



## Prefrontal direct current stimulation modulates resting EEG and event-related potentials in healthy subjects: A standardized low resolution tomography (sLORETA) study

D. Keeser<sup>a,1</sup>, F. Padberg<sup>a,\*</sup>, E. Reisinger<sup>a</sup>, O. Pogarell<sup>a</sup>, V. Kirsch<sup>a</sup>, U. Palm<sup>a</sup>, S. Karch<sup>a</sup>, H.-J. Möller<sup>a</sup>, M.A. Nitsche<sup>b</sup>, C. Mulert<sup>a,c</sup>

<sup>a</sup> Department of Psychiatry and Psychotherapy, Ludwig-Maximilian University Munich, Germany

<sup>b</sup> Department of Clinical Neurophysiology, Georg-August University, Goettingen, Germany

<sup>c</sup> University Medical Center Hamburg-Eppendorf, Department of Psychiatry and Psychotherapy, Psychiatry Neuroimaging Branch (PNB), Hamburg, Germany

### ARTICLE INFO

#### Article history:

Received 30 July 2010

Revised 3 November 2010

Accepted 2 December 2010

Available online 10 December 2010

#### Keywords:

Transcranial direct current stimulation (tDCS)

sLORETA

Major depression

Therapy

Cognition

Prefrontal

### ABSTRACT

Prefrontal transcranial direct current stimulation (tDCS) with the anode placed on the left dorsolateral prefrontal cortex (DLPFC) has been reported to enhance working memory in healthy subjects and to improve mood in major depression. However, its putative antidepressant, cognitive and behavior action is not well understood. Here, we evaluated the distribution of neuronal electrical activity changes after anodal tDCS of the left DLPFC and cathodal tDCS of the right supraorbital region using spectral power analysis and standardized low resolution tomography (sLORETA). Ten healthy subjects underwent real and sham tDCS on separate days in a double-blind, placebo-controlled cross-over trial. Anodal tDCS was applied for 20 min at 2 mA intensity over the left DLPFC, while the cathode was positioned over the contralateral supraorbital region. After tDCS, EEG was recorded during an eyes-closed resting state followed by a working memory (n-back) task. Statistical non-parametric mapping showed reduced left frontal delta activity in the real tDCS condition. Specifically, a significant reduction of mean current densities (sLORETA) for the delta band was detected in the left subgenual PFC, the anterior cingulate and in the left medial frontal gyrus. Moreover, the effect was strongest for the first 5 min ( $p < 0.01$ ). The following n-back task revealed a positive impact of prefrontal tDCS on error rate, accuracy and reaction time. This was accompanied by increased P2- and P3- event-related potentials (ERP) component-amplitudes for the 2-back condition at the electrode Fz. A source localization using sLORETA for the time window 250–450 ms showed enhanced activity in the left parahippocampal gyrus for the 2-back condition. These results suggest that anodal tDCS of the left DLPFC and/or cathodal tDCS of the contralateral supraorbital region may modulate regional electrical activity in the prefrontal and anterior cingulate cortex in addition to improving working memory performance.

© 2010 Elsevier Inc. All rights reserved.

### Introduction

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation method that shifts neuronal resting membrane potentials towards depolarization or hyperpolarization, depending on whether anodal or cathodal stimulation is applied, leading to changes of cortical excitability and other functional parameters (Nitsche et al., 2008, 2003a,b). More recently, Nitsche and Paulus (2000, 2001) revisited this approach in humans and demonstrated that anodal tDCS increases and cathodal tDCS decreases motor cortex excitability (Nitsche and Paulus, 2000, 2001). When applied for 9–13 min, tDCS

produces post-stimulation effects in the human motor cortex that are stable for up to 1 h and longer (Nitsche et al., 2003c; Nitsche and Paulus, 2001). As demonstrated in animal experiments, the primary mechanism of tDCS appears to be a subthreshold modulation of neuronal resting membrane potential (Purpura and McMurtry, 1965). Accordingly, pharmacologically blocking voltage-dependent ion channels in humans abolishes any effect of depolarizing anodal tDCS on cortical excitability, but does not influence the impact of hyperpolarizing cathodal tDCS (Nitsche et al., 2003a). Pharmacological studies have proven that tDCS related effects depend on changes of NMDA receptor-efficacy (Liebetanz et al., 2002). Recently, Stagg et al. (2009) demonstrated changes in GABA levels after anodal tDCS using magnetic resonance spectroscopy (MRS), suggesting that anodal excitatory effects do affect GABAergic inhibition in addition to NMDA-receptor dependency (Stagg et al., 2009). Based on initial studies, combining tDCS and EEG, a direct impact of tDCS on oscillatory activity was observed (Ardolino et al., 2005; Marshall et al., 2004). During slow-wave sleep (SWS) bilateral frontal

\* Corresponding author. Department of Psychiatry and Psychotherapy, Ludwig-Maximilians University Munich, Nussbaumstrasse 7, D-80336 Munich, Germany. Fax: +49 89 51603930.

E-mail address: [padberg@med.uni-muenchen.de](mailto:padberg@med.uni-muenchen.de) (F. Padberg).

<sup>1</sup> Both authors contributed equally to the manuscript.

sinusoidal anodal tDCS reduced the average power in the theta and alpha-1-bands in frontal, central and parietal electrode locations (Marshall et al., 2004). Compared to placebo stimulation, frontal anodal tDCS during SWS-rich sleep distinctly increased the retention of word pairs (Marshall et al., 2004). Ardolino et al. (2005) also found a widespread impact of tDCS on the EEG (Ardolino et al., 2005). Increasing amounts of delta and theta activity were found after cathodal DC stimulation (15 min, 1.5 mA) to the right motor cortex, extending beyond the primary stimulation site (Ardolino et al., 2005). These EEG pilot studies are indicative of possible large-scale network changes following tDCS. Using positron emission tomography, Lang et al. (2005) showed that anodal tDCS increased the rCBF in widespread cortical and subcortical areas in comparison to cathodal tDCS, while cathodal stimulation entailed an excitability decrease of the metabolic activity in the corresponding areas (Lang et al., 2005).

One mode of tDCS application, namely anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) and cathodal stimulation of the right supraorbital region, has been associated with working memory enhancement and improvement in other cognitive domains (Boggio et al., 2006; Dockery et al., 2009; Elmer et al., 2009; Ferrucci et al., 2008; Fertonani et al., 2010; Fiori et al., 2010; Fregni et al., 2005; Kincses et al., 2004; Marshall et al., 2004; Ohn et al., 2008).

Memory processes of healthy subjects were enhanced after left anodal DLPFC tDCS with the cathode placed on the right frontocortical regions (Fregni et al., 2005; Kincses et al., 2004; Marshall et al., 2004, 2005; Ohn et al., 2008). Moreover, prefrontal tDCS is supposed to modulate pain perception (Boggio et al., 2009, 2008b), seems to influence social behavior (Knoch et al., 2008) and shows an impact on risk taking behavior (Beeli et al., 2008a,b; Fecteau et al., 2007a,b). Prefrontal tDCS may even influence the desire for specific foods (Fregni et al., 2008) and the reaction time to lies (Priori et al., 2008).

In depressed subjects promising pilot data of prefrontal tDCS were reported, suggesting a therapeutic action of real tDCS compared to sham tDCS (Boggio et al., 2007, 2008a; Ferrucci et al., 2009; Fregni et al., 2006; Rigonatti et al., 2008), whereas the effect of one single tDCS-session on healthy subjects had no mood-altering effects (Koenigs et al., 2009).

The mechanism of action of prefrontal tDCS is not completely understood and to date there has been no study about the effects of prefrontal tDCS on resting EEG. Moreover, as prefrontal tDCS seems to influence a wide range of disorders and behaviors, resting state EEG and source analysis techniques may help to better understand prefrontal tDCS induced post-stimulation effects. Furthermore, TMS, MRS and imaging studies are only an indirect proof of the neuronal activity and were predominantly applied to the motor cortex in the past to test the effects of tDCS on brain physiology. We therefore investigated the effects of anodal tDCS of the left DLPFC and cathodal tDCS of the supraorbital region in a placebo-controlled cross-over study in healthy subjects, applying resting state EEG with spectral power analysis and standardized low resolution tomography (sLORETA). Following resting-state EEG all healthy subjects underwent a working memory task (n-back) with event-related potential (ERP) recording. As prefrontal tDCS has been found to influence working memory performance, we intended to replicate this behavioral finding and hypothesized that neurophysiological correlates should be detectable in ERPs related to cognitive processes.

**Methods and materials**

*Subjects*

Ten healthy subjects (five women, five men, mean age = 28.89 years, SD = 2.67) participated in this study. All subjects underwent a semi-

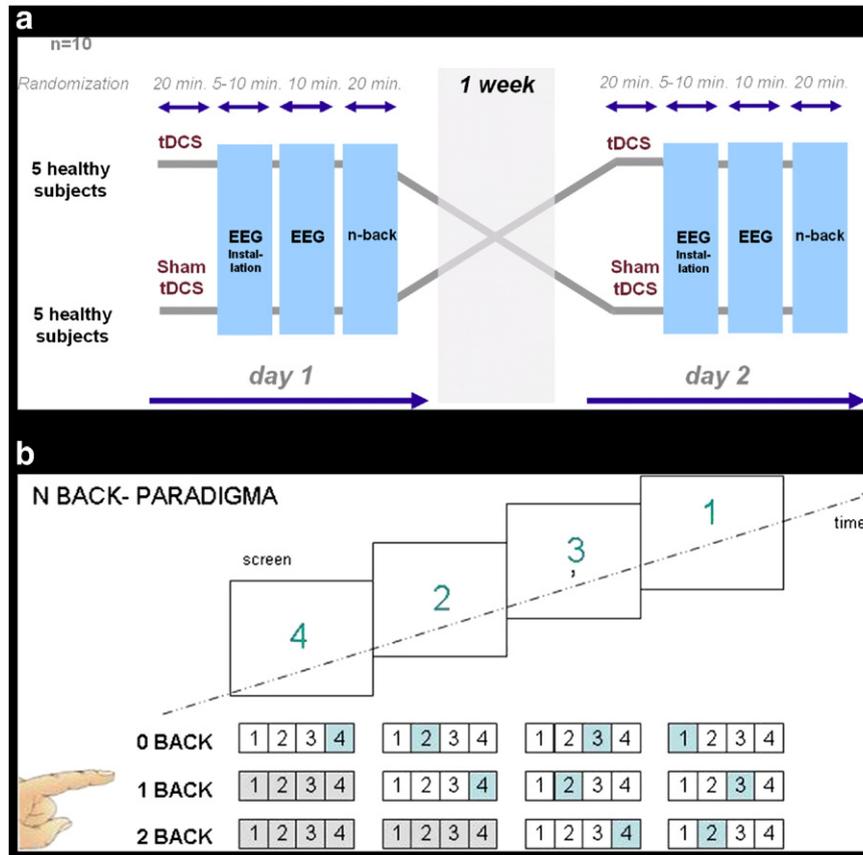


Fig. 1. a) experimental design (prior to the experiments the healthy subjects were introduced and trained to the n-back-task). b) n-back working memory paradigm.

structured interview (including the M-CIDI-S interview and a semantic word fluency task (Wittchen and Müller, 1998) showing that they were without history of neurological and/or psychiatric diseases and free of medication affecting the central nervous system. All subjects were right-handed (Edinburgh handedness test (Oldfield, 1971)) and homogenous with regard to education (university masters degree or medical students). This study was approved by the local ethics committee of the Faculty of Medicine, Ludwig-Maximilian University Munich, Germany. Written informed consent was obtained from each subject and they were paid for their participation. All subjects underwent single sessions of active anodal tDCS and sham tDCS on separate days in randomized order with both conditions counterbalanced across subjects and with an intersession interval of at least 1 week (see Fig. 1a). In addition, mood changes were assessed using the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) before and after tDCS and after the end of EEG recording.

#### tDCS

An Eldith DC stimulator approved for use in humans was used for active stimulation (Neuroconn, Ilmenau, Germany). For sham tDCS, a custom-built placebo stimulator (Neuroconn, Ilmenau, Germany) was used, which was indistinguishable from the active tDCS device to both the operator who administered tDCS and the subjects participating in the trial. Two water-soaked sponge electrodes were used for stimulation ( $7 \times 5$  cm,  $35$  cm<sup>2</sup>). The anode was placed above the left DLPFC with the center above F3 (10–20 system) and the cathode above the right supraorbital region, as previously reported (Fregni et al., 2006). Each tDCS condition was applied for 20 min (15 s ramp in and 15 s ramp out) at 2 mA stimulation intensity. The impedance was controlled by the device, normally ranging below 10 k $\Omega$ , limited by the voltage at less than 26 V.

