embedded in an electro cap (actiCAP) and BrainAmp DC equipment (Brain Products, Gilching, Germany). The sampling frequency was 1000 Hz. Reference electrodes were placed on the right and left mastoids. Vertical and horizontal electrooculography (EOG) was conducted by placing electrodes above and below the participant's left eye, and electrodes at 1 cm from the right and left eyes.

2.1.4 EEG analyses

We analyzed EEG data with MATLAB software (R2015b, Mathworks Inc., Natick, MA, USA) to perform all the analysis. First, the EEG data was segmented into 8.0 s epochs (-7.5 s to 0.5 s from the onset of keypress) in all sessions. Next, to get the time-frequency amplitudes, we conducted the wavelet analyses for the original EEG signals s (t) using Morlet's function (t, f) in the time domain (SD σt) and the frequency domain (SD σf) around its centre frequency (f):

$$w(t,f) = (\sigma_t \sqrt{\pi})^{-\frac{1}{2}} \exp(-t^2 / 2\sigma_t^2) \exp(i2\pi ft)$$

with $\sigma_f = 1/(2\pi\sigma_t)$

We used a wavelet that was characterised by a constant ratio (f ⁄ σf = 7), with f ranging from 2–15 Hz (0.5-Hz steps). The amplitude was calculated by subtracting the baseline data measure in the intervals from the current keypress to the next riddle presentation (1.5-s time window) for each frequency band. To compare "giving-up" and "problem-solving" conditions, the Mann-Whitney U test was used.

2.2 EXPERIMENT 2

2.2.1 Participants

Ten healthy participants consented and participated in experiment 2, and nine participants completed the experiment. One participant reported a transient headache and withdrew from the experiment. We excluded one participant from the analysis because of too many EEG artefacts. Eight participants were included in the analysis (four women and four men, aged 18-39 years; mean age 25.0 ± 6.1 years). All participants gave written informed consent before participation. This study was approved by the Research Ethics Committee of the University of Tsukuba and performed in accordance with the Declaration of Helsinki.

2.2.2 Task procedure

In a sound-proofed, electric-shielded room, participants sat on a chair, placed their chin on a chinrest, and wore earplugs throughout the sessions. During each trial, participants were instructed to solve Japanese crossword puzzles presented on a computer display and to press keyboard buttons when they gave up on solving the puzzles (giving-up) or when they solved the puzzles (problem-solving). The problems were selected from a royalty-free question bank on the Internet, and the difficulty of the problems was randomised. All participants completed four sessions (5 minutes per session) and were allowed to work at their own pace. Up to 30 puzzles were prepared and distributed over four sessions.

2.2.3 Application of rTMS delivery

rTMS was applied during the sessions of problem-solving tasks with the following conditions: alpha-TMS and theta-TMS for rTMS stimulation, and no-TMS and sham-TMS for the control; the order of conditions was counterbalanced across participants. We first conducted the task without rTMS (no-TMS) and identified the individual alpha and theta frequencies for each participant to determine the stimulation frequency of alpha and theta conditions, which were the peak amplitudes of 4-6 Hz and 9-13 Hz, respectively (Figure 4-1). For the theta- and alpha-TMS conditions, we applied TMS for 1 second at intervals of the 1 second divided by the determined theta and alpha stimulation frequencies, respectively (e.g. 250 milliseconds in the case of 4 Hz).

For the control, sham stimulation was conducted by applying TMS pulses at 15 cm from the top of the participant's head (sham-TMS).

rTMS was applied using a figure-of-eight coil with a 70-mm wing diameter that was connected to a biphasic stimulator (Magstim Rapid MRS1000/50, Magstim Company Ltd., Whitland, United Kingdom). We used the flexible arm of a camera stand to fix the coil in the same position and direction for the duration of each session. We targeted the stimulation site as the frontal areas and located the TMS coil over the Fz electrode, according to the results of experiment 1. The intensity of TMS was 95% of the motor threshold of each participant, which was determined before the task instruction was given. We placed the TMS coil tangential to the scalp, with the handle pointing prerolaterally over the frontal area.

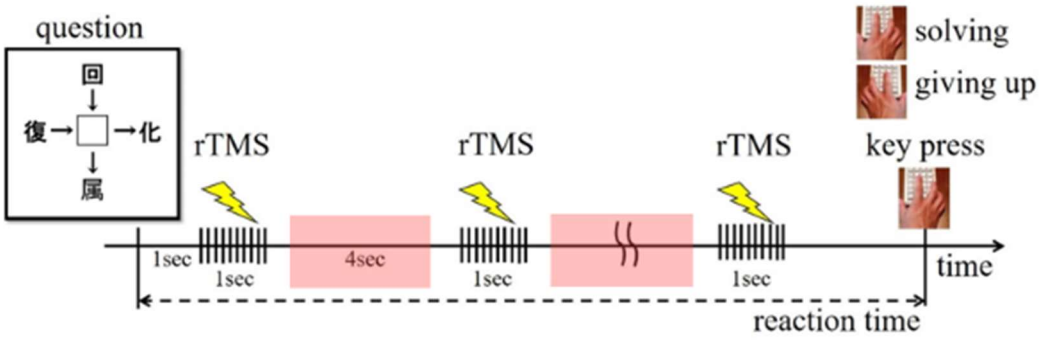

Figure 4-1. Experimental design. Seven seconds from the onset of keypress. The pink rectangles indicate the time window when participant's averaged EEG amplitudes were calculated

