Peripersonal space : a multisensory interface for body-objects interactions

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PERIPERSONAL SPACE : A MULTISENSORY INTERFACE FOR BODY-OBJECTS INTERACTIONS

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A Fede,
perché questo spazio
mi ha preso nel tempo
che a volte era suo

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L’ESPACE PERIPERSONNEL: UNE INTERFACE MULTISENSORIELLE POUR LES INTERACTIONS ENTRE LE CORPS ET LES OBJETS

Notre habilité à interagir avec les objets du monde nécessite l’intégration d’informations provenant de différents canaux sensoriels, dans le cadre de la construction d’une représentation de l’espace en particulier des informations visuelles et tactiles. L’espace péripersonnel et l’intégration visuo-tactile ont été l’objet d’importantes recherche récemment. Des études neurophysiologiques chez le primate non-humain ont montré l’existence de neurones bimodaux activés à la fois par des stimulations tactiles et par des stimulations visuelles si ces dernières étaient présentées près d’une partie du corps (par exemple la main). Il a été proposé que ces neurones bi-modaux constituent le substrat neuronal de la représentation de l’espace péripersonnel. Les études neuropsychologiques menées chez des patients présentant une extinction cross-modale consécutive à une lésion pariétale droite ont permis de suggérer l’existence du même type de représentation de l’espace péripersonnel chez l’homme. Les données issues des études en neuroimagerie fonctionnelle sont venues par la suite conforter cette idée. Plus récemment, à travers l’utilisation d’outils, des données acquises chez le primate humain et non humain ont révélé les propriétés dynamiques de cette représentation spatiale.

Selon notre hypothèse la représentation de l’espace péripersonnel est une interface présidant aux interactions du corps avec les objets du monde externe.

Nous avons donc évalué le rôle et l’état de l’espace péripersonnel lors de l’exécution de mouvements volontaires vers des objets (comme une simple saisie) et lors de mouvements involontaires d’évitement. Lors d’une première série d’expériences nous avons étudié les coordonnées spatiales du codage des objets qui soudainement se rapprochent du corps grâce à la mesure des potentiels évoqués moteurs. Cette étude a révélé que l’espace péripersonnel joue un rôle dans la représentation des objets approchant le corps et dans la sélection des mouvements appropriés en réponse. Lors d’une seconde série d’expériences nous avons utilisé un paradigme d’interférence visuo-tactile couplé à l’enregistrement cinématique des mouvements de saisie afin d’examiner la représentation de l’espace péripersonnel lors de l'exécution d'actions volontaires. Cette approche novatrice nous a permis de mettre en évidence que l'action volontaire induit un recodage en ligne de l'interaction visuo-tactile dans l'espace de préhension. Ce recodage de l'action s'effectue en coordonnées centrées sur la partie du corps qui exécute l'action.

En conclusion nos études expérimentales démontrent que l'espace péripersonnel est une interface multisensorielle qui a été sélectionnée à travers l'évolution non seulement pour la gestion des mouvements d'évitement et de défense mais également pour l'exécution d'actions volontaires.

PERIPERSONAL SPACE: A MULTISENSORY INTERFACE FOR BODY-OBJECTS INTERACTIONS

Our ability to interact with the environment requires the integration of multisensory information for the construction of spatial representations. The peripersonal space (i.e., the sector of space closely surrounding one's body) and the integrative processes between visual and tactile inputs originating from this sector of space have been at the center of recent years investigations. Neurophysiological studies provided evidence for the presence in the monkey brain of bimodal neurons, which are activated by tactile as well as visual information delivered near to a specific body part (e.g., the hand). Neuropsychological studies on right brain-damaged patients who present extinction and functional neuroimaging findings suggest the presence of similar bimodal systems in the human brain. Studies on the effects of tool-use on visual-tactile interaction revealed similar dynamic properties of the peripersonal space in monkeys and humans.

The functional role of the multisensory coding of peripersonal space is, in our hypothesis, that of providing the brain with a sensori-motor interface for body-objects interactions. Thus, not only it could be involved in driving involuntary defensive movements in response to objects approaching the body, but could be also dynamically maintained and updated as a function of manual voluntary actions performed towards objects in the reaching space.

We tested the hypothesis of an involvement of peripersonal space in executing both voluntary and defensive actions. To these aims, we joined a well known cross-modal congruency effect between visual and tactile information to a kinematic approach to demonstrate that voluntary grasping actions induce an on-line re-weighting of multisensory interactions in the peripersonal space. We additionally show that this modulation is hand-centred. We also used a motor evoked potentials approach to investigate which coordinates system is used to code the peripersonal space during motor preparation if real objects rapidly approach the body. Our findings provide direct evidence for automatic hand-centred coding of visual space and suggest that peripersonal space may also serve to represent rapidly approaching and potentially noxious objects, thus enabling the rapid selection of appropriate motor responses.

These results clearly show that peripersonal space is a multisensori-motor interface that might have been selected through evolution for optimising the interactions between the body and the objects in the external world.

INTRODUCTION

> *"Space is not a sort of ether in which all things float...*
> *The points in space mark, in our vicinity, the varying range of our aims and our gestures*"
>
> (Merleau-Ponty)

Research in the last four decades has brought a considerable advance in our understanding of how the brain synthesises perceptual information arising from different sensory modalities. Indeed, many cortical and subcortical areas, also beyond those traditionally considered to be 'associative', have been shown to be involved in multisensory interaction and integration (Ghazanfar and Schroeder 2006). Visuo-tactile interaction is of particular interest because of the prominent role played by vision in guiding our actions and anticipating their tactile consequences in everyday life. In this thesis, we focus on the functional role that visuo-tactile processing may play in driving two types of body-object interactions: avoidance and approach. We will first review some basic features of visuo-tactile interactions, as revealed by single units recording studies in monkeys. These will prove to be relevant for interpreting the subsequent human evidence. A crucial point that will be stressed is that these neuronal populations have not only sensory, but also motor-related activity that qualifies them as multisensory-motor interfaces. Evidence will then be presented for the existence of functionally homologous processing in the human brain, both from neuropsychological research in brain-damaged patients and in healthy people. The original experimental contribution of this dissertation is focussed on healthy humans and supports the idea that the human motor system is provided with a multisensory interface that allows for continuous monitoring of the space near the body (i.e., peripersonal space). We will provide evidence of the involvement of the peripersonal space representation in rapid reaction to approaching objects. We further demonstrate that multisensory processing can be modulated on-line as a consequence of acting voluntarily on objects. This indicates that, far from being passive, the monitoring of peripersonal space is an active process subserving actions between our body and objects located in the space around us.

Chapter I

Multisensory perception

During the 60's and 70's, research about perception focussed on the single sensory modalities in order to investigate the sensory processing and the relative brain pathways for the elaboration of a perceptual event. The very fruitful investigation of Hubel and Wiesel's Nobel prize awarded research in Physiology, for example, brought to discover the hierarchical organisation of the visual system. The main characteristics is the gradual construction of the visual perception, proceeding from a primary sensory area (V1, area 17 of Broadmann, in the occipital lobe) to areas of higher level (V2, V3, V4, V5/MT) where the simple visual features of the visual input progressively converge in more and more complex perceptions. The visual system hierarchical organisation became thus a model for the other sensory modalities, whose primary sensory areas have been then localised: in the temporal lobe for audition (A1, areas 41-42 of Broadmann) and in post-central gyrus for somatosensation (S1, areas 1, 2 and 3 of Broadmann, in the parietal lobe; Figure 1.1). Even if in a milder fashion, the brain elaboration of audition and touch also proceeds in a primary-to-secondary sensory areas pathway[1].

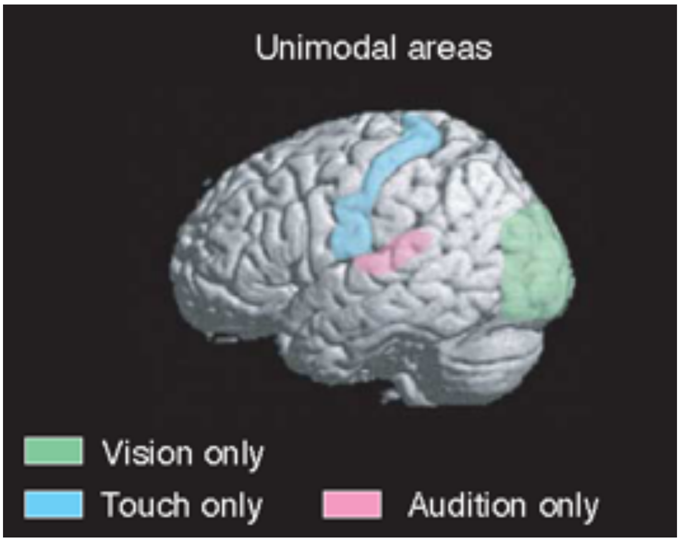

Fig. 1.1 Primary and secondary unimodal areas in the human brain: visual areas in the occiptal lobe, somatosensory areas in the post-central gyrus and auditory areas in superior temporal gyrus. From Macaluso and Driver 2005.