#### EEG recording

Acute effects of tDCS on the EEG were assessed using a Neuroscan Synamps apparatus together with an electrode cap with 32 electrodes. The recordings took place approximately 5–10 min after each tDCS treatment session with 25 electrodes (all referred to channel Cz). Electrode skin impedance was always less than 5 k $\Omega$ . The electrodes were placed according to the International 10/20 system (Jaspers, 1958) with the additional electrodes FC1, FC2, FC5, FC6, CP5 and CP6. The electrooculogram was measured below the left eye and Fpz served as ground electrode. The subjects were instructed to remain in an alert state with their eyes closed in a sound-attenuated room. The EEG was recorded for 10 min with a sampling rate of 1000 Hz and an analogous bandpass filter (0.16–200 Hz). Offline, we changed the sampling rate to 250 Hz and used a 70 Hz low-pass filter. Before analysis, artifact detection was performed automatically (threshold 70 microvolt ( $\mu$ V)) and visually involving all EEG channels and EOG with the exclusion of all EEG segments that contained obvious eye or muscle artifacts or a decrease in alertness. Additionally, the EEG was analyzed four times independently by two experienced neurophysiologists blinded to the stimulation condition. After relation to the average reference, spectral analysis was performed for 25 electrodes (due to electrode and/or muscle artifacts in some subjects, it was necessary to exclude the electrodes T1, T2, P09 and P10 in the whole sample). The EEG was Fourier-transformed for at least 2-second epochs using the Brain Vision Analyzer software Version 1.05. Epochs were reduced to an average of 160 artifact-free epochs (2 min and 40 s) for the entire sample. The EEG epochs were acquired choosing the best quality, excluding blinking, muscle and electrode artifacts. At least 100 artifact-free segments were required from each subject for fast Fourier transformation and power spectral analysis (PSD) of the Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–25 Hz) and Gamma (30–40 Hz) frequency bands. Repeated-measure analy-

ses of variance (ANOVAs) were used to test for differences between the conditions (anodal vs. sham) in EEG absolute power ( $\mu$ V<sup>2</sup>). Multivariate normal distribution was checked with the Mauchly test of sphericity, and the Greenhouse-Geisser correction was applied, when necessary. A  $p$  value <0.05 was considered significant. Student's  $t$ -tests were used for post hoc analysis (single electrode comparisons). Statistics were performed using the SPSS 13.0 software (Statistical Package for Social Sciences, SPSS Inc, Chicago).

#### sLORETA

We performed a current density analysis in 3-D Talairach/MNI space of the scalp-recorded electrical activity using the sLORETA/eLORETA software package (Pascual-Marqui, 2002). LORETA images represent the electrical activity of each voxel in the neuroanatomic Talairach/MNI space as amplitude of the computed current source density ( $\mu$ A/mm<sup>2</sup>). LORETA estimates the distribution of electrical neural activity in the 3-D space, based on the measurements of a dense grid of electrodes, which are placed on the entire scalp surface covering the brain. The first version of LORETA (Pascual-Marqui et al., 1994) has been validated extensively in the past using PET (Pae et al., 2003; Pizzagalli et al., 2004; Zumsteg et al., 2005b), functional magnetic resonance imaging fMRI (Mulert et al., 2004; Vitacco et al., 2002) and intra-cerebral recordings (Zumsteg et al., 2005a, 2006). Moreover, even deep structures with mesial hippocampal and subcallosal cingulate foci could be correctly classified with LORETA in the past (Pizzagalli et al., 2004; Zumsteg et al., 2005b). Pizzagalli et al. (2004) demonstrated a highly correlated correspondence between LORETA measures of activation in subgenual cingulate and PET measures of glucose metabolism (Pizzagalli et al., 2004). These results can also be applied on sLORETA (Pascual-Marqui, 2002), which is an advanced version of the previous LORETA method.

The version of LORETA used in the present study, sLORETA (Pascual-Marqui, 2002), estimates the current source density distribution for epochs of brain electrical activity on a dense grid of 6239 voxels at 5 mm spatial resolution. The effects of tDCS on sLORETA were obtained for both experimental conditions (real and sham tDCS) and compared between groups with  $t$ -statistical non-parametric mapping, using the implemented statistical nonparametric mapping (SnPM) tool. The significance level applied to the data was set at  $p < 0.05$  (significant effect) and  $p < 0.10$  (statistical trend).

#### n-back task

Prior to tDCS experiments (study design, see Fig. 1a) a baseline n-back task was conducted on a separate day. Following EEG recordings after real or sham tDCS, all subjects underwent the same working memory n-back task (see Figs. 1a,b). In the n-back paradigm figures of cardinal numbers 1–4 were presented in pseudorandomized order on the screen with an interval of 1800 ms between stimuli. Each number was presented for 400 ms. The easiest task consisted of simply pressing the key that appeared immediately on the screen (0-back). For 1-back the number which was presented a passageway before had to be pressed. 2-back required to press the

**Table 1**

PANAS mean ratings and standard deviations before and after real or sham stimulation.

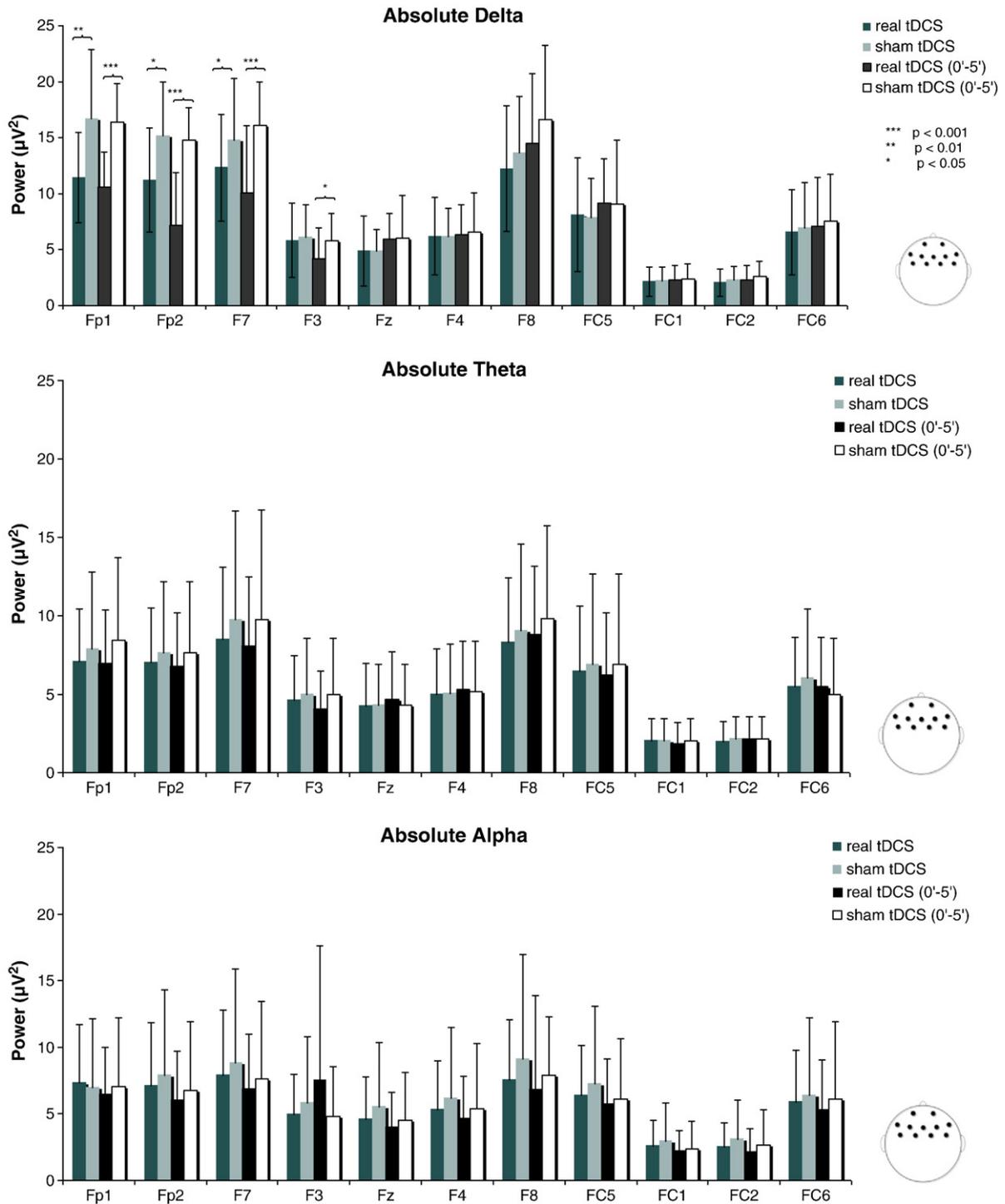
	Real tDCS and EEG		Sham tDCS and EEG	
	Before	After	Before	After
PANAS				
Positive affect	26.80 (5.14)	27.60 (5.69)	28.00 (5.14)	27.10 (3.84)
Negative affect	11.40 (2.55)	11.50 (2.17)	11.60 (2.01)	11.10 (1.91)

button according to the number presented two trials back. The different conditions were presented in 6 blocks and every block consisted of 14 trials. The subjects were informed about all tasks at the beginning by displaying 0-, 1-, and 2-back on the center of the screen between blocks and as headline during the whole experiment. Stimulus presentation was computerized (Presentation, Version 9.13). In order to ensure that participants can principally perform the task, they could practice several minutes before the recording started.

ERP recording

Eye artifact correction

Eye artifact and brain activities were considered as concurrent overlapping processes and separated using the principle of multiple source artifact correction in BESA 5.1.4.40 software (MEGIS, Graefelfing, Germany): Therefore first a provided surrogate model (BR\_BrainRegions.LR.bsa) consisting of a set of dipole sources was placed



**Fig. 2.** Effect of real vs. sham tDCS on absolute power ( $\mu V^2$ ) as a function of single frontal electrode comparisons for the frequency bands Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), Beta (12–30 Hz) and Gamma (30–40 Hz). Resting state EEG after real and sham tDCS is given for the frontal electrodes. The green bars show the whole mean EEG record (10 min), black and white bars represent the first 5 min (0'-5') of EEG recording. The head in the lower corner right indicates the chosen electrodes. Even electrode numbers represent the right frontal hemisphere, odd numbers the left frontal hemisphere. Note tDCS was applied to the left DLPFC.

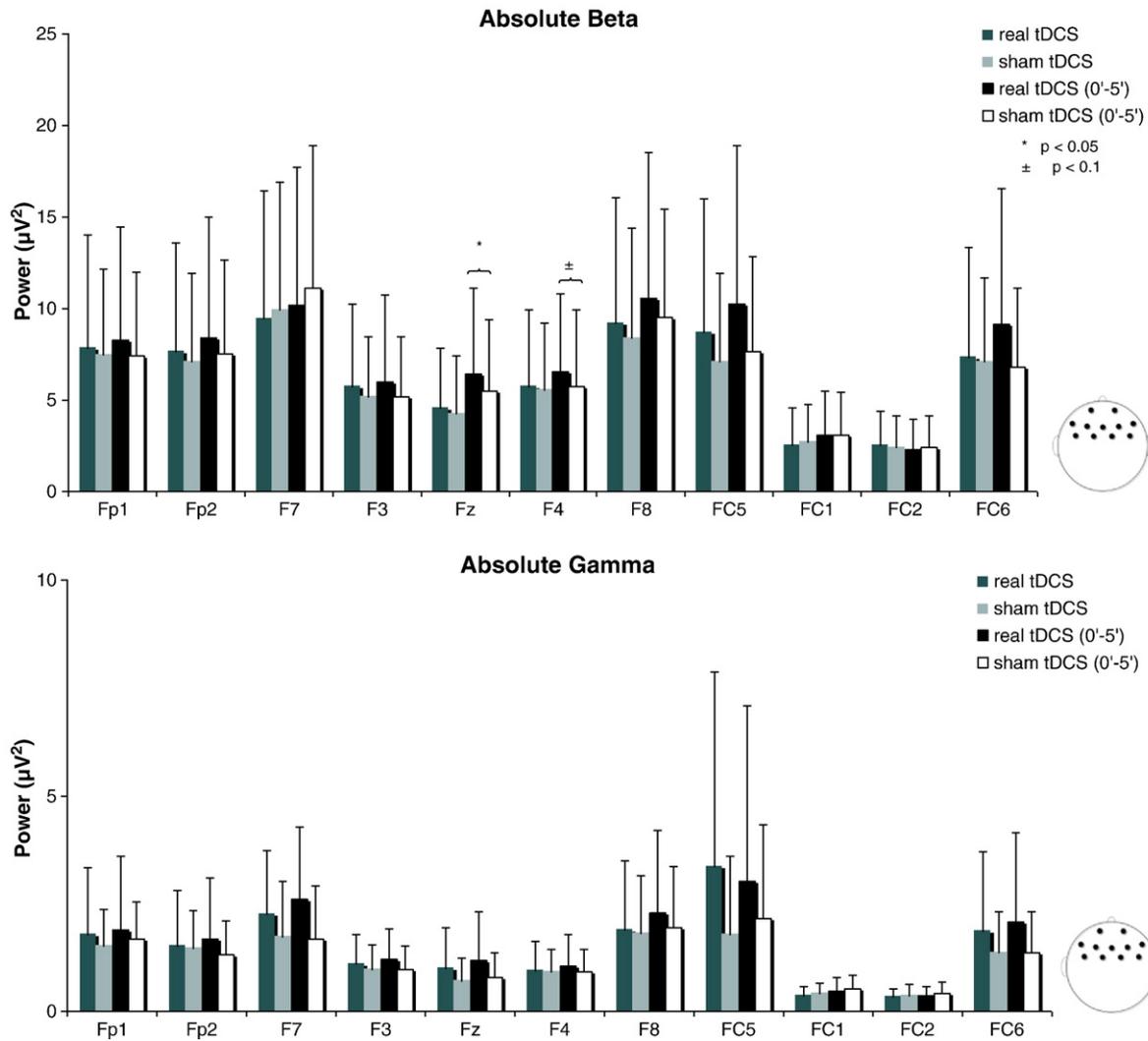


Fig. 2 (continued).

