31st Annual International Conference of the IEEE EMBS
Minneapolis, Minnesota, USA, September 2-6, 2009

An Investigation on The Effects of Single Pulse Transcranial Magnetic Stimulation in A Modified Maximum Entropy Auditory Stimulation Paradigm

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Abstract— **In this paper, we intend to investigate further the effects of single pulse TMS (sTMS) on auditory attention through an experimental design that combines a modified version of maximum entropy stimulation paradigm. Single pulses of TMS with 4.4s inter-stimulus interval (ISI) were applied to the left temporal lobe of subjects while three randomized auditory stimuli with constant ISI of 1.1s were delivered to the contra–lateral side within the TMS stimulation duration. Our main focus was to examine the time course of the auditory late responses (ALRs) due to TMS stimulation by a phase clustering on the unit circle measure and an adaptive shift–invariant feature extraction method. In the attention scheme, a significant difference in the phase stability between TMS and no–TMS was found in the range of the N1 wave of ALRs. However, the difference occurs only for the data after 1.1s. Furthermore, there is an absence of differences in the amplitude of the ALR. In addition, the effects of TMS and attention can also be discriminated very well and illuminate the effects of TMS in auditory attention. It is concluded that even sTMS might have the potential to alter the attentional states and the effects can last about 1s, at least when considering the large–scale neural correlates of attention in ALR sequences.**

I. INTRODUCTION

Transcranial magnetic stimulation (TMS) is a noninvasive method to excite neurons in the brain with weak electric currents which are induced in the tissue by rapidly changing magnetic fields (electromagnetic induction). TMS has become an important method for studying the conductivity and excitability of the corticospinal system, abnormal cortical circuitry in neurological diseases, and the reorganization of sensorimotor and visual systems after peripheral and central lesions. Some examples are found in functional relevance of cortical areas in cognitive task performance [1], altered cortical excitability in neurological diseases [2], and treatment of neuropsychiatric disorders (e.g., depression, schizophrenia and anxiety disorders) [3], [4]. Some studies proved that TMS therapies (especially rTMS) are able to induce the treatment of various neurological diseases such as Parkinson's disease and Stroke [5], [6]. There are also treatments of psychiatric diseases with TMS such as bipolar mania [7] and post–traumatic stress disorder [4].

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Brain mapping is also possible with TMS. For instance, the effects of TMS on the electroencephalographic (EEG) activity were studied by [8] and the effects of the stimulus intensity by [9]. Many studies tried to find the early and middle latency evoked potential (less than 50ms) [8], [9] but some authors also focused on slow cortical potentials (SCPs) such as the effects of TMS on SCPs elicited during performance of a feedback and reward task [10]. High frequency repetitive TMS may induce cortical excitation while low frequency TMS may provoke cortical inhibition [11].

Furthermore, the effects of TMS to the attentional process have been reported by many researchers [12], [13], [14], [15]. Most of the research was focused on visual or spatial attention. Studies on the effects of TMS to auditory attention by using EEG are still lacking, with only a few results reported (e.g., [16], [17], [18], [19]). Especially, rTMS has the potential advantage of disrupting brain activity for the duration of train of pulses, making it much easier to detect processing changes in studies of cognitive function as well as in studies of sensory and motor function. Nevertheless, few studies have shown that rTMS can induce generalized seizures even in people with no known history of epilepsy [20]. On the contrary, some safety studies have suggested that single pulse TMS (sTMS) can be used without risk of side effects, such as epileptic seizures or transitory memory impairment in all normal subjects [21]. Although sTMS has been reported to induce seizures in patients with epilepsy, it has been safely applied to diverse patient groups, including those with spinal cord injuries (SCI), Parkinson's disease and multiple sclerosis. Reviews and guidelines for the safe use of rTMS can be found in [22], [23].