On the other hand, we are used to live in a world where each event is a composition of different

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[1] Recently also for the visual system a more parallel processing of visual features has been revealed (See Van Essen 2005 for a review).

sensory inputs and where the multisensoriality is the rule. When we are talking with a friend or just watching a movie or looking for our ringing cell-phone in order to grasp it, we are simply receiving and automatically integrating information coming from different sensory modalities. The visible mouth movements of my friend talking bring visual information that can interact with its related audible counterpart; similarly the visual information of the ringing cell-phone is integrated without any effort to the sound coming from it, sometime possibly helping to find its location. Moreover, the form of the telephone I can be aware of through vision, creates automatically expectations about the tactile feedback I will receive when my hand will enter in contact with it. These everyday life's examples clearly point out the fact that the peripherally separated perceptual channels have to converge at a certain level of the sensory elaboration in order to give the unitary perception of world events we are used to experience.

The necessary revolution in perception research arrived thus with the discovery of brain cortex regions where the "separated" sensory input could converge and interact bringing to more elaborated form of perception. For the convergence of information they allow, these areas are referred to as "associative" areas; but also as "higher-level" areas, to underline that

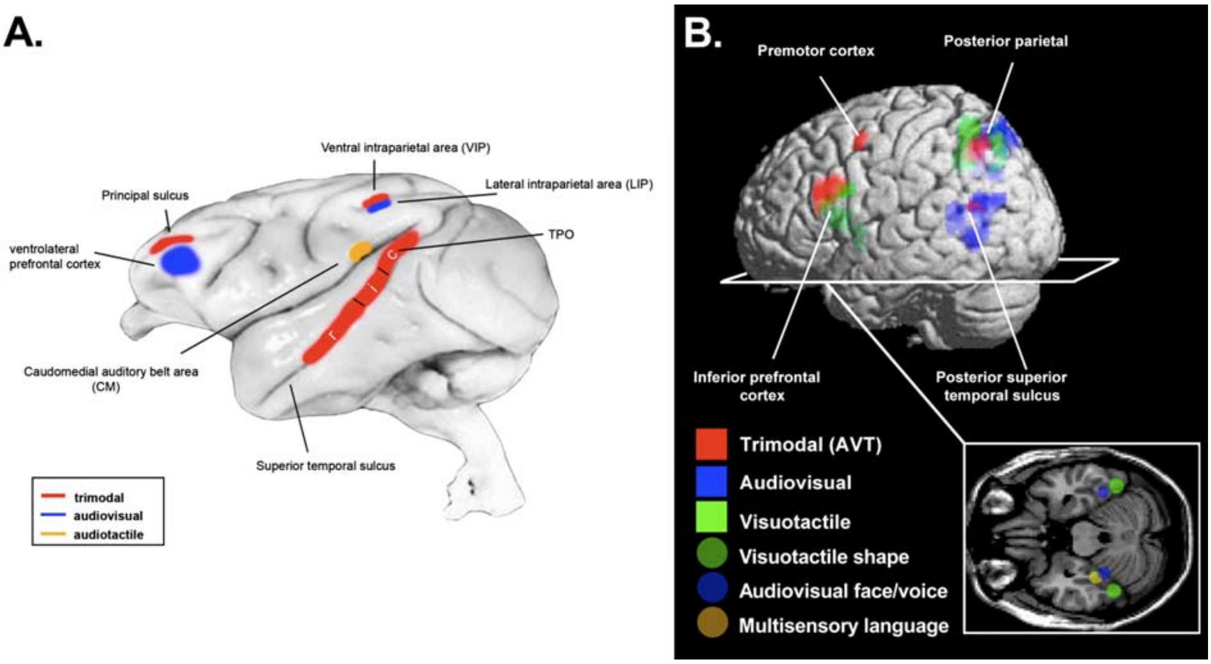

Fig. 1.2 Some of the multisensory areas in the non-human (panel A) and human (panel B) primates' brain. Three main regions are recognisable: posterior parietal cortex, prefrontal premotor cortex, superior temporal sulcus. From Driver and Noesselt 2008.

here arises the first form of cognition rather than a ‘mere’ perception. We refer to them as “multisensory” areas, underlining the fact that in these parts of the brain the integration of different sensory modalities takes place (Figure 1.2).

Further advancements in the research about perception were the discovery of direct influences of the so-defined multisensory areas over the primary and secondary sensory areas, but also very early interactions between different “low-level” areas. These evidence brought to a drastic reconsideration of the multisensoriality of the brain, till the provocative question of Ghazanfar and Schroeder (2006): “Is the neocortex essentially multisensory?”.

In this first chapter I will present examples of multisensory perception that can reflect different mechanisms in the brain. We will see how pervasive it is but also that, despite the essential multisensory nature of perception in terms of “final” product, we still can consider the functional specialisation of the brain areas as a fundamental principle of the brain organisation. I will maintain the word “integration” for the multisensory phenomena based on a proved convergence of different sensory inputs on the same cell. Multisensory “interaction” is by contrast any other multisensory phenomenon arising by a feedback influence from high- to low-level areas or by direct modulations between primary or secondary areas of different sensory modalities. Multisensory, when referred to brain areas, will mean the areas of convergence of different sensory input over single cells, as opposed to unisensory areas.

1. Multisensory perception in human behaviour

The multisensory perception in everyday life is more the rule than the exception. The interaction between different sensory modalities arises so automatically, requiring no conscious processing, that we can often experience illusions when contrasting information are coming from different sensory channels. The phenomenon of “Ventriloquism”, for instance, is an example of mislocalisation of a sound toward the position of a temporally correlated moving visual object (Driver 1996; Calvert et al. 2004). The more the sound and the visual object are ‘compatible’, the stronger is the illusion: a speaking voice can be attributed to a visible simultaneously moving mouth even if the two events are spatially separated (Lewald and Guski 2003). The multisensory perception is so ineluctable that such an illusion would arise also when we are aware about the spatial separation between the origin of the sound and the visual object. We can thus without any effort enjoying a movie in a cinema, for example. Strong crossmodal integration can also occur when visual and auditory stimuli are not static, in particular, in case of apparent motion (Soto-Faraco et al. 2002; see Soto-Faraco et al. 2004 for a similar audio-tactile effect). This kind of study showed that the apparent motion in vision strongly modulates the perception of the direction of auditory apparent motion. Also for this dynamic situation however, spatial and temporal constraints are present for the occurrence of this crossmodal effect (Soto-Faraco et al. 2002).

A different illusion can arise when incompatible auditory and visual events are simultaneously presented. For instance from the association of an auditory presented phoneme and visible mouth movements corresponding to a different sound originates a phenomenon typically termed the “McGurk effect” (McGurk and McDonald 1976). The experienced effect is a synthesis of discordant visual and auditory information so that the syllable *da* is the final perception of hearing *ba* while watching a silent mouth moving as for saying *ga*. This is another example of how vision and audition are tightly interconnected and how the final unitary perception is based on information coming from different modalities. The McGurk illusion is considered to be the result of an automatic and involuntary process leading to the seamless integration of the acoustic and the visual sources of information (Soto-Faraco et al. 2004). Recently, Soto-Faraco and Alsius (2009), provided evidence of the fact that, when presented with desynchronised audiovisual speech syllables, observers are nonetheless able to detect the temporal mismatch while experiencing the McGurk illusion. This interesting finding supports the idea that, contrary to previous assumptions, it seems possible to gain access to information about the individual sensory components of a perception resulting from a multisensory integration.

These illusions are representative for their pervasive presence in our everyday life but it is logical to think that such phenomena can also arise with other pairs of sensory modalities. Ventriloquism may indeed also arise between tactile and visual events and is more commonly referred to as “visual capture of touch” (Pavani et al. 2000). Also a “tactile capture of audition” has been proved (Caclin et al. 2002) since the apparent location of a sound can be biased toward the location of a concurrent tactile stimulation. The synchrony between the stimuli appears a fundamental parameter. Similarly in the “parchement-skin illusion” (Jousmäki and Hari 1998), perturbing the sound as hands are rubbed together can affect the perception of skin texture and moistness. Also in these cases, illusions appear to be dependent on the spatial and temporal association between the two sensory inputs.

In the presented multisensory illusions, the brain is confronted with concurrent information coming from two modalities but providing information about the same external property. Often indeed, the auditory input jointly with the visual ones, both bring the spatial information necessary, for example, to the localisation of a multisensory event. It appears thus extremely adaptive that the brain might synthesise the different sensory information. By contrast, recent examples of multisensory influences in perception show different types of phenomena. Rather than different modalities providing independent information about the same external sensory property, multisensory research also showed that stimulation in one modality can affect the judgement of a property logically pertinent only to another modality. Touch at a given location for instance, can improve judgements about the colour of a visual stimulus delivered nearby, although touch itself does not convey any information about this visual property (Spence et al. 2004). Other example of such a multisensory effect in behaviour is the case of single flashes that can be illusory perceived as being double whenever associated with two auditory signals (Shipley 1964; Shams et al. 2000). Again, a visuo-tactile form of the “double-flash illusion” exists (Violentyev et al. 2005), where perceiving two touches delivered simultaneously with a single flash induces the illusion to perceive a double flash.

