Alma Mater Studiorum – Università di Bologna

DOTTORATO DI RICERCA IN

Cognitive Neuroscience

Ciclo XXIX

Settore Concorsuale di afferenza: 11/E1

Settore Scientifico disciplinare: M-PSI/02

The role of the subcortical dorsal visual pathway in the recovery of visual field defects

Presentata da: **Dott. Paolo Antonino Grasso**

Coordinatore Dottorato

Prof.ssa Monica Rubini

Relatore

Prof.ssa Elisabetta Làdavas

Esame finale anno 2017

Alla mia famiglia

Table of Contents

Abstract

Lateralized post-chiasmatic lesions to the primary visual pathway result in loss of vision over the visual field retinotopically corresponding to the site of the lesion. Previous studies showed that a systematic audio-visual training could constitute an efficient tool for the rehabilitation of such disturbances as revealed by ameliorated clinical performances in various visual domains. The first part of the present dissertation aim to shed light on the substrates underlying multisensory mediated recovery of visual field defects. Experiment 1 and Experiment 2, demonstrated that a sustained audio-visual training can promote stable plastic neural changes within the cortex, likely reflecting an enhanced activity of those neural circuits connecting superior colliculus to cortical areas within the dorsal stream. The second part of the present dissertation aimed to shed light on the functionality and the characteristics of extrageniculate circuits targeting extrastriate visual areas within the dorsal stream. Experiment 3 and Experiment 4, suggested that these connections remain responsive even when a lesion prevents visual processing within the primary visual channel and that these connections could play a relevant role in the rapid processing of salient visual stimuli.

Overall, the present experimental evidence suggest that visual processing depends on a variety of neural circuits and that a lesion to the primary visual pathway do not abolish the visual processing mediated by alternative routes. Moreover, activity within these routes could be exploited in a rehabilitative perspective, as revealed by ameliorated clinical performances and stable plastic neural changes induced by a systematic multisensory audio-visual training in hemianopic patients.

CHAPTER 1

General introduction

Vision is undoubtedly the dominant sense for humans. It enables us to interact with the surrounding environment to the point that our choices are in most of the cases highly driven by our visual experience. This happens because vision is the most reliable source of information and it strongly guides our daily behaviors in localizing, reaching and avoiding objects in the space.

However, vision is not the only sense we own to gather information from the environment. Most of the inputs arising from the external world are indeed multisensory in their nature and consequently the same event or object is represented by our system as the product of a synergic interaction of different sensory experiences.

The possibility to simultaneously perceive the same event in different sensory modalities constitute a strong advantage for our system. For example, at the neural level, we now know that several brain structures are specialized for the processing of combined sensory inputs and that brain responses to multisensory stimuli are generally more pronounced with respect to the single unisensory counterparts. In addition, the importance of experiencing various sensory inputs at the same time become clearer in the case of loss, or weakness, of information in one of the sensory modalities. In this case, the impaired sensory modality can greatly benefit from the information arising from the other sensory signals which can significantly boost the processing of the impaired input.

In this introductive chapter, I will firstly provide a description of the organization of visual system and of the consequences of lesions occurring at various stages of visual elaboration. I will then review the extent literature about evidence of preserved visual capacities still retrievable despite the presence of a visual field defect and the possible neural substrates subserving these capacities. I will then shift the focus of attention to the basic properties and the neural substrates governing the integration of different sensory modalities with a particular interest for the integration of audio-visual percepts. Finally, I will review the extent literature about existing protocols for the rehabilitation of visual field defects with a particular focus to a relatively novel approach exploiting audio-visual multisensory integration mechanisms.

1.1 Visual system and visual field defects

Organization of the visual system

The primary visual pathway is the pathway conveying visual information from the retina to primary visual cortex through the lateral geniculate nucleus (LGN) of the thalamus (i.e. retino-geniculo-striate pathway). This pathway is generally conceived of as a *parallel hierarchical system*. It is hierarchical because visual information is sequentially processed at various stages of the visual hierarchy. Neural fibers originating from ganglion cells of the retina convey most of the information to the LGN, which in turns projects to primary visual cortex (V1) where the basic features of a visual scene are processed (Figure 1). From V1 visual information then flows through a cortical hierarchy

to higher order visual areas including V2, V3, V4 and V5 where other features of the visual scene are processed like color, orientation, motion and spatial frequency. The primary visual pathway is also conceived of as parallel because neural fibers are usually divided into two segregated systems based on anatomical and functional characteristics. A magnocellular system originating from large receptive field ganglion cells of the retina well suited to respond to large moving objects and a parvocellular system originating from small receptive field ganglion cells of the retina specialized for the analysis of fine details and stationary stimuli. After V1, magnocellular and parvocellular systems are recombined into two cortical pathways. A dorsal pathway flowing towards parietal cortex and dominated by magnocellular inputs mainly processing information about space, motion and action and a ventral pathway dominated by parvocellular inputs and flowing towards temporal lobes mainly implicated in object identification and perception (Goodale & Milner, 1992).

As the other systems, also the visual system works on a crossed wires organization. Fibers originating from the two nasal hemiretinas (carrying information from the contralateral peripheral field) cross over at the optic chiasm, while fibers from the two temporal hemiretinas (carrying information from the contralateral medial field) do not cross. Consequently, fibers originating from the nasal hemiretina of the left eye and from temporal hemiretina of the right eye reach the right LGN via the optic tract and the reverse occur for the left LGN. From the LGN signals are then conveyed via the optic radiations, which send signals to striate cortex into two separate divisions. The lower division carries information arising from the upper quadrant of the contralateral visual hemifield and terminate in the lower part of calcarine sulcus while the upper division carries information

originating from the lower quadrant and terminates in the upper part of calcarine sulcus (Figure 1).

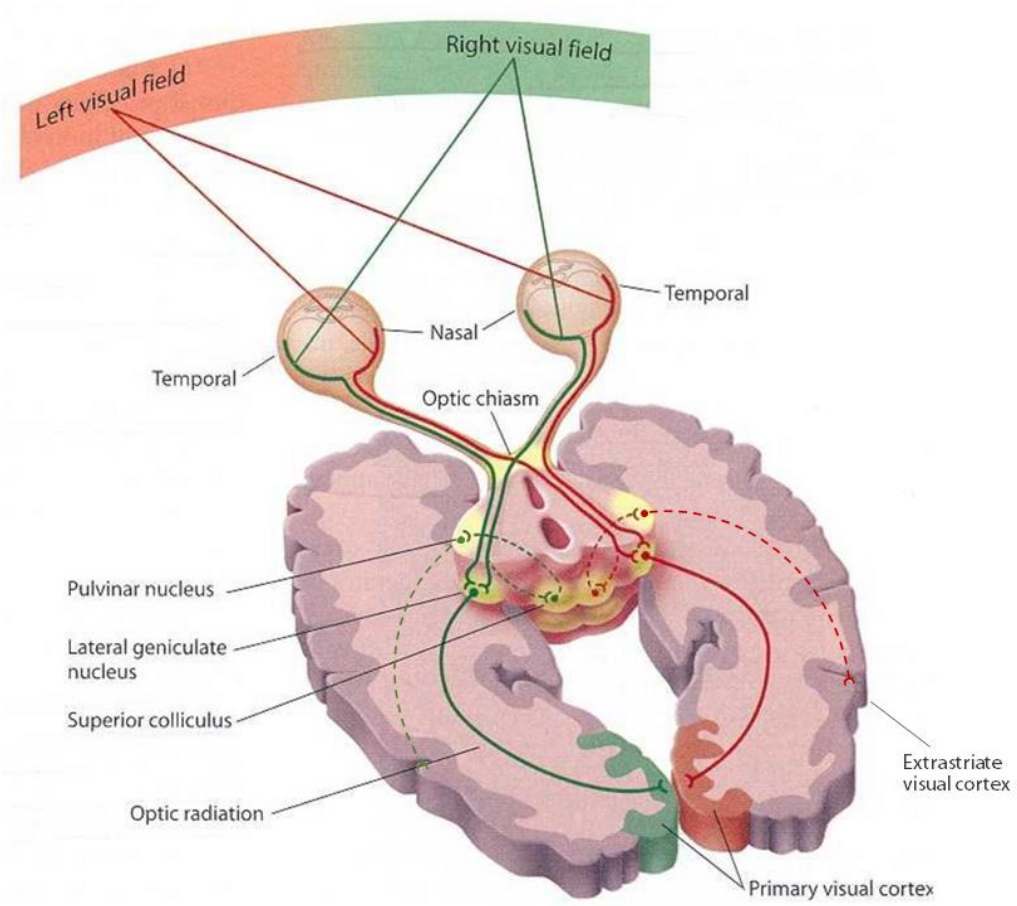

Figure 1. Organization of the visual pathways. Neural fibers originating from the two temporal hemiretinas project to the ipsilateral side, while the two nasal hemiretinas cross over at the optic chiasm. Visual input arising from each visual hemifield is thus projected to the contralateral lateral geniculate nucleus (LGN) and primary visual cortex (retino-geniculo-striate pathway – solid lines). A small percentage of the optic nerve fibers project to the superior colliculus (SC) and pulvinar which in turn project to higher order visual cortices (retino-colliculo-extrastriate pathway – dotted lines) (readapted from Gazzaniga et al., 2009).

Apart from the LGN a small percentage of neural fibers originating from the retina reach other subcortical nuclei like the superior colliculus (SC) and the pulvinar (PV) which in turn send visual information directly to extrastriate visual areas bypassing V1 (i.e. retino-colliculo-extrastriate pathway) (Figure 1). Given the significant role played by SC in the

control of eye movements (Mohler & Wurtz, 1976, 1977; D. A. Robinson, 1972), this secondary route is generally thought to be implicated in the control of orienting behaviors towards objects of interest and is thought to mediate preserved orienting behaviors in the direction of unseen visual stimuli in hemianopic patients (L. Weiskrantz, 1986). In addition, evidence of direct projections from intralaminar layers of LGN and extrastriate areas have been reported. Even if in the normal brain, the functionality of these secondary pathways is mostly hidden, these secondary routes could be of a great relevance when a lesion occur to the primary visual route.

Characteristics and etiology of visual field defects

In the light of the hierarchical organization of the visual system described in previous paragraph, it is easy to imagine that lesions occurring at different sites of the primary visual pathway can evolve into different visual field defects. For example, peripheral lesions occurring at the level of the eye (e.g. glaucoma, macular degeneration) or the optic nerve (e.g. optic neuritis) are associated with the loss of vision from one eye whereas chiasmatic and post-chiasmatic lesions are mostly associated with the loss of vision over half of the visual field in both eyes. The latter condition, termed hemianopia, could be distinguished into heteronymous or homonymous. Heteronymous hemianopia is the loss of half of the visual field in different sides of both eyes and is usually caused by a lesion corresponding to the optic chiasm mostly caused by tumor (e.g. pituitary tumor). Homonymous hemianopia instead corresponds to the loss of half of the visual field on the same side of both eyes and can result from damages occurring at the level of the optic tract, optic radiation or primary visual cortex. Moreover, less extensive lesions in the

same areas can result in a less extensive loss of visual field. In particular, lesions occurring in the upper branch of the optic radiation (Meyer's loop) or to the upper part of primary visual cortex mainly result in the loss of vision over the inferior portion of the contralateral visual field (inferior quadrantopia) while lesions occurring in the lower branch of the optic radiation or in the lower part of primary visual cortex mainly result in the loss of vision over the superior portion of the contralateral visual field (superior quadrantopia) (Figure 2).

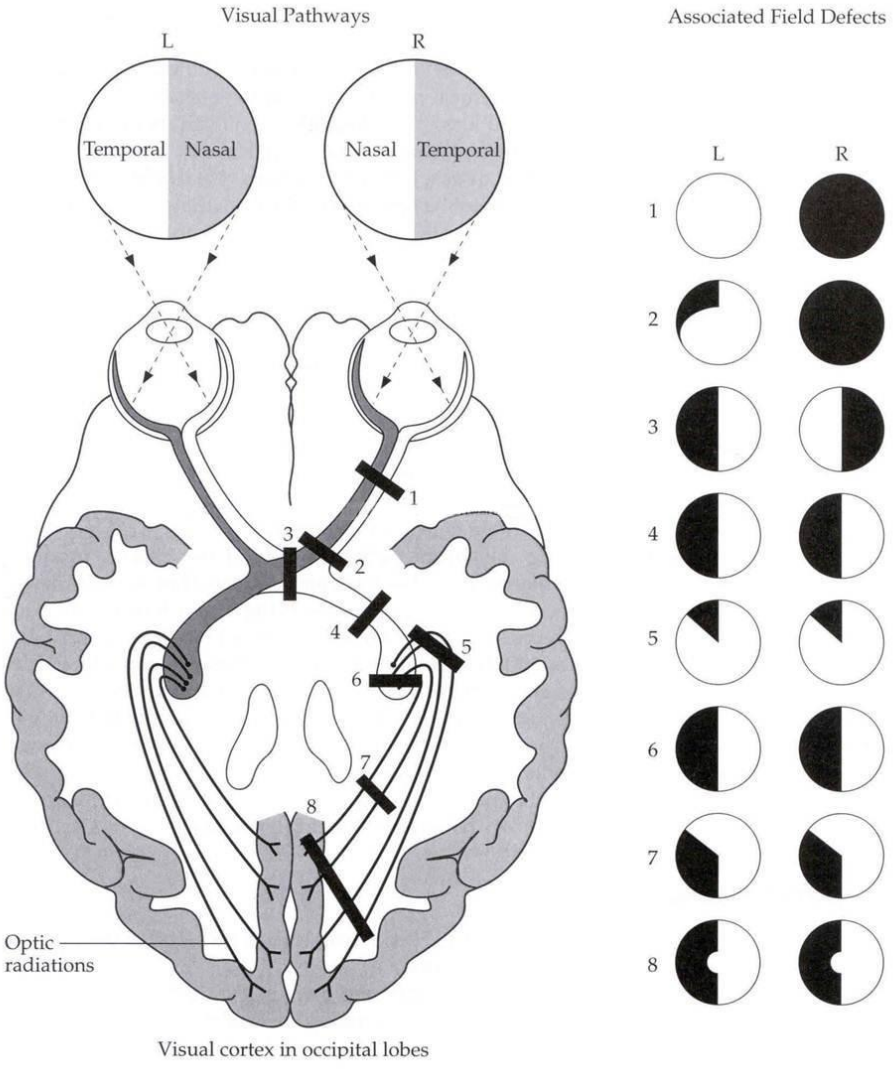

Figure 2. Schematic representation of visual field defects resulting from lesions occurring at different sites of the primary visual pathway (retino-geniculo-striate pathway). On the left are represented the different locations where lesions occur while on the right are the associated visual field defects.

Homonymous hemianopia can result from several pathological conditions such as ischemia, arteriovenous malformation, tumor, hemorrhage, abscess, anoxia or demyelination. Lesions of the occipital lobe (43%) or optic radiations (31%) are the most common causes, while smaller percentages are associated to damage of the optic tract (10%) or the LGN (1.2%, Zhang et al., 2006). Ischemic pathologies such as infarction of the posterior cerebral artery (PCA) or the middle cerebral artery (MCA) are the most common causes of homonymous hemianopia since branches of the two arteries supply striate and extrastriate visual areas. Also trauma and tumors are quite common causes while more rarely, homonymous hemianopia results from pathological conditions, such as multiple sclerosis, leading to demyelination of the optic radiations (Zhang et al., 2006).

1.2 Residual visual capacities after lesions to the primary visual pathway

Residual visual abilities in hemianopia

Although the ability to consciously perceive visual stimuli in the blind field is lost after lesions to the striate cortex or the neural pathway feeding it, some hemianopic patients have demonstrated residual visual functions, in the absence of awareness (for a review, see Cowey, 2010). Such phenomenon have been classically termed blindsight, and might involve the ability to implicitly detect or discriminate specific visual features of stimuli presented in the blind field (L Weiskrantz, Warrington, Sanders, & Marshall, 1974). First reports of residual visual abilities after lesions to striate cortex arose in the turn of the nineteenth century when some studies described patients with visual field defects caused

by stroke or penetrating head wounds at the level of primary visual cortex who could still detect flickering or moving objects in their otherwise blind visual field (Riddoch, 1917). Later in time, Poppel et al. (1973) reported that occipital lesioned patients could still direct their eyes towards the approximate position of briefly presented flashes in the blind visual field. A year later, Perenin and Jeannerod (1975) further showed that patients with visual field defects could also perform accurately in the manual localization of stimuli presented in their blind visual field. Authors suggested the involvement of subcortical routes bypassing V1 in the generation of this phenomenon since it was only evident in those patients suffering a post-geniculate lesion to the primary visual pathway and was conversely absent in patients with lesions anterior to the optic chiasm. Blindsight patients usually report having no visual experience in their blind visual field but when forced choice paradigms are used, an above chance level performance can be shown. This happens for a wide range of visual stimuli (for a review: Cowey, 2010).

Several studies demonstrated that the detection and the discrimination of moving stimuli presented in the blind visual field constitute one of the most preserved ability. For example Magnussen and Mathiesen (1989) reported evidence from a patient whose entire striate and extrastriate cortices where removed but could nevertheless show an above chance level performance in the detection of grating stimuli moving in the horizontal direction and an at chance performance when stimuli remained static. Blythe et al. (1986) also reported evidence of preserved abilities to detect the displacement of visual targets in the blind field but an inability to discriminate their spatial structures suggesting that only features related to the dorsal “where” pathway could be determined above chance level. As previously said, one possibility is that the preserved sensitivity to stimuli moving in the blind visual field could be reached through the recruitment of a route

bypassing V1. This would also be suggested by the results from a positron emission tomography study (PET) on GY (Barbur, Watson, Frackowiak, & Zeki, 1993), an hemianopic patient showing impressive preserved abilities to accurately discriminate motion stimuli on his blind visual field. In this study, authors showed an activation of area V5 without a concurrent activation of area V1 when moving stimuli where presented in his blind visual field, thus suggesting that visual input could reach V5 without firstly passing through V1.

Some studies reported that also the capacity to determine the orientation of a stimulus could be preserved in some patients experiencing lesion to primary visual pathway. For example, Perenin (1978) showed a preserved above chance ability to discriminate between squares and triangles presented in the blind visual field of a sample of hemianopic patients likely reflecting a preserved ability to discriminate between line orientation as opposed to form. Indeed a study of Weiskrantz (1987) described a patient that could successfully discriminate between different forms when differences in the orientation cues were large (e.g. discriminating between diamonds and squares), but not when differences in orientation cues were less evident (e.g. discriminating between a rectangle and a square). Interestingly, in a later study Perenin and Rosetti (1996) reported a patient that was not able to discriminate above chance level between different rectangular shapes, but was nonetheless extremely accurate when asked to perform reaching and grasping movements in the direction of the same unseen stimulus.

The discrimination of colors could also be preserved after lesions to the primary visual pathway. For example Brent et al. (1994) reported that patient GY could accurately identify large colored stimuli presented in his blind visual field in a forced choice paradigm. In another study (Danckert, Maruff, Kinsella, de Graaff, & Currie, 1998)

authors reported a significant congruency effect[1] for color when color-congruent stimuli appeared in the blind visual field of a patient with an occipital damage. Interestingly this was not found to be true in a patient with a thalamic lesion that instead showed no facilitation for color-congruent stimuli appearing in his blind visual field, thus suggesting a crucial role played by the thalamo-extrastriate neural pathway.

Finally another stimulus feature that seem to be preserved in hemianopic patients is the ability to implicitly process emotional stimuli in the absence of awareness, the so-called affective blindsight (for a review: Tamietto and de Gelder, 2010). On the one hand, these patients can perform above chance level both on task directly requiring them to discriminate the emotional content of faces presented in the blind visual field (de Gelder, Vroomen, Pourtois, & Weiskrantz, 1999; Pegna, Khateb, Lazeyras, & Seghier, 2005). On the other hand, a congruency effect for faces have been shown in the presence of emotionally identical pairs of unseen/seen stimuli (de Gelder, Pourtois, van Raamsdonk, Vroomen, & Weiskrantz, 2001).

In the light of evidences showing a variety of preserved visual abilities in blindsight patients, one important question to be asked is whether also patients that do not exhibit a striking ability to detect or discriminate above chance level visual stimuli presented in their blind visual field could nonetheless show evidence of an implicit visual processing of these stimuli. Previous studies seem to suggest that this could be the case. For example, Bertini et al. (2013) tested the congruency effect found in blindsight patients with emotionally congruent pairs of seen/unseen stimuli described before (de Gelder et al.,

[1] The congruency effect refers to a faster reaction time to a target stimulus when an identical stimulus is concurrently presented in another portion of space. In hemianopic patients, faster responses to seen targets presented in the intact field while unseen stimuli are presented in the blind field are thought to represent indirect evidence of implicit visual processing in the blind field.

2001) in a group of hemianopic patients who performed at chance when directly asked to detect or discriminate visual signals presented in the blind field. Authors showed a response facilitation (i.e. reduced reaction times) when unseen fearful faces where presented in the blind visual field together with happy faces in the intact field that was interpreted as adaptive mechanisms for the implementation of efficient defensive responses. Intriguingly, the fear-related behavioral facilitation has also been reported at the electrophysiological level. Cecere et al. (2014) showed that unseen fearful faces presented in the blind field of hemianopic patients increased the amplitude of the early N170 component elicited by seen happy faces in the intact hemisphere possibly reflecting an enhanced structural encoding of faces presented in the intact field.

These results suggest that also patients that do not show above chance level performances in the detection or discrimination of visual stimuli presented in the scotoma can nevertheless show evidence of a preserved processing when visual stimuli contain an emotional valence. However, it remains to be investigated whether this preserved processing could also be shown for other types of visual stimuli that do not have an emotional content. In chapter 3, I will present a study reporting electrophysiological evidence of implicit visual processing of motion stimuli presented in the blind visual field of a group of hemianopic patients without blindsight.

Neuroanatomical correlates of residual visual abilities in hemianopia

A great dispute still exist on what are the neural mechanisms involved in the residual visual abilities that some patients evidence despite the loss of vision due to a lesion to the primary visual pathway.

Some authors argued that implicit visual processing would be mainly mediated by the presence of preserved “islands” of primary visual cortex that are still capable to process visual information. This hypothesis arise from the fact that not all hemianopic patients show preserved visual abilities in the scotopic area and that some researchers demonstrated a link between intact islands of striate cortex and portions of visual field exhibiting residual visual functions (Fendrich, Wessinger, & Gazzaniga, 2001). However, this hypothesis has been questioned by studies revealing a preserved neural activity in extrastriate visual areas in the absence of activation of primary visual cortex (P Stoerig, Kleinschmidt, & Frahm, 1998) and by evidence of residual visual abilities even after a complete loss of the striate cortex (M. T. Perenin, 1978).

It is possible that residual visual abilities are rather mediated by the activity of preserved secondary pathways connecting subcortical structures to extrastriate visual areas bypassing primary visual cortex. One possibility is that a network of projections between the SC, PV and extrastriate visual areas (i.e. retino-colliculo-extrastriate pathway) could mediate the residual visual functions. Indeed, SC receive direct input from the retina and contains a representation of the entire visual field (Schiller, 1972). On the one hand the SC is known to play a significant role in orienting behaviors and would consequently explain the ability of some hemianopic patients to orient a motor action (saccade or grasping movement) in the direction of an unseen target in their blind visual field (L Weiskrantz et al., 1974). On the other hand, several studies revealed the important role played by this secondary pathway in non-conscious visual processing. For example, V1 lesioned monkeys showed abilities to discriminate motion, simple shape or patterns and to localize visual stimuli in their blind visual field (Ptito, Herbin, Boire, & Ptito, 1996), while these abilities were abolished after the removal of the ipsilateral SC (Rodman,

Gross, & Albright, 1990). In a similar way, neurons of the dorsal extrastriate MT area showed a preserved motion direction-selective response even after ablation of striate cortex (Rodman, Gross, & Albright, 1989), but this response was abolished after removal of the ipsilateral SC (Rodman et al., 1990). In addition, more recently Leh et al., (2006) revealed an association between the presence of ipsilateral and contralateral intact fibre tracts connecting SC to various cortical areas (association areas, primary visual cortex, parietal cortex and prefrontal areas) and the presence of residual visual abilities in the blind visual field.

Alternatively, recent evidence support the idea that residual visual abilities could be mediated by connections between interlaminar layers of LGN and extrastriate visual areas. In a recent study Schmid et al. (2010) used fMRI and behavioral measures to test the role of LGN activity in residual visual abilities and V1-independent cortical activation in macaque monkeys with chronic lesions to primary visual cortex. They found a V1-independent preserved activity in various extrastriate and higher order cortical areas that was abolished after temporarily inactivation of LGN. In addition, the ability to detect high contrast visual stimuli in the scotoma was abolished after LGN inactivation. In line with this, a recent diffusion tensor imaging (DTI) study showed intact white matter pathway between the LGN and area hMT+ in human subjects experiencing residual visual abilities in their blind visual field (Ajina, Pestilli, Rokem, Kennard, & Bridge, 2015).

In summary, even if it is still controversial what are the exact neural pathways mediating implicit visual processing in the blind visual field of hemianopic patients, it seems clear that hierarchical models of the visual system cannot account for the behavioral and imaging evidence of residual visual processing in the absence of V1. A more complex

organization in which parallel connections can directly activate extrastriate visual areas seems more appropriate.

1.3 Audio-visual multisensory integration in the normal and lesioned brain

Subcortical and cortical structures mediating audio-visual multisensory integration

One of the most known and studied site of convergence of multiple sensory inputs is the SC. This structure, placed on the midbrain, is present in all mammals and is known to receive and integrate inputs from different sensory modalities. The superficial layers of SC are known to mainly respond to visual stimulation, while deeper layers respond to the combination of visual, auditory and tactile stimuli. Multisensory integration at the level of SC neurons is known to follow three major rules. The responses of neurons from deeper layers are enhanced when different sensory stimuli originate approximately from the same spatial position (*spatial rule*), occur at approximately the same time (*temporal rule*) and when at least one of the two stimuli can elicit only a weak neural response when presented alone (*inverse effectiveness*).

The *spatial rule* is a consequence of the overlapping of receptive fields from different modalities on multisensory neurons of SC, which results in an increased firing rate when stimuli originating from different modalities are displayed approximately in the same region of space. This could have the advantage of helping neurons integrating more easily the sensory information arising from the most stimulated region of space and thus potentially more relevant. Conversely, when stimuli from different sensory modalities are

presented with a considerable spatial disparity, the firing rate of SC multisensory neurons is decreased.

The *temporal rule* could instead be a consequence of the timing necessary for the information to be processed from different modalities. Signals originating from different sensory modalities often require different amount of time to be processed and a relatively "large" time window in which different sensory signals can still be integrated in a multisensory percept could be necessary. Indeed, while a neural spike last only a few milliseconds, the corresponding voltage current generated could last several hundreds of milliseconds, thus allowing in this time period the integration of multiple stimuli originating from different sensory inputs. Consequently, two components of a multisensory stimulus are integrated if presented at approximately the same time, while not integrated when excessively spaced over time. The temporal coincidence leads to an enhanced firing rate of SC multisensory neurons, while an excessive temporal disparity will result in a decreased firing rate.

The *inverse effectiveness* rule constitutes a highly adaptive and functional mechanism. When one (or both) component of a multisensory signal is weak, SC neurons produce a stronger firing rate. This enable the system to compensate for the lack of input in one of the two modalities that is partly overcome by the presence of a spatially and temporally congruent stimulus in another sensory modality (Làdavas, 2008).

Apart from SC, multisensory audio-visual integration mechanisms are known to occur also in various cortical sites. Dorsal posterior parietal cortex (PPC) have been shown to represent a site of convergence of multisensory audio-visual pairs and to retain audio-visual integrative responses similar to those recorded in SC neurons (Colby, Duhamel, & Goldberg, 1993; Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994; Schlack,

Hoffmann, & Bremmer, 2002; B E Stein & Meredith, 1993). The great part of multisensory integration studies in the cortex arise from researches on cats in which the anterior ectosylvian sulcus (AES), a portion of cortex lying at the junction between parietal, temporal and frontal lobes, is known to contain a large number of multisensory neurons revealing similar characterization of SC neurons. These neurons present overlapping receptive fields from different sensory modalities and show superadditive and decreasing responses to the presentation of spatiotemporally aligned or misaligned audio-visual pairs respectively (B E Stein & Wallace, 1996). Significant interactions between AES neurons and deep layers of SC have been documented in cats with AES neurons strongly influencing the multiplicative integration effect of SC neurons (W. Jiang & Stein, 2003). In primates and humans, posterior parietal cortices, particularly the lateral intraparietal part (LIP), are known to contain multisensory neurons. This area shows superadditive BOLD responses in the presence of audio-visual stimuli presented in spatial and temporal coincidence, while a decreased BOLD activity when audio-visual pairs are in spatial disparity (for a review see G A Calvert, 2001).

In addition, superior temporal cortical areas have shown to be involved in the processing of multisensory audio-visual stimuli. For example, an fMRI study revealed that superior temporal sulcus (STS) show superadditive cortical activation in response to the presentation of synchronous audio-visual speech while the asynchronous presentation showed a similar activity to those induced by the presentation of each single modality (G.A. Calvert, Campbell, & Brammer, 2000). Furthermore, increase in BOLD signals have been documented in STS during the presentation of bimodal audio-visual or audio-tactile stimuli with respect to unisensory stimuli (Stevenson & James, 2009) and

superadditive response in STS has been found during the presentation of weak bimodal stimulations (Beauchamp, Yasar, Frye, & Ro, 2008).

Behavioral benefits of audio-visual integration in the normal brain

As previously described, the SC neurons show clear evidence of enhanced responses to multisensory audio-visual pairs presented in spatial and temporal coincidence, as opposed to unisensory stimuli, especially when one (or both) of the two stimuli is weak and thus hard to detect or localize. Evidence that this is also observable at the behavioral level come from studies on normal subjects showing enhanced detection of hard to localize auditory or visual stimuli when these are presented in spatio-temporal register with visual or auditory stimuli. In a study of Frassinetti et al. (2002), subjects were asked to localize masked visual stimuli that could be presented either alone or together with an auditory stimulus presented in spatial and temporal coincidence or alternatively with a spatial or temporal disparity. Despite subjects were instructed to ignore the auditory stimulus, the detection of subthreshold masked visual stimuli was found to be significantly improved by the concurrent presentation of the auditory stimulus when this was presented in spatial and temporal register with the visual one, while no improvement was found when the auditory stimulus was presented in spatial or temporal disparity. In a similar way, Bolognini et al. (2007) showed that also the localization of auditory stimuli can benefit of the concurrent presentation of visual stimuli at detection threshold. In this study, subjects were asked to localize an auditory stimulus that could be presented with a concurrent supra-threshold or at threshold visual stimulus. The visual stimulus position could vary in regards to the spatial disparity from the auditory stimulus. While the supra-

threshold visual stimulus in spatial disparity induced the classical ventriloquism effect (i.e. a mislocalization of the perceived auditory source in the direction of the visual source), the at threshold visual stimulus only influenced the auditory localization when the two stimuli were spatially coincident resulting in an enhanced auditory localization. Taken together these results suggest that the detection of weak sensory signals can critically benefit from the congruent presentation of other signals in different sensory modalities strongly resembling the rules governing responses at the level of single neurons of SC (B E Stein & Meredith, 1993). Interestingly, the behavioral advantage of concurrently presented audio-visual pairs seems to be strongly mediated by the SC. In a simple reaction time task, Leo, Bertini, Di Pellegrino, & Làdavas (2008) asked participants to respond to the presentation of audio-visual stimuli (in spatial coincidence or in spatial disparity) or auditory and visual stimuli presented alone. Results revealed that, while the presentation of audio-visual stimuli always induced a faster response with respect to the single unisensory condition, the behavioral advantage of presenting audio-visual pairs in spatial and temporal coincidence was only evident when the visual stimulus was a red long-wavelength stimulus visible to the SC and was conversely absent when the stimulus used was a purple short-wavelength stimulus to which SC is blind (Sumner, Adamjee, & Mollon, 2002).

Audio-visual multisensory integration in hemianopia

As evident from studies reported in previous paragraphs, the behavioral and neural advantage of concurrently presented audio-visual pairs is boosted when one of the two sensory stimuli is weak. This property of the processing of multisensory stimuli could be

of great relevance when one of the two sensory modality is critically impaired because of a lesion occurring to primary sensory cortices (Làdavas, 2008). In line with this, previous evidence showed that patients suffering a lesion to primary visual cortex could benefit from audio-visual integration mechanisms during the detection and localization of stimuli presented in the blind visual field. Some studies investigated the effects of the concurrent presentation of audio-visual stimuli in the blind visual field as opposed to the presentation of auditory or visual stimuli alone, during detection or localization tasks. For example, Leo, Bolognini, Passamonti, Stein, & Làdavas (2008) tested the hypothesis that auditory localization could benefit from the presentation of a concurrent visual stimulus in the blind visual field. A group of hemianopic patients was tested with hard to localize auditory stimuli that could be presented either alone or together with a visual stimulus appearing in spatial and temporal register or at different temporal or spatial disparities with the auditory stimulus. The results showed an improved auditory localization performance in the blind visual field for audio-visual stimuli presented in spatial and temporal register, suggesting that covert visual processing could remain active in hemianopia. In a similar way, Frassinetti, Bolognini, Bottari, Bonora, & Làdavas, (2005) reported a significant improvement in the detection of visual stimuli presented in the blind field of hemianopic patients, when auditory stimuli were presented in spatial and temporal coincidence. In this study, a sample of hemianopic patients were asked to detect the occurrence of visual stimuli in their blind visual field that could be presented either alone or together with an auditory stimulus presented in spatial coincidence or in spatial disparity with the visual stimulus. Patients showed a greater detection of stimuli presented in spatial alignment with the auditory ones with respect to both visual stimuli alone and audio-visual stimuli presented in spatial disparity. Interestingly, patients reporting lower

detection accuracy in the unisensory visual condition displayed the highest enhancement with in the audio-visual condition, a finding consistent with the inverse effectiveness rule of SC neurons (B E Stein & Meredith, 1993).

Overall, this evidence showed that hemianopic patients can successfully integrate unseen visual information with auditory information, suggesting an implicit visual processing of stimuli presented in the blind visual field. This processing could be presumably mediated by the retino-colliculo-extrastriate pathway, which is preserved in these patients and plays a pivotal role in crossmodal enhancement of perception.

Even more intriguingly, multisensory facilitation effects were found to generalize to localization performances in the unisensory domain after exposure to a short audio-visual stimulation. In a study of Passamonti et al. (2009), a group of patients with visual field defects caused by lesion to primary visual cortex (hemianopic patients) or temporoparietal cortex (neglect patients,) were asked to localize weak sounds before and after a short session (~4 minutes) of repetitive audio-visual stimulation of their blind visual field. The audio-visual stimulation session was performed either with audio-visual stimuli presented in spatial coincidence or in spatial disparity. The results revealed improved auditory localization performances in the blind visual field for both group of patients when exposed to the spatially coincident audio-visual stimulation session (multisensory enhancement aftereffect). A bias in the localization of auditory stimuli in the direction of previously presented visual stimuli (ventriloquism aftereffect) was instead selectively shown in neglect patients. These findings suggest that while ventriloquism aftereffect requires the integrity of the geniculo-striate circuit (preserved only in neglects patients), the multisensory enhancement aftereffect is instead implemented along the

colliculo-extrastriate circuit that is generally spared both in neglect and hemianopic patients.

1.4 Rehabilitation of visual field defects: compensatory, restorative and multisensory based approaches

Compensatory and restorative approaches for the rehabilitation of visual field defects

Visual field defects tend to improve in the first 2-3 months after the insult and some spontaneous recovery is likely to be observed in this period. However, after the third month, further spontaneous improvements are usually not expected and a rehabilitative approach is necessary to help patients dealing with the visual deficit. Two are the main lines of approach in the field of visual treatment: compensatory and restitutive approaches.

The major aim of compensatory approaches for hemianopia is to make patients develop more efficient and automatic oculomotor strategies in the direction of the blind visual field. Hemianopic patients generally exhibit a reduced scanning behavior in the direction of their blind field together with a pattern of disorganized and inefficient visual search. Several trainings have been thus developed over the past decades aiming to compensate for these aspects. Most of these trainings include a series of exercises designed to stimulate compensatory oculomotor behaviors in the direction of the blind field. Some trainings require patients to search for a visual target embedded in a set of distractors (Kerkhoff et al., 1992; Pambakian, Mannan, Hodgson, & Kennard, 2004), while other

trainings stimulate patients to make large and fast saccades in the direction of targets presented alone (Nelles et al., 2001; Zihl, 1995). The efficacy of compensatory trainings is considered good. Patients usually report improved performances in the accuracy of scanning behaviors and reduced exploration times together with better performances in daily life activities (Zihl & Von Cramon, 1985). These trainings could act inducing a spatial bias during visual search as a consequence of the repetitive visual scanning behavior in the direction of the blind field. Interestingly, a study comparing the effects of a compensatory training based on saccadic exploration with the effects of an attentional training (i.e. a training without the saccadic component) revealed a similar pattern of results for the two type of trainings, thus suggesting that attention could play a crucial role in the rehabilitative effect (Lane, Smith, Ellison, & Schenk, 2010).

Restorative approaches base their rationale to the idea that visual system is plastic and a repetitive photostimulation can potentially induce a neural reorganization. These approaches usually work by stimulating the transition zone, which is the border area between the intact field and the blind field, through the presentation of thousands of visual stimuli over weeks and months. Studies using this technique reported an enlarged visual field in central vision (Kasten, Wust, Behrens-Baumann, & Sabel, 1998; Mueller, Mast, & Sabel, 2007) together with functional improvements in various domains (Mueller I, Poggel A, 2003). However, controversies arose about the real efficacy of restorative approaches. Some studies argued that the effects shown could be the result of more effective eye movements instead of a real expansion of the visual field (Reinhard et al., 2005) even if studies controlling for eye movements argue against this as the explanation of the restorative effects (Marshall, Chmayssani, O'Brien, Handy, & Greenstein, 2010).

In summary, while compensatory approaches mainly aim to develop efficient ocular scanning strategies enabling patients to compensate for the loss of vision without extending the area of intact visual field, restitutive approaches have the major aim to extend the visual perimetry promoting neural reorganization through an intensive stimulation of the border area between the blind and the intact visual field. Interestingly, despite the diversity, both methods were found to be efficient in the rehabilitation of visual field defects leading to significant improvements in various functional domains together with an altered activation in striate and extrastriate cortex suggesting that cortical reorganization mechanisms could be promoted by both type of approaches.(Marshall et al., 2008; Nelles et al., 2007).

Multisensory based approach for the rehabilitation of visual field defects

A novel approach for the rehabilitation of visual field defects has been proposed in the last decade. This approach is a compensatory approach based on the combination of saccadic training and multisensory audio-visual stimulation.

Animal research revealed that the lack of compensatory eye movements in the direction of objects of interest in the blind visual field strongly depends from interaction between the SC and the cortex. Indeed, SC is not only extremely important for multisensory integration mechanisms (B E Stein & Meredith, 1993) but also for the programming and execution of eye movements and orienting behaviors (Gandhi & Katnani, 2011). Cats rendered blind by complete unilateral visual cortex ablation showed an attenuated visual responsiveness of deep SC neurons together with a lack of SC-mediated behavioral orienting in the direction of the contralateral blind hemifield. After one month of audio-

visual multisensory stimulation, authors reported a re-emergence of visual orienting behaviors in the direction of the blind visual field that correlated with a reinstatement of visual responsiveness of deep SC neurons. Notably, the reinstatement of visual responsiveness in SC neurons was found to be mediated by training-induced alterations of descending inputs from AES association cortex and SC (H. Jiang, Stein, & McHaffie, 2015). These findings indicate that the visual responsiveness in the deeper layers of ipsilesional SC can be reversed by a simple cross-modal training paradigm.

Similar results have been demonstrated in hemianopic patients. Bolognini et al. (2005) attempted to exploit multisensory integration mechanisms to rehabilitate patients with visual field defects. In this study, a group of patients with chronic visual field defects underwent an intensive audio-visual training (4h daily, over two weeks). During the training, patients were seated in front of a concave ellipse in which eight LED lights associated with eight loudspeakers were positioned at increasing eccentricities with respect to a central fixation point (Figure 3). Patients were instructed to explore their entire visual field and to detect the presence of visual targets that could be either presented alone (unisensory condition) or together with a sound (multisensory condition). To boost oculomotor exploration towards the blind visual field, a greater proportion of stimuli were presented in the blind visual field to favor patients' orienting behavior in that direction. After the training patients showed progressive amelioration of both visual detection and visual exploration abilities together with a post-training reduction in self-perceived disability (Bolognini et al., 2005). Notably, patients showed improved visual performances only when they could use eye movements to compensate for the loss of vision, while no improvement was found in detection tasks when asked to maintain their eyes on a central fixation cross. This suggests that the amelioration of visual performance

observed after training did not rely on an enlargement of the visual field but are likely mediated by an increased activation of the oculomotor system increasing orienting responses towards the blind visual field.

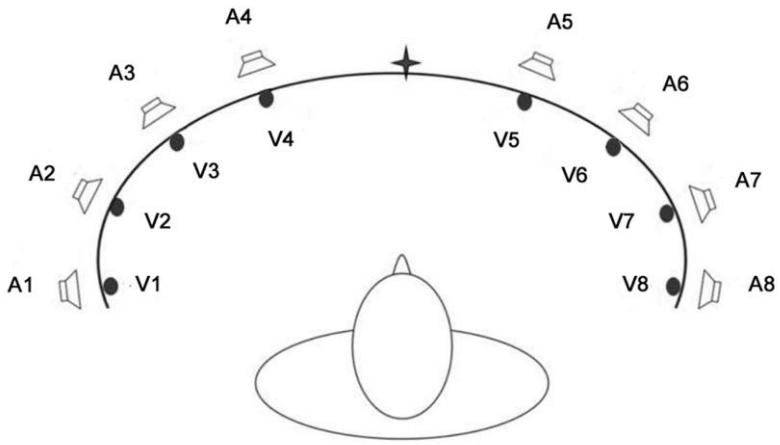

Figure 3. Schematic bird's eye view of the apparatus used by Bolognini et al., (2005) for the audio-visual training in hemianopic patients. Eight LEDs (V1-V8) were associated with eight loudspeakers (A1-A8) positioned at increasing eccentricities with respect to the center of the visual field (readapted from Bolognini et al., 2005).

