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# Non-invasive alternating current stimulation induces recovery from stroke

Anton Fedorov[a,1], Yulia Chibisova[b,1], Aneta Szymaszek[a,c], Mikhail Alexandrov[b], Carolin Gall[a] and Bernhard A. Sabel[a,*]

[a]*Institute of Medical Psychology, Otto-von-Guericke-University Magdeburg, Leipziger Str., 44, 39120 Magdeburg, Germany*

[b]*Mechnikov Medical Academy, Department of Neurology, Neurosurgery and Medical Genetics, Piskarevsky pr., 47, Saint-Petersburg, Russia*

[c]*Nencki Institute of Experimental Biology, Laboratory of Neuropsychology, 3 Pasteur St., Warsaw, Poland*

**Abstract**. *Background:* Recovery of post-stroke deficits can be achieved by modulating neuroplasticity with non-invasive brain stimulation. To evaluate potential effects of repetitive transorbital alternating current stimulation (rtACS) on stroke recovery we carried out a randomized, drug-controlled clinical trial.

*Methods:* Ninety-eight patients that had suffered ischemic stroke 21.4 months earlier were randomly assigned to either group D ($n = 30$) receiving conventional drug therapy, group ACS ($n = 32$) treated for 12 days with rtACS, or group D/ACS ($n = 36$) receiving combined drug therapy/rtACS. Stroke severity level (SSL) was assessed by the NIH-NINDS stroke scale before and after treatment and at a 1-month follow-up to evaluate motor impairments (weakness, ataxia), sensory loss, visual field defects, and cortical deficits (aphasia, neglect). At each time point standard EEG recordings (10–20 system) were conducted.

*Results:* Before therapy SSL was moderate ($9.18 \pm 0.78$) without significant group difference ($F = 0.86$, $p = 0.43$). After 12 days of treatment, SSLs of groups ACS and D/ACS significantly improved by 22.5% and 25.1% over baseline, respectively, with no such change in the control group D ($+3\%$). SSL improvements were mainly due to recovery of motor, sensory, and speech functions. After 1-month follow-up, an additional improvement of 9.7% and 9.4% was seen for the group ACS and D/ACS which led to a total change of $+32.3\%$ and $+34.7\%$ over baseline. EEG recordings revealed greater interhemispheric synchrony between both temporal lobes which were positively correlated with clinical outcome.

*Conclusions*: Non-invasive rtACS applied to post-stroke patients can modulate brain plasticity and induce recovery from neurological deficits long after the early post lesion recovery is over.

Keywords: Stroke, alternating current stimulation, recovery, aphasia, restoration

## 1. Introduction

Because at least 30% of post-stroke patients suffer from long lasting neurological deficits in different functional domains new therapeutic approaches are needed to facilitate rehabilitation. With regard to motor function deficits incomplete recovery is attributed to maladaptive plasticity that results from interhemispheric competition (Sprague, 1966; Calford and Tweedale, 1990; Ferbert et al., 1992). Here, the motor cortex of the intact hemisphere has abnormally high levels of excitation and by interhemispheric inhibition it suppresses the analogous motor area of the lesioned hemisphere, thus limiting adaptive plasticity.

Non-invasive brain stimulation techniques such as transcranial magnetic stimulation (TMS) or transcranial direct current stimulation (tDCS) have been used

[1]These authors contributed equally to this manuscript.

*Corresponding author: Bernhard A. Sabel, PhD, Institute of Medical Psychology, Otto-von-Guericke-University Magdeburg, Leipziger Str. 44, 39120 Magdeburg, Germany. Tel.: +49 391 672 1800; Fax: +49 391 672 1803; E-mail: bernhard.sabel@med.ovgu.de.

to study plasticity effects in the areas of verbal fluency, motor learning and perceptual thresholds (Pascual-Leone et al., 2000; Wassermann and Grafman, 2005). There is a need for safe stimulation protocols to allow the use of these techniques in neurorehabilitation (Paulus, 2003). TMS can activate or suppress activity in cortical regions directly and provides up- or down-regulation of neuronal excitability, depending on the specific stimulation parameters (Pascual-Leone et al., 2000; Maeda et al., 2000; Siebner and Rothwell, 2003). TDCS can also enhance or depress excitability in the stimulated region for minutes to 1–2 hours depending on the duration and polarity of stimulation, where activation of both long term potentiation (LTP)- and long term depression (LTD)-like mechanisms can be achieved by altering sodium and calcium-dependent channels and N-methyl-D-aspartate-receptor activity (Wassermann and Grafman, 2005; Nitsche et al., 2005; Gandiga et al., 2006).

