

# Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: A pilot study<sup>1</sup>

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**Abstract.** *Background and Purpose:* Preliminary reports suggest that central stimulation may enhance the effect of conventional physical therapies after stroke. This pilot study examines the safety and methodology of using transcranial direct stimulation (tDCS) with robot-assisted arm training (AT), to inform planning a larger randomised controlled trial.

*Subjects:* Ten patients, after an ischaemic stroke 4–8 weeks before study onset, no history of epilepsy, participated. Eight had a cortical lesion and 2 had subcortical lesions: all had severe arm paresis and, co-incidentally, 5 had severe aphasia.

*Methods:* Over six weeks, they received thirty 20 min-sessions of AT. During the first 7 minutes, 1.5mA of tDCS was applied with the anode over the lesioned hemisphere and the cathode above the contralateral orbit. Arm and language impairment were assessed with the Fugl-Meyer motor score (FM, full range 0–66) and the Aachener Aphasia Test.

*Results:* No major side effects occurred. Arm function of three patients (two with a subcortical lesion) improved significantly, with FM scores increasing from 6 to 28, 10 to 49 and 11 to 48. In the remaining seven patients, all with cortical lesions, arm function changed little, FM scores did not increase more than 5 points. Unexpectedly, aphasia improved in 4 patients.

*Conclusions:* These procedures are safe, and easy to use in a clinical setting. In future studies, patients should be stratified by degree of arm weakness and lesion site, also the unexpected aphasia improvement warrants following-up.

**Keywords:** Stroke, rehabilitation, aphasia, plasticity, brain stimulation, recovery of function

## 1. Introduction

Stroke affects almost 1 million subjects in the European community each year. While most patients regain walking ability, a severe upper limb paresis with no volitional hand and finger activity, affecting a third of stroke survivors, has a poor prognosis [10].

Central stimulation, in combination with a suitable behavioural therapy, may be a new treatment option to promote brain recovery. In animal experiments, Plautz et al have shown that coupled forced use of the paretic hand with implanted electrical stimulation to the ip-

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**Conflict of interest:** Reha-Stim holds the national patent on the arm trainer Bi-Manu-Track, the company is owned by Beate Brandl-Hesse, the spouse of the first author.



Fig. 1. A right hemiparetic patient while training with the computerized arm trainer in addition to the transcranial direct current stimulation. The anodal electrode is placed over the presumed hand area of the lesioned left hemisphere, the cathodal electrode above the contralateral orbita..

silesional M1 lead to significant behavioural improvements with large-scale expansions of the hand representation into areas previously representing proximal forelimb movements [16]. Adkins-Muir and Jones found similar results in lesioned rats [1]. In stroke patients, D-Amphetamine improved the motor status in patients with stroke when paired with physical therapy, but not when given in a manner unrelated to such therapy [12].

Potential candidates of physical central stimulation to be combined with peripheral physical therapy, are repetitive transcranial magnetic [19], epidural [3] and transcranial direct current stimulation, tDCS [14,15]. Erb successfully combined tDCS and muscle faradisation to improve motor outcome in chronic stroke patients in the late 19th century [4]. Recently, interest in this inexpensive method rose again, when Nitsche and Paulus showed that anodal (cathodal) tDCS stimulation of the hand area resulted in a significant and persistent elevation (depression) in cortical excitability in healthy subjects [14,15]. Polarity-driven alterations of resting membrane potentials were regarded as the crucial mechanisms of the DC-induced after effects [11]. Motor learning and verbal fluency improved in healthy [9], and fine motor skills in mildly affected chronic stroke subjects [8] following a single session of tDCS.

The present pilot study intended to study the safety and possible clinical effects of multiple sessions of tDCS in combination with physical therapy in subacute stroke patients suffering from severe upper limb

paresis. Robot-assisted arm training with the Bi-Manu-Track, offering a standardized treatment procedure, served as physical therapy. A recent controlled trial had shown a superior effect of the arm trainer as compared to electrical stimulation of the paretic wrist extensors in a comparable patient group [7].

