Effect of Phase-Locked Transcranial Alternating Current Stimulation on Vocal tremor

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Abstract— **Vocal tremor can be found in 30% of patients with essential tremor, causing significant communication difficulties. To develop more efficient and safer treatments with less side effects for vocal tremor, this study investigated the potential of transcranial alternating current stimulation (tACS) that is temporally synchronized with tremor envelope. Three female patients with vocal tremor received tACS over the cerebellum during their phonation. Patients received phase-locked stimulation of both in-phase and out-phase with respect to the tremor, and the changes in voice characteristics was evaluated. The results showed that out-phase stimulation significantly reduced tremor amplitude intensity (AtrI). After the treatment, the patients' subjective ease of phonation improved. These findings suggest that tACS, especially out-phase stimulation, can be an effective treatment for vocal tremor and warrants further study.**

I. Introduction

Vocal tremor refers to the tremor occurring in the muscles of the larynx, vocal tract, and other vocal organs, characterized by rhythmic movements causing pitch perturbation and amplitude perturbation of the voice in the range of 4-8 Hz. Among patients with essential tremor, a condition where tremors occur without underlying diseases such as stroke or Parkinson's disease[1], 30% of them experience this symptom [2]. The trembling of the voice leads to significant communication difficulties for patients, affecting their social life. Traditional treatments, such as voice therapy and pharmacotherapy, have certain symptom-relieving effects but are limited by insufficient efficacy or high risk of side effects, emphasizing the necessity for developing new treatment methods [3-5].

Recently, electrical stimulation therapy has gained attention as an innovative treatment for brain dysfunction and neurological disorders. Among these, transcranial alternating current stimulation (tACS) has shown potential as a non-invasive neural modulation technique for treating neurological diseases [6-10]. By applying weak alternating currents through electrodes placed on the scalp, tACS modulates neuronal activity and influences related neural network functions. Its unique advantage lies in the ability to adjust the frequency and intensity of stimulation in a non-invasive manner, allowing flexible intervention in neural activity [11]. Recent reports suggest that tACS, by stimulating the cerebellum, the central pattern generator, could potentially reduce upper limb tremor symptoms in the treatment of essential tremor[12]. Therefore, tACS holds great potential for a treatment option of vocal tremor.

Previous studies have used accelerometers attached to the affected limb to extract tremor frequency and phase. Sinusoidal current phase or at some phase difference with respect to the limb movement, was applied to the cerebellum [12-14]. When a sinusoidal tACS is applied at the same frequency as the patient's tremor, the tremor is entrained by the stimulus, maintaining a constant phase difference. This phase difference varies from patient to patient and is referred to as the entrainment phase. Studies have also reported that phase-locked stimulation using the entrainment phase as the phase difference suppresses tremor amplitude [13]. Based on these previous studies on the treatment effect of tACS on motor tremor, we investigated the feasibility of tACS for the treatment of vocal tremor. analysis has been used to aid in the evaluation of vocal tremor focuses primarily on two aspects: frequency and amplitude. For example, studies on PD have found that the amplitude tremor intensity index (ATrI) is significantly higher in the PD group than in the control group [15]. Another study in essential tremor have shown that both ATrI and frequency tremor intensity index (FTrI) are significantly increased in patients [16]. Based on these studies, we used ATrI and FTrI from previous research as indices to assess tremor by comparing the intensity of vocal tremor before and after treatment. Using this approach, we investigated the potential of transcranial alternating current stimulation (tACS) for the treatment of vocal tremor.

II. METHOD

A. Participant

An experiment was conducted on three female patients with vocal tremor at Kobe City Medical Center General Hospital (Table 1). The study was approved by the Certified Review Board of Kyoto University, and Kobe City Medical Center General Hospital was registered as a collaborating research facility for this specified clinical research. Written informed consent was obtained from all participants, and the experimental procedures were conducted in accordance with the ethical guidelines approved by the Ethics Committee of the Certified Review Board of Kyoto University (approval number: jRCTs052210211). This study was also registered in the Japan Registry of Clinical Trials (jRCT ID: jRCTs052210211).

