Flavia Mancini

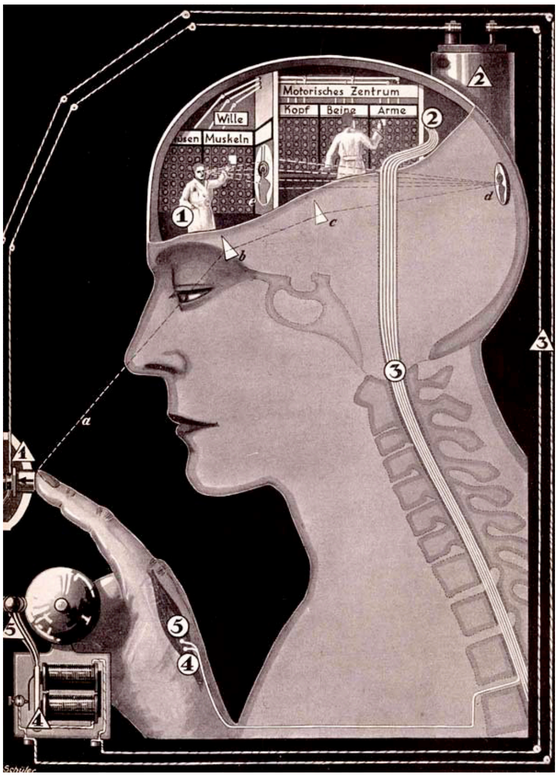
Multisensory modulation of bodily senses

Doctoral thesis promoted by:
Prof. G. Vallar & Prof. E. Bricolo

University of Milano-Bicocca, Department of Psychology
Doctoral program in Experimental Psychology, Linguistics, and Cognitive Neuroscience, XXIII cycle: 2008-2011.

I, Flavia Manicni, confirm that the work presented in this thesis is my own.

Where information has been derived from other sources, I confirm that this has been indicated in the thesis.



Fritz Kahn, *The workings of the nervous system*. 7407, p. 24.

Doctoral thesis promoted by:

Professor Giuseppe Vallar

Professor Emanuela Bricolo

Department of Psychology, University of Milano-Bicocca

Table of Contents

Summary 6

Introduction 7

Multisensory convergence 9

Multisensory modulation 11

Visual modulation of touch 13

Visual modulation of pain 21

Visual modulation of touch 28

1. Visuo-haptic interactions: a psychophysical investigation of the Judd illusion 28

Introduction 28

Exp. 1 29

Method 30

Results 33

Discussion 38

Exp. 2 39

Method 39

Results 41

Discussion 43

General Discussion 43

2. Visuo-haptic interactions in Unilateral Spatial Neglect 46

Introduction 46

Method 50

Results 60

Discussion 63

3. Crossmodal processing in Occipito-Temporal cortex: a TMS study of the Judd illusion 71

Introduction 71

Method 73

Results 78

Discussion 84

Visual modulation of pain 89

4. The visually-induced analgesia 89

Introduction 89

Method 90

Results 94

Discussion 96

5. EEG oscillations related to visually-induced analgesia 98

Introduction 98

Method 99

Results 103

Discussion 107

6. tDCS modulation of the visually-induced analgesia 110

Introduction 110

Method 111

Results 116

Exp. 1: Anodal/excitatory tDCS 116

Exp. 2: Cathodal/inhibitory tDCS 118

Discussion 119

General Discussion 122

Visual modulation of touch 123

Visual modulation of pain 130

Acknowledgments 139

References 140

Summary

The human perceptual system is essentially multisensory. I studied how vision modulates the bodily senses, particularly the multisensory modulation of the visual context on touch and pain. I used a combination of behavioural, neurostimulation and electro-physiological techniques to investigate the neural correlates of contextual multisensory interactions.

I first demonstrated that the visual context modulates touch: task-irrelevant visual arrowheads influence spatial representations of stimuli perceived by touch, depending on the spatial coincidence between visual and tactile sensory inputs (Chapter 1). These visuo-tactile interactions do not require spatial attention to occur, being preserved in brain-damaged patients with attentional deficits (Chapter 2). Importantly, the occipito-temporal cortex is causally involved in merging visual and tactile inputs in multisensory representations of shape (Chapter 3).

I then showed that the visual context can also modulate pain perception: in particular, I demonstrated that viewing one's own body in comparison to viewing an object is analgesic, increasing contact heat-pain thresholds of 3.2 °C (Chapter 4). This 'visually-induced analgesia' is reflected in enhancements of sensory cortical rhythms, possibly due to active inhibition of somatosensory processing (Chapter 5). In addition, changes in the excitability of the extrastriate visual cortex are involved in multisensory modulation of pain (Chapter 6).

Taken together, these results indicate that the visual context modulates the processing of touch and pain. Visual cortical areas mediate visual-somatosensory contextual interactions.

Introduction

A traditional view in neuroscience and neuropsychology has been that distinct cognitive, sensory and motor functions can be localized in distinct areas of the brain (Gazzaniga, 2000). For example, many sensory-specific areas have been identified, areas that respond to stimulation in one but not another sensory modality. This ‘functional specialization’ approach has however been challenged by the growing amount of evidence of interactions between different sensory modalities.

Indeed, to perceive the external and internal environment our brain uses multiple sources of sensory information obtained from several modalities including vision, touch, pain, and audition. All these different sources of information have to be efficiently merged to form a coherent and robust percept. The development of multiple sensory channels and the coexistence of different sensory modalities enhance individuals’ likelihood of survival (Ernst & Bulthoff, 2004).

The ability of our brain to assemble these types of information and then to sinergically use them in combination is based on Multisensory Integration, whereby the final perceptual result is more than the sum of the unimodal components (Stein & Meredith, 1993). During my doctorate, I investigated some of the mechanisms that underlie the merging of the senses in the brain, in particular how vision modulates somatosensory processing and which are the neural correlates of this modulation.

Crossmodal illusions have been used to demonstrate modulatory interactions between different sensory modalities. For instance, the "ventriloquist effect" consists in the phenomenon whereby perceived location of a sound can shift towards its apparent visual source (McGurk & MacDonald, 1976). These modulatory interactions usually arise with anomalous or incongruent multisensory combinations:

namely, when different information is obtained from different sensory modalities but signals in one modality influence the processing of signals in another.

Multisensory interactions arise also, and more obviously, when the same information regarding a sensory event is processed by different sensory modalities: namely, when there is *convergence* across multisensory inputs. Facilitatory and inhibitory crossmodal effects highlight the impact of multisensory congruence. For instance, visual detection can be enhanced at the location of a sound (McDonald, Teder-Salejarvi, & Hillyard, 2000).

Most previous multisensory research has focused on cases of convergence between inputs from different sensory modalities, how "events" across modalities are fused into a unified representation (Ernst & Banks, 2002; Stein & Meredith, 1993). The type of interaction that occurs when activity from one sensory modality *modulates* activity in another modality has been less studied. Modulating inputs can be single sensory "events" (Shams, Kamitani, & Shimojo, 2000) or continuous "contexts". Perceptual contexts can be considered the background of discrete sensory events. Less importance has been recognised to the context in the somatosensory literature, however previous evidence suggests that somatosensory processing could be modulated by the perceptual context in other modalities (e.g., Kennett, Taylor-Clarke, & Haggard, 2001). During my doctorate, I studied the influence of the visual context on tactile and pain processing, using a combination of behavioural, neurostimulation and electro-physiological techniques.

In the touch domain (Chapters 1-3), I investigated how the visual context influences the representation of shapes explored only by touch (i.e., haptically). To this aim, I used a well-known visual illusion, the Judd variant of the Müller-Lyer illusion (Coren & Gircus, 1978), under unimodal (visual or haptic) and crossmodal visuo-haptic presentation.

In the pain domain (Chapters 4-6), I investigated the effect of the visual context, manipulating the content of the visual information available when feeling pain. Most of previous studies investigated the effect of viewing a threating stimulus on pain responses but neglected the role of viewing beyond the stimulus, to one's own body itself. However, looking at one's own body has been demonstrated able to affect both touch (Kennett, et al., 2001) and pain (Longo, Betti, Aglioti, & Haggard, 2009). I focussed my research on the link between viewing one's own body and pain and on the neural correlates of this interaction.

Multisensory convergence

The mechanism of multisensory convergence occurs when multimodal neurons receive information from different sensory modalities and synthesize these inputs in a harmonious percept (Stein & Meredith, 1993).

The neural basis of multisensory interactions has been studied using both intra-cranial recordings (mainly in animals) and non-invasive electrophysiological or haemodynamic measures in humans. Independently of the technique applied, two main approaches have been used to identify the neural underpinnings of multisensory convergence.

The simplest approach is to measure brain activity during stimulation of particular modalities, and then determine whether any regions respond to stimulation of more than one modality (Bremmer et al., 2001; Mouraux, Diukova, Lee, Wise, &

Iannetti, 2011). Alternatively, the brain response to the concurrent stimulation of several modalities has been studied, to reveal more complex pattern of spatial and temporal dynamics of interaction.

Multisensory convergent interactions follow three general rules (Stein & Meredith, 1993). First, in order to treat stimuli from different modalities as referring to the same external event, they should show *spatial coincidence*. Second, these stimuli should also arise at approximately the same time, i.e. they should be *temporally coincident*. Third, the activity of multisensory neurons shows a response gradient based on the efficacy of the modality-specific stimuli: whereas the pairing of weakly effective stimuli results in a vigorous enhancement of the multisensory neuronal activity, the combination of highly effective stimuli results in little increase in the neuron's response. This property reflects the '*inverse effectiveness rule*'.

Interactions between different modalities have been demonstrated at the level of single neurons. Convergence at the single neuron level consists in the ability of the neuron to respond to inputs from multiple modalities. Concurrent stimulation in multiple modalities can lead both to enhanced and depressed responses, as compared to unimodal baselines (Driver & Spence, 2000; Stein & Meredith, 1993). Crossmodal facilitation can have an effect on perception, e.g. detection thresholds. For example, Frassinetti et al. (Frassinetti, Pavani, & Ladavas, 2002) found that sensitivity to visual stimuli below luminance threshold is increased by a simultaneous accessory sound burst presented at the same spatial location. This effect was eliminated when the two sensory inputs were separated in space or offset by more than 500 ms.

In non human primates, multisensory convergence has been demonstrated in several brain areas, as the superior colliculus (Meredith & Stein, 1986), putamen (Graziano & Gross, 1993), premotor cortex (Graziano, Yap, & Gross, 1994), parietal areas such as area 7b (Hyvarinen, 1981), and ventral intraparietal area (Avillac, Ben Hamed, & Duhamel, 2007).

Neuroimaging evidence in humans supports this sensory-convergence, showing the recruitment of the intraparietal sulcus, the posterior part of the superior temporal sulcus, and the ventral premotor cortex (Bremmer, et al., 2001; Macaluso & Driver, 2001).

Multisensory modulation

In contrast with mechanisms of convergence, mechanisms of modulation do not necessarily require congruency or redundancy of the sensory inputs, as in the case of the ventriloquist effect discussed above. Multisensory modulation is observed when processing of information in one sensory modality influences the effects of processing in another modality, thus involving lateral interactions between different sensory pathways.

One of the functions of multisensory modulation is maximize information delivered from the different sensory modalities to improve sensory estimates (Ernst & Bulthoff, 2004). To do that, the human brain has to reconstruct the environment from the incoming stream of –often-ambiguous – sensory information and has to constantly process, analyse, and combine different sources of sensory information. A simple example in everyday life is what happens when sitting on a train and looking out the window at a neighbouring train. If the other train starts moving, there is an ambiguous situation, so that it is hard to distinguish visually which of the two trains is actually moving. To solve this ambiguity, the brain can use information from other sensory modalities other than vision, like from proprioception and vestibular system. In this case, multisensory information helps correcting an ambiguity induced by a given sensory modality and allows reliable estimates of sensory events.

Multisensory modulation might arise from feedback influences from multimodal areas on predominantly unimodal regions. Indeed, it has been demonstrated that areas classically considered purely unisensory can show multisensory responses. For example, regions in the extra-striate visual cortex are closely involved in tactile discrimination of orientation (Sathian, Zangaladze, Hoffman, & Grafton, 1997; Zangaladze, Epstein, Grafton, & Sathian, 1999) and haptic object recognition (Amedi, Malach, Hendler, Peled, & Zohary, 2001). Similarly, unisensory visual input can modulate activity in unisensory-specific auditory areas, for example during silent lip-reading (Calvert et al., 1997).

Two neural models of multisensory modulation have been formulated. The first model postulates direct anatomical connections between sensory-specific areas, while the second involves top-down modulatory projections from multisensory areas to sensory-specific regions (Macaluso, 2006).

The first model is based on evidence of fast multisensory modulatory effects (Foxe et al., 2000; Shams, Iwaki, Chawla, & Bhattacharya, 2005). For example, consistent with direct anatomical connections between sensory-specific areas, somatosensory responses in the auditory cortex have been reported in monkeys (Fu et al., 2003; Kayser, Petkov, Augath, & Logothetis, 2005).

The second approach combines feed-forward hierarchical convergence of signals from primary areas into multisensory areas, with modulatory feedback projections from these associative higher-level regions toward sensory-specific cortices (Macaluso & Driver, 2005). In support of this view, neuroimaging studies of effective connectivity demonstrate functional coupling between sensory-specific and multisensory cortical areas (Deshpande, Hu, Stilla, & Sathian, 2008; Macaluso, Frith, & Driver, 2000). The two proposals are not mutually exclusive, and the engagement of top-down influences may in fact follow some interactions based on direct connections (Ghazanfar & Schroeder, 2006).

Most of the studies investigated the multisensory modulation of spatially or temporally defined discrete sensory events. The influence of a continuous sensory context on another sensory modality has been mainly neglected and the mechanisms underlying are almost unknown. The object of study of the present thesis is the multisensory influence of the visual context on somatosensory processing of touch and pain. In the following sections, I will discuss previous studies on the relation between vision and bodily senses that guided and motivated my doctoral research.

Visual modulation of touch

A large body of evidence indicates that vision modulates touch. Different levels of complexity of the sensory inputs have been investigated, from single passively perceived sensory events to more complex actively explored patterns of stimuli.

In the case of passive touch, the influence of both discrete and continuous visual inputs has been demonstrated. For example, visual flashes influence the number of perceived taps on the hand, and vice versa (Violentyev, Shimojo, & Shams, 2005). Continuous visual contexts, like vision of the body, are able to modulate the spatial discrimination (Kennett, et al., 2001) and detection (J. A. Harris, Arabzadeh, Moore, & Clifford, 2007) of single tactile events.

Not only the visual modulation of passive touch has been studied, but also that of active dynamic touch (i.e., haptics), which is the object of study in part of this thesis (Chapters 1-3). Active touch is crucial in the perception of complex external stimuli, like objects. To study how vision and touch are integrated in complex perceptual tasks like shape recognition, cases of ambiguity or discrepancy between visual and tactile stimuli are often introduced. In a classical experiment using a minifying lens, Rock and Victor (1964) demonstrated that when subjects feel an object that is visually minified by the lens, the perceived size of the object grasped is reduced accordingly. The combination of visual and haptic information follows statistically optimal rules (Ernst & Banks, 2002; Ernst & Bulthoff, 2004): sensory cues are weighted according to their reliability (variance), so that 'better' cues are weighted more; the combined estimate reduces variance with respect to the unimodal estimate, therefore facilitating perception. Interestingly, optimal estimation probabilistic models can explain phenomena of visual capture as described by Rock and Victor (1964). Since the variance of visual size estimates is smaller than the variance of haptic estimates, visual cues are weighted more than haptic cues and bias final sensory estimates (Ernst & Banks, 2002).

As for the neural correlates of visual-haptic interactions, responses to tactile stimuli have been demonstrated in cortical regions beyond the somatosensory cortex. Visual areas are involved in a variety of somatosensory tasks in the sighted, including tactile perception of two-dimensional patterns and motion, and haptic perception of three-dimensional objects (Sathian & Lacey, 2007). The specific case of visuo-tactile interactions during shape processing is addressed in Chapters 1-3. Chief among the several cortical areas implicated in visuo-haptic shape processing is a portion of the lateral occipital complex (LOC), an object-selective area in the ventral visual pathway (Grill-Spector, 2003; Malach et al., 1995). That region, called LOtv, responds selectively to objects in both vision and touch (Amedi, Jacobson, Hendler, Malach, & Zohary, 2002; Amedi, et al., 2001; Deshpande, et al., 2008; T. W. James et al., 2002; Peltier et al., 2007).

Case studies support the view that the LOC is necessary for both haptic and visual shape perception. Feinberg et al. (1986) reported a patient with a lesion to the left occipito-temporal cortex, likely including the LOC, who exhibited both tactile and visual agnosia (inability to recognize objects), although somatosensory cortex and somatosensation were spared. Another patient with bilateral lesions to LOC was unable to learn new objects explored by either vision or touch (T.W. James, James, & Humphrey, 2006).

Multisensory shape selectivity also occurs in parietal cortical regions, particularly in an anterior region in the cortex of the intraparietal sulcus and in the postcentral sulcus (Stilla & Sathian, 2007).

The convergence of visual and haptic shape-selective activity in the extra-striate visual cortex opened an ongoing debate on whether the representation of shape there created is multisensory, i.e. a representation that can be encoded and retrieved by multiple sensory systems (Lacey, Tal, Amedi, & Sathian, 2009). In alternative, shape representations might be first processed in a modality-specific fashion, leading to independent visual and tactile representations of shape. It has been suggested that LOC builds a multisensory representation of shape, since it is involved in the processing of shapes explored only by touch (Lacey, et al., 2009).

Although it is accepted that visual cortical areas are recruited during touch, an important issue regards whether this recruitment depends on top-down inputs mediating visual imagery or engagement of modality-independent representations by bottom-up somatosensory inputs (Deshpande, et al., 2008). Neuroimaging studies investigating effective connectivity in humans during haptic perception of shape and texture revealed a variety of interactions between areas generally regarded as somatosensory, multisensory, visual and motor. Bottom-up somatosensory inputs from the ipsilateral post-central sulcus and ipsilateral posterior insula feed into visual cortical areas, including the ipsilateral LOC. In addition, top-down inputs from left postero-supero-medial parietal cortex influence the ipsilateral LOC (Deshpande, et al., 2008).

Other studies compared activations evoked by visual imagery with haptic shape processing of both familiar and unfamiliar objects, under the assumption that visual imagery would play a more relevant role in mediating tactile responses in visual cortex when familiar than unfamiliar shapes are perceived. Activations evoked by visual imagery overlapped more extensively, and their magnitudes were more correlated, with those evoked during haptic shape perception of familiar, compared to unfamiliar, objects (Lacey, Flueckiger, Stilla, Lava, & Sathian, 2010). Task-specific analyses of functional and effective connectivity showed that the visual imagery and familiar haptic shape tasks activated similar networks, whereas the unfamiliar haptic shape task activated a different network. Visual imagery and familiar haptic shape networks involved top-down paths from prefrontal cortex into the LOC, whereas the unfamiliar haptic shape network was characterized by bottom-up, somatosensory inputs into the LOC (Deshpande, Hu, Lacey, Stilla, & Sathian, 2010).

Taken together, these data suggest that shape representations in the LOC are flexibly accessible, either top-down or bottom-up, according to task demands, and that visual imagery is more involved in LOC activation during haptic shape perception when objects are familiar, compared to unfamiliar.

However, findings that LOC is involved in tactile shape recognition do not provide direct evidence that this region plays a causal role in multisensory processing. To study visuo-haptic interactions in LOC under the hypothesis of shared processing of vision and touch in that region, I used a variant of the Müller-Lyer illusion (see below) in a crossmodal spatial task (Chapters 1-2) and I investigated the causal role of LOC in mediating these multisensory interactions using a non invasive neurostimulation technique (Chapter 3).

The crossmodal Müller-Lyer illusion

Arrowheads at the ends of a line may affect its estimated length (Müller-Lyer, 1889). Outward-oriented arrowheads bring about an illusory lengthening of it, while inward-oriented arrowheads reduce the perceived extent of the segment. The Müller-Lyer illusion and its variants have been extensively investigated in the visual modality, and interpreted according to purely visual theoretical frameworks (Coren & Girgus, 1978). The finding that similar illusory effects occur also in touch (for a review, see Gentaz & Hatwell, 2004), even in congenitally blind participants (Heller et al., 2002), challenges these classical visual accounts (Over, 1967; Rudel & Teuber, 1963), opening an ongoing debate as to whether modality-specific or shared processes underlie the visual and haptic Müller-Lyer illusion.

Contrary to purely visual interpretations, the haptic illusion is not dependent upon visual experience, being equally powerful both in congenitally blind and in visually-unimpaired participants (Heller, et al., 2002), although the merits of comparing illusions in vision and in touch have been questioned (Gregory, 1967).

The hypothesis of a common representation of the Müller-Lyer illusion is supported by the finding that haptic and visual illusions occur with the same magnitude (Over, 1966; Suzuki & Arashida, 1992), correlate with each other (Frisby & Davies, 1971; Gentaz, Camos, Hatwell, & Jacquet, 2004), and are affected in a similar fashion by a number of experimental manipulations. Particularly, the angle of the arrowheads influences both the visual and the haptic judgements of the Müller-Lyer illusion (Over, 1966). Furthermore, the visual and the haptic illusions are reduced by the same amount with instructions suggesting the use of body-centred cues (Millar & Al-Attar, 2002). As for crossmodal effects, the decrement of the illusion with practice transfers between the visual and the haptic Brentano variants of the Müller-Lyer illusion (namely, a combined form of the Müller-Lyer figure, which includes both the inward and the outward configurations, Rudel & Teuber, 1963), with the initial magnitude of the illusory effects being identical in touch and vision, as noted above (Over, 1966; Suzuki & Arashida, 1992). Finally, the view of the arrowheads of the Brentano illusion alone affects the estimated length of isolated sticks in the haptic domain. Participants, in fact, underestimate the length of a line explored only by touch when it is located behind the visible outward-fins. Conversely the length of the line is overestimated when the visible fins project inwards (Gallace & Spence, 2005).

In line with the view that some of the mechanisms underlying the visual and haptic Müller-Lyer illusions are supra-modal, rather than modality-specific, the strength of the illusion in touch does not depend on exploration mode (Heller et al., 2005), movement time, distinctiveness of the fins, and external-reference information

(Millar & Al-Attar, 2002). Particularly, different exploratory conditions (i.e., tracing, free exploration, grasping and measuring) do not influence haptic judgements, even though tracing with the index finger reduces the strength of the haptic illusion (Heller, et al., 2005).

Although this set of results seems to support the hypothesis of a shared representation of the Müller-Lyer illusion, the processes underlying the crossmodal transfer remain unclear, and no direct comparison between unimodal and crossmodal conditions has been reported. I directly addressed these issues in two psychophysical experiments presented in Chapter 1, providing evidence of visual modulation of tactile bisection.

Since the mechanisms underlying crossmodal contextual modulations are still unknown, I used the visuo-tactile illusion demonstrated in Chapter 1 to investigate them. I first explored whether they depend on spatial attention, testing the processing of unimodal and crossmodal illusions in right brain damaged patients with/without attentional disorders, specifically Unilateral Spatial Neglect (Chapter 2). Then, I examined the causal role of occipital and parietal regions in conveying the unimodal and crossmodal illusory effects, using a neurostimulation technique to virtually interfere with the functioning of these regions in neurologically unimpaired adults (Chapter 3).

The neural correlates of the haptic and crossmodal illusion have in fact never been investigated so far. As for the visual modality, neuropsychological evidence from brain-damaged patients suggests the crucial involvement of the extra-striate visual cortex in the generation of the visual Müller-Lyer illusion (Daini, Angelelli, Antonucci, Cappa, & Vallar, 2002). More recently, a fMRI study (Weidner & Fink, 2007) investigated the hemodynamic response associated to the processing of the

Brentano illusion in the visual modality. The authors manipulated parametrically the strength of the perceived illusion by varying the angles of the illusion-inducing fins, comparing a landmark-like judgement task with a luminance control task. Areas that correlated with the strength of the Müller-Lyer illusion were explored by looking at the regressor representing the parametric modulation of the strength of the illusion. Weidner & Fink (2007) found bilateral activations in the *lateral occipital cortex*, and in the right superior parietal lobule (Superior Parietal Cortex, SPC). In a successive MEG study, the time course of the processing of the visual Müller-Lyer illusion was investigated (Weidner, Boers, Mathiak, Dammers, & Fink, 2010). An early activation in the visual areas, occurring between 85 and 130 ms after stimulus onset, was found, followed by a later activation (at 195-220 ms) along the ventral visual pathway in the right superior temporal cortex; activations took place also in the right inferior parietal cortex, and in the right frontal cortex. Based on these sources of evidence, Weidner and coworkers suggest that ventral stream areas (lateral occipital and inferior temporal) may be involved in forming object representations, including size-invariant shape, whereas dorsal stream areas (the posterior parietal cortex) may subsequently integrate these object representations into spatial frames of reference (Weidner, et al., 2010; Weidner & Fink, 2007). Finally, an event-related potential study suggests that higher level cognitive control, based on activity in the anterior cingulate and in the superior frontal cortices, may contribute to the Müller-Lyer illusory effects (Qiu, Li, Zhang, Liu, & Zhang, 2008).

The hypothesis of a multisensory representation of the Müller-Lyer illusion predicts that the brain regions (i.e., the occipito-temporal cortex bilaterally, and the right SPC) activated by the visual illusion in the Weidner & Fink's (2007) study would be involved also in the processing of the haptic and crossmodal illusions.

These regions indeed participate in multisensory processing, and their role has been investigated in Chapter 3.

Neuroimaging studies have shown that the SPC is involved in visual (Corbetta, Shulman, Miezin, & Petersen, 1995; Yantis & Serences, 2003), and crossmodal spatial attention and localization (Bushara et al., 1999; Molholm et al., 2006). The SPC contributes also to the transformation of multisensory inputs into a common spatial frame of reference (Tanabe, Kato, Miyauchi, Hayashi, & Yanagida, 2005).

On the other hand, as discussed above, the LOC is a visual area implicated in object recognition (Grill-Spector, 2003; Malach, et al., 1995), which seems to compute category- and viewpoint-independent shape representations (e.g., Kourtzi & Kanwisher, 2001; Pourtois, Schwartz, Spiridon, Martuzzi, & Vuilleumier, 2009). Crucially, recent neuroimaging studies have highlighted the involvement of this area in tactile processing, with the LOC responding to both familiar and unfamiliar shapes presented not only in the visual, but also in the tactile modality (Amedi, et al., 2002; Amedi, et al., 2001; Deshpande, et al., 2008; T. W. James, et al., 2002; Peltier, et al., 2007). These findings indicate that the LOC may subserve crossmodal processing (Beauchamp, 2005). I tested this hypothesis in the study presented in Chapter 3.

Visual modulation of pain

Despite the fact that multimodal integration of nociception has received less attention than touch, there is evidence that nociceptive processing is largely modulated by other sensory modalities, like vision (see below) and proprioception

(Gallace, Torta, Moseley, & Iannetti, 2011). This claim is supported by clinical neuropsychology studies.

Hoogenraad et al. (1994) reported a case of a neglect patient with a right parietal lesion who suffered from hemianesthesia for both nociception and touch specifically when the stimulus was applied while the patient had his eyes closed. In contrast, when the patient had his eyes open and saw the sensory testing tool approaching his contralesional limb, he reported a sensation of burning pain in the arm. It has also been shown that patients suffering from complex regional pain syndrome (CRPS) tend to neglect their affected limb (Legrain, Bultitude, De Paepe, & Rossetti, in press). More importantly, their neglect symptoms are reduced by the vision of the limbs (Moseley, Parsons, & Spence, 2008) and influenced by the posture (Moseley, Gallace, & Spence, 2009), thus suggesting that neglect symptoms of CRPS do not depend on a pure somatotopic representation of pain (Legrain, et al., in press). Intriguingly, when CRPS patients are asked to point in the dark what they estimate to be the midline of their body, they neglect the opposite side of space, that is the side of the healthy limb (Sumitani et al., 2007). When the visual field of the patients is shifted by prismatic glasses toward the hemispace corresponding to the side of the affected limb, CRPS symptoms including neglect symptoms *and* pain are alleviated (Bultitude & Rafal, 2010; Sumitani, et al., 2007). Taken together, this neuropsychological evidence suggests that vision and spatial representations can, somehow, modulate chronic pain.

Studies on neurologically unimpaired participants provide further evidence of this form of modulation. It is common knowledge that the experienced level of pain strongly depends on the context in which nociceptive stimuli occur. Attention, expectations, motivation are well known examples of contextual modulation (Wiech, Ploner, & Tracey, 2008). Beside psychological contexts, *multisensory perceptual* contexts also modulate acute pain. Multimodal interactions between vision and pain depend on the content of what is seen while being in pain, i.e. the specific visual context. The effect of different types of visual contexts on acute pain can be considered: i) vision of one's own body; ii) vision of someone else's body; iii) vision of the threatening stimulus; iv) other visual inputs.

i. Vision of one's own body

Recent evidence has demonstrated that simply looking at one's own body is analgesic (Longo, et al., 2009). Passive vision of the hand in comparison of an object in the same spatial location reduced both the N2/P2 complex of laser evoked potentials and corresponding pain ratings in healthy participants (Longo, et al., 2009).

The visual context was presented in two ways. Neurologically unimpaired participants looked either directly at their stimulated hand or at an image of that hand manipulated through the mirror illusion (Ramachandran, Rogers-Ramachandran, & Cobb, 1995). In this latter condition, the stimulated hand was placed behind a mirror aligned with the participant’s sagittal plane and the illusion of seeing that hand was created while the participant was actually seeing the mirror-reflected image of the opposite hand. This illusion was created in order to disambiguate whether the effect was driven by viewing one's own hand, or the threatening stimulus over the hand (i.e. the laser beam). The mirrorbox illusion technique induces the impression that the participants' hand contralateral to stimulation, which is reflected in a mirror aligned with their sagittal plane, is actually their stimulated hand. In this way, the effect of vision of the body can be isolated from the effect of viewing the source of pain (Longo, et al., 2009). As compared to control situations in which the stimulated hand was out of sight and masked by a neutral object, or the participants were viewing the experimenter's hand, participants rated the laser stimuli as less intense and these stimuli also evoked nociceptive ERPs of smaller amplitude (i.e., reduced N2/P2 complex).

This 'visually-induced analgesia' can be considered a form of multisensory modulation in which the visual representation of the body has effects on pain processing. Since the mechanisms underlying visual modulation of pain are unknown, I investigated them in three different ways.

First, in a psychophysical experiment I studied the role of the visual appearance of the body in modulating acute pain in healthy participants (Chapter 4).

Second, I examined the influence of the visual context on patterns of distributed brain responses induced by thermal stimuli, studying changes in cortical EEG oscillations (Chapter 5).

Third, I tested hypotheses about the neural networks underlying the visually-induced analgesia, modulating the excitability of occipital and centro-parietal regions by non invasive neurostimulation in healthy individuals (Chapter 6).

Even if pain has been the object of the studies presented in Chapters 4-6, it is relevant to note that the effect of vision of the body is not specific for pain, but modulates other somatosensory submodalities. As for the tactile modality, viewing the hand has been demonstrated to have a different effect on spatial acuity, enhancing tactile two points-discrimination (Kennett, et al., 2001) and stimulus intensity, but also reducing tactile detection (J. A. Harris, et al., 2007). At least as for stimulus intensity, the similarity of effects for tactile detection and for pain levels may suggest a common neural pathway underlying visual modulation of somatosensory processing. There is evidence that viewing the body can influence tactile processing in early somatosensory cortex (Cardini, Longo, & Haggard, 2011; Fiorio & Haggard, 2005). This suggests that modulation of cortical pain-related activity could occur. One possibility is that the neural correlates of visually-induced analgesia may involve an inhibitory link between visual and pain centres in the cerebral cortex, possibly relayed via intermediate multisensory representations of the body in posterior parietal areas.

Importantly, visual modulation of pain is specific for particular visual contexts, given that only viewing one's own body but not an object has an effect on pain perception. Hence, visual areas specific for representing the body are likely to mediate these effects. In line with this proposal, neuroimaging evidence shows that occipital-temporal areas, including the "Extrastriate Body Area" (Downing, Jiang, Shuman, & Kanwisher, 2001) and the fusiform body area (Peelen & Downing, 2005), are preferentially activated by the view of bodies and body parts (Orlov, Makin, & Zohary, 2010). The role of these regions has been investigated in a study presented in Chapter 6.

ii. Vision the body of another person

The analgesic effect of viewing the body seems to require the recognition of personal identity. A previous study found no modulation of pain ratings and laser evoked potentials when viewing the hand of another person (Longo, et al., 2009). However, viewing photographs of one’s partner reduced heat pain ratings (Master et al., 2009). The latter modulation is likely to be related to the affective content of the visual stimulus rather than crossmodal perceptual interactions, in line with other studies reporting analgesia induced by the affective and pleasant values of pictures (de Tommaso et al., 2009; de Wied & Verbaten, 2001; Kenntner-Mabiala & Pauli, 2005).

Another source of modulation is related to seeing someone else in pain while feeling pain, which reduces the N1/P1 LEPs but does not modulate later components such the N2/P2 (e.g., Valeriani et al., 2008).

iii. Vision of the threatening stimulus

Vision of physical threat can activate the pain matrix, in absence of nociceptive inputs (Lloyd, Morrison, & Roberts, 2006). In a neuroimaging experiment, participants looked at a visible rubber hand placed over their real hand that was stimulated with either a threatening or an innocuous probe (Lloyd, et al., 2006). Superior and inferior parietal regions (BA5/7 and BA40), mid-cingulate (BA24) and anterior insula increased their activity in response to observing a painful versus non-painful stimulus. This effect was only evident when the rubber hand was in a spatially congruent (vs. incongruent) position with respect to the participants' own hand. Multisensory interactions are indeed known to occur under specific conditions of spatial and temporal coincidence (Stein, Huneycutt, & Meredith, 1988; Stein & Stanford, 2008).

A further study shows that viewing physical threat applied to a rubber hand that is illusory felt as one's own activates brain areas associated with anxiety and interoceptive awareness, such as the insula and anterior cingulate cortex. Also, the stronger the feeling of ownership of the artificial hand, the stronger was the threat-evoked neuronal responses in the areas reflecting anxiety (Ehrsson, Wiech, Weiskopf, Dolan, & Passingham, 2007).

Again, the pain modulation induced by vision of the threatening stimulus is likely to be affective-motivational rather than perceptual. However, the two components are difficult to dissociate, given that pain sensation has necessarily an emotional and affective value, being unpleasant (Auvray, Myin, & Spence, 2010).

iv. Other visual inputs

A systematic study of multisensory interactions between visual and nociceptive inputs is still lacking, differently from touch literature. Research in the pain domain has been mainly focused on visual attentional and distraction manipulations, which are not the object of this section. The role of eye orientation on pain perception has been investigated. Honoré et al. (1995) did not find clear effects of eye orientation on pain threshold and tolerance. A successive study reported that unpleasantness but not pain thresholds increased when the gaze line was directed towards the side ipsilateral to stimulation in comparison to contralateral (Naveteur, Mars, & Crombez, 2005). More research is needed in this field, to disentangle the effects of the visual context, gaze line, and attention orientation.

Visual modulation of touch

1. Visuo-haptic interactions: a psychophysical investigation of the Judd illusion

[This research has been published in: Mancini, F., Bricolo, E., Vallar, G. (2010). Multisensory integration in the Müller-Lyer illusion: From vision to haptics. *Quarterly Journal of Experimental Psychology,* 63, 818-830]

Introduction

This study aimed first at comparing illusory effects across different presentation conditions, unimodal (visual and haptic), and bimodal (visuo-haptic). Second, the role of visual information on haptic spatial representations was investigated, in order to assess whether vision or touch leads, or, on the contrary, if the two sensory modalities are integrated into a unified percept.

A manual bisection task was used in the present study, with identical stimulus material (i.e., 3D plastic shapes on wooden boards) in the visual and haptic modalities. The illusory stimulus was the Judd variant of the Müller-Lyer illusion (Gillam, 1980; Holding, 1970; Judd, 1899; Vallar & Daini, 2002, 2006). The *Judd* or *Holding* variant of the Müller-Lyer illusion consists of a horizontal line with two arrowheads oriented in the same direction (one inwards, and one outwards), which produce a displacement of the perceived centre either leftwards or rightwards depending on the orientation of the arrowheads. Previous studies found that when neurologically unimpaired participants were required to place a mark on the horizontal shaft at the mid-point, they placed it more towards the 'tail' end, outward-oriented with respect to the shaft (see Ellis, Flanagan, & Lederman, 1999, who used a grasping balancing task; Mon-Williams & Bull, 2000, who used a line bisection task).

Exp. 1

The experiment investigated the hypothesis of modality-specific vs. common processes underlying the visual and haptic forms of the Judd variant of the Müller-Lyer illusion, using a manual bisection task under visual, haptic, and visuo-haptic presentations. Were the visual and haptic variants processed by shared mechanisms, the hypothesis predicted no differences between the two unimodal conditions, as well as transfer of the illusion from vision to haptics in the bimodal condition. Particularly, with both visual and haptic unimodal presentations, a bisection error towards the 'tail' of the Judd figure was expected, either leftwards or rightwards, according to the left-sided or right-sided position of the 'tail'. With a crossmodal presentation of the stimulus and a haptic bisection, we expected the error being modulated by the visual arrowheads, suggesting that the visual illusion, irrelevant for the bisection task, transferred crossmodally to haptics. Conversely, were the illusion processed in a modality-specific fashion by independent components, no transfer in the bimodal task was expected: the haptic bisection would have been performed unimodally, with no illusory effects induced by the visual stimulus.