2.2.4 EEG recording

Brain activity was measured using 27 active scalp electrodes embedded in an electro cap (actiCAP) and BrainAmp DC equipment (Brain Products, Germany). The sampling frequency was 1000 Hz. Reference electrodes were placed on the right and left mastoids. Vertical and horizontal electrooculography (EOG) was recorded by electrodes placed above and below the left eye, and electrodes placed 1 cm from the right and left eyes.

2.2.5 EEG analyses

We analyzed only the Fz data. We used the same methods as the analyses for Experiment 1, expect for the rejection of the TMS artifacts and the epoch segmentations. The EEG data were segmented into 4-sec time windows (from 0.5-s to 3-sec after the last rTMS) which were shown in Figure 4-2. To reduce the TMS-related artifact, we removed the EEG data from -1 to 4 ms from TMS onset using linear interpolation, according to previous study [17]. The statistical differences were evaluated by the Mann-Whitney U-tests.

3 RESULTS

3.1 RESULTS OF EXPERIMENT 1

3.1.1 Behavioural results

The response time (RT), which corresponds to the duration from stimulus onset to keypress response in the giving-up condition, was measured as the cognitive and behavioural response, and that in the problem-solving condition was measured as the control response. Participant-averaged RTs (± standard deviation [s.d.]) for giving-up and problem-solving conditions were as follows: 57.65 ± 13.60 seconds and 24.70 ± 8.38 seconds, respectively. There were significant difference between conditions（z = -3.306, $p < 0.001$）.

3.1.2 EEG results

To examine temporal activity of alpha and theta frequencies during the giving-up process, time-frequency analyses were conducted based on EEG data for the 7.0 seconds from the onset of stimulation to the keypress for each condition, and the data were compared to highlight the distinctive giving-up oscillatory behaviour. Figure 4-2 presents the participant-averaged time-frequency amplitudes of the Fz electrodes for giving-up (A), problem-solving (B), and their statistically significant differences between a p-value of 0.05 and 0.00 (C). There were intermittent increases in the alpha amplitude for both conditions, and an acute increase of the theta amplitude along with elevated alpha activity around 1 second before the keypress response was distinctive of giving-up.

