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Visual search improvement in hemianopic patients after audio-visual stimulation

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One of the most effective techniques in the rehabilitation of visual field defects is based on implementation of oculomotor strategies to compensate for visual field loss. In the present study we develop a new rehabilitation approach based on the audio-visual stimulation of the visual field. Since it has been demonstrated that audio-visual interaction in multisensory neurons can improve temporally visual perception in patients with hemianopia, the aim of the present study was to verify whether a systematic audio-visual stimulation might induce a long-lasting amelioration of visual field disorders. Eight patients with chronic visual field defects were trained to detect the presence of visual targets. During the training, the visual stimulus could be presented alone, i.e. unimodal condition, or together with an acoustic stimulus, i.e. crossmodal conditions. In the crossmodal conditions, the spatial disparity between the visual and the acoustic stimuli were systematically varied (0, 16 and 32° of disparity). Furthermore, the temporal interval between the acoustic stimulus and the visual target in the crossmodal conditions was gradually reduced from 500 to 0 ms. Patients underwent the treatment for 4 h daily, over a period of nearly 2 weeks. The results showed a progressive improvement of visual detections during the training and an improvement of visual oculomotor exploration that allowed patients to efficiently compensate for the loss of vision. More interesting, there was a transfer of treatment gains to functional measures assessing visual field exploration and to daily-life activities, which was found stable at the 1 month follow-up control session. These findings are very promising with respect to the possibility of taking advantage of human multisensory capabilities to recover from unimodal sensory impairments.

Keywords: multisensory integration; visual field defect; oculomotor compensation; rehabilitation

Abbreviations: RT = reaction time; SC = superior colliculus; SOA = stimulus onset asynchrony

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Introduction

Visual field defects are common consequences of posterior brain injury. Nearly 80% of patients with unilateral post-chiasmal brain damage acquired a homonymous visual field defect (Zihl, 1994), in which there is the loss of vision in one hemifield, which corresponds retinotopically to the damaged area (Zihl and Kennard, 1996). Spontaneous complete recovery from scotoma is very unusual, occurring in <20% of all patients. Recovery depends on the underlying pathology: homonymous visual field defects from vascular disease seem to have a poor prognosis for a spontaneous recovery, while a more remarkable recovery from scotoma often occurs after traumatic damage (Zihl and von Cramon, 1985). Recovery of vision normally occurred within 8–12 weeks, after that further recovery is negligible (Pambakian and Kennard, 1997; Zihl, 2000).

Impairments in visual exploration and reading represent the most common consequences of visual field disorders. Patients with visual field disorders exhibit impairments of visual orientation and a typical defective oculomotor scanning behaviour. Consequently, patients omit objects and relevant parts of scene located in their blind hemifield (Zihl, 1995, 2000; Zihl and Hebel, 1997; Hildebrandt *et al.*, 1999; Pambakian *et al*, 2000; Tant *et al.*, 2002). Moreover, visual field sparing of <5° is typically associated with impaired reading, which constituted a major source of visual disability. It is well known that parafoveal field regions form a 'perceptual window' for reading, subserving letter identification and playing a crucial role in both text recognition and guidance of eye movements in reading (Chedru *et al*, 1973; Zihl, 1995; Pambakian *et al*, 2000). Thus, parafoveal field loss affects reading at the sensory level, preventing patients from perceiving a word as a whole and impairing the visual guidance of eye movements in reading. As a consequence, the reading performance, i.e. correctly read words, is markedly reduced (Poppelreuter, 1971/1990; Morris *et al.*, 1990; Zihl, 1995, 2000).

Patients with visual field defects complain about many difficulties in daily-life activity: as the visual field defect restricts the patient's overview, they complain of difficulties with noticing persons or relevant objects, avoiding obstacles, driving, walking and many other activities (Pambakian and Kennard 1997; Zihl, 2000).

Some of the most useful approaches to the treatment of hemianopia are based on making up for visual field loss by oculomotor compensation. Usually, the training involves psychophysical techniques based on a top-down mechanism, aimed at strengthening the patient's attention for the blind hemifield and improving their ability to explore the visual field with saccadic movement (Zihl, 1981, 1995, 2000; Kerkhoff *et al.*, 1992, 1994; Pambakian and Kennard, 1997; Kerkhoff, 1999, 2000; Nelles *et al.*, 2001; Pambakian *et al.*, 2004). Two procedures have been used: a training to enlarge saccade amplitudes or a training to implement visual search by using search paradigms. With these trainings, some authors have obtained an amelioration of explorative eye movements and of visual exploration, that enabled hemianoptic patients to overcome and efficiently compensate for the visual field loss (Zihl, 1980, 1981, 2000; Kerkhoff *et al.*, 1992, 1994; Pambakian and Kennard 1997; Kerkhoff, 1999, 2000; Nelles *et al.*, 2001; Pambakian *et al.*, 2004). These procedures, however, require patients to voluntarily maintain attention oriented to the affected hemifield. Moreover, in patients with additional lesion to the striate cortex, such as injury to the thalamus, parieto-occipital structures and white matter, the treatment effect was smaller (Zihl, 2000).

In the present study we developed a new approach to the compensatory visual field training based mainly on a bottom-up mechanism, involving a multisensory integration mechanism, that seems to be very promising because it does not require patients' ability to voluntarily maintain attention oriented to the affected field (Pizzamiglio *et al.*, 1992; Làdavas *et al.*, 1994), which may be difficult for brain-damaged patients.

Neurophysiological studies in animals (Stein and Meredith, 1993) have shown, in superior colliculus (SC) and regions of cortex, the existence of neurons responding to stimuli from different sensory modalities. In particular, multisensory neurons form a major component of the output circuitry of SC, since nearly three-quarters of the SC's neurons with descending efferent projections to brain stem motor areas are multisensory. Thus, multisensory integration might play a significant role in behaviours mediated by SC, as the attentive and orientation behaviours as well as saccadic eye movements (Stein, 1998).

Recent behavioural studies in humans have documented that audio-visual interaction can improve visual detection (Frassinetti *et al.*, 2002*a*, *b*; Bolognini *et al.*, 2005*a*), and visual localization (Hairston *et al.*, 2003) and reduce saccadic reaction times (RTs) (Harrington and Peck, 1998; Hughes *et al.*, 1998; Colonius and Arndt, 2001; Corneil *et al.*, 2002; Arndt and Colonius, 2003). In particular, it has been found that a sound, spatially and temporally coincident to a visual stimulus, can improve visual perception in the blind hemifield of hemianopic patients (Frassinetti *et al.*, 2005). Based on these findings, we investigated the possibility to induce a long-lasting amelioration of visual field defects by using a training based on a systematic audio-visual stimulation of the visual field. For this purpose, eight patients with homonymous hemianopia or quadrantopia underwent the audio-visual training over a period of 2 weeks.

The improvement of patients' performance in the training sessions was assessed by measuring in each session the percentages of visual detections in the unimodal and crossmodal conditions. Furthermore, to evaluate the effect of the audio-visual training on visual disorders, different visual abilities, i.e. visual detections, visual exploration and reading abilities, were assessed before and after the treatment. In particular, to assess whether the improvement is due to an enlargement of the visual size or to the ability to compensate for visual field loss by using eye movements, visual detection in the blind hemifield was measured using different tests under two different conditions: Eye-Movements Condition and Fixed-Eyes Condition. If the improvement is due to a restitution of visual field, one might expect an amelioration in each condition. On the other hand, if the improvement is to be ascribed only to the implementation of oculomotor compensatory strategies, without a restitution of visual field, one might expect an improvement only in the Eye-Movements Condition.

