



## Effects of transcranial direct current stimulation (tDCS) on behaviour and electrophysiology of language production

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### ABSTRACT

Excitatory anodal transcranial direct current stimulation (A-tDCS) over the left dorsal prefrontal cortex (DPFC) has been shown to improve language production. The present study examined neurophysiological underpinnings of this effect. In a single-blinded within-subject design, we traced effects of A-tDCS compared to sham stimulation over the left DPFC using electrophysiological and behavioural correlates during overt picture naming. Online effects were examined during A-tDCS by employing the semantic interference (SI)-Effect – a marker that denotes the functional integrity of the language system. The behavioural SI-Effect was found to be reduced, whereas the electrophysiological SI-Effect was enhanced over left compared to right temporal scalp-electrode sites. This modulation is suggested to reflect a superior tuning of neural responses within language-related generators. After –(offline) effects of A-tDCS were detected in the delta frequency band, a marker of neural inhibition. After A-tDCS there was a reduction in delta activity during picture naming and the resting state, interpreted to indicate neural disinhibition. Together, these findings demonstrate electrophysiological modulations induced by A-tDCS of the left DPFC. They suggest that A-tDCS is capable of enhancing neural processes during and after application. The present functional and oscillatory neural markers could detect positive effects of prefrontal A-tDCS, which could be of use in the neuro-rehabilitation of frontal language functions.

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### 1. Introduction

Alterations of language production, as expressed via difficulties in word finding or naming, are a hall mark symptom of Alzheimer's disease (AD) and aphasia, but they also occur during normal aging (Burke & Shafto, 2004; Burke & MacKay, 1997). Within these sub-populations the improvement of language production skills is therefore of particular interest.

According to the following neuro-cognitive network model (Friston, Frith, Liddle, & Frackowiak, 1991; Frith, Friston, Liddle, & Frackowiak, 1991), language production requires the interplay of at least two structures: the temporally distributed “representational” system and the prefrontal “executive” system that is able to modify (i.e., inhibit/excite) the responsiveness of neurons in the representational system. In other terms, generating specific kinds of words (e.g., animals) is viewed to involve cognitive

control of the dorsal prefrontal cortex (DPFC) on neural activations within the representational system. Likewise, in patients with word finding difficulties (i.e., anomia), the frontal influence on representational regions can be impaired (Biegler, Crowther, & Martin, 2008).

Following this language production model, the excitation and recuperation of prefrontal regions can be expected to improve language production skills. Indeed, word production can be influenced by the application of non-invasive excitatory neuro-stimulatory techniques, as delivered via transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) (e.g., Cerruti & Schlaug, 2009; de Vries et al., 2010; Floel, Rosser, Michka, Knecht, & Breitenstein, 2008; Sparing, Dafotakis, Meister, Thirugnanasambandam, & Fink, 2008). Particularly though, high-frequency repetitive (r) TMS over the left and right DPFC has been shown to improve naming in AD patients (Cotelli et al., 2011, 2006; Cotelli, Manenti, Cappa, Zanetti, & Miniussi, 2008). In a similar way anodal (A)-tDCS over the left DPFC results in a better naming performance in healthy participants (Fertonani, Rosini, Cotelli, Rossini, & Miniussi, 2010; Iyer et al., 2005) and aphasic patients (Baker, Rorden, & Fridriksson, 2010).

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Such promising findings suggest an application of the practicable and safe prefrontal A-tDCS in the neuro-rehabilitation of language functions. Yet, the neural underpinnings of this effect remain elusive. Most commonly behavioural markers are used to quantify stimulation-induced effects. These measures are selected during (thereafter termed online) and shortly after (thereafter termed offline) tDCS delivery. For a better understanding of stimulation-evoked neural modulations, it is however necessary to include also neuro-physiological markers that are sensitive to specific functional processes.

The weak direct currents applied in tDCS are able to induce polarity-dependent neuro-modulatory changes (Schlaug, Renga, & Nair, 2008). Dependent on the electrode that is placed over the brain regions of interest (i.e., anode or cathode), increasing or decreasing cortical excitability has been found (Priori, 2003; see Utz, Dimova, Oppenlander, & Kerkhoff, 2010 for current review). As shown in animal models (e.g., Creutzfeldt, Fromm, & Kapp, 1962; Purpura & McMurtry, 1965) and in humans (Nitsche & Paulus, 2001), anodal tDCS induces a de-polarization, whereas cathodal tDCS seems to cause a hyper-polarization of the resting membrane potentials in the underlying brain tissue. In humans, neural excitability changes as promoted by tDCS have mostly been traced in primary sensory and motor systems by electroencephalogram (EEG). As such neural activity changes have been reported using visual (Accornero, Li, La Riccia, & Gregori, 2007; Antal, Kincses, Nitsche, Bartfai, & Paulus, 2004) and sensory (Dieckhofer et al., 2006; Matsunaga, Nitsche, Tsuji, & Rothwell, 2004) event-related potentials (ERPs) as well as motor-related spectral EEG parameters (Antal, Varga, Kincses, Nitsche, & Paulus, 2004; Polania, Nitsche, & Paulus, 2011). Two recent studies on working memory combined EEG and tDCS to track offline neuro-modulatory correlates of A-tDCS over the left DPFC (Keeser et al., 2011; Zaehle, Sandmann, Thorne, Jancke, & Herrmann, 2011). Both studies reported poststimulatory changes in neural oscillations with reductions in slow-wave delta activity during task performance and the resting state or amplifications of the theta and alpha frequency power, respectively.

To our best knowledge, the present study is the first report of synchronous tDCS–EEG in the assessment of language production. According to the above-mentioned literature one can expect that prefrontal A-tDCS as compared to sham stimulation (S-tDCS) influences neural activity patterns within the functional language circuit. It is the scope of the study to gain more insights into the online and offline neuro-modulatory changes and thus support the generation of more powerful hypotheses on existing tDCS effects. We therefore sample the following electrophysiological markers during and after tDCS application using suitable online and offline paradigms:

Online A-tDCS effects are assessed by the semantic interference (SI)-Effect. The SI-Effect can be related to the functional integrity of the language production system mainly due to two reasons: The marker emanates mainly from the involvement of left-hemispheric temporal-to-prefrontal language-related neural generators (Maess, Friederici, Damian, Meyer, & Levelt, 2002; Schnur et al., 2009) and is found to be exaggerated in aphasic patients with reduced frontal inhibitory functions (Biegler et al., 2008). Semantic interference is robustly evoked in semantic blocking paradigms (Abdel Rahman & Melinger, 2007, 2011; Damian, Vigliocco, & Levelt, 2001), where subjects have to name repeatedly presented pictures of objects displayed in semantically homogeneous (e.g., cherries among grapes, pear, orange) or heterogeneous (e.g., cherries among fly, cocktail, bed, edding) contexts. Employing the semantic blocking paradigm, different demands are posed on the language system: When objects are named in the presence of categorical similar objects (i.e., homogenous blocks), the target word must be selected from co-activated and competing alternatives. Such lexical-semantic competition is reduced when the

target object appears among semantically unrelated objects (i.e., heterogeneous blocks). The two conditions therefore induce a pronounced difference in semantic interference within the language system. This SI-Effect that can be traced in verbal performance (Abdel Rahman & Melinger, 2011; Schnur et al., 2009) and left temporo-parietal electroencephalic (Aristei, Melinger, & Rahman, 2011) or magneto encephalic (Maess et al., 2002) brain signatures during language production.

