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Neural basis of visual deficits recovery: visual residual functions and multisensory integration

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Introduction

The possession of multiple ways of sensing the world offers many potential benefits (Stein and Meredith, 1993; Spence and Driver, 2004). The existence of specialized sensory organs is useful in encoding and decoding different aspects of external information about biologically significant event and their collective activity leads to the identification and interpretation of objects or events of interest. However, even greater advantages might be achieved by the combination of sources of information. In fact, the integrated product derived by the synergistic activation of different sensory channels is more effective than information derived from each single modality to guide behaviour towards environmental salient stimuli. The interaction among senses, the consequent fusion of sensory information and the deriving behavioural benefits have been object of a wide corpus of studies investigating the phenomenon described as “multisensory integration”. Among the other behavioural advantages, 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 unisensory processing, improving the perception of sensory events difficult to be perceived due to the unisensory defect. For example, it has been shown that, in patients with somatosensory deficits, visual information pertaining to the body might affects tactile sensation (Serino et al., 2007). In particular, in these patients, tactile thresholds on the arm were improved by viewing their own arms, but not by viewing a natural object or another body part.

As far as audio-visual integration is concerned, the pioneering investigations were conducted at the level of single neuron in Superior Colliculus (SC) on cats (Stein and Meredith, 1993). Superior Colliculus is a midbrain structure where multisensory neurons are particularly abundant. Multisensory neurons are constituted by multiple receptive fields, each one responding to a specific sensory modality and aligned in spatial register with one other. When stimuli of different modalities reach the multisensory neurons of SC, multisensory integration (i.e. a statistically significant difference between the number of impulses evoked by the crossmodal combination and the number evoked by the most effective of these stimuli individually) might occur. In order to produce response enhancement, stimuli must be presented within the space encoded by their overlapping receptive fields and linked in time. These properties depend on the organization of the receptive fields of the multisensory cells. The multisensory neurons have each of their unisensory receptive fields overlapping in the space. Consequently, visual and auditory stimuli originating in close spatial proximity will fall within the excitatory receptive fields of a visual-auditory multisensory neuron, enhancing one another. In contrast, if a sensory stimulus falls within the inhibitory region of the multisensory receptive field, it will depress neuron responses to the other sensory stimulus. Moreover, the effectiveness of the modality-specific signals has been shown to be a major determinant of multisensory enhancement. Notably, the activity of multisensory neurons in SC shows a response gradient based on the efficacy of the modality-specific stimuli: whereas the pairing of weakly effective stimuli results in a vigorous enhancement of the 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 has a great behavioural relevance, considering the survival value of the ability to detect minimal signals. In fact, minimal cues from different sensory modalities are easier to be detected in combination than they are individually. As a consequence, stimuli that are unlikely to produce either neural or behavioural responses when presented separately, show the greater advantages from the multisensory combination. According to this property, the beneficial effects of combining different sensory modalities might be more evident at the behavioural level when at least one sensory processing is too weak to induce a behavioural response; thus, a concurrent stimulation of other senses might enhance the response of the weak sensory system. This would be the case of impaired unisensory processing resulting from brain lesions that, in line with the inverse effectiveness principle, might be improved by a stimulation involving a spared sensory modality. Multisensory neural circuits, normally associated with both the deprived and nondeprived senses, retaining their responsiveness to cross-modal stimuli, might constitute the neural basis subserving the recovery of impaired sensory modalities (Làdavas, 2008). Patients with unilateral damage to the striate cortex, demonstrating visual field defects contralateral to the site of the lesion, represent an ideal model for testing this hypothesis, since they present an impairment limited to a single sensory modality and a sparing of the neural sites thought to be involved in multisensory integration.

The hypothesis that multisensory stimulation might be effective in improving visual field defects will be discussed in the present dissertation. In the first chapters (chapters 1 and 2), the neural substrate of multisensory integration in humans will be examined, providing evidence of the existence of a retino-collicular-extrastriate pathway underlying the synthesis of audio-visual stimuli. In the first chapter, evidence from literature addressing the crucial role of the SC in mediating multisensory spatial orienting both in animals and humans will be provided. In addition, paralleling the results of SC deactivation studies in cats, a study testing patients with collicular lesions in a multisensory task will be presented. The second chapter will discuss the cortical contribution to the multisensory processing. Literature concerning the effects of cortical deactivation on multisensory integrative abilities in animals will be revised. Moreover, neuroimaging studies in humans revealing a network of cortical areas activated in response to multisensory stimulation will be presented. In addition, since the patterns of cortical activation revealed in neuroimaging studies might reflect just an epiphenomenon, not disambiguating the causal involvement of these cortical areas in mediating multisensory processes, recent experimental evidence in humans, investigating the role of temporo-parietal cortex, occipital cortex and posterior parietal cortex in multisensory integration will be provided by inducing cortical virtual lesions by theta-burst stimulation. Chapters 3 and 4 will discuss the possibility of exploiting multisensory integration in order to enhance the unisensory visual impairment of patients with visual field defect. Since the retino-colliculo–extrastriate pathway constitutes the neural circuit responsible of multisensory orienting behavior, the third chapter will demonstrate that this alternative visual pathway is not only anatomically spared, but also functionally active in hemianopic patients. Evidence of immediate (i.e. on line) effects of multisensory integration, depending on the retino-colliculo-extrastriate pathway, and visual residual abilities for fearful stimuli (i.e. affective blindsight), depending on the connection of the retino-colliculo-extrastriate pathway with amygdala, will be provided. Finally, chapter 4 will demonstrate long-lasting effects of multisensory integration in hemianopic patients. Evidence of short term effects will be provided, showing that patients with visual field defect might demonstrate a multisensory enhanced auditory localization, after passive exposure to spatially coincident audio-visual stimulation. On the other hand, long-term effects of multisensory stimulation will be discussed. Evidence of the therapeutical efficacy of a systematic multisensory stimulation will be provided, showing the long-lasting clinical improvements due to the implementation of efficient oculomotor strategies in hemianopic patients after an audio-visual training regimen. Moreover, the results of a study investigating different patterns of improvement after the audio-visual training in patients with lesions to the occipital cortex and patients with lesions involving also other cortical areas, will be presented, in order to disambiguate the contribution of the retino-colliculo-extrastriate pathway in mediating the beneficial effects of multisensory integration.

CHAPTER 1

The role of Superior Colliculus in multisensory integration

The Superior Colliculus (SC) is a midbrain structure receiving convergent inputs form different sensory modalities and, therefore, widely studied as a crucial region of multisensory integration. SC is dived into two functionally distinct regions. The superficial layers are mainly unisensory with neurons responding exclusively to visual stimuli. On the other hand, the deep layers are multisensory, since they contain unisensory neurons for different modalities (visual, auditory and somatosensory) and multisensory neurons responding to each possible combination of these senses (Meredith and Stein, 1993). In this chapter, literature on electrophysiological studies in animal and psychophysics and neuroimaging investigations in humans, providing evidence of the relevance of SC in integrating different sensory signals, will be examined. At the end of the present chapter, experimental data (Experiment 1) exploring the multisensory abilities of patients with SC lesions will be presented.

1. EVIDENCE OF THE ROLE OF SC IN MEDIATING MULTISENSORY INTEGRATION IN ANIMALS

Electrophysiological studies on the SC of cats showed that multisensory neurons exhibit significant changes in their responses when presented with stimuli from multiple sensory modalities (Meredith and Stein, 1983, 1986b; King and Palmer, 1985; Wallace et al., 1996). Enhanced or depressed responses might be observed depending on the spatial, temporal and physical characteristics of the stimuli that are combined (Meredith and Stein, 1986a; 1986b; Meredith et al., 1987; Kadunce et al., 1997). On the other hand, behavioural studies on cats demonstrated that the same factors governing multisensory integration at the level of single SC neurons also govern multisensory orientation behaviors (Stein et al., 1988): multisensory stimulus combinations enhancing neural activity in SC neurons were also able to enhance behavioral performance, while combinations inducing depression in the activity of SC neurons resulted in degraded performance (Stein et al., 1988; 1989). The observation of the parallels between neuronal activity and behavior suggested that changes in the responses of multisensory SC neurons were directly responsible for changes in behavior. Evidence supporting this hypothesis is provided by animal studies on SC lesions. To test the relevance of SC activity in mediating multisensory orienting responses, the performance of cats in an audio-visual orientation task was studied before and after excitotoxic lesions of the multisensory layers of the SC (Burnett et al., 2004). The results showed different effects of SC lesions on unisensory and multisensory behavior. SC lesions induced a transient deficit in the orienting behavior towards modality-specific visual or auditory stimuli, lasting a maximum of 5 weeks, after which animals returned to performance levels equivalent to those seen prior to the lesion, therefore suggesting that the integrity of the SC is not necessary for the performance of unisensory orienting tasks. In contrast, SC lesions resulted in a permanent loss in the animal's ability to integrate visual and auditory inputs in order to enhance the orientation performance towards spatially coincident audio-visual pairs of stimuli, underscoring the essential role of the SC in the generation of these integrated responses. Moreover, the observation that the loss of multisensory integrative behavior was absolute, even when lesions to the multisensory layers of the SC were not complete and significant sparing tissue could be seen after lesion, led to a subsequent study investigating the physiological changes induced by the lesions (Burnett et al., 2007). The results revealed that the multisensory behavioral deficits seen following SC lesions were the combined result of loss of multisensory neurons and a loss of the integrative abilities in the remaining neurons. Taken together, these findings strengthened and provided confirmation in animals of the crucial role of SC in synthesizing different inputs deriving from different sensory channels in order to regulate multisensory orienting responses.

2. EVIDENCE OF THE ROLE OF SC IN MEDIATING MULTISENSORY INTEGRATION IN HUMANS

The supporting evidence on the crucial role of SC in mediating multisensory integration comes mainly from single-unit recordings in the cat and from studies on animal lesions (Stein and Meredith 1993; Burnett et al. 2004; 2007). Although the SC has provided an influential model for studies of multisensory integration in animals, the question concerning whether SC has the same pivotal role in mediating multisensory integration in humans, or other cortical areas might substitute its function, has been just recently addressed.

During a neuroimaging study, Calvert and colleagues (Calvert et al., 2001) reported a superadditive enhanced BOLD signal in the SC when subjects were presented with synchronous audio-visual stimuli, compared to asynchronous. Although the enhanced activity reported in this study revealed an involvement of SC in processing auditory and visual stimuli presented in temporal coincidence, it did not disambiguate the specific role of this subcortical structure in multisensory integration: in particular, no evidence of the causal involvement of SC in mediating multisensory orienting behavior can be derived from neuroimaging studies.

More recently, the role of SC in mediating multisensory responses in healthy humans has been directly tested with a redundant signal paradigm using stimuli visible and invisible to both the retino-collicular and magnocellular pathways (Leo et al., 2008a), exploiting the fact that neurophysiological studies have consistently reported that there are no projections to the SC from S cones (Marrocco and Li, 1977; Schiller and Malpeli, 1977; de Monasterio, 1978). There is evidence that the S cones mediate primarily colour perception (Mollon,1982), and their signals are carried by morphologically distinct types of retinal ganglion cells, which project to the koniocellular layers of the lateral geniculate nucleus and thence to layers 2 and 3 of the striate cortex (Dacey and Lee 1994; White et al. 1998). As well, S-cone stimuli cannot reach the SC via corticotectal projections (i.e. projections running from visual cortex to the SC), because S-cone stimuli are invisible also to the magnocellular pathway, which feeds these projections. However, even if an S-cone input to the magnocellular pathway, or even to the SC, exists (Stockman et al., 1991; Calkins, 2001), it is small and, more importantly, it is not chromatically opponent and can therefore be masked with luminance noise (Mollon, 1982; Birch et al., 1992). Although recent findings on primates have questionated the absence of responses to isoluminant-color stimuli in the SC (White et al., 2009), fMRI investigations on humans have reported a lack of activation of SC in presence of purple stimuli (Tamietto et al., 2009a), therefore supporting the hypothesis that stimuli uniquely detected by S cones remain invisible to the SC. Taking advantage of these neurophysiological properties, Leo and collaborators demonstrated that audio-visual multisensory responses varied as a function of the color of visual stimuli. They presented red, long-wavelength stimuli visible to the SC, and purple, short-wavelength stimuli invisible to the SC, coupled with auditory stimuli presented in spatial coincidence or at spatial disparity in a speeded detection task, where subjects were asked to respond to both visual and auditory stimuli. The stimuli were displayed at peripheral spatial locations, in order to increase the component of spatial orienting of the task. When red, long-wavelength stimuli were used, RTs to spatially coincident AV stimuli were significantly faster than RTs to the spatially disparate AV stimuli. In striking contrast, when purple, short-wavelength stimuli were used, no significant RT difference was evident between coincident and disparate audiovisual conditions. This finding demonstrates a spatially specific audio-visual integration effect for red but not for purple visual stimuli. More stringent evidence for the role played by the SC in multisensory spatial integration derived from a second analysis based on Miller's race inequality model (Miller, 1982). According to this model, the redundancy gain (i.e.

the advantage in reaction times with double relative to single stimuli) may be due either to a probabilistic race between signals transmitted along different neural channels (statistical facilitation), or to a neural coactivation (multisensory integration) mechanism resulting from the convergence of the incoming signals onto one or more brain centers. Miller's Test showed a significant violation of the race model for spatially coincident audio-visual stimuli, but only when a red long wavelength stimulus, visible to the SC, was used. Together, the present findings reveal that short wavelength stimuli, to which the SC is blind, do not produce audio-visual integration across corresponding locations in space, indicating that the SC may play a key role in integrating stimuli from separate modalities into a unified representation of space for the purpose of spatial orienting. Similar results have been recently reported by Maravita and colleagues (Maravita et al., 2008). In addition, this finding was strengthen by the observation that, in a second manipulation of the experimental setting, where the spatial component of the task was reduced by presenting the audio-visual pairs of stimuli at a central location, instead of at peripheral locations, a significant violation of race inequality was found both when auditory stimuli were paired with long or short-wavelength visual stimuli.

The role of SC in audio-visual orienting response was then confirmed by the results of another recent study (Bertini et al., 2008), also exploiting stimuli visible and invisible to the SC and showing how the multisensory effect depends on the hemifield where stimuli are presented: stimulation of the temporal hemifield leads to a greater multisensory response enhancement (i.e., shorter reaction times), comparing to the stimulation of the nasal hemifield. It is worth noting that neuroanatomical studies on cats support this behavioural finding; it has been shown that 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). Therefore, the asymmetry observed in this multisensory effect appears to be linearly related to the asymmetry of the afferent fibres to the SC. These findings are consistent with the results of a recent fMRI study, which revealed an increased activation of the SC in response to visual stimuli presented in the temporal hemifield than in the nasal hemifield, whereas no differential activity was observed in the lateral geniculate nucleus (LGN) or in the retinotopic cortical areas V1 and V3 (Sylvester et al., 2007) and strengthen the corpus of evidence supporting the pivotal role of SC in mediating multisensory spatial integration in humans.

Overall, evidence from both lesion studies on cats and neuroimaging and psychophysics investigations in humans supported the hypothesis of the crucial role of SC in mediating multisensory orienting behavior. However, in humans, the striking evidence of animals' lesions studies, directly demonstrating a loss of multisensory behavior after SC lesions (Burnett et al., 2004; 2007), has never been assessed or tested. The experiment reported in the following section will present data on patients with SC lesions performing a multisensory task, therefore, providing lesional evidence of the role of SC in multisensory behavior also in humans.

3. EXPERIMENT 1 - EVIDENCE OF THE ROLE OF SC IN MEDIATING MULTISENSORY INTEGRATION IN HUMANS WITH COLLICULAR LESIONS

Lesions to the superior colliculus in humans are mainly due to surgical removal of tumors in the pineal region. Since SC is a crucial oculomotor structure, clinical descriptions of these patients consistently reported oculomotor deficits involving spontaneous saccades and reflexive visually-guided saccades (Pierrot-Deseilligny et al., 1991; Heywood and Ratcliff, 1975). In particular, a typical clinical feature, classically described in literature, is represented by a specific up-gaze palsy: patients with SC lesions usually demonstrate defective saccades on the vertical line (Logan and Eustace, 1985; Ebner et al., 1990; Bolzani et al., 1996). As previously documented, the SC is also known to play a major role in multisensory behavior. Studies on cats (Burnett et al., 2004; 2007) reported that, after a lesion to the SC, animals lost multisensory enhanced localization behavior. However, clinical investigations on patients with lesions to the SC have never examined the multisensory integrative abilities of these patients. In this study, in order to verify the effects of a disruption of SC in humans, integrative responses of patients with collicular lesions were compared with the responses of healthy subjects and of patients with subcortical lesions not involving the SC. Patients participating in the experiment were selected based on CT scan and MRI reconstructions and they were preliminary submitted to a saccadic localization task with oculography in order to ascertain the critical presence of defective saccades on the vertical line. Obviously, the presence of defective saccades was expected in patients with the lesion involving the SC, and not in the control groups, i.e. patients with subcortical lesions not involving the SC and healthy subjects.

The multisensory integrative abilities were then compared to subjects' capacity to integrate stimuli from the same sense (i.e. unisensory integration). Recent electrophysiological studies aimed at exploring the relationship between multisensory and unisensory integration on multisensory neurons of cats (Alvarado et al., 2007a; Alvarado et al., 2007b), reported that the integration of stimuli from different modalities is more effective in enhancing neuronal responses than the integration of stimuli from the same modality. Likewise, recent evidence suggested that similar computations are reflected in overt orienting behaviour of cats (Gingras et al., 2009), where multiple stimuli from the same sensory modality only marginally enhanced localization compared to cross-modal stimuli combinations. In humans, while behavioural responses to multisensory stimulation have been extensively studied, the issues concerning the behavioural effects of the presentation of stimuli of the same sensory modality have never been investigated.

In order to explore multisensory and unisensory integrative responses in humans and to investigate the role of SC lesions in these abilities, healthy subjects, patients with subcortical lesions not involving SC and patients with collicular lesions were tested with a redundant signals paradigm for simple reaction time, in which the observer must initiate a response as quickly as possible following the detection of any stimulus onset. Subjects were presented with modality-specific stimuli (visual or auditory), cross-modal stimulus pairs (visual-auditory) and within-modal stimulus pairs (double-visual). Since the pioneering work of Todd (Todd, 1912) it is known that people typically respond faster to double targets than to a single target, a phenomenon known as redundant target effect (RTE). The RTE has been explained by two alternative models: the *race model* (*statistical facilitation*) (Raab, 1962) and the *neural coactivation model* (Miller, 1982, 1986). The former postulates that two stimuli are processed in separate channels and the fastest stimulus wins the race and triggers the response. In contrast, the neural coactivation model postulates the existence of a neural convergence among the redundant stimuli suggesting therefore that the double stimuli, integrated into a unified percept, are processed faster than the fastest single stimulus in the pair. To qualify the nature of the RTE, Miller (Miller, 1982) devised a mathematical method (race inequality test) that, using the cumulative frequency distribution (CFD) of RTs in the single versus double-target condition, sets an upper limit for the CDF when redundant target are presented (Miller, 1982, 1986) using the formula:

$$p(t < t_0 \mid \mathrm{AV}) \le p(t < t_0 \mid \mathrm{A}) + p(t < t_0 \mid \mathrm{V}).$$

When comparing the cumulated reaction time distributions to modality-specific and cross-modal stimuli, the race model predicts that for reaction time bins (t) shorter than a particular reaction time (t0), the probability (p) for the reaction time to a cross-modal stimulus (audio-visual, AV) is smaller than or equal to the summed probabilities for the modality-specific stimulus components (auditory and visual stimuli, A and V). If the limit predicted by the model is violated, then an explanation relying on statistical facilitation is no longer tenable, and the RTE can be attributed to a neural coactivation mechanism.

In the present study, the presentation of cross-modal pairs of stimuli is expected to exhibit different modulations in the three groups of subjects. In particular, in the control healthy subjects and the group of patients with subcortical lesions not involving the SC, cross-modal stimulation should significantly reduce reaction times and the RTE is expected to be explained by a neural coactivation mechanism, in line with previous psychophysics evidence (Leo et al., 2008a). In contrast, the expectation concerning patients with collicular lesions is that they should demonstrate only partial benefits from the cross-modal stimulation and, even if a reduction of the RTs for cross-modal stimulus pairs compared to modality-specific stimuli had to be found, the RTE is expected to be explained by a mechanism of statistical facilitation, not involving neural coactivation, result which would be consistent with studies on SC lesions on cats (Burnett et al., 2004; 2007).

Moreover, modality-specific and cross-modal stimulation should differentially affect behaviour, with within-modal pairs of stimuli being less effective than cross-modal pairs in reducing reaction times, mimicking the animal model on unisensory and multisensory integration (Alvarado et al., 2007b). More specifically, in all the groups tested, even if unisensory combinations of stimuli induced a significant reduction of the reaction times compared to single stimuli, this RTE is expected to be explained by a statistical facilitation mechanism and not by a neural coactivation mechanism.

Materials and method

Subjects

Three groups of subjects took part into the experiment:

1) A control group of six healthy subjects with no neurological history (mean age: 59 years; 4 females)

2) A group of six patients with subcortical lesions not involving SC (mean age: 64 years; 4 females). Three patients, recruited at least after 5 months after the surgery, reported lesions to hypophysis due to removal of pituitary adenoma, while three patients demonstrated degenerative lesions to the basal ganglia. Lesions of patients with lesions to hypophysis were documented by CT scan or MRI (see table 1)
3) A group of six patients with SC lesions (mean age: 34 years; all females). The lesions were documented by CT scan or MRI and were due to removal of tumor in the pineal gland. All the patients were recruited at least after 5 months after the surgery (see table 2)

Case	Sex	Age	Years of Education	Time since onset (months)	Cause of lesion	Lesion site
P1	F	72	5	6	tumor	pituitary adenoma
P2	F	60	8	6	tumor	pituitary adenoma
P3	M	65	5	8	tumor	pituitary adenoma
P4	F	69	5	24	degenerative	basal ganglia
P5	M	70	13	12	degenerative	basal ganglia
P6	F	46	8	30	degenerative	basal ganglia

Table 1 Summary of clinical, demographic and lesional data for patients with subcortical lesions not involving SC

All the participants were right handed and had normal or corrected-to-normal vision and showed normal hearing thresholds, as measured by audiometry in each ear, with no sign of interaural asymmetry. Subjects were naïve as to the purpose of the study. All subjects gave their informed consent to participate in the study, which was performed with approval of the local ethics committee and in accordance with the Declaration of Helsinki.

Case	Sex	Age	Years of Education	Time since onset (months)	Cause of lesion	Lesion site
P1	F	34	8	48	tumor	pineal gland
P2	F	32	17	30	tumor	pineal gland
P3	F	16	11	48	tumor	pineal gland
P4	F	17	11	45	tumor	pineal gland
P5	F	59	8	12	tumor	pineal gland
P6	F	47	13	72	tumor	pineal gland

Table 2 Summary of clinical, demographic and lesional data for patients with SC lesions

Saccadic localization task

To assess the functional properties of the SC in the patients group, before the experimental task, patients were submitted to a saccadic localization task where eye movements were recorded, in order to ascertain the involvement of SC in the lesions of the patients. 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 (accuracy 0.5°). 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. During calibration, subjects were asked to fixate (for at least three seconds) successively on each one of a series of small dots arranged on three horizontal lines. To prevent head movements, a head stabilization device was used. In the experimental task, a black background on a PC monitor was presented to subjects. Each trial consisted of a central fixation point appearing for 500 ms and a visual target appearing for 200 ms. Targets consisted of white squares (stimulus size: $0.5^{\circ} \times 0.5^{\circ}$) randomly appearing on the vertical or horizontal medial line in four positions: to the left, to the right, above or below (i.e. left, right, top, bottom) the central fixation point. Targets could appear at a distance from the central fixation point ranging from 1° to 7°. Subjects were asked maintain the gaze on the central fixation point and to perform eye movements as accurate as possible at each target presentation. Data from eye movements recordings were quantitatively analyzed computing the localization error on each trial expressed in degree (i.e. the difference between the endpoint of the first saccade and the actual target position). Each subject's mean localization errors were analyzed in a two-way ANOVA with Group as between subjects factor (normal subjects, patients with subcortical lesions not involving the SC, patients with SC lesions) and Position as within subjects factor (left, right, top, bottom). Post hoc comparisons were conducted with Newman-Keuls test.

Redundant signal paradigm

Apparatus

The apparatus (Figure 1) consisted of a 110 cm (radius) perimetry containing an array of red light emitting diodes (LEDs) separated by 2.5° and loudspeakers separated by 10°. These LEDs were at eye level, and the speakers were centered 1.3 cm above eye level. Each visual stimulus complex consisted of two horizontally-displaced (2.5°) LEDs. As a general convention we reference the stimulus aligned with the loudspeaker within each visual complex with a "V_1", and the rightmost (left side of the apparatus) or leftmost (right side of the apparatus) stimulus with a "V_2". The physical limitation of the apparatus displaced the visual-auditory complex in the vertical dimension. A fixation LED was positioned at the centre of the apparatus, in alignment with the speakers. An adjustable chin mount was positioned at the centre of the perimetry. Offset 15 cm from the centre of the semicircle was a joystick style yoke comprised of handles and two buttons. The entire apparatus was set in a dark, sound-attenuated room. The experiment was controlled via a PC.

