tDCS clinical research - highlights: Cognitive Enhancement

Neuroelectrics White Paper WP201305

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Is transcranial current stimulation (tCS, including direct current, tDCS, alternating current, tACS, or random noise stimulation tRNS) effective for Cognitive Enhancement? Under what conditions? With what montages?

Recent results suggest that tCS technology can be used to enhance cognitive abilities in the healthy such as our ability to concentrate and carry out complex mental tasks or to improve our learning abilities in everything from piano to sharp-shooting (see Kadosh's Lab and our blog on this topic for some examples).

We focus here on a compilation of the recent literature on this (quite wide) topic. We have relied on Google Scholar and also PubMed to carry out the search, including the terms of tDCS, tACS, tRNS (**from March 2012 and till Sep 2013**).

We advance that there is currently a high intensity in the research community probing this question in addition to using tCS for pure, fundamental research. As you can read below, there quite a few encouraging results in this area (in both mathematics, problem solving, motor), although study group sizes (the famous *N*) are still relatively small. We try to highlight group sizes 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.**

Neuroelectrics' main interests lie in medical applications such as stroke-recovery, depression or cognitive enhancement to offset mild cognitive impairment (MCI) in the elderly. Recent results, however, suggest that tCS can be used to enhance cognitive abilities in the healthy, potentially raising some ethical concerns. The research community is very much aware of this aspect of the field. A recent report by Kadosh et al. at Oxford tackles this issue and calls for the community to address these concerns now before the applications mature. The growing *neuroethics* community is providing much needed support in this regard.

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

Update (2012-2013)

Language

Transcranial direct current stimulation over multiple days improves learning and maintenance of a novel vocabulary

The majority of tDCS studies have assessed effects of single stimulation sessions that are mediated by transient neural modulation. Studies assessing the **impact of multiple stimulation sessions** on learning that may induce long-lasting behavioural and neural changes are scarce and have not yet been accomplished in the language domain in healthy individuals. The present study probed the potential of atDCS to enhance **language learning** over multiple days by employing an explicit word learning paradigm. **40 healthy** young participants were randomized to learning with either simultaneous atDCS or **sham** stimulation (N = 20/ group; comparable regarding demographic variables and neurocognitive status). All participants acquired a novel vocabulary (familiar and novel object picture – non-word pairs) over five consecutive days. Two memory tasks (free recall; forced choice recognition tasks) were administered immediately after each training session. A one week follow-up tested the maintenance of learning success. *Linear mixed effects model analysis revealed superior learning during atDCS compared to sham stimulation for both familiar and novel objects. atDCS yielded a steeper learning curve and significantly more pronounced learning at the end of the training during the recall task. During the recognition task, the atDCS group reached ceiling levels earlier and overall learning success was greater. For both tasks, beneficial atDCS effects were maintained during the follow-up assessment.* The present study provides direct evidence that *atDCS administered during multiple learning sessions facilitates language learning and that effects are maintained over time.*

Facilitation of Inferior Frontal Cortex by Transcranial Direct Current Stimulation Induces Perceptual Learning of Severely Degraded Speech

Perceptual learning requires the generalization of categorical perceptual sensitivity from trained to untrained items. For **degraded speech,** perceptual learning modulates activation in a left-lateralized network, including inferior frontal gyrus (IFG) and inferior parietal cortex (IPC). Here we demonstrate that facilitatory anodal transcranial direct current stimulation (tDCSanodal) can induce perceptual learning in healthy humans. In a **sham**-controlled, parallel design study, **36 volunteers** were allocated to the three following intervention groups: tDCSanodal over left IFG, IPC, or sham. Participants decided on the match between an acoustically degraded and an undegraded written word by forced same-different choice. Acoustic degradation varied in four noise-vocoding levels (2, 3, 4, and 6 bands). Participants were trained to discriminate between minimal (/Tisch/-FISCH) and identical word pairs (/Tisch/-TISCH) over a period of 3 d, and tDCSanodal was applied during the first 20 min of training. Perceptual sensitivity (d') for trained word pairs, and an equal number of untrained word pairs, was tested before and after training. Increases in d' indicate perceptual learning for untrained word pairs, and a combination of item-specific and perceptual learning for trained word pairs. Most notably for the lowest intelligibility level, perceptual learning occurred only when tDCSanodal was applied over left IFG. For trained pairs, improved d' was seen on all intelligibility levels regardless of tDCS intervention. Over left IPC, tDCSanodal did not modulate learning but instead introduced a response bias during training. Volunteers were more likely to respond "same," potentially indicating enhanced perceptual fusion of degraded auditory with undegraded written input. *Our results supply first evidence that neural facilitation of higher-order language areas can induce perceptual learning of severely degraded speech.*

Mathematics

Long-Term Enhancement of Brain Function and Cognition Using Cognitive Training and Brain Stimulation

Noninvasive brain stimulation has shown considerable promise for enhancing cognitive functions by the long-term manipulation of neuroplasticity. However, the observation of such improvements has been focused at the behavioral level, and enhancements largely restricted to the performance of basic tasks. Here, we investigate whether transcranial random noise stimulation (TRNS) can improve learning and subsequent performance on **complex arithmetic tasks**. TRNS of the bilateral dorsolateral prefrontal cortex (DLPFC), a key area in arithmetic, was uniquely coupled with near-infrared spectroscopy (NIRS) to measure online hemodynamic responses within the prefrontal cortex. **25 participant**s were matched for age and gender and randomly assigned to either the **TRNS** or **sham** group. *Five consecutive days of TRNS-accompanied cognitive training enhanced the speed of both calculation- and memory-recall-based arithmetic learning. These behavioral improvements were associated with defined hemodynamic responses consistent with more efficient neurovascular coupling within the left DLPFC. Testing 6 months after training revealed long-lasting behavioral and physiological modifications in the stimulated group relative to sham controls for trained and nontrained calculation material.* These results demonstrate that, depending on the learning regime, TRNS can induce long-term enhancement of cognitive and brain functions.

Enhancing performance in numerical magnitude processing and mental arithmetic using transcranial Direct Current Stimulation (tDCS)

The ability to accurately process numerical magnitudes and solve mental arithmetic is of highest importance for schooling and professional career. Although impairments in these domains in disorders such as developmental dyscalculia (DD) are highly detrimental, remediation is still sparse. The posterior parietal cortex (PPC) is known to be crucially involved in numerical magnitude processing and mental arithmetic. In this study, we evaluated whether tDCS has a beneficial effect on **numerical magnitude processing and mental arithmetic.** Due to the unclear lateralization, we stimulated the left, right as well as both hemispheres simultaneously in two experiments **(with 21 and then 16 subjects)**. *We found that left anodal tDCS significantly enhanced performance in a number comparison and a subtraction task, while bilateral and right anodal tDCS did not induce any improvements compared to sham. Our findings demonstrate that the left PPC is causally involved in numerical magnitude processing and mental arithmetic. Furthermore, we show that these cognitive functions can be enhanced by means of tDCS. These findings encourage to further investigate the beneficial effect of tDCS in the domain of mathematics in healthy and impaired humans.*

Memory

Testing the limits: Investigating the effect of tDCS dose on working memory enhancement in healthy controls.

There is a rapidly growing evidence base showing that anodal tDCS applied to the left prefrontal cortex (PFC) is able to enhance aspects of cognitive functioning, in particular working memory (WM). This has led to both excitement and concerns regarding the possibility of 'electrodoping' in order to greatly improve one's cognitive performance. We investigated the behavioural and neurophysiological effects of increasing the current (or 'dose') of tDCS on the degree of WM improvement in healthy controls. Single sessions of 1 mA, 2 mA and sham anodal tDCS to the left PFC were undertaken over a period of three weeks. Participants underwent a WM task at three time points post-stimulation (0, 20 and 40 min) with concurrent electrophysiological (EEG) recordings. *Our results showed that while active tDCS can enhance behavioural* *performance, with neurophysiological findings indicating improve efficiency of cognitive processing; we showed that 1 mA produced the most significant effects. These findings are somewhat unexpected as tDCS dose effects in cognitive enhancement have been shown previously in patient populations. Our results provide valuable information regarding the potential limits of tDCS induced cognitive enhancement in healthy controls, as well as providing additional insights into the possible mechanisms of action of tDCS.*

The role of timing in the induction of neuromodulation in perceptual learning by transcranial electric stimulation.