In another study conducted in a different set of patients, Passamonti et al., (2009) showed that, after the audio-visual training, hemianopic patients also improved in various oculomotor parameters recorded during visual search and reading tasks. Authors recorded eye-movements by means of an eye-tracking device and reported pre and post measures of oculomotor scanning with respect to the same audio-visual training used by Bolognini et al., (2005). Results showed significant post-training oculomotor improvements as revealed by reduced fixations, refixations and scanpath length leading to shorter search times in visual search tasks. In addition, improved performances in reading tasks were also reported with a reduced number of progressive and regressive saccades. Notably

these effects could not be ascribed to simple practice effects, as the performance of a group of healthy subjects was not influenced by the repetitions of the task.

Interestingly, post-training clinical improvements remained stable over time as revealed by follow-up sessions at one month (Bolognini et al., 2005) and one year after the training (Passamonti, Bertini, et al., 2009). Overall, the behavioral and oculomotor changes reported suggest that the audio-visual training could represent an effective methodology to reinstate long-lasting oculomotor strategies that could compensate for the loss of vision. However, little is known about the neural changes mediating the effects of the multisensory training. Given the important role played by SC in the programming and execution of saccades as well as in audio-visual multisensory integration processing, authors proposed that the improvements might be due to an enhanced activity in the pathway connecting SC to dorsal extrastriate areas (i.e. retino-colliculo-extrastriate) that is known to be usually preserved in hemianopic patients.

In chapter 2, I will shed light on the electrophysiological changes associated to the exposure to a systematic audio-visual training. I will firstly present a study aiming to investigate the long-term electrophysiological changes induced by a complete course of audio-visual multisensory training on hemianopic patients. Recent evidence revealed that multisensory audio-visual training might also induce plastic changes within attentional networks (Dundon, Làdavas, Maier, & Bertini, 2015) as revealed by a reduction of P3 component of the EEG signal during detection of visual stimuli presented in the intact field. However, the study did not disambiguate whether reported modulations in the EEG signal represent long-term changes ascribing to persistent plastic neural changes induced by the audio-visual training or rather reflect a short term change in visuo-spatial attentional resources allocation that is mainly independent by the long-term clinical

improvements found in previous studies (Bolognini et al., 2005; Passamonti, Bertini, et al., 2009). If changes in the electrophysiological signal reported by Dundon et al. (2015) represent long-term plastic neural changes induced by the training, it would be plausible to observe similar changes also at a follow up session given that the audio-visual training was found to produce long-lasting clinical effects (Bolognini et al., 2005; Passamonti, Bertini, et al., 2009). To address this issue I used the same paradigm used by Dundon et al., (2015) and electrophysiological measures were recorded at various time intervals from the audio-visual training.

I will then report further evidence of the neural modulations induced by a systematic audio-visual training presenting results from a study investigating whether the audio-visual training promote changes within the dorsal or ventral visual processing. Given the existing functional connections between SC and various cortical areas ascribed to the dorsal stream (Krauzlis, Lovejoy, & Zénon, 2013; Lyon, Nassi, & Callaway, 2010), it would be plausible to hypothesize that the training could also induce plastic changes within the dorsal stream. To test this hypothesis I recorded EEG measures while a group of healthy participants performed a visual task relying on a dorsal processing (i.e. motion discrimination task) and a visual task relying on ventral processing (i.e. orientation discrimination task) before and after a short version of the same audio-visual training used for hemianopic patients. Further, the specific role of audio-visual integration processes was tested by comparing results obtained from a group of participants receiving a spatially coincident audio-visual training with results from a different group of participants receiving a training with spatially disparate audio-visual cues.

In chapter 3, I will present two studies investigating the characteristics of extrageniculate visual processing. Lesions to the primary visual pathway usually leave unaffected the

other visual routes. However, both the functionality and the characteristics of visual processing mediated by extrageniculate routes remains unclear. I will firstly present an EEG study investigating implicit visual processing on hemianopic patients that do not show residual visual capacities in their blind visual field. This allowed to cast out the possiblity that the recorded signal could be explained by a preserved geniculo-striate functioning (Fendrich et al., 2001). EEG data were recorded while patients were presented with lateralized moving or static stimuli intruding their blind visual field. Given that the processing of motion on V5 area is both dependent from geniculo-striate inputs and from extrageniculate inputs (Gross, 1991; Rodman et al., 1989, 1990) it would be plausible to hypothesize an implicit processing of motion stimuli while no preserved processing of static stimuli should be expected.

I will then present a transcranial magnetic stimulation (TMS) study in a group of healthy participants, which aimed to investigate whether different stimulus features could differentially recruit geniculo-striate and extrageniculate inputs to V5 area. I tested whether the direct extrageniculate pathway to V5 area is mainly active when fast moving stimuli have to be processed while the indirect geniculo-striate route is recruited by slow moving stimuli. Indeed, fast moving stimuli could potentially represent dangerous stimuli and would consequently require a faster cortical processing. If it was the case, one would expect fast motion to be processed earlier with respect to slow motion. I tested this hypothesis applying V5-TMS at different stimulus onset asynchronies (SOAs) while a group of healthy participants performed a motion discrimination task.

CHAPTER 2

Electrophysiological effects of a systematic audio-visual stimulation on hemianopic patients and healthy participants

2.1 Experiment 1: Compensatory recovery after multisensory stimulation in hemianopic patients: behavioral and neurophysiological components

Introduction

As widely described in Chapter 1 (see *Visual system and visual field defects*), damage to the visual structures located behind the chiasma, including primary visual cortex (V1), surrounding extrastriate cortices and optic radiations, lead to a loss of visual perception in up to one half of the contralesional visual field.

Interestingly, behavioral evidences on low level visual perceptual tasks (i.e. grayscales task, Mattingley et al., 1994), has shown that, in association with the perceptual deficit, hemianopic patients could also exhibit an attentional bias in the direction of the ipsilesional visual hemifield (J B Mattingley et al., 1994; Tant, Kuks, Kooijman, Cornelissen, & Brouwer, 2002). In this task, patients are presented with two vertically aligned horizontal bars filled with scales of gray going from white to black. The two bars are identical but mirror reversed and patients are asked to report which of the two is perceived as darker in an eyes-moving free context. Results reveal that hemianopic patients have similar performances to those of neglect patients showing a bias towards

selecting the bar with the darker side ipsilateral to their lesion (Tant et al., 2002). The authors interpreted the result as the evidence of an unbalanced hyperactivation of the intact hemisphere as a consequence of the continuous asymmetric visual input due to the loss of vision over half of the visual field. In this view, hemianopics' visual performances, could be worsened by the presence of a concurrent attentional bias towards the ipsilesional visual field (Poggel, Kasten, Müller-Oehring, Bunzenthal, & Sabel, 2006), resulting in a poorer attitude to implement compensatory ocular strategies to explore the blind visual field. If it was the case, improving visual scanning behavior towards the blind field might co-occur with a reduction of the attentional bias towards the ipsilesional visual field.

As described in Chapter 1 (see *Rehabilitation of visual field defects: compensatory, restorative and multisensory based approaches*), a recent rehabilitative approach (Bolognini et al., 2005; Làdavas, 2008; Passamonti, Bertini, et al., 2009) has revealed that a systematic audio-visual multisensory stimulation of the blind visual field can reinstate more efficient and organized orienting responses towards the blind field, leading to significant ameliorations also in daily life activities. A possibility is that the audio-visual training could have boosted compensatory saccadic eye-movements towards the blind field reducing, at the same time, the attentional bias towards the intact visual field (Tant et al., 2002).

A recent study confirmed this hypothesis (Dundon et al., 2015) revealing that the exposure to the same audio-visual rehabilitative protocol used in previous studies (Bolognini et al., 2005; Làdavas, 2008; Passamonti, Bertini, et al., 2009) improves visual scanning behaviors towards the blind field, and concurrently reduces the attentional bias towards the ipsilesional visual field. During a simple visual detection paradigm with

electroencephalography, hemianopic patients showed a post-training attenuation of the P3 component in response to visual stimuli presented in their intact visual field. The amplitude of P3 component is known to be modulated by the amount of attention allocated to processing or manipulating the stimulus (Isreal, Chesney, Wickens, & Donchin, 1980; Johnson, 1986) and the post-training reduction in P3 amplitude could thus represent an attenuation of visual attention towards the intact field, which might co-occur with a shift of spatial attention towards the blind visual field. These results suggest a critical role of multisensory audio-visual training in reducing attentional processing of stimuli presented in the intact field.

However, while the ameliorative effects of the training on clinical measures of visual detection, visual exploration and oculomotor behaviors have been shown to remain stable also after several months from the training (Bolognini et al., 2005; Passamonti, Bertini, et al., 2009), it remains to be investigated whether also the associated re-allocation of attentional resources could show the same pattern of results.

Thus, aim of the present study was to assess whether pairing gaze-evoking auditory cues with undetectable visual cues in a perimetry device reinstates long-lasting basic visual and visuomotor competencies in hemianopic patients, and whether these ameliorations are accompanied by long-term modulation of visual spatial attention. Replicating the post-treatment results from behavioral (Bolognini et al., 2005; Passamonti, Bertini, et al., 2009) and electrophysiological measures (Dundon et al., 2015) at a follow-up session would confirm that a complete course of multisensory stimulation in the blind visual field is able not only to reinstate long-term compensatory saccadic eye movements towards the blind field, but also to induce long-term modulation of visuospatial attention allocation indicating long-term plastic changes in the neural structures involved in the recovery.

Patients underwent a course of multisensory treatment for two weeks. Behavioral performance and electrophysiological measures were tested at four time points: baseline 1 (before training), baseline 2 (2 weeks after baseline 1, and immediately before training to control for possible practice effects), post (immediately after training) and follow-up (8 months after training, on average).

Materials and methods

Participants

Ten patients (2 females, mean age = 49.8 years, SD = 13.7) with chronic visual field deficits (mean time since lesion at the first evaluation = 6.4 months; Table 1) took part to the study. Patients' selection was contingent on reported visual field defects, and the availability of a full visual perimetry (Figure 4) and CT/MRI scans of the lesion (Figure 5). Right-lesioned patients were screened using the Behavioral Inattention Test for the assessment of neglect (Wilson, Cockburn, & Halligan, 1987) to ensure performance was in the normal range. All patients showed normal hearing and normal or corrected-to normal-visual acuity. Patients were informed about the procedure and the purpose of the study, and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the Psychology Department at the University of Bologna.

ID	Sex	Age	Education	Onset	Lesion Site	Aetiology
P1	M	57	13	7	Left Occipital	Ischaemic
P2	M	39	13	3	Left Occipital	Ischaemic
P3	M	44	13	3	Left Temporo-Occipital	Ischaemic
P4	M	33	13	11	Left Temporal	Ischaemic
P5	M	50	8	6	Left Thalamus and Temporo-Occipital	Ischaemic
P6	F	54	18	7	Left Temporo-Occipital	Ischaemic
P7	F	37	13	12	Right Temporo-Parietal-Occipital	Ischaemic
P8	M	69	8	3	Right Temporo-Occipital	Ischaemic
P9	M	41	11	9	Right Temporo-Occipital	AVM
P10	M	74	23	3	Right Temporo-Parietal-Occipital	Hemorrhagic

Table 1. Demographic and clinical data of patients: M=Male; F=Female; Age in years; Education in years; Onset of lesion prior to treatment in months; AVM = Arteriovenous malformation.

Experimental design

Patients completed both a clinical and an oculomotor assessment at three time points, i.e., before treatment (B), immediately after treatment (P) and in a follow-up session (F; mean time after training = 8 months, SD = 3.02 months). Notably, the clinical and oculomotor measures used in the present study have been demonstrated to be resistant to practice effects, as shown by patients' stable performance in test-retest assessments (Bolognini et al., 2005; Dundon et al., 2015; Passamonti, Bertini, et al., 2009). As a consequence, to reduce the testing time and patient fatigue, patients were not tested with a second control baseline in the present study.

Instead, EEG measures were collected at four time points: baseline 1, i.e., before treatment (B1), control baseline 2, i.e., two weeks after B1 and immediately before treatment (B2), immediately after treatment (P) and in a follow-up session (F; mean time after training = 8 months, SD = 3.02 months). The second baseline (B2) was included to control for any possible effects of merely repeating the test (i.e., practice effects).

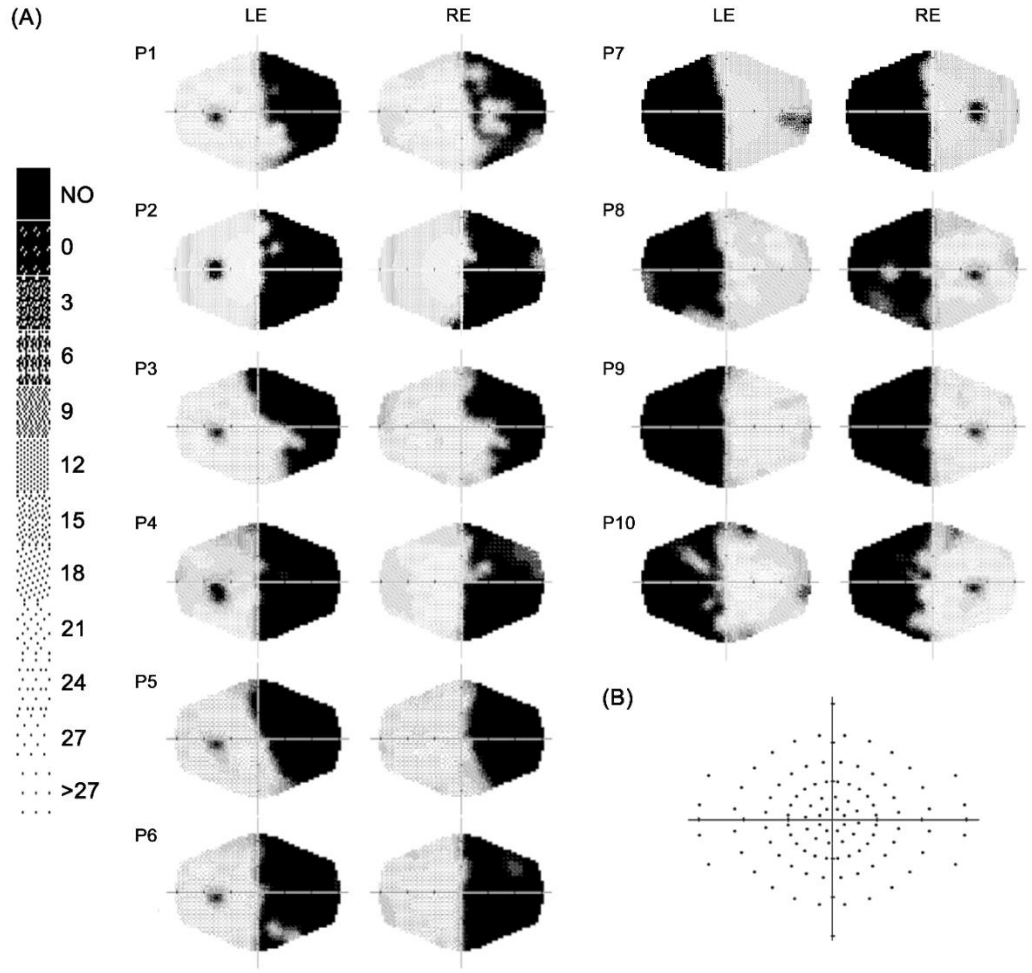

Figure 4. (A) Computerized automated visual perimetry (Medmont M700 automated perimetry apparatus, Melbourne, Australia). Axial hash marks denote ten visual degree increments; color map reports decibel values; LE = left eye, RE = right eye. (B) Schematic view of the visual field maps, depicting the locations of visual stimulation.

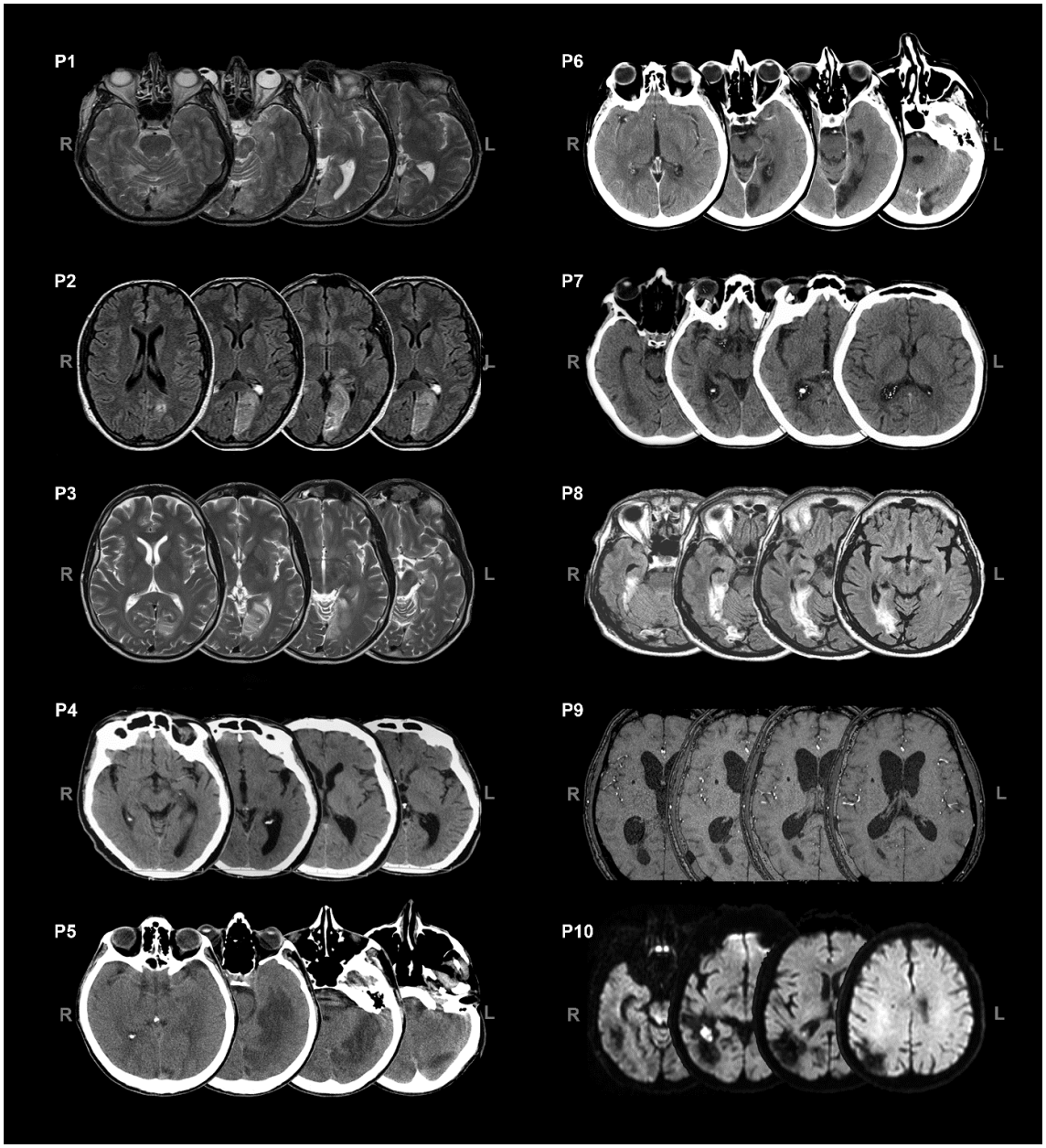

Figure 5. Axial views of CT/MRI scans of the patients. L = left, R = right.

Clinical measures

Patients completed a neuropsychological examination (Bolognini et al., 2005; Passamonti, Bertini, et al., 2009) to measure visual detection, visual scanning, reading abilities and self-perceived disability in daily activities.

Visual detection - Unisensory visual test - In a light-attenuated room, patients detected the presence of a light stimulus (red LED; luminance: 90 cd/m^2; diameter: 0.5 cm) presented on the horizontal meridian of the training apparatus (height: 30 cm, length: 200 cm; Figure 7A), by pressing a button. The visual stimulus could appear at one of eight eccentricities (56°, 40°, 24° and 8° bilaterally). Patients could move their eyes, while the head remained fixed. An experimenter monitored when eyes were centered and administered the light stimulus (100ms). Patients performed three blocks of 120 trials (12 trials at each eccentricity and 24 catch trials, i.e., no light stimulus). The percentage of correctly detected targets (accuracy) at each eccentricity constituted the outcome metric.

Visual search – E-F test (modified from Zihl, 2000; Bolognini et al., 2005) – A personal computer running C.I.R.O. software (http://www.cnc.unibo.psice.unibo/ciro) was used to control stimulus presentation and record responses. One target stimulus (green capital F; 2° × 2°; RGB values: 0, 163, 0) and 20 distractors (green capital E; 2° × 2°; RGB values: 0, 163, 0) were displayed on a projector screen (NEC V260X projector) randomly within a 52° × 45° array on a black background (RGB values: 0, 0, 0). Patients (at a distance of 120 cm from the projector screen) responded as quickly as possible if the target was present or not, with one of two buttons on the mouse. Patients performed one block of 20 trials - 16 target-present trials and 4 target-absent trials (i.e., catch trials). Response time and accuracy were recorded, and inverse efficiency scores (IES = response time divided by the percentage of accurate detections) were computed.

Visual search – Triangles test (modified from Zihl, 2000; Bolognini et al., 2005) – Using the same procedure as above, patients were asked to count targets (yellow triangles; 2° × 2°; RGB values: 253, 253, 110), amongst distractors (yellow squares; 2° × 2°; RGB values: 253, 253, 110) displayed against a black background (RGB values: 0, 0,

0). Patients pressed a button when they were able to indicate the number of targets in the array, which marked the response time. They then verbally declared their response, which was noted by the experimenter on a response sheet. Inverse efficiency scores (IES = response time divided by the percentage of accurate detections) were computed.

Reading text task (Bolognini et al., 2005) – The text, in Italian, was a short story (330 syllables). Four different stories were counterbalanced between subjects and testing sessions. The texts chosen were equivalent with respect to graphical and lexical characteristics (font: Arial 40; 6–8 lines for each paragraph; 5–6 words per line; distance between lines: 1.5 cm) and were presented on a computer monitor (visual scene: 30° × 24°). Subjects were asked to read aloud, and reading time was measured (syllables/sec).

Self-report - Activities of Daily Living Inventory (ADL; modified from (Bolognini et al., 2005; Kerkhoff et al., 1992). Patients were asked to complete a ten-item, five-point Likert scale questionnaire exploring the dimensions of visual impairment in daily life. Raw mean scores constituted the outcome metric.

Oculomotor measures

Eye movements were assessed while patients performed the *Visual search – Number test* (modified from Bolognini et al., 2005). Eight stimulus arrays were presented, depicting the numbers 1 to 15 (2° × 2°; printed in red, RGB values: 251, 0, 55) on a black background (RGB values: 0, 0, 0), in random positions. Patients identified each number in ascending order while eye movements were recorded.

Eye movements were recorded using a Pan/Tilt optic eye-tracker (Eye-Track ASL-6000) which registers real-time gaze at 60 Hz. The recording was performed in a dimly lit room.

The patient's dominant eye was illuminated with invisible infrared light, and the reflections were recorded by a video camera positioned 60 cm from the eye. During the task, the position of patient's eye in the visual scene was monitored online by the experimenter. Before collecting data from each patient, the equipment was calibrated using a nine-point grid. During calibration procedure, patients were asked to fixate successively on each of a series of small dots arranged on three lines. Fixation time at each dot position was at least three seconds.

Data from eye movement recordings were quantitatively analyzed with respect to the number of fixations and saccadic speed (saccadic amplitude/saccadic duration). In addition, mean exploration time was taken as a behavioral measure of visual exploration.

EEG measures

EEG data were recorded at B1, B2, P and F while patients performed a simple visual detection task. During the task, patients were placed 57 cm away from a 17" PC monitor (refresh rate: 60Hz). Stimuli were presented on a PC running Presentation software (Version 0.60, www.neurobs.com). A target stimulus (white, RGB values: 255, 255, 255; 1° diameter circle) appeared against a black background (RGB values: 0, 0, 0) at one of six locations: 15° right or left of the central fixation cross, and on the midline (i.e., horizontally aligned with the central fixation cross), or in the upper or lower quadrant (i.e., 13° above or below the midline). Each trial consisted of a central fixation cross (1000 ms), followed by a gap (800 to 1200 ms), a target (100 ms) and a response window (1000 ms, Figure 6). To control for false positives, 14.3% of trials were catch trials, i.e., a fixation cross followed by a gap, but no stimulus. Patients were instructed to maintain

central eye-fixation throughout the entire trial, and to detect the presence of the stimulus, pressing a response button as quickly as possible.

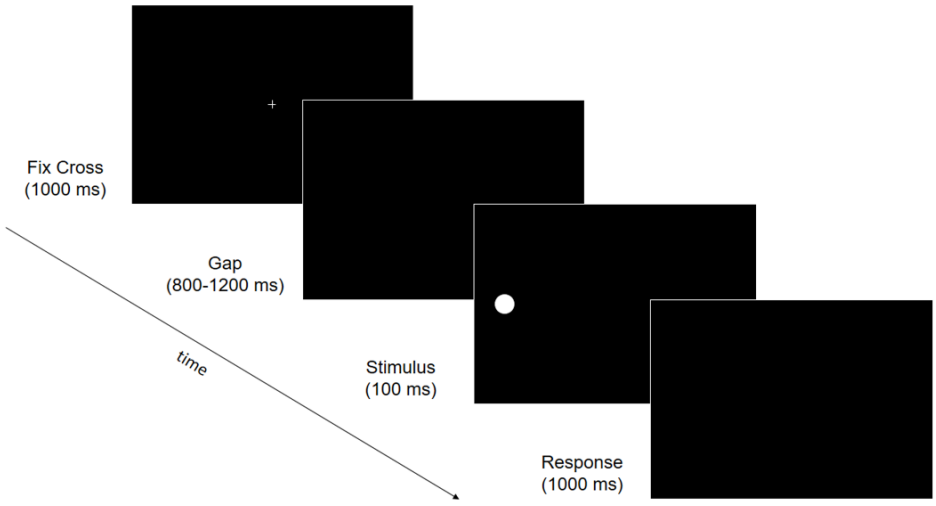

Figure 6. Trial structure of the EEG behavioral task. Fixation cross (1000 ms) was followed by a gap ranging from 800 to 1200 ms. A stimulus was then presented for 100 ms at one of six possible locations (upper, median or lower, 15 degrees to the right or left visual field) followed by a response window of 1000 ms in which participants were asked to press space-bar when they detected the visual stimulus.

Patients performed 27 blocks of 30 trials (an average of 115 trials at each visual location, and 115 catch trials). EEG data were 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) and the right mastoid. The left mastoid was used as reference, while the ground electrode was positioned on the right cheek. Vertical and horizontal electrooculogram (EOG) components were recorded from above and below the left eye, and from the outer canthus of both eyes. Data were recorded with a band-pass filter 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, offline filtered with a 40 Hz low-pass filter, and then analyzed using custom routines in Matlab

7.12.0.635 (R2011a; The Mathworks, Natic, MA, USA) and EEGLAB v10.2.5.8b (Delorme & Makeig, 2004). Data from all electrodes were re-referenced offline to the average of both mastoids. Stimulus triggers were located within the continuous EEG waveform and used to anchor the epochs (-200 ms to 900 ms; baseline window -100 ms to 0 ms pre-stimulus). Epochs containing artifacts were excluded using methods from the EEGLAB toolbox (Delorme, Sejnowski, & Makeig, 2007). Epochs with large EEG peaks (greater than an individually adjusted threshold, mean 242 μV) and with improbable data (joint probability of a trial > 5* SD) were also excluded (mean: 41.9 epochs per participant per session). Remaining vertical EOG artifacts were corrected using a regression approach (Gratton, Coles, & Donchin, 1983). Finally, epochs were discarded if horizontal saccadic movements (> 30 μV on horizontal EOG channels) were registered 0 ms to 200 ms post-stimulus onset, to control for eye-movements explaining stimulus detection (mean: 55.8 epochs per participant per session). In total, 12% of epochs were excluded. Remaining epochs were averaged. The P3 component was quantified as the mean amplitude in a time window between 370 and 410 ms post stimulus presentation.

Epochs were averaged for the entire group: electrodes were swapped cross-hemispherically for patients with lesions to the left hemisphere. Thus, the data were analyzed as if all participants were right-lesioned. Scalp topography at B1 in the chosen time window showed a maximal positive inflection over electrodes CP1, P3 and Pz (Figure 9A). Data from these electrodes were therefore used for statistical analysis.

Given that early sensory components such as the visual N1 can be modulated by visual spatial attention (for a review: Hillyard et al., 1998), we also analyzed this component. The N1 was quantified as the mean amplitude in a time window between 170 and 210 ms. Scalp topography at B1 in the chosen time window showed a maximum negative

inflection (Figure 9B) over electrodes C3, CP5 and P7; data from these electrodes were used for the statistical analysis.

Training

During a full course of training (10 days; 4 hours of training per day), patients were presented with three different kinds of sensory stimulation (Figure 7A): (i) unisensory visual (UV; 100 ms red LED light; luminance: 90 cd/m^2; diameter: 0.5 cm), (ii) unisensory auditory (UA; 100 ms, 80 dB white noise) and (iii) multisensory audio-visual (MAV; UV and UA simultaneously at the same location). Patients fixated centrally and performed visual explorations, while the head remained stationary. Patients explored for stimuli and responded with a button-press when any visual stimulus (UV or MAV) was observed. Stimuli were disproportionately allocated to the hemianopic side, to encourage exploration of this field. (For further details on the training protocol, please see: Bolognini et al., 2005; Dundon et al., 2015; Passamonti et al., 2009; for the apparatus, see also the "Visual detection - Unisensory visual test" paragraph). Patients performed approximately 30 blocks per day, of 48 trials each (12 UV; 12 UA and 24 MAV).

Results

Repeated measures ANOVAs were conducted to test training effects on clinical, oculomotor and electrophysiological measures. To compensate for violations of

sphericity, Greenhouse-Geisser corrections (Greenhouse & Geisser, 1959) were applied whenever appropriate; corrected *p*-values (but uncorrected degrees of freedom) are reported. Partial eta-squared (η_p^2) effect sizes are also reported. *Post-hoc* comparisons were conducted using the Newman-Keuls test.

Clinical measures

Visual detection - Unisensory visual test: A 2×3×4 ANOVA, with visual field (hemianopic, intact), session (B, P, F) and location (56°, 40°, 24°, 8°) as within-subjects factors, was performed on raw accuracy scores. The main effects of visual field ($F(1,9) = 51.85$, $p = 0.00005$, $\eta_p^2 = 0.852$), session ($F(2, 18) = 30.31$; $p = 0.000003$, $\eta_p^2 = 0.771$) and location ($F(3,27) = 127.83$, $p = 0.0000000004$, $\eta_p^2 = 0.934$) were significant. Notably, the three-way interaction between visual field, session and location was also significant ($F(6,54) = 3.21$; $p = 0.048$, $\eta_p^2 = 0.262$). Thus, two separate ANOVAs were run, for the hemianopic and intact visual fields, respectively, with the factors session (B, P, F) and location (56°, 40°, 24°, 8°). The ANOVA on the hemianopic field revealed a significant effect of session ($F(2,18) = 36.52$; $p = 0.000001$, $\eta_p^2 = 0.804$): accuracy scores significantly increased from B (37.6%) to P (66.4%; $p = 0.0002$) and from B to F (68.3%; $p = 0.0001$). No significant difference was instead observed between P and F ($p = 0.637$). Also, the main effect of location was significant ($F(3,27) = 49.61$; $p = 0.000002$, $\eta_p^2 = 0.846$): accuracy was significantly lower at 56° (27.2%), compared to 40° (57.6%; $p = 0.0001$), 24° (70.2%; $p = 0.0001$) and 8° (74.8%; $p = 0.0002$), and also lower at 40° compared to 24° ($p = 0.007$) and 8° ($p = 0.001$). The session x location interaction was not significant ($F(6,54) = 1.82$; $p = 0.156$, $\eta_p^2 = 0.163$). The ANOVA on the intact field

revealed a significant interaction between session and location ($F(6,54) = 6.65$; $p = 0.004$, $\eta_p^2 = 0.426$). Post-hoc comparisons revealed that at 56°, compared to B (86.2%), accuracy was significantly reduced at P (58.8%, $p = 0.0001$) and at F (63.8%; $p = 0.0002$), while no significant difference was found between P and F ($p = 0.32$). At the remaining three stimulus locations, accuracy was unchanged across all three testing sessions (all p-values > 0.352, Figure 7B). An ANOVA with the factor session (B, P, F) comparing the percentages of false alarms revealed no significant differences between sessions ($F(2,18) = 1.38$; $p = 0.272$, $\eta_p^2 = 0.166$; B: 0%; P: 2%; F: 1%).

Visual search – E-F test: An ANOVA with the factor session (B, P, F), looking at the effect of treatment on IES, revealed a significant main effect of session ($F(2,18) = 4.47$, $p = 0.042$, $\eta_p^2 = 0.332$): Compared to B (3242 ms), IES at P (2902 ms) and at F (2875 ms) were significantly lower ($p = 0.023$ and $p = 0.039$, respectively; Figure 7C), reflecting a post-treatment improvement in scanning efficiency, with no difference between P and F ($p = 0.844$). The same ANOVA computed on the percentage of false alarms revealed no significant effect of session ($F(2,18) = 0.995$, $p = 0.344$, $\eta_p^2 = 0.117$; B: 0%; P: 5%; F: 0%).

Visual search – Triangles test: An ANOVA with the factor session (B, P, F), looking at the effect of treatment on IES, revealed a significant main effect of session ($F(2,18) = 7.29$, $p = 0.022$, $\eta_p^2 = 0.447$). Compared to B (11390 ms), IES at P (8274 ms) and at F (7894 ms) were significantly lower ($p = 0.006$ and $p = 0.007$, respectively; Figure 7D), reflecting more efficient visual scanning at post-treatment and follow-up sessions. No difference was observed between P and F ($p = 0.709$). The same ANOVA computed on the percentage of false alarms revealed no significant effect of session ($F(2,18) = 0.00$, $p = 1.00$, $\eta_p^2 = 0.000$; B: 0%; P: 0%; F: 0%).

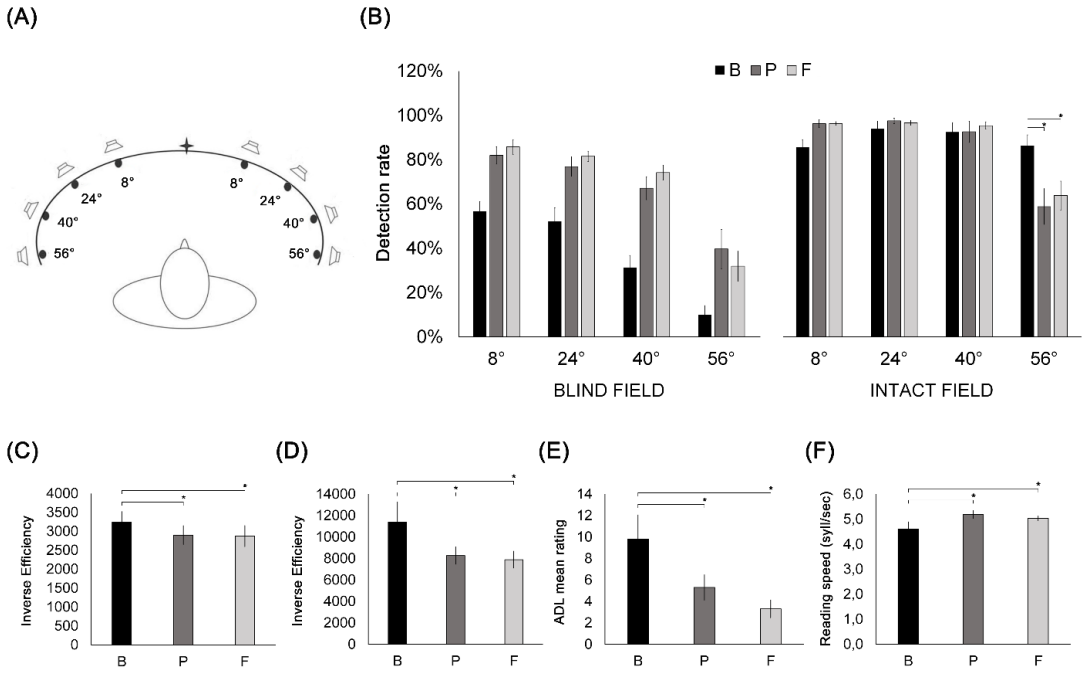

Figure 7. (A) Schematic bird's eye representation of the apparatus used for the Visual detection - Unisensory visual test and the audio-visual training. Patients were placed at the center of a concave ellipse (200 cm in width and 30 cm in height) in which 8 LED lights and 8 piezoelectric loudspeakers were positioned at increasing eccentricities (8°, 24°, 40° and 56° to the left and to the right) with respect to the center. During the Visual detection - Unisensory visual test, only LED stimuli were used. (B) Results of the Visual detection - Unisensory visual test. Detection rates (% correct stimulus detections) are depicted as a function of stimulus eccentricity (8, 24, 40 and 56 degrees) and visual field (blind field, intact field), at B (black bars), P (dark grey bars) and F (light grey bars) sessions. (C) Visual search. Inverse efficiency scores (reaction time/accuracy) for the E-F test as a function of testing session (B, P, F). (D) Visual search. Inverse efficiency scores (reaction time/accuracy) for the Triangles test as a function of testing session (B, P, F). (E) Mean ratings from the Activity of Daily Living inventory as a function of testing session (B, P, F). (F) Reading text task. Reading speed (syllables/second) as a function of testing session (B, P, F). Error bars report standard error of the mean. Asterisks indicate significant comparisons ($p < 0.05$).

ADL – An ANOVA with the factor session (B, P, F), looking at the effect of treatment on ADL scores, revealed a significant main effect of session ($F(2,18) = 13.21$, $p = 0.003$, $\eta_p^2 = 0.595$). ADL scores were significantly lower at P (5.3) and at F (3.3), compared to B (9.8; $p = 0.003$ and $p = 0.0004$, respectively), showing a significant improvement in the quality of patients' daily living, both immediately after treatment and

at the follow-up session. In contrast, ADL scores were not significantly different between P and F ($p = 0.14$; Figure 7E).

Reading text task – An ANOVA with the factor session (B, P, F) looked at the effect of treatment on reading speed. There was a significant main effect of session ($F(2,18) = 4.68$, $p = 0.047$, $\eta_p^2 = 0.341$), showing significantly improved reading speed at P (5.19 syll/sec) and at F (5.03 syll/sec), compared to B (4.61 syll/sec; $p = 0.02$ and $p = 0.04$, respectively; Figure 7F), while no difference was found between P and F ($p = 0.44$).

Oculomotor measures

ANOVAs with the factor session (B, P, F) were conducted separately for each oculomotor parameter measured (see the above section *Oculomotor measures*). The ANOVA on the number of fixations revealed a significant main effect of session ($F(2,18) = 5.23$, $p = 0.038$, $\eta_p^2 = 0.367$). The number of fixations was significantly reduced at P (73.6) and at F (70.2) compared to B (80.9, $p = 0.044$ and $p = 0.014$, respectively). No significant difference was found between P and F ($p = 0.329$, Figure 8A). Also, the ANOVA on mean saccadic speed revealed a significant main effect of session ($F(2,18) = 6.22$, $p = 0.013$, $\eta_p^2 = 0.408$). Saccades were significantly faster at P (64.81°/s) and at F (64.00°/s) compared to B (50.45°/s, $p = 0.015$ and $p = 0.008$ respectively; Figure 8B). No significant difference was found between P and F ($p = 0.862$).

In addition, the ANOVA conducted on mean exploration times revealed a significant main effect of session ($F(2,18) = 9.19$, $p = 0.007$, $\eta_p^2 = 0.50$). Mean exploration time was significantly lower at P (23.5 s) and at F (23.2 s) compared to B (27.2 s; $p = 0.002$ and $p = 0.003$, respectively), while no difference was observed between P and F ($p = 0.766$).

This indicates a significant post-treatment improvement in visual exploration that was maintained at the follow-up session (Figure 8C).

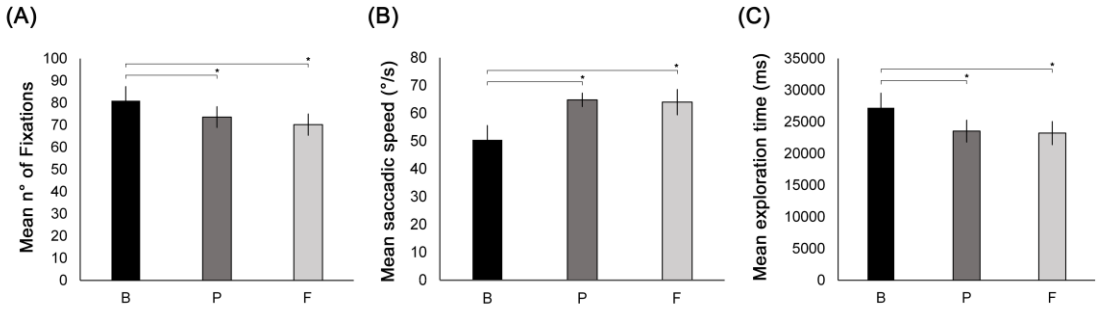

Figure 8. Oculomotor measures recorded during the Number visual search test. Mean number of fixations (A), mean saccade speed (B) and mean exploration time (C) are reported as a function of testing session (B, P, F). Error bars report standard error of the mean. Asterisks indicate significant comparisons ($p < 0.05$).

EEG measures

Behavioral Data – Given the requirement of eye-fixation, patients, as expected, detected a low number of stimuli in the hemianopic field (6% at B1, 6% at B2, 7% at P and 7% at F). Analyses on accuracy, response times and detection sensitivity were therefore performed only for stimuli presented in the intact visual field, using 4 x 3 ANOVAs with session (B1, B2, P, F) and location (upper, middle, lower) as factors. Neither accuracy ($F(3,27) = 1.24$, $p = 0.304$, $\eta_p^2 = 0.121$; B1 = 98%, B2 = 97%, P = 98%, F = 98%), response time ($F(3,27) = 1.02$, $p = 0.375$, $\eta_p^2 = 0.102$; B1 = 418.5 ms, B2 = 422.9 ms, P = 408.7 ms, F = 406.3 ms) nor detection sensitivity ($F(3,27) = 0.94$, $p = 0.417$, $\eta_p^2 = 0.094$; B1 = 4.75, B2 = 4.78, P = 4.75, F = 4.55) changed across sessions,

nor were there any significant interactions involving session and location (all *p*-values > 0.105).

