Tailoring brain–machine interface rehabilitation training based on neural reorganization: towards personalized treatment for stroke patients

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Electroencephalogram (EEG)-based brain–machine interface (BMI) has the potential to enhance rehabilitation training efficiency, but it still remains elusive regarding how to design BMI training for heterogeneous stroke patients with varied neural reorganization. Here, we hypothesize that tailoring BMI training according to different patterns of neural reorganization can contribute to a personalized rehabilitation trajectory. Thirteen stroke patients were recruited in a 2-week personalized BMI training experiment. Clinical and behavioral measurements, as well as cortical and muscular activities, were assessed before and after training. Following treatment, significant improvements were found in motor function assessment. Three types of brain activation patterns were identified during BMI tasks, namely, bilateral widespread activation, ipsilesional focusing activation, and contralesional recruitment activation. Patients with either ipsilesional dominance or contralesional dominance can achieve recovery through personalized BMI training. Results indicate that personalized BMI training tends to connect the potentially reorganized brain areas with event-contingent proprioceptive feedback. It can also be inferred that personalization plays an important role in establishing the sensorimotor loop in BMI training. With further understanding of neural rehabilitation mechanisms, personalized treatment strategy is a promising way to improve the rehabilitation efficacy and promote the clinical use of rehabilitation robots and other neurotechnologies.

Key words: brain–machine interaction; closed-loop training; neural reorganization; personalized treatment; stroke rehabilitation.

Introduction

Stroke remains the leading cause of long-term disability for adults (Group 2020), which results in motor impairment contralateral to the affected brain hemisphere (hemiparesis). Robot-assisted training enables stroke patients to perform repetitive tasks in high intensity, which is considered to be a significant factor contributing to rehabilitation recovery (Staubli et al. 2009). Although previous studies with robot-assisted training have shown promise for improving recovery outcome, a clinical trial with 770 patients did not support the better rehabilitation performance using robot-assisted training in routine clinical practice (Rodgers et al. 2019).

As the understanding of the basic mechanisms of robot-assisted rehabilitation is further exploited, another trend is to combine different types of neurotechnologies to facilitate recovery. Electroencephalogram (EEG)-supported brain–machine interface (BMI) training combines robot-assisted training and BMI technology (Coscia et al. 2019; Micera et al. 2020), which is hypothesized that closing the loop between cortical activity and actual movement can restore functional corticospinal (Naros et al. 2020) and corticomuscular connections (Chaudhary et al. 2016). Previous studies have shown that BMI training achieved better motor improvements compared with the group with only robot-assisted training (Cervera et al. 2018; Khan et al. 2020). Various kinds of robots have been combined with BMI for rehabilitation training, such as MIT-Manus (Ang et al. 2010; Varkuti et al. 2013; Ang et al. 2015), WAM robot arm (Gomez-Rodriguez et al. 2011a, 2011b; Meyer et al. 2012; Xu et al. 2015), and robotic hand exoskeleton (Ang et al. 2014; Frolov et al. 2017; Cantillo-Negrete et al. 2018). Besides, enhancing BMI performance and improving its clinical application have been the focus of research, such as adding multi-sensory information (Shu et al. 2019; Choi et al. 2020; Stieger et al. 2020; Zhang et al. 2021) and reducing BMI calibration time (Zou et al. 2019). Benefits of BMI training are manifested not only in motor function improvements assessed by Fugl-Meyer (Bhagat et al. 2020; Cheng et al. 2020) but also in brain functional connectivity changes measured by EEG (Brauchle et al. 2015;
Tsuchimoto et al. 2019) and functional magnetic resonance imaging (fMRI; Varkuti et al. 2013) following with brain cortical changes (Bhagat et al. 2020).

