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Audio-visual stimulation improves oculomotor patterns in patients with hemianopia

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A B S T R A C T

Patients with visual field disorders often exhibit impairments in visual exploration and a typical defective oculomotor scanning behaviour. Recent evidence [Bolognini, N., Rasi, F., Coccia, M., & Làdavas, E. (2005b). Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain*, *128*, 2830–2842] suggests that systematic audio-visual stimulation of the blind hemifield can improve accuracy and search times in visual exploration, probably due to the stimulation of Superior Colliculus (SC), an important multisensory structure involved in both the initiation and execution of saccades. The aim of the present study is to verify this hypothesis by studying the effects of multisensory training on oculomotor scanning behaviour. Oculomotor responses during a visual search task and a reading task were studied before and after visual (control) or audio-visual (experimental) training, in a group of 12 patients with chronic visual field defects and 12 controls subjects. Eye movements were recorded using an infra-red technique which measured a range of spatial and temporal variables. Prior to treatment, patients' performance was significantly different from that of controls in relation to fixations and saccade parameters; after Audio-Visual Training, all patients reported an improvement in ocular exploration characterized by fewer fixations and refixations, quicker and larger saccades, and reduced scanpath length. Overall, these improvements led to a reduction of total exploration time. Similarly, reading parameters were significantly affected by the training, with respect to specific impairments observed in both left- and right-hemianopia readers. Our findings provide evidence that Audio-Visual Training, by stimulating the SC, may induce a more organized pattern of visual exploration due to an implementation of efficient oculomotor strategies. Interestingly, the improvement was found to be stable at a 1 year follow-up control session, indicating a long-term persistence of treatment effects on the oculomotor system.

1. Introduction

Patients with posterior visual pathway lesions may develop homonimous hemianopia (HH), a visual field defect (VFD) in which half of the visual field is blind. In the majority of patients (about 70%), field sparing does not exceed 5° (Zihl, 1989). As a consequence, patients show difficulties in detecting stimuli and finding objects in the visual space that correspond to the affected field region, often complaining about having a limited overview, bumping into obstacles, missing or misreading words, hurting people in busy places. These complaints are partly due to a common underlying defective mechanism, namely a visual scanning deficit.

Registration of eye movements has been successfully employed to assess visual scanning deficit (Zangemeister, Meienberg, Stark, & Hoyt, 1982; Zangemeister & Oechsner, 1996; Tant, Cornelissen, Kooijman, & Brouwer, 2002) and reading disabilities in patients with visual field defects (Trauzettel-Klosinski & Brendel, 1998; Behrmann, Shomstein, Black, & Barton, 2001). On the basis of ocular recordings, Zihl (1995) estimated that nearly 60% of HH patients do not show effective compensatory oculomotor behaviour. In a relatively simple stimulus display (*dot counting task*), subjects exhibited longer scanning times and scanpaths, higher numbers of fixations and refixations and, at least in part, longer fixation durations and shorter saccadic amplitudes. Differential hemifield performance has been reported by several studies, revealing a higher number of fixations and hypometric saccades in the hemianopic field (Chedru, Leblanc, & Lhermitte, 1974; Ishiai, Furukawa, & Tsukagoshi, 1987; Meienberg, Zangemeister, Rosenberg, Hoyt, & Stark, 1981; Zihl, 1995, 1999, 2000; Tant et al., 2002).

In addition to impairments in visual exploration, reading disabilities can constitute a severe handicap in patients with hemianopic field defects, especially when they are asked to read a text. Text reading needs the integration of perceptual and motor processes,

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requiring the reader to direct the eyes along the array of words. Patients with hemianopia have reading difficulties that reflect the laterality of the visual field defect; patients with right-hemianopia (RH) are more disabled than those with left-hemianopia (LH) (Eber, Metz-Lutz, Bataillard, & Collard, 1987; Gassel, & Williams, 1963; Remond, Lesevre, & Gabersek, 1957; Schoepf & Zangemeister, 1993). Left VFD causes difficulties in finding the beginning of a new line, while right-hemianopia leads to more severe reading difficulties characterized by prolonged fixations, inappropriately small amplitude saccades to the right, and many saccadic regressions, mainly due to the loss of the anticipatory parafoveal scanning process (De Luca, Spinelli, & Zoccolotti, 1996; Trauzettel-Klosinski & Rheinard, 1998; Leff, Scott, Rothwell & Wise, 2001; Wang, 2003).

The improvement of these disabilities has been, therefore, the predominant aim in the rehabilitation of these patients. Visual search and reading impairments have been classically treated by training patients to enlarge saccadic amplitude and efficiently explore their blind area, with the support of search paradigms and computerized reading programs (Zihl, 1981, 1995, 2000; Zihl & Kennard, 1996; Kerkhoff, Munssinger, Haaf, Eberle-Strauss, & Stogerer, 1992; Kerkhoff, Munbinger, & Meier, 1994; Pambakian & Kennard, 1997; Pambakian, Mannan, Hodgson, & Kennard, 2004). The common assumption of this kind of methods, sometimes called "awareness enhancement training", is that the patient is trained to be aware of the deficit and to use compensatory eye movements for scanning the blind field. Because these procedures rely on top-down mechanisms, requiring patients to voluntary maintain attention oriented to the affected hemifield, the amount of amelioration strongly depends on additional lesions to the striate cortex, such as injury to the thalamus, parieto-occipital structures and white matter (Zihl, 2000).Considering these limitations, Bolognini, Rasi, Coccia, & Làdavas (2005b) developed a new approach to compensatory rehabilitation of VFD, based mainly on a bottom-up mechanism involving audio-visual integration processes. Neurophysiological studies in animals (Stein & Meredith, 1993; Stein, Jiang, & Standford, 2004) have shown, in Superior Colliculus (SC) and regions of cortex, the existence of neurons responding to stimuli from different sensory modalities that may play a significant role in spatial orientation and saccadic eye movements (Stein, 1998). Behavioural studies have shown, in humans, the existence of an integrated audio-visual system that can be successfully activated to enhance visual detection in normal subjects (Frassinetti, Bolognini, & Làdavas, 2002; Bolognini, Frassinetti, & Làdavas, 2005a) and in patients with VFD (Frassinetti, Bolognini, Bottari, Bonora, & Làdavas, 2005), in accordance with the spatial and temporal constraints observed at neural level (Stein and Meredith, 1993) (for a review, see Làdavas, 2008).

