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Feasibility of single and combined with other treatments using transcranial direct current stimulation for chronic stroke: A pilot study

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Abstract

Objectives: This pilot study aimed to investigate the safety and efficacy of transcranial direct current stimulation (tDCS) for chronic stroke in adult and pediatric patients. We also aimed to verify the efficacy of botulinum toxin A and peripheral neuromuscular electrical stimulation combined therapy involving bilateral tDCS in adult patients with chronic stroke.

Methods: We conducted a pilot study applying an unblinded, non-randomized design. Eleven patients were recruited, and classified into three groups. Group I-a involved bilateral transcranial direct current stimulation and intensive occupational therapy for chronic stroke in adult patients. Group I-b involved bilateral tDCS and intensive occupational therapy for chronic stroke in pediatric patients. Group II involved bilateral tDCS, peripheral neuromuscular electrical stimulation, and intensive occupational therapy after botulinum toxin A injection for chronic stroke in adult patients. Clinical evaluations to assess motor function and spasticity were performed at baseline as well as in 2-week and 4-month follow-up visits. The questionnaire included questions regarding the presence of tDCS side effects, such as headache, redness, pain, itching, and fever.

Results: There were clinically meaningful changes in total Fugl–Meyer Assessment Upper Extremity (FMA-UE) scores at the 2-week follow-up and in the Action Research Arm Test (ARAT) scores at 4-month follow-up in Group I-b. In addition, Group II showed significant improvement in total FMA-UE scores in the 2-week follow-up ($p < 0.05$) but not on the ARAT scores ($p > 0.05$). However, Group II showed improvements in total Motor Activity Log scores at both follow-up visits ($p < 0.05$). No serious adverse events were reported.

Conclusion: The results of this study indicate that tDCS therapy is a potential treatment in pediatric patients with chronic stroke. Furthermore, our data indicate that botulinum toxin A and peripheral neuromuscular electrical stimulation combined therapy may enhance the efficacy of tDCS on motor function.

Keywords

Transcranial direct current stimulation, rehabilitation, stroke, upper limb

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Introduction

Previous longitudinal studies have reported that between 30% and 66% of patients experience upper limb paralysis 6 months after suffering from a stroke.[1–3] Recent studies have demonstrated the efficacy of various treatments for patients with chronic stroke, who experience upper limb paralysis, including botulinum toxin A (BTX-A) treatment, functional electrical stimulation therapy, and robotic therapy for functional motor recovery.[4–6] In addition, repetitive transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), have been reported to induce

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long-term effects on cortical excitability, lasting for months after the intervention.[7,8]

tDCS modulates cortical excitability which influences neural plasticity.[9] Anodal tDCS (anodal electrode placed over standard scalp coordinates for motor ipsilesional M1, the cathodal electrode over the contralesional supraorbital ridge) also modulates cortical excitability in motor areas within affected hemisphere.[9,10] Furthermore, bilateral tDCS, which stimulates both hemispheres simultaneously, could affect excitatory and inhibitory synaptic transmission in the bilateral motor cortex in patients with chronic stroke.[9,11–13] By modulating cortical excitability, tDCS may alter maladaptive neural plasticity after stroke.[9] Moreover, peripheral neuromuscular electrical stimulation (PNMES) enhances the effects of tDCS on cortical excitability, relative to tDCS alone.[14,15] Furthermore, rehabilitation therapy using PNMES combined with BTX-A has been shown to be an effective treatment in chronic stroke or spinal cord injury.[16]

However, no studies have examined the efficacy of the use of bilateral tDCS with PNMES and BTX-A therapy in patients with stroke and upper limb paralysis. Therefore, based on the results of each combination therapy effect from previous studies, we predicted that a new multiple combination of adding BTX-A to existing tDCS and PNMES combination therapy would result in more effective results. In addition, tDCS may help improve upper limb paralysis in pediatric patients with chronic stroke. Since tDCS alone has been rarely used in pediatrics, our pilot study aimed to investigate the safety and efficacy of tDCS in adult and pediatric patients with chronic stroke. We also aimed to verify the efficacy of BTX-A and PNMES combined therapy involving bilateral tDCS in adult patients with chronic stroke.

Methods

Study design

We conducted a pilot study applying an unblinded, non-randomized design. This study included patients with chronic stroke (>6 months from stroke onset) experiencing paralysis in an upper limb. Patients between 6 and 85 years old were included. We also excluded patients with epilepsy, complete paralysis, and/or severe pain, as well as those who were unable to follow directions due to cognitive impairment and/or aphasia. All participants provided written informed consent. Our institutional review board approved the study. Patient characteristics are summarized in Table 1.

