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Effect of tDCS on Cognitive Function of Patients With Stroke: A Systematic Review and Meta–Analysis

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Abstract

Objective : This study aimed to analyze the effect of transcranial direct current stimulation (tDCS) on cognitive function recovery in patients with stroke.

Methods: Data published in Korean and foreign academic journals from 2009 to 2019 were searched using the NDSL, RISS, PubMed, and CINAHL databases. A total of 11 experimental research articles were selected based on the inclusion and exclusion criteria. A qualitative assessment was conducted, and a meta-analysis of nine results from seven of the stuides was performed using the Comprehensive Meta-Analysis 3.0 program.

- **Results**: Based on the results of the meta-analysis, the attention and memory effect sizes were 0.725 and 0.796, respectively, which were both considered a "medium effect size". Statistically significant changes were observed in both the areas (p<0.05).
- **Conclusion**: The results of this study confirmed that tDCS can be useful in the rehabilitation of patients with stroke with limited cognitive function. In addition, the application methods differed, indicating that a formalized tDCS protocol is required.

Keywords: Cognition, Stroke, tDCS, transcranial Direct Current Stimulation

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I. Introduction

Cognition is the ability to adapt to one's environment by understanding, judging, and determining the circumstances that occur within the environment (Yoo, Chun, Oh, & Chun, 1997; Whealtley, 2001). Cognitive functions can be divided into subfunctions such as attention and memory, and executive functions, and the combination of low and high functions allows an individual to think and act functionally in the environment (Wheatley, 2001). In addition, prior studies have revealed the correlation between the ability to perform daily life activities or quality of life, one of human cognitive and functional abilities (Lee, Kim, & Kim, 2015). Cognitive impairment leads to a reduction in activities of daily living (ADL), in addition to damage, and can cause further problems such as reduced participation and poor quality of life (Oros, Popescu, Iova, Michancea, & Iova, 2016).

Cognitive disorders are primarily caused by brain disorders, such as neurodegeneration or stroke, due to aging. Stroke rehabilitation, post-recovery deterioration management, and recurrence prevention are not only important, especially since stroke prevalence tend to increase with age and in patients with cardiovascular diseases, but also advances in medical technology (Chung & Kim, 2015). The incidence of cognitive impairment is high in 44% of patients after stroke and remains high 3 years after diagnosis (Patel, Coshall, Rudd, & Wolfe, 2002). Therefore, it is important to immediately identify the signs of cognitive impairment after stroke and manage it in a timely manner to prevent long-term functional damage (Oh & Jung, 2017).

Meanwhile, Diller et al. (1993) proposed cognitive

rehabilitation to improve cognitive impairment in occupational therapy, and brain plasticity theory became the basic theory of cognitive rehabilitation. As structural and functional changes are also observed in the adult cerebral cortex, brain plasticity theory-based cognitive rehabilitation programs are being developed and implemented to maximize the residual cognitive function and achieve neurological compensation in patients with impaired functions (Kim, 2001). In particular, noninvasive brain stimulation has been highlighted as a valid alternative to existing treatments, with the development of neuroimaging techniques such as functional magnetic resonance imaging (fMRI) and computerized tomography (CT).

The use of noninvasive brain stimulation in neurological diseases such as stroke allows the adjustment of the excitation and plasticity of the cerebral cortex. Among the noninvasive brain stimulation techniques, transcranial direct current stimulation (tDCS) involves the attachment of anodal electrodes or cathodal electrodes to the scalp, affecting the excitation of the cerebral cortex by allowing constant century and positive currents to flow through the scalp. It is a simple and safe procedure (Zaghi, Acar, Hultgren, Boggio, & Fregni, 2010). In neurological disorders, tDCS was initially used to examine the motor function of stroke patients and was later used to study the degree of language impairment, cognitive impairment, etc. in stroke patients. A previous cognitive rehabilitation study of stroke patients reported that the use of tDCS has been increasing and has improved the attention, memory, and executive functions of the said patient group (Chi, Fregni, & Snyder, 2010; Kang, Baek, Kim, & Paik, 2009; Smith & Clithero, 2009). In addition,

work therapy also demonstrates that tDCS is effective in cognitive function as tDCS is performed for cognitive rehabilitation for stroke patients (An & Kwon, 2019; Bae, Jeong, Lee, & Kim, 2012). Although it is likely that tDCS will be routinely used for cognitive rehabilitation in stroke patients as its effects have already been verified in previous studies, the application of this technique in the occupational therapy clinical setting remains challenging due to heterogeneous research methods.