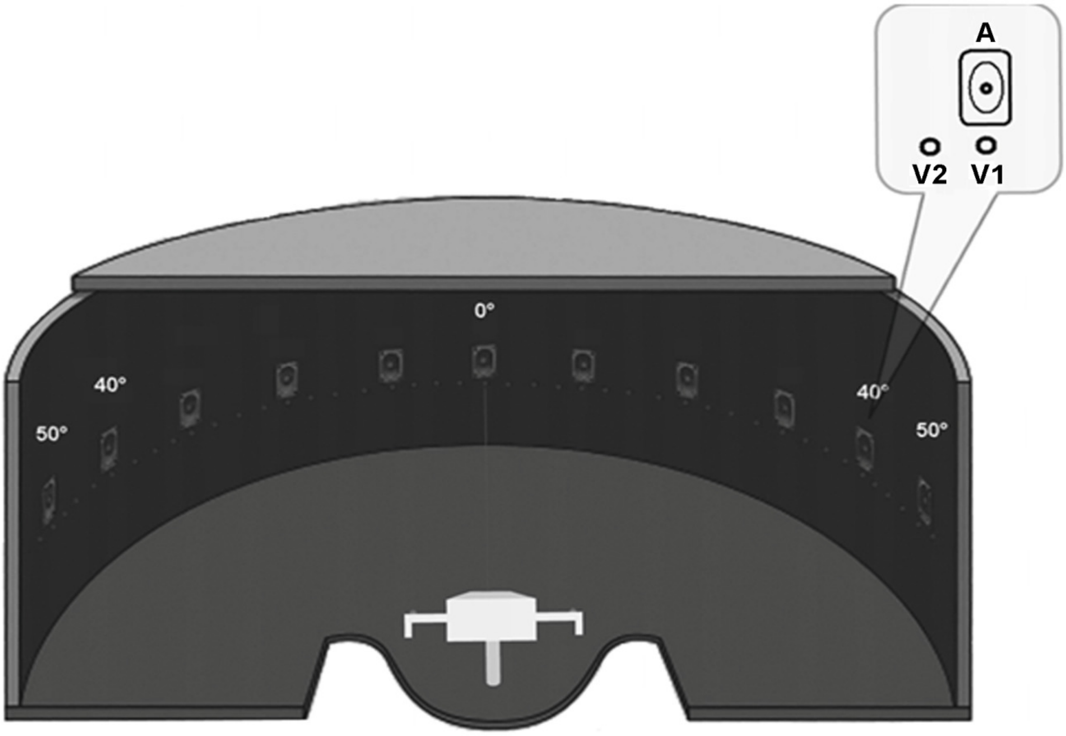

Figure 1 Schematic view of the experimental apparatus. The balloon on the top right corner represents a magnified view of a loudspeaker (A) and the corresponding visual stimulus complex (V_1 was the LED aligned with the loudspeaker; V_2 was the leftmost LED).

Stimuli

Stimuli consisted of lighting of LEDs (660 nm l at 0.003 ft cd) and broadband white noise bursts delivered from a speaker. White noise bursts were presented at 64.4 dB SPL (A scale) measured from the chin mount at the centre of the apparatus. The intensity of both visual and auditory stimuli was fixed across subjects. The intensity levels for both visual and auditory stimuli were chosen on the basis of a pilot study, in order to elicit 100% of detections and a mean localization error < 3° for all subjects.

Five trial conditions were randomly interleaved:

1) Modality-specific Visual Condition (V), consisting of a single visual stimulus (i.e. V_1);

2) Modality-specific Auditory Condition (A), consisting of a single auditory stimulus;

3) Cross-modal Audio-Visual Condition (AV), consisting of spatiotemporally coincident audio-visual stimulus pairs (i.e. A and V_1);

4) Within-modal double-visual Condition (VV), consisting of spatiotemporally coincident double-visual stimuli (i.e., V_1 and V_2);

5) Catch-Trial Condition (CT), consisting of no stimulus.

Pairs of visual stimuli were generated by two horizontally-displaced red light-emitting diodes (LEDs, 2.5°) with the same intensity level. This displacement ensured that subjects could clearly perceive each visual component of the pair. The duration of both modality-specific stimuli, cross-modal stimulus pairs, and within-modal stimulus pairs was 50 ms. Stimuli were presented at four locations along the azimuth: ±40°, ±50° from midline. The location of a green light-emitting fixation diode (fixation LED) is referenced as midline, with target locations based on this framework. By convention, negative values referenced locations left of fixation, and positive values referenced locations to the right of fixation.

Procedure

Subjects dark-adapted for 10 min prior to beginning each block of trials. In each trial, the lighting of the fixation LED lasted 1000 ms and then, after an interval which duration was randomised in a 250-1000 ms time window, a 50 ms stimulus was presented. On Catch-Trial Conditions no stimuli were presented after fixation offset. Subjects were instructed to hold constant fixation on the fixation LED, and to respond by pressing a response button with a finger of the dominant hand as quickly as possible to any stimulus onset. They were required not to push the button when no stimuli were detected. The experiment was subdivided into five blocks of trials with an overall number of 1000 trials for each participant. There were 200 trials for each type of stimulus condition and 200 catch trials in which only the fixation LED was turned on without the target stimuli. All the stimulus conditions and the catch trials were randomly interleaved.

Statistical analysis

For each subject, the average RTs were calculated and their distributions were recorded for each stimulus condition. RTs more than 2 standard deviations above or below the mean were considered outliers and discarded (4.75% of trials). Before performing statistical analysis, assumption of normality for reaction times was tested by Shapiro-Wilk's test. This confirmed that subjects' RT distributions were Gaussian for each stimulus condition. RTs in each group of subjects were then analyzed with a one-way ANOVA with Condition (V, A, AV, VV) as within-subject factors. Newman-Keuls test was used for post-hoc comparisons.

Moreover, whenever a significant reduction of RTs for pairs of stimuli, compared to single stimuli, was found, Miller's test of the race model was implemented by using RMITest software (Miller, 1982; Ulrich et al., 2007), in order to determine if the observed RTE could be explained by a statistical facilitation or by a neural coactivation mechanism. The software computes the estimated cumulative density functions (CDFs) of RTs for each stimulus condition and the estimated race model inequality bound. It also computes a *t*-test at each percentile to see whether the race model violation is statistically significant. The difference between the cumulative probability for the double stimuli and the sum of the cumulative probability for the single stimuli indicates the magnitude of violation.

Results

Saccadic localization task

Results of the two-way ANOVA with Group as between subjects factor (normal subjects, patients with subcortical lesions not involving the SC, patients with SC lesions) and Position as within subjects factor (left, right, top, bottom) revealed a significant main effect of Group [F (2,15) = 4.06, p = .04] accounted by a significantly greater mean localization error in patients with SC lesions (6.2°) compared to control subjects (5.1°; p = .05) and to subjects with subcortical lesions not involving the SC (4.6°; p = .03). A significant main effect of Position was also found [F (3,45) = 40.01, p < .001], explained by a significantly greater mean localization error for upwards saccades (6.9), compare to downwards (3.5°; p < .001), leftwards (5.4°; p < .001) and rightwards saccades (5.4°; p < .001). More importantly, a significant Group x Position interaction was found [F (6,45) = 2.11, p < .01]. Post hoc comparisons revealed that patients with SC lesions demonstrated a significant greater mean localization error in upwards saccades (8.1°) compared to healthy control subjects (6.1°; p = .04) and to patients with subcortical lesions not involving SC (6.4°; p = .04). Moreover, rightward saccades resulted significantly more inaccurate in SC patients (7°) compared to patients with no SC lesions (4.5°; p = .03). In contrast, no significant difference was found between patients with subcortical lesions not involving SC and healthy control subjects (all Ps > .07). Overall, these results highlighted a significant impairment in SC patients in upwards saccades, compared to healthy control subjects and patients with subcortical lesions not involving SC. These data are consistent with clinical findings showing a specific impairment in upwards saccades in patients with SC.

Redundant signal paradigm

Control healthy subjects

In the one-way ANOVA performed on the mean RTs observed in the group of control healthy subjects, a significant effect of the main factor Condition [F (3,15) = 25.66, p < .001] was found (Figure 2a). Responses to audio-visual stimuli (AV: 278 ms) were significantly faster than responses to modality-specific visual (404 ms; p < .001), modality-specific auditory (329 ms; p = .006) and within-modal stimuli (VV: 383 ms; p < .001). In contrast, responses to within-modal stimuli (VV: 435 ms) were not significantly different compared to modality-specific visual stimuli (p = .2).

Moreover, Miller's test of the race model revealed a significant violation of the limit predicted by the model, indicating the presence of a neural coactivation mechanism underlying the facilitation observed with audio-visual stimuli compared to modality-specific visual and auditory stimuli. In Figure 2b asterisks represent the percentiles where a significant violation occurred.

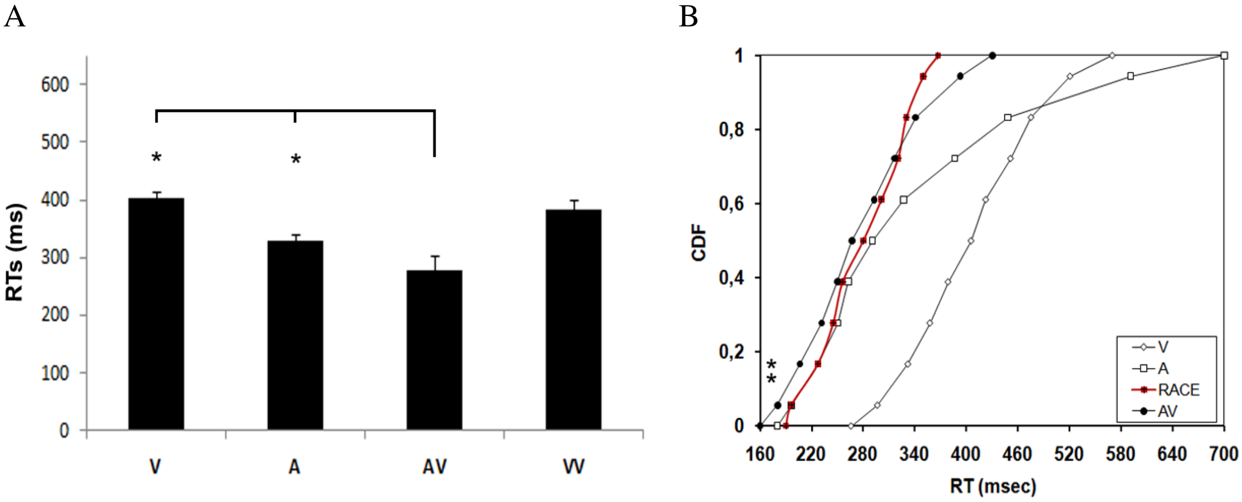

Figure 2 Healthy control subjects. Panel A: Mean RTs (S.E.M. indicated) for each condition of stimulation (V = modality-specific visual condition; A = modality-specific auditory condition; AV = cross-modal audio-visual condition; VV = within-modal double-visual condition). Asterisks indicate a p value <.05. Panel B: Violation of the race inequality test for the cross-modal audio-visual condition (AV). Asterisks represent a significant violation.

Patients with subcortical lesions non involving SC

Results of the one-way ANOVA performed on the mean RTs showed a significant effect of the main factor Condition [F (3,15) = 6.72, p = .004; Figure 3a]. In particular, RTs to audio-visual stimuli (AV: 329 ms) were significantly faster compared to RTs to modality-specific visual (438 ms; p = .006), modality-specific auditory (397 ms; p = .04) and within-modal stimuli (VV: 452 ms; p < .004). In contrast, responses to within-modal stimuli were not significantly different compared to modality-specific visual stimuli (p = .7).

Moreover, the implementation of Miller's test of the race model, testing the computational mechanism underlying the RTE observed in the audio-visual condition, revealed a significant violation of the bound predicted by the model, suggesting the existence of a neural coactivation mechanism. In Figure 3b asterisks represent the percentiles where a significant violation occurred.

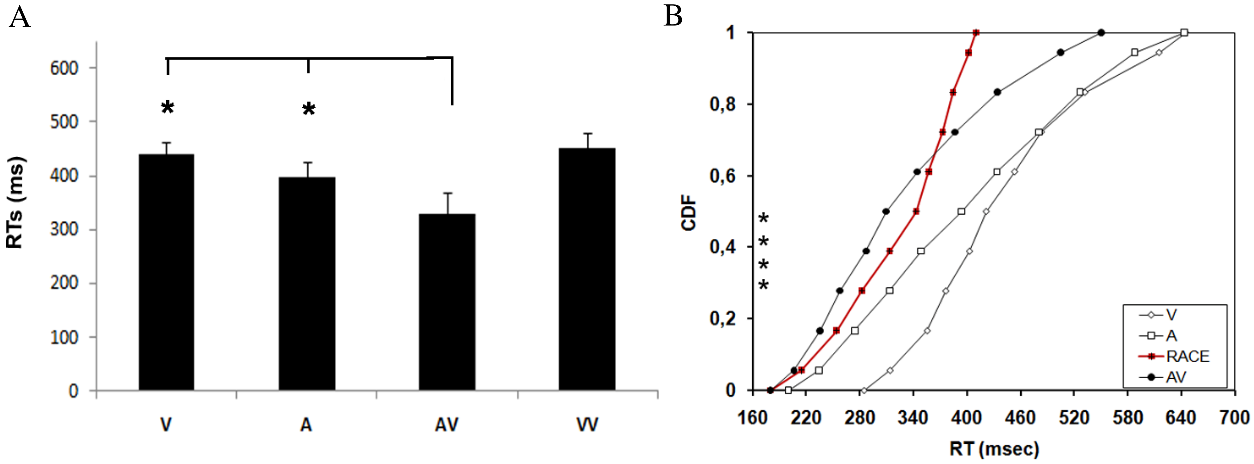

Figure 3 Patients with subcortical lesions not involving SC. Panel A: Mean RTs (S.E.M. indicated) for each condition of stimulation (V = modality-specific visual condition; A = modality-specific auditory condition; AV = cross-modal audio-visual condition; VV = within-modal double-visual condition). Asterisks indicate a p value <.05. Panel B: Violation of the race inequality test for the cross-modal audio-visual condition (AV). Asterisks represent a significant violation.

Patients with lesions to the SC

The one-way ANOVA performed on the mean RTs revealed a significant effect of the main factor Condition [F (3,15) = 9.3, p = .001; Figure 4a]. Post-hoc comparisons revealed that responses to audio-visual stimuli (AV: 413 ms) were significantly faster than responses to both modality-specific visual (527 ms; p < .001) and auditory stimuli (490 ms; p < .004). In addition, responses to audio-visual stimuli were also significantly faster compared to responses to within-modal stimuli (VV: 505 ms; p = .001). In contrast, no significant difference between the within-modal condition compared to the modality-specific visual condition (p = .35) was observed.

In addition, data were analyzed with Miller's test of the race model, in order to determine whether the RTE for audio-visual stimuli could be explained in terms of a race or a neural coactivation model. No significant violation of race inequality was found, indicating the presence of a statistical facilitation mechanism (Figure 4b).

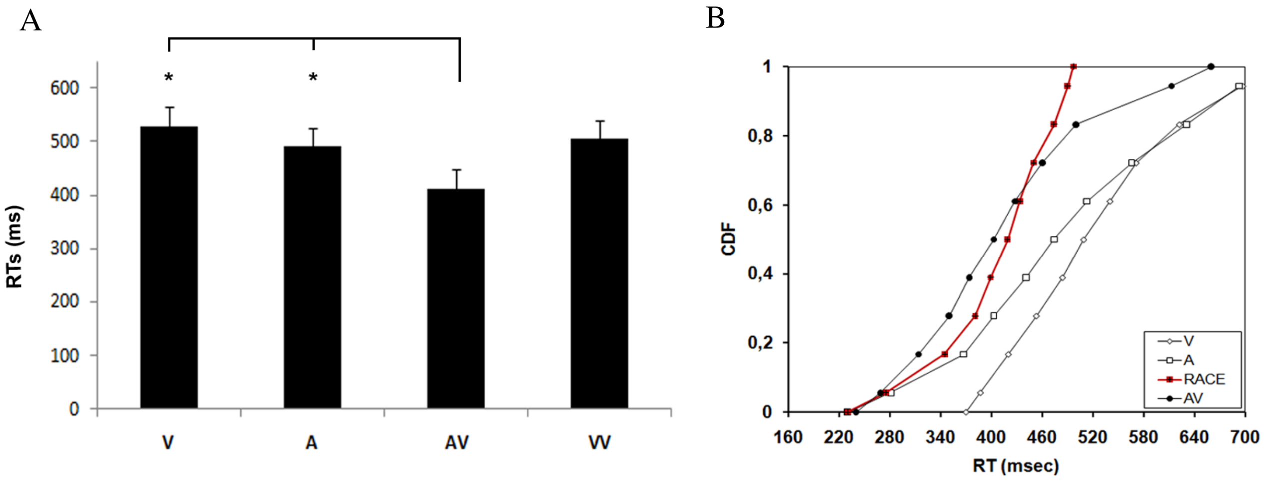

Figure 4 Patients with SC lesions. Panel A: Mean RTs (S.E.M. indicated) for each condition of stimulation (V = modality-specific visual condition; A = modality-specific auditory condition; AV = cross-modal audio-visual condition; VV = within-modal double-visual condition). Asterisks indicate a p value <.05. Panel B: Violation of the race inequality test for the cross-modal audio-visual condition (AV).

Discussion

Multisensory integrative effects in humans have been extensively investigated, both in healthy subjects and in patients with different cortical lesions (Frassinetti et al., 2002a; 2002b; 2005). However, patients with specific lesion to the SC, the midbrain structure known to play a pivotal role in integrating inputs from different sensory modalities, have never been tested in multisensory tasks. Moreover, although the behavioural advantages of multisensory integration are very well known, the effects of unisensory integration (i.e. the integration of signals from the same sense) have never been addressed in humans. The present study aimed to investigate these unexplored issues, testing healthy control subjects, patients with subcortical lesions not involving the SC and patients with collicular lesions in a redundant signal paradigm with cross-modal and within-modal pairs of stimuli. Notably, a preliminary saccadic localization task confirmed that the selection of patients based on the CT scan and MRI reconstruction was accurate. Indeed, patients with collicular lesions, were specifically impaired in upwards saccades, compared to healthy subjects and patients with subcortical lesions not involving SC, as suggested by literature regarding collicular lesions (Logan and Eustace, 1985; Ebner et al., 1990; Bolzani et al., 1996).

The performance in the redundant signal paradigm of normal subjects highlighted a different impact of multisensory compared to unisensory integration on behavioural responses. In particular, the presence of co-occurring audio-visual stimuli in spatial coincidence significantly reduced reaction times compared to modality-specific visual or auditory stimuli. Moreover, this RTE (i.e. the RT advantage with double relative to single stimuli) was to be ascribed to a neural coactivation mechanism, as revealed by the significant violation of the Miller's race inequality model (Miller, 1982). In contrast, no effect on reaction times was observed with within-modal pairs of double visual stimuli, therefore suggesting that modality-specific stimulation does not significantly affect behavioural responses. The observation that unisensory integration is less effective compared to multisensory integration in modulating behaviour is consistent with previous electrophysiological findings in cats revealing that the processes underlying multisensory and unisensory integration in superior colliculus neurons are substantially different (Alvarado et al., 2007a; Alvarado et al., 2007b). When integrating the information contained in multiple cues from different senses, multisensory neurons in cat's superior colliculus (SC) show enhanced responses that are equal to or greater than the sum of the responses to the individual modality specific component stimuli (Diederich and Colonius, 2004; Jiang et al., 2001; Kadunce et al., 1997; King and Palmer, 1985; Meredith and Stein, 1983; Peck, 1987; Perrault et al., 2005; Stanford et al., 2005; Wallace et al, 1996). In contrast, this was rarely observed when these same neurons integrated multiple inputs from the same sense. Instead, most responses were found to be subadditive, with responses to within-modal pairs substantially lower than the sum of their component responses (Alvarado et al., 2007b). Moreover, behavioural studies on cats highlighted a similar result, reporting that enhancement in localization performances was significantly greater in presence of cross-modal pairs of stimuli, compared to within-modal combinations (Gingras et al., 2009). The results obtained on control healthy subjects were also confirmed by the behavioural responses observed in patients with subcortical lesions not involving the SC. In fact, presentation of within-modal pairs of stimuli was not effective in modulating reaction times, while presentation of cross-modal pairs induced a reduction in reaction times. This RTE was explained by a neural coactivation mechanism, suggesting that when SC is intact, in spite of the presence of a subcortical lesion, patients retain the ability to demonstrate multisensory integrative effects.

In contrast, patients with SC lesions revealed a different pattern of results, as far as the integrative effects are concerned. Similarly to healthy subjects and patients with intact SC, responses were affected by the presentation of cross-modal stimuli and not affected by the presentation of within-modal pairs of stimuli. However, the observed RTE for audio-visual stimuli was not significantly different compared to the bound predicted by the Miller's test and, therefore, no violation of the race model was found. This finding suggests that, in contrast with control subjects, the RTE observed on patients with collicular lesions is subserved by a mechanism of statistical facilitation, where, in a probabilistic race between signals transmitted along different neural channels, the fastest triggers the response. This observation is in line with animal results showing that SC lesions in cats induced a complete loss of multisensory enhanced orienting behaviour (Burnett et al., 2004; 2007). In the same vein, previous evidence in humans (Leo et al., 2008a; Bertini et al., 2008; Maravita et al., 2008) revealed the presence of a neural coactivation mechanism only when subjects were presented with auditory stimuli coupled with visual stimuli visible to the SC (i.e. long wavelength stimuli), suggesting a relevant role of this subcortical structure in mediating audio-visual orienting behaviour. Moreover, neuroimaging studies revealed superadditive enhancement and depressions in the BOLD signal in SC, during the presentation of synchronous and asynchronous audio-visual stimuli (Calvert et al., 2001). However, the present findings provide more striking and direct evidence of the essential role of SC in mediating audio-visual integration, since the investigation on patients with superior colliculus lesions offers the unique opportunity to directly test the role of this midbrain structure in mediating multisensory orienting behaviour and to replicate the lesional studies conducted on cats (Burnett et al., 2004; 2007).

Overall, the present study revealed a differing impact of multisensory compared to unisensory integration on behavioural performances, with multisensory integration being more effective in speeding responses compared to unisensory integration. Moreover, the ability of integrating signals from different sensory channels was found to be strictly dependent on the activity of SC, since patients with collicular lesions failed to demonstrate multisensory integrative abilities, paralleling the findings described in lesioned cats.

CHAPTER 2

The role of cortex in multisensory integration

It is widely held that the SC plays a central role in the integration of information from different sensory modalities and the generation of spatial orienting responses. In animals, the supporting evidence comes mainly from animal lesions, and, most compellingly, from single-unit recordings in the cat (Stein and Meredith, 1993; Burnett et al., 2007). In humans, behavioural data (Leo et al., 2008a; Bertini et al., 2008), neuroimaging studies (Calvert et al., 2001) and the previously presented evidence on patients with collicular lesions have confirmed the pivotal role of this midbrain structure in generating multisensory orienting behavior. However, a wide corpus of studies, both in animals and in humans, provided evidence of a concurrent critical contribution of the cortex in mediating multisensory integrative effects. Research has mainly focused on associative polisensory areas where signals of different modalities converge. In the present chapter, the role of cortex in multisensory integration will be addressed, presenting evidence in animals and in humans and, finally, reporting experimental data concerning the cortical circuits underlying ventriloquism effect and multisensory integration revealed by theta-burst stimulation (Experiment 2).

1. EVIDENCE OF CORTICAL CONTRIBUTIONS TO MULTISENSORY INTEGRATION IN ANIMALS

Animal researches on the cortical contribution to multisensory integration have mainly focused on the role and the properties of the anterior ectosylvian sulcus (AES) of cats. AES is an associative cortex, composed of somatosensory, auditory and visual subregions, heavily projecting to the multisensory neurons of the SC (Stein et al., 1983; McHaffie et al., 1988; Meredith and Clemo, 1989; Wallace et al., 1993) and where multisensory neurons are particularly abundant. Multisensory neurons of AES demonstrate many similarities with the multisensory neurons in SC. Cortical multisensory neurons have multiple receptive fields, one for each sensory input, and these receptive fields are in spatial register with one other. Moreover, similarly to SC, multisensory enhancement in AES requires spatial and temporal concordance and exhibit inverse effectiveness (Wallace et al., 1992; Stein and Wallace, 1996).

Early investigations suggested an involvement of this cortical area in multisensory mediated behaviour (Wilkinson et al., 1996). Wilkinson et al. (1996) found that during reversible deactivation of AES cats' ability to locate and approach modality-specific targets remained unaffected, whereas the enhanced performance in presence of multisensory audio-visual targets was severely disrupt. Further evidence supported the role of cortex in multisensory integration, showing that SC neurons require cortical inputs to integrate the information they receive from different senses (Jiang et al., 2001; Alvarado et al., 2009). Electrophysiological recordings revealed that, after deactivation of AES and of the adjacent area constituted by the rostral lateral suprasylvian sulcus (rLS), multisensory integrative abilities of the multisensory neurons in the SC were disrupted, while their capacity to respond to stimuli from different senses remained intact. In particular, authors reported that after disruption of the cortical influences, the responses evoked by cross-modal pairs of stimuli in spatial coincidence were not different from those evoked by a single modality stimulus, thus demonstrating a loss of multisensory enhancement. This effect was stronger after deactivation of AES, since a greater number of multisensory neurons in the SC depend solely on AES, compared to rLS (Jiang et al., 2001). Similarly, AES deactivation was also responsible of the loss of the typical effect of multisensory depression when audio-visual stimuli were presented at spatial disparity (Jiang and Stein, 2003). In further studies exploring the role of AES subregions, selective and combined deactivation of the visual (AEV) and auditory (FAES) subregions of AES revealed that a synergistic activity of the converging cortical inputs is required in order for multisensory enhancement to occur. In fact, the disruption of either the AEV or the FAES, similarly to the simultaneous disruption of both, abolish audio-visual multisensory enhancement (Alvarado et al., 2009). Overall, these findings provide evidence, at least in cats, that SC neurons, where modality-specific inputs from different sensory channels converge, are able to demonstrate integration of these different sensory inputs only in presence of descending inputs from the associative cortex AES, favouring the hypothesis of a central role of the cortex in multisensory integration.