The goal of this work was to investigate how different types of tES (tDCS and tRNS) can modulate behavioral performance in the healthy adult brain in relation to their timing of application. We applied tES protocols before (offline) or during (online) the execution of a **visual perceptual learning (PL) task.** PL is a form of i**mplicit memory** that is characterized by an improvement in sensory discrimination after repeated exposure to a particular type of stimulus and is considered a manifestation of neural plasticity. Our aim was to understand if the timing of tES is critical for the induction of differential neuromodulatory effects in the primary visual cortex (V1). We applied high-frequency tRNS, anodal tDCS and sham tDCS on V1 before or during the execution of an orientation discrimination task. The experimental design was between subjects and performance was measured in terms of d' values. The ideal timing of application varied depending on the stimulation type. *tRNS facilitated task performance only when it was applied during task execution, whereas anodal tDCS induced a larger facilitation if it was applied before task execution. The main result of this study is the finding that the timing of identical tES protocols yields opposite effects on performance.*

<u>Motor</u>

Task-specific effect of transcranial direct current stimulation on motor learning

When applied to the human primary motor cortex (M1), tDCS has beneficial effects on motor skill learning and consolidation in healthy controls and in patients. However, it remains unclear whether tDCS improves motor learning in a general manner or whether these effects depend on which motor task is acquired. Here we compare whether the effect of tDCS differs when the same individual acquires (1) a Sequential Finger Tapping Task (SEQTAP) and (2) a Visual Isometric Pinch Force Task (FORCE). Both tasks have been shown to be sensitive to tDCS applied over M1, however, the underlying processes mediating learning and memory formation might benefit differently from anodal transcranial direct current stimulation (anodal-tDCS). **30 healthy subjects** were **randomly assigned** to an **anodal**-tDCS group or **sham**-group. Using **a double-blind, sham-controlled cross-over design,** tDCS was applied over M1 while subjects acquired each of the motor tasks over three consecutive days, with the order being randomized across subjects. *We found that anodal-tDCS affected each task differently: the SEQTAP task benefited from anodal-tDCS during learning, whereas the FORCE task showed improvements only at retention. These findings suggest that anodal-tDCS applied over M1 appears to have a task-dependent effect on learning and memory formation.*

Effect of transcranial direct current stimulation (tDCS) during complex whole body motor skill learning

The aim of the study was to investigate tDCS effects on motor skill learning in a complex whole body dynamic balance task (DBT). We hypothesized that tDCS over the supplementary motor area (SMA), a region that is known to be involved in the control of multi-joint whole body movements, will result in polarity specific changes in DBT learning. In a **randomized sham-controlled, double-blinded parallel design**, we applied 20min of tDCS over the supplementary motor area (SMA) and prefrontal cortex (PFC) while subjects performed a DBT. *Anodal tDCS over SMA with the cathode placed over contralateral PFC impaired motor skill learning of the DBT compared to sham. This effect was still present on the second day of training.* Reversing the polarity (cathode over SMA, anode over PFC) did not affect motor skill learning neither on the first nor on the second day of training. To better disentangle whether the impaired motor skill learning was due to a modulation of SMA or PFC, we performed an additional control experiment. Here, we applied anodal tDCS over SMA together with a larger and presumably more ineffective electrode (cathode) over PFC. Interestingly this alternative tDCS electrode setup did not affect the outcome of DBT learning. *Our results provide novel evidence that a modulation of the (right) PFC seems to impair complex multi-joint motor skill learning.* Hence, future studies should take the positioning of both tDCS electrodes into account when investigating complex motor skill learning.

Polarity Independent Effects of Cerebellar tDCS on Short Term Ankle Visuomotor Learning.

Most studies using tDCS for facilitating lower limb motor coordination have applied tDCS to the lower limb motor cortex (M1). As the cerebellum is also critically involved in movement control, it is important to dissociate the effect of tDCS on the cerebellum and M1 with respect to lower limb motor control before we begin the application of tDCS as a neuromodulatory tool. The purpose of this study was to determine the effects of cerebellar vs. motor cortical tDCS on short term ankle visuomotor learning in healthy individuals. **8 healthy individuals** practiced a skilled ankle motor tracking task while receiving either facilitatory anodal tDCS to cerebellum, inhibitory cathodal tDCS to cerebellum, facilitatory anodal tDCS to M1, inhibitory cathodal tDCS to M1 or **sham** stimulation. Pre- and post-measures of changes in cortical excitability of the tibialis anterior muscle and measures of tracking accuracy were assessed. *Anodal cerebellar, cathodal cerebellar, and anodal M1 stimulation improved target-tracking accuracy of the ankle. This was not dependent on the observed changes in motor cortical excitability of the tibialis anterior muscle.* Polarity independent effects of tDCS on cerebellum were observed. The present study shows that modulation effects of tDCS can occur because of changes in the cerebellum, a structure implicated in several forms of motor learning, providing an additional way in which tDCS can be used to improve motor coordination.

Is motor learning mediated by tDCS intensity?

Although tDCS has been shown to improve **motor** learning, previous studies reported rather small effects. Since physiological effects of tDCS depend on intensity, the present study evaluated this parameter in order to enhance the effect of tDCS on skill acquisition. **The effect of different stimulation intensities of anodal tDCS (atDCS) was investigated in a double blind, sham controlled crossover design.** In each condition, **13 healthy subjects** were instructed to perform a unimanual motor (sequence) learning task. *Our results showed (1) a significant increase in the slope of the learning curve and (2) a significant improvement in motor performance at retention for 1.5 mA atDCS as compared to sham tDCS. No significant differences were reported between 1 mA atDCS and sham tDCS; and between 1.5 mA atDCS and 1 mA atDCS.*

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.*

Primary motor and premotor cortex in implicit sequence learning--evidence for competition between implicit and explicit human motor memory systems.

Implicit and explicit memory systems for motor skills compete with each other during and after motor practice. Primary motor cortex (M1) is known to be engaged during implicit motor learning, while dorsal premotor cortex (PMd) is critical for explicit learning. To elucidate the neural substrates underlying the interaction between **implicit and explicit motor memory systems**, adults underwent a **randomized** crossover experiment of anodal transcranial direct current stimulation (AtDCS) applied over M1, PMd or **sham** stimulation during implicit motor sequence (serial reaction time task, SRTT) practice. We hypothesized that M1-AtDCS during practice will enhance online performance and offline learning of the implicit motor sequence. In contrast, we also hypothesized that PMd-AtDCS will attenuate performance and retention of the implicit motor sequence. Implicit sequence performance was assessed at baseline, at the end of acquisition (EoA), and 24 h after practice (retention test, RET). M1-AtDCS during practice significantly improved practice performance and supported offline stabilization compared with Sham tDCS. *Performance change from EoA to RET revealed that PMd-AtDCS during practice attenuated offline stabilization compared with M1-AtDCS and sham stimulation.*

Site-specific effects of mental practice combined with transcranial direct current stimulation on motor learning.

