

Blinding in electric current stimulation in subacute neglect patients with current densities of 0.8 A/m²: A cross-over pilot study

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Research note

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Abstract

Objective Transcranial direct current stimulation (tDCS) is a promising adjuvant technique to improve standard care neglect therapy in patients suffering from stroke. Current densities in tDCS are modeled by tissue distribution in the brain. Therefore, we hypothesized that higher current densities are needed in aged stroke population to counteract age related brain volume loss. Here it is still unresolved whether blinding of participants can be achieved. Our aim was to test whether stroke patients with left-sided hemineglect are able to differentiate beyond chance active tDCS from sham stimulation at a current density of 0.8 A/m^2 . Therefore, we investigated 12 early subacute stroke patients with left-sided hemineglect in a cross-over design with two stimulation settings (active/sham stimulation in randomized order). Stimulation was performed simultaneous to standard care neglect therapy with 0.8 A/m^2 and progress of neglect symptomatology was monitored during inpatient rehabilitation.

Results Our sample exhibited higher odds of correct guessing an active tDCS condition compared to wrongly judge an active tDCS condition as sham stimulation (Odds ratio 10.00, 95%CI: 0.65 - 154.40, $p = 0.099$). Therefore, we must question the feasibility of blinding success in studies with current densities of 0.8 A/m^2 . Assessment in multisession protocols still warrants further investigation.

Introduction

Large right hemispheric stroke often results in a multimodal neglect (1,2). Although symptoms persist for more than a year in 30 – 40 % of patients, and the poor prognostic outcome of neglect (3), only few therapies have been established in clinical practice (4). A study combining conventional rehabilitation therapy and transcranial direct current stimulation (tDCS) showed a beneficial effect on the rehabilitation of neglect symptoms in stroke (5).

The effect of tDCS on cortical excitability is known to be modulated by different parameters such as the stimulation site, duration and current density (in A/m^2) (6,7,8). In neglect patients different current densities ($0.29 - 0.8 \text{ A/m}^2$) have been applied (9,10). The rationale behind is modulating a right hemispheric network by tDCS, but according to head modelling simulation studies (11) electric fields are affected by the amount of different tissue types in the brain. Considering the age-related natural loss of brain tissue (12) we hypothesize that higher current densities in tDCS are needed to observe clinically relevant effects. However, higher current densities might prevent effective blinding of sham stimulation protocols e.g. due to elicited sensory discomfort.

In this pilot study we investigated whether neglect patients can discriminate between real active (atDCS) and sham stimulation (stDCS) beyond chance when current densities of 0.8 A/m^2 are applied.

Methods

A cross-over, double-blinded intervention pilot study was performed to assess the feasibility of blinding procedure and the recovery of visuospatial functioning in patients with first-time ever stroke within the

right hemisphere. This pilot study closely agrees with CONSORT-Guidelines (Additional file 3).

The study was conducted within the neurological rehabilitation ward of the Kliniken Beelitz GmbH in Brandenburg, Germany. All patients were pre-screened for eligibility. Inclusion criteria comprised: ischemic or hemorrhagic stroke within the right hemisphere (confirmed by neuro-imaging), early subacute phase (> 7 and < 56 days after stroke onset), age ≥ 18 years, right-handed (13), and residual visuospatial neglect symptoms. Major exclusion criteria included: history of stroke, severe cognitive impairment, epilepsy and the presence of a pacemaker (for details see table 1).

Procedures

The presence of visuospatial neglect (VSN) was tested at screening visit using selected tests from the Behavioral Inattention Test battery (BIT, German version: Star Cancellation, Figure Copying, and Line Bisection (14)). Only patients with impaired performance in at least two of these tests, and confirmed VSN diagnosis by the treating neuropsychologist entered the baseline visit, which was scheduled approximately one week after the screening visit to account for spontaneous recovery of neglect symptoms. Subsequently, an atDCS and stDCS session were applied in randomized order (48 h wash-out period in between) during standard care neuropsychological therapy (30 min, exploration tasks) by the treating therapist. On the last day of the hospital stay patients were re-assessed (follow-up).