2. EVIDENCE OF CORTICAL CONTRIBUTIONS TO MULTISENSORY INTEGRATION IN HUMANS

Although a wide range of evidence supports in humans, as well as in animals, the critical role of SC in mediating multisensory integration, growing evidence suggests that substantial audio-visual processing is also occurring in the cortex. For example, BOLD response in human fMRI studies has been demonstrated to parallel the electrophysiological characteristics of multisensory integration at the neuronal level (Calvert et al., 2000; 2001). In other words, superadditive audio-visual gains and corresponding decrements in BOLD signal were found to mimic the response enhancements and depressions recorded in multisensory neurons in response to spatially coincident and disparate audio-visual pairs (Calvert et al., 2000; 2001). In animals, studies on cats have investigated the multisensory properties of the associative cortex AES

(Jiang et al., 2001; Jiang and Stein, 2003; Alvarado et al., 2009) and primate research has focused on the properties of the superior temporal (Benevento et al., 1977; Seltzer and Pandya, 1978; Barraclough et al., 2005), inferior parietal (Dong et al., 1994) and intraparietal (Colby et al., 1993; Duhamel et al., 1998; Schlack et al., 2002) cortices where sensory information from many different modalities converges. Similarly, neuroimaging and evoked-potential studies in humans, investigating the cortical correlates of multisensory integration, have mainly explored temporal and parietal cortices.

Temporal cortical areas, such as superior temporal sulcus (STS) and superior temporal gyrus (STG), have been reported to show superadditive activation during presentation of spatially congruent pairs of auditory and visual speech signals (Calvert et al., 2001; Wright et al., 2003) and in presence of bimodal congruent letter-sound pairs (van Atteveldt et al., 2007). STS also revealed enhanced activation with semantically congruent visual objects and sounds (Beauchamp et al, 2004; Stevenson et al., 2007; Meienbrock et al., 2007; Werner and Noppeney, 2009), as well as non-semantic simple audio-visual stimuli (Noesselt et al., 2007).

On the other hand, posterior parietal cortex (PPC) demonstrated superadditive enhancement and decrease in BOLD signal during the presentation of simple synchronous and asynchronous audio-visual stimuli, respectively (Calvert et al., 2001). Increased activity in PPC was also found during presentation of semantically congruent images and sounds in spatial coincidence (Meienbrok et al., 2007). In the same vein, early audio-visual interactions in PPC were found during an ERPs study (Molholm et al., 2002).

In addition to temporal and parietal cortices, neuroimaging studies also revealed a consistent contribution of frontal cortices during presentation of synchronous simple audio-visual stimuli (Calvert et al., 2001), during multisensory object categorization (Adams and Janata, 2002) and during detection of semantic inconsistencies in audio-visual objects (Laurienti et al., 2003).

Moreover, exceeding the classical view of sensory organization, multisensory related activations have been also found within low-order regions of sensory cortices, typically considered unisensory (Ghazanfar and Schroeder, 2006). These activations might represent feedback top-down influences from high-order cortical areas, affecting unisensory encoding (Foxe and Schroeder, 2005), or, alternatively, might reflect an early stage of multisensory interactions (Giard and Peronnet, 1999).

Although the existence of this wide corpus of studies, demonstrating a network of cortical activation during audio-visual processing, to date, it is still not clear whether this cortical activation is necessary in order to integrate audio-visual multisensory signals or if it reflects an epiphenomenon. This issue needs therefore to be further investigated, in order to ascertain the causal involvement of cortical areas in multisensory process. To this aim, transcranial magnetic stimulation (TMS) and, in particular, inhibitory continuous theta burst stimulation (cTBS), provides the unique opportunity of transiently and non-invasively inhibiting the brain activity of selected cortical areas and, therefore, of investigating their influence on behavioural performances during controlled experimental tasks.

3. EXPERIMENT 2 - INDEPENDENT MECHANISMS FOR VENTRILOQUISM AND MULTISENSORY INTEGRATION AS REVEALED BY THETA-BURST STIMULATION

The influence of visual cues on auditory perception has been extensively investigated and studies have documented either beneficial (i.e. multisensory integration) or detrimental influences (i.e. visual bias) of visual events on auditory localization (Corneil et al., 2002; Bolognini et al., 2007; Alais and Burr, 2004; Recanzone and Sutter, 2008). As far as the multisensory integration effect is concerned, it is well known that localization of an auditory stimulus is enhanced by the presence of a co-occurring spatial coincident visual stimulus (Corneil et al., 2002; Bolognini et al., 2007; Leo et al., 2008b; Passamonti et al., 2009a). This perceptual enhancement can well highlight the benefit deriving from the integration of cross-modal stimuli (Hairston et al., 2003a; Bolognini et al., 2005a; Bertini et al., 2008; Leo et al., 2008a) and it is reminiscent of the response properties of multisensory cells in the superior colliculus, as described in several neurophysiological studies in non-human mammals (Meredith and Stein, 1983; Meredith and Stein, 1986a, 1986b; Stein and Meredith, 1993; Kadunce et al., 2001), suggesting a pivotal role of this subcortical structure in mediating multisensory integration. Notably, however, evidence on cats suggests that cortical areas (i.e. the anterior ectosylvian sulcus, AES) are essential for multisensory response in collicular neurons and for multisensory mediated orienting behavior (Stein and Stanford, 2008); however, to date, information about the possible human cortical homologue of AES is meager. Imaging studies in humans have revealed that temporoparietal areas (i.e. superior temporal sulcus and superior temporal gyrus, extending into inferior parietal cortex, here referred as temporo-parietal cortex, TPC) and the intraparietal sulcus in the posterior parietal cortex (PPC) consistently show multisensory enhanced response to audio-visual stimuli presented with temporal and spatial coincidence (Calvert et al., 2000; Calvert et al., 2001, Molholm et al., 2002; Meienbrock et al., 2007), mimicking the response properties of collicular multisensory neurons (Laurienti et al., 2005). Nevertheless, to date it is not clear whether activity in these temporal and parietal cortical regions is essential for multisensory perceptual benefit or it reflects an epiphenomenon. While presenting simultaneous spatial coincident auditory and visual stimuli can enhance auditory spatial localization, presenting simultaneous but spatially discrepant auditory and visual stimuli is known to mostly induce a perceptual translocation of the sound towards the visual stimulus, i.e. a detrimental effect of visual events on auditory localization (Howard and Templeton, 1966; Thurlow and Jack, 1973; Welch and Warren, 1980; Bertelson and Radeau, 1981; Spence and

Driver, 2000; Slutsky and Recanzone, 2001; Hairston et al., 2003b; Lewald and Guski, 2003; Vroomen and De Gelder, 2004). Behavioral studies on healthy participants and brain damage patients suggest that mechanisms underlying the 'ventriloquism' effect are at least partially distinct from those underlying multisensory integration (Bolognini et al., 2007; Leo et al., 2008b; Passamonti et al., 2009a); indeed, reduction in perceptual saliency of visual stimuli (Hairston et al., 2003b; Bolognini et al., 2007) and lesions to the occipital cortex (OC) (Leo et al., 2008b; Passamonti et al., 2009a) are known to reduce ventriloquism without affecting multisensory perceptual enhancement. In the present research we tested the hypothesis that differential neural networks are critically involved in ventriloquism and audio-visual multisensory enhancement. In three experiments we asked subjects to localize an auditory stimulus that was presented alone (modality-specific stimulation) or with a concurrent hard-to-detect visual stimulus at various spatial disparities (audio-visual stimulations). This way, we derived indices of visual bias and multisensory integration from auditory localization performance. Importantly, in each experiment, the localization task was carried out in two counterbalanced sessions that were performed well within the inhibition window created by off-line repetitive transcranial magnetic stimulation (TMS) or outside the influence of TMS (baseline). Magnetic stimulation was performed by means of continuous theta-burst (cTBS), a novel TMS protocol known to suppress cortical excitability for up to 60 minutes (Huang et al., 2005). By showing how auditory localization was affected by "virtual lesions" to the right temporo- parietal cortex (rTPC), right occipital cortex (rOC) and right posterior parietal cortex (rPPC) we were able to test the critical role of these three regions in multisensory integration and ventriloquism.

Materials and Method

Subjects

Forty-two right-handed healthy participants free from any contraindication to TMS (Wassermann, 1998) took part in the experiment and were assigned to three experimental groups. A first group comprised 12 subjects (age range: 21-18 years; 7 females) who were submitted to cTBS on right temporo-parietal cortex (rTPC, Experiment 1). The second group included 12 subjects (age range: 21-27 years; 9 females) submitted to cTBS on the right occipital cortex (rOC, Experiment 2). The third group comprised 18 subjects (age range: 21-31 years; 11 females) submitted to cTBS on the right posterior parietal cortex (rPPC, Experiment 3). All had normal hearing and normal or corrected-to-normal vision and were naive as to the purpose of the experiment. Participants received course credits for their participation and gave informed consent prior to beginning. The experimental procedures were approved by the Ethical Committee of the Department of Psychology, University of Bologna. The experiment was carried out according to the principles laid out in the 1964 Declaration of Helsinki.

Experimental Apparatus

The apparatus consisted of a semicircular perimetry (radius 110 cm) containing an array of red light-emitting diodes (LEDs) and speakers (Figure 5). A central LED, positioned at the eye level, constituted the central fixation point (0°). A set of 26 LEDs was placed at the same level, at eccentricities ranging from 20° to 80° to the left and the right of the fixation point. Each LED was separated by 5° of visual angle. A set of 8 speakers was positioned 1.3 cm above the LEDs array at 20°, 40°, 60° and 80° of eccentricity to the left and the right of the central fixation point.

A joystick style yoke comprised of handles, two buttons and a laser pointer was mounted 5 cm from the center of the semicircle. A personal computer and a multifunction card controlled the stimuli display and the response acquisition, receiving input from the yoke and the buttons. The entire apparatus was enclosed in a dimly lit, sound-attenuated room.

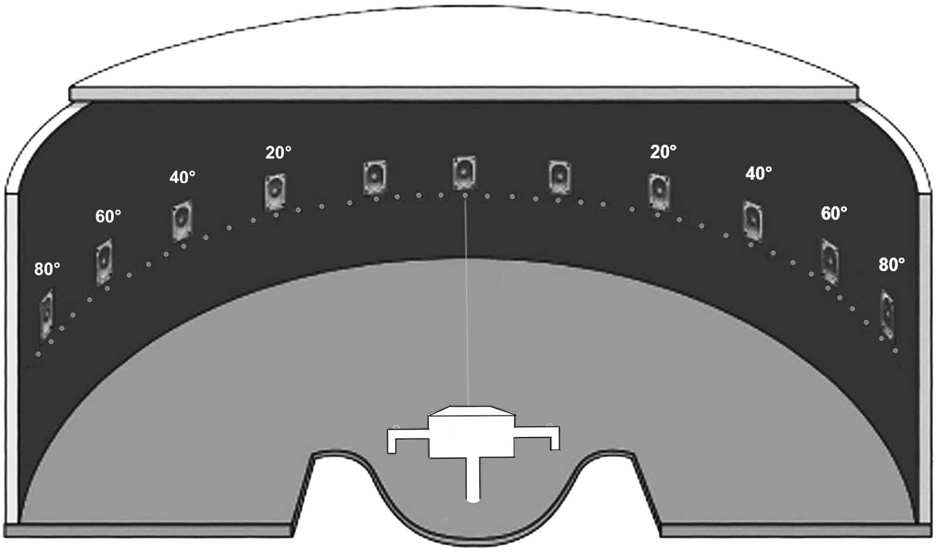

Figure 5 Schematic view of the experimental apparatus

Experimental procedure

In each experiment subjects dark-adapted for 10 minutes prior to beginning the testing procedure. In order to set the auditory and visual intensities, each subject's ability to localize auditory stimuli (auditory intensity setting procedure) and to detect visual stimuli (visual intensity setting procedure) was measured before the experimental task. In the auditory intensity setting procedure, subjects were instructed to localize a pure tone (2000Hz) delivered from a speaker, by rotating the yoke and pointing with the laser pointer. Each trial consisted of the illumination of the central fixation point for 800 ms, a random delay (100-1000 time window) and the presentation of the auditory stimulus (100 ms). In each block, all the 8 possible auditory positions were tested and 10 trials for position were presented. After each block, auditory localization performance was evaluated by assessing the mean localization absolute error (i.e., unsigned difference between actual and reported location). The initial intensity of the pure tone was 56.1 dB and was gradually reduced with step of 1.3 dB in each block, in order to reach a localization error within 8° in about 50% of the trials. During the visual intensity setting procedure, subjects were asked to detect the presence of a visual stimulus consisting of the illumination of an LED, by pressing a button. In each trial, the central fixation point appeared for 800 ms and then, after a random delay (100-1000 ms time window), the visual stimulus was presented for 100 ms. The 26 visual stimulus positions were tested individually, in separate blocks. Each block consisted of 20 trials and 10 catch trials (i.e. trials in which no visual stimulus was presented). The intensity of the visual stimuli was initially set at 0.016/fc and then, was gradually reduced with step of 0.002/fc in each block, to reach a hit rate of about 50%. Once stimuli intensities were set, subjects performed the experimental task in two counterbalanced sessions, within (Post-cTBS session) and outside (baseline) the inhibition time window created by the cTBS. Participants were presented with hard-to-detect visual stimuli (100 ms illumination of a red LED, intensity range 0.001-0.016 /fc) and hard-to-localize auditory stimuli (100 ms pure tone 2000 Hz, intensity range 52.2-56.1 dB).

Two possible stimuli combinations were used:

- Modality-specific Auditory Condition (A-UNI): the auditory stimulus was presented alone.
- Cross-modal Audio-Visual Condition (AV): the auditory stimulus was presented at each location concurrently with a temporally coincident task-irrelevant visual stimulus. The visual stimulus was either spatially coincident (SP, same position) or spatially disparate (SD) with the auditory target. Disparities of 15° (SD-15) or 30° (SD-30) in the nasal (N) or temporal (T) directions were used. For each trial, subjects were asked to fixate the central fixation point and then to judge the spatial position of the auditory stimulus, by pointing with the laser pointer, and

to ignore any accompanying visual stimulus. The auditory stimuli could be presented in any of the 8 possible auditory positions.

During each session of the experiment, 16 trials for each of the 5 stimulus combination (A-UNI, AV-SP, AV-SD-15N, AV-SD-15T, AV-SD-30) were randomly presented at each of the 4 spatial positions (60° right, 40° right, 40° left, 60° right) resulting in a total of 160 trials for hemifield. Localization performance was based on data recorded at these positions. To increase uncertainty judgments we presented a total of 32 stimuli for hemifield at more central (20°) and peripheral (80°) locations (these included 8 A-UNI, 8 AV-SP, 8 AV-SD-15 and 8 AV-SD-30 stimuli for hemifield). However, these data were not included in the analysis.

Transcranial Magnetic Stimulation

In a preliminary part of the experiments, before performing the auditory and visual intensity setting procedures (see above), we assessed the individual intensity threshold for phosphene perception in the right visual cortex. Participants wore a lycra cup, were blindfolded and adapted to darkness for 10 min to enhance the excitability of their visual cortex (Boroojerdi et al., 2000; Fernandez et al., 2002). TMS was performed by means of a 70 mm figure-eight stimulation coil connected to a Magstim Rapid2 (The Magstim Company, Carmarthenshire, Wales, UK). The coil was oriented so that the induced current was lateral-to-medial, optimal for stimulating the visual cortex (Kammer et al., 2001). Five participants in the rTPC Experiment (42% of the total), five participants in the rOC Experiment (42%) and seven participants in the rPPC Experiment (39%) did not report phosphenes during single-pulse TMS. In the remaining subjects, by using a slightly suprathreshold intensity we roughly marked the scalp area in which single-pulse TMS elicited phosphenes and then, within this area, we localized the hotspot. Phosphene Threshold (PT) was determined by delivering in random order, about 10 pulses at various intensities with increments of 2-3%. PT values (mean maximum stimulator output ± st.dev.) were comparable in the three experiments (rTPC, Experiment 1: 59.4 ± 7.5%; rOC, Experiment 2: 61.4 ± 9.7%; rPPC, Experiment 3: 59.3 ± 7.5%; F(2,22) = 0.14, P =.87). After the assessment of PT and the auditory and visual intensity setting procedures (see above), participants performed the experimental task in two different sessions (Post-cTBS, Baseline) lasting 20-25 min each. In the Post-TBS session, the task was performed within the inhibition window created by 40 sec of continuous TBS (cTBS) on rTPC, rOC or rPPC; cTBS consisted of bursts of 3 TMS pulses delivered at 50 Hz, with each train burst repeated every 200 ms (5 Hz) for a total of 600 pulses. This TMS protocol is known to suppress the excitability of the stimulated site for about 30-60 minutes (Huang et al., 2005; Franca et al., 2006). After cTBS, participants rested for 5 minutes before running the task to allow the cTBS effect to reach its maximum level (Huang et al., 2005). Pulse intensity was comparable in the three experiments (rTPC, Experiment 1: 48.5 ± 4.3%; rOC, Experiment 2: 48.7 ± 5.0%; rPPC, Experiment 3: 48.4 ± 4.3%; F(2,39) = 0.02, P = 0.98) and was set as it follows: i) in those subjects with PT < 64% of maximum stimulator output (6, 6 and 8 subjects in rTPC, rOC and rPPC Experiment, respectively) the intensity was 80% of PT; ii) in those subjects with higher PT (1, 2 and 3 in rTPC, rOC and rPPC Experiment, respectively) or reporting no phosphene (5, 4 and 7) pulse intensity was set at the maximum allowed by the stimulator (51%). In all the experiments, task performance in the Baseline session was recorded before cTBS (in half of participants) or at least 2 h after cTBS to be sure that all the interferential effects had faded away (in the remaining subjects). This procedure was aimed at counterbalancing the two experimental sessions. Coil position was identified on each participant's scalp with the SofTaxic Navigator system (Electro Medical Systems, Bologna, Italy) as in previous research (Avenanti et al., 2007; Bolognini and Maravita, 2007; Bolognini et al., 2009). Skull landmarks (nasion, inion, and two preauricular points) and about 100 points providing a uniform representation of the scalp were digitized by means of a Polaris Vicra digitizer (Northern Digital Inc, Ontario, Canada). Coordinates in Talairach space (Talairach and Tournoux, 1988) were automatically estimated by the SofTaxic Navigator from an MRI-constructed stereotaxic template. Figure 2-4 illustrate site reconstructions displayed on a standard template from MRIcro (v1.40; http://www.mricro.com; Rorden and Brett, 2000). In the rTPC Experiment, we targeted the superior temporal gyrus at the board with the inferior parietal cortex (x = 63.7, y = - 31.3, and z = 14.9, corresponding to Brodmann's area 42/39, Figure 6a). This site was chosen based on imaging studies showing multisensory activity in superior temporal and inferior parietal regions (Calvert et al., 2000; Wright et al., 2003 Beauchamp et al., 2004; Stevenson et al., 2007; Noesselt et al., 2007; Meienbrock et al., 2007; Werner and Noppeney, 2009). In the rOC Experiment we identified the scalp locations that corresponded best to the visual cortex (coordinates: x = 19.1, y = - 98.2, and z = 0.9, corresponding to Brodmann's area 17, in the middle occipital gyrus, see Figure 7a). In the rPPC Experiment we targeted the rPPC site where auditory and visual information are likely to be merged (x = 43.7, y = -43.3, and z = 47.3, corresponding to Brodmann's area 40, in the depth of the intraparietal sulcus, see Figure 8a); this location was chosen by averaging the coordinates of the right intraparietal cortex sites found in three previous brain imaging studies (Bushara et al., 2001; Bremmer et al., 2001; Calvert et al., 2001).

Statistical Analysis

Performance was evaluated for responses to auditory stimuli presented at 40° and 60° to the right and the left of the central fixation point. The other auditory positions were not analyzed (i.e. 20° and 80°) in order to not produce a nasal or temporal response bias in the data set. In fact, auditory judgments more central than 20° and more peripheral than 80° were not possible for technical reasons. Auditory localization performances were analyzed for each experiment separately according to two parameters:

Multisensory enhancement index (MEI). The multisensory response enhancement for spatially coincident audio-visual stimuli was computed with the formula (modified from Meredith and Stein, 1983):

$$\text{MEI} = (\text{Err SP-AV} - \text{Err A-UNI}) / \text{Err A-UNI}$$

where Err SP-AV indicates the mean localization error for spatially coincident audio-visual stimuli and Err A-UNI represents the mean localization error in the modality-specific auditory condition. Negative values of MEI indicate that the localization error in the modality-specific condition is greater than the localization error in the SP-AV condition (i.e. presence of a multisensory enhancement), while positive values indicate the opposite. This index was calculated to quantify and compare the magnitude of multisensory enhancement across the sessions.

Data were collapsed across positions (40°, 60°) to increase statistical power and analyzed with an ANOVA with Session (Baseline vs Post-cTBS) and Hemifield (Contralateral vs Ispilateral to the stimulated site) as within-subjects factors.

Visual Bias. The percentage of Visual Bias was calculated for each trial where audio-visual stimuli were presented in spatial disparity, according to the following formula (Hairston et al., 2003b; Wallace et al., 2004; Leo et al., 2008b):

$$\%\ \text{Visual Bias} = [(\text{Err SD-AV} - \text{Err A-UNI}) / \Delta\ \text{AV}] * 100$$

where Err SD-AV represents the localization error in a given trial with audio-visual disparity, Err A-UNI represents the mean localization error in the modality-specific auditory condition and Δ AV represents the actual visual-auditory disparity. The resulting percentage score represents the degree of visual bias of sound location, in other words the “pull” that the visual signal has over the auditory target. A score of 100% indicates a complete bias, wherein the subject localizes the sound at the visual stimulus site, while positive scores less that 100% represents position judgments between the visual and auditory stimuli.

Data were collapsed across positions (40°, 60°) and disparities (15°N, 15°T, 30°) to increase statistical power and then analyzed with an ANOVA with Session (Baseline vs Post-cTBS) and Hemifield (Contralateral vs Ispilateral to the stimulated site) as factors within subjects. Although the same experimental procedure was used in the three experiments, visual bias and multisensory enhancement indices were higher in subjects of rTPC Experiment. To eliminate differences between groups, a total of 12 subjects with no sign of multisensory enhancement (4 subjects with mean MEI across conditions > 0) or with low (under the 20th percentile, 6 subjects) or very high visual bias (higher than 2 st.dev from the mean, 2 subjects) were removed from the main analysis. In the following section, the results from the ANOVAs conducted on the remaining 30 participants are reported (rTPC, Experiment 1: 9 subjects; rOC, Experiment 2: 10 subjects; rPPC, Experiment 3: 11 subjects). Crucially, analyses conducted on the entire sample lead to the same statistical results (Main effect of Session in the ANOVA performed on MEI in the rTPC experiment: F(1,11)= 11.25, P = .006; Session x Hemifield interaction in the ANOVA performed on the visual bias in the rOC experiment: F(1,11) = 12.45, P = .005. In the remaining ANOVAs, no main effect or interaction was significant: all Fs < 1.49; Ps > .25; see table 3).

	Experiment 1 Virtual lesions to rTPC	**Experiment 2 Virtual lesions to rOC**	**Experiment 3 Virtual lesions to**
MEI			
Session	($F_{1,11}$= 11.25, P = .006)	($F_{1,11}$= 0.08, P = .79)	($F_{1,17}$= 0.01, P = .92)
Hemifield	($F_{1,11}$= 1.32, P = .28)	($F_{1,11}$= 0.05, P = .82)	($F_{1,17}$= 0.23, P = .64)
Session x Hemifield	($F_{1,11}$= 3.44, P = .09)	($F_{1,11}$= 0.27, P = .61)	($F_{1,17}$= 0.08, P = .79)
Visual Bias			
Session	($F_{1,11}$= 0.12, P = .74)	($F_{1,11}$= 0.40, P = .54)	($F_{1,17}$= 0.02, P = .89)
Hemifield	($F_{1,11}$= 1.49, P = .25)	($F_{1,11}$= 2.07, P = .18)	($F_{1,17}$= 0.16, P = .69)
Session x Hemifield	($F_{1,11}$= 0.44, P = .52)	($F_{1,11}$= 12.45, P = .005)	($F_{1,17}$= 0.19, P = .67)

Table 3 Statistical values of the ANOVAs conducted on the entire sample of subjects.

Results

Experiment 1: Virtual lesion to rTPC

Overall, participants in Experiment 1 showed multisensory enhancement effects as indicated by the mean MEI computed across conditions (Figure 6b): one-sample t-test revealed that MEI was significantly different from zero (one-sample t-test: t(8)=-6.23, P = .0002), indicating that presenting simultaneous spatially coincident visual stimuli improved localization accuracy of auditory stimuli. The Session x Hemifield ANOVA performed on MEI revealed a significant main effect of Session [F(1,8)= 9.75, P = .014], accounted by the lower multisensory enhancement (less negative MEI) after cTBS over rTPC compared to baseline (-0.26 vs -0.31). No main effect of Hemifield [F(1,8) = 1.14, P= .32] or interaction Session x Hemifield were found [F(1,8) = 3.34, P = .11]. However, planned comparisons revealed that most of the reduction of the multisensory enhancement occurred in the left hemifield, contralateral to the stimulated site (-0.33 vs -0.18, P = .009), while no change in MEI seemed to occur in the ipsilateral hemifield (-0.29 vs -0.33, P = .59). After cTBS, multisensory enhancement in the left contralateral hemifield was marginally lower than in the right ipsilateral hemifield (-0.18 vs -0.33, P = .07). Importantly, one-sample t-test revealed that after cTBS over rTPC, multisensory enhancement in the left contralateral hemifield was still significantly different from 0 [t(8)= -3.33, P = .01], indicating that cTBS was capable of reducing but not of eliminating the multisensory enhancement. All participants in the first experiment showed a conspicuous visual bias (one-sample t-test against zero calculated on mean visual bias index computed across conditions: t(8) = 7.35, P <. 0001; see Figure 6c). The Session x Hemifield ANOVA on the percentage of visual bias revealed no significant effect or interaction (all Fs < 0.62, Ps > .45), indicating that cTBS over rTPC did not affect ventriloquism. In sum, this first experiment shows that in the Baseline session (outside the inhibitory effect of cTBS over rTPC) auditory localization performance was strongly improved by the presentation of a spatially coincident visual stimulus (multisensory enhancement effect) and decreased by the presentation of a spatially disparate visual stimulus that induced a perceptual translocation of the sound towards the visual stimulus (visual bias effect). Crucially, suppressing the activity of rTPC by means of cTBS disrupted multisensory integrative enhancement but not ventriloquism.