We included 11 patients (four males and seven females; mean age 43.5 ± 5.1 years) including 7 cases of hemorrhagic stroke and 4 cases of ischemic stroke. All study participants were right handed. There were six cases of right upper limb paralysis and five cases of left upper limb paralysis. All of four ischemic stroke cases had a lesion in the middle cerebral arterial territtory, and three hemorrhagic stroke patients had a lesion in the putamen, two stroke patients had a lesion in the subcortical, and other two patients had lesions were in the thalamus and pontine. These treatment programs were initiated on 54.9 ± 23.2 days from stroke onset. Of the included cases, data from 1 patient (Case 1) was published previously.[13]

Five patients, included in Group I, underwent bilateral tDCS therapy alongside intensive occupational therapy (OT) (Group I-a: two adults; Group I-b: three children). Group II included six adult patients in chronic stroke who underwent BTX-A and PNMES combined therapy involving bilateral tDCS.

Each rehabilitation session lasted 60 min. Sessions were performed twice daily for 10 days so that all patients completed 20 sessions for the 2-week intervention period in the hospital. In Group I, tDCS started at the same time as the intensive OT for 25 min; and a 45-min only intensive OT was performed after the tDCS. In Group II, patients were given a BTX-A injection. Following this, patients simultaneously underwent intensive OT for 25 min using tDCS, and PNMES (25 min). Meanwhile, intensive OT was continued as well, and finally alone intensive OT (10 minutes) was performed (Figure 1). Intensive OT involved task-oriented training. The content of the task-oriented training mainly consisted of the task on the desk. The difficulty of the task was adjusted for each patient depending on the extent of their upper limb paralysis and their rehabilitation goals. Examples of activities included gripping or picking up blocks or pegs, varying in size; as well as using a keyboard and playing cards. The activities performed by each patient were recorded. In addition, patients were instructed to increase their use of upper limb paralysis. After the 2-week intervention period, patients presented as outpatients and were given exercises to complete at home. Patients were encouraged to use their paralyzed upper limbs depending on their individual rehabilitation needs. Daily activities involved tasks related to their own rehabilitation goals from the activities of daily living (ADL) and instrumental activities of daily living (IADL) tasks.

Clinical evaluations were performed at baseline and in 2-week and 4-month follow-up visits conducted after the intervention. We used the following clinical outcome measures to evaluate upper limb function, including the Fugl–Meyer Assessment Upper Extremity (FMA-UE; range: 0–66) and the Action Research Arm Test (ARAT; range: 0–57).[17,18] Limb functioning used during daily activities were assessed using the Motor Activity Log (MAL; range: 0–5).[19]

Table 1. Demographics and clinical characteristics.

Group	Case	Age (years)	Sex	Handedness	Diagnosis	Lesion location	Interval from onset (months)	BTX-A injection sites (units)	
I-a	1	71	F	R	Hemorrhage	Left putamen	18	N/A	
	2	58	F	R	Ischemic	Right MCA	31	N/A	
Mean (±SD)		64.5 ± 9.2					24.5 ± 9.2		
I-b	3	9	F	R	Ischemic	Left MCA	91	N/A	
	4	8	M	R	Hemorrhage	Right subcortical	101	N/A	
	5	8	F	R	Ischemic	Right MCA	104	N/A	
Mean (±SD)		8.3 ± 0.6					98.7 ± 6.8		
II	6	49	M	R	Hemorrhage	Left pontine	52	PM:20, Bra:10	FCR:30, FCU:30, FDS:20, FDP:20, ADP:20
	7	64	M	R	Hemorrhage	Left thalamus	135	PM:20, Tri:20	FCR:20, PT:20, FDS:30, FDP:20, ADP:20
	8	68	F	R	Hemorrhage	Right subcortical	14	PM:20, Bra:10, Bi:20, Tri:20	FCR:10, PT:20
	9	53	F	R	Hemorrhage	Right putamen	18	PM:30, Bra:10, Bi:20, Tri:20	FCR:30, FCU:30, FDS:30, FDP:30
	10	46	F	R	Hemorrhage	Left putamen	12	PM:20, Bra:20	FCR:20, FCU:20, FDS:25, FDP:25, ADP:20
	11	67	M	R	Ischemic	Left MCA	18	PM:10, Bra:20, Bi:10, Tri:20	FCR:20, FDS:30, FDP:30
Mean (±SD)		57.8 ± 9.7					41.5 ± 48.1		

MCA: middle cerebral artery; BTX-A: Botulinum toxin A; PM: pectoralis major; Bra: brachialis; Bi: biceps brachii; Tri: triceps brachii; FCR: flexor carpi radialis; FCU: flexor carpi ulnaris; ADP: adductor pollicis; FDS: flexor digitorum superficialis; FDP: flexor digitorum profundus; PT: pronator teres.

The severity of spasticity symptoms were evaluated using the Disability Assessment Scale (DAS; range: 0–12).[20] DAS evaluations were conducted with patients who had received BTX-A injections. The questionnaire included questions regarding the presence of tDCS side effects, such as headache, redness, pain, itching, and fever.

The effective change in this pilot study was defined as the minimal clinically important difference (MCID) for endpoints with established values, and the MCID for FMA-UE, ARAT and MAL were 4.25, 5.7 and 0.5 points, respectively.[21,22] Furthermore, the statistically significant difference in the amount of change from the baseline within the group and the presence or absence of serious adverse events were used as reference indicators of feasibility.

