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**Prism adaptation in rehabilitation? No additional effects of prism adaptation on neglect recovery in the subacute phase post-stroke - A randomised controlled trial**

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## **Abstract**

*Background.* Patients with neglect ignore or respond slower to contralesional stimuli. Neglect negatively influences independence in activities of daily life (ADL). Prism adaptation (PA) is one of the most frequently studied treatments, yet there is little evidence regarding positive effects on neglect behaviour in ADL. *Objective.* To assess whether PA in the subacute phase ameliorates neglect in situations of varying complexity. *Methods.* 70 Neglect patients admitted for inpatient stroke rehabilitation received either PA or sham adaptation (SA) for two weeks, with full access to standard treatment. There were seven time-dependent measurements (baseline and 1-4, 6 and 14 weeks after start of treatment). The primary outcome was change of neglect as observed during basic ADL with the Catherine Bergego Scale (CBS). Secondary outcomes were changes in performance on a dynamic multitask (i.e. the Mobility Assessment Course; MAC), and a static paper-and-pencil task (i.e. a shape cancellation task; SC). *Results.* 34 patients received PA and 35 SA. There were significant time-dependent improvements in performance as measured with the CBS, MAC, and SC [all  $F > 15.57$ ,  $p < .001$ ]. There was no significant difference in magnitude of improvement between groups on the CBS, MAC, and SC [all  $F < 2.54$ ,  $p > .113$ ]. *Conclusions.* No beneficial effects of PA over SA in the subacute phase post-stroke were observed, which was comparable for situations in varying complexity. Heterogeneity of the syndrome, time post-stroke onset and the content of the treatment as usual are discussed. Basic knowledge on subtypes and recovery patterns would aid the development of tailored treatment. *Trial registration.* #NTR3278.

**Keywords:** stroke, rehabilitation, hemispatial neglect, clinical trial, prism adaptation, Catherine Bergego Scale, Mobility Assessment Course, treatment

## ***Introduction***

A frequent post-stroke disorder in lateralized attention is visuospatial neglect ('neglect'). Patients with neglect ignore—or respond slower to—contralesional stimuli, without being aware of it.<sup>1,2</sup> Of all stroke patients, 20-80% shows neglect, depending on the moment and task used.<sup>3</sup> Generally, spontaneous recovery occurs within the first three months post-stroke onset, but in 40% of neglect patients, the disorder is still present one year later.<sup>4</sup> Neglect patients need more help in daily life activities (ADL) compared to patients without neglect, and are less likely to be discharged home.<sup>5,6</sup> Adequate treatment of neglect is, therefore, of great importance.

The current neglect treatment is mainly visual scanning training, a *compensatory* treatment with emphasis on top-down strategies.<sup>7</sup> Its effectivity, however, remains unproven.<sup>8</sup> Additionally, several *restorative* treatments have been developed, of which prism adaptation (PA) is the most frequently studied (i.e. 16 randomised controlled trials [RCT's]).<sup>9-24</sup> The PA paradigm was developed by Rossetti and colleagues,<sup>9</sup> and their PA procedure is used in most studies. During PA, patients wear prism glasses that produce an ipsilesional lateral shift of the visual field. Adaptation to this optical shift requires a set of successive visuo-motor pointing movements. When the prisms are removed, attention is automatically shifted contralesional. Of RCT's that included neuropsychological neglect tasks,<sup>9,10,12-24</sup> in 60% PA diminished neglect as measured with at least one of these pen-and-paper tasks.<sup>9,10,12-15,17,18,24</sup> There is, however, little evidence regarding whether PA diminishes neglect in ADL, as paper-and-pencil tasks lack the dynamics and complexity of daily life.<sup>25</sup> Of RCT's that included measures at the level of (basic) ADL,<sup>16,17,19,21-23</sup> in only 33% neglect behaviour decreased more after PA compared to no or control treatment.<sup>17,19</sup> This inconsistency between results is probably due to the lack of comparability between studies (e.g. treatment procedure, intensity, tasks) or a general lack of methodological quality (e.g. small groups [11-43], no right-sided

neglect, measures of ADL in only 38% of studies, follow-up measurements in only 25% of studies). In sum, it is uncertain whether PA should be implemented in rehabilitation. The effectiveness of other rehabilitation interventions (e.g. limb activation training, optokinetic stimulation, eye patching) also remains unproven.<sup>8</sup> More high-quality (i.e. adequate statistical power, randomization, ADL measures, follow-up), pragmatic RCT's in a clinical setting are needed.<sup>8,26</sup>

We conducted an RCT in which the aforementioned issues were considered. Our primary aim was to determine whether treatment with PA in the subacute phase ameliorated neglect behaviour in basic ADL (as measured with the Catherine Bergego Scale; CBS) to a larger extent compared to sham adaptation (SA). In addition, in order to eliminate the influence of compensation strategies, we used the Mobility Assessment Course (MAC), a dynamic multitask.<sup>25</sup> Finally, a cancellation task was included, which is a widely used measure for neglect.<sup>27</sup> We included stroke patients with left- and right-sided neglect. Patients with right-sided neglect have not been included in prior trials. Finding a treatment for this group of patients is, however, necessary, as consequences of left- versus right-sided neglect in ADL are largely comparable.<sup>28</sup>

We included patients in the subacute phase post-stroke. A general consideration for early treatment is the plasticity of the brain. Spontaneous neurobiological recovery occurs within all domains and lasts around 90 days.<sup>4,29</sup> The main part of recovery during this critical period is likely driven by spontaneous recovery and effects of rehabilitation interventions are much smaller. They may, however, improve or extend the duration of neuroplasticity.<sup>29-31</sup> A more specific consideration is that patients with neglect ignore one side of their body or space in the acute phase post-stroke, and learn not to use this side of the body or hemifield. Early treatment might minimize this learned non-use, and larger effects of PA could potentially be obtained.<sup>13</sup>

## ***Methods***

### *Research design*

A single centre, randomised, double-blind (i.e. regarding the primary outcome), parallel-group study with an allocation ratio of 1:1 (i.e. an equal number of patients was allocated to each group) was conducted (for the trial protocol, see Ten Brink et al.<sup>32</sup>). A rehabilitation physician was consulted by the investigator regarding the inclusion and exclusion criteria (see below). Patients gave written informed consent. The nurses, physical therapist, and occupational therapist who filled in the CBS were blind to the treatment conditions. The investigator (AFTB) who treated and tested the patients regarding the secondary outcomes was not blind to the treatment since she had to put on the goggles. If possible, tests were computerized in order to increase objectivity. Patients could not be (completely) blinded to the treatment since they had to wear the goggles. However, patients were not explicitly told which treatment they received, and none of them expressed any awareness of assigned condition (after informal enquiry). Patients were tested at baseline and after 1, 2, 3, 4, 6 and 14 weeks from the start of treatment. The MAC was assessed at baseline and after 2, 4, and 14 weeks.

