tDCS clinical research - highlights: Stroke

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Author: G. Ruffini (PhD), L. Dubreuil Vall

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G. Ruffini, L. Dubreuil Vall, Neuroelectrics Barcelona SL

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A stroke that affects the cerebral cortex may have a wide range of effects depending on the location of the lesion. The clinical strategies for treating stroke typically involve**s stabilization** of the patient, **preservation** of function in the brain area and **adaptation** of the patient to diminished function. There are some hints that **electrical stimulation of the brain may in itself promote recovery or preservation of brain tissue** (see, e.g., [1]), although to date a relatively small number of published studies have focused on improving specific functions through the use of single or repeated sessions of anodal stimulation.

Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) effective for the treatment of stroke? Under what conditions? With what montages? We focus here on a compilation of the recent literature on this topic. We have relied on Google Scholar and also PubMed to carry out the search, including the terms of tDCS, tACS, tRNS as well as Stroke (**from March 2012 and until March 2015**).

We advance that there continues to be a high intensity in the research community probing this question in addition to using tCS for pure, fundamental research. At the same time, study group sizes are slowly increasing (and they have to!), and this is good news. As you can read below, there quite a few encouraging results in this area, although study group sizes (the famous *N*) are still relatively small. We try to indicate group size and the use of a sham-controlled, double-blind experimental technique. **The conclusion is that there is very interesting progress in this area, and that there is likely to be more in the future.**

In what follows we concentrate on interesting, study-oriented papers with patients, and leave reviews to the end. In order to make the reading lighter, we have edited the abstracts a bit (just click on the title link if you are interested in the paper).

We provide first an overview of earlier papers, then focus on recent data.

1. Overview

The main motivation behind the use of non-invasive brain stimulation for stroke recovery is to support relearning of compromised abilities by enhancement of pathologically-reduced cortical excitability and activity, directly by excitability-enhancing brain stimulation of the lesioned area, or indirectly, by reducing excitability of the non-lesioned contralateral hemisphere – since this has inhibitory connections with the lesioned one [2]. Specifically, the respective excitability enhancements are thought to promote relearning of functions by enhancing learning-related long-term potentiation (LTP) (which is the likely physiological basis of learning and memory formation [3]) and via this mechanism promote recovery.

We recall here the logic regarding **anodal versus cathodal stimulation**. Anodal stimulation over an area produces electric fields directed generally inward into the brain in the subjacent cortex. The direction of the

electric field with respect to the orientation of the neuron is a significant parameter in the alteration of the trans-membrane potential, especially of elongated neurons such as pyramidal cells. For this reason we may loosely say that anodal stimulation is excitatory, since long cortical neurons are generally aligned perpendicular to the cortical surface, etc. The opposite applies to cathodal stimulation. However, these are approximate statements. The geometry of the cortical surface is complex, as are the generated electric fields. For this reason, biophysical modeling of electric fields an their interactions with neurons is an important tool to carefully define montages. If interested in the topic, see this paper on biophysical modeling and this one on the electric field generated by focal tDCS.

Despite these subtleties, **tDCS has been repeatedly shown to modulate learning in healthy humans** [e.g., 4, 5] and animals, (see this nice HIVE paper). Function-specific treatment trials have so far addressed recovery of motor function, language and of memory and cognition. An early study of a small number of patients with unilateral motor deficit found an improvement in the affected hand function after a single application of 20 min of 2 mA anodal tDCS over the lesioned area [6]. In addition, we also know that recovery may be enhanced if the stimulation is applied bilaterally, with the unaffected hemisphere concurrently down-regulated using cathodal stimulation [7]. The same technique may be used to ameliorate visuospatial attention deficits in neglect patients [8].

Another interesting study on **post-stroke aphasia** found an improvement in picture naming after a single 10 min session of 2 mA tDCS over Broca's area, but only after cathodal and not anodal stimulation [9]. A second study tested five daily 20 min sessions of 1 mA anodal tDCS to a target location defined by functional imaging of each patient's spared ability [10]. These authors found that anodal stimulation was effective in aiding recovery. On first sight, these results would appear to contradict each other and further work is no doubt required to address the substantial differences between the two studies' methods. One explanation for the diverging outcome might be that the electrode arrangement differed in both studies, with different positions of the return electrode. Since tDCS effects depend on electric field direction [11, 12] different electrode positions might have resulted in different alterations of cortical excitability. This highlights the need for careful, complete specification of electrode montages in all future studies and careful modeling of the resulting electric fields in the brain.

More recently, the effects of anodal stimulation in the affected vs. cathodal in the contralateral hemisphere (both with combined robotic arm rehabilitation) have been studied in more depth, showing that both produce similar, in not identical results [16].

Although the approaches taken in such trials do not allow researchers to determine the effect of tDCS alone, they do mimic more closely the likely treatment pathway for a patient, where tDCS will probably be combined with other therapies.

A crucial direction of **future research** will be to determine the factors that best predict recovery in stroke patients, and to shape optimal therapy combinations for each patient [13, 14]. Paired tDCS-robot therapy seems like a promising route. Both fMRI and EEG (prior, during, post tDCS) can provide interesting data as well, guiding in the future the choice of the most effective montages and protocols.

A relatively recent meta-analysis of studies on stroke and tDCS concludes that, although the efficacy of anodal tDCS depends on current density and duration of application, there is a pattern of motor function

improvement following anodal tDCS that encourages further research [15]. Since the studies conducted so far are in most cases exploratory pilots with a relatively small numbers of subjects, future studies should explore the validity of the results in larger samples. Judging by the number of ongoing (declared) clinical studies on the subject, we should learn much more soon.

We provide next an updated list of recent publications on this subject.

2. Update (2014-2015)

A number of studies by now strongly suggest the efficacy of tDCS in stroke. The studies in our search show in general positive results. We have analyzed 47 papers meeting our criteria, from 2005 to 2015. The total number of subjects in these studies was 873, with 65% of subjects in studies with positive outcomes. If we restrict the analysis to papers dealing with chronic stroke the percent of subjects in studies with a positive outcome increases to 82% (231 out of 281 subjects). If we further restrict the analysis to those studies with chronic patients in which tDCS was administered concurrently with therapy, the positive rate increases further to 84% (156 out of 186 subjects were in studies with positive results). The analogous rate for non-chronic stroke patients is low, of 44% (207 out of 470 patients). Finally, focusing only on studies with non-acute or subacute only patients, the rate is of 88%

Based on this results, we conclude that there is sufficient evidence for tDCS in chronic stroke. In this sense we come to the same conclusion as in the meta-analysis by [Marquez2013a]: "Transcranial direct current stimulation is likely to be effective in enhancing motor performance in the short term when applied selectively to patients with stroke". Our results agree with those of [Butler2013a], who carried out a meta-analysis of upper limb chronic stroke patients (N=100), indicating an overall positive effect.

CHRONIC STROKE META-ANALYSIS

Butler AJ, Shuster M, O'Hara E, Hurley K, Middlebrooks D, Guilkey K., A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors., J Hand Ther. 2013 Apr-Jun;26(2):162-70;

Prior reviews on the effects of anodal transcranial direct current stimulation (a-tDCS) have shown the effectiveness of a-tDCS on corticomotor excitability and motor function in healthy individuals but nonsignificant effect in subjects with stroke. PURPOSE: To summarize and evaluate the evidence for the efficacy of a-tDCS in the treatment of upper limb motor impairment after stroke. METHODS: A meta-analysis of randomized controlled trials that compared a-tDCS with placebo and change from baseline. RESULTS: A pooled analysis showed a significant increase in scores in favor of a-tDCS (standard mean difference [SMD]=0.40, 95% confidence interval [CI]=0.10-0.70, p=0.010, compared with baseline). A similar effect was observed between a-tDCS and sham (SMD=0.49, 95% CI=0.18-0.81, p=0.005).
CONCLUSION: This meta-analysis of eight randomized placebo-controlled trials provides further evidence that a-tDCS may benefit motor function of the paretic upper limb in patients suffering from chronic stroke. LEVEL OF EVIDENCE: Level 1a.