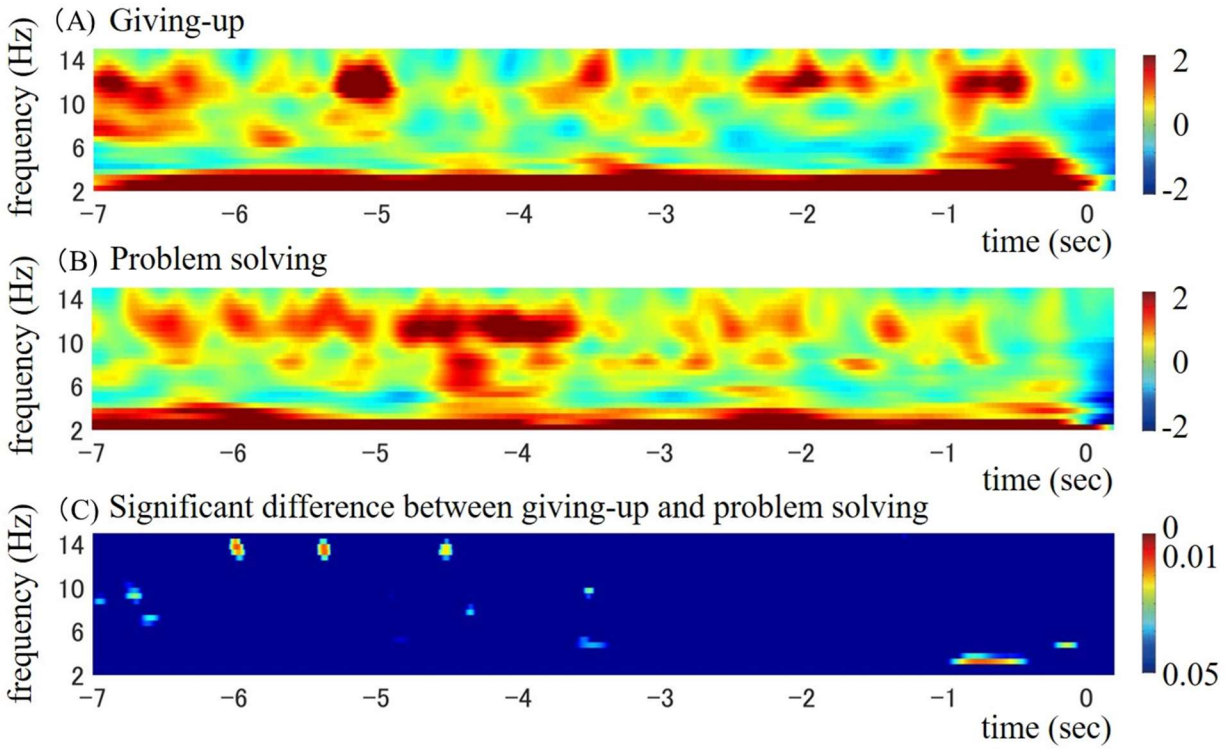

Figure 4-2. Time-frequency maps of frontal (Fz) amplitudes for 7 seconds from the onset of keypress: (A) giving-up condition and (B) solved condition. (C) Statistically significant differences between the conditions.

3.2 Results of Experiment 2

3.2.1 Modulatory effects on behaviour

The RT under no-TMS condition was considered as baseline response and sham-TMS condition was considered as control stimulation.

Participant-averaged RTs (± s.d.) for giving-up under no-TMS, alpha-TMS, theta-TMS, and sham-TMS conditions were as follows: 50.099 ± 6.266 seconds, 62.270 ± 5.307 seconds, 41.730 ± 2.746 seconds, and 44.600 ± 2.580 seconds, respectively (Figure 4-3 [on the left]). There was no significant difference between sham-TMS and no-TMS condition (z= -0.423, p= 0.672), suggesting that both conditions could be considered as control. There was a shortening trend of RT in the theta-TMS condition compared to the sham-TMS condition (z = -1.741, p = 0.082), and RT was significantly prolonged in the alpha-TMS condition compared to the sham-TMS and no-TMS conditions (z = 3.461, p < 0.001; z = -2.771, p = 0.006, respectively).

Participant-averaged RTs (± s.d.) for problem solving under no-TMS, alpha-TMS, theta-TMS, and sham-TMS conditions were as follows: 17.904 ± 3.799 seconds, 29.695 ± 3.031 seconds, 19.455 ± 2.821 seconds, and 20.330 ± 2.325 seconds, respectively (Figure 4-3 [on the right]). There was no significant modulatory effect on RT for problem-solving under alpha- and theta-TMS conditions compared to the sham-TMS condition (z = 0.101, p = 0.920; z = -0.602, p = 0.548, respectively).

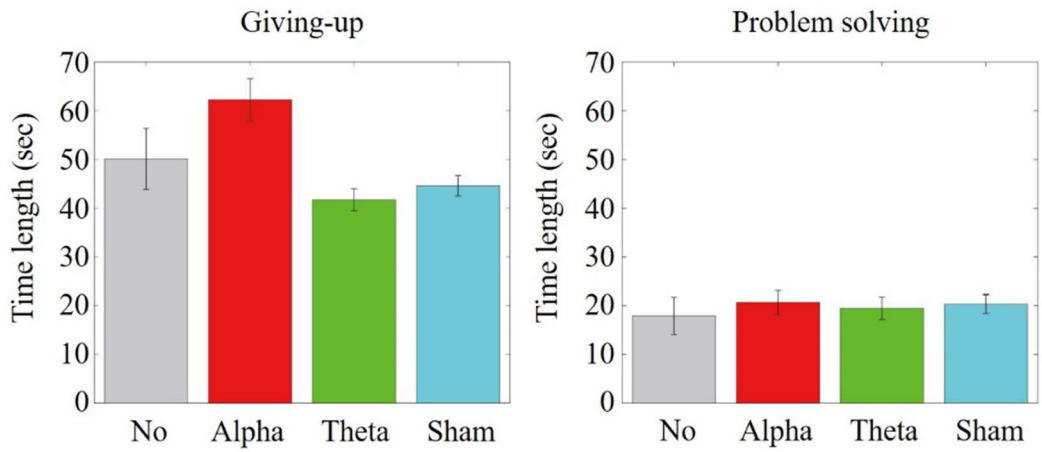

Figure 4-3. Modulatory effects of repetitive transcranial magnetic stimulation (rTMS) on giving-up and problem-solving behaviours in the rTMS condition.

