Study protocol

Randomized controlled trial of combined optokinetic stimulation and cueing-based reading therapy to treat hemispatial neglect following stroke (OKS-READ study)

PD Dr. med. Björn Machner

Department of Neurology - University of Lübeck

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1.1 Principle Investigator – Contact details

Name, Academic Degree:	Björn Machner, PD Dr. med.
Position:	Consultant Neurologist
Date of Birth, Nationality:	20.03.1980, German
Institution and Department:	University of Lübeck Department of Neurology
Address:	Ratzeburger Allee 160 23538 Lübeck Germany
Phone:	+49-451-50075827
Fax:	+49-451-50043404
E-mail:	Bjoern.Machner@neuro.uni-luebeck.de

1.2 Study summary

Title:	A randomized, controlled trial of combined optokinetic stimulation and cueing-based reading therapy in hemispatial neglect following stroke
Objectives:	To assess the effect of a combined treatment with optokinetic stimulation (OKS) and cueing-based reading therapy (READ) on hemispatial neglect and neglect-related functional disability in right-hemisphere stroke patients.
Study design:	This study will be a mono-centric, randomized, controlled, clinical trial. Using a crossover design with two arms, patients will either receive the intervention therapy first and then the control treatment or they will start in the control arm and then switch to the intervention. Each treatment phase consists of 15 therapy sessions lasting 30 to 45 minutes. Each patient will be assessed at 6 test sessions: • T1 and T2 as baseline measurement (min. 24 hours between the two sessions) • T3 after the first treatment phase • T4 before the second treatment phase • T5 after the second treatment phase • T6 as follow-up two weeks after T5.
Planned Sample Size:	30 recruited subjects who completed all test sessions (plus an expected drop-out of n=6). An interim analysis is planned after successful inclusion of 22 subjects.
Setting:	Neurological Rehabilitation Center (Bad Segeberg, Germany)
Participants:	Eligible participants are in-patients with a right hemisphere stroke, signs of hemispatial neglect in at least one screening test and the ability to read and understand German language. Exclusion criteria are a pre-existing dementia, other structural lesions of the brain besides the unilateral stroke, low vision (corrected <0.7) and the inability to give informed consent.
Intervention:	The intervention consists of a combination of optokinetic stimulation (OKS) and an adaptive, cueing-based reading (READ) therapy. Within the intervention session, the OKS will always be performed first (at least 15 minutes) followed by the reading therapy (at least 15 minutes). During the control phase, patients will receive a general neuropsychological treatment without specifically targeting spatial attention. Each phase will contain 15 individual therapy sessions applied within a period of max. 28 days.
Primary outcome:	Composite score of different established neuropsychological tests assessing spatial neglect and a clinical score of neglect-related functional disability (Catherine Bergego scale)
Data Analysis Plan:	The difference in the primary outcome parameters between the intervention and control phase will be analyzed using adequate statistical tests for this within-subject crossover design (independent t-test of the intra-individual differences between intervention and control).

2 Introduction

2.1 Background and objectives

Every two seconds, someone in the world is having a stroke (Stroke association 2018). In Germany the lifetime prevalence of having a stroke in adults between 40 and 79 years is 2.9 %. With growing age, the prevalence increases up to 7.2% at the age of 70 to 79 (Busch et al. 2013). Hemispatial neglect represents one of the major cognitive disorders following a stroke (Parton et al. 2004). Neglect is typically defined as the impaired or lost ability to respond to sensory stimuli presented in the contralesional hemispace. It can appear in all modalities, impairing seeing, hearing, feeling and smelling (Kerkhoff 2004). Neglect patients predominantly explore the ipsilesional space in the room, miss or react less to objects, people or obstacles in the contralesional hemispace and search repeatedly in the same areas in the room (perseveration). Neglect represents a supramodal “secondary” disorder with symptoms that are not explained by a primary sensory or motor impairment (Kerkhoff 2004).

Neglect is thought to be a multicomponent deficit (Milner und McIntosh 2005; Parton et al. 2004) and the combination and severity of each of the deficits varies strongly between patients (Parton et al. 2004). Neglect patients frequently deny that there is anything wrong with their perception, which itself is a core symptom of the syndrome called anosognosia (Parton et al. 2004; Kerkhoff 2004). Due to this heterogeneity, the anosognosia and the numerous phenomena occurring with the syndrome, neglect is difficult to treat.

