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Transcranial Direct Current Stimulation Improves Audioverbal Memory in Stroke Patients

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Objective: The aim of this study was to investigate whether anodal transcranial direct current stimulation over the left temporoparietal area improved audioverbal memory performance in stroke patients.

Design: Twelve stroke patients with audioverbal memory impairment participated in a single-masked, crossover, and sham-controlled experiment. The anodal or sham transcranial direct current stimulation was applied during the Rey Auditory Verbal Learning Test, which evaluates the ability to recall a list of 15 heard words over five trials. The number of correctly recalled words was compared between the anodal and sham conditions and the influence of transcranial direct current stimulation on serial position effect of the 15 words was also examined.

Results: The increase in the number of correctly recalled words from the first to the fifth trial was significantly greater in the anodal condition than in the sham condition ($P < 0.01$). There was a significant difference ($P < 0.01$) between the anodal and sham conditions in the number of correctly recalled words within the first five words (primacy region) over the second to fifth trial trials, but not in the middle (next five words) or recency (last five words) regions.

Conclusions: Anodal transcranial direct current stimulation over the left temporoparietal area improved audioverbal memory performance and induced the primacy effect in stroke patients.

Key Words: Serial Position Effect, Primacy Effect, Brain Stimulation, Short-Term Memory

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Post-stroke memory impairment is more common in older stroke survivors than it is in younger stroke survivors.[1] Patients with a stroke or transient ischemic attack have higher incidence of dementia and greater whole brain atrophy than do healthy controls.[2] It is noteworthy that, over 3 yrs, patients also show a decline in verbal memory, with fewer declines in other cognitive functions.[2] As stroke prevalence increases in Japan,[3] a method for improving memory impairment and preventing stroke recurrence is required.

Transcranial direct current stimulation (tDCS) is a noninvasive brain stimulation technique that involves application of a weak direct current (1–2 mA) on the scalp, which can induce temporary changes in cortical excitability. The effect of tDCS varies depending on the polarity of the electrode; anodal polarization increases cortical excitability, whereas cathodal polarization decreases it.[4–6] In a clinical study of chronic stroke patients, anodal tDCS over the lower limb primary motor cortex in the affected hemisphere temporarily facilitated the force of knee extension.[7]

With respect to cognitive function, tDCS has been shown to enhance verbal fluency[8] and language learning[9] in healthy participants. tDCS of the prefrontal cortex affects working memory, which is capable of transiently storing and manipulating information necessary for complex tasks such as language comprehension, learning, and reasoning in healthy participants.[10,11] In a study of stroke patients who had cognitive deficits, 30 mins of anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) improved the patients' accuracy in a two-back working memory task.[12]

To the authors' knowledge, only one report has described the effects of tDCS on audioverbal memory. Elmer and colleagues auditorily presented healthy participants with a word list to memorize and applied sham, anodal, or cathodal tDCS to the right or left DLPFC, which is considered to be related to working memory. They found impairment of short-term verbal learning after cathodal tDCS application over the left DLPFC, whereas no improvement was demonstrated by anodal tDCS application over either DLPFC.[13] However, it remains necessary to examine whether stimulation to an area other than the DLPFC might improve audioverbal memory.

Dupont and colleagues[14] performed functional magnetic resonance imaging and reported that during verbal memory tasks, healthy participants exhibited significant activation in the left inferior parietal and superior temporal cortices (corresponding to the Wernicke area) in addition to the left occipital cortex and bilateral ventrolateral frontal cortex. Maeshima and colleagues[15] reported two patients with traumatic brain injuries in the left temporal and parietal lobes who demonstrated verbal memory impairment. Leff and colleagues[16] found that the left

superior temporal gyrus is a shared substrate for auditory verbal memory and speech comprehension in stroke patients. Therefore, it was hypothesized that stimulation to the left temporoparietal (TP) area would enhance audioverbal memory in patients after stroke. To evaluate this hypothesis, it was investigated whether anodal tDCS over the left TP area improved audioverbal memory in stroke patients with memory impairment.

