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Title: Perceptual post-effects of left neck muscle vibration with visuo-haptic feedback in healthy individuals: a potential approach for treating spatial neglect.

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Abstract

Among the techniques used to reduce spatial neglect's symptoms, left neck muscle vibration (NMV) is alluring because it does not require the patient's attentional co-operation. The aim of this study was to determine the type of NMV-associated feedback that induced the most intense and longest-lasting egocentric post-effects. Eighty-seven healthy individuals were randomly assigned to four intervention groups: "neck muscle vibration, blindfolded" (NMV), "neck muscle vibration with vision" (NMV+V), "neck muscle vibration and visual finger-pointing" (NMV+P), and "visual finger-pointing" (P). An eyes-closed finger-pointing subjective straight-ahead (SSA) test was carried out before the intervention, immediately afterwards, and 30 minutes afterwards. The results showed that only the NMV+P intervention induced a lasting leftward bias of SSA. In addition, the deviation reported in this intervention group differed significantly from those observed in the other interventions. The combination of visuo-haptic feedback and neck-somatosensory stimulation may enable a full, lasting intermodal recalibration, which could be potentiated by the attention level engaged during voluntary pointing. These outcomes highlighted that the NMV technique could easily integrate into routine occupational therapy sessions for treating various aspects of neglect disorders.

Keywords: neck muscle vibration, visuo-haptic feedback, combined intervention, straight-ahead, intermodal calibration, neglect rehabilitation

Introduction

Unilateral spatial neglect (USN) is a perplexing neuropsychological syndrome that affects several domains of spatial cognition and also impacts functional domains [1]. The damaged brain networks (mostly in the right hemisphere) appear to affect the whole system of spatial coordinates relative to the patient's body [2]. More specifically, these patients fail to detect and respond to stimuli located contralaterally to the hemispheric lesion. Moreover, many studies of egocentric perception in people with left USN have shown that the subjective straight-ahead (SSA) is deviated to the right [3,4]. This impairment can contribute to long-term disability.

Several rehabilitation approaches have been developed to reduce spatial neglect. Conventionally, these approaches can be categorized as "top-down" (based on the patient being consciousness of their impairment) or "bottom-up" (based on sensory manipulation). "Bottom-up" sensory stimulation is alluring because it does not require much attentional cooperation by the patient; this is notably an important advantage in early-phase rehabilitation [5–7].

Neck muscle vibration (NMV) has been described by Saevarsson et al. [8] as a passive-restorative intervention technique and has shown promising results in patients with left USN. This proprioceptive stimulation (application of 80-100 Hz vibration to the belly of a muscle) generates muscle spindle and Ia afferent fiber responses that are interpreted centrally as a change in muscle length [9]. In healthy individuals, left-side NMV affects the whole egocentric coordinate system and induces (i) a rightward illusory motion of a stationary visual target, and (ii) a leftward deviation of the visually estimated SSA [10–12]. These perceptual egocentric effects are also observed in patients with various perceptive or sensorimotor impairments [13,14] and they are reportedly more intense in patients with USN [14] and in patients with spatial cognition disorders [13] than in healthy individuals. In patients with left

USN, the effects of left-side NMV might lead to improved sensorimotor coordination. Moreover, some studies have found that left-side NMV produces a lasting reduction in the symptom of spatial neglect [5,15–17].