Finally, to evaluate the transfer of the training's gain to daily life, a questionnaire investigating the most impaired daily activities was given to the patients before and after the treatment.

Subjects and methods

Subjects

Selection of patients was based on complete availability of visual perimetry (*see* Fig. 1A and B). Eight patients with chronic visual field defect participated in the study. They gave informed consent to participate according to the Declaration of Helsinki (International Committee of Medical Journal Editors, 1991) and the Ethical Committee of the Department of Psychology, University of Bologna.

Details concerning sex, age, length of illness, lesion sites and the presence of visual field defect are reported in Table 1. The patients had suffered unilateral lesion in the right or left posterior hemisphere, as confirmed by MRI scanning (*see* Fig. 2A and B). The lesion of each patient was reconstructed and areas involved by the lesion were also coded using the method introduced by Damasio and Damasio (1989) (*see* Table 2).

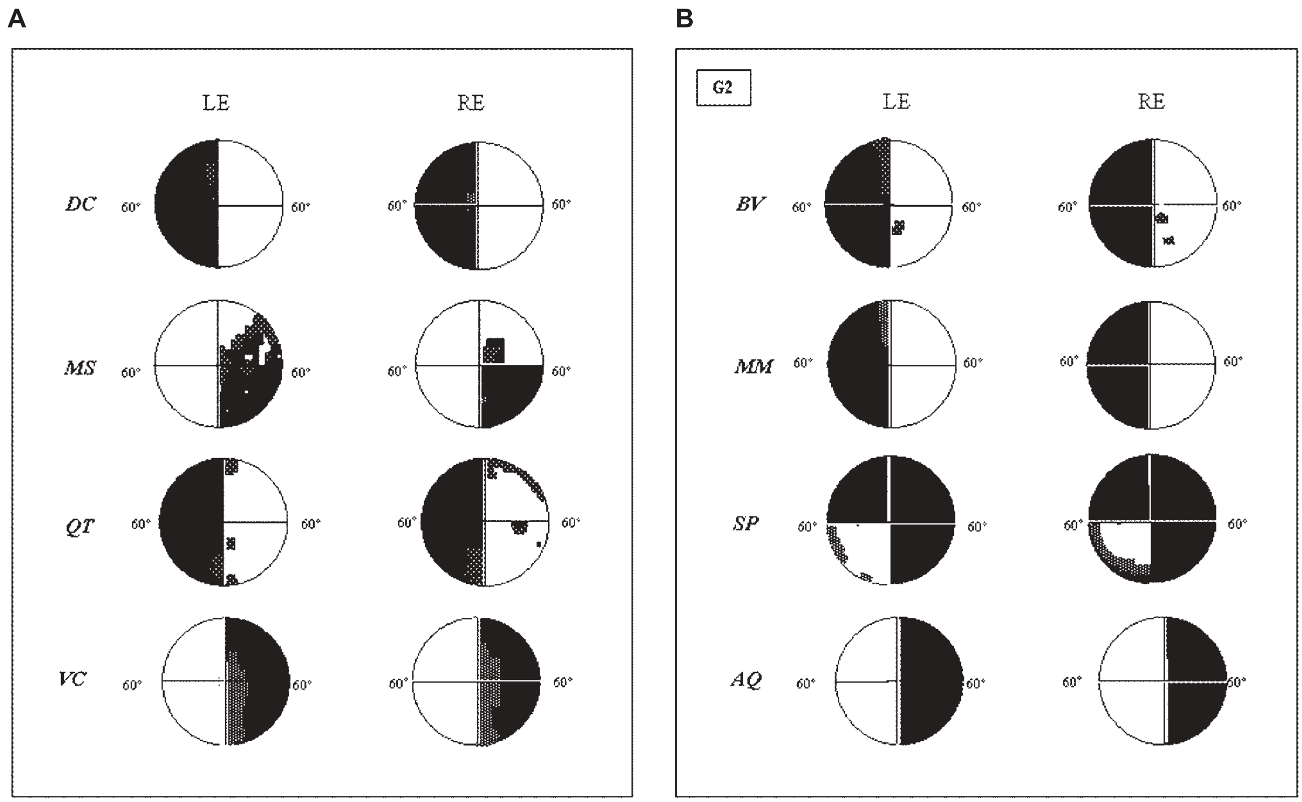

Fig. 1 (**A**) The figure depicts the reconstruction of the visual field based on the computerized perimetry for each patient of G1. LE = left eye; RE = right eye. Black areas: regions of lost vision; black with white dots areas: amblyopic regions; white areas: intact regions. (**B**) The figure depicts the reconstruction of the visual field based on the computerized perimetry for each patient of G2. LE = left eye; RE = right eye. Black areas: regions of lost vision; black with white dots areas: amblyopic regions; white areas: intact regions.

Table 1 Summary of the clinical data

Group	Patient	Age/sex	Onset of illness (months)	Lesion site	Visual field defect
G1	DC	77, F	10	Right occipital	Left homonymous hemianopia
	MS	42, F	12	Left parietal-occipital	Right lower quadrantanopia
	QT	70, M	4	Right occipital	Left homonymous hemianopia
	VC	40, F	13	Left temporo-occipital	Right homonymous hemianopia
G2	MM	47, F	7	Right occipital	Left homonymous hemianopia
	BV	55, M	15	Right temporo-parietal	Left homonymous hemianopia
	SP	56, F	24	Not available	Right homonymous hemianopia
	AQ	70, M	11	Left temporo-occipital	Right homonymous hemianopia

Patients showed a normal hearing, as measured by audiometry in each ear, with no sign of asymmetry between ears, and a normal or corrected binocular visual acuity for near and far space. Patients with neglect were excluded from the study.

All patients underwent a neuropsychological examination of visual field disorders that consisted in the assessment of: (i) visual detections; (ii) visual scanning; (iii) hemianopic dyslexia; (iv) self evaluation questionnaire of activities of daily living.

Assessment of visual field disorders

Assessment of visual detections

In order to investigate whether patients were able to compensate for the visual field loss by using eye movements, patients underwent each test under two conditions. In the Eye-Movements Condition, patients were free to use eye movements to detect the visual target. Otherwise, in the Fixed-Eyes Condition, eye movements were not allowed and the fixation was monitored by the experimenter.

Unimodal visual test. Visual detections were assessed by using the apparatus employed for the presentation of the training procedure (*see* Subjects and methods). A visual target was presented for 100 ms in different spatial positions, at 8, 24, 40 and 56° from either side of the central fixation point. 120 trials were presented: 12 trials for each of the 8 visual positions and 24 trials in which no visual stimulus was presented, i.e. catch trials. The total number of trials was equally distributed in three blocks. Patients were instructed to press a