3.2.2 Modulatory effects on oscillatory activity

In order to measure the modulatory effects of rTMS on oscillatory activity for giving-up, we calculated participant-averaged alpha and theta amplitudes in between stimulations (500 milliseconds post-stimulation and 1 second pre-stimulation, as shown in Figure 4-1) as rTMS-induced oscillatory amplitudes for alpha-, theta-, and sham-TMS conditions (Figure 4-4). The greatest increase of the theta amplitude was induced by theta-TMS, and the greatest increase of the alpha amplitude was induced by alpha-TMS. The participant-averaged theta amplitude was significantly higher for the theta- and alpha-TMS conditions compared to the sham-TMS condition ($z = 3.095$, $p < 0.002$; $z = 3.053$, $p < 0.003$, respectively). Moreover, there was no significant difference between the theta- and alpha-TMS conditions ($z = 1.189$, $p = 0.235$). These results suggested that not only theta-TMS but also alpha-TMS has increasing effect of theta amplitude. The participant-averaged alpha amplitude was significantly different for the alpha-TMS condition compared to the sham- and theta-TMS conditions ($z = 4.463$, $p = 0.001$; $z = 3.704$, $p = 0.001$, respectively).Moreover, the alpha amplitude for the alpha-TMS was significantly higher than those for the theta-TMS ($z = 2.631$, $p < 0.009$).

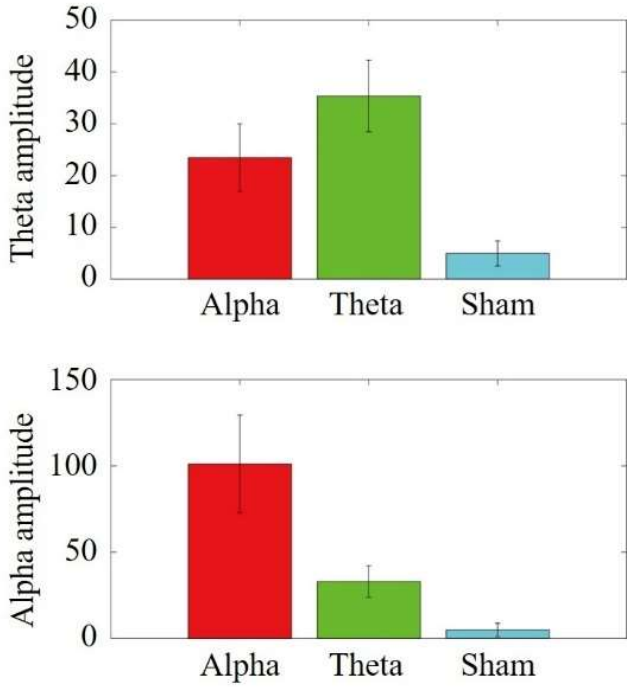

Figure 4-4. Modulatory effects of repetitive transcranial magnetic stimulation (rTMS) on oscillatory amplitudes for the rTMS conditions (theta amplitude [on the top] and, alpha amplitude [on the bottom]).

In order to further illustrate the effects of stimulation frequency on rTMS-induced behaviour and oscillatory activity, we examined the relationship between rTMS-induced giving-up RTs and participant-averaged amplitudes for each rTMS condition (Figure 4-5). Our study showed that in the theta-TMS condition, there was a significant correlation between RT and the theta amplitude (r = -0.380, p < 0.021), suggesting that the greater increasing effect in the theta amplitude, the greater shortening effect in RT occurs. Although it was weak, a similar effect was found for prolonging the effect of RT for increasing the alpha amplitude in the alpha-TMS condition, as there was a positive but not significant correlation between RT and the alpha amplitude (r = 0.245, p = 0.379).