Biguer et al [10] suggested that perceptual effects are optimized when the NMV technique is applied in darkness. In the literature, however, most studies of NMV-based rehabilitation for USN maintained normal ambient light conditions, and patients were allowed or instructed to keep their eyes open [5,15,17]. This raises the important question of whether or not the visual feedback-context during NMV influences the magnitude of any induced post-effects. Furthermore, the passive nature of NMV means that it can be easily combined with other passive techniques (*e.g.* vestibular, optokinetic or transcutaneous electrical nerve stimulation), or with active techniques (*e.g.* prism adaptation and visual exploration training). Likewise, several studies have reported that post-effects in patients with USN were stronger and longer lasting when treatments with converging effects were combined [7,8,14,18,19]. In some "top-down" interventions combined with NMV, patients have to be strongly aware of their spatial impairment so that they can compensate actively for the resulting spatial bias [7,20]. This requires patients with left USN to engage substantial attentional resources. However, an implicit awareness of spatial bias during performance can be easily induced by (for instance) asking the patient to reach specific visual targets in their peripersonal space with their arm. Awareness of bias between the arm's final position and the target's position would be facilitated by visual and haptic feedback. In a preliminary study [16], we described the effectiveness of treatment based on left-side NMV and visuo-haptic feedback in an patient with left USN. A generalized, lasting (24-hour) reduction in neglect symptoms (including better wheelchair navigation) was observed. However, it was not clear whether the treatment effect was due the repeated reaching movements, the left-side NMV, and/or the visuo-haptic feedback. The lack of theoretical knowledge on the influence of sensory feedback during the application of NMV has led to a diversity of environmental contexts in the application of this technique. However, it is not known which of these environments provides the strongest or longest-lasting post-effects.

The present study's primary objective was to describe and compare the perceptual post-effects induced by left-side NMV (*i.e.* deviation of the SSA immediately after stimulation and its persistence at 30 minutes) under visual or visuo-haptic contexts in a large group of healthy individuals. Thereafter, the objective will be to propose the sensory feedback context that was associated with the greatest post-effects and that might be of relevance in patients with left USN. Our hypothesis was that visuo-haptic feedback-context associated with the NMV technique would induce the most promising post-effects.

Materials and methods

Participants

Eighty-seven right-handed, right dominant eye, normal-sighted, healthy young adults (including 39 women, age: 21.4±2.2, respectively: mean±standard deviation) were recruited in the study. They were randomly assigned to four independent groups (random drow computed with a Matlab script), each of which corresponded to a single type of intervention: a "neck muscle vibration, blindfolded" group (NMV: n=21, including 5 women; 21.3±2.8); a "neck muscle vibration with vision" group (NMV+V: n=22, including 6 women; 20.7±1.7); a "neck muscle vibration with visual finger-pointing" group (NMV+P: n=24, including 15 women; 22.2±2.3); and a "visual finger-pointing" group (P: n=20, including 13 women; 20.8±1.1). None of the participants had a history of central nervous system disease or psychiatric, neurological, ocular, oculomotor or vestibular disorders. None of the participants complained of dizziness or vertigo during the study. The study was carried out in agreement with the French and European legislation and the Declaration of Helsinki.

Experimental devices

The participant sat comfortably in a chair in front of a wooden device placed on a table. He/she placed their chin on a height-adjustable chinrest, so that the head remained vertically aligned with their trunk throughout the experiment. Five light targets (LEDs, 0.3 cm in diameter) were placed at specific lateral locations 50 cm in front of the participant: straight-ahead, 10 degrees to the left and to the right, and 20 degrees to the left and to the right (*i.e.* -10 deg, -20 deg, 0 deg, 10 deg, and 20 deg).

Vibratory stimulators (VB115, Vibrasens®, Techno Concept, Manosque, France) were fixed bilaterally over the belly of the upper trapezius muscle and fastened with straps.

Experimental design

- The SSA task and the test sessions

During a test session, the participant's chin was always placed on the chinrest in order to align the participant's straight-ahead with the zero-degree direction of the wooden device. The right index finger positioned at the base of the chinrest (in front of the sternum). The blindfolded participant was asked to indicate their SSA with the right index as quickly as possible. The final index position had to be maintained for at least 2 seconds, before a return to the starting position at the base of the chinrest. Twenty pointing movements were carried out in each test session. Three test sessions were performed: before the intervention (Pre), immediately afterwards ($Post_0$), and 30 minutes afterwards ($Post_{30}$).