Although patients who received BMI training generally obtained better recovery compared with control groups, the recovery mechanism of BMI training and conditions to construct closed-loop training are not fully understood. Moreover, few study has discussed the BMI training from the perspective of neurophysiological characteristics of stroke patients, which are different from healthy subjects and can determine the training efficiency to a large extent. Studies with healthy subjects showed major brain activation in contralateral sensorimotor area during unilateral upper limb movement (Pfurtscheller and Berghold 1989). However, there are no guidelines for selecting suitable brain regions to implement BMI training for stroke patients. For example, sensorimotor rhythm of the ipsilesional motor cortex (Ramos-Murcia1day et al. 2013) and the contralesional motor cortex (Bundy et al. 2017) were used respectively for decoding motor intention in different studies. Furthermore, for stroke patients with different degree of impairment, increased brain activation related to movement of paralyzed upper limb can be found in premotor cortex, supplementary motor area, or even unaffected hemisphere (Di Pino et al. 2014), which also evolves during rehabilitation process (Feydy et al. 2002). Specifically, according to a longitudinal study, recruitment and focusing are 2 main patterns of brain activation poststroke (Feydy et al. 2002). Although ipsilesional hemisphere’s activities plays an important role in motor recovery (Ramos-Murcia1day et al. 2013), for some patients with serious primary motor cortex deficits, there will be persistent recruitment in the contralesional hemisphere (Feydy et al. 2002), whose compensation matters more for motor rehabilitation (Johansen-Berg et al. 2002; Bundy et al. 2017).

EEG study explored the compensation mechanism of stroke that the severity of motor disability was related to the presence of different compensation mechanisms in the contralesional hemisphere (Barios et al. 2021). The positive contralesional compensation was also found in a lidocaine test of rats with large infarct (Biermaksie et al. 2005). Therefore, for each stroke patient, BMI training should be individualized based on personalized neural reorganization patterns not only due to BMI control principle, but also more importantly to stimulate the personalized sensorimotor loop to facilitate recovery.

We hypothesize that tailoring BMI training according to different patterns of neural reorganization can contribute to a personalized trajectory to rehabilitation for heterogeneous stroke patients, and proposed a personalized neural reorganization-based BMI rehabilitation training method.

Materials and methods
Experiment design and study protocol

This case series study was approved by the Ethical Committee of Beijing Rehabilitation Hospital of Capital Medical University and registered at Chictr.org (ChiCTR2000030709). All participants provided written informed consent. Sixty-nine stroke survivors enrolled for eligibility assessment based on the inclusion criteria (Supplement 1). Among these patients, 13 patients completed the 2-week training and were included in analysis in this study. The recruitment, intervention, and follow-ups details following Consolidated Standards of Reporting Trials were shown in eFigure 1 (Supplement 1). Patients’ detailed information was shown in Table 1.

The experiment was conducted based on an end-effector upper limb robot controlled by EEG-based BMI system. The experiment setup was shown in eFigure 3 (Supplement 1). EEG was recorded using ANT eego™. Surface electromyography (sEMG) from biceps and triceps muscles of the paralyzed arm was monitored. As shown in Fig. 1A, the BMI training protocol consisted of 2 calibration sessions, 10 therapy sessions and 2 assessments. After the first calibration, the personalized BMI training was conducted for 10 sessions, 5 times per week, lasting for 2 weeks. Assessments were performed before and immediately after the 2-week treatment. During BMI training, patients were presented with a reciprocating push-pull task on a display to train flexion and extension of the paralyzed upper limb. A total of 80 training trials were conducted in each day. The assessments consist of Fugl-Meyer upper extremity motor score (FMU) test, neural activities measured by EEG, muscle activation measured by sEMG, and motor function as determined from the robot kinematic data. Neural activities assessment consists of activation patterns and lateralization index (LI). Motor function is comprised of 5 scoring items describing the active movement performance.

Personalized BMI training based on neural reorganization patterns

Personalized BMI training was proposed based on both the BMI control principle and the basic recovery mechanism for stroke patients that the closed loop between motor intention and actual movement should be stimulated in a personalized manner according to neural reorganization.