CHRONIC STROKE STUDIES

Lefebvre S, Dricot L, Laloux P, Gradkowski W, Desfontaines P, Evrard F, Peeters A, Jamart J, Vandermeeren Y, Neural substrates underlying stimulation-enhanced motor skill learning after stroke., Brain. 2015 Jan;138(Pt 1):149-63.

Nineteen chronic hemiparetic stroke patients participated in a double-blind, cross-over randomized, sham-controlled experiment with two series. Each series consisted of two sessions: (i) an intervention session during which dual transcranial direct current stimulation or sham was applied during motor skill learning with the paretic upper limb; and (ii) an imaging session 1 week later, during which the patients performed the learned motor skill. The motor skill learning task, called the 'circuit game', involves a speed/accuracy trade-off and consists of moving a pointer controlled by a computer mouse along a complex circuit as quickly and accurately as possible. Relative to the sham series, dual transcranial direct current stimulation applied bilaterally over the primary motor cortex during motor skill learning with the paretic upper limb resulted in (i) enhanced online motor skill learning; (ii) enhanced 1-week retention; and (iii) superior transfer of performance improvement to an untrained task. The 1-week retention's enhancement driven by the intervention was associated with a trend towards normalization of the brain activation pattern during performance of the learned motor skill relative to the sham series. A similar trend towards normalization relative to sham was observed during performance of a simple, untrained task without a speed/accuracy constraint, despite a lack of behavioural difference between the dual transcranial direct current stimulation and sham series. Finally, dual transcranial direct current stimulation applied during the first session enhanced continued learning with the paretic limb 1 week later, relative to the sham series. This lasting behavioural enhancement was associated with more efficient recruitment of the motor skill learning network, that is, focused activation on the motor-premotor areas in the damaged hemisphere, especially on the dorsal premotor cortex. **Dual transcranial direct current stimulation applied during motor skill learning with a paretic upper limb resulted in prolonged shaping of brain activation, which supported behavioural enhancements in stroke patients.**

Vestito L1, Rosellini S1, Mantero M1, Bandini F2., Long-term effects of transcranial direct-current stimulation in chronic post-stroke aphasia: a pilot study., Front Hum Neurosci. 2014 Oct 14;8:785

Three aphasic patients underwent anodal tDCS (A-tDCS, 20 min, 1.5 mA) and sham stimulation (S-tDCS) over the left frontal (perilesional) region, coupled with a simultaneous naming training (on-line tDCS). Ten consecutive sessions (5 days per week for 2 weeks) were implemented. In the first five sessions, we used a list of 40 figures, while in the subsequent five sessions we utilized a second set of 40 figures differing in word difficulty. At the end of the stimulation period, we found a significant beneficial effect of A-tDCS (as compared to baseline and S-tDCS) in all our subjects, regardless of word difficulty, although with some inter-individual differences. In the follow-up period, the percentage of correct responses persisted significantly better until the 16th week, when an initial decline in naming performance was observed. Up to the 21st week, the number of correct responses, though no longer significant, was still above the baseline level. **These results in a small group of aphasic patients suggest a long-term beneficial effect of on-line A-tDCS.**

Au-Yeung SS1, Wang J, Chen Y, Chua E., Transcranial direct current stimulation to primary motor area improves hand dexterity and selective attention in chronic stroke., Am J Phys Med Rehabil. 2014 Dec;93(12):1057-64.

Ten stroke survivors with some pinch strength in the paretic hand received three different tDCS interventions assigned in random order in separate sessions-anodal tDCS targeting the primary motor area of the lesioned hemisphere (M1lesioned), cathodal tDCS applied to the contralateral hemisphere (M1nonlesioned), and sham tDCS-each for 20 mins. The primary outcome measures were Purdue pegboard test scores for hand dexterity and response time in the color-word Stroop test for selective attention. Pinch strength of the paretic hand was the secondary outcome. Cathodal tDCS to M1nonlesioned significantly improved affected hand dexterity (by 1.1 points on the Purdue pegboard unimanual test, P = 0.014) and selective attention (0.6 secs faster response time on the level 3 Stroop interference test for response inhibition, P = 0.017), but not pinch strength. The outcomes were not improved with anodal tDCS to M1lesioned or sham tDCS. Thus, **Twenty minutes of cathodal tDCS to M1 nonlesioned can promote both paretic hand dexterity and selective attention in people with chronic stroke.**

Viana RT1, Laurentino GE1, Souza RJ1, Fonseca JB1, Silva Filho EM1, Dias SN1, Teixeira-Salmela LF2, Monte-Silva KK1., Effects of the addition of transcranial direct current stimulation to virtual reality therapy after stroke: a pilot randomized controlled trial. NeuroRehabilitation. 2014;34(3): 437-46.

This pilot double-blind randomized control trial aimed to determine whether or not tDCS, combined with Wii virtual reality therapy (VRT), would be superior to Wii therapy alone in improving upper limb function and quality of life in chronic stroke individuals. **Twenty** participants were randomly assigned either to an experimental group that received VRT and tDCS, or a control group that received VRT and sham tDCS. The therapy was delivered over 15 sessions with 13 minutes of active or sham anodal tDCS, and one hour of virtual reality therapy. The outcomes included were determined using the Fugl-Meyer scale, the Wolf motor function test, the modified Ashworth scale (MAS), grip strength, and the stroke specific quality of life scale (SSQOL). Minimal clinically important differences (MCID) were observed when assessing outcome data. RESULTS: Both groups demonstrated gains in all evaluated areas, except for the SSQOL-UL domain. Differences between groups were only observed in wrist spasticity levels in the experimental group, where more than 50% of the participants achieved the MCID. **These findings support that tDCS, combined with VRT therapy, should be investigated and clarified further.**

Sunwoo H1, Kim YH, Chang WH, Noh S, Kim EJ, Ko MH., Effects of dual transcranial direct current stimulation on post-stroke unilateral visuospatial neglect., Neurosci Lett. 2013 Oct 25;554:94-8.

Based on the interhemispheric inhibition model of unilateral visuospatial neglect (USN) after stroke, the effects of dual-mode transcranial direct current stimulation (tDCS) over the parietal cortices were assessed in a double-blind random-order cross-over experiment. **Ten chronic** right hemispheric stroke patients (4 men; mean age: 62.6 years) with USN were recruited. All participants underwent three randomly arranged tDCS sessions: (1) dual-mode, anodal tDCS over the right posterior parietal cortex (PPC) and cathodal tDCS over the left PPC; (2) single-mode, anodal tDCS over the right PPC; and (3) sham mode. Each session lasted 20min. Before and immediately after the stimulation, a line bisection test and star cancelation test were carried out. In the line bisection test, significant improvements were observed after both the dual- and the single-mode tDCS ($p<0.05$), but not after sham stimulation. Statistical analysis showed a significant interaction between time and tDCS mode, where the dual tDCS had a stronger effect than the single or sham

stimulation modes ($p<0.05$). The star cancelation test did not show any significant change. **These results suggest that dual tDCS over the bilateral PPC is an effective method for the treatment of USN in stroke patients.**

Danzl MM, Chelette KC, Lee K, Lykins D, Sawaki L., Brain stimulation paired with novel locomotor training with robotic gait orthosis in chronic stroke: a feasibility study., NeuroRehabilitation. 2013;33(1):67-76.