2. Multisensory attention

The presence of a sensory event can produce a shift of attention toward its location. This shift could be either voluntary, “endogenous”, or “exogenous”, as it is driven by the sudden appearance of a stimulus in the environment, in an involuntary fashion (Posner 1980). A part of the multisensory research focussed on how the presence of multisensory information can affect and drive attention in space (Driver and Spence 2000; Macaluso and Driver 2005). The basic question authors asked was whether a shift of attention occurring in one modality (i.e., vision) could then affect the detection of a spatially coincident stimulus in another modality (i.e., tactile; see Figure 1.3; Spence and Driver 1996; 1997a; 1997b; Driver and Spence 1998; Spence et al. 1998). A cross-modal facilitatory effect is generally present when the target is presented in the position where a spatially non-predictive cue appeared. The cue in one modality induces thus an involuntary orienting of attention which facilitates the detection of a stimulus presented in the same spatial location, but in another modality (Driver and Spence 1998; McDonald et al. 2000). However, the temporal interval between cue and target appears to be fundamental. When the cue-to-target interval exceeds 200 ms (or more, depending on the stimuli and task) an inverse effect arises, known as the "inhibition of return" (Posner and Cohen 1984; Klein 2000; Driver and Spence 1998; Spence and Driver 1998a; 1998b; Spence et al. 2000). In this case, the attention is initially exogenously shifted toward the position of the cue and then, since nothing happens there, attention shifts back inducing a facilitatory effect for the opposite spatial position compared to the previously cued ones. These studies suggest that attention can be shifted supramodally and thus enhance or inhibit perception in particular spatial locations as a function of the spatial position of the cue.

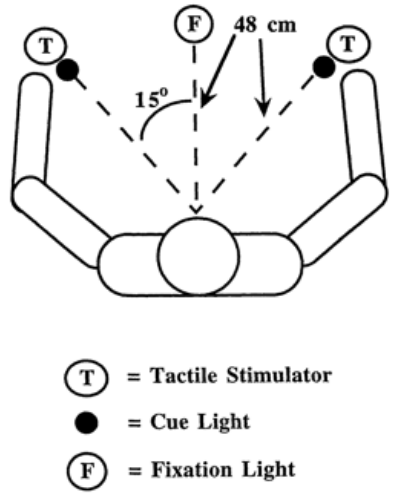

Fig. 1.3 Example of paradigm for the study of cross-modal shift of attention. After the presentation of a visual cue, a tactile target is delivered in the same spatial position or in the opposite one. Facilitatory and inhibitory effects have been shown depending on the spatial disparity between sensory inputs. From Spence et al. 1998.

Attention can also be shifted in space through centrally symbolic cues such as arrows (left or right), for example, or numbers, in virtue of their magnitude (Dehaene et al. 1993). Numbers seem indeed to be represented on a spatially oriented "mental number line" where smaller digits find their place on the left and larger on the right side. As a consequence of this spatial arrangement, the vision of a task irrelevant digit has been proved to shift attention in a visual detection task (Fischer et al. 2005) in a Posner-like fashion, even though evidence has been provided against the automaticity of this effect (Galfano et al. 2006). The case is possible that the vision of a digit might shift attention also cross-modally, for instance, modulating tactile perception. We have investigated this hypothesis and the study is presented hereafter as an example of this thesis contribution to multisensory shifts of attention.

2.1. The spatial organization of numbers

My research experience, though mainly focussed on the investigation of multisensory properties of peripersonal space, has brought me to study also a more general kind of visuo-tactile interaction. In my first experimental contribution presented here, I investigated the effects of a visual shift of attention on the tactile modality. In particular I investigated a shift of attention induced by a visually presented numerical cue.

We are used to learn counting on our fingers and the digital representation of numbers we develop is still present in adulthood in our counting motor behaviour. By virtue of such an association between anatomy and digit magnitude we establish tight functional correspondences between fingers and numbers. However, it has long been known that numerical information is also spatially arranged along an oriented mental number line, where digits are organised from left to right as a function of their magnitude.

In the following study, I investigated touch perception in order to disambiguate whether number representation is embodied on the hand (“1” thumb; “5” little finger) or disembodied in the extrapersonal space (“1” left; “5” right). In two experiments, the number spatial representations have been directly contrasted each other using a single centrally located effector (the foot) and a simple postural manipulation of the hand (palm-up vs. palm-down). Results show that visual presentation of a number (“1” or “5”) shifts attention cross-modally, modulating the detection of tactile stimuli delivered on the little finger or thumb. When the hand rests palm-down, subjects perform better in reporting tactile stimuli delivered to the little finger after presentation of number “5” than number “1.” Crucially, this pattern reverses (better performance after number “1” than “5”) when the hand is in a palm-up posture, in which the position of the fingers in external space, but not their relative anatomical position, is reversed. The human brain can thus use either space- or body-based representation of numbers, but in case of competition, the former dominates the latter, showing the stronger role played by the mental number line organisation.

CROSS-MODAL SHIFT OF ATTENTION

Touch perception reveals the dominance of spatial over digital representation of numbers

P.N.A.S. (2008)

Touch perception reveals the dominance of spatial over digital representation of numbers

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We learn counting on our fingers, and the digital representation of numbers we develop is still present in adulthood [Andres M, *et al.* (2007) *J Cognit Neurosci* 19:563–576]. Such an anatomy–magnitude association establishes tight functional correspondences between fingers and numbers [Di Luca S, *et al.* (2006) *Q J Exp Psychol* 59:1648–1663]. However, it has long been known that small-to-large magnitude information is arranged left-to-right along a mental number line [Dehaene S, *et al.* (1993) *J Exp Psychol Genet* 122:371–396]. Here, we investigated touch perception to disambiguate whether number representation is embodied on the hand (''1'' = thumb; ''5'' = little finger) or disembodied in the extrapersonal space (''1'' = left; ''5'' = right). We directly contrasted these number representations in two experiments using a single centrally located effector (the foot) and a simple postural manipulation of the hand (palm-up vs. palm-down). We show that visual presentation of a number (''1'' or ''5'') shifts attention cross-modally, modulating the detection of tactile stimuli delivered on the little finger or thumb. With the hand resting palm-down, subjects perform better when reporting tactile stimuli delivered to the little finger after presentation of number ''5'' than number ''1.'' Crucially, this pattern reverses (better performance after number ''1'' than ''5'') when the hand is in a palm-up posture, in which the position of the fingers in external space, but not their relative anatomical position, is reversed. The human brain can thus use either space- or body-based representation of numbers, but in case of competition, the former dominates the latter, showing the stronger role played by the mental number line organization.

mental number line | tactile perception

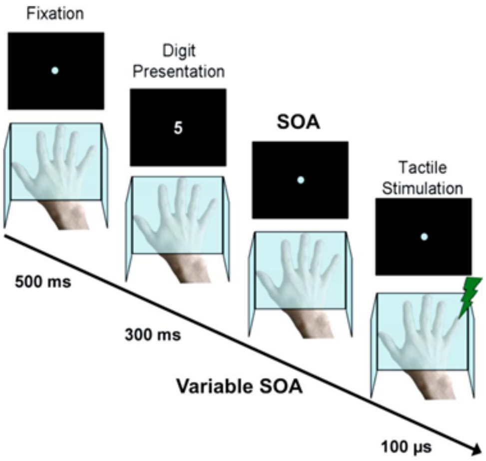

Fig. 1. Experimental setup and procedures. The subjects' right hands lay in front of them with their middle finger aligned with the central fixation point on the monitor. After a fixation period of 500 ms, a number appeared for 300 ms in the center of the monitor. A tactile stimulus was delivered either to the thumb or the little finger at a variable interval from number onset: four SOAs were possible in the first experiment (550, 800, 1,050, or 1,300 ms after onset of the task-irrelevant number) and two in the second experiment (250 ms or 550 ms after onset of the task-irrelevant number). The subjects were instructed to respond to the tactile stimulus as quickly as possible, by pressing a centrally located pedal with their right foot.

It has long been considered that literate humans associate numbers (e.g., "1" and "5") with fingers (e.g., thumb and little finger) by virtue of learning processes such as counting on fingers. Such an embodied finger-counting strategy, developed during numerical acquisition in childhood, might result in a finger–number association still present in adulthood when the same numerical manipulations can be carried out mentally (1, 2). Accordingly, activation of the precentral gyrus and parietal areas participating in hand-shaping control and finger movements (3) are commonly reported during numerical tasks (4–9) and have been suggested to underlie implicit finger-counting strategies (4–6). Neuropsychological studies of Gerstmann's syndrome (10, 11) and transcranial magnetic stimulation (TMS) approaches in healthy subjects (3, 12, 13) have also suggested tight functional correspondences between fingers and numbers. However, a disembodied form of numerical representation is also well established: Numbers are represented in a spatial format along the so-called "mental number line," whereby smaller numbers occupy relatively leftward locations compared with larger numbers (14, 15). This phenomenon, which has become known as the spatial numerical association of response codes (SNARC) effect, suggests that magnitude information may be analogically arranged from left to right (in most Western cultures): In parity judgment tasks, large numbers are responded to faster with the right hand (and small numbers faster with the left hand) by virtue of the spatial compatibility between the location of a given number on the mental number line and the location of the correct response effector in external space. Neuropsychological evidence from neglect patients and TMS studies on subjects bisecting numerical intervals has further supported the left-to-right spatial organization of numbers (16–21). Moreover, visual attention and action can be enhanced according to the magnitude of a visually presented number, larger numbers boosting performance on the right and smaller numbers on the left side (22, 23). The few existing attempts to contrast hand-/finger-based (embodied) and space-based (disembodied) representations of numbers have led to mixed results. Dominance of the space-based representation has been suggested by Dehaene *et al.* (14), who asked subjects to perform a crossed-hand version of their original parity-judgement task and found that the SNARC effect did not depend on the left–right hand identity but the left–right hand location in the response space. In

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Author contributions: C.B. and A.F. designed research; C.B. performed research; R.S. contributed new reagents/analytical tools; C.B., M.I., and A.F. analyzed data; and C.B., M.I., S.M.G., Y.R., and A.F. wrote the paper.