While both left-sided and right-sided neglect can occur, the former is much more frequent and severe and persists more often up to the chronic stage (Bowen et al. 1999; Parton et al. 2004). A left-sided neglect is caused by a lesion in the right hemisphere, commonly cerebral infarction or hemorrhages. The brain areas predominantly injured in neglect patients are the right temporo-parietal junction and ventral frontal cortex, but neglect also occurs after damage to subcortical regions (thalamus, basal ganglia) and fronto-parietal white matter tracts (Parton et al. 2004; Bartolomeo und Chokron 2002; Milner und McIntosh 2005; Verdon et al. 2010; Doricchi und Tomaiuolo 2003). The prevalence of a left-sided neglect after a right-hemispheric brain lesion is hard to determine and depends on the criteria to diagnose neglect and on the phase of stroke patients are assessed in (Bowen et al. 1999). In the acute phase 28 to 53% of all right hemispheric patients suffer from neglect (Kerkhoff 2004). While some patients recover spontaneously, one third of the right hemispheric patients still suffer from neglect three months after the lesion.

Since neglect patients have a worse rehabilitation outcome than other stroke patients without neglect (even worse than patients with aphasia and hemiparesis), they require especially intense rehabilitation therapy (Kerkhoff 2004; Mainetti et al. 2013). Neglect not only impairs cognitive functions but affects motor recovery and the social rehabilitation of the patient (Bartolomeo und Chokron 2002; Denes et al. 1982). It is a major independent predictor for poor functional outcome (loss of independence) after a stroke (Parton et al. 2004). If neglect remains untreated, it leads to a worse general rehabilitation outcome (Kerkhoff et al. 2012) and massive impairments in everyday life (Katz et al. 1999). Hence, the burden of the disease and the demand for a successful treatment of neglect is high.

2.2 Scientific background and explanation of rationale

Over the last years, different interventional approaches were investigated to treat spatial neglect but there is no single therapy that reached wide acceptance or an establishment in clinical practice. This is due to different reasons: There is certainly a lack of high-quality studies. Common problems are a small sample size, lack of adequate blinding, lack of transfer of effects to the everyday life of patients or missing evidence for a persistence of effects at follow up (Azouvi et al. 2017). Thus, Kerkhoff and Schenk (Kerkhoff und Schenk 2012) claimed that the aim of future neglect therapy research should be to identify the best treatment, the best treatment combination, the best therapy frequency and patient specific predictors for therapy success.

Beside medication and non-invasive brain stimulation treatments, most interventions are so-called "cognitive" rehabilitation interventions. These can be further differentiated into top-down and bottom-up interventions. Top-down interventions encourage awareness of the disability and potential compensatory strategies and include visual scanning therapy, any form of feedback of cueing or mental practice or imagery. Bottom-up interventions address the impairment directly and do not require awareness or behavioral change. They include for example prisma adaptation or hemifield eye patching (Bowen et al. 2002).

There is evidence that combined therapy approaches may be more effective in treating the multicomponent neglect syndrome than monotherapies (Saevarsson et al. 2011). Due to the variety of neglect symptoms even within a single patient a monotherapy approach is probably not able to improve all the symptoms. Currently there is too little knowledge about which therapy is the best for which symptom, so that a general combined therapy covering a broad spectrum of symptoms is preferable (Saevarsson et al. 2011). Combining therapies with different underlying mechanism of action could be a powerful approach to address the variety of symptoms. Following this reasoning, Kortte and Hillis (Kortte und Hillis 2011) argue that a combination of a bottom-up and a top-down approach could be the most effective combined therapy for neglect patients.

For this study we chose a combined therapy consisting of smooth pursuit eye movements elicited by optokinetic stimulation (OKS) and an adaptive reading therapy (READ). Each of these therapies, when applied as a monotherapy, has previously shown promising results in improving the neglect syndrome and functional disability (Kerkhoff et al. 2014; Turgut et al. 2018). There are several reasons why we are confident that a combination of OKS and READ could be highly effective: Firstly, OKS is commonly classified as a bottom-up approach while the reading therapy can be considered as predominantly top-down approach. Therefore, although both therapies include components of the other approach, we follow the argument outlined above of combining bottom-up and top-down approaches. Secondly, there are concrete synergies between the two therapies. OKS facilitates the reading capacity of the neglect patients at least for a short time (Kerkhoff 2004), so that the reading won't be that exhausting and frustrating for the patients. At the same time, many patients are eager to regain their reading ability, so

the reading therapy with individualized texts will improve the patients' motivation. This in turn could result in increased engagement during the rather monotonous OKS task. Finally, both therapies are feasible and practicable, so - if the combined approach proves effective - therapists could easily apply them in their patients.

In the following, detailed information on each of the two therapeutic approaches are provided.

OKS

During OKS-therapy the patients watch a display with stimuli moving coherently towards the neglected hemispace. The patients should follow the stimuli with their eyes. Many studies demonstrated that OKS can reduce the neglect symptoms. One session of OKS can reduce the neglect directly afterwards (Keller et al. 2009) and a repetitive stimulation over several days can have long-term benefits for the neglect patients (Hill et al. 2015). Kerkhoff and colleagues (Kerkhoff et al. 2014) showed that the stimulation reduced not only the visual, but also the auditory neglect symptoms. In the same paper, they also demonstrated that the neglect was not only reduced in standard neglect tests but also in activities of daily life (ADLs).