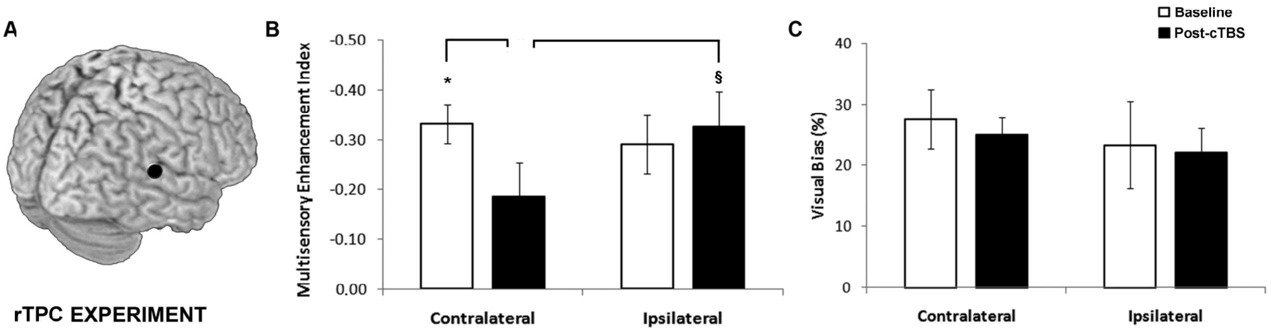

Figure 6 Experiment 1: (A) Brain location of the coil position to induce virtual lesion of the right temporo-parietal cortex (rTPC, mean Talairach coordinates: x = 63.7, y = -31.3, and z = 14.9). (B) Multisensory enhancement index (MEI). (C) Visual bias. White and black histograms represent MEI and visual bias during baseline and after cTBS (post-cTBS), respectively. Error bars indicate s.e.m. *: P < .05; § P = 0.07.

Experiment 2: Virtual lesions to rOC

One-sample t-tests against zero indicate that participants in the second experiment showed multisensory enhancement [t(9) = -4.79, P = .0009) and visual bias effects across sessions [t(9) = 7.50, P < .0001]. The Session x Hemifield ANOVA conducted on MEI showed no main effects or interaction (all Fs < 1.31, Ps > .28), indicating that TMS did not affect multisensory integration (Figure 7b).

By contrast, the Session x Hemifield ANOVA on visual bias revealed a significant double interaction [F(1,9) = 7.71, P = .021; Figure 3c], but not main effects of Session or Hemifield (all Fs < 0.59, Ps > .46). Post-hoc analysis revealed that compared to baseline, cTBS over rOC brought about a significant decrease in the percentage of visual bias in the left (contralateral) hemifield (25% vs 16%, P = .03). In contrast, in the ipsilateral hemifield no difference was found (21% vs 25%, P = .26). The double interaction was also accounted by higher visual bias after cTBS in the ipsilateral with respect to the contralateral hemifield (25% vs 16%, P = .033; Figure 7c). No other significant comparisons were found (Ps > .18). Importantly, one-sample t-test revealed that after cTBS over rOC visual bias in the left (contralateral) hemifield was still significantly different from 0 [t(9) = 4.04, P = .003], indicating that cTBS was capable of reducing but not of eliminating the visual bias.

These findings indicate that suppressing the excitability of the rOC leads to a reduction of visual bias in the left hemifield (contralateral to the stimulated site) but does not change multisensory integration.

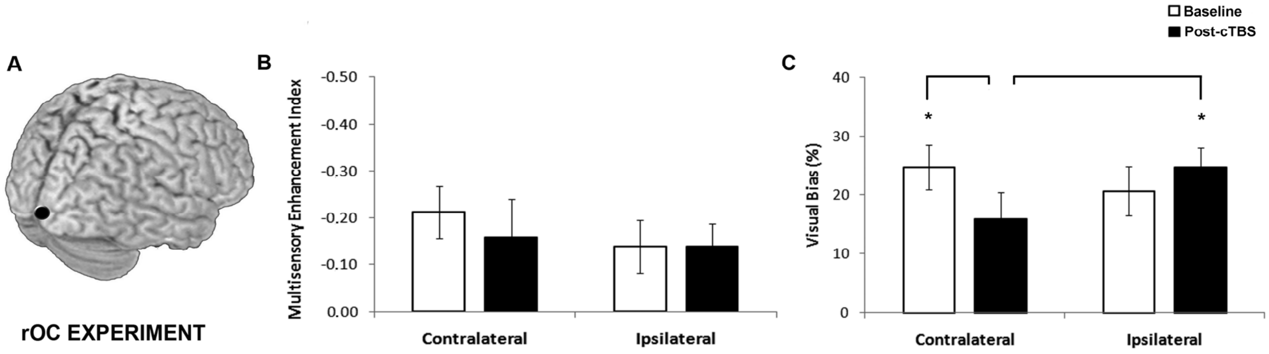

Figure 7 Experiment 2: (A) Brain locations of the coil position to induce virtual lesion of the right occipital cortex (rOC, mean Talairach coordinates: x = 19.1, y = -98.2, z = 0.9). (B) Multisensory enhancement index (MEI). (C) Visual bias. White and black histograms represent MEI and visual bias during baseline and after cTBS (post-cTBS), respectively. Error bars indicate s.e.m. *: P < .05.

Experiment 3: Virtual lesions to rPPC

One-sample t-tests against zero indicate that participants in the third experiment showed multisensory enhancement [t(10) = -4.45, P = .001] and visual bias effects across sessions [t(10) = 6.92, P < .0001]. However, the Session x Hemifield ANOVAs on MEI (all Fs < 1.66; Ps > .23; Figure 8b) and on visual bias (all Fs < 0.26; Ps > .62; Figure 8c) did not show any significant main effect or interaction. Thus, suppressing the activity in the rPPC by means of cTBS did not affect multisensory integration or ventriloquism.

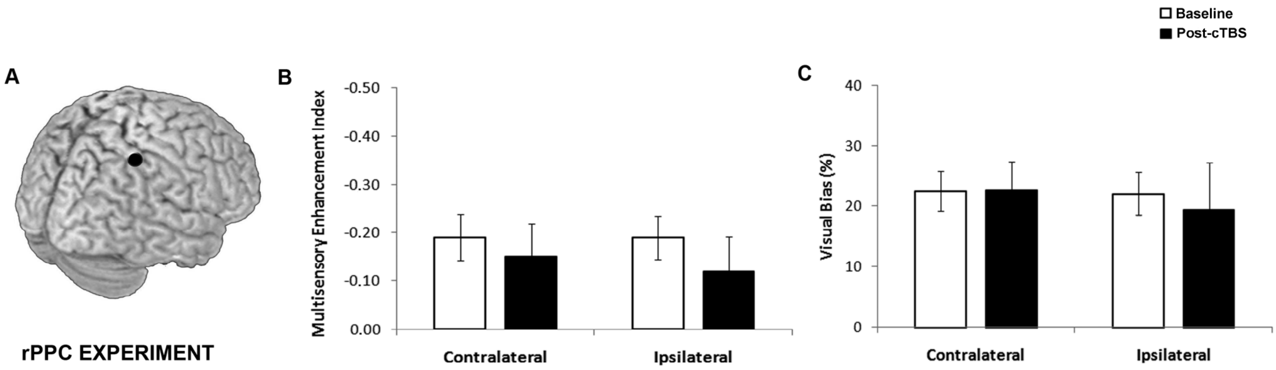

Figure 8 Experiment 3: (A) Brain locations of the coil position to induce virtual lesion of the intraparietal sulcus in the right posterior parietal cortex (rPPC, mean Talairach coordinates: x = 43.7, y = -43.3, and z = 47.3). (B) Multisensory enhancement index (MEI). (C) Visual bias. White and black histograms represent MEI and visual bias during baseline and after cTBS (post-cTBS), respectively. Error bars indicate s.e.m.

Discussion

The ability to determine accurately the location of a sound source has a great adaptive value in many species and represents a complex computational process, typically less accurate and reliable than visual localization (Corneil et al., 2002; Bolognini et al., 2007; Alais and Burr, 2004; Recanzone and Sutter, 2008). As a consequence, a visual cue is often able to either enhance (i.e. multisensory integration) or bias (i.e. ventriloquism) auditory localization performances. In three TMS experiments, we tested the causative role of rTPC, rOC and rPPC in multisensory integration and visual bias effects during an auditory localization task. The audio-visual multisensory enhancement in auditory localization, observed in the baseline sessions, was disrupted by cTBS-induced virtual lesions of rTPC, but remained unaffected by virtual lesions to rOC or rPPC. By contrast, the ventriloquism effect (i.e. the perceptual translocation of the sound towards the visual stimulus) found in the baseline session was reduced by cTBS-induced virtual lesions of rOC, but not by virtual lesions to rTPCor rPPC. The present double dissociation clearly demonstrates that multisensory integration and ventriloquism are functionally independent phenomena relying on different cortical networks.

Multisensory Integration

The enhanced auditory localization performance, observed in the baseline sessions when spatially coincident audio-visual stimuli were presented, attested the presence of a multisensory integrative effect (Corneil et al., 2002; Bolognini et al., 2007; Leo et al., 2008b; Passamonti et al., 2009a). This multisensory effect was reduced after cTBS over rTPC. The reduction appeared to be greater in the contralateral hemifield compared to the ipsilateral, although the interaction was not significant. In contrast, multisensory effect remained unaffected by stimulation of rOC or rPPC. The finding that rTPC is involved in multisensory integration is well in keeping with previous neuroimaging evidence, showing enhanced BOLD signal during processing of a wide range of auditory and visual stimuli, including ‘semantic’ combinations of audio-visual stimuli (e.g. matching vocal sounds and mouth movements, Calvert et al., 2001; Wright et al., 2003; visual objects that match environmental sounds, e.g. Beauchamp et al., 2004; Stevenson et al., 2007; Meienbrock et al., 2007; Werner and Noppeney, 2009) as well as non-semantic audio-visual stimuli (Noesselt et al., 2007). In keeping, additional evidence from non-human primates has highlighted the superior temporal and inferior parietal cortex as important multisensory sites (Stein and Stanford, 2008). Neuroanatomical and electrophysiological studies have described neurons within these temporo-parietal regions receiving convergent inputs from visual, auditory and somatosensory cortices (Jones and Powell, 1970; Seltzer and Pandya, 1978, Cusick, 1997; Zhong and Rockland, 2003; Rozzi et al., 2006) and responding to stimulations in more than one sensory modality (Desimone and Gross, 1979; Bruce et al., 1981; Hikosaka et al., 1988; Dong et al., 1994). Our findings expand these evidence by showing that rTPC is critical for multisensory-related improvement in auditory localization.

The observation that rOC inhibition does not compromise the multisensory integration effect is consistent with previous studies on hemianopic patients with occipital lobe damage. These patients show an improvement of auditory localization responses when ‘unseen’ visual stimuli (i.e. presented in the hemianopic visual field) are presented simultaneously at the same location as the auditory stimuli (Leo et al., 2008b); in a similar vein, ‘unseen’ visual stimuli can improve hemianopic patients’ response time to simultaneous and spatially coincident sounds (Frassinetti et al., 2005). In addition, a recent study on hemianopics (Passamonti et al., 2009a) also revealed an improvement of auditory localization after a period of passive exposure to audio-visual stimuli presented at the same location, demonstrating a perceptual learning effect due to multisensory integration. The retention of the ability to integrate audio-visual stimuli when the visual cortex is damaged or inhibited is also in agreement with neurophysiological recordings on cats, indicating that temporary deactivation of the visual cortex (Wilkinson et al., 1996) and other primary cortices (Wallace and Stein, 1994) does not disrupt multisensory enhancement in the superior colliculus neurons responses or in orientation behavioral performances (Stein and Stanford, 2008).

Similarly to rOC, also rPPC suppression did not alter the multisensory enhanced localization accuracy. In keeping, in a recent TMS study, suppression of right PPC by means of low-frequency rTMS did not affect audio-visual multisensory enhancement of response time in a speeded detection task (Bolognini et al., 2009). Moreover, evidence indicates that brain damage patients with parietal lesions retain multisensory enhancement for spatially coincident audio-visual stimuli both in response time (Frassinetti et al., 2005) and perceptual learning (Passamonti et al., 2009a). Thus, previous and present findings are consistent in showing that the parietal lobe, as well as the occipital lobe, does not play a critical role in audio-visual integration.

Studies on multisensory integration in non-human mammals have widely reported the critical role of superior colliculus (Stein and Meredith, 1993) and the relevance of associative cortical areas (i.e. the anterior ectosylvian sulcus, AES), showing that the ability of superior colliculus neurons to integrate multisensory signals is disrupted after AES deactivation (Wallace and Stein, 1994; Jiang et al., 2001; Alvarado et al., 2007a,b; 2009). However, to date, a putative human homologue of AES has not been clearly identified. Imaging studies in humans suggest an involvement of several cortical areas including the temporo-parietal and posterior parietal cortices in mediating audio-visual multisensory integration (for a review: Calvert, 2001; Stein and Stanford, 2008). However, the prominent role of rTPC, but not of rPPC, in audio-visual multisensory integration described in this study suggests that neural activity in posterior parietal areas detected with fMRI or PET during audio-visual stimulation (Bushara et al., 2001; Bremmer et al., 2001; Calvert et al., 2001) may reflect epiphenomenic activity with no crucial behavioral consequences for auditory localization. In light of these considerations, it could be suggested that temporo-parietal regions more than intraparietal cortex may represent a possible human homologue of AES.

Ventriloquism Effect

The perceptual translocation of the sound towards a spatially disparate visual stimulus, observed in the baseline sessions, attested the presence of ventriloquism effect, a very well known phenomenon documented in previous studies (Howard and Templeton, 1966; Thurlow and Jack, 1973; Bertelson and Radeau, 1981; Spence and Driver, 2000; Slutsky and Recanzone, 2001; Hairston et al., 2003b; Lewald and Guski, 2003; Vroomen and De Gelder, 2004).

This effect was reduced by cTBS over rOC, but not over rTPC or rPPC, supporting the hypothesis that cortical visual processing in the occipital cortex modulates ventriloquism effect. Neuroimaging evidence on humans (Pekkola et al., 2005; Lehmann et al., 2006; Martuzzi et al., 2007; Meyer et al., 2007; Besle et al., 2009) and intracortical recordings on animals (Bizley et al., 2007; Kayser et al., 2009) have suggested that visual information can have both excitatory and inhibitory effects on the activity of auditory cortex at relatively early stages, supporting the idea of the existence of direct projections from visual to auditory cortex (Bonath et al., 2007). These projections and the inherent higher reliability of visual localization over auditory localization might, therefore, be responsible of the perceptual bias in auditory localization produced by spatially incongruent audio-visual stimuli. The decrease in ventriloquism effect after rOC suppression is in line with behavioural evidence showing that decreasing the saliency of visual stimuli may reduce ventriloquism (Hairston et al., 2003b), at variance with multisensory integration (Bolognini et al., 2007; for a review see Làdavas, 2008). In addition, it is worthwhile to remember that hemianopic patients do not show visual bias in the hemianopic field, although they retain the multisensory integrative effects (Leo et al., 2008b; Passamonti et al., 2009a). Based on previous evidence and on present findings, we posit that cTBS induced suppression of rOC excitability decreases the weight of visual information in the auditory cortex and this may reduce the bias in auditory localization[1]. Notably, this reduction was greater in the contralateral compared to the ipsilateral hemifield.

The findings that suppression of rTPC or rPPC does not change ventriloquism effect is in keeping with imaging studies disclosing a preferential activation in temporo-parietal regions for audio-visual stimuli presented at spatial coincidence rather than at spatial disparity (Meienbrock et al., 2007); moreover, brain damage patients with parietal lesions typically show visual bias, further suggesting that parietal regions are not critical for ventriloquism (Bertelson et al., 2000; Passamonti et al., 2009a). Taken together, previous studies in brain damage patients (Bertelson et al., 2000; Leo et al., 2008b; Passamonti et al., 2009a), neuroimaging evidence (Meienbrock et al., 2007) and the present experiment in healthy subjects demonstrate the prominent role of rOC, but not of rTPC or rPPC, in modulating ventriloquism.

Concluding Remarks

Overall, the present study provides causative evidence for the functional independence of multisensory integration and ventriloquism effect during auditory localization and suggests the existence of partially different neural circuits subserving the two phenomena. Temporo-parietal regions are critically involved in mediating the integration of audio-visual stimuli at the same spatial location, but not in the mislocalization of sounds towards spatially disparate visual stimuli. In contrast, suppression of occipital cortex reduces visual bias but not multisensory integration, confirming that this area is selectively involved in weighting visual information in ventriloquism. These findings further suggest that TMS represents an ideal tool for disclosing

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[1] A previous study has shown that cTBS over the visual cortex increases the threshold for evoking visual phosphenes by means of single-pulse TMS over the same site, demonstrating that cTBS can suppress the excitability of the visual cortex (Franca et al., 2006). To the best of our knowledge, our study provides the first evidence that cTBS-induced suppression of visual cortical excitability has clear behavioural consequences. This suppressive effect of visual processing is however in keeping with previous TMS studies using online occipital stimulation (Amassian et al., 1989; Kammer et al., 2005; Romei et al., 2007; Romei et al., 2009).

multisensory interactions in the human brain (Romei et al., 2007; Bolognini and Maravita, 2007; Romei et al., 2009; Serino et al., 2009; Azañón and Haggard, 2009).

CHAPTER 3

Evidence of the functional activity of the retino-colliculo-extrastriate pathway in patients with visual field defect

In the previous chapters, evidence of the neural circuit underlying multisensory integrative behavior have been provided, revealing that SC is necessary for integrating audio-visual stimuli into a unified percept and that extrastriate temporo-parietal regions of the cortex are causally involved in modulating these effects. One of the most important behavioural advantages of multisensory integration is represented by the possibility of integrating sensory inputs from different sensory modalities in order to enhance an impaired unisensory processing, improving the perception of sensory events difficult to be perceived due to the unisensory defect. Therefore, these integrative abilities might constitute an ideal basis for a multisensory-mediated approach to the recovery of unisensory deficits. This approach might be especially useful in the case of unisensory visual impairments due to visual field defects. Homonymous visual field defects are due to damage to the geniculo-striate pathway, producing a loss of vision contralateral to the side of the lesion (i.e. homonymous hemianopia) and retinotopically corresponding to the damaged area. However, in hemianopic patients, the alternative visual pathway constituted by the retino-colliculo-extrastriate pathway is spared, at least anatomically (Figure 9). As a consequence, the possibility of recovering the impaired visual modality using multisensory integrative abilities in hemianopic patients should depend on the functionality of this spared circuit.

In the present chapter, abilities directly depending on the activity of the retino-colliculo-extrastriate pathway will be demonstrated in hemianopic patients. In particular, evidence of the immediate (i.e. online) effects of multisensory integration and demonstration of the existence of visual residual abilities for fearful stimuli (i.e. affective blindsight) will be presented, providing evidence of the functional sparing of the retino-colliculo-extrastriate pathway in hemianopic patients (Experiment 3).

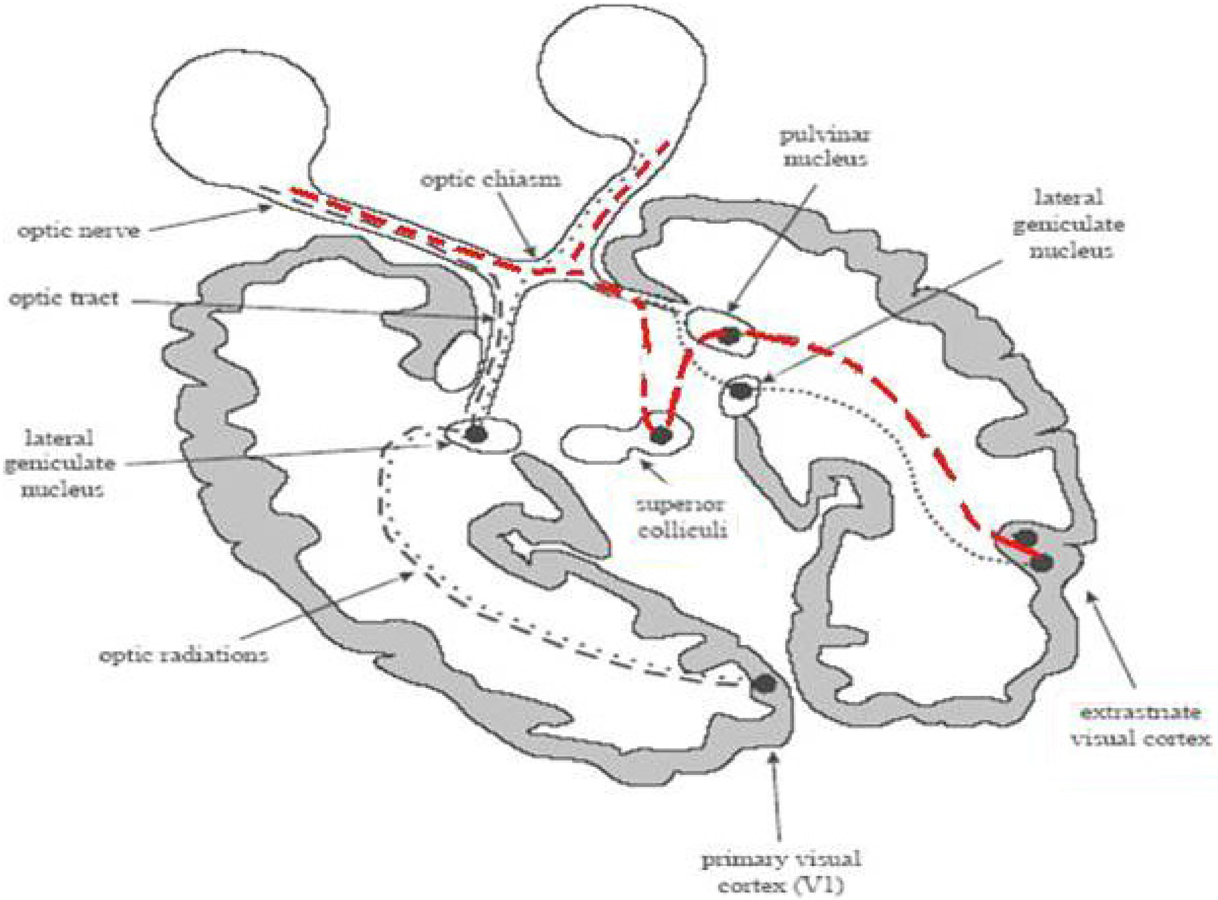


Figure 9 Visual pathways. In black, the retino-geniculo-striate pathway; in red, the retino-colliculo-extrastriate pathway. (readapted from Dankert and Rossetti, 2005).

1. IMMEDIATE EFFECTS OF MULTISENSORY INTEGRATION ON HEMIANOPIC PATIENTS

The influence of an auditory stimulus on visual detection in the blind field

The possibility that multisensory audio-visual stimulation in patients with hemianopia might improve perception of visual events presented in the blind visual field, in accordance with the rules governing multisensory integration at the neuronal level in SC, have been tested with a detection task (Frassinetti et al., 2005). In this experiment, hemianopic patients were presented with single visual stimuli, single auditory stimuli and pairs of audio-visual stimuli and they were asked to respond to any visual presentation. According to the temporal principle of multisensory integration (Meredith et al., 1987), audio-visual pairs were presented simultaneously. In order to test whether the spatial principle governing the multisensory integration at the single neuron level (Meredith and Stein, 1986a) also governs multisensory integrative behaviour in patients with visual deficit, audio-visual pairs were presented either at the same spatial location or at a spatial disparity. Results revealed that the association of a sound with a visual stimulation increased the patients' ability to consciously perceive the presence of visual stimuli in the blind field. In particular, this effect was evident only when auditory and visual stimuli were presented at the same spatial position, but not when a spatial disparity was present between the stimuli, consistent with the spatial properties regulating multisensory effects in the multisensory neurons (Meredith and Stein, 1986a). In addition, patients demonstrated greater multisensory effects as their ability in detecting modality-specific visual stimuli decreased. In fact, a negative correlation between patients' responses to single visual stimuli and the amount of multisensory enhancement (i.e. the difference between the performance with audio-visual stimuli and the performance with single visual stimuli) was found. This behavioural feature appears to have parallels in the electrophysiological response properties of multisensory cells in SC described as the inverse effectiveness principle (Meredith and Stein, 1983). Overall, these findings provided evidence that, in patients with visual field defects, the ability of detecting visual stimuli presented in the blind field might be enhanced by the concurrent presentation of auditory stimuli in spatial coincidence and that this effect might be due to a sparing of the retino-collicular extrastriate pathway. In the same study, also patients with posterior parietal damage demonstrating unilateral neglect (i.e. an orienting deficit to visual stimuli presented contralaterally to the lesioned hemisphere) have been tested and they exhibited performances similar to the ones reported by hemianopic patients (Frassinetti et al., 2002b): detection of visual stimuli presented in the neglected field was found to be increased by the simultaneous presentation of spatially coincident auditory stimuli, thus demonstrating a retention of the ability of integrating audio-visual stimuli in patients with unilateral neglect. Notably, a third group of patients tested in this study, reporting wide lesions to the occipital and the parietal cortices and exhibiting both hemianopia and neglect, did not demonstrate any improvement in visual detection mediated by the concurrent presence of an auditory stimulus. Overall, these findings suggested that, when the lesion was extended and involved both striate and extrastriate areas, no effect of audio-visual integration can be found. In contrast, when the lesion was confined to the occipital areas or to the parietal areas, visual and auditory stimuli could be integrated into a unified percept and could improve visual detection, due to the sparing of the retino-colliculo-extrastriate pathway. The results of Frassinetti and colleagues' study highlighted that damage to the geniculo-striate pathway does not eliminate responses from the multisensory systems and that audio-visual interaction can induce perception of visual stimuli presented in the impaired hemifield of hemianopic patients.