Experimental and clinical evidence from different non-invasive brain stimulation protocols revealed that neurological outcome does not only depend on the applied current parameters but that different mechanisms of synaptic plasticity are involved. According to the theory of "homeostatic plasticity" (Abraham and Bear, 1996; Turrigiano and Nelson, 2004; Rich and Wenner, 2007), LTP/LTD like stimulation effects strongly correlated with time-averaged postsynaptic activity. Whereas low levels of postsynaptic thresholds initiate LTP, high threshold levels, in contrast, lead to LTD.

Considering both mechanisms, interhemispheric competition and homeostatic plasticity, we have carried out an exploratory study to treat patients with chronic neurological impairments after stroke using repetitive transorbital alternating current stimulation (rtACS). This rtACS approach has been studied for two decades in Russia (Chibisova et al., 2001; Fedorov et al., 2005, 2010) and recently also in Germany (Sabel et al., 2010; Gall et al., 2010). By using repetitive pulses we wished to induce LTP-like enhancement of synaptic plasticity which was accomplished by transorbital current pulses at frequencies in the alpha and beta range which are capable to induce well defined phosphenes in most patients at current levels (200–400 $\mu$A) far below those needed for transcranial stimulation (1000 $\mu$A or greater) (Kanai et al., 2008). Based on the prior experience, these phosphenes were expected to produce clinically beneficial effects (Chibisova et al., 2001; Fedorov et al., 2005, 2010; Sabel et al., 2010; Gall et al., 2010). Most recently, in an independent line of research, other investigators have also observed that trains of transcranial ACS produce phosphenes in a frequency-dependent manner which is a sign that ACS activates the visual cortex (at least) (Antal et al., 2008; Kanai et al., 2010; Schutter et al., 2010). Zaehle et al. (2010) reported that transcranial ACS applied within the individual alpha frequency range over the visual cortex of 10 healthy subjects elevated the alpha power measured at parieto-central electrodes. Increased individual alpha power was shown to be relevant for enhancing cognitive performance (Klimesch et al., 2003; Hanslmayr et al., 2005).

We have recently applied rtACS sessions in the alpha range to evaluate efficacy in patients with optic neuropathies (Sabel et al., 2010; Gall et al., 2010). Here, rtACS led to visual function improvements which were accompanied by neuronal network reorganization as shown by EEG power spectra changes across different brain sites (unpublished observations). These findings suggest that rtACS induces excitability changes, though the precise mechanisms (excitation or inhibition) are currently not known. While it remains to be determined if trains of ACS pulses induce homeostatic plasticity changes, rtACS presumably alters brain activity towards normal levels by increasing synchronization in the brain network. Interestingly, even with the transorbital electrode montage, EEG power spectra changes were noted in areas well beyond the visual pathway.

Whatever the mechanism(s) might be, given the widespread EEG changes we have seen across the brain in several non-visual regions after transorbital stimulation, we now wished to determine whether (visual) phosphene inducing rtACS can also affect non-visual functional loss after stroke.

We have therefore applied rtACS to stroke patients and measured clinical recovery several years after the spontaneous recovery phase was over. It was hypothesized that rtACS might re-balance interhemispheric excitation and inhibition by brain network synchronization (Murase et al., 2004) as it is also known in other domains such as attention, memory and language (Oliveri et al., 2001; Hilgetag et al., 2001; Naeser et al., 2005). As we now show, phosphene-inducing rtACS improves several non-visual neurological functions in stable stroke patients such as locomotion, sensory and language functions.