There has been an increasing interest in the use of tDCS for cognitive rehabilitation of stroke patients. There is a growing interest in tDCS in cognitive rehabilitation in stroke patients, but there is a lack of classification of tDCS-based cognitive rehabilitation applied to stroke patients and introduction to practicality in clinical sites. Therefore, in this study, we aimed to systematically analyze the tDCS-based cognitive rehabilitation technique used in stroke patients at home and abroad and to determine their effect sizes using a meta-analysis to provide information and evidence that can be utilized in domestic clinical or research areas.

II. Methods

1. Study design

In this work, studies of transcranial direct current stimulation (tDCS) based cognitive rehabilitation conducted on stroke patients were independently considered by two evaluators, and results were integrated through Comprehensive Meta Analysis 3.0 program.

2. Search strategies

1) Study search and data collection

Between January 2009 and August 2019, the articles published in National Digital Science Library, Research Information Sharing Service (RISS), PubMed, and Cumulative Index of Nursing and Allied, in both Korean and foreign academic journals, were searched. The search term used for all four academic journals were "transcranial Direct current stimulation", "tDCS", "cognition" and "stroke".

2) Inclusion criteria and exclusion criteria

Studies that reported the effects of tDCS on the cognitive function of stroke patients, studies written in Korean and English, and studies that measured the cognitive function of stroke patients using standardized assessment tools were included. In contrast, studies related to the development of research, intervention protocols, or evaluation tools where no specialties are available; animal experiment research, posters; literature reviews; and meta-analyses were excluded.

3. Study selection process

The literature was collected and selected in the order of the search results, removing duplicates and screening titles, abstracts, and full-texts; the study selection process is presented in Figure 1.

4. Qualitative level of studies

In order to select the relevant studies, the Traditional Single-Hierarchy Evidence Model

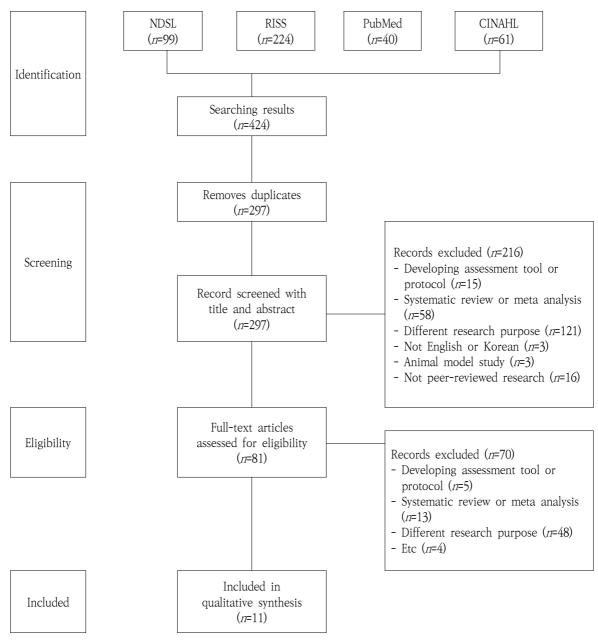


Figure 1. Flow Diagram for Study Selection

(Arbesman, Scheer, & Lieberman, 2008) was used to evaluate the quality of the study. Systematic consideration, meta-analysis, and random control studies were classified as Level I studies, while case studies, technical considerations, and qualitative studies were classified as Level V studies, with the lowest qualitative level.