- Procedure for each intervention

Each participant was equipped with a vibratory stimulator on each upper trapezius muscle, and the head position was maintained on the chinrest. In the NMV, NMV+V and NMV+P groups, only the left-side vibrator was activated (vibration frequency: 100 Hz; vibration amplitude: 300 µm) throughout the 15-minute session; the right vibrator was never activated. In the NMV group, the blindfolded participants did not have to perform any specific activities during the left-side proprioceptive stimulation of the neck, other than an informal discussion with the investigator. In the NMV+V group, the stimulation conditions were the same as in the NMV group, except that participants were not blindfolded and could keep their eyes open. In the NMV+P group, the participants were asked to point as quickly as possible at one of the five light targets (-10 deg, -20 deg, 0 deg, 10 deg, and 20 deg) with the right index finger. After the target had been indicated, the participant had to return the index finger to the starting position at a natural speed. Five blocks of 50 successive pointing trials were performed. Each pointing direction was presented 10 times, in random order. Each block lasted for approximatively 2.5 minutes, and there was a 30-seconds rest period between successive blocks. In the P group, the participants performed the same finger-pointing task as the NMV+P group but in the absence of any vibratory stimulation; this enabled us to check the possible training effect of repeated finger-pointing on post-effects in the NMV+P group.

Data reduction and statistical analysis

As previously mentioned, the participant's objective straight-ahead was perfectly aligned with the zero-degree direction of the wooden device. For each trial, the direction indicated by the blindfolded participant with their index finger (corresponding to their SSA) was visually measured thanks to a circular degree scale located on the edge of the wooden device. The precision of this measurement was ±0.5 degrees. Leftward and rightward errors were assigned negative and positive values, respectively.

For each test session, quantitative data were expressed as the medians (*M*) [interquartile range (*IQR*)]. Under all the four stimulation conditions, the data were not normally distributed (Shapiro-Wilk test, *ps*<0.05) and heterogeneity of group-variances occurred (Levene's test, *ps*<0.05). Therefore, non-parametric statistical analyses were computed. For the study participants as a whole and then for each group, Friedman's test was used to analyze the effect of the period (Pre; $Post_0$; $Post_{30}$) on the median SSA values. When Friedman's test was significant (with an alpha level of 0.05), post-hoc Wilcoxon's signed-rank tests (with a Bonferroni-adjusted alpha level of 0.017) was used to assess pairwise comparisons between each of the three periods (Pre; $Post_0$; $Post_{30}$). Kruskal-Wallis tests were used to compare the intervention groups. Firstly, a Kruskal-Wallis test was performed on the SSA's sums of ranks in each group (NMV; NMV+V; NMV+P and P) at Pre, in order to ensure that the SSA values were equivalent at baseline level. Secondly, the effect of the intervention was computed for each participant at $Post_0$ and at $Post_{30}$ respectively by subtracting the baseline level from mean SSA after intervention (*i.e.* respectively mean SSA at $Post_0$ minus mean SSA at Pre and mean SSA at $Post_{30}$ minus mean SSA at Pre). Therefore, leftward and rightward SSA variations were assigned negative and positive difference values, respectively. In order to analyze the effect of the intervention type on SSA variations, Kruskal-Wallis tests were performed on the SSA Post-Pre differences' sums of ranks in each group (NMV; NMV+V; NMV+P and P), *i.e.* $Post_0$-Pre and $Post_{30}$-Pre SSA's differences. When Kruskal-Wallis test was significant (with an alpha level of 0.05), post-hoc pairwise comparisons between groups were computed and *p*-value adjusted with the Steel-Dwass-Critchlow-Fligner (SDCF) method [21].

Results

The median [IQR] values of the SSA at Pre, $Post_0$ and $Post_{30}$ periods are depicted as a boxplot in Figure.

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Please insert Figure here

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In the Pre period, the median SSA did not differ significantly [$H(3, N=87)=2.38$; $p=0.50$] when comparing the NMV group ($M_{NMV/Pre}=+3.45$ deg; $IQR_{NMV/Pre}=3.85$), the NMV+V group ($M_{NMV+V/Pre}=+2.88$ deg; $IQR_{NMV+V/Pre}=5.10$), the NMV+P group ($M_{NMV+P/Pre}=+3.63$ deg; $IQR_{NMV+P/Pre}=2.50$) and the P group ($M_{P/Pre}=+2.53$ deg; $IQR_{P/Pre}=4.50$).

