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# Transcranial direct current stimulation to the parietal cortex in hemispatial neglect: A feasibility study

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ABSTRACT

*Objectives:* Prior research suggests that dampening neural activity of the intact, presumably overactive hemisphere, combined with increasing neural activity in the damaged hemisphere, might restore cortical interhemispheric balance and reduce neglect. In the present study we repeatedly applied a relatively new technique, transcranial direct current stimulation (tDCS), to the posterior parietal cortex to modulate spontaneous neural activity levels in a polarity dependent fashion to find evidence for improvements in severe hemispatial neglect in chronic patients.
*Methods:* Eighty-nine patients were initially identified from our databases as having neglect, after thoroughly screening databases, consulting medical practitioners and baseline testing, only five met our inclusion criteria and agreed to participate. Sixty-five patients were excluded as they did not meet safety criteria for tDCS (epilepsy, metal implants), suffered from other medical conditions (i.e., heart disease, epilepsy, current psychiatric disorder) or displayed only mild neglect at baseline testing. Five patients with severe chronic hemispatial neglect were enrolled in a double-blind, placebo-controlled treatment program. TDCS or placebo was applied for 20 minutes over the left (cathodal) and right (anodal) posterior parietal cortex at an intensity of 2 mA on five consecutive days. Treatment conditions were separated by a four week wash-out period. Baseline corrected change in performance on the conventional subtests of the Behavioral Inattention Test (BIT) was our primary endpoint.
*Results:* No treatment-related effects were observed for the BIT change scores and performance on individual subtests. Moreover, patients' performance somewhat improved only during the stimulation period (day one vs day five, irrespective of whether it was placebo or tDCS), but not thirty days later, indicating a practice effect.
*Discussion:* The present study does not provide evidence that tDCS to the posterior parietal cortex improves chronic hemispatial neglect. As a result of in- and exclusion health and safety criteria the majority of patients were excluded, which indicates that performing large randomized controlled trials is not feasible in chronic neglect patients.



## 1. Introduction

One of the most debilitating syndromes following stroke is visuospatial neglect (Heilman et al., 1985). Patients suffering from neglect do not attend to, respond to and mostly ignore information on the contralesional side of space (usually ignoring the left side following right hemispheric damage) (Halligan and Marshall, 1991; Robertson, 1999; Vallar and Bolognini, 2014; Bolognini et al., 2009). Several studies indicate that neglect is a predictor of poor functional outcome (Cherney et al., 2001; Nys et al., 2005;

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Jehkonen et al., 2006; Nijboer T. et al., 2013, Nijboer T.C. et al., 2013; Nijboer et al., 2014). The majority of neglect patients show spontaneous recovery of neglect in the sub-acute stage (10–12 weeks). However, about 40% of the patients are still not fully recovered after one year (Karnath et al., 2011; Rengachary et al., 2011; Nijboer et al., 2013).

Starting in the 1970s, many (experimental) attempts have been made to treat hemispatial neglect and they include prism adaptation, optokinetic stimulation, limb activation and eye patching procedures. These techniques have all shown to be effective to some extent (Luaute et al., 2006). Nonetheless, most of these effects are short-lived and/or do not consistently generalize to situations outside the research setting. This makes understanding the underlying mechanisms of neglect in order to better facilitate treatment an important research goal.

Several influential models suggest that neglect results from an imbalance between the two hemispheres (Heilman et al., 1985; Heilman and Valenstein, 1979; Heilman and Watson, 1977; Kinsbourne, 1974; Kinsbourne, 1987). Both Heilman (1985) and Kinsbourne (1987) proposed that the right and left hemispheres allocate attention to their contralateral side, that is, left hemisphere to the right side and the right hemisphere to the left side of the visual space. Moreover, the right hemisphere is able to direct attention to both sides of the visual space. Kinsbourne (1974) further proposed that attention systems in both hemispheres inhibit each other via transcallossal pathways. A lesion in the right hemisphere will therefore not only result in reduced activity of the attentional system in that hemisphere, but due to loss of transcallosal inhibition by the damaged right hemisphere, will cause over-activation of the attentional system in the left hemisphere as well. Arguably, the lateralized deficits frequently observed in neglect are a direct result of a dominating attentional system in the left hemisphere and therefore a rightward attentional bias. In contrast, the right hemisphere can better compensate for the damaged left hemisphere, since it is proposed to be capable of allocating attention to both sides.

Restoring the interhemispheric balance by modulating brain activity can be achieved through the use of non-invasive brain stimulation (NBIS) techniques, such as transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (Nitsche et al., 2008; Hesse et al., 2011). Both TMS and tDCS have been explored as a possible means for treating neglect patients. Several studies have demonstrated that TMS can be effective in ameliorating lateralized deficits using both low-frequency rTMS of the contralesional (overactive) hemisphere (Brighina et al., 2003; Shindo et al.; 2006; Koch et al., 2008; Song et al., 2009), and high frequency protocols (20 Hz) over the ipsilesional hemisphere (Kim et al., 2010). Although the effects seem promising, most of these studies are proof of principle studies and the number of sufficiently powered randomized controlled trials is still limited (Fasotti and van Kessel, 2013; Muri et al., 2013). Moreover, it is unknown whether a daily application of TMS is feasible in a clinical setting (Muri et al., 2013).

TDCS is another transcranial stimulation method that can have positive effects on treating neglect by way of simultaneously hypo- and hyperpolarizing cortical tissue by delivering a constant, low intensity current overlying to the sites of interest. TDCS is safe, well tolerated and not associated with serious adverse events (Nitsche et al., 2008). Together with the fact that tDCS devices are portable and relatively cheap, this makes tDCS an attractive method for professionals to use in the clinic or at home.