The current study tested whether tDCS, using different electrode montages, can increase the neuroplastic **effects of mental imagery on motor learning. 18 healthy right-handed adults** underwent a **randomised sham**-controlled crossover experiment to receive mental training combined with either sham or active anodal tDCS of the right primary motor cortex (M1), right supplementary motor area, right premotor area, right cerebellum or left dorsolateral prefrontal cortex (DLPFC). Motor performance was assessed by a **blinded** rater using: non-dominant handwriting time and legibility, and mentally trained task at baseline (pre) and immediately after (post) mental practice combined with tDCS. *Active tDCS significantly enhances the motor-imagery-induced improvement in motor function as compared with sham tDCS.* There was a specific effect for the site of stimulation such that effects were only observed after *M1 and DLPFC stimulation* during mental practice. *These findings provide new insights into motor imagery training and point out that two cortical targets (M1 and DLPFC) are significantly associated with the neuroplastic effects of mental imagery on motor learning.*

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. Two different motor sequences, matched for their degree of complexity, were tested in a counterbalanced order during as well as 90 minutes and 24 hours after the intervention. Potential underlying mechanisms were evaluated with transcranial magnetic stimulation. *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.*

Problem solving / learning / Other

Brain stimulation enables the solution of an inherently difficult problem

Certain problems are inherently difficult for the normal human mind. Yet paradoxically they can be effortless for those with an unusual min*d. We discovered that an atypical protocol for non-invasive brain stimulation enabled the solution of a problem that was previously unsolvable.* The majority of studies over the last century find that no participants can solve the nine-dot problem – a fact we confirmed. But with 10 min of right lateralising tDCS, more than 40% of participants did so. *Specifically, whereas no participant solved this extremely difficult problem before stimulation or with* ***sham*** *stimulation,* ***14 out of 33*** *participants did so with cathodal stimulation of the left anterior temporal lobe together with anodal stimulation of the right anterior temporal lobe*. This finding suggests that our stimulation paradigm might be helpful for mitigating cognitive biases or dealing with a broader class of tasks that, although deceptively simple, are nonetheless extremely difficult due to our cognitive makeup.

Non-invasive brain stimulation improves object-location learning in the elderly.

Remembering the location of objects, an integral part of everyday life, is known to decline with advancing age and early in the course of neurodegenerative dementia. Here, we aimed to test if object-location learning and its retention could be modified by noninvasive brain stimulation. In a group of **20 elderly** (mean age 62.1 years) right-handed individuals, we applied tDCS (20 minutes, 1 mA) over the right temporoparietal cortex, while subjects acquired the correct position of buildings on a street map using an associative learning paradigm. Each subject participated in a **randomized** and balanced order in 1 session of anodal tDCS and 1 session of **sham** stimulation, in a **double-blind** design with 2 parallel versions of the task. Outcome measures were learning success at the end of each session, and immediate as well as delayed (1 week) free recall. *We found that subjects performed comparably in the learning task in the 2 conditions, but showed improved recall 1 week after learning with anodal tDCS compared with learning with sham stimulation. In conclusion, retention of object-location learning in the elderly may be modulated by noninvasive brain stimulation, a finding of potential relevance not only for normal aging but also for memory deficits in pathological aging.*

TDCS guided using fMRI significantly accelerates learning to identify concealed objects.

The accurate identification of obscured and concealed objects in complex environments was an important skill required for survival during human evolution, and is required today for many forms of expertise. Here we used tDCS guided using neuroimaging to increase learning rate in a novel, minimally guided discovery-learning paradigm. **96 subjects** identified threat-related objects concealed in naturalistic virtual surroundings used in real-world training. A variety of brain networks were found using functional magnetic resonance imaging (fMRI) data collected at different stages of learning, with two of these networks focused in right inferior frontal and right parietal cortex. *Anodal 2.0 mA tDCS performed for 30 min over these regions in a series of single-blind, randomized studies resulted in significant improvements in learning and performance compared with 0.1 mA tDCS.* This difference in performance increased to a factor of two after a one-hour delay. A dose-response effect of current strength on learning was also found. T*aken together, these brain imaging and stimulation studies suggest that right frontal and parietal cortex are involved in learning to identify concealed objects in naturalistic surroundings. Furthermore, they suggest that the application of anodal tDCS over these regions can greatly increase learning, resulting in one of the largest effects on learning yet reported.*

Improved multitasking following prefrontal tDCS

We have a limited capacity for mapping sensory information onto motor responses. This processing bottleneck is thought to be a key factor in determining our ability to make two decisions simultaneously – i.e., to multitask. Previous functional imaging research has localised this bottleneck to the posterior lateral prefrontal cortex (pLPFC) of the left hemisphere. Currently, however, it is unknown whether this region is causally involved in multitasking performance. We investigated the role of the left pLPFC in **multitasking** using tDCS. The behavioural paradigm included single- and dual-task trials, each requiring a speeded discrimination of **visual stimuli alone, auditory stimuli alone, or both visual and auditory stimuli**. Reaction times for single- and dual-task trials were compared before, immediately after, and 20 min after anodal stimulation (excitatory), cathodal stimulation (inhibitory), or sham stimulation. *The cost of responding to the two tasks (i.e., the reduction in performance for dual- vs single-task trials) was significantly reduced by cathodal stimulation, but not by anodal or sham stimulation.*

Mood and cognitive function following repeated transcranial direct current stimulation in healthy volunteers: A preliminary report

Although mood and cognitive function have been reported to change following transcranial direct current stimulation (tDCS) in patients with neurological and psychiatric diseases, little is known about the effects of repeated tDCS on mood and cognition in healthy humans. **We recruited 11 healthy male participants** for this **single-blind, sham-controlled crossover trial**. We used Profile of Mood States, brief-form (POMS), and CogHealth (Detection Task, Identification Task, One Back Task, One Card Learning Task and Continuous Monitoring Task) to evaluate the changes in mood and cognitive function, respectively, before and immediately after 4-daily, 20min, 1mA sham or anodal tDCS over the left dorsolateral prefrontal cortex (DLPFC). *While there were no significant changes in six factors of POMS and performance (speed and accuracy) of CogHealth between sham and anodal stimulation, the accuracy of One Card Learning was increased at the end of the experiment. Signal detection analyses revealed that both hit rate and discriminability were improved in this task. These results suggest that 4-daily anodal tDCS over left DLPFC may not change mood and cognitive function in healthy subjects, and further support the safety of tDCS. A slight improvement in a visual recognition and learning task at the end of experiment may be susceptible to practice effects.*

Anodal tDCS to V1 blocks visual perceptual learning consolidation.

This study examined the effects of visual cortex transcranial direct current stimulation (tDCS) on **visual processing and learning**. Participants performed **a contrast detection task** on two consecutive days. Each session consisted of a baseline measurement followed by measurements made during active or sham stimulation. On the first day, one group received anodal stimulation to primary visual cortex (V1), while another received cathodal stimulation. Stimulation polarity was reversed for these groups on the second day. The third (control) group of subjects received **sham** stimulation on both days. No improvements or decrements in contrast sensitivity relative to the same-day baseline were observed during real tDCS, nor was any within-session learning trend observed. *However, task performance improved significantly from Day 1 to Day 2 for the participants who received cathodal tDCS on Day 1 and for the sham group.* No such improvement was found for the participants who received anodal stimulation on Day 1, indicating that anodal tDCS blocked overnight consolidation of visual learning, perhaps through engagement of inhibitory homeostatic plasticity mechanisms or alteration of the signal-to-noise ratio within stimulated cortex. *These results show that applying tDCS to the visual cortex can modify consolidation of visual learning.*

Modulating human procedural learning by cerebellar transcranial direct current stimulation.

