University of Milano-Bicocca

DOCTORAL PROGRAM IN

EXPERIMENTAL PSYCHOLOGY, LINGUISTICS AND COGNITIVE NEUROSCIENCE
(XXVI cycle)

The "multisensory" visual cortex: cross-modal shaping of visual cortical responses and perception

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Academic Years: 2011-2014

Declaration

I declare that the work presented in this thesis is my own.
Where information has been derived from other sources, I confirm that this has been reported in the thesis.

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Table of contents

Summary

In our daily life, multisensory cues impact our sensory systems, shaping our perception of sensory events: the integration of information from the different sensory channels represents a relevant function of the primate and human brain. Seminal models defer neural mechanisms of multisensory integration into late cortical stages, after sensory-specific processing has been completed. However, more recent anatomical studies suggest that this view may be over-simplistic, since the substrate for multisensory integration is not constrained to the heteromodal areas of multisensory convergence; rather, multisensory integration may even occur in the early stages of sensory processing, rising the intriguing hypothesis that most of cerebral cortex is essentially multisensory.

The present dissertation inquires the causal involvement of classical 'sensory-specific' visual areas in multisensory processing. Using a combination of behavioral, neuromodulatory, and neuropsychological evidence, I investigated the behavioral and brain signatures of a causal link between visual cortical excitability and multisensory perception. In parallel, I provide a characterization of the impact of distinct cross-modal stimuli on phenomenal visual experience.

By measuring visual cortical excitability via Transcranial Magnetic Stimulation in healthy, neurologically unimpaired participants, the first study shows facilitatory effects by spatially-specific bimodal and trimodal stimuli on visual cortical responses, which, in turn, improve visual perception. Moreover, by using transcranial Direct Current Stimulation, I

elucidate the role played by higher-order multisensory cortices in mediating such cross-modal influences on visual perception, finding the presence of regional cortical preferences for auditory or somatosensory influences on visual responses.

The second study, again in healthy participants, further extends these findings by showing that multisensory influences on vision not only express themselves through an enhancement of visual perception, but they can also bring about phenomenological changes in the conscious visual experience, namely a cross-modal illusion, when incongruent auditory cues are provided. Cross-modal illusory effects show a specific time-course, compatible with the occurrence of early visual-auditory interactions in the primary visual cortex.

At complement with evidence in healthy participants, the third study investigates how a well-known cross-modal effect, the Sound-Induced Flash Illusion, is processed by brain-damaged patients either with visual half-field deficits, following a retro-geniculate damage to the visual pathways, or with defective report of visual stimuli, contralateral to a cerebral hemispheric lesion (most frequently involving the posterior-inferior parietal lobe, the superior-posterior temporal lobe, or both) due to unilateral spatial neglect. The perception of this cross-modal illusion is defective in patients with visual field defects, but not in those with unilateral spatial neglect, further supporting the involvement of low-level stages of visual processing in integrating multisensory cues.

Overall, this set of experiments illustrates a causal link between the cross-modal modulation of visual perception and the activity of the primary visual cortical areas, which represent a key site for multisensory integration.

Chapter 1

Introduction

Being endowed with more than one sense enhances the individual's ability to adapt to a changing environment: the specific signals provided by each sensory channel are useful in different circumstances, but when combined together they maximize the chances of detecting and identifying events or objects of interest in the surrounding environment (Stein & Stanford, 2008). Moreover, having multiple sensory channels allows functionally replacing (at least in part) one with another, if necessary, as for example in sensory impairments. At the same time, since each sense is tuned to a specific form of energy, it gives rise to a distinct perceptual experience of the external world (e.g. the perception of color is unique to the visual system, as the perception of pitch is specifically related to the auditory system). However, despite these diversities, and their anatomo-functional independence, in our daily life we use them synergistically, without any conscious effort (Stein & Meredith, 1993). For instance, while we are riding a bike, our brain continuously combines the different information derived from the visual (looking at the road), somatosensory (feeling the pad beneath the bicycle pedal) and auditory (hearing the noises of road traffic) modalities and automatically translates them into an integrated motor command to regulate the ongoing riding. This intrinsic ability of our perceptual system to assemble multiple sources of information and then to use them in combination has been described with the term

Multisensory Integration. Integrating inputs from multiple sensory sources partially transforms their modality-specific features, to create a final perceptual experience that tells more about external event than what would be predicted by the sum of the individual sensory components (Stein & Meredith, 1993). From a neural perspective, this perceptual advantage can be explained by the statistically higher number of neural impulses evoked by multisensory stimuli in multisensory neurons, as compared to that evoked by the most effective stimulus alone (Meredith & Stein, 1983). This mechanism has clear behavioral advantages: it allows the brain to amplify minimal signals and reduce their ambiguity, thereby improving the ability of detecting and identifying environmental events and orienting toward them (e.g., Calvert, 2001; Stein & Meredith, 1993; Spence & Driver, 2004).

Despite the acknowledged impact of multisensory integration on subjective perceptual experiences, the investigation of human perception has traditionally focused on its unimodal counterpart (Schroeder & Foxe, 2005). Indeed, the most of the knowledge about mechanisms of multisensory integration has been provided by pioneering investigations of the physiological responses of single multisensory neurons in a number of brain regions, particularly in the midbrain and in the cerebral cortex of cats and monkeys (Stein & Meredith, 1993). In particular, in the Superior Colliculus (SC), a midbrain structure involved in attentive and orientation behavior, the majority of neurons responds to stimuli from different sensory modalities (Stein & Meredith, 1993). Multisensory integration in SC neurons follows three simple rules: the neural responses to multisensory stimuli is enhanced when the stimuli from the different senses come from approximately the same location (the '*spatial rule*') and at approximately the same time (the '*temporal rule*'), and when at least one of the stimuli is by itself only weakly effective in exciting the neuron (the '*inverse*

effectiveness rule'). Following this seminal evidence on the SC, neurophysiological and brain imaging studies have then identified several cortical regions showing multisensory responses in both humans and non-human primates (Ghazanfar & Schroeder, 2006; Calvert et al., 2004), including the upper bank of the Superior Temporal Sulcus (STS) (Padberg et al., 2003; Schmahmann & Pandya, 1991; Barraclough et al., 2005; Beauchamp, 2005), several regions of the Posterior Parietal Cortex (PPC), namely the Inferior Parietal Lobe (IPL) and the Ventral Intraparietal Area (VIP) (Cohen & Andersen, 2004; Duhamel et al., 1998; Maravita et al., 2003; Molholm et al., 2006; Sereno & Huang, 2006), and premotor and prefrontal cortical regions (Barbas et al., 2005; Sugihara et al., 2006).

This evidence has led to a hierarchical model of cross-modal convergence, occurring in higher-order, specialized brain areas where sensory information is combined and synthesized according to various constraints. Following this model, no integration between sensory items can occur before each signal is extensively processed through modality-specific, self-contained cortical pathways, deferring every convergence among senses until late in the cortical perceptual processing stream (Schroeder & Foxe, 2005). This view largely reflects a modular approach to the study of perceptual functions, a hallmark of cognitive research from the 1960s through the 1980s, which fractioned behavioral functions into independent modules, holding a high degree of functional specialization and competing one with the other during processing (Fodor, 1983; Pascual-Leone & Hamilton, 2001).

However, the adoption of neurophysiological and functional-imaging techniques [e.g. positron emission tomography (PET), functional magnetic resonance (fMRI), event-related potentials (ERPs) and magnetoencephalography (MEG)] has led to the increasing realization that multisensory influences might be much more pervasive than classical views assumed

and may even affect brain regions and neural responses traditionally considered modality-specific (Driver & Noesselt, 2008; Schroeder & Foxe, 2005). Accordingly, behavioral evidence shows that the phenomenal experiences and perceptual judgments within one modality can be dramatically affected by stimulation in another modality (Driver & Spence, 2000). Cross-modal illusions are a case in point, since they reveal how perception in one sensory domain can be qualitatively altered by a stimulus in another modality (Stein, 1998). Moreover, multisensory interactions can affect how we direct attention in space, for example, improving the perceptual judgment of a visual stimulus when it is coupled with a tactile or auditory cue at the same location (Macaluso et al., 2002; 2003).

This cohort of neuroimaging and behavioral evidence has compelled classical models to move beyond a modular paradigm of sensory processing, embracing the idea that multisensory integration processes may extend until primary stages of sensory processing (Calvert et al., 1999; Foxe et al., 2000; Ghazanfar & Schroeder, 2006).

This challenging assumption naturally raises two main questions: (1) Are primary sensory (unimodal) cortical areas engaged in early multisensory integration? (2) Which are the cortical mechanisms that sustain the interactions between senses in primary sensory areas?

As noted above, neuroimaging and electrophysiological studies in the human brain has provided some clues in response to the first question. For instance, ERPs studies has detected audio-visual interactions at an early time window during visual processing (40 msec), and at scalp locations mostly corresponding to primary visual areas (Giard & Perronet, 1999); additionally, a growing number of fMRI evidence showed activation of primary auditory, visual and somatosensory cortices in response to cross-modal stimulation

(Macaluso et al., 2002; 2003; Calvert et al., 1997; 2000; Amedi et al., 2002; Watkins et al., 2007).

However, despite their remarkable spatial and temporal resolution, these techniques show pattern of functional activity correlated to a given task, without assessing whether a given brain area is necessary for the function under investigation (Bolognini & Ro, 2010). Conversely, non-invasive brain stimulation (NIBS) techniques, by transiently and reversibly altering brain activity, may allow the assessment of the causal role of a targeted brain area in a specific task/behavior (Pascual-Leone et al., 2000).

For this reason, I took advantage of two NIBS techniques, namely *Transcranial Magnetic Stimulation* (TMS) and *transcranial Direct Current Stimulation* (tDCS) to investigate how multisensory stimuli can shape visual cortical and perceptual responses, in order to: (1) Demonstrate a causal link between cross-modal influences on visual perception and early cortical responses and (2) Shed light on the involvement of higher-order multisensory cortices in these low-level effects.

In the present Chapter, I will firstly provide an overview of the current literature about multisensory interactions in traditionally considered "modality-specific" brain areas, focusing on recent TMS evidence about the effects of cross-modal stimuli within early visual cortical areas. Finally, I will discuss some new theoretical frameworks that take into account the mechanisms by which cross-modal interactions occur in primary sensory cortices.

1.1. Multisensory influences in early sensory areas

Cross-modal interactions in space

Several examples of multisensory effects on unisensory processing have been provided in the domain of cross-modal spatial attention, where the stimulation of, or attention to, one sensory modality, i.e. the "modulatory" cue, has been shown to affect activity in areas dedicated to a different modality, in a spatially-specific manner (Macaluso & Driver, 2001). The modulatory cue may render a particular region of space salient for a second stimulus in another modality, to facilitate the processing of the latter when occurring in that specific portion of space (Driver & Spence, 2000; Frassinetti et al., 2002). Accordingly, several lines of evidence have shown that voluntarily directing endogenous attention to a spatially non-predictive tactile cue can lead to enhanced judgments not only for co-localized tactile stimuli but also for visual targets presented near to the location of the tactile cue, as compared to those presented elsewhere, affecting visual properties orthogonal to the nature of the tactile stimulus (Driver & Spence, 1998; Spence et al., 2000; Kennet et al., 2001). Similarly, when an auditory target is expected at a particular location in space, the subjects' response (both speed and accuracy) is enhanced on the side of the expected stimulus also for the visual modality, although the visual target is uninformative (Spence & Driver, 1996). Cross-modal stimuli can also serve as exogenous attentional cues: when a peripheral salient sound cues a visual target on the same side, visual discrimination and detectability are increased, relative to trials where the auditory cue and the visual target are on the opposite sides (Spence & Driver, 1997; McDonald et al., 2000; Frassinetti et al., 2002). These behavioral findings nicely demonstrate that spatial information may be shared across multiple representations, in a spatially coherent manner (Macaluso & Driver, 2001).

Through a series of elegant neuroimaging investigations, Macaluso and colleagues explored the neural correlates of either endogenous or exogenous cross-modal interactions

in space (Macaluso et al., 2000a; 2000b; 2003). From the one hand, by using an endogenous paradigm during Positron Emission Tomography (PET) scanning (Macaluso et al., 2000a), the authors reported that voluntarily orienting attention to a specific location in space activated the anterior part of the contralateral Inferior Parietal Sulcus (IPS), irrelevantly of the target modality. This result corroborates the idea that the attentional selection of a region in space occurs at a multisensory level and indicates the IPS as a putative structure for supporting such a function (Spence et al., 2000; Macaluso & Driver, 2001). Multisensory responses were also found in other human associative areas, including the IPL, the posterior part of the STS, and the ventral Premotor Cortex (vPM) (Bremmer et al., 2001; Macaluso & Driver, 2001), in line with electrophysiological findings in non-human primates (Meredith & Stein, 1983; Graziano & Gross, 1995). This evidence is consistent with multisensory spatial integration occurring through converging feed-forward sensory pathways (Driver & Spence, 2000; Stein & Meredith, 1993). However, further evidence shows that this is only part of the story. Indeed, during the spatial attention task not only the activity of higher-order multisensory areas, but also that of low-level sensory-specific areas was increased (Macaluso et al., 2000b; Macaluso et al., 2003): spatially congruent visuo-tactile stimuli (e.g. a brief flash in the left or the right hemifield near one hand together with a congruent vibration) also enhanced the neural activity in the contralateral occipital visual cortex, relative to the activation brought about by unimodal visual stimuli (Macaluso et al., 2000b). Within the audio-visual domain, ERPs studies reported similar cross-modal activations in primary sensory areas: spatially predictive auditory cues modulated visual-evoked neural activity, first in the superior temporal cortex, and then in the ventral occipital cortex (15–25 msec later) (McDonald et al., 2003); moreover, directing endogenous tactile attention (Eimer &

Driver, 2000; Eimer & van Velzen, 2005; Eimer, 2001) or auditory attention (Eimer & Schröger, 1998) in a specific position of the external space increased visual ERPs evoked by an irrelevant visual stimulus.

Importantly, in all these works the spatial alignment of cross-modal stimuli in external space is a crucial factor for evoking such low-level cross-modal effects (Macaluso et al., 2002). However, not only spatial, but also temporal and semantic constraints govern multisensory interactions, in particular when auditory and visual modalities are engaged.

Timing constraints and Cross-modal Illusions

Beyond the spatial domain, multisensory effects can influence 'sensory-specific' perception in many other ways. For instance, when a listener sees the lip movements while he listens to a story, and the information provided by the visual and auditory channels is semantically and temporally congruent, speech processing and its intelligibility are strongly increased (Calvert et al., 1999; 2000). FMRI evidence has shown a remarkable correlation between the presentation of audio-visual synchronized stimuli and an increased activity in the posterior ventral bank of the left STS, but also in the left primary auditory cortex (A1) and in the primary visual cortex (V1) (Calvert et al., 1999; 2000). Crucially, no increase of activation was observed for paired, but desynchronized, auditory and visual stimuli, emphasizing the impact of temporal constraints on this multisensory phenomenon. Temporal synchrony acts as a cue to combine signals that are perceived in different modalities but that are likely to originate from a single multisensory event (see also Stein & Meredith, 1993, for related works in animal models).

Temporally coincident speech cues can still be combined even if slightly mismatched, but the resulting synthesis yields an entirely different percept (Stein & Stanford, 2008). For instance, in the McGurk effect (McGurk & MacDonald, 1976) watching lip-movements alters the way in which a phoneme is heard for a particular sound (Massaro, 1999) while, in the ventriloquist effect, the same visual stimulus can alter the apparent location of sounds, capturing the latter towards its position (Howard & Templeton, 1966; Bertelson, 1999). Further effects were reported for other cross-modal pairings: in the Parchment-skin effect, perturbing the sound made by rubbing hands together can affect the perception of skin texture (Jousmäki & Hari, 1998), while altering the color of drinks or food can modify the perception of their flavor (DuBose et al., 1980). Within the visual domain, a number of illusory phenomena have been described, revealing robust and vigorous influences of non-visual sensory inputs on visual perception. An example regards the sound-induced changes of visual motion perception: when two identical visual objects (e.g., two vertical bars) continuously move toward each other, coincide, and continue along the same linear path of motion, they can be perceived as either streaming through each other or colliding and bouncing back along the same, but now reversed, path (Sekuler et al., 1997). Intriguingly, the number of trials perceived as "collision trials" greatly increases if a sound is presented at the exact moment when the two visual stimuli overlap, inducing a qualitative change in visual perception. Neuroimaging evidence has reported an increased activity in parietal and prefrontal cortices related to the trials where a collision is perceived, together with a concurrent decrease in auditory and visual areas (Bushara et al., 2003).

Another example of qualitative alteration of visual perception induced by concurrent sounds is represented by the *Sound-Induced Flash Illusion* (SIFI). This intriguing phenomenon

has been firstly described by Shams, Kamitani and Shomojo in 2000, and involves the perception of multiple flickering flashes of light, when multiple sounds are presented in temporal coincidence with a single flash (Shams et al., 2000; 2002). The SIFI is a surprisingly simple but robust effect and has been associated with a change in perceptual sensitivity rather than a mere auditory-driven bias of perception (Rosenthal et al., 2009; Watkins et al., 2006; 2007; Wozny et al., 2008), therefore reflecting cross-modal interactions at a perceptual level. To note, a similar visual illusion can be also induced by tactile stimuli (Violentyev et al., 2005).

Cross-modal illusions represent an extreme example of how perception can be modified by cross-modal interactions. However, why should a perceptual system be misled by another one? At first sight, such cross-modal interactions may seem "tricky" phenomena, involving a sub-optimal representation of the external world; rather, they could be interpreted as the result of our perceptual system efforts to come up with a reliable esteem of the external event, through a weighted average of the contribution of each sensory modality based on its reliability/validity with respect to the specific situation (Helbig & Ernst, 2007; Ernst & Banks, 2002). Accordingly, the final aim of this process is to provide an optimal percept, which minimizes the noisiness of each sensory information. However, the 'best guess' can also be wrong sometimes and result in perceptual errors, namely illusions (Ernst & Bülthoff, 2004).

Collectively, this evidence reveals vigorous interactions among senses, occurring in a variety of domains and affecting neural responses in sensory-specific cortical regions and related perception. These interactions offer a completely new perspective for the study of perception: in particular, the demonstration that the visual system undergoes qualitative

and quantitative changes by cross-modal inputs as much as other sensory modalities do, discards another steady point of the traditional/modular approach, which considered vision as the dominant modality (Boring, 1947), impenetrable by other sensory inputs. Conversely, visual processing appears to function as part of a larger network that benefits from information provided by a variety of sources and modalities, and where interactions among senses represent the rule rather than the exception. In this context, both the cross-modal illusions and the cross-modal facilitatory spatial effects offer a cohort of experimental paradigms to study early multisensory effects in low-level sensory-specific cortices. However, it remains to be clarified whether and how these effects causally engage early processing in primary sensory regions, in particular within early visual areas. In line with the aim of the present thesis, the next step will be the description of some previous TMS works, which have tested the modulatory effects of cross-modal stimuli directly within the early visual areas, by means of TMS-induced phosphenes.

1.2. Phosphene perception as a marker of early cross-modal effects in the visual cortex

The investigation of the cross-modal modulation of phosphene perception represents a valuable approach to disclose how cross-modal interactions alter visual cortical excitability, in turn verifying the causal involvement of early visual areas in multisensory interactions.

The application of single-pulse TMS (sTMS) to the occipital areas can elicit phosphenes, namely bright spots of light appearing in specific regions of the visual field, which reflect the retinotopic organization of human visual cortex (McKeefry et al., 2009;

Fernandez et al., 2002). Phosphenes are generated by TMS of virtually all early visual areas, including the striate cortex (V1), the extrastriate areas (V2/V3), and cortico-cortical tracts projecting from V2/V3 back to V1 (Kammer et al., 2005). Because the sTMS output threshold needed to generate phosphenes, namely the *Phosphene Threshold* (PT) provides a direct measure of visual cortical excitability (Kammer et al., 2005), the study of cross-modal influences on phosphene perception can provide a more direct measure of early visual cortical responses to non-visual stimuli (for a review, see Bolognini & Maravita, 2011).

By using this approach, it has been shown that peripheral cross-modal stimuli can modify the excitability of the visual cortex in such a way that phosphene perception can be induced using a lower sTMS intensity. Such cross-modal modulation of phosphenes follows strict spatial and temporal constraints, and it becomes behaviorally relevant especially under conditions of sub-threshold sTMS intensity, suggesting that this type of cross-modal interactions depends on the relative physiological salience of visual information (Bolognini et al., 2010a; Romei et al., 2007; 2009; Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007). A few examples in this regard. A touch occurring at the same spatial location of the perceived TMS-induced phosphene facilitates its detection (Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007). Crucially such facilitation is strictly dependent on the spatial alignment of visual and somatosensory stimuli: the facilitatory effect of touch on phosphene perception is abolished when the hand is located far away from the phosphene (i.e., in the opposite hemifield or even in the opposite quadrant of the same hemifield) (Bolognini & Maravita, 2007). This effect is in agreement with findings on cross-modal spatial effects investigated with fMRI, demonstrating enhanced activity in early visual areas in response to spatially coincident visuo-tactile stimuli (Macaluso et al., 2000b, see above). Moreover, the

touch-induced facilitation of phosphenes is maximal when the peripheral somatosensory stimulus preceded the occipital TMS by 60 msec (Ramos-Estebanez et al., 2007), in line with ERP evidence for cross-modal tactile modulation of visual responses (Eimer, 2001). Finally, these cross-modal sensory interactions can be revealed only when phosphene perception is at or below threshold (Ramos-Estebanez et al., 2007), broadly in line with the *"inverse effectiveness rule"* of multisensory integration, which predicts that the salience of the unimodal signals represents a major determinant of the advantage resulting from their integration (Holmes & Spence, 2005; Meredith & Stein, 1983).

Cross-modal modulation of phosphene perception has also been reported when auditory, instead of somatosensory, stimuli were paired with the TMS pulse (Romei et al., 2007; 2009; Bolognini et al., 2010a). Romei and colleagues in 2009 showed that acoustically structured looming sounds selectively and pre-perceptually increased visual cortical excitability, as indexed by the individual PT, with enhancing effects starting when TMS followed the auditory stimulus by 80 msec (Romei et al., 2009). Subsequently, Bolognini and colleagues showed that a maximal facilitation of visual cortical excitability could be obtained when sounds (20 msec bursts of white noise) were aligned with the peripheral position of the induced phosphenes and preceded the TMS pulse by 40 msec (Bolognini et al., 2010a). Finally, a recent work revealed that the stimulus-selective, acoustical modulation of phosphenes, driven by high-pitch and narrowband sounds, exerted its maximal effect when the TMS pulse followed the sound onset by 30 msec, although remarkable influences were still observed at a delay of 90 msec (Spierer et al., 2013). Despite these works report slight differences with respect to the latency of auditory modulation in the visual cortex, which might in principle be explained by methodological factors such as the type of auditory

stimulus or the temporal and spatial features of the combined stimuli (Bolognini & Maravita, 2011), they are broadly in line with previous ERPs studies in humans, showing relatively early influences of auditory stimuli on visual perception (Giard & Perronet, 1999; Molholm et al., 2002; Cappe et al., 2010; Raij et al., 2010). Crucially, different timing might also be suggestive of distinct mechanisms mediating the transmission of cross-modal inputs to low-level visual areas.

