The effects of computer-aided cognitive rehabilitation combined with virtual reality technology on event-related potential P300 and cognitive function of patients with cognitive impairment after stroke

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Abstract. – OBJECTIVE: The aim of this study was to explore the effects of computer-aided cognitive rehabilitation (CACR) combined with virtual reality (VR) technology on event-related potential P300 and cognitive function in patients with cognitive impairment after stroke.

PATIENTS AND METHODS: Clinical data from 94 patients with post-stroke cognitive impairment, admitted to our hospital from January 2020 to March 2023, were retrospectively analyzed. Of them, 45 patients received routine rehabilitation training (Control group), and 49 patients received CACR combined with VR technology (Observation group). Cognitive rehabilitation status, event-related potential P300 examination status, biochemical indices levels, and daily living activity scores of the two groups were evaluated and compared.

RESULTS: After treatment, cognitive function significantly improved in the Observation group compared to the Control group. The amplitude of P300 in the Observation group was significantly higher, and the latency was significantly lower compared to the Control group. The levels of brain-derived neurotrophic factor (BDNF) in the Observation group were significantly higher ($p<0.05$), while the levels of cystatin C (Cys-C) and neuron-specific enolase (NSE) were significantly lower than those in the Control group ($p<0.05$ each). Patients in the Observation group demonstrated a significantly higher ability to perform daily living activities compared to the Control group ($p<0.05$).

CONCLUSIONS: Compared with conventional rehabilitation training, the combination of CACR and VR technology in the treatment of stroke-induced cognitive impairment is more effective in improving patients' cognitive function, regulating BDNF, Cys-C, and NSE levels, and enhancing patients' ability to perform daily living activities.

Key Words:
Computer-aided cognitive rehabilitation, Cognitive impairment, Virtual reality, Stroke.

Introduction

Stroke is a common type of brain tissue damage caused by a sudden obstruction or rupture of cerebral blood vessels[1]. Patients may have varying degrees of brain tissue damage and often experience different types of sequelae after successful treatment, with cognitive impairment being the more common[1,2]. Cognitive impairment after stroke is often accompanied by varying degrees of memory impairment, dementia, etc., seriously affecting the quality of life and physical and mental health[3,4]. Therefore, there is a great need to find efficient and feasible treatment plans for stroke patients[2,4].

The current clinical rehabilitation training measures for cognitive impairment after stroke are often not systematic and inefficient, making it difficult for patients to fully benefit from them[5]. In recent years, with the continuous development

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and improvement of computer technology, computer-aided cognitive rehabilitation (CACR) has become increasingly popular[6]. It is attractive for patients and encourages them to actively carry out repetitive and targeted training through games, generating positive brain stimulation and effectively aiding in the reconstruction of damaged brain function[6,7]. Virtual reality (VR) technology is also an important rehabilitation training method for stroke patients[8]. During the training period, the patient's movements are presented on the screen[9], and the patient interacts with the environment presented on the computer screen (immersive rehabilitation)[8,9].

At present, there is limited literature on the application of CACR combined with VR technology in the treatment of cognitive impairment after stroke. The aim of the current study is to retrospectively analyze the data of patients with post-stroke cognitive impairment who received CACR combined with VR technology treatment to clarify the effectiveness of CACR combined with VR technology for the rehabilitation of stroke patients.

Patients and Methods

Patients

Clinical data from 94 patients (52 males and 41 females) with post-stroke cognitive impairment, admitted to the Second Rehabilitation Hospital of Shanghai from January 2020 to March 2023, were retrospectively analyzed. The age of the patients ranged from 49 to 80 years, with an average age of 64.7±7.2 years. The course of the disease ranged from 2 to 9 months, with an average of 5.35±1.97 months. A total of 45 patients received routine rehabilitation training treatment and were assigned to the Control group; 49 patients received CACR combined with VR technology treatment and were assigned to the Observation group. The Ethics Committee of the Second Rehabilitation Hospital of Shanghai approved this study, No. 2020-30-01, Date: 2020-03-01.

Inclusion Criteria

- Meets the diagnostic criteria for cognitive impairment after stroke[10];
- Stable vital signs and clear consciousness;
- The mini-mental state examination (MMSE) score is less than 27 points;
- Not receiving any other relevant treatment before the inclusion in the study;
- Complete clinical data;
- Received two months of treatment.