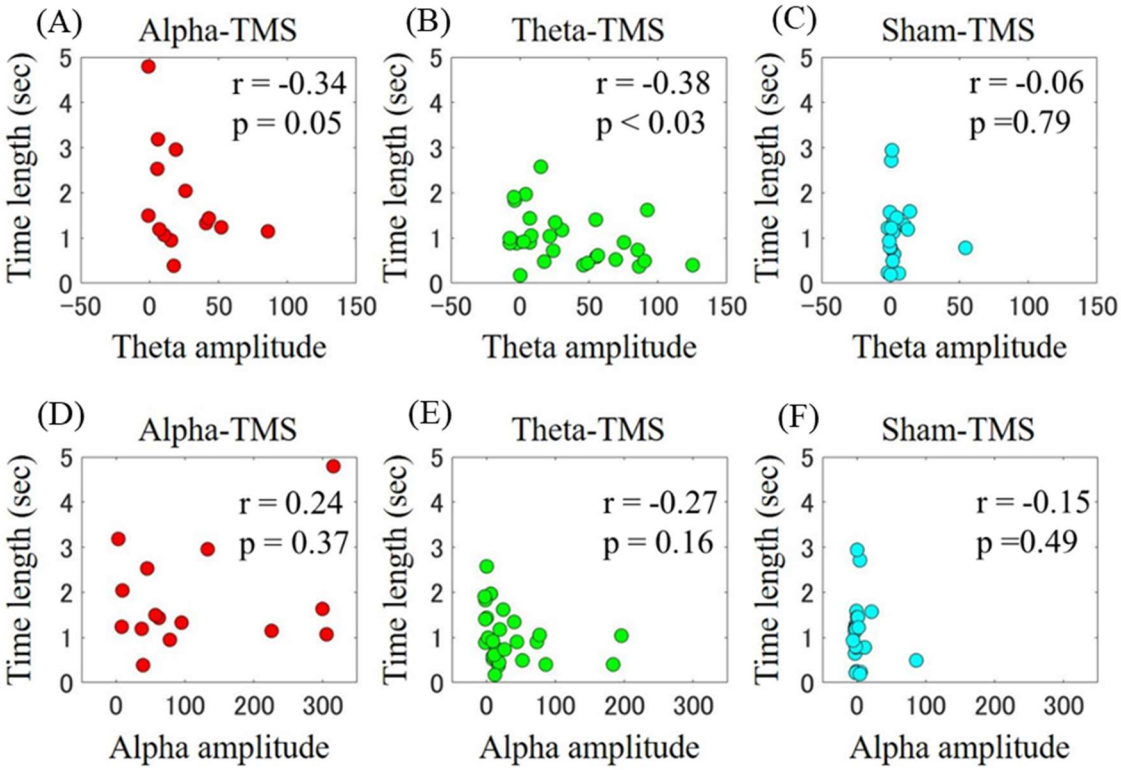

Figure 4-5. Relationship between response time (RT) and oscillatory amplitude induced by repetitive transcranial magnetic stimulation (TMS) conditions. Scatter plots between RT and the theta amplitude under the (A) alpha-TMS condition, (B) theta-TMS condition, and (C) sham-TMS condition are shown. Scatter plots between RT and the alpha amplitude under the (D) alpha-TMS condition, (E) theta-TMS condition, and (F) sham-TMS condition are shown.

4 DISCUSSION

The main goal of the current study was to modulate giving-up behaviours and their cognitive functions using TMS-EEG, selectively. We first investigated the correlations between the EEG oscillatory cognitive giving up processes. We then conducted online rTMS to examine the frequency-dependent stimulation effects of rTMS on the performance of problem-solving tasks and ongoing oscillatory activity. It was hypothesised that the frontal theta rhythm would be associated with the giving-up process, while the frontal alpha rhythm would be associated with the problem-solving process. According to the results of Experiment 1, we hypothesised that rTMS at the theta frequency would induce ongoing theta activity and accelerate giving-up behaviour while rTMS at the alpha frequency would induce ongoing alpha activity and slow down giving-up behaviour.

There was an acute increase in the theta amplitude right before the giving-up response, which was distinctive of giving-up and consistent with our first hypothesis. This may reflect the decision-making process to disengage from the goal and quit problem-solving as a type of conflict resolution as the frontal theta amplitude is associated with the cognitive processes of decision-making, conflict resolution, and action monitoring.

This study's results also showed an intermittent increase in the alpha amplitude for the giving-up and problem-solving conditions, which suggests its involvement with the cognitive processes of problem-solving, as hypothesised. These results are consistent with those of a previous study in which frontal alpha-band activity was related to creative problem-solving. Considering that creative thinking is related to cognitive flexibility and the ability to develop alternative concepts or strategies, the observed increase in the alpha amplitude along with the theta amplitude before the giving-up response could be explained by the fact that their activities were involved with conflict resolution. That is, a choice between quitting and continuing problem-solving.

There was a trend for shortening in giving-up RT when rTMS induced an increase in theta activity and a significant prolongation of giving-up RT when rTMS induced an increase in alpha activity. This was consistent with our second hypothesis. The results confirm an association between the cognitive processes of giving-up and the theta amplitude as well as problem-solving with the alpha amplitude in the frontal area. The increase in the theta activity is responsible for deciding to give up, and the increase in the alpha activity is associated with problem-solving. To our knowledge, this is the first study to investigate the neural oscillatory correlations of giving-up. There are, however, other possible explanations. For instance, we cannot rule out the possibility that prolongation of giving-up RT occurred due to inattention to the task. Indeed, many studies have suggested that event-related synchronisation of alpha activity reflects inhibition [19].

This study also demonstrates the effectiveness of using stimulation frequency and target location, which are relevant to selective modulation. Furthermore, this has important implications for developing the effective therapeutic use of rTMS. It has been suggested that rumination, or repetitive negative thinking, is a risk factor and an important therapeutic target for depression [20-21]. Additionally, effective giving-up behaviour is associated with less of a tendency to ruminate [8]. Therefore, the study's implications regarding the effective means to encourage or discourage giving-up behaviour could be used in therapeutic options for depression.