For the study participants as a whole (*i.e.* independently of any group effect), the median SSA was significantly modified by the intervention, as indicated by the significant Friedman's test result [$\chi^2(2, N=87)=7.27$; $p=0.026$]. We noted that the median SSA was initially oriented toward the right in the Pre period ($M_{Pre}=+3.30$ deg; $IQR_{Pre}=4.10$) but tended to be slightly deviated leftwards immediately after the interventions ($M_{Post0}=+2.45$ deg; $IQR_{Post0}=4.40$; $z=2.25$; $p=0.024$) and then 30 minutes afterwards ($M_{Post30}=+2.50$ deg; $IQR_{Post30}=4.85$; $z=2.49$; $p=0.013$). However, only the NMV+P intervention contributed significantly to these results; only in this group did the period have a significant effect on the median SSA [$\chi^2(2, N=24)=24.25$; $p<0.001$]. More precisely, the SSA was significantly deviated leftwards immediately after the intervention ($M_{NMV+P/Post0}=+1.43$ deg; $IQR_{NMV+P/Post0}=2.13$; $z=3.96$; $p<0.001$) and then 30 minutes afterwards ($M_{NMV+P/Post30}=+2.00$ deg; $IQR_{NMV+P/Post30}=2.83$; $z=3.64$; $p<0.001$), relative to the Pre values ($M_{NMV+P/Pre}=+3.63$ deg; $IQR_{NMV+P/Pre}=2.50$). The difference between the median SSA at $Post_0$ and at $Post_{30}$ did not reach the level of significance ($z=1.90$; $p=0.057$). In contrast, the three other interventions did not influence significantly the SSA over the course of the three test periods, as shown by the non-significant results of Friedman's test in the NMV group [$\chi^2(2, N=21)=2.57$; $p=0.28$], the NMV+V group [$\chi^2(2, N=22)=0.71$; $p=0.70$] and the P group [$\chi^2(2, N=20)=0.70$; $p=0.70$].

This differential effect of the type of intervention was corroborated by the Kruskal-Wallis analyses computed on the Post–Pre SSA differences. Immediately after the intervention, the SSA variation differed significantly across the groups [$H(3, N=87)=25.16$; $p<0.001$]. SDCF pairwise comparison method revealed that the SSA variations were significantly higher in the NMV+P group ($M_{NMV+P/Post0-Pre}=-2.43$ deg; $IQR_{NMV+P/Post0-Pre}=1.18$) than in the NMV group ($M_{NMV/Post0-Pre}=+1.25$ deg; $IQR_{NMV/Post0-Pre}=3.95$, $p<0.001$), in the NMV+V group ($M_{NMV+V/Post0-Pre}=-0.25$ deg; $IQR_{NMV+V/Post0-Pre}=2.35$, $p<0.001$) or in the P group ($M_{P/Post0-Pre}=-0.80$ deg; $IQR_{P/Post0-Pre}=2.93$, $p=0.016$). Other comparisons between groups were not significant ($ps>0.05$). Thirty minutes afterwards, the group effect on SSA variations was also significant [$H(3, N=87)=8.02$; $p=0.046$]. The median SSA's $Post_{30}$–Pre changes were larger (in absolute) in the NMV+P group ($M_{NMV+P/Post30-Pre}=-1.73$ deg; $IQR_{NMV+P/Post30-Pre}=2.10$) than in the NMV group ($M_{NMV/Post30-Pre}=+0.05$ deg; $IQR_{NMV/Post30-Pre}=2.15$), in the NMV+V group ($M_{NMV+V/Post30-Pre}=-0.83$ deg; $IQR_{NMV+V/Post30-Pre}=3.65$) or in the P group ($M_{P/Post30-Pre}=-0.53$ deg; $IQR_{P/Post30-Pre}=3.85$). However, only NMV group differed significantly from the NMV+P group ($p=0.016$; $p>0.05$ for all other pairwise comparisons) concerning this SSA $Post_{30}$–Pre change.