Brain (2005), **128,** 2830–2842

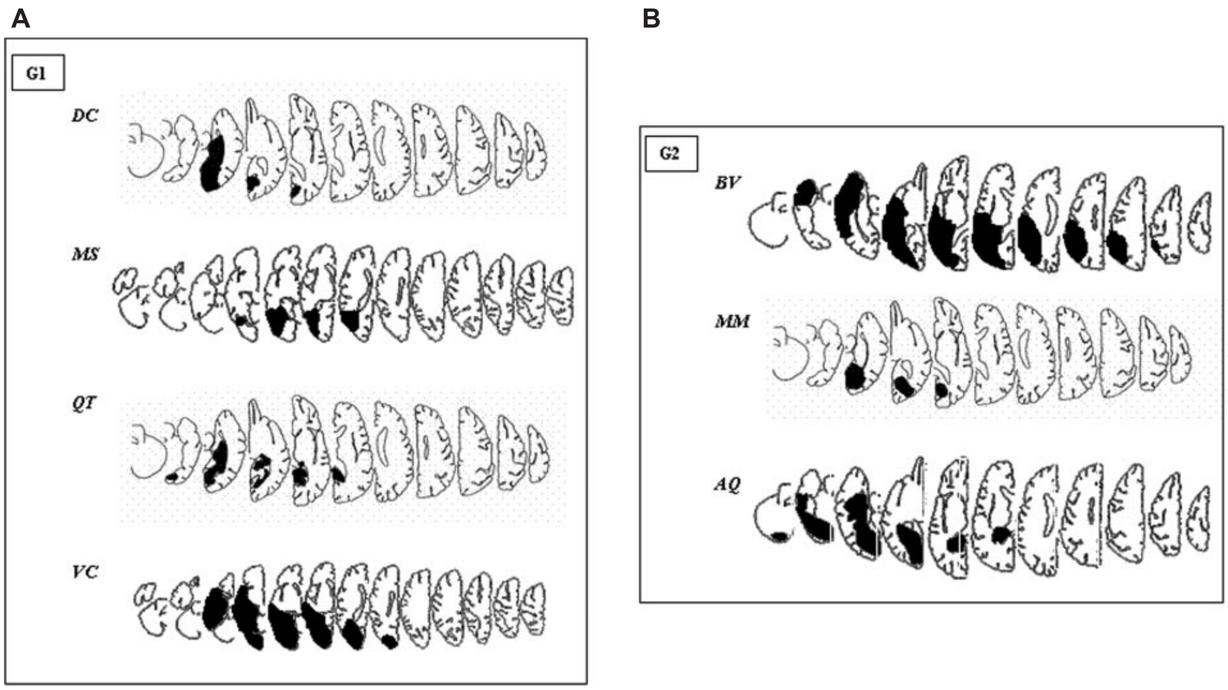

Fig. 2 The figure depicts the graphical reconstruction of the lesion according to Damasio and Damasio's atlas (1989) for each patient of (**A**) G1 and (**B**) G2.

Table 2 Summary of lesion data: anatomical areas involved (x) by lesion are coded using the method introduced by Damasio and Damasio (1989)

Group	Patient	Frontal lobe		Temporal lobe										Parietal lobe					Occipital lobe						
		F2	F8	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	P1	P2	P3	P5	P6	O1	O2	O3	O4	O5	O6	O7
G1	DC										x	x							x	x	x	x			
	MS						x												x		x	x	x	x	x
	QT	x									x	x							x	x	x			x	x
	VC			x		x		x	x	x	x	x						x		x	x	x	x	x	x
G2	BV		x	x	x		x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x	
	MM																		x	x	x	x			x
	SP	Not available																							
	AQ			x		x	x					x	x						x	x	x	x		x	x

response button after the detection of the targets and visual detections for each spatial position were recorded.

Computerized visual field test. The stimulus array was of 52° × 45° (horizontally and vertically, respectively), projected on the wall. The viewing distance was 120 cm. Targets were white dots (1°), presented for 100 ms at different positions on a black background. The fixation point was a red cross presented on the centre of the slide. The total number of targets presented was 96, i.e. 24 targets for each quadrant of the visual field. The task was to press a response button after the detection of the target. Visual detections and RTs were measured.

Assessment of visual scanning

Visual search test. This test consisted three subtests: the E–F test, the Triangles test and the Number test. Patients were shown the stimulus arrays (52° × 45°, horizontally and vertically respectively) projected on slides at a distance of 120 cm and they were required to actively explore the visual field by using eye, but not head, movements to search for visual targets.

E–F test (modified from Zihl, 2000). Each stimulus array contained 21 stimuli, distributed at random over the array. The stimuli consisted of green letters, projected on a black background. 20 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 centre of the slide (i.e. fixation point) and to search, after the disappearance of the cross, for a single target (i.e. the green letter 'F') embedded among distracters (the green letters 'E'). They had to report the presence of the target, by pressing a 'yes' key response if the target was present and a 'no' key response if it was absent. Correct responses and RTs were recorded.

Triangles test (modified from Zihl, 2000). Patients were shown stimulus arrays, each containing 21 stimuli, distributed at random over the array and presented on a black background. Different shapes of the same size were used as stimuli: yellow squares as distracters and yellow triangles as targets. The number of targets presented in each trial varied from 0 to 13. As the number of targets increased, the number of distracters decreased, thus in each stimulus array there were always 21 stimuli. The total number of trials was 20. Patients were instructed to fixate a red cross presented in the centre of the slide (i.e. fixation point) and, after the disappearance of the cross, to search and report the total number of targets. Moreover, after having found a target, patients had to indicate it by using a light pointer.

Correct responses and time for searching performance were recorded.

Number test (modified from Zihl, 2000). Eight stimulus arrays, each containing 15 numbers (from number 1 to 15) distributed at random over a black background, were presented. The task was to point to the individual numbers in an ascending order using a light pointer.

Time for error-free searching performance was recorded.

Assessment of hemianopic dyslexia

Only dyslexia for single word reading task was assessed. Stimuli comprised 48 letter strings, 24 of 9 and 24 of 11 letters in length. Each string was always composed of upper-case letters (0.7×0.7 cm; $0.95^\circ \times 0.95^\circ$) separated by a single character space (0.7×0.7 cm; $0.95^\circ \times 0.95^\circ$). Stimuli were printed in white against a black background, and they were displayed horizontally at the centre of the video screen, one at the time. Half of the stimuli (n = 24) were common Italian words, and the remaining half (n = 24) were non-words generated by changing two letters of each word. The substituted letters were located at the beginning and at the end of the stimulus. All non-word strings were pronounceable and orthographically legal. Compound words were not used. Word and non-word stimuli were presented separately. Subjects received the two lists in separate block of trials. A fixation cross was presented in the centre of the video screen. After the central cross was extinguished, the stimulus was displayed for a maximum of 4000 ms. The subject's task was to look at the string and to report verbally what he had read. Responses were recorded.

ADL—self evaluation questionnaire of activities of daily living (modified from Kerkhoff et al., 1994)

A questionnaire based on 10 items describing the most frequent visual impairments of patients with visual field defect was completed by patients. The following items were presented: 1, seeing obstacles; 2, bumping into objects/obstacles; 3, losing the way; 4, finding objects on the table; 5, finding objects in the room; 6, finding objects in the supermarket; 7, walking in a crowd; 8, reading; 9, to go upstairs/downstairs on the staircase; 10, crossing the streets. For each item, patients had to judge on a five point scale to what extent they experienced the problem in question. The scale was as follows: 0, no problem; 1, rare problem; 2, partially relevant problem; 3, frequent problem; 4, very frequent problem. To minimize the tendency of the patients to respond in a socially desirable manner after the training, they were not informed about their ratings at the beginning of the training.

Audio-visual training

Apparatus and stimuli

The apparatus consisted of a semicircular structure in which the visual and the acoustical stimuli were positioned. The apparatus was a plastic horizontal arc (height 30 cm, length 200 cm) fixed on the table surface.

The acoustical stimuli were eight piezoelectric loudspeakers (0.4 W, 8 Ω), located horizontally at the subject's ear level, at an eccentricity of 8, 24, 40, 56° in the hemianopic hemifield and in the intact hemifield. The loudspeakers were covered by a strip of black fabric, attached to a plastic arc, preventing any visual cues about their position. The sounds were created by a white-noise generator (80 dB). Six visual stimuli were located directly in front of the loudspeakers: the light displays, poking out of the black fabric, were placed at an eccentricity of 24, 40 and 56° to either side of the fixation point. Note that we refer to the auditory positions by labels A1–A8 moving from left to right, and similarly we described the corresponding visual stimuli positions by labels V1–V6 (*see* Fig. 3).

