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Behavioral and functional changes in neglect after multisensory stimulation

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Abstract

The present cohort study investigated whether systematic multisensory audio-visual stimulation might improve clinical signs of neglect. To this aim, patients with neglect (n=7) and patients with neglect associated with hemianopia (n=12) were exposed to a course of audio-visual stimulation with spatially and temporally coincident audio-visual pairs of stimuli for 10 daily training sessions (4 hours of training per day), over two weeks. Performance on neuropsychological tests assessing neglect was measured before training, immediately after the training and months after the training at a follow-up session. The results showed significant post-training improvements in clinical signs of neglect, which were stable at the follow-up. These findings suggest that intensive and prolonged multisensory audio-visual stimulation affects orientation towards the neglected hemifield, therefore inducing long-term improvements in visual exploration and neglect symptoms in both patients with neglect and patients with neglect associated with hemianopia. Previous evidence from hemianopic patients suggests that these post-training effects might be mediated by activity in spared subcortical structures, such as the superior colliculus, which are relevant to multisensory integrative processing and spatial orientation.

Keywords

Neglect; Hemianopia; Audio-visual stimulation; Rehabilitation; Superior colliculus

Introduction

The failure to explore, respond to or orient towards stimuli presented in the contralesional side of space in right hemisphere brain-damaged patients is called hemispatial neglect (Heilman et al., 2000). Although this spatial bias is often observed in the visual modality, other sensory modalities and motor functions can be equally affected (e.g., Pavani et al., 2003; Coslett et al., 1990). Similarly, the deficit can concern different sectors of space (i.e. personal or extrapersonal space; Làdavas et al., 1997a; Guariglia & Antonucci, 1992; Bisiach et al., 1986; Committeri et al., 2007). As a result, patients suffer enduring difficulties in their everyday lives, such as impaired reading, navigation and visual exploration. Neglect is also an issue in neuropsychological diagnosis and rehabilitation of cognitive functions; for example, both psychometric testing and computer-based training methods require sufficient vision to identify stimuli. A certain amount of spontaneous recovery may occur in the first 2–3 months post-lesion. However, such spontaneous recovery might be partial, and in more than 25% of cases, neglect persists several years after lesion onset (Pantano et al., 1996; Katz et al., 1999; Farnè et al., 2004). Hence, there is a need for treatment.

Converging evidence has shown that the multifaceted neglect syndrome can be interpreted as a disorder of spatial attention, resulting from lesions involving right fronto-parietal and subcortical networks. Although in some circumstances, contralesional spatial attentional disorders might be observed in left hemisphere-damaged patients – i.e., in the post-lesional acute stage (Stone et al., 1993) or when patients engage in multitasking with attentional load (Blini et al., 2016) – the evidence that spatial neglect is more commonly observed and more severe after right-hemispheric lesions suggests a functional asymmetry of the underling mechanisms allocating spatial attention. The prevalence of the syndrome after lesions to the right hemisphere has been suggested to depend on the dominance of the right hemisphere in attentional allocation; that is, the right hemisphere mediates shifts of attention to both hemifields, while the left hemisphere can shift attention only to the right hemifield (Heilman & Abell, 1980). Alternatively, interhemispheric rivalry or competition has been proposed as a crucial mechanism underlying the expression of the deficit (Kinsbourne, 1977); because interhemispheric fibers have inhibitory effects (Sprague, 1966; Sherman, 1974; Wallace et al., 1989), their loss, due to the damage of the right hemisphere, would result in relative hyperexcitation of the intact left hemisphere. This perspective postulates that each hemisphere has an attentional vector biased towards the contralateral hemifield, with the rightward bias of the left hemisphere being stronger than the leftward bias of the right hemisphere (Kinsburne, 1977). As a result of the hyperactivation of the left hemisphere, with concurrent hypoactivation of the damaged right hemisphere, patients direct their attention towards the "ipsilesional field" (Làdavas, 1990; Làdavas et al., 1990; Barbieri & De Renzi, 1989) and the "contralesional field" lacks sufficient attentional resources to process stimuli presented in that portion of the space.

A wide range of evidence seems to confirm the attentional asymmetry between the two hemispheres. For instance, TMS over parietal cortex has been used to entrain alpha oscillations (Thut et al., 2011) and the changes in alpha power have been shown to be behaviorally relevant (Romei et al., 2010), with right posterior parietal cortex (PPC) stimulation impairing visual detection in the left hemifield but enhancing visual detection in the right hemifield. In addition, stimulation of the right dorsal network (i.e., the PPC and the frontal eye fields) led to changes in task performance in the vast majority of studies, whereas stimulation of the left dorsal network failed to have an effect. Overall, this evidence seems indicative of the right hemisphere's dominance in attentional control (for a review, see Duecker & Sack, 2015).

Stemming from this theoretical background, neglect can be considered as the result of unbalanced excitability between the two hemispheres. If this explanation is correct, restoration should be conceived as a rebalancing act between the two hemispheres. A recent technique that has been safely applied to change patterns of hemispheric activation in brain-damaged patients is prism adaptation (PA), which has been shown to ameliorate neglect symptoms in large samples of patients (Frassinetti et al., 2002b; Serino et al., 2006; Làdavas et al., 2011; Làdavas et al., 2015). PA requires the patient to perform a series of pointing movements toward a visual target while wearing prismatic goggles. These goggles induce a deviation of the visual field toward the right. To compensate, the patient has to orient the pointing movement toward the left, resulting in a leftward drift of sensorimotor coordinates. It has been hypothesized that under prism exposure, due to eye–hand coordination, the leftward deviation of hand movements also induces a leftward deviation of the oculomotor system (Angeli et al., 2004; Ferber et al., 2003) and a consequent shift of visual attention toward the left, thus mediating the recovery of visual neglect (Frassinetti et al., 2002b; Serino et al., 2006; Làdavas et al., 2011; for a review, see De Wit et al., 2018).

These findings suggest that the leftward drift of sensorimotor coordinates, including eye movements, is able to reduce the attentional bias towards the ipsilesional field in such a way that spatial attention is more equally distributed between the two hemispaces, and to reduce the unbalanced excitability between the two hemispheres. Thus, gaze field improvement in the neglected hemispace can be accomplished by the enhancement of saccadic or other orienting responses.

Another way to reset the gaze field by enhancement of saccadic responses and other orienting behaviors is by using multisensory stimulation in the impaired visual field. Pioneering studies on animals (Stein & Meredith, 1993) have revealed enhanced neural responses in the multisensory neurons of the superior colliculus (SC) – an important neural structure for the programming and execution of eye movements (Gandhi & Katnani, 2011; Krauzlis et al., 2013) – when auditory and visual stimuli are presented in spatial and temporal coincidence (spatial and temporal principles of multisensory integration). Such enhanced neural responses in the SC are synergistic, i.e., the response to the combination of auditory and visual stimuli exceeds the sum of the responses to each individual sensory stimulus (multisensory enhancement). Moreover, combinations of weakly effective unisensory stimuli induce a more robust enhancement of multisensory neuronal activity (i.e., the inverse efficacy principle; Stein & Stanford, 2008).

Crucially, converging evidence suggests the presence of multisensory benefits at the behavioral level, both in animals' orienting responses (Gingras et al., 2009) and in a wide range of perceptual tasks in humans (for a review, see Alais et al., 2010). In particular, behavioral studies of healthy participants have shown that multisensory integrative mechanisms can improve both detection (Frassinetti et al., 2002a; Bolognini et al., 2005a; Bertini et al., 2008; Leo et al., 2008a; Maravita et al., 2008) and localization (Hairston et al., 2003; Lovelace et al., 2003; Alais and Burr, 2004; Bolognini et al., 2007; Leo et al., 2008b; Bertini et al., 2010) of audio-visual pairs consisting of degraded unisensory stimuli. Interestingly, repeated exposure to coincident audio-visual stimulus pairs effectively facilitates visual learning (Kim et al., 2008; Grasso et al., 2016a). Moreover, enhanced activation in extrastriate cortical areas has been found after stimulation with coincident audio-visual stimuli (Shams and Kim, 2012). This is not surprising because heteromodal associative cortices in the cat (i.e., AES, rLS; Jiang et al., 2001; Jiang and Stein, 2003) support integrative processing in the SC. In line with this finding, the inferior parietal (Dong et al., 1994) and intraparietal cortices (Colby et al., 1993; Duhamel et al., 1998; Schlack et al., 2002) have been suggested as sites of convergence of many different sensory modalities in primates. Additionally, imaging studies in humans have confirmed the involvement of the SC and posterior cortical areas, including the temporo-parietal and posterior parietal cortices, in mediating audio-visual multisensory integration (for a review, see Calvert, 2001; Stein and Stanford, 2008).

More importantly from the perspective of the present study, animal studies have shown that combined audio-visual stimulation is effective at reinstating visual responses in the multisensory layers of the ipsilesional SC. Specifically, some visually unresponsive neurons in the SC became responsive to visual stimuli after repeated exposure to spatio-temporally coincident cross-modal cues (Yu et al., 2009; 2012). Notably, this recovery could not be induced by training the animals with visual or auditory cues alone. Also, studies on hemianopic cats have revealed that training with pairs of spatially and temporally coincident audio-visual stimuli can recover orienting abilities, discrimination and visual awareness of visual patterns in the blind hemifield (Jiang et al., 2015; Dakos et al., 2019). In line with these animal studies, in a series of studies in human patients, Làdavas and colleagues demonstrated that audio-visual integration can increase perceptual performance in patients with unisensory defects, such as hemianopia (Bolognini et al., 2005b; Leo et al., 2008b; Passamonti et al., 2009; Dundon et al., 2015; Grasso et al., 2016b) and neglect (Frassinetti et al., 2002a; Frassinetti et al., 2005).

