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Efficacy of Unilateral and Bilateral Parietal Transcranial Direct Current Stimulation on Right Hemispheric Stroke Patients With Neglect Symptoms: A Proof-of-Principle Study

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HIGHLIGHTS

- Comparison of bi- and unilateral transcranial direct current stimulation (tDCS).
- Line bisection but not exploration task benefits from single bi-lateral stimulation.
- Investigation of adjunctive bilateral tDCS in larger multi-session trials.

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Efficacy of Unilateral and Bilateral Parietal Transcranial Direct Current Stimulation on Right Hemispheric Stroke Patients With Neglect Symptoms: A Proof-of-Principle Study

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ABSTRACT

Different transcranial direct current stimulation (tDCS) protocols have been tested to improve visuospatial neglect (VSN). So far, methodological heterogenity limits reliable conclusions about optimal stimualtion set-up. With this proof-of-principle study behavioral effects of two promising (uni- vs. bilateral) stimulation protocols were directly compared to gain more data for an appropriate tDCS protocol in subacute neglect patients. Notably, each tDCS set-up was combined with an identical sham condition to improve comparability. In a double-blind sham-controlled cross-over study 11 subacute post-stroke neglect patients received 20 minutes or 30 seconds (sham) tDCS (2 mA, 0.8 A/m^2) parallel to neglect therapy randomized in unilateral (anode-reference: P4-Fp2 10-20 electroencephalography [EEG] system) and bilateral manner (anode-cathode: P4-P3) and 48h wash-out in-between. Before and immediately after stimulation performance were measured in cancellation task (bell test), and line bisection (deviation error). Significant difference between active and assigned sham condition was found in line bisection but not cancellation task. Particularly, deviation error was reduced after bilateral tDCS (hedges g^* = 0.6) compared to bilateral sham, no such advantage were obtained for unilateral stimulation (hedges g^* = 0.2). Using a direct comparison approach findings add further evidence that stimulating both hemispheres (bilateral) is superior in alleviating VSN symptoms than unilateral stimulation in subacute neglect.

Keywords: Hemispatial Neglect; Transcranial Direct Current Stimulation; Stroke; Anodal and Cathodal tDCS; Proof-of-Principle Study

INTRODUCTION

Visuospatial neglect (VSN) is a disabling condition which frequently occurs after large right-hemispheric stroke [1,2]. VSN is characterized by attentional deficits, and a reduction or loss of visuospatial functions [3]. It persists in 30%–40% of patients for more than a year, is associated with poor prognostic outcome [4,5], and high burden on patients in their daily

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Conflict of Interest

The authors have no potential conflicts of interest to disclose.

lives. Established treatment options for VSN show limited efficacy [6], and warrants the search for new treatment strategies. Since cortical reorganization mainly occurs during the first months after stroke [7], the subacute stage (less than 6 months post stroke; [8]) seems to be highly susceptible for treatment to support remission.

In the last years the potential of transcranial direct current stimulation (tDCS) in the treatment of VSN has been tested [9]. TDCS is a non-invasive, painless and easy to handle method to modulate cortical excitability by subthreshold alteration of resting membrane potential [10,11] in targeted brain areas. Various theories on the neuronal mechanisms underlying VSN have been proposed. They are not mutual exclusive, but rather reflect the heterogeneous symptoms in VSN. One classical theory (rivalry theory of Kinsbourne [12-14]) postulates that both parietal lobes may exert reciprocal interhemispheric inhibition. Similarly, Corbetta et al. [15] postulated that spatial neglect is caused by structural and functional dysfunction of two interacting fronto-parietal attention networks (right-lateralized ventral and bilateral dorsal attention network) including specialized nodes that mediates spatial attention, visuomotor behavior (eye-hand coordination) and vigilance [16,17]. Thus, lesions impact functionally connected regions and evoke lesion-induced imbalance in interhemispheric inhibition which results in hypoactivity of the lesioned (affected) and hyperactivity of the intact hemisphere of the brain. To restore the disrupted hemispheric balance so far tDCS was mainly applied over posterior parietal cortex (PPC) with different protocols to i) inhibit the unaffected (cathodal tDCS), ii) to activate the affected hemisphere (anodal tDCS) or iii) to simultaneously activate the affected and inhibit the intact hemisphere (bilateral tDCS). Beneficial effects have been found for anodal [18-20], cathodal [21] as well as bilateral [22,23] protocols.

To date, there is no general agreement about the optimal stimulation site or mode in the treatment of VSN. The limited number of available studies and methodological heterogeneity of usually small-scale studies render definitive conclusions about the choice of intervention difficult [24,25]. Because of impairments in vigilance in severely affected post-stroke patients, neglect associated comorbidities, and safety criteria of tDCS a low recruiting rate can be anticipated in studies with subacute neglect patients [26,27]. Accordingly, a proof-of-principle cross-over study was conducted to gain more exploratory data for an appropriate tDCS protocol to be used in a future multi-session study in post-stroke subacute neglect patients. With tDCS short-term effects have already been observed with single application of brain stimulation, especially when tDCS was administered in conjunction with training [28]. Thus, a randomized double-blind sham-controlled study was designed and different stimulation conditions were applied in each subject to reduce some sources of known variability [29-31]. The following 2 tDCS set-ups were tested for their effectiveness: stimulation (activation) of right lesioned hemisphere, and stimulation of both hemispheres (activation of affected right and inhibition of intact left side). A striking difference from previous studies was that each active tDCS montage was combined with its own identical sham set-up rather than using a single sham condition for all comparisons to improve comparability between conditions. Parietal stimulation was applied and performance in widely used tests measuring VSN symptoms was assessed. Each tDCS set-up was administered once during a computer-assisted neglect treatment therapy in subacute neglect patients. Effectiveness was assessed by comparing performance in target cancellation and line bisection task immediately after the end of treatment between active and assigned sham tDCS condition.

