Brain-computer interface training based on visual and motor feedback improves convalescent stroke patients with hemiplegia: a randomized clinical trial

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Research Article

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Brain-computer interface training based on visual and motor feedback improves convalescent stroke patients with hemiplegia: a randomized clinical trial

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Abstract

Background: Modern stroke rehabilitation integrates exercise therapy, occupational therapy, and other technological interventions. This study investigated the short-term intervention effect of brain-computer interface (BCI) training based on visual and motor feedback on cognition, psychology, limb movement, and brain function in convalescent stroke patients with hemiplegia.

Methods: Convalescent stroke patients with hemiplegia (n=98) were randomly assigned to one of three groups: conventional exercise rehabilitation (Control), conventional exercise + conventional motor imagery (MI), and conventional exercise + BCI-based MI (BCI) groups, while MI and BCI patients imagined the upper limb swimming and lower limb cycling during the rehabilitation, and treated for six times a week for two weeks. The training effects were evaluated by the mini-mental state examination (MMSE), Hamilton Depression Scale (HAM-D), Fugl-Meyer Assessment (FMA), six min walking distance (6MWD), modified Barthel index (MBI), and transcranial magnetic stimulator before and after the intervention.

Results: (1) After intervention: All indicators of the three groups were significantly improved compared with those before intervention (P<0.05) except for the MEP amplitude in Control group and MI group. (2) Differences before and after intervention: All items in BCI group were the largest in the three groups, in which MMSE, HAMD, and FMA items in BCI group were significantly different
from those in the other two groups (P < 0.05), and the MEP latency in BCI group was significantly different from that in MI group (P < 0.05).

**Conclusion:** This randomized controlled trial demonstrated that all three types of interventions could significantly improve convalescent stroke patients with hemiplegia, while BCI-based MI training with both visual and motor feedback was a better choice for clinical rehabilitation of patients to recover cognition, psychology, and limb movement. Mechanistically, BCI-based MI training also improved the excitability of the non-lesional cerebral hemisphere and the conductivity of the descending neural pathway.

**Keywords:** Brain-computer interface, Cognition, Limb movement, Motor imagery, Stroke

1 Introduction

Brain tissue ischemia or hemorrhage causes stroke, recognized as the second most frequent cause of death in the world, with an estimated more than 12.2 million new cases and more than 6.5 million stroke-related deaths in 2019 [1]. Currently, over 101 million stroke patients are alive globally [1]. Thus, diagnosis and treatment of stroke-related central nervous system injury and sequelae are hot topics of rehabilitation research and clinical management [2–5]. Exercise therapy is the most crucial conventional rehabilitation among all treatment options to restore the motor function of patients after stroke [6]. Active exercises, if possible, are more effective than passive exercises for their recovery [7, 8]. However, active exercises may not be an option for patients with severely paralyzed limbs (≤ grade 1 of the muscle strength assessed by the manual muscle test, MMT) [9]; passive exercises are the only option. In this regard, recently developed motor imagery (MI) therapy, a mentally rehearsed task for movement imagination (repetitively imagining body movements or mentally repeating imagined action) without physical performance [10], could be an alternative to active exercise [8], by which the “command function” of the cerebral cortex and the conduction function of the neural pathway between the brain nerve and the peripheral nerve could be repeatedly strengthened. Thus, MI therapy is a substitute for active exercise for patients with severely paralyzed limbs [11, 12], although conventional MI therapy lacks limb motor feedback to the brain, and its rehabilitation effect may be limited [13, 14].

To improve the effectiveness of the MI therapy on recovery of patients, the brain-computer interface (BCI) technique has been recently developed to integration with MI due to the availability of novel science and technology [15, 16]. This technique detects the electroencephalogram (EEG) signals from patients during their MI, and the EEG signals will control a rehabilitation training device that can drive the limb movements for rehabilitation training [17]. The most important feature of the BCI-based technique is to synchronously activate the cerebral cortex and somatic sensation bidirectionally. According to the Hebbian plasticity theory [18] proposed in the 1940s as the basic nerve function remodeling theory, a positive feedback modality will form if a stimulus and feedback are present simultaneously. The persistence and repetition of this positive feedback could lead to continuous promotion of neuronal excitability [18, 19]. During BCI-based rehabilitation, the patient’s MI and limb movement can be achieved simultaneously, and the MI can be enhanced by motor sensory feedback (i.e., somatosensory activation). Moreover, BCI-based MI training does not depend on patients’ internal neural channels, so it is suitable for active rehabilitation in stroke patients at various stages (like acute or recovery stage and complete soft paralysis or spasticity stage) [20–25]. Thus, further study and clinical trials using the BCI-based module could help stroke patients improve their cognition, psychology, and limb movement abilities.

This study utilized a novel BCI system, i.e., the L-B300 EEG Acquisition and Rehabilitation Training System from Zhejiang Mailian Medical Technology Co., Ltd. (Hangzhou, China), and this system offers the following advantages: 1) It provides both visual and motor feedback [25], whereas most other BCI rehabilitation systems adopt single feedback modality, such as systems based on vision [26], kinesthetic sense [27],
or perception[28], and 2) It provides a high-time efficiency, with real-time feedback taking only 110 ms, which is smaller than that of other systems (200 ms[29] and 300 ms[30]). In rehabilitation, having more and faster feedback could potentially improve patient outcomes[13]. Indeed, scholars assume that BCI-based MI training is more effective than conventional MI. However, very few studies have compared the efficacy of the two methods. In our previous study, we initially treated eight stroke patients to assess the performance of this BCI module[31]. In this randomized and controlled trial, we enrolled 98 stroke patients and divided them into Control, conventional MI, and BCI-based MI rehabilitation. We monitored motor state percentage (MSP) and effective training revolutions (ETRs) to conduct a more in-depth and rigorous investigation into the performance of this BCI module. Meanwhile, we collected data from patients, measuring and evaluating their performance on the mini-mental state examination (MMSE)[32], the Hamilton Depression Scale (HAM-D)[33, 34], the Fugl-Meyer Assessment (FMA) score for the FMA-Upper Extremity (FMA-UE) and the FMA-Lower Extremity (FMA-LE)[35], the six min walking distance (6MWD)[36], the modified Barthel index (MBI)[37], and tested the brain function using the transcranial magnetic stimulator (CR Technology Co., Ltd., Daejeon, Korea)[38]. We expect to provide useful information regarding BCI-based MI training as a choice for our stroke patients.