## 2. Method

### *2.1. Subjects*

Ninety-eight patients were enrolled in a randomized, drug-controlled clinical trial at the Human Brain

Table 1
Patients' demographics

| Patients samples ($n = 98$) | | Group D ($n = 30$) | Group ACS ($n = 32$) | Group D/ACS ($n = 36$) |
|---|---|---|---|---|
| Average age (M ± SD) | | 58.9 ± 9.2 | 57.3 ± 7.6 | 61.1 ± 8.3 |
| Sex | Male ($n = 37$) | 14 | 12 | 11 |
| | Female ($n = 61$) | 16 | 20 | 25 |
| Stroke area | ICA ($n = 52$) | 19 | 17 | 16 |
| | VA ($n = 46$) | 11 | 15 | 20 |
| Average stroke age (months, M ± SD) | | 22.7 ± 1.8 | 21.4 ± 4 | 20 ± 2.9 |

Group D: controls without rtACS; Group ACS: rtACS only; Group D/ACS: rtACS combined with drugs; ICA: internal carotid artery; VA: vertebral artery.

Institute and Mechnikov Medical Academy (Saint-Petersburg, Russia) which was approved by the local Ethical Committee. Patients gave written informed consent. Ischemic stroke patients were included if lesions were older than 6 months. Patients had either ischemic cortical or subcortical stroke, with different neurological deficits including sensory, motor, and cognitive impairments; 23 patients had aphasia (motor, sensory and mixed forms). The mean patients' age was 59.0 ± 8.4 years; mean lesion age was 22.1 ± 8.3 months (see Table 1 for demographics). Lesion location and size were documented by MRI.

Exclusion criteria were heart pacemakers, epileptic seizure within the last 3 years, photosensitive epilepsy as determined by EEG, mental diseases (schizophrenia etc.), presence of a non-operable tumor, blood pressure above 160 mm/Hg, and diabetes mellitus (respectively diabetic retinopathy). Taking into account that arterial hypertension is associated with a high risk of stroke recurrence and, on the other hand, undesirable blood pressure fluctuations may occur during rtACS these patients were excluded. Also patients with diabetes mellitus were excluded because these may suffer from retinopathy with the risk of retinal hemorrhages or detachment during rtACS.

### *2.2. Neurologic examination*

Patients were examined immediately before and after the treatment, and after a 1-month treatment free follow-up period. Physicians examining the patients were blinded as to the treatment condition. Neurological deficits and stroke severity were assessed with the National Institutes of Health Stroke Scale (NIH-NINDS) to quantify motor impairments (weakness, ataxia), sensory loss, visual field defects, and cortical deficits (aphasia, neglect). NIH-NINDS sections devoted to the acute phase of stroke were not analyzed. For statistical analysis of pre- and post-stimulation measurements paired T-test was used.

## 3. Clinical evaluation

Patients were assigned to one of 3 groups: groups D ("control group") received a combination of drug therapies for 18 days (see below) ($n = 30$), group ACS received rtACS only ($n = 32$), and group D/ACS a combination of both ($n = 36$). For randomization patients were sorted according to their family name and consecutively assigned to one group at a time in that sequence. As part of the basic therapeutic ischemic stroke management different antiplatelet agents in standard recommended doses were chronically administered to each patient (including aspirin alone or the combination of aspirin with dipyridamole or clopidogrel). For groups D and D/ACS additional drugs (depending on the patients individual requirements) included: (i) vasodilatator Vinpocetine ($\alpha$-adrenoblocker and as a potential blocker of excitotoxicity) or Nicergoline (Sermion, selective antagonist $\alpha$ adrenergic receptor); (ii) cognition enhancers (nootropic function) Piracetam (pyroglutamate) or Choline alfoscerate (parasympathomimetic precursor of acetylcholine neurotransmitter), (iii) metabolic enhancers to improve oxygen and glucose or (iv) anti-depressants (Fluoxetine), oral and intrathecal spasticity drugs (e.g. Baclofen) or pain reliever with anti-inflammatory effects (Ibuprofen). The drug selection was made individually by the attending physician to achieve optimized clinical effects, with no systematic differences between groups (Table 2).