Based on these findings, a recent study (Bolognini et al., 2005b) from our laboratory has shown that multisensory integration might offer a unique approach for the stimulation of the SC, leading to the possibility that systematic bimodal stimulation, affecting orientation towards the blind hemifield and modulating the processing of visual events, might improve visual exploration with long-lasting effects. In other words, we assessed the possibility that a crossmodal training regime reinforces the innate ability of the brain to perceive multisensory events, an ability normally masked when unimodal processing of sensory events is sufficient for their perception (Frassinetti et al., 2005). In this study, patients with chronic visual field defects were trained to detect the presence of visual targets that could be presented alone, or together with an acoustic stimulus, in various multisensory conditions. The treatment allowed patients to efficiently compensate for the loss of their vision, by improving visual detection and visual search time. This improvement is probably mediated by the intact Superior Colliculus, an important oculomotor structure involved in both the initiation and execution of saccades as well as in target selection (Krauzlis, Liston, & Carello, 2004). Moreover, since sensory maps within the SC are in register with premotor maps, multisensory information can be translated directly into an appropriate orientation response toward the blind hemifield. Indeed, studies of normal subjects suggest that audio-visual stimulation improves both saccade accuracy and saccade timing (Corneil, Van Wanrooij, Munoz, & Van Opstal, 2002; Colonius & Arndt, 2001).

Thus, in the light of previous evidence (Bolognini et al., 2005b), the present study was aimed to address four novel issues.

The first aim was to verify the effect of multisensory training on patients' oculomotor scanning, which has never been assessed before. Thus, oculomotor responses during a visual search task and a reading text task were studied both before and after the experimental training in a group of 12 patients with chronic hemianopia. We examined the eye movements patterns with particular regard to the following variables: number and duration of fixations, refixations, saccadic amplitude and duration, length of scanpath (for the visual search task); number of progressive and regressive saccades, return sweep, duration of fixations and saccadic amplitude (for the reading task).

In the previous study (Bolognini et al., 2005b) a significant amelioration of visual exploration was observed after the Audio-Visual Training, compared to the condition in which no training was provided. However, this study did not rule out the possibility that a similar improvement can be obtained by using a unimodal stimulation. Thus, the second aim of the present study was to verify the specific effects of unimodal stimulation (control training) and bimodal stimulation (experimental training) in the amelioration of patients' performance. The testing paradigm comprised five different Sessions (S1, S2, S3, S4, S5). Patients underwent a Control Visual Training, consisting of visual stimulation of the visual field, in the period occurring between S1 and S2, and Audio-Visual Training, consisting of audio-visual stimulation, between S2 and S3. We hypothesized that systematic audio-visual stimulation of the visual field, activating multisensory neurons in the SC, might affect orientation toward the blind hemifield and improve oculomotor exploration. No beneficial effects were expected after the visual control training, due to the lesion of the retino-genicolo-striate pathway.

The third aim was to evaluate the long-lasting effects of Audio-Visual Training. Since in the previous study (Bolognini et al., 2005b) follow-up assessment was limited to one month after the end of the training, in the present study patients were evaluated at three months (S4) and 1 year (S5) after the end of the treatment.

Finally, the fourth aim was to compare the performance of the hemianopic patients to that of a control group of healthy subjects, who were not given any training, but did perform the same experimental tasks as patients in five different sessions. The inclusion of healthy individuals allowed us to verify if patients' oculomotor pattern can reach normal levels after training, and to monitor the influence of a "practice effect" due to the repetition of the experimental tasks.

Moreover, in addition to eye-movement recording, patients were given a clinical assessment of VFD at each session (Bolognini et al., 2005b) to evaluate the effects of the two training on different visual abilities. Visual detections were measured under two different conditions in order to test visual field size and the ability to compensate for visual field loss by using eye movements (Fixed-Eyes Condition and Eye Movements Condition, respectively). Visual exploration and impairments of daily life activities (ADL) were tested as well.

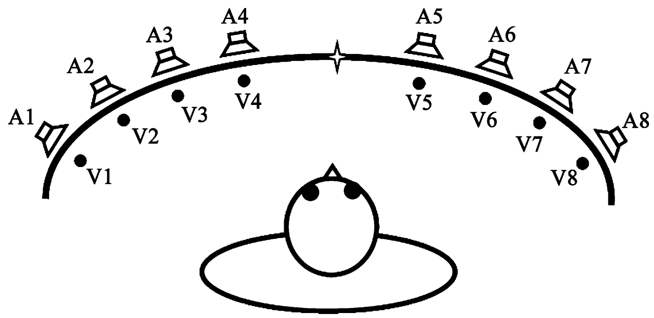

Fig. 1. A schematic bird-view of the training apparatus. V1–V8 = visual stimuli; A1–A8 = auditory stimuli.

2. Methods

2.1. Subjects

A group of hemianopic patients and a control group of healthy subjects took part in the study. All the subjects gave informed consent to participate in the study 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.

2.1.1. Patient selection

Selection of patients was based on complete availability of visual perimetry data. A total of 12 right-handed patients with chronic visual field deficits due to a postchiasmatic lesion were recruited and trained. Patients were recruited at least five months after the onset of their hemianopia, when their field defects were stable. Patients with coexisting eye movement pathologies or other cognitive impairments were excluded. All patients showed a normal hearing, as measured by audiometry in each ear, with no sign of asymmetry between ears. Moreover, all were able to correctly localize sounds. The binocular visual acuity of all patients was normal or corrected to normal by contact lenses. The patients' pathologies varied: seven had cerebral infarctions, one had arteriovenous malformations (AVMs) that had bled, one had a temporal lobectomy, and three had traumatic brain injury. The brain lesions of each patient were confirmed by CT and MRI, and all lesions were coded using the method introduced by Damasio and Damasio (1989). Details concerning sex, age, years of education, length of illness, lesion sites, degrees of macular sparing and the presence of visual field defect are reported in Table 1.