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contrast, finger-based dominance has been suggested by Di Luca *et al.* (24), who asked subjects to perform a visuomotor finger-number compatibility task and found better performance when the mapping was congruent with the prototypical finger-counting strategy. In addition, a certain degree of flexibility in number representation has been recently suggested (25–28), because the mapping between numbers and space can vary to some extent with instructional context (25) and task demands (17).

Previous findings are thus not definitive with regard to number representation, because both the embodied and the disembodied hypotheses have received empirical support. In this study, we used a previously undescribed approach to disambiguate between such representations within a corporeal modality, by investigating the attentional effects induced by numbers on the perception of touches delivered to the fingers. A postural manipulation of the hand (palm-up vs. -down) allowed us to directly contrast the embodied and disembodied representations of numbers. A further manipulation was critically introduced to avoid any left–right arrangement in the response space, potentially favoring a space-based representation, and any motor bias in the response effector, potentially favoring a finger-based representation: Subjects had to respond to tactile stimulation by pressing a centrally located pedal with the foot.

Results and Discussion

Participants performed a simple tactile detection task by making speeded foot-pedal responses to a tactile stimulus delivered to either the thumb or little finger of their right (preferred and counting) hand. Tactile intensity was set in a previous session to obtain an equal detection probability for the two fingers [see supporting information (SI) *Experiment 1*, *Supporting Procedures* and *Supporting Results*, Table S1, and Fig. S1]. In the first experiment, the task instructions were given as to emphasize the fingers (i.e., "you will feel a touch on either your thumb or little finger"). At a variable stimulus onset asynchrony (SOA), an electrocutaneous stimulus followed the presentation of a task-irrelevant number ("1," "2," "4," or "5") on a screen in front of their hand (Fig. 1). The tactile task was performed with the unseen hand passively resting either in a palm-down or -up posture.

Two main results were found: First, visual presentation of a number cross-modally affects tactile performance. Second, this numerical cueing of touch does not follow a number–finger association, but a number–space association, akin to the mental number

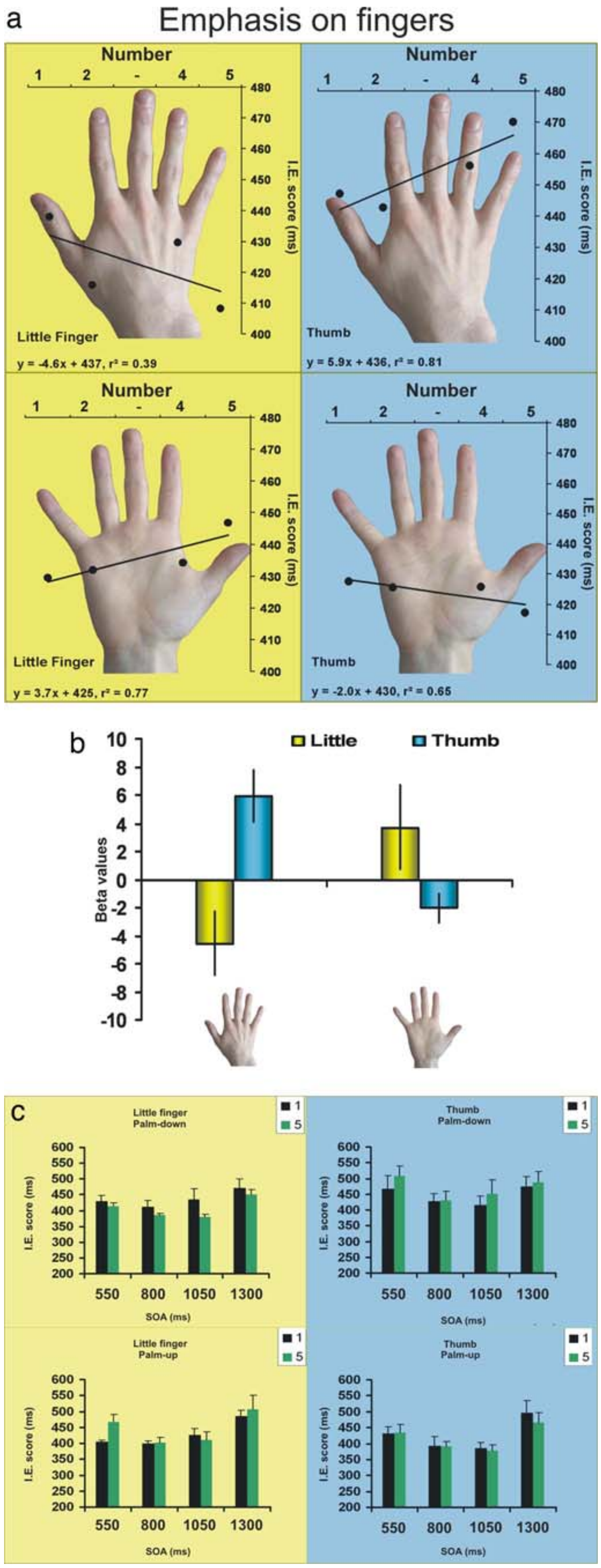

Fig. 2. Visual numerical cueing of touch is modulated by hand posture: emphasis on fingers. (*a*) Regression lines of the inverse efficiency score as a function of number magnitude for all conditions. Regression equations reflect the averaged data in each image. Performance for the thumb (blue) in palm-down posture (*Upper*), decreased as a function of number magnitude from the smallest (''1'') to the largest (''5'') number ($y = +5.9x + 436$, $r^2 = 0.81$); the pattern is opposite for the same stimulus on the same thumb but in palm-up posture (*Lower*, $y = -2.0x + 430$, $r^2 = 0.65$). Little-finger results (yellow) mirror those for the thumb ($y = -4.6x + 437$, $r^2 = 0.39$, palm-down posture, *Upper*; $y = +3.7x + 425$, $r^2 = 0.77$ palm-up posture, *Lower*). (*b*) Beta values of the regression lines (mean ± SEM) relating the inverse efficiency score to number magnitude are presented for the palm-down (left side of the graph) and the palm-up posture (right side) for little finger (yellow bars) and thumb (blue bars) [finger × posture interaction, $F(1,13) = 9.80$, $P < 0.01$]. Hand posture modulates the visual numerical cueing of touch. Indeed, for stimuli applied to the thumb, positive beta values in the palm-down posture become negative in the palm-up posture (+5.94 ± 2.10 vs. −2.04 ± 2.53, respectively). The opposite is true for the little finger (−0.55 ± 1.95 vs. +3.70 ± 2.58, respectively). (*c*) Time course of the visual numerical cueing of touch. Inverse efficiency scores (mean + SEM) for stimuli to the little finger (yellow) and thumb (blue) after presentation of number ''1'' (black bars) and ''5'' (green bars) are presented for each SOA (550, 800, 1,050, and 1,300 ms). The spatial bias induced by the number is not modulated by time: in the palm-down posture (*Upper*), the pattern of performance for touches delivered to the little finger was better after number ''5'' than number ''1,'' whereas performance for touches delivered to the thumb was better after number ''1'' than number ''5.'' The reversed pattern is observed in the palm-up posture (*Lower*), irrespective of the SOA.

line (14). A descriptive illustration of the results for all experimental conditions including all of the numbers (“1,” “2,” “4,” and “5”) is provided by Fig. 2*a*. When the right hand was in the palm-down posture, placed centrally with the middle finger aligned with the visually presented number, subjects’ detection of brief tactile stimuli applied to the little finger improved as a function of the preceding number magnitude. The larger the number, the better the performance in terms of inverse efficiency (IE) score, jointly indexing accuracy, and response latency. The opposite pattern of results was found when the same little finger was stimulated with the hand in the palm-up posture. In this condition, subjects’ tactile performance actually decreased as the preceding number increased. The statistical comparison showed a significant finger × posture interaction [$F(1,13) = 9.80$; $P < 0.01$]: Fig. 2*b* shows that for stimuli applied on the little finger, a difference was present between the slopes of IE regression lines in the palm-down and -up position (-0.55 vs. $+3.70$, respectively; $P < 0.05$; Fig. 2*b*, yellow bars). Results for the thumb mirrored those for the little finger (Fig. 2b, blue bars). When the hand was in the palm-down posture, subjects’ detection improved as a function of the number’s magnitude. For the thumb, the smaller the preceding number, the better the performance, because the regression line has a positive slope. On the contrary, when the hand was in the palm-up position, subjects’ detection of brief stimuli on the thumb tended to worsen with decreasing magnitude of the presented number ($+5.94$ vs. -2.04 for the palm-down and -up postures, respectively; $P = 0.053$, Fig. 2*b*).