MATERIALS AND METHODS

Procedure and participants

The study was conducted within the early rehabilitation ward of the Kliniken Beelitz GmbH in Brandenburg, Germany. All patients admitted to the clinic were pre-screened for eligibility (**Fig. 1**). Patients were included when they matched the following criteria: first-time ever stroke (ischemic or hemorrhagic, confirmed by neuroimaging, 7–70 days post stroke) within the right brain hemisphere, symptoms of visual neglect, age ≥ 18 years, and right-handed. In case of neglect symptoms, severity was tested by using the German version of the Behavioral Inattention Test (BIT) [32]. Only patients with a BIT-score < 130 were further included. In addition, the treating neuropsychologist confirmed the diagnosis of neglect. Major exclusion criteria were a history of stroke, history of epileptic seizure, severe cognitive impairment, unable to consent, or the presence of a pacemaker, shunt or scar tissue at the stimulation sites. All patients provided informed written consent prior to participation. The study was approved by the local Ethic Committee (State Medical Association Brandenburg; S 15(a)/2018), is registered at the German Clinical Study Registry (DRKS00016853), agrees with CONSORT-Guidelines, and was conducted according to the latest version of the Declaration of Helsinki.

This double-blind, sham-controlled study consisted of 4 treatment sessions (t1–t4). Each of the session included the application of one of the two active or respective sham tDCS protocols during neglect therapy (for details see below). Before and after each treatment session performance in two frequently used neglect tasks, namely a target cancellation task (bells test) [33], and line bisection task (LBT taken from the BIT) were tested. The Center of Cancellation index (CoC) obtained from the bells test served as primary outcome measure. The 4 treatment sessions were conducted sequentially in randomized order. In order to balance feasibility and after-effects a wash-out phase of at least 48 hours in-between (cross-over design) were chosen. The length of the intersession interval is comparable to other studies in subacute neglect patients [24,25]. Two visits before treatment (screening: v1, baseline: v2) and one visit after completion of all four treatment sessions (follow-up: v3) were performed.

Patients who met inclusion/exclusion criteria underwent a screening visit v1 (n = 15). Visit v1 included assessment of stroke-related neurologic deficits (NIH stroke scale [34]), visual impairments (e.g., hemianopsia), global cognition (Montreal Cognitive assessment, MoCA [35]), socio-demographic data, and handedness [36]. Before any treatment, the following measures were applied at baseline (v2): i) the Catherine-Bergego-Scale (CBS; an observational scale performed by nursing staff to evaluate existence and extend of unilateral neglect behavior during different activities of daily living (ADL) [37], ii) 4 paper-pencil tests to measure neglect symptoms: line cancellation, text reading, figure copying, clock drawing all taken from the BIT (for details see below), iii) the Barthel-Index (BI) [38] assessed during clinical routine. To account for spontaneous recovery of neglect symptoms baseline measures were scheduled approximately 1 week after the screening visit v1. Baseline visit comprised 60 minutes. After completion of all 4 treatment sessions baseline tests were repeated (v3) on the last day of the hospital stay (**Fig. 1**). During the course of the study 4 patients had to be excluded due to screening failure (n = 1), withdrawal of consent (n = 1), and medical conditions (second stroke during hospital stay [n = 1], optic atrophy [n = 1]).

Neglect therapy and brain stimulation

An interventional session (**Fig. 2A**) comprised the administration of tDCS simultaneous to conventional neglect treatment therapy. As neglect treatment therapy (duration 20 minutes)