10 subjects with stroke were recruited and randomized to active tDCS or sham tDCS for 12 sessions. Both groups participated in identical locomotor training with a robotic gait orthosis (RGO) following each tDCS session. RGO training protocol was designed to harness cortical neuroplasticity. Data analysis included assessment of functional and participation outcome measures and qualitative thematic analysis. Eight subjects completed the study. Both groups demonstrated trends toward improvement, but the active tDCS group showed greater improvement than the sham group. Qualitative analyses indicated beneficial effects of this combined intervention. CONCLUSIONS: It is feasible to combine tDCS targeting the LE motor cortex with our novel locomotor training. **It appears that tDCS has the potential to enhance the effectiveness of gait training in chronic stroke.**

Giacobbe V1, Krebs HI, Volpe BT, Pascual-Leone A, Rykman A, Zeiarati G, Fregni F, Dipietro L, Thickbroom GW, Edwards DJ., Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: the dimension of timing., NeuroRehabilitation. 2013;33(1):49-56.

We used a within-subjects repeated-measurement design in **12 chronic (>6 months) stroke survivors**. Twenty minutes of anodal tDCS was delivered to the affected hemisphere before, during, or after a 20-minute session of robotic practice. Sham tDCS was also applied during motor practice. Robotic motor performance and corticomotor excitability, assessed through transcranial magnetic stimulation (TMS), were evaluated pre- and post-intervention. RESULTS: Movement speed was increased after motor training (sham tDCS) by ~20%. Movement smoothness was improved when tDCS was delivered before motor practice (~15%). TDCS delivered during practice did not offer any benefit, whereas it reduced speed when delivered after practice (~10%). MEPs were present in ~50% of patients at baseline; in these subjects motor practice increased corticomotor excitability to the trained muscle. CONCLUSIONS: **In a cohort of stroke survivors, motor performance kinematics improved when tDCS was delivered prior to robotic training,** but not when delivered during or after training. The temporal relationship between non-invasive brain stimulation and neurorehabilitation is important in determining the efficacy and outcome of this combined therapy.

Olma MC1, Dargie RA, Behrens JR, Kraft A, Irlbacher K, Fahle M, Brandt SA., Long-Term Effects of Serial Anodal tDCS on Motion Perception in Subjects with Occipital Stroke Measured in the Unaffected Visual Hemifield., Front Hum Neurosci. 2013 Jun 24;7:314

This study aimed to examine whether serial anodal tDCS over the visual cortex can exogenously induce long-term neuroplastic changes in the visual cortex. However, when the visual cortex is affected by a cortical lesion, up-regulated endogenous neuroplastic adaptation processes may alter the susceptibility to tDCS. To this end, motion perception was investigated in the unaffected hemifield of subjects with unilateral visual cortex lesions. **Twelve subjects** with occipital ischemic lesions participated in a within-subject, sham-controlled, double-blind study. MRI-registered sham or anodal tDCS (1.5 mA, 20 min) was applied on five consecutive days over the visual cortex. Motion perception was tested before and after stimulation sessions and at 14- and 28-day follow-up. After a 16-day interval an identical study block with the other stimulation

condition (anodal or sham tDCS) followed. Serial anodal tDCS over the visual cortex resulted in an improvement in motion perception, a function attributed to MT/V5. This effect was still measurable at 14- and 28-day follow-up measurements. Thus, this may represent **evidence for long-term tDCS-induced plasticity** and has implications for the design of studies examining the time course of tDCS effects in both the visual and motor systems.

Lefebvre S1, Thonnard JL, Laloux P, Peeters A, Jamart J, Vandermeeren Y., Single session of dual-tDCS transiently improves precision grip and dexterity of the paretic hand after stroke. Neurorehabil Neural Repair. 2014 Feb;28(2):100-10.

In all, **19 chronic hemiparetic** individuals with mild to moderate impairment participated in a double-blind, randomized trial. During 2 separate cross-over sessions (real/sham), they performed 10 precision grip movements with a manipulandum and the Purdue Pegboard Test (PPT) before, during, immediately after, and 20 minutes after dual-tDCS applied simultaneously over the ipsilesional (anodal) and contralateral (cathodal) primary motor cortices. RESULTS: **The precision grip performed with the paretic hand improved significantly 20 minutes after dual-tDCS, with reduction of the grip force/load force ratio by 7% and in the preloading phase duration by 18% when compared with sham.** The dexterity of the paretic hand started improving during dual-tDCS and culminated 20 minutes after the end of dual-tDCS (PPT score +38% vs +5% after sham). The maximal improvements in precision grip and dexterity were observed 20 minutes after dual-tDCS. These improvements correlated negatively with residual hand function quantified with ABILHAND. **One bout of dual-tDCS improved the motor control of precision grip and digital dexterity beyond the time of stimulation. These results suggest that dual-tDCS should be tested in longer protocols for neurorehabilitation and with moderate to severely impaired patients.** The precise timing of stimulation after stroke onset and associated training should be defined.

Lefebvre S1, Laloux P, Peeters A, Desfontaines P, Jamart J, Vandermeeren Y., Dual-tDCS Enhances Online Motor Skill Learning and Long-Term Retention in Chronic Stroke Patients., Front Hum Neurosci. 2013 Jan 9;6:343.

Eighteen chronic stroke patients participated in a randomized, cross-over, placebo-controlled, double bind trial. During separate sessions, dual-tDCS or sham dual-tDCS was applied over 30 min while stroke patients learned a complex visuomotor skill with the paretic hand: using a computer mouse to move a pointer along a complex circuit as quickly and accurately as possible. A learning index involving the evolution of the speed/accuracy trade-off was calculated. Performance of the motor skill was measured at baseline, after intervention and 1 week later.
RESULTS: After sham dual-tDCS, eight patients showed performance worsening. In contrast, dual-tDCS enhanced the amount and speed of online motor skill learning compared to sham ($p < 0.001$) in all patients; this superiority was maintained throughout the hour following. The speed/accuracy trade-off was shifted more consistently after dual-tDCS ($n = 10$) than after sham ($n = 3$). More importantly, 1 week later, online enhancement under dual-tDCS had translated into superior long-term retention (+44%) compared to sham (+4%). The improvement generalized to a new untrained circuit and to digital dexterity. **A single-session of dual-tDCS, applied while stroke patients trained with the paretic hand significantly enhanced online motor skill learning both quantitatively and qualitatively, leading to successful long-term retention and generalization. The combination of motor skill learning and dual-tDCS is promising for improving post-stroke neurorehabilitation.**

Stagg CJ, Bachtiar V, O'Shea J, Allman C, Bosnell RA, Kischka U, Matthews PM, Johansen-Berg H., Cortical activation changes underlying stimulation-induced behavioural gains in chronic stroke., Brain. 2012 Jan;135(Pt 1):276-84.

Patients at least 6 months post-first stroke participated in a behavioural experiment **(n = 13**) or a functional magnetic resonance imaging experiment **(n = 11),** each investigating the effects of three stimulation conditions in separate sessions: anodal stimulation to the ipsilesional hemisphere; cathodal stimulation to the contralesional hemisphere; and sham stimulation. Anodal (facilitatory) stimulation to the ipsilesional hemisphere led to significant improvements (5-10%) in response times with the affected hand in both experiments. This improvement was associated with an increase in movement-related cortical activity in the stimulated primary motor cortex and functionally interconnected regions. Cathodal (inhibitory) stimulation to the contralesional hemisphere led to a functional improvement only when compared with sham stimulation. We show for the first time that **the significant behavioural improvements produced by anodal stimulation to the ipsilesional hemisphere are associated with a functionally relevant increase in activity within the ipsilesional primary motor cortex in patients with a wide range of disabilities following stroke**.