We have recently shown that TMS is capable of increasing neural correlates of attention reflected in ALRs in normal subjects [24]. This paper will focus on the investigation of the effects of sTMS in auditory attention by examining the time course of ALRs through an experimental design that integrates a modified maximum entropy stimulation paradigm. Single pulses of TMS with 4.4s ISI were applied to the left temporal lobe of subjects while three auditory stimuli with constant ISI of 1.1s were delivered to the contra–lateral side within the TMS stimulation duration. Neural correlates of attention reflected in ALRs were analyzed by a phase clustering on the unit circle measure that has been confirmed to be linked to attention [25] and an adaptive shift–invariant feature extraction method by optimized filter banks. Our

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assumption is that the sTMS could increase and synchronize the phase of ALRs particularly in the attention scheme. Furthermore, we expect that the differences among classes can be separated well by the proposed feature extraction method.

II. METHODOLOGY

A. Experimental Procedure

Ten student volunteers (3 females, 7 males, aged 26±4.5) from Saarland University participated in the experiments. All of them had normal hearing and no history of any neurological disorders. The magnetic stimulation was applied by using a figure–of–eight TMS coil from Magstim Super Rapid System. Biphasic magnetic pulses (duration 250μs) were delivered over the left temporal lobe with 4.4s inter-stimulus interval (ISI). The TMS intensity was determined as 100% of individual motor threshold. The TMS stimulation is combined with an adjusted maximum entropy stimulation paradigm of auditory attention described in [25].

In each experiment, a total of 50 TMS stimulation were presented and every TMS pulse is followed by 3 auditory stimuli with a fixed ISI of 1.1s in randomized order. For the first measurement, subjects were required to pay attention to the auditory stimuli which were delivered to the right ear and detect the target tones in the attention scheme. For the second measurement, experiments were conducted without TMS stimulation. EEG signals were sampled with 512Hz and acquired through the g.USBamp system (Guger Technologies Austria) which allows to record DC signals or TMS spikes without saturation. Single sweeps, i.e., the responses to the individual tones, were recorded using electrodes placed at the left and right mastoid, the vertex, and the upper forehead. Electrodes impedances were strictly maintained below 5kΩ in all measurements.

In preparing the data for the further analysis, the recorded responses were bandpass filtered (cut–off frequencies: 1Hz–30Hz) and then segmented into pre-stimulus 200ms to 800ms post-stimulus for each single sweeps. An artifact filter was used to remove responses that exceeded 50μV.

B. Phase stability measure (phase clustering on the unit circle)

We employed the time–scale coherence measures based on the complex wavelet transform. The quality and stability of the response over the stimulus sequences are evaluated in terms of the time-resolved phase information. According to [26], the phase stability $\Gamma_{s,\tau}$ of a sequence $\mathcal{F} = \{f_m \in L^2(\mathbb{R}) : m = 1, \dots, M\}$ of M sweeps is defined by:

$$\Gamma_{s,\tau}(\mathcal{F}) = \frac{1}{M}\left|\sum_{m=1}^{M} e^{\imath \arg((\mathcal{W}_\psi f_m)(s,\tau))}\right|. \quad (1)$$

In this study, we used the 4th–derivative of the complex Gaussian function as wavelet. In general, Eq. (1) yields a value in the range of 0 and 1. We have a perfect phase stability for a particular s and τ for $\Gamma_{s,\tau} = 1$ and a decreasing stability for smaller values.

C. Adaptive Feature Extraction by Optimized Filter Banks

In order to extract the differences between attended ERPs with and without TMS, the proposed morphological shift–invariant local discrimination bases (MSLDB) algorithm as introduced in [27] is used. A combination of the morphologically adapted filter banks with the shift–invariant technique gives a powerful adaptive feature extraction. Instead of applying predefined libraries of standard wavelets, this algorithm introduces the selection of a local discriminant bases (LDB) from a parameter space which contains all paraunitary filter banks of a given order with at least one vanishing moment of the highpass filter. In other words, the wavelet shape is adapted through all subjects to give the most discriminant features of the classes.

The proposed algorithm uses an approximate shift–invariant wavelet packet decomposition (WPD). The idea of this technique extends the typical WPD equation [27] where the coefficients($y[\cdot]$) are calculated as follow:

$$y[\cdot] = \begin{cases} \sum\limits_{k\in\mathbb{Z}} x[k]h^{(\theta)}[2\cdot - k], & \text{if } \mathcal{M}(u[\cdot]) \geq \mathcal{M}(u[\cdot - 1]) \\ \sum\limits_{k\in\mathbb{Z}} x[k]h^{(\theta)}[2\cdot - k - 1], & \text{else} \end{cases} \quad (2)$$

$x[\cdot]$ is the input signal, $h^{(\theta)}[\cdot]$ is the adaptable wavelet which depends on the lattice angles θ and $\mathcal{M}(\cdot)$ is the information cost function like entropy or energy of filtered signal ($u[\cdot]$).