Method

Participants

Twenty-four neurologically unimpaired participants (fifteen males/nine females) took part in the experiment (mean age 22.64 years, range 19-34 years). All participants were right-handed (Oldfield, 1971), with normal or corrected-to-normal vision. Participants were naïve as to the purpose of the study, and received course credits for their participation in the experiment, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

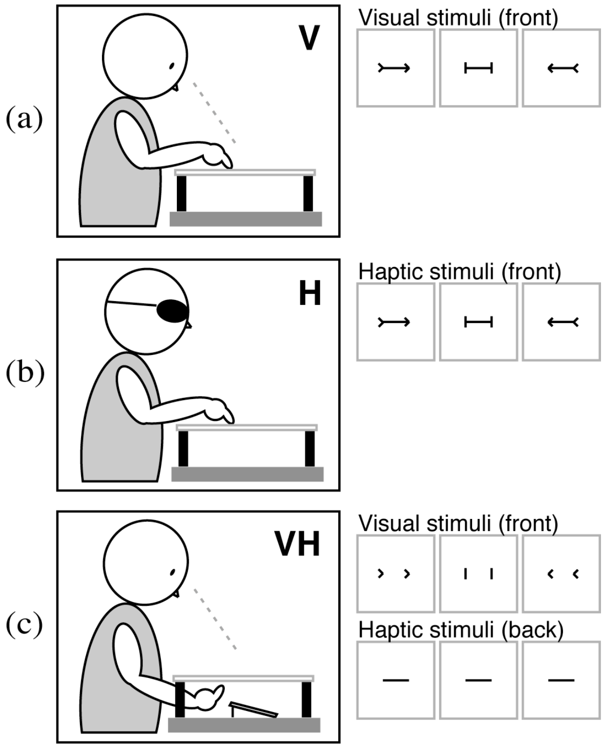


Figure 1-1. *Stimuli and apparatus.* Under visual (V, a), haptic (H, b), and crossmodal visuo-haptic (VH, c) presentations, three types of stimuli were administered: leftward outgoing/rightward ingoing fins, which brought about a leftward displacement of the shaft's perceived centre; a baseline control stimulus with vertical ends; leftward ingoing/rightward outgoing fins, which brought about a rightward displacement of the shaft's perceived centre. In the visuo-haptic condition (c) the ends were glued on the front of the board, and the horizontal shaft to be bisected on the back, in the correspondent positions.

Stimuli and Apparatus

Stimuli consisted of three types of black 3D figures with blurred contours made of melted plastic beads: a baseline control (a line with vertical ends), and right- and left-displaced Judd illusions (see Figure 1-1, A-B). Previous studies had shown that the Müller-Lyer illusion was still present with blurred stimuli (Coren & Girgus, 1978). The melting plastic beads blurred stimuli, low-cost and easy to build up, had curved intersections between the shaft and the fins. By contrast, wooden and metal stimuli would have had sharper intersections, clearly detectable by touch, and, therefore, introducing a possible bias on the amplitude of the tactile illusion.

Each stimulus included a horizontal shaft (10 or 12 cm long), and two identical ends, vertical (length: 25 mm; height: 10 mm, thickness: 1 mm), or angled at 45° (length of each fin: 35 mm; height: 10 mm, thickness: 1 mm). All stimuli, both with vertical and angled ends, were 50 mm high. Each stimulus configuration was located in the centre of a white wooden board (40 x 40 cm, thickness 0.8 cm). Under visual and haptic presentation, both the arrowheads and the horizontal shaft were glued on the front of the board (see Figure 1-1, a-b). Conversely, in the crossmodal condition the horizontal shaft was positioned on the backside of the board centrally, and the arrowheads on the front-side in the correspondent positions (Figure 1-1, c).

The experiment was performed in a normally illuminated and quiet room with patients being comfortably seated in front of a table. Each board was presented individually, with its centre aligned with the mid-sagittal plane of the participant's trunk, and placed flat on a wooden support at the height of 12 cm from the table top. In the crossmodal condition, a mirror was placed on the table under the board. The mirror reflected the shaft on the backside and was seen by the experimenter only.

Procedure

Participants received instructions to bisect with their index finger the horizontal shaft of each stimulus, using their left or right hand in separate blocks. The task was performed under visual, haptic, or visuo-haptic conditions of stimulus presentation. The three conditions were assessed in three separate sessions on three non-consecutive days, in a counterbalanced order across participants. The three modalities generated six presentation orders, each given to four participants.

In the *visual condition,* participants received instructions to touch the mid-point of the shaft without exploring haptically the stimulus, and to close their eyes immediately after the bisection response, while the experimenter measured their bisection error to the nearest mm.

In the *haptic condition*, blindfolded participants scanned the shapes (arrowheads and shafts) haptically, using their whole hand (left or right in separate blocks), and then set the mid-point of the shaft with their index finger. Each trial started with the experimenter placing the palm of the participant's open hand centrally over the stimulus. Participants received instructions not to use timing strategies, such as counting, while exploring the stimulus. No time limits were given.

In the *visuo-haptic condition*, participants received instructions to look at the arrowheads on the front side of the board, simultaneously palpate with the whole hand the shaft glued on the backside of the board, and then set its mid-point using their index finger. Participants did not see their forearm, which was covered by the wooden support (see Figure 1-1, c).

In all presentation conditions (visual, haptic, visuo-haptic) the two lengths of the shaft (10, 12 cm), and the three types of stimulus configuration (baseline neutral; leftward outgoing/rightward ingoing fins; leftward ingoing/rightward outgoing fins) generated six possible stimuli. Each type of stimulus was presented 10 times, for a total of 60 trials subdivided into two blocks of 30 trials each, with each block including five trials for each stimulus. The task was performed with the left or the right hand in an ABBA design, for a total amount of 120 trials for each participant. Half of the participants started with the right hand, half with the left hand. For each participant, a different random sequence was used for each block. Two practice trials, one baseline and one illusion stimulus, selected at random, were administered at the beginning of each session (visual, haptic, visuo-haptic), and were not included in any subsequent analysis.

After each response, using a ruler, the experimenter measured to the nearest mm the bisection error, namely, the distance between the subjective midpoint set by each participant and the objective centre of the shaft. A rightward deviation of the subjective midpoint carried a plus sign, a leftward deviation a minus sign. A percent error as related to the length of each shaft (10, 12 cm) was subsequently computed.

Data analysis

For each participant, the average percent errors on the illusory stimuli were corrected for the average percent errors on the baseline stimuli, as follows: [Illusion score = percent error illusion minus percent error baseline]. Scores exceeding ±3 SD from the group mean were excluded from the analyses. The scores were submitted to a repeated-measures analysis of variance with two within-subjects main factors (*Modality*: visual, haptic, visuo-haptic; and *Stimulus:* leftward outgoing/rightward ingoing fins, leftward ingoing/rightward outgoing fins). The between-subject main factor of *order of presentation* of the three modalities, with six levels, was not significant, and did not interact with the other within-subjects factors in a preliminary analysis of variance. Accordingly, it was not included in the subsequent analyses.

Results

Figure 1-2 shows the percent error in the three presentation modalities, and for the two directions of the illusion. In all modalities stimuli with leftward outgoing/rightward ingoing fins brought about a leftward error, stimuli with leftward ingoing/rightward outgoing fins a rightward error. The magnitude of the error was smaller in the bimodal condition.

A repeated-measures analysis of variance showed a significant effect of the *Stimulus* main factor, $F(1,23) = 111.689$, $MSE = 1225.1$, $p < .001$, $\eta^2 = .623$, and no significant effect of the *Modality* main factor, $F < 1$. The *Stimulus* by *Modality* interaction was significant, $F(2,46) = 22.33$, $MSE = 99.47$, $p < .001$, $\eta^2 = .101$. Post hoc pairwise comparisons showed no differences between visual and haptic modalities with both leftward outgoing/rightward ingoing, $p = .632$, and leftward ingoing/rightward outgoing stimuli, $p = .488$. Conversely, significant differences were found between the visual and the bimodal conditions with both leftward outgoing/rightward ingoing, $p < .001$, and leftward ingoing/rightward outgoing stimuli, $p < .001$. The differences between the haptic and the bimodal conditions with both leftward outgoing/rightward ingoing, $p < .001$, and leftward ingoing/rightward outgoing stimuli, $p < .001$, were significant (Bonferroni adjusted alpha levels were set as .004).

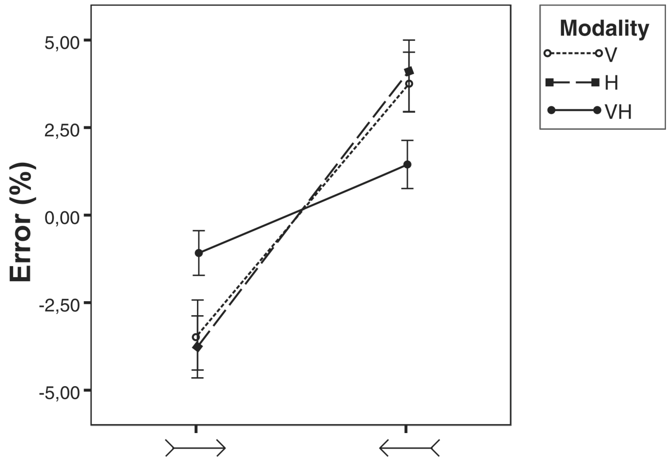


Figure 1-2. Exp. 1. Mean percent error (SE) in shaft bisection, by stimulus type (leftward outgoing/rightward ingoing, and leftward ingoing/rightward outgoing fins), and presentation modality (Visual, V; Haptic, H, Visuo-Haptic, VH).

These findings were explored in more detail by three analyses of variance, one for each modality, including the main factors of *Stimulus* (leftward outgoing/rightward ingoing, leftward ingoing/rightward outgoing fins), *Hand* (left, right), and *Shaft length* (10, 12 cm).

Figure 1-3 shows the percent error by modality (visual, haptic, visuo-haptic), stimulus type (leftward outgoing/rightward ingoing, leftward ingoing/rightward outgoing fins), hand (left, right), and shaft length (10, 12 cm). The illusory effects were present with both shaft lengths, reduced in size in the visuo-haptic modality, and slightly larger with the shorter 10 cm shaft.

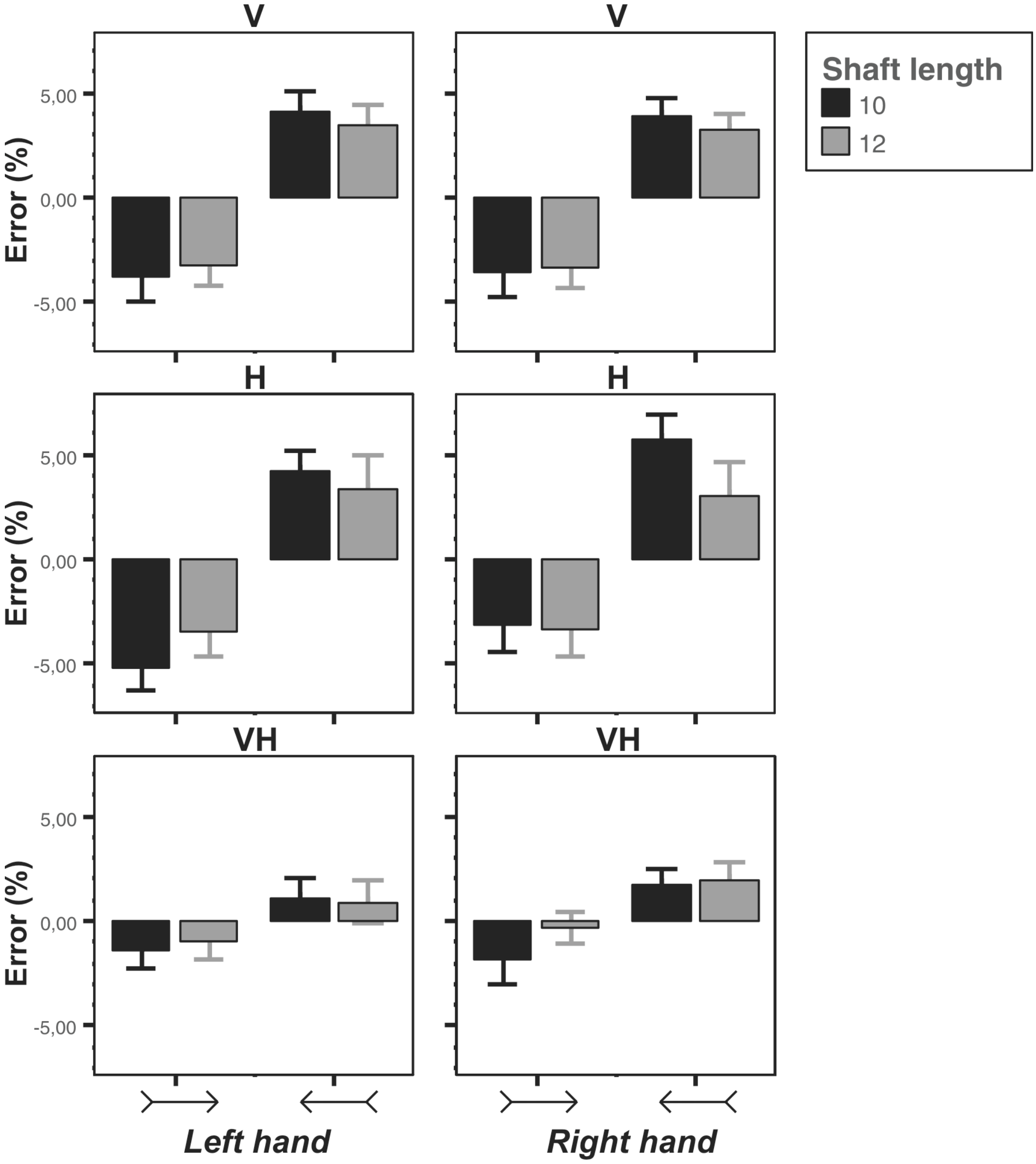


Figure 1-3. Exp. 1. Mean percent error (SE) in shaft bisection, by stimulus type (leftward outgoing/rightward ingoing, and leftward ingoing/rightward outgoing fins), presentation modality (V, H, VH), hand (left, right), and shaft length (10, 12 cm).

In the visual modality, the main effect of the *Stimulus* factor was significant, $F(1,23) = 66.616$, $MSE = 2448.23$, $p < .001$, $\eta^2 = .994$. The main effects of both the *Shaft length* and the *Hand* factors were not significant, $F < 1$. The *Stimulus* by *Shaft length* interaction was significant, $F(1,23) = 20.394$, $MSE = 13.65$, $p < .001$, $\eta^2 = .006$. Post hoc pairwise comparisons showed a significant difference between the short and long shaft for the leftward ingoing/rightward outgoing stimuli, $p = .005$, but not for the leftward outgoing/rightward ingoing configuration, $p = .078$ (Bonferroni adjusted alpha levels were set as .012); the bisection error was slightly larger for 10 cm (mean = 3.97%, SEM = .44) than for 12 cm (mean = 3.32%, SEM = .41) leftward ingoing/rightward outgoing stimuli. None of the other interactions was significant, $F < 1$.

In the haptic modality, the main effect of the *Stimulus* factor was significant, $F(1,23) = 97.256$, $MSE = 2940.08$, $p < .001$, $\eta^2 = .944$. The main effects of both the *Shaft length*, $F(1,23) = 2.053$, $MSE = 13.65$, $p = .165$, $\eta^2 = .004$, and the *Hand*, $F(1,23) = 3.401$, $MSE = 35.63$, $p = .078$, $\eta^2 = .011$, factors were not significant. The *Stimulus* by *Shaft length* interaction was significant, $F(1,23) = 25.596$, $MSE = 77.41$, $p < .001$, $\eta^2 = .025$. Post hoc pairwise comparisons showed a significant difference between the short and long shaft for leftward ingoing/rightward outgoing stimuli, $p < .001$, but not for the leftward outgoing/rightward ingoing configuration, $p = .091$ (Bonferroni adjusted alpha levels were set as .012); as under visual presentation, the bisection error was slightly larger for 10 cm (mean = 4.95%, SEM = .41) than for 12 cm (mean = 3.15%, SEM = .65) leftward ingoing/rightward outgoing stimuli. The *Hand* by *Shaft Length* interaction was significant, $F(1,23) = 5.805$, $MSE = 43.71$, $p = .024$, $\eta^2 = .014$. Pairwise comparisons showed a significant difference between the left and the right hand for 10 cm stimuli, $p < .001$, but not for 12 cm stimuli, $p = .897$

(Bonferroni adjusted alpha levels were set as .012); larger error occurred at 10 cm with the right (mean = 1.31%, SEM = .29) than with the left hand (mean = -.51%, SEM = .33). None of the other interactions was significant, $F < 1$.

In the visuo-haptic modality, the main effect of the *Stimulus* factor was significant, $F(1,23) = 24.756$, $MSE = 307.88$, $p < .001$, $\eta^2 = .296$. The main effects of the *Shaft length*, $F(1,23) = 2.218$, $MSE = 10.96$, $p = .150$, $\eta^2 = .011$, and of the *Hand*, $F(1,23) = 2.080$, $MSE = 9.40$, $p = .163$, $\eta^2 = .009$, factors were not significant. The *Stimulus* by *Shaft length* interaction was significant, $F(1,23) = 13.731$, $MSE = 11.34$, $p = .001$, $\eta^2 = .005$. Post hoc pairwise comparisons showed a marginal effect towards a difference between the short and the long shaft for leftward outgoing/rightward ingoing stimuli, $p = .020$, while for leftward ingoing/rightward outgoing stimuli no significant difference was found, $p < .978$ (Bonferroni adjusted alpha levels were set as .012); the bisection error was slightly larger for 10 cm (mean = -1.61%, SEM = .39) than for 12 cm (mean = -.65%, SEM = .33) leftward outgoing/rightward ingoing stimuli. The *Hand* by *Stimulus* interaction was significant, $F(1,23) = 4.680$, $MSE = 5.48$, $p = .041$, $\eta^2 = .005$. Pairwise comparisons showed a trend towards significance between the left and the right hand for leftward ingoing/rightward outgoing stimuli, $p = .023$, but not for leftward outgoing/rightward ingoing stimuli, $p = .778$ (Bonferroni adjusted alpha levels were set as .012); a larger error was found when bisecting leftward ingoing/rightward outgoing stimuli with the right (mean = 1.79%, SEM = .34) than with the left hand (mean = 1.01%, SEM = .40). The *Hand* by *Shaft length,* $F(1,23) = 1.966$, $MSE = 8.07$, $p = .174$, $\eta^2 = .008$, and the *Stimulus* x *Hand* x *Shaft length,* $F(1,23) = 1.038$, $MSE = 1.80$, $p = .319$, $\eta^2 = .002$, interactions were not significant.

Since many trials were administered to each participant (120 per session, 360 total), the effects of repeated exposure to the stimuli and of practice were investigated by dividing the trials into two blocks for each presentation condition (block 1: trials 1-60; block 2: trials 61-120). A repeated measures within-subjects analysis of variance with three main factors (*Modality*: visual, haptic, visuo-haptic; *Stimulus:* leftward outgoing/rightward ingoing fins, leftward ingoing/rightward outgoing fins; *Block*: 1, 2) failed to reveal any effect of block (all, $F < 1$); only the interaction Stimulus by Block was significant, $F(1,23) = 5.801$, $MSE = 3.76$, $p = .024$, $\eta^2 = .001$, but the post-hoc tests were not significant (Bonferroni adjusted alpha levels were set as .012).

Discussion

Arrowheads affected line bisection in all three presentation conditions: the subjective mid-point was shifted towards the tail end, consistent with the effect of the Judd illusion. The illusory effect was equally powerful in both unimodal conditions (visual and haptic), with an approximately 4% magnitude effect. In the bimodal condition the illusion was still present, even though reduced (~2%), as compared to the unimodal conditions. This result indicates that the view of the arrowheads of the Judd configuration shifts the subjective mid-point of a line perceived haptically. Such shift, however, is smaller than the shift observed under unimodal presentation.

Exp. 2

Exp. 2 aimed at assessing whether the illusory effects found in the bimodal task of Exp. 1 indeed reflected a visuo-haptic integrative process (i.e., the merging of visual and tactile signals into a unified percept), by manipulating the spatial correspondence of the visual and haptic components of the stimulus. In fact, one relevant factor for multisensory integration is spatial coincidence, with integration becoming poorer when the spatial separation between the relevant signals increases (Gepshtein, Burge, Ernst, & Banks, 2005; Stein, 1998).

In Exp. 2, we presented the bimodal condition alone (namely, the visible arrowheads on the frontside, and the shaft on the backside of the board, out of sight), varying the horizontal position of the shaft with respect to the arrowheads. If the illusory effects observed in the bimodal condition of Exp. 1 were based on the merging of visual and haptic information, this integration should be broken by the absence of spatial coincidence.

Method

Participants

Twenty neurological unimpaired participants (nine males/eleven females) took part in the experiment (mean age 24 years, range 20-33 years). All participants were right-handed (Oldfield, 1971), with normal or corrected-to-normal vision. Participants were naïve as to the purpose of the study, and received course credits for their participation in the experiment, which was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Stimuli and Apparatus

The same stimulus material of the bimodal task of Exp. 1 was used: double-face wooden boards with the plastic ends on the front visible side, and a 12 cm shaft on the back side. Exp. 2 differed from Exp. 1 in the spatial position of the shaft glued on the back of the board and aligned with its centre on the vertical axis. The shaft was positioned centrally, shifted leftwards or rightwards, with a 25% offset (3 cm) with respect to the centre of the board on the horizontal plane (Figure 1-4). This offset was chosen, in order to have the shaft still partially superimposed over the two fins. As in Exp. 1, the ends were placed centrally on the front of the board, and three stimuli were used: leftward outgoing/rightward ingoing fins, leftward ingoing/rightward outgoing fins, and one baseline non-illusory stimulus with vertical ends.

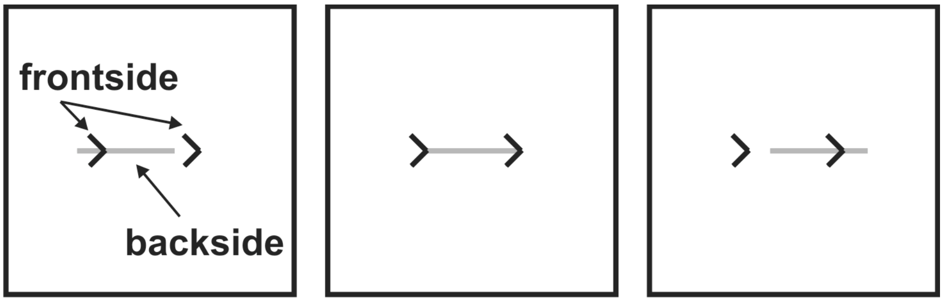


Figure 1-4. Exp. 2. Examples of experimental stimuli. The shaft glued on the backside on the board was positioned either at the centre of the display, or shifted leftwards or rightwards, with a 25% offset (3 cm).

Procedure

As in Exp. 1 the participants' task was to set the mid-point of the horizontal shaft with their index finger. Participants used their right hand, as no major differences related to the hand used had been found in Exp. 1. Participants received no information as to the position of the shaft, and they were given instructions to explore it with the whole hand, before performing the bisection. Each trial started with the experimenter placing the participants' right hand open centrally over the shaft. Participants saw the arrowheads on the front side, and, at the same time, palpated the invisible shaft glued on the backside of the board, and then set its midpoint using their right index finger. Each of the three stimulus types was presented 10 times for each spatial position of the shaft (leftward shifted, rightward shifted, central) for a total of 90 trials, presented in a random order.

The random sequence was different for each participant. Two practice trials, one baseline and one illusory stimulus selected at random, were administered at the beginning of the experiment, and were not included in any further analysis.

The bisection error was measured to the nearest mm, and scored as in Exp. 1. Scores exceeding ±3 SD from the group mean were excluded from the analyses. Then, scores were submitted to a repeated-measures analysis of variance with two within-subjects main factors *Shaft Position* (left shift, right shift, centre) and *Stimulus* (leftward outgoing/rightward ingoing fins, leftward ingoing/rightward outgoing fins).

Results

Figure 1-5 shows the percent deviation for the three positions of the shaft and for the two illusory conditions. The illusory effects, namely a leftward error with leftward outgoing/rightward ingoing fins, and a rightward error with leftward ingoing/rightward outgoing fins, were present only when the two ends of the shaft glued on the back of the board were aligned with the vertices of the two fins (Figure 1-5, centre). When the shaft was shifted leftwards and rightwards no illusory effects took place. A repeated-measures analysis of variance showed a significant main effect of the factor *Stimulus*, $F(1,19) = 4.49$, $MSE = 18.10$, $p = .047$, $\eta^2 = .036$, while the main factor *Shaft Position* was not significant, $F(2,38) = 2.485$, $MSE = 15.03$, $p =$

.097, $\eta^2 = .06$. The interaction *Stimulus* by *Shaft Position* was significant, $F(2,38) = 18.39$, $MSE = 36.46$, $p < .001$, $\eta^2 = .145$. Post hoc pairwise comparisons showed no significant difference between the leftward outgoing/rightward ingoing and the leftward ingoing/rightward outgoing stimuli when the shaft was shifted away from the centre, both leftwards, $p = .442$, and rightwards, $p = .656$. Conversely, the difference between the leftward outgoing/rightward ingoing (mean = -1.60%, SEM = .64), and the leftward ingoing/rightward outgoing stimuli (mean = 1.39%, SEM = .48) was significant when the shaft was positioned in the centre of the board, $p < .001$ (Bonferroni adjusted alpha levels were set as .008).

The effects of repeated exposure to the stimuli and of practice were investigated by dividing the trials into two blocks (1: trials 1-45, 2: trials 46-90), and then performing an analysis of variance differing from the one reported above in that the main factor Block was added. The main effect of Block and its interactions were not significant, all $F < 1$.

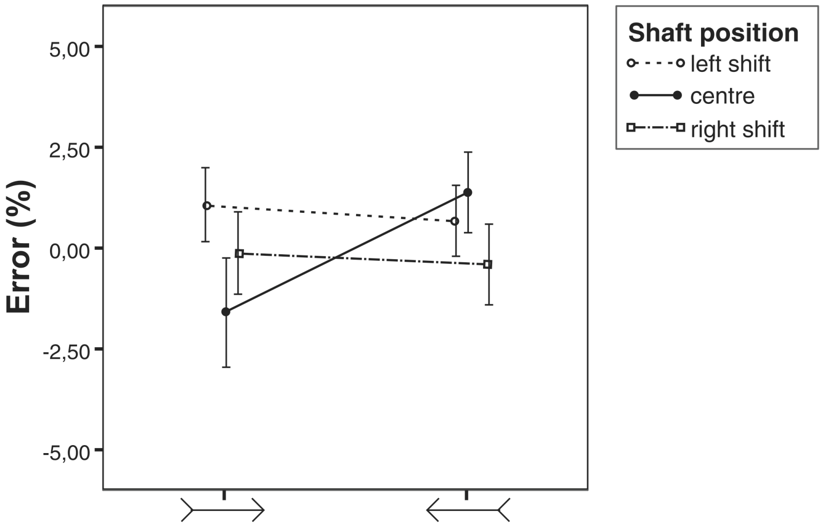


Figure 1-5. Exp. 2. Mean percent error (SE) in shaft bisection, by stimulus type (leftward outgoing/rightward ingoing, and leftward ingoing/rightward outgoing fins), and position of the horizontal shaft (left and right shift, centre).

Discussion

Visual arrowheads affected haptic bisection, only when the shaft was aligned with them. The mislocation of the shaft with respect to the arrowheads impeded the crossmodal transfer of the illusion. These findings provide evidence that the bias induced by the arrowheads on haptic bisection has the characteristics of a multisensory effect, and it is based on spatial coincidence rules.

General Discussion

In the present study we have demonstrated that the visual and haptic Judd versions of the Müller-Lyer figure bring about illusory effects that are comparable in size. In a multisensory condition, where the arrowheads are visible and the shaft is bisected haptically, the illusory effects are still present, albeit reduced in size (Exp. 1). This multisensory illusory effect requires the spatial correspondence of the arrowheads and the shaft, being disrupted by a misalignment of these component parts of the Judd figure (Exp. 2).

Spatial proximity is a relevant factor for multisensory integration (Gepshtein, et al., 2005), and the present results extend this view to the generation of crossmodal illusory effects. These findings make also unlikely an interpretation of the results of Exp. 1 (visuo-haptic condition) as the mere (unimodal) influence of the visual fins on the directional movement of the upper limb in the haptic bisection task, with the illusory effects of the bimodal condition of Exp. 1 reflecting only the visual processing of the fins. The finding that the visual arrowheads, irrelevant for the bisection task, affect haptic bisection only when the shaft is aligned with them indicates, first, that the visual illusion transfers crossmodally from vision to haptics, and, second, that this transfer crucially depends on the spatial coincidence of the visual and haptic stimuli.

It may be noted that, in the context of a Gestalt-based theoretical framework, the effects of displacing the shaft in the crossmodal condition of Exp. 2 may be seen as a disruption of the perceptual organization (see a recent review of these principles in the visual domain in Kubovy & van den Berg, 2008) of the component parts of the Judd figure. Future studies may test other spacing intervals, addressing the question of which is the minimum interval capable of breaking down the crossmodal transfer of the illusion.

When spatial proximity is maintained, the comparable illusory effects observed with visual and haptic Judd stimuli, as assessed by a line bisection task, are in line with the results of previous studies using judgement tasks on the Müller-Lyer figure (Over, 1966; Suzuki & Arashida, 1992). In the visuo-haptic condition condition of Exp. 1 the size of the illusory effects is reduced, with a greater bisection accuracy, as compared with the two unimodal conditions. This reduction may be caused by different factors.

Firstly, crossmodal integration may require additional processing resources (see discussion in Santangelo & Spence, 2008), decrementing the level of performance. However, in the present study the participants' accuracy was actually higher rather than lower, resulting in a smaller error with a reduced illusory effect.

A second account could be in terms of the completeness of the stimulus. In the unimodal visual presentation participants looked at the complete 'arrowheads and shaft' configuration, while in the bimodal condition only the arrowheads were presented visually. This could have reduced the size of the illusory effect in the bimodal condition. However, the size of the visual Müller-Lyer illusion, as assessed by different paradigms, is not affected by the presence/absence of the horizontal shaft interposed between the wings (Blessing & Svetlik, 2007; Coren & Girgus, 1974).

Thirdly, participants may combine visual and haptic inputs, improving accuracy. Specifically, they might use tactile information about the mid-point of the line to correct the shift produced by the visual arrowheads. Evidence from brain-damaged patients (Rorden, Heutink, Greenfield, & Robertson, 1999), and neurologically unimpaired participants (Serino, Padiglioni, Haggard, & Ladavas, 2009; Taylor-Clarke, Kennett, & Haggard, 2002), indicates that vision may improve tactile detection, supporting an interpretation of this sort for the present observation that in the bimodal visuo-haptic condition the illusory 'error' is reduced in size.

2. Visuo-haptic interactions in Unilateral Spatial Neglect

[This research has been published in: Mancini, F., Bricolo, E., Mattioli, F.C., Vallar, G. (2011) Visuo-haptic interactions in unilateral spatial neglect: the crossmodal Judd illusion. *Frontiers in Perception Science*]

Introduction

Unilateral Spatial Neglect (USN) is a frequent neuropsychological syndrome occurring after lesions to the right hemisphere. USN is characterised by the patients' failure to report sensory events taking place in the portion of space contralateral to the side of the lesion (contralesional), and to explore through motor acts that portion of space (Halligan, Fink, Marshall, & Vallar, 2003; Heilman, Watson, & Valenstein, 2003; Husain, 2008; Vallar, 1998). A rightward bias in line bisection is considered one of the signatures of USN (Bisiach, Bulgarelli, Sterzi, & Vallar, 1983; Bisiach, Capitani, Colombo, & Spinnler, 1976; Schenkenberg, Bradford, & Ajax, 1980), which has been mainly investigated in the visual modality, with fewer studies assessing the haptic modality and reporting controversial results.

The aim of this study was twofold: i) to compare the severity of left USN, as assessed by a line bisection task, in unimodal visual and haptic conditions, entirely comparable except for the availability of unisensory information; ii) to assess the patients' ability to combine information from different sensory modalities, i.e. vision and haptics. To this aim, we used a line bisection task involving the processing of a crossmodal illusion that we had previously used in neurologically unimpaired individuals (Mancini, Bricolo, & Vallar, 2010).

As assessed by motor exploratory tasks, USN may occur in both the visual and the tactile modality (Beschin, Cazzani, Cubelli, Della Sala, & Spinazzola, 1996; De Renzi, Faglioni, & Scotti, 1970; Haeske-Dewick, Canavan, & Homberg, 1996). Evidence has however been provided to the effect that USN may be less severe and even absent in the tactile modality, in the absence of visual input. An early and seminal observation is provided by Gilliatt and Pratt (1952) about a right-brain-damaged patient who showed severe left USN, when required to circle pins using a pencil with eyes open; conversely, with eyes closed, the patient explored the whole board up to the extreme left. A number of subsequent studies found a visuo-haptic difference, with USN being more severe in the visual modality for spatial exploratory tasks (Chedru, 1976, in right-brain-damaged patients with a visual-half-field deficit; Gentilini, Barbieri, De Renzi, & Faglioni, 1989; Schindler, Clavagnier, Karnath, Derex, & Perenin, 2006; Villardita, 1987). However, in the study by Chedru (1976) right-brain-damaged patients without visual half-field deficits showed a more severe USN when blindfolded. Importantly, there is evidence that the deficit may be modality-specific (Cubelli et al.'s 1991 re-analysis of the data of Gentilini, et al., 1989; Vallar, Rusconi, Geminiani, Berti, & Cappa, 1991). Particularly, in their reanalysis Cubelli et al. (1991) reported four right-brain-damaged patients who showed a disproportionate rightward bias with open eyes, but not with eyes closed, in a task requiring to explore a keyboard; three patients showed the opposite pattern (rightward bias with eyes closed), while five patients were impaired in both conditions. Other studies found a double dissociation between visual and tactile USN, reporting patients with a defective performance either in the visual or in the tactile modality (Barbieri & De Renzi, 1989; Perani, Vallar, Cappa, Messa, & Fazio, 1987, Appendix 2; Vallar, Rusconi, et al., 1991).

In line bisection tasks, the available studies indicate that the rightward bias appears to be confined to the visual modality (Chokron et al., 2002; Fujii, Fukatsu, Kimura, Saso, & Kogure, 1991; Hjaltason, Caneman, & Tegner, 1993). In haptic bisection, no rightward bias has been found, with left USN being almost absent (for a review, see Brozzoli, Demattè, Pavani, Frassinetti, & Farnè, 2006; Gainotti, 2010).

Taken together, these findings indicate that USN may be more severe in the visual than in the tactile modality. The deficits may also be modality-specific in exploratory tasks, conjuring up a double dissociation between vision and touch (Vallar, 2000) and suggesting the existence of modality-specific attentional and representational components (Vallar, 1998). In line with this idea, a rehabilitation study showed that a 6-weeks visual attention training improved visual but not tactile detection of left-sided targets (Làdavas, Menghini, & Umiltà, 1994). Finally, it is also well known that visual and tactile extinction to double simultaneous stimulation may occur independent of each other after unilateral brain damage (Hillis et al., 2006; Vallar, Rusconi, Bignamini, Geminiani, & Perani, 1994).

The evidence for modality-specificity, currently framed in the broader context of a multi-componential attentional/representational account of the USN deficit (Barbieri & De Renzi, 1989; Vallar, 1998), may be contrasted with an early interpretation of the syndrome in terms of a higher-order sensory impairment, hypothesized as a defective "spatial summation" and termed "amorphosynthesis" (with the primary function of "morphosynthesis" being the recognition of form, Denny-Brown, Meyer, & Horenstein, 1952). *"The loss of visual components of such* *morphosynthesis in addition to tactile factors, is the basis of unawareness of part of extrapersonal space and unawareness of self, without disorder of the concept of space or of body schema. Such unawareness differs considerably from simple loss of sensation"* (ibidem, p. 470). While the very concept of amorphosynthesis is admittedly vague, it appears to suggest the impairment of a higher-order spatial factor, related to different sensory modalities, rather than modality-specific.

In our experimental task we used a well-known optical illusion, the Judd figure, that has proven to be crossmodal (Mancini, Bolognini, Bricolo, & Vallar, 2011). Visual illusions are a tool for investigating implicit processing in USN, since illusory effects arising from the left side of space can be preserved and do not require perceptual awareness to occur (see Vallar & Daini, 2006, for a review). Although the Müller-Lyer illusion has proven to be useful for studying implicit processing in the contralesional space in patients with left USN, these investigations have been confined to the visual modality: haptic and crossmodal illusory effects have not been investigated so far (Vallar & Daini, 2006). We therefore examined right brain-damaged patients with and without left USN in the bisection of the Judd variant of the Müller-Lyer illusion under visual, haptic, and visuo-haptic presentation. We aimed at assessing whether visuo-tactile interactions were preserved in these patients. The ability of right-brain-damaged patients with left USN to combine visuo-haptic information could also provide an experimental assessment of the "amorphosynthesis" hypothesis.

