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Congruent movement training as a rehabilitation method to ameliorate symptoms of neglect—proof of concept

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Abstract

Stroke patients with visuospatial neglect (VSN) have difficulties responding to visual information located in the contralesional hemifield, affecting many daily life activities (ADL) such as eating, reading and mobility. Visual Scanning Therapy (VST) is widely used in clinical practice to ameliorate symptoms of VSN. Yet, not all patients benefit from this training and many training sessions are needed in order to achieve stable results. One potentially promising improvement to the VST is based on the theory that different effectors of the motor systems (e.g., eyes, hands) independently allocate attention during the programming of the movement (i.e., Pre Motor Theory of Attention (PMT)). Here, we studied this direct implementation of the PMT and tested whether a congruent movement training (CMT: congruent -i.e., executed at the same time to the same location-eye and pointing movements) is more effective to attenuate symptoms of neglect compared to VST. This study can be seen as a proof of concept. Attenuation of neglect symptoms was found in the CMT group after just 5 h of training in the subacute phase of neglect. In contrast, no training effects were found in the VST group. These findings indicate the potential of CMT which is a minimal yet crucial-upgrade of the standard VST protocol that can be easily implemented in the clinic.

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1. Introduction

Visuospatial neglect (VSN) is a complex disorder characterized by lateralized impairments of visual attention in the absence of motor or sensory deficits (Heilman & Valenstein, 1979; Posner et al., 1984; Kinsbourne, 1987). These lateralized impairments result in the ignorance of most visual information located in the contralesional hemifield, which affects many daily life situations, such as eating, getting dressed and mobility (Katz et al., 1999a; Nijboer et al., 2013; Bosma et al., 2019). VSN occurs in ~25–50% of stroke patients (Appelros et al., 2002) and has a more attenuated recovery pattern than other deficits after stroke (Katz et al., 1999b). In addition,
patients with VSN often have a prolonged stay in the clinic, as neglect also has a negative impact on recovery from additional non-neglect symptoms, such as hemiparesis (Nijboer et al., 2014). VSN is chronic for a high proportion of patients; about 30–40% of the patients show signs of neglect one year post-stroke (Nijboer et al., 2013; Karnath et al., 2011). Furthermore, patients with neglect need more help in daily life activities (ADL) compared to patients without neglect (Nijboer et al., 2013, 2014; Bosma et al., 2019). It is therefore of great importance to optimize treatment of neglect.

In the first few months after stroke, spontaneous recovery up to 70% of the initial state post stroke may occur in VSN (Nijboer et al., 2013; Winters et al., 2017). Yet, ~10–30% of the VSN patients do not show such biological recovery patterns (Winters et al., 2017). Non-spontaneous (additional) improvements rely on specific behavioral treatments. Visual Scanning Therapy (VST) is the most frequently used treatment for neglect in the clinic. During VST, patients are trained to make systematic large eye movements to their contralesional hemifield, in order to explore the neglected side of space. Oculomotor performance is often affected in neglect patients. Besides the asymmetry in (disorganized) search patterns (Ten Brink et al., 2016), fixation characteristics (e.g., cumulative fixation duration) can be abnormal in visual exploration task with more random fixations (Behrmann et al., 1997; Chèdru et al., 1973). VST may help to relearn how to explore the visual world, as proper fixation behavior is essential for detailed processing of visual information (Müri et al., 2009).

Many studies have investigated this treatment using a number of different versions (Bowen et al., 2013; Kerkhoff & Schenk, 2012). While there is some evidence that symptoms of neglect can indeed be attenuated after treatment (Antonacci et al., 1995; Weinberg et al., 1977; Luukkainen-Markkula et al., 2009), other studies reported no significant effects of VST compared to general non-specific control treatments (Robertson et al., 1990). Indeed, many patients actually do not show a positive treatment outcome after VST (Bowen et al., 2013; Kerkhoff & Schenk, 2012). There is evidently still much room for improvement in using VST as the treatment of neglect.