According to Kerkhoff, smooth pursuit training modulates and reduces neglect in at least three ways: Firstly, it activates a cortico-subcortical network, including many brain regions which are involved in gaze and attention shift (occipitotemporal, parietal, insular, occipital cortex, basal ganglia, cerebellum, and brain stem). Thus, activating these brain regions can lead to more accurate behavior in space. Secondly, SPT may activate the vestibulo-ocular system via optokinetic nystagmus. Through this mechanism, SPT may recalibrate the egocentric spatial orientation and correct the ipsilesional neglect bias into a more symmetrical midline position. Third, the dynamic features inherent in moving displays that elicit smooth pursuit eye movement may increase perceptual saliency of contralesional targets.

One OKS study that instructed patients to refrain from pursuit eye movements yielded a negative result (Pizzamiglio et al. 2004) which highlights the importance of smooth pursuit eye movements as a therapeutic ingredient of the OKS training.

To perform smooth pursuit eye movements during OKS and follow the stimuli accurately it is important to be able to predict where and with which velocity the stimuli is moving. Therefore, smooth pursuit eye movements also have an active component, which is why it is thought to use top-down processes as well. Heide and colleagues (Heide et al. 1996) showed that in stroke patients damage to the parietal or frontal lobes can lead to deficits in performing smooth pursuit eye movements. In combination with areas such as the cerebellum, the medial superior temporal and middle temporal areas are most involved in processing, predicting and relaying visual information (Krauzlis 2004). Thimm and colleagues (Thimm et al. 2009) could show that after three weeks of OKS training the neglect patients showed increased activation of bilateral parietooccipital regions when performing a spatial attention task. Moreover, this increase, e.g. in the bilateral precuneus which is known to be involved in performing smooth pursuit eye movements (Petit und Haxby 1999), was related to the amelioration of neglect symptoms.

In our study we record the eye movements of the patients during the OKS. This will not only allow us to control patients' adherence to the OKS task. It will also allow us to answer the following questions: Is OKS able to reduce neglect symptoms even if the patients are impaired in following the OKS with their eyes? Do the patients improve in executing smooth pursuit eye movements during the OKS therapy? Is the accuracy in performing smooth pursuit eye movements during the OKS a predictor for its success in ameliorating neglect symptoms and functional disability?

Cueing-based reading therapy

The second part of the intervention in our study will be an adaptive, cueing-based reading therapy.
Cueing as a therapy approach for neglect patients attempts to use cues to shift the patient's attention to the neglected side (Posner 1980; Pizzamiglio et al. 1992). The cues used can differ in modality (visual, auditory, etc.) as well as in *how* the shift of attention is provoked. If the cue elicits an automatic shift of attention like a moving bright light, then the cue and the shift of attention would be classified as *exogenous*. But there are also *endogenous* cues, which require effort on the side of the patient, for example when he or she is asked to search for a special object on the left.

In our study, we will apply cues while the patient is reading words or a whole text out loud. The basic approach is derived from the reading therapy used by Turgut and colleagues (Turgut et al. 2018). This study showed that the neglect in stroke patients was reduced after an intense three-week therapy. Compared to a neuropsychological treatment that was not neglect-specific, the patients' performance improved in standard neuropsychological bedside tests for spatial neglect but also in activities of daily living. Both, exogenous and endogenous cues were implemented.
Usually, a reading therapy would be classified as a top-down approach. However, by additionally using exogenous cues to direct the patient's attention to the left, bottom-up processes are utilized as well. The patients' anosognosia often goes along with reduced compliance to rehabilitation. We are convinced that our reading therapy, which uses both bottom-up and top-down influences, has a good chance of overcoming this problem by keeping the patient motivated. Patients are generally aware that their reading ability suffered from the stroke and are eager to regain this skill. Furthermore, we will construct the therapy in an adaptive manner to keep the difficulty at an appropriate level for the individual patient.

2.3 Specific objectives and hypotheses

We hypothesize that a combined therapeutic intervention consisting of OKS and READ applied in 15 sessions within 21 days, will significantly reduce neglect symptoms of right-hemispheric stroke patients and their neglect-related functional disability. The reduction will be greater than the improvement of symptoms during a control treatment of the same duration and frequency, a general neuropsychological rehabilitation without specifically targeting the neglect and spatial attention. The outcome will be measured by use of a computerized neuropsychological test battery and a clinical scale of neglect-related functional impairment in the activities of daily living, both directly after the intervention/control phase (immediate effects) and at a follow-up 8 weeks after study inclusion (long-term effects). We

expect the positive effects to emerge directly after the two-week intervention and to persist up to the follow-up measurement. We further speculate that those patients that receive the OKS-READ intervention first (and the control therapy second) will show greater improvement at follow-up than those patients that started with the control therapy (advantage of an early versus delayed treatment).

