tDCS clinical research - highlights: Stroke

Neuroelectrics White Paper WP201302

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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 till Sep 2013**).

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.

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.

Update (2012-2013)

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!

Review papers

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.*