It is perhaps not surprising that not all patients benefit from standard VST, given the complexity and heterogeneity of neglect; not all patients show comparable neglect behavior. Additionally, other consequences of stroke that often co-occur (e.g., hemiparesis) may interfere with treatment. An increasing number of studies have therefore explored the beneficial effects of using a combination of experimental treatment (e.g., prism adaptation, non-invasive [brain] stimulation or non-specific contralesional arm movements (Limb Activation Therapy: LAT) Combinations have indeed yielded greater attenuation of neglect symptoms than single VST (Polanowska et al., 2009; Schindler et al., 2002; Schröder et al., 2008; Robertson et al., 2002), although a recent Cochrane review showed that the benefits of current rehabilitation techniques are unclear and that no approach can currently be supported (Bowen et al., 2013).

One potentially promising improvement to the VST is based on the idea that the motor system consists of a collection of different effector systems (e.g., eyes, hands, legs) that can each independently allocate attention. According to the Pre Motor Theory of Attention (PMT), the planning of a movement is both necessary and sufficient for attentional orienting (Rizzolatti et al., 1987). There is ample evidence that planning and executing an eye movement-as trained during VST-will lead to a concurrent shift of attention (Deubel & Schneider, 1996; Hanning et al., 2018; Jonikaitis & Deubel, 2011; Khan et al., 2011). Interestingly, several studies have provided evidence that congruent eye and hand-movements (directed to the same special location at the same time) lead to larger shift of attention than the execution of a single eye or hand movement (Jonikaitis & Deubel, 2011; Hanning et al., 2018). Furthermore, previous studies on novel rehabilitation techniques for neglect have shown beneficial effects of visuomotor feedback training, such as pointing (for a review see Harvey et al., 2012) and grasping-to-lift rods at the centre (Harvey et al., 2003; Rossit et al., 2019). Based on these results, we tested a theoretically grounded hypothesis that a congruent movement training (CMT), in which congruent eye- and pointing movements are made to the contralesional hemifield, allocate more attention to the contralateral hemifield than a training with single eye movement as provided during standard VST. In this study, we explored 1) whether CMT results in greater attenuation of VSN symptoms than VST. CMT is a minimal -yet important- upgrade of standard VST and can easily be implemented in the clinic if proven to have beneficial effects. In addition, 2) we collected eye movement data during several neglect outcome measures in order to explore whether fixation patterns are different for VSN patients compared to healthy individuals and whether training can improve a potential fixation imbalance. Finally, 3) we explored whether the performance during the training task is predictive for training outcome as assessed during the VSN tests.

2. Materials and methods

The study procedures were preregistered prior to data collection (https://www.trialregister.nl/trial/6818), and all deviations from protocol are reported in the manuscript. We report how we determined our sample size, all data exclusions (if any), all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study.

2.1. Participants

Patients with visuospatial neglect after stroke were included during admittance to the Hoogstraat Rehabilitation center or the Parkgraaf rehabilitation center. As part of usual care, patients were tested on the presence of neglect assessed during a neuropsychological neglect screening. This screening included a digitized shape cancellation test (Aglioti et al., 1997), a digitized line bisection test (McIntosh et al., 2005) and the Catherine Bergego Scale (CBS) (Azouvi et al., 2003; Ten Brink et al., 2013). Patients were included if at least one of these three tests were deviant from normal range (i.e., omission difference of 2 or more between contralesional and ipsilesional side at shape cancellation test, >2 of 4 lines deviant on line bi-section test (8 repetitions of 4 different lines) or CBS score ≥ 6). As we used a digitized version of the shape cancellation and line bisection test, we calculated cut-off scores based on a group of thirty healthy controls. Further inclusion criteria were: 1) the
neglect was caused by stroke, 2) age between 18 and 85 and 3) sufficient ability to comprehend and to communicate as assessed by a psychologist. Patients with traumatic head injury, severe aphasia (lack of understanding and/or production of speech) and/or insufficient understanding of the task were excluded. All these inclusion/exclusion criteria were established prior to data analysis. Also, when expected discharge was within four weeks, patients were excluded to minimize dropouts. Seven age matched healthy controls were included to obtain cutoff scores for the eye movement data.