2 Methods

2.1 Study population

In this randomized controlled clinical trial, we recruited 98 hemiplegic patients after their first stroke from the Department of Rehabilitation Medicine, the Second Affiliated Hospital of Anhui Medical University, between December 2020 and December 2021. The inclusion criteria were 1) Hemiplegic patients between 18 and 80 years old, diagnosed by an imaging assessment, like CT or MRI, after the first cerebral infarction or cerebral hemorrhage event; 2) More than one week of disease course, according to a previous study[39]; 3) Patients with stable vital signs; 4) Weak muscle strength of the upper (Triceps brachii) and lower limbs (The quadriceps) on the hemiplegic side (≤ grade 4 of MMT) following a previous study[9], but without an obvious dysfunction of the contralateral limbs; 5) Patients being able to sit for 30 min without support; and 6) Patients with clear awareness and ability to complete the motor imagery.

However, patients with the following were excluded from the current study, i.e., 1) Craniotomy and/or skull repair surgery; 2) More than one history of cerebral infarction or cerebral hemorrhage; 3) Shorter disease course (≤ 1 week); 4) Complication of severe heart disease or carrying a heart pacemaker; 5) Continuous deterioration and unstable vital signs; 6) A poor cognitive level (< 21 scores of the MMSE) and non-cooperation of rehabilitation therapy; 7) Motor dysfunction in the contralateral limbs; 8) Inability to sit alone for 30 min; or 9) Participation in other clinical trials. This clinical trial was approved by the Ethics Review Board of The Second Affiliated Hospital, Anhui Medical University, with an approval number of YX2020-103(F1). This study followed the ethical standards of the 1975 Helsinki Declaration (revised in 2008) after obtaining written informed consent from each enrolled patient.

2.2 Randomization and rehabilitation

These 98 patients were randomly divided into three groups by a random number table method, i.e., conventional exercise rehabilitation (Control), conventional exercise + conventional MI (MI), and conventional exercise + BCI-based MI (BCI) groups, and treated for six days a week for two weeks. The treatment of the control patients was to first place patients in a favorable position for respiratory exercise (5 min daily for six days a week) and active/assisted/passive movement of the limbs (30-45 min daily for six days a week), and patients were then subjected to routine occupational therapy, like orthesis and orthotic device, and drug treatment, like oral or intramuscular injection of antispasmodic drugs. In contrast, the MI group of patients was subjected to conventional exercise plus conventional MI training tasks in a comfortable and quiet environment. The latter training was set to let patients watch a 1-minute swimming video and then complete a 1-minute swimming movement of bilateral upper
limbs under the manual assistance from the investigator; after that, instructed patients to close their eyes for the imagination of swimming movement of bilateral upper limbs for 15 min and rest for 5 min. Patients were then subjected to a review of a 1-minute cycling video, performance of a 1-minute cycling movement with assistance by a robot, closure of the eyes, and then imagination for 15-minute cycling of bilateral lower limbs. During the treatment, the investigator would verbally prompt the patient to strengthen the MI for 10 s at the beginning and 10 min after the beginning of the MI. Such 1-minute swimming/cycling training review and simulation steps were only implemented in the first three MI training sessions. Both the upper limb swimming MI training and the lower limb cycling MI training were performed once in the morning and once in the afternoon.

The BCI group of patients was subjected to conventional exercise plus BCI-based MI training using the L-B300 EEG Acquisition and Rehabilitation Training System (Zhejiang Mailian Medical Technology Co., Ltd. Hangzhou, China). The equipment includes four major components, i.e., an electrode cap for signal acquisition, an amplifier for EEG signals (to filter and identify EEG signals through an integrated circuit and then convert the EEG signals to Bluetooth signals), a display (to convert the Bluetooth signals to video), and a motor robot (the rehabilitation training gear receives the Bluetooth signals and converts them into a mechanical movement). During rehabilitation, patients were required to wear an 8-lead EEG cap per the electrode placement principles of the 10/20 international standard lead system [40], electrodes of which were localized over the left and right prefrontal lobes (FP1 and FP2), left and right frontal lobes (F3 and F4), left and right central regions (C3 and C4), frontal midline (Fz), and central midline (Cz), respectively. In contrast, the left and right ear clip electrodes (A1 and A2) were set as the reference electrode and the bias electrode, respectively (Fig.1.B). Except for the left and right ear clip electrodes (A1 and A2, dry electrodes), the remaining eight electrodes (FP1, FP2, F3, F4, C3, C4, Fz, and Cz) were wet, utilizing normal saline as a conductive medium.

The bilateral upper/lower limbs of patients were fixed onto the corresponding left and right rotary shafts in the system for upper/lower limb rehabilitation, i.e., this system provides a training mode entirely driven by the patient’s MI and displays the visual feedback platform between the machine and the patient. Before and during the upper/lower limb exercise training, a virtual character will be displayed for the corresponding exercise preparation and training, for example, a virtual character showing swimming during upper limb training, whereas a virtual character showing cycling during lower limb training. The Patient can perform the corresponding MI tasks according to the type of virtual character shown on the display and follow the corresponding voice reminders.