## 2. Materials and methods

### 2.1. Subjects

The pilot study, approved by the local ethical committee, included ten subacute stroke patients. The inclusion criteria were

- first time supratentorial, ischaemic stroke,
- stroke interval between 4 and 8 weeks at study onset,
- age < 80 years,
- in-patient participating in a comprehensive rehabilitation programme,
- severe flaccid arm paresis with no (MRC 0) or minimal (MRC 1) volitional hand and finger extensor activity,
- Fugl Meyer upper limb motor assessment score (0–66) < 18, and
- written informed consent (in patients with aphasia: in cooperation with the speech therapist and relatives)

Exclusion criteria were:

- Preceding epileptic fits,
- an EEG suspect of elevated cortical excitability,
- a sensitive scalp skin,
- severe cognitive impairment,
- metallic implants within the brain,
- previous brain neurosurgery,
- medications altering the level of cortical excitability (e.g. antiepileptics, neuroleptics, benzodiazepines, antidepressants), and
- medications with a presumed positive or negative effect on brain plasticity (e.g. Dopamine, Fluoxetine, D-Amphetamine).

They were 3 men, 7 women, the age ranged from 32 to 76 years, the mean age was 63.3 years. Six (four) subjects presented a hemiparesis right (left). Eight subjects had suffered a cortical infarct due to an ischemia in the territory of the middle cerebral artery (MCA), and two subjects had suffered a subcortical infarct due to an ischemia in the territory of the Aa lenticulostriatæ. Five out of 10 patients were aphasic, global in three and Wernicke-type in two cases.

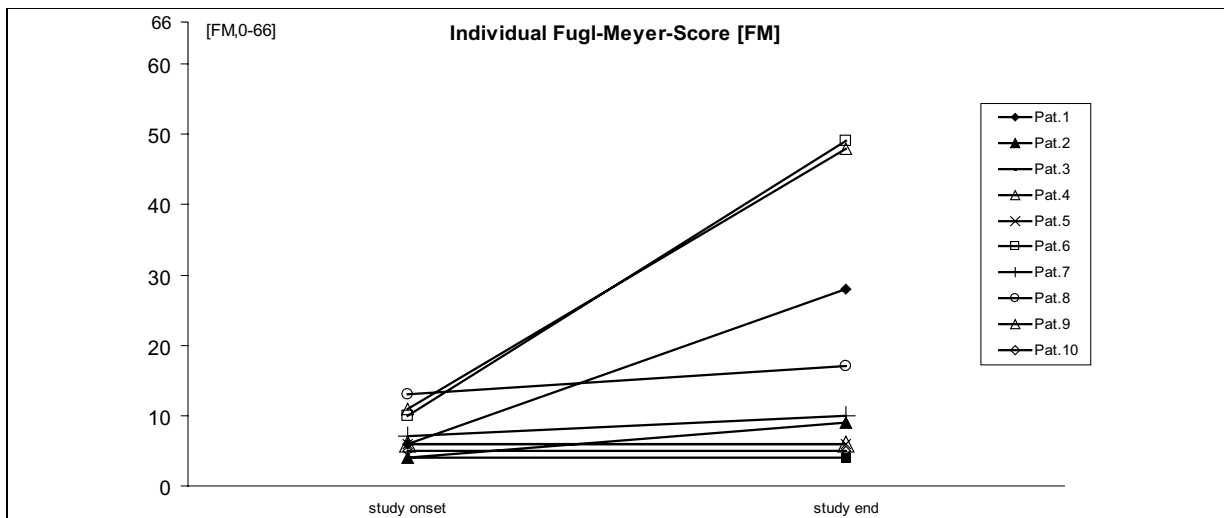


Fig. 2. Fugl-Meyer upper limb motor assessment score (FM, 0–66) of each patient before and after the six-week intervention.

## 2.2. Treatment

the specific treatment protocol of each session consisted of 20 min of robot assisted arm training (AT), additionally the patients received tDCS in the first seven minutes of the AT, i.e. the arm training and tDCS were applied simultaneously for 7 min. After this period, the tDCS stimulator was switched off, the electrodes remained in place so that the AT went on without interruption. The patients sat in a comfortable, height-adjustable armchair with the back supported.

tDCS was applied via saline-soaked surface sponge electrodes (35 cm<sup>2</sup>), connected to a battery-driven constant current stimulator<sup>1</sup> (Fig. 1). The intensity was 1.5 mA. The anodal electrode was placed over the presumed hand area of the lesioned hemisphere (C3, res. C4 according to the 10–20-system), the cathodal electrode was placed above the contralateral orbita. The tDCS protocol followed the work of Nitsche and Paulus, who had reported a lasting facilitation of the hand area of healthy subjects for up to 20 minutes following 7 min of tDCS [14,15] Originally, the authors had intended to determine the hand area of the lesioned hemisphere by transcranial magnetic stimulation, but a consistent CMAP of the paretic M. abductor digiti minimi could not be recorded in these severely affected stroke patients.