EEG Data – No worthwhile ERPs were elicited by stimuli in the hemianopic field (Figure 9C). Therefore, only ERPs elicited by stimuli presented in the intact field were analyzed. A 4×3×3 ANOVA with the factors session (B1, B2, P, F), electrode (Pz, P3, CP1) and location (upper, middle, lower) compared the effect of treatment on the P3 component elicited by stimuli presented in the intact visual field. The main effect of session was significant ($F(3,27) = 7.61$, $p = 0.0008$, $\eta_p^2 = 0.458$). The mean P3 amplitude at session P (7.19 μV) was significantly lower than at B1 (9.25 μV; $p = 0.002$) and at B2 (9.05 μV; $p = 0.002$). The mean P3 amplitude at session F (7.99 μV) was also significantly lower than the mean P3 amplitudes at B1 ($p = 0.04$) and B2 ($p = 0.04$). There was no significant difference in P3 amplitude between B1 and B2 ($p = 0.689$), or between P and F ($p = 0.117$, Figure 9A).

To control for other possible effects of the training on early sensory components that are known to be modulated by visuo-spatial attention (i.e., the N1 component; for a review: Hillyard et al., 1998), a 4×3×3 ANOVA with the factors session (B1, B2, P, F), electrode (C3, CP5, P7) and location (upper, middle, lower) was conducted on the N1 component elicited by stimuli presented in the intact visual field. The results revealed no main effect of session ($F(3,27) = 1.23$, $p = 0.317$, $\eta_p^2 = 0.120$), suggesting that the mean N1 amplitude remained constant over the four testing sessions (B1 = -2.88 μV; B2 = -2.18 μV; P = -1.99 μV; F = -2.19 μV).

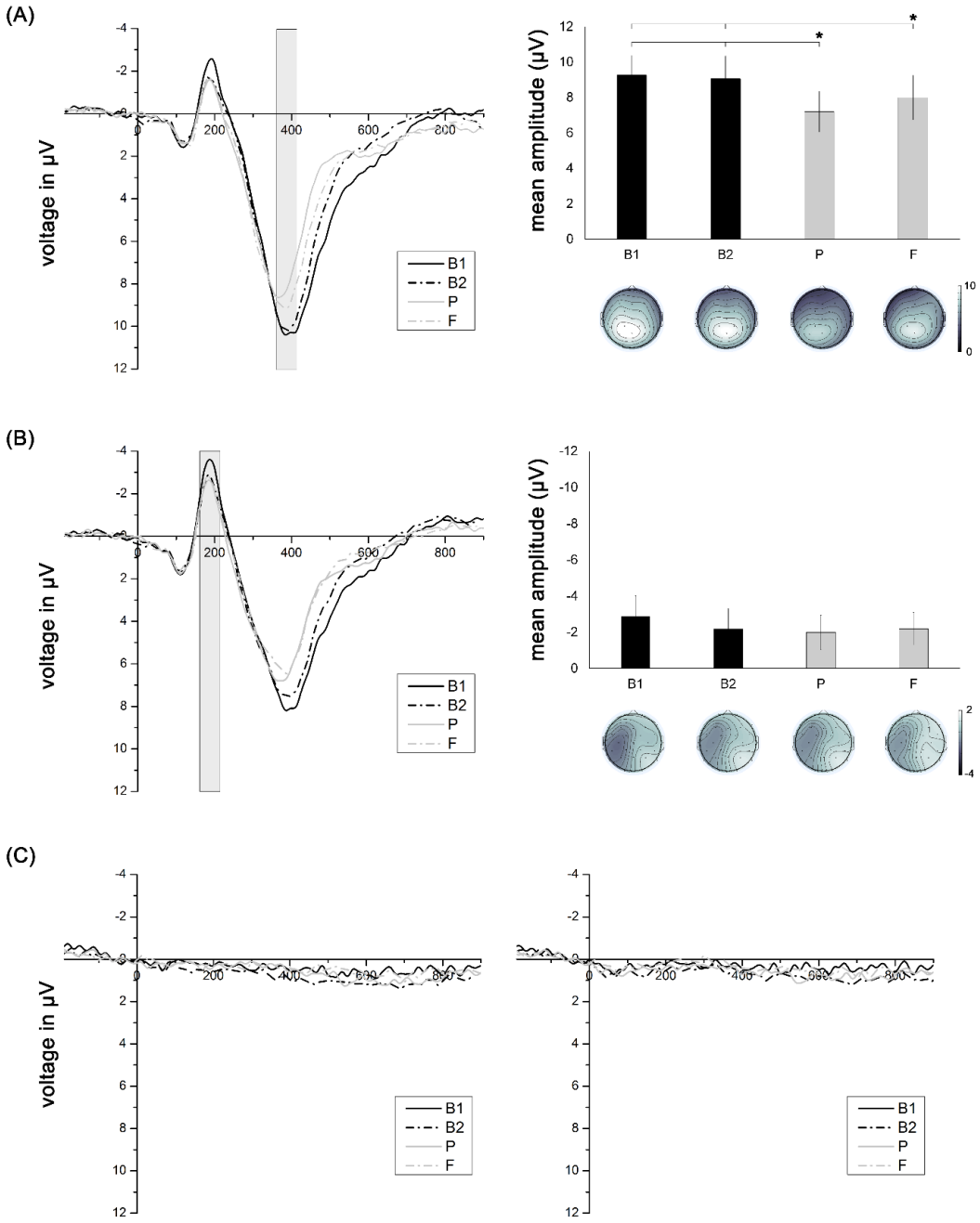

Figure 9. (A) Left panel depicts grand average ERPs averaged across electrodes Pz, P3 and CP1, elicited by stimuli presented in the intact visual field, as a function of session (B1, B2, P, F). Right panel depicts mean P3 amplitudes (with corresponding topographies) measured in a time window between 370 and 410 ms as a function of testing session (B1, B2. P, F). Asterisks connected with lines indicate significant comparisons ($p < 0.05$). (B) Left panel depicts grand average ERPs averaged across electrodes C3, CP5 and P7, elicited by stimuli presented in the intact visual field, as a function of session (B1, B2, P, F). Right panel depicts mean N1 amplitudes (with corresponding topographies) measured in a time window between 170 and 210 ms as a function of testing session (B1, B2. P, F). (C) Grand average ERPs elicited by stimuli presented to the blind visual field averaged across electrodes Pz, P3 and CP1 (left panel) and across electrodes C3, CP5 and P7 (right panel), as a function of testing session (B1, B2, P, F).

Discussion

In everyday life, hemianopic patients continuously experience asymmetric visual inputs, which could lead to an imbalance of attentional resource allocation towards the intact visual field (Tant et al., 2002). Multisensory audio-visual stimulation can reduce this attentional imbalance and improve clinical signs of hemianopia. Indeed, the present results confirm previous findings (Bolognini et al., 2005; Dundon et al., 2015; Passamonti, Bertini, et al., 2009) and provide new evidence for the long-term efficacy of the audio-visual training in both ameliorating visual performance and reducing the attentional bias towards the ipsilesional visual field. At the behavioral level, an improvement in visual search abilities, an increase in visual detection in the hemianopic field and improvements in self-perceived disability in daily life activities were observed at both the P and F sessions. Furthermore, oculomotor parameters during visual search revealed a reduction in the number of fixations, an increase in mean saccadic speed and a reduction in the mean exploration time at P and F sessions, suggesting the implementation of more organized visual exploration strategies. At the electrophysiological level, a reduction in the posterior-parietal P3 component elicited by simple visual detection in the periphery of the intact visual field was found both at the P session and at the F session. In addition, no differences were found between B1 and B2 sessions, or between P and F sessions, dismissing any possible explanation of the results as practice effects, and confirming the long-term duration of the modifications induced by the training.

A likely neural substrate driving the observed improvements in clinical and oculomotor parameters is the spared retino-collicolo-dorsal extrastriate pathway, which is known to

play a critical role in integrating audio-visual stimuli (Bertini, Leo, Avenanti, & Làdavas, 2010; Bertini, Leo, & Làdavas, 2008; G A Calvert, 2001; Leo, Bolognini, et al., 2008; Maravita, Bolognini, Bricolo, Marzi, & Savazzi, 2008; Meienbrock, Naumer, Doehrmann, Singer, & Muckli, 2007; Nardo, Santangelo, & Macaluso, 2014; B E Stein & Meredith, 1993). In addition, the SC is relevant to the execution and initiation of saccades and target selection (Krauzlis, Liston, & Carello, 2004), and contributes to oculomotor planning (Arikuni, Sakai, Hamada, & Kubota, 1980; Barbas & Mesulam, 1981). These observations are in line with electrophysiological findings showing that hemianopic cats, after similar audio-visual training, can recover visual orienting and visual responsiveness in the SC neurons. In addition, repeated exposure to audio-visual pairs has been shown to increase multisensory responses in the SC (L. Yu, Rowland, Xu, & Stein, 2012; Liping Yu, Stein, & Rowland, 2009; Liping Yu, Xu, Rowland, & Stein, 2014). Interestingly, systematic multisensory stimulation can also uncover the responsiveness of the SC neurons to stimuli in a single sensory modality (L. Yu et al., 2012; Liping Yu et al., 2009), showing that audio-visual stimulation can be effective at inducing plastic changes in the responses of SC neurons.

In addition, the neural network involving the SC, extrastriate and dorsal-parietal cortices is known to have a crucial role not only in orienting movements of the eyes and the head towards visual stimuli, but also in controlling visual spatial attention (Krauzlis et al., 2013). This seems in line with the present finding of a reduction in the amplitude of the P3 component in response to stimuli presented in the intact field, which seems to reflect a reallocation of spatial attentional resources after audio-visual training. Indeed, although no consensus has been reached on the exact processes underlying the P3 (Kok, 2001), this component has been interpreted as an index of attentional resource allocation (Isreal et

al., 1980; Wickens, Kramer, Vanasse, & Donchin, 1983), specifically within a late stage of cortical visual processing involving endogenous attention (Hopfinger & West, 2006). Moreover, attentional orienting has been consistently shown to influence P3 amplitude (see Polich, 2007 for review). The reduced P3 amplitude in the present study was associated with a post-treatment reduction in detection accuracy at the most peripheral eccentricity (56°) of the intact hemifield in the unisensory visual test. This corroborates the hypothesis of a reduction in attentional resource allocation toward the intact field after training. Indeed, the implementation of a more efficient oculomotor strategy after training might have increased compensatory saccadic planning towards the hemianopic field, inducing a consequent shift of attention from the intact to the blind field. This seems in line with evidence suggesting that preparation of saccades evokes visual attentional shifts towards the targeted location of the saccades (for a review: Zhao et al., 2012).

The observation that improvements at the clinical, oculomotor levels as well as electrophysiological changes found after training, were stable at the follow-up session is extremely relevant to the neural plasticity of the visual system. Indeed, these findings reveal that systematic audio-visual stimulation with hemianopic patients can induce a long-term implementation of efficient compensatory oculomotor strategies and a long-lasting reallocation of attentional resources, therefore suggesting a stable plastic change of the neural circuit (i.e., the retino-colliculo-dorsal pathway) subserving these effects. This seems in line with recent electrophysiological findings showing that when the neurons of the SC, deprived of any early sensory experience, are repeatedly exposed to spatially coincident audio-visual stimuli, they acquire stable multisensory integrative responses, which are maintained without further multisensory experience for more than one year (J. Xu, Yu, Rowland, Stanford, & Stein, 2012).

Overall, these results show that systematic audio-visual multisensory stimulation can promote long-term plastic changes in hemianopic patients, with stable and long-lasting beneficial effects resulting in ameliorations in their quality of life.

2.2 Experiment 2: Audio-visual multisensory training enhances visual processing of motion stimuli in healthy participants: an electrophysiological study

In previous experiment, I showed that the exposure to an intensive audio-visual multisensory training can significantly improve hemianopic patients' performances on various domains. I firstly replicated results from previous studies (Bolognini et al., 2005; Dundon et al., 2015; Passamonti, Bertini, et al., 2009) showing that, when free to explore their entire visual field, patients show post-training increased performances on visual search and visual detection tasks, together with a pattern of more organized oculomotor behavior. Interestingly, electrophysiological data confirmed, at a follow up session of ~8 months, a reduction of P3 component during the detection of briefly presented visual stimuli in the intact field, suggesting a multisensory mediated long-lasting reduction of attentional resources allocation towards the intact visual field possibly reflecting the counterpart of a greater resources allocation in the direction of the blind visual field.

This result suggests that the audio-visual multisensory training could have boosted the activity of those cortical and subcortical structures mediating audio-visual integration and visuo-spatial attentional processes. A likely candidate subserving both mechanisms is the network of connections between SC and cortical areas ascribed to the dorsal stream like dorsal posterior parietal and dorsal extrastriate cortices (Behrmann, Geng, & Shomstein, 2004; Krauzlis et al., 2013; Lyon et al., 2010; Nardo et al., 2014). If this is the case, we should expect an influence on visual processing within the dorsal stream, while leaving unaffected the visual processing within the ventral stream. Thus, I will present electrophysiological data from a study investigating this point through a comparison of the effects of the audio-visual training on a task relying on the activity of dorsal cortices and a control task relying on striate and ventral extrastriate cortices.

Introduction

Previous studies documented that a repetitive audio-visual stimulation could enhance the unisensory visual responses of SC neurons (L. Yu et al., 2012). Following cross-modal exposure trials, SC neurons showed an increased sensitivity to both cross-modal configurations and to the single unisensory components. The present study aimed to test whether similar mechanisms could also be observed in the cortex. In particular, I tested whether the exposure to a repetitive audio-visual stimulation might specifically enhance activity within the dorsal stream, as a consequence of a massive stimulation of its connections to the SC. Indeed, the SC is known to be robustly connected to higher order cortical areas within the dorsal stream, while projections relayed to the ventral stream are less documented (Krauzlis et al., 2013; Lyon et al., 2010). A systematic audio-visual stimulation could thus potentially enhance not only SC responses (L. Yu et al., 2012; Liping Yu et al., 2009, 2014), but also neural responses within those cortical areas receiving most collicular projections (Lyon et al., 2010).

To test this hypothesis, a group of healthy participants were tested before and after audio-visual training with two tasks: a Motion discrimination task, relying on activation of the dorsal-MT pathway (Kolster *et al.*, 2010; Tootell *et al.*, 1995; Watson *et al.*, 1993; Zeki *et al.*, 1991), and an Orientation discrimination task, relying on activation of the striate and early ventral extrastriate cortices (Boynton & Finney, 2003; Fang *et al.*, 2005; Kamitani & Tong, 2005; Murray *et al.*, 2006; Yacoub *et al.*, 2008; Swisher *et al.*, 2010). The Motion discrimination task, in which participants were asked to discriminate the motion direction of random-dot kinematograms, was selected based on the idea that motion processing involves both the dorsal extrastriate area MT and the SC (Kolster *et*

al., 2010), therefore suggesting a shared neural pathway with audio-visual multisensory integration. In contrast, the Orientation discrimination task, in which participants were asked to report the tilt of Gabor patches, entails the activation of striate and early ventral extrastriate cortices (Fang *et al.*, 2005), and does not involve the neural structures mediating audio-visual integration. During each task, EEG was recorded to measure electrophysiological correlates of motion and orientation discrimination.

In addition, to test the role of multisensory integrative processes in activating the colliculo-dorsal extrastriate pathway, one group of participants received training with concurrent audio-visual stimuli presented in the same spatial position, i.e., following the multisensory integrative principles of spatial and temporal coincidence (B E Stein & Meredith, 1993), while a control group received training with audio-visual stimuli presented at a spatial disparity of 32°, preventing optimal integration of the two sensory modalities. If audio-visual integration relies on activity in the colliculo-dorsal extrastriate pathway, then systematic stimulation with spatially coincident audio-visual stimuli should enhance activation of that pathway, resulting in a post-training increase in motion discrimination, which typically requires the activation of dorsal extrastriate cortices. Specifically, an increase in the amplitude of early visual evoked potentials, reflecting the visual discrimination process (i.e., the N1 component), might be expected. No effect of the audio-visual stimulation should be conversely expected in the orientation discrimination task which do not require a specific activation of dorsal cortices. No effect should also be expected after training with audio-visual pairs presented in spatial disparity.

Materials and methods

Participants

Thirty-two healthy volunteers took part in the study (20 females; mean age: 23.5 years; range: 19-33 years). All subjects were right-handed, had normal or corrected-to-normal vision and had no history of neurological or psychiatric disorders. Participants were informed about the procedure and the purpose of the study, and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the Psychology Department at the University of Bologna.

Experimental design

Each participant underwent two visual tasks, the Motion discrimination task and the Orientation discrimination task (see *Motion discrimination task* and *Orientation discrimination task* sections below). EEG was recorded during both tasks. Each task was performed before (Pre-training session) and after (Post-training session) audio-visual training (Figure 10). Experimental blocks of the Motion discrimination and Orientation discrimination tasks were interleaved, and the order of block presentation was counterbalanced between participants. Two experimental sessions were performed on two separate days. On the first day, participants performed the Motion and Orientation discrimination titration procedures (see *Motion discrimination titration procedure* and *Orientation discrimination titration procedure* sections below). Then, on the same day, they completed the Pre-training session, in which EEG was recorded during the Motion

discrimination and Orientation discrimination tasks. On the second day of testing (two or three days after the Pre-training session), participants completed the Audio-Visual training (see *Audio-Visual training* section below) and the Post-training session, in which EEG was again recorded during the Motion discrimination and Orientation discrimination tasks.

For the audio-visual training, participants were randomly assigned to two different groups, each of which received a different type of training: the AV-SC group received multisensory training in which audio-visual stimuli were presented in spatial coincidence, i.e., according to the principles of optimal multisensory integration (B E Stein & Meredith, 1993), while the AV-SD group, received a control training procedure in which audio-visual stimuli were presented in spatial disparity (see *Audio-Visual training* section below).

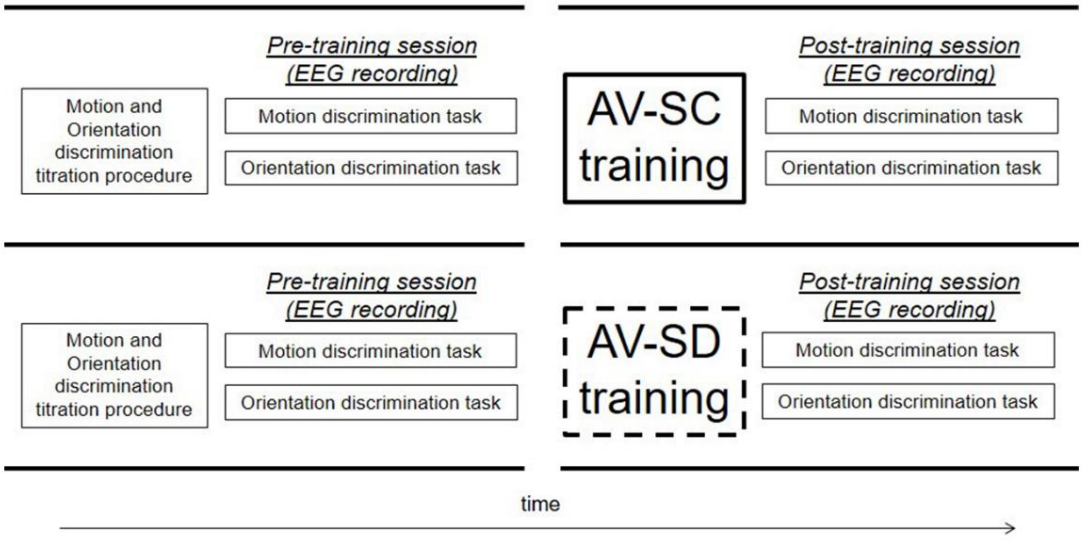

Figure 10. Schematic representation of the experimental design.

Motion discrimination titration procedure

The titration procedure was performed to select the stimulus difficulty level (i.e., the coherence level) at which participants performed with a discrimination accuracy around 60-65%, in order to avoid possible floor and ceiling effects during the subsequent Motion discrimination task.

Participants were seated in a dimly lit and sound controlled room in front of a 19" monitor (60 Hz refresh rate) at a distance of 57 cm. Stimuli consisted of modified random dot kinematograms (Gummel, Ygge, Benassi, & Bolzani, 2012), i.e., small white dots moving within a circular frame (5° diameter), displayed on a black background (velocity 2.2 °/s; lifetime: 8 frames; number: 150; density: 14.5 dots/deg^2). Stimuli were randomly presented 15° to the right or to the left of the centre of the screen. In each trial, dots moved in one of the four cardinal directions, and participants were asked to discriminate the direction of motion (vertical or horizontal) by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand.

Each trial (Figure 11A) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the motion stimulus (530 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms).

The titration procedure consisted of 13 experimental blocks, each one composed of 80 trials. In 40 trials, the stimulus was presented in the right visual field, and in the remaining

40 trials the stimulus was presented in the left visual field. In each block, motion stimuli were presented at a different level of coherence in order to test participants' motion perception performance. The 13 blocks corresponded to 13 consecutive levels of coherence. Starting from 100% coherence in the first block, the number of coherently moving dots was decreased at a rate of 20.6% in each subsequent block by substituting a percentage of the coherent dots with noise dots moving in a Brownian manner. Starting from the first block, in which all the dots moved coherently in a specific direction (100% coherence), the number of coherently moving dots decreased until reaching 6.3% coherence in block 13. The titration procedure was administered twice before the Pre-training session, in order to minimise learning effects. Performance during the second titration procedure was used to select the coherence level to be used in the Motion discrimination task.

Orientation discrimination titration procedure

The titration procedure was performed to select the stimulus difficulty level (i.e., the tilt orientation) at which participants performed with a discrimination accuracy around 60-65%, in order to avoid possible floor and ceiling effects during the subsequent Orientation discrimination task.

The setup was similar to the one used in the Motion discrimination titration procedure. Stimuli consisted of circular, equiluminant Gabor patches (7°), displayed on a grey background. The Gabor patches were composed of a 2D sinusoidal luminance grating with a spatial frequency of 3.5 cycles per degree. They were randomly presented 15° to the right or to the left of the centre of the screen. Participants were asked to discriminate

the tilt orientation from the vertical axis of the Gabor patch (clockwise or anti-clockwise) by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand.

Each trial (Figure 11B) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the Gabor patch (250 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms).

The titration procedure consisted of 13 experimental blocks, each one composed of 80 trials. In 40 trials, the stimulus was presented in the right visual field, and in the remaining 40 trials the stimulus was presented in the left visual field. In each block, the Gabor patches were presented at a different tilt orientation from the vertical axis, in order to test participants' orientation discrimination performance. The 13 blocks corresponded to 13 different degrees of tilt, in which tilt orientation decreased at a rate of 29.3% of the previous level. Tilt orientation from the vertical axis reduced from 16° in block 1 to 0.25° in block 13. The titration procedure was administered twice, in order to minimise learning effects. Performance during the second titration procedure was used to select the degree of tilt to be used in the orientation discrimination task.

Motion discrimination task

The Motion discrimination task was performed both before (Pre-training session) and after (Post-training session) the Audio-Visual training, and EEG was recorded in both

sessions. Stimuli consisted of the same modified random dot kinematograms (Gummel *et al.*, 2012) used in the Motion discrimination titration procedure. In each trial, dots moved in one of the four cardinal directions, and participants were asked to discriminate the direction of motion (vertical or horizontal) by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand.

For each participant, the kinematograms were set at the coherence rate corresponding to 60-65% accuracy in the Motion discrimination titration procedure (see above; mean coherence rate: 15.8%). Stimuli were randomly presented 15° to the right or to the left of the centre of the screen.

Each trial (Figure 11A) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the motion stimulus (530 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms).

Participants completed 6 blocks, consisting of 80 trials per block, i.e., 40 trials with stimuli presented in the right visual field and 40 trials with stimuli presented in the left visual field. In total, participants underwent 480 trials (240 trials per side of presentation). Behavioural performance was measured by computing inverse efficiency scores (IES = mean reaction times/proportion of correct responses).

Orientation discrimination task

The Orientation discrimination task was performed both before (Pre-training session) and after (Post-training session) Audio-Visual training, and EEG was recorded in both sessions. Stimuli consisted of the same circular, equiluminant Gabor patches used in the Orientation discrimination titration procedure. In each trial, a Gabor patch was presented with either a clockwise or anti-clockwise tilt from the vertical axis, and participants were asked to discriminate the tilt orientation by pressing one of two vertically aligned response buttons on the keyboard. Response buttons were counterbalanced between subjects. During the task, participants kept their gaze at the centre of the screen, and were instructed to respond as quickly as possible using the index and middle fingers of their right hand. For each participant, the tilt was set at the orientation corresponding to 60-65% accuracy in the Orientation discrimination titration procedure (see above; mean tilt orientation: 1°). Stimuli were randomly presented 15° to the right or to the left of the centre of the screen. Each trial (Figure 11B) started with a blank screen with a central fixation cross (1000 ms), and then a blank screen of random duration ranging from 150 ms to 300 ms. This was followed by presentation of the Gabor patch (250 ms), and then another blank screen, during which participants' responses were recorded (maximum duration 2000 ms). Participants completed 6 blocks, consisting of 80 trials per block, i.e., 40 trials with stimuli presented in the right visual field and 40 trials with stimuli presented in the left visual field. In total, participants underwent 480 trials (240 trials per side of presentation). Behavioural performance was measured by computing inverse efficiency scores (IES = mean reaction time/proportion of correct responses).

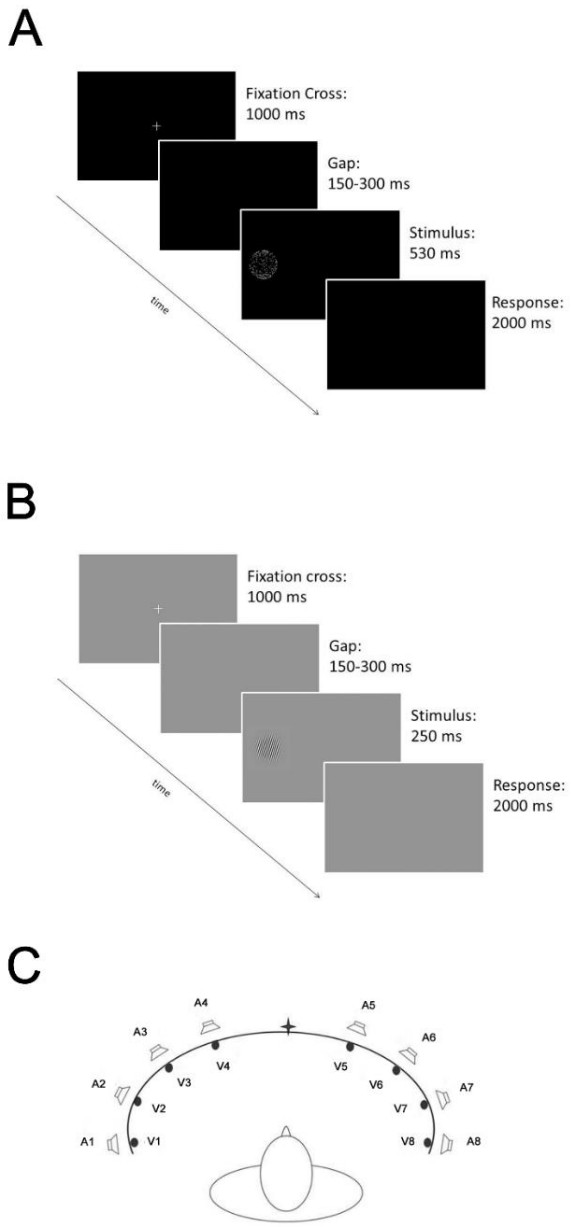

Figure 11. Experimental tasks and Audio-Visual training. (A) Motion discrimination task. (B) Orientation discrimination task. (C) A schematic bird's-eye view of the apparatus used for multisensory training, depicting the locations of visual (V1-V8) and auditory (A1-A8) stimuli. Stimuli were positioned at 8, 24, 40 and 56 visual degrees of eccentricity into both the left and right visual fields, on an elliptical apparatus.

Audio-Visual training

Participants sat on a comfortable chair with their head placed on a chin rest positioned at the centre of the training apparatus. The apparatus consisted of a concave ellipse, 200 cm wide by 30 cm high, placed on a table. Visual and auditory stimuli were delivered at eight

positions along the median line at 8°, 24°, 40° and 56° of eccentricity to the right and to the left of the centre (Figure 11C). Auditory stimuli consisted of 100 ms bursts of white noise at 80 dB, emitted by hidden piezoelectric loudspeakers (A1-A8 in Figure 11C). Visual stimuli consisted of 100 ms flashes of red LED light (luminance at 90 cd/m^2; V1-V8 in Figure 11C). Three different kinds of sensory stimulation were administered: (i) unisensory visual stimulation, in which only visual stimuli were presented at the 24°, 40° and 56° positions on the apparatus; (ii) unisensory auditory stimulation, in which only auditory stimuli were presented at the 24°, 40° and 56° positions on the apparatus; (iii) multisensory audio-visual stimulation, in which auditory and visual stimuli were coupled. Participants were asked to press a response button when they detected a visual stimulus and to perform eye movements towards the position of the visual stimulus. Trials with unisensory auditory stimuli could be considered catch trials, since no response was required. In contrast, participants had to respond to the visual stimuli on both unisensory visual and multisensory audio-visual trials. Whereas multisensory audio-visual stimuli were used to increase the activity of the SC-dorsal MT pathway, the role of the unisensory visual trials was to make the task less predictable and to increase participants' attentional engagement.

Half of the participants received multisensory training with audio-visual pairs of stimuli presented in spatial coincidence, i.e., auditory and visual stimuli were presented in the same spatial position at 24°, 40° or 56° on the apparatus (AV-SC group). The remaining half received multisensory training with audio-visual pairs, in which the visual stimulus was presented at the 24°, 40° or 56° position on the apparatus, and the auditory stimulus was presented at a spatial disparity of 32° within the same hemifield (AV-SD group).

Audio-visual stimulus pairs were disproportionately allocated to one side of the visual field, i.e., participants received 75% of the audio-visual pairs in either the left or the right visual field (trained hemifield), while the remaining 25% were delivered on the other side (untrained hemifield). Unisensory visual and auditory stimuli were equally distributed on both sides. The side in which participants received 75% of the audio-visual pairs (i.e., the trained hemifield) was counterbalanced between participants.

Participants performed 38 blocks of trials. Each block consisted of 12 unisensory visual stimuli (6 in the left and 6 in the right visual field; i.e, 2 per each spatial position), 12 unisensory auditory stimuli (6 in the left and 6 in the right visual field; i.e., 2 per each spatial position) and 24 multisensory audio-visual stimuli (18 in the trained hemifield, i.e. 6 per each spatial position; 6 in the untrained hemifield, i.e., 2 per each spatial position).

EEG recording and ERP analysis

EEG was recorded during the Motion discrimination and Orientation discrimination tasks with Ag/AgCl electrodes (Fast 'n Easy Electrodes, Easycap, Herrsching, Germany) from 27 electrodes sites on the scalp (Fp1, Fp2, F7, F3, Fz, F4, F8, FC5, FC1, FC2, FC6, T7, C3, Cz, C4, T8, CP5, CP1, CP2, CP6, P7, P3, Pz, P4, P8, O1, O2) and one on the right mastoid. The electrode on the left mastoid was used as the reference, while the ground electrode was placed on the right cheek. Impedances were kept below 10 KΩ. All electrodes were off-line re-referenced to the average of both mastoids. Vertical and horizontal electrooculogram data (EOG) were 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 digitised at a sampling rate of 500 Hz and off-line filtered with a 40-Hz low-pass filter.

ERP data were analysed using custom routines in Matlab 7.12.0.635 (R2011a; The Mathworks, Natic, MA, USA) and EEGLAB v10.2.5.8b (Delorme & Makeig, 2004; http://www.sccn.ucsd.edu/eeglab). Segments of 200 ms before and 900 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 with incorrect responses were rejected (Motion discrimination task: pre-training 38%, post-training 36%; Orientation discrimination task: pre-training 38%, post-training 35%). In addition, epochs contaminated with large artefacts were identified using the following methods from the EEGLAB toolbox (Delorme et al., 2007): (1) an epoch was excluded whenever the voltage on a channel exceeded an individually adjusted threshold (Motion discrimination task: pre-training 280 μV, post-training 275 μV; Orientation discrimination task: pre-training 281 μV, post-training 280 μV) to remove epochs with large voltage peaks (mean excluded epochs: motion discrimination task, pre-training 3.3%, post-training 2.3%; Orientation discrimination task, pre-training 3.1%, post-training 3.4%); (2) an epoch was excluded whenever the joint probability of a trial exceeded five standard deviations to remove epochs with improbable data (mean excluded epochs: Motion discrimination task, pre-training 1.7%, post-training 2%; Orientation discrimination task, pre-training 1.5%, post-training 1.7%). Remaining vertical EOG artefacts were corrected using a multiple adaptive regression method (Automatic Artifact Removal Toolbox Version 1.3; http://kasku.org/projects/eeg/aar.htm; Gratton *et al.*, 1983), based on the least mean squares algorithm. Finally, epochs were discarded from the analysis when saccadic movements (>30 μV in the horizontal EOG channels) were registered in a time window

between 0 and 530 ms following stimulus onset in the Motion discrimination task (mean excluded epochs: pre-training 2.1%, post-training 3.3%) and between 0 and 250 ms following stimulus onset in the Orientation discrimination task (mean excluded epochs: pre-training 1.2%, post-training 1.8%). The remaining epochs (mean epochs: Motion discrimination task, pre-training 54.9%, post-training 57.4%; Orientation discrimination task, pre-training 56.2%, post-training 58.1%) were averaged separately for each participant, each session and each hemifield of stimulus presentation.

ERP channels were swapped cross-hemispherically for participants in which the trained hemifield was the right visual field. In this way, the entire participant sample was analysed as if the trained hemifield was the left side.

The N1 component was quantified as the mean amplitude in a time window of 140 – 180 ms post-stimulus presentation (Figures 12C, 12D, 12E, 12F; Figures 13C, 13D, 13E, 13F). Scalp topographies for the N1 component were also calculated as the mean amplitude in a time window of 140 – 180 ms post-stimulus presentation. Scalp topographies of the mean N1 amplitude in the Pre-training session (Figure 12A and Figure 13A) and the Post-training session (Figure 12B and Figure 13B), both in the Motion and the Orientation discrimination tasks, showed a maximal negative deflection over electrodes FC1, FC2 and Cz; data from these electrodes were used for statistical analysis. Mean N1 amplitudes were analysed with 2x2x3x2 ANOVAs with Time (Pre-training, Post-training), Hemifield (Trained hemifield, Untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables, and with Group (AV-SC group, AV-SD group) as a between-subjects variable. The ANOVAs were performed separately for each experimental task (Motion discrimination task, Orientation discrimination task). 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. Post-hoc comparisons were performed using the Newman-Keuls test.

Results

Behavioural results

IES in the Motion discrimination and the Orientation discrimination tasks were analysed with two separate 2x2x2 ANOVAs with Time (Pre-training, Post-training) and Hemifield (Trained hemifield, Untrained hemifield) as within-subjects factors and Group (AV-SC group, AV-SD group) as a between-subjects factor.

The analysis on IES in the Motion discrimination task revealed a main effect of Time ($F(1,30) = 9,38$, $p = 0.004$; $\eta_p^2 = 0.24$), showing a significant improvement in performance in the Post-training session (1336 ms), compared to the Pre-training session (1423 ms). No other main effects (all p values > 0.118) or interactions (all p values > 0.223) were significant.

In contrast, the analysis on IES in the Orientation discrimination task revealed no significant main effects (all p values > 0.097) or interactions (all p values > 0.181).

Electrophysiological results

The ANOVA on mean N1 amplitudes elicited in the Motion discrimination task (Figure 12) revealed a significant Hemifield x Electrode interaction ($F(2,60) = 25.17$, $p < 0.001$, $\eta_p^2 = 0.46$). For stimuli presented in the trained hemifield, the contralateral FC2 electrode showed a significantly greater N1 amplitude (-2.29 μV) compared to both ipsilateral FC1 (-2.01 μV, $p = 0.002$) and central Cz (-2.13 μV, $p = 0.030$). For stimuli presented in the untrained hemifield, the contralateral FC1 electrode showed a significantly greater N1 amplitude (-2.31 μV) compared to both ipsilateral FC2 (-1.85 μV, $p < 0.001$) and central Cz (-2.11 μV, $p = 0.003$).

More importantly, the Time x Hemifield x Group interaction was significant ($F(1,30) = 4.80$, $p = 0.036$, $\eta_p^2 = 0.13$). Post-hoc comparisons revealed that, in the group who received coincident audio-visual training, a significantly greater N1 amplitude was observed in response to stimuli presented in the trained hemifield in the Post-training session (-3.02 μV), compared to the Pre-training session (-1.96 μV, $p = 0.003$; Figure 12C, 12G). In contrast, in the same group of participants, no significant difference between the Pre-training session (-1.93 μV) and the Post-training session (-2.19 μV, $p = 0.747$) was found in response to stimuli presented in the untrained hemifield (Figure 12D, 12G). Notably, in the group who received spatially disparate audio-visual training, no significant differences in N1 amplitude were found between the Pre-training session and the Post-training session, either in response to stimuli presented in the trained hemifield (Pre-training: -1.84 μV; Post-training: -1.74 μV, $p = 0.702$; Figure 12E, 12H), or in response to stimuli presented in the untrained hemifield (Pre-training: -2.00 μV; Post-training: -2.23 μV, $p = 0.644$; Figure 12F, 12H). No other main effects (all p values > 0.163) or interactions (all p values > 0.090) were significant.

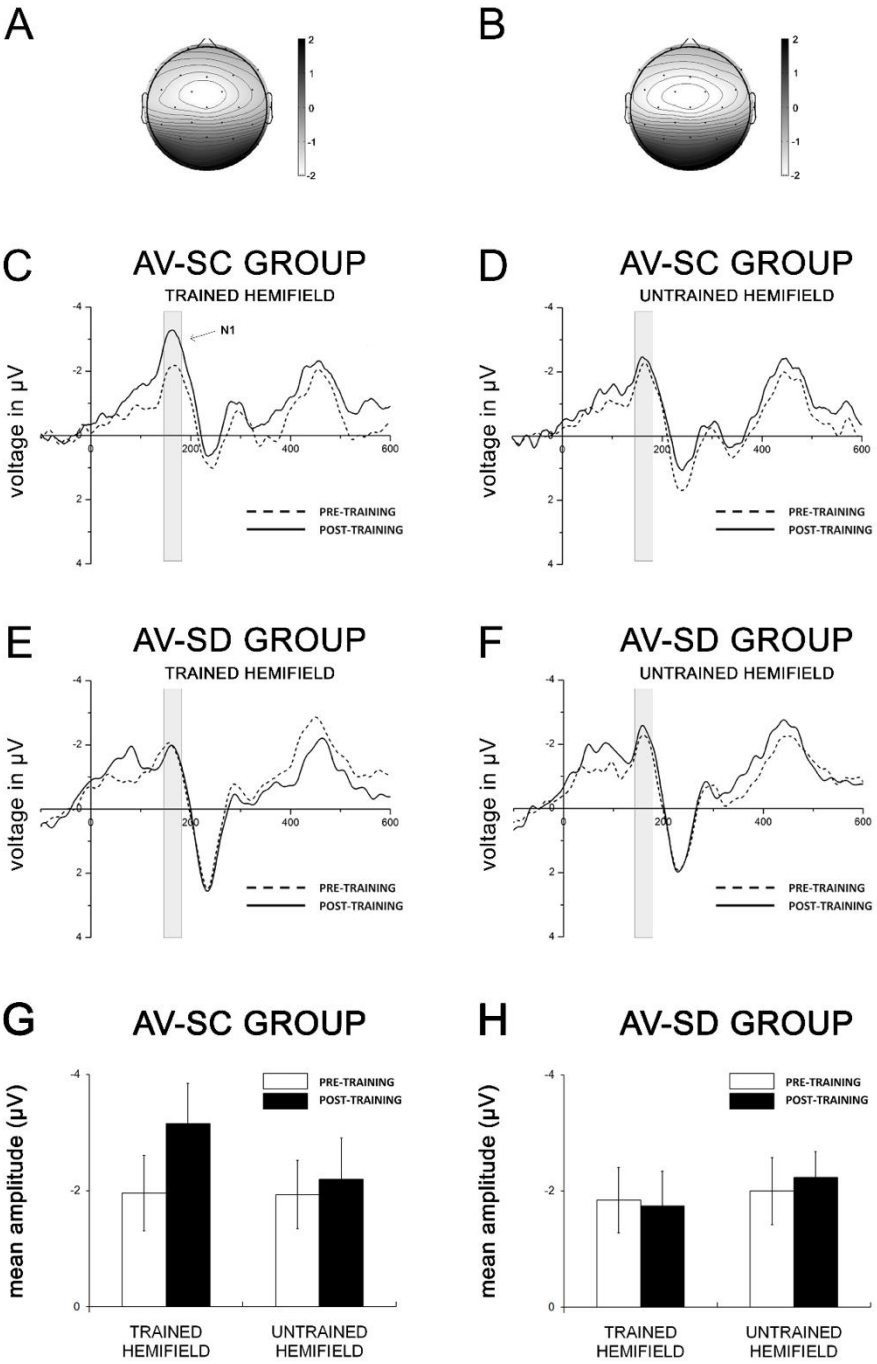

Figure 12. Motion discrimination task. (A) and (B) represent scalp topographies of the mean N1 amplitude in a time window between 140 – 180 ms, averaged over stimuli presented in the trained hemifield and the untrained hemifield, in the Pre-training session (A) and the Post-training session (B) for both the AV-SC (Audio-Visual training with stimuli in spatial coincidence) and the AV-SD (Audio-Visual training with stimuli in spatial disparity) groups. Grand-average ERPs averaged across electrodes FC1, FC2 and Cz, elicited by motion stimuli in the Pre-training session and the Post-training session, in the trained (C) and untrained (D) hemifields in the AV-SC group, and in the trained (E) and untrained (F) hemifields in the AV-SD group. Mean N1 amplitudes elicited by motion stimuli in the Pre-training and Post-training sessions, presented in the trained and untrained hemifields in the AV-SC group (G) and the AV-SD group (H), averaged across electrodes FC1, FC2 and Cz in a time window between 140 ms and 180 ms.

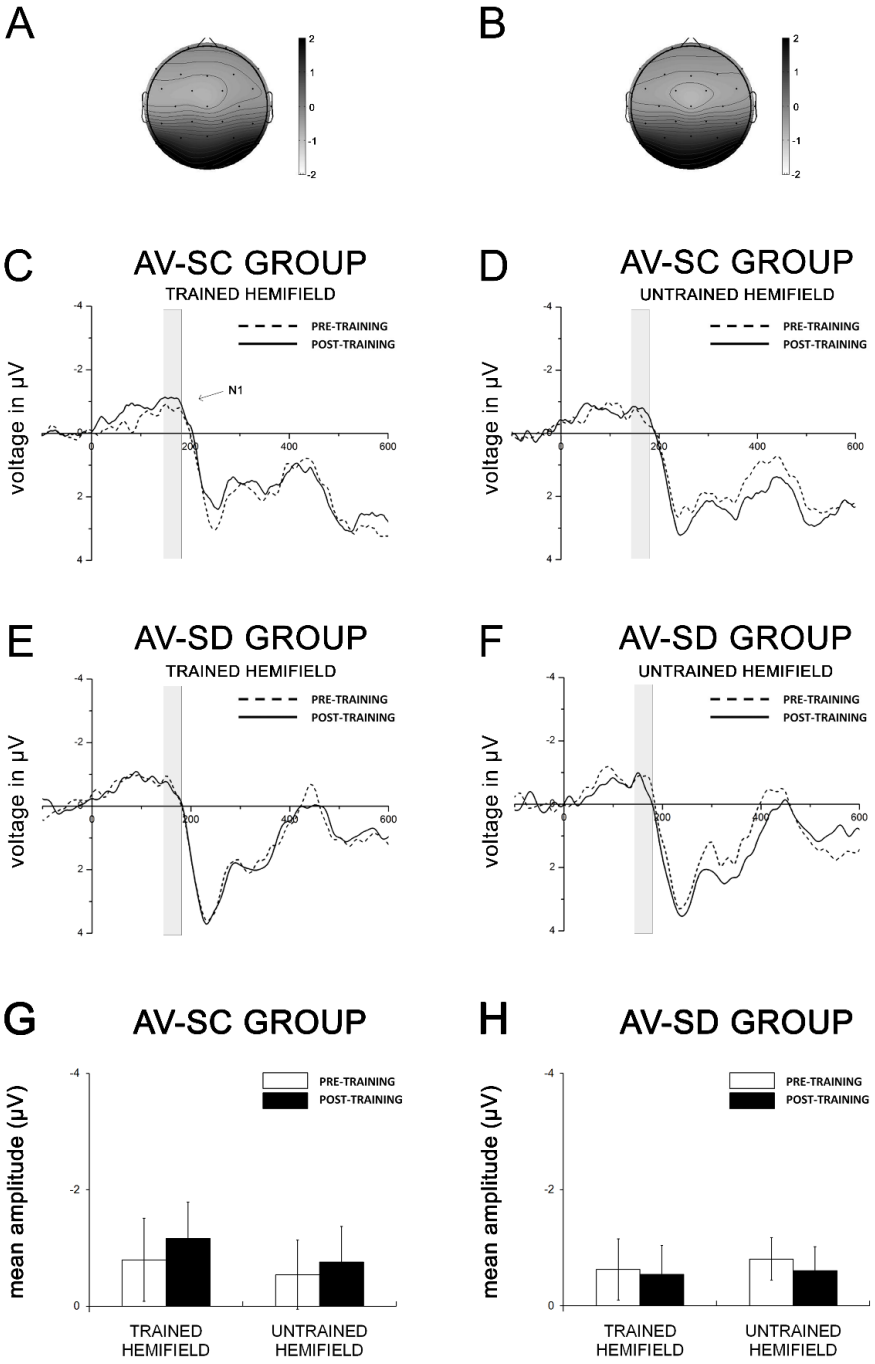

Figure 13. Orientation discrimination task. (A) and (B) represent scalp topographies of the mean N1 amplitude in a time window between 140 – 180 ms, averaged over stimuli presented in the trained hemifield and the untrained hemifield in the Pre-training session and the Post-training session for both the AV-SC (Audio-Visual training with stimuli in spatial coincidence) and the AV-SD (Audio-Visual training with stimuli in spatial disparity) groups. Grand-average ERPs averaged across electrodes FC1, FC2 and Cz, elicited by orientation stimuli in the Pre-training session and the Post-training session, in the trained (C) and untrained (D) hemifields in the AV-SC group, and in the trained (E) and untrained (F) hemifields in the AV-SD group. Mean N1 amplitudes elicited by orientation stimuli in the Pre-training and Post-training sessions, presented in the trained and untrained hemifields in the AV-SC group (G) and the AV-SD group (H), averaged across electrodes FC1, FC2 and Cz in a time window between 140 ma and 180 ms.

The ANOVA on mean N1 amplitudes elicited in the Orientation discrimination task (Figure 13) revealed only a significant Hemifield x Electrode interaction ($F(2,60) = 16.42$, $p < 0.001$, $\eta_p^2 = 0.35$). For stimuli presented in the trained hemifield, the contralateral FC2 electrode showed a significantly greater N1 amplitude (-0.91 μV) compared to ipsilateral FC1 (-0.61 μV, $p = 0.011$). For stimuli presented in the untrained hemifield, the contralateral FC1 electrode showed a significantly greater N1 amplitude (-0.86 μV) compared to ipsilateral FC2 (-0.45 μV, $p < 0.001$). In contrast with the results of the Motion discrimination task, the Time x Hemifield x Group interaction was not significant ($F(1,30) = 0.003$, $p = 0.961$, $\eta_p^2 = 0.00008$). In addition, no other significant main effects (all p values > 0.713) or interactions (all p values > 0.266) were found.

To ascertain whether there were any differences in N1 enhancement during motion discrimination between participants who received audio-visual training in the left visual hemifield and those who received training in the right visual hemifield (Corral & Escera, 2008; Sosa, Clarke, & McCourt, 2011; Sosa, Teder-Sälejärvi, & McCourt, 2010), a 2x2x3x2x2 ANOVA with Time (Pre-training, Post-training), Hemifield (Trained hemifield, Untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables and Group (AV-SC group, AV-SD group) and Trained side (Left, Right) as between subjects variables was performed. Again, the Time x Hemifield x Group interaction was significant ($F(1,28) = 5.07$, $p = 0.032$, $\eta_p^2 = 0.15$), confirming a significant post-training increase in N1 amplitude in response to stimuli presented in the trained hemifield in the group who received coincident audio-visual training (Pre-training: -1.96 μV; Post-training: -3.02 μV; $p = 0.002$). No significant difference was found in response to stimuli presented in the untrained hemifield (Pre-training: -1.93 μV; Post-training: -

2.19 μV; p = 0.730). Moreover, no significant differences were found in the group who received spatially disparate audio-visual training (all p values > 0.469). Importantly, the Time x Hemifield x Group x Trained side interaction was not significant ($F(1,28) = 1.70$, $p = 0.203$, $\eta_p^2 = 0.06$), suggesting a similar post-training N1 enhancement in participants who received training in the left hemifield and the right hemifield.

In addition, to control for possible hemispheric differences in N1 enhancement during motion discrimination, mean N1 amplitudes recorded from the lateralised electrodes FC1 (in the hemisphere ipsilateral to the trained hemifield) and FC2 (in the hemisphere contralateral to the trained hemifield) were analysed with a 2x2x2x2 ANOVA with Time (Pre-training, Post-training), Hemifield (Trained hemifield, Untrained hemifield) and Hemishpere (ipsilateral, contralateral) as within-subjects variables, and with Group (AV-SC group, AV-SD group) as a between-subjects variable. Similar to the previous analyses, the Time x Hemifield x Group interaction was significant ($F(1,30) = 5.42$, $p = 0.027$, $\eta_p^2 = 0.15$), and post-hoc comparisons confirmed a significant post-training increase in N1 amplitude in response to stimuli presented in the trained hemifield in the group who received coincident audio-visual training (Pre-training: -2.00 μV; Post-training: -3.06 μV; p = 0.002). No significant difference was found in response to stimuli presented in the untrained hemifield (Pre-training: -2.01 μV; Post-training: -2.25 μV; p = 0.624). In addition, no significant differences were found in the group who received spatially disparate audio-visual training (all p values > 0.526). Neither the main effect of Hemisphere ($F(1,30) = 1.23$, $p = 0.276$, $\eta_p^2 = 0.04$) nor the Time x Hemifield x Hemisphere x Group interaction ($F(1,30) = 0.09$, $p = 0.759$, $\eta_p^2 = 0.003$) was significant, suggesting no hemispheric differences in the observed N1 enhancement.

An additional control analysis was performed to ascertain that the N1 increase after spatially coincident Audio-Visual training was not influenced by the preceding C1 component. Two separate 2x2x3x2 ANOVAs for each experimental task were performed on C1 amplitudes, quantified as the most negative peak in a time window of 70-130 ms post-stimulus onset, with Time (Pre-training, Post-training), Hemifield (Trained hemifield, Untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables, and with Group (AV-SC group, AV-SD group) as a between-subjects variable. The ANOVA on mean C1 amplitudes elicited in the Motion discrimination task revealed a significant effect of Time ($F(1,30) = 17.6$, $p < 0.001$, $\eta_p^2 = 0.37$), showing a significant increase in C1 amplitude in the Post-training session (-1.55 μV) compared to the Pre-training session (-1.01 μV). Notably, the Time x Hemifield x Group interaction was not significant ($F(1,30) = 0.45$, $p = 0.508$, $\eta_p^2 = 0.01$), suggesting that the observed C1 increase might reflect perceptual learning due to practice effects (Bao, Yang, Rios, He, & Engel, 2010; Pourtois, Rauss, Vuilleumier, & Schwartz, 2008). In addition, the main effect of Electrode was significant ($F(2,60) = 15.14$, $p < 0.001$, $\eta_p^2 = 0.33$), showing significantly greater C1 amplitudes over electrode Cz (-1.45 μV) compared to both FC1 (-1.2 μV, $p < 0.001$) and FC2 (-1.18, $p < 0.001$). No other significant main effects (all p values > 0.388) or interactions (all p values > 0.260) were found.

In the Orientation discrimination task, a significant main effect of Electrode ($F(2,60) = 24.94$, $p < 0.001$, $\eta_p^2 = 0.45$) was found, revealing greater C1 amplitudes over electrode Cz (-1.00 μV) compared to both FC1 (-0.66 μV, $p < 0.001$) and FC2 (-0.69, $p < 0.001$). No other significant main effects (all p values > 0.907) or interactions (all p values > 0.070) were found.

Finally, to test possible differences at a later time window post-stimulus onset, mean P2 component amplitudes were analysed with a 2x2x3x2 ANOVA for each experimental task, with Time (Pre-training, Post-training), Hemifield (Trained hemifield, Untrained hemifield) and Electrode (FC1, FC2, Cz) as within-subjects variables and Group (AV-SC group, AV-SD group) as a between-subjects variable. The P2 component was quantified as the most positive peak in a time window between 220-260 ms post-stimulus onset. Overall, the P2 component was not significantly modulated by audio-visual training. Indeed, the ANOVA on mean P2 amplitudes elicited in the Motion discrimination task revealed no significant main effect of Time ($F(1,30) = 1.04$, $p = 0.398$, $\eta_p^2 = 0.03$) or Group ($F(1,30) = 0.93$, $p = 0.343$, $\eta_p^2 = 0.03$). In addition, no significant Time x Hemifield x Group interaction was found ($F(1,30) = 0.009$, $p = 0.924$, $\eta_p^2 = 0.0003$).

Similarly, the ANOVA on mean P2 amplitudes elicited in the Orientation discrimination task revealed no significant effect of Time ($F(1,30) = 0.21$, $p = 0.650$, $\eta_p^2 = 0.007$) or Group ($F(1,30) = 0.7$, $p = 0.408$, $\eta_p^2 = 0.023$). The Time x Hemifield x Group interaction was also non-significant ($F(1,30) = 1.45$, $p = 0.237$, $\eta_p^2 = 0.046$).

Discussion

The results of the present study show an enhancement of the N1 component in a Motion discrimination task extensively involving the dorsal MT pathway (Kolster *et al.*, 2010; Tootell *et al.*, 1995; Watson *et al.*, 1993; Zeki *et al.*, 1991) after exposure to a training with spatially coincident audio-visual stimuli. The effect was found to be spatially

selective to the portion of space receiving the greater amount of audio-visual stimulation as it was found only in response to stimuli presented in the trained hemifield (receiving 75% of total audio-visual stimulation), while no effect was found in response to stimuli presented in the untrained hemifield (receiving 25 % of total audio-visual stimulation). Notably, no effect was found in an Orientation discrimination task involving the ventral extrastriate pathway. Furthermore, participants who received a control training with spatially disparate audio-visual stimuli showed no effects in either task suggesting that the effect was strongly dependent to multisensory integration rules (B E Stein & Meredith, 1993).

The observed N1 enhancement might reflect increased motion discrimination ability (Vogel & Luck, 2000) after the spatially coincident audio-visual training. Indeed, the N1 component is an early visual-evoked potential, which has been associated with visual discrimination processes (Mangun & Hillyard, 1991; Martínez et al., 1999; Vogel & Luck, 2000) and might be related to attentional preparation for discriminating task-relevant features (Chen, Li, Qiu, & Luo, 2006; Pinal, Zurrón, & Díaz, 2014).

The enhanced processing of motion stimuli might reflect increased activity in the retino-colliculo-dorsal MT pathway due to the intensive two-hour training with spatially coincident audio-visual stimuli. Indeed, a wide range of evidence suggests that both motion processing and audio-visual integration share common neural circuits. On the one hand, primate studies suggest the existence of a functional pathway from the SC to cortical area MT (Berman & Wurtz, 2010, 2011; Lyon et al., 2010), in which motion signals are processed (Zeki, 1974; Maunsell & Van Essen, 1983a, 1983b; Albright, 1984). Similarly, evidence from humans suggests the involvement of the SC (Schneider & Kastner, 2005) and the dorsal extrastriate area MT in motion processing (Kolster *et al*.,

2010; Tootell *et al.*, 1995; Watson *et al.*, 1993; Zeki *et al.*, 1991). On the other hand, converging evidence reveals the pivotal role of the human SC in integrating spatio-temporally coincident audio-visual stimuli (Calvert, 2001; Bertini *et al.*, 2008; Leo *et al.*, 2008; Maravita *et al.*, 2008), and the relevance of the dorsal temporo-parietal and posterior parietal cortices in mediating orienting behaviour towards audio-visual stimuli (Bertini et al., 2010; Meienbrock et al., 2007; Nardo et al., 2014). Interestingly, a similar audio-visual training administered to hemianopic cats induced a recovery of visual orienting behaviour towards the hemianopic field, co-occurring with the reinstatement of visual responsiveness in the SC (H. Jiang et al., 2015), suggesting that coincident audio-visual stimulation might induce plastic changes in the SC. The plasticity of the colliculo-dorsal pathway is also supported by the observation that repeated audio-visual stimulation favours the development (J. Xu et al., 2012; Jinghong Xu, Yu, Rowland, Stanford, & Stein, 2014; Liping Yu, Rowland, & Stein, 2010) and enhancement (L. Yu et al., 2012; Liping Yu et al., 2009, 2014) of multisensory integrative responses in the SC. Intriguingly, repeated exposure to multisensory pairs can also increase neuronal responses to stimuli in a single sensory modality (L. Yu et al., 2012; Liping Yu et al., 2009). This is in line with the finding of the present study in which the audio-visual training affected responses to purely visual stimuli. Enhanced motion processing was observed only in response to the trained hemifield (i.e., the hemifield in which 75% of the coincident audio-visual stimuli were presented), while no change was found in the untrained hemifield, in which participants received only 25% of audio-visual stimuli. This seems to suggest a lateralised activation of the colliculo-dorsal MT pathway after the Audio-Visual training, in line with previous evidence showing that the SC contains a representation of the contralateral auditory and visual space (for a review: King, 2004).

Interestingly, we can speculate that the lack of any effect in the untrained hemifield might be due to an insufficient amount of multisensory stimulation presented in that hemifield. However, further studies are needed to investigate the exact quantity of stimulation needed to boost activity in the colliculo-dorsal MT pathway.

Notably, the post-training N1 enhancement observed in response to motion stimuli was detected over anterior fronto-central electrodes. Visual stimulus presentation is known to elicit a complex of temporally overlapping negative waves (the "N1 complex") in the 135-200 ms time window, both with posterior occipito-parietal and anterior fronto-central scalp distributions (Di Russo et al., 2005, 2012; Di Russo, Martinez, & Hillyard, 2003; Di Russo, Martínez, Sereno, Pitzalis, & Hillyard, 2002; Mangun & Hillyard, 1991; Martínez et al., 1999). Interestingly, the neural sources of the anteriorly distributed N1 component have been shown to be located in the superior parietal cortex (Di Russo et al., 2005, 2003, 2002), therefore corroborating the hypothesis that the observed N1 enhancement might reflect an increase in the activity of dorsal cortical areas. Indeed, a wide range of evidence suggests the existence of a network of cortical areas interconnected with the SC, including dorsal posterior parietal areas (Harting, Huerta, Frankfurter, Strominger, & Royce, 1980; Krauzlis et al., 2013; D. L. Robinson & Petersen, 1992).

Interestingly, no effect was found after training with audio-visual stimuli presented at a spatial disparity of 32°, suggesting that the combination of auditory and visual stimuli per se is not sufficient to enhance motion processing. In order to activate the colliculo-dorsal MT pathway and enhance motion discrimination, audio-visual pairs must be presented in spatial coincidence. Indeed, although spatial coincidence seems to play a marginal role in non-spatial tasks (e.g. Bertelson & Vroomen, 1994; Doyle & Snowden, 2001), spatial

alignment has been widely demonstrated to be crucial for multisensory enhancement in tasks requiring an orienting response (either overt or covert; for a review: Spence, 2013), as in the present audio-visual training. In line with this idea, electrophysiological studies in animals report that SC responses are enhanced only in the presence of spatially coincident audio-visual stimuli (B E Stein & Meredith, 1993), while audio-visual pairs presented in spatial disparity might depress SC responses (Kadunce, Vaughan, Wallace, Benedek, & Stein, 1997). Similarly, studies in humans have revealed enhanced activity in the SC (G A Calvert, 2001) and dorsal cortical areas with spatially coincident audio-visual stimuli, compared to spatially disparate stimuli (Macaluso, *et al.*, 2004; Meienbrock *et al.*, 2007; for a review: Calvert, 2001; Stein & Stanford, 2008). The finding that the N1 was only enhanced after training with stimuli presented in spatial coincidence rules out a possible role of saccadic eye movements in mediating the post-training effect. Indeed, in order to obtain an orienting response during the training and, therefore, to enhance the spatial component of the task, participants were asked to perform eye movements towards the visual and audio-visual stimuli. However, the saccadic response per se cannot account for the post-training N1 enhancement since saccadic eye movements were also performed in the control training procedure with spatially disparate audio-visual stimuli, after which no N1 enhancement was found.

Notably, the observed increase in the N1 component was not influenced by changes in the preceding C1 component. Indeed, the amplitude of the C1 component in the Motion discrimination task was increased after training, irrespectively of the type of training (spatially coincident vs. spatially disparate) and the hemifield in which stimuli were presented (trained vs. untrained). This general increase in C1 amplitude is in line with the finding that behavioural performance on the Motion discrimination task improved after

training, regardless of the type of training and the side of stimulus presentation. Both these findings might reflect a practice effect in motion processing. In line with this hypothesis, it has been shown that increases in stimulus-evoked activity as early as the C1 might aid perceptual performance, resulting in perceptual learning (Bao et al., 2010; Pourtois et al., 2008; Rauss, Schwartz, & Pourtois, 2011). Indeed, a wide range of evidence has shown better performance on visual perception tasks, including motion discrimination (Saffell & Matthews, 2003; Lu *et al.*, 2004), after repeated exposure to visual (for a review: Fahle, 2005) and audio-visual stimuli (Kim *et al.*, 2008; Shams & Kim, 2012).

At a later stage of visual processing related to task relevance evaluations (i.e., the P2 component; Potts *et al.*, 1996; Potts & Tucker, 2001; Potts, 2004), no effects of audio-visual training were found. This suggests that audio-visual training specifically affects the early visual discrimination process, but has no effect on higher order cognitive processes. The specific activation of the colliculo-dorsal MT pathway after the coincident Audio-Visual training is also suggested by the lack of any effects on orientation discrimination. Indeed, unlike with motion discrimination, both animal (Hubel & Wiesel, 1968; Hubel *et al.*, 1977; Vogels & Orban, 1994; De Weerd *et al.*, 1999) and human studies have revealed that grating orientation discrimination elicits activation in a visual pathway involving the striate cortex (Kamitani & Tong, 2005; Swisher et al., 2010; Yacoub et al., 2008) and early ventral extrastriate cortices (Boynton & Finney, 2003; Fang et al., 2005; Murray et al., 2006; Tong et al., 2012).

As a consequence, it seems reasonable that systematic, coincident audio-visual training, activating the colliculo–dorsal pathway, would have effects on a Motion discrimination

task, which relies on the same pathway, but not on an Orientation discrimination task, which relies on early ventral visual areas.

Overall, these results suggest that systematic audio-visual stimulation with spatially coincident stimuli enhances post-training functionality of the colliculo-dorsal MT pathway. Even though the post-training effects were only observed at the electrophysiological level, it is possible that increasing the duration of training might also induce changes at the behavioural level. Although the present study did not systematically investigate the duration of this post-training enhancement, which was observed immediately after audio-visual training (i.e., within two hours), electrophysiological evidence from animals suggests that the effects of repetitive audio-visual stimulation might outlast the exposure period and remain stable over a long period of time (i.e., more than 16 months after stimulation; Xu *et al.*, 2012). This would also be in line with results from the study presented in previous experiment revealing long-term electrophysiological changes (~8 months after stimulation) induced by the exposure to a systematic audio-visual stimulation on hemianopic patients (Grasso, Làdavas, & Bertini, 2016).

CHAPTER 3

Subcortical visual processing in hemianopic patients and healthy participants

In previous chapter, I showed that the exposure to a multisensory spatially coincident audio-visual training can induce a selective enhanced processing of visual stimuli relying on the activity of the dorsal pathway as measured by a post-training enhancement of early visual N1 component. Conversely, the processing of stimuli relying on the activity of striate and early ventral extrastriate cortices was not influenced by the training. I hypothesized that this result could be driven by a boosted activity within the dorsal stream as a consequence of an increased recruitment of connections with SC (Krauzlis et al., 2013; Lyon et al., 2010) induced by a prolonged coincident audio-visual stimulation. This interpretation is also suggested by the lack of enhanced visual processing in both dorsal and ventral pathway after an audio-visual training violating the basic principles of multisensory integration (B E Stein & Meredith, 1993).

The improved clinical performances of hemianopic patients after exposure to the same audio-visual training (Bolognini et al., 2005; Dundon et al., 2015; Grasso et al., 2016; Passamonti, Bertini, et al., 2009) could thus be driven by an improved functionality of the colliculo-dorsal circuit. However, it is not clear whether V1 lesioned patients that do not show residual residual visual capacities (i.e. blindisght) can still show a preserved functionality of this pathway. In the next experiment, I will therefore present a study aiming to investigate this point by comparing the electrophysiological activity induced by the presentation of visual stimuli relying or not relying on the activity of the colliculo-dorsal route in a group of hemianopic patients without blindsight.

3.1 Experiment 3: Electrophysiological evidence of implicit processing of motion stimuli presented in the blind field of hemianopic patients without blindsight

Introduction

Unilateral post-chiasmatic lesions to primary visual pathway lead to loss of vision over half of the visual field retinotopically corresponding to the site of the lesion. When visual stimuli are presented in the blind visual field, hemianopic patients are usually unaware of the presence of a stimulus. However, when forced to provide a response of detection or discrimination of visual stimuli in the scotopic area, some patients are still capable to perform above chance level (see *Residual visual capacities after lesions to the primary visual pathway* in Chapter 1). As widely described in Chapter 1, the neural origin of this phenomenon, termed blindsight, is still unclear. Some authors proposed that residual visual abilities are mediated by preserved "islands" of primary visual cortex that are still responsive to visual stimulation (Fendrich et al., 2001), others argued that blindsight is mediated by the activity of subcortical connections to extrastriate visual areas bypassing the lesional site (Ajina et al., 2015; Bridge, Thomas, Jbabdi, & Cowey, 2008; Ffytche, Guy, & Zeki, 1996; Holliday, Anderson, & Harding, 1997; Leh et al., 2006).

However, blindsight is the exception rather than the rule since only a minority of hemianopic patients report evidence of residual visual abilities in their blind visual field. This lead to hypothesize that it could rather be the result of a peculiar situation possibly arising from plastic reorganization of the visual system after lesions to primary visual pathway occurring early in time (Bridge et al., 2008; Leh et al., 2006; Rees, 2008; Tamietto, Pullens, De Gelder, Weiskrantz, & Goebel, 2012). Furthermore, blindsight

patients sometimes report experiencing glimpses of awareness when high contrasted stimuli are presented in their blind visual field, casting some doubt on the complete loss of primary visual cortex functioning (Silvanto, Cowey, Lavie, & Walsh, 2005).

The aim of the present study was to investigate whether hemianopic patients that do not show residual visual abilities in their blind visual field, could show evidence of implicit visual processing of "specific" stimuli presented in the scotopic area. To date a few studies already revealed that this could be the case (Bertini et al., 2013; Cecere et al., 2014). In these studies authors reported behavioral (Bertini et al., 2013) and electrophysiological (Cecere et al., 2014) evidence of visual processing of fearful faces presented in the blind visual field interpreted as the result of the activation of the subcortical colliculo-pulvinar-amygdala network. It remained to be investigated whether also stimuli that do not contain an emotional valence could show a preserved processing possibly arising from the activity of subcortical spared visual pathways bypassing the lesioned site.

To investigate this point, in the present study I recorded EEG activity while a group of hemianopic patients without blindsight were presented with lateralized visual stimuli in their blind or intact visual field. Stimuli consisted of dots that could either move or remain static. Moving stimuli were chosen based on evidence that the processing of motion on dorsal MT area depends both on inputs from primary visual cortex and from SC (Rodman et al., 1989, 1990) and could thus potentially elicit an electrophysiological activity even in the absence of V1. Electrophysiological responses to the presentation of moving stimuli was compared to that elicited by the presentation of both static stimuli and a control condition of no stimulus presentation (i.e. blank condition). The prediction was that, when presented in the blind visual field, only stimuli that could rely on the activity

of a secondary subcortical pathway (i.e. motion stimuli) bypassing the lesioned site, could be capable to elicit an electrophysiological activity providing evidence of a preserved processing.

Electrophysiological activity was quantified in the time-frequency domain (i.e., event-related spectral perturbations, ERSPs). The analysis was a priori focused on the alpha (8-12 Hz) and low-beta (15-25 Hz) bands given the reported association of these frequencies with sensory processing and attentional mechanisms (Bauer, Kennett, & Driver, 2012; Klimesch, 2012; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes Da Silva, 2004; Pfurtscheller, Neuper, & Mohl, 1994). In addition, an analysis in the time-domain (i.e., event-related potentials, ERPs) was also performed. Specifically, the time-frequency based approach enabled to measure both the phase-locked and the not phase-locked changes in the electrophysiological signal (see Figure 14) thus allowing to measure task-relevant dynamics in the EEG signal not retrievable with a time-based approach (Michael X Cohen, 2011; Herrmann & Knight, 2001; Pfurtscheller & Lopes, 1999).

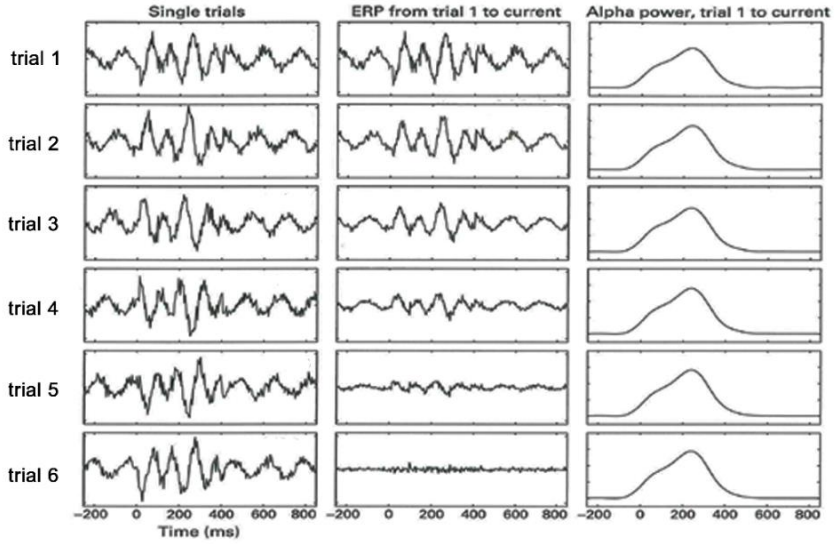

Figure 14. Trial averaging of non-phase locked signal in the time domain (second column) and in the time frequency domain (third column). The first column shows simulated trials with a jittered temporal response with respect to time 0. Trial averaging critically affect response in the time domain but not in the time-frequency domain.

Material and methods

Participants

Eleven patients (5 females, mean age = 50.9 years, SD = 12.4) with chronic visual field defects at the time of present evaluation (mean time since lesion = 13.5 months; Table 1) took part to the study. Patients were recruited based on reported visual field defects, the availability of a full visual field perimetry (Figure 15) and CT/MRI scans of the lesion. Right-lesioned patients were screened using the Behavioral Inattention Test neglect assessment (Wilson et al., 1987) to ensure performance was in the normal range. All patients showed normal or corrected-to-normal visual acuity. Patients were informed about the procedure and the purpose of the study, and gave written informed consent. The study was designed and performed in accordance with the ethical principles of the Declaration of Helsinki, and was approved by the Ethics Committee of the Psychology Department at the University of Bologna.

Experimental Procedure

Patients were firstly tested on forced choice tasks (see *Forced Choice Tasks* section below) to ensure an at chance level performance of detection and discrimination of visual stimuli in the blind visual field. After forced choice tasks, patients took part to the main experimental session (see *Experimental Session* section below) in which EEG were recorded.

ID	Sex	Age	Education	Onset	Lesion Site	Aetiology
P1	M	60	8	47	Left Occipital	Ischaemic
P2	M	50	13	7	Left Temporo- Parietal-Occipital	Ischaemic
P3	M	71	n.d.	3	Left Temporo-Occipital	Ischaemic
P4	M	45	13	7	Left Temporal	Hemorragic
P5	F	58	8	18	Left Posterior Temporal	Tumor
P6	F	58	13	28	Left Fronto-Temporal-Insular	AVM
P7	F	33	16	5	Right Temporo-Parietal-Occipital	Ischaemic
P8	M	58	8	5	Right Temporo-Parietal-Occipital	Abscess
P9	F	57	8	22	Right Temporo-Parietal-Occipital	Ischaemic
P10	M	32	13	3	Right Occipital	AVM
P11	F	38	13	4	Right Temporo-Parietal-Occipital	Tumor

Table 2. Demographic and clinical data of patients: M=Male; F=Female; Age in years; Education in years; Onset of lesion prior to treatment in months; AVM = Arteriovenous malformation.

Stimuli and Apparatus

Stimuli used both on *Forced Choice Tasks* and the *Experimental Session* consisted of 300 white dots (dot size: 2 x 2 pixels) on a black background presented within a circle area of 5° x 5° of visual angle on a 24'' LCD monitor (refresh rate: 60 Hz, 1920 x 1080 pixel resolution). Stimuli were presented at an eccentricity of 20° from the center of the screen and could either move (with maximum coherence at a velocity of 8°/s) or remain static. For patients with quadrantopia, stimuli were presented in the upper (upper quadrantopia) or lower (lower quadrantopia) part of the screen in order to ensure presentation in the blind visual field. During the *Forced Choice Tasks* stimuli were always presented within the blind visual field, while during the *Experimental Session* stimuli were half presented

in the blind visual field and half presented in the intact visual field. The experiment was conducted in a sound controlled room with participants seated at a viewing distance of 57 cm from the monitor. A computer running Presentation software (version 0.60) controlled stimuli presentation.

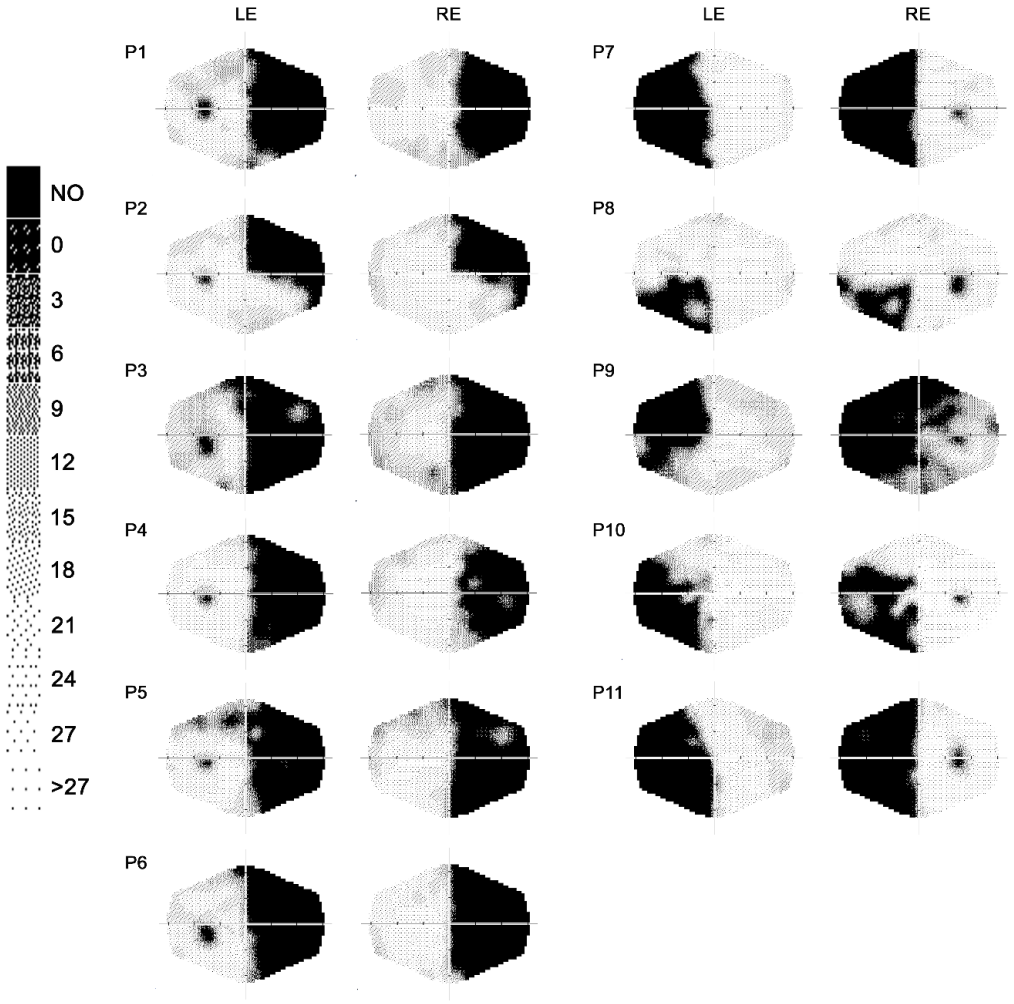

Figure 15. Computerised automated visual perimetry (Medmont M700 automated perimetry apparatus, Melbourne, Australia). Axial hash marks denote ten visual degree increments. Colourmap reports decibel values corresponding to each point in the grey scale; LE=Left Eye; RE= Right Eye.

Forced Choice Tasks

Patients were tested on three separate two-alternative forced-choice (2AFC) direct tasks requiring detection or discrimination of stimuli presented in the scotopic area. In the *motion detection task*, moving stimuli or catch trials (i.e. blank screen) were randomly presented. Similarly, in the *static detection task*, static stimuli or catch trials were randomly presented. In the *discrimination task*, patients were randomly presented with either moving stimuli or static stimuli. For each of the three-forced choice task, trial structure consisted of a blank screen (1000ms) with a central fixation cross followed by the presentation of a target stimulus (2000ms). After stimulus presentation, a blank screen with a central question mark appeared and patients were asked to provide a verbal response that was manually recorded by the experimenter. During the task, patients were instructed to maintain their eyes on the central fixation cross. Eye movements were monitored by means of an eye-tracker and trials in which an eye movement was registered were discarded from the analysis. In the *motion detection task* and *static detection task* patients were asked to indicate whether or not a stimulus appeared in the blind field (50% valid trials, 50% catch trials) while in the *discrimination task* patients were asked to indicate whether a moving or static stimulus appeared in their blind visual field (50% moving stimuli, 50% static stimuli). Each of the three tasks consisted in the presentation of 100 trials equally distributed between the two alternatives. Mean percentage of correct responses was computed for each task and accuracy was compared to chance level (50% accuracy) by means of a binomial test.

Experimental Session

Each trial started with the presentation of a fixation cross (2000 or 3000ms) than a lateralized visual stimulus (moving or static dots) could appear either in the blind or in the intact visual field for 2000ms. In addition, blank trials (no stimulus presentation) were included. At the end of stimulus presentation, a small dot appeared (100ms) either above or below the fixation cross followed by a response time window of 2000ms (Figure 16).

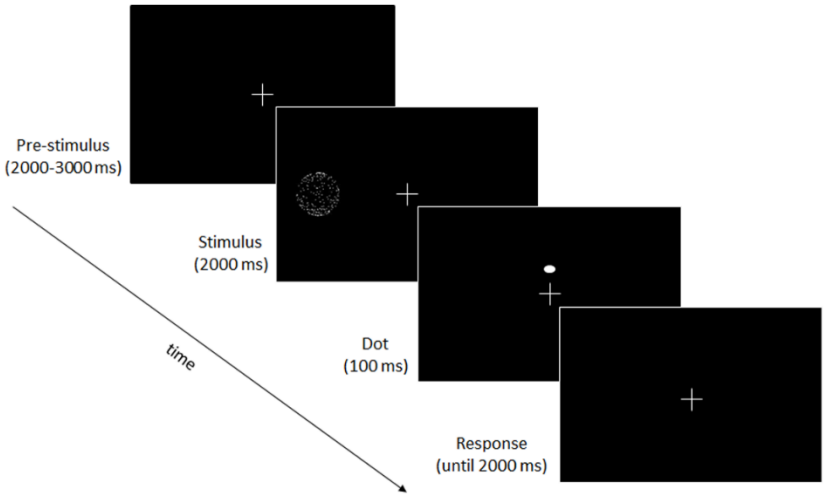

Figure 16. Schematic representation of the experimental paradigm. A trial began with the presentation of a fixation cross at the center of the monitor (2000-3000ms) followed by the presentation of lateralized visual stimuli (moving or static dots) appearing either on the intact or on the blind visual field. An additional control condition (blank condition) in which no stimuli appeared was also included. Patients were instructed to maintain their eyes on the central fixation cross and to respond to the presentation of a small dot (100ms) either appearing above or below fixation.

Patients were instructed to maintain central eye-fixation throughout the entire trial ignoring the presence of lateralized visual stimuli and to respond whether the central dot appeared above or below the fixation cross by respectively pressing the upward or downward arrow on the keyboard. Request to respond to the position of the dot allowed minimizing eye movements in the direction of lateralized visual stimuli and concurrently

reducing attentional drop. The Experimental Session was divided into five blocks. Each block consisted of the presentation of 40 lateralized moving stimuli (half-presented in the blind visual field and half-presented in the intact visual field), 40 lateralized static stimuli (half-presented in the blind visual field and half-presented in the intact visual field) and 20 catch trials.

EEG Recording and pre-processing

EEG data were recorded with Ag/AgCl electrodes (Fast'n Easy-Electrodes, Easycap, Herrsching, Germany) from 59 electrode sites (Fp1, AF3, AF7, F1, F3, F7, FC1, FC3, FC5, FT7, C1, C3, C5, T7, CP1, CP3, CP5, TP7, P1, P3, P5, P7, PO3, PO7, O1, Fp2, AF4, AF8, F2, F4, F8, FC2, FC4, FC6, FT7, C2, C4, C6, T8, CP2, CP4, CP6, TP8, P2, P4, P6, P8, PO4, PO8, O2, FPz, AFz, Fz, FCz, Cz, CPz, Pz, POz, Oz) and the right mastoid. The left mastoid was used as reference, while the ground electrode was positioned on the right cheek. Vertical and horizontal electrooculogram (EOG) components were recorded from above and below the left eye, and from the outer canthus of both eyes. Data were recorded with a band-pass filter 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 1000 Hz and then analyzed using custom routines in Matlab 7.12.0.635 (R2011a; The Mathworks, Natic, MA, USA) and EEGLAB v10.2.5.8b (Delorme & Makeig, 2004).

Data from all electrodes were re-referenced offline to the average of both mastoids and offline filtered with a band-pass filter of 1-40 Hz. Continuous EEG waveform were segmented in epochs from -1000ms to 2000ms considering the onset of lateralized

stimulus presentation (moving, static, and blank) and baseline corrected to the pre-stimulus interval (1000ms). Epochs containing horizontal eye-movements that could explain stimulus detection were excluded by visual inspection, while vertical EOG artefacts were corrected through an independent component analysis (ICA). Remaining epochs were divided into five separate datasets based on stimulus type and side of presentation (1. moving stimulus presented in the blind field, 2. moving stimulus presented in the intact field, 3. static stimulus presented in the blind field, 4. static stimulus presented in the intact field and 5. blank presentation).

Time-frequency domain analysis

For each dataset, a time-frequency (TF) analysis based on a continuous wavelet transform of the signal (Morlet's wavelets) between 4 and 40 Hz (1 Hz step) was performed (baseline window: -500 to 0 ms pre stimulus). Epochs were then averaged and electrodes were swapped cross-hemispherically for patients with lesions to the left hemisphere. Thus, the data were analyzed as if all participants were right-lesioned.

When presented in the intact visual field, both moving and static stimuli showed the greater event-related desynchronization (ERD) over contralateral posterior electrodes in a time range between 200 and 800ms post stimulus onset for the alpha range (8-12 Hz) (Figure 17A) and between 200 and 500ms post stimulus onset for the low-beta range (15-25 Hz) (Figure 19A). For both moving and static stimulus presentation, scalp topographies in the chosen time windows showed the maximum contralateral ERD across electrodes O1, PO3, PO7, P3, P5, P7 in the alpha range (see scalp topographies on Figure 17A) and across electrodes O1, PO3, PO7, P1, P3, P5 in the low-beta range (see scalp

topographies on Figure 19A). These electrodes were then chosen to represent responses of the intact hemisphere, while electrodes O2, PO4, PO8, P4, P6, P8 in the alpha range and electrodes O2, PO4, PO8, P2, P4, P6 in the low-beta range, were chosen to represent responses of the lesioned hemisphere. Data were then separately averaged across electrodes of the intact and the lesioned hemisphere, and subsequently averaged across the chosen time windows in the alpha (8-12 Hz) and low-beta (15-25 Hz) range.

Two separate 2 x 3 ANOVA with factors Hemisphere (Intact, Lesioned) and Stimulus Type (Moving, Static, Blank) were conducted for stimuli presented in the intact visual field and for stimuli presented in the blind visual field. All post-hoc comparisons were conducted using the Newman-Keuls test.

Time-domain analysis

For each trace, epochs were averaged and electrodes were swapped cross-hemispherically for patients with lesions to the left hemisphere. Thus, the data were analyzed as if all participants were right-lesioned.

When presented in the intact visual field, both moving and static visual stimuli elicited an ERP response mainly showing a negative inflection (N1) peaking around 200ms (see Figure 21A) and a positive inflection (P3) peaking around 300ms (see Figure 22A). The N1 component was then quantified as the mean amplitude in a time window between 180 and 210ms post-stimulus onset. Scalp topography in the chosen time window showed the maximal contralateral negative inflection over electrodes FC1, FC3, C1, C3, CP3, CP5 in response to both moving and static stimulus presentation. These electrodes were then chosen to represent the N1 component over the intact hemisphere, while electrodes FC2,

FC4, C2, C4, CP4, CP6 were chosen to represent the N1 component over the lesioned hemisphere. Data from these electrodes were therefore averaged and used for the statistical analysis. The same procedure was used for P3 that was quantified as the mean amplitude in a time window between 280 and 340ms post-stimulus onset. Scalp topography in the chosen time window showed the maximal contralateral positive inflection over electrodes P3, P5, P7, PO3, PO7, O1 in response to both moving and static stimulus presentation. These electrodes were then chosen to represent the P3 component over the intact hemisphere, while electrodes P4, P6, P8, PO4, PO8, O2 were chosen to represent the P3 component over the lesioned hemisphere. Data from these electrodes were therefore averaged and used for the statistical analysis.

Two separate 2 x 3 ANOVA with factors Hemisphere (Intact, Lesioned) and Stimulus Type (Moving, Static, Blank) were conducted for stimuli presented in the intact visual field and for stimuli presented in the blind visual field. All post-hoc comparisons were conducted using the Newman-Keuls test.

Results

Forced Choice Tasks

For each patient and for each task, the percentage of correct responses was calculated (see Table 3) and compared to the chance level (50% correct). Performances did not significantly differ from chance level in any of the tasks (*motion detection task*: all ps >

0.11; *static detection task*: all ps = 0.11; *discrimination task*: all ps = 0.16) revealing that the patients were not aware of the presence of stimuli in the blind visual field.

	Motion detection	**Static detection**	**Discrimination**
P1	54%	58%	51%
P2	51%	53%	54%
P3	57%	54%	49%
P4	54%	46%	57%
P5	54%	49%	52%
P6	55%	51%	48%
P7	58%	57%	57%
P8	52%	53%	52%
P9	57%	53%	53%
P10	51%	55%	51%
P11	52%	54%	56%

Table 3. Individual percentage of correct answers in each of the three forced choice tasks.

Time frequency-domain results

The ANOVAs compared the ERD response over the intact and lesioned hemispheres elicited by moving, static or blank stimulus presented either in the intact visual field or in the blind visual field.

Alpha range (8-12 Hz)**.** The ANOVA on the intact visual field showed a significant main effect of Stimulus Type ($F(2,20) = 14.804$, $p < 0.001$). The post-hoc analysis revealed that both moving (-1.41 dB; $p < 0.001$) and static (-1.04 dB; $p = 0.001$) stimuli presentation elicited a significantly greater desynchronization in the alpha range with respect to blank condition (-0.05 dB), while no difference was shown between moving and static stimuli presentation ($p = 0.173$). The interaction between Hemisphere and Stimulus Type was also significant ($F(2,20) = 4.256$, $p = 0.029$) and was explained by a

greater ERD of the contralateral intact hemisphere as compared to the ipsilateral lesioned hemisphere, for both moving (intact: -1.81 dB, lesioned: -1.01 dB; $p = 0.008$) and static (intact: -1.36 dB, lesioned: -0.73 dB; $p = 0.036$) stimuli presentation but not for the blank condition (intact: 0.01 dB, lesioned: -0.11 dB; $p = 0.627$). Furthermore, both in the intact and in the lesioned hemisphere, moving (intact: $p = 0.0001$, lesioned: $p = 0.003$) and static (intact: $p = 0.0002$, lesioned: $p = 0.016$) stimuli elicited a greater ERD with respect to blank condition. In summary, when presented in the intact visual field both moving and static stimuli elicited, as expected, a greater desynchronization in the alpha range with respect to the blank condition, while no difference was evidenced between moving and static stimuli presentation, suggesting that the two type of stimuli were comparable in terms of evoked response in the alpha range (Figure 17A, 17C and Figure 18). The ANOVA for stimuli presented in the blind visual field showed a significant main effect of Stimulus Type ($F(2,20) = 7.295$, $p = 0.004$). The post-hoc analysis revealed that moving stimuli elicited a significantly greater desynchronization (-0.53 dB) with respect to both static stimuli presentation (-0.15 dB; $p = 0.009$) and blank condition (-0.05 dB; $p = 0.004$), while no difference was shown between static stimuli presentation and blank condition ($p = 0.449$). Interestingly, also the interaction between Hemisphere and Stimulus Type was significant ($F(2.20) = 7.407$, $p = 0.004$). The post-hoc analysis revealed that, in the intact ipsilateral hemisphere, moving stimuli presentation elicited a significantly greater desynchronization (-0.65 dB) with respect to both static stimuli presentation (-0.07 dB; $p < 0.001$) and blank condition (0.01 dB; $p < 0.001$), while, for the lesioned contralateral hemisphere, moving stimuli presentation elicited a significantly greater response (-0.37 dB) with respect to blank condition (-0.11 dB; $p = 0.043$) but not to static stimuli presentation (-0.24 dB; $p = 0.210$).

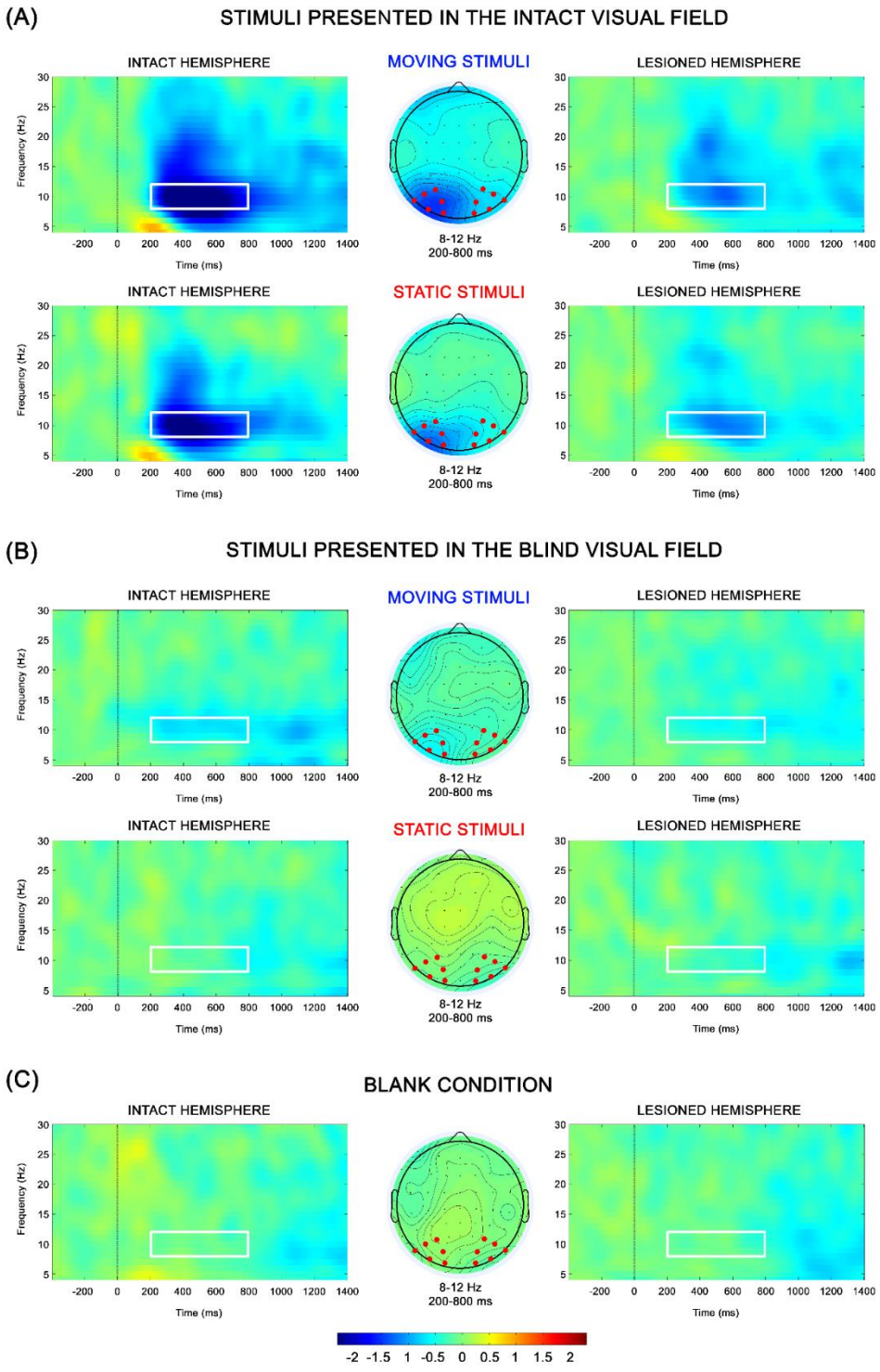

Figure 17. (A-B) Frequency plots depicting event-related desynchronization (ERD) in response to moving (upper panels) or static (lower panels) stimuli presented in the intact (A) and blind (B) visual field. (C) Frequency plots depicting ERD in response to the control condition (blank condition) of no stimulus presentation. Left panels always represent ERD responses averaged across posterior electrodes of the intact hemisphere (left ROI on the corresponding topographies), while right panels represent ERD response averaged across posterior electrodes on the lesioned hemisphere (right ROI on the corresponding topographies). Topographies depict ERD in the alpha range (8-12 Hz) in a time window between 200 and 800ms post stimulus onset.

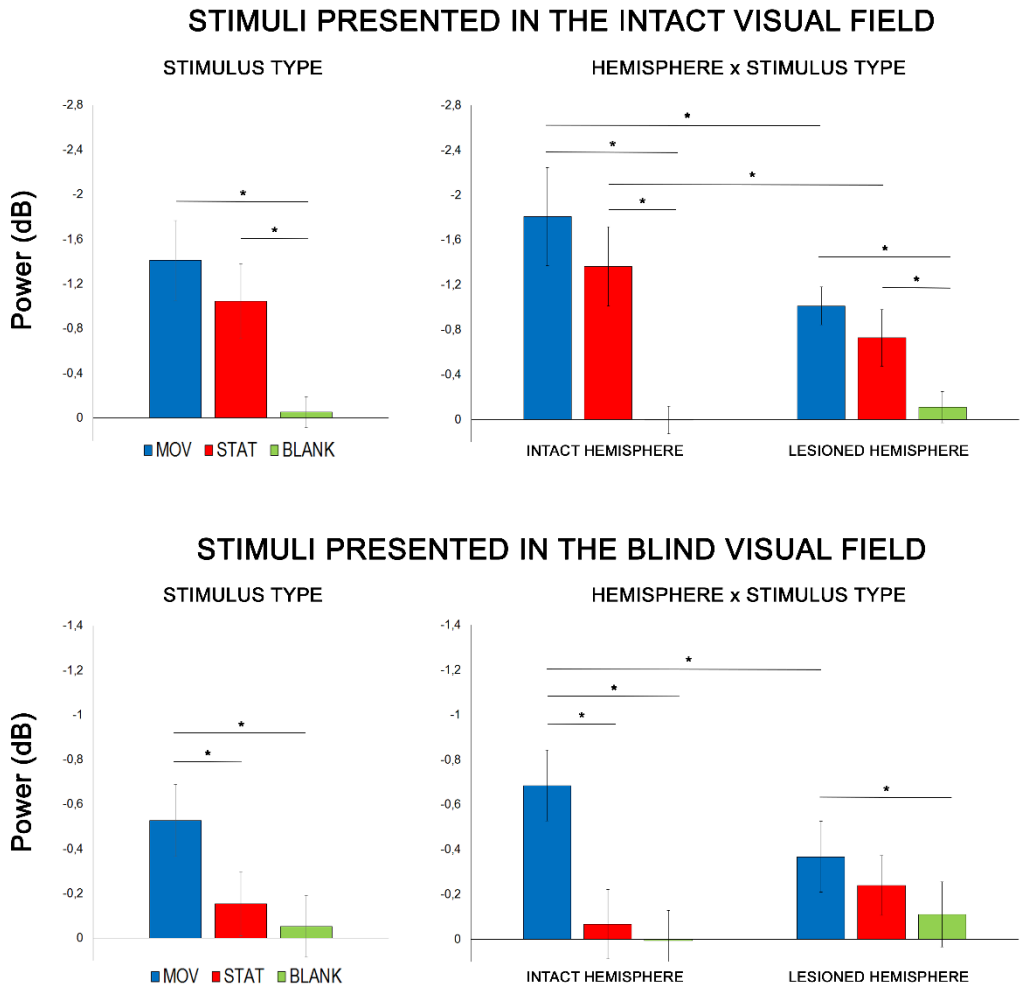

Figure 18. Event-related desynchronization (ERD) in the alpha range (8-12 Hz) in response to stimuli presented in intact visual field (upper plots) and in the blind visual field (lower plots) averaged between 200 and 800ms post stimulus onset. Left plots show ERD responses averaged across selected electrodes of the two hemispheres (intact and lesioned), while right plots show ERD response separately for the intact and lesioned hemispheres. Blue bars always depict ERD in response to moving stimuli, red bars to static stimuli and green bars to blank condition (no stimulus). Error bars represent standard error.

No difference was instead shown between static stimulus presentation and blank condition neither for the intact hemisphere ($p = 0.471$) nor for the lesioned hemisphere ($p = 0.204$). In addition, a greater ERD for the intact with respect to lesioned hemisphere was shown in response to moving stimuli ($p = 0.004$) but not to static stimuli ($p = 0.21$) and blank condition ($p = 0.47$).

In summary, when presented in the blind visual field only moving stimuli were capable to elicit a greater desynchronization in the alpha range with respect to the blank condition and this response was mainly driven by activity in the intact hemisphere (Figure 17B, 17C and Figure 18).

Low-Beta range (15-25 Hz). The ANOVA on the intact visual field showed a significant main effect of Stimulus Type ($F(2,20) = 13.705$, $p < 0.001$). The post-hoc analysis revealed that both moving (-0.83 dB; $p < 0.001$) and static (-0.80 dB; $p < 0.001$) stimuli presentation elicited a significantly greater desynchronization in the low-beta range with respect to blank condition (-0.03 dB) but no difference was shown between moving and static stimuli presentation ($p = 0.828$). The interaction between Hemisphere and Stimulus Type was also significant ($F(2,20) = 6.616$, $p = 0.006$) and was explained by a greater ERD response in the intact hemisphere for both moving (intact: -0.99 dB, lesioned: -0.68 dB; $p = 0.004$) and static (intact: -0.94 dB, lesioned: -0.67 dB; $p = 0.013$) stimuli presentation but not for blank condition (intact: 0.01 dB, lesioned: -0.07 dB; $p = 0.312$). Furthermore, both in the intact and in the lesioned hemisphere moving (intact: $p = 0.0001$, lesioned: $p = 0.0001$) and static (intact: $p = 0.0001$, lesioned: $p = 0.0001$) stimuli elicited a greater ERD with respect to blank condition (Figure 19A, 19C and Figure 20). The ANOVA on the blind visual field showed a significant main effect of Stimulus Type ($F(2,20) = 4.321$, $p = 0.027$). The post-hoc analysis revealed that moving stimuli (-0.28 dB) elicited a significantly greater desynchronization with respect to both static stimuli (-0.06 dB; $p = 0.03$) and blank presentation (-0.03 dB; $p = 0.034$), while no difference was shown between static stimuli and blank presentation ($p = 0.709$). Both the main effect of Hemisphere ($F(1,10) = 3.178$, $p = 0.105$) and the interaction Hemisphere x Stimulus Type were not significant ($F(2,20) = 0.582$, $p = 0.568$) (Figure 19B, 19C and Figure 20).

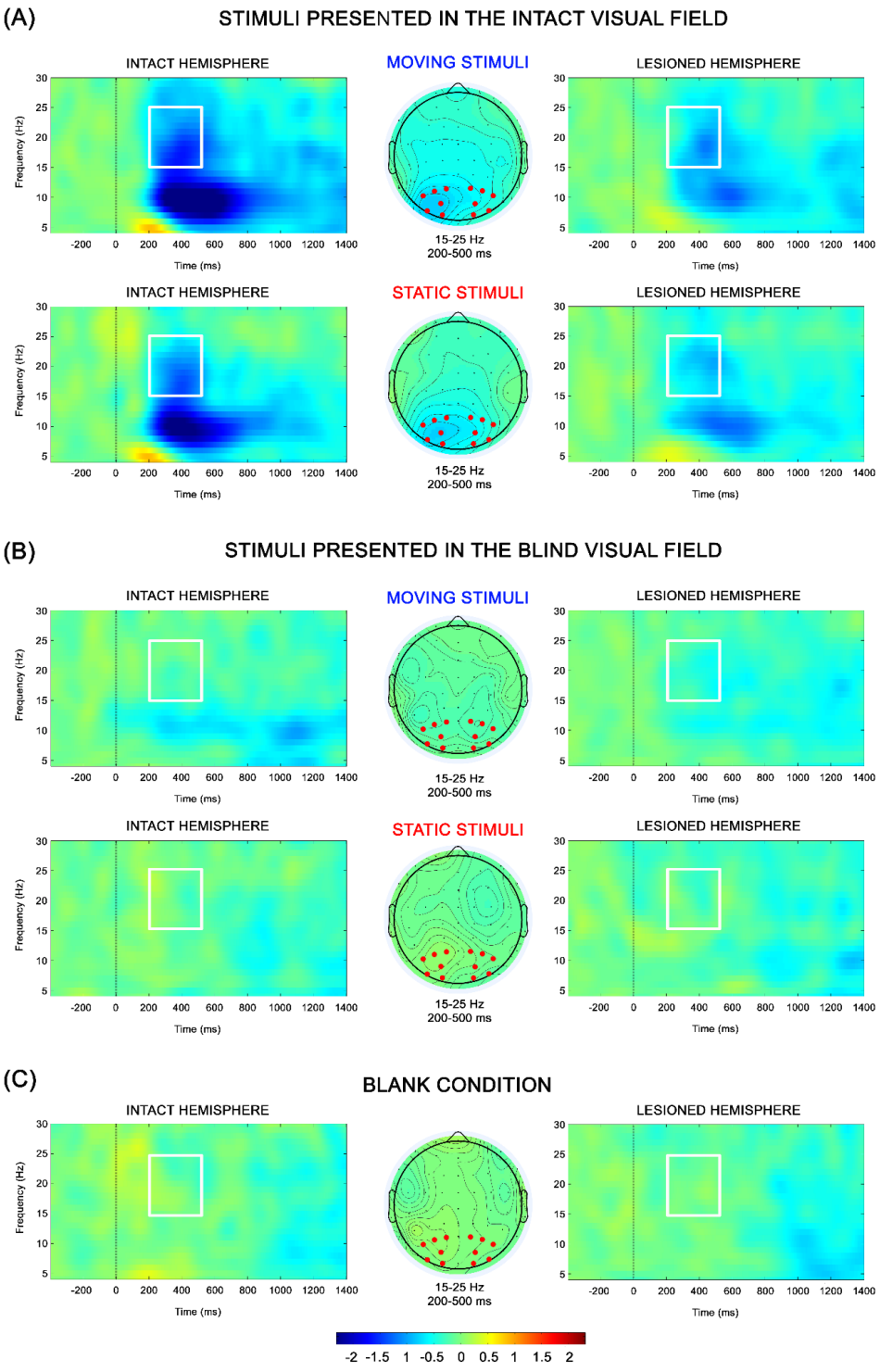

Figure 19. (A-B) Frequency plots depicting event-related desynchronization (ERD) in response to moving (upper panels) or static (lower panels) stimuli presented in the intact (A) and blind (B) visual field. (C) Frequency plots depicting ERD in response to the control condition (blank condition) of no stimulus presentation. Left panels always represent ERD response averaged across posterior electrodes of the intact hemisphere (left ROI on the corresponding topographies), while right panels represent ERD response averaged across posterior electrodes on the lesioned hemisphere (right ROI on the corresponding topographies). Topographies depict ERD in the low-beta range (15-25 Hz) in a time window between 200 and 500ms post stimulus onset.

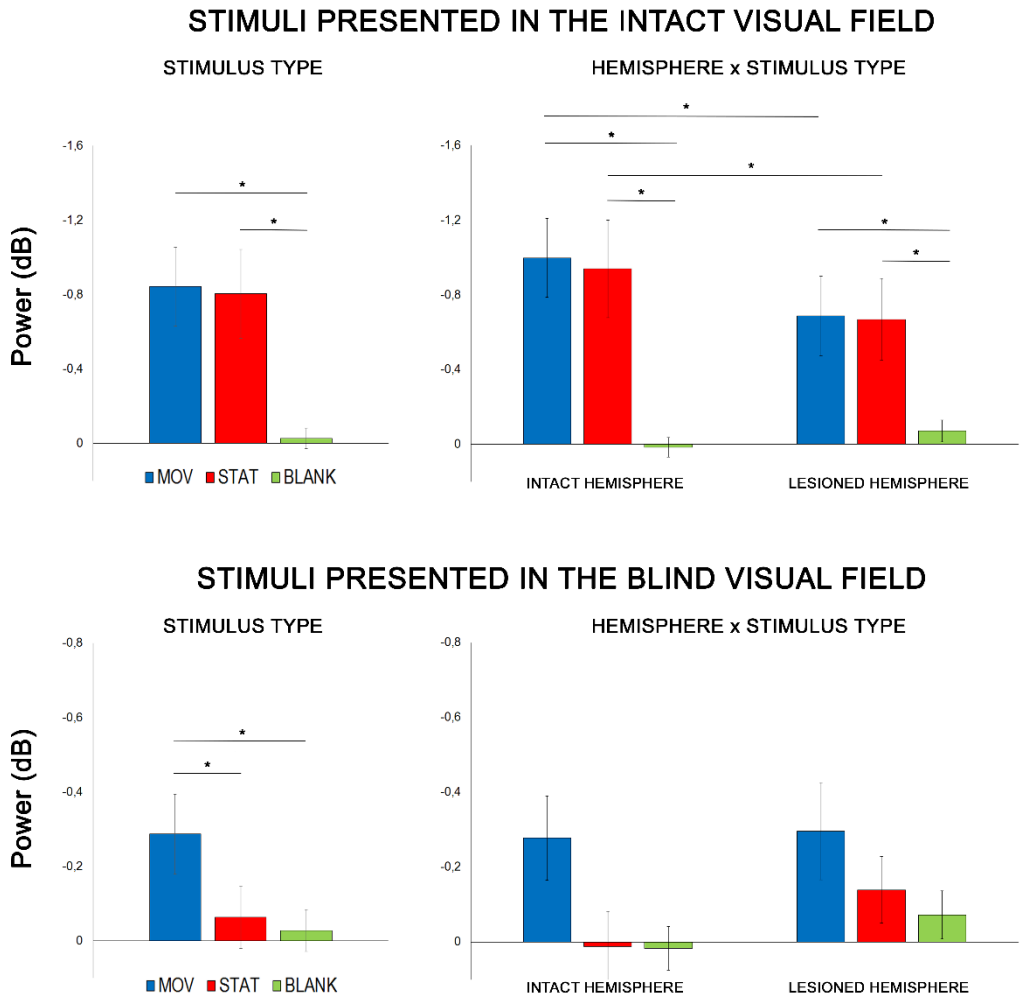

Figure 20. Event-related desynchronization (ERD) in the low-beta range (15-25 Hz) in response to stimuli presented in intact visual field (upper plots) and in the blind visual field (lower plots) averaged between 200 and 500ms post stimulus onset. Left plots show ERD responses averaged across selected electrodes of the two hemispheres (intact and lesioned), while right plots show ERD response separately for the intact and lesioned hemispheres. Blue bars always depict ERD in response to moving stimuli, red bars to static stimuli and green bars to blank condition (no stimulus).

Time-domain results

No worthwhile ERPs were elicited by stimuli presented in the blind visual field (Figure 21B and 22B). Therefore, only ERPs elicited by stimuli presented in the intact field were analyzed. The ANOVA compared the ERP response over the intact and lesioned hemispheres elicited by moving, static or blank stimulus presentations.

N1 component. The main effect of Hemisphere ($F(1,10) = 10.109$, $p = 0.009$) was significant revealing a higher N1 component in the intact hemisphere (-1.33 μV) with respect to the lesioned hemisphere (-0.81 μV). Also the main effect of Stimulus Type ($F(2,20) = 3.903$, $p = 0.037$) was significant. The post-hoc analysis revealed that both moving (-1.39 μV; $p = 0.045$) and static (-1.66 μV; $p = 0.041$) stimuli presentation elicited a significantly higher N1 component with respect to the blank condition (-0.17 μV) but no difference was shown between moving and static stimuli presentation ($p = 0.633$). The interaction between Hemisphere and Stimulus Type was not significant ($F(2,20) = 1.964$, $p = 0.166$).

P3 component. The main effect of Hemisphere ($F(1,10) = 5.072$, $p = 0.048$) was again significant revealing a higher P3 component in the intact hemisphere (1.53 μV) with respect to the lesioned hemisphere (0.51 μV). The main effect of Stimulus Type was significant ($F(2,20) = 9.826$, $p = 0.001$). Also in this case the post-hoc analysis revealed that both moving (1.37 μV; $p = 0.002$) and static (1.57 μV, $p = 0.002$) stimuli presentation elicited a higher P3 component with respect to the blank condition (0.13 μV) while no difference was shown between moving and static stimuli presentation ($p = 0.577$). The interaction between Hemisphere and Stimulus Type ($F(2,20) = 4.930$, $p = 0.018$) was significant. The post-hoc analysis revealed that, in the intact hemisphere, both moving (2.04 μV; $p = 0.001$) and static (2.42 μV; $p < 0.001$) stimuli presentation elicited a significantly higher P3 component with respect to the blank condition (0.12 μV) and no difference between them ($p = 0.372$), while no significant differences was evidenced over the lesioned hemisphere (all p-values > 0.19).

Overall, the analysis of ERP elicited by stimuli presented in the intact visual field revealed that both moving and static stimuli presentation were able to elicit a greater response with

respect to the blank condition, while no significant difference was shown between the response elicited by moving and static stimuli presentation suggesting that the two type of stimuli were comparable in terms of evoked response amplitudes.

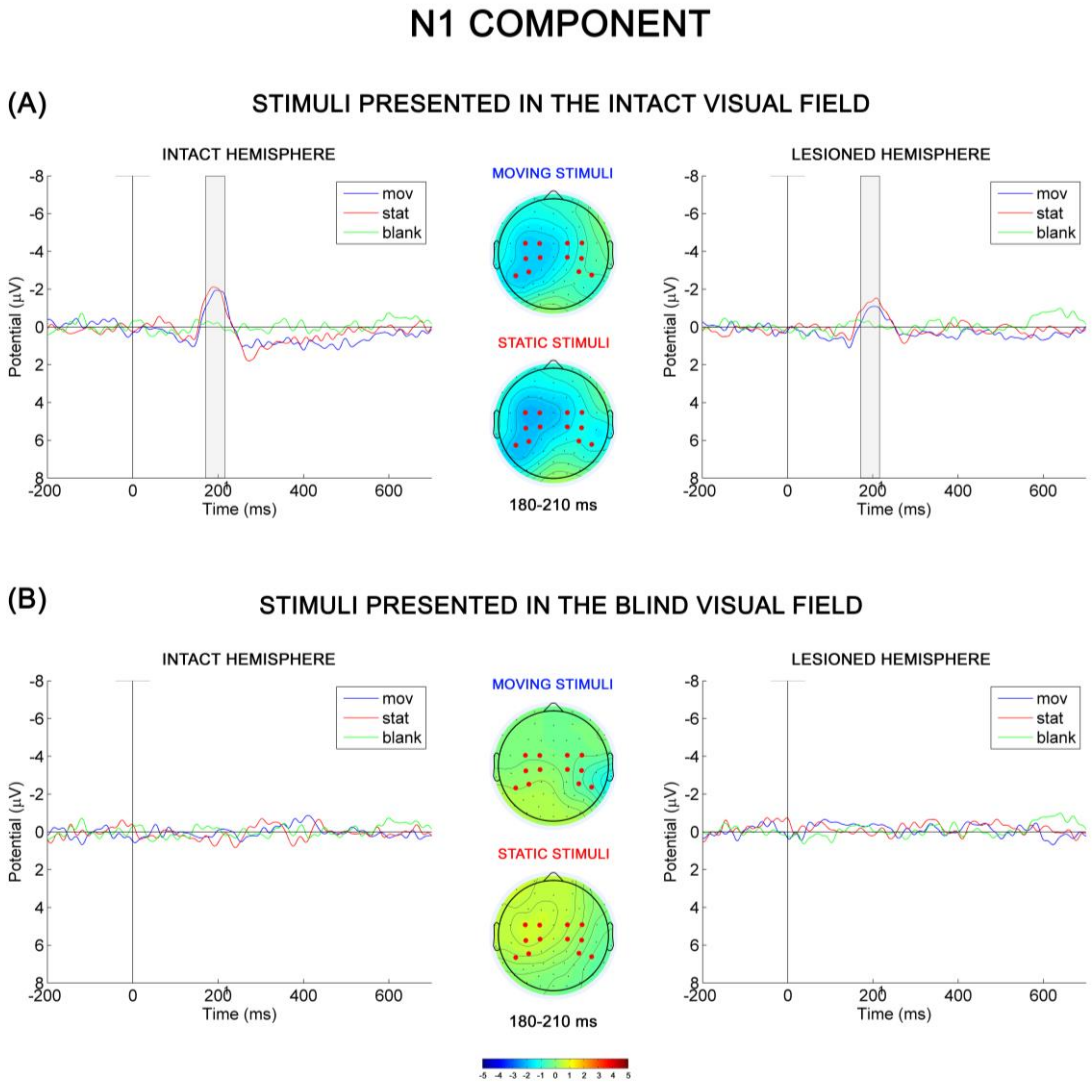

Figure 21. Event-related potentials (ERPs) elicited by the presentation of visual stimuli in the intact (A) and in the blind (B) visual field. Left and right panels represent respectively ERPs averaged across electrodes of the intact (left ROI on the corresponding topographies) and lesioned (right ROI on the corresponding topographies) hemispheres, in response to the presentation of moving stimuli (blue line), static stimuli (red line) or blank condition (green line). Topographies depict EEG activity averaged in a time window between 180 and 210ms after the presentation of moving (upper topography) or static (lower topography) stimuli in the intact (A) or blind (B) visual field.

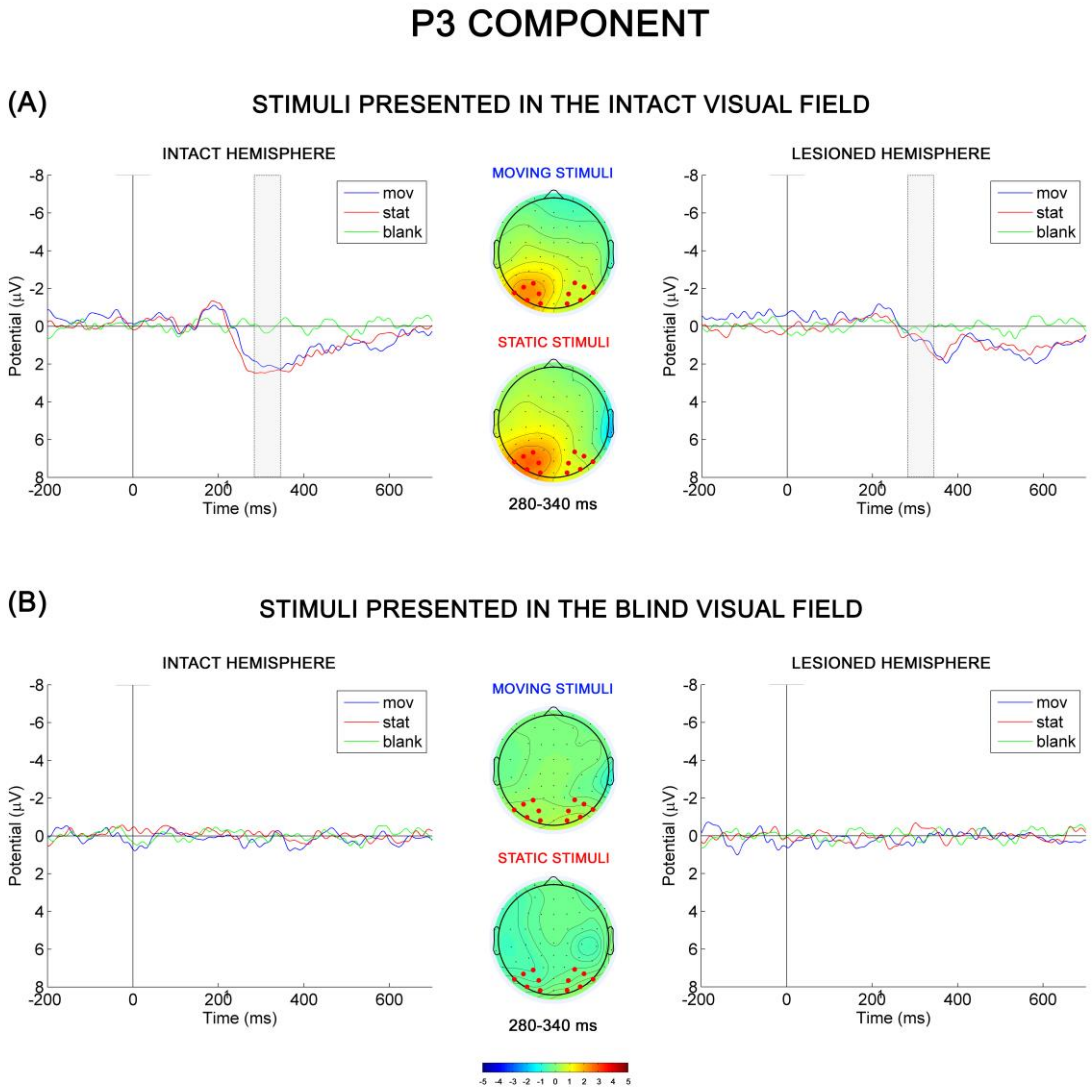

Figure 22. Event-related potentials (ERPs) elicited by the presentation of visual stimuli in the intact (A) and in the blind (B) visual field. Left and right panels represent respectively ERPs averaged across electrodes of the intact (left ROI on the corresponding topographies) and lesioned (right ROI on the corresponding topographies) hemispheres, in response to the presentation of moving stimuli (blue line), static stimuli (red line) or blank condition (green line). Topographies depict EEG activity averaged in a time window between 280 and 340ms after the presentation of moving (upper topography) or static (lower topography) stimuli in the intact (A) or blind (B) visual field.

Discussion

The present study aimed to investigate the presence of implicit visual processing in the blind visual field of a group of hemianopic patients without blindsight. The major aim was to test whether stimuli that could rely on the activity of a subcortical route bypassing the lesioned site (i.e. motion stimuli) could show evidence of a preserved processing (without stimulus awareness), as indexed by a measurable electrophysiological response. During experimental sessions, motion or static stimuli were randomly presented in the intact or blind visual field together with a control condition (i.e. blank condition) in which no stimulus was shown. Importantly, none of the patients participating to the present experiment showed above chance level performances in any of the direct forced choice tasks aimed to evaluate residual visual capacities in the blind visual field.

The analysis in the time-frequency domain, revealed, as expected, a greater ERD in the alpha (8-12 Hz) and low-beta (15-25 Hz) band when a stimulus (moving or static) was presented in the intact visual field as compared to the condition in which no stimulus was presented (blank condition). The desynchronization was mainly evident over posterior electrodes sites placed in the intact contralateral hemisphere and no significant difference in ERD amplitude was evident between the presentations of moving and static stimuli. Interestingly, an ERD in the alpha and low-beta band was also evident when moving stimuli were presented in the blind visual field and was significantly greater with respect to ERD measured during both static stimulus presentation and blank condition that did not differ each other. Also in this case ERD was mainly confined over posterior electrodes of the intact ipsilateral hemisphere. Indeed, electrophysiological activity

elicited by moving stimuli presented in the blind visual field was significantly larger over electrodes of the intact hemisphere with respect to electrodes of the lesioned hemisphere. An ERD in the alpha and low-beta band is generally thought to represent the electrophysiological correlate of an activated cortical area (Neuper & Pfurtscheller, 2001; Pfurtscheller et al., 1994). Brain regions that are active during a task usually exhibit a reduced synchronization (i.e. desynchronization), while regions that are not involved exhibit an enhanced synchronization (Pfurtscheller & Lopes Da Silva, 2004).

Moreover, desynchronization and synchronization (ERS) in the alpha band are generally observed over posterior brain regions during tasks requiring a shift of visuo-spatial attention. When covertly attending to a specific portion of space, a decrease in alpha activity is observed in cortical regions contralateral to the attended location, while an increase in alpha activity is observed in ipsilateral cortical regions. These modulations are thought to reflect the correlate of an enhanced (ERD) or a reduced (ERS) cortical readiness to respond to the spatial location (Kelly, Lalor, Reilly, & Foxe, 2006; Sauseng et al., 2005; Thut, 2006). The same holds true during task requiring attention to a specific sensory modality in which an ERS has been observed over cortical regions associated with the sensory modality to be ignored (Foxe & Snyder, 2011). Similarly, a modulations of activity in the low-beta band has also been found over posterior cortices during attentional tasks (Bauer et al., 2012; Siegel, Donner, Oostenveld, Fries, & Engel, 2008).

The significant decrease in the alpha and low-beta band associated with the presentation of a stimulus in the intact visual field shown here could thus be interpreted as the evidence of cortical activation reflecting stimulus processing or shift of visuo-spatial attention induced by stimulus appearance. A similar process was observed when stimuli were presented in the blind visual field where patients had no awareness of stimulus

presentation. However, it is interesting to point out that, when presented in the blind visual field, a significant ERD was only found in the presence of a moving stimulus while no relevant ERD has been elicited by static stimuli presentation. This result seems to suggest that even patients that do not show residual visual abilities in their blind visual field can nevertheless show an implicit visual processing of some stimulus features. The lack of a significant electrophysiological activity in response to the presentation of a static stimulus suggests that the activity would be specifically linked to the processing of motion. Even if the present data cannot account for the cortical or subcortical generators of these oscillations, one possible interpretation is that this could be the result of the involvement of the pathway connecting SC to dorsal extrastriate areas (i.e. colliculo-dorsal extrastriate). This pathway is usually spared in hemianopic patients and is also thought to play a role in the processing of motion signals given that the activity in dorsal area V5/MT partly depends on input from V1 and partly depends on input originating from the SC (Gross, 1991; Rodman et al., 1989, 1990). In addition, the relative lateralization of the electrophysiological activity over electrodes placed in the intact hemisphere suggests that the implicit visual processing of motion in the blind visual field may originate from the intact hemisphere. We could speculate that the activation of ipsilateral intact hemisphere could have been reached via interhemispheric connections between subcortical ipsilesional structures and cortical contralesional striate and extrastriate areas, similar to those observed in blindsight patients (Bridge et al., 2008; Leh et al., 2006; Tamietto et al., 2012) or could have alternatively reached contralesional cortices via intercollicular circuitry (Rushmore & Payne, 2003).

At the electrophysiological level, both the SC and MT area are known to robustly respond to transient flickering or moving stimuli (Marrocco & Li, 1977; Schneider & Kastner,

2005) while being weakly activated by stationary stimuli and changes in luminance contrast (Kastner et al., 2004; Schneider & Kastner, 2005). Conversely, both LGN and V1 are known to be sensitive to changes in luminance contrast and to show maintained responses to static stimuli (Kastner et al., 2004; McLelland, Ahmed, & Bair, 2009; McLelland, Baker, Ahmed, & Bair, 2010).

The processing of static stimuli could thus mainly require the integrity of the geniculo-striate pathway as opposed to moving stimuli that could also benefit from the activity of the SC-dorsal MT route generally spared in hemianopic patients.

The lack of a significant desynchronization in response to static stimuli presentation also cast out the possibility that the activity shown in response to moving stimuli could be explained by a simple change of luminance. Moving and static stimuli were indeed comparable both in terms of emitted light and in terms of elicited ERD magnitude when presented in the intact visual field.

The analysis in the time domain, revealed the presence of a negative (N1) and a positive (P3) component in response to the presentation of stimuli (moving or static) in the intact visual field, while no measurable event related potentials (ERPs) were evident when no stimulus was presented (blank condition). The amplitude of both N1 and P3 did not differ between the presentations of moving or static stimuli. Contrary, when stimuli were presented in the blind visual field, no measurable ERPs were elicited. The presentation of both moving and static stimuli did not evoke any measurable component neither in the intact nor in the lesioned hemisphere and was visually comparable to the activity recorded in the blank condition. This result is in line with previous findings of studies investigating the electrophysiological aspects of visual functions in hemianopic

patients without blindsight that found no evidence of activity elicited by stimuli presented in the blind visual field (Dundon et al., 2015; Grasso et al., 2016).

Methodological considerations

As previously said, the activity induced by the presentation of the moving stimuli in the blind visual field was only evident in the time-frequency domain. This result seems to suggest that the analysis in the time-frequency domain could constitute a more sensitive approach to investigate implicit visual processing. A possible explanation of the discrepancy found between the two analysis, could dwell in the possibility with time-frequency analysis to measure both the phase-locked and the not phase locked response of the EEG signal. Indeed, task-related information can be lost during ERP averaging (Mike X Cohen, 2014) since ERPs result from the alignment of the phases of ongoing oscillations (Makeig et al., 2002) and are measurable only in the case of a strictly phase locked and time-locked activity. One possibility is that the presentation of a motion stimulus in the blind visual field elicited loosely timed state changes in the oscillatory activity, mainly related to attentional mechanisms that are not shown in the time-domain but are instead still retrievable in the time frequency-domain (Michael X Cohen, 2011; Herrmann & Knight, 2001).

