Combined Effects of Electroacupuncture and Behavioral Training on Learning-Memory Ability and Event-Related Potential P300 in Rats with Mid/Advanced Cerebral Infarction

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Abstract

Background: The effectiveness of the combination of electroacupuncture (EA) and behavioral training (BT) for mid/advanced cerebral infarction (M/ACI) and related mechanisms remains unclear. This study aimed to investigate the combined effects on the learning-memory ability and event-related potential P300 in rats with M/ACI.

Methods: Eighty rats with M/ACI were divided into Group Model (M), Group EA, Group BT, and Group EA-BT (n = 20) according to the random number with five healthy rats in Group Control (CON). On the 6th week after modeling, EA, BT, and EA-BT were given to Group EA, Group BT, and Group EA-BT, respectively, whereas Group M and Group CON were not given any intervention. Y-maze test and P300 were recorded before and after the intervention.

Results: After intervention, the P300 latency was lower and the amplitude was higher in the Group EA-BT, Group EA, and Group BT than before (for latency, t = −7.638, −4.334, and −5.916; for amplitude, t = 8.125, 3.846, and 5.238; P < 0.01), with Group EA-BT superior to Group EA (for latency, t = −3.708; for amplitude, t = 3.653; P < 0.01) and Group BT (for latency, t = −2.067; for amplitude, t = 2.816; P < 0.05), with no significant difference between Group BT and EA (for latency, t = −1.439; for amplitude, t = 1.075; P > 0.05). While the performances of Y-maze tests in the Group EA-BT, Group EA, and Group BT were all better than before (t = 10.359, 4.520, and 7.791, P < 0.01), with Group EA-BT better than Group EA (t = 5.627, P < 0.01) and Group BT (t = 2.913, P < 0.01) respectively, and Group BT better than Group EA (t = 2.912, P < 0.01).

Conclusion: EA or BT can affect P300 in rats with M/ACI, and the combination of these two methods can significantly improve the learning-memory ability.

Key words: Cerebral Infarction; Electroacupuncture; Event-Related Potentials; Exercise Therapy; P300; Rats

Introduction

Cognition refers to the psychological process of an individual realizing and understanding things.[1] Approximately 50% of patients with stroke may have certain cognitive dysfunction, especially learning-memory disorder.[2] Recently, a large number of studies have already confirmed that early electroacupuncture (EA) or behavioral training (BT) can improve the learning-memory ability. The principal underlying mechanism is centered around the ability of EA or BT to reduce the pathological damage to brain neurons, regulate neuronal regeneration and apoptosis, and maintain intracellular free radicals, extra- and intracellular ion homeostasis, and cytokine expression.[3-6] However, whether the above treatment is effective against mid/advanced cerebral infarction (M/ACI) has rarely been reported. P300,
an endogenous component of event-related potential (ERP), can reflect the process of information, memory, judgment, and reasoning inside the brain, and it has become an important index for the auxiliary diagnosis of cognitive impairment. P300 has been successfully extracted in many mammals. In this study, we prepared rat M/ACI models and used EA/BT treatment, aiming to observe the changes in P300 and to explore its possible neuro-electrophysiological mechanisms, thus providing a theoretical basis for M/ACI patients’ clinical return to community rehabilitation.

**Methods**

**Modeling and electrode implantation**
A total of 85 healthy male Wistar rats were purchased from the Experimental Animal Center, the Third Military Medical University, Chongqing, China, which weighed 250 ± 50 g and aged 12 months. First, all rats were fed for 2 days to acclimatize them to the environment and then anesthetized by intraperitoneally injecting a mixture of 25% urethane (Shanghai Hengyuan Biotechnology Co., Ltd., China) and 1% chloralose (Shanghai Yangguang Biotechnology Co., Ltd., China) (3 ml/kg). They were then fixed onto one brain stereotaxic instrument (Shanghai Mobiledatum Co., Ltd., China, RD1617-1ss), and right cerebral middle artery ischemia was induced using the suture-embolus method. The rat’s scalp was then cut open to expose the cranium. One micro screw electrode (1.0 mm in diameter) was then fixed using dental cement onto the skull surface 7.0 mm posterior and 1.0 mm levo-lateral to the zero point (the Bregma point) to record the P300 of the parietal lobe. A successful molding is determined when the rat exhibits the following appearances: the rat’s left anterior limb adducts and inflects when awake, homolateral Homer signs are positive, and the rat exhibits left circling when crawling or inclining to the left when standing. If any rats died in the modeling process or later due to different reasons, the rats should be supplemented timely to ensure a stable total number of rats. The rats were raised in cages and then divided into the Group Model (M), Group EA, Group BT, and Group EA-BT using the random number table (n = 20); five healthy rats were grouped into the Group CON. This study was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health. The animal use protocol has been reviewed and approved by the Institutional Animal Care and Use Committee of Sichuan Academy of Medical Sciences.