To further establish the dominant role played by the space-based organization of numbers, an additional analysis of tactile performance was run by focusing on those conditions with presentation of numbers “1” and “5” (i.e., excluding conditions “2” and “4”). The four-way ANOVA revealed a significant main effect of SOA on tactile performance [$F(3,39) = 15.35$; $P < 0.01$]. Newman–Keuls posthoc test revealed that subjects’ performance was worst in the longer SOA (1,300 ms), compared with shorter ones (550, 800, and 1,050 ms; $P < 0.01$ for all comparisons). However, the variable SOA was not involved in any significant interaction (Fig. 2*c*). The hypothesis of an embodied representation of numbers predicts that the thumb is more closely associated with, and thus would be more efficiently primed by, number “1” than number “5,” independently of the hand’s posture, with the opposite association for the little finger. Contrary to these predictions, a significant posture × finger × number interaction [$F(1,13) = 14.43$; $P < 0.01$] confirmed that the numerical cueing of touch is mapped in extrapersonal

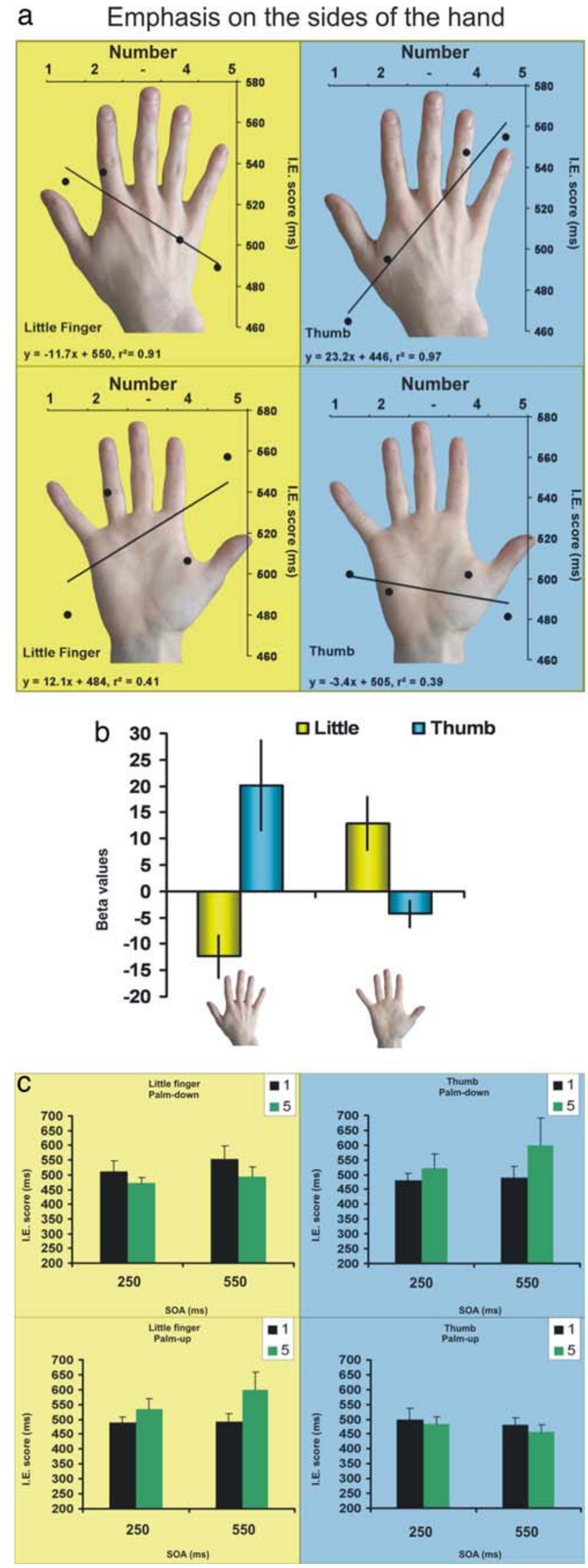

Fig. 3. Visual numerical cueing of touch is modulated by hand posture: emphasis on the sides of the hand. (*a*) Regression lines of the inverse efficiency score as a function of number magnitude for all conditions. Regression equations reflect the averaged data in each image. Performance for the thumb (blue) in palm-down posture (*Upper*), decreased as a function of number magnitude from the smallest (“1”) to the largest (“5”) number ($y = +23.2x + 446$, $r^2 = 0.97$); the pattern is opposite for the same stimulus on the same thumb but in palm-up posture (*Lower*, $y = -3.4x + 505$, $r^2 = 0.39$). Little-finger results (yellow) mirror those for the thumb ($y = -11.7x + 550$, $r^2 = 0.91$, palm-down posture, upper row; $y = +12.1x + 484$, $r^2 = 0.41$ palm-up posture, *Lower*). (*b*) Beta values of the regression lines (mean ± SEM) relating the inverse efficiency score to number magnitude are presented for the palm-down (left side of the graph) and palm-up postures (right side) for little finger (yellow bars) and thumb (blue bars) [finger × posture interaction, $F(1,12) = 6.02$; $P < 0.03$]. Hand posture modulates the visual numerical cueing of touch, also when emphasis in task instruction is given to the side (left or right) of the hand. For stimuli applied to the thumb, positive beta values in the palm-down posture become negative in the palm-up posture ($+23.2 \pm 12.6$ vs. -3.4 ± 4.9, respectively). The opposite is true for the little finger (-1.69 ± 7.3 vs. $+12.12 \pm 6.6$, respectively). (*c*) Time course of the visual numerical cueing of touch. Inverse efficiency scores (mean + SEM) for stimuli to the little finger (yellow) and thumb (blue) after presentation of number “1” (black bars) and “5” (green bars) are presented for each SOA: 250 ms (i.e., during number presentation) and 550 ms (i.e., after number presentation). Even at the shortest SOA, the spatial bias induced by the number on tactile perception shifts according to whether the hand is in the palm-down (*Upper*), or the palm-up posture (*Lower*).

space. Subjects' performance was better in perceiving a touch on the thumb after number "1" than "5" in the palm-down posture (IE score: 447 vs. 470 ms, respectively; $P < 0.05$), but the opposite tendency was obtained when the hand posture was reversed (IE score: 428 vs. 417 ms, respectively). Similarly, when considering the little finger, subjects' performance mirrored that of the thumb: In the palm-down posture, stimuli on the little finger were detected more efficiently when preceded by number "5" than "1" (408 vs. 439 ms, respectively; $P < 0.05$), but the opposite was true in the palm-up posture, in which performance was better when touches were preceded by number "1" than "5" (429 vs. 447 ms, respectively; $P < 0.05$). The same significant pattern of results was also obtained when subjects' accuracy was separately tested, and response latencies showed the same tendency. In other words, the same touch delivered to the same little finger was better perceived if preceded by number "5" than "1" in the palm-down posture but was better perceived if preceded by number "1" than "5" in the palm-up posture.

To further explore the potential role played by instructional and task-setting variables, we performed a second experiment whereby tactile stimuli were always delivered on the thumb or little finger, but the side of the hand was stressed (i.e., "you will feel a touch on either the left or right side of your hand"). Moreover, to provide a finer description of the time course of the effect of numerical cueing of touch, a shorter SOA was tested: tactile stimuli were delivered either 550 ms (i.e., as the shortest SOA in the first experiment) or 250 ms after number onset (i.e., when the task-irrelevant number was still present on the screen; see *Methods* for details).

Results replicated the findings of the previous experiment. As shown in Fig. 3*b*, tactile performance was cross-modally affected by the visual presentation of a number, and numerical cueing of touch again followed a number–space association, as revealed by the significant finger × posture interaction [$F(1,12) = 6.02$; $P < 0.03$]. In the palm-down posture, subjects' tactile detection at the little finger improved with increasing number magnitude; the opposite pattern was observed in the palm-up posture. For stimuli applied on the little finger, the slopes of IE regression lines in the palm-down and -up position differed (-1.69 vs. $+12.12$, respectively; $P < 0.04$; Fig. 3*b*, yellow bars). Again, results for the thumb mirrored those for the little finger (Fig. 3*b*, blue bars). When the hand was in the palm-down posture, subjects' detection improved with decreasing number magnitude; the opposite tendency was present when the hand was in the palm-up position ($+23.22$ vs. -3.35 for the palm-down and -up postures, respectively; $P = 0.07$; Fig. 3*b*). When considering only the numbers "1" and "5," the ANOVA revealed a significant posture × finger × number interaction [$F(1,12) = 8.20$; $P < 0.01$], which further confirmed that the numerical cueing of touch was mapped in extrapersonal space. Fig. 3*c* illustrates that this effect was also present at the shortest SOA, because neither was this variable significant nor was it involved in any interaction (Fig. 3*c*), thus suggesting a rather early space-based mapping of numbers.

