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A Novel Synchronized Stimulation Method to Improve the Tactile Localization Ability of Post-Stroke Patients

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ABSTRACT

Introduction: Transcranial electrical stimulation (tES) has shown promise in enhancing post-stroke patients' neural plasticity and functional abilities. However, determining the optimal protocol for this method remains an open question. Our study proposes a novel approach: synchronized stimulation that combines mechanical and electrical stimuli. We hypothesize that this approach will enhance tactile localization ability in post-stroke patients.

Methods: We recruited a total of 23 patients and conducted four different types of experiments involving periodic mechanical stimulation on their fingertips. The primary objective was to assess the participant's ability to localize the location of the mechanical stimulation accurately. In one experiment, only mechanical stimulation was administered. Electrical stimulations were combined with mechanical stimulation in the remaining three experiments. The electrical stimulations comprised of one of the following protocols: (1) (tES) pulses administered solely for the initial five seconds of the session, (2) continuous (tES) pulses throughout the entire duration of the mechanical stimulation, and (3) (tES) pulses synchronized precisely with the timing of the mechanical stimulation.

Results: A noteworthy enhancement in tactile localization ability was observed when the electrical and mechanical stimulations were synchronized. Conclusion: Our findings demonstrate that the integration of electrical brain stimulation with simultaneous mechanical stimulation of the fingertips resulted in enhanced neural activities. This synchronized integration holds the potential to improve perception and may serve as a vital approach in the treatment of post-stroke patients.

Keywords: Stimulation, (tES), Tactile Localization, Synchronization, Post-Stroke Patients.

INTRODUCTION

Patients who have suffered a stroke often experience a range of impairments that severely affect their day-to-day functioning (1). Among the challenges faced by post-stroke individuals are unilateral motor weakness, limb hemiparesis, spasticity, and coordination difficulties, which lead to a significant decline in motor abilities (1). Restoring motor function following a stroke is a complex task due to pathophysiological and clinical factors (2). Different types of treatment are suggested for post-stroke rehabilitation. Physical therapy is commonly used and has been shown to improve brain plasticity. Physical factor therapy is another mean of rehabilitation in these patients which is done by using a stimulation (8-10**) Various forms of stimulation, including electrical stimulation, have emerged as effective approaches in post-stroke rehabilitation (3,4). Electrical stimulation techniques, such as neuromodulator non-invasive brain stimulation (NIBS) with transcranial electrical stimulation (tES), have gained attention as experimental therapies for promoting motor recovery after a stroke (5).

Noninvasive brain stimulation (NIBS) is a neuromodulatory technology that focuses on the local cerebral cortex. This technique regulates the neural excitability of neurons which results in improved clinical functions (NIBS1). As this method has become more popular, multiple clinical research studies have been conducted (NIBS1, 18,19**), but due to the low number of participants, it’s not yet standardized as a single treatment method. As this method has recently gained attention, studies are trying to achieve the best possible technique for using NIBS (NIBS1).

As said above, NIBS has been applied clinically in various forms. These include repetitive transcranial magnetic stimulation (rTMS), and transcranial electrical stimulation (tES) (NIBS1). The application of tES in post-stroke motor recovery was introduced in 2005 and has since been widely utilized (6, 7, and 8). Recent advancements, such as the closed-loop EEG-tES method, have shown promising applications in this field (9). Furthermore, novel approaches like multichannel network-based tES, particularly employing a 5-channel tES scheme, have demonstrated improved efficacy in healthy subjects, suggesting potential benefits for future stroke rehabilitation cases (10).

In addition to motor deficits, post-stroke patients often experience impairments in their tactile abilities, including reduced touch detection and localization. Some individuals with focal brain lesions may exhibit tactile detection capability, but they struggle with accurately localizing tactile stimuli on the skin surface. The process of perceiving the location of touch involves intricate neural mechanisms. When an object is touched, signals from touch receptors and proprioceptors in the muscles are transmitted via neurons to the dorsal horn of the spinal cord. From there, the signals are relayed through the spinal cord to reach the thalamus and subsequently the primary somatosensory cortex (S1 region) (11, 12). Recent studies propose that conscious detection plays a crucial role in the localization of tactile stimuli (13), although there are contrasting findings (14, 15, 16), and the underlying mechanism of tactile localization remains poorly understood.