Method

Participants

Fourteen right-brain-damaged (RBD) patients (see Table I) and 14 neurologically unimpaired participants (C) took part in the study. RBD patients were subdivided into two groups, with and without left USN (N+/N-), as assessed by a standard neuropsychological battery (Table II). Even if a perusal of Table I suggests that N+ patients may be older (as previously found in larger series of patients, Gottesman et al., 2008; Leibovitch et al., 1998), the age of the participants of the three groups was comparable as assessed by a one-way analysis of variance [$F(2,25) = 3.16$, $p > 0.60$]. Each participant gave informed written consent to take part in the experiment, which had been approved by the Ethics Committee of the IRCSS Istituto Auxologico Italiano.

The patients' demographic and neurological data are summarized in Table I. All 14 RBD patients had unilateral stroke lesions in the right hemisphere. All patients were right-handed, and had no history or neurological evidence of previous neurological diseases, psychiatric disorders, or dementia. All patients had a normal or corrected-to-normal vision. Contralesional motor, somatosensory, and visual half-field deficits, including extinction to tactile and visual double stimuli, were assessed by a standard neurological exam (Bisiach & Faglioni, 1974). Visual field defects were also assessed by kinetic Goldmann perimetry, and by a computerized program testing six different positions in both the left and right hemi-fields, at different eccentricities (3°, 6°, 12° of visual field). The visual field of two N- patients (P10 and P14) was tested with our customised program only.

Table I. Demographical and neurological data of 14 right-brain-damaged patients with (N+) and without (N-) USN, and of 14 control (C) neurologically unimpaired participants. M/F: male/female. I/H: ischemic/hemorrhagic. M/SS/V: left motor/somatosensory/visual half-field deficits. e: contralesional extinction.
+/-: presence/absence of impairment.

Patient	**Sex**	**Age** (years)	**Education** (years)	**Months post-onset**	**Aetiology**	**Neurological deficit**		
						M	**SS**	**V**
N+								
1	M	63	17	16	I	+	+	+
2	M	77	17	23	I	+	e	e
3	F	83	13	12	I	+	+	+
4	F	72	7	22	I	+	-	-
5	M	70	17	1.5	I	+	+	+
6	M	66	5	14	H	+	+	+
7	M	71	17	4	I	+	+	e
Mean		*71.71*	*13.29*	*13.21*				
(SD)		*(6.68)*	*(5.23)*	*(8.21)*				
N-								
8	F	41	10	2	H	+	-	-
9	M	63	17	15	I	+	-	-
10	M	38	13	1.5	I	+	-	-
11	F	77	8	10	I	-	-	-
12	M	74	12	24	I	+	-	-
13	M	37	13	1	I	+	-	-
14	M	39	6	1	I	+	-	-
Mean		*52.71*	*11.29*	*7.79*				
(SD)		*(17.96)*	*(3.64)*	*(8.99)*				
C								
15	F	72	8					
16	M	58	17					
17	F	60	8					
18	M	52	13					
19	M	52	8					
20	M	65	5					
21	F	53	13					
22	M	66	13					
23	M	73	17					
24	M	85	16					
25	F	70	13					
26	F	85	13					
27	F	36	8					
28	F	41	13					
Mean		*62.00*	*11.79*					
(SD)		*(14.64)*	*(3.77)*					

The lesion site and size were assessed by CT or MRI scan. Lesions were mapped for each right-brain-damaged patient using the MRIcro software (Rorden & Brett, 2000) and were drawn manually onto selected horizontal slices of a standard template brain. Figure 2-1 shows the overlapped lesion maps of the 14 right-brain-damaged patients, subdivided into showing and not showing left USN. In N+ patients the maximum overlap involved the right putamen, and the insular and frontal inferior orbital cortices (7 patients); in N- patients the maximum overlap was observed over the right rolandic operculum, the superior temporal pole and the insula (3 patients).

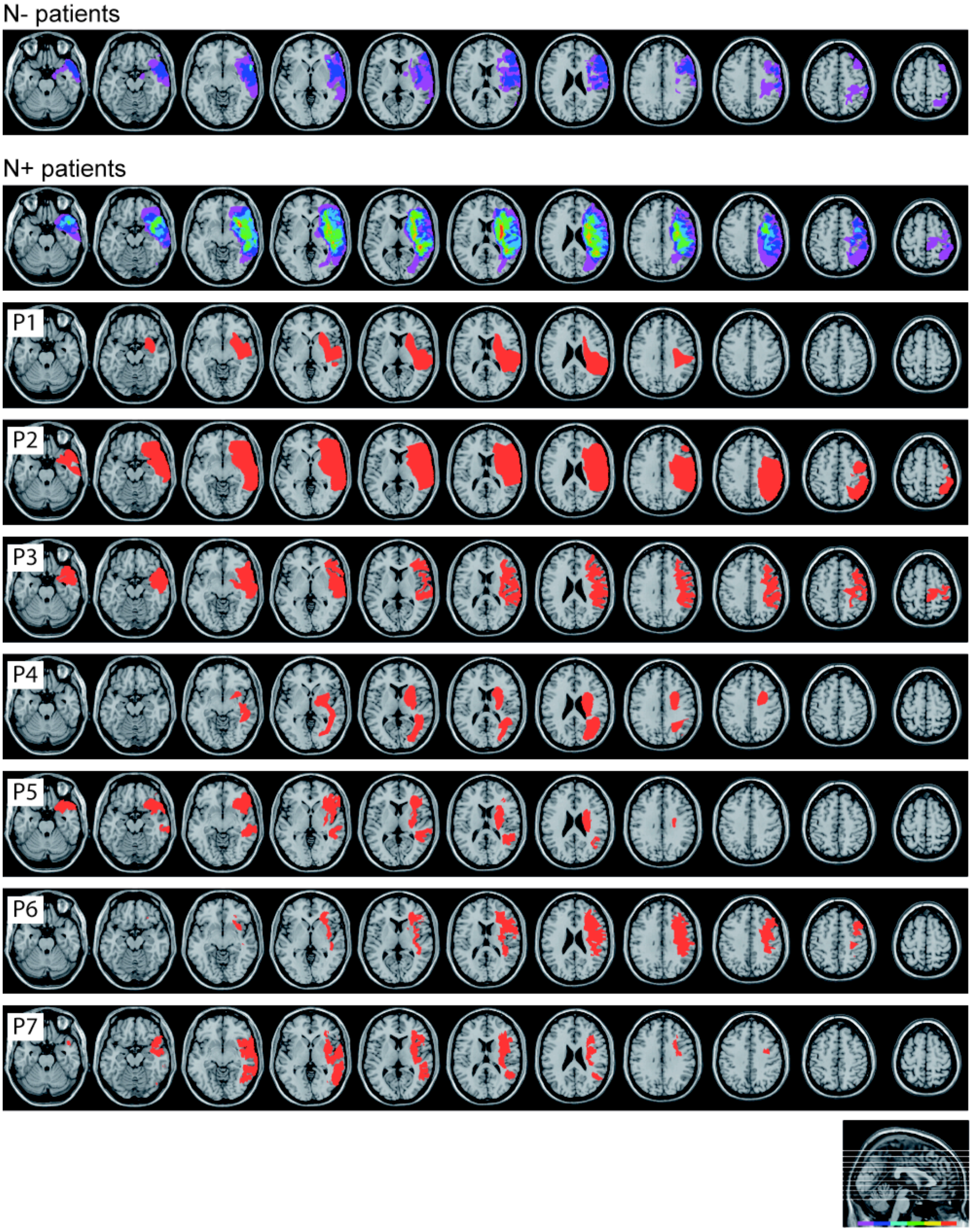


Figure 2-1. *Lesion site of patients with and without USN*. Superimposed overlapping brain lesions (first two rows), and lesional mapping for each USN patient (P1-P7). The lesions were mapped using MRIcro software (http://www.sph.sc.edu/comd/rorden/mricro.html).

Overall, lesions were more extensive in the N+ group (mean volume of the lesion = 126 cc, SD ± 79.51, range 74.44 - 282.76 cc) than in the N- group (mean volume of the lesion = 41.04 cc, SD ± 54.24, range 1.22 - 129.16 cc), in line with previously reported evidence in large series of patients (Hier, Mondlock, & Caplan, 1983a, 1983b; Leibovitch, et al., 1998).

Baseline neuropsychological assessment

The diagnostic battery assessing the presence of left USN included three visuomotor exploratory tasks (line, letter, and bell cancellation), a reading task, a line bisection task, two copying tasks, and one drawing from memory task (Table II). Patients used their right unaffected hand to perform the tasks. In all tasks, the centre of the sheet was aligned with the mid-sagittal plane of the patient's trunk. The Mini Mental State Examination (MMSE) was also given (Grigoletto, Zappala, Anderson, & Lebowitz, 1999).

i. *Line bisection*. The patients' task was to mark with a pencil the mid-point of six horizontal black lines (two 10 cm, two 15 cm, and two 25 cm in length, all 2 mm in width), presented in a random fixed order. Each line was printed at the centre of an A4 sheet. The length of the left-hand side of the line (i.e., from the left end of the line to the participant's mark) was measured to the nearest millimetre. This measure was converted into a standardized score (percentage deviation), namely: measured left half minus objective half/objective half * 100 (Rode, Michel, Rossetti, Boisson, & Vallar, 2006). This transformation yields positive numbers for marks placed to the right of the physical centre, negative numbers for marks placed to the left of it. The mean percentage deviation score of 65 neurologically unimpaired participants, matched for age (mean = 72.2, SD ± 5.16, range 65 to 83), and years of education (mean = 9.5, SD ± 4.48, range 5 to 18) was 1.21% (SD ± 3.48, range -16.2% to + 6.2%). A percentage deviation score higher than 8.20 was considered as indicative of left USN (Fortis et al., 2010).

ii. *Line cancellation* (Albert, 1973). The participants' task was to cross out all of the 21 black lines printed on an A4 sheet with no distracters. The score was the difference between numbers of omissions in the left- (range 0–11) and in the right- (range 0–10) hand-sides of the sheet. Neurologically unimpaired participants perform this task without errors.

iii. *Letter cancellation* (Diller & Weinberg, 1977). The participants' task was to cross out all of 104 H letters (53 in the left-hand-side, and 51 in the right-hand-side of the sheet), printed on an A3 sheet, together with other letter distracters. In neurologically unimpaired participants the maximum difference between omission errors on the two sides of the sheet is two (Vallar, Rusconi, Fontana, & Musicco, 1994).

iv. The Bells Test (Gauthier, Dehaut, & Joanette, 1989). The participants' task was to cross out all of 35 bells (15 in the left-hand-side, 5 in the middle, and 15 in the right-hand-side of the sheet), printed on an A3 sheet, together with other 280 distracters. In neurologically unimpaired participants the maximum difference between omission errors on the two sides of the sheet is four (Vallar, Rusconi, Fontana, et al., 1994).

v. Sentence reading (Pizzamiglio et al., 1992). Six sentences of different lengths were presented one per time, printed centrally on a A4 sheet. The score was the number of correctly read sentences (range 0–6). Normal participants and patients with right brain damage without USN make no errors on this test. Right-brain-damaged patients with USN make omission errors, substitution errors, or both, in the left half of the sentence.

vi. *Drawing*. Patients were required to copy two figures [a daisy and a complex figure with two trees in the left-hand-side, two pine trees in the right-hand-side, and a house in the centre of an A4 sheet (Gainotti, Messerli, & Tissot, 1972)], and to draw from memory the hours of a clock in a circular quadrant (diameter 12 cm), printed on an A4 sheet. Omission errors were calculated as follows:

a. *Daisy* (range 0–2): 2 (flawless copy); 1.5 (partial omission of the left-hand-side of the daisy); 1.0 (complete omission of the left-hand-side of the daisy); 0.5 (complete omission of the left-hand-side of the daisy, and partial omission of the right-hand-side of the daisy); 0 (no drawing, or no recognizable element). The mean number of omissions of 148 neurologically unimpaired participants (mean age = 61.89, SD ± 11.95, range 40 to 89) was 1.99 (SD ± 0.12, range 1 to 2). Accordingly, the presence of a partial or complete omission of the left-hand side of the daisy (score lower than 1.5) was considered as indicative of left USN.

b. *Five-element complex drawing* (range 0–10): 2 (for each flawless copied element); 1.5 (for each partial left-sided omission of one component, e.g., some branches of the left-hand-side of a tree); 1.0 (for each left-hand-side omission of one component); 0.5 (for each complete omission of the left-hand-side, and partial omission of the right-hand-side of the component); 0 (no drawing, or no recognizable element). The horizontal ground line was not considered for scoring. The mean score of 148 neurologically unimpaired participants (mean age = 61.89, SD ± 11.95, range 40 to 89) was 9.89 (SD ± 0.23, range 9.5-10). Accordingly, a score lower than 9.5 indicated a defective performance.

c. *Clock drawing from memory* (range 0–12): 1 (for each element in the correct position); 0 (for each omission or translocation of an element from one side to the other; elements ‘‘12’’ and ‘‘6’’ were scored as translocated when displaced in the right- or left-hand-side quadrants). The mean score of 148 neurologically unimpaired participants (mean age = 61.89, SD ± 11.95, range 40 to 89) was 11.55 (SD ± 1.17, range 0 to 6). Accordingly, a score lower than 9 indicated a defective performance. Also, neurologically unimpaired participants made no translocations.

vii. *Corsi’s Block tapping test* (Orsini et al., 1987). Nine white cubes were arranged over a 23 by 28 cm board. The examiner tapped sequences of increasing length in a fixed order, with the patients’ task being to tap the same ordered sequence, immediately after presentation. The test continued until the patient failed at a given length (less than three out of five sequences were correctly recalled). The spatial span score was the length of the longest sequence correctly recalled. Scores adjusted for gender, age, and education were computed.

viii. *Corsi’s block tapping vertical test*. This was a modified version of the standard Corsi’s block tapping test, adapted for USN patients (Ronchi, Posteraro, Fortis, Bricolo, & Vallar, 2009). Nine white cubes were arranged over a vertical board 60 cm high and 14 cm wide; the distance between each cube was 1.5 cm. The procedure was identical to that used for the standard Block tapping test of Orsini et al. (1987). Control data were provided by 14 neurologically unimpaired right-handed C participants, matched for age and education (mean age 62 years, range 36-85, mean education 11.7 years): the mean span was 3.38 (SD ± 1.07, range 2-6).

ix. *Modified version of the Benton Tactile Form Assessment* (Benton, 1994). We adapted the original version in order to administer the test to USN patients (symmetrical stimuli, central presentation of the visual comparisons). Participants were required to match a shape, explored haptically with the right hand and out of sight, to a visual sketch of the shape to be chosen among five stimuli, printed in a vertical column on an A4 sheet. Eighteen shapes, subdivided in three sections, were presented: nine filled and nine unfilled. A score of 2 was assigned to each correct response given within 30 sec, 1 within 60 sec, and 0 for wrong or out-of-time responses. The mean score of the control group (C) was 30.91 out of 36 (SD ± 4.18, range 26-36).

For the Benton Tactile Form Assessment and the Corsi's block tapping vertical test, the patients' performances were compared with those of control participants by t tests (Crawford & Garthwaite, 2002).

Stimuli, Apparatus and Procedure

Stimuli, apparatus and procedure were identical to a previous study we conducted in neurologically unimpaired participants (Mancini, et al., 2010) (see Chapter 1). Stimuli consisted of three types of black plastic figures (Figure 1-1, a-c): a baseline control (a line with vertical ends), and two illusory figures (leftward outgoing/rightward ingoing fins, which brought about a leftward displacement of the shaft's perceived centre; leftward ingoing/rightward outgoing fins, which brought about a rightward displacement of the shaft's perceived centre).

Each type of stimulus was presented 8 times, for a total of 48 trials. For each participant and for each session, a different random sequence was used. Two practice trials, one baseline and one illusory stimulus selected at random, were administered at the beginning of each session (visual, haptic, visuo-haptic), and were not included in any subsequent analyses.

After each response, using a ruler, the experimenter measured to the nearest mm the bisection error, namely, the distance between the subjective midpoint set by each participant and the objective centre of the shaft. A rightward deviation of the subjective midpoint carried a plus sign, a leftward deviation a minus sign. A percent error as related to the length of each shaft (10, 12 cm) was subsequently computed.

Data analysis

In order to assess the presence of USN in each sensory modality, in the baseline bisection task, percent errors were first submitted to three analyses of variance (ANOVA), one per Presentation Modality, with one within-subjects main factor (*Shaft Length*: 10, 12 cm), and one between-subjects main factor (*Group*: N+, N-, C).

For each participant, average percent errors in each illusory stimulus condition were corrected for the average percent error in the baseline stimulus. Illusory effects were investigated by three separate ANOVAs (one per Presentation Modality) with two within-subjects main factors (*Stimulus:* leftward outgoing/rightward ingoing fins, leftward ingoing/rightward outgoing fins; *Shaft Length*: 10, 12 cm), and one between-subjects main factor (*Group*: N+, N-, C). A posteriori contrasts among means were evaluated by Scheffé's test.

Table II. Clinical data of 14 right-brain-damaged patients with (N+) and without (N-) USN. Mini Mental State Examination, Drawing tests, Corsi's Block Tapping tests, Tactile Form Recognition: raw scores. Target cancellation: numbers of left- minus right-hand-side omissions. Line Bisection: percent displacement (+/- rightward/leftward). Sentence Reading: number correct. n.a.: not assessed. ^{1}Arabian patient. *: defective performance.

Patient	MMSE	Cancellation tests			Line Bisection (%)	Sentence reading	Drawing			Corsi's Block Tapping Test		Tactile Form Recognition
		Line	Letter	Bells			Daisy	Complex	Clock	Standard	Vertical	
N+												
1	30	0	2	1	+11.4	6	2	5.5*	11	3*	3	30
2	29	0	20*	16*	+3.8	6	1.5	10	12	4	2	25
3	26	2*	6*	10*	+3.8	4*	1.5	4*	2*	3	1*	10*
4	27	2*	-1	3	+10.2	6	2	9*	11	3	2	20*
5	29	0	36*	7*	+1.1	6	1.5	4.5*	6*	2*	1*	16*
6	28	7*	34*	6*	+50.4*	0*	1.5	4*	8*	2*	2	14*
7	28	1*	32*	7*	+2.4	4*	2	5*	12	4	2	25
N-												
8	30	0	0	0	+4.4	6	2	10	12	4	2	28
9	29	0	0	-2	-2.3	6	2	10	12	6	2	33
10	30	0	0	0	-2	6	2	10	12	4	3	29
11	27	0	0	0	-5.6	6	2	10	12	4	3	24
12	27	0	-1	-2	-5.6	6	2	10	12	4	3	22*
13	28	0	0	1	+0.8	6	2	10	12	4	4	36
14	n.a.^{1}	0	1	4	+0.2	6	2	10	11	4	4	34

Results

Baseline errors

The bisection of the baseline stimulus (a shaft with vertical ends) was deviated rightwards in the N+ group in the visual modality, indicating the presence of visual USN. No difference across the three groups was found under unimodal haptic and crossmodal visuo-haptic presentations (see Figure 2-2).

In the *visual condition*, the analysis of variance revealed a significant main effect of Group [F(2,25) = 20.32, $p < 0.0001$, $\eta^2 = 0.399$]. The main effect of Shaft Length was significant [F(1,25) = 5.31, $p = 0.030$, $\eta^2 = 0.161$], indicating larger rightwards errors with 12 cm stimuli compared with 10 cm. The interaction Shaft Length by Group was not significant [F(2,25) = 1.32, $p = 0.285$, $\eta^2 = 0.080$]. The differences between N+ patients and both N- ($p < 0.0001$) and C participants ($p < 0.0001$) were significant; no difference was found between the N- and C groups.

In the *haptic condition*, the main effect of Group was not significant ($F < 1$). The main effect of Shaft Length was significant [F(1,25) = 6.09, $p = 0.021$, $\eta^2 = 0.151$], since the 10 cm stimulus was bisected more leftwards than the 12 cm one. The interaction Shaft Length by Group was significant [F(2,25) = 4.55, $p = 0.021$, $\eta^2 = 0.226$]. The difference between short and long stimuli was significant only in the N+ group ($p = 0.001$): in particular, N+ patients bisected the longer line more rightwards than the shorter line.

In the *visuo-haptic condition*, the main effect of Group was not significant ($F < 1$). Also the main effect of Shaft Length [F(1,25) = 1.13, $p = 0.298$, $\eta^2 = 0.042$] and its interaction with Group ($F < 1$) were not significant.

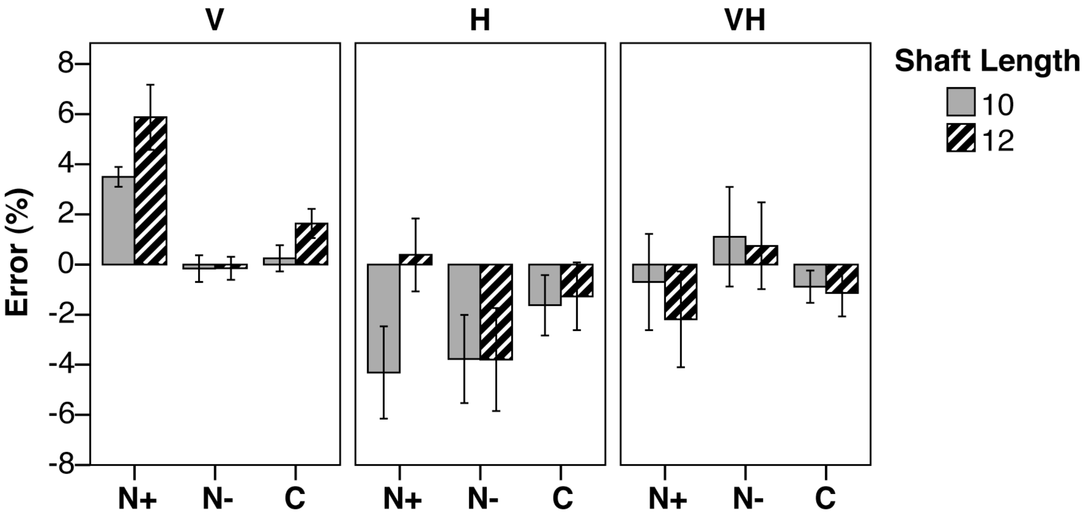


Figure 2-2. ***Baseline errors*****. Mean percent error (± SEM) in shaft bisection in the baseline condition, by Shaft Length (10, 12 cm), Group (N+/ N-, patients with/without USN; C, neurologically unimpaired control participants), and presentation Modality (Visual, V; Haptic, H, Visuo-Haptic, VH). Negative/positive score: leftward/rightward error.**

Illusory effects

In each modality and in each group, stimuli with leftward outgoing/rightward ingoing fins brought about a leftward error, stimuli with leftward ingoing/rightward outgoing fins elicited a rightward error (Figure 2-3). The figure does not show the effect of Shaft Length, which did not provide results of interest for the purposes of the present study.

In the *visual condition*, the analysis of variance did not reveal a significant main effect of Group [F(2,25) = 2.51, p = 0.101, η^2 = 0.148]; the main effect of Stimulus [F(1,25) = 138.88, p < 0.0001, η^2 = 0.772], and its interaction with the main effect of Shaft Length [F(1,25) = 6.60, p = 0.017, η^2 = 0.004] were significant. Post-hoc comparisons did not show any significant difference between the two lengths for both the leftward outgoing/rightward ingoing (p = 0.322), and the leftward ingoing/rightward outgoing stimuli (p = 0.236). The main effect of Shaft Length and all the interactions with Group were not significant (F < 1).

In the *haptic condition*, there was a trend towards significance for the main effect of Group [F(2,25) = 3.11, $p = 0.062$, $\eta^2 = 0.182$]. N- patients bisected the stimuli overall more rightwards than both the N+ ($p = 0.035$) and the C ($p = 0.037$) participants. The main effect of Stimulus [F(1,25) = 45.663, $p < 0.0001$, $\eta^2 = 0.501$] and its interaction with the main effect of Shaft Length [F(1,25) = 4.96, $p = 0.035$, $\eta^2 = 0.006$] were significant. The difference between the two lengths was close to significance in the leftward ingoing/rightward outgoing stimulus ($p = 0.076$). The main effect of Shaft Length and its interaction with the main effect of Group was not significant ($F < 1$). The Stimulus by Group [F(2,25) = 1.50, $p = 0.243$, $\eta^2 = 0.033$], and Stimulus by Length by Group [F(2,25) = 1.43, $p = 0.258$, $\eta^2 = 0.003$] interactions were not significant.

Finally, in the *visuo-haptic condition*, the main effect of Group was significant [F(2,25) = 5.92, $p = 0.008$, $\eta^2 = 0.321$]. The difference between the N+ and the C groups was significant ($p < 0.009$), but not among the other groups. In particular, the corrected bisection of the illusory stimuli made by N+ patients was shifted overall more rightwards than the bisection made by C participants. The main effect of Stimulus [F(1,25) = 113.01, $p < 0.0001$, $\eta^2 = 0.622$] was significant. The main effect of Shaft Length ($F < 1$), and the Stimulus by Group [F(2,25) = 2.18, $p = 0.123$, $\eta^2 = 0.025$], Stimulus by Shaft Length [F(1,25) = 1.68, $p = 0.206$, $\eta^2 = 0.004$], Shaft Length by Group ($F < 1$), and Stimulus by Shaft Length by Group [F(2,25) = 1.36, $p = 0.274$, $\eta^2 = 0.007$] interactions were not significant.

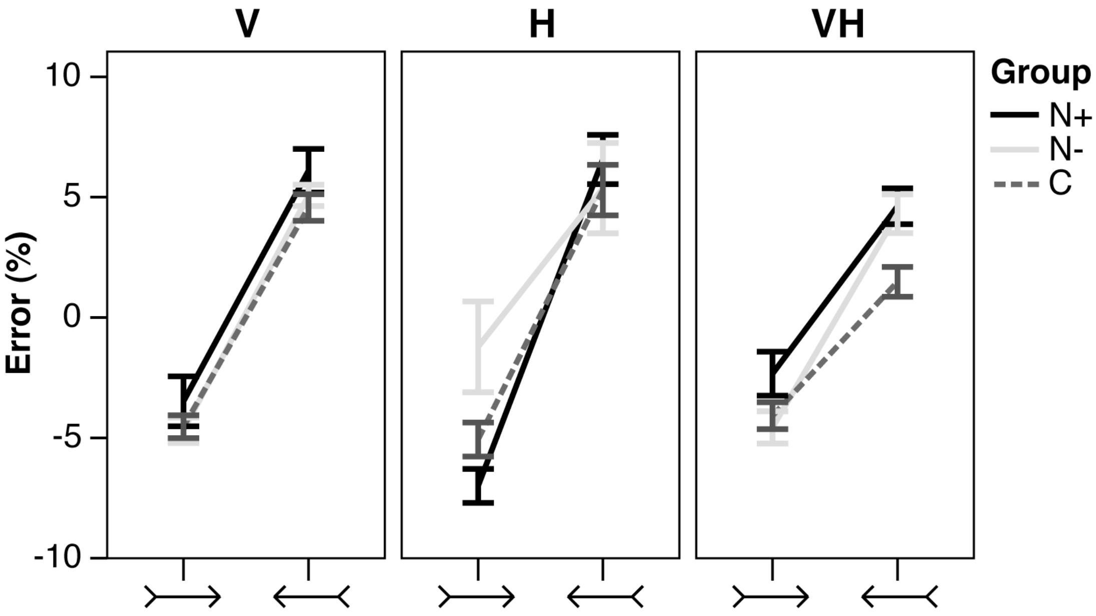


Figure 2-3. ***Illusory effects.*** **Mean percent error (± SEM) in shaft bisection in the illusory conditions, by Stimulus type (leftward outgoing/rightward ingoing, and leftward ingoing/rightward outgoing fins), Group (N+, N-, C), and presentation Modality (V, H, VH). Negative/positive score: leftward/rightward error.**

Discussion

The present study yielded three main findings. (1) The rightward bias in bisection characteristic of patients with USN was present only in the visual modality, not in the haptic and visuo-haptic conditions. (2) Illusory effects were preserved in each modality, revealing that the processing of the Judd illusion is independent of the presence of spatial attentional deficits. (3) Visual and tactile inputs were properly integrated by right-brain-damaged patients with left USN.

USN within and between sensory modalities

Our results support the view that left USN can be modality-specific. In the present study, USN (as evaluated by a bisection task) was present in the visual modality only, since USN patients showed a preserved performance in the haptic and crossmodal presentation conditions. It may be noted, however, that in the haptic modality USN patients did make a more rightward error with the longer stimulus (Figure 2-2), unlike patients without USN and control participants. This pattern might be taken as possible evidence of a minor tactile USN. In the visuo-haptic condition (visual illusion and haptic line bisection), illusory effects were biased rightwards in USN patients as compared with control participants (Figure 2-3), possibly indicating transfer of the visual USN in the tactile domain.

Overall, these results are in line with the evidence, reviewed in the introduction, that USN is absent or less severe in the tactile than in the visual modality: a number of studies report almost preserved tactile bisection in patients with visual USN (Chokron, et al., 2002; Fujii, et al., 1991; Hjaltason, et al., 1993). We cannot exclude that in the present experiment the use of short lines (under 12 cm) might have hidden deficits in the haptic bisection: particularly, this is suggested by the fact that USN patients show a small rightward bias (see Figure 2-2) in the haptic bisection of longer (12 cm), but not of smaller lines (10 cm). However, longer rods have been used in previous studies that do not report a greater rightward error in haptic line bisection in USN patients than in control participants (Chokron, et al., 2002, 20 and 22 cm; Fujii, et al., 1991, four lengths from 8 to 20 cm in 4 cm steps; Hjaltason, et al., 1993, 20 and 40 cm). Interestingly, the experiment of Hjaltason et al. (1993) includes a visuo-tactile task, in which participants indicate the perceived midpoint after having ran the index finger along the rod. Even in that condition (which differs from the visual one in that tactile exploration of the rod is required), right-brain-damaged patients with left USN show no significant rightward error. In our visuo-haptic condition, the line to bisect is explored only haptically, and participants are allowed to see its ends.

It is possible that our selection criteria for USN, based on visual tasks, may have prevented the inclusion of patients with haptic USN, accounting for the present results, at least in part, in terms of selection bias. However, it should be noted that previous studies reporting the absence of USN in haptic line bisection, as we did, adopted similar selection criteria, namely the presence of visual USN (Chokron, et al., 2002; Fujii, et al., 1991; Hjaltason, et al., 1993). In any case, in the baseline experimental task we assessed visual and haptic (as well as visuo-haptic) line bisection, replicating the previously reported visuo-haptic dissociation.

The rightward bias exhibited by right-brain-damaged USN patients in visual bisection can not be traced back to initial rightward biases or a general position preference for the side ipsilateral to the side of the lesion (ipsilesional) (Campbell & Oxbury, 1976; Costa, 1976), since the shafts are short (10 and 12 cm) and the participants' hand covers the whole stimulus at the beginning of each trial.

Multisensory interactions have been rarely investigated in USN. One area of research involves the effects of physiological stimulations that improve a number of manifestations of the USN syndrome (Chokron, Dupierrix, Tabert, & Bartolomeo, 2007; Kerkhoff, 2003; Rode, Klos, Courtois-Jacquin, Rossetti, & Pisella, 2006; Vallar, Guariglia, & Rusconi, 1997). Vestibular stimulation ameliorates left-sided somatosensory deficits (Bottini et al., 2005; Vallar, Bottini, Rusconi, & Sterzi, 1993; Vallar, Sterzi, Bottini, Cappa, & Rusconi, 1990). Prism adaptation improves tactile deficits (Maravita et al., 2003). Optokinetic stimulation may either ameliorate or worsen proprioceptive deficits of position sense in right-brain-damaged patients with left USN (Vallar, Antonucci, Guariglia, & Pizzamiglio, 1993; Vallar, Guariglia, Magnotti, & Pizzamiglio, 1995). Also auditory USN, as indexed by a contralesional left-sided deficit with dichotic stimuli, is ameliorated by prism adaptation (Jacquin-Courtois et al., 2010). The effects of these stimulations are essentially similar across sensory modalities and depend on the characteristics of the sensory stimulations (Chokron, et al., 2007; Kerkhoff, 2003; Rode, Klos, et al., 2006; e.g., side, left vs. right, and type, warm vs. cold stimulation, in the case of caloric vestibular stimulation: see reviews in Vallar, et al., 1997). Importantly, these stimulations are thought to modulate spatial processing or attention (damaged or biased ipsilaterally in USN) rather than being considered as an index of preserved multisensory integration. In particular, the typical paradigm of these studies involves the assessment of a physiological stimulation on the patients' performance in a unimodal task.

More direct evidence comes from the finding that in right-brain-damaged patients the detection of visual stimuli presented in the left "neglected" side of space is improved by the concomitant presentation of stimuli in another sensory modality (i.e., auditory), depending on the temporal and spatial coincidence of the sensory inputs (Frassinetti, Bolognini, Bottari, Bonora, & Ladavas, 2005; Frassinetti, Pavani, et al., 2002). Differently from the effects of the sensory stimulations discussed above, these effects have been interpreted as based on the integrative contribution of multisensory neurons and neural networks, spared in patients with USN (Stein & Stanford, 2008). In particular, since these crossmodal effects have been found both in patients with sensory deficits (namely, hemianopia) and with visuo-spatial deficits (namely, USN), the underlying mechanisms might involve preserved multisensory integration, with effects similar to those found in neurologically unimpaired participants (Bolognini, Frassinetti, Serino, & Ladavas, 2005; Frassinetti, Bolognini, & Ladavas, 2002). These studies investigated the multisensory integration of multiple sources of information about the same stimulus, i.e. coincident visual and auditory targets. A different form of integration is the *combination* between non-redundant sensory inputs, necessary to form a robust and coherent representation (Ernst & Bulthoff, 2004). The present study aimed specifically at investigating whether multisensory combination is preserved in USN, using the transfer of the illusion from vision to haptics as an index of effective integration.

The present results suggest that multisensory interactions, over or above contralesional unimodal sensory deficits, are preserved in right-brain-damaged patients with USN, and are therefore independent of the presence of spatial deficits. This conclusion is further supported by two findings: first, patients exhibit visual but not, or minor, haptic USN; second, illusory effects are not modality-specific. Interestingly, in the visuo-haptic condition (Figure 2-3), the finding that N+ patients showed a greater overall rightward bias with respect to control participants may be taken as a further evidence of visuo-haptic integration, as if visual USN crossmodally affects tactile bisection. The preserved multisensory interactions reported here do not extend to other haptic processes, such as shape recognition, that was defective in four out of seven N+ patients and in one out of seven N- patients. Overall, shape recognition and crossmodal integration appear to rely on largely independent processes, which, in turn, do not involve the spatial attentional resources defective in USN.

Consequently, results from the present visuo-haptic paradigm do not lend support to the "amorphosynthesis" hypothesis of Denny-Brown and coworkers (1952), even though this account was formulated in rather vague terms. More recently, Brandt et al. (2009) proposed that USN reflects the damage of a multisensory integration center for attention and orientation (MSO) in the temporo-parietal cortex. The MSO is assumed to be bilateral, but the center localized in the right hemisphere is held to be dominant, in that it exerts a greater inhibition of the contralateral left MSO, and a greater excitation of the ipsilateral visual cortex. The net result is that a right-sided temporo-parietal lesion of the MSO brings about visual USN mainly though a reduced activity of the right-sided visual cortex, that is further inhibited by the contralateral visual cortex. This model considers USN mainly as a visual phenomenon and therefore could seem in accordance with the present results at first analysis. However, USN has been also found also in tactile (Smania & Aglioti, 1995; Vallar, Bottini, et al., 1993; Vallar, Bottini, Sterzi, Passerini, & Rusconi, 1991) and auditory (Bisiach, Cornacchia, Sterzi, & Vallar, 1984; Jacquin-Courtois, et al., 2010; Vallar, Guariglia, Nico, & Bisiach, 1995) modalities, in line with the multicomponential nature of the disorder (Vallar, 1998). Also, the multisensory integration features of the MSO center do not appear supported by the present results, which clearly reveal preserved visuo-haptic interactions in right-brain-damaged patients with left USN.

Processing of the Müller-Lyer illusion

The illusory effects are preserved in each sensory condition, and independent of the presence of USN. Preserved leftwards illusory effects have been already demonstrated in the visual modality (Daini, et al., 2002; Vallar & Daini, 2006), in striking contrast with the evidence that the explicit processing of the left-sided portion of the stimuli is defective, as assessed by the verbal report of the left-sided fins (Mattingley, Bradshaw, & Bradshaw, 1995) and by same-different judgments (Olk, Harvey, Dow, & Murphy, 2001; Ro & Rafal, 1996). Here we demonstrate for the first time that also tactile and crossmodal illusory effects are preserved in right-brain-damaged patients with left visual USN. Therefore, the Judd illusion can be a powerful tool in evaluating residual multimodal visual, haptic, and crossmodal processes.

Clinical implications

USN includes both perceptual and premotor components, with the former involving a defective conscious spatial representation of sensory and internally generated events in the contralesional side, the latter an impairment in performing movements in a contralesional direction ("directional hypokinesia"), and a general ipsilesional bias (Vallar & Mancini, 2010). The present study did not aim ad disentangling perceptual and premotor components of USN. This requires specific paradigms that would contrast perception and action in a more or less compatible way. Nevertheless, we believe that the rightward bias we found in visual bisection of baseline stimuli is likely to be mainly perceptual in nature for three main reasons. i) The stimuli (10 and 12 cm in length) fit comfortably into the participants' hand, which was placed over the stimulus at the beginning of the trial, thus minimizing the need of manual exploration. ii) The preserved illusory effects, as assessed by manual line bisection, involve both rightward and leftward shifts, performed by the unaffected right hand. iii) Premotor pathological mechanisms appear to be less frequent determinants of USN that the perceptual deranged components (Gallace, Imbornone, & Vallar, 2008; Vallar & Mancini, 2010).