B. Vowel Selection

Previous research by Nieuwhof et al. discussed the amplitude uniformity of tremor patterns in the upper limbs and the efficacy of tACS stimulation, indicating that tACS treatment is more effective for non-jerky sinusoidal tremor patterns than for jerky tremor patterns [6]. Therefore, patients were first asked to pronounce the Japanese vowels "/a/", "/i/", "/u/", "/e/", and "/o/" to determine the vowel whose tremor sound envelope was closest to a sinusoidal wave. The selected vowel was then used consistently during the experiment. The vowels used by each patient are listed in Table 2.

An anode was placed on the cerebellum on the same side as the affected limb tremor, and a cathode was placed on the shoulder of the opposite side. The anode electrode was centered over the midpoint between the inion and the mastoid process [17-19]. The peak-to-peak amplitude of the tACS was -1.5 to +1.5 mA. The stimulation frequency used ranged between 4 and 6 Hz, matching the frequency of the patient's vocal tremor. Fig. 1 shows the electrode placement on the patient.

C. Electrode Arrangement and Stimulation

Fig. 2 shows a schematic representation of the experimental system. A microphone and the amplifier recorded the voice of the patient. The voice signal was captured and analyzed in real-time by an in-house developed MATLAB Simulink program to generate stimulation waveforms. The generated stimulation waveform was sent to the tACS stimulation device (DC-STIMULATOR PLUS, neuroConn, Ilmenau, Germany) as an analog voltage waveform via an I/O terminal board (MF634 and TB621, HUMUSOFT, Prague, Czech Republic). The stimulation voltage waveform was modulated to the current signal with the external input function of the tACS stimulation device, which was provided to the patient.

The analog input signal at the amplifier output and the analog input signal to the tACS device were recorded with an oscilloscope and used to investigate the relationship between the voice signal and the tACS signal. The sampling frequency in the oscilloscope and the MATLAB Simulink program was 10000 Hz and 11025 Hz, respectively. The data recorded by the oscilloscope were used to analyze the phase difference between the stimulus waveform and the tremor envelope. The voice data were also recorded as wave files in the Simulink program, which were used to determine ATrI and FTrI.

Table 1. Participant demographic information

Patient	Age (year)	Sex	Diagnosis	Affect-ed Side	VHI -10
1	80	F	Vocal tremor	Left	25
2	74	F	Vocal tremor	Left	66
3	73	F	Vocal tremor	Left	23

VHI-10: Voice Handicap Index-10

Table 2. Vowels used by each patient

Patient	Vowel
Patient 1	/u/
Patient 2	/a/
Patient 3	/o/

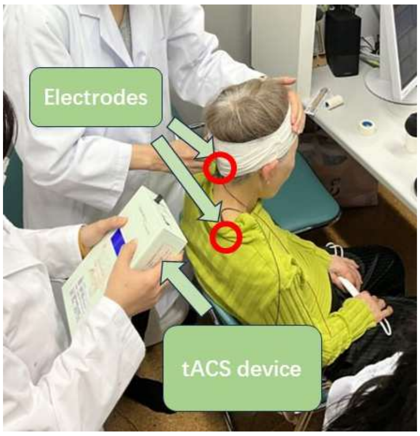


Fig. 1. Preparation of tACS electrodes with a patient

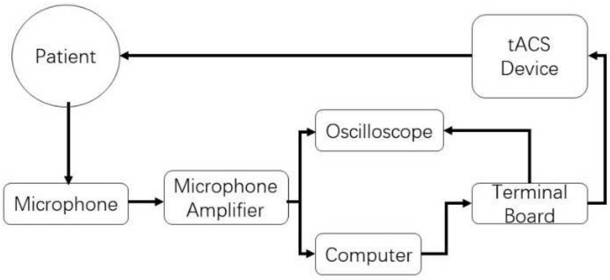


Fig. 2. Overview of the experimental system.