Following an a priori power analysis (with effect size $d = 1$; power = .8) a total sample size of 28 patients are required (actual power of .824). Therefore, we aim to include 14 patients per group.

Written informed consent was obtained from all patients according to the Declaration of Helsinki. The study was approved by the Medical Ethical Committee of University Medical Centre Utrecht (NL64626.041.18).

2.2. Procedure

A more detailed description of the protocol used in this study can be found in Elshout et al. (Elshout et al., 2019). In short, half of the patients included received standard VST and the other half received CMT in this randomized controlled trial. Patients were randomly assigned to one of the training paradigms based on a predetermined list, generated using Matlab (The Math Works, Inc.), that has paired each training variant to a patient number. Patients were included in chronological order of neglect diagnosis based on the neuropsychological neglect screening. Each patient was tested on several neglect tests (Elshout et al., 2019) on two separate consecutive days prior to training to assess baseline performances. For this study, we focus on our primary VSN tests including a shape cancellation task, line bi-section test and the CBS. Next, each patient received ten 30-min sessions of VST or CMT (5 h in total), along their general rehabilitation program, during their admittance to the rehabilitation center. Note that every patient received the same amount of training hours, so the number of trials completed during the training itself varied between patients. After completion of all ten sessions, post measurements of all neglect tests were performed on two separate consecutive days. Digitized tests on a 27-inch computer screen (Iiyama ProLite monitor with resolution of 2400 × 1350 pixels and refresh rate of 60 Hz) were used (except CBS) that allowed for more precise analysis and to minimize unintended influences of the researchers who were not blinded to treatment type. The nurses who filled out the CBS were blinded to treatment type.

2.3. Outcome measures

Our primary outcome measure is the improvement on neglect symptoms between post-training and baseline measurements on three VSN tests. As patients are included based on the presence of neglect symptoms on one of the three neglect tests, they might not show neglect symptoms on each task. As a result of this, not every patient will improve on each test (e.g., no omission difference on shape cancellation test prior to training cannot further improve) and each patient may improve on (a combination of) different tests. Therefore, we calculated a combined neglect improvement score, which consisted of 1) the number of omission differences (between contralesional and ipsilesional side of the figure) on the shape cancellation test, plus 2) the mm deviation from center on the line bi-section test, plus 3) the CBS score. This composite score allows us to capture the overall improvement of neglect symptoms for each patient, as no patient has perfect scores on all three tests.

Our secondary outcome measure is the imbalance between the number of fixations on the contralesional versus the ipsilesional side of the screen, during the shape cancellation and line bi-section test. Therefore, eye movement data was collected (sampled at 250 Hz) during the shape cancellation and line bi-section task using an Eyelink 1000 (SR Research Ltd Ottawa ON).

Additionally, demographical parameters (age, gender) were collected from the patients’ medical records. Furthermore, the following stroke-related parameters were captured: Time since lesion, aetiology, side of neglect, Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005), Barthel Index (Collin et al., 1988) and Motricity Index (Collin & Wade, 1990; Kwakkel et al., 1999). These demographical and stroke related characteristics were used to check for differences between groups as the groups are not matched during inclusion.

2.4. Training

A detailed description of the training can be found in Elshout et al. (Elshout et al., 2019). Briefly, during experimental treatment (CMT) patients are instructed to make congruent eye and pointing movements during a game-like task on a touchscreen 15-inch laptop (HP Envy ×360) (Fig. 1). Patients have to match a grid consisting of nine filled circles with different colors (template grid) that is shown at the top corner of the screen in their affected hemifield. A grid of nine empty circles (target grid) is placed beneath the template grid. By pressing a button placed in the ipsilesional hemifield, a filled circle with specific color is presented and can be placed at a corresponding location in the target grid. This is repeated until all locations of the target grid are filled. Then, feedback is automatically provided about time needed to complete the target grid and percentage of correct placed targets. This exercise requires repetitive coordinated eye and hand movements towards the contralesional hemifield.