The visual stimulus consisted of the illumination of the red LED (luminance 90 cd m^{-2} each). The visual stimulus and the acoustical target had the same duration of 100 ms. Timing of stimuli was controlled by an ACER 711TE laptop computer, using a custom program (XGen-Experimental Software, http://www.psychology.nottingham.ac.uk/staff/cr1/) and a custom hardware interface.

Training procedure

Patients sat on a chair in a low illuminated and sound attenuated room, at ~70 cm in front of the apparatus, facing straight ahead, with their body midline aligned with the centre of the apparatus.

To present visual targets in the blind region of the visual hemifield, the central fixation point was moved along the central vertical axis of the apparatus. The fixation point was on the median plane for patients with homonymous hemianopia (*see* Fig. 3), 30° above the semicircular structure used for stimuli presentation in case of patients with inferior quadrantopia and 30° below for patients with superior quadrantopia.

Patients were required to look at the fixation point, a white triangle (1°), and to explore the blind hemifield by shifting their gaze towards the visual stimulus, without head movements. They were instructed to detect the presence of the visual target by pressing a button and to ignore the auditory stimuli, since they were not predictive of the presence of the visual target. Before each trial, fixation

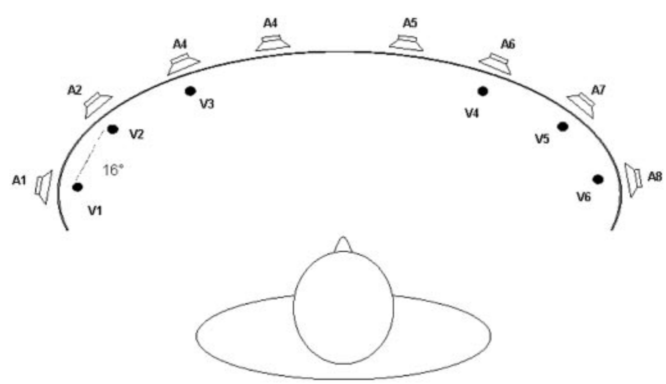

Fig. 3 Bird's eye schematic view of the position of loudspeakers and light displays.

was monitored visually by the experimenter standing behind the apparatus, facing the subject. The experimenter starts each trial only after the correct posture was achieved. The treatment was carried out under binocular conditions.

Three different kinds of sensory stimulation were presented: (i) unimodal visual condition, in which only the visual target was present; (ii) unimodal auditory condition, in which only the auditory stimulus was present, i.e. catch trial; (iii) crossmodal visual-auditory condition: a sound presented together with the visual target. In the crossmodal conditions, the sound could be presented either in the same position of the visual stimulus, i.e. spatially coincident crossmodal condition (SP), or in a different position, i.e. spatially disparate crossmodal condition, at 16 and 32° of nasal (16n, 32n respectively) or temporal (16t, 32t respectively) disparity from the visual target.

During the training, the hemianopic hemifield was more intensively stimulated than the intact hemifield. For each block, 48 trials were presented: 9 unimodal visual trials (6 trials for the hemianopic hemifield and 3 for the intact hemifield); 8 unimodal auditory trials (6 for the hemianopic hemifield and 2 for the intact hemifield); 8 crossmodal spatially coincident trials (6 for the hemianopic hemifield and 2 for the intact hemifield); 23 crossmodal spatially disparate trials (20 for the hemianopic hemifield and 3 for the intact hemifield). The number of blocks varied for each patient, depending on individual progress in each stimulus onset asynchrony (SOA) session (*see* below).

Since visual exploration in hemianopic patients is usually difficult and time-consuming, the training was rendered less difficult by having different temporal intervals between the two stimuli. Thus, the training was divided in six sessions with different temporal intervals (SOA) between the acoustic and the visual stimulus. The treatment started with 500 ms of SOA, i.e. the auditory stimulus preceded the visual target 500 ms, and the SOA was reduced in steps of 100 ms (i.e. 400, 300, 200 and 100 ms) up to the last session of the training, in which the stimuli were simultaneous (i.e. 0 ms of SOA). Each SOA session terminated when a hit ratio of at least 50% in unimodal visual condition was obtained. Once the patient reached this criterion, the next SOA session began.

The treatment finished when patients detected >50% of unimodal visual stimuli for three consecutive blocks of trials in the simultaneous presentation of audio-visual stimuli (last SOA session). This percentage, although it represents a low level of performance, was positively correlated with visual scanning amelioration in a pilot experiment aimed to establish the criterion for the end of the treatment. It is worthwhile to remember that due to the target exposition time (100 ms), the task was very difficult for the patients.

Each daily session lasted ~4 h, separated by frequent breaks according to the patients' performance and tiredness. All patients completed the training in 2 weeks.

Testing procedure

Treatment efficacy was evaluated by using a multiple-baseline design. Each patient was tested before the treatment, after treatment and after a resting period of 1 month. The aim of having different patients' visual abilities evaluations was 2-fold: (i) to provide a pre-treatment and a post-treatment performance assessment; (ii) to monitor a possible spontaneous recovery of the visual disabilities. Therefore, patients were divided in two groups. The first group (G1) underwent the first evaluation of the visual field deficits before the treatment (i.e. baseline), the second evaluation immediately at the end of the treatment (i.e. post-training) and a third evaluation was conducted after 1 month from the end of the treatment (i.e. 1 month). By contrast, the second group (G2) underwent a first evaluation of the visual field deficits 1 month before starting the training (i.e. baseline 1) and immediately before the treatment (i.e. baseline 2). No treatment was provided in the period occurring between the two baselines. Finally, an assessment of visual field disorders was carried out immediately at the end of the treatment (i.e. post-training).

Results

All the analyses were carried out using different ANOVAs. Whenever necessary, pairwise comparisons were conducted using Newman–Keuls test.

Audio-visual training

In order to assess the relative improvement of visual abilities during the training sessions, the different spatial positions on the hemianopic hemifield (V1, V2, V3) were collapsed and one between group (G1 and G2) ANOVA was conducted on the percentages of visual detections, converted in arcsine values, in unimodal visual conditions before the treatment and in training sessions. There were also very few (<9%) false positives on catch trials, so these too were not analysed statistically. The main factor was Session: baseline, i.e. patients' performance before the treatment, and training sessions (i.e. SOA 500, 400, 300, 200, 100 and 0 ms). Note that in the baseline session the audio-visual stimulation was temporally coincident, i.e. 0 ms of SOA. Session was the only significant effect [$F(6,36) = 20.01$, $P < 0.000001$]: in each group, the difference between the baseline and each training session was significant ($P < 0.0002$ in all comparisons) (*see* Fig. 4).

Assessment of visual detections

For each group of patients (G1 and G2), the improvement of visual detections was assessed by using a two-way ANOVA on the percentages of visual detections to stimuli presented in the hemianopic hemifield in two tests (Unimodal Visual Field test and Computerized Visual Field test). Since all patients had an almost correct performance in the intact hemifield (near 100% of visual detections), the analyses were conducted only for the impaired hemifield. The main factors were Condition (Eye Movements and Fixed-Eyes) and Session with the following conditions: for group G1, there were baseline, post-training, 1 month post-training conditions; for G2, there were baseline 1, baseline 2 and post-training conditions. In the Unimodal Visual test, the interaction Condition × Session was significant in G1 [$F(2,6) = 5.19$, $P < 0.05$] and in G2 [$F(2,6) = 15.01$, $P < 0.005$] (*see* Fig. 5A and B).