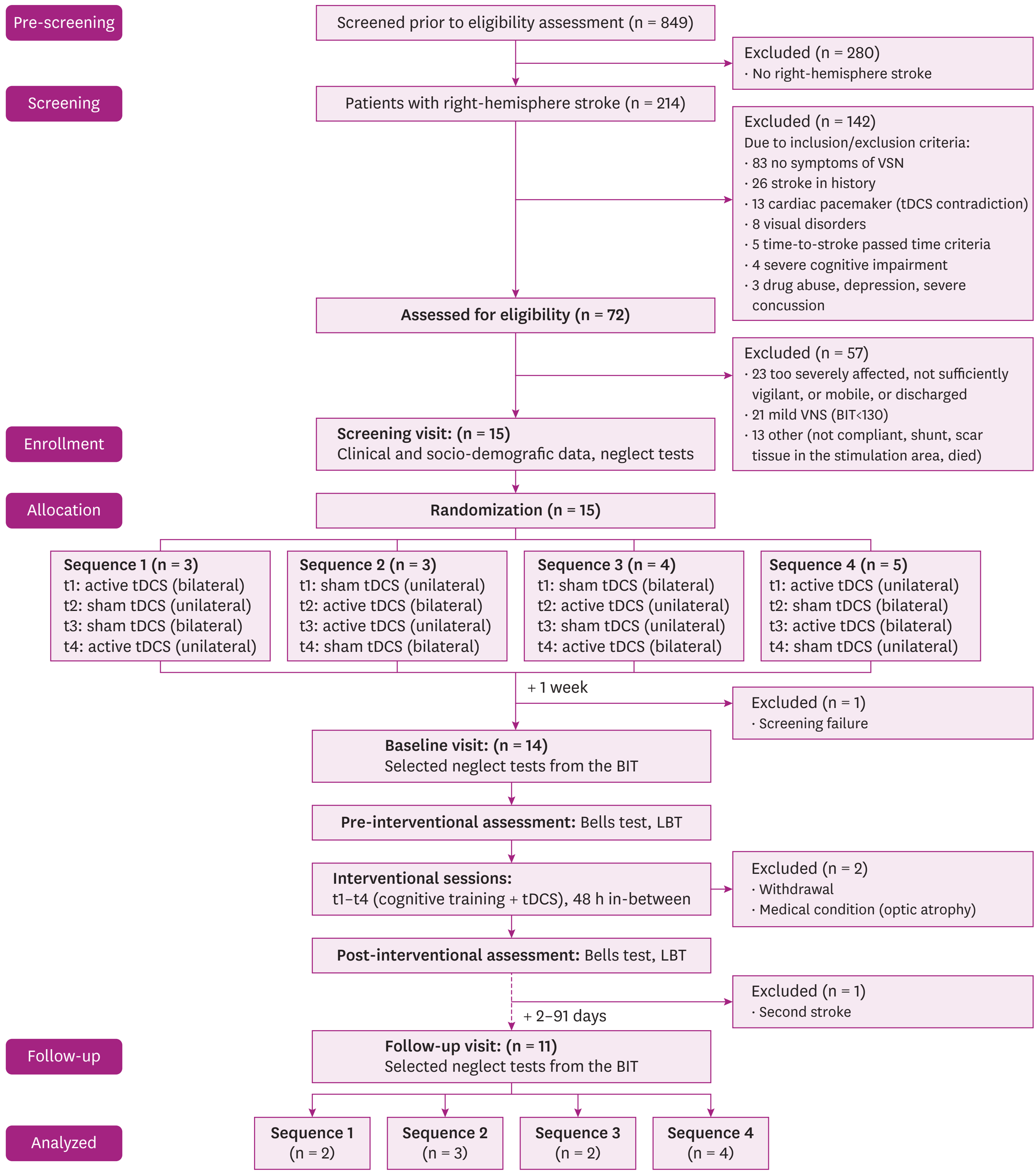

Fig. 1. Flow diagram of the study. Patients (n = 849) admitted to the clinic were pre-screened according to inclusion and exclusion criteria. Out of 214 patients with right hemisphere stroke 15 could be included in the study and underwent a screening visit. Patients were then randomized to one of four possible sequences. Sequences comprised a balanced order of the four different treatment sessions t1–t4 (active or sham non-invasive brain stimulation applied in a uni- or bilateral manner during a cognitive training program). After 1 week 14 patients (one screening failure) underwent a baseline visit before performing treatment session t1–t4. After the end of all treatment sessions and shortly before discharge a follow-up visit was conducted. Three patients had to be excluded due to withdrawal (n = 1) and medical conditions (n = 2) leaving 11 patients for analysis.
tDCS, transcranial direct current stimulation.

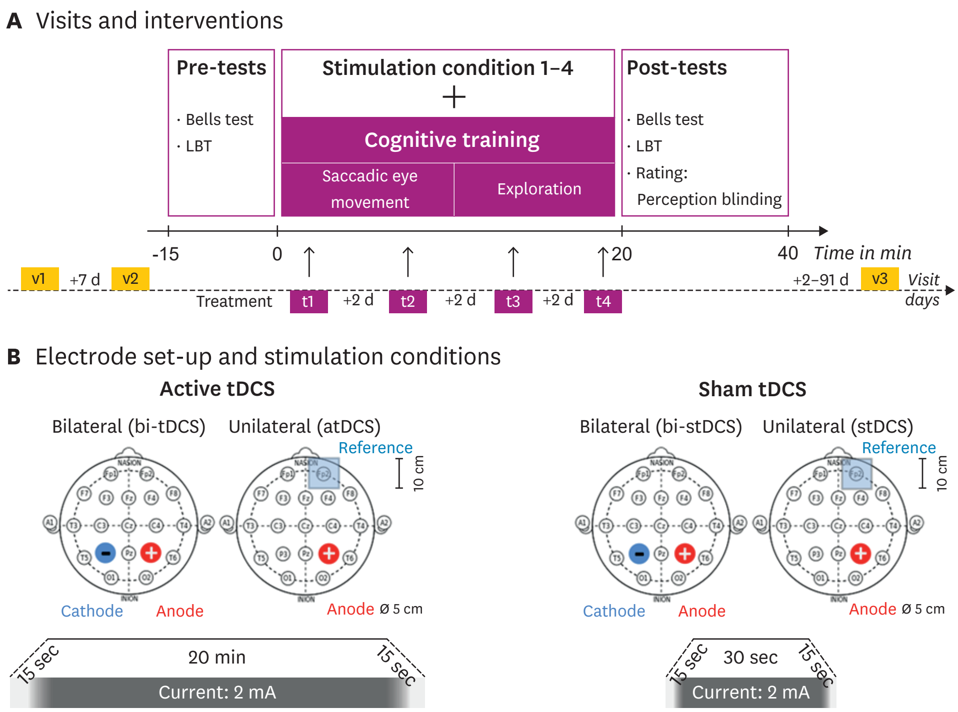

Fig. 2. Study overview. (A) Timeline of visits and interventions. The study started with a screening visit (v1) scheduled one week before baseline (v2) to test for presence and severity of neglect symptoms. At baseline selected neglect tests were applied and repeated at follow-up visit (v3) to monitor long-term changes. After baseline patients performed four interventional treatment (t) sessions (t1–t4) in randomized order. Each treatment session comprised non-invasive tDCS which was conducted during a cognitive training (including a 10 minutes saccadic eye movement and 10 minutes exploration training task). Before and after each treatment session the bells test and LBT were performed. Furthermore, after each treatment session patients were ask to rate whether and, if so, to what extent predetermined side effects of tDCS were perceived and to guess which stimulation (real or sham) they received. (B) Electrode montages. Left: Active (real) tDCS was administered for 20 minutes and current (2 mA) was ramped up and down within 15 seconds. The anode (diameter 5 cm) was mounted at P4 (red circle) according to the EEG 10–20 system. In the bilateral set-up the cathode (diameter 5 cm) was attached to P3 (blue circle). In the unilateral set-up a larger reference electrode (10 × 10 cm) was used to render the stimulation density functionally ineffective. The reference electrode was placed ipsilesional at Fp2 (light blue square). The bilateral set-up intended to activate the affected right and simultaneously inhibit the intact left hemisphere whereas the unilateral set-up aimed to achieve an up-regulation of injured hemisphere. Right: In the sham condition the same bi- and unilateral set-up was used, but sham tDCS was administered for only 30 seconds. Current (2 mA) was also ramped up and down within 15 seconds.
tDCS, transcranial direct current stimulation; LBT, line bisection task; EEG, electroencephalography.

