Alma Mater Studiorum – Università di Bologna
University College London

DOTTORATO DI RICERCA IN

Cognitive Neuroscience

Ciclo XXV
Settore Concorsuale di afferenza: AREA 11
Settore scientifico-disciplinare: M-PSI/02

Residual visual processing following real or virtual lesions to primary visual pathways

Presentata da: **Dott. Roberto Cecere**

Coordinatore Dottorato

Prof.ssa Elisabetta Làdavas

Relatore

Prof.ssa Elisabetta Làdavas

Esame finale anno 2013

Alla mia famiglia

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Abstract

Lesions to the primary geniculo-striate visual pathway cause blindness in the contralesional visual field. Nevertheless, previous studies have suggested that patients with visual field defects may still be able to implicitly process the affective valence of unseen emotional stimuli (affective blindsight) through alternative visual pathways bypassing the striate cortex. These alternative pathways may also allow exploitation of multisensory (audio-visual) integration mechanisms, such that auditory stimulation can enhance visual detection of stimuli which would otherwise be undetected when presented alone (crossmodal blindsight).

The present dissertation investigated implicit emotional processing and multisensory integration when conscious visual processing is prevented by real or virtual lesions to the geniculo-striate pathway, in order to further clarify both the nature of these residual processes and the functional aspects of the underlying neural pathways.

The present experimental evidence demonstrates that alternative subcortical visual pathways allow implicit processing of the emotional content of facial expressions in the absence of cortical processing. However, this residual ability is limited to fearful expressions. This finding suggests the existence of a subcortical system specialised in detecting danger signals based on coarse visual cues, therefore allowing the early recruitment of flight-or-fight behavioural responses even before conscious and detailed recognition of potential threats can take place.

Moreover, the present dissertation extends the knowledge about crossmodal blindsight phenomena by showing that, unlike with visual detection, sound cannot

crossmodally enhance visual orientation discrimination in the absence of functional striate cortex. This finding demonstrates, on the one hand, that the striate cortex plays a causative role in crossmodally enhancing visual orientation sensitivity and, on the other hand, that subcortical visual pathways bypassing the striate cortex, despite affording audio-visual integration processes leading to the improvement of simple visual abilities such as detection, cannot mediate multisensory enhancement of more complex visual functions, such as orientation discrimination.

Introduction

About 500 million years ago, simple organisms started developing primitive visual systems allowing the ability to detect light, which led to the first forms of visually-guided behaviours (Land & Nilsson, 2002). Since then, the sense of vision has become more and more powerful and sophisticated through evolution, boosting animals' abilities in locating food and preys in the environment, detecting potential threats and recognising and interacting with conspecifics.

Humans are probably the most vision-based species among mammals, with a remarkable ability to process visual information. The importance of vision in humans is evidenced by the considerable proportion of the central nervous system devoted to the analysis of visual information, as well as by the complexity of visual neural circuitry, which is far greater than the other senses (Kandel et al., 2000). The primary visual cortex, located in the occipital lobe, is the main cerebral area responsible for visual perception. This area, also known as the striate cortex, or simply visual area 1 (V1), receives inputs from retinal photoreceptors through the lateral geniculate nucleus of the thalamus, building up visual images and giving rise to the conscious visual experience of the world. A lesion to the striate cortex or to the retino-geniculate pathway feeding it with input results in blindness. However, given that the striate cortex is only one component of a complex system of multiple areas and functionally distinct networks for visual processing, a lesion to the retino-geniculo-striate pathway might not affect vision *in toto*, thus leaving intact the ability to partially elaborate visual information or specific features of stimuli. In fact, a large body of literature has provided evidence that selective damage to specific components of visual processing

may spare other visual functions mediated by different brain areas and neural networks.

I. Primary visual pathways and consequences of their lesion

Vision is a complicated process, which requires numerous components of the eye and brain to work synergically in order to build an internal representation of the external world. The visual system encompasses a large network of subcortical structures and cortical areas and its modular organisation affords the analysis of visual information at different levels of complexity, ranging from the simple detection of a stimulus to the recognition of faces or emotional expressions.

In this section, a general description of the central visual pathways will be provided, particularly focusing on the retino-geniculo-striate route. Moreover, disorders following lesions to this pathway will be discussed.

The first step of visual processing is the retina, the internal membrane of the eye containing photosensitive ganglion cells that capture light and transduce it into neural impulses, which are subsequently sent downstream to the central nervous system for deeper analysis. The central part of the retina, where visual acuity is maximal, is called the fovea. The medial part of each retina is termed the nasal hemiretina, whereas the lateral part is termed the temporal hemiretina. The portion of space that can be seen when both foveas are fixed on a single point constitutes the visual field (Kandel et al., 2000). Light from the left visual hemifield is captured by the nasal hemiretina of the left eye and the temporal hemiretina of the right eye (i.e. the right part of each eye). Light from the right visual hemifield is captured by the temporal hemiretina of the left eye and the nasal hemiretina of the right eye (i.e. the left part of

each eye). Similarly, the upper half of the visual field projects onto the lower half of the retina, whereas the lower half of the visual field projects onto the upper half of the retina. Two classes of ganglion cells form the retina: M (magnocellular) cells, with large receptive fields, have poor spatial acuity but are specialized in detecting movement; P (parvocellular) cells, with small receptive fields, are more sensitive to colour and fine details of stimuli than to movement. These two classes of cells serve as the origin of two parallel pathways (M and P) in the visual system (Merigan & Maunsell, 1993).

Axons of the retinal ganglion cells, carrying the electric signal triggered by light, bundle together and exit through the optic disc, forming the optic nerve (see Figure 1). The fibres originating from the two nasal hemiretinae then cross to the opposite side at the optic chiasm, whereas those from the temporal hemiretinae do not cross. As a result, after the optic chiasm, the axons from the left portion of each retina (representing the right visual hemifield) converge into the left optic tract, whereas axons from the right portion of each retina (representing the left visual hemifield) converge into the right optic tract. The axons of the optic tracts, each of which carries a complete representation of the contralateral visual hemifield, project to four subcortical structures (see Figure 1): i) the suprachiasmatic nucleus of the hypothalamus, controlling circadian rhythms; ii) the pretectum, controlling pupillary reflex; iii) the superior colliculus (SC), involved in the rapid and automatic direction of gaze and head towards a target; iv) the lateral geniculate nucleus (LGN) of the dorsal thalamus, a fundamental relay structure in the visual system.

Through the optic tract, the LGN receives the majority (about 90%; Silveira & Perry, 1991) of retinal fibres and it is the main structure carrying afferent visual input to the striate cortex. Axons of the retinal ganglion cells terminate in an orderly manner

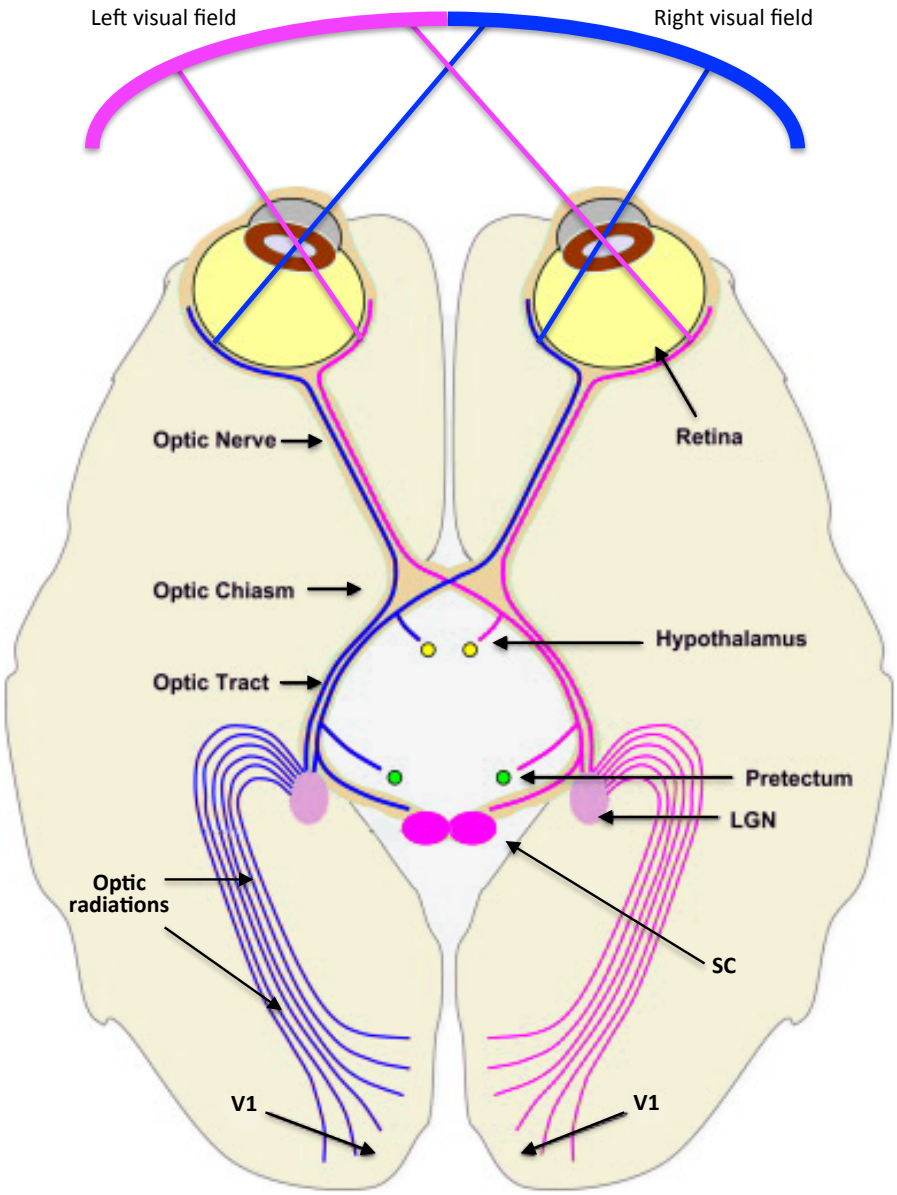

Figure 1. Schematic view of human visual pathways from the retina to the central nervous system. Retinal ganglion cell projections terminate at four subcortical structures: the hypothalamus, the pretectum, the superior colliculus (SC) and the lateral geniculate nucleus (LGN) of the thalamus. From the LGN, through the optic radiations, visual information from the contralateral visual hemifield reaches the primary visual cortex (V1). The pink and blue lines represent, respectively, the flow of visual information from the left and right visual fields (readapted from Liu et al., 2011)

within each LGN, providing a retinotopic representation of the contralateral visual hemifield. However, the retina is not equally represented in the LGN (as well as in the striate cortex), given that the foveal area is coded by a larger number of neurons than

the more peripheral areas. Neurons in the LGN are organized in six layers of cells: the upper layers (1 - 4) receive projection from the retinal P cells, whereas the lower layers (5 and 6) are targeted by retinal M cells. More recently, a third class of neurons has been identified in the intralaminar space of the primate LGN (Norton & Casagrande, 1982; Hendry & Yoshioka, 1994), the K (koniocellular) cells, involved in some aspects of colour perception. Axons of neurons in the LGN project ipsilaterally onto the striate cortex, forming the optic radiations (see Figure 1). Each of the two optic radiations reaches the striate cortex through two branches: 1) the temporal branch, carrying input from the upper quadrant of the contralateral visual hemifield, reaches the inferior portion of the striate cortex; 2) the parietal branch, carrying input from the lower contralateral quadrant, terminates in the superior portion of the striate cortex.

The striate cortex (V1; Brodmann area 17) lies in the medial surface of the occipital lobe, around the calcarine fissure, and it serves as the core of the human visual system. Like the SC and the LGN, the striate cortex contains a retinotopic map of the visual field, with each half of the visual field only represented in the contralateral striate cortex. Cells in V1 are organised in six layers, containing neurons with different properties and connections. Cells in layer 4 receive, separately for each eye, most of projection from the M and P layers of the LGN and convey these inputs to the other layers of the striate cortex. Pyramidal neurons of the superficial layers (1 - 3) send projections to extrastriate cortical areas, whereas neurons in the deeper layers (5 and 6) project back to subcortical structures like the SC and the LGN.

As revealed by pioneering animal studies by Hubel and Weisel (1959; 1977), neurons of mammalian striate cortex show different properties than cells in the retina and the LGN. Indeed, whereas the latter have centre-surround receptive fields and respond

best to a circular spot of light, most of V1 neurons are edge detectors, strongly responding to dark/light bars with a specific orientation. Beyond orientation-sensitive neurons, other types of cells exist in V1, which can code colours (the so-called *blobs*) and the direction of motion. Neurons in the striate cortex are organised in columns formed by cells with similar functional properties. Orientation-sensitive cells form the orientation columns, whereas cells receiving input from only one eye form the ocular dominance columns, important for binocular vision.

Orientation and ocular dominance columns, together with blobs, form small functional modules, each of which codes the basic visual properties (e.g. form and colour) of stimuli in a specific portion of the visual fields. All of these functional modules are organised in an orderly manner and combined to give a representation of the whole visual field, giving rise to what we experience as vision.

After primary processing in the striate cortex, visual information is sent to a large number of higher-order visual areas (extrastriate areas) for a deeper analysis. From V1, and after reaching secondary visual areas (V2 and V3), the flow of visual information follows two main routes (Ungerleider & Mishkin, 1982; Goodale & Milner, 1992): 1) a *dorsal stream*, terminating in the posterior parietal cortex; 2) a *ventral stream*, reaching the inferior temporal cortex.

The dorsal and ventral stream can be respectively seen as an extension of the magnocellular and parvocellular pathways, two parallel routes originating in the retina (see above). The dorsal stream (also known as the *where* pathway), mainly receiving input from the M cells (Livingstone & Hubel, 1984; Zeki & Shipp, 1988), allows the location of objects in space, motion and depth perception, and plays a major role in visually guided behaviour. The ventral stream (or the *what* pathway) is fed with input by the P cells (Livingstone & Hubel, 1984; Zeki & Shipp, 1988) and it is crucial for

object recognition.

Beyond the visual pathways described above, other functional routes bypassing the striate cortex exist, purportedly mediating residual visual abilities when lesions to the geniculo-striatal pathway prevent primary visual processing. Evidence about the functional properties of these alternative visual pathways will be discussed further in this section.

Lesions involving primary visual pathways may result in a variety of pathologies depending on the specific stage at which the flow of visual information is interrupted. Since the present thesis will focus on residual visual abilities after lesions to the retino-geniculo-striate pathway, only visual field defects following deafferentation or destruction of the striate cortex will be considered here.

Visual field defects may ensue either from peripheral (pre-chiasmatic) or central (post-chiasmatic) damage to the visual system. The most common aetiologies of peripheral visual field defects are specific pathologies involving the retina (e.g. glaucoma or macular degeneration) or the optic nerve (e.g. neuritis). Central visual field defects may follow vascular, tumoral, traumatic and anoxic lesions to the striate cortex or to any of its afferent fibres and structures. Given that inputs from the retina reach the visual structures and the areas of the central nervous system in an orderly fashion, thus maintaining the retinal spatial relationships, the site of a lesion can often be inferred by a careful clinical evaluation of patients with visual field defects. Figure 2 shows a schematic representation of visual field defects resulting from lesions at different points along the retino-striatal pathway.

As a general definition, a defect involving large portions of the visual field is termed

anopsia or *anopia* (Purves et al., 2008). The addition of a prefix specifies the affected area (e.g. *hemianopia* or *quadrantopia* indicate the involvement of a half or a quadrant of the visual field, respectively). Visual field defects in small circumscribed areas are called *scotomas* (Purves et al., 2008).

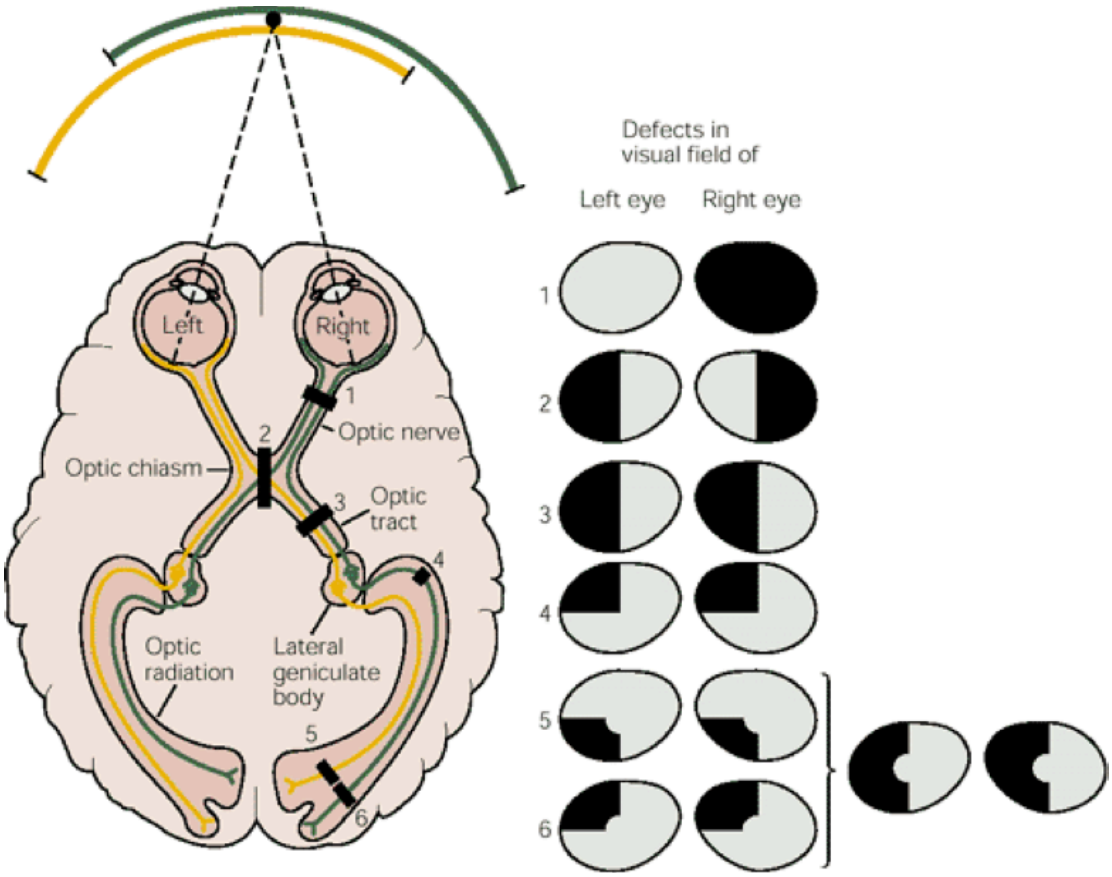

Figure 2. Schematic representation of visual field defects resulting from lesions at different points along the retino-striatal pathway. The figure on the left shows the different locations where lesions can occur. The right panel indicates the visual field defects associated with each specific lesion site illustrated in the figure on the left. (1) Loss of vision in the right eye. (2) Bitemporal heteronomous hemianopia. (3) Left homonymous hemianopia. (4) Upper left quadrantopia. (5) Lower left quadrantopia with macular sparing. (6) Upper left quadrantopia with macular sparing. When both temporal and parietal branches of the right optic radiations (5 and 6 in the left figure) are lesioned, this will result in left hemianopia with macular sparing (rightmost panel) (readapted from Kandel et al., 2000).

Pre-chiasmatic lesions involving the retina or one of the optic nerves cause loss of vision limited to the eye of origin. A lesion at the level of the optic chiasm interrupts

the fibres coming from each nasal hemiretina, resulting in bitemporal hemianopia, a non-homonymous defect (i.e. affecting two different visual hemifields in the two eyes) involving the temporal halves of both visual fields. All lesions after the optic chiasm cause homonymous deficits (i.e. affecting the same visual hemifield in each eye) in the contralateral visual hemifield. A lesion of the optic tract, carrying input from the contralateral hemifield of both eyes (see above), causes homonymous defects that are usually incongruent, i.e. the blind areas have different shapes in the two eyes. Lesions to the LGN are very rare and their outcome depends on the aetiology. Partial lesions usually produce incongruent homonymous defects, whereas vascular lesions typically result in a congruent wedge-shaped defect (Luco et al., 1992). When the optic radiations are damaged, different types of visual field defects can result, depending on the affected fibres. In particular, the involvement of the temporal branch leads to upper contralateral quadrantopia, whereas the interruption of the parietal branch causes lower contralateral quadrantopia. If the lesion affects the whole bundle of fibres forming the optic radiation, this will result in a contralateral hemianopia. Direct damage to the striate cortex produces defects in different portions of the contralateral visual field, depending on the involved area and on the type and extension of the lesion. Visual defects after damage to V1 range from simple scotomas to cortical blindness (i.e. complete loss of vision in the whole visual field), including all the types of homonymous anopias. Due to the large representation of the fovea in the striate cortex, central vision can be spared in some cases of anopia following a V1 lesion. In some other cases, the aetiology of the lesion is related to specific visual deficits. For instance, anoxia typically produces widespread neural loss within the striate cortex (Caine & Watson, 2000), which can cause multiple scotomic areas and even complex syndromes like visual agnosia.

II. Implicit visual processing in patients with visual field defects

The striate cortex is the main recipient of visual input in human visual system, and its lesion or denervation yields loss of visual awareness and chronic blindness (Leopold, 2012). Nevertheless, since the visual system can rely on multiple parallel pathways for processing visual information (e.g. see Cowey, 2010a), losing the ability to consciously perceive visual stimuli does not necessarily implicate that all visual abilities are lost. In fact, since the first reports of spared perception of flickering and moving stimuli after occipital lesions (Riddoch, 1917; Holmes, 1918), there has been growing evidence that patients with visual field defects, despite their clinical blindness, may still display some residual functions at different levels of visual processing.

Low-level functions such as reflexive responses are usually preserved in clinically blind patients. For instance, the pupil still reacts to changes in illumination levels (Magoun & Ranson, 1935; Bender & Krieger, 1951; Brindley et al., 1969) and even to equiluminant spatial patterns (Weiskrantz, 1990). The blink reflex in response to a flash of light is also still present (Bender & Krieger, 1951; Hackley & Johnson, 1996). Moreover, tracking eye movements (optokinetic nystagmus) can be elicited in blind patients by a unidirectional moving visual scene (Pizzamiglio et al., 1984; Heide et al., 1990), although this residual ability is still controversial (see: Stoerig & Cowey, 1997). The persistence of reflexive responses despite cortical blindness has been also well documented in monkeys (for reviews, see Stoerig & Cowey, 1997; Cowey, 2010a).

Beyond the simple reflexive responses described above, some patients with lesions to

the primary visual pathway may also retain the ability to detect, localise and even discriminate visual stimuli in their blind field, in the absence of any conscious perception. The term *blindsight* was coined to describe this paradoxical ability of patients with visual field defects (Sanders et al., 1974; Weiskrantz et al., 1974). Blindsight patients can show different degrees of awareness for stimuli presented in their blind field and this observation led Weiskrantz (1998) to the distinction between type 1 blindsight (total lack of awareness) and type 2 blindsight (feeling that something occurred in the blind visual field).

Both direct and indirect behavioural approaches have been used to infer the presence of blindsight abilities in patients with geniculo-striatal lesions.

Direct methods simply require a patient to make a direct response to stimuli presented in his blind field, for example indicating the position or guessing the content of unseen stimuli, usually in a forced-choice paradigm. In such a type of task, blindsight patients display above-chance performance, which can be considered as proof of a certain degree of knowledge about visual stimuli that they deny seeing.

When forced to do so, blindsight patients can localise stimuli they cannot consciously perceive. For example, Pöppel et al. (1973) showed that patients with occipital lesions could perform saccadic eye movements towards spots of light that were briefly flashed at different positions in their blind visual field, a result that was also replicated by later studies (Sanders et al., 1974; Weiskrantz et al., 1974; Perenin & Jeannerod, 1978; Zihl, 1980). These findings were further extended by other studies showing that clinically blind patients could localise the position of a stimulus in the blind field by manual pointing (Weiskrantz et al., 1974; Perenin & Jeannerod, 1975; 1978; Bridgeman & Staggs, 1982). In particular, the study by Perenin and Jeannerod (1975)

investigated pointing abilities in a group of eight patients suffering from hemianopia, resulting either from post-geniculate (n=6) or post-chiasmatic lesions (n=2). Despite none of the patients being able to detect stimuli in the blind field, when they were asked to perform a manual pointing towards unseen stimuli, results showed a different performance according to the patients' lesional profile. Indeed, whereas, on the one hand, patients with post-geniculate lesions could point to stimuli in their blind field with good accuracy, on the other hand, patients with pre-chiasmatic lesions failed in such a task. This led the authors to postulate that residual visual abilities displayed by patients with post-geniculate lesions could depend on spared retino-colliculo and retino-geniculo projections to extrastriate visual areas, which are interrupted in the case of pre-chiasmatic lesions.

More recent studies further confirmed that visually-guided behaviours might survive post-geniculate lesions, by showing that patients with visual field defects could retain the ability to perform reaching and grasping movements towards stimuli they could not see, accordingly with the position, form and orientation of the target (Jeannerod, 1981; 1994; Perenin & Rossetti, 1996; Marcel, 1998). For instance, a single-case study (Perenin & Rossetti, 1996) investigated the residual abilities to process the orientation and size of unseen objects in a hemianopic patient, depending on different response modalities. To test the former aspect, the patient was presented with a slot of variable orientation; to test the latter aspect, he was presented with rectangular objects with the same surface but different length. His performance was then tested in three different tasks: i) a motor task, where he had to "post" a card in the slot and grasp a rectangle with a thumb-index pinch; ii) a verbal task, requiring forced-choice guessing about orientation and size; iii) a matching task, in which he had to match the orientation of the slot by rotating his wrist and indicate the size of the rectangle by

opening his fingers. The patient did not display blindsight abilities in both the verbal and the matching task, as shown by his chance-level performance. However, in the motor task, requiring the execution of actions towards the unseen stimuli, the patient performed above the chance level. As suggested by the authors, these results demonstrate that different response modalities tap dissociable systems for processing visual information, dealing with "what" an object is and "how" to grasp it. Moreover, compared to the "what" pathway, the neural pathway responsible for visuo-motor transformations seems to rely to a lesser extent on conscious vision (i.e. input from V1).

Some patients with visual field defects may also retain the ability to perform reliable detection of stimuli in their blind visual field (Stoerig et al., 1985; Stoerig & Poppel, 1986; Weiskrantz et al., 1991; Magnussen & Mathiesen, 1989). To assess this residual ability in a hemianopic patient, Stoerig and colleagues (1985) employed a signal detection paradigm requiring the discrimination between a condition in which a small circular target was briefly presented within his blind hemifield (target condition), and a condition in which no such target was presented (no-target condition). The analysis on sensitivity scores (d') revealed that the patients could perform above chance level in discriminating between the target and the no-target condition. The possibility that the above-chance performance could stem from an effect of light scattering from the blind to the intact visual field was also ruled out, by demonstrating that the patient could not detect stimuli that were presented within the retinal blind spot. Another study confirmed these findings (Stoerig & Poppel, 1986), also reporting a better discriminative ability for circular spots of light presented at higher eccentricities. As suggested by the authors, this eccentricity-dependent effect could be explained by the fact that the size of the employed visual stimuli could have better fit the receptive

fields of more peripheral retinal ganglion cells, which are larger than the receptive fields of more central cells. A single-case study (patient BN; Magnussen & Mathiesen, 1989), using a forced-choice paradigm with high-contrast gratings as stimuli, failed to report above-chance detection when stationary stimuli were presented. However, in another condition where the black/white bands within the grating were moving horizontally, the patient performed above chance. In the authors' opinion, the lesion profile of BN could account for the different pattern of results between the stationary and moving conditions. Indeed, since the patient's whole occipital lobe had been removed (i.e. including extrastriate occipital areas), she could only rely on the activity of the superior colliculus, whose neurons are known to be optimally activated by moving stimuli (Goldberg & Wurtz, 1972).

Studies using direct tasks have shown that blindsight patients can not only detect motion, but that they can also discriminate the displacement of unseen targets (Blythe et al., 1986; Blythe et al., 1987) and the direction of unseen moving stimuli (Barbur et al., 1980; Perenin, 1991; Weiskrantz et al., 1995). Of particular interest is the study by Perenin (1991), where motion direction discrimination performance in a two-alternative forced choice (2AFC) task was compared between patients with cortical blindness/hemianopia due to striatal lesions and patients with hemianopia following hemispherectomy. Results showed that patients with striatal lesions could discriminate the direction of motion above chance, whereas hemispherectomised patients could not. Crucially, hemispherectomised patients are, by definition, deprived of cortical areas in the hemisphere contralateral to the blind hemifield, whereas in patients with striatal lesions, cortical extrastriate areas are still intact. For this reason, any difference found between these groups of patients can be reasonably attributed to spared cortical areas. Based on this observation, Perenin (1991) suggested that the

above-chance discrimination of motion direction, which was only evident in patients with striatal lesions, most likely required the contribution of intact extrastriate areas related to motion perception (i.e. V5/MT). In support of this hypothesis, a study using positron emission tomography (PET) showed activation of the extrastriate area V5, but not of V1, in a hemianopic patient (GY) who could reliably discriminate the direction of motion of stimuli within his blind field (Barbur et al., 1993).

Despite having lesions to the primary visual pathway, blindsight patients can also distinguish the colour of stimuli presented in their blind field (Stoerig & Cowey, 1992; Brent et al., 1994). For example, the study by Brent and colleagues (1994) tested the patient GY in a triple-choice paradigm asking to indicate the colour of light flashes presented in his hemianopic field. Many different triplets of colours were tested and in most cases the patient demonstrated above-chance discriminative ability, though his performance was more robust for long-wavelength stimuli (e.g. red, orange and yellow) than for short-wavelength stimuli (e.g. green, blue and purple). Noteworthy, to exclude that the ability to discriminate wavelengths was due to differences in apparent brightness, the task was also performed with each of the coloured stimuli randomly presented at three possible different luminance levels. Also after this manipulation, the same results were obtained.

Some studies reported a few cases of blindsight patients (i.e. GY and DB) who can also discriminate the orientation of unseen stimuli (Weiskrantz et al., 1974; Weiskrantz, 1987; Morland et al., 1996). For example, the patient DB displayed above-chance performance in 2AFC tasks requiring to guess the orientation (horizontal vs. vertical or diagonal vs. vertical) of lines presented in his scotoma (Weiskrantz et al., 1974). These results were confirmed and extended by a follow-up study (Weiskrantz, 1987), which tested many orientation differences and also

excluded possible effects due to light scatter by showing that DB could not discriminate the orientation of lines presented within his retinal blind spot. As well, the patient GY tested by Morland and colleagues (1996) reported reliable discrimination performance for unseen flickering bars of various orientations, but not if bars were smaller than 10 visual degrees. In contrast, when tested with equiluminant gratings, GY's performance fell to chance level.

In Weiskrantz et al. (1974) the patient DB was proven to be also able to discriminate simple forms (i.e. X versus O) presented in his blind field. However, the follow-up of this study (Weiskrantz, 1987) strongly suggested that this form discrimination ability could only be based on the ability to discriminate the orientations of components of X and O figures. Indeed, when differences between these components were reduced, e.g. using "straight" and "curved" triangles as stimuli, DB was no longer able to discriminate forms.

Evidence reviewed so far shows that blindsight patients are able to discriminate relatively simple aspects of unseen stimuli, such as motion direction, colour or orientation. However, in direct tasks these patients may also display above-chance ability in discriminating far more complex features of stimuli within their blind visual field. For instance, in a study by Morris and colleagues (2001) the patient GY could reliably discriminate the gender of unseen faces. Moreover, a restricted number of cases (patients GY, DB and TN) also reported above-chance discrimination of the emotional expression of both faces (GY and DB: de Gelder et al., 1999; 2002; Tamietto et al., 2009; TN: Pegna et al., 2005) and bodies (GY and DB; Tamietto et al., 2009) presented in the blind visual field. This latter ability has been referred to as *affective blindsight* (de Gelder et al., 1999).

Direct tasks have been widely used to assess blindsight, however such methodologies

are not bias-free, and the use of different tasks to test the ability to see a stimulus (yes/no task) and the ability to guess its nature (forced-choice task) might lead to spurious results, possibly reflecting a shift in the response criterion, rather than actual blindsight (Campion et al., 1983; also see: Cowey, 2010a, for an overview). For this reason, indirect tasks, which are free of response biases, represent a more reliable and sensitive method for studying the implicit processing of unseen stimuli (Marzi et al., 2004).