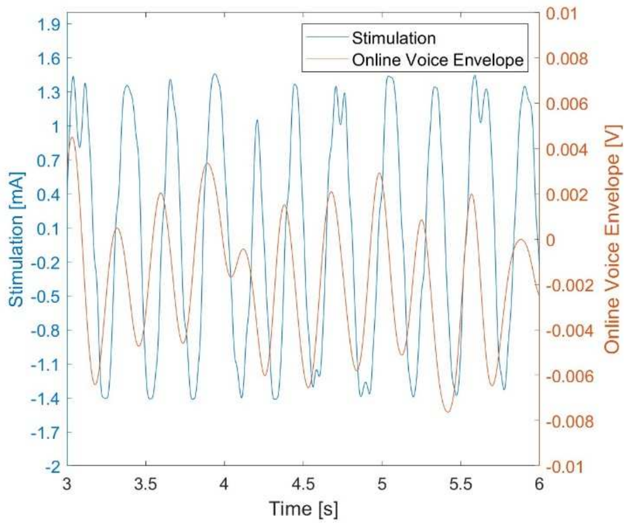
The oscilloscope simultaneously recorded the voice signal from the amplifier and the tACS waveform.

D. *Experimental Protocol*

The experiment consisted of a single session of an entrainment experiment and two sessions of a phase-locked stimulation experiment. Entrainment experiments were conducted to determine individual entrainment phase and phase-locked stimulation experiments were conducted to determine whether entrainment phase in-phase or entrainment out-phase stimulation was more effective. The entrainment experiment session was conducted with two pre-tACS non-stimulation voice measurements, three voice measurements under non-phase-synchronized tACS, and two post-tACS non-stimulation voice measurements. The inherent frequency of the patient's vocal tremor was calculated from the first two voice measurements. In the entrainment experiments, we applied a sinusoidal stimulus to the patients that was not phase-locked but had the same frequency as their voice amplitude tremor. The entrainment phase was determined by calculating the phase difference between the envelope of the sound waveform and the tACS stimulus waveform at its peak using the Hilbert transform. The phase differences were determined for each cycle of the tACS stimulus and presented in a histogram.

The phase-locked experiment consisted of in-phase and out-phase stimulation sessions. Each session consisted of three voice measurements under phase-synchronized alternating current stimulations, followed by two non-stimulation voice measurements. For the in-phase stimulation, the phase deviation between the stimulation waveform and the patient's voice envelope was maintained at the entrainment phase. For the out-phase stimulation, the phase deviation between the stimulation waveform and the patient's voice envelope was maintained at the antiphase of the entrainment phase (i.e. phase shift of π from the entrainment phase). The order of in-phase and out-phase stimulations was randomized. Fig. 3(a) shows an example of the entrainment phase in-phase stimulation waveform and the voice envelope. Fig. 3(b) shows a histogram of the phase difference between the envelope of the patient's voice and the stimulation waveform, calculated by the Hilbert transform. The horizontal axis represents the phase difference, and the vertical axis represents the frequency of occurrence of that phase difference. Fig. 3(b) indicates that in this task, the actual phase difference between the envelope and the stimulation waveform is close to the target phase difference.

(a)



(b)

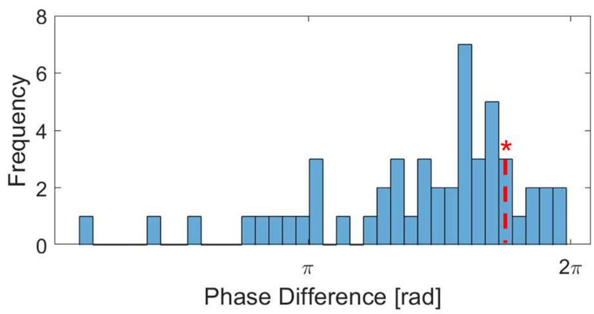


Fig. 3. Example of entrainment phase in-phase stimulation experiment.

(a) Voice envelope and the corresponding tACS waveform. In this example, the entrainment phase was set to 5.45 rad. (b) Histogram of the phase difference between the voice envelope and the stimulation waveform recorded in this experiment (results from single measurement). *:5.45 rad.