Exclusion Criteria

- Patients with other cerebrovascular diseases;
- Patients with a previous history of mental illness;
- Patients with significant intellectual impairment prior to stroke;
- Long-term medication treatment for patients that may affect their mental state.

Regular Rehabilitation Training

1) Patients were encouraged to communicate more with others and were provided targeted treatment based on their psychological characteristics. Effort was made to alleviate negative emotions and reduce physical and mental burden; 2) Functional training, including retelling and naming exercises (referring to voice prompts, retelling different animal and item names), memory exercises (including building block arrangement exercises, recalling recent events, identifying and memorizing photos, etc.) were conducted.

CACR Combined with VR Technology

CACR

RehaCom computer-assisted cognitive rehabilitation training instrument from Beijing Oupeide Technology Co., Ltd. was used. It consists of the following 7 modules: 1) Attention – patients were provided with 2 images and guided to quickly find and mark the differences; 2) Graphic Memory – patients were provided with a set of images based on the patient's cognitive ability state, and asked them to remember their order. The order of the images was then changed, and patients were instructed to sort the images again based on their memory status; 3) Search ability – patients were presented with multiple identifiers on the computer screen, and asked to quickly search after giving instructions for one identifier; 4) Spatial manipulation ability – patients were presented with different three-dimensional shapes, and were instructed to observe the graphic features from multiple angles including left and right, up and down, and front and back; 5) Reactive behavior – presenting different traffic signs to patients, guiding them to quickly evaluate the significance represented by the signs in the shortest possible time; 6) Logical ability – providing patients with a set of regular images or numbers to guide them in finding the shapes or numbers that should appear in the blank spaces; 7) Computational ability – patients were guided to start practicing simple addition, subtraction, multiplication, and division algorithms; if the patient answered well, the difficulty was increased appropriately.

VR technology

The equipment selected was the STB-110 99PAL machine of Man&tel Company in South Korea, which includes 5 exercise modules: 1) Image pairing exercise – presenting multiple randomly arranged graphics on the display screen without order, requiring patients to remember the same image position within 30 seconds. The same images are then searched through the nine sensing boards under the patient's feet; 2) Obstacle runway – 1 kitten is displayed on the display screen, guiding the patient to use their feet to control nine different colored sensing boards under their feet, in order to manipulate the kitten on the display screen to avoid different obstacles on the runway; 3) Jigsaw Exercise – presenting different fragments of a certain image on the display screen, guiding patients to use complete background information prompts for puzzle training; 4) Picking Fruits – the display screen displays a fruit tree with different types of fruits on it; the patient picks the corresponding fruit according to the instructions on the left side of the screen and puts the fruit into the fruit basket; 5) Algorithm Exercise – arithmetic questions appear on the display screen, with 1 or 2 small squares above and unordered numbers in the middle. Patients are guided to calculate the answer and move the number representing the answer into the box by hand.

Patients received the appropriate treatment 6 times a week for a total of 8 weeks.

Observation Indicators

1) Cognitive function - assessed using the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment Scale (MoCA), with a total average score of 30 points. A higher score indicated better cognitive function. 2) For the event-related potential P300 examination (Model: Nuampa40; Neuroscan Corporation; Texas, USA), a recording electrode was placed at the central midpoint, and a reference electrode was placed at the lower edge of the mastoid processes behind both ears. The impedance between the skin and the electrode did not exceed 5 kQ, and the stimulus selection was 85 dB, 1,000 Hz pure tone with a probability of occurrence of 0.8. The bias stimulus was 95 dB, 2,000 Hz pure tone with a probability of occurrence of 0.2, and the stimulus interval was 1.5 seconds. Patients were assisted in wearing headphones and were instructed to click the left mouse button if they heard deviant stimuli. Amplitude and latency of P300 waves were recorded. 3) Chemical indicators – 4 ml of fasting venous blood was taken, and the supernatant was centrifuged (3,000 r/minute, 15 minutes). Serum levels of brain-derived neurotrophic factor (BDNF), cystatin C (Cys-C), and neuron-specific enolase (NSE) were measured by enzyme-linked immunosorbent assay (ELISA) using the appropriate commercial kits from Shanghai Enzymes Biotechnology Co., Ltd. 4) Activity of Daily Living Ability – Activity of Daily Living Ability was assessed based on the Modified Barthel Index (MBI) assessment, that includes a total of 100 points, with higher scores indicating better activity of daily living.

