

Differential Amplitude of Low-Frequency Fluctuations in brain networks after BCI Training with and without tDCS in Stroke

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Abstract— Mapping the brain alterations post stroke and post intervention is important for rehabilitation therapy development. Previous work has shown changes in functional connectivity based on resting-state fMRI, structural connectivity derived from diffusion MRI and perfusion as a result of brain-computer interface-assisted motor imagery (MI-BCI) and transcranial direct current stimulation (tDCS) in upper-limb stroke rehabilitation. Besides functional connectivity, regional amplitude of local low-frequency fluctuations (ALFF) may provide complementary information on the underlying neural mechanism in disease. Yet, findings on spontaneous brain activity during resting-state in stroke patients after intervention are limited and inconsistent. Here, we sought to investigate the different brain alteration patterns induced by tDCS compared to MI-BCI for upper-limb rehabilitation in chronic stroke patients using resting-state fMRI-based ALFF method. Our results suggested that stroke patients have lower ALFF in the ipsilesional somatomotor network compared to controls at baseline. Increased ALFF at contralesional somatomotor network and alterations in higher-level cognitive networks such as the default mode network (DMN) and salience networks accompany motor recovery after intervention; though the MI-BCI alone group and MI-BCI combined with tDCS group exhibit differential patterns.

I. INTRODUCTION

More than half of the survived stroke patients age 65 and over suffer from reduced mobility [1]. Many new techniques have been utilized for post-stroke rehabilitation, such as robotics [2], brain-computer interface [3], non-invasive brain

stimulation [4], virtual reality [5], and wearable devices [6]. Motor Imagery has been proved to be beneficial for post-stroke rehabilitation in many studies [7]. It solved a critical problem for rehabilitation that it is difficult or even impossible for patients to move the stroke-impaired limb [8]. It provides a practical, accessible way to modulate activity in the motor network after stroke [9]. EEG-based BCI detects and uses a patient's neural signals as inputs to provide real-time feedback, effectively enabling users to modulate their brain activity [3, 10]. This is a promising therapy for patients with motor impairment, as they can control external devices such as computers and robots during rehabilitative tasks without relying on residual muscle control. Several studies have shown the functional benefits of BCI in motor recovery [11, 12]. By combining MI and BCI, the stroke-impaired limb of a patient can move driven by a robotic arm via neural signals from motor imagery of the arm [13]. It is a promising tool for improving motor recovery in stroke patients as it provides multisensory feedback and facilitates integration with motor learning [14].

Another promising technique for stroke rehabilitation is transcranial direct current stimulation (tDCS). TDCS is a non-invasive brain stimulation technique that uses constant, low direct current delivered via electrodes on the head [15]. TDCS has been shown effective on primary motor cortex [15, 16]. There are studies suggested that tDCS may improve the detection accuracy of motor imagery [17, 18]. Thus it is hypothesized that combining MI-BCI with tDCS may further improve the motor function recovery post stroke.

This study investigated the effect of MI-BCI and MI-BCI combined with tDCS from the perspective of spontaneous fluctuations in BOLD signals of resting-state fMRI. Amplitude of low-frequency fluctuation (ALFF) was measured as the activity of brain regions [19]. We hypothesized that stroke patient would have lower ALFF in the ipsilesional somatomotor network compared to controls at baseline. Increased ALFF both ipsilesional and contralesional somatomotor network and alterations in higher-level cognitive networks such as the default mode network (DMN) and salience network would accompany motor recovery after intervention; though the MI-BCI alone group and MI-BCI combined with tDCS group would exhibit differential patterns.

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II. METHODS

A. Ethics Statement

Ethics committee approval was obtained from the National Healthcare Group Domain Specific Review Board.