The first step was to recognize the personalized activation pattern for each patient, as shown in Fig. 1B. Event-related desynchronization (ERD) can represent an electrophysiological correlate of activated cortical areas involving in processing of motor-related behavior (Pfurtscheller and Lopes da Silva 1999; Takahashi et al. 2012; Shu et al. 2019; Choi et al. 2020), which supports the EEG-based neural reorganization recognition. Previous simultaneous EEG–fMRI has also proven that decrease in EEG sensorimotor rhythm amplitude correlates inversely with fMRI activation (Zich et al. 2015). Upper limb-related movement is directly dependent upon sensorimotor activities of 8–13 Hz (Ramos-Murcia1day et al. 2013; Jia et al. 2020). Therefore, EEG was used to recognize activated brain regions and EEG-based motor intention recognition was used in online BMI training. ERD was...
Table 1. Patients information.

| Subject | Gender | Age (years) | Stroke type | Location | Lesion side | TFO (days) |
|---------|--------|-------------|-------------|----------|-------------|------------|
| S1      | M      | 35          | Isch.       | C and SC | Right       | 81         |
| S2      | M      | 55          | Isch.       | SC       | Left        | 41         |
| S3      | M      | 51          | Isch.       | SC       | Left        | 39         |
| S4      | M      | 59          | Isch.       | SC       | Left        | 40         |
| S5      | M      | 59          | Isch.       | SC       | Right       | 61         |
| S6      | F      | 65          | Isch.       | SC       | Left        | 82         |
| S7      | F      | 65          | Hem.        | SC       | Left        | 95         |
| S8      | F      | 57          | Isch.       | SC       | Left        | 58         |
| S9      | M      | 54          | Isch.       | SC       | Left        | 92         |
| S10     | M      | 60          | Isch.       | C and SC | Left        | 35         |
| S11     | M      | 67          | Isch.       | SC       | Left        | 35         |
| S12     | F      | 58          | Isch.       | SC       | Left        | 51         |
| S13     | M      | 58          | Isch.       | SC       | Right       | 42         |

Hem., hemorrhagic stroke; Isch., ischemic stroke; C, cortical; SC, subcortical; TFO, time from onset.

calculated based on BMI calibration sessions following the modified ERD calculation method (Li et al. 2019; Jia et al. 2021). BMI calibration was detailed in Supplement 1. The second step was to train the classifier using the data from the individually selected channels for motor intention recognition and conduct personalized BMI training, as shown in Fig. 1C. During clinical practice, to minimize negative influences of signal noise contamination on BMI system, a denoising algorithm for ERD-based motor intention recognition algorithm was used in this BMI system (Jia et al. 2020).

Analysis of EEG-based lateralization index
ERD distributions and ERD-based LI were assessed before and after the 2-week treatment, in order to quantify changes in neural activities following BMI training and explore the relationship between neural reorganization pattern and motor recovery. ERD-distribution map
describes the changes of activation pattern following the treatment and ERD-based LI describes the activation lateralization, indicating whether contralesional or ipsilesional hemisphere plays the dominative role.

sEMG recording and analysis
During functional assessments, sEMG was recorded from 2 locations on the paralyzed arm: (i) biceps brachii (BB) and (ii) brachioradialis (BR). Patients were required to try their best to pull the robot using the affected arm without any assistance. Muscle activation is defined as 2 states: “activated” and “inactivated” (Hwang and Jeon 2015).

Statistical analysis
The outcomes of the proposed individualized neural reorganization-based BMI therapy were assessed with 3 indicators, namely FMU, neural activities measured by EEG, and motor exercise performance based on robot-based movement assessment. Considering data’s normality and non-normality, paired sample t-test and Wilcoxon signed rank test were used respectively with 95% confidence interval. Two-sided $P < 0.05$ indicated statistical significance.