The findings of both experiments clearly demonstrate that the human brain takes into account magnitude information presented in the visual modality when processing tactile stimuli at the fingers, but in so doing, it refers to an extrapersonal spatial representation of numbers. Indeed, very similar and consistent results were observed both when task instructions emphasized the (left or right) sides of the hand (second experiment), and the (little finger or thumb) fingers of the hand (first experiment), as further confirmed by the omnibus ANOVA run on data from the common SOA (550 ms from number onset), whereby the between-subject variable emphasis was not involved in any interaction. Therefore, even when emphasis was given to fingers and might have in principle favored a finger-based numerical representation, the results were clear in showing a space-based dominance in number representation. When compared with previous studies, it is noteworthy that the present findings were obtained within a best-suited approach to disambiguate between number representations: First, number magnitude was totally task-irrelevant, at odds with previous visuomotor number-finger mapping task (24); second, a single centrally located effector was used, at variance with SNARC tasks whereby two left–right horizontally aligned effectors are typical used (14, 17); finally, the foot was used as response effector, i.e., a body part that is not used to learn counting.

Here, the case for a connection between space and numbers (29) was studied in direct reference to the body. Our manipulation of hand posture (30) was effective in distinguishing between the spatial reference frames in which tactile perception is biased by numerical cueing. By using an embodied approach based on tactile perception, we not only show that number-based attentional cueing crosses sensory modalities but also demonstrate that number-based tactile priming is early mapped according to an extrapersonal spatial representation, thus providing a compelling support for the dominant role played by the spatial representation of numbers known as the "mental number line."

Methods

Subjects. The first experiment was run on 14 (7 female, mean age 30.9; SD 10.1, range 20–51 years) neurologically healthy subjects. Thirteen (7 female, mean age 29.3; SD 8.1, range 21–51 years) healthy subjects participated in the second experiment. Three subjects took part in both experiments. All participants gave their informed consent to take part in this study, which was approved by the local ethics committee. They were asked to show how they usually count with their fingers, without specifying in the request which hand to use first. However, to induce subjects to use both hands, they were asked to count up to "8." Only subjects who used the conventional (for Italian and French subjects) counting system (1, thumb; 2, index; 3, middle; 4, ring; 5, little finger) starting from the right thumb were admitted to the experimental session. Subjects were all right-handed according to the Edinburgh Handedness Inventory. They had normal or corrected visual acuity, reported no somatosensory problems, and were naïve as to the purpose of the study.

Apparatus and Procedure. Both experiments were run with the same setup and procedures were identical, unless otherwise stated. A personal computer (Dell, Optiplex GX270, Intel Pentium 4) equipped with a visual stimulus generator (ViSaGe, Cambridge Research Systems) was used to control stimulus presentation and response collection. Arabic numerals ("1," "2," "4," or "5") were presented singly at the center of a cathode ray tube monitor (Eizo FlexScan T931; resolution, 800 × 600 pixels; refresh rate, 160 Hz), located 57 cm from the subjects' eyes, subtending 1 × 1° of visual angle. Subjects' right hidden hands lay in front of them, the middle finger aligned with the vertical meridian of the monitor, where a fixation point appeared. Thumb and little finger were thus to the right or to the left with respect to the middle finger. Two different postures could be assumed: Hand pronation (palm-down posture) or supination (palm-up posture). Subject's fixation and eye movements were constantly monitored throughout each trial via an eye-tracking system (Cambridge Research Systems; 250 Hz). After the subject succeeded in keeping the fixation within a (nonvisible) circular window centered on the fixation point (2.5° side by side) for 500 ms, one of the four equiprobable numbers ("1," "2," "4," or "5") appeared (300 ms). In the first experiment, a brief (100-μs) electrocutaneous stimulus was equiprobably delivered via self-adhesive disposable electrodes (Neuroline 700-K, Ambu) to the thumb or little finger at one of four possible SOAs (550, 800, 1,050, or 1,300 ms). In the second experiment, the electrocutaneous stimulus was equiprobably delivered to the thumb or little finger at one of two possible SOAs: 550 ms (i.e., same as the shortest SOA in the first experiment) or 250 ms (i.e., 300 ms earlier than the first SOA, when the number was still present on the screen). In both experiments, subjects had to respond as fast as possible to the tactile stimulation by pressing a central foot pedal with their right foot. Eye movements were monitored up to the foot-pedal response. If central fixation was broken at any time during the trial, the trial was aborted and randomly reintroduced to ensure that the same number of trials was recorded for each condition. The tactile stimulus intensity was set to obtain ≈80% correct detections for both fingers with a titration procedure that was run in a preexperimental session (see *SI Experiment 1* and *SI Experiment 2*). Each stimulator (DS7A, Digitimer) current was varied independently for each finger so that detection performance was comparable between the two fingers. Subjects were told that the number was totally irrelevant for the tactile detection task. To ensure that number magnitude was processed (see *SI Experiment 1* and *SI Experiment 2, Number Magnitude*, and Table S2), they were also told they could be asked without warning which number appeared in the immediately preceding trial.

Accuracy and reaction time (RT) were combined in the IE score, a standard way to combine RT and accuracy data into a single performance measure, computed as the median RT divided by the proportion of correct trials for a given condition; a higher IE value indicates worse performance, just as for RT and error measures. The IE score was submitted to a four-way ANOVA with SOA, posture, finger, and number (''1'' vs. ''5'') as variables. Each posture was further analyzed by a three-way ANOVA. Regression line beta values between IE score and numbers were also calculated and submitted to a three-way ANOVA with SOA, posture, and finger as within-subject variables. Significant sources of variance were explored by Newman–Keuls posthoc tests and planned comparisons.

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Supporting Information

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SI Experiment 1

Supporting Procedures. To obtain ≈80% correct detections for both fingers, the stimulus intensity was set individually for each subject and each stimulated finger in a preliminary session before the main experiment. The setup was the same used as for the main session, but the procedure differed as depicted in the Fig. S1. The fixation point was presented for 500 ms, after which, if the subject succeeded in keeping fixation, a tactile stimulus was delivered either to the thumb or the little finger. No number stimuli were presented.

The titration block used to set the intensity consisted of 15 trials, where 5 stimulations to the thumb and 5 to the little finger were randomly intermingled with 5 trials in which no tactile stimulus was delivered (catch trials). The intensity was first set at 0.10 mA for both constant current stimulators, each delivering electrocutaneous square wave pulses to one finger. At the end of the first preliminary block, the experimenter varied the stimulator current, independently for each finger, to reach a detection performance of 80% for each of them. Thus, the intensity was increased or reduced depending on whether the performance was below or above the criterion. The first step was 2 mA, then the step amplitude was halved at every direction reversal. The same block of trials and procedure was then repeated until the criterion of 80% of accuracy was met for each finger. The same procedure was applied for each hand posture (palm-up, palm-down). Table S1 below reports the stimulus intensity used for each subject for both fingers and postures.

Supporting Results. ***Electrocutaneous current intensity.*** A statistical analysis (ANOVA) with finger (thumb vs. little finger) and posture (palm-up vs. palm-down) as variables showed that, to have the same performance in terms of accuracy a different intensity had to be set for thumb (3.79 mA) and little finger (2.61 mA) [$F(1,13) = 7.13$; $P < 0.05$)]. No difference was present between the two postures.

Number Magnitude. To ensure that number magnitude was processed, subjects were told they could be asked, without warning, which number had been presented in the immediately preceding trial. Two of such probing situations were randomly interspersed within each block of trials. All subjects answered without error to this request in each block (100% accuracy), except one (subject 9) who made two errors reporting an incorrect number (83% accuracy).

Catch Trials. Each experimental block consisted of 160 trials: 4 repetitions for each combination of number, delay and finger (128) plus 32 trials (20%), where after the visual presentation of the number no electric pulse was delivered (catch trials). False alarms rate was on average 1.16% without difference across conditions.

SI Experiment 2

Supporting Procedures. Subjects started the experimental session alternatively with the hand in the palm-down or palm-up posture. The experiment consisted of a unique session of four experimental blocks (two for each posture), postures being counterbalanced across blocks. The same procedures and criterion (80% accuracy independently for both fingers) as for the first experiment were used in the second experiment to set the tactile stimulations intensity before the experimental session. As in the first experiment, stimulus intensity was not varied during the experimental session, but in the second experiment it was set in the palm-down posture for six subjects and with the hand in the palm-up posture for the remaining seven subjects. Table S2 below reports the stimulus intensity used for each subject for each finger.

Supporting Results. ***Electrocutaneous current intensity.*** Similar to the first experiment, a statistical analysis (ANOVA) with posture (palm-up vs. palm-down) as between-subject variable and finger (thumb vs. little finger) as within-subject variable showed that a difference in tactile stimulus intensity was set to obtain the same detection performance for thumb (4.38 mA) and little finger (2.94 mA) [$F(1,11) = 81.98$; $P < 0.001$)]. No difference was found between postures.

Number Magnitude. Subjects performed errorless when requested to report which number had been presented in the immediately preceding trial in each block (100% accuracy), except one subject (subject 11) who made one error reporting an incorrect number (4 instead of 5) (75% accuracy).

Catch Trials. Each experimental block consisted of 160 trials: 8 repetitions for each combination of number, delay and finger (128) plus 32 trials (20%), where after the visual presentation of the number no electric pulse was delivered (catch trials). False alarms rate was on average 2,49% without difference across conditions.

