

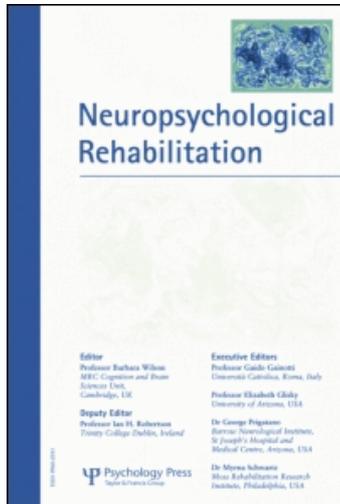
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Styrmir Saevarsson^{abc}; Árni Kristjánsson^{bd}; Ulrike Halsband^a

^a Department Neuropsychology, University of Freiburg, Germany ^b Faculty of Psychology, School of Health Sciences, University of Iceland, Iceland ^c Center for Advanced Brain Imaging, Georgia Institute of Technology & Georgia State University, USA ^d Institute of Cognitive Neuroscience, University College, London, UK

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Strength in numbers: Combining neck vibration and prism adaptation produces additive therapeutic effects in unilateral neglect

Styrmir Saevarsson^{1,2,3}, Árni Kristjánsson^{2,4}, and Ulrike Halsband¹

¹*Department Neuropsychology, University of Freiburg, Germany;* ²*Faculty of Psychology, School of Health Sciences, University of Iceland, Iceland;* ³*Center for Advanced Brain Imaging, Georgia Institute of Technology & Georgia State University, USA;* ⁴*Institute of Cognitive Neuroscience, University College, London, UK*

Unilateral neglect is a multifaceted disorder. Many authors have, for this reason, speculated that the best treatment for neglect will involve combinations of different therapeutic techniques. Two well-known interventions, neck vibration (NV) and prism adaptation (PA), have often been considered to be among the most effective treatments for neglect. Here, two experiments were performed to explore possible additive benefits when these interventions are used in combination to treat chronic neglect. Both experimental groups received NV for 20 minutes, while the second group received simultaneous PA. The effects of treatment were measured with a time-restricted and feedback-based visual search task, which has previously been found to abolish

Correspondence should be sent to Styrmir Saevarsson, Center for Advanced Brain Imaging, 831 Marietta St., Atlanta, GA 30332, USA. E-mail: saevarsson@gatech.edu

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the beneficial effects of PA, and with standard neglect tests. Baseline and intervention measures were performed on separate days. Findings for both groups indicated improved visual search following intervention, but the patients that underwent the combined intervention (NVPA) showed clear improvements on visual search paper and pencil neglect tests unlike the NV-only group. Overall, our results suggest that PA strengthens the effects of NV and that feedback-based tasks do not abolish the beneficial effects of PA, when NV is applied simultaneously. The results support the view that the most effective treatment for neglect will involve the combination of different treatments.

Keywords: Unilateral neglect; Prism adaptation; Neck vibration; Combined approach; Feedback.

INTRODUCTION

Unilateral neglect involves a number of different symptoms that vary greatly among patients. Patients suffering from neglect may fail to react to stimuli in their contralesional hemifield (Heilman, Valenstein, & Watson, 2003) and show abnormal visual search behaviour which is not confined to a single hemifield (Husain et al., 2001; Malhotra et al., 2005; but see Kristjánsson & Vuilleumier, in press). The symptoms can involve both motor deficits and impairments of visual imagery (Mesulam, 1981). In line with this, Danckert and Ferber (2006) have suggested that the neglect disorder involves a combination of different but interacting impairments of spatial working memory, attentional orienting and exploratory motor behaviour. Many others have speculated that neglect involves disrupted operation of a network for attentional orienting (e.g., Mesulam, 1981). The lesions that typically cause neglect are in the inferior parietal cortex, medial temporo-parietal junction (e.g., Mort et al., 2003; Vallar, 1993; Vallar & Perani, 1987) and superior temporal cortex (Karnath, Berger, Kuker, & Rorden, 2004; Karnath, Ferber, & Himmelbach, 2001) among other areas (e.g., Saevarsson, Kristjánsson, Hildebrandt, & Halsband, 2009a). All these brain regions have been shown to be parts of a network responsible for attentional orienting (Corbetta & Shulman, 2002; Geng et al., 2006; Kristjánsson, Vuilleumier, Schwartz, Macaluso, & Driver, 2007; Ruff, Kristjánsson, & Driver, 2007).

Recovery from neglect

Recovery from neglect can occur only a few days following stroke, or many years later, and neglect can in many cases be chronic (Martin, 2006). Stroke is currently one of the leading causes of human disability (Paul, Sturm, Dewey, Donnan, & Macdonell, 2005) and since neglect is a deficit that is observed in

about one out of every three stroke patients (Appelros, Karlsson, Seiger, & Nydevik, 2002; Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Pedersen, Jørgensen, Nakayama, Raaschou, & Olsen, 1997), it has a major impact on health services all over the world. Effective therapeutic treatments of neglect would therefore be of great value.

