Electrical stimulation of the motor cortex enhances treatment outcome in post-stroke aphasia

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Transcranial direct current stimulation has shown promise to improve recovery in patients with post-stroke aphasia, but previous studies have only assessed stimulation effects on impairment parameters, and evidence for long-term maintenance of transcranial direct current stimulation effects from randomized, controlled trials is lacking. Moreover, due to the variability of lesions and functional language network reorganization after stroke, recent studies have used advanced functional imaging or current modeling to determine optimal stimulation sites in individual patients. However, such approaches are expensive, time consuming and may not be feasible outside of specialized research centres, which complicates incorporation of transcranial direct current stimulation in day-to-day clinical practice. Stimulation of an ancillary system that is functionally connected to the residual language network, namely the primary motor system, would be more easily applicable, but effectiveness of such an approach has not been explored systematically. We conducted a randomized, parallel group, sham-controlled, double-blind clinical trial and 26 patients with chronic aphasia received a highly intensive naming therapy over 2 weeks (8 days, 2 × 1.5 h/day). Concurrently, anodal-transcranial direct current stimulation was administered to the left primary motor cortex twice daily at the beginning of each training session. Naming ability for trained items (n = 60 pictures that could not be named during repeated baseline assessments), transfer to untrained items (n = 284 pictures) and generalization to everyday communication were assessed immediately post-intervention and 6 months later. Naming ability for trained items was significantly improved immediately after the end of the intervention in both the anodal (Cohen’s d = 3.67) and sham-transcranial direct current stimulation groups (d = 2.10), with a trend for larger gains in the anodal-transcranial direct current stimulation group (d = 0.71). Treatment effects for trained items were significantly better maintained in the anodal-transcranial direct current stimulation group 6 months later (d = 1.19). Transfer to untrained items was significantly larger in the anodal-transcranial direct current stimulation group after the training (d = 1.49) and during the 6 month follow-up assessment (d = 3.12). Transfer effects were only maintained in the anodal-transcranial direct current stimulation group. Functional communication was significantly more improved in the anodal-transcranial direct current stimulation group at both time points compared to patients treated with sham-transcranial direct current stimulation (d = 0.75–0.99). Our results provide the first evidence from a randomized, controlled trial that transcranial direct current stimulation can improve both function and activity-related outcomes in chronic aphasia, with medium to large effect sizes, and that these effects are maintained over extended periods of time. These effects were achieved with an easy-to-implement and thus clinically feasible motor-cortex montage that may represent a promising ‘backdoor’ approach to improve language recovery after stroke.
tDCS enhances aphasia recovery

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Abbreviations: CETI = Communicative effectiveness index; M1 = primary motor cortex; PCQ = Partner Communication Questionnaire; tDCS = transcranial direct current stimulation

Introduction

More than 15 million people worldwide suffer from stroke each year (Feigin et al., 2014), of whom approximately one-third show language impairment (aphasia, Laska et al., 2001; Dickey et al., 2010). It is estimated that aphasia persists in up to 40% of these patients for more than 1 year after stroke (Pedersen et al., 1995; Lazar and Antoniello, 2008). Chronic language impairments are among the most devastating consequences of stroke by affecting vocational reintegration, social life and psychological wellbeing on the individual level and by placing major burdens on the healthcare system (Code and Herrmann, 2003; Dickey et al., 2010). Intensive and deficit-oriented treatment can improve aphasia even in the chronic stage, but treatment effect sizes are often modest (Brady et al., 2012). Thus, there is a pressing need to explore new strategies to enhance treatment efficacy in chronic aphasia.