The idea of combination therapy using NIBS with other forms of therapy is clinically being pursued and studied. This research focuses on enhancing the localization ability of stroke patients, as poor tactile abilities are commonly addressed through mechanical stimulation in the form of physical therapy. However, electrical stimulation has also demonstrated effectiveness in improving tactile function in post-stroke cases. Recently, simultaneous mechanical and electrical stimulation has gained attention as a potential intervention for stroke patients (17). Abdullahi, et al. 2023 showed the superiority of using NIBS alongside constraint-induced movement therapy (CIMT) (combination CIMT). Previous studies have reported noticeable improvements in the motor abilities of stroke patients when electrical stimulation is synchronized with rehabilitation movement frequency (17, 18). In this study, we applied simultaneous mechanical and electrical stimulations to a group of stroke patients and observed a significant improvement in their tactile localization performance. Furthermore, we hypothesized that synchronizing these two types of stimulations would yield even greater effectiveness. To validate this hypothesis, we compared the localization abilities of patients across different experimental conditions. The experiment involving synchronized stimulation showed a remarkable enhancement in tactile ability compared to the other experimental setups.

METHODS

Participants

This study involved the participation of 23 patients who had experienced a stroke within the past 2 to 6 months and were between the ages of 25 and 75. Ethical approval was obtained from the Iran Medical Ethics Committee, and all patients provided informed consent to be part of the study. All participants exhibited a low level of tactile localization ability in either the right or left half of their bodies, to the extent that they had difficulty localizing any mechanical stimulation applied to their fingertips on the affected body side. However, they were capable of detecting the presence of these stimulations. The patients also agreed not to receive any medication or physical therapy during the experiment.

Experimental protocol, Intervention

The experimental protocol consisted of four experiments conducted on a group of 23 patients, with each experiment performed within a 24-hour time frame. We've used the Omini tES device in a controlled environment with present medical staff. Patients were told safety regards and cautions. Our rubber electrodes were 5 × 5 cm in diameter. For those patients experiencing a deficiency in the right half of the body (left hemisphere injury), the cathode was placed to S1-right, and the anodal was connected to S1-right. For patients with deficiency in the left half of the body (right hemisphere injury), the electrodes were connected in a reverse manner.

In the first experiment, referred to as the tES stimulation, the group received tES pulses (9). A 2.5mA current was applied during the whole test time, simultaneously with intensive mechanical stimulations applied to their fingertips (experiment 1 in Figure 1). To perform the mechanical stimulation, each finger was stimulated with a needle on the tip of the fingers of their hands. Each finger was stimulated approximately 10 times within a 5-second interval, and a time interval of 20 seconds was considered between the stimulations. During these 20-second intervals, the patients were instructed to localize the preceding stimulation (say the name of the stimulated finger), and the responses of subjects were recorded. The trial was considered correct if the subject referred to the name of the stimulated finger. Otherwise, the trial was considered as a wrong trial. Each individual received a total of 50 mechanical stimulations, with the sequence of fingertip stimulations selected randomly from a uniform distribution for each trial. The performance of each patient was measured by the percentage of correct trials that is summation of correct trials divided by all trial numbers. This index is considered the correct localization (CL).

In the second experiment, the same mechanical stimulations were applied without any tES stimulation, and the results were recorded. This experiment served as the control condition and was referred to as the No- tES stimulation (experiment 2 in Figure 1).

In the third experiment, similar to the first, tES-sham stimulation was applied with a 2.5mA electrical current for only a duration of 5 seconds, (experiment 3 in Figure 1).

Finally, in the fourth experiment, the same protocol as the first experiment was followed, with the only difference being that the 2.5mA current was applied only during the application of physical stimulation. The electrical current was disconnected between each set of two mechanical stimulations, thereby synchronizing the electrical stimulation with the mechanical stimulation (experiment 4 in Figure 1). This experimental setup was referred to as tES-sync stimulation.