Statistical analysis

Within-group comparisons were conducted to investigate changes in clinical symptoms (FMA-UE, ARAT, and MAL) before and after treatment using the Wilcoxon signed-rank test. All analyses were performed using SPSS, version 21.0 (IBM Corp., Armonk, NY, USA). The significance threshold was set to $p < 0.05$.

tDCS-supported rehabilitation

We used the DC-STIMULATOR PLUS system (neuroConn GmbH, Germany) to perform tDCS. The anodal electrode was placed over standard scalp coordinates for the ipsilesional M1; whereas the cathodal electrode was placed over standard scalp coordinates for the contralesional M1 (C3 or C4 points according to the 10–20 system). Bilateral tDCS using electrodes (size of 5×7 cm; 35 cm^2) using a constant current intensity of 2.5 mA for 25 min (Figure 2). Our protocol used current densities below 25 mA/cm^2 which should not induce damage even when high-frequency stimulation is applied for several hours.[23,24] The tDCS protocol that we used has been described previously (Figure 3).[13,25]

PNMES-supported rehabilitation

We used an electromyography (EMG)-controlled electrical stimulator, which is also known as an *integrated volitional control electrical stimulator* (IVES) (OG GIKEN Co, Japan). The IVES is a portable, two-channel neuromuscular stimulator that promotes wrist extension, finger extension, and shoulder flexion during coordinated movement. The system consists of two instruments: a setting/input system and a stimulator.[26–28]

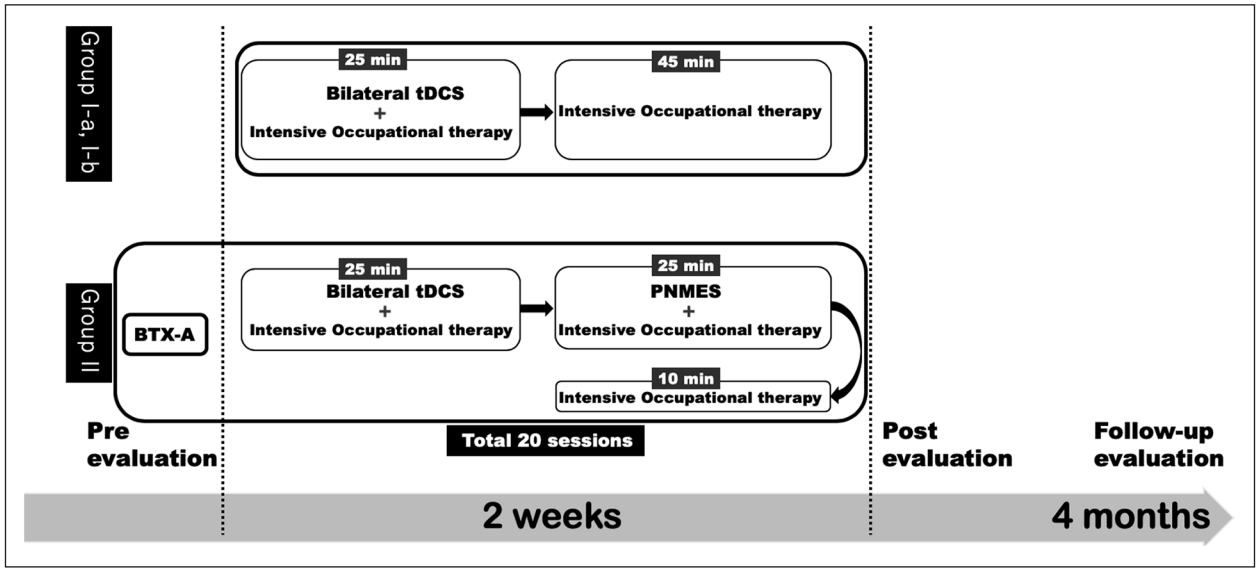

Figure 1. Study protocol in Groups I, bilateral tDCS started at the same time as the intensive occupational therapy for 25 min; and a 45-min-only intensive occupational therapy was performed after bilateral tDCS. Study protocol for combined therapy involving bilateral tDCS. Patients in Group II received BTX-A therapy 25 min prior to bilateral tDCS, which was immediately followed by a 25-min PNMES. Intensive occupational therapy was also provided simultaneously and performed alone for 10 min.
BTX-A: botulinum toxin A; tDCS: transcranial direct current stimulation; PNMES: peripheral neuromuscular electrical stimulation.