Tanaka S1, Takeda K, Otaka Y, Kita K, Osu R, Honda M, Sadato N, Hanakawa T, Watanabe K., Single session of transcranial direct current stimulation transiently increases knee extensor force in patients with hemiparetic stroke., Neurorehabil Neural Repair. 2011 Jul-Aug;25(6):565-9.

In this double-blind, crossover, sham-controlled experimental design, **8 participants with chronic subcortical stroke** performed knee extension using their hemiparetic leg before, during, and after anodal or sham tDCS of the LL motor cortex representation in the affected hemisphere. Affected hand-grip force was also recorded. RESULTS: The maximal knee-extension force increased by 21 N (13.2%, $P < .01$) during anodal tDCS compared with baseline and sham stimulation. The increase persisted less than 30 minutes. Maximal hand-grip force did not change. CONCLUSIONS:
Anodal tDCS transiently enhanced knee extensor strength. The modest increase was specific to the LL. **Thus, tDCS might augment the rehabilitation of stroke patients when combined with lower extremity strengthening or functional training.**

Geroin C, Picelli A, Munari D, Waldner A, Tomelleri C, Smania N., Combined transcranial direct current stimulation and robot-assisted gait training in patients with chronic stroke: a preliminary comparison, Clin Rehabil. 2011 Jun;25(6):537-48.

Thirty patients with chronic stroke. All patients received ten 50-minute treatment sessions, five days a week, for two consecutive weeks. Group 1 (n = 10) underwent a robot-assisted gait training combined with transcranial direct current stimulation; group 2 (n = 10) underwent a robot-assisted gait training combined with sham transcranial direct current stimulation; group 3 (n = 10) performed overground walking exercises. No differences were found between groups 1 and 2 for all primary outcome measures at the after treatment and follow-up evaluations. A statistically significant improvement was found after treatment in performance on the six-minute walking test and the 10-m walking test in favour of group 1 (six-minute walking test: 205.20 ± 61.16 m; 10-m walking test: 16.20 ± 7.65 s) and group 2 (six-minute walking test: 182.5 ± 69.30 m; 10-m walking test: 17.71 ± 8.20 s) compared with group 3 (six-minute walking test: 116.30 ± 75.40 m; 10-m walking test: 26.30 ± 14.10 s). All improvements were maintained at the follow-up evaluation.

In the present pilot study transcranial direct current stimulation had no additional effect on robot-assisted gait training in patients with chronic stroke. Larger studies are required to confirm these preliminary findings.

Lindenberg R1, Renga V, Zhu LL, Nair D, Schlaug G., Bihemispheric brain stimulation facilitates motor recovery in chronic stroke patients., Neurology. 2010 Dec 14;75(24):2176-84.

In this sham-controlled randomized trial, we investigated whether noninvasive modulation of regional excitability of bilateral motor cortices in combination with physical and occupational therapy improves motor outcome after stroke.

Twenty chronic stroke patients were randomly assigned to receive 5 consecutive sessions of either 1) bihemispheric transcranial direct current stimulation (tDCS) (anodal tDCS to upregulate excitability of ipsilesional motor cortex and cathodal tDCS to downregulate excitability of contralesional motor cortex) with simultaneous physical/occupational therapy or 2) sham stimulation with simultaneous physical/occupational therapy. Changes in motor impairment (Upper Extremity Fugl-Meyer) and motor activity (Wolf Motor Function Test) assessments were outcome measures while functional imaging parameters were used to identify neural correlates of motor improvement. The improvement of motor function was significantly greater in the real stimulation group (20.7% in Fugl-Meyer and 19.1% in Wolf Motor Function Test scores) when compared to the sham group (3.2% in Fugl-Meyer and 6.0% in Wolf Motor Function Test scores). The effects outlasted the stimulation by at least 1 week. In the real-stimulation group, stronger activation of intact ipsilesional motor regions during paced movements of the affected limb were found postintervention whereas no significant activation changes were seen in the control group. **The combination of bihemispheric tDCS and peripheral sensorimotor activities improved motor functions in chronic stroke patients that outlasted the intervention period. This novel approach may potentiate cerebral adaptive processes that facilitate motor recovery after stroke.** This study provides Class I evidence that for adult patients with ischemic stroke treated at least 5 months after their first and only stroke, bihemispheric tDCS and simultaneous physical/occupational therapy given over 5 consecutive sessions significantly improves motor function as measured by the Upper Extremity Fugl-Meyer assessment (raw change treated 6.1 ± 3.4, sham 1.2 ± 1.0).

Baker JM1, Rorden C, Fridriksson J., Using transcranial direct-current stimulation to treat stroke patients with aphasia., Stroke. 2010 Jun;41(6):1229-36.

Ten patients with chronic stroke-induced aphasia received 5 days of anodal tDCS (1 mA for 20 minutes) and 5 days of sham tDCS (for 20 minutes, order randomized) while performing a computerized anomia treatment. tDCS positioning was guided by a priori functional magnetic resonance imaging results for each individual during an overt naming task to ensure that the active electrode was placed over structurally intact cortex. Results revealed significantly improved naming accuracy of treated items ($F[1,9]=5.72$, $P<0.040$) after anodal tDCS compared with sham tDCS. Patients who demonstrated the most improvement were those with perilesional areas closest to the stimulation site. Crucially, this treatment effect persisted at least 1 week after treatment. **Our findings suggest that anodal tDCS over the left frontal cortex can lead to enhanced naming accuracy in stroke patients with aphasia and, if proved to be effective in larger studies, may provide a supplementary treatment approach for anomia.**

Celnik P1, Paik NJ, Vandermeeren Y, Dimyan M, Cohen LG., Effects of combined peripheral nerve stimulation and brain polarization on performance of a motor sequence task after chronic stroke., Stroke. 2009 May;40(5):1764-71.

Nine chronic stroke patients completed a blinded crossover designed study. In separate sessions, we investigated the effects of single applications of PNS+tDCS, PNS+tDCS(Sham), tDCS+PNS(Sham), and PNS(Sham)+tDCS(Sham) before motor training on the ability to perform finger motor sequences with the paretic hand. PNS+tDCS resulted in a 41.3% improvement in the number of correct key presses relative to PNS(Sham)+tDCS(Sham), 15.4% relative to PNS+tDCS(Sham), and 22.7% relative to tDCS+PNS(Sham). These performance differences were maintained 1 and 6 days after the end of the training. **These results indicate that combining PNS with tDCS can facilitate the beneficial effects of training on motor performance beyond levels reached with each intervention alone, a finding of relevance for the neurorehabilitation of motor impairments after stroke.**

Boggio PS1, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F., Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients., Restor Neurol Neurosci. 2007;25(2):123-9.

We tested the motor performance improvement in stroke patients following 4 weekly sessions of sham, anodal- and cathodal tDCS (experiment 1) and the effects of 5 consecutive daily sessions of cathodal tDCS (experiment 2). A blinded rater evaluated motor function using the Jebsen-Taylor Hand Function Test. There was a significant main effect of stimulation condition ($p=0.009$) in experiment 1. Furthermore there was a significant motor function improvement after either cathodal tDCS of the unaffected hemisphere ($p=0.016$) or anodal tDCS of the affected hemisphere ($p=0.046$) when compared to sham tDCS. There was no cumulative effect associated with weekly sessions of tDCS, however consecutive daily sessions of tDCS (experiment 2) were associated with a significant effect on time ($p< 0.0001$) that lasted for 2 weeks after treatment. **The findings of our study support previous research showing that tDCS is significantly associated with motor function improvement in stroke patients; and support that consecutive daily sessions of tDCS might increase its behavioral effects. Because the technique of tDCS is simple, safe and non-expensive; our findings support further research on the use of this technique for the rehabilitation of patients with stroke.**

Hummel FC1, Voller B, Celnik P, Floel A, Giraux P, Gerloff C, Cohen LG., Effects of brain polarization on reaction times and pinch force in chronic stroke., BMC Neurosci. 2006 Nov 3;7:73.