Transcranial direct current stimulation (tDCS) may be a promising tool to achieve this goal (Monti et al., 2013; Floël, 2014; de Aguiar et al., 2015). During tDCS, a weak electrical current is delivered to the scalp using two surface electrodes to induce a polarity-dependent shift in neuronal resting membrane potential within the targeted cortical region, thereby promoting changes in cortical excitability (Stagg and Nitsche, 2011). Moreover, the after-effects of tDCS involve induction of synaptic plasticity that mimic long-term potentiation, which is critical for learning, neuroplasticity and rehabilitation (Stagg and Nitsche, 2011). Transcranial DCS has an excellent safety profile and thus far no serious side effects have been reported even in stroke populations, while a placebo stimulation condition (‘sham-tDCS’) allows effective blinding of participants (Fregni et al., 2015).

In the language domain, proof-of-concept studies that exploited transient effects of single stimulation sessions have demonstrated that excitatory (‘anodal’) tDCS administered to perisylvian regions in the left hemisphere can improve language processing in healthy individuals (for reviews see Floël, 2012; Monti et al., 2013). Moreover, multi-session tDCS has been shown to induce more permanent behavioural and neural modulations. For example, studies in healthy individuals have shown that five to 10 sessions of anodal-tDCS can enhance language, motor and cognitive learning compared to sham-tDCS with maintenance of effects for up to 12 months (Dockery et al., 2009; Reis et al., 2009; Cohen Kadosh et al., 2010; Meinzer et al., 2014a). Thus, anodal-tDCS could be a viable and cost-effective way to enhance treatment efficacy in aphasia. However, to date, there is a lack of randomized clinical trials testing the effectiveness of tDCS to improve both linguistic impairment and functional communication, and the long-term maintenance of potential beneficial effects in aphasia (Elsner et al., 2015).

Moreover, the choice of stimulation sites in patients with post-stroke aphasia is complicated by variable lesion sizes and locations as well as interindividual differences in functional language network reorganization. Consequently, studies that employed ‘uniform’ stimulation sites targeting left hemispheric language regions in aphasia patients resulted in highly variable stimulation effects (for review see de Aguiar et al., 2015). Recently, more sophisticated approaches have emerged that involved pretreatment mapping of spared language regions using functional MRI (Baker et al., 2010; Fridriksson et al., 2011), modelling of current flow on an individual basis (Dmochowski et al., 2013) and systematic exploration of optimal montages using experimental conditions prior to treatment (Shah-Basak et al., 2015). However, from a pragmatic point of view, determining the optimal stimulation on an individual basis is time consuming, expensive and may require expertise frequently not available outside of specialized research settings. This complicates the incorporation of tDCS in day-to-day clinical practice and underscores the need to explore the effectiveness of alternative stimulation sites that are easy to administer and feasible in clinical environments.

Such a stimulation site could feature a functionally connected ancillary system to facilitate processing of the residual language network, i.e. the primary motor system. Previous research has suggested a tight link between linguistic functions and activation of the motor (action) system (Willems and Hagoort, 2007; Pulvermüller and Fadiga, 2010). Numerous studies have demonstrated that pre-activation of the motor system by behavioural...
Manipulations can facilitate language processing on different levels (e.g., semantic processing, lexical retrieval) in healthy individuals (Hadar et al., 1998; Holle and Gunter, 2007; Dick et al., 2009) and patients with aphasia (Hanlon et al., 1990; Hesse et al., 2007; Meinerz et al., 2011; Benjamin et al., 2014; Harnish et al., 2014). Moreover, two recent studies in healthy individuals demonstrated that tDCS administered to the primary motor cortex (M1) can facilitate (anodal-tDCS, Meinerz et al., 2014c) or impair (inhibitory cathodal-tDCS, Liu et al., 2010) language processing. In aphasia, a cross-over, sham-tDCS controlled, single case report demonstrated significantly improved naming ability when anodal-tDCS was administered to the left M1 (Datta et al., 2011).

Therefore, evidence from behavioural, brain imaging and brain stimulation studies suggest that M1 stimulation by anodal-tDCS may represent a promising and clinically feasible approach to enhance language therapy outcome in post-stroke aphasia. This hypothesis was tested in the present randomized, sham-tDCS controlled, clinical trial that assessed both short- and long-term outcome of intensive language training in combination with M1-tDCS on impairment and disability parameters.