5. Providing evidence

The literature on the effects of tDCS on the cognitive function of stroke patients was analyzed and presented based on the number of study participants, duration and frequency of treatment, experimental group-control intervention characteristics, evaluation tools used, and clinical effects.

6. Analysis method

1) Statistical heterogeneity

In the meta-analysis, heterogeneity means that the variations in the study results indicate abnormalities in sampling, which cannot be explained by chance: hence, statistical tests such as the chi-square test (Q statistics) and Higgin's I 2 statistical method are used to confirm heterogeneity (Kang, 2015). In this study, heterogeneity tests were conducted using the chi-square test method.

2) Effect size

Effect size refers to a quantitative index used to summarize research results in meta-analysis, reflecting the magnitude or strength of the relationship between two variables in each study. The methods used to integrate effective sizes in meta-analysis are fixed effect models and random effect models. Assuming the same population, the fixed effects model only accounts for changes in each parameter by the amount of variation in the study, while the variable effect model takes into account further changes between studies (Kang, 2015). In this study, according to the definition of effect size provided by Cohen (1988), the absolute value of the effect is less than 0.2 for small, 0.5-0.8 for medium, and 0.8 for large effect sizes.

3) Publication bias

Publication bias occurs when statistically significant studies have increased likelihood of being published than statistically insignificant studies. Therefore, the meta-analysis of published studies will more likely to overestimate the results than the actual effect size. In this study, publication expedients bias was reviewed using Funnel plot (Jang & Kim, 2019).

III. Results

1. Analysis of results

After searching for relevant literature from four databases, 424 articles were found. A total of 127 duplicate literature were removed, and 216 were excluded after reviewing the titles and abstracts. The full-text of the remaining 81 articles were reviewed, and finally 11 literature were selected based on the inclusion and exclusion criteria (Figure 1).

2. Characteristics of the studies

1) Quality of study

Based on the assessment of the qualitative level of 11 selected literature, eight studies (73%) were classified as Level I studies, while three were classified as Level II studies (27%) (Table 1).

2) General characteristics of the study subjects

A total of 378 stroke patients were recruited in the selected 11 papers to explore the effects of tDCS. A variety of patients were included, with acute to chronic conditions, and the general characteristics of the study patients are presented in Appendix 1.

Evidence level	Definition	Frequency n(%)
Ι	Systematic reviews Meta-analyses Randomized controlled trials	8(73)*
П	Two group non-randomized controlled studies	3(27)+
Ш	One group non-randomized controlled studies	0(0)
IV	Single subject studies Survey	0(0)
V	Case reports Narrative literature reviews Qualitative research	0(0)
	Total	11(100)

Table 1. Level of Evidence for Studies

* : Bae (2012); D'Agata et al. (2016); Hosseinzadeh et al. (2018); Park et al. (2013); Saidmanesh et al. (2012); Shaker et al. (2018); Yun. (2012); Yun et al. (2015)

+ : Au-Yeung et al. (2014); Jo et al. (2009); Yi et al. (2016)

3) Types of interventions and results of intervention

Six (Au-Yeung, Wang, Chen, & Chua, 2014; Hosseinzadeh et al., 2018; Jo et al., 2009; Saidmanesh, Pouretemad, Amini, Nillipour, & Ekhtian, 2012; Yi et al., 2016; Yun, 2012) of the 11 studies using tDCS alone examined the effects of tDCS on the cognitive function of stroke patients, while five other studies (Bae, 2012; D'Agata et al., 2016; Park, Koh, Choi, & Ko, 2013; Shaker, Sawan, Fahmy, Ismail, & Elrahman, 2018; Yun, Chun, & Kim, 2015) used intervention programs combining tDCS and cognitive training activities. The type of intervention program applied in each individual study is given in Appendix 1. In the case of stimulation locations, the researchers differed, indicating that DLPFC was used as the most stimulation location. Although the purpose of the study or the assessment tools used differed between studies, the experimental group, which received the tDCS intervention, had at least one significant result (Appendix 1).