The same significant effect of the interaction Condition × Session was obtained in the Computerized Visual Field test in G1 [$F_{(2,6)} = 25.85$, $P < 0.001$], while it was marginally significant in G2 [$F_{(2,6)} = 4.31$, $P < 0.06$] (*see* Fig. 6A and B).

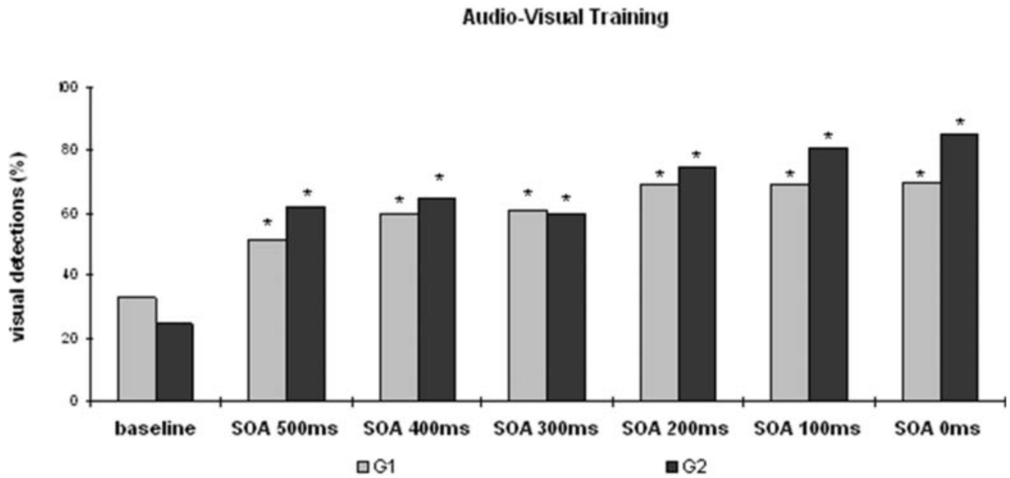

Fig. 4 Audio-visual training. Mean percentages of visual detections in the unimodal conditions in the baseline and in the training sessions. Grey bars represent the performance of G1; black bars represent the performance of G2. The asterisk indicates a significant difference between the baseline and the training session ($P < 0.002$ in all comparisons).

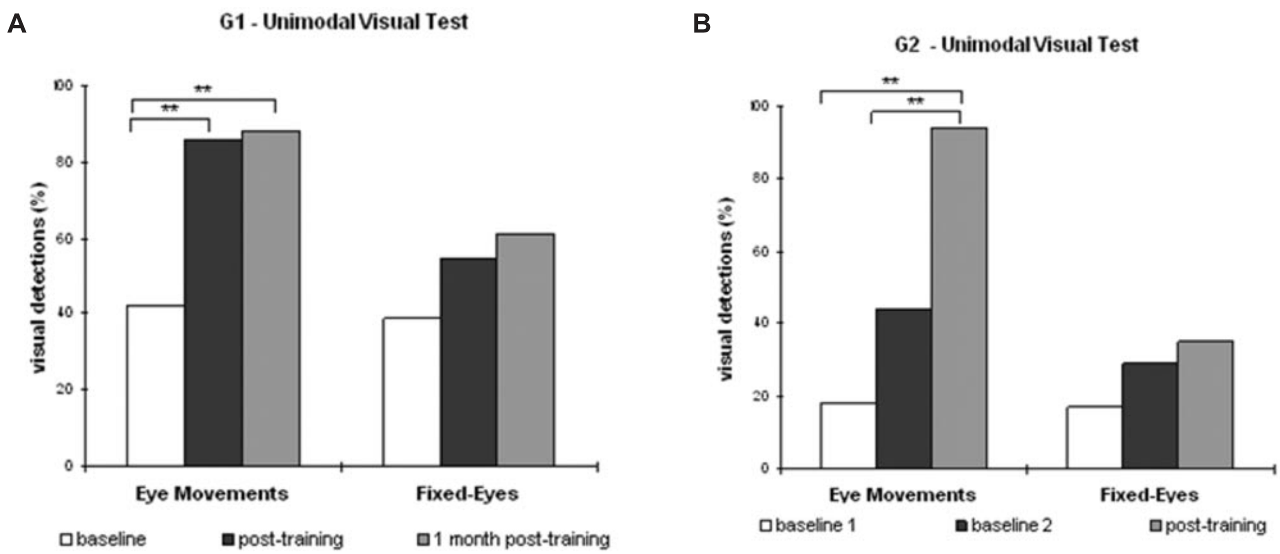

Fig. 5 Unimodal visual test. (**A**) Mean percentages of visual detections in the different evaluations for the group G1. White bars = baseline; black bars = post-training; grey bars = 1 month post-training. On the left, patients' performance in Eye Movement Condition; on the right, patients' performance in Fixed-Eyes Condition. The asterisk indicates a significant difference between conditions: $^{**}P < 0.005$.
(**B**) Mean percentages of visual detections in the different evaluations for G2. White bars = baseline 1; black bars = baseline 2; grey bars = post-training. On the left, patients' performance in Eye Movement Condition; on the right, patients' performance in Fixed-Eyes Condition. The asterisk indicates a significant difference between conditions: $^{**}P < 0.005$.

Assessment of visual exploration

For each subtest of the Visual Search test, percentages of correct responses and RTs were analysed separately for the two groups of patients (i.e. G1 and G2) by using different one-way ANOVAs with Session as main factor (for G1, baseline, post-training, 1 month post-training conditions; for G2, baseline 1, baseline 2 and post-training). For E–F test, the main factor Session was significant in G1 and G2 both when correct responses and RTs were considered (*see* Table 3) and the significant *post-hoc* comparisons are reported in Fig. 7A–D. The same effects of Session was obtained in the Triangles test for G1, whereas in G2 the effect of Session was significant only when correct responses were considered (*see* Table 3 and Fig. 7A–D).

For the Number test, analysis of RTs showed a significant effect of Session for both G1 and G2 (*see* Table 3): in G1, compared to the baseline (73 s), RTs significantly decreased in the post-training (34 s, $P < 0.0003$) and in 1 month post-training condition (40 s, $P < 0.0003$), without differences between the last two conditions. In G2 [$F_{(2,6)} = 6.86$, $P < 0.03$], in post-training condition patients were faster (44 s) compared to baseline 1 (70 s, $P < 0.03$) and to baseline 2 (65 s, $P < 0.03$), without significant differences between the two baselines.