Materials and methods

Experimental design

We conducted a randomized, parallel-group, sham-tDCS controlled, double-blind, single centre, clinical trial to investigate whether anodal-tDCS administered to M1 can improve the effectiveness of intensive therapy in patients with chronic post-stroke aphasia and word-finding problems. All patients received an established naming therapy, either with anodal or sham-tDCS. The primary outcome variable was treatment success for specifically trained items. Secondary outcomes comprised transfer to untrained items and generalization to everyday communication ability. All outcome measures were assessed before and immediately after the end of the intervention and during a 6 month follow-up period. Figure 1 illustrates the design of the study. The trial was registered (clinicaltrials.gov NCT01924702), approved by the ethics committee of the Charité University Hospital (Berlin, Germany) and conducted in accordance with the Declaration of Helsinki. Patients received a reimbursement for their participation.

Patient sample

Our study group consisted of 26 right-handed, native German speakers with chronic aphasia (>12 months post-stroke) and impaired naming ability due to a single infarction or haemorrhage in the left hemisphere. Aphasia type and severity was determined using the standardized Aachen Aphasia Test (AAT, Huber et al., 1983). None of the subjects presented with oral apraxia, as indicated by a score of <2 errors during 10 imitation tasks involving the lips, cheeks and tongue (Götze and Zenz, 2005). Apraxia of speech was assessed using the Hierarchic Wordlists (Liepold et al., 2003). Seven patients (anodal-tDCS: n = 3, sham-tDCS: n = 4) had mild apraxia of speech, characterized by minor impairment of rhythm, stress or intonation. Co-morbid motor impairment (hemiparesis/hemiplegia of the right arm and leg) was present in 14 patients (n = 7 in each stimulation group, see Table 1). Patients with contraindications for tDCS (e.g., cardiac pacemaker, history of seizures), a history of alcohol or drug abuse, other severe neurological, psychiatric or medical conditions were excluded (n = 1 due to cerebral glioma, n = 1 due to history of progressive multifocal leukoencephalopathy, n = 1 due to severe neuropathic pain). Patients on antidepressant or antipsychotic medication were excluded as such medication may interfere with tDCS effects (Stagg and Nitsche, 2011).

Of 89 patients that were screened, 26 were eligible and participated in the study between August 2013 and May 2015 at the Charité University Hospital, Berlin, Germany. Four patients were not available for the follow-up assessment due to reasons unrelated to the study (n = 2/stimulation group; Fig. 2). After providing written informed consent, patients were randomly assigned to the stimulation groups, with stratification factor ‘naming impairment severity’ (i.e. mean naming performance on repeated baseline assessments, see below). For stratification, a list with 26 cells was created (n = 13/stimulation conditions) and consecutive patients were randomly assigned to open cells or matched pairwise until all cells were filled. The resulting stimulation groups were matched for naming impairment severity, sex, time since stroke and education. Table 1 details clinical and demographic characteristics of the sample. At the time of the study, none of the participants received drugs other than lipid- or blood pressure lowering, anti-platelet and thyroid hormone replacement medication, which remained unchanged during participation. All patients scored within normal ranges on the Beck Depression Inventory. Figure 3 illustrates the lesions in the two stimulation groups. Lesions were drawn on high-resolution T1-weighted MRI acquired prior to the treatment (n = 24.

Figure 1 Study design.
patients, one patient from each group could not be scanned due to claustrophobia), normalized and rendered on a standard brain template as an overlay plot. Lesion sizes were comparable in both groups ($t(22) = 1.34, P = 0.19$, Table 1). While some patients had lesions affecting parts of M1, the hand motor cortex and underlying white matter tracts were spared in all patients.