Results
Clinical outcomes
Figure 2A shows the detailed breakdown of motor recovery evaluated with FMU before and after the 2-week treatment. Patients had a mean [SD] FMU improvement 5.92 [4.27]. Paired sample t-test analysis proved that significant improvement in FMU was found before (5.23 [2.65]) and after (11.15 [4.47]) the 2-week treatment ($P < 0.05$). Eight scoring items of FMU were analyzed separately. Results showed that significant improvements were found in combined synergies, extensor synergy and flexor synergy pre-treatment and post-treatment ($P < 0.05$). No statistically significant improvements were found in the other scoring items of FMU. Figure 2B and C shows that patients were grouped into ipsilesional lateralization and contralesional lateralization pre-treatment. Results show that patients in both groups have improvements except S7.

Behavioral outcomes
In Fig. 3, boxplots compare 5 scoring items of motor function between pre-treatment and post-treatment. Results showed that movement deviation and movement deviation ratio were significantly lower after the treatment. Active range of motion was significantly higher after the treatment. Interaction force intended to be higher than before. No statistical improvements were found in average speed. Mean [SD] values for movement deviation decreased from 26.6 [26.1] to 12.8 [9.1] mm ($P < 0.05$) and movement deviation ratio from 3.74 [3.09] to 0.85 [0.87] ($P < 0.05$), which suggests better performance of combined synergies. Mean [SD] values of active range of motion increased from 85.1 [44.2] mm to 199.2 [59.8] mm ($P < 0.05$), which suggests better control of extensor and flexor synergy. Mean [SD] values of interaction force increased from 2.70 [0.86] N to 3.38 [1.61] N ($P < 0.1$), which suggests the output of muscular activities increased.

Neural activities assessment
Figure 4 shows the activation patterns pre-treatment and post-treatment. All the patients showed activation in unilateral or bilateral sensorimotor area. There are 3 main brain activation patterns poststroke, namely bilateral widespread activation, ipsilesional focusing activation and contralesional recruitment activation. Ipsilesional activation is the main neural reorganization pattern in this study. S9 shows typical focusing on ipsilesional hemisphere, and S11 shows recruitment on contralesional hemisphere pre-treatment and post-treatment persistently. FMU was assessed by Mann–Whitney U test between the 2 groups, namely ipsilesional hemisphere lateralization group and contralesional hemisphere lateralization group. No significant differences were found in FMU between the 2 groups before ($U = 20, P = 1.0$) and after ($U = 17.5, P = 1.0$) the 2-week treatment. FMU changes pre-treatment and post-treatment between the 2 groups were also not statistically different ($U = 10.5, P = 0.5$). The results indicate that stroke patients with either ipsilesional dominance or contralesional dominance can achieve recovery following personalized neural reorganization.

Muscle activities assessment
Figure 5 shows the comparison of muscle activation between pre-treatment and post-treatment. Participants can be grouped into 4 categories based on the changes of muscle activation. (i) For S2, S8, and S13, BB and BR were both activated during active flexion task pre-treatment and post-treatment. (ii) For S3 and S6, BB and BR stayed activated during active flexion task. BR was inactivated before the treatment and was activated post-treatment. Correspondingly, FMU improvements were accompanied with BR activation. (iii) For S4 and S12, both BB and BR stayed inactivated pre-treatment, and BB was activated during active flexion task and BR was inactivated pre-treatment and was activated post-treatment. For S7 with no FMU improvements, both BB and BR were inactivated. FMU improvements were correlated with target muscles reactivation.

Discussion
This study explicitly explores the hypothesis that designing personalized BMI for stroke patients according to different types of neural reorganization patterns promisingly contributes to motor rehabilitation. Following BMI training, evident improvements were found in
Fig. 2. Detailed breakdown of motor recovery measured with FMU. (A) Breakdown of FMU scores by subscales, by averaging across participants. (B) Individual FMU scales for participants with ipsilesional hemisphere lateralization pre-treatment. (C) FMU scales for participants with contralesional hemisphere lateralization pre-treatment.