Offline tDCS effects are examined during picture naming (Fertonani et al., 2010) and the resting state (Keeser et al., 2011) by the delta band activity – an established spectral marker of neural integrity. This low frequency activity is viewed to reflect a quantitative marker of neural inhibition, indicating the amount of unspecific neural processes. The later assumption is mostly derived from the delta power and synchronicity excess in psychiatric (e.g., Boutros et al., 2008; Koenig et al., 2005) as well as neurologic (aphasia, Spironelli & Angrilli, 2009; Szelies, Mielke, Kessler, & Heiss, 2002) disorders. Furthermore, hypofrontality in schizophrenia is related to delta power increase (Spironelli, Angrilli, Calogero, & Stegagno, 2011; Winterer et al., 2000), while language recovery in aphasia is associated with delta power decreases (Hensel, Rockstroh, Berg, Elbert, & Schonle, 2004; Meinzer et al., 2004) – suggesting a sensitivity of the delta band to the integrity and recuperation of neural responses in frontal regions including the language system. Here, the delta band activity is sampled during overt picture naming, as well as the eyes closed resting state EEG and thereafter quantified by its global spectral power (PWR) and global field synchronization (GFS). While the PWR is indicative of the signal strength across all electrode channels for a given frequency, the GFS represents a single reference-independent EEG marker that reflects the amount of synchronized activity (Jann et al., 2009; Koenig et al., 2001, 2005).

This single-blinded crossover placebo-controlled A-tDCS–EEG study is apt to enrich the pilot literature on stimulation-induced neuromodulations within the language system. For the online experiment a difference effect is analysed in order to control for stimulation-induced artefacts. The offline paradigms are adapted from prior research approaches to increase comparability. The selected biomarkers constitute established indices of specific language-related functions (i.e., the SI-Effect) and global neural processes (i.e., delta activity). We anticipate that the application of A-tDCS over the left DPFC leads to enhanced prefrontal processes. These changes in neural activity patterns are expected to modulate the selected electrophysiological markers in an excitatory way. The observed A-tDCS effects are discussed within the neuro-cognitive model of language production (Friston et al., 1991; Frith et al., 1991).

The A-tDCS effects are anticipated to be subtle; a challenge for clinical as well as experimental tDCS applications. Recent studies have denoted factors that influence the efficacy of tDCS like genetic predisposition (Antal et al., 2010), electrode position (Moliadze, Antal, & Paulus, 2010), stimulation duration and intensity (see Nitsche et al., 2008 for review). In behavioural measures the detection of tDCS effects has been optimized using data normalizations (Fertonani et al., 2010) and absolute response time cutoffs (Ross, McCoy, Volk, Coslett, & Olson, 2010). In order to improve the signal-to-noise-ratio the present study employs a large number of stimuli and absolute thresholds in behavioural data analysis. Because this is the first study to examine neurobiological underpinnings of prefrontal A-tDCS on language production, it is considered as a hypothesis-generating study.

## 2. Materials and methods

### 2.1. Subjects

Twenty volunteers (10 females), aged from 19 to 31 years (mean age 23.5, SD 3.7) were studied after obtaining ethical committee approval and written informed

**Table 1**  
Overview of the study procedure.

Order	Procedural phase	tDCS	Duration	Session 1		Session 2	
				Paradigm	Duration	Paradigm	Duration
1	Training period	No		Semantic blocking	10 min	Picture naming	5 min
2	Pre-experiment	Yes	7 min				
<i>Technical break ~1 min</i>							
3	Online experiment	Yes	30 min	Semantic blocking	30 min	Semantic blocking	30 min
<i>Technical break ~1–2 min</i>							
4	Offline experiment	No		Picture naming	2 min	Picture naming	2 min
				Resting EEG	4 min	Resting EEG	4 min
5	Post-experiment	No		Stimulation questionnaire	5 min	Stimulation questionnaire	5 min

consent. All participants had a similar level of education (mean duration of education 13 years, SD 1.6) and were native Swiss-German or German speakers. According to the Oldfield Handedness Questionnaire the subjects were right-handed and reported normal or corrected-to-normal visual acuity. Neurological (e.g., migraine) and psychiatric (e.g., depression) screenings were negative. Subjects were further instructed to omit the intake of coffee, alcohol, nicotine and tea up to 6 h before the assessments. Note, for the online (during tDCS) experiment the behavioural data of all subjects was analysed, while the ERP data of two subjects (2 females) had to be excluded, due to technical problems during the synchronous tDCS–EEG measurements. For the offline (after tDCS) experiment, the EEG and behavioural datasets of all 20 subjects were included. All subjects received payment after completion of the study.

## 2.2. Stimuli

The stimulus set consisted of 75 colored 207 × 207 pixel photographs of common objects originating from 15 common living and non-living semantic categories (for examples see below).

## 2.3. Experimental paradigms

The present study employed two experimental paradigms as described below: For the online experiment the established semantic blocking paradigm was employed. During the offline experiment, the simple picture naming task was assessed (e.g., Fertonani et al., 2010).

**Semantic blocking paradigm:** Each of the 75 object picture was presented in a categorically homogeneous block consisting of 5 objects from the same semantic category (e.g., “fruits”: apple, cherries, grapes, pear, and orange) and in a categorically heterogeneous block consisting of 5 semantically unrelated objects (e.g., cherry [fruits], fly [insects], cocktail [beverages], bed [furniture] and pen [stationery]). There were 15 homogeneous and 15 heterogeneous groups, within each block visual similarity and phonological overlap of pictures and their names were minimized. During the semantic blocking paradigm, each of the homogenous and heterogeneous blocks was presented in 5 consecutive naming cycles (here referred to as block repetitions 1 to 5) with the 5 pictures appearing randomly and in sequential order during each naming cycle. All together, the paradigm therefore included 750 trials, i.e., 15 homogeneous blocks × 5 pictures × 5 block repetitions and 15 heterogeneous blocks × 5 pictures × 5 block repetitions. During each trial a single object picture was displayed for at most 2000 ms on a computer screen, followed by a fixation cross in the middle of the screen for another 1500 ms. Subjects overtly named each object; vocal reaction time (vRT) was measured starting from picture presentation-onset by using a microphone. Presentation was terminated by the verbalisation (if vRT < 2000 ms) or after 2000 ms, which resulted in the appearance of the fixation cross. In session 1, a specific pseudo-randomized order of homogeneous and heterogeneous blocks was created for each participant; while for session 2 the individualised order was reversed. After block 7, 16 and 24 a self-paced short break was administered.