a standardized computer-assisted visual exploration and saccadic eye movement training task (10 minutes each) from the cognitive rehabilitation software RehaCom (version 5.6.2; Hasomed GmbH, Magdeburg, Germany) was conducted. tDCS was administered by a direct current stimulator (StarStim tES; Neuroelectrics, Barcelona, Spain) via saline-soaked sponge electrodes mounted on an EEG-Cap with an intensity of 2 mA and current density of 0.8 A/m^2. This intensity was previously shown to be well tolerated in neglect patients [27]. According to a proposed categorization [39] we used the following two electrode montages: a unilateral bipolar and a bilateral bipolar balanced montage (**Fig. 2B**). The bilateral bipolar balanced montage (hereinafter simply referred to as bilateral set-up) was applied to up-regulate the lesioned right and down-regulate the unaffected left hemisphere in parallel. The unilateral bipolar montage was applied to activate (anodal stimulation) the lesioned right hemisphere (hereinafter simply referred to as unilateral set-up). Electrode positions for each set-up was guided by the international 10–20 EEG system. During bilateral stimulation (bi-tDCS) one sponge disk electrode with a diameter of 5 cm (25 cm^2) was attached to the left and one to the right posterior parietal cortex (PPC; anode: P4, cathode: P3). During unilateral stimulation (atDCS) of the right PPC a sponge disk electrode with a diameter of 5 cm (25 cm^2) was positioned at P4 (anode), and the passive 10 cm x 10 cm reference electrode (100 cm^2)

was placed on the ipsilesional supraorbital region (Fp2). Note, that the use of an enlarged reference electrode renders the stimulation density of reference electrode functionally ineffective [40]. In each set-up tDCS was delivered for 20 min (active tDCS: bi-tDCS, atDCS) or 30 seconds (sham tDCS: bi-stDCS, stDCS) in a ramp-like fashion with a 15 seconds (fade in/fade out) interval at the beginning and the end of the stimulation. Neglect therapy was combined with each of the four tDCS conditions resulting in four interventional sessions in total (t1–t4). The order of interventions was randomized across the patients.

Control of blinding and side effects

After each tDCS session patients were asked to self-rate perceived sensation of itching, pain, burning, heat, taste of metal, or fatigue during stimulation on a 4-point scale (not, mild, moderate, strong). Patients had to judge if they had received active or sham stimulation ("Do you think you received an active or sham stimulation?"). When patients were uncertain (inconclusive), they were motivated when possible to make a clear decision in order to reduce the number of inconclusive answers. Similarly, the blinded assessor was required to rate after each stimulation session whether the patient had received active or sham stimulation. The occurrence of skin-redness was also documented.

Assessments and outcomes

The primary outcome was the CoC index obtained from the bells target cancellation task. The bells test is a paper-pencil task consisting of 35 bells (targets), which are arranged in seven columns (5 targets per column) to assure equal target distribution across a sheet of paper (DIN A4), and which are mixed with 264 distractors (objects). The patient's task was to find and cross out all the bells. The CoC – index was determined according to the procedure described by Rorden and Karnath [41] using software (https://github.com/neurolabusc/Cancel). CoC-index takes into account side and number of omissions in relation to the distance to the center of the Din A4 sheet of paper, and varies on a normalized scale between −1 and 1. A value of 0 means that all targets have been identified by the patients, a value near 1 is related to identification of rightmost, and −1 to leftmost targets.

As secondary outcomes the time to complete the bells test (in second), and performance in the LBT were measured. In the LBT participants were required to bisect each of three lines by placing a mark trough each line as close to the center as possible using their unaffected hand. Length of each horizontal line was 20 cm and the lines were distributed in a staircase manner on a Din A4 sheet of paper with increasing distance (1.4–8.3 cm) to the right margin. Deviation of the mark from the true center of each line was recorded.

For monitoring long-term changes in VSN symptoms during inpatient rehabilitation neglect tests assessed at baseline (v2) were repeated at follow-up (v3). The test battery comprised the line cancellation task (to cross out all of the 40 lines (each 2.5 cm long) evenly distrusted across a Din A4 sheet of paper), text reading (to read aloud a short three-column newspaper article), figure copying (to copy a star, diamond, and flower), and the clock drawing task (to draw a clock with hands and dial). All tests were taken from the BIT. Performance in these paper-pencil tasks were scored according to the procedure described in the manual. Moreover, the CBS was applied to determine neglect severity in everyday activities. Therefore, the nursing staff rated impairment in performance of ADL in relation to 10 categories (e.g., face care, cleaning after meals) on a 4-point scale (no, mild, moderate or severe neglect).

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Data aggregation and statistical analysis

Effects of different stimulation conditions (tDCS vs. sham) under different set-ups (unilateral vs. bilateral) on performance were analyzed by separate linear mixed models (LMM; random intercept models, random intercept for individuals) [42] for the primary (CoC), and each secondary (bell time, LBT performance) outcome. Therefore, bisection of the lines was aggregated to a mean deviation score (LBT in cm) by averaging the respective deviation from the center over the three lines. Repeated measurements (44 data points in total, 11 patients) observed during the 4 treatment sessions (t1–t4) represent level one units in the model, and these measures were nested in the different individuals representing level 2 units. Thus, for each outcome under each stimulation condition one measure per individual was considered. The LMM included set-up (bilateral, unilateral) and stimulation (tDCS, sham) as fixed factors. The measurement conducted before any intervention served as baseline, and was accounted as covariate in the LMM. Further, 'visit' was incorporated as covariate into the LMM to adjust for sequence effects in a cross-over design for the four treatment sessions (dummy coded variable: 1, 2, 3, and 4). Estimated marginal means of the pair-wise comparisons (mean differences and 95% confidence intervals [CIs]) are reported to compare modulation of active compared to sham tDCS, respectively, for the bilateral and unilateral configuration. Effect size for the total model and for each of the fixed effects were determined by computing semi partial R^2 ($R^2_{\beta*}$) [43] to infer the amount of variance explained by the model. Hedges g^* [44] was calculated as effect size for the pairwise comparisons between conditions using baseline adjusted means for calculation. Calculation was performed by using an online tool retrieved from: https://matheguru.com/stochastik/effektstarke.html.