Here we tested the effects of tDCS on pinch force (PF) and simple reaction time (RT) tasks in patients with chronic stroke in a double-blind cross-over Sham-controlled experimental design. Anodal tDCS shortened reaction times and improved pinch force in the paretic hand relative to Sham stimulation, an effect present in patients with higher impairment. **tDCS of M1affected hemisphere can modulate performance of motor tasks simpler than those previously studied, a finding that could potentially benefit patients with relatively higher impairment levels**.

Hummel F1, Cohen LG. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke., Neurorehabil Neural Repair. 2005 Mar;19(1):14-9.

This manuscript reports the effects of transcranial DC stimulation (tDCS), a technique that enhances cortical plasticity in healthy humans, on motor function in a patient with chronic subcortical ischemic stroke. tDCS but not sham applied in a double-blind protocol to motor regions of the affected hemisphere led to

improvements in pinch force, Jebsen-Taylor Hand Function Test, and simple reaction times in the paretic hand that outlasted the stimulation period for at least 40 min. These changes were accompanied by increased corticomotor excitability identified by enhanced recruitment curves and reduced intracortical inhibition to transcranial magnetic stimulation. **These results document a beneficial effect of noninvasive brain stimulation on motor function in a human patient with stroke and raise the hypothesis of its potential application in neurorehabilitation.**

Hummel F1, Celnik P, Giraux P, Floel A, Wu WH, Gerloff C, Cohen LG., , Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke., Brain. 2005 Mar;128(Pt 3):490-9.

This double blind, Sham-controlled, crossover study was designed to test the hypothesis that non-invasive stimulation of the motor cortex could improve motor function in the paretic hand of patients with chronic stroke. Hand function was measured using the Jebsen-Taylor Hand Function Test (JTT), a widely used, well validated test for functional motor assessment that reflects activities of daily living. JTT measured in the paretic hand improved significantly with non-invasive transcranial direct current stimulation (tDCS), but not with Sham, an effect that outlasted the stimulation period, was present in every single patient tested and that correlated with an increment in motor cortical excitability within the affected hemisphere, expressed as increased recruitment curves (RC) and reduced short-interval intracortical inhibition. **These results document a beneficial effect of non-invasive cortical stimulation on a set of hand functions that mimic activities of daily living in the paretic hand of patients with chronic stroke, and suggest that this interventional strategy in combination with customary rehabilitative treatments may play an adjuvant role in neurorehabilitation.**

3. Update (2012-2013)

3.1 Studies

Effects of dual transcranial direct current stimulation on post-stroke unilateral visuospatial neglect

This was a **double blind** experiment with **10 chronic right hemispheric stroke** patients with neglect were treated with tDCS over the post parietal cortex (PPC). In the line bisection test, significant improvements were observed after both the dual- and the single-mode tDCS ($p < 0.05$), but not after sham stimulation. Statistical analysis showed a significant interaction between time and tDCS mode, where the dual tDCS had a stronger effect than the single or sham stimulation modes ($p < 0.05$). *Results suggest that dual tDCS over the bilateral PPC is an effective method for the treatment of USN in stroke patients.*

Long-term effects of serial anodal tDCS on motion perception in subjects with occipital stroke measured in the unaffected visual hemifield

12 subjects with occipital ischemic lesions participated in a within-subject, **sham-controlled, double-blind study.** Serial anodal tDCS over the visual cortex resulted in an improvement in motion perception, a function attributed to MT/V5. This effect was still measurable at 14- and 28-day follow-up measurements. *Thus, this may represent evidence for long-term tDCS-induced plasticity and has implications for the design of studies examining the time course of tDCS effects in both the visual and motor systems.*

Anodal transcranial direct current stimulation in early rehabilitation of patients with post-stroke non-fluent aphasia: A randomized, double-blind, sham-controlled pilot study.

Recent research in patients with chronic aphasia shows an association between excitatory anodal tDCS (A-tDCS) of the stroke-affected left hemisphere coupled with speech and language therapy (SLT) and better language performance. The present study aimed to investigate this association during the early post-stroke rehabilitation period, when adaptive changes are most possible on neurophysiological and behavioral levels. We **randomized 24 patients with non-fluent aphasia** to receive 15 consecutive sessions (5 days/week for 3 weeks) of Anodal tDCS (1 mA, 10 min; n = 14) or **sham** tDCS (S-tDCS: 1 mA, 25 sec; n = 10) over Broca's area followed by 45-min SLT. Naming ability was assessed before the rehabilitation, after its completion, and three months later. *Both groups significantly improved after the therapy. There were no statistically significant between-group differences in the short-term or long-term tDCS effects on naming accuracy and naming time. The A-tDCS group obtained* ***higher effect sizes in naming time****, both post-treatment and at the 3-month follow-up, suggesting potential benefits of the stimulation.* Conclusions: *The findings provide only weak evidence for A-tDCS-related language gains during early neurorehabilitation of post-stroke aphasia. Further research is needed to explore the effectiveness of this kind of neuromodulation.*

Transcranial direct current stimulation (tDCS) of Broca's area in chronic aphasia: a controlled outcome study.

It is still unclear whether tDCS should be applied at rest (off-line) or combined with behavioral treatment strategies (on-line), therefore, this study investigates the effect of repeated sessions of off-line tDCS on language recovery in post-stroke chronic aphasic patients. **8 post-stroke patients** with different type and degree of chronic aphasia underwent two weeks of off-line anodal tDCS (2 mA intensity for 20 min a day) on Broca's area and two weeks of sham stimulation as a control condition. No significant difference between anodal tDCS and sham stimulation, both for object and action naming tasks, was found. *With the exception of one patient, the overall results suggest that in chronic aphasic patients the off-line tDCS protocol applied in this study is not effective in improving noun and verb naming abilities.*

tDCS stimulation segregates words in the brain: evidence from aphasia

A number of studies have already shown that modulating cortical activity by means of tDCS improves noun or verb naming in aphasic patients. However, it is not yet clear whether these effects are equally obtained through stimulation over the frontal or the temporal regions. In the present study, the same group of aphasic subjects participated in **two randomized double-blind experiments** involving two intensive language treatments for their noun and verb retrieval difficulties. **7 aphasic subjects** (5 men and 2 female) who had suffered a single left hemisphere stroke were included in the study. During each training, each subject was treated with tDCS (20 min, 1 mA) over the left hemisphere in three different conditions: anodic tDCS over the temporal areas, anodic tDCS over the frontal areas, and sham stimulation, while they performed a noun and an action naming tasks. *Results showed a significant greater improvement in noun naming after stimulation over the temporal region, while verb naming recovered significantly better after stimulation of the frontal region.*

Transcranial Direct Current Stimulation Improves Swallowing Function in Stroke Patients

We investigated whether noninvasive brain stimulation to the pharyngeal motor cortex combined with intensive swallowing therapy can improve dysphagia. **A total of 20 patients who had dysphagia** for at least 1 month after stroke were **randomly assigned** to receive **10 sessions lasting 20 minutes each of either 1-mA anodal tDCS** or a **sham** procedure to the ipsilesional pharyngeal motor cortex, along with simultaneous

conventional swallowing therapies. We evaluated swallowing function with the Dysphagia Outcome and Severity Scale (DOSS) before, immediately after, and 1 month after the last session. *The improvements in the anodal tDCS group were significantly greater than those in the sham tDCS group* (P = .029 after the last session, and P = .007 1 month after the last session). *Anodal tDCS to the ipsilesional hemisphere and simultaneous peripheral sensorimotor activities significantly improved swallowing function as assessed by the DOSS.*

Effects of transcranial direct current stimulation (tDCS) on post-stroke dysphagia.