Neuroimaging studies suggest that the cerebellum contributes to human cognitive processing, particularly **procedural learning.** This type of learning is often described as implicit learning and involves automatic, associative, and unintentional learning processes. Our aim was to investigate whether cerebellar tDCS influences procedural learning as measured by the serial reaction time task (SRTT), in which subjects make speeded key press responses to visual cues. A preliminary modeling study demonstrated that our electrode montage (active electrode over the cerebellum with an extra-cephalic reference) generated the maximum electric field amplitude in the cerebellum. We enrolled **21 healthy subjects** (aged 20-49 years). Participants did the SRTT, a visual analogue scale and a visual attention task, **before and 35 min after** receiving 20-min anodal and **sham** cerebellar tDCS in a randomized order. To avoid carry-over effects, experimental sessions were held at least **1 week apart.** *For our primary outcome measure (difference in RTs for random and repeated blocks) anodal versus sham tDCS, RTs were significantly slower for sham tDCS than for anodal cerebellar tDCS ($p = 0.04$), demonstrating that anodal tDCS influenced implicit learning processes. When we assessed RTs for procedural learning across the one to eight blocks, we found that RTs changed significantly after anodal stimulation (interaction "time" × "blocks 1/8": anodal, $p = 0.006$), but after sham tDCS, they remained unchanged ($p = 0.094$).* No significant changes were found in the other variables assessed.

Bifrontal tDCS prevents implicit learning acquisition in antidepressant-free patients with major depressive disorder.

The findings for implicit (procedural) learning impairment in major depression are mixed. We investigated this issue using tDCS. **28 age- and gender-matched, antidepressant-free depressed subjects** received a single-session of active/sham tDCS. We used a bifrontal setup - anode and cathode over the left and the right dorsolateral prefrontal cortex (DLPFC), respectively. The probabilistic classification-learning (PCL) task was administered before and during tDCS. *The percentage of correct responses improved during sham; although not during active tDCS.* ***Procedural or implicit learning*** *acquisition between tasks also occurred only for sham.* We discuss whether DLPFC activation decreased activity in subcortical structures due to the depressive state. The deactivation of the right DLPFC by cathodal tDCS can also account for our results. *To conclude, active bifrontal tDCS prevented implicit learning in depressive patients.*

Enhancement of object detection with transcranial direct current stimulation is associated with increased attention.

We previously found that tDCS improves learning and performance in a task where subjects learn to **detect potential threats indicated by small target objects hidden in a complex virtual environment**. In the present study, we examined the hypothesis that these effects on learning and performance are related to changes in attention. The effects of tDCS were tested for three forms of attention (alerting, orienting, and executive attention) using the Attention Network Task (ANT), which were compared with performance on the object-learning task. Participants received either 0.1 mA (**N = 10**) or 2.0 mA (**N = 9**) tDCS during training and were tested for performance in object-identification before training (baseline-test) and again immediately after training (immediate test). Participants next performed the Attention Networks Task (ANT), and were later tested for object-identification performance a final time (delayed test). *Alerting, but not orienting or executive attention, was significantly higher for participants receiving 2.0 mA compared with 0.1 mA tDCS ($p < 0.02$). Furthermore, alerting scores were significantly correlated with the proportion of hits ($p < 0.01$) for participants receiving 2.0 mA.*

Unilateral prefrontal direct current stimulation effects are modulated by working memory load and gender.

Recent studies revealed that anodal tDCS to the left dorsolateral prefrontal cortex (DLPFC) may improve **verbal working memory** (WM) performance in humans. In the present study, we evaluated executive attention, which is the core of WM capacity, considered to be significantly involved in tasks that require active maintenance of memory representations in interference-rich conditions, and is highly dependent on DLPFC function. We investigated verbal WM accuracy using a WM task that is highly sensitive to executive attention function. We were interested in how verbal WM accuracy may be affected by WM load, unilateral DLPFC stimulation, and gender, as previous studies showed gender-dependent brain activation during verbal WM tasks. We utilized a modified verbal n-Back task hypothesized to increase demands on executive attention. We examined "online" WM performance while participants received tDCS, and implicit learning performance in a post-stimulation WM task. Significant lateralized "online" stimulation effects were found only in the highest WM load condition revealing that males benefit from left DLPFC stimulation, while females benefit from right DLPFC stimulation. High WM load performance in the left DLPFC stimulation was significantly related to post-stimulation recall performance. *Our findings support the idea that lateralized stimulation effects in high verbal WM load may be gender-dependent.* Further, our post-stimulation results support the idea that increased left hemisphere activity may be important for encoding verbal information into episodic memory as well as for facilitating retrieval of context-specific targets from semantic memory.

Anodal transcranial direct current stimulation (tDCS) over supplementary motor area (SMA) but not pre-SMA promotes short-term visuomotor learning.

While there is increasing knowledge about the importance of the primary motor cortex (M1) in **short- and long-term motor skill learning,** little is known about the role of secondary motor areas such as the supplementary and pre-supplementary motor area (SMA/pre-SMA) especially in short-term motor performance. Since SMA but not pre-SMA is directly connected to M1, we hypothesize that anodal tDCS over SMA but not pre-SMA will facilitate visuomotor learning. We applied anodal tDCS (tDCS(anodal)) over left SMA, pre-SMA or M1 **(n=12 in each group)** while subjects performed a visuomotor pinch force task (VPFT) with their right hand and compared VPFT performance relative to **sham** (tDCS(sham)). *For the* *first time, we could show that apart from tDCS(anodal) over left M1 also SMA but not pre-SMA stimulation promotes short-term improvements in visuomotor learning relative to tDCS(sham).*

Modulating behavioral inhibition by tDCS combined with cognitive training.

Cognitive training is an effective tool to improve a variety of cognitive functions, and a small number of studies have now shown that brain stimulation accompanying these training protocols can enhance their effects. In the domain of **behavioral inhibition,** little is known about how training can affect this skill. As for tDCS, it was previously found that stimulation over the right inferior frontal gyrus (rIFG) facilitates behavioral inhibition performance and modulates its electrophysiological correlates. This study aimed to investigate this behavioral facilitation in the context of a learning paradigm by giving tDCS over rIFG repetitively over four consecutive days of training on a behavioral inhibition task (stop signal task (SST)). **22 participants took part; ten participants were assigned to receive anodal tDCS (1.5 mA, 15 min), 12 were assigned to receive training but not active stimulation**. *There was a significant effect of training on learning and performance in the SST, and the integration of the training and rIFG-tDCS produced a more linear learning slope. Better performance was also found in the active stimulation group.* Our findings show that tDCS-combined cognitive training is an effective tool for improving the ability to inhibit responses. The current study could constitute a step toward the use of tDCS and cognitive training as a therapeutic tool for cognitive control impairments in conditions such as attention-deficit hyperactivity disorder (ADHD) or schizophrenia.

Transcranial direct current stimulation augments perceptual sensitivity and 24-hour retention in a complex threat detection task.

We have previously shown that transcranial direct current stimulation (tDCS) improved performance of a complex **visual perceptual learning task** (Clark et al. 2012). However, it is not known whether tDCS can enhance perceptual sensitivity independently of non-specific, arousal-linked changes in response bias, nor whether any such sensitivity benefit can be retained over time. We examined the influence of stimulation of the right inferior frontal cortex using tDCS on perceptual learning and retention in **37 healthy participants,** using signal detection theory to distinguish effects on perceptual sensitivity (d') from response bias (ß). *Anodal stimulation with 2 mA increased d', compared to a 0.1 mA sham stimulation control, with no effect on ß. On completion of training, participants in the active stimulation group had more than double the perceptual sensitivity of the control group. Furthermore, the performance enhancement was maintained for 24 hours.* The results show that tDCS augments both skill acquisition and retention in a complex detection task and that the benefits are rooted in an improvement in sensitivity (d'), rather than changes in response bias (ß).

Impact of tDCS on performance and learning of target detection: interaction with stimulus characteristics and experimental design.