Statistical Analysis

Collected data were entered into Microsoft Excel and analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and PRISM 8.0 software (La Jolla, CA, USA). According to the distribution normality evaluated by the Shapiro-Wilk test, continuous variables were reported as mean and standard deviation or median and interquartile spacing. The normality of the data was evaluated using the Shapiro-Wilk test. The data of normal distribution were expressed by mean ± standard deviation, and a *t*-test was used. The data of non-normal distribution were expressed by median and interquartile interval and analyzed by Wilcoxon test. The counting data were represented by the number of use cases, using the Chi-square test or Fisher's exact probability method. A *p*-value lower than 0.05 was considered statistically significant.

Results

There was no significant difference in the general information such as age, gender, stroke type, course of disease, and education level between the two groups ($p>0.05$) (Table I).

Before the treatment, MMSE and MoCA scores in the two groups were comparable ($p>0.05$). After the treatment, MMSE and MoCA scores in the two groups increased compared to before treatment and were significantly higher in the Observation group compared to the Control group ($p<0.05$) (Figure 1).

Before the treatment, there was no significant difference in the amplitude and latency of P300 between the two groups ($p>0.05$). After the treatment, the amplitude of P300 in both groups increased, while the latency decreased compared to those before the treatment. P300 amplitude of the

Table I. Comparison of two sets of baseline data.

Group	Gender (male/ female)	Age (year)	Course of disease (month)	Stroke type		Education level	
				Cerebral hemorrhage	Cerebral infarction	Below High School	High school and above
Observation-group (n=49)	25/24	65.5±7.4	5.55±1.80	14	35	26	23
Control-group (n=45)	27/17	63.9±7.0	5.13±2.14	9	35	30	14
χ^2/t	1.006	1.082	1.013	0.821		2.212	
p	0.316	0.282	0.314	0.365		0.137	

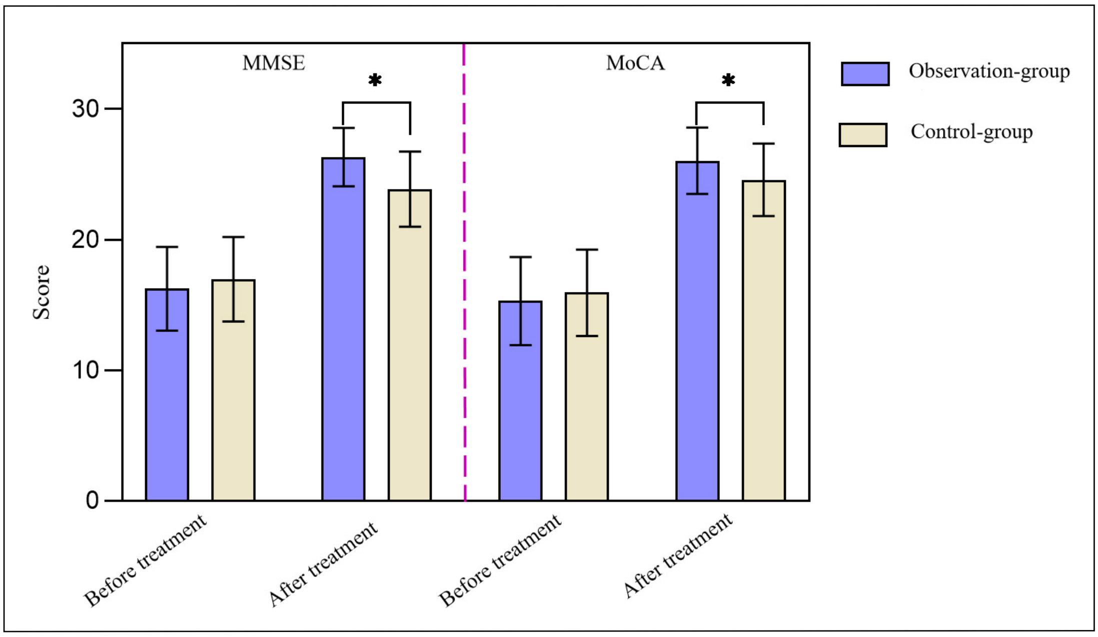

Figure 1. Comparison of cognitive function rehabilitation between two groups. * indicates a comparison between the two groups, $p<0.05$.