Discussion

The present study's objectives were to compare the egocentric post-effects induced by left-side NMV under various sensory feedback contexts in a large group of healthy individuals and to select the context that induced the most intense, persistent perceptual post-effects. Although the environment in which NMV is applied has never been investigated *per se*, it has a fundamental impact on the technique's effectiveness. This impact is important with regard to improving the rehabilitation of spatial neglect. Firstly, our results showed that the SSA in healthy right-handed participants is deviated slightly rightwards [3,22]. Secondly, our study's main finding is that only the "NMV with visuo-haptic feedback" intervention induced a leftward deviation of the egocentric frame of reference for at least 30 minutes. These perceptual post-effects were not attributable to the visuomotor training induced by repeated pointing. Lastly, and regardless of whether or not visual feedback was present during left-side NMV, we did not see a post-effect on the SSA in the absence of haptic feedback.

A neural mechanism favorable to an intermodal updating process

Although the study's psychophysical data cannot provide direct evidence of the neural mechanisms induced by the "NMV with visuo-haptic feedback" intervention, they (and the literature data in the field of neurophysiology) enable us to form a number of hypotheses. The effects induced seem relatively similar to those induced by other "bottom-up" interventions (*e.g.* vestibular stimulation) and that might result from neuroplastic changes in the contralateral (right) hemisphere. However, several studies [17,23] have shown that somatosensory stimulation of the neck not only activates the contralateral hemisphere non-specifically but also activates many vestibular neurons in the parieto-insular vestibular cortex. As described in the monkey by Grüsser et al. [24,25], these neurons are known to (i) have bilateral receptive fields, (ii) participate in the multisensory integration of vestibular, optokinetic and somatosensory inputs, and (iii) contribute to the construction and updating of internal representations of head and body positions in space [17]. Vallar et al. [17] hypothesized that somatosensory stimulation of the neck has specific effects (possibly mediated by multimodal vestibular units) and may account for the reduction in neglect. Indeed, the left-side NMV might counteract the (rightward) ipsilesional distortion of egocentric representations caused by (right) parietal lesions in patients with left USN. To do so, the vibratory stimulation might activate right hemisphere units with bilateral receptive fields. This neuronal process might underlie the perceptual effects observed in the present study.

A number of psychophysiological studies have corroborated the neurophysiological outcomes described above. Indeed, several studies have shown that the unilateral NMV provokes postural adjustments [26,27], illusory body motion [9,28], and illusory motion of a bright stationary target in an otherwise dark environment [10,29]. From a mechanical point of view, Strupp et al. [13] showed horizontal eye deviation towards the vibrated side in patients with subacute unilateral vestibular lesions and also in healthy-participants, *i.e.* shifting the gaze off a stationary target so that it seems to move to the opposite side; this is congruent with the apparent target motion usually reported by participants. Lackner and Levine [29] referred to this phenomenon as a "propriogyral illusion", in order to emphasize its similarity to the "oculogyral illusion" elicited by vestibular stimulation [30]. Here, the visual component of illusory motion reflects the effect of proprioceptive stimulation of the neck on the neural representation of the direction of gaze, and highlights the importance of neck input for eye movement control [31,32]. Moreover, Strupp et al. [13] proposed that the effect of unilateral NMV on SSA resulted from changes in eye position and was possibly mediated by the cervico-ocular reflex. These observations suggest that the neck region has a strong influence on the central representation of body orientation [17,33]. Thus, the somatosensory stimulation induced by unilateral NMV may have specific directional effects (deviation towards the stimulated side) on egocentric coordinates. Although this mechanism might account for the temporary improvement in neglect, it does not explain the persistence of post-effects with visuo-haptic feedback observed in the present study.

Overall, reaching a visual target requires proper sensory matching between the somatosensory afferences from the effector arm and visual afferences from the actual target position. Furthermore, asking someone to focus their attention on the visual target to reach, would activate the visual pathways, the posterior parietal areas and the motor cortices [34,35]. According to Conte et al. [35], the attentional processes engaged would potentiate mechanisms of short-term plasticity in cortical motor areas. Thereby, two independent mechanisms, possibly complementary, might be the cause of the persistence of the post-effect. Firstly, the combination of visuo-haptic and neck-somatosensory stimulation could produce a lasting multisensorial updating process, *i.e.* complete intermodal recalibration. Secondly, the activation of attentional processes for the fulfilment of a sensory-motor task coupled to neck-somatosensory stimulation could potentiate the motor cortices' plasticity. It is also quite conceivable, through the neurophysiological and psychophysiological mechanisms presented above, that the addition of neck-somatosensory stimulation could activate a process of persistent intermodal recalibration which would be potentiated by the sensory-motor attention engaged by the individual during voluntary action.