During control treatment (VST), patients have to compare a template grid consisting of nine filled circles with different colors placed in their ipsilesional hemifield with a target grid, also consisting of nine filled circles with different colors that was placed in their contralesional hemifield. The instruction was to report how many items were differently colored at each grid location (ranging from zero to a maximum of nine targets). Feedback about performance (percentage correct responses and time needed) was provided afterwards. In order to perform this task, eye movements between both grids have to be made. Crucially, no pointing movements are made during VST.

2.5. Analyses

Parametric tests were used if the data were normally distributed and non-parametric test were used if the data were not normally distributed. To check for differences in demographic
and stroke related characteristics between both groups, non-parametric Mann–Whitney U and chi-square test were performed. In addition, a Mann–Whitney U test was used to compare baseline performance on the neglect outcome variables. As we have a clear hypothesis driven research question, we used an one-sampled t-test against a hypothesized training effect of 0 (i.e., no training effect) to test whether each training paradigm resulted in an improvement of neglect symptoms. An independent sampled t-test (one sided) was used to test whether CMT is more effective than VST.

To explore whether the test outcome on the shape cancellation and line bi-section test is reflected in the eye movement patterns, we calculated a fixation index by dividing the percentage of fixations at the contralesional hemifield by the percentage of fixations at the ipsilesional hemifield. Since patients may either make fewer eye movements to the contralesional hemifield or more compensational eye movements towards the contralesional hemifield, we defined the absolute deviation from 1 as the fixation index. The data of the CMT and VST group were compared against the data of the healthy control group, using an independent sample t-test (one-sided). Only patients in which we could collect at least 75% of eye movement data during each test were used in this analysis.

A training index was calculated in order to study how well the patients improved on the training task itself and to test the relation between training performance and training effect. The training index is defined by the sum of the relative improvements on error rate and time needed to complete the training task. The improvement on error rate and time needed was based on the difference between the second half of training results and the first half of the training results. The maximum improvement achievable was set by the average training results of the first five repetitions of the training task. Spearman’s correlation is used to test the relationship between training performance and training effects.

Alpha was set to .05. The study analyses were not pre-registered.

### 3. Results

Twenty patients with VSN were included. One patient of the VST group was excluded from analyses since the patient was discharged from the rehabilitation center before post measurements could be completed.

Demographics and stroke related characteristics of the remaining 19 patients (ten patients in the CMT group and nine patients in the VST group) are provided in Table 1. There were no differences between groups with respect to either demographics, stroke related characteristics, or baseline performances (all Z < −1.97; all t < 1.26; all p > .05).

The mean age of the healthy control group (2 male) was 54.6 (5.1) and was not different from either the VST or the CMT group (Z = −.05, p = .96 and Z = −.25, p = .81, respectively).

#### 3.1. Is CMT more effective than VST to attenuate symptoms of neglect?

The CMT group showed an averaged composite score of −5.99 (SE = 2.43), which is significant lower than 0 (t (9) = −2.46, p = .036), indicating a positive training effect (Fig. 2A). In contrast, the VST group had an average composite score of 2.7 (SE = 5.2) which is not different from 0 (t (8) = .52, p = .62) indicating no training effect in this group. At the individual level, seven of the ten patients from the CMT group showed an improvement of neglect symptoms. Three of the nine patients from the VST group showed an improvement in neglect symptoms. However, we lacked the power to firmly conclude that CMT is more effective than VST (t (17) = −1.57, p = .068).

Overall, the CMT group had lower scores -which represent attenuation of neglect symptoms-on post measurements on all three VSN tests (Fig. 2B–D). On average, patients had 2.1 less omissions during the shape cancellation test, deviated 2.07 mm less from center during the line bi-section task and had a 6.25 lower CBS score. The VST group, however, showed a more diverse pattern and on average, patients only improved on the line bi-section task (1.4 mm), and performed slightly lower in the other tests.
worse at the shape cancelation task (1.78 more omissions) and CBS (3.23 higher CBS score).