Overall, the available evidence on the cross-modal modulation of phosphene perception suggests the existence of somatosensory-driven or auditory-driven sensitivity changes on low-level visual cortical excitability (Bolognini & Maravita, 2011). Nevertheless, we are still far from a complete characterization of these early modulatory phenomena.

1.3. Possible cortical mechanisms for multisensory influences on sensory-specific cortices

Regarding the potential origins and the neural mechanisms subtending cross-modal interactions in primary sensory areas, a number of potential accounts have been proposed (see Figure 1 for a schematic depict of the two main explanatory proposals). The hypotheses put forward range from the extreme idea that all brain areas may be inherently multisensory, all containing at least some multisensory neurons (Allman & Meredith, 2007), to models of brain connectivity, some of them emphasizing the role of feed-back modulatory influences from higher-level multisensory zones to primary sensory areas, or of direct feed-forward projections between primary sensory cortices (Driver & Noesselt, 2008).

With respect to the first account, although recent evidence speaks in favor of a good permeability of the different sensory systems to cross-modal influences, it is largely implausible that all cortical areas are inherently multisensory. Indeed, functional specialization is a very basic principle of brain organization and regional preference for the processing of specific sensory signals cannot be denied (Krubitzer et al., 1997, Macaluso & Driver, 2005; Van Essen et al., 1992).

The second main account proposes that multisensory effects on sensory-specific cortices may reflect feed-back influences from high-order heteromodal areas (Figure 1-A). This perspective retains the traditional distinction between multisensory and sensory-specific regions, with unisensory signals converging in higher-order multimodal areas through feed-forward projections, but also assumes the existence of modulatory, feed-back projections conveying multisensory information from heteromodal regions of the temporal, parietal and frontal cortices to primary sensory areas, like V1 and A1 (Jones & Powell, 1970; Meredith & Stein, 1983; Giard & Peronnet, 1999; Calvert, 2001; Macaluso, 2006; Meienbrock et al., 2007; Driver & Noesselt, 2008; Macaluso & Driver 2001). To note, analogous feed-back modulatory projections are invoked by models of attentional control, assuming top-down modulatory influences from a fronto-temporo-parietal attentional control network, which shows a supramodal nature, to posterior sensory areas (Kastner & Ungerleider, 2001). Consequently, this model has been proposed for explaining the cross-modal effects in spatial attention (Calvert et al., 1999; Macaluso & Driver 2001; Macaluso, 2006). Indeed, fMRI studies have detected multisensory attentional effects in heteromodal parietal areas (Macaluso & Driver 2001; Bremmer et al., 2001), which correlated with the increased activity in primary sensory areas, like V1 (Macaluso et al., 2000b; Macaluso & Driver, 2005).

The third account relies on recently discovered direct connections between sensory-specific areas (Figure 1-B). Recent neuroanatomical studies on non-human primates have documented the existence of dense monosynaptic projections from the primary or associative auditory cortices (A1) into primary visual areas (Falchier et al., 2002; Rockland & Ojima, 2003; but see also Cappe & Barone, 2005, for other anatomical projections between visual, auditory, and somatosensory areas). Similarly, electrophysiological works reported somatosensory responses in auditory regions adjacent to A1 (Fu et al., 2004; Kayser et al., 2005; Schroeder et al., 2001; Schroeder & Foxe, 2002). In humans, further support to the existence of these direct connections has been provided by ERPs reports of relatively early interactions (<50 msec post stimulus onset) between sensory modalities (Giard & Peronnet, 1999; Molholm et al., 2002; Senkowski et al., 2007; Foxe et al., 2000). Effects at such short latencies apparently rule out any modulatory role of multimodal areas in higher-order associative cortices, suggesting that some direct connections from primary sensory cortices are likely to mediate rapid interactions between low-level sensory areas without invoking multisensory regions (Cappe & Barone, 2005).

Finally, it has been proposed that a number of thalamic structures, including the posterior (PO) and postero-medial (PM), limitans (LIM), suprageniculate (SG) nuclei of thalamus, as well as the magnocellular (MGm) division of the medial geniculate nucleus (De la Mothe et al., 2006; Hackett et al., 2007) could play a key role in multisensory processing (Ghazanfar & Schroeder, 2006; Cappe et al., 2009a; 2009b). In particular, the pulvinar nucleus, among the other thalamic structures, seems to be a good candidate for mediating integrative processes, given the multisensory responses characteristic of its neurons (Avanzini et al., 1980; Gattass et al., 1978) and its extensive connectivity with a number of

sensory and motor cortical regions (Cappe et al., 2009a; 2009b; Budinger et al., 2006). However, the function of thalamic structures and their relevance for multisensory integration is still matter of debate. Thalamic nuclei could serve as a relay between different sensory and/or premotor cortices, providing a "cortico-thalamo-cortical" route through which sensory information is transferred among remote cortical areas. Recently, Lakatos and colleagues also suggested that thalamic structures might work as synchronizers of oscillatory activity among distant sensory structures, matching the temporal patterns (i.e. the rhythms) of cross-modal information, in terms of frequency and phase (Lakatos et al., 2007). Accordingly, the visual or somatosensory information could drive oscillations in auditory cortex into the ideal phase for the auditory input, with the result of an enhanced auditory cortical response (Lakatos et al., 2007).

In conclusion, different pathways are likely to mediate multisensory interactions at low-level cortical stages of sensory processing. Modulatory feed-back from higher-order areas might be important for controlling spatially-specific multisensory processing. On the other hand, coarse, non-specific cross-modal interactions may rather rely on faster direct cortico-cortical projections (Macaluso, 2006). The current scientific literature seems to indicate that these mechanisms are not mutually exclusive or 'rival'; rather, they may coexist, being differentially recruited according to the specific multisensory phenomenon, or they could even take charge of situation when one of these mechanisms is out of order (Bolognini et al., 2013).

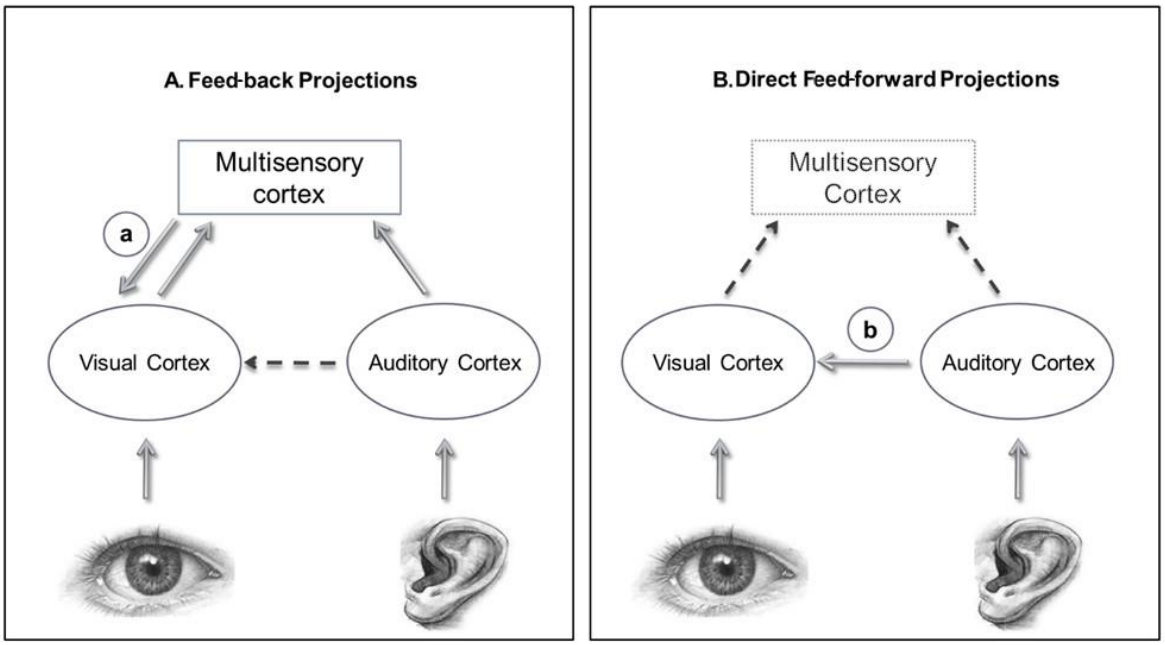


Figure 1. Cortical mechanisms of multisensory influences on sensory-specific cortices. A. Feed-back Projections: Feed-forward convergence from sensory-specific to multisensory areas are combined with feed-back projections (a) from the latter to the former. B. Direct feed-forward projections: Stimuli from one modality can activate cortices of a different modality, via direct anatomical connections (b) between sensory-specific brain areas.

1.4. Concluding remarks and specific aims

In the last decades there has been a revolution in multisensory research, driven by the realization that multisensory processing may extend far beyond established higher-order areas of multisensory convergence up to sensory-specific cortical regions and perception. This novel view has been supported by behavioral, neuroanatomical and brain imaging evidence, and to a less extent by TMS studies. Understanding under which conditions our ability to integrate inputs from different sensory modalities can be increased (or decreased)

and delineating the mechanisms supporting this phenomenon will pave the way to a better elucidation of multisensory interactions, but also to the development of novel approaches for potentiating multisensory processing in the healthy and damaged brain.

The following chapters will provide a characterization of cross-modal interactions in early visual cortex in the healthy and in the damaged brain. Through a series of studies, I will provide evidence of quantitative and qualitative alteration of visual cortical activity and subjective perceptual experience induced by cross-modal stimuli. To this aim, I will use two different paradigms, namely the cross-modal induction of phosphenes and the *Sound-Induced Flash Illusion* (SIFI).

In Chapter 2, I will illustrate the facilitatory effects of spatially-specific auditory, tactile and audio-tactile stimuli on TMS-induced phosphenes. These multisensory effects will be quantified in terms of an increased detectability and brightness of the visual events. Moreover, by applying tDCS over cortical sites putatively mediating these cross-modal spatial interactions, I aim at exploring whether and how the multisensory influences on phosphenes could be further modulated, thus providing evidence for the causal involvement of these areas in early cross-modal spatial effects.

In Chapter 3, I will use the same TMS-based approach to understand whether visual perception, beyond being facilitated, can also be misled by non-congruent auditory events, driving in turn to phenomenological changes in subjective visual experience. Accordingly, I will take advantage of a well-known audio-visual illusion, namely the SIFI, and I will attempt to replicate it in the phosphene domain.

Finally, In Chapter 4, I will investigate how the SIFI is perceived by brain-damaged patients with visual field deficits or unilateral spatial hemineglect (USN). By doing so, I will complement my investigation about the role played by the visual cortex and associative areas in multisensory perception through a neuropsychological perspective.

Chapter 2

Cross-modal enhancement of visual cortical excitability

[This research has been published in: Convento, S., Vallar, G., Galantini, C., & Bolognini, N. (2013) Neuromodulation of early multisensory interactions in the visual cortex. *Journal of Cognitive Neuroscience*, 25, 685–696]

2.1. Aim of the study

In humans, strong support for the causal involvement of low-level sensory areas in multisensory processing has been provided by studies investigating the cross-modal modulation of phosphene perception (Bolognini & Maravita, 2007; 2011; Bolognini et al., 2010a; Ramos-Estebanez et al., 2007; Romei et al., 2007; 2009; 2012; Spierer et al., 2013). As discussed in Chapter 1, these studies show that early cross-modal interactions obey to temporal and spatial congruency rules, and they also reveal the dynamics and stimulus-related selectivity of these effects (Bolognini et al., 2010a; Romei et al., 2009), paving the way to its cortical characterization.

To date, a direct comparison between the effects of different cross-modal combinations on phosphene perception, including the impact of a trimodal stimulation, is still lacking. Moreover, the cortical network mediating the cross-modal influences on phosphene perception has not been determined yet. As far as cross-modal spatial effects on phosphene perception are concerned, it has been nicely demonstrated that interfering with

cortical activity in the PPC via repetitive TMS (rTMS) selectively disrupts the spatial remapping of visuo-tactile interactions, providing the first, and to date the only, evidence of a causal involvement of cross-modal modulatory influences from this area on V1 activity (Bolognini & Maravita, 2007). Whether this parietal effect is specific for body-related visuo-tactile interactions or it extends to other sensory combinations is still unknown.

To this aim, I have performed a first experiment aimed at comparing the effects of different combinations of bimodal (i.e., an auditory or tactile stimulus combined with the occipital sTMS pulse) and trimodal (i.e., an auditory-tactile stimulation combined with the occipital sTMS pulse) stimuli on sub-threshold phosphene perception. At difference with previous studies, beyond testing phosphene detectability, I have also examined the cross-modal modulation of the perceived phosphene brightness. In this regard, there is evidence showing that cues from one sensory modality can substantially alter perceptual judgments in another modality: Stein and co-workers (1996) reported the enhancement of the perceived intensity of a visual target by an auditory cue, with most pronounced influences at the lowest intensities of the visual stimulus (Stein et al., 1996). Since judgments of the intensity of a stimulus are assumed to depend on the population of neurons activated along a modality-specific pathway and the frequency at which they discharge (Orban, 1984; Barlow et al., 1978; Papaioannou & White, 1972), it follows that phosphene brightness may likely represent an index of the intensity of the visual signal, shedding more light on the mechanisms by which cross-modal interactions affect visual cortical responses.

Then, a series of following experiments (2-3) further explored the possibility of boosting the cross-modal influences on phosphene perception through the neuromodulation

of areas putatively mediating such multisensory interactions. To this aim, I took advantage of tDCS.

tDCS is a NIBS technique that involves the delivery of weak, constant direct currents via electrodes applied on the scalp, in correspondence with target cortical areas (Wassermann & Grafman, 2005). TDCS can up- or down-regulate neural activity in the stimulated regions in a polarity-dependent manner, with anodal stimulation enhancing cortical excitability of the underlying cortical areas and cathodal stimulation decreasing it (Nitsche & Paulus, 2000; 2001; Brunoni et al., 2012). The mechanisms of action of tDCS rely on the modulation of neuronal signalling by influencing the permeability of ion channels or shifting electrical gradients. This electrical variation, in turn, modulates the resting membrane threshold (Ardolino et al., 2005). Chemical neurotransmission, either pre- or post-synaptic, may also play a role in tDCS effects (Liebetanz et al., 2002). In humans, tDCS has been successfully used to facilitate modality-specific visual and tactile perception (for recent reviews, see Utz et al., 2010; Vallar & Bolognini, 2011; Zimerman & Hummel, 2010), and to affect plasticity (Nitsche et al., 2003; 2004; Kuo et al., 2008; Fritsch et al., 2010) . However, fewer studies have used this technique to modulate multisensory interactions (Bolognini et al., 2010a; 2010b; 2010c).

Here, tDCS was used to increase auditory and/or tactile influences on visual cortical excitability, as measured by TMS-induced phosphenes. To this aim, anodal tDCS was applied over the occipital, temporal or parietal cortices. The following considerations guided the choice of these cortical targets. First, the occipital cortex is the cortical area for phosphene induction, and previous studies have shown that its stimulation by anodal tDCS improves phosphenes perception (Antal et al., 2003a; 2003b; 2004). Hence, the hypothesis was that

anodal tDCS of the occipital cortex could facilitate phosphene perception, regardless of the presence of cross-modal stimuli. Instead, the stimulation of the temporal and of the parietal cortices should specifically affect the cross-modal influences of sounds and touches on phosphene perception, plausibly through the modulation of feed-back influences from these multisensory convergence zones to visual areas, or by directly facilitating cross-modal inputs from primary somatosensory and auditory areas (Driver & Noesselt, 2008; Macaluso, 2006). In both circumstances, a tDCS facilitation of phosphene perception under cross-modal conditions was expected.

2.2. Experiment 1

2.2.1. Materials and methods

Participants

Twenty-six healthy volunteers took part at this study. Given the subjective nature of phosphene perception, only participants who consistently reported phosphenes at a preliminary evaluation (i.e. training session, see below) entered the experimental part. Consequently, twelve out of the thirty-eight initially screened participants were excluded.

Eight volunteers (3 males, mean age = 23.6, range = 19-34) participated in Experiment 1. All participants had normal hearing and normal or corrected-to-normal vision. None of them had neurological, psychiatric, or other relevant medical problems, nor any

contraindication to NIBS (Rossi et al., 2009). Accepted recommendations for the safe use of TMS and tDCS were applied (Rossi et al., 2009).

Participants were all naïve to the experimental procedure, and to the purpose of the study. They gave informed consent prior to be enrolled in the study, which was carried out according to the guidelines of the ethical committee of the University of Milano-Bicocca, and in accordance with the ethical standards of the Declaration of Helsinki (British Medical Journal, 1991, Vol. 302, p. 1194).

Training Session

To determine the optimal site of occipital stimulation for inducing reliable phosphenes, an initial training prior to the first experimental session was conducted for all participants. The training consisted in a functional mapping procedure of the occipital cortex (Fernandez et al., 2002); this type of protocol has been previously used to probe visual cortical excitability (Bolognini & Maravita, 2007; Bolognini et al., 2010a; Romei et al., 2007; 2008a; 2008b; Silvanto et al., 2009).

During the mapping procedure, participants sat in a darkened room, wearing a specially designed blindfold to accomplish total darkness, and an elastic swimming cap to mark the stimulation sites. With the aim of facilitating phosphene perception, all participants were adapted to darkness for the first 10 min (Fernandez et al., 2002). Subsequently, single-pulse TMS (sTMS) was delivered over the occipital cortex using a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Whitland, UK), connected with a 70

mm figure-of-eight-shaped coil (maximum field strength, 2.2 T). Firstly, we determined in each participant the optimal scalp site over which the occipital sTMS pulse induced a phosphene. To this aim, the stimulation site was determined by moving the coil in steps over the right occipital pole, while the subject was stimulated with a supra-threshold TMS intensity until he/she observed a sharply delineated phosphene, clearly restricted to the left visual field ("hot spot"). At this coil position, different stimulator intensities were tested in steps of 3% in order to determine the individual Phosphene Threshold (i.e., PT), namely, the minimum intensity of the sTMS needed to evoke a phosphene on 50% of trials (i.e. 5 out of 10 trials). The mean PT was of 66% [Standard deviation (SD) ± 8%] of maximum stimulator output in Experiment 1, of 65.5% (SD ± 8%) in Experiment 2, and of 63% (SD ± 5%) and 61% (SD ± 4%) in Experiment 3-A and 3-B, respectively.

Then, the TMS coil position was kept constant for each participant across the different experimental sessions. To this aim, the coil location was marked on the elastic swimming cap placed over the head of the participants. Only the occipital cortex of the right hemisphere was stimulated, with phosphenes being induced in the left visual hemifield. The optimal stimulation site across participants was localized on average 2.6 cm above the inion (SD = 1 cm) and 2 cm to the right of the midline (SD = 0.6 cm). During the experimental session, participants remained blindfolded and sTMS was applied at the previously determined optimal scalp location for phosphene induction, at the individual PT.

The training session also allowed us to monitor the reliability of phosphene perception over time. Actually, the optimal occipital coil position, as well as the shape, size, and spatial location of the perceived phosphenes, remained constant over repeated trials in participants selected for the experiment.

S*timuli and procedure*

The experimental apparatus, stimuli and procedures described below were maintained constant across the 3 experiments.

The auditory stimulus consisted in a 250 msec (55-75 dB) looming sound (Romei et al., 2009) delivered from an external loudspeaker, which was spatially aligned with the visual field quadrant where phosphenes appeared (Bolognini et al., 2010a). The choice of a structured looming, namely a rapidly approaching, behaviourally salient stimulus (Schiff et al., 1962; Neuhoff, 1998; Ball & Tronick, 1971) was driven by the evidence that this type of sound is best suited to enhance visual cortex excitability (Romei et al., 2009).

The tactile signal consisted in 15-msec supra-threshold vibrations (namely, two 5-msec on-phases, interleaved with one 5-msec off-phase-interval) released through a custom-made electromagnetic solenoid, attached to the participants' left index finger. Participants were required to place their left hand in the same visual field quadrant of phosphenes (see, Bolognini & Maravita, 2007). Hence, both the auditory and the tactile stimulus were presented at the same spatial location as the perceived phosphene (see Figure 2.1), with respect to both the vertical and the horizontal meridians, in accordance with previous reports from our laboratory, showing that cross-modal influences on phosphene perception are spatially-specific (Bolognini et al., 2010a; Bolognini & Maravita, 2007).

The looming sound always preceded the sTMS pulse by 40 msec, while the tactile vibration preceded the sTMS pulse by 60 msec. These inter-stimulus intervals (ISIs) were chosen in line with previous works, showing the temporal profile of cross-modal interactions in the visual cortex, by using phosphene induction via sTMS (Bolognini et al., 2010a; Ramos-

Estebanez et al., 2007; Romei et al., 2009). Finally, catch trials, namely tactile, auditory, or audio-tactile stimuli without sTMS, were randomly presented.

Experiment 1 consisted in two blocks, each including 60 trials: 12 Unimodal trials (only TMS), 24 Bimodal trials (12 visuo-tactile and 12 visuo-auditory), 12 Trimodal (visuo-audio-tactile) and 12 Catch trials without sTMS (4 auditory, 4 tactile and 4 audio-tactile). In every trial, the sTMS pulse was delivered at individual PTs, as previously determined during the training.

Each block lasted approximately 7 min and was separated from the other by a brief rest period of some min. Within each block, the stimuli were presented in a random order with an inter-trial interval between 4 and 5 sec to avoid any possible carry-over effect of TMS on visual cortical excitability (Walsh & Pascual-Leone, 2003).

Participants were instructed to press on the keyboard of a PC the button “1” with the index finger of their right hand when they saw a phosphene, and to press the button “2” with the middle finger of their right hand, to indicate that they did not see any phosphene. Only for Experiment 1, whenever the phosphene was present, participants were asked to indicate its level of brightness on a 5-point scale (1 = faint gleam percept; 5 = very bright phosphene). The subject’s rating for each trial was manually scored by the experimenter. The time required for completing the task was about 20 min. The experimental setup is depicted in Figure 2.1.

Stimulus presentation, timing and response recording were under computer control (E-prime Software, Psychology Software Tools, Pittsburgh, PA).