## 4. EEG recording and analysis

We used a computer controlled EEG (Encephalan-131, Russia) with electrode montage according to the 10–20 system, i.e. from 19 sites, with impedances below 10 k$\Omega$. Earlobe electrodes served as reference. Statistical analyses were performed on 120 sec. of spontaneous EEG records which were filtered off-line, segmented and baseline corrected (sampled at 250 Hz,

Table 2
Summary of applied drugs, theirs dosage per course for groups D and D/ACS

| Drug name | Dosage per course | Group D | Group D/ACS | Group difference |
|---|---|---|---|---|
| Vinpocetine, | Min | 210 | 200 | |
| 5 mg | Max | 630 | 700 | |
| | Average | 420 ± 148.5 | 450 ± 176.8 | ns. |
| Nicergoline, | Min | 315 | 210 | |
| 10 mg | Max | 525 | 525 | |
| | Average | 420 ± 74.2 | 367.5 ± 111.4 | ns. |
| Piracetam, | Min | 19.2 | 20.8 | |
| 0.8 g | Max | 28.8 | 31.2 | |
| | Average | 24.0 ± 3.3 | 26 ± 3.6 | ns. |
| Choline alfoscerate, | Min | 6.3 | 6.6 | |
| 0.3 g | Max | 25.2 | 26.4 | |
| | Average | 15.7 ± 6.7 | 16.5 ± 7.0 | ns. |
| Fluoxetine, | Min | 60 | 50 | |
| 20 mg | Max | 240 | 150 | |
| | Average | 150 ± 63.6 | 100 ± 35.4 | ns. |
| Baclofen, | Min | 105 | 95 | |
| 10 mg | Max | 210 | 190 | |
| | Average | 157.5 ± 37.1 | 142.5 ± 33.6 | ns. |

low-pass filter was set at 50 Hz). Here, 15–20 artifact-free EEG segments ($\sim$ 6 sec) were extracted from each record and averaged. Auto-power spectra and cross-power spectra were computed by Hamming windowed Fast Fourier transformation procedure. Cross-power spectra were calculated between all possible channel pairs on the scalp. The coherence function was measured by the correlation between two signals as a function of their frequency components. Of all possible frequency bands, the coherence analysis was limited to broad-band coherence values for the main frequency bands delta (0.5–3.5 Hz), theta (4–7.5 Hz), alpha (8–12.5 Hz) and beta (13–25 Hz). Coherence values for pre- vs. post-rtACS EEG measurements were then compared within groups (Wilcoxon signed rank test).

### *4.1. Alternating current stimulation procedure*

RtACS was generated by an alternating current stimulation device (BrainStim, Russia) and applied via multizone active electrodes (9 steel half sphere contact zones, 0.14 cm$^2$ each) placed on the eyelids. The passive electrode was positioned on the wrist of the right arm. Bipolar square pulses (5–20 msec phase) were delivered as train of pulses (2–9) for each active electrode. Current intensity threshold was established by inducing phosphenes and they were typically between 200–400 $\mu$A, i.e. well below 1000 $\mu$A. Inter-pulse intervals ranged from 23–190 ms applied to both eyes separately. A treatment lasted 30–40 min. daily and was given for 12 consecutive days. The neurologist providing clinical examinations was blinded as to which group the patients belonged.

## 5. Results

### *5.1. Stroke severity levels (SSL)*

Neurological examination showed a moderate (9.18 ± 0.78) SSL for all groups before treatment without significant between group differences (one – way ANOVA, F = 0.86, $p$ = n.s., see Table 3).

After 12 days of treatment, SSL values of the ACS and D/ACS group decreased by 2.01 (22.5%, $p = 0.042$) and 2.6 (25.1%, $p = 0.035$), respectively. The control group D only showed a slight improvement of 0.27 (3%, n.s.). After a 1-month treatment-free follow-up, an additional improvement of the SSL was observed by 0.67 (9.7%, $p = 0.064$) and 0.73 (9.4%, $p = 0.078$) for the ACS and D/ACS group, respectively, i.e. a change of $+32.3\%$ ($p = 0.019$) and $+34.7\%$ ($p = 0.023$) over baseline. Decreased SSL values were mainly due to recovery of motor and sensory neurological domains, but also due to improvements in speech functions, which was also analyzed separately (Table 3).