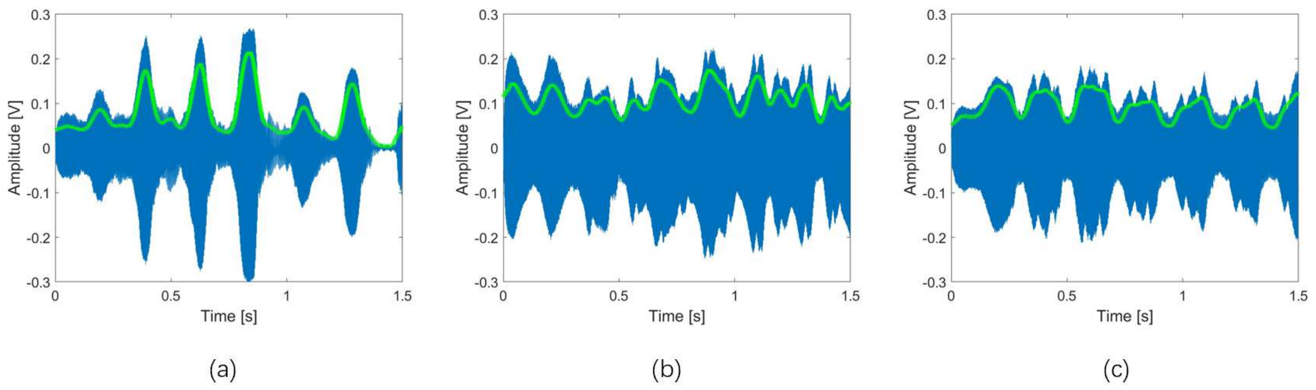


Fig. 4. tACS-related changes in patient voice characteristics. Figures show patient voice and its envelope waveforms (blue and green lines, respectively). Results from patient 1 is presented. (a) Before treatment. (b) After treatment with in-phase tACS. (c) After treatment with out-phase tACS.

E. Voice Signal Analysis

The initial 1.5 seconds of the voice waveform and its envelope were extracted to qualitatively observe the changes in voice amplitude. This duration was chosen based on the longest continuous voice period among all patients. To evaluate tremor changes, the FTrI and ATrI were calculated using the tremor2.06 algorithm of the voice processing program Prrat [20-21]. The definition of FTrI and ATrI is shown in Equation (1). The peaks and troughs of the voice envelope waveform were identified and set as maxima and minima, respectively, with the number of maxima and minima represented as *m* and *n*, respectively.

$$(\mathrm{F,A})\mathrm{TrI} = \left(\frac{\sum_{i=0}^{m} |max_i|}{m} + \frac{\sum_{j=0}^{n} |min_j|}{n} \right) \div 2 \qquad (1)$$

ATrI represents the vibration amplitude of the power value at the tremor frequency, indicating the intensity of the amplitude tremor. Thus, a higher ATrI indicates a greater amplitude tremor. FTrI indicates the intensity of changes in the tremor frequency, with a higher FTrI indicating greater variability in tremor frequency.

For patients from whom data could be obtained, subjective ratings of ease of voice production on a scale of 0-100 were obtained both before the intervention on arrival and after stimulation. On this scale, 0 represents the most difficult voice production, while 100 represents no difficulty at all.

III. Results

A. tACS-derived Changes in Voice Envelope Waveforms

Figure 4 shows the voice envelope of a representative patient (patient 1) measured on arrival and after in-phase and out-phase tACS treatment. In the pre-treatment state (Fig. 4a), a vocal tremor is evident, as indicated by the strong oscillations in the envelope waveform. In contrast, the post-treatment state shows a significant reduction in the amplitude of these oscillations (Fig. 4bc), indicating an improvement in the vocal tremor. Both in-phase and out-phase stimulation resulted in a comparative improvement in vocal tremor for this patient. While the responsiveness varied among patients, the amplitude variations of the voice envelope waveform were generally suppressed, and the envelope of the voice waveform became flatter after both in-phase and out-phase entrainment stimulation.

B. FTrI and ATrI

Figures 5 and 6 show the results of the voice signal analysis. The FTrI decreased in two out of three patients with both in-phase and anti-phase stimulation compared to the pre-stimulation state, although no significant changes were obtained across all patients. The ATrI decreased significantly after the out-phase stimulation compared to the pre-stimulation state (paired t-test, $p < 0.05$).