### Selection of treatment items

Naming ability was evaluated during two baseline assessments using a standardized battery of pictures ($n = 344$, Menke et al., 2009; Meinzer et al., 2010; Floel et al., 2011). The pictures were presented in random order on a laptop computer split into eight sets with short breaks in between. Pictures were presented for 3 s followed by a blank screen (up to 27 s) and patients were asked to name each picture as accurately as possible. Responses were recorded and subsequently analysed based on the first valid response (Dell et al., 1997). Sixty pictures that could not be named correctly during both assessments were selected for each patient and trained during therapy (trained items). Those items only comprised non-responses, unrelated semantic errors, phonologically unrelated errors and neologisms. Minor articulatory errors due to mild apraxia of speech that was present in some of the patients were not scored as errors during any of the assessments. The remaining 284 pictures (which included correct responses, omissions, semantic and phonemic paraphasias and other utterances) remained untrained (untrained items) and served to assess transfer effects (Table 1 details baseline naming performance for individual patients).

### Treatment

Participants underwent an established computer-assisted naming treatment that followed the method of ‘vanishing cues’ (Abel et al., 2005) and was administered over 2 weeks (4 days/week, $2 \times 1.5$ h/day). This procedure has previously been shown to be highly effective to improve naming ability in chronic patients with aphasia (Menke et al., 2009; Meinzer et al., 2010; Floel et al., 2011). It is based on an associative learning procedure that aims at strengthening associations between target words (object pictures) and auditory and graphemic cues by using a shaping approach. Across five difficulty

### Table 1 Details of demographic and clinical characteristics of patients in the two stimulation groups

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<th>Type of stroke</th>
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A = anodal-tDCS; S = sham-tDCS; M = male; F = female; TSS = time since stroke (months); I = ischaemic; H = haemorrhagic; AAT = Aachen Aphasia Test (subtests): TT = Token Test (error score); RT = repetition; WL = written language; Na = naming; Co = comprehension.

*Patients with comorbid hemiparesis/hemiplegia.

*Score represents the mean number of correct responses during the two baseline assessments.
levels, cues were gradually reduced depending on improved naming ability. Initially, all patients were presented with pictures in combination with its spoken and written word form and patients were asked to repeat the name (Level 1). This was repeated until the patient scored >80% correct responses. At the second and third levels, the picture was only cued with the first two phonemes and graphemes or the first phonemes and graphemes, respectively. Level 4 minimized cueing to the first grapheme. No cues were provided at Level 5. The 80% correct criterion applied for progression to the next level. Whenever performance was <80% correct (Levels 2–5), a training block of Level 1 was interspersed to provide patients with the complete visual and auditory target word forms. The treatment was supervised by an experienced speech therapist, who was blind to the stimulation conditions and who scored each patient’s responses as correct or incorrect (the first valid response was scored, minor articulatory difficulties were not scored as errors).

Transcranial direct current stimulation

Transcranial DCS was administered using a battery driven stimulator (DC-Stimulator Plus®, NeuroConn). Stimulation duration and intensity complied with current safety recommendations (Fregni et al., 2015). The anode (5 × 7 cm²) was placed over the left M1 representation of the hand as in our previous studies (C3 of the 10–20 EEG system) (Lindenberg et al., 2013; Meinzer et al., 2014c). Figure 4 details the placement and orientation of the anode on a standard brain and on an individual MRI. The cathode (10 × 10 cm²) was positioned over the right supraorbital region. The large size of this reference electrode renders the stimulation over this area functionally ineffective. Twenty minutes of anodal-tDCS (1 mA) were administered at the beginning of each of the two daily treatment sessions. The current was ramped up and down for 10 s at the beginning and end of each stimulation session. During sham-tDCS, the current was ramped up and remained at 1 mA only for 30 s before ramping down, which does not affect neural functions, but assures effective blinding of participants due to the initial tingling sensation on the scalp (Gandiga et al., 2006).