The study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October) and in accordance with the Medical Research Involving Human Subjects Act (WMO). The study was approved by the Medical Ethical Committee of the University Medical Centre Utrecht.

### *Participants*

Stroke patients with a clinical diagnosed symptomatic stroke (first or recurrent, ischemic or intracerebral hemorrhagic lesion) admitted consecutively to De Hoogstraat Rehabilitation

Centre in Utrecht, the Netherlands, were considered for inclusion. Patients had to be aged between 18 and 85 years, and have sufficient comprehension and communication skills. Patients were not included in case of interfering psychiatric disorders or substance abuse; when they were physically or mentally unable to participate; or when the expected discharge was <3 weeks.

### *Neglect screening*

All patients were screened for neglect per usual care within the first two weeks after admission. Patients could enroll when they showed neglect on the SC, line bisection, *or* CBS (see ‘Primary outcome’, a CBS score of  $\geq 6$  was used as a threshold for neglect<sup>33</sup>). The SC (see ‘Static task – SC’) and line bisection were administered on a computer monitor.<sup>34</sup> The line bisection task consisted of three horizontal lines (22° long, 0.2° thick) that were presented upper right, lower left, and in the horizontal and vertical center. The stimulus presentation was approximately 19° wide and 5.7° high. Patients had to mark the midpoint.

The thresholds for neglect were based on the mean plus three standard deviations of 28 healthy individuals.<sup>34</sup> The SC omission difference score ranged from 0 to 1.05, resulting in a threshold of  $\geq 2$ . The line bisection deviations ranged from -0.77 to 0.81°, -0.85 to 0.48° and -0.89 to 0.42° for the three lines respectively. A deviation outside normal range on  $\geq 2$  lines was used as a threshold.

### *Apparatus*

The treatment and the SC were administered using a 22-inch interactive WACOM (PL2200) tablet screen (1920 × 1080), with a screen size of 477.64mm × 268.11mm.<sup>35</sup> The tablet screen was oriented horizontally and slightly tilted (18°) with an adjustable stand. Patients had to respond to stimuli by drawing on or pointing at the screen with a digital stylus. DiagnoseIS

(developed by Metrisquare, the Netherlands) was used to program the SC. The tablet was controlled by a laptop (Samsung NP300E5A-S01NL).

### *Intervention*

The PA procedure was adapted from Rossetti and colleagues.<sup>9</sup> Patients wore a pair of goggles fitted with wide-field point-to-point prismatic lenses, inducing an ipsilesional optical shift of 10° (PA) or goggles with plain lenses (SA). Exposure consisted of  $\pm 100$  fast pointing movements to three stimuli (red, yellow, blue) presented on a horizontal axis at a distance of  $\pm 65$ cm.<sup>35</sup> The left and right stimuli were located 10° away from the body midline. The investigator indicated which stimulus was the target. A board was held under the chin to prevent viewing of the hand at its starting position, but allowing an unobstructed view of the targets and terminal errors. The coordinates of the touch responses were recorded.

Immediately after ending the adaptation phase (either PA or SA), the aftereffect of adaptation was measured. The goggles were removed and patients were instructed to look at the central visual target. After a few seconds, patients had to point to the central target with closed eyes to prevent online adjustment of the pointing movement due to visual feedback. For successful PA, a contralesional shift of  $\pm 3$ cm from the target was required. For patients in the PA group, the procedure was repeated once with  $\pm 50$  pointing movements when the aftereffect was less than 3cm.<sup>1</sup>

The treatment was performed in the rehabilitation centre once a day, each working day, for two weeks in addition to usual care. Usual care differed per patient, and contained  $\pm 4-6$  therapy's (e.g. physical, occupational, speech; 30-60 min) per working day. Neglect treatment consisted of psycho-education and visual scanning training (i.e. search tasks and

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<sup>1</sup> In the PA group, 12 patients obtained an aftereffect of less than 3cm in  $>50\%$  of sessions (despite the 50 additional pointing movements). In the SA group, 1 patient pointed more than 3cm next to the target in  $>50\%$  of sessions.



reading), 1-hr per week, 1-6 weeks (3 on average). In addition, during the other therapies and during ALD, patients were occasionally stimulated to attend their neglected side.

### *Randomisation*

Before the start of the study, the investigator put 70 printed cards with the treatment condition (35 PA and 35 SA) in envelopes. After completion of the baseline assessment, the investigator opened an envelope and allocated the patient based on the treatment written on the card.

### *Primary outcome*

The CBS is an observation scale for neglect behaviour in ADL.<sup>33,36</sup> Neglect severity was scored for each of 10 items on a scale of 0 (no neglect) to 3 (severe neglect) by a nurse, physical therapist and occupational therapist. Items that were impossible to score (e.g. because patients were unable to independently perform the activity, or the situation was not observed) were considered invalid and were not included in the total score. For the first four items, the score provided by the nurse was used, for the last six items, the average score of the three disciplines was used. The total score was the sum of the (weighted) item scores, divided by the number of valid items, multiplied by 10 (resulting in a total score ranging from 0 to 30).<sup>33,36</sup> In case five items or less were observed, the total score was considered not reliable, and therefore a missing value.

### *Secondary outcomes*

*Dynamic task - MAC.* Patients were instructed to walk or navigate their wheelchair independently at a leisurely pace through a corridor, without stopping or turning back (see Ten Brink et al.<sup>25</sup> for a detailed description). Meanwhile, patients had to point out targets (12 per side, yellow, 10x10cm). It was emphasized that there was no time limit, and finding all

targets was the main goal. Task assessment lasted approximately 5 minutes. The asymmetry score was computed as the absolute difference between the number of omissions left versus right.

*Static task - SC.* The SC consisted of 54 small targets, 52 large distractors, and 23 words and letters.<sup>35</sup> Patients were instructed to cancel all targets. No time limit was given. The absolute difference in the number of omissions between the left and right side of the stimulus field (asymmetry score) was computed.

#### *Patient characteristics*

We reviewed the patient's medical record and captured demographic (age, gender) and stroke related characteristics (date stroke, stroke history, stroke type, lesion side). Global cognitive functioning was screened with either the Mini-Mental State Examination (MMSE)<sup>37</sup> or the Montreal Cognitive Assessment (MoCA).<sup>38</sup> We converted MMSE scores into MoCA scores to create a single, pooled MoCA score  $([1.124 * \text{MMSE}] - 8.165)$ .<sup>39</sup> Quality of communication was determined with the 'Stichting Afasie Nederland' test (SAN),<sup>40</sup> an observation scale for language communication. Muscle strength was measured by the Motricity Index, a short task to assess the loss of strength in the arm and leg.<sup>41</sup> Independence in ADL was assessed using the Barthel Index.<sup>42</sup> Independence in walking was evaluated with the Functional Ambulation Categories (FAC).<sup>43</sup>

#### *Data analyses*

*Power.* An effect size of 0.70 standard deviations was used to estimate the necessary sample size. To identify a difference with a power of 80% and alpha .05 (2-sided), 35 patients per group (70 patients in total) were required for sufficient statistical power.<sup>32</sup>

*Demographic and stroke related characteristics.* Non-parametric Mann-Whitney and Chi-square tests were used to compare demographic and stroke related characteristics between groups. Baseline neglect variables were compared with a *t*-test when data was normally distributed, and with a Mann-Whitney test when data were not normally distributed.