Several limitations make it impossible to validate the neuromodulatory effects of rTMS found in this study. Firstly, the small sample size and number of trials did not allow us to conduct elaborate analyses or make conclusions regarding the results. In particular, we used the Mann-Whitney U-tests for our statistical evaluation due to the limited number of trials for each rTMS condition. Therefore, we could not provide conclusive results regarding the effects of frequency-dependent stimulation. More specifically, although the *p*-values indicated significant differences in condition (e.g., Figure 4-3 and 4-5), it should be noted that multiplicity issues have not been taken into account. Further studies with a larger sample size and trials are needed to provide more definitive evidence regarding the frequency-specific effects of rTMS. Notably, recent studies have indicated the importance of calculating effect size in quantitative studies [22]. Secondly, the present study did not employ a control site or frequency for comparing the rTMS paradigm. Therefore, there may be an alternative explanation for our results which suggest the importance of detecting task-relevant stimulation target site and frequency. Also, we did not use a neuronavigation system to locate the target site. Recent research that compared the behavioural effects of major targeting methods demonstrated that individualised functionally guided rTMS showed the largest effects, while scalp measurement localisation led to the smallest [23]. Considering that detecting a task-relevant stimulation target site is one way to individualise target location, using a functional neuronavigation could have increased the neuromodulatory effects of this study. Therefore, future work should investigate effective methods. An example of this is the co-registration of functional magnetic resonance imaging with EEG for assessment and stimulation.

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CHAPTER 5: GENERAL CONCLUSIONS

This dissertation was designed to illustrate the utility of the TMS-EEG approach for the evaluation and modification of cognitive functions (or cognitive enhancement). In order to achieve this, three experimental studies were conducted. In the first study, we examined whether TMS-induced EEG oscillatory information can be used to evaluate the network properties of cognitive processes. This information is essential to elucidate the neural mechanisms underlying cognitive functions. Cognitive enhancement is closely related to the treatment of mental disorders, as such, in the second study we examined whether TMS-induced EEG oscillatory information is useful for evaluating disease- and treatment-states in depression. The characteristics of cognitive impairments vary depending on the individual. Therefore, it is important that selective modification of a cognitive function is individualizable. Thus, in the final study, we investigated whether modulating TMS-induced oscillatory activity can selectively change performance of the relevant cognitive function.

1 OVERVIEW OF FINDINGS

2.1 CHARACTERIZING NETWORK PROPERTIES OF COGNITIVE FUNCTION WITH TMS-EEG

In Chapter 2, we showed that TMS-induced phase-locking information can be used to evaluate the directionality of information transmission in the cortical network associated with a cognitive function. We found that a single pulse of TMS modulates the global phase synchronization of a cortical network (i.e. PLV) in the direction of information flow. This was shown by increased TMS-induced theta phase synchronization when TMS was delivered to sensory but not frontal areas, during WM tasks. This finding is supported by previous findings that TMS-induced neural activity propagates through a cortical network by manipulating brain activation not only in TMS-targeted areas [1–3] but also in relevant non-TMS targeted areas [4–6]. Global phase synchronization suggests that the areas affected by TMS are functionally correlated and support neural communication and information transmission [7].

2.2 CHARACTERIZING NEURAL CHANGES IN DEPRESSION WITH TMS-EEG

In Chapter 3, we demonstrated that the TMS-induced phase-locking information can be used to evaluate the characteristics of a cortical network before and after the treatment of depression. The results showed that changes in the TMS-induced phase synchronization of a cortical network (i.e. PLV) could be used to evaluate depressive states and treatment effects of ECT. TMS-induced

alpha band PLV was negatively correlated with depression severity, and changes in TMS-induced alpha band PLV were positively correlated with the reduction in depression severity. Furthermore, the results suggest that the intensity and speed of information transmission could be evaluated from TMS-induced phase-locking information between two nodes of the cortical network (i.e. PLF). In particular, we found that changes in the TMS-induced PLF peak latencies between visual and motor areas were positively correlated with treatment effects.

2.3 Modification of Cognitive Performance with TMS-EEG

In Chapter 4, the study's findings suggest that we can selectively modulate TMS-induced oscillatory activity by tuning the stimulation frequency and inducing changes in cognitive performance. In particular, theta-frequency rTMS application induced an increase in theta amplitudes. Further, it led to shortening RTs for giving-up, a cognitive process associated with depression. Alpha-frequency rTMS application induced an increase in alpha amplitudes and prolonged giving-up RTs. These findings are consistent with earlier studies, which suggested that rTMS induces local entrainment of ongoing endogenous oscillatory activity during a task. This impacts cognitive performance and depends on the function of the oscillation [8-10]. Indeed, the stimulation frequencies–theta and alpha–were determined by examining EEG oscillatory activity during the giving-up task in the first experiment of this study. The findings elucidated the neural mechanisms underlying the cognitive processes of giving-up: the increase in theta activity may be associated with making a decision to give up, and the increase in the alpha activity may be associated with problem-solving thinking..

2 Implications and Suggestions For Future Research

The findings of this dissertation have several implications for future practice. In general, they support the idea that TMS-EEG is a useful approach for both the characterization and the modulation of cognitive functions. In particular, the TMS-induced phase-locking information of distant areas (i.e. calculated PLV and PLF) related to cognitive function could be used to evaluate the characteristics of a cortical network of cognitive function (e.g. directionality, intensity, and intra-network information transmission speed). In addition, such characteristic evaluations could feasibly be used to assess the severity of mental disorders and the therapeutic effects of various treatments. Furthermore, the effective modulation of TMS-induced amplitudes and the consequent changes in cognitive performance could be achieved by selecting stimulation frequencies and target locations that are relevant to cognitive functions. Since the neural-oscillatory basis of cognitive processes is largely unknown, oscillatory information obtained from EEG recordings could be useful for determining stimulation frequencies and locations. The use of TMS-induced phase-locking information for evaluating the neural correlates of cognitive processes may allow us to select even more effective targets for rTMS modulation, rather than simply evaluating TMS-induced amplitudes.