Figure 2 The CONSORT diagram details the flow of participants in the randomized, sham-tDCS controlled treatment phase and during the follow-up (f-u) period.

Figure 3 Structural lesions. The structural lesions of the patients in both stimulation groups (anodal-tDCS; sham-tDCS, n = 12/group) as an overlay plot rendered on a standard brain template. Colours indicate number of patients with lesions in a given area.
Outcome measures

All outcome measures were assessed immediately before and after the end of the intervention and after 6 months. Assessors were blind to the stimulation conditions. Dependent variables were the mean change of naming ability for trained items (primary outcome) and untrained items (secondary outcome) from baseline to both endpoints (immediate post-test, 6 months follow-up). Within-therapy effects were probed by confrontation naming of trained items (without cues) after each treatment day (Days 1–8). Other secondary endpoints comprised ratings of the quality of everyday communication that were assessed by the German versions of two questionnaires that have demonstrated reliability and validity to assess the impact of treatment on everyday communication ability in aphasia, i.e. the Communicative Effectiveness Index (CETI, Lomas et al., 1989) and the Partner Communication Questionnaire (PCQ, Blomert, 1993). Ratings were completed by the patients’ primary reference person (e.g. partner or other family member). The CETI assesses the quality of everyday communication relative to the patients’ premorbid status on a scale from 1–10 (1 = much worse, 10 = same as before
stroke) for 16 items. In the PCQ, partners rate current verbal communication abilities in 46 situations (scale 0–5, 0 = not possible, 5 = possible).

**Statistical analyses**

Given that effects of M1-tDCS in aphasia have not been tested, the sample size calculation was based on our previous cross-over study in healthy older adults that showed beneficial effects of this montage on word retrieval (Meinzer et al., 2014c).

This showed that 26 participants were required ($\alpha < 0.05$, two-sided power 80%, including 15% dropout rate). Linear mixed effect models were calculated separately for all outcome measures (primary: trained items, secondary: untrained items, CETI, PCQ). Models included all time points (pre, post, follow-up) with Time and Stimulation as fixed effects; patients were included as random factor. As baseline AAT scores of the repeating subtest of the AAT were different in the two stimulation groups (Table 1), this variable was included as covariate in the analyses. Significant effects were followed up by post hoc paired and unpaired $t$-tests as appropriate. Pearson correlation assessed whether changes in naming ability (trained items, untrained items) were associated with ratings of improved everyday communication ability (CETI, PCQ). Effect sizes were calculated for significant results (Cohen’s d).

**Results**

All patients believed that they had received anodal-tDCS when questioned after the end of the 2-week treatment period. The stimulation was tolerated well. Only mild sensations (e.g. itching, tingling, slight burning feeling) during the initial ramping up were reported.

**Within treatment effects**

Naming performance for trained items, as assessed immediately after the end of each treatment day, improved across the 2-week training period [Time $F(7,168) = 24.3$, $P < 0.001$; mean = 34.5, standard error (SE) = 3.4, confidence interval (CI) = 27.4–41.6, $d = 2.79$] with comparable gains in the two groups [Stimulation $F(1,23) = 1.4$, $P = 0.2$; interaction Time $\times$ Stimulation $F(7,168) = 0.9$, $P = 0.5$].

**Trained items**

Across the three assessments (pre, post, follow-up), there were significant main effects for Time [$F(2,45.3) = 102.1$, $P < 0.0001$] and Stimulation [$F(1,22.9) = 6.7$, $P = 0.017$] and a significant interaction of Time $\times$ Stimulation [$F(2,45.5) = 5.9$, $P = 0.005$] for trained items. Post hoc paired $t$-tests showed that both treatment groups performed above baseline immediately after the training [$t(25) = 10.4$, $P < 0.0001$] and during the 6-month follow-up assessment [$t(21) = 7.7$, $P < 0.001$]. The immediate treatment effect tended to be larger in the group that had received anodal-tDCS [post–pre $t(24) = 1.8$, $P = 0.08$] and gains were significantly better maintained in this group during the follow-up assessment [follow-up–pre $t(20) = 2.8$, $P = 0.01$]. This was explained by a steeper decrease of naming scores 6 months after the training in the sham-tDCS group [follow-up–post $t(20) = 3.9$, $P = 0.0008$; see Fig. 5A and Table 2 for details of effects and effect sizes].