Finally, the present findings that USN can be absent in the tactile domain, as assessed by bisection tasks, and does not affect crossmodal visuo-haptic interactions, support the importance of including a multimodal assessment in diagnostic batteries, and of setting up multisensory-based rehabilitation approaches rather than the traditional visual ones (Pizzamiglio, Guariglia, Antonucci, & Zoccolotti, 2006;

Schroder, Wist, & Homberg, 2008). The most important functions of multisensory integration are likely to be maximizing information delivered from the different sensory modalities, reducing the variance in the multisensory sensory estimate, in order to increase its reliability (Ernst & Bulthoff, 2004). Left USN may cause a bias in one modality, but the brain can take advantage of other preserved sensory modalities to help correcting it. Treatments that support these processes should be encouraged.

3. Crossmodal processing in Occipito-Temporal cortex: a TMS study of the Judd illusion

[This research has been published in: Mancini, F., Bolognini, N., Bricolo, E., Vallar, G. (2010). Visuo-haptic interactions in the occipito-temporal cortex: a TMS study of the Müller-Lyer illusion. *Journal of Cognitive Neuroscience*, 23:1987-97]

Introduction

In the previous two chapters, I showed that the Judd illusion may occur within and across modalities, and that is independent of the presence of spatial deficits. The present experiment investigated the neural correlates of this crossmodal illusion.

The aim of the present study was to explore the involvement of the (extra-striate) occipital-temporal and parietal areas found to be activated by the visual Müller-Lyer illusion (Weidner & Fink, 2007) in both the unisensory (visual and haptic), and the crossmodal (visuo-haptic) processing of this illusory figure (see Introduction).

To this aim, we used Transcranial Magnetic Stimulation (TMS), which may provide insight into the causal role of particular regions of the cerebral cortex in specific behaviours (Pascual-Leone, Walsh, & Rothwell, 2000). In particular, low frequency repetitive TMS (rTMS) can be used to transiently disrupt ongoing neuronal activity in a localized cortical area, by briefly inducing an electrical field in the tissue below the magnetic coil (Walsh & Cowey, 2000). Here, low-frequency 1 Hz rTMS was applied over the occipito-temporal or superior parietal cortices, either of the right hemisphere or of the left hemisphere, in two groups of neurologically unimpaired participants. These stimulation sites were selected on the basis of previous neuroimaging evidence, showing the involvement of the left and the right lateral occipital cortices, and the right SPC, in the visual processing of the Müller-Lyer illusion (Weidner & Fink, 2007).

In the present study, we investigated the role of the above discussed visual and parietal areas in the processing of the Judd variant of the Müller-Lyer illusion, under three conditions of stimulus presentation: unimodal visual, unimodal haptic, and crossmodal visuo-haptic.

If the occipito-temporal cortex is involved in the processing of the Müller-Lyer illusion independent of the modality of the sensory input, low-frequency rTMS over that region would be expected to interfere with the generation of the illusion, reducing illusory effects in each condition of stimulus presentation.

As for the parietal cortex, an asymmetric effect of rTMS over this region may be predicted. On the basis of the study by Weidner & Fink (2007), rTMS over the right SPC should affect the magnitude of the illusion, at least in the visual modality. Instead, the left SPC should not be functionally relevant for the present task (Weidner & Fink, 2007): therefore it was chosen as a control site for testing the specificity of rTMS stimulation.

Method

Participants

Twenty naïve healthy volunteers (12 females, mean age 25, range 20-40 years) took part in the study. All were right-handed (Oldfield, 1971), and had a normal or corrected-to-normal vision. None of the participants had neurological, psychiatric, or other relevant medical problems or any contraindication to TMS (Rossi, Hallett, Rossini, & Pascual-Leone, 2009). All participants gave written informed consent, and received course credits for their participation. The protocol was carried out in accordance with the ethical standards of the Declaration of Helsinki (BMJ 1991; 302:1194), and was approved by the Ethical Committee of the University of Milano-Bicocca.

Stimuli and apparatus

Stimuli consisted of three types of black 3D plastic figures (Figure 1-1, a-c): two illusory figures (leftward outgoing/rightward ingoing fins, which brought about a leftward displacement of the shaft's perceived centre; leftward ingoing/rightward outgoing fins, which brought about a rightward displacement of the shaft's perceived centre), and one baseline control stimulus (a shaft with vertical ends). For this task, we used only one shaft length (12 cm).

Procedure

Participants were required to bisect with the index finger the horizontal shaft of each stimulus, using either their right or left hand in different groups. Throughout all experimental conditions, participants who were administered a right hemisphere rTMS used the ipsilateral right hand, participants who were administered a left hemisphere rTMS the ipsilateral left hand. The task was performed under three sensory input conditions, given in different blocks: visual, haptic, or visuo-haptic. The experimenter who administered the behavioural tasks was blind to the TMS experimental condition.

The behavioral procedure was identical to the previous studies (Chapters 1-2). The presentation condition (visual, haptic, visuo-haptic) was blocked and counterbalanced across participants and experimental sessions. Approximately 2 min rest breaks were given between each block. Within each block, the three stimulus configurations (baseline neutral; leftward outgoing/rightward ingoing fins; leftward ingoing/rightward outgoing fins) were repeated randomly six times, for a total of 18 trials per block, and 54 per session. Two practice trials, one baseline and one illusory stimulus selected at random, were administered at the beginning of each block (visual, haptic, or visuo-haptic), and not included in the analyses.

The 20 participants were randomly assigned to one of two groups, right- and left-hemisphere stimulated, each group comprising 10 participants. Participants performed the tasks using the hand ipsilateral to the stimulated hemisphere, namely the right hand in the right-hemisphere group, and the left hand in the left-hemisphere group. For each participant, the experimental task was repeated in three different sessions, given in a counterbalanced order across participants, and performed over different days (the inter-session interval was at least 48 hours): a baseline session with no rTMS, and two rTMS sessions (rTMS over the occipito-temporal or the superior parietal cortex). In both rTMS sessions, the 1-Hz stimulation was applied for 20 min before the participant was tested on the task. The duration of the task was about 13 min, with each experimental session lasting about 33 min.

rTMS

Low-frequency (1Hz) off-line rTMS was delivered using a Magstim Super Rapid magnetic stimulator (Magstim, Whitland, UK) and a figure-of-eight coil (7 cm diameter). Off-line rTMS may transiently modulate neural excitability, with the net effect being dependent on stimulation frequency. From a physiological point of view, low frequency rTMS (1Hz) generally results in inhibition of the stimulated area (Chen et al., 1997). Similar effects have been found also in behavioural experiments (e.g., Bolognini, Miniussi, Savazzi, Bricolo, & Maravita, 2009; Knecht, Ellger, Breitenstein, Bernd Ringelstein, & Henningsen, 2003; Merabet et al., 2004; Pascual-Leone, et al., 2000). rTMS was delivered for 20 min at a fixed intensity, 65% of the maximum output of the stimulator. These parameters were compatible with the aim of the present experiment, which was to interfere with the normal functioning of stimulated areas (Bolognini & Maravita, 2007; Bolognini, et al., 2009; Boroojerdi, Prager, Muellbacher, & Cohen, 2000; Cappelletti, Barth, Fregni, Spelke, & Pascual-Leone, 2007; I. M. Harris & Miniussi, 2003).

The targeted stimulation sites were the occipito-temporal and the superior parietal cortices, using the stereotaxic coordinates of Weidner & Fink (2007) in the right hemisphere in one group of participants, and in the left hemisphere in a second group (see Figure 3-1). The targeted areas were localized using the SofTaxic Evolution navigator system (Version 1.0, http://www.emsmedical.net). This system allows the reconstruction of the cerebral cortex in Talairach coordinates, with an accuracy of ≈1 cm, on the basis of digitized skull landmarks (nasion, inion, and two preauricular points), and other 30 uniformly distributed points that are mapped on the scalp (3D Fastrak Polhemus digitizer). An estimation of the cerebral volume of each participant was obtained by ‘Point-based Warping’ to an MRI template and a 3D virtual reconstruction based on the points recorded from the subject's scalp. Following this procedure, the lateral occipital cortex was localized for each participant with Talairach coordinates (Talairach & Tournoux, 1988) corresponding on average to X= +/-36, Y= -76, Z= -1 (Weidner & Fink, 2007); the right/left SPC corresponded on average to Talairach coordinates X= +/-14, Y= -61, Z= 66 (Weidner & Fink, 2007). The choice of these stimulation sites and coordinates (original Montreal Neurological Institute – MNI - coordinates were converted in Talairach coordinates using SPM5) was based upon a previous fMRI study (Weidner & Fink, 2007), as discussed above. On each session, the correct site was marked on the participant's cap; the coil was positioned on that site, and was supported and held in place by a mechanical device.

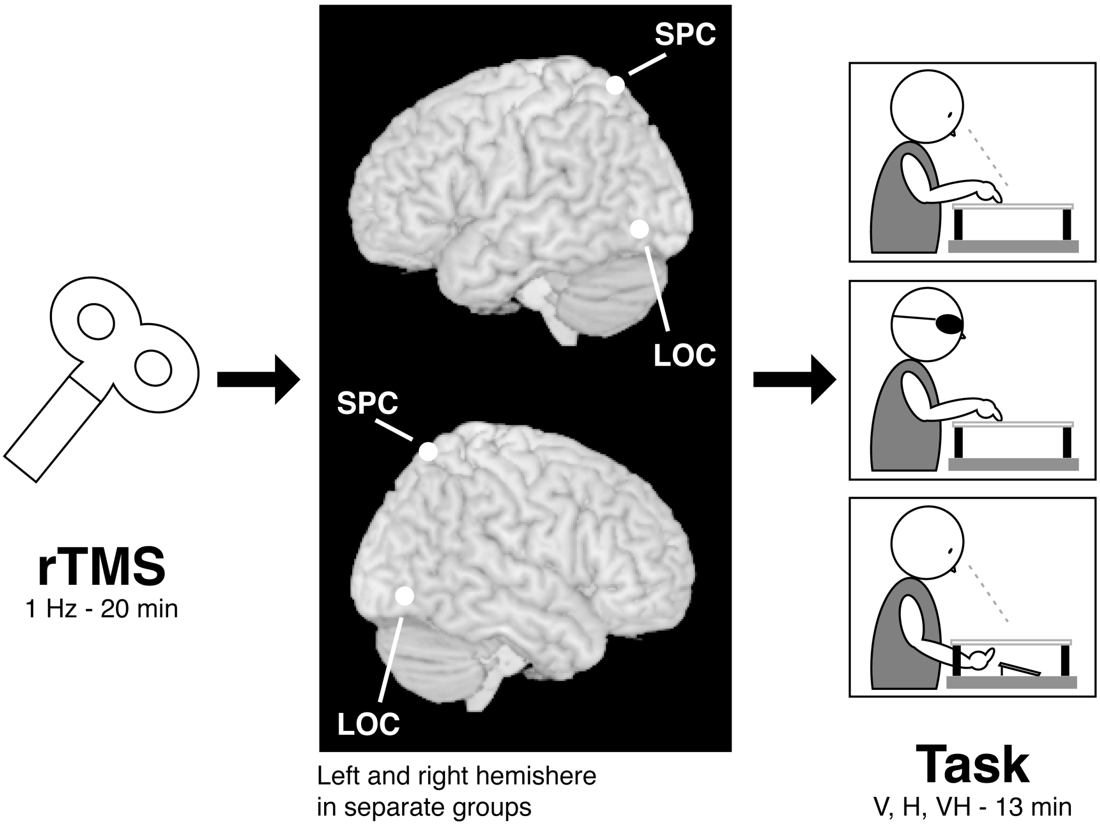


Figure 3-1. ***Procedure*****.** **Repetitive low-frequency TMS was administered to the occipito-temporal (at the level of the LOC) and the SPC, separately for the right and the left hemisphere in two different groups of participants. The experimental task was administered and performed with the hand ipsilateral to the stimulated hemisphere. The task was given alone ('no rTMS' condition), and after 20 minutes of rTMS.**

Data analysis

The bisection error (mm) was computed as the difference between the subjective mid-point of the horizontal shaft, marked by each participant, and its objective centre; positive values indicated a rightward displacement, while negative values indicated a leftward displacement from the objective centre of the line.

Preliminarily, we assessed whether the participant's response was influenced by the hand used to perform the task, by conducting an analysis on the corrected illusion errors in each presentation condition, in the 'no rTMS' session only (i. e., for each participant the average bisection error for each of the two illusory stimuli minus the baseline average bisection error in the 'no rTMS' session). A repeated-measures analysis of variance (ANOVA) was performed with two within-subjects main factors (*Stimulus*: leftward ingoing/rightward outgoing, leftward outgoing/rightward ingoing; *Modality*: visual, haptic, visuo-haptic), and one between-subjects factor (*Hand*: left, right).

The effects of rTMS stimulation on illusion magnitude were then assessed. An illusion magnitude score was computed as follows, individually for each participant and experimental condition: $I = (\text{error}_{\text{right illusion}} - \text{error}_{\text{left illusion}})$, namely: the difference between the bisection errors (mm) in the leftward ingoing/rightward outgoing and the leftward outgoing/rightward ingoing stimuli. Positive values indicated that the illusory effect was present (i. e., the leftward ingoing/rightward outgoing stimulus had been bisected more rightwards than the leftward outgoing/rightward ingoing stimulus). Negative values indicated shifts in a direction opposite to that of the expected illusory effect (i.e., the leftward ingoing/rightward outgoing stimulus had been bisected more leftwards than the leftward outgoing/rightward ingoing stimulus).

Finally, a 0 score marked a null illusory effect (i.e., the leftward ingoing/rightward outgoing stimulus had been bisected at the same point as the leftward outgoing/rightward ingoing one). The illusion scores were submitted into a repeated-measures ANOVA with two within-subjects main factors (*Session*: no rTMS; rTMS: occipito-temporal, superior parietal; *Modality*: visual, haptic, visuo-haptic), and one between-subjects factor (*Hemisphere*/*Hand*: left, right).

Finally, the specificity of the effect of rTMS on illusion processing was assessed by a similar ANOVA performed on the average bisection errors of the baseline stimulus only (vertical ends).

Results

Crossmodal Judd illusion

As shown in Figure 3-2, the expected (see Mancini, et al., 2010) illusory effects were present in the 'no rTMS' condition; in every modality, stimuli with leftward outgoing/rightward ingoing fins brought about a leftward error, and stimuli with leftward ingoing/rightward outgoing fins a rightward error. The illusory effects were slightly reduced under the crossmodal visuo-haptic presentation, as compared with the unimodal visual and haptic conditions, in line with a previous study using a similar procedure (Mancini, et al., 2010).

The analysis of variance performed on the corrected bisection errors of the illusory stimuli in the 'no rTMS' condition (i. e., illusion – baseline) showed that the main factors of stimulus [$F(1,18)= 189.66$, $p< 0.001$, $\eta^2= 0.76$], and of modality [$F(2,36)= 4.78$, $p= 0.014$, $\eta^2= 0.01$] were significant, as well as their interaction

[F(2,36)= 9.26, *p*= 0.001, η^2= 0.07]. Importantly, the main factor of hand was not significant [F(1,18)= 2.28, *p*= 0.15, η^2= 0.09], as well as its interactions with the stimulus [F(1,18)= 1.21, *p*= 0.28, η^2= 0.005], and the modality [F(2,36)= 1.87, *p*= 0.17, η^2= 0.001] main factors. The hand by stimulus by modality interaction was not significant (F< 1). Bonferroni post-hoc comparisons were performed to explore the stimulus by modality interaction (see Figure 3-2). For the stimulus with leftward outgoing/rightward ingoing fins, the differences between the visual and haptic (*p*= 0.048), and between the haptic and visuo-haptic presentation conditions (*p*< .001) were significant; for the stimulus with leftward ingoing/rightward outgoing fins only the difference between the visual and visuo-haptic modalities attained the significance level (*p*= 0.024).

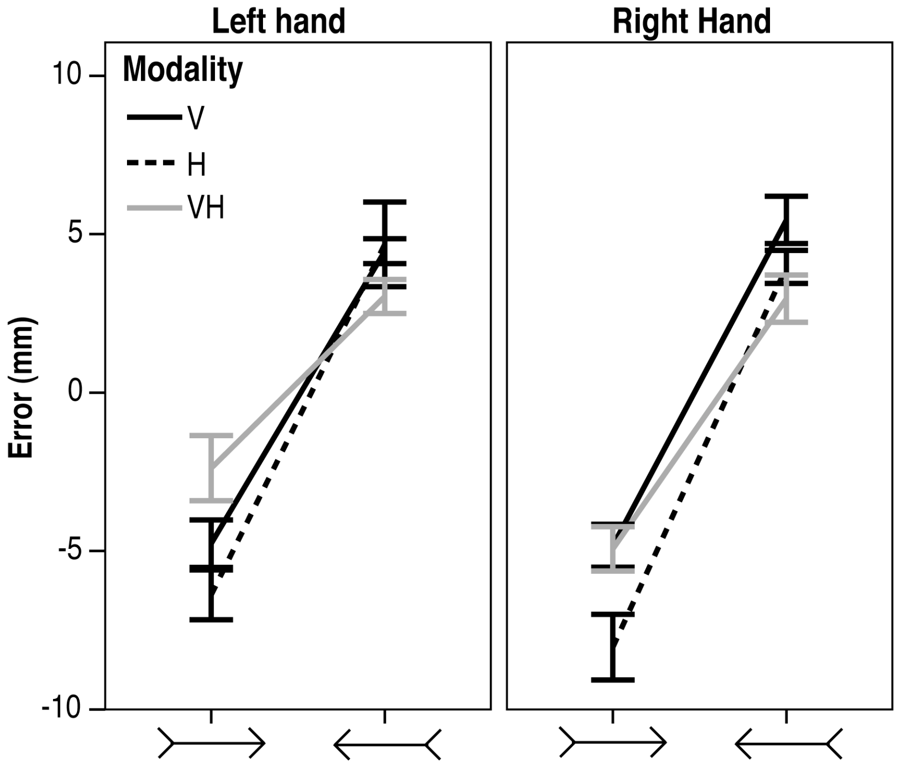


Figure 3-2. ***Results: Judd illusion in the 'no rTMS' session.*** **Mean bisection error in mm (SE), adjusted for the baseline error, by Modality (Visual, V; Haptic, H; Visuo-Haptic, VH), Stimulus type (leftward outgoing/rightward ingoing, and leftward ingoing/rightward outgoing fins), and Hand (left, right). Negative/positive score: leftward/rightward error.**

Effect of rTMS

The effects of rTMS on the illusion magnitude (i.e., right illusion – left illusion) are shown in Figure 3-3.

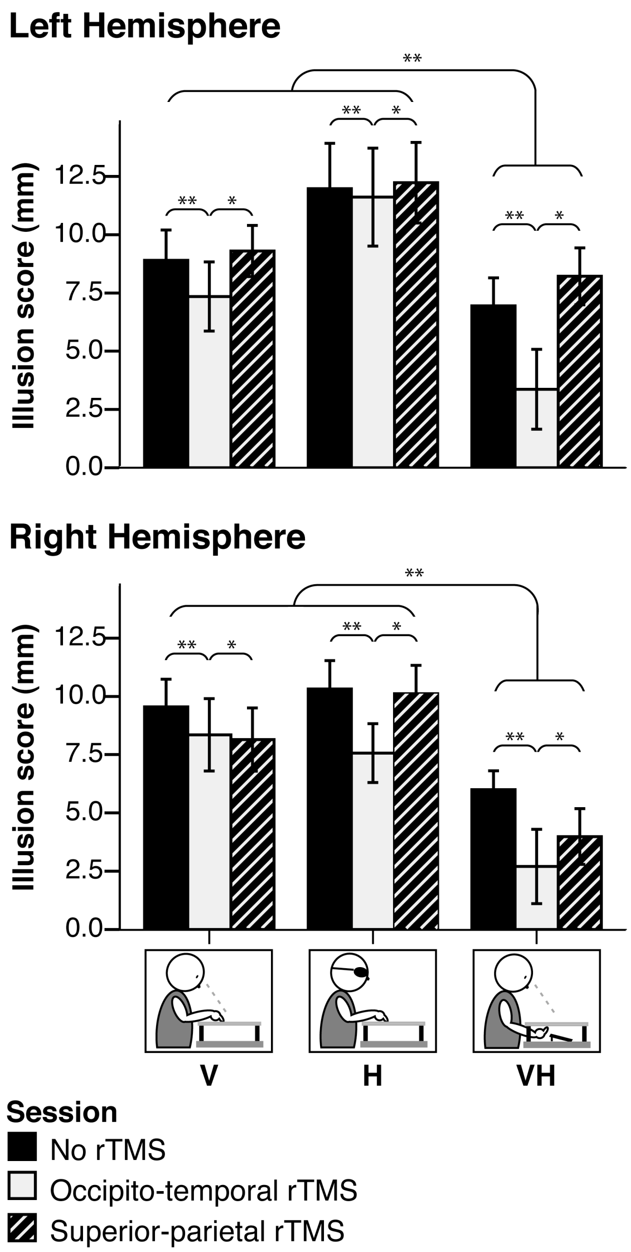


Figure 3-3. ***Results: Judd illusion after rTMS interference.*** **Mean illusion scores in mm (SE) by Modality (Visual, V; Haptic, H; Visuo-Haptic, VH), Session (no rTMS; rTMS: occipito-temporal, superior parietal), and group (Left Hemisphere/Hand; Right Hemisphere/Hand). The asterisks indicate a significant difference between conditions: * $p < 0.05$, ** $p < 0.01$.**

Overall, the illusion scores decreased after occipito-temporal rTMS, but not after superior parietal rTMS. The analysis of variance on the illusion scores revealed significant effects of the main factors of session [F(2,36)= 9.26, p= 0.001, η^2= 0.07], and of modality [F(2,36)= 20.61, p< 0.0001, η^2= 0.31]. Crucially, the interaction between session and modality was not significant [F(4,72)= 1.20, p= 0.32, η^2= 0.01]. The main effect of hemisphere/hand was not significant [F(1,18)= 1.53, p= 0.23, η^2= 0.01], as well as its interactions with the main factors of session (F< 1), and modality [F(2,36)= 1.25, p= 0.30, η^2= 0.02]. The hemisphere/hand by session by modality interaction was not significant [F(4,72)= 1.71, p= 0.157, η^2= 0.01].

Bonferroni post-hoc comparisons on the session factor showed a significant difference between the 'no rTMS' condition and the occipito-temporal rTMS (p= 0.001), with the illusion scores being decreased after occipito-temporal stimulation (mean 6.83, SEM 0.94) with respect to the 'no rTMS' condition (mean 9.32, SEM 0.68). Conversely, the difference between the baseline 'no rTMS' condition and superior parietal stimulation (mean 8.67, SEM 0.67) was not significant (p= 0.911), indicating a null effect of superior parietal rTMS on the illusion magnitude. The difference between the superior parietal and occipito-temporal sites of stimulation was also significant (p= 0.024), with the illusion scores after occipital-temporal rTMS being lower than after superior parietal rTMS. Thus, results highlight an involvement of the bilateral occipital-temporal cortex in the processing of the visual, haptic, and visuo-haptic illusion, while both the right and the left SPC seem to play no relevant role in any presentation condition[1].

---

[1] An inspection of the data (Figure 3-3) may suggest that in the visual (and the visuo-haptic) conditions the illusion scores were reduced also after right SPC rTMS, in line with the study by Weidner and Fink Weidner, R., & Fink, G. R. (2007). The neural mechanisms underlying the Müller-Lyer illusion and its interaction with visuospatial judgments. *Cerebral Cortex, 17*, 878-884.. Therefore, in the right hemisphere/hand group, we directly compared, by one-tailed t-tests, the illusion scores in the 'no rTMS' and in the SPC rTMS sessions, in both the visual and the visuo-haptic presentation conditions; no significant differences were found, for both the visual (t_9= 1.660), and the visuo-haptic (t_9= 1.391) modalities.

Finally, Bonferroni post-hoc comparisons on the modality factor showed that the illusory effects were comparable in size ($p = 0.22$) in vision (mean 8.78 SEM 0.78), and in touch (mean 10.77, SEM 0.99), but reduced in the visuo-haptic condition (mean 5.26, SEM 0.77), as compared to both the unimodal visual and haptic presentation conditions (both $p < 0.0001$). The reduced illusory effects in the visuo-haptic condition, as compared with the two unimodal conditions, confirm previously reported evidence (Mancini, et al., 2010).

Specificity of the involvement of the occipito-temporal cortex in the crossmodal Judd illusion

In order to control for the specificity of the effect of rTMS on the illusion, and consequently to rule out an interpretation in terms of interference with general object-representation processes, an ANOVA on the bisection errors of the baseline stimulus alone (vertical ends) was performed. Table III shows the average bisection error scores for the baseline non-illusory stimulus in the three TMS conditions, and in the three input modalities. Importantly, the main factors of session, modality, and their interaction were not significant (all F< 1). However, the between-subjects factor hemisphere/hand was significant [$F(1,18) = 4.44$, $p = 0.049$, $\eta^2 = 0.19$], as the stimulus was bisected more rightwards with the left (mean 0.74, SEM 0.71), than with the right hand (mean -1.39, SEM 0.71). The hemisphere/hand by modality interaction was significant [$F(2,36) = 19.63$, $p < 0.0001$, $\eta^2 = 0.38$]. Post-hoc pairwise comparisons showed a significant difference between the visuo-haptic and the two unimodal presentation conditions, for each hemisphere/hand ($p < 0.05$); the difference between the two unimodal conditions was not significant. For the left hand, the baseline stimulus was bisected rightwards in the visuo-haptic (mean 4.21, SEM 1.49), and leftwards in the visual (mean -1.02, SEM 0.38), and haptic (mean -0.95, SEM 1.12) conditions. On the contrary, for the right hand, the baseline stimulus was bisected leftwards in the visuo-haptic (mean -5.30, SEM 1.49), and rightwards in the visual (mean 0.68, SEM 0.38), and haptic (mean 0.47, SEM 1.12) conditions. Finally, the hemisphere/hand by session, and hemisphere/hand by session by modality interactions were not significant (all F< 1). Overall, these results indicate that the effects of occipito-temporal rTMS were specific for the illusory stimuli.

Table III. Baseline stimulus: mean (SE) bisection error (mm) by Modality (Visual, V; Haptic, H; Visuo-Haptic, VH), Session (no rTMS; rTMS: occipito-temporal, superior parietal), and group (Left Hemisphere/Hand; Right Hemisphere/Hand). Negative/positive score: leftward/rightward error.

Modality	V	H	VH
Left Hemisphere/Hand			
No rTMS	-1.20 (0.51)	-1.27 (1.85)	3.82 (1.69)
occipito-temporal	-0.42 (0.59)	-0.52 (1.56)	4.20 (2.24)
superior parietal	-1.45 (0.57)	-1.07 (1.19)	4.60 (2.41)
Right Hemisphere/Hand			
No rTMS	0.22 (0.31)	0.98 (0.71)	-4.78 (0.97)
occipito-temporal	0.82 (0.27)	-0.37 (1.69)	-5.60 (1.45)
superior parietal	1.00 (0.41)	0.78 (0.88)	-5.52 (1.07)

Discussion

The present study investigated the neural correlates of the Judd illusion, contrasting for the first time visual, haptic, and crossmodal illusory effects in a manual bisection task. We found that rTMS over either the left or the right occipito-temporal cortex, at the level of the LOC, interferes with the processing of the unisensory, visual and haptic, and the crossmodal visuo-haptic illusion in a similar fashion. Conversely, rTMS administered over either the left or the right SPC does not affect illusion scores in any modality. Overall, these findings suggest that the left and right occipito-temporal cortices are causally involved in the processing of the Judd illusion. We show that this visual area, traditionally considered as modality-specific (Grill-Spector, 2003), plays a multisensory role (Beauchamp, 2005; Lacey, et al., 2009), being causally implicated not only in the visual (Weidner, et al., 2010; Weidner & Fink, 2007), but also in the haptic and crossmodal visuo-haptic processing of the illusion.

The main finding of the study is that both the left and the right occipito-temporal cortices are involved in the processing of the Judd variant of the Müller-Lyer illusion. The rTMS interference with the processing of the illusion is not modality-specific, supporting the hypothesis of a multisensory representation of the Müller-Lyer illusion in this region. As far as the visual modality is concerned, these findings are in line with the results of previous neuroimaging studies that used other variants of the visual Müller-Lyer illusion (Weidner, et al., 2010; Weidner & Fink, 2007). Here we demonstrate the causal bilateral involvement of the occipito-temporal cortex in processing the illusion across different sensory modalities, namely: not only visual, but also haptic and crossmodal visuo-haptic.

In this study the visual and haptic Judd illusions are equally powerful, whereas the crossmodal illusory effects are smaller than the unimodal effects (marginal differences emerged from the analysis in the 'no rTMS' condition), in line with recent evidence (Mancini, et al., 2010). The decrement of the illusion in the crossmodal condition has been considered the likely marker of the multisensory integration of the visual and haptic components of the stimuli (see Chapter 1 and General Discussion). Finally, the occipito-temporal rTMS interference was comparable among the three presentation conditions, in line with the hypothesis of shared processes in the two assessed modalities.

One issue might be relevant to the interpretation of our data. We aimed at stimulating the lateral occipital cortex, which was activated by the visual Müller-Lyer illusion in a previous study (Weidner & Fink, 2007). Other areas within the occipito-temporal cortex might be also relevant in the processing of the crossmodal variant of the illusion, such as the LOtv, which is activated by haptic shape processing (Amedi, et al., 2002; Amedi, et al., 2001). LOtv is localised slightly more laterally (Talairach coordinates, mean ± SD, –45 ± 5, –62 ± 6, –9 ± 3) (Amedi, et al., 2001) than the region targeted in the present experiment. The use of group-based coordinates for coil positioning might have reduced the spatial accuracy of our rTMS effects (Sack et al., 2009; Sparing, Buelte, Meister, Paus, & Fink, 2008), hence resulting in the stimulation of nearby regions of the occipito-temporal cortex, such as LOtv. fMRI-guided TMS studies may provide additional information concerning the selective involvement of different regions of the occipito-temporal cortex (i.e., LOC vs. LOtv) in the unimodal and crossmodal processing of the illusion.

In addition to the lateral occipital cortex, in the study by Weidner and Fink (2007) the visual Müller-Lyer illusion activates also the right SPC. This activation may reflect spatial processing, rather than the illusory effects *per se*, possibly the integration and updating of a size-invariant representation of shape, which is illusory biased, into a spatial reference frame (Weidner & Fink, 2007). In the study presented in Chapter 3, we did not find any significant involvement of the SPC in the processing of the illusion, regardless of stimulus modality. Our rTMS study differs from the fMRI experiment by Weidner and Fink (2007) in a number of important respects, that may have influenced the results: Weidner and Fink (2007) used the Brentano variant of the Müller-Lyer illusion and a perceptual judgment task; we used the Judd illusion and a manual bisection task. Importantly, however, there is a convergence as to the cerebral area responsible of the illusory effects in the visual modality, namely the occipito-temporal cortex.

Moreover, in line with our null effect of the superior parietal stimulation, the previous neuropsychological study shows that patients with right parietal cortical lesions exhibit preserved unimodal and crossmodal illusory effects. The illusory effects occur independently of the presence of spatial and attentional deficits, like unilateral spatial neglect. However, when the patients' right-sided posterior parietal lesions extend to the occipital regions, patients show impaired visual illusory effects (Daini, et al., 2002). These findings in brain-damaged patients are consistent with the current results that the stimulation of the parietal cortex alone does not elicit significant effects.

It should also be noted that the different physiology of the cortical regions targeted in the present study (i.e., gyral/sulcal geometry with respect to the plane of TMS pulse propagation) could make them not equally susceptible to rTMS interference (Walsh & Cowey, 2000; Wassermann et al., 2008). For all these reasons, the null effect of right superior parietal stimulation should be interpreted with caution.

Finally, other multisensory regions in the posterior parietal cortex, as the intra-parietal sulcus (IPS, Peltier, et al., 2007), might play a role in the processing of the illusion.

The bisection of the baseline stimulus with vertical ends is not affected by any condition of TMS stimulation, indicating that the TMS interference over the occipital-temporal cortex is specific for the illusion. Particularly, right superior parietal rTMS does not impair bisection. There is evidence that TMS interference over the posterior parietal cortex, of which the SPC is a component part, may affect line bisection performance, eliciting a 'neglect-like' bias in healthy participants (Fierro et al., 2000; Oliveri & Vallar, 2009, right supramarginal gyrus). Furthermore, neuroimaging activation studies indicate a role of the entire posterior parietal cortex (both the inferior and the superior parietal lobule) in bisection tasks (Ciçek, Deouell, & Knight; Fink et al., 2000; Fink et al., 2003). However, neuropsychological evidence indicates that damage to the SPC is associated with optic ataxia, rather than with unilateral spatial neglect, of which the rightward bias in line bisection is one of the main manifestations (Coulthard, Parton, & Husain, 2006). Finally, anatomo-clinical correlation studies in right-brain-damaged patients with spatial neglect indicate that the rightward bias in line bisection is associated with posterior lesions, specifically at the junction between the right middle temporal and the middle occipital gyri (Rorden, Fruhmann Berger, & Karnath, 2006), and lesions to the inferior parietal lobule (Verdon, Schwartz, Lovblad, Hauert, & Vuilleumier, 2010).

In summary, TMS and neuroimaging studies suggest an involvement of the posterior parietal cortex (both the inferior and the superior parietal lobule, and the IPS) in line bisection tasks. The available evidence from brain-damaged patients highlights the role of the inferior parietal lobule, in line with the present finding that rTMS interference with the SPC does not affect line bisection performance.

Visual modulation of pain

4. The visually-induced analgesia

[This research has been published in: Mancini, F., Longo, M. R., Kammers, M., Haggard, P. (2011) Visual distortion of body size modulates pain perception. *Psychological Science*, 22, 325-330]

Introduction

Pain can be caused by peripheral stimuli (e.g., burning one's fingers), by chronic bodily states (e.g., back pain), or by mechanisms entirely within the brain (e.g., phantom limb pain). The pain level generated by a peripheral stimulus varies dramatically across individuals and across situations, so the subjective aspect of pain cannot be ignored (Eisenberger & Lieberman, 2004; Melzack & Wall, 1965).

Simple perceptual factors can influence pain. For example, just looking at one's own body reduces both reported intensity and neural responses to painful stimuli, compared to viewing a neutral object (Longo, et al., 2009). This visually-induced analgesia demonstrates that acute pain can be modulated by specific visual contexts. This raises the possibility that manipulating the visual appearance of the body might further modulate pain. Indeed, visually-specified size of the body may affect levels of chronic pain in certain clinical populations (Moseley, et al., 2008; Ramachandran, Brang, & McGeoch, 2009). In the present study, we investigated whether manipulating the visual size of the body modulates experimentally-induced pain in healthy participants.

Previous studies of crossmodal pain modulation generally relied on pain intensity ratings. Such ratings reflect a combination of sensory-discriminative and post-perceptual affective-motivational components of pain (Auvray, et al., 2010; Melzack & Casey, 1968). We used contact heat-pain thresholds as a more purely sensory measure of pain perception (Yarnitsky, Sprecher, Zaslansky, & Hemli, 1995). Heat-pain thresholds were measured while participants viewed their own hand or a neutral object, which appeared either visually reduced, at real size, or enlarged.

Method

Participants

Eighteen healthy right-handed volunteers (11 females, mean age 27.1, SD 4.1) participated for payment. Procedures were approved by the local ethics committee.

Thermal stimuli

Thermal stimulation of the dorsum of the left hand, just proximal to the knuckle of the index finger (first metacarpal space), was delivered by a 13 mm diameter Peltier-type thermode (NTE-2A, Physitemp Instruments Inc). The probe was held by a mechanical arm to control contact pressure.

Thresholds for heat pain were estimated with the method of limits (Yarnitsky, et al., 1995). The probe temperature was increased from normal skin temperature (constant 32°C, maintained for 20 sec) at 2°C/sec. Participants pressed a foot pedal with their right foot when they first perceived the stimulation as being painful. For safety, maximum temperature was limited to 50°C.

Procedure

We used the mirror box technique (Ramachandran, et al., 1995) to induce the impression that the participant's right hand, which was reflected in a mirror aligned with their sagittal plane, was actually their stimulated left hand. Participants sat at a table, with the left hand behind the mirror and the right hand in front. The tips of each index finger were 20 cm from the mirror. One group of participants (n = 9) looked into the mirror towards their left hand, and saw the reflection of their right hand, appearing where they felt their left hand to be. For a second group (n = 9), the right hand was occluded by a box, and participants saw the reflection of an approximately hand-sized wooden block placed over it (approx. 3 cm over the hand). The viewed size of the hand/object was manipulated by exchanging three mirrors (Figure 4-1): a convex mirror giving 2x reduction (0.5x magnification), a normal mirror, and a concave mirror giving 2x magnification. The different visual sizes (reduced, real size, enlarged) were tested in randomised blocks. Vision of the hand and object were tested in separate groups of participants, to avoid problems of pain habituation/sensitization (Green, 2004).