The shift–invariant discriminant measure ($\mathfrak{D}$) of feature ($\mathcal{E}$) between two classes $\mathbf{a}_1$ and $\mathbf{a}_2$ can be written as a Fisher's distance [28] which includes the mean ($\bar{\mathcal{E}}$) for each subject and variance (σ^2) within the classes:

$$\mathfrak{D}(\mathbf{a}_1, \mathbf{a}_2) = \frac{\left|\bar{\mathcal{E}}_{a_1} - \bar{\mathcal{E}}_{a_2}\right|}{\sigma^2_{\mathcal{E}_{a_1}} + \sigma^2_{\mathcal{E}_{a_2}}} \quad (3)$$

The feature also has to be shift–invariant such as energy ($\mathcal{E}_a = \sum_{i=1}^{n} a^2[i]$) or entropy ($\mathcal{E}_a = \sum_{i=1}^{n} a^2[i]\log a^2[i]$) of each sequence ($a$) where n is the length of the sequence. The sequences from each classes are normalized to get more robust distances.

III. RESULTS AND DISCUSSION

We divided the auditory responses into 3 sets and termed these sets as first sweeps (i.e., all first responses after the TMS stimulation), second sweeps (i.e., all second responses after the TMS stimulation) and third sweeps (i.e., all third responses after the TMS stimulation). Our study was focused on the N1 wave that is commonly used in paradigms related to auditory attention [29], [30]. This wave is assumed to reflect selective attention to basic stimulus characteristics, initial selection for later pattern recognition, and intentional discrimination processing. Its amplitude is enhanced by increased attention to the stimuli [29]. In order to elucidate the time dependant effects induced by TMS, we analyze and discuss the data of first sweeps and the third sweeps.

Fig. 1 depicts the averaged ALR across subjects in the attention scheme, with and without TMS stimulation was applied. There is no difference in the amplitude of grand averaged ALR between the TMS and no TMS data for both first and third sweeps.

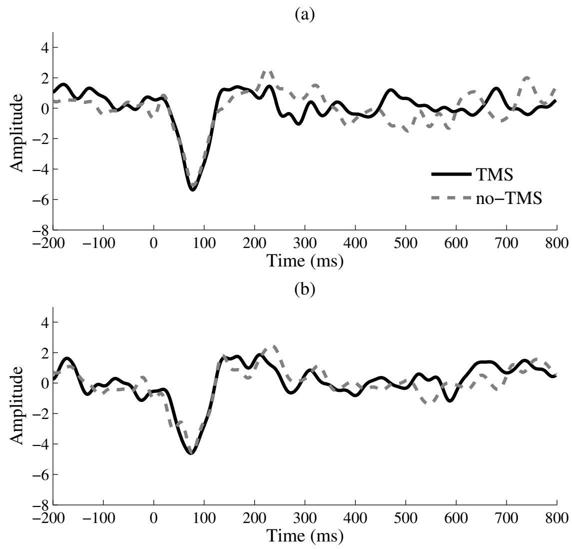

Fig. 1. Amplitude of grand averaged ALR in the attention scheme. (a) first sweeps and (b) third sweeps. Note: solid line represents data with TMS and dash line denotes data without TMS.

The phase stability across sweeps was evaluated and shown in Fig. 2. The scale shown here is $s = 40$ as example. For this scale, the temporal resolution is rather satisfactory for ALRs and the differences in this frequency band are also clearly noticeable [24]. It is remarkable that the most significant difference is found within the time interval between 70–130ms where the N1 wave is located (ANOVA, p<0.01). The neural activity reflected in these waves is presumably associated with the auditory cortex [31], [32]. However, this difference is observed only in the first sweeps of the data which means the data after 1.1 seconds.