FMU, motor function and target muscles reactivation. The results indicate that personalized BMI training tends to connect the potentially reorganized brain areas with event-contingent proprioceptive feedback. To the best of our knowledge, this is the first study on subacute stroke patients that tails BMI training to achieve a personalized trajectory to motor rehabilitation.

Motor deficits poststroke are reflected by lack of self-sensation (Cheng et al. 2020), which is manifested by patient’s inability to control movements even though their muscles, efferent neuro, and afferent neuro are intact. Patients participating in this study reported they were regaining self-sensations during training. Accordingly, improvements of motor task performance were
found in movement deviation, movement deviation ratio, range of motion and interaction force, which proved the enhancement of motor functional abilities. The results listed above can prove that the self-sensorimotor loop gradually established. In the assessment of motor task, no requirement of completion time was given to the patients. Thus, it was natural that there was no difference in average speed before and after the treatment. Moreover, 1 main factor that influences the motor improvements is the form of training. In this study, extension and flexion movement during line tracking task was repeatedly trained with event-contingent proprioceptive feedback. FMU tests showed significant improvements in combined synergies, extensor synergy, and flexor synergy, but no statistical improvements in the other scoring items. The listed 3 scoring items were correlated with the specific form of training tasks in this study, which further validated the efficacy of the proposed method to some extent.

Although numerous studies have verified the advantages of BMI training compared with robot-assisted training alone, individual responses to BMI interventions are still complicated. In addition, no norms or guidelines exist for selecting suitable brain areas to implement BMI training. Patients without satisfied BMI performance would be excluded from BMI training which was partly due to failing to select suitable brain areas for decoding motor intention. The channels selection will not only affect the decoding accuracy, but also influence whether the closed loop is actually established. The hypothesis behind BMI training is that establishing the connection between motor intention and actual movement can close the loop between the potentially reorganized brain area and the paralyzed limb. Therefore, the channels selection

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**Fig. 3.** Improvements in motor function between pre-treatment and post-treatment. Motor function was analyzed from trajectory, speed and force data collected during participants’ active movement. Exercise performance is comprised of 5 scoring items, namely movement deviation, movement deviation ratio, active range of motion, average speed, and interaction force.

**Fig. 4.** Comparison of activation patterns between pre-treatment and post-treatment. Each topography was drawn with ERD values in the alpha-mu rhythm. (A) Participants with ipsilesional hemisphere lateralization pre-treatment. (B) Participants with contralesional hemisphere lateralization pre-treatment. The cross indicates the side of the paralyzed upper limb.
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directly determines the source of the control signal that affects whether the closed loop can be constructed accurately. Considering various alterations across stroke patients, this study proposed a personalized BMI training method that each patient’s altered brain activation pattern was recognized and involved in the design of BMI system. Different BMI strategies were set according to each subject’s personalized neural reorganization. S1 and S11, with cortical and subcortical lesion, showed completely contralesional recruitment pre-treatment, so that EEG from contralesional brain areas was decoded for BMI training. The hypothesis behind is that for these patients with completely contralesional recruitment, compensation should be enhanced, which is beneficial for motor recovery. The dynamic changes of cortical functional reorganization should also be considered in long-term BMI training. (Feydy et al. 2002) reported the cortical reorganization process of stroke patients over a period of 1–6 months after stroke. Besides, the differences of lesion could affect neural reorganization process. For S1, besides contralesional recruitment, ipsilesional reorganization was also found after the 2-week training. Therefore, in the follow-up training, contralesional and ipsilesional neural activities should be considered in BMI design for S1. However, accurate prognosis of activation patterns process is hard and designing the BMI system based on the current neural recombination pattern is a better choice to promote the construction of the internal closed loop. Dynamic changes in cortical functional reorganization should be tracked to adjust the BMI system inputs.