3 Methods

3.1 Trial design

The study will be a randomized controlled trial. We implement a crossover design with two treatment phases (Figure 1). After a screening (T0) and the fulfilment of the inclusion criteria for the study, the baseline measurement is conducted at two different time points (T1, T2) separated by at least 24 hours. One group of patients (IC) receives the intervention first and then the control therapy. The other patients receive the control treatment first and then the intervention (group CI). During the intervention and the control phase the patients receive 15 therapy sessions within a 28-day period, each session lasting between 30 and 45 minutes. We will assess neglect severity directly after the first phase (T3) and again right before the beginning of the second phase (T4). After finishing the second therapy phase there will be another neglect assessment (T5). Two weeks later, we will measure the long-term effects of the therapy at the follow-up assessment (T6).

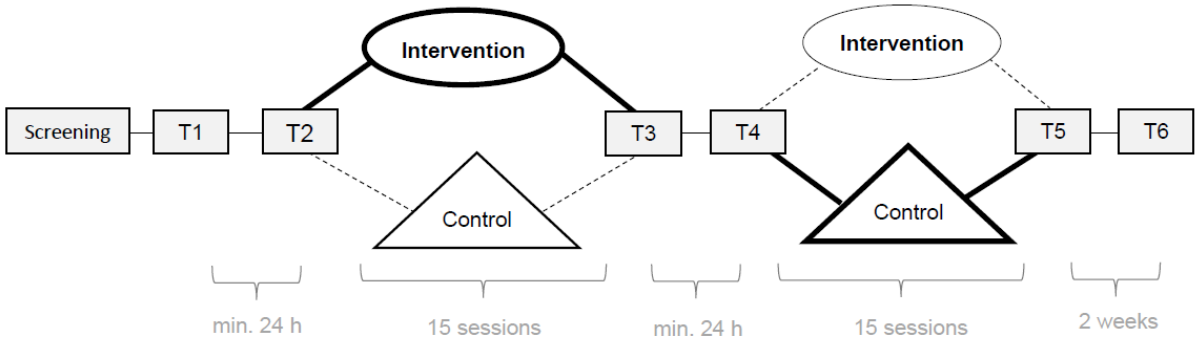

Figure 1. Study design: randomized controlled trial with crossover. There are two randomized groups of patients. One receives the intervention first, and then the control therapy (IC, bold). The other receives the control therapy first and then the intervention (CI). Assessments (T 1-6) will be performed directly before and after each therapy phase and at a 2-week follow up.

4 Participants

4.1 Eligibility criteria for participants

Inclusion criteria are

- a first-time stroke in the right hemisphere (confirmed by cranial CT or MRI) within the last six months,
- a left-sided hemispatial neglect (as detected in at least one subtest of the screening test battery, see also “Outcome” section),
- the ability to read and understand German language and
- the ability to give informed consent.

Patients are excluded from the study if they have any of the following:

- dementia
- structural lesions of the brain besides the unilateral stroke (e.g. multiple or bilateral stroke lesions, hydrocephalus, inflammatory lesions, etc.)
- low vision (corrected <0.7) due to ophthalmological diseases.

4.2 Settings and locations where the data are collected

The data will be collected at the neurological rehabilitation center (NRC) in Bad Segeberg, Germany. The patients will be recruited from three different wards.

The diagnostic and therapy sessions will always take place in the same room in the NRC, where the computer, screens, eye tracker, etc. will be permanently installed.

5 Interventions

5.1 Intervention therapy

<u>OKS</u>

At the beginning of each session the patients will receive OKS for at least 15 minutes. The stimuli are presented on a computer screen in front of the patients. There will be a black background with a pattern of 70 stimuli (size 0.5°/ 0.75°/ 1°), which coherently and continuously move to the left (Figure 2). Both, the stimuli (squares, dots, triangles and stars) and the velocity (7 – 13 ° per sec.) change every 45 seconds (see figure 2 for an example). The patients will be instructed to continuously choose one stimulus dot and follow it with their eyes until it has reached the left side of the screen and then to jump to the right edge of the screen and start again. This instruction and the rather slow stimulus speeds have been shown to successfully elicit smooth pursuit eye movements (look-nystagmus) which appears crucial for the therapeutic effect of OKS (Kerkhoff & Schenk, 2012).

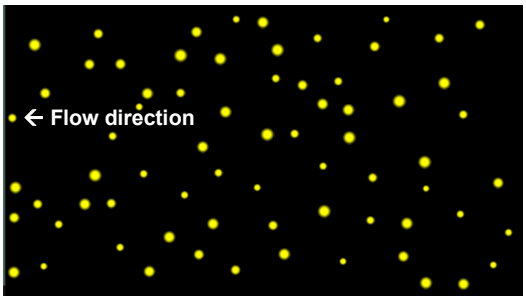

Figure 2. Optokinetic Stimulation (OKS).