Table 2

Statistical non-parametric comparisons between current source density values of real vs. sham tDCS stimulations using sLORETA. Results for the delta- and beta-1-band activity.

	Region	XYZ (MNI)				Brodmann area	T-value
<b>a) 0'-10'</b>							
Real vs. sham	Medial frontal gyrus	-5	20	-20	25		-4.16*
	Subcallosal gyrus	-5	20	-15	25		-4.14*
	Anterior cingulate	-5	20	-10	32		-4.11*
	Medial frontal gyrus	-5	-25	-20	25		-4.06±
	Rectal gyrus	-10	20	-25	11		-4.01±
<b>b) 0'-5'</b>							
Delta	Anterior cingulate	-5	20	-5	25		-5.45**
	Anterior cingulate	-5	25	-5	24		-5.43**
	Anterior cingulate	-5	20	-10	32		-5.32**
	Anterior cingulate	-5	25	-10	32		-5.30**
	Subcallosal gyrus	-5	25	-15	25		-5.22
	Medial frontal gyrus	-6	20	-20	11		-5.13
beta	Cingulate gyrus	10	20	40	32		3.53±

0'-10' = 10 min of EEG recording after tDCS.

0'-5' = first 5 minutes of EEG recording (Note: for delta-band only t-values of  $p < 0.01$  are shown).

\*  $p$ -value  $< 0.05$ .

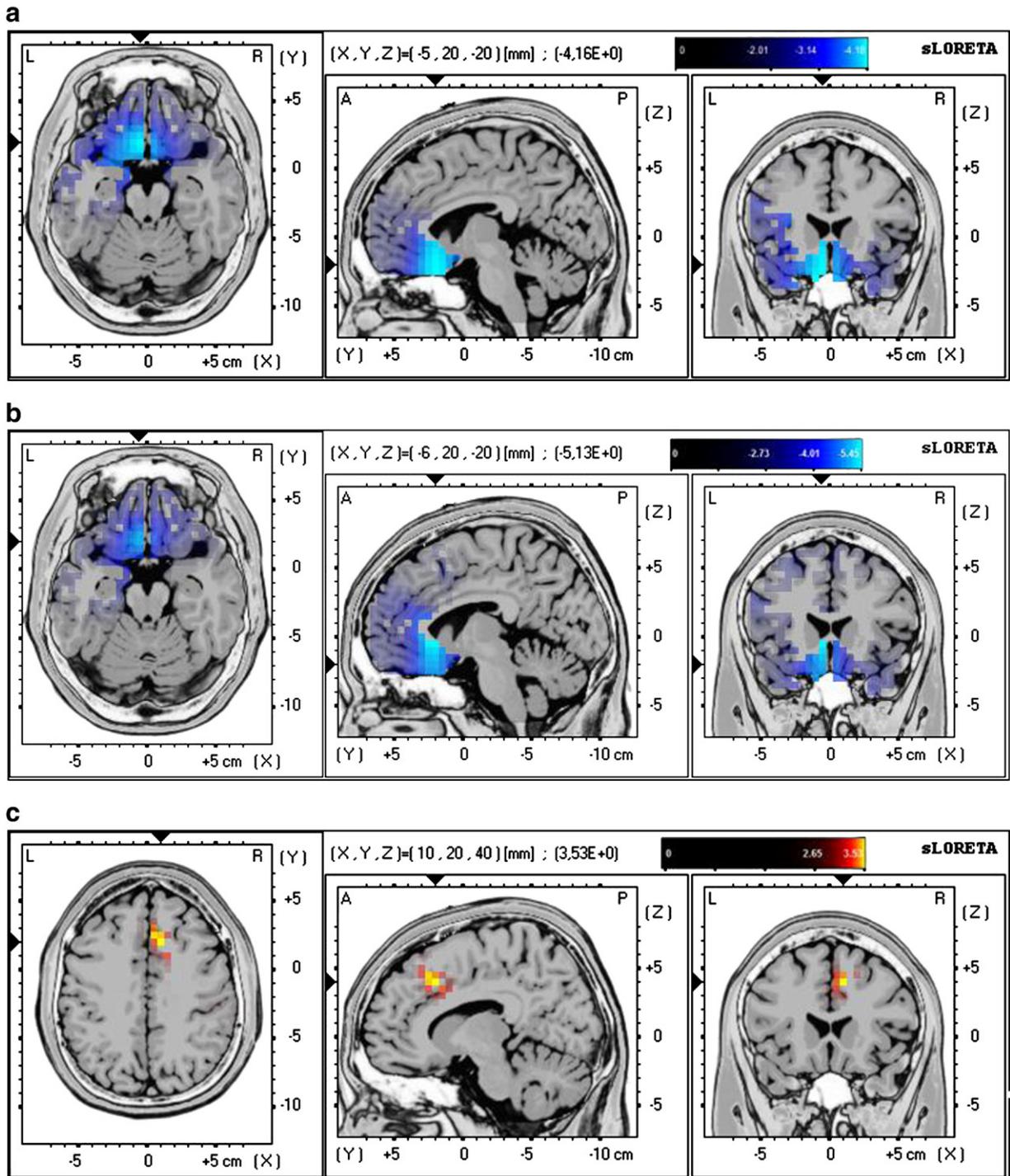
±  $p$ -value  $< 0.10$ .

\*\*  $p$ -value  $< 0.01$ .

according to the locations of the EEG generators. Eye artifacts pattern search was automatically performed. In the next step, the surrogate dipole model was combined with the source model of the eye artifact. After that the artifact was subtracted from the data.

#### ERP averaging

Corrected data were exported into Brain Vision Analyzer 1.05 (Brainproducts, Munich, Germany), re-referenced to common average after channels T01, T02, P09, P10 were excluded from further analysis. Then data were filtered (low pass filter 30 Hz, 48 dB/oct; high pass filter 0.53 Hz, 48 dB/oct) and segmented (100 ms pre-stimulus baseline to 600 ms post stimulus). We analyzed all components at all channels and selected the P2- and P3-components for the electrodes Fz, Cz and Pz for further statistical analysis. This selection was done to restrict our analysis to a more global view on ERPs. As midline areas are well-known to show replicable components and activations during working memory tasks, P2- and P3- peak amplitudes were determined prior to analysis for the experimental conditions by defining the peak within a classified time window for P2 (100–250 ms after a stimulus) and P3 (260–400 ms after stimulus). All sweeps were automatically excluded from averaging if the voltage exceeded  $70 \pm \mu\text{V}$  in any of the 25 channels at any point during the averaging period.



**Fig. 3.** The effect of real tDCS vs. sham tDCS on the mean current source density analyzed by sLORETA. a) for the whole resting-state EEG (10 min): a significant ( $p < 0.042$ ) reduction was detected for the deltaband (1–6.5 Hz) and localized in the subgenual prefrontal cortex ( $xyz = -5, 20, -20$ ; BA 25). b) for the time period 0–5 min a significant ( $p = 0.001$ ; two-tailed) reduction was detected on the mean current source density analyzed by sLORETA. For the deltaband (1–6.5 Hz). The strongest effects were localized in the subgenual prefrontal cortex ( $xyz = -6, 20, -20$ ; BA 25). c) for the time period 0–5 min a significant trend ( $p < 0.10$ ) was detected in the gyrus cingulate ( $xyz = 10, 20, 40$ ; BA 32) of the beta 1 band (13–18 Hz). Note there was no significant difference in any other frequency band for the time period 5–10 min, indicating that real vs. sham tDCS had only a significant effect up to 15 min after stimulation and 5 min after EEG recording on the resting-state EEG.

#### sLORETA

To enhance the spatial sensitivity of our ERP procedure, we used the following time windows on the EEG source analysis: i) –150–50 ms ii) 50–250 ms iii) 260–450 ms and iv) 450–650 ms. We used all scalp electrodes in a source localization analysis using sLORETA. This was done separately for all 0-, 1- and 2-backs. The significance level was set to  $p < 0.10$  and  $p < 0.05$ .

#### Statistics

We used analysis of variance for repeated measures (ANOVA) to investigate if there was a difference between real and sham tDCS. Data are reported as means and standard deviations. Mauchly's test was used to test for sphericity, and the Greenhouse–Geisser correction was applied if necessary. The Wilcoxon signed rank test (nonparametric test) was used for the ERP statistics because our sample was reduced to seven subjects due to artifacts. Given the exploratory character of the

**Table 3**  
Changes in miss rate, accuracy, error rate and reaction time after real and sham tDCS.

n-back	Baseline			Sham			Real		
	0-back	1-back	2-back	0-back	1-back	2-back	0-back	1-back	2-back
Miss rate	0.05 ± 0.06	0.09 ± 0.06	0.18 ± 0.12	0.04 ± 0.05	0.12 ± 0.07	0.18 ± 0.11	0.04 ± 0.05	0.13 ± 0.10	0.20 ± 0.11
Accuracy	0.95 ± 0.06	0.85 ± 0.09	0.66 ± 0.17	0.95 ± 0.05	0.84 ± 0.10	0.67 ± 0.13	0.96 ± 0.05	0.83 ± 0.14	0.73 ± 0.13 <sup>ab</sup>
Error rate	0.00 ± 0.00	0.05 ± 0.04	0.15 ± 0.09	0.03 ± 0.005	0.03 ± 0.03	0.14 ± 0.06	0.01 ± 0.004	0.04 ± 0.05	0.08 ± 0.06 <sup>ab</sup>
Reaction time (ms)	523.5 ± 46.5	289.2 ± 43.0	568.0 ± 250.4	509.6 ± 57.2	294.2 ± 93.1	438.9 ± 163.7	463.2 ± 27.2 <sup>ab</sup>	253.4 ± 48.2 <sup>c</sup>	386.5 ± 150.0 <sup>c</sup>

Values are mean ± standard deviation.

<sup>a</sup> $p < 0.05$  vs. baseline.

<sup>b</sup> $p < 0.05$  vs. placebo.

<sup>c</sup> $p < 0.10$  vs. baseline.

study, statistical significance levels were set to  $p = 0.05$  and  $p < 0.10$  (statistical trend) and not corrected for multiple comparisons. Correlations were calculated using Pearson's correlation coefficient with a significance level of  $p < 0.05$  and a statistical trend ( $p < 0.1$ ). All statistical analyses were performed using the SPSS 13.0 software (Statistical Package for Social Sciences, SPSS Inc, Chicago) or the implemented statistical sLORETA nonparametric mapping (SnPM) tool (Pascual-Marqui et al., 2002). The SnPM analysis tool includes a correction for multiple comparisons and does not require any assumption of Gaussianity (Diener et al., 2010).

## Results

### Distinguishability of DC stimulators

All subjects were asked if they perceived a difference between the stimulation conditions and if they could specifically discern real from placebo tDCS. Nobody was able to distinguish real and sham tDCS, nor did the reported sensations differ between stimulation conditions.

### Mood changes

No side effects of stimulation were reported. There were no significant differences in the PANAS before and after tDCS (see Table 1). The Positive Affect Scale showed no main effects for time ( $F(1,9) = 0.02$ ,  $p = 0.96$ , n.s.) and stimulation condition (anodal vs. sham) ( $F(1,9) = 0.11$ ,  $p = 0.75$ , n.s.) nor for the interaction time x condition ( $F(1,9) = 1.99$ ;  $p = 0.19$ , n.s.). On the Negative Affect Scale, there was no main effects for time ( $F(1,9) = 0.211$ ;  $p = 0.66$ , n.s.), stimulation condition ( $F(1,9) = 0.01$ ,  $p = 0.91$ , n.s.) and the interaction time x condition ( $F(1,9) = 0.64$ ;  $p = 0.44$ , n.s.).