The subjects were completely blind to the types of stimulations being administered.

Statistical analysis

All experiments were conducted on each participant, resulting in paired data for analysis. To investigate the impact of electrical stimulation on the ability of patients to correct localization, the effect was compared across four groups: No-tES, tES-sham, tES, and tES-sync. We used the CL measurement to quantify the ability of subjects in tactile localization of their hands' fingers. In order to demonstrate that the effect of tES-sync was superior to the other stimulations, pairwise comparisons were performed between the four groups using Wilcoxon signed-rank tests. The correct localization (CL) distributions were found to pass the normality test, indicating that normal distributions could be assumed for CL values in different experiments.

To examine potential differences in the mean of CL responses among the different experiments, a repeated measure analysis of variance (ANOVA) was conducted. Post-hoc analysis with Bonferroni correction was applied to compare the means of CL values between different experiments in pairwise comparisons (19). All statistical analyses were performed using MATLAB version 2021 and SPSS software version 22.0.

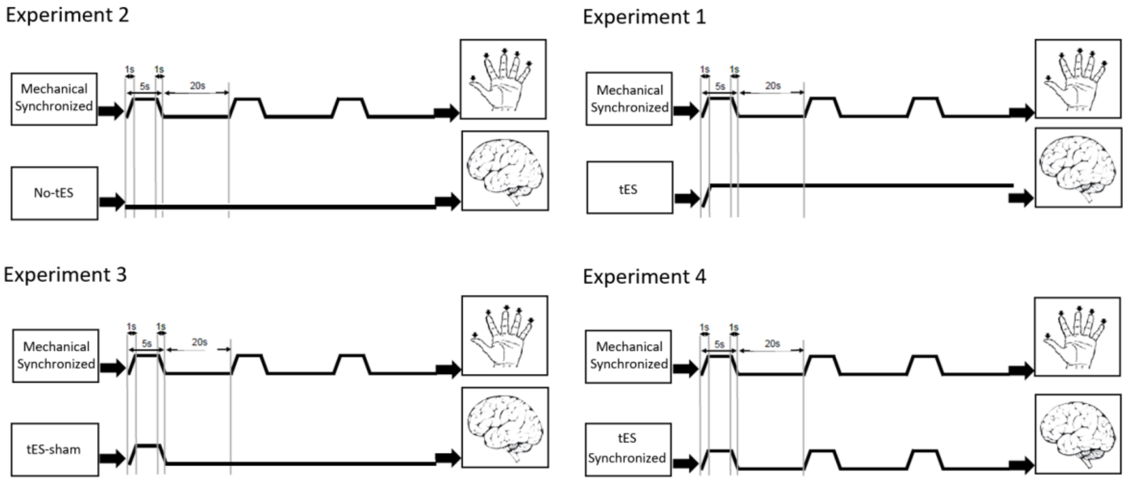

Figure 1. Different types of the applied stimulations. Only mechanical stimulation was applied in the first experiment. In the second experiment, a sham electrical stimulation was applied besides the mechanical stimulation. In the third experiment, a steady electrical stimulation was applied besides the mechanical stimulation. In the last experiment, an electrical stimulation was applied in a synchronized manner with the mechanical stimulation.

RESULTS

To evaluate the impact of the proposed stimulation method on improving tactile localization ability in patients, we measured the percentage of correct localization (CL) in each experiment. All CL distributions passed the normality test (Kolmogorov–Smirnov test, P No-tES=0.200, P tES-sham=0.200, P tES=0.144, P tES-sync=0.160). To assess the differences in localization abilities among the four experiments, a repeated measure ANOVA model was employed (9). The results revealed a significant difference among the different stimulation schemes (RMANOVA, F (3, 66) = 22.408, P<0.001). Further analysis using repeated measures ANOVA with Greenhouse-Geisser correction also showed a statistically significant difference in the mean of CL between the four experiments.