Participants were first familiarised with contact heat by stimulating a skin region not used in the experiment (the centre of the hand dorsum). Next, in each of the three blocks, participants were instructed to look into the mirror and fixate the hand/object continuously. After 10 min of fixation, four heat-pain staircase measurements were obtained from the left hand at 1 min intervals. A fake thermode probe was simultaneously applied to the right hand or to the neutral object, at the location corresponding to where the stimulation was felt on the left hand, so that participants always saw an object touching the hand or block, corresponding to the location where they felt the heat. Three minutes of rest were allowed between blocks.

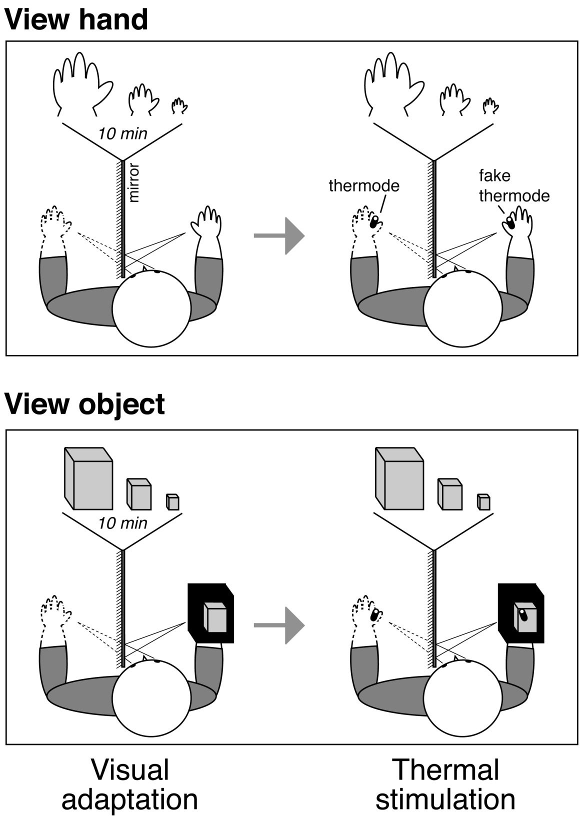
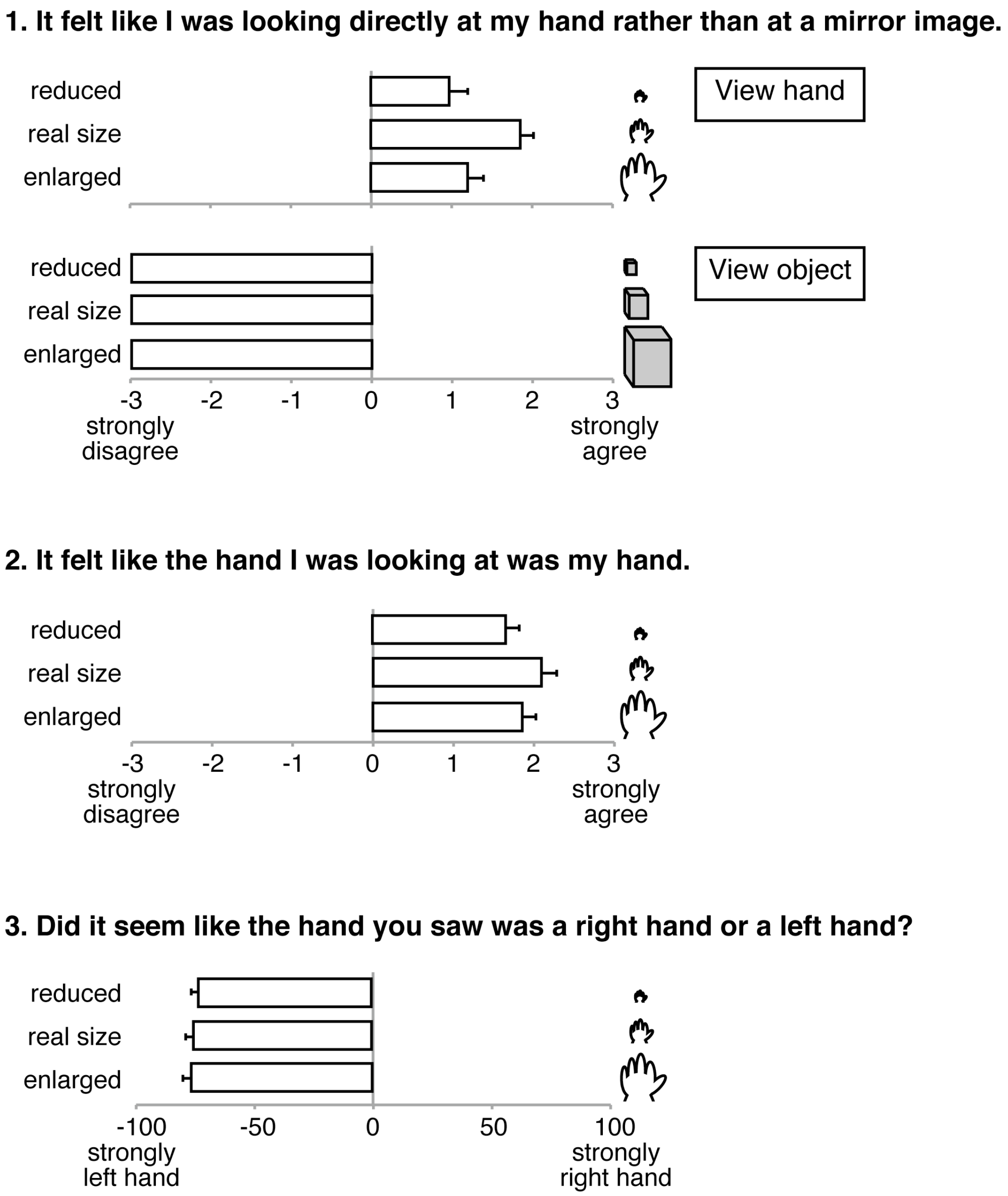


Figure 4-1. ***Stimuli, apparatus and procedure.*** **Participants gazed towards their left hand. A mirror aligned with the mid-sagittal plane ensured that they viewed either their right hand (which appeared to be their left) or a neutral object in front of the mirror. After a 10 minute adaptation phase, a thermode probe applied gradually-increasing contact heat to the left hand. To avoid perceptual conflict, a fake thermode probe was simultaneously applied to the right hand, or to the object, at the location corresponding to where the stimulation was felt on the left hand. Participants pressed a foot pedal when the left hand stimulation became painful.**

Three additional measures were collected.

First, we administered an established questionnaire (Longo, et al., 2009) to check that the mirror box indeed induced a compelling visual illusion of viewing their left hand directly (Figure 4-2).


1. It felt like I was looking directly at my hand rather than at a mirror image.

2. It felt like the hand I was looking at was my hand.

3. Did it seem like the hand you saw was a right hand or a left hand?

Figure 4-2. ***Mirror box illusion questionnaire.*** **Item 1 was given in both the view hand and object conditions, items 2 and 3 only in the hand condition. For items 1 and 2, participants rated their agreement using a 7-point Likert scale, +3 indicating "strongly agree" and -3 "strongly disagree". Item 3 required dichotomous responses, after which participants indicated the strength of the feeling that the hand was a right/left hand using a 0-100 scale. Right hand responses were coded positively, left hand responses negatively, yielding scores between -100 (strong left hand) to 100 (strong right hand). Error bars indicate +/- 1 SEM.**

Second, to check that visual manipulations of hand size were effective, participants judged the size they felt their left hand was, using a specially-designed apparatus. Participants adjusted the distance between two visual points to match the distance between the index and little finger knuckles of their left hand, immediately before and after each block.

Finally, to assess whether pain thresholds could have changed due to changes in skin temperature, an infrared thermometer was used to measure skin temperature immediately before and after viewing the hand/object.

Results

Questionnaire responses

Agreement or disagreement with each questionnaire item (Figure 4-2) was tested by comparing the overall mean score with 0 using t tests. The mirrors produced the illusion of viewing one's own left hand when viewing the right hand (item 1: $t_8 = 3.41$, $p = 0.009$; item 2: $t_8 = 5.13$, $p = 0.001$; item 3: $t_8 = -12.71$, $p < 0.001$) but not the object (all ps > 0.50).

ANOVAs on each questionnaire item tested effects of visual size. None showed significant visual size effects (item 1: $F_{2,30} = 1.27$, $p = 0.297$, $\eta_p^2 = 0.08$; items 2 and 3: $F < 1$), indicating that visual size manipulation did not influence the illusion of viewing one's hand.

Hand size estimates

Differences in hand size estimates before and after visual exposure were analysed using repeated measure ANOVA with a between-subjects factor (*visual context*: hand, object) and a within-subjects factor (*visual size*: reduced, real size, enlarged), using Greenhouse–Geisser corrections where deviation from sphericity was observed. The ANOVA showed no main effect of visual context ($F < 1$), but a significant effect of size ($F_{2,30}$ = 8.78, p = 0.003, η_p^2 = 0.35), and a significant interaction ($F_{2,30}$ = 9.95, p = 0.002, η_p^2 = 0.38) (Figure 4-3, left panel). Simple effects showed that this interaction arose because visual size distortions influenced represented hand size when viewing the hand ($F_{2,16}$ = 13.23, $p < 0.001$, η_p^2 = 0.62) but not the object ($F < 1$). Bonferroni-corrected follow-up testing in the view-hand condition confirmed that seeing the hand as bigger increased represented hand size (p = 0.003), while seeing the hand as smaller shrank it (p = 0.002), relative to the control condition (actual size). All comparisons between visual size conditions when viewing the object were non-significant (ps > 0.30). These results indicate that the size at which the body was viewed influenced representations of actual body size.

Pain thresholds

We first investigated whether viewing the hand at natural size produced a visual analgesia similar to that reported previously (Longo et al., 2009). We confirmed that viewing the hand via the non-distorting mirror indeed increased heat-pain thresholds (mean 44.90°C, SEM 0.98), relative to the view object condition (mean 41.69°C, SEM 1.07) (t_{16} = 2.14, p = 0.048).

We then explored the effects of visual size of the hand and object. ANOVA revealed significant main effects of both visual context ($F_{1,16}$ = 5.20, p = 0.037, η_p^2 = 0.24), and visual size ($F_{2,32}$ = 4.16, p = 0.025, η_p^2 = 0.21) on heat pain thresholds. Crucially, there was a significant interaction between these two factors ($F_{2,32}$ = 4.58, p = 0.018, η_p^2 = 0.22). Simple effects analyses showed that visual size modulated pain thresholds when participants saw their hand ($F_{2,16}$ = 10.18, p = 0.001, η_p^2 = 0.56). Bonferroni follow-up tests showed that this arose because visual enlargement of size increased the analgesic effect of viewing the body (p = 0.032), whereas visual reduction decreased the analgesic effect (*p* = 0.043), relative to the real size condition (Figure 4-3, right panel). In contrast, simple effects showed that visual size of the object had no effect on pain thresholds (*F* < 1).

Because pain thresholds depend on baseline skin temperature, we also investigated whether the different visual conditions induced changes in skin temperature, and thus influenced pain thresholds indirectly. However, no significant main effects or interaction were found (*F* < 1).

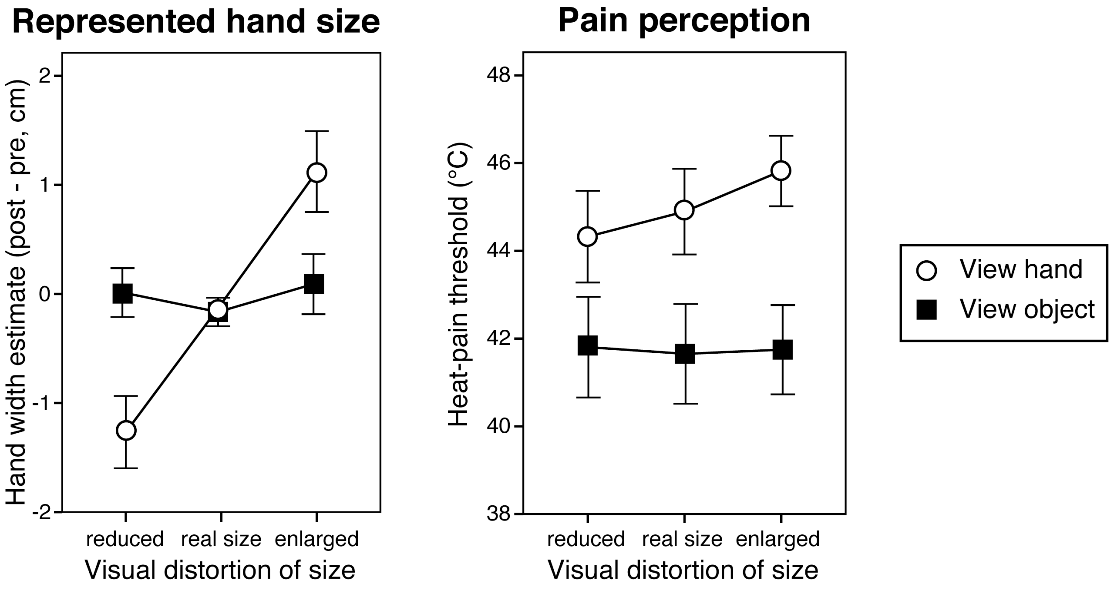


Figure 4-3. Mean changes in hand width estimates (post – pre visual exposure, cm) and heat-pain thresholds (°C), as a function of visual context (hand, object) and visual distortion (reduced, real size, enlarged). Error bars indicate +/- 1 SE.

Discussion

This study yielded three main findings: (1) Viewing the body versus viewing a neutral object is analgesic, inducing specific effects on sensory-discriminative processing of pain. Contact heat-pain thresholds are increased by an average 3.2°C.

(2) The size at which the hand is *viewed* alters the size the hand is *represented*. (3) Viewing an enlarged hand increases the analgesic effect of seeing the hand, whereas viewing a reduced hand decreases it. In other words, a stimulus needs to be hotter to feel painful when applied to a body part that is seen as bigger than its actual size. Conversely, a stimulus need be less warm to produce pain when applied to a body part that is viewed as smaller than actual size. Our findings cannot be explained by changes in skin temperature or scale-dependence of the mirror box illusion that we used to alternate vision of hand or object at a single spatial location.

Interestingly, a previous study of body size effects on chronic pain reported an apparently opposite effect to ours. Moseley and coworkers (2008) reported that chronic pain ratings and swelling evoked by movement in patients with complex regional pain syndrome (CRPS) increased when viewing the limb enlarged, and decreased when viewing the limb reduced. However, different neurophysiological mechanisms underlie acute and chronic pain (Apkarian, Bushnell, Treede, & Zubieta, 2005; Moseley, Sim, Henry, & Souvlis, 2005). The links between the two mechanisms may be inhibitory, with acute pain inhibiting chronic pain (Baliki, Geha, Fields, & Apkarian, 2010). Further, different therapies relieve the two forms of pain (Chou & Huffman, 2007; Wiffen, McQuay, Edwards, & Moore, 2005). Importantly, CRPS alters the territory of the affected limb in somatosensory brain regions (Maihofner, Handwerker, Neundorfer, & Birklein, 2003), and involves a complex pattern of disorders, including impaired body image and sense of ownership (Lewis, Kersten, McCabe, McPherson, & Blake, 2007). These physiological and psychological aspects of CRPS may mediate the visual size effects.

5. EEG oscillations related to visually-induced analgesia

[This research was done in collaboration with: Matthew Longo, Elisa Canzoneri, Giuseppe Vallar and Patrick Haggard]

Introduction

Viewing the body reduces pain but the neural basis of this analgesic effect is not clear yet. It is known that viewing the body can also influence tactile processing in early somatosensory cortex, possibly increasing intracortical inhibition (Cardini, et al., 2011; Fiorio & Haggard, 2005). This suggests that similar mechanisms could occur during visually-induced analgesia, modulating sensory pain-related activity.

We studied the neural correlates of multisensory modulation of pain by investigating modulations of induced EEG oscillations. Event-related desynchronization (ERD) and synchronization (ERS) are generated by reciprocal coupling between excitatory and inhibitory neurons (Hari & Salmelin, 1997). Crucially, these oscillations reflect phases of low vs. high excitability.

Relative reductions in alpha and beta power, reflecting desynchronisation of neural activity, are linked to increases in cortical excitability (Neuper, Wortz, & Pfurtscheller, 2006). Specifically, nociception is associated with suppression of alpha and beta rhythms in contralateral somatosensory cortex, indicating activation of these regions by nociceptive inputs (e.g., Crone et al., 1998; Mouraux, Guerit, & Plaghki, 2003; Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2006b). Conversely, synchronised (alpha) activity is interpreted to reflect either the idling (Pfurtscheller & Lopes da Silva, 1999) or relative inhibition of sensorimotor systems (Klimesch, Sauseng, & Hanslmayr, 2007). GABA agonists such as benzodiazepines robustly increase beta-band EEG power over motor cortex (e.g., Hall, Barnes, Furlong, Seri, & Hillebrand, 2010; Jensen et al., 2005).

Here, we investigated for the first time the effect of multisensory modulation on pain-related EEG oscillations. We compared the perception of ramps of thermal stimuli in two visual contexts (viewing one's own hand vs. viewing a neutral object at the same spatial location). The stimuli increased gradually to reach one of two different temperature levels, corresponding to perceptions of mild warmth or of painful heat.

Previous studies suggested that viewing the body reduces pain levels (Longo, et al., 2009; Mancini, Longo, Kammers, & Haggard, 2011). We therefore hypothesised that vision of the body would inhibit somatosensory cortex activations associated with pain, producing analgesia. This visually-induced inhibition of somatosensory cortex would therefore be associated with relative *increases* in EEG alpha and beta oscillations over the contralateral hemisphere (Klimesch, et al., 2007).

Method

Participants

Ten healthy right-handed individuals (mean age 25 years, range 19-32 years) participated for payment. Informed consent was obtained from all participants. The study was approved by the UCL ethics committee and conducted in accordance with the principles of the Declaration of Helsinki.

Thermal stimuli

Thermal stimulation was delivered to the fingertip of either the left index or middle finger by a 13 mm diameter Peltier-type thermode (NTE-2A, Physitemp Instruments Inc). A mechanical arm helped in maintaining the probe in position and in controlling contact pressure. On each trial, the probe temperature was initially set at normal skin temperature (32 °C), maintained for 3-5 sec. Then, the temperature was gradually increased during an 8 sec ramp to reach a final stimulus temperature, either in the warm (38, 39, 40 °C) or in the painful range (46, 47, 48 °C) in a randomised order. These temperatures were chosen as appropriate to stimulate C- (warm range) and A-delta fibers (pain range) in the glabrous skin of the hand (Gybels, Handwerker, & Van Hees, 1979). The final temperature was then maintained at a steady level for 4 sec, until a beep marked the end of the trial (Figure 5-1, a). Skin temperature was measured by an infrared thermometer at the beginning of 10% of the trials selected at random, to check that it remained stable across the session (average SD across trials 1.1°C, SD across subjects 0.4 °C).

Procedure

We used the mirror box technique (Ramachandran, et al., 1995) to induce the visual illusion that the participants' right hand, reflected in a mirror aligned with their sagittal plane, was actually their stimulated left hand. Participants sat at a table, with the left hand behind the mirror and the right hand in front, gazing towards their left hand (see Figure 5-1, a). The tips of the index fingers were 20 cm from the mirror.

Two visual conditions, ‘hand-view’ and ‘object-view’ were presented in different blocks in an ABBA order (initial condition counterbalanced across participants). In the ‘hand-view’ condition, participants looked into the mirror towards their left hand, and saw the reflection of their right hand. A questionnaire administered after the experiment confirmed that participants felt they saw their left hand in this condition (Longo, et al., 2009) and therefore that the illusion provided by the mirror was successful. In the ‘object-view’ condition, the right hand was occluded by a box, and participants saw the reflection of an approximately hand-sized wooden block placed on top of it (approx. 3 cm above the hand). Each condition was repeated 40 times.

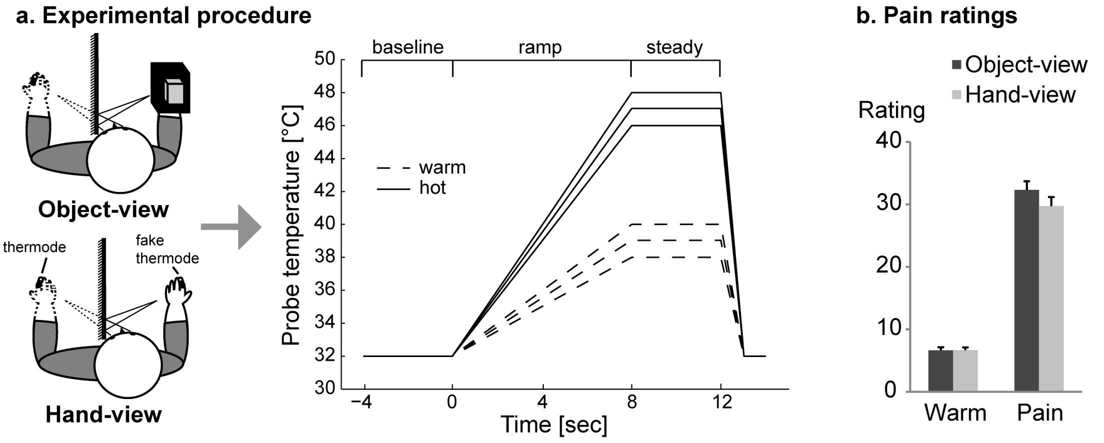


Figure 5-1. (a) Experimental procedure. Participants gazed towards the left hand, and saw the reflection of their right hand or a wooden block via a mirror. The left index and middle fingertips were stimulated with a thermode. The thermode probe was maintained at skin temperature (32 °C) for 3-5 sec, then gradually increased to one of three warm or three painful temperatures (randomised). The final temperature was maintained steady for 4 sec. A beep signalled the end of the trial, and participants then rated the stimulus intensity using a numerical scale. (b) Mean (+/- SEM) subjective ratings of pain intensity.

Electrophysiological recordings

A SynAmps 2 amplifier system and Scan 4.3 software (Neuroscan, El Paso, TX) were used to record electroencephalographic (EEG) data. Twenty-six scalp electrodes were recorded (FP1, FP2, F3, Fz, F4, T7, C5, C3, Cz, C4, C6, T8, CP5, CP3, CPz, CP4, CP6, P7, P5, P3, Pz, P4, P6, P8, O1, O2), according to the 10-20 International EEG System. The online reference electrode was AFz and the ground electrode was placed on the chin. Electrode impedances were kept below 5 KΩ. The left and right mastoids were also recorded and used for offline re-referencing. Horizontal electroculogram (EOG) was recorded from bipolar electrodes placed on the outer canthi of each eye, and vertical EOG was recorded from bipolar electrodes placed above and below the right eye. EEG signals were amplified and digitized at 500 Hz.

EEG analyses

EEG data were pre-processed with EEGLAB (http://sccn.ucsd.edu/eeglab/) (Delorme & Makeig, 2004). Data were downsampled to 250 Hz, and re-referenced to the average of the mastoids. Epochs of 14 sec were extracted from the raw EEG data from 2 sec before to 12 ms after the onset of the ramp. Epochs containing stereotyped artefacts were corrected using blind source separation with independent component analysis (Jung et al., 2000). A few further epochs were rejected by visual inspection, on the grounds of eyeblinks and movements. On average, 5.97% (SD 6.48) of epochs were rejected.

EEG oscillations were quantified using SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). A complex Morlet wavelet decomposition of the EEG signal was performed across a 0.1–30 Hz frequency range. The wavelet decomposition was performed for each trial, sensor and participant. The power at each frequency was corrected for a baseline period defined as the 2 sec immediately before the onset of the stimulus ramp. Absolute, uncorrected, power was used for some analyses. Time-frequency data were averaged across trials of the same task type to produce an average time-frequency map for each sensor for each condition.

Time-frequency data at each electrode were then averaged across two frequency bands of particular interest, alpha (8–13 Hz) and beta (15–25 Hz), for each participant. Two regions of interest were defined over contralateral (average of electrodes C4, C6, CP4, CP6, P4, P6) and ipsilateral centro-parietal cortices (average of electrodes C3, C5, CP3, CP5, P3, P5) to measure pain-induced alpha and beta oscillations (Crone, et al., 1998; Hauck, Lorenz, & Engel, 2007; Mouraux, et al., 2003; Raij, Forss, Stancak, & Hari, 2004; Stancak, Polacek, Vrana, & Mlynar, 2007). Factorial anovas were performed on both the absolute and baseline-corrected alpha and beta power, comparing effects of visual context (hand, object), stimulus intensity (warm, painful) and hemisphere (contralateral, ipsilateral).

Results

Pain intensity ratings

Analysis of variance (ANOVA) on intensity ratings revealed significant main effects of visual context ($F_{(1,9)} = 5.80$, $p = 0.039$) and stimulus intensity (warm vs. pain, $F_{(1,9)} = 47.07$, $p < 0.0001$), as well as an interaction of these factors ($F_{(1,9)} = 5.90$, $p = 0.038$). Viewing the hand significantly reduced subjective intensity ratings for painful stimuli ($t_{(9)} = 2.58$, $p = 0.032$) compared to viewing a neutral object. In contrast, visual context did not influence perceived intensity of non-painful warm stimuli ($t_{(9)} = 0.03$, $p = 0.979$) (Figure 5-1, b). These results replicate previous findings of visually-induced analgesia (Longo, et al., 2009; Mancini, Longo, et al., 2011).

EEG oscillations at rest

We investigated the effect of visual context on spontaneous oscillations during the 2 sec pre-stimulus baseline period, by comparing the absolute power in the left and right centro-parietal regions using a 2x2 ANOVA with factors of hemisphere and visual context.

In the alpha band, viewing the hand reduced absolute spectral power ($F_{(1,9)} = 7.40$, $p = 0.024$), relative to viewing the object. There was a near-significant effect of hemisphere, with lower oscillatory power contralaterally than ipsilaterally ($F_{(1,9)} = 4.39$, $p = 0.066$). The interaction between visual context and hemisphere was not significant ($F_{(1,9)} = 3.83$, $p = 0.082$), indicating that the effects of the visual context were not strongly lateralised.

Conversely beta absolute power was not significantly modulated by the visual context ($F_{(1,9)} = 1.63$, $p = 0.233$). There was a significant effect of hemisphere in the beta band, in the same direction as in the alpha band ($F_{(1,9)} = 8.82$, $p = 0.016$). The interaction was not significant in the beta band ($F < 1$).

Stimulus-induced EEG oscillations in the alpha band (8-13 Hz)

These analyses used measures of relative EEG power during the steady phase of warm/painful stimulation, with baseline-correction for the prestimulus period. An ANOVA with factors of visual context, hemisphere and stimulus intensity was applied. Viewing the hand increased stimulus-induced alpha-band power compared to the neutral view condition ($F_{(1,9)} = 32.24$, $p < 0.0001$). There was also a significant main effect of hemisphere ($F_{(1,9)} = 5.64$, $p = 0.042$), with less induced power over the contralateral (mean ± SEM, 0.93 ± 0.33 dB) than ipsilateral (mean ± SEM, 1.11 ±

0.34 dB) centro-parietal cortex. Finally, alpha power was lower for painful compared to merely warm stimuli (stimulus intensity: $F_{(1,9)} = 7.19$, $p = 0.025$), suggesting an inverse relation between sensory intensity and EEG oscillations. All the interactions were non-significant ($F < 1$), indicating that the effects of stimulus intensity and visual context were independent and bilateral (Figure 5-2 and 5-3, a).

To check whether visual effects on stimulus-induced oscillations could simply reflect differences between visual conditions in baseline power, we performed an analysis of covariance with the difference between the absolute power in the two visual contexts during the baseline. The covariate was not significant ($F < 1$), and the main effect of visual context remained significant even after adjustment for the covariate ($F_{(1,8)} = 12.23$, $p = 0.008$), indicating that the visual modulation of stimulus-induced oscillations are not simply due to changes in baseline power.

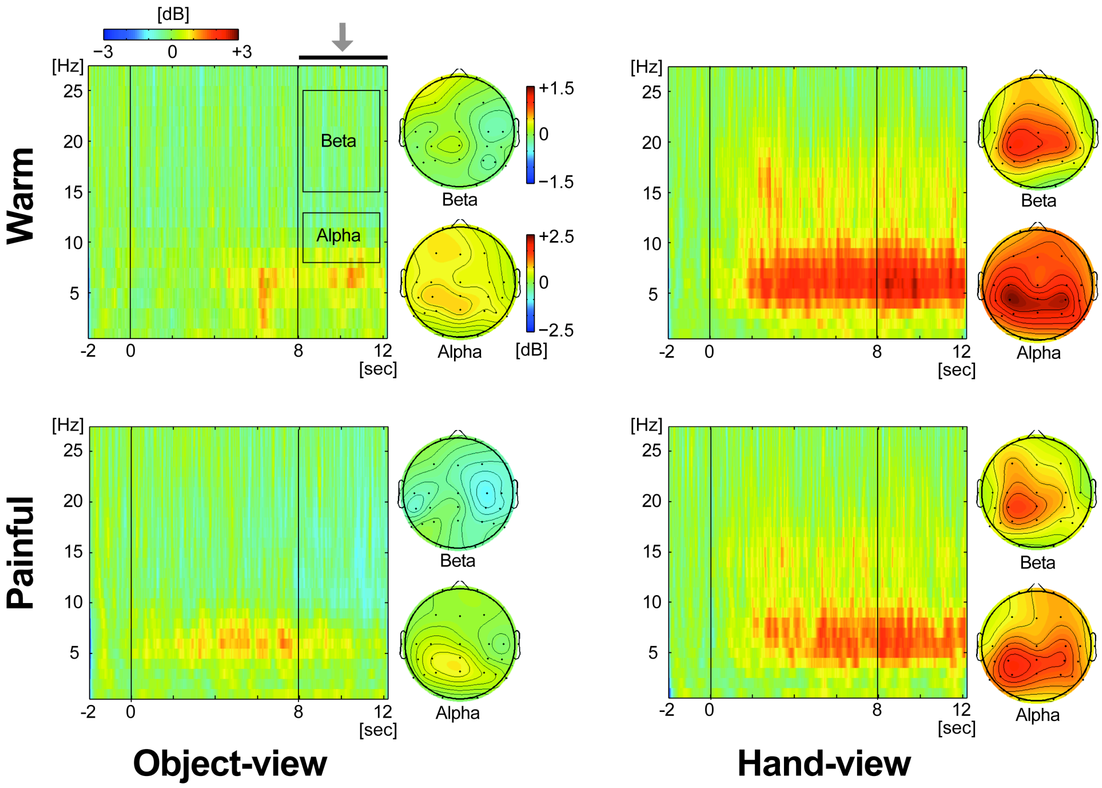
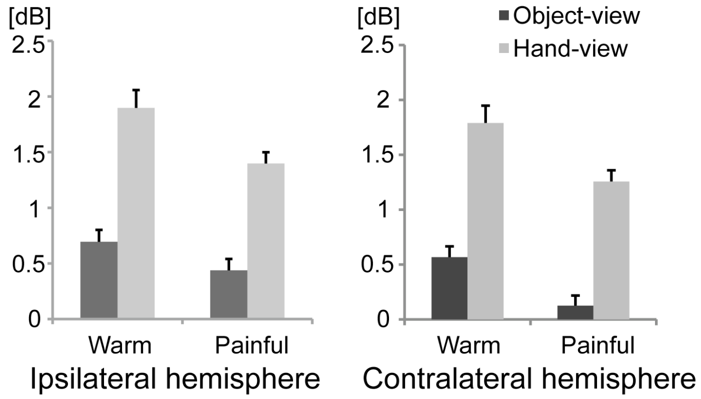


Figure 5-2. Grand mean time-frequency representations of EEG spectral power over the contralateral centro-parietal cortex. Baseline-rescaled responses were averaged across 10 subjects and 6 central-parietal electrodes in the right hemisphere, contralateral to stimulation. Topographical maps represent average oscillatory power during the steady period (8-12 sec after the ramp onset) in the alpha (8-13 Hz) and beta (15-25 Hz) bands.

a. Relative alpha power



b. Relative beta power

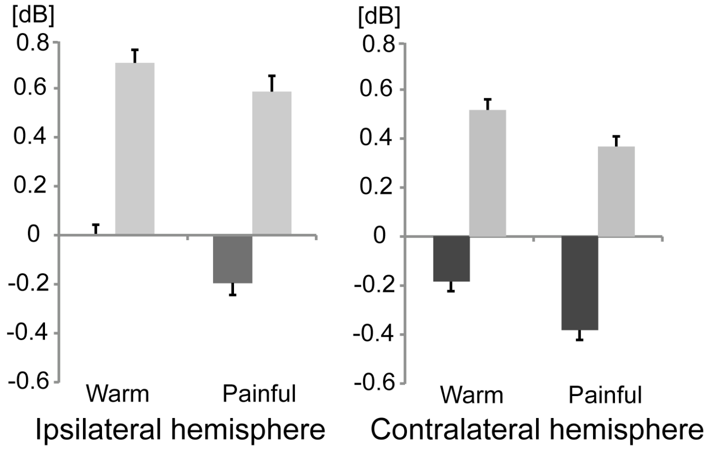


Figure 5-3. (a) Mean (+/- SEM) baseline-rescaled alpha power during the steady-stimulus period in a ROI over the centro-parietal cortex ipsilateral and contralateral to stimulation (b) Beta power, same conventions as a.

Stimulus-induced EEG oscillations in the beta band (15-25 Hz)

Viewing the hand increased beta oscillations compared to viewing the neutral object ($F_{(1,9)}$ = 38.16, p < 0.0001). There was a near-significant effect of hemisphere ($F_{(1,9)}$ = 4.33, p = 0.067), with less induced power over the contralateral (mean ± SEM, 0.08 ± 0.10 dB) than ipsilateral (mean ± SEM, 0.26 ± 0.14 dB) centro-parietal cortex. As in the alpha band, pain reduced beta oscillations in comparison to warm stimuli (stimulus intensity: $F_{(1,9)}$ = 13.30, p = 0.005), and there were no significant interactions (all F < 1) (Figure 5-2 and 5-3, b). We performed an ANCOVA as before, adding as a covariate the difference between the absolute power in the two visual contexts during the baseline. As in the alpha band, the covariate was not significant (F< 1). Further the main effect of visual context survived adjustment for the covariate ($F_{(1,8)} = 28.52, p = 0.001$).

Discussion

The present study yielded three main findings regarding multisensory modulation of EEG rhythms over centro-parietal cortex. (1) Viewing the body modulates spontaneous oscillations, reducing absolute power in the alpha, but not in the beta band, during the baseline period before thermal stimulation. (2) Painful stimuli reduce both alpha and beta spectral power in comparison to non-painful warm stimuli, possibly reflecting increased bilateral activation of centro-parietal cortex with more intense thermal stimulation. (3) Stimulus-related oscillations are crossmodally modulated by visual context: thermally-induced alpha and beta power are relatively enhanced, when viewing one's own hand in comparison to a neutral object.

This pattern of results suggests that viewing the body results either in reduced cortical excitation following thermal stimulation (Pfurtscheller, Stancak, & Neuper, 1996) or in active inhibition of the cortical response (Klimesch, et al., 2007).

Visual presetting of centro-parietal circuits

We found that simply viewing the body reduced spontaneous alpha oscillations over the sensorimotor cortex bilaterally during a baseline period prior to any thermal stimulation. Conversely, beta oscillations were not significantly altered by the visual context during the baseline period.

Previous studies have shown that observation of body movements may result in decreased alpha power (event-related desynchronization) over somatosensory cortex (for a review, see Pineda, 2005). The present study demonstrates suppression of alpha oscillatory activity for passive observation of one's own static hand. Whereas previous interpretations focussed on 'motor resonance' and simulation of body movements of others, attention to part of one's own body may also be involved. For example, spatial attention decreases alpha power in primary somatosensory cortex (Jones et al., 2010).

Pain processing

In the present study we additionally found stimulus-induced power decreases bilaterally in the alpha and beta bands when stimuli were painfully hot, compared to merely warm.

We interpret these as a relative suppression of alpha and beta rhythms linked to pain, in line with previous findings (Crone, et al., 1998; Hauck, et al., 2007; Mouraux, et al., 2003; Ploner, et al., 2006b; Raij, et al., 2004; Stancak, et al., 2007). Further, pain-induced oscillatory power correlates negatively with the excitability of somatosensory cortex (Ploner, Gross, Timmermann, Pollok, & Schnitzler, 2006a). Therefore, alpha and beta suppression induced by painful stimulation presumably reflects stronger centro-parietal activations with more intense thermal stimuli.

Interestingly, pain-related relative suppression was less clearly contralateral in our data than in some previous reports (e.g., Stancak, et al., 2007) (but see Crone, et al., 1998).

Multisensory modulation of pain

Viewing the hand reduced the level of pain experienced during thermal stimulation, compared to viewing the neutral object. This finding extends reports of visually-induced analgesia reported previously (Longo, et al., 2009; Mancini, Longo, et al., 2011). Moreover, viewing the hand led to greater alpha and beta stimulus-induced power associated with thermal stimulation, compared to viewing the object. This indicates that stimulus-induced oscillations are modulated by visual context, and in particular are enhanced by the view of one's own body. EEG modulations were largely bilateral. We interpret this relative *increase* in stimulus-induced oscillatory power as evidence of a *reduced* or inhibited cortical response to thermal stimulation when viewing the body (Klimesch, et al., 2007).

These visual modulations of stimulation-induced oscillations are not just an artefact of visual modulations of baseline EEG activity, for three reasons. First, we found visual effects on stimulation-induced oscillatory power even in the beta band, where visual conditions did not significantly influence baseline EEG power. Second, we found that the difference in relative power during stimulation did not covary significantly with the absolute power during baseline. Third, the difference in relative power during stimulation remained significant even after adjustment for the covariate.

6. tDCS modulation of the visually-induced analgesia

[This research was done in collaboration with: Nadia Bolognini, Patrick Haggard, and Giuseppe Vallar]

Introduction

The mechanisms underlying visual modulation of pain are unknown. One possibility may be an inhibitory link between visual and pain centres in the cerebral cortex, possibly relayed via intermediate multisensory representations of the body in posterior parietal areas. The lateral occipital cortex houses an "Extrastriate Body Area" (EBA), which is selectively tuned for viewing one's own body and other bodies (Downing, et al., 2001). Direct or indirect feedback (e.g., Macaluso, 2006) from visual areas representing the body, as EBA, to somatosensory areas (e.g., SI) and pain networks may underlie the analgesia induced by viewing one's own body. We directly tested this hypothesis by modulating the level of excitability of the extrastriate visual cortex and examining the resulting effect on visually-induced analgesia.

Transcranial direct current stimulation (tDCS) is a non-invasive technique of brain stimulation that can modulate cortical excitability by polarizing brain tissue in a polarity-dependent fashion, with anodal stimulation generally increasing excitability, and cathodal stimulation generally reducing excitability (Brunoni et al., in press; Nitsche et al., 2003; Nitsche & Paulus, 2001). When delivered to specific cortical areas, tDCS can alter physiological, perceptual, and higher-order cognitive processes (Antal, Nitsche, & Paulus, 2001; Nitsche & Paulus, 2001; Vallar & Bolognini, 2011). tDCS alters activity of cortical areas situated under the electrodes, but also of distant areas, probably through interconnections of the primary stimulated area with these structures (Polania, Nitsche, & Paulus, 2011).

The behavioural task was to rate the intensity of a painful sensation elicited by trains of electrical shocks on the left hand in two different visual contexts: participants were required to look at their own left hand or at an object (a wooden block occluding the left hand). In two separate experiments, we investigated the effect of anodal (Exp. 1) and cathodal (Exp. 2) tDCS over the occipital cortex (extrastriate visual), and the centro-parietal cortex (over the primary somatosensory cortex, SI) which contributes to sensory processing of nociceptive stimuli (Tracey, 2011).

We expected that tDCS over the occipital cortex would not modulate pain generally, but it would specifically boost the analgesic effect of viewing the body (increasing or decreasing pain processing depending on the tDCS polarity). Conversely, tDCS over the centro-parietal cortex might induce analgesia independently of the visual context, according to some previous reports (see reviews in Lefaucheur et al., 2008; Vallar & Bolognini, 2011).

Method

Participants

Twenty-four naïve right-handed participants (mean age 23.4, SD ± 4.4; 17 females) took part in the two experiments (n = 12 each). All were free of medical disorders, substance abuse or dependence, central nervous system effective medication, and psychiatric and neurological disorders (Poreisz, Boros, Antal, & Paulus, 2007), and participated on the basis of informed consent. Guidelines of the ethical committees of the University of Milano-Bicocca (Milan, Italy) and the Declaration of Helsinki (BMJ 1991; 302: 1194) were followed.

Stimuli

For stimulation we used a custom planar concentric electrode, consisting of a central metal cathode (Diameter: 0.5 mm), an isolation insert (D: 5 mm), and an external anode ring (D: 6 mm), and providing a stimulation area of 19.6 mm^2. The electrode was applied along the digital nerve path, approximately on the second metacarpal space of the left hand. In each trial, a 500 ms train of electrical shocks at 10 Hz was generated by a Digitimer DS7A electrical stimulator (http://www.digitimer.com/) under computer control.

By virtue of its concentric design and small anode-cathode distance, this somatosensory stimulating electrode produces high current density at low current intensities. It can therefore selectively depolarize the superficial layer of the dermis containing nociceptive Aδ-fibers without reaching the deeper Aβ-containing layers (Kaube, Katsarava, Kaufer, Diener, & Ellrich, 2000). Pinprick-like painful sensation is generally produced between 0.6 and 1.6 mA. Mean onset latencies of blink reflexes and pain-related evoked potentials for such stimulation were found to be compatible with conduction velocities of Aδ-fibers (Katsarava et al., 2006; Katsarava, Ellrich, Diener, & Kaube, 2002).

At the beginning of each session, the individual threshold for painful pinprick sensations was identified by two ascending and descending stimulation sequences in

0.1 mA steps. The mean threshold was 0.52 mA, SD ± 0.26 mA. Two different intensities (+0.20 mA and +0.70 mA above individual pain thresholds) were then selected and used in the main experiments (low intensity stimulus: mean 0.70 mA, SD ± 0.26 mA; high intensity stimulus: mean 1.18 mA, SD ± 0.32 mA).

Procedure

Participants sat at a table with their hands resting palm down on the desktop, gazing towards their left hand (see Figure 6-1). A black cape hid from sight their arms and right hand, so that participants could see only their left hand. Two visual conditions, 'hand-view' and 'object-view', were presented in different blocks in an ABBA order (initial condition counterbalanced across participants and sessions). In the 'hand-view' condition, participants gazed towards their left hand. In the 'object-view' condition, the left hand was occluded by a box, and participants looked at a hand-sized wooden block placed on top of it (approx. 3 cm above the hand). Participants were instructed to fixate the hand/object continuously. In each trial, a 500 ms train of 5 shocks at either low or high intensity was administered. Participants were asked to verbally rate the intensity of the stimulus using a pain scale, from 0 (just noticeable) to 100 (worst pain imaginable) (Ohnhaus & Adler, 1975). The intensity of the stimulus was randomised within each block. Each condition was repeated 4 times per block, for a total of 8 repetitions per behavioural test (32 total trials, taking approx. 10 min). The test was repeated before and after each of the three tDCS sessions (see below).

tDCS

In two different experiments, either anodal (Exp. 1) or cathodal (Exp. 2) stimulation (2 mA/35 cm^2) was administered. The tDCS stimulation was delivered by a battery-driven constant current stimulator (http://www.eldith.de/products/stimulator), using a pair of surface saline-soaked sponge electrodes. A constant current of 2 mA intensity was applied, complying with current safety guidelines (Poreisz, et al., 2007). The stimulating current was ramped up during a 10 sec fade-in phase, then held constant at 2 mA for 10 min, and then ramped down during a 10 sec fade-out phase. The duration of the tDCS stimulation was chosen on the basis of previous literature, as effects on cortical excitability sufficiently enduring to cover the duration of our experimental task (Nitsche & Paulus, 2001). The experimental task was initiated in the last 2 min of tDCS, as shown in Figure 6-1.

Each participant performed three sessions of tDCS (occipital, centro-parietal, and sham stimulation), separated by at least 90 min and presented in counterbalanced order across participants. In different sessions, the active electrode (to which polarity refers) was placed over one of the targeted areas in the right hemisphere, according to the 10-20 system for EEG electrode placement. For *occipital* stimulation (O), the active electrode was placed between O2 and PO8 in order to stimulate the extra-striate visual cortex including visual body-specific regions (Downing, et al., 2001). For *centro-parietal* stimulation (CP), the active electrode was placed between CP4 and C4, in close proximity to the primary somatosensory cortex (Geyer, Schleicher, & Zilles, 1999; Overduin & Servos, 2004). For both areas, the reference electrode was placed over a contralateral supra-orbital region (Fp3), as this montage has proven to be effective in previous tDCS experiments (Dasilva, Volz, Bikson, & Fregni, 2011; Vallar & Bolognini, 2011).

For sham stimulation, the electrodes were placed over one of the target areas, the current was ramped up over 30 sec, and then immediately switched off. This ensured that participants could feel the initial itching sensation at the beginning of tDCS, prevented any effective modulation of cortical excitability by tDCS, and allowed for a successful blinding of participants (Gandiga, Hummel, & Cohen, 2006). The experimenter himself was also blinded to the tDCS condition. For each experiment, six participants received sham stimulation at the occipital site, and six at the centro-parietal site.

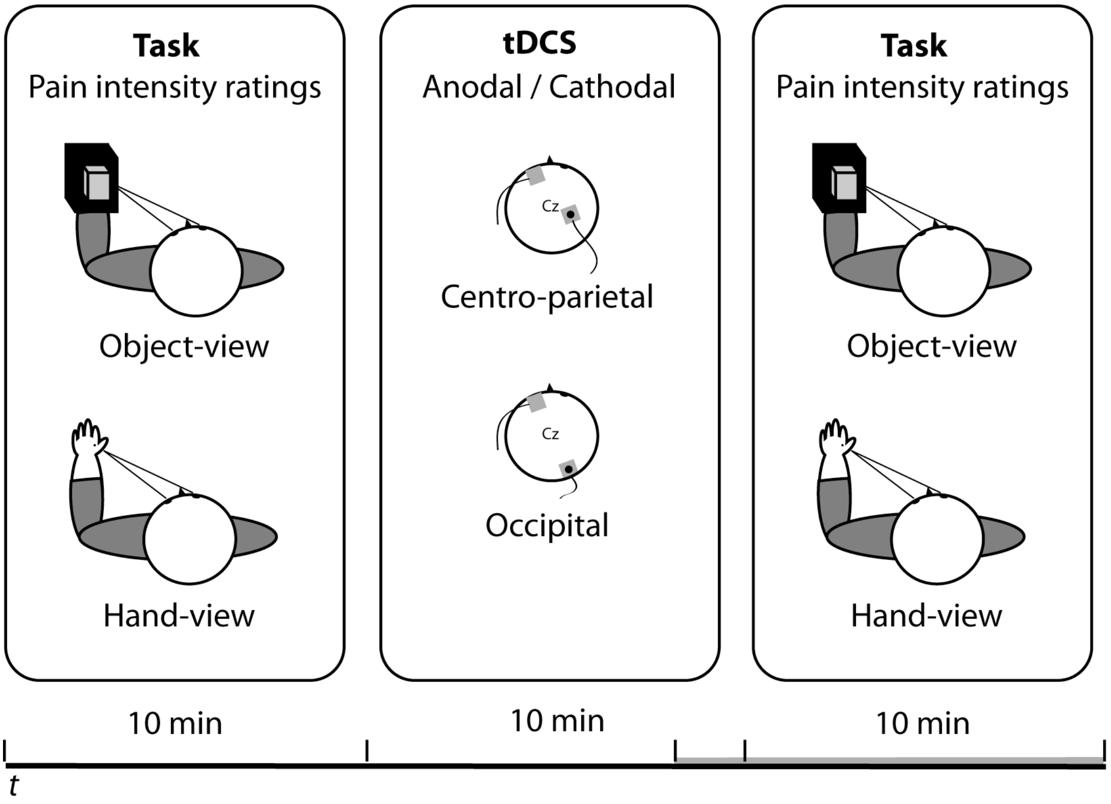


Figure 6-1. ***Stimuli and procedure.*** **Two sessions of the same behavioural task were administered before and after 10 min of tDCS over either the right occipital or the centro-parietal cortex. During the behavioral task, participants were required to look at their own left hand or at an object in the same spatial location while verbally rating the intensity of electrical shocks delivered on their left hand.**

Data analyses

For each experiment, we submitted pain ratings into repeated-measures analyses of variance (ANOVAs) with factors of stimulation *session* (active tDCS over occipital cortex, active tDCS over centro-parietal cortex, sham tDCS), *time* (pre- and post-tDCS), and visual *context* (hand-view, object-view).

We then explored the modulation of the analgesic effect of viewing the body (see below), calculating an index of visual analgesia as the difference between the pain ratings (on a 0-100 scale) in the object-view and hand-view conditions. A positive difference value indicates higher pain levels in the object-view condition, namely analgesia induced by viewing the body, while a negative value indicates hyperalgesia. Analgesia indices were submitted to repeated-measures analyses of variance (ANOVAs) with two within-subjects factors of session and time.

Results

Exp. 1: Anodal/excitatory tDCS

The pain rating data for each condition are reported in Table IV.

The ANOVA on raw pain ratings revealed a significant main effect of visual context ($F_{1,11} = 19.18$, $p < 0.001$, $\eta^2_p = 0.64$): pain ratings were reduced in the hand-view in comparison to the object-view condition, replicating the finding that viewing one's own body is analgesic (Longo, et al., 2009; Mancini, Longo, et al., 2011). The main effects of session ($F_{2,22} = 2.89$, $p = 0.08$, $\eta^2_p = 0.21$) and of time ($F < 1$) were not significant, nor was their interaction ($F_{2,22} = 2.26$, $p = 0.13$, $\eta^2_p = 0.17$); this indicates that anodal tDCS over either the contralateral occipital or centro-parietal cortex did not modulate overall pain levels. Importantly, the interactions of session by context ($F_{2,22} = 3.62, p < 0.04, \eta^2_p = 0.25$), time by context ($F_{1,11} = 6.01, p < 0.03, \eta^2_p = 0.35$), and session by time by context ($F_{2,22} = 4.68, p < 0.02, \eta^2_p = 0.30$) were all significant, suggesting that tDCS modulations were specific for the visual context. These interactions with context were explored by an additional ANOVA on the analgesia index, given the difference between hand and object conditions.

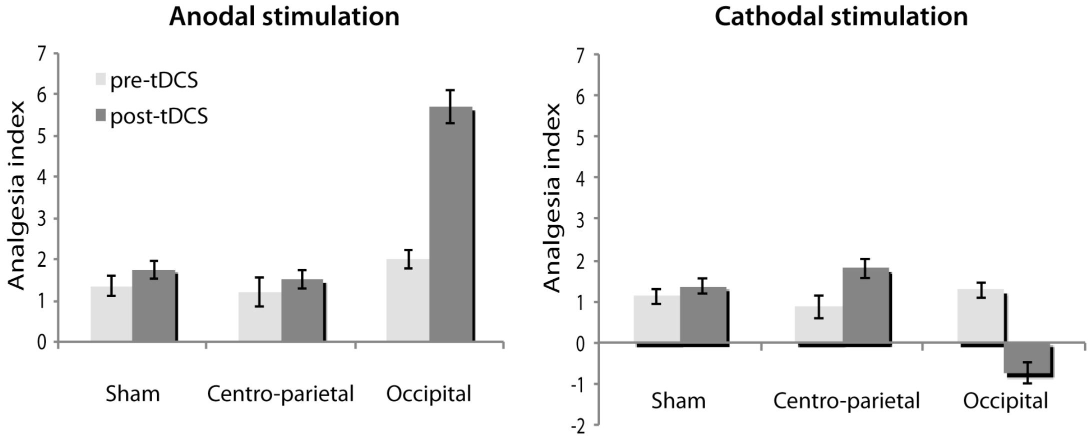


Figure 6-2. ***Results*****. Mean analgesia index (± SEM) by tDCS polarity by stimulation site, and by time. The analgesia index represents the difference between pain ratings (0-100) in the object-view and in the hand-view conditions. A positive difference indicates that viewing the body induces analgesia, while a negative difference means that viewing the body induces hyperalgesia.**

Figure 6-2 (left-hand side) shows the modulation of the analgesia index by anodal stimulation. Note the clear increase in analgesia by occipital anodal tDCS. Figure 6-3 shows these modulations in the individual participants. The anova on the analgesia indices revealed significant main effects of session ($F_{2,22} = 3.62$, $p < 0.04$, $\eta^2_p = 0.25$) and time ($F_{1,11} = 6.01$, $p < 0.03$, $\eta^2_p = 0.35$). Also the time by session interaction was significant ($F_{2,22} = 4.68$, $p < 0.02$, $\eta^2_p = 0.30$). Post-hoc comparisons showed that the difference between the pre- and the post-tDCS conditions was significant only for occipital stimulation ($p < 0.01$). The analgesic effect of viewing the body was increased by anodal stimulation of the extrastriate visual cortex, but not of the centro-parietal cortex (p = 0.85).

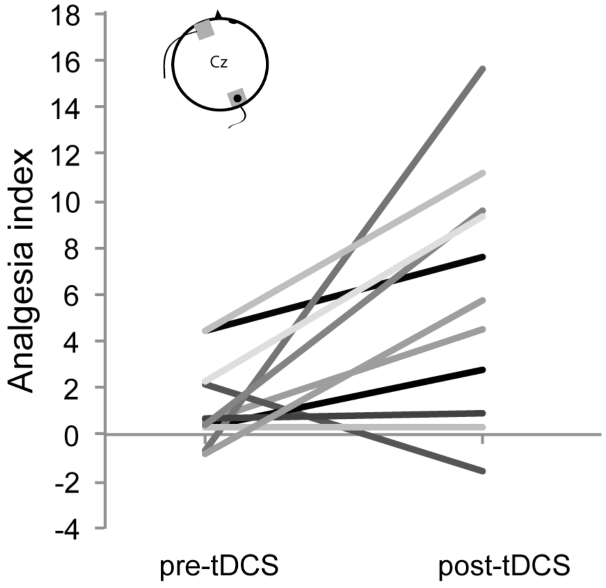


Figure 6-3. ***Results*****. Analgesia index before and after anodal stimulation of the right occipital cortex, for each participant. Positive/negative values: visually-induced analgesia/hyperalgesia.**

Exp. 2: Cathodal/inhibitory tDCS

Figure 6-2 (right-hand side) shows the modulation of the analgesia index by cathodal stimulation. The ANOVA on raw pain ratings again revealed a significant visually-induced analgesia (context: $F_{1,11} = 8.15$, $p < 0.02$, $\eta^2_p = 0.43$). The main effect of session was not significant ($F_{2,22} = 1.12$, $p = 0.34$, $\eta^2_p = 0.09$), but there was a significant effect of time ($F_{1,11} = 5.19$, $p < 0.04$, $\eta^2_p = 0.32$). No interactions were significant (context by session: $F_{2,22} = 1.43$, $p = 0.26$, $\eta^2_p = 0.11$; time by context: $F < 1$; session by time: $F < 1$; session by time by context: $F_{2,22} = 2.04$, $p = 0.15$, $\eta^2_p = 0.16$). Therefore, cathodal stimulation did not modulate pain levels at any site (Table 6-1 and Figure 6-2). There was a significant pain habituation in the post- in comparison to the pre-stimulation session, independently of the tDCS session (see Table IV).

Table IV. Mean (± SEM) pain ratings by polarity (anodal, cathodal), time (pre-, post-tDCS), stimulation site (sham, Centro-Parietal cortex, Occipital cortex), and visual context (object-view, hand-view).

Anodal tDCS

	Pre-tDCS		**Post-tDCS**	
	Object-view	**Hand-view**	**Object-view**	**Hand-view**
Sham	49.55 (1.86)	48.20 (1.75)	51.35 (2.26)	49.60 (2.14)
Centro-Parietal	49.19 (2.06)	47.97 (2.15)	42.96 (2.09)	41.45 (2.03)
Occipital	39.46 (1.78)	38.11 (1.75)	41.09 (1.70)	34.82 (1.47)

Cathodal tDCS

	Pre-tDCS		**Post-tDCS**	
	Object-view	**Hand-view**	**Object-view**	**Hand-view**
Sham	33.05 (2.02)	31.92 (2.11)	30.03 (2.01)	28.67 (1.97)
Centro-Parietal	37.04 (2.11)	36.17 (2.15)	33.44 (2.03)	31.64 (1.98)
Occipital	33.43 (2.32)	32.16 (2.42)	29.48 (2.20)	30.23 (2.26)

Discussion

Viewing one's own body reduces the level of acute pain caused by an electrocutaneous stimulus, relative to viewing the object. This replicates previous findings obtained using different nociceptive stimuli (Longo, et al., 2009; Mancini, Longo, et al., 2011). The novel finding of the present study is that the visually-induced analgesia can be modulated by the level of excitability in the contralateral extrastriate occipital cortex. Specifically, experimentally increasing excitability of this area by means of anodal tDCS enhanced the analgesic effect of viewing the body. This effect was specific for stimulation site, since stimulation of the centro-parietal cortex did not modulate visual analgesia. The effect was also specific for the polarity of stimulation, since cathodal tDCS did not have significant effects on pain perception.

In contrast to the anodal effect, cathodal stimulation of the occipital cortex did not modulate visual analgesia. There are many other examples in both the motor and sensory systems where the effects of tDCS have been limited to one polarity of stimulation (see for a recent review Vallar & Bolognini, 2011). This is because, beyond the effect of the current polarity, many other factors contribute to the tDCS effects, including the orientation of the electric field (e.g., Nitsche & Paulus, 2000), and the background level of activity in the system when tDCS is applied. Further experiments are required to address the potential role of these additional factors with respect to the absence of cathodal modulation.

Our study also demonstrates that the tDCS effects were specific for the stimulation of the occipital cortex. Neither anodal nor cathodal stimulation of the centro-parietal cortex modulated pain levels in any visual condition. This may be surprising, since centro-parietal stimulation should influence activity in somatosensory cortical areas involved in pain (Valentini et al., in press). A previous report showed that cathodal, but not anodal, stimulation of contralateral SI can reduce pain ratings and the N2 component of nociceptive laser evoked potentials (Antal et al., 2008). On the other hand, there is also evidence of analgesic effects of cathodal (Csifcsak et al., 2009; Terney et al., 2008) and anodal (Boggio, Zaghi, Lopes, & Fregni, 2008) stimulation of contralateral primary motor cortex in healthy participants (see reviews in Lefaucheur, et al., 2008; Vallar & Bolognini, 2011). Given these previous reports, one might predict reduced pain ratings in both view-hand and view-object conditions following centro-parietal cathodal stimulation.

Anatomical factors may explain the ineffectiveness of our centro-parietal stimulation. First, our tDCS active electrode was located slightly more posteriorly (between CP4 and C4) than in previous studies (over C3/4: Boggio, et al., 2008; Csifcsak, et al., 2009), and the current intensity and the duration of the stimulation were also different (e.g., 1 mA for 15 minutes: Antal, et al., 2008). Further, no single primary nociceptive or pain cortex has been so found so far, and it remains unclear whether S1 contributes to the coding of pain levels. An extensive network, of which S1 is only one node, responds to nociceptive stimulation (Tracey, 2011). Moreover, the region in the operculo-insular cortex where nociceptive responses are found is relatively small, its location varies considerably across individuals (Baumgartner et al., 2010), and its contribution to pain intensity remains unclear (Iannetti & Mouraux, 2010; Oertel et al., 2011).

The current literature does not provide a clear view of tDCS modulation of pain. Many authors suggest that the somatosensory cortex is only indirectly involved (e.g., Dieckhofer et al., 2006; Matsunaga, Nitsche, Tsuji, & Rothwell, 2004). Analgesic effects of tDCS are mostly associated with anodal stimulation of the primary motor cortex, while the effects of tDCS stimulation of SI appear controversial at least in patients (Lima & Fregni, 2008; Tracey, 2011). Also, tDCS effects on pain may be not based on modulations of focal activity, but on connectivity changes (Dieckhofer, et al., 2006; Matsunaga, et al., 2004).

General Discussion

The human perceptual system is essentially multisensory (Stein & Meredith, 1993), and is incessantly at work merging information from different modalities, in order to build up a robust percept. Ernst and Bülthoff (2004) draw a distinction between ‘sensory combination’ (i.e., interactions between sensory signals that are not redundant, may be in different units and coordinate systems, or about complementary aspects of the same environmental property), and ‘sensory integration’ (i.e., interactions between redundant signals, in the same unit and coordinate systems, and about the same aspect of the environmental property). In this thesis I investigated a particular form of multisensory combination, through which a continuous perceptual context modulates the processing of bodily senses, particularly touch and pain.

In the case of touch, with the help of the Judd illusion, I demonstrated that visual flankers can bias tactile spatial judgements (Chapter 1, Exp. 1), depending on the spatial coincidence between the visual and tactile inputs (Chapter 1, Exp. 2). These multisensory interactions are independent of spatial attention, given that are preserved in brain-damaged patients with spatial attentional deficits such as USN (Chapter 2). The occipito-temporal cortex plays a causal role in integrating visual and tactile sensory information, and in the processing of multisensory shape representations (Chapter 3).

In the case of pain, I showed that the perceptual context strongly influences pain. Viewing one's own body in comparison to an object increases contact heat pain thresholds, an effect we called 'visually-induced analgesia'. The visual appearance of the body, like its perceived size, further modulates pain, revealing a linear relationship between visual body size and pain (Chapter 4). At the neural level, visually-induced analgesia is reflected in an enhancement of alpha and beta pain-induced EEG oscillations over the centro-parietal cortex bilaterally, possibly due to crossmodal inhibition of this region (Chapter 5). Excitability shifts in the extra-striate visual cortex are involved in generating the visually-induced analgesia, given that the visually-induced analgesia is boosted by anodal/excitatory occipital stimulation (Chapter 6).

Taken together, these results clearly indicate that the visual context is able to shape the representation of external objects and events in contact with the body, and to modulate their neural processing. The extra-striate visual cortex, including object- and body-specific areas, is causally involved in contextual multisensory modulation of somatosensation.

Visual modulation of touch

The Judd illusion

To study visuo-tactile interactions, I used unimodal and crossmodal versions of the Judd illusion in bisection tasks. The bias induced by the illusion is comparable in the visual and tactile modality, and reduced in a crossmodal condition where the illusion was only visual (Chapter 1). The decrement of the illusion in the crossmodal condition has been considered the likely marker of the multisensory integration of the visual and haptic components of the stimuli, in the sense that tactile bisection is at the same time biased by the visual flankers *and* improved by the exploration of the tactile rod.

In an early study using an apparatus broadly similar to the present one, Walker (1971) found that visual flankers affect tactile length judgements. The present finding that the view of irrelevant arrowheads affects the setting of the subjective midpoint in a haptic bisection task, with a displacement toward the 'tail' of the Judd figure differs from a recent observation by Gallace and Spence (2005) in neurologically unimpaired participants. Using a haptic judgement task about the length of sticks positioned behind the visible Brentano variant of the Müller-Lyer illusion, they found that sticks placed behind the outward-oriented fins configuration (always presented on the right hand-side) are perceived as shorter, while sticks positioned behind the inward-oriented fins (presented on the left hand-side) are perceived as not different in length from the reference stick and, therefore, comparatively longer than their right-sided counterpart. This pattern is opposite to what typically happens in vision (e.g., Vallar, Daini, & Antonucci, 2000). In a second experiment, no visual illusion was presented and an opposite pattern was found, namely, a relative underestimation of the length of the standard stick when it was presented on the left, and a relative overestimation when the standard stick was presented on the right. While these asymmetrical effects suggest an influence of the visual illusion on the haptic perception of extent, a more precise interpretation is unclear [see the discussion of Gallace and Spence, 2005, in terms of underestimation of extent on the left-hand side of space, and of 'pseudoneglect' (Jewell & McCourt, 2000)].

It should be noted, however, that Gallace and Spence did not use a classical Brentano illusion, in which the shaft extends up to the tips of each fin, but a configuration where the two sticks behind the fins were shorter, leaving a gap between them and the arrowheads. This configuration appears indeed very similar to the so-called 'reverse Müller-Lyer illusion', widely described in the visual domain

(Fellows, 1967; Pressey & Bross, 1973; Taya & Ohashi, 1992). In the reverse Müller-Lyer illusion the arrowheads are displaced farther away from the ends of the shaft. This displacement of the fins makes the shaft between the inward-oriented fins configuration to appear longer than the one between the wings-out shape. By contrast, if the shaft extends up to the arrowheads, as in the classical Müller-Lyer figure, the classical pattern of the Müller-Lyer figure occurs, with inward-oriented fins shortening the shaft, and outward-oriented fins lengthening it. Consistent with the present results, Gallace and Spence's findings may then be the result of a 'linear' crossmodal transfer of a reverse Müller-Lyer illusion.

The spatial rule

The crossmodal transfer of the illusion from vision to haptics depends on the spatial coincidence between the visual and tactile sensory inputs. Particularly, we varied the horizontal position of the shaft with respect to the arrowheads: it could be shifted in the congruent or incongruent direction of the side expanded by the illusion, with a 25% offset. Only when the visual arrowheads are aligned with the shaft they are able to affect its haptic bisection. The misalignment of the shaft with respect to the arrowheads, even when it is in the direction expanded by the illusion, disrupts the crossmodal transfer of the illusory effects (Chapter 1, Exp. 2).

In line with these findings, spatial coincidence is known to be a relevant factor in multisensory integration, with integration becoming poorer when the spatial separation between the relevant signals increases (Gepshtein, et al., 2005; Stein, 1998; Stein & Meredith, 1993). This is important because it supports the view that the effects reported derive from the multisensory combination of visual and tactile sensory inputs, rather than motor modulation or visual imagery.

Independency of spatial attention

Many multisensory interactions reported in the literature depend on attention. Instead, the visual bias on touch caused by the Judd illusion is independent of spatial attention, since it is fully preserved in right brain-damaged patients with Unilateral Spatial Neglect (Chapter 2).

The visual-tactile interactions studied may be largely non-spatial in nature, suggesting that the illusion might elicit a bias in mechanisms involved in crossmodal shape representation in ventral stream networks (Mancini, Bolognini, et al., 2011; Vallar & Mancini, 2010).

In support to this view, visual ventral regions are not a lesional correlate of USN, as assessed by line bisection tasks. In our patients the cortico-subcortical lesions mainly involve frontal and centro-parietal regions, relatively sparing the extra-striate visual cortex (see Figure 2-1). Anatomo-clinical correlation studies in right-brain-damaged patients with USN show that the rightward bias in line bisection is associated with posterior lesions (Binder, Marshall, Lazar, Benjamin, & Mohr, 1992): specifically, to the inferior parietal lobule (Karnath, Fruhmann Berger, Zopf, & Kuker, 2004; Mort et al., 2003; Verdon, et al., 2010), and at the temporo-occipital junction (Rorden, et al., 2006).

The task used to assess the illusory effects, rod bisection, should also be considered. In studies performed in neurologically unimpaired participants other response effectors have been investigated, such as saccadic eye movements, visually-guided pointing, and grasping, with different results. Saccades are biased by the illusion, suggesting no dissociation between this type of action and perception (see the metanalysis of Bruno, Knox, & de Grave, 2010). As for visual effects, the prediction could be made that USN patients, being sensitive to illusory effects as assessed by line bisection, would exhibit a modulation of saccades by illusory stimuli. Beside saccades, the visual illusion can also affect grasping movements (Bruno & Franz, 2009). Conversely, visually-guided pointing is not affected by the illusion (see the metanalysis of Bruno, Bernardis, & Gentilucci, 2008). This finding is taken as broadly consistent with the distinction between vision-for-perception and vision-for-action (Gangopadhyay, Madary, & Spicer, 2010; Milner & Goodale, 2006), with the illusion arising in the visual perceptual ventral stream and not affecting the vision-for-action dorsal stream. However, the positive effects on saccades and grasping "do not appear to support independent spatial representations for vision-for-action and vision-for-perception" (Bruno & Franz, 2009).

Neural correlates

The mechanisms underlying the processing of the visual Müller-Lyer illusion and its variants may be closely linked to those associated with object perception, as suggested by recent neuroimaging evidence on the visual illusion (Weidner, et al., 2010).

In Chapter 3, I showed that rTMS over either the left or the right occipito-temporal cortex, at the level of the LOC, interferes with the processing of the unisensory, visual and haptic, and the crossmodal visuo-haptic illusion in a similar fashion. Conversely, rTMS administered over either the left or the right SPC does not affect illusion scores in any modality.

Our findings suggest that the Müller-Lyer illusion may elicit a bias in mechanisms involved in crossmodal shape processing. Within the visual ventral stream, the LOC is an object-selective area that responds to objects not only in vision, but also in touch (Amedi, et al., 2002; Amedi, et al., 2001; Deshpande, et al., 2008; T. W. James, et al., 2002; Peltier, et al., 2007).

The LOC may build a multisensory representation of objects (Tal & Amedi, 2009). In particular, a sub-region of the LOC, the lateral occipital tactile-visual region (LOtv, Amedi, et al., 2002; Amedi, et al., 2001), contains a modality-independent representation of geometric shape that can be flexibly addressed either bottom-up, from direct sensory inputs, or top-down, from prefrontal and parietal regions, irrespective of the modality of the sensory input, and depending on object familiarity (Deshpande, et al., 2010; Lacey, et al., 2009). This neural network concerned with multisensory representations of objects might be implicated also in the processing of illusions, such as the Müller-Lyer figure and its variants, within and across different sensory modalities.

It is still controversial whether the LOC's recruitment in haptic shape processing is purely multisensory or is also mediated by *visual imagery*. The role of visual imagery has been investigated in a series of fMRI studies using connectivity analyses. Particularly, visual imagery may mediate the recruitment of LOC in haptic shape processing of familiar objects, through top-down paths from prefrontal cortex to LOC. Conversely, the unfamiliar shape network is mainly characterized by bottom-up, somatosensory inputs to LOC (Deshpande, et al., 2010; Deshpande, et al., 2008; Lacey, et al., 2010). Importantly, activation of LOC during haptic shape processing has been demonstrated also in congenitally blind people (Amedi, Raz, Azulay, Malach, & Zohary, 2010; Amedi et al., 2007; Pietrini et al., 2004). This indicates that visual imagery is not an obligatory condition for the haptic recruitment of the visual cortex.

With reference to the Judd illusion, tactile illusory effects are preserved in congenitally blind people (Heller, et al., 2002), indicating that they are not dependent on visual experience. In addition, I showed that the crossmodal transfer of the illusion from vision to haptics depends on the spatial coincidence between the visual and tactile sensory inputs (Chapter 1). The absence of illusory effects for spatially incongruent stimuli suggests that imagery itself cannot explain the influence of the visual illusion on haptic bisection (in particular, the condition where the shaft is shifted in the direction expanded by the visual illusion does not elicit any bisection bias). Instead, the illusory effect is likely to result from the crossmodal combination of the sensory inputs, being dependent on the spatial coincidence between them.

In conclusion, the present results indicate the existence of a common multisensory neural substrate of the Judd variant of the Müller-Lyer illusion, showing the critical involvement of the occipito-temporal cortex in constructing a representation shared by the visual, haptic, and visuo-haptic illusion. These findings indicate that the occipito-temporal cortex is implicated in crossmodal shape processing, both of illusory and of non-illusory figures (Amedi, et al., 2002; Amedi, et al., 2001). Growing evidence indicates that this visual region, traditionally considered unisensory, plays a crossmodal role in perception (Beauchamp, 2005; Kim & James, 2010; Lacey, et al., 2009). The study presented in Chapter 3 may provide a new insight on the multisensory involvement of the occipito-temporal cortex in perception, through a classical visual illusion.

Open questions

It remains still unclear how unisensory information reaches multisensory associative regions as LOC. For instance, the visual and the haptic versions of the

Judd illusion could be processed either by independent, modality-specific mechanisms with similar encoding strategies, and only at a later stage integrated in a supra-modal representation. Alternatively, an early coding system may be shared by vision and touch. This issue reflects a more general question, as to whether vision and touch create multiple independent or common multisensory representations (Lacey, Campbell, & Sathian, 2007; Newell, 2004).

Be as they may, the present studies show that visual information irrelevant for the bisection task affects the spatial representation of a rod perceived haptically. This may indicate that vision and touch are integrated automatically (e.g. Bresciani, Dammeier, & Ernst, 2006), at least in the paradigm used in the present study (see also for a recent review Santangelo & Spence, 2008).

Visual modulation of pain

The fact that pain depends on the context in which occurs can be commonly experienced in everyday life: expectations, attention and motivation strongly change pain levels. The influence of the psychological context has indeed been extensively investigated. However, the set of studies presented in this thesis shows that also lower-level perceptual factors, previously neglected by the scientific community, play an important role in pain perception. Indeed, a pain sensation is formed on a body part, at a specified time and space location, in an organism and in a particular psychological context. The context in which a sensation occurs can be conceptualised in a hierarchical way, in order to differentiate between processing levels of increasing complexity, from perceptual to cognitive. The present thesis attempted to investigate the role of the visual context on pain perception.

When we feel acute pain on our body, our gaze is commonly directed toward either (or both) the stimulus causing pain or/and to our body. It is well known that viewing the threatening stimulus enhances pain responses, thus having an hyperalgesic effect, possibly due to increased arousal and emotional top-down modulation (Dowman, 2011; Wiech, et al., 2008). Surprisingly, looking beyond the stimulus at the body part in which pain is felt has the opposite effect, being analgesic (Longo, et al., 2009).

Visually-induced analgesia: psychophysical evidence

In Chapter 4, I demonstrated that viewing one's body modulates the 'sensory-discriminative' components of pain experience (Auvray, et al., 2010; Melzack & Casey, 1968), increasing contact heat pain thresholds of 3.2 °C in comparison to viewing an object in the same spatial location.

Previous studies of visual analgesia measured pain intensity ratings (Longo, et al., 2009). These are confounded by post-perceptual 'affective-motivational' components of pain (Melzack & Casey, 1968), such as task demands and response biases (Iannetti, Hughes, Lee, & Mouraux, 2008). Further, recent reviews have questioned how much of 'pain' is specific to nociceptive stimulation, and how much reflects general salience and arousal mechanisms (Iannetti, et al., 2008; Legrain, Iannetti, Plaghki, & Mouraux, 2011). However, our measures of pain thresholds suggest that viewing the body modulates sensory processes specific to pain *perception*.

Not just viewing the body but also how the body is seen influences pain. Using concave and convex mirrors to alter the visual size of the hand and of the object viewing during nociceptive stimulation, I demonstrated that the visually-induced analgesia is enhanced by viewing one's own hand as magnified and reduced when the hand is minified. Visual distortions of the object size did not have any effect on pain.

This suggests a plastic and flexible link between representations of the body (particularly, its perceived size) and pain perception. Previous studies demonstrated that alterations of afferent input cause changes in the perceived size of affected body parts (Gandevia & Phegan, 1999). Here, I demonstrate an additional causal relationship in the opposite direction. That is, altering the perceived size of a body part causes changes in pain sensory processing.

Viewing the body was previously reported to improve tactile acuity (Kennett, et al., 2001). This tactile modulation was further enhanced by visual enlargement. I found a visually-induced increase in heat-pain threshold, which is further enhanced by visual enlargement. Interestingly, reduction of visual hand size decreased heat-pain thresholds. This bidirectional modulation rules out explanations based simply on attention, expectations or novelty. Visual distortion of one's own body is unusual in everyday life, so it might plausibly lead to a non-specific arousal effect. However, such non-specific attentional effects should be similar for increased or decreased scales. My results rather indicate a specific, proportional relation between visual body size and pain perception.

The results from the present studies are surprising as, based on the findings from studies on spatial attention, one should expect that looking at the hand would direct spatial attention in a crossmodal way to that location (Eimer & Driver, 2000), amplify nociceptive processing (Legrain, Guerit, Bruyer, & Plaghki, 2002), and therefore increase pain (Van Ryckeghem et al., 2011). However, the similar effects of viewing the body on touch and pain suggest a common mechanism independent of attention. For example, visual and multisensory areas that represent one's own body and peripersonal space might modulate networks of inhibitory interneurons in early somatosensory areas (Longo, et al., 2009), hypothesis tested in Chapters 5 and 6.

Previous psychophysical (Kammers, de Vignemont, & Haggard, 2010) and clinical (Ramachandran, et al., 2009) studies confirm links between body representation and pain sensation. Representation of one's own body is initially created by integrating multisensory inputs. Once established, however, such body representations may attribute, interpret (Tsakiris, Haggard, Franck, Mainy, & Sirigu, 2005) and modulate (Kennett, et al., 2001) sensory inputs, in order to optimise perception of novel events (Coslett & Lie, 2004), and provide a spatiotemporally continuous sense of self. Visual analgesia might be another example of self-related modulation.

EEG correlates of visually-induced analgesia: inhibition of the centro-parietal cortex

In Chapter 5, I studied changes in EEG oscillatory activity related to visual modulation of pain, by comparing cortical oscillations during warm or painful contact heat, while participants viewed either their own hand or a neutral object in the same location. EEG oscillations reflect phases of low vs. high excitability occurring in neuronal networks (Neuper, et al., 2006).

Time-frequency analysis revealed that painful, as opposed to warm, stimulation is associated with reduced alpha (8-13 Hz) and beta (15-25 Hz) power.

Classically, such decreases in oscillatory power indicate increases in sensory cortical activation. These event-related oscillatory changes are further modulated by the visual context: viewing one's own body increases stimulation-induced alpha and beta oscillatory activity bilaterally, relative to viewing a neutral object.

The relative increase in alpha and beta power during visual analgesia can be considered a form of multisensory event-related synchronisation. Alpha ERS has been classically interpreted as cortical idling (Pfurtscheller, et al., 1996). In the present case it may indicate a reduced stimulus-related activity of the centro-parietal cortex due to viewing the hand. However, more recent models consider alpha ERS as reflecting active inhibition (Klimesch, et al., 2007). This latter view would suggest that specific inhibitory processes could underlie visual analgesia.

Interestingly, vision of the body has indeed been shown to modulate somatosensory intracortical inhibition (Cardini, et al., 2011). The fronto-parietal alpha rhythm may also play an active role in the mechanisms of top-down modulation, attention and consciousness (Palva & Palva, 2007). Thus, alpha ERS might reflect active modulation of pain processing networks.

These effects may depend on the representations of the body and peripersonal space maintained by the posterior parietal cortex (e.g., Avillac, Deneve, Olivier, Pouget, & Duhamel, 2005). Parietal multisensory areas might in turn modulate networks of inhibitory interneurons in early somatosensory areas (Longo, et al., 2009). This increased somatosensory inhibition might then be responsible for reduced pain levels.

GABAergic interneurons may play an important role in visual analgesia. Previous studies show that GABAergic mechanisms underlie increases in pain levels (Lefaucheur, Drouot, Menard-Lefaucheur, Keravel, & Nguyen, 2006; Schwenkreis et al., 2003) particularly following nerve injury (Basbaum, Bautista, Scherrer, & Julius, 2009). Further, GABA agonists are an effective treatment for chronic central pain (Canavero & Bonicalzi, 1998). Critically, inhibitory GABAergic networks also contribute to the generation of sensorimotor beta rhythm. For example, the GABAergic agonist benzodiazepine increases 20-Hz oscillations in the human motor cortex (e.g., Hall, et al., 2010; Jensen, et al., 2005). I suggest that viewing the body might produce top-down modulation of GABAergic inhibitory intracortical networks, resulting in alpha and beta synchronisation.

Importantly, modulation of the stimulation-induced oscillatory power was largely bilateral and independent of stimulus type, being present equally for warm and painfully hot stimuli. However, we did not find any modulation of intensity ratings for mild warm stimuli, possibly because of a floor effect: we asked our participants to rate pain and not just perceived temperature. Thermal sensitivity modulation needs to be further investigated in future studies. Viewing the body also influences other somatosensory systems: in touch it has been demonstrated to have a different effect on spatial acuity, enhancing tactile two points-discrimination (Kennett, et al., 2001), and stimulus intensity, reducing tactile detection (J. A. Harris, et al., 2007). At least as for stimulus intensity, the similarity of effects for tactile detection and for pain levels may suggest a common neural pathway underlying visual modulation of somatosensory processing.

Taken together, these results possibly indicate that visual modulation of pain involves changes in sensory EEG rhythms. In particular, cortical inhibition of centro-parietal cortex underlies visually-induced analgesia. This interpretation is supported by reduced pain ratings when viewing the body.

tDCS modulation of visually-induced analgesia: the role of the visual cortex

Chapter 5 suggests that viewing the body inhibits the centro-parietal cortex. In Chapter 6, investigated which neural structures drive this modulatory influence. I modulated the excitability of the extrastriate visual cortex and centro-parietal cortex by either anodal or cathodal tDCS. I found that the analgesic effect of viewing the body is enhanced selectively by anodal stimulation of the occipital cortex. The effect is specific for the polarity and the site of stimulation, suggesting that visually-induced analgesia may be related to excitability shifts in the extrastriate visual cortex.

The present results support the hypothesis that the mechanisms underlying visually-induced analgesia may involve an inhibitory interaction between visual areas and pain networks. This modulation is triggered by the activation of specific visual representations of the body, since the visual cortex stimulation did not modulate overall pain levels but only the specific analgesic effect of viewing the body. Hence, visual areas specific for representing the body are likely to mediate these effects.

In line with this proposal, neuroimaging evidence shows that occipital-temporal areas, including EBA (Downing, et al., 2001) and the fusiform body area (Peelen & Downing, 2005), are preferentially activated by the view of bodies and body parts (Orlov, et al., 2010). Anodal tDCS may boost neural responses to viewing the hand in these body-specific visual areas, producing a neural drive that inhibits processing in pain networks.

Our data cannot reveal what intermediate processing stages, if any, contribute to this inhibitory link. However, the posterior parietal cortex acts as a site of both convergence and modulation between visual and somatosensory regions (e.g., Avillac, et al., 2007), and thus may represent an important intermediate relay.

Interestingly, the analgesic effect of viewing the body may require recognition of personal identity. A previous study found no modulation of pain ratings and laser evoked potentials when viewing the hand of another person (Longo, et al., 2009). However, viewing photographs of one's partner reduced heat pain (Master, et al., 2009).

It is still controversial whether EBA is able to assign body identity, and contributes to discriminating self from other (Hodzic, Muckli, Singer, & Stirn, 2009; Myers & Sowden, 2008; Saxe, Jamal, & Powell, 2006). The recognition of identity seems also to involve other multisensory associative regions in the posterior parietal cortex, including the inferior parietal lobule and the inferior parietal sulcus (Hodzic, Kaas, Muckli, Stirn, & Singer, 2009). These regions are connected with visual body areas and therefore may also be involved in the visually-induced analgesia we show here. New studies are needed to shed further light on their role in pain modulation. Our findings clearly indicate that the source of this modulation involves the occipital cortex; higher integrative regions may be also involved, however.

It is worth noting that EBA may itself be a multisensory area, since it is activated by haptic as well as by visual body perception (Kitada, Johnsrude, Kochiyama, & Lederman, 2009). This suggests that the body representations formed in EBA might be partly amodal, as indeed are representations of non-body objects in other visual areas (Lacey, et al., 2009; Mancini, Bolognini, et al., 2011). Interestingly, a previous study investigated the relation between body representations and pain observation. Lamm and Decety (2008) compared EBA activation during observation of pain, but found no difference relative to a control condition not involving pain.

Clinical implications

The finding that viewing the body is analgesic suggests new possibilities to modulate acute pain crossmodally by manipulating the visual context.

Cognitive therapies that aim to relieve physical pain are generally focused on the painful stimulus itself, for example modulating expectations and attention towards pain sources. In the studies here presented I show that the multisensory context in which pain occurs, in this case the body and its appearance, is also important. Looking beyond the painful stimulus, to the body itself, may have novel therapeutic implications.

Moreover, I demonstrated that multisensory interactions can be facilitated by anodal tDCS. In particular, cortical excitability shifts induced by tDCS can modulate visual-nociceptive interactions, enhancing visual analgesia. tDCS is becoming extremely popular in the treatment of neuropathic and chronic pain (Brunoni, et al., in press; Fregni, Freedman, & Pascual-Leone, 2007; Lefaucheur, et al., 2008; Zaghi, Heine, & Fregni, 2009). Mounting evidence suggests that other sensory modalities including touch (Drew & MacDermott, 2009; Inui, Tsuji, & Kakigi, 2006), and vision (Mancini, Longo, et al., 2011) can significantly modulate pain. The present findings suggest to extend the range of regions targeted by tDCS in pain therapies, increasing the efficacy of both tDCS and multisensory therapies, by an approach involving combined tDCS and crossmodal stimulation.

Acknowledgments

My gratitude goes to my PhD supervisors, Prof. Giuseppe Vallar and Prof. Emanuela Bricolo, who first initiated me to research. With a unique combination of knowledge, expertise, trust and friendship, they supported me during my undergraduate studies and in all the different phases of this doctoral program.

I gratefully thank Prof. Patrick Haggard for his fine competence and for the support he demonstrated me during my visiting research work at the Institute of Cognitive Neuroscience (University College London).

I would like to thank my colleagues and co-authors, for the assistance they unfailingly provided at every stage of the research projects, particularly: Matthew Longo, Nadia Bolognini, Marjolein Kammers, and Flavia Caterina Mattioli.

My sincere thanks also go to all those who participated in the experiments and the hospital staff at Auxological Institute (Milano) and Spedali Civili (Brescia) for their assistance.

Finally, I am grateful to other teachers and collaborators who have been important for my scientific development, among them: Renato Michieli, Hans Spinnler, Denis Pelli, Marty Sereno, and Giandomenico Iannetti.

And, of course, thanks to whom I miss most, my family: thanks for your endless love and unconditional support.

References

Albert, M. L. (1973). A simple test of visual neglect. *Neurology, 23*, 658–664.

Amedi, A., Jacobson, G., Hendler, T., Malach, R., & Zohary, E. (2002). Convergence of visual and tactile shape processing in the human lateral occipital complex. *Cerebral Cortex, 12*, 1202-1212.

Amedi, A., Malach, R., Hendler, T., Peled, S., & Zohary, E. (2001). Visuo-haptic object-related activation in the ventral visual pathway. *Nature Neuroscience, 4*, 324-330.

Amedi, A., Raz, N., Azulay, H., Malach, R., & Zohary, E. (2010). Cortical activity during tactile exploration of objects in blind and sighted humans. *Restorative Neurology and Neuroscience, 28*, 143-156.

Amedi, A., Stern, W. M., Camprodon, J. A., Bermpohl, F., Merabet, L., Rotman, S., et al. (2007). Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. *Nature Neuroscience, 10*, 687-689.

Antal, A., Brepohl, N., Poreisz, C., Boros, K., Csifcsak, G., & Paulus, W. (2008). Transcranial direct current stimulation over somatosensory cortex decreases experimentally induced acute pain perception. *Clinical Journal of Pain, 24*, 56-63.

Antal, A., Nitsche, M. A., & Paulus, W. (2001). External modulation of visual perception in humans. *NeuroReport, 12*, 3553-3555.

Apkarian, A. V., Bushnell, M. C., Treede, R. D., & Zubieta, J. K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *European Journal of Pain, 9*, 463-484.

Auvray, M., Myin, E., & Spence, C. (2010). The sensory-discriminative and affective-motivational aspects of pain. *Neuroscience and Biobehavioral Reviews, 34*, 214-223.

Avillac, M., Ben Hamed, S., & Duhamel, J. R. (2007). Multisensory integration in the ventral intraparietal area of the macaque monkey. *Journal of Neuroscience, 27*, 1922-1932.

Avillac, M., Deneve, S., Olivier, E., Pouget, A., & Duhamel, J. R. (2005). Reference frames for representing visual and tactile locations in parietal cortex. *Nature Neuroscience, 8*, 941-949.

Baliki, M. N., Geha, P. Y., Fields, H. L., & Apkarian, A. V. (2010). Predicting value of pain and analgesia: nucleus accumbens response to noxious stimuli changes in the presence of chronic pain. *Neuron, 66*, 149-160.

Barbieri, C., & De Renzi, E. (1989). Patterns of neglect dissociation. *Behav Neurol, 2*, 13-24.

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell, 139*, 267-284.

Baumgartner, U., Iannetti, G. D., Zambreanu, L., Stoeter, P., Treede, R. D., & Tracey, I. (2010). Multiple somatotopic representations of heat and mechanical pain in the operculo-insular cortex: a high-resolution fMRI study. *Journal of Neurophysiology, 104*, 2863-2872.

Beauchamp, M. S. (2005). See me, hear me, touch me: multisensory integration in lateral occipital-temporal cortex. *Current Opinion in Neurobiology, 15*, 145-153.

Benton, A. L. (1994). Neuropsychological assessment. *Annual Review of Psychology, 45*, 1-23.

Beschin, N., Cazzani, M., Cubelli, R., Della Sala, S., & Spinazzola, L. (1996). Ignoring left and far: an investigation of tactile neglect. *Neuropsychologia, 34*, 41-49.

Binder, J., Marshall, R., Lazar, R., Benjamin, J., & Mohr, J. P. (1992). Distinct syndromes of hemineglect. *Archives of Neurology, 49*, 1187-1194.

Bisiach, E., Bulgarelli, C., Sterzi, R., & Vallar, G. (1983). Line bisection and cognitive plasticity of unilateral neglect of space. *Brain and Cognition, 2*, 32-38.

Bisiach, E., Capitani, E., Colombo, A., & Spinnler, H. (1976). Halving a horizontal segment: a study on hemisphere-damaged patients with cerebral focal lesions. *Schweiz Arch Neurol Psychiatr, 118*, 199-206.

Bisiach, E., Cornacchia, L., Sterzi, R., & Vallar, G. (1984). Disorders of perceived auditory lateralization after lesions of the right hemisphere. *Brain, 107*, 37-52.

Bisiach, E., & Faglioni, P. (1974). Recognition of random shapes by patients with unilateral lesions as a function of complexity, association value and delay. *Cortex, 10*, 101-110.

Blessing, S., & Svetlik, M. (2007). How the statistical structure of the environment affects perception of the Müller-Lyer illusion. In D. S. McNamara & J. G. Trafton (Eds.), *Proceedings of the 29th Annual Cognitive Science Society* (pp. 827-832). Austin, TX: Cognitive Science Society.

Boggio, P. S., Zaghi, S., Lopes, M., & Fregni, F. (2008). Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. *European Journal of Neurology, 15*, 1124-1130.

Bolognini, N., Frassinetti, F., Serino, A., & Ladavas, E. (2005). "Acoustical vision" of below threshold stimuli: interaction among spatially converging audiovisual inputs. *Experimental Brain Research, 160*, 273-282.

Bolognini, N., & Maravita, A. (2007). Proprioceptive alignment of visual and somatosensory maps in the posterior parietal cortex. *Current Biology, 17*, 1890-1895.

Bolognini, N., Miniussi, C., Savazzi, S., Bricolo, E., & Maravita, A. (2009). TMS modulation of visual and auditory processing in the posterior parietal cortex. *Experimental Brain Research, 195*, 509-517.

Boroojerdi, B., Prager, A., Muellbacher, W., & Cohen, L. G. (2000). Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. *Neurology, 54*, 1529-1531.

Bottini, G., Paulesu, E., Gandola, M., Loffredo, S., Scarpa, P., Sterzi, R., et al. (2005). Left caloric vestibular stimulation ameliorates right hemianesthesia. *Neurology, 65*, 1278-1283.

Brandt, T., Glasauer, S., Strupp, M., & Dieterich, M. (2009). Spatial neglect: hypothetical mechanisms of disturbed interhemispheric crosstalk for orientation. *Annals of the New York Academy of Sciences, 1164*, 216-221.

Bremmer, F., Schlack, A., Shah, N. J., Zafiris, O., Kubischik, M., Hoffmann, K., et al. (2001). Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. *Neuron, 29*, 287-296.

Bresciani, J. P., Dammeier, F., & Ernst, M. O. (2006). Vision and touch are automatically integrated for the perception of sequences of events. *Journal of Vision, 6*, 554-564.

Brozzoli, C., Demattè, M. L., Pavani, F., Frassinetti, F., & Farnè, A. (2006). Neglect and extinction: within and between sensory modalities. *Restorative Neurology and Neuroscience, 24*, 217-232.

Bruno, N., Bernardis, P., & Gentilucci, M. (2008). Visually guided pointing, the Muller-Lyer illusion, and the functional interpretation of the dorsal-ventral split: conclusions from 33 independent studies. *Neuroscience and Biobehavioral Reviews, 32*, 423-437.

Bruno, N., & Franz, V. H. (2009). When is grasping affected by the Muller-Lyer illusion? A quantitative review. *Neuropsychologia, 47*, 1421-1433.

Bruno, N., Knox, P. C., & de Grave, D. D. (2010). A metanalysis of the effect of the Muller-Lyer illusion on saccadic eye movements: no general support for a dissociation of perception and oculomotor action. *Vis Res, 50*, 2671-2682.

Brunoni, A. R., Nitsche, M. A., Bolognini, N., Bikson, M., Wagner, T., & Merabet, L. (in press). Clinical research with Transcranial Direct Current Stimulation (tDCS): Challenges and future directions. *Brain stimulation*.

Bultitude, J. H., & Rafal, R. D. (2010). Derangement of body representation in complex regional pain syndrome: report of a case treated with mirror and prisms. *Experimental Brain Research, 204*, 409-418.

Bushara, K. O., Weeks, R. A., Ishii, K., Catalan, M. J., Tian, B., Rauschecker, J. P., et al. (1999). Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans. *Nature Neuroscience, 2*, 759-766.

Calvert, G. A., Bullmore, E. T., Brammer, M. J., Campbell, R., Williams, S. C., McGuire, P. K., et al. (1997). Activation of auditory cortex during silent lipreading. *Science, 276*, 593-596.

Campbell, D. C., & Oxbury, J. M. (1976). Recovery from unilateral visuo-spatial neglect? *Cortex, 12*, 303-312.

Canavero, S., & Bonicalzi, V. (1998). The neurochemistry of central pain: evidence from clinical studies, hypothesis and therapeutic implications. *Pain, 74*, 109-114.

Cappelletti, M., Barth, H., Fregni, F., Spelke, E. S., & Pascual-Leone, A. (2007). rTMS over the intraparietal sulcus disrupts numerosity processing. *Experimental Brain Research, 179*, 631-642.

Cardini, F., Longo, M. R., & Haggard, P. (2011). Vision of the body modulates somatosensory intracortical inhibition. *Cerebral Cortex, 21*, 2014-2022.

Chedru, F. (1976). Space representation in unilateral spatial neglect. *Journal of Neurology, Neurosurgery, and Psychiatry, 39*, 1057-1061.

Chen, R., Classen, J., Gerloff, C., Celnik, P., Wassermann, E. M., Hallett, M., et al. (1997). Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology, 48*, 1398-1403.

Chokron, S., Colliot, P., Bartolomeo, P., Rhein, F., Eusop, E., Vassel, P., et al. (2002). Visual, proprioceptive and tactile performance in left neglect patients. *Neuropsychologia, 40*, 1965-1976.

Chokron, S., Dupierrix, E., Tabert, M., & Bartolomeo, P. (2007). Experimental remission of unilateral spatial neglect. *Neuropsychologia, 45*, 3127-3148.

Chou, R., & Huffman, L. H. (2007). Nonpharmacologic therapies for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Annals of Internal Medicine, 147*, 492-504.

Ciçek, M., Deouell, L. Y., & Knight, R. T. (2009). Brain activity during landmark and line bisection tasks. *Frontiers in human neuroscience, 3*, 7.

Corbetta, M., Shulman, G. L., Miezin, F. M., & Petersen, S. E. (1995). Superior parietal cortex activation during spatial attention shifts and visual feature conjunction. *Science, 270*, 802-805.

Coren, S., & Gircus, J. S. (1978). *Seeing is deceiving: The psychology of visual illusions*. Hillsdale, New Jersey: Lawrence Erlbaum.

Coren, S., & Girgus, J. S. (1974). Transfer of illusion decrement as a function of perceived similarity. *Journal of Experimental Psychology, 102*, 881-887.

Coren, S., & Girgus, J. S. (1978). Visual illusions. In R. Held, H. W. Leibowitz & H.-L. Teuber (Eds.), *Handbook of sensory physiology*. *Perception* (Vol. 8, pp. 548-568). Berlin, Heidelberg, New York: Springer.

Coslett, H. B., & Lie, E. (2004). Bare hands and attention: evidence for a tactile representation of the human body. *Neuropsychologia, 42*, 1865-1876.

Costa, L. D. (1976). Interset variability on the Raven coloured progressive matrices as an indicator of specific ability deficit in brain-lesioned patients. *Cortex, 12*, 31-40.

Coulthard, E., Parton, A., & Husain, M. (2006). Action control in visual neglect. *Neuropsychologia, 44*, 2717-2733.

Crawford, J. R., & Garthwaite, P. H. (2002). Investigation of the single case in neuropsychology: confidence limits on the abnormality of test scores and test score differences. *Neuropsychologia, 40*, 1196-1208.

Crone, N. E., Miglioretti, D. L., Gordon, B., Sieracki, J. M., Wilson, M. T., Uematsu, S., et al. (1998). Functional mapping of human sensorimotor cortex with electrocorticographic spectral analysis. I. Alpha and beta event-related desynchronization. *Brain, 121*, 2271-2299.

Csifcsak, G., Antal, A., Hillers, F., Levold, M., Bachmann, C. G., Happe, S., et al. (2009). Modulatory effects of transcranial direct current stimulation on laser-evoked potentials. *Pain Medicine, 10*, 122-132.

Cubelli, R., Nichelli, P., Bonito, V., De Tanti, A., & Inzaghi, M. G. (1991). Different patterns of dissociation in unilateral spatial neglect. *Brain and Cognition, 15*, 139-159.

Daini, R., Angelelli, P., Antonucci, G., Cappa, S. F., & Vallar, G. (2002). Exploring the syndrome of spatial unilateral neglect through an illusion of length. *Experimental Brain Research, 144*, 224-237.

Dasilva, A. F., Volz, M. S., Bikson, M., & Fregni, F. (2011). Electrode positioning and montage in transcranial direct current stimulation. *Journal of Visualized Experiments, 23*, 2744.

De Renzi, E., Faglioni, P., & Scotti, G. (1970). Hemispheric contribution to exploration of space through the visual and tactile modality. *Cortex, 6*, 191-203.

de Tommaso, M., Calabrese, R., Vecchio, E., De Vito Francesco, V., Lancioni, G., & Livrea, P. (2009). Effects of affective pictures on pain sensitivity and cortical responses induced by laser stimuli in healthy subjects and migraine patients. *International Journal of Psychophysiology, 74*, 139-148.

de Wied, M., & Verbaten, M. N. (2001). Affective pictures processing, attention, and pain tolerance. *Pain, 90*, 163-172.

Delorme, A., & Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *Journal of Neuroscience Methods, 134*, 9-21.

Denny-Brown, D., Meyer, J. S., & Horenstein, S. (1952). The significance of perceptual rivalry resulting from parietal lesion. *Brain, 75*, 433-471.

Deshpande, G., Hu, X., Lacey, S., Stilla, R., & Sathian, K. (2010). Object familiarity modulates effective connectivity during haptic shape perception. *NeuroImage, 49*, 1991-2000.

Deshpande, G., Hu, X., Stilla, R., & Sathian, K. (2008). Effective connectivity during haptic perception: a study using Granger causality analysis of functional magnetic resonance imaging data. *NeuroImage, 40*, 1807-1814.

Dieckhofer, A., Waberski, T. D., Nitsche, M., Paulus, W., Buchner, H., & Gobbele, R. (2006). Transcranial direct current stimulation applied over the somatosensory cortex - differential effect on low and high frequency SEPs. *Clinical Neurophysiology, 117*, 2221-2227.

Diller, L., & Weinberg, J. (1977). Hemi-inattention in rehabilitation. The evolution of a rational remediation program. In E. A. Weinstein & R. P. Friedland (Eds.), *Hemi-inattention and Hemisphere Specialization* (pp. 62–82). New York: Raven Press.

Dowman, R. (2011). The role of somatic threat feature detectors in the attentional bias toward pain: effects of spatial attention. *Psychophysiology, 48*, 397-409.

Downing, P. E., Jiang, Y., Shuman, M., & Kanwisher, N. (2001). A cortical area selective for visual processing of the human body. *Science, 293*, 2470-2473.

Drew, L. J., & MacDermott, A. B. (2009). Neuroscience: Unbearable lightness of touch. *Nature, 462*, 580-581.

Driver, J., & Spence, C. (2000). Multisensory perception: beyond modularity and convergence. *Current Biology, 10*, R731-735.

Ehrsson, H. H., Wiech, K., Weiskopf, N., Dolan, R. J., & Passingham, R. E. (2007). Threatening a rubber hand that you feel is yours elicits a cortical anxiety response. *Proceedings of the National Academy of Sciences of the United States of America, 104*, 9828-9833.

Eimer, M., & Driver, J. (2000). An event-related brain potential study of cross-modal links in spatial attention between vision and touch. *Psychophysiology, 37*, 697-705.

Eisenberger, N. I., & Lieberman, M. D. (2004). Why rejection hurts: a common neural alarm system for physical and social pain. *Trends in Cognitive Sciences, 8*, 294-300.

Ellis, R. R., Flanagan, J. R., & Lederman, S. J. (1999). The influence of visual illusions on grasp position. *Experimental Brain Research, 125*, 109-114.

Ernst, M. O., & Banks, M. S. (2002). Humans integrate visual and haptic information in a statistically optimal fashion. *Nature, 415*, 429-433.

Ernst, M. O., & Bulthoff, H. H. (2004). Merging the senses into a robust percept. *Trends in Cognitive Sciences, 8*, 162-169.

Feinberg, T. E., Rothi, L. J., & Heilman, K. M. (1986). Multimodal agnosia after unilateral left hemisphere lesion. *Neurology, 36*, 864-867.

Fellows, B. J. (1967). Reversal of the Müller-Lyer illusion with changes in the length of the inter-fins line. *Quarterly Journal of Experimental Psychology, 19*, 208-214.

Fierro, B., Brighina, F., Oliveri, M., Piazza, A., La Bua, V., Buffa, D., et al. (2000). Contralateral neglect induced by right posterior parietal rTMS in healthy subjects. *NeuroReport, 11*, 1519-1521.

Fink, G. R., Marshall, J. C., Shah, N. J., Weiss, P. H., Halligan, P. W., Grosse-Ruyken, M., et al. (2000). Line bisection judgments implicate right parietal cortex and cerebellum as assessed by fMRI. *Neurology, 54*, 1324-1331.

Fink, G. R., Marshall, J. C., Weiss, P. H., Stephan, T., Grefkes, C., Shah, N. J., et al. (2003). Performing allocentric visuospatial judgments with induced distortion of the egocentric reference frame: an fMRI study with clinical implications. *NeuroImage, 20*, 1505-1517.

Fiorio, M., & Haggard, P. (2005). Viewing the body prepares the brain for touch: effects of TMS over somatosensory cortex. *European Journal of Neuroscience, 22*, 773-777.

Fortis, P., Maravita, A., Gallucci, M., Ronchi, R., Grassi, E., Senna, I., et al. (2010). Rehabilitating patients with left spatial neglect by prism exposure during a visuomotor activity. *Neuropsychology, 24*, 681-697.

Foxe, J. J., Morocz, I. A., Murray, M. M., Higgins, B. A., Javitt, D. C., & Schroeder, C. E. (2000). Multisensory auditory-somatosensory interactions in early cortical processing revealed by high-density electrical mapping. *Brain research. Cognitive brain research, 10*, 77-83.

Frassinetti, F., Bolognini, N., Bottari, D., Bonora, A., & Ladavas, E. (2005). Audiovisual integration in patients with visual deficit. *Journal of Cognitive Neuroscience, 17*, 1442-1452.

Frassinetti, F., Bolognini, N., & Ladavas, E. (2002). Enhancement of visual perception by crossmodal visuo-auditory interaction. *Experimental Brain Research, 147*, 332-343.

Frassinetti, F., Pavani, F., & Ladavas, E. (2002). Acoustical vision of neglected stimuli: interaction among spatially converging audiovisual inputs in neglect patients. *Journal of Cognitive Neuroscience, 14*, 62-69.

Fregni, F., Freedman, S., & Pascual-Leone, A. (2007). Recent advances in the treatment of chronic pain with non-invasive brain stimulation techniques. *Lancet Neurology, 6*, 188-191.

Frisby, J. P., & Davies, I. R. (1971). Is the haptic Müller-Lyer a visual phenomenon? *Nature, 231*, 463-465.

Fu, K. M., Johnston, T. A., Shah, A. S., Arnold, L., Smiley, J., Hackett, T. A., et al. (2003). Auditory cortical neurons respond to somatosensory stimulation. *Journal of Neuroscience, 23*, 7510-7515.

Fujii, T., Fukatsu, R., Kimura, I., Saso, S., & Kogure, K. (1991). Unilateral spatial neglect in visual and tactile modalities. *Cortex, 27*, 339-343.

Gainotti, G. (2010). The role of automatic orienting of attention towards ipsilesional stimuli in non-visual (tactile and auditory) neglect: a critical review. *Cortex, 46*, 150-160.

Gainotti, G., Messerli, P., & Tissot, R. (1972). Qualitative analysis of unilateral spatial neglect in relation to laterality of cerebral lesions. *Journal of Neurology, Neurosurgery, and Psychiatry, 35*, 545–550.

Gallace, A., Imbornone, E., & Vallar, G. (2008). When the whole is more than the sum of the parts: evidence from visuospatial neglect. *Journal of Neuropsychology, 2*, 387-413.

Gallace, A., & Spence, C. (2005). Examining the crossmodal consequences of viewing the Müller-Lyer illusion. *Experimental Brain Research, 162*, 490-496.

Gallace, A., Torta, D. M., Moseley, G. L., & Iannetti, G. D. (2011). The analgesic effect of crossing the arms. *Pain, 152*, 1418-1423.

Gandevia, S. C., & Phegan, C. M. (1999). Perceptual distortions of the human body image produced by local anaesthesia, pain and cutaneous stimulation. *Journal of Physiology, 514*, 609-616.

Gandiga, P. C., Hummel, F. C., & Cohen, L. G. (2006). Transcranial DC stimulation (tDCS): a tool for double-blind sham-controlled clinical studies in brain stimulation. *Clinical Neurophysiology, 117*, 845-850.

Gangopadhyay, N., Madary, M., & Spicer, F. (2010). *Perception, action and consciousness. Sensorimotor dynamics and the two visual systems*. Oxford: Oxford University Press.

Gauthier, L., Dehaut, F., & Joanette, Y. (1989). The bells test: a quantitative and qualitative test for visual neglect. *International Journal of Clinical Neuropsychology, 11*, 49-54.

Gazzaniga, M. (2000). *The new cognitive neurosciences*: MIT Press.

Gentaz, E., Camos, V., Hatwell, Y., & Jacquet, A. Y. (2004). The visual and haptic Müller-Lyer illusions: correlation study. *Current Psychology Letters, 13*.

Gentaz, E., & Hatwell, Y. (2004). Geometrical haptic illusions: the role of exploration in the Müller-Lyer, vertical-horizontal, and Delboeuf illusions. *Psychonomic Bulletin & Review, 11*, 31-40.

Gentilini, M., Barbieri, C., De Renzi, E., & Faglioni, P. (1989). Space exploration with and without the aid of vision in hemisphere-damaged patients. *Cortex, 25*, 643-651.

Gepshtein, S., Burge, J., Ernst, M. O., & Banks, M. S. (2005). The combination of vision and touch depends on spatial proximity. *Journal of Vision, 5*, 1013-1023.

Geyer, S., Schleicher, A., & Zilles, K. (1999). Areas 3a, 3b, and 1 of human primary somatosensory cortex. *NeuroImage, 10*, 63-83.

Ghazanfar, A. A., & Schroeder, C. E. (2006). Is neocortex essentially multisensory? *Trends in Cognitive Sciences, 10*, 278-285.

Gillam, B. (1980). Geometric illusions. *Scientific American, 242*, 102-111.

Gilliatt, R. W., & Pratt, R. T. (1952). Disorders of perception and performance in a case of right-sided cerebral thrombosis. *Journal of Neurology, Neurosurgery, and Psychiatry, 15*, 264-271.

Gottesman, R. F., Kleinman, J. T., Davis, C., Heidler-Gary, J., Newhart, M., Kannan, V., et al. (2008). Unilateral neglect is more severe and common in older patients with right hemispheric stroke. *Neurology, 71*, 1439-1444.

Graziano, M. S., & Gross, C. G. (1993). A bimodal map of space: somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. *Experimental Brain Research, 97*, 96-109.

Graziano, M. S., Yap, G. S., & Gross, C. G. (1994). Coding of visual space by premotor neurons. *Science, 266*, 1054-1057.

Green, B. G. (2004). Temperature perception and nociception. *Journal of Neurobiology, 61*, 13-29.

Gregory, R. L. (1967). Comments on the inappropriate constancy scaling theory of the illusions and its implications. *Quarterly Journal of Experimental Psychology, 19*, 219-223.

Grigoletto, F., Zappala, G., Anderson, D. W., & Lebowitz, B. D. (1999). Norms for the Mini-Mental State Examination in a healthy population. *Neurology, 53*, 315-320.

Grill-Spector, K. (2003). The neural basis of object perception. *Current Opinion in Neurobiology, 13*, 159-166.

Gybels, J., Handwerker, H. O., & Van Hees, J. (1979). A comparison between the discharges of human nociceptive nerve fibres and the subject's ratings of his sensations. *Journal of Physiology, 292*, 193-206.

Haeske-Dewick, H. C., Canavan, A. G., & Homberg, V. (1996). Directional hyperattention in tactile neglect within grasping space. *J Clin Exp Neuropsychol, 18*, 724-732.

Haggard, P. (2009). Neuroscience. The sources of human volition. *Science, 324*, 731-733.

Hall, S. D., Barnes, G. R., Furlong, P. L., Seri, S., & Hillebrand, A. (2010). Neuronal network pharmacodynamics of GABAergic modulation in the human cortex determined using pharmaco-magnetoencephalography. *Human Brain Mapping, 31*, 581-594.

Halligan, P. W., Fink, G. R., Marshall, J. C., & Vallar, G. (2003). Spatial cognition: evidence from visual neglect. *Trends in Cognitive Sciences, 7*, 125-133.

Hari, R., & Salmelin, R. (1997). Human cortical oscillations: a neuromagnetic view through the skull. *Trends in Neuroscience, 20*, 44-49.

Harris, I. M., & Miniussi, C. (2003). Parietal lobe contribution to mental rotation demonstrated with rTMS. *Journal of Cognitive Neuroscience, 15*, 315-323.

Harris, J. A., Arabzadeh, E., Moore, C. A., & Clifford, C. W. (2007). Noninformative vision causes adaptive changes in tactile sensitivity. *Journal of Neuroscience, 27*, 7136-7140.

Hauck, M., Lorenz, J., & Engel, A. K. (2007). Attention to painful stimulation enhances gamma-band activity and synchronization in human sensorimotor cortex. *Journal of Neuroscience, 27*, 9270-9277.

Heilman, K. M., Watson, R. T., & Valenstein, E. (2003). Neglect and related disorders. In K. M. Heilman & E. Valenstein (Eds.), *Clinical neuropsychology* (4 ed., pp. 296-346). New York: Oxford University Press.

Heller, M. A., Brackett, D. D., Wilson, K., Yoneyama, K., Boyer, A., & Steffen, H. (2002). The haptic Müller-Lyer illusion in sighted and blind people. *Perception, 31*, 1263-1274.

Heller, M. A., McCarthy, M., Schultz, J., Greene, J., Shanley, M., Clark, A., et al. (2005). The influence of exploration mode, orientation, and configuration on the haptic Müller-Lyer illusion. *Perception, 34*, 1475-1500.