Adaptive, cueing-based reading therapy

The second part of each therapy session in the intervention condition is the cueing-based reading therapy, which will last at least 15 minutes. The task of the patient is to read out loud words or a text presented on a paper in front of them. Like Turgut and colleagues (Turgut et al. 2018), we will use exogenous and endogenous cues to facilitate an attentional shift to the left while the patients are reading. To give exogenous cues, the therapist will highlight words at the beginning of the line or when they were omitted. Endogenous cues are verbal instructions which require intrinsic actions by the patient. For example, the therapist will name the first letter of the omitted word and ask the patient to search for it or to establish eye contact with the therapist. The therapist will always sit on the left side of the patient because he or she also functions as a cue. The cues will be inserted depending on the severity of neglect (Table 1) estimated by the therapist (adaptive therapy). If the reading ability increases and neglect dyslexia symptoms decrease, the cueing will be reduced, and the task difficulty will be increased by adapting font size and line spacing. Following the protocol established by Turgut et al., the reading material will be chosen depending on the patient's preference to increase the patient's motivation and adherence to the therapy.

	Exogenous Cues	Endogenous Cues
Severe – Moderate	● Colored highlight of most of the first letters in a word/first word in a line ● Colored highlight of the first letter of omitted words	● Therapist asks to search for marked letter/ word ● Therapist asks to search for her index finger, which is positioned at the beginning of the line ● Therapist asks for eye contact
Moderate	● Colored highlight of the first letter of omitted words if necessary	● Therapist names first letter of omitted word and asks to search for it (if necessary, add colored marking) ● Indirect request for eye contact
Moderate – Mild	● Colored highlight of the first letter of omitted words if necessary	● Therapist names first letter of omitted word and asks to search for it (less need for colored marking)
Mild		● Therapist asks to search further to the left ● If a word is omitted, therapist asks to read the sentence again

Table 1. READ Cueing Protocol. Adapted from Turgut et al. (2018), modified for the present study.

5.2 Control therapy

During the control therapy the patients will also receive neuropsychological treatment, but without targeting visuospatial attention. Examples for components implemented are supporting conversations, diagnostic assessments (e.g. memory diagnostics) and training of memory and executive functions.

6 Outcomes

6.1 Performance in a computerized neuropsychological test battery

The neuropsychological assessment of neglect severity will happen by use of a largely investigator-independent computerized test battery presented on a computer tablet with 17 inches touch screen.

In the screening phase, patients will be confronted with a brief version of the neuropsychological test battery to detect signs of hemispatial neglect. This version will include the following subtests: Bells cancellation (Gauthier et al. 1989), line bisection, and figure copying (Ogden 1985). Additionally, patients will perform a reading task taken from the German version of the Behavioral Inattention Test (BIT).

After the enrolment, during the further course of the study the patients will repeatedly perform a more extensive version of the computerized test battery that includes 11 subtests. The tests are executed at a tablet screen with touch screen. During the performance of some of these tests (Table 2) eye movements will be recorded by use of a non-invasive, video-based remote eye tracking device (EyeLink Portable Duo).

The subtests (and parameters that will be analyzed) are the following:

I. *Word reading*: 40 words are successively presented in the center of the screen. We will use two different sets of words composed by Reinhart and Kerkhoff (Reinhart und Kerkhoff 2016). The sets will be presented alternately (Set 1: T1, T3, T5; Set 2: T2, T4; T6). The patient is asked to read the words out loud. The number of correct words is counted. An audio file of the patient's performance will be recorded.

II. The *Menu reading* task is a subtest of the BIT for assessing functional reading. 24 words are presented in 4 columns simultaneously. The words are predominantly compound words (e.g. "Erbsensuppe", engl.: "pea soup"). The patient is asked to read the words out loud. The number of correct words is counted. An audio file of the patient's performance will be recorded.

III. *Text reading*: We will use one out of six texts (Kerkhoff et al. 2012) for each test session. Each text consists of 180 words and is presented on the tablet screen. The order of the texts will be always

the same (T1: Text A; T2: Text B; T3: Text C; …). The patient is asked to read the text out loud. The number of correct words is counted. An audio file of the patient's performance will be recorded.

IV. *Free viewing*: We will use 60 different pictures, downloaded from the free-to-use web-based photo stock Pixabay (Figure 3, Appendix A1). They contain for example landscapes, shelfs with books, food, etc.. We will split them up randomly into 6 sets à 10 pictures. At each test session the patients will be confronted with one of the sets, including the 10 pictures in a random order, each being presented for 10 seconds. The patients will be instructed to just look at the pictures and we will record the eye movements. The median of all gaze points (fixations) will be analysed with a special regard to the neglect-typical rightward bias.

Figure 3. Examples for pictures of the Free viewing task.