**Picture naming paradigm:** The set of 75 pictures was presented randomly with the trial chronometry as described above.

## 2.4. Transcranial direct current stimulation (tDCS)

Transcranial DCS was delivered by a battery-driven direct current stimulator (Magstim Eldith 1 Channel DC Stimulator Plus, Germany). The stimulation electrodes were surrounded by a flat sponge soaked in an isotonic NaCl solution and coated with Aqua Sonic™ ultrasound transmission gel in order to ease skin irritation. A-tDCS was delivered over the left DPFC via a 5 cm × 7 cm electrode that was placed halfway between the EEG points F3 and AF3 of the 10–20 EEG system (Fitzgerald, Maller, Hoy, Thomson, & Daskalakis, 2009). Fixation of the head electrode was realized by an EEG cap. The extra-encephalic cathodal tDCS reference electrode (7 cm × 7 cm), proven safe in healthy subjects (Vandermeeren, Jamart, & Osseman, 2010), was affixed on the right shoulder with a skin-friendly cello tape. Before the experiment, a constant direct current of 1.5 mA was applied for 7 min (=pre-experimental tDCS) during a resting state. Subsequently, the

30 min online tDCS experiment was conducted (adding up to a total of 37 min tDCS): Subjects were instructed to start the experiment after around 1 min (this onset duration was determined by the sham condition) via a mouse button press. During Sham (S)-tDCS the procedure was exactly the same, with the exception that the tDCS was turned off after 60 s during both, the pre-experimental and experimental t-DCS. At the beginning and at the end of each tDCS condition there was a ramping period of 10 s. The study design was single-blinded. As such, the subjects were kept naïve about when and how often A-tDCS was applied. Potential tDCS side effects were assessed with a questionnaire (see below) at the end of each session.

## 2.5. Procedure

The measurements took place at the Department of Psychiatric Neurophysiology, University Hospital of Psychiatry in Bern. The present study employs a single-blinded within-subject placebo-controlled design. The overview of the study procedure is provided in Table 1: Each of the participants passed therefore 2 study sessions (here termed sessions 1 and 2) within an interval of 2–4 days. During each session A-tDCS or sham stimulation was applied in counterbalanced order. Sessions lasted at most 2 h, each starting with a training period in order to familiarize subjects with the experimental setting and adjust the sensitivity of the microphone if needed. In the following the different procedural phases are describe in their temporal order for the A-tDCS example:

1. Training phase: For the training phases of session 1 and 2, subjects were instructed to name all 75 objects using one specific term for each object with respect to their native (German and Swiss German) tongue. In session 1 only, a training version of the semantic blocking paradigm (requiring two naming cycles lasting ~10 min) was further performed to obtain a stable baseline performance. After the training period, the EEG electrodes were mounted.
2. Pre-experimental phase: Participants received a 7 min A-tDCS, as reported in prior online protocols (Fecteau et al., 2007). During this period artefact electrodes as well as technical failures were corrected.
3. Online experimental phase: The online experiment was started after a technical break of approximately 1 min and A-tDCS was delivered for 30 min. Participants were instructed to name objects fast and correctly, while avoiding noise (e.g., coughing) and movements.
4. Offline experimental phase: The offline phase was started approximately 1–2 min after the end of the online experiment. During the technical break the EEG acquisition was re-started and electrode signals were re-checked. In the first part of the offline experiment, the picture naming paradigm was conducted lasting around 2 min. Participants named 75 objects without explicit speed instruction. In the second part, a 4 min eyes closed resting state EEG was recorded.
5. Post-experimental phase: The stimulation questionnaire was completed.

## 2.6. Behavioural data acquisition and analysis

### 2.6.1. Stimulation questionnaire

Perceptual sensations induced by the A- and S-tDCS conditions were assessed with a translated and adapted version of the standardized questionnaire published by Fertonani and colleagues (2009). Items, each representing a distinct perceptual sensation, were chosen with respect to possible tDCS side effects (Poreisz, Boros, Antal, & Paulus, 2007). Subjects were asked to evaluate the intensity of each sensation item on a 5-point rating scale (0 = none to 5 = strong; missings were treated as 0) and indicate, whether the sensation influenced their performance (5-point rating scale), and when it started and ended (beginning = 1, middle = 2, end = 3 of the experiment). For each sensation item a single-tailed paired *t*-test was calculated to test for differences between the stimulation conditions. Finally, subjects provided their naïve judgment concerning the stimulation condition using five categories, i.e., no stimulation/only beginning/only at the end/during the whole experiment/others. To compare the observed counts to the expected counts under the null hypothesis (equal distribution)  $\chi^2$  tests were employed. Overall, the questionnaire was included

to measure possible differences in awareness between the stimulation conditions and thus evaluate the single-blinded design.

### 2.6.2. Behavioural data acquisition and analysis

Stimulus presentation and response recording were conducted using E-Prime software Version 2.0 (Psychology Software Tools Inc., Pittsburgh, Pennsylvania, USA). The object pictures appeared centrally on a grey-shaded monitor screen mounted at a constant eye-to-screen distance. Participants viewed the display in an electrically shielded and dimly lit EEG cabin maintaining a comfortable position with their arms resting on a table and their mouth in proximity to the microphone. The microphone was plugged to the E-prime response box recording the verbal response times (vRT) with respect to the picture onset. Naming errors, tip of the tongue phenomena and accidental triggering of the voice key by e.g., non-verbal sounds were encoded manually as error trials by the experimenter.