The aim of this dissertation was to establish an effective approach (methods and/or systems) for cognitive enhancement. Accordingly, there are a few ideas that I would like propose towards this goal that would utilize TMS-EEG for evaluation and modification:

1. Individualized interventions could be developed to improve cognitive functions and mental health (Figure 5-1). Specifically, rTMS-induced neuromodulation could be used to enhance cognitive functions, given TMS parameters that are individualized for maximum impact. There are several cognitive dysfunctions related to mental problems. For example, as discussed in Chapter 4, the cognitive processes behind giving-up may be closely related to rumination–a key feature of depression. In the proposed system, (1) we would first assess impairments in cognitive function and disease states by using single-pulse TMS-EEG for evaluation. We would then (2) determine TMS parameters in accordance with individual characteristics such as head form, natural frequencies, and modification interests, in order to use rTMS to modulate the target cognitive function. Personalized TMS parameters should include target frequencies, target locations, stimulation sites, etc. During application, brain activity would be monitored using EEG to ensure that TMS affects the proper target location and induces the correct frequencies. (3) After TMS intervention, we would examine the neuromodulatory effects of rTMS on the targeted cognitive function and evaluate any resultant mental health issues, using single-pulse TMS-EEG. Along with the examination, we would use evaluation methods such as measures for clinical symptoms, questionnaires, and behavioural markers for subjective and objective changes in real-life settings. For example, in the case of modifying giving-up functions using rTMS, we would need to ensure that the intervention reduced ruminative thinking and depressive states in real-life settings, and not only in hospital or laboratory settings.

As the neural-oscillatory basis of cognitive processes is largely unknown, several steps would be involved in developing a system for TMS-EEG medical intervention. We would need to investigate the neural mechanisms underlying various cognitive functions, especially those that are relevant to mental health issues. Furthermore, more effective intervention systems would necessarily rely on engineering development (* in Figure 5-1). For instance, with further investigation into the neuromodulatory effects of rTMS, we should be able to build databases for procedures and parameters suited for each cognitive function or for individual factors. Using this information, a device or system could be developed that automatically selects and installs TMS intervention parameters on an individual basis. This would allow efficient distribution of the system to clinical settings.

Figure. 5-1: A schematic diagram of a personalized intervention system using TMS-EEG

2. The TMS approach could also be combined with therapeutic approaches such as cognitive interventions. Cognitive interventions are techniques and therapies practiced in clinical settings. They result in behavioural modification by, for example, teaching flexible thinking skills and methods for emotion control. In clinical psychology, evidence-based cognitive interventions include cognitive-behavioural therapy (CBT), mindfulness-based approaches, acceptance and commitment therapy (ACT), and metacognitive therapy (MCT) [11-14]. Although these approaches are known to be effective in clinical settings, the neural mechanisms underlying their effects are largely unknown. However, recent studies have suggested that these approaches affect cognitive functions and neural activity [11-14]. For example, it has been suggested that the attention training technique (ATT) increases frontoparietal alpha and beta oscillatory activities, which are associated with executive functions such as top-down attentional control [13]. It can be considered that using rTMS to target oscillatory activity and locations relevant to the therapies' effects would accelerate these effects. Alternatively, it may also be possible that these cognitive interventions would accelerate the rTMS effects. In short, these interventions could benefit each other in combination. Recent reviews have pointed out this possibility [11-14], but few studies have examined it. As this dissertation has suggested, future development has many challenges to overcome and more investigation is needed. However, there are practical engineering approaches that can be considered for implementation (* in Figure 5-2). For instance, with further investigation of the neural and therapeutic effects of cognitive interventions, we should be able to build a database for procedures and parameters suitable for combined therapy. Furthermore, a device or system could be created to help patients monitor their cognitive function, brain activity, and emotional states. This could provide alerts for check-ups and encourage individuals to engage in the at-home elements of their therapies. This approach would be effective when implemented along with the development of the system described in the first proposal.