### Single electrode comparisons

We conducted repeated-measures ANOVA for our main region of interest, i.e. the prefrontal cortex. A three-way repeated-measures ANOVA with condition (anodal, sham), lead (Fp1, Fp2, F7, F3, F4, F8, FC5, FC1, FC2, and FC6) and frequency band (delta, theta, alpha, beta, gamma) as within-subjects factors on the absolute EEG power revealed significant main effects of lead ( $F(1.55,13.92) = 40.21$ ,  $p = 0.0004$ ), condition x lead ( $F(12.35,3.79) = 7.66$ ,  $p = 0.019$ ), lead x frequency ( $F(3.82,34.34) = 16.94$ ,  $p = 0.0001$ ) and condition x frequency x lead ( $F(3.82,34.39) = 3.17$ ,  $p = 0.027$ ). Post-hoc ANOVAs for each frequency band showed that significant condition x lead interactions were found in the delta frequency band ( $F(5,45) = 9.84$ ,  $p = 0.001$ ). The EEG power at each lead for real and sham tDCS in the delta, theta, alpha, beta and gamma band are shown in Fig. 2. Prefrontal real tDCS induced a significant decrease in delta power at the Fp1, Fp2 and F7 electrodes (Fp1:  $t(9) = -3.32$ ,  $p = 0.009$ ; Fp2:  $t(9) = -2.47$ ,  $p = 0.036$ ; F7:  $t(9) = -2.66$ ,  $p = 0.026$ ). Analysis of the first 5 min of EEG recording (0–5 min) identified a stronger main effect of lead ( $F(1.51,13.60) = 47.59$ ,  $p = 0.0002$ ), condition x lead ( $F(4.4,39.55) = 16.59$ ,  $p = 0.0009$ ), lead x

frequency ( $F(3.65,32.81) = 7.78$ ,  $p = 0.0008$ ) and condition x frequency x lead ( $F(4.39,39.50) = 8.33$ ,  $p = 0.001$ ). We detected again a condition x lead interaction for the delta frequency band. Real tDCS decreased activity at the frontal leads Fp1, Fp2, F3 and F7 (Fp1:  $t(9) = -8.49$ ,  $p = 0.0001$ ; Fp2:  $t(9) = -5.5$ ,  $p = 0.0003$ ; F3:  $t(9) = -3.15$ ,  $p = 0.01$ ; F7:  $t(9) = -5.58$ ,  $p = 0.0003$ ) and a statistical trend was identified for FC5 (FC5:  $t(9) = -2.05$ ,  $p = 0.07$ ). Additionally, prefrontal tDCS had an effect on the beta band where it significantly increased activity at Fz (Fz:  $t(9) = 2.31$ ,  $p = 0.046$ ) and F4 (F4:  $t(9) = 2.15$ ,  $p = 0.061$ ).

### sLORETA results

In order to further localize the changes in delta activity, sLORETA was applied. SnPM showed a reduced left frontal delta (1–6.5 Hz) activity in the real tDCS condition compared to sham tDCS. Specifically, we detected a decrease in current densities (sLORETA) in real tDCS compared to sham tDCS for the delta band localized in the left subgenual PFC/medial frontal gyrus, Brodmann area, BA 25 ( $t = -4.16$ ,  $p < 0.05$ ), in the subcallosal gyrus, BA 47 ( $t = -4.14$ ,  $p < 0.05$ ), in the anterior cingulate (ACC), BA 32 ( $t = -4.11$ ,  $p < 0.05$ ), in the medial frontal gyrus, BA 25 ( $t = -4.06$ ,  $p < 0.10$ ) and in the left rectal gyrus, BA 11 ( $t = -4.01$ ;  $p < 0.079$ ) (Table 2a, Fig. 3a). We did not find significant results for any other frequency band.

To further elucidate if there were any time effects we looked at the sLORETA time course. We found a strong statistical effect ( $p < 0.01$ ) in the delta band and a statistical trend ( $p < 0.10$ ) in the beta band when we analyzed the first 5 minutes of EEG recording (see Table 2b, Figs. 3b,c). There was not any significant effect or trend for the later time window 5–10 min. The strongest effect for the source localization was found in the subgenual PFC ( $t = -5.13$ ,  $xyz = -6, 20, -20$ ; BA 25) for the delta frequency (1–6.5 Hz). A statistical trend of increased activity was found in the rostral ACC ( $t = 3.53$ ,  $xyz = 5, 20, 40$ ; BA 32) for the beta-1-band (13–18 Hz).

### n-back task: behavioral results

We analyzed the different memory load of the n-back tasks (0-, 1-, 2-back) and all n-backs combined using a two-way repeated-measures ANOVA, with 'condition' (baseline, anodal, sham) and behavioral n-back subcategories for miss rate, accuracy, error rate, reaction time as within-subjects factor (see summary, Table 3). For the combined n-backs accuracy condition the analysis revealed that there were significant differences between condition ( $F(2,18) = 6.53$ ,  $p = 0.007$ ). Post-hoc analyses, with a Bonferroni correction for multiple comparisons, indicated that error rate was significantly lower after real tDCS ( $M = 0.04 \pm 0.03$ ) compared to sham tDCS ( $M = 0.06 \pm 0.03$ ), with  $p = 0.037$  and baseline assessment ( $M = 0.07 \pm 0.04$ ), with  $p = 0.027$ . Analyzing results of the single n-back conditions, we found a significant effect between conditions only for 2-back ( $F(2,18) = 7.43$ ,  $p = 0.004$ ). There was a significant lower error rate in the 2-back task after real stimulation ( $M = 0.08 \pm 0.06$ ) in contrast to sham tDCS ( $M = 0.14 \pm 0.06$ ,  $p = 0.013$ ) and baseline ( $M = 0.15 \pm 0.09$ ,  $p = 0.018$ ), suggesting

that real tDCS especially influences error rate in conditions with higher memory load.

Additionally, real tDCS significantly reduced reaction time ( $M = 366.40 \pm 57.1$ ) as compared to baseline ( $M = 460.23 \pm 95.3$ ), ( $F(2,18) = 8.70$ ,  $p = 0.002$ ), but not to sham stimulation ( $M = 414.26 \pm 82.6$ ,  $p = 0.19$ ). Comparison between the single n-backs revealed that there was a significant effect of condition for the 0-back ( $F(2,18) = 11.17$ ,  $p = 0.001$ ) and 2-back task ( $F(2,18) = 8.70$ ,  $p = 0.002$ ). Regarding the 0-back condition, real DC stimulation ( $M = 463.19 \pm 27.2$ ) reduced the reaction time significantly as compared to sham tDCS ( $M = 509.62 \pm 57.2$ ,  $p = 0.006$ ) or baseline assessment ( $M = 523.49 \pm 46.5$ ,  $p = 0.002$ ). For the 1-back condition, real tDCS ( $M = 253.38 \pm 48.2$ ) reduced reaction time only trendwise as compared to baseline performance ( $M = 289.2 \pm 43.0$ ;  $p = 0.062$ ) but did not differ from sham tDCS ( $M = 294.23 \pm 93.1$ ). We found a similar result for the 2-back condition where we detected a significant effect for condition ( $F(2,18) = 4.76$ ,  $p = 0.022$ ), but only a statistical trend ( $p = 0.084$ ) after real tDCS ( $M = 386.51 \pm 150.0$ ) vs. baseline ( $M = 567.99 \pm 250.4$ ) and no difference ( $p = 0.19$ ) compared to sham tDCS ( $M = 438.94 \pm 163.7$ ).

Finally, there was a significant effect of condition for the 2-back accuracy ( $F(2,18) = 4.97$ ,  $p = 0.019$ ), driven by better accuracy after real stimulation ( $M = 0.73 \pm 0.13$ ) as post hoc contrasts showed that accuracy was significantly enhanced ( $p = 0.024$ ) compared to sham stimulation ( $M = 0.67 \pm 0.13$ ) and non-significantly improved as compared to baseline performance ( $M = 0.66 \pm 0.17$ ,  $p = 0.13$ ).

#### *n-back task: ERP results*

Three subjects were excluded from the analysis because of artifacts or due to ERP outliers. Table 4 shows ERP amplitudes and latencies for P2 and P3 amplitudes at midline electrodes (Fz, Cz and Pz).

Only in the 2-back task P2 potentials were significantly increased at electrode Fz after real DC stimulation ( $5.55 \pm 1.45 \mu\text{V}$ ) compared to sham ( $4.02 \pm 1.51 \mu\text{V}$ ,  $p = 0.046$ , Wilcoxon signed rank test) and baseline ( $3.62 \pm 1.66 \mu\text{V}$ ,  $p = 0.018$ , Wilcoxon signed rank test) conditions. After real tDCS we found a significantly reduced P2 latency ( $202 \pm 32$  ms,  $p = 0.042$ ) at Cz compared to baseline. (Fig. 4c). All results incl. trends are shown in Table 4.

Only in the 2-back condition the P3 potentials were significantly higher at Fz after prefrontal stimulation ( $2.10 \pm 1.05 \mu\text{V}$ ) compared to sham stimulation ( $0.61 \pm 0.81 \mu\text{V}$ ,  $p = 0.047$ , Wilcoxon signed rank test). Two trends were found for increased voltage at Pz after real tDCS ( $9.58.61 \pm 2.78 \mu\text{V}$ ,  $p = 0.063$ , Wilcoxon signed rank test) for the 0-back condition if compared to baseline ( $8.12 \pm 1.74 \mu\text{V}$ ) and for the 2-back condition if real tDCS ( $7.64 \pm 2.17 \mu\text{V}$ ) was compared to baseline ( $6.63 \pm 1.14 \mu\text{V}$ ,  $p = 0.084$ ). The latency after sham stimulation ( $328 \pm 44$  ms) compared to real tDCS ( $315 \pm 23$ ) at Cz showed a significant difference ( $p = 0.027$ , Wilcoxon signed rank test). All results are shown in Table 4.

#### *Correlation of P2 and P3 results with memory performance after tDCS*

Analyses of post-tDCS findings revealed no significant correlations between the P2-amplitude and miss rate, accuracy, error rate or reaction time.

Interestingly, Pearson linear correlation analysis showed a significant negative correlation between the P3 amplitude at electrode Pz and error rate for the 2-back condition ( $r = -0.78$ ,  $p = 0.04$ ) at baseline. In regard to higher memory effort (2-back) higher voltage at Pz was significantly associated with reduced error rate ( $r = -0.79$ ,  $p = 0.04$ ) and reduced reaction time ( $r = -0.87$ ,  $p = 0.011$ ) after prefrontal tDCS. These results are shown in Table S1 (Supporting Information).

#### *Memory effect on sLORETA*

We looked on the averaged ERPs within the time windows:  $-150$  to  $50$  ms,  $50-250$  ms,  $250$  ms– $450$  ms and  $450-650$  ms for all 0-back, 1-back and 2-back separately. We did not find any significant effects for the 0-back and 1-back condition. For the 2-back condition there was a significant effect ( $p < 0.05$ , two-tailed) in the left parahippocampal gyrus ( $t = 7.41$ ,  $xyz = -15, -3, -21$ ; BA 35) for the time window  $250-450$  ms compared to sham tDCS (see Fig. 5).

#### **Discussion**

##### *EEG study*

Our results suggest that anodal tDCS above the left DLPFC with the cathode placed supraorbitally on the contralateral side may influence regional electrical activity in the surface EEG and deeper in the prefrontal lobe as revealed by sLORETA. However, the underlying mechanisms are not well understood and several hypotheses might be discussed, e.g. neuroplastic effects by prolonged weak depolarization/hyperpolarization, effects on connected networks or even brain conductivity heterogeneities.

As a matter of fact, other brain stimulation studies of the left DLPFC showed a similar modulation of regional brain activity in the subgenual PFC. In several studies combining rTMS with functional neuroimaging and magnetoencephalography (MEG) (Kimbrell et al., 1999; Maihöfner et al., 2005; Speer et al., 2000), particularly slow magnetoencephalographic (MEG) activity (2–6 Hz) in the PFC decreased after rTMS of the left DLPFC (Maihöfner et al., 2005). Regarding brain stimulation studies of the primary motor cortex, anodal tDCS increased the rCBF in widespread cortical and subcortical areas as compared to cathodal tDCS, while cathodal stimulation entailed an excitability decrease of the metabolic activity in the corresponding areas (Lang et al., 2005). However, the strongest effects in that study were not seen in the motor cortex but in the supplementary motor area, suggesting large-scale network changes due to DC stimulation (Lang et al., 2005). Applying BOLD fMRI, Baudewig and colleagues found changes of cortical activity by not primarily in the areas under the tDCS electrodes (Baudewig et al., 2001), but rather in closely connected brain regions, suggesting a complex spatial distribution of the tDCS action. However, previous neuroimaging studies did not investigate possible tDCS effects on frontal brain regions. For tDCS-induced EEG alterations, it was shown that cathodal tDCS of the primary motor cortex increases slow-wave delta and theta EEG activity, while anodal stimulation reduces it, again also in regions outside the electrode placements (Ardolino et al., 2005). Another study has recently shown that anodal prefrontal compared to sham stimulation with 1 mA has an effect for up to 10 min after the end of stimulation on functional near-infrared spectroscopy (Merzagora et al., 2009). This is in line with our result showing that prefrontal stimulation with 2 mA had an impact on EEG activity for up to 15 min after the end of DC stimulation. Our results show that tDCS of the prefrontal cortex influences cortical dynamics in the frontal network with a pronounced activation in the medial frontal gyrus, the ACC and the subgenual cortex. These results are compatible with those of a recent prefrontal rTMS study that found a significant reduction of the PET binding potential in almost the same regions of the left DLPFC (BA 25, 11 and 32) after 10 Hz repetitive TMS stimulation (Cho and Strafella, 2009).