Interestingly, previous evidence revealed that the occurrence of two visual stimuli, although presented in the same spatial position, does not improve visual detection performance in neglect patients (Làdavas et al., 1994). More precisely, a noninformative visual cue presented in the neglected left hemispace before the appearance of the visual target did not ameliorate visual responses in that hemispace. This evidence stresses the importance of the multisensory integrative system in improving perceptual performance after brain lesion, exploiting the spared retino-colliculo-extrastriate pathway. Indeed, the preserved responsiveness of this neural circuit to audio-visual stimuli might constitute the neural basis for the behavioral compensation observed with multisensory stimulation (Làdavas, 2008; Bertini et al., 2016). Both hemianopia and neglect are characterized by a lack of compensatory eye movements towards objects of interest presented in the impaired field (Zhil, 1999; Pambakian et al., 2000). This ability depends on interactions between the SC in the midbrain and the visual cortex, with the SC being extremely important for multisensory integration (Stein and Meredith, 1993) and the programming and execution of eye movements (Gandhi and Katnani, 2011; Krauzlis et al., 2013). Thus, the activation of this neural circuit by multisensory stimulation could be fundamental to the recovery of visual impairments after brain damage. Accordingly, after training hemianopic patients with audio-visual stimulation, a long-lasting improvement in oculomotor exploration was found (Passamonti et al., 2009), which was characterized by fewer fixations and re-fixations, faster and larger saccades and a reduced scanpath length, leading to a shorter exploration time compared to pre-treatment performance. Similarly, the training significantly affected oculomotor reading parameters, reducing both progressive and regressive saccades. In other words, the audio-visual treatment induces an increased activation of the visual responsiveness of the oculomotor system, thus reinforcing orienting behavior towards the blind hemifield.

However, the available evidence so far has shown only a short-term improvement of visuospatial attention allocation induced by multisensory stimulation in neglect patients (Frassinetti et al., 2002a; 2005). In addition, the amelioration was not evident when left hemispatial neglect was associated with left hemianopia. A possible explanation for the lack of audio-visual integration in neglect patients with hemianopia is that the simultaneous impairment of areas involved in visual spatial attention and primary sensory visual processing prevents cross-modal integration, probably due to the influence of these cortical areas on the SC. Indeed, it is possible that the ability of the SC to synthesize cross-modal inputs is modulated by cortical influences (Jiang et al., 2001; Wilkinson et al., 1996). Alternatively, it is possible that recovery of function after concurrent damage to "polysensory cortices" involved in spatial attention and "sensory-specific" cortices involved in visual processing requires repetitive multisensory stimulation in order to be stably implemented and to produce generalized benefits for patients with both neglect and hemianopia. In other words, we hypothesize that, in order to induce multisensory plasticity in neglect patients with hemianopia, the stimulation needs to be regular, intensive and prolonged.

Thus, the aim of the present study is to verify whether pairing gaze-evoking auditory cues with undetectable visual cues in the contralesional field reinstates long-lasting basic visual and visuomotor abilities in neglect patients, and whether this amelioration can also be accomplished in patients with both neglect and elementary visual deficits, i.e., hemianopia. Neglect patients with and without hemianopia underwent a daily course of multisensory treatment for two weeks, and their behavioral performance was tested at three time points: before training, immediately after training and at a follow-up. Patients were required to detect brief flashes of light either in a unimodal condition (i.e., only visual stimuli were presented) or in a cross-modal condition (i.e., a sound was presented simultaneously with the visual target). Importantly, the multisensory stimulation was administered only in spatial and temporal coincidence (i.e., no temporal or spatial disparities were used).

Indeed, single neuron recordings (Stein & Meredith, 1993) and behavioral evidence in humans (Frassinetti et al., 2002; Bolognini et al., 2005a) suggest that multisensory integration is minimal, if not absent, in conditions with temporal and spatial disparity. Consequently, the presence of such a disparity during training could reduce the effectiveness of multisensory learning and, as a result, the possibility of reinforcing the efficiency of audio-visual responses (Stein & Rowland, 2020).

Methods

Participants

Nineteen right-brain-damaged patients with chronic left hemispatial neglect participated in the study. All patients were right-handed and had normal or corrected-to-normal visual acuity. Patients were selected based on their defective performance on at least one visuo-spatial neglect scale of the BIT (Conventional or Behavioural Scale; Wilson et al., 1987) or the Fluff test (Cocchini et al., 2001). The required sample size of the study was calculated with G*Power 3.1.9.6. The effect size used to calculate the sample size was estimated from previous studies investigating the effects of the audio-visual (AV) training (Passamonti et al., 2009; Dundon et al., 2015; Grasso et al., 2016). This calculation determined that a sample of 18 participants was required to investigate the effect of the training in two groups with a power of 95% at a 5% significance.

All patients' lesions were confirmed by computed tomography (CT) or magnetic resonance imaging (MRI) scans. The location and extent of patients' brain lesions were established from those scans using MRIcro. Lesions documented by the most recent clinical CT or MRI scan were traced onto the T1-weighted MRI template provided with MRIcro software (Rorden & Brett, 2000; Rorden, Karnath, & Bonilha, 2007, with the exception of N2 and NH12 whose scans were not available; see Figure 1).

Patients were classified into two separate groups – based on both clinical signs and lesion site – as showing neglect only (Neglect group: N1, N2, N3, N4, N5, N6, N7) or both neglect and hemianopia (Neglect + Hemianopia group: NH1, NH2, NH3, NH4, NH5, NH6, NH7, NH8, NH9, NH10, NH11, NH12). Clinical and demographic details are reported in Table 1. The two groups did not differ in terms of age (N: M = 63 years, SD = 12; NH: M = 60 years, SD = 13; t_{17}= 0.45; p = 0.66), lesion onset (N: M = 9.6 months, SD = 3.6; NH: M = 16 months, SD = 8,9; t_{17}= -1.81; p = 0.09) or lesion volumes (N: M = 171873 voxel, SD = 140927; NH: M = 162902, SD = 115887; t_{15}= 0.14; p = 0.56). Patients were informed about the procedure and the purpose of the study and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Regional Health Service Romagna (CEROM; n.2300). Anonymized data supporting the claims in this paper cannot be publicly archived due to ethical restrictions. Researchers seeking access to the data should contact the corresponding author [CB] who is responsible for considering and granting access requests.

Please insert Figure 1 and Table 1 about here

Neuropsychological assessment

All patients underwent a neuropsychological assessment including standardized tests for visuo-spatial deficits (see below). All tests were administered before the audio-visual training (baseline session) and immediately after the audio-visual training (post-training session) at the Center for Studies and Research in Cognitive Neuroscience, an outpatient facility. In addition, 10 patients out of 19 (N1, N2, N5, N6, N7, NH1, NH3, NH6, NH9, NH10) were also tested approximately 6.5 months (range 3-18 months) after the training to test long-term effects of the training. The remaining 9 patients, who were not available to perform the follow-up session, were mainly patients unable to reach the outpatient facility, which was located outside their region of residence.

Testing sessions required approximately 3h per patient distributed over 2 days to minimize fatigue. For each patient, a neglect assessment was performed by a neuropsychologist who did not administer the treatment to the same patient. Performance was analyzed with a series of ANOVAs (see below). To compensate for violations of sphericity, Greenhouse-Geisser corrections were applied whenever appropriate and corrected p-values (but uncorrected degrees of freedom) are reported. When significant main effects or interactions were found, post-hoc comparisons were run with Newman-Keuls tests. The cut-off for significance was set at 0.05.

Behavioral Inattention Test (BIT)

BIT (Wilson et al., 1987) is composed of two scales consisting of conventional and behavioral tests. The Conventional scale includes cancellation tasks, figure and shape copying, line bisection and drawing from memory. The Behavioral scale includes tests simulating daily life activities, such as scanning a picture, dialing a telephone, reading a menu or an article, telling and setting the time, sorting coins or cards, copying addresses and sentences and map navigation. The cut-off scores of the Conventional and Behavioral scales are 129 (range 0–146) and 69 (range 0–81), respectively. To test training effects, two separate ANOVAs were conducted on BIT Conventional and BIT Behavioral scores with Group (N, NH) and Session (Baseline, Post-training) as factors. In addition, to test long-term effects of the training, ANOVAs with Session (Baseline, Post-training, Follow-up) as a factor were run on the subset of patients tested at a follow-up session.