B. Subjects

19 stroke patients who had their first-ever subcortical stroke at least 9 months before recruitment (53.42 ± 10.38 yrs old, 14 males, 2 left-handed) and 11 age-matched healthy subjects (56.73 ± 4.47 yrs old, 6 males, all right-handed) were recruited for this study. Exclusion criteria included a history of seizures, major depression, and implants that may be triggered, moved, or heated by electrical current (eg, intracranial shunts, pacemakers, metal cranial implants).

C. Study Design

Figure 1 shows the timeline of the study. All healthy controls underwent two MRI scan sessions and all patients underwent three MRI scan sessions. 19 patients were randomized into two groups, respectively, tDCS group who received 20-minute tDCS prior to MI-BCI training and sham group who received sham-tDCS. Each MI-BCI training consisted of 160 trials and each trial last for 12 seconds. The subject was prepared with a visual cue for 2 seconds and the subjects will be instructed to perform motor imagery by another visual cue. A movement feedback was provided by the MIT-Manus robot if motor imagery was detected.

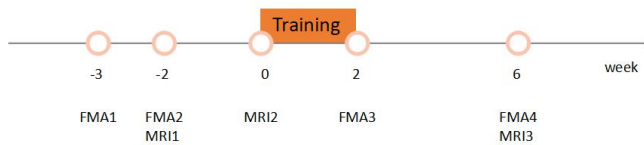


Figure 1 Timeline of the training, assessment of FMA and MRI

D. Motor Function Assessment

Motor function of the affected upper limb for stroke patients was evaluated by the upper extremity component of the Fugl-Meyer assessment (FMA). Each subject underwent four assessments according to the timeline in Figure 1. The two assessments before training (FMA1 and FMA2) were averaged as the pre-training score (baseline). The latter assessments (FMA3 and FMA4) were the post-training scores.

E. Image Acquisition

MRI data were collected using a 3T scanner (TIM Trio, Siemens, Germany) with a 32 channel head array coil. T1-weighted images were acquired with a magnetization prepared rapid gradient-echo (MPRAGE) sequence in the sagittal view with $T_I = 900$ ms, $T_R = 1900$ ms, $T_E = 2.5$ ms, and voxel size = 1mm isotropic. T2-weighted images were acquired with fluid-attenuated inversion recovery (FLAIR) sequence in the coronal view with $T_R = 9320$ ms, $T_E = 82$ ms, and voxel size = $0.9 \times 0.9 \times 3$ mm³.

7-minute block resting-state fMRI scan (240 volumes, 33 slices, voxels, $T_R = 1.725$ s, $T_E = 30$ ms, interleaved-ascending acquisition). During resting-state fMRI, subjects were required to remain awake and eye-closed.

F. Image Processing

Preprocessing was performed using FMRIB software library and AFNI. Standard preprocessing steps include segmentation, registration, and normalization to standard space. Especially, the images of patients with lesion in the right hemisphere were flipped over. Thus that the lesion appeared on the left side for all subjects. Preprocessing for resting-state fMRI include slice time correction, 3D motion correction, mean-based intensity normalization, spatial smoothing and temporal band-pass filtering between 0.009-0.01Hz.

Structural MRI data were visually checked for motion artifacts. Quality control (QC) criteria for resting-state fMRI data was set as the maximum 4mm movement. After quality control, 16 patients out of 19 passed the first scan session (MRI1). 18 patients passed the second scan session (MRI2). 16 patients passed the third scan session (MRI3). 9 healthy controls out of 11 passed the first scan session (MRI1) and 11 passed the second scan session (MRI2).

MRI2 of stroke patients were used as pre-training (baseline) and MRI3 were used as post-training. MRI2 of healthy control were used as the baseline.

G. Statistical Analysis

ALFF map of each subject was calculated individually using Dpabi Toolkit [20]. Group analysis was performed with regard to the healthy control group, patients group, sham group, and tDCS group. The whole-brain ALFF maps of 18 patients pre-training and 11 healthy controls were compared to investigate the brain alteration post stroke. Comparisons between pre-training and post-training were performed for tDCS and sham group separately. The effect of MI-BCI with and without tDCS were then investigated by group and time interaction. Results were reported at the height threshold of $p < 0.01$ and cluster-level of $p < 0.05$, GRF corrected.