The influence of visual stimuli presented in the blind field on auditory localization

The influence of auditory stimuli on perception of visual stimuli in hemianopic patients has been demonstrated by the previous study by Frassinetti and colleagues (Frassinetti et al., 2005). However, the audio-visual integrative abilities in hemianopic patients might be tested also by measuring the influence of an unseen visual stimulus on auditory localization performances, exploiting the fact that a visual cue is often able to either bias (i.e. ventriloquism; Howard and Templeton, 1966) or enhance (i.e. Bolognini et al., 2007) auditory localization performances. Cross modal localization in hemianopic patients has been examined by comparing the effects of visual stimuli presented in the blind and the intact field on these patients' ability to locate hard-to-localize sounds (Leo et al., 2008b). Auditory targets were presented alone (modality-specific auditory condition) or with a visual stimulus (cross-modal condition) presented at various spatial (0°, 16°, 32°) and temporal (0 ms, 500 ms) disparities. The results of this study showed that visual information on the blind field of hemianopic patients can significantly improve their auditory localization performance only under two critical circumstances, i.e. the presentation of auditory and visual stimuli at the same spatial position and in temporal coincidence, consistent with the principles governing multisensory integration in the neurons of SC. Surprisingly, the advantage in auditory localization when a visual stimulus was presented simultaneously at the same spatial location was as great in the hemianopic field, where the visual stimulus was not consciously perceived, as it was in the intact field, where, in contrast, the stimulus was seen. Notably, the typical effect of perceptual translocation of a sound towards a spatially disparate visual stimulus (i.e. ventriloquism effect) was evident in the intact field, whereas it was completely lost in the hemianopic field, therefore suggesting that damage to the visual cortex disrupted the ventriloquism effect. Overall, this study further confirmed that patients with striate cortex lesions retained visual-auditory integrative effects. Again, a likely explanation of this result is that a lesion of the visual cortex does not prevent the integration of auditory and visual stimuli, and the integrative effects observed depended on the activity of the spared secondary visual pathway, consisting of the retino-colliculo-extrastriate pathway.

The findings presented so far have provided evidence of the functional activity of the retino-colliculo-extrastriate pathway in patients with hemianopia, demonstrating the retention of their integrative abilities. Another evidence of the functional activity of the secondary visual pathway in hemianopic patients is provided by the existence of visual residual abilities for emotional stimuli in the blind field in absence of awareness, a capacity which is thought to be mediated by the retino-colliculo-extrastriate pathway and its connections with amygdala, as suggested by recent neuroimaging studies (Morris et al., 2001; Andino et al., 2009).

2. EXPERIMENT 3 - AFFECTIVE BLINDSIGHT FOR FEARFUL FACES: EVIDENCE FROM A REDUNDANT TARGET PARADIGM IN PATIENTS WITH HEMIANOPIA

The capacity of demonstrating visual perceptual abilities without acknowledged perceptual awareness has been termed blindsight, emphasizing the apparent dissociation between functional visual processing and subjective visual experience. Since early reports of blindsight, a wide range of visual residual functions has been described. They include target detection and localisation by saccadic eye movements (Poppel, 1973), manual pointing (Weiskrantz, 1974) or verbal response (Dodds et al., 2002) and the ability to discriminate colours (Stoerig, 1987; Stoerig and Cowey, 1992), the direction of motion and relative velocity (Barbur et al., 1980; Weiskrantz et al., 1995) and the orientation of visual stimuli (Weiskrantz, 1986). However, such visual residual abilities do not only apply for relatively simple stimulus features, but might also concern the emotional content of the unseen visual stimulus (De Gelder et al., 1999; 2001), a phenomenon known as affective blindsight.

Although investigated in a small number of cases, the experimental evidence on these affective visual residual abilities are quite consistent. Patients with hemianopia demonstrated the ability of correctly guess above the chance level the emotional valence of facial expressions presented in the blind field (De Gelder et al., 1999). Moreover, a significant redundant target effect (RTE; i.e. the advantage on reaction times with double compared to single stimuli) was observed with presentation of faces within the blind and the intact visual field with congruent emotional expressions (De Gelder et al., 2001). More recently, it has been shown that passive exposure to either seen or unseen bodily or facial expressions resulted in highly comparable physiological responses reflecting the affective valence and the arousal components of the stimuli (Tamietto et al., 2009b). It is worth noting that the patients described in literature, exhibiting affective blindsight, were the same tested in the classical blindsight investigations and demonstrating also visual residual abilities for other features of the unseen visual stimuli (such as position, orientation, shape, color; for a recent review see Cowey, 2010)

As previously mentioned, affective blindsight is thought to be mediated by a neural circuit bypassing the striate cortex, impaired in patients with visual field defects. Given that the superior colliculus is implicated in non-striatal visual functions in both monkeys (Mohler and Wurtz, 1977; Miller et al., 1980; Rodman et al., 1989) and humans (Sahraie et al., 1997), it has been proposed that the residual visual abilities of patients exhibiting blindsight might depend on the collicular visual pathway (Weiskrantz et al., 1974; Barbur et al., 1980). In particular, there is evidence that visual residual functions concerning the discrimination of emotional expressions, most notably fearful faces, depend on a neural circuit projecting visual inputs from the retina to the SC and the pulvinar and, then, to the amygdala where the emotional content might be implicitly recognized (Morris et al., 1999; Morris et al., 2001).

Since this alternative visual pathway including amygdala is supposed to be intact in the majority of patients with visual field defects and considering the great adaptive advantage of implicitly recognizing emotional stimuli, affective blindsight capacities should be evident in a wide population of hemianopic patients and not only in those hemianopic patients showing also other forms of blindsight. However, up to date, experimental investigations have never investigated the existence of visual residual abilities for emotional stimuli on a large scale and, as a consequence, the true incidence of affective blindsight is still unknown. A methodological limit in literature investigating affective blindsight involves patients' selection: in fact, patients examined are very limited in number and, since the majority of them have been repeatedly tested for all the forms of blindsight, they might not be naive to the purpose of the experiments. In addition, both direct methods of investigation (i.e. where patients are asked to perform a response to an unseen stimulus presented in the blind field) and indirect methods (i.e. where implicit visual processing in the blind field is indirectly derived by patients' responses to a seen visual stimulus in the intact field) have been equally employed, but a direct comparison of their efficacy in highlighting visual residual functions is still missing.

The aim of the present study was to estimate the presence of visual residual abilities and, indirectly, the functional activity of the retino-colliculo-extrastriate pathway in a group of ten hemianopic patients, never submitted to any similar task. Patients were presented with stimuli constituted by emotional faces (fearful or happy), neutral faces (male or female), or geometrical shapes (circle or square). Based on the hypothesis that the spared secondary visual pathway connected with the amygdala is able to implicitly process stimuli with emotional valence, patients are expected to demonstrate visual residual abilities only in presence of emotional stimuli, especially fearful faces. Patients underwent both direct and indirect methods of investigation. As for direct methods, they were submitted to a two alternative forced choice task (2AFC) where they were asked to guess some features of targets (i.e. the emotional valence, the gender or the shape of the stimuli) presented in the blind field. In contrast, as an indirect method, a redundant signals paradigm for simple reaction times was used. In this task, targets were presented both in the intact and in the blind field, but patients were instructed to quickly respond to targets presented only in the intact field.

Materials and method

Subjects

Ten patients (8 males, 2 females; mean age: 52.4, range: 21-65) with postgeniculate lesions resulting in deafferentation or destruction of left (n =5) or right (n=5) striate cortex participated in the study. In all the patients, MRI scanning confirmed the lesions and automated or manual perimetry documented the visual field defect. Details of lesions are given in Table 4 and CT scan or MRI reconstructions (MRIcro; Rorden and Brett, 2000) are reported in Figure 10. All patients were at a chronic stage of illness (> 5 months). A formal neuropsychological assessment performed before the experiment showed no other cognitive impairment except homonymous hemianopia. All patients were clinically blind and unable to consciously detect any target feature in the contralesional visual field, describing their visual experience in the blind field as complete darkness. All patients gave written informed consent before participation, and the study was approved by the local ethics committee.

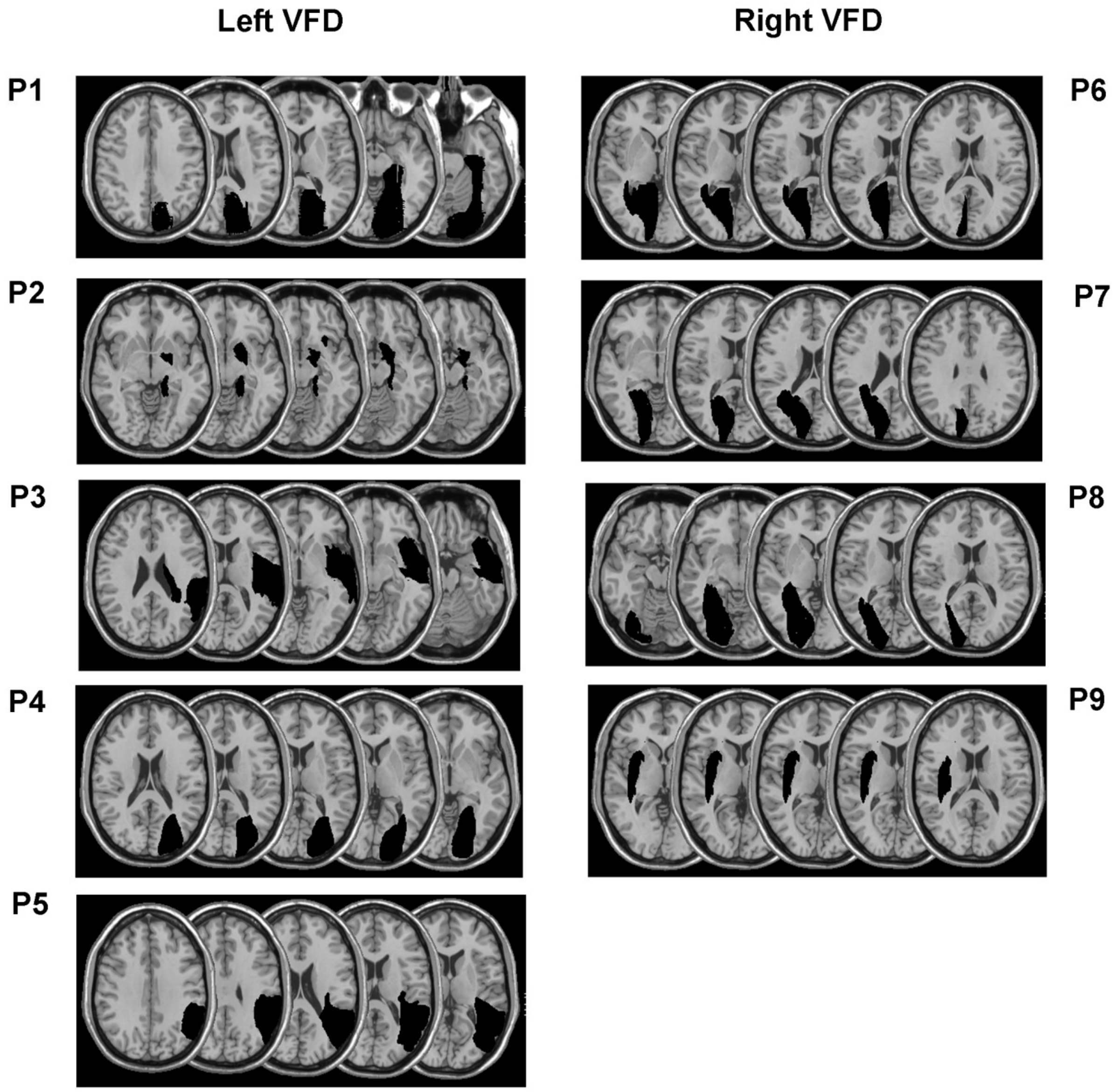


Figure 10 Lesion reconstruction images from CT and MRI, superimposed on the normalized MNI template http://www.bic.mni.mcgill.ca/cgi/icbm_view). Images from patients P10 were not available. The lesions are shown in the corresponding hemisphere (i.e. a right lesion is viewed in the right hemisphere).

Case	**Sex**	**Age**	**Years of Education**	**Time since onset (months)**	**Cause of hemianopia**	**Side of VFD**	**Degrees of macular sparing**	**Lesion site**
P1	M	41	18	55	vascular	Left	0°	Right temporo-parieto-occipital
P2	M	21	13	6	trauma	Left	0°	Right frontal-temporal
P3	M	47	17	17	vascular	Left	<5°	Right fronto-parieto-temporal
P4	F	76	4	8	vascular	Left	<5°	Right temporo-occipital
P5	M	53	11	7	vascular	Left	0°	Right temporo-parietal
P6	M	39	8	100	AVMs	Right	0°	Left temporo-occipital
P7	F	39	18	107	vascular	Right	<5°	Left parieto-occipital
P8	M	72	8	6	vascular	Right	<5°	Left temporo-occipital
P9	M	53	18	18	vascular	Right	<5°	Left occipito-temporal
P10	M	41	17	12	vascular	Righ	<5°	Left temporo-occipital

Table 4 Summary of clinical, demographic and lesional data

Experimental design

Patients underwent two different experiments. Experiment A consisted in a two alternative forced-choice task (2AFC). This experiment was aimed to investigate covert processing of unseen stimuli and patients were asked to guess features (i.e. emotional valence, gender and shape) of a target stimulus presented in the blind field (direct method). Experiment B consisted of a redundant signal paradigm, aimed to measure the effect on reaction times to a target presented in the intact field of a congruent (i.e. an identical image) or incongruent (i.e. an opposite image) stimulus presented in the blind field (indirect method). Each experiment consisted of three separate sessions, testing different categories of stimuli: emotional faces (fear vs happiness), neutral faces of different gender (male vs female) and geometrical shapes (circle vs square). Eye gaze fixation was controlled throughout the experiments with infrared oculography. The experiments and the sessions within each experiment were presented in a counterbalanced order.

Apparatus and Stimuli

Patients sat in a dimly lit and sound attenuated room in front of a PC monitor. Eye movements were monitored using a Pan/Tilt optic eye tracker (Eye-Track ASL-6000) which registers real-time gaze at 60 Hz (accuracy 0.5°). 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 the beginning of the experimental tasks, the equipment was calibrated for each subject using a nine-point grid. During calibration, 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.

The experimental tasks were displayed using EPRIME software. Three different categories of stimuli, in three separate sessions for each experiment, were used. The first category of stimuli (Emotion), critical for testing the presence of affective blindsight, comprised two types of images of human faces expressing opposite emotions (fear vs happiness). The second category of stimuli (Gender) comprised two types of images of neutral human faces of different gender (males vs females). The faces used were static black and white pictures selected from the Pictures of Facial Affect series (Ekman and Friesen, 1975). Finally, the third category of stimuli (Object) included two types of images of different geometrical shapes (circle vs square).

Experiment A: two alternative forced-choice task (2AFC)

Procedure

Patients underwent three separate sessions of 2AFC task, testing different categories of stimuli (emotion, gender, object). They were instructed to fixate a central fixation point and they were asked to guess, between two choices, which type of image was presented in the blind field (for the session with emotion stimuli: fear or happiness; for the session with gender stimuli: male or female; for the session with object stimuli: circle or square). Each session was constituted by one block of trials. For each block, a total of 180 trials were presented, 90 for each type of image. Images appeared pseudorandomly at 11° from the fixation cross in the blind field. In the intact field no image was presented. In each trial (2250 ms duration), a fixation cross appeared for 500 ms, then, stimuli were presented for 1500 ms, followed by a blank screen for 250 ms. At the end of each presentation, a sound prompted subjects to verbally respond. Subjects' verbal responses were manually recorded. A new trial started only when patients were fixating at the central fixation cross and the onset was manually controlled by the experimenter (Figure 11).

Results

The percentage of correct responses for each patient in each session was computed and compared to the chance level with a chi-square test. All the patients exhibited responses at chance level in every session (all χ^2s < 2.45; all Ps $> .12$). Only in one case, a patient demonstrated a percentage of correct responses slightly above the chance level, although not significant, in the session where emotional stimuli were presented (63%; $\chi^2(1) = 3.43$; $p = .064$).

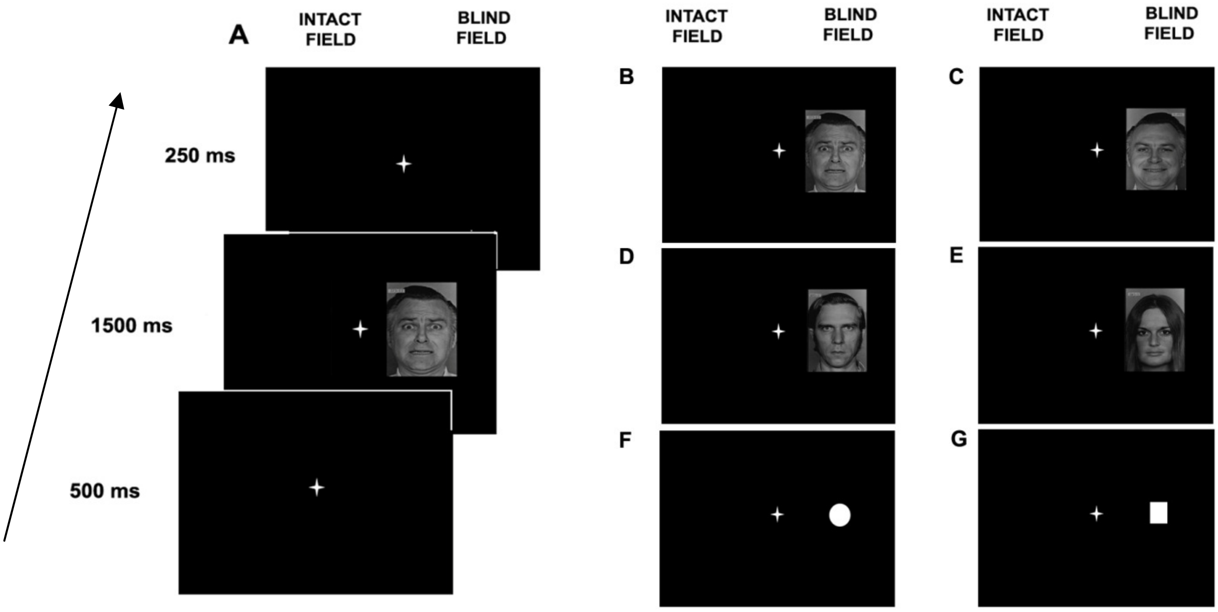


Figure 11 Procedure and stimuli for the experiment A. Panel A: a typical trail of experiment A. Panel B-G: stimuli for the experiment A (B: fear; C: happiness; D: male; E: female; F: circle; G: square)

Experiment B: redundant signal paradigm

Procedure

Patients underwent three separate sessions of redundant signal paradigm, testing different categories of stimuli (emotion, gender, object). Patients were instructed to maintain their gaze on the fixation cross and to detect the stimulus target presented in the intact visual field as quickly as possible, by pressing a response button. No direct response towards stimuli presented in the blind field was required and the presence of implicit processing of unseen visual stimuli was inferred from the reaction times to stimuli presented in the intact field. For each session, three blocks of trial for each type of image as a target were performed (for the session with emotional faces: 3 block with fear as a target and 3 blocks with happiness as a target; for the session with neutral faces: 3 blocks with male as a target and 3 blocks with female as a target; for the session with object stimuli: 3 blocks with circle as a target and three block with square as a target). Target images were presented under three different conditions:

1) Unilateral: target stimuli were coupled with a scrambled image
2) Bilateral Congruent: target stimuli were coupled with identical images
3) Bilateral Incongruent: target stimuli were coupled with opposite images

Stimuli appeared pseudorandomly at 11° to the left and the right of the fixation cross. Scrambled stimuli had the same rectangular shape, size, luminance, and spatial frequency of the target stimuli and they were constituted by randomly swapping small parts (18×18 pixels) of target pictures. For each block, a total of 36 trials were presented, 12 for each condition. Each trial was constituted by a fixation cross appearing for 500 ms, followed by the images appearing for 200 ms and a blank screen for 250 ms. A new trial began after an intertrial interval of random duration comprised between 1000 and 2000 ms (Figure 12).

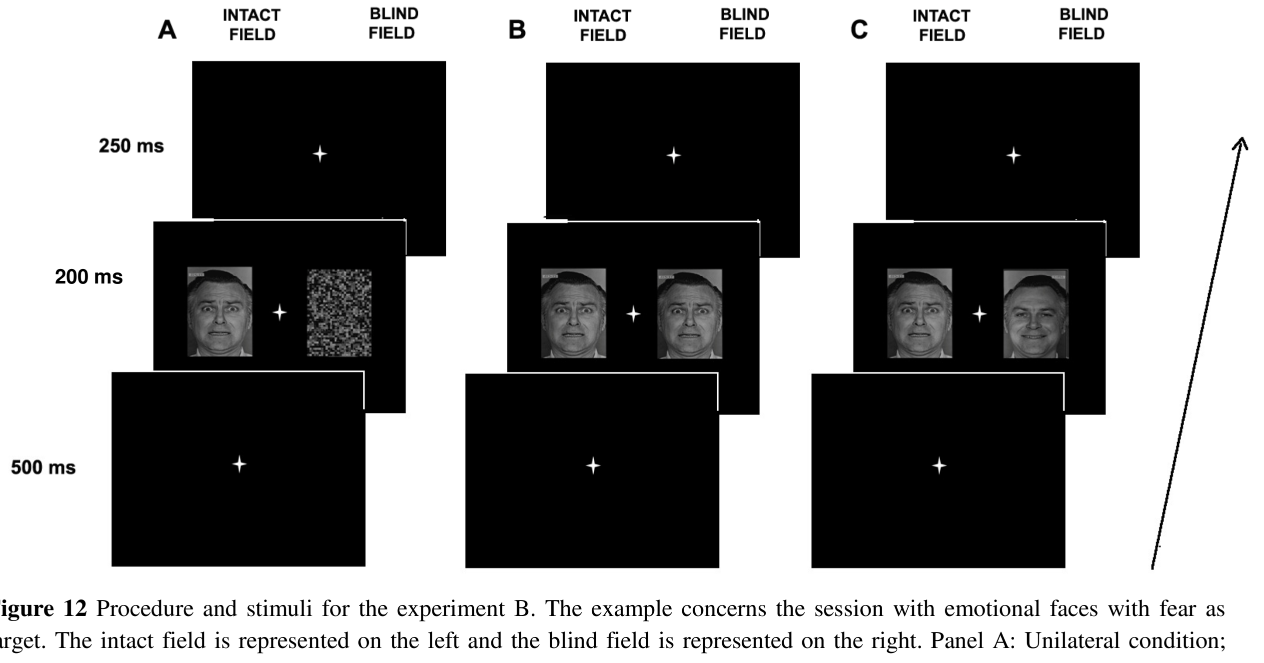


Figure 12 Procedure and stimuli for the experiment B. The example concerns the session with emotional faces with fear as target. The intact field is represented on the left and the blind field is represented on the right. Panel A: Unilateral condition; Panel B: Bilateral congruent condition; Panel C: Bilateral incongruent condition.

Results

The average RTs of the responses to the each target was calculated. RTs more than 2 standard deviations above or below the mean were considered outliers and discarded (3.75% of trials). Three separate two-way ANOVAs were calculated for each session (emotion, gender, object) with Image Type (in the session emotion: fear vs happiness; in the session gender: male vs female; in the session object: circle vs square) and Condition (Unilateral, Bilateral Congruent, Bilateral Incongruent) as within subjects factors. Newman-Keuls test was used for post-hoc comparison.

The ANOVA conducted on the RTs to emotional stimuli revealed a significant main effect of Image Type [F(1,9): 23.82, $p < .001$] explained by significantly faster RTs to fearful faces (607 ms) compared to happy faces (695 ms). More importantly, a significant two-way interaction Image Type x Condition [F(2,18): 7.54, $p = .004$] was found (Figure 13a). Post hoc comparisons revealed that, when the image target was a fearful face, a significant reduction of RTs in the bilateral congruent condition (590 ms) compared to the unilateral (614 ms, $p = .02$) and the bilateral incongruent (616 ms; $p = .04$) conditions was found. No significant difference was found between the unilateral condition and the bilateral incongruent condition ($p=.8$). On the other side, when the image target was a happy face, a significant reduction of RTs was observed in the incongruent condition (678 ms) compared to the unilateral (701 ms, $p=.02$) and the congruent condition (705 ms; $p = .03$). Notably, the reduction of RTs was evident every time a fearful face was presented in the blind field, suggesting a specific effect of fearful stimuli in mediating implicit visual processing.

In contrast, in the ANOVA conducted on response times to neutral faces, no significant effect was found (all Ps > .4; Figure 13b). No difference was observed in RTs when the target was a male face between the unilateral condition (490 ms), the bilateral congruent condition (496 ms) or the bilateral incongruent condition (486 ms). Similarly, when the target was a female face, no differences were found between the unilateral (492 ms), the bilateral congruent (494 ms) or the bilateral incongruent (500 ms) conditions. In the same vein, the ANOVA on the RTs registered during presentation of geometrical shapes, revealed no significant effect (all Ps > .2; Figure 13c). When the target stimulus was a circle, no significant difference was found between the unilateral condition (442 ms) and the bilateral congruent (444 ms) or the bilateral incongruent (454 ms); when the target was a square, RTs to unilateral stimuli (443 ms) were not significantly different compared to RTs to bilateral congruent stimuli (448 ms) or bilateral incongruent stimuli (455 ms).