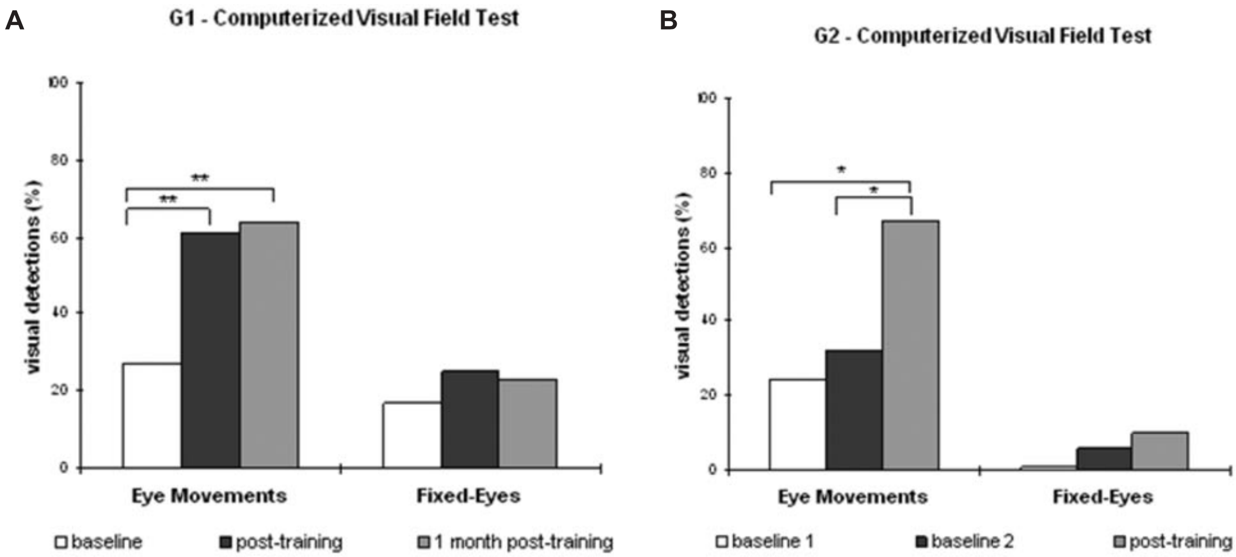

Fig. 6 Computerized visual field test. (**A**) Mean percentages of visual detections in the different evaluations for G1. White bars = baseline; black bars = post-training; grey bars = 1 month post-training. On the left, patients' performance in Eye Movement Condition; on the right, patients' performance in Fixed-Eyes Condition. The asterisk indicates a significant difference between conditions: **$P < 0.005$. (**B**) Mean percentages of visual detections in the different evaluations for G2. White bars = baseline 1; black bars = baseline 2; grey bars = post-training. On the left, patients' performance in Eye Movement Condition; on the right, patients' performance in Fixed-Eyes Condition. The asterisk indicates a significant difference between the conditions: *$P < 0.05$.

Table 3 Main effects of the analysis for the audio-visual training and for tests for assessing visual field disorders

Group	Main effects			
	G1		G2	
	Correct responses	RTs	Correct responses	RTs
E–F test	Session $F_{(2,6)} = 14.99$, $P < 0.005$	Session $F_{(2,6)} = 64.82$, $P < 0.0009$	Session $F_{(2,6)} = 44.69$, $P < 0.0003$	Session $F_{(2,6)} = 8.64$, $P < 0.02$
Triangles test	Session $F_{(2,6)} = 8.55$, $P < 0.02$	Session $F_{(2,6)} = 18.13$, $P < 0.003$	Session $F_{(2,6)} = 10.7$, $P < 0.01$	Session $F_{(2,6)} = 1.08$, $P = 0.4$
Number test	–	Session $F_{(2,6)} = 68.44$, $P < 0.00007$	–	Session $F_{(2,6)} = 6.86$, $P < 0.03$
	Total score			
ADL	Session $\chi^2(4,2) = 6.53$, $P < 0.04$		Session $\chi^2(4,2) = 6.5$, $P < 0.04$	

Assessment of hemianopic dyslexia

The percentages of correct responses (i.e. correctly read letter strings) were analysed separately for each group using different ANOVAs with Session as main factor: the effect of Session was significant in both G1 [$F(2,6) = 9.28$, $P < 0.01$] and G2 [$F(2,6) = 60.25$, $P < 0.0001$] (*see* Fig. 8).

ADL

The total rating of the mean subjects' disability in the three evaluations were analysed by using a non-parametric test (Kendall). In both groups a significant difference was found (*see* Table 3). Single comparisons, conducted by using the Wilcoxon signed-rank test, revealed in G1 a marginal significant difference between the baseline (score = 16) and post-training evaluations (post-training score = 6, $P < 0.06$; 1 month post-training score = 5, $P < 0.06$), without differences between the two last conditions (*see* Fig. 9A). In G2, only a marginal significant effect was found comparing the post-training (score = 11) and the two baselines (baseline 1, score = 27; baseline 2, score = 24, $P < 0.06$ in both comparisons) (*see* Fig. 9B).

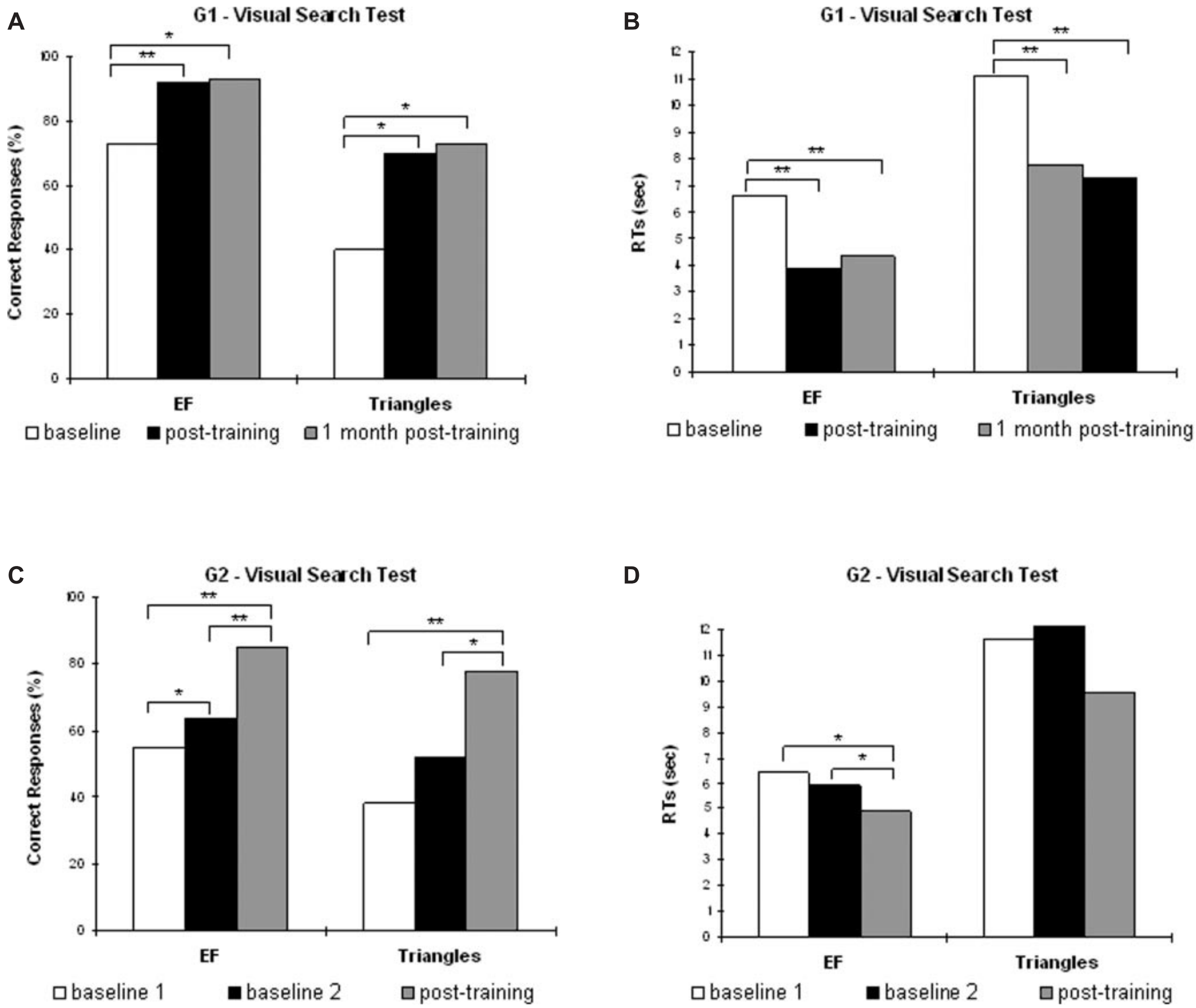

Fig. 7 E–F and triangles tests. (**A**) Mean percentages of correct responses in each evaluation for G1. White bars = baseline; black bars = post-training; grey bars = 1 month post-training. The asterisk indicates a significant difference between conditions: *$P < 0.05$; **$P < 0.005$. (**B**) Mean RTs in each evaluation for group G1. White bars = baseline; black bars = post-training; grey bars = 1 month post-training. The asterisk indicates a significant difference between conditions: **$P < 0.005$. (**C**) Mean percentages of correct responses for G2. White bars = baseline 1; black bars = baseline 2; grey bars = post-training. The asterisk indicates a significant difference between the conditions: *$P < 0.05$; **$P < 0.005$. (**D**) Mean RTs in each evaluation for G2. White bars = baseline 1; black bars = baseline 2; grey bars = post-training. The asterisk indicates a significant difference between conditions: *$P < 0.05$.