We have previously found that transcranial direct current stimulation (tDCS) over right inferior frontal cortex (RIFC) enhances performance during learning of a difficult **visual target detection task** (Clark et al., 2012). In order to examine the cognitive mechanisms of tDCS that lead to enhanced performance, here we analyzed its differential effects on responses to stimuli that varied by repetition and target presence, differences related to expectancy by comparing performance in **single- and double-blind task designs**, and individual differences in skin stimulation and mood. Participants were trained for 1h to detect target objects hidden in a complex virtual environment, while anodal tDCS was applied over RIFC at 0.1 mA or 2.0 mA for the first 30 min. Participants were tested immediately before and after training and again 1h later. Higher tDCS current was associated with increased performance for all test stimuli, but was greatest for repeated test stimuli with the presence of hidden-targets. This finding was replicated in a second set of subjects using a double-blind task design. Accuracy for target detection discrimination sensitivity (d'; Z(hits)-Z(false alarms)) was greater for 2.0 mA current (1.77) compared with 0.1 mA (0.95), with no differences in response bias (β). *Taken together, these findings indicate that the enhancement of performance with tDCS is sensitive to stimulus repetition and target presence, but not to changes in expectancy, mood, or type of blinded task design.* The implications of these findings for understanding the cognitive mechanisms of tDCS are discussed.

Left lateralizing transcranial direct current stimulation improves reading efficiency.

Poor reading efficiency is the most persistent problem for adults with developmental **dyslexia**. Previous research has demonstrated a relationship between left posterior temporal cortex (pTC) function and reading ability, regardless of dyslexia status. In this study, we tested whether enhancing left lateralization of pTC using tDCS improves reading efficiency in adults without dyslexia.25 **right-handed adults** with no history of learning disorder participated. **Real and sham** "Left lateralizing" tDCS were applied to the pTC in separate sessions. Standardized word and nonword reading tests were given immediately after stimulation. *Modeling of the induced electrical field confirmed that tDCS was likely to increase left pTC excitability and reduce right pTC excitability as intended. Relative to sham, real tDCS induced improvements in word reading efficiency in below average readers. Enhancing left lateralization of the pTC using tDCS improves word reading efficiency in below-average readers.* This demonstrates that left lateralization of the pTC plays a role in reading ability, and provides stimulation parameters that could be used for a trial of tDCS in adults with developmental dyslexia. Such short-term gains could amplify the effect of appropriate reading interventions when performed in conjunction with them.

Oppositional transcranial direct current stimulation (tDCS) of parietal substrates of attention during encoding modulates episodic memory.

In the present study, we attempted to modulate activation of cortical substrates of **attention during learning** by physiological intervention, using transcranial direct current stimulation (tDCS). To effect adversarial modulation, we applied anodal stimulation directed toward left intraparietal sulcus/superior parietal cortex (IPS/SPL; a substrate of selective attention) and cathodal stimulation directed toward right inferior parietal cortex (IPL; a substrate of orienting). *Such stimulation during study of verbal materials led to superior subsequent recognition memory relative to the opposite polarity of stimulation.*

FUNDAMENTAL RESEARCH

Transcranial direct-current stimulation modulates synaptic mechanisms involved in associative learning in behaving rabbits.

tDCS is a noninvasive brain stimulation technique that has been successfully applied for modulation of cortical excitability. tDCS is capable of inducing changes in neuronal membrane potentials in a polarity-dependent manner. When tDCS is of sufficient length, synaptically driven after-effects are induced. **The mechanisms underlying these after-effects are largely unknown**, and there is a compelling need for animal models to test the immediate effects and after-effects induced by tDCS in different cortical areas and evaluate the implications in complex cerebral processes. *Here we show in **behaving rabbits** that tDCS applied over the somatosensory cortex modulates cortical processes consequent to localized stimulation of the whisker pad or of the corresponding area of the ventroposterior medial (VPM) thalamic nucleus.* With longer stimulation periods, poststimulation effects were observed in the somatosensory cortex only after cathodal tDCS. *Consistent with the polarity-specific effects, the acquisition of classical eyeblink conditioning was potentiated or depressed by the simultaneous application of anodal or cathodal tDCS, respectively, when stimulation of the whisker pad was used as conditioned stimulus, suggesting that tDCS modulates the sensory perception process necessary for associative learning.* We also studied the putative mechanisms underlying immediate effects and after-effects of tDCS observed in the somatosensory cortex. Results when pairs of pulses applied to the thalamic VPM nucleus (mediating sensory input) during anodal and cathodal tDCS suggest that *tDCS modifies thalamocortical synapses at presynaptic sites.* Finally, we show that *blocking the activation of adenosine A1 receptors prevents the long-term depression (LTD) evoked in the somatosensory cortex after cathodal tDCS.*

Anodal transcranial direct current stimulation over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding.

We report three studies of the effects of anodal transcranial direct current stimulation (tDCS) over auditory cortex on audition in humans. Experiment 1 examined whether tDCS enhances rapid frequency discrimination learning. Human subjects were trained on a frequency discrimination task for 2 days with anodal tDCS applied during the first day with the second day used to assess effects of stimulation on retention. This revealed that tDCS did not affect learning but did degrade frequency discrimination during both days. Follow-up testing 2-3 months after stimulation showed no long-term effects. Following the unexpected results, two additional experiments examined the effects of tDCS on the underlying mechanisms of frequency discrimination, place and temporal coding. Place coding underlies frequency selectivity and was measured using psychophysical tuning curves with broader curves indicating poorer frequency selectivity. Temporal coding is determined by measuring the ability to discriminate sounds with different fine temporal structure. We found that tDCS does not broaden frequency selectivity but instead degraded the ability to discriminate tones with different fine temporal structure. T*he overall results suggest anodal tDCS applied over auditory cortex degrades frequency discrimination by affecting temporal, but not place, coding mechanisms.*

Dynamic modulation of intrinsic functional connectivity by transcranial direct current stimulation.

Recent evidence suggests that bilateral tDCS over both primary sensorimotor cortices (SM1) yields more prominent effects on motor performance in both healthy subjects and chronic stroke patients than unilateral tDCS over SM1. To better characterize the underlying neural mechanisms of this effect, we aimed to explore changes in resting-state functional connectivity during both stimulation types. In a **randomized single-blind**

crossover design, 12 healthy subjects underwent functional magnetic resonance imaging at rest before, during, and after 20 min of unilateral, bilateral, and sham tDCS stimulation over SM1. Eigenvector centrality mapping (ECM) was used to investigate tDCS-induced changes in functional connectivity patterns across the whole brain. *Uni- and bilateral tDCS over SM1 resulted in functional connectivity changes in widespread brain areas compared with sham stimulation both during and after stimulation.* Whereas bilateral tDCS predominantly modulated changes in primary and secondary motor as well as prefrontal regions, unilateral tDCS affected prefrontal, parietal, and cerebellar areas. No direct effect was seen under the stimulating electrode in the unilateral condition. The time course of changes in functional connectivity in the respective brain areas was nonlinear and temporally dispersed. *These findings provide evidence toward a network-based understanding regarding the underpinnings of specific tDCS interventions.*

Beyond the silence: Bilateral somatosensory stimulation enhances skilled movement quality and neural density in intact behaving rats.

It is thought that a close dialogue between the primary motor (M1) and somatosensory (S1) cortices is necessary for skilled motor learning. The extent of the relative S1 contribution in producing skilled reaching movements, however, is still unclear. Here we used anodal tDCS, which is able to alter polarity-specific excitability in the S1, to facilitate skilled movement in intact behaving rats. We hypothesized that the critical role of S1 in reaching performance can be enhanced by bilateral tDCS. Pretrained rats were assigned to control or stimulation conditions: (1) UnAno: the unilateral application of an anodal current to the side contralateral to the paw preferred for reaching; (2) BiAno1: bilateral anodal current; (3) BiAno2: a bilateral anodal current with additional 30ms of 65µA pulses every 5s. Rats received tDCS (65µA; 10min/rat) to the S1 during skilled reach training for 20 days (online-effect phase). After-effect assessment occurred for the next ten days in the absence of electrical stimulation. Quantitative and qualitative analyses of online-effects of tDCS showed that UnAno and BiAno1 somatosensory stimulation significantly improve skilled reaching performance. Bilateral BiAno1 stimulation was associated with greater qualitative functional improvement than unilateral UnAno stimulation. tDCS-induced improvements were not observed in the after-effects phase. Quantitative cytoarchitectonic analysis revealed that somatosensory tDCS bilaterally increases cortical neural density. *The findings emphasize the central role of bilateral somatosensory feedback in skill acquisition through modulation of cortico-motor excitability.*

Cerebellar modulation of human associative plasticity.