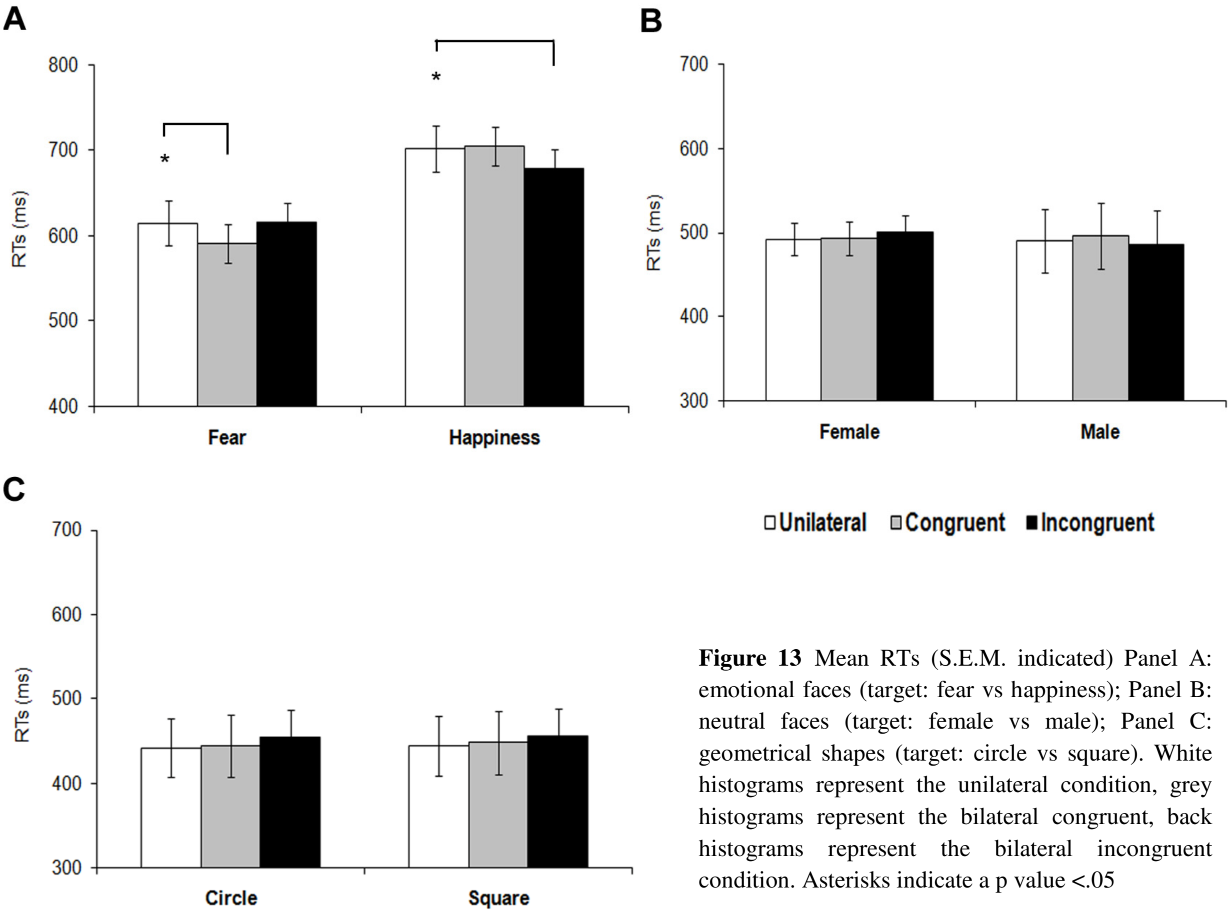


Figure 13 Mean RTs (S.E.M. indicated) Panel A: emotional faces (target: fear vs happiness); Panel B: neutral faces (target: female vs male); Panel C: geometrical shapes (target: circle vs square). White histograms represent the unilateral condition, grey histograms represent the bilateral congruent, back histograms represent the bilateral incongruent condition. Asterisks indicate a p value <.05

Discussion

In the present study, a group of ten hemianopic patients demonstrated visual residual abilities in the blind field for stimuli with an emotional valence, consistent with the presence of affective blindsight. During the presentation of neutral human faces and of geometrical shapes, no effects of an implicit processing of the unseen visual stimuli were observed, both with direct and indirect methods of investigation. In contrast, when emotional human faces were presented, hemianopic patients exhibited abilities of implicit recognition of the emotional content of unseen visual stimuli. Notably, this effect was evident only under two circumstances: 1) when the emotional faces presented in the blind field were constituted by faces expressing fear; 2) when an indirect method of investigation, such as a redundant signal paradigm, was used.

The finding that effects of implicit processing of unseen visual stimuli were observed only in presence of fearful faces in the blind field suggests a specific effect of this type of emotion on affective blindsight. In particular, when fearful faces were presented in the blind field, an effect of target redundancy (i.e. faster reaction times for bilateral stimuli, compared to unilateral) was found. This was observed both when the target stimulus presented in the intact field was a fearful face (i.e. congruent condition) and a happy face (incongruent condition), demonstrating that the effect was not related to the congruency or incongruence of the images presented bilaterally, but specifically due to the implicit processing of fearful stimuli. Instead, the presentation of happy faces in the blind field did not induce any effect on reaction times, in line with the lack of effects found with neutral faces and geometrical shapes. The finding of a preferential effect for fearful faces in blindsight is consistent with previous studies demonstrating the existence of a neural circuit bypassing the striate cortex underlying the implicit processing of fear related stimuli (Morris et al., 2001; Andino et al., 2009; Figure 14).

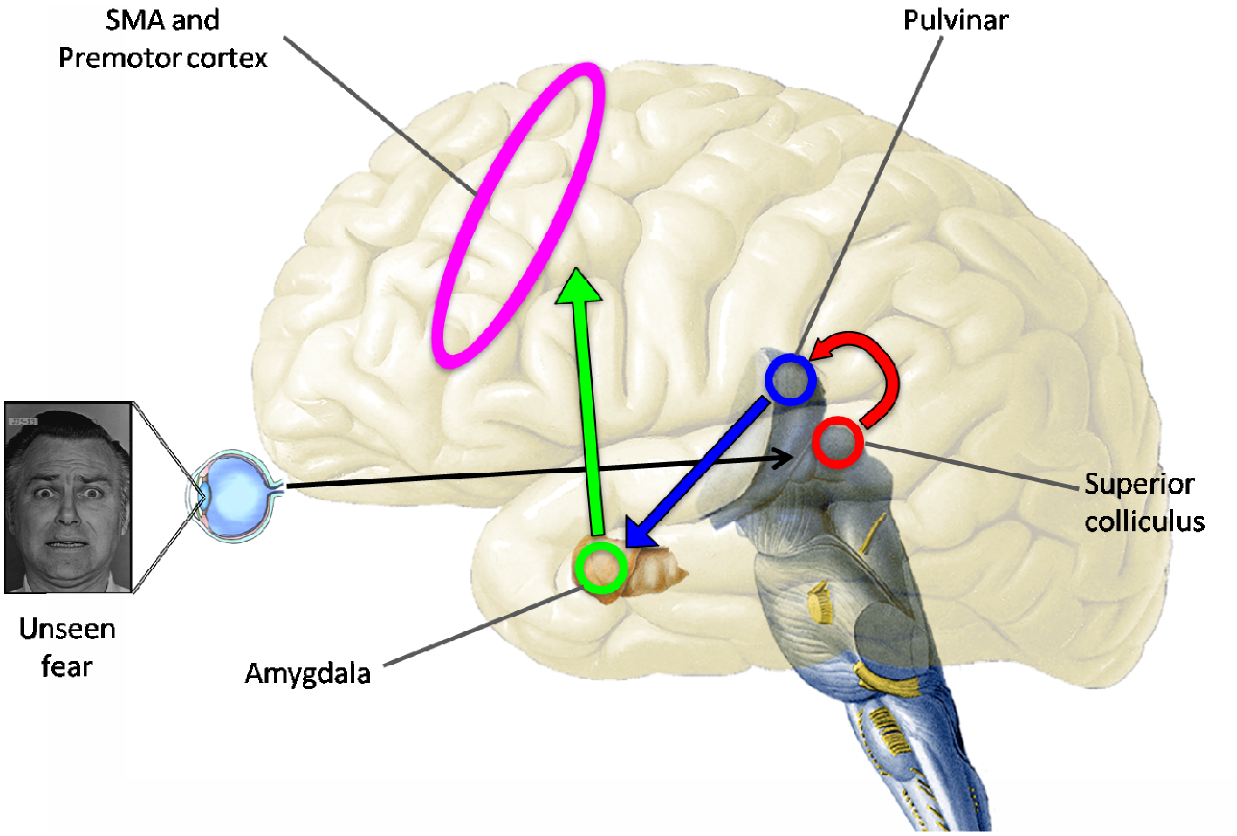


Figure 14 Schematic view of the retino-colliculo-amygdala pathway mediating affective blindsight.

Functional neuroimaging evidence (Morris et al., 2001) revealed a co-varying pattern of increased activation during presentation of fearful faces in superior colliculus, pulvinar and amygdala, supporting the existence of a retino-colliculo-thalamo-amygdala pathway subserving an implicit recognition of fearful stimuli. An EEG investigation (Andino et al., 2009), focusing on the cortical correlates and the temporal properties related to unseen fearful faces, proposed a slightly different extrastriate visual pathway. The EEG pattern of activation, revealed in this study, displayed an early change at 70 ms in superior temporal sulcus (STS), independent of the type of the emotion. Patterns of activation specific to fearful faces appeared only at a later stage, at approximately 120 ms, starting in frontal regions, such as inferior frontal gyrus, anterior cingulate, orbito-frontal cortex and superior frontal gyrus, and then spreading into middle temporal structures, including the amygdala. In this view, retinal signals are supposed to reach extrastriate areas by a subcortical route and then, after transiting in frontal areas, to activate amygdala. However, both of these pathways (see Morris et al., 2001 and Andino et al., 2009), might be responsible of the effects observed in the present study.

In humans, the existence of this fear system, functioning independently of the geniculo-striate visual system and in absence of normal visual awareness, is consistent with the presence in animals of a similar amygdala-based pathway, which is present in many species, including mammals, and has a long evolutionary history and a great importance for survival (Morris et al., 2001; Le Doux, 1996). This parallel visual system, specialized in analyzing threatening stimuli, might play a crucial role in coordinating efficient protective motor responses. A recent study supporting this view demonstrated that presentation of stimuli expressing fear produced, beside the activation of structures associated with emotion, activations of circuits mediating actions (De Gelder et al., 2004; Figure 14). The reduction of reaction times in presence of fearful stimuli in the blind field, observed in the present study, might be explained by a readiness to response mediated by this complex subcortical-cortical network. This pathway, even processing a limited range of spatial frequencies and not accessing to awareness, is still sufficient to mediate visual residual abilities for fearful stimuli and to sustain rapid orientation and detection of potentially dangerous signals.

The observation that evidence of implicit visual processing was found only when an indirect method of investigation was used favours the hypothesis that these methods might be more sensitive in testing blindsight, compared to direct methods. Results of the present study show a strong dissociation between tasks, since no patients performed over the chance level in the 2AFC task, whereas all the patients, as a group, demonstrated a significant effect of implicitly processed visual stimuli on reaction times. Direct methods of investigation of blindsight, such as two alternative forced choice tasks, have been questioned not only for their sensitivity, but also because they might be ambiguous in establishing the presence of the phenomenon (Azzopardi and Cowey, 1997). In fact, asking patients to make counterintuitive guesses about unseen targets might be subject to response bias, masking the actual presence of visual residual abilities. In contrast, using indirect procedures involving bilateral presentation of stimuli, the conclusions about the implicit processing of the stimuli presented in the blind field, are entirely based on bias free responses to stimulation occurred in the intact field.

The results presented in the present study revealed that visual residual abilities in hemianopic patients might be underestimated. In particular, based on the present results, affective blindsight for fearful stimuli might be observed in wide population of patients with visual field defect. The observation, in a group of hemianopic patients, that potentially threatening stimuli, such as fearful faces, are preferred in the implicit visual processing and induce faster reaction times is consistent with this view. The neural circuit underlying these unaware visual abilities might be constituted by a pathway conveying visual inputs from the retina to the pulvinar and the superior colliculus, in order to reach the amygdala, a crucial structure for the processing of fear related stimuli, and other cortical areas involved with motor preparation. Notably, the observation that, in a large number of hemianopic patients, a subcortical-cortical pathway bypassing the striate cortex subserve the implicit ability of recognizing fearful visual stimuli, might constitute a neural basis for a therapeutical intervention. In fact, the systematic stimulation of this spared and functional pathway might improve and consolidate these visual residual abilities.

CHAPTER 4

Multisensory based approach to the recovery of visual field defects

The human innate ability of integrating information from different sensory modalities offers several behavioural advantages. In particular, one of the functional properties described in multisensory neurons of the SC, i.e. the inverse effectiveness rule, makes these neurons well–suited to detect sensory events when at least one sensory system is damaged. This principle, in fact, postulate the existence of an inverse relationship between the response evoked by modality-specific signals and the enhancement evoked by pairs of audio-visual stimuli, resulting in vigorous multisensory enhancements when weakly effective modality-specific stimuli are paired. As a consequence, multisensory integration might represent an innovative and efficient approach to the rehabilitation of unisensory defects, such as visual field defects. Recent electrophysiological evidence (Yu et al., 2009) revealed that multisensory responses in SC neurons of adult cats show signs of plasticity after exposure to audio-visual combinations of stimuli, therefore suggesting that adult SC neurons might adapt their response properties to multisensory experience and supporting the idea of neuronal plasticity induced by multisensory stimulation.

Homonimous hemianopia, a visual field defect (VFD) in which half of the visual field is blind, is common in patients with post-chiasmal lesions. In the majority of patients (about 70%), if a central visual field sparing exists, it does not exceed 5° (Zihl, 1989). As a consequence of the visual field loss, hemianopic patients show difficulties in detecting stimuli and finding objects in the visual space corresponding to the affected field region and they often complain about having a limited overview, bumping into obstacles, hurting people in busy places. These complaints are partly due to a common underlying defective mechanism, namely a visual scanning deficit. On the basis of ocular recordings, Zhil (1995) estimated that nearly 60% of patients with hemianopia do not show effective compensatory oculomotor behavior. In a relatively simple stimulus display (dot counting task), subjects exhibited longer scanning times and scanpaths, higher number of fixations and refixations and, at least in part, longer fixation durations and shorter saccadic amplitudes. Differential hemifield performances have also been reported by several studies, revealing a higher number of fixations and hypometric saccades in the heminaopic field (Chedru et al., 1974, Ishiai et al., 1987; Meienberg et al., 1981; Zhil, 1995, 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. Patients with hemianopia show reading difficulties that reflect the laterality of the visual field defect and, usually, patients with right-hemianopia (RH) are more disabled than those with left-hemianopia (LH) (Eber et al., 1987; Gassel and Williams, 1963; Remond et al., 1957; Schoepf and 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 et al., 1996; Trauzettel-Klosinski and Rheinard, 1998; Leff et al., 2001; Wang, 2003).

Spontaneous complete recovery from visual field defect is very unusual, occurring in less than 20% of all patients. Recovery depend on the underlying pathology: 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 (Zhil and von Cramon, 1985). Recovery of vision normally occurs within 8-12 weeks, after that further recovery is negligible (Pambakian and Kennard, 1997; Zihl, 2000). The rehabilitation of these patients, in order to reduce the disabilities consequent to visual field defects, constitutes therefore a crucial clinical aim. Visual search and reading impairments have been classically treated with psychophysical techniques aimed to oculomotor compensation. Two procedures have been mainly 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 amelioration of explorative eye movements and of visual exploration, enabling 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). However, 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. These procedures rely on top-down mechanisms and require patients to voluntary maintain attention oriented to the affected hemifield. In this view, multisensory integration might constitute an innovative and efficient theurapeutical approach based on a bottom-up mechanism. In fact, a systematic audio-visual stimulation, depending on the activity of a neural circuit spared in hemianopic patients (i.e. the retino-colliculo-extrastriate pathway), might affect orientation toward the blind hemifield and modulate the processing of visual events, improving visual exploration, possibly with long lasting effects.

In the previous chapter, evidence of the functional activity of the retino-colliculo-extrastriate pathway in hemianopic patients has been provided. Due to the sparing and the functionality of this pathway, representing the neural basis of multisensory integrative effects in humans, hemianopic patients have demonstrated to show immediate (i.e. on line) effects of multisensory integration. In the present chapter, evidence demonstrating that multisensory integration might induce also off-line, short-term effects on behavior of hemianopic patients will be presented, discussing data on the after effects of ventriloquism. In addition, long-lasting effects of multisensory integration on patients with visual field defect will be described, reporting clinical amelioration due to a systematic audio-visual stimulation and, therefore, demonstrating the therapeutical efficacy of a multisensory based approach to the recovery of visual field defects (Experiment 4).

1. SHORT TERM EFFECTS OF MULTISENSORY INTEGRATION IN HEMIANOPIC PATIENTS

The study by Leo and colleagues previously presented (Leo et al., 2008b) have demonstrated that visual stimuli, although not explicitly detected by hemianopic patients, can exert some effects on auditory spatial processing. It is worth pointing out that this finding revealed an immediate or on-line effect of auditory–visual stimulation.

A recent study (Passamonti et al., 2009a) investigated whether cross-modal stimulation under the same circumstances can also induce off-line changes in spatial processing (i.e. perceptual learning) in patients with visual awareness impairments. For instance, in healthy subjects, prolonged exposure to a ventriloquism-like situation leads to a remapping of auditory localization (i.e., the ventriloquism after-effect; AE); the apparent location of sounds, presented unimodally after a period of exposure to spatially incongruent sound–flash pairs, is displaced in the direction of the preceding visual stimulus (Canon, 1970; Radeau and Bertelson, 1974; Recanzone, 1998; Lewald, 2002; Frissen et al., 2003). It is generally agreed that AEs to such discrepant sensory inputs reflect a visually-driven recalibration process that results in a short-term reduction in the perceived discrepancy. This kind of perceptual learning is thought to play an important role in achieving and maintaining a coherent intersensory representation of space (Held, 1965; Welch, 1978). The study of Passamonti and colleagues explored AEs of audio-visual adaptation in patients with impairment of visual awareness due to a lesion of striate cortex (i.e., hemianopic patients) or parietal cortex (i.e., neglect patients). Patients were asked to localize weak sounds before and after a brief session (4 minutes) of a passive audio-visual adaptation, which consisted of either spatially disparate or spatially coincident adapting stimuli. The results revealed that, after exposure to spatially disparate stimuli presented in the normal field, all patients exhibited the usual shifts in sound localization toward the visual attractor. In contrast, when the same kind of adaptation was given within the affected field, a consistent shift was still evident in neglect patients but not in patients with hemianopia, therefore suggesting a key role of the geniculostriate circuit for adaptation to spatially disparate audio-visual stimuli. However, more importantly, when adaptation comprised spatially coincident stimuli, hemianopic and neglect patients exhibited significant AEs regardless of the adapted hemifield. Such AEs resulted in a reduction of the auditory localization error compared to baseline (i.e. after effect of multisensory enhancement). In other words, auditory localization performance was clearly enhanced after a passive adaptation to spatially coincident stimuli, even though visual stimuli were not overtly processed (i.e., adaptation occurred in the affected field). This evidence ruled out any possible involvement of geniculo-striate circuits in mediating AEs of multisensory enhancement. In fact, due to the damage to visual cortex, the *off-line* improvement observed in those patients may be explained only by a covert processing of visual stimuli, probably mediated by the spared collicular-extrastriate pathway (Leo et al., 2008b). The enhancement in auditory localization after exposure to spatially coincident audio-visual stimuli represents a short-term effect due to multisensory integration, indicating that perceptual learning induced by a cross-modal stimulation is possible when one of the sensory modalities is impaired.

2. LONG-TERM EFFECTS OF MULTISENSORY INTEGRATION IN HEMIANOPIC PATIENTS

The observation that patients with visual field defects retain multisensory integrative abilities within their blind field, demonstrating both on-line immediate effects and off-line short-term effects of integration of audio-visual stimuli, indicates that hemianopic patients might reveal also long-term effects of multisensory integration. In this view, Bolognini and colleagues (2005b) tried to take advantage of the audio-visual integrative abilities of hemianopic patients to rehabilitate their visual field defect. It was hypothesized that a systematic audio-visual stimulation of the visual field, activating multisensory neurons in the SC, would affect orientation toward the blind hemifield and improve oculomotor exploration with long-lasting effects (Liversedge and Findlay, 2000; Gitelman et al., 2002). In this study, patients with chronic visual field defects were trained to detect the presence of visual targets, that could be presented alone (i.e. modality-specific condition) or together with an acoustic stimulus (i.e. cross-modal conditions). Patients underwent the treatment 4 hours daily, for nearly 2 weeks. After the treatment, patients were assessed with a battery of tests that showed a progressive improvement in visual detection and visual search time. These gains allowed patients to efficiently compensate for the loss of their vision. Moreover, the improvement in visual exploration was stable at 1-month (Bolognini et al., 2005b) and 1-year (Passamonti et al., 2009b) follow-up sessions. 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.

The crucial role of 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 detection

(Bolognini et al., 2005b; Passamonti et al., 2009b). In a computerized visual field test, a significant increase in visual detection's accuracy was found in the blind field after the training, when patients were allowed to use eye movements to perform the task (eye-movement condition). Importantly, such amelioration resulted from an enhanced perceptual sensitivity (d') and not from a change in response criterion (β) (Passamonti et al., 2009b). In contrast, a weak or no amelioration at all was found in the same test when patients were constrained to strictly maintain their gaze on the fixation point (fixed-eye condition). To be noted, in the computerized visual field test visual stimuli were randomly presented in the whole visual field for a duration of 100 ms, so reducing the possibility to foveate the target. The discrepancy between these two conditions (eye-movement vs fixed-eye) 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.

To directly assess the specific effects of audio-visual training on oculomotor scanning behaviour, the 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 twelve patients with chronic visual field defects (Passamonti et al., 2009b). Eye movements were recorded using an infrared recording technique, with respect to a range of spatial and temporal variables. Results showed that prior to treatment, patients' performance was significantly different from that of healthy controls in relation to fixation and saccade parameters (Jahnke et al., 1995; Zihl and Kennard, 1996; Pambakian et al., 2000; Tant et al., 2002). After audio-visual training, all patients reported an improvement in oculomotor exploration, which was characterized by fewer fixations and refixations, faster and larger saccades, and a reduced scanpath length, leading to a shorter exploration time. Similarly, reading parameters were significantly affected by the training with respect to the specific impairments observed in both left and right hemisphere–damaged patients (Leff et al., 2000). In contrast, the control visual training was not sufficient to significantly affect the impaired oculomotor responses. After visual training, in fact, patients did not show any improvement in oculomotor exploration and in visual detection, as assessed by computerized visual field test. Taken together, these findings provide evidence that a training regimen based on a multisensory stimulation, such as the audio-visual training, may improve clinical signs of hemianopia with long lasting effects, encouraging a more organized pattern of visual exploration, due to the implementation of efficient oculomotor strategies. However, whether this improvement might be ascribed to the specific stimulation of the retino-colliculo-extrastriate pathway needs to be further investigated.

3. EXPERIMENT 4 - CORTICAL CORRELATES OF VISUAL FIELD DEFECTS IMPROVEMENTS AFTER AUDIO-VISUAL STIMULATION

Previous studies have provided evidence that a systematic audio-visual stimulation induce long-lasting improvements in visual detection, visual exploration, reading abilities and daily life disabilities in patients with visual field defect (Bolognini et al., 2005b; Passamonti et al., 2009b). This improvement was evident only when patients were allowed to perform eye movements, therefore suggesting that it might depend on a mechanism of oculomotor compensation. An interesting question concerns the neural mechanism underlying the implementation of efficient oculomotor strategies. It has been hypothesized that this oculomotor compensation might be due to a bottom-up mechanism activated by cross-modal stimulation of a neural circuit responsible of automatic shifts of attention and saccadic eye movements, which might be represented by the retino-colliculo-extrastriate pathway. The multisensory properties of SC have been extensively reported (Meredith and Stein, 1993), but it is also worth noting that the SC is involved in both the initiation and the execution of saccades, and in target selection (Krauzlis et al., 2004). Studies on normal subjects suggested that audio-visual stimulation improves both saccade accuracy and saccade timing (Corneil et al., 2002; Colonius and Arndt, 2001). In fact, because sensory maps within the SC are in spatial register with premotor maps, multisensory information can be translated directly into an appropriate orientation response toward the blind hemifield, rendering this midbrain structure the ideal candidate to explain the multisensory mediated oculomotor compensation. In addition to the SC, also extrastriate temporo-parietal areas have been shown to be causally involved in the modulation of audio-visual multisensory orienting behaviour (Bertini et al., in press). The retino-colliculo-extrastriate pathway, involved in multisensory integration, spatial orienting and oculomotor behaviour, is usually anatomically spared in hemianopic patients and, as previously demonstrated, is functionally able to mediate multisensory immediate effects and visual residual abilities. Based on this body of knowledge, the hypothesis of a bottom-up mechanism mediating the clinical improvements of hemianopic patients after the audio-visual training and depending on the activity of the spared retino-colliculo-extrastriate pathway seems quite reasonable. However, the experimental evidence on the audio-visual training provided so far, testing a relatively small number of patients, has never addressed this issue.

In the present study, in order to investigate the mechanisms underlying the compensation of visual field defects after audio-visual stimulation, twenty-eight patients with chronic visual field defect due to post-chiasmal lesions were submitted to the audio-visual training (Bolognini et al., 2005b; Passamonti et al., 2009b); clinical and oculomotor parameters were tested in three sessions (before, immediately and one year after the training). To highlight possible differential effects of different cortical lesions on the recovery mediated by the audio-visual training, the performances of patients with lesions involving only the occipital lobe were compared to performances of patients with lesions extending also to different cortical areas (such as extrastriate areas). In fact, if the retino-colliculo-extrastriate pathway is responsible of the bottom-up mechanism mediating the implementation of compensatory oculomotor strategies, patients with lesions limited to the occipital cortex are expected to demonstrate greater improvements after the training, since an occipital lesion does not compromise the functionality of the secondary visual pathway.

Materials and method

Subjects

A group of twenty-eight right-handed patients with chronic visual field deficits due to a postchiasmatic lesion 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.