The AT was performed with the robot-assisted Bi-Manu-Track,<sup>2</sup> described in detail before [6] It en-

abled the bilateral mirror-like practice of a forearm pronation or a wrist extension flexion, the change of the movement direction required to tilt the device and to exchange the handles. The amplitude, speed and resistances could be set individually. Within one 20 min session both cycles were trained for 10 min, their sequence changed every day. Initially, the patients practised each cycle 100 times in a passive manner, to be followed by an active – passive mode, i.e. the non-paretic was driving the paretic extremity, for another 100 times. If possible, the paretic extremity had to overcome an initial isometric resistance actively. The dual stimulation paradigm (tDCS + AT) was applied every workday for six weeks, i.e. 30 session.

The ongoing comprehensive rehabilitation programme consisted of 45 min individual physiotherapy every workday and 30 min individual occupational therapy 4 times a week, following the Bobath concept. Therapy primarily aimed at the restoration of mobility and the daily living competence, stressing the compensatory use of the non-affected upper extremity. Treatment of aphasia included three to four 30-min syndrome-specific speech therapy sessions every week.

## 2.3. Assessment

Primary outcome parameter was the sensory and motor integrity and the degree of synergy involved in executing movements, assessed by the Fugl-Meyer Motor Assessment Score, FM, 0–66, 0 = no integrity, 66 = full integrity). A proximal shoulder/elbow (0–42) and a distal wrist/hand subscore (0–24) were calculated.

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Secondary was the upper limb muscle strength, assessed with the help of the MRC (0–5, 0 = plegic, 5 = full power). A sum score of three proximal (shoulder abduction, elbow flexion and extension) and five distal (flexion and extension of the hand and fingers, and thumb flexion) muscle groups (0–40) was calculated. Two physiotherapists assessed the outcome parameters before and after the treatment period. To ensure blinded evaluation of the FM, videos of the assessment, the patients sat on a chair and a mirror was placed 45° behind them, were sent to an experienced therapist on maternity leave.

Patient #2 was global aphasic, his communicative abilities improved to an unexpected level during the study, so that the authors asked the speech therapist to assess a second Aachen Aphasia Test (AAT) at study end, in addition to the routinely assessed AAT at rehabilitation onset. This assessment procedure of aphasia was continued in the four subsequent aphasic patients. The AAT consisted of five subtests: Token test, repetition, written language, confronting name and comprehension. Based on the prospective data of a low (up to 4 × 30 min per week) and a high intensity (6 × 90 min per week) group of aphasic patients, Poeck et al had reported critical gains of improvements of the raw values for each of the five subtest exceeding spontaneous recovery in subacute patients [17]. They assumed, in line with the literature [5], that a low-frequency speech therapy did not result in a relevant improvement beyond spontaneous recovery.

#### 2.4. Safety

Safety assessments included the:

- ongoing clinical observation of the in-patients (the principal investigator, a consultant neurologist, was clinically responsible for the participating patients),
- notification of the therapeutic team of potential risks, particularly epileptic fits, burning of the scalp skin, and clinical deterioration,
- EEG recordings 3 and 6 weeks after study onset to detect any changes in cortical excitability, evaluated by an independent consultant,
- No prescription of any medication altering cortical excitability or with a presumed positive or negative effect on brain plasticity (see also exclusion criteria).

Table 1

Individual results of the total Fugl-Meyer upper limb motor assessment score (0–66), and its proximal (0–42) and distal (0–24) subscores

FM	Study onset			Study end		
	total (0–66)	proximal (0–42)	distal (0–24)	total (0–66)	proximal (0–42)	distal (0–24)
Pat #1	6	6	0	28	16	12
Pat #2	4	4	0	9	7	2
Pat #3	4	4	0	4	4	0
Pat #4	6	6	0	6	6	0
Pat #5	6	6	0	6	6	0
Pat #6	10	8	2	49	32	17
Pat #7	7	7	0	10	8	2
Pat #8	13	11	2	17	13	4
Pat #9	11	9	2	48	30	18
Pat #10	5	5	0	5	5	0
Mean	7.2	6.6	0.6	18.2	12.7	5.5
SD	3.1	2.2	0.9	17.2	10.3	7.3

### 3. Results

Major side effects did not occur, four patients noticed a slight itching under the electrodes and two subjects a bearable headache in the first week immediately following tDCS. The EEGs recorded after the third and sixth week did not detect any elevated cortical excitability, i.e. the basic rhythm showed no change and no typical potentials for epilepsy were observed.