*Outcome analyses.* The analyses were conducted by the available-case, intention-to-treat method; that is, all data were included in the analysis, and the data were analysed with all patients remaining in the treatment group in which they were initially randomised. A linear mixed effects model analysis was performed in IBM SPSS Statistics version 23<sup>44</sup> for each outcome measure separately. We choose this approach as it is appropriate for repeated measures in a heterogeneous group, the variable ‘time’ is treated as a continuous measure (which is an advantage since intervals differed between measurements), patients with missing data are included, and covariates can be introduced.<sup>45</sup> The linear mixed effects model used a heterogeneous first-order autoregressive covariance structure and included a random intercept for each patient. Missing data were handled by a maximum likelihood algorithm under the assumption that the missingness was random. The predictors of theoretical interest were the effects of time and group, and the interaction between time and group. These predictors were included in the basic model. The quadratic relation of time, baseline score, number of days post-stroke, gender, and age were introduced as potential covariates (fixed effects). This was regardless whether or not these variables differed between groups, to enhance the fit of the model. To statistically compare the fit of each new model with the old model, the change in -2 log-likelihood ( $\chi^2_{\text{Change}} = -2LL_{\text{old}} - -2LL_{\text{new}}$ ) was assessed in light of the number of additional parameters ( $df_{\text{Change}} = k_{\text{Old}} - k_{\text{New}}$ ).<sup>46</sup> The coefficients of the best performing model were

reported (thus, the included covariates could differ between final models, depending on their significance). Significance was set to  $p = .05$ .

Secondary analyses were performed in subgroups of patients with right-sided brain damage and moderate to severe neglect on the given task (resulting in different subgroups per task), to compare current results to prior studies and to correct for possible ceiling effects in the outcome measures. Moderate to severe neglect was defined as a CBS baseline score of  $\geq 7$ ,<sup>16</sup> MAC asymmetry score of  $\geq 3$ ,<sup>25</sup> and SC asymmetry score of  $\geq 4$ .<sup>24</sup> Finally, analyses were repeated with the size of the absolute aftereffect (average of all sessions) as factor, instead of group.

## ***Results***

### *Patient characteristics*

Recruitment to the trial was carried out from November 2013 to November 2016, the final follow-up measurement took place March 2017. A total of 581 stroke patients were admitted to the rehabilitation wards during the period of recruitment (Figure 1). 70 Patients were included in the study, of which one patient quit during the baseline measurement and was not randomised nor treated. Two patients in the PA group did not complete the treatment due to illness or early discharge (both after five sessions).

The groups were comparable with respect to patient characteristics (Table 1; see Supplementary Table 1 for characteristics of patients with right brain damage). As patients could be included based on abnormal performance on one of neglect tasks (Supplementary Table 2), not all patients showed neglect on all outcome measures when they entered the trial. SC scores at baseline were not normally distributed, so a non-parametric test was used. Overall, scores on neglect measures at baseline were comparable between groups. Raw mean scores for separate patient groups (i.e. overall group, right-sided lesions, and left-sided

lesions) are depicted in Table 2. Within the right-sided lesions group, patients in the SA group obtained higher baseline CBS scores compared to patients in the PA group.

*Primary outcome: influence of PA on basic ADL*

CBS scores could not be obtained after 14 weeks, as most patients were discharged home. The final model included baseline score, days post-stroke and gender as confounders (Table 3). Overall, CBS scores improved over time [ $F(1, 239) = 38.90, p < .001$ ]. There was no main effect of experimental condition [ $F(1, 148) = 2.54, p = .113$ ], indicating that the effects of PA and SA on the CBS scores were comparable. Additionally, no interaction effect [ $F(1, 239) = 2.28, p = .133$ ] was observed, indicating that the pattern of improvement through time was comparable for PA and SA (Figure 2).

Sub-analyses for patients with right-sided brain damage and moderate to severe neglect ( $n = 21$  in the PA group,  $n = 21$  in the SA group), and with aftereffect as factor, resulted in similar findings (Supplementary Table 3-4).

*Secondary outcomes: influence of PA on lateralized attention*

The final model for the **MAC** included the confounder baseline score (Table 4). Overall, patients improved over time regarding MAC scores [ $F(1, 110) = 17.53, p < .001$ ]. No effect of experimental condition was found [ $F(1, 129) = 0.70, p = .406$ ], indicating that the effects of PA and SA on the MAC scores were comparable. In addition, no interaction effect was seen [ $F(1, 110) = 0.04, p = .851$ ], indicating that the pattern of improvement on MAC scores through time was comparable between groups. Comparable results were obtained when analyses were performed for patients with right-sided brain damage and moderate to severe neglect ( $n = 15$  in the PA group,  $n = 20$  in the SA group), and with aftereffect as factor (Supplementary Table 5-6).

The final model for the SC included the confounder baseline score (Table 5). Overall, scores on the SC improved over time [ $F(1, 311) = 15.57, p < .001$ ]. There was no effect of group [ $F(1, 105) = 0.19, p = .661$ ], indicating that SC scores did not differ between patients who received PA compared to SA. Furthermore, no interaction effect was seen [ $F(1, 311) = 3.65, p = .057$ ], indicating that PA and SA had no differential effects on the pattern of improvement. Similar results were found when analyses were performed for patients with right-sided brain damage and moderate to severe neglect ( $n = 12$  in the PA group,  $n = 14$  in the SA group), and with aftereffect as factor (Supplementary Table 7-8).

### ***Discussion***

In the current study, 69 stroke patients received ten sessions of either PA or SA during their admission for inpatient rehabilitation. We measured neglect behaviour in situations of varying complexity. Overall, a time-dependent improvement of neglect behaviour was observed on all measures (i.e. CBS, MAC and SC), but no differences were found between PA and SA groups. Comparable results were found when we subsequently performed sub-analyses including only patients with moderate to severe neglect and right hemisphere lesions, or with aftereffect as a factor.