2.1.2. Control subjects

The control group comprised 12 right-handed healthy subjects (7 female, 5 male; mean age: 40 years; mean years of education: 13) with no history of neurological disease.

2.2. Training paradigm

All the patients underwent Control Visual Training and subsequently Audio-Visual Training.

Both training were performed on a semicircular structure in which LEDs and loudspeakers were mounted at eight locations along the azimuth (8°,24°,40°,56° right and left from the central fixation point) (see Fig. 1). Audio-Visual Training comprised systematic audio-visual stimulation of the intact and affected visual fields, for 4 h daily over a period of 2 weeks. Patients were asked to detect the presence of visual targets, which consisted of illumination of a LED for 100 ms, by moving their eyes towards them; these visual targets could be presented either alone or together with an acoustic stimulus (a 100-ms white noise burst). In the audio-visual conditions, the two stimuli could be presented at either the same spatial position or at positions with a spatial disparity (16° and 32° of disparity); furthermore, the temporal interval between the sound and the light was gradually reduced from 300 to 0 ms over the sessions, as visual detection in the blind field reached 50% accuracy in the unimodal visual condition (for more details, see Bolognini et al., 2005b). During the training, the blind hemifield was more intensively stimulated than the intact hemifield. Control Visual Training consisted of systematic visual stimulation of the visual field; it was also carried out for a similar amount of time. The apparatus, task, and procedures were the same as during the Audio-Visual Training, but in this case *only* visual stimuli were presented.

2.3. Testing paradigm

Clinical and eye movements assessments were conducted in five sessions.

Session 1 (S1) was the initial evaluation; Session 2 (S2) occurred two weeks later. During that two weeks, patients underwent Control Visual Training. After the second assessment, patients underwent Audio-Visual Training and were then tested again, immediately at the end of the treatment (S3), three months later (S4) and yet again 1 year later (S5). The assessment at each session was carried out by a different investigator, who was not aware of the type of treatment; moreover, patients were not aware of the possible different impact of the two treatments on hemianopic deficits. Control Subjects performed the same tasks on the same schedule as the patients.

2.4. Clinical assessment

Patients underwent a neuropsychological examination of visual field disorders in five different sessions (see Testing Paradigm). The assessment consisted of evaluating visual detection ability (Computerized Visual Field Test, performed in two conditions: *Fixed-Eyes* and *Eye Movements Condition*), visual exploration (Triangle Test) and impairment in daily life activities (ADL) (for details, see Bolognini et al., 2005b).

2.5. Assessment of eye movements responses

2.5.1. Apparatus

Eye movements were recorded in a dimly lit room using a Pan/Tilt optic eye-tracker (Eye-Track ASL-6000) which registers real-time gaze at 60 Hz. The recording was performed in a dimly lit room. The subject's dominant eye was illuminated by invisible infra-red light, and the reflections were recorded by a video-camera positioned 60 cm from the eye. During the tasks, the position of subject's eye in the visual scene was monitored on-line by the experimenter. Before collecting data from each subject, the equipment was calibrated using a nine-point grid. Subjects were asked to fixate successively on each of a series of small dots arranged on three lines in the form of a square. Fixation time at each dot position was at least three seconds. To prevent head movements a head stabilization device was used.

2.5.2. Stimuli and experimental tasks

Number test (modified from Bolognini et al., 2005b). In this visual search task, eight stimulus arrays (56° × 48°, horizontally and vertically respectively) each containing 15 numbers (from 1 to 15, stimulus size 2° × 2°) distributed at random over a black background, were presented. The subjects were asked to count the numbers in an ascending order by moving the eyes on each target.

Data from eye movements recordings were quantitatively analyzed with respect to the following parameters: number of fixations, duration of fixation, saccade duration, saccade amplitude, scanpath length (sum of the saccadic amplitudes), and refixations.

In addition, mean exploration time was taken as behavioural measure of ocular efficacy.

Reading text task. The text, in Italian, was a short story (330 syllables). Four different stories were counterbalanced between subjects and testing sessions. The texts chosen were equivalent with respect to the graphical and lexical characteristics (font: Arial 40; 6–8 lines for each paragraph; 5–6 words per line; distance between lines: 1.5 cm) and were presented on a computer monitor (visual scene: 30° × 24°). Subjects were asked to read aloud to obtain both accuracy and reading time. The following variables were evaluated: number of saccades in the reading direction, number of regressions (backward saccades), number of saccades during the return sweep (additional to the one necessary to start a new line), mean duration of fixation, and amplitude of reading saccades.

3. Results

3.1. Clinical assessment

Data obtained from Computerized Visual Field Test, Triangle Test and ADL were analysed with a series of ANOVAs. Whenever necessary, pairwise comparisons were conducted using Newman–Keuls tests. Only significant interactions are discussed.

3.1.1. Analysis of visual detection (computerized visual field test)

The analyses were conducted only for the impaired hemifield in the two task conditions (*Fixed-Eyes* and *Eye Movements*). Both percentage of correct detections and signal detection measures were analyzed. This latter analysis was done in order to distinguish between perceptual (d') and response bias processes (β). The main factors were Group (LH: left-hemianopic patients, RH: right-hemianopic patients) and Session (S1, S2, S3, S4, S5). No significant effects of main factors were found in the *Fixed-Eyes Condition*. In contrast, a significant main effect of Session was found for the *Eye Movements Condition* in both the percentage of visual detections [$F(4, 50) = 6.33$, $p < .001$] and d' measure [$F(4, 50) = 8.05$, $p < .0001$]. On the contrary, β measure remained stable along sessions in both task conditions. Visual detections and perceptual sensitivity

Table 1
Summary of clinical, demographic and lesional data for experimental patients.