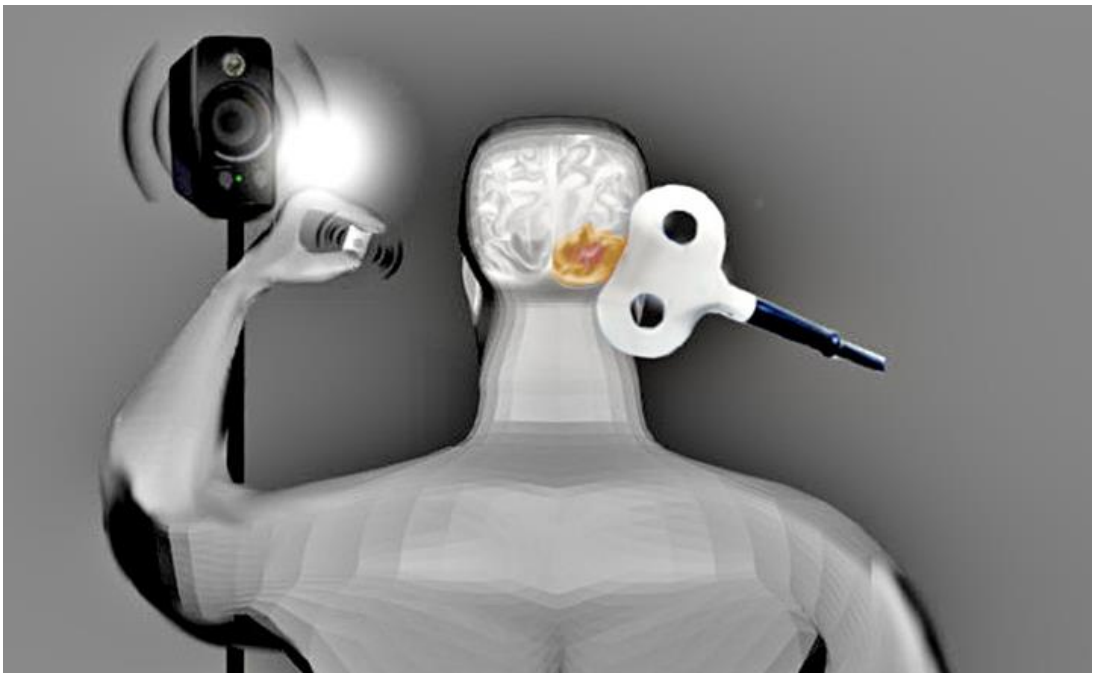


Figure 2.1. 3D representation of the experimental setup in Experiment 1. The looming sound was presented throughout an external loudspeaker, while the tactile vibration was released through a custom-made electromagnetic solenoid attached to the participant's left index finger. Both the looming sound and the tactile vibration were spatially aligned with the TMS-induced phosphene (bright circle). The TMS pulse was delivered over the right occipital cortex.

Statistical Analysis

Statistical analyses were performed using the Statistica Software (Statsoft, Version 6.0, StatSoft Italia SRL). The mean phosphene detection rate (PDR), namely the percentage of phosphenes computed as number of detections divided by the number of trials for each stimulus condition (the primary outcome measure) was used as index of visual cortical responses in the different sensory conditions. Before running the analyses, the PDR was transformed into the arcsine of the square root of the raw values, to normalize the data

distribution (Zubin, 1935).

The mean level of perceived brightness, namely the average of brightness ratings in trials where a phosphene was detected, was also computed, in order to quantify the perceived intensity of the visual precepts under the different sensory conditions. At difference with PDR, brightness values were normally distributed, thus no transformation was applied for this data.

PDR and mean brightness were analysed via one-way repeated-measures Analyses of Variance (ANOVA). When necessary, post-hoc multiple comparisons were performed by using the Student–Newman–Keuls test. The effect size in the ANOVAs was also measured by computing the partial Eta Squared ($p\eta^2$), which expresses the degree of association between an effect and the dependent variable, namely the proportion of the total variance that is attributable to a main factor or to an interaction (Cohen, 1973).

2.2.2. Results

PDR and mean reported brightness in the different trials were submitted to 2 one-way repeated-measures ANOVAs with *Condition* [4 levels: *Unimodal* (sTMS alone); *Bimodal Visuo-Acustic* (sTMS plus sound); *Bimodal Visuo-Tactile* (sTMS plus touch); *Trimodal* (sTMS plus sound and touch)] as main within-subject factor.

As predicted, both PDR and level of brightness vigorously increased in all cross-modal conditions as compared to the unimodal one, with the highest values registered in the trimodal condition (Figure 2.2).

Indeed, a significant main effect of *Condition* ($F_{3, 21} = 5.23$, $p < 0.001$, $p\eta^2 = 0.78$) emerged from the ANOVA on PDR, for which an increase of phosphene detection was evident for every cross-modal combination of stimuli, as compared with the unimodal one: sTMS alone = 39% vs. sTMS combined with sound = 49% ($p < 0.05$); sTMS combined with touch = 67%, ($p < 0.001$); sTMS combined with sound and touch = 77% ($p < 0.001$).

Across the cross-modal conditions, significant differences were found between the effects of sound and touch ($p < 0.01$), although it was the audio-tactile combination to induce the largest facilitation on visual responses ($p < 0.05$, for all comparisons).

The analysis of phosphene brightness showed again a significant effect of *Condition*, ($F_{3, 21} = 5.67$, $p < 0.01$, $p\eta^2 = 0.44$): as compared with the unimodal stimulus (mean rating = 0.70), an increase of phosphene brightness emerged when sTMS was paired either with touch (1.22, $p < 0.05$), or with an audio-tactile stimulus (1.41, $p < 0.01$), while the coupling with sound did not lead to a significant intensification (1.01, $p = 0.1$). To date, the effects of auditory and tactile stimuli were not significantly different ($p = 0.1$).

With respect to catch trials, participants committed only 2% false alarms (i.e., less than 3 false visual detections over 60 trials), with no differences among conditions; consequently, these data were not further analysed.

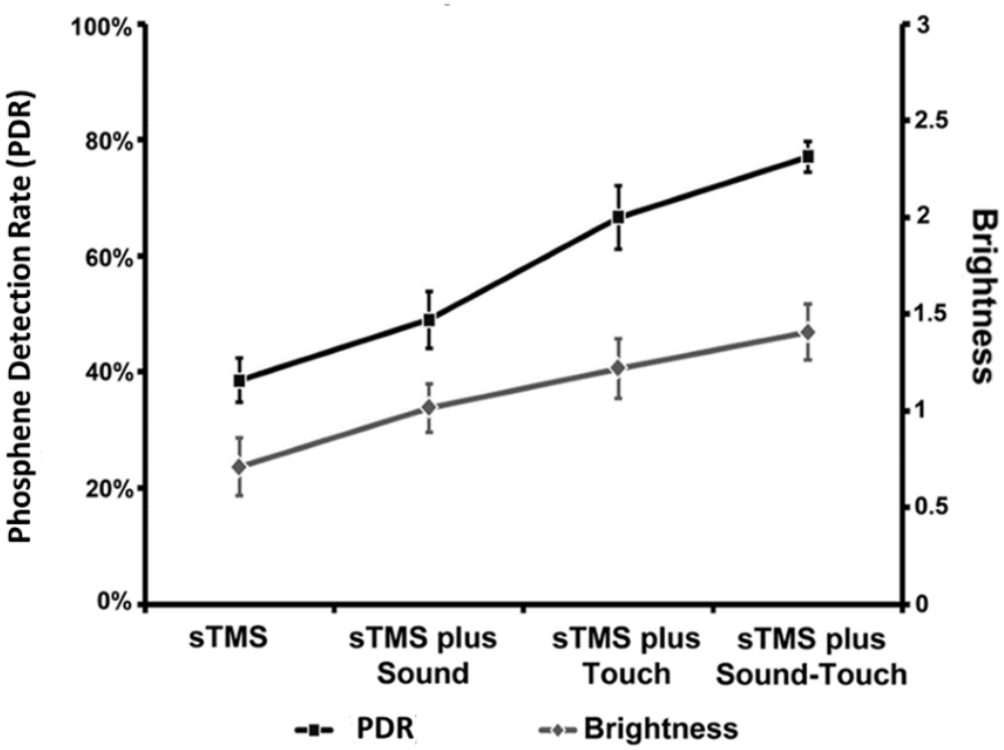


Figure 2.2. **Results of Experiment 1**. Mean phosphene detection rate (PDR), (left ordinate, black line) and mean perceived brightness (right ordinate, grey line) by sensory condition (abscissa: Unimodal: occipital sTMS alone; Cross-modal: sTMS plus Sound, plus Touch, plus Sound and Touch). Error bars= standard error of measure (S.E.M.)

2.3. Experiment 2

2.3.1. Materials and Methods

Participants

Eight participants were tested in Experiment 2 (2 males, mean age = 23.8, range = 19 - 34); six of them participated also in Experiment 1.

Experimental Procedures

The same general procedure of Experiment 1 was adopted in the second experiment. The main difference was that the phosphene detection task was now performed after the delivery of 10 min of anodal tDCS.

A double-blinded, sham-controlled design was adopted, which comprised 4 tDCS sessions randomized across participants, namely: 1) Active tDCS of the right temporal cortex; 2) Active tDCS of the right parietal cortex; 3) Active tDCS of the right occipital cortex; 4) Sham (i.e. placebo) tDCS.

Moreover, participants were now required to detect phosphenes, without judging their brightness. The global duration of each session was about 30 min.

Transcranial Direct Current Stimulation (tDCS)

tDCS was delivered by a battery-driven, constant current stimulator (Eldith Ltd., Germany, www.eldith.de/products/stimulator) through a pair of saline-soaked sponge electrodes (5 cm × 5 cm, 25 cm^2). tDCS can be set to deliver either active (i.e. real), or sham (i.e. placebo) modes of stimulation, through the use of codes set through the device. Such codes were previously selected by an external operator, who did not take part to data collection; in this way, the device was only activated by the experimenter, who remained unaware with respect of the mode of delivered stimulation (active vs. sham). Overall, this method has been shown to be reliable for keeping both the experimenter and the participant blind to sham and active tDCS (Gandiga et al., 2006), and it is commonly used in

tDCS clinical and experimental investigations (e.g., Nitsche et al., 2008; Brunoni et al., 2012; 2013)

In every experimental session, a constant current of 2mA intensity was applied for 10 min before the beginning of the phosphene detection task, in compliance with current safety data (Poreisz et al., 2007). Current intensity was gradually increased at the beginning and decreased at the end of the stimulation (namely, fade-in/fade-out phases = 10 msec) in order to diminish its perception and minimize the possibilities for participants to discriminate the type of stimulation to which they were subjected.

For the stimulation of the temporal cortex, the active electrode was placed over T4: the regions beneath T4 are Broadmann areas (BA) 22 and 42 (Talairach & Tournoux, 1988) corresponding mostly to the Superior Temporal Gyrus (STG) and to a less extent to the Middle Temporal Gyrus (MTG) (Herwig et al., 2003). For parietal stimulation, the active electrode was placed over P4, a location that overlies the PPC, close to the intraparietal sulcus (Herwig et al., 2003). For both these stimulation sites, the reference electrode was placed over the contralateral supraorbital area, in line with previous experimental works, showing the effectiveness of this montage (Bolognini et al., 2011a; Nitsche et al., 2008).

For occipital stimulation, the active anodal electrode was placed over O2, a site overlying the primary visual cortices, whereas the reference electrode was placed over Cz, in the light of previous studies, which have proved this electrode arrangement to be effective to achieve current-driven excitability changes in the occipital cortex (Bolognini et al., 2011a; Antal et al., 2004).

Each participant underwent four different tDCS sessions: three sessions during which

active tDCS was applied over one of the three target areas of the right hemisphere (namely, the same hemisphere of the occipital sTMS for phosphene induction) and one session with the delivery of sham tDCS.

For sham tDCS, the electrodes were arranged over one of the target areas (the electrodes montage was randomized across participants; Bolognini et al., 2011a). The same parameters of the active stimulation were used, but the stimulator was turned off after 30 sec; this ensured that participants could feel an itching sensation at the beginning of tDCS, while no effective stimulation was delivered, thus allowing a successful blinding for the active vs. sham stimulation (Gandiga et al., 2006).

The tDCS sessions were separated by at least 60 min to avoid carry-over effects by the previous stimulation (Boggio et al., 2009; Ragert et al., 2008; Sparing et al., 2008; Fregni et al., 2005).

Statistical Analyses

The PDR was analysed via a two-way repeated-measures ANOVA, with *tDCS Session* (sham tDCS; occipital tDCS; parietal tDCS; temporal tDCS) and *Condition* (same as Experiment 1) as within-subject factors.

2.3.2. Results

Figure 2.3 shows the effects of tDCS on phosphene detection for every sensory

condition and each stimulation site. In line with Experiment 1, cross-modal stimuli facilitated phosphene perception. Accordingly, the ANOVA showed a significant main effect of *Condition* ($F_{3, 21} = 4.05$, $p < 0.05$, $p\eta^2 = 0.37$), for which an increase of phosphene detection was found in every cross-modal condition, as compared with the unimodal ones ($p < 0.05$, for every comparison). We also observed a significant interaction between *tDCS Session* and *Condition* ($F_{9, 63} = 2.35$, $p < 0.05$, $p\eta^2 = 0.26$), while the main effect of *tDCS Session* was not significant ($F_{3,21} = 0.34$, $p = 0.8$, $p\eta^2 = 0.05$). In order to better delineate how visual responses in the different sensory conditions were affected by tDCS application, we run 4 one-way ANOVAs, one for each sensory condition (sTMS, sTMS plus sound, plus touch, plus sound and touch). A significant difference emerged from the ANOVA on the unimodal condition [i.e., sTMS alone, ($F_{3, 21} = 6.05$, $p < 0.01$, $p\eta^2 = 0.46$)], where, as compared with Sham tDCS (42%), an increment of phosphene detection occurred after occipital tDCS (63%, $p < 0.01$) but not after temporal tDCS (43%, $p = 0.9$). Crucially, a significant modulation of unimodal detection also occurred after parietal tDCS (58%, $p < 0.05$), with no difference as compared to the perceptual gain observed after occipital stimulation ($p = 0.4$).

However, when cross-modal conditions were analysed, the ANOVA did not reveal any tDCS-specific modulation, neither for sTMS combined with sound ($F_{3, 21} = 1.81$, $p = 0.2$, $p\eta^2 = 0.2$), with touch ($F_{3, 21} = 0.79$, $p = 0.5$, $p\eta^2 = 0.1$), nor with sound plus touch ($F_{3, 21} = 0.75$, $p = 0.5$, $p\eta^2 = 0.1$).

We also conducted 4 separate one-way ANOVAs, one for each tDCS Session (sham, occipital, temporal, and parietal tDCS) to delineate the modulatory effects on the different sensory conditions within each tDCS session. Significant differences emerged for Sham tDCS ($F_{3, 21} = 7.39$, $p < 0.01$, $p\eta^2 = 0.5$), and for temporal tDCS ($F_{3, 21} = 3.85$, $p < 0.02$, $p\eta^2 = 0.35$): in

both sessions, phosphene detection increased in every cross-modal condition, as compared with the unimodal one ($p < 0.05$ for all comparisons). Conversely, no differences were found for occipital ($F_{3, 21} = 1.68$, $p = 0.2$, $p\eta^2 = 0.19$), nor parietal tDCS ($F_{3, 21} = 1.04$, $p = 0.4$, $p\eta^2 = 0.17$).

To date, in each tDCS session, participants committed less than 3% false alarms, with no differences among conditions; these data were no further analysed.

To summarize the results of Experiments 1 and 2, phosphene perception improved when sub-threshold occipital sTMS was coupled with an auditory stimulus, a tactile stimulus, or both, presented at the expected retinotopic location of the phosphene (Experiment 1). The neuromodulation of the occipital and parietal activity significantly affected phosphene detection, but only in the unimodal condition; moreover, the facilitatory effect induced by occipital tDCS was comparable with that induced by cross-modal stimuli, suggesting similar effects on visual cortical excitability (i.e., Experiment 2). Conversely, tDCS did not seem to affect phosphene perception in cross-modal conditions, although data inspection pointed toward a trend for tDCS-specific facilitatory effects with respect to the type of processed stimulus.

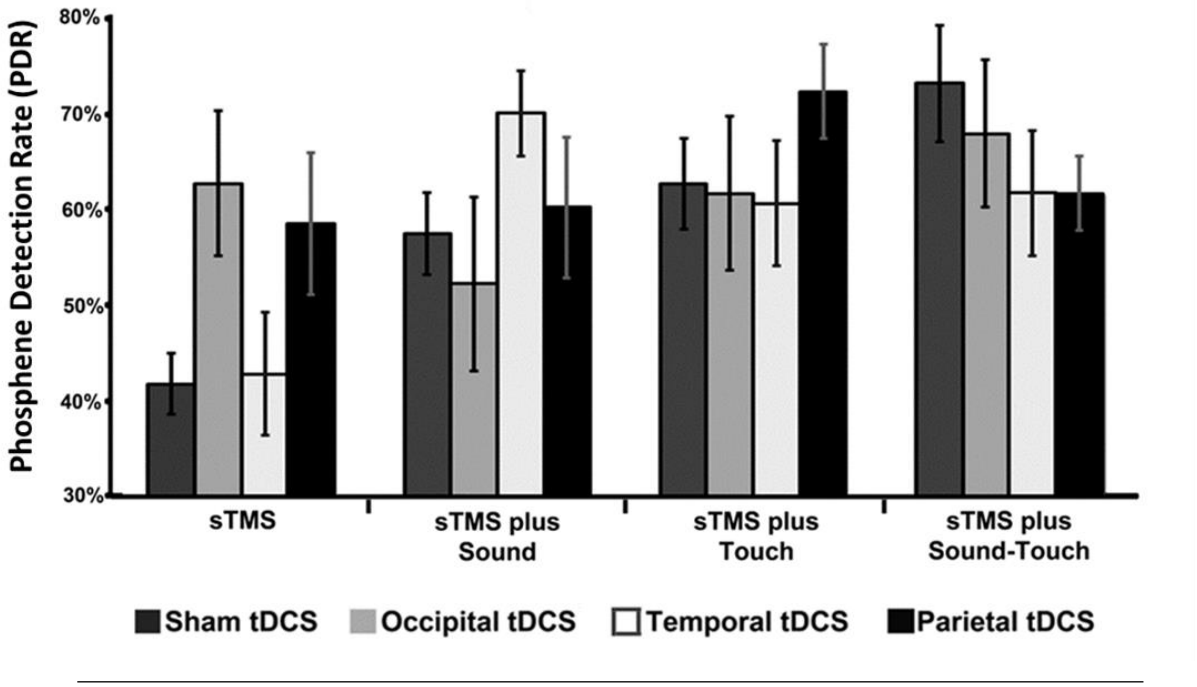


Figure 2.3. Results of Experiment 2. Mean PDR (± S.E.M.) (ordinate) in each tDCS Session (Sham tDCS, dark grey bars; Occipital tDCS, light grey bars; Temporal tDCS, white bars; Parietal tDCS, black bars) for the Unimodal (Occipital sTMS) and Cross-modal (sTMS plus sound, plus touch, plus sound and touch) conditions (abscissa).

2.4. Experiment 3

2.4.1. Materials and Methods

Participants

Twenty-four subjects (3 males, mean age = 23.7, range = 19-34) took part at Experiments 3; eight of them had previously participated at Experiment 2.

Stimuli and Procedures

In the light of Experiments 1 and 2, it might be conjectured that cross-modal stimulation per se induced a significant increment of phosphene perception, with a ceiling effect that might have precluded any further improvement by anodal tDCS. To verify this hypothesis, two additional experiments (Experiments 3-A and 3-B) were performed. The same procedure of Experiment 2 was adopted, but now the PT was measured on cross-modal, rather than unimodal, conditions. Specifically, PT was now determined considering the minimum stimulator output needed to evoke a phosphene in the 50% of the trials when the TMS pulse was coupled with a sound or a touch. The PT was determined separately for the auditory and the tactile conditions. Consequently, we ran two different experiments: Experiment 3-A, where the PT was determined for the cross-modal condition with sound paired to sTMS and Experiment 3-B, in which the PT was determined for the cross-modal condition with touch paired to sTMS. The mean PT under cross-modal conditions was of 63% (SD = 5%) of maximum stimulator output in Experiment 3-A and of 61% (SD = 4%) in Experiment 3-B. Noteworthy, for those subjects who participated also at Experiment 2, the PT in Experiments 3 was significantly lower (59%) as compared with that in Experiment 2 (65%, $t = 2.3$, $p < 0.05$).

All participants took part to 4 tDCS Sessions (Sham, occipital, parietal, and temporal tDCS), which order was randomized across subjects. All tDCS parameters were kept constant with respect to Experiment 2 (see above). As for the experimental task, during the two experiments, only the cross-modal condition for which PT was determined was presented, namely, the sTMS plus sound condition for Experiment 3-A and the sTMS plus touch

condition for Experiment 3-B. The task included 12 stimulation trials and 12 catch trials, for a total duration of about 5 min.

2.4.2. Results

For each of the two experiments, the PDR was submitted to a one-way ANOVA, with *tDCS Session* (Sham, occipital, parietal, and temporal tDCS) as main within-subject factor. The effects of tDCS on sub-threshold cross-modal phosphenes are shown in Figure 2.4. The rate of cross-modal detections increased after both parietal and temporal tDCS, but the effect was specific with respect to the cross-modal stimulus. In Experiment 3-A, where we coupled sTMS with sound, the ANOVA showed a significant difference among *tDCS Sessions* ($F_{3, 33} = 3.28$, $p < 0.05$, $p\eta^2 = 0.22$), with an increase of cross-modal PDR only after temporal tDCS (66%, $p < 0.05$ for all comparisons), as compared with sham tDCS (48%), occipital tDCS (53%), and parietal tDCS (52%). Occipital and parietal tDCS did not differ from sham tDCS ($p = 0.8$), nor from each other ($p = 0.9$). Also in Experiment 3-B (touch paired with sTMS) a significant main effect of *tDCS Session* was present ($F_{3, 33} = 3.36$, $p < 0.05$, $p\eta^2 = 0.23$), but in this case a significant increase of phosphene perception selectively emerged after parietal tDCS (77%, $p < 0.05$ for all comparisons), as compared with sham tDCS (57%), occipital tDCS (55%), and temporal tDCS (62%). Occipital and temporal tDCS differed neither from sham tDCS ($p = 0.9$), nor from each other ($p = 0.6$).

In conclusion, a selective modulation of cross-modal phosphenes after the neuromodulation of the parietal and the temporal cortices was found: temporal tDCS increased phosphene perception when the cross-modal stimulation was auditory

(Experiment 3-A), whereas it was parietal tDCS to increase phosphene perception when the cross-modal stimulus was tactile (Experiment 3-B).