Word/non-word reading test (Làdavas et al., 1997b)

Stimuli consisted of 55 concrete Italian words (≥ 3 syllables) and 55 legal non-words obtained by substituting two letters at the beginning and at the end of the letter string. Words and non-words were of different lengths: 6 letters (10 stimuli), 7 letters (16 stimuli), 8 letters (34 stimuli), 9 letters (22 stimuli), 10 letters (18 stimuli) or 11 letters (10 stimuli). The stimuli, printed in upper-case 18-point Palatino font, were located at the center of a piece of paper (A4 size). Each piece of paper was presented horizontally, one at a time. The patients were instructed to read the letter string aloud. Omitting or misreading one or more letters was considered an error for the whole letter string. The proportion of correct responses was recorded. Training effects were tested using two separate ANOVAs on the number of correct responses to words and non-words, with Group (N, NH) and Session (Baseline, Post-training) as factors. In addition, ANOVAs with Session (Baseline, Post-training, Follow-up) as a factor were run on the subset of patients tested at a follow-up.

Reading text task

The text consisted of a short story in Italian. Four different stories were counterbalanced between subjects and testing sessions (syllable range: 328-391). All the texts had the same graphical and lexical characteristics (font: Arial 40; 6–8 lines per paragraph; 5–6 words per line; distance between lines: 1.5 cm) and were presented on a computer monitor (visual scene: 30°×24°) at a distance of ~70 cm. Patients were asked to read aloud, and both errors and reading time (syll/sec) were taken into account. Training effects were tested using two separate ANOVAs on errors and reading time, with Group (N, NH) and Session (Baseline, Post-training) as factors. Moreover, an ANOVA with Session (Baseline, Post-training, Follow-up) as a factor was run on the subset of patients tested at a follow-up.

Fluff Test (Cocchini et al., 2001)

All patients (except N5) were seated and blindfolded while six pieces of adhesive paper were attached by the experimenter to their clothing on the left part of their body (chest, shoulder, elbow, wrist, knee and hip). Patients were asked to remove all the paper pieces in 2 minutes. The task was performed in two conditions: Non-visual (i.e., with the patient blindfolded during the task) and Visual (i.e., with the patient not blindfolded). The number of pieces removed was recorded and analyzed with an ANOVA with Group (N, NH), Session (Baseline, Post-training) and Condition (Non-visual, Visual) as factors. An ANOVA with Session (Baseline, Post-training, Follow-up) and Condition (Non-visual, Visual) as factors was also conducted on patients who performed a follow-up session.

Computerized visual field test

Patients were presented with a stimulus array of 52° x 45° (horizontally and vertically, respectively) projected on the wall at a viewing distance of 140 cm. Targets consisted of white dots (1°) presented for 100 ms at different positions on a black background. A red fixation cross (0.5°) was presented at the center of the screen. The total number of targets presented was 96, i.e., 48 targets in each hemifield. Patients were asked to press a response button when they detected a target. The task was performed under two different conditions: when eye movements were prevented and patients had to keep their gaze on a central fixation cross (Fixation) and when patients were allowed to perform eye movements (Eye movement). The experimenter monitored the patients' gaze throughout the task. Visual detection rates were measured. Two separate ANOVAs were conducted on performance in the Fixation and Eye Movement conditions. The factors were Group (N, NH), Session (Baseline, Post-training) and Visual field (Left, Right). An ANOVA with Session (Baseline, Post-training, Follow-up) and Visual Field (Left, Right) as factors was also conducted on patients who performed a follow-up session.

Visual search test

The visual search test consisted of two subtests: the E–F test and the Triangles test (modified from Zhil, 2000 and Bolognini et al., 2005). In both subtests, the stimulus arrays (52° horizontally x 45° vertically) were displayed on a projector screen at a distance of 112 cm and patients were required to actively explore the visual field by using eye movements, but not head movements, to search for visual targets. The experimenter monitored patients' posture throughout the tasks. Before beginning each task, stimuli were shown to patients to ensure they had no problems in discriminating or recognizing colors, letters and shapes.

In the E-F subtest, each stimulus array contained 21 randomly distributed stimuli. The stimuli consisted of green letters projected on a black background. Twenty trials were presented: 16 trials in which the target was present and 4 in which the target was absent. Patients were instructed to fixate the red cross located in the center of the slide (2° x 2° fixation point) and to search, after the disappearance of the cross, for a single target (i.e., the green letter 'F'; 2° x 2°) embedded among distracters (the green letter 'E'; 2° x 2°). They had to report the presence of the target by pressing a 'yes' key if the target was present and a 'no' key if it was absent. Correct responses were recorded.

In the Triangle subtest, patients were asked to count targets (2° x 2° yellow triangles) amongst distractors (2° x 2° yellow squares) displayed against a black background. Patients pressed a button when they were able to indicate the number of targets in the array and then verbally declared their response, which was noted by the experimenter on a response sheet. Correct responses were analyzed with separate ANOVAs for each subtest with Group (N, NH) and Session (Baseline, Post-training) as factors. ANOVAs with Session (Baseline, Post-training, Follow-up) as a factor were also conducted on patients who performed a follow-up session.

Activities of Daily Living Inventory (ADL; modified from Kerkhoff et al., 1992; Bolognini et al., 2005b)

All patients and a close relative (except N6, NH5, NH7 and NH12, whose relatives' responses were not available) were asked to separately complete a 10-item questionnaire on a 5-point Likert scale exploring visual impairment in daily life. Raw mean scores constituted the outcome metric and were analyzed with two separate ANOVAs for the scores obtained by patients and relatives, with Group (N, NH) and Session (Baseline, Post-training) as factors. Two ANOVAs with Session (Baseline, Post-training, Follow-up) as a factor were also conducted on patients who performed a follow-up session (except N6 in the ANOVA on relatives' scores).

Unisensory visual detection task

An additional task was performed by patients to test their ability to visually explore and detect visual stimuli. The task used the same experimental apparatus as the audio-visual training (see below; Figure 2), but during this test, patients were presented only with visual stimuli. Differently from the other clinical tests, this task was performed twice before training and once after training. Specifically, the task was performed during the baseline session when patients were also performing the other clinical tests (i.e., baseline 1), immediately before the audio-visual training (baseline 2, ~ two weeks after baseline 1) and immediately after the audio-visual training (post-training session). The different time schedule of this task specifically aimed to verify not only the training outcomes, but also that patients could comply with a task similar to the one used during training. We also used this testing schedule to check that patients' performance was stable over time before the training.

In a light-attenuated room, patients detected a light stimulus (red LED; diameter: 0.5 cm; luminance: 90 cd/m2) presented on the horizontal meridian of the treatment apparatus (height: 30 cm, length: 200 cm) by pressing a button. The visual stimulus could appear for 100 ms at one of six eccentricities (56°, 40° and 24° bilaterally). Patients were asked to keep their head fixed and oriented towards the center of the apparatus, to fixate centrally and to perform saccadic eye movements towards visual stimuli. Patients had to press a response button when they detected the visual stimulus. Patients performed four blocks of 144 trials (16 trials at each eccentricity and 48 catch trials, i.e., no light stimulus). The accuracy (i.e., the percentage of correctly detected targets) at each eccentricity was analyzed with an ANOVA with Group (N, NH), Session (Baseline 1, Baseline 2, Post-training), Visual field (Left, Right) and Position (56°, 40°, 24°) as factors.

Audio-visual training

Similarly to previous studies using the same training procedure with hemianopic patients (Bolognini et al., 2005b; Passamonti et al., 2009; Dundon et al., 2015; Grasso et al., 2016b), the audio-visual training consisted of 10 daily training sessions (4 hours of training per day). Patients sat in front of a semicircular structure (i.e., a plastic horizontal arc; height: 30 cm, length: 200 cm; Figure 2) with LEDs (red LEDs; diameter: 0.5 cm; luminance: 90 cd/m^2) and loudspeakers located on the horizontal meridian at eccentricities of 24°, 40° and 56° in the left and right visual fields. Three different kinds of sensory stimulation were randomly presented during the training: i) unisensory visual (V; 100ms red LED light); ii) unisensory auditory (A; 100ms, 80dB white noise); and iii) multisensory audio-visual (AV; simultaneous presentation of V and A at the same spatial location). Patients were asked to keep their head fixed and oriented towards the center of the apparatus. They were required to fixate centrally and to perform saccadic eye movements towards visual stimuli. Patients had to press a response button when they saw any visual stimulus (V or AV), which was presented on the apparatus for 100 ms. In contrast, trials with unisensory auditory stimuli (A) were used to control for false alarms. An experimenter monitored eye gaze and administered the stimuli when the eyes were fixated centrally. Patients performed approximately 30 blocks of stimulation per day. Each block consisted of a total of 48 trials (12 V, 12 A, 24 AV). Patients were allowed to rest during the daily training session and frequent breaks were scheduled between blocks.

Please insert Figure 2 about here

Results

Behavioral Inattention Test (BIT)

The ANOVA on the BIT Conventional scores revealed a significant Session effect ($F_{1,17} = 22.55$; $p = 0.0002$; $\eta_p^2 = 0.57$), with significantly higher scores in the post-training session (M = 130.2; SD = 18.58) compared to the baseline (M = 117.4; SD = 24.42; $p = 0.00002$). No significant effect of Group ($F_{1,17} = 0.08$; $p = 0.78$; $\eta_p^2 = 0.005$) or Group X Session interaction ($F_{1,17} = 1.68$; $p = 0.21$; $\eta_p^2 = 0.09$) was found (Figure 3). Similarly, the ANOVA on the subset of participants who underwent the follow-up session revealed a significant effect of Session ($F_{2,18} = 10.01$; $p = 0.001$; $\eta_p^2 = 0.527$), with both the post-training session (M = 127.9; SD = 24.73; $p = 0.002$) and the follow-up session (M = 129; SD = 27.38; $p = 0.002$) showing increased scores compared to the baseline (M = 116.6; SD = 32.19; Figure 10). No significant difference was found between the post-training and the follow-up session ($p = 0.72$).