For the online experiment, the behavioural SI-Effect was analysed. Using the semantic blocking paradigm it has been repeatedly demonstrated that the SI-Effect is observed only after first presentation (Abdel Rahman & Melinger, 2007; Damian et al., 2001). From the second presentation onwards interference effects are found to remain present and also stable over subsequent repetitions (Abdel Rahman & Melinger, 2011). Because our main interest was the presence and potential modulation of the SI-Effect, and because analyses across all presentations except for the first one is a well-established procedure in the blocking paradigm, all analyses were carried out on the collapsed data over the repetitions 2–5. Further, error rates were not statistically analysed because they are known to be at floor (Maess et al., 2002). As mentioned earlier tDCS effects on the vRTs were expected to be small relative to the large data variability (see also, Fertonani et al., 2010). Response times  $\leq 1000$  ms are known to be more stable and less susceptible to failure processes (Ratcliff, 1993). Hence, stimulation effects could be expected to occur for shorter vRTs. We therefore performed the statistical analyses using two different absolute cut-offs (Ratcliff, 1993):  $<300/>1300$  ms (Maess et al., 2002) and  $<300/>1000$  ms. Selected individual trials of a given subject and experimental condition were averaged using the median due to the robustness of this measure towards the positive skew of RT distributions (McCormack & Wright, 1964). Subsequently, each of the vRT data obtained during online and offline experiments were subjected to an omnibus repeated measures analysis of variance (rm ANOVA). Huynh-Feldt corrected values are reported. Significant main effects and interactions of interest were assessed in a post-hoc analysis by means of paired *t*-tests. In accordance with our scope, we calculated the SI-Effect, i.e., measured as the difference ( $\Delta$ ) between the vRTs of the homogenous and the heterogeneous conditions.

For the offline vRT data of the picture naming paradigm, the median of individual correct trials per subject and experimental condition were computed. A two-tailed paired *t*-test was then conducted on the vRT data in the A-tDCS compared to the S-tDCS condition.

## 2.7. EEG/ERP data acquisition and analysis

The EEG recording was done with a Nihon Kohden Neurofax EEG-1100G and amplifier system (Nihon Kohden, Tokyo, Japan). The recording electrodes were positioned in the electrode cap according to the extended 10–20 system (74 channel montage, Easycap, Falk Minow, Munich, Germany). Two additional electrodes placed beneath the eyes of the participant recorded vertical eye movements (vEOG). C3 and C4 served as EEG recording reference; the ground electrode was placed on the scalp and impedances were kept below 20 kOhms. As stated above, the tDCS electrode was positioned underneath the electrode cap. In consequence, the offline and online EEG data were recorded from a 65 channel recording montage; the following 9 electrode positions were not included during any of the experiments: Fp1, AF7, AF3, F7, F5, F3, F1, FC3, FC1. The EEG was recorded with a band-pass filter of 0.016–120 Hz and digitized at 500 Hz sampling rate.

### 2.7.1. Online tDCS experiment

On the basis of visual inspection of the EEG data for artefacts, 13 additional electrodes were discarded (i.e., Fpz, AFz, Fz, FCz, Cz, F9, FT9, FT7, FC5, T7, C5, C3, C1) due to the tDCS-induced signal contamination. The EEG signals from the remaining 52 scalp electrodes were submitted to an independent component analysis (ICA) to extract artefacts introduced by speech-related muscle activity (e.g., Tran, Craig, Boord, & Craig, 2004) as well as vertical and horizontal eye movements. During word production, the scalp-recorded EEG is contaminated with electromyographic (EMG) activity of cranial muscles involved in the articulation process. The main EMG artefact is not a tonic and continuous activity. Rather it is expressed by short bursts as produced during the articulation itself (Vos et al., 2010) – therefore speech-related artefacts can be expected to exhibit a temporal consistency with the onset of the verbal response (measured by the vRT, criterion 1) and a high factor loading at frontal scalp electrode sites (criterion 2, Vos et al., 2010) including EOG electrode positions (Shackman et al., 2009). The obtained ICs were inspected visually and removed (i.e., 1–3 ICs per subject) when coinciding with these criteria. Thereafter, the EEG data were inspected for sparse/a-rhythmic artefacts, e.g., amplifier bursts, biting artefacts, blinks and electrode jumps. Bad electrodes were replaced by linear interpolation if needed. The continuous EEG was then recalculated to common average reference (Lehmann & Skrandies, 1980; Murray, Brunet, & Michel, 2008), band-pass filtered at 0.5 Hz (12 db/octave) to 18.0 Hz (24 db/octave) including

a 50 Hz notch filter, and segmented into epochs from 0 to 1000 ms post picture onset. Further, a baseline correction using the 400 ms pre-stimulus interval was applied.

The individual averages and grand-mean averages were computed for each experimental condition of interest. As stated above, our main interest concerned the SI-Effect that can be observed in the blocking paradigm only after the first presentation. Therefore the data was averaged across correct trials over repetitions 2 to 5. Prior studies using neuroscientific methods in the blocking paradigm (Maess et al., 2002; Schnur et al., 2009), including an ERP study with the same materials as used here but an independent subject group (Abdel Rahman et al., unpublished data) clearly demonstrate the feasibility of extracting SI-Effects from collapsed ERP data. The SI-Effect of interest was estimated between 200 and 400 ms post stimulus onset in correspondence with previous studies (Aristei et al., 2011; Costa, Strijkers, Martin, & Thierry, 2009). ERP data was pooled over left and right temporo-parietal electrode sites of interest (Aristei et al., 2011), referred to as scalp-Region-of-Interest (ROI). Note, due to methodological caveats of synchronous tDCS-EEG recordings, the ERP analysis can only be conducted remote from the stimulations site. The present ROIs included the mean amplitudes (mAmplitude) of correct response over the electrode sites of P7/TP7 for the left and P8/TP8 for the right side for each subject and experimental condition of interest over the time window of interest (200–400 ms). The obtained amplitude measures were submitted to a rm ANOVA. Huynh-Feldt corrected values are reported. Significant main effects and interactions of interest were explored in a post-hoc analysis using paired *t*-tests and a probability criterion of  $\alpha < 0.05$ .

### 2.7.2. Offline tDCS experiment

In this condition, electrode FC5 had to be discarded from the 65-channel recording montage due to the tDCS sponge. In rare cases, bad electrodes were further replaced by linear interpolation. For the picture naming paradigm, the ICA-driven artefact removal procedure (see above) was applied, to eliminate mainly speech-related muscle movements from the EEG data. The continuous EEG was then re-computed and inspected for sparse artefacts (see above). For the resting state (eyes closed) EEG data, infrequent artefacts were removed in the semiautomatic artefact correction procedure. The EEG data obtained from the picture naming task and the resting state were then re-calculated to common average reference and a 50 Hz notch filter was applied. Subsequently, the artefact-free EEGs were segmented into equally sized epochs, i.e., for the picture naming paradigm epochs ranged from 0 to 2000 ms with respect to the picture-onset, for the resting state EEG the segments lasted 2000 ms. A complex Fast Fourier Transformation (FFT) was applied to the segments of the two data pools. In the following step the PWR (the measure of global spectral power) and GFS (the measure of global spectral synchronicity) were calculated for each subject and stimulation condition. The GFS (e.g., Koenig et al., 2005) is independent of the PWR and constitutes a global measure that does not provide spatial information of synchronized activity. High GFS values for a given frequency indicate that brain activity at the frequency is phase locked, that is, synchronized; changes in the GFS reflect modulations in neural synchronization. Each global measure was compared using paired two-tailed *t*-tests between stimulation conditions (A-tDCS vs. S-tDCS) for each data set (picture naming and resting state). The delta frequency band (1–4 Hz) was analysed in the main focus; for completeness exploratory analyses of the remaining frequency bands, i.e., theta (4.5–7.5 Hz), alpha (8–12 Hz), beta (12.5–30 Hz), gamma (35–45 Hz), were conducted.