3.2. How does training affect fixation characteristics during shape cancellation and line bi-section test?

Reliable eye movement data could be obtained for seven patients of the CMT group and six patients of the VST group during the shape cancellation test (Fig. 3A). The fixation index of both the CMT (M = .46, SE = .11) and VST group (M = .43, SE = .03) deviated from the healthy control group (M = .19, SE = .03) prior to training (t (12) = 2.121, p = .036; t (11) = 4.844, p < .001, respectively). After training, the fixation index of the CMT group was reduced to .31 (SE = .12) and the VST group was reduced to .36 (SE = .09), which then did not differ anymore from the healthy control group (t (12) = .878, p = .20; t (11) = 1.602, p = .08, respectively). In addition, five of the seven patients showed a more balanced fixation index after CMT, against three of the six patients in the VST group. Fig. 3C and D shows two example datasets of a patient with a low fixation index (Fig. 3C1 and 2) and a patient with a high fixation index (Fig. 3D1 and 2), showing a strong preference for the ipsilesional hemifield.

During the line bi-section tests, we were able to collect reliable data of six patients in both the CMT and the VST group (Fig. 3B). The fixation index of both the CMT (M = .94, SE = .19) and VST group (M = .46, SE = .14) fell within normal range prior to training (t (11) = 1.716, p = .06; t (11) = .716, p = .25, respectively) with respect to the healthy control group (M = .57, SE = .1). Although the fixation index of the CMT group was reduced to .67 (SE = .09), the fixation index of the VST group increased to .62 (SE = .15). However, both were still not different from the healthy controls (CMT: t (11) = .726, p = .24; VST: t (11) = .217, p = .42). In the CMT group, four of the six patients showed a more balanced fixation index, whereas in the VST group only one patient showed a more balanced fixation index.

### Table 1 – Demographical characteristics and stroke related characteristics.

|                        | VST  | CMT  | P-value |
|------------------------|------|------|---------|
| Neglect side (% left)  | .9   | .89  | .937    |
| Gender (% male)        | 40   | 66.7 | .370    |
| Age (years)            | 58.7 (4.2) | 59.2 (4) | .842 |
| Time post stroke (days)| 76.8 (9) | 102.6 (21.8) | .400 |
| MoCA                   | 20.4 (1.4) | 18.1 (2.4) | .815 |
| Barthel Index          | 9.3 (1) | 10.4 (2) | .694 |
| Motricity Index arm    | 26.5 (11.8) | 59.9 (11.2) | .050 |
| Moiricity Index leg    | 55.8 (14) | 72.4 (11.1) | .505 |
| Baseline Shape Canc    | 4.2 (1.7) | 8.6 (3) | .228 |
| Baseline Line Bi-sec (mm) | 12.6 (3.5) | 15.3 (3.8) | .605 |
| Baseline CBS           | 11.4 (1.5) | 12.2 (2.8) | .816 |

Fig. 2 – Total training effect. The red lines indicate the means and the green/blue bars are the 95% CI. A) The colored circles resemble the individual composite scores consisting of the difference score on the shape cancellation test plus the difference score on the line bi-section test plus the difference score on the CBS. A value of zero indicates no difference in neglect symptoms before and after training. A lower composite score indicates less pronounced neglect symptoms after training. B) Performance on the shape cancellation test before and after training. A lower composite score indicates less pronounced neglect symptoms after training. C) Performance on the line bi-section test before and after training. D) CBS scores before and after training. Higher scores in B, C and D reflect more severe neglect.
In conclusion, a more balanced fixation pattern after training was found during the shape cancellation test in both the CMT and VST group. Fixation behavior during the line bi-section test fell within normal range prior to and after training.

3.3. Is performance on the training task predictive for VSN outcome?

Overall, patients in the CMT group improved by about 26% (SE = 5%) on the training task and the VST group improved by
18% (SE = 6%), which is not significantly different from each other (t (18) = 1.03, p = .316) (Fig. 4A). As both groups improved to a similar extent on the training task and to increase power, we combined both groups to study the relation between performance on the training task and outcome on the combined neglect score.