Establishing the sensorimotor loop has been considered as the underlying mechanism of BMI training. Some factors have been identified influencing the formation, and we addressed that personalization is an important factor based on this study. Following the training, target muscle reactivation can further evidence the sensorimotor loop formation. Motor units were formed by muscle fibers and their innervating spinal motor neurons. Therefore, multiunit activity from spinal motor neurons can be reflected by slightly delayed sEMG recordings from the corresponding muscle (van Elswijk et al. 2010). Furthermore, these spinal motor neurons receive input from motor cortex contralateral to the corresponding muscle (van Elswijk et al. 2010). We can speculate that sEMG activities following motor intention reflect unobstructed transmission of information, which remains consistent with previous work (van Elswijk et al. 2010; Keil et al. 2014; Khademi et al. 2018). Due to brain lesions, this pathway from cerebral cortex to corresponding muscle motor units may be functionally suppressed. By accurately recognizing the motor intention and offering concurrent positive neural feedback (Ramos-Murguialday et al. 2013), the sensorimotor loop could be activated. With positive BMI feedback training, motor function was improved as expected. Nonetheless, the formation of the closed loop still needs further exploration in the future.

Our original idea is to show for heterogeneous patients that patients can achieve recovery in a personalized manner. Therefore, patients recruited in this study consist of different lesion types and locations. It is due to the heterogeneous lesions that we can study the effect of the personalized BMI training on different neural reorganization patterns. Results also proved that personalized neural reorganization-based BMI training worked for heterogeneous stroke patients. Undeniably, motor rehabilitation is affected by many kinds of factors and this study provides a solution to individual differences.

To date, EEG and EMG supported neural interfaces have been used to implement rehabilitation training

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**Fig. 5.** Comparison of muscle activation state between pre-treatment and post-treatment. For each participant, sEMG from BB and BR was measured before and after the treatment.
based on reading motor intention from cortical activities and muscular activities respectively. Future studies can explore the relationship between EEG and EMG, or corticomuscular coherence (Chen et al. 2018), which may represent the formation of the sensorimotor loop and serve as a possible indicator to initiate the closed-loop training. Unfortunately, there are still amounts of patients who cannot generate motor-related cortical activities so that to be excluded from BMI training, even with the proposed personalized BMI training. Noninvasive brain stimulation, such as repetitive transcranial magnetic stimulation and transcranial electrical stimulation, has the potential to enhance motor-related cortical activities by entraining brain oscillations (Helfrich et al. 2014; Koch et al. 2019; Jia et al. 2021), which can be the personalized treatment for the excluded patients before BMI training. In conclusion, with further understanding of neural rehabilitation mechanism, personalized intervention strategy is a promising way to promote the rehabilitation efficacy and clinical use of rehabilitation robots and other neurotechnologies.

The first limitation of this study is the absence of a control group. This study mainly investigated the influence of different brain areas for BMI decoding on patient’s recovery. Previous studies have proven that BMI training achieved better motor improvements compared with robotic training alone (Cervera et al. 2018). If a control group had been set, EEG from the ipsilesional or contralesional hemisphere would have been used for motor intention recognition referring to previous study. However, results showed that both ipsilesional and contralesional dominance were both found in this study, which means overlaps would exist between groups. The overlaps will confuse the study. Secondly, the sample size of this study was relatively small, but it was considerable as the average of the experimental groups in similar studies (Mihara et al. 2013; Pichirolli et al. 2015; Cervera et al. 2018; Carino-Escobar et al. 2019). Nevertheless, future studies with substantial patients are still needed to explore the constraints of the proposed method.

**Conclusions**

This study proposed a personalized BMI training based on neural reorganization patterns. During the personalized BMI training, potentially reorganized brain areas were connected with event-contingent proprioceptive feedback. Analysis of clinical and behavioral outcomes demonstrated that most patients achieved significant improvements. The results indicate that tailoring BMI training for patient based on different types of neural reorganization patterns contributes to a personalized trajectory to motor rehabilitation.

**Supplementary material**

Supplementary material is available at Cerebral Cortex online.

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