Observation group was significantly greater, and the latency was significantly lower than that of the Control group ($p<0.05$) (Table II).

There was no significant difference in serum BDNF, Cys-C, and NSE levels between the two groups before the treatment ($p>0.05$). After the treatment, serum BDNF levels in the two groups increased, while Cys-C and NSE levels decreased compared to the pre-treatment levels. Serum BDNF levels in the Observation group were significantly higher, and the levels of Cys-C and NSE were significantly lower than those in the Control group ($p<0.05$) (Table III).

Before the treatment, there was no significant difference in MBI scores between the two groups ($p>0.05$). After the treatment, the MBI scores of both groups increased compared to before the treatment and were markedly higher in the Observation group ($p<0.05$) (Figure 2).

Discussion

The results of our study show that compared with conventional rehabilitation therapy, patients with cognitive impairment after stroke who receive rehabilitation therapy using CACR combined with VR technology have better cognitive function rehabilitation effects. The main reason for this is that the CACR system is an intelligent interactive system with sound and visual feedback, and can accurately distinguish the cognitive

Table II. Comparison of P300 examination results of two groups of event-related potentials.

Time	Group	n	Amplitude (μV)	Latency (ms)
Before treatment	Observation group	49	5.77±1.11	436±46
	Control group	45	5.45±1.18	425±50
	t		1.321	1.158
	p		0.190	0.250
After treatment	Observation group	49	7.70±1.29	347±38
	Control group	45	6.66±1.26	369±39
	t		3.948	-2.673
	p		<0.001	<0.001

Table III. Comparison of serum biochemical index levels between two groups.

Time	Group	n	BDNF (ng/ml)	Cys-C (mg/L)	NSE (ng/ml)
Before treatment	Observation group	49	5.48±0.68	1.38±0.38	15.90±3.64
	Control group	45	5.63±0.74	1.49±0.39	16.91±3.75
	t		-1.065	-1.396	-1.319
	p		0.290	0.166	0.191
After treatment	Observation group	49	8.60±1.21	0.82±0.30	6.75±2.44
	Control group	45	7.50±1.00	1.21±0.35	9.30±2.51
	t		4.730	-5.659	-4.947
	p		<0.001	<0.001	<0.001

function level of the patients and provide them with rich, scientific, and reasonable training content. This method is perceived as entertaining and fun, thus ensuring patients' interest in practicing it[6,7]. VR technology mainly utilizes computer simulation of virtual scenes to provide patients with rich training content. It is imaginative, interactive, and immersive. Patients are encouraged to provide feedback and interactive connections in touch, hearing, vision, and other aspects in order to achieve the recovery and reconstruction of damaged functions[8,9]. Bian et al[11] pointed out that compared to conventional rehabilitation training, rehabilitation training based on VR technology