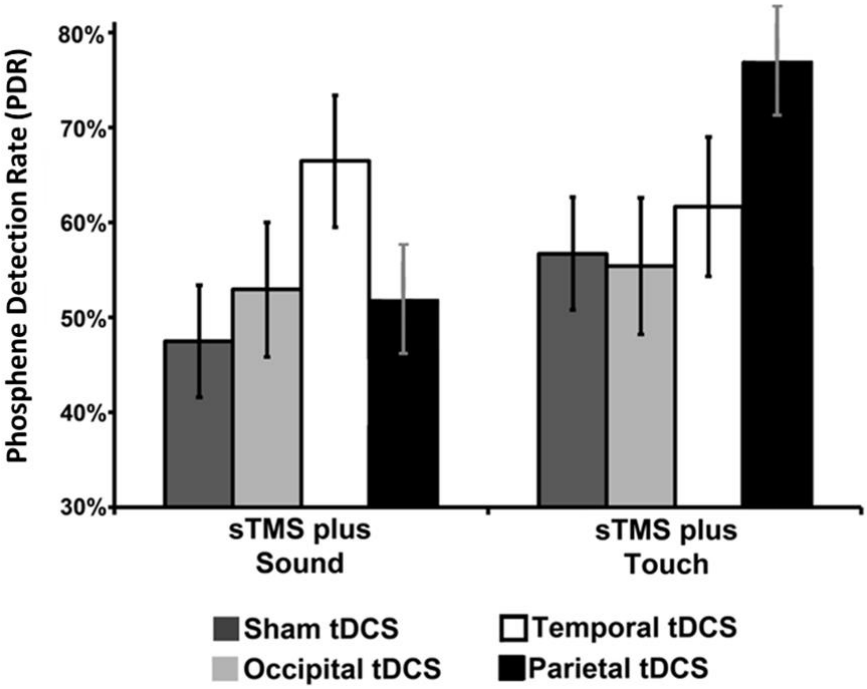


Figure 2.4. Results of Experiment 3. Mean PDR (± S.E.M.) (ordinate) in each tDCS session (Sham tDCS, dark grey bars; Occipital tDCS, light grey bars; Temporal tDCS, white bars; Parietal tDCS, black bars), for the two cross-modal conditions (abscissa): sTMS plus Sound in Experiment 3-A, and sTMS plus Touch, in Experiment 3-B.

2.5. Discussion

The results of the Experiments 1, 2 and 3 demonstrate that cross-modal interactions can affect processing in low-level visual areas, thereby facilitating phosphene perception. In particular, as compared with previous works on this phenomenon (Bolognini & Maravita,

2007; 2011; Bolognini et al., 2010a; Romei et al., 2007; 2009; Ramos-Estebanez et al., 2007), the main novel finding is that brain stimulation can facilitate visual responses as measured through phosphene perception in a specific manner, being dependent on the cortical area targeted by tDCS and on the type of sensory input to be processed (unimodal vs. cross-modal).

In Experiment 1, where the aim was to characterize the influences of redundant temporally- and spatially-congruent auditory, tactile, and audio-tactile stimuli on the participants' ability to detect phosphenes and to judge their brightness, we observed a significant facilitation for both our measures in every cross-modal condition. This result replicates previous evidence showing that the stimulation of the somatosensory (Bolognini & Maravita, 2007; Ramos-Estebanez et al., 2007) and the auditory (Romei et al., 2007; 2009; 2012; Spierer et al., 2013; Bolognini et al., 2010a) modalities can boost visual cortical excitability, but it also provides the intriguing evidence that delivering a trimodal stimulation, namely an occipital sTMS pulse coupled with an audio-tactile stimulus, maximizes the cross-modal benefit on vision. This result is in agreement with evidence related to the redundant signal effect for cross-modal stimuli (Diederich & Colonius, 2004; Todd, 1912), showing that a trimodal (visual-auditory-tactile) stimulus combination reduces latencies as compared not only to unimodal stimuli, but also to bimodal stimuli. The effect of adding a third modality might plausibly be related to a co-activation mechanism (Miller, 1982; 1986), for which the different sensory signals jointly contribute to a common pool of activation to initiate the behavioural response; therefore, the more the sensory signals (as in the case of trimodal stimuli), the faster, on average, the response as compared to unimodal (and bimodal) signals (Miller, 1986). This, in turn, implies a possible contribution from

trimodal multisensory neurons, sensitive to visual, auditory, and somatosensory inputs (Stein & Meredith, 1993).

Moreover, Experiment 1 disclosed the enhancing effects of redundant auditory and/or tactile information on the mean level of perceived brightness, with the maximal enhancement occurring again for trimodal stimuli.

Through the subsequent experiments, we demonstrated that anodal tDCS can facilitate phosphene perception in both unisensory and cross-modal conditions, but in a pretty selective manner. First, we showed that anodal tDCS of the occipital cortex enhances phosphene detection, when phosphenes are probed by sTMS given alone (unimodal condition). This result is in agreement with previous evidence concerning the effects of anodal tDCS on the excitability of the visual cortex, as measured by either phosphene induction (Antal et al., 2003a; 2003b), or the modulation of visual-evoked potentials (Antal et al., 2004). The novel result is that the benefit induced by occipital tDCS on phosphene perception becomes comparable to that induced by cross-modal stimuli. This finding indicates that it is possible to effectively up-regulate visual cortical excitability either by applying low currents to the occipital pole or by presenting an external, non-visual stimulus. The final finding is that occipital and parietal stimulations yield a similar facilitation of phosphene perception under sensory-specific visual conditions. The involvement of the parietal cortex is not entirely unexpected, as phosphene perception is not a strictly local phenomenon; rather, it involves an extensive recurrent processing within a wide array of posterior areas (Taylor et al., 2010).

In Experiment 3, by lowering phosphene perception below threshold in cross-modal conditions, the facilitatory effects of temporal and parietal tDCS became apparent. Crucially,

enhancing the excitability of these areas via tDCS did not induce a global facilitation of response to all cross-modal pairings, but it selectively increased phosphene perception depending on the stimulated area and the cross-modal pairing to be processed. Accordingly, it was the tDCS of the temporal cortex to increase phosphene detection when the paired stimulus was a sound, while parietal tDCS increased it when the paired stimulus was a touch (Experiments 3-A and 3-B, respectively). This evidence highlights the existence of regional preferences in parietal and temporal areas for specific pairings of two modalities (Driver & Noesselt, 2008). Instead, no modulation of sub-threshold phosphene perception in cross-modal conditions was induced by occipital tDCS.

Chapter 3

Illusory phosphenes by auditory stimulation

[This research has been published in Bolognini, N., Convento, S., Fusaro, M., & Vallar, G. (2013). The sound-induced phosphene illusion. *Experimental Brain Research*, 231, 469-478]

3.1. Aim of the study

In the previous Chapters, through an overview of the evidence in literature and a series of experiments, the effects of spatial cross-modal interactions on early visual processing has been documented: in the presence of a spatially- and temporally-congruent auditory and/or tactile cues, the level of visual cortical excitability, as measured through TMS-induced phosphenes, is affected, with the larger perceptual effects, the more the cross-modal stimuli. The observed modulation is facilitatory in nature, since it leads to a substantial improvement in the detection of sub-threshold visual events, plausibly through an intensification of the signal in early visual areas.

However, our sensory systems do not always integrate external stimuli properly and multisensory integration can affect sensory-specific judgments in multiple ways (Driver & Noesselt, 2008). In specific circumstances, when the information provided by the different modalities is incoherent, one sense may dominate another one and influence its processing, thus inducing phenomenological changes of perception, namely illusions.

Cross-modal illusions represent the flip side of sensory coherence and have been used to elucidate the mechanisms underlying multisensory integration, since their effects are often greater than those of congruent stimuli (see for a review: Recanzone, 2003). However, the neurophysiological processes underlying such phenomena are still not fully understood.

The SIFI (Shams et al., 2000; 2002) represents a striking example of how sounds can pervasively affect visual perception: when a single flash is presented along with two or more beeps, observers often report seeing two or more flashes, i.e., the *Fission illusion*. A complementary *Fusion illusion* may also occur, where two flashes fuse into one when accompanied by one beep (Shams et al., 2000; Andersen et al., 2004). However, Fusion effects are consistently weaker, as compared to the Fission ones (Andersen et al., 2004; Innes-Brown & Crewther, 2009; Shams et al., 2000), and more related to individual differences in visual processing (Mishra et al., 2008; Shams & Kim, 2011).

The illusory effects exerted by sounds on visual phenomenal experience must be driven by functional connections between different sensory and associative brain regions. Although the debate concerning the cortical circuitries involved this illusory phenomenon is still open, evidence of a rapid, a dynamic functional interplay between primary auditory and visual cortical areas was demonstrated (Shams et al., 2001; Watkins et al., 2006). First, electrophysiological studies documented an early, extensive modulation of visual evoked potentials (VEPs) by sound in the illusion trials (Shams et al., 2001). Second, neuroimaging studies have shown that the SIFI is associated with the activation of the retinotopic V1, driven by the concurrent auditory stimulation: when a single flash is perceived incorrectly as two flashes, neural activity in V1 increases, while when a double flash is incorrectly

perceived as a single flash, V1 activity decreases (Watkins et al., 2006; 2007). Accordingly, it has been claimed that the level of activation of V1 plausibly reflects the subjective visual perception, rather than the physical visual stimulus (Watkins et al., 2006; 2007).

The evidence provided by the above-mentioned studies has a major limitation: it cannot demonstrate a causal link between cortical responses in V1 and sound-induced changes in visual perception, thus limiting any possible assumption concerning the causal role of the visual areas in this cross-modal phenomenon.

Therefore, in the present study, we aimed at using TMS to create a physiological variant of the sound-induced flash, namely the *Sound-induced Phosphene Illusion* (SIPI) in order to directly test the effects of sound within early visual areas and demonstrate its influence on conscious visual experience, as indexed by phosphenes. In particular, in the light of the results emerged from the previous experiments (Experiments 1-3, Chapter 1), we sought to understand whether sounds, beyond enhancing visual cortical excitability and facilitating visual perception, can even mislead it, giving rise to an illusory phosphene.

To this aim, in a first experiment (Experiment 4), we compared Fission and Fusion illusions brought about by the standard version of the SIFI (Shams et al., 2000) and by a phosphene version of the same task (namely the phosphene task) in which external flashes were replaced by sTMS-induced phosphenes. If the illusory effects actually reflect early auditory-driven modulations in low-level visual areas, where phosphenes originate, then phenomenological changes at the level of phosphene perception should be detected in the illusory conditions.

A parallel aim of the present study concerned the elucidation of the temporal profile of auditory-driven effects on visual cortical excitability. Indeed, featuring the temporal window within which sounds can alter visual cortical responses and perception, thus inducing an illusory phosphene, could help us shedding light on the putative cortical mechanisms supporting this perceptual phenomenon. Accordingly, in a subsequent experiment (Experiment 5) we manipulated the stimulus onset asynchrony (SOA) between the TMS pulse and the auditory inputs. This design was based on previous observations about the temporal profile of the standard Fission illusion with flashes, which show how this effect progressively degrades when the time interval between the two sounds is larger than 100 msec (Shams et al., 2002). I reasoned that the degree at which the impact of auditory stimuli on visual cortical excitability and phosphene perception decreases as the SOA grows, could disclose the time constraints of sound-driven changes within early visual areas. If early, direct connections between primary sensory areas are essential for the illusion to occur, then any illusory effect on phosphene perception should be broken down as the SOA overtakes an early time window of 100 msec, in line with previous brain imaging studies showing timing for audio–visual interactions in V1 (Raij et al., 2010).

3.2. Experiment 4

3.2.1. Materials and Methods

Participants

Thirteen healthy right-handed participants (mean age = 23 ± 4; 10 females), with normal or corrected-to-normal vision and normal hearing, entered Experiment 4. Participants gave their informed consent prior to be enrolled in the study, which was carried out according to the guidelines of the ethical committee of the University of Milano-Bicocca, and the Declaration of Helsinki (BMJ 1991; 302: 1194). Participants were naïve to the experimental procedure and to the purpose of the study. All the accepted recommendations for the use and safety of TMS were applied (Rossi et al., 2009).

Participants underwent the two different tasks, namely the flash task, taken from the original study of Shams and collaborators (Shams et al., 2000), which was aimed at verifying the presence of the Fission and Fusion illusions in the participants, and the experimental task, i.e., the phosphene task. The two tasks were given in a random order across participants.

Experimental Tasks

Flash task

We used the standard version of the SIFI task, with stimuli and procedures taken from the original study of Shams and collaborators (Shams et al., 2000; Bolognini et al., 2011a).

In a dimly illuminated room, subjects sat ~57 cm in front of a CRT computer monitor (Samsung SyncMaster 1200NF: resolution 1,024 × 768, refresh rate 60 Hz), with their eyes aligned with the center of the screen and their head supported by a chinrest. Each trial began with the appearance of a white fixation cross, displayed at the center of a black

screen (luminance: 0.02 cd/m^2). At the eccentricity of 5° of visual field, a white disk subtending 2° was flashed 1–2 times. Single and double flashes (V) were presented alone or accompanied with 0–2 beeps (B) (i.e., V1B0, V1B1, V1B2, i.e., Fission trials; V2B0, V2B1, V2B2, i.e., Fusion trials). Hence, the total number of conditions was 6.

Each flash (luminance: 118 cd/m^2) was set to display for one refresh period of the monitor (i.e., 16.7 msec, hence considering the typical persistence of the CRT phosphors, it would be about 2.7 msec) (Elze, 2010), and the duration of each beep was of 7 msec. Auditory stimuli were presented through headphones (i.e., intensity of 80 dB SPL, frequency of 3.5 kHz, duration of 7 msec) against a continuous background noise. The background mask was added with the aim of preventing any auditory interference related to the noise of the TMS pulses in the subsequent phosphene task (see below). The background mask was fixed at an intensity of 80 dB and delivered with specific closed-back, circumaural headphones (Sennheiser HD 280 Pro), with a 32 dB attenuation of external noise. In this way, by measuring the Sound Pressure Level (SPL) related to the TMS click at 80% of the maximum stimulator output with a sound level meter (PCE-999, PCE Italia srl; www.pce-italia.it), and considering the mean distance of the coil from the participants' ears, the intensity of the noise mask and the sound attenuation provided by the headphones, we were able to ensure that the perceived intensity of the TMS click never exceeded 30 dB, minimizing any external, acoustic facilitation concerning the number of delivered pulses.

The first beep was followed after 40 msec by the first flash. The SOA was of 67 msec between two flashes and 80 msec between two beeps. The interval between beeps was increased as compared to the standard version of the task. This choice was driven by the

results of a pilot experiment, where we observed that, with the background noise mask, 80 msec of SOA were necessary for subjects to clearly perceive the two beeps.

Participants were asked to judge the number of flashes seen on the screen. Each condition was repeated 16 times, for a total of 96 trials (inter-trial interval of 5 sec), presented in a random order within two separate blocks. The total duration of the task was about 12 min. At the beginning of the task, 12 practice trials were also administered, and not included in the subsequent analysis. Stimulus presentation and responses recording were under computer control (E-prime Software, Psychology Software Tools).

Phosphene Task

An overview of the experimental setup is presented in Figure 3.1. The procedure was identical to that of the flash task, and the only difference was that external flashes were replaced by phosphenes induced by single-pulse and double-pulse TMS delivered to the occipital cortex. TMS was delivered using a Magstim Super Rapid Transcranial Magnetic Stimulator (Magstim Company, Whitland, UK) connected with a 70 mm figure-of-eight-shaped coil (maximum field strength, 2.2 T).

Prior to the experimental task, participants underwent a training session consisting in a functional mapping procedure for the determination of the optimal site of occipital stimulation for inducing reliable phosphenes and for the definition of the individual phosphene threshold (i.e., PT, see Chapter 2, Paragraph 2.2.1 ‘Materials and Methods’, for details on the training procedure). The mean PT was of 65% (SD ± 4%) of maximum stimulator output. The optimal TMS coil position was over the occipital pole centered on

average 2.8 cm above the inion and 2.4 cm lateral to the midline. The Talairach coordinates (Talairach & Tournoux, 1988) of the stimulated site (x = 18, y = 85, z = − 4) were estimated with the SofTaxic Navigator system (E.M.S., Bologna, Italy, www.emsmedical.net; details are described in Bolognini et al., 2011b; Rossetti et al., 2012) and mainly corresponded to early visual areas. Shape, size, and position of the perceived phosphenes varied somewhat across participants, but were constant for each participant throughout the experimental session.

After the initial training, we ensured that each participant could report the percept of one or two phosphenes, after the delivery of single-pulse and double-pulse TMS (inter-pulses interval = 50 msec), respectively. To this aim, 10 trials of single-pulse and double-pulse TMS were randomly delivered at an intensity of 110% of the individual PT, to the previously determined optimal scalp location for phosphene induction. By delivering pulses at 110% of PT, we ensure the consistency of phosphene perception through the different trials. The choice of the inter-pulse interval was driven by previous evidence in literature (Kammer & Baumann, 2010), showing that double-pulse TMS over the occipital areas, when delivered at an interval of 50 msec, elicited a reliable perception of two distinct phosphenes in every participant; to date the second phosphene appeared at the same retinotopic location of the first one. Additionally, during this preliminary session, when phosphenes were detected, participants were also asked to report their spatial location and rate their level of brightness on a 10-point scale (1 = faint gleam percept, to 10 = very bright phosphene); the experimenter scored the participants' rating manually. The mean level of phosphene brightness was of 4.9, and the spatial location of phosphenes was at a mean eccentricity of 17° (SD ± 7°) in the hemifield contralateral to TMS.

During the experimental task, subjects remained blindfolded. Single-pulse occipital TMS (110% of the individual PT) was presented alone or paired with 1-2 beeps for the Fission illusion (i.e., V1B0, V1B1, V1B2), while double-pulse TMS was combined with 0-1-2 beeps for the Fusion illusion (i.e., V2B0, V2B1, V2B2). The SOA was of 50 msec between two TMS pulses and of 80 msec between two beeps. Auditory stimuli were presented through headphones, against a continuous background noise (see the previous Paragraph, "*Flash Task",* for more details).

Participants were instructed to report the number of seen phosphenes. During the experimental task, each condition was repeated 16 times, for a total of 96 trials, presented in a random order within two separate blocks. An inter-trial interval of 5 sec was used in order to avoid any possible carry-over effect of TMS on visual cortical excitability. The total duration of the task was about 15 min. At the beginning of the task, 12 practice trials (two trials for each stimulus type) were administered, and not included in the subsequent analysis. Stimulus presentation and response recording were under computer control (E-prime Software, Psychology Software Tools).

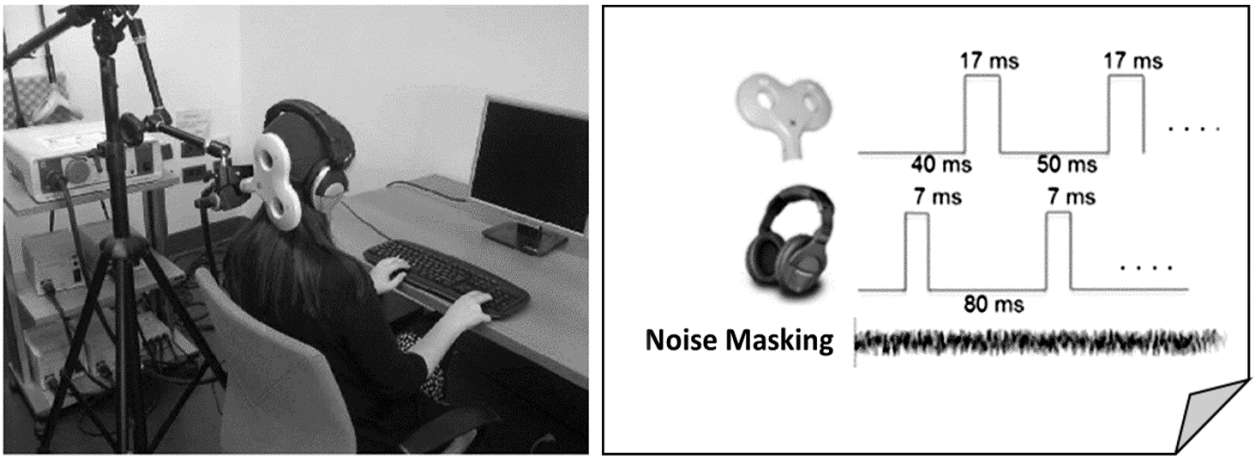


Figure 3.1. Experimental setup for the SIPI in Experiment 4. Phosphenes were induced by the delivery of single-pulse and double-pulse TMS over the occipital pole via a 70 mm figure-of-eight TMS coil. Single pulse TMS was presented alone or paired with 1–2 beeps, for the Fission illusion, while double-pulse TMS was presented alone or paired with 1–2 beeps, for the Fusion illusion. Auditory stimuli were presented through headphones against a continuous background noise.

Control for TMS interfering effects

The contact of the coil with the head typically produces TMS clicks, and participants may hear bone conducted vibrations and feel pulses on their skin, which, in turn, may interfere with the illusory effects in the phosphene task by offering a sort of perceptual "anchor" to solve the ambiguity related to cross-modal trials. Although the delivery of a background noise through closed-back headphones minimized the influence of TMS clicks, we could not unequivocally rule out the possibility that both the sound and the scalp sensations related to the TMS might have biased responses during the experimental task. Therefore, a control task was performed on a new cohort of thirteen healthy right-handed

participants (mean age = 23 ± 3; 9 females), in order to assess the participants' ability to discriminate such sensations during the phosphene task.

The procedure was similar to that of the phosphene task (see above), namely single and double TMS pulses (110% of the individual PT) were randomly delivered with 1–2 beeps (i.e., V1B1, V1B2, V2B1, V2B2); 8 trials for each stimulus condition were presented. However, after each trial, participants were required to report not only the number of seen phosphenes, but also of heard auditory TMS clicks, and of felt pulses on the scalp, as well to judge the intensity of the TMS stimulation on a 0−10 scale, with 0 indicating that "the TMS pulse was not perceived at all" and 10 indicating "a very intense TMS pulse". Intermediate values (1–9) could also be used.

Statistical Analyses

The mean number of perceived visual stimuli, being either flashes or phosphenes, in the different experimental conditions was used as main outcome for the analyses. We conducted a comprehensive analysis of variance (ANOVA), with 2 within-subject factors: *Task* (flash, phosphene), and *Stimulus* (V1B0, V1B1, V1B2, V2B0, V2B1, V2B2).

For the control task, the mean number of seen phosphenes, TMS clicks, felt pulses, and the mean TMS intensity, in the different experimental conditions (V1B1, V1B2, V2B1, V2B2) were submitted to 4 one-way ANOVAs.

When significant effects emerged in ANOVAs, post-hoc comparisons were carried out with Bonferroni correction.

The effect size in the ANOVAs was measured by calculating the partial eta squared ($p\eta^2$). Statistical analyses were performed using Statistica for Windows (release 6.0; StatSoft).

3.2.2. Results

Overall, the results of Experiment 4 show a remarkable influence exerted by two sounds on visual performance: on average, a single visual stimulus, being either a flash or a phosphene, was incorrectly reported as double when coupled with two rapid beeps. However, the reverse effect, namely two visual stimuli reported as one stimulus (Fusion illusion), was reported only in the case of flash stimuli. The results of phosphene and flash tasks are shown in Figure 3.2-a.