The FM (0–66) improved significantly over time (Wilcoxon test,  $p = 0.018$ ), the initial (terminal) mean (SD) FM was  $7.2 \pm 3.1$  ( $18.2 \pm 17.2$ ). The same applied to the MRC sum score (0–40), it improved from a mean of  $3.0 \pm 3.1$  to  $7.6 \pm 6.9$ ,  $p = 0.027$ .

Three patients profited markedly, starting from an initial score of 6, 10 and 11, they gained +22, +39, and +37 FM scores respectively (Fig. 2). Their proximal and distal subscores improved to a comparable extent (Table 1). They became able to use their paretic hand functionally, for instance to open a door by pushing the door handle while standing, or to stretch the paretic arm forward, pick up an object like a tooth paste from the table and to release it again. Two patients (#6, #9) could even turn the top of a tooth paste with the affected hand. Two patients had suffered a stroke in the territory of the Aa lenticulostriatae, the third patient exhibited two smaller ischaemic zones in the frontal and parietal cortex due to cardioembolic stroke.

The remaining seven patients, who all had suffered a MCA territory infarct with cortical involvement, did not improve (4 cases) or gained no more than 5 FM scores (Fig. 2), the paretic upper extremity remained non-functional.

Among the three global aphasic patients, one remained global, two transformed into a Wernicke syn-

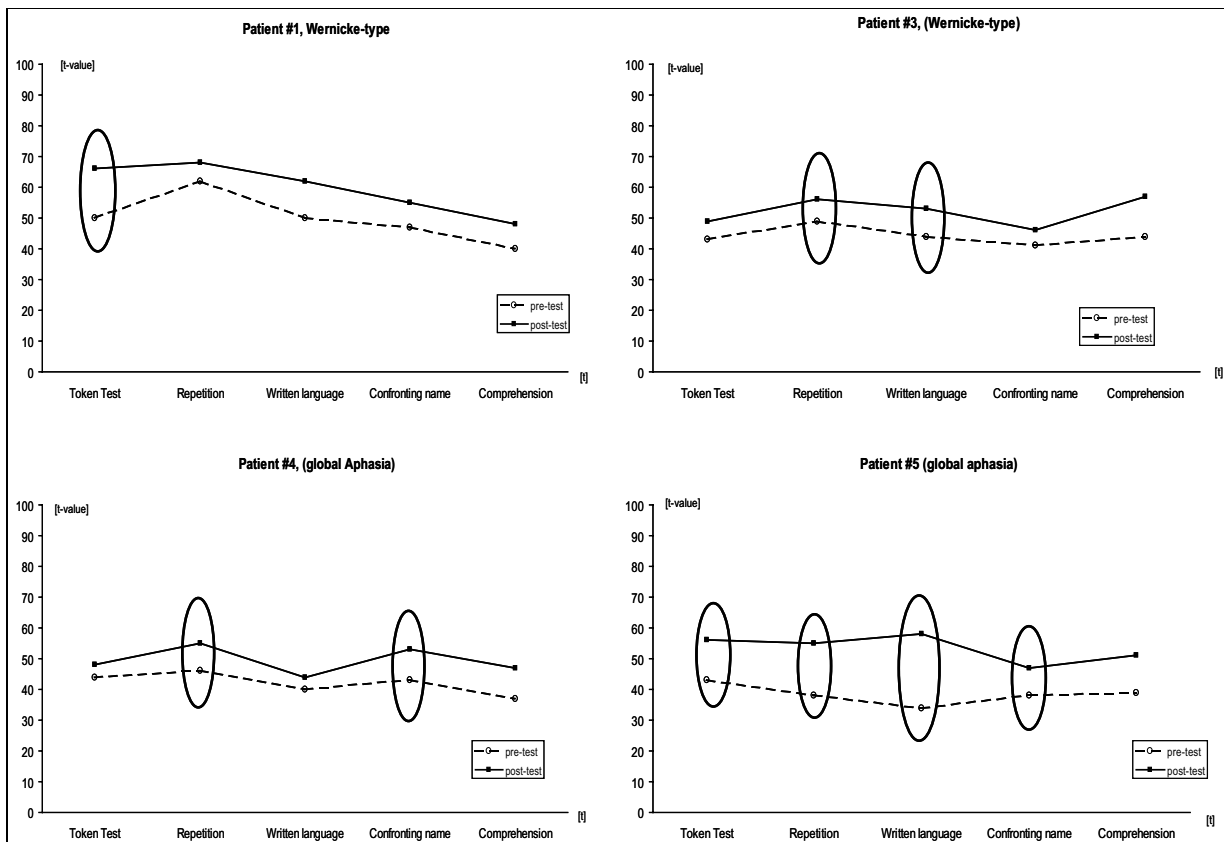


Fig. 3. Shows the t-values of the five subtests of the Aachen Aphasia Test (AAT) of the four aphasic patients, whose improvements exceeded the critical difference at least in one of the five AAT subtests (circles) indicating a definite treatment effect.

