Randomized Controlled Trial on Hemifield Eye Patching and Optokinetic Stimulation in Acute Spatial Neglect

Björn Machner, MD; Inga Könemund; Andreas Sprenger, PhD; Janina von der Gablentz, MD; Christoph Helmchen, MD

Background and Purpose—Right hemisphere stroke patients frequently experience spatial neglect, a severe lack of awareness for contralesional hemispace. Although neglect counts among the strongest predictors for poor functional outcome after stroke, there is no established therapy, particularly not for the acute stage.

Methods—In a randomized controlled trial, we compared the combined treatment of hemifield eye patching and repetitive optokinetic stimulation in acute stroke patients with neglect to the spontaneous course. Outcome measures were a neuropsychological test battery for neglect as well as scales of functional independence and clinical impairment. Outcomes were assessed at baseline (day 1), post treatment (day 8), and at 1-month follow-up (day 30).

Results—Final analysis included 21 acute right hemisphere stroke patients with neglect (23 enrolled, 2 lost to follow-up) allocated either to the treatment (1 week hemifield eye patching and daily sessions of optokinetic stimulation, n=11) or the control group (no neglect-specific treatment, n=10). At baseline, both groups did not differ in neuropsychological test performance, clinical impairment, or functional disability. At the post treatment session, both groups had improved in all these measures, and results were stable or further improved at follow-up. However, there was no significant difference in this change between the treatment and the control group.

Conclusions—An early intervention of combined hemifield eye patching and optokinetic stimulation in acute stroke patients with spatial neglect has no additive effect to the spontaneous remitting course of the disorder.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01617343.

Key Words: hemispatial neglect ■ rehabilitation ■ stroke

Spatial neglect represents a severe cognitive disorder affecting two thirds of patients with acute right hemisphere stroke.1,2 Although there is spontaneous remission in some patients within days, others show persisting neglect signs even after years.2,3 Because of the profound lack of awareness for contralesional hemispace, neglect patients are severely impaired in the activities of daily living.2,4 In fact, spatial neglect constitutes one major predictor for poor functional outcome after stroke.3,4

Despite promising experimental approaches, an established therapy for neglect in clinical practice is still lacking.5 There is a clear need for a neglect treatment that is easily applicable, well tolerated, and effective, inducing long-lasting improvement not only in neuropsychological test performance but also in patients’ functional independence.

We aimed to establish such an intervention for acute stroke patients with neglect by combining 2 bottom-up stimulation techniques: hemifield eye patching (HEP) and repetitive optokinetic stimulation (OKS). HEP is supposed to reduce the salience of hyperattended ipsilesional stimuli and thereby countering the interhemispheric attentional imbalance in neglect patients.6,7 HEP may be regarded as a visual type of constraint-induced (forced use) therapy, an approach proven effective in motor rehabilitation.8 OKS, inducing contralesional smooth pursuit eye movements and a visual motion percept, is supposed to work as a correcting input signal for the ipsilesionally shifted subjective egocentric midline in neglect patients.9,10

We a priori hypothesized that HEPOKS in acute stroke patients with neglect induces greater remission of neglect than in the spontaneous course. Beneficial effects, reflected by improvements in neuropsychological tests and functional disability scales, were expected to develop during the treatment period and be persistent at follow-up.

Methods

Subjects

The randomized controlled trial was conducted at the Department of Neurology, University Hospital Schleswig-Holstein, Lübeck, Germany. The study was approved by the local Ethics Committee.
Intervention
After obtaining informed consent according to the Declaration of Helsinki, patients were randomized by a third party (Institute of Medical Biometry and Statistics, University of Lübeck) and allocated to either of 2 parallel groups. Patients in the treatment group received HEP-OKS in addition to the usual stroke care (physio-, speech, and occupational therapy), whereas patients in the control group had usual care only. HEP was applied by spectacle frames containing noncorrective lenses of which the right half was patched with dark nontranslucent tape. Participants were instructed to wear the glasses all-day for 7 days and only to remove them for the OKS treatment sessions. Investigators, care providers, and patients’ relatives regularly checked on correct use of the glasses. The daily OKS sessions (15 minutes each) were applied at the bedside. Seventy colored geometric objects were coherently moving on an 18.4″ notebook monitor from right to left at varying speed (8–12°/s).