Indirect methods for assessing implicit visual processing in clinically blind patients consist of tasks requiring a patient to respond to a (seen) stimulus in the intact visual field while another (unseen) stimulus is presented in the blind visual field. If the response to the seen stimulus is affected in some way by the presentation of the unseen stimulus, this can be considered as proof of implicit processing of visual information presented in the blind visual field. A widely used indirect approach is the redundant target paradigm, based on the so-called redundant target effect (RTE; Todd, 1912). In such a paradigm, healthy subjects usually respond faster (i.e. RTE) when two identical stimuli are presented bilaterally (i.e. in both visual fields, while the participant is fixating a central point) compared to unilateral stimulus presentation. Some hemianopic patients can show a typical RTE when a stimulus in the intact visual field is coupled with an identical stimulus in the blind visual field, demonstrating that implicitly processed unseen stimuli can elicit a summation effect that leads to faster reaction times. Marzi and colleagues (1986) employed a redundant target paradigm to test a group of patients with post-chiasmatic lesions. In a task where brief flashes of light could be presented either unilaterally, in the intact visual field, or bilaterally, in both the intact and blind field, authors found a spatial

summation effect in the bilateral condition (i.e. blindsight), but, noteworthily, only in one patient out of twenty. Another study (Tomaiuolo et al., 1997) used a similar paradigm on four patients with hemianopia resulting from hemispherectomy. Similarly to the study by Marzi et al. (1986), results did not show a summation effect at the group level, whereas a single case analysis revealed an RTE for bilateral stimulus presentation in two out of the four tested patients. A single-case study on the hemianopic patient GY (de Gelder et al., 2001), showing above-chance discriminative ability in direct tasks for a wide range of stimulus features (see above), reported faster reaction times and earlier electrophysiological responses (i.e. P1 component of event-related potentials) to bilateral versus unilateral presentation of checkerboards. The same gain on RTs was evident when GY was presented bilaterally with emotionally congruent pairs of faces, compared both to emotionally incongruent pairs and to a single face presented only in the intact visual field (i.e. affective blindsight).

Other studies used different indirect approaches to assess blindsight abilities. For example, Rafal and co-workers (1990) tested three hemianopic patients with lesions to the striate cortex to verify whether distractors presented in the blind field could affect (i.e. delay) oculomotor responses to targets in the intact field. During the experimental task, the patients initially fixated a central cross that was flanked by two dim squares, one falling in the sighted field and one in the blind field, and they were instructed to perform a saccadic movement towards the target square in their intact visual field as soon as it became brighter. In each trial, the distractor square in the blind field was also illuminated, but, in different conditions, its onset could slightly anticipate (distractor condition) or occur well after (no-distractor condition) the target illumination. All tested patients showed a delay of saccadic movements towards the target in the distractor condition versus the no-distractor condition, suggesting that

stimuli in the blind visual field could be processed through an extrageniculate visual pathway, most likely involving the spared retino-collicular projections.

Another line of indirect evidence of residual processing of unseen stimuli comes from studies evidencing that a full circle, with one half falling in the blind field, can appear more complete than a half circle presented only in the intact field (Warrington, 1962; Torjussen, 1976).

Interestingly, a study using an indirect paradigm (Marcel, 1998) suggested even higher level cognitive processing in blindsight patients; i.e., that unseen stimuli can influence the processing of consciously perceived stimuli up to the semantic level.

In this study, two hemianopic patients (TP and GY) were presented, in their intact visual field, with a polysemous (i.e. with more than one possible meaning) word and required to indicate its meaning. For example, the polysemous word "BANK" may indicate either "the bank of a river" or "the place where money is kept". To test whether the semantic attribution to the seen polysemous words could be biased by unseen words, in each trial the presentation of the seen word (e.g. BANK) was preceded by the presentation, in the blind visual field, of a word indicating a specific meaning (e.g. RIVER or MONEY). The results showed that the attributed meaning to the seen word strictly depended on the priming word presented in the blind visual field, suggesting that blindsight patients can process unseen stimuli even at the semantic level. However, the robustness of the results provided by this study has been questioned (Cowey, 2010a), due to the scarce control of eye movements.

When the striate cortex or the neural pathway feeding it with visual input is lesioned, the ability to consciously perceive visual stimuli is permanently lost. Nevertheless, the existence of blindsight phenomena clearly demonstrates that some basic visual

functions, such as localisation, detection or discrimination of motion, colours and orientation, might be carried out even in the absence of awareness. For this to be possible, one or more alternative visual pathways must exist, allowing visual processing without the contribution of V1. In fact, there are at least ten identified pathways conveying visual input from the eye to the central nervous system (Cowey, 2010a). Among these pathways, those directly projecting from subcortical structures in the midbrain to the extrastriate cortex, thereby bypassing the striate cortex, are assumed to mediate blindsight abilities (Weiskrantz, 2009). A large body of evidence coming from studies on both human and non-human primates strongly supports this idea, pointing to the SC, LGN and pulvinar, as fundamental subcortical structures relaying inputs to extrastriate areas (for reviews, see: Stoerig & Cowey, 1997; Cowey, 2010a; 2010b; Leopold, 2012).

III. Implicit emotional processing in patients with visual field defects

Since the first report of a hemianopic patient (GY) who was able to process the emotional valence of stimuli presented in his blind visual field (de Gelder et al., 1999), a specific line of research has focused on the study of the implicit processing of affective signals in the absence of explicit visual awareness, a phenomenon known as *affective blindsight*.

The seminal study by de Gelder and colleagues (de Gelder et al., 1999) investigated the covert recognition of affect by testing GY in various tasks and with different types of dynamic and static emotional faces. The dynamic stimuli consisted of silent video fragments showing a face pronouncing the same sentence but with different facial expressions (happy, sad, angry, fearful). When tested in 2AFC tasks, GY displayed above-chance performance in discriminating various pairs of dynamic emotional faces

(i.e. happy/sad, angry/sad, angry/fearful). Strikingly, the patient could discriminate among the same dynamic stimuli with high accuracy even in a four-alternative forced choice paradigm. To ascertain whether GY's performance could depend on the dynamic nature of stimuli, he was further tested in 2AFC tasks with static emotional faces. Under this condition, the patient had much more difficulties and he was not as reliable as he was with videos. However in another experiment, when electroencephalography (EEG) was recorded while GY was presented with static happy and fearful faces in his blind field, results showed that unseen emotional faces elicited the same event-related potential (ERP) components (P1 and N1) in occipital areas that were elicited by stimuli presented in his intact visual field. Based on these latter findings, authors concluded that GY's affective blindsight abilities could stem from the activation of extrastriate areas in the ventral stream via alternative neural pathways bypassing V1.

More recent works have only reported a few more cases of patients with occipital lesions who are able to guess the affective valence of stimuli presented within their field defect. For example, a study tested such an ability for GY and another famous blindsight patient (DB), reporting that they performed above chance in discriminating fearful versus happy facial expressions, as well as negative (e.g. spiders) versus positive (e.g. bunnies) pictures (de Gelder et al., 2002). A more recent study on patients GY and DB (Tamietto et al., 2009) extended these results, reporting above-chance performance when the patients had to discriminate not only between unseen fearful and happy faces, but also between unseen fearful and happy body postures. Another study (Pegna et al., 2005) demonstrated that the patient TN, suffering from complete cortical blindness due to bilateral destruction of V1, could nevertheless discriminate between angry vs. happy, sad vs. happy and fearful vs. happy faces, as

tested by means of 2AFC tasks. In contrast to GY and DB (see de Gelder et al., 2002), when affective stimuli consisted of threatening/non-threatening animals or pleasant/unpleasant scenes, TN performed at chance, suggesting a specific affective blindsight for faces in this patient.

Affective blindsight abilities in patients with visual field defects have also been investigated in indirect tasks not requiring a direct response to stimuli presented in the blind visual field. In a study by de Gelder and colleagues (2001) the patient GY underwent two experiments testing how emotional faces presented in his blind field could influence the response to faces presented in his intact field. In the first experiment, GY had to categorise by double choice the emotion conveyed by a seen half-face stimulus, which could be angry or fearful and angry or sad in different blocks. In each trial, the seen half face was coupled with another half face in the blind field (resulting in a whole-face stimulus), which could be emotionally congruent, incongruent or neutral. GY was faster in categorising the seen emotion when coupled with an unseen congruent emotion, suggesting that he could implicitly process the affective valence of unseen stimuli. The second experiment confirmed this finding using a go/no-go task with whole-face stimuli. In this case, GY was asked to respond to fearful or sad faces presented in the intact visual field, which could be coupled either with emotionally congruent or incongruent faces in the blind field. Again, consistent with the hypothesis that non-conscious emotional processing is still possible after striatal lesions, results showed faster responses to seen fearful and angry faces when paired with emotionally congruent faces. In support of these behavioural findings, a study using functional magnetic resonance imaging (fMRI; Morris et al., 2001) reported that GY, when presented with fearful or fear-conditioned faces in his blind field, displayed enhanced BOLD (blood oxygen level-dependent) signal in the

amygdala, a core subcortical structure for the analysis of fearful stimuli, including fearful faces (Adolphs et al., 1994; Adolphs et al., 1995; Morris et al., 1996; LeDoux, 1996). Similarly, another fMRI study on a cortically blind patient (TN) with affective blindsight, showed enhanced amygdala activity in the presence of unseen fearful faces and, although to a lesser extent, also in the presence of happy and angry faces, compared to neutral faces (Pegna et al., 2005).

Further indirect evidence of implicit emotional processing in patients with striatal lesions has been provided by a study using electromyography (EMG) to explore emotional contagion in the absence of awareness (Tamietto et al., 2009). In this study, two hemianopic patients (GY and DB), discriminating above chance between unseen happy and fearful facial and bodily expressions, were presented with faces and bodies in their intact or blind visual field. During the passive exposure to seen and unseen emotional stimuli, EMG responses were recorded from two facial muscles, namely the zygomaticus major (ZM) and the corrugator supercilii (CS), which are respectively involved in smiling and frowning (i.e. in happy and fearful expressions). To measure the contingent changes in arousal, pupil dilatation was also measured. Results showed that the presentation of happy faces and bodies specifically enhanced EMG responses recorded from the ZM, whereas fearful faces and bodies increased EMG activity in the CS. Notably, the emotion-specific EMG modulations were equally elicited by conscious (seen) and unconscious (unseen) stimuli, and both seen and unseen fearful stimuli induced an increased pupil dilatation, suggesting that emotional signals can be processed in the absence of conscious vision and influence autonomic responses. This is consistent with studies using fear-conditioning paradigms, which have reported that patients with visual field defects produce an increased startle reflex in response to unseen conditioned stimuli, demonstrating that

the striate cortex and visual awareness are not necessary to acquire a reliable aversive response to visual cues (Hamm et al., 2003; Anders et al., 2004). Interestingly, the study by Tamietto et al. (2009) also found that unseen emotions induced faster muscular reactions with respect to seen emotions, in line with the hypothesis that unconscious emotional signals can be processed through a fast route bypassing the cortex (LeDoux, 1996).

Implicit emotional processing can also be evident in a crossmodal context; studies have shown that unseen emotional faces can influence responses to conscious affective stimuli in another sensory (e.g. auditory) modality. De Gelder and co-workers (2002) shed light on this aspect by testing, in the blindsight patients GY and DB, the electrophysiological responses elicited by emotionally charged voices which were paired with seen and unseen emotional stimuli. During the experimental task, the patients were presented with emotional faces (fearful or happy) or pictures (negative or positive) either in their intact or in their blind field, then, after 900 ms, they heard an emotional voice, on which they were required to perform a task-irrelevant gender decision. The tone of the heard voice could be emotionally congruent or incongruent with the visual stimulus. The EEG recorded during the task showed that when a voice was paired with an emotionally incongruent face, auditory ERPs (i.e. the N1 component) decreased. Importantly, this crossmodal effect was evident with both seen and unseen emotional faces, demonstrating that conscious vision was not needed for this crossmodal effect to arise. In contrast, unseen emotional non-face pictures were not effective in modulating the EEG responses to voices, suggesting a specificity of the effect for unseen faces.

The literature reviewed in the previous section demonstrates that basic visual

functions can survive lesions to the primary visual pathway responsible for conscious vision, thanks to alternative routes carrying visual information about stimulus location, movement or colour to extrastriate areas specialised in evaluating these aspects of visual stimuli. In this section, evidence was discussed about the possibility that even more complex stimulus features, such as the affective valence, can be processed in the absence of awareness. Akin to other blindsight abilities, the residual ability to implicitly process emotional stimuli implicates the existence of neural pathways conveying visual information to areas involved in the evaluation of the affective valence of a stimulus (see Chapter 1 for a detailed description of the neural bases of implicit emotional processing). One of the most credited theories (LeDoux, 1996) postulates the existence of a dual route for emotional processing, providing visual input to a subcortical structure that plays a central role in the appraisal of emotional signals: the amygdala. In this model, visual information can reach the amygdala through a cortical, geniculo-striate, "high road", and a subcortical "low road", directly projecting from the thalamus to the amygdala.

Patients with visual field defects represent a valuable model to study the functionality of the "low road" for emotional processing, since the "high road" is not functional in such patients because of the lesion to the geniculo-striate pathway. So far, the majority of studies investigating implicit emotional processing in the absence of awareness (i.e. affective blindsight) tested a very restricted group of blind patients (GY, DB and, in one study, TN), attributing their implicit abilities to the activity of the spared "low road". However, these patients display the unusual ability to discriminate an impressive number of features of visual stimuli in their blind field (see above) above chance level, which raises the suspicion that their cortical "high road" could still be functional to some extent. This suspicion is strengthened by a

number of observations. For example, in one case (GY) the lesion occurred very early in life (7 years age; e.g. see de Gelder et al., 2002), which could have caused a functional reorganisation within visual pathways involving extrastriate areas. In another case (DB), the use of metal clips in the surgical procedure prevented precise determination of the areas affected by the lesion, and extent thereof, using MRI (e.g. see de Gelder et al., 2002). Moreover, both GY and DB have been extensively tested over years and, during testing, have often reported the feeling that something occurred in their blind visual field (i.e. Type II blindsight). If all of these observations are taken into account, it seems reasonable that the effects reported in these patients could not stem solely from the activity of the subcortical "low road", but also from the partial contribution of the cortical "high road" for emotional processing.

Thus, to exclude any possible confound, the studies presented in Chapter 1 (Experiments 1 and 2) tested the implicit emotional processing in patients with post-geniculate lesions who were completely naïve to the experimental procedures and did not display any form of residual knowledge about stimuli within their blind field, i.e. performing at chance in direct tasks. This allowed the possibility of any residual cortical processing to be ruled out in the tested patients, ensuring that the observed effects exclusively reflected the activity of the spared subcortical networks (i.e. the "low road") for implicit emotional processing. Moreover, to further disentangle the differential role of the cortical and subcortical networks in emotional processing, brain stimulation was used in Experiment 3 to selectively interfere with occipital areas (i.e. a crucial node of the cortical "high road") of healthy subjects. This virtual lesion approach allowed a direct comparison between the effects observed when the cortex is intact and those arising when its activity is disrupted.

IV. Multisensory integration in patients with visual field defects.

Blindsight phenomena demonstrate that the implicit processing of visual stimuli (i.e. without acknowledged awareness) can affect behaviour in several ways and, interestingly, they show that task-irrelevant, unseen stimuli can modulate the response to consciously perceived stimuli. Subcortical networks not involving V1 are thought to mediate all of these implicit effects and interactions. The superior colliculus, which is a critical structure in these networks mediating blindsight (see above), contains multimodal neurons responding to inputs from multiple sensory channels (visual, auditory and tactile), thus playing an important role in multisensory integration (Stein & Meredith, 1993). The combination of multiple sensory signals (i.e. multisensory integration) has been shown to elicit a more powerful neural activation in the SC than the activation produced by inputs from a single modality, and as a result, perception and behavioural responses are enhanced when multisensory cues are provided (Stein, 1998). Furthermore, by virtue of the so-called *inverse effectiveness rule* (Stein & Meredith, 1993), the weaker the unisensory inputs, the greater the response elicited by their integration. This would suggest that when one sensory process is too weak to induce a behavioural response, the concurrent stimulation through different sensory channels might improve the responsiveness of the weak sensory system (Làdavas et al., 2012). Moreover, it is worth noting that multisensory integration is an automatic process and can occur in the absence of meaningful relationships between sensory inputs and without any perceptual awareness (Stein & Meredith, 1993).

Taken together, these observations suggest that, in patients with unisensory deficits following brain damage, the presentation of stimuli in one intact sensory modality might crossmodally enhance perception in the modality that is impaired because of a lesion to primary sensory areas (Làdavas, 2008; Làdavas et al., 2012).

In patients with deficits in the auditory representation of space, due to right-hemisphere lesions, the presentation of visual cues can ameliorate the impaired ability to localise sounds. A study by Bolognini et al. (2005c) tested a patient with a right-hemisphere lesion without neglect but with a deficit in auditory localisation, aiming to verify whether stimulation through the intact visual channel could induce a recovery of impaired auditory functions. The patient's accuracy in indicating the position of sounds was tested under two conditions: i) a unimodal condition, where sounds were presented alone; and ii) a crossmodal condition, where sounds were accompanied by visual stimuli, which could be presented either in the same spatial location of sounds or in a non-coincident position. Results showed that, compared to the unimodal condition, the patient's performance improved in the crossmodal condition, but only if visual stimuli were presented in spatiotemporal coincidence with sounds. The spatio-temporal specificity of the effect respected both the *spatial* (Meredith & Stein, 1986) and *temporal* (Meredith et al., 1987) *rules* of multisensory integration in the SC, leading authors to hypothesise a role of the colliculo-extrastriate pathway in mediating the crossmodal auditory improvement.

Notably, the visually induced enhancement of auditory localisation can even occur when a visual stimulus is not consciously perceived because of a geniculo-striatal lesion, in a sort of "crossmodal blindsight". This was shown by a study (Leo et al., 2008) testing a group of hemianopic patients in a similar paradigm to the one used by Bolognini and colleagues (2005c). Here, again, the authors found that unseen visual stimuli could enhance auditory localisation only when presented in the same position as the sounds. These results show that visual stimuli can not only be processed in the absence of awareness, but also that their unconscious perception can influence other senses through multisensory mechanisms. Moreover, since the geniculo-striate

pathway is not functional in hemianopic patients, this study confirmed the hypothesis that the colliculo-exstrastriate pathway, which is preserved in these patients, plays a pivotal role in mediating the crossmodal enhancement of perception. Another study on patients with post-geniculate lesions (Passamonti et al., 2009b) demonstrated that unseen stimuli not only exert online effects on auditory localisation (Leo et al., 2008), but also prolonged, offline effects. Passamonti and colleagues (2009b) asked a group of hemianopic patients to localise weak sounds after passively exposing them to a brief (4 minutes) audio-visual adaptation session. The adaptation phase could be carried out in the intact or in the blind visual field, with audio-visual stimuli that could be either spatially coincident or spatially disparate. Results revealed long-lasting effects of adaptation on the auditory localisation both when the audio-visual stimuli were presented in the intact and in the blind visual field. However, in line with Leo et al. (2008), the adaptation in the blind visual field produced an offline enhancement of auditory localisation only when audio-visual stimuli were presented in spatial coincidence.

A number of studies also demonstrated that audition can improve vision, when conscious perception of visual stimuli is prevented by a lesion to the primary visual pathway. Frassinetti and colleagues (2005) asked a group of hemianopic patients to perform a visual detection task while fixating a central point. Visual stimuli could be presented alone (unimodal condition) or together with a sound (crossmodal condition). In the crossmodal condition, sounds could be spatially coincident or disparate. Patients' detection sensitivity (d') for stimuli within their field defect significantly improved when accompanied by a sound (i.e. crossmodal condition), but only when this was presented in the same spatial location as the visual stimulus. This

is in line with the spatial rule (Meredith & Stein, 1986) of multisensory integration in the SC; and, since all stimuli were concurrently presented, the temporal principle (Meredith et al., 1987) was also respected. Interestingly, patients performing worst in the unimodal condition displayed the highest improvement with audio-visual stimulation, which is consistent with the inverse effectiveness rule (Stein & Meredith, 1993). Based on these observations, the authors highlighted the possible critical role of the colliculo-extrastriate pathway in mediating the crossmodal visual enhancement, also suggesting the possibility of using crossmodal stimulation to induce long-lasting visual improvements in patients with visual field defects.

Following this line of reasoning, a study by Bolognini and colleagues (2005b) attempted to exploit multisensory integration mechanisms to rehabilitate patients with visual field defects, hypothesising that systematic stimulation of neurons in the SC, critically involved in automatic saccadic movements, might promote oculomotor exploration towards the blind visual field with long-lasting effects. In this study, a group of patients with chronic visual field defects underwent an intensive training (4 hours daily, over 2 weeks) requiring them to detect visual targets that could be presented alone (unisensory condition) or together with a sound (multisensory condition). Following the treatment sessions, patients showed progressive amelioration in both visual detection and oculomotor exploration, which allowed them to compensate for their blindness. The effect of treatment was stable over time, as demonstrated by follow-up sessions carried out 1 month (Bolognini et al., 2005b) and 1 year (Passamonti et al., 2009a) after the treatment.

The studies reviewed above clearly demonstrate that the ability to detect a visual stimulus can be enhanced in patients with visual field defects via auditory stimulation.

The colliculo-extrastriate pathway, spared in these patients, has been pointed out as the possible neural basis mediating this type of crossmodal enhancement. These observations raise the intriguing question of whether even higher-order abilities can be affected by the concurrent presentation of sounds in patients with visual field defects.

A previous study (Leo et al., 2011) has already shown that sounds signalling approach (looming sounds) can improve healthy subjects' ability to discriminate the orientation of visual stimuli. However, it is not clear whether such an improvement stemmed from the activity of the colliculo-extrastriate pathway (i.e. akin to the sound-induced detection enhancement evident in patients with visual field defects) or from intact primary visual areas. Indeed, accumulating evidence suggests that not only the SC, but also low-level sensory cortices, classically regarded as unisensory, show multisensory properties, and their activity can be directly modulated by stimuli from different modalities (Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007; Driver & Noesselt, 2008).

In Chapter 2 a single case study will be presented, exploring the possibility to use looming sounds to enhance orientation sensitivity in the blind visual field of a patient with occipital lesions. In addition, testing a patient with a partial field defect offers the opportunity to compare his performance between the intact and the blind visual field, which are subtended by spared and lesioned V1, respectively. Such a comparison will allow clarification about the neural basis of the sound-induced orientation sensitivity improvement, investigating the possible role of the visual cortex in such a crossmodal effect.

CHAPTER 1

Implicit processing of emotional faces with and without cortical contribution

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1.1 Neural bases of implicit emotional processing in humans

Evidence reported by studies on patients with affective blindsight strongly suggest that primary visual areas and explicit perceptual awareness are not necessary for emotional signals (e.g. emotional faces) to be processed and to elicit autonomic and behavioural responses. For this to be possible, a network should exist that directly conveys visual input from the retina to structures and areas in the brain evaluating the emotional significance of stimuli, without involving the cortex. The amygdala is a subcortical structure that is widely regarded as a central component of the emotional system, being involved in both the evaluation and response to emotionally salient stimuli (Dolan, 2002; Zald, 2003; Phelps & LeDoux, 2005). In particular, it has been suggested that the amygdala could play a pivotal role in Pavlovian fear conditioning (Wilensky et al., 2006), as well as in fear recognition (Whalen, 1998; Davis & Whalen, 2001; Zald, 2003; Öhman, 2005), especially from faces (Adolphs et al., 1994; 1995; Calder et al., 1996; Broks et al., 1998; Sprengelmeyer et al., 1999; Anderson & Phelps, 2000; Hariri et al., 2002; Graham et al., 2007; Loughead et al., 2008). Based on evidence from animal fear-conditioning studies, Joseph LeDoux (1996) first hypothesized the existence, in the brain, of a dual-route system for processing affective signals, in particular fearful ones. According to LeDoux's theory, sensory information about threatening stimuli might reach the amygdala through two

parallel pathways: a cortical *"high road"*, conveying inputs to the amygdala via the sensory thalamus and the cortex, and a subcortical *"low road"*, directly projecting from the thalamus to the amygdala. These two segregated networks would exist for each sensory modality. However, in line with the topic of the present dissertation, their role in visual processing will be specifically discussed here. In LeDoux's conceptualization, the "high road" and the "low road" would be characterised by different functional properties, both in terms of processing speed and accuracy. On the one hand, the indirect, cortical "high road" to the amygdala would provide a detailed analysis of visual fearful stimuli, allowing their conscious perception and recognition, as well as the production of a behavioural response that is appropriate to the context. However, as this fine-grained processing would require the contribution of multiple areas, it would also entail a cost in terms of processing speed. On the other hand, the direct, subcortical "low road" to the amygdala would grant a high-speed processing of potential threats and enable quicker motor reactions, although, without the cortical contribution, the stimulus would not reach the level of consciousness and its features would be only coarsely elaborated. In accordance with LeDoux's proposal that the "high road" and "low road" would provide, respectively, a detailed and coarse visual analysis, an fMRI study (Vuilleumier et al., 2003) reported that high-spatial-frequency face stimuli are more likely to activate cortical areas, whereas low-spatial-frequency fearful faces specifically trigger subcortical structures such as the SC and the pulvinar. Moreover, in support of the dual-route model (LeDoux, 1996), a recent study using a Bayesian model comparison (Garrido et al., 2012) demonstrated that the higher amygdala responses found when unpredicted sounds were coupled with fearful faces were better explained by a dual model (calling for both a cortical and a fast subcortical pathway to the amygdala) than by a single cortical model.

Whereas it is widely accepted that the cortical "high road" relies on the well-known primary visual pathway from the thalamic LGN to cortical visual areas (see part I in this section) and from there to the amygdala, direct anatomical evidence about the existence, in humans, of the subcortical "low road" is still scarce. Some authors argued against the existence of a single subcortical route for the non-conscious perception of emotions, proposing a multiple-road model (Pessoa & Adolphs, 2010). However, converging evidence from animal models and lesion and neuroimaging studies on humans point to a subcortical network, encompassing the SC, the thalamic pulvinar and the amygdala (Figure 3), as the possible anatomical substrate of the "low road", bypassing primary visual areas and purportedly mediating the implicit visual processing of affective stimuli.

Studies on rats using anterograde tracers, revealed the presence of direct colliculo-thalamic and thalamo-amygdaloid connections (Linke et al., 1999) and suggested the existence of two routes to the amygdala, one cortical and one subcortical, mediating fear conditioning (Shi & Davis, 2001). Similar projections, from the SC to the thalamic pulvinar and from there to the amygdala, have been identified in the tree shrew, a prototypical primate (Chomsung et al., 2008; Day-Brown et al., 2010), as well as in monkeys (Jones & Burton, 1976; Romanski et al., 1997). In humans, fMRI studies on healthy participants reported that subliminally perceived (i.e. backward-masked) fearful signals elicited enhanced activity in the SC, pulvinar and amygdala, with increased functional connectivity within these neural sites, suggesting that a direct subcortical network to the amygdala might underlie implicit fear processing (Morris et al., 1999; Liddell et al., 2005; L. M. Williams et al., 2006a). Similar results were obtained in a study on a hemianopic patient, demonstrating that the colliculo-

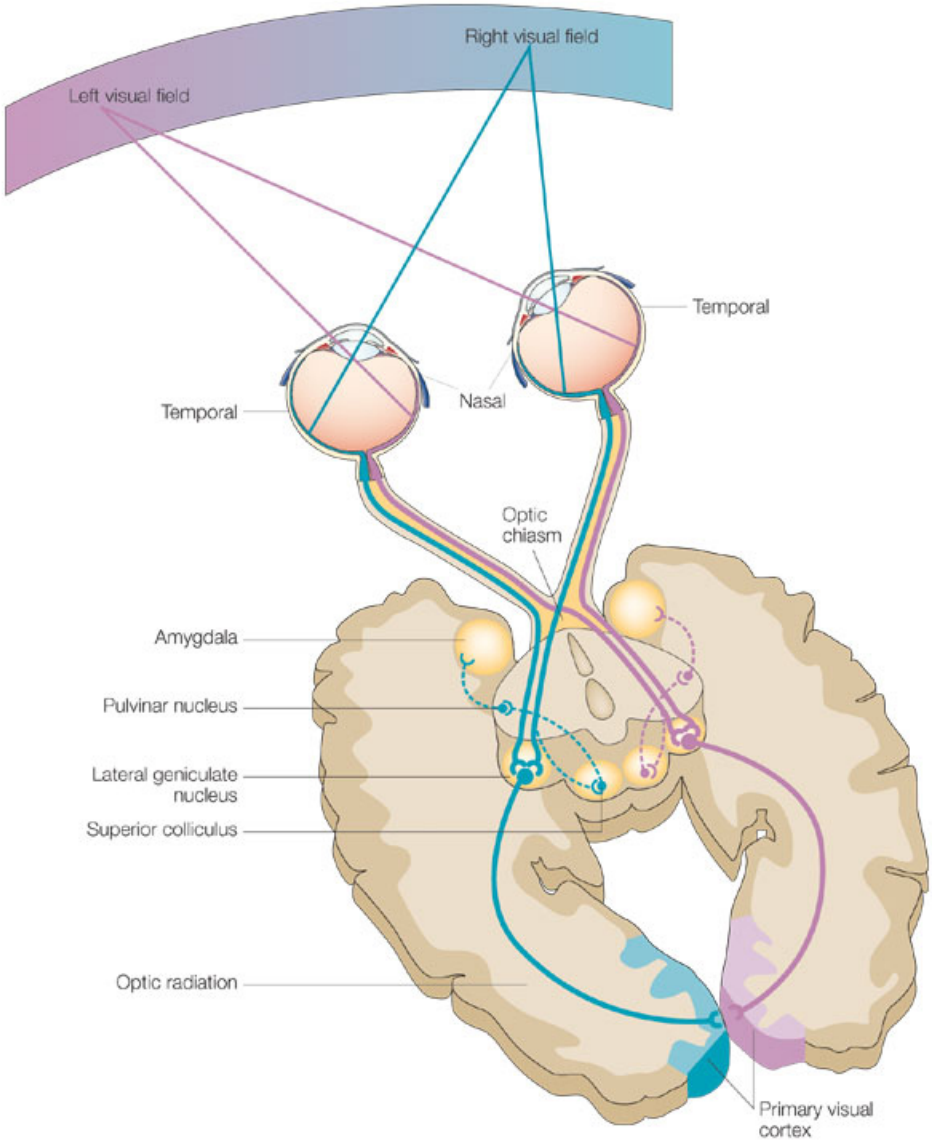

Figure 3. Schematic representation of primary and subcortical visual pathways. Solid lines represent the primary, retino-geniculo-striate visual pathway. Dashed lines represent the subcortical, retino-colliculo-pulvinar visual pathway to the amygdala (readapted from Hannula et al., 2005).

pulvinar-amygdala network is still functional, even when visual stimuli cannot be consciously perceived because of a striatal lesion (Morris et al., 2001).

In further support of the role of the pulvinar in conveying visual information towards the amygdala, it has been shown that in patients with a pulvinar lesion, both automatic responses to visual threat (Ward et al., 2005) and its recognition (Ward et al., 2007) is

impaired. First direct evidence about the existence of colliculo-pulvinar projections to the amygdala in humans came from a recent study by Tamietto et al. (2012) using diffusion tensor imaging (DTI), a non-invasive magnetic resonance-based technique for tracing white matter fibres connecting areas and structures in the brain (Le Bihan & Johansen-Berg, 2012). The authors found fibre connections between the SC and amygdala via the pulvinar, both in a blindsight patient (GY) with unilateral destruction of V1 and in healthy controls. Interestingly, qualitative and quantitative modifications of the connections within this network were found in the patient's lesioned hemisphere, compared to both his intact hemisphere and healthy controls. These results suggest that the destruction of the striate cortex induces structural and functional reorganisation of visual pathways, resulting in strengthened connections within the spared subcortical route to the amygdala.

The literature reviewed here provides compelling evidence about the existence of a subcortical "low road" that possibly mediates residual implicit processing of emotional stimuli, when conscious visual perception is prevented by a lesion to the primary geniculo-striatal pathway. Nevertheless, the functional properties of this subcortical colliculo-pulvinar-amygdala route are still debated, since it is not clear whether it specifically mediates responses to potential threat or to emotional stimuli in general, or, even more generally, to unspecific novel and relevant events in the environment (Garrido, 2012).

1.2 Experiment 1 - Unseen fearful faces facilitate motor responses to seen stimuli in patients with visual field defects

A variety of studies on both animals and humans have focused on the neural bases of emotional processes. Special attention has been paid to fear processing, because of its

relevance for survival and consequent evolutionary advantage (Öhman & Wiens, 2003). Due to the prominent role fear plays in mediating adaptive responses, it has been suggested that a dual-route system for fear perception evolved to facilitate optimal detection and response to dangerous stimuli (LeDoux, 1996). According to this theory (see section 1.1), fearful stimuli might be processed both by (i) a "high road", involving cortical as well as sub-cortical networks, which enables a slower, conscious and detailed processing of stimulus features and context, and by (ii) a short-latency, sub-cortical "low-road", allowing the perception of threatening stimuli automatically and without awareness. As highlighted in section 1.1, neuroimaging studies on both blindsight patients (Morris et al., 2001) and healthy subjects (e.g. see: Morris et al., 1999; Liddell et al., 2005) supported the existence of the "low road" for emotional processing, pointing to the superior colliculus, the pulvinar and the amygdala as part of this subcortical network (for a critical perspective on the "low road" hypothesis, see: Pessoa & Adolphs, 2010).