We investigate the effects of tDCS combined with swallowing training on post-stroke dysphagia. **16 patients with post-stroke dysphagia,** diagnosed using video fluoroscopic swallowing (VFSS), were randomly assigned into two groups: (1) anodal tDCS group (1 mA for 20 min), or (2) sham group (1 mA for 30 s). Patients received anodal tDCS or sham over the pharyngeal motor cortex of the affected hemisphere during 30 min of conventional swallowing training for 10 days. Functional dysphagia scale (FDS) scores based on VFSS were measured at baseline and immediately and 3 months after the intervention. After the intervention, FDS scores improved in both groups without significant differences. However, *3 months after the intervention, anodal tDCS elicited greater improvement in terms of FDS compared to the sham group* (β = -7.79, p = 0.041). Thus, *Anodal tDCS applied over the affected pharyngeal motor cortex can enhance the outcome of swallowing training in post-stroke dysphagia. Our results suggest that non-invasive cortical stimulation has a potential role as an adjuvant strategy during swallowing training in patients with post-stroke dysphagia.*

Combined central and peripheral stimulation to facilitate motor recovery after stroke: the effect of number of sessions on outcome.

The objective was to assess the efficacy of multiple treatment sessions on motor outcome. The study examined the effects of two 5-day intervention periods of bihemispheric tDCS and simultaneous occupational/physical therapy on motor function in a **group of 10 chronic stroke patients.** The first 5-day period yielded an increase in Upper-Extremity Fugl-Meyer (UE-FM) scores by 5.9 ± 2.4 points (16.6% ± 10.6%). The second 5-day period resulted in further meaningful, although significantly lower, gains with an additional improvement of 2.3 ± 1.4 points in UE-FM compared with the end of the first 5-day period (5.5% ± 4.2%). The overall mean change after the 2 periods was 8.2 ± 2.2 points (22.9% ± 11.4%). *The results confirm the efficacy of bihemispheric tDCS in combination with peripheral sensorimotor stimulation. Furthermore, they demonstrate that the effects of multiple treatment sessions in chronic stroke patients may not necessarily lead to a linear response function, which is of relevance for the design of experimental neurorehabilitation trials.*

Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand.

In the present study, we tested the capacity of cathodal tDCS applied over the contralesional motor cortex during training to enhance the acquisition and retention of complex sequential finger movements of the paretic hand. **12 well-recovered chronic patients** with subcortical stroke attended 2 training sessions during which either cathodal tDCS or a sham intervention were applied to the contralesional motor cortex **in a double-blind, crossover design.** *tDCS facilitated the acquisition of a new motor skill compared with sham stimulation (P=0.04) yielding better task retention results. A significant correlation was observed between the tDCS-induced improvement during training and the tDCS-induced changes of intracortical inhibition (R(2)=0.63). These results indicate that tDCS is a promising tool to improve not only motor behavior, but*

also procedural learning. They further underline the potential of noninvasive brain stimulation as an adjuvant treatment for long-term recovery, at least in patients with mild functional impairment after stroke.

Dual-tDCS Enhances Online Motor Skill Learning and Long-Term Retention in Chronic Stroke Patients.

The aim of this trial was to test the hypothesis that dual-tDCS applied bilaterally over the primary motor cortices (M1) improves online motor skill learning with the paretic hand and its long-term retention. **18 chronic stroke** patients participated in a **randomized, cross-over, placebo-controlled, double bind trial.** During separate sessions, dual-tDCS or sham dual-tDCS was **applied over 30 min while stroke patients learned a complex visuomotor skill** with the paretic hand: using a computer mouse to move a pointer along a complex circuit as quickly and accurately as possible. A learning index involving the evolution of the speed/accuracy trade-off was calculated. Performance of the motor skill was measured at baseline, after intervention and 1 week later. After sham dual-tDCS, eight patients showed performance worsening. In contrast, *dual-tDCS enhanced the amount and speed of online motor skill learning compared to sham ($p < 0.001$) in all patients; this superiority was maintained throughout the hour following. The speed/accuracy trade-off was shifted more consistently after dual-tDCS ($n = 10$) than after sham ($n = 3$). More importantly, 1 week later, online enhancement under dual-tDCS had translated into superior long-term retention (+44%) compared to sham (+4%). The improvement generalized to a new untrained circuit and to digital dexterity. Conclusion: A single-session of dual-tDCS, applied while stroke patients trained with the paretic hand significantly enhanced online motor skill learning both quantitatively and qualitatively, leading to successful long-term retention and generalization. The combination of motor skill learning and dual-tDCS is promising for improving post-stroke neurorehabilitation.*

Transcranial direct current stimulation (tDCS) and robotic practice in chronic stroke: The dimension of timing

Combining tDCS with robotic therapy is a new and promising form of neurorehabilitation after stroke, however the effectiveness of this approach is likely to be influenced by the relative **timing** of the brain stimulation and the therapy. The objective was to measure the kinematic and neurophysiological effects of delivering tDCS before, during and after a single session of robotic motor practice (wrist extension). We used a within-subjects, **sham-controlled** repeated-measurement design in **12 chronic (>6 months) stroke survivors**. Motor performance kinematics **improved when tDCS was delivered prior to robotic training,** but not when delivered during or after training. *The temporal relationship between non-invasive brain stimulation and neurorehabilitation is important in determining the efficacy and outcome of this combined therapy.*

Predicting behavioural response to TDCS in chronic motor stroke

tDCS of primary motor cortex (M1) can transiently improve paretic hand function in chronic stroke. However, responses are variable so there is incentive to try to improve efficacy and or to predict response in individual patients. Both excitatory (Anodal) stimulation of ipsilesional M1 and inhibitory (Cathodal) stimulation of contralesional M1 can speed simple reaction time. Here we tested whether combining these two effects simultaneously, by using a bilateral M1–M1 electrode montage, would improve efficacy. We tested the physiological efficacy of Bilateral, Anodal or Cathodal tDCS in changing motor evoked potentials (MEPs) in the healthy brain and their behavioural efficacy in changing reaction times with the paretic hand in chronic stroke. **13 chronic stroke patients** (3 females, mean: 66 years, range 30–80 years) with

hemiparesis subsequent to first-ever unilateral stroke were recruited *Findings indicate the superiority of Anodal or Cathodal over Bilateral TDCS in changing motor cortico-spinal excitability in the healthy brain and in speeding reaction time in chronic stroke. Although patients were in the chronic phase,* ***time since stroke*** *was a positive predictor of behavioral gain from Cathodal TDCS.*

Single session of dual-tDCS transiently improves precision grip and dexterity of the paretic hand after stroke

We explored whether dual-hemisphere tDCS (dual-tDCS) in participants with chronic stroke can improve fine hand motor function in 2 important aspects: precision grip and dexterity. **19 chronic hemiparetic individuals** with mild to moderate impairment participated in a **double-blind, randomized trial**. During 2 separate cross-over sessions (real/sham), they performed 10 precision grip movements with a manipulandum and the Purdue Pegboard Test (PPT) before, during, immediately after, and 20 minutes after dual-tDCS applied simultaneously over the ipsilesional (anodal) and contralateral (cathodal) primary motor cortices. *Conclusions: One bout of dual-tDCS improved the motor control of precision grip and digital dexterity beyond the time of stimulation. These results suggest that dual-tDCS should be tested in longer protocols for neurorehabilitation and with moderate to severely impaired patients. The precise timing of stimulation after stroke onset and associated training should be defined.*

The ABC of tDCS: Effects of Anodal, Bilateral and Cathodal Montages of Transcranial Direct Current Stimulation in Patients with Stroke—A Pilot Study

Previous studies have demonstrated that anodal and cathodal stimulation can improve motor performance in terms of dexterity and manual force. The objective of this study was to determine whether different electrodes' setups (anodal, cathodal, and simultaneous bilateral tDCS) provide different motor performance and which montage was more effective. As secondary outcome, we have asked to the patients about their satisfaction, and to determine if the bilateral tDCS was more uncomfortable than unilateral tDCS. **9 patients with stroke in subacute phase** were enrolled in this study and randomly divided in three groups. *tDCS was an effective treatment if compared to Sham stimulation.* In particular, anodal stimulation provided the higher improvement in terms of manual dexterity. Cathodal stimulation seemed to have a little effect in terms of force improvement, not observed with other setups. Bipolar stimulation seemed to be the less effective. No significant differences have been noted for the different set-ups for patients' judgment. *These results highlight the potential efficacy of tDCS for patients with stroke in subacute phase.*

Transcranial direct current stimulation of the affected hemisphere does not accelerate recovery of acute stroke patients.