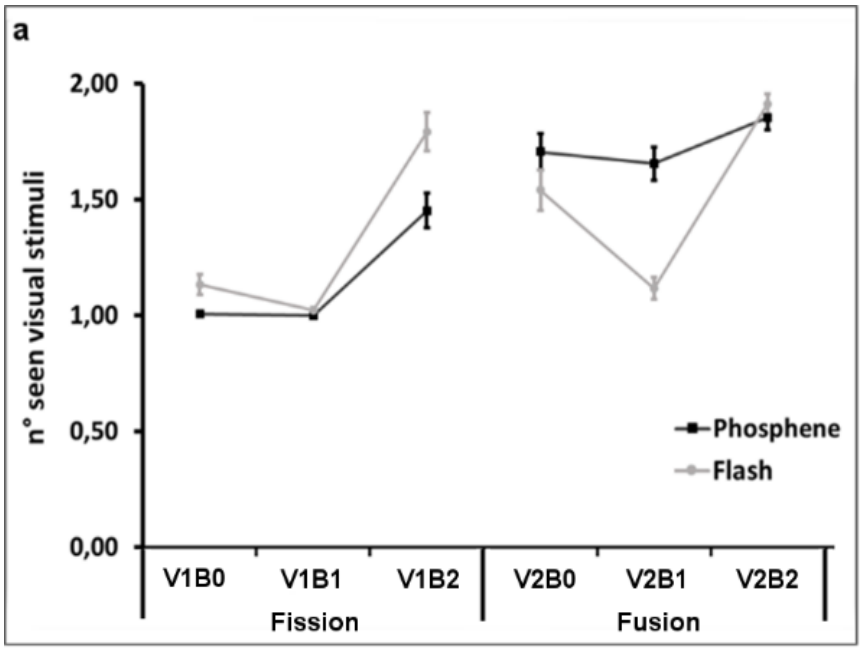
Accordingly, the ANOVA showed a significant main effect of *Stimulus* ($F_{5,60} = 97.89$, $p < 0.0001$, $p\eta^2 = 0.89$). The main effect of *Task* did not reach significance ($F_{1,12} = 0.32$, $p = 0.58$, $p\eta^2 = 0.26$), while the *Task* by *Stimulus* interaction was significant ($F_{5,60} = 23.31$, $p < 0.0001$, $p\eta^2 = 0.66$). Post-hoc comparisons showed that in the flash task, when a single flash was presented, increasing the number of beeps increased the number of perceived flashes, with the differences between the V1B2 versus the V1B0 and the V1B1 conditions being significant at $p < 0.0001$; the two last conditions did not differ from each other ($p = 0.98$). When two flashes were presented, the number of counted flashes decreased in presence of a single beep, as compared with both 0 and 2 beeps (V2B1 vs. V2B0 and V2B2, $p < 0.0001$).

A partially different pattern of results emerged from the phosphene task; here, while increasing the number of beeps increased the number of seen phosphenes (V1B2 vs. V1B0 and V1B1, all ps < 0.001, with the difference between V1B0 and V1B1 being not significant, p = 1) confirming the occurrence of a Fission effect also for TMS-evoked visual percepts. Instead, the presence of a single beep did not reduce the number of perceived visual events as expected for the Fusion illusion, with the differences between V2B1, V2B0, and V2B2 failing to attain the significance level (all ps > 0.50). Accordingly, a significant difference between flash and phosphene tasks emerged only for the V2B1 condition (p < 0.0001), with participants showing the Fusion illusion in the flash, but not in the phosphene task.

Importantly, the number of reported phosphenes in Fission trials (i.e., V1B2) was not significantly different from the number of seen phosphenes when two TMS pulses were actually delivered (phosphene condition V2B0, p = 0.15) or from the number of seen flashes when two physical flashes were presented (flash condition V2B0, p = 1). Finally, there was no difference in the number of seen visual stimuli induced by presenting double flashes and by delivering double-pulse TMS (V2B0, flash vs. phosphene, p = 0.77; V2B2, flash vs. phosphene p = 1).

To further examine the relation between the illusory effects in the flash and phosphene tasks, Pearson correlations were performed considering both Fission (i.e., number of flashes reported in V1B2 trials minus number of flashes reported in V1B0 trials, with positive values indicating an increase in seen stimuli by double beeps) and Fusion effects (i.e., number of flashes reported in V2B1 trials minus number of flashes reported in V2B0 trials, with negative values indicating a reduction in seen stimuli by a single beep). A

positive correlation between the participants' responses in the two tasks was found for the Fission illusion (R_{13} = 0.63, p = 0.024): individuals who reported more than one phosphene by double beeps in the phosphene task also reported to see more than one flash by double beeps in the flash task, indicating the existence of a similar perceptual phenomenon regardless of the type of the visual stimulus (flash vs. phosphene) (Figure 3.2-b). Instead, no correlation between tasks was found for the Fusion illusion (R_{13} = −0.18, p = 0.55), confirming the dissociation between the two tasks as already emerged in the ANOVA.



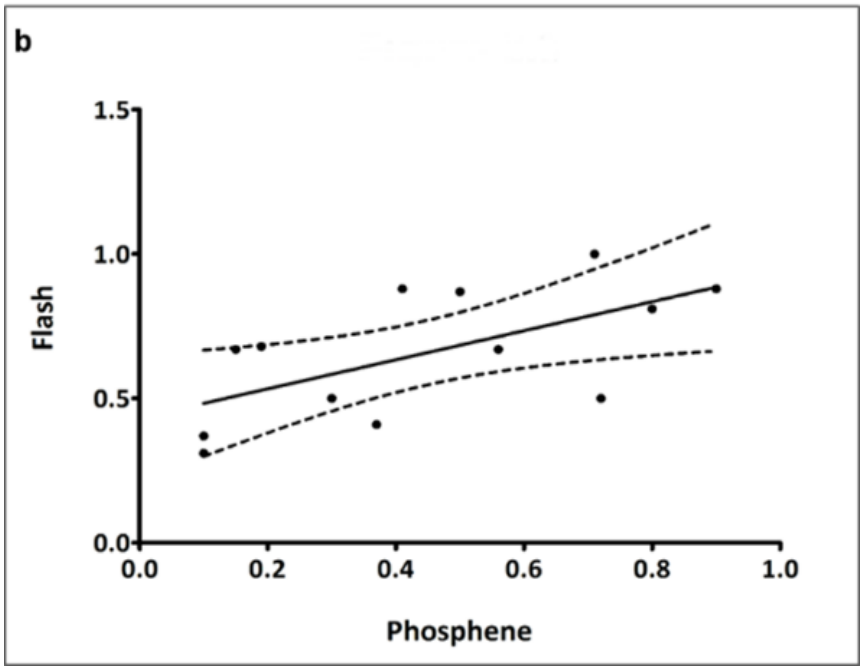


Figure 3.2. Results of Experiment 4.

(a): Average number of perceived visual stimuli (ordinate) in each stimulus condition (abscissa: V= visual stimulus, B= beep), in the phosphene (dark grey line) and flash (light grey line) tasks. Error bars= S.E.M.

(b): Pearson correlation analysis between the magnitude of the Fission illusion in the Flash task (ordinate) and in the Phosphene task (abscissa).

Control Task

As shown in Figure 3.3, the number of seen phosphenes, but also of felt pulses on the scalp, and the perceived intensity of the TMS stimulation varied depending on the stimulus condition, differently from the number of heard TMS click, which never showed any remarkable change across the different conditions. Accordingly, the ANOVAs showed a significant main effect of S*timulus* in the report of phosphenes ($F_{3,36} = 3.16$, $p < 0.05$, $p\eta^2 = 0.36$), felt touches ($F_{3,36} = 12.04$, $p < 0.0001$, $p\eta^2 = 0.50$), and TMS intensity ($F_{3,36} = 12.79$, $p < 0.0001$, $p\eta^2 = 0.52$), but not for reported TMS clicks ($F_{3,36} = 2.17$, $p = 0.11$, $p\eta^2 = 0.15$). Post-hoc comparisons revealed that, overall, participants felt more pulses on the scalp during double-pulse stimulation, than during single-pulse stimulation (V1B1 vs. V2B1, $p = 0.0007$; V1B2 vs. V2B2, $p = 0.05$), and TMS intensity was judged to be stronger in the double-pulse TMS conditions (V2B1 = 3.40; V2B2 = 3.56), than in single-pulse TMS conditions (V1B1 = 2.77, $p = 0.0039$; V1B2 = 2.73, $p < 0.0001$).

When the number of seen phosphenes was considered, a significant difference emerged between V1B1 and V1B2 conditions, confirming once again the occurrence of the Fission illusion in phosphene perception ($p = 0.05$; Figure 3.3-a). Intriguingly, the same significant difference was present also for felt scalp sensations, where two rapid beeps paired with single-pulse TMS increased the number of felt touches on the scalp, as compared to one-beep trials (V1B1 vs. V1B2, $p = 0.006$; Figure 3.3-b).

Conversely, when double TMS pulses were delivered, phosphenes (V2B1 vs. V2B2, $p = 1$) and felt scalp sensations (V2B1 vs. V2B2, $p = 0.93$) were not modulated by beeps.

Perceived TMS intensity was never modulated by the number of beeps (V1B1 vs. V1B2, p = 1; V2B1 vs. V2B2, p = 1; Figure 3.3-d).

In line with these results, it may be argued that the absence of a Fusion effect in the phosphene task could be explained by the ability of participants to discriminate the number of felt scalp sensations in the trials where double TMS pulses were delivered; in other words, being able to discriminate two TMS pulses on the scalp might have provided subjects with a further clue concerning the number of physically presented stimuli, preventing the Fusion illusion to arise. However, being able of distinguishing between single and double TMS pulses on the scalp should have biased visual responses, not only when double TMS pulses were delivered, but also when single TMS pulse was presented.

In order to better delineate the impact of felt scalp sensations versus that of delivered beeps on participants' visual responses and to rule out any influence by heard TMS clicks and TMS perceived intensity on the observed effects, Pearson correlation analyses were performed considering the number of seen phosphenes, beeps, felt auditory and somatosensory sensations by TMS, and the perceived TMS intensity.

The number of seen phosphenes was associated with the number of beeps only in Fission trials (R_{13} = 0.55, p = 0.026), but not in Fusion trials (R_{13} = 0.20, p = 0.45). Even more importantly, the number of seen phosphenes did not correlate with the number of felt pulses or with the TMS intensity, nor with the number of heard TMS clicks (all ps > 0.2), suggesting that even though subjects had a feeling about the number of received TMS pulses from scalp sensations, this did not exert any influence on the number of reported visual conscious experiences.

Moreover, accordingly with the ANOVA results, the number of felt touches on the scalp reported by participants positively correlated with the number of presented beeps (R_{13} = 0.48, p = 0.013), namely, increasing the number of beeps increased the number of felt touches on the scalp. This result confirms that the number of beeps biased the participants' report of the somatic sensations induced by TMS. Conversely, in Fusion trials (R_{13} = 0.25, p = 0.20), no correlation was found between the felt scalp sensations and the number of beeps.

Finally, no significant correlation was found between the number of beeps and the heard TMS pulses (Fission trials: R_{13} = 0.28, p = 0.17; Fusion trials: R_{13} = 0.55, p = 0.79), nor the perceived TMS intensity (Fission trials: R_{13} = 0.037, p = 0.86; Fusion trials: R_{13} = 0.059, p = 0.76).

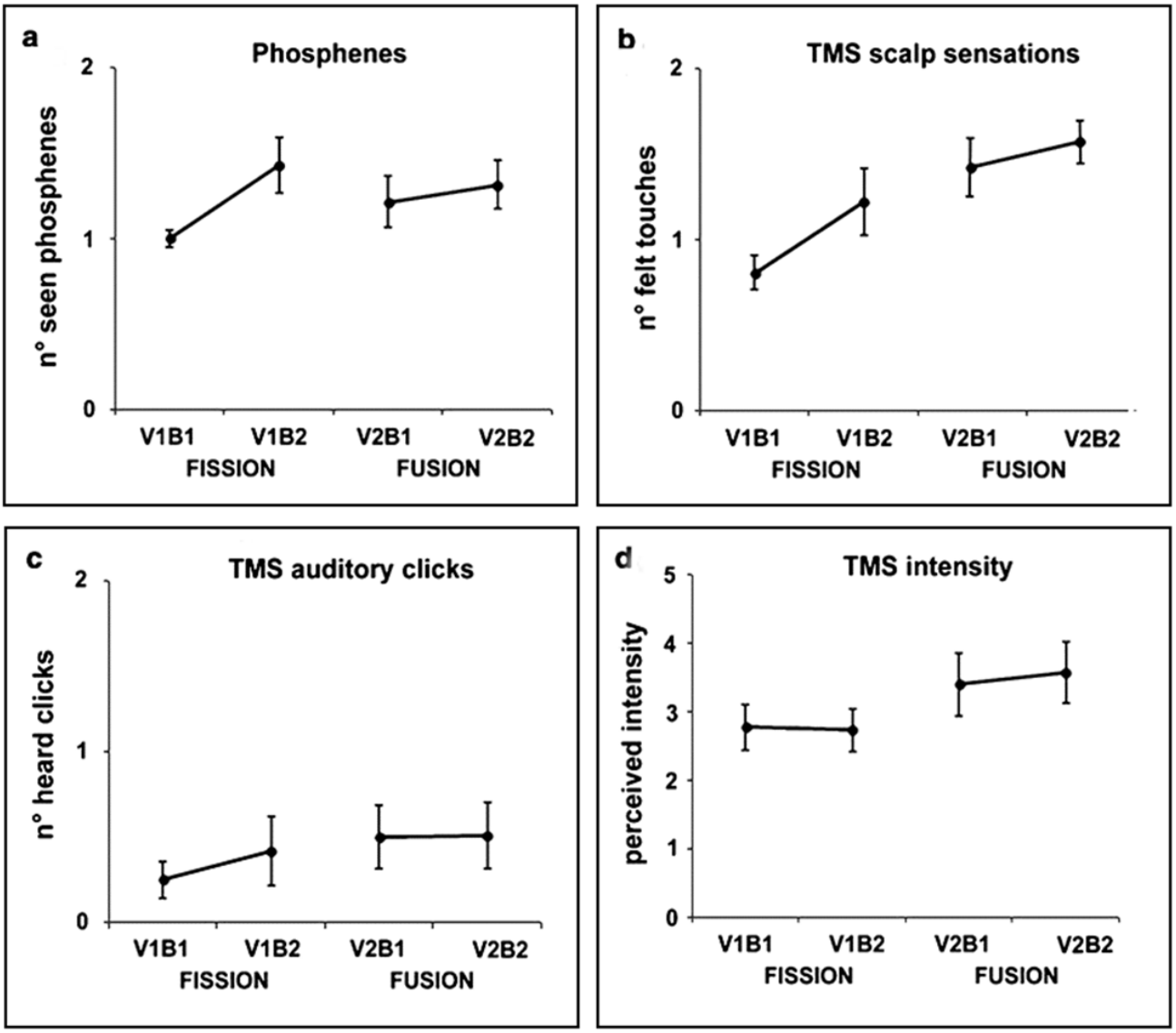


Figure 3.3. Results of the Control Experiment. Average number (ordinate) of perceived phosphenes **(a)**, TMS-induced felt touches **(b)**, heard auditory clicks **(c)**, and perceived TMS intensity **(d)** in each stimulus condition (abscissa, V= visual stimulus, B= beep). Error bars= S.E.M.

3.3. Experiment 5

3.3.1. Materials and methods

Participants

Ten healthy participants (mean age = 24.5 ± 4; 6 females) entered Experiment 5. They were right-handed, with normal or corrected-to-normal vision and normal hearing. Participants gave their informed consent prior to be enrolled in the study, which was carried out according to the guidelines of the ethical committee of University of Milano-Bicocca, and the Declaration of Helsinki (BMJ 1991; 302: 1194).

Experimental task

To measure the temporal window within which sounds could alter visual cortical responses evoked with TMS, I capitalized on the phosphene paradigm used in Experiment 4. Hence, I maintained the same experimental procedure of Experiment 4, included the training session. The only difference was that the phosphene task now comprised only Fission trials (i.e., V1B2), and the SOA between the single-pulse TMS and beeps was systematically varied, so that one beep was always physically simultaneous with the TMS pulse, while the timing of the other beep changed, from trial to trial, with the following SOAs: 40, 80, 160, and 240 msec either before (−) or after (+) the single-pulse TMS. 16 trials were given in a random order for each SOA, for a total of 128 trials (total duration of the task = about 14 min).

In line with Experiment 4, only the right hemisphere was stimulated, and phosphenes were induced in the contralateral, left visual hemifield, at a mean eccentricity of 15° (± 8°). The mean PT was of 63% (SD ± 2%) of maximum stimulator output, and the mean level of reported phosphene brightness was of 5.1.

Statistical Analyses

Participants' mean responses were submitted to a one-way repeated-measures ANOVA, with *SOA* (+/-40, 80, 160, 240 msec) as a within-subject factor. Post-hoc comparisons were carried out using the Bonferroni test, and the effect size was computed by calculating the relative eta-squared index ($p\eta^2$).

3.3.2. Results

As shown in Figure 3.4, the effects of double beeps on phosphene perception started degrading from ± 80 msec. Indeed, the ANOVA showed a main effect of *SOA* ($F_{7,63} = 12.49$, $p < 0.0001$, $p\eta^2 = 0.58$): the number of reported phosphenes was significantly higher when the first beep preceded the single-pulse TMS and the second beep by −40 msec (1.63, $p < 0.002$ for all comparisons) and −80 msec (1.44, $p < 0.0008$ for all comparisons) with respect to the SOAs of −160 msec (1.21) and −240 msec (1.06). In a specular way, a higher number of phosphenes was reported when it was the second beep to follow the single TMS pulse and the first beep by +40 msec (1.62, $p < 0.0038$ for all comparisons) and +80 msec (1.52, p <

0.036 for all comparisons) as compared to SOAs of +160 msec (1.28), and +240 msec (1.24). The number of visual events reported at SOAs of ± 80 msec and ± 40 msec did not differ statistically from each other (p = 0.69). From a visual inspection of the data, a reduction between these two SOAs is evident, suggesting that the effect of sound on visual perception starts decreasing as far as the time lag between the two sounds recedes from an optimal interval of about 40 msec. Finally, no difference was found between the SOAs of ± 160 and ± 240 msec (p = 1).

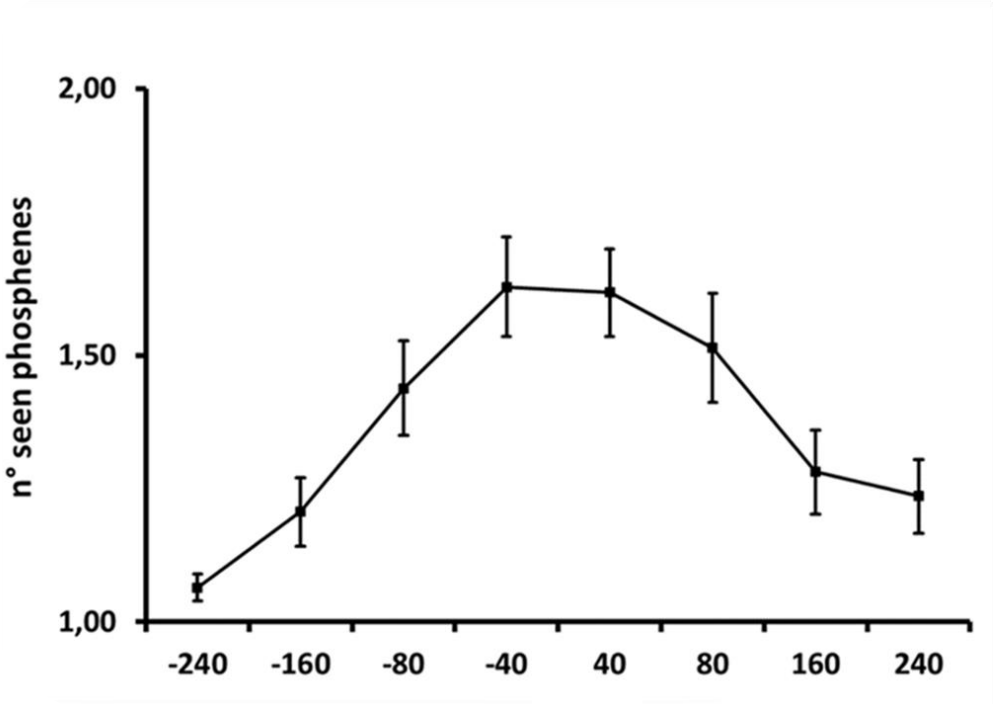


Figure 3.4. Results of Experiment 5. Average number (± S.E.M.) of seen phosphenes in Fission trials (i.e., V1B2, ordinate) for each SOA (abscissa) during the SIPI.

3.4. Discussion

The present study yields two main findings. Firstly, I demonstrated that sounds can alter visual cortical responses to create a striking phosphene illusion: when a phosphene induced by a single-pulse TMS to the occipital cortex is accompanied by two beeps, about two phosphenes are seen, giving rise to an illusory effect that we labelled as *the Sound-Induced Phosphene Illusion* (SIPI). The illusory perception of two phosphenes driven by the double beep mimics the effect induced by actually stimulating visual cortical areas with two TMS pulses, consistently with a prominent role of auditory-driven signals within early visual areas, where phosphenes originate. Additionally, the pattern of responses associated with the perception of an illusory, second phosphene was comparable to that related to the perception of an illusory, second flash, indicating that the modulation of visual activity exerted by sound occurred in the same visual cortical areas that are involved in representing a real visual stimulus.

It is important to remark that since the SIPI reflects sound-induced changes in visual cortex excitability, namely phosphene perception, it cannot be explained by inferential cognitive processes, such as deploying a decision strategy for responding to ambiguous or conflicting experiences; additionally, generating this illusion does not require experience of any specific bimodal context.

The second main finding regards the temporal window of the SIPI. The Fission illusion in phosphene perception is characterized by an early modulation of visual cortical activity, within ± 80 msec, that is: the SIPI occurs when one beep preceded or followed the TMS pulse

and the other beep by 40 msec or 80 msec. After this early time window, the modulatory effects of sounds on phosphenes remarkably decrease. This evidence is consistent with the temporal profile of the standard Fission illusion with flashes, which starts degrading when the time interval between the two sounds is larger than 100 msec (Shams et al., 2002). Moreover, electrophysiological evidence in humans shows that the Fission flash illusion is characterized by an early modulation of visual cortical activity, as early as 35–65 msec from the onset of the visual stimulus, followed by a later modulation, at about 150 msec post-stimulus (Shams et al., 2005; Mishra et al., 2007). A similar early time window (75–120 msec of delay between auditory and occipital TMS stimuli) also characterizes the auditory enhancement of phosphene perception (Romei et al., 2007; 2009).

Noteworthy, the results from the control task rule out the possibility that TMS-related sensations interfered with the illusory effects. Indeed, participants were unable to reliably discriminate between single and double TMS pulses with respect to the number of heard clicks, confirming that the auditory setting used in the main experiment was effective in masking the TMS clicks. Crucially, in Fission trials, the number of seen phosphenes was associated with the number of presented beeps, but not with the number of heard TMS clicks, nor with felt scalp sensations, nor with TMS intensity.