V. *Posner paradigm*: We will implement a version of the classical Posner task (Posner 1980). During the task, the display shows a dark-gray background with a light-gray fixation cross at the center and two light-gray square frames, positioned on the horizontal meridian at either side with. The cue consists of one of the rectangle frames turning yellow for 300ms. After a delay of 150 or 400 ms, the target (a light gray asterisk) appears within one of the two frames and remains present until a response (press the space-bar) is made, or 2 s have elapsed. In 75 % of the cases the target appears in that frame, which before had turned yellow (valid trial). Each block consists of 40 trials, and there will be a maximum of 3 blocks. Reaction times and eye movements will be recorded in order to calculate an index of lateralized spatial attention (bias).

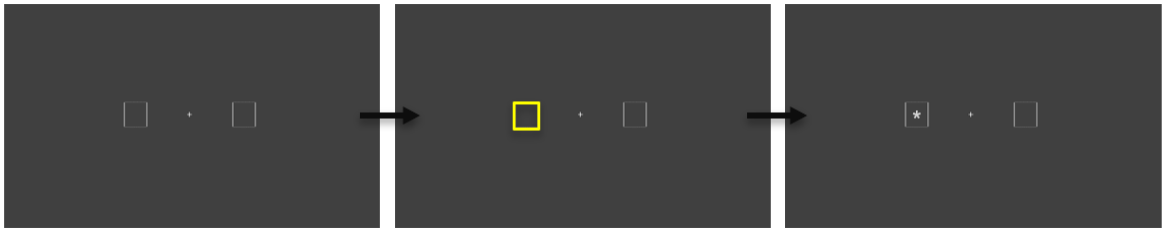

Figure 4. Example of a valid trial (cue and target at the same side, here: left) of the Posner task. The patient is asked to press the space-bar when the target (asterisk) appears.

VI. *Visual search:* The patients will perform a visual search task while eye movements are recorded (Machner et al. 2018). Each trial will start with a central fixation cross, followed by the presentation of a naturalistic image of a desk scene (Figure 5). On the desk, there are 30 different every-day

objects (pen, coin, key, etc.). The patients will be instructed to search for a paperclip that could be either red or blue. As soon as they find the target, they should press a response button. Each trial will be finished after a maximum of 12 s or earlier by a button press upon target detection. In 80% of the images there will be a target present, 20 % are no-target trials. At each test session there will be 15 trials. The median of gaze points, reaction times and the number of detected targets will be recorded in order to analyze the extent of the rightward spatial attention bias.

Figure 5. Desk task stimulus.

VII. The *Bells test* is a cancellation test, which consists of 35 targets (bells) and 280 distractors. The stimuli are presented on a tablet screen in the same size as in the paper-and-pencil (PnP)-version. The patient will be asked to tick the bells with a stylus/ pen. Ticked stimuli will be marked with a red circle (figure 6). Maximum time for processing will be 7 minutes. Dependent variables will be the point of beginning (pob, distance of the left border of the screen), the Center of Cancellation (CoC, calculated as in (Rorden und Karnath 2010), the relative test performance (100 * (bells circled / 35)) and the oculomotor median.

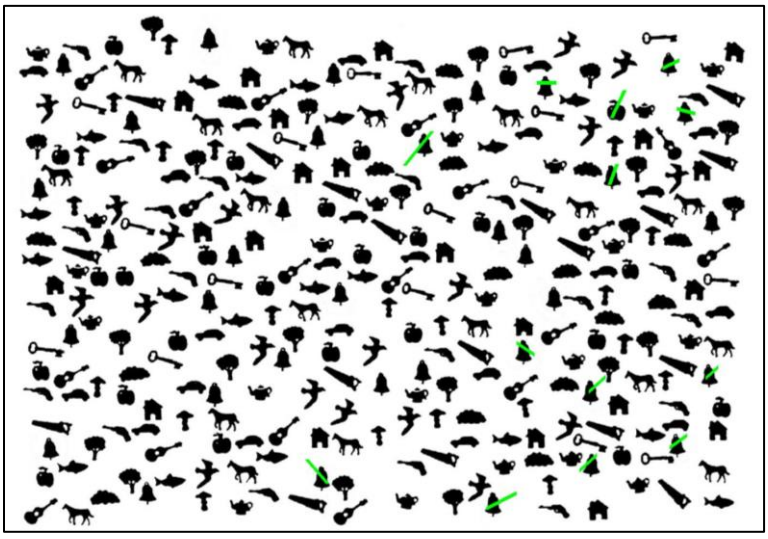

Figure 6. The bells test. Stimuli ticked by the patients will be marked with a green line irrespective of whether they are targets (bells) or distractors.

VIII. In the *line bisection* task 3 lines, each 20 cm long, are successively presented on the tablet. The patient is instructed to mark the middle of each line. Mean deviation from the center will be assessed.