It is generally accepted that tDCS has both short-lasting membrane effects and longer-lasting synaptic effects (see Stagg and Nitsche, 2011 for details), and dual stimulation (either facilitatory or inhibitory) fits well into Kinsbourne's model of hemispheric rivalry. However, effects of tDCS in neglect patients have been reported in only few studies (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2013; Brem et al., 2014). Ko et al. (2008) studied the consequences of a single 20 min session of anodal tDCS at 2 mA of the right PPC in fifteen sub-acute stroke patients with spatial neglect, and found improvement on a line bisection test and a cancellation task. Sunwoo et al. (2013) also tested the effect of single session tDCS in ten neglect patients but used both anodal stimulation over the right PPC and cathodal stimulation over the left PPC (2.0 mA, 20 min), only cathodal over the left PPC and placebo control. They found significant improvements after both dual-mode tDCS and only cathodal tDCS on a line bisection test as opposed to the placebo condition. The effect of dual-mode stimulation was stronger than cathodal tDCS only. Sparing et al. (2009) also used dual application of tDCS in a cross-over design with two sessions of tDCS (1.0 mA, 10 min) in ten neglect patients and reported improvement on a line bisection test but not on a visual detection task. Thus, using tDCS in a manner consistent with reducing the imbalance in attention allocation has been proven successful to some extent (single session, limited tasks). However, the research on multiple sessions remains relatively scarce. Only one recent single case study has used multiple treatment sessions. Brem et al., (2014) combined dual-mode tDCS with cognitive neglect therapy during treatment of a single patient in the post-acute phase. During the course of four weeks, either cognitive therapy only was given (weeks 1 and 4) or it was combined with either placebo or dual-mode tDCS (week 2) or dual mode tDCS only (week 3). Compared to placebo stimulation, improvements were observed for covert attention to the left side after biparietal tDCS as well as qualitative improvements on line bisection and copying. In the current study we focussed on the effects of multiple sessions of dual stimulation tDCS without concomitant cognitive training in chronic stroke patients. We aimed to study both the feasibility and efficacy of multiple sessions of tDCS in a placebo controlled treatment program. TDCS or placebo 'stimulation' was applied, each for a period of five consecutive days. Similar to previous studies with dual-mode tDCS, we hypothesized that tDCS applied to the left (cathodal) and right (anodal) posterior parietal cortex would improve activity causing a shift in attention and reductions in neglect.

## 2. Methods

### 2.1. Ethics statement

The ethical institutional review board of the University Medical Center Utrecht approved this study. All patients gave written informed consent prior to participation and received further information when needed. All study procedures have been conducted according to the principles which are outlined in the Declaration of Helsinki.

### 2.2. Subjects

Patients were recruited via advertisements on social media and from several healthcare institutions, such as 'Stichting zorggroep Noord-West Veluwe', 'Stichting Nieuw Unicum', 'de Hoogstraat Revalidatie' and the University Medical Center in Utrecht, The Netherlands. Inclusion was verified by a tDCS screening questionnaire and was based on the following criteria: (1) left hemispatial neglect after right hemispheric lesion, (2) right-handed, (3) older than the age of 18, (4) more than four months after stroke. Exclusion was based on the following criteria: (1) severe language and communication disorders, (2) bilateral cortical damage, (3) psychiatric disorders, (4) alcohol and/or drug addiction, (5) epilepsy, (6) eczema or damages on the scalp, (7) metal or

**Table 1**
Patient demographics.

| Pt[a] | Gender | Age | Time post-stroke (Y,M) | Etiology | Lesion location | Mobility[b] | Barthel index | BIT-C[c] |
|---|---|---|---|---|---|---|---|---|
| **AB** | M | 52 | (2,4) | Hemorrhage | rP,BG[d] | Impaired | 15 | 136 |
| **BO** | M | 69 | (1,0) | Ischemia | rO, TH, CI[e] | Intact | 18 | 111.5 |
| **BU** | F | 65 | (1,4) | Hemorrhage | rP | Intact | 10 | 131 |
| **VO** | F | 76 | (7,2) | Hemorrhage | rT, C[f] | Impaired | 18 | 56 |
| **WE** | M | 62 | (12,4) | Ischemia | rP, T | Impaired | 14 | 71 |

[a] Patient AB, WE were recruited from social media; BU, BO from the Hoogstraat Revalidatie; VO from Stichting Noord-West Veluwe.
[b] Mobility: AB, BO, WE, VO were left hemiplegic, only VO was permanently in a wheelchair.
[c] BIT-C= baseline measures on the Conventional Behavioral Inattention Test.
[d] r=right hemisphere, P= Parietal, BG=Basal Ganglia.
[e] O= Occipital, TH=Thalamus, CI=Capsula Interna.
[f] T=Temporal; C=Central.

other foreign parts in the head. We identified 89 patients who exhibited neglect shortly after the stroke. After thoroughly screening our databases i.e. checking medical background and neglect severity and consulting medical practitioners/doctors for stimulation contra-indications, approximately half of the patients had to be excluded and were not further invited. Thereafter about 47 patients were invited by letter, 19 did not respond/did not want to participate. Of these 28 potential candidates only 5 out could be included (see Table 1 for patient demographics and Table 2 for reasons for exclusion). This table contains patients who were excluded after checking the medical background/consultation with medical practitioners as well as the patients who were excluded after sending letters to them. It does not include the 19 patients who did not want to participate. Patients were considered to suffer from neglect when the aggregate score on the conventional tasks was 129 or lower (total range 0–146) on the baseline and/or pre-treatment session (i.e., baseline and the pre-test).

**Table 2**
Primary reason of exclusion for 65 patients who were identified from our databases.

| Reason exclusion | Number of patients excluded |
|---|---|
| Medical conditions* | 21 |
| Epilepsy | 12 |
| (Metal) implants | 11 |
| Bilateral lesions | 5 |
| Mild neglect at baseline testing | 9 |
| Nursing home** | 4 |
| Preliminary termination | 1 |
| Eczema | 1 |
| Language problems | 1 |
| Total Exclusion | 65 |

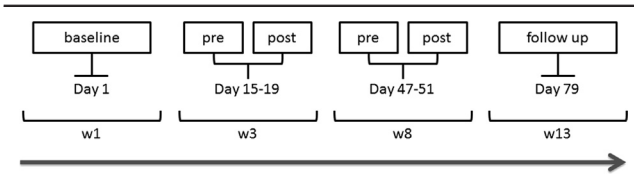
* Medical conditions included mental retardation, suffering from severe aphasia, tumor, alcohol addiction, COPD, PTSD, depression, delusions, severe heart conditions, pacemaker.
** We did not have permission to conduct our study at the nursing home where these patients were residing, which is why these patients could not participate.