The study of patients with visual field defects offers a unique opportunity to investigate the nature of the emotional processes mediated by the "low road" to the amygdala. Indeed, in these patients cortical visual processing (i.e. the "high road") is interrupted by a lesion to the geniculo-striate pathway responsible for conscious vision, hence any kind of implicit emotional processing evident for stimuli within their field defect can be reasonably attributed to the activity of the spared "low road" pathway.

A number of previous studies on clinically blind patients have provided evidence for implicit processing of the affective valence of visual stimuli in the absence of perceptual awareness (i.e. affective blindsight; see Introduction). For example, a

restricted number of cases (i.e. patients GY, DB and TN) demonstrated the remarkable ability to perform above chance level in direct tasks (i.e. forced-choice paradigms) requiring the discrimination of the emotional content of faces presented in their blind field (de Gelder et al., 1999; 2002; Pegna et al., 2005; Tamietto et al., 2009). Notably, the above-chance discriminative ability of these patients was evident for a wide range of emotions, including fear, anger, sadness and happiness.

In indirect tasks (i.e. redundant target paradigms), where the implicit processing of unseen stimuli is inferred from the effect exerted on the response to seen targets, some of these patients (GY and DB) displayed faster RTs when emotionally congruent pairs of faces were concurrently presented in the intact and blind fields (i.e.: fearful-fearful or sad-sad), compared to incongruent pairs (i.e.: fearful-sad or sad-fearful) and unilaterally presented faces (i.e. single fearful or sad face presented in the intact field only) (de Gelder et al., 2001). Another study investigating emotional contagion in hemianopic patients (GY and DB) also showed an implicit effect of unseen emotions, by demonstrating that happy and fearful faces and bodies presented in the blind visual field could trigger fast, automatic and emotion-specific EMG responses (Tamietto et al., 2009).

In the literature investigating implicit emotional processing in patients with visual field defects, the majority of evidence came from the study of two blindsight patients, namely GY and DB (see Introduction for a detailed review). The implicit effects observed in these patients have been attributed to the activity of the colliculo-pulvinar-amygdala pathway for emotions. Indeed, the reported implicit effects are consistent with LeDoux's hypothesis that a subcortical "low road" can mediate emotional processing automatically and without awareness. However, before making any inference about the exclusive subcortical nature of any observed effect, it is

crucial to demonstrate the absence of any form of cortical processing in the tested patients. Unfortunately, this appears not to be the case for patients GY and DB.

Noteworthy, both GY and DB demonstrated above-chance performance over an impressive range of direct tasks, testing localisation (e.g. Weiskrantz et al., 1974), detection (e.g. Weiskrantz et al., 1991) and motion perception (e.g. Weiskrantz et al., 1995) abilities, as well as the discrimination of colour (e.g. Brent et al., 1994), orientation (e.g.: Weiskrantz et al., 1974; Morland et al., 1996) and of the gender (e.g. Morris et al., 2001) and emotional expression (e.g. Tamietto et al., 2009) of faces. The above-chance performance displayed by GY and DB in direct tasks raises the suspicion that these patients, despite V1 lesions, can still recruit, to some extent, cortical areas belonging to the "high road" for emotional processing. Accordingly, Stoerig and Cowey (1997), suggested that explicit blindsight functions are likely to depend on the presence of functional extrastriate cortical areas ipsilateral to the lesion. Indeed, as shown by studies on hemidecorticated patients (Perenin, 1991; King et al., 1996; Stoerig et al., 1996), when the cortex is totally ablated there is no evidence of blindsight in direct tasks. In addition, a number of observations further support the hypothesis that the "high road" could still be functional in GY and DB. For example, in the case of GY, due to the early occurrence of the lesional event (7 years age; e.g. see de Gelder et al., 2002), plasticity phenomena could have promoted a functional reorganisation within visual pathways involving extrastriate areas. On the other hand, in the case of DB, cortical areas affected by the lesion could never be precisely determined by MRI because of the presence of metal clips in his brain (e.g. see de Gelder et al., 2002). Moreover, both GY and DB have been extensively tested over years and, during testing, have often reported the feeling that something occurred in their blind visual field (i.e. Type II blindsight). Finally, the congruency-dependent

effects displayed by GY and DB in tasks with redundant emotional stimuli (de Gelder et al., 2001) are strikingly alike the congruency-dependent effects reported in healthy subjects, when tested in similar tasks with masked facial expressions to mimic the hemianopic deficit (Tamietto & de Gelder, 2008a). This parallel with healthy subjects, who cannot consciously perceive stimuli because of the masking procedure, but still have intact cortex, further strengthens the idea that blindsight patients can rely on cortical processing, despite their visual unawareness.

Taken together, all these observations strongly suggest that the performance of patients with affective blindsight could not stem exclusively from the activity of the subcortical "low road", but also from the partial contribution of the cortical "high road" for emotional processing. Thus, to exclude any possible confound and investigate the specific role of the subcortical networks in implicit emotional processing, it is critical to test patients with lesions to the geniculo-striate pathway, in whom the presence of residual cortical processing can be ruled out.

For this reason, the present study will test patients with visual field defects without any awareness for stimuli presented in the blind field, that is, performing at the chance level in direct tasks. The aim here is to assess whether such patients, who can only rely on the "low road" for emotional processing, demonstrate visual residual abilities for emotional stimuli in an indirect task. According to findings in the literature on classical blindsight patients (e.g.: de Gelder et al., 1999; 2001), implicit visual processing for emotional stimuli should be evident regardless of the type of emotion presented in the blind field. However, considering its potential adaptive value (Öhman & Wiens, 2003), a specific implicit visual processing for fearful stimuli might be expected. In fact, recent fear conditioning studies on patients with visual field defects have provided evidence for implicit processing of unseen visual stimuli

that had been previously conditioned with an aversive event (Hamm et al., 2003; Anders et al., 2004; 2009), suggesting that fear-related stimuli might be preferentially processed at the implicit level.

To directly assess their discriminative ability for unseen visual stimuli, in Experiment 1a patients will be tested in 2AFC tasks, where emotional faces (happy or fearful), neutral faces of either gender (male or female) and geometrical shapes (circle or square) will be presented to their blind visual field. In addition, to investigate implicit visual processing of emotional stimuli in indirect tasks, in Experiments 1b and 1c patients will perform go/no-go tasks with redundant stimuli, consisting of emotional faces, neutral faces, or geometrical shapes. If an alternative neural circuit specialised in fear perception is active and functional in patients with visual field defects, a specific effect (i.e., faster RTs) is expected when fearful faces, but not happy and scrambled faces, are presented in the blind field. In contrast with patients tested in classical blindsight investigations, no general congruency effect should be evident when fearful faces are not presented to patients performing at chance in 2AFC tasks.

Materials and Methods

Patients

Eight right-handed patients with chronic visual field defects (4 females; mean age: 48.9; range: 28-69) participated in Experiments 1a, 1b and 1c. Five patients reported a right visual field defect, whereas three patients reported a left visual field defect, as documented by an automated perimetry test (Medmont M700, Melbourne, Australia). All patients presented post-geniculate lesions resulting in deafferentation or destruction of the striate cortex, as confirmed by computed tomography (CT) or

magnetic resonance imaging (MRI) scanning. CT/MRI scans and clinical details and are reported in Figure 4 and Table 1, respectively. All patients had normal or corrected-to-normal visual acuity and no coexisting neurological and psychiatric disorder or cognitive deficit.

In accordance with the Declaration of Helsinki, patients provided written informed consent to participate to the study, approved by the Departmental Ethical Committee.

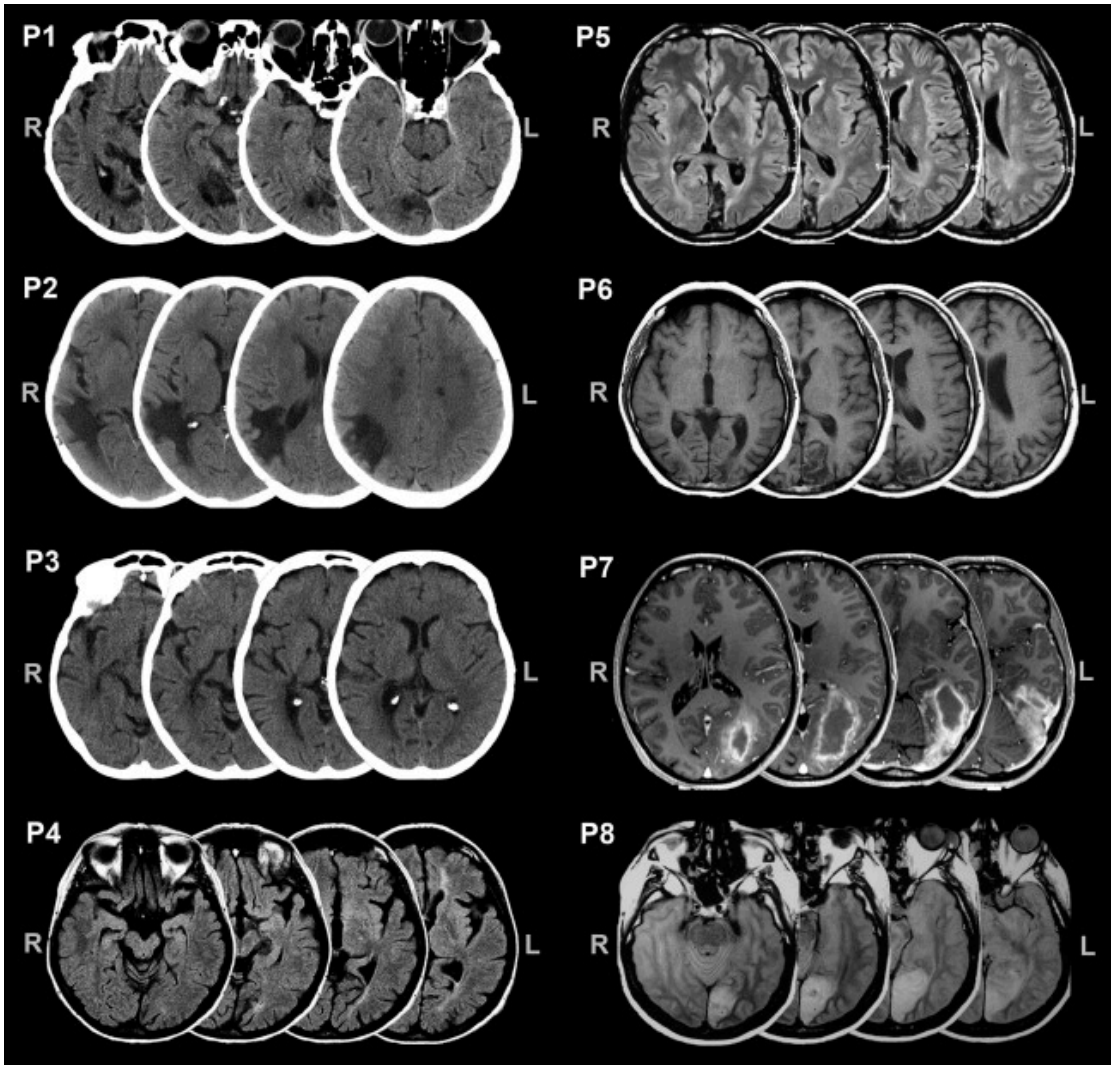

Figure 4. CT or MRI scans of patients in axial views. R = right; L = left.

Case	Sex	Age	Years of Education	Time since onset (months)	Cause of hemianopia	Side of VFD	Lesion site
P1	M	69	5	6	vascular	Left	Right temporal-occipital
P2	M	59	13	8	traumatic	Left	Right temporal-parietal-occipital
P3	F	56	16	55	vascular	Left	Right temporal-occipital
P4	F	40	17	238	traumatic	Right	Left temporo-occipital
P5	M	34	11	7	vascular	Right	Left parietal-occipital
P6	F	44	8	8	vascular	Right	Left parieto-occipital
P7	F	29	13	7	vascular (AVM)	Right	Left temporal-parietal-occipital
P8	M	60	13	7	vascular	Right	Left occipital

Table 1. Summary of clinical, demographic and lesional data of patients. M = male; F = female; VFD = visual field defect; AVM = arteriovenous malformation.

Apparatus

During the experimental sessions patients sat in a dimly lit and sound attenuated room in front of a 17" LCD monitor (refresh rate 60 Hz) at a distance of 57 cm. Eye movements were monitored using a Pan/Tilt optic eye-tracker (Eye-Track ASL-6000; sampling rate 60 Hz). Stimulus presentation was controlled by a PC running Presentation software (Version 0.60, www.neurobs.com). Patients were asked to hold constant fixation on a central white cross subtending a visual angle of 2°. For patients with quadrantopia (P1: upper left quadrantopia; P6; lower right quadrantopia; P7: upper right quadrantopia), the fixation cross was placed at the centre, on either the upper or lower edges of the screen, in order to ensure the presentation of stimuli in the blind field. The central fixation cross and the stimuli were presented against a uniform black background.

Experiment 1a: stimuli, procedure and data analysis

Patients underwent four separate sessions of a 2AFC task where different materials were used as stimuli. In the *visual detection* task (Figure 5a), the stimulus consisted of

a white dot (2° diameter). In the *emotional* task (see Figure 5b), 12 greyscale photographs (Ekman & Friesen, 1976) of six different identities (3 females), showing fearful or happy expressions (7.5° x 11°), were used as stimuli. In the *gender* task (see Figure 5c), stimuli consisted of 6 greyscale photographs (Ekman & Friesen, 1976) of different faces (3 females) with a neutral expression (7.5° x 11°). In the *shape* task (see Figure 5d), white-coloured squares and circles (5° x 5°) were used as stimuli. The trial structure (2250 ms duration) consisted of a blank screen with a central fixation cross (500 ms), followed by the target stimuli (1500 ms) and a subsequent blank screen (250 ms; see Figure 5). After the presentation of each stimulus, a sound prompted patients to verbally respond and responses were manually recorded. A new trial began when patients were fixating at the central fixation cross and the onset was manually controlled by the experimenter. Patients were instructed to keep fixation on a central cross during the task. Trials where eye movements occurred were discarded from the analysis (2%).

Stimuli were randomly presented in the blind visual field, whereas no stimuli were shown in the intact field. In the visual detection task patients were asked to indicate whether or not a white dot was presented in the blind field (50% valid trials, 50% catch trials). In the remaining three tasks they were required to guess which of two types of images were presented in the blind field: fearful vs. happy faces in the emotional task, male vs. female faces in the gender task and circle vs. square in the shape task. Sessions were performed in a counterbalanced order.

In each of the four experimental tasks, patients performed a single block of 180 trials (90 trials for each of the two possible choices). For each task, the mean percentage of correct responses was computed and the accuracy was compared to the chance level (50% correct responses) using a binomial test.

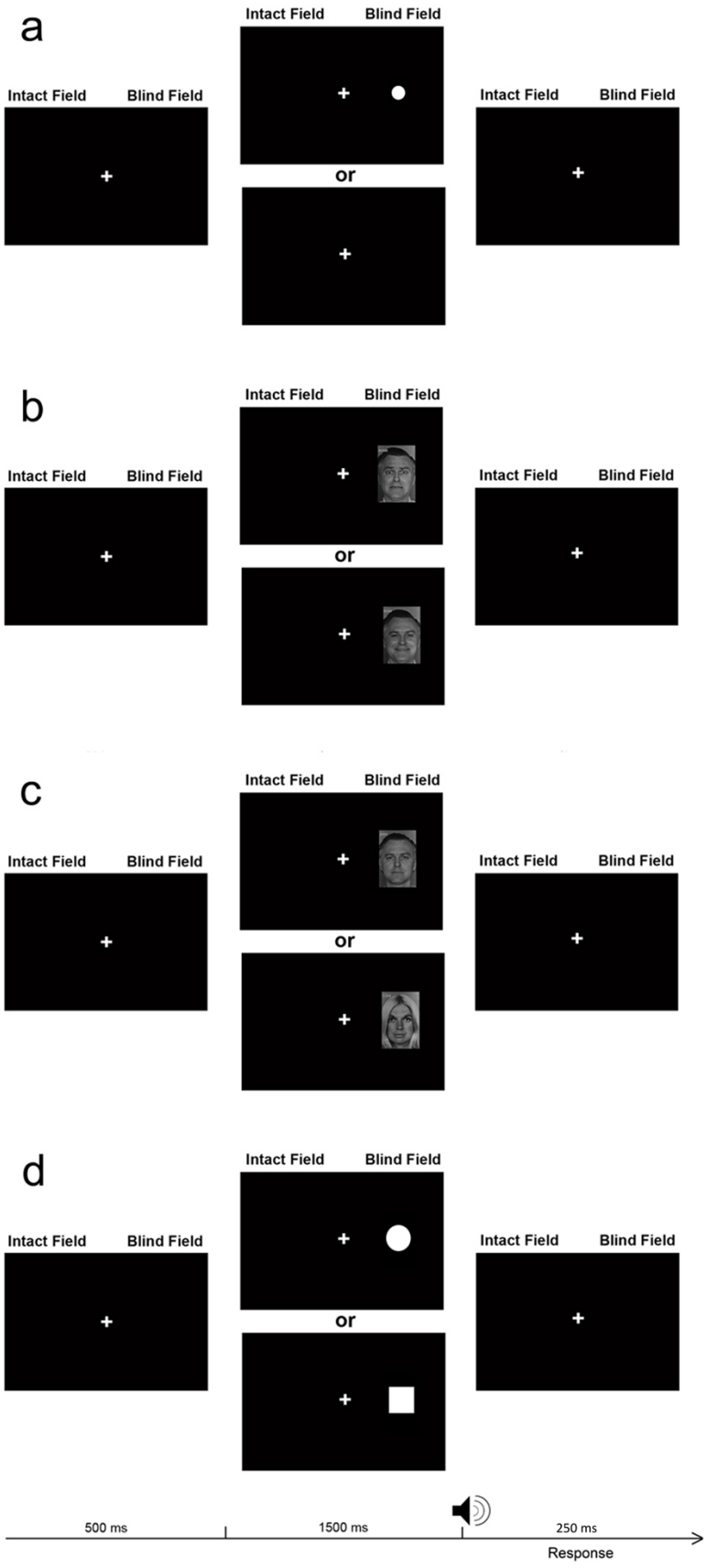

Figure 5. Schematic representation of trial structure and stimuli of Experiment 1a. (a) Visual detection task. (b) Emotional task. (c) Gender task. (d) Shape task.

Experiment 1b: stimuli, procedure and data analysis

Patients underwent a go/no-go task with redundant stimuli, during three separate sessions, involving several different types of stimulus material (see Figure 6). In the *emotional* task, stimuli consisted of 18 greyscale photographs (Ekman & Friesen, 1976) of six different identities (3 females) showing fearful or happy expressions (7.5° x 11°) and scrambled images made by randomly swapping small parts (18 x 18 pixels) of the same emotional faces. The scrambled images had the same rectangular shape, size, luminance and spatial frequency as the emotional faces. In the *gender* task, stimuli consisted of 6 greyscale photographs (Ekman & Friesen, 1976) of different faces (3 females) with a neutral expression (7.5° x 11°) and scrambled images made by randomly swapping small parts (18 x 18 pixels) of the same neutral faces. The scrambled images had the same rectangular shape, size, luminance and spatial frequency as the neutral faces. In the *shape* task, solid white squares and circles (5° x 5°) were used, as well as a scrambled shape made by randomly swapping small parts (10 x 10 pixels) of an irregular shape of the same size and colour as the stimuli. The structure of each trial consisted of a blank screen with the central fixation cross (500 ms), followed by the stimuli (200 ms) and a subsequent blank screen (1000 ms; see Figure 6). A new trial automatically began after an inter-trial interval of random duration (500-800 ms).

Patients attended three different sessions, where they separately performed an emotional task, a gender task and a shape task, administered in a counterbalanced order. Throughout the sessions patients were asked to keep central fixation. Trials with eye movements were discarded from the analysis (6%). In each session (emotional, gender or shape task) patients performed 6 blocks of trials. In half of the blocks, they were asked to quickly respond to a specific target presented in the intact

field (by pressing the spacebar on a keyboard) while ignoring the non-target; in the remaining half of the blocks, the categories of target and non-target stimuli were swapped (i.e. the previous non-target stimulus became the target). For example, during the emotional task, targets consisted of fearful faces in 3 blocks, whereas no response was required for happy faces; in the remaining 3 blocks, the targets were happy faces, with no response required for fearful faces. In the gender task, targets were female faces or male faces. In the shape task, targets were circles or squares. For each task, a total of 216 trials were presented (108 for each type of target; 18 for each condition). Target stimuli were presented in the intact field and coupled with concurrent stimuli in the blind field. Pairs of stimuli appeared pseudo-randomly at 10° to the left and to the right of the fixation cross.

In the emotional task, target stimuli presented in the intact field could be coupled with three different types of images in the blind field (see Figure 6a): (i) a scrambled image, in the unilateral condition; (ii) an identical face with the same emotional expression, in the bilateral congruent condition; and (iii) an identical face with a different emotional expression, in the bilateral incongruent condition. Similarly, in the gender task, target stimuli in the intact field were coupled in the blind field with: (i) a scrambled image, in the unilateral condition; (ii) an identical face, in the bilateral congruent condition; (iii) a face of the opposite gender, in the bilateral incongruent condition (see Figure 6b). Finally, in the shape task, target stimuli in the intact field were coupled in the blind field with: (i) a scrambled shape, in the unilateral condition; (ii) an identical shape, in the bilateral congruent condition; and (iii) the alternative shape, in the bilateral incongruent condition (see Figure 6c).

To control for outliers, trials with RTs exceeding 1.5 standard deviations above or below the mean of each condition (10% of the trials in the emotional task; 11% of the

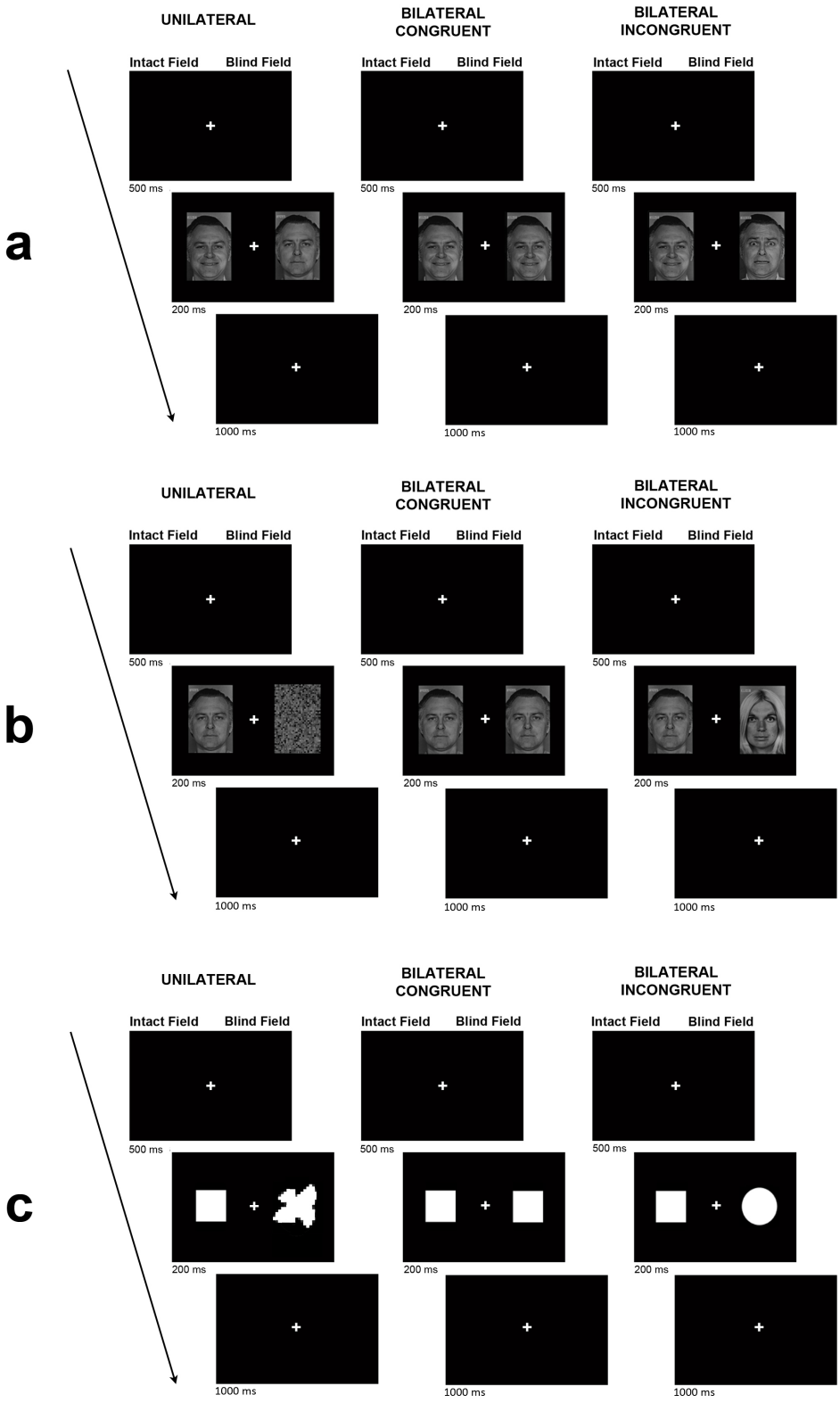

Figure 6. Schematic representation of trial structure and stimuli of the Experiment 1b, in the unilateral (leftmost column), bilateral congruent (central column) and bilateral incongruent (rightmost column) conditions. (a) Emotional task (example of a trial with a happy face as a target); (b) Gender task (example of a trial with a male face as a target); (c) Shape task (example of a trial with a square as a target).

trials in the gender task; 10% of the trials in the shape task) were excluded. Mean error rates were: 9% (±7%) in the emotional task, 4% (±6%) in the gender task and 1% (±0.7%) in the shape task. RTs in each task were analysed with three separate ANOVAs: (i) Target Emotion (fear, happiness) by Condition (unilateral, bilateral congruent, bilateral incongruent); (ii) Target Gender (male, female) by Condition (unilateral, bilateral congruent, bilateral incongruent); (iii) Target Shape (circle, square) by condition (unilateral, bilateral congruent, bilateral incongruent). Significant effects were analysed using a Newman-Keuls Test.

Experiment 1c: stimuli, procedure and data analysis

Patients underwent a go/no-go task with redundant neutral and emotional stimuli (see Figure 7). Stimuli consisted of 18 greyscale photographs (Ekman & Friesen, 1976) of six different identities (3 females) showing fearful, happy or neutral expressions (7.5° x 11°) and scrambled images made by randomly swapping small parts (18 x 18 pixels) of the same neutral faces. The original pictures were modified using Photoshop CS5 (Adobe Systems Inc.), extracting an oval area centred on the face, in order to remove the hairline and create an identical facial contour for each stimulus. The scrambled images had the same oval shape, size, luminance and spatial frequency as the neutral faces. The structure of each trial consisted of a blank screen with a central fixation cross (500 ms), followed by the stimuli (200 ms) and a subsequent blank screen (1000 ms; see Figure 7). A new trial automatically began after an inter-trial interval of random duration (500-800 ms).

Trials with eye movements were discarded from the analysis (5%). Patients performed 6 blocks of trials. In half of the blocks, they were asked to quickly respond to a female neutral face in the intact field (by pressing the spacebar on a keyboard)

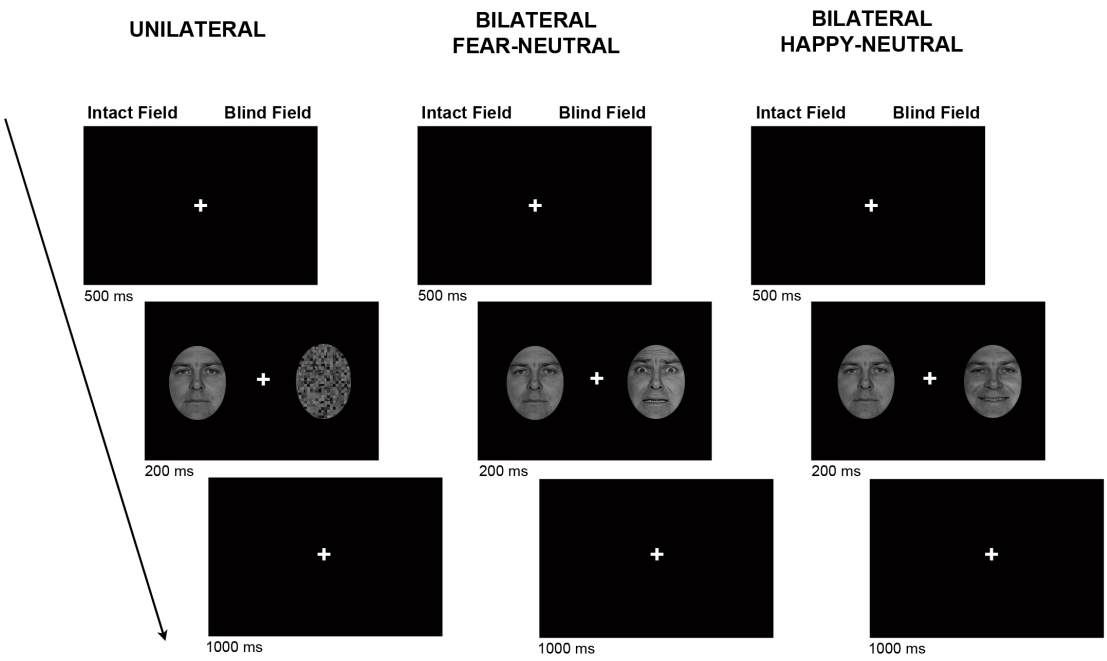

Figure 7. Schematic representation of trial structure and stimuli of the Experiment 1c, The figure depicts examples of unilateral (leftmost column), bilateral fear-neutral (central column) and bilateral happy-neutral (rightmost column) conditions, when the target is a male face.

and to not respond to the non-target male neutral face; vice versa in the remaining half of the blocks. A total of 216 trials were presented (108 for each type of target; 18 for each condition). Target stimuli were presented in the intact field and coupled with concurrent stimuli in the blind field. Pairs of stimuli appeared pseudo-randomly at 10° to the left and to the right of the fixation cross.

Target stimuli were presented in the intact field, consisting of neutral faces of male or female actors; the simultaneously presented image in the blind field was either: (i) a scrambled image, in the unilateral condition; (ii) an identical face with a fearful expression, in the bilateral fear-neutral condition; (iii) an identical face with a happy expression, in the bilateral happiness-neutral condition. To control for outliers, trials with response times exceeding 1.5 standard deviations above or below the mean were excluded from the analysis (9%). The mean error rate was 7% (±5%). Responses to male and female targets were collapsed and RTs were analysed with a one-way

ANOVA with Condition (unilateral, bilateral fear-neutral, bilateral happiness-neutral) as the main factor.

Results

Experiment 1a: chance-level performance for stimuli presented in the blind field

Experiment 1 was designed to test whether the patients were able to detect the presence or discriminate the nature of stimuli presented in the blind field. To this end, patients were first asked to guess about the presence of small dots presented in the blind field (visual detection task). In the three remaining tasks, patients were asked to guess the type of image presented in the blind field. For each task, different stimuli were presented: emotional faces (happy or fearful), gender faces (male or female) and geometrical shapes (circle or square).

For each patient and each task, the percentage of correct responses was computed and compared to the chance level (50% correct responses) with a binomial test. Performance did not significantly differ from chance level in the visual detection task (see Table 2 and Figure 8; all ps>0.3). Since patients are often reluctant to report the presence of stimuli in their blind field, the "present" and "absent" responses were also compared to the chance level with a binomial test, in order to assess whether a response bias was present. The results revealed no significant difference from chance (all ps>0.14; see Table 3). Performances also did not significantly differ from chance level in the remaining discrimination tasks (emotional task: all ps>0.1; gender task: all ps>0.1; shape task: all ps>0.3), indicating that patients were not aware of the presence and the nature of stimuli presented in the blind field (see Table 2 and Figure 8).

Case	Visual Detection Task	Emotional Task	Gender Task	Shape Task
P1	53%	50%	56%	46%
P2	53%	56%	50%	53%
P3	53%	47%	50%	47%
P4	47%	56%	48%	50%
P5	49%	55%	52%	49%
P6	51%	47%	49%	51%
P7	51%	50%	48%	48%
P8	54%	54%	53%	53%

Table 2. Percentage of correct responses in the four sessions of Experiment 1a (2AFC). Results are reported for each patient separately.

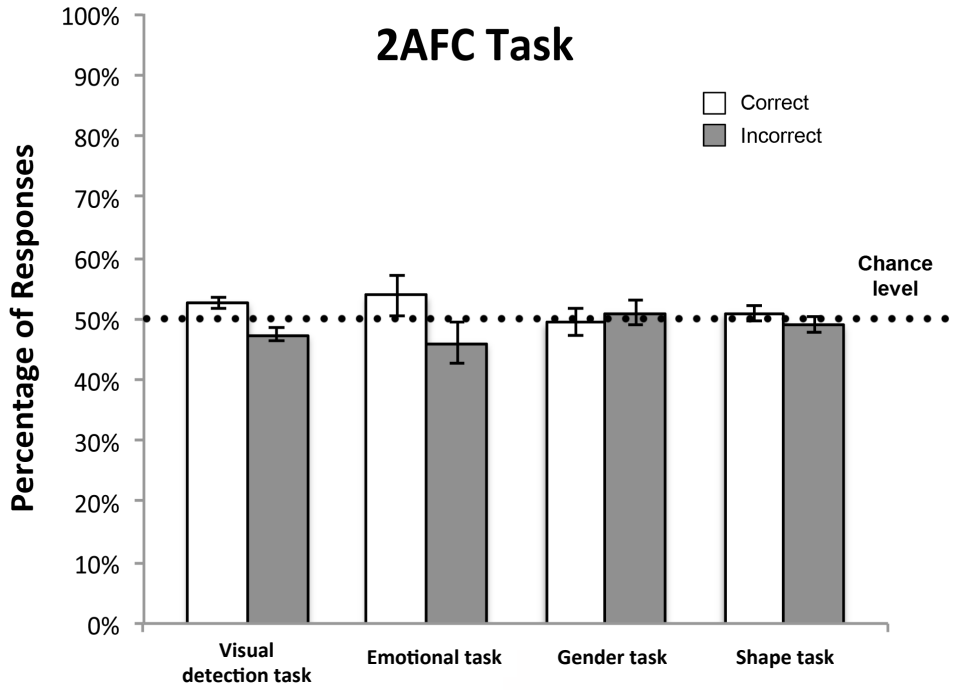

Figure 8. Mean percentage of correct (white columns) and incorrect (grey columns) responses for each session of Experiment 1a (2AFC). From left to right: visual detection task, emotional task, gender task, shape task. The dotted line indicates the chance level. Error bars represent the standard error of the mean (s. e. m). Patients' performances did not differ significantly from chance level in any session.

Case	Response Present	Response Absent	P value
P1	50%	50%	1
P2	47%	53%	0.37
P3	44%	56%	0.14
P4	53%	47%	0.37
P5	49%	51%	0.88
P6	53%	47%	0.46
P7	54%	46%	0.23
P8	55%	45%	0.19

Table 3. Percentage of "present" and "absent" responses in the visual detection session of the two-alternative forced choice task. Results are reported for each patient separately.

Experiment 1b: implicit visual processing for unseen fearful faces in an emotional discrimination task.

Experiment 1b employed an indirect method to investigate the presence of implicit visual processing of emotional stimuli presented in the blind field. Patients participated in a go/no go task, performed in three separate sessions, with redundant stimuli consisting of emotional faces (fear or happiness), neutral faces of different gender (male or female) or geometrical shapes (circle or square). Participants were presented with images displayed concurrently in both intact and blind fields and were instructed to quickly respond to the target image in the intact field and to withhold responses to the non-target images.

For instance, in the emotional task, when the target image in the intact field was a fearful face, in the blind field three different types of image could appear: a scrambled image (Fs; unilateral); an identical fearful face (Ff; bilateral congruent); or a happy face (Fh; bilateral incongruent). Similarly, when the target image in the intact field was a happy face, three different images could be presented in the blind field: a

scrambled image (Hs; unilateral); an identical happy face (Hh; bilateral congruent); or a fearful face (Hf; bilateral incongruent). RTs were analysed with a 2 (Target Emotion: fear vs. happiness) x 3 (Condition: unilateral vs. bilateral congruent vs. bilateral incongruent) ANOVA.

Results revealed no significant main effect of Target Emotion ($F_{(1,7)}$=0.62, p=0.45) or Condition ($F_{(2,14)}$=0.63, p=0.55). In contrast, a significant interaction Target Emotion x Condition ($F_{(2,14)}$=10.75, p=0.001) was found. Post hoc comparisons revealed a significant reduction of reaction times for the condition where patients were asked to respond to a happy face presented in the intact field whilst a fearful face was presented in the blind field (Hf: 586 ms), compared to all the remaining conditions (Fs: 614 ms, p=0.05; Ff: 618 ms, p=0.05; Fh: 641 ms, p=0.002; Hs: 629 ms, p=0.01; Hh: 611 ms, p=0.03; see Figure 9a). No additional significant comparison was observed (all ps>0.1). In order to ensure that that the observed effect was not due to the different lesional profiles of the participating patients, we divided the sample into two subgroups: group 1 (P1, P2, P3 and P4) comprising patients with spared primary visual areas, whereas group 2 (P5, P6, P7 and P8) comprising patients with lesions to the primary visual areas. Again, reaction times were analysed with a 2 (Group: group 1 vs group 2) x 2 (Target Emotion: fear vs. happiness) x 3 (Condition: unilateral vs. bilateral congruent vs. bilateral incongruent) ANOVA. Results revealed no significant main effect of group ($F_{(1,6)}$=0.02, p=0.9) nor significant interactions between the factor group and the factors Target Emotion or Condition (all ps>0.32). Due to the small size of the groups, we also performed non-parametric tests. For each subject in the two groups, five indices were separately computed representing the gain in ms produced by the Hf condition, compared to each of the other five conditions. The five indices were obtained calculating the difference between RTs in the Hf condition and

RTs in the other conditions (Hf-Fs; Hf-Ff; Hf-Fh; Hf-Hs; Hf-Hh). Groups 1 and 2 were then compared on each of these new indices with a Kolmogorov-Smirnov test (e.g. Hf-Fs group 1 vs Hf-Fs group 2). No significant group differences were observed for any index (all ps>0.1).

In the remaining sessions, where gender faces and geometrical shapes were presented, the ANOVAs on RTs revealed no significant main effect (all Fs<1.59; all ps> .24),

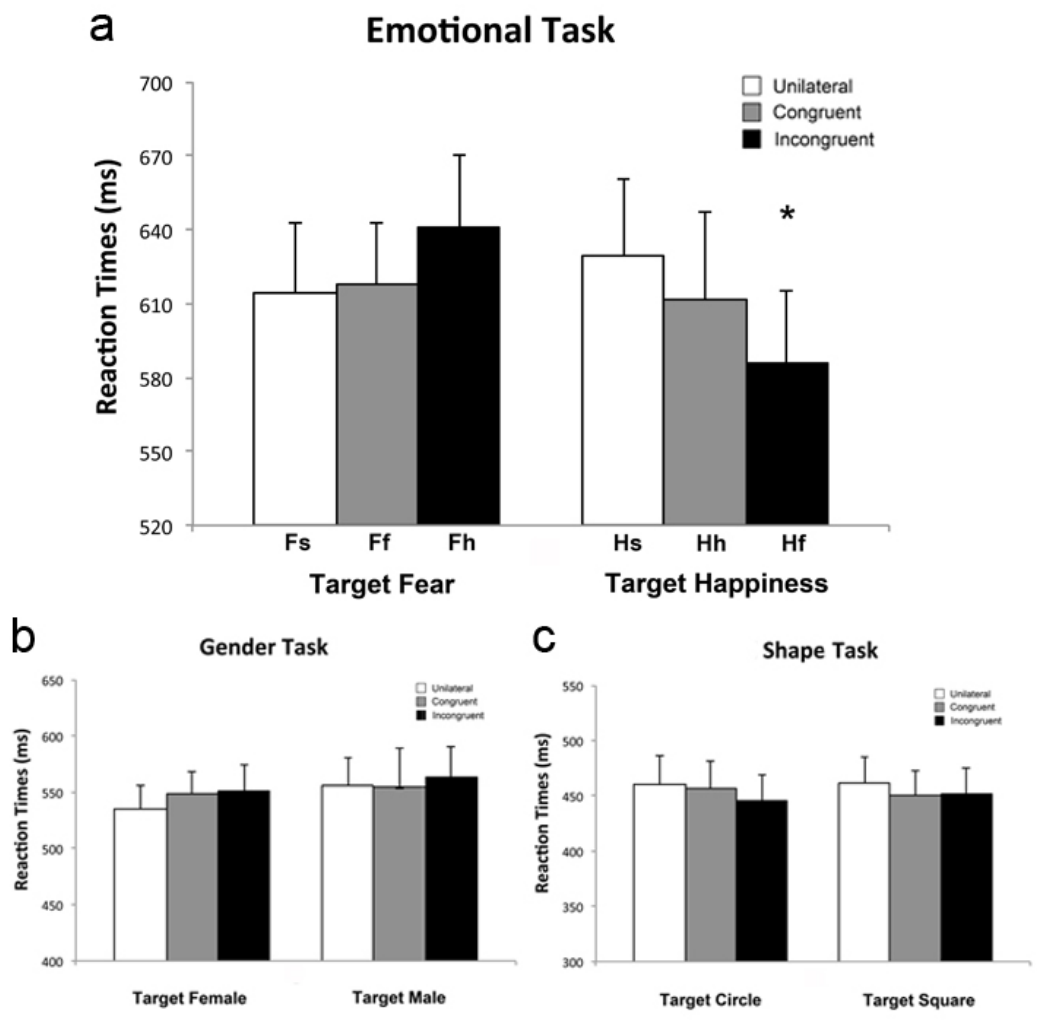

Figure 9. Mean RTs for each condition (unilateral, bilateral congruent, bilateral incongruent) of the three sessions of Experiment 1b (go/no-go task). Panel a: emotional task; Panel b: gender task; Panel c: geometrical shapes task. Error bars represent the standard error of the mean (SEM). Asterisks indicate a p value <0.05. In the emotional task, reaction times were significantly slower in the conditions where fearful faces were presented in the blind field while happy faces were concurrently presented in the intact field (Hf), compared to all the remaining conditions (Fs, Ff, Fh, Hs and Hh).

or interaction (all Fs<0.6; all ps>0.56), revealing the absence of any effect due to implicit visual processing of stimuli presented in the blind field (Figure 9b and c).

Patients' performances in the emotional task revealed faster reaction times only when happy faces were presented in the intact field while fearful faces were concurrently presented in the blind field. In order to test whether the observed effect for unseen fearful face presentation was also evident in a task where the emotional content of stimuli was task-irrelevant, patients were also tested in a go/no go gender discrimination task where neutral faces were presented in the intact field while emotional faces were concurrently presented in the blind field (Experiment 1c).

Experiment 1c: implicit visual processing for unseen fearful faces in a gender discrimination task.

In Experiment 1c, patients undertook a go/no go task with redundant stimuli. They were presented with images displayed concurrently in the intact and in the blind field and were instructed to quickly respond to the target image in the intact field (female or male) and to not respond to the other image category. Target images in the intact field were neutral female or male faces, whereas in the blind field different types of images were presented: a scrambled image (unilateral condition); an identical face expressing fear (bilateral fear-neutral condition); or an identical face expressing happiness (bilateral happiness-neutral condition). Reaction times were analysed with a one-way ANOVA with Condition (unilateral, bilateral fear-neutral, bilateral happiness-neutral) as the main factor.

Results revealed a significant main effect of Condition ($F_{(2,14)}$=5.03, p=0.02) and post-hoc analysis showed a significant reduction of reaction times in the bilateral fear-neutral condition (566 ms), compared to the unilateral (595 ms; p=0.03) and the

bilateral happiness-neutral condition (590 ms; p=0.03; see Figure 10).

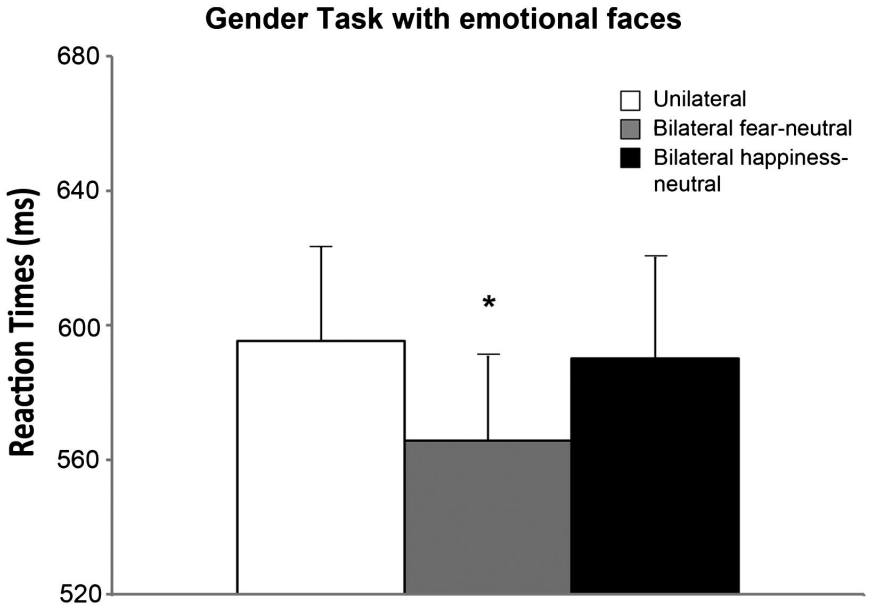

Figure 10. Mean RTs for each condition (unilateral, bilateral fear-neutral, bilateral happiness-neutral) of Experiment 1c (go/no-go task). Error bars represent the standard error of the mean (SEM). Asterisks indicate faster RTs in the bilateral fear-neutral condition, compared to the unilateral and to the bilateral happiness-neutral conditions (all ps<0.05).

Discussion

The aim of the present study was to test the functionality of the "low road" for emotional processing by investigating the implicit effects of unseen emotions in patients with visual field defects, in whom the "high road" is not functional due to a lesion to the geniculo-striate visual pathway.

Results showed that, in such patients, behavioural responses to seen stimuli were specifically facilitated by the concurrent presentation of fearful faces in their blind field, both in emotional and non-emotional tasks. In particular, in an emotion discrimination task, patients' simple manual responses to happy faces in their intact field were faster when fearful faces were concurrently presented in their blind field. The facilitative behavioural effect elicited by unseen fearful faces was also found

when the emotional content of the stimuli was task-irrelevant, i.e. when patients responded to the gender of neutral faces in the intact field. Specifically, patients were faster in responding to the gender component of seen neutral stimuli when a fearful face was concurrently presented in the blind field.

The specific facilitative effect of unseen fearful faces observed here in hemianopic patients suggests that when the primary visual pathway (i.e. the "high road") has been damaged by lesion, the only visual information available at the implicit level is that related to fear, acting as a warning signal able to boost the motor system. In fact, fearful faces are known to be an optimal cue to engage orientation and rapid detection of potentially dangerous signals, and neuroimaging studies on healthy volunteers have revealed that the presentation of stimuli expressing fear could induce activation of the circuits mediating actions, suggesting a specific role of fear-related stimuli in facilitating defensive (i.e. "flight-or-fight") motor responses (de Gelder et al., 2004).

Thus, the behavioural advantage found here in the presence of unseen fearful faces might reflect the implementation of a reactive mechanism, which rapidly and specifically alerts the motor system in the presence of threatening stimuli. Furthermore, the observation that this facilitation was evident both during an emotional task and during a task where the emotional content of stimuli was task-irrelevant, suggests the great adaptive value of this mechanism, which allows the fast motor recruitment whenever a potential threat is detected, independently of the context. This would be in line with the hypothesis (LeDoux, 1996) that the "low road" for emotional processing only provides coarse and rapid visual processing, in order to preventively activate the motor system in any potentially dangerous situation. The more accurate but slower "high road" would intervene only at a later stage, evaluating the appropriateness of the response relative to the context.

Converging anatomical and neuroimaging studies (see section 1.1 for an extensive review) support the hypothesis of a "low road" for emotional processing, by demonstrating the existence of a subcortical visual network encompassing the SC, the pulvinar and the amygdala. Within this subcortical network, direct projections from the SC and the pulvinar convey visual input to the amygdala (Tamietto et al., 2012), which is known to modulate behavioural, autonomic and endocrine components of emotional responses (LeDoux, 1996), and to play a pivotal role in a continuous vigilance system, monitoring the environment for stimuli signalling increases in threat probability (Whalen, 2007). Given that the amygdala is a core component of the "low road" for emotional processing, and considering its relevance in fear processing, it is not surprising that hemianopic patients, who can only rely on the subcortical networks bypassing the lesioned V1, here displayed a specific effect for unseen fearful faces. Moreover, this finding is also consistent with the observation that the colliculo-pulvinar-amygdala network is preferentially activated by the unconscious perception of fearful faces, both in patients with visual field defects (Morris et al., 2001) and healthy subjects (Morris et al., 1999).

It is worth noting that the facilitative effect of unseen fearful faces on RTs was evident in the experimental condition where happy faces were presented as a target in the intact field, but no effect was observed when congruent fearful faces were displayed in the intact field. This result suggests that the presentation of fearful faces in the intact field (i.e. conscious perception) might have inhibited the activation of the subcortical visual pathway, as well as the fast motor response triggered by the implicit processing of unseen fearful stimuli. In line with this hypothesis, it has been observed that conscious fear perception elicited negative functional connectivity within visual

pathways to the amygdala (L. M. Williams et al., 2006a). In other words, when a fearful face is presented in the intact field, an inhibitory modulation of the amygdala might downregulate parallel visual inputs to this subcortical structure, favouring the deployment of selective attentional resources towards the observed salient threatening stimuli. Alternatively, the observation of the facilitative effect of unseen fearful faces only with co-ocurring seen happy faces, i.e. in an emotionally ambiguous condition, might be explained by the active engagement of the amygdala in ambiguous environmental circumstances (Whalen, 1998; 2007), even in the absence of biologically relevant stimuli (Herry et al., 2007). Indeed, a greater activation of the amygdala was found in the presence of an unpredictable series of auditory tones, compared to a predictable series (Herry et al., 2007). In the same vein, the involvement of the amygdala in modulating a vigilance system for detecting fear and ambiguity might be in line with the reduction of RTs during the concurrent presentation of emotional unseen fearful faces and non-emotional seen neutral faces (Experiment 1c). However, further studies are needed, in order to disentangle these alternative explanations.

In Experiments 1b and 1c the fear-specific RT facilitation was evident in a sample of patients who displayed no subjective awareness of the presence of stimuli in their blind fields and, furthermore, did not demonstrate blindsight abilities in direct tasks. In fact, when patients were asked to discriminate the emotional valence of the target in the blind field in a 2AFC task, their performance was at the chance level. Likewise, they showed chance-level performance in 2AFC tasks requiring the detection of the presence of a simple stimulus or the discrimination of the gender of neutral faces or geometrical shapes.

Overall, the pattern of the present behavioural results is in contrast with previous studies where two blindsight patients (GY and DB) were tested with a similar go/no go experimental paradigm (de Gelder et al., 2001), which revealed a summation effect comparable to healthy subjects' performance (Tamietto & de Gelder, 2008a), with faster responses in the bilateral congruent conditions (fear-fear; sad-sad) compared to the unilateral or bilateral incongruent conditions.

Notably, GY and DB differed from the patients of the present study in many respects. Indeed, when tested in 2AFC tasks with emotional stimuli in the blind field, GY and DB could discriminate the emotional valence of many types of facial expressions (i.e. fearful, angry, sad and happy) above chance (de Gelder et al., 1999; 2002; Pegna et al., 2005; Tamietto et al., 2009). Moreover, as previously highlighted in the present dissertation, they demonstrated visual residual functions in the absence of any subjective awareness for several other visual features, (for reviews, see: Weiskrantz, 1986a; 2001; 2009; Cowey, 2010a).

Such behavioural performances suggest that the blindsight patients described in literature might have specific visual residual abilities, uncommon in typical patients with visual field defect, which might be ascribed to a peculiar functional and anatomical reorganization of the visual system. The results of the present study further support the idea that the unusual above-chance emotional discrimination observed in blindsight patients, as well as the congruency-dependent facilitative effect they show in indirect tasks, might reflect higher order cognitive processes that require the contribution of some spared extrastriate areas involved in the cortical "high road" for emotional processing, in addition to the activation of the subcortical "low road" pathway. On the other hand, the fear-specific implicit visual processing observed in the patients of the present study could represent an automatic, low-order process,

solely dependent upon the activation of the “low road” subcortical circuit.

In summary, the present findings support the view that fear plays a specific role in implicit visual processing, probably mediated by the activity of the secondary “low road” visual pathway for fear perception (LeDoux, 1996). In particular, the observation that unseen fearful faces facilitated motor responses to consciously perceived stimuli might be explained by the activity of this automatic subcortical pathway for fear processing, spared in patients with visual field defects. This “low road” represents an alternative pathway for coarse and rapid processing of fear-related visual information and its activity is mainly evident when the primary cortical “high road” for conscious fear perception is disrupted by a lesion. The existence of two distinct mechanisms for fear processing has adaptive value for survival, ensuring the detection of stimuli that might indicate a potential threat. This detection may come by way of detailed and slow visual analysis or through coarse and rapid visual processing, thereby enabling the implementation of efficient defensive responses.

1.3 EXPERIMENT 2 - Unseen fearful faces modulate face encoding in patients with visual field defects

The first study presented in this chapter (Experiment 1; data published in: Bertini et al., 2012) provided behavioural evidence that hemianopic patients with no explicit residual abilities (i.e. performing at chance in direct tasks) within their field defect can nevertheless implicitly process unseen fear-related stimuli. In particular, results showed that RTs to both emotional (i.e. happy) and neutral targets in the intact visual field were selectively reduced when fearful (vs. happy and neutral) faces were concurrently presented in the blind visual field, suggesting that unconsciously

perceived fearful faces can trigger rapid motor reactions to seen stimuli, purportedly via a subcortical colliculo-pulvinar-amygdala circuit bypassing the lesioned striate cortex. Interestingly, no RT facilitation was found in the presence of unseen fearful faces when coupled with seen fearful faces, suggesting that the conscious perception of fear might have inhibited the activation of the "low road" for emotional processing. Thus, when the striate cortex is damaged, unseen fearful faces that are implicitly processed by the subcortical "low road" seem to modulate the explicit processing of seen faces, which is mediated by cortical circuits (i.e. the "high road"). Intriguingly, this modulation of cortical activity by subcortical circuits could be evident not only at the behavioural level (see: Experiment 1; Bertini et al., 2012) but also at the electrophysiological level, during the visual processing of faces.

Results of Experiment 1 also suggest that the implicit perception of fearful faces mediated by subcortical networks is a fast process, enabling rapid behavioural responses in the presence of unseen fearful faces. Therefore, at the electrophysiological level, any modulation by unseen fearful faces should be evident at an early stage of facial processing, consistent with the time course of its behavioural effect.

Moreover, Experiment 1 also outlined the possibility that the automatic responses to unseen fear could be suppressed when a consciously perceived (i.e. more salient) threat demands more attention. This would suggest a dynamic interplay between the "high road" and the "low road" for emotional processing, whereby not only could the subcortical processing influence cortical activity, but the cortex could also down-regulate subcortical activity when necessary. This is feasible in light of the fact that the "high" and the "low road" do not exhibit a complete anatomical segregation, as both require the crucial contribution of the amygdala. In further support of this

hypothesis, an fMRI study (L. M. Williams et al., 2006a) showed that, whereas the processing of unseen fearful stimuli relies on excitatory feedforward connections within the colliculus-pulvinar-amygdala circuit, conscious fear perception elicits negative functional connectivity within the visual pathways to the amygdala.

The use of EEG would be an ideal approach to investigating the hypotheses outlined above. In particular: i) the possibility that unseen fearful faces influence face processing in hemianopic patients could be investigated by testing whether ERPs elicited by seen faces can be modulated by unseen fearful faces; ii) the high temporal resolution of EEG could provide further evidence that the "low road" pathway conducts a coarse and extremely rapid visual analysis by testing whether the effect of unseen fearful faces is already evident at the early stages of face processing, i.e. the stage of facial encoding; iii) the interactions between the "high road" and the "low road" could be further explored by testing whether differential ERP modulations by unseen fearful faces are evident in the presence and in the absence of seen fearful faces.

To shed light on these issues, in the present study scalp EEG will be recorded in two groups of patients with hemianopia due to left or right lesions, respectively, and who do not show any residual perceptual ability for visual stimuli presented in their blind field, as tested by 2AFC tasks. During the experimental task, event-related potentials (ERPs) will be recorded while the patients respond to emotional faces presented in their intact visual field, which may be coupled with emotional (i.e. happy or fearful) or neutral faces in their blind visual field. In particular, to explore the impact of the fast and implicit emotional processing mediated by the "low road" on face perception, the present study will focus on the N170 component of ERPs, which has been suggested to reflect the rapid structural encoding of faces (Bentin et al., 1996; Bentin

& Deouell, 2000; Itier & Taylor, 2004) and to be modulated by emotional expressions (Batty & Taylor, 2003; Stekelenburg & de Gelder, 2004; Pegna et al., 2008; 2011).

In particular, an ERP study on healthy subjects (Batty & Taylor, 2003) found that the conscious perception of various types of positive and negative emotional faces elicited an increased N170 component recorded from occipito-temporal sites, compared to neutral and surprised faces, with the greatest enhancement elicited by fearful faces. Another study on healthy subjects using backward masked faces (Pegna et al., 2008) reported N170 enhancement also in response to subliminally perceived fearful faces versus non-fearful faces. The source localisation analysis showed that unseen fearful faces increased activation of extrastriate areas, particularly in the right hemisphere.

According to the suggested specialization of the "low road" pathway in processing unseen fearful stimuli (Bertini et al., 2012) and the notion that the conscious perception of fear might inhibit visual inputs to the amygdala (L. M. Williams et al., 2006a), in the present study a modulation of the N170 elicited by faces in the intact field is expected only when seen happy faces are coupled with unseen fearful faces in the blind visual field. In contrast, no ERP modulation is expected when seen faces are coupled with unseen happy or neutral faces in the blind field, or when seen fearful faces are paired with unseen fearful faces.

Importantly, testing both left and right hemianopic patients will also disclose possible lateralization effects in the modulation of face encoding by implicitly processed fearful faces. Indeed, right hemisphere dominance for the regulation of emotional responses has been reported since early studies on cerebral asymmetries in emotional processing (Gainotti, 1972; Gainotti et al., 1993). In addition, more recent evidence has suggested that withdrawal behaviours from potentially dangerous environmental

stimuli are associated with right hemisphere processing (Davidson, 1993; Davidson et al., 2000). These findings, together with data showing preferential right amygdala activation for unconsciously perceived fearful faces, (Morris et al., 1999; de Gelder et al., 2005; Pegna et al., 2005; L. M. Williams et al., 2006b), as well as a right-lateralised enhanced N170 component in response to unseen fearful faces (Pegna et al., 2008), favour the hypothesis that the activity of the "low road" and the consequent implicit processing of fearful faces might be observed only when the right hemisphere is intact. According to this line of evidence, it could be predicted that a modulation of the N170 component in the presence of seen happy faces coupled with unseen fearful faces should be evident only in patients with right hemianopia, i.e. reporting a lesion to the left hemisphere.

Materials and Methods

Patients

Seven patients (3 females; mean age 50.1; range 28-72) with right chronic visual field defect and seven patients (1 female; mean age 52; range 40-59) with left chronic visual field defect gave their written informed consent to participate in the study, which was approved by the Departmental Ethics Committee and was designed in accordance with the ethical principles of the Declaration of Helsinki. All patients presented deafferentation or destruction of primary visual areas consequent to post-geniculate lesions, as documented by CT and MRI scans (see Figure 11 for CT or MRI scans and Table 4 for lesion details). All patients suffered from complete right or left homonymous hemianopia, except for P5 who had a lower right quadrantopia, P6 and P7 who had upper right quadrantopia and P14 who had lower left quadrantopia.

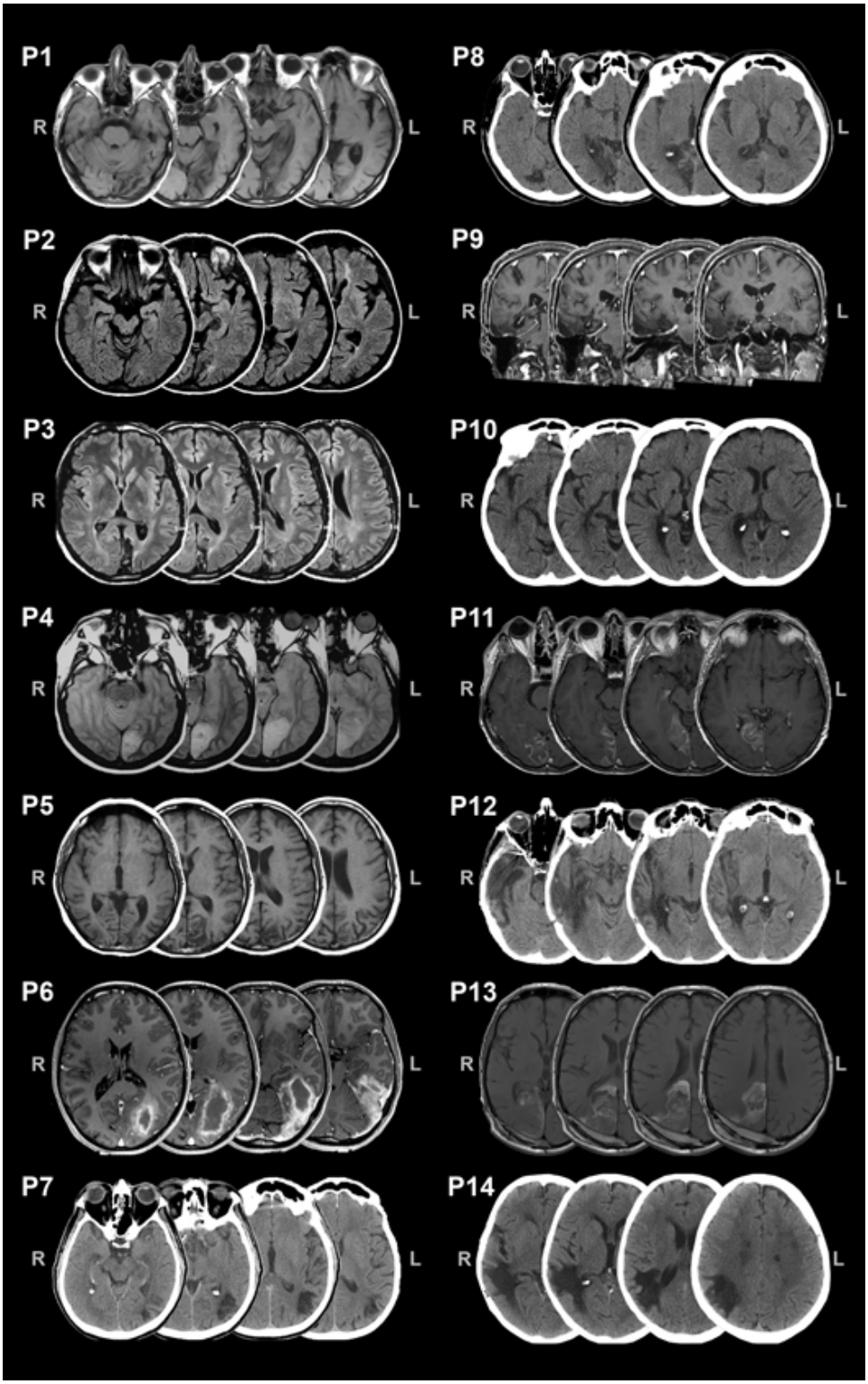

Figure 11. CT or MRI scans of patients. All the scans are presented in axial views except for those of P9, which are presented in coronal views. R: right; L: left.

Case	Sex	Age	Time since onset (months)	Visual Field Defect	Etiology	Lesion site
P1	M	72	22	Right hemianopia	vascular	L temporal-occipital
P2	F	40	239	Right hemianopia	traumatic	L temporal-occipital
P3	M	34	7	Right hemianopia	vascular	L parietal-occipital
P4	M	60	7	Right hemianopia	vascular	L occipital
P5	F	44	8	Lower right quadrantopia	vascular	L parietal-occipital
P6	F	29	8	Upper right quadrantopia	vascular (AVM)	L temporal-parietal-occipital
P7	M	72	10	Upper right quadrantopia	vascular	L temporal-parietal-occipital
P8	M	56	12	Left hemianopia	vascular	R temporal-parietal-occipital
P9	M	48	34	Left hemianopia	vascular	R temporal-occipital
P10	F	56	55	Left hemianopia	vascular	R temporal-occipital
P11	M	47	3	Left hemianopia	vascular	R temporal-parietal-occipital
P12	M	40	7	Left hemianopia	vascular (AVM)	R temporal-parietal
P13	M	58	4	Left hemianopia	astrocytoma	R parietal-occipital
P14	M	59	9	Lower left quadrantopia	vascular	R temporal-parietal-occipital

Table 4. Summary of clinical, demographic and lesional data of patients. M = male; F = female; L = left; R= right AVM = arteriovenous malformation.

The presence of visual field blindness was confirmed by automated perimetry (Medmont M700, Melbourne, Australia), whereas visual acuity in the intact visual field was normal or corrected-to-normal in all patients. None of the participants presented any coexisting neurological or psychiatric disorder or cognitive deficit.

Apparatus

During the experimental sessions patients were placed 57 cm distant from a 17" LCD monitor (refresh rate 60 Hz) in a quiet and dimly lit room. Eye movements were constantly monitored by a Pan/Tilt optic eye-tracker (Eye-Track ASL-6000; sampling rate 60 Hz) during the test of residual visual abilities, whereas an electrooculogram (EOG) was used during EEG recording. Stimuli were presented on a PC running Presentation software (Version 0.60, www.neurobs.com). Patients were asked to hold their gaze on a central fixation crosshair subtending an angle of 2°. For patients with

quadrantopia, the fixation spot was displaced upwards or downwards to ensure the display of stimuli in the blind field.

Test of residual visual abilities

Patients' residual visual abilities in the blind field were tested in four separate sessions of a 2AFC task using different stimuli (see Figure 5, p. 54). In the *visual detection* task (Figure 5a), the stimulus was a white dot (2° diameter). In the *emotional* task (Figure 5b), stimuli consisted of 12 greyscale photographs (6 males) showing happy or fearful facial expressions. In the *gender* task (Figure 5c), 6 greyscale photographs of male and female models with a neutral expression were used. The pictures displayed both in the emotional and in the gender task were the same size (7.5° x 11°) and were taken from the Pictures of Facial Affect set (Ekman & Friesen, 1976). In the *shape* task (Figure 5d), solid white squares (5° x 5°) and circles (5° diameter) were used as stimuli. All stimuli in all sessions were presented at 10° eccentricity from the fixation spot. In each of the 4 experimental sessions a single block of 180 trials (90 trials x 2 possible choices) was administered. Stimuli were displayed in the blind visual field in a random order, whereas no stimuli were presented to the intact visual field. In the *visual detection* task patients were asked to indicate the presence of a white dot in the blind visual field (50% catch trials). The remaining three tasks required them to guess the image presented to the blind visual field, choosing between two possibilities: fearful vs. happy faces in the *emotional* task, male vs. female faces in the *gender* task and circle vs. square in the *shape* task. Each trial (2250 ms total duration) began with a central fixation crosshair (2°) on a black background (500 ms), followed by the presentation of the target stimulus in the blind visual field (1500 ms) and then finally by a blank screen (250 ms). At the end of

the stimulus presentation a sound prompted patients to verbally respond (see figure 5, p. 54). During the task patients were instructed to mantain fixation on the central crosshair and a new trial was manually launched only when they were keeping their gaze on the fixation spot. Trials where eye movements occurred were discarded from the analysis (<2%). The percentage of correct responses given by each patient was compared to the chance level (50% correct responses) by means of a binomial test.

EEG experiment: behavioural task

The electroencephalogram (EEG) was recorded while the patients performed a double-choice discrimination task with redundant stimuli consisting of eighteen greyscale photographs of faces (3 females; 7.5° x 11°) showing fearful, happy or neutral expressions (Ekman & Friesen, 1976). All stimuli were displayed against a uniform black background, 10° distant from the central fixation. Patients were required to discriminate between faces displaying fearful or happy expressions (target emotions), presented in their intact visual field, by pressing one of two vertically-arranged buttons on a keyboard.

The target seen stimuli were always coupled, in the blind field, with a face of the same identity showing a neutral, fearful or happy expression (see Figure 12). This resulted in 6 possible conditions: 1) target fearful face-neutral face in the blind field (Fn); 2) target fearful face-fearful face in the blind field (Ff); 3) target fearful face-happy face in the blind field (Fh); 4) target happy face-neutral face in the blind field (Hn); 5) target happy face-happy face in the blind field (Hh); 6) target happy face-fearful face in the blind field (Hf). Patients were instructed to respond as quickly and accurately as possible to target fearful and happy faces, respectively, by pressing the upper button with the middle finger or the lower one with the index finger of their

right hand. A central fixation crosshair (2°) was always present on the screen. Each trial started with a fixation period (1500 ms) followed by the display of two faces, one to the left and one to the right of the fixation spot (400 ms). After stimulus offset, responses were recorded during a maximal time interval of 1600 ms (see Figure 12). As soon as a response occurred, a new trial started. Each experimental block consisted of 36 trials (6 trials per condition). A total of 36 experimental blocks were run (1296 total trials, 216 trials per condition), split into two separate sessions of approximately 1 hour each.

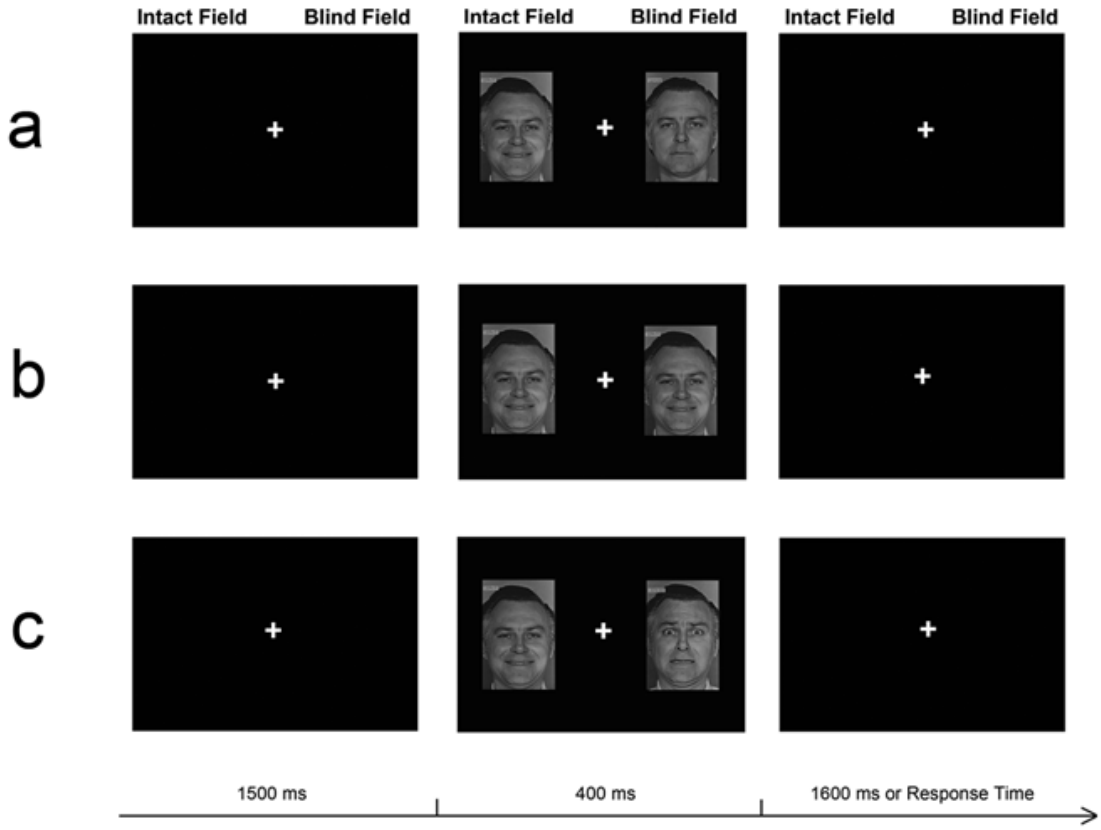

Figure 12. Schematic representation of the trial structure of the behavioural task. The figure depicts examples of neutral (panel a), congruent (panel b) and incongruent (panel c) trials, when the target is a happy face.

Behavioural data analysis

Response time was defined as the time interval between the onset of the stimulus and the subsequent button press. To control for outliers, trials were excluded (<1.5%) on which the response time was 3 standard deviations above or below the condition mean. RTs and error rates were subjected to three-way repeated-measures ANOVAs with the between-subjects variable Group (left-sided lesion, right-sided lesion), and the within-subjects variables Target Emotion (fear, happiness) and Condition (neutral, congruent, incongruent).

EEG experiment: Event-related potentials

The EEG was recorded with Ag/AgCl electrodes (Fast'n Easy-Electrodes, Easycap, Herrsching, Germany) from 27 electrode sites (Fp1, F3, F7, FC1, FC5, C3, T7, CP1, CP5, P3, P7, O1, Fz, Cz, Pz, Fp2, F4, F8, FC2, FC6, C4, T8, CP2, CP6, P4, P8, O2) as well as from the right mastoid. The left mastoid was used as a reference electrode, and the ground electrode was placed on the right cheek. All electrodes were off-line re-referenced to the average of both mastoids. Vertical and horizontal electrooculogram (EOG) was recorded from above and below the left eye and from the outer canthi of both eyes. EEG and EOG were recorded with a band-pass of 0.01-100 Hz and amplified by a BrainAmp DC amplifier (Brain Products, Gilching, Germany). The amplified signals were digitized at a sampling rate of 500 Hz, and off-line filtered with a 30 Hz low-pass filter. ERP data were additionally filtered with a 16 Hz low-pass filter for visualization.

Event-related potentials (*ERPs) data analysis*

ERP data were analysed using custom routines in MATLAB 7.0.4 (The Mathworks,

Natic, MA, USA) as well as EEGLAB 5.03 (Delorme & Makeig, 2004), an open source toolbox for EEG data analysis (EEGLAB toolbox for single-trial EEG data analysis, Swartz Center for Computational Neurosciences, La Jolla, CA; http://www.sccn.ucsd.edu/eeglab). Segments of 200 ms before and 500 ms after stimulus onset were extracted from the continuous EEG. The baseline window ran from -100 ms to 0 ms relative to stimulus onset. Epochs contaminated with large artifacts were identified using two methods from the EEGLAB toolbox (Delorme et al., 2007): 1) An epoch was excluded whenever the voltage on an EOG channel exceeded an individually adjusted threshold (mean 126 μV) to remove epochs with large EOG peaks; 2) An epoch was excluded whenever the joint probability of a trial exceeded five standard deviations to remove epochs with improbable data. The mean percentage of epochs excluded in this way was 16.28%. Remaining horizontal and vertical EOG artifacts were corrected by an eye movement correction procedure (Automatic Artifact Removal Toolbox Version 1.3; http://www.cs.tut.fi/~gomezher /projects/eeg/aar.htm) based on a linear regression method (Gratton et al., 1983). Finally, epochs were discarded from the analysis when saccadic movements were registered in a time window of 200 ms following stimulus onset (11.6 %) to make sure that faces displayed in the blind field could not be seen due to eye movements. The remaining epochs (mean: 156 epochs per condition) were averaged separately for each participant and each condition. For patients with lesions in the right hemisphere, hemispheres were swapped. In this way, all patients' lesions were considered to be on the left side for all analyses and Figures, except for the scalp topographies displayed in Figures 13a and 13d (p. 86), where un-swapped data are shown for better understanding. The N170 amplitude was quantified using a peak-to-peak measure. The difference was taken between the most positive peak in a time window of 50 ms

to 150 ms following stimulus onset and the most negative peak in a time window of 150 ms to 250 ms following stimulus onset. This method ensured that observed N170 modulation was not a function of modulation of the immediately preceding P1 component (e.g., Goffaux et al., 2003; Rossion et al., 2003). The P1 is thought to reflect low-level properties of visual stimuli (e.g., Rossion & Caharel, 2011) and differences in this earlier component could affect the subsequent N170 (Rossion & Jacques, 2008). However, it is important to note that using a simple peak amplitude measure in the time window of the N170 produced essentially the same results as the peak-to-peak measure. Peak-to-peak amplitudes were subjected to a four-way repeated-measures ANOVA with the between-subjects variable Group (left-sided lesion, right-sided lesion) and the within-subjects variables Electrode (P8, P4, O2), Target Emotion (fear, happiness), and Condition (neutral, congruent, incongruent). The significant interaction between Group, Electrode, Target Emotion and Condition was further examined by three-way ANOVAs with Electrode (P4, P8, O2), Target Emotion (fear, happiness), and Condition (neutral, congruent, incongruent) as within-subjects variables, computed separately for the two groups of patients. To compensate for violations of sphericity, Greenhouse-Geisser corrections were applied whenever appropriate (Greenhouse & Geisser, 1959), and corrected p values (but uncorrected degrees of freedom) are reported.

Results

Test of residual visual abilities

During screening, participants underwent four experiments (visual detection task, emotional task, gender task, shape task; see Methods) to determine if they could guess above chance regarding the presence and content of stimuli presented in their blind

field. Results of the binomial test showed that the percentage of correct responses did not significantly differ from chance (50% correct responses) in any of the patients across all tasks (Table 5; visual detection task: all ps>0.3; emotional task: all ps>0.14; gender task: all ps>0.1; shape task: all ps>0.3).

Case	Visual Detection Task	Emotional Task	Gender Task	Shape Task
P1	52%	44%	47%	47%
P2	52%	56%	47%	50%
P3	48%	55%	53%	48%
P4	53%	54%	53%	53%
P5	49%	47%	48%	51%
P6	51%	50%	47%	47%
P7	50%	45%	50%	52%
P8	53%	50%	56%	48%
P9	48%	46%	46%	51%
P10	53%	47%	50%	47%
P11	52%	51%	46%	51%
P12	51%	48%	47%	49%
P13	47%	51%	53%	52%
P14	54%	55%	50%	53%

Table 5. Percentage of correct answers in the four sessions of the test of residual visual abilities. Results are reported for each patient separately.

EEG experiment: behavioural and ERP results

During EEG recording, patients were required to classify the emotional expression of target faces displaying either a happy or a fearful expression. The target faces presented in their intact visual field could be coupled with a neutral, emotionally congruent or emotionally incongruent face in the blind visual field.

For the behavioural task, the three-way ANOVAs on RTs and error rates with the between-subjects variable Group (left-sided lesion, right-sided lesion), and the within-subjects variables Target Emotion (fear, happiness) and Condition (neutral, congruent, incongruent) showed no significant main effects (RT: all ps>0.09; error rates: all ps > 0.32) or interactions (RT: all ps>0.13; error rates: all ps>0.1). The mean RT was 792 ms, and the mean error rate was 11.7%. Neither RTs, nor error rates were significantly different between the two patient groups (p>0.34, and p>0.33, respectively).

To determine a region of interest (ROI) for the N170 component, we first visually examined the grand average scalp topographies of both patient groups, identifying the most negative peak in a time window of 140 ms to 200 ms following stimulus onset. It is evident from the topographies (Figures 13a and 13d) that the N170 was largest over the intact brain areas in both groups and small over the lesioned hemisphere, probably because of the large lesions in occipito-parietal areas (see Figure 11, p. 76). For this reason, only data from the intact hemisphere were analysed. Note that, except for the topographies shown in Figures 13a and 13d, hemispheres were swapped for patients with right-sided lesions for comparison with patients with left-sided lesions in all analyses (see Methods). Because the topography of the most negative peak in the time window of the N170 reached a maximum on channels P4, P8, and O2, these channels were chosen as a ROI for the N170 analyses. Grand average waveforms for the representative electrode P8 are depicted in Figures 13b, 13c, 13e, and 13f, where a clear N170 component is visible in all experimental conditions.

Peak-to-peak N170 component amplitudes were subjected to a four-way repeated-measures ANOVA, with the between-subjects variable Group (left-sided lesion, right-

sided lesion) and the within-subjects variables Electrode (P4, P8, O2), Target Emotion (fear, happiness), and Condition (neutral, congruent, incongruent).

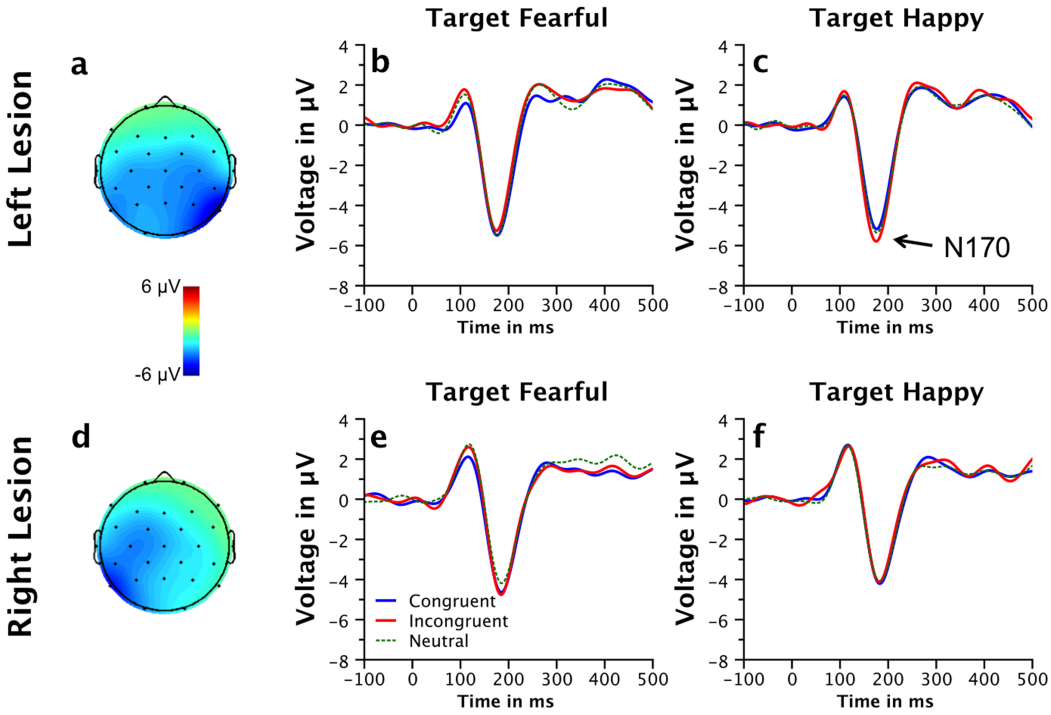

Figure 13. Grand average ERPs elicited by happy and fearful target faces presented in the intact field as a function of Condition (neutral, congruent, incongruent). ERP waveforms at the representative electrode P8 (panels b, c, e, and f), and scalp topographies of the most negative peak in a time window of 150 to 250 ms following stimulus onset averaged over all conditions (panels a and d) are shown. µV = microvolt.

The ANOVA revealed a three-way interaction between Group, Target Emotion and Condition ($F_{(2,24)}$=6.02, p<0.01). No further main effects (all ps>0.11) or interactions (all ps>0.28) were significant. To further examine the interaction between Group, Target Emotion and Condition, three-way ANOVAs with Electrode (P4, P8, O2), Target Emotion (fear, happiness), and Condition (neutral, congruent, incongruent) as within-subjects variables were computed for the two groups of patients separately. The ANOVA for the patients with left-sided lesions revealed a trend towards a main effect of Condition ($F_{(2,12)}$=4.83, p<0.07), explained by a larger N170 amplitude for

the incongruent pairs (Fh and Hf: 7.57 μV), followed by the neutral (Fn and Fh: 7.11 μV) and the congruent (Ff and Hh: 6.77 μV) pairs. Importantly, this main effect was qualified by a significant interaction between Target Emotion and Condition ($F_{(2,12)}$=6.92, p<0.03). No further main effects (all ps>0.32) or interactions (all ps>0.64) reached significance. Post-hoc tests showed that the N170 amplitude was larger when the target image in the intact field was a happy face coupled with a fearful face in the blind field (Hf: 7.95 μV), compared to the remaining conditions (Fn: 7.15 μV, p<0.01; Ff: 6.97 μV, p=0.007; Fh: 7.20 μV, p<0.006; Hn: 7.07 μV, p<0.01; Hh: 6.57 μV, p<0.001; see Figure 14a), which were not statistically different from each other (all ps>0.1).

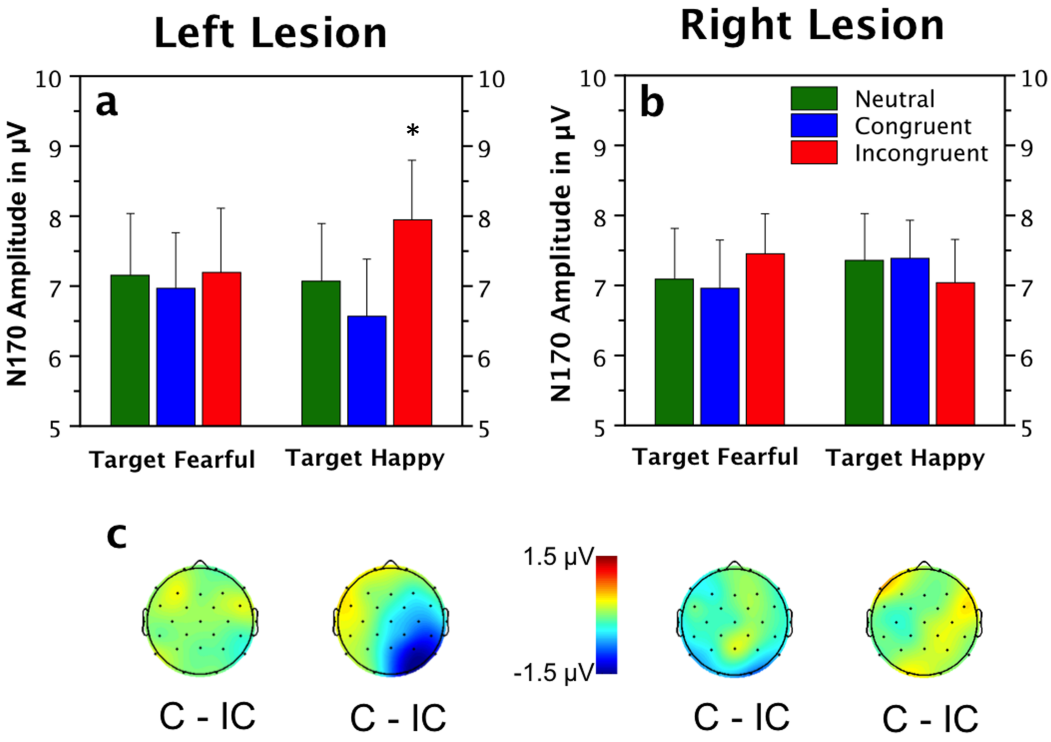

Figure 14. Peak-to-peak N170 values elicited by happy and fearful target faces presented in the intact field as a function of Condition (neutral, congruent, incongruent) averaged over electrodes P4, P8, and O2 (panels a and b) and scalp topographies of the difference in peak-to-peak N170 amplitudes between congruent and incongruent trials (panel c) are shown. The asterisk indicates a p value <0.01. In patients with left hemisphere lesion, the N170 amplitude was significantly higher in the Hf condition, compared to all the remaining conditions (Fn, Ff, Fh, Hn and Hh). C = Congruent Condition; IC = Incongruent Condition; μV = Microvolt. See text for details.

In contrast, the ANOVA for the patients with right-sided lesions did not reveal any significant main effects (all ps>0.23) or interactions (all ps>0.51). Of particular interest, the interaction between Target Emotion and Condition was not significant (p>0.51) (Figure 14b). Figure 14c shows grand average scalp distributions of the difference in peak-to-peak N170 amplitude between the congruent and the incongruent conditions for both patient groups as a function of Target Emotion.A clear negativity over right occipito-temporal brain areas is visible for happy targets in the group with left-sided lesions, demonstrating that these patients showed larger N170 amplitudes only when a fearful face in the blind field was presented concurrently with a happy face in the intact field.

Discussion

The main aim of the present study was to test whether the activity of the subcortical system (i.e. the "low road") for fast and unconscious visual processing of fearful stimuli can modulate cortical visual processing of consciously perceived faces. To this end, the present work investigated the effects of emotional faces presented in the blind field of hemianopic patients on the processing of faces presented concurrently in their intact field, as measured by the N170 component of the ERPs elicited by these faces. The N170 component is thought to represent the visual encoding of faces (Bentin et al., 1996; Bentin & Deouell, 2000; Itier & Taylor, 2004), Consequently, an enhancement of this component suggests an enhancement of facial encoding. In patients with visual field defects due to lesions in the left hemisphere, the N170 elicited by a happy face in the intact visual field was selectively increased when a fearful face was concurrently presented in the blind visual field. No such

enhancement was evident when the seen faces were coupled with unseen happy or neutral faces and, likewise, unseen fearful faces did not elicit a higher N170 component when concurrently presented with seen fearful faces.

The present study confirmed and extended the behavioural findings of Experiment 1 by providing electrophysiological evidence that, in the absence of conscious, cortically-mediated visual processing, non-conscious visual information about fear-related stimuli can still influence the activity of extrastriate areas mediating face processing, most likely via a subcortical colliculo-pulvinar-amygdala network bypassing the striate cortex.

Previous EEG studies (Batty & Taylor, 2003) demonstrated that a wide range of facial emotions (i.e. fear, sadness, disgust, anger, and happiness), when consciously perceived, can modulate the N170 amplitude. By contrast, other studies on healthy subjects reported that, under conditions of subliminal presentation (i.e. non-conscious perception), only fearful faces increased the N170 amplitude (Pegna et al., 2008), even when they are task-irrelevant and completely unattended (Pegna et al., 2011). The present findings contribute to this line of evidence by demonstrating for the first time that even when cortical processing is totally prevented by a lesion (i.e. in patients with visual field defects), unseen fearful faces still elicit a larger N170, suggesting that without the "high road", only threat-related signals can implicitly modulate face processing via the spared subcortical "low road". In addition, the observation that this fear-specific modulatory effect occurs at the stage of facial encoding, i.e., at a fairly early stage of visual processing, favours the hypothesis that the "low road" visual pathway performs a fast and coarse visual analysis in the absence of awareness (LeDoux, 1996). Considered from an evolutionary point of view, the observation that only fear-related stimuli are processed in a fast and non-conscious way is not at all

surprising. Indeed, the rapid detection of stimuli signalling potential threats would be highly advantageous for survival, boosting perception and thereby enabling the early activation of defensive behaviours before the source of danger has even been recognised (Öhman & Wiens, 2003).

Paralleling the behavioural data of Experiment 1, the modulatory effect exerted by unseen fearful faces on the N170 was not evident when another fearful face was presented in the intact visual field. As previously suggested (see Discussion of Experiment 1), this could be accounted for by two hypotheses.

One possibility is that the "high road" activity in response to the seen fearful face might have inhibited the activity of the subcortical "low road" to the amygdala engaged by the unseen fearful face, thus preventing early modulation of extrastriate areas and promoting more detailed analysis of the seen stimulus. In line with this hypothesis, previous studies have shown that conscious visual perception relies on re-entrant cortical feedback (Lamme & Roelfsema, 2000), which presumably reflects an inhibitory modulation over subcortical areas (Bush & Sejnowski, 1996; L. M. Williams et al., 2006a). Accordingly, conscious fear perception has been shown to elicit negative functional connectivity within visual pathways to the amygdala (L. M. Williams et al., 2006a), down-regulating parallel visual inputs to this subcortical structure and favouring deployment of selective attentional resources towards the salient threatening stimulus.

Alternatively, it could be that an unseen fearful face paired with a seen happy face is the only condition capable of enhancing the N170. Indeed, this condition could have yielded higher amygdala activation due to the presence of unseen fear in an emotionally ambiguous situation (i.e. happy-face/fearful-face pairing). This would be

in line with the suggested role of the amygdala in constantly monitoring the environment to boost vigilance as soon as something unpredicted or ambiguous occurs (Whalen, 1998; Herry et al., 2007; Whalen, 2007), as well as with the observation of sustained amygdala activity and enhanced attention towards emotional faces in the presence of unexpected and unpredicted events (Herry et al., 2007).

In the present study, patients with hemianopia due to left and right lesions were tested to explore possible lateralised effects of non-conscious fear. Notably, the modulation of the N170 by unseen fearful faces was evident only in patients with left hemispheric lesions, whereas no effect was observed in patients with right lesions. These findings suggest that the implicit visual processing of unseen threatening signals mediated by the "low road" might only occur when the right hemisphere is intact. This is consistent with previous evidence showing increased connectivity between the right amygdala and the other components of the "low road", i.e. the pulvinar and the SC (Morris et al., 1999), as well as greater right amygdala responses when fearful faces are presented subliminally to healthy participants (L. M. Williams et al., 2006b) or to the blind hemifield of patients with striatal lesions (de Gelder et al., 2005; Pegna et al., 2005). In addition, these findings are in line with the hypothesis of right hemisphere dominance in withdrawal behaviours (i.e. defensive responses) — often associated with negative emotions such as fear — which aim to increase the distance between the individual and the source of aversive stimulation (Davidson, 1993; Davidson et al., 2000).

Another finding from the present study that requires explanation is the lack of behavioural effects (i.e. motor facilitation) in the presence of unseen fearful faces. This result appears to contradict the results of Experiment 1 (Bertini et al., 2012), in

which simple manual responses to seen stimuli were facilitated when unseen fearful faces were presented concurrently. This discrepancy could be explained by differences in the tasks used in Experiments 1 and 2 to assess implicit processing of fear in hemianopic patients, which were, respectively, a go/no-go task and a double-choice task. Because go/no-go tasks require participants to respond only to pre-specified targets while ignoring non-targets, they tap more automatic components of the behavioural response and have been shown to be more sensitive to low-level effects, e.g. the redundancy gain on RTs (Grice & Canham, 1990; Grice & Reed, 1992). On the other hand, double-choice tasks, which require the production of an appropriate response according to the seen target, involve decisional processes that are probably mediated by higher-order cortical areas. Consistent with this idea, studies using choice RT tasks to study the effects of unilaterally and bilaterally presented emotional faces failed to find any differential behavioural effect between these conditions (Schweinberger et al., 2003).

The observation that only a low-level task (i.e. go/no-go) can reveal the behavioural gain elicited by the implicit processing of fearful stimuli (see Experiment 1) is consistent with the hypothesis that the emotional processing mediated by the subcortical pathway is automatic and reflexive. This underscores, once more, the adaptive value of the "low road" for rapidly detecting coarse features of threat-related stimuli, allowing automatic orientation of attention and deployment of reflexive motor reactions even before conscious recognition of the danger can occur.

1.4 EXPERIMENT 3 - Differential contribution of cortical and subcortical visual pathways to the implicit processing of emotional faces

Experiments 1 and 2 investigated the implicit emotional processing mediated by the

subcortical “low road” to the amygdala by testing hemianopic patients in whom the cortical “high road” is disrupted by a lesion. To further control for the possibility of residual cortical functionality, chance-level performance in direct tasks requiring the discrimination of visual stimuli within the field defect was considered an inclusion criterion. The converging results of Experiments 1 and 2 demonstrated that, in the absence of cortical processing, only a specific residual ability to implicitly process unseen fearful stimuli is evident, which could reasonably ensue from the activity of the alternative subcortical visual pathway (i.e. the “low road”) that conveys rough visual information about fear to the amygdala.

Notably, the fear-specific behavioural (Experiment 1) and electrophysiological (Experiment 2) facilitations found in hemianopic patients are not consistent with results from studies on classical blindsight patients, which report implicit processing of emotional stimuli in general (e.g. see: Pegna et al., 2005; Tamietto et al., 2009) and congruency-dependent facilitations in behavioural tasks (e.g. see de Gelder et al., 2001). Moreover, the effects observed in blindsight patients show striking similarities to those reported for neurologically healthy subjects, in whom backward masking procedures were used to interrupt conscious perception of visual stimuli.

For example, EMG studies investigating implicit emotional contagion in healthy subjects showed that passive exposure to backward-masked angry and happy faces could trigger distinct patterns of activation in facial muscles mimicking the unconsciously perceived facial expressions (Dimberg et al., 2000). Similar emotionally-congruent muscular reactions were found in normal observers during the presentation of masked happy and fearful bodily expressions (Tamietto & de Gelder, 2008b). These emotion-unspecific implicit effects in healthy subjects are consistent

with results from blindsight patients showing that happy and fearful faces and bodies presented in their blind field trigger specific muscular reactions according to the emotional content of the unseen stimuli (Tamietto et al., 2009). Moreover, another behavioural study (Tamietto & de Gelder, 2008a) on healthy participants using a redundant target paradigm with emotional seen and masked faces reported faster RTs when seen faces (fearful or happy) were coupled with emotionally congruent masked faces, replicating the congruency effects found by de Gelder and colleagues (2001) using the same paradigm on the blindsight patient GY.

As previously suggested in this chapter, the different performances observed in hemianopic patients (Bertini et al., 2012; also see Experiments 1 and 2) and in blindsight patients (e.g. see de Gelder et al., 2001; Tamietto et al., 2009) might reflect different cognitive processes, thus raising the question of the possible contributions of different neural networks to implicit processing of emotional stimuli. In particular, the fear-specific facilitation reported in hemianopic patients with no discriminative abilities for unseen stimuli might reflect a low-level process, exclusively relying on the "low road". On the other hand, the emotion-unspecific and congruency-dependent facilitations in blindsight patients might reflect a high-level cognitive process, requiring the contribution of both the "low road" and some spared occipital areas of the cortical "high road". Consistent with this hypothesis, blindsight patients display above-chance performance in tasks explicitly requiring them to discriminate stimuli within their blind visual field (see Introduction for a detailed review), a residual ability that has been suggested to arise from the activation of cortical extrastriate areas ipsilateral to the striatal lesion (Stoerig & Cowey, 1997). In addition, as described above, their behavioural performance highly resembles that of healthy subjects, in

whom cortical areas are still intact and functional and might contribute somewhat to implicit visual processing of unseen stimuli.

Taken together, these observations suggest that, even in the absence of conscious visual experience, occipital areas involved in the "high road" might also play a role in the unconscious processing of emotions, contributing, for example, to the congruency effects seen in blindsight patients and healthy subjects. To investigate this possibility, one could use brain stimulation to selectively interfere with the occipital areas of healthy subjects and compare the implicit effects of unseen emotional stimuli after occipital interference to those observed when no inhibitory stimulation is delivered. Such an approach would disentangle the effects exclusively mediated by the "low road" from those which also receive a contribution from the "high road" for emotional processing.

The present study will use cathodal-inhibitory transcranial direct current stimulation (tDCS) to modulate activity in healthy occipital cortex in order to infer cortical contributions to implicit processing of emotional faces. Following sham or active cathodal tDCS over occipital cortex, healthy participants will perform a go/no-go task with redundant stimuli, responding to seen emotional faces (fearful or happy) concurrently displayed with neutral, emotionally congruent or emotionally incongruent backward-masked faces (Experiment 3a). To exclude any nonspecific effects of tDCS, another group will be tested with the same task after sham or active cathodal tDCS over a control site, namely the vertex (experiment 3b).

Following sham stimulation, faster responses for pairs of emotionally congruent stimuli are expected, in line with literature on healthy participants (Tamietto & de Gelder, 2008a). In contrast, the suppression of activity in occipital cortex should

disrupt congruency-dependent facilitation and yield a specific reduction of reaction times for unseen (masked) fearful faces, consistent with evidence from hemianopic patients (Bertini et al., 2012).

Materials and Methods

Participants

Twenty-six right-handed healthy volunteers (21 females; mean age: 24 years; range: 21-28 years) participated in Experiment 3a, whereas twenty-four healthy volunteers (21 females; mean age: 24 years; range 21–31 years) participated in Experiment 3b. All participants gave their written consent and completed a tDCS safety screening form before taking part in the study, which was approved by the Departmental Ethics Committee.

Brain stimulation procedure

Brain stimulation has been proven to be effective in suppressing occipital cortex excitability, thus interfering with visual processing (Bertini et al., 2010). Transcranial direct current stimulation is a non-invasive method for delivering weak polarizing electrical current to the human cortex, focally altering neural resting membrane potential and inducing prolonged changes in synaptic efficiency. Specifically, anodal tDCS enhances cortical excitability, whereas cathodal stimulation reduces it. In the visual domain, it has been shown that tDCS is able to modulate the amplitude of visual evoked potentials (Antal et al., 2004a), modify the perception of phosphenes (Antal et al., 2003a; 2003b), and affect contrast sensitivity (Antal et al., 2001) and motion detection (Antal et al., 2004b). In particular, cathodal tDCS has been proven to significantly decrease static and dynamic contrast sensitivity (Antal et al., 2001)

and increase the threshold for static phosphenes (Antal et al., 2003a).

Before undergoing the behavioural task, participants received either active cathodal or sham tDCS over the left occipital cortex (Experiment 3a) or the vertex (Experiment 3b). In each experiment, the order of the tDCS sessions was counterbalanced and at least one week was allowed between sessions. A direct current of 2 mA intensity was delivered by a battery-driven, constant-current stimulator (ELDITH DC-Stimulator, Neuroconn, Ilmenau, Germany), through a pair of rubber electrodes in 5 cm x 7 cm saline-soaked sponges. The impedance was kept at ≤ 5 KΩ during stimulation. In the active tDCS sessions, cathodal stimulation was applied for 900 seconds (15 minutes; fade in-out duration: 30 sec). This duration has been shown to produce a 20-minute aftereffect at 1 mA intensity (Antal et al., 2004a). In the sham sessions, the direct current was delivered for 30 seconds in order to reproduce the early sensations of active stimulation, and then it was switched off.

To inhibit left occipital areas in Experiment 3a, the cathodal electrode was placed over left O1 (according to the EEG 10/20 system), and the anodal electrode was placed over Cz. The Oz-Cz montage has been shown to be the optimal stimulating electrode arrangement for suppressing activity in the visual cortex compared to several other electrode montages, such as the left O1-right O2 montage or the Oz-left mastoid montage (Antal et al., 2004a). In Experiment 3b, the positions of the electrodes were swapped by placing the cathode over Cz and the anode over O1. Stimulation was delivered only to the left hemisphere to avoid right hemisphere suppression, as there is a wide range of evidence in the literature for the involvement of the right hemisphere in processing emotional facial expressions (for a review, see Adolphs, 2002).

Experimental task

Before each experimental session, participants underwent two training blocks of the behavioural go/no-go task (one with fearful faces and one with happy faces as targets). After the practice, participants received brain stimulation (active cathodal tDCS or sham tDCS) over O1 (Experiment 3a) or Cz (Experiment 3b), followed by a go/no-go task with redundant stimuli. The same task was used in both Experiment 3a and 3b, and it was carried out in ~16 minutes to stay within the 20-minute temporal window of the tDCS aftereffect (Antal et al., 2004a). Each session lasted 90 minutes overall and included training, brain stimulation, the experimental task and a final check of the effectiveness of the masking procedure.

During the go/no-go task, participants sat in front of a 17" LCD monitor (sampling rate 60 Hz), at a distance of 57 cm. Participants were asked to respond by pressing a button on a standard keyboard. A computer running E-Prime software (E-Prime 1.1, Psychology Software Tools Inc.) displayed the stimuli and recorded RTs. Participants' eye movements were monitored online throughout the experiment with an infrared eye-tracking system (Eye-Track ASL-6000; sampling rate 60 Hz). Trials with eye movements (less than 1% in total) were marked online by the experimenter via a mouse button press and subsequently discarded from analyses.

Stimuli consisted of 18 grayscale photographs (7.5° x 11°) from the Pictures of Facial Affect set (Ekman & Friesen, 1976), featuring 6 different identities (3 males), each of whom were pictured displaying a fearful, a happy and a neutral facial expression.

In each trial, target stimuli consisted of fearful or happy faces displayed for 200 ms in the left visual field (LVF), ipsilateral to the stimulated site. Concurrently, backward-masked fearful, happy or neutral faces were presented in the right visual field (RVF), contralateral to the stimulated site. The stimulus/mask compounds consisted of a

fearful, happy or neutral face presented for 33 ms and then immediately replaced by a mask (167 ms) to prevent conscious perception. The mask consisted of a neutral face of a different identity than the previous stimulus. Targets and stimulus/mask compounds were always presented at 10° to the left and to the right of the central fixation cross, respectively. The 33 ms stimulus onset asynchrony (SOA) used for the masking procedure was proven to be effective in preventing conscious perception by a preliminary pilot experiment, consistent with previous studies (Esteves & Öhman, 1993; Morris et al., 1998; Whalen et al., 1998; Etkin et al., 2004).

Each trial started with a blank screen and a central fixation cross (500 ms), followed by the presentation of the target and stimulus/mask compound (200 ms) and a subsequent blank screen with a central fixation cross (1000 ms). Inter-trial intervals ranged between 500 ms and 800 ms.

While fixating the central cross, participants were asked to respond with their right hand as quickly and accurately as possible to the target emotional face in the LVF (fearful or happy), which was paired with the masked face in the RVF (fearful, happy or neutral; see Figure 15). In half of the blocks the target faces in the LVF were fearful faces and the non-targets in the RVF were happy faces, whereas in the other half the target/non-target emotional faces were reversed. As a result, there were six possible conditions of stimulus presentation: 1) target fearful face/masked neutral face (Fn); 2) target fearful face/masked fearful face (Ff); 3) target fearful face/masked happy face (Fh); 4) target happy face/masked neutral face (Hn); 5) target happy face/masked happy face (Hh); 6) target happy face/masked fearful face (Hf).

In each tDCS session, 8 experimental blocks (4 with happy faces and 4 with fearful faces as targets) were run in a counterbalanced order. Each block consisted of 36 trials (18 valid trials, 6 repetitions per condition), resulting in 288 trials overall (144 valid

trials, 24 repetitions per condition). At the end of each experimental session, a forced triple-choice task, also used in the pilot experiment to set the SOA parameters, was carried out to check the effectiveness of the masking procedure (see below).

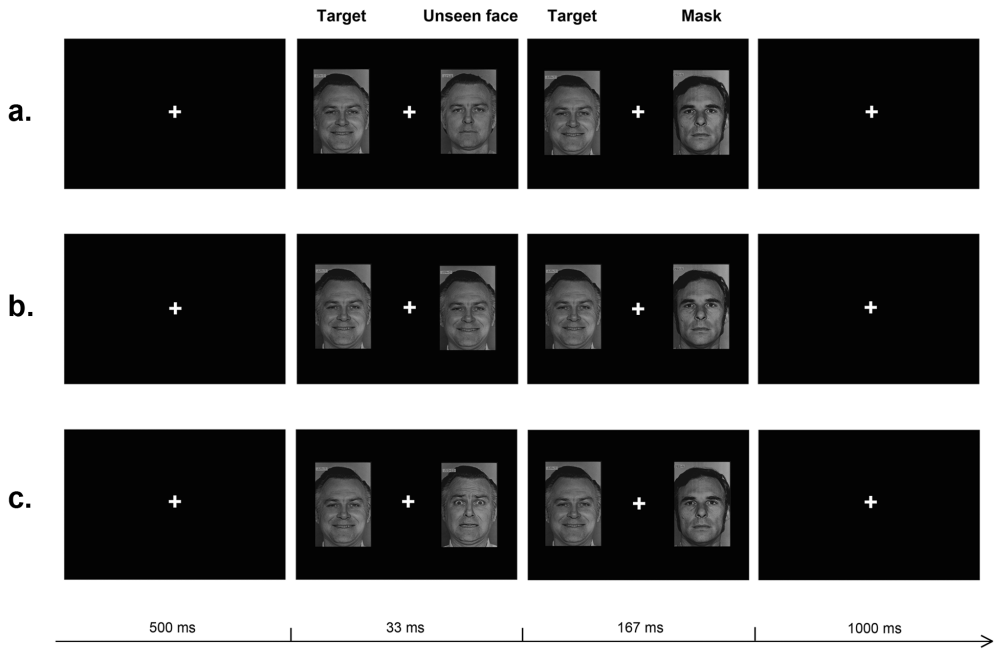

Figure 15. Schematic representation of the experimental task used in Experiments 3a and 3b. The figure depicts examples of neutral (panel a), congruent (panel b) and incongruent (panel c) trials, when the target is a happy face. In each trial, the target face was displayed for 200 ms in the left visual field. Concurrently, backward-masked neutral, emotionally congruent or emotionally incongruent faces were presented in the right visual field. The stimulus/mask compounds consisted of fearful, happy or neutral faces presented for 33 ms and then immediately replaced by a neutral face (167 ms) to prevent conscious perception.

Analysis of masking procedure effectiveness

After performing the behavioural go/no-go task in Experiments 3a and 3b, the effectiveness of the backward masking procedure in preventing conscious perception was checked in each participant using a forced triple-choice task with the same masked stimuli used throughout the experiments. A single block of 144 trials (lasting ~8 minutes) was run, in which participants were required to fixate a central cross and to discriminate masked fearful, happy and neutral faces by pressing different keys on

a standard keyboard. All stimuli were presented unilaterally in the RVF at 10° eccentricity from the fixation cross. Stimulus display and SOA parameters were the same as in the experimental sessions. Sensitivity (d') scores were computed for each participant, and those with discriminative ability significantly above chance were excluded from the main statistical analysis (2 out of 26 participants in Experiment 3a; all d'>0.7, all ps<0.03).

Since half of the trials in the task used to test masking effectiveness fell inside the aftereffect window of cathodal (Experiment 3a) or anodal (Experiment 3b) tDCS over O1, an additional analysis was performed to control for possible differential effects of cathodal and anodal stimulation on perceptual sensitivity (i.e. masking effectiveness). For each participant from the two groups that received cathodal (Experiment 3a) or anodal (Experiment 3b) tDCS over O1, we split the 144-trial block into 2 parts (72 in-window trials and 72 out-window trials) and computed d' in each of the four resulting conditions (cathodal group/in-window, cathodal group/out-window, anodal group/in-window and anodal group/out-window). None of the participants had resulting d' values significantly above chance (all ps>0.74). d' values were entered into an ANOVA with Time (in-window, out-window) as a within-subjects factor and Group (cathodal, anodal) as a between-subjects factor. Neither the main effects (all Fs<0.8; all ps>0.37) nor the interaction ($F_{(1, 46)}$=0.09; p=0.76) was significant. Moreover, d' values between the in-windows of the cathodal and anodal tDCS groups were directly compared, and they were not significantly different between the two groups (t=-0.31; p=0.99). In summary, analyses did not show any differences in sensitivity either between trials falling inside and outside the tDCS aftereffect window, or between cathodal and anodal tDCS.

Data analysis

To control for outliers, RTs exceeding 1.5 standard deviations above or below each participant's condition mean were removed from the analyses. The rejection rates resulting from this procedure were: 11% of the trials in the O1 active cathodal, O1 sham and Cz active cathodal tDCS sessions, and 10% of the trials in the Cz sham tDCS session. Statistical analyses were performed on RTs for correct responses; mean error rates were: 5% (±7%) in the O1 active cathodal, 4% (±6%) in the O1 sham, 3% (±4%) in the Cz active cathodal and 4% (±5%) in the Cz sham tDCS sessions.

All RTs from both Experiments 3a and 3b were entered into a general four-way ANOVA with Session (active cathodal tDCS, sham tDCS), Target Emotion (fear, happiness) and Condition (neutral, congruent, incongruent) as within-subjects factors and Experiment (target area O1, target area Cz) as a between-subjects factor. The results revealed a significant Session by Condition by Experiment interaction ($F_{(2, 92)}=3.33$; $p=0.04$). Therefore, data from Experiments 3a and 3b were analysed separately in two three-way ANOVAs with Session (active cathodal tDCS, sham tDCS), Target Emotion (fear, happiness) and Condition (neutral, congruent, incongruent) as within-subjects factors. All resulting significant effects and interactions were further analysed using the Duncan post-hoc test.

Results

Experiment 3a: sham vs. active cathodal tDCS over the occipital cortex

In Experiment 3a, participants received, in two separate sessions, either active cathodal or sham tDCS over left occipital areas prior to the execution of a behavioural go/no-go task. Reaction times were recorded in response to target emotional faces (fearful of happy) presented in the LVF, ipsilateral to the stimulated site, which were

coupled with masked emotional faces (emotionally congruent, emotionally incongruent or neutral) presented in the RVF, contralateral to the stimulated site.

The results of the 2 x 2 x 3 ANOVA on RTs with Session (active cathodal tDCS over left O1, sham tDCS), Target Emotion (fear, happiness) and Condition (neutral, congruent, incongruent) as within-subjects factors revealed a significant three-way interaction ($F_{(2, 46)}$=3.59, p=0.036). To further investigate the three-way interaction, two separate analyses for the sessions with cathodal tDCS over O1 and sham tDCS were carried out by means of two 2 x 3 ANOVAs with Target Emotion (fear, happiness) and Condition (congruent, incongruent, neutral) as within-subjects factors.

When placebo stimulation was delivered (sham tDCS session), the Target Emotion by Condition ANOVA showed a significant main effect of Condition ($F_{(2, 46)}$=8.69, p=0.0006). As revealed by post-hoc comparisons, RTs were significantly faster in the congruent conditions (Ff and Hh, mean RT 502 ms), compared to both the neutral conditions (Fn and Hn, mean RT 507 ms, p=0.04) and the incongruent conditions (Fh and Hf, mean RT 513 ms, p=0.0002; see Figure 16). Moreover, RTs in the incongruent conditions were slower than in the neutral condition (p=0.04; see Figure 16). The main effect of Target Emotion and the Target Emotion by Condition interaction were not significant ($F_{(1, 23)}$=0.26, p=0.61; $F_{(2, 46)}$=0.74, p=0.48, respectively).

In summary, when participants received sham stimulation, RTs were maximally facilitated by emotionally congruent pairs of target and masked faces, whereas the presence of emotionally incongruent pairs significantly delayed RTs.

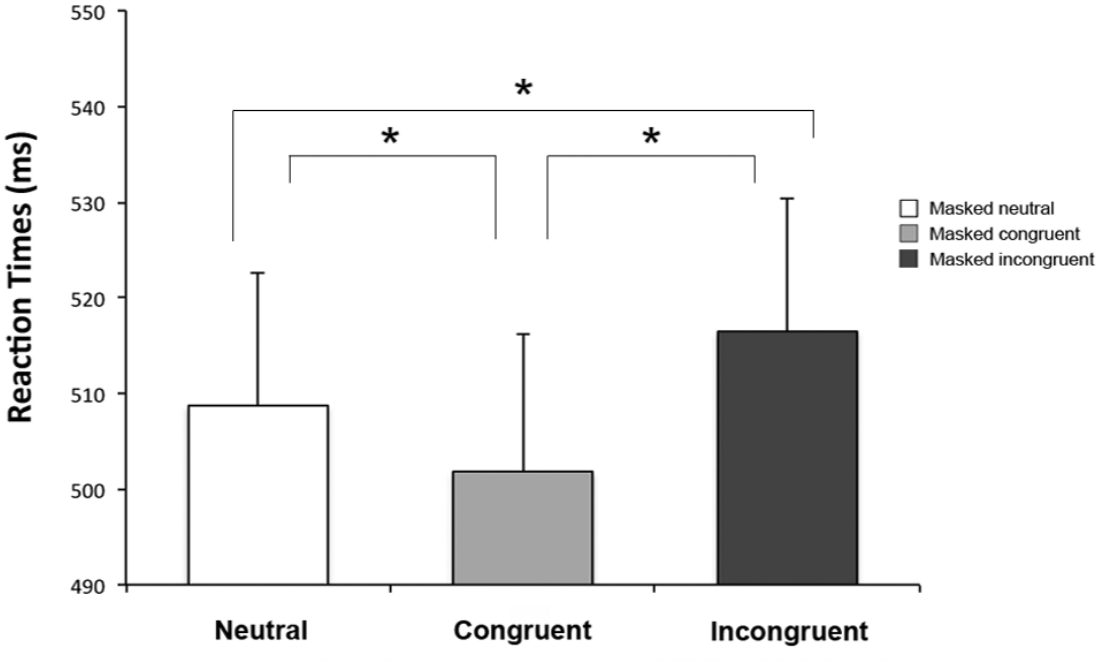

Figure 16. Experiment 3a – Sham tDCS over O1. Mean RTs are reported for the neutral condition (Fn, Hn), the congruent condition (Ff, Hh) and the incongruent condition (Fh, Hf). Error bars represent the standard error of the mean (SEM). Asterisks indicate significantly faster RTs in the congruent condition than in the neutral and incongruent conditions (all *p*s ≤ 0.04) and significantly slower RTs in the incongruent than in the neutral condition ($p = 0.04$).

After suppressing activity in occipital areas (active cathodal tDCS over left O1), results of the Target Emotion (fear, happiness) by Condition (congruent, incongruent, neutral) ANOVA showed a significant interaction between the two factors ($F_{(2, 46)}=5.58$, $p=0.007$). Post-hoc comparisons revealed a significant reduction of RTs in the condition where target happy faces were coupled with masked fearful faces (Hf, mean RT 510 ms) compared to all remaining conditions (Ff, mean RT 520 ms, $p=0.049$; Fh, mean RT 520 ms, $p=0.05$; Hn, mean RT 527 ms, $p=0.001$; Hh, mean RT 521 ms, $p=0.036$) except the Fn condition (mean RT 516 ms, $p=0.26$; see Figure 17). Main effects of Target Emotion ($F_{(1, 23)}=0.02$, $p=0.88$) and Condition ($F_{(2, 46)}=1.15$, $p=0.32$) were not significant.

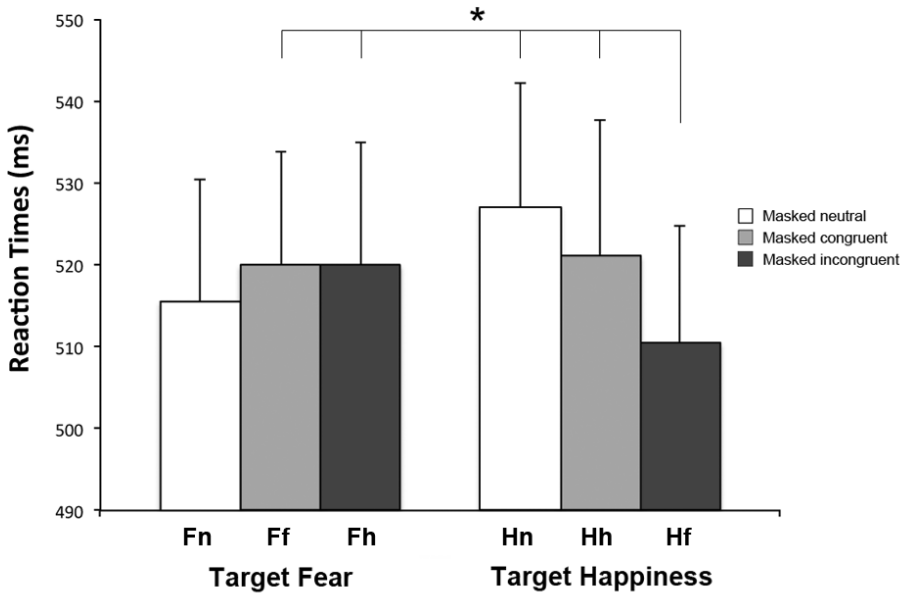

Figure 17. Experiment 3a – Active tDCS over O1. Mean RTs are reported for each condition (neutral, congruent, incongruent) when the targets were fearful faces (columns on the left) and happy faces (columns on the right). Error bars represent the standard error of the mean (SEM). The asterisk indicates significantly faster RTs in response to a target happy face coupled with a masked fearful face (Hf) compared to Ff, Fh, Hn and Hh conditions (all ps≤0.05).

In order to reveal the specific effects of inhibiting left occipital areas and exclude any nonspecific confounding effects of the stimulation procedure, data from the session in which tDCS was applied over left O1 were sham-normalised: mean RTs recorded during the sham tDCS session were subtracted from mean RTs recorded following tDCS over left O1 for each subject, in each separate condition (ΔRT = active cathodal tDCS over left O1 – sham tDCS), in accordance with procedures used in other studies (Romei et al., 2010; 2011). This index represents the difference between performance after active cathodal tDCS and performance in a normal physiological state (sham tDCS). Negative ΔRT values correspond to faster RTs. Normalised RTs (ΔRTs) were entered in a 2 x 3 ANOVA with Target Emotion (fear, happiness) and Condition (neutral, congruent, incongruent) as within-subjects factors. A main effect of Condition was evident ($F_{(2, 46)}$=6.51, p=0.003), whereas the main effect of Target Emotion was not significant ($F_{(1, 23)}$=0.08, p=0.78). More interestingly, and paralleling

the results on raw data, the analysis highlighted a significant Target Emotion by Condition interaction ($F_{(2, 46)}$=3.58, p=0.036). Post-hoc comparisons showed that, following tDCS over left O1, participants were significantly faster when responding to a target happy face in the LFV coupled with a masked fearful face in the RVF (Hf condition, mean ΔRT = -6 ms), compared to all the remaining conditions (Fn, mean ΔRT = 10 ms, p=0.026; Ff, mean ΔRT = 18 ms, p=0.002; Fh, mean ΔRT = 11 ms, p=0.024; Hn, mean ΔRT = 18 ms, p=0.002; Hh, mean ΔRT = 19 ms, p=0.002; see Figure 18). Taken together, these results show that when the activity of occipital areas (O1) is suppressed, the RT facilitation for emotionally congruent pairs (either fearful or happy) of target and masked faces disappears and a specific facilitative effect is evident in the presence of masked fearful faces.

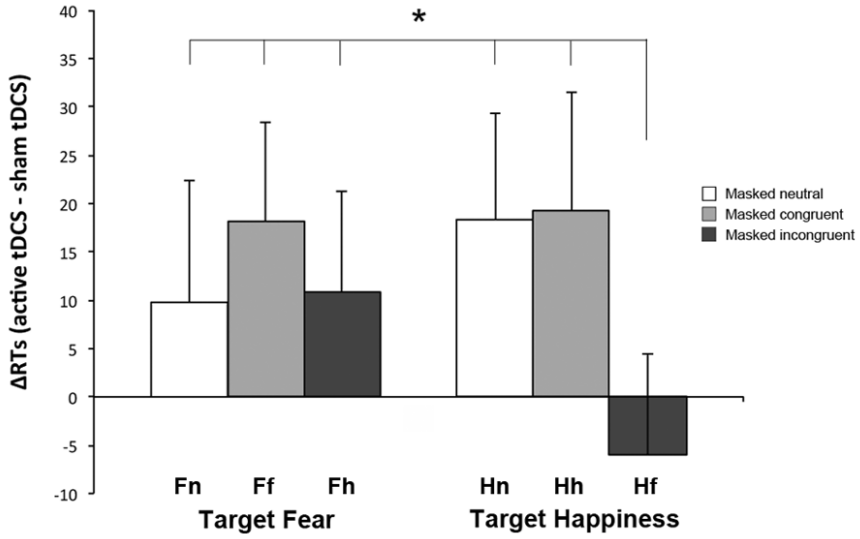

Figure 18. Experiment 3a – Active tDCS over O1: sham-normalised data. Mean normalised RTs (ΔRTs) are reported for each condition (neutral, congruent, incongruent) when the targets were fearful faces (columns on the left) and happy faces (columns on the right). Error bars represent the standard error of the mean (SEM). The asterisk indicates significantly faster RTs in response to a target happy face coupled with a masked fearful face (Hf) relative to all the remaining conditions (Fn, Ff, Fh, Hn and Hh, all ps<0.03).

Experiment 3b: sham vs. active cathodal tDCS over the vertex

To ensure that the effects reported in Experiment 3a are specifically due to suppression of O1 activity, it is crucial to demonstrate that the inhibition of a different, non-visual area does not provide the same outcome. For this reason, in a control experiment, a group of healthy participants was tested with the same go/no-go task used in Experiment 3a in two separate sessions, one after receiving sham tDCS and another after active cathodal tDCS over a control area, namely the vertex (Cz). The Session (active cathodal tDCS over Cz, sham tDCS) by Target Emotion (fear, happiness) by Condition (congruent, incongruent, neutral) repeated-measures ANOVA revealed only a main effect of Condition ($F_{(2, 46)}$=7.79, p=0.001). Post-hoc comparisons showed faster RTs in the congruent conditions (Ff and Hh, mean RT 546 ms) compared to both neutral (Fn and Hn, mean RT 553 ms, p=0.01) and incongruent conditions (Fh and Hf, mean RT 556 ms, p=0.0005), which did not differ statistically from each other (p=0.2; see Figure 19).

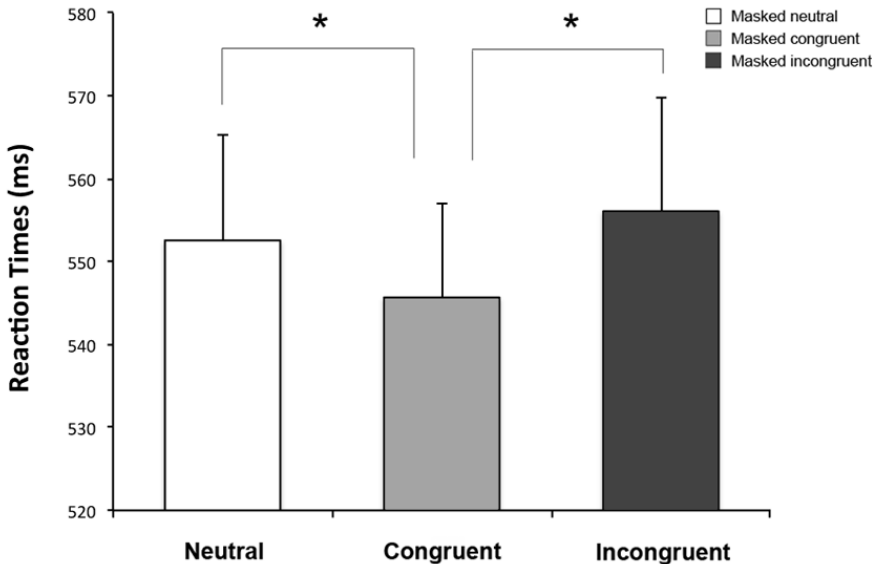

Figure 19. Experiment 3b – Sham and active tDCS over Cz. Mean RTs are reported for the neutral condition (Fn, Hn), the congruent condition (Ff, Hh) and the incongruent condition (Fh, Hf). Error bars represent the standard error of the mean (SEM). Asterisks indicate significantly faster RTs in the congruent condition compared to the neutral and incongruent conditions (all ps<0.01).

Interestingly, no other main effect (Session: $F_{(1, 23)}$=0.1, p=0.76; Emotion: $F_{(1, 23)}$=3.35, p=0.08) or interaction (all Fs<0.71, all ps>0.5) was significant, suggesting that active cathodal tDCS over the vertex does not affect RTs compared to sham stimulation. Overall, the control Experiment 3b revealed contrasting findings to experiment 3a, inasmuch as performances were similar between the sham session and the session where tDCS was applied over the vertex, i.e., faster RTs with pairs of emotionally congruent target and masked faces. Notably, this pattern of results was similar to the participants' performance during the sham session of experiment 3a.

Discussion

Recent studies have revealed different implicit effects of unseen emotional stimuli between patients with blindsight (de Gelder et al., 1999; 2001) and patients with hemianopia (Bertini et al., 2012; see also Experiments 1 and 2). This observation suggests that these two patient groups might recruit different visual pathways during emotional implicit processing. The present study was designed to investigate the cortical contribution to implicit visual processing of emotional faces using backward masking and active cathodal tDCS over healthy occipital cortex (Experiment 3a), with stimulation at the vertex (Experiment 3b) as a control condition.

After sham stimulation over the occipital cortex (Experiment 3a), results revealed a reduction of reaction times to seen emotional target faces, ipsilateral to the stimulated site, when they were concurrently presented with emotionally congruent masked faces, contralateral to the stimulated site. Reaction times were speeded up by both happy and fearful congruent pairs of target and masked faces. This congruency-dependent effect, also found in previous studies testing healthy participants (Tamietto & de Gelder, 2008a) and blindsight patients (de Gelder et al., 2001), suggests that,

although backward masking prevents conscious discrimination of emotional faces, some implicit visual processing is still possible, and this results in a response facilitation for pairs of emotionally congruent stimuli.

However, after active cathodal tDCS over occipital sites (Experiment 3a), the facilitative effect for emotionally congruent pairs of faces disappeared, suggesting that such a congruency effect requires the contribution of the occipital visual cortex. Notably, the suppression of activity in the occipital cortex not only disrupted the congruency-dependent facilitation, but also revealed a significant reduction of RTs when consciously perceived target happy faces, ipsilateral to the inhibited site, were coupled with masked fearful faces, contralateral to the inhibited site. This pattern of results is in line with results of Experiment 1 on hemianopic patients (Bertini et al., 2012).

The control experiment (Experiment 3b), in which both sham and active cathodal tDCS were applied over the control site (vertex), again revealed a reduction in RTs for congruent pairs of emotional stimuli, confirming the crucial role of the occipital cortex in mediating the congruency-dependent facilitation of response times.

The facilitation elicited by pairs of emotionally congruent seen/masked faces observed during both the sham sessions (in Experiments 3a and 3b) and the session in which the vertex was inhibited (in Experiment 3b), suggests that the backward-masked faces were visually processed in the absence of any conscious perception. In fact, though backward masking prevents conscious perception by interrupting the re-entrant feedback projections from higher to lower visual areas, it leaves intact the feed-forward sweep of visual information (Lamme & Roelfsema, 2000). The implicit processing of masked emotional signals requires the contribution of the "low road", as suggested by neuroimaging studies showing enhanced activity of the subcortical

pathway to the amygdala during subliminal presentation of fearful faces (Whalen et al., 1998; Liddell et al., 2005) or faces expressing negative emotions (Morris et al., 1999) and decreased BOLD signal intensity in response to masked happy faces (Whalen et al., 1998). However, the observation from the present study that the congruency-dependent facilitation specifically disappeared after inhibition of the occipital cortex suggests that this effect might rely not only on the activity of the "low road" circuit, but also on the contribution of the occipital cortex and, possibly, of other visual areas from the cortical "high road".

Interestingly, the congruency-dependent facilitation observed when the occipital cortex was not inhibited is in contrast with results from hemianopic patients with no explicit blindsight abilities (Bertini et al., 2012; also see Experiment 1), but in line with the performance of blindsight patients when tested in similar go/no-go tasks with emotional faces (de Gelder et al., 2001). Indeed, the blindsight patient GY showed faster RTs when presented with bilateral congruent pairs of sad or fearful faces compared to unilateral or bilateral incongruent pairs (de Gelder et al., 2001). The parallel between the present results and data on blindsight patients strongly suggests that in these patients, notwithstanding the lesions to the primary visual cortex, the ability to implicitly process emotional stimuli might be mediated not only by the activity of the subcortical "low road" visual pathway, but also by some spared cortical visual areas of the "high road", akin to healthy subjects for whom backward masking prevents awareness but occipital cortex is functional (i.e. not inhibited). This preserved ability to rely on spared areas of the "high road" could also explain blindsight patients' unusual residual capacity to perform above-chance discrimination of the emotional valence (e.g. see de Gelder et al 1999) and many other features (for reviews, see Weiskrantz, 1986b; 2001; Cowey, 2010a) of unseen stimuli. In support

of this hypothesis, previous studies reported sustained hemodynamic responses in the ipsilesional lateral occipital cortex and in the posterior fusiform gyrus of blindsight patients during the presentation of images of natural objects in their blind visual field (Goebel et al., 2001).

The present results also showed that suppressing activity in the occipital cortex eliminated the congruency-dependent facilitation and revealed a specific response facilitation for pairs of target happy faces and masked fearful faces. Interestingly, this fear-specific facilitative effect is in line with the results of Experiment 1 on hemianopic patients (Bertini et al., 2012), in which unseen fearful faces facilitated behavioural responses to faces presented in the intact field, both during emotional and non-emotional tasks. These converging results suggest that when the occipital cortex is damaged or inhibited and visual processing of emotional faces is mainly dependent on the activation of the "low road" subcortical route, fearful faces are the only stimuli that are visually processed and capable of mediating a behavioural response.

Overall, the results of the present study clarify the contribution of the occipital cortex to implicit visual processing of emotional faces. In particular, occipital areas seem to play a crucial role in mediating high-order implicit visual processes, such as the congruency-dependent facilitative effects observed here. In contrast, the fear-specific facilitation observed after inhibition of occipital areas might be mainly mediated by the activation of the subcortical pathway (i.e. the "low road"), bypassing these cortical areas. Evidence for the anatomical substrate of the subcortical "low road" has been provided by animal (Chomsung et al., 2008; Day-Brown et al., 2010) and human (Tamietto et al., 2012) studies demonstrating the existence of a direct visual pathway encompassing the SC, the thalamus and the amygdala, which are well known to be involved in emotional and implicit visual processing. Due to the crucial involvement

of the amygdala, this neural circuit is preferentially activated by fear-related signals and, therefore, might have great relevance for survival, with consequent evolutionary advantage. Indeed, this pathway, which is activated rapidly and automatically (Luo et al., 2010), is presumably involved in implementing adaptive defensive behaviours (de Gelder et al., 2004).

The present findings also extend the results from Experiments 1 and 2, providing further support for the hypothesis that the different behavioural performances observed in blindsight and hemianopic patients might be ascribed to different lesional profiles. Patients described in classical blindsight studies demonstrate high-order visual processing, similar to the performance of healthy participants when conscious visual processing is prevented by backward masking. This finding suggests that their performance might rely on a peculiar functional and anatomical reorganization of the visual system, allowing first for contributions from the sub-cortical "low road", but also from the cortical "high road" by way of some spared occipital areas. In contrast, hemianopic patients show fear-specific behavioural and electrophysiological effects (see Experiments 1 and 2), akin to the facilitation observed here in healthy participants when (i) conscious visual processing was prevented by backward masking and (ii) the occipital cortex was inhibited by tDCS. These fear-specific effects, arising when the cortical "high road" is disrupted by real (Experiments 1 and 2) or virtual (the present study) lesions, might reflect an automatic, low-order process, mainly dependent upon the activation of the subcortical "low road" for emotional processing.

CHAPTER 2

Audio-visual interactions in patients with visual field defects

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The previous chapter focused on the residual ability to implicitly process the affective valence of visual stimuli following lesions to the primary visual pathway, a phenomenon known as affective blindsight.

The present chapter aims to further explore aspects of visual processing in the absence of conscious vision, namely multisensory integration of audio-visual inputs and the possible beneficial effects of auditory stimulation on impaired visual perception. In particular, based on previous findings showing that the presentation of sounds can improve simple visual detection in hemianopic patients (Frassinetti et al., 2005), the study presented here will investigate, in a patient with occipital lesions, the possibility of using auditory stimulation to enhance a more complex visual function, i.e. the discrimination of orientation.

2.1 EXPERIMENT 4 - Crossmodal enhancement of visual orientation sensitivity by looming sounds requires intact striate cortex

From an evolutionary perspective, multisensory integration represents a successfully adaptive mechanism, whereby information from several sensory modalities is integrated to produce a more robust and coherent sensory percept (Stein & Meredith, 1993; Stein et al., 1993). The integration of information carried by different senses has been shown to induce higher neural activation than inputs from a single sensory modality (Stein & Meredith, 1993; for a review, see Stein & Stanford, 2008). More

importantly, neural responses to multisensory inputs are superadditive, i.e. they are greater than the mere sum of the responses produced by individual unisensory inputs (Meredith & Stein, 1986). Multisensory integration results in perceptual gain in many circumstances, for example by reducing perceptual ambiguity (MacLeod & Summerfield, 1990), enhancing visual detection (Frassinetti et al., 2002; Bolognini et al., 2005a) and speech perception (Sumby & Pollack, 1954; Reisberg, 1987), and speeding up responses (Gielen et al., 1983; Molholm et al., 2002).

Vision is a paramount sense in humans, and it has been long considered a self-contained modality that prevails against and unidirectionally influences the other senses (Ernst & Bulthoff, 2004; Shams & Kim, 2010). However, more recent accounts have challenged the visual dominance hypothesis, showing that audition can crossmodally influence vision; for example, audition can both improve and bias visual performance, in the latter case producing sound-induced visual illusions (for a review, see: Shams & Kim, 2010). Indeed, in healthy subjects, the presentation of sounds can enhance visual detection (Driver & Spence, 1998; McDonald et al., 2000; Vroomen & de Gelder, 2000; Frassinetti et al., 2002; Bolognini et al., 2005a; de Haas et al., 2013), phosphene (i.e. visual percepts induced by TMS) perception (Romei et al., 2007; 2009; 2012; 2013; Bolognini et al., 2010; Convento et al., 2012) and even visual orientation sensitivity (Leo et al., 2011). Interestingly, the visual perceptual gain produced by concurrent auditory stimulation, like any type of multisensory effect, obeys the so-called inverse effectiveness rule (Stein & Meredith, 1993), which refers to a higher neural response (i.e. perceptual gain) in multisensory neurons when one or more unisensory inputs are weak or degraded. As a corollary of this rule, when the visual sensory channel is too weak to induce a behavioural response, concurrent stimulation through different sensory (e.g. auditory) channels might improve its

responsiveness (Làdavas et al., 2012). These observations suggest that patients with visual field defects might particularly benefit from multisensory integration. In other words, visual perception in their blind field might improve via auditory stimulation. Interestingly, previous studies on these patients demonstrated that sound can crossmodally enhance visual detection sensitivity (d') for visual stimuli that are not consciously perceived because of geniculo-striatal lesions (Frassinetti et al., 2005), also suggesting a role of the SC, a classical subcortical multisensory structure (Stein & Meredith, 1993), in mediating this crossmodal enhancement in the absence of cortical contribution. Other studies on hemianopic patients (Bolognini et al., 2005b) further extended these findings by demonstrating that audio-visual stimulation can not only produce online visual enhancement (Frassinetti et al., 2005) but also a long-lasting improvement of visual abilities.

Auditory stimuli with different characteristics can crossmodally modulate vision in different ways. Approaching (looming) sounds seem particularly efficient in modulating visual processing in animals (Maier et al., 2004; 2008) as well as in humans (Romei et al., 2009; 2013; Leo et al., 2011; Canzoneri et al., 2012). Looming sounds have indeed been shown to induce perceptual biases and to be more salient than other dynamic (e.g. receding) sounds, both in monkeys (Ghazanfar et al., 2002; Maier & Ghazanfar, 2007) and humans (Small, 1977; Neuhoff, 1998; Seifritz et al., 2002; Bach et al., 2008). A behavioural study on healthy subjects by Leo and colleagues (2011) reported that spatiotemporally congruent looming sounds, versus receding and stationary sounds, improved orientation sensitivity (d') for Gabor patches presented at the individual orientation discrimination threshold and in peripheral view. Unfortunately, the paradigm used in this study could not discern whether the crossmodal effect was mediated by classically multisensory subcortical

structures (e.g. the SC; Stein & Meredith, 1993) or by the primary visual cortex, as suggested by more recent studies (Romei et al., 2009). In fact, converging evidence suggests that multisensory interactions might not only occur in subcortical structures (Stein & Meredith, 1993; Nishijo et al., 1988; Nagy et al., 2006; Hackett, 2012) and higher associative cortices (e.g. superior temporal and intraparietal sulci; Ghazanfar & Schroeder, 2006; Kayser & Logothetis, 2007), but also at the level of early (primary) sensory areas (Giard & Peronnet, 1999; Molholm et al., 2002; Martuzzi et al., 2007; Kayser et al., 2007; Romei et al., 2007; 2012; Wang et al., 2008; Noesselt et al., 2010; Raij et al., 2010; Van der Burg et al., 2011; Cappe et al., 2012; Murray et al., 2012). According to a recent study using single-pulse TMS over the occipital pole, looming sounds can selectively increase primary visual cortex excitability as early as ~80 ms after sound onset, relative to stationary or receding sounds (Romei et al., 2009). In support of these findings, Tyll et al. (2013) found that audiovisual looming (vs. receding and unisensory) signals enhance fMRI responses in low-level visual and auditory areas in addition to multisensory areas.

Based on previous reports on hemianopic patients that showed a sound-induced improvement in visual detection of stimuli in their blind field (Frassinetti et al., 2005), the present study aims to address whether it is also feasible to use auditory stimulation to enhance a more complex visual function, i.e. orientation discrimination, in the blind field of a patient with occipital lesions. To this end, in a modified version of the paradigm used by Leo et al. (2011), the patient will be asked to perform a line orientation discrimination task, in which visual targets will be presented in his intact and blind visual fields, either unimodally (without sound) or coupled with auditory stimuli, namely looming, receding or stationary sounds. In line with results from Leo

et al.'s study (2011), if any sound-induced visual enhancement is observed, it should be specific for looming sounds, whereas receding and static sounds should not affect visual orientation sensitivity compared to unimodal visual presentation. Importantly, the lesional approach of the present study will also help clarify whether the crossmodal enhancement of orientation sensitivity is subcortically or cortically mediated. Indeed, if, as expected, a crossmodal visual enhancement is evident in the intact visual field, which is subtended by spared striate cortex, but also in the blind field, which is subtended by damaged striate cortex, then the effect must be exclusively mediated by areas and networks bypassing the lesioned V1. Otherwise, if crossmodal enhancement of orientation sensitivity is specific for stimuli in the intact visual field, with no crossmodal effect observed in the blind visual field, this would point to a causative role of the striate cortex in this type of crossmodal interaction.

Materials and Methods

Case history

SDV is a 44-year-old right-handed man who had a cardiac arrest due to electrocution, with consequent cerebral anoxia affecting bilateral occipital cortex, 3 years before participating in the present study. Following that event, SDV suffered cortical blindness for almost 10 months, then partially recovered his vision, especially in the periphery of the visual field. A campimetry test (Medmont M700 automated perimetry, Melbourne, Australia) performed before the experimental testing showed a complete loss of central vision, covering an area of 5 visual degrees (VD) around the fovea, plus the presence of multiple scotomic areas (see Figure 20).

Despite his central visual field defect, SDV was able to perceive movement, see colours, navigate, interact with the environment and with people, and independently

carry out basic everyday life activities (feeding, dressing, etc.). However, since the incident, he had shown typical signs of visual form agnosia. Indeed, SDV could no longer read or recognise objects and familiar faces (prosopagnosia) by vision, whereas his tactile and auditory recognition abilities were preserved and he was still able to identify people by their voices.

In accordance with the Declaration of Helsinki, SDV gave his written informed consent for participation in the study, which was approved by the Departmental Ethics Committee.

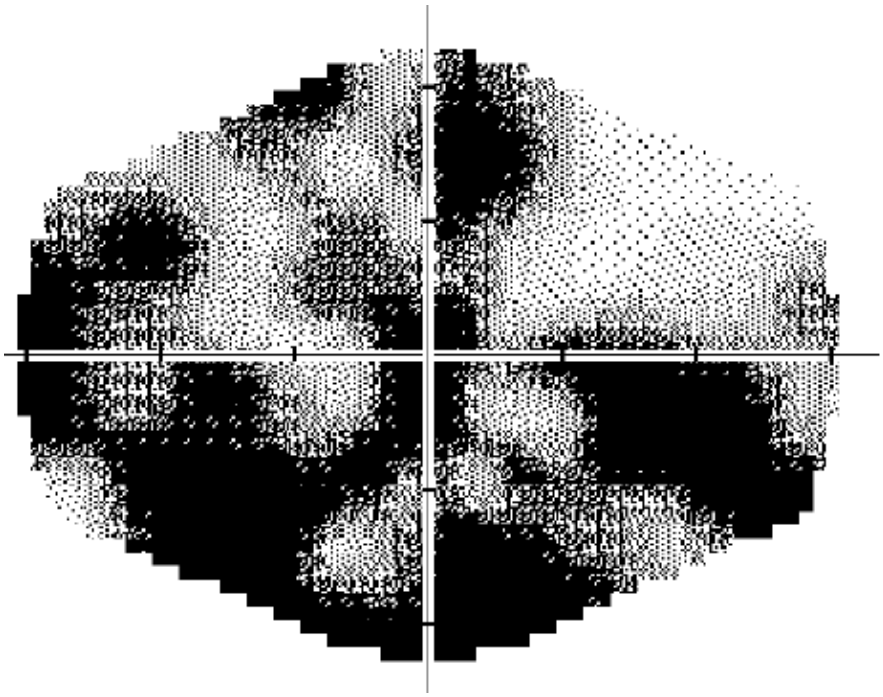

Figure 20. SDV's visual field (right eye) as shown by the perimetry test performed at the time of experimental testing. The picture displays SDV's visual field up to 30 deg to the right and the left of the fixation point and up to 10 deg above and below the fixation point.

Brain lesion

Image acquisition. Structural magnetic resonance imaging (MRI) was performed in a 3T scanner (Allegra, Siemens Medical Solutions, Erlangen, Germany) with a maximum gradient strength of 40 mT/m, using a standard quadrature birdcage head

coil for both the RF (radio frequency) transmission and RF reception. SDV underwent an MRI protocol including axial, coronal and sagittal T2-weighted turbo spin-echo (TSE) sequences (TR = 3900 ms, TE = 96 ms), and axial fluid-attenuated inversion recovery (FLAIR) sequences (TR = 8500, TE = 109, inversion time = 200) covering the whole brain. Twenty-four 5-mm gapless sections and a 230x230 matrix were obtained using all the available MRI techniques. The axial and the coronal sections ran, respectively, parallel and perpendicular to a line joining the anterior and posterior commissures (AC–PC line). Whole-brain T1-weighted images were obtained on the sagittal plane using a modified driven equilibrium Fourier transform (MPRAGE) sequence optimized for gray-white contrast (TR= 7.92 ms TE= 2.4 ms, 176 consecutive slices, flip angle 15◦, FoV 256, voxel-size $1mm^3$). All of the images were assessed visually by a neuroradiologist. Ten healthy males (mean age: 43.7; range: 39-50 years) underwent the same imaging protocol, including whole-brain T1-weighted images, with the purpose of quantitatively assessing SDV's grey and white matter reduction in comparison to a non-lesioned, age-matched control group.

Voxel-based morphometry (VBM) analysis. Image pre-processing was conducted using the VBM toolbox implemented in SPM8b (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/) running on MATLAB 7.7 (MathWorks, Natick, MA). First, the images were segmented into tissue classes: grey matter (GM), white matter (WM) and cerebrospinal fluid (Ashburner & Friston, 2000; 2005; Good et al., 2001). After that, a high-dimensional DARTEL normalization (Ashburner, 2007) modulating for nonlinear effects was applied to the tissue-classified GM and WM maps. Finally, the maps were smoothed using a Gaussian smoothing kernel of 8-mm full width at half-maximum, resulting in a final

voxel size of 1.5 mm^3. The resulting smoothed and modulated GM and WM images were used in the statistical analysis to assess GM and WM volume changes. Differences in GM and WM between groups (patient and healthy controls) were assessed by means of a two-sample t-test design implemented in SPM8b. Because normalization of nonlinear effects had only been applied during VBM pre-processing, which corrects for differences in GM, WM, and intracranial volumes (Buckner et al., 2004), there was no further need to control for these variables in the statistical model.

When performing the second level statistics, the comparison was masked by a region of interest (ROI) covering the area of injury (see Figure 21b) to evaluate a possible GM or WM decrease outside the area primarily affected by the lesion. The ROI was manually traced over the T1-weighted image using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron/), considering the area of the lesion in T2-weighted and FLAIR images; the lesion area was then smoothed and binary coded (0 for the voxels covering the lesion; 1 for the rest of the image). All voxels with a value of 0 were excluded from the analysis. First, a non-corrected threshold ($p<0.001$) was used to perform an exploratory analysis. Then the final results were corrected for multiple comparisons using a family-wise error rate (FWER) correction set at $p < 0.05$. The MNI (Montreal Neurological Institute) coordinates of significant clusters were converted into Talairach coordinates using a nonlinear MNI to Tailarach conversion algorithm (http://www.bioimagesuite.org/Mni2Tal/index.html). VBM methods and statistical analyses were performed following the rules for reporting VBM studies described by Ridgway et al. (2008).

Results of structural MRI. Neuroradiological MRI examination revealed two

encephalomalacic areas, hyperintense on T2-weighted images, involving GM and WM of both the occipital lobes, corresponding to BA (Brodmann area) 17-18, and to part of BA 19. The lesion extended rostrally to the superior parietal lobes, corresponding to BA 30-31 and part of BA 7. In addition, a diffuse hyperintensity on T2-weighted images was present around both the ventricles, which appeared enlarged, extending through the callosum body. The posterior part of the callosum body had reduced thickness. Adjacent sulci were prominent and the occipital horns of both ventricles were enlarged, reflecting loss of cerebral tissue volume. A diffuse, moderate enlargement of the subarachnoid spaces and sulci was also present and especially evident in the mesial superior frontal and superior parietal lobes bilaterally (See Figure 21).

Results of VBM analysis. The lesion ROI is shown in Figure 21b. After masking the brain lesion, the patient presented reduced GM in the right precuneus (BA 7) and in the parietal WM (posterior part of the superior longitudinal fasciculus) ($p<0.001$ uncorrected results). However, when corrected for multiple comparisons (FWER), the two-sample t-test did not show significant differences between the patient and the control group.

In summary, SDV suffered extensive lesions in the occipital lobe, involving BA 17, 18 and part of 19. There were no significant GM or WM reductions in areas outside the lesion.

Experimental apparatus

During the experimental session, SDV sat on a comfortable chair with his head placed

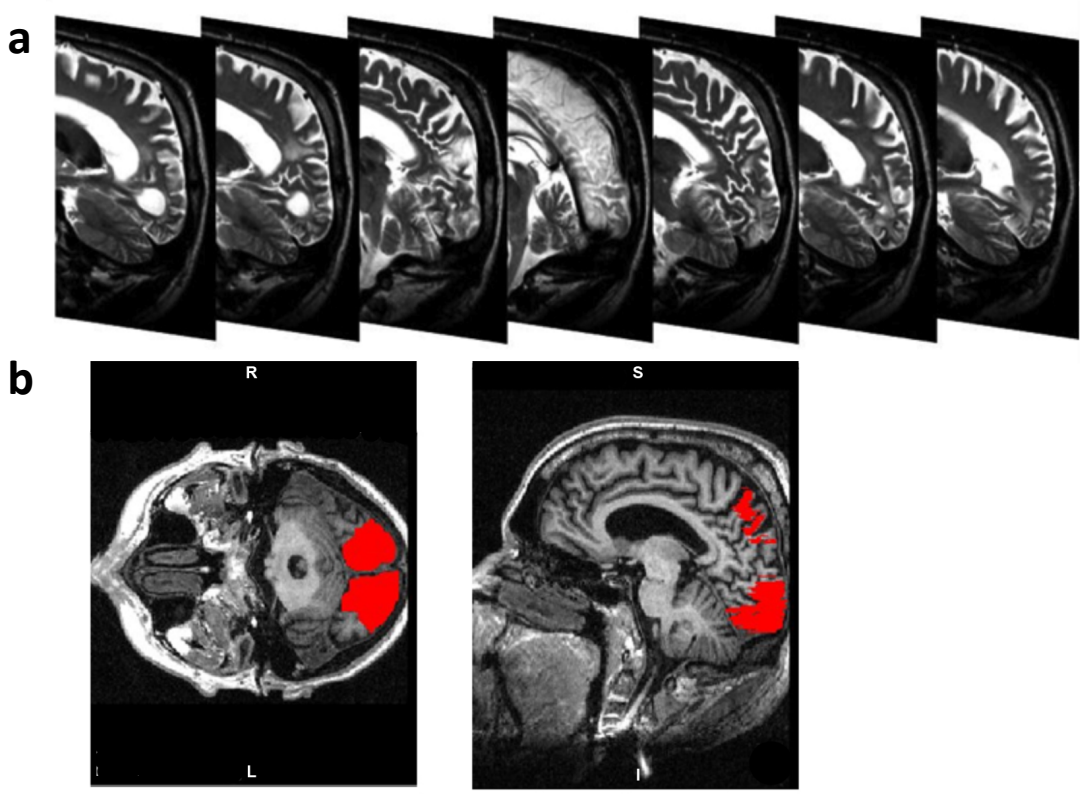

Figure 21. Structural MRI and lesion analysis. (a) Sagittal view of SDV's MRI scans. (b) Lesion region of interest (in red) that was used as an explicit mask in the statistical analysis.

on a chin rest 57 cm away from the screen in a dimly lit room. Visual stimuli were presented on a 17" LCD display with a refresh rate of 60 Hz. Auditory stimuli in the main experiment were delivered by two small PC speakers placed at the bottom of the screen, one aligned with the centre of the screen (i.e. the fixation point) and the other at 10 VD (visual degrees) eccentricity on the right, matching the (vertical) spatial locations of visual target stimuli presented during the task (see Figure 22, p. 127). Eye movements were monitored online using an infrared Pan/Tilt optic eye-tracker (Eye-Track ASL-6000; sampling rate 60 Hz). Stimulus presentation and data recording were implemented on a PC running Psychophysics Toolbox 3 (Kleiner et al., 2007) on Matlab r2007b (The MathWorks Inc., Natick, MA). SDV's vocal responses were collected by the experimenter using a standard keyboard.

Stimuli

Visual target stimuli consisted of solid white lines (2x0.2 VD), which were presented for 250 ms either in a vertical or a tilted position (see Figure 22, p.127). Auditory stimuli were adapted from previous works (Leo et al., 2011) and consisted of complex sounds of 250 ms duration with a triangular waveform (frequency: 400 Hz; sampling rate: 44.1 kHz). Three types of sounds could be presented during the main experiment: 1) looming sound, gradually rising in intensity from 55 dB to 75 dB; 2) receding sound, gradually decreasing in intensity from 75 dB to 55 dB; 3) stationary sound, with intensity fixed at 75 dB.

Pilot experiment

The aim of the present study was to test whether SDV's orientation discriminative ability would benefit from audio-visual integration in the areas of the visual field subtended by intact V1 and lesioned V1, i.e. where he could see and where he was blind, respectively. For this reason, before participating in the study, SDV's ability to discriminate the orientation of a line was assessed in 7 different positions in his visual field (at the centre, 0 VD, and at 5, 10 and 15 VD eccentricity in both the left and right visual fields) to identify where he performed best and worst. Visual stimuli were presented unimodally in this task. One experimental block was run for each position (7 blocks total) and, in each of the 50 trials, the patient was presented with either a vertical (0°) or a horizontal (90° tilted) line. The patient was asked to report the perceived orientation (vertical vs. tilted). SDV's accuracy and sensitivity (d') scores at each stimulus eccentricity are summarised in Table 6.

As expected, when lines were presented centrally, i.e. in the patient's blind visual field, his performance (48% accuracy) did not differ statistically from chance (d'=-

0.1; p<0.84). At higher eccentricities SDV's performance was better, with the best performance at 10 VD eccentricity in the right visual field (79% accuracy; d'=1.64; p<0.002). Thus, in the main experiment, auditory and visual stimuli were presented at 10 VD to the right (the "intact" spot, where audio-visual enhancement was expected) and at the central fixation point (the "lesioned" spot, where audio-visual enhancement had to be tested).

	Left Visual Field			**Centre**	**Right Visual Field**		
Eccentricity	*-15vd*	*-10vd*	*-5vd*	*0vd*	*5vd*	*10vd*	*15vd*
Accuracy	58%	73%	70%	48%	64%	79%	68%
d prime value	0.43	1.33	1.09	-0.1	0.72	1.64	0.94
c value	0.37	-0.3	-0.29	0.2	0.11	-0.12	-0.11

Table 6. Results of the pilot experiment. SDV's accuracy, d' and c values for orientation discrimination of vertical and horizontal lines presented at the centre of the visual field and at 5, 10 and 15 visual degrees eccentricity in the left and right visual fields.

Orientation threshold estimation

As noted above, when asked to discriminate the orientation of lines (vertical vs. horizontal) presented within his foveal scotoma, SDV performed at chance. For this reason, in the main experiment, the difference between vertical and tilted lines presented at fixation was set at 90° (i.e. the maximal possible difference). However, most likely because of visual form agnosia, even where the patient performed best, i.e. at 10 VD eccentricity to the right, his accuracy (79%) did not reach 100%. To avoid ceiling effects and to allow a margin of improvement for stimuli presented at 10 VD, we titrated the vertical-tilted orientation difference before the experimental task to result in 65% accuracy. The orientation difference between vertical and tilted lines presented at 10 degrees eccentricity in the main experiment was set at this threshold

value. The threshold was estimated following a two-step procedure.

First, a staircase procedure was used to roughly determine the minimal perceived difference between vertical and tilted lines. To this end, vertical or tilted lines (250 ms duration) were initially presented with the maximal orientation difference (i.e. 90°). SDV had to indicate the perceived orientation. After 3 consecutive correct responses, the vertical-tilted orientation difference was reduced by 50%; otherwise, if SDV made an error, the orientation difference was raised to the midpoint of the last error trial and the preceding correct trial. This procedure was carried on until the orientation difference between the last correct trial and the last error trial reached 2° (e.g. last correct 22°; last error 20°); the middle value (e.g. 21°) was considered to be the minimal perceived difference between vertical and tilted lines.

In the following step, constant stimuli were used to adjust the orientation discrimination threshold to 65% accuracy. A series of 24 stimuli (12 vertical, 12 tilted) was presented, with the tilted line orientation set at the value identified in the first step (e.g. 21°). If the patient scored between 63% and 67% in 3 consecutive blocks of 24 stimuli, this orientation value was considered to be the threshold and was used in the main experiment. Otherwise, the orientation value was raised or lowered until SDV reached a stable performance (around 65%) over three consecutive blocks.

Procedure

The main experiment was designed to test whether SDV's orientation discrimination ability can be crossmodally modulated by the presence of task-irrelevant sounds and, if so, whether the modulation occurs only in sighted areas of the visual field (subtended by spared V1) or also in blind areas (subtended by lesioned V1). To test the influence of sound on the patient's visual performance, he was asked to

discriminate the orientation (vertical or tilted) of a line when presented either unimodally or coupled with sounds. To test the location-specificity of the effect, visual and auditory stimuli were presented, in different blocks, at 10 VD eccentricity in the right visual field and at 0 VD (i.e. at fixation), that is, the two areas of the visual field previously identified to be where the patient's discriminative ability was best and worst, respectively (see Pilot experiment).

As shown in Figure 22, each trial started with a red fixation dot (0.2 VD diameter) on a uniform grey background. Stimulus presentation was triggered by the experimenter after checking the patient's eye position. If eye movements were registered during the stimulus presentation, the trial was removed and subsequently repeated, interspersed among the following trials. In each trial, either a vertical or a tilted line could be presented (250 ms duration) in four possible conditions: 1) coupled with a looming sound; 2) coupled with a receding sound; 3) coupled with a stationary sound; 4) without sound presentation. After each stimulus presentation, SDV verbally reported the perceived orientation (vertical vs. tilted) and his response was collected by the experimenter. All auditory stimuli were presented temporally and spatially (on the same vertical line) coincident with the visual stimuli, and the patient was instructed to focus on visual stimuli and to ignore the sounds. In different blocks, stimuli were presented at two possible positions in SDV's visual field, namely 10 VD eccentricity to the right and at the central fixation point. Each block comprised 96 trials (24 trials per condition) and a total of 40 blocks (20 blocks for each tested position) were run (480 trials x 4 conditions x 2 positions = 3840 total trials). The 40 experimental blocks were split into 4 sessions of 10 blocks each (5 blocks for each tested position). The vertical line stimulus (0° orientation) was the same in all tested positions, whereas the tilted line stimulus had different orientations between 0 VD and 10 VD.

Indeed, in blocks at 0 VD eccentricity tilted lines were always horizontal (90° orientation), whereas in blocks at 10 VD the orientation of tilted lines was thresholded before each session using the procedure described above (see Orientation threshold estimation; mean orientation across the 4 blocks: 21.25°; SD: 1.5°).

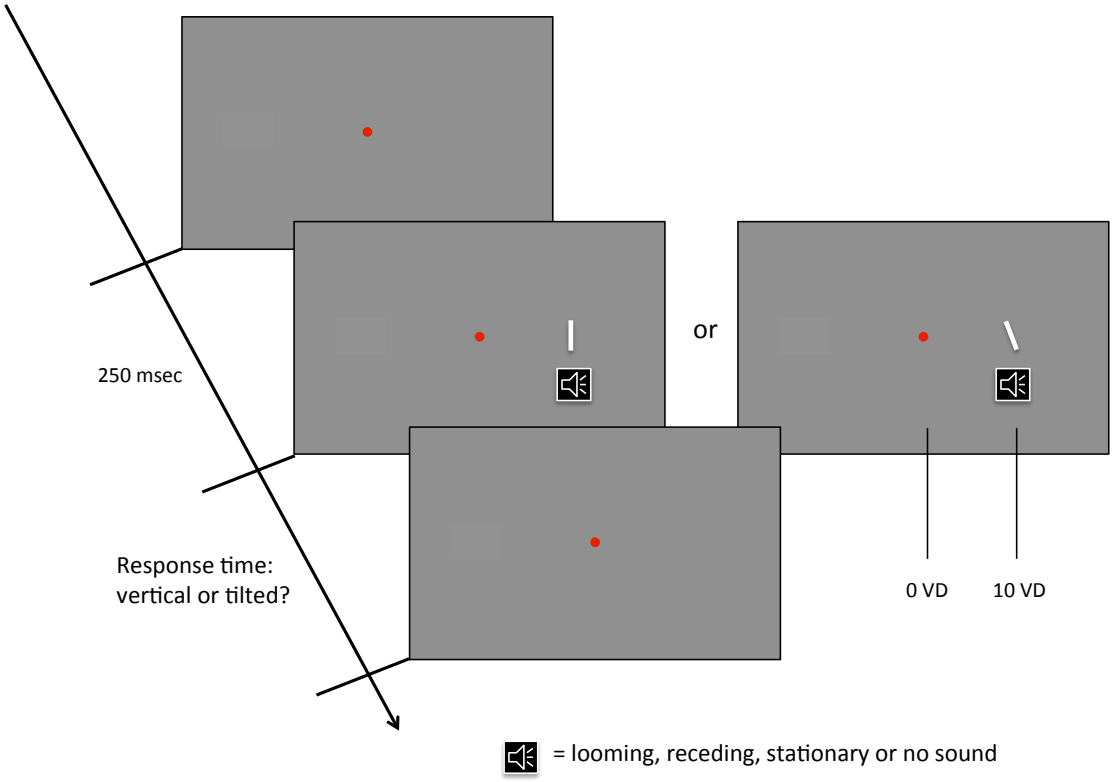

Figure 22. Schematic representation of the procedure of the main experiment. The figure depicts examples of trials in the condition where lines were presented at 10 VD eccentricity to the right. While maintaining fixation on a central dot, SDV was presented with either a vertical or a counter-clockwise tilted line, unimodally (without sound) or paired with a concurrent looming, receding or static sound. On each trial SDV verbally reported the perceived orientation of the line (vertical or tilted).

Data analysis and Results

The numbers of hits, misses, correct rejections and false alarms were calculated for each condition (looming, receding, stationary and no sound) in the two tested positions (10 VD and 0 VD eccentricity). Accuracy (% correct responses), sensitivity (d') and criterion (c) scores are reported in Table 7. Differences in sensitivity between conditions were analysed by paired 2-tailed Fisher's tests. Overall sensitivity for

stimuli presented at 10 VD eccentricity (d'=1.03) was significantly above chance (p=0.0001) and higher than for stimuli presented at 0 VD (d'=-0.09; p=0.0001), where SDV's performance did not differ from chance (p=0.27). For stimuli presented at 10 VD, sensitivity was significantly higher in the looming sound condition (d'=1.35) than in the receding (d'=0.88; p=0.007), stationary (d'=1.01; p=0.05) and no sound (d'=0.93; p=0.02) conditions, which did not differ from each other (all ps>0.44; see Figure 23A). Interestingly, for stimuli presented at fixation, there was no difference in sensitivity between conditions (all ps>0.19; see Figure 23B), and d' did not differ from chance in any of the conditions (all ps>0.15).

