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Master's thesis

Evaluating the Effectiveness of a Neuropsychological Therapy Program in Combination with FES in Ameliorating (Allocentric) Neglect

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Are there deviations of the Master's thesis from the proposed plan?
☐No
☒Yes, please explain below the deviations
Using mixed ANOVAs instead of Linear Mixed models. Surpassing 10.000 words.

Abstract

Spatial neglect can be divided into multiple subtypes, two of which include egocentric (space-based) and allocentric neglect (object-based). Although allocentric neglect in particular has been linked to poor functional outcomes, current treatment approaches often only show effectiveness for treating egocentric but not allocentric neglect.

This study aimed to compare the effectiveness of a combination of Functional electrical stimulation (FES) of the contralesional arm and exercise-based (allocentric) neglect therapy to a general neuropsychological therapy with FES in ameliorating (allocentric) neglect. Furthermore, the effectiveness of FES independent of treatment was investigated by comparison of an allocentric neglect therapy with FES to a general neuropsychological therapy without FES. Additionally, neuroanatomical correlates of allocentric and egocentric neglect were investigated.

Employing an AB/BA cross-over design, patients with right-hemispheric lesions and left-sided neglect underwent treatment for several weeks. The allocentric neglect therapy with FES did not prove more effective than the other two treatment options in treating allocentric neglect, nor was it superior in ameliorating egocentric neglect or at improving functional independence. While there were treatment-independent improvements of egocentric neglect and functional independence over time, allocentric severity remained unchanged. Furthermore, while no benefit of the combination of FES and allocentric neglect therapy over and beyond a general neuropsychological therapy could be established, important insights regarding its feasibility were gained. Finally, a significant lesion cluster associated with allocentric neglect, located in the anterior parts of the brain, could be identified.

Although the present study could not establish a successful treatment approach for allocentric neglect, it allowed for the identification of multiple areas for future research on allocentric neglect recovery and treatment.

Keywords: Allocentric neglect, egocentric neglect, FES, rehabilitation

Evaluating the Effectiveness of a Neuropsychological Therapy Program in Combination with FES in Ameliorating (Allocentric) Neglect

Unilateral spatial neglect is a neuropsychological syndrome which occurs as a consequence of unilateral brain lesions, especially right-hemispheric (RH) lesions (Gammeri et al., 2020), often following cerebrovascular events such as a stroke. It is characterised by an impaired awareness of contralesional stimuli (Gammeri et al., 2020) such that patients fail to attend, orient, or respond to the contralesional side of stimuli or to stimuli presented on the contralesional side of space. For instance, they might only groom the ipsilesional side of their body, eat only from one side of the plate or bump into objects and door frames (Gammeri et al., 2020). A recent systematic review reported the prevalence of neglect occurring post-stroke to be around 30 percent across various studies (Esposito et al., 2021). Given the high incidence of strokes (around 12.2 million strokes per year globally; Feigin et al., 2022), alleviating the severity of neglect is an important target for neuropsychological rehabilitation.

This is particularly true due to the severe impairment neglect is associated with. Patients with neglect following RH stroke have slower recovery rates, in particular showing fewer improvements in functional activities such as self-care or walking, and require longer hospital stays than patients without a neglect (Gillen et al., 2005). In fact, the severity of unilateral spatial neglect serves as an independent predictor for functional outcomes at the end of inpatient rehabilitation in RH stroke patients (Di Monaco et al., 2011). As such, identifying and developing effective rehabilitation programs for spatial neglect is important (Katz et al., 1999; Kerkhoff & Schenk, 2012).

However, the identification and treatment of neglect is not straightforward given that neglect is not a homogenous syndrome: there are multiple subtypes of neglect which may differ regarding impairment in daily activities, recovery rates and effectiveness of interventions (Williams et al., 2021). Moreover, Williams and colleagues (2021) show that definitions of neglect subtypes as well as the assessment tools used for identifying neglect are

inconsistent across studies, thus making it difficult to generalise findings. Similarly, Moore et al. (2021) highlight the need for neglect research to clearly differentiate between subtypes and to adequately represent behavioural diversity instead of treating neglect as a unitary syndrome.

Two commonly reported subtypes of neglect are egocentric and allocentric neglect. Egocentric neglect is considered space-based, whereby patients fail to attend to stimuli presented on the contralesional side of their body, while allocentric neglect is object-based, whereby patients neglect the contralesional side of the object itself, regardless of the object's position in space (Leyland et al., 2017).

While egocentric and allocentric neglect commonly occur in conjunction, studies have shown a clear distinction between the symptoms, whereby some patients may only be affected by one of the subtypes (Bickerton et al., 2011; Moore et al., 2021). Supporting this, MRI studies have shown differences in lesion location for the two subtypes: Generally, egocentric neglect has been associated with damage to anterior regions as well as subcortical regions, such as postcentral, middle frontal, superior temporal and supramarginal gyri, insula, and putamen, while allocentric neglect has been associated with lesions in posterior cortical regions, such as the superior and middle temporal gyri, superior and inferior parietal cortices and middle temporal and middle occipital gyrus (Chechlacz et al., 2010; Kenzie et al., 2015). In addition, Grimsen and colleagues (2008) suggest egocentric information processing to be associated with the dorsal pathway, linked to spatial orientation, and allocentric information processing to be associated with the ventral pathway, regarding object recognition and identification. While there has been some overlap between lesion sites in grey and white matter for allocentric and egocentric neglect, overall, there is evidence to suggest allocentric and egocentric neglect to be dissociated (Chechlacz et al., 2010; Marsh & Hillis, 2008).

Apart from neuroanatomical differences, patients affected by either subtype differ with respect to the severity of their functional impairments. Bickerton and colleagues (2011) report

patients with solely allocentric neglect to be generally more impaired in activities of daily living than those with egocentric neglect. Similarly, patients presenting with chronic allocentric neglect report higher levels of functional impairment, with the severity of allocentric neglect at the acute stage being predictive of poor functional outcomes 6 months post-stroke (Moore et al., 2021).

Finally, the recovery rate of these two subtypes appears to be different. Moore et al. (2021) investigated the recovery trajectories of neglect subtype in stroke survivors 6 months after stroke and found egocentric neglect to follow a proportional recovery trajectory, with the rate of recovery being similar for those severely affected and those less severely impaired. The severity of egocentric neglect at the acute stage served as a significant predictor for the severity of chronic egocentric neglect. Conversely, for allocentric neglect, the recovery pattern was not proportional, with the recovery rate differing among patients, such that some showed no improvements or even a worsening. Importantly, allocentric patients who recovered did not differ from those who did not recover with regard to the severity of allocentric neglect at the acute time.

The reviewed literature highlights that differentiating between subtypes may be important for research purposes as well as for clinical practice and allocentric neglect specifically may serve as an important target for rehabilitation due to its non-proportional recovery pattern and profound impact on patients' quality of life.

A promising approach to treating neglect in general may be via sensory modulation (Kerkhoff, 2003). Karnath and Dieterich (2006) propose neglect to be linked to damage in a "multisensory cortex" in which auditory, vestibular, visual and neck proprioceptive information is converged for higher-order spatial representations and the position of one's body in space. They argue that this integration of multimodal sensory information into spatial representations may be disturbed, potentially explaining the orientation bias observed in patients. Based on this assumption, sensory modulation of these modalities as a way to reduce

the orientation-bias observed in neglect may be a route of rehabilitation for spatial neglect (Karnath et al., 2006; Kerkhoff et al., 2012). Indeed, treatment approaches such as optokinetic stimulation (Pizzamiglio et al.,1990), neck-muscle vibration (Karnath et al., 1993), vestibular stimulation (for example, Rode et al., 1992), prism adaptation (Rossetti et al., 1998) or even non-invasive brain stimulation such as Transcranial Magnetic Stimulation (Brighina et al., 2003) or transcranial Direct Current Stimulation (tDCS; Sparing et al., 2009) show some promising results. However, treatments such as tDCS have often been unsuitable for patients in early rehabilitation settings, who may present with a risk for epilepsy or a craniotomy (Turgut et al., 2018). In a feasibility study on applying multiple sessions of tDCS in left-sided neglect patients, Smit and colleagues (2015) comment on the large number of patients that had to be excluded prior to the experiment, suggesting tDCS to not be feasible for large-scale studies on neglect treatment.

As an alternative to tDCS, Functional Electrical Stimulation (FES) could potentially be a feasible form of stimulation, in particular for an early-rehabilitation setting, as it is safe and easily administered (Eskes & Butlers, 2006). First evidence suggests FES to be a potentially promising treatment for neglect: Eskes and Butlers (2006) found improvements in visual scanning performance in some neglect patients following passive movement caused by FES. Likewise, Harding and Riddoch (2009) investigated the effectiveness of FES stimulation of the left forearm in four patients with right-sided brain lesions by applying stimulation to the ipsilesional arm for a period of 4 weeks, followed by another treatment period during which stimulation was applied to the contralesional arm. The authors found a reduction in neglect symptoms as well as general improvements in functional recovery in three of those patients, with improvements coinciding with the application of contralesional FES treatment. Finally, in a randomised-controlled study of 40 participants, comparing left-hand electrical stimulation combined with visual scanning to sham stimulation with visual scanning, Polanowska et al. (2009) found the group of patients having received FES to show greater improvements on

cancellation tasks than the group having received sham-stimulation after one month of treatment. However, an immediate effect of FES treatment could not be observed. The authors hypothesise that electrical stimulation of the left hand may indirectly exert a positive effect on RH brain regions involved in spatial attention. These findings provide first evidence for the potential rehabilitative effect of FES on neglect symptoms. However, it is not yet clear what effect FES stimulation may have on allocentric neglect recovery.

In sum, while there are multiple approaches to treating neglect, it is important to note that many interventions appear to focus on ameliorating egocentric neglect and may therefore be less effective or even ineffective in treating allocentric neglect (Moore et al., 2021). Indeed, prism adaptation, for instance, has been shown to have no effect on the rehabilitation of allocentric neglect (Abbruzzese et al., 2019, Gossmann et al., 2013), while in the case of FES, its effectiveness for treating allocentric neglect is still unknown. Generally, treatments specifically targeting allocentric neglect are not yet well researched (Moore et al., 2021), thus showing a gap in the literature.

Based on the lack of allocentric treatment options, the present study investigated the effectiveness of a non-invasive exercise-based therapy program developed at the Klinikum Bremen-Ost aimed at improving neglect in general and allocentric neglect specifically. During the intervention patients worked on exploring the left side of objects as well as on their visuoconstructive skills and skills relevant for daily living such as folding clothes and tying shoes, all with the aim of improving the (visual) attention of the left side of objects specifically. The treatment was developed based on clinical experience by researchers at the Klinikum Bremen-Ost regarding the problems of allocentric neglect and may be the first of its kind. This therapy was evaluated compared to a placebo therapy consisting of general (standard) neuropsychological therapy with no particular focus on neglect, but with a focus on memory, attention, and executive functioning, depending on the patient's needs. The therapy was offered to inpatient early-rehabilitation patients presenting with left-sided neglect early

on in their recovery process. In addition, the effectiveness of FES of the left arm as a way to alleviate both egocentric and allocentric neglect was investigated.

The aim of the present study was thus two-fold: Firstly, the effectiveness of a combination of specific allocentric neglect therapy and FES was investigated by comparison to a general neuropsychological therapy with FES. Secondly, the effectiveness of FES independent of the type of treatment was investigated by comparing the combination of specific allocentric neglect therapy and FES to a historical control group having received a general neuropsychological training (comparable to the general neuropsychological therapy described earlier) without FES. Based on this, it was hypothesised that (1) a combination of a specific allocentric neglect therapy and FES will be more effective in treating (allocentric) neglect in patients early in their recovery process than a combination of general neuropsychological therapy and FES and (2) a combination of a specific allocentric neglect therapy and FES will be more effective in treating (allocentric) neglect than a general neuropsychological intervention without FES.

This study may be one of the few to investigate a therapy form aimed specifically at improving allocentric neglect. Additionally, this study took place in an intensive inpatient setting, with patients being early on in their recovery process. Findings from this study may provide important insights regarding the effectiveness of early rehabilitation neglect therapies and may be a first step towards the specific treatment of allocentric neglect.

Methods

Participants

Based on a priori power analysis, the aim was to include at least 12 participants who followed both treatment forms, namely a therapy specifically targeted at allocentric neglect in combination with FES (Therapy A) as well as a general neuropsychological therapy in combination with FES (Therapy B). The final sample consists of 16 patients, with 10 having received both rounds of therapy and six having received only one round of therapy. All

patients were recruited at the early-rehabilitation unit of the Klinikum Bremen-Ost between 2020 and 2022 and presented with left-sided ego- and/or allocentric neglect following a right-hemispheric cerebrovascular event. Potential participants were assessed two times (T1 and T2) prior to the beginning of the therapy with at least two days between assessments. They were included if they showed a neglect at the second point of assessment (T2), as judged clinically. Following a cross-over design (AB/BA), patients were then randomly allocated to either receive Therapy A first, followed by Therapy B or vice versa, with each therapy followed by another assessment (T3 and T4), resulting in a total of four assessments. With group allocation taking place after the initial assessment, the researcher providing the therapy was blind to the group allocation during the first two assessments (T1 and T2). Patients were included in the final analysis if they completed at least one of the two therapy programs. Exclusion criteria for participation or data analysis included a clinical diagnosis of a progressive neurodegenerative disease, normal pressure hydrocephalus, the inability to receive FES due to medical reasons, an inability to actively participate for at least 30 minutes of therapy or having participated in less than 80 percent (12 units) of one round of therapy. Patients did not receive compensation for their participation but may have benefitted from receiving additional therapy on top of their regular program at the rehabilitation unit.

Data collection took place in two waves. The data used for this study is a combination of data collected by researchers at the Klinikum Bremen-Ost during 2020 and 2021 and data collected between January 2022 and July 2022 following the same methodology. This combination allowed for a larger sample size.

Figure 1 shows a flow chart of the recruitment process in 2022 of the second wave. During the period of January 2022 and July 2022, 13 patients were approached for initial assessment. Of those, four were excluded after the first and second assessment either due to an inability to complete the assessment, due to having no clinically relevant neglect, or due to medical reasons preventing them from receiving regular FES. In total, nine patients started the

first round of therapy, of which only six completed the third assessment (T3), with three patients having to stop the therapy either due to an early release or due to illnesses (such as COVID-19) rendering them unable to continue the required number of therapy sessions. Of those completing the third assessment, four started the second round of therapy, with the other patients being released from the rehabilitation unit beforehand. Only three patients were present for the final assessment. The final sample of this data collection entering the final analysis was n = 6, consisting of all patients who completed at least one of the therapy programs.

Figure 1

Patient Recruitment Second Wave

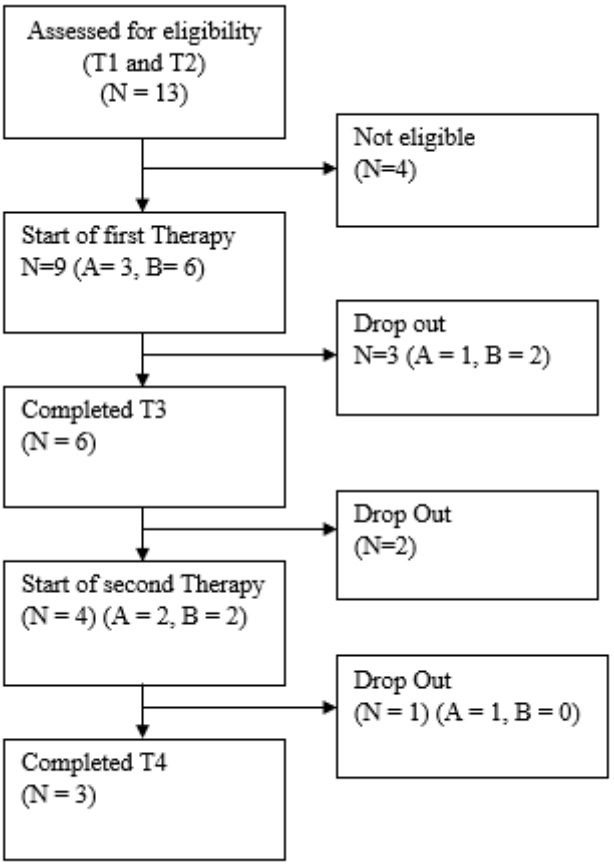
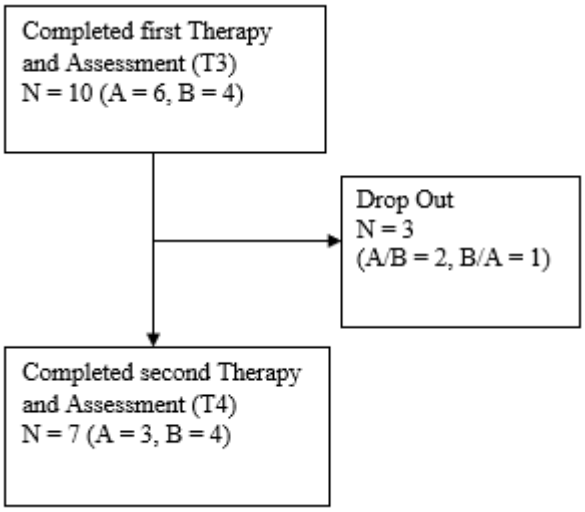


Figure 2

Patient Recruitment First Wave



Note. Total Sample of both waves consists of N = 16, with A/B = 8, B/A = 8.

The dataset provided by previous data collection consisted of 10 participants, of which seven completed both forms of therapy, and three completed one round of therapy. Figure 2 gives a short overview of the recruitment of the first wave of participants. Combining both recruitment waves resulted in a total sample of *N* = 16 patients having completed at least one round of therapy, with an equal number of participants having followed the A/B and the B/A sequence. Participants' age ranged from 37 to 83 years of age (*M* = 66.75, *SD* = 14.74, *Mdn* = 71) for the total sample.

The historical control group used for the second research question consists of 14 patients having received 30 minutes of general neuropsychological therapy not focused on allocentric neglect for five days a week for a duration of three weeks in addition to the regular

program offered at the rehabilitation unit. The data was collected between 2016 and 2017 by researchers at the Klinikum Bremen-Ost.

This study is a continuation of a research project started in 2020 which has received ethical approval and was registered in the German Clinical Trials Register (DRKS, Deutsches Register Klinischer Studien). All participants and/or their legal representatives were debriefed and provided written informed consent.

Instruments

Primary Outcome Measures

Apples Cancellation Task (Bickerton et al., 2011). The Apples Cancellation Task was used to assess both egocentric and allocentric neglect. It consists of a DIN-A4 page showing a total of 150 apples spread evenly over the page. Of those, 50 complete apples serve as target stimuli, with the rest being distractors in the form of apples with left- or right-sided openings spread out in between. The page can be divided into 5 invisible sections, with one being in the middle and two sections on each side respectively. Each section contains the same number of targets (10 per section) and distractors. The paper is placed horizontally in front of the patient's midline. The patient is then asked to cross out all targets while ignoring the distractor items.

Left-sided egocentric neglect is demonstrated by patients identifying more targets on the right than on the left, while allocentric neglect is demonstrated by falsely crossing the distractor items. For egocentric neglect, the total number of omissions is recorded as a primary measure. For allocentric neglect, allocentric severity is recorded by dividing the total of allocentric errors (distractors being falsely identified as targets) by the number of correctly identified targets (in line with Moore et al., 2021).

As additional secondary measures, the asymmetry scores were calculated. For egocentric neglect, the asymmetry score is calculated by subtracting the targets identified in the right sections from the correct hits in the left sections. For allocentric neglect, the

asymmetry score is calculated by subtracting the number of allocentric errors with a right-sided opening from the left-sided errors.

Functional Independence Measure (FIM; Granger et al, 1986). The FIM is a measure for the patient's ability to independently perform activities of daily living, as well as their cognitive (communication, social behaviour) functions (Houlden et al., 2006) and is scored by the personnel of the clinic every week. It consists of 18 items that receive a score between 1 (total assistance) to 7 (complete independence). Total higher scores indicate higher degrees of independence.

Secondary Outcome Parameters

Early-Rehabilitation Barthel Index (Schönle, 1995). Similar to the FIM, the Barthel-Index is used to assess functional abilities, specifically on how well patients can take care of themselves without assistance. The expansion by Schönle (1995) additionally takes into account aspects relevant for the care of patients in early rehabilitations settings, for example the need for intensive care monitoring or requiring supervision due to dysphagia. Higher scores similarly indicate lower needs of assistance and show higher functional abilities. This index was scored by healthcare professionals at the clinic every week.

Line Bisection Task (in accordance with Gossmann et al., 2013). For the Line Bisection Task, a DIN-A4 paper is placed in front of the patients, depicting three differently oriented lines (length of 21 cm each). The task hereby is to mark the middle of each individual line. The mean deviation from the actual middle was used as an outcome measure (egocentric), as well as the asymmetry calculated by subtracting the deviation on the first line from the deviation on the third line (allocentric neglect).

Clock Drawing Task. The Clock Drawing Task was taken from the Behavioural Inattention Task (Wilson, Cockburn, & Halligan, 1987). The patient is presented with a horizontal DIN-A4 page depicting a big circle in which the patient is asked to note the letters of a clock. The drawings were scored (0 = normal, 1 = deviations, 2 = complete omission of

the left side) by a clinician who was blind to the patient, condition, and time of the assessment.

Reading Task. Four different short texts were used to assess the reading ability of the patients. A different text was used at each assessment to avoid previous knowledge affecting performance. The texts consisted of around 60 words each, describing different events, like a news article. The texts were taken from the Rivermead Behavioural Memory Test (Wilson, Cockburn, & Baddeley, 1985; German translation: Beckers, Behrends, & Canavan, 1992). The total number of omitted words was used to assess reading ability.

Procedure

Assessments

For the baseline measurements, patients were assessed on four diagnostic tests (Apples Cancellation Task, Line Bisection, Clock Drawing, and Reading) twice (T1 and T2) with at least two days in-between assessments. The first assessment (T1) served as a control for a potential retest effect, while the second assessment (T2) was used in the analysis as the pre-diagnostic of the first round of therapy. During the first assessments, the researcher was blind to the condition the patient would be allocated to; using a coding list, patients were randomly assigned to either receive neglect therapy (Therapy A) or a general neuropsychological therapy (Therapy B) first. The coding list was concealed so that the researcher would only be able to see one group allocation at a time, thus preventing knowledge about future group allocations. The assessment was followed by around 3 weeks or 15 units of therapy. The therapy (either A or B) was offered daily for five days per week for around 45 minutes per day. For the data to be included in the final analysis, the patient had to complete at least 80 percent (12 units) of one round of the therapy sessions. Following this, patients were assessed on the above-mentioned diagnostic tests for a third time (T3). Afterwards, patients received another round of therapy as described above, this time following the not yet received form of therapy. Finally, patients completed a final assessment (T4).

Therapy

The therapy sessions were built to vary between FES stimulation and exercise-based therapy. Specifically, each session started out with 5 minutes of FES stimulation, followed by around 10 minutes of either specific neglect therapy or by general neuropsychological therapy. This pattern was repeated three times, resulting in around 45 minutes of therapy.

Specific Neglect Therapy. Therapy A consisted of three parts, with each therapy session including one or more tasks from each part. The tasks were adjusted to the individual patient depending on their skill level, for example by adjusting the difficulty of the required tasks. The therapy was aimed at improving allocentric neglect specifically, thus the focus was on integrating, constructing, and manipulating different objects.

The first part consisted of exercises focused on skills needed in everyday life. Patients practised detangling and folding a long-sleeved T-shirt, closing the buttons of the T-shirt, threading shoelaces in a sneaker shoe, and tying the shoelaces.

The second part focused on visually integrating objects and included three tasks with varying difficulty. Firstly, three reading tasks with different difficulty levels were offered, all presented on a computer screen. The first reading task consisted of a text presented in columns alternating on either the left or right half of the computer screen. The second text was presented in a column in the middle of the computer screen, with the background being split into two sections of different colours, such that the left background was yellow while the right background was green. For the third and most difficult task, the text was presented in front of the previously described split background, with a large gap in the middle, thus the text was separated by both the colour of the background and the column in which it was presented. In order to read the text correctly, one had to ignore the colour and column split and instead focus on following each individual line of text. Next to the reading task, a clock with movable hands was used for which patients were asked to tell the time or set the clock to show a specific time. The final task consisted of worksheets showing different geometric figures for

which patients had to identify individual segments (a right angle, a diagonal line etc.). Patients thus had to segment each complete object into its individual parts to describe its properties.

The third and final part was aimed at actively constructing objects. Firstly, Grid Pattern (Nikitin) dice were used which patients tried to place according to a visual template depicting pictures. Here again patients had to segment the presented pictures according to colour and form as depicted on the individual dice in order to build the form presented to them. Similarly, another task consisted of placing wooden geometrical figures into printed-out templates, like a puzzle. Finally, drawing tasks included completing the right half of an object while being presented with the left half (thus mirroring the left half), or having to copy a picture or geometrical figure.

General Neuropsychological Therapy. Therapy B was tailored towards the patient's need with regard to cognitive deficits other than neglect and consisted of tasks and exercises commonly used at the neuropsychological therapy sessions at the rehabilitation unit. For instance, patients may have received memory training, i.e., practising to learn and recall a list of words, attention training, using for example the rehabilitation software RehaCom ® (HASOMED GmbH, Magdeburg, Germany) with exercises for alertness or improving reaction time, or executive functions training, using planning exercises such as calculating the number of ingredients for a meal or planning a day with pre-defined activities at certain times.

Functional Electrical Stimulation (FES). For applying FES, the RehaMove2 (HASOMED GmbH, Magdeburg, Germany) was used. For the stimulation, two surface electrodes were placed on the extensors of the left forearm, with the goal of causing an upward movement of the left hand. In the first treatment session, the strength of the stimulation was set according to the patient's comfort. The strength was successively increased until an upward movement was reached, or the patient felt too much discomfort.

The maximum amperage allowed to use was 90 mA. The strength of the stimulation was readjusted throughout the therapy sessions if needed.

During the therapy session, patients received 3x5 minutes of stimulation to their left arm. The active stimulation happened for 5 seconds, with 5 seconds of rest in between each stimulation for the whole 5 minutes. During the stimulation the patient's task was to actively focus on their left hand and copy the movement of the left hand with their right hand, if possible.

Lesion Mapping

For exploratory purposes, the neuroanatomical correlates of egocentric and allocentric neglect in this particular sample were investigated. Similarly, as an additional variable of interest, the lesion size of the participants was recorded. Neuroimaging data was available for 15 of the 16 participants. The data was taken from the internal data bank of the Klinikum Bremen-Ost. When possible, MRI scans of the patients' brains were used, however, for most of the sample only CCT images were available.

The cerebral lesions shown on the available brain images of patients were manually delineated in the open-source software MRIcron (https://www.nitrc.org/projects/mricron/; Rorden & Brett, 2000). For this, the standard template ch2.nii.gz was used. Starting at layer 94, lesions were manually mapped on the template taking 6-layered steps up and down. The resulting lesion maps were then combined in an overlay. The mean voxel size of the lesion map of each individual patient was retrieved through the descriptive functions of MRIcron, serving as a proxy for lesion size.

Following this, a voxel-based lesion-symptom analysis (VLSM) was performed in the open-source statistical software NPM (https://www.nitrc.org/projects/mricron/; Rorden et al., 2007). Since higher scores are considered as better performance in the software, instead of using the number of omissions on the Apples Cancellation Task to represent egocentric neglect, the accuracy score (number of correctly identified targets on the Cancellation Task)

of each patient was used. For allocentric neglect, the variable "Allocentric Severity" was multiplied by 10 in order to arrive at integer numbers. As a higher score represents more severe allocentric neglect, the magnitude was inverted by subtracting the integer values from 100, so that higher scores would indicate better performance for allocentric neglect. The values for both the egocentric and the allocentric variable were taken from the second point of assessment (T2), prior to the start of the first round of therapy. Following the analysis, the aal.nii.gz template (Tzourio-Mazoyer et al., 2002) was used to identify the areas showing significant lesions clusters.

Statistical Analysis Plan

The analysis was performed in SPSS, Version 26.0.

Variables of Interest

The variables of interest include the pre and post tests for the primary and secondary outcome measures, as well as the difference scores between assessment 2 and 3 (T3-T2), and assessment 3 and 4 (T3-T4).

Missing Data and Outliers

Firstly, the data was explored with regard to missing values, which were imputed if possible. Outliers were identified graphically using boxplots; however, it was decided to not remove them as they represent valid impairments by the patients we were aiming to treat. Additionally, removing outliers would have reduced the sample further, which may have led to a decrease in power.

Mixed ANOVA

For the main analysis mixed-design ANOVAs were used. For this, two groups were formed consisting of all participants who underwent treatment A (Group A), and all having received treatment B (Group B). Most patients were included in both groups as they had undergone both conditions. The pre and post measures for the groups consisted of the patient's performance on the primary and secondary outcome measures on T2, T3, and/or T4.

For example, a patient who firstly received therapy A and then therapy B would be included in Group A with T2 as pre-measure and T3 as post-measures, as well as be included in Group B with T3 as pre-measure and T4 as post-measure.

In order to assess the first hypothesis, that is, that a specific allocentric neglect therapy with FES (Therapy A) will be more effective in ameliorating neglect than a general neuropsychological therapy with FES (Therapy B), a mixed-design 2 (Time: Pre- and Post-test) x 2 (Group: Treatment A, Treatment B) ANOVA was used.

For the second hypothesis, namely that a specific allocentric neglect therapy with FES (Therapy A) would be more effective in treating neglect than a general neuropsychological therapy without FES (Therapy H; based on the historical control group), another mixed-design 2 (Time: Pre- and Post-test) x 2 (Group: Treatment A, Treatment H) ANOVA was used.

The assumptions of a mixed-design ANOVA were given by design or assessed with formal statistical testing. The assumption of normality was assessed using the Shapiro-Wilks test as well as visual depictions such as QQ-plots. For the homogeneity of covariances, Box's test was used, while homogeneity of error variances was assessed with Levene's test of equal variances.

As the design was a cross-over design, there was the possibility of a sequence effect. It may have been possible for the order of the received therapy to have an effect. To explore this possibility, a mixed-design 2 (Period 1 and 2: T3-T2 and T4-T3) x 2 (Sequence: A/B, B/A) ANOVA was conducted, including only participants who completed both rounds of therapy. As dependent variables, the difference between assessment 3 and 2 (T3 – T2) of the primary outcome measures was calculated to represent the change during the first treatment period (Period 1) while the difference between assessment 3 and 4 (T4-T3) represented the change during the second treatment period (Period 2). The interaction would represent the effect of the sequence of the treatment while a main effect of time would represent an effect of the

period when treatment was applied, irrespective of the treatment itself. ***Correlations of Correlations of Neglect Recovery***

To explore the recovery of neglect further, Spearman's correlations between the difference scores of the primary outcome parameters for egocentric and allocentric neglect and the variables Age and Lesion Size were investigated.

Results

Missing Values

A general summary of all outcome measures at each assessment revealed missing data.

Firstly, some data was missing for T1, however, since T1 was only assessed to limit the influence of retest effects, the missingness in these variables was not further regarded. For T2, there was no missing data. For T3, one participant missed values for the primary outcome variable "Allocentric Severity" as well as for the secondary outcome variables "Line Bisection Mean" and "Line Bisection Allocentric". This particular participant had a continuous cognitive decline throughout their rehabilitation stay and was not cognitively able to complete these measures. In order to still include the participant, some of the missing data was imputed. For the Line Bisection Task, the patient was only able to identify one of the three lines for T3, and none of the lines for T4. As such, the missing data was imputed using the value 10.5, the most extreme deviation possible on the line bisection task. The "Line Bisection Mean" and "Line Bisection Allocentric" were then calculated with these numbers. For the "Allocentric Severity" no appropriate imputation could be identified, therefore the patient was removed from the analysis for this particular variable. For T4, missingness was primarily related to the fact that not all participants underwent the second therapy and thus did not complete T4. Of the participants completing T4, there was the same participant mentioned previously having missing values for the three previously mentioned measures which were imputed or discarded as described above.

Descriptive Statistics

Table 1 shows the sample characteristics of the three groups entering the analysis. Group A consisted of the patients having received the specific allocentric neglect therapy with FES (Therapy A), while Group B consisted of those who received the general neuropsychological therapy with FES (Therapy B). Group H referred to the historical control group. As can be seen, the samples were equal in size as well as close in age and sex distribution.

Table 1

Sample Characteristics for Groups A, B and H

	A (n = 13)	B (n= 13)	H (n=14)
Age (Mean (SD))	70,08 (13,04)	67,77 (15,23)	67,00 (14,04)
Percent Female (%)	38,5	38,5	28,6
Aetiology (count)			
ischemic	9	8	12
haemorrhage	4	4	1
SAB	0	0	
ICB	0	1	
Mixed	1	1	
Basal Ganglia	3	2	
Other	0	1	1

Note. SAB = subarachnoid haemorrhage, ICB = intracerebral haemorrhage. Brackets indicate standard deviation.

Main Analysis

For the main analysis, the assumption of normality was violated for multiple variables. Given the small sample size, this was to be expected. Due to the fact that ANOVA in general is rather robust to violations of normality (Glass et al.,1972) as well as the fact that small samples may show non-normality even when coming from a normally distributed population (Altman & Bland, 1995), the analysis was performed without any additional transformations or removal of outliers.

Generally, the assumptions of equal covariances and error variance were met, save for a few variables that showed a significant Box's test, indicating a violation of equal covariances as well as one variable showing a violation of the assumption of homogeneity of error variance. Box's test is easily affected by non-normality; therefore, a violation may be expected given our sample. Regarding the homogeneity of variance, studies have shown the F-test to be robust to violation in cases of equal sample sizes (Blanca et al., 2017). Based on the robustness of the ANOVA and the previously mentioned points, the analysis was performed despite those assumption violations. Nevertheless, one should employ caution when interpreting the results.

While alternative methods exist, for example robust ANOVA or non-parametric tests, these options may result in a loss of power, a particular concern given the small sample size. Thus, the possibility of using non-parametric tests was discarded. However, readers should be aware that there are alternative methods for analysis than the one presented in this study.

Neglect Therapy with FES (A) vs General Neuropsychological Therapy with FES (B)

A vs B, Primary Outcome Measures

Table 2 shows the mean and standard deviation of the pre- and post-tests of the primary outcome parameters as well as the results of the Shapiro-Wilks test for normality.

Table 2

A vs B: Descriptive Statistics and Shapiro-Wilks Test

Variable	Group(*n*)		Mean	SD	Median	Min	Max	Shapiro-Wilk	df	*p*
Omissions	A*(13)*	Pre	36,69	11,95	39,00	4	50	0,812	13	**,009***
		Post	26,62	13,43	25,00	4	50	0,969	13	,199
	B*(13)*	Pre	32,46	12,79	36,00	9	48	0,913	13	,884
		Post	24,62	16,67	26,00	3	50	0,905	13	,157
Allocentric Severity	A*(12)*	Pre	0,83	0,97	0,56	0,02	3,50	0,770	12	**,004***
		Post	0,41	0,59	0,17	0	2,00	0,721	12	**,001****
	B*(12)*	Pre	0,51	0,69	0,22	0	2,00	0,763	12	**,004***

FIM	A*(13)*	Post	0,56	1,01	0,09	0	3,50	0,623	12	**,000****
		Pre	45,00	16,1	38,00	27	78	0,883	13	,078
		Post	51,85	15,64	49,00	33	80	0,898	13	,131
	B*(13)*	Pre	43,08	11,29	47,00	25	57	0,899	13	,124
		Post	54,31	14,1	53,00	31	78	0,979	13	,972

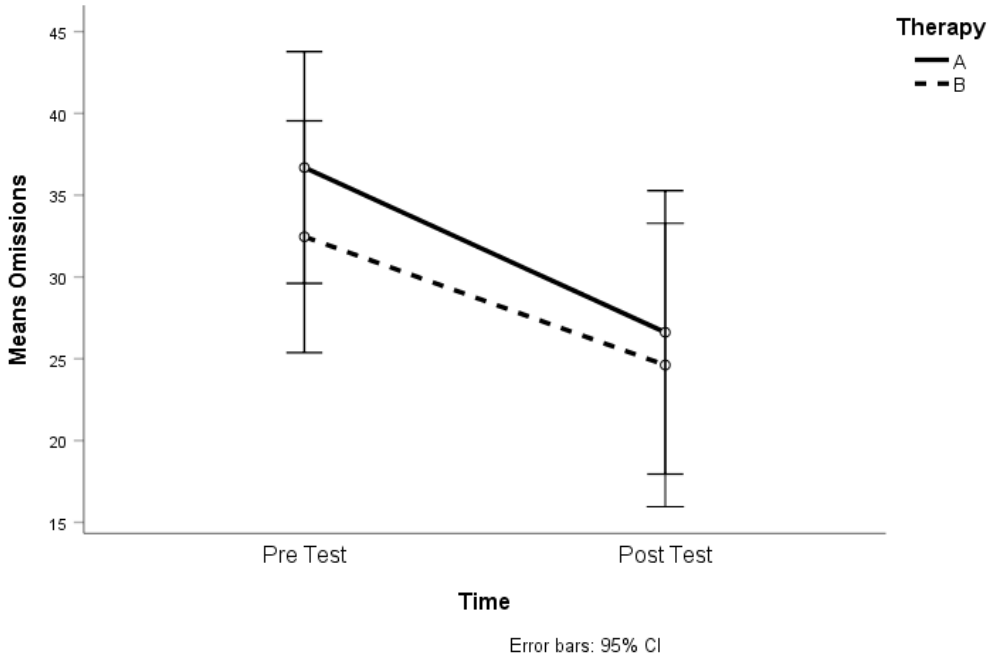
Note. * Test is significant at the 0.05 level, ** Test is significant at the 0.001 level

Egocentric Neglect: Omissions. The results revealed a significant main effect for time, F (1, 24) = 28.46, p < 0.001, $\eta p^2 = 0.543$. The main effect for group, F (1, 24) = 0.365, p = 0.551, $\eta p^2 = 0.015$, and the interaction Time x Group, F (1, 24) = 0.441, p = 0.513, ηp^2 = 0.018, were not statistically significant.

As such, it seems that, while there was a general reduction in omissions on the Apples Cancellation Task over time, as can be seen visually in Figure 3, there was no significant difference between the groups, thus not supporting the idea that the specific neglect therapy would be superior to the general neuropsychological therapy in ameliorating egocentric neglect.

Figure 3

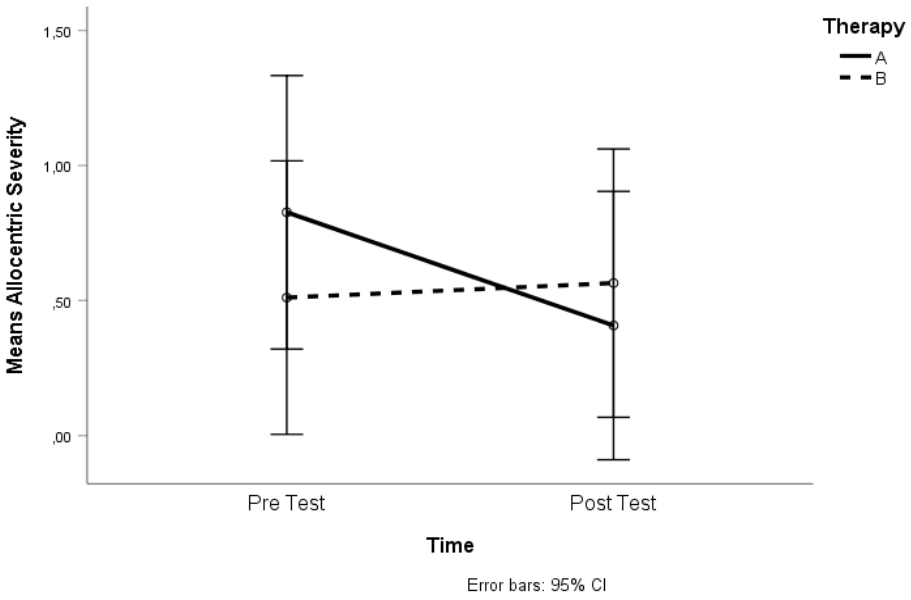
Group Comparison A vs B, Omissions



Allocentric Neglect: Allocentric Severity. The analysis showed no statistically significant main effect for time, F (1, 22) = 1.068, p = 0.313, ηp^2 = 0.046, nor for group, F (1,22) = 0.073, p = 0.789, ηp^2 = 0.003. Similarly, the interaction between time and group was non-significant, F (1,22) = 1.790, p = 0.195, ηp^2 = 0.075. Figure 4 shows the two variables over time, separated by group. Based on the visual depiction allocentric severity appears to slightly decline for Group A, however, the error bars show a great overlap between the two groups. Generally, there seems to be no significant change in allocentric neglect over time, with the treatments seemingly not differing significantly with regard to their impact on allocentric severity. This evidence is not in support of our hypothesis.

Figure 4

Group Comparison A vs B, Allocentric Severity



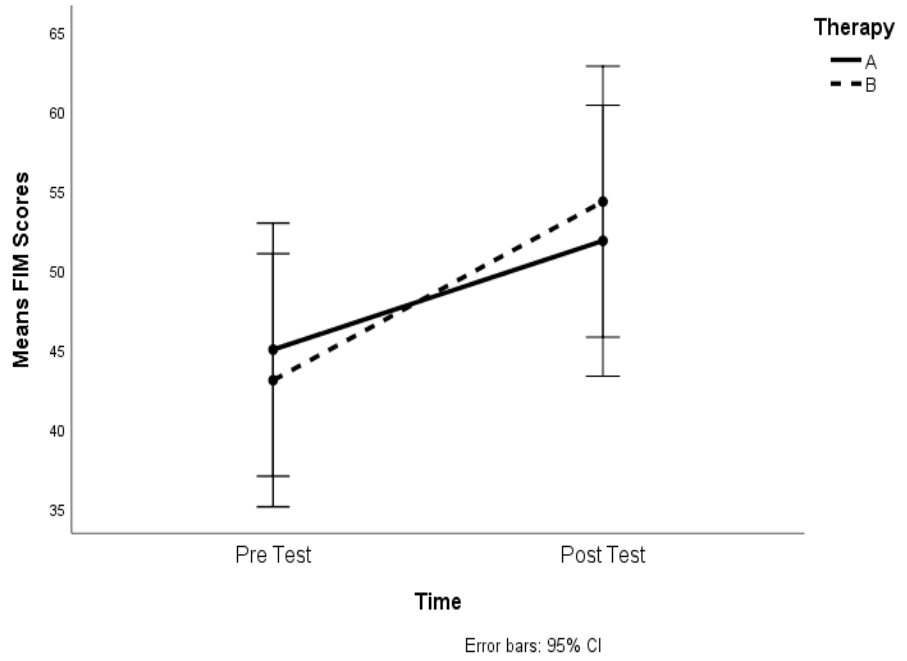
Functional Independence Measure (FIM). The results show a significant main effect for time, F (1, 24) = 59.973, p < 0.001, ηp^2 = 0.714. However, the main effect for group, F (1,24) = 0.002, p = 0.962, ηp^2 = 0, and the Time x Group interaction, F (1, 24) = 3.528, p = 0.073, ηp^2 = 0.128, were non-significant.

Patients showed a clear improvement in functional abilities during their rehabilitation stay, as can be seen visually in Figure 5, however, there is no evidence supporting the notion

that the neglect treatment could be superior to the general neuropsychological treatment in supporting the increase in functional independence.

Figure 5

Group Comparison A vs B, FIM



In sum, the results suggest an overall decrease in egocentric neglect, as represented by a decrease in omissions over time on the Apples Cancellation Task, as well as an increase in functional independence over time, however, this seems to be independent of treatment type. No improvements could be found for allocentric neglect, thus there is no evidence to support our first hypothesis.

A vs B, Secondary Outcome Parameters

Table 3 shows the results of the analysis for the secondary outcome measures.

Table 3

A vs B, Secondary Outcomes, Mixed-ANOVA results

	Group A		Group B		*p*	ηp2	*p*	ηp2	*p*	ηp2
Outcome	Pre (SD)	Post (SD)	Pre (SD)	Post (SD)	(Time)	(Time)	(Group)	(Group)	(Time*Group)	(Time*Group)
Apples Cancellation Task										

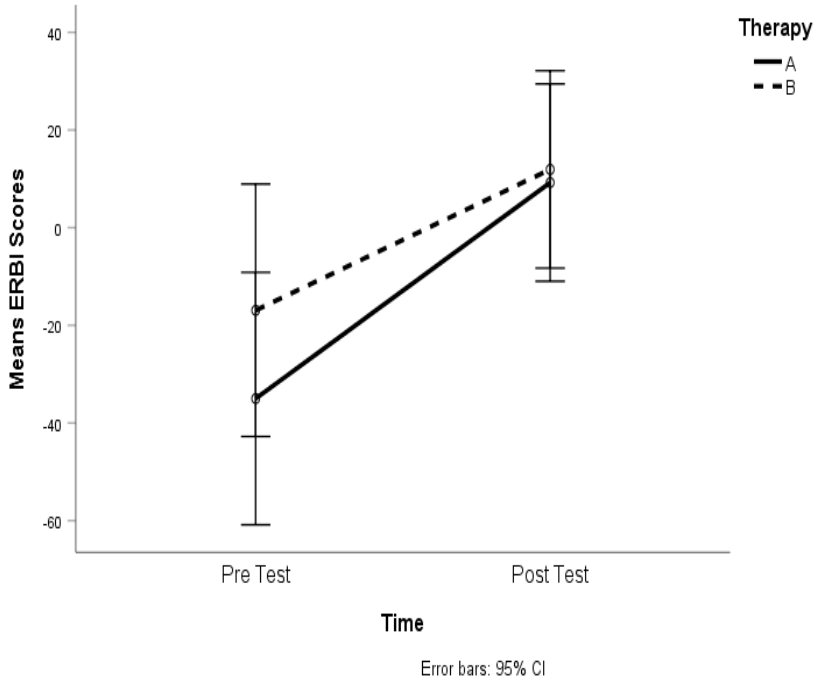
EgoAsymmetry	-7,08 (5,41)	-7,85(7,45)	-9,15(4,43)	-7,08(7,37)	,597	,012	,763	,004	,255	,054
AlloAsymmetry	2,31(4,05)	1,77(4,00)	1,15(2,44)	2,39(4,07)	,624	,010	,835	,002	,217	,063
ERBI	-35,00 (50,21)	9,23(32,27)	16,92(39,45)	11,92(38,12)	**,000****	,476	,460	,023	,335	,039
Line Bisection										
Mean (cm)	3,2 (3,1)	2,5 (3,5)	2,3 (2,7)	2,9 (2,96)	,790	,003	,839	,002	**,024***	,195
Allocentric (cm)	1,7(1,9)	1,2(1,6)	1,1(1,8)	2,1(1,9)	,640	,009	,793	,003	,164	,079
Clock	0,92(0,70)	0,58(0,64)	0,81(0,78)	0,65(0,63)	,083	,120	,935	,000	,493	,020
Reading	18,00(21,99)	13,08(22,06)	23,00(26,58)	14,77(22,09)	**,020***	,204	,705	,006	,538	,016

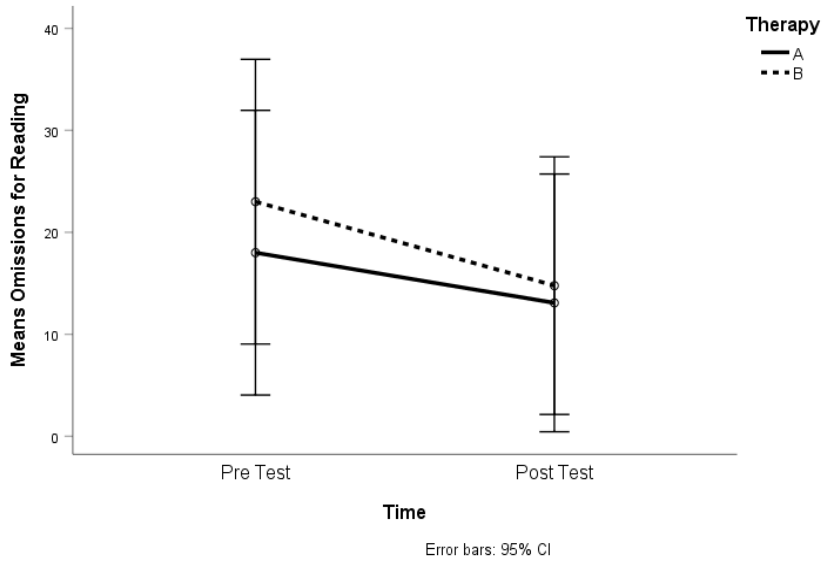
Note. * Significant at the 0.05 level; ** Significant at the 0.001 level

As can be seen, there was a significant main effect of time for reading ability and functional disability as assessed by the ERBI. Figures 6 and 7 show the two variables respectively, indicating a general improvement in functional abilities as well as a reduction in omissions on the reading task over time, regardless of treatment condition.

Figures 6 and 7

Group Comparison A vs B, ERBI and Reading

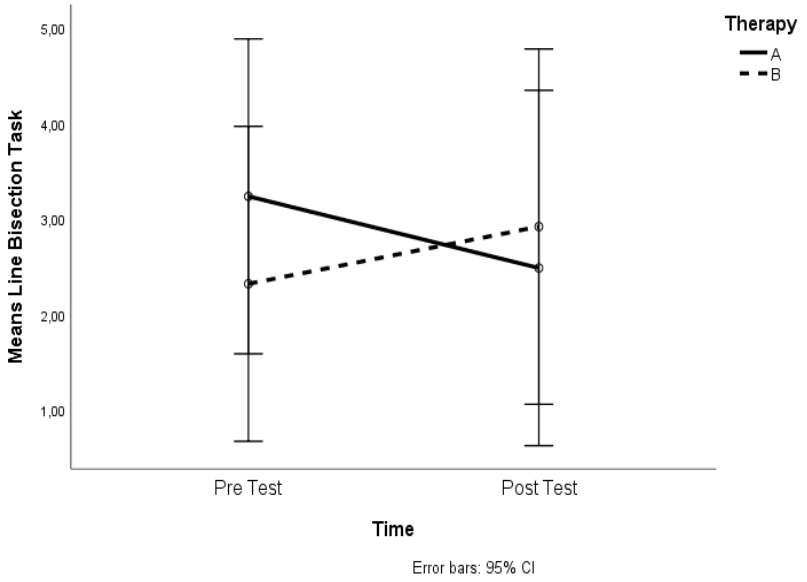




The significant interaction effect of the Line Bisection task was further investigated with post-hoc tests. A post-hoc one-way analysis of variance was performed to investigate the potential effect of the between-subjects factor “Group”. The results of the Welch-ANOVA showed no significant difference between the two treatment conditions for either point in time (Pre-A vs Pre-B and Post- A vs Post B, $p > 0.5$). For the potential effect of the within-subjects factor, a post-hoc repeated measures ANOVA with Pre- and Post-test as within-subjects factor was conducted. There was no significant main effect of time for group A, F (1,12) = 3.592, p =0.082, ηp^2 =0.230, nor for group B, F (1,12) =2.287, p = 0.156, ηp^2 = 0.160. While graphically one can identify a potential interaction between Time and Condition (see Figure 8), the post-hoc tests do not reveal significant effects of time or group, thus making it difficult to adequately interpret the result as it does not become clear where potential differences lie.

Figure 8

Group Comparison A vs B: Line Bisection Mean



In sum, patients only showed an improvement over time in their reading ability, which may be connected to the improvement of egocentric neglect, as well as an improvement over time in functional abilities, which is in line with the improvements over time on the FIM described earlier. Post-hoc tests following the significant interaction for the Line Bisection Mean showed no significant differences for Time, nor was there a significant difference between the groups for each point in time, thus making it difficult to interpret. The lack of improvement on allocentric measures is in line with the findings for the primary outcome measures but did not support our hypothesis. Interestingly, the measure for egocentric asymmetry did not show an improvement, despite the significant improvement on omissions in the Apples Cancellation Task. In general, it seems that the specific neglect therapy in combination with FES was not more effective than the general neuropsychological therapy with FES in ameliorating ego- and allocentric neglect.

Sequence and Period Effect

Given the cross-over design, there may have been a period effect. For instance, patients may have generally improved more in the first period than in the second, regardless of the provided treatment. Similarly, the sequence of the received therapy may have had an

effect. To test this, firstly, the differences between assessment T3 and T2 as well as assessment T4 and T3 were calculated for each patient. The mean of the difference scores can be found in Table 4 for the primary outcome parameters. The sample for this analysis was reduced to n = 10, as six patients did not undergo both forms of therapy and thus did not complete the assessment at T4.

Table 4

AB vs BA, Mean and SD for the Difference Scores

Variable	Group	Diff.	Mean	SD
Omissions	AB (n =5)	T3 - T2	-10,40	9,76
		T4 - T3	-8,80	8,56
	BA (n=5)	T3 - T2	-5,80	10,43
		T4 - T3	-6,00	14,71
Allocentric Severity	AB (n =5)	T3 - T2	-0,10	0,58
		T4 - T3	-0,28	0,42
	BA (n=4)	T3 - T2	0,70	1,06
		T4 - T3	-1,00	1,41
FIM	AB (n =5)	T3 - T2	9,60	6,19
		T4 - T3	7,60	3,85
	BA (n=5)	T3 - T2	13,20	8,56
		T4 - T3	4,40	4,93

In the following, a mixed-design 2 (Period: T3-T2, T4-T3) x 2 (Sequence: AB/BA) ANOVA was performed. It should be noted that this comparison was done with 5 patients per sequence, thus the ANOVA may very likely have been underpowered, and results should be considered with caution. Additionally, normality was violated for Allocentric Severity and for the FIM. Unless otherwise specified, other assumptions were met.

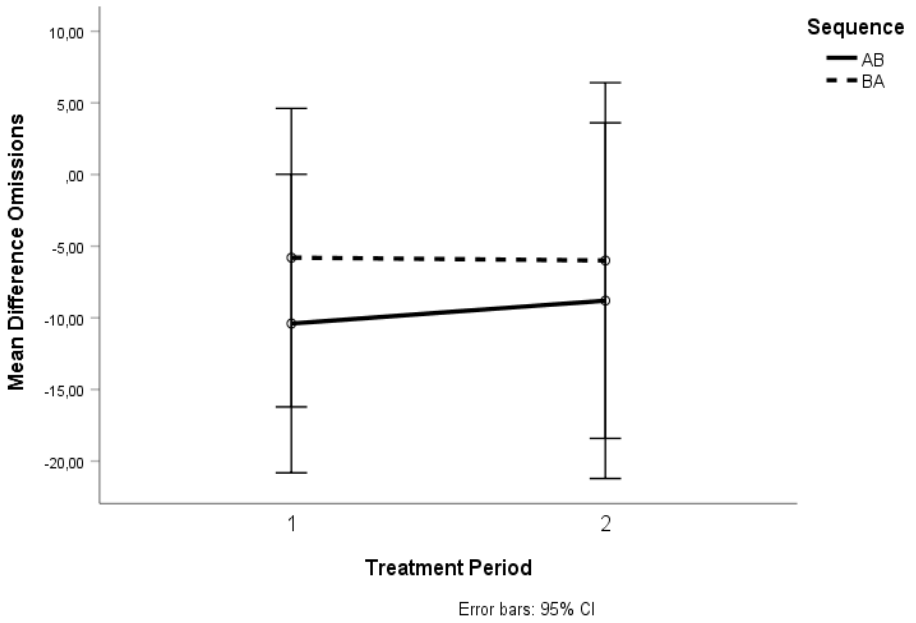
Omissions

The analysis showed the main effect for time to be non-significant, F (1,8) = 0.013, p = 0.911, ηp^2 = 0.002. It thus seems that there is no statistically significant difference between the changes during the first and second period for egocentric neglect. Moreover, the interaction between period and sequence was not significant, F (1, 8) = 0.022, p =0.885, ηp^2=

0.003, thus there is no indication that the sequence of received therapy may have had a significant effect on the change in egocentric neglect. Figure 9 depicts the comparison of difference scores by Group.

Figure 9

Group Comparison AB vs BA: Omissions

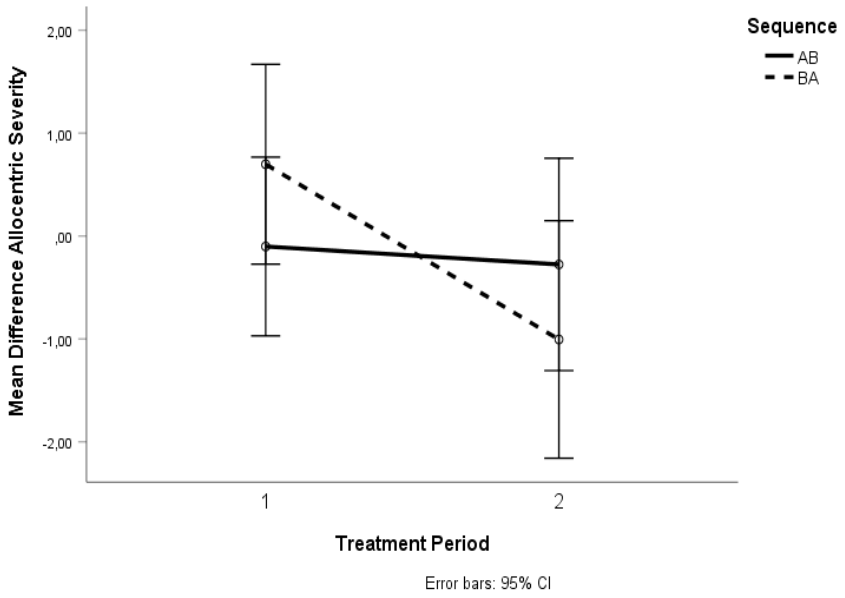


Allocentric Severity

In addition to the normality violation, Box's test suggests a violation of the assumption of equal covariances (p = .010), thus the results should be interpreted with caution. The analysis showed no significant main effect for time, F (1,7) = 2.524, p = 0.156, ηp^2 = 0.265, suggesting no difference between the treatment periods. Nevertheless, Figure 10 hints at potential differences between the change in Period 1 and Period 2 for the B/A sequence. However, the interaction between time and group was non-significant, F (1,7) = 1.674, p = 0.237, ηp^2 = 0.193.

Figure 10

Group Comparison AB vs BA: Allocentric Severity

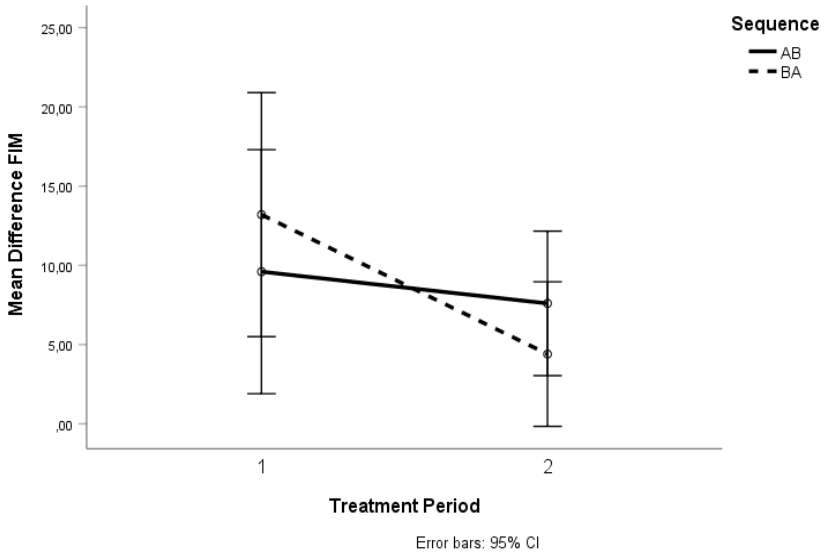


FIM

The main effect for time was not significant, F (1, 8) = 4.715, p = 0.062, ηp^2 = 0.371, suggesting that the difference scores for functional independence did not differ between the first and second treatment period. Likewise, the interaction between period and sequence was not significant, F (1,8) = 1,869, p = 0.209, ηp^2 = 0.189. Similar to Allocentric Severity, the visual depiction of the analysis hints at potential differences in the difference scores for Period 1 and 2 for the sequence B/A (see Figure 11).

Figure 11

Group Comparison AB vs BA: FIM



In sum, the results suggest that the sequence of treatment did not significantly affect the change in neglect and functional independence. Similarly, in both treatment periods the difference scores did not differ significantly. However, given the very limited sample size for this comparison, the results need to be interpreted cautiously as the effects may not have been detected due to limited power.

Neglect Therapy with FES vs General Neuropsychological Therapy without FES

To analyse the hypothesis that a specific neglect therapy in combination with FES would be more effective in ameliorating neglect than a general neuropsychological therapy without FES, patients having undergone the neglect therapy (Group A) were compared to the historical control group (Group H), using mixed-design ANOVAS as described above. Unless otherwise specified, the assumptions of equal covariances and homogeneity of variances were given. The normality assumption was violated for multiple variables.

A vs H, Primary Outcome Parameters

Table 5 shows the descriptive statistics for the Pre and Post-tests for the primary outcome parameters of both groups, as well as the results of the Shapiro-Wilks test for each variable.

Table 5

A vs H, Descriptive Statistics and Shapiro-Wilk Test

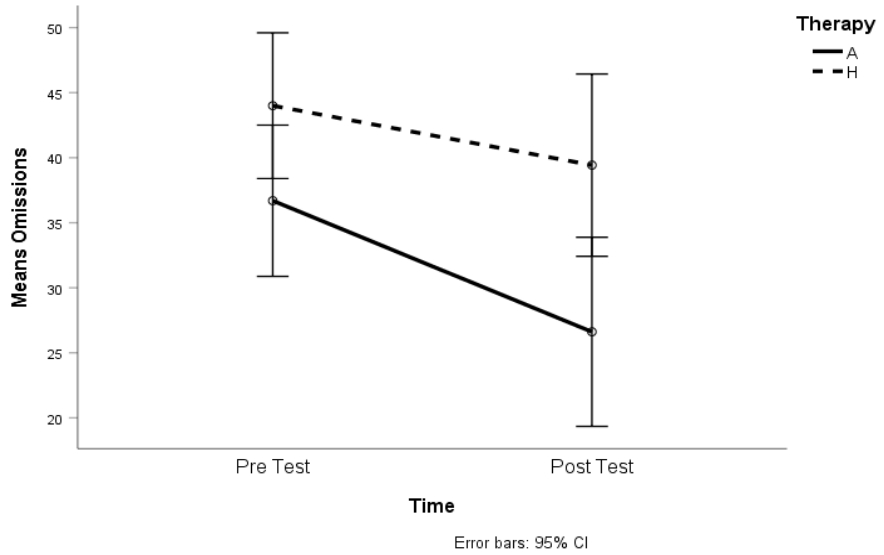
Variable	Group		Mean	SD	Median	Min	Max	Shapiro-Wilk	df	*p*
Omissions	A (n =13)	Pre	36,69	11,95	39,00	4	50	,812	13	**,009***
		Post	26,62	13,43	25,00	4	50	,969	13	,884
	H (n=14)	Pre	44,00	8,21	46,50	20	50	,722	14	**,001***
		Post	39,43	12,04	43,50	5	48	,706	14	**,000****
Allocentric Severity	A (n =12)	Pre	0,83	0,97	0,56	0,02	3,50	,770	12	**,004***
		Post	0,41	0,59	0,17	0	2,00	,721	12	**,001***
	H (n=14)	Pre	1,00	0,85	0,88	0	2,50	,911	14	,162
		Post	1,14	0,99	0,91	0,09	4,00	,818	14	**,008***
FIM	A (n=13)	Pre	45,00	16,1	38,00	27	78	,883	13	,078
		Post	51,85	15,64	49,00	33	80	,898	13	,124
	H (n=14)	Pre	36,36	13,54	33,00	19	66	,925	14	,259
		Post	52,93	24,997	48,00	15	99	,942	14	,446

Note. * Significant at the 0.05 level; ** Significant at the 0.

Omissions. The analysis revealed a significant main effect for time, F (1, 25) = 17.432, $p < 0.001$, $\eta p^2 = 0.411$, as well as for group, F (1,25) = 6,091, $p = 0.021$, $\eta p^2 = 0.196$. The interaction between time and group was not statistically significant, F (1,25) = 2.462, p = 0.129, $\eta p^2 = 0.090$. As with the previous comparison between A and B, there seems to be a general improvement over time (see Figure 12), however, the results suggest that the type of therapy may have not made a statistically significant difference. The main effect of the group can be seen with Group H generally having more omissions than Group A. In sum, these results are not in line with our hypothesis.

Figure 12

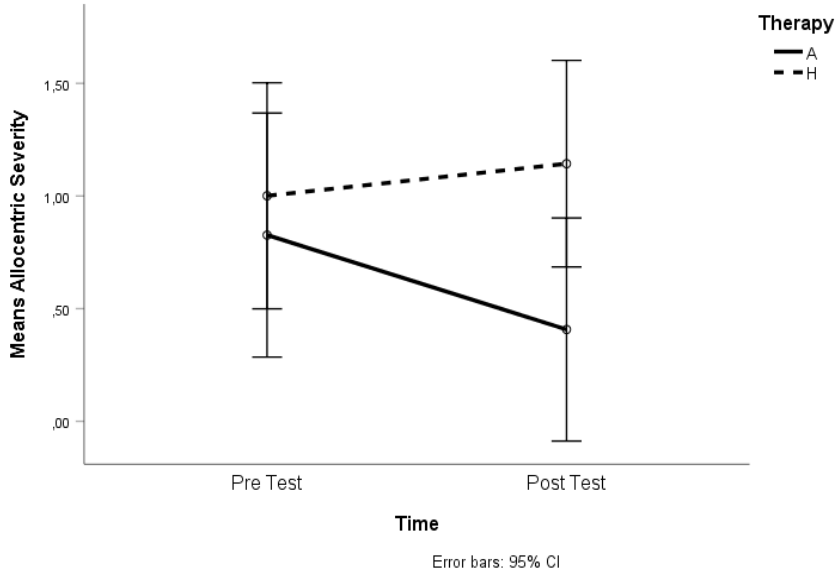
Group Comparison A vs H: Omissions



Allocentric Severity. There was no statistically significant main effect for time, F (1,24) = 0.579, p = 0.454, ηp^2 = 0.024, nor for group, F (1,24) = 2,455, p = 0.130, ηp^2 = 0.093. Likewise, the interaction between time and group did not reach statistical significance, F (1,24) = 2.388, p = 0.135, ηp^2 = 0.090. Overall, these results are in line with the previous comparison between Therapy A and B, suggesting no significant improvement in allocentric neglect over time, and no difference regarding the treatment applied. Interestingly, the graphical depiction (Figure 13) of the two groups may suggest a slight improvement for Group A, however, based on the non-significant results of the ANOVA, our hypothesis is not supported.

Figure 13

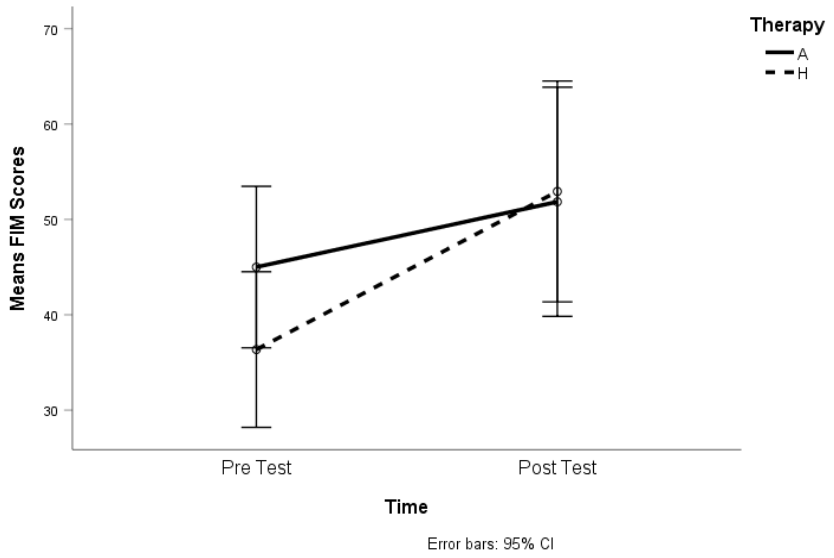
Group Comparison A vs H, Allocentric Severity



Functional Independence Measure. For the measure of functional independence, there was a violation of the assumption of equal covariances (Box's test, $p < .001$). There was a statistically significant main effect for time, F (1, 25) = 15,122, p = 0.001, ηp^2 = 0.377, with Figure 14 suggesting a general improvement in functional independence over time for both groups. There was no statistically significant main effect for group, F (1,25) = 0.357, p = 0.556, ηp^2 = 0.014, and no significant interaction between time and group, F (1,25) = 2,608, p = 0.119, ηp^2 = 0.094.

Figure 14

Group Comparison A vs H: FIM



Taken together, these results suggest that there was a general improvement over time for egocentric neglect and functional independence, but not for allocentric neglect, thus there is no evidence supporting the hypothesis that a specific neglect treatment with FES may be more effective than a general neuropsychological treatment without FES.

A vs H, Secondary Outcome Measures

The results of the analysis can be found in Table 7. For the variables of allocentric asymmetry as well as ERBI, the assumption of equal covariances was violated. Furthermore, the assumption of homogeneity was violated for the ERBI variable.

Table 7

A vs H, Secondary Outcome Measures, ANOVA Results

	Group A		Group H							
Outcome	Pre (SD)	Post (SD)	Pre (SD)	Post (SD)	*p* (Time)	ηp2 (Time)	*p* (Group)	ηp2 (Group)	*p* (Time*Group)	ηp2 (Time*Group)
Apples Cancellation Task										
AlloAsymmetry	2,31(4,05)	1,77(4,00)	2,36 (6,68)	3,93(4,03)	,670	,007	,449	,023	,387	,030
ERBI	-35,00(50,21)	9,23(32,27)	84,64(20,8)	16,07(50,92)	**,000****	,636	**,008***	,247	,166	,075

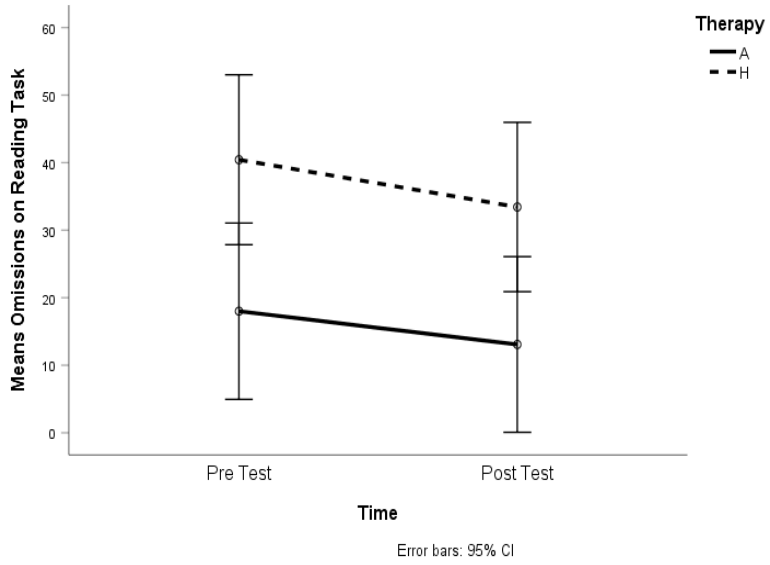
Line Bisection Task										
Mean (cm)	3,2	2,5	5,7	6,3	,859	,001	**,017***	,216	,159	,081
Allocentric (cm)	1,7	1,2	1,2	1,8	,858	,001	,971	,000	,220	,062
Clock	0,92	0,58	1,58	1,50	,084	,119	**,001***	,367	,263	,052
Reading	18,00	13,08	40,43	33,43	**,036***	,165	**,017***	,207	,702	,006

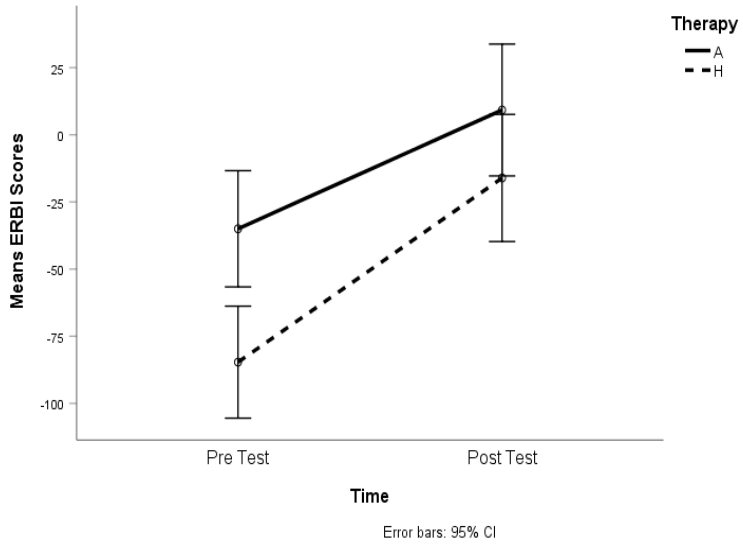
Note. * Significant at the 0.05 level; ** Significant at the 0.

As can be seen in Table 7, there was a significant main effect of time for Reading, showing a reduction in omitted words with time for both groups (see Figure 15) as well as a main effect of time for ERBI (see Figure 16). Additionally, there were significant main effects of group for the variables ERBI, Line bisection Mean, Clock, and Reading, with the historical control group generally performing worse than group A, both on the pre- and post-tests, as seen graphically.

Figure 15 and 16

Group Comparison A vs H: Reading and ERBI





Due to the violations of assumptions, one has to be cautious when drawing conclusions from the results. Generally, the potential improvement in reading ability over time is in line with a general improvement of egocentric neglect, with patients now potentially exploring more of the left side of the page than before. Apart from this finding, the groups generally do not seem to have improved significantly on these measures.

Overall, it thus appears that the neglect therapy in combination with FES was not more effective than a general neuropsychological training without FES, thus our hypothesis is not supported by the results of the performed analysis.

Correlations with Neglect Recovery

For exploratory purposes, the association between Age and allocentric/egocentric Neglect Recovery, as represented by the difference between T2 and T3 as well as the difference between T3 and T4 was investigated. Additionally, the association between Lesion Size and Neglect Recovery was explored. An inspection of the scatterplots of each potential correlation revealed potential non-linearity, therefore, two-tailed Spearman-rho correlations were performed.

Age was not significantly correlated with the difference between assessments for egocentric neglect (T3-T2 Omissions: Spearman's ρ = - 0.130, p = 0.631; T4-T3 Omissions: Spearman's ρ = 0.138, p = 0.705) nor with allocentric neglect (T3-T2 Allocentric Severity: Spearman's ρ = - 0.166, p = 0.555; T4-T3 Allocentric Severity: Spearman's ρ = 0.641, p = 0.063).

Lesion Size, as assessed via the mean voxels provided by MRIcron, was not significantly correlated with the change in egocentric neglect (T3-T2 Omissions: Spearman's ρ = -0.303, p = 0.273; T4-T3 Omissions: ρ = -0.184, p = 0.635). Furthermore, Lesion Size did not significantly correlate with the change in allocentric neglect (T3-T2 Allocentric Severity: Spearman's ρ = -0.154, p = 0.599; T4-T3 Allocentric Severity: Spearman's ρ = 0.193, p = 0.647).

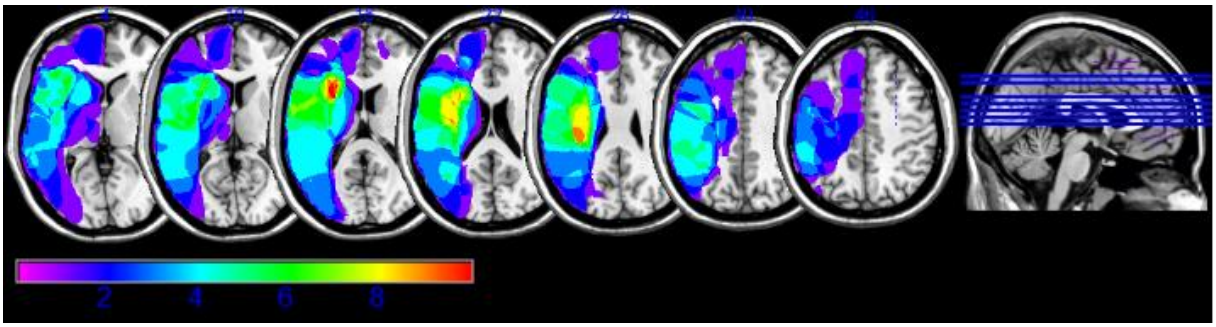
In conclusion, there appears to be no association between Age and neglect recovery as assessed with difference scores, or between lesion size and neglect recovery. However, due to the presence of outliers potentially affecting the correlation, caution should be applied.

Voxel-based Lesion-Symptom Analysis (VLSM) for Egocentric and Allocentric Neglect

A general lesion overlay of all participants can be found in Figure 17, depicting all lesioned areas across patients. Higher lesion overlap is found primarily in the insula, with some overlap in the precentral gyrus and the opercular part of the inferior frontal gyrus.

Figure 17

Lesion Overlay of all 15 participants showing the distribution of right-hemispheric damage.

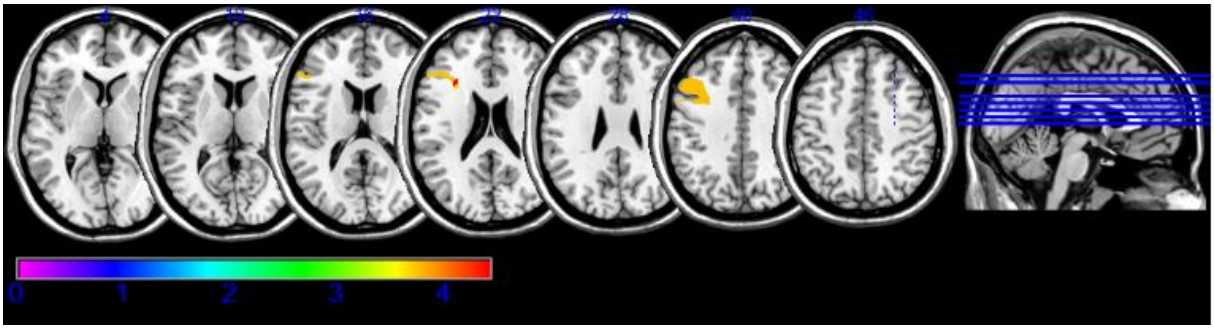


A VLSM analysis for continuous behavioural data was conducted for each predictor variable, using two-sample t-tests and the Brunner-Munzel test. For the analysis, only voxels damaged in more than 10 percent of the sample (at least 2 patients) were included. To account for multiple comparisons, the false discovery rate (FDR = .01) correction was applied, as well as the family-wise error correction, as default by MRIcron.

There was no significant lesion cluster for egocentric neglect according to both the two-sample t-tests as well as for the Brunner-Munzel test. For allocentric neglect, there was a significant lesion cluster, based on the t-test with a FDR correction. A lesion overlay can be found in Figure 18. Based on the automated anatomical labelling map (AAL, Tzourio-Mazoyer et al., 2002), the lesion cluster appears to be located in the Middle Frontal Gyrus, Precentral Gyrus, and Inferior Frontal Gyrus, both in the opercular and triangular part.

Figure 18

Lesion Overlay based on t-test results for Allocentric Severity



Discussion

The purpose of the current study was to investigate the effectiveness of (1) a specific allocentric neglect therapy with FES compared to a general neuropsychological therapy with FES and (2) a specific allocentric neglect therapy with FES compared to a general neuropsychological therapy without FES. Based on the results, there was no improvement on allocentric neglect measures over time, nor did the treatments differ in their effectiveness regarding the treatment of allocentric neglect.

The results reveal general improvements on some measures for egocentric neglect over time, such as a reduction in omissions on both the Apples Cancellation Task as well as on the Reading Task, and improvements in functional independence, both evidenced by the FIM and ERBI. However, for both comparisons no treatment appeared to be more effective than the other. While there was a significant interaction for the Line Bisection Task Mean (thus the egocentric measure) between Therapy A and B, post-hoc tests did not reveal significant differences between the two treatment conditions nor between the pre- and post-tests, thus the concrete mechanisms remain unsolved.

In general, therefore, the results do not provide evidence in favour of either of our hypotheses.

Allocentric Neglect Therapy

This study attempted to ameliorate allocentric neglect specifically via a combination of exercise-based therapy and FES. Unfortunately, we found no evidence for its effectiveness in comparison to a general neuropsychological therapy. However, there are multiple aspects regarding the content, assessment and feasibility of the treatment which could be adjusted to better target allocentric neglect specifically and which may inform the development of future treatments.

Content

As patients received exercises from each of the three parts of therapy as described earlier every day, it is difficult to disentangle the individual effectiveness of each exercise. However, some important observations could be made.

Part 1. Although subjects particularly appreciated practising daily activities such as folding t-shirts and tying shoelaces, these exercises may not be well-suited to specifically tackle allocentric neglect symptoms. In fact, folding a t-shirt may have equally been affected by egocentric neglect, as it required an exploration not only of the object itself but also the left side of space in which the shirt was partly placed. The object-specificity may have been rather given by the shoe, as the object is smaller and could therefore be placed outside the neglected space. Interestingly, the sample demonstrated a general improvement in functional independence but not in allocentric neglect. Given that allocentric neglect has been connected to functional impairment (Bickerton et al., 2011), this finding is surprising and raises the question of which aspects of functional abilities are specifically impaired due to allocentric neglect. This could provide insight into exercises that may need adjustments to adequately represent functional impairments associated with allocentric neglect.

Part 2. This part consisted of telling time on a clock, which most patients had no trouble with, as well as reading tasks and a segmentation task. Except for the most difficult reading task, patients often performed quite well and as such, these exercises were often substituted with exercises from other parts so that patients would continuously be challenged.

There were exceptions of patients who struggled with the clock, in which case it was necessary to remain flexible and attempt different modifications. For example, one patient was not able to even identify the numbers of the clock but an attempt of visually following the minute hand (red coloured) of the clock which was then successively moved further to the left and naming the number pointed at was (sometimes) possible. There was also variability among patients in their ability to perform the segmentation task, however, it often appeared that many patients struggled to understand the instructions but performed relatively well once the task was understood. These examples highlight the variability of behavioural manifestation of the impairment in the different patients. Therefore, it may be helpful for future studies to identify more of the specific behavioural consequences and cognitive mechanisms that are unique to allocentric neglect in order to judge the appropriateness of these exercises and identify those patients who may benefit the most from each exercise.

Regarding the reading task, it often appeared that the first task in which the text was presented in a left-sided column alternating with a text presented in a right-sided column was often more difficult than the second text which was presented in the middle of the screen with a split-coloured background. When attempting to read the third text (split by column and colour), many patients followed the column instead of continuing the text on the right side. Even the hint that one needs to switch between the differently coloured sides did not help. It seems that the colour of the background was not used as a reference-frame. Creating a new reference-frame, ignoring both the unusual separation in columns and colours was impossible for most patients unless provided with a lot of correction and cueing from the therapist. Bickerton and colleagues (2011) report egocentric neglect to potentially result in a failure to use separate elements of an object to guide spatial attention and to monitor the already-attended-to elements. They link this to the finding that patients showing purely egocentric neglect had slower reading times than those with allocentric neglect. It may thus be that the reading tasks targeted egocentric neglect more than allocentric neglect. This may be

additionally true for the assessment of reading ability, which took into consideration omissions of words. To assess allocentric neglect, counting reading errors may have been a more informative measure.

Part 3. Except for the wooden figures, the visuoconstructive exercises were particularly difficult and often required extensive help from the therapist, though there was considerable variability among patients. While some patients performed well on any drawing exercise but not on the Nikitin dice, others showed the opposite pattern. For instance, one patient who showed only an egocentric neglect was almost incapable of drawing the right side of an object, which was somewhat unexpected given that this exercise appears to be more object-based than needing a space-based reference frame. However, Bickerton and colleagues (2011) found egocentric neglect to be associated with more difficulties on a figure copying task than allocentric neglect. It may therefore be that the drawing exercises not only targeted allocentric neglect but to the same extent targeted egocentric neglect. Here again it may be beneficial to investigate the behavioural consequences of egocentric and allocentric neglect specifically to judge the exercises' appropriateness in targeting each subtype as well as other mechanisms (such as motor ability or working memory) that may affect performance on them.

Assessment Instruments

Regarding allocentric neglect, it appears that skills worked on during the therapy sessions, for example the visual exploration of the contralesional side of objects, may have not transferred well to the diagnostic tests. One aspect that was consistent between patients was the need for cueing from the therapist. Whether that was auditory or visual through e.g., a neon-coloured marker, many patients needed cueing to be able to solve or even attempt some exercises. However, no cueing was available during diagnostic tests and patients continued to commit allocentric errors. It seems that the focus on the left side of objects did not become automatic but was only possible when patients' attention was directed to it actively. Since anosognosia may co-occur with neglect (Appelros et al., 2007), expecting patients to actively

remind themselves to focus and investigate the left-side of the targets in the Apples Cancellation Task may have been too advanced. Future adjustment focusing on how to develop a certain automatization may be helpful. Additionally, it also seemed that exploration was impaired as patients often went over the same few apples repeatedly. Some patients also did not seem to follow a specific exploration strategy (for example starting left to right or top to bottom of the page) but explored randomly without a clear goal in mind. As such, the impairment on the Apples Cancellation Task may have been affected by a disturbed exploration behaviour which could be included in adjustments of the presented treatment.

Both the Apples Cancellation Task as well as Line Bisection Task are commonly employed assessment methods for neglect. Since the therapy sessions included the visual exploration of both space and objects, these two assessments appear to be appropriate outcome measures. It is surprising that in this sample there were improvements in egocentric neglect on measures regarding the omissions of Apples and Words, but no improvement on the egocentric asymmetry scores or on the egocentric measure of the Line Bisection Task. It could be beneficial to investigate covariates (for example hemianopsia) that may influence the performance on some but not all neglect tasks. The same applies to the Clock Drawing Task. Based on the fact that few patients showed problems with telling time from the clock used during treatment sessions, performance on the task may have been affected by other variables such as executive dysfunction that were not considered in this design. Finally, while the Reading Task may accurately reflect the reduction of space-based errors (fewer omissions of words), allocentric neglect may have been better represented by reading errors.

Finally, two measures were used for the assessment of functional independence. For both, there was an improvement over time, however, as discussed previously, the lack of improvement on allocentric neglect is surprising. It could be interesting to take a closer look at the different subscales of the FIM to disentangle the specific impairments patients experienced and the scales' association with both egocentric and allocentric neglect to judge

the appropriateness of both the treatment exercises as well as the use of the FIM as an outcome measure for functional impairment in relation to allocentric neglect.

Feasibility of Treatment

Compliance. Overall, patient compliance was very good. Every patient who was approached during recruitment voiced interest in participating, and those following the treatments consistently participated to their abilities. While motivation seemed to decrease with time, this often appeared to be related to a general dissatisfaction with being in a hospital as well as a lack of visitors due to the strict COVID-19 regulations. Additionally, patients who were severely affected and rather early in their rehabilitation process often found the sessions exhausting and required many breaks in between. On the other hand, patients who were generally more "fit" and closer to being released to the next rehabilitation phase showed great motivation and conscientiousness regarding the therapy sessions.

Duration. Setting the study at around 7 weeks posed some issues. Due to the fact that the therapy sessions were quite intensive, and patients had to be able to be mobilised regularly, many patients newly arriving to the rehabilitation unit were not yet able to participate. On the other hand, participants who were very well capable of following such an intensive program often were about to be released, thus many patients only completed one round of therapy before being released. Additionally, the sessions themselves were too long for many patients. Few were able to actively work for 45 minutes, and it became evident that reducing the time to 30 minutes was beneficial for many patients. It was also helpful to allow patients small breaks in between exercises. Finally, providing therapy sessions daily may have been overwhelming. It is questionable whether clinics would have the resources to provide 45-minute sessions to patients daily.

Improvements and Future Direction

The therapy program investigated in the present study represents a first attempt at treating allocentric neglect with an exercise-based intervention. Several adjustments could be

made both to the treatment itself as well as to the study design. Firstly, while overall the exercises appear to have targeted neglect, some adjustments could be considered in order to focus the therapy more on allocentric neglect. One could test the individual exercises regarding their effectiveness in treating ego- and allocentric neglect as well as determining the best combination of exercises. Since therapy sessions did not follow a rigid format but rather followed the patient's ability and compliance there was variability between patients and within patients. Reducing the number of exercises, focusing on a few and following these regardless of patients' ability and over a longer period of time may provide insight into the effectiveness of individual exercises and their combinations. However, this rigid form may not adequately represent the clinical reality, which should be kept in mind.

Furthermore, including more exercises specific for functional impairments, perhaps in combination with occupational therapy may additionally be helpful as these exercises were experienced positively by patients. Inspecting the correlation between the specific scales of the FIM and both egocentric and allocentric neglect may give an indication of the different functional impairments related to either one type of neglect which could then be specifically targeted.

Finally, this treatment was focused on the exploration and manipulation of objects. In a case study investigating the responsiveness of two patients to either a visual scanning training or a spatio-motor training, Pachalska and colleagues (2004) found allocentric neglect to be more effectively treated by a visual scanning training. As such, the focus on exploration of objects in this treatment seems justified, however, one could adjust the treatment to include fewer exercises and a more systematic and conscious exploration as well as encouraging patients to critically examine the difference between complete and incomplete objects, as described by Pachalska and colleagues (2004). Furthermore, Bickerton et al. (2011) found allocentric neglect to be correlated with difficulties in gesture imitation, which could further be explored in future studies and treatments.

With regard to the study design, there are several adjustments that could be made. Spatial neglect in general shows great spontaneous recovery within the first weeks post-stroke: for example, Nijboer et al. (2013) found 54 % of patients to recover within 12 weeks post-stroke, suggesting time post-stroke to be an important factor for consideration for rehabilitation research.

In the present study, a lack of baseline, which is difficult to establish in post-acute settings, prevents drawing proper conclusions about the spontaneous recovery. However, it may well have overridden any differences between the treatments. Additionally, as the recovery of allocentric neglect is not yet well-researched, the timing of the treatment may have not been optimal. Applying the treatment for a longer period and potentially with patients already at a later point of rehabilitation may reveal new insights. Furthermore, patients were not investigated separately regarding "pure" forms of neglect or a combination of egocentric and allocentric neglect. A combination of the two subtypes has been shown to be related to different lesions than "pure" forms (Chechlacz et al., 2010; Bickerton et al., 2011). It could be possible that patients presenting with both ego- and allocentric neglect differ in their impairment and in their responsiveness to different treatments. As this analysis was comparing group levels, potential individual differences may have not been taken into account. Differentiating more clearly between the different subtypes and combinations of neglect types may provide important additional insights helping to adjust the treatment to the needs of the patients.

In summary, while this study was unable to establish the effectiveness of an allocentric neglect treatment above and beyond standard neuropsychological therapy, multiple insights were gained which may inform the development of future treatments specifically aimed at allocentric neglect.

FES

In addition to the exercise-based treatment, the effectiveness of FES was investigated by means of comparison to a historical control group. Specifically, FES was used as an alternative to tDCS, which often is not feasible in an early rehabilitation setting due to strict safety regulations (Turgut et al., 2018)

Feasibility

The application of FES was very feasible. The apparatus used for applying the stimulation was portable, allowing for flexibility regarding the place of administration. Except for one patient, none voiced any strong discomfort with the stimulation. However, for many patients no movement could be achieved. For some this may have been due to spasticity, others may have needed stronger stimulation for a movement to happen. While experiencing no movement was often de-motivating for patients, those for whom a movement could be achieved often assumed an effectiveness of the treatment. The movement of the hand was a good way to guide patients' attention to the left side of their body. Even those for whom no active movement could be achieved, searching for example for some twitches on the stimulated arm helped keeping patients focused on their left side. Some patients also voiced their personal impression that FES treatment had been helpful in improving their attention to the left side of space.

Generally, it became evident that this was not an easy task for patients, and all had to make a conscious effort to focus their gaze on their left hand, let alone copy that movement with the right hand. Many patients could only focus for a minute or even just a few seconds before having their gaze drift away. Only few patients (with primarily egocentric neglect) who were closer to being released to the next rehabilitation phase were able to remind themselves independently to move their gaze back and copy the movement. Most patients required the therapist to remind them or cue them back to their own hand.

FES was considered as an alternative to tDCS. While our study does not allow for the conclusion that a combination of exercise-based therapy with FES is more effective than a

treatment without FES, the fact that it was easily administered opens the options for future studies investigating FES as a potential treatment. In this sample, three patients would have not been able to receive tDCS treatment. They were however able to receive FES. Of those not being able to receive FES, for one patient this was due to medical reasons which would also have prevented the use of tDCS, while only one could not receive FES due to heightened sensitivity, making FES unbearable. As such, FES appears to be a feasible option for sensory stimulation for early rehabilitation patients and future studies may further investigate the use of FES as a treatment option in post-acute rehabilitation settings.

Treatment Potential

Based on the group comparison between Therapy A and the historical control group, the effectiveness of FES to treat egocentric and/or allocentric neglect could not be established.

This is not in line with previous studies showing improvements in neglect symptoms when applying FES (see for example Harding et al., 2009; Polanowska et al., 2009). However, these studies showed variability in the responsiveness of FES, which may have also been the case in our sample. In the study of Harding and Riddoch 2009), the patient not benefitting from FES showed reduced proprioception and skin sensation. Potentially, patients in our sample may have differed in their proprioception and skin sensations as well, evidenced by the varying tolerance for FES. Additionally, Polanowoska and colleagues (2009) found improvements only after a month-long application. In this sample, six participants did not complete a second round of therapy, thus only receiving three weeks of FES, which may have additionally affected the results.

FES was considered as an alternative to tDCS, which has been argued to reduce spatial neglect via modulating interhemispheric balance (Smit et al., 2015; Sparing et al., 2009). Polanowska and colleagues (2009) hypothesised that stimulation of the left hand via FES may similarly lead to an increase in activation in the right hemisphere. They argue that due to the somatosensory fields of the hand being localised in the parietal region, the electrical

stimulation of the hand may have had positive effects on the brain regions involved in spatial attention. In line with this, Kaelin-Lang and colleagues (2002) found electrical stimulation to the ulnar nerve at the wrist to increase corticomotoneuronal excitability outlasting the stimulation period of 2 hours, primarily in the motor cortex. Given that previous literature seems to suggest that electrical stimulation of the hand may result in a modulation of the right-hemisphere, it is surprising that no treatment effect could be found in this sample. As mentioned above, the variability in this sample regarding the length of application and responsiveness to FES as well as the potential of spontaneous recovery overriding differences between groups may have affected results. Whether FES indeed results in a modulation of the right-hemisphere, and thus may function as an alternative to tDCS, would require additional studies employing neuroimaging techniques in order to determine the effect of FES on neuronal activation more closely.

An additional factor to consider is the fact that this study investigated the combination of FES and exercised-based therapy. There have been disagreements in the literature regarding the effectiveness of combining treatments focusing on sensory modulation, with some finding good add-on effects, and others showing no additional benefits (Kerkhoff & Schenk, 2012; Luauté et al., 2006). While some studies suggest FES to be a potentially effective treatment for neglect on its own (Eske et al., 2006; Harding et al., 2009) as well as in combination with visual scanning (Polanowska et al., 2009), future studies are needed to disentangle the individual effectiveness as well as the effectiveness of different combinations of treatments.

Improvement and Future Directions

In sum, research on FES is still in its infancy. While this study showed FES to be a feasible form of sensory stimulation for patients in an early rehabilitation setting, a combination of specific allocentric neglect therapy and FES was not more effective in ameliorating neglect than a general neuropsychological training. As research on FES is just at

its beginning, future studies should focus on determining the best circumstances of stimulation. For instance, while in this study stimulation was individually adjusted to the patient to result in movement of the hand, Polanowska and colleagues (2009) used a maximum of 15mA. Similarly, stimulation in this study was 15 minutes per day, split in 5 minute units, while Polanowska et al. (2009) used 30 minute stimulation, and Kaelin-Lang and colleagues (2002) used a two-hour stimulation to show the increase in corticomotoneuronal excitability. Investigating the appropriate magnitude of stimulation as well as stimulation and treatment duration are important steps in order to apply FES effectively.

From a feasibility standpoint, FES may well represent an alternative to tDCS for an early rehabilitation setting. However, whether it can serve as an alternative regarding the modulation of the right-hemisphere and as a treatment alternative for neglect cannot be concluded yet and may be investigated in a direct comparison, focusing on feasibility and effectiveness both assessed behaviourally and with neuroimaging or electrophysiological measures.

Improvements of Egocentric but not Allocentric Neglect

An interesting finding of the present study is the fact that egocentric neglect seems to have improved with time, independent of treatment condition, whereas allocentric neglect has not. In general, multiple studies have shown many patients to demonstrate good recovery of visual neglect within six months (see for example Demeyere & Gillebert, 2019; Moore et al. 2021) In fact, Farné et al. (2004) report around 43 percent of patients spontaneously improved within two weeks. In addition, Stone et al. (1992) report visual neglect to quickly recover within the first 10 days post-stroke, with recovery plateauing around three months. Based on these findings, it is possible that the improvements on egocentric neglect in this study may have been due to spontaneous recovery. The fact that allocentric neglect did not improve with time may be in line with the finding that allocentric neglect does not follow a proportional

recovery (Moore et al., 2021). Additionally, the presented studies reporting recovery rates for neglect for the post-acute phase did not focus on allocentric neglect specifically but used measures more indicative of egocentric neglect. Given that in this sample there is an improvement of egocentric neglect over time, regardless of treatment, but no improvement for allocentric neglect opens the possibility for future research to investigate the exact timeframe of allocentric neglect recovery, as having a clearer understanding of the recovery trajectory of allocentric neglect may inform the right timeframe in which treatment should be provided. For example, one could speculate that allocentric neglect recovery starts at a later point in time than egocentric neglect. Additionally, monitoring the recovery trajectory more closely may reveal variables associated with chronic allocentric neglect (since allocentric neglect severity at the acute stage appears to not be predictive of chronic allocentric neglect, see Moore et al., 2021) which may inform potential interventions.

Neglect Recovery

In this sample, age of the patients did not correlate with neglect recovery. This is not in line with Ringman and colleagues (2004) who found the frequency of neglect both at the acute stage and three months post stroke to increase with age. Similarly, Knoflach and colleagues (2012) found younger patients to show a better recovery of functional outcomes following a stroke than older patients. While age may predict the frequency and severity of the initial neglect (Gottesman et al., 2008; Suarez et al., 2020), it may not be related to the rate of neglect recovery per se.

Lesion size and neglect recovery also did not correlate. There are multiple studies linking specific lesion areas to the presence of chronic neglect (e.g., Karnath et al., 2011). Larger lesions have a higher probability to include affected areas than smaller lesions (Karnath et al., 2004) that may be relevant for neglect recovery, and it is thus surprising to find no correlation between lesion size and neglect recovery. Additionally, Ringman and colleagues (2004) found larger lesion size to be associated both with neglect at the acute stage

as well as three months post stroke. Contrary to that, Karnath and colleagues (2011) did not find a difference in lesion volume between those patients recovering and those presenting with chronic neglect. Potentially, lesion size may affect the occurrence of neglect, but not the rate of recovery. However, future studies are needed to corroborate this speculation.

In sum neither of the two variables were related to the change in neglect recovery during the different treatment periods. Following the previously mentioned idea of following the recovery trajectories of allocentric neglect more closely may reveal variables associated with the change in neglect recovery at a given point in time.

Neuroanatomical Differences

The analysis of neuroanatomical differences for allocentric and egocentric neglect revealed a small significant lesion cluster in the anterior parts of the brain only for allocentric neglect. Specifically, the lesion cluster was located in the Middle Frontal Gyrus, Precentral Gyrus, and Inferior Frontal Gyrus, both the opercular and triangular part. This is not in line with findings positioning allocentric neglect rather in the posterior regions, in particular temporal and parietal areas (Chechlacz et al., 2010; Kenzie et al., 2015). The lesions sites identified in this sample have rather been connected to egocentric neglect (Kenzie et al., 2015). Other studies used different assessment instruments (e.g., Kentie et al., 2015) or focused on the presence of allocentric neglect in general instead of the severity (e.g., Chechlacz et al. 2010), thus the disagreements of the results may be related to those differences. However, given that in the present study, tests with a more conservative correction (permutation thresholding) resulted in a non-significant result, as well as the fact that the sample was very small compared to previous studies, and that manual delineation may be prone to human- error, one should apply caution when interpreting the results. A larger sample may be beneficial in addition to separating patients into groups according to neglect type or combination of neglect types to gather meaningful information on neuroanatomical differences.

Importance and Implications

The findings in this study have important implications for future research. Mainly, multiple areas for which future research is required could be identified, specifically to investigate the recovery trajectory, behavioural manifestations, and cognitive mechanism of allocentric neglect. Additionally, the insights gained regarding the feasibility of an exercise-based training as well as the application of FES in an early rehabilitation setting may inform future treatment developments.

Limitations

As previously mentioned, this study did not separate patients according to allocentric and egocentric neglect and a combination of those two subtypes. Patients with combined neglect may respond differently to treatment and future investigations may want to focus on clear distinctions. As the study took place in an early rehabilitation unit, no long-term baseline could be established, thus spontaneous recovery may account for the presented results. As previously described, time after stroke is an indicator for neglect recovery (Nijboer et al., 2013). In this sample, time post-stroke was not controlled for. Similarly, the presence of hemianopsia was not considered. These are variables that future analyses could take into consideration in order to gain a more thorough understanding of aspects affecting the recovery process and treatment responsiveness. Additionally, the sample was rather small. This makes it difficult to make generalisations but also provides the opportunity for investigating individual patients and their recovery more in depth. The huge variability in this sample may have overridden any treatment effect, however this also represents the clinical reality of patients showing different impairments and strengths. Potentially, a series of case studies may be helpful in identifying those patients that do or do not respond well to treatments, which may then inform future interventions**.** Finally, from a statistical standpoint, multiple assumptions were violated. As described above, these violations may not have been impactful, however, the results nonetheless need to be considered with caution. Using a different

approach, for example linear mixed modelling, may provide a more accurate analysis of the obtained data.

Conclusion

In sum, the proposed allocentric neglect therapy with FES was not more effective in treating allocentric neglect and showed no superiority to a general neuropsychological treatment with FES nor to a general treatment without FES. While the application of the therapy and the use of FES provide some insight into the feasibility of these types of interventions in early-rehabilitation settings, the effective treatment of allocentric neglect could not be established. This highlights the need for continued research on allocentric neglect specifically, as a greater understanding of the cognitive processes and behavioural consequences of allocentric neglect and its recovery may help in the development Fof future treatments specifically aimed at allocentric neglect.

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