Outcome Measures and Assessments
We prespecified 2 primary outcome measures: (1) mean performance (accuracy) in the neuropsychological test battery and (2) neglect-related functional disability measured by the Catherine Bergego Scale.12 Secondary outcome measures were scores from the individual neuropsychological subtests and further scales of clinical impairment and functional disability (Barthel index, modified Rankin scale, and National Institutes of Health Stroke Scale).

Participants were assessed at 3 time points (figure 1): baseline (day 1), post treatment (day 8), and follow-up (day 30). The follow-up assessment took place at 1 of 3 Clinics for Neurological Rehabilitation in Lübeck’s surrounding area.

Statistics
Statistics were performed using SPSS 22.0 (IBM Corp). The design of the study required 2×3 ANOVAs with repeated measures, with group (treatment versus control) as between-group factor and session (baseline, post treatment, and follow-up) as within-group factors. In case of significant main effects, the ANOVA was followed by post hoc t tests investigating absolute differences (Bonferroni corrected).

Additional details concerning methods, randomization process, and sample size calculation can be found in the online-only Data Supplement.

Results
Recruitment and Baseline Characteristics
From 23 patients randomized (Figure I in the online-only Data Supplement), 2 patients were lost to follow-up, leaving 21 evaluable patients for final analyses (n=11 treatment, n=10 control). At baseline, study groups did not differ significantly in demographic, clinical, and neuropsychological characteristics except for 1 paper–pencil subtest (Table). Lesion overlap analyses are provided in Figure II in the online-only Data Supplement.

Outcomes
Figure 2 shows the group results for the 2 primary outcome measures. Table I in the online-only Data Supplement provides the statistical analyses from the according ANOVAs.

For neuropsychological test accuracy, there was no significant main effect of group or the interaction group*session, but only of session (F(2,18)=32.8, P<0.001). In both groups, neuropsychological test accuracy improved similarly between baseline and post treatment (treatment: d=21±4%, P<0.001; control: d=19±6%, P<0.05). Between post treatment and follow-up, there was additional improvement in the treatment group (d=14±4%, P<0.01) and stable effects in the control group (d=3±4%; P>0.05).

For Catherine Bergego Scale score, there was no significant main effect of group or the interaction group*session, but...
only of session ($F(2,18)=45.2, P<0.001$). Within both groups, the Catherine Bergego Scale score decreased equally between post-treatment and follow-up session (treatment: $d=−9.0±1.9$, $P<0.01$; control: $d=−8.2±1.8$, $P<0.01$).

Primary outcome analyses separately for each participant revealed that there was significant improvement in individual patients, independent of the allocated intervention (Figure III in the online-only Data Supplement). This reflects an individual variability in the spontaneous remission of neglect and not a dichotomy of responders and nonresponders to treatment.

Results of the secondary outcome measures are provided in Figure IV and Table I in the online-only Data supplement.

**Discussion**

In this randomized controlled trial on acute stroke patients with spatial neglect, we compared an early, 1-week intervention of HEP and OKS (treatment) to the spontaneous course (control). Patients in both groups showed an equal improvement in neuropsychological test performance and neglect-related functional disability over time, independent of the allocated intervention. Data indicate that the HEPOKS intervention had no additive effect to the spontaneous remission of neglect in our acute stroke patients.

**Did the study or the intervention fail?**

The study fulfilled all requirements of a randomized controlled trial, for example, applying adequate randomization, comparing a treatment to a no-treatment group with similar baseline characteristics and assessing established and relevant outcome measures. By contrast, the positive result of a previous study on HEP in subacute neglect patients was derived from the parallel improvement in 2 experimental groups (HEP versus Visual Scanning Training) without comparison to no-treatment. However, spontaneous remission of neglect must be necessarily taken into account before attributing any improvement to an intervention. Other positive studies on HEP did not refer to group differences at baseline which could have explained significant improvements.