Amplitude increases in low frequency oscillations are related to a decreased BOLD signal in fMRI studies – hence an excitatory shift in neuronal activity from lower to higher frequencies would result in reduced delta and theta activity and increased beta and gamma amplitudes. Recently, reduced delta power and increased beta power were significantly ( $r = -0.73$  and  $r = 0.53$ ) correlated to increased functional connectivity in a simultaneous EEG-fMRI study (Hlinka et al., 2010). Here we provide further proof that a more alert state (may established via excitatory anodal Direct Current brain stimulation) leads to reduced delta power and increased beta power,

**Table 4**  
Effects of real and sham tDCS on P2- and P3-ERP-components and latencies for the midline electrodes Fz, Cz, and Pz.

n-back electrode	Baseline									Sham			
	0-back			1-back			2-back			0-back			1-back
	Fz	Cz	Pz	Fz									
P2 – Voltage ( $\mu$ V)	3.51 $\pm$ 1.7	3.67 $\pm$ 1.7	none	3.73 $\pm$ 2.0	4.47 $\pm$ 1.5	4.74 $\pm$ 0.8	3.62 $\pm$ 1.7	none	none	3.62 $\pm$ 1.9	3.85 $\pm$ 1.6	none	3.91 $\pm$ 2.7
P2 – latency (ms)	180 $\pm$ 11	196 $\pm$ 37	none	178 $\pm$ 14	197 $\pm$ 29	228 $\pm$ 25	189 $\pm$ 14	none	none	179 $\pm$ 6	202 $\pm$ 37	none	182 $\pm$ 10
P3 – Voltage ( $\mu$ V)	1.91 $\pm$ 0.6	4.90 $\pm$ 1.5	8.12 $\pm$ 1.7	0.81 $\pm$ 1.0	3.6 $\pm$ 1.2	4.0 $\pm$ 2.6	0.81 $\pm$ 1.0	5.43 $\pm$ 1.6	6.63 $\pm$ 2.9	1.57 $\pm$ 1.6	4.79 $\pm$ 1.8	9.47 $\pm$ 1.4	1.10 $\pm$ 1.0
P3 – latency (ms)	385 $\pm$ 97	342 $\pm$ 25	322 $\pm$ 42	384 $\pm$ 83	359 $\pm$ 61	308 $\pm$ 80	359 $\pm$ 97	342 $\pm$ 27	313 $\pm$ 35	390 $\pm$ 111	350 $\pm$ 30	314 $\pm$ 12	385 $\pm$ 93

None = no component was detected.

Values are mean  $\pm$  standard deviation.

<sup>a</sup> $p < 0.05$  vs. Baseline.

<sup>b</sup> $p < 0.05$  vs. Sham.

<sup>c</sup> $p < 0.10$  vs. Baseline.

<sup>d</sup> $p < 0.10$  vs. Sham.

supporting the results of Hlinka and colleagues (Hlinka et al., 2010) on another experimental domain (non-invasive brain stimulation).

Our study provides first pilot data of tDCS-associated excitability changes within the DLPFC, extending the previous results of motor cortex tDCS studies induced (Nitsche et al., 2005).

Additionally, we found activations in a widespread area of the prefrontal cortex that could play an important role in revealing the functional anatomy of effects induced by prefrontal tDCS. In summary, existing neuroimaging, TMS and EEG studies support the hypothesis that tDCS alters the level of neural excitability (Nitsche et al., 2003a, 2002, 2005; Nitsche and Paulus, 2000).

On a functional level we did not find an immediate influence of prefrontal tDCS on mood. The results in the PANAS questionnaire did not differ between real and sham stimulation. These data are consistent with a previous study of Koenigs et al. 2009 that did not find any significant mood effects of bifrontal tDCS in a double-blind crossover study where participants underwent a single session of anodal, sham and cathodal tDCS (Koenigs et al., 2009).

The finding that prefrontal tDCS particularly modulates delta activity in the medial frontal cortex, the ACC and the subgenual cortex (SGC) of healthy subjects could form a link to previously reported effects of prefrontal tDCS on depression, risk taking behavior, impulsiveness, pain modulation and craving (Beeli et al., 2008a,b; Boggio et al., 2008b; Fecteau et al., 2007a,b).

The SGC, where we observed the strongest effect of anodal tDCS (BA 25), plays a central role in the neurobiology of depression and affective disorders (Hajek et al., 2008). Neuroimaging studies reveal an interaction between changes of regional brain activity in this area and the severity of depression (Drevets et al., 2002; Hajek et al., 2008; Pizzagalli et al., 2004), although the direction of these changes does vary across methodologies and patient populations (Hajek et al., 2008; Mayberg et al., 2000, 2005).

Using LORETA, two previous studies demonstrated an increase of delta activity in the subgenual PFC in patients with major depression (Pae et al., 2003; Pizzagalli et al., 2001, 2004). Moreover, Pizzagalli et al. (2004) reported that EEG delta-activity tended to decrease in the subgenual PFC of melancholic subjects in contrast to non-melancholic subjects after antidepressant treatment, as demonstrated by LORETA. Thus, one might speculate that the antidepressant effect of anodal tDCS above the left DLPFC and right cathodal tDCS supraorbitally reported elsewhere (Boggio et al., 2008a; Ferrucci et al., 2009; Fregni et al., 2006; Rigonatti et al., 2008) may be mediated by the tDCS effects on the SGC observed here. Furthermore, a recent study revealed that nucleus accumbens (NAcc) responses were inversely associated with rostral ACC resting delta activity and the authors mentioned that available animal data suggest that dopamine release in the NAcc is associated with decreased delta activity (Wacker et al., 2009). Cho and Straffella also provided first evidence of extrastriatal dopamine modulation in the subgenual and orbitofrontal cortex following

acute rTMS of the left DLPFC (Cho and Straffella, 2009). McCormick and colleagues found that a normalization of subgenual theta activity after electroconvulsive therapy was associated with decreased psychotic symptoms in patients with depression and psychotic disorders (McCormick et al., 2009).

Our sLORETA results could also be interpreted in a way that the pain system is modulated by prefrontal tDCS, as pilot data indicate a significant increase of pain thresholds after prefrontal tDCS, and the ventral and rostral area of the ACC has a predominant role in endogenous pain control (Boggio et al., 2008b).

Several methodological considerations are necessary. Firstly, we found a significant effect in the delta spectral power and a statistical trend in the beta-1-band in the source analysis of areas in the prefrontal cortex. Whereas the values in the delta band are clearly significant we found only a statistical trend in the beta band. However, we measured the EEG approximately 10 min after tDCS stimulation and this time lag may have contributed to the lesser effect on the EEG. This assumption is further confirmed by the fact that the EEG analysis of the whole time window (10 min) showed weaker statistical results than the first 5 min.

Secondly, our sample size was relatively small. Acknowledging the limited spatial resolution and precision of sLORETA, it must be pointed out that our findings are preliminary and functional imaging techniques with more precise localization (e.g. fMRI or PET) are needed in order to confirm our present results.

#### *n-back behavioral results*

In addition to EEG, we introduced a working memory (n-back) paradigm in this experiment to obtain behavioral data as positive control for our EEG findings. Indeed, prefrontal tDCS enhanced performance in the n-back-task. It is important to emphasize that the task was carried out not immediately, but 20–40 min after tDCS. Our findings are in line with a prior study looking on a verbal memory n-back task after prefrontal tDCS revealing a significant change in accuracy 30 min after completing tDCS (Ohn et al., 2008). Different to this previous study (Ohn et al., 2008) we used a non-verbal n-back task and stimulated with 2 mA for 20 min whereas Ohn et al. stimulated with 1 mA for 30 min. In contrast to previous studies (Fregni et al., 2005; Ohn et al., 2008) we found significant effects on the reaction time after prefrontal stimulation. This is in accordance with early work on frontal DC stimulation that found enhanced response speed in a simple reaction paradigm after anodal stimulation of the vertex, a region more posterior compared to our stimulation site but still within the frontal brain (Elbert et al., 1981). Nitsche and colleagues found that anodal stimulation of the primary motor cortex of healthy subjects resulted in reduced RTs in implicit motor learning (Nitsche et al., 2003d). In contrast, other studies could not detect any effect on reaction time (Fregni et al., 2005) or even found a worsening

					Real								
2-back					0-back			1-back			2-back		
Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz	Fz	Cz	Pz
4.5 ± 1.0	5.45 ± 1.5	4.02 ± 1.5	none	none	↑4.11 ± 2.1 <sup>c</sup>	3.70 ± 1.4	none	3.85 ± 1.8	5.11 ± 2.1	5.25 ± 1.2	↑5.55 ± 1.5 <sup>a,b</sup>	none	none
204 ± 29	228 ± 31	187 ± 13	none	none	181 ± 9	200 ± 37	none	178 ± 6	↓202 ± 32 <sup>a</sup>	221 ± 31	190 ± 22	none	none
4.44 ± 2.5	4.31 ± 2.8	0.61 ± 0.8	5.54 ± 1.9	7.14 ± 2.2	2.0 ± 0.9	5.46 ± 1.4	↑9.58 ± 2.8 <sup>c</sup>	1.28 ± 1.0	4.1 ± 2.2	4.62 ± 2.6	↑2.1 ± 1.1 <sup>b,c</sup>	5.88 ± 1.6	↑7.64 ± 2.2 <sup>c</sup>
373 ± 101	310 ± 47	360 ± 120	340 ± 23	328 ± 4	390 ± 91	333 ± 26	313 ± 29	382 ± 92	366 ± 90	304 ± 42	361 ± 97	340 ± 23	↓315 ± 4 <sup>d</sup>

(Marshall et al., 2005). As Elbert and colleagues detected an RT-interaction only in the second half of their experiment we speculate about the possibility that the effects of prolonged weak tDCS might had a delayed effect on the domain of behavioral reaction time. This view might be supported by reports that found higher task accuracy

and faster reaction times in later repeated sessions (Dockery et al., 2009) suggesting a possible strengthening of connections in time course. In addition, prefrontal tDCS was associated with improved reaction time in naming processing (Fertonani et al., 2010; Fiori et al., 2010) and in probabilistic learning (Hecht et al., 2010).