Assessment of neglect

Impaired visual search is one of the most common and important symptoms of neglect (e.g., Behrmann, Ebert, & Black, 2004; Husain et al., 2001, Kristjánsson & Vuilleumier, in press; Kristjánsson, Vuilleumier, Malhotra, Husain, & Driver, 2005; Saevarsson, Jóelsdóttir, Hjaltason, & Kristjánsson, 2008a). Many different types of visual search tasks have been found to be useful to assess neglect since they mimic, in many ways, the cognitive requirements of daily life. Standard neglect tests, such as line bisection, copy and free-hand drawing, or cancellation tasks, are also very useful because of their ease of use and their sensitivity to the different symptoms of neglect (e.g., Robertson & Halligan, 1999).

Therapy for neglect

Neglect therapy has seen rapid development over the last few decades despite limited understanding of the disorder's multimodal aetiology. Many different treatments have been developed but only a handful of interventions have, however, been found to be of value in treating the disorder. In a comprehensive review of the literature, Luauté, Halligan, Rode, Rossetti, and Boisson (2006a) recommended only six interventions that have been shown conclusively to result in the improvement of neglect. These include prism adaptation (PA) and neck vibration (NV) associated with an extensive exercise programme, visual scanning, mental imagery and video feedback training. Of those, PA and NV are probably the most extensively studied therapies for the disorder.

Neck vibration

Neck vibration has been explored extensively over the past three decades. In a pioneering study, Lackner and Levine (1979) showed, for healthy observers, how applying vibration to the posterior neck muscle produces a proprioceptive illusion of egocentric coordinates in space. Karnath, Christ, and Hartje (1993) reported how this illusion could be used to produce positive after-effects in neglect patients. Karnath, Fetter, and Dichgans (1996) argued that the improvement of neglect by manipulating neck, optokinetic and vestibular proprioceptive input is caused by general correction of the underlying neural transformation process (e.g., Gonshor & Jones, 1976a, 1976b, 1980; Karnath, Reich, Rorden, Fetter, & Driver, 2002; Lackner, 1988; Rorden,

Karnath, & Driver, 2001). This process converts the afferent input of the peripheral sensory organs into a body and ego-centric coordinate frame (Jeannerod & Biguer, 1987; Karnath & Dieterich, 2006). Two studies have indicated that NV, when applied repeatedly, produces long-lasting therapeutic benefits in neglect. Schindler, Kerkhoff, Karnath, Keller, and Goldenberg (2002) observed therapeutic effects of NV when the method was used in combination with conventional exploration training. Johannsen, Ackermann, and Karnath (2003) have shown similar effects with standard neglect tests when NV is used in isolation. As of yet little is known about the influence of feedback based tasks on NV effects, but feedback has sometimes been found to abolish therapeutical effects of prism adaptation on neglect (Morris, Kritikos, Berberovic, Pisella, Champers, & Mattingley, 2006; Saevarsson et al., 2009a; see further discussion below). One advantage of the neck vibration technique is that it is minimally dependent upon the patient's cooperation. It is also important to note that some patients seem to show no improvement following NV (Johannsen et al., 2003).

Prism adaptation

Prism adaptation has been studied since the 19th century (Helmholtz, 1962) while Ivo Kohler was, most likely, the first to study it systematically (Spillmann & Wooten, 1984). In the context of hemispatial neglect, Rossetti, Rode, Pisella, Farnè, and Boisson (1998) reported that right diverting prisms produced positive after-effects on neglect symptoms. A couple of studies have revealed longer-term (lasting for more than one day) beneficial effects following repeated application of PA (e.g., Frassinetti, Angeli, Meneghello, Avanzi, & Làdavas, 2002; Humphreys, Watelet, & Riddoch, 2006).

It has been suggested that visuo-motor adaptation following PA ameliorates pathological spatial reference frames, visuo-motor calibration, and higher order visuo-spatial representations (e.g., Danckert & Ferber, 2005; Redding & Wallace, 2006; Saevarsson, Kristjánsson, & Hjaltason, 2009b; Serino, Angeli, Frassinetti, & Làdavas, 2006). Probably the biggest drawback to PA is that the beneficial effects following treatment easily disappear, with high cognitive load, 1–2 hours after adaptation. Saevarsson et al. (2009a) also found that feedback and time restrictions in visual search abolished the beneficial effects of PA, while the effects lasted longer without trial-by-trial feedback upon response during the visual search task. The effects of prism adaptation have also been studied in relation to other interventions. The results of a pilot study, where PA and hemifield patching were simultaneously applied, suggest that the combined use of the two treatments produces additive therapeutic effects (Saevarsson, Kristjánsson, & Halsband, 2008b). On the other hand, Keller, Lefin-Rank, Löscher, and Kerkhoff (2009) reported results from another pilot study and found that when PA is

sequentially applied along with optokinetic stimulation (but critically not at the same time, in contrast to Saevarsson et al., 2008b), it produces less improvement than when optokinetic stimulation is applied on its own. These heterogeneous findings might, however, be explained by differences in therapeutic design since in the former the methods were applied simultaneously, while in the latter study the treatments were applied one after the other which may have caused fatigue and subsequently lessened any therapeutic improvements. Furthermore, similarly to other interventions, PA has not been found to help all neglect patients (see, e.g., Vuilleumier, 2007).