## 3. Results

### 3.1. Stimulation questionnaire

All subjects tolerated the tDCS well and reported only marginal perceptual sensations (Table 2). Single-tailed paired *t*-tests for each item indicated higher sensation intensity in the A-tDCS compared to the sham condition regarding itchiness, skin flush and warmth/heat (the latter two items concerning the right shoulder tDCS reference electrode). Overall, the experienced sensations started at the beginning of the experiment, did not last long, nor affected cognitive performance in the A- or S-tDCS conditions. For each study session, 8 out of 20 subjects indicated the appropriate stimulation condition (each  $\chi^2$  test:  $p > 0.05$ ). Only 4 out of 20 participants provided the correct answer twice, i.e., at the end of each stimulation session ( $\chi^2$  test:  $p > 0.05$ ). According to the questionnaire data, potential confounding influences due to subjects' expectations as well as perceptual sensations between A-tDCS and sham stimulation can be considered negligible. There was no reason to reject the single-blinded character of this study on the basis of these results.

**Table 2**  
Overview of the stimulation questionnaire data.

Scale items	S-tDCS	A-tDCS	Comparison	
			t-Value	p-Value < 0.05
<i>Intensity rating (5-point scale): 0 = none, 1 = mild, 2 = moderate, 3 = considerable, 4 = strong</i>				
Itchiness	0.90/0.91	1.25/1.02	1.79	*
Pain	0.05/0.22	0.20/0.41		
Burning	0.65/0.67	0.80/0.95		
Warmth/heat	0.20/0.41	0.35/0.49	1.83	*
Pinching	0.75/0.79	0.75/0.79		
Iron Taste	0.05/0.22	0.05/0.22		
Fatigue	0.50/0.83	0.75/1.07		
Skin Flush	0.16/0.38	0.42/0.61	2.03	*
Effect on performance	0.15/0.37	0.25/0.44		
<i>Duration rating (3-point scale): 1 = begin, 2 = middle, 3 = end of the assessment</i>				
Start	1.20/0.70	1.25/0.64		
End	1.00/0.69	1.35/0.67		

M/SD = mean/standard deviation, S = sham, A = anodal.

### 3.2. Online tDCS experiment

#### 3.2.1. Behavioural data

The vRT data of correct responses is provided in Table 3. The overall absolute error rate was low (1.4%). The cutoff threshold for vRT of <300/>1300 ms vRT led to 0.91% reduction of all correct response trials, while the cutoff <300/>1000 ms resulted in the removal of 3.2% of all correct answers. The omnibus rm ANOVA was conducted on the vRT data (cutoffs <300/>1300 ms) and the within subject factors (i.e., factor levels in parenthesis) “category” [homogenous, heterogeneous] and “stimulation” [A-tDCS, S-tDCS]. The statistical analysis of the vRT data with the cutoffs <300 ms/>1300 ms yielded the expected main effects of the factors “category” ( $F_{1,19} = 257.91, p < 0.05$ ), i.e., the behavioural SI-Effect. There was no significant effect of factor “stimulation” ( $p = 0.9$ ); however, there was a trend in the interaction of the factors “stimulation”  $\times$  “category” ( $F_{1,19} = 3.09, p < 0.1$ ). The rm ANOVA on the vRT data (cutoffs <300 ms and >1000 ms) confirmed the above-mentioned main effect. Important for the present research question, a significant interaction of the factors “stimulation”  $\times$  “category” ( $F_{1,19} = 5.21, p < 0.05$ ) was obtained. The further assessment of this interaction using a post-hoc paired t-test confirmed that the behavioural SI-Effect ( $\Delta vRT_{\text{homogeneous}} - vRT_{\text{heterogeneous}}$ ) was reduced during the A-tDCS compared to sham stimulation ( $t_{19} = 2.28, p < 0.05$ ).

#### 3.2.2. ERP data

The omnibus rm ANOVA on the mean amplitudes over the analysis window of interest and scalp-ROIs (see Fig. 1A) was calculated on the factors “category” [homogenous, heterogeneous], “scalp-ROI” [left, right] and “stimulation” [A-tDCS, S-tDCS]. This statistical analysis indicated a significant main effect to the factor “category” ( $F_{1,17} = 8.87, p < 0.05$ ) confirming the expected differences in ERP signature between homogenous and heterogeneous categories. Furthermore, a significant interaction of “category”  $\times$  “ROI” ( $F_{1,17} = 14.23, p < 0.05$ ) and “ROI”  $\times$  “stimulation” ( $F_{1,17} = 18.22, p < 0.05$ ) as well as a significant triple interaction of “stimulation”  $\times$  “ROI”  $\times$  “category” ( $F_{1,17} = 5.18,$

$p < 0.05$ ) were obtained. In accordance with our assumptions, only the interactions regarding the electrophysiological SI-Effect ( $\Delta m\text{Amp}_{\text{heterogeneous}} - m\text{Amp}_{\text{homogeneous}}$ ) were explored by conducting a post-hoc analysis using paired t-tests (see Fig. 1B): This SI-Effect was significantly increased ( $t_{17} = 3.78, p < 0.05$ ) over the left ( $M = 0.60 \mu\text{V}, SD = 0.64 \mu\text{V}$ ) compared to the right ( $M = -0.07 \mu\text{V}, SE = 0.37 \mu\text{V}$ ) scalp-ROI. For the left scalp-ROI, the SI-Effect was further enhanced ( $t_{17} = 2.12, p \leq 0.05$ ) during A-tDCS ( $M = 0.76 \mu\text{V}, SE = 0.90 \mu\text{V}$ ) compared to sham stimulation ( $M = 0.41 \mu\text{V}, SE = 0.50 \mu\text{V}$ ). During the critical time window, the influence of confounding speech-related artefacts can be considered to be minimal because the mean amplitude between 200 and 400 ms of the measured EOG signals (channels beneath the left and right eye above cranial muscles) were statistically non-differentiable (as assessed by rm ANOVA) for the experimental conditions.