A significant effect of Session ($F_{1,17} = 20.11$; $p = 0.0003$; $\eta_p^2 = 0.54$) was also found in the ANOVA on BIT Behavioral scores, with increased scores post-training (M = 70.79; SD = 13.19) compared to baseline (M = 59.16; SD = 16.18; $p = 0.0003$). No significant effect of Group ($F_{1,17} = 0.06$; $p = 0.81$; $\eta_p^2 = 0.003$) or Group X Session interaction ($F_{1,17} = 0.0006$; $p = 0.98$; $\eta_p^2 < 0.001$ was found (Figure 3). Again, the analysis investigating follow-up effects revealed a significant effect of Session ($F_{2,18} = 10.57$; $p = 0.0009$; $\eta_p^2 = 0.54$), explained by higher scores in the post-training session (M = 69; SD = 17.3; $p = 0.001$) and the follow-up session (M = 69.7; SD = 15.13; $p = 0.002$) compared to baseline (M = 58; SD = 19.86). No significant difference was found between the post-training and the follow-up session ($p = 0.97$; Figure 10).

Please insert Figure 3 about here

Word/non-word reading test (Làdavas et al., 1997b)

The ANOVA on correct responses in the word reading task showed a significant main effect of Session ($F_{1,17} = 5.09$; $p = 0.038$; $\eta_p^2 = 0.23$), demonstrating an increase in accuracy in the post-training session ($M = 53.37$; $SD = 4.47$) compared to the baseline ($M = 49.32$; $SD = 11.6$; $p = 0.044$). In contrast, the ANOVA did not reveal any significant effect of Group ($F_{1,17} = 0.03$; $p = 0.87$; $\eta_p^2 = 0.002$) or Group X Session interaction ($F_{1,17} = 0.39$; $p = 0.54$; $\eta_p^2 = 0.023$; Figure 4). In the ANOVA investigating follow-up effects, the main effect of Session was not significant ($F_{2,18} = 2.47$; $p = 0.144$; $\eta_p^2 = 0.215$; Figure 10).

Similarly, the ANOVA on correct responses in the non-word reading task revealed a significant main effect of Session ($F_{1,17} = 28.68$; $p < 0.0001$; $\eta_p^2 = 0.63$), showing a higher number of correct responses post-training ($M = 47.79$; $SD = 7.79$) compared to baseline ($M = 40$; $SD = 13.9$; $p < 0.0001$). Again, no significant effect of Group ($F_{1,17} = 1.08$; $p = 0.31$; $\eta_p^2 = 0.059$) or Group X Session interaction ($F_{1,17} = 3.74$; $p = 0.07$; $\eta_p^2 = 0.18$) was found (Figure 4). The post-training improvement was also confirmed by the ANOVA on the subset of participants who underwent a follow-up session; there was a significant main effect of Session ($F_{2,18} = 8.05$; $p = 0.012$; $\eta_p^2 = 0.472$), explained by an increased number of correct responses in the post-training session ($M = 47.6$; $SD = 9.72$; $p = 0.004$) and the follow-up session ($M = 45.8$; $SD = 11.1$; $p = 0.007$) compared to baseline ($M = 38.4$; $SD = 17.84$). No difference was found between the post-training session and the follow-up session ($p = 0.47$; Figure 10).

Reading text task

The ANOVA on errors showed a significant main effect of Session ($F_{1,17} = 6.08$; $p = 0.025$; $\eta_p^2 = 0.26$), with a post-training decrease in errors ($M = 0.89$; $SD = 1.52$) compared to baseline ($M = 2.5$; $SD = 3.49$; $p = 0.022$). No significant main effect of Group ($F_{1,17} = 1.58$; $p = 0.23$; $\eta_p^2 = 0.085$) or Group X Session interaction ($F_{1,17} = 0.01$; $p = 0.92$; $\eta_p^2 = 0.0006$) was found (Figure 4). The ANOVA exploring follow-up effects revealed a trend toward significance of the factor Session ($F_{2,18} = 4.36$; $p = 0.059$; Figure 10).

The ANOVA analyzing reading speed revealed a significant main effect of Session ($F_{1,17} = 8.51$; $p = 0.01$; $\eta_p^2 = 0.033$), showing a post-training increase in reading speed (M = 3.43 syll/sec; SD = 1.43) compared to baseline (M = 3.1 syll/sec; SD = 1.4; $p = 0.011$). On the contrary, no significant effect of Group ($F_{1,17} = 0.001$; $p = 0.97$; $\eta_p^2 = 0.00008$) or Group X Session interaction ($F_{1,17} = 0.35$; $p = 0.56$; $\eta_p^2 = 0.02$) was found (Figure 4). Similarly, the ANOVA investigating follow-up effects revealed a significant effect of Session ($F_{2,18} = 3.68$; $p = 0.046$; $\eta_p^2 = 0.291$). Post-hoc comparisons confirmed a significant increase in reading speed post-training (M = 3.51 syll/sec; SD = 1.45) compared to baseline (M = 3.06 syll/sec; SD = 1.3; $p = 0.04$), and a trend towards an increased reading speed in the follow-up session (M = 3.36 syll/sec; SD = 1.45) compared to baseline, as well ($p = 0.09$; Figure 10).

Please insert Figure 4 about here

Fluff Test

The ANOVA revealed a significant effect of Condition ($F_{1,6} = 4.65$; $p = 0.047$; $\eta_p^2 = 0.23$), with a trend towards more accurate performance in the visual condition (M = 5.39; SD = 0.80) than the non-visual condition (M = 5.06; SD = 1.12; $p = 0.059$). More importantly, there was a significant effect of Session ($F_{1,16} = 13.33$; $p = 0.002$; $\eta_p^2 = 0.45$), explained by improved performance in the post-training session (M = 5.44; SD = 0.77) compared to baseline (M = 5.06; SD = 1.12; $p = 0.0009$). No other main effects or interactions were significant (all p-values > 0.09; Figure 5). Similarly, the ANOVA investigating follow-up effects revealed a significant main effect of Condition ($F_{1,8} = 6.13$; $p = 0.038$; $\eta_p^2 = 0.434$), again with better performance in the visual condition (M = 5.63; SD = 0.56) than the non-visual condition (M = 5.22; SD = 1.05; $p = 0.039$). As in the previous analysis, a significant effect of Session ($F_{2,16} = 5.82$; $p = 0.035$; $\eta_p^2 = 0.421$) was found. Post hoc comparisons to baseline (M = 5.11; SD = 1.02) revealed significantly improved performance in the follow-up session (M = 5.72; SD = 0.75; $p = 0.01$) and a trend towards improved performance in the post-training session (M = 5.44; SD = 0.7; $p = 0.08$). No significant difference was found between the post-training and the follow-up sessions ($p = 0.14$). Finally, the Condition X Session interaction was not significant ($F_{2,16} = 1.93$; $p = 0.181$; $\eta_p^2 = 0.194$; Figure 10).

Please insert Figure 5 about here

Computerized visual field test

In the Fixation condition, the ANOVA revealed a significant effect of Visual field ($F_{1,17} = 65.38$; $p < 0.0001$; $\eta_p^2 = 0.79$), with a significantly higher proportion of correct responses in the right visual field (M = 91%; SD = 12%) than the left visual field (37%; SD = 31%; p = 0.0002). In addition, a significant effect of Session ($F_{1,17} = 8.21$; $p = 0.011$; $\eta_p^2 = 0.33$) was found, with more correct responses in the post-training session (M = 66%; SD = 36%) than the baseline session (M = 61%; SD = 36%; p = 0.02). More interestingly, a significant Visual field x Session interaction ($F_{1,17} = 4.5$; $p = 0.049$; $\eta_p^2 = 0.21$) was found, revealing a post-training increase in detection rate only in the left visual field (baseline: M = 32%; SD = 28%, post-training: M = 41%; SD = 34%; p = 0.027), not the right visual field (baseline: M = 90%; SD = 10%, post-training: M = 91%; SD = 13%; p = 0.61). No other significant main effects or interactions were found (all p-values > 0.13; Figure 6). However, the ANOVA exploring follow-up effects revealed only a significant effect of Visual field ($F_{1,9} = 25.18$; $p = 0.0007$; $\eta_p^2 = 0.737$), and no effect of Session ($F_{2,18} = 2.27$; $p = 0.16$; $\eta_p^2 = 0.2$) or Visual field X Session interaction ($F_{2,18} = 2.71$; $p = 0.11$; $\eta_p^2 = 0.232$; Figure 10).