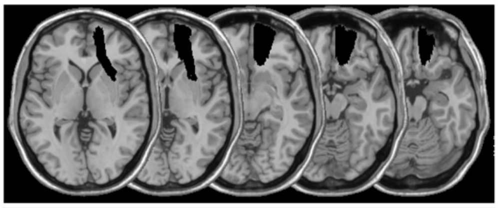
Selection of patients was based on complete availability of visual perimetry data. Patients were recruited at least three months after the onset of their hemianopia, when their field defects were stable. Patients with coexisting eye movement pathologies or other cognitive impairments were excluded. All 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: twenty-two had cerebral infarctions, three had arteriovenous malformations that had bled, one had a temporal lobectomy, and two had traumatic brain injury. 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 5. The brain lesions of each patient were confirmed by CT scan and MRI, and each lesion was reconstructed using MRIcro software (Rorden and Brett 2000; Figure 15). In order to test differential cortical contributions on the effects of the audio-visual training (see Statistical Analysis), patients were divided on the basis of their CT scan - MRI reconstruction in two groups: patients with occipital lesion (9 patients) and patients with lesions involving occipital lobe and extending to other cortical areas (19 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	41	13	3	vascular	left	0°	Right fronto-temporal	**P16**	M	39	8	100	AVMs	right	0°	Left temporo-occipital
P2	F	23	13	3	vascular	Left	<5°	Right occipital	**P17**	F	39	18	107	vascular	Right	<5°	Left parieto-occipital
P3	F	35	8	144	vascular	Left	0°	Right occipital	**P18**	M	33	18	9	vascular	Right	<5°	Left parieto-occipital
P4	M	56	18	14	vascular	Left	<5°	Right temporo-occipital	**P19**	M	72	8	6	vascular	Right	<5°	Left temporo-occipital
P5	M	37	16	30 years	epilepsy	Left	<5°	Right fronto-temporal-parietal-occipital	**P20**	M	53	18	18	vascular	Right	<5°	Left temporal
P6	M	41	18	55	vascular	Left	0°	Right temporo-parieto-occipital	**P21**	M	64	13	5	vascular	Right	0°	Left occipital
P7	F	31	18	24	vascular	Left	<5°	Right fronto-temporal-parietal-occipital	**P22**	M	42	15	17	vascular	Right	<5°	Left temporo-occipitaal
P8	M	52	17	34	AVMs	Left	0°	Right temporo-parietal-occipitaal	**P23**	F	36	8	30	vascular	Right	<5°	Left fronto-temporo-parietal-occipital
P9	M	21	13	3	trauma	Left	0°	Right frontal-temporal	**P24**	M	63	5	3	vascular	Right	0°	Left occipital
P10	M	62	13	3	vascular	Left	<5°	Right occipital	**P25**	M	75	8	6	vascular	Right	0°	Left occipital
P11	M	60	8	15	vascular	Left	<5°	Right fronto-temporo-parietal	**P26**	M	22	11	45	trauma	Right	0°	Left fronto-parieto-occipital
P12	M	56	13	6	vascular	Left	0°	Right occipital	**P27**	M	45	13	15	AVMs	Right	0°	Left parieto-occipital
P13	F	65	5	3	vascular	Left	<5°	Right occipital	**P28**	M	36	18	13	vascular	Right	0°	Left occipital
P14	M	47	17	17	vascular	Left	<5°	Right fonto–temporo-parietal									
P15	F	62	8	32	vascular	Left	0°	Right fronto-temporal									

Table 5 Summary of clinical, demographic and lesional data. M: male; F: female; AVMs: arteriovenous malformations; VFD: visual field defect.

A – Patients LEFT VFD

P1



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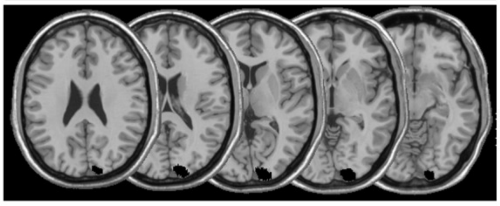

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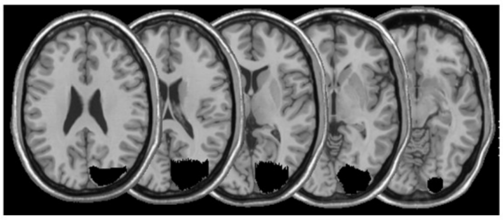

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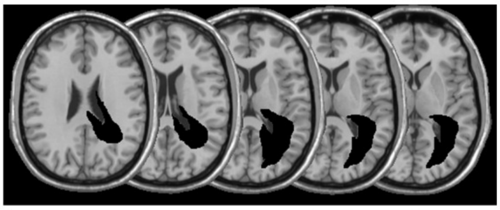

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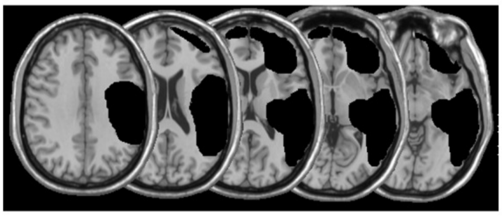

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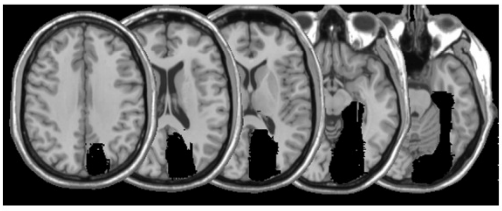

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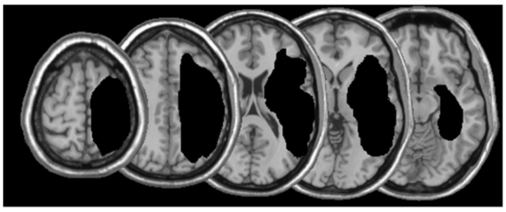

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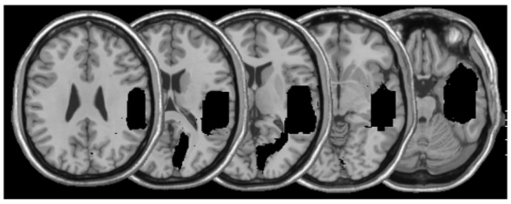
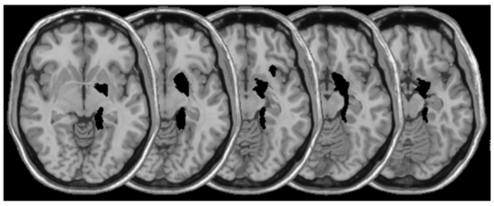
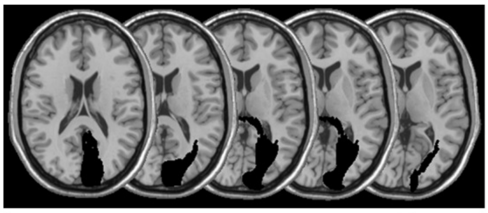


P9



P10



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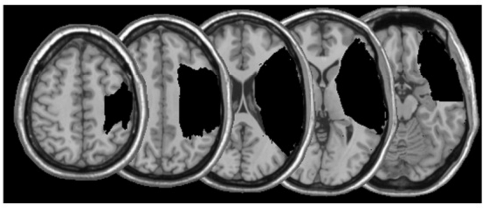

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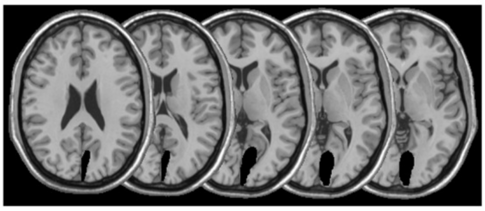

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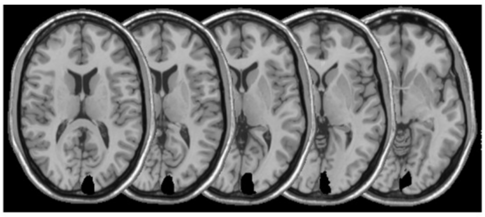

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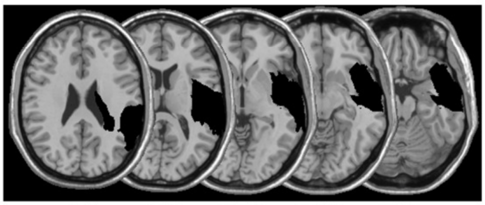
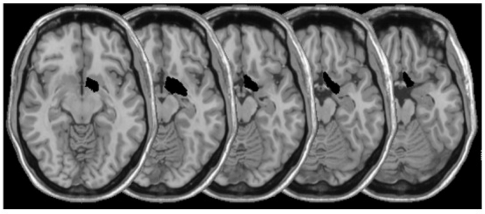


P15



B – Patients RIGHT VFD

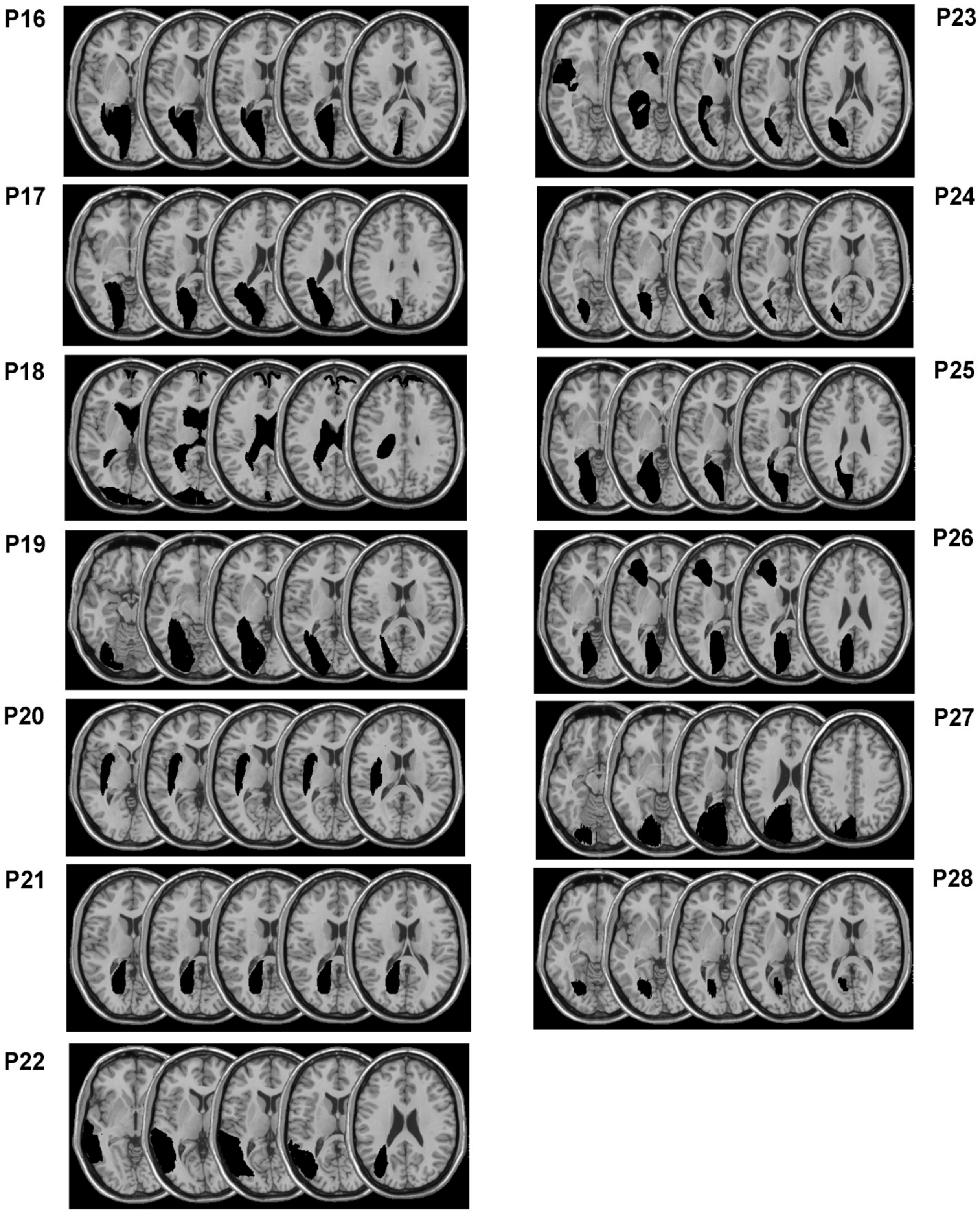


Figure 15 Lesion reconstruction images from CT and MRI, superimposed on the normalized MNI template http://www.bic.mni.mcgill.ca/cgi/icbm_view). Panel A: lesion reconstructions of patients with left visual field defect. Panel B: lesion reconstructions of patients with right visual field defect. The lesions are shown in the corresponding hemisphere (i.e. a right lesion is viewed in the right hemisphere).

Training paradigm

All the patients underwent Audio-Visual Training, 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 Figure 16). 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 modality-specific visual condition (for more details, see Bolognini et al., 2005b). During the training, the blind hemifield was more intensively stimulated than the intact hemifield.

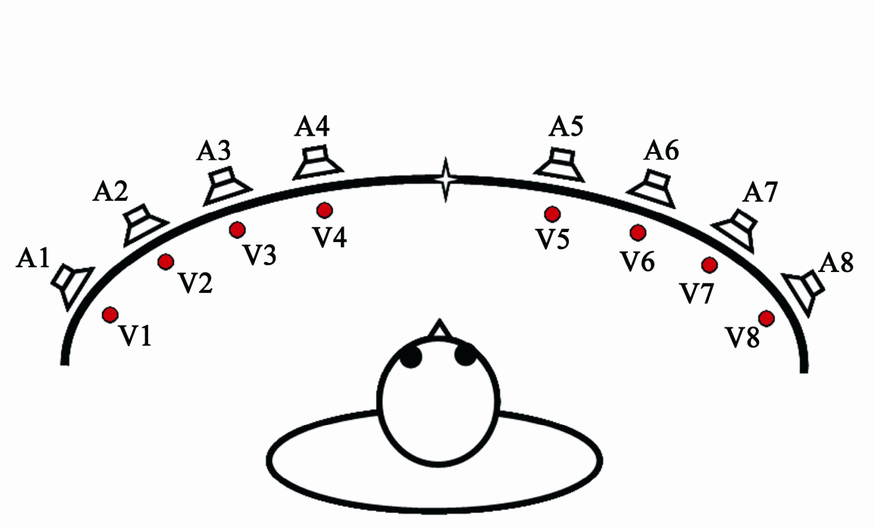


Figure 16 A schematic view of the training apparatus. V1–V8 = visual stimuli; A1–A8 = auditory stimuli.

Testing sessions

Clinical tests and eye movements assessments were conducted in three sessions. Session 1 (S1) was the initial evaluation, Session 2 (S2) occurred immediately after the audio-visual training, while Session 3 (S3) was performed 1 year after the audio-visual training. The assessment at each session was carried out by a different investigator.

Clinical assessment

Clinical assessment consisted of a neuropsychological examination of visual field disorders. Computerized Visual Field Test: This test consisted of an evaluation of visual detection ability The stimulus array was of 52° x 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. D prime and beta indices for the detections into the blind field were measured. The task was performed 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 (Figure 17a).
Triangle Test (modified from Zhil, 2000): Patients were shown with 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. The total number of trials in

this test 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. Patients' visual exploration abilities were measured calculating the percentage of correct responses (Figure 17b).

ADL questionnaire (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, in order to assess the subjectively perceived impairment in daily life activities.

Assessment of eye movements responses

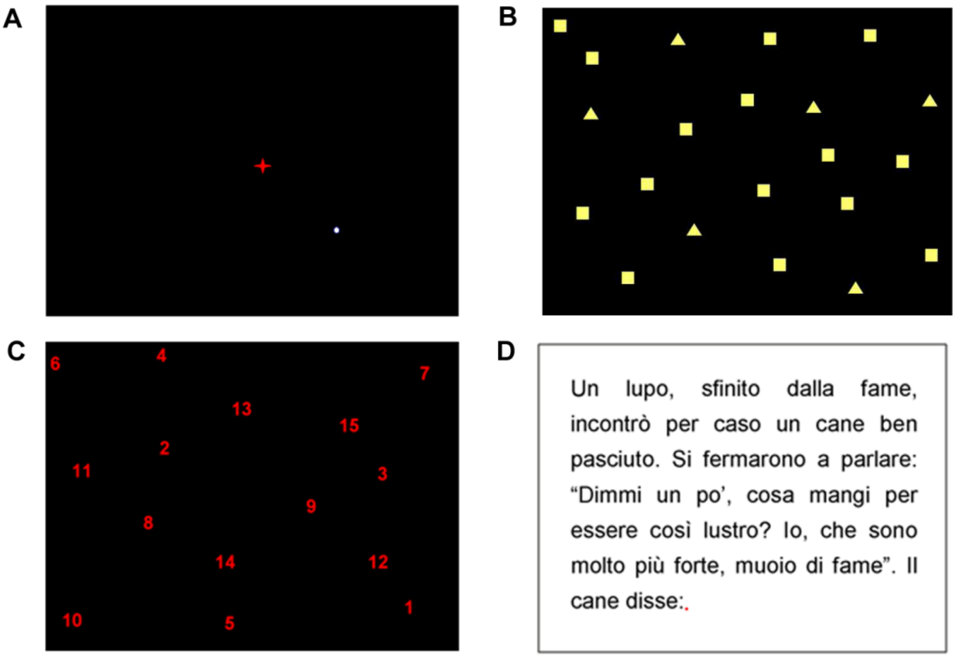
Apparatus

Eye movements were recorded in a dimly lit room using a Pan/Tilt optic eyetracker (Eye-Track ASL-6000) which registers real-time gaze at 60 Hz (accuracy 0.5°). 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 one of a series of small dots arranged on three horizontal lines. Fixation time at each dot position was at least three seconds. To prevent head movements, a head stabilization device was used.

Stimuli and experimental tasks

Number test (modified from Bolognini et al., 2005b). In this visual search task, eight stimulus arrays ($56^{\circ} \times 48^{\circ}$, horizontally and vertically respectively) each containing 15 numbers (from 1 to 15, stimulus size 2° × 2°) randomly distributed 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 according to two parameters: number of fixations and saccade amplitude. In addition, mean exploration time was taken as behavioural measure of ocular efficacy (Figure 17c).

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 reading time, as behavioral measure. The following variables were evaluated: number of saccades in the reading direction (progressive saccades), number of regressions (backward saccades) and amplitude of reading saccades (Figure 17d).



Un lupo, sfinito dalla fame, incontrò per caso un cane ben pasciuto. Si fermarono a parlare: “Dimmi un po’, cosa mangi per essere così lustro? Io, che sono molto più forte, muoio di fame”. Il cane disse:.

Figure 17 (A) Computerized visual field test; (B) Triangle test; (C) Number test; (D) Reading text task

Statistical analysis

Data obtained in each parameter from clinical and eye movements assessments were analyzed with separate ANOVAs with Cerebral Area (occipital vs other cortical lesions) as between group factor and Session (S1, S2, S3) as within group factor. Whenever necessary, pairwise comparisons were conducted with Newman-Keuls test.

Based on previous findings (Passamonti et al., 2009b), showing different reading oculomotor patterns in right and left hemianopic patients, reading text task parameters were analyzed with separate ANOVAs with Cerebral Area (occipital vs other cortical lesions) and Side of hemianopia (RH: right hemianopic patients, LH left hemianopic patients) as between subjects factor and with Session (S1, S2, S3) as within group factor. Whenever necessary, pairwise comparisons were conducted with Newman-Keuls test.

Results

Clinical Assessment

Computerized Visual Field Test in the Fixed-eyes condition: Results of the ANOVA conducted on d prime and beta for the detections in the blind field showed no significant effects (all Fs < 1.31; all Ps >.26), suggesting that the ability of patients of detecting visual stimuli and the response criterion were not affected by the audio-visual treatment when they were not allowed to explore the visual scene with the eye-movements (D prime: S1 = 1.15; S2 = 1.21; S3 = 1.31; Beta: S1 = 6.66; S2 = 6.93; S3 = 7.4; Figure 18a).

Computerized Visual Field Test in the Eye Movements condition: the ANOVA conducted on d prime for detections in the blind field revealed a significant main effect of Session [F(2,52) = 31.23; p<.001], accounted by a significant increase of perceptual sensitivity in S2 (2.66) and S3

(2.72) compared to S1 (2.01; all Ps < .001), as suggested by post-hoc comparisons. In addition, a significant effect of the main factor Cerebral Area [F(2,26) = 4.35; p = .05] was found, explained by a higher d prime in patients with occipital lesions (2.74) compared to patients with lesions involving also other cortical areas (2.34). More importantly, a significant Cerebral Area x Session interaction was found [F (2,52) = 3.29; p = .04]. As revealed by post hoc comparisons, an increase in perceptual sensitivity was found immediately at the end and one year after the audio-visual treatment, both for occipital patients (S1 = 2.07; S2 = 3.1; S3 = 3.05; all Ps < .001) and for patients with lesions including other cortical areas (S1 = 1.99; S2 = 2.46; S3 = 2.58; all Ps <.001). However, notably, the performance in S2 and S3 was significantly higher in patients with occipital lesions compared to the performance in S2 and S3 of patients with lesions extending to other cortical areas (S2: p = .04; S3: p =.05), whereas their performance at the baseline session was not significantly different (S1: p = .73). This pattern of results clearly demonstrated that the audio-visual training was more effective in hemianopic patients with occipital lesions (Figure 18b).

On the other hand, results of the ANOVA on the beta index revealed no significant effect (all F < 0.9; all P > .3), indicating that the improvements observed in d prime indices were due to an enhancement in perceptual sensitivity and could not be ascribed to a more liberal response criterion.

In order to rule out the hypothesis that occipital patients and patients with lesions involving other cortical areas might demonstrate different profile of improvement in perceptual sensitivity due to different extensions of the lesions (i.e. occipital patients reporting smaller lesions compared to patients with lesions involving other cortical areas), supplemental ANOVAs on d prime and beta indices were conducted, dividing patients in two groups according to the extension of the lesion. Based on CT scan and MRI reconstruction with MRIcro (Rorden and Brett, 2000), patients were divided in two groups: a first group, comprising 13 patients with lesions extending over 10% of the entire brain (extended lesions), and a second group, comprising 15 patients with lesions not exceeding the 10% of the entire brain (limited lesions). D prime and beta indices were analyzed with two separate ANOVAs with Extension of the lesion (extended lesion vs limited lesion) as between subjects factor and Session (S1, S2, S3) as within subjects factor. Relative to perceptual sensitivity, results revealed only a significant effect of Session [F (2,52) = 28.04; p < .001], with d prime index increasing in S2 (2.65) and S3 (2.72) compared to S1 (1.99; all Ps < .001). No significant effect of Extension or interaction Extension x Session (all Fs < 3.49; all Ps > .08) was found, thus suggesting that the extension of the lesion does not play a crucial role in modulating the increase of perceptual sensitivity in the Computerized Visual Field Test. The ANOVA on the response criterion revealed no significant effect (all Fs < 1.72; all Ps > .2).

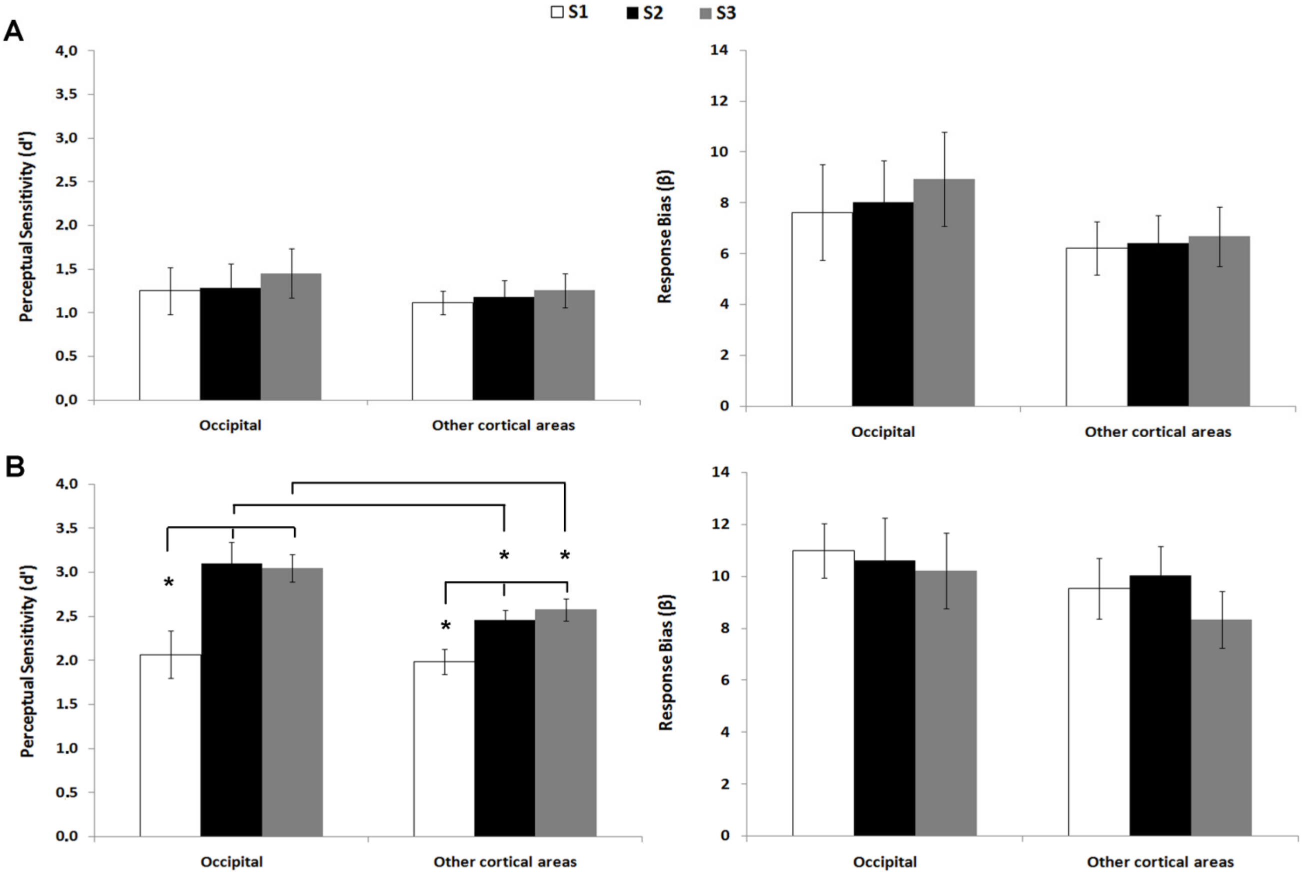


Figure 18 Computerized visual field test: perceptual sensitivity (d') and response bias (β). Panel A: fixed-eye condition. Panel B: eye movement condition. White histograms represent baseline (S1); black histograms represent the session immediately after the audio-visual training (S2); grey histograms represent the session one year after the training (S3). Error bars indicate s.e.m. Asterisks indicate a p value <.05

Triangle Test: in the ANOVA conducted on the percentage of correct responses, only the main factor Session resulted significant [F (2,52) = 24.9; Ps <.001] and post-hoc comparisons revealed a significant increase of correct responses in S2 (90%) and S3 (91%) compared to S1 (71%; all Ps < .001; Figure 19a).