A significant moderate relation between the training index and the neglect composite score was found (r.s (17) = –0.45, p = .05), indicating that patients who showed the largest improvements during training also showed the largest improvements on the composite neglect score (Fig. 3B).

4. Discussion

In the current study, we tested the theoretically grounded hypothesis that a training with congruent eye and pointing movements (CMT) is more effective in ameliorating VSN compared to a training with eye movements only (VST). CMT is a direct implementation of the PMT which predicts that each effector of the motor system has its own representation of space, and can potentially independently direct attention (Rizzolatti et al., 1987). As more effectors of the motor system agree on a goal directed action endpoint (motor congruency), more attentional resources will be allocated accordingly as our brain has more evidence that this location is important. This is the first study that translated the principle of congruence in the motor system into a rehabilitation method to treat VSN using a relatively minor -yet crucial-upgrade of standard VST. Significant improvement of averaged neglect symptoms was observed after CMT but not after VST. Additionally, more individual patients showed attenuation of VSN after CMT than VST.

Even with a relatively low amount of training hours, we found significant training effects for CMT and not VST, which shows its potential for use in the clinical practice. Stable VST training effects are usually found after at least 40 h of training (Antonucci et al., 1995; Kerkhoff, 1998), which is eight times more than the 5 h used in this study. This short amount of training hours is likely also the reason for the lack of profound training effects and the large diversity in individual training outcome after VST. In the VST group, only performance on the line bi-section test improved unlike the shape cancellation test and CBS. In addition, a more balanced fixation was observed during the shape cancellation test, while the opposite pattern was found during the line bi-section test, which underscores the variability of group and individual treatment outcomes in the VST group. Considering the small group sizes (patient and healthy controls) these eye tracking data are explorative and needed to be verified in larger sample sizes. The variability of (individual) treatment outcome has often been reported after VST (Bowen et al., 2013) and may relate to the specificity of VST (Kerkhoff, 1998). In contrast, the CMT group showed remarkably similar improvements on all three neglect tests with a similar pattern in the fixation data during the shape cancellation and line bi-section tests, suggesting non-specific training effects. Also, more patients improved in the CMT group than in the VST group, even though no difference in demographical, stroke related characteristics nor baseline performances were found between the two groups. Yet, the generalizability of CMT needs to be examined in future studies also taken into account improvements on non-visual associated neglect symptoms such as in the tactile or auditory domain.

Previous studies have shown that combinations of different therapies tend to attenuate symptoms of VSN more than the effect of a single therapy (Polanowska et al., 2009; Schindler et al., 2002; Robertson et al., 2002; Samuel et al., 2000). CMT can also be regarded as a combination of therapies, namely the combination of training of goal-directed eye movements with the training of making goal-directed hand movements. Especially the goal-directed nature of this CMT makes this training different from LAT, that can also ameliorate symptoms of VNS (Robertson et al., 2002; Samuel et al., 2000). The implementation of congruent eye and pointing movements (motor actions executed at the same time to the same location) is unique to CMT and builds on the findings that different effectors of the

Fig. 4 — Training performance. A) The training index is a combined measure of the relative improvement on error rate and time needed to complete the training task. In other words, patients could improve by being more accurate (higher % correct answers) and/or being faster without compromising accuracy. Higher scores indicate better training performance. B) Relation between training performance and improvement of neglect after training based on the composite score (shape cancellation test, line bi-section test and CBS). A negative training effect as plotted on the y-axis indicate attenuation of neglect symptoms.
motor system can synergistically boost attention in healthy subjects during the programming of both movements (Jonikaitis & Deubel, 2011; Hanning et al., 2018). Our findings are in line with other studies using different kind of visuo-motor training to ameliorate symptoms of neglect (for review see Harvey & Rossit, 2012). The principle underlying motor congruency may be related to the multisensory system, which consists of a collection of different senses that can synergistically facilitate perception of the environment when the right conditions are met (approximately same location (spatial rule) and the same time (temporal rule), space and inverse effectiveness) (Calvert et al., 2004; Spence & Squire, 2003; van der Stoop et al., 2017). As the goal-directed behavior fits especially the spatial rule and the PMT stresses the congruency between eye and pointing movements, CMT is therefore potentially more effective (either in magnitude of training effect or in number of patients with VSN that could benefit from it) than non-congruent LAT, although this remains to be tested.