**Electroacupuncture**
Each rat in Group EA was fixed onto one self-made mouse plate, kept in a sober state, cut local fur, and disinfected. After that, two No. 28 1-inch filiform needles were obliquely inserted into the Baihui acupoint (0.5 inch in depth) and Dazhui acupoint (0.5 inch in depth), respectively, referring to the common rat acupoint positioning method in “rat acupoints” and “experimental acupuncture.” The needle handles were then connected with one G6805-C EA instrument (Guangzhou Hongxing Medical Instrument Co., Ltd., China). Electrical stimulation was provided using the following parameters: frequency 16 Hz and dilatational wave. The current intensity was used such that the rat could keep quiet and tolerate it (2 mA).

**Behavioral training**

**Drum-mesh training**
The rat was placed into one 100 cm long and 60 cm diameter circular mesh instrument, which was handedly rotated so that the rat will passively run for training its grip, rotation, and walking abilities.

**Balance training**
The rat was placed onto one 150 cm long and 2 cm wide square stick (5 cm above the ground) and induced its walk using food to train its balance.

**Screen training**
The rat was placed onto one screen (mesh, 1 cm × 1 cm, and width, 50 cm × 40 cm); the screen was 80 cm above the ground with 12 cm sponge paving below. The screen was changed from horizontal to vertical and then kept for 5 s; the rat was observed whether it fell from the screen or used its front claw to seize the screen. The longer the rat stayed on the screen, the better the muscle strength (training the rat’s grasp and muscle strength).

The above trainings began on the 6th week after the modeling. EA was performed once a day (15 min), and BT was performed twice a day: once in the morning and once in the afternoon (15 min each session, for 2 weeks). The rats in Group M and Group CON were quietly raised in cages without any intervention.

**Y-maze study test**
The Y-maze study test was performed in all groups 2 weeks after the intervention. It is a single maze with three isometric arms (Zhangjiagang Biomedical Instrument Factory, China) with a signal light at the top of each arm to prompt “danger.” Six seconds after the signal light brightened, this arm was dangerous due to connection with 36 V AC to stimulate the ability of the rats to run away from the bright arm to the dark arm. There will always be a safe arm during the training, which will be irregularly changed. The experiment is carried out in a quiet, dark environment. At the beginning of the experiment, each rat was placed in the maze and a 5 min adaption was provided before the experiment. If the rat goes from one electrified arm (lighted arm) to another electrified arm, it is marked as a mistake; if the rat goes from one electrified arm (lighted arm) to one un-electrified arm (dark arm), it is marked as correct. Each rat is trained for six segments (10 times per segment) in 1 day, with 2 min rest between segments. The number of correct running is recorded.

**Target acoustic stimulation training**
Before testing P300, the target acoustic stimulation training was performed in each rat. The training method was as follows: the rat was first placed in a quiet and relatively dark bar-climbing training box with 5 min adjustment time, and then the test was started according to the method by Yamaguchi et al. The
non-target stimulation frequency was 2 kHz and accounted for 80% of the total stimuli. The target stimulation frequency was 8 kHz, which accounted for 20% of the total stimuli and randomly distributed among the non-target stimuli. The target and non-target stimuli both lasted for 50 ms, with a stimulus interval and intensity of 2 s and 80 dB, respectively. After the target stimulation, the rat was immediately administered square wave stimulation under its feet (wave width 5 ms, frequency 64 Hz) to stimulate it to climb the bar to avoid the electric stimulation. Each rat was continuously trained for 2 days until the active bar-climbing rate reached 90% with target stimulation, and then, the P300 test can be performed.