Case	Sex	Age	Years of Education	Time since onset (months)	Cause of hemianopia	Side of VFD	Degrees of macular sparing	Lesion site	Case	Sex	Age	Years of Education	Time since onset (months)	Cause of hemianopia	Side of VFD	Degrees of macular sparing	Lesion site
P1	M	37	15	30 years	Craniotomy	Left	0°	Right temporo-parieto-occipital	P7	M	42	18	6	Vascular	Right	<5°	Left temporo-parieto-occipital
P2	M	62	5	5	Vascular	Left	0°	Right occipital	P8	M	63	5	6	Vascular	Right	0°	Left temporo-occipital
P3	F	65	5	6	Vascular	Left	<5°	Right occipital	P9	M	35	13	16 years	Trauma	Right	0°	Left optic tract
P4	M	41	8	7	Vascular	Left	0°	Not available	P10	M	45	13	12	AVMs	Right	0°	Left parieto-occipital
P5	F	35	8	8	Vascular	Left	<5°	Right occipital	P11	M	22	13	30	Trauma	Right	0°	Left fronto-temporo-occipital
P6	F	32	18	24	Vascular	Left	<5°	Right fronto-temporo-parieto-occipital	P12	M	33	13	42	Trauma	Right	0°	Not available

	Case frontal lobe														Temporal lobe											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
P1																	X			X	X	X	X		X	
P2																										
P3																										
P5																										
P6	X	X				X		X	X									X				X	X		X	
P7																	X			X			X		X	
P8																	X			X				X	X	
P9																										
P10																										
P11	X	X				X	X		X															X	X	X

	Parietal lobe						Occipital lobe							Sub-cortical structures			
	P1	P2	P3	P4	P5	P6	O1	O2	O3	O4	O5	O6	O7	BG	IC	Th	OT
P1	X	X		X	X	X				X	X	X	X	X	X	X	
P2							X	X	X	X		X	X				
P3							X	X	X	X							
P5							X	X		X	X						
P6	X	X		X	X	X	X	X	X	X	X	X					
P7					X				X	X	X	X	X				
P8							X		X	X		X	X				
P9																	X
P10	X	X	X	X	X	X	X	X	X	X	X	X	X				
P11							X	X	X	X							

significantly increased in S3 (67%; d': 2.48) compared to S2 (47%; d':1.84; $p < .01$), while no significant changes were found when compared S3 to S4 (72%; d': 2.65; $p > .7$) and to S5 (71%; d': 2.48; $p > .7$). Again, no differences were found when comparing S1 (42%; d':1.77) to S2 ($p > .7$).

3.1.2. Analysis of visual exploration (triangle test)

The only main effect of Session was significant [$F(4, 50) = 12.39$, $p < .0001$]. Compared to the baseline (S1: 71% of correct responses), no significant difference was observed in S2 (70%; $p > .8$), while accuracy significantly improved in S3 (93%), S4 (94%), and S5 (93%) ($p < .003$ in all comparisons).

3.1.3. Analysis of ADL

A significant effect of the main factor Session was found [$F(4, 50) = 18.84$, $p < .0001$]. Compared to S1 (score:15), subjective perceived disability was significantly reduced at S3 (6; $p < .001$), while no differences were observed between S1 and S2 (15; $p > .9$), nor between S3 and S4 (5; $p > .5$), S3 and S5 (4; $p > .7$).

3.2. Analysis of eye movements

To study differences between control subjects and patients' oculomotor behaviour and to investigate the differences between the two stimulation types (visual and audio-visual), we compared oculomotor data collected during the *visual search task* and the *reading task* using two MANOVAs (Wilks' multivariate test), with Group (Controls, LH: left-hemianopic patients, RH: right-hemianopic patients) as a between-subjects factor and Session (S1, S2, S3, S4, S5) as a within-subjects factor.

When significant multivariate effects were observed, the univariate effects were inspected with a series of ANOVAs.

3.2.1. Visual search task (number test)

The MANOVA showed a significant Group x Session interaction [$F(56, 538) = 1.40$, $p < .03$]. Univariate ANOVAs confirmed the same interaction for each parameter [smallest F-value $(8, 105) = 2.12$, $p < .04$], except for the duration of fixation.

At S1, patients took more time than control subjects to explore the visual display, and also produced more fixations and refixations, resulting in a longer scanpath. Moreover, their saccades were slower and shorter in amplitude ($p < .05$ in all comparisons). No significant differences were found between S1 and S2 ($p > .4$ in all comparisons), suggesting that the Control Visual Training did not significantly affect the oculomotor responses of patients. On the contrary, comparing the patients' performance in S2 and S3, i.e. before and after the Audio-Visual Training, we observed significantly fewer fixations, saccadic duration was markedly reduced, and mean saccadic amplitude was significantly increased. As a consequence, visual scanning appeared to be much better organized, due to a significant reduction of the length of scanpath, refixations and search times ($p < .05$ in all comparisons). No significant differences were found when results obtained in S3 were compared to S4 and S5 ($p > .2$ in all comparisons), thus suggesting the stability of the results at three months and 1 year after the end of the Audio-Visual Training. Moreover, in the sessions after the Audio-Visual Training patients showed the same performance as control subjects on most parameters ($p > .2$ in all comparisons), except for the number of fixations, the total exploration time and the length of scanpath, all of which remained impaired ($p < .05$ in all comparisons), although improved compared to baseline. Performance of normal subjects was stable across sessions, so suggesting that practice did not appreciably affect oculomotor responses ($p > .8$ in all comparisons). (see Fig. 2 and Table 2)