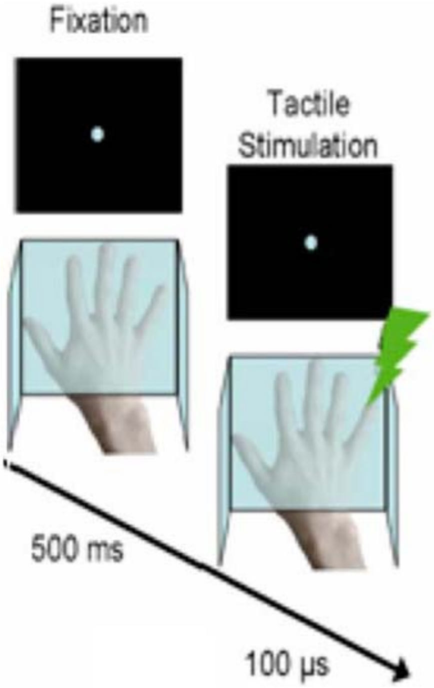

Fig. S1. Timing of stimuli presentation for the preliminary titration session. The figure illustrates the example of a tactile stimulus delivered to the little finger (green symbol) in the palm-down posture. As in the experimental sessions, the subjects were instructed to respond to the tactile stimulus as quickly as possible regardless of the finger stimulated, by pressing a pedal with their right foot.

Table S1. Stimulus intensity for each subject's thumb and little finger for the two hand postures

	Stimulus intensity, mA			
	Thumb		Little finger	
Subjects	Palm down	Palm up	Palm down	Palm up
1	3.5	3.6	2	2.1
2	3.4	3.3	1.9	1.5
3	2.7	2.6	1.8	1.8
4	7.5	7.7	4.2	4.3
5	4.8	4.8	3.6	3.6
6	3.7	3.7	3	3
7	7	6.8	1.9	1.6
8	2.4	2.4	4.1	4.1
9	5.6	5.6	3	3
10	2	2.1	2	2
11	3.2	3	2.4	2.5
12	2.5	2.3	2.2	2.2
13	3	3	2.8	2.9
14	2	2	1.8	1.8
Mean	3.81	3.78	2.62	2.60
SD	1.77	1.79	0.85	0.91

Table 2. Stimulus intensity for each subject's thumb and little finger

	Stimulus intensity, mA	
Subjects	Thumb	Little finger
1	3.9	2.7
2	4.1	2.5
3	4.3	3.0
4	4.7	3.3
5	5.3	3.3
6	4.1	2.6
7	4.7	2.7
8	1.9	1.9
9	4.5	3.5
10	6.1	4.4
11	5.9	4.1
12	4.2	2.2
13	3.2	2.1
Mean	4.38	2.94
SD	1.09	0.75

From subjects 1 to 6, intensity was set with the hand in the palm-down posture; from 7 to 13, intensity was set with the hand was in the palm-up posture.

2.1.1. Discussion

The study presented here reveals that visuo-tacile interactions in healthy humans may be modulated by relatively abstract information about quantities and that, in some cases, the somatotopic coding of touch 'loses' against more 'space-based' coding of touch (Azañón and Soto-Faraco 2008). The visual information, in this case a semantic symbol as a number, can affect the perception of information coming from the somatosensory channel. It is clear from this example that the interaction between the two modalities has a spatial nature, even at this high-cognitive level. This study is an evidence of cross-modally driven shift of attention.

3. Multisensory integration through anatomical convergence

Perhaps, the simplest approach for thinking of an interplay between different sensory modalities is to imagine a point of convergence for inputs coming from the different sensory channels. In other words, the information coming from the external world, initially elaborated in the unisensory regions of the brain at a certain level have to converge on the same area. A large body of evidence is now available from single-cell and tracing studies in animals and from neuroimaging studies in humans showing numerous multisensory convergence zones in the brain. In particular the animal models revealed cortical and subcortical structures where the single units receive afferent inputs from different senses. The pioneering and influential series of studies conducted on the superior culliculus (SC) in the cat (Meredith and Stein 1983; 1986), made of this structure a model for the multisensory integration. In humans too, neuroimaging studies revealed the presence of possible areas of sensory convergence.

Deep layers of the SC, in addition to other subcortical regions such as basal ganglia (Nagy et al. 2006), has been shown to receive inputs from somatosensory, auditory, and visual areas (Stein and Meredith 1993). Activity in deep SC neurons is thus dependent on the presence of information coming from more than one sense and on spatial and temporal relation between inputs of different modalities. Three general rules can describe the neural activity of this structure.

1. The spatial proximity between sensory information. Activity of SC neurones is maximal when stimuli of different modalities are presented in the same location. The integration diminishes with increasing spatial discrepancy between the visual and auditory information, for example.
2. The temporal synchrony between sensory information. Also the temporal relation appears to play a fundamental role in the multisensory integration, allowing it when the different sensory information are presented simultaneously rather than temporally separated.
3. The "inverse effectiveness" rule. Activity of SC neurones appears to be dependent on the intensity of the sensory signals. In particular the best response is associated with the presence of one sensory input with a weak signal. The bi- or trimodal interplay at the cellular level can be larger when each unisensory input alone elicits a relatively weak neural discharge (Stein and Meredith 1993; but see Holmes 2007c for a critical discussion about the law of inverse effectiveness in behaviour). However, both super- or sub-additive responses can be observed for multisensory co-stimulation, as compared to stimulating either sense individually (see Figure 1.4).

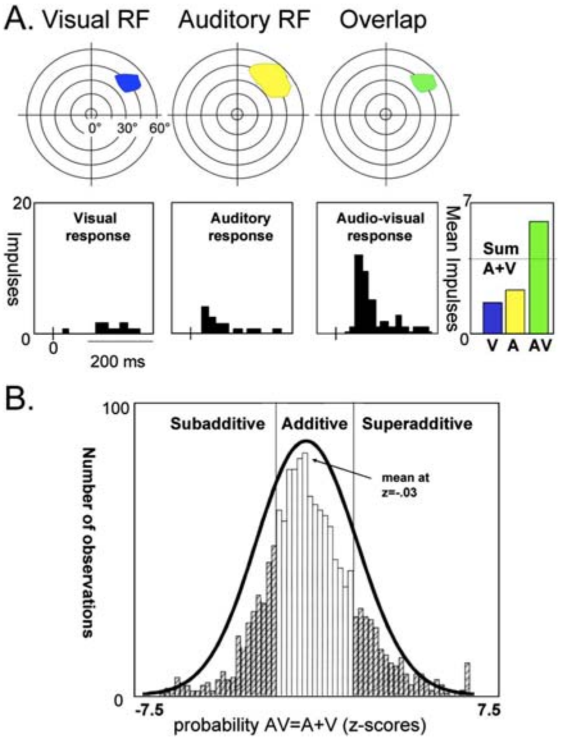

Fig. 1.4 Example of audio-visual integration cell in SC. **A.** The bar graph shows a super-additive response where the multisensory response of the cell (green bar) is higher than the sum of the unisensory responses (blue and yellow bars). **B.** Distribution of the numbers of cells presenting linear and non-linear responses to multisensory stimulation. From Driver and Noesselt 2008.

Turning to cortical regions in non-human primates (Kaas and Collins, 2004 for a review), the upper bank of the superior temporal sulcus is known to have bidirectional connections with unisensory auditory, visual and somatosensory cortices (Padberg et al. 2003; Schmahmann and Pandya 1991) and to contain multisensory neurons (Bruce et al. 1981) that, similarly to the SC, receive inputs from different sensory modalities converging on the same single cell. Several regions within parietal and frontal areas also present a multisensory convergence of information (see the second chapter of this dissertation).

One of the most elegant research in humans focussing on cross-modal integration is represented by a series of studies conducted in fMRI (functional Magnetic Resonance Imaging, Macaluso and Driver 2001; Macaluso et al. 2000; Macaluso and Driver 2005 for a review). This constitutes one of the first research investigating which areas in the human brain present an activity correlated with a detection task performed on stimulation coming from different modalities. A region corresponding to IPS (Intraparietal sulcus) appeared to be activated both for a visual and for a tactile detection task (Macaluso and Driver 2001). These results are in agreement with the results coming from an independent research by another group showing an activation of parietal regions in response to visual or tactile stimulations (Bremmer et al. 2001).

4. Multisensory interactions through feedback on unisensory areas and inter-connections among unisensory areas

As noted in the introduction, the revolutionary advance in multisensory research is the discovery that the multisensoriality exists “beyond modularity and convergence” (Driver and Spence 2000). The interplay between different modalities can indeed arise not only through a convergence mechanism which integrates the information coming from different senses in the same neuron. Other mechanisms have been recently proposed, following some studies whose results showed the existence of modulations of unisensory low-level areas from the activity of multisensory high-level areas, or as a result of direct early modulations from different low-level unisensory areas (Figure 1.5).