For monitoring long-term changes performance in pre- and post-intervention assessed tests and scores (v2 and v3) were analyzed by Wilcoxon signed rank test. Hedges g^* is reported as effect size for differences in means and r for differences in medians ($r = z/\sqrt{[N]}$). Reported sensations, skin redness and guessing answers (blinding integrity) were grouped according to the categories "active" (bi-tDCS, atDCS) and "sham" (both sham conditions) tDCS. Sensations were further aggregated into a new dichotomous variable "any sensation" (present /absent) and proportions of patients under active (bilateral and unilateral) and sham (bilateral and unilateral) tDCS were compared by a non-parametric McNemar test for reported "any sensation" and obszerved skin redness (dependent variables). Blinding integrity was controlled by determining odds ratios (OR). Guessing answers after each interventional session were coded as: a) active, b) inconclusive, c) sham. Binary logistic mixed models were applied to estimate if guessing of the stimulation condition was associated with an active stimulation condition by accounting for the clustered data structure (repeated measures, random intercept model; melogit command in Stata). Patient's judgements were included as independent (nominal: active, inconclusive, non-active), the actual stimulation condition as dependent variable (coded: active tDCS: 1, stDCS: 0). To evaluate assessor's judgments separate binomial tests which refer to the proportion of correct responses about stimulus condition were applied for active and sham tDCS.

All statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS, version 26; IBM Corp., Armonk, NY, USA) or Stata Statistical Software, Release 15 [45], and the free statistical software R [46]. All secondary analyses were done within an exploratory framework without adjustment for multiple testing.

RESULTS

Of 15 included patients data of 11 (aged 54 to 83 years, 6 female, 11 years of education on average) were available for final analysis. On average, patients were tested within 1 month after stroke. Nearly half of them (46%) were additionally diagnosed with hemianopsia, and most of the patients (82%) suffered from an ischemic stroke. **Table 1** shows characteristics of these patients and summarizes the performance in selected neurological scales and neglect tests (BIT score) at inclusion.

Selected neglect tests were repeated at screening and baseline visit (one week in-between) to control for spontaneous remission. The z-scores of conducted Wilcoxon tests were all ≤ 1 suggesting that no substantial improvement occurred within one week. Monitoring of VSN symptoms and functional scores during inpatient rehabilitation (v2 vs. v3; see also **Table 2**) revealed increased performance in figure copying task (r = 0.8) and text reading (r = 0.7), but not in clock drawing and line cancellation task (both r's < 0.1) during the hospital stay. Furthermore, an increase in functional scores related to ADLs (BI: Hedges g* = 1.3, CSB: r = 0.8) was observed. The mean difference delay between visit v2 and v3 was 57 days (standard deviation = 29).

Table 1. Patient demographic and clinical characteristics (n = 11)

Characteristics	No. (%)	Mean ± SD	Median [IQR]	Min, Max
Female sex	6 (54.5)			
Age in years	11 (100.0)	71 ± 9	69 [65–79]	54, 83
Education in years	11 (100.0)	12 ± 2	11 [10–12]	10, 16
Ischemic stroke	9 (81.8)			
Time from stroke in days	11 (100.0)	32 ± 15	28 [22–45]	13, 65
MoCA sum score	11 (100.0)	17 ± 5	17 [15–22]	8, 24
BIT sum score	11 (100.0)	64 ± 37	55 [34.5–103.5]	15, 120
NIHSS	11 (100.0)		11 [6–14]	6, 15
mRS	11 (100.0)		5 [4–5]	3, 5
Presence of hemianopsia	5 (45.5)			

SD, standard deviation; IQR, interquartile range; MoCA, Montreal Cognitive Assessment (max, 30 points); BIT, Behavioral Inattention Test (lower scores indicate more severe visual impairment); NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Score.

Table 2. Comparison of performance in selected neglect tests and functional scores at inclusion and shortly before discharge from clinic

Test/Scale	Visit	No.	Median [IQR]	Min, Max	v2 vs. v3 z-score	Hedges g* or r
Figure copying test	v2	11	1 [0–7]	0, 7	−2.4*	0.8
	v3	10	6 [2–8]	2, 7		
Clock drawing	v2	11	2 [1–2]	0, 3	−0.1	0.03
	v3	10	2 [2–2]	0, 3		
Text reading	v2	9	44 [14–104]	0, 136	−2.2*	0.7
	v3	10	94 [55–139]	65, 135		
Line canceling	v2	11	32 [17–36]	12, 36	−0.3	0.1
	v3	10	35 [23–36]	17, 36		
CBS	v2	10	12 [9–16]	2, 22	−2.4*	0.8
	v3	10	6 [2–9]	0, 12		
BI	v2	11	10 [5–25]	5, 50	−2.5†	1.3
	v3	10	32.5 [21.25–63.75]	5, 90		

IQR, interquartile range; v2, baseline visit; v3, follow-up visit; CBS, Catherine-Bergego Scale (higher scores indicate more extend unilateral neglect symptoms); BI, Barthel Index.
p ≤ .05, †p ≤ .01; Effect size: Hedges g interpretation: 0.2–0.3 'small effect', 0.3–0.5 'moderate effect', ≥ 0.8 'strong effect', r (for median differences) interpretation: 0.3 'small effect', 0.3–0.5 'moderate effect', > 0.5 'strong effect'.

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Cutoff scores have been previously defined for neglect tests. According to these scores 9 out of 11 patients showed pathological performance in both, cancellation task (cutoff: CoC = 0.083) [47], and LBT (cutoff: ≥ 6.5 mm) [48]. Two patients exhibited spatial neglect primarily in bells test (CoC: 0.728 and 0.548), but performed close to LBT cutoff score (LBT: 5 and 6 mm deviation from the true center).