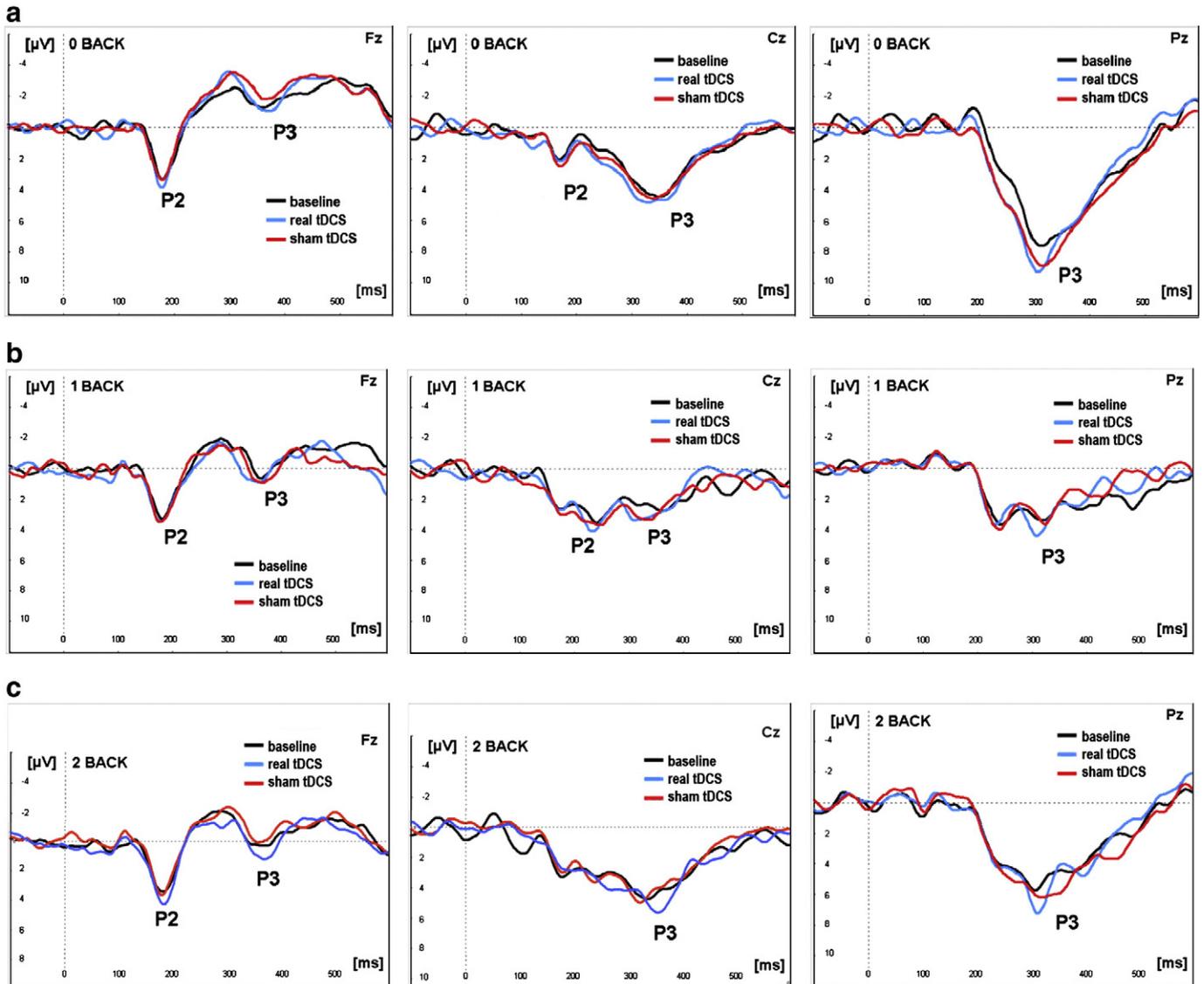
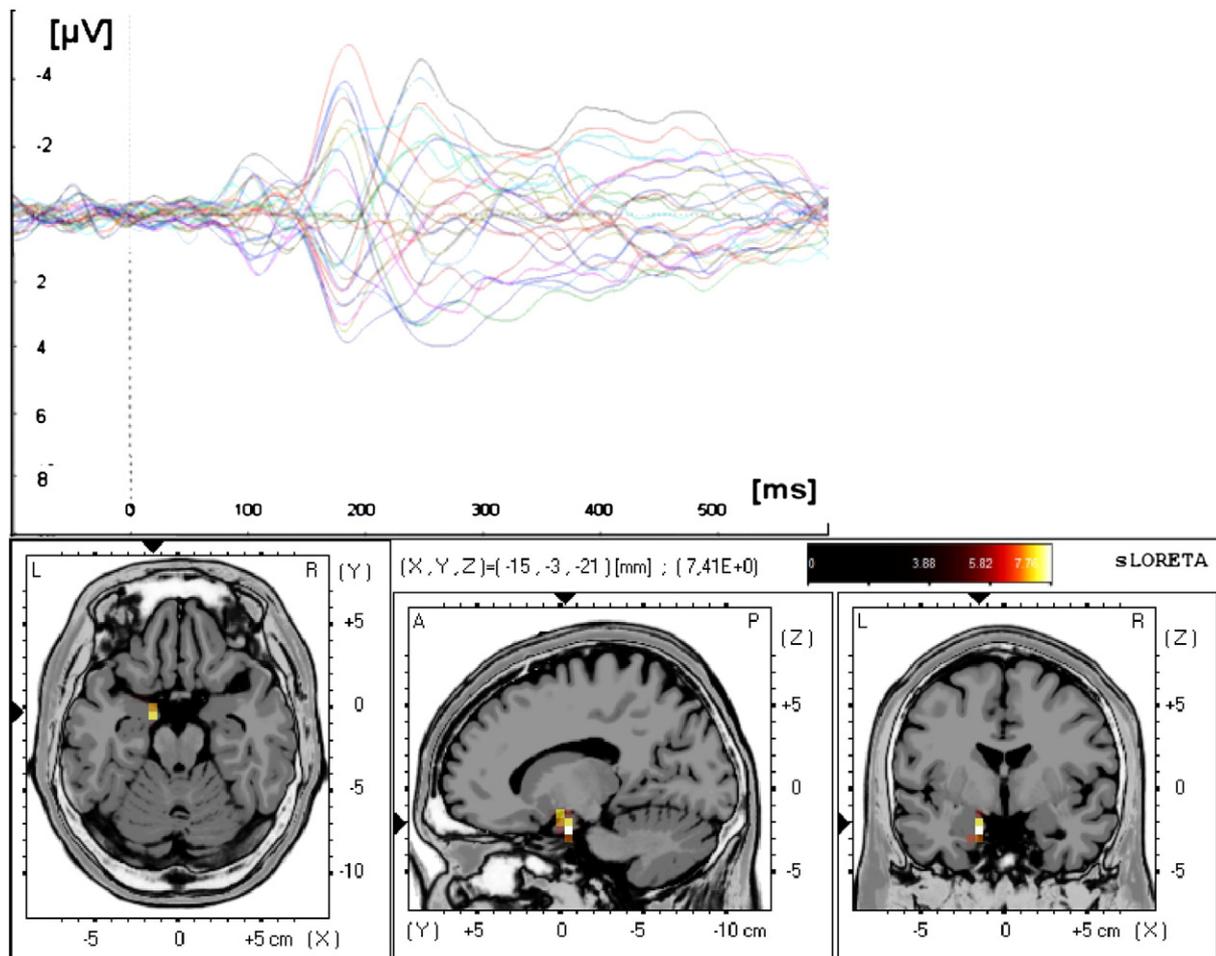


Fig. 4. ERP group averages for the n-back tasks. Here shown for the conditions baseline, real and sham for the midline electrodes Fz, Cz, Pz, time-window: 100 ms pre-stimulus baseline to 600 ms post stimulus. a) 0-back. b) 1-back. c) 2-back.



**Fig. 5.** sLORETA source localisation of 2-back memory retrieval as compared by real vs. sham tDCS. All electrodes were used for the source localisation in the time window 250–450 ms post-stimulus, see picture above for the baseline activations. Statistical comparison shows that the maximal activation stimulus appears in the left parahippocampal gyrus ( $xyz = -15, -3, -21$ ; BA 35) on a significant level of  $p < 0.05$ .

Furthermore, we observed an effect of prefrontal tDCS especially on the 2-back task. Correspondingly, several studies in the past found stronger activations of functional brain processes on higher working memory load (Braver et al., 1997; Callicott et al., 1999). Real tDCS of the prefrontal cortex seems to influence the accuracy and error rate for higher memory load (2-back), whereas it reduces the reaction time especially in the lower memory load (0-back) condition. We suggest that Direct Current (DC) stimulation prior to task condition contributed to increased efficient network dynamics more capable of higher task demands, whereas it seems to increase RTs on lower memory – load tasks that are more automatically processed.

#### *n-back ERP study results*

As expected, we found an influence of tDCS on ERPs during the n-back task.

**P2:** We found an increase of P2 amplitudes at Fz after real tDCS compared to sham and baseline conditions for the 2-back task. Increased P2 amplitudes have previously been associated with demanding memory load (Klaver et al., 1999).

**P3:** The amplitudes of P3 showed a significant increase at Fz after real tDCS compared to sham tDCS and baseline during the 2-back condition. This suggests that prefrontal real tDCS contributed to the P3-amplitude increase as it is known that structures such as the DLPFC and the anterior cingulate cortex, among other regions, are involved in the generation of the P3-component (Benar et al., 2007; Halgren et al., 1998; Menon et al., 1997; Mulert et al., 2004). As we found modified activity in parts of these

structures after prefrontal tDCS or during the n-back task as shown by sLORETA, it is possible that prefrontal tDCS is directly related to this increase of the P3 amplitude. While the P3 component is produced by a distributed network of brain processes associated with attention and memory operations, it is observed in any task that requires stimulus discrimination. It has been suggested recently that the P3 component could occur from the initial need to enhance focal attention during stimulus detection relative to the contents of working memory (Polich, 2007).

In our examination of memory recall in the 2-back condition by sLORETA we detected significant higher activation of the left parahippocampal gyrus after real tDCS. This effect was found between 250 and 450 ms post stimulus, whereas there was no significant difference in other latency periods. These results could be interpreted to mean that prefrontal tDCS influences the frontal cortex via fronto-hippocampal and fronto-parietal connections, as we see increased frontal and parietal activations after prefrontal tDCS. Past studies have found direct neuronal activity between the medial prefrontal cortex and the hippocampus in rodents during spatial working memory tasks (Jones and Wilson, 2005; Siapas et al., 2005) and there is evidence for a fronto-parietal network (Laufs, 2008; van den Heuvel et al., 2009). One major effect of the parahippocampal activation might be the updating of the working memory processes, as this region is well-known for its role in episodic memory (Johnson et al., 2008; Kumari et al., 2003; Ramsay et al., 2009). Reciprocal connections between the dorsolateral prefrontal cortex (including the ACC) and the parahippocampal region are known (Goldman-Rakic et al., 1984). Assuming a

higher order network that mediates memory processes, tDCS might influence the whole network during the resting state period, making it easier to get the network activated during consecutive task performance. The role of the parahippocampal gyrus could be the representation activation of the cardinal numbers during memory delays (2-back). Hence, the stronger activity in the parahippocampal gyrus would explain the significant better accuracy and miss rate after real compared to sham stimulation.

An interesting finding of this study is the delayed impact of DC stimulation on the EEG. It seems that prefrontal tDCS directly influenced neuronal activity in the resting state for a certain time period, and might have kept the network more activated explaining the subsequent better performance and increased cognitive ERP amplitudes during the higher memory requirement of the 2-back task. There was consistency between improved behavioral performance and increased ERP amplitudes for the 2-back condition. Moreover shorter latencies may indicate reduced reaction time in the n-back task. Since tDCS stimulation affected the Fz- and Pz-electrode a strengthening of the frontal to parietal connectivity by real tDCS is possible. During rest we found increased high-frequency EEG activity in the gyrus cingulate. It is plausible that prefrontal tDCS induces activity changes in a broader network via top-down modulation starting at frontal cortical structures.

Thus, our results are in line with previous studies showing an effect of prefrontal tDCS on n-back tasks in healthy subjects (Fregni et al., 2005; Ohn et al., 2008) and in neurological/psychiatric patients (Boggio et al., 2006; Jo et al., 2009; Kang et al., 2009).

Previous studies did not differentiate between single n-backs and might have missed the effect of prefrontal tDCS on memory load. Other authors have reported effects on additional memory categories (Elmer et al., 2009; Kincses et al., 2004; Marshall et al., 2004), as well as on other cognitive domains (Cerruti and Schlaug, 2009; Dockery et al., 2009; Elmer et al., 2009; Fecteau et al., 2007a; Fertonani et al., 2010; Fiori et al., 2010; Iyer et al., 2005; Marshall et al., 2006; Palm et al., 2009; Priori et al., 2008; Sparing et al., 2007; Wassermann and Grafman, 2005). In summary our findings suggest that prefrontal tDCS influences and accelerates cortical EEG activity and may thus help explain the recently reported broad range of behavioral tDCS effects.

### Limitations

One limiting aspect of our study is the small sample size and time-delay for the cognitive task. Due to these facts and the exploratory nature of our n-back study, we did not correct for multiple comparisons and might hereby have increased the possibility of type II errors. At the same time the risk of type I error was decreased, taking the preliminary character of our n-back study into account. Upcoming studies must corroborate our results. We also like to mention that we did not control for the hormonal status of our female subjects. Despite the pseudorandomized order and the cross-over design it might be criticized that we only performed baseline n-back on a separate day once and not before each experimental condition.

Another limitation is the lack of varying and controlling active electrode positions. The bipolar electrode positions may have resulted in effective stimulation of two brain regions. In addition to anodal tDCS of the left DLPFC, the right frontopolar cortex was stimulated with cathodal tDCS. In our study we used the electrode size of  $7 \times 5 \text{ cm}^2$  as most behavioral and clinical prefrontal tDCS studies up to date have used these electrode sizes. A neurobiological interpretation is complicated by two possible stimulation sources (anode/cathode). Future studies may encounter this important topic by increasing electrode size to reduce the effects of anode/cathode electrode or to use an extracephalic region (Vandermeeren et al., 2010).