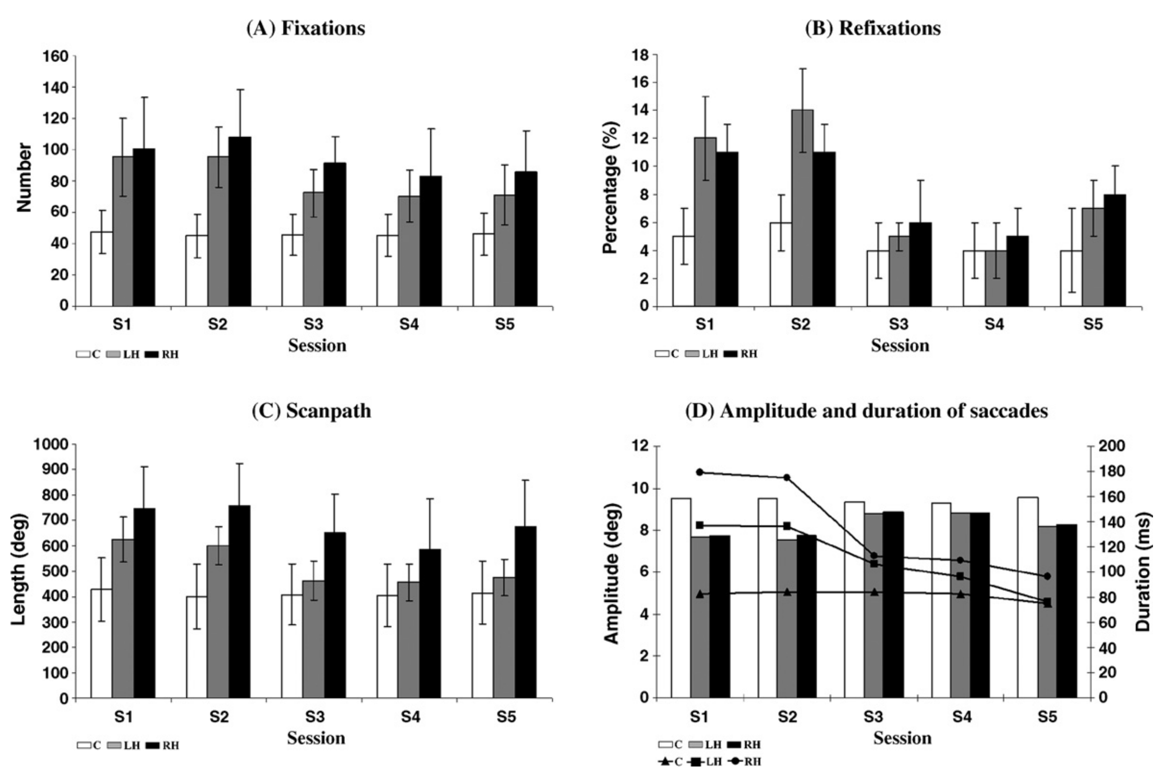

Fig. 2. Visual search task. Eye movements' parameters ((A) number of fixations; (B) number of refixations; (C) length of scanpath; (D) amplitude and duration of saccades) in the five sessions (S1 = baseline; S2 = after visual training; S3 = after Audio-Visual Training; S4 = 3 months after Audio-Visual Training; S5 = 1 year after Audio-Visual Training). For graphs (A)–(D): white bars = control subjects; grey bars = left-hemianopic patients; black bars = right-hemianopic patients. For graph (D): bars represent saccadic amplitude; lines represent saccadic duration (triangles = control subjects; squares = left-hemianopic patients; circles = right-hemianopic patients).

Table 2
Visual search task.

		S1	S2	S3	S4	S5
Number of fixations	C	47 (13)	45 (13)	42 (13)	43 (13)	46 (13)
	LH	95(24)	95 (19)	65 (15)	60 (16)	71 (18)
	RH	100 (32)	107 (30)	80 (26)	83 (29)	85 (26)
Duration of fixation (ms)	C	185 (31)	188 (36)	178 (31)	188 (31)	181 (31)
	LH	195 (14)	192 (17)	188 (15)	183 (21)	188 (21)
	RH	206 (34)	208 (29)	210 (34)	202 (31)	192 (31)
Saccadic amplitude (°)	C	9.50 (.6)	9.50 (.8)	9.33 (.3)	9.32 (.2)	9.53 (.9)
	LH	7.69 (.7)	7.54 (.8)	8.80 (.5)	8.85 (.3)	8.20 (1.4)
	RH	7.72 (.4)	7.77 (.5)	8.87 (.5)	8.83 (.4)	8.33 (.5)
Saccadic duration (ms)	C	83 (9)	84 (9)	84 (11)	83 (10)	74 (10)
	LH	130 (30)	131 (30)	89 (13)	84 (15)	76 (17)
	RH	171 (60)	168 (62)	94 (27)	98 (18)	96 (28)
Length of scanpath (°)	C	428 (123)	400 (129)	408 (118)	404 (123)	415(124)
	LH	624 (90)	600 (76)	461 (76)	456 (72)	476 (70)
	RH	746 (165)	756 (169)	648 (153)	587 (198)	675 (183)
Rate of refixations (%)	C	5 (2)	6 (1)	4 (2)	4 (2)	4 (3)
	LH	12 (3)	14 (3)	5 (1)	4 (2)	7 (2)
	RH	11 (2)	11 (2)	6 (3)	5 (2)	8 (2)
Exploration time (s)	C	12 (3)	12 (4)	13 (3)	11 (2)	12 (3)
	LH	28 (5)	27 (4)	20 (3)	20 (3)	20 (4)
	RH	33 (7)	34 (4)	25 (5)	23 (5)	28 (6)

Mean values for each session (S1, S2, S3, S4, S5) in controls (C), left-hemianopic patients (LH) and right-hemianopic patients (RH). Standard errors between parentheses.

3.2.2. *Reading task*

MANOVA revealed a significant Group × Session interaction [$F(56, 538) = 2.00$, $p < .0001$], which was replicated by Univariate ANOVAs for every variable measured [smallest F-value $(8, 105) = 2.00$, $p < .05$].