Another relevant finding is the absence of Fusion effects in phosphene perception: two phosphenes by a double-pulse TMS did not fuse into one when accompanied by one beep. This finding indicates that the Fusion illusion does not take place in early visual areas, at variance with the Fission illusion. The control experiment, again, is important to rule out other interpretations. Overall, it allows excluding that the absence of Fusion effects in phosphenes perception is merely due to interference effects provoked by the TMS

stimulation. Indeed, although participants could discriminate single and double TMS pulses based on the related scalp sensations and TMS intensity (but not with respect to the TMS clicks, which were indistinguishable across conditions), the number of seen phosphenes was not associated with these TMS effects, but only with the number of beeps.

It is worth mentioning that through the control task we also found Fission effects on the somatosensory sensations, namely increasing the number of beeps led to a parallel increase in felt touches on the scalp induced by the magnetic pulses. Through correlation analysis, we observed that this effect was related to the number of beeps, but not with other TMS-related effects, i.e., clicks and intensity of TMS. Again, Fusion effects did not occur with respect to such scalp sensations. This result is in line with previous evidence showing that tactile stimuli can lead to a tactile-induced flash illusion (Violentyev et al., 2005), and that task-irrelevant auditory stimuli can modulate the tactile perception of sequences of taps delivered on the skin (Bresciani et al., 2005). Therefore, the auditory modulation of the felt TMS pulses on the scalp is suggestive of an auditory-driven Fission effect occurring not only in visual but also in somatosensory domain, which deserves further investigation.

To summarize, the present findings enrich the results of Chapter 2, showing that sounds cannot only enhance the excitability of primary visual areas, thus facilitating phosphenes detection, but they can also alter visual activity in such a way that conscious visual experience is misled, in turn giving rise to an illusory phosphene. Overall, this evidence further substantiates the claim that responses in primary visual areas reflect subjective perception, rather than the mere presence of a physical stimulus (Watkins et al., 2006; 2007).

Chapter 4

Audio-visual interactions in brain-damaged patients: Clues from Hemianopia and Unilateral Spatial Neglect

4.1. Aim of the study

Through the Experiments described so far, I demonstrated that cross-modal signals can affect visual cortical responses and related conscious perception in different ways, either by facilitating, or by misleading it. By using TMS, I provided evidence that early cross-modal responses directly involve low-level visual areas, while by means of tDCS, I demonstrated regional preferences in higher-order heteromodal cortices in supporting auditory and somatosensory influences on visual perception.

To complete this investigation, in the present study I will seek neuropsychological evidence of cross-modal influences on visual perception in patients with visual field defects, i.e. hemianopia or quadrantanopia, or unilateral spatial neglect (USN).

Visual field defects consist in the loss of part of the contralesional visual field resulting from unilateral post-chiasmal damage, including V1, which manifests as an impairment of conscious vision in the portion of the visual field that corresponds retinotopically to the damaged visual area (Zihl & Kennard, 1996). Visual field defects may be different with respect to the extension of the blind region and to the gravity of the

disorder: the term homonymous hemianopia refers to the loss of vision in the entire contralesional hemifield, while in quadrantanopia, the deficit regards only one quadrant of the contralesional hemifield (upper or lower quadrantanopia).

USN is a neuropsychological syndrome typically due to lesions to the right hemisphere. It is characterized by the patients' failure to detect and report sensory events occurring in the portion of space contralateral to the side of the lesion (contralesional), and to explore that portion of space through motor acts (Halligan et al., 2003; Heilman et al., 2003; Husain, 2008; Vallar, 1998; Vallar & Bolognini, 2014). USN has risen particular interest in the multisensory research field, since the areas that are typically affected in this syndrome, namely the posterior-inferior parietal, the posterior-superior temporal regions, the temporo-parietal junction, and the inferior frontal lobes, play a fundamental role in the multisensory representation of space (Halligan et al., 2003; Pavani et al., 2003; Vallar & Bolognini, 2012). Accordingly, a lesion to these associative areas could virtually impair all the sensory modalities, jointly or separately, as well their integration (Brozzoli et al., 2006; Vallar & Bolognini, 2012; Pavani et al., 2003).

Previous neuropsychological evidence has revealed that the multisensory enhancement of sensory-specific perception is still possible in spite of focal damages to either primary visual areas or heteromodal association cortices, suggesting that the cross-modal facilitation of unimodal perception as well as the integration of unisensory spatial inputs into a supramodal spatial representation may likely occur in absence of awareness of the visual stimulus or of the ability to voluntary orient attention in the side of space contralateral to the side of the lesion (Frassinetti et al., 2005; Schendel & Robertson, 2004; Bolognini et al., 2012; Mancini et al., 2011). On the other hand, when information provided

by the different senses is incongruent, a spared visual processing seems to be necessary for cross-modal interactions to occur. For instance, studies exploring the Ventriloquist illusion in brain-damaged patients with hemianopia or USN have shown that, when spatially incongruent audio-visual stimuli are presented in the affected hemifield, the typical auditory bias toward the visual event, namely the "visual capture" of sound, is disrupted in hemianoptic patients but not in in the presence of NSU (Leo et al., 2008; Passamonti et al., 2009). However, when the same stimuli are spatially aligned, the visual enhancement of auditory localization is spared in hemianoptic patients (Leo et al., 2008). This evidence suggests that the neural underpinning allowing the integration of congruent or incongruent audio-visual stimuli are different. In particular, the hypothesis put forward is that geniculo-striate circuits, including primary visual areas, are crucial for the illusory capture of sound by vision (i.e., inability of integrating incongruent visual-auditory cues in hemianopia), while the extra-geniculate pathway, which comprises the SC, is relevant for the multisensory enhancement effects on visual processing (i.e., spared auditory facilitation of visual perception in the blind hemifield of hemianoptic patients) (Bolognini et al., 2013). Moreover, there is some evidence indicating spared multisensory mechanisms in patients with lesions affecting heteromodal areas, such as the PPC, which may even compensate for unisensory perceptual and spatial disorders (Frassinetti et al., 2005; Bolognini et al., 2005).

In the light of such neuropsychological evidence, and following the results obtained in the previous experiments, I have taken advantage of the SIFI to assess whether auditory information can affect visual perception in face of low-level perceptual deficit featuring hemianopia and of the higher-order visuo-spatial disorder characteristic of NSU. This

approach will also offer clues on the causal contribution of primary visual areas (i.e., hemianopia) and higher-order associative cortices (i.e., USN) to the generation of the SIFI.

4.2. Experiment 6

4.2.1. Materials and Methods

Participants

Thirty-two right-handed participants were recruited in the Department of Neurorehabilitation Sciences of the IRCCS Istituto Auxologico Italiano (Milan, Italy). They were all naïve as to the purpose of the experiment and they all provided written informed consent to the protocol, which was approved by the Ethical Committee of the hospital, and carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302:1194).

Three groups of participants entered this study.

1) Twelve neurologically healthy controls (5 males; mean age = 65.41 ± 9.17 years, range = 50-82; mean years of schooling = 9.83 ± 3.83, range = 5-18), with no history or evidence of neurological or psychiatric diseases;

2) Twelve brain-damaged patients with visual helf-field defect (7 males; mean age = 48.66 ± 15.77 years, range = 25-77; mean years of schooling = 13.08 ± 4.05, range = 5-18). Patients were all tested in a chronic stage of illness (duration of disease = 32.48 ± 51.78 months, range = 3-192 months), when minimal spontaneous changes in visual sensitivity are

expected (Zhang et al., 2006). All patients suffered from a cerebral stroke: 6 (50%) of them had suffered a lesion of the left hemisphere and an associated right homonymous hemianopia, while for the other 6 the lesion affected the right hemisphere, and was related to a left-sided visual field defect (i.e., 4 patients with left homonymous hemianopia, and 2 with quadrantanopia). Contralateral visual field deficits were assessed by a standard visual field perimetry (i.e., Goldmann Perimetry);

3) Eight patients with left USN due to right-hemisphere cortical and/or subcortical lesions (4 males; mean age = 71.33 ± 10.96 years, range = 51-83; mean years of schooling = 11.8 ± 4.05, range = 5-18). Again, patients were all tested in a chronic stage of illness (duration of disease = 2.85 ± 3.68 months, range = 1-12 months). Seven of them had a history of vascular disease, while one patient suffered from brain tumor (parasellar meningioma). The presence of USN was assessed at the baseline neuropsychological evaluation by using a battery of standardized tests, which are described below. The diagnosis of USN was determined on the basis of a defective performance (i.e., below the cut-off score) in at least 3 out of the 5 clinical tests of cancellation and drawing.

All participants had normal or corrected-to-normal visual acuity. Brain-damaged patients were fully oriented in time and space, as clinically assessed, and they had no history or evidence of previous neurological or psychiatric disorders, nor dementia. Patients' demographic and clinical characteristics are summarized in Table I.

Neuropsychological assessment

One week before the experimental session, all patients underwent a standard neurological examination for the assessment of contralesional motor, somatosensory, and visual field deficits (Bisiach & Faglioni, 1974) and a battery of tests assessing the presence USN, including:

1. Cancellation tasks: Letter cancellation (Diller & Weinberg, 1977), Stars cancellation (Wilson et al., 1987), Bells cancellation (Gauthier et al., 1989); these tests assess the patient's ability to explore the two halves of a paper sheet, to cross out all the targets embedded into an array of distractors. In neurologically healthy participants the maximum difference between omission errors on the two sides of the sheet is 2 targets for the Letter task, 4 targets for the Bell task, and 1 target for the Stars Task (Vallar et al., 1994);

2. Line bisection: The patient is required to mark with a pencil the midpoint of 6 horizontal black lines (two lines of each of the following lengths: 10 cm, 15 cm, 25 cm; all lines are of 2 mm in width), presented in a random order. Each line is printed centrally on an A4 sheet. The length of the line, i.e. from the left end of the line to the participant's mark, is measured to the nearest millimeter and then converted into a standardized score (percentage of deviation) namely: measured left half *minus* objective half *divided by the* objective half *per* 100 (Rode et al., 2006). This transformation yields positive scores for rightward deviations, and negative numbers for leftward deviations. A percentage deviation score higher than +8.20% is considered as indicative of left USN (Fortis et al., 2010);

3. The Clock-Drawing Test (Ishiai et al., 1993) assesses the capacity of drawing from memory the numbers of a clock inside a printed circle (diameter = 12 cm). The total

score ranges from 0 to 12. A score lower than 9 indicates a defective performance (Mancini et al., 2011);

4. Five-element Complex Drawing (Gainotti et al., 1972) assesses the ability of the patients to copy a complex figure consisting of 5 elements (from left to right: 2 trees, 1 house, and 2 pine trees). The total score ranges from 0 to 10. According to normative data, a score lower than 10 indicates a defective performance (Fortis et al., 2010).

Patients used their right, unaffected, hand to perform every task. In all tasks, the center of the sheet was aligned with the mid-sagittal plane of the patient's trunk. Moreover, when USN signs were present, patients also underwent two supplementary clinical tasks in order to have a more comprehensive evaluation of their visuo-spatial disorder, namely a sentence reading test comprising 6 sentences (range score = 1-6) (Pizzamiglio et al., 1992) and a test assessing the presence of personal neglect in which patients were asked to reach 6 body parts of the right-side of their body, by using their right hand (range score = 0-18) (Bisiach et al., 1986).

Hemianoptic patients did not show comorbidity with USN symptoms, as confirmed by a performance above cut-off in at least 5 over the 6 NSU tests. The patients' individual scores are shown in in Table I.

Patient	Group	Duration of disease (months)	Aetiology	Age / Sex	Neurological Disease			Line Bisection	Cancellation Tasks			Drawing Tasks		Reading	Personal Neglect
					M	V	SS		Bells	Letters	Stars	Complex Figure	Clock		
P1	LH	353	H	69, M	-	+	-	2,40%	35/35	104/104	56/56	10/10	8/10*	n.a.	n.a.
P2	LH	993	H	25, F	-	+	-	6,80%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P3	LH	311	H	49, M	-	+	-	8,60%*	29/35*	104/104	56/56	10/10	12/12	n.a.	n.a.
P4	LH	288	I	77, F	+	+	+	- 2,00%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P5	LH	5760	H	28, M	-	+	-	- 1,00%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P6	LH	372	I	45, F	-	+	-	- 4,00%	27/35*	104/104	55/56	10/10	12/12	n.a.	n.a.
P7	RH	90	I	46, M	-	+	-	- 10,20%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P8	RH	183	I	34, M	-	+	-	- 10,20%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P9	RH	423	I	45, F	-	+	-	- 18,80%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P10	RH	1105	I	65, M	-	+	-	- 0,60%	33/35	102/104	54/56	10/10	12/12	n.a.	n.a.
P11	RH	1260	H	48, F	-	+	-	- 10,00%	35/35	104/104	56/56	10/10	12/12	n.a.	n.a.
P12	RH	555	H	53, M	+	+	+	- 5,00%	25/35*	102/104	56/56	10/10	12/12	n.a.	n.a.
P13	USN	30	H	51, F	+	+	+	6,20%	34/35	46/104*	45/56*	9/10*	12/12	6	17
P14	USN	59	H	69, M	-	-	-	0,40%	24/35*	102/104	56/56	10/10	10/12*	6	9*
P15	USN	358	I	74, M	-	-	-	9,80%*	27/35*	78/104*	41/56*	7,5/10*	12/12	6	18
P16	USN	33	TUMOR	72, M	+	+	+	77,40%*	0/35*	4/104*	7/56*	3/10*	8/12*	0*	18
P17	USN	47	I	83, F	+	-	-	6,60%	30/35*	95/104*	48/56*	9/10	10/12*	6	18
P18	USN	44	H	76, M	-	-	-	6,20%	19/35*	104/104	55/56	8,5/10*	3/12*	6	n.a.
P19	USN	50	I	73, M	+	-	-	29,60%*	3/35*	12/104*	6/56*	0,5/10*	3/12*	0*	17*
P20	USN	64	I	76, M	+	+	-	22,20%*	13/35*	28/104*	20/56*	10/10	9/12*	6	18

Table I. Demographic, neurological and clinical data of 6 left-brain-damaged patients with hemianopia (P1-P6, group LH), 6 right-brain-damaged patients with hemianopia (P7-P12, group RH) and 8 right-brain-damaged patients with NSU (P13-P20, group NSU). I/H: ischemic/hemorrhagic. M/V/SS: contralateral motor/somatosensory/visual half-field deficits. +/-: presence/absence of impairment. n.a.: not available. *: defective performance

Lesion data

Brain images were available for 17 out of the 20 brain-damaged patients enrolled in the study. Lesions were assessed by CT scans in 9 patients, and by MRI scans in 8 patients. The regions of interest (ROIs), defining the location and size of the lesion for each patient, were reconstructed by means of a template technique, by manually drawing the lesion on the standard template from the Montreal Neurological Institute (Rorden & Brett, 2000). ROIs

were created by mapping the regions on each 2D slice of a 3D volume. Figure 4.1 shows the transverse sections of the ROIs for each patient together with an overlay lesion plot for both NSU (Figure 4.1-a) and hemianoptic (Figure 4.1-b) patients, respectively. The mean volume of the lesion for USN patients was of 78.1 ± 100.6 cc^3 (range = 4.2–264.4 cc^3), while in hemianoptic patients it was of 22.12 ± 20.21 cc^3 (range = 1.2–58.1 cc^3).

(a) NSU Patients

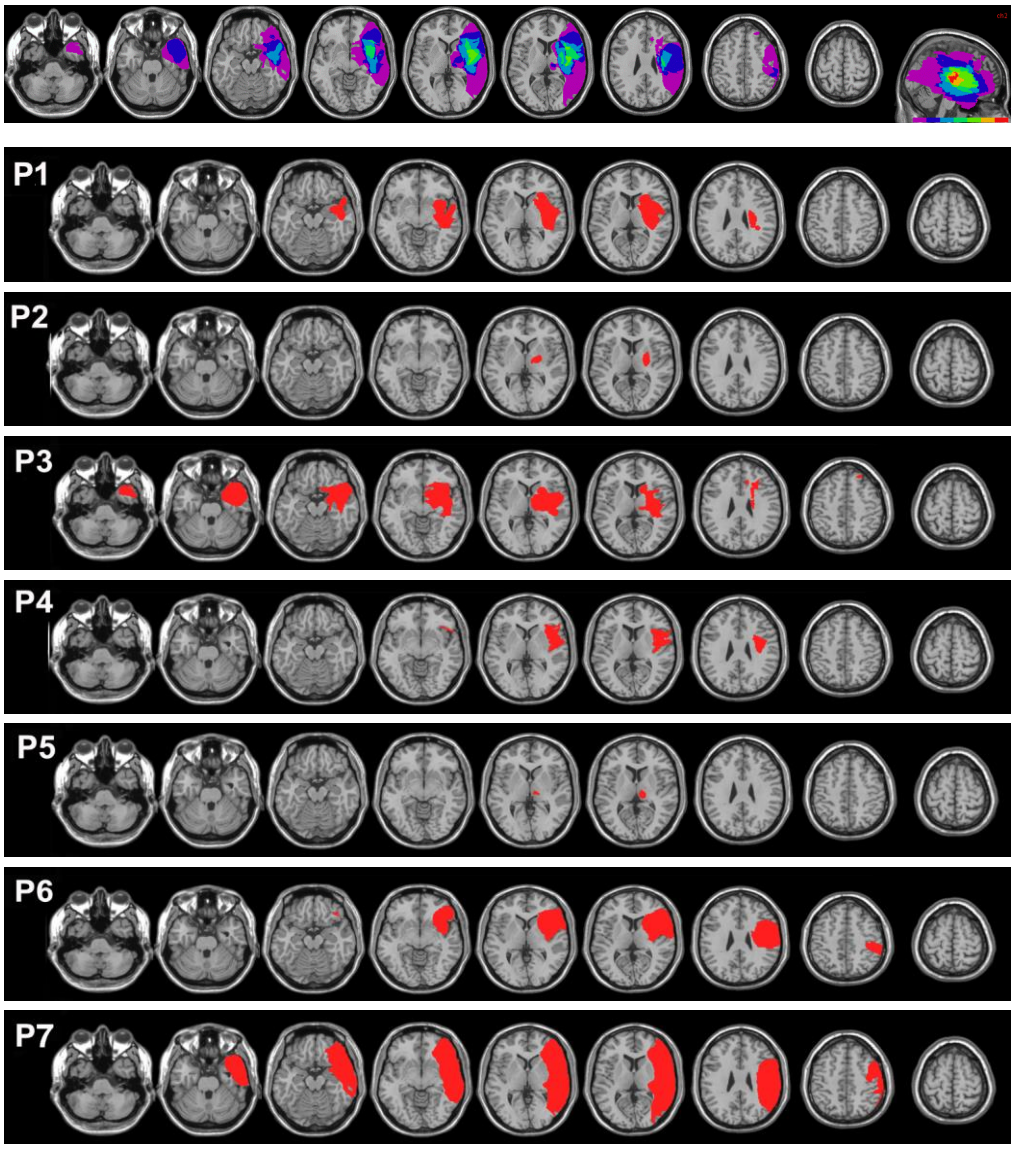


Figure 4.1-a. Lesion site of patients with USN. Overlay lesion plot (first row) and lesional mapping for each USN patient (P1-P7).

(b) Hemianoptic Patients

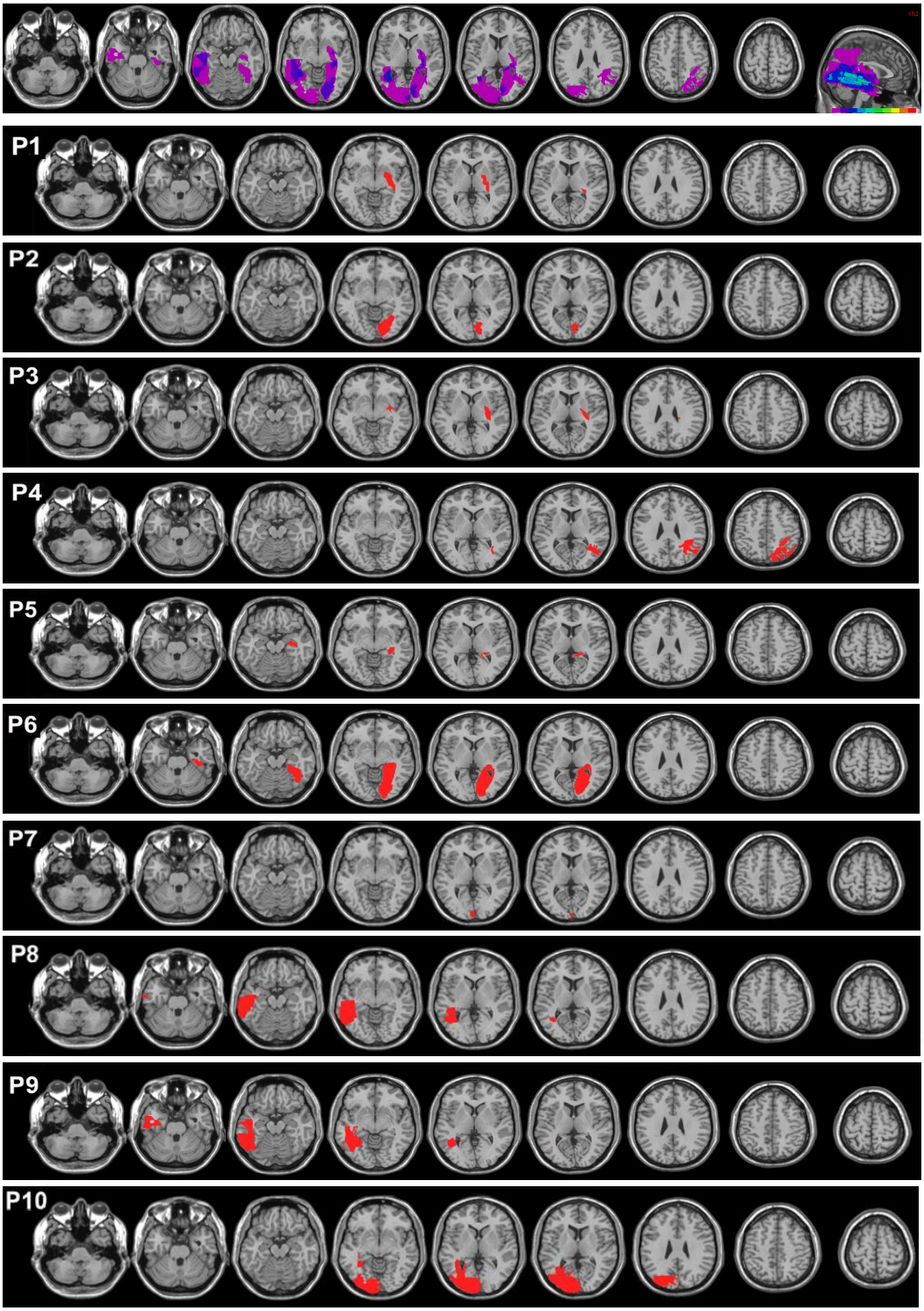


Figure 4.1-b. Lesion site of patients with hemianopia. Overlay lesion plot (first row) and lesional mapping for each patient (P1-P6, right-brain-damage, left hemianopia; P7-P10, left-brain-lesion, right hemianopia).