Possible applications of NMV-based interventions in rehabilitation

Firstly, the non-invasive application of the neck vibrator device is an easy procedure to implement. However, the main advantage of the NMV technique is the weak requirement for attentional co-operation by the patient while obtaining significant changes in their representation of egocentric space [7]. The NMV technique is known as a passive restorative intervention but it may facilitate the visuospatial detection of objects – a process that usually requires significant attentional resources in patients with USN – thanks to its incidental effect on eye position [13]. The present study corroborated the post-effects induced by combining left-side NMV with visual finger-pointing, as shown previously in an patient with left USN [16]. These results suggest that sensorimotor self-activation during left neck-proprioceptive stimulation will obtain the most promising post-effects. The transfer of this intervention directly into rehabilitation sessions might further increase the intensity and/or the impact of the outcomes. To do so, reaching towards a target is very much like the motor activities executed during standard rehabilitation sessions in patients with USN. Consequently, the addition of the NMV technique during occupational therapeutic sessions might readily enhance the therapeutic effects obtained by standard treatments, without needing to add additional, specific sessions as is sometimes suggested [36].

Lastly, the “NMV with visuo-haptic feedback” intervention involved voluntary movements with the participant’s dominant (right) arm in the present study. Therefore, this intervention is not similar to the so-called “limb activation” therapy used in the cases of neglect [37,38]. In limb activation therapy, the patient with left USN is asked to perform voluntary movements in peripersonal space with their contralesional limb (the left one). Robertson et al.’s report on these patients showed that moving the left limb in the neglected hemispace significantly reduced the degree of neglect [39]. However, they also found that adding right limb movements in the neglected hemispace abolished or at least dramatically limited this benefit. In order to explain this “motor extinction” effect, Robertson et al. suggested that “*the right hand movements are more perceptually salient than those of the left hand, and hence “overshadow” the latter.*”

In the light of these outcomes and with a view to applying the NMV technique during occupational therapeutic sessions for USN, it might be advantageous to combine the NMV technique with limb-activation. However, in the early stages of neglect, many patients have immense difficulty moving the limbs of the neglected hemi-body [7]. Therefore, as a first step and in order to maintain motivation levels, these patients should be allowed to move only their ipsilateral (right) arm in their peripersonal space. The therapist will check the patient never moves both arms at the same time in the neglected hemispace. At present, there are no literature data on whether ipsilateral arm movements in the neglected hemispace induce less benefits than contralesional arm movements in the neglected hemispace; this topic warrants evaluation.

Conclusion

Our present results clearly emphasize the potential of combing visuo-haptic feedback with left-side NMV to optimize a lasting leftward egocentric deviation. The transfer of this combined intervention is realistic and relevant into rehabilitation sessions for various reasons. The first is that the NMV technique is an easy procedure to implement and painless, and requires a weak attentional co-operation by the patient. The second is that repeated reaching movements are very much like the motor activities executed during standard rehabilitation sessions in patients with USN. Consequently, our findings argue in favor of including the NMV technique in rehabilitation sessions for patients with USN.

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Author Contributions: H.C. conceived and managed the study. H.C. and S.C. designed the experiment, collected and processed the data, and analyzed the results. H.C., J-M.B., G.C. and S.C. discussed the results, wrote the manuscript, and reviewed the manuscript for critical content.

Declaration of interest: The authors declare that they have no conflict of interest.