ADL questionnaire: the ANOVA on the subjectively perceived disability index revealed a significant main effect of Session [F (2,52) = 59.1; P < .001], showing that the disability index decreased significantly in S2 (6) and S3 (5), compared to S1 (12), as revealed by post hoc comparisons. Moreover, a significant interaction Cerebral Area x Session was found [F (2,52) = 6.1; P < .001]. Post hoc comparisons showed that in the baseline session (S1) occipital patients perceived a greater impairment in daily activities (17) compared to patients with lesions extending to other cortical areas (10; P = .002). However, a significant amelioration of the perceived disability index was found immediately at the end and one year after the audio-visual treatment, both for occipital patients (S1 = 17; S2 = 7; S3 = 6; all Ps < .001) and for patients with lesions including other cortical areas (S1 = 10; S2 = 6; S3 = 5; all Ps < .002; Figure 19b).

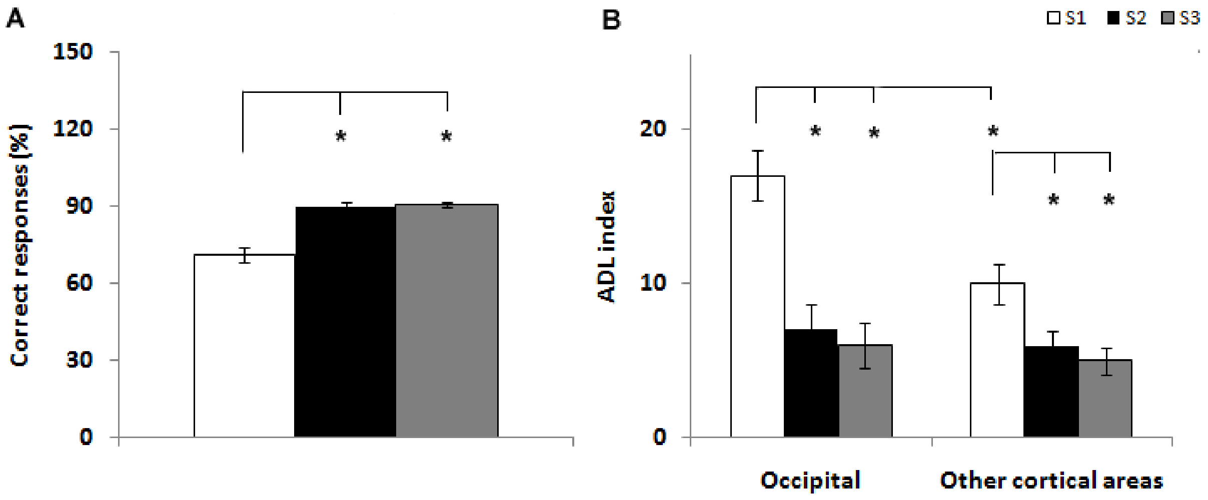


Figure 19 Panel A: Triangle Test; Panel B: ADL Questionnaire; White histograms represent baseline (S1); black histograms represent the session immediately after the audio-visual training (S2); grey histograms represent the session one year after the training (S3). Error bars indicate s.e.m. Asterisks indicate a p value <.05

Assessment of eye movements responses

Number test. The ANOVAs conducted on the number of fixations and the mean exploration times revealed a main effect of Session (all F > 7.4; all Ps < .001), accounted by a significant decrease in S2 and S3, compared to S1, of the number of fixations (S1 = 100; S2 = 84; S3 = 86; all Ps < .001; Figure 20a) and of the mean exploration times (S1 = 28 sec.; S2 = 23 sec.; S3 = 24 sec.; all Ps < .001; Figure 20c). In the same vein, the ANOVA conducted on the amplitude of saccades showed a significant effect of Session [F (2,52) = 5.5; P < .007] and post hoc comparisons demonstrated that the amplitude of saccades significantly increased in S2 (8.2°) and S3 (8.2°), compared to S1 (7.6°; Figure 20b). Also, a significant effect of Area was found, indicating that patients with lesions including other cortical areas (7.6°) were, overall, more compromised than occipital patients (8.7°). No other significant effect or interaction was found (all < 1.2; all Ps >.3).

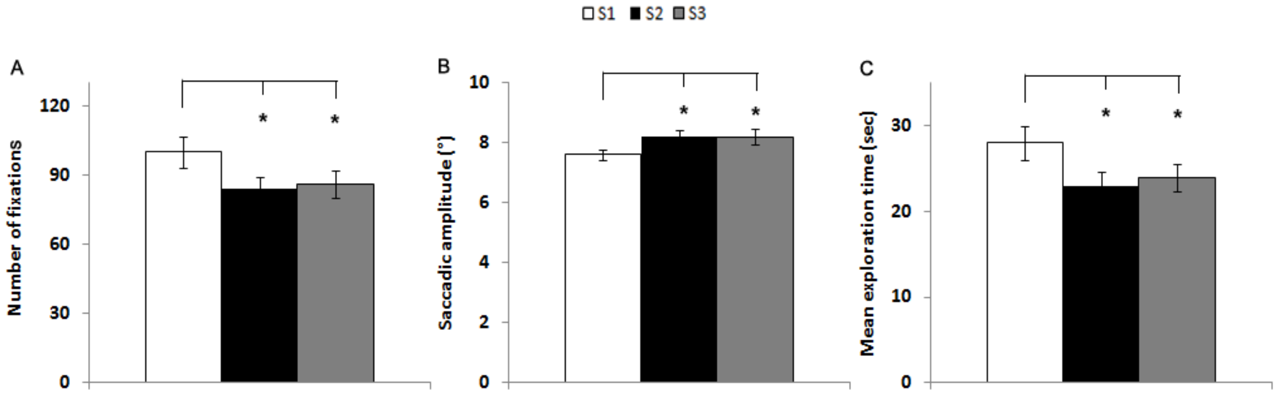


Figure 20 Number Test. Panel A: Number of fixations; Panel B: Saccadic amplitude; Panel C: Mean exploration time. White histograms represent baseline (S1); black histograms represent the session immediately after the audio-visual training (S2); grey histograms represent the session one year after the training (S3). Error bars indicate s.e.m. Asterisks indicate a p value <.05

Reading text task. The ANOVAs conducted on each parameter of the reading text task (i.e. number of progressive saccades, number of regressions, amplitude of reading saccades and reading time) showed a significant effect of Session (all Fs > 4.5; all Ps < .01). Post hoc comparisons for each parameters revealed a significant improvement in S2 and S3, compared to S1 (progressive saccades: S1 = 10.3; S2 = 9.1; S3 = 8.5; all Ps < .007; regressions: S1 = 2.3; S2 = 1.9 ; S3 = 1.5; all Ps < .05; amplitude of reading saccades: S1 = 3.6°; S2 = 3.9° ; S3 = 4°; all Ps < .04; reading time: S1 = 3.4 syll/sec.; S2 = 3.6 syll/sec. ; S3 = 4 syll/sec; all Ps < .05; Figure 21). Moreover, in each parameter, a significant effect of Side of hemianopia was found (all Fs > 4; all Ps <.05), revealing a greater defective reading behavior of right hemianopic patients compared to left hemianopic patients (progressive saccades: RH = 12.6; LH = 6.4, regressions: RH = 2.4; LH = 1.5; amplitude of reading saccades: RH = 2.6°; LH = 4.9°; reading time: RH = 2.6 syll/sec; LH = 4.6 syll/sec.; all Ps <.03). No other significant effect or interaction was found (all Fs < 2.8; all Ps >.08).

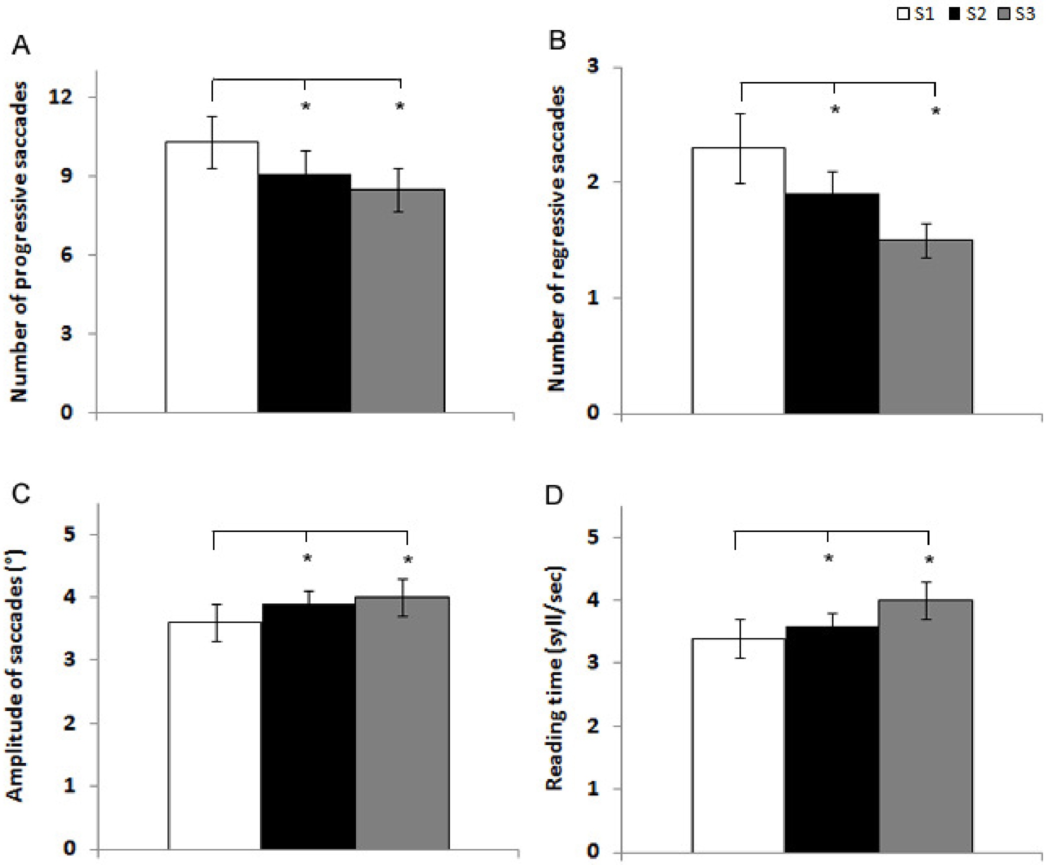


Figure 21 Reading text task. Panel A: Number of progressive saccades; Panel B: Number of regressive saccades; Panel C: Amplitude of reading saccades; Panel D: Reading time. White histograms represent baseline (S1); black histograms represent the session immediately after the audio-visual training (S2); grey histograms represent the session one year after the training (S3). Error bars indicate s.e.m. Asterisks indicate a p value <.05

Discussion

The present study confirmed the effectiveness of audio-visual stimulation in improving clinical signs and oculomotor deficits in hemianopic patients, showing long-lasting improvements (up to one year after the treatment) in visual detections, visual exploration and oculomotor patterns. Notably, the audio-visual training did not enlarge the field of vision, as suggested by the lack of improvements in visual detections when eye movements were not allowed (Computerized Visual Field – Fixed eyes condition). In contrast, the beneficial effects found when patients were free to perform eye movements suggest that the improvement might be ascribed to a compensatory mechanism due to the enhancement of the responsiveness of the oculomotor system. These results are in line with previous evidence reporting clinical (Bolognini et al., 2005b) and oculomotor (Passamonti et al., 2009b) improvements in hemianopic patients after audio-visual stimulation. Moreover, the present study put some light on the neural circuitries underlying the compensation of the visual field defect mediated by the audio-visual stimulation, by showing different patterns of improvement in patients with different cortical lesions. In particular, patients with lesions to the occipital lobe revealed a stronger improvement in visual detections when eye movements were allowed compared to patients with lesions involving also different cortical areas. It is worth noting that the improvement and the differing effect of cortical lesions were evident only for the perceptual sensitivity index and not for the response criterion.

However, the greater improvement in visual detections might have been due to the extension of the lesions (i.e. occipital patients demonstrating smaller lesions compared to patients with lesions involving other cortical areas). This hypothesis was ruled out by the absence of differences in the performances of patients with lesions involving less than 10% and more than

10% of the entire brain, indicating that the greater beneficial effect observed in occipital patients cannot be ascribed to the extension of the lesion, but is probably related to the site of the lesion.

Notably, this differential pattern of improvement was mainly evident in a task very high demanding in terms of spatial orienting behaviour. In fact, in the Computerized visual field test, patients were required to detect small dots briefly appearing (100 ms) on a wide projection screen by performing rapid eye movements. The execution of this task, therefore, mainly relies on bottom-up mechanisms, regulating reflexive orienting eye movements. This finding is consistent with the hypothesis that the compensation of the visual field defects after the audio-visual training might depend on the systematic stimulation of the retino-colliculo-extrastriate pathway. It is worth remembering the very well known role of SC in coding spatial locations for guiding saccades and shifts of attention towards peripheral visual locations (Kustov and Robinson, 1996; Ignashchenkova et al., 2004) and in mediating multisensory orienting behaviour (Leo et al., 2008a). Moreover, extrastriate parietal areas such as the parietal eye fields (PEF), connected with the SC and the frontal eye fields (FEF), are known to be involved in the execution of saccades externally triggered towards a suddenly appearing peripheral target (i.e. reflexive visually guided saccades) (Arikuni et al., 1980; Barbas and Mesulam, 1981; Pierrot-Deseilligny et al., 2004). Therefore, the activation of the retino-colliculo-extrastriate pathway after an intensive and systematic audio-visual stimulation might have been responsible for the enhanced responsiveness of the oculomotor system. This interpretation is in line with the findings that patients with lesions to the occipital cortex and a complete sparing of the retino-colliculo-extrastriate pathway demonstrated the greater improvement in a task requiring bottom-up visual orienting abilities.

However, it is worth noting that patients with lesions involving other cortical areas demonstrated also a significant improvement after the audio-visual training in visual detections compared to the baseline, although this improvement was significantly lower compared to the one demonstrated by occipital patients. In addition, the performance in visual search and reading abilities, as well as in daily life activities, resulted significantly improved in all the patients with no differences between patients with lesions involving the occipital cortex or other cortical regions. A possible explanation is that performance in these tasks might engage the high order correlates of visual exploration, such as spatial attention and strategic oculomotor planning, depending on top-down mechanisms. Therefore, the activation of strategic attentional processes involved with the learning of efficient compensatory oculomotor strategies might have masked the specific contribution of the retino-colliculo-extrastriate pathway. Taken together, these findings suggest that a systematic audio-visual stimulation is effective in compensating visual field defects. The audio-visual training, activating the spared retino-colliculo-extrastriate pathway in hemianopic patients, improve orientation towards the blind field and enhance the responsiveness of the oculomotor system, allowing patients to efficiently performing eye movements in order to compensate for the visual field defect. As a consequence, patients with lesions involving exclusively the occipital cortex exhibit the greater beneficial effects in tasks requiring bottom-up visual orienting. Overall these findings provide further evidence that multisensory integration can enhance the impaired unisensory processing, improving the perception of sensory events difficult to be perceived due to the unisensory defect.

Concluding remarks

Perception of the external world often depends on integrating different sensory information. When the primary modality of information is weak, for example, when viewing a dimply lit scene or when listening to speech in a noisy environment, we can benefit from the information derived from our other senses. Indeed, we typically receive a rich and simultaneous flow of information from all our senses, so our comprehension of the events of the external world is always the product of an integrated, multisensory perception. This integration of multiple sensory cues (i.e. multisensory integration) provides animals with enormous response flexibility, so that their reaction to the presence of one stimulus can be altered by the presence of another in a different modality. In humans, multisensory integration might be clearly beneficial, for example, in producing response enhancement, when the signal from a specific sensory modality is weak, or when a sensory system is deprived of its modality-specific brain area (Calvert et al., 2004; Làdavas et al., 2008). This would be the case of impaired unisensory processing resulting from brain lesions that might be improved by a stimulation involving a spared sensory modality. Multisensory neural circuits, normally associated with both the deprived and nondeprived senses and retaining their responsiveness to cross-modal stimuli, might, therefore, represent the neural correlates of an efficient sensory compensation after damage to one sensory system. The present project was aimed to test this hypothesis in patients with visual field defects due to post-chiasmal lesions.

In the first two chapters of the present dissertation the neural circuit responsible of multisensory integration has been discussed. The crucial role of superior colliculus (SC) has been addressed providing evidence both from animals and humans. In animals, pioneering studies on multisensory integration (Meredith and Stein, 1993) revealed that SC is particularly rich of neurons responding to more than one modality and that presentation of auditory and visual stimuli might significantly enhance the firing rate in these multisensory neurons. Moreover, studies on cats with lesions to the SC provided evidence of the essential activity of this midbrain structure to mediated multisensory effects, demonstrating the loss of multisensory enhanced orienting behaviour after deactivation of SC (Burnett et al., 2004; 2007). In the same vein, evidence in humans (Leo et al., 2008a; Bertini et al., 2008; Maravita et al., 2008) revealed the presence of multisensory integrative effects due to a neural coactivation mechanism only when subjects were presented with auditory stimuli coupled with visual stimuli visible to the SC (i.e. long wavelength stimuli), Moreover, neuroimaging studies revealed superadditive enhancement and depressions in the BOLD signal in SC, during the presentation of synchronous and asynchronous audio-visual stimuli (Calvert et al., 2001). Although these findings suggested a relevant role of this subcortical structure in mediating audio-visual orienting behaviour, the striking evidence of animals' lesions studies, directly demonstrating a loss of multisensory behavior after SC lesions was still missing. Experimental evidence (Experiment 1) presented in the first chapter aimed to provide this direct evidence, testing, in a multisensory task, patients with collicular lesions, patients with subcortical lesions not involving the SC and healthy control subjects. The results revealed that, in contrast with healthy subjects and patients with subcortical lesions not involving SC, patients with SC lesions were not able to exhibit multisensory effects due to neural coactivation mechanisms. Paralleling the evidence of studies on cats with SC, patients with collicular lesions demonstrated a loss of multisensory enhancement, providing the first lesional evidence in humans of the essential role of SC in mediating audio-visual integration.

Although a wide range of evidence supports in animals and in humans the critical role of SC in mediating multisensory integration, growing evidence suggests that substantial audio-visual processing is also occurring in the cortex. Studies on cats have mainly focused on the contribution of the anterior ectosylvian sulcus (AES), demonstrating that SC neurons exhibit effects of integration of different sensory stimuli only in presence of descending inputs from this associative cortex AES (Jiang et al., 2001; Alvarado et al., 2009). Neuroimaging and evoked-potential studies, in order to find a possible human homologous for AES, reported superadditive activation in several cortical areas, such as the superior temporal sulcus (STS), the superior temporal gyrus (STG; Calvert et al., 2001; Wright et al., 2003), the posterior parietal cortex (PPC; Calvert et al., 2001; Molholm et al., 2002) and frontal cortical regions (Calvert et al, 2001; Adams and Janata, 2002; Laurienti et al., 2003). However, these enhanced BOLD signals might represent an epiphenomenal activation and do not disambiguate the causal involvement of these cortical areas in the multisensory processing. The experiment presented in the second chapter (Experiment 2) aimed to investigate the role of the temporo-parietal cortex, the occipital cortex and the posterior parietal cortex in multisensory integration, inducing virtual lesions by inhibitory theta-burst stimulation on these cortical areas. The results revealed that only temporo-parietal cortex was causally involved in modulating the integration of audio-visual stimuli at the same spatial location.

Taken together, these findings suggest that multisensory audio-visual integration in humans is mediated by a subcortical-cortical network including the SC and temporo-parietal regions. The possibility of exploiting the activity of this neural circuit in order to enhance unisensory defective processing has been discussed in the second part of the dissertation. In fact, in the perspective of a multisensory-based approach to the recovery of unisensory defects, the sparing of this colliculo-extrastriate circuit results extremely relevant. In patients with hemianopia, since the cortical lesion causing the visual defect affects the occipital lobe, the retino-colliculo extrastriate pathway is usually anatomically spared. In the third chapter evidence of the functional activity of this circuit in hemianopic patients has been provided. Previous studies have reported that hemianopic patients are able to demonstrate immediate (online) effects of audio-visual integration, ability strictly depending on the functionality of the spared retino-colliculo-extrastriate pathway. In this view, both influences of an auditory stimulus on visual detection in the blind field (Frassinetti et al., 2005) and influences of visual stimuli presented in the blind field on auditory localization (Leo et al., 2008b) have been presented. Moreover, the existence in hemianopic patients of visual residual abilities for emotional stimuli in the blind field in absence of awareness (i.e. affective blindsight) has been examined in Experiment 3. The results revealed the presence of implicit recognition of the fearful content of unseen visual stimuli in a wide population of patients with visual field defect. Since affective blindsight is thought to be mediated by the retino-colliculo-extrastriate pathway and its connections with amygdala, as suggested by recent neuroimaging studies (Morris et al., 2001; Andino et al., 2009), this evidence provided further confirmation of the functional activity of this spared neural circuit. In order to exploit the sparing of the retino-colliculo-extrastriate pathway and to use cross-modal stimulation as a therapeutic tool for the recovery of unisensory defects, hemianopic patients should demonstrate not only immediate on-line behavioural effects of multisensory integration, but also off-line effects. In the fourth chapter, evidence of short term and long-term effects of multisensory integration on behavioural performances of hemianopic patients has been discussed. In a study investigating the effects of passive exposure to spatially coincident audio-visual stimuli, Passamonti and colleagues (Passamonti et al., 2009a) found a significant enhancement in auditory localization, demonstrating a perceptual learning due to a short-term effect of multisensory integration. On the other hand, long lasting effects of multisensory integration have been provided by the studies testing the efficacy of a systematic audio-visual training on hemianopic patients. Bolognini and colleagues (Bolognini et al., 2005b) submitted a group of hemianopic patients to an intensive audio-visual stimulation regimen, reporting, after the training, significant improvements in clinical signs and visual exploration deficits, due to the implementation of efficient oculomotor strategies. Moreover, in a subsequent study (Passamonti et al., 2009b), these effects were found to be stable up to one year after the training. These results demonstrated that a systematic audio-visual stimulation is effective in inducing long-lasting clinical improvements in patients with visual field defect. Moreover, experimental evidence reported in the fourth chapter (Experiment 4) revealed that the activity of the spared retino-colliculo-extrastriate pathway is responsible of the clinical amelioration observed after the audio-visual training, as suggested by the greater improvement of patients with cortical lesions limited to the occipital cortex, compared to patients with lesions extending to other cortical areas, observed in the tasks high demanding in terms of spatial orienting. In fact, the intensive multisensory stimulation of the retino-collicluo-extrastriate pathway might have affected orientation toward the blind field and modulated the processing of visual events, resulting in effective oculomotor compensation of the visual field defect.

In conclusion, in the present dissertation the relevance of the colliculo-extrastriate pathway in mediating multisensory orienting responses and the possibility of exploiting this pathway for sensory compensation, after damage to the geniculo-striate pathway, have been discussed. The results presented, overall, demonstrated that a multisensory training might reinforce the innate ability of our brain to perceive multisensory events, an ability normally hidden when unisensory processing of the sensory events is sufficient for their perception, and, therefore, might constitute an effective and innovative approach for the rehabilitation of unisensory visual impairments.

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Glossary

2AFC: two alternative forced choice.
A: modality-specific auditory stimuli (Experiment 1).
A-UNI: modality-specific auditory stimuli (Experiment 2).
AE: ventriloquism after effect.
AES, anterior ectosylvian sulcus.
AV: cross-modal audio-visual stimuli (Experiment 1 and 2).
CT: catch trial condition (Experiment 1).
cTBS: continuous theta-burst stimulation.
LGN: lateral geniculate nucleus.
LH: left hemianopia.
MEI: multisensory enhancement index.
N: nasal (Experiment 2).
OC: occipital cortex.
PPC: posterior parietal cortex.
PT: phosphene threshold.
rOC: right occipital cortex.
rPPC: right posterior parietal cortex.
rLS: rostral lateral suprasylvian sulcus.
RH: right hemianopia.
RTE: redundant target effect.
rTPC: right temporo-parietal cortex.
S1: session 1 – baseline evaluation (Experiment 4).
S2: session 2 – evaluation immediately after audio-visual training (Experiment 4).
S3: session 3 – evaluation one year after the audio-visual training (Experiment 4).
SC: superior colliculus.
SD-AV: spatially disparate audio-visual stimuli (Experiment 2).
SP-AV: spatially coincident audio-visual stimuli (Experiment 2).
STG: superior temporal gyrus.
STS: superior temporal sulcus.
T: temporal (Experiment 2).
TPC: temporo-parietal cortex.
TMS: transcranial magnetic stimulation.
V: modality-specific visual stimuli (Experiment 1).
VFD: visual field defect.
VV: within-modal double-visual stimuli (Experiment 1).