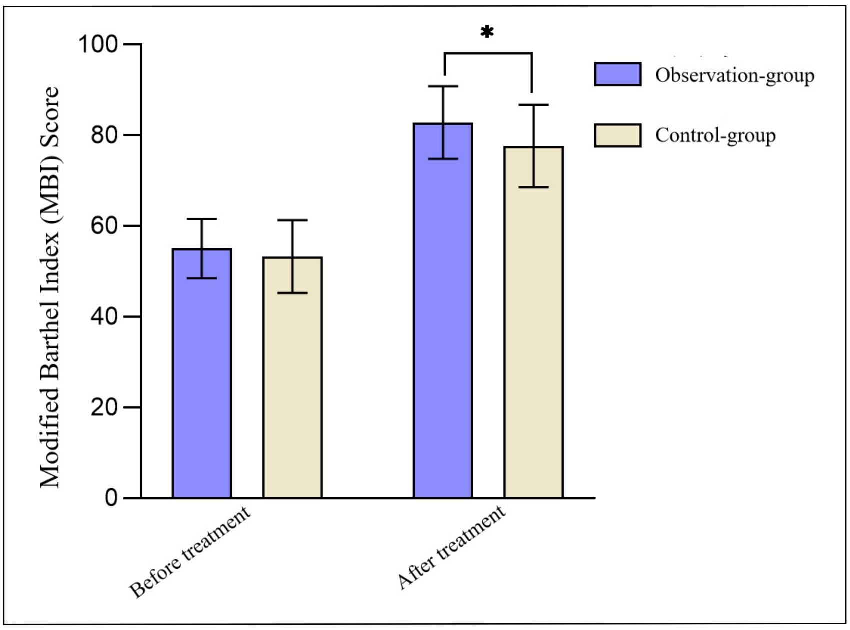

Figure 2. Comparison of MBI scores between two groups. *indicates a comparison between the two groups, $p<0.05$.

can provide patients with virtual game scenarios, through the integration of three-dimensional vision, touch, and hearing simulation scenarios. Such activities enhance patients' attention during training, keep them motivated, and encourage thinking, movement, visual organization, and other functions, thus ensuring the effectiveness of body functional rehabilitation. He et al[12] showed that the use of CACR technology can improve cognitive function in patients with cognitive impairment after the stroke, and can help to enhance their daily living activities. This is consistent with the results of our study. Zhang et al[13] combined acupuncture and other related treatments with CACR technology to treat patients with cognitive impairment after the stroke and showed that it can significantly improve the overall treatment efficiency. Nie et al[14] also confirmed that using CACR technology to treat patients with post-stroke cognitive impairment on the basis of conventional cognitive rehabilitation training can effectively improve their cognitive function. Amirthalingham et al[15] showed that compared to conventional rehabilitation training, VR technology can more effectively improve the body function of stroke patients. Errante et al[16] found that VR technology can effectively improve patients' motor ability and enhance the effectiveness of treatment in stroke patients. The results of our study are consistent with these research findings, confirming the value of CACR combined with VR technology in treating cognitive impairment after stroke.

Onatsu et al[17] showed that NSE is a specific enzyme widely distributed in the neuroendocrine system and brain neurons. It can participate in glycolysis and accounts for approximately 1.5% of soluble proteins in the whole brain. The expression level of NSE is usually low. However, in the event of brain tissue damage and the accompanying loss of cell membrane integrity, NSE is released into the cerebrospinal fluid and enters the bloodstream due to damage to the blood-brain barrier. Therefore, measuring blood levels of NSE can evaluate the degree of brain neuron damage in patients. Liu et al[18] showed that BDNF is a neurotrophin, widely distributed in the central nervous system, and plays an important role in the process of neuron growth and survival, differentiation, repair after injury, regeneration, etc. It is closely related to neural function and cognitive function. Su et al[19] pointed out that Cys-C is a low-molecular-weight cysteine protease inhibitor. The expression of brain cathepsin that is abnormally increased in a damaged brain can damage nerve cells, causing an abnormal increase in Cys-C content. The degree of increase is positively correlated with the degree of brain tissue damage. The results of our study showed that after the treatment, the levels of Cys-C and NSE in the Observation group were lower than those in the Control group, while the levels of BDNF were significantly higher than those in the Control group. Our results further confirm that CACR and VR techniques have high application value in patients with cognitive impairment after the stroke, and may improve disease treatment effectiveness and promote good disease outcomes.

Limitations

This is a single-center retrospective analysis with a small sample size and a certain selection bias. The conclusions of this study need to be validated through multicenter, large-scale, and long-term follow-up studies.

Conclusions

Compared with conventional rehabilitation training alone, the combination of CACR and VR technology can effectively improve cognitive function, regulate BDNF, Cys-C, and NSE levels in patients with cognitive impairment after stroke, and enhance their daily living activities.

Authors' Contributions

JS and SM conceived and designed the study, ZH, JX and HX collected data and performed data analysis. JS and SM wrote the draft of this manuscript. JH edited the manuscript.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Approval

The Ethics Committee of the Second Rehabilitation Hospital of Shanghai approved this study, No. 2020-30-01, Date: 2020-03-01.

Informed Consent

Written informed consent was obtained from the patient or legal guardian.

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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