Stimuli, Apparatus and Procedures

The same apparatus and procedures of the SIFI (Shams et al., 2000) used in previous experiments (see for details, Chapter 3, Paragraph 3.2.1) were entailed. During the experimental session, participants were presented with the following 11 stimulus combinations (V = flash stimulus; B = beep stimulus): V1B0, V1B1, V1B2, V1B3, V1B4 (Fission Trials), and V2B0, V2B1, V3B0, V3B1, V4B0, V4B1 (Fusion Trials). Each condition was repeated 10 times, for a total of 110 trials, in a random order, for a duration of 10 min. At the beginning of each session, 11 practice trials were administered, but not included in subsequent analyses. The task was to report verbally the number of seen flashes.

Statistical Analyses

In order to assess the presence of the Fission and Fusion illusions in the three experimental groups, two repeated-measures ANOVAs, one for each illusory effect, were performed. For the Fission illusion, participants' mean visual responses to one flash (V1) trials (combined with 0–4 beeps) were submitted to a two-way ANOVA, with the 5-level *Beep* as main within-subject factor and the 3-level *Group* (Hemianopia, USN, Control) as between-subjects factor. For the Fusion illusion, the mean number of seen flashes was analyzed through a 3-way ANOVA, with *Beep* (1 vs. 2) and *Flash* (1-4) as main within-subject factors, and *Group* as between-subjects factor (Hemianopia, USN, Control).

Omissions, i.e. trials where patients failed in seeing any flash, never exceeded 3% and thus were excluded from analyses.

The same ANOVA's models were used in order to assess hemispheric asymmetries in the performance of hemianoptic patients, by comparing the patients with hemianopia due to left-hemisphere (N = 6) and right-hemisphere damages (N = 6). Accordingly, patients' responses in Fission and Fusion trials were submitted to two ANOVAs, which now included *Group* (Left Hemianopia, Right Hemianopia) as between-subjects factor.

For significant main effects and interactions, post-hoc multiple comparisons were conducted with the Bonferroni test. For each ANOVA, a measure of the effect size, as assessed by calculating the partial Eta Squared ($p\eta^2$) was also reported.

4.2.2. Results

Fission Illusion

When a single visual stimulus was flashed on the display, increasing the number of beeps significantly increased the number of reported flashes in NSU patients and healthy controls. However, this effect was significantly reduced in the hemianoptic patients (Figure 4.2-a).

The ANOVA revealed a main effect of *Beep* ($F_{4,116} = 105.02$, $p < 0.0001$, $p\eta^2 = 0.78$): the Fission illusion emerged when 1 flash was coupled with 2 (1.84), 3 (2.27) and 4 beeps (2.37), as compared to the 0 beep (1.22, $p < 0.0001$) and 1 beep trials (1.18, $p < 0.0001$) (with no differences between V1B0 and V1B1 trials, $p > 0.9$). The main effect of *Group* ($F_{2,29} = 6.83$, $p = 0.004$, $p\eta^2 = 0.32$) showed that hemianoptic patients, overall, reported less seen flashes

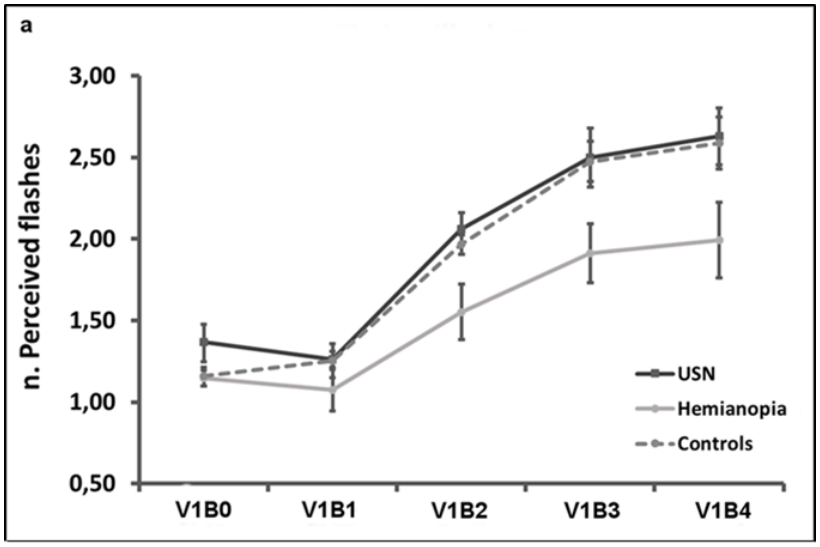
(1.53), as compared to healthy controls (1.89, p = 0.01) and USN patients (1.96, p = 0.008), with no differences between the latter (p = 0.9). Crucially, a significant *Group* by *Beep* interaction emerged ($F_{8,116}$ = 2.41, p = 0.02, $p\eta^2$ = 0.14). In order to clarify how the three groups diverged with respect to each beep condition, we run 5 additional one-way ANOVAs, one per each stimulus condition, with *Group* as between-subjects factor. No significant effect of *Group* was found for the V1B1 condition ($F_{2,29}$ = 1.72, p = 0.2, $p\eta^2$ = 0.08), nor for the V1B0 condition ($F_{2,29}$ = 3.29, p = 0.07, $p\eta^2$ = 0.18). Instead, the main effect of *Group* reached the significance in the critical illusory trials, namely: V1B2 ($F_{2,29}$ = 7.76, p = 0.002, $p\eta^2$ = 0.34), V1B3 ($F_{2,29}$ = 5.57, p = 0.009, $p\eta^2$ = 0.28), and V1B4 ($F_{2,29}$ = 4.18, p = 0.02, $p\eta^2$ = 0.22). Post-hoc comparisons showed that for every illusory trial, hemianoptic patients always reported a lower number of perceived flashes as compared to the other two groups ($p < 0.05$ for all comparisons); NSU patients and controls never differed from each other ($p > 0.9$ for all comparisons).

The ANOVA comparing hemianoptic patients with a left-hemisphere damage and a right-hemisphere damage showed no main effect of *Group* ($F_{1,10}$ = 1.35, p = 0.3, $p\eta^2$ = 0.12), nor a significant *Group* by *Beep* interaction ($F_{1,10}$ = 0.45, p = 0.5, $p\eta^2$ = 0.04); instead, the main effect of *Beep* was significant ($F_{1,10}$ = 30.68, $p < 0.0001$, $p\eta^2$ = 0.75).

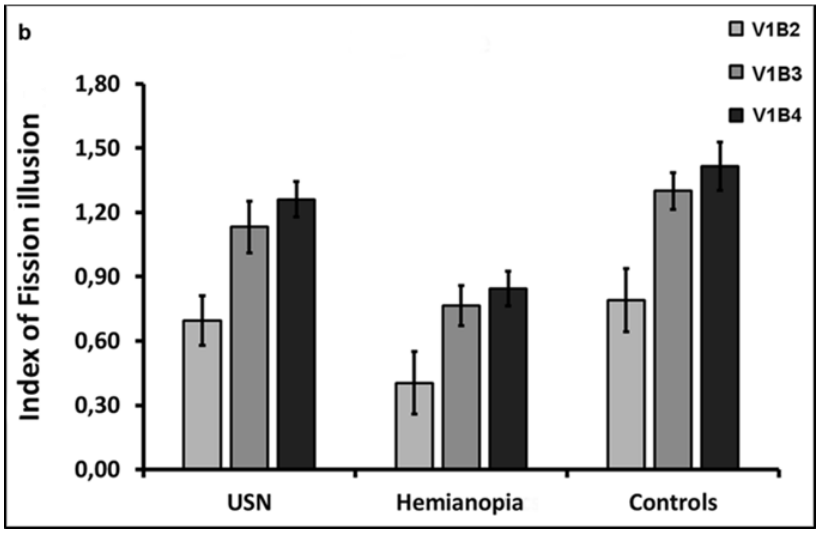
In order to better describe the differences among the three groups with respect to the illusory trials, an index of the Fission illusion was computed by subtracting the mean number of seen flashes in V1B0 trials from each of the multiple-beep trials (V1B2, V1B3, V1B4). Then, these indexes were submitted to a repeated-measures ANOVA with *Illusion Trial* as within-subject factor (V1B2, V1B3, V1B4) and *Group* (Hemianopia, USN, Control) as between-subjects factor. Results are depicted in Figure 4.2-b. In line with the previous

analysis, a significant main effect of *Group* ($F_{2,29}$ = 4.37, p = 0.02, $p\eta^2$ = 0.23) and of *Illusion Trial* ($F_{2,58}$ = 44.02, p < 0.0001, $p\eta^2$ = 0.60) emerged. Instead, the *Group* by *Illusion Trial* interaction was not significant ($F_{4,58}$ = 0.51, p = 0.72, $p\eta^2$ = 0.03). When the main effect of *Group* was explored by post-hoc comparisons, the results showed that the Fission illusion index was significantly reduced in hemianoptic patients, as compared to controls only (p = 0.02). There was no difference between USN patients and healthy controls (p = 0.8).

Figure 4.2. Results of Experiment 6, Fission Illusion.



(a) Average number of perceived flashes (ordinate) in each stimulus condition (abscissa: V= visual stimulus, B= beep) in USN patients (black line), hemianoptic patients (grey line) and controls (dashed grey line). Error bars= S.E.M.



(b) Mean Index of the Fission Illusion (ordinate) in USN, hemianoptic patients and controls (abscissa) in each illusory trial (V1B2: light grey bar; V1B3: dark grey bar: V1B4: black bar). Error bars= S.E.M.

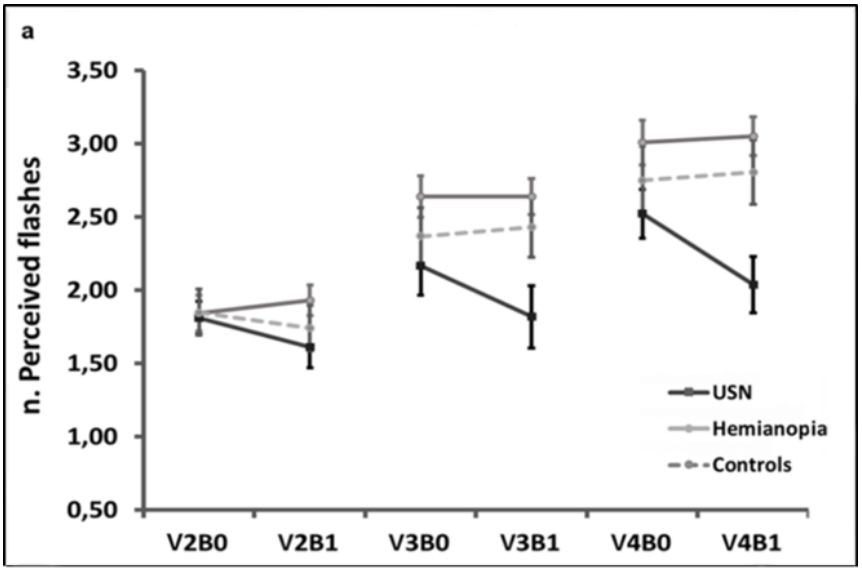
Fusion Illusion

Regarding the Fusion illusion, the results showed that only USN, but not hemianoptic patients, showed an amplification of this illusory effect as compared to controls (Figure 4.3-a).

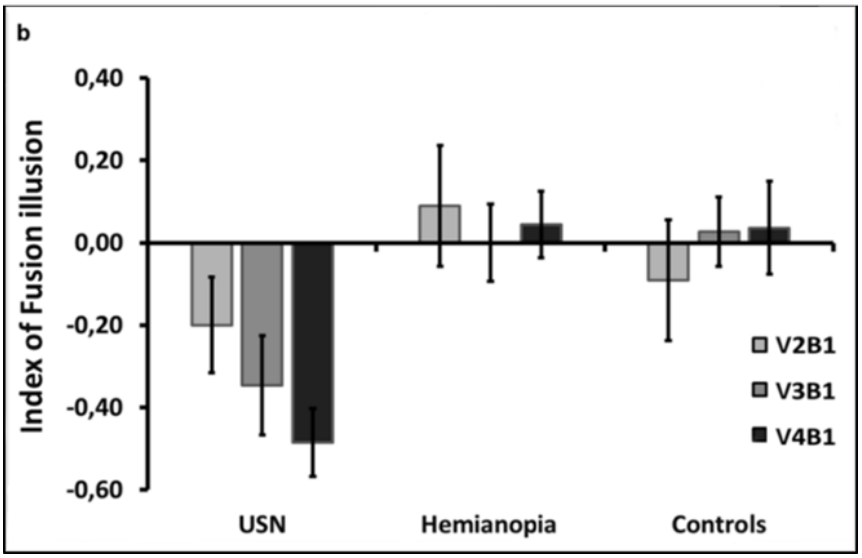
The ANOVA showed a significant effect of *Flash* ($F_{2,58}$ = 146.01, p < 0.0001, $p\eta^2$ = 0.83), indicating that the more flashes were presented, the more were reported (p < 0.0001 for all comparisons). The significant effect of *Beep* ($F_{1,29}$ = 4.38, p = 0.04, $p\eta^2$ = 0.13) revealed an apparently marginal effect of the sound on visual perception (0 beep trials = 2.35; 1 beep trials = 2.28). The significant *Flash* by *Group* interaction ($F_{4,58}$ = 5.33, p = 0.001, $p\eta^2$ = 0.27) showed that in USN patients a significant difference was present only between 2 flashes (1.71) and 4 flashes (2.28) trials (p < 0.0001), while for hemianoptic patients and controls differences were significant at all the three levels (Hemianoptic patients: 2 flashes = 1.89 vs. 3 flashes = 2.64 vs. 4 flashes = 3.03; Controls: 2 flashes = 1.80 vs. 3 flashes = 2.40, vs. 4 flashes = 2.78; all ps < 0.001). More relevant is the significant *Group* by *Beep* interaction ($F_{2,29}$ = 6.11, p = 0.006, $p\eta^2$ = 0.30): the presence of 1 beep significantly reduced the number of reported flashes only in USN (p = 0.01, the mean number of seen flashes was 2.17 in 0 beep trials vs. 1.82 in 1 beep trials), while in the control and hemianoptic groups the sound did not influence visual performance (p = 0.98 for all comparisons). Noteworthy, the main effect of *Group* was nearly significant ($F_{2,29}$ = 3.08, p = 0.06, $p\eta^2$ = 0.17). The *Flash* by *Beep* ($F_{2,58}$ = 0.33, p = 0.71, $p\eta^2$ = 0.01) and the *Flash* by *Beep* by *Group* ($F_{4,58}$ = 2.14, p = 0.08, $p\eta^2$ = 0.13) interactions were not significant. In line with the analyses conducted on the Fission effect, a repeated-measures ANOVA was performed for the index of the Fusion illusion, measured as the difference between 0 beep and 1 beep trials (i.e., 0 beep minus 1 beep, with negative values indicating the presence of the Fusion effect), with *Illusion Trial* (V2B1, V3B1, V4B1) as main within-subject factor and *Group* as between-subjects factor. The results (depicted in Figure 4.3-b) showed a main effect of *Group* ($F_{2,29}$ = 6.09, p = 0.006, $p\eta^2$ = 0.30), with the USN patients presenting a larger Fusion effect (-0.50) as compared to controls (0.01) and hemianoptic patients (0.04) (p < 0.05 for both comparisons). The main effect of *Illusion Trial*

($F_{2,58}$ = 0.33, p = 0.71, $p\eta^2$ = 0.01), and the *Illusion Trial* by *Group* interaction ($F_{4,58}$ = 2.13, p = 0.09, $p\eta^2$ = 0.13) did not reach significance.

Figure 4.3. **Results of Experiment 6, Fusion Illusion.**



(a) Average number of perceived flashes (ordinate) in each stimulus condition (abscissa: V= visual stimulus, B= beep) in USN patients (black line), hemianoptic patients (grey line) and controls (dashed grey line). Error bars= S.E.M.



(b) Mean Index of the Fusion Illusion (ordinate) in USN, hemianoptic patients and controls (abscissa) in each illusory trial (V2B1: light grey bar; V3B1: dark grey bar; V4B1: black bar). Error bars= S.E.M.

Lesion Size and Location

The size of the occipital, parietal, temporal and frontal lobe lesions (cc^3) in USN and hemianoptic patients, quantified by the estimated number of damaged voxel in each lobe (Bolognini et al., 2012; 2014 *in press*; Rorden & Brett, 2000), was correlated with the indexes of the Fission and the Fusion effects using non-parametric Spearman's rank correlation. Indexes of the Fission and the Fusion effects were calculated by averaging the index of each effect among the three illusory trials, namely, V1B2, V1B3, V1B4 for the Fission illusion, and V2B1, V3B1, V4B1 for the Fusion illusion.

A significant negative correlation (R_{17} = - 0.60, p = 0.01) emerged only between the size of the occipital lesion and the mean index of the Fission effect: the larger the extent of the damage affecting the occipital cortex, the smaller the Fission illusion. Other tested correlations did not reach significance: Fission illusion: parietal lesion (R_{17} = - 0.34, p = 0.2), temporal Lesion (R_{17} = - 0.13, p = 0.6), frontal lesion (R_{17} = 0.02, p = 0.9); Fusion illusion: occipital lesion (R_{17} = 0.15, p = 0.5), parietal lesion (R_{17} = - 0.24, p = 0.3), temporal lesion (R_{17} = - 0.10, p = 0.7), frontal lesion (R_{17} = - 0.35, p = 0.1).

4.3. Discussion

The present study investigated the perception of the SIFI in patients with hemianopia or USN. The results show that the Fission illusion was selectively reduced in patients with visual field defects, while in patients with USN the presence of multiple sounds affected visual perception in the same way as observed in neurologically healthy controls. A different

pattern of results emerged for the Fusion illusion, which was reliable only in NSU patients, while it was absent in hemianoptic patients and heathy controls.

The finding of a reduced Fission in hemianoptic patients represents a nice and strong complementary result to the evidence obtained in the previous experiments on the Fission illusion in phosphene perception (cfr. Experiment 4, Chapter 3). Now, the neuropsychological results confirm that having an intact visual cortex is necessary for regular Fission effects to occur. Accordingly, the amount of the lesion affecting the occipital cortex negatively correlated with the patients' perception of the Fission illusion: the larger the occipital damage, the smaller the illusory Fission by sounds. This finding is in line with previous reports showing that the Fission illusion varies according to the level of excitability of the occipital cortex, which could be altered by a pathological condition of over-activation as in chronic migraine (Brighina et al., 2014, *in press*), or by the non-invasive electrical stimulation of the cortex via tDCS (see Experiment 3 described in Chapter 2, but also Bolognini et al., 2011a).

Of great relevance is also the preserved Fission illusion in USN patients. In face of impaired spatial awareness, affecting both visual and auditory perception (Bertelson et al., 2000; Phan et al., 2000), pre-attentive sensory processing (Treisman & Gelade, 1980) is often preserved in these patients (Driver & Mattingly, 1998). Accordingly, the spared activity in primary visual areas might have allowed the emergence of the Fission illusion. Overall, it seems that the dysfunction of the dorsal attentional network, affected in USN, did not abolish the auditory influences on visual perception, as revealed by a preserved Fission illusion here, and by a spared facilitatory auditory effects on contralesional visual perception

and a preserved spatial ventriloquism in previous studies (Frassinetti et al., 2005; Bertelson et al., 2000).

The causal role of higher-order areas in the SIFI as assessed by means of NIBS in previous works appears controversial. By altering the excitability of the right PPC via tDCS, Bolognini and collaborators failed in finding any significant modulation of the SIFI, while they observed a significant increase of the Fission illusion after the anodal stimulation of the right STG, and a decrease of the same effect after the cathodal stimulation of the same area (Bolognini et al., 2011a). The involvement of the superior temporal cortex in the Fission illusion is further supported by fMRI and EEG evidence (Watkins et al., 2007; Mishra et al., 2007).

Conversely, two recent TMS works testing the contributions of two sub-regions of the parietal cortex, the Angular Gyrus (AG) and the supramarginal Gyrus (SMG), in the SIFI showed a reduced sensitivity to the Fission illusion after the disruption of the right AG, but not of the right SMG (Kamke et al., 2012; Hamilton et al., 2013). Kamke and colleagues (2012) specifically called upon an alteration of an attention-related cortical network to explain the observed reduction of the SIFI when the right AG was knocked out by TMS.

On the bases of the present results in hemianoptic and NSU patients, I argue that a dysfunction of higher-order network involved in spatial attention consequent to brain injury does not seem to impact the Fission illusion, strengthening the hypothesis that the SIFI is more likely related to low-level cross-modal interactions between visual and auditory modalities.

The second important finding is related to the Fusion illusion, which was stronger in NSU patients, than in hemianoptic patients and healthy controls. Although the Fusion and the Fission illusions may appear as complementary phenomena, behavioral, neuroimaging and electrophysiological evidence points to different neural correlates (Andersen et al., 2004; Innes-Brown & Crewther, 2009; Shams et al., 2000; Mishra et al., 2008; Watkins et al., 2007). Indeed, the Fusion is a weaker phenomenon as compared to the Fission Illusion and it shows a larger degree of inter-individual variability in healthy subjects (Mishra et al., 2008; Andersen et al., 2004; Shams et al., 2000), which likely explains its variability in my experiments. Second, from a neural perspective, the Fission illusion results from auditory-induced changes of activity in A1, V1 and superior temporal areas, occurring within 90-150 msec post stimulus onset. Instead, the Fusion illusion is associated to a different spatio-temporal profile, namely a cross-modal modulation of the activity of superior temporal areas starting at around 80–112 msec after the second flash and followed by a delayed (at 228–248 msec) modulation in the extrastriate visual cortex (Mishra et al., 2007; 2008; Watkins et al., 2007). This spatio-temporal profile indicates that the Fusion illusion does not primarily rely on the activity in V1, in line with the results on phosphenes perception (Experiment 4, Chapter 3), showing that the perceptual Fission of a single phosphene by multiple beeps is not matched by a Fusion of double phosphenes by a single beep. The present results in brain-damaged patients further support the dissociation between Fusion and Fission effects, pointing to a causal link between the activity in areas damaged in USN, but not featuring hemianopia, and the likelihood of the Fusion illusion to occur.

However, no significant correlation emerged between the size of the parietal, the temporal nor the frontal lobe lesions and the size of the Fusion illusion. This null result might

have been caused by the small sample size, and the heterogeneity of lesion profile of our patients. More generally, it is worth mentioning that in the present study, USN patients showed heterogeneous right hemispheric damages, mainly involving frontal and temporal areas (with a maximal region of overlay in the insular cortex, see Figure 4.1-a) and, to a less extent, parietal areas. To note, temporal and parietal areas play a distinct role in attentional and cognitive control, as well as in multisensory processing (Chambers et al., 2004a; 2004b; Gobel et al., 2001). Hence, it will be of great interest for future research to further explore how the Fission and Fusion illusions are altered in larger samples of USN patients. Such investigation would allow obtaining more insights on the neural substrate of such cross-modal illusory effects.