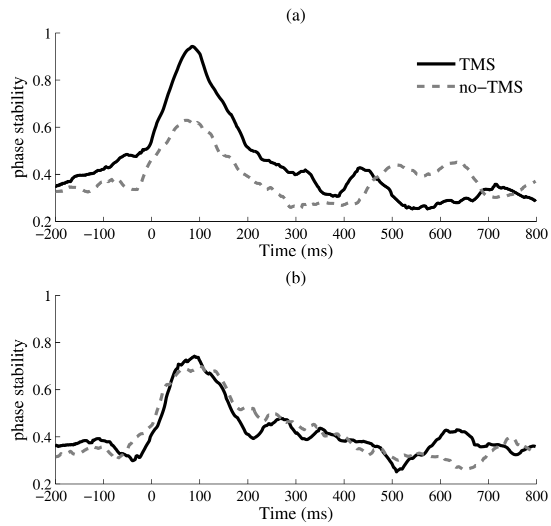

Fig. 2. Normalized averaged phase stability in the attention scheme for $s = 40$ as example. (a) first sweeps and (b) third sweeps. Note: solid line represents data with TMS and dash line denotes data without TMS.

Fig. 3 illustrates an overview of the most discriminant feature of ALRs in the range of the N1 wave with and without TMS in the attention scheme for all of the subjects. It shows that the feature of most subjects can be separated very well using this technique even though two of them give only small differences. The feature is selected comprehensively so that only the most discriminant feature is extracted from the signals.

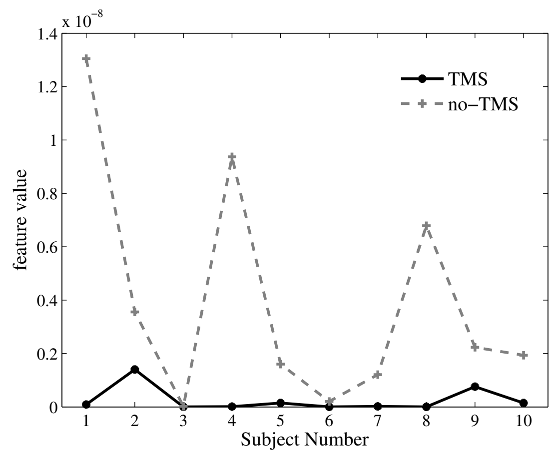

Fig. 3. The most discriminant feature of attended ALRs in the range of the N1 wave with and without TMS for all of the subjects.

We suggest that the increase of phase stability in attention scheme is due to the phase reset processes induced by magnetic stimulation. The results shown are quite surprising and exciting that the effects of even a single pulse TMS could last for reasonably long (i.e., after 1 second of the stimulation) and have not been reported elsewhere. Meanwhile, the no–change of the amplitude of the N1 wave with magnetic stimulation could be explained to reflect an inhibitory processes [33]. Besides that, it has been suggested that rTMS can suppress cognitive activities, showing an inhibitory effect on neurophysiological processes (i.e., amplitude of the N1 wave is decreased after rTMS) [18]. We propose that the similar effect could also apply to sTMS. Anyway, we have to take note that all the studies before are dealing with the responses immediately after the stimulation which is not the same case in our study. In addition, we speculate that the magnetic stimulation (sTMS in our study) could induce effects on thalamocortical system for neural correlates of auditory attention [34], [35].

IV. CONCLUSION AND FUTURE WORK

We have presented a study on the effects of sTMS in auditory attention by examining the ALRs with a phase stability measure and an adaptive shift–invariant feature extraction method. Results support the fact that sTMS might activates an involvement of the corticothalamic feedback loops for neural correlates of auditory attention. It is concluded that sTMS might modulate the level of attention and its influence can last rather long, at least when considering the large–scale neural correlates of attention in ALR sequences. Since the ERP has an important relationship with EEG, one of the interesting topics in the future could be the assessment of TMS induced cortical oscillations.

V. ACKNOWLEDGMENT

This work has been supported by the Universiti Teknikal Malaysia Melaka, the Faculty of Biomedical Engineering and Health Science at Universiti Technologi Malaysia and the German Federal Ministry of Education and Research (BMBF), Grant FZ:17N1208. Additionally, the authors would like to thank Louise Castra for supporting the data acquisition.

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