How do these results relate to earlier findings? We evaluated five RCT's (of which two recent),<sup>22,24</sup> that were comparable to ours regarding the time post-stroke onset (1-2 months on average), intensity of the treatment (4 to 20 sessions) and inclusion of a control group (SA).<sup>13,16,19,22,24</sup> Only two of these used the CBS to measure neglect behaviour in ADL. In these studies, no beneficial effects of PA over SA were reported.<sup>16,19</sup> These results should, however, be interpreted with caution, as it was estimated by Turton and colleagues<sup>16</sup> that inclusion of at least 32 patients in total is necessary in order to observe clinically relevant treatment effects on the CBS, which was not the case in these studies. In our study –with a

larger sample of patients ( $n = 69$ )– , however, no treatment effects were found either. Two prior studies used the Functional Independence Measure. Here, long-term positive effects of PA were seen in one study (for mild neglect only),<sup>19</sup> but not in another.<sup>22</sup> Although all early studies (including ours) reported improvement in basic ADL over time, it is uncertain to what extent this change is related to an actual improvement of the core deficit in neglect: lateralized inattention. As only basic activities are observed, improvement could relate to the use of compensatory strategies, especially since many of these basic activities are practiced daily during inpatient rehabilitation. In all five studies, the lateralized attention deficit was measured with (different) neuropsychological neglect tasks. In general (with the exception of positive findings on few tasks), no beneficial effects of PA were found directly after treatment<sup>16,19</sup> or during follow-up compared to SA.<sup>13,16,19,22,24</sup> With cancellation tasks, in which no time limit is provided, compensation strategies are quite easily incorporated. Results on dynamic multitasks in a daily life environment, such as the MAC in our RCT, have not been reported yet. Visual search while moving (MAC) is not used in daily routines, such as basic ADL, and it is more dynamic in nature compared to neuropsychological tests.<sup>25</sup> Nevertheless, no difference was seen between groups on MAC performance in the current study. As it is a fairly new test, it remains to be seen to what extent this task is insensitive to compensation strategies or leaves less room for compensation. In sum, in most *early onset* RCT's, little beneficial effects of PA over SA are reported. This is in sharp contrast with the RCT's in the later and/or chronic phase, in which positive effects of PA compared to SA (or no treatment) were reported on at least one outcome measure in all studies,<sup>9–11,14,17,18</sup> but one.<sup>20</sup> Note that this is a rough comparison, as studies differed regarding treatment characteristics, such as intensity. Looking at studies with low (1 session in total)<sup>9,11,47</sup> versus high (5 sessions per week)<sup>16,20</sup> intensity does, however, not suggest that a higher intensity results in better outcome.

It has been argued that SA (the control treatment) is a form of visuomotor training and could, therefore, also diminish neglect.<sup>18</sup> The SA procedure requires the patient to plan and perform a series of movements toward stimuli in the ipsilesional and contralesional field. Half of the movements (i.e. towards contralesional stimuli) might train the orientation of the sensorimotor system towards the neglected side. The study of Serino et al.,<sup>14</sup> however, indicated that patients wearing sham goggles improved only a little, while their performance on neuropsychological tests greatly improved when they subsequently received PA. In several other studies, no improvement was found in the SA group while the PA group improved.<sup>9,11,17</sup> It seems, therefore, more likely that other factors lead to recovery of patients receiving SA.

Timing of treatment, therefore, seems to be the crucial factor for significant beneficial effects of PA. In the first 3 months post-stroke, a neglect patient group is more heterogeneous compared to a later stage. There are two important mechanisms that may enhance the heterogeneity: first, spontaneous neurobiological recovery in the first 3 months post-stroke onset is variable between patients.<sup>4,48</sup> About half of patients with neglect in the first week post-stroke, does not show neglect as measured with a cancellation task 12 weeks later.<sup>4</sup> Second, treatment responsiveness on the existing multidisciplinary rehabilitation program could differ between patients. Especially the visual scanning training may have the largest impact on the use of compensation strategies to avoid impairment during (simple) activities in daily living due to the lateralized attention deficit (see above). In the chronic phase, therefore, the group is more homogeneous compared to the early phase, as the quick-recovering patients are not included.

Evaluating intervention effects (of PA or other interventions) for neglect on a group level in such a heterogeneous group might not be the most appropriate approach. Future studies should focus on tracing factors that determine individual differences between patients (e.g. data-driven [cluster] analyses), hence patterns of recovery at subgroup level (e.g. van



Mierlo et al.<sup>49</sup>). Subsequently, the choice of treatment could be based on this knowledge (several examples exist in literature on drug treatment<sup>50</sup>). Such studies are needed in rehabilitation research too, as data-driven analyses allow the generation of new hypotheses. This is necessary, as the current approach has not resulted in evidence -or only to a limited extent- on beneficial effects of neglect treatment in the subacute phase post-stroke onset.

Contrary, a theory-driven approach could be used to diminish heterogeneity of the syndrome, when the focus of the study is aimed at specific subtypes of neglect, such as region specific neglect,<sup>34,51</sup> or distinctions between perceptual awareness versus neglect in action planning and execution.<sup>26,52</sup> In addition, patients who are likely to benefit from PA could be differentiated based on brain properties. Lesion data or data regarding brain networks could be used into both a theory-driven approach, as different neglect subtypes likely have a different neuroanatomical basis, as well as a data-driven approach, based on patterns of recovery in patients with different lesion locations.<sup>12,53-55</sup> For example, lesions in the cerebellum,<sup>54</sup> or (wide) lesions in the occipital lobe<sup>12</sup> seem to limit the effect of PA. Notwithstanding the theoretical importance of such distinctions, analysing smaller subgroups was currently not feasible statistically. Future trials should include measures that allow differentiation between such subtypes and/or lesion sites to reveal which patients benefit from the studied treatment.

Finally, since neglect is a multifaceted disorder, the best treatment might involve combinations of different therapeutic techniques.<sup>56,57</sup> A review study regarding this topic concluded that combined treatments led to larger beneficial effects compared to individual treatments (the phase of treatment was not specified).<sup>47</sup> However, more basic knowledge on the best timing of neglect treatment and individual recovery patterns is needed first to aid the development of evidence-based tailored treatment.

### ***Strengths and limitations***

A large number of neglect patients was included and almost no patients dropped out during treatment or were lost to follow-up. This can be considered a strength, as the treatment should eventually be integrated within the current rehabilitation program. This was the first study in which patients with right-sided neglect after left hemisphere lesions were included. The strength of the study (i.e. all neglect patients in the subacute phase were included) is, however, at the same time a limitation, as the heterogeneity of the group could have prevented us from finding (subtle) effects of PA. Patients were tested only for neglect, thus, visual field defects were not detected. Positive effects of PA on neglect in patients with comorbid hemianopia, however, have been reported.<sup>13</sup> In addition, as patients were randomized, we did not expect comorbid visual field defects to affect our results.

An important drawback of a study that is performed as part of an existing rehabilitation programme is the lack of control regarding other treatments. In the current rehabilitation centre, neglect treatment consisted of 1 hr of visual scanning training per week, in combination with efforts made by the complete team during every day, throughout the admission (e.g., physical and occupational therapists, as well as nursing staff trying to enhance attention for the neglected side). The intensity of the usual care might therefore differ between individual patients, depending on the severity of neglect and treatment sessions (physical, occupational, etc.) per day. At group level, however, estimations are that the groups received largely comparable amounts of neglect training and feedback on a daily basis.

A final limitation is the difference between SA and PA groups at baseline, for patients with right-sided lesions. Patients in the SA group obtained higher CBS scores (indicating more severe neglect) compared to patients in the PA group. SA patients had, therefore, more ‘potential of rehabilitation’, which could, possibly, have affected our results. In order to minimize this effect, we have corrected for baseline score in our models.

## ***Conclusions***

No time-dependent beneficial effects were found in a large sample of neglect patients after PA compared to SA, in the subacute phase post-stroke. Possibly, PA is no effective treatment for neglect in the subacute phase. It could, however, also relate to the heterogeneity of the neglect syndrome, enhanced by neurobiological recovery or standard treatment effects. To conclude, we found no evidence that PA should replace the current treatment for neglect in the subacute phase post-stroke.

## ***Conflict of Interest Statement***

The authors declare that there is no conflict of interest.

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**Table 1.** Median (IQR) demographic and stroke related characteristics at admission, and mean (SD) neglect variables at baseline, split per group.<sup>1</sup>

	<i>n</i>	PA	<i>n</i>	SA	Comparison
		<i>Median (IQR)</i>		<i>Median (IQR)</i>	
Age, years	34	59.31 (14.45)	35	61.48 (13.37)	$U = 594.0, z = -0.012, p = .990$
Sex, % man	34	74	35	69	$\chi^2(1, N = 69) = 0.21, p = .650$
Time post-stroke onset (at baseline), days	34	41.50 (39.00)	35	37.00 (37.00)	$U = 566.0, z = -0.348, p = .728$
Length of stay, days	34	89.50 (55.00)	35	99.00 (50.00)	$U = 497.5, z = -1.170, p = .242$
Stroke history, % first	32	84	29	90	$\chi^2(1, N = 61) = 0.37, p = .542$
Stroke type, %	28		29		$\chi^2(1, N = 57) = 1.23, p = .541$
- Ischemic		68		76	
- Intracerebral haemorrhage		29		17	
- Subarachnoid haemorrhage		4		7	
Lesion side, %	34		33		$\chi^2(1, N = 67) = 0.40, p = .819$
- Left		21		21	
- Right		77		73	
- Bilateral		3		6	
Neglect side, % left	34	82	35	77	$\chi^2(1, N = 69) = 0.29, p = .591$
MoCA (0-30)	27	19.94 (6.80)	29	18.81 (5.60)	$U = 383.0, z = -0.140, p = .889$
SAN (1-7)	28	6.00 (2.00)	32	6.00 (2.40)	$U = 389.5, z = -0.905, p = .366$
Barthel Index (0-20)	28	7.75 (6.00)	32	7.00 (7.00)	$U = 409.0, z = -0.579, p = .562$
Motricity Index arm (0-100)	25	39.00 (76.00)	28	0.00 (75.00)	$U = 312.5, z = -0.712, p = .476$
Motricity Index leg (0-100)	26	72.00 (83.00)	29	52.00 (75.00)	$U = 345.5, z = -0.542, p = .588$
Functional Ambulation Categories (0-5)	33	2.50 (2.00)	35	3.00 (1.50)	$U = 536.5, z = -0.512, p = .609$
<i>Neglect variables at baseline</i>					
SC, absolute asymmetry	34	2 (7)	35	1 (12)	$U = 577.5, z = -0.214, p = .831$
		<i>Mean (SD)</i>		<i>Mean (SD)</i>	
CBS	34	12.83 (6.62)	34	15.43 (7.54)	$t(66) = -1.51, p = .136$
MAC, absolute asymmetry	33	3.91 (3.52)	33	5.30 (3.49)	$t(64) = -1.61, p = .112$

Abbreviations: CBS, Catherine Bergego Scale; IQR, interquartile range; MAC, Mobility

Assessment Course; MoCA, Montreal Cognitive Assessment; PA, prism adaptation; SA,

sham adaptation; SAN, Stichting Afasie Nederland; SC, shape cancellation task.

<sup>1</sup>Group sizes differ among measures due to missing data.



**Table 2.** Mean (SD) neglect scores per week, split for experimental group and lesion side.<sup>1</sup>

	Group	Week 0		Week 1		Week 2		Week 3		Week 4		Week 6		Week 14	
		n	M (SD)	n	M (SD)	n	M (SD)	n	M (SD)	n	M (SD)	n	M (SD)	n	M (SD)
<u>CBS</u>															
<i>Overall group</i>	PA	34	12.83 (6.62)	30	12.19 (6.03)	29	11.74 (6.46)	28	10.22 (6.00)	29	9.02 (5.54)	28	9.46 (5.46)	-	-
	SA	34	15.43 (7.54)	35	12.31 (8.26)	34	11.97 (8.34)	33	11.68 (7.88)	32	10.88 (7.25)	30	11.04 (7.94)	-	-
<i>Right-sided lesions</i>	PA	26	13.76 (6.70)*	22	13.38 (5.81)	21	12.92 (6.02)	20	11.84 (5.38)	21	10.41 (4.84)	21	10.53 (4.93)	-	-
	SA	23	18.08 (7.23)	24	15.03 (8.06)	23	14.01 (8.45)	24	13.46 (7.91)	22	12.91 (7.42)	21	13.53 (8.06)	-	-
<i>Left-sided lesions</i>	PA	7	8.45 (4.55)	7	7.61 (4.74)	7	6.39 (3.20)	7	4.31 (2.82)	7	3.64 (3.48)	6	4.21 (3.01)	-	-
	SA	7	10.86 (5.02)	7	8.07 (5.08)	7	7.60 (5.94)	6	6.87 (6.00)	7	6.36 (4.14)	7	4.87 (2.33)	-	-
<u>MAC, absolute asymmetry</u>															
<i>Overall group</i>	PA	33	3.91 (3.52)	-	-	29	3.94 (3.26)	-	-	27	3.27 (3.07)	-	-	21	2.51 (2.28)
	SA	33	5.30 (3.49)	-	-	34	4.12 (3.61)	-	-	30	4.53 (3.46)	-	-	28	3.03 (2.67)
<i>Right-sided lesions</i>	PA	25	4.48 (3.64)	-	-	22	4.74 (3.27)	-	-	21	3.91 (3.18)	-	-	17	2.99 (2.27)
	SA	24	6.12 (3.18)	-	-	24	5.13 (3.38)	-	-	22	5.41 (3.39)	-	-	19	3.73 (2.47)
<i>Left-sided lesions</i>	PA	7	1.29 (0.95)	-	-	7	1.43 (1.51)	-	-	6	1.03 (0.94)	-	-	4	0.50 (0.58)
	SA	5	3.69 (4.52)	-	-	6	1.99 (3.95)	-	-	6	2.17 (2.86)	-	-	6	1.33 (2.80)
<u>SC, absolute asymmetry</u>															
<i>Overall group</i>	PA	34	4.56 (5.72)	34	3.41 (5.05)	31	4.03 (6.66)	29	3.10 (4.91)	28	2.50 (3.93)	29	3.03 (4.79)	22	1.14 (1.98)
	SA	35	6.31 (8.41)	35	5.80 (7.72)	35	4.63 (6.40)	34	4.53 (7.02)	32	4.06 (7.09)	33	2.85 (5.87)	32	2.16 (4.54)
<i>Right-sided lesions</i>	PA	26	5.08 (5.48)	26	3.62 (4.74)	24	5.17 (7.20)	22	4.00 (5.35)	22	3.05 (4.27)	23	3.74 (5.16)	18	1.28 (2.16)
	SA	24	8.75 (9.11)	24	8.00 (8.45)	24	6.33 (7.02)	24	6.08 (7.84)	23	5.13 (7.86)	23	3.87 (6.81)	22	3.00 (5.29)
<i>Left-sided lesions</i>	PA	7	0.57 (0.79)	7	0.57 (1.13)	7	0.14 (0.39)	7	0.29 (0.49)	6	0.50 (0.84)	6	0.33 (0.52)	4	0.50 (0.58)
	SA	7	1.43 (2.51)	7	1.14 (1.35)	7	0.86 (2.27)	7	1.00 (1.41)	7	1.57 (4.16)	7	0.57 (0.79)	7	0.43 (0.54)