Analysis of tDCS-related effects

Primary outcome

LMM analysis revealed for CoC index no significant differences between active and sham tDCS neither for bilateral (mean difference and 95% CI: 0.02 [−0.11,0.16], g^* = 0.1) nor for unilateral (mean difference and 95%CI: −0.05 [−0.19, 0.08], g^* = 0.2) set-up (**Table 3**).

Secondary outcomes

Regarding the secondary outcomes a stimulation effect was limited to LBT performance (**Table 3**). Overall, semi partial R^2 was 0.9 and indicated that the model explained the LBT data in a sufficient way. Comparisons of estimated marginal means (see also **Figure 3**) revealed a beneficial tDCS effect on line bisection deviance for the bilateral set-up. Here, deviation after active (bi-tDCS) stimulation was less than after respective sham (bi-stDCS) stimulation (mean difference and 95% CI: −1.12 [−2.14, −0.10], g^* = 0.6). Calculating the effect for the unilateral set-up revealed no substantial advantage of active (atDCS) compared to respective sham (stDCS) stimulation on LBT performance (mean difference and 95% CI: −0.21 [−1.23, 0.82], g^* = 0.2).

Sensations of stimulation and blinding integrity

The following sensations were perceived most frequently: burning (36%), fatigue (32%), itching (27%), and heat (18%). The distribution was rather balanced among stimulation conditions (**Table 4**). Specifically, patients reported sixteen times sensation of burning (7 under active stimulation), twelve times sensation of itching (7 under active stimulation), eight times sensation of heat (5 under active stimulation), and fourteen times sensation of fatigue (7 under active stimulation). Most of reported sensations were rated as mild or moderate under both, active and sham tDCS, indicating that levels of comfort were comparable under the different stimulation conditions. Overall, marginal proportions of reporting any sensations under active or sham stimulation were not substantially different (McNemar test: p = 1.00). No other adverse events were reported after or during the study period.

Table 3. Results of linear mixed models analysis with fixed factor set-up, and tDCS condition for primary (CoC derived from bells test) and secondary (time in completing bells test, line bisection) outcomes and baseline and visits as covariates

Outcome	Primary				Secondary							
	Bells test: CoC index				Time (sec) completing bells test				LBT: deviation from center			
	No.	Estimate	95% CI	R^2	No.	Estimate	95% CI	R^2	No.	Estimate	95% CI	R^2
Model total data points	44			0.53	28			0.33	44			0.90
Individuals	11				11				11			
Constant		0.33	−0.005, 0.66			168	64, 273			−1.26	−2.93, 0.40	
Bi-hemisph. set-up (ref.: unilateral)		−0.06	−0.20, 0.07	0.02		−1	−88, 85	0.00		0.64	−0.83, 1.66	0.04
tDCS condition (ref.: sham)		−0.05	−0.19, 0.08	0.01		−33	−119, 52	0.04		−0.21	−1.23, 0.82	0.01
Bilateral set-up × tDCS condition		0.08	−0.12, 0.27	0.01		15	−107, 137	0.004		−0.91	−2.36, 0.54	0.04
Covariates												
Baseline		0.57	0.07, 1.06	0.51		0.22	0.03, 0.42	0.27		1.27	1.01, 1.53	0.89
Visit		−0.04	−0.08, 0.003	0.07		−13	−41, 14	0.06		−0.32	−0.65, 0.002	0.09
Estimated marginal means	df	Mean diff	95% CI	p	df	Mean diff	95% CI	p	df	Mean diff	95% CI	p
Set-up		stim−sham				stim−sham				stim−sham		
Bilateral	29	0.02	−0.11, 0.16	0.75	22	−19	−107, 69	0.67	**29**	**−1.12**	**−2.14, −0.10**	**0.03**
Unilateral	29	−0.05	−0.19, 0.08	0.42	22	−33	−119, 52	0.43	29	−0.21	−1.23, 0.82	0.69

tDCS, transcranial direct current stimulation; CoC, Center of Cancellation index; LBT, line bisection task; CI, confidence interval.

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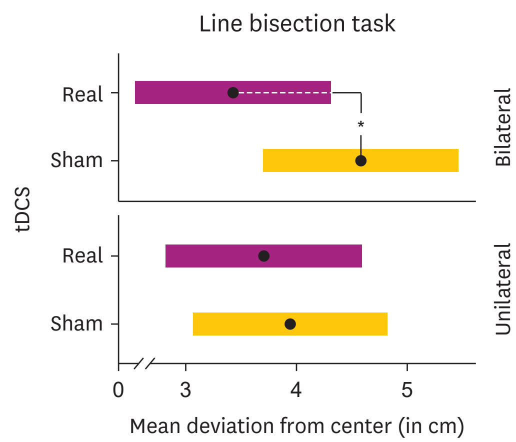

Fig. 3. Deviation from the center (in cm) in the LBT. Depicted means are adjusted for baseline LBT performance and sequence effects for the four treatment sessions (dummy coded variable: 1, 2, 3, and 4). The upper panel shows results for the bilateral (simultaneous activation of injured and inhibition of intact hemisphere) and the lower panel for the unilateral (activation of injured hemisphere) set-up. Black circles indicate mean deviation from the true center and bars represent 95% CI. Dark grey filled bars correspond to active (real) and light grey filled bars to sham tDCS condition. The least deviation (best performance) is achieved by bilateral tDCS stimulation which is less than in respective sham condition (effect size hedges g^* = 0.6). For the unilateral set-up no substantial benefit was observed between active and corresponding sham condition (effect size hedges g^* = 0.2). Total number of 11 subacute stroke patients was included.
LBT, line bisection task; CI, confidence interval; tDCS, transcranial direct current stimulation.
*$p < 0.05$.