Further post-hoc analyses were conducted to investigate the effect of different kinds of stimulation conditions. We compared the CL distributions among pairs of different stimulation schemes considering a Bonferroni correction. The average CL without any electrical stimulation was approximately 25% (mean±SEM, 0.257±0.033, Figure 2 & Table 1). Similarly, the CL in the tES-sham stimulation was around 24% (mean±SEM, 0.240±0.034, Figure 2 & Table 1). There was no significant difference in CL between tES-sham and No- tES stimulations (mean±SEM, ΔCL No-tES & tES-sham=0.017±0.011, Wilcoxon signed-rank test, P No-tES & tES-sham=0.855, Figure 3F).

Table 1. The mean, standard error of the mean, and 95% confidence interval of CL in four experiments.

Group name	Mean	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
No-tES	0.257	0.033	0.188	0.327
tES-sham	0.240	0.034	0.171	0.310
tES	0.265	0.032	0.199	0.332
tES-sync	0.365	0.030	0.303	0.428

Table 2. The mean differences, standard errors of mean differences of CL between each pair of experiments, P-value based on Bonferroni correction, and 95% confidence interval for differences. The significant p-values are shown by boldface numbers. (*. The mean difference is significant at the .05 level)

Type of stimulations		Mean Difference	Std. Error	P-value	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
No-tES	tES-sham	0.017	0.011	0.855	-0.015	0.048
	tES	-0.008	0.010	1.000	-0.036	0.021
	tES-sync	-0.108*	0.022	**0.000**	-0.171	-0.044
tES-sham	No-tES	-0.017	0.011	0.855	-0.048	0.015
	tES	-0.024	0.012	0.306	-0.059	0.010
	tES-sync	-0.124*	0.022	**0.000**	-0.190	-0.059
tES	No-tES	0.008	0.010	1.000	-0.021	0.036
	tES-sham	0.024	0.012	0.306	-0.010	0.059
	tES-sync	-0.100*	0.019	**0.000**	-0.155	-0.045
tES-sync	No-tES	0.108*	0.022	**0.000**	0.044	0.171
	tES-sham	0.124*	0.022	**0.000**	0.059	0.190
	tES	0.100*	0.019	**0.000**	0.045	0.155

The CL increased to 26% in the tES stimulation (mean±SEM, 0.265±0.032, Figure 2 & Table 1). Although there was a clear trend of improvement with tES, it did not reach significance compared to No-tES, but it was significantly higher than tES-sham stimulation (mean±SEM, ΔCL tES _No-tES=0.008±0.010, Wilcoxon signed-rank test, P tES_No-tES =1.000; mean±SEM, ΔCL tES_ tES-sham=0.024±0.012, Wilcoxon signed-rank test, P tES_ tES-sham=0.0306, Figure 3B&D).

The CL significantly increased to 36% in the tES-sync stimulation (mean±SEM, 0.365±0.030, Figure 2 & Table 1), representing a 44% increase compared to No-tES stimulation. There was a significant difference between CL in the tES-sync stimulation and both No-tES and tES-sham stimulations (mean±SEM, ΔCL tES-sync_Without-tES =0.108±0.022, Wilcoxon signed-rank test, P tES-sync_Without-tES=0.000; mean±SEM, ΔCL tES-sync_ tES-sham=0.124±0.022, Wilcoxon signed-rank test, P tES-sync_ tES-sham=0.000, Figure 3A&C). Additionally, the proposed stimulation method performed significantly better than tES alone (mean±SEM, ΔCL tES-sync_ tES=0.100±0.019, Wilcoxon signed-rank test, P tES-sync_ tES=0.000, Figure 3E). These results demonstrate the superior effectiveness of synchronized electrical and mechanical stimulations compared to other methods in enhancing tactile localization ability in post-stroke patients.

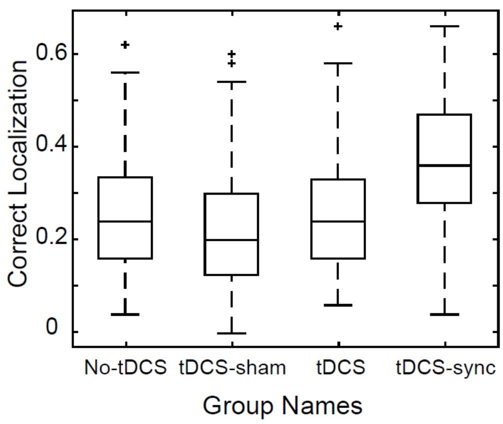

Figure 2- Statistical measurements of four experiments. The central lines indicate the median and the bottom and top edges of the boxes show the 25th and 75th percentiles, respectively.