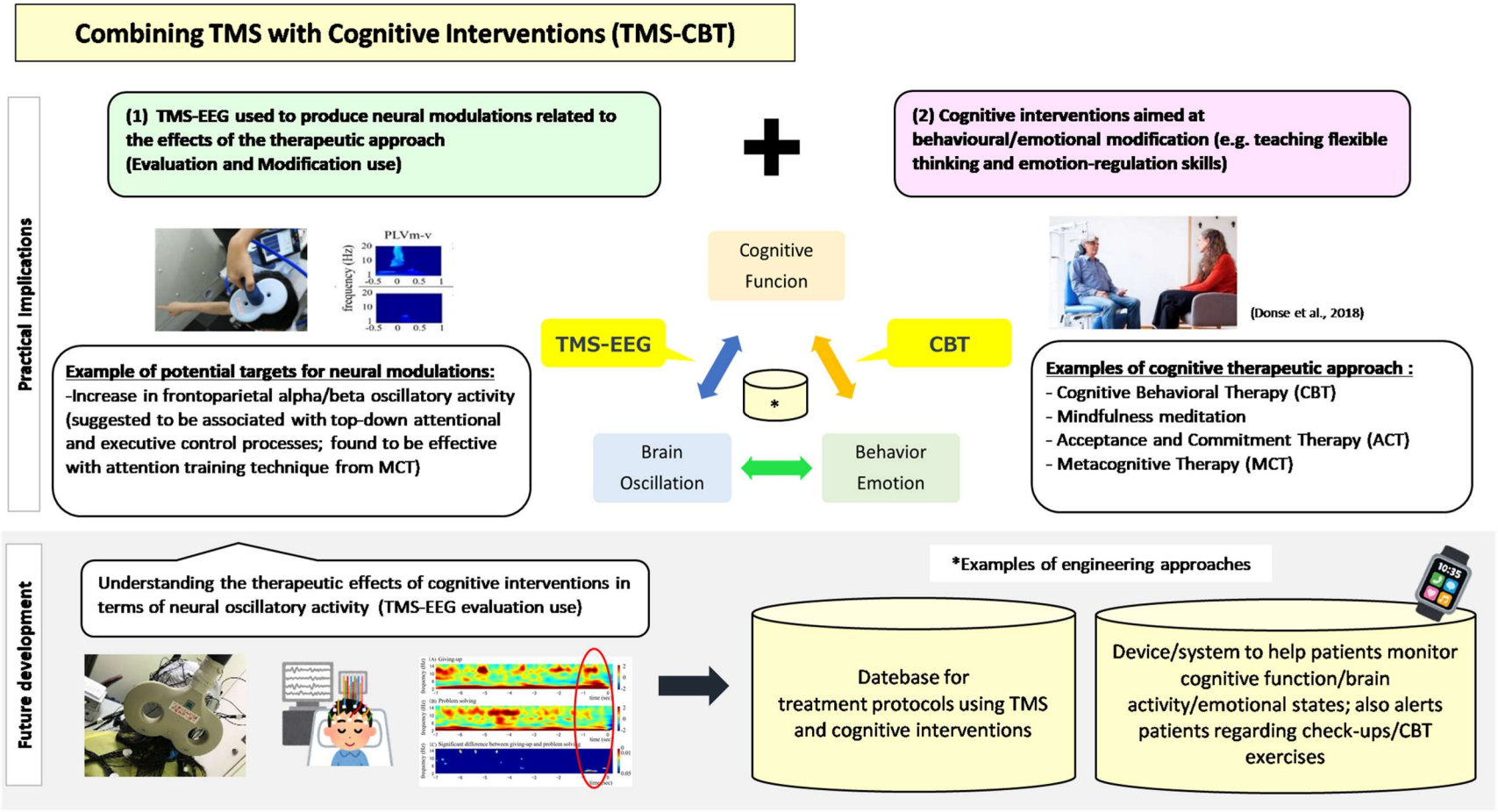

Figure. 5-2: A schematic diagram of TMS-CBT

As described above and in Chapter 1, there were several critical issues that hampered progress in achieving the aforementioned goals and prospects. For instance, there remains a paucity of evidence regarding the use of the TMS-EEG approach for inducing cognitive function modification and on the possible effectiveness of employing stimulation frequencies and target locations that are associated with cognitive functions. The findings of this dissertation provide a better understanding of the TMS-EEG approach and its effective usage for the evaluation and modification of cognitive functions. This dissertation represents one of the first attempts to thoroughly examine the effectiveness of using stimulation frequency and target location specific to cognitive function. To better understand the implications of these results, however, further research should address the effects of other factors that affect the neuromodulatory effects of TMS on cognitive functions.

3 CONCLUSIONS

Despite remarkable advances in technology and the accumulation of research towards understanding the relationship between the brain, mind, and behaviour, there still exists considerable uncertainty in the field. This dissertation illustrated not only how the TMS-EEG approach may help us to take a step further but also that there is a long way to go to fully understand the brain. Using the TMS-EEG approach, we have been able to elucidate how information is transferred within a WM network (by evaluating TMS-induced PLVs), how information transmission in the network is impaired and improved in depression (by evaluating the relationship between TMS-induced phase-locking information and symptoms), and how we can change cognitive performance related to depression (by modulating TMS-induced amplitudes). To enable us to selectively control the neuromodulatory effects of cognitive functions, we still need to elucidate the mechanisms underlying cognitive function.

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