Table 4. Frequency of reported sensations after active and sham tDCS in bi- and unilateral stimulation

Sensation	Active tDCS		Sham tDCS	
	Bilateral	Unilateral	Bilateral	Unilateral
Itching	2	4	3	3
Pain	1	0	1	1
Burning	4	3	5	4
Heat	2	3	1	2
Taste	0	0	0	1
Fatigue	4	3	5	2
Other	1	1	1	1
Frequency of any reported sensation*	8	8	7	7

Frequency is given as number of patients who reported this sensation perceived after tDCS stimulation.
tDCS, transcranial direct current stimulation.
*Proportions of patients who reported any sensations between active (bilateral, unilateral) and sham (bilateral, unilateral) tDCS were compared by McNemar test. Marginal proportions were not substantially different from each other (p = 1.00).

Each patient was asked after each stimulation session whether they believed they had received active or sham tDCS resulting in a total of 44 judges. The OR of correct guessing an active tDCS condition compared to wrongly judge an active tDCS condition as sham was 1.33 (95% CI: 0.38, 4.62; p = 0.65). The assessor was also required after each stimulation session to rate the applied condition according to active or sham. The binomial tests revealed, that neither after the active (59% correct assignments, p = 0.52) nor sham (68% correct assignments, p = 0.13) tDCS the assessor has identified the correct stimulation condition reliably about chance. Skin redding occurred after both stimulation conditions, but marginal proportions were not substantially different (McNemar test: p = 0.25). Specifically, 4 out of 11 patients showed skin redding after both, active as well as sham tDCS, and 3 patients only after active tDCS. Taken together, reported sensations and OR suggest that applied tDCS was well tolerated and that blinding procedure was successful.

DISCUSSION

The purpose of this double-blind proof-of-principle study was to gain information whether parietal applied bi- or unilateral tDCS administered during standard computer-assisted neglect treatment would be more effective in treating neglect symptoms when compared to an identical sham control for uni- and bilateral set-up. The results of this study will be used to establish the stimulation parameters for a subsequent larger multi-session study. The effect of tDCS on the tests defined as primary and secondary outcomes parameters were as follows: while there were no effects seen in the bells cancellation task in terms of either the CoC measure (primary outcome) or time taken to complete the bells task (secondary outcome), an effect of moderate effect size on LBT performance (secondary outcome parameter) was observed for bi- but not for unilateral set-up when comparing active tDCS to the corresponding sham condition (bi-tDCS vs. bi-stDCS; atDCS vs. stDCS). Overall, both tDCS set-ups were well tolerated despite the current density of 0.8 A/m^2, which is higher compared with other published studies, and no evidence was found for compromised blinding.

In accordance with Sunwoo et al. [22], who also directly compared efficacy of a bi- and unilateral tDCS protocol on VNS, our results show a superiority of the bilateral compared to the unilateral stimulation setting (exploratory analysis). Our current findings are supported by a recently conducted meta-analysis [25] that was performed on the very limited available data and indicate larger effect size for bilateral compared to unilateral applications. It is possible that simultaneous anodal (right) and cathodal (left) stimulation of both hemispheres is more effective because it has a greater impact on the entire network, or even on both tightly linked attentional systems, the right-laterized ventral and non-lateralized dorsal system [15]. Some evidence for differentially induced effects by uni- and bilateral stimulation are provided by imaging data in motor studies [49]. Specifically, these studies suggest that bilateral stimulation evoke more complex modulations in both hemispheres [50] while unilateral stimulation causes more local modulations [51]. However, to substantiate this assumption, in future studies recording of brain activity (EEG or functional magnetic resonance imaging [fMRI]) simultaneous to tDCS in neglect patients would be helpful.

Contrary to Sunwoo et al. [22] and a number of other previous studies [18,52] we could not demonstrate an impact on improving VSN symptoms by unilateral anodal stimulation of the lesioned hemisphere. Given the randomization of treatment order and wash-out phase (longer than in Sunwoo et al. [22]), carry-over effects seems an unlikely explanation for the lack of unilateral stimulation effect. However, differences might be due to other decisive variations in tDCS set-up as well as the sample studied. In fact, in Sunwoo's study [22] a dual mode with two independent devices (two tDCS circuits) was applied to stimulate the hemispheres, and they used a contra—and not ipsilesional—reference electrode in their montage. However, reference electrodes are probably not completely inert and may thus affect electric field orientation [53-55] which in turn may lead to differences in neurobiological effects. Similarly, using an active sham condition could provoke unintended biological effects [56]. Consequently, existing inconsistencies between active sham conditions in comparative (uni- vs. bilateral) studies [22,50,57] may also contribute to conflicting results. Two other randomized controlled studies have applied tDCS in subacute patients and found a beneficial effect of unilateral anodal compared to sham stimulation. However, they did not compare bi- to unilateral set-up and different with regard to other important methodological aspects such as the use of a contralesional reference [18], or implementation of a very short intersession interval [52] rendering a direct comparison to our study difficult.

With regard to the studied sample, phase of recovery has to take into account. In contrast to Sunwoo et al. [22] the present study focused on the subacute phase after stroke, which is supposed to be the most intense phase of plasticity. Depending on the underlying dynamic recovery processes [58] and associated shifts in activation between hemispheres [59,60] efficacy of uni- or bilateral stimulation may therefore change over time. Albeit the contribution of the contralesional hemisphere in recovering has not been fully elucidated lesion size and thus residual intra- and interhemispheric structural and functional reserve are considered a critical parameters influencing effectivity of tDCS [61-63]. Particularly, in large lesions the risk to stimulate over necrotic tissue is increased and may hamper efficacy, possibly affecting unilateral (shunting of electrical current) more than bilateral application in which cathodal stimulation of healthy hemisphere is at least maintained. In sum, transcallosal inhibition can be addressed with uni- or bilateral approaches. The anode is the shared element in both protocols. While transient depolarization of the affected parietal hemisphere might be helpful in some cases, concurrent hyperpolarization of the intact hemisphere might provide additional benefit especially during subacute phase as has been shown here and in other studies. A future challenge will be to identify residual functional and structural integrity and to individually customize tDCS protocols.