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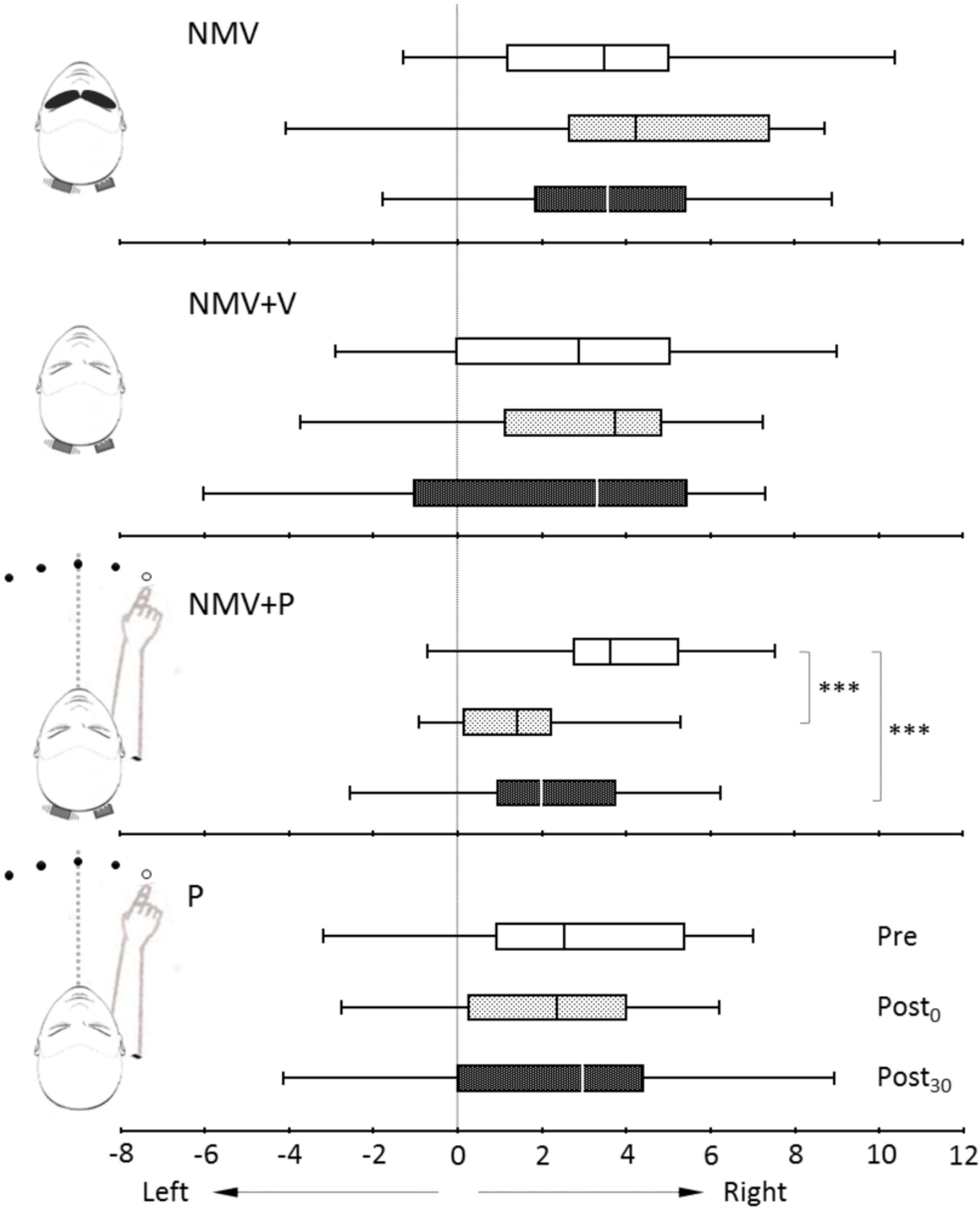
Figure legend

Figure. Median ([IQR] and range) visual angle errors (in degree) during the blindfolded subjective straight-ahead (SSA) finger-pointing test before each intervention (Pre), immediately afterwards ($Post_0$), and 30 minutes afterwards ($Post_{30}$): “neck muscle vibration, blindfolded” (NMV), “neck muscle vibration with vision” (NMV+V), “neck muscle vibration with visual finger-pointing” (NMV+P), and ‘visual finger-pointing’ (P). ***: $p<0.001$


NMV
NMV+V
NMV+P
***
***
P
Pre
Post$_0$
Post$_{30}$
-8
-6
-4
-2
0
2
4
6
8
10
12
Left
Right