But is our study result really a proof for failure of the therapeutic approach in general? There is good evidence for a beneficial impact of HEP and OKS when applied as monotherapies in chronic neglect patients. That the concurrent application of HEP and OKS caused interferences in our study, is still unlikely, as these interventions act complementary based on their theoretical rationale.

The acute stage of stroke may be better explanation. Our patients were certainly not generally too ill for this bottom-up treatment; tolerance and adherence to therapy was good (no discontinuation). But there was strong spontaneous remission of neglect in individual subjects of the control group, which makes it a strong competitor for any intervention, especially in studies with a moderate sample size. However, neither absolute group values nor individual analyses pointed to a clinically relevant effect of the HEPOKS intervention missed by our study that would have emerged in a larger study sample.

**Conclusions**

In this randomized controlled trial, the early intervention of combined HEPOKS had no additive therapeutic effect to the spontaneous remission of spatial neglect in acute stroke patients. We emphasize that this result does not exclude beneficial effects of this therapeutic approach in chronic neglect patients. In the absence of a neglect-specific treatment for the acute stage of stroke, affected patients should receive occupational therapy and physiotherapy as usual care.

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**Disclosures**

None.

**References**

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Supplemental Methods

Neuropsychological test battery – procedure, analysis, cut-offs and calculation of relative scores

The following paper-and-pencil tests were presented at the bedside on an A4 horizontal sheet of paper. The cut-off scores were derived from: Azouvi et al., A battery of tests for the quantitative assessment of unilateral neglect, Restorative Neurology and Neurosciences, 24, 273–285 (2006).

In order to receive one composite score as the primary outcome, the absolute scores from each patient in each subtest were first transformed into relative scores of test accuracy between 0 to 100% (see online supplement for detail). The mean of these finally constituted the “Neuropsychological test accuracy” of each participant.

Line bisection

Patients were instructed to mark the centre of 3 lines of 20 cm length. Mean deviation from the centre was assessed (between 0 mm and 100 mm), and the relative score was calculated:

Line bisection performance [%] = 100 – deviation [mm].

The cut-off* for pathological line bisection was set at > 6.5 mm deviation from the centre.

Star cancellation

Patients were asked to cross out 56 small stars presented among 65 distractors. We measured the total number of stars circled and calculated the relative test performance:

Star cancellation performance [%] = 100 * (stars circled / 56).

The cut-off for pathological Star cancellation performance was set at ≥ 6 omissions in total, with left minus right omissions ≥2.

Bells Test

In this cancellation task, patients were asked to circle bells (targets, n=35) that were presented among 280 other real-life objects serving as distractors. We measured the total number of bells circled (max. 35) and calculated relative test performance:

Bells test performance [%] = 100 * (bells circled / 35).
The cut-off for pathological Bells cancellation performance was set at ≥ 6 omissions in total, with left minus right omissions ≥2.

Text reading

Patients were asked to read out loud a text containing 140 words, displayed in three separate columns. The number of correct words was counted and relative test performance was calculated:

Text reading performance [\%] = 100 * (words read correctly / 140).

The cut-off for pathological reading performance was set at ≥ 1 word omission.

Figure copying

Patients were asked to copy the Ogden scene, i.e. drawing a tree, a fence, a house and a second tree. The five level scale ranged from 0 (no omissions) to 4 (omission of one left sided object and at least one left part of another object). The relative test performance in the Figure copying task was transformed as the following:

Ogden scene score 0 = 100% test accuracy, 1 = 75%, 2 = 50%, 3 = 25%, 4 = 0%.

The cut-off for pathological figure copying was set at ≥ 1 point.

Scales of clinical impairment and functional disability

Functional disability and clinical impairment of patients were assessed using the following scales: Catherine Bergego Scale (details below), Barthel Index, modified Rankin Scale, and the National Institute of Health Stroke Scale (http://www.ninds.nih.gov/doctors/NIH_Stroke_Scale.pdf).

The Catherine Bergego Scale (CBS) is a scale to assess neglect-related functional disability. It is based on direct observation of the neglect patient’s functioning in 10 real-life situations. For each of ten items there is a score of spatial bias between 0 (no neglect) and 3 (severe neglect), the maximum total score is 30 points.

