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 Neglect after stroke is a disabling disorder and its rehabilitation is a major challenge. Transcranial direct current stimulation (tDCS) seems to be a promising adjuvant technique to improve standard care neglect therapy. Since electric fields are influenced by age-related factors higher current densities are probably needed for effective treatment in aged stroke patients. The validation of treatment efficacy requires sham-controlled experiments but increased current densities might comprise blinding. Therefore, we conducted a pilot study to test sham adequacy when using current density of 0.8 A/m^2. Whether especially neglect patients who mainly suffer from perceptual and attentional deficits are able to differentiate beyond chance active from sham tDCS was investigated in a cross-over design (active/sham stimulation, randomized order) in 12 early subacute patients with left-sided hemineglect. Stimulation was performed simultaneous to standard care neglect therapy with 0.8 A/m^2. Progress of neglect symptomatology was also monitored during inpatient rehabilitation.

Results 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) were observed. Therefore, blinding success remains debatable in neglect studies with current densities of 0.8 A/m^2 and still warrants further investigation.

Introduction

Large right hemispheric stroke often results in a multimodal neglect (1,2). Parietal or fronto-temporo-parietal networks are frequently affected, which also compromise multi-sensory integration areas, and are linked to attentional and perceptual deficits (3). Despite symptoms persist for more than a year in 30 – 40 % of patients, and the poor prognostic outcome of neglect (4), only few therapies have been established in clinical practice (5). A couple of small studies indicate that transcranial direct current stimulation (tDCS) might be a promising tool for future treatment (6), which warrants further investigation.

tDCS modulates cortical excitability and network strengthening and suppression (7), but it's effectiveness could be influenced by numerous parameters such as the stimulation site, duration and current density (in A/m^2) (8–10), or interindividual heterogenenity (7). According to head modelling simulation studies (11) electric fields can be affected by different tissue types in the brain. Considering the age-related natural and lesion induced loss of brain tissue (12) higher current densities may be necessary to observe clinically relevant effects in patients.

Evaluation of new treatment strategies requires double-blind sham-controlled studies. tDCS, even if mild, can evoke sensations (itching, burning), and may accordingly compromise blinding, particularly at higher currents. Despite age-related altered processing of perceptual or sensory information (13) robustness of blinding has been mainly tested in healthy young subjects with conflicting results (14–16). Nevertheless, whether results, even obtained in healthy older adults (16) apply to brain-damaged neglect patients, who are mainly suffer from perceptual and attentional deficits, remain unknown. So far, different current

densities (0.29 – 0.8 A/m²) have been administered in neglect patients (17,18). Methodological heterogeneity and/or no information about controlling effective blinding challenge conclusive remarks. Therefore, the aim of the present pilot study was to investigate whether neglect patients can discern active (atDCS) and sham stimulation (stDCS) beyond chance using high current densities of 0.8 A/m² to assure adequacy of sham procedure before it is applied in larger trials.

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 cm²) 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/m²). 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). Median NIHSS was 7 [2 – 10]. Three patients showed signs of anosognosia and two

patients were later suspected to have hemianopia. In all but Line Cancellation test, patients showed impaired performance in neglect tests at baseline (for details see table 2).

[Insert table 2 here]

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 guessed correctly was 80.0% (95%CI: 30.9 % - 97.3 %). If sham was guessed the marginal probability of actually having an atDCS condition (wrong guessing) 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 atDCS four and after stDCS one out of 12 patients reported the presence of any sensations, but marginal proportions were not substantially different (p = .25). Specifically, 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. The remaining 5 patients stated “no idea” when asked about received stimulation condition (see also Table 3). No other adverse events were reported after intervention or during the study period.

[Insert table 3 here]

Mean difference between baseline and follow-up was 40 days (26). No significant improvement in performance from baseline to follow-up 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 an atDCS versus stDCS stimulation

protocol applying a high current density (0.8 A/m²). Results (high Odds ratio, range and direction of CI) suggested good guesses about the atDCS condition, though not statistically significant, which was probably due to small sample size. Therefore, effective blinding remains debatable. Further, recovery from visuospatial functioning could be at least demonstrated for performance in Line Bisection test.

Despite the used high current density only few sensations of mild intensity were reported by patients, mostly itching and burning as in other studies (25,26). Because stimulation mode assignment (when a sensation has been perceived) was rather uncertain, it is unlikely that these sensations could fully account for the measured Odds ratio. Previous studies using comparable stimulation intensity (2 mA, 20 min/30 min), but lower current density (0.57 A/m²) could demonstrate successful blinding in young (15) and old (16) healthy subjects in a cross-over design, but they have also found that subjects have tended to identify stimulation mode more correctly in the second of two sessions. This result was probably due to increased experience with tDCS in a within-subject design and might also explain the observed higher odds of correctly identifying the atDCS condition in our study. It should be noted that experience need not be limited to sensations caused by tDCS itself, but may also include any subjective changes (e.g., performance, symptom reduction), and this may be particularly relevant in the clinical population (27). However, age-related differences in sensation and perception (13), and complaints about it (28) render a translation of results obtained in healthy (young) to clinical (brain-damaged) subjects difficult. Although, in one study chronic stroke patients (suffering from motor dysfunction) did not differ in discomfort or stimulus identification from healthy controls (29), conclusions are limited considering marked deficits in neglect patients (perception, attention), differences in stimulus parameters (1 mA, 0.4 A/m² vs. 2 mA, 0.8 A/m²), and phase (chronic vs. subacute). Overall, results may indicate that blinding could be more a concern of 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, strategies to prevent and control blinding efficacy across studies, remain 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 (30). 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 (31). The additional use of computer-based tests in future studies might provide further information about possible subtle changes in neglect symptoms (32).

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 hemorraghic 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

This is a list of supplementary files associated with this preprint. Click to download.

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- Additionalfile3CONSORT2010Checklist.doc
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