The randomization list was generated by a self-written script (Additional file 1) using R-statistical software (random generator). A stimulation protocol for atDCS and stDCS were programmed and performed by the same assessor (TR). Patients and treating therapists were blinded to the stimulation protocol.

tDCS was applied by a StarStim tDCS stimulator (Neuroelectrics, Barcelona, Spain) via electrodes (round electrodes, 25 cm^2) mounted over both posterior parietal cortices (P4-anode; P3-cathode, bi-hemispheric protocol) determined with the international 10-20 EEG System with an intensity of 2 mA (current density: 0.8 A/m^2). tDCS was delivered for 20 min (atDCS) or 30 s (stDCS) in a ramp-like fashion with a 15 s (fade in/fade out) interval at the beginning and the end of the stimulation.

Assessments

After each tDCS session patients were ask (by TR): "Do you think you received an active or sham stimulation or are you undecided?" to assess blinding success, and for the sensation of itching, pain, burning, heat, taste of metal, or fatigue during stimulation. Adverse events were monitored throughout the hospital stay and were noted if they could be related to the intervention.

At baseline demographic and clinical data were recorded including impairment caused by stroke using the National Institute of Stroke Scale (NIHSS) (15). Global cognitive functioning were assessed by the Montreal Cognitive Assessment (MoCA) (17). Neglect symptoms were assessed at baseline and follow-up (Star-, Letter-, and Line Cancellation, Line Bisection, Figure Copying and Text Reading).

Statistical Analysis

To demonstrate the feasibility of blinding procedures 12 patients were included. Eligible patients were hypothesized to be around 6 % of all stroke patients admitted to the clinic. An adequate number was intended to acquire long-term data which should guide sample size calculations of clinically relevant differences in future trials.

Each patient evaluated stimulation mode twice for stDCS and atDCS. Answers were coded as: a) sham, b) indifferent, c) active. Binary logistic mixed models were applied to estimate if guessing of the stimulation condition was associated with tDCS-stimulation condition by accounting for the clustered data structure (repeated measures, random intercept model) (melogit command in stata). Patients judgements were included as independent (nominal), the actual stimulation condition as dependent variable (coded: atDCS: 1, stDCS: 0).

All analyses were performed in an exploratory framework with descriptive statistics presenting mean (SD) or median [IQR] depending on the distribution of the data. Changes between baseline and follow-up were analysed using paired t-tests or Wilcoxon signed rank test where appropriate. Cohen's d with confidence intervals (CI) are reported as effect size. Analyses were not corrected for multiple testing.

All programming and analyses were done using R-Statistical Software Version 3.4.4 (18) or Stata Statistical Software, Release 15 (19).

Results

From July, 23rd 2018 until February, 2nd 2019 686 patients were screened for eligibility. Twelve patients (3 %) met all inclusion and exclusion criteria and gave written consent to participate. Three patients could not be assessed at follow-up due to early discharge ($n = 2$) or severe progression of visual impairment (for details see Additional file 2: Figure S1).

Median time from stroke onset to inclusion was 26 [16 – 46] days, between screening and baseline visit 5 (3) days without signs of spontaneous recovery. Patients (7 females) were between 65 and 83 years old (median 77). NIHSS was 7 [2 – 10]. Three patients showed signs of anosognosia and two patients were later on suspected to have hemianopsia. In all but Line Cancellation test, patients showed impaired performance in neglect tests at baseline (for details see table 2).

Each patient evaluated both conditions (atDCS and stDCS) resulting in a total of 24 judges. Four out of twelve times the atDCS and five out of twelve times the stDCS protocol were identified correctly. Twelve times out of 24 ratings patients were indifferent, six times when evaluating stDCS and six times when evaluating the actDCS protocol (table 3). Marginal probabilities for having an atDCS condition if active was guessed was 80.0% (95%CI: 30.9 % - 97.3 %). If sham was guessed the marginal probability of

actually having the atDCS condition was 28.6 % (95%CI: 7.2 % - 67.3 %). If the judgement was indifferent the marginal probability of having an atDCS condition was 50.0 % (95%CI: 24.4 % - 75.6 %). The odds ratio of correct guessing an atDCS condition compared to wrongly judge an atDCS condition as sham was 10.00 (95%CI: 0.65 - 154.40, $p = 0.099$). Wash-out phase between intervention sessions was 3 (2) days.

After intervention patients reported three times sensations of itching (all during atDCS) and of burning (one during stDCS and two during atDCS), and one time the sensation of heat (during atDCS). In two of the seven cases patients correctly guessed atDCS stimulation. In all other cases patients were indifferent. No other adverse events were reported after intervention or during the study period.

Mean difference between baseline and follow-up was 40 days (26), and no significant improvement was revealed, but a large effect size in the Line Bisection test was observed (Cohen's $d = 1.0$, 95%CI: -0.2 - 2.1) (table 2).

Discussion

Considering that reliable blinding plays a pivotal role in placebo-controlled clinical trials, and higher current densities in tDCS are probably needed to observe clinically relevant effects in brain damaged subjects, this study aimed to assess the effectiveness of blinding of a stDCS versus atDCS stimulation protocol applying a high current density of 0.8 A/m^2 . Patients were not able to detect both intervention sessions correctly beyond chance, but presented with higher odds of correctly identifying atDCS in comparison to wrongly judging the atDCS condition as sham. Recovery from visuospatial functioning could be at least demonstrated for performance in Line Bisection test.

Our findings resemble those of previous studies (20, 21) who studied successful blinding in young (20), and old (21) healthy subjects with a similar stimulation intensity (2 mA , $20\text{min}/30\text{min}$), but lower current density (0.57 A/m^2) in a cross-over design. In both studies only operators were able to reliably distinguish atDCS from stDCS, mainly because of skin reddening evoked by atDCS. However, probably due to increased experience with tDCS in a within-in subject design participants have tended to identify stimulation mode more correctly in the second of two sessions. This might also explain the observed higher odds of correctly identifying the atDCS condition in our study. Therefore, effective blinding using a current density of 0.8 A/m^2 may appear questionable. Given that double blinding is considered as gold-standard, strategies to prevent and control for violation of blinding should be implemented, e.g. by reducing skin reddening, or by assessing outcomes by others than the operator.

An association between stronger stimulation and larger sensations, which could accordingly compromise subject blinding, have been reported in healthy subjects (22,23). O'Connell et al. (23) observed more precise guessing in atDCS and stDCS sessions (cross-over design) in young subjects (0.57 A/m^2 , 20 min), but this could have been provoked by the short ramping period in sham condition compared to others (5 s

vs 15 s). Short ramping might result in a greater contrast between stDCS and atDCS regarding to sensations such as itching and burning. Further, knowledge about receiving both stimulation conditions (cross-over design) might have influenced the judgments (20, 22, 23). Besides, age-differences in perception and sensation of tDCS-related skin effects have been reported previously (24, 25), and also differences between young and older adults in complaining about adverse effects may exits (26). The latter may be even more relevant in clinical (brain damaged) populations. Moreover, in clinical populations correct guessing can also be associated with treatment effects (symptom reduction) under atDCS compared to stDCS, especially in the context of repeated sessions (27). Overall, results may indicate that blinding could be more a concern of younger adults, and cross-over designs, however, caution is required when interpreting, evaluating, and comparing robustness of blinding in different studies. In addition to a number of study-related parameters (intensity, ramping, design), individual characteristics, age-related alterations, or specifics of the population under study must be considered. Since systematic research is lacking, control of blinding across studies is strongly recommended to improve our understanding about successful blinding procedures.

Recovery of neglect symptoms (secondary outcome) was limited to Line Bisection, although this test is not specific to VSN (28). So far it is unknown why it was most sensitive to assess improvement in the present study, but the heterogeneous symptoms presented in VSN are associated with different cognitive demands and dissociations between tests are frequently observed (29).

Limitations

- Small sample size
- Single-session intervention
- No assessment of blinding success of rater

Abbreviations

atDCS: active transcranial direct current stimulation

stDCS: sham stimulation

VSN: visuospatial neglect

BIT: Behavioral Inattention Test battery

NIHSS: National Institute of Stroke Scale

MoCA: Montreal Cognitive Assessment

SD: standard deviation

IQR: interquartile range

CI: confidence interval

CT: computer tomography

MRI: magnetic resonance imaging

Declarations

Ethical approval and consent to participate

The study design was approved by the ethics committee of the State Chamber of Physicians of Brandenburg, Germany (*S9(a)2018*) and conducted in line with the CONSORT extension for randomized pilot and feasibility trials and procedures were carried out in accordance to the Declaration of Helsinki. All subjects gave written informed consent. The study is registered with the German Clinical Trials Register (*DRKS00014700*).

Consent for publication

Not applicable

Availability of data and material

Data and analysis scripts are freely available for researchers on request to reproduce current findings or for further analysis.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

TR and AG designed the study. TR and AG were responsible for the interpretation of data. TR, NK, and AG contribute to drafting and revising of the manuscript. AG obtained funding. TR performed acquisition of data, and had study supervision. TR and UG did the statistical analysis. All authors read and approved the final manuscript.

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Tables

Table 1: Inclusion and Exclusion criteria

Inclusion criteria
Ischemic or hemorrhagic stroke in the right hemisphere (confirmed by CT or MRI)
Early subacute phase after stroke (defined as 7 to 56 days after stroke onset)
Minimum 18 years of age
Signs of visuospatial neglect
Right-handed
Able to understand the scope and content of the trial
Exclusion criteria
Severe alcohol or narcotic abuse, severe psychiatric disease like depression or psychosis (if not in remission)
History of stroke
Severe cognitive impairment
Visual impairment which cannot be corrected with any optical aid or decreased visual field due to hemianopia.
Use of medications primarily affecting the central nervous system including antidepressants, neuroleptics, sedatives, Alpha-1 blockers, psychostimulants
Pregnancy
Epileptic activity
History of severe traumatic brain injury or surgery
Pacemaker
Participation in any intervention trial

MRI = magnetic resonance imaging | CT = computer tomography

Table 2: Baseline characteristics and assessment of neglect at follow-up visit

	Baseline N = 12	Follow-Up N = 9 ¶	p-value	Effect size, CI §
Age in years, median [IQR]	77 [68 – 83]	-		
Female sex, n (%)	7 (58)	-		
Ischemic stroke, n (%)	9 (75)	-		
Time from stroke in days, median [IQR]	26 [16 – 46]	-		
NIHSS at inclusion, median [IQR]	7 [2 – 10]	-		
MoCA sum score, mean (SD)	18 (5)	20 (6)	0.12	0.2 [-0.1 to 0.5]
Star cancellation test, mean (SD)	32 (13)	41 (16)	0.65	0.2 [-0.6 to 0.9]
Letter cancellation test, mean (SD)	25 (7)	32 (9)	0.13	0.6 [-0.2 to 1.4]
Line cancellation test, median [IQR]	35 [28 – 36]	36 [34 – 36]	0.46	0.37 [-0.4 to 1.1]
Line bisection test in cm, mean (SD)	2.6 (2)	0.5 (1.2)	0.07	1.0 [-0.2 to 2.1]
Figure copying test, median [IQR]	3 [2 – 4]	6 [4 – 7]	0.1	0.5 [0.0 to 1.1]
Text reading test, median [IQR]	90 [86 – 133]	117 [87 – 136]	0.83	0.2 [-0.5 – 0.8]

¶ Data of one patient could not be analysed due to bad performance of patient.

§ Effect sizes are calculated using Cohen's d.

| One test could not be rated due to bad performance of the patient.

Table 3: Distribution of guessing between active and sham stimulation among patients

		Guess			Total
		False	Uncertain	Correct	
Sham tDCS	n	1	6	5	12
	%	8.3	50.0	41.7	100.0
Active tDCS	n	2	6	4	12
	%	16.7	50.0	33.3	100.0
Total	n	3	12	9	24
	%	12.5	50.0	37.5	100.0

Supplementary Files

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