DISCUSSION

Our findings provide valuable insights into the effectiveness of different stimulation methods in improving tactile localization ability in post-stroke patients. The results indicate that the application of a tES sham, which does not involve actual electrical stimulation, does not significantly impact the patients' localization ability. However, when a steady tES stimulation is applied, there is a noticeable increase in the patient's ability to localize physical stimulation, although the improvement is not statistically significant compared to the absence of electrical stimulation.

In contrast, the synchronized application of tES stimulation with mechanical stimulation significantly enhances tactile localization ability compared to steady tES stimulation alone. This enhancement is also observed when there is no electrical stimulation involved. These observations are based on the performance of the patients in the four experimental conditions.

It is worth noting that electrical stimulation slightly decreased the correct localization ability of patients, as evident from the comparison between tES-sham and No-tES experiments. However, this difference is not statistically significant. The slight decrease in performance could be attributed to the discomfort experienced by the patients due to the electrodes placed on their brains.

The marginally significant effect of steady electrical stimulation on tactile localization (P tES_ tES-sham=0.035, Figure 3E) highlights the potential of tES in modulating neural firing probabilities. Our results suggest that the failure in localizing touch stems from insufficient neural activity in the S1 area of the brain triggered by mechanical stimulation alone. In contrast, the electrical pulses generated by tES stimulate the brain area, increasing the probability of generating action potentials in response to mechanical stimulation and facilitating successful localization perception. However, due to the adaptation effect in the brain, the impact of steady tES on enhancing neural activity in response to mechanical stimulation is less pronounced compared to synchronized tES.

Overall, our study demonstrates that synchronized electrical and mechanical stimulation yields superior results in improving tactile localization ability in post-stroke patients. These findings highlight the potential of simultaneous stimulation methods in the treatment and rehabilitation of patients with impaired sensory perception.