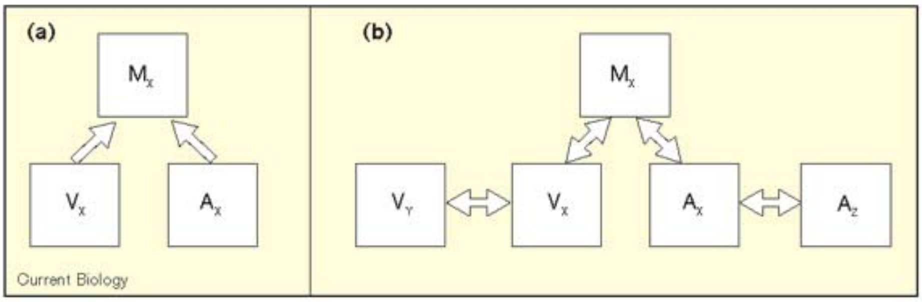

Fig. 1.5 Schematic representation of **a)** multisensory integration and **b)** multisensory feedback interaction from integration areas over unisensory areas. From Driver and Spence 2000.

4.1. Back-projections from multisensory higher-level to unisensory lower-level areas

The “new look” in this field is based on studies showing that once believed sensory-specific areas can be influenced by multisensory interactions. Some evidence was present in the early 70’s (Fishman and Micheal 1973; Morrell 1972; Spinelli et al. 1968) showing a modulation of the visual regions response as a consequence of the presence of auditory information. However due to the technological limits of these early studies one cannot exclude non-specific confounding factors. More recent researches have clearly showed that traditionally considered unisensory regions can be influenced by multisensory interactions (Macaluso et al. 2000; Macaluso et al. 2002). Several fMRI studies have now reported modulation of traditional unisensory areas (usually defined as occipital for the visual system, post-central for tactile sensation and temporal for the auditory information) due to multisensory co-stimulation (Amedi et al. 2002; Buchel et al. 1998; Calvert et al. 1999; 2001; Macaluso et al. 2000; Martuzzi et al. 2007; Miller and D'Esposito 2005). Using high-resolution fMRI in monkeys, together with separate mapping of specific auditory-cortex regions, Kayser and colleagues (2005) observed increased BOLD signal in secondary auditory cortex due to the presence of tactile stimulations. Even primary auditory areas were affected during the presence of visual information (Kayser et al. 2007).

Also in human, evidence has been found in favour of a modulation of primary sensory areas in case of multisensory stimulation. Auditory cortex, for instance, appears to be differentially modulated when subjects perceived audiovisual speech stimuli as synchronous

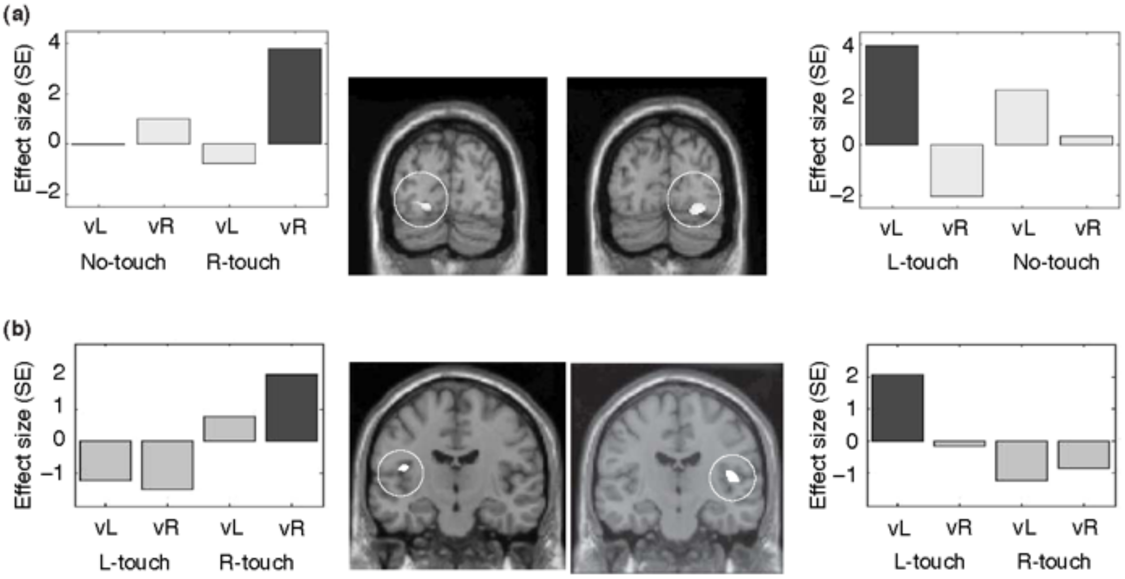

Fig. 1.6 Spatially-specific stimulus-driven crossmodal influences on unimodal cortices. **(a)** Task-irrelevant tactile stimulations modulated visual responses in contralateral occipital areas, with higher activity when the visual event was presented together with a spatially congruent tactile stimulus on the same side (dark bars), even though these areas did not respond to touch alone. **(b)** Activity in the parietal operculum increased for contralateral tactile stimuli when presented with a visual stimulus at the same location (dark bars). From Macaluso and Driver 2005.

or asynchronous (Miller and D’Esposito 2005). Similarly, a neuroimaging study provided evidence of modulation of auditory cortex activity induced by the vision of silent speech (Calvert et al. 1997). An elegant work on modulation of unisensory by multisensory areas is Macaluso’s series of studies in fMRI on visuo-tactile interactions. These experiments investigated which areas in the brain might present an activity correlated to the execution of very simple cross-modal spatial tasks when both visual and tactile information are simultaneously present (Macaluso et al. 2000; Macaluso et al. 2002; Spence and Driver 2004). Typically, a visual stimulation was presented on the right or left side of space. On half of the trials, a concurrent tactile stimulus was delivered to the right or left hand of the participants, instructed to report only where they perceived the visual information trying to ignore the touches. Thus, visual and tactile information could be presented in a congruent or incongruent spatial arrangement, on a trial-by-trial basis. The behavioural performance showed a cross-modal facilitation effect when both sensory modalities were stimulated at the same side with respect to when the same stimuli were presented on opposite sides. More interestingly, the behavioural facilitation was accompanied by an increased activity in occipital regions contralateral to the stimulated side when the visual information was presented together with the tactile one. Similarly, in a subsequent study (Macaluso et al. 2002), tactile responses in the parietal operculum have been shown to be analogously modulated by adding a visual stimulus: maximal activity was observed when the contralateral tactile information was coupled with the visual stimulation at the same location (Figure 1.6).

These studies provide evidence in favour of a possible modulation of relatively low-level areas through backward projections coming from areas of multisensory convergence.

4.2. Early interactions between unisensory areas

Several electrophysiological studies showed very early modulation of event related potentials (ERP) arising over visual cortex when a bimodal auditory-visual stimulation was present, already at 40 ms after the stimulus presentation (Giard and Perronet 1999). A similar modulation of ERP recorded over unisensory regions has been described for concurrent audition and touch, as early as 50 ms after the stimulus presentation (Figure 1.7; Foxe et al.

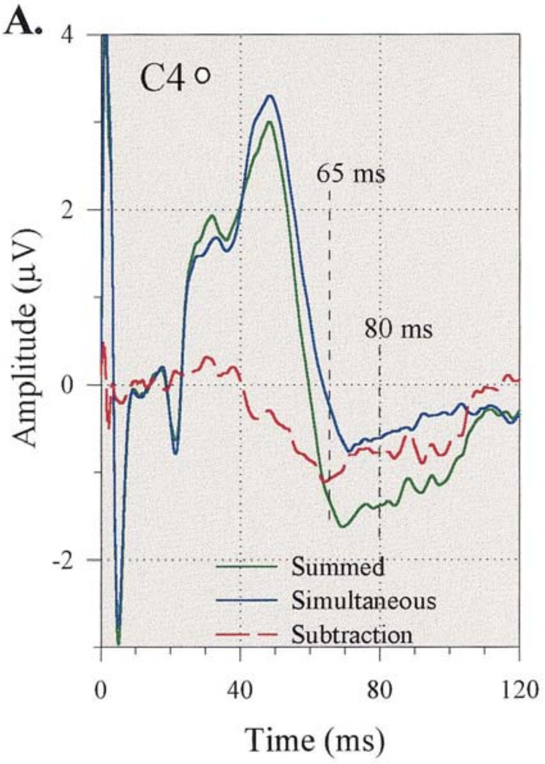

Fig. 1.7 Early multisensory interaction between audition and touch. The simultaneous auditory and tactile inputs presentation elicits a higher early component (50 ms) than the sum of the unisensory stimulation, supporting the idea of an early interaction between unisensory areas. From Foxe et al. 2000.

2000; Molholm et al. 2002). Effects at such short latencies do not readily fit with backward projections via longer pathways from multisensory areas. Thus they are presumably suggesting some direct connections between sensory-specific areas. Evidence in favour of this possibility comes from retrograde tracing studies in monkeys, showing for example direct connections between primary auditory and visual cortex (Falchier et al. 2002). Moreover, electrophysiology has also demonstrated some response to somatosensory stimuli in a region closely adjacent to the primary auditory cortex (Fu et al. 2003; Lakatos et al. 2007).

5. Conclusion

The multisensory research presented in this chapter clearly shows how pervasive might be the presence of multisensory mechanisms in the brain. It is obvious that the brