Audiovisual Integration in Patients with Visual Deficit

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Abstract

■ In the present study, we investigated the possibility that bimodal audiovisual stimulation of the affected hemifield can improve perception of the visual events in the blind hemifield of hemianopic patients, as it was previously demonstrated in neglect patients. Moreover, it has been shown that ''heteromodal'' and ''sensory-specific'' cortices are involved in cross-modal integration. Thus, the second aim of the present study was to examine whether audiovisual integration influences visual detection in patients with different cortical lesions responsible of different kinds of visual disorders. More specifically, we investigated cross-modal, audiovisual integration in patients with visual impairment due to a visual field deficit (e.g., hemianopia) or visuospatial attentional deficit (e.g., neglect) and patients with both hemianopia and neglect. Patients were asked to detect visual stimuli presented alone or in combination with auditory stimuli that could be spatially aligned or not with the visual ones. The results showed an enhancement of visual detection in cross-modal condition (spatially aligned condition) comparing to unimodal visual condition only in patients with hemianopia or neglect; by contrast, the multisensory integration did not occur when patients presented both deficits. These data suggest that patients with visual disorders can enormously benefit the multisensory integration. Moreover, they showed a different influence of cortical lesion on multisensory integration. Thus, the present results show the important adaptive meaning of multisensory integration and are very promising with respect to the possibility of recovery from visual and spatial impairments. ■

INTRODUCTION

Visual field defects are common consequences after posterior brain injury. Homonymous hemianopia is a visual field defect, resulting from unilateral postchiasmatic damage, which determines a loss of vision in the hemifield that corresponds retinotopically to the damaged area (Zihl & Kennard, 1996). Homonymous field disorders can be different according to the extension of the blind region and to the gravity of the disorder. In hemianopia, there is a loss of vision in one hemifield; in quadrantopia, the deficit regards only one quadrant of the contralesional hemifield (upper or lower quadrantopia); and in the paracentral scotoma, there is a loss of vision in the parafoveal field region. Concerning the quality of the disorder, hemianopic patients can exhibit complete and persistent cortical blindness or a relative defect, in which the patients can exhibit residual conscious vision due to the island of relative impaired or amblyopic zones.

Furthermore, hemianopic patients can show ''blind'' visual functions, as neuroendocrine responses, reflexive responses, and behavioral responses to not consciously perceived stimuli, the so-called blindsight phenomena (Stoering & Cowey, 1997). In previous findings, two methodologically distinct classes of visual responses have been demonstrated: the implicit responses and the direct (or explicit) responses. In the implicit response, there is the implicit processing of a visual stimulus in the blind field, which affects the response to a second stimulus presented in the normal field. In contrast, the direct responses represent the highest level of visual function after striate cortical damage in the absence of conscious perception and require to directly respond to stimuli presented in the scotoma (Stoering & Cowey, 1997; Stoering, 1996; Weiskrantz, 1986). Investigation of direct response commonly uses forced-choice methods, in which the patients are asked to guess whether a visual stimulus has been presented in the blind area. Using this method, it has been demonstrated that hemianopic patients can retain some visual abilities such as localization of visual targets in the impaired field when asked to perform saccadic eye movement or pointing response (Stoering & Cowey, 1997). Moreover, Schendel and Robertson (2004) have recently found in a hemianopic patient an amelioration of explicit visual detection when the patient's left hand was located in the ''blind hemifield.''

Neurophysiological and neuropsychological studies have suggested that blindsight could be mediated by the spared striate cortex as well as by the extrastriate visual cortex and by neural pathways involving subcortical nuclei such as the superior colliculus (SC), the

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lateral geniculate nucleus, and the pulvinar (Ro, Shelton, Lee, & Chang, 2004; Nelles et al., 2002; Schonfeld et al., 2002; Rausch, Widdig, Eysel, Penner, & Tegenthoff, 2000; Azzopardi & Cowey, 1998; Stoering & Cowey, 1997; Mohler & Wurtz, 1977).

Some of the structures mediating the blindsight phenomena, such as the SC, are ''heteromodal'' areas; they receive converging projections from different senses and contain multisensory neurons. As a consequence, it seems possible that the interaction between different sensory inputs occurring within the SC can affect the unimodal processing of visual information in the blind hemifield. Multisensory neurons form a major component of the output circuitry of the SC; nearly three-quarters of the SC's neurons with descending efferent projections to the brainstem motor areas are multisensory. Consequently, multisensory integration might play a significant role in behaviors mediated by the SC, as the attentive and orientation behaviors (Stein, 1998). Recent studies in normal subjects (Bolognini, Frassinetti, Serino, & Làdavas, 2005; Frassinetti, Bolognini, & Làdavas, 2002) and in neglect patients (Frassinetti, Pavani, & Làdavas, 2002) have provided evidence that audiovisual interaction in multisensory neurons can modulate human behavior by enhancing visual processing of below-threshold stimuli and of neglected stimuli.

Thus, in the present study, we investigated the possibility that bimodal audiovisual stimulation of the hemianopic hemifield can improve perception of the visual events in the blind hemifield of hemianopic patients. The expectation of an enhancement of visual processing is also based on an important and adaptive property of multisensory integration: The auditory input might enhance the multisensory response to unseen visual inputs because multisensory interaction is modulated by the efficacy of the unimodal 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 (the so-called inverse effectiveness rule). In animal studies, the effectiveness of the unimodal signals has been shown to be a major determinant of the advantage resulting from multisensory integration (Stein & Meredith, 1993).

In addition to the inverse effectiveness rule, multisensory integration in SC neurons is also governed by spatial and the temporal rules (Stein & Meredith, 1993).

The spatial rule depends on the spatial organization of multisensory neurons' receptive fields. Indeed, each multisensory SC neuron has multiple receptive fields, one for each modality to which it is responsive, which are in spatial register with one another. Consequently, visual and auditory inputs originating from the same event, and thus from the same location, can fall within the receptive fields of a given multisensory neuron. The responses elicited by this combination of stimuli are likely to be significantly greater than those induced by either stimulus alone and can exceed the sum of the neuron's modality-specific responses (Wallace, Meredith, & Stein, 1998; Wallace, Wilkinson & Stein, 1996; Meredith & Stein, 1986a, 1986b). However, when stimuli originate from different events, and thus from different locations (i.e., the stimuli are spatially disparate), and the visual stimulus falls within a neuron's receptive field, but the auditory stimulus falls outside its receptive field, the auditory stimulus will either have no effect on the neuron's response, or will depress responses to the visual stimulus (Kadunce, Vaughan, Wallace, Benedek, & Stein, 1997). These observations indicate that enhancement and depression are dynamic properties that depend on the relative spatial relationships between stimuli and the receptive fields of the neuron (''spatial rule'').

Another critical factor influencing multisensory integration in the SC is the temporal disparity among combinations of different sensory stimuli. Maximal level of response enhancement is generated by overlapping the peak discharge periods evoked by each modality and the magnitude of this enhancement decays monotonically to zero as the peak discharge periods become progressively more segregated in time. Moreover, by increasing the temporal disparity, the same stimulus combinations that previously produced enhancement can often produce depression (''temporal rule'') (Meredith, Nemitz, & Stein, 1987).

Thus, the first aim of the present study was to investigate the possibility that bimodal audiovisual stimulation of the hemianopic hemifield can improve perception of the visual events in the blind hemifield of hemianopic patients, in accordance with the rules governing multisensory integration at neuronal level in the SC.

As far as the cerebral structures involved in cross-modal integration are concerned, recent studies suggest that, although a characteristic property of many SC neurons is their ability to integrate information from different sensory modalities (Stein & Meredith, 1993), the capability to synthesize cross-modal inputs, and thereby produce an enhanced multisensory response, requires functional inputs from the cortex. The possible role of the cortex in multisensory integration has been demonstrated by neurophysiological (Jiang, Wallace, Jiang, Vaughan, & Stein, 2001) and behavioral studies (Jiang, Jiang, & Stein, 2002; Wilkinson, Meredith, & Stein, 1996) in animals. These data, in accordance with those found in humans by using functional magnetic resonance imaging (fMRI) and electrophysiological techniques, show the role of subcortical (SC) and cortical structures in the synthesis of cross-modal cues (Calvert, Hansen, Iversen, & Brammer, 2001; Calvert, Campbell, & Brammer, 2000; Calvert, Brammer, et al., 1999; Giard & Peronnet, 1999). These studies have demonstrated that ''heteromodal'' areas, namely, fronto-temporal areas (Giard & Peronnet, 1999), and a network of brain areas, including the insula, the claustrum, the superior temporal sulcus, the intraparietal sulcus, and several frontal regions (Calvert, Hansen, et al., 2001), as well as ''sensory-specific'' visual and auditory cortices (Calvert, Brammer, et al., 1999; Giard & Peronnet, 1999), are involved in cross-modal integration.

Thus, the second aim of the present study was to examine whether audiovisual integration influences visual detection in patients with different cortical lesions responsible for different kinds of visual disorders. More specifically, we investigated cross-modal, audiovisual integration in patients with visual impairment due to a visual field deficit (e.g., hemianopia) or visuospatial attentional deficit (e.g., neglect), that is, patients who usually fail to report, respond, or orient to visual stimuli presented contralaterally to the lesioned hemisphere (Halligan, Fink, Marshall, & Vallar, 2003) and patients with both hemianopia and neglect. Patients with hemianopia usually present with a lesion in the visual areas, whereas patients with neglect without hemianopia present with a lesion in the fronto-temporo-parietal areas. To this aim, three subgroups of patients were selected for this study: patients with neglect (N+H−), patients with hemianopia (N−H+), and patients with neglect and hemianopia (N+H+).

To examine whether audiovisual interaction can affect visual processing in hemianopia and neglect, detections of visual stimuli presented in the impaired field were studied under two different conditions: the unimodal visual condition, in which only the visual target was present, and the cross-modal conditions, in which an auditory stimulus was presented simultaneous to the visual target. Visual targets had a duration of 100 msec and could appear in different spatial locations, at 8°, 24°, 40°, 56° to either sides of the central fixation point. The patients were instructed to ignore the auditory cue, which was not predictive of the visual location, and to indicate the presence of the visual target by pressing a button. Furthermore, to assess if the improvement of visual detection in the cross-modal conditions was mediated by a multisensory mechanism, the spatial disparity between the visual and the auditory stimuli was systematically varied. The response activity of the multisensory neurons is modulated by the spatial arrangement of the bimodal stimulation, as only stimuli from different sensory modalities presented in the same position or in close spatial proximity interact, producing multisensory response enhancement, whereas spatially disparate stimuli produce depression or no change in neuronal multisensory activity (Stein & Meredith, 1993). To test the spatial specificity of multisensory integration, in the cross-modal conditions the sound was presented at the same spatial position as the visual stimulus or at one of the remaining seven spatial positions. Moreover, as predicted by the ''inverse effectiveness rule,'' the spatially specific improvement in cross-modal, audiovisual conditions should be greater when visual detection in unimodal visual condition is more impaired.

RESULTS

To investigate the influence of audiovisual interaction on a visual impairment due to a visuospatial attentional deficit (e.g., neglect) or to a visual field deficit (e.g., hemianopia), it is necessary to compare the number of visual detections made in unimodal condition to those made in cross-modal conditions in patients with neglect (N+H−), with hemianopia (N−H+), and with both neglect and hemianopia (N+H+). To this aim, statistical analyses were conducted on the patients' correct performance in responding to the three most peripheral locations in the LVF, where neglect patients' performance was impaired. Moreover, for each patient with hemianopia, only impaired visual locations in the hemianopic hemifield, LVF or RVF, were considered for the analysis. Because patients' performance was errorless for visual stimuli presented in the intact hemifield or in the spared regions of the affected hemifield, the results for the corresponding visual positions were not analyzed. We refer to visual positions in the neglected and in the blind hemifield as V1 (56° from the central fixation point), V2 (40°), and V3 (24°), independent of the hemifield affected by the brain damage (right or left).

To reduce the number of comparisons, mean percentages of correct responses in each spatial position (V1, V2, and V3) were collapsed. Two-way analyses of variance (ANOVAs), one for nasal and one for temporal positions, were carried out on mean percentage of correct responses and converted in arcsine values. As far as nasal positions are concerned, only trials in V1 and V2 were considered for the analysis, because they are the only visual positions in which the acoustic stimulus could be presented at 16° and 32° of nasal disparity in the same hemifield of the visual stimulus. In other words, V3 was not considered for this analysis because at 32° of nasal disparity the acoustic stimulus was presented in the opposite visual field.

One between-group (N+H−, N−H+, and N+H+) ANOVA was conducted with Condition as the main factor: unimodal condition, in which only a visual stimulus was presented in V1 and V2, and cross-modal conditions, in which an auditory stimulus was presented either in the same position of the visual one (i.e., the spatially coincident cross-modal condition), or at 16° or 32° of *nasal* disparity from the visual stimulus (i.e., spatially disparate conditions).

As far as temporal positions are concerned, one-way ANOVA was conducted similarly to the previous one with the exception that only trials in V2 and V3 were considered for the analysis as they are the only visual positions in which the acoustic stimulus could be presented at 16° of *temporal* disparity from the visual stimulus. In this respect, V1 could not be analyzed because of the lack of a condition in which the acoustic stimulus could be presented at 16° of temporal disparity. Thirty-two degrees of temporal spatial disparity was not considered because this position was present only for V3.

Whenever necessary, pairwise comparisons were conducted using the Scheffé test. The level of significance was always set at $p <. 05$.

Nasal Positions

The ANOVA revealed a significant effect of Group [$F(2,18) = 16.26$, $p < .00009$]: neglect patients with hemianopia (N+H+ = 1%) were less accurate than neglect patients without hemianopia (N+H− = 34%, $p < .0001$) and patients with only hemianopia (N−H+ = 22%, $p < .007$). The last two groups were not significantly different ($p = .17$). Condition was also significant [$F(3,54) = 12.92$, $p < .000002$]: compared to unimodal visual condition (10%), detection accuracy increased in cross-modal conditions when the two stimuli were presented in the same position (29%, $p < .000003$), but not when stimuli were presented at a disparity of 16° (19%, $p = .15$) or 32° (18%, $p = .37$). Moreover, detection accuracy increased in spatially coincident cross-modal condition comparing to spatially disparate conditions ($p < .006$ and $p < .001$, at 16° and 32°, respectively).

Interestingly, the interaction Group × Condition was significant [$F(6,54) = 9.71$, $p < .0000001$]. In neglect patients without hemianopia, detection accuracy (18%) increased by presenting an auditory stimulus in the same spatial position (49%, $p < .001$). In contrast, no beneficial effect was observed when the two stimuli were presented at a disparity of 16° and 32° (36%, $p = .22$ and 34%, $p = .39$, respectively). Also in hemianopic patients without neglect, detection accuracy (9%) increased when audiovisual stimuli were presented in the same spatial position (36%, $p < .0002$), but not when the two stimuli were presented at a disparity of 16° and 32° (22%, $p = .52$ and 20%, $p = .73$, respectively). In contrast, in patients with both neglect and hemianopia, visual detection accuracy (4%) did not significantly improve in cross-modal conditions when an auditory stimulus was presented in the same spatial position (1%, $p = .88$) or at a disparity of 16° and 32° (0% and 0%, $p = .62$ in both comparisons) (see Figure 1A).

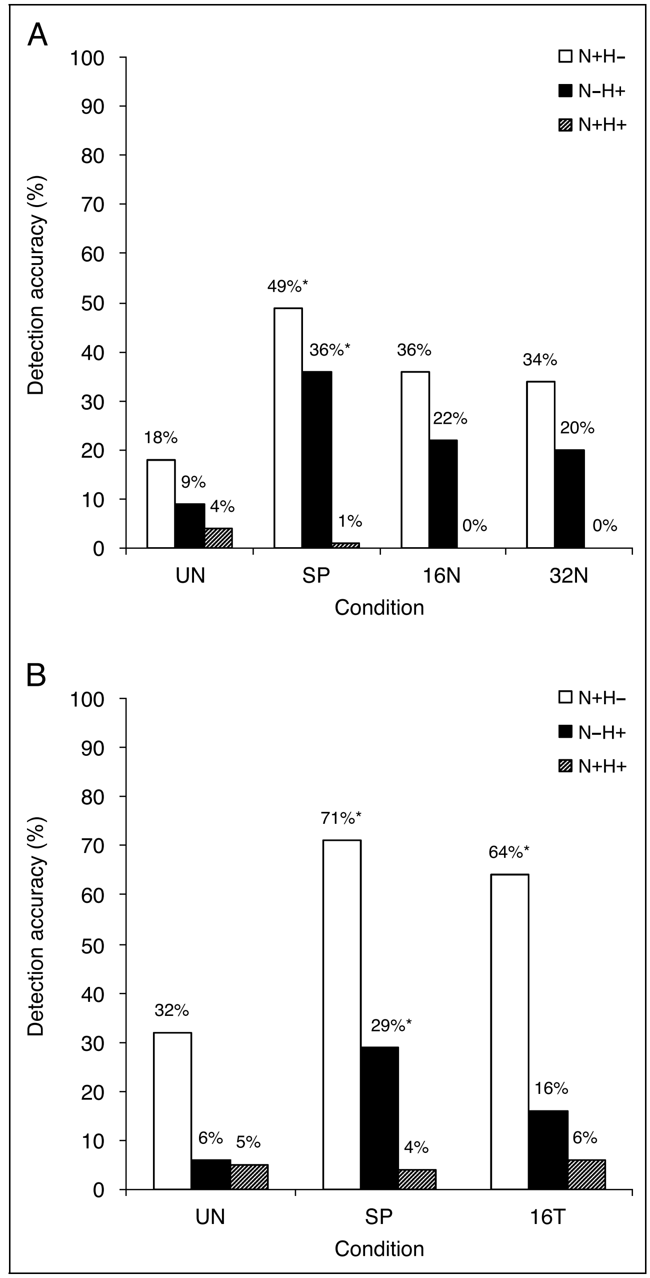

Figure 1. Mean percentage of correct visual detection in neglect patients without hemianopia (N+H−), in hemianopic patients without neglect (N−H+), and in neglect patients with hemianopia (N+H+), for unimodal visual condition and cross-modal visual–auditory conditions in which an auditory stimulus was presented either in the same position (SP) or in a *nasal* position at 16° or 32° (16N and 32N) from the visual stimulus (A) or in a *temporal* position at 16° (16T) from the visual stimulus (B); asterisks (*) indicate significant pairwise comparisons between unimodal and cross-modal conditions.

Temporal Positions

One hemianopic patient, included in the previous analysis, was excluded by the present analysis because she presented a visual deficit only in V1 (the most peripheral spatial position). The ANOVA revealed a significant effect of Group [$F(2,17) = 24.63$, $p < .00001$]: hemianopic patients (N−H+ = 17%) and neglect patients with hemianopia (N+H+ = 5%) were less accurate than neglect patients without hemianopia (N+H− = 56%, $p < .0008$ and $p < .00001$, respectively). No significant differences were found between the first two groups

(p = .22). Condition was significant [$F(2,34) = 19.41$, $p < .000002$]: comparing to unimodal visual condition (14%), detection accuracy increased in cross-modal conditions both when the two stimuli were spatially coincident (35%, $p < .000004$) and were presented at a disparity of 16° (28%, $p < .0006$). No difference was found between the two cross-modal conditions (p = .23).

The interaction Group × Condition was also significant [$F(4,34) = 6.70$, $p < .0004$]. In neglect patients without hemianopia, visual detection accuracy (32%) increased by presenting an auditory stimulus in the same spatial position (71%, $p < .001$) or at a spatial disparity of 16° (64%, $p < .005$). In hemianopic patients without neglect, visual detection accuracy (6%) significantly improved when audiovisual stimuli were presented in the same spatial position (29%, $p < .02$), but not at spatial disparity of 16° (16%, $p = .86$). Finally, in patients with both neglect and hemianopia, visual detection accuracy (5%) did not significantly improve in cross-modal conditions when an auditory stimulus was presented in the same or in a different position (4% and 6%, $p = 1.0$ in both comparisons) (see Figure 1B).

Inverse Effectiveness Rule

To verify whether minor visual detection accuracy in unimodal condition is associated with greater levels of multisensory enhancement (i.e., inverse effectiveness), a Pearson correlation analysis was conducted in patients who showed cross-modal effects (i.e., N+H− and N−H+) between the percentage of correct responses in unimodal visual condition and the magnitude of multisensory enhancement. Multisensory enhancement was calculated using the formula adapted from Meredith and Stein (1983).

$$[(\mathrm{CM} - \mathrm{SM}_{\max})/\mathrm{SM}_{\max}] \times 100$$

where CM is the mean percentage of correct responses in cross-modal condition when the acoustic stimulus was presented in the same position of the visual stimulus and $\mathrm{SM}_{\max}$ is the mean percentage of correct responses in unimodal visual condition. A negative correlation was found between the percentage of correct responses in unimodal visual condition and the magnitude of multisensory enhancement ($r = -0.72, p < .02$). This means that the less effective the unimodal visual stimuli, the bigger the magnitude of the enhancement audiovisual stimuli generate in combination.

Anatomical Correlates of Audiovisual Integration

Taken together, these results showed cross-modal effects in neglect patients without hemianopia and in hemianopic patients without neglect, but not in neglect patients with hemianopia. A possible explanation of these data is that the integrative multisensory effect depends on the extension and/or on the localization of the lesion.

To verify whether the characteristics of the lesion influence the integrative effects, the lesion of each patient was reconstructed and areas involved by lesion were coded using the method introduced by Damasio and Damasio (1989) (see Figure 2 and Table 1).

To assess whether lesion extension influences cross-modal effects, a Pearson correlation analysis was conducted between the number of cortical areas involved by

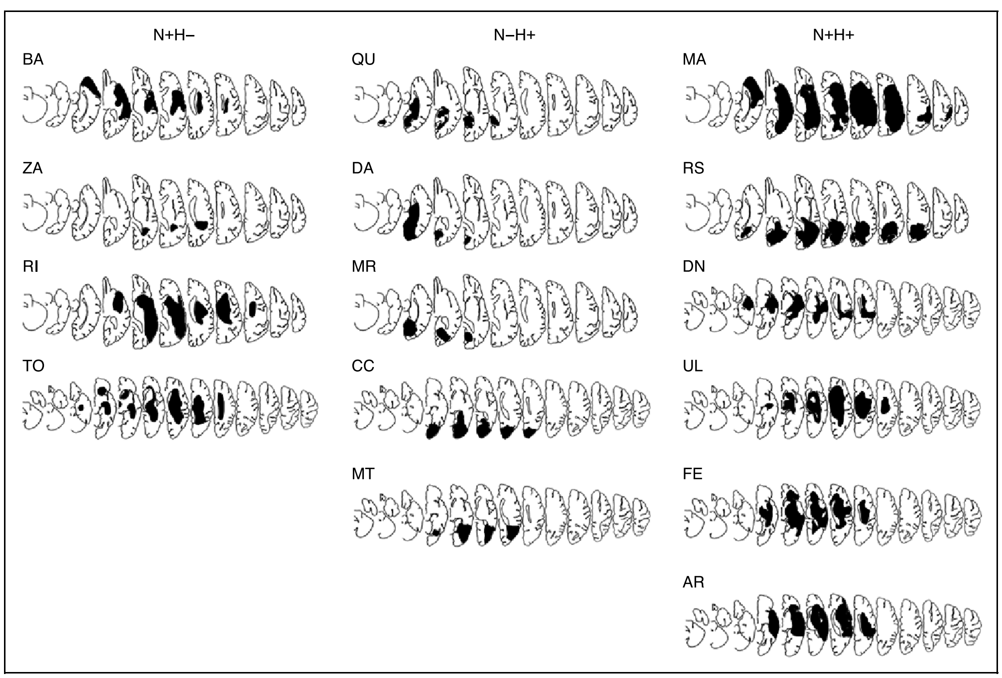

Figure 2. Individual maps in neglect patients without hemianopia (N+H−), in hemianopic patients without neglect (N−H+), and in neglect patients with hemianopia (N+H+). Templates were taken from Damasio and Damasio (1989).

Table 1. Summary of Lesion Data for Neglect Patients without Hemianopia (N+H−), Hemianopic Patients without Neglect (N−H+), and Neglect Patients with Hemianopia (N+H+)

Group	*Patient*	*F1*	*F2*	*F6*	*F7*	*F8*	*F9*	*F10*	*F14*	*T1*	*T3*	*T4*	*T6*	*T7*	*T8*	*T9*	*T10*	*T11*	*T12*	*P1*	*P2*	*P3*	*P4*	*P5*	*P6*	*O1*	*O2*	*O3*	*O4*	*O5*	*O6*	*O7*	*BG1,2*	*BG3,4*	*IC*	*TH*
N+H−	BA					x	x	x			x	x		x	x	x			x						x						x					
N+H−	ZA					x						x				x				x				x							x					
N+H−	RI	x	x			x	x	x			x	x		x	x	x				x	x			x	x					x	x			x	x	
N+H−	TO	x	x	x			x	x	x		x			x	x	x	x							x	x						x	x	x	x	x	x
N+H−	AR			x		x	x		x		x		x	x	x	x		x		x				x							x			x	x	
N−H+	QU		x														x	x								x	x	x			x	x				
N−H+	DA																x	x								x	x	x	x							
N−H+	MR																									x	x	x	x			x				
N−H+	CC																	x								x	x	x	x	x	x	x				
N−H+	MT												x													x		x	x	x	x	x				
N+H+	MA	x	x	x	x	x	x	x			x	x	x	x	x	x			x	x	x	x		x	x				x	x	x					
N+H+	RS		x									x				x				x	x		x	x	x	x	x	x	x	x	x	x				
N+H+	DN						x			x	x			x	x	x		x		x				x				x			x	x		x		
N+H+	UL	x	x			x	x	x			x		x	x	x	x				x				x	x						x	x	x	x	x	x
N+H+	FE	x		x	x	x	x		x		x		x	x	x	x	x	x						x				x			x	x	x	x	x	

Anatomical areas involved (x) by lesion are represented with the coding system of Damasio and Damasio (1989).

the lesion and the magnitude of multisensory enhancement. A negative correlation was found between the number of cortical areas involved by lesion and the magnitude of multisensory enhancement ($r = -.78$, $p < .004$). This means that the smaller the lesion, the bigger the magnitude of the enhancement audiovisual stimuli generate in combination. Thus, lesion extension seems to play a role in cross-modal integration. However, because the size of the lesion was calculated on the number of damaged cortical areas, it is interesting to verify the localization of damaged areas in patients who integrated versus patients who did not integrate.

As shown by Figure 2 and Table 1, neglect patients' lesion is mainly confined to the fronto-temporal and parietal lobe, and hemianopic patients' lesion is mainly confined to the occipital lobe, whereas in neglect patients with hemianopia, lesion could involve both fronto-temporo-parietal areas and occipital areas. Thus, it seems that the damage of both networks, one involved in the visuospatial attentional system (i.e., frontal, temporal, and parietal areas) and the other involved in the primary sensory visual system (i.e., occipital areas), prevents audiovisual integration.

Finally, the two characteristics of lesion (extension and localization) were considered together, comparing the average of damaged areas for each lobe in neglect patients with and without hemianopia. These data (see Table 1) showed that, not only neglect patients with hemianopia have far more lesioned occipital areas than neglect patients without hemianopia (3.17 vs. 1.5), they also have, on average, more lesioned areas in the frontal (4 vs. 3.75), temporal (5.5 vs. 4.5), parietal (3 vs. 2.25), and subcortical (1.67 vs. 1.5) structures. So, the greater lesion size across the whole brain in neglect patients with hemianopia might also contribute to the lack of cross-modal integration in addition to what is likely the major contributor, which is the occipital lobe.

DISCUSSION

The results of the present study highlight the importance of audiovisual interaction in inducing perception of visual stimuli presented in the impaired hemifield of hemianopic and neglect patients. These results confirm previous data in neglect patients without hemianopia (Frassinetti, Pavani, et al., 2002) and, more interestingly, extend these findings to patients with hemianopia.

Indeed, this is the first demonstration of visual awareness due to an auditory modulation of visual processing in the blind area of hemianopic patients: The acoustic modality affected the damaged visual modality, thus inducing an improvement of vision in the hemianopic hemifield. Thus, associating a sound to the visual stimulation, the patients' ability to consciously perceive the presence of the visual stimuli in the blind field increased.

The second interesting finding of the present study was the characteristic of the enhanced behavioral performance: The sound improved the detection of the visual target only when it was presented in the same spatial position as the visual target, but not when there was a spatial disparity between the stimuli (i.e., 16° and 32°). A possible explanation for these effects can be found by considering the functional characteristics of multisensory neurons in the SC. In the SC, only stimuli from different sensory modalities spatially coincident or at close spatial proximity interact, producing an enhancement of the multisensory response, whereas with spatially disparate stimuli, the integration of the visual and auditory information cannot take place. In the spatially disparate conditions, the increment of correct responses found in the present study in both neglect patients without hemianopia and in hemianopic patients without neglect was very little and never significant. This effect can be easily explained with a generalized arousal phenomenon: The presence of two stimuli, instead of one, might have produced greater activity throughout the brain by increasing neural sensitivity to any and all stimuli (see Robertson, Mattingley, Rorden, & Driver, 1998). This general arousal phenomenon was not observed in neglect patients with hemianopia. A possible explanation of the lack of this effect is that the simultaneous presence of a sensory deficit (hemianopia) and of a general attentional deficit (Husain & Rorden, 2003; Robertson, 2001) prevents the effect of the auditory cue. Thus, a general sound can produce a little amelioration of visual detection when the deficit is due to a sensory or attentional impairment, such as in hemianopic and in neglect patients, but not when it is due to the impairment of both functions, such as in neglect patients with hemianopia. Although such a principle might have played a role in our study, it is important to note that it cannot explain solely the pattern of results, mainly the large and significant effects found when the two stimuli were presented on the same spatial positions.

In neglect patients without hemianopia, a significant improvement was also found when the auditory stimulus was presented at 16° of disparity in a temporal position. This finding can be explained with the characteristic of multisensory neurons' receptive fields. Indeed, auditory receptive fields that are larger than visual receptive fields (Jay & Sparks, 1987; King & Hutchings, 1987; Middlebrooks & Knudsen, 1984; King & Palmer, 1983; Knudsen, 1982) are rarely symmetric, that is, their temporal borders often extend more into the peripheral space than the medial borders (Stein & Meredith, 1993). It is worth noting that hemianopic patients did not show integrative effects in cross-modal conditions at 16° of disparity in a temporal position. The influence of the auditory stimulus to visual stimuli located at a disparity of 16° was also previously found in neglect patients without hemianopia (Frassinetti, Pavani, et al., 2002) when visual stimuli were presented below threshold. Thus, it seems that when vision is impaired or visual stimuli are degraded, the cross-modal effects occur only in the case of specific spatial correspondence between audiovisual stimuli, whereas when there is an attentional deficit, the size of area where the cross-modal integration occurs is larger.

Another interesting finding of the present study is the correlation between multisensory integration and unimodal visual impairment. Patients showed an increase of multisensory enhancement as unimodal visual stimulus detection decreased, as pointed out by the negative correlation found between patients' performance in unimodal visual condition and the magnitude of multisensory enhancement, calculated on the difference between the cross-modal, spatially aligned condition and the unimodal condition. In other words, the improvement observed in cross-modal, spatially aligned condition was bigger when the visual stimuli in the unimodal condition were less effective. This behavioral feature of cross-modal processing in humans appears to have parallels in the electrophysiological response properties of multisensory cells in the SC of nonhuman mammals (i.e., the inverse effectiveness role). Indeed, visually responsive multisensory neurons in the SC show proportionately greater response enhancement with progressively less effective (e.g., lower intensity) stimuli (Kadunce, Wallace, Benedek, & Stein, 1994; Stein & Meredith, 1993). This makes intuitive sense because potent unimodal stimuli need no enhancement to be effective.

After the demonstration of the effect of cross-modal integration on visual unimodal impairment, it is worthwhile to make a few considerations on possible mechanisms underlying such effects, mainly in relation to the improvement of visual detection in patients with hemianopia, that is the novel finding of the present study.

Some patients with lesions of the primary visual (striate) cortex (V1) demonstrate residual visual capacity but without acknowledged perceptual awareness. This phenomenon, named blindsight, reveals that retinal pathways, other than those to the striate cortex, are crucially involved in vision. It has been suggested that the extrageniculate visual pathway from the retina to the SC, which is involved with visual coding and with the generation of saccadic eye movements, may be responsible for this blindsight phenomenon (Ro et al., 2004; Rafal, Smith, Krantz, Cohen, & Brennan, 1990). A similar mechanism could be responsible for visual detection in patients with hemianopia. More precisely, audiovisual, spatially coincident stimuli can activate the SC, which is involved in audiovisual integration and may mediate visual processes.

However, it is important to note a relevant difference between blindsight phenomenon and visual detection in hemianopic patients found in the present study. Indeed, blindsight is an example of "implicit processing" in the absence of explicit knowledge (for reviews, see Stoering & Cowey, 1997; Weiskrantz, 1996). By contrast, here hemianopic patients explicitly detected visual stimuli, thus being *aware* of their presentation in a significant number of trials. Thus, the characteristic of their visual responses suggests another interpretation of the present findings. Being aware of visual stimuli, their responses probably are mediated by cortical areas. These cortical areas might be multimodal areas. In this respect, it has been demonstrated that "polysensory" (Calvert, Hansen, et al., 2001; Calvert, Campbell, et al., 2000; Giard & Peronnet, 1999) and "sensory-specific" cortices (Calvert, Brammer, et al., 1999; Giard & Peronnet, 1999) are involved in cross-modal integration.

One way to verify the role of the SC in cross-modal integration is to use different kinds of visual stimuli. Indeed, it has been shown that visual pathways originating from short-wave sensitive cones (i.e., purple color) do not send or send very few afferents to the SC (Sumner, Adamjee, & Mollon, 2002). As a consequence, if the hypothesis that the SC mediates cross-modal integration is correct, we should not obtain cross-modal effects in hemianopic patients when using purple stimuli as the SC does not receive S-cones input. By contrast, if the spared cortex mediates cross-modal effects in patients with visual field deficit, we should observe these effects also when using purple stimuli.

Finally, the last finding of the present study shows that neglect patients with hemianopia did not show an improvement in cross-modal as compared to unimodal visual condition, independent of the spatial relationship between auditory and visual stimuli. A possible explanation for the lack of audiovisual integration in neglect patients with hemianopia is that the simultaneous impairment of areas involved in visual spatial attention and primary sensory visual processing prevents cross-modal integration, probably due to the influence of these cortical areas on the SC. Indeed, it is possible that the ability of the SC to synthesize cross-modal inputs is modulated by cortical influences (Stein, Laurienti, Wallace, & Stanford, 2003; Jiang, Wallace, et al., 2001; Wilkinson et al., 1996). Alternatively, if we accept the other interpretation (i.e., multisensory cortical neurons might be directly involved in cross-modal integration), then we can hypothesize that the simultaneous damage of "polysensory cortices," involved in spatial attention, and of "sensory-specific" cortices, involved in visual processing, prevents audiovisual integration in neglect patients with hemianopia. Indeed, a negative correlation was found between the number of damaged areas and the magnitude of multisensory enhancement. When the lesion is mainly confined to the fronto-temporo-parietal areas (neglect patients) or to the occipital areas (hemianopic patients), the visual and auditory stimuli were integrated, whereas when the lesion involved all the previous lobes, although in different measures, stimuli were not integrated (neglect patients with hemianopia).

In conclusion, the results of the present study underline the relevance of cross-modal integration in enhancing visual processing in neglect patients and in patients with visual field deficits. The possibility of a sound improving the detection of the visual stimuli is very promising with respect to the possibility to take advantage of the brain's multisensory capabilities for a rehabilitation approach of visual attention deficit and of visual field defect. Based on the results of the present study, multisensory integration might offer a unique approach for the stimulation of the SC, which is frequently spared in lesions causing neglect and hemianopia. A systematic bimodal stimulation, affecting orientation towards the blind hemifield and modulating the processing of visual events, can improve visual exploration, perhaps with long-lasting effects. A cross-modal training might reinforce the innate ability of our brain to perceive multisensory events, hidden in the normal condition in which the unimodal process of the sensory events is sufficient for their perception.

METHODS

Subjects

Twenty-one brain-damaged patients were recruited from different hospitals. They were naïve as to the purpose of the experiment and they gave informed consent to participate in the study according to the Declaration of Helsinki (BMJ 1991;302:1194) and the Ethical Committee.

Patients were divided into three groups with the following characteristics:

(a) Neglect patients without hemianopia (N+H−): 7 patients, 4 men and 3 women, with a mean age of 70 years.
(b) Patients with only hemianopia (N−H+): 7 patients, 3 men and 4 women, with a mean age of 46 years.
(c) Neglect patients with hemianopia (N+H+): 7 patients, 5 men and 2 women, with a mean age of 67 years.

Patients were fully oriented in time and space and were right handed. The presence of visual neglect was assessed by using a battery of clinical tests: letter cancellation, bell cancellation (Gauthier, Dehaut, & Joanette, 1989), and line bisection. In each test, the severity of neglect in the two groups of neglect patients (N+H− and N+H+) was comparable (p = .89, .38, .59 for letter cancellation, bell cancellation, and line bisection, respectively). Visual field cuts were examined by means of Goldmann perimetry. All patients showed a normal hearing threshold as measured by audiometry test in each ear, with no sign of asymmetry between ears. Moreover, patients always detected auditory stimuli regardless of their spatial position.

Apparatus

The apparatus consisted of eight piezoelectric loudspeakers (0.4 W, 8 Ω), arranged horizontally at the subject's ear level. Loudspeakers were mounted on a vertical plastic support (height 30 cm, length 150 cm) that was held in place by four wooden stands fixed to the table surface and arranged in semicircle. Each loudspeaker was located at an eccentricity of 8°, 24°, 40°, and 56° from a central fixation point, in either hemifields. A strip of black fabric attached to the plastic grid was used to conceal the loudspeakers preventing any visual cues about their position. Eight LEDs were visible, poking out from the black fabric. Each LED was placed directly in front of each loudspeaker (see Figure 3).

Auditory stimuli presented through loudspeakers were white-noise bursts, lasting 100 msec. Visual stimuli presented by means of LEDs (luminance 80 cd m^{-2})

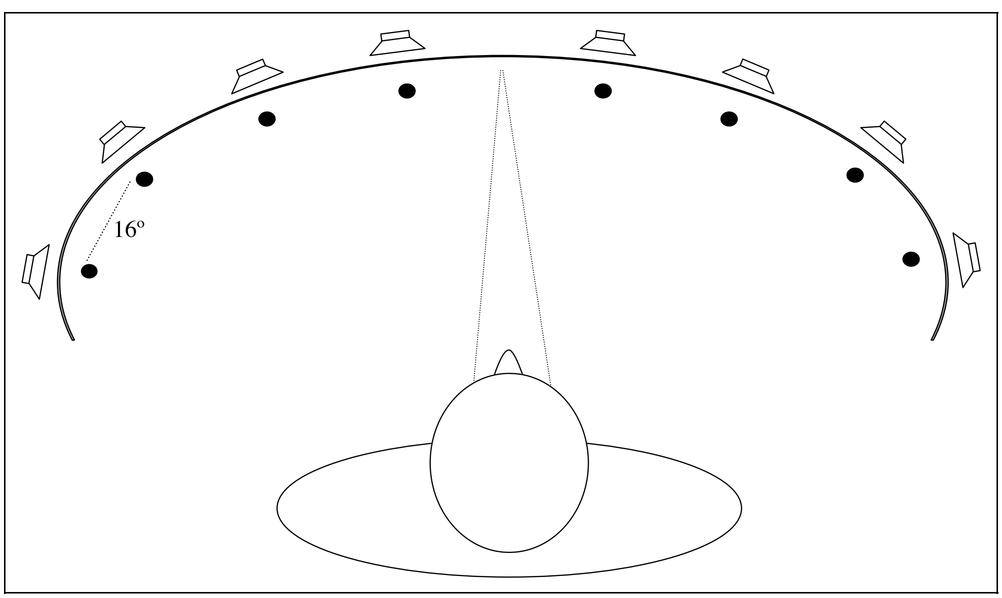

Figure 3. Bird's eye schematic view of the position of light displays (black circles) and loudspeakers (trapezoids).

were single flash, lasting 100 msec. Timing of stimuli and responses was controlled by an ACER 711TE laptop computer using a custom program (XGen Experimental Software, www.psychology.nottingham.ac.uk/staff/cr1/) and a custom hardware interface.

Procedure

Patients sat in a dimly lit room, approximately 70 cm in front of the semicircular display, with their body-midline aligned with its center. They were instructed to keep their head straight and fixate a small yellow triangle (1°), located in the center of the display, throughout the entire experiment. One experimenter who stood behind the apparatus facing the patient checked fixation visually. The experimenter started a trial only when the correct head posture and eye position were achieved.

In each trial, three different combinations of visual and auditory stimuli could be presented: (1) a single visual stimulus (unimodal visual condition), (2) a single auditory stimulus (unimodal auditory condition, i.e., catch trials), and (3) a visual stimulus and an auditory stimulus presented simultaneously (cross-modal condition). In cross-modal conditions, for each visual position the auditory stimulus could be presented either in the same location as the visual target or in one of the remaining seven positions. The auditory and the visual stimuli were simultaneously presented.

For each spatial position, there were the following types of trials: 8 unimodal visual trials, 64 cross-modal trials (8 trials for each of the 8 auditory stimulus positions), and 24 unimodal auditory catch trials. The total number of trials (768 trials, i.e., 96 trials for each of the 8 positions) was equally distributed in 16 experimental blocks (48 trials each) given in a random order and run in two sessions. Each session lasted approximately 2 hr and was run on two consecutive days.

Patients were instructed to verbally detect the presence of visual stimuli (light) and ignore auditory stimuli. Patients who erroneously responded to auditory stimuli for more than 10% of trials were excluded from the investigation. Patients considered in the present study almost never responded to the auditory stimuli, also when they were presented in the impaired space (3%, 2%, and 0% for N+H−, N−H+, and N+H+, respectively).

Anatomical Correlates of Audiovisual Integration

To better investigate the anatomical correlates of audiovisual integration and to address the question of what areas critically contribute to cross-modal integration, the cerebral lesion of 15 out of the 21 patients investigated (4N+H−, 5N−H+, 6N+H+) were available and were reconstructed using the method introduced by Damasio and Damasio (1989) (see Figure 2). Therefore, lesion location of each patient was coded using the 41 regions adopted from template A18 or A20 (depending on slice angle) of Damasio and Damasio (see Table 1). Subcortical regions (internal capsule, thalamus, and basal ganglia) not appearing in the template were also coded (see Buxbaum et al., 2004).

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