**Transfer to untrained items**

For untrained items, there were significant effects for Time [$F(2,44)=38.43$, $P < 0.001$] and Time $\times$ Stimulation [$F(2,44)=18.1$, $P < 0.0001$]. Baseline performance was comparable in both stimulation groups [$t(24) = 0.94$, $P = 0.93$]. Generalization of treatment effects to untrained items were found in both groups immediately after the training [paired $t$-test post–pre $t(25) = 5.8$, $P < 0.0001$], but this effect was significantly larger in the anodal-tDCS group [post–pre: $t(24) = 3.8$, $P = 0.0009$].

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**Figure 5 Details of outcome measures for impairment measures.** (A) Trained ($n = 60$) and (B) untrained items ($n = 284$) that were assessed immediately before (pre) and after the end of the treatment (post) and 6 months later (follow-up, f-u). Trained items could not be named correctly during repeated baseline assessments. Thus, pretreatment scores for these items are zero for each patient. Data represent means and standard errors of the mean; asterisk indicates significant improvement compared to baseline assessments and interactions (Time $\times$ Stimulation).
were better maintained in the anodal-tDCS group [follow-up-pre \( t(20) = 7.3, P < 0.0001 \)], and only in this group, performance was still above baseline level at the 6-month follow-up assessment [anodal-tDCS \( t(10) = 7.5, P < 0.0001 \); sham-tDCS \( t(10) = -1.2, P = 0.29 \); Fig. 5B and Table 2].

**Everyday communication**

The primary reference person of each patient rated communicative effectiveness higher than at baseline immediately after the training and at the follow-up assessment in both stimulation groups and for both rating scales [CETI: Time \( F(2,44.5) = 32.4, P < 0.0001 \), post-pre/follow-up-pre \( t(25/21) = 6.3/6.0, \) both \( P < 0.0001 \); PCQ: Time \( F(2,44.1) = 20.52, P < 0.0001 \), post-pre/post-pre/follow-up-pre \( t(25/21) = 4.5/4.3, \) both \( P < 0.0004 \)]. In addition, there was a significant interaction of Time x Stimulation in the CETI, that was explained by significantly higher ratings for patients in the anodal-tDCS group immediately after the end of the treatment [post-pre \( t(24) = 2.2, P = 0.037 \), follow-up-pre, \( t(20) = 2.0, P = 0.055 \)]. PCQ ratings were higher in the anodal-tDCS group during the follow-up [post-pre \( t(24) = 1.9, P = 0.06 \); follow-up-pre \( t(20) = 2.3, P = 0.03 \); Fig. 6A and B, and Table 2].

**Correlation between objective and subjective measures of language ability**

Improvement of trained items was not correlated with ratings of everyday communication ability immediately after the treatment or 6 months later (all \( r = 0.09–37, P = 0.1–0.6 \)). However, the degree of improvement for untrained items was positively correlated with ratings of improved everyday communication immediately after the end of the treatment (CETI \( r = 0.43, P = 0.024 \)) and during the follow-up (CETI \( r = 0.43, P = 0.043 \); PCQ \( r = 0.55, P = 0.008 \)).