TDCS-related effects were primarily observed in LBT performance, but not in cancellation task (e.g., Sunwoo et al. [22]). Although LBT may not be specific to the diagnosis of neglect (e.g., Sperber and Karnath [64]), bisection bias is nevertheless considered a core aspect of the heterogeneous neglect symptomatology (see also McIntosh et al. [65]). In fact, our results are consistent with other findings which showed that LBT is often the most sensitive test in neglect patients responding to parietal tDCS (cf. Olgiati and Malhotra [24]). Several reasons may account for this finding. Both tasks differ with respect to cognitive load and demands, which is also confirmed by some factorial analysis [65,66] where the 2 clinical tests load on different components reflecting different aspects of the neglect. While LBT requires exploration of line length, visual judgment, and low attentional control in the neglected hemifield, cancellation tasks are more difficult and require a systematic exploration of the intact and neglected visual field, high attentional control to suppress distractors during search (executive component), and more time-on-task. The latter is likely to be a particularly important aspect in more severely impaired patients. This view of different cognitive components is further supported by a lesion-symptom mapping analysis performed by Verdon et al. [66]. Based on their factorial analysis, the authors interpreted a bisection task as perceptual visuospatial and a cancellation task as explorative visuospatial component. For the first task they identified the right inferior parietal lobule, for the second the dorsolateral prefrontal cortex as neuronal correlate. It remains to be tested whether stimulation of other, perhaps prefrontal targets, may be more effective in improving performance on cancellation tasks. However, a fronto-parietal network has been suggested as neuronal basis [67,68] for spatial neglect. Many different cortical or subcortical lesions contribute to spatial neglect, but as proposed by Corbetta et al. [15,69] focal lesions can also cause dysfunction in remote neural systems beyond the site of injury, especially if these regions serve as specialized nodes for spatial processing. Thus, stimulating these critical parietal nodes may be most promising to restore normal network function. Alternatively, it is conceivable that depending on task and task demands beneficial tDCS effects may be measurable at different time points after stimulation ends, or after repeated sessions which was not tested in the present study. In sum, depending on task- and patient-related factors different tests may be differentially sensitive to a single application of parietal tDCS. While less complex tasks such as line bisection may benefit from short-term single interventions, more complex (cancellation) tasks may not.

Due to lesion caused loss of brain tissue higher current densities might be necessary for clinically relevant effects [70] with the risk of increased side effects and reduced subject blinding. Similar to our previous study [29] patients tolerated the procedure well, and, even more clearly than in our earlier study, integrity of blinding could be demonstrated. Blinding success was inferred from the fact that correct guessing was not substantially increased compared to wrongly judge tDCS as sham stimulation (OR and 95% CI, current study: 1.33 [0.38, 4.62]; previous study: 10 [0.65, 154.4]). Differences in OR between studies might be explained by a reduction of inconclusive answers in the present compared to our previous study, among other factors. It should be noted that validity of typical post-training guesses has been recently questioned as sensitive measure for blinding [71] and instead 'online probe questions' during the course of stimulation is recommended by these authors. Besides the strongest sensations of stimulation might occur during the initial period [72], which is why at the beginning a very brief (sham) stimulation is applied in placebo condition to provoke comparable sensations, study of Turner et al. [71] is subjected to some limitations. Most importantly, in study of Turner et al. [71] young healthy subjects were studied who (due to study design) were even more attentive to possible sensations while their motor cortex was stimulated. Older adults and neglect patients in particular, however, are assumed to be less sensitive and thus blinding is probably of greater concern in healthy young subjects [29,73,74]. Nevertheless, this highlights that blinding and assessing of blinding in tDCS research is still poorly studied in different populations and deserve further investigation in future studies.

Several limitations should be acknowledged when interpreting results of this study. First, the study was faced with the problem of a small, heterogeneous post-stroke patient sample size that result in low statistical power and, consequently, rather weak effects along with limited generalizations. However, the study was designed from the beginning as proof-of-principle study to gain preliminary evidence for an appropriate tDCS set-up for subsequent use in a larger study. Furthermore, the sample studied is representative of our clientele to be examined in a larger future trial. Second, the transfer of results from single session to a planned multi-session application is, in fact, not uncritical as additional factors could influence the tDCS effect, especially when tDCS is used in conjunction with a training task. Nevertheless, single-session applications are considered suitable to verify immediate probably short-lived effects given the basic idea of a multi-session design that induced effects after one session become larger and/or more sustained with each bout of stimulation [75]. Third, this study focused on a purely behavioral outcome. The underlying functional changes in neuronal networks are certainly of great interest to clarify the predictors of tDCS and mechanisms of the respective effects. However, clinically meaningful effects should manifest in behavioral changes.

CONCLUSION

TDCS is increasingly discussed as an encouraging approach for the treatment of VSN. Following the interhemispheric rivalry model, excitatory and inhibitory protocols were previously tested in a series of small-scale, methodologically heterogeneous studies without consensus about optimal stimulation protocols. Behavioral results of the direct comparison of two different, promising tDCS set-ups (bi- vs. unilateral tDCS) tend to favor a bilateral mode of parietal stimulation in subacute neglect patients. However, the results remain exploratory. The efficacy of adjunctive bilateral tDCS to improve outcomes in subacute neglect patients should be systematically investigated in studies with larger sample size that would also allow stratification of patients for example with respect to neuronal (size and location of the lesion, transcallosal integrity) as well as behavioral indices like neglect subtypes (symptom-leading aspects), and/or severity of hemineglect. Further, heterogeneous samples not only resemble naturally occurring patient samples in clinics, but careful and systematic assessing of various clinical characteristics like stroke etiology, cognitive (visual working memory), visual (hemianopsia), or emotional deficits would also add information on potentially confounding or modulating factors. Together with accumulating knowledge of the underlying neuronal and functional changes, this may improve our understanding when tDCS is adaptive or when it may be maladaptive in terms of affecting reorganization processes in neglect patients, with the ultimate goal to match the "right" patient to the "right" treatment (personalized approach).

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