Targeting the different symptoms and mechanisms of neglect

Given the neglect syndromes' multifaceted nature, many authors have speculated that to maximise therapeutic effects, different interventions might be applied in combination (e.g., Kerkhoff, 2001; Rossetti & Rode, 2002; Saevarsson, Halsband, & Kristjánsson, 2010; Saevarsson et al., 2009b). For instance, if two effective neglect interventions are applied, which lead to different clinical effects and physiological changes, it would not be wild speculation to suggest that a treatment approach where the two are applied in combination would be more likely to produce more general beneficial effects compared to when they are used alone. Note, however, that the combined approach may not be optimal in all cases, if it, say, increases the patients' fatigue level, such as when two active interventions are used in combination. In such situations, sequential application of interventions might be more beneficial (Saevarsson et al., 2010).

Johannsen et al. (2003) have suggested that the combination of NV and PA might increase the therapeutic effects of these methods; that they could bolster each others' effects. This combination is of interest for many reasons. Firstly, these two interventions are among the few methods that have been found to be of clinical value (Luauté et al., 2006a). Secondly, a combination of an *active* intervention like PA (with high attentional load and therefore likely to tire the patients) and a *passive* one like NV (with minimal attentional load and thus less likely to tire the patients) is also suitable for many patients because of their low fitness level. Furthermore, both have been found to affect many distinct neglect mechanisms and symptoms (e.g., Johannsen et al., 2003; Rossetti & Rode, 2002; Schindler & Kerkhoff, 2004), and to lead to different modulations of neural activity (e.g., Bottini et al., 2001; Luauté et al., 2006b) which suggests that the two treatments may affect different neural or functional mechanisms. It is of interest in this context that there is good evidence that neglect can occur *without* motor and somatosensory deficits that underpin the differentiation between egocentric/personal and extrapersonal components of the disorder. This might explain why some patients show little improvement following

interventions that target the egocentric or extrapersonal aspects of neglect (Karnath et al., 2003; Vallar, 1998). As explained earlier, the stimulation of the neck muscles is believed to modulate, or “correct”, the neural generation of the displaced ego-/body-centred frame. On the other hand, PA is believed to ameliorate pathological higher order visuo-spatial representations. In other words, NV may apply better to the egocentric aspects of neglect, while PA may address the extrapersonal factors of neglect.

The current questions

The aim of the current study was to investigate possible benefits of using NV and PA in combination (NVPA), compared to when NV is used in isolation. Importantly, the results will also be compared to the results of a companion study (Saevarsson et al., 2009a) where the benefits of PA, applied on its own, were measured with the same feedback-based visual search task as we use here as well as largely the same standard neglect tests. Thus the results of Saevarsson et al. can serve as a PA-only comparison group for the current study since the experimental groups are comparable and the assessment of neglect was the same. Saevarsson et al. found no beneficial effects of PA upon performance on a visual search task where feedback was provided upon performance (see also Morris et al., 2006), while, importantly, they also showed that PA resulted in improved performance when no feedback was provided upon response.

Here, we compare and contrast the therapeutic benefits of these two most promising interventions for neglect on performance of the same tasks in a combined and isolated way which has not been done in past studies. Our reasoning was that if the two treatments target (at least partly) different aspects of neglect, the therapeutic benefits might be additive, resulting in more improvement and/or longer lasting amelioration of the symptoms when both are applied.

METHODS

Participants

Twelve patients with chronic neglect participated in the study. Patients N1, N2, N3, N4, N5, and N6 participated in experiment 1 (NV) and patients N7, N8, N9, N10, N11, and N12 in experiment 2 (NVPA). All were stroke victims except patient N4 who had neural tissue injury due to a brain tumour. They were randomly assigned to the two experiments by coin-toss with the only constraint that there should be six patients in each group. Table 1 shows general demographic and clinical information on the patients. Our main inclusion criteria were a right hemisphere injury, intact left

TABLE 1
Demographic and clinical information on the patients participating in the study

<i>Experiment</i>	<i>Patient</i>	<i>Gender</i>	<i>Age (years)</i>	<i>Months between stroke and experiment</i>	<i>Ocular deviation</i>	<i>Cephalic deviation</i>	<i>Hemiplegia to left</i>	<i>Days between baseline and experiment</i>
1	N1	Female	47	29	+	+	+	2
1	N2	Male	71	18	-	-	+	5
1	N3	Female	63	57	-	+	+	8
1	N4	Female	65	6	+	+	+	1
1	N5	Male	62	49	-	-	+	3
1	N6	Female	83	15	+	+	+	7
2	N7	Male	56	43	+	+	+	6
2	N8	Male	68	35	+	+	+	12
2	N9	Male	80	9	+	+	+	2
2	N10	Female	79	10	-	-	+	1
2	N11	Male	61	3	-	+	+	6
2	N12	Male	64	7	-	-	+	7