Abbreviations: CBS, Catherine Bergego Scale; MAC, Mobility Assessment Course; PA, prism adaptation; SA, sham adaptation; SC, shape cancellation task.

<sup>1</sup>Group sizes differ among measures due to missing data. In addition, patients with bilateral lesions are not depicted separately (they are part of the overall group). \*Significant difference ( $p < .05$ ) between PA and SA groups at baseline (Week 0).



**Table 3.** Fixed-effect predictors and covariates for predicting the CBS total score across week 1 to 6 ( $n = 69$ ).

Predictor	$\beta$	SE $\beta$	95% CI	$p$
Group (PA) <sup>1</sup>	1.81	1.14	-0.44 to 4.05	.113
Time	-0.53	-0.16	-0.83 to -0.22	.001
Time * Group	-0.34	0.22	-0.78 to 0.10	.133
Baseline CBS	0.74	0.06	0.61 to 0.86	< .001
Days post-stroke	0.04	0.02	0.00 to 0.07	.024
Gender (male)	-1.98	0.98	-3.92 to -0.02	.047

Abbreviations: CBS, Catherine Bergego Scale; PA, prism adaptation.

<sup>1</sup>The Beta coefficient for the predictor ‘Group’ indicates that the predicted CBS score is on average 1.81 points higher for the PA group compared to the SA group, although this effect is not significant.

**Table 4.** Fixed-effect predictors and covariates for predicting the MAC asymmetry score across assessment in week 2, 4 and 14 ( $n = 69$ ).

Predictor	$\beta$	SE $_{\beta}$	95% CI	$p$
Group (PA) <sup>1</sup>	0.45	0.54	-0.62 to 1.53	.406
Time	-0.11	0.04	-0.18 to -0.04	.003
Time * Group	-0.01	0.06	-0.12 to 0.10	.851
Baseline MAC	0.65	0.06	0.53 to 0.77	< .001

Abbreviations: MAC, Mobility Assessment Course; PA, prism adaptation.

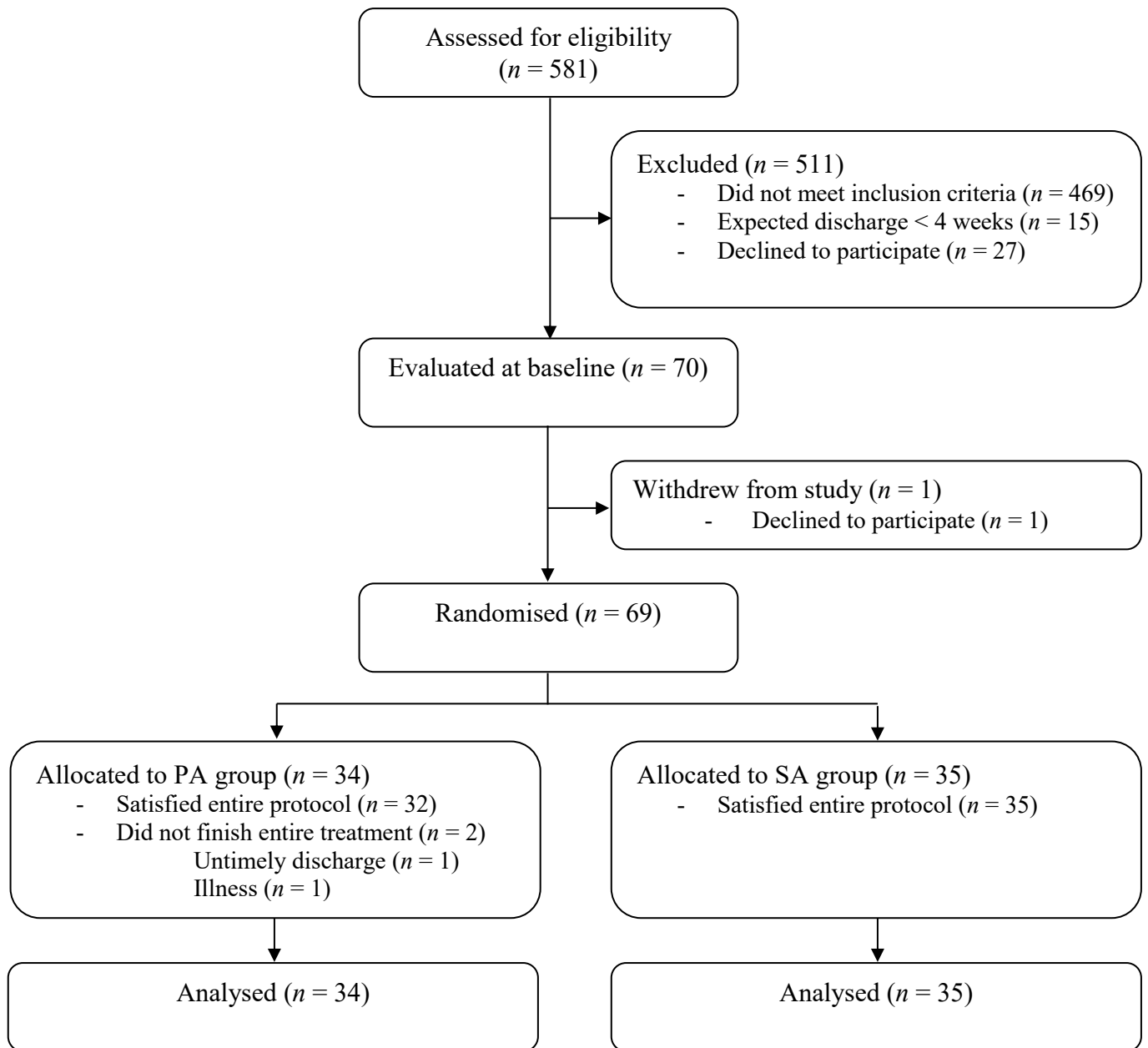
<sup>1</sup>The Beta coefficient for the predictor ‘Group’ indicates that the predicted MAC asymmetry score is on average 0.45 points higher for the PA group compared to the SA group, although this effect is not significant.