### 3.3. Offline tDCS experiment

#### 3.3.1. EEG data

A summary of the results is provided in Fig. 1C. During the picture naming paradigm, a significant reduction in the delta frequency GFS after A-tDCS compared to S-tDCS ( $t_{19} = -2.64, p < 0.05$ ) was obtained. During the resting state (eyes closed) EEG data, the delta PWR was reduced after A-tDCS ( $t_{19} = -3.45, p < 0.05$ ) and there was a trend for a reduction in the delta GFS ( $t_{19} = -1.98, p < 0.1$ ). No other effects concerning the remaining frequency bands were observed in the exploratory analysis.

#### 3.3.2. Behavioural data

There was no significant effect ( $p > 0.05$ ) in the vRTs of the picture naming paradigm obtained after A-tDCS compared to S-tDCS (see Table 3).

## 4. Discussion

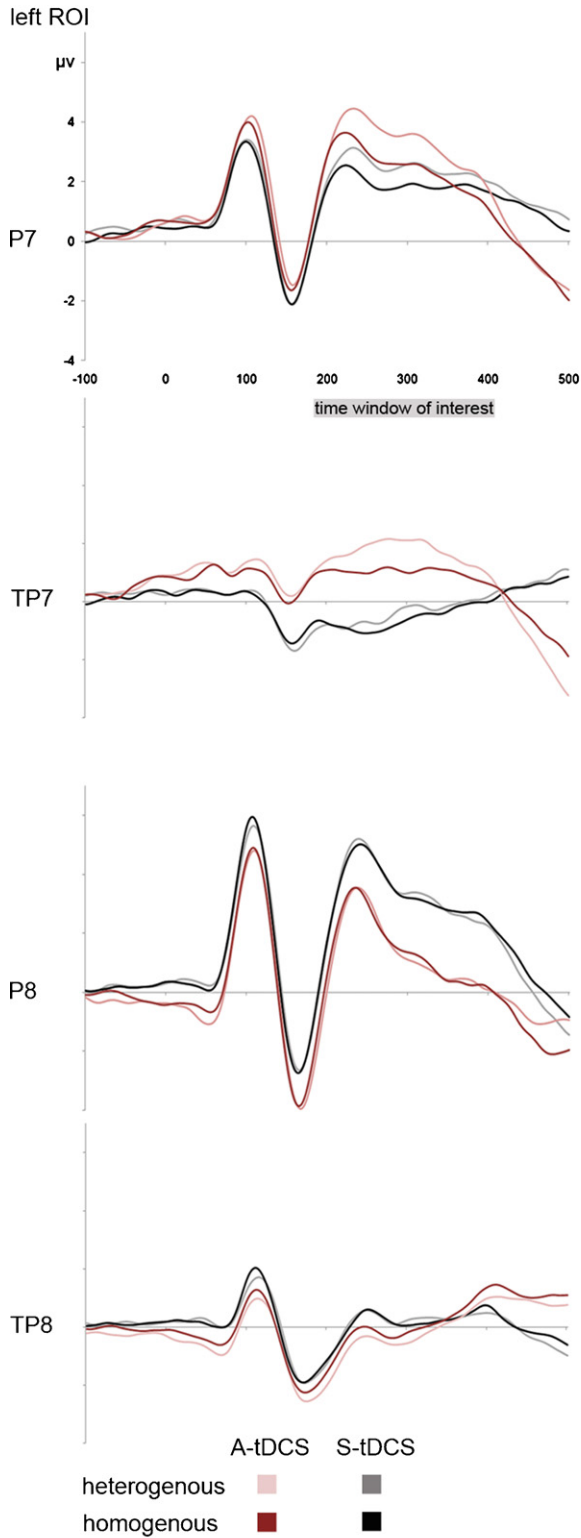
Recent studies have demonstrated positive effects of prefrontal A-tDCS and high-frequency rTMS on language functions

**Table 3**  
Overview of the behavioural data.

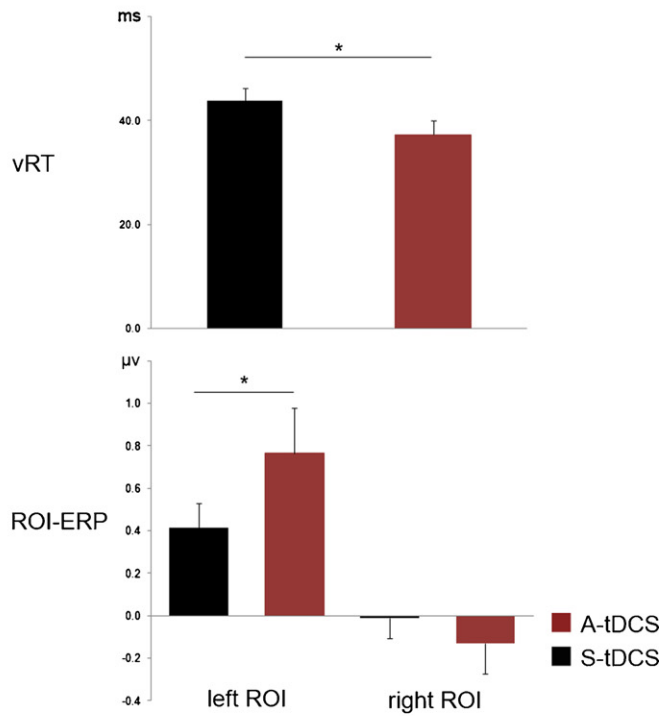
		S-tDCS	A-tDCS
Semantic blocking	homogenous	627.83/66.74	625.89/71.53
	heterogeneous	583.99/67.16	588.64/71.68
SI-Effect		43.84/10.90	37.26/12.26
Picture naming		689.45/65.41	692.40/72.90

M = mean vRT (in ms)/SD = standard deviation, S = sham, A = anodal.