We utilized Mscore (a specific EEG signal) to measure the intensity of the patient’s MI [25]. In particular, for the upper limb swimming training rehabilitation, patients were subjected to a review of a 1-minute swimming video and completion of a 1-minute swimming movement of bilateral upper limbs under manual assistance from the investigator. The swimming review and simulation were only carried out for the first three BCI training sessions. After that, patients sat in a comfortable position, wore the electrode cap, watched the screen, and imagined their left and right upper limbs’ swimming forward alternately, during which the EEG signal was collected, processed, and displayed by the system for the upper limb rehabilitation. When the Mscore reached the pre-set threshold, the virtual character on the display would begin swimming forward, and the upper limb rehabilitation training gear would start to rotate the patient’s upper limbs; when the Mscore fell below the pre-set threshold, the virtual character and the upper limb rehabilitation training gear would stop moving. The system would timely remind the patient with sound to focus on MI to make the Mscore reach the pre-set threshold again to continue the training. The total duration of one upper limb swimming BCI training was 15 min. After resting for 5 min, patients were subjected to lower limb cycling BCI training for 15 min, and the procedure was similar to upper limb swimming BCI training. During the rehabilitation process, the system employed voice reminders to encourage patients to maintain their focus on MI and complete the training without exerting any force on their limbs (Fig.1.C). Both the upper limb swimming BCI training and the lower limb cycling
BCI training were performed once in the morning and once in the afternoon.

2.3 Data recording and assessments

The BCI system can record data on the MSP, i.e., the percentage of the time that the patient’s motor intention intensity exceeds the selected threshold during the BCI-based MI training process, and the ETRs, i.e., the average number of rehabilitation training gear rotations manipulated by MI per minute during each training session[25]. Moreover, the vital signs of patients, including the level of blood pressure, respiration, pulse, and blood oxygen concentration value, were monitored. The occurrence/recurrence events of epilepsy, cerebral hemorrhage, cerebral infarction, and pulmonary embolism were recorded.

The following six assessments were completed before and after rehabilitation: 1) The MMSE assesses the cognitive functions of patients on a scale ranging between 0 and 30 points. The higher the score, the better the cognitive function of the patient; however, the normal value is related to the level of the patient’s education, e.g., >17 for illiteracy, >20 for primary school education, >22 for secondary and technical school education, and >24 for college education, according to a previous study[32]; 2) The Hamilton Depression Scale (HAM-D), a questionnaire initially designed by Hamilton in 1960[33] and improved after that[34], is used to evaluate the severity of depression. This study adopted the 24-item version of the HAM-D with a total score of 76. The lighter the disease, the lower the score. If the total score is over 35, the patient could suffer from severe depression; if the total score is between 21 and 35, the patient would be diagnosed with depression; if the total score is between 8 and 20, the patient may have depression; if the total score is less than 8, the patient should not have depression or related symptoms; 3) The FMA score for the FMA-Upper Extremity (FMA-UE) includes nine major items (i.e., reflex, shoulder, elbow, wrist, and hand functions and other four major items) and 33 sub-items (each is divided into three levels with a score of 0, 1 and 2) for a total 66 scores. The higher the score, the better the upper limb function. The FMA-Lower Extremity (FMA-LE) consists of five major items and 17 sub-items, 0-2 points for each sub-item, 34 scores in total. The higher the score, the better the lower limb function[35]; 4) The six min walking distance (6MWD): a most widely used submaximal exercise test to assess patients’ systemic and complete response during exercise. The test let the patient walk back and forth for 6 min along a 30-meter straight horizontal route at the fastest speed, and the total walking distance on the unit of a meter (m) was recorded[36]; 5) The MBI evaluates the activity of daily living (ADL), like personal hygiene, self-bathing, feeding, toilet-using ability, stair climbing, dressing, bowel and bladder control, transfer between chairs and beds, and ambulation, for a total score of 100 points. The higher the total score, the stronger the ADL[37]; and 6) The brain function was tested using the transcranial magnetic stimulator (TMS; CR Technology Co., Ltd., Daejeon, Korea) containing a figure-8 coil (12.5 cm in diameter, 3.0 T in maximum intensity). The motor-evoked potential (MEP) induced with the stimulator exciting the primary motor cortex (M1) in the non-lesional cerebral hemisphere was the surface electromyogram (sEMG) signals recorded on the surface of the abductor pollicis brevis in the contralateral hand. The amplitude and latency of the MEP were utilized to assess the excitability of the cortex (M1) in the non-lesional cerebral hemisphere and the conductivity of the descending neural pathway, respectively[38].

In particular, patients sat comfortably with the surface electrode over the abductor pollicis brevis in the non-affected hand. According to the international EEG 10-20 system positioning method, the approximate position of the M1 area in the non-lesional cerebral hemisphere was determined. The figure-8 coil was then put to the surface of the skull and moved up and down at a distance of 1 cm each time to find the exact position where the maximum MEP amplitude was induced. Moreover, the resting motor threshold (RMT) was then measured by a gradual decrease in the stimulus intensity at this position to find the exact position where the maximum MEP amplitude was induced. The MEP amplitude ≥ 50 μV recorded over the contralateral abductor pollicis brevis for at least five times in 10 consecutive stimulations. Five MEPs were collected under the RMT intensity stimulation, and the mean values of their amplitudes and latencies were calculated for analysis[38].
2.4 Statistical analyses

The quantitative data with a normal distribution were expressed as mean±standard deviation and analyzed using the analysis of variance test among multiple data groups; if the difference was significant, the least significant difference method (LSD) was used for pairwise comparison. The paired sample t-test was used to compare the quantitative data before and after intervention in one group. Moreover, the categorical data were analyzed using the chi-square test. Cohen’s d-test was performed to assess the effect size in different groups, with the threshold values of small, medium, and large effects being 0.20, 0.50, and 0.80, respectively [41–43]. All statistical analyses were performed using the SPSS 25.0 software (SPSS, Chicago, IL, USA), and a P<0.05 was considered statistically significant.