**P300 test**

P300 of each rat was recorded starting from the 4th day of electrode implantation until the end of the intervention: each rat was placed in one restriction cage, which was then placed in a self-made P300 test box. The front wall of the box was fitted with one auditory-stimulating speaker, and one myoelectricity-evoking potential meter (Keypoint, Dantec Co., Denmark) was used for the recording according to hearing oddball program (based on the frequency and intensity of acoustic stimulation by Yamaguchi, the reference electrode was connected to the ear, and the tail was grounded). The parameters of the recording and reference electrodes were as follows: electrode impedance, <2 KΩ; bandpass, 0.5–100 Hz; sensitivity, 20 µA; scanning time, 1000 ms; and averagely 30 times of superimposition. When the rat was quiet and appeared to have a stable and reliable P300 waveform, the peak-peak amplitude was recorded as the P300 value of the parietal lobe (from the previous peak of P3 until the peak of this P3); simultaneously, the peak latency was also measured.

**Statistical analysis**

The data were analyzed using the SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Numerical data were described using mean ± standard deviation. T-test analysis was used to estimate the changes in learning-memory ability and P300 within groups before and after the intervention, while one-way analysis of variance was used to compare the changes among groups. The level of significance was considered to be less than 0.05.

**Results**

**Comparison of learning-memory ability**

Before the intervention, the performance of the four intervention groups (Group M, Group EA, Group BT, and Group EA-BT) in Y-maze tests was poorer than that of Group CON ($t = 6.939, 6.980, 7.174, and 7.007, P < 0.01$), implying that models with learning-memory dysfunction were successfully identified. After the intervention, the performance of Group EA-BT, Group EA, and Group BT in Y-maze tests was significantly better than the performance before the intervention ($t = 10.359, 4.520$, and $7.791, P < 0.01$), with Group EA-BT performing better than Group EA ($t = 5.627, P < 0.01$) and Group BT ($t = 2.913, P < 0.01$), and Group BT performing better than Group EA ($t = 2.912, P < 0.01$). The difference in the intragroup comparison in the Group M was not statistically significant ($t=0.855, P > 0.05$), but the correction times represented an increasing trend [Table 1].

**Determination and comparison of P300**

**Determination of P300**

P300 can be extracted from each group, and the waveform in the Group M showed relatively poor differentiation. Figure 1 shows the P300 waveforms of all groups.

**Comparison of P3 among different groups**

The difference between Group BT and Group EA (for latency, $t = −1.439$; for amplitude, $t = 1.075; P > 0.05$). The difference in the intragroup comparison before intervention was not statistically significant, the P300 latency was longer, and the amplitude was smaller in the four intervention groups (Group M, Group EA, Group BT, and Group EA-BT) than the Group CON (for latency, $t = 6.289, 5.874, 6.015, and 4.770$; for amplitude, $t = 5.492, 6.415, 6.106, and 6.398, P < 0.01$). After the intervention, the latency was significantly lower and the amplitude was significantly higher in the Group EA-BT, Group EA, and Group BT than those before the intervention (for latency, $t = −7.638, −4.334, and −5.916$; for amplitude, $t = 8.125, 3.846, and 5.238; P < 0.01$), and those in Group EA-BT were significantly higher than those in Group EA (for latency, $t = −3.708$; for amplitude, $t = 3.653; P < 0.01$) and Group BT (for latency, $t = −2.067$; for amplitude, $t = 2.816; P < 0.05$), respectively. No statistically significant difference was observed in the Group M (for latency, $t = −1.847$; for amplitude, $t = 0.846, P > 0.05$), but the P300 latency and amplitude represented an improving trend [Table 2].