In the Eye movement condition, the ANOVA revealed a significant effect of Visual field ($F_{1,17} = 77.46$; $p < 0.0001$; $\eta_p^2 = 0.82$), with a significantly higher proportion of correct responses in the right visual field (M = 86%; SD = 15%) than the left visual field (M = 57%; SD = 26%; p = 0.0002). In addition, a significant effect of Session ($F_{1,17} = 14.24$; $p = 0.002$; $\eta_p^2 = 0.46$) was found, showing an increase in correct responses in the post-training session (M = 79%; SD = 19%) compared to baseline (M = 65%; SD = 30%; p = 0.002). Importantly, a significant Visual field x Session interaction ($F_{1,17} = 16.72$; $p = 0.0008$; $\eta_p^2 = 0.5$) was found, showing a post-training increase in detection rate only in the left visual field (baseline: M = 45%; SD = 28%, post-training: M = 70%; SD = 17%; p = 0.0002), not the right visual field (baseline: M = 85%; SD = 14%, post-training: M = 87%; SD = 17%; p = 0.57). No other significant main effects or interactions were found (all p-values > 0.16; Figure 6). The ANOVA exploring follow-up effects confirmed a significant main effect of Visual field ($F_{1,9} = 25.31$; $p = 0.0007$; $\eta_p^2 = 0.738$), revealing a significantly higher proportion of correct responses in the right visual field (M = 87%; SD = 16%) than the left visual field (M = 66%; SD = 28%; p = 0.0008). In addition, a significant effect of Session ($F_{1,18} = 7.18$; $p = 0.022$; $\eta_p^2 = 0.444$) was found, showing an increase in correct responses in both the post-training session (M = 81%; SD = 22%; $p = 0.008$) and the follow-up session (80%; SD = 22%; $p = 0.006$) compared to baseline (M = 68%; SD = 30%). No significant difference was found between the post-training and follow-up sessions ($p = 0.7$). Importantly, a significant Visual field x Session interaction ($F_{2,18} = 8.53$; $p = 0.005$; $\eta_p^2 = 0.487$) was found, revealing an increase in detection rate only in the left visual field, both in the post-training session (M = 74%; SD = 20%; $p = 0.0002$) and the follow-up session (M = 72%; SD = 26%; $p = 0.0002$) compared to baseline (M = 51%; SD = 33%). In contrast, no significant differences between sessions were found in the right visual field (all p-values > 0.29; Figure 10).

Please insert Figure 6 about here

Visual Search Test

The ANOVA conducted on correct responses in the E-F subtest revealed a significant main effect of Session ($F_{1,17} = 14.44$; $p = 0.001$; $\eta_p^2 = 0.46$), showing a higher proportion of correct responses in the post-training session (M = 84%; SD = 14%) compared to baseline (M = 72%; SD = 19%; $p = 0.0006$). No other main effects or interactions were significant (all p-values > 0.16; Figure 7). Similarly, the analysis of patients who also participated in the follow-up session showed a significant main effect of Session ($F_{2,18} = 14.36$; $p = 0.0002$; $\eta_p^2 = 0.615$), with more correct responses in both the post-training session (M = 86%; SD = 12%; $p = 0.0004$) and the follow-up session (M = 87%; SD = 14%; $p = 0.0005$) compared to baseline (M = 70%; SD = 21%; Figure 10).

The results of the ANOVA on performance in the Triangle Test showed a significant main effect of Session ($F_{1,16} = 34.75$; $p < 0.0001$; $\eta_p^2 = 0.68$), explained by an increase in the proportion of correct responses in the post-training session (M = 58%; SD = 16%) compared to baseline (M = 41%; SD = 14%; $p = 0.0002$). No other main effects or interactions were significant (all p-values > 0.91; Figure 7). This pattern of results was also confirmed by the ANOVA exploring follow-up effects, which revealed a significant main effect of Session ($F_{2,18} = 23.65$; $p < 0.0001$; $\eta_p^2 = 0.724$). Post hoc comparisons showed a significant increase in correct responses in both the post-training session (M = 56%; SD = 15%; $p = 0.0003$) and the follow-up session (M = 62%; SD = 12%; $p = 0.0002$) compared to baseline (M = 41%; SD = 14%; Figure 10).

Please insert Figure 7 about here

Activities of Daily Living Inventory

The ANOVA on the raw scores obtained from patients revealed a significant main effect of Session ($F_{1,17}$ = 16.08; p = 0.0009; η_p^2 = 0.49), with a reduction in subjectively perceived disability scores in the post-training session (M = 5.26; SD = 4.82) compared to baseline (M = 10.95; SD = 7.53; p = 0.0008). No other main effects or interactions were significant (all p-values > 0.16; Figure 8). Similarly, the ANOVA exploring follow-up effects showed a significant main effect of Session ($F_{2,18}$ = 12.36; p = 0.005; η_p^2 = 0.579), and post hoc comparisons revealed a significant reduction in subjectively perceived disability scores in both the post-training session (M = 6.2; SD = 4.57; p = 0.0009) and the follow-up session (M = 5.4; SD = 3.78; p = 0.0008) compared to baseline (M = 12.7; SD = 7.79; Figure 10).

The ANOVA on the scores obtained from relatives also revealed a significant main effect of Session ($F_{1,13}$ = 11.57; p = 0.005; η_p^2 = 0.47), showing lower subjectively perceived disability scores post-training (M = 8.47; SD = 5.88) compared to baseline (M = 14.87; SD = 11.1; p = 0.005). No other main effects or interactions were significant (all p-values > 0. 13; Figure 8). Similarly, the ANOVA on patients who participated in a follow-up session showed a significant main effect of Session ($F_{2,14}$ = 9.94; p = 0.014; η_p^2 = 0.587). Post hoc comparisons showed a significant reduction in subjectively perceived disability scores in both the post-training session (M = 10.25; SD = 4.98; p = 0.006) and the follow-up session (M = 7.25; SD = 3.76; p = 0.002) compared to baseline (M = 19.75; SD = 10.91; Figure 10).

Please insert Figure 8 about here

Unisensory visual detection task

The ANOVA on visual detection accuracy revealed a significant main effect of Visual field ($F_{1,17}$ = 107.17; p < 0.0001; η_p^2 = 0.86), showing significantly higher accuracy in the intact right visual field (M = 87%, SD = 17%) compared to the neglected left field (M = 40%; SD = 34%; p = 0.0002). There was also a significant main effect of Position ($F_{2,34}$ = 32.26; p < 0.0001; η_p^2 = 0.65), revealing a decrease in accuracy at larger eccentricities (56° position: M = 49%, SD = 39% vs. 40° position: M = 67%; SD = 35%; $p = 0.0001$; vs. 24° position: M = 74%; SD = 30%; $p = 0.0001$). In addition, a significant effect of Session was found ($F_{2,34} = 21.24$; $p < 0.0001$; $\eta_p^2 = 0.56$), showing a significant increase in accuracy in the post-training session (M = 76%; SD = 31%) compared to both baseline 1 (M = 58%; SD = 39%; $p = 0.0001$) and baseline 2 (M = 58%; SD = 35%; $p = 0.0001$). No difference was found between the two baselines ($p = 0.98$). More importantly, a significant Session x Visual field interaction was found ($F_{2,34} = 27.19$; $p < 0.0001$; $\eta_p^2 = 0.62$). Post hoc comparisons revealed a significant post-training increase in accuracy in the neglected left hemifield (M = 62%; SD = 34%) compared to both baseline 1 (M = 26%; SD = 28%; $p = 0.0001$) and baseline 2 (M = 32%; SD = 29%; $p = 0.0001$). Importantly, performance at baseline 1 and baseline 2 did not differ ($p = 0.08$). No significant differences were found post-training in the intact visual field (M = 89%, SD = 20%) compared to baseline 1 (90%: SD = 13%; $p = 0.77$) and baseline 2 (M = 83% SD = 17%; $p = 0.15$). Also, performance in the intact visual field did not differ between the two baselines ($p = 0.19$). No other relevant interactions were found (all p-values > 0.33; Figure 9).

Please insert Figures 9 and 10 about here

Discussion

The present study aimed to test whether the short-term visual detection improvements found in neglect patients after multisensory stimulation in a previous study (Frassinetti et al., 2002a) could persist in the long term, and whether those improvements could also be achieved in neglect patients with hemianopia.

Neglect patients with and without hemianopia were exposed to audio-visual stimulation for 4 hours a day for two weeks. These training sessions induced a long-term improvement that was maintained overall for at least 6.5 months after treatment. This is the first study in which audio-visual stimulation was applied as a daily treatment in these patients and long-lasting effects were reported. The improvement was consistent across a wide range of visual spatial tasks in the BIT, including both conventional tests, such as stimulus cancellation, and behavioral tests, comprising activities very similar to those carried out in daily life. Visual detection improvements were mainly evident in the neglected left hemifield, while no change was found in the intact right hemifield, suggesting that the training recovered visual attention towards the neglected hemifield without affecting attentional allocation toward the intact field. Amelioration was found in tests assessing both extrapersonal and personal space. Finally, improvements were also found when considering the patients' subjectively perceived disability in their daily life activities.

Importantly, the improvement was highly consistent across post-training sessions. This indicates that the training has widespread effects on the recovery of neglect which remain active after treatment, and that the audio-visual stimulation triggers plastic changes related to multisensory integration and space representation.