drome after therapy. Among the two Wernicke-type patients, one patient remained Wernicke-type while the second transformed into an anomic aphasia. Four patients exceeded the critical differences of spontaneous recovery at least in one to four of the five subtests of the AAT (Fig. 3).

#### 4. Discussion

No persistent side effects occurred, the protocol of 30 sessions of 7 min tDCS integrated into 20 min of robot arm training proved viable in the severely affected subacute patients. Repeated EEG recordings, independently evaluated, could not detect an elevated level of cortical excitability and none of the patients deteriorated clinically during the study. Given the relatively low current densities delivered to the skin, the expected dispersion of the current in the brain, and the likelihood of substantial current shunting through the skin and the CSE, noxious effects were unlikely a priori.

The pilot study lacked any control group, it included a small number of patients, who were still in the phase of spontaneous recovery, accordingly no conclusions can be drawn until a study with an appropriate control group is carried out. Which preliminary findings are worth following up in future studies?

Lesion site may influence the outcome of the combined treatment approach. Two out of 10 participating subjects had suffered a subcortical stroke, they both belonged to a subgroup of three patients, who showed the most FM improvement. The third subject exhibited two smaller ischaemic zones in the frontal and parietal cortex due to cardioembolic stroke.

Starting from an initial score of 6, 10 and 11 they gained 22, 39 and 37 points and became functionally, even to turn the top of a tooth paste in two cases. The remaining seven patients, all of them had suffered a cortical stroke, did not gain more than 5 FM scores

Given the poor prognosis of the severe upper limb paresis [10], the upper limb motor outcome of those 3 subjects is encouraging. The preceding RCT [7] on the

effect of the arm trainer alone also showed a significant improvement in the experimental group. But on an individual basis none of the patients gained more than + 29 FM scores. So, at least in two subjects, one may speculate on an additional effect of tDCS. For the MIT-Manus, another upper limb robot, Aisen et al. reported maximum individual FM gains of + 22 in their controlled study [2].

Unexpectedly, we observed that four of the five aphasic patients, all of them had suffered a MCA infarct with cortical involvement, improved their communication skills considerably. The AAT gains corresponded to those reported by Poeck et al. for patients participating in a high intensive speech therapy programme totalling 9 hours per week [17]. In contrast, patients of the present study only received 120 min per week which rarely results in an improvement beyond spontaneous recovery according to literature reviews [5]. Lacking any confirmatory studies, explanations of this unexpected effect must be premature. Nevertheless, the authors want to hint at the findings of Saur et al., who showed that an up-regulation of the brain activity both in the Broca and its homologous area correlated with the improvement of aphasia in the sub-acute phase [18]. Furthermore, a close relationship between hand and speech areas seems to exist; healthy subjects, for instance, improved their verbal fluency following repetitive transcranial magnetic stimulation of the hand area [13].

Was the computerized arm trainer the appropriate behavioural therapy to be combined with tDCS? The authors suggest further studies to evaluate the effect of tDCS and a regular rehabilitation program. Any active training programmes, such as CIMT for instance, could not be applied due to the severity of the paresis in this subgroup of sub-acute stroke patients. Electrical stimulation of the peripheral nerves or muscles would have been an alternative. However, the preceding RCT on the arm trainer had resulted in a superior FM result of the machine as compared to the electrical stimulation of the paretic wrist extensors. Most probable explanation was a higher repetition rate of movements trained which on the other hand should have conferred a larger afferent input to the primary sensorimotor cortex. The bilateral approach of the machine intended to additionally facilitate the paretic side. At the moment the authors cannot exclude that a unilateral passive movement of the paretic side would have not been a more appropriate therapy to be combined with tDCS.

In conclusion, exposure to direct current polarization of the frontal cortex in combination with a robot-

assisted arm training seems safe in sub-acute stroke patients. Given the pilot character of the study, no conclusions can be drawn until a study with an appropriate control group is carried out. The findings that the lesion site could have influenced the motor outcome and the unexpected speech improvement may be worth following in future controlled trials. The appropriate physical therapy to be combined with tDCS is another open question.

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