### *5.2. Speech functions*

Patients with aphasia were separately analyzed with respect to their speech functions (groups D: $n = 6$; ACS: $n = 8$; D/ACS $n = 7$). The clinical effects on aphasia after rtACS included a facilitation of selection of words, decreased number of pauses during conversation, improved speed of speech and an increased loudness of voice.

Table 3
Results of SSL assessment (NIH-NINDS stroke scale) for ischemic post-stroke patients before, after 12 days and 1 month follow-up

| NIH-NINDS scale | Group D, $n = 30$ | | Group ACS, $n = 32$ | | | Group D/ACS, n=36 | | |
|---|---|---|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | Follow Up | Pre | Post | Follow Up |
| Facial palsy | 1.56 | 1.50 | 1.50 | 1.25 | 1.33 | 1.85 | 1.50 | 1.23* |
| Motor arm right | 0.75 | 0.70 | 1.17 | 1.00 | 0.67* | 0.88 | 0.88 | 0.83 |
| Motor arm left | 0.44 | 0.44 | 0.17 | 0.17 | 0.17 | 0.63 | 0.25* | 0.17* |
| Motor leg right | 0.63 | 0.57 | 1.25 | 1.00 | 0.67* | 1.00 | 0.88 | 0.88 |
| Motor leg left | 0.50 | 0.50 | 0.17 | 0.17 | 0.17 | 0.63 | 0.25* | 0.17* |
| Limb ataxia | 1.38 | 1.38 | 1.50 | 1.00* | 1.00* | 1.67 | 1.38* | 1.43 |
| Sensory | 1.13 | 1.13 | 1.08 | 0.91 | 0.82 | 1.25 | 1.00 | 0.87* |
| Formerly neglect | 1.13 | 1.13 | 1.08 | 1.00 | 1.00 | 1.25 | 1.00 | 1.00 |
| Dysarthria | 0.50 | 0.45 | 0.58 | 0.33* | 0.33* | 0.88 | 0.38* | 0.33* |
| Aphasia | 0.25 | 0.20 | 0.42 | 0.08* | 0.08* | 0.33 | 0.25 | 0.13* |
| SSL | 8.27 | 8.0 | 8.92 | 6.91* | 6.24* | 10.37 | 7.77* | 7.04* |

SSL: Stroke severity level. Significant differences between post minus pre or follow-up minus pre measurements are marked with * ($p < 0.05$).

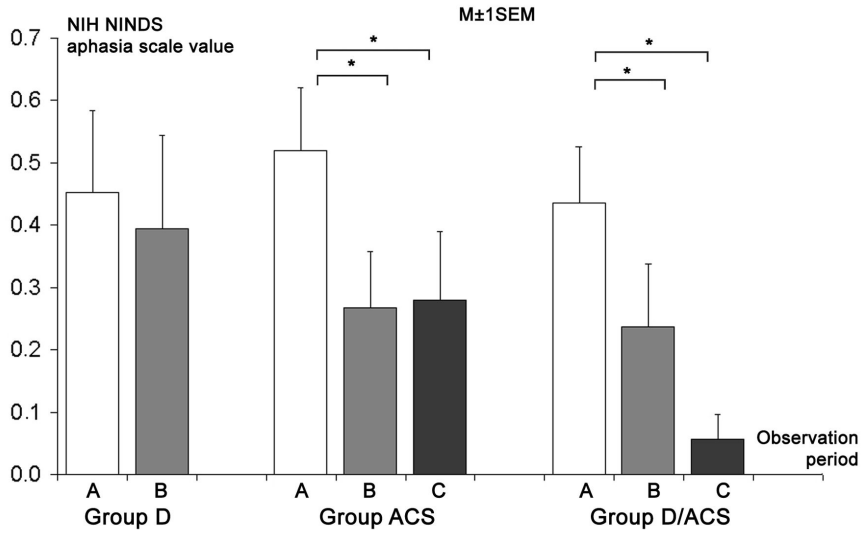


Fig. 1. Aphasia subscale of the NIH-NINDS for control group D, group ACS and group D/ACS displayed as M ± SEM before therapy (A), after 12 days (B) and one month follow-up (C). * $p < 0.05$.