PARTICIPANTS AND METHODS

Participants

Twelve stroke patients with an audioverbal memory deficit participated in this study (eight men and four women, 71.5 ± 7.4 yrs old); all patients were right handed. The inclusion criteria were as follows: (1) no seizure disorder, (2) no intracranial metal insertion or cardiac pacemaker, (3) no intake of medication that affects the central nervous system (antipsychotics or antidepressants), and (4) no cognitive decline (including memory deficit) before stroke onset. All participants were evaluated with the Japanese version of the Mini-Mental Status Examination and Frontal Assessment Battery to screen cognitive function. Verbal memory was also tested with paired-associate learning of nouns. In the test, 10 word pairs were presented aurally and patients were instructed to memorize each pair. Then, one word from each pair was presented and patients were required to recall the word's pair. The trial was repeated three times for 10 easy-association pairs (e.g., sky-star) and 10 distant pairs (e.g., bud-tiger). Because the easy pairs are semantically associated, the number of the correctly recalled words reflects the retrieval process by the existing neural network. The distant pairs consist of less semantically similar words, and the number of correctly recalled words thus reflects the learning process to associate words. According to previous work,[17] recollection of fewer than 10 easy pairs or 0 distant pairs was considered to be abnormal.

Written informed consent was obtained from both the participants and their caregivers before study inclusion, and the protocol was approved by the local ethics committee of Tokyo Bay Rehabilitation Hospital. The participants' demographic and clinical characteristics are shown in Table 1.

Audioverbal Memory Task

The Rey Auditory Verbal Learning Test (RAVLT)[18] was modified and used for an audioverbal memory task in this study. A list of 15 common words was aurally presented to the participants one by one every 2 secs (encoding procedure: 30 secs). After presentation of the 15 words (Table 2, list A), the participants were asked to repeat as many words as they could (recall procedure: 1 min). This encoding-recall procedure was repeated five times (T1–T5). Thereafter, a different list of 15 words (Table 2, list B) was presented aurally and the participants were again asked to recall as many words as possible (interference: TB). Next, they were asked to recall 15 words from list A without presentation (T6 recall: 1 min). The subjects were then shown 50 words at a time and were asked to determine whether or not any of the 50 words presented in list A (T6 recognition: 1 min). In this study, two different word lists that are common in clinical practice were used (Table 2, list no. 1 and 2). A custom-made MATLAB program (MathWorks, Natick, MA) was used for the aural presentations, which were recorded before the trials, and for the time setting.

tDCS Application

The DC Stimulator Plus (NeuroConn; Ilmenau, Germany) was used to deliver a direct current through two sponge surface electrodes placed onto the scalp. For the anodal TP stimulation, a 7 × 5–cm saline-soaked electrode was placed over the TP area, including the Wernicke area, as determined by the international 10-10 electroencephalogram system corresponding to Cp5. The cathodal electrode (5 × 10 cm) was placed over the right supraorbital area. In this study, the current intensity

TABLE 1. Demographic and characteristics of the participants

Patient Number	Age (Years)	Sex	Duration After Stroke (Months)	Lesion	MMSE Score	FAB Score	Verbal Paired Associate Learning	
							Easy Pairs	Distant Pairs
1	75	M	3	Rt thalamic hemorrhage	23	10	8	0
2	81	M	5	Rt cerebellar infarction	25	15	8	0
3	76	M	3	Brainstem infarction	30	13	9	0
4	78	M	6	Multiple lacunar infarction	28	17	9	1
5	78	F	12	Rt frontal infarction	25	17	9	1
6	58	M	12	Lt frontal hemorrhage	27	16	5	0
7	66	F	3	Lt caudate hemorrhage	23	13	6	0
8	60	M	3	Bilateral thalamic hemorrhage	24	15	8	1
9	72	F	6	Multiple lacunar infarction	28	17	9	0
10	76	M	3	Rt frontal infarction	29	13	9	0
11	72	M	12	Multiple lacunar infarction	25	16	8	0
12	66	F	12	Multiple lacunar infarction	29	17	9	1
Mean ± SD	71.5 ± 7.40	M = 7 F = 5	6.7 ± 4.1	Hemorrhage = 4 Infarction = 8	26.3 ± 2.5	14.9 ± 2.2	8.1 ± 0.9	0.3 ± 0.4

M indicates male; F, female; Rt, right; Lt, left; MMSE, Mini-Mental State Examination; FAB, Frontal Assessment Battery.