The “+” symbol refers to presence of a particular symptom and the “-” sign denotes that the particular patient did not have the symptom designated in the column headings.

hemisphere, intact cerebellum, an overall stable health condition, and significantly impaired performance on more than three of nine neuropsychological neglect tests (see below). The baseline measurements were used as study-inclusion criteria. Patients with hemianopia were excluded from the study. Extinction and hemianopia were assessed via clinical confrontation. All patients were right-handed except for patient N12 who was ambidextrous. Three patients (N5, N6, and N10) were found to suffer from extinction neglect. The patients were tested either at rehabilitation centres (N4, N5, N10, and N11) or in their homes (N1, N2, N3, N6, N7, N8, N9, and N12). All brain injuries were imaged with MRI and/or CT and plotted with MRICroN (<http://www.sph.sc.edu/comd/rorden/mricron/>) on a T1-weighted template (see Figure 1).

Stimuli

All 12 neglect patients in the study performed a single feature (pop-out) computerised visual search task and paper and pencil neglect tests, before and after the therapeutic interventions. In the visual search task, the participants searched for a green target circle among blue distractor circles and responded by key press whether the target was present or not. The diameter of all the circles was 0.6 arc deg and the viewing distance was kept as close to 67 cm from the monitor display as possible. The dimensions of the search

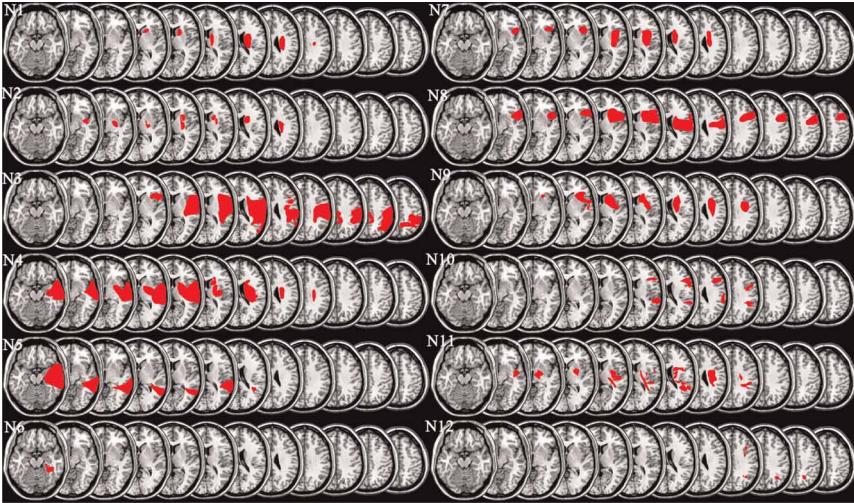


Figure 1. The location of the brain injuries of the 12 patients participating in the study. The figure shows 12 axial slices of the brains of each patient where the neural tissue damages are indicated in red colour. [To view this figure in colour, please visit the online version of this Journal.]

display on the monitor were 13.7 arc deg (vertically) by 19.5 arc deg (horizontally). The target was present on the screen on half of the trials of the search task (25% in the left and 25% in the right visual field). Forty-eight stimuli were presented on each trial, a target, and 47 distractors (a target-present trial) or 48 distractors (a target-absent trial). The stimuli on the left and right (50% on each side) were separated by a vertical 5.2 arc degree gap at the middle of the screen to increase the distinction between the hemifields. The search display was visible for 3500 ms and was followed by strong auditory and visual feedback (visual: “*Richtig*” was presented for correct and “*Falsch*” for wrong; auditory: high frequency tone for wrong responses and low frequency tone for correct responses). Following the visual search task, the patients performed the nine standard neglect tests. Four of these tests were visual-search based (Albert’s, digit, star and letter cancellation tests) and five tests were non-visual search based (free drawings of a clock and a flower; copy drawing of a Greek cross and a house, along with a line-bisection task). The tests were only assessed on the left side. The search-based tests were scored according to percentages of crossed out targets. The drawing tests were assessed according to percentages of correct lines and location of drawing; each stroke on the left side of an image was counted as a point, each omitted stroke was counted as a zero point, and each clearly misplaced or distorted stroke was counted as half a point. The deviation of the line-bisection test was measured in millimeters and the deviation was scored in percentages, where 100% indicated perfect bisection while 0%

indicated maximal deviation to the right side (Halsband, Gruhn, & Ettlinger, 1985; Wilson, Cockburn, & Halligan, 1987). We also recorded patient's reports of changes of the light spot. The open-loop task was analysed by recording the average pointing error of each patient.

Apparatus

A 600 Hz neck vibration apparatus (experiments 1 and 2) and 10 degree right shifted prism lenses (experiment 2) were used. An adaptation box was used for the prism adaptation, as well as an IBM T41 Thinkpad with a 15 inch LCD screen to present the visual search task and collect responses (the participants pressed one of two buttons on a keypad). Photoshop 7.0 pro was used to design the visual search stimuli and E-prime 1.1 for stimulus presentation.