Compared to control subjects at S1, both groups of patients demonstrated reduced reading speed (LH patients: $p < .0001$; RH patients: $p < .009$). RH readers were impaired with respect to the following variables: number of errors, progressive saccades, regressions per line, duration of fixation and saccadic amplitude ($p < .001$ in all comparisons). In contrast, LH readers were only impaired in the return sweep, producing at least 1 saccade more than that necessary to find the new line ($p < .001$).

No significant differences were found in patients between S1 and S2 ($p > .5$ in all comparisons). In contrast, all patients showed a significant reduction of reading time between S2 and S3 (LH patients: $p < .01$; RH patients: $p < .02$) and an overall improvement in performance. RH patients made fewer errors, fewer progressive saccades and fewer regressions; they showed a shorter duration of fixation, and a clear enlargement in mean saccadic amplitude ($p < .05$ in all comparisons). In contrast, only the number of saccades during the return sweep decreased in LH patients ($p < .02$). Furthermore, no significant differences were found in any parameters between S3, S4 and S5 ($p > .3$ in all comparisons), suggesting a long-lasting effect of the Audio-Visual Training.

As in the Visual Search Task, the ocular responses of controls were stable across sessions ($p > .7$ in all comparisons). When comparing patients to controls at S3, S4 and S5, only LH readers showed a complete normalisation of all parameters ($p > .1$ in all comparisons); despite their clear improvements, RH patients remained significantly different from both controls and LH patients ($p < .05$ in all comparisons) (see Fig. 3 and Table 3)

4. Discussion

Unilateral damage to visual cortex of the occipital lobe can render patients to be unaware of contralesional visual information due to hemianopia. However, it has been shown that they may retain neuroendocrine, reflexive and other behavioural responses to visual stimuli (Weiskrantz, 1986). Although they do not have conscious vision, they may accurately localize visual stimuli in the hemianopic field with the hand or eye movements, or show multisensory localization behaviour (Leo, Bolognini, Passamonti, Stein, & Làdavas, 2008a). In the last study, it was shown that visual information in the blind field affects auditory localization performance, although patients remained unaware of both the presence of the visual stimulus in their blind field and of its effects on their auditory responses. One explanation that has been postulated for these different forms of residual vision is based on the involvement of the retinotectal or secondary visual pathway, which is usually intact in patients with hemianopia. Visual information can be transmitted through the retinotectal pathway, or some other subcortical pathway (e.g. retino-pulvinar, see Williams, Azzopardi, & Cowey, 1995), to extrastirate visual cortex. This information seems to be sufficient to drive visually guided behaviour without awareness. Furthermore, the SC, in addition to generating accurate visually guided saccades or orienting responses to unseen targets, is an important neural structure for multisensory integration. Recent findings provided evidence of the pivotal role of SC in mediating multisensory integration in humans when orienting responses are required (Leo, Bertini, di Pellegrino, & Làdavas, 2008b). By using stimuli visible (red stimuli) and invisible (purple stimuli) to the SC, it has been demonstrated that, when subjects were presented with peripheral visual stimuli, multisensory integration effects occurred only with stimuli visible to the SC. This important result suggests that the activity of the SC is necessary when spatial orienting responses are required. In addition, it seems that the stimulation of the temporal hemifield leads to a greater multisensory response enhancement, compared to stimulation of the nasal hemifield (Bertini, Leo, & Làdavas, 2008), thus reflecting the anatomical differences according to which the nasal hemiretina (processing the temporal hemifield) has a stronger direct input to the SC than the temporal hemiretina (processing the nasal hemifield) (Sherman, 1974).

Taken together, these studies strongly suggest that intact retinotectal functioning may be crucial for these different forms of residual vision (see also Ro & Rafal, 2006, for a review) and that the recruitment or training of these retinotectal pathways may