**Discussion**

In this study, to emphasize the combined effects of EA and BT on learning-memory ability and ERP P300 in rats with M/ACI, BT, including drum-mesh training, balance training, and screen training, was administered to rats in Group BT, and EA was administered at the Baihui and Dazhui acupoints to rats in Group EA. BT combined with EA was administered to rats in Group EA-BT, and then cognition testing using the Y-maze test was performed.

| Groups   | $n$ | Before intervention | After intervention |
|----------|----|---------------------|--------------------|
| Model    | 20 | 19.16 ± 10.32       | 22.14 ± 11.67      |
| EA       | 20 | 18.92 ± 10.33       | 34.07 ± 10.86$^*$  |
| BT       | 20 | 19.23 ± 9.87        | 43.67 ± 9.97$^*$$^\dagger$ |
| EA-BT    | 20 | 19.09 ± 10.22       | 53.13 ± 10.56$^*$$^\ddagger$ |
| CON      | 5  | 55.62 ± 11.36$^*$   |                     |

Comparison between Group CON and other groups after modeling, $^p<0.01$; Intragroup comparison of before and after intervention, $^\dagger$P<0.01; Comparison between Group EA-BT and Group EA after intervention, $^\ddagger$P<0.01; Compared with Group BT, $^\ddagger$P<0.01; Comparison between Group BT and Group EA, $^\ddagger$P<0.01. EA: Electroacupuncture; BT: Behavioral training; CON: Control.
to assess their learning and memory abilities. P300 was recorded to observe the corresponding electrophysiological changes in the brain. The results showed that the learning and memory abilities of rats in Group EA-BT, Group BT, and Group EA after the intervention were all significantly improved than before the intervention, with Group EA-BT having superior abilities than Group EA ($P < 0.01$) and Group BT ($P < 0.05$), and Group BT having superior abilities than Group EA ($P < 0.01$). Meanwhile, the P300 latency was significantly shorter, and amplitude was significantly higher in Group EA-BT, Group BT, and Group EA after the intervention than before the intervention, with Group EA-BT having superior latency and amplitude than Group EA ($P < 0.01$) and Group BT ($P < 0.05$), and

![Figure 1: Comparison of P300. (a) Group Model before and after modeling; (b) Group EA before and after treatment; (c) Group BT before and after treatment; (d) Group EA-BT before and after treatment; (e) Group CON. EA: Electroacupuncture; BT: Behavioral training; CON: Control.](image)

| Groups     | n   | Before intervention | After intervention |
|------------|-----|---------------------|--------------------|
|            |     | Latency (ms)        | Amplitude ($\mu$V)| Latency (ms) | Amplitude ($\mu$V) |
| Model      | 20  | 437.27 ± 38.57      | 7.14 ± 2.08       | 401.19 ± 41.52 | 7.64 ± 1.63 |
| EA         | 20  | 432.36 ± 40.11      | 7.23 ± 1.64       | 371.90 ± 47.79 | 9.59 ± 2.20 |
| BT         | 20  | 435.34 ± 40.12      | 7.19 ± 1.78       | 349.39 ± 51.10 | 10.30 ± 1.97 |
| EA-BT      | 20  | 437.21 ± 54.48      | 7.15 ± 1.68       | 318.42 ± 43.32 | 12.15 ± 2.18 |
| CON        | 5   | 309.16 ± 49.77*     | 13.08 ± 2.52*     |                |                |

Comparison between Group CON and other groups after modeling, *$P<0.01$; Intragroup comparison of before and after intervention, †$P<0.01$; Comparison between Group EA-BT and Group EA after intervention, ‡$P<0.01$; Compared with Group BT, §$P<0.01$; Comparison between Group BT and Group EA, ||$P>0.05$. EA: Electroacupuncture; BT: Behavioral training; CON: Control.
Group BT having superior latency and amplitude than Group EA ($P < 0.01$). These outcomes imply that both BT and EA can improve the learning and memory ability in rats with M/ACI. Further, the combination of these two methods may improve the learning and memory ability while causing more corresponding changes in P300 latency and amplitude in the brain.

P300 is the most typical and commonly used component of ERP, closely related to the cognitive process, and regarded as the window of “peeping” psychological activities. P300 includes exogenous (P1, N1, and P2) and endogenous components (N2 and P3). The exogenous components are mainly involved in the sensory process and are more influenced by the physical properties of the stimuli. The endogenous components are mainly involved in the cognitive process, which are more influenced by psychological factors and are related to the cognitive process such as attention and memory. The latency of P3 represents the speed at which the brain classifies, encodes, and identifies the external stimuli and can reflect the speed of the neural activity and processing. The P3 amplitude reflects the degree of effective resource mobilization during information processing in the brain. Therefore, P300 provides a reliable and objective electrophysiological testing index for cognitive processes.

With the development of comprehensive studies on the neuro-electrophysiological mechanisms of P300, P300 is also actively recorded from many mammals by mimicking human behavioral responses to target stimuli. When testing animals, the P300 electrode can be placed inside the calvarium or at the cranial top; the positions used in the former method include the cerebral cortex, hippocampus, medial geniculate body, or thalamus. The electrode placed at the cranial top refers to the international standard of 10–20 electrode coordination method. The basic waveforms of P300 recorded from different electrode sites are similar. A number of studies have shown that the cranial electrode can record P300 in a satisfactory manner and is the most convenient method for this purpose. Therefore, the study used the cranial electrode method for recording.

In this study, P300 was measured on the 4th day after the rats were successfully made into cerebral infarction (CI) model. The latency was significantly prolonged, and the amplitude was significantly decreased when compared with the Group CON. Prolonged latency represents impairment of the brain’s execution function, and decreased amplitude indicates that the brain’s information-processing speed slowed down. The extent of effectively mobilizing the resources also weakened, suggesting that the rats with CI had different degrees of cognitive impairment in the early stages. The mechanism is that CI-induced pathological changes degenerate the limbic system, such as the hippocampus and amygdala, and the frontal-subcortical structural nerve cells that are closely related to the identification and learning functions, to reduce the cortical cerebral waking state and the cerebral activation or excitability and to weaken its ability toward processing external information and regulating behaviors.

Acupuncture is one of the essences of traditional Chinese medicine and has a history of more than 2000 years; acupuncture and traditional Chinese medicine believe that “when lesions were located in the brain, the first treatment target should be the Du Meridian.” The Baihui and Dazhui acupoints belong to the Du channel; the former is located at the top of the head and in the intersection between five important channels (the Du channel, Taiyang Bladder Channel of Foot, Shaoyang Sanjiao Channel of Hand, Shaoyang Gallbladder Channel of Foot, and Jueyin Liver Channel of Foot), which commands the Yang inside the whole body and connects the brain in vivo. The Dazhui acupoint lies close to the head and is the intersection of the Du channel and SanYang of hand and foot. Treatment targeting these two acupoints can simultaneously restore consciousness, realize resuscitation, calm Liver-Wind, dredge in vivo channels, and activate arteries and veins; therefore, they have been long used in treating forgetfulness and dementia. Animal experiments have confirmed that continuous EA stimulation can improve the cerebral blood flow, confront free radical damage, inhibit cell apoptosis, reduce nerve cell damage, regulate neurotransmitters, promote angiogenesis, regulate vasoactive substances, promote secretion and metabolism of brain neurotransmitters, and regulate the inhibitory status of the ischemic cortex, thus increasing its compensatory function, promoting the ordering of EEG activities, and improving the basic electrical activities of the cortical cells. The experimental rats’ brain perception capacity can thus be increased, their brain execution function is enhanced, and their ability of processing external information and regulating behaviors are also promoted. In this study, we have found that the P latency in the M/ACI rats is shortened, while the amplitude is increased, and the learning-memory ability in the Y-maze is also improved.

The same BT can also shorten the P3 latency in the M/ACI rats while increasing the amplitude and improving the learning-memory ability in the Y maze. The mechanism may be due to the following: (1) promoting cerebral angiogenesis in CI rats, improving the blood supply to the cerebral ischemic areas, and reducing the number of ischemia-caused necrotic neurons; therefore, the adjacent noninjury area can occur functional reorganization, which plays important roles in recovering the cognitive function and (2) improving the link and transfer of neural networks and promoting the reconstruction of the functional loop in the injured brain area, thus, the curvature of the hippocampal synaptic interface and the thickness of the posterior synaptic intense masses can be increased, the percentage of perforated synapse can be increased, and the transfer function among different active areas can thus be greatly enhanced. Meanwhile, the changes in the opening conductance level, duration, and probability of the N-methyl-D-aspartic acid receptor channel further enhance the synaptic transmission function, significantly further speed up the long-term.
potentiation potential formation rate that can reflect the learning-memory sensitivity,\textsuperscript{[32]} reorganize the cortical function, allocate more resources to attention, and increase the processing speed.

In this study, we also found that the latency of P3 in Group BT is shorter while the amplitude is higher than that in Group EA, and the increase of P3 amplitude reflects that BT causes the increase of resource allocation to attention. This may be because EA is only a passive input stimulus while lacking active attention input; BT such as drum-mesh training, balance training, and screen training can achieve the active participation of the rats' vision and tactile sensation. Furthermore, the joint and posture stimuli can make the neurons gain sensation, movement, and attention information, thus promoting the formation of new effective neural pathways to speed up the auditory information processed in the brain through selection, attention, classification, coding, and recognition. The brain can increase the degree of mobilizing effective resources, with shortened P3 latency and increased amplitude electrophysiologically and better Y maze learning-memory performance behaviorally than Group EA.

This study found that the performance of learning and memory in Group BT-EA was better than Group BT and Group EA, which promotes more corresponding changes of P300 latency and amplitude in the brain. This represented that the combination of these two methods can enable them to mobilize the simultaneous excitation of more neurons so that the central nervous network link during cognitive activities is strengthened and more cognitive processing resources can be mobilized to complete the current cognitive tasks to significantly improve the overall cognition of the brain and prominently enhance its learning-memory ability.

This study suggests that EA combined with BT can significantly improve the learning-memory ability in MACI rats. This method is simple and practical and is suitable in studying patients with mid-/advanced stroke. In our future studies, we will explore the effects of different ways, intensities, movement duration, and acupuncture points and stimulation degrees on the cognitive function. We believe that, through continuous research and exploration, the mechanism of EA-BT toward cognitive function in MACI patients will become increasingly clear.

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Conflicts of interest
There are no conflicts of interest.

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电针结合行为训练对脑梗死中晚期大鼠学习记忆能力和事件相关电位P300的影响

摘要

背景：电针结合行为训练对中晚期脑梗死的影响及相关机制仍不清楚。本研究的目的是探讨电针结合行为训练对脑梗死中晚期大鼠学习记忆能力和事件相关电位P300的影响。

方法：80只脑梗死中晚期大鼠按随机数字表法分成模型组、电针组、训练组、联合组，每组各20只；对照组为5只健康大鼠。于造模后第6天，分别给予电针组、训练组、联合组以电针+行为训练，而模型组和对照组不给予任何干预。分别于干预前后记录Y-迷宫分辨学习能力和P300。

结果：干预后，联合组、电针组、训练组P300与干预前比较其潜伏期均减小，波幅均增大（潜伏期：t = −7.638, −4.334, −5.916；波幅：t = 8.125, 3.846, 5.238；P < 0.01）；且联合组优于电针组(潜伏期：t = −3.708；波幅：t = 3.653；P < 0.01)和训练组(潜伏期：t = −2.067；波幅：t = 2.816；P < 0.05)，而电针组和训练组之间差异无统计学意义(潜伏期：t = −1.439；波幅：t = 1.075；P > 0.05)。Y-迷宫结果显示联合组、电针组、训练组学习记忆能力分别较干预前改善(t = 10.359, 4.520, 7.791；P < 0.01)，且联合组优于电针组(t = 5.627, P < 0.01)和训练组(t = 2.913, P < 0.01)，训练组优于电针组(t = 2.912, P < 0.01)。

结论：电针或行为训练均影响脑梗死中晚期大鼠P300，两者联合使用可显著提高学习记忆能力。