Overall, 51 patients were excluded because of criteria specifically related to tDCS (medical conditions, epilepsy, metal implants, eczema, bilateral lesions). Nine patients no longer showed neglect at baseline testing (see Table 2). Four patients were residing in a nursing home where we did not have permission to test the patient. We excluded one patient during the tDCS treatment condition (see Table 2; preliminary termination). The patient became emotional, and felt morose. Although we could not establish a causal relation between the patient's emotional state and tDCS, we nonetheless stopped the treatment, since non-invasive brain stimulation of the parietal cortex has been linked to changes in emotional state and mood (Schutter and van Honk, 2005; Schutter et al., 2009).

### 2.3. Study design

Patients were seen 12 times within 79 days, see Table 3 for the exact timeline. Baseline testing or screening took place on day 1, then the first condition (either experimental or placebo) started two weeks later. Four weeks later,[1] the other condition took place. During both periods, patients performed pre- and post-stimulation assessment daily for 5 consecutive days. Pre- and post-stimulation assessment consisted of conventional BIT tasks (see Section 2.4).

**Table 3**
Timeline of the study design. Patients are tested 12 times within a 79 days time frame on the BIT-C. Only in week 3 and 8 tDCS was applied in between the pre-post BIT assessment (See text for details).




### 2.4. Task, stimuli and procedure

Patients were treated and tested at home or at the nursing residence. We ensured that all measurements were conducted in a quiet room and that patients were seated as comfortable as possible. All tests were presented directly in front of the subjects' mid-sagittal plane, and stimulus-sheets were fixed to the table in order to prevent movement of the material. The order of tests was randomized between the days, but was the same within one day (pre- and post-assessment). In all sessions the six conventional tasks of the Behavioral attention test were administered, consisting of Star Cancellation (SC), Letter Cancellation (LC), Line Crossing (LiC) Line Bisection (LB), Figure and Shape Copying (FSC-A&B) and Representational Drawing (RD). We utilized the standard procedure and outcome measures provided by the BIT-Conventional test (see manual BIT for details).[2] We only administered the conventional subtests of the BIT and not the complete BIT including

[1] This was however not the case for patient BU because of other illness and treatment. She had a six months interval, instead of four weeks, in between the treatment sessions.
[2] Only for the LB we obtained a different procedure. Patients performed this test twice (twice before and after treatment). Outcome measures were the average deviation in mm and were for each separate LB assessment converted into a score provided by the BIT-C (either 0,1,2,3). Thereafter these separate LB assessments were averaged (e.g. average line 1a and 1b; 2a and 2b etc.).

behavioral subtests). The conventional subtests are usually administered to diagnose the presence or absence of neglect and provides a range (0–146) and a clear cut off score. Additionally, another outcome measure, other than provided by the BIT, was the horizontal Center of Cancellation (CoC). The CoC is an indicative measure of severity of neglect, since it obtains information about the location of canceled items. Specifically, a positive CoC-score indicates lateralized deficits on the (far) left and vice versa. A CoC-score towards zero means a more symmetrical spatial error distribution. Calculations for the CoC were adapted from Dalmaijer et al. (2014). For the statistical analyses, we derived a composite BIT score (range 0–146) for each measurement (pre-assessment and post-assessment), consisting of just one outcome measure. Also, a *clustered* composite score was calculated; the cancellation tests were clustered, as well as the line bisection and the drawing tests, according to norms provided by the BIT-C. Assessment and stimulation lasted approximately one hour.

### 2.5. Transcranial direct-current stimulation (tDCS)

In between the pre- and post-BIT assessments, tDCS or placebo 'stimulation' was applied, for 20 min in a double blind procedure. A battery-driven direct current stimulator (NeuroConn DC-Stimulator; serial number 0096) was used to deliver the electrical current. The stimulation parameters were set at a current of 2000 μA, and a resistance of $<10$ kOhm. This was applied for 1200 s with ramping up in 30 s and ramping down in 30 s. Electrodes were located over the posterior parietal lobe, corresponding with P3 (left undamaged hemisphere, cathodal electrode) and P4 (right damaged hemisphere, anodal electrode) according to the international 10/20 EEG system (Fig. 1). A tight cap was used in order to maximize contact between the scalp and the entire surface of the electrode. In a double-blind procedure the experimenter entered a previously determined code, which referred to either tDCS or placebo. Resistance was monitored during stimulation to ensure that resistance remained lower than 10 kOhm. All patients sat in an upright position during tDCS-treatment and tolerated the treatment with tDCS without any adverse side-effects. Most patients reported a slight tingling sensation beneath the right (anodal) electrode at the onset (during the ramping-up) of tDCS. The skin, underneath the electrode, was checked for possible skin burns or abrasion prior to each and after each tDCS application. During placebo condition, 30 s of real stimulation at the onset was given. Patients VO, AB and WE received tDCS in the first week, and placebo in the second (see Table 4). This order was reversed for patient BU and BO. Pt. AB was convinced that he received tDCS stimulation the second week, and pt. BU thought the first week, which was in both cases incorrect. Medication was monitored and was kept stable during the treatment weeks.

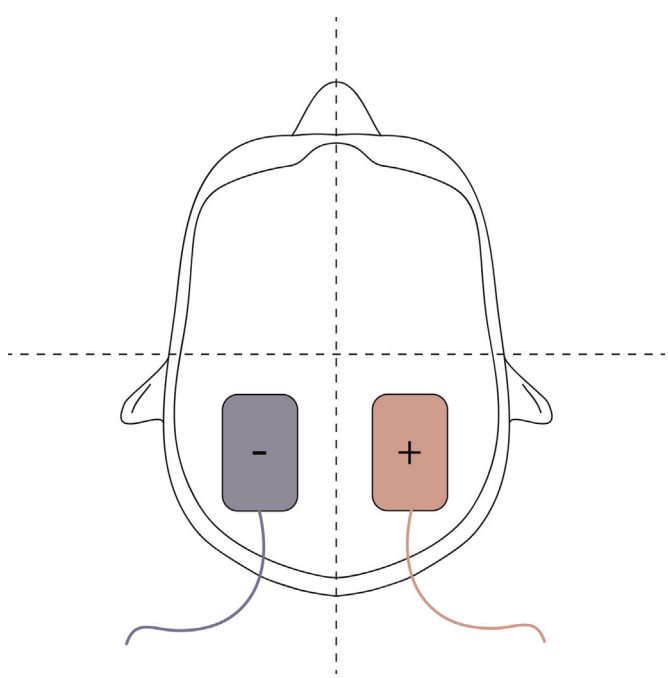



**Fig. 1.** tDCS set up. Red+= anodal electrode (excitatory); Blue −= cathodal electrode (inhibitory).

**Table 4**
Type and order of tDCS stimulation administered and blind check.

| Pt | TDCS | Placebo | Correct |
|---|---|---|---|
| **VO** | 1 | 2 | No* |
| **BU** | 2 | 1 | No |
| **AB** | 1 | 2 | No |
| **BO** | 2 | 1 | No* |
| **WE** | 1 | 2 | Yes* |

* Pt. VO, WE and BO could not disentangle the two treatment weeks but when giving a forced choice, WE was correct and VO and BO were incorrect.