Discussion

It is well recognized that the possession of multiple ways of sensing the world offers many potential benefits (Stein and Meredith, 1993; Spence and Driver, 2004). In the last years, a vast body of evidence has been provided about the ability of our brain to take advantage from the integration of information derived from different sensory modalities (*see* Stein and Meredith, 1993; Calvert *et al.*, 2004; Spence and Driver, 2004). The mechanism of multisensory integration might become particularly important when a sensory modality is damaged; the possibility to integrate sensory inputs from different sensory modalities, related to the same external event, can enhance the impaired unimodal processing, improving the perception of sensory events difficult to be perceived unimodally due to the unimodal sensory defect.

Multisensory neurons have been identified in different brain structures, such as the SC plus regions of cortex (Stein and Meredith, 1993). In multisensory neurons of SC, stimulus combinations produce significant increase over unimodal response and can influence overt behaviour (Stein, 1998). Furthermore, the activity of multisensory neurons of SC shows a response gradient based on the efficacy of the unimodal stimuli: whereas the pairing of weakly effective stimuli results in a vigorous enhancement of the

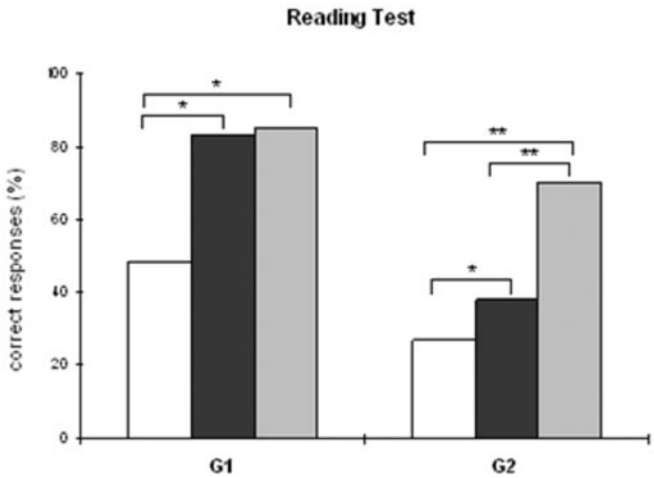

Fig. 8 Reading test. Percentages of correct responses in each evaluation. On the left, G1: white bars = baseline; black bars = post-training; grey bars = 1 month post-training. On the right, G2: white bars = baseline 1; black bars = baseline 2; grey bars = post-training. The asterisk indicates a significant difference between the conditions: **P* < 0.05; ***P* < 0.005.

multisensory neuronal activity, the combination of highly effective stimuli results in little increase in the neuron's response. This property is called 'inverse effectiveness rule'. The presence of an inverse relationship between stimulus effectiveness and multisensory enhancement makes intuitive sense if one considers that the survival value in this system lies in the ability to detect minimal signals. Stimuli that are unlikely to produce either neural or behavioural responses by themselves, benefit most from the multisensory combination. Minimal cues from different sensory modalities are easier to detect in combination than they are individually. In animal studies, the effectiveness of the unimodal signals has been shown to be a major determinant of the advantage resulting from multisensory integration (Stein and Meredith, 1993).

According to this property, at the behavioural level, the beneficial effects of combining different sensory modalities might be more evident when at least one sensory processing is weakly effective to induce a behavioural response; thus, a concurrent stimulation of other senses might enhance the response of the weak sensory system. Recent studies in brain-damaged patients (Frassinetti, 2002*b*; Schendel and Robertson, 2004; Bolognini *et al.*, 2005*b*) support this

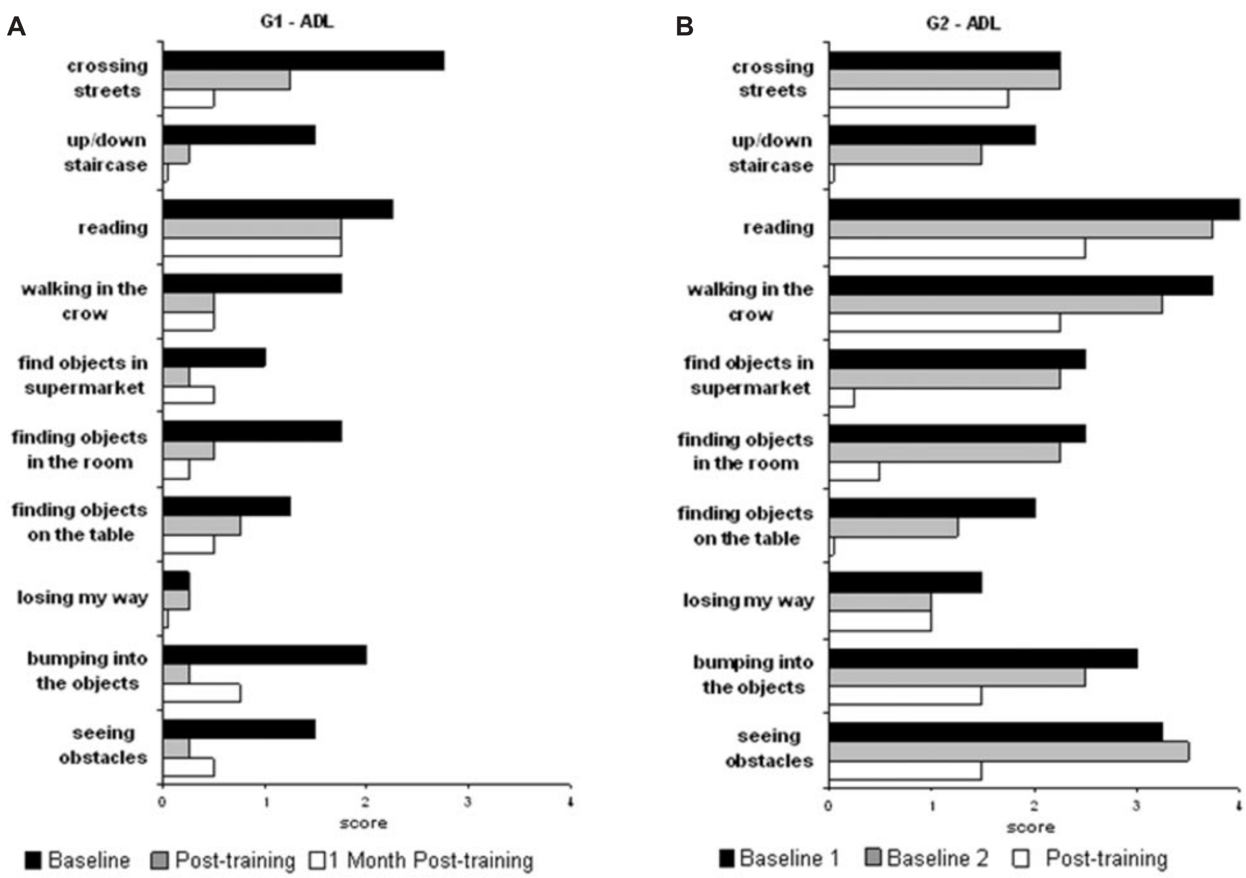

Fig. 9 ADL. (**A**) Mean score for G1 in each item of the questionnaire. Black bars = baseline; grey bars = post-training; white bars = 1 month post-training. (**B**) Mean score for G2 in each item of the questionnaire. Black bars = baseline 1; grey bars = baseline 2; white bars = post-training.

hypothesis by demonstrating that the sensory information from a not impaired modality can improved the impaired processing of information derived from a damaged sensory system. In particular, in patients with hemianopia, audio-visual interaction in multisensory neurons can improve temporally visual perception in the blind hemifield (Frassinetti *et al*., 2005).