When averaging the NIH-NINDS aphasia values (Fig. 1) the severity of speech deficits was not reduced in the control group D. However, in groups treated with rtACS (group ACS and D/ACS) a reduction from 0.52 to 0.27 and 0.44 to 0.24 was noted, i.e. an improvement of 0.25 (51.9%, $p = 0.025$) and 0.20 (54.5%, $p = 0.029$), respectively (Fig. 1). At 1-month follow-up, the speech deficits severity was stable in the ACS group compared to the assessment immediately post-treatment, but group D/ACS showed a trend of further improvement (0.06; 25%, $p = 0.075$). The final score for this group had significantly improved at final outcome when compared to baseline ($p = 0.009$).

### 5.3. EEG results

Visual inspection of the EEG data revealed typical pattern of bioelectrical activity changes across the evaluation period. Initially, focal theta-waves were seen in the projection of the temporal and/or frontal lobes of the intact hemisphere. After rtACS in the lesioned side we noted periodically bilateral synchronization which finally (at follow up) had developed to a symmetrically distribution between both hemispheres. The findings can be interpreted as temporal limbic system involvement. Taking into account that the projection of the limbic system onto the scalp surface corresponds well with

the central line electrodes we measured the changes of coherence values between T3 and T4 temporal brain sites of both hemispheres. Coherence function was calculated for theta-activity which reflects deep brain structure activities. The coherence function dynamics are shown in Fig. 2.

Coherence values at baseline for temporal sites of both hemispheres showed no significant difference between groups. After the 12-day treatment course, coherence for the control group (D) was increased by only 0.07 (15.9%, ns), whereas both ACS groups showed increased coherence values of 0.14 (31.4%, $p = 0.06$) and 0.17 (37%, $p = 0.03$) for the ACS and D/ACS group, respectively. Follow-up examinations confirmed improvements of interhemispheric interaction as indicated by coherence values $> 0.7$ ($p < 0.01$) for both ACS groups. This was not seen in the control group D. Nonparametric correlation analyses (Spearman rank test) revealed that the difference of the pre- and post-rtACS coherence value between T3-T4 channels was correlated with changes of SSL only in the ACS and D/ACS group ($r = 0.29$, $p = 0.048$ and $r = 0.34$, $p = 0.02$), but not in the control group D ($r = 0.04$, n.s.).

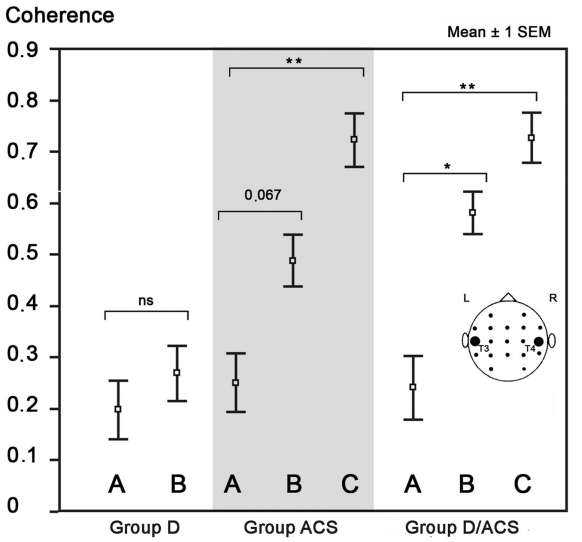


Fig. 2. Coherence dynamics during rtACS. T3-T4 sites coherence function changes for control group (I), group ACS (II) and group D/ACS. Averaged coherence values displayed as M ± SEM before therapy (A), after 12 days (B) and one month follow-up (C). * - difference between A&B at $p < 0.05$, ** - difference between A&C at $p < 0.05$.