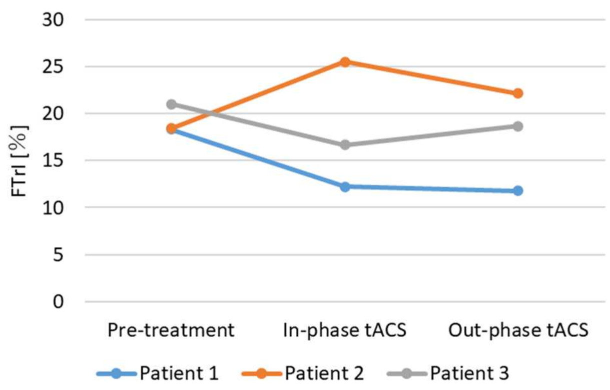


Fig. 5. FTrI changes before treatment, after in-phase stimulation, and after out-phase stimulation treatments.

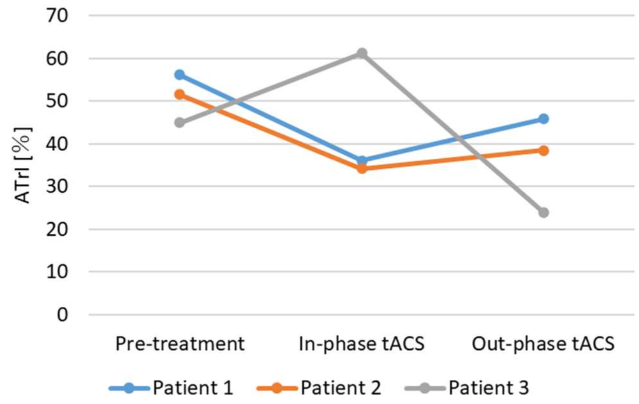


Fig. 6. ATrI changes before treatment, after in-phase stimulation, and after out-phase stimulation treatments.

C. Questionnaire

Subjective ratings for ease of voice production were obtained from patients 1 and 3 (Table 3). Both patients showed improvement in voice production after tACS treatment.

Table 3. Ease of voice production (scale of 100)

Patient	**Before treatment**	**After in-phase stimulation**	**After out-phase stimulation**
Patient1	25	60	Not available
Patient3	30	40	35-45

IV. Discussion

The current results demonstrated he potential of tACS as a treatment option for vocal tremor patients. We investigated the effect of both in-phase and out-phase stimulations to explore the effective treatment protocol. Although previous tACS research on patients with hand tremors showed clinical effectiveness of in-phase stimulation [12,14], statistically significant improvements in the vocal tremor amplitude were found in the out-phase stimulation. This difference may be related to the relationship between the site of the tremor and the cerebellum. For upper limb tremors, stimulation is applied to the cerebellum on the same side as the affected limb, but for vocal tremors, the relationship with the left and right cerebellum is not yet clear. Furthermore, the decrease in ATrI with in-phase stimulation is larger in patients 1 and 2, besides patient 3, indicating that the optimal phase might vary depending on the pathological condition of the patients. A similar tendency was observed in the FTrI, two out of three patients showed improved frequency tremor, but the other one showed its exaggeration regardless of the phase of stimulation. Further studies should measure both cerebellums and increase the number of patients to evaluate the therapeutic effect.

To date, the etiology of essential tremor is not clearly understood. However, a number of studies have shown that essential tremor is closely related to the central motor network that controls voluntary movements and the associated neural network, with the olivocerebellar-thalamic pathway playing an important role within this network [22]. Schnitzler et al. reported that in patients with essential upper limb tremor, upper limb tremor activity recorded by electromyography showed coherence with the electrophysiological activity of the primary motor cortex, possibly involving associated neural pathways of the primary motor cortex, thalamus, premotor cortex, cerebellum, and brainstem [23]. Therefore, the reason for the changes in tremor amplitude and frequency due to the application of tACS to the cerebellum may be due to the disruption of the coherence between cerebellar and skeletal muscle activities via the central motor network caused by the electrical stimulation.

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