### Safety aspects

Finally, tDCS was well tolerated and the only side effect reported was an initial itching sensation. Previously reported skin lesions occurring after a longer clinical trial (5 days later) were not observed (Palm et al., 2008). This is in line with other previously conducted safety studies (Iyer et al., 2005; Poreisz et al., 2007; Tadini et al., 2010) and there have not been any reports of skin lesions for single 2 mA sessions.

### Conclusion

In conclusion, we have shown that anodal/cathodal tDCS of the left DLPFC/right frontopolar region increases neuronal activation, corroborated by EEG results showing decreased localized delta-theta and enhanced beta activity both associated with a more alert state (Barry et al., 2009; Kilner et al., 2005) and increased functional connectivity (Hlinka et al., 2010). We further speculate that the increased activation in the prefrontal region and parahippocampal area led to the improvement in the n-back task. Combining tDCS and EEG should further contribute to our understanding of the neurophysiological mechanisms underlying the action of tDCS on behavioral measures. Given the likely effects on various cognitive and affective domains, prefrontal tDCS might have an impact in many clinical fields.

Supplementary materials related to this article can be found online at doi:10.1016/j.neuroimage.2010.12.004.

### Acknowledgments

This study is part of the Ph.D. thesis of Daniel Keeser at the Faculty of Medicine of the Ludwig-Maximilians University of Munich (in preparation). We gratefully acknowledge T. Sprenger for his invaluable advise, and thank M. Hartmann, D. Bars und H.J. Engelbregt for critically reading our manuscript.

### References

- Ardolino, G., Bossi, B., Barbieri, S., Priori, A., 2005. Non-synaptic mechanisms underlie the after-effects of cathodal transcutaneous direct current stimulation of the human brain. *J. Physiol.* 568, 653–663.
- Barry, R.J., Clarke, A.R., Johnstone, S.J., Brown, C.R., 2009. EEG differences in children between eyes-closed and eyes-open resting conditions. *Clin. Neurophysiol.* 120, 1806–1811.
- Baudewig, J., Nitsche, M.A., Paulus, W., Frahm, J., 2001. Regional modulation of BOLD MRI responses to human sensorimotor activation by transcranial direct current stimulation. *Magn. Reson. Med.* 45, 196–201.
- Beeli, G., Casutt, G., Baumgartner, T., Jancke, L., 2008a. Modulating presence and impulsiveness by external stimulation of the brain. *Behav. Brain Funct.* 4, 33.
- Beeli, G., Koeneke, S., Gasser, K., Jancke, L., 2008b. Brain stimulation modulates driving behavior. *Behav. Brain Funct.* 4, 34.
- Benar, C.G., Schon, D., Grimault, S., Nazarian, B., Burle, B., Roth, M., Badier, J.M., Marquis, P., Liegeois-Chauvel, C., Anton, J.L., 2007. Single-trial analysis of oddball event-related potentials in simultaneous EEG-fMRI. *Hum. Brain Mapp.* 28, 602–613.
- Boggio, P.S., Ferrucci, R., Rigonatti, S.P., Covre, P., Nitsche, M., Pascual-Leone, A., Fregni, F., 2006. Effects of transcranial direct current stimulation on working memory in patients with Parkinson's disease. *J. Neurol. Sci.* 249, 31–38.
- Boggio, P.S., Berman, F., Vergara, A.O., Muniz, A.L., Nahas, F.H., Leme, P.B., Rigonatti, S.P., Fregni, F., 2007. Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. *J. Affect. Disord.* 101, 91–98.
- Boggio, P.S., Rigonatti, S.P., Ribeiro, R.B., Myczkowski, M.L., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2008a. A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression. *Int. J. Neuropsychopharmacol.* 11, 249–254.
- Boggio, P.S., Zaghi, S., Lopes, M., Fregni, F., 2008b. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *Eur. J. Neurol.* 15, 1124–1130.
- Boggio, P.S., Zaghi, S., Fregni, F., 2009. Modulation of emotions associated with images of human pain using anodal transcranial direct current stimulation (tDCS). *Neuropsychologia* 47, 212–217.
- Braver, T.S., Cohen, J.D., Nystrom, L.E., Jonides, J., Smith, E.E., Noll, D.C., 1997. A parametric study of prefrontal cortex involvement in human working memory. *NeuroImage* 5, 49–62.

- Callicott, J.H., Mattay, V.S., Bertolino, A., Finn, K., Coppola, R., Frank, J.A., Goldberg, T.E., Weinberger, D.R., 1999. Physiological characteristics of capacity constraints in working memory as revealed by functional MRI. *Cereb. Cortex* 9, 20–26.
- Cerruti, C., Schlaug, G., 2009. Anodal transcranial direct current stimulation of the prefrontal cortex enhances complex verbal associative thought. *J. Cogn. Neurosci.* 21, 1980–1987.
- Cho, S.S., Strafella, A.P., 2009. rTMS of the left dorsolateral prefrontal cortex modulates dopamine release in the ipsilateral anterior cingulate cortex and orbitofrontal cortex. *PLoS ONE* 4, e6725.
- Diener, C., Kuehner, C., Flor, H., 2010. Loss of control during instrumental learning: a source localization study. *Neuroimage* 50, 717–726.
- Dockery, C.A., Hueckel-Weng, R., Birbaumer, N., Plewnia, C., 2009. Enhancement of planning ability by transcranial direct current stimulation. *J. Neurosci.* 29, 7271–7277.
- Drevets, W.C., Bogers, W., Raichle, M.E., 2002. Functional anatomical correlates of antidepressant drug treatment assessed using PET measures of regional glucose metabolism. *Eur. Neuropsychopharmacol.* 12, 527–544.
- Elbert, T., Lutzenberger, W., Rockstroh, B., Birbaumer, N., 1981. The influence of low-level transcranial DC-currents on response speed in humans. *Int. J. Neurosci.* 14, 101–114.
- Elmer, S., Burkard, M., Renz, B., Meyer, M., Jancke, L., 2009. Direct current induced short-term modulation of the left dorsolateral prefrontal cortex while learning auditory presented nouns. *Behav. Brain Funct.* 5, 29.
- Fecteau, S., Knoch, D., Fregni, F., Sultani, N., Boggio, P., Pascual-Leone, A., 2007a. Diminishing risk-taking behavior by modulating activity in the prefrontal cortex: a direct current stimulation study. *J. Neurosci.* 27, 12500–12505.
- Fecteau, S., Pascual-Leone, A., Zald, D.H., Liguori, P., Theoret, H., Boggio, P.S., Fregni, F., 2007b. Activation of prefrontal cortex by transcranial direct current stimulation reduces appetite for risk during ambiguous decision making. *J. Neurosci.* 27, 6212–6218.
- Ferrucci, R., Mameli, F., Guidi, I., Mrakic-Sposta, S., Vergari, M., Marceglia, S., Cogiamanian, F., Barbieri, F., Scarpini, E., Priori, A., 2008. Transcranial direct current stimulation improves recognition memory in Alzheimer disease. *Neurology* 71, 493–498.
- Ferrucci, R., Bortolomasi, M., Vergari, M., Tadini, L., Salvoro, B., Giacopuzzi, M., Barbieri, S., Priori, A., 2009. Transcranial direct current stimulation in severe, drug-resistant major depression. *J. Affect. Disord.* 118, 215–219.
- Fertonani, A., Rosini, S., Cotelli, M., Rossini, P.M., Miniussi, C., 2010. Naming facilitation induced by transcranial direct current stimulation. *Behav. Brain Res.* 208, 311–318.
- Fiori, V., Coccia, M., Marinelli, C.V., Vecchi, V., Bonifazi, S., Ceravolo, M.G., Provinciali, L., Tomaiuolo, F., Marangolo, P., 2010. Transcranial direct current stimulation improves word retrieval in healthy and nonfluent aphasic subjects. *J. Cogn. Neurosci.* doi:10.1162/jocn.2010.21579.
- Fregni, F., Boggio, P.S., Nitsche, M., Bermpohl, F., Antal, A., Feredoes, E., Marcolin, M.A., Rigonatti, S.P., Silva, M.T., Paulus, W., Pascual-Leone, A., 2005. Anodal transcranial direct current stimulation of prefrontal cortex enhances working memory. *Exp. Brain Res.* 166, 23–30.
- Fregni, F., Boggio, P.S., Nitsche, M.A., Marcolin, M.A., Rigonatti, S.P., Pascual-Leone, A., 2006. Treatment of major depression with transcranial direct current stimulation. *Bipolar Disord.* 8, 203–204.
- Fregni, F., Orsati, F., Pedrosa, W., Fecteau, S., Tome, F.A., Nitsche, M.A., Mecca, T., Macedo, E.C., Pascual-Leone, A., Boggio, P.S., 2008. Transcranial direct current stimulation of the prefrontal cortex modulates the desire for specific foods. *Appetite* 51, 34–41.
- Goldman-Rakic, P.S., Selemon, L.D., Schwartz, M.L., 1984. Dual pathways connecting the dorsolateral prefrontal cortex with the hippocampal formation and parahippocampal cortex in the rhesus monkey. *Neuroscience* 12, 719–743.
- Hajek, T., Kozeny, J., Kopecek, M., Alda, M., Hoschl, C., 2008. Reduced subgenual cingulate volumes in mood disorders: a meta-analysis. *J. Psychiatry Neurosci.* 33, 91–99.
- Halgren, E., Marinkovic, K., Chauvel, P., 1998. Generators of the late cognitive potentials in auditory and visual oddball tasks. *Electroencephalogr. Clin. Neurophysiol.* 106, 156–164.
- Hecht, D., Walsh, V., Lavidor, M., 2010. Transcranial direct current stimulation facilitates decision making in a probabilistic guessing task. *J. Neurosci.* 30, 4241–4245.
- Hlinka, J., Alexakis, C., Diukova, A., Liddle, P.F., Auer, D.P., 2010. Slow EEG pattern predicts reduced intrinsic functional connectivity in the default mode network: an inter-subject analysis. *Neuroimage* 53, 239–246.
- Iyer, M.B., Mattu, U., Grafman, J., Lomarev, M., Sato, S., Wassermann, E.M., 2005. Safety and cognitive effect of frontal DC brain polarization in healthy individuals. *Neurology* 64, 872–875.
- Jaspers, H.H., 1958. The ten twenty electrode system of the international federation. *Electroencephalogr. Clin. Neurophysiol.* 10, 371–375.
- Jo, J.M., Kim, Y.H., Ko, M.H., Ohn, S.H., Joen, B., Lee, K.H., 2009. Enhancing the working memory of stroke patients using tDCS. *Am. J. Phys. Med. Rehabil.* 88, 404–409.
- Johnson, J.D., Muftuler, L.T., Rugg, M.D., 2008. Multiple repetitions reveal functionally and anatomically distinct patterns of hippocampal activity during continuous recognition memory. *Hippocampus* 18, 975–980.
- Jones, M.W., Wilson, M.A., 2005. Theta rhythms coordinate hippocampal-prefrontal interactions in a spatial memory task. *PLoS Biol.* 3, e402.
- Kang, E.K., Baek, M.J., Kim, S., Paik, N.J., 2009. Non-invasive cortical stimulation improves post-stroke attention decline. *Restor. Neurol. Neurosci.* 27, 645–650.
- Kilner, J.M., Mattout, J., Henson, R., Friston, K.J., 2005. Hemodynamic correlates of EEG: a heuristic. *Neuroimage* 28, 280–286.
- Kimbrell, T.A., Little, J.T., Dunn, R.T., Frye, M.A., Greenberg, B.D., Wassermann, E.M., Repella, J.D., Danielson, A.L., Willis, M.W., Benson, B.E., Speer, A.M., Osuch, E., George, M.S., Post, R.M., 1999. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol. Psychiatry* 46, 1603–1613.
- Kincses, T.Z., Antal, A., Nitsche, M.A., Bartfai, O., Paulus, W., 2004. Facilitation of probabilistic classification learning by transcranial direct current stimulation of the prefrontal cortex in the human. *Neuropsychologia* 42, 113–117.
- Klaver, P., Smid, H.G., Heinze, H.J., 1999. Representations in human visual short-term memory: an event-related brain potential study. *Neurosci. Lett.* 268, 65–68.
- Knoch, D., Nitsche, M.A., Fischbacher, U., Eisenegger, C., Pascual-Leone, A., Fehr, E., 2008. Studying the neurobiology of social interaction with transcranial direct current stimulation—the example of punishing unfairness. *Cereb. Cortex* 18, 1987–1990.
- Koenigs, M., Ukeberuwa, D., Campion, P., Grafman, J., Wassermann, E., 2009. Bilateral frontal transcranial direct current stimulation: failure to replicate classic findings in healthy subjects. *Clin. Neurophysiol.* 120, 80–84.
- Kumari, V., Gray, J.A., ffytche, D.H., Mitterschiffhaller, M.T., Das, M., Zachariah, E., Vythelingum, G.N., Williams, S.C., Simmons, A., Sharma, T., 2003. Cognitive effects of nicotine in humans: an fMRI study. *Neuroimage* 19, 1002–1013.
- Lang, N., Siebner, H.R., Ward, N.S., Lee, L., Nitsche, M.A., Paulus, W., Rothwell, J.C., Lemon, R.N., Frackowiak, R.S., 2005. How does transcranial DC stimulation of the primary motor cortex alter regional neuronal activity in the human brain? *Eur. J. Neurosci.* 22, 495–504.
- Laufs, H., 2008. Endogenous brain oscillations and related networks detected by surface EEG-combined fMRI. *Hum. Brain Mapp.* 29, 762–769.
- Liebetanz, D., Nitsche, M.A., Tergau, F., Paulus, W., 2002. Pharmacological approach to the mechanisms of transcranial DC-stimulation-induced after-effects of human motor cortex excitability. *Brain* 125, 2238–2247.
- Maihöfner, C., Ropohl, A., Reulbach, U., Hiller, M., Elstner, S., Kornhuber, J., Sperling, W., 2005. Effects of repetitive transcranial magnetic stimulation in depression: a magnetoencephalographic study. *NeuroReport* 16, 1839–1842.
- Marshall, L., Molle, M., Hallschmid, M., Born, J., 2004. Transcranial direct current stimulation during sleep improves declarative memory. *J. Neurosci.* 24, 9985–9992.
- Marshall, L., Molle, M., Siebner, H.R., Born, J., 2005. Bifrontal transcranial direct current stimulation slows reaction time in a working memory task. *BMC Neurosci.* 6, 23.
- Marshall, L., Helgadottir, H., Molle, M., Born, J., 2006. Boosting slow oscillations during sleep potentiates memory. *Nature* 444, 610–613.
- Mayberg, H.S., Brannan, S.K., Tekell, J.L., Silva, J.A., Mahurin, R.K., McGinnis, S., Jerabek, P.A., 2000. Regional metabolic effects of fluoxetine in major depression: serial changes and relationship to clinical response. *Biol. Psychiatry* 48, 830–843.
- Mayberg, H.S., Lozano, A.M., Voon, V., McNeely, H.E., Seminowicz, D., Hamani, C., Schwab, J.M., Kennedy, S.H., 2005. Deep brain stimulation for treatment-resistant depression. *Neuron* 45, 651–660.
- McCormick, L.M., Yamada, T., Yeh, M., Brumm, M.C., Thatcher, R.W., 2009. Antipsychotic effect of electroconvulsive therapy is related to normalization of subgenual cingulate theta activity in psychotic depression. *J. Psychiatr. Res.* 43, 553–560.
- Menon, V., Ford, J.M., Lim, K.O., Glover, G.H., Pfefferbaum, A., 1997. Combined event-related fMRI and EEG evidence for temporal-parietal cortex activation during target detection. *NeuroReport* 8, 3029–3037.
- Merzagora, A.C., Foffani, G., Panyavin, I., Mordillo-Mateos, L., Aguilar, J., Onaral, B., Oliviero, A., 2009. Prefrontal hemodynamic changes produced by anodal direct current stimulation. *Neuroimage* 49, 2304–2310.
- Mulert, C., Jager, L., Schmitt, R., Bussfeld, P., Pogarell, O., Moller, H.J., Juckel, G., Hegerl, U., 2004. Integration of fMRI and simultaneous EEG: towards a comprehensive understanding of localization and time-course of brain activity in target detection. *Neuroimage* 22, 83–94.
- Nitsche, M.A., Paulus, W., 2000. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *J. Physiol.* 527 (Pt 3), 633–639.
- Nitsche, M.A., Paulus, W., 2001. Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology* 57, 1899–1901.
- Nitsche, M.A., Liebetanz, D., Tergau, F., Paulus, W., 2002. Modulation of cortical excitability by transcranial direct current stimulation. *Nervenarzt* 73, 332–335.
- Nitsche, M.A., Fricke, K., Henschke, U., Schlittler, A., Liebetanz, D., Lang, N., Henning, S., Tergau, F., Paulus, W., 2003a. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. *J. Physiol.* 553, 293–301.
- Nitsche, M.A., Liebetanz, D., Antal, A., Lang, N., Tergau, F., Paulus, W., 2003b. Modulation of cortical excitability by weak direct current stimulation—technical, safety and functional aspects. *Suppl. Clin. Neurophysiol.* 56, 255–276.
- Nitsche, M.A., Nitsche, M.S., Klein, C.C., Tergau, F., Rothwell, J.C., Paulus, W., 2003c. Level of action of cathodal DC polarisation induced inhibition of the human motor cortex. *Clin. Neurophysiol.* 114, 600–604.
- Nitsche, M.A., Schauenburg, A., Lang, N., Liebetanz, D., Exner, C., Paulus, W., Tergau, F., 2003d. Facilitation of implicit motor learning by weak transcranial direct current stimulation of the primary motor cortex in the human. *J. Cogn. Neurosci.* 15, 619–626.
- Nitsche, M.A., Seeber, A., Frommann, K., Klein, C.C., Rochford, C., Nitsche, M.S., Fricke, K., Liebetanz, D., Lang, N., Antal, A., Paulus, W., Tergau, F., 2005. Modulating parameters of excitability during and after transcranial direct current stimulation of the human motor cortex. *J. Physiol.* 568, 291–303.
- Nitsche, M.A., Cohen, L.G., Wassermann, E.M., Priori, A., Lang, N., Antal, A., Paulus, W., Hummel, F., Boggio, P.S., Fregni, F., Pascual-Leone, A., 2008. Transcranial direct current stimulation: state of the art 2008. *Brain Stimul.* 1, 206–223.
- Ohn, S.H., Park, C.I., Yoo, W.K., Ko, M.H., Choi, K.P., Kim, G.M., Lee, Y.T., Kim, Y.H., 2008. Time-dependent effect of transcranial direct current stimulation on the enhancement of working memory. *NeuroReport* 19, 43–47.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Pae, J.S., Kwon, J.S., Youn, T., Park, H.J., Kim, M.S., Lee, B., Park, K.S., 2003. LORETA imaging of P300 in schizophrenia with individual MRI and 128-channel EEG. *Neuroimage* 20, 1552–1560.

- Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Nitsche, M., Reisinger, E., Padberg, F., 2008. Skin lesions after treatment with transcranial direct current stimulation (tDCS). *Brain Stimul.* 1, 386–387.
- Palm, U., Keeser, D., Schiller, C., Fintescu, Z., Reisinger, E., Baghai, T.C., Mulert, C., Padberg, F., 2009. Transcranial direct current stimulation in a patient with therapy-resistant major depression. *World J. Biol. Psychiatry* 10, 632–635.
- Pascual-Marqui, R.D., 2002. Standardized low-resolution brain electromagnetic tomography (sLORETA): technical details. *Meth. Find. Exp. Clin. Pharmacol.* 24 (Suppl D), 5–12.
- Pascual-Marqui, R.D., Michel, C.M., Lehmann, D., 1994. Low resolution electromagnetic tomography: a new method for localizing electrical activity in the brain. *Int. J. Psychophysiol.* 18, 49–65.
- Pascual-Marqui, R.D., Esslen, M., Kochi, K., Lehmann, D., 2002. Functional imaging with low-resolution brain electromagnetic tomography (LORETA): a review. *Meth. Find. Exp. Clin. Pharmacol.* 24 (Suppl C), 91–95.
- Pizzagalli, D., Pascual-Marqui, R.D., Nitschke, J.B., Oakes, T.R., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Koger, J.V., Benca, R.M., Davidson, R.J., 2001. Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am. J. Psychiatry* 158, 405–415.
- Pizzagalli, D.A., Oakes, T.R., Fox, A.S., Chung, M.K., Larson, C.L., Abercrombie, H.C., Schaefer, S.M., Benca, R.M., Davidson, R.J., 2004. Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Mol. Psychiatry* 9 (325), 393–405.
- Polich, J., 2007. Updating P300: an integrative theory of P3a and P3b. *Clin. Neurophysiol.* 118, 2128–2148.
- Poreisz, C., Boros, K., Antal, A., Paulus, W., 2007. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res. Bull.* 72, 208–214.
- Priori, A., Mameli, F., Cogiamanian, F., Marceglia, S., Tiriticco, M., Mrakic-Sposta, S., Ferrucci, R., Zago, S., Polezzi, D., Sartori, G., 2008. Lie-specific involvement of dorsolateral prefrontal cortex in deception. *Cereb. Cortex* 18, 451–455.
- Purpura, D.P., McMurtry, J.G., 1965. Intracellular activities and evoked potential changes during polarization of motor cortex. *J. Neurophysiol.* 28, 166–185.
- Ramsay, T.Z., Liptrot, M.G., Skimminge, A., Lund, T.E., Sidaros, K., Christensen, M.S., Baare, W., Paulson, O.B., Jernigan, T.L., 2009. Regional activation of the human medial temporal lobe during intentional encoding of objects and positions. *Neuroimage* 47, 1863–1872.
- Rigonatti, S.P., Boggio, P.S., Myczkowski, M.L., Otta, E., Fiquer, J.T., Ribeiro, R.B., Nitsche, M.A., Pascual-Leone, A., Fregni, F., 2008. Transcranial direct stimulation and fluoxetine for the treatment of depression. *Eur. Psychiatry* 23, 74–76.
- Siapas, A.G., Lubenov, E.V., Wilson, M.A., 2005. Prefrontal phase locking to hippocampal theta oscillations. *Neuron* 46, 141–151.
- Sparing, R., Dafotakis, M., Meister, I.G., Thirugnanasambandam, N., Fink, G.R., 2007. Enhancing language performance with non-invasive brain stimulation—A transcranial direct current stimulation study in healthy humans. *Neuropsychologia* 46, 261–268.
- Speer, A.M., Kimbrell, T.A., Wassermann, E.M., Repella, J.D., Willis, M.W., Herscovitch, P., Post, R.M., 2000. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biol. Psychiatry* 48, 1133–1141.
- Stagg, C.J., Best, J.G., Stephenson, M.C., O’Shea, J., Wylezinska, M., Kincses, Z.T., Morris, P.G., Matthews, P.M., Johansen-Berg, H., 2009. Polarity-sensitive modulation of cortical neurotransmitters by transcranial stimulation. *J. Neurosci.* 29, 5202–5206.
- Tadini, L., El-Nazer, R., Brunoni, A.R., Williams, J., Carvas, M., Boggio, P., Priori, A., Pascual-Leone, A., Fregni, F., 2010. Cognitive, mood, and electroencephalographic effects of noninvasive cortical stimulation with weak electrical currents. *J. ECT.* doi:10.1097/YCT.0b013e3181e631a8.
- van den Heuvel, M.P., Mandl, R.C., Kahn, R.S., Hulshoff Pol, H.E., 2009. Functionally linked resting-state networks reflect the underlying structural connectivity architecture of the human brain. *Hum. Brain Mapp.* 30, 3127–3141.
- Vandermeeren, Y., Jamart, J., Osseman, M., 2010. Effect of tDCS with an extracephalic reference electrode on cardio-respiratory and autonomic functions. *BMC Neurosci.* 11, 38.
- Vitacco, D., Brandeis, D., Pascual-Marqui, R., Martin, E., 2002. Correspondence of event-related potential tomography and functional magnetic resonance imaging during language processing. *Hum. Brain Mapp.* 17, 4–12.
- Wacker, J., Dillon, D.G., Pizzagalli, D.A., 2009. The role of the nucleus accumbens and rostral anterior cingulate cortex in anhedonia: integration of resting EEG, fMRI, and volumetric techniques. *Neuroimage* 46, 327–337.
- Wassermann, E.M., Grafman, J., 2005. Recharging cognition with DC brain polarization. *Trends Cogn. Sci.* 9, 503–505.
- Watson, D., Clark, L.A., Tellegen, A., 1988. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J. Pers. Soc. Psychol.* 54, 1063–1070.
- Wittchen, H.U., Müller, N., 1998. M-CIDI-S. *Gesundheitswesen* 60, 95–100.
- Zumsteg, D., Friedman, A., Wennberg, R.A., Wieser, H.G., 2005a. Source localization of mesial temporal interictal epileptiform discharges: correlation with intracranial foramen ovale electrode recordings. *Clin. Neurophysiol.* 116, 2810–2818.
- Zumsteg, D., Wennberg, R.A., Treyer, V., Buck, A., Wieser, H.G., 2005b. H2(15)O or 13NH3 PET and electromagnetic tomography (LORETA) during partial status epilepticus. *Neurology* 65, 1657–1660.
- Zumsteg, D., Lozano, A.M., Wennberg, R.A., 2006. Depth electrode recorded cerebral responses with deep brain stimulation of the anterior thalamus for epilepsy. *Clin. Neurophysiol.* 117, 1602–1609.