## 6. Discussion

Both animal and human studies show that non-invasive brain stimulation with tDCS or TMS can modulate plasticity in post-stroke recovery (Ward and Cohen, 2005; Gerloff et al., 2006). The results of the present study using an alternating current stimulation protocol are in line with findings by different research groups which showed that inhibition of cortical excitability of the primary motor area (Ml) of the contralesional hemisphere promotes recovery of function of the affected hand after stroke. These studies reported significant improvements of motor function of the affected hand after inhibitory TMS over the contralesional Ml (Mansur et al., 2005; Takeuchi et al., 2005; Nowak et al., 2009). Application of inhibitory (1 Hz) TMS over the contralesional M1 reduced the inhibitory effect onto lesioned M1 which led to improvement of motor functions of the affected hand in subcortical stroke (Kirton et al., 2008). The combination of anodal tDCS over the ipsilesional Ml with peripheral nerve stimulation of the affected hand seems more effective than anodal tDCS alone (Celnik et al., 2009). Fregni et al. (2005) showed that tDCS significantly improved hand function in the Jebsen-Taylor Hand Test in chronic stroke patients.

Even stroke-induced cognitive deficits were diminished by stimulation of the frontal lobe as indicated by an increased speed in reaction time (Marshall et al., 2005) and improvement of working memory (Fregni et al., 2005; Jo et al., 2009). In the language domain, Martin et al. (2004) observed improvements in the ability to name objects and people after inhibition of anterior parts of the inferior frontal gyrus. Further, significant improvements (34%) in picture naming were observed after cathodal tDCS over the left frontotemporal areas in patients with non-fluent aphasia (Monti et al., 2008).

The neurological improvements we have seen after rtACS can not be explained by spontaneous recovery because all patients were treated in the chronic phase ($22.1 \pm 8.3$ months after stroke), i.e. well after the initial recovery phase. When applied for 12 days rtACS led to partial recovery in different neurological functions. These improvements were stable at a 1-month follow-up. At follow-up some patients even showed additional recovery. Decreased SSL scores and improvements in aphasic symptoms were observed. Because there was greater interhemispheric EEG coherence (synchrony) between the temporal lobes of both hemispheres we propose that changes of interhemispheric balance are possible mechanisms of rtACS-induced recovery. Specifically, before treatment, coherence function of the theta range revealed functional (frequency) links, located only on the side of the in-

tact hemisphere but absent on the stroke side. After 12 daily rtACS sessions, coherence analysis revealed newly formed interhemispheric links of the intact hemisphere with the lesioned side (in the projection zone of the limbic system) and this was accompanied by fewer functional links on the intact side. After 1-month follow-up the coherence analysis confirmed new functional connections between temporal sites of both hemispheres. Our overall interpretation is that rtACS is not only able to modulate activity in selected brain regions of the intact hemisphere, but it modulates the damaged hemisphere as well. The combined modulation in both hemispheres may contribute to the recovery of neurological functions. We presume that rtACS-induced recovery from stroke is mediated by the recruitment of pre-existing network elements (Chen et al., 2001; Hummel et al., 2003) and the strengthening of synaptic plasticity in a more widely distributed network, i.e. the effect is not limited to localized regions.

This interpretation is in line with behavioral experiments indicating that both hemispheres contribute to recovery of function after stroke (Cramer, 2004). Because in the present study the correlation links were located in temporal lobes, i.e. the projection zone of limbic structures, we postulate that recovery is not simply due to cortical plasticity but that structures located deep in the brain also contribute to recovery but this requires further experimentation.

In any event, our data are in agreement with other studies where improved interhemispheric interactions (balance) were observed during recovery from brain injury (Ward et al., 2003; Carter et al., 2010).

The observed improvements of aphasic symptoms are in line with findings of language learning studies with healthy subjects that showed with coherence measures that brain structures involved in learning – such as the hippocampus – mediate initial learning of lexical, semantic and syntactic knowledge (Classen et al., 1998; Miltner et al., 1999; Chen et al., 2001). We suspect that coherence in the investigated stroke patients is likely caused by activity of sensorimotor and premotor cortices in the intact hemispheres, signifying integration of both areas into a functioning network.

The present study was not designed to answer the question whether recovery after stroke is based on certain cellular mechanisms of recovery such as axonal sprouting or the formation of new synapses. Whatever the mechanism may be, non-invasive brain stimulation is a promising approach to improve neurological functions in patients after stroke. However, further studies are required to better understand the mechanisms induced by rtACS and larger scale double-blind, sham-controlled clinical trials are now warranted.

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