3 Results

3.1 Characteristics of patients

This randomized and controlled clinical trial recruited 98 patients with hemiplegia after the first stroke, and they all completed this study without any dropouts. During enrollment, we divided them into Control (n=34), MI (n=32), and BCI (n=32) groups. There were no statistically significant differences in the patient’s gender and age, disease course, numbers of cerebral hemorrhage/cerebral infarction, left/right hemiplegia, and upper/lower limb muscle (i.e., triceps brachii and the quadriceps) strength equal to or less than grade 1 of the MMT, and days of rehabilitation treatment among the three groups (all P>0.05; Table A1).

3.2 Feasibility and safety of BCI system

All BCI patients completed the BCI-based MI training. According to statistics, the average system response time of this system was 291.93 ms. The MSP and the ETRs during the upper limb BCI rehabilitation were 57.33±28.05 % and 33.22±12.88 r/min, and during the lower limb BCI rehabilitation, they were 60.91±26.05% and 19.09±6.95 r/min, respectively, indicating that the BCI-based MI training is feasible for patients. In particular, we divided the BCI rehabilitation days of the upper and lower limbs into five training periods of assessment (T1-T5). The total training days for each person were then divided by 5, leading to the T1 period as the first 1/5 time period. However, if the quotient was not an integer, its integer was taken by the rounding method, i.e., if a patient was treated for a total of 13 days, we divided 13 by 5, resulting in a quotient of 2.6, and we then set the T1 period as the first three days; after that, we set the T2 period as [13 x (2/5) - 3]=2.2 days (its integer was 2) and then, Days 4 and 5 were set as the T2 period of assessment. The MSPs and ETRs measured as the mean ± standard deviation in each period during the upper and lower limb training were calculated, and the data are shown in Fig. A1.

Regarding the BCI module safety, we found that all vital signs from these patients were stable. No patient experienced any apparent discomfort,
epilepsy, cerebral hemorrhage, cerebral infarction, or pulmonary embolism during the BCI-based rehabilitation, indicating that the BCI module is relatively safe and reliable.

3.3 MMSE of cognition level in patients

The MMSE questionnaire assesses the cognitive impairment of patients[44]. Our measurement data showed no statistically significant difference in the MMSE scores at the baseline among these three groups of patients (P>0.05 using the ANOVA test). The MMSE in each group was significantly improved after intervention (all P<0.01 using the paired t-test). However, the MMSE scores showed significant differences between the BCI group and the Control group and between the MI group and the Control group of patients after intervention (both P<0.05). Nevertheless, there was no significant difference observed between the MI group and the BCI group of patients after intervention (P>0.05; Table 1). The difference in the MMSE score before and after intervention and the effect size (Cohen’s d) in BCI patients were the largest among these three groups of patients (Table 1).

3.4 Hamilton Depression Scale (HAM-D) analysis

HAM-D is a questionnaire to evaluate the severity of depression[33, 34]. Our data exhibited no statistical difference in the HAM-D scores at the baseline among these three groups of patients; however, the BCI group of patients had the best HAM-D score after the intervention, although the differences did not reach statistical significance between the BCI group and the other two groups (P>0.05 using the ANOVA test; Table 2). Moreover, these interventions also improved HAM-D scores in all three groups of patients (all P<0.01 using the paired t-test; Table 2). The difference in the HAM-D score before and after intervention and the effect size (Cohen’s d) in BCI patients were the most significantly improved among these three groups of patients (Table 2).

3.5 FMA of patients’ limb movement function

The FMA assesses the limb movement function in patients[45]. The FMA-Masses of Limb (FMA-LE) data showed no statistically significant difference at the baseline among all three groups of patients (all P>0.05 using the ANOVA test; Table 3); however, the interventions significantly improved the FMA-LE scores in all three groups of patients (all P<0.01 using the paired t-test) and the BCI patients had the best improvement followed by the MI and Control patients (both P<0.01; Table 3). The effect size (Cohen’s d) in the BCI group for the FMA-UE score was the largest among the three groups (Table 3).

Furthermore, there was no statistically significant difference in the FMA-LE score at the baseline among the three groups of patients (all P>0.05 using the ANOVA test; Table 4). The interventions significantly improved the FMA-LE scores in all three groups of patients (all P<0.01 using the paired t-test), while BCI patients showed a significantly higher FMA-LE score than the Control patients (P<0.05; Table 4). In the differences in the FMA-LE scores before and after the intervention, the BCI group was significantly higher than the Control and MI groups (both P<0.01 using the LSD test; Table 4). For the FMA-LE assessment, the effect size in the BCI group was the largest among those of the three groups (Table 4).

3.6 The six min walking distance (6MWD) analysis of the physical ability

The 6MWD assesses systemic and complete response during exercise in patients[36]. In this study, we assessed each patient for the 6MWD score and found no statistically significant difference in the 6MWD at the baseline among the three groups (all P>0.05 using the ANOVA test; Table 5). However, the 6MWD score in each group of patients was significantly improved after intervention (all P<0.01 using the paired t-test). The differences before and after intervention were BCI>MI>Control groups, although there was no statistically significant difference (all P>0.05 using the ANOVA test; Table 5). For the 6MWD assessment, the effect size (Cohen’s d) in
### Table 1  Comparison of the MMSE scores among these three groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference before and after intervention</th>
<th>Pre- and post-intervention comparison</th>
<th>Cohen’s d</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34</td>
<td>25.56±1.40</td>
<td>25.85±1.18#*</td>
<td>0.29±0.52**</td>
<td>-3.273 0.002</td>
<td>0.56</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>26.00±1.48</td>
<td>26.66±1.00</td>
<td>0.66±0.79*</td>
<td>-4.714 0.000</td>
<td>0.83</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCI</td>
<td>32</td>
<td>25.47±2.88</td>
<td>26.75±1.95</td>
<td>1.28±1.40</td>
<td>-5.190 0.000</td>
<td>0.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>0.533</td>
<td>0.023</td>
<td>0.000</td>
<td>- -</td>
<td>-</td>
<td></td>
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</tr>
</tbody>
</table>

Note: *P<0.05 and **P<0.01 compared with the BCI group, and #P<0.05 compared with the MI group of patients.