Procedure

Baseline measurements and post-therapy measures were performed on different days. The between-session interval was kept as short as possible. The patients started by performing the visual search task, followed by the standard paper-and-pencil neglect tests. Each patient finished 480 to 640 visual search trials before and after therapy. On the day of intervention, both groups performed the open loop task (see below) before and after intervention. The neck vibration apparatus was adjusted to all patients before they performed the open-loop task. The testing procedure lasted about one and a half to two hours each day. The measurement process with the computerised visual search lasted approximately 60–90 minutes and 20–30 minutes for the standard tests. The experimenter was seated to the right of each participant at the time of all measurements.

For the open loop task, the patients were instructed to perform non-visible pointings straight forward from the midline with their right hand while blindfolded with sleeping glasses. Participants were asked to return their hand to the starting position in front of their chest. This test was performed by both groups to confirm the induced spatial representation shifts produced by both interventions. This is, to our knowledge, the first time that performance on an open-loop task has been measured following the application of NV.

NV was applied for 20 minutes on the left posterior neck muscle of the patient. The location at the neck was found by asking the patients to monitor a small green light 2 metres in front of them. While the apparatus was adjusted, the patients were asked openly if they noticed any changes in their perception of the light. If a patient reported an alteration (e.g., the light point moving to the right side at the time of stimulation and to the left side when the NV module was removed), the NV module was applied at that exact location. The NV module was glued with medical tape to the patients' neck muscles (for further details see, e.g., Karnath et al., 1993, and

http://www.vibraneck.de/_english/vibraneck/aerzte_und_therapeuthen.htm). Both groups of patients underwent NV while seated in front of an adaptation box. The NVPA group underwent PA treatment simultaneously to the NV. The patients in this group were asked to perform rapid pointing movements approximately four times per minute while wearing 10 degree right shifted prism glasses. Participants were only able to see their pointing for the last 1–2 cm before their finger reached the dots of the adaptation box. Pointing errors reduced with repeated pointing until the landing point was aligned with the dots.

Data analysis and ethical issues

The accuracy scores on the visual search task were estimated with log-linear analyses. Wilcoxon matched-pairs signed rank tests were used to analyse reaction times for the three conditions of the visual search task (right-hemifield targets, left-hemifield targets and target-absent trials). The accuracy and RT of the standard neglect tests were analysed with paired *t*-tests. The critical alpha-level (*p*) was set at .05. Finally, we compared the outcome of the two procedures (NV only, experiment 1 and NV and PA, experiment 2), with a mixed-design ANOVA. The study was approved by the ethics committee of the University of Freiburg, and was performed in accordance with the Declaration of Helsinki.

RESULTS

Experiment 1: Neck vibration only

Visual search performance

The purpose of the first experiment was to explore the effects of neck-vibration only, on performance on a feedback-based visual search task, in addition to performance on standard neglect tests. Figure 2 shows

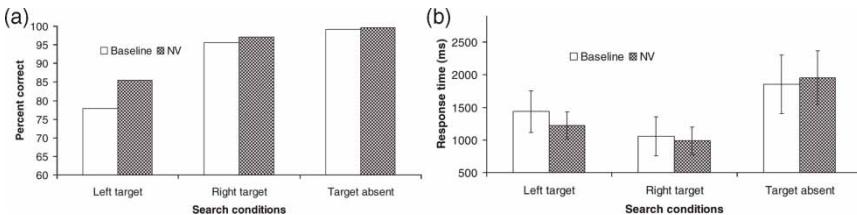


Figure 2. Results for the visual search task in experiment 1. Panel A shows average percent correct and panel B the average reaction times for the three conditions of visual search. The error bars indicate the standard deviations. The grey bars show the performance following NV.

the average percent correct (panel A) and the average RTs (panel B) for the six patients on the visual search task.

The patients in the NV-only group showed only an improvement in terms of accuracy for left targets, $\chi^2(1) = 16.471$, $p < .001$, on the day of the intervention; no difference was found for right sided targets, $\chi^2(1) = 2.896$, *ns*, nor the target absent condition, $\chi^2(1) = 0.08$, *ns*. The RTs became significantly faster for left and right targets and slower on the target-absent trials, $t(653) = 21.350$, $p < .001$; $t(802) = 7.166$, $p < .001$; $t(1665) = -28.015$, $p < .001$) for reasons that are unknown to us at present.

Standard neglect tests

Figure 3 shows the average percent correct (panel A) and RTs (panel B) on the nine neglect tests for the six patients. No significant difference in performance on these standard neglect tests was found for average percent correct, all: $t(23) = -0.809$, *ns*; VS: $t(23) = -0.30$, *ns*; non-VS: $t(29) = -1.157$, *ns*, nor RTs, all: $t(53) = 1.144$, *ns*; VS: $t(23) = 0.23$, *ns*; non-VS: $t(29) = 1.323$, *ns*, for the standard neglect tests before and after NV treatment.