III. RESULTS

The results of FMA showed significant improvement for both sham group and tDCS group (Figure 2). The analysis was performed based on the ground truth of effectiveness of training.

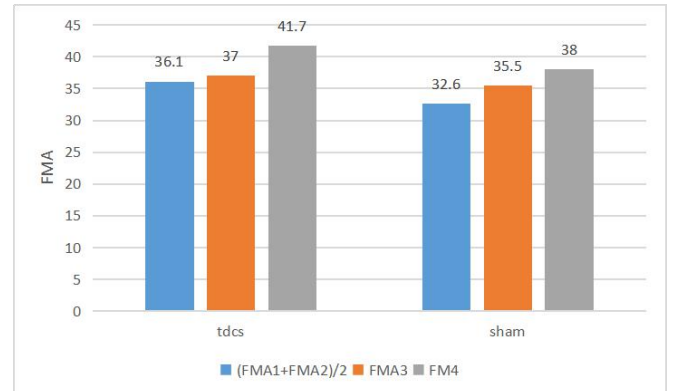


Figure 2 Both tDCS group and sham group gained an increase in FMA score after training

A. Patients vs Healthy Control

The whole-brain ALFF maps of 18 patients pre-training and 11 healthy controls were compared to investigate the brain alteration after stroke. Reduced ALFF was observed at the ipsilesional somatomotor network (Precentral_L, Postcentral_L, Paracentral_Lobule_L, and Supp_Motor_Area_L). Increased ALFF were observed at Default Mode Network (Posterior cingulate cortex, precuneus, angular gyrus, and part of the prefrontal cortex) and Saliience network (Insula).

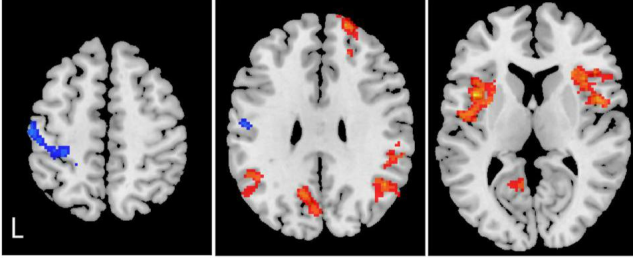


Figure 3 Reduced ALFF at ipsilesional somatomotor network and increased ALFF in the DMN and saliience network compared to healthy control

B. Pre-training vs Post-training

Comparison between pre-training and post-training was performed for tDCS group and sham group separately. Stroke patients with MI-BCI with and without tDCS had divergent ALFF changes after the intervention. For sham group, as shown in Figure 4 a), increased ALFF were observed at the contralesional somatomotor network (Precentral_R, Postcentral_R, Paracentral_Lobule_R, and Supp_Motor_Area_R). And reduced ALFF were observed at default mode network (Posterior cingulate cortex, precuneus, angular gyrus). For tDCS group, as shown in Figure 4 b), only reduced ALFF was observed at angular gyrus and part of temporal gyrus.

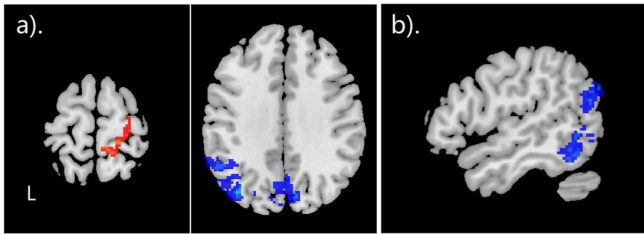


Figure 4 a). Increased ALFF in the contralesional somatomotor network and reduced ALFF in the DMN in sham group. (B) Decreased ALFF in the Angular gyrus and temporal gyrus in tDCS group.