### Table 2  Comparison of the HAM-D scores among these three groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference before and after intervention</th>
<th>Pre- and post-intervention comparison</th>
<th>Cohen’s d</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34</td>
<td>18.18±1.96</td>
<td>16.91±2.35</td>
<td>-1.26±1.24**</td>
<td>5.954 0.000</td>
<td>1.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>18.16±2.19</td>
<td>17.19±1.80</td>
<td>-0.97±1.12**</td>
<td>4.888 0.000</td>
<td>0.86</td>
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<tr>
<td>BCI</td>
<td>32</td>
<td>17.97±3.10</td>
<td>15.84±3.26</td>
<td>-2.13±1.34</td>
<td>8.894 0.000</td>
<td>1.59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>0.932</td>
<td>0.087</td>
<td>0.001</td>
<td>- -</td>
<td>-</td>
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</table>

Note: **P<0.01 compared with the BCI group of patients.

the BCI group was the largest among the three groups (Table 5).

### 3.7 MBI analysis of the daily living activity in patients

The MBI score evaluates personal hygiene, self-bathing, feeding, etc., a total of ten aspects of daily activities[37]. Our data showed no statistically significant difference in the MBI scores at the baseline among the three groups (all P>0.05 using the ANOVA test; Table 6). However, the interventions significantly improved the MBI scores in all three groups of patients (all P<0.01 using the paired t-test; Table 6). The differences before and after intervention were BCI>Control>MI groups, although there was no statistically significant difference (all P>0.05 using the ANOVA test; Table 6). For the MBI score, the effect size (Cohen’s d) in the BCI group was the largest among the three groups (Table 6).

### 3.8 Analysis of amplitude and latency of motor-evoked potentials (MEP) at non-lesion side

In this study, we utilized the transcranial magnetic stimulator to induce the MEP and recorded the MEP amplitude (µV) and latency (ms) to assess the excitability of the primary motor cortex (M1) in the non-lesional cerebral hemisphere and the conductivity of the descending neural pathway according to a previous study[38]. MEP was not collected in 12, 15, and 11 patients within the Control, MI, and BCI groups, respectively, because MEP could not be elicited, or MEP could not be detected due to a skull defect or metal skull repair from these patients. Our data showed no statistically significant difference in the MEP amplitude and latency at the baseline among the three groups of patients (all P>0.05 using the ANOVA test; Table 7). However, the MEP amplitude in the BCI group was significantly increased after intervention (P<0.01 using the paired t-test; Table 7). The differences in the MEP amplitude before and after intervention were BCI>Control>MI groups, although there was no statistically significant difference among them (all
Table 3  Comparison of the FMA-UE scores among these three groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference before and after intervention</th>
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<td></td>
<td>T</td>
<td>P</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>17.71±10.53</td>
<td>21.88±10.71</td>
<td>4.18±2.41**</td>
<td>-10.124</td>
<td>0.000</td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>20.50±12.02</td>
<td>24.31±12.61</td>
<td>3.81±2.15**</td>
<td>-10.046</td>
<td>0.000</td>
</tr>
<tr>
<td>BCI</td>
<td>32</td>
<td>18.66±7.89</td>
<td>25.81±8.09</td>
<td>7.16±3.54</td>
<td>-11.439</td>
<td>0.000</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>0.538</td>
<td>0.320</td>
<td>0.000</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: **P<0.01 compared with the BCI group of patients.

Table 4  Comparison of the FMA-LE scores among these three groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference before and after intervention</th>
<th>Pre- and post-intervention comparison</th>
<th>Cohen’s d</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>P</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>14.68±7.55</td>
<td>17.76±7.60*</td>
<td>3.09±1.90**</td>
<td>-9.493</td>
<td>0.000</td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>15.06±8.72</td>
<td>18.38±8.32</td>
<td>3.31±2.24**</td>
<td>-8.383</td>
<td>0.000</td>
</tr>
<tr>
<td>BCI</td>
<td>32</td>
<td>16.28±6.44</td>
<td>21.63±6.28</td>
<td>5.34±2.57</td>
<td>-11.749</td>
<td>0.000</td>
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<tr>
<td>P</td>
<td>-</td>
<td>0.676</td>
<td>0.086</td>
<td>0.000</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Note: *P<0.05 and **P<0.01 compared with the BCI group of patients.

P>0.05 using the ANOVA test; Table 7). Furthermore, regarding the MEP latency, the three groups of patients significantly improved after intervention (all P<0.05 using the paired t-test; Table 7). For the MEP amplitude and latency, the effect sizes in the BCI group were the largest among those of the three groups (Table 7).

4 Discussion

In this study, we designed a randomized controlled clinical trial with three arms, i.e., BCI, MI, and Control groups. The former two corresponded to bidirectional and top-down stimulation modes, respectively. In the Control group, patients could use active exercise training as a bidirectional stimulation when the limbs could move autonomously. However, only passive exercise training (bottom-up stimulation mode) could be used for their limbs with muscle strength ≤ grade 1 of MMT. This study included three stimulation modes for the first time and compared multiple indicators under unified control conditions. Upon completing this short rehabilitation period (six days a week for two weeks), our data showed that 1) All three types of rehabilitations could significantly improve the functions of convalescent stroke patients with hemiplegia; 2) The BCI-based MI training with both visual and motor feedback even helped the patients to better recover cognition, psychology, and limb movement; and 3) The BCI-based MI training also improved the excitability of the non-lesional cerebral hemisphere and the conductivity of the descending neural pathway. In conclusion, BCI-based MI training with both visual and motor feedback could be a future choice for the clinical rehabilitation of stroke patients with hemiplegia. Future studies with a larger sample size from different institutions will validate the findings from our current study.