To summarize, in the present study we extended the previous findings by demonstrating that the integrity of visual processing, and hence of primary visual areas is a crucial factor for the Fission illusion to occur. The Fission effect can arise even in the presence of a dysfunction to a higher-order supramodal network responsible for spatial attention functions (i.e., USN). This evidence indicates that a top-down attentional control is not compulsory for the binding of visual and auditory signals (Werkhoven et al., 2009; Kamke et al., 2012), in accordance with what previously observed in the visuo-haptic domain, where the visual bias on touch featuring a well-known cross-modal illusion, namely the Judd variant of the Müller-Lyer illusion (Coren & Gircus, 1978), was found to be preserved in right brain-damaged patients with NSU (Mancini et al., 2011). Conversely, the Fusion illusion is not altered in face of impaired visual perception and cortical activity; rather, this illusion seems more related to the activity of a higher-order network, which however determines an increase, rather than a decrease, of such Fusion effect.

Chapter 5

General Discussion

The series of experiments described in the present doctoral thesis demonstrates the causal implication of low-level visual areas in early multisensory interactions, providing novel clues on the cortical mechanisms through which cross-modal stimuli interact with and affect visual perception.

In Chapter 2, through a set of three Experiments, I described the effects of spatially congruent auditory and/or tactile cues on visual cortical and behavioral responses, as indexed by TMS-induced phosphenes, demonstrating that the more sensory inputs are combined (i.e., trimodal vs. bimodal stimuli), the greater the multisensory benefits on phosphene perception (Experiment 1). This perceptual facilitation is likely related to a multisensory amplification of the intensity of the neural signal within the visual cortex (Experiment 1). Such multisensory-mediated improvement of visual perception can be selectively increased by up-regulating the excitability of temporal and parietal areas via tDCS, thus confirming the causal implication of these areas in mediating the observed facilitation of visual perception by non-visual cues (Experiments 2-3).

In Chapter 3, by reproducing the SIFI with TMS-induced phosphenes, I showed that visual cortical activity can be altered by temporally incoherent sounds, with a consequent misleading of subjective visual experiences, namely the illusory perception of multiple

phosphenes (Experiment 4). The auditory induction of the phosphene illusion occurs within a precise temporal window featured by early audio-visual interactions (Experiment 5), which supports a neural account implying a rapid audio-visual interplay occurring during the earliest stages of visual processing and not requiring a higher-order control.

Finally, in Chapter 4 (Experiment 6), I provided further support to this claim by showing that the perception of the SIFI is disrupted in brain-damaged patients with visual field defects but not in those with spatial attention disorders, with the Fission illusory effects specifically associated with the integrity of occipital areas.

Taken together, the results of these experiments demonstrate that cross-modal influences on visual perception are causally related to early cross-modal interactions that can take place in primary visual areas. Feed-back projections from temporal and parietal heteromodal regions plausibly refine such cross-modal influences on visual cortical activity and perception; instead, feed-forward connections between primary sensory areas, such as from A1 and S1 to V1, likely subtend a rapid, although rougher, exchange of sensory information across the different perceptual systems.

5.1. Cross-modal interactions in the visual cortex

By directly inquiring visual cortical excitability via TMS and using phosphene perception as perceptual index of occipital activation, in Experiments 1-5 I demonstrated that cross-modal stimuli can modulate visual conscious perception exactly where it generates, namely within early visual areas.

It has been proposed that multisensory mechanisms in primary sensory cortices are modulatory in nature, namely they change the probability of neuronal firing in response to an appropriately timed input from a different modality, while those in higher-order regions are more likely driving-type inputs, i.e., directly causing the neurons to respond (Musacchia & Schroeder, 2009). Accordingly, attending to a visual stimulus presented in isolation modulates the ongoing oscillatory activity in the supragranular laminae of A1; the opposite modulation is observed with attended auditory stimuli in V1 (Lakatos et al., 2008; Musacchia & Schroeder, 2009). Phase resetting, in which a sensory stimulus causes ongoing oscillations across different areas to become phase-locked, has been suggested to represent the key mechanism of the cross-modal modulation of early visual activity (Senkowski et al., 2007; Pasalar et al., 2010). In other words, synchronization of neuronal activity within and across different cortical areas is the way for binding sensory information offered by specialized cortical regions (Antal et al., 2004; Engel & Singer, 2001; Lakatos et al., 2007). Evidence in this sense has been provided by studies using phosphene induction. Romei and collaborators (2012) showed that a salient sound can phase-lock visual alpha activity, with direct consequences on phosphene perception. In particular, the auditory enhancement of phosphenes shows a rapidly cycling pattern with roughly ~100 msec peak-to-peak interval, with two peaks of increased visual cortical excitability between 75–105 and 195–225 msec after the sound, consistent with the ~10 Hz nature of occipito-parietal alpha activity linked to visual perception. Auditory stimulation, without occipital TMS, also shows ~10 Hz alpha phase locking from 50 to 250 msec following auditory stimulus onset, not only over the auditory cortex, but also for posterior parietal-occipital sites including the visual cortex. Finally, a ~10 Hz pattern was found also for EEG-derived measures of occipital cortex

reactivity to TMS pulses. These cyclical visual phenomena in both perceptual and EEG measures after sound onset suggest a cross-modally triggered phase locking of perceptually relevant oscillatory alpha activity over occipito-parietal areas. This likely represents the neural mechanism through which cross-modal stimuli affect phosphene perception (Romei et al., 2012).

In Experiment 1, the modulatory effects of redundant auditory and tactile inputs on visual activity express themselves through an increased probability to detect sub-threshold phosphenes, spatially coincident with the sound and touch locations; such multisensory enhancement is maximized by the simultaneous presentation of both sound, touch and the TMS occipital pulse (i.e. the trimodal condition). Intriguingly, cross-modal cues do not only increase phosphene detection, but also enhance phosphene brightness as compared to unimodal stimulation. Brightness perception strictly depends on the intensity of the neural signal within early visual areas (Orban, 1984; Barlow et al., 1978; Papaioannou & White, 1972). Accordingly, studies using intracranial electrical stimulation of the visual cortex have reported a monotonic increase of the perceived brightness of phosphenes as the frequency of electrical pulses increased up to 200 Hz (Evans et al., 1979). It follows that the physiological correlates of the augmented phosphene brightness plausibly relies on a cross-modal intensification of the sensory signal within the visual cortex. Such signal amplification may, in turn, reflect a top-down perceptual-attentional enhancement of visual processing driven by feed-back pathways from higher-order multisensory areas within the parietal and temporal cortices (Driver & Spence, 2000; Macaluso, 2006).

A remarkable facilitation of unimodal phosphene perception can also be observed in Experiment 2, where occipital activity is enhanced via tDCS. Recent EEG studies, investigating

changes of activity in a resting brain during anodal tDCS of the PPC reported a significant alteration of ongoing brain activity, specifically in the alpha-band rhythm (Spitoni et al., 2013; Mangia et al., 2014). Accordingly, the neuromodulatory influences on unimodal visual responses observed in Experiment 2, plausibly rely on transient and reversible changes of visual cortical activity driven by tDCS, which, in turn, are functionally akin to the modulatory effects brought about by multisensory stimuli. This evidence strongly suggests that we can effectively regulate visual cortical ongoing activity either by increasing it via tDCS or by presenting external cross-modal stimuli.

The mechanisms supporting the multisensory enhancement of visual perception may also be called into question for explaining the alteration of visual perception featuring cross-modal illusions. In the SIPI (Experiments 4, 5), multiple auditory signals, paired to the occipital TMS pulse, affect visual cortical responses. Here, however, the auditory modulation of occipital does not result in an enhancement of phosphene perception; rather, it determines the illusory perception of multiple visual events. Previous neuroimaging studies have shown that the SIFI is associated with the activation of the retinotopic V1 by the concurrent auditory stimulation: when a single flash is perceived incorrectly as two flashes, neural activity in V1 increases, while when a double flash is perceived incorrectly as a single flash, V1 activity decreases (Watkins et al., 2006; 2007). In a more recent MEG study, Keil and colleagues (2014) highlighted that a complex pattern of alpha-band and beta-band phases synchrony in a network comprising temporal and occipital areas may play an important role in determining the perception of this audio-visual illusion.

Collectively, these pieces of evidence suggest that both cross-modal spatially and/or temporally congruent and incongruent cross-modal information affect phosphene

perception by modulating visual cortical excitability. However, they diverge with respect to the induced phenomenal experience: a facilitation of visual perception and cortical excitability results from coherent pairings of cross-modal stimuli, while incoherent ones alter the visual experience.

5.2. Visual cortical excitability and integrity affect cross-modal interactions

The evidence discussed so far points at the visual cortex as a key cortical site where cross-modal stimuli converge and interact, in turn modulating visual perceptual and neural responses. This area not only represents a passive structure, where activity can be modulated and/or optimized by non-visual signals, but it may rather actively determine the extent of early cross-modal interactions, depending on its level of activation. In support to this proposal are recent reports of altered multisensory effects on visual perception in the presence of variation of visual cortical excitability. For instance, Brighina and collaborators demonstrated that the SIFI is dramatically reduced in patients suffering from chronic migraine, a condition suggested to be related to a state of pathologic hyperexcitability of the visual cortex (Brighina et al., 2014, *in press*). In particular, the authors observed that in migraine patients the Fission illusion was greatly reduced, especially during the migraine attack, and almost abolished when a single flash was combined with two beeps; instead, the Fusion illusion was less consistently reported in both migraine groups, but not completely disrupted.

On the other hand, Bolognini and colleagues (2011a) reported that modulating visual cortical excitability with tDCS altered the Fission, but not the Fusion, illusion in neurologically healthy subjects. Anodal tDCS decreased the Fission effect, while the cathodal stimulation increased it (Bolognini et al., 2011a).

In Experiment 3, the facilitatory effects of congruent cross-modal stimuli are counteracted by the anodal stimulation of the occipital cortex. This evidence is reminiscent of the "inverse effectiveness rule" of multisensory integration. In multisensory neurons of the SC of the cat, the salience of the unimodal signals represents a major determinant of the advantage resulting from their integration (Holmes & Spence, 2005; Meredith & Stein, 1983). In this perspective, the level of excitability in visual areas might predict the extent of cross-modal interactions, with larger multisensory effects for reduced visual activity (Bolognini et al., 2010a).

If from the one hand an altered visual excitability at baseline modifies the impact of cross-modal interactions on visual perception, a different scenario opens up when visual activity is at least partially knocked out by a brain injury. In this case, specific cross-modal interactions may be abolished (Leo et al., 2008; Passamonti et al., 2009). Accordingly, when testing the SIFI in patients suffering from damages to early visual areas, the Fission illusion is reduced, as compared to healthy individuals (Experiment 6), suggesting that the degree by which sounds impact visual responses varies not only in function of its excitability, but also of its integrity. Therefore, a sub-optimal visual processing may favor cross-modal interactions that can strengthen or alter visual perception; however, the disruption of visual functions may also prevent some (but not all) specific cross-modal interactions. Indeed, although the integrity of early visual areas may be necessary for the occurrence of specific

cross-modal phenomena, such as the Fission illusion, in other cases a visual loss might be compensated by alternative, spared multisensory mechanisms, allowing the survival of other multisensory phenomena (Frassinetti et al., 2005; Schendel & Robertson, 2004; Bolognini et al., 2012; Mancini et al., 2011). These compensatory mechanisms seem to reflect a functional reorganization of multisensory networks aimed at balancing the loss of a sensory modality and sustaining impaired sensory processing through adaptive cross-modal plasticity (Bolognini et al., 2013).

The evidence of preserved multisensory phenomena in face of visual cortical damages rises another important question: why is the integrity of early visual areas critical for some multisensory effects but not for others? Answering this question requires re-considering the causal role played by the visual cortex as part of a larger network, where cross-modal influences on low-level visual activity can be mediated either by feed-back projections from higher-order structures, or by direct connections between low-level sensory areas.

5.3. Routes for cross-modal influences on visual areas

Non-visual inputs may access the visual cortex through different neural pathways. Anatomical studies in non-human primates, as well as neuroimaging and electrophysiological investigations in humans, have demonstrated the existence of both feed-forward and feed-back projections to the primary sensory cortices, including V1. As described in details in Chapter 1, evidence of fast cortico-cortical routes for direct influences between senses has been provided by anatomical tracing studies in animals (macaque: Falchier et al., 2002;

Rockland & Ojima, 2003; ferret: Bizley et al., 2007), while examples of top-down modulatory influences from heteromodal areas have been chiefly documented by electrophysiological recordings in macaques (Bizley et al., 2007; Brosch et al., 2005; Ghazanfar et al., 2005), and by human neuroimaging studies (Macaluso et al., 2002; Macaluso & Driver, 2005; Noesselt et al., 2007; for a more detailed overview, please refer to Chapter 1, Paragraph 1.3). The existence of such alternative pathways through which cross-modal stimuli can affect neural activity in primary, sensory-specific, areas is suggestive that each route may subserve specific multisensory functions.

Direct connections between primary sensory cortices, but also thalamo-cortical gating (de la Mothe et al., 2006), may support early cortical interactions among senses in V1. Accordingly, cross-modal interactions in primary sensory areas arise as early as 50 msec post stimulus onset (e.g., Giard & Peronnet, 1999; Molholm et al., 2002; Senkowski et al., 2007). In particular, audio-visual activations in V1 occurs around 53 msec after the auditory stimulation, that is only 10 msec after the V1 activation brought by visual stimuli; this cross-modal effect strongly suggests that the auditory input is provided to V1 directly by A1 (Raij et al., 2010). The type of multisensory information driven by such short-latency cross-modal responses in primary sensory cortices is plausibly simple in nature (Musacchia & Schroeder, 2009). In other words, cross-modal interactions in primary sensory areas should support relatively non-specific multisensory effects (e.g., arousal, alerting, or overall weighting of one modality relative to another), rather than particular relationships between stimuli from different sensory modalities (e.g., relative location or semantic/associative links) (Driver & Noesselt, 2008).

In this perspective, results from Experiments 4-5-6 suggest that the SIFI may

represent an example of these effects. Firstly, because the Fission illusion with phosphenes is characterized by an early modulation of visual cortical activity (within ± 80 msec of interval between the TMS pulse and the second sound). After this early interval, the illusion dramatically decays. This short time window is consistent with the temporal profile of the standard Fission illusion with flashes, which starts degrading when the time interval between the two sounds is larger than 100 msec (Shams et al., 2002). Electrophysiological studies also reveal that the perception of the Fission illusion is linked to an early modulation of visual cortical activity, elicited as rapidly as 35–65 msec after the delivery of the second sound, plausibly reflecting audio-visual activity in V1, and followed by a later modulation localized in the superior temporal area (Mishra et al., 2007; 2010).

Secondly, as observed in Experiment 4, the sound-induced illusory phosphene actually appears in the peripheral left visual hemifield, at a mean eccentricity of about 17°. Accordingly, direct projections from primary auditory cortices to V1 seem to terminate preferentially in portions representing the peripheral visual field (Falchier et al., 2002).

Lastly, the evidence emerged from Experiment 6 of a preserved Fission illusion in face of a dysfunction of a dorsal network of higher-order areas (responsible for the spatial attentional deficit in NSU patients), along with its disruption consequent to occipital lesions (featuring patients with visual field disorders), further points to an early multisensory processing in V1 as the most likely functional substrate of the sound-induced Fission of illusory flashes or phosphenes.

An alternative way by which multisensory stimuli may change the activity of primary sensory cortices relies on top-down modulatory feed-back projections (Calvert et al., 1999; Macaluso & Driver, 2001). This account retains the traditional distinction between

multisensory and sensory-specific regions, as defined by their feed-forward inputs (e.g., Mesulam, 1998), but postulates that the former areas would now be able to influence the latter via feed-back projections (Driver & Noesselt, 2008). This prediction implicates that multisensory phenomena mediated by this route necessarily hold a longer temporal profile relative to multisensory interactions in V1. Accordingly, a later modulation in primary sensory cortices, picking up around 100-200 msec after stimuli onset, has been associated to a number of multisensory effects (McDonald et al., 2005; Bizley et al., 2007; Bonath et al., 2007). These effects, at difference from those arising from rapid, feed-forward cross-modal interactions, often involve some top-down attentional control (Kastner et al., 1999; Macaluso et al., 2003), undergo the influences of posture (Macaluso et al., 2002; Kennett et al., 2001) and are associated to functional activations in supramodal association areas (Macaluso et al., 2000b; 2003). Accordingly, some authors propose that modulatory back-projections from multisensory to unimodal brain areas could mediate cross-modal spatial effects in primary sensory areas (Macaluso & Driver, 2005). This proposal implies that interfering with activity in these supramodal regions should prevent a higher-order, plausibly attentional, control over early multisensory effects. Causal evidence in this sense has been provided by a previous study targeting the right PPC by rTMS: the disruption of the PPC activity selectively impaired the spatial remapping of visuo-tactile interactions across postures, but it did not entirely abolish visuo-tactile interactions, which were still evident, although deprived of their spatial specificity (Bolognini & Maravita, 2007). In the same vein, in the present Experiment 3 an enhancement of the cross-modal facilitation by sounds or touches on phosphene perception was obtained after the anodal tDCS of the STG and of the PPC, respectively. This intriguing result deserves a couple of considerations. First, in such

experiment the auditory and tactile stimuli were spatially coincident to the phosphene locations, a choice dictated by evidence showing the importance of the spatial alignment of sensory signals for effectively activating V1 (e.g., Macaluso et al., 2000b; Bolognini et al., 2010a). The spatial congruency of cross-modal signals is relevant to prompt their behavioral relevance, leading supramodal attentional mechanisms to enhance cross-modal interactions through feed-back modulatory connections. In this respect, the selectivity of the target areas relative to the type of cross-modal effect (i.e., tactile vs. auditory enhancement of visual cortical responses) might reflect a regional preferences of the PPC and the STG for one modality over the others or for specific cross-modal combinations (Driver & Noesselt, 2008; Kayser et al., 2005; Kayser & Logothetis, 2007; Ghazanfar & Schroeder, 2006). Within the PPC and along the STG there are heteromodal sub-regions where inputs from the different senses converge and integrate (Driver & Noesselt, 2008; Stein & Stanford, 2008; Macaluso, 2006; Teder-Sälejärvi et al., 2005; Andersen, 1997). Posterior parietal sub-regions seem mainly involved in updating the relative position of extrapersonal visual and somatosensory stimuli for allowing effective visuo-tactile interactions related to body and peripersonal space representations (Vallar & Maravita, 2009; Bolognini & Maravita, 2007; Macaluso, 2006; Maravita et al., 2003). The STG is primarily involved in the integration of audio-visual speech and non-speech stimuli (Bolognini et al., 2011a; Beauchamp et al., 2004; Calvert, 2001), as well as in the multisensory enhancement of detection sensitivity for low-contrast visual stimuli by co-occurring sounds (Noesselt et al., 2010; Beauchamp et al., 2004; Calvert, 2001). More importantly, both PPC and STG have been shown to send feed-back projections to occipital areas (Chambers et al., 2004b; Macaluso et al., 2000b; McDonald et al., 2003). Therefore, the neuromodulation of STG and PPC via tDCS might target specific cross-modal

interactions in these areas, facilitating the cross-modal shift of attention toward the spatial location of phosphenes cued by touch or by sound.

An important point to consider concerns the low spatial resolution of tDCS (Brunoni et al., 2012; Vallar & Bolognini, 2011; Nitsche et al., 2008). Although computer-based modeling studies indicate that direct functional effects of tDCS are restricted to the area under the active electrode (Wagner et al., 2007; Miranda et al., 2006), it is possible that the parietal and temporal stimulation might have affected activity also in primary somatosensory and auditory areas, respectively, hence modulating cross-modal interactions mediated by direct, feed-forward connections between these sensory regions and V1.

What seems to be clear from the results of Experiment 3 is that tDCS can be used to up-regulate cortical excitability in parietal and temporal areas to reinforce auditory and tactile influences on visual perception. Since enhanced multisensory facilitation occurred after parietal and temporal tDCS, but not after occipital tDCS (Experiment 3), it follows that for modulating the cross-modal influences on visual cortical excitability the best approach consists of targeting the areas where the cross-modal influences originate (i.e., PPC and STG), rather than the areas where these influences terminate (namely, V1).

Concluding Remarks

In the last decade, the research on multisensory processing has led to the realization that multisensory influences can be much more pervasive than classical views assumed and may extend to brain regions, neural responses, and judgments classically marked as modality-specific. By focusing on the visual domain and using NIBS techniques, in the

present doctoral thesis I have provided novel support to the view that visual perception can be improved or altered by non-visual stimuli, with such behavioral effects being caused by cross-modal changes in visual cortical excitability. The cross-modal effects on visual perception and cortical activity can be further enhanced by boosting the auditory and tactile influences from temporal and parietal areas through their non-invasive electrical stimulation, while damages to visual cortical areas may preclude some interactions among cross-modal stimuli. Collectively, this evidence argues against a modular paradigm of perceptual processes, showing that dynamic and vigorous exchanges and integration of sensory information are possible as early as in putative, modality-specific sensory cortices, such as V1.

It would be a challenge for future research to better characterize the role of different cortical circuits (feed-back vs. feed-forward connections) in supporting distinct phenomena of multisensory perception. This investigation is likely to require the combination neuromodulatory techniques and concurrent measures of functional neural activity, in order to outline the causal interplay between remote but interconnected regions of the brain, rather than the function of single brain region(s).

Acknowledgements

I would like to express my gratefulness to all the people who took part to this work and supported me during my doctoral studies.

My deepest and most sincere gratitude goes to my Supervisor and Mentor, Nadia Bolognini. She firstly initiated me to research and supported me during the different phases of my undergraduate and doctoral studies with a unique mix of patience, trust, knowledge and friendship. She truly inspired me with her passion and dedication for science and I will always be grateful for her teaching. A better guidance would not have been possible.

My heart-felt thanks to Professor Vallar, who has been a Mentor for me as well, and supported my scientific growth with his outstanding knowledge and expertise. Working with him has been an honor for me.

My gratefulness also goes to my colleagues and friends, Angela Rossetti, Irene Senna, Martina Fusaro, Chiara Galantini, Carlotta Casati, Mirella Manfredi, Roberta Ronchi, Elena Olgiati, Luca Zigiotto, Cristina Russo, Francesco Marini, Manuela Malaspina, Elena Calzolari, Daniele Romano, and Marjan Persuh. Everyone, his own way, supported and encouraged me, helping me growing up as a researcher and as a person as well. THANK YOU for your precious help and friendship.

I would also like to express my gratitude to all the people who participated to the data collection for this doctoral thesis, from the staff of the Neuropsychological Laboratory at the Auxological Institute (Milan), to the undergraduate students who flanked me during

the data collection, to all the over 100 experimental participants. You made this work possible.

Finally, I would like to dedicate this work to my father: thank you for your endless love and inestimable, ceaseless support.

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