Conclusions

In the present study, I have shown electrophysiological evidence of implicit visual processing in the scotopic area of a group of hemianopic patients without blindsight. The

electrophysiological response to stimulus presentation was only recorded in the presence of a moving stimulus, while no measurable activity has been shown in the presence of a static stimulus. This result suggests that the implicit visual processing shown in the present study could be mainly related to the activation of spared neural connections between SC and dorsal extrastriate MT area bypassing the lesion.

3.2 Experiment 4: Early V5 processing decoupled from awareness with fast but not slow motion: TMS evidence for dynamic deployment of parallel routes depending on motion velocity

In previous experiment, I reported electrophysiological evidence of implicit preserved processing of visual stimuli presented in the blind visual field of a group of hemianopic patients without blindsight. The electrophysiological activity was shown only in response to motion stimuli while no relevant activity was recorded when static stimuli were presented. This result suggests that a lesion to the primary visual pathway would leave, at least partly, unaffected the processing of motion signals also in those patients not showing any residual visual capacity when tested with direct tasks. I hypothesized that the preserved response could be the result of the activity of subcortical direct connections between SC and dorsal MT area known to be generally preserved after lesions to primary visual pathway. Indeed the processing of motion in MT is known to be partly dependent on input from the primary visual cortex and partly dependent on input from the SC (Gross, 1991; Rodman et al., 1989, 1990). However, it is not clear whether the fast-direct input to MT via the SC can be activated by all motion stimuli or rather show a selectivity for those stimuli potentially containing a greater salience and thus requiring a faster elaboration.

In the next experiment, I will present results from a transcranial magnetic stimulation (TMS) study on healthy participants investigating the effect of motion velocity on timing of V5/MT processing. I will show that stimuli moving at fast velocities reach V5/MT at earlier latencies with respect to stimuli moving at slow velocities thus suggesting the recruitment of segregated pathways to V5/MT depending on motion velocity.

Intoduction

Perception of motion is an important characteristic of our visual system, since motion stimuli are in many cases also behaviorally relevant. One of the most prominent area in the processing of motion signals is a relatively small portion of dorsal extrastriate visual cortex, area MT/V5. In monkeys, lesions to this area lead to severe impairments in motion direction discrimination (W. T. Newsome & Pare, 1988; W. Newsome, Wurtz, Dürsteler, & Mikami, 1985) and TMS applied over this area in humans results in transient impairments of motion processing (Beckers & Hömberg, 1992; d'Alfonso et al., 2002; Hotson, Braun, Herzberg, & Boman, 1994; Sack, Kohler, Linden, Goebel, & Muckli, 2006; Walsh, Ellison, Battelli, & Cowey, 1998).

Based on hierarchical models of visual processing in primates, V5 can be considered a relatively late stage in the processing stream. After activating the retina, visual information reaches the thalamus where the magnocellular layers of LGN convey most of the motion information to primary visual cortex V1 (Felleman & Van Essen, 1991; Maunsell & Van Essen, 1983; Van Essen & Maunsell, 1983), which in turn projects to V5. This pathway is thought to support awareness of visual motion through recurrent feedback to V1 (Bullier, 2001; Lamme, 2001; Pascual-Leone & Walsh, 2001). However, this is not the only route by which motion information can reach V5. The existence of functional connections between subcortical structures such as the superior SC and PV to V5 has been widely documented in primates (Berman & Wurtz, 2010, 2011; Lyon et al., 2010; Rodman et al., 1990) and the involvement of both SC (Schneider & Kastner, 2005) and V5 (Tootell et al., 1995; Watson et al., 1993; S. Zeki et al., 1991) in the processing of motion signals suggests the existence of similar functional connections also in humans.

As previously discussed in the present thesis (see *Residual visual capacities after lesions to the primary visual pathway* in Chapter 1), this alternative pathway could mediate the presence of residual visual capacities to detect or discriminate moving stimuli after lesions to the primary visual pathway (Petra Stoerig, 2006; Lawrence Weiskrantz, 1996). However, some studies revealed that not all moving patterns elicit an above-chance level performance in these patients. In particular, a study reported that blindsight patient G.Y. with intact V5 but lesioned V1 could more easily detect or discriminate fast-moving (>6°/s) than slower moving stimuli (Barbur et al., 1993). This was interpreted as evidence of an increased recruitment of the subcortical connection bypassing V1 by fast motion. In accordance with this, another study showed a preserved early EEG response to fast motion but not slow motion when stimuli were presented in GY's blind hemifield (Ffytche et al., 1996) even if this result was challenged by similar follow-up studies in the same patient (Benson, Guo, & Hardiman, 1999; Holliday et al., 1997). Conversely, slow moving stimuli may mostly rely on the activity of the geniculo-striate pathway and consequently may need the integrity of V1. In accordance with this, a double-dissociated pattern of performance was reported in a patient with bilateral V5 lesions but intact V1, who showed higher reliability in the detection and discrimination of slow moving (<6°s) than fast moving stimuli (Hess, Baker, & Zihl, 1989; Zihl, von Cramon, & Mai, 1983). Taken together these results suggest that parallel motion input to V5 could depend on stimulus characteristics, a phenomenon that was termed dynamic parallelism (Ffytche, Guy, & Zeki, 1995; Ffytche et al., 1996).

Nonetheless, the existence of two segregated pathways that could be differentially activated by the presence of fast versus slow moving signals is still a matter of debate. To date no consistent evidence for dynamic parallelism in healthy participants has been

reached. While a study combining EEG and MEG measurements revealed earlier evoked responses to fast moving stimuli over V5 as compared to V1, and a reverse temporal pattern when slow moving stimuli were presented (Ffytche et al., 1995), a subsequent MEG study using a variety of stimulus parameters found no evidence of an early V5 response that could be explained by a direct subcortical input (Anderson, Holliday, Singh, & Harding, 1996). Likewise, while intracranial recordings from area V5A in monkeys revealed an earlier response latency to fast than slow moving stimuli (52 vs. 60ms; Kawano et al., 1994), a subsequent study on V1 lesioned macaque monkeys showed no differential latencies in area MT to slow versus fast motion (Azzopardi, Fallah, Gross, & Rodman, 2003).

In the present TMS study, I tested the hypothesis of dynamic parallelism in two groups of healthy participants by transiently interfering with V5 or V1/V2 processing, respectively. Participants were asked to judge the direction of motion of a patch of dots moving at either 23°/s (fast motion) or 4.4°/s (slow motion) while applying double-pulse TMS at different stimulus onset asynchronies (SOAs). In addition to assessing the TMS-induced objective performance changes, participants were also asked to provide a trial by trial rating of their confidence in perceiving the motion stimuli (awareness) in order to examine possible dissociations between TMS interference with objective and subjective measures. In case of dynamic parallelism for motion processing, one would expect TMS to differentially interfere with fast versus slow motion processing when V5 or V1/V2 is being stimulated. More specifically, one would expect V5-TMS interference with objective measures to occur at earlier latencies or being stronger for fast than slow moving stimuli, suggesting the involvement of a more direct pathway to V5 for the processing of fast motion (i.e. colliculo-extrastriate). In addition, one may expect these V5-TMS effects

on motion processing to be more decoupled from subjective awareness (confidence ratings) in case of fast than slow moving stimuli, suggesting that fast motion processing relies less on primary visual cortex function. The reverse could occur for V1/V2-TMS, which may conversely show an earlier time window or stronger TMS interference with slow than fast moving stimuli, and greater coupling of these V1/V2-TMS effects to subjective awareness of these changes, given the crucial role played by V1/V2 in visual awareness (e.g. Silvanto et al., 2005) and the finding of slow motion perception mostly relying on V1/V2 integrity (Hess et al., 1989; Zihl et al., 1983).

Materials and methods

Participants

Twelve participants took part in Experiment 1 (two males; mean age: 25.1, SD: 3.9), and twelve participants in Experiment 2 (three males; mean age 25.1, SD: 3.8), nine of whom participated in both experiments. The selection of participants to Experiment 1 or 2 was based on consistent perception of moving (Experiment 1) or static (Experiment 2) phosphenes (see *Transcranial Magnetic Stimulation and Functional Localization* section for further details). All participants were naïve to the purpose of the study, were right-handed (apart from one left-hander participant who took part in both experiments) and had normal or corrected to normal vision. No participant presented with contraindications for TMS (Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009), nor with a history of neurological or psychiatric disorders. Before taking part in

the experiment, all participants provided written informed consent. The study was approved by the ethics committee of the College of Science and Engineering, University of Glasgow.

Experimental design

Each experiment consisted of three sessions conducted on three separate days (see Figure 23A). The first day served to determine TMS location and intensity per participant (see below, *Transcranial Magnetic Stimulation and Functional Localization*) and to equate task complexity across participants and conditions for the following sessions (see *Titration*). The experimental sessions were performed on the second and third day. For those participants who took part in both experiment 1 and 2, order of experiments was randomized (5 participants starting with one experiment and 4 with the other).

Transcranial Magnetic Stimulation and Functional Localization

TMS was administered using a Magstim Rapid2 Plus1 stimulator and a figure-of-eight coil. Double pulse TMS with an inter-pulse interval of 26.7ms was used both during the functional localization phase and during the experimental sessions.

Experiment 1 examined the effect of TMS over motion area V5. I chose to stimulate left V5 in all participants based on previous TMS studies showing more interference with motion processing after left than right hemispheric interventions (Anand, Olson, & Hotson, 1998; Beckers & Hömberg, 1992). Left V5 was localized individually at day 1 by establishing for each participant the site over which TMS most strongly induced the perception of moving phosphenes. To this end, a 6 x 6 cm grid of thirty-six points centered

3 cm above and 3 cm to the left of the inion was firstly drew on an elastic cap. Starting 3 cm dorsal and 4 cm lateral from the inion, the coil was then moved across the grid in 1 cm steps in order to find the site from which most reliable moving phosphenes were induced. On average, this was 3.3 cm above and 2.6 cm lateral from the inion (center of coil).

Experiment 2 examined the effects on TMS over early visual areas (V1/V2). In analogy to experiment 1, V1/V2 was localized at day 1 by establishing for each participants the site over which TMS induced the perception of static phosphenes covering the center of the visual field. To this end, a 4 x 4 cm grid of sixteen points centered 2 cm above the inion was firstly drew on an elastic cap. Starting from 2 cm above the inion, the coil was then moved across the grid in 1 cm steps in order to find the site from which most reliable static phosphenes were induced. On average, this was 2.6 cm above the inion (coil center).

For both V5 and V1/V2 localization, TMS intensity was initially set to 50% of maximum stimulator output (MSO) and then gradually increased or decreased following a staircase procedure based on the participants' report of phosphenes. Nine participants perceived both moving and static phosphenes, and therefore participated in both experiments. Six participants perceived either moving (n=3) or static phosphenes (n=3) and therefore took part in experiment 1 or 2 only. Coil orientation was individually chosen based on each participant's most consistent reports of phosphenes. This resulted in the coil handle oriented upward for both V5 and V1 stimulation in the majority of participants.

During the experimental sessions, the stimulator output was set to 10% below the individual defined phosphene threshold (PT) in order to avoid phosphene perception. The average stimulator output used was 36% MSO for V5 stimulation and 40% MSO for V1 stimulation.

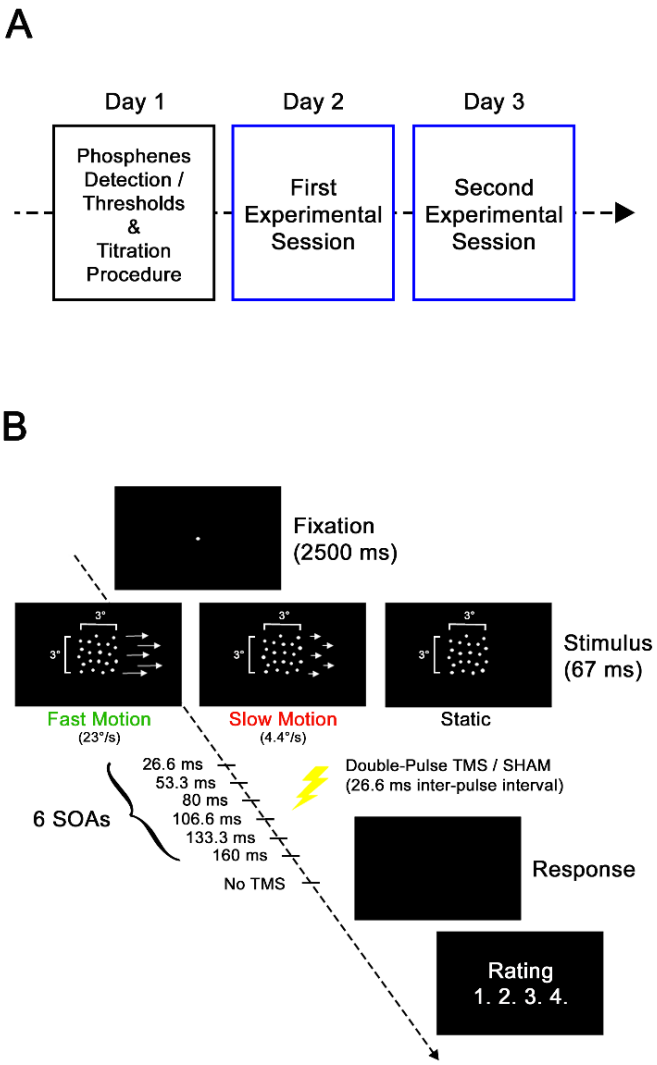

Figure 23. Experimental design and stimuli employed in two TMS experiments targeting area V5 or V1/V2 respectively (Experiment 1 and 2), while healthy participants had to discriminate direction of fast vs. slow moving visual stimuli. (A) Experimental design: Each experiment consisted of three sessions. Session 1 (at day 1) served to identify areas V5 or V1/V2 by induction of moving vs. static TMS phosphenes respectively, and to equate task complexity across conditions (fast motion and slow motion) for the following sessions. Session 2 and 3 served for data acquisition to examine TMS interference with fast vs slow visual motion processing (TMS intensity < phosphene threshold, trials equally split across day 2 and 3). (B) Schematic representation of a trial. Each trial began with a fixation cross (2500ms) followed by the presentation of a stimulus (fast motion, slow motion or static, 67ms, 5 frames). Real or SHAM double pulse TMS was then applied at one of six possible stimulus onset asynchronies (SOAs) or, alternatively, no TMS was delivered. Participants were asked to report the perceived direction of motion (by 2AFC) and to rate their awareness of motion on a four point scale (1 - "I did not perceive any motion at all", 2 - "I might have perceived motion but I did not have any idea of its direction", 3 - "I did not actually see the direction of the motion, but I may have been able to sense or guess its direction", 4 - "I saw the direction of the motion").

Coherent motion stimuli, task and Apparatus

Eighty white dots (dot size: 3 x 3 pixels) were presented within an area of 3° x 3° of visual angle (squared) at the center of a black CRT monitor (19'', refresh rate: 75 Hz, 1280 x 1024 pixel resolution). A percentage of dots could move either rightward or leftward (coherent motion) over five frames (66.7ms) at either 23°/s (fast motion) or 4.4°/s (slow motion), while the remaining percentage of dots moved in a random manner. In addition, during the experimental sessions static stimuli were also presented (see Figure 23B). The experiment was conducted in a dimly lit and sound controlled room with participants seated with their head placed on a chinrest at a viewing distance of 57 cm from the monitor. A computer running E-Prime software (Version 2.0) controlled stimulus presentation and manual response collection.

Titration

In both experiments, a titration curve was established at day 1 per motion velocity condition to individually adjust stimulus properties (i.e. motion coherence levels) for equating task difficulty between fast and slow motion stimuli for the subsequent experimental sessions.

Each trial began with a fixation cross (2500ms) followed by the presentation of a left- or rightward moving stimulus (either fast or slow motion; see *Coherent motion stimuli, task and Apparatus* section above). After the presentation of the motion stimulus, participants were asked to indicate the perceived direction of motion (by a 2AFC), or to guess if not perceived. Stimuli were randomly presented at one of 12 coherence levels (ranging from a minimum of 8% to a maximum of 62% of dots moving coherently). Participants

performed three blocks of titration, each composed of 384 trials equally distributed across the two velocity conditions (fast motion, slow motion) and the twelve levels of coherence. The coherence level at which each participant performed at an accuracy of 75-85% (average over the three titration blocks) was then selected for the experimental sessions. On average, stimuli were presented at 23% of coherence for fast motion and 35% for slow motion.

Experimental Session

For each participant, slow motion and fast motion stimuli were set at the coherence rate established during titration (see *Titration* section above). In addition, static catch stimuli (80 white dots presented centrally for 66.7ms within 3° x 3° of visual angle on black background) were included in the experimental sessions (see Figure 23B).

In order to control for eye blinks during stimulus presentation, two electrodes were placed above and below the participants' left eye and EOG activity was continuously recorded. Before the beginning of each experimental session, the location and the intensity of TMS was checked to confirm the validity of the parameters determined in the previous session (see *Transcranial Magnetic Stimulation and Functional Localization* section above).

Each trial started with a fixation cross (2500ms) followed by the presentation of a stimulus (66.7ms; fast motion, slow motion or static). Double-pulse TMS with an inter-pulse interval of 26.7ms was then delivered at six different delays from motion stimulus onset (SOAs: 26.7, 53.3, 80, 106.6, 133.3 and 160 ms) in either an active TMS block or a sham TMS block (see Figure 23B), the latter to control for a potential influence of the TMS click on task performance. As an addition control condition, no TMS trials were

also included. Participants were first asked to judge whether they perceived a rightward or a leftward motion and then to rate their perceptual awareness on the same four-points rating scale previously used by Koivisto et al. (2010): 1) “I did not perceive any motion at all”, 2) “I might have perceived motion but I did not have any idea of its direction”, 3) “I did not actually see the direction of the motion, but I may have been able to sense or guess its direction”, 4) “I saw the direction of the motion”. When a static stimulus was perceived, participants were instructed to guess in response to the first prompt and then select the first point of the perceptual awareness rating scale (“I did not perceive any motion at all”).

A total of 24 stimuli were presented for each SOA (and no TMS) and for each type of stimulus (fast motion, slow motion and static) administered across 12 blocks. On six blocks, participants received TMS while on the remaining six blocks a control SHAM stimulation was administered in which the coil was positioned perpendicular to the scalp. The order of TMS and SHAM blocks were pseudo-randomized across participants within experimental sessions and half of the blocks (n=6) were administered during the first experimental session (day 2), while the other half (n=6) were administered during the second experimental session (day 3).

Analysis

Only eye blink free trials (as assessed by EOG in a post-stimulus time window ranging from 0-100ms from stimulus onset) and trials with reaction times < 3sd from the mean were considered. Inverse efficiency scores (IES = mean reaction times/proportion of correct responses) were computed as a measure of objective performance, while the mean

of rating scale scores (RSS = sum of rating scores/number of trials) was used as a measure of subjective performance. These measures were analyzed per experiment using 2 x 2 x 6 repeated-measure Analyses of Variance (ANOVAs) with the within-subject factors Stimulation (TMS, SHAM), Motion Velocity (fast motion, slow motion) and TMS SOA (26.7, 53.3, 80, 106.6, 133.3 and 160 ms). When appropriate, main effects and interactions were followed up by simple tests.

Further tests included analysis of SHAM trials and static trials for control purposes using 2 x 6 ANOVAs with the within-subject factors Motion Velocity (fast motion, slow motion) and TMS SOA (6 levels). No TMS trials were analyzed with a two-tailed t-test comparing performances between fast and slow motion. Correlation analyses (using Spearman rank correlations) were performed to examine possible relationships between the effects of TMS on objective and subjective motion perception (or the absence thereof).

Results

Experiment 1 (V5-TMS)

Figure 24 illustrates task performance in terms of both the objective measure (2AFC response, Figure 24A) and subjective measures (confidence ratings, Figure 24B) and for both the fast and slow motion stimuli (left vs. right panels) under V5-TMS (colored lines) as compared to SHAM (black line).

Objective Measures

Regarding objective performance (Figure 24A), the 2x2x6 ANOVA revealed a significant Stimulation x Velocity x SOA interactions ($F(5,55) = 2.967$, $p = 0.019$), suggesting that V5-TMS had differential effects on motion processing over SOAs depending on motion velocity (left vs. right panels). I therefore conducted two separate 2x6 ANOVAs, one per motion velocity. For fast motion trials (Figure 24A, left panel), a significant Stimulation x SOA interaction ($F(5,55) = 2.826$, $p = 0.024$) was found. This was explained by significant TMS effects (TMS vs. SHAM) at the 2nd, 4th and 6th SOA, where TMS impaired motion detection relative to SHAM (2nd SOA: 1003.96 vs 898.27ms; $t(11) = 2.402$, $p = 0.035$, 4th SOA: 895.73 vs, 805.15ms; $t(11) = 2.086$, $p = 0.061$; 6th SOA: 805.77 vs. 691.54ms; $t(11) = 2.739$, $p = 0.019$). Importantly, this effect was not driven by outliers, as TMS interference relative to SHAM was observed in the majority of participants (see inset in Figure 24A, left panel illustrating single subject data for 2nd SOA). The same 2x6 ANOVA on slow motion trials (Figure 24A, right panel) also revealed a significant Stimulation x SOA interaction ($F(5,55) = 2.723$, $p = 0.028$) which however was explained by a significant TMS effect (TMS vs. SHAM) at the 3rd SOA only, where TMS impaired performance relative to SHAM (883.85 vs. 783.54ms; $t(11) = 3.036$, $p = 0.011$). Again, TMS interference relative to SHAM was observed in the majority of participants (see inset in Figure 24A, right panel for individual data). In addition, the overall 2x2x6 ANOVA revealed a significant main effect of SOA ($F(5,55) = 12.073$, $p < 0.001$, linear decrease of IES over time) and a significant Stimulation x SOA interaction ($F(5,55) = 2.522$, $p < 0.039$) that was explained by a significant TMS effect over the 3rd SOA (916.42 vs, 817.87ms; $t(11) = 2.212$, $p = 0.049$) when both velocities are collapsed.

To rule out that differences in performance between the two motion velocities may have been driven by differences in task complexity, a 2 x 6 ANOVA on SHAM block trials only, with Motion Velocity and SOA as within subject factors was also run. The main effect of Velocity ($F(1,11) = 0.070$, $p = 0.796$) and the interaction Velocity x SOA ($F(5,55) = 0.675$, $p = 0.644$) were both far from significant, whereas the main effect of SOA was again significant ($F(5,55) = 9.061$, $p < 0.001$). No difference between the two velocities was also evidenced on no TMS trials ($t(11) = -1.356$, $p = 0.202$). Overall, this therefore confirms that participants' performances for the two types of stimuli were equated, as intended by the pre-experimental titration session.

To examine whether TMS over V5 selectively disrupted motion processing, or interfered with visual processing in general, I also analyzed performance on the trials with static stimuli using a 2 x 6 ANOVA with Stimulation and SOA as within subject factors. The main effect of Stimulation, SOA and the interaction Stimulation x SOA were all far from significance (all *p-values* > 0.30) suggesting that TMS over V5 did interfere with motion processing, without affecting visual processing in general (in contrast to V1/V2-TMS, see below).

Overall, present data set indicates that V5-TMS interferes with motion processing at differential time points after motion onset, depending on velocity of motion, with fast motion being processed around 30ms earlier than slow motion (50 vs 80ms post-motion onset).

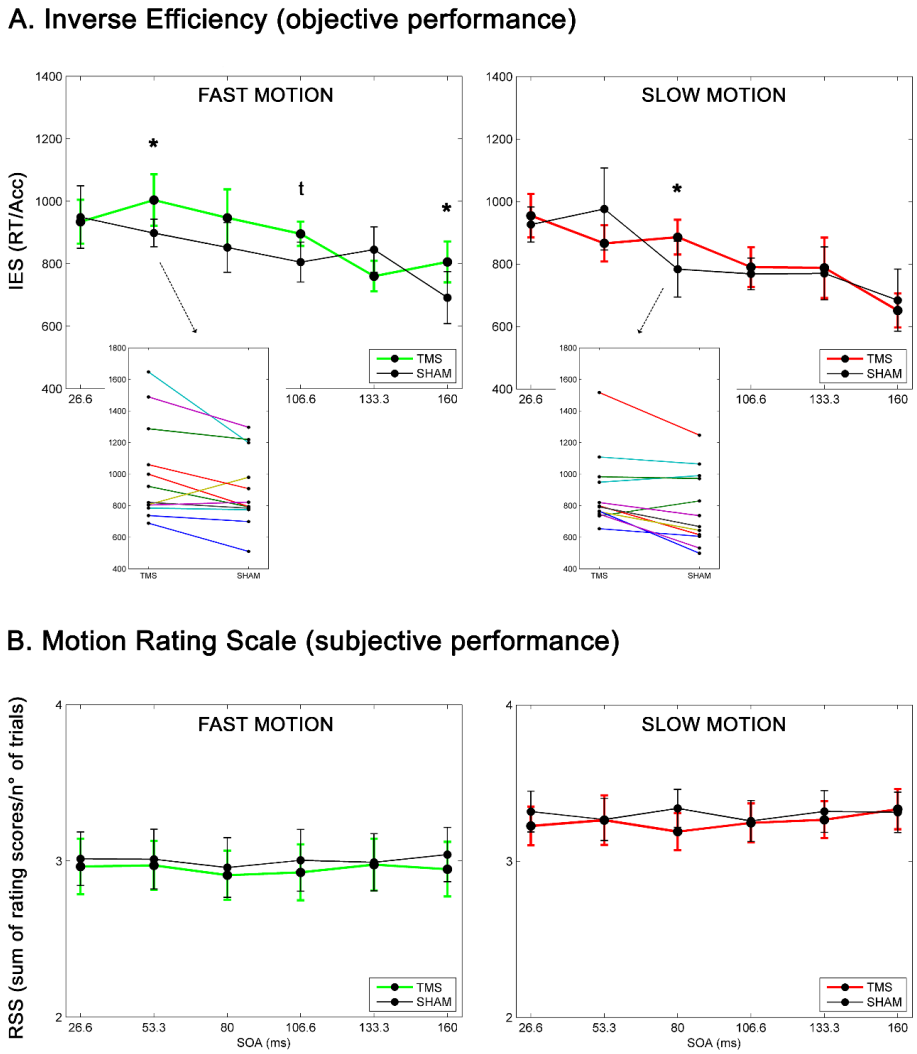

Figure 24. Interference of V5-TMS (Experiment 1) with objective and subjective motion perception. A: Objective performance (Inverse Efficiency Scores, IES) and **B:** Subjective performance (motion Rating Scale Scores, RSS) during TMS (colored lines) versus SHAM (black lines) at each SOA for fast motion (left panel) and slow motion (right panel). Error bars represent 95% confidence interval corrected for a within subjects design (Cousineau, 2005). Note that V5-TMS interfered with fast vs. slow motion at an earlier (2^{nd}) vs. later (3^{rd}) SOA for objective performance (in A). Insets on the upper panels represent single participants' trends in TMS and SHAM blocks over the 2^{nd} SOA for fast motion (left inset) and 3^{rd} SOA for slow motion (right inset).

Subjective Measures

The analysis of subjective performance (Figure 24B) using the 2 x 2 x 6 ANOVA with Stimulation, Velocity and SOA as within subject factors revealed a main effect of

Velocity $F(1,11) = 4.927$, $p = 0.048$). On average, participants assigned lower confidence rating scores to perception of fast motion stimuli (mean = 2.97) than to slow motion stimuli (mean = 3.27). No other main effects (all *p-values* > 0.18) or interactions were significant (all *p-values* > 0.40).

Correlations between Objective and Subjective Measures

To investigate the relationship between objective and subjective measures, I examined correlations between SHAM normalized measures of objective effects on perception (i.e. IES on TMS blocks – IES on SHAM blocks) (Figure 25A) and SHAM normalized measures of subjective changes (i.e. RSS on TMS blocks – RSS on SHAM blocks) (Figure 25B) across participants on SOAs in which behavioral performances were found to be significantly affected by TMS (i.e. the 2nd, 4th and 6th SOA of the fast motion stimuli and the 3rd SOA of the slow motion stimuli). The correlation results are illustrated in Figure 25C. While in the fast motion trials, the behavioral performance decrease did not significantly correlate with a decrease in subjective measures at any of the relevant SOAs (2nd SOA: Spearman $r(10) = 0.133$, $p = 0.681$; 4th SOA: $r(10) = -0.237$, $p = 0.457$; 6th SOA: $r(10)=0.360$, $p = 0.249$) (see Figure 25C, left panel for 2nd SOA), a significant correlation was found on the 3rd SOA of slow motion trials (Spearman $r(10) = -0.648$, $p = 0.022$) (see Figure 25C, right panel). Therefore, while objective measures of disrupted fast motion perception by V5-TMS were decoupled from subjective measures (changes in the absence of awareness), objective and subjective measures correlated in regards to V5-TMS disrupted slow motion perception (the more TMS interfered with objective performance, the lower was the confidence ratings).

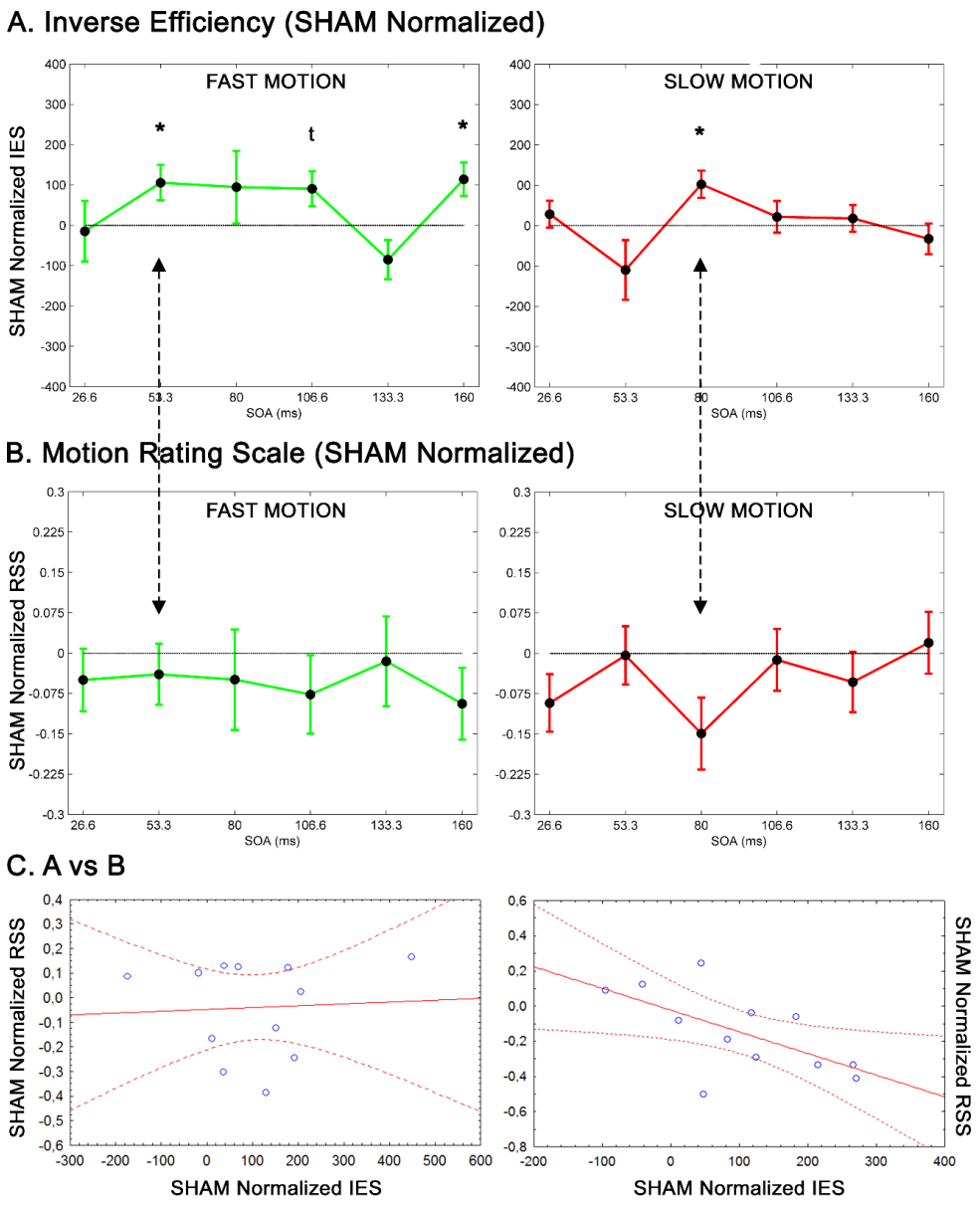

Figure 25. Relationship between interference of V5-TMS (Experiment 1) with objective vs. subjective performance (SHAM-normalized). A: SHAM normalized performance (i.e. TMS–SHAM) for objective and B: subjective measures in fast motion (left panel) and slow motion trials (right panel). C: Correlation scatterplots (95% confidence intervals) between SHAM normalized objective and subjective performances (A. vs B.) on the 2nd SOA for fast motion (left inset) and the 3rd SOA for slow motion (right inset).

Experiment 2 (V1/V2-TMS)

Figure 26 illustrates task performance in terms of both the objective measure (2AFC response, Figure 26A) and subjective measures (confidence ratings, Figure 26B) and for both the fast and slow motion stimuli (left vs. right panels) under V1/V2-TMS (colored lines) as compared to SHAM (black line).

Objective Measures

Analysis of the objective performance measures (Figure 26A) made evident a significant main effect of Stimulation ($F(1,11) = 6.342$, $p = 0.028$) revealing that V1/V2-TMS induced a general decrease of performance over all velocities and all SOAs with respect to SHAM stimulation (981.59 vs. 917.32ms), which was independent of SOA. In accordance with this, no significant interactions were also found between Stimulation x SOA ($F(5,55) = 0.487$, p=0.785), Stimulation x Velocity ($F(1,11) = 3.483$ p=0.09) and Stimulation x Velocity x SOA ($F(5,55) = 1,496$, p=0.206). Also a significant main effect of SOA was found ($F(5,55) = 5.538$, $p < 0.001$) explained by a linear decrease on IES measures from earlier to later SOAs, which was independent of Stimulation (no interaction Stimulation and SOA), replicating the SOA effect found in Experiment 1 (Figure 24A) which is likely driven by an unspecific effect of the TMS click on performance. No other main effects (all *p-values* > 0.21) or interactions were significant (all *p-values* > 0.28). To control for possible differences in performance between the two velocities due to differences in task complexity, a 2 x 6 ANOVA with Velocity and SOA was again conducted on SHAM trials only. The main effect of Velocity ($F(1,11) = 0.147$, $p = 0.708$) and the interaction Velocity x SOA ($F(5,55) = 0.938$, $p = 0.464$) were both far

from significant, whereas the main effect of SOA was again significant ($F(5,55) = 2.821$, $p = 0.024$). No difference between the two velocities was also evidenced on no TMS trials (t(11)) = -1.208, p = 0.252) confirming that performances in processing the two type of stimuli in the absence of TMS were equated as intended. To investigate whether TMS had interfered with motion processing, or affected visual processing in general, an additional 2 x 6 ANOVA with Stimulation and SOA as within subject factors was conducted on static trials. The main effect of Stimulation was significant ($F(1,11) = 5.091$, $p = 0.045$), suggesting that TMS over V1 had interfered also with the processing of static stimuli (TMS vs. SHAM: 583.48 vs. 532.89ms). The main effect of SOA was also significant ($F(5,55) = 17.078$, $p < 0.001$) explained by a linear decrease of IES measures from earlier to later SOAs, while the Stimulation x SOA interaction was not significant ($F(5,55) = 0.690$, $p = 0.633$).

Overall, this indicates that while V5-TMS had interfered with motion processing at specific time points, V1/V2-TMS interfered with general visual processing in a much larger time window after stimulus onset (~27-160ms). As a consequence, inferences on the implication of V1/V2-TMS in motion processing are limited with present data set.

Subjective Measures

The 2 x 2 x 6 ANOVA with Stimulation, Velocity and SOA as within subject factors was also conducted on RSS measures (see Figure 26B). A slight trend toward a significant main effect of Velocity ($F(1,11) = 3.366$, $p = 0.093$) and SOA ($F(5,55) = 2.211$, $p = 0.066$) were evidenced. No other significant main effects (all *p-values* > 0.25) or interactions were found (all *p-values* > 0.18).

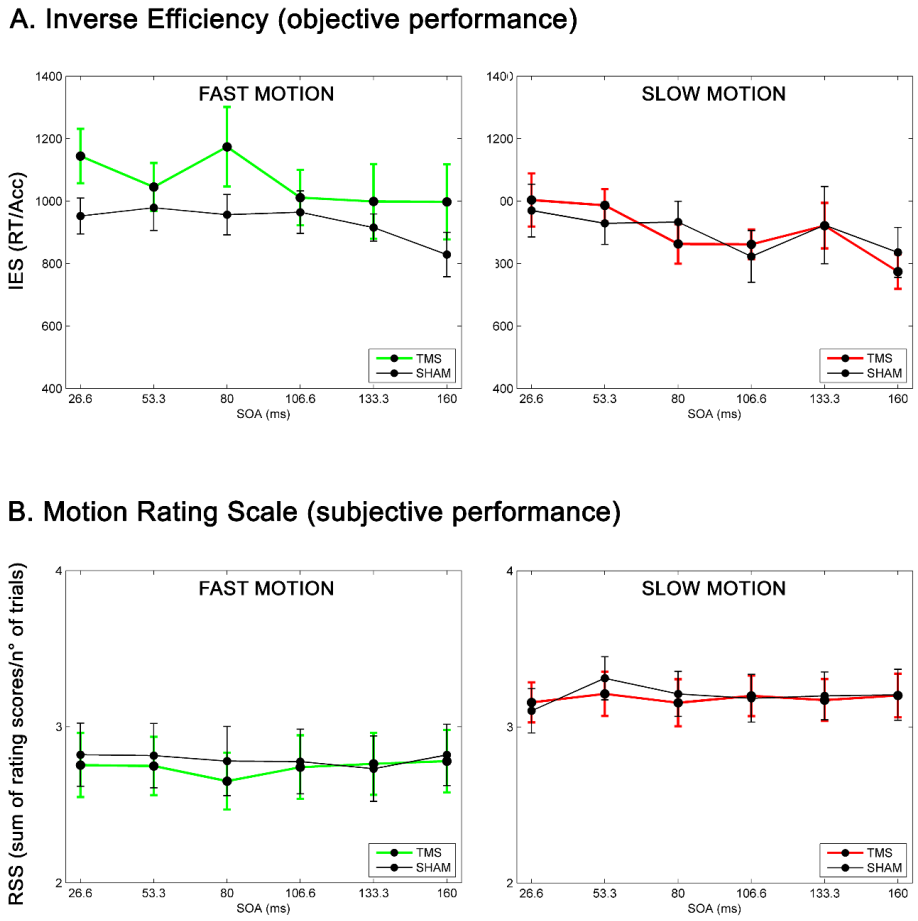

Figure 26. Interference of V1/V2-TMS (Experiment 2) with objective and subjective motion perception. A: Objective performance (Inverse Efficiency Scores, IES) and B: Subjective performance (motion Rating Scale Scores, RSS) during TMS (colored lines) versus SHAM (black lines) at each SOA for fast motion (left panel) and slow motion (right panel). Error bars represent 95% confidence interval corrected for a within subjects design (Cousineau, 2005).

Correlations between Objective and Subjective Measures

Again, correlations between SHAM normalized measures of objective effects on perception (i.e. IES on TMS blocks – IES on SHAM blocks) (Figure 27A) and SHAM normalized measures of subjective changes (i.e. RSS on TMS blocks – RSS on SHAM blocks) (Figure 27B) were examined. Because there was no effect of SOA but V1/V2-TMS tended to disrupt performance over all SOAs relative to SHAM, I correlated objective and subjective measures collapsed across SOAs. The analysis did not reveal any

significant correlation between the two measures neither for fast motion stimuli (Spearman: r (10) = -0.426, p = 0.167) (Figure 27C, left panel), nor for slow motion (Spearman: r (10) = -0.055, p = 0.862) (Figure 27C, right panel).

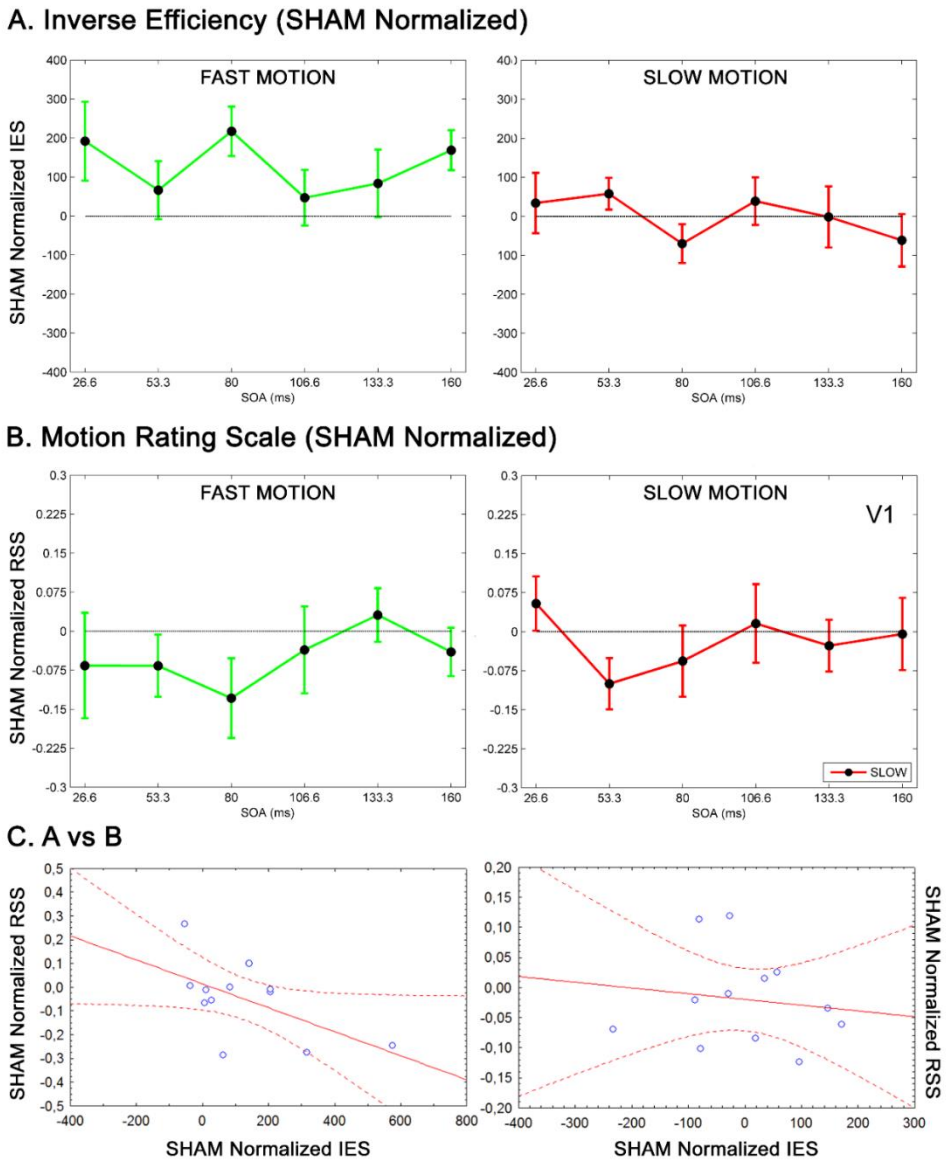

Figure 27. Relationship between interference of V1/V2-TMS (Experiment 2) with objective vs. subjective performance (SHAM-normalized). A: SHAM normalized performance (i.e. TMS–SHAM) for objective and B: subjective measures in fast motion (left panel) and slow motion trials (right panel). Note that V1/V2-TMS tended to interfere with motion processing across all SOAs in fast motion trials (but less so with slow motion stimuli) C: Correlation scatterplots (95% confidence intervals) between SHAM normalized objective and subjective performances (A. vs B.) for fast motion (left inset) and slow motion (right inset) collapsed across SOAs.