To date, stroke rehabilitation mechanisms include the following four types (Fig.1. A), i.e., 1) The exercise training of effectors (such as limb muscles) using conventional upper/lower limb rehabilitation training devices could send a continuous bottom-up signal to the injury area of the brain, thereby stimulating the brain[46, 47]; 2) Direct current or magnetic stimulation of the corresponding cerebral cortex produces a top-down signal to the injury area of the brain[48, 49]; 3) Bidirectional stimulation of brain and peripheral effectors generates both top-down and bottom-up signals to the injury area of the brain simultaneously[50, 51]; and 4) BCI-based creation of an external channel can strengthen (for patients...
Table 5  Comparison of the 6MWD scores among these three groups of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference before and after intervention</th>
<th>Pre- and post-intervention comparison</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>P</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>78.32±8.17</td>
<td>84.32±8.78</td>
<td>6.00±7.98</td>
<td>-4.381</td>
<td>0.000</td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>97.68±83.71</td>
<td>105.44±89.07</td>
<td>7.75±7.36</td>
<td>-5.955</td>
<td>0.000</td>
</tr>
<tr>
<td>BCI</td>
<td>32</td>
<td>110.75±73.48</td>
<td>119.44±78.16</td>
<td>8.69±6.92</td>
<td>-7.101</td>
<td>0.000</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>0.256</td>
<td>0.248</td>
<td>0.333</td>
<td>-</td>
<td>-</td>
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</tbody>
</table>

Table 6  Comparison of the MBI scores among these three groups of patients

<table>
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<tr>
<th>Group</th>
<th>N</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Difference before and after intervention</th>
<th>Pre- and post-intervention comparison</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>T</td>
<td>P</td>
</tr>
<tr>
<td>Control</td>
<td>34</td>
<td>53.97±18.70</td>
<td>60.29±17.36</td>
<td>6.32±3.55</td>
<td>-10.392</td>
<td>0.000</td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>60.47±22.91</td>
<td>66.25±22.54</td>
<td>5.78±3.14</td>
<td>-10.418</td>
<td>0.000</td>
</tr>
<tr>
<td>BCI</td>
<td>32</td>
<td>61.88±14.24</td>
<td>68.59±13.15</td>
<td>6.72±3.27</td>
<td>-11.641</td>
<td>0.000</td>
</tr>
<tr>
<td>P</td>
<td>-</td>
<td>0.198</td>
<td>0.161</td>
<td>0.529</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

with less severe damage to the internal descending neural channel) or re-achieve (for patients with grievous damage to the internal descending neural channel) cortical control over effectors, resulting in voluntary limb movement, thereby enhancing or generating both top-down and bottom-up stimulations of the injury area in the brain\[25, 31, 52]\.

Our previous study revealed that the MSP and ETRs are useful for evaluating BCI system performance\[25\]. MSP assesses the proportion of the effective MI duration in BCI-based MI training by the recorded duration of motor control-related brain regions’ effective activation in terms of EEG signals and the descending control signals. Moreover, the ETRs can reflect the degree of limb terminal activation and the bottom-up sensory signal intensity. Thus, these two parameters can measure the intensity of bidirectional synchronous activation. In our current study (Fig.A1, a), over 24-28 training sessions in two weeks, the MSP and ETRs of the 32 convalescent stroke patients with hemiplegia showed an overall upward trend during the five upper limb training periods, while during the lower limb training periods, both the MSP and ETRs showed the maximum values in the first period, and then exhibited a slight downward trend. The reasons for these results are as follows: in China, most people have been cycling since childhood, and many have never been able to swim all their lives\[53\]. In all five assessment training periods (T1-T5), both the MSP and ETRs during the lower limb training were the largest in the first training period of assessment (T1), which indicated that the patients were easy to perform cycling MI at the beginning; in the subsequent training periods of assessment, both the MSP and the ETRs decreased slightly, which may be related to the state of lower limb training of patients at that time. In the initial assessment period (T1), the patient’s proficiency in upper limb swimming MI was not as high as that in lower limb cycling MI. Therefore, the MSP in this period during upper limb training was less than that during lower limb training. However, as the number of training sessions increased, the proficiency in upper limb swimming MI gradually improved, resulting in both the MSP and ETRs during upper limb training showing upward trends. Regardless of the training periods of assessment, the ETRs during upper limb training were all greater than the ETRs during lower limb training, which is explained by the fact that the upper limbs are more flexible than the lower limbs. Compared with driving the lower limbs, the equipment could more easily drive the upper limbs to do more rotations. In addition, regarding the BCI module safety, we found that all vital signs from these patients were
Table 7 Comparison of the MEP amplitude and latency among these three groups of patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group</th>
<th>N</th>
<th>Detected</th>
<th>Undetected</th>
<th>Before intervention</th>
<th>After intervention</th>
<th>Differences before and after intervention</th>
<th>Pre- and post-intervention comparison QT</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEP amplitude (µV)</td>
<td>Control</td>
<td>22</td>
<td>12</td>
<td>35.92±12.07</td>
<td>36.31±11.05</td>
<td>0.38±5.31</td>
<td>-0.331</td>
<td>0.744</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>17</td>
<td>15</td>
<td>33.76±14.12</td>
<td>33.90±14.12</td>
<td>0.14±3.96</td>
<td>-0.143</td>
<td>0.888</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>BCI</td>
<td>21</td>
<td>11</td>
<td>31.73±11.99</td>
<td>34.39±11.57</td>
<td>2.66±2.65</td>
<td>-4.587</td>
<td>0.000</td>
<td>1.00</td>
</tr>
<tr>
<td>P</td>
<td>0.517</td>
<td>-</td>
<td>0.556</td>
<td>0.800</td>
<td>0.113</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MEP Latency (ms)</td>
<td>Control</td>
<td>22</td>
<td>12</td>
<td>38.90±10.28</td>
<td>36.98±9.04</td>
<td>-1.92±3.29</td>
<td>2.748</td>
<td>0.012</td>
<td>0.59</td>
</tr>
<tr>
<td></td>
<td>MI</td>
<td>17</td>
<td>15</td>
<td>39.40±10.11</td>
<td>38.27±10.05</td>
<td>-1.13±1.71</td>
<td>2.715</td>
<td>0.015</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td>BCI</td>
<td>21</td>
<td>11</td>
<td>39.48±8.34</td>
<td>36.41±8.18</td>
<td>-3.07±2.63</td>
<td>5.349</td>
<td>0.000</td>
<td>1.17</td>
</tr>
<tr>
<td>P</td>
<td>0.517</td>
<td>-</td>
<td>0.978</td>
<td>0.815</td>
<td>0.089</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Note: *P<0.05 compared with the BCI group of patients.