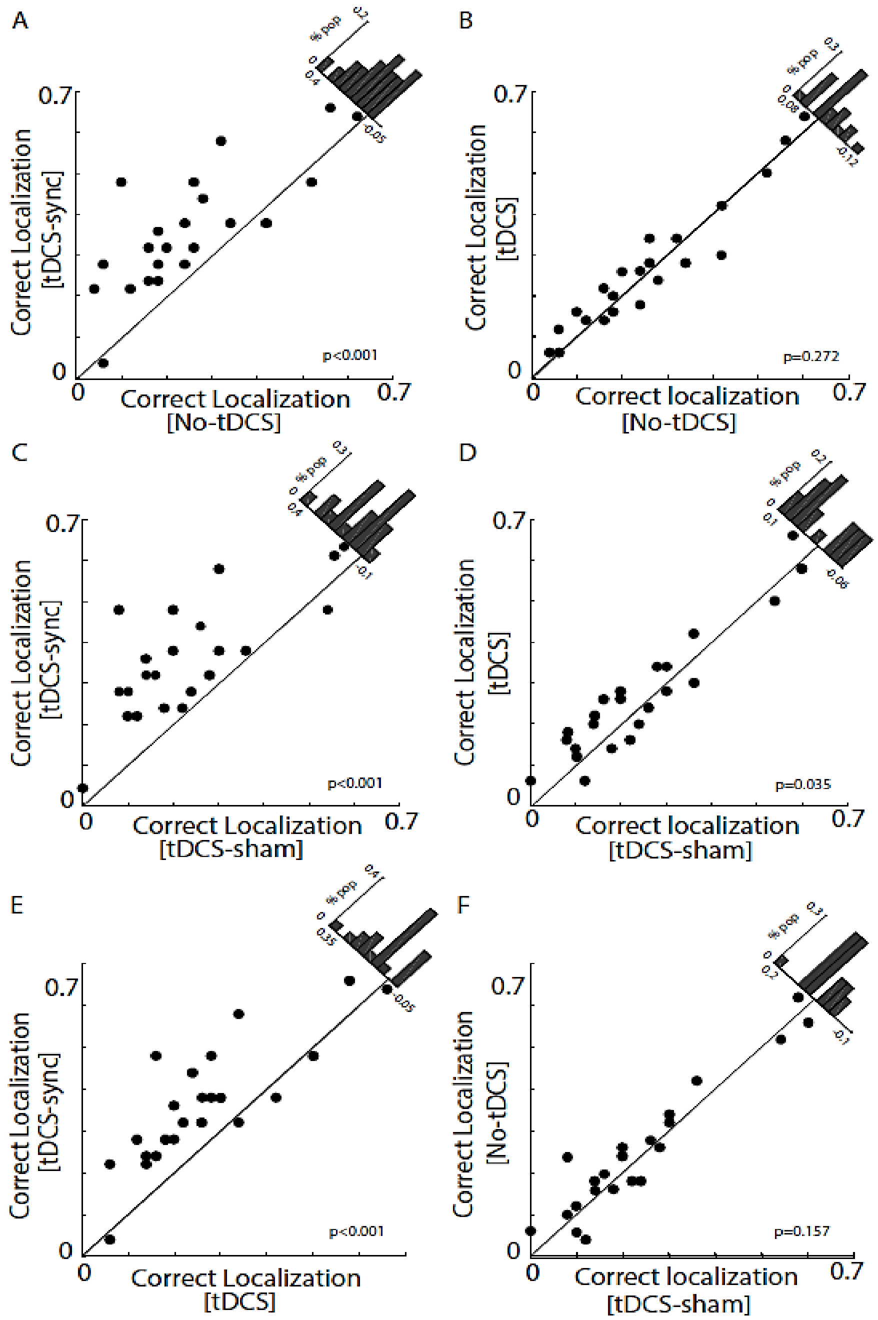

Figure 3_ CL is significantly increased by means of synchronized localization. A) Scatter plot of CL values for No- tES experiments vs. tES-sync experiment. B) Scatter plot of CL values for No-tES experiments vs. tES experiment. C) Scatter plot of CL values for No-sham experiments vs. tES-sync experiment. D) Scatter plot of CL values for tES-sham experiments vs. tES experiment. E) Scatter plot of CL values for tES experiments vs. tES-sync experiment. F) Scatter plot of CL values for No-tES experiments vs. tES -sham.

CONCLUSION

In conclusion, our study introduces a novel treatment approach for enhancing the localization ability of post-stroke patients by synchronizing mechanical stimulation with tES stimulation of the somatosensory region. Building upon our previous findings that demonstrated the effectiveness of synchronizing AC stimulation with physical therapy in improving motor function in stroke patients, (16) we propose that synchronization can serve as a fundamental principle for enhancing various aspects of stroke patients' abilities.

Considering the neuroplasticity-altering effects of tES, (24, 25) we anticipate that the long-term treatment of stroke patients using this synchronized stimulation approach will yield promising results. Exploring the long-term effects and benefits of synchronized stimulation in stroke patients represents a compelling avenue for future research.

Overall, our findings offer valuable insights into the potential of synchronized stimulation as a novel treatment strategy to enhance the localization ability of post-stroke patients. Further investigations into the broader application of synchronization in stroke rehabilitation hold significant promise for improving patient outcomes and quality of life.

COMPETING INTERESTS

The authors declare that they have no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE CONSENT FOR PUBLICATION:

Ethics approval was obtained for this study, and all participants provided informed consent to participate. Additionally, consent for publication was obtained from the participants, ensuring their anonymity and confidentiality.

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Availability of data and materials

All datasets and materials utilized in this study are available upon request.

AUTHORS' CONTRIBUTIONS

All authors contributed to the conception and design of the study. Zahra Bahmani and Mohammad Rostami conducted the data collection and analysis. Maryam Ahmadi drafted the initial manuscript and all authors critically reviewed and edited the manuscript. All authors have read and approved the final version of the manuscript.

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