**Discussion**

This randomized, controlled clinical trial investigated for the first time the combined effects of tDCS and intensive aphasia therapy on both impairment measures and functional communication in post-stroke aphasia and also addressed the long-term maintenance of tDCS effects. The main results of this trial are: (i) immediately after the end of the intervention, naming ability for trained material was significantly improved in both active (Cohen’s \( d = 3.67 \)) and sham-tDCS groups (\( d = 2.10 \)), with numerically larger gains in the anodal-tDCS group (\( d = 0.71 \)). These large treatment gains were maintained in both stimulation groups during the 6-month follow-up assessment, which underscores the effectiveness of the intervention. However, the maintenance of treatment effects was superior in the anodal-tDCS group, accumulating in a large between-group effect size 6 months later (\( d = 1.19 \)); (ii) importantly, we also observed significant transfer effects to untrained material in both stimulation groups, which were significantly larger in the anodal-tDCS group immediately after the end of the intervention (\( d = 1.49 \)) and even more pronounced at the 6-month follow-up assessment (\( d = 3.12 \)). Transfer effects were only maintained in the group that had received anodal-tDCS; and (iii) we also demonstrated that anodal-tDCS resulted in enhanced generalization to measures of everyday communication ability that were confirmed during both the short-term and long-term follow-up assessments (\( d = 0.75–0.99 \)). This finding corroborates the functional relevance of the observed improvement on impairment measures, which was also reflected by the positive correlation between improved functional communication and performance on untrained...
materials in the short- and long-term. Thus, our study provides the first evidence from a randomized, controlled trial that anodal-tDCS can induce gains in both function and activity-related outcomes in post-stroke aphasia and that these effects are maintained over extended periods of time. Importantly, these effects were achieved with a M1-tDCS montage that can be easily implemented into standard clinical settings and may represent a novel ‘backdoor’ approach to improve language recovery after stroke.

Long-term effects of transcranial DCS

Studies in healthy individuals have demonstrated beneficial effects of repeated tDCS sessions on motor and cognitive learning that were maintained for up to 12 months (Dockery et al., 2009; Reis et al., 2009; Cohen Kadosh et al., 2010; Meinzer et al., 2014a). Unlike single tDCS session effects that are mediated by transient neural modulations (Stagg and Nitsche, 2011), repeated stimulation sessions administered concurrently with training are thought to act via mechanisms similar to long-term potentiation, which is critical for neuroplasticity and memory consolidation (Reis et al., 2009, 2015; Fritsch et al., 2010). However, while an increasing number of studies demonstrated that tDCS can enhance immediate treatment outcome in aphasia (de Aguiar et al., 2015), only few studies addressed whether these effects are maintained over time, using relatively short follow-up periods of 1–4 weeks (Fridriksson et al., 2011; Floël et al., 2011; Fiori et al., 2011; Marangolo et al., 2013). To date, only one study assessed maintenance of tDCS effects over several months (Vestito et al., 2014). In this study, three patients with chronic aphasia received 10 days of naming therapy with either anodal- or sham-tDCS administered to left frontal regions. Here, anodal-tDCS induced superior immediate treatment effects that were maintained for up to 4 months. In-line with those previous studies, the present randomized, controlled trial confirmed that beneficial training effects are maintained for at least 6 months. Importantly, we demonstrated for the first time that repeated tDCS sessions not only resulted in enhanced long-term improvement for specifically trained materials but also in enhanced maintenance of transfer effects to untrained materials and measures of functional communication.

The majority of previous tDCS studies in aphasia only assessed stimulation effects after the end of the training when acute stimulation effects had ceased (de Aguiar et al., 2015). In the present study, we also assessed performance for trained items immediately after each training day. Interestingly, there were no significant differences between the stimulation groups with regard to naming ability across the training period and significant between-group stimulation effects only emerged during the follow-up assessments. Our findings are thus in line with data from animal models (Fritsch et al., 2010) and healthy individuals (Reis et al., 2009, 2015; Cohen Kadosh et al., 2010; Meinzer et al., 2014a) suggesting that multisession tDCS improves memory consolidation by impacting on plasticity-related protein synthesis, which is thought to be enhanced by concurrent application of tDCS during training.