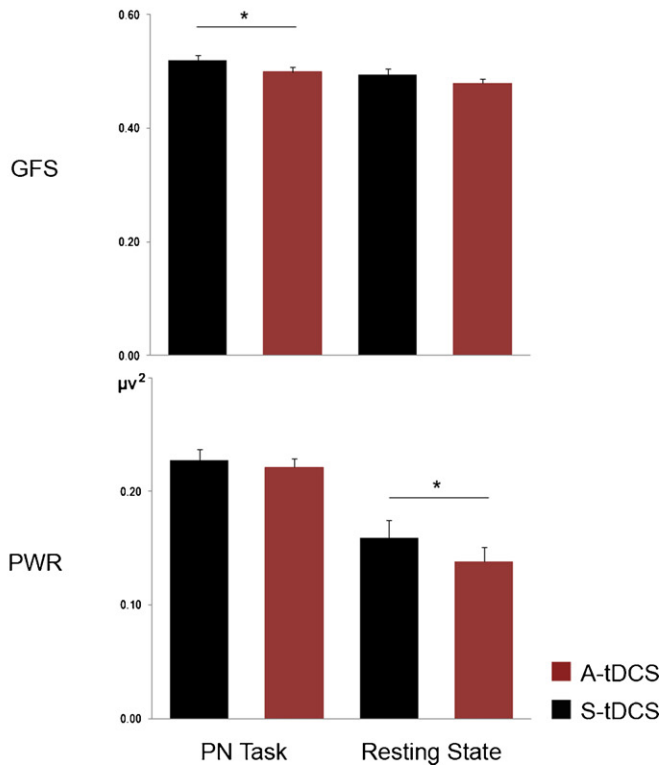
A) ROI Electrode waveforms



B) Online results: SI-Effect



C) Offline results: Delta activity



**Fig. 1.** Overview of main results. (A) Average-referenced waveforms for the left (P7, TP7) and right (P8, TP8) scalp-ROIs are depicted across the experimental conditions of interest, i.e., category (heterogeneous/homogenous) and stimulation conditions (A-tDCS/S-tDCS). Color codes and the time window of interest are specified. The xy-scale provided for P7 applies for all ROI graphs. (B) The graphs show the online results. The Semantic Interference (SI)-Effects are depicted for verbal responses (mean vRT [in ms] with SE [standard error of the mean]) and ROI-ERPs (mean amplitude [in µV] with SE). During A-tDCS compared to sham stimulation the behavioural SI-Effect was significantly reduced, while the ERP SI-Effect was significantly enhanced over the left scalp-ROI (see asterisks). (C) The graphs display the offline results. The delta activity specified by the global field synchronization (GFS, mean values with SE) and global spectral power (PWR, mean values with SE) is plotted for the picture naming (PN) task and the resting state. The delta GFS is decreased during picture naming and the PWR is diminished during the resting state following A-compared to S-tDCS.

in healthy subjects (Fertonani et al., 2010) and patient populations (Baker et al., 2010). In the present combined EEG–tDCS study we examined neurophysiological and behavioural correlates of this putative therapeutic effect. Our findings provide first indication of online (during tDCS) and offline (after tDCS) modulations evoked by prefrontal A-tDCS compared to sham stimulation within selected ERP/EEG markers during language production: Online A-tDCS influenced the semantic interference. Offline A-tDCS induced a reduction in the delta activity as measured by the global delta power and field synchronization. In the following we discuss these observed effects within the neuro-cognitive network model of language production (Friston et al., 1991; Frith et al., 1991).

#### 4.1. Online tDCS effects

Replicating prior studies (Aristei et al., 2011; Maess et al., 2002; Schnur et al., 2009), the SI-Effect was consistently obtained in the current semantic blocking paradigm. The effect refers to the difference in the dependent variables (here, verbal RTs and ERPs) evoked by overt picture naming in semantically homogeneous and heterogeneous contexts. Critically, homogenous context is believed to pose a higher demand on language production components due to increased neural interference and/or competition of categorically related representations (Abdel Rahman & Melinger, 2007, 2011; Damian et al., 2001) within the representational system.

It is of significance that the present behavioural and electrophysiological SI-Effects are sensitive to online anodal (vs. sham) tDCS modulations. Interestingly though, there was a divergence in the observed modulations of the SI-Effects: while the electrophysiological SI-Effect was enhanced over the left, but not over the right scalp-ROIs, the behavioural SI-Effect was reduced during A-compared to S-tDCS (i.e., after noise reduction of the vRT data). For the possible interpretation of these online effects within the neural model of language production (Friston et al., 1991; Frith et al., 1991) the following preliminary interpretation could be considered: There is evidence that the measured SI markers emanate from different language-related neural generators. The behavioural SI-Effect is found to be enhanced in aphasic patients with frontal verbal inhibition deficits (Biegler et al., 2008), i.e., suggesting a prefrontal source of this effect. The physiological SI-Effect was previously related to activity changes in the left-lateralized temporal generators using MEG (Maess et al., 2002). Within the train of thought, anodal tDCS over the left DPFC might influence different neural processes via a propagation of neuro-stimulatory effects within functionally connected neural networks (Boros, Poreisz, Munchau, Paulus, & Nitsche, 2008; Lang, Nitsche, Paulus, Rothwell, & Lemon, 2004). The tDCS-induced reduction of the behavioural SI-Effect could be related to alterations, i.e., elevation, of prefrontal inhibitory functions. The increased electrophysiological SI-Effect during A-tDCS suggests a superior tuning in neural responses within the temporally distributed representational system.

Overall, it can be concluded that the SI markers are responsive to A-tDCS induced neuro-modulatory changes within the language system. A possible interpretation of our observations is a functional relation between the behavioural and ERP SI-Effects. However, at present, this postulation is not supported by the data as indicated by an exploratory posthoc correlation analysis. Prospective research will be needed to draw more direct and confident conclusions on the underlying neural generators by incorporating source localization techniques. For the current montage the required uniform sampling of the head surface (Michel et al., 2004) is constraint.

#### 4.2. Offline tDCS effects

In line with the recent findings (Keeser et al., 2011; Polania et al., 2011; Zaehle et al., 2011), the current study tracks offline A-tDCS effects in the oscillatory EEG activity. Spectral oscillations are recordable in the scalp-EEG and reflect neural activity within large-scale cortico-cortical and cortico-subcortical functional neural circuits (Uhlhaas, Roux, Rodriguez, Rotarska-Jagiela, & Singer, 2010) presumed to be involved in higher-order mental functions (Uhlhaas & Singer, 2006, 2010). Here, we specifically demonstrate a reduction in the slow-wave delta band activity following A-tDCS compared to S-tDCS, i.e., in the global field synchronicity during overt picture naming and in the global spectral power during the resting-state. Our findings are comparable with Keeser et al. (2011), who previously reported a reduction of delta resting state power after anodal tDCS of the left DPFC. In an analogous way Maihofner et al. (2005) found a decrease in prefrontal slow-wave magnetoencephalographic activity after repeated sessions of rTMS over the left DPFC. In general, the delta band is viewed as a surrogate of neural inhibition (Spironelli & Angrilli, 2009), i.e., the amount of neurons *not* engaged in specific cognitive processes. In healthy subjects delta activity is increased during states of reduced vigilance and alertness (Braboszcz & Delorme, 2011), while it has been related to frontal lobe dysfunctions in patients (Spironelli et al., 2011; Winterer et al., 2000). Accordingly, the observed decreases in delta activity suggest that A-tDCS over the left DPFC may excite (or disinhibit) neural processes in prefrontal regions, potentially reflecting a boost of neuro-computational resources.