Similarly to a previous study conducted by Bolognini and colleagues (2005) , the results from the unisensory visual task – which was performed twice before training at an interval of two weeks – show that visual exploration abilities were stable in this sample of patients, thus suggesting that the post-training outcomes were not merely due to spontaneous recovery. This also suggests that practice effects or learned test responses did not play a relevant role in the observed post-training improvements. This is also in line with previous results with hemianopic patients where the effects of unisensory visual stimulation training were tested (Passamonti et al., 2009). Specifically, hemianopic patients did not show any improvement in performance after training with unisensory visual stimuli. In the same vein, the occurrence of two visual stimuli, although presented in the same spatial position, did not improve visual detection in neglect patients (Làdavas et al., 1994). More precisely, a noninformative visual cue presented in the left hemifield before the visual target did not ameliorate visual responses, therefore corroborating the relevance of multisensory stimulation and suggesting that the improvements found in the present study could be specifically ascribed to audio-visual training.

Thus, the results of the present study suggest that systematic multisensory stimulation can affect orientation towards the neglected hemifield, thereby improving the processing of visual events and visual exploration. Similar evidence was found in hemianopic cats trained with audio-visual stimuli, who recovered the ability to discriminate and orient towards visual patterns in the previously blind hemifield (Jiang et al., 2015; Dakos et al., 2019). In addition, this amelioration was accompanied by a reinstatement of visual responses in the multisensory layers of the ipsilesional SC (Yu et al., 2009; 2012). Thus, converging evidence from previous studies and the present study suggests that when unisensory visual processing is impaired due to a brain lesion, areas dedicated to visuo-spatial processing, such as the retino-colliculo-extrastriate pathway – a neural substrate mediating visual exploration, oculomotor activity and multisensory integration, and functionally spared in hemianopic and neglect patients (Tamietto et al., 2012) – can reinstate visual behavior. More precisely, audio-visual stimulation may enhance activity within this spared network and recruit additional cortical areas responsible for oculomotor planning, such as the frontal eye fields, which are known to be strongly connected to the SC and involved in spatial orienting behaviors (for a review, see Krauzlis et al., 2013).

Overall, the results of the present study show that cross-modal training reinforced the innate ability of the brain to perceive multisensory events, which is masked under normal conditions in which unimodal processing of sensory events is sufficient for their perception. Cross-modal events are a common feature of normal environments, and patients are exposed to thousands of such events in the contralesional space every day.

Thus, an obvious question is why this everyday exposure is insufficient for rehabilitation, while series of exposures to visual and auditory stimuli during training were able to ameliorate neglect. One possible answer is that this might be due to the high density of cross-modal events in each of the exposure sessions, relative to that which is generally found in everyday environments. Another possible answer, not incompatible with the previous one, is that the cross-modal stimuli in each training session were always congruent in space and time, and their spatiotemporal relationship remained constant within and across exposure sessions. In contrast, visual, auditory and audio-visual cues in an everyday environment vary substantially in their cross-modal spatiotemporal relationships. Such variation may degrade the effectiveness of the stimuli in guiding changes in the underlying circuit, as suggested by animal studies revealing that plastic changes in the responses of the SC and interconnected circuits occur according to Hebbian principles after repetitive and spatiotemporally coincident audio-visual pairs (for a review, see Stein & Rowland, 2020).

This factor could also explain why, in a previous study (Frassinetti et al., 2005) where audio-visual stimulus pairs were presented at the same position and at disparities of 16° and 32°, neglect patients with hemianopia did not show visual detection improvements in the cross-modal condition compared to the unimodal visual condition. The different outcomes of that previous study (Frassinetti et al., 2005) and the present study underscore the relevance of following multisensory integration principles for achieving the desired amelioration in patients with spatial perception deficits. Other factors that could explain the difference between the two studies include the frequency and duration of the experimental sessions; in Frassinetti et al.'s study (2005) only 64 cross-modal trials (8 trials for each of the 8 auditory stimulus positions) were delivered in two days (1 hour per day), whereas patients in the present study were repeatedly presented with audio-visual stimulus pairs in the neglected hemifield on a daily basis (4 hours per day) for two weeks.

In conclusion, the results of the present study highlight the relevance of spared subcortical circuits to the recovery of visual functions after brain lesions. These findings also reveal that visuo-spatial disorders related to neglect can be recovered by means of systematic audio-visual stimulation, therefore documenting the importance of multisensory integration systems for constructing spatial representations.

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ID	Sex	Age (years)	Onset (months)	Etiology
N1	M	59	10	Ischemic
N2	F	77	4	Ischemic
N3	F	72	7	Hemorrhagic
N4	M	67	14	Ischemic
N5	M	42	10	Ischemic
N6	F	69	8	Hemorrhagic
N7	M	57	14	Ischemic
NH1	M	58	21	Ischemic
NH2	F	35	2	Hemorrhagic
NH3	M	65	15	Ischemic
NH4	M	48	8	Ischemic
NH4	M	67	21	Traumatic
NH5	M	60	29	Ischemic
NH6	M	49	21	Hemorrhagic
NH7	M	81	11	Ischemic
NH8	M	77	6	Hemorrhagic
NH9	F	58	14	Ischemic
NH10	M	65	13	Ischemic
NH11	M	65	31	Ischemic

Table 1. Patient demographic and clinical data.

Figure legends

Figure 1. Locations of patients' brain lesions. The image shows the lesions of the neglect patients (N) and neglect + hemianopia patients (NH) projected onto four axial slices of the standard MNI brain. In each slice, the left hemisphere is on the left side. The positions of the axial slices are marked by white lines on the sagittal view of the brain.

Figure 2. Schematic bird's eye view of the apparatus used for the audio-visual training and the unisensory visual detection task. Patients were placed at the center of a concave ellipse (200 cm wide and 30 cm high) in which six LED lights and six piezoelectric loudspeakers were positioned at increasing eccentricities (24°, 40° and 56° to the left and to the right) with respect to the center. During the unisensory visual detection task, only LED stimuli were used.

Figure 3. Training effects on patients' performance in the BIT battery, including both the BIT conventional scale (cut-off: 129) and the BIT behavioral scale (cut-off: 69). N: Neglect patients; NH: Neglect + Hemianopia patients. Error bars represent Standard Error of the Mean (S.E.M.).

Figure 4. Training effects on patients' performance in reading words (number of correct words on a total of 55), nonwords (number of correct nonwords on a total of 55) and text (number of errors and reading speed). N: Neglect patients; NH: Neglect + hemianopia patients. Error bars represent standard error of the mean (S.E.M.).

Figure 5. Training effects on patients' performance in the Fluff Test, averaged across the visual and non-visual conditions. N: Neglect patients; NH: Neglect + hemianopia patients. Error bars represent standard error of the mean (S.E.M.).

Figure 6. Training effects on patients' performance in the computerized visual field test in the left and right visual fields, showing both the fixation and the eye movement conditions. N: Neglect patients; NH: Neglect + hemianopia patients. Error bars represent standard error of the mean (S.E.M.).

Figure 7. Training effects on patients' performance in the visual search test, including both the E-F subtest and the Triangle subtest. N: Neglect patients; NH: Neglect + hemianopia patients. Error bars represent standard error of the mean (S.E.M.).

Figure 8. Training effects on the Activities of Daily Living Inventory (ADL) scores provided by both patients and their relatives. N: Neglect patients; NH: Neglect + hemianopia patients. Error bars represent standard error of the mean (S.E.M.).

Figure 9. Training effects on patients' performance in the unisensory visual detection task. Performance is reported at baseline 1, baseline 2 and the post-training session. N: Neglect patients; NH: Neglect + hemianopia patients. Error bars represent standard error of the mean (S.E.M.).

Figure 10. Performance of the subset of patients tested at a follow-up session in all the clinical tests. Performance is reported at baseline, post-training and follow-up sessions. Error bars represent standard error of the mean (S.E.M.).