Based on these findings, we have tried to take advantage of the existence of integrated audio-visual system to rehabilitate patients with visual field defects. A systematic audio-visual stimulation of the visual field, activating multisensory neurons in SC, which is frequently spared in lesions causing visual field cuts, might affect orientation towards the blind hemifield and improve oculomotor exploration with long-lasting effects.

The results of the present study support this hypothesis. During the training, we observed a progressive improvement of patients' performance, as documented by the increase of visual detections in the unimodal conditions during the different sessions of the training. Since patients were instructed to use saccadic eye movements for the detection of visual targets, the amelioration of patients' performance can be explained with the implementation of the oculomotor system: multisensory integration might have enhanced the responsiveness of the oculomotor system, reinforcing orientation towards the blind hemifield and oculomotor visual exploration mediated by multisensory structures, such as the SC. Thus, the multisensory implementation of the oculomotor system allows patients to detect the presence of visual events in the affected areas both with a bimodal and unimodal stimulation.

The important role of the oculomotor system in mediating the amelioration induced by the audio-visual training is also suggested by the results obtained by patients in tests assessing visual disorders. In all tests assessing visual detections (i.e. Unimodal Visual test and Computerized Visual Field test), when patients were let free to use eye movements to perform the tasks (Eye-Movements Condition), we found an important increase of accuracy in the blind area after the training. In contrast, a weak or no amelioration at all was found in the same tests under the condition with fixed-eyes. The discrepancy between the two conditions suggests that the amelioration in visual perception induced by the training is not due to an enlargement of the visual field, but it is mostly mediated by the oculomotor system. Our findings are in line with a previous study on patients with hemianopia (Nelles *et al*., 2001), in which saccades were trained with compensatory visual field training on a large training board: after the training, the authors found a marked improvement of detections and RTs only when patients use explorative eye movements, but not with eyes fixating.

In the present study, the improvement obtained after the treatment did not only involve visual detections, but also the visual scanning behaviour. The improvement of patients' performance was highly consistent across all the tests assessing visual exploration (Visual Search tests), both in terms of accuracy and search times, as documented by the nearly error-free performance and the reduction of visual scanning times obtained after the treatment. Patients' visual search behaviour became more efficient and faster after the treatment, probably implying an enlargement of the search field, defined as size of the visual field that a patient can actively scan via eye movements (Kerkhoff *et al*., 1994).

The amelioration of visual exploration had also positive consequences on hemianopic dyslexia: after the training, we observed an improvement of single word reading performance in all patients. Other forms of reading performance were not evaluated. Furthermore, the efficacy of the audio-visual treatment was confirmed by patients' subjective improvements in daily life, with positive outcomes on their private life: the reduced scores on self-evaluation questionnaire (i.e. ADL) obtained by patients indicate the transfer effects of training to daily activities, which were perceived by patients before the treatment as strongly impaired by the visual field loss. As patients' reports indicate, there was a clear treatment effect on the reduction of visual handicap in everyday life. Thus, patients learned to use the regained visual capacities to cope with the visual field defect, ensuring a gradual transfer and automatization of the compensatory strategies in daily life.

Finally, the treatment effects were maintained: in group G1, after 1 month from the end of the treatment, the amelioration remained stable. This amelioration cannot be ascribed to a spontaneous recovery of visual disorders for two reasons. First, it is important to note that all patients were in a chronic stage of illness since stroke occurred at least 4 months before the experiment was conducted. Second, in group G2, patients' performance did not markedly improve between the two baseline conditions, that were run before the treatment and 1 month apart from each other. In conclusion, when both groups were considered (i.e. G1 and G2), a significant improvement of visual abilities was found only after the audio-visual training (i.e. post-training).

The results of the present study suggested that audio-visual training can induce a long-lasting (at least 1 month) activation of visual responsiveness of the oculomotor system, maybe mediated by the intact SC (*see* Table 2). The SC is an important oculomotor structure involved in the execution and initiation of saccades and in target selection (Krauzlis *et al*., 2004); moreover, SC is part of the colliculo-geniculo-pulvinar-extrastriate pathways that mediates some residual visual functions in hemianopia (Stoerig and Cowey, 1997). Since the sensory maps of SC are in register with the premotor maps, crossmodal information can be translated directly into an appropriate orientation response towards the blind hemifield.

Furthermore, SC is also involved in spatial orientation and in crossmodal spatial attention (Krauzlis *et al*., 2004; Spence and Driver, 2004; Stein *et al*., 2004): audio-visual interaction in multisensory neurons of SC can also mediate an exogenous shift of crossmodal attention towards the blind hemifield. Since patients with visual defects usually direct their focus of attention to the intact hemifield, the auditory cue, interacting with the visual input in multisensory neurons of SC, can reverse this tendency by inducing an exogenous shift of crossmodal spatial attention towards the blind hemifield.

An interesting question raised is whether the amelioration of oculomotor search behaviour is the result of learning or can be explained directly by the activation of saccadic eye movements via multisensory neurons located in the SC. It is possible to speculate that both mechanisms are involved in the use of the oculomotor system to substitute the lost visual field. The activation of the multisensory neurons is very important for the implementation of visual enhancement in the blind field (Frassinetti *et al.*, 2005). However, for a permanent amelioration of visual search, a prolonged and systematic training is required; this might suggest a contribution of some top-down mechanisms in the achievement of oculomotor compensatory strategies. This issue needs further investigation. For example, one way to verify the role of SC in the compensation of hemianopia is to use different kinds of visual stimuli. Indeed it has been shown that visual pathways originating from short wave sensitive cones (i.e. purple colour) do not send or send very few afferents to SC (Sumner *et al.*, 2002). As a consequence, if the hypothesis that SC mediates the effects found in the present study is correct, we should not obtain an improvement in visual search tasks when using purple stimuli since SC does not receive S-cones input. By contrast, if other mechanisms are responsible for the oculomotor compensation, we should observe these effects also when using purple stimuli.

The major novelty of the audio-visual training used in the present study is that it is based on the human innate ability to integrate information from different sensory modalities. The functional property of multisensory neurons, i.e. inverse efficacy rule, makes them well-suited to detect sensory events when at least one sensory system is damaged. In conclusion, the audio-visual training represents an innovative and efficient approach to the rehabilitation of visual field deficits, based on the multisensory system. A systematic audio-visual stimulation of the blind hemifield for a short period of time (2 weeks) can improve oculomotor visual exploration and crossmodal spatial attention, inducing the implementation of efficient oculomotor strategies that allow patients to compensate for the loss of vision.

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