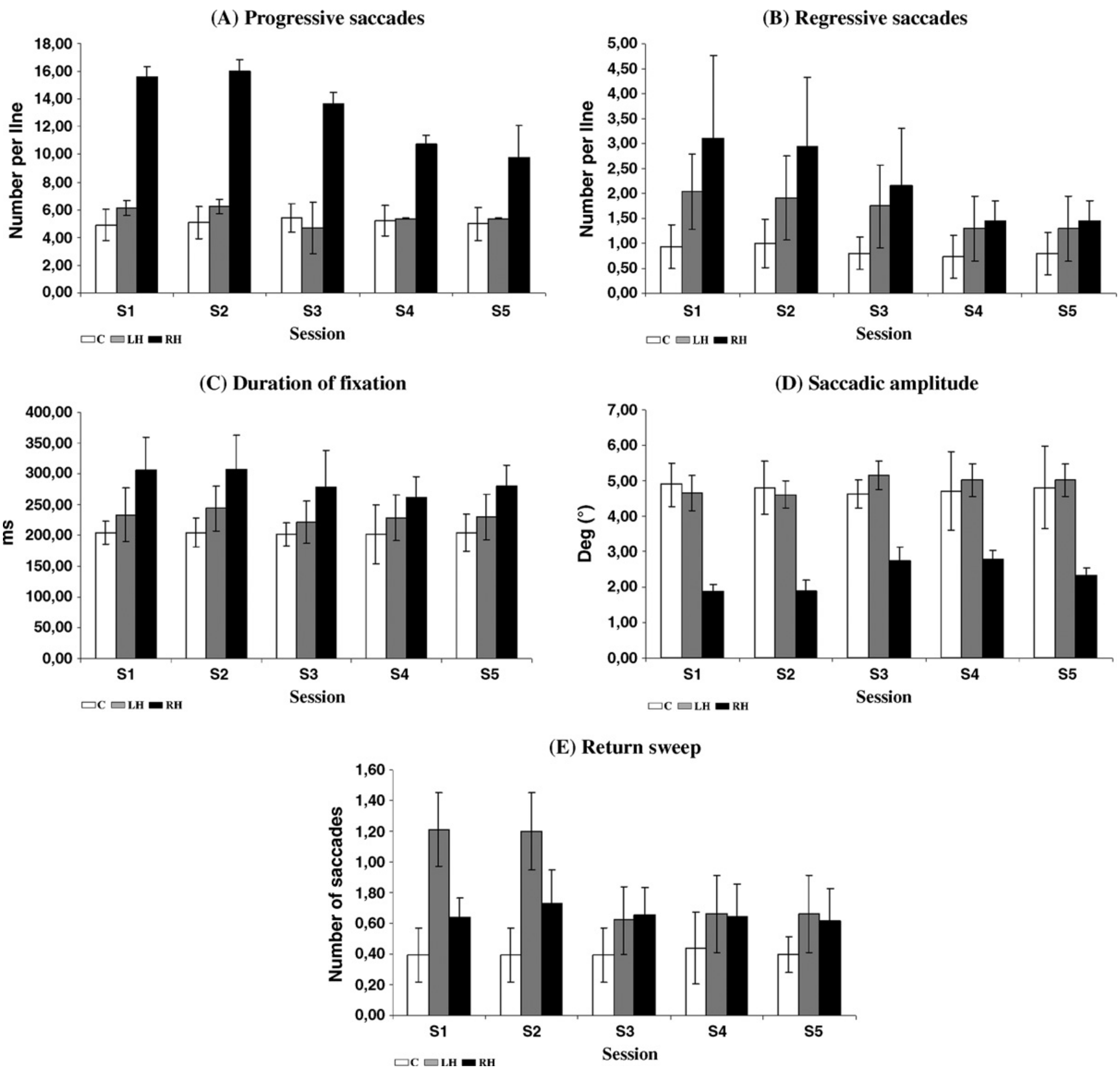

Fig. 3. Reading task. Eye movements' parameters ((A) number of progressive saccades; (B) number of regressive saccades; (C) duration of fixation; (D) saccadic amplitude; (E) return sweep) in the five sessions (S1 = baseline; S2 = after visual training; S3 = after Audio-Visual Training; S4 = 3 months after Audio-Visual Training; S5 = 1 year after Audio-Visual Training). White bars = control subjects; grey bars = left-hemianopic patients; black bars = right-hemianopic patients.

be advantageous in the restoration of visual function after primary visual cortex damage. Since most of the patients with visual cortex damage have an intact Superior Colliculus, it might be possible to train them to use their retinotectal functions to activate the extrastriate cortex processes, thereby enhancing visual awareness. Since one of the major functions of the SC is its ability to integrate multisensory information when an orienting responses is required, systematic audio-visual stimulation should improve visual processing in patients with hemianopia. A study from our laboratory demonstrated the validity of this assumption: intensive multisensory stimulation allowed patients to compensate for the loss of their vision by improving visual detection and visual search time (Bolognini et al., 2005b). These behavioural modifications are thought to result from the synergistic activation of cortical and subcortical multisensory areas, which play a pivotal role by determining oculomotor orienting behaviour towards peripheral locations.

To verify this hypothesis, the responsiveness of the oculomotor system was tested directly in the present study by comparing the effects of two different kinds of stimulation (Audio-Visual vs. Control Visual Training) on oculomotor responses. Based on eye movement data collected before the training, our results highlight the clear difficulty patients had organising their ocular scanning in a systematic way, both in the visual search and reading tasks. In the *visual search task*, both LH and RH patients, compared to controls, made a higher number of fixations and refixations, leading to a longer scanpath and smaller and slower saccades, resulting in time-consuming exploration (Chedru et al.,1974; Jahnke, Denzler, & Liebelt, 1995; Zihl, 1995; Pambakian et al., 2000; Tant et al., 2002). In the *text reading task*, the two groups of patients showed differing oculomotor deficits. Compared to control subjects, RH patients made prolonged fixations, inappropriately low amplitude saccades to the right, and many progressive and regressive saccades; as a consequence, their reading was markedly inaccurate and slow. In contrast, LH patients reported difficulties in the return sweep, leading to a slight, but significant, reduction of their reading speed (Zihl, 1995; De Luca et al., 1996; Trauzettel-Klosinski and Rheinard, 1998; Leff et al., 2000; Leff et al., 2001).

The results of the present study showed that these oculomotor deficits were differentially affected by the two training protocols. Control Visual Training proved ineffective in ameliorating either the clinical signs of hemianopia or the impaired oculomo-

Table 3
Reading task.

		S1	S2	S3	S4	S5
Number of progressive saccades per line	C	4.9 (1.1)	5.1 (1.2)	5.4 (1.0)	5.2 (1.1)	4.9 (1.1)
	LH	6.1 (.5)	6.2 (.5)	4.7 (1.9)	5.4 (.0)	5.3 (.0)
	RH	15.6 (.7)	16.0 (.8)	13.6 (.8)	10.7 (.6)	9.8 (2.2)
Number of regressive saccades per line	C	.9 (.4)	1.0 (.5)	.8 (.3)	.7 (.4)	.8 (.4)
	LH	2.0 (.7)	1.9 (.8)	1.7 (.8)	1.3 (.6)	1.3 (.6)
	RH	3.1 (1.6)	2.9 (1.4)	2.2 (1.1)	1.4 (.4)	1.4 (.4)
Duration of fixation (ms)	C	205 (18)	205 (23)	202 (18)	202 (48)	204 (29)
	LH	233 (44)	244 (37)	221 (35)	229 (37)	230 (36)
	RH	306 (54)	308 (55)	278 (60)	262 (34)	280 (34)
Saccadic amplitude (°)	C	4.89 (.6)	4.80 (.7)	4.62 (.4)	4.71 (1.1)	4.80 (1.1)
	LH	4.65 (.5)	4.61 (.4)	5.16 (.4)	5.01 (.4)	5.00 (.4)
	RH	1.87 (.2)	1.90 (.3)	2.75 (.4)	2.79 (.2)	2.32 (.2)
Return sweep (*n*)	C	.39 (.2)	.39 (.7)	.39 (.2)	.44 (.2)	.40 (.1)
	LH	1.21 (.2)	1.20 (.2)	.62 (.2)	.66 (.2)	.65 (.2)
	RH	.64 (.1)	.73 (.2)	.66 (.2)	.64 (.2)	.62 (.2)
Reading speed (syll/s)	C	6.0 (.9)	6.3 (1.1)	6.1 (.9)	5.8 (2.0)	5.8 (1.2)
	LH	4.0 (.7)	4.1 (.8)	5.8 (.4)	4.8 (.6)	4.8 (.5)
	RH	1.6 (.7)	1.4 (.6)	6.0 (.6)	3.2 (.7)	3.4 (.7)
Errors (*n*)	C	.2 (.6)	.2 (.6)	.2 (.4)	.1 (.3)	.0 (.2)
	LH	1.8 (1.3)	1.2 (1.2)	.3 (.5)	.5 (.5)	.5 (.5)
	RH	5.6 (3.2)	4.7 (3.2)	2.7 (1.9)	1.8 (1.5)	1.8 (1.4)