Discussion

In the present study, I used TMS in a group of healthy participants to test the hypothesis of dynamic parallelism which posits that fast parallel input to V5 by-passing V1 depends on stimulus characteristics (Ffytche et al., 1995, 1996). To this end, I interfered with V5- or V1/V2-processing in two separate TMS-experiments (targeting V5 or V1/V2 respectively) while participants performed a motion discrimination task on fast (23°/s) or slow (4.4°/s) moving stimuli. Altogether, the present results are in support of dynamic parallelism for motion processing. The results are discussed separately for each experiment below, alongside methodological considerations.

Evidence for segregated motion input into V5 as a function of motion velocity

Results from the present experiment revealed that fast and slow moving stimuli show different timing in regards to processing by V5. When interfering with V5 by TMS, an early (~50ms) decrease of 2AFC performance when fast moving stimuli were processed and a later decrease (~80ms) with slow moving stimuli was found. No interference with the processing of static stimuli was found by V5-TMS in any of the tested SOAs, confirming the role of V5 for the processing of motion signals (Beckers & Hömberg, 1992; d'Alfonso et al., 2002; Hotson et al., 1994; Sack et al., 2006; Walsh et al., 1998). Interestingly, the early V5-TMS induced decrease of 2AFC performance in the fast motion trials did not correlate with a change in motion awareness as revealed by subjective motion rating scales, while the later decrease in the slow motion trials was significantly correlated with a change in motion awareness. These results suggest that fast

moving stimuli could reach V5 through a more direct pathway than slow moving stimuli, given the time difference in V5-TMS interference (~30ms) found between the two conditions. The latencies of arrival to V5 area found in the present study also match previous electrophysiological findings evidencing that fast motion elicit an early component originating in V5 with an onset at approximately 40ms and peaking at 70ms, while slow motion elicit a component with an onset of approximately 60ms and peaking at 100ms (Pitzalis, Strappini, de Gasperis, Bultrini, & Di Russo, 2013). One possibility is that fast motion information is mainly conveyed the direct route connecting the SC to V5 bypassing V1 (i.e. a colliculo-dorsal extrastriate route). In monkey, the existence of a functional connection between SC and V5 for motion processing has been widely documented (Berman & Wurtz, 2010, 2011; Lyon et al., 2010; Rodman et al., 1990). In humans, a similar connection has also been suggested, given that both SC (Schneider & Kastner, 2005) and V5 (Tootell et al., 1995; Watson et al., 1993; S. Zeki et al., 1991) are known to play a role in the processing of motion signals. Furthermore, a relative specialization of SC to respond to fast moving stimuli has been reported (Tohmi, Meguro, Tsukano, Hishida, & Shibuki, 2014; Waleszczyk, Wang, Benedek, Burke, & Dreher, 2004; Wallace, McHaffie, & Stein, 1997) and an above-chance level performance in the detection or discrimination of moving stimuli in the scotopic area (despite absence of awareness) has been documented specifically for fast moving stimuli after lesion to V1 (Barbur et al., 1993), which lends support to the notion that direct pathways may be selectively involved in the processing of fast motion patterns. Conversely, slow moving stimuli may reach V5 only after processing in V1 (i.e. implicating a geniculo-striate route) as also suggested by the preserved ability to perceive slow motion after bilateral V5 lesions (Hess et al., 1989; Zihl et al., 1983). The present finding of a dissociation between

fast and slow moving stimuli with respect to the correlation between TMS-interference with objective and subjective measures of motion processing is providing further support to these notions. The fact that the early TMS-interference with fast motion processing did not correlate with a change in motion awareness is indicative of a decoupling between objective and subjective analysis of fast motion signals that resemble the decoupling shown in blindsight patients' performances on motion detection or discrimination tasks (Riddoch, 1917; L. Weiskrantz, 1986), while the presence of such a correlation for slow moving stimuli suggests coupling to awareness and provides further support for V1 involvement with this type of motion stimulus.

Altogether, the present results are in line with the idea that collicolo-extrastriate and geniculo-striate pathways are selectively activated by different stimulus velocities, corroborating the view of a dynamic parallelism in the processing of motion signals (Ffytche et al., 1995, 1996). In this view, fast moving stimuli primarily rely on the activation of a direct route to V5, and the processing of stimuli through this route is decoupled to some extent from their conscious experience, suggesting that this pathway is sufficient to implement implicit sensorimotor transformations necessary to quickly respond to the presence of a moving target, but not to provide a complete analysis, including awareness of it. The existence of a faster pathway specialized for the analysis of fast moving stimuli also makes sense in the perspective of an evolutionary advantage. Fast moving stimuli constitute more dangerous events and consequently require the implementation of faster motor responses occurring before or even in the absence of awareness. This is less important for slow moving stimuli that may reach V5 through a slower and less direct pathway, which preserves the coupling between objective and subjective experience of motion and allows for a more in depths analysis.

Interestingly, the processing of fast moving stimuli by V5-TMS was not influenced only at the second SOA (i.e. 53.3ms). A decrease of performance was also evidenced at the third and fourth SOAs (i.e. 79.8ms and 106.6ms) suggesting a relatively long lasting involvement of V5 in the processing of fast motion. This was not true for slow moving stimuli that conversely showed a more time-restricted decrement of performance over the third SOA (i.e. 79.8sm). Finally, another decrease of performance at the latest SOA (i.e. 160ms) was also evidenced in the fast motion trials. The long latency of occurrence suggests that this could represents feedback signals from higher frontal regions such as frontal eye fields and parietal cortex that are known to exert a top-down control in visual processing (Foxe & Simpson, 2002; Laycock, Crewther, Fitzgerald, & Crewther, 2007; Ruff et al., 2006; Silvanto, Lavie, & Walsh, 2006), albeit I acknowledge the speculative nature of this interpretation. A similar decrease should also be expected for slow motion trials. However, if we consider a constant time lag between the processing of the two velocities, this should be expected in a time window beyond the SOAs here considered (i.e. ~190ms).

No selective interference of V1/V2-TMS with motion processing

When TMS was applied over V1/V2, an unspecific decrease of performance irrespective of stimulus velocity and SOAs was found. One possibility is that, TMS applied over this area interfered with general visual processing as also suggested by a significant decrease in the performance on catch trials (i.e. static stimuli). Indeed, even if V1 exhibit responses to patterns of motion (McKeefry, Watson, Frackowiak, Fong, & Zeki, 1997; G A Orban, Kennedy, & Bullier, 1986), the role of this area is not strictly confined to the analysis of

a motion signal. It is thus reasonable to think that TMS applied over V1 could cause a broader interference with visual processing. Nonetheless, it is noteworthy that previous TMS studies were able to find a more restricted window of interference with motion processing when TMS was applied over V1 (Beckers & Hömberg, 1992; Beckers & Zeki, 1995; Laycock et al., 2007; Silvanto, Lavie, & Walsh, 2005) although the consistency in regards to the timing of this window across these studies is limited. Some studies reported early interference at ~60-70ms (Beckers & Hömberg, 1992; Beckers & Zeki, 1995), while others found a later window of interference evidenced not earlier than ~100-120ms post stimulus onset (Hotson et al., 1994; Silvanto, Lavie, et al., 2005). One explanation for the discrepancy between present and previous findings in regards to the time-window of V1-interference are differences in the stimulation protocol used. The present study used a double-pulse stimulation protocol with a relative large inter-pulse interval (i.e. 26.7ms) that could have had a much more detrimental effect when applied over V1. In accordance with this, a previous study using a similar stimulation protocol (Koivisto et al., 2010) also showed a temporally unspecific disruption of motion processing over the majority of tested time intervals when TMS was applied over V1, and a much more temporally selective disruption when TMS was applied over V5.

Methodological considerations

As to the optimal design for studying the role and the timing of V5 and V1/V2 in the processing of motion stimuli by TMS, I would like to point out the control conditions implemented in the present study which I consider important for enabling to discard possible confounds potentially influencing the result (and which have not always been

implemented by the many past TMS studies on the same topic, none of which however dissociating between fast and slow motion processing). Firstly, results obtained with TMS were always compared with a control SHAM condition that enabled to exclude the influence of the auditory click associated with TMS on the participants' performance. Secondly, the use of concurrent EOG recordings enabled to exclude TMS-induced eye-blinks as the origin of the performance decrease in the presence of a TMS pulse. Finally, the inclusion of static stimuli (catch trials) allow to pinpoint interference with motion processing per se, as opposed to visual processing in general.

Conclusions

Altogether, the present results support the idea that fast moving and slow moving stimuli are not processed by the same pathway, corroborating that parallel processing of motion signals through segregated routes is dynamically deployed depending on motion characteristics (dynamic parallelism). The latency difference in V5 processing between fast and slow moving stimuli (~50ms vs 80ms) suggest an extra relay for slow motion stimuli, likely involving V1 (given the decoupling of objective from subjective changes to motion processing for fast but not slow moving stimuli). This would be in line with the idea that motion signals can reach V5 through two segregated pathways.

CHAPTER 4

General discussion

There is no doubt that humans are visual creatures. We constantly rely on our visual system to the point that most of our daily choices and behaviors are indeed driven by visual experience. However, human species is endowed with a variety of sensory channels working in concert and constantly providing our system a redundant description of the surrounding environment.

The importance of experiencing different sensory inputs at the same time become increasingly relevant when one of these inputs is weak or lost. The impaired sensory modality can indeed greatly benefit from the concurrent presentation of a congruent signal arising from a different sensory channel, which can lead to an enhanced processing of the otherwise subthreshold sensory component. For example, as described in Chapter 1 (see *Audio-visual integration in the normal and lesioned brain*), hemianopic patients show enhanced detection performances of visual stimuli presented in the scotopic area when these are associated with a sound and the same holds true when healthy participants are presented with hard to detect visual cues (Frassinetti et al., 2005, 2002; Làdavas, 2008). Similar mechanisms are also observed at the neural level. For example, multisensory neurons of the SC show progressively enhanced responses with progressively less effective pairs of stimuli, a phenomenon called inverse effectiveness (B E Stein & Meredith, 1993) and similar responses are also observed in the cortex (for a review Calvert, 2001). In addition, long-term multisensory mediated perceptual facilitation of unisensory signals has also been reported in hemianopic patients possibly reflecting a sustained activation of those cortical and subcortical areas mediating multisensory

integrative mechanisms (Passamonti, Frissen, & Làdavas, 2009). In line with this, it has been shown that SC neurons repeatedly exposed to concordant audio-visual pairs can enhance their responsiveness to the individual visual and auditory components (L. Yu et al., 2012).

A relatively recent approach for the rehabilitation of visual field defects based on a combination of audio-visual stimulation and saccadic training has shown to induce significant improvements in various visual domains. After a complete course of multisensory audio-visual training, patients reported long-lasting ameliorations in visual search and reading abilities together with reduced disabilities in daily life activities (Bolognini et al., 2005). Furthermore, the training also promoted improved oculomotor scanning behaviors characterized by fewer fixations, reduced scanpath length leading to shorter search times during visual search. Importantly, the improvements were critically dependent on the use of paired audio-visual multisensory stimulation since no ameliorations were reported when a control unisensory training was used (Passamonti, Bertini, et al., 2009). This suggests that the ameliorative effects could be driven by a boosted recruitment of the SC, which is well implicated in multisensory integration mechanisms (B E Stein & Meredith, 1993) as well as saccades execution and oculomotor planning (Arikuni et al., 1980; Barbas & Mesulam, 1981; Krauzlis et al., 2004). In addition, the intensive multisensory stimulation could have also enhanced activity in those cortical areas receiving collicular projections and involved in audio-visual multisensory integration processes (Bertini et al., 2010; Krauzlis et al., 2013; Maravita et al., 2008; Meienbrock et al., 2007; Nardo et al., 2014).

However, while associated clinical and behavioral improvements have been widely demonstrated, it remains to be clarified what are the substrates of the effects induced by

a sustained audio-visual training. Experiment 1 and 2 of the present dissertation were designed to clarify this point on hemianopic patients and healthy participants.

In Experiment 1, a group of hemianopic patients was exposed to a complete course of the same multisensory training used in previous studies (Bolognini et al., 2005; Dundon et al., 2015; Làdavas, 2008; Passamonti, Bertini, et al., 2009). As expected, after the training patients reported ameliorated performance on visual search tasks, a more efficient pattern of oculomotor behaviors and reduced disabilities in daily life activities that remained stable also at a ~8 months follow up session. In addition, a reduced P3 component of the electrophysiological signal in response to simple visual stimuli briefly presented in the periphery of the intact visual field (Dundon et al., 2015) was confirmed at the follow up session. This result clearly revealed that the audio-visual training induced stable changes in the processing of visual stimuli that were evident also after several months. Critically P3 amplitude was not reduced at the baseline 2, designed to control for possible effects due to the repetition of the test. Given that the amplitude of the P3 component is modulated by the amount of attentional resources allocation (Isreal et al., 1980; Wickens et al., 1983), the present result suggests that the audio-visual training could have led to a stable reduction of attentional resources allocation in the direction of the intact visual field. This would be in line with results from previous studies reveling that hemianopic patients also exhibit a maladaptive attentional bias in the direction of their intact visual field similar to that shown by neglect patients and possibly reflecting an hyperactivation of the intact hemisphere (Jason B. Mattingley et al., 2004; Tant et al., 2002). It is possible that the audio-visual training induced a reduction of the attentional bias in the direction of the intact visual field in favour of a greater allocation of attentional resources towards

the blind visual field, as also suggested by the post-training increase of accuracy performances in the blind visual field during the unisensory visual detection task. Indeed, when free to move their eyes patients showed an increase in the detection of visual stimuli briefly presented in their blind visual field together with a concurrent reduction of the detection of stimuli presented in the peripheral site of the intact visual field. The post-training implementation of a more efficient oculomotor strategy might have increased compensatory saccadic planning towards the hemianopic field, inducing a consequent shift of attention from the intact to the blind field. This seems in line with evidence suggesting that preparation of saccades evokes visual attentional shifts towards the targeted location of the saccades (for a review Zhao et al., 2012).

The lack of a significant modulation of early components of the electrophysiological signal (P1 or N1) could look odd since these components are usually known to be influenced by visuo-spatial attentional shifts (Mangun & Hillyard, 1991). However, early and late stages of attention can have separate effects on the electrophysiological signal. When early (exogenous) and late (endogenous) attentional mechanisms overlap, for example in the case of a stimulus appearing in the covertly attended location, both the early and the late stages of the electrophysiological signal are likely to be influenced. Contrary, when exogenous and endogenous attentional mechanisms are separated, early and late components can be separately affected (Hopfinger & West, 2006). The audio-visual training on hemianopic patients could have thus selectively induced a long-lasting modulation of post-perceptual attentional mechanisms while leaving unchanged the early mechanisms.

A likely neural substrate driving the reported changes might be the SC. Indeed, SC is known to be also part of a network of brain areas implicated in spatial attention and plays

a crucial role both in the implementation of the motor consequences of attention and in the process of target selection that precedes movement (Krauzlis et al., 2004, 2013; Sprague, 1966). In addition, the intensive audio-visual stimulation could have also induced a modulation in those cortical areas receiving collicular projections and involved in multisensory integration processes and attentional mechanisms (Behrmann et al., 2004; Bertini et al., 2010; Krauzlis et al., 2013; Maravita et al., 2008; Meienbrock et al., 2007; Nardo et al., 2014). A likely candidate is the network of connections between the SC and cortical areas within the dorsal stream, like dorsal posterior parietal cortices, which is known to be involved in both multisensory integrative processes (G A Calvert, 2001; Nardo et al., 2014; B E Stein & Meredith, 1993) and in the control of orienting behaviors and attentional mechanisms (Behrmann et al., 2004; Krauzlis et al., 2013; Krauzlis, 2004). As a consequence, it is plausible to hypothesize that the multisensory training could also selectively influence neural activity within the dorsal stream.

To further examine this point, in Experiment 2 a group of healthy participants was exposed to a shorter version of the same audio-visual training and electrophysiological measures were recorded before and after the training while subjects performed two lateralized visual discrimination tasks: a motion discrimination task and an orientation discrimination task. Results revealed that the audio-visual training enhanced the early visual processing during the execution of a motion discrimination task greatly relying on the activity of the dorsal stream (Kolster et al., 2010; Tootell et al., 1995; Watson et al., 1993; S. Zeki et al., 1991), as indexed by a post-training enhancement of the N1 component. Furthermore, the N1 enhancement was only evident in response to stimuli presented in the previously trained hemifield (i.e. the hemifield receiving 75% of audio-

visual stimulation), suggesting a spatial selectivity of the effect. Conversely, no enhanced processing was evident when subjects performed an orientation discrimination task involving striate and ventral extrastriate cortices (Fang et al., 2005; Kamitani & Tong, 2005; Swisher et al., 2010; Yacoub et al., 2008). The effect was found to be strongly dependent to multisensory integration rules (B E Stein & Meredith, 1993) given that participants receiving a control training in which audio-visual pairs were always presented in spatial disparity, showed no effect in either tasks. The N1 enhancement might reflect increased motion discrimination ability (Vogel & Luck, 2000) after the spatially coincident audio-visual training given that this component has been associated with visual discrimination processes (Mangun & Hillyard, 1991; Martínez et al., 1999; Vogel & Luck, 2000). It is possible that the repeated exposure to the audio-visual training could have increased the activity of the network of connections between SC and dorsal cortices, leading to an enhanced visual processing within the dorsal stream. Indeed, on the one hand previous studies revealed that repeated audio-visual stimulation can induce plastic changes in responses of SC neurons (L. Yu et al., 2012) and that the exposure to multisensory pairs can also increase neuronal responses to stimuli in a single sensory modality (Schroeder & Foxe, 2005; Shams, Wozny, Kim, & Seitz, 2011).

Taken together results from Experiment 1 and 2 showed that a systematic audio-visual training can induce significant and stable changes in the electrophysiological responses of the brain to unisensory visual stimuli. Results from Experiment 1 revealed that an audio-visual training in hemianopic patients improve visual search and orienting behaviors in the direction of the blind visual field, while concurrently reducing the attentional processing of visual stimuli presented in the intact visual field. Further, results from Experiment 2 showed that the audio-visual training on healthy participants

selectively enhances visual discriminatory processes related to activity within the dorsal stream. Both results could be ascribed to changes occurring within the network of connections between SC and the dorsal cortices.

Experiment 3 and 4 of the present dissertation were designed to explore the functionality and the characteristics of extrageniculate visual processing on both hemianopic patients and healthy participants. Indeed, our visual system is endowed with an incredibly complex organization composed of multiple visual pathways. Even if the majority of visual information is conveyed by the pathway connecting retina to LGN of the thalamus and then to primary visual cortex (i.e. retino-geniculo-striate pathway), alternative circuits are also present. This complex organization has several advantages. On the one hand, prevent the system to a complete loss of the visual function in the case of damage to the primary visual channel and on the other hand afford the system with different processing levels and speeds.

In Experiment 3, I reported electrophysiological evidence of implicit visual processing of stimuli presented in the blind field of hemianopic patients without blindsight, that could likely reflect the activity of alternative visual routes bypassing the lesional site. To date, most of the studies investigating preserved visual processing in hemianopic patients, were mainly aimed to shed light on the fascinating phenomenon of blindsight as a model for studying the properties of alternative routes to the primary visual channel (for a review Cowey, 2010). However, blindsight is the exception rather than the rule likely resulting from a very peculiar reorganization of the visual system and thus it might be risky to

generalize results from these patients to a wider population of V1-lesiond patients. Blindsight patients show surprising abilities to accurately respond to several stimulus features in their blind visual field in some cases also associated to glimpses of consciousness, which cast some doubt on the complete loss of primary visual cortex functioning. Conversely, investigating implicit visual processing in patients who do not show residual visual capacities in their blind visual field allows to undoubtedly exclude the involvement of primary visual cortex since feedback signals to this area are thought to be an essential component of consciousness (Bullier, 2001; Lamme, 2001; Silvanto, Cowey, et al., 2005). Surprisingly, to date only few studies aimed to investigate the presence of implicit visual processing in hemianopic patients that do not report residual visual abilities in their blind field. These studies showed evidence of implicit visual processing of emotional stimuli supposed to reflect the activity of the subcortical colliculo-pulvinar-amygdala network (Bertini et al., 2013; Cecere et al., 2014). In Experiment 3, I showed that also the processing of motion could be preserved in these patients. Indeed, moving dots presented in the scotopic area of a group of hemianopic patients induced a significant modulation of the electrophysiological signal as indexed by an event-related desynchronization in the alpha (8-12 Hz) and low-beta (15-25 Hz) generally associated with sensory processing and attentional mechanisms (Bauer et al., 2012; Klimesch, 2012; Neuper & Pfurtscheller, 2001; Pfurtscheller & Lopes Da Silva, 2004; Pfurtscheller et al., 1994; Thut, 2006). No modulation of the electrophysiological signal was instead shown by the presentation of static stimuli that induced an electrophysiological response statistically comparable to the control condition of no stimulus presentation (i.e. blank condition). These results suggest that also hemianopic patients that do not show striking residual visual capacities to detect or discriminate

stimuli above chance level in their blind visual field, can nevertheless show preserved visual processing of some stimulus features. The lack of a relevant modulation of the electrophysiological signal, when static stimuli were presented, suggests that the activity would be mainly related to the processing of motion. Indeed, the two types of stimuli (moving and static dots) induced comparable electrophysiological responses when presented in the intact visual field thus discarding the possibility that the difference could be ascribed to a mere luminance difference. Even if the present data cannot account for the cortical or subcortical generators of the activity reported, it is possible that it results from the recruitment of the subcortical pathway connecting SC to dorsal MT area and bypassing the lesional site. Indeed, the processing of motion on dorsal MT area is both dependent on signals supplied from the primary visual cortex and from signals originating from SC (Gross, 1991; Rodman et al., 1989, 1990). Furthermore, electrophysiological evidence revealed that both SC and dorsal MT area robustly respond to the presence of flickering or moving stimuli (Marrocco & Li, 1977; Schneider & Kastner, 2005), while being weakly activated by stationary stimuli (Kastner et al., 2004; Schneider & Kastner, 2005). It is thus reasonable to hypothesize that the implicit processing of motion described in the present thesis would result from the activity of this secondary route. In addition, these results on the one hand confirm the view of a prominent role of primary visual cortex for the conscious analysis of visual stimuli (Bullier, 2001; Lamme, 2001; Silvanto, Cowey, et al., 2005) while on the other hand lend support to the notion that the unconscious processing of some stimulus features could be preserved in the absence of V1 contribution.

In Experiment 4, I tried to better characterize the properties of the subcortical processing of motion stimuli revealed in previous experiment. In particular, I tested whether the recruitment of subcortical visual route to V5/MT area depends on motion characteristics, with more "salient" stimuli being processed by the fast subcortical SC-dorsal MT route while less salient stimuli reaching V5 through the pathway relaying on primary visual cortex. Studies on patients suggested that this could be the case since V1-lesioned patient G.Y. could only reliably detect stimuli moving at fast velocities (>6°/s) while bilateral V5-lesioned patient L.M. reported residual perception of stimuli moving at very slow speeds (Barbur et al., 1993; Ffytche et al., 1995; Hess et al., 1989; Zihl et al., 1983). In Experiment 4, I lent support to this notion by using TMS to interfere on V5 while a group of healthy participants performed a motion discrimination task. I reported evidence of an earlier interference with the processing of fast motion stimuli (i.e. 23°/s) at ~50ms post stimulus onset and a later interference at ~80ms when stimuli moved at a slower velocity (i.e. 4.4°/s). I interpreted this result as evidence of the recruitment of parallel segregated routes to V5 differentially activated by the velocity of motion. The fast SC-dorsal MT direct route would be mainly activated by fast moving objects as also suggested by the relative specialization of SC to respond to fast motion (Tohmi et al., 2014; Waleszczyk et al., 2004; Wallace et al., 1997). In addition, the early decrease of performance shown during fast motion trials did not correlate with a subjective awareness of the decremented performance as measured by a trial-by-trial subjective rating of motion performance. Conversely, slow motion trials showed a strong correlation between objective and subjective measures of the decrease of performance. This result would lend further support to the idea that the processing of slow motion require a first step of analysis on primary visual cortex greatly associated to conscious perception (Bullier, 2001; Lamme,

2001; Silvanto, Cowey, et al., 2005), while fast motion would quickly activate V5 area without the processing of V1.

Taken together, results from Experiment 3 and 4 provided novel findings on the characteristics of visual processes mediated by extrageniculate routes. For the first time, I showed that also hemianopic patients that do not report residual visual capacities in the scotopic area could show evidence of a preserved processing of motion signals likely mediated by the functionality of the SC-dorsal MT visual pathway (Experiment 3). This secondary route could be mainly involved in a fast coarse elaboration of motion sufficient to quickly execute an appropriate motor response but not to provide a complete analysis of the stimulus. This would be particularly important in the case of potentially dangerous stimuli like fast moving objects (Experiment 4). The direct SC-dorsal MT pathway might miss some fine perceptual aspects of the processing in V1 in favor of a faster transfer of information for an earlier detection of motion and implementation of rapid orienting behaviors.

In conclusion, in the present dissertation I described the relevant role played by extrageniculate neural circuits targeting cortical areas within the dorsal stream and how activity within these circuits can be efficiently modulated by a non-invasive stimulation based on a systematic exposure to paired audio-visual cues. The reported results revealed that these connections could play a relevant role in the rapid processing of salient visual stimuli requiring a fast elaboration and that these connections remain responsive even when a lesion prevent visual processing within the primary visual channel. Furthermore, I showed that a sustained audio-visual stimulation could be capable to significantly

reinforce activity of these connections. These results are particularly relevant in the perspective of a deeper comprehension of the neural mechanisms underpinning multisensory mediated recovery from visual field defects (Bolognini et al., 2005; Làdavas, 2008; Passamonti, Bertini, et al., 2009). They show, for the first time, that a systematic audio-visual training can induce stable plastic neural changes within the cortex, likely reflecting modulated responses in SC neurons (e.g. H. Jiang et al., 2015). Furthermore, these results somehow mirror previous animal evidence (L. Yu et al., 2012) and lend further support to the idea that the visual system could retain plastic properties until adulthood, that are highly exploitable in a rehabilitative perspective.

References

Ajina, S., Pestilli, F., Rokem, A., Kennard, C., & Bridge, H. (2015). Human blindsight is mediated by an intact geniculo-extrastriate pathway. *eLife*, *4*(OCTOBER2015). http://doi.org/10.7554/eLife.08935

Albright, T. D. (1984). Direction and orientation selectivity of neurons in visual area MT of the macaque. *Journal of Neurophysiology*, *52*, 1106–1130.

Anand, S., Olson, J. D., & Hotson, J. R. (1998). Tracing the timing of human analysis of motion and chromatic signals from occipital to temporo-parieto-occipital cortex: A transcranial magnetic stimulation study. *Vision Research*, *38*(17), 2619–2627. http://doi.org/10.1016/S0042-6989(98)00025-X

Anderson, S. J., Holliday, I. E., Singh, K. D., & Harding, G. F. (1996). Localization and functional analysis of human cortical area V5 using magneto-encephalography. *Proceedings. Biological Sciences / The Royal Society*, *263*(1369), 423–31. http://doi.org/10.1098/rspb.1996.0064

Arikuni, T., Sakai, M., Hamada, I., & Kubota, K. (1980). Topographical projections from the prefrontal cortex to the post-arcuate area in the rhesus monkey, studied by retrograde axonal transport of horseradish peroxidase. *Neuroscience Letters*, *19*(2), 155–160. http://doi.org/10.1016/0304-3940(80)90187-1

Azzopardi, P., Fallah, M., Gross, C. G., & Rodman, H. R. (2003). Response latencies of neurons in visual areas MT and MST of monkeys with striate cortex lesions. *Neuropsychologia*, *41*(13), 1738–1756. http://doi.org/10.1016/S0028-3932(03)00176-3

Bao, M., Yang, L., Rios, C., He, B., & Engel, S. A. (2010). Perceptual learning increases the strength of the earliest signals in visual cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*, 15080–15084. http://doi.org/10.1523/JNEUROSCI.5703-09.2010

Barbas, H., & Mesulam, M.-M. (1981). Organization of afferent input to subdivisions of area 8 in the rhesus monkey. *The Journal of Comparative Neurology*, *200*(3), 407–431. http://doi.org/10.1002/cne.902000309

Barbur, J. L., Watson, J. D., Frackowiak, R. S., & Zeki, S. (1993). Conscious visual perception without V1. *Brain*, *116 (Pt 6*, 1293–1302. http://doi.org/10.1093/brain/116.6.1293

Bauer, M., Kennett, S., & Driver, J. (2012). Attentional selection of location and modality in vision and touch modulates low-frequency activity in associated sensory cortices. *Journal of Neurophysiology*, *107*(9), 2342–2351. http://doi.org/10.1152/jn.00973.2011

Beauchamp, M. S., Yasar, N. E., Frye, R. E., & Ro, T. (2008). Touch, sound and vision in human superior temporal sulcus. *NeuroImage*, *41*(3), 1011–1020. http://doi.org/10.1016/j.neuroimage.2008.03.015

Beckers, G., & Hömberg, V. (1992). Cerebral visual motion blindness: transitory akinetopsia induced by transcranial magnetic stimulation of human area V5. *Proceedings of the Royal Society B*, *249*(1325), 173–178. http://doi.org/10.1098/rspb.1992.0100

Beckers, G., & Zeki, S. (1995). The consequences of inactivating areas V1 and V5 on visual motion perception. *Brain*, *118*(1), 49–60. http://doi.org/10.1093/brain/118.1.49

Behrmann, M., Geng, J. J., & Shomstein, S. (2004). Parietal cortex and attention. *Current Opinion in Neurobiology*. http://doi.org/10.1016/j.conb.2004.03.012

Benson, P. J., Guo, K., & Hardiman, M. J. (1999). Cortical Evoked Potentials Due to Motion Contrast in the Blind Hemifield. *Neuroreport*, *10*(17), 3595–3600. http://doi.org/10.1097/00001756-199911260-00024

Berman, R. A., & Wurtz, R. H. (2010). Functional identification of a pulvinar path from superior colliculus to cortical area MT. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*, 6342–6354. http://doi.org/10.1523/JNEUROSCI.6176-09.2010

Berman, R. A., & Wurtz, R. H. (2011). Signals conveyed in the pulvinar pathway from superior colliculus to cortical area MT. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *31*, 373–384. http://doi.org/10.1523/JNEUROSCI.4738-10.2011

Bertelson, P., & Vroomen, J. (1994). Exploring the relation between McGurk interference and ventriloquism. *Proceedings of the Third …*, *94*, 559–562. Retrieved from http://www.narcis.nl/publication/RecordID/oai:wo.uvt.nl:148924

Bertini, C., Cecere, R., & Làdavas, E. (2013). I am blind, but I " see" fear. *Cortex*, *49*(4), 985–993. http://doi.org/10.1016/j.cortex.2012.02.006

Bertini, C., Leo, F., Avenanti, A., & Làdavas, E. (2010). Independent mechanisms for ventriloquism and multisensory integration as revealed by theta-burst stimulation. *European Journal of Neuroscience*, *31*(10), 1791–1799.

Bertini, C., Leo, F., & Làdavas, E. (2008). Temporo-nasal asymmetry in multisensory integration mediated by the Superior Colliculus. *Brain Research*, *1242*, 37–44.

Blythe, I. M., Bromley, J. M., Kennard, C., & Ruddock, K. H. (1986). Visual discrimination of target displacement remains after damage to the striate cortex in humans. *Nature*, *320*(6063), 619–621. http://doi.org/10.1038/320619a0

Bolognini, N., Leo, F., Passamonti, C., Stein, B. E., & Làdavas, E. (2007). Multisensory-mediated auditory localization. *Perception*, *36*, 1477–1485. http://doi.org/10.1068/p5846

Bolognini, N., Rasi, F., Coccia, M., & Làdavas, E. (2005). Visual search improvement in hemianopic patients after audio-visual stimulation. *Brain*, *128*(12), 2830–2842. http://doi.org/10.1093/brain/awh656

Boynton, G. M., & Finney, E. M. (2003). *Orientation-specific adaptation in human visual cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience* (Vol. 23).

Brent, P. J., Kennard, C., & Ruddock, K. H. (1994). Residual colour vision in a human hemianope: spectral responses and colour discrimination. *Proceedings. Biological Sciences / The Royal Society*, *256*(1347), 219–225. http://doi.org/10.1098/rspb.1994.0073

Bridge, H., Thomas, O., Jbabdi, S., & Cowey, A. (2008). Changes in connectivity after visual cortical brain damage underlie altered visual function. *Brain*, *131*(6), 1433–1444. http://doi.org/10.1093/brain/awn063

Bullier, J. (2001). Feedback connections and conscious vision. *Trends in Cognitive Sciences*. http://doi.org/10.1016/S1364-6613(00)01730-7

Calvert, G. A. (2001). Crossmodal processing in the human brain: insights from functional neuroimaging studies. *Cerebral Cortex*, *11*, 1110–1123. http://doi.org/10.1093/cercor/11.12.1110

Calvert, G. A., Campbell, R., & Brammer, M. J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. *Current Biology*, *10*(11), 649–657. http://doi.org/10.1016/S0960-9822(00)00513-3

Cecere, R., Bertini, C., Maier, M. E., & Làdavas, E. (2014). Unseen Fearful Faces Influence Face Encoding : Evidence from ERPs in Hemianopic Patients. *Journal of Cognitive Neuroscience*, *26*(11), 2564–2577. http://doi.org/10.1162/jocn

Chen, A., Li, H., Qiu, J., & Luo, Y. (2006). The time course of visual categorization: Electrophysiological evidence from ERP. *Chinese Science Bulletin*, *51*, 1586–1592. http://doi.org/10.1007/s11434-006-1586-2

Cohen, M. X. (2011). It's about Time. *Frontiers in Human Neuroscience*, *5*(2), 1–15. http://doi.org/10.3389/fnhum.2011.00002

Cohen, M. X. (2014). Analyzing Neural Time Series Data: Theory and Practice. *MIT Press*. http://doi.org/10.1017/CBO9781107415324.004

Colby, C. L., Duhamel, J. R., & Goldberg, M. E. (1993). Ventral intraparietal area of the macaque: anatomic location and visual response properties. *Journal of Neurophysiology*, *69*, 902–914.

Corral, M. J., & Escera, C. (2008). Effects of sound location on visual task performance and electrophysiological measures of distraction. *Neuroreport*, *19*(15), 1535–1539. http://doi.org/10.1097/WNR.0b013e3283110416\r00001756-200810080-00018 [pii]

Cousineau, D. (2005). Confidence intervals in within-subject designs: A simpler solution to Loftus and Masson's method. *Tutorials in Quantitative Methods for Psychology*, *1*(1), 42–45. http://doi.org/no DOI found

Cowey, A. (2010). The blindsight saga. *Experimental Brain Research*. http://doi.org/10.1007/s00221-009-1914-2

d'Alfonso, A. A., van Honk, J., Schutter, D. J., Caffe, A. R., Postma, A., & de Haan, E. H. (2002). Spatial and temporal characteristics of visual motion perception involving V5 visual cortex. *Neurol.Res.*, *24*(3), 266–270.

Danckert, J., Maruff, P., Kinsella, G., de Graaff, S., & Currie, J. (1998). Investigating form and colour perception in blindsight using an interference task. *Neuroreport*, *9*(13), 2919–25. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9804291

De Gelder, B., Pourtois, G., van Raamsdonk, M., Vroomen, J., & Weiskrantz, L. (2001). Unseen stimuli modulate conscious visual experience: evidence from inter-hemispheric summation. *Neuroreport*, *12*(2), 385–391. http://doi.org/10.1097/00001756-200102120-00040

De Gelder, B., Vroomen, J., Pourtois, G., & Weiskrantz, L. (1999). Non-conscious recognition of affect in the absence of striate cortex. *Neuroreport*, *10*(18), 3759–3763. http://doi.org/10.1097/00001756-199912160-00007

De Weerd, P., Peralta, M. R., Desimone, R., & Ungerleider, L. G. (1999). Loss of attentional stimulus selection after extrastriate cortical lesions in macaques. *Nature Neuroscience*, *2*, 753–758. http://doi.org/10.1038/11234

Delorme, A., & Makeig, S. (2004). EEGLAB: An open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods*, *134*(1), 9–21. http://doi.org/10.1016/j.jneumeth.2003.10.009

Delorme, A., Sejnowski, T., & Makeig, S. (2007). Enhanced detection of artifacts in EEG data using higher-order statistics and independent component analysis. *NeuroImage*, *34*, 1443–1449. http://doi.org/10.1016/j.neuroimage.2006.11.004

Di Russo, F., Martinez, A., & Hillyard, S. a. (2003). Source analysis of event-related cortical activity during visuo-spatial attention. *Cerebral Cortex*, *13*(5), 486–499. http://doi.org/10.1093/cercor/13.5.486

Di Russo, F., Martínez, A., Sereno, M. I., Pitzalis, S., & Hillyard, S. a. (2002). Cortical sources of the early components of the visual evoked potential. *Human Brain Mapping*, *15*(2), 95–111. http://doi.org/10.1002/hbm.10010

Di Russo, F., Pitzalis, S., Spitoni, G., Aprile, T., Patria, F., Spinelli, D., & Hillyard, S. a. (2005). Identification of the neural sources of the pattern-reversal VEP. *NeuroImage*, *24*(3), 874–886. http://doi.org/10.1016/j.neuroimage.2004.09.029

Di Russo, F., Stella, A., Spitoni, G., Strappini, F., Sdoia, S., Galati, G., … Pitzalis, S. (2012). Spatiotemporal brain mapping of spatial attention effects on pattern-reversal ERPs. *Human Brain Mapping*, *33*(January 2011), 1334–1351. http://doi.org/10.1002/hbm.21285

Dong, W. K., Chudler, E. H., Sugiyama, K., Roberts, V. J., & Hayashi, T. (1994). Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys. *Journal of Neurophysiology*, *72*, 542–564.

Doyle, M. C., & Snowden, R. J. (2001). Identification of visual stimuli is improved by accompanying auditory stimuli: the role of eye movements and sound location. *Perception*, *30*(7), 795–810. http://doi.org/10.1068/p3126

Dundon, N. M., Làdavas, E., Maier, M. E., & Bertini, C. (2015). Multisensory stimulation in hemianopic patients boosts orienting responses to the hemianopic field and reduces attentional resources to the intact field. *Restorative Neurology and Neuroscience*. http://doi.org/DOI 10.3233/RNN-140457

Fahle, M. (2005). Perceptual learning: specificity versus generalization. *Current Opinion in Neurobiology*, *15*(2), 154–60. http://doi.org/10.1016/j.conb.2005.03.010

Fang, F., Murray, S. O., Kersten, D., & He, S. (2005). Orientation-tuned FMRI adaptation in human visual cortex. *Journal of Neurophysiology*, *94*, 4188–4195. http://doi.org/10.1152/jn.00378.2005

Felleman, D. J., & Van Essen, D. C. (1991). Distributed hierarchical processing in the primate cerebral cortex. *Cerebral Cortex*, *1*(1), 1–47. http://doi.org/10.1093/cercor/1.1.1-a

Fendrich, R., Wessinger, C. M., & Gazzaniga, M. S. (2001). Speculations on the neural basis of islands of blindsight. In *Progress in Brain Research* (Vol. 134, pp. 353–366). http://doi.org/10.1016/S0079-6123(01)34023-2

Ffytche, D. H., Guy, C. N., & Zeki, S. (1995). The parallel visual motion inputs into areas v1 and v5 of human cerebral cortex. *Brain*, *118*(6), 1375–1394. http://doi.org/10.1093/brain/118.6.1375

Ffytche, D. H., Guy, C. N., & Zeki, S. (1996). Motion specific responses from a blind hemifield. *Brain*, *119*(6), 1971–1982. http://doi.org/10.1093/brain/119.6.1971

Foxe, J. J., & Simpson, G. V. (2002). Flow of activation from V1 to frontal cortex in humans: A framework for defining "early" visual processing. *Experimental Brain Research*, *142*(1), 139–150. http://doi.org/10.1007/s00221-001-0906-7

Foxe, J. J., & Snyder, A. C. (2011). The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Frontiers in Psychology*, *2*(JUL). http://doi.org/10.3389/fpsyg.2011.00154

Frassinetti, F., Bolognini, N., Bottari, D., Bonora, A., & Làdavas, E. (2005). Audiovisual integration in patients with visual deficit. *Journal of Cognitive Neuroscience*, *17*, 1442–1452. http://doi.org/10.1162/0898929054985446

Frassinetti, F., Bolognini, N., & Làdavas, E. (2002). Enhancement of visual perception by crossmodal visuo-auditory interaction. *Experimental Brain Research*, *147*(3), 332–343. http://doi.org/10.1007/s00221-002-1262-y

Gandhi, N. J., & Katnani, H. A. (2011). Motor functions of the superior colliculus. *Annual Review of Neuroscience*, *34*, 205–31. http://doi.org/10.1146/annurev-neuro-061010-113728

Gazzaniga, M. S., Ivry, R. B., & Mangun, G. R. (2009). Cognitive Neuroscience: The Biology of the Mind. *The Quarterly Review of Biology*. http://doi.org/10.1086/603482

Goodale, M. A., & Milner, A. D. (1992). Separate visual pathways for perception and action. *Trends in Neurosciences*. http://doi.org/10.1016/0166-2236(92)90344-8

Grasso, P. A., Làdavas, E., & Bertini, C. (2016). Compensatory Recovery after Multisensory Stimulation in Hemianopic Patients: Behavioral and Neurophysiological Components. *Frontiers in Systems Neuroscience*, *10*, 45. http://doi.org/10.3389/fnsys.2016.00045

Gratton, G., Coles, M. G. H., & Donchin, E. (1983). A new method for off-line removal of ocular artifact. *Electroencephalography and Clinical Neurophysiology*, *55*(4), 468–484. http://doi.org/10.1016/0013-4694(83)90135-9

Greenhouse, S. W., & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika*, *24*, 95–112. http://doi.org/citeulike-article-id:6139128

Gross, C. G. (1991). Contribution of striate cortex and the superior colliculus to visual function in area MT, the superior temporal polysensory area and inferior temporal cortex. *Neuropsychologia*, *29*(6), 497–515. http://doi.org/10.1016/0028-3932(91)90007-U

Gummel, K., Ygge, J., Benassi, M., & Bolzani, R. (2012). Motion perception in children with foetal alcohol syndrome. *Acta Paediatrica (Oslo, Norway : 1992)*, *101*, e327–32. http://doi.org/10.1111/j.1651-2227.2012.02700.x

Harting, J. K., Huerta, M. F., Frankfurter, A. J., Strominger, N. L., & Royce, G. J. (1980). Ascending pathways from the monkey superior colliculus: An autoradiographic analysis. *Journal of Comparative Neurology*, *192*, 853–882. http://doi.org/10.1002/cne.901920414

Herrmann, C. S., & Knight, R. T. (2001). Mechanisms of human attention: Event-related potentials and oscillations. In *Neuroscience and Biobehavioral Reviews* (Vol. 25, pp. 465–476). http://doi.org/10.1016/S0149-7634(01)00027-6

Hess, R. H., Baker, C. L., & Zihl, J. (1989). The "motion-blind" patient: low-level spatial and temporal filters. *Journal of Neuroscience*, *9*(May), 1628–1640.