stable and no single patient experienced noticeable side effects. To sum up, this BCI module is safe and reliable for patients.

One essential data generated in this trial was to show the effectiveness of all three interventions on patients, indicating the importance of exercise therapy in stroke patients. Indeed, a previous review and meta-analysis revealed that physical therapy-based rehabilitation training was able to enhance upper limb movement ability, increase muscle strength, and improve the quality of life, but reduce limb pain in stroke patients with hemiplegia[6], while exercise-based rehabilitation also improved the balance and gait in stroke patients[7]. Moreover, our current study also demonstrated that BCI-based MI training was even better in improving different parameters in these patients, further indicating that new technologies, such as tele-rehabilitation, robotic-assisted systems, virtual and augmented reality, wearable sensors, and smartphone apps have indeed accelerated stroke rehabilitation [54]. In the current study, we confirmed that BCI-based MI training improved the scores of MMSE, HAM-D, FMA-UE, and FMA-LE in these stroke patients with hemiplegia, although it may not improve all parameters we have assessed, including the 6MWD and MBI scores in the patients, which could be due to the short duration of the intervention. These measurements helped us assess patients’ cognition, depression, motor function, and quality of life. Thus, a future long-term intervention must be proposed for their proficiency to help stroke patients with hemiplegia. As we know, BCI-based MI not only plays a positive role in the recovery of motor functions of patients but also has an impact on the cognitive and psychological functions of patients; for example, different previous studies demonstrated that BCI was able to significantly improve the cognitive functions in the elderly and children and also possessed a capability to help prevent Alzheimer’s disease and treat the attention deficit hyperactivity disorder (ADHD) in children[55–57]. It is because in BCI-based MI training, many cognitive activities, like attention and target switching ability, are required from tested patients during the active movement rather than passive movement; thus, the repeated and high-intensity output of a specific brain signal during continuous training under external feedback stimulation could be important for neuromodulation in cognitive training[58].

In this study, the MEP was the sEMG signal generated by the excited contraction of the target muscle after the action potential induced through TMS stimulation of the M1 area in the non-lesional cerebral hemisphere was transmitted to the target muscle. The MEP amplitude is positively correlated with the excitability of the stimulated brain region, while the MEP latency is negatively correlated with the conductivity of the descending neural pathway[38, 59]. The study results revealed the following: 1) After intervention, the MEP amplitude increased in all three groups, but only the BCI group exhibited a significant increase, signifying the substantial enhancement of the excitability of the M1 area in the non-lesional cerebral hemisphere through BCI-based MI training; 2) After intervention, the MEP latency decreased significantly in all three groups, with the BCI group experiencing the most notable reduction, suggesting that the BCI-based MI training also significantly improved the conductivity of the descending neural pathway. MI is mainly an activity at the brain level. During BCI-based MI training, real-time visual and motor
feedback continuously enhanced MI, and "brain instructions" were kept generating and transmitted downward to the target muscles, thereby improving the conductivity of the descending neural pathway by strengthening the function of synapses\[60\].

The BCI group showed advantages over the Control and MI groups in a short period. The main reasons are as follows: 1) In this study, each group had such patients [Upper/lower limb muscle strength \(\leq\) 1 grade of MMT (n): Control 10/7 (29.4/20.6%), MI 9/7 (28.1/21.9%), BCI groups 14/5 (43.8/15.6%)] (Table A1). For stroke patients with limb muscle strength \(\leq\) 1 grade of MMT in the Control group and the MI group, the paralyzed limbs could not carry out effective active exercise training due to the lack of BCI system; in the BCI group, patients could use the L-B300 EEG Acquisition and Rehabilitation Training System to execute completely active exercise training even if their limbs with muscle strength \(\leq\) grade 1 of MMT, as long as they had clear consciousness and could perform MI; in addition, there were timely visual and motor feedback during BCI-based MI training (the feedback time was only 110 ms), which undoubtedly enhanced the efficacy. 2) For stroke patients with muscle strength >grade 1 of MMT in the three groups, although the paralyzed limbs could all carry out (partially) active exercise training, the Control group only had conventional exercise. In contrast, the BCI group had both conventional exercise and sufficient intensity of BCI-Based MI training. Furtherly, there was real-time visual and motor feedback during the BCI-based MI training process. Hence, the efficacy of the BCI group was better than that of the Control group. Though the MI group also had conventional MI training, due to the absence of real-time visual and motor feedback, patients could not feel the effect of conventional MI training in time, resulting in low motivation and enthusiasm for training. Even some patients who fell asleep during conventional MI training could not be found timely. Hence, its training intensity and efficacy were difficult to be guaranteed. The MI training intensity for patients in the BCI group could be shown by the progress bar on the right side of the display screen in real-time (updated every 110 ms). When the intensity of the patient’s MI (i.e., Mscore) reached a certain threshold, the virtual character on the display screen would start the corresponding movement; meanwhile, the rotary shafts of the system drove the patient’s limb movement; however, when the intensity of the patient’s MI fell below the pre-set threshold, the virtual character and the rotary shafts stopped moving\[31\]. These phenomena could be easily observed or detected by patients themselves, researchers, and the BCI system, which could remind patients to focus on the BCI-based MI training again and ensure the training intensity of MI; at the same time, because patients could easily feel the effect of the MI training (i.e., controlling the movement of the virtual character and the rotary shafts through MI), their motivation and enthusiasm were very high. It is precisely because of the advantages of the BCI-based MI training that the curative effect of the BCI group was generally better than those of the Control and MI groups.