### 2.6. Data-analyses

For each patient a composite score on the conventional tasks of the BIT was calculated for each day. To recall, the composite score was derived on the summed performance on the SC, LC, LiC, LB, FSC-A, FSC-B, and RD (see Wilson et al., 1987, for details). For the treatment days (either placebo/sham or tDCS) a baseline corrected difference score was calculated by subtracting the post- from the pre-assessment scores. Note that in the result section day 1 reflects the first treatment day (day 15 in timeline). The real baseline was only used as a screening for the presence of neglect.

Due to the small sample size, normality did not hold and non-parametric tests were performed. To assess immediate effects of tDCS, performance during tDCS vs. placebo condition was tested with a Wilcoxon signed rank test (Wilcoxon, 1945). This analysis was conducted with the average (day 1 till 5) BIT-C pre-post assessment difference score as dependent variable. Similar analyses were performed with clustered BIT-C and the CoC as dependent measures.

Intermediate (difference score day 1 pre-test and day 5 post-test) and follow-up effects (difference score day 1 pre-test and day 30 pre-test) between tDCS and placebo treatment were tested on the *total* BIT-C-composite, the *clustered* BIT-C-composite and the CoC, with a Wilcoxon signed rank test.

In order to assess whether the BIT conventional scores changed over the course of the 5 treatment days as a function of tDCS or placebo 'stimulation', two separate Friedman tests (for the placebo and for the tDCS condition) were conducted with time (day 1 till 5) as within subject factor on both the aggregate BIT score and the CoC of the Star cancellation.

Lastly, in order to test whether individual patients were perhaps differentially sensitive to tDCS treatment, a Wilcoxon signed rank test was conducted for each patient separately. Difference score between pre- and post-assessment (day 1 till 5) was taken as dependent variable and tDCS condition (tDCS vs. placebo) as independent variable. In all non-parametric statistics we reported the Exact Test instead of the Asymptotic Test, which is more conservative with smaller samples (Bellera et al., 2010). Alpha level of significance was set at 0.05 (two-tailed).

## 3. Results

### 3.1. Immediate effects of tDCS versus placebo on the BIT Conventional total composite score

In order to assess the immediate effects of tDCS on performance, the difference between tDCS stimulation and placebo was tested with a related Samples Wilcoxon signed rank test. Dependent measure was the pre-post assessment difference score (averaged over day 1 till 5). As can be seen in Fig. 2, there seems a slight difference between treatment and placebo on the average performance, in favor of the placebo condition. However, this did not reach significance ($Z=-1{,}483$, $p=.188$). Inspection of the individual patient data suggests that this difference was mostly evident in the performance of patient AB (see Fig. 3[3]).

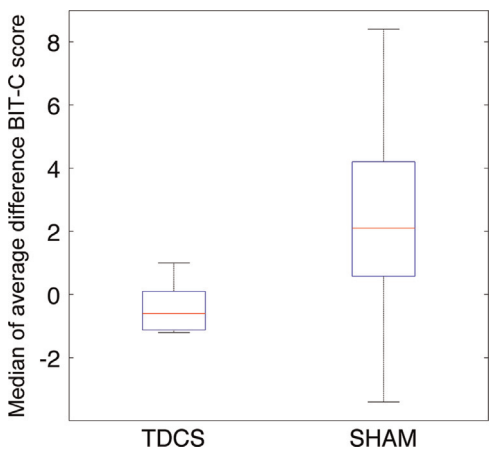



**Fig. 2.** The median of all patients' average difference scores (post–pre) on the BIT-C across five days for the tDCS and placebo/sham condition. A positive value indicates an improvement after treatment. Whiskers represent the most extreme data points. Note that the treatment-weeks were separated by 4 weeks. VO, AB and WE received tDCS stimulation in the first week (in timeline: day 15–19) and BU and BO in the second week (in timeline: day 47–51).

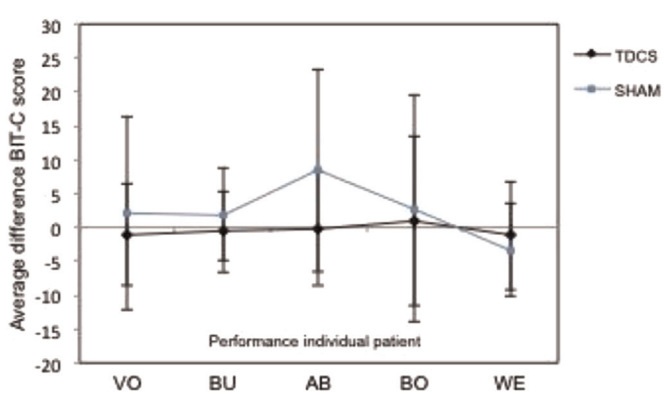



**Fig. 3.** Difference score (post–pre) on the BIT-C, averaged over the different treatment conditions (tDCS vs. placebo) for each individual patient. A positive value indicates an improvement after treatment. Error bars represent standard deviations.

[3] In Fig. 3 we present averages instead of the medians, because in the Wilcoxon Rank test these averages were converted into medians.