Paired associative stimulation (PAS) is a method commonly used in human studies of motor cortex synaptic plasticity. It involves repeated pairs of electrical stimuli to the median nerve and transcranial magnetic stimulation (TMS) of the motor cortex. If the interval between peripheral and TMS stimulation is around 21–25 ms, corticospinal excitability is increased for the following 30–60 min via a long term potentiation (LTP)-like effect within the primary motor cortex. Previous work has shown that PAS depends on the present and previous levels of activity in cortex, and that it can be modified by motor learning or attention. *Here we show that simultaneous transcranial direct current stimulation (TDCS; 2 mA) over the cerebellum can abolish the PAS effect entirely.* Surprisingly, the effect is seen when the PAS interval is 25 ms but not when it is 21.5 ms. There are two implications from this work. First, the cerebellum influences PAS effects in motor cortex; second, LTP-like effects of PAS have at least two different mechanisms. The results are relevant for interpretation of pathological changes that have been reported in response to PAS in people with movement disorders and to changes in healthy individuals following exercise or other interventions.

Differential effects of dual and unihemispheric motor cortex stimulation in older adults.

Bihemispheric transcranial direct current stimulation (tDCS) is thought to upregulate excitability of the primary motor cortex (M1) using anodal stimulation while concurrently downregulating contralateral M1 using cathodal stimulation. This "dual" tDCS method enhances motor learning in healthy subjects and facilitates motor recovery after stroke. However, its impact on **motor system activity and connectivity remains unknown.** Therefore, we assessed neural correlates of dual and unihemispheric anodal tDCS effects in **20 healthy older subjects** in a randomized, **sham**-controlled study using a cross-over design. Participants underwent tDCS and simultaneous functional magnetic resonance imaging during a choice reaction time task and at rest. Diffusion tensor imaging (DTI) allowed us to relate potential functional changes to structural parameters. *The resting-state analysis demonstrated that, compared with sham, both dual and anodal tDCS decreased connectivity of right hippocampus and M1 (contralateral to the anode position) while increasing connectivity in the left prefrontal cortex. Notably, dual but not anodal tDCS enhanced connectivity of the left dorsal posterior cingulate cortex. Furthermore, dual tDCS yielded stronger activations in bilateral M1 compared with anodal tDCS when participants used either their left or right hand during the motor task. The corresponding tDCS-induced changes in laterality of activations were related to the microstructural status of transcallosal motor fibers.*

A Comparison between Uni- and Bilateral tDCS Effects on Functional Connectivity of the Human Motor Cortex.

Transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) has been shown to induce changes in motor performance and learning. Recent studies indicate that tDCS is capable of modulating widespread neural network properties within the brain. However the temporal evolution of online- and after-effects of tDCS on functional connectivity (FC) within and across the stimulated motor cortices (M1) still remain elusive. In the present study, two different tDCS setups were investigated: (i) unilateral M1 tDCS (anode over right M1, cathode over the contralateral supraorbital region) and (ii) bilateral M1 tDCS (anode over right M1, cathode over left M1). **In a randomized single-blinded cross-over design, 12 healthy subjects underwent functional magnetic resonance imaging at rest before, during and after 20 min of either bi-, unilateral, or sham M1 tDCS.** Seed-based FC analysis was used to investigate tDCS-induced changes across and within M1. We found that bilateral M1 tDCS induced (a) a decrease in interhemispheric FC during stimulation and (b) an increase in intracortical FC within right M1 after termination of the intervention. While unilateral M1 tDCS also resulted in similar effects during stimulation, no such changes could be observed after termination of tDCS. *Our results provide evidence that depending on the electrode montage, tDCS acts upon a modulation of either intracortical and/or interhemispheric processing of M1.*

Effect of serotonin on paired associative stimulation-induced plasticity in the human motor cortex.

Serotonin modulates diverse brain functions. Beyond its clinical antidepressant effects, it improves motor performance, learning and memory formation. These effects might at least be partially caused by the impact of serotonin on neuroplasticity, which is thought to be an important foundation of the respective functions. In principal accordance, selective serotonin reuptake inhibitors enhance long-term potentiation-like plasticity induced by transcranial direct current stimulation (tDCS) in humans. As other neuromodulators have discernable effects on different kinds of plasticity in humans, here we were interested to explore the impact of serotonin on paired associative stimulation (PAS)-induced plasticity, which induces a more focal kind of plasticity, as compared with tDCS, shares some features with spike timing-dependent plasticity, and is thought to be relative closely related to learning processes. **In this single-blinded, placebo-controlled,**

randomized crossover study, we administered a single dose of 20 mg citalopram or placebo medication and applied facilitatory- and excitability-diminishing PAS to the left motor cortex of **14 healthy subjects**. Cortico-spinal excitability was explored via single-pulse transcranial magnetic stimulation-elicited MEP amplitudes up to the next evening after plasticity induction. *After citalopram administration, inhibitory PAS-induced after-effects were abolished and excitatory PAS-induced after-effects were enhanced trendwise, as compared with the respective placebo conditions. These results show that serotonin modulates PAS-induced neuroplasticity by shifting it into the direction of facilitation, which might help to explain mechanism of positive therapeutic effects of serotonin in learning and medical conditions characterized by enhanced inhibitory or reduced facilitatory plasticity, including depression and stroke.*

High-frequency TRNS reduces BOLD activity during visuomotor learning.

We investigated the effects of tDCS and tRNS in the early and later stages of visuomotor learning, as well as associated brain activity changes using functional magnetic resonance imaging (fMRI). We applied anodal and cathodal tDCS, low-frequency and high-frequency tRNS (lf-tRNS, 0.1-100 Hz; hf-tRNS 101-640 Hz, respectively) and **sham** stimulation over the primary motor cortex (M1) during the first 10 minutes of a visuomotor learning paradigm and measured performance changes for 20 minutes after stimulation ceased. Functional imaging scans were acquired throughout the whole experiment. *Cathodal tDCS and hf-tRNS showed a tendency to improve and lf-tRNS to hinder early learning during stimulation, an effect that remained for 20 minutes after cessation of stimulation in the late learning phase.* Motor learning-related activity decreased in several regions as reported previously, however, there was no significant modulation of brain activity by tDCS. In opposition to this, hf-tRNS was associated with reduced motor task-related-activity bilaterally in the frontal cortex and precuneous, probably due to interaction with ongoing neuronal oscillations. *This result highlights the potential of lf-tRNS and hf-tRNS to differentially modulate visuomotor learning and advances our knowledge on neuroplasticity induction approaches combined with functional imaging methods.*

The effect of transcranial direct current stimulation on the motor suppression in stop-signal task.

This study examined whether tDCS of the primary motor cortex alters the response time in motor suppression using the stop-signal task (SST). **40 healthy subjects** were enrolled in this study. The subjects were assigned randomly to either the tDCS condition or **sham** control condition. All subjects performed a stop-signal task in three consecutive phases: without, during or after the delivery of anodal tDCS on the primary motor cortex (the pre-tDCS motor phase, on-tDCS motor phase, and after-tDCS motor phase). *The response times of the stopping process were significantly lower in each SST motor phase during or after tDCS ($p < 0.05$) and shorter immediately during delivery of the tDCS, whereas there was no change after the delivery of tDCS compared to sham condition. In contrast, the response times of the going process were similar under the two conditions ($p > 0.05$). No subjects complained of any adverse symptoms or signs.*

Reorganizing the intrinsic functional architecture of the human primary motor cortex during rest with non-invasive cortical stimulation.