However, our current study has some limitations. For example, the duration of rehabilitation intervention is too short, so a future long-term treatment should be scheduled. Moreover, the number of cases is also relatively small (just more than 30 cases in each group). In addition, although we performed six different assessments to evaluate cognition, psychology, limb movement, and brain function in the patients, the parameter reflecting brain function was only the MEP in the non-lesional cerebral hemisphere but lacked the MEP in the lesional cerebral hemisphere. Thus, a future study with a larger patient population will extend the intervention process and duration and add the MEP in the lesional cerebral hemisphere.

5 Conclusion

Scholars suggest BCI-based Motor Imagery (MI) training is more effective than conventional MI, but few studies directly compare them. In our randomized controlled clinical trial with BCI, MI, and Control groups, using bidirectional, top-down, and bottom-up stimulation modes, we assessed cognition, psychology, limb movement, and brain function. Results demonstrate that the BCI-based MI training for convalescent stroke patients with hemiplegia is feasible, safe, and effective. Mechanistically, BCI-based MI enhanced M1 area excitability and improved the descending neural pathway conductivity. After intervention, MEP amplitude increased significantly only in the
BCI group, indicating substantial enhancement of non-lesional cerebral hemisphere excitability. MEP latency decreased significantly in all groups, with the BCI group showing the most notable reduction, suggesting improvement of the descending neural pathway conductivity. These findings provide key insights into the comparative effectiveness and mechanisms of BCI-based MI training for neurorehabilitation. In addition, this system related MI visualization and controllability can help patients to enhance MI intensity that can be detected spatially and temporally to provide feasibility for rehabilitation therapists to timely interfere in patients’ MI and also create an effective tool for future research on the mechanism of the spike-timing dependent plasticity (STDP)\cite{61,62}.

6 Acknowledgment

We want to thank our clinical staff for their help in managing and caring for our patients. We would also like to thank Medjaden Inc. for the scientific editing of this manuscript.

7 Declarations

7.1 Ethics approval and consent to participate

This clinical trial was approved by the Ethics Review Board of The Second Affiliated Hospital, Anhui Medical University, with an approval number of YX2020-103(F1). This study followed the ethical standards of the 1975 Helsinki Declaration (revised in 2008) after obtaining written informed consent from each enrolled patient.

7.2 Consent for publication

Not applicable.

7.3 Availability of data and materials

The datasets are available from the url: https://dx.doi.org/10.21227/2a9x-vk53.

7.4 Competing interests

The authors declare that they have no competing interests.

7.5 Funding

This work was supported in part by a grant from The Research Center for Translational Medicine, The Second Affiliated Hospital of Anhui Medical University (2022ZHYJ01).

7.6 Authors’ contributions

Conceptualization, Y.Y., TT.W., and ZZ.C.; methodology, W.G.; software, ST.Z.; validation, YF.H., YQ.M., and ZZ.C.; formal analysis, TT.W.; investigation, ST.Z.; resources, GN.L.; data curation, XJ.W.; writing—original draft preparation, Y.Y.; writing—review and editing, YF.H.; visualization, P.L.; supervision, SQ.Z.; project administration, SQ.Z.; funding acquisition, YF.H. All authors have read and agreed to the published version of the manuscript.

Appendix A Supplementary Figure and Table

References


[2] Skidmore ER, Shih M. Stroke rehabilitation: recent progress and future promise. OTJR:
Table A1  Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Male/Female(n)</th>
<th>Age (years)</th>
<th>Course of disease(d)</th>
<th>Cerebral Hemorrhage infarction(n)</th>
<th>Left/right hemiplegia(n)</th>
<th>Upper/lower limb muscle strength ≤ 1 grade(n)</th>
<th>Rehabilitation treatment time (days)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>34</td>
<td>21/13</td>
<td>55.71±12.54</td>
<td>107.06±96.82</td>
<td>17/17</td>
<td>15/19</td>
<td>10.7</td>
<td>12.56±20.66</td>
<td>0.812</td>
</tr>
<tr>
<td>MI</td>
<td>32</td>
<td>22/10</td>
<td>54.63±11.11</td>
<td>86.94±76.51</td>
<td>15/17</td>
<td>17/15</td>
<td>9.7</td>
<td>12.69±17.38</td>
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<td>32</td>
<td>20/12</td>
<td>53.94±11.48</td>
<td>90.28±76.48</td>
<td>10/22</td>
<td>16/16</td>
<td>14.5</td>
<td>12.66±4.45</td>
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<td>P</td>
<td></td>
<td>0.812</td>
<td>0.827</td>
<td>0.581</td>
<td>0.262</td>
<td>0.758</td>
<td>0.503</td>
<td>0.746</td>
<td>0.262</td>
</tr>
</tbody>
</table>


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- VideosandPictures.zip