4) tDCS

In 11 studies, tDCS was performed for 26 minutes, with an average strength of 1.77 mA, using a 28.64-cm² electrode (Table 2).

3. Results of meta-analysis

1) Statistical heterogeneity

For meta-analysis, the values of five attention and four memory areas were utilized in seven papers with data values among 11 papers. The Q-statistical test was used to incorporate the results by selecting a random effects model with an overall significance level of more than 0.05 (Table 3).

Study	Active tDCS mode (Target cortical area)	Intensity (mA)	Duration (mins)	Electrode size(cm²)
Au-Yeung et al. (2014)	Anode (M1 _{lesioned}) & Cathode (M1 _{unlesioned})	1	20	35
Bae (2012)	Anode (Left-F3) & Cathode (Right-Supraorbital)	1	20	35
D'Agata et al. (2016)	Anode (C3 or C4) & Cathode (Opposite to Anode)	1.5	20	25
Hosseinzadeh et al. (2018)	Anode (Left-STG) & Cathode (Right-STG)	2	30	35
Jo et al. (2009)	Anode (Left-DLPFC) & Cathode (Right-supraorbital)	2	30	25
Park et al. (2013)	Anode (bilateral prefrontal cortex)	2	30	25
Saidmanesh et al. (2012)	Anode(Left-DLPFC) & Cathode(Right-DLPFC)	2	20	25
Shaker et al. (2018)	Anode (F3, F4-DLPFC) & Cathode (Contralateral supraorbital area)	2	30	35
Yi et al. (2016)	Anode (Right-PPC) & Cathode (Left-PPC)	2	30	25
Yun (2012)	Anode (LATL) & Anode (RATL)	2	30	25
Yun et al. (2015)	Anode (Left-FTAS) & Anode (Right-FTAS)	2	30	25
	Mean	1.77	26.36	28.64

Table 2. Characteristics of Transcranial Direct Current Stimulation

DLPFC=dorsolateral prefrontal cortex; FTAS=fronto-temporal anode stimulation; LATL=left anterior temporal lobe; PPC=posterior parietal cortex; RATL=right anterior temporal lobe; STG=superior temporal gyrus

Table 3. Effect Size by Attention and Memory

		Effect	size			Heterog	geneity	
	Study (<i>n</i>)	Effect size	Ζ	р	Q value	df(Q)	р	I^2
Fixed								
Attention	5	0.732	3.808	0.000	12.932	4	0.012	69.070
Memory	4	0.796	4.071	0.000	2.375	3	0.498	0.000
Overall	9	0.764	5.569	0.000	15.362	8	0.052	47.924
Random								
Attention	5	0.725	2.053	0.000				
Memory	4	0.796	4.071	0.000				
Overall	9	0.779	4.556	0.000				

2) Calculation of effect size

The application of tDCS to stroke patients showed that the attention was 0.725 (95% confidence interval [CI]: 0.033-1.417) for medium effect size and the memory was 0.796 (95% CI: 0.413-1.180) for medium effect size. Both the attention and memory have positive effects; that is, the experimental group showed better results than the control group, which were considered statistically significant (p<0.05) (Figure 2).

3) Results of publication bias

The nine values used in the meta-analysis were all distributed within the area except for one value, but showed a tendency to be visually asymmetrical, indicating that there was a publication bias (Figure 3).

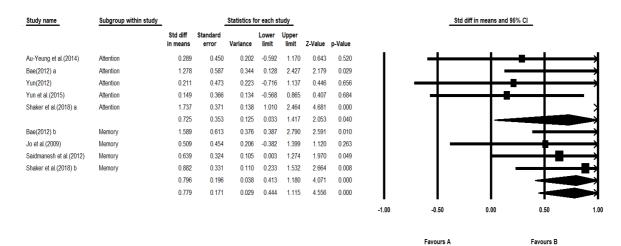
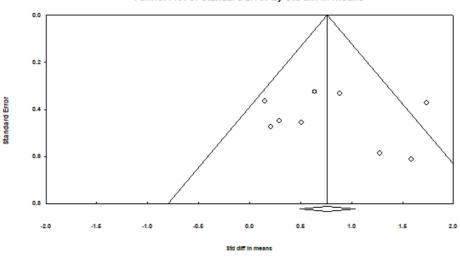


Figure 2. Forest Plot Showing Attention and Memory



Funnel Plot of Standard Error by Std diff in means

Figure 3. Funnel Plot of Standard Error by Std diff in means

IV. Discussion

This study systematically analyzed the studies examining the effects of tDCS on the cognitive function of stroke patients. In addition, a metaanalysis was performed to determine the effect size for attention and memory.

In this study, the results of the meta-analysis showed that the effect sizes for attention and memory were 0.725 and 0.796, which is close to 0.8, the largest effect size defined by Cohen (1988), and that tDCS was highly effective in improving the cognitive function of stroke patients.

As reported in the 11 papers presented, the mean used in each study was 1.77 mA in strength, 26.36 minutes in stimulation time, and 28.64 cm² in area size, which was different for each study. In addition, the total duration, session, and mode of the study differed among studies, and it could be seen that the assessments used and computerization cognitive programs were in various forms. In particular, this study has shown that there are differences in design and methods among studies, even though the effects of cognitive function in the same area are seen in this study, suggesting that a formal protocol is needed to use tDCS as part of rehabilitation for improving cognitive function in stroke patients in future clinical settings.

The tDCS normally applied in tDCS is 1-2 mA and the area size is 25 cm². In addition, the 30-minute continuous tDCS is known to be safe for the human body (Kim, 2014), but there are no formal guidelines or protocols for how to apply tDCS, so it is not clear which method is most effective. Kim (2014) and Chae (2018) suggested that further research will be needed because the number of cognitive function-related studies is small, the number of subjects is small, and only short-term effects are analyzed, compared to the studies of motor function and language function applied with tDCS to stroke patients in Korea. Through this, it is thought that tDCS application study of cognitive function in stroke patients should be done in depth and formalized protocol development is needed.

In stroke patients, decreased cognitive function is one of the major factors affecting the successful rehabilitation of stroke patients, and recovery of cognitive function is important (Trombly & Radomski, 2002). Traditional cognitive rehabilitation methods do not directly stimulate the brain, which causes the development of lesions; however, treatments associated with brain stimulation have recently gained considerable interest as a result of a growing number of studies showing that benefits of brain stimulation. Other methods are used to deliver magnetic or electrical stimulation to specific areas of the brain in patients with stroke without surgical treatment, and technologies to improve cognitive function using noninvasive methods are being sought (Kim, 2014). Unlike conventional rehabilitation treatments, tDCS is among the noninvasive brain stimulation methods and is used to treat patients with brain injury, which can cause the development of brain lesions; it is a safe method for brain nerve rehabilitation in patients with brain injury (Erk et al., 2010).

In rehabilitation, the occupational therapist assesses whether cognitive damage to clients affects the performance of daily activities and helps them perform independent roles through systematic training (Allen, 1982). In order to improve cognitive function, which is considered important in the field of occupational therapy, attempts are needed to improve not only existing cognitive rehabilitation but also new cognitive function, and it is also important to prepare basic data in expanding the work of occupational therapists. Therefore, it is believed to be important to continue to carry out relevant studies with interest in tDCS, which can be used as a new treatment like this.

The studies included in the meta-analysis might not provide corroborative results on the effects tDCS on cognitive function due to the existence of a publication bias. In addition, the meta-analysis was performed without separately classifying the different studies included and the interventions used. Moreover, results were calculated without distinguishing stroke patients with acute condition from those with chronic condition, which may affect the generalizability of the results.

The 11 studies analyzed in this literature have shown significant improvements in at least one of the different evaluation tools for assessing cognitive function in the experimental group. This study, which reports the effects of tDCS on stroke patients, could serve as a basis for developing future rehabilitation intervention plans or research plans to improve the cognitive functions of stroke patients.

V. Conclusion

A meta-analysis was conducted in this study after examining the studies published from 2009 to 2019 in Korea and abroad to determine the effects of tDCS in stroke patients. Through these studies, tDCS was found to effectively improve the attention and memory of stroke patients. Moreover, we found that different techniques have been used to perform tDCS, suggesting that a standard tDCS protocol should be established and tDCS should be performed.

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국문초록

뇌졸중 후 인지장애에 대한 경두개 직류 자극: 체계적 고찰 및 메타분석

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- **목적**: 본 연구의 목적은 뇌졸중 환자의 인지기능 회복에 대한 경두개 직류자극(tDCS)의 효과를 살펴본 연구를 분석하기 위함이다.
- **연구방법**: 2009년부터 2019년까지 국내외 학술지에 게재된 논문들을 NDSL, RISS, PubMed, CINAHL을 통해 검색하였다. 선정기준과 배제기준을 통해 총 11개의 실험연구 논문이 선정되었다. 이를 질적 평가를 시행하고, 이 중 7편의 논문에서 9개의 결과값에 대해 메타분석을 실시하였다.
- **결과**: 메타 분석을 실시한 결과 효과크기는 attention 0.725, memory 0.796으로 모두 '보통 효과크기'를 보였다. 두 영역 모두 통계적으로 유의한 변화가 있던 것으로 분석되었다(p<0.05)
- **결론**: 본 연구 결과를 통하여 인지기능이 제한된 뇌졸중 환자에게 tDCS는 효과가 있음을 알 수 있었다. 또한, tDCS 적용법이 연구 간 서로 상이함을 알게 되었으며 이에 따라 정형화된 tDCS 프로토콜과 전문가 양성이 필요할 것으로 보인다.

주제어: 경두개 직류 전기자극, 뇌졸중, 인지, tDCS

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		Patients			Intervention	l		Outcome
Study	Stage of	Sample	size	Ē	C	Ĵ	*	
	stroke	EG	CG		בכ	0	Assessment	Inesul
				a-tDCS	c-tDCS	s-tDCS	Ċ	
Au-Yeung et al. (2014) Chronic	Chronic	10		Total : single session20 mins per session	session session		level 1~3)	 - Significantly increased selective attention in c-tDCS.
				GT + CC	GT + CCT + tDCS	GT + CCT GT		- Significant difference was identified
Bae (2012)	Chronic	2	7	- GT : 5 times/wk, 4wks - CCT & tDCS : 3 times/ - 30 mins per session	GT : 5 times/wk, 4wks CCT & tDCS : 3 times/wk, 4wks 30 mins per session	łwks	DST WMPT	between GT and EG(DST). - GT and EG were significant difference at 4 wks in word memory, and picture memory(WMPT).
D'Agata et al. (2016)	Chronic 16	16 8	10	rTMS, tDCS+MT	tDCS + MT, rTMS	s-tDCS + MT	MMSE FBDS AM SST	 Significant difference was identified CF with immediate recall, delayed recall and Nelson MCST in the tDCS
			•	rTMS: 10 sessions, 2wkstDCS + MT: 10 sessions,	rTMS: 10 sessions, 2wks tDCS + MT: 10 sessions, 2wks	ks	CF Nelson MCST	+ MT group.
a-tDCS=anodal mode of tDCS: AM=attentional matrices: Test: FBDS=Forward and Backward Digit Span: GT=Gene Card Sorting Test: SST=Short Story Test: s-tDCS=sham n Test: Assessment*=only involved cognitive function test	DCS; AM=a Backward L tort Story T ivolved cog	ttentional 1 Jigit Span; 'est: s-tDCS nitive func	natrices; GT=Gen S=sham r tion test	CCT=Computer eral therapy; MN mode of tDCS; tl	ized Cognitive T fSE=Mini Mental DCS=transcranial	'raining; CF=copy of State Examination; I direct current stim	figure: c-tDCS= Nelson MCST=N alation: wk=week	a-tDCS=anodal mode of tDCS: AM=attentional matrices: CCT=Computerized Cognitive Training: CF=copy of figure: c-tDCS=cathodal mode of tDCS: DST=Digit Span Test: FBDS=Forward and Backward Digit Span: GT=General therapy: MMSE=Mini Mental State Examination: Nelson MCST=Nelson Modified version of the Wisconsin Card Sorting Test: SST=Short Story Test: s-tDCS=sham mode of tDCS: tDCS=transcranial direct current stimulation: wk=week: WMPT=Working Memory Performance Test: Assessment*=only involved cognitive function test

Appendix 1. Characteristics of Analyzed Studies

	1	Patients		Intervention	ntion		Outcome
Study	Stage of	Sample	e size	Ц	Ĵ	A 000000000 *	4 0 0
	stroke	EG	DO	5	20	Assessinent	Kesul
				a-tDCS c-tDCS	s-tDCS control		- There are significant increase between
Hosseinzadeh et al. (2018) Chronic 25 25	Chronic	25 25	25 25	- Total : 3 times/wk 4wks	sk	TMT	tDCS groups versus control or sham groups.
				- 30 mins per session			 a-tDCS was more effective than c-tDCS significantly.
				a-tDCS	s-tDCS	Two-back	- Significant interaction effect of tDCS
Jo et al. (2009)	Chronic	10	10	- Randomly assigned to a-tDCS and within 48 hours of a washout period	Randomly assigned to a-tDCS and s-tDCS within 48 hours of a washout period	verbal WM task	type and time on the recognition accuracy.
		\ \	۱	a-tDCS + CACR	s-tDCS + CACR	S-CNT	- Use of the tDCS with CACR to prefrontal cortex may provided
Park et al. (2015)	Acute	0	n	- Total : 5 times/wk, a week - 30 mins per session	week	K-MMSE	effects in improving visual and auditory attention.
				tDCS	s-tDCS		
Saidmanesh et al. (2012) Chronic	Chronic	20	20	Total: 10 sessions20 mins per session		2-Back test	 working memory improves significantly in tDCS group.

WM=working memory; Assessment*=only involved cognitive function test

	·	Patients			Intervention			Outcome
Study	Stage of	Sample	le size	C F		C	*.	- - -
	stroke -	EG	CG	- EG		CG	Assessment	Kesult
				tDCS + CTP	CTP	s-tDCS + CPT		- Significant improvement in the scores
Shaker et al. (2018)	Chronic	20	20	Total : 3sessions/wk, 4wks30 mins per session	ns/wk, 4wks ession		RehaCom	or attention and concentration, figural memory, logical reasoning, reaction behavior in EG.
				a-tDCS	c-tDCS	s-tDCS	HCLAR	- Improvement in the MVPT, SCT and
Yi et al. (2016)	Subacute	10 10	10	- Total : 5 times/wk, 3wks - 30 mins per session	s/wk, 3wks ession		LBT SCT	LDI were greater in the tUCS groups than sham group. Significant improvement in VLT of CNT in the LS group.
				LS	RS	s-tDCS	DST	шуу ј- шит -;;;;
Yun (2012)	Chronic	9	6	Total : 5 times/wk, 3wks30 mins per session	s/wk, 3wks ession		K-MMSE VLT	- significant improvement in VLI of CNI in the LS group.
				L-FTA	R-FTA	s-tDCS		
Yun et al. (2015)	Subacute	15 15	15	+ CACR	+ CACR	+ CACR	K-MMSE	- Applying tDCS to the left temporal lobe
				- Total : 5 times/wk, 3wks - 30 mins per session	s/wk, 3wks ession		CNI	effectively improved auditory memory.

stimulation; SCT=Star Cancellation Test; wk=week; VLT=Verbal Learning Test; Assessment*=only involved cognitive function test