**Table 5**
The median and significance level of all patients' average difference scores (post–pre) on the clusters (cancellation, line bisection, drawing) of the BIT-C across five days for the tDCS and placebo condition. The most extreme data-points are shown in parentheses (lower, upper).

| Test | tDCS | Placebo | Z-statistic | *p*-Value |
|---|---|---|---|---|
| **Cancellation test** | −.06 (−1.4,0.2) | 2.4 (−3.6,7.6) | −1.483 | .188 |
| **Line Bisection test** | −.4 (−1.3,0.8) | 0 (−1,0.9) | −.674 | .625 |
| **Drawing test** | .4 (0,3) | 0 (−0.2,0.8) | −.944 | .438 |

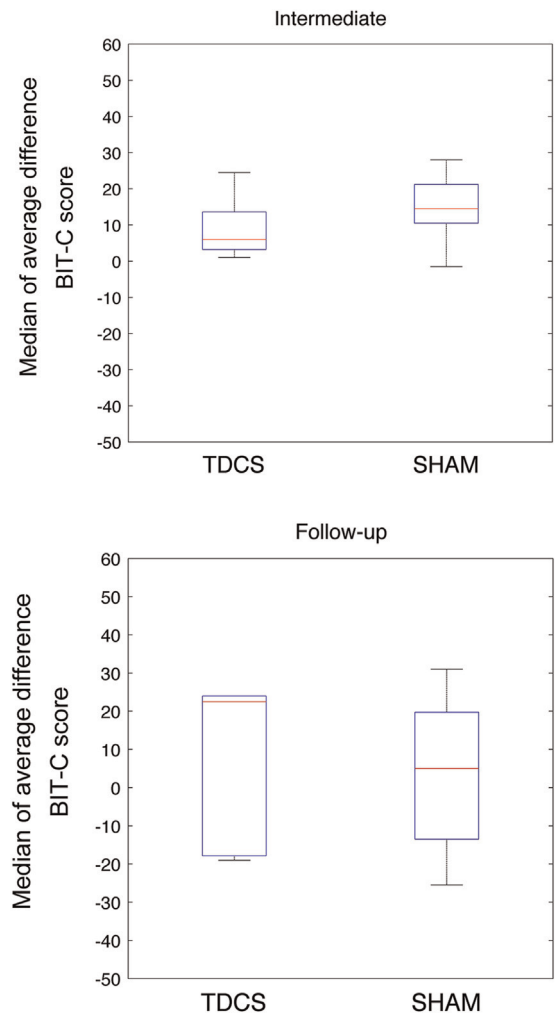



**Fig. 4.** Intermediate (top panel) and follow-up (bottom panel) median of the difference scores (post–pre) on the BIT-C for the different treatment conditions (tDCS vs placebo), see text for details. A positive value indicates an improvement after treatment. Whiskers represent the most extreme data points.

### 3.2. Immediate effects of tDCS treatment on the clustered composite score

We divided the overall composite (baseline-corrected difference score) in the clustered composites (cancellation, drawing and line bisection). All three clusters did not differ significantly between treatment and placebo, as can be seen in Table 5.

### 3.3. Direct effects of tDCS treatment on the center of cancellation

The horizontal spatial distribution of the cancelled items (as assessed with the CoC) in the star cancellation did, on average, not

**Table 6**
Median average difference 'intermediate' and 'follow-up' scores and significance level for the clustered BIT-Conventional tests. The most extreme data-points are shown in parentheses (lower, upper).

| Test | TDCS | Placebo | Z-statistic | *p*-Value |
|---|---|---|---|---|
| **Cancellation Tests** | | | | |
| *Intermediate* | 5 (2,21) | 15 (−2,28) | −.944 | .438 |
| *Follow-up* | 30 (−20,23) | 2 (−22,34) | −.135 | 1.000 |
| **Line Bisection Test** | | | | |
| *Intermediate* | 0 (−1.5,1) | −0.5 (−2.5,2) | −.271 | .875 |
| *Follow-up* | 0.5 (−1,2.5) | −1.5 (−4,4) | −.948 | .375 |
| **Drawing Tests** | | | | |
| *Intermediate* | −3 (−5,1) | 1 (−1,2) | −1.761 | .125 |
| *Follow up* | 0 (−2,3) | −1 (−2,3) | −.756 | .625 |

differ between treatment conditions ($Z=-.674$, $p=.625$) indicating that there was no (horizontal) shift in the location of cancellations.

### 3.4. Intermediate and follow-up effects of tDCS treatment on the BIT Conventional composite score

Intermediate and follow-up treatment effects were assessed with a related samples Wilcoxon signed rank test, using the averaged BIT-C-composite difference score. Intermediate performance consisted of a difference score between day 1 pre-test and day 5 post-test. The follow up performance consisted of a difference score between day 1 pre-test and day 30 pre-test. As can be seen in Fig. 4, patients' performance, on average, improved from day 1 till day 5 (top panel), and day 1 till day 30 (bottom panel), hence the positive scores. However, both the intermediate difference score ($Z=-.944$, $p=.438$) and follow-up difference score ($Z=-135$, $p=1.000$) performances did not differ significantly between tDCS and placebo. Interestingly, a one sample Wilcoxon ranks test against zero revealed a significant effect in the intermediate difference score performance ($Z=-2.601$, $p=.006$) as opposed to the follow-up difference score performance ($Z=-.765$, $p=.477$), indicating an improvement as a function of repeated testing and not as a function of time.

### 3.5. Intermediate and follow-up effects of tDCS treatment on the clustered BIT Conventional composite scores

Visual inspection of the data (see Table 6) suggested an improvement after either treatment for the cancellation tests, hence the positive value. However, tDCS and placebo did not differ significantly from each other. Furthermore, a one sample Wilcoxon ranks test against zero revealed a significant practice effect of only the intermediate performance, for only the Cancellation tests ($Z=-2.652$, $p=.006$), but not for other clusters ($Z<-1.125$, $p>.283$), indicating that the aforementioned effects of repeated testing were mainly driven by performance on the cancellation tests.

### 3.6. Intermediate and follow up effects of tDCS treatment on the Center of Cancellation

Horizontal spatial distribution of the cancelled items (as assessed with the CoC) in the star cancellation did not differ between treatment conditions in the intermediate condition ($Z=-.674$, $p=.625$) and follow-up condition ($Z=-.674$, $p=.625$), indicating that there was, on average, no (horizontal) shift in the location of cancellations.