We performed in our stroke unit a single-centre **randomized**, **double-blind, sham-controlled study** to investigate safety and efficacy of anodal tDCS of the affected hemisphere in acute stroke patients. The second day from stroke onset, **50 acute stroke patients received either five-daily sessions of anodal (n=25) at 2mA for 20min or sham tDCS (n=25) to the ipsilesional primary motor cortex (M1).** Motor deficit was assessed by the short form of the Fugl-Meyer motor scale (FM) and overall neurological deficit by the National Institute of Health Stroke Scale (NIHSS) at onset, at 5days after stroke and after 3months. *No side effects were detected during either TDCS or sham. In both groups, there was a significant improvement in NIHSS and FM scores, which did not significantly differ when comparing TDCS and sham. Conclusions Five-daily sessions of anodal TDCS to the ipsilesional M1 appear to be safe in acute stroke patients but do not improve clinical outcome.*

Brain stimulation paired with novel locomotor training with robotic gait orthosis in chronic stroke: A feasibility study.

The objective was to investigate the feasibility of combining tDCS to the lower extremity (LE) motor cortex with novel locomotor training to facilitate gait in subjects with chronic stroke and low ambulatory status, and to obtain insight from study subjects and their caregivers to inform future trial design. **Double-blind, randomized controlled study** with additional qualitative exploratory descriptive design. One-month follow-up. **10 subjects with stroke** (**8** subjects completed the study) were recruited and randomized to active tDCS or sham tDCS for 12 sessions. Both groups participated in identical locomotor training with a robotic gait orthosis (RGO) following each tDCS session. RGO training protocol was designed to harness cortical neuroplasticity. *Both groups demonstrated trends toward improvement, but the active tDCS group showed greater improvement than the sham group. Qualitative analyses indicated beneficial effects of this combined intervention. It is feasible to combine tDCS targeting the LE motor cortex with our novel locomotor training. It appears that tDCS has the potential to enhance the effectiveness of gait training in chronic stroke. Insights from participants provide additional guidance in designing future trials.*

Effects of anodal and cathodal transcranial direct current stimulation combined with robotic therapy on severely affected arms in chronic stroke patients.

The purpose of this study was to examine the effects of combined therapy using transcranial direct current stimulation (tDCS) with robot-assisted arm training (AT) for impairment of the upper limb in chronic stroke patients, and to clarify whether differences exist in the effect of anodal tDCS on the affected hemisphere (tDCS(a) + AT) and cathodal tDCS on the unaffected hemisphere (tDCS(c) + AT). Subjects in this **randomized**, **double-blinded, crossover** study comprised **18 chronic stroke** patients with moderate-to-severe arm paresis. Each patient underwent 2 different treatments: tDCS(a) + AT; and tDCS(c) + AT. Each intervention was administered for 5 days, and comprised AT with 1 mA of tDCS during the first 10 min. *Both interventions showed significant improvements in FMUL and MAS, but not in MAL. Distal spasticity was significantly improved with tDCS(c) + AT compared with tDCS(a) + AT for right hemispheric lesions (median -1 vs 0), but not for left hemispheric lesions.* Conclusion: *Although this study demonstrated that combined therapy could achieve limited effects in the hemiplegic arm of chronic stroke patients, a different effect of polarity of tDCS was seen for patients with right hemispheric lesions.*

Improvement of the working memory and naming by transcranial direct current stimulation.

32 healthy adults (15 males and 17 females, mean age 37.3±13.0 years) were enrolled in this study. The subjects were divided into four groups randomly. They underwent **sham** or anodal tDCS over the left or right prefrontal cortex, for 20 minutes at a direct current of 1 mA. Before and immediately after tDCS, the subjects performed the Korean version of the mini-mental state exam (K-MMSE) and stroop test (color/word/interference) for the screening of cognitive function. For working memory and language evaluation, the digit span test (forward/backward), the visuospatial attention test in computer assisted cognitive program (CogPack®) and the Korean-Boston Naming Test (K-BNT) were assessed before tDCS, immediately after tDCS, and 2 weeks after tDCS. RESULTS: *The stroop test (word/interference), backward digit span test and K-BNT were improved in the left prefrontal tDCS group compared with that of the sham group ($p<0.05$). Their improvement lasted for 2 weeks after stimulation.* Conclusion: *tDCS can induce verbal working memory improvement and naming facilitation by stimulating the left prefrontal cortex. It can also improve the visuospatial working memory by stimulating the right prefrontal cortex. Further studies which are lesion and symptom specific tDCS treatment for rehabilitation of stroke can be carried out.*

Transcranial direct current stimulation and EEG-based motor imagery BCI for upper limb stroke rehabilitation.

Clinical studies had shown that EEG-based motor imagery Brain-Computer Interface (MI-BCI) combined with robotic feedback is effective in upper limb stroke rehabilitation, and tDCS combined with other rehabilitation techniques further enhanced the facilitating effect of tDCS. This motivated the current clinical study to investigate the effects of combining tDCS with MI-BCI and robotic feedback compared to sham-tDCS for upper limb stroke rehabilitation. The stroke patients recruited were randomized to receive 20 minutes of tDCS or **sham**-tDCS prior to 10 sessions of 1-hour MI-BCI with robotic feedback for 2 weeks. *The results showed no evident differences between the online accuracies on the evaluation part from both groups, but the offline analysis on the therapy part yielded higher averaged accuracies for subjects who received tDCS (**n=3**) compared to sham-tDCS (**n=2**). The results suggest towards tDCS effect in modulating motor imagery in stroke, but a more conclusive result can be drawn when more data are collected in the ongoing study.*

Safety and Efficacy of Transcranial Direct Current Stimulation in Acute Experimental Ischemic Stroke (in mice)

Cathodal stimulation **in mice** was able, if applied in the acute phase of stroke, to preserve cortical neurons from the ischemic damage, to reduce inflammation, and to promote a better clinical recovery compared with sham and anodal treatments. This finding was attributable to the significant decrease of cortical glutamate, as indicated by nuclear magnetic resonance spectroscopy. Conversely, anodal stimulation induced an increase in the postischemic lesion volume and augmented blood brain barrier derangement. "*Our data indicate that transcranial direct current stimulation exerts a measurable neuroprotective effect in the acute phase of stroke. However, its timing and polarity should be carefully identified on the base of the pathophysiological context to avoid potential harmful side effects."*

Focal tDCS in Chronic Stroke patients: A pilot study of physiological effects using TMS and concurrent EEG

In this pilot (in which I participated) we report the first study investigating feasibility and proof-of-concept of tDCS in **15 chronic stroke patients** using EEG recording simultaneously with tDCS. We are working on a publication at the moment - stay tuned!