Randomization and allocation

The randomization and allocation were performed by a “third party” at the Institute of Medical Biometry and Statistics (IMBS), University of Lübeck, Lübeck, Germany. The principle investigator sent a fax including identification parameters of the eligible patient (no name and initials) to the IMBS. A staff member at the IMBS with no clinical involvement in the trial randomized the patient online using a computerized permuted block technique with varying block size and assigned the unique patient identification number (PID). The randomization result and PID was documented on the fax and sent back to the investigator.
The study investigators had no influence on the randomization and due to the varying block size no knowledge about the upcoming allocation, thus preventing a selection bias. Due to the nature of a cognitive intervention trial, both the investigators and the patients were aware (not “blind”) of the allocated arm throughout the study.

**Sample size**

We based our initial estimation of the sample size on the results from previous studies applying either OKS or HEP as a monotherapy in chronic stroke patients. As the main parameter for this calculation we chose the difference (improvement) in the performance of the neuropsychological test battery between Day 1 (Baseline) and Day 8 (Post Treatment). Expecting a between-group difference of 30% (effect size) and a within-group standard deviation of 35%, 22 experimental subjects and 22 control subjects would be needed to study, associated with 80% power of the study and a Type I error of 0.05 (independent t-test, PS Power and Sample Size Calculations Program). An interim analysis was planned after recruitment of 50% of the patients.

In this interim analysis, independent t-test revealed no significant difference in the improvement of performance between treatment (21.1% ±4.2, n=11) and control (18.4% ±6.0, n=10) group (mean difference=2.7% ±7.2; t(19)=0.38; p=0.71; 95% confidence interval -12.3 to 17.7). Based on this negative result with respect to the originally targeted effect size of at least 30%, the trial was discontinued early and final analyses were performed on the basis of the 21 evaluable study subjects enrolled so far.

**Supplemental Results**

**Secondary outcomes**

Figure IV illustrates how both study groups improved over time in all the secondary outcome measures. This change was not statistically different (Table I) between the treatment and the control group for all but one measure:

In the Star cancellation task, the ANOVA revealed a significant main effect of the interaction group*session (F(2,18)=6.1; p=0.008). Subsequent t-tests revealed a significant increase of total cancellations from baseline to post-treatment only in the treatment group (22.8±4.9; p=0.003). However, this “greater improvement” was based on their lower number of cancellations at baseline (Table 1, main manuscript) and not a better performance at the post-treatment session (Figure IV).
Supplemental Figure Legends

Figure I: Flow of participants.

Figure II: Lesion overlap analyses.
Lesion overlaps are shown separately for patients in the treatment and the control group. The range of the rainbow color scale derives from the absolute number of patients, each color represents a defined number of patients having lesions in this area.

Lesion normalization and mapping on a standard brain was performed using SPM 8 and the MRICron software (http://www.mccauslandcenter.sc.edu/micro/mricron/).

Figure III: Individual primary outcomes for each participant in the two study groups.
Results from the neuropsychological test battery for neglect (upper row, “mean test accuracy”) and the Catherine Bergego Scale (lower row, “CBS score”) at the 3 different time points (Baseline, Post-Treatment, Follow-up) are depicted separately for each patient of the treatment (left) and the control group (right). In both study arms there are patients who improve significantly while others show less improvement.

e-Figure IV: Results of secondary outcome measures.
Results are shown for the different scales of clinical impairment and disability (Barthel, NIHSS, Rankin) as well as for the individual subtests from the neuropsychological test battery (Text reading, Star and Bells cancellation, Ogden scene copying, Line bisection). Error bars represent ±1 standard error.
Supplemental Table I: Statistical analyses of differences in primary and secondary outcomes between and within the two study groups.