C. tDCS group vs sham group

The effect of MI-BCI with and without tDCS were investigated by group and time interaction. Time interaction is similar to the results of pre-training and post-training in sham group. Increased ALFF were observed at contralesional somatomotor network (Precentral_R, Postcentral_R, Paracentral_Lobule_R and Supp_Motor_Area_R). And reduced ALFF were observed at default mode network (Posterior cingulate cortex, precuneus, angular gyrus). Group interaction indicated that the alteration of ALFF in tDCS group and sham group divergent at default mode network ((Posterior cingulate cortex, precuneus, and angular gyrus) and partially temporal gyrus).

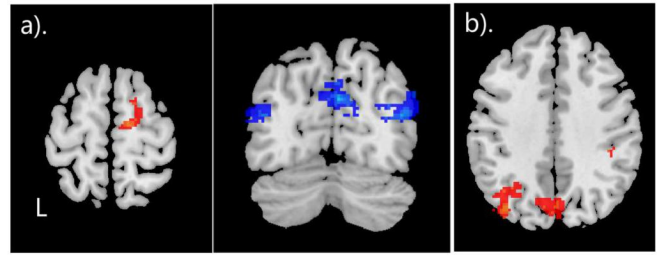


Figure 5 a). Increased ALFF in the contralesional somatomotor network and reduced ALFF in the DMN measured by time interaction. b). Group interaction at default mode network and partially temporal gyrus.

IV. DISCUSSION

A. Compensatory Motor Function

While the comparison between patients and healthy controls suggested decreased ALFF at the ipsilesional somatomotor network, comparisons between pre-training and post-training indicated improvement at the contralesional hemisphere. Reduced ALFF at the ipsilesional somatomotor network was observed in previous studies [21]. Increased ALFF was reported at some other regions after rehabilitation other than the contralesional somatomotor network. But compensatory motor function recovery was studied from the perspective of functional connectivity in both human and animal studies. Contralesional motor cortex will impact the motor function of the impaired limbs [22, 23]. Our results provide further evidence for compensatory motor function at the contralesional hemisphere.

B. Abnormal Cognitive Networks

Abnormal default mode network and saliience network were observed in stroke patients. The abnormal increase was reduced after training. Default mode network and saliience network are reported to be related to higher cognitive functions. Aberrant functional connectivity of default mode network and saliience network was reported at post-stroke depression, post-stroke memory loss, schizophrenia, and Parkinson's Disease [24, 25]. Our results provide evidence for correlation of motor function and higher cognitive functions.

C. Effect of tDCS

Although both tDCS group and sham group obtained an increase of motor function as assessed by the FMA scores, the interaction of ALFF is different. While the sham group gained improvements on affected regions observed in the comparison between patients and healthy control, tDCS group did not obtain significant improvements at corresponding regions. Supported the interaction map between tDCS group and sham group showed different interaction. The results indicate that tDCS has a different mechanism on stroke rehabilitation with MI-BCI, which is concordant with another study which investigated the effect of tDCS from the perspective of PET and DTI [26]. On the contrary to our study of sham group, a study of tDCS therapy

showed decreased ALFF at somatomotor network at ipsilesional hemisphere, which further indicates the different mechanism of MI-BCI only therapy and MI-BCI combined with tDCS therapy [27].

V. CONCLUSION

Our findings demonstrated MI-BCI with and without tDCS intervention exhibited different neuroplasticity mechanism in terms of spontaneous regional activity in stroke patients underlying comparable motor improvement. The effects of MI-BCI and tDCS were not additive but instead might be conflicting. Future work should study the relationship between brain changes and motor recovery for these two intervention strategies in a larger sample of stroke.

ACKNOWLEDGMENT

This study was supported by National Medical Research Council, Singapore, grant #NIG09MAY022 and intramural research program of the Singapore Bioimaging Consortium, A*STAR, Singapore. The analysis was carried out at NTU Institute for Health Technologies, Interdisciplinary Graduate School, Nanyang Technological University, Singapore.

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