Mean values for each session (S1, S2, S3, S4, S5) in controls (C), left-hemianopic patients (LH) and right-hemianopic patients (RH). Standard errors between parentheses.

tor responses in hemianopic patients, probably because the visual stimulation, presented only for 100 ms, was weakly effective to "pull" patients attention and eye movements into the scotoma. This evidence suggests that unimodal visual stimulation is insufficient to significantly affect the impaired oculomotor responses. This does not imply that other types of "unimodal training" with more salient visual stimuli and with more active visual exploration might be effective in improving visual search strategy (Zihl, 1995; Pambakian et al., 2004). In contrast to unimodal training, the multisensory stimulation provided by the Audio-Visual Training helped patients on every behavioural dimension tested; they showed improvement in the clinical tests as well as in the ocular responses recorded during visual search. In addition, RH patients gained a more accurate reading performance, producing fewer progressive and regressive saccades, larger in amplitude, and a reduced duration of fixation, while in LH patients the number of saccades during the return sweep decreased significantly. After the training, however, when compared to controls, only LH patients obtained an almost complete normalization of defective ocular responses, while in the reading task RH patients still showed an impairment of the ocular responses, despite the clear benefit gained. Moreover, the improvement observed after the Audio-Visual Training was long-lasting, as revealed by the maintenance of the results one year after the end of training, and it cannot be ascribed to a practice effect. In fact, performance of control healthy subjects remained stable along time, despite the repetition of the experimental tasks.

It is worth noting that the treatment did not improve the field of vision, since no relevant change in visual field size was observed after Audio-Visual Training. In fact, when patients were not allowed to move the eyes (*Fixed-Eyes Condition*), no significant difference was observed in perceptual sensitivity. The amelioration was found only when patients' behaviour relied on other visual processing mechanisms, such as the coding within the SC for reflexive eye movements. The improvement found, therefore, can be ascribed to the implementation of an oculomotor compensatory behaviour. This hypothesis is supported by an increase of perceptual sensitivity when patients were free to move the eyes (*Eye movements Condition*) and by the improvement obtained in test assessing visual exploration ("*Triangle*" Test). These data indicate that the deleterious physiological consequences of visual cortex lesions can be ameliorated by cross-modal training, which enhances the responsiveness of the oculomotor system.

Neurophysiological studies in animals and humans have shown that multisensory neurons form the major output circuitry of the SC (see Stein and Meredith, 1993, for a review) and may play a significant role in orienting behaviour (Stein, Meredith, Huneycut, & McDade, 1989). In fact, since the sensory and premotor maps in SC are in spatial register, audio-visual information can be translated directly into an appropriate orientation response. In particular, the behavioural significance of multisensory integration to facilitate orienting has been recently addressed in the saccadic system (see Colonius & Arndt, 2001, for a review). Corneil et al. (2002) reported that saccades generated to low-intensity bimodal stimuli presented in close temporal and spatial proximity combine the properties of both visual saccades (i.e., accuracy) and auditory saccades (i.e., short latency) in an optimal fashion. We may, therefore, suppose that the intensive bimodal stimulation provided by our Audio-Visual Training has affected the spatial and temporal aspects of saccades generated by patients. This may explain, at least in part, the enlargements of saccadic amplitude and the reduction of saccadic duration observed after the training. The benefit of multisensory stimulation may be further increased by using trimodal stimuli. In fact, there is evidence from healthy subjects that additional tactile stimulation can result in faster responses to near-threshold stimuli (Diederich & Colonius, 2004). So far, however, no study has addressed the effects of a trimodal training paradigm on hemianopic patients's behaviour.

Although the SC has been demonstrated to be crucial in mediating multisensory integration, other cortical areas may have a specific influence in modulating its activity. Neuroanatomical and neurophysiological studies in animals have demonstrated strong linkages among the Superior Colliculus, posterior parietal cortex, and frontal eyes fields (FEF) for the control of eye movements (Arikuni, Sakai, Hamada, & Kubota, 1980; Barbas & Mesulam, 1981). Furthermore, data from neuroimaging in humans have reported a common activation of these areas during visual search (Gitelman, Parrish, Friston, & Mesulam, 2002).

Thus, Audio-Visual Training might have affected several higher order cognitive correlates of visual exploration, such as spatial attention and strategic oculomotor planning, as suggested by the reduction of fixation, refixation rates and, consequently, the length of scanpath. Training may have enhanced the preparation and execution of eye movements by stimulating the activity of the frontal eyes fields (FEF), which represents a descending input pathways to the SC (for a review, see Liversedge & Findlay, 2000).

Our data, taken together, lead to the conclusion that an efficient oculomotor compensation may be induced by this specific Audio-Visual Training, with long-lasting effects on the network subserving oculomotor exploration, as suggested by the maintenance of training effects one year later the end of the training. This more organized pattern of ocular exploration may well explain the improvements observed in other behavioural measures used in clinical evaluation and daily-life activities. Overall, results obtained by eye movement recordings seem to be promising with respect to the efficacy of Audio-Visual Training as a valid compensatory method for visual field disorders.

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