<table>
<thead>
<tr>
<th></th>
<th>Between-group analyses (ANOVA with repeated measures)</th>
<th>Within-group analyses (t-test)</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Main Effects</td>
<td>Treatment Group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group</td>
<td>Session</td>
<td>Group*Session</td>
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<tr>
<td><strong>Primary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropsychological test accuracy</td>
<td>F (1,19)=0.2; p=0.662</td>
<td>F (2,18)=33.5; p&lt;0.001</td>
<td>F (2,18)=1.7; p=0.207</td>
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<td>CBS score</td>
<td>F (1,19)=0.0; p=0.927</td>
<td>F (2,18)=45.2; p&lt;0.001</td>
<td>F (2,18)=0.04; p=0.957</td>
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<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Barthel Index</td>
<td>F (1,19)=0.0; p=0.898</td>
<td>F (2,18)=26.2; p&lt;0.001</td>
<td>F (2,18)=1.9; p=0.166</td>
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<td>NIHSS score</td>
<td>F (1,19)=0.0; p=0.857</td>
<td>F (2,18)=22.6; p&lt;0.001</td>
<td>F (2,18)=1.4; p=0.260</td>
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<td>Rankin score</td>
<td>F (1,19)=0.0; p=0.917</td>
<td>F (2,18)=14.4; p&lt;0.001</td>
<td>F (2,18)=0.03; p=0.949</td>
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<td>Bells cancellations</td>
<td>F (1,19)=0.1; p=0.821</td>
<td>F (2,18)=20.7; p&lt;0.001</td>
<td>F (2,18)=0.8; p=0.44</td>
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<td>Stars cancellations</td>
<td>F (1,19)=0.4; p=0.512</td>
<td>F (2,18)=26.1; p&lt;0.001</td>
<td>F (2,18)=6.1; p=0.008</td>
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<td>Line bisection error</td>
<td>F (1,19)=1.7; p=0.204</td>
<td>F (2,18)=3.8; p=0.031</td>
<td>F (2,18)=0.4; p=0.662</td>
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<td>Ogden score</td>
<td>F (1,19)=0.1; p=0.709</td>
<td>F (2,18)=15.0; p&lt;0.001</td>
<td>F (2,18)=2.6; p=0.097</td>
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<td>Reading errors</td>
<td>F (1,19)=0.7; p=0.400</td>
<td>F (2,18)=13.7; p&lt;0.001</td>
<td>F (2,18)=0.3; p=0.747</td>
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</table>

Statistical significant results (p<0.05) are bold typed. Within-group analyses show mean differences d (±standard error) between baseline and post-treatment session (Post) and between post-treatment and follow-up session.
Flow of participants

Enrollment

Assessed for eligibility (n=40)

Excluded (n=17)
  Not meeting inclusion criteria (n=17)
  Declined to participate (n=0)
  Other reasons (n=0)

Randomized (n=23)

Allocated to intervention:
  HEPOKS + usual care (n=12)
  Received allocated intervention (n=12)

Allocated to control:
  usual care only (n=11)
  Received usual care (n=11)

Follow-Up

Lost to follow-up
  (n=1, due to pulmonary embolism)
Discontinued intervention (n=0)

Lost to follow-up
  (n=1, due to second stroke)
Discontinued intervention (n=0)

Analysis

Allocated to intervention:
  HEPOKS + usual care (n=12)
  Received allocated intervention (n=12)

Allocated to control:
  usual care only (n=11)
  Received usual care (n=11)

Analysis

Allocated to intervention:
  HEPOKS + usual care (n=12)
  Received allocated intervention (n=12)

Allocated to control:
  usual care only (n=11)
  Received usual care (n=11)

Analyzed (n=11)
  Excluded from analysis (n=0)

Analyzed (n=10)
  Excluded from analysis (n=0)
Lesion overlap analyses

Figure II
Individual primary outcomes of participants in the two study groups

**Figure III**

Treatment

Control

<table>
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<tr>
<td>5</td>
<td>0</td>
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</tbody>
</table>

Mean test accuracy [%]

CBS score

Follow-upPostBaseline Follow-upPostBaseline

Subject ID

1 4 6 9 10 12 15 16 18 19

Subject ID

1 4 6 9 10 12 15 16 18 19
Secondary outcomes for the two study groups

- **Barthel Index [%]**
- **Rankin score**
- **NIHSS score**
- **Text reading errors [n]**
- **Star cancellations [n]**
- **Bells cancellations [n]**
- **Ogden scene score**
- **Line bisection deviation [%]**

Control vs. Treatment