TABLE 2. Word lists of RAVLT

| | List 1 | | | | | | List 2 | | | | | |
| | List A | | | List B | | | List A | | | List B | | |
	Japanese	Phonologic Symbol	Meaning	Japanese	Phonologic Symbol	Meaning	Japanese	Phonologic Symbol	Meaning	Japanese	Phonologic Symbol	Meaning
Primacy	雨	/ame/	Rain	机	/tukue/	Desk	すずめ	/suzume/	Sparrow	さんま	/saNma/	Pacific saury
	学校	/gaQkoR/	School	帽子	/boRsi/	Hat	さくら	/sakura/	Cherry blossoms	銀	/giN/	Silver
	太陽	/TaiyoR/	Sun	手紙	/tegami/	Letter	リンゴ	/riNgo/	Apple	海	/umi/	See
	薬	/kusuri/	Medicine	山	/yama/	Mountain	はさみ	/hasami/	Scissors	牛	/usi/	Cattle
	家	/ie/	House	窓	/mado/	Window	大根	/daikoN/	White radish	キャベツ	/kjabetu/	Cabbage
Middle	時計	/tokeR/	Clock	本	/hoN/	Book	森	/mori/	Forest	ひばり	/hibari/	Skylark
	風	/kaze/	Wind	財布	/saihu/	Wallet	膝	/hiza/	Knee	カマキリ	/kamakiri/	Mantis
	鉛筆	/eNpitu/	Pencil	酒	/sake/	Liquor	マグロ	/maguro/	Tuna fish	ボールペン	/boRrupeN/	Ballpoint pen
	桜	/sakura/	Cherry blossoms	羊	/hituzi/	Sheep	野球	/yakjuR/	Baseball	サッカー	/saQkaR/	Soccer
	秋	/aki/	Autumn	月	/tuki/	Moon	トンボ	/toNbo/	Dragonfly	赤	/aka/	Red
Recency	魚	/sakana/	Fish	車	/kuruma/	Car	ピアノ	/piano/	Piano	スミレ	/sumire/	Violet
	鏡	/kagami/	Mirror	雷	/kaminari/	Thunder	靴下	/kutusita/	Socks	帽子	/boRsi/	Hat
	顔	/kao/	Face	子供	/kodomo/	Child	緑	/midori/	Green	足	/asi/	Foot
	船	/hune/	Ship	靴	/kutu/	Shoes	馬	/uma/	Horse	笛	/hue/	Pipe/Flute
	電話	/deNwa/	Telephone	海	/umi/	Sea	鉄	/tetu/	Iron	ぶどう	/budoR/	Grape

/N/ = moraic nasal; /R/ = long vowel; /Q/ = geminate consonant.

was gradually increased to 2 mA in 15 secs, maintained constantly for 9.5 mins, and then decreased to diminish in 15 secs. For the anodal stimulation, tDCS was applied from the second encoding trial (T2) until the end of the T6 recognition session (approximately 10 mins). The electrode placement was identical for the sham stimulation, except that the stimulator was turned off after the first 15 secs. In the sham stimulation, the inspector pretended to maintain the stimulation until the end of the session, and no patient realized that the stimulation had stopped. Therefore, the participants were under the illusion that they had also received 10-min stimulation in the sham condition. The participants were asked whether they felt any sensations by tDCS after the second trial, and all of them reported to have felt nothing in either condition.

Each participant underwent the two tDCS conditions within 7 days of a washout period. The order of the two conditions was randomly assigned for each participant. The word list (list 1 or list 2) not used in the first condition was used for the second condition. A procedure was arranged that was counterbalanced between participants to eliminate a possible effect with respect to both the order of the tDCS condition and presentation of list 1 or 2.

Data Analyses

The number of recalled words in each trial was counted. For each trial, the number of correctly recalled or recognized words was compared between the anodal and sham conditions with a paired *t* test. Bonferroni correction was used for multiple comparisons among trials.

Verbal learning ability was defined as the number of words recalled at T5 minus the number recalled at T1[18,19] and was compared between the anodal and sham conditions with a paired *t* test.

To investigate the influence of tDCS on the serial position effect within the list, the 15 words for each trial were grouped
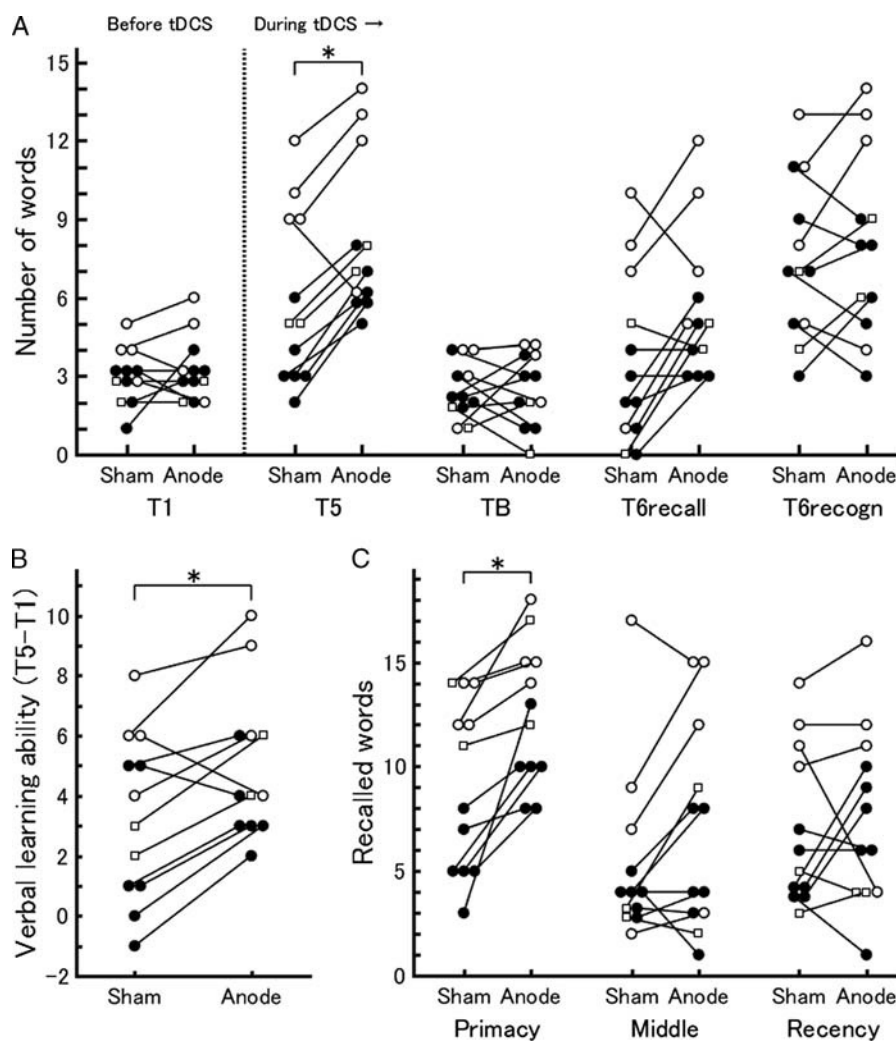
FIGURE 1. *A,* The number of recalled words of RAVLT. Each 10-min anodal stimulation (from T2 to T6 recognition) and 15-sec sham stimulation was applied from the second encoding process (T2). *B,* Verbal learning ability, calculated as the number of words recalled at T5 minus those at T1. *C,* Sum of the number of the recalled words over the four learning trials during tDCS (from T2 to T5) as a function of the order of word presentation (primacy, five words; middle, five words; and recency, five words). White circles: patients with lacunar infarction. White squares: patients with cerebellar or brainstem infarctions. *Bonferroni-corrected *P* < 0.05.

in the first third (words 1–5, primacy region), middle (words 6–10, middle region), and final third (words 11–15, recency region). For each group, the sum of the correctly recalled number of words from T2 to T5 during tDCS stimulation in the anodal condition was compared with that during the sham condition with a paired *t* test. Bonferroni correction was used for multiple comparisons among groups.

RESULTS

Figure 1*A* shows the numbers of correctly recalled (T1, T5, TB, and T6 recall) or recognized (T6 recognition) words in the anodal and sham conditions. At T1, before tDCS, the number of correctly recalled words was not significantly different between the anodal and sham conditions. Paired *t* test with Bonferroni correction revealed the number of recalled words to be significantly different between the anodal and sham conditions at T5 (mean ± SD: anode, 8.2 ± 3.1; sham: 5.9 ± 3.3; *t* = 4.3, corrected *P* < 0.05), but not at TB, T6 recall, or T6 recognition. Although there were significant differences in word recall at T2 (anode, 5.3 ± 2.6; sham, 4.3 ± 2.1; *t* = 3.0, corrected *P* < 0.05) and T3 (anode, 6.5 ± 2.2; sham, 5.5 ± 2.5; *t* = 3.3, corrected *P* < 0.05), these significances disappeared when the 10 cases excluding the 2 patients with lesions beneath the tentorium were analyzed.

The verbal learning ability score of the anodal condition was significantly higher than that of the sham condition (Fig. 1*B*; anode, 5.0 ± 2.5; sham, 3.3 ± 2.8; *t* = 3.4, *P* < 0.01).

Figure 1*C* shows the sum of the correctly recalled words from T2 to T5 in the three serial positions. There was a significant difference between the anodal and sham stimulation in the primacy region (anode, 12.5 ± 3.4; sham, 9.2 ± 4.1; *t* = 4.2, corrected *P* < 0.01), but not in the middle (anode, 7.0 ± 5.0; sham, 5.3 ± 4.2; *t* = 1.9, *P* = 0.04) and recency (anode, 7.6 ± 4.2; sham, 7.0 ± 3.8; *t* = 0.6, *P* = 0.29) regions.

DISCUSSION

Whether anodal tDCS over the left TP area would improve the audioverbal memory function of stroke patients with an audioverbal memory deficit was investigated. The number of recalled words on the RAVLT was significantly improved in the anodal condition compared with that in the sham condition. In the information-processing model of memory, memory is divided into the stages of attention, encoding, storage, and retrieval.[20] Because the task applied in the present study requires an increase of the recalled by moving through each of these stages in each trial of RAVLT, one of these stages might be enhanced by anodal tDCS.

In the audioverbal memory task, RAVLT, participants are presented a list of 15 words auditorily and are asked to recall as many words as possible repeatedly. The scores of the fifth trial (T5) and verbal learning ability score (T5 minus T1) increased. Because the learning ability score maximally loaded on the "acquisition" factor,[21] the attention and encoding stages might be enhanced in the present study. On the other hand, the scores in TB, T6 recall, and T6 recognition were not affected by tDCS. This suggests a limited effect of tDCS on the TP area. Specifically, it is possible that through repetition of memorization and recall, there is only a memory-enhancing effect of

tDCS for short retention periods. Meinzer et al.[22] administered the anodal tDCS over the TP area during a 5-day training of language learning, and reported a significant enhancement of verbal memory functions immediately and 1 wk after training in healthy, young individuals. This could show that to enhance the storage ability of memory function and to observe a prolonged effect, several days of training combined with tDCS treatment might be necessary.

The influence of tDCS on the serial position effects (primacy, middle, and recency regions of five words each) was also examined. Serial position effects in memory refer to the tendency for increased performance in free recall of words at the beginning (primacy effect) and end (recency effect) of a memorized list compared with those positioned in the middle in immediate testing.[23] Memory is first stored as short-term memory and then transferred into long-term memory by rehearsal; thus, more extensive rehearsal with a greater amount of selective attention enhances the primacy effect.[24] That the primacy effect was more significant in the anodal than sham condition suggests that tDCS may specifically enhance the selective attention stage of memory.

Elmer and colleagues[13] applied sham, anodal, and cathodal tDCS to the right or left DLPFC, considered to be related to working memory. According to their results, cathodal tDCS application on the left DLPFC impaired short-term verbal learning, which was not improved with anodal tDCS. The results of this study suggest that anodal tDCS over the left TP area is more effective than that over the DLPFC in improving audioverbal memory in stroke patients with memory impairment. Cerebral activities in the left inferior parietal and superior temporal cortices (corresponding to the Wernicke area) are known to play an important role in verbal memory.[14] Indeed, patients with left temporal-parietal lobe injuries demonstrate audioverbal memory impairment.[15] Therefore, the enhancement of cortical excitability produced with anodal tDCS over the left TP area might result in promoting memory retention.

This promoting effect could be the result of stimulation of the Wernicke area, given that the tDCS electrode was placed on Cp5 of the international 10-10 system of electroencephalograph sensor placement.[9] Considering the size of the electrodes, however, it is also possible that regions around the Wernicke area were also stimulated. Furthermore, although localization based on the 10-10 system is convenient, it is not sufficiently accurate to reach a definite conclusion of the specific region being stimulated. Increased accuracy could be achieved by using a small electrode and the stimulus localization method, which uses an optical navigation system based on magnetic resonance imaging.

Because the cathodal electrode was placed over the right supraorbital area in this study, the possible effect of reduced interhemispheric inhibition from the right prefrontal cortex must be considered when interpreting the results.[25,26] The prefrontal cortex is known to control visual and auditory attention by a top-down mechanism of action. Hopfinger et al.[27] demonstrated that superiorfrontal, inferiorparietal, and superiortemporal cortices are part of a voluntary attentional control network. Therefore, cathodal stimulation over the right supraorbital area may lead to a relative increase in cortical excitability of the left DLPFC. This might facilitate top-down control processes from the prefrontal cortex to the left inferior parietal

and posterior temporal lobes, which could promote memory retention. To confirm this hypothesis, it is necessary to examine the specific polarity under the conditions of cathode stimulation over the left TP area.

In the present research, the anode was placed at the posterior TP junction (Cp5 of the 10-10 EEG system), and the cathode was placed at the upper right orbital area for stimulation. These locations were chosen based on previous research on working memory language learning.[9,10,13,28] Datta et al.[28] reported that the electric current flowed through a wide area of the frontal lobe when 7 × 5–cm electrodes were placed with the anode on the region, including the left primary motor cortex and the cathode on the upper right orbital area. Electrodes of the same size were used, and it is possible that the electrical current flowed through a wide area, including the bilateral frontal lobes. Furthermore, the stimulated area in the present study is perhaps even less certain because the brain injury sites of the participants varied, owing the limited sample size. To overcome this limitation, future investigations should assess a larger number of patients with the same brain lesion sites.

The patients examined in this study had various damaged areas, including some with lesions beneath the tentorium, which were thought to have little effect on memory ability. When 10 cases were analyzed excluding those with brainstem and cerebellar lesions, the significant difference for T2 and T3 disappeared; however, the difference in T5 persisted, and the effect of the anodal stimulation was significantly higher than the sham condition. In the patient with a brainstem lesion (no. 3) and the patient with a cerebellar lesion (no. 2), results for the stimulated T2–T5 were similar compared with the other patients; the anode group showed a value greater than or equal to that of the sham group. Among the four multi-infarct patients, three cases (no. 4, 9, and 12) exhibited results similar to the other patients, whereas the remaining case (no. 11) showed either the same value or a lesser value for the anodal stimulation compared with the sham in cases T2–T5. As this case had lower scores than the other three on the Mini-Mental Status Examination and Frontal Assessment Battery, low cognitive function may be the reason why a memory enhancement effect following tDCS was not observed. One consideration to make is that memory decline could be related to not only stroke but also aging and might be caused by vascular or Alzheimer-type pathologies.[1,2] Because the T1 scores in this study were less than standard score (approximately 7 or more in healthy participants in their 80s),[29] the direct and/or indirect influences of stroke may not be negligible. Hereafter, it will be necessary to perform TP area functional monitoring or to assess comparatively younger patients who are less likely to be affected by age-related memory decline. On the other hand, a memory-enhancing effect has also been seen in healthy participants by anodal tDCS over the TP area.[30] Therefore, the tDCS application in the present study could be a strength when it is the aim to maintain or improve audioverbal memory in wide range of stroke patients.

Performing the RAVLT in patients with Alzheimer disease tends to yield a flatter learning curve than in healthy control participants.[31,32] This indicates that the ability of transferring memory from short- to long-term storage by rehearsal (repetition of short-term memory) is impaired in Alzheimer disease. In mild Alzheimer disease, impairment in the primacy effect precedes the progression of dementia, whereas recall of recent items is relatively less impaired.[31–33] The results of this study showed that anodal tDCS upregulates the primacy effect, which indicates a potential therapeutic modality for the cognitive deficits of Alzheimer disease. On the other hand, the flattened learning curve of stroke patients observed in the sham condition could have been due to low initiation or could indicate that the learning curve is affected by attention impairment with fluctuations in concentration between repeated trials. This study's results demonstrated improvement of the learning curve under the anodal condition, suggesting that tDCS over the TP area may be effective to improve aprosexia.

CONCLUSIONS

In stroke patients, significant enhancement of audioverbal memory was observed after anodal tDCS stimulation over the left TP area. Because a significant primacy effect was observed, which is related to improved attention at higher serial positions, tDCS might improve memory function mainly through increasing attention.

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