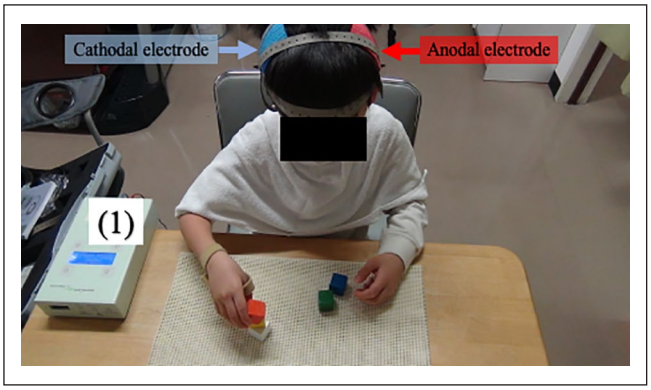

Figure 2. Bilateral tDCS with intensive occupational therapy: (1) DC-STIMULATOR PLUS system (neuroConn GmbH, Germany) for transcranial direct current stimulation.
tDCS: transcranial direct current stimulation.

Two self-adhesive surface electrodes were positioned on the extensor digitorum communis muscles in order to detect the myographic activity triggering the electrical pulse in the same muscle.[28] IVES therapy sessions were conducted twice daily for 10 days. When IVES (power-assist mode) could not pick up voluntary EMG signals, we selected the normal mode. Stimulation was applied at a frequency of 35 Hz at intervals of 50 µs (duty cycle: ON for 4 s, OFF for 4 s). When the IVES lamp turned ON, patients needed to be conscious of their finger extension movements. Stimulation intensity was set to the level where each patient reported mild paresthesia and muscle contractions in the absence of discomfort.

Results

Baseline characteristics

We included total 11 patients in this study, Group I-a included two patients (two females; mean age: 64.5 ± 9.2 years; mean interval from stroke onset: 24.5 ± 9.2 months), Group I-b included three patients (one male and two females; mean age: 8.3 ± 0.6 years; mean interval from stroke onset: 98.7 ± 6.8 months), Group II included six patients (three males and three females; mean age: 57.8 ± 9.7 years; mean interval from stroke onset: 41.5 ± 48.1 months). The mean baseline total Fugl-Meyer Assessment Upper Extremity (FMA-UE) score in Group I-a was 55.0 ± 4.2, while the mean proximal and distal FMA-UA scores were 36.0 ± 1.4 and 19.0 ± 2.8, respectively. The mean baseline total FMA-UE score in Group I-b was 42.7 ± 11.0, while the mean proximal and distal FMA-UA scores were 34.0 ± 4.6 and 8.7 ± 6.4, respectively. The mean baseline total FMA-UE score in Group II was 37.5 ± 14.2, while the mean proximal and distal FMA-UA scores were 27.7 ± 7.4 and 9.8 ± 7.4, respectively. The mean baseline ARAT scores in Group I-a, Group I-b, and Group II were 26.0 ± 5.7, 21.3 ± 12.1, and 19.3 ± 19.3, respectively.

The mean amount of use (AOU) score in Group II was 0.9 ± 0.7, while the mean quality of movement (QOM) score was 1.0 ± 0.8. The mean baseline DAS score was 3.0 ± 1.3.

Clinical outcomes

The mean total FMA-UE scores in Group I-a were 55.5 ± 4.9 and 52.0 ± N/A at the 2-week and 4-month follow-up,

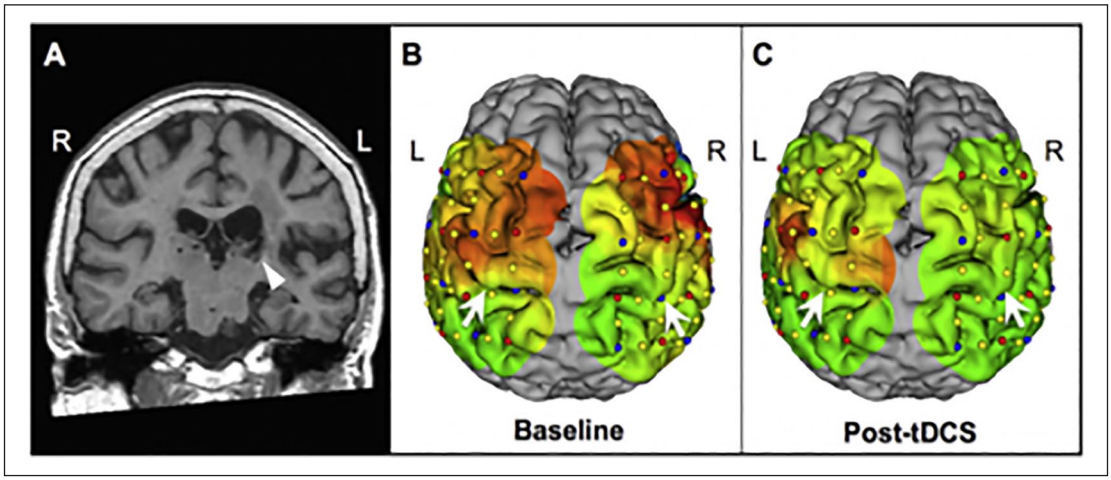

Figure 3. (A) Coronal view of a T1-weighted image. The arrow indicates a post-hemorrhagic lesion in the left thalamus. (B) and (C) Functional near-infrared spectroscopy (fNIRS) results showing oxyhemoglobin levels during right fist closure and opening over a 3D reconstructed image of the patient's brain. Red and green indicate higher and lower functional activity levels, respectively. Arrows indicate the central sulci. Following all tDCS sessions, activity in the right hemisphere was reduced.
This figure is adapted from Morishita et al.'s study[13] with permission.

respectively. The mean total FMA-UE scores in Group I-b were 47.0 ± 12.3 and 46.3 ± 12.9 at the 2-week and 4-month follow-up, respectively. The mean total FMA-UE scores in Group II were 39.5 ± 14.9 and 38.0 ± 13.5 at the 2-week and 4-month follow-up, respectively. The mean proximal FMA-UA scores in Group I-a were 36.0 ± 1.4 and 35.0 ± N/A at the 2-week and 4-month follow-up, respectively. The mean proximal FMA-UA scores in Group I-b were 35.3 ± 5.1 and 35.0 ± 5.6 at the 2-week and 4-month follow-up, respectively. The mean proximal FMA-UA scores in Group II were 28.3 ± 7.5 and 28.3 ± 7.5 at the 2-week and 4-month follow-up, respectively. The mean distal FMA-UA scores in Group I-a were 19.5 ± 3.5 and 17.0 ± N/A at the 2-week and 4-month follow-up, respectively. The mean distal FMA-UA scores in Group I-b were 11.7 ± 7.2 and 11.3 ± 7.5 at the 2-week and 4-month follow-up, respectively. The mean distal FMA-UA scores in Group II were 11.2 ± 7.8 and 9.7 ± 7.2 at the 2-week and 4-month follow-up, respectively.

The mean total FMA-UE scores and the proximal FMA-UA scores in Group II significantly improved compared to baseline total FMA-UE scores at the 2-week follow-up ($p=0.041$), the proximal FMA-UA scores at the 2-week follow-up ($p=0.046$) and at 4-month follow-up ($p=0.046$), respectively. Total FMA-UE scores at the 4-month follow-up ($p=0.339$), distal FMA-UA scores at the 2-week follow-up ($p=0.063$) and the 4-month follow-up ($p=0.713$) were unchanged. The mean ARAT scores in Group I-a were 30.5 ± 9.2 and 26.0 ± N/A in the 2-week and the 4-month follow-up, respectively. The mean ARAT scores in Group I-b were 25.3 ± 15.0 and 27.3 ± 14.0 at the 2-week and the 4-month follow-up, respectively. The mean ARAT scores in Group II were 21.7 ± 19.5 and 22.7 ± 20.2 at the 2-week ($p=0.180$) and 4-month follow-up ($p=0.138$), respectively (Table 2).

There appeared to be meaningful improvements in Group I-b. These data indicate that there were clinically meaningful changes in total FMA-UE scores in the 2 week and in ARAT scores in the 4 month follow-up in Group I-b. Moreover, Group II also showed significant improvement in total FMA-UE scores in the 2-week and proximal FMA-UA in the 2-week and 4-month follow-up. However, when both Group I-a and Group II were combined, no clinically meaningful improvements in motor function were observed.

The mean AOU scores in Group II increased to 1.2 ± 0.8 in the 2 week ($p=0.027$) and 1.4 ± 0.7 4 month follow-ups ($p=0.046$); whereas the mean QOM scores in Group II increased in the 2-week (1.3 ± 0.7; $p=0.042$) and 4-month follow-up (1.6 ± 0.9; $p=0.026$). Improvements in total MAL (AOU and QOM) scores in Group II were also observed at each follow-up visit. Most patients exhibited improvements in use of the affected limb following therapy. The mean DAS score in Group II decreased to 2.2 ± 0.4 and 2.4 ± 1.5 in the 2-week and 4-month follow-up, respectively. Thus, improvements in DAS scores (i.e. spasticity levels) were observed at each follow-up visit (Table 3).

Skin redness and mild itchiness were reported by five patients; however, no serious adverse events were noted (e.g. seizure) during tDCS therapy.

Discussion

This pilot study investigated the safety and efficacy of tDCS in adult and pediatric patients with chronic stroke. We also aimed to verify the efficacy of BTX-A and PNMES combined therapy involving bilateral tDCS in adult patients with chronic stroke. Our results demonstrated the feasibility of tDCS in 11 cases, including three pediatric patients. However, functional improvements in the impaired limb were only

Table 2. Upper limb paralysis function.

Group	Case	FMA-UE									ARAT		
		Total (0-66)			Proximal (0-42)			Distal (0-42)			Total (0-57)		
		Pre	Post	4M	Pre	Post	4M	Pre	Post	4M	Pre	Post	4M
I-a	1	58	59	N/A	37	37	N/A	21	22	N/A	30	37	N/A
	2	52	52	52	35	35	35	17	17	17	22	24	26
Mean (±SD)		55.0 ± 4.2	55.5 ± 4.9	52.0 ± N/A	36.0 ± 1.4	36.0 ± 1.4	35.0 ± N/A	19.0 ± 2.8	19.5 ± 3.5	17.0 ± N/A	26.0 ± 5.7	30.5 ± 9.2	26.0 ± N/A
I-b	3	39	42	41	33	34	34	6	8	7	17	21	23
	4	34	38	37	30	31	30	4	7	7	12	13	16
	5	55	61	61	39	41	41	16	20	20	35	42	43
Mean (±SD)		42.7 ± 11.0	47.0 ± 12.3	46.3 ± 12.9	34.0 ± 4.6	35.3 ± 5.1	35.0 ± 5.6	8.7 ± 6.4	11.7 ± 7.2	11.3 ± 7.5	21.3 ± 12.1	25.3 ± 15.0	27.3 ± 14.0
II	6	54	56	56	33	34	34	21	22	22	56	56	57
	7	30	34	31	26	27	27	4	7	4	11	11	11
	8	46	47	48	34	34	34	12	13	14	23	27	34
	9	23	24	24	19	20	20	4	4	4	3	3	6
	10	22	22	24	19	19	19	3	3	5	7	7	5
	11	50	54	45	35	36	36	15	18	9	16	26	23
Mean (±SD)		37.5 ± 14.2	39.5* ± 14.9	38.0 ± 13.5	27.7 ± 7.4	28.3* ± 7.5	28.3* ± 7.5	9.8 ± 7.4	11.2 ± 7.8	9.7 ± 7.2	19.3 ± 19.3	21.7 ± 19.5	22.7 ± 20.2

FMA-UE: Fugl–Meyer assessment (FMA) upper extremity, ARAT: Action Research Arm Test.
*$p < 0.05$ (Wilcoxon signed-rank test).

Table 3. Use of impaired upper limb and affecting of muscle tone in ADL.

Group	Case	MAL						DAS		
		Amount of use (0-5)			Quality of movement (0-5)			(0-12)		
		Pre	Post	4M	Pre	Post	4M	Pre	Post	4M
I-a	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	2	1.5	2.5	2.2	2.0	2.8	2.5	N/A	N/A	N/A
Mean		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
I-b	3	0.6	1.4	1.7	0.6	1.4	1.7	N/A	N/A	N/A
	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mean		N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
II	6	0.9	1.9	2.4	1.6	2.2	2.9	4	2	1
	7	0.5	0.6	0.8	0.5	0.7	0.8	2	2	2
	8	2.0	2.2	2.2	2.1	2.1	2.3	2	2	2
	9	1.4	1.6	1.3	1.1	1.4	1.4	3	N/A	N/A
	10	0.5	0.6	0.8	0.7	0.9	1.0	2	2	2
	11	0	0.5	1.1	0	0.7	0.9	5	3	5
Mean (±SD)		0.9 ± 0.7	1.2* ± 0.8	1.4* ± 0.7	1.0 ± 0.8	1.3* ± 0.7	1.6* ± 0.9	3.0 ± 1.3	2.2 ± 0.4	2.4 ± 1.5

MAL: Motor Activity Log; AOU: amount of use; QOM: quality of movement; DAS: Disability Assessment Scale.
*$p < 0.05$ (Wilcoxon signed-rank test).

observed on specific clinical measures for a subset of patients (Group I-b and Group II).

Previous research indicates that an MCID in patients with chronic stroke can be indexed by a change greater than 4.25 points on the FMA-UE or a change greater than 5.7 points on the ARAT scale.[21,22] In our cohort, only Group I-b achieved an MCID for the FMA at the 2-week follow-up and Group I-b achieved an MCID for the ARAT in the 4-month follow-up. The MCID for the MAL is greater than 0.5 points.[22] The increased use of upper limb paralysis may induce greater changes in neuroplasticity that may be linked to functional recovery. In functional assessments, Group I-b achieved MCID on clinical assessments during follow-up. Similarly, Group II achieved an MCID of 4-month follow-up assessment.

Improvements in total FMA-UE and proximal FMA-UA scores in Group II were observed at the 2-week follow-up. Previous studies have reported that tDCS is effective when administered in combination with other modalities such as upper limb robot therapy and virtual reality therapy,[29] suggesting that combined therapy involving tDCS may enhance upper limb function. Therefore, Group II may have had an enhanced effect of treatment.

Several studies have shown that childhood is a time where brain anatomy and connectivity change significantly.[30–33] There is also evidence of changes in brain plasticity during childhood.[33–37] Since tDCS may promote plasticity,[34] children receiving tDCS may have shown improved clinical outcomes due to changes in synaptic plasticity. However, it is not possible to determine whether changes in the 4-month follow-up visit are due to changes in plasticity due to treatment or due to normal neurodevelopment in childhood.

Interestingly, improvements in DAS scores were observed in the 4-month follow-up, even after the effects of BTX-A therapy had faded. Motivation for continuing self-training was important. MAL scores indicated that our rehabilitation program motivated Group II patients to use their affected limb after completing the 2-week treatment program. Previous studies have reported that the recovery of motor function after a stroke depends on the level of use of the affected limb.[38] Therefore, the program of Group II may have enhanced the effect of treatment.

Functional interhemispheric imbalances inhibit the recovery of upper limb paralysis.[9,39,40] A previous study suggested inhibitory signals from the ipsilesional hemisphere suppressed activity in the contralesional hemisphere in patients with stroke. This abnormal signaling pattern prevented functional motor recovery.[41] The two tDCS electrodes were placed symmetrically to address this interhemispheric imbalance. Moreover, our previous functional near-infrared spectroscopy studies have indicated that this procedure suppresses abnormal activity in the ipsilesional hemisphere (Figure 3).[13,25]

Although our data demonstrate the potential treatment of tDCS therapy either alone or in combination with other therapeutic modalities, there are several important limitations that require consideration. We only included 11 patients, and the sample was further split into pediatric and adult patients. Another limitation of the study was that different protocols for different age were used. In addition, the number of modalities is very large to study the effects of this study Group II. It should also be noted that cortical stimulation using tDCS may have promoted neuroplasticity.[41] Moreover, pediatric patients may have experienced spontaneous recovery over time since changes in neuroplasticity are shown in

children.[30–37] Nonetheless, our results highlight the need for further studies involving a larger number of cases, a control group subjected to sham stimulation (control) and a uniform treatment protocol.

Conclusion

The results of this study demonstrate that tDCS therapy is a potential treatment for chronic stroke in pediatric patients. Furthermore, our data indicate that BTX-A and PNMES treatment combined therapy involving tDCS may support the recovery of motor function. Additional, rigorously designed studies are required to verify our findings.

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Declaration of conflicting interests

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Ethical approval

Ethical approval for this study was obtained from institutional review board (IRB) named "Fukuoka University-Medical Ethics Review Board" (IRB approval number: 15-2-07).

Informed consent

Written informed consent was obtained from all subjects for this study. We have obtained written informed consent from the legally authorized representatives of subjects who were either minor or if they did not have the decisional capacity to provide the informed consent.

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References

1. Heller A, Wade DT, Wood VA, et al. Arm function after stroke: measurement and recovery over the first three months. *J Neurol Neurosurg Psychiatry* 1987; 50(6): 714–719.
2. Wade DT, Langton-Hewer R, Wood VA, et al. The hemiplegic arm after stroke: measurement and recovery. *J Neurol Neurosurg Psychiatry* 1983; 46(6): 521–524.
3. Sunderland A, Tinson D, Bradley L, et al. Arm function after stroke. An evaluation of grip strength as a measure of recovery and a prognostic indicator. *J Neurol Neurosurg Psychiatry* 1989; 52(11): 1267–1272.
4. Sheean G, Lannin NA, Turner-Stokes L, et al. Botulinum toxin assessment, intervention and after-care for upper limb hypertonicity in adults: international consensus statement. *Eur J Neurol* 2010; 17(Suppl 2): 74–93.
5. Lo AC, Guarino PD, Richards LG, et al. Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med* 2010; 362: 1772–1783.
6. Saita K, Morishita T, Hyakutake K, et al. Combined therapy using botulinum toxin A and single-joint hybrid assistive limb for upper-limb disability due to spastic hemiplegia. *J Neurol Sci* 2017; 373: 182–187.
7. Dimyan MA and Cohen LG. Neuroplasticity in the context of motor rehabilitation after stroke. *Nat Rev Neurol* 2011; 7(2): 76–85.
8. Pekna M, Pekny M and Nilsson M. Modulation of neural plasticity as a basis for stroke rehabilitation. *Stroke* 2012; 43(10): 2819–2828.
9. Lüdemann-Podubecká J, Bösl K, Rothhardt S, et al. Transcranial direct current stimulation for motor recovery of upper limb function after stroke. *Neurosci Biobehav Rev* 2014; 47: 245–259.
10. Nitsche M and a Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J Physiol* 2000; 527Pt3: 633–639.
11. Lindenberg R, Renga V and Zhu LL. Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients. *Neurology* 2010; 75: 2176–2184.
12. Bolognini N, Vallar G, Casati C, et al. Neurophysiological and behavioral effects of tDCS combined with constraint-induced movement therapy in poststroke patients. *Neurorehabil Neural Repair* 2011; 25(9): 819–829.
13. Morishita T, Hyakutake K, Saita K, et al. Pain reduction associated with improved functional interhemispheric balance following transcranial direct current stimulation for post-stroke central pain: a case study. *J Neurol Sci* 2015; 358: 484–485.
14. Takebayashi T, Takahashi K, Moriwaki M, et al. Improvement of upper extremity deficit after constraint-induced movement therapy combined with and without preconditioning stimulation using dual-hemisphere transcranial direct current stimulation and peripheral neuromuscular stimulation in chronic stroke. *Front Neurol* 2017; 8: 568–568.
15. Uy J and Ridding MC. Increased cortical excitability induced by transcranial DC and peripheral nerve stimulation. *J Neurosci Methods* 2003; 127: 193–197.
16. Tsuchiya M, Morita A and Hara Y. Effect of dual therapy with botulinum toxin A injection and electromyography-controlled functional electrical stimulation on active function in the spastic paretic hand. *J Nippon Med Sch* 2016; 83(1): 15–23
17. Fugl -Meyer AR, Jääskö L, Leyman I, et al. The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand J Rehabil Med* 1975; 7: 13–31.
18. Lyle RC. A performance test for assessment of upper limb function in physical rehabilitation treatment and research. *Int J Rehabil Res* 1981; 4(4): 483–492.

19. van der Lee JH, Beckerman H, Knol DL, et al. Clinimetric properties of the motor activity log for the assessment of arm use in hemiparetic patients. *Stroke* 2004; 35(6): 1410–1414.
20. Brashear A, Zafonte R, Corcoran M, et al. Inter- and intrarater reliability of the Ashworth scale and the disability assessment scale in patients with upper-limb poststroke spasticity. *Arch Phys Med Rehabil* 2002; 83(10): 1349–1354.
21. Page SJ, Fulk GD and Boyne P. Clinically important differences for the upper-extremity Fugl-Meyer scale in people with minimal to moderate impairment due to chronic stroke. *Phys Ther* 2012; 92(6): 791–798.
22. van der Lee JH, Wagenaar RC, Lankhorst GJ, et al. Forced use of the upper extremity in chronic stroke patients. *Stroke* 1999; 30(11): 2369–2375.
23. Equation P and Equation L. Letters to the editor. *Clin Neurophysiol* 1971; 10: 231–233.
24. McCreery DB, Agnew WF, Yuen TG, et al. Charge density and charge per phase as cofactors in neural injury induced by electrical stimulation. *Biomed Eng IEEE Trans* 1996; 37: 996–1001.
25. Morishita T and Inoue T. Brain stimulation therapy for central post-stroke pain from a perspective of interhemispheric neural network remodeling. *Front Hum Neurosci* 2016; 10: 166.
26. Hara Y, Ogawa S and Muraoka Y. Hybrid power-assisted functional electrical stimulation to improve hemiparetic upper-extremity function. *Am J Phys Med Rehabil* 2006; 85(12): 977–985
27. Hara Y, Ogawa S, Tsujiuchi K, et al. A home-based rehabilitation program for the hemiplegic upper extremity by power-assisted functional electrical stimulation. *Disabil Rehabil* 2008; 30(4): 296–304.
28. Muraoka Y. Development of an EMG recording device from stimulation electrodes for functional electrical stimulation. *Front Med Biol Eng* 2002; 11(4): 323–333.
29. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). *Clin Neurophysiol* 2017; 128(1): 56–92.
30. Huttenlocher PR. Synaptic density in human frontal cortex-develop-mental changes and effects of aging. *Brain Res* 1979; 163: 195–205.
31. Huttenlocher PR and de Courten C. The development of synapses in striate cortex of man. *Hum Neurobiol* 1987; 6(1): 1–9.
32. Casey BJ, Giedd JN and Thomas KM. Structural and functional brain development and its relation to cognitive development. *Biol Psychol* 2000; 54(1–3): 241–257.
33. Rapoport JL and Gogtay N. Brain neuroplasticity in healthy, hyperactive and psychotic children: insights from neuroimaging. *Neuropsychopharmacology* 2008; 33(1): 181–197.
34. Brunoni AR, Nitsche MA, Bolognini N, et al. Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimul* 2012; 5(3): 175–195.
35. Kolb B and Teskey GC. Age, experience, injury, and the changing brain. *Dev Psychobiol* 2012; 54(3): 311–325.
36. Stortelder F and Ploegmakers-Burg M. Adolescence and the reorganization of infant development: a neuro-psychoanalytic model. *J Am Acad Psychoanal Dyn Psychiatry* 2010; 38(3): 503–531.
37. Kessler SK, Woods AJ, Minhas P, et al. Dosage considerations for transcranial direct current stimulation in children: a computational modeling study. *PLoS One* 2013;8: e76112.
38. Wolf SL, Winstein CJ, Miller JP, et al. Retention of upper limb function in stroke survivors who have received constraint-induced movement therapy: the EXCITE randomised trial. *Lancet Neurol* 2008; 7(1): 33–40.
39. Ward NS and Cohen LG. Mechanisms underlying recovery of motor function after stroke. *Arch Neurol* 2004; 61: 1844–1848.
40. Simonetta-Moreau M. Neuromodulation corticale non invasive (NIBS) et récupération motrice post-AVC. *Ann Phys Rehabil Med* 2014; 57: 530–542.
41. Grefkes C and Fink GR. Connectivity-based approaches in stroke and recovery of function. *Lancet Neurol* 2014; 13(2): 206–216.