The primary motor cortex (M1) is the main effector structure implicated in the generation of voluntary movements and is directly involved in motor learning. The intrinsic horizontal neuronal connections of M1 exhibit short-term and long-term plasticity, which is a strong substrate for learning-related map reorganization. tDCS applied for few minutes over M1 has been shown to induce relatively long-lasting plastic alterations and to modulate motor performance. Here we test the hypothesis that the relatively long-lasting synaptic modification induced by tDCS over M1 results in the alteration of associations among populations of M1 neurons which may be reflected in changes of its functional architecture. fMRI resting-state datasets were acquired immediately before and after 10 minutes of tDCS during rest, with the anode/cathode placed over the left M1. For each functional dataset, grey-matter voxels belonging to Brodmann area 4 (BA4) were labelled and afterwards BA4 voxel-based synchronization matrices were calculated and thresholded to construct undirected graphs. Nodal network parameters which characterize the architecture of functional networks (connectivity degree, clustering coefficient and characteristic path-length) were computed, transformed to volume maps and compared before and after stimulation. At the dorsolateral-BA4 region cathodal tDCS boosted local connectedness, while anodal-tDCS enhanced long distance functional communication within M1. Additionally, the more efficient the functional architecture of M1 was at baseline, the more efficient the tDCS-induced functional modulations were. *In summary, we show here that it is possible to non-invasively reorganize the intrinsic functional architecture of M1, and to image such alterations.*

The effect of transcranial direct current stimulation: a role for cortical excitation/inhibition balance?

Transcranial direct current stimulation (tDCS) is a promising tool for cognitive enhancement and neurorehabilitation in clinical disorders in both cognitive and clinical domains (e.g., chronic pain, tinnitus). Here we suggest the potential role of tDCS in modulating cortical excitation/inhibition (E/I) balance and thereby inducing improvements. We suggest that part of the mechanism of action of tDCS can be explained by non-invasive modulations of the E/I balance.

REVIEWS

Transcranial alternating current stimulation: a review of the underlying mechanisms and modulation of cognitive processes

Brain oscillations of different frequencies have been associated with a variety of cognitive functions. Convincing evidence supporting those associations has been provided by studies using intracranial stimulation, pharmacological interventions and lesion studies. The emergence of novel non-invasive brain stimulation techniques like repetitive transcranial magnetic stimulation (rTMS) and transcranial alternating current stimulation (tACS) now allows to modulate brain oscillations directly. Particularly, tACS offers the unique opportunity to causally link brain oscillations of a specific frequency range to cognitive processes, because it uses sinusoidal currents that are bound to one frequency only. Using tACS allows to modulate brain oscillations and in turn to influence cognitive processes, thereby demonstrating the causal link between the two. Here, we review findings about the physiological mechanism of tACS and studies that have used tACS to modulate basic motor and sensory processes as well as **higher cognitive processes like memory, ambiguous perception, and decision making.**

Sensing, assessing, and augmenting threat detection: behavioral, neuroimaging, and brain stimulation evidence for the critical role of attention.

Rapidly identifying the potentially threatening movements of other people and objects-biological motion perception and action understanding-is critical to maintaining security in many civilian and military settings. A key approach to improving threat detection in these environments is to sense when less than ideal conditions exist for the human observer, assess that condition relative to an expected standard, and if necessary use tools to augment human performance. Action perception is typically viewed as a relatively "primitive," automatic function immune to top-down effects. However, recent research shows that **attention** is a top-down factor that has a critical influence on the identification of threat-related targets. In this paper we show that detection of motion-based threats is attention sensitive when surveillance images are obscured by other movements, when they are visually degraded, when other stimuli or tasks compete for attention, or when low-probability threats must be watched for over long periods of time-all features typical of operational security settings. Neuroimaging studies reveal that action understanding recruits a distributed network of brain regions, including the superior temporal cortex, intraparietal cortex, and inferior frontal cortex. Within this network, attention modulates activation of the superior temporal sulcus (STS) and middle temporal gyrus. The dorsal frontoparietal network may provide the source of attention-modulation signals to action representation areas. Stimulation of this attention network should therefore enhance threat detection. *We show that transcranial Direct Current Stimulation (tDCS) at 2 mA accelerates perceptual learning of participants performing a challenging threat-detection task. Together, cognitive, neuroimaging, and brain stimulation studies provide converging evidence for the critical role of attention in the detection and understanding of threat-related intentional actions.*

Learning, memory, and transcranial direct current stimulation.

Transcranial direct current stimulation (tDCS) has been the subject of many studies concerning its possible cognitive effects. One of the proposed mechanisms of action for neuromodulatory techniques, such as transcranial magnetic stimulation and tDCS is induction of long-term potentiation (LTP) and long-term depression (LTD)-like phenomena. LTP and LTD are also among the most important neurobiological processes involved in memory and learning. This fact has led to an immediate interest in the study of possible effects of tDCS on memory consolidation, retrieval, or learning of various tasks. This review analyses published articles describing beneficial or disruptive effects of tDCS on memory and learning in normal subjects. The most likely mechanisms underlying these effects are discussed.

Effects of transcranial electrical stimulation on cognition.

Alterations of cortical excitability, oscillatory as well as non-oscillatory, are physiological derivates of cognitive processes, such as perception, working memory, learning, and long-term memory formation. Since noninvasive electrical brain stimulation is capable of inducing alterations in the human brain, these stimulation approaches might be attractive tools to modulate cognition. Transcranial direct current stimulation (tDCS) alters spontaneous cortical activity, while transcranial alternating current stimulation (tACS) and transcranial random noise stimulation (tRNS) are presumed to induce or interfere with oscillations of cortical networks. Via these mechanisms, the respective stimulation techniques have indeed been shown to modulate cognitive processes in a multitude of studies conducted during the last years. In this review, we will gather knowledge about the potential of noninvasive electrical brain stimulation to study and modify cognitive processes in healthy humans and discuss directions of future research.

Enhancing motor skill learning with transcranial direct current stimulation - a concise review with applications to stroke.

In the past few years, there has been a rapid increase in the application of non-invasive brain stimulation to study brain-behavior relations in an effort to potentially increase the effectiveness of neuro-rehabilitation. Transcranial direct current stimulation (tDCS), an emerging technique of non-invasive brain stimulation, has shown to produce beneficial neural effects in consequence with improvements in motor behavior. tDCS has gained popularity as it is economical, simple to use, portable, and increases corticospinal excitability without producing any serious side effects. As tDCS has been increasingly investigated as an effective tool for various disorders, numerous improvements, and developments have been proposed with respect to this technique. tDCS has been widely used to identify the functional relevance of particular brain regions in motor skill learning and also to facilitate activity in specific cortical areas involved in motor learning, in turn improving motor function. Understanding the interaction between tDCS and motor learning can lead to important implications for developing various rehabilitation approaches. This paper provides a concise overview of tDCS as a neuromodulatory technique and its interaction with motor learning. The paper further briefly goes through the application of this priming technique in the stroke population.

Clinical applications of noninvasive electrical stimulation: problems and potential.

Both transcranial direct current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) can produce lasting aftereffects on cortical function that are thought to be due to the initial stages of synaptic potentiation/depression. They can also interact with processes of normal learning, to increase or decrease the rate of learning and retention. These features have spurred a number of investigators to test whether there is any clinical therapeutic potential for the methods to improve recovery of function after damage to the brain by injury or disease. The only condition where there is sufficient evidence is in certain forms of depression where excitatory rTMS is a recommended treatment protocol; there is insufficient evidence for any other condition. The problem facing investigators is the variety of possible paradigms that can be applied. Particularly for tDCS, only a small range of possible parameters has been tested, even in healthy volunteers; in addition, it is unclear whether stimulation should be applied at the same time as a behavioral therapy or whether stimulation should be applied at rest. Present trials give some evidence that can be used to address these questions, but until they are answered more securely it will be difficult to reach a consensus about "standard" protocols that can then be tested widely in multicenter trials.