IX. The *Hearts Cancellation* task (figure 7) is part of the Oxford Cognitive Screen (Demeyere et al. 2015). It's a cancellation task consisting of 50 targets (hearts without a gap), and 100 distractors (50 hearts with a gap on the left, 50 hearts with a gap on the right). The patient's task is to tick all the hearts *without* a gap. Maximum time for processing will be 5 minutes. The number of ticked targets and distractors is counted and will be used to calculate the spatial bias with regards to the whole test sheet (egocentric) and with regards to the individual objects (allocentric).

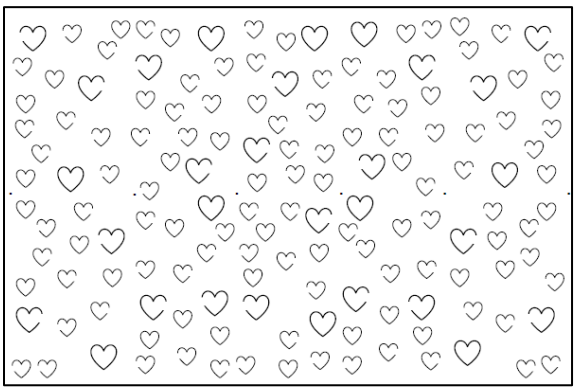

Figure 7. Hearts Cancellation Task. The targets are the ones without a gap, the others are distractors with a gap on the left or on the right side.

X. *Figure copying*: Patients are asked to copy the Ogden scene (Ogden 1985), i.e. drawing a tree, a fence, a house and a second tree. Performance is evaluated on a five-level scale ranging from 0 (no omissions) to 4 (omission of at least one left sided object and a left part of another object).

XI. *Clock drawing:* The task is part of the BIT, in which the patient has to write the numbers of a clock (from 1 to 12) clockwise in an empty circle (xx cm in diameter). Then we ask the patient to add two pointers at the right place so that the clock shows "10 past 11". The scoring will be a value between 1 (perfect performance) and 6 (no representation of a clock).

There are several benefits of executing the neglect assessment digitally. On the one hand test execution is more standardized and the evaluation of the data is less time-consuming for the therapist. On the other hand, which is even more important, more parameter can be recorded, like reaction times, order of processing or eye movements. Several studies have shown, that computerized tasks measuring reaction times are more sensitive than standard paper-and-pencil tasks. Those digital performed reaction time tasks can reveal an ipsilesional spatial attention bias in patients without clinical signs of neglect. To uncover this "hidden" neglect is essential, because it can have an impact on everyday life situation, for example during orientation in traffic (Machner et al. 2018).

	Subtests	Eye movement recordings	Audio file recording	Evaluation/ Scoring
I	Reading: word	x	x	manually
II	Reading: menu	x	x	manually
III	Reading: text	x	x	manually
IV	Free viewing	x		digital
V	Posner-Task	x		digital
VI	Visual search	x		digital
VII	Bells-Test			digital
VIII	Line bisection			digital
IX	Heart Cancellation task			digital
X	Clock test			manually
XI	Figure copying			manually

Table 2. Overview of the subtests included in the neuropsychological test battery (including information on eye movement and audio file recordings)

6.2 Functional impairment as assessed by a clinical scale for neglect-related disability

We will assess the neglect-related impairments in activities of daily living (ADL) using the German version of the Catherine Bergego Scale (CBS) (Bergego et al. 1995). To obtain information about the degree of anosognosia the patient her-/himself will fill out the CBS, so that we can compare the patient's score and the value scored by the investigator (care-providers on the ward). Notably, the investigator version of the CBS will be evaluated by therapeutic staff not involved in the study to ensure a maximum of objectivity.

In addition, we will score the Barthel Index (BI) and the Functional Independence Measurement (FIM) as an assessment of the patients' overall ability in ADLs.

6.3 Definition of primary and secondary outcome measures

As relevant outcome measures we will calculate the within-subject difference between the test sessions T3 and T5 for the following parameters:

Primary outcome:

I. Composite score of the performance in the neuropsychological test battery (mean of the normalized values of the different subtests, range: 0 - 100%) as a measure of neglect severity and the ipsilesional spatial attention bias

II. Score of the Catherine Bergego Scale (investigator version, range: 0-30 points) as a measure of neglect-related functional disability

Secondary outcome:

I. Performance in the individual subtests of the computerized test battery
II. Anosognosia (difference between CBS_other and CBS_self)
III. Non-neglect specific functional outcome scores (BI, FIM)

7 Sample size

Based on the successful inclusion of 30 patients in this two-arms crossover study, the probability is 80 percent (power) that the study will detect a treatment difference at a two-sided 0.05 significance level, if the true difference between treatments is 0.25 units (25% effect size). This is based on the assumption that the within-patient standard deviation of the response variable is 0.33 (33% standard deviation). With respect to an estimated drop-out rate of 20%, we are going to enroll 36 patients in total.

8 Randomisation

8.1 Method used to generate the random allocation sequence

The random allocation sequence will be generated using a web-based randomization tool (https://www.sealedenvelope.com/simple-randomiser/v1/lists).

8.2 Type of randomization

A permuted block technique with randomly varying block lengths will be used to randomize patients into either the IC (Intervention first) or the CI (Control treatment first) group. The ratio will be 1:1 (balanced randomization).

9 Implementation of the allocation process

The random allocation sequence list will be stored at the office of an employee of the University of Lübeck, Dept. of Neurology, who has no direct clinical involvement in the trial. After successful screening, check of the inclusion and exclusion criteria and reception of the patient's informed consent, the investigator at the Rehabilitation Centre will contact the keeper of the generated randomization list at the University of Lübeck via email, he will provide the patient's study ID and whether the necessary preconditions for the allocation are fulfilled (inclusion/exclusion criteria checked, informed consent obtained) and finally ask for the randomized allocation. The keeper of the list will then tell the randomization result, i.e. whether the patient is allocated to the IC or the CI group.
Notably, the therapist at the Rehabilitation Center is never aware of the order of the sequence nor the block lengths, hence he is not able to predict the randomization result (no selection bias).

10 Blinding

Due to the implicit constraints of cognitive interventions (no placebo possible as opposed to drug studies), neither the patient himself nor the therapist of the study can be blinded to the patient's allocation arm. However, the assessment of the functional impairment (CBS score as a primary outcome) will be performed by rehabilitation staff who are blind to the patient's allocation. Furthermore, the assessment of the neglect severity by use of a computerized neuropsychological test battery is robust and objective and largely independent of the investigator who is administering the test.

11 Statistical methods

11.1 Statistical methods used to compare groups for primary and secondary outcomes

Statistical analyses will follow the rules of proper use of the crossover design in clinical studies (Wellek and Blettner 2012). First, the intra-individual difference (Delta) between the outcome results of the two treatment phases (I and C) will be calculated for each patient in the two study groups (IC and CI). Next, an independent t-test will be applied to assess a significant difference between the intra-individual Delta of study group IC and the ones of study group CI.

This way of statistically analyzing the efficacy of an intervention investigated by a crossover design applies to all the primary and secondary outcome measures in our study.

11.2 Methods for additional analyses, such as subgroup analyses and adjusted analyses

There are no pre-specified subgroups.

12 Data monitoring (Interim Analysis)

An interim analysis will be performed on the primary endpoints when n=22 patients have been randomized and have successfully completed the trial. This number is derived from an adjusted sample size calculation with an assumed higher effect size of 30% (see also section 7 Sample size; current assumption 25% effect size). The statistical method used for the interim analysis is the same approach as stated above (section 11.1 Statistical methods). In case of superiority or inferiority of the intervention (vs. control treatment) at this stage, the study will be prematurely terminated. We do not plan to stop the trial at this stage for other reasons (e.g. futility).

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Appendix

A1 Stimuli for the free viewing task

List of pictures downloaded at https://pixabay.com/ (title and number).

1	Animal	3437467	**31**	Flea_market	1681489
2	Auto	3091234	**32**	Food	1679815
3	Avenue	2215317	**33**	Fruit_basket	1114060
4	Away	3024773	**34**	Home	1438326
5	Bathroom	3563272	**35**	Houses	1622066
6	Berries	1546125	**36**	Kitchen	1566964
7	Bookcase	3532950	**37**	Kitchen	2565105
8	Bookcase	3532957	**38**	Landscape	3714664
9	Books	2463779	**39**	Living_room	670237
10	Bowling	596766	**40**	Marbles	1659398
11	Bowling_shoes	2779989	**41**	Music	2060616
12	Breads	387544	**42**	Nuclear_waste	1471361
13	Bridge	192982	**43**	Parking	825371
14	Cafe	3537801	**44**	Pier	349672
15	California	106943	**45**	Potatoes	411975
16	Christmas	1075121	**46**	Raspberry	2023404
17	Church	3481187	**47**	Road	220058
18	Closet	3725417	**48**	Salt_harvesting	3060093
19	Clubs	518192	**49**	Sand	1573326
20	Cock	2522623	**50**	Shelf	1853439
21	Coffee	751619	**51**	Still_life	562357
22	Coffee	2390136	**52**	Still_life	851328
23	Colorful	2653188	**53**	Store	984393
24	Computer	627220	**54**	Summer	814679
25	Countryside	2326787	**55**	Summer	2391348
26	Daisy	324403	**56**	Tray	2546077
27	Dolls_kitchen	546966	**57**	Wash	1141774
28	Fashion	1031469	**58**	Wheelie_bin	2270582
29	Flea_market	851970	**59**	Woodland	656969
30	Flea_market	851978	**60**	Workshop	984022