### 3.7. Short-term effects of tDCS over the five treatment days on the conventional composite BIT scores

As can be seen in Fig. 5, the overall composite *difference* score (i.e. difference between post-pre-assessment) fluctuated over time (e.g. a positive score indicates an improvement after either tDCS or placebo treatment). Generally, these fluctuations were more pronounced in the placebo-week as opposed to the week with tDCS and they were mostly visible in the data of patients AB, BO and VO. The Friedman test on time (day 1, day 2, day 3, day 4, day, day 5) showed that the overall composite score was not affected by time in the tDCS treatment condition ($\chi 2$ (4)=.687, $p=.965$), nor in the placebo condition ($\chi 2$ (4)=2.880, $p=.613$).

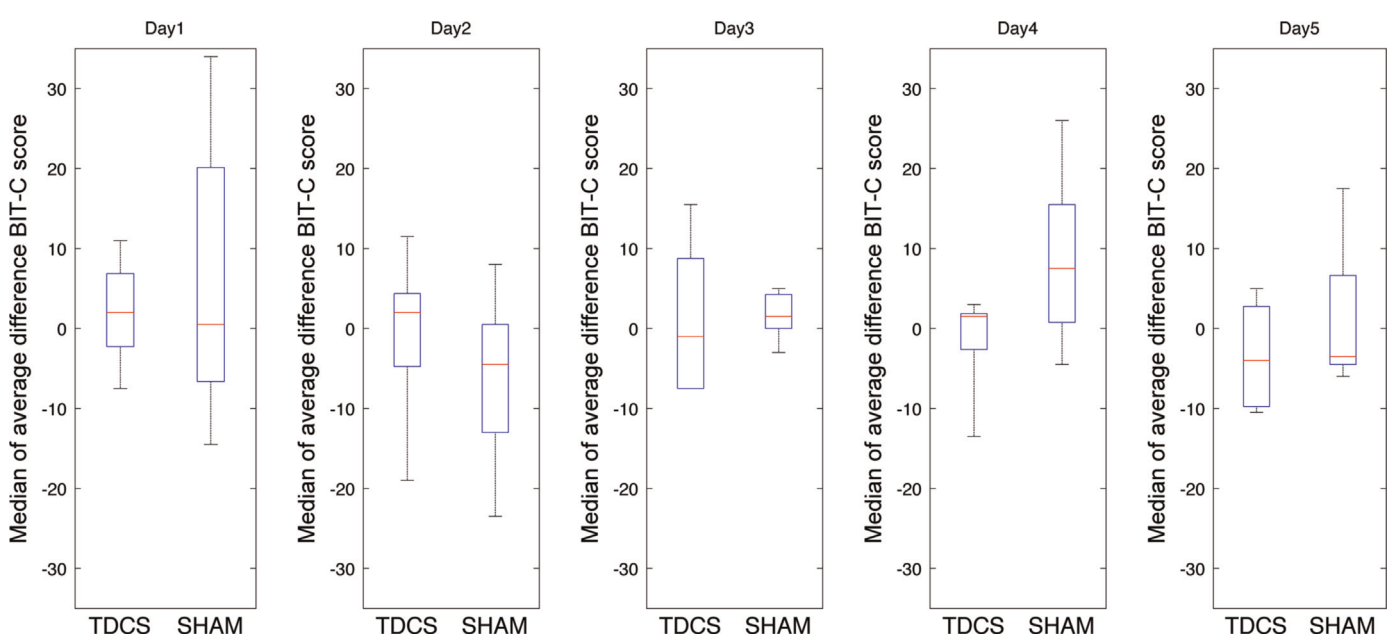



**Fig. 5.** The median of the averaged difference score (post- minus pre-assessment) on the BIT-C for the different treatment conditions (tDCS vs placebo) over the 5 treatment days. A positive value indicates an improvement after treatment. Whiskers represent the most extreme data points.

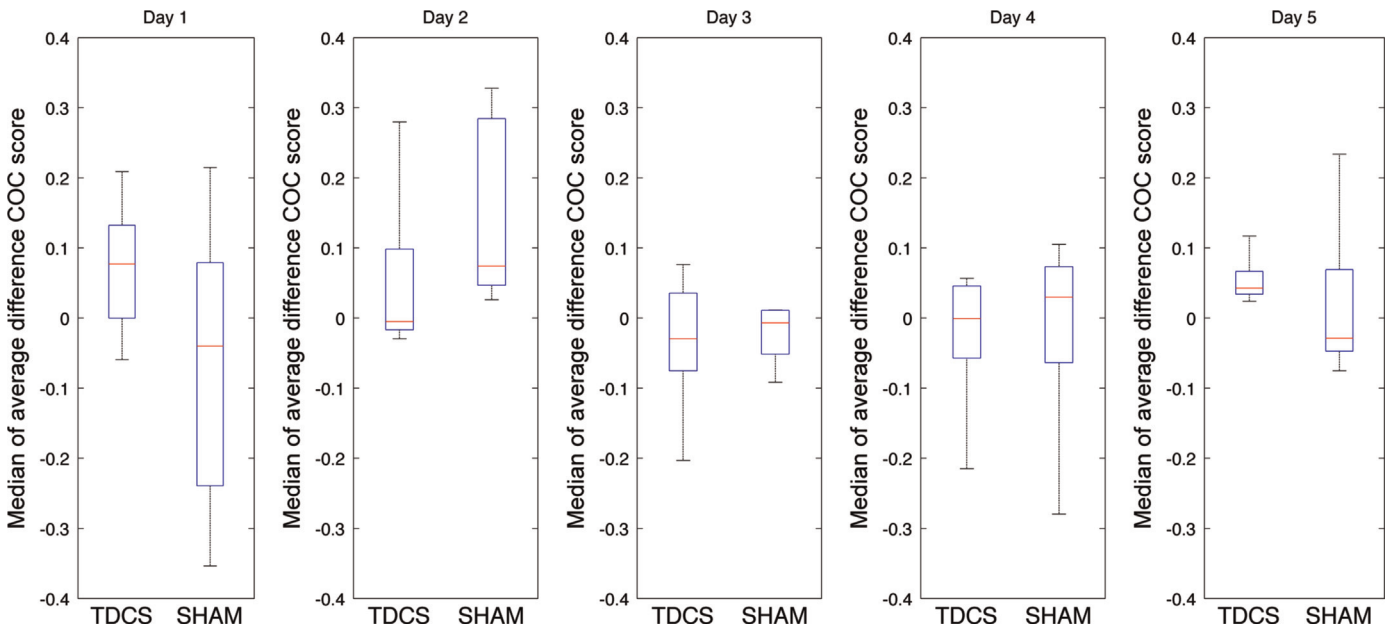



**Fig. 6.** The median of average difference Score of the Center of Cancellation of the Star Cancellation. A positive difference CoC-score represents a shift to the right and vice versa. Whiskers represent the most extreme data points.

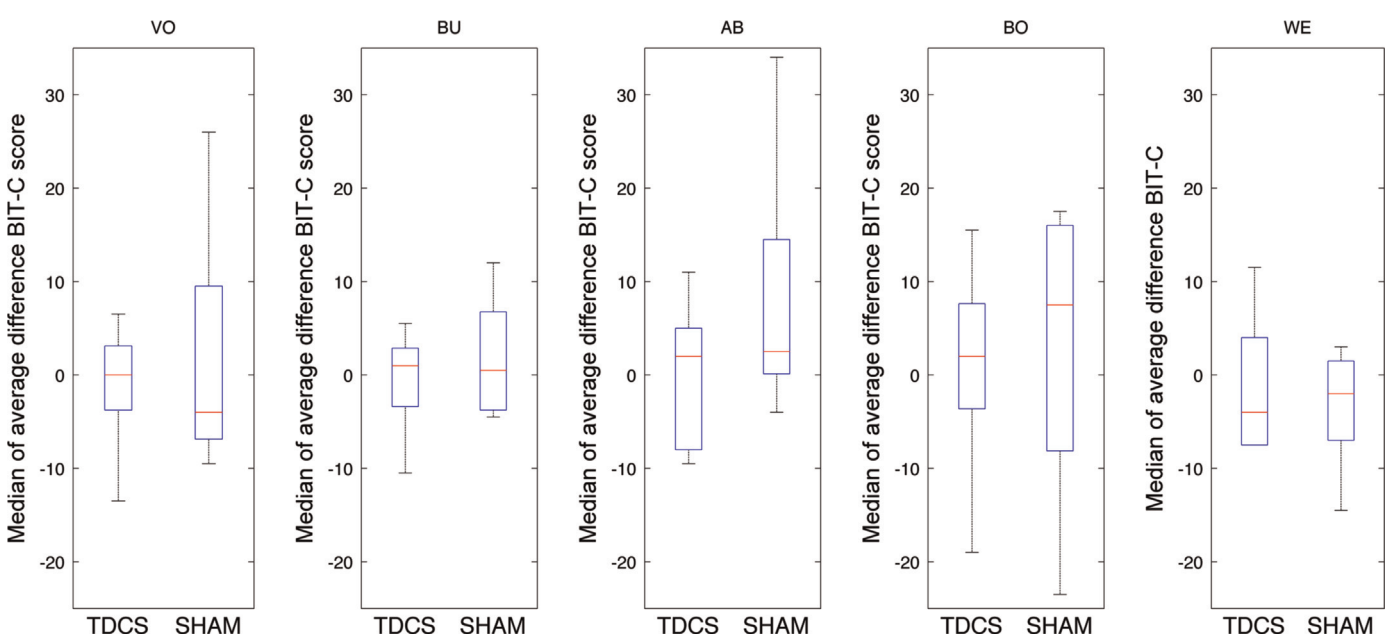



**Fig. 7.** The median of the averaged difference scores and significance level for the BIT-Conventional tests for each individual patient. Whiskers represent the most extreme data points.

### *3.8. Short-term effects of tDCS treatment on the center of cancellation*

No effects of day in the tDCS treatment condition ($\chi 2$ (4)= 6.240, $p$=.183) and placebo condition ($\chi 2$ (4)=7.360, $p$=.112) on the horizontal spatial distribution of the cancelled items (as assessed with the CoC) in the star cancellation (see Fig. 6).

### *3.9. Individual differences between tDCS and placebo*

Lastly, in order to test whether individual patients were perhaps differentially sensitive to tDCS treatment, a Wilcoxon signed rank test between tDCS and placebo was conducted for each patient separately. Again, as can be seen in Fig. 7, the difference in treatment was mostly evident, albeit not significant, in patient AB (see Table 7).

**Table 7**
Z-statistic and significance level for the BIT-Conventional tests for each individual patient.

| Pt | Z-statistic | *p*-Value |
|---|---|---|
| **VO** | −.674 | .625 |
| **BU** | −.944 | .438 |
| **AB** | −1.753 | .125 |
| **BO** | −.405 | .813 |
| **WE** | −.271 | .875 |

## 4. Discussion

The aim of the current study was to evaluate the feasibility and both short-term and long-term effects of multiple sessions of tDCS on hemispatial neglect. We hypothesized that tDCS would rebalance the attention systems in the left and right hemisphere, and, as a result, would enhance attentional processing in the contralesional hemispace in order to reduce lateralized deficits. We used the conventional subtests of the BIT to assess the effects of multiple and daily applications of biparietal tDCS.

Analyses of the BIT-Conventional composite scores did not reveal a significant tDCS treatment effect on performance. More specifically, there was neither an effect on the deviation from the actual center on the line-bisection, nor in the number of cancellations, or a shift in location of these cancellations after tDCS as compared to placebo 'stimulation'. There was however an improvement during treatment. More specifically, patients' performance somewhat improved in the cancellation tasks in both the placebo and tDCS treatment weeks (day one vs day five), but not thirty days later, indicating a practice effect. This finding indicates that learning effects due to repeated testing can confound or possibly even explain improvements in neglect especially in open-label studies and studies without proper control conditions.

Unlike the recent promise of single session tDCS (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2013) and multiple session tDCS in a single patient (Brem et al., 2014), no robust amelioration of lateralization deficits across clinical measures were found in our patients. It should be noted however, that Sparing et al. (2009), only found improvement on a line bisection task, and not on visual search. Generally, most effects were found on the line bisection in the previous studies. Interestingly, we did not find such an effect across multiple sessions. One could speculate that a lack of statistical power could be the main cause of our lack of results, since we had only five participants. However, one other study did find effects of tDCS in only a single patient (Brem et al., 2014). Individual trends were not present in our data. However, considering the large variation in our data, we cannot rule out a statistical power issue here. Another important difference with previous studies is that all studies, but one (Sunwoo et al., 2013), assessed and stimulated the patients in the sub-acute stage ( < six months post-stroke), and we performed our measurements in the chronic stage. As a result of the inclusion of chronic patients there may have been less room for neurological improvement indicating that patients might have reached a plateau level in recovery. However when including patients in the sub-acute stage, tDCS could have facilitated neurological recovery, as the brain is especially sensitive to neurological reorganization during the first 3 months post-stroke (Robertson and Murre, 1999; Murphy and Corbett, 2009; Kwakkel et al., 2004; Nijboer et al., 2013).