Action mechanisms of transcranial direct current stimulation in Alzheimer's disease and memory loss.

The pharmacological treatment of Alzheimer's disease (AD) is often limited and accompanied by drug side effects. Thus alternative therapeutic strategies such as non-invasive brain stimulation are needed. Few studies have demonstrated that transcranial direct current stimulation (tDCS), a method of neuromodulation with consecutive robust excitability changes within the stimulated cortex area, is beneficial in AD. There is also evidence that tDCS enhances memory function in cognitive rehabilitation in depressive patients, Parkinson's disease, and stroke. tDCS improves working and visual recognition memory in humans and object-recognition learning in the elderly. AD's neurobiological mechanisms comprise changes in neuronal activity and the cerebral blood flow (CBF) caused by altered microvasculature, synaptic dysregulation from ß-amyloid peptide accumulation, altered neuromodulation via degenerated modulatory amine transmitter systems, altered brain oscillations, and changes in network connectivity. tDCS alters (i) neuronal activity and (ii) human CBF, (iii) has synaptic and non-synaptic after-effects (iv), can modify neurotransmitters polarity-dependently, (v) and alter oscillatory brain activity and (vi) functional connectivity patterns in the brain. It thus is reasonable to use tDCS as a therapeutic instrument in AD as it improves cognitive function in manner based on a disease mechanism. Moreover, it could prove valuable in other types of dementia. Future large-scale clinical and mechanism-oriented studies may enable us to identify its therapeutic validity in other types of demential disorders.

The neuroethics of non-invasive brain stimulation.

Transcranial direct current stimulation (TDCS) is a brain stimulation tool that is portable, painless, inexpensive, apparently safe, and with potential long-term efficacy. Recent results obtained from TDCS experiments offer exciting possibilities for the enhancement and treatment of normal or impaired abilities, respectively. We discuss new neuroethical problems that have emerged from the usage of TDCS, and also focus on one of the most likely future applications of TDCS: enhancing learning and cognition in children with typical and atypical development.

Neuroenhancement: Enhancing brain and mind in health and in disease.

Humans have long used cognitive enhancement methods to expand the proficiency and range of the various mental activities that they engage in, including writing to store and retrieve information, and computers that allow them to perform myriad activities are now commonplace in the internet age. Neuroenhancement describes the use of neuroscience-based techniques for enhancing cognitive function by acting directly on the human brain and nervous system, altering its properties to increase performance. Cognitive neuroscience has now reached the point where it may begin to put theory derived from years of experimentation into practice. This special issue includes 16 articles that employ or examine a variety of neuroenhancement methods currently being developed to increase cognition in healthy people, and in patients with neurological or psychiatric illness. This includes transcranial electromagnetic stimulation methods, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), along with deep brain stimulation, neurofeedback, behavioral training techniques, and these and other techniques in conjunction with neuroimaging. These methods can be used to improve attention, perception, memory and other forms of cognition in healthy individuals, leading to better performance in many aspects of everyday life. They may also reduce the cost, duration and overall impact of brain and mental illness in patients with neurological and psychiatric illness. Potential disadvantages of these techniques are also discussed. Given that the benefits of neuroenhancement outweigh the potential costs, these methods could potentially reduce suffering and improve quality of life for everyone, while further increasing our knowledge about the mechanisms of human cognition.

Battery powered thought: Enhancement of attention, learning, and memory in healthy adults using transcranial direct current stimulation

This article reviews studies demonstrating enhancement with transcranial direct current stimulation (tDCS) of attention, learning, and memory processes in healthy adults. Given that these are fundamental cognitive functions, they may also mediate stimulation effects on other higher-order processes such as decision-making and problem solving. Although tDCS research is still young, there have been a variety of methods used and cognitive processes tested. While these different methods have resulted in seemingly contradictory results among studies, many consistent and noteworthy effects of tDCS on attention, learning, and memory have been reported. The literature suggests that although tDCS as typically applied may not be as useful for localization of function in the brain as some other methods of brain stimulation, tDCS may be particularly well-suited for practical applications involving the enhancement of attention, learning, and memory, in both healthy subjects and in clinical populations.

Transcranial cerebellar direct current stimulation (tcDCS): Motor control, cognition, learning and emotions.

The neurological manifestations of cerebellar diseases range from motor to cognitive or behavioral abnormalities. Experimental data in healthy subjects extend the cerebellar role to learning, emotional and mood control. The need for a non-invasive tool to influence cerebellar function in normal and pathological conditions led researchers to develop transcranial cerebellar direct current stimulation (tcDCS). tcDCS, like tDCS, depends on the principle that weak direct currents delivered at around 2mA for minutes over the cerebellum through surface electrodes induce prolonged changes in cerebellar function. tcDCS modulates several cerebellar skills in humans including motor control, learning and emotional processing. tcDCS also influences the cerebello-brain interactions induced by transcranial magnetic stimulation (TMS), walking adaptation, working memory and emotional recognition. Hence tcDCS is a simple physiological tool that can improve our physiological understanding of the human cerebellum, and should prove useful also in patients with cerebellar dysfunction or psychiatric disorders and those undergoing neurorehabilitation to enhance neuroplasticity.

Noninvasive brain stimulation to modulate neuroplasticity in traumatic brain injury.

Based on a literature search, we describe the pathophysiological events following TBI and the rationale for the use of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) in this setting. The pathophysiological mechanisms occurring after TBI vary across time and therefore require differential interventions. Theoretically, given the neurophysiological effects of both TMS and tDCS, these tools may: 1) decrease cortical hyperexcitability acutely after TBI; 2) modulate long-term synaptic plasticity as to avoid maladaptive consequences; and 3) combined with physical and behavioral therapy, facilitate cortical reorganization and consolidation of learning in specific neural networks. All of these interventions may help decrease the burden of disabling sequelae after brain injury. Evidence from animal and human studies reveals the potential benefit of NBS in decreasing the extent of injury and enhancing plastic changes to facilitate learning and recovery of function in lesioned neural tissue. However, this evidence is mainly theoretical at this point. Given safety constraints, studies in TBI patients are necessary to address the role of

NBS in this condition as well as to further elucidate its therapeutic effects and define optimal stimulation parameters.

Non-invasive Cerebellar Stimulation-a Consensus Paper.

There is a consensus amongst the panel of experts that both TMS and tDCS can effectively influence cerebellar functions, not only in the motor domain, with effects on visually guided tracking tasks, motor surround inhibition, motor adaptation and learning, but also for the cognitive and affective operations handled by the cerebro-cerebellar circuits. Verbal working memory, semantic associations and predictive language processing are amongst these operations. Both TMS and tDCS modulate the connectivity between the cerebellum and the primary motor cortex, tuning cerebellar excitability. Cerebellar TMS is an effective and valuable method to evaluate the cerebello-thalamo-cortical loop functions and for the study of the pathophysiology of ataxia. In most circumstances, DCS induces a polarity-dependent site-specific modulation of cerebellar activity. Paired associative stimulation of the cerebello-dentato-thalamo-M1 pathway can induce bidirectional long-term spike-timing-dependent plasticity-like changes of corticospinal excitability. However, the panel of experts considers that several important issues still remain unresolved and require further research. In particular, the role of TMS in promoting cerebellar plasticity is not established. Moreover, the exact positioning of electrode stimulation and the duration of the after effects of tDCS remain unclear. Future studies are required to better define how DCS over particular regions of the cerebellum affects individual cerebellar symptoms, given the topographical organization of cerebellar symptoms. The long-term neural consequences of non-invasive cerebellar modulation are also unclear. Although there is an agreement that the clinical applications in cerebellar disorders are likely numerous, it is emphasized that rigorous large-scale clinical trials are missing. Further studies should be encouraged to better clarify the role of using non-invasive neurostimulation techniques over the cerebellum in motor, cognitive and psychiatric rehabilitation strategies.