Hillyard, S. a, Vogel, E. K., & Luck, S. J. (1998). Sensory gain control (amplification) as a mechanism of selective attention: electrophysiological and neuroimaging evidence. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, *353*(1373), 1257–1270. http://doi.org/10.1098/rstb.1998.0281

Holliday, I. E., Anderson, S. J., & Harding, G. F. A. (1997). Magnetoencephalographic evidence for non-geniculostriate visual input to human cortical area V5. *Neuropsychologia*, *35*(8), 1139–1146. http://doi.org/10.1016/S0028-3932(97)00033-X

Hopfinger, J. B., & West, V. M. (2006). Interactions between endogenous and exogenous attention on cortical visual processing. *NeuroImage*, *31*(2), 774–789. http://doi.org/10.1016/j.neuroimage.2005.12.049

Hotson, J., Braun, D., Herzberg, W., & Boman, D. (1994). Transcranial magnetic stimulation of extrastriate cortex degrades human motion direction discrimination. *Vision Research*, *34*(16), 2115–2123. http://doi.org/0042-6989(94)90321-2 [pii]

Hubel, D., & Wiesel, T. (1968). Receptive fields and functional architecture of monkey striate cortex. *The Journal of Physiology*, 215–243.

Hubel, D., Wiesel, T. N., & Stryker, M. P. (1977). Orientation columns in macaque monkey visual cortex demonstrated by the 2-deoxyglucose autoradiographic technique. *Nature*, *269*(5626), 328–330.

Isreal, J. B., Chesney, G. L., Wickens, C. D., & Donchin, E. (1980). P300 and tracking difficulty: Evidence for multiple resources in dual-task performance. *Psychophysiology*, *17*(3), 259–273. http://doi.org/10.1111/j.1469-8986.1980.tb00146.x

Jiang, H., Stein, B. E., & McHaffie, J. G. (2015). Multisensory training reverses midbrain lesion-induced changes and ameliorates haemianopia. *Nature Communications*, *6*(May 2015), 7263. http://doi.org/10.1038/ncomms8263

Jiang, W., & Stein, B. E. (2003). Cortex controls multisensory depression in superior colliculus. *J Neurophysiol*, *90*(0022-3077 (Print)), 2123–2135. http://doi.org/10.1152/jn.00369.2003

Johnson, R. (1986). A triarchic model of P300 amplitude. *Psychophysiology*. http://doi.org/10.1111/j.1469-8986.1986.tb00649.x

Kadunce, D. C., Vaughan, J. W., Wallace, M. T., Benedek, G., & Stein, B. E. (1997). Mechanisms of within- and cross-modality suppression in the superior colliculus. *Journal of Neurophysiology*, *78*, 2834–2847. http://doi.org/citeulike-article-id:411545

Kamitani, Y., & Tong, F. (2005). Decoding the visual and subjective contents of the human brain. *Nature Neuroscience*, *8*, 679–685. http://doi.org/10.1038/nn1444

Kasten, E., Wust, S., Behrens-Baumann, W., & Sabel, B. A. (1998). Computer-based training for the treatment of partial blindness. *Nature Medicine*, *4*(9), 1083–1087.

Kastner, S., O'Connor, D. H., Fukui, M. M., Fehd, H. M., Herwig, U., & Pinsk, M. a. (2004). Functional imaging of the human lateral geniculate nucleus and pulvinar. *Journal of Neurophysiology*, *91*(1), 438–448. http://doi.org/10.1152/jn.00553.2003

Kawano, K., Shidara, M., Watanabe, Y., & Yamane, S. (1994). Neural activity in cortical area MST of alert monkey during ocular following responses. *Journal of Neurophysiology*, *71*(6), 2305–2324.

Kelly, S. P., Lalor, E. C., Reilly, R. B., & Foxe, J. J. (2006). Increases in alpha oscillatory power reflect an active retinotopic mechanism for distracter suppression during sustained visuospatial attention. *Journal of Neurophysiology*, *95*(6), 3844–51. http://doi.org/10.1152/jn.01234.2005

Kerkhoff, G., Munssinger, U., Haaf, E., Eberle-Strauss, G., Stogerer, E., Haff, E., … Stogerer, E. (1992). Rehabilitation of homonymous scotomata in patients with postgeniculate damage of the visual system: saccadic compensation training. *Restorative Neurology & Neuroscience*, *4*(4), 245–254. http://doi.org/10.3233/RNN-1992-4402

Kim, R. S., Seitz, A. R., & Shams, L. (2008). Benefits of stimulus congruency for multisensory facilitation of visual learning. *PloS One*, *3*(1), e1532. http://doi.org/10.1371/journal.pone.0001532

King, A. J. (2004). The superior colliculus. *Current Biology*. http://doi.org/10.1016/j.cub.2004.04.018

Klimesch, W. (2012). Alpha-band oscillations, attention, and controlled access to stored information. *Trends in Cognitive Sciences*. http://doi.org/10.1016/j.tics.2012.10.007

Koivisto, M., Mäntylä, T., & Silvanto, J. (2010). The role of early visual cortex (V1/V2) in conscious and unconscious visual perception. *NeuroImage*, *51*(2), 828–834. http://doi.org/10.1016/j.neuroimage.2010.02.042

Kok, A. (2001). On the utility of P3 amplitude as a measure of processing capacity. *Psychophysiology*, *38*(3), 557–577. http://doi.org/10.1016/S0167-8760(98)90168-4

Kolster, H., Peeters, R., & Orban, G. A. (2010). The retinotopic organization of the human middle temporal area MT/V5 and its cortical neighbors. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*, 9801–9820. http://doi.org/10.1523/JNEUROSCI.2069-10.2010

Krauzlis, R. J. (2004). Activity of rostral superior colliculus neurons during passive and active viewing of motion. *Journal of Neurophysiology*, *92*(2), 949–58. http://doi.org/10.1152/jn.00830.2003

Krauzlis, R. J., Liston, D., & Carello, C. D. (2004). Target selection and the superior colliculus: Goals, choices and hypotheses. In *Vision Research* (Vol. 44, pp. 1445–1451). http://doi.org/10.1016/j.visres.2004.01.005

Krauzlis, R. J., Lovejoy, L. P., & Zénon, A. (2013). Superior colliculus and visual spatial attention. *Annual Review of Neuroscience*, *36*, 165–82. http://doi.org/10.1146/annurev-neuro-062012-170249

Làdavas, E. (2008). Multisensory-based approach to the recovery of unisensory deficit. *Annals of the New York Academy of Sciences*. http://doi.org/10.1196/annals.1440.008

Lamme, V. A. F. (2001). Blindsight: The role of feedforward and feedback corticocortical connections. *Acta Psychologica*, *107*(1-3), 209–228. http://doi.org/10.1016/S0001-6918(01)00020-8

Lane, A. R., Smith, D. T., Ellison, A., & Schenk, T. (2010). Visual exploration training is no better than attention training for treating hemianopia. *Brain*, *133*(6), 1717–1728. http://doi.org/10.1093/brain/awq088

Laycock, R., Crewther, D. P., Fitzgerald, P. B., & Crewther, S. G. (2007). Evidence for Fast Signals and Later Processing in Human V1/V2 and V5/MT+: A TMS Study of Motion Perception. *Journal of Neurophysiology*, *98*(3), 1253–1262. http://doi.org/10.1152/jn.00416.2007

Leh, S. E., Johansen-Berg, H., & Ptito, A. (2006). Unconscious vision: New insights into the neuronal correlate of blindsight using diffusion tractography. *Brain*, *129*(7), 1822–1832. http://doi.org/10.1093/brain/awl111

Leo, F., Bertini, C., Di Pellegrino, G., & Làdavas, E. (2008). Multisensory integration for orienting responses in humans requires the activation of the superior colliculus. *Experimental Brain Research*, *186*(1), 67–77. http://doi.org/10.1007/s00221-007-1204-9

Leo, F., Bolognini, N., Passamonti, C., Stein, B. E., & Làdavas, E. (2008). Cross-modal localization in hemianopia: New insights on multisensory integration. *Brain*, *131*, 855–865. http://doi.org/10.1093/brain/awn003

Lyon, D. C., Nassi, J. J., & Callaway, E. M. (2010). A Disynaptic Relay from Superior Colliculus to Dorsal Stream Visual Cortex in Macaque Monkey. *Neuron*, *65*, 270–279. http://doi.org/10.1016/j.neuron.2010.01.003

Macaluso, E., George, N., Dolan, R., Spence, C., & Driver, J. (2004). Spatial and temporal factors during processing of audiovisual speech: A PET study. *NeuroImage*, *21*, 725–732. http://doi.org/10.1016/j.neuroimage.2003.09.049

Magnussen, S., & Mathiesen, T. (1989). Detection of moving and stationary gratings in the absence of striate cortex. *Neuropsychologia*, *27*(5), 725–728. http://doi.org/10.1016/0028-3932(89)90117-6

Makeig, S., Westerfield, M., Jung, T. P., Enghoff, S., Townsend, J., Courchesne, E., & Sejnowski, T. J. (2002). Dynamic brain sources of visual evoked responses. *Science*, *295*(5555), 690–694. http://doi.org/10.1126/science.1066168

Mangun, G. R., & Hillyard, S. A. (1991). Modulations of sensory-evoked brain potentials indicate changes in perceptual processing during visual-spatial priming. *Journal of Experimental Psychology. Human Perception and Performance*, *17*(4), 1057–1074. http://doi.org/10.1037/0096-1523.17.4.1057

Maravita, A., Bolognini, N., Bricolo, E., Marzi, C. a, & Savazzi, S. (2008). Is audiovisual integration subserved by the superior colliculus in humans? *Neuroreport*, *19*(3), 271–275. http://doi.org/10.1097/WNR.0b013e3282f4f04e

Marrocco, R. T., & Li, R. H. (1977). Monkey superior colliculus: properties of single cells and their afferent inputs. *Journal of Neurophysiology*, *40*(4), 844–60. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=407333

Marshall, R. S., Chmayssani, M., O'Brien, K. a, Handy, C., & Greenstein, V. C. (2010). Visual field expansion after visual restoration therapy. *Clinical Rehabilitation*, *24*, 1027–1035. http://doi.org/10.1177/0269215510362323

Marshall, R. S., Ferrera, J. J., Barnes, A., Xian Zhang, O'Brien, K. a, Chmayssani, M., … Lazar, R. M. (2008). Brain activity associated with stimulation therapy of the visual borderzone in hemianopic stroke patients. *Neurorehabilitation and Neural Repair*, *22*(2), 136–144. http://doi.org/10.1177/1545968307305522

Martínez, a, Anllo-Vento, L., Sereno, M. I., Frank, L. R., Buxton, R. B., Dubowitz, D. J., … Hillyard, S. a. (1999). Involvement of striate and extrastriate visual cortical areas in spatial attention. *Nature Neuroscience*, *2*(4), 364–369. http://doi.org/10.1038/7274

Mattingley, J. B., Berberovic, N., Corben, L., Slavin, M. J., Nicholls, M. E. R., & Bradshaw, J. L. (2004). The greyscales task: A perceptual measure of attentional bias following unilateral hemispheric damage. *Neuropsychologia*, *42*(3), 387–394. http://doi.org/10.1016/j.neuropsychologia.2003.07.007

Mattingley, J. B., Bradshaw, J. L., Nettleton, N. C., & Bradshaw, J. A. (1994). Can task specific perceptual bias be distinguished from unilateral neglect? *Neuropsychologia*, *32*(7), 805–817. http://doi.org/10.1016/0028-3932(94)90019-1

Maunsell, J. H., & Van Essen, D. C. (1983). Functional properties of neurons in middle temporal visual area of the macaque monkey. I. Selectivity for stimulus direction, speed, and orientation. *Journal of Neurophysiology*, *49*, 1127–1147.

Maunsell, J. H., & van Essen, D. C. (1983). The connections of the middle temporal visual area (MT) and their relationship to a cortical hierarchy in the macaque monkey. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *3*, 2563–2586.

McKeefry, D. J., Watson, J. D., Frackowiak, R. S., Fong, K., & Zeki, S. (1997). The activity in human areas V1/V2, V3, and V5 during the perception of coherent and incoherent motion. *NeuroImage*, *5*(1), 1–12. http://doi.org/10.1006/nimg.1996.0246

McLelland, D., Ahmed, B., & Bair, W. (2009). Responses to static visual images in macaque lateral geniculate nucleus: implications for adaptation, negative afterimages, and visual fading. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(28), 8996–9001. http://doi.org/10.1523/JNEUROSCI.0467-09.2009

McLelland, D., Baker, P. M., Ahmed, B., & Bair, W. (2010). Neuronal responses during and after the presentation of static visual stimuli in macaque primary visual cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(38), 12619–31. http://doi.org/10.1523/JNEUROSCI.0815-10.2010

Meienbrock, A., Naumer, M. J., Doehrmann, O., Singer, W., & Muckli, L. (2007). Retinotopic effects during spatial audio-visual integration. *Neuropsychologia*, *45*(3), 531–539. http://doi.org/10.1016/j.neuropsychologia.2006.05.018

Mohler, C. W., & Wurtz, R. H. (1976). Organization of monkey superior colliculus: intermediate layer cells discharging before eye movements. *Journal of Neurophysiology*, *39*(4), 722–44. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=823302

Mohler, C. W., & Wurtz, R. H. (1977). Role of striate cortex and superior colliculus in visual guidance of saccadic eye movements in monkeys. *Journal of Neurophysiology*, *40*(1), 74–94.

Mueller I, Poggel A, K. S. (2003). Vision restoration therapy after brain damage: Subjective improvements of activities of dailz life and their relationship to visual field enlargements. *Visual IMpairment Research*, *5*(3), 157 – 178. http://doi.org/10.1080/13882350390486929 Vision

Mueller, I., Mast, H., & Sabel, B. a. (2007). Recovery of visual field defects: a large clinical observational study using vision restoration therapy. *Restorative Neurology and Neuroscience*, *25*(5-6), 563–572.

Murray, S. O., Olman, C. A., & Kersten, D. (2006). Spatially specific FMRI repetition effects in human visual cortex. *Journal of Neurophysiology*, *95*, 2439–2445. http://doi.org/10.1152/jn.01236.2005

Nardo, D., Santangelo, V., & Macaluso, E. (2014). Spatial orienting in complex audiovisual environments. *Human Brain Mapping*, *35*, 1597–1614. http://doi.org/10.1002/hbm.22276

Nelles, G., De Greiff, A., Pscherer, A., Stude, P., Forsting, M., Hufnagel, A., … Diener, H. C. (2007). Saccade induced cortical activation in patients with post-stroke visual field defects. *Journal of Neurology*, *254*(9), 1244–1252. http://doi.org/10.1007/s00415-007-0511-1

Nelles, G., Esser, J., Eckstein, A., Tiede, A., Gerhard, H., & Diener, H. C. (2001). Compensatory visual field training for patients with hemianopia after stroke. *Neuroscience Letters*, *306*(3), 189–192. http://doi.org/10.1016/S0304-3940(01)01907-3

Neuper, C., & Pfurtscheller, G. (2001). Event-related dynamics of cortical rhythms: Frequency-specific features and functional correlates. In *International Journal of Psychophysiology* (Vol. 43, pp. 41–58). http://doi.org/10.1016/S0167-8760(01)00178-7

Newsome, W. T., & Pare, E. B. (1988). A selective impairment of motion perception following lesions of the middle temporal visual area (MT). *The Journal of Neuroscience*, *8*(6), 2201–2211. http://doi.org/http://www.ncbi.nlm.nih.gov/pubmed/3385495

Newsome, W., Wurtz, R., Dürsteler, M., & Mikami, a. (1985). Deficits in visual motion processing following ibotenic acid lesions of the middle temporal visual area of the macaque monkey. *The Journal of Neuroscience*, *5*(3), 825–40. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/3973698

Orban, G. A., Dupont, P., Vogels, R., De Bruyn, B., Bormans, G., & Mortelmans, L. (1996). Task dependency of visual processing in the human visual system. *Behavioural Brain Research*. http://doi.org/10.1016/0166-4328(95)00195-6

Orban, G. A., Kennedy, H., & Bullier, J. (1986). Velocity sensitivity and direction selectivity of neurons in areas V1 and V2 of the monkey: influence of eccentricity. *Journal of Neurophysiology*, *56*(2), 462–480.

Pambakian, a L. M., Mannan, S. K., Hodgson, T. L., & Kennard, C. (2004). Saccadic visual search training: a treatment for patients with homonymous hemianopia. *Journal of Neurology, Neurosurgery, and Psychiatry*, *75*(10), 1443–1448. http://doi.org/10.1136/jnnp.2003.025957

Pascual-Leone, A., & Walsh, V. (2001). Fast backprojections from the motion to the primary visual area necessary for visual awareness. *Science*, *292*(5516), 510–512. http://doi.org/10.1126/science.1057099

Passamonti, C., Bertini, C., & Làdavas, E. (2009). Audio-visual stimulation improves oculomotor patterns in patients with hemianopia. *Neuropsychologia*, *47*(2), 546–555. http://doi.org/10.1016/j.neuropsychologia.2008.10.008

Passamonti, C., Frissen, I., & Làdavas, E. (2009). Visual recalibration of auditory spatial perception: Two separate neural circuits for perceptual learning. *European Journal of Neuroscience*, *30*(6), 1141–1150. http://doi.org/10.1111/j.1460-9568.2009.06910.x

Pegna, A. J., Khateb, A., Lazeyras, F., & Seghier, M. L. (2005). Discriminating emotional faces without primary visual cortices involves the right amygdala. *Nature Neuroscience*, *8*(1), 24–25. http://doi.org/10.1038/nn1364

Perenin, M. T. (1978). Visual function within the hemianopic field following early cerebral hemidecortication in man - II. Pattern discrimination. *Neuropsychologia*, *16*(6), 697–708. http://doi.org/10.1016/0028-3932(78)90004-0

Perenin, M. T., & Jeannerod, M. (1975). Residual vision in cortically blind hemiphields. *Neuropsychologia*, *13*(1), 1–7. http://doi.org/10.1016/0028-3932(75)90041-X

Perenin, M. T., & Rosetti, Y. (1996). Grasping without form discrimination in a hemianopic field. *NeuroReport*, *7*, 793–797.

Pfurtscheller, G., & Lopes Da Silva, F. H. (2004). EEG Event-Related Desynchronization (ERD) and Event-Related Synchronization (ERS). In *Electroencephalography : Basic Principles, Clinical Applications, and Related Fields* (pp. 1003–1016). http://doi.org/10.1016/S0013-4694(97)88021-6

Pfurtscheller, G., & Lopes, F. H. (1999). Event-related EEG / MEG synchronization and desynchronization : basic principles. *Clinical Neurophysiology*, *110*, 1842–1857. http://doi.org/10.1016/S1388-2457(99)00141-8

Pfurtscheller, G., Neuper, C., & Mohl, W. (1994). Event-related desynchronization (ERD) during visual processing. *International Journal of Psychophysiology*, *16*(2-3), 147–153. http://doi.org/10.1016/0167-8760(89)90041-X

Pinal, D., Zurrón, M., & Díaz, F. (2014). Effects of load and maintenance duration on the time course of information encoding and retrieval in working memory: from perceptual analysis to post-categorization processes. *Frontiers in Human Neuroscience*, *8*, 165. http://doi.org/10.3389/fnhum.2014.00165

Pitzalis, S., Strappini, F., de Gasperis, M., Bultrini, A., & Di Russo, F. (2013). Spatio-Temporal Brain Mapping of Motion-Onset VEPs Combined with fMRI and Retinotopic Maps. *PLoS ONE*, *7*(4). http://doi.org/10.1371/journal.pone.0035771

Poggel, D. A., Kasten, E., Müller-Oehring, E. M., Bunzenthal, U., & Sabel, B. A. (2006). Improving residual vision by attentional cueing in patients with brain lesions. *Brain Research*, *1097*(1), 142–148. http://doi.org/10.1016/j.brainres.2006.04.011

Polich, J. (2007). Updating P300: An integrative theory of P3a and P3b. *Clinical Neurophysiology*. http://doi.org/10.1016/j.clinph.2007.04.019

Poppel, E., Held, R., & Frost, D. (1973). Residual Visual Function after Brain Wounds involving the Central Visual Pathways in Man. *Nature*, *243*, 295–296. http://doi.org/10.1038/243295a0

Potts, G. F. (2004). An ERP index of task relevance evaluation of visual stimuli. *Brain and Cognition*, *56*(1), 5–13. http://doi.org/10.1016/j.bandc.2004.03.006

Potts, G. F., Liotti, M., Tucker, D. M., & Posner, M. I. (1996). Frontal and inferior temporal cortical activity in visual target detection: Evidence from high spatially sampled event-related potentials. *Brain Topography*, *9*(1), 3–14. http://doi.org/10.1007/BF01191637

Potts, G. F., & Tucker, D. M. (2001). Frontal evaluation and posterior representation in target detection. *Cognitive Brain Research*, *11*(1), 147–156. http://doi.org/10.1016/S0926-6410(00)00075-6

Pourtois, G., Rauss, K. S., Vuilleumier, P., & Schwartz, S. (2008). Effects of perceptual learning on primary visual cortex activity in humans. *Vision Research*, *48*, 55–62. http://doi.org/10.1016/j.visres.2007.10.027

Ptito, M., Herbin, M., Boire, D., & Ptito, A. (1996). Neural bases of residual vision in hemicorticectomized monkeys. *Progress in Brain Research*, *112*, 385–404.

Rauss, K., Schwartz, S., & Pourtois, G. (2011). Top-down effects on early visual processing in humans: A predictive coding framework. *Neuroscience and Biobehavioral Reviews*. http://doi.org/10.1016/j.neubiorev.2010.12.011

Rees, G. (2008). The anatomy of blindsight. *Brain*. http://doi.org/10.1093/brain/awn089

Reinhard, J., Schreiber, a, Schiefer, U., Kasten, E., Sabel, B. a, Kenkel, S., … Trauzettel-Klosinski, S. (2005). Does visual restitution training change absolute homonymous visual field defects? A fundus controlled study. *The British Journal of Ophthalmology*, *89*(1), 30–35. http://doi.org/10.1136/bjo.2003.040543

Riddoch, G. (1917). Dissociation of visual perceptions due to occipital injuries, with especial reference to appreciation of movement. *Brain*, *40*(1), 15–57. http://doi.org/10.1093/brain/40.1.15

Robinson, D. A. (1972). Eye movements evoked by collicular stimulation in the alert monkey. *Vision Research*, *12*(11), 1795–1808. http://doi.org/10.1016/0042-6989(72)90070-3

Robinson, D. L., & Petersen, S. E. (1992). The pulvinar and visual salience. *Trends in Neurosciences*, *15*, 127–132. http://doi.org/10.1016/0166-2236(92)90354-B

Rodman, H. R., Gross, C. G., & Albright, T. D. (1989). Afferent basis of visual response properties in area MT of the macaque. I. Effects of striate cortex removal. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *9*(6), 2033–2050.

Rodman, H. R., Gross, C. G., & Albright, T. D. (1990). Afferent basis of visual response properties in area MT of the macaque. II. Effects of superior colliculus removal. *J. Neurosci.*, *10*(4), 1154–1164.

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *120*(12), 2008–39. http://doi.org/10.1016/j.clinph.2009.08.016

Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J. D., … Driver, J. (2006). Concurrent TMS-fMRI and Psychophysics Reveal Frontal Influences on Human Retinotopic Visual Cortex. *Current Biology*, *16*(15), 1479–1488. http://doi.org/10.1016/j.cub.2006.06.057

Rushmore, R. J., & Payne, B. R. (2003). Bilateral impact of unilateral visual cortex lesions on the superior colliculus. *Experimental Brain Research*, *151*(4), 542–547. http://doi.org/10.1007/s00221-003-1513-6

Sabel, B. A., & Kasten, E. (2001). Rehabilitation of Visual Disorders After Brain Injury, Edited by Josef Zihl, Psychology Press 1999, ISBN 0863778984. *Neuropsychologia*. http://doi.org/10.1016/S0028-3932(00)00145-7

Sack, A. T., Kohler, A., Linden, D. E. J., Goebel, R., & Muckli, L. (2006). The temporal characteristics of motion processing in hMT/V5+: Combining fMRI and neuronavigated TMS. *NeuroImage*, *29*(4), 1326–1335. http://doi.org/10.1016/j.neuroimage.2005.08.027

Saffell, T., & Matthews, N. (2003). Task-specific perceptual learning on speed and direction discrimination. *Vision Research*, *43*(12), 1365–1374. http://doi.org/10.1016/S0042-6989(03)00137-8

Sauseng, P., Klimesch, W., Stadler, W., Schabus, M., Doppelmayr, M., Hanslmayr, S., … Birbaumer, N. (2005). A shift of visual spatial attention is selectively associated with human EEG alpha activity. *European Journal of Neuroscience*, *22*(11), 2917–2926. http://doi.org/10.1111/j.1460-9568.2005.04482.x

Schiller, P. H. (1972). The role of the monkey superior colliculus in eye movement and vision. *Investigative Ophthalmology*, *11*, 451–460.

Schlack, A., Hoffmann, K. P., & Bremmer, F. (2002). Interaction of linear vestibular and visual stimulation in the macaque ventral intraparietal area (VIP). *European Journal of Neuroscience*, *16*, 1877–1886. http://doi.org/10.1046/j.1460-9568.2002.02251.x

Schmid, M. C., Mrowka, S. W., Turchi, J., Saunders, R. C., Wilke, M., Peters, A. J., … Leopold, D. a. (2010). Blindsight depends on the lateral geniculate nucleus. *Nature*, *466*(7304), 373–377. http://doi.org/10.1038/nature09179

Schneider, K. A., & Kastner, S. (2005). Visual responses of the human superior colliculus: a high-resolution functional magnetic resonance imaging study. *Journal of Neurophysiology*, *94*, 2491–2503. http://doi.org/10.1152/jn.00288.2005

Schroeder, C. E., & Foxe, J. (2005). Multisensory contributions to low-level, "unisensory" processing. *Current Opinion in Neurobiology*. http://doi.org/10.1016/j.conb.2005.06.008

Shams, L., Wozny, D. R., Kim, R., & Seitz, A. (2011). Influences of multisensory experience on subsequent unisensory processing. *Frontiers in Psychology*, *2*(OCT). http://doi.org/10.3389/fpsyg.2011.00264

Siegel, M., Donner, T. H., Oostenveld, R., Fries, P., & Engel, A. K. (2008). Neuronal Synchronization along the Dorsal Visual Pathway Reflects the Focus of Spatial Attention. *Neuron*, *60*(4), 709–719. http://doi.org/10.1016/j.neuron.2008.09.010

Silvanto, J., Cowey, A., Lavie, N., & Walsh, V. (2005). Striate cortex (V1) activity gates awareness of motion. *Nature Neuroscience*, *8*(2), 143–4. http://doi.org/10.1038/nn1379

Silvanto, J., Lavie, N., & Walsh, V. (2005). Double dissociation of V1 and V5/MT activity in visual awareness. *Cerebral Cortex*, *15*(11), 1736–1741. http://doi.org/10.1093/cercor/bhi050

Silvanto, J., Lavie, N., & Walsh, V. (2006). Stimulation of the human frontal eye fields modulates sensitivity of extrastriate visual cortex. *Journal of Neurophysiology*, *96*(2), 941–5. http://doi.org/10.1152/jn.00015.2006

Sosa, Y., Clarke, A. M., & McCourt, M. E. (2011). Hemifield asymmetry in the potency of exogenous auditory and visual cues. *Vision Research*, *51*(11), 1207–1215. http://doi.org/10.1016/j.visres.2011.03.012

Sosa, Y., Teder-Sälejärvi, W. a, & McCourt, M. E. (2010). Biases of spatial attention in vision and audition. *Brain and Cognition*, *73*(3), 229–35. http://doi.org/10.1016/j.bandc.2010.05.007

Spence, C. (2013). Just how important is spatial coincidence to multisensory integration? Evaluating the spatial rule. *Annals of the New York Academy of Sciences*, *1296*(1), 31–49. http://doi.org/10.1111/nyas.12121

Sprague, J. M. (1966). Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. *Science (New York, N.Y.)*, *153*(743), 1544–1547. http://doi.org/10.1126/science.153.3743.1544

Stein, B. E., & Meredith, M. A. (1993). *The Merging of the Senses*. Cambridge, MA: The MIT Press.

Stein, B. E., & Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nature Reviews. Neuroscience*, *9*, 255–266. http://doi.org/10.1038/nrn2377

Stein, B. E., & Wallace, M. T. (1996). Comparisons of cross-modality integration in midbrain and cortex. *Progress in Brain Research*, *112*, 289–299. http://doi.org/10.1016/S0079-6123(08)63336-1

Stevenson, R. A., & James, T. W. (2009). Audiovisual integration in human superior temporal sulcus: Inverse effectiveness and the neural processing of speech and object recognition. *NeuroImage*, *44*(3), 1210–1223. http://doi.org/10.1016/j.neuroimage.2008.09.034

Stoerig, P. (2006). Blindsight, conscious vision, and the role of primary visual cortex. *Progress in Brain Research*, *155*, 217–34. http://doi.org/10.1016/S0079-6123(06)55012-5

Stoerig, P., Kleinschmidt, a, & Frahm, J. (1998). No visual responses in denervated V1: high-resolution functional magnetic resonance imaging of a blindsight patient. *Neuroreport*, *9*(1), 21–5. http://doi.org/10.1097/00001756-199801050-00005

Sumner, P., Adamjee, T., & Mollon, J. D. (2002). Signals invisible to the collicular and magnocellular pathways can capture visual attention. *Current Biology*, *12*(15), 1312–1316. http://doi.org/10.1016/S0960-9822(02)01020-5

Swisher, J. D., Gatenby, J. C., Gore, J. C., Wolfe, B. a, Moon, C.-H., Kim, S.-G., & Tong, F. (2010). Multiscale pattern analysis of orientation-selective activity in the primary visual cortex. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*, 325–330. http://doi.org/10.1523/JNEUROSCI.4811-09.2010

Tamietto, M., & de Gelder, B. (2010). Neural bases of the non-conscious perception of emotional signals. *Nature Reviews. Neuroscience*, *11*(10), 697–709. http://doi.org/10.1038/nrn2889

Tamietto, M., Pullens, P., De Gelder, B., Weiskrantz, L., & Goebel, R. (2012). Subcortical connections to human amygdala and changes following destruction of the visual cortex. *Current Biology*, *22*(15), 1449–1455. http://doi.org/10.1016/j.cub.2012.06.006

Tant, M. L. M., Kuks, J. B. M., Kooijman, a C., Cornelissen, F. W., & Brouwer, W. H. (2002). Grey scales uncover similar attentional effects in homonymous hemianopia and visual hemi-neglect. *Neuropsychologia*, *40*(8), 1474–1481. http://doi.org/10.1016/S0028-3932(01)00197-X

Thut, G. (2006). α-Band Electroencephalographic Activity over Occipital Cortex Indexes Visuospatial Attention Bias and Predicts Visual Target Detection. *Journal of Neuroscience*, *26*(37), 9494–9502. http://doi.org/10.1523/JNEUROSCI.0875-06.2006

Tohmi, M., Meguro, R., Tsukano, H., Hishida, R., & Shibuki, K. (2014). The extrageniculate visual pathway generates distinct response properties in the higher visual areas of mice. *Current Biology*, *24*(6), 587–597. http://doi.org/10.1016/j.cub.2014.01.061

Tong, F., Harrison, S. A., Dewey, J. A., & Kamitani, Y. (2012). Relationship between BOLD amplitude and pattern classification of orientation-selective activity in the human visual cortex. *NeuroImage*, *63*, 1212–1222. http://doi.org/10.1016/j.neuroimage.2012.08.005

Tootell, R. B., Reppas, J. B., Kwong, K. K., Malach, R., Born, R. T., Brady, T. J., … Belliveau, J. W. (1995). Functional analysis of human MT and related visual cortical areas using magnetic resonance imaging. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *15*, 3215–3230.

Van Essen, D. C., & Maunsell, J. H. R. (1983). Hierarchical organization and functional streams in the visual cortex. *Trends in Neurosciences*. http://doi.org/10.1016/0166-2236(83)90167-4

Vogel, E. K., & Luck, S. J. (2000). *The visual N1 component as an index of a discrimination process. Psychophysiology* (Vol. 37).

Vogels, R., & Orban, G. A. (1994). Activity of inferior temporal neurons during orientation discrimination with successively presented gratings. *Journal of Neurophysiology*, *71*, 1428–1451.

Waleszczyk, W. J., Wang, C., Benedek, G., Burke, W., & Dreher, B. (2004). Motion sensitivity in cat's superior colliculus: Contribution of different visual processing

channels to response properties of collicular neurons. *Acta Neurobiologiae Experimentalis*, *64*(2), 209–228.

Wallace, M. T., McHaffie, J. G., & Stein, B. E. (1997). Visual response properties and visuotopic representation in the newborn monkey superior colliculus. *Journal of Neurophysiology*, *78*(5), 2732–2741.

Walsh, V., Ellison, A., Battelli, L., & Cowey, A. (1998). Task-specific impairments and enhancements induced by magnetic stimulation of human visual area V5. *Proceedings. Biological Sciences / The Royal Society*, *265*(1395), 537–43. http://doi.org/10.1098/rspb.1998.0328

Watson, J. D. G., Myers, R., Frackowiak, R. S. J., Hajnal, J. V., Woods, R. P., Mazziotta, J. C., … Zeki, S. (1993). Area V5 of the Human Brain: Evidence from a Combined Study Using Positron Emission Tomography and Magnetic Resonance Imaging. *Cerebral Cortex*, *3*, 79–94. http://doi.org/10.1093/cercor/3.2.79

Weiskrantz, L. (1986). *Blindsight: A Case Study and Implications*. *Oxford University Press*. http://doi.org/10.1093/acprof

Weiskrantz, L. (1987). Residual vision in a scotoma: A follow-up STUDY of "form" discrimination. *Brain*, *110*(1), 77–92. http://doi.org/10.1093/brain/110.1.77

Weiskrantz, L. (1996). Blindsight revisited. *Current Opinion in Neurobiology*. http://doi.org/10.1016/S0959-4388(96)80075-4

Weiskrantz, L., Warrington, E. K., Sanders, M. D., & Marshall, J. (1974). Visual capacity in the hemianopic field following a restricted occipital ablation. *Brain: A Journal of Neurology*, *97*(4), 709–728. http://doi.org/10.1093/brain/97.1.709

Wickens, C., Kramer, A., Vanasse, L., & Donchin, E. (1983). Performance of concurrent tasks: a psychophysiological analysis of the reciprocity of information-processing resources. *Science (New York, N.Y.)*, *221*(4615), 1080–1082. http://doi.org/10.1126/science.6879207

Wilson, B., Cockburn, J., & Halligan, P. (1987). Development of a behavioral test of visuospatial neglect. *Archives of Physical Medicine and Rehabilitation*, *68*(2), 98–102.

Xu, J., Yu, L., Rowland, B. a., Stanford, T. R., & Stein, B. E. (2012). Incorporating Cross-Modal Statistics in the Development and Maintenance of Multisensory Integration. *Journal of Neuroscience*, *32*(7), 2287–2298. http://doi.org/10.1523/JNEUROSCI.4304-11.2012

Xu, J., Yu, L., Rowland, B. a., Stanford, T. R., & Stein, B. E. (2014). Noise-rearing disrupts the maturation of multisensory integration. *European Journal of Neuroscience*, *39*(October), 602–613. http://doi.org/10.1111/ejn.12423

Yacoub, E., Harel, N., & Ugurbil, K. (2008). High-field fMRI unveils orientation columns in humans. *Proceedings of the National Academy of Sciences of the United States of America*, *105*, 10607–10612. http://doi.org/10.1073/pnas.0804110105

Yu, L., Rowland, B. a, & Stein, B. E. (2010). Initiating the development of multisensory integration by manipulating sensory experience. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *30*(14), 4904–4913. http://doi.org/10.1523/JNEUROSCI.5575-09.2010

Yu, L., Rowland, B. a., Xu, J., & Stein, B. E. (2012). Multisensory plasticity in adulthood: cross-modal experience enhances neuronal excitability and exposes silent inputs. *Journal of Neurophysiology*, (October 2012), 464–474. http://doi.org/10.1152/jn.00739.2012

Yu, L., Stein, B. E., & Rowland, B. A. (2009). Adult plasticity in multisensory neurons: short-term experience-dependent changes in the superior colliculus. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *29*(50), 15910–15922. http://doi.org/10.1523/JNEUROSCI.4041-09.2009

Yu, L., Xu, J., Rowland, B. a, & Stein, B. E. (2014). Multisensory Plasticity in Superior Colliculus Neurons is Mediated by Association Cortex. *Cerebral Cortex (New York, N.Y. : 1991)*, 1–8. http://doi.org/10.1093/cercor/bhu295

Zeki, S. M. (1974). Functional organization of a visual area in the posterior bank of the superior temporal sulcus of the rhesus monkey. *The Journal of Physiology*, *236*, 549–573.

Zeki, S., Watson, J. D., Lueck, C. J., Friston, K. J., Kennard, C., & Frackowiak, R. S. (1991). A direct demonstration of functional specialization in human visual cortex. *The Journal of Neuroscience*, *11*, 641–649. http://doi.org/10.1.1.211.5726

Zhang, X., Kedar, S., Lynn, M. J., Newman, N. J., & Biousse, V. (2006). Homonymous hemianopia in stroke. *Journal of Neuro-Ophthalmology : The Official Journal of the North American Neuro-Ophthalmology Society*, *26*(3), 180–183. http://doi.org/10.1016/j.ajo.2006.10.017

Zhao, M., Gersch, T. M., Schnitzer, B. S., Dosher, B. A., & Kowler, E. (2012). Eye movements and attention: The role of pre-saccadic shifts of attention in perception, memory and the control of saccades. *Vision Research*, *74*, 40–60. http://doi.org/10.1016/j.visres.2012.06.017

Zihl, J. (1995). Visual scanning behavior in patients with homonymous hemianopia. *Neuropsychologia*, *33*(3), 287–303. http://doi.org/10.1016/0028-3932(94)00119-A

Zihl, J., & Von Cramon, D. (1985). Visual field recovery from scotoma in patients with postgeniculate damage: A REVIEW of 55 cases. *Brain*, *108*(2), 335–365. http://doi.org/10.1093/brain/108.2.335

Zihl, J., von Cramon, D., & Mai, N. (1983). Selective disturbance of movement vision after bilateral brain damage. *Brain : A Journal of Neurology*, *106 (Pt 2)*, 313–340. http://doi.org/10.1093/brain/106.2.313

Glossary

2AFC: Two alternative forched choice

ADL: Activity of daily living (Experiment 1)

AES: Anterior ectosylvian sulcus

ANOVA: Analysis of variance

AV-SC: Audio-visual spatially coincident training (Experiment 2)

AV-SD: Audio-visual spatially disparate training (Experiment 2)

AVM: Arteriovenous malformation

B: Baseline (Experiment 1)

B1: Baseline 1 (Experiment 1)

B2: Baseline 2 (Experiment 1)

BOLD: Blood oxygenation level dependent

CRT: Cathode ray tube

CT: Computed tomography

dB: Decibel

DC: Direct coupled

DTI: Diffusion tensor imaging

EEG: electroencephalogram

EOG: Electrooculogram

ERD: Event-related desynchronization

ERP: Event related potential

ERS: Event-related synchronization

ERSP: Event-related spectral perturbation

F: Follow-up (Experiment 1)

fMRI: Functional magnetic resonance imaging

hMT+: Human middle temporal

Hz: Hertz

ICA: Independent component analysis

IES: Inverse efficiency score

MCA: Middle cerebral artery

MT: Middle temporal

LED: Light emitting diode

LCD: Liquid crystal display

LGN: Lateral geniculate nucleus

LIP: Lateral intra parietal

MAV: Multisensory audio-visual (Experiment 1)

MEG: Magnetoencephalography

MRI: Magnetic resonance imaging

MSO: Maximum stimulator output

P: Post (Experiment 1)

PCA: Posterior cerebral artery

PET: Positron emission tomography

PPC: Posterior parietal cortex

PV: Pulvinar

ROI: Region of interest

RSS: Rating scale score (Experiment 4)

SC: Superior colliculus

SD: Standard deviation

SOA: Stimulus onset asynchrony

STS: Superior temporal sulcus

TF: Time frequency

TMS: tanscranial magnetic stimulation

UA: Unisensory auditory (Experiment 1)

UV: Unisensory visual (Experiment 1)

V1: Primary visual cortex

µV: Microvolt

η_p^2: Partial eta square