Hier, D. B., Mondlock, J., & Caplan, L. R. (1983a). Behavioral abnormalities after right hemisphere stroke. *Neurology, 33*, 337-344.

Hier, D. B., Mondlock, J., & Caplan, L. R. (1983b). Recovery of behavioral abnormalities after right hemisphere stroke. *Neurology, 33*, 345-350.

Hillis, A. E., Chang, S., Heidler-Gary, J., Newhart, M., Kleinman, J. T., Davis, C., et al. (2006). Neural correlates of modality-specific spatial extinction. *Journal of Cognitive Neuroscience, 18*, 1889-1898.

Hjaltason, H., Caneman, G., & Tegner, R. (1993). Visual and tactile rod bisection in unilateral neglect. *Cortex, 29*, 583-588.

Hodzic, A., Kaas, A., Muckli, L., Stirn, A., & Singer, W. (2009). Distinct cortical networks for the detection and identification of human body. *NeuroImage, 45*, 1264-1271.

Hodzic, A., Muckli, L., Singer, W., & Stirn, A. (2009). Cortical responses to self and others. *Human Brain Mapping, 30*, 951-962.

Holding, D. H. (1970). Notes and discussion. A line illusion with irrelevant depth cues. *American Journal of Psychology, 83*, 280-282.

Honoré, J., Hénon, H., & Naveteur, J. (1995). Influence of eye orientation on pain as a function of anxiety. *Pain, 63*, 213-218.

Hoogenraad, T. U., Ramos, L. M., & van Gijn, J. (1994). Visually induced central pain and arm withdrawal after right parietal lobe infarction. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*, 850-852.

Husain, M. (2008). Hemispatial neglect. In P. J. Vinken & G. W. Bruyn (Eds.), *Handbook of clinical neurology* (Vol. 88, pp. 359-372). Amsterdam: Elsevier.

Hyvarinen, J. (1981). Regional distribution of functions in parietal association area 7 of the monkey. *Brain Research, 206*, 287-303.

Iannetti, G. D., Hughes, N. P., Lee, M. C., & Mouraux, A. (2008). Determinants of laser-evoked EEG responses: pain perception or stimulus saliency? *Journal of Neurophysiology, 100*, 815-828.

Iannetti, G. D., & Mouraux, A. (2010). From the neuromatrix to the pain matrix (and back). *Experimental Brain Research, 205*, 1-12.

Inui, K., Tsuji, T., & Kakigi, R. (2006). Temporal analysis of cortical mechanisms for pain relief by tactile stimuli in humans. *Cerebral Cortex, 16*, 355-365.

Jacquin-Courtois, S., Rode, G., Pavani, F., O'Shea, J., Giard, M. H., Boisson, D., et al. (2010). Effect of prism adaptation on left dichotic listening deficit in neglect patients: glasses to hear better? *Brain, 133*, 895-908.

James, T. W., Humphrey, G. K., Gati, J. S., Servos, P., Menon, R. S., & Goodale, M. A. (2002). Haptic study of three-dimensional objects activates extrastriate visual areas. *Neuropsychologia, 40*, 1706-1714.

James, T. W., James, K. H., & Humphrey, G. K. (2006). Do visual and tactile object representations share the same neural substrate? In M. A. Heller & S. Ballesteros (Eds.), *Touch and blindness. Psychology and neuroscience.* (pp. 139-155). Mahwah, New Jersey: Lawrence Erlbaum Associates.

Jensen, O., Goel, P., Kopell, N., Pohja, M., Hari, R., & Ermentrout, B. (2005). On the human sensorimotor-cortex beta rhythm: sources and modeling. *NeuroImage, 26*, 347-355.

Jewell, G., & McCourt, M. E. (2000). Pseudoneglect: a review and meta-analysis of performance factors in line bisection tasks. *Neuropsychologia, 38*, 93-110.

Jones, S. R., Kerr, C. E., Wan, Q., Pritchett, D. L., Hamalainen, M., & Moore, C. I. (2010). Cued spatial attention drives functionally relevant modulation of the mu rhythm in primary somatosensory cortex. *Journal of Neuroscience, 30*, 13760-13765.

Judd, C. H. (1899). A study of geometrical illusions. *Psychol Rev, 6*, 241-261.

Jung, T. P., Makeig, S., Humphries, C., Lee, T. W., McKeown, M. J., Iragui, V., et al. (2000). Removing electroencephalographic artifacts by blind source separation. *Psychophysiology, 37*, 163-178.

Kammers, M. P., de Vignemont, F., & Haggard, P. (2010). Cooling the thermal grill illusion through self-touch. *Current Biology, 20*, 1819-1822.

Karnath, H. O., Fruhmann Berger, M., Zopf, R., & Kuker, W. (2004). Using SPM normalization for lesion analysis in spatial neglect. *Brain, 127*, E10.

Katsarava, Z., Ayzenberg, I., Sack, F., Limmroth, V., Diener, H. C., & Kaube, H. (2006). A novel method of eliciting pain-related potentials by transcutaneous electrical stimulation. *Headache, 46*, 1511-1517.

Katsarava, Z., Ellrich, J., Diener, H. C., & Kaube, H. (2002). Optimized stimulation and recording parameters of human 'nociception specific' blink reflex recordings. *Clinical Neurophysiology, 113*, 1932-1936.

Kaube, H., Katsarava, Z., Kaufer, T., Diener, H., & Ellrich, J. (2000). A new method to increase nociception specificity of the human blink reflex. *Clinical Neurophysiology, 111*, 413-416.

Kayser, C., Petkov, C. I., Augath, M., & Logothetis, N. K. (2005). Integration of touch and sound in auditory cortex. *Neuron, 48*, 373-384.

Kennett, S., Taylor-Clarke, M., & Haggard, P. (2001). Noninformative vision improves the spatial resolution of touch in humans. *Current Biology, 11*, 1188-1191.

Kenntner-Mabiala, R., & Pauli, P. (2005). Affective modulation of brain potentials to painful and nonpainful stimuli. *Psychophysiology, 42*, 559-567.

Kerkhoff, G. (2003). Modulation and rehabilitation of spatial neglect by sensory stimulation. *Progress in Brain Research, 142*, 257-271.

Kim, S., & James, T. W. (2010). Enhanced effectiveness in visuo-haptic object-selective brain regions with increasing stimulus salience. *Human Brain Mapping, 31*, 678-693.

Kitada, R., Johnsrude, I. S., Kochiyama, T., & Lederman, S. J. (2009). Functional specialization and convergence in the occipito-temporal cortex supporting haptic and visual identification of human faces and body parts: an fMRI study. *Journal of Cognitive Neuroscience, 21*, 2027-2045.

Klimesch, W., Sauseng, P., & Hanslmayr, S. (2007). EEG alpha oscillations: the inhibition-timing hypothesis. *Brain Research Reviews, 53*, 63-88.

Knecht, S., Ellger, T., Breitenstein, C., Bernd Ringelstein, E., & Henningsen, H. (2003). Changing cortical excitability with low-frequency transcranial magnetic stimulation can induce sustained disruption of tactile perception. *Biological Psychiatry, 53*, 175-179.

Kourtzi, Z., & Kanwisher, N. (2001). Representation of perceived object shape by the human lateral occipital complex. *Science, 293*, 1506-1509.

Kubovy, M., & van den Berg, M. (2008). The whole is equal to the sum of its parts: a probabilistic model of grouping by proximity and similarity in regular patterns. *Psychological Review, 115*, 131-154.

Lacey, S., Campbell, C., & Sathian, K. (2007). Vision and touch: multiple or multisensory representations of objects? *Perception, 36*, 1513-1521.

Lacey, S., Flueckiger, P., Stilla, R., Lava, M., & Sathian, K. (2010). Object familiarity modulates the relationship between visual object imagery and haptic shape perception. *NeuroImage, 49*, 1977-1990.

Lacey, S., Tal, N., Amedi, A., & Sathian, K. (2009). A putative model of multisensory object representation. *Brain Topography, 21*, 269-274.

Làdavas, E., Menghini, G., & Umiltà, C. (1994). A rehabilitation study of hemispatial neglect. *Cognitive Neuropsychology, 11*, 75-95.

Lamm, C., & Decety, J. (2008). Is the extrastriate body area (EBA) sensitive to the perception of pain in others? *Cerebral Cortex, 18*, 2369-2373.

Lefaucheur, J. P., Antal, A., Ahdab, R., Ciampi de Andrade, D., Fregni, F., Khedr, E. M., et al. (2008). The use of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to relieve pain. *Brain stimulation, 1*, 337-344.

Lefaucheur, J. P., Drouot, X., Menard-Lefaucheur, I., Keravel, Y., & Nguyen, J. P. (2006). Motor cortex rTMS restores defective intracortical inhibition in chronic neuropathic pain. *Neurology, 67*, 1568-1574.

Legrain, V., Bultitude, J. H., De Paepe, A., & Rossetti, Y. (in press). Pain, body, and space. What do patients with complex regional pain syndrome really neglect? *Pain*.

Legrain, V., Guerit, J. M., Bruyer, R., & Plaghki, L. (2002). Attentional modulation of the nociceptive processing into the human brain: selective spatial attention, probability of stimulus occurrence, and target detection effects on laser evoked potentials. *Pain, 99*, 21-39.

Legrain, V., Iannetti, G. D., Plaghki, L., & Mouraux, A. (2011). The pain matrix reloaded: a salience detection system for the body. *Progress in Neurobiology, 93*, 111-124.

Leibovitch, F. S., Black, S. E., Caldwell, C. B., Ebert, P. L., Ehrlich, L. E., & Szalai, J. P. (1998). Brain-behavior correlations in hemispatial neglect using CT and SPECT: the Sunnybrook Stroke Study. *Neurology, 50*, 901-908.

Lewis, J. S., Kersten, P., McCabe, C. S., McPherson, K. M., & Blake, D. R. (2007). Body perception disturbance: a contribution to pain in complex regional pain syndrome (CRPS). *Pain, 133*, 111-119.

Lima, M. C., & Fregni, F. (2008). Motor cortex stimulation for chronic pain: systematic review and meta-analysis of the literature. *Neurology, 70*, 2329-2337.

Lloyd, D., Morrison, I., & Roberts, N. (2006). Role for human posterior parietal cortex in visual processing of aversive objects in peripersonal space. *Journal of Neurophysiology, 95*, 205-214.

Longo, M. R., Betti, V., Aglioti, S. M., & Haggard, P. (2009). Visually induced analgesia: seeing the body reduces pain. *Journal of Neuroscience, 29*, 12125-12130.

Macaluso, E. (2006). Multisensory processing in sensory-specific cortical areas. *Neuroscientist, 12*, 327-338.

Macaluso, E., & Driver, J. (2001). Spatial attention and crossmodal interactions between vision and touch. *Neuropsychologia, 39*, 1304-1316.

Macaluso, E., & Driver, J. (2005). Multisensory spatial interactions: a window onto functional integration in the human brain. *Trends in Neuroscience, 28*, 264-271.

Macaluso, E., Frith, C. D., & Driver, J. (2000). Modulation of human visual cortex by crossmodal spatial attention. *Science, 289*, 1206-1208.

Maihofner, C., Handwerker, H. O., Neundorfer, B., & Birklein, F. (2003). Patterns of cortical reorganization in complex regional pain syndrome. *Neurology, 61*, 1707-1715.

Malach, R., Reppas, J. B., Benson, R. R., Kwong, K. K., Jiang, H., Kennedy, W. A., et al. (1995). Object-related activity revealed by functional magnetic resonance imaging in human occipital cortex. *Proceedings of the National Academy of Science USA, 92*, 8135-8139.

Mancini, F., Bolognini, N., Bricolo, E., & Vallar, G. (2011). Cross-modal Processing in the Occipito-temporal Cortex: A TMS Study of the Muller-Lyer Illusion. *Journal of Cognitive Neuroscience, 23*, 1987-1997.

Mancini, F., Bricolo, E., & Vallar, G. (2010). Multisensory integration in the Müller-Lyer illusion: From vision to haptics. *Quarterly Journal of Experimental Psychology, 63*, 818-830.

Mancini, F., Longo, M. R., Kammers, M. P., & Haggard, P. (2011). Visual distortion of body size modulates pain perception. *Psychological Science, 22*, 325-330.

Maravita, A., McNeil, J., Malhotra, P., Greenwood, R., Husain, M., & Driver, J. (2003). Prism adaptation can improve contralesional tactile perception in neglect. *Neurology, 60*, 1829-1831.

Master, S. L., Eisenberger, N. I., Taylor, S. E., Naliboff, B. D., Shirinyan, D., & Lieberman, M. D. (2009). A picture's worth: partner photographs reduce experimentally induced pain. *Psychological Science, 20*, 1316-1318.

Matsunaga, K., Nitsche, M. A., Tsuji, S., & Rothwell, J. C. (2004). Effect of transcranial DC sensorimotor cortex stimulation on somatosensory evoked potentials in humans. *Clinical Neurophysiology, 115*, 456-460.

Mattingley, J. B., Bradshaw, J. L., & Bradshaw, J. A. (1995). The effects of unilateral visuospatial neglect on perception of Müller-Lyer illusory figures. *Perception, 24*, 415-433.

McDonald, J. J., Teder-Salejarvi, W. A., & Hillyard, S. A. (2000). Involuntary orienting to sound improves visual perception. *Nature, 407*, 906-908.

McGurk, H., & MacDonald, J. (1976). Hearing lips and seeing voices. *Nature, 264*, 746-748.

Melzack, R., & Casey, K. L. (1968). Sensory, motivational and central control determinants of pain: a new conceptual model. In D. Kenshalo (Ed.), *The skin senses* (pp. 423-439). Springfield, IL: C.C. Thomas.

Melzack, R., & Wall, P. D. (1965). Pain mechanisms: a new theory. *Science, 150*, 971-979.

Merabet, L., Thut, G., Murray, B., Andrews, J., Hsiao, S., & Pascual-Leone, A. (2004). Feeling by sight or seeing by touch? *Neuron, 42*, 173-179.

Meredith, M. A., & Stein, B. E. (1986). Visual, auditory, and somatosensory convergence on cells in superior colliculus results in multisensory integration. *Journal of Neurophysiology, 56*, 640-662.

Millar, S., & Al-Attar, Z. (2002). The Müller-Lyer illusion in touch and vision: implications for multisensory processes. *Perception and Psychophysics, 64*, 353-365.

Milner, A. D., & Goodale, M. (2006). *The visual brain in action* (2nd ed.). Oxford: Oxford University Press.

Molholm, S., Sehatpour, P., Mehta, A. D., Shpaner, M., Gomez-Ramirez, M., Ortigue, S., et al. (2006). Audio-visual multisensory integration in superior parietal lobule revealed by human intracranial recordings. *Journal of Neurophysiology, 96*, 721-729.

Mon-Williams, M., & Bull, R. (2000). The Judd illusion: evidence for two visual streams or two experimental conditions? *Experimental Brain Research, 130*, 273-276.

Mort, D. J., Malhotra, P., Mannan, S. K., Rorden, C., Pambakian, A., Kennard, C., et al. (2003). The anatomy of visual neglect. *Brain, 126*, 1986-1997.

Moseley, G. L., Gallace, A., & Spence, C. (2009). Space-based, but not arm-based, shift in tactile processing in complex regional pain syndrome and its relationship to cooling of the affected limb. *Brain, 132*, 3142-3151.

Moseley, G. L., Parsons, T. J., & Spence, C. (2008). Visual distortion of a limb modulates the pain and swelling evoked by movement. *Current Biology, 18*, R1047-1048.

Moseley, G. L., Sim, D. F., Henry, M. L., & Souvlis, T. (2005). Experimental hand pain delays recognition of the contralateral hand--evidence that acute and chronic pain have opposite effects on information processing? *Brain research. Cognitive brain research, 25*, 188-194.

Mouraux, A., Diukova, A., Lee, M. C., Wise, R. G., & Iannetti, G. D. (2011). A multisensory investigation of the functional significance of the "pain matrix". *NeuroImage, 54*, 2237-2249.

Mouraux, A., Guerit, J. M., & Plaghki, L. (2003). Non-phase locked electroencephalogram (EEG) responses to CO2 laser skin stimulations may reflect central interactions between A partial partial differential- and C-fibre afferent volleys. *Clinical Neurophysiology, 114*, 710-722.

Müller-Lyer, F. C. (1889). Optische Urteilstäuschungen. *Archiv für Physiologie, 2 (Suppl.)*, 263-270.

Myers, A., & Sowden, P. T. (2008). Your hand or mine? The extrastriate body area. *NeuroImage, 42*, 1669-1677.

Naveteur, J., Mars, F., & Crombez, G. (2005). The effect of eye orientation on slowly increasing pain. *European Journal of Pain, 9*, 79-85.

Neuper, C., Wortz, M., & Pfurtscheller, G. (2006). ERD/ERS patterns reflecting sensorimotor activation and deactivation. *Progress in Brain Research, 159*, 211-222.

Newell, F. N. (2004). Cross-modal object recognition. In G. A. Calvert, C. Spence & B. E. Stein (Eds.), *The Handbook of Multisensory Processes* Cambridge, MA: MIT Press.

Nitsche, M. A., Liebetanz, D., Antal, A., Lang, N., Tergau, F., & Paulus, W. (2003). Modulation of cortical excitability by weak direct current stimulation--technical, safety and functional aspects. *Supplements to Clinical Neurophysiology, 56*, 255-276.

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *Journal of Physiology, 527*, 633-639.

Nitsche, M. A., & Paulus, W. (2001). Sustained excitability elevations induced by transcranial DC motor cortex stimulation in humans. *Neurology, 57*, 1899-1901.

Oertel, B. G., Preibisch, C., Martin, T., Walter, C., Gamer, M., Deichmann, R., et al. (2011). Separating brain processing of pain fromthat of stimulus intensity. *Human Brain Mapping*.

Ohnhaus, E. E., & Adler, R. (1975). Methodological problems in the measurement of pain: a comparison between the verbal rating scale and the visual analogue scale. *Pain, 1*, 379-384.

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia, 9*, 97-113.

Oliveri, M., & Vallar, G. (2009). Parietal versus temporal lobe components in spatial cognition: Setting the mid-point of a horizontal line. *Journal of neuropsychology, 3*, 201-211.

Olk, B., Harvey, M., Dow, L., & Murphy, P. J. (2001). Illusion processing in hemispatial neglect. *Neuropsychologia, 39*, 611-625.

Orlov, T., Makin, T. R., & Zohary, E. (2010). Topographic representation of the human body in the occipitotemporal cortex. *Neuron, 68*, 586-600.

Orsini, A., Grossi, D., Capitani, E., Laiacona, M., Papagno, C., & Vallar, G. (1987). Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital J Neurol Sci, 8*, 539-548.

Over, R. (1966). A comparison of haptic and visual judgments of some illusions. *American Journal of Psychology, 79*, 590-595.

Over, R. (1967). Haptic illusions and inappropriate constancy scaling. *Nature, 214*, 629.

Overduin, S. A., & Servos, P. (2004). Distributed digit somatotopy in primary somatosensory cortex. *NeuroImage, 23*, 462-472.

Palva, S., & Palva, J. M. (2007). New vistas for alpha-frequency band oscillations. *Trends in neurosciences, 30*, 150-158.

Pascual-Leone, A., Walsh, V., & Rothwell, J. (2000). Transcranial magnetic stimulation in cognitive neuroscience - virtual lesion, chronometry, and functional connectivity. *Current Opinion in Neurobiology, 10*, 232-237.

Peelen, M. V., & Downing, P. E. (2005). Selectivity for the human body in the fusiform gyrus. *Journal of Neurophysiology, 93*, 603-608.

Peltier, S., Stilla, R., Mariola, E., LaConte, S., Hu, X., & Sathian, K. (2007). Activity and effective connectivity of parietal and occipital cortical regions during haptic shape perception. *Neuropsychologia, 45*, 476-483.

Perani, D., Vallar, G., Cappa, S., Messa, C., & Fazio, F. (1987). Aphasia and neglect after subcortical stroke. A clinical/cerebral perfusion correlation study. *Brain, 110*, 1211-1229.

Pfurtscheller, G., & Lopes da Silva, F. H. (1999). Event-related EEG/MEG synchronization and desynchronization: basic principles. *Clinical Neurophysiology, 110*, 1842-1857.

Pfurtscheller, G., Stancak, A., Jr., & Neuper, C. (1996). Event-related synchronization (ERS) in the alpha band--an electrophysiological correlate of cortical idling: a review. *Int J Psychophysiol, 24*, 39-46.

Pietrini, P., Furey, M. L., Ricciardi, E., Gobbini, M. I., Wu, W. H., & Cohen, L. G. (2004). Beyond sensory images: Object-based representation in the human ventral pathway. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 5858-5663.

Pineda, J. A. (2005). The functional significance of mu rhythms: translating "seeing" and "hearing" into "doing". *Brain Res Brain Res Rev, 50*, 57-68.

Pizzamiglio, L., Antonucci, G., Judica, A., Montenero, P., Razzano, C., & Zoccolotti, P. (1992). Cognitive rehabilitation of the hemineglect disorder in chronic patients with unilateral right brain damage. *Journal of Clinical Experimental Neuropsychology, 14*, 901-923.

Pizzamiglio, L., Guariglia, C., Antonucci, G., & Zoccolotti, P. (2006). Development of a rehabilitative program for unilateral neglect. *Restorative Neurology and Neuroscience, 24*, 337-345.

Ploner, M., Gross, J., Timmermann, L., Pollok, B., & Schnitzler, A. (2006a). Oscillatory activity reflects the excitability of the human somatosensory system. *NeuroImage, 32*, 1231-1236.

Ploner, M., Gross, J., Timmermann, L., Pollok, B., & Schnitzler, A. (2006b). Pain suppresses spontaneous brain rhythms. *Cerebral Cortex, 16*, 537-540.

Polania, R., Nitsche, M. A., & Paulus, W. (2011). Modulating functional connectivity patterns and topological functional organization of the human brain with transcranial direct current stimulation. *Human Brain Mapping, 32*, 1236-1249.

Poreisz, C., Boros, K., Antal, A., & Paulus, W. (2007). Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Research Bulletin, 72*, 208-214.

Pourtois, G., Schwartz, S., Spiridon, M., Martuzzi, R., & Vuilleumier, P. (2009). Object representations for multiple visual categories overlap in lateral occipital and medial fusiform cortex. *Cerebral Cortex, 19*, 1806-1819.

Pressey, A. W., & Bross, M. (1973). Assimilation theory and the reversed Müller-Lyer illusion. *Perception, 2*, 211-217.

Qiu, J., Li, H., Zhang, Q., Liu, Q., & Zhang, F. (2008). The Müller-Lyer illusion seen by the brain: An event-related brain potentials study. *Biological psychology, 77*, 150-158.

Raij, T. T., Forss, N., Stancak, A., & Hari, R. (2004). Modulation of motor-cortex oscillatory activity by painful Adelta- and C-fiber stimuli. *NeuroImage, 23*, 569-573.

Ramachandran, V. S., Brang, D., & McGeoch, P. D. (2009). Size reduction using Mirror Visual Feedback (MVF) reduces phantom pain. *Neurocase, 15*, 357-360.

Ramachandran, V. S., Rogers-Ramachandran, D., & Cobb, S. (1995). Touching the phantom limb. *Nature, 377*, 489-490.

Ro, T., & Rafal, R. D. (1996). Perception of geometric illusions in hemispatial neglect. *Neuropsychologia, 34*, 973-978.

Rock, I., & Victor, J. (1964). Vision and Touch: An Experimentally Created Conflict between the Two Senses. *Science, 143*, 594-596.

Rode, G., Klos, T., Courtois-Jacquin, S., Rossetti, Y., & Pisella, L. (2006). Neglect and prism adaptation: a new therapeutic tool for spatial cognition disorders. *Restorative Neurology and Neuroscience, 24*, 347-356.

Rode, G., Michel, C., Rossetti, Y., Boisson, D., & Vallar, G. (2006). Left size distortion (hyperschematia) after right brain damage. *Neurology, 67*, 1801-1808.

Ronchi, R., Posteraro, L., Fortis, P., Bricolo, E., & Vallar, G. (2009). Perseveration in left spatial neglect: drawing and cancellation tasks. *Cortex, 45*, 300-312.

Rorden, C., & Brett, M. (2000). Stereotaxic display of brain lesions. *Behav Neurol, 12*, 191-200.

Rorden, C., Fruhmann Berger, M., & Karnath, H. O. (2006). Disturbed line bisection is associated with posterior brain lesions. *Brain Research, 1080*, 17-25.

Rorden, C., Heutink, J., Greenfield, E., & Robertson, I. H. (1999). When a rubber hand 'feels' what the real hand cannot. *NeuroReport, 10*, 135-138.

Rossi, S., Hallett, M., Rossini, P. M., & Pascual-Leone, A. (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology, 120*, 2008-2039.

Rudel, R. G., & Teuber, H.-L. (1963). Decrement of visual and haptic Müller-Lyer illusion on repeated trials: A study of crossmodal transfer. *Quarterly Journal of Experimental Psychology, 15*, 125-131.

Sack, A. T., Cohen Kadosh, R., Schuhmann, T., Moerel, M., Walsh, V., & Goebel, R. (2009). Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. *Journal of Cognitive Neuroscience, 21*, 207-221.

Santangelo, V., & Spence, C. (2008). Is the exogenous orienting of spatial attention truly automatic? Evidence from unimodal and multisensory studies. *Consciousness and Cognition, 17*, 989-1015.

Sathian, K., & Lacey, S. (2007). Journeying beyond classical somatosensory cortex. *Canadian Journal of Experimental Psychology, 61*, 254-264.

Sathian, K., Zangaladze, A., Hoffman, J. M., & Grafton, S. T. (1997). Feeling with the mind's eye. *NeuroReport, 8*, 3877-3881.

Saxe, R., Jamal, N., & Powell, L. (2006). My body or yours? The effect of visual perspective on cortical body representations. *Cerebral Cortex, 16*, 178-182.

Schenkenberg, T., Bradford, D. C., & Ajax, E. T. (1980). Line bisection and unilateral visual neglect in patients with neurologic impairment. *Neurology, 30*, 509-517.

Schindler, I., Clavagnier, S., Karnath, H. O., Derex, L., & Perenin, M. T. (2006). A common basis for visual and tactile exploration deficits in spatial neglect? *Neuropsychologia, 44*, 1444-1451.

Schroder, A., Wist, E. R., & Homberg, V. (2008). TENS and optokinetic stimulation in neglect therapy after cerebrovascular accident: a randomized controlled study. *European Journal of Neurology, 15*, 922-927.

Schwenkreis, P., Janssen, F., Rommel, O., Pleger, B., Volker, B., Hosbach, I., et al. (2003). Bilateral motor cortex disinhibition in complex regional pain syndrome (CRPS) type I of the hand. *Neurology, 61*, 515-519.

Serino, A., Padiglioni, S., Haggard, P., & Ladavas, E. (2009). Seeing the hand boosts feeling on the cheek. *Cortex, 45*, 602-609.

Shams, L., Iwaki, S., Chawla, A., & Bhattacharya, J. (2005). Early modulation of visual cortex by sound: an MEG study. *Neuroscience Letters, 378*, 76-81.

Shams, L., Kamitani, Y., & Shimojo, S. (2000). Illusions. What you see is what you hear. *Nature, 408*, 788.

Smania, N., & Aglioti, S. (1995). Sensory and spatial components of somaesthetic deficits following right brain damage. *Neurology, 45*, 1725-1730.

Sparing, R., Buelte, D., Meister, I. G., Paus, T., & Fink, G. R. (2008). Transcranial magnetic stimulation and the challenge of coil placement: a comparison of conventional and stereotaxic neuronavigational strategies. *Human Brain Mapping, 29*, 82-96.

Stancak, A., Polacek, H., Vrana, J., & Mlynar, J. (2007). Cortical oscillatory changes during warming and heating in humans. *Neuroscience, 147*, 842-852.

Stein, B. E. (1998). Neural mechanisms for synthesizing sensory information and producing adaptive behaviors. *Experimental Brain Research, 123*, 124-135.

Stein, B. E., Huneycutt, W. S., & Meredith, M. A. (1988). Neurons and behavior: the same rules of multisensory integration apply. *Brain Research, 448*, 355-358.

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

Stein, B. E., & Stanford, T. R. (2008). Multisensory integration: current issues from the perspective of the single neuron. *Nature Reviews. Neuroscience, 9*, 255-266.

Stilla, R., & Sathian, K. (2007). Selective visuo-haptic processing of shape and texture. *Human Brain Mapping*.

Sumitani, M., Rossetti, Y., Shibata, M., Matsuda, Y., Sakaue, G., Inoue, T., et al. (2007). Prism adaptation to optical deviation alleviates pathologic pain. *Neurology, 68*, 128-133.

Suzuki, K., & Arashida, R. (1992). Geometrical haptic illusions revisited: haptic illusions compared with visual illusions. *Perception & Psychophysics, 52*, 329-335.

Tal, N., & Amedi, A. (2009). Multisensory visual-tactile object related network in humans: insights gained using a novel crossmodal adaptation approach. *Experimental Brain Research, 198*, 165-182.

Talairach, J., & Tournoux, P. (1988). *A co-planar stereotactic atlas of the human brain*. Stuttgart: Thieme Verlag.

Tanabe, H. C., Kato, M., Miyauchi, S., Hayashi, S., & Yanagida, T. (2005). The sensorimotor transformation of cross-modal spatial information in the anterior intraparietal sulcus as revealed by functional MRI. *Brain Research. Cognitive Brain Research, 22*, 385-396.

Taya, R., & Ohashi, Y. (1992). The reversed Muller-Lyer illusion and figure-ground organization theory. *Perception, 21*, 611-626.

Taylor-Clarke, M., Kennett, S., & Haggard, P. (2002). Vision modulates somatosensory cortical processing. *Current Biology, 12*, 233-236.

Terney, D., Bergmann, I., Poreisz, C., Chaieb, L., Boros, K., Nitsche, M. A., et al. (2008). Pergolide increases the efficacy of cathodal direct current stimulation to reduce the amplitude of laser-evoked potentials in humans. *Journal of Pain and Symptom Management, 36*, 79-91.

Tracey, I. (2011). Can neuroimaging studies identify pain endophenotypes in humans? *Nature reviews. Neurology, 7*, 173-181.

Tsakiris, M., Haggard, P., Franck, N., Mainy, N., & Sirigu, A. (2005). A specific role for efferent information in self-recognition. *Cognition, 96*, 215-231.

Valentini, E., Hu, L., Chakrabarti, B., Aglioti, S. M., Hu, Y., & Iannetti, G. D. (in press). The primary somatosensory cortex largely contributes to the early part of the cortical response elicited by nociceptive stimuli. *NeuroImage, 59*, 1571-1581.

Valeriani, M., Betti, V., Le Pera, D., De Armas, L., Miliucci, R., Restuccia, D., et al. (2008). Seeing the pain of others while being in pain: a laser-evoked potentials study. *NeuroImage, 40*, 1419-1428.

Vallar, G. (1998). Spatial hemineglect in humans. *Trends in Cognitive Sciences, 2*, 87-97.

Vallar, G. (2000). The methodological foundations of human neuropsychology: studies in brain-damaged patients. In F. Boller, J. Grafman & G. Rizzolatti (Eds.), *Handbook of Neuropsychology* (2nd ed., Vol. 1, pp. 305-344). Amsterdam: Elsevier.

Vallar, G., Antonucci, G., Guariglia, C., & Pizzamiglio, L. (1993). Deficits of position sense, unilateral neglect and optokinetic stimulation. *Neuropsychologia, 31*, 1191-1200.

Vallar, G., & Bolognini, N. (2011). Behavioural facilitation following brain stimulation: Implications for neurorehabilitation. *Neuropsychological Rehabilitation*, 1-32.

Vallar, G., Bottini, G., Rusconi, M. L., & Sterzi, R. (1993). Exploring somatosensory hemineglect by vestibular stimulation. *Brain, 116*, 71-86.

Vallar, G., Bottini, G., Sterzi, R., Passerini, D., & Rusconi, M. L. (1991). Hemianesthesia, sensory neglect, and defective access to conscious experience. *Neurology, 41*, 650-652.

Vallar, G., & Daini, R. (2002). Illusions in neglect, illusions of neglect. In H. O. Karnath, A. D. Milner & G. Vallar (Eds.), *The cognitive and neural bases of spatial neglect* (pp. 209-224). Oxford: Oxford University Press.

Vallar, G., & Daini, R. (2006). Visual perceptual processing in unilateral spatial neglect: the case of visual illusions. In T. Vecchi & G. Bottini (Eds.), *Imagery and spatial cognition: Methods, models and cognitive assessment* (pp. 337-362). Amsterdam/Philadelphia: John Benjamins Publishing Company.

Vallar, G., Daini, R., & Antonucci, G. (2000). Processing of illusion of length in spatial hemineglect: a study of line bisection. *Neuropsychologia, 38*, 1087-1097.

Vallar, G., Guariglia, C., Magnotti, L., & Pizzamiglio, L. (1995). Optokinetic stimulation affects both vertical and horizontal deficits of position sense in unilateral neglect. *Cortex, 31*, 669-683.

Vallar, G., Guariglia, C., Nico, D., & Bisiach, E. (1995). Spatial hemineglect in back space. *Brain, 118*, 467-472.

Vallar, G., Guariglia, C., & Rusconi, M. L. (1997). Modulation of the neglect syndrome by sensory stimulation. In P. Thier & H.-O. Karnath (Eds.), *Parietal* *lobe contributions to orientation in 3D space* (pp. 555-578). Heidelberg: Springer-Verlag.

Vallar, G., & Mancini, F. (2010). Mapping the neglect syndrome onto neurofunctional streams. In N. Gangopadhyay, M. Madary & F. Spicer (Eds.), *Perception, action, and consciousness. Sensorimotor dynamics and two visual systems* (pp. 183-215). Oxford: Oxford University Press.

Vallar, G., Rusconi, M. L., Bignamini, L., Geminiani, G., & Perani, D. (1994). Anatomical correlates of visual and tactile extinction in humans: a clinical CT scan study. *Journal of Neurology, Neurosurgery, and Psychiatry, 57*, 464-470.

Vallar, G., Rusconi, M. L., Fontana, S., & Musicco, M. (1994). Tre test di esplorazione visuo-spaziale: taratura su 212 soggetti normali. *Archivi di Psicologia, Neurologia e Psichiatria, 55*, 827-841.

Vallar, G., Rusconi, M. L., Geminiani, G., Berti, A., & Cappa, S. F. (1991). Visual and nonvisual neglect after unilateral brain lesions: modulation by visual input. *International Journal of Neuroscience, 61*, 229-239.

Vallar, G., Sterzi, R., Bottini, G., Cappa, S., & Rusconi, M. L. (1990). Temporary remission of left hemianesthesia after vestibular stimulation. A sensory neglect phenomenon. *Cortex, 26*, 123-131.

Verdon, V., Schwartz, S., Lovblad, K. O., Hauert, C. A., & Vuilleumier, P. (2010). Neuroanatomy of hemispatial neglect and its functional components: a study using voxel-based lesion-symptom mapping. *Brain, 133*, 880-894.

Villardita, C. (1987). Tactile exploration of space and visual neglect in brain-damaged patients. *Journal of Neurology, 234*, 292-297.

Violentyev, A., Shimojo, S., & Shams, L. (2005). Touch-induced visual illusion. *NeuroReport, 16*, 1107-1110.

Walker, J. T. (1971). Visual capture in visual illusions. *Perception & Psychophysics, 10*, 71-74.

Walsh, V., & Cowey, A. (2000). Transcranial magnetic stimulation and cognitive neuroscience. *Nature Reviews Neuroscience, 1*, 73-79.

Wassermann, E. M., Epstein, C. M., Ziemann, U., Walsh, V., Paus, T., & Lisanby, S. H. (Eds.). (2008). *The Oxford handbook of transcranial stimulation*. New York: Oxford University Press.

Weidner, R., Boers, F., Mathiak, K., Dammers, J., & Fink, G. R. (2010). The temporal dynamics of the Müller-Lyer illusion. *Cerebral Cortex, 20*, 1586-1595.

Weidner, R., & Fink, G. R. (2007). The neural mechanisms underlying the Müller-Lyer illusion and its interaction with visuospatial judgments. *Cerebral Cortex, 17*, 878-884.

Wiech, K., Ploner, M., & Tracey, I. (2008). Neurocognitive aspects of pain perception. *Trends in Cognitive Sciences, 12*, 306-313.

Wiffen, P. J., McQuay, H. J., Edwards, J. E., & Moore, R. A. (2005). Gabapentin for acute and chronic pain. *Cochrane database of systematic reviews, 3*, CD005452.

Yantis, S., & Serences, J. T. (2003). Cortical mechanisms of space-based and object-based attentional control. *Current Opinion in Neurobiology, 13*, 187-193.

Yarnitsky, D., Sprecher, E., Zaslansky, R., & Hemli, J. A. (1995). Heat pain thresholds: normative data and repeatability. *Pain, 60*, 329-332.

Zaghi, S., Heine, N., & Fregni, F. (2009). Brain stimulation for the treatment of pain: A review of costs, clinical effects, and mechanisms of treatment for three different central neuromodulatory approaches. *Journal of pain management, 2*, 339-352.

Zangaladze, A., Epstein, C. M., Grafton, S. T., & Sathian, K. (1999). Involvement of visual cortex in tactile discrimination of orientation. *Nature, 401*, 587-590.