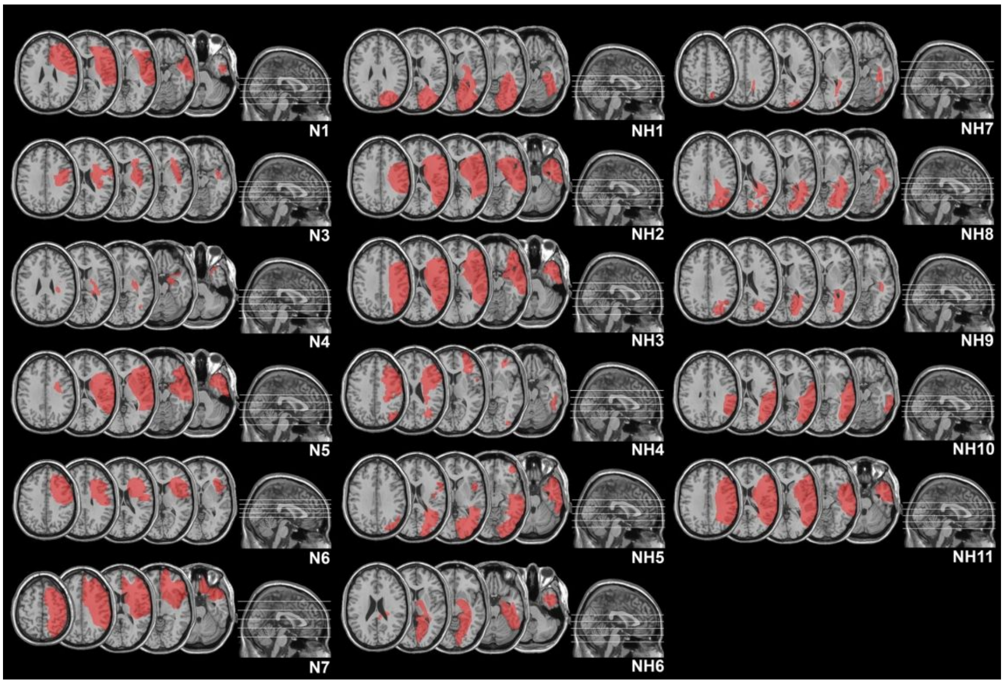

Figure 1

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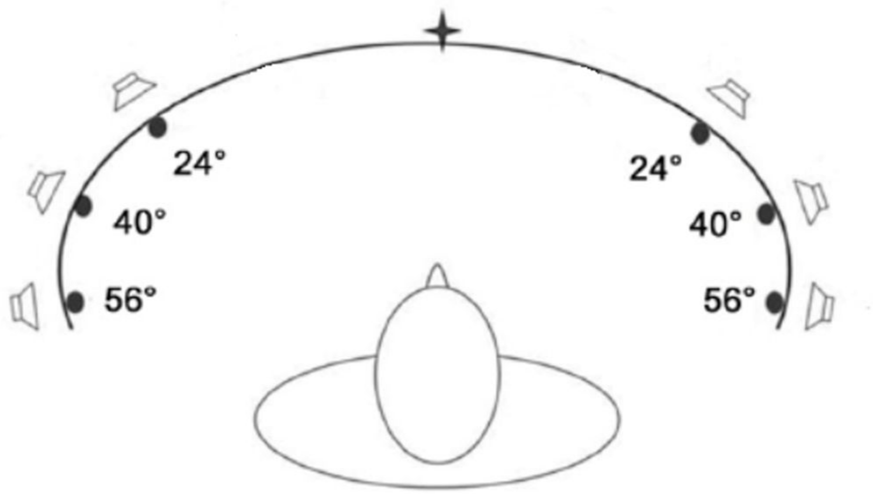

Figure 2

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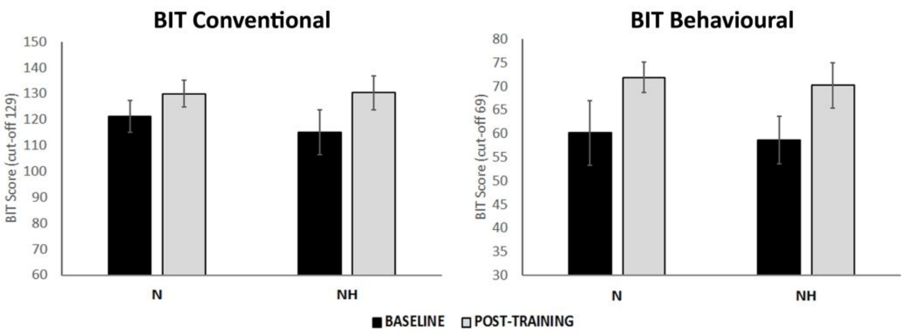

Figure 3

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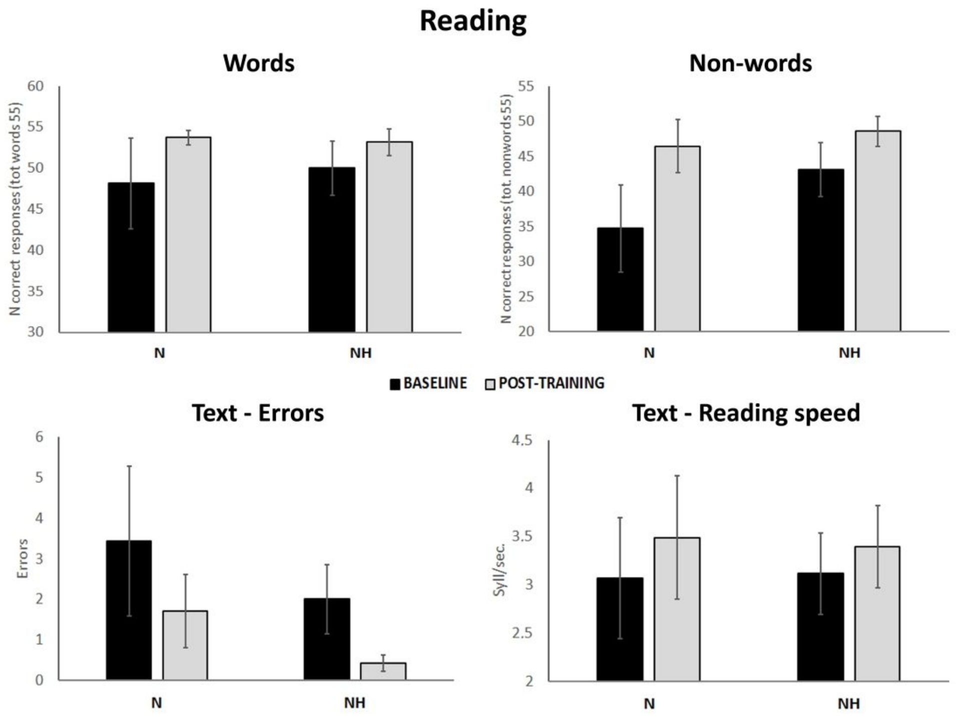

Figure 4

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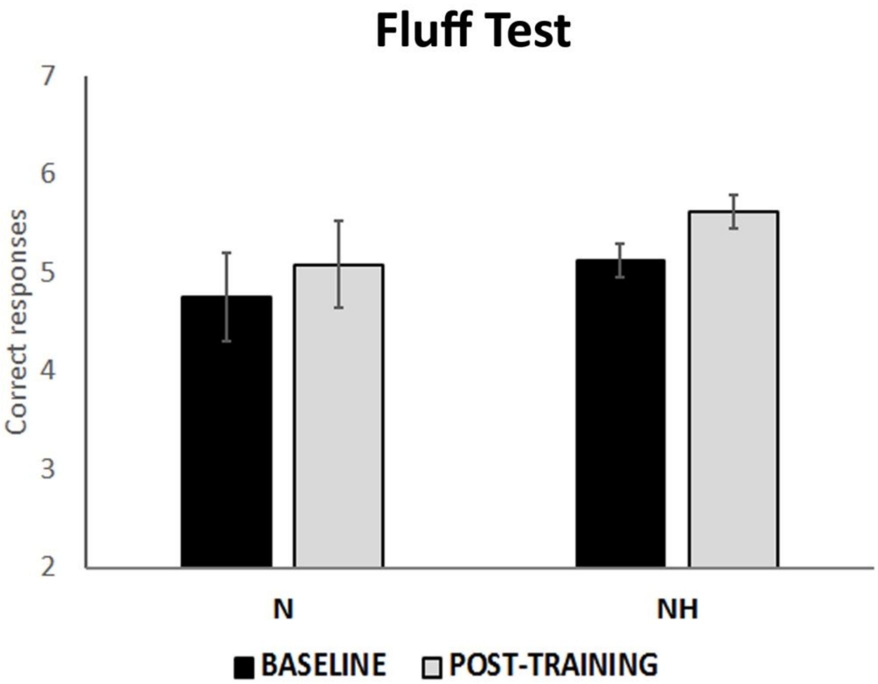

Figure 5

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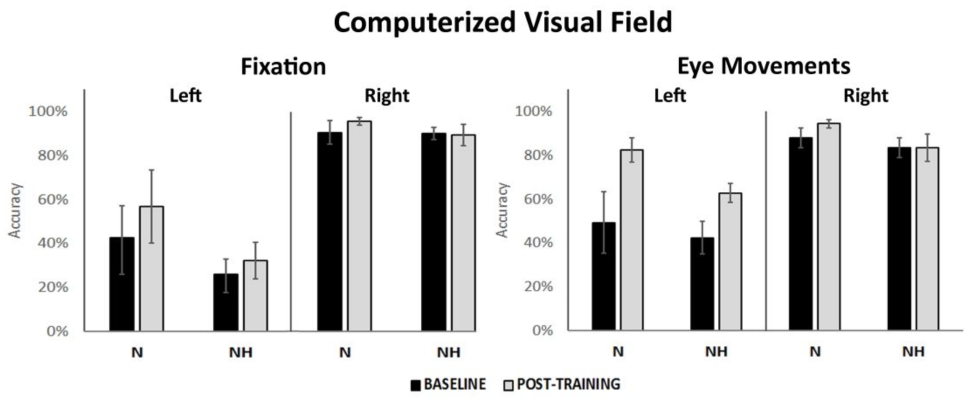