Importantly, the timing of effects in our study differed compared to previous studies in healthy young individuals, where significant stimulation effects were found already during the training phase and ‘forgetting-rates’ during the follow-up periods were similar in active versus sham-tDCS groups (Dockery et al., 2009; Reis et al., 2009, 2015; Cohen Kadosh et al., 2010; Meinzer et al., 2014a). This may in part be related to the advanced age of our patient group (on average 60 years of age) and recent research emphasized that tDCS effects may be stronger during follow-up periods in older versus younger participants (Floël et al., 2012; Park et al., 2014; Jones et al., 2015). Indeed, long-term effects of tDCS 6 months after the end of the intervention were larger than the immediate post-training effects for all outcome measures. Moreover,
enhanced maintenance of training effects in the anodal-tDCS group were driven mainly by larger performance decrements in the sham-group. Importantly, none of the previous studies in healthy individuals addressed long-term maintenance of transfer effects to untrained materials. In the present study, we were able to demonstrate that these were only maintained in the anodal-tDCS group 6 months after the end of the treatment. Thus, the profound effects of tDCS on consolidation of treatment effects in the present study further emphasize the potential of tDCS to aid recovery from aphasia after stroke or other neurological conditions.

**M1-transcranial DCS to enhance aphasia recovery**

Unlike previous tDCS studies in aphasia that targeted domain-specific language regions (Monti et al., 2013; de Aguiar et al., 2015), beneficial effects of tDCS were achieved by stimulating the primary motor system that is functionally connected with the language network (Willems and Hagoort, 2007; Pulvermüller and Fadiga, 2010). From a pragmatic point of view, M1-tDCS is easy to administer and cost and labour-efficient because it does not require identification of residual language regions on an individual basis by means of pretreatment functional imaging. Thus, the present study provides evidence for the effectiveness of an alternative stimulation site that can easily be implemented in clinical practice. From a theoretical perspective, recent research has emphasized a critical role of ancillary or functional brain regions engaged by a given task (i.e. in our study, a larger language-motor network). For example, previous studies that combined functional imaging with (intrascanner) tDCS showed specific modulation of activity in task-relevant regions (e.g. premotor cortex) may also be effective to enhance language treatment outcome in aphasia.

This study provided the first evidence that M1-tDCS can induce long-lasting improvement of language function and communication after stroke, however, these findings need to be confirmed in larger, multicentre trials and in routine clinical settings. While this was beyond the scope of our study, our trial provides the basis for such an endeavour in the future. Future studies should also assure blinding of the treating clinicians, which was not implemented in the present study mainly for safety reasons. However, given that the computerized treatment only required minimal involvement of the therapist and that assessors were fully blinded to the stimulation conditions, we believe that this did not substantially affect the outcome of the present study. In addition, we chose to target impaired word retrieval because effective treatment approaches for naming impairment are available (Menke et al., 2009; Meinzer et al., 2010; Floel et al., 2011) and word production impairment is the most frequent symptom in acute (Lazar and Antonioli, 2008) and chronic aphasia (Klebcic et al., 2011). However, future studies could explore whether M1-tDCS can also improve other aphasis symptoms. Nonetheless, the relevance of improving naming impairment for aphasia recovery is demonstrated by concomitant improvement of functional communication using reliable and valid proxy measures of functional communication (Lomas et al., 1989; Blomert, 1993). In the future, this could be complemented by analysis of connected speech samples, to provide additional evidence generalization of treatment effects.
Conclusion

This randomized, sham-tDCS controlled trial demonstrated for the first time that multi-session tDCS can induce long-lasting improvement of treatment outcome for trained and untrained materials as well as functional communication. Importantly, these add-on effects were achieved with an easy to administer and therefore clinically feasible M1-tDCS montage, thereby providing a novel 'backdoor' approach to enhance language recovery after stroke.

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