The absence of behavioural after-effects was unexpected, considering prior reports of prefrontal anodal effects on naming performance (Baker et al., 2010; Fertonani et al., 2010; Iyer et al., 2005), however, Huey et al. (2007) also reported null effects. The efficacy of tDCS may vary – the reasons for which can be, e.g., methodological factors, such as the tDCS inter-electrode distance (Moliadze et al., 2010), protocol characteristics (Fricke et al., 2011) and the stimulation duration (Nitsche et al., 2008). Albeit we observed stimulation-induced neuro-oscillatory modulations, in our opinion mainly two methodological parameters could have rendered their magnitude too low to provoke concurrent behavioural changes: The inter-electrode distance is negatively associated with magnitude and duration of stimulation-induced after-effects (Moliadze et al., 2010). In related studies, Fertonani et al. (2010) as well as Baker et al. (2010) have likewise implemented an extra-encephalic reference, however, with the use of a higher stimulation intensity and multiple tDCS sessions, respectively. Further, recent findings demonstrated a time-dependency of homeostatic plasticity, a term that refers to the efficacy of repeated tDCS sessions on neural plasticity. Fricke et al. (2011) showed for the primary motor cortex that a 1 min break reduced the after-effects of a 5 min anodal tDCS protocol, when it was preceded by a 7 min preconditioning tDCS as applied in the current study. As a third parameter, the stimulation duration seems to be positively related to occurrence and duration of after-effects (Nitsche & Paulus, 2000, 2001). While there is still very limited data on stimulation durations exceeding 20 min, previous studies reported reliable neurophysiological (Clark, Coffman, Trumbo, & Gasparovic, 2011) and behavioural (Clark et al., 2012) after-effects.

In line with previous reports, our findings support the view that tDCS-induced modifications of neural oscillations could be an important mechanism that influences executive functions. There is first evidence that stimulation-induced oscillatory changes are functionally significant as previously demonstrated using working memory tasks (Keeser et al., 2011; Zaehle et al., 2011). Future studies in the field of language production will be needed to establish the proposed brain-behaviour relationship.

#### 4.3. Synthesis and outlook

From the current observations we argue that A-tDCS over the DPFC results in excitation of frontally mediated neural processes (indicated by decreased delta activity) and language functions (derived from the reduced behavioural and the enhanced ERP SI-Effects). Some of the present behavioural and electrophysiological parameters are known to be sensitively altered in neurological and psychiatric disorders that exhibit language dysfunctions (Biegler et al., 2008; Koenig et al., 2005; Spironelli & Angrilli, 2009; Winterer et al., 2000). This study additionally demonstrates that these parameters are sensitive to stimulation induced neuromodulations within the language system. For the clinical implementation of our findings, we therefore suggest a possible application of these markers in the neuro-rehabilitation of language abilities.

#### 4.4. Methodological caveats and challenges

The present synchronous tDCS–EEG approach could prove of value for prospective studies assessing higher order cognition. Yet, a careful methodological evaluation of the following critical points is required. (1) *Scalp electrodes*: The synchronous tDCS–EEG setup leads to a discounting of the number of EEG channels and therefore demands a suitable experimental paradigm. (2) *Stimulation artefacts*: Compared to the sham stimulation, online A-tDCS induced a power increase over a number of frequency bands that was differently expressed across EEG channels (data not shown). Differences in measured EEG signals between critical stimulation conditions and/or electrode sites could as such represent tDCS-induced artefacts. In the present study we tried to bypass this limitation: The SI-Effect was compared between A- and S-tDCS conditions as measured remote from the stimulation site at selected scalp-ROIs. In our opinion, the obtained effects can therefore not be explained by a mere stimulation-induced artefact but rather represent local changes in neural activity patterns. (3) *tDCS electrode montage*: In order to maximize the number of EEG electrode channels, an extracephalic tDCS reference electrode site was chosen in the present and prior studies (Accornero et al., 2007). This tDCS setup improves the focality of the cortical stimulation (Nitsche et al., 2008) and is more optimal for EEG recordings. At the same time the montage is known to alter the effectiveness of tDCS due to increasing scalp-reference-electrode distance (Moliadze et al., 2010) and associated alterations in the current flow.

#### 4.5. tDCS protocol and safety aspects

The present tDCS protocol (intensity: 1.5 mA, current density: 0.04 mA/cm<sup>2</sup>, duration: 30 min experimental tDCS, 7 min pre-experimental tDCS) differed in some respects from previous stimulation studies on language-related functions: e.g., 2 mA, 0.06 mA/cm<sup>2</sup>, 10 min (Fertonani et al., 2010) and 1 mA/20 min (0.04 mA/cm<sup>2</sup>, Baker et al., 2010; Iyer et al., 2005; 0.03 mA/cm<sup>2</sup>, Floel et al., 2008). The following reasons can be provided: The present tDCS protocol yielded prolonged stimulation duration to parallel time requirements of semantic blocking. Although a similar duration has been applied elsewhere (2 mA, 0.18 mA/cm<sup>2</sup>, 30 min: Bullard et al., 2011; Clark et al., 2011, 2012), the available data about safety limits is still restricted (Nitsche et al., 2008). Transcranial DCS side effects are minor, when stimulation intensities up to 2 mA and 20 min applications are used (see Utz et al., 2010 for review; Poreisz et al., 2007). With longer stimulation duration an increase in side effects (mainly heat and skin flush) could be expected. Due to considerations of safety and blinding the current amperage intensity was set to 1.5 mA for the given stimulation duration; further side effects were monitored: Besides a rapidly resolving itchiness, subjects reported skin flush/heat following active stimulation.

This observation could be accounted for by stimulation-induced vasodilatation (Durand, Fromy, Bouye, Saumet, & Abraham, 2002) known to react directly proportional to the total electrical charge (Grossmann et al., 1995). Overall, however, frequency and magnitude of adverse effects were minimal and comparable to previous safety reports (see above).

#### 5. Conclusion

The present exploratory study tracks neuro-modulatory effects of A-tDCS at the left DPFC during overt picture naming. We report A-tDCS induced modulations within selected electrophysiological markers known to indicate the integrity of specific language-related activation processes (vRT and ERP SI-Effects) and more unspecific neural inhibition (delta band activity). As such, the present electrophysiological markers could prove to be useful add-on biomarkers to trace and explain neuro-rehabilitatory effects of prefrontal A-tDCS on language production.

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