To the best of our knowledge, only Brem et al. (2014) applied more than 10 sessions in a single case study. The other studies (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2013) showing positive results administered less tDCS sessions than we did. Five sessions of tDCS applied in the chronic stage might nonetheless be insufficient to induce reliable changes and could be one of the reasons we did not find a difference between tDCS and placebo. Moreover, it has recently been observed that, following neurostimulation, the sensorimotor cortex reorganizes differently in chronic and subacute stroke patients, suggesting that these stages reflect different mechanisms of neuroplasticity (Yarossi et al., 2014) and may require different stimulation parameters. Furthermore, although tDCS as a monotherapy has been shown effective before (Ko et al., 2008; Sparing et al., 2009; Sunwoo et al., 2013), the functional networks recruited might be too diffuse, especially when tests are administered offline. If tDCS is implemented as an adjuvant therapy, next to scanning training or prism adaptation for instance, it might recruit the attentional networks necessary for improving neglect. Several authors studying rehabilitation for motor (Bolognini et al., 2009; Miniussi and Vallar, 2011; Sandrini and Cohen, 2013) and language problems (de Aguiar et al., 2014) have recently stressed the importance of combining a behavioral intervention with non-invasive brain stimulation.

In recent studies, the effect of tDCS has been questioned (Horvath et al., 2014, 2015). In a systematic review, the authors evaluated the effectiveness of tDCS in literature (Horvath et al., 2015). Instead of including studies with behavioral outcome measures, they included studies utilizing neurophysiological outcome measures in mostly healthy subjects, such as motor evoked potentials (MEP) combined with TMS, event related potentials (ERP's), EEG and fMRI. Reliable effects were found only on corticospinal excitability as measured with MEP. They concluded that tDCS could not reliably induce a physiological effect in healthy subjects, and of all the aforementioned measures motor evoked potentials were the most sensitive to tDCS. It should be noted that the number of available studies included in the meta-analyses for the different neurophysiological outcomes, except for the MEP, was very limited, which makes it difficult to draw definite conclusions. The results indicate that the neurophysiological effects of tDCS are difficult to quantify. How do we interpret these findings in light of behavioral findings? In another study, Horvath et al. (2014) further stated eminent indicators that could cause variability between subjects and inconsistencies in effectiveness, both neurophysiological and behaviorally. Yet, a recent review shows that tDCS has reliable behavioral effects in healthy volunteers (for a review see Coffman et al., 2014). The observed variability in efficacy are most likely due to individuals' unique anatomy, skull thickness, subcutaneous fat levels, cerebrospinal fluid density, scalp to cortex distance and other factors that determine the flow of current and how much electricity reaches the cortical surface (Stagg and Nitsche, 2011). In addition, the effects also depend on differences in physiological susceptibility to exogenous electric currents of the brain itself. Although we have no anatomical information about our included patients, individual variability could explain some of our null-findings, that is, despite placing the electrodes in a standardized way, individual variability in the above factors and additionally in lesion characteristics, may have precluded any behavioral effects.

In terms of the feasibility of conducting randomized controlled trials involving multiple consecutive sessions of tDCS, patients tolerate the daily applications well. Most reported sensations were underneath the anode electrode at the onset of the stimulation, the ramping up phase, in both the tDCS and placebo condition. Although skin burns underneath the electrodes have been reported in repeated applications on the same scalp locations (Loo et al., 2011; Frank et al., 2010; Palm et al., 2008), our patients did not show any physical aversive effects during and after treatment. When the resistance exceeded levels of 10 kOhm, a small amount of conduction gel was added or the site of the electrodes was massaged gently. One patient showed dryness of skin underneath the stimulated area, and we used a lubricant after the stimulation session to prevent skin damage.

Apart from the lack of efficacy, another important issue which hampers evaluation of tDCS in our study was our large number of a priori excluded patients. Most patients were excluded on the bases of unstable medical conditions. Medical conditions in our sample included mental retardation, epilepsy, suffering from severe aphasia, tumor, alcohol and or drug addiction, COPD, PTSD, delusions, and severe heart conditions. Generally, there is little information available about the exact in- and exclusion criteria for stimulation techniques in stroke patients. Nitsche et al. (2008) state that patients should be excluded when displaying an

unstable medical history, but what does that mean? Unstable in the sense of psychological problems or neurological problems, and to what extent? Also, tDCS has not directly been associated with an increased risk of epilepsy in healthy individuals, but literature is not sure what might happen when applying dual tDCS, especially with the anode electrode, in epileptic vulnerable people (Nitsche et al., 2008). We therefore also excluded patients whom did not have epilepsy themselves, but with family records of epilepsy. Perhaps this has been somewhat too conservative. So far, there have only been a few studies investigating tDCS in neglect. This might reflect the difficulties in studying this set-up in this patient population and the relative small sample sizes, which ranged from a single case to fifteen patients. Unfortunately however, the number of excluded patients prior to treatment is usually not reported. It is particularly interesting to note that other studies with stroke patients with language problems (see for a review de Aguiar et al., 2014) or motor problems (for a review see Floel, 2014) usually have larger samples. Unfortunately, again, the number of patients that has been excluded a priori is usually not reported. However, it may be that since chronic hemispatial neglect is often associated with more comorbidity, this hampers research with stimulation techniques and possible routine clinical application, to a larger extent than other post-stroke cognitive problems. This again underscores the fact that displaying neglect after stroke is not only a predictor of poor functional outcome, it is also very difficult to treat.

In conclusion, the present study does not provide evidence that tDCS to the posterior parietal cortex improves hemispatial neglect in severe chronic neglect patients. Due to the strict in- and exclusion health and safety criteria the majority of patients were excluded and this suggests that performing large randomized controlled trials is not feasible in chronic neglect patients.

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