4.1. Clinical considerations and limitations

Neglect is a heterogeneous disability with a variety of symptoms ranging from mild to severe neglect. Our sample of neglect patients in both the CMT and VST group was recruited in the subacute phase from two different rehabilitation centers (specialized and geriatric rehabilitation) and covers patients with mild and severe neglect. In the Netherlands, a patient is admitted to a rehabilitation centre if (a) discharge to home is expected in view of the prognosis and availability of the caregivers, but not from the hospital within 5 days; (b) the patient is capable of participating in therapy; (c) the patient is vital enough; (d) a multidisciplinary approach is essential to reach the complex rehabilitation goals; and (e) discharge to home is expected to be within 3 months. Older patients (75 years or older) or patients with more severe stroke or comorbidities are more likely to be admitted to geriatric rehabilitation. As we included from both types of rehabilitation, in mainly the subacute phase post-stroke onset, our sample is therefore a good representation of VSN patients admitted for either regular rehabilitation or geriatric rehabilitation.

The subacute phase is generally considered to be the group in which training is most beneficial, so we feel that it is important to investigate feasibility and outcome of intervention in especially this stage post-stroke onset. All patients were able to perform the training task and almost all patients, except for two patients in the VST group, improved on the training task taken both error rate and time needed to complete the task into account. Many patients also reported to enjoy performing the task and competed with themselves to improve their error score and/or time. These are important observations to confirm feasibility of this computerized training task in these subacute neglect patients. A significant linear relation was found between performance on the training task and attenuation of neglect symptoms based on the composite score. This suggests that our training task is not a general task, but specifically targeting VSN.

For clinical impact, implications and implementation it is also important to discuss the limitations of the current study. Our sample was too small to perform analyses on subgroups (e.g., different number of days post-stroke onset, differences in severity of stroke or VSN itself, severity of comorbidity), to study whether different subgroups of VSN benefit to a different extent.

All individual patients had their own rehabilitation schedules as other therapies were not withheld during our training. This may have influenced the results of the training. However, such interference should have affected both CMT and VST similarly as patients were randomly assigned to one of the two groups. Similarly, we cannot rule out that spontaneous recovery may have occurred (Nijboer et al., 2013; Winters et al., 2017), although again such potential spontaneous neurobiological recovery is likely to occur to a similar extent in both the CMT and VST group. Also, although we have inspected the medical records and excluded patients that may suffer from hemianopia or extinction, we cannot rule out the possibility that one of the patients also had hemianopia, as neglect and hemianopia are notoriously difficult to disentangle. It is difficult to speculate how training performance could be different for a patient with neglect or a patient with hemianopia exclusively as both deficits are treated with VST and all primary outcome measures can potentially improve in the same way.

Although we do find more pronounced attenuation of VSN symptoms after CMT, we are cautious in firmly concluding that CMT is more effective than VST. This cautious note is based on the relative small sample size; based on our a priori power calculation, fourteen patients should have been included per condition, instead of ten (Elshout et al., 2019). Due to a slow inclusion rate and a national forced inclusion stop for several months*, we had to complete the study with a smaller sample size. Still, we found reliable positive training results for CMT compared to VST, even with such a relatively small sample size.

In conclusion, CMT is a simple upgrade of VST, easy to implement, and may produce more pronounced and more stable attenuation of VSN symptoms than VST, even with short treatment procedures.

* Due to the COVID-19 pandemic.

Data availability

The conditions of our ethics approval do not permit archiving or sharing of the data obtained in this study with any individual outside the author team under any circumstances. Materials for the study that can be shared are publicly available at https://osf.io/4mrv5/.

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Open practices

The study in this article earned Preregistered and Open Materials badges for transparent practices. Materials for this study are available at https://osf.io/4mrv5/.
Declaration of competing interest

All authors declare that they have no competing interests.

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