Position	Condition	Accuracy	d'	c
10 VD	*Looming sound*	75%	1,35	-0,05
	Receding sound	67%	0,88	0,14
	Stationary sound	69%	1,01	-0,01
	No sound	67%	0,93	-0,28
0 VD	*Looming sound*	49%	-0,06	-0,01
	Receding sound	50%	-0,02	-0,03
	Stationary sound	45%	-0,23	0,12
	No sound	49%	-0,04	-0,06

Table 7. Results of the main experiment. SDV's accuracy, d' and c values for orientation discrimination between vertical and tilted lines presented at fixation (blind visual field) and at 10 VD eccentricity in the right visual field (sighted visual field), in the looming sound, receding sound, static sound and no sound conditions.

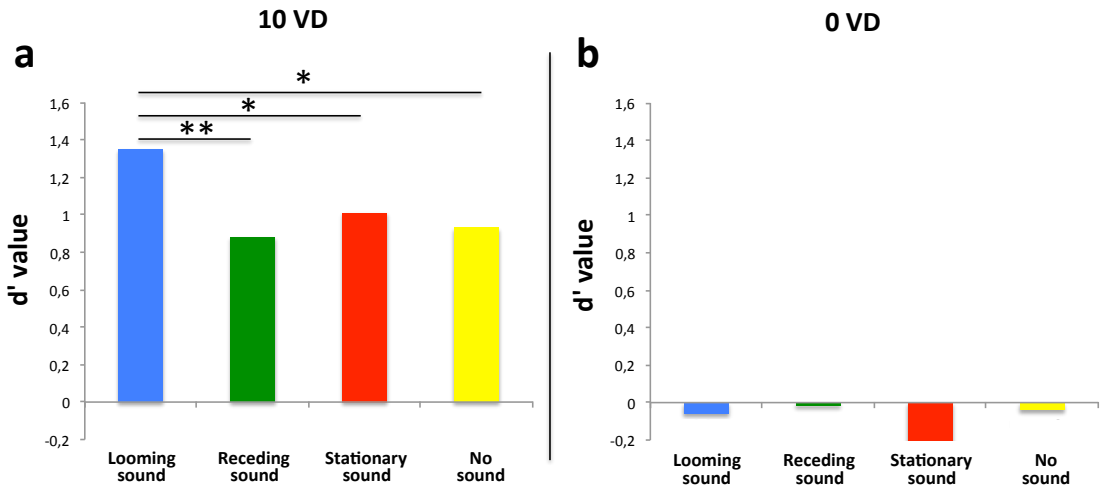

Figure 23. Results of the main experiment. SDV's orientation sensitivity scores (d') for each condition (looming, receding, stationary and no sound) when visual stimuli were presented at 10 VD eccentricity in the right visual field (panel a) or at 0 VD eccentricity (panel b). Single asterisks indicate a p value <0.05; double asterisks indicate a p value <0.01. As indicated by the asterisks, only looming sounds in the sighted visual field (10 VD eccentricity on the right) significantly enhanced visual sensitivity in the visual orientation discrimination task compared to all other conditions.

In summary, results showed that SDV's orientation discrimination ability was specifically enhanced by a co-occurring looming sound, but only when audio-visual stimuli were presented in a relatively preserved location of his visual field (i.e. 10 VD eccentricity to the right). Notably, looming sounds enhanced SDV's accuracy for lines at threshold orientation discrimination (~21°) up to 75%, i.e. almost his best performance (79%) with lines of maximal orientation difference (90°).

Discussion

The present study was inspired by previous works reporting, on the one hand, that auditory stimulation (white-noise bursts) can improve visual detection sensitivity in the blind field of patients with visual deficits (Frassinetti et al., 2005) and, on the other hand, that looming sounds can enhance orientation sensitivity for visual stimuli in normally-sighted subjects (Leo et al., 2011). Basing on these findings, the patient SDV, presenting bilateral occipital lesion and consequent visual field defect, was

tested to assess whether looming sounds could improve his orientation sensitivity for solid lines presented in his intact and blind visual fields. Looming sounds, instead of white-noise sounds, were used in the present study because it was previously shown that white-noise sounds are not effective at enhancing visual processing in an orientation discrimination task (Leo et al., 2011).

In line with Leo et al. (2011), results revealed that SDV's visual orientation sensitivity significantly improved when the visual stimuli were paired with looming sounds versus receding and stationary sounds. The specific effect yielded by looming sounds is in agreement with evidence that looming signals benefit from preferential processing in the brain (e.g. Cappe et al., 2012) and improve behaviour in multisensory contexts (e.g. Cappe et al., 2009; 2012).

However, in the present study looming sounds specifically enhanced orientation sensitivity for visual stimuli presented in the preserved portion of SDV's visual field (i.e. 10 VD eccentricity to the right), whereas none of the sounds coupled with visual stimuli presented in the patient's blind visual field (i.e. the fovea) affected his ability to discriminate line orientation, as demonstrated by his chance-level performance. This latter finding suggests that, when the striate cortex is damaged, looming sounds are ineffective at crossmodally enhancing line orientation discrimination. This negative result is apparently in contrast with previous reports showing that auditory stimulation can improve visual processing, namely detection, in the blind field of patients with lesions to the primary visual pathway (Frassinetti et al., 2005). However, this discrepancy might be explained by substantial differences in both the tasks and the stimuli used in the two studies. The task employed by Frassinetti et al. (2005) required the detection of briefly flashed single spots of light, whereas in the present study the patient was asked to discriminate the orientation of vertical versus tilted

lines. The different visual tasks and stimuli used in the two studies might have tapped areas and networks in the visual system with completely different properties. Indeed, single spots of light are known to be particularly efficient in activating neurons with centre-surround receptive fields (Hubel & Weisel, 1959; 1977), which are abundant in the SC (Goldberg & Wurtz, 1972), a subcortical structure with multisensory properties capable of driving multisensory integration without cortical contribution (Stein & Meredith, 1993). On the other hand, light-dark lines and edges seem to generate a preferential response in V1 neurons, which are triggered by specific line orientations and are only weakly activated by simple spots of light (Hubel & Weisel, 1959; 1977).

If these observations are taken into account, it seems reasonable that the crossmodal mechanisms improving visual detection performance in Frassinetti et al. (2005) largely depended on subcortical networks without involving primary visual areas, which were lesioned or deafferentated in the tested patients. Instead, the visual improvement found here likely stemmed from audio-visual interactions at the level of early visual areas, as suggested by the fact that looming sounds enhanced visual processing, but only within areas of the visual field subtended by intact striate cortex. In other words, primary visual areas might represent a critical node for such crossmodal interactions as those leading to the improved orientation discrimination observed here.

Several studies have already suggested that multisensory interactions might occur at the level of early visual areas (Giard & Peronnet, 1999; Molholm et al., 2002; Martuzzi et al., 2007; Romei et al., 2007; 2012; Noesselt et al., 2010; Raij et al., 2010; Van der Burg et al., 2011). In keeping with this hypothesis, a TMS study (Romei et al., 2009) showed that looming sounds, compared to other types of sounds, selectively

enhance visual processing by rapidly increasing visual cortex excitability. More recent EEG (Cappe et al., 2012) and fMRI (Tyll et al., 2013) studies shed further light on the neural underpinnings of the crossmodal effects of looming sounds by revealing superadditive responses to audio-visual stimuli in a broad network of areas, including early sensory cortices (auditory and visual) as well as multisensory convergence areas such as STS (Tyll et al., 2013). Thus, the question remains whether any modulation of orientation sensitivity by looming sounds is primarily determined by differential activity in early visual areas or in brain areas other than V1 (e.g. STS). The results of present study seem to support the first hypothesis. Indeed, if areas outside V1, and not V1 itself, were primarily responsible for the crossmodal interactions improving orientation sensitivity, such an improvement would be observed in SDV also in the absence of conscious vision, i.e. without intact V1. However, this was not the case, as SDV was not able to discriminate the orientation of a line in his blind field, neither alone, nor paired with looming sounds. This would speak in favour of the hypothesis that early visual areas are necessary for this type of crossmodal interaction. However, future studies will need to address the question of whether and to what extent STS, and or its interaction with V1, contributes to the crossmodal effects produced by looming sounds. For example interventional studies can be used that transiently and selectively interfere with STS activity while assessing the impact of looming sounds on visual processing.

According to Cappe and co-workers (2012), the behavioural gain resulting from the integration of looming signals might reflect early multisensory interactions in low-level sensory areas. Romei et al. (2013) have recently argued that the effects of looming sounds on visual cortex excitability are evident not only early in time but also at later stages of signal processing, and that top-down attentional mechanisms

can account for such late effects. These findings are in line with a broad literature suggesting that looming signals are particularly salient stimuli that attract attentional resources (Schiff et al., 1962; 1965; Neuhoff, 1998; Ghazanfar et al., 2002; Seifritz et al., 2002; Graziano & Cooke, 2006; Bach et al., 2008; 2009). The present study cannot ascertain to what extent the observed visual enhancement by looming sounds depended on sensory or attentional processes. Nevertheless, the observation that looming sounds differentially affected orientation sensitivity in the sighted and the blind fields of SDV cannot be merely attributed to a differential deployment of spatial attention. Indeed, in each block of the experimental task, visual stimuli were presented in only one of the two possible positions (0 VD or 10 VD) and SDV was informed about the position where the stimuli would appear and instructed to focus his attention on that spot throughout the block. Notably, SDV had to maintain fixation during the whole task; therefore, when visual stimuli were presented in his intact field (10 VD eccentricity to the right), he covertly attended them, whereas when they were presented in his blind field (i.e. in the fovea), visual stimuli were overtly attended. This should have enhanced any attentional effect in the blind field, but that was not the case.

In conclusion, whatever the underlying process, the present results clearly show that when the striate cortex is lesioned, sounds cannot enhance orientation sensitivity, neither by early multisensory interactions nor by late attentional modulations, suggesting that primary visual areas play a fundamental role in this specific audio-visual integrative process.

General discussion

Humans are endowed with the remarkable ability to perform a deep and detailed analysis of visual information, which is further strengthened by the brain's ability to merge signals conveyed by multiple sensory modalities. Thus, when visual input is somehow weak or degraded, converging inputs from other senses can aid perception. Such complex visual abilities are mirrored by an equally complex visual system, which, through evolution, has developed multiple parallel neural pathways that, on the one hand, afford visual processing at different levels of detail and speed and, on the other hand, also prevent the total loss of visual functions when the brain is damaged. Indeed, thanks to the existence of multiple visual pathways, even when geniculo-striate lesions permanently disrupt the conscious visual experience of the external world, spared visual networks can still process some features of visual stimuli that are no longer explicitly perceived.

The present dissertation sought to clarify some aspects of residual visual functions following lesions to the primary visual pathway for conscious vision, focusing i) on the implicit processing of emotional signals conveyed by unseen stimuli and ii) on the multisensory integration of auditory and unseen visual stimuli.

The ability to perceive affective signals coming from the external world is fundamental for optimal interaction with the environment. Analysing a visual stimulus in detail entails a long and complicated process, requiring the participation of a large number of brain areas. However, in some cases, the rapid and automatic processing of visual information can be critical for survival. For example, the fast

detection of an imminent threat could be extremely advantageous, allowing early recruitment of autonomic responses and prompt deployment of flight-or-fight reactions (Öhman & Wiens, 2003). Joseph LeDoux (1996) first conceptualised the existence of two parallel visual pathways for fear processing, both feeding input to the amygdala, a fundamental subcortical structure for the analysis of fearful signals (Whalen, 1998; Davis & Whalen, 2001; Zald, 2003; Öhman, 2005). In this dual-route model, visual information can reach the amygdala through: (i) a cortical, geniculo-striate "high road", providing conscious and detailed, though slow, visual processing; (ii) a subcortical, colliculo-pulvinar "low road" for rough but fast analysis of stimuli.

To investigate the specific role of the "low road" in emotional processing, a number of previous studies have tested both patients with visual field defects, in whom, theoretically, the "high road" is lesioned but the "low road" is still functional, and healthy subjects, in whom conscious perception provided by the "high road" is prevented by experimental manipulation. These studies have provided useful insights into the functional properties of the "low road", but the evidence reported so far on this topic has been controversial, making it difficult to disentangle whether this pathway is specifically triggered by fearful stimuli, as suggested by LeDoux's model, or, alternatively, by emotions in general. For instance, a small number of patients, despite their blindness, have demonstrated above-chance discriminative ability (affective blindsight) for various facial emotional expressions in their blind field (e.g. fearful, sad, angry, happy; see: de Gelder et al., 1999; Pegna et al., 2005; Tamietto et al., 2009), as well as implicit effects (e.g. automatic facial muscular reactions) for both unseen fearful and happy faces and body postures (Tamietto et al., 2009), suggesting that the "low road" could mediate non-conscious processing of affective stimuli regardless of the type of emotion. On the other hand, a considerable number of

imaging studies have reported activation of the "low road" for unseen fearful stimuli (Whalen et al., 1998; 2004; Morris et al., 1999; 2001; M. A. Williams et al., 2004; Liddell et al., 2005; Pegna et al., 2005; L. M. Williams et al., 2006a) and, among those comparing subcortical activity elicited by different types of unseen emotions, some reported fear-specific effects (Whalen et al., 1998; 2004), while others also found a response to positive-valenced stimuli (M. A. Williams et al., 2004; Pegna et al., 2005). Moreover, it is worth noting that results from studies on affective blindsight patients might be spurious, because it is not clear whether their unusual residual visual abilities ensue exclusively from the contribution of subcortical networks (i.e. the "low road"). Indeed, blindsight patients are reportedly able to perform above-chance guessing about many different features of unseen visual stimuli (see Introduction), a fact that seems to be the exception rather than the rule in clinically blind patients. This suggests that blindsight patients might benefit from a peculiar post-lesion functional reorganisation, possibly involving spared extrastriate areas. Considering all these observations and controversial results, it is quite surprising that implicit emotional processing had not yet been studied in patients with visual field defect showing no residual cortical visual processing, i.e. no above-chance discriminative ability for unseen stimuli.

The studies presented in the first chapter of the present dissertation provide an original contribution to the debate on the functions of the "low road" and the "high road" in emotional processing by testing i) hemianopic patients with no residual capacity to discriminate stimuli in their blind field (Experiments 1 and 2) and ii) healthy subjects, in whom conscious perception in one visual field was prevented by means of a masking technique and cortical activity was suppressed by brain stimulation (Experiment 3).

In Experiment 1, hemianopic patients performing at chance in 2AFC tasks were tested in two go/no-go tasks with redundant stimuli to assess whether behavioural responses to seen faces in the intact visual field could be influenced by emotional faces presented in the blind visual field. The results revealed a facilitatory effect on RTs to seen happy faces exerted by unseen fearful faces but not by unseen happy or scrambled faces, suggesting that, when the "high road" is lesioned, only fear can be implicitly processed by the "low road". Moreover, the same fear-specific facilitation was also evident when patients responded to non-emotional stimuli (i.e. neutral faces), pointing to a general, task-independent facilitatory effect of unseen fear, i.e. to a role of the "low road" in alerting the motor system whenever a potential threat is perceived.

Interestingly, Experiment 1 also revealed that unseen fearful faces did not speed up responses to seen fearful faces. In other words, conscious fear seemed to inhibit the fast responses typically triggered by unconscious fear. One possible explanation could be that, when a fearful stimulus is consciously perceived, visual input conveyed by the "low road" to the amygdala is suppressed in order to promote further processing of the more salient seen threat, as also suggested by a previous fMRI study showing negative functional connectivity within visual pathways to the amygdala in the presence of conscious fear (L. M. Williams et al., 2006a). This would open the possibility for complex dynamic interactions between the "high" and the "low road", which is further supported by the fact that these two routes for emotional processing are not fully anatomically segregated.

Experiment 2 corroborated and extended the results of Experiment 1, providing evidence that the implicit perception of fearful signals is not only manifest at the behavioural level (Experiment 1), but also impacts the early electrophysiological

response to consciously perceived emotional faces. This was achieved by testing the influence of unseen emotional faces on the early ERP component (N170) typically elicited by seen faces. Scalp EEG was recorded in two groups of patients with left and right hemisphere lesions while they performed a double-choice task in which target faces (fearful or happy) in the intact visual field were paired with emotional faces (fearful, happy or neutral) in the blind field. Paralleling the behavioural findings of Experiment 1, the results showed that the N170 component elicited by seen happy faces was specifically enhanced by the concurrent presentation of unseen fearful faces, whereas no such ERP modulation by unseen fearful faces was evident in response to consciously perceived fearful faces. Notably, the modulatory effects were already evident at early stages of visual facial processing (i.e. the stage of facial encoding), favouring the hypothesis that subcortical visual pathways (i.e. the "low road") operate a fast and coarse visual analysis in the absence of awareness. Interestingly, the fear-related N170 increase was only evident in patients with left hemisphere lesions, suggesting that unseen fearful signals processed by the "low road" can only modulate the early stages of facial processing when the right hemisphere is intact. This is consistent with reports of increased connectivity between the right amygdala and the other components of the "low road", i.e. the pulvinar and the SC (Morris et al., 1999), as well as higher right amygdala activation in the presence of unseen fearful faces (de Gelder et al., 2005; Pegna et al., 2005; L. M. Williams et al., 2006b). In addition, these findings are concordant with the hypotheses of right-hemisphere dominance in emotional processing (Borod et al., 1998; Gainotti, 2000) and in withdrawal behaviours, which are often associated with negative emotions such as fear (Davidson, 1993; Davidson et al., 2000).

In summary, Experiments 1 and 2 supported the existence of a subcortical visual

pathway that, bypassing V1, allows emotional processing in the absence of visual awareness. More importantly, they demonstrated that behavioural (Experiment 1) and electrophysiological (Experiment 2) responses to seen happy faces were specifically affected by the concurrent presentation of unseen fearful faces, suggesting that in hemianopic patients only fear-related signals (and not general emotional signals) can be implicitly processed through the subcortical "low road".

Such results disagree with studies on blindsight patients, which report a congruency-dependent facilitation (i.e. faster RTs) for emotionally identical pairs of seen/unseen faces (sad or fearful; de Gelder et al., 2001) and reduced ERPs in response to emotionally incongruent pairs of voices and unseen faces (de Gelder et al., 2002). These congruency-dependent effects are strikingly similar to those reported in healthy subjects when tested in indirect tasks with redundant seen/masked emotional faces (Tamietto & de Gelder, 2008a). The discrepancy with data on hemianopic patients, on the one hand, and the similarity with healthy subjects' performance, on the other hand, strengthens the above-mentioned hypothesis that the effects evident in blindsight patients might stem from high-order processes, involving not only the "low road", but also, to some extent, components of the "high road". In contrast, the fear-specific effect evident in hemianopic patients might reflect a low-level reactive mechanism that is exclusively mediated by the "low road", allowing early recruitment of motor areas when any type of potential threat is detected, as also suggested by previous studies (e.g. de Gelder et al., 2004).

To disentangle the effects depending on the joint activity of the "high" and the "low road" and those yielded by the mere activity of the "low road", tDCS was used in Experiment 3 to perturb healthy volunteers' occipital areas (i.e. a pivotal node of the "high road") prior to the execution of a go/no-go task, in which target seen emotional

faces (fearful or happy) were coupled with backward-masked emotionally congruent, incongruent or neutral faces to approximate hemianopia.

Performing such a task under normal physiological conditions (i.e. after sham tDCS) yielded a congruency effect (i.e. faster RTs in the presence of identical pairs of seen/unseen emotional faces), in line with previous studies that used a similar paradigm with blindsight patients (de Gelder et al., 2001) and healthy subjects (Tamietto & de Gelder, 2008a). On the other hand, when activity in occipital areas was suppressed by cathodal tDCS, congruency effects disappeared and participants showed faster responses to seen happy faces when coupled with unseen fearful faces, perfectly matching the results from hemianopic patients in Experiments 1 and 2 (also see Bertini et al., 2012). These findings clearly suggest that: (i) when only the "low road" is active and functional, only fearful faces can be processed in the absence of visual awareness; (ii) the congruency-dependent facilitation elicited by pairs of seen/unseen emotional faces requires the contribution of occipital cortex (i.e. the "high road"). The causative role of occipital areas in determining congruency effects was further confirmed by a control experiment (Experiment 3b), in which cathodal inhibitory tDCS at a control site (i.e. the vertex) had the same outcome as sham stimulation. In addition, the results of Experiment 3 suggest that the backward masking technique, despite abolishing conscious perception by interrupting re-entrant feedback to V1 (Lamme & Roelfsema, 2000), is not sufficient to totally prevent cortical activation during implicit emotion perception. In other words, the lack of conscious visual perception does not always exclude the possibility that cortical components of the "high road" could be nevertheless engaged by unseen emotional stimuli. Following this line of reasoning, blindsight patients, notwithstanding lesions to the striate cortex, might be able to recruit cortical areas of the "high road" during

implicit perception of emotions, akin to healthy subjects in whom visual awareness is prevented by backward masking. This could be driven by post-lesion plasticity phenomena promoting functional reorganisation within visual pathways.

In summary, the first chapter of the present thesis demonstrated that, when the striate cortex is damaged or denervated, some residual visual processing of the emotional content of unseen stimuli is still possible, most likely by means of a subcortical colliculo-pulvinar-amygdala network that is spared by the lesion.

Based on anatomical evidence, previous animal (e.g. see: Chomsung et al., 2008; Day-Brown et al., 2010) and human (Tamietto et al., 2012) studies demonstrated the existence of a subcortical, colliculo-pulvinar visual pathway to the amygdala, bypassing V1 and mediating responses to unconsciously perceived emotional stimuli. The experiments reported in the first chapter of the present dissertation extend knowledge about the functional aspects of this "low road", providing converging evidence that the subcortical colliculo-pulvinar-amygdala network is specialised for detecting coarse fearful signals, as well as for enhancing face processing and early activation of motor areas in response to such signals. This fear-induced perceptual boost and motor readiness could represent an adaptive mechanism that quickly enable defensive behaviours, well before conscious recognition of dangers.

The first chapter also shed light on some functional properties of the cortical "high road" for emotional processing, demonstrating that occipital areas are able to extract emotional information from unseen faces and to elicit faster responses to seen faces, depending upon their emotional congruence with unseen stimuli.

From an evolutionary perspective, in the context of threat detection, it is extremely useful to have a fear detection system that can automatically trigger fast motor responses based only on a coarse visual analysis, because, in potentially dangerous

situations, it is far less risky to quickly react to a stimulus that is not really harmful (i.e. a false positive) than to react too late to a stimulus that is actually harmful (i.e. a false negative) (LeDoux, 1996; Öhman & Mineka, 2001). As well, it is highly advantageous to be endowed with a more detailed, though slower, visual pathway for emotional processing, allowing the extraction of emotional signals from more complex stimuli and situations and, by consequence, the production of behavioural responses that are more appropriate to the context.

When the primary visual pathway responsible for conscious vision is lesioned, this ability to perform high-order processing of emotional stimuli is lost, but residual visual functions mediated by alternative visual pathways still allow implicit processing of coarse features of fear-related stimuli.

Moreover, a number of studies in the literature have demonstrated that, thanks to the residual visual functions provided by alternative visual pathways that bypass V1, multisensory integration processes are also still available after striatal lesions, allowing unseen visual stimuli to influence auditory perception and, vice-versa, allowing auditory stimuli to aid visual perception, a phenomenon which could be referred to as "crossmodal blindsight". The superior colliculus, which, as a part of the "low road" to the amygdala, also plays a role in emotional processing, is an important subcortical component of the visual system, directly conveying visual input from the retina to cortical extrastriate areas, thus bypassing the striate cortex and mediating a number of visual functions in the absence of awareness (see Introduction). Interestingly, neurons in the superior colliculus respond not only to visual stimuli, but also to signals conveyed by other sensory modalities (e.g. audition), a property that suggests that the SC also plays an important role in multisensory integration (Stein &

Meredith, 1993). The integration of signals from the auditory and visual sensory modalities can improve visual perception, for example enhancing visual detection (Driver & Spence, 1998; McDonald et al., 2000; Vroomen & de Gelder, 2000; Frassinetti et al., 2002; Bolognini et al., 2005a; de Haas et al., 2013), phosphene perception (Romei et al., 2007; 2009; 2012; 2013; Bolognini et al., 2010; Convento et al., 2012) and orientation discrimination (Leo et al., 2011). Moreover, multisensory integration is particularly effective at improving visual perception when visual inputs are weak or degraded (i.e. the inverse effectiveness rule), and its effects are evident even in the absence of awareness of the stimuli to be integrated (Stein & Meredith, 1993). Based on this evidence, as well as on the observation that the SC is spared by lesions involving the geniculo-striate pathway, it seems reasonable to hypothesize that, exploiting multisensory properties of the SC, visual perception in the blind field could be enhanced in patients with visual field defects by concurrent auditory stimulation. In keeping with this hypothesis, Frassinetti and co-workers (2005) found that detection sensitivity for stimuli presented in the blind hemifield of hemianopic patients was improved by the presentation of spatiotemporally coincident sounds, also suggesting that this crossmodally-induced visual enhancement could be mediated by direct colliculo-extrastriate projections, which were spared in the tested patients. More recently, a study on healthy subjects (Leo et al., 2011) reported that orientation sensitivity for threshold stimuli is also enhanced by the concurrent presentation of auditory stimuli, namely looming sounds. An interesting question arising from these previous observations is whether the residual ability of patients with visual field defects to integrate audio-visual stimuli might not only improve visual detection and localisation, but also the discrimination of specific features of unseen stimuli, such as their orientation.

The single case study (Experiment 4) reported in the second chapter of the present dissertation aimed to test whether auditory stimulation could be exploited in a patient with V1 lesions to not only improve simple visual detection of unseen stimuli (Frassinetti et al., 2005), but also a more complex visual ability, such as orientation discrimination, in line with results on normal subjects (Leo et al., 2011). To this end, Experiment 4 tested the impact of looming sounds on orientation discrimination performance for lines presented in the patient's intact and in blind fields, respectively subtended by intact and lesioned V1. This allowed the investigation of: (i) whether orientation sensitivity can be enhanced by concurrent auditory stimulation; (ii) whether the striate cortex plays a role in determining the orientation sensitivity enhancement by looming sounds or whether, as for visual detection, this process can be mediated by the alternative colliculo-exstrastriate pathway, bypassing V1.

In line with Leo et al. (2011), results showed that looming sounds enhanced the patient's performance, but only for lines presented in his relatively preserved visual field, whereas no effect of sound was evident for lines presented within his foveal scotomas. In other words, looming sounds were effective in crossmodally enhancing orientation sensitivity only in areas of the patient's visual field that were subtended by intact V1. These findings demonstrate that, when the striate cortex is lesioned, concurrently presented sounds can enhance the detection of spots of light (Frassinetti et al., 2005; Làdavas, 2008) but not the ability to discriminate the orientation of lines. This suggests that multisensory integration processes leading to improved detection (Frassinetti et al., 2005; Làdavas, 2008) and orientation (Leo et al., 2011) sensitivity could be carried out by different visual areas and networks. In particular, whereas sound-induced detection improvement is likely mediated by subcortical structures (e.g. the SC) that are usually spared by geniculo-striate lesions, V1 might play a

causative role in the sound-induced enhancement of orientation sensitivity, as suggested by the absence of crossmodally-induced visual sensitivity enhancement for stimuli presented in blind areas of the visual field, which are subtended by lesioned V1. This hypothesis is consistent with the different properties shown by neurons in the SC and in the primary visual cortex. Indeed, neurons in the SC have centre-surround receptive fields that are maximally activated by simple spots of light (Hubel & Weisel, 1959; 1977). By contrast, neurons in V1 are edge detectors that are preferentially activated by lines with specific orientations, showing only a modest response to spots of light (Hubel & Weisel, 1959; 1977).

Moreover, in keeping with the suggestion that V1 might be a critical area mediating the orientation sensitivity enhancement by looming sounds, several studies have provided evidence that multisensory interactions might occur at the level of early visual areas (Giard & Peronnet, 1999; Molholm et al., 2002; Martuzzi et al., 2007; Romei et al., 2007; 2012; Noesselt et al., 2010; Raij et al., 2010; Van der Burg et al., 2011). For example, it has been shown that the presentation of looming sounds increases visual cortex excitability (Romei et al., 2009), and that audio-visual stimuli engage a broad network of areas, including early sensory (auditory and visual) cortices (Tyll et al., 2013). Consistent with these findings, an EEG study by Cappe and colleagues (2012) showed that the behavioural gain produced by the audio-visual integration of looming signals could be explained by the early activation of sensory areas.

However, a recent study (Romei et al., 2013) demonstrated that looming sounds affect visual cortex excitability not only at early stages but also at a later stage of processing, which led the authors to hypothesise that top-down attentional mechanisms could enhance V1 activity and play a role in the crossmodal effects

exerted by looming sounds. This explanation seems plausible in light of previous evidence suggesting that looming signals are particularly salient stimuli that attract attentional resources (Schiff et al., 1962; 1965; Neuhoff, 1998; Ghazanfar et al., 2002; Seifritz et al., 2002; Graziano & Cooke, 2006; Bach et al., 2008; 2009). Unfortunately, the design of Experiment 4 does not allow the discrimination of the specific roles of sensory and attentional mechanisms in the visual enhancement by looming sounds, a topic that, in any case, is far beyond the scope of chapter 2 and the present dissertation.

Notwithstanding these limitations, the data presented in chapter 2 demonstrate that when the striate cortex is lesioned, the ability to discriminate the orientation of visual stimuli cannot be enhanced by concurrent looming sounds, neither through early multisensory interactions nor through late attentional modulations, thus suggesting that primary visual areas play a crucial role in determining whether the presentation of auditory stimuli will crossmodally affect visual orientation sensitivity.

Concluding remarks

In conclusion, the present dissertation has discussed the different roles of subcortical and cortical visual pathways in both implicit emotional processing and multisensory integration. To reveal the specific contributions of each pathway to these processes, real or virtual lesion approaches were used, testing both patients with lesions to the primary visual pathway and healthy subjects in whom cortical visual processing was perturbed by means of transcranial direct current stimulation.

With respect to emotional processing in the absence of visual awareness, results revealed that, when lesions to occipital areas prevent conscious visual perception, subcortical visual pathways, most likely involving the superior colliculus, the thalamic pulvinar and the amygdala, are able to implicitly and coarsely process emotional facial expressions, but this residual ability is limited to fearful expressions. Instead, cortical areas, most likely extrastriate cortices, would be able to evaluate high-order features of stimuli, such as the emotional correspondence between seen and unseen emotional faces, as suggested by evidence that the occipital cortex has a causative role in mediating behavioural facilitations in response to congruent pairs of seen/unseen faces, regardless which emotion they express.

Further studies are needed to investigate whether the subcortical visual pathway for fear perception specifically processes unseen fearful faces or whether it can be also engaged by different types of unseen fearful stimuli, e.g. fearful body postures.

As far as multisensory integration is concerned, it was shown here that, in the presence of occipital lesions, it is not possible to enhance visual orientation discrimination in the blind field via concurrent auditory stimulation. This suggests

that the occurrence of such crossmodal effects requires intact primary visual areas and, on the other hand, that subcortical (e.g. colliculo-extrastriate) visual pathways bypassing the striate cortex, despite affording the integration of audio-visual stimuli and the improvement of simple visual abilities such as detection and localisation, cannot mediate multisensory enhancement of more complex visual functions, such as orientation discrimination.

Future studies using brain stimulation to transiently and selectively impair V1, versus other cortical areas involved in multisensory integration (e.g. STS), would help to clarify the specific role of different areas in this process, as well as to further confirm the causative role of primary visual areas in multisensory enhancement of orientation sensitivity. A deeper understanding of these aspects would also be extremely valuable in terms of the rehabilitation of patients with visual fields defects, allowing the exploitation of multisensory integration in treatments aiming to ameliorate not only simple functions, but also more complex visual abilities.

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Glossary

2AFC = two-alternative forced-choice

ANOVA = analysis of variance

AVM = arteriovenous malformation

BA = Brodmann area

BOLD = blood-oxygen-level-dependent

CS = corrugator supercilii

CT = computed tomography

DTI = diffusion tensor imaging

EEG = electroencephalography or electroencephalogram

EMG = electromyography

EOG = electrooculogram

ERP = event-related potential

fMRI = (functional magnetic resonance imaging)

FWER = family-wise error rate

GM = grey matter

Hz = hertz

kHz = kilohertz

kΩ = kiloohms

LGN = lateral geniculate nucleus

LVF = left visual field

M = magnocellular

mA = milliampere

MEG = magnetoencephalography

MNI = Montreal Neurological Institute

MRI = (magnetic resonance imaging)

MRI = magnetic resonance imaging

P = parvocellular

RF = radiofrequency

ROI = region of interest

RT = reaction time

RTE = redundant target effect

RVF = right visual field

SC = superior colliculus

SEM = standard error mean

V1 = Visual area 1

VBM = voxel-based morphometry

VD = visual degrees

VFD = visual field defect

WM = white matter

ZM = zygomaticus major

μV = microvolts