3.1 Review papers (until 2013)

Review of transcranial direct current stimulation in poststroke recovery.

Motor impairment, dysphagia, aphasia, and visual impairment are common disabling residual deficits experienced by stroke survivors. In this review, we summarize characteristics of tDCS (method of stimulation, safety profile, and mechanism) and its application in the treatment of various stroke-related deficits, and we highlight future directions for tDCS in this capacity.

Transcranial direct current stimulation (tDCS) for improving aphasia in patients after stroke.

To assess the effects of tDCS for improving aphasia in patients after stroke. We searched the Cochrane Stroke Group Trials Register (April 2013), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library, March 2012), MEDLINE (1948 to March 2012), EMBASE (1980 to March 2012), CINAHL (1982 to March 2012), AMED (1985 to April 2012), Science Citation Index (1899 to April 2012) and seven additional databases. We also searched trials registers and reference lists, handsearched conference proceedings and contacted authors and equipment manufacturers. **We included five trials involving 54**

participants. None of the included studies used any formal outcome measure for measuring functional communication, that is measuring aphasia in a real-life communicative setting. All five trials measured correct picture naming as a surrogate for aphasia. There was no evidence that tDCS enhanced SLT outcomes. No adverse events were reported and the proportion of dropouts was comparable between groups.
AUTHORS' CONCLUSIONS: *Currently there is no evidence of the effectiveness of tDCS (anodal tDCS, cathodal tDCS) versus control (sham tDCS). However, it appears that cathodal tDCS over the non-lesioned hemisphere might be the most promising approach.*

Novel methods to study aphasia recovery after stroke.

The neural mechanisms that support aphasia recovery are not yet fully understood. It has been argued that the functional reorganization of language networks after left-hemisphere stroke may engage perilesional left brain areas as well as homologous right-hemisphere regions. In this chapter, we summarize how noninvasive brain stimulation can be used to elucidate mechanisms of plasticity in language networks and enhance language recovery after stroke. We review recent studies that used TMS or tDCS to promote language recovery after stroke. Most of these studies applied noninvasive brain stimulation over contralateral right-hemisphere areas to suppress maladaptive plasticity. However, some studies also suggest that right-hemisphere regions may beneficially contribute to recovery in some patients. More recently, some investigators have targeted perilesional brain regions to promote neurorehabilitation. *In sum, these studies indicate that language recovery after stroke may integrate left- as well as right-hemisphere brain regions to a different degree over the time course of recovery. Although the results of these preliminary studies provide some evidence that noninvasive brain stimulation may promote aphasia recovery, the reported effect sizes are not striking. Future studies on larger patient collectives are needed to explore whether noninvasive brain stimulation can enhance language functions at a level that is clinically relevant.*

Systematic review of parameters of stimulation, clinical trial design characteristics, and motor outcomes in non-invasive brain stimulation in stroke.

This article presents an up-to-date systematic review of the treatment effects of rTMS and tDCS on motor function. A literary search was conducted, utilizing search terms "stroke" and "transcranial stimulation." Investigation of PubMed English Database prior to 01/01/2012 produced 695 applicable results. Studies were excluded based on the aforementioned criteria, resulting in 50 remaining studies. They included 1314 participants (1282 stroke patients and 32 healthy subjects) evaluated by motor function pre- and post-tDCS or rTMS. Heterogeneity among studies' motor assessments was high and could not be accounted for by individual comparison. *Pooled effect sizes for the impact of post-treatment improvement revealed consistently demonstrable improvements after tDCS and rTMS therapeutic stimulation.* Most studies provided limited follow-up for long-term effects. Conclusion: *It is apparent from the available studies that non-invasive stimulation may enhance motor recovery and may lead to clinically meaningful functional improvements in the stroke population. Only mild to no adverse events have been reported. Though results have been positive results, the large heterogeneity across articles precludes firm conclusions.*

Disruption of motor network connectivity post-stroke and its noninvasive neuromodulation.

New data from longitudinal studies in which rTMS of the lesioned or contralesional motor cortex was combined with motor training showed ambiguous effects: some patients improved whereas others did not show any rTMS effect (compared with control stimulation). *In contrast, novel studies using tDCS point to a more consistent effect on distal upper limb function, especially for inhibitory (cathodal) tDCS applied over contralesional M1.* Neuroimaging data reveal that the effects of rTMS/tDCS on the functional architecture of

the motor system depend upon lesion location, degree of impairment and number of treatment sessions. Furthermore, analyses of regional brain activity and motor network connectivity allow prediction of the behavioural effects of brain stimulation. SUMMARY: *rTMS and tDCS can be used to modulate stroke-induced changes of motor network activity and connectivity thereby improving hand motor function. The interindividual variability in response to brain stimulation calls for the identification of treatment-associated surrogate markers, which may be provided by neuroimaging.*

Non-invasive cerebral stimulation for the upper limb rehabilitation after stroke: a review.

Numerous studies have recently been published on improving upper-limb motor function after stroke. There has been a particular interest in brain stimulation techniques, which could promote brain plasticity. In this review, tDCS and rTMS are presented as techniques that could be relevant in Physical Medicine and Rehabilitation (PM&R) centers in the future. We are presenting a comprehensive literature review on the studies using tDCS or rTMS for upper-limb rehabilitation after a stroke. *Both techniques have shown their ability to modify cortical excitability and to transitorily improve upper-limb function after one single stimulation session. The first placebo-controlled, blinded therapeutic trials, which included repeated daily sessions, seem quite promising, and deserve to be validated by further trials.*

Can tDCS enhance treatment of aphasia after stroke?

Recent advances in the application of tDCS in healthy populations have led to the exploration of the technique as an adjuvant method to traditional speech therapies in patients with post-stroke aphasia. This review aims to highlight our current understanding of the methodological and theoretical issues surrounding the use of tDCS as an adjuvant tool in the treatment of language difficulties after stroke. CONCLUSIONS: *Preliminary evidence shows that tDCS may be a useful tool to complement treatment of aphasia, particularly for speech production in chronic stroke patients. The potential of tDCS is to optimise language rehabilitation techniques and promote long-term recovery of language. A stimulating future for aphasia rehabilitation!*

Transcranial Direct Current Stimulation in Stroke Rehabilitation: A Review of Recent Advancements

This is a critical review paper. An interesting point is that because evaluation of tDCS is being conducted mainly in academia, studies are not widely standardized regarding variables and population samples, therefore limiting generality of conclusions. These findings are also limited by small sample sizes and experimental design. Although animal studies are useful for exploring physiological aspects of tDCS mechanisms, differences in cortical architecture as compared to humans may pose problems in translating findings from animal research to humans (i.e., positioning of electrodes, stimulation parameters, etc.). *Thus, despite multiple studies showing benefits of tDCS, the jury is still out whatever these results will translate into real-world benefits.*

A meta-analysis of the efficacy of anodal transcranial direct current stimulation for upper limb motor recovery in stroke survivors.

To summarize and evaluate the evidence for the efficacy of a-tDCS in the treatment of upper limb motor impairment after stroke. A meta-analysis of randomized controlled trials that compared a-tDCS with placebo and change from baseline. RESULTS: *A pooled analysis showed a significant increase in scores in favor of a-tDCS (standard mean difference [SMD]=0.40, 95% confidence interval [CI]=0.10-0.70, p=0.010, compared with baseline). A similar effect was observed between a-tDCS and sham (SMD=0.49, 95%*

CI=0.18-0.81, p=0.005). CONCLUSION: This meta-analysis of eight randomized placebo-controlled trials provides further evidence that a-tDCS may benefit motor function of the paretic upper limb in patients suffering from chronic stroke. LEVEL OF EVIDENCE: Level 1a.