Figure 6

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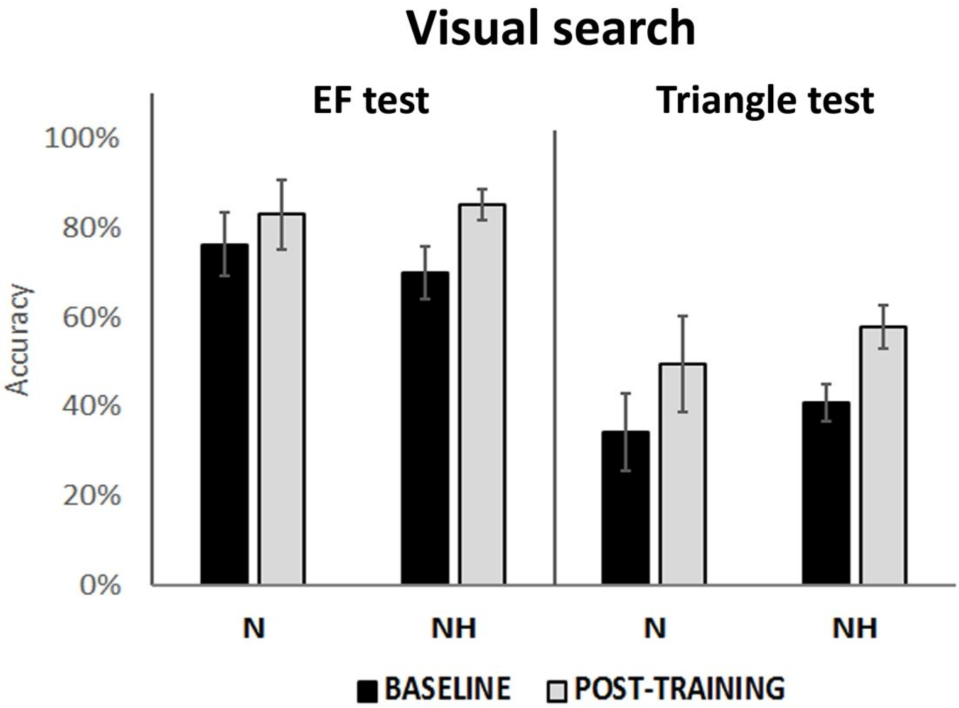

Figure 7

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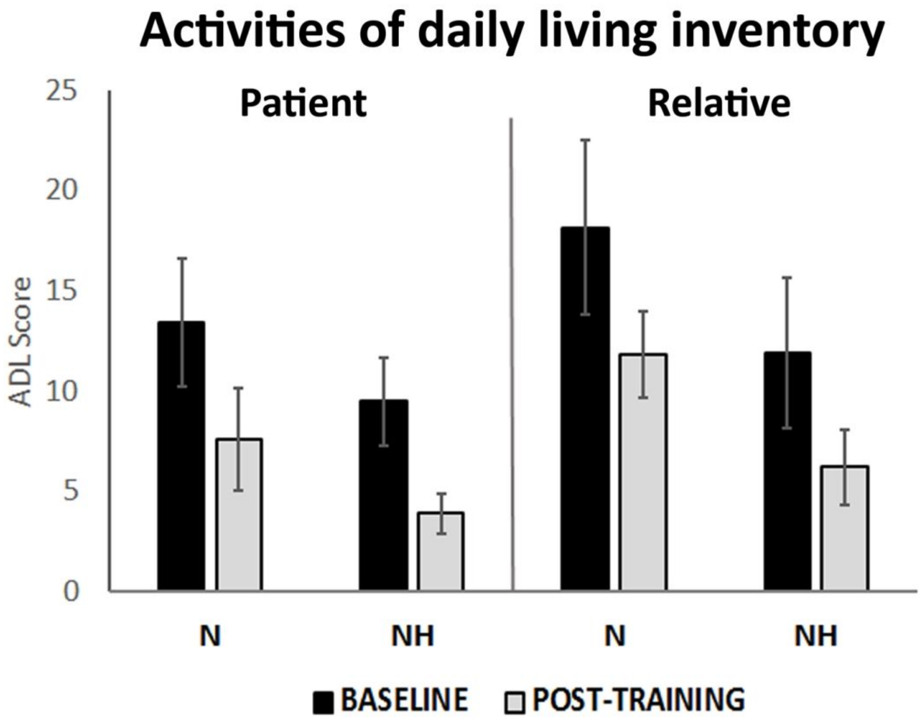

Figure 8

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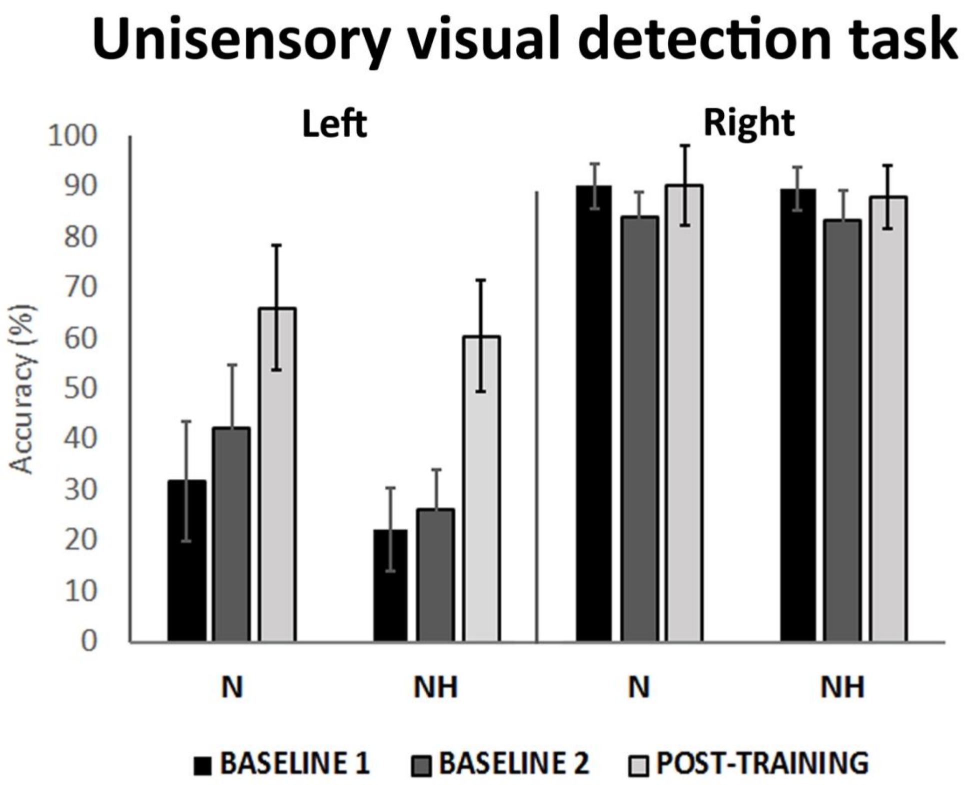

Figure 9

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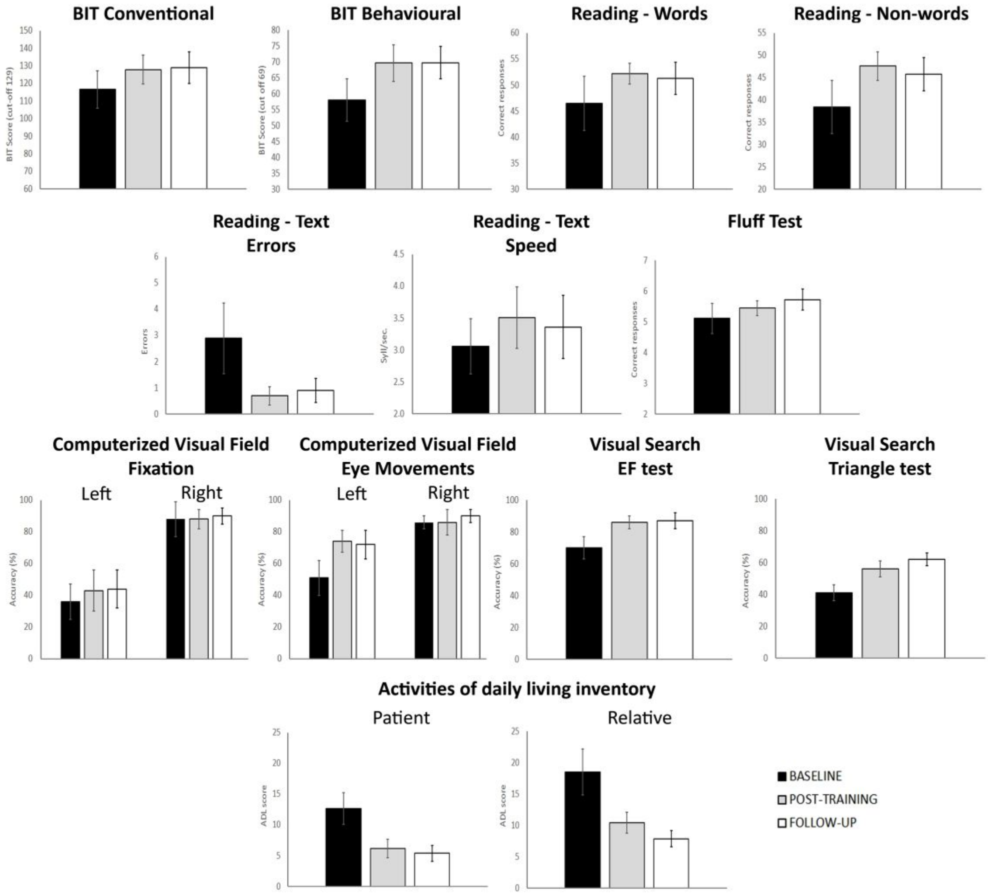

Figure 10

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