**Table 5.** Fixed-effect predictors and covariates for predicting the SC asymmetry score across week 1 to 14 ( $n = 69$ ).

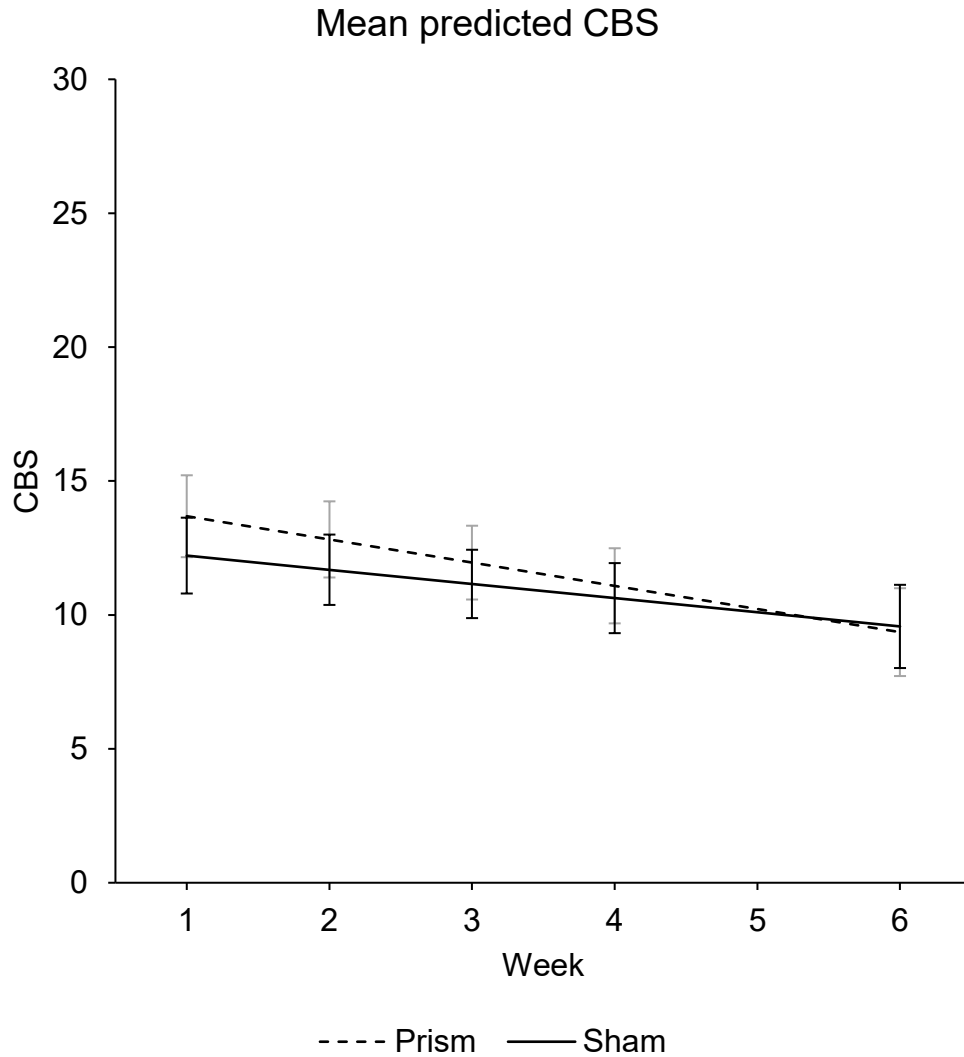
Predictor	$\beta$	$SE_{\beta}$	95% CI	$p$
Group (PA) <sup>1</sup>	-0.42	0.95	-2.29 to 1.46	.661
Time	-0.27	0.06	-0.38 to -0.15	< .001
Time * Group	0.17	0.09	-0.01 to 0.35	.057
Baseline SC	0.50	0.06	0.38 to 0.62	< .001

Abbreviations: PA, prism adaptation; SC, shape cancellation task.

<sup>1</sup>The Beta coefficient for the predictor ‘Group’ indicates that the predicted SC asymmetry score is on average 0.42 points lower for the PA group compared to the SA group, although this effect is not significant.



**Figure 1.** Participant flow through the study.



**Figure 2.** The average model predicted CBS scores and confidence intervals across assessment sessions for each group: PA (dashed line) and SA (solid line). The assessment session in week 1 occurred after one week of treatment and the assessment session in week 2 occurred after two weeks of treatment. Lower scores indicate less severe neglect. Note that scores were corrected for the confounders in the model, including the baseline CBS score. The linear mixed effects model analysis takes into account the underlying model of the data, correcting for covariates (e.g. baseline score and days post-stroke) and missing data, therefore, reporting these data points are preferred over observed means.

Abbreviations: CBS, Catherine Bergego Scale, PA, prism adaptation; SA, sham adaptation.

**Supplementary Table 1.** Median (IQR) demographic and stroke related characteristics at admission, for right brain damaged patients only, split per group.<sup>1</sup>

	<i>n</i>	PA	<i>n</i>	SA	Comparison
Age, years	26	61.46 (12.49)	24	62.09 (13.04)	$U = 304.0, z = -0.155, p = .877$
Sex, % man	26	73.1	24	62.5	$\chi^2(1, N = 50) = 0.64, p = .423$
Time post-stroke onset (at baseline), days	26	41.50 (45.00)	24	43.50 (39)	$U = 308.0, z = -0.078, p = .938$
Length of stay, days	26	85.50 (70.00)	24	108.50 (49.00)	$U = 231.5, z = -1.563, p = .188$
Stroke history, % first	24	87.5	20	85.0	$\chi^2(1, N = 44) = 0.06, p = .810$
Stroke type, %	23		19		$\chi^2(1, N = 42) = 0.66, p = .720$
- Ischemic		69.6		78.9	
- Intracerebral haemorrhage		26.1		15.8	
- Subarachnoid haemorrhage		4.3		5.3	
Neglect side, % left	26	100	24	100	-
MoCA (0-30)	21	21.00 (6.40)	22	18.81 (6.00)	$U = 193.5, z = -0.913, p = .361$
SAN (1-7)	22	6.00 (1.30)	21	6.00 (2.00)	$U = 214.0, z = -0.437, p = .662$
Barthel Index (0-20)	21	8.00 (7.00)	22	6.25 (7.00)	$U = 173.0, z = -1.412, p = .158$
Motricity Index arm (0-100)	18	66.50 (80.80)	18	7.00 (56.50)	$U = 119.0, z = -1.414, p = .157$
Motricity Index leg (0-100)	19	75.00 (74.00)	18	52.00 (75.00)	$U = 142.0, z = -0.901, p = .368$
Functional Ambulation Categories (0-5)	25	3.00 (2.30)	24	2.75 (2.00)	$U = 253.5, z = -0.942, p = .346$

Abbreviations: IQR, interquartile range; MoCA, Montreal Cognitive Assessment; PA, prism

adaptation; SA, sham adaptation; SAN, Stichting Afasie Nederland.

<sup>1</sup>Group sizes differ among measures due to missing data.



**Supplementary Table 2.** Percentage of patients with abnormal performance on neglect measures, administered during the neglect screening.

<b>Task</b>	<b>Overall group (<i>N</i> = 69)</b>	<b>Right-sided lesions (<i>n</i> = 50)</b>	<b>Left-sided lesions (<i>n</i> = 14)</b>
CBS only	29.0	20.0	50.0
SC only	0.0	0.0	0.0
LB only	1.4	2.0	0.0
CBS and SC	18.8	20.0	21.4
CBS and LB	13.0	10.0	21.4
SC and LB	1.4	2.0	0.0
CBS, SC and LB	36.2	46.0	7.1

Abbreviations: CBS, Catherine Bergego Scale; LB, line bisection task; SC, shape cancellation task.

**Supplementary Table 3.** Fixed-effect predictors and covariates for predicting the CBS across week 1 to 6, including patients with neglect at baseline (CBS  $\geq$  7) and right hemispherical damage ( $n = 42$ ).

Predictor	$\beta$	SE $_{\beta}$	95% CI	$p$
Group (PA) <sup>1</sup>	1.77	1.58	-1.36 to 4.89	.265
Time	-0.59	0.22	-1.04 to -0.14	.009
Time * Group	-0.35	0.32	-0.98 to 0.29	.281
Baseline CBS	0.85	0.11	0.63 to 1.06	< .001
Days post-stroke	0.04	0.02	0.00 to 0.07	.049
Gender (male)	-2.22	1.28	-4.81 to 0.36	.090

Note.  $n = 21$  in the PA group,  $n = 21$  in the SA group.

Abbreviations: CBS, Catherine Bergego Scale, PA, prism adaptation; SA, sham adaptation.

<sup>1</sup>The Beta coefficient for the predictor ‘Group’ indicates that the predicted CBS score is on average 1.77 points higher for the PA group compared to the SA group, although this effect is not significant.

**Supplementary Table 4.** Fixed-effect predictors and covariates for predicting the CBS across week 1 to 6, including the variable aftereffect instead of group ( $n = 69$ ).

Predictor	$\beta$	SE $_{\beta}$	95% CI	$p$
Aftereffect in mm	0.03	0.03	-0.03 to 0.09	.287
Time	-0.68	0.11	-0.91 to -0.46	< .001
Baseline CBS	0.74	0.06	0.62 to 0.87	< .001
Days post-stroke	0.03	0.02	0.00 to 0.06	.027
Gender (male)	-1.79	0.96	-3.71 to 0.13	.068

Abbreviations: CBS, Catherine Bergego Scale.

**Supplementary Table 5.** Fixed-effect predictors and covariates for predicting the MAC asymmetry score across week 2, 4 and 14, including patients with neglect at baseline (asymmetry score  $\geq 3$ ) and right hemispherical damage ( $n = 35$ ).

Predictor	$\beta$	$SE_{\beta}$	95% CI	$p$
Group (PA) <sup>1</sup>	0.15	0.84	-1.52 to 1.83	.856
Time	-0.16	0.05	-0.27 to -0.05	.005
Time * Group	-0.04	0.09	-0.22 to 0.14	.660
Baseline MAC	0.58	0.14	0.30 to 0.86	< .001

Note.  $N = 15$  in the PA group,  $N = 20$  in the SA group.

Abbreviations: MAC, Mobility Assessment Course, PA, prism adaptation; SA, sham adaptation.

<sup>1</sup>The Beta coefficient for the predictor ‘Group’ indicates that the predicted MAC asymmetry score is on average 0.15 points higher for the PA group compared to the SA group, although this effect is not significant.

**Supplementary Table 6.** Fixed-effect predictors and covariates for predicting the MAC asymmetry score across week 2, 4 and 14, including the variable aftereffect instead of group ( $n = 69$ ).

Predictor	$\beta$	$SE_{\beta}$	95% CI	$p$
Aftereffect in mm	-0.01	0.01	-0.04 to 0.02	.539
Time	-0.13	0.03	-0.18 to -0.07	< .001
Baseline MAC	0.65	0.06	0.53 to 0.77	< .001

Abbreviations: MAC, Mobility Assessment Course.

**Supplementary Table 7.** Fixed-effect predictors and covariates for predicting the SC asymmetry score across week 1 to 14, including patients with neglect at baseline (asymmetry score  $\geq 4$ ) and right hemispherical damage ( $n = 26$ ).

Predictor	$\beta$	$SE_{\beta}$	95% CI	$p$
Group (PA) <sup>1</sup>	-0.13	2.41	-5.01 to 4.75	.958
Time	-0.51	0.13	-0.77 to -0.24	< .001
Time * Group	0.12	0.23	-0.34 to 0.57	.605
Baseline SC	0.30	0.16	-0.03 to 0.64	.075

Note.  $n = 12$  in the PA group,  $n = 14$  in the SA group.

Abbreviations: PA, prism adaptation; SA, sham adaptation; SC, shape cancellation task.

<sup>1</sup>The Beta coefficient for the predictor ‘Group’ indicates that the predicted SC asymmetry score is on average 0.13 points lower for the PA group compared to the SA group, although this effect is not significant.

**Supplementary Table 8.** Fixed-effect predictors and covariates for predicting the SC asymmetry score across week 1 to 14, including the variable aftereffect instead of group ( $n = 69$ ).

Predictor	$\beta$	$SE_{\beta}$	95% CI	$p$
Aftereffect in mm	0.02	0.03	-0.04 to 0.07	.519
Time	-0.20	0.05	-0.29 to -0.11	< .001
Baseline SC	0.49	0.06	0.38 to 0.61	< .001

Abbreviations: SC, shape cancellation task.