Open-loop tests

The open-loop tests revealed a significant pointing error to the left side for patients N2, N4, N5, and N6 (3.2° , 5.8° , 2.4° , and 8.9° , respectively; $p < .05$) but not for patients N1 and N3 (1.5° and 1.0° , respectively; $p > .05$), when the pre- and post- conditions were compared. This result certainly warrants further attention in future, since it strongly indicates that NV causes recalibration similar to that seen for PA (see, e.g., Saevarsson et al., 2009). Patients N1, N2, N3, and N4 reported seeing changes in the lights, but patients N5 and N6 did not.

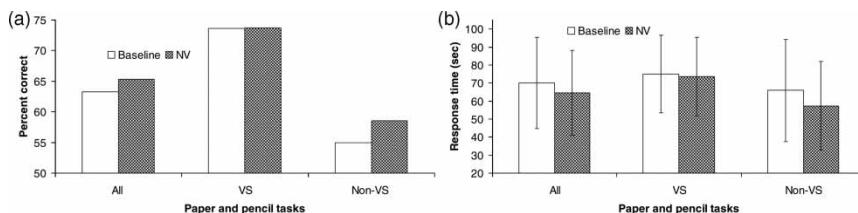


Figure 3. The results for the standard neglect tests on experiment 1. Panel A shows average percent correct and panel B indicates average reaction times for the standard neglect task. Both panels include results for all tests, visual search tests and non-visual search standard neglect tests. Performance following NV treatment is shown in grey.

Experiment 2: Combination of neck vibration and prism adaptation

Visual search performance

The aim with experiment 2 was to explore the effects of combining neck vibration and prism adaptation (NVPA) on feedback-based visual search in addition to performance on standard paper and pencil neglect tests. Figure 4 shows the average percent correct (panel A) and the RTs (panel B) for the visual search task. Log linear analysis revealed significant improvements in accuracy for both left, $\chi^2(1) = 21.986$, $p < .001$, and right, $\chi^2(1) = 10.786$, $p < .001$, targets after NVPA but not for the target absent conditions, $\chi^2(1) = 0.624$, *ns*. The RTs became faster for left and right trials and slower for the target absent condition, $t(522) = 7.588$, $p < .001$; $t(696) = 6.655$, $p < .001$; $t(1416) = -27.289$, $p < .001$.

Standard neglect tests

In contrast to the results of experiment 1 where the patients received NV only, NVPA was found to improve overall scores on standard neglect tests, $t(53) = -2.466$, $p < .05$. A non-significant trend was found for VS-based tasks, $t(23) = -1.779$, $p = .089$, and non-VS based tasks, $t(23) = -1.704$, $p = .099$, on these tests between the days of the experiment. No difference was found for the RTs for the three test categories, all: $t(53) = 1.99$, *ns*; VS: $t(23) = -2.58$, *ns*; non-VS: $t(29) = 0.723$, *ns*; Figure 5).

Open-loop tests

Open-loop tests showed pointing errors to the left for patients N8, N9, N11, and N12 (18.6° , 10.1° , 14.9° , and 0.2° , respectively; $p < .05$). No significant difference was found for subjects N7 and N10 (1.0° to right and 1.5° to left, respectively; $p > .05$) when the two conditions were compared, although there was a slight trend towards leftwards pointing errors for both. Patients

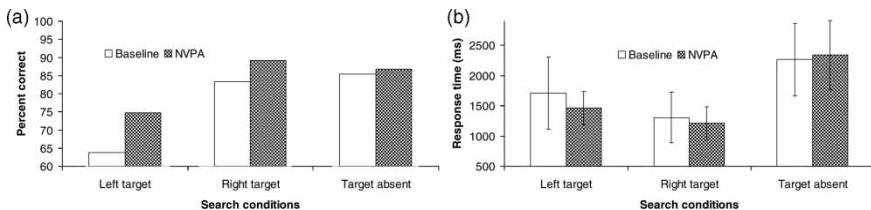


Figure 4. The results for the visual search task in experiment 2. Panel A shows the mean percent correct scores and panel B shows average reaction times for the three visual search conditions, before and after NVPA. The error bars show the standard deviations. Performance following NVPA therapy is shown in grey.

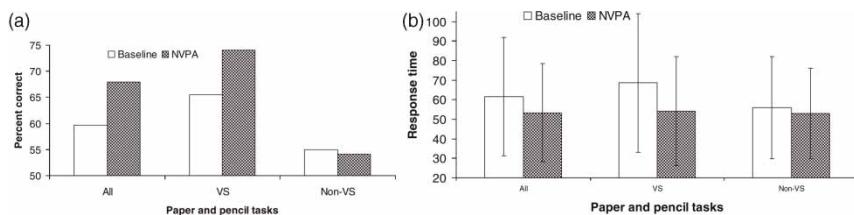


Figure 5. The results for the standard neglect test in experiment 2. Panel A shows mean percent correct scores on standard neglect tests before and after NVPA. Panel B shows the average time to finish each test. Both panels show results for all nine tests, four visual search tests and five non-visual search neglect tests. The error bars present the standard deviations. Performance following NVPA therapy is shown in grey.

N7, N8, N9, N11, and N12 reported seeing light changes induced by the neck vibration while N10 did not.

Taken together, the most notable result from the current experiments is that both groups showed improved performance on the computerised visual search task following their treatment. Interestingly, Saevarsson et al. (2009a) and Morris et al. (2006) have reported no benefits from PA on comparable tasks, but note that Saevarsson et al. found benefits from PA on tasks *not* involving feedback. Furthermore, the NVPA group showed improvement on standard neglect tests following treatment while the NV group did not. This result suggests that added therapeutical benefits are seen for neglect patients when PA and NV are applied in combination compared to NV only.

Comparison of the results for the two experiments

To compare the effects of the two treatment types we performed cross-experiment ANOVAs on the outcome variables with one between-subjects factor (treatment type: Neck vibration only [NV] versus neck vibration combined with prism adaptation [NVPA]) and one within-subjects factor (treatment: Pre- or post-treatment).

For the computer-based visual search task there was a significant effect of treatment upon accuracy, $F(1, 10) = 21.89$, $p = .0009$, but no interaction between the effect of treatment and treatment type, $F(1, 10) = .674$, $p > .4$. For the response times on the visual search task, neither term was significant, $F_s < 1.3$; $p_s > .2$.

For the response times on the paper and pencil visual search tests, there was a significant effect of treatment, $F(1, 10) = 5.57$, $p = .04$, in addition to a significant interaction between treatment type and the effect of treatment, $F(1, 10) = 7.90$, $p = .18$, which shows how the effects of NVPA treatment were significantly stronger than for neck vibration only. The results for accuracy for the visual search paper and pencil tests were comparable.

We found a significant effect of treatment, $F(1, 10) = 5.99, p = .034$, and a significant interaction between treatment effect and treatment type, $F(1, 10) = 5.76, p = .037$, again showing that the effect of treatment was significantly stronger for NVPA upon performance on the visual search-based paper and pencil tests.

For the non-visual search-based tests the effect of treatment upon accuracy was significant, $F(1, 10) = 4.96, p = .05$, but the interaction between treatment type and the effect of treatment was not, $F(1, 10) = 0.99, p = .34$. The same pattern was seen for the response times for the non-visual search-based paper and pencil tests, where the effect of treatment was significant, $F(1, 10) = 6.78, p = .027$, but not the interaction between treatment type and the effect of treatment, $F(1, 10) = 0.59, p > .4$.

Overall, these between-experiment ANOVAs support our main conclusions here. The beneficial effect of NVPA is notably higher than the effect of NV upon visual search-based paper and pencil neglect tests. Both NV and NVPA treatment lead to improved performance on feedback-based visual search tasks; which is very notable in the light of the fact that PA on its own only leads to benefits when feedback is not provided on a trial-by-trial basis in visual search.

DISCUSSION

There is a growing impetus in the literature on hemispatial neglect towards using a battery of rehabilitation procedures to treat the various neglect symptoms rather than focusing on single methods (see, e.g., Kerkhoff, 2001; Saevarsson et al., 2010). In the current study we have answered this call by directly comparing the therapeutic effects of neck vibration applied on its own with the effects of applying simultaneously neck vibration and prism adaptation upon neglect. We measured performance during feedback-based visual search and with standard neglect tests and we compared these results with the results of a companion study where PA was applied on its own and performance was measured with identical tests (Saevarsson et al., 2009a).

Our main results are that the beneficial effect of neck vibration and prism adaptation (NVPA) in combination is notably higher than the effect of neck vibration (NV) alone upon visual search-based paper and pencil neglect tests. Also, both NV and NVPA treatment lead to improved performance on feedback-based visual search tasks. This result is of note since our companion study (Saevarsson et al., 2009a) shows that prism adaptation applied on its own only leads to visual search benefits when feedback is not provided on a trial-by-trial basis. This suggests that the simultaneous application of NV along with PA may counteract de-adaptation effects from feedback upon the effects of PA when applied on its own.

The current study is the first to assess the beneficial effects of applying NV and PA in conjunction. One interpretation of the findings is that the NVPA combination improves visual search and other deficits measured with standard tests of neglect for at least 90 to 120 minutes following treatment. When NV was applied on its own, it was found to result in moderate improvements on the visual search task but not on the standard neglect tests. This might be interpreted as reflecting that NV does not lead to improvements on standard neglect tests but this seems unlikely in light of studies which suggest that it does (e.g., Karnath et al., 1993). The therapeutic effects might therefore last for a maximum of 60–90 minutes, or the same time it took to finish the computerised visual search task. In addition, similar light changes induced by NV were found (for the majority of patients) as in previous studies on the effects of NV (e.g., Johannsen et al., 2003). The open-loop test revealed comparable findings to preceding reports on the effects of PA for both experimental groups (e.g., Sarri et al., 2008). Finally, it is of note that our results indicate that neck vibration can lead to similar pointing errors as prism adaptation, a very interesting finding which certainly warrants further study in the future.

Relation to previous studies

Our results suggest that the effects of NV can be prolonged with the simultaneous application of PA, and they fall in line with the findings of Karnath et al. (1993) who reported short-term effects of NV on neglect. Schindler et al. (2002) found an improvement of neglect symptoms when NV was combined with visual exploration training, two months following the termination of the intervention. These authors also reported improvements lasting 1.4 years following sequential application of NV. Morris et al. (2006) and Saevarsson et al. (2009a) have shown that patients who undergo PA do not show benefits on similar neglect tasks as those used in the current study, nor on feedback-based visual search. However, we found that NV led to improved visual search performance on a visual search task where feedback was provided (see experiment 1) in contrast with previous findings reported for PA only (Morris et al., 2006; Saevarsson et al., 2009a, experiment 1). The results suggest that the therapeutic effects of NV do persist at least for some time when feedback upon search performance is provided in contrast to what has been observed for PA on comparable tasks (see Saevarsson et al., 2009a for detailed discussion).

More generally, the results lend support to the view that combining treatments can be a more effective way of treating neglect than focusing on one therapeutic approach, and that this may lead to longer lasting therapeutic benefits than otherwise. As reviewed earlier, NV and PA are among a handful of intervention techniques for neglect that have been shown to

improve neglect symptoms in the daily life of patients (Luauté et al., 2006a). Our results suggest that applying NV and PA in combination leads to more general therapeutic effects than when either NV or PA are used on their own.

Physiological effects of neck vibration and prism adaptation

Modulations of brain activity following NV and PA applied on their own have been explored with functional imaging in neglect patients. The results of PET studies conducted by Luauté et al. (2006b; see also Luauté et al., 2009) and Bottini et al. (2001) indicate that modulations of neural activity following NV and PA, applied on their own, show more differences than similarities in terms of changes in brain activity of neglect patients. This suggests that the two techniques may indeed affect different aspects of the neglect disorder. Both interventions were found to produce modulations in the left fusiform gyrus but PA produced activation while NV resulted in *deactivation* of this area. Furthermore, NV was found to affect activity in the right insula and the somatosensory area II of the perisylvian cortex. PA increased the activity in the left temporal medial cortex, the left temporo-occipital cortex, the left thalamus, the right posterior parietal cortex, and the right cerebellum. We can only speculate which modulations of brain activity might occur following NVPA treatment, since no functional brain imaging studies have been performed to date to investigate this. The current results strongly argue that neuroimaging following the combined use of NV and PA would be of great interest to uncover which neural networks are affected by the therapy approach.

The extensive modulations in both hemispheres following NV and PA applied in isolation might explain why NV, when combined with PA, seems to lead to longer lasting therapeutic effects than either one applied on its own. Two different methods may affect the same brain mechanisms more strongly when they are applied in combination. However, another possibility is that the physiological effects following PA or NV are non-overlapping. Hence, using the two in conjunction may be a more comprehensive and effective treatment than using either on its own, affecting a larger part of the networks damaged in neglect. These are intriguing questions for future investigations.

Limitations of the current study

Although the patients were randomly assigned to the two experimental groups we should note that there was a slight difference between the two groups in terms of clinical and demographic data. For instance, the NVPA experimental group showed stronger symptoms of neglect than the NV group. This may actually make it all the more surprising that a larger improvement was seen for the NVPA group than the NV group, although our current data do not allow us to make strong claims with regard to this issue.

Conclusions and future directions

The current findings may have some important implications regarding the therapeutic nature of both NV and PA, which count among the most promising rehabilitation procedures for unilateral neglect. When NV and PA are combined, they seem to produce superior effects in terms of length and generality of effects, compared to when NV and PA are used on their own. A more general conclusion that we might draw from the results is that using two treatments in combination is more effective than using either on its own. A likely reason for this is that neglect tends to involve a conglomeration of symptoms, some of which may be best treated with NV while others may respond more strongly to PA treatment.

Our findings here call for further studies. It would be interesting to explore the effects of NVPA on groups of patients with more homogenous lesions. Different symptoms of neglect (e.g., motor vs. visual modalities) might also be explored in this context. Furthermore, it would be of great importance to explore the effects of NVPA with other tasks involving visual attention, such as in attentional cueing paradigms (Carrasco, Williams, & Yeshurun, 2002; Kristjánsson, Mackeben, & Nakayama, 2001; Kristjánsson & Sigurdardóttir, 2008; Nakayama & Mackeben, 1989; Posner, 1980; see, e.g., Kristjánsson, 2006 for review) to test the generality of the attentional benefits that the improved visual search performance in the current study suggests. Testing NV and PA with measures of function in daily life such as walking and wheelchair navigation (e.g., Turton et al., 2009) would also be of great interest. Exploring the therapeutic effects when the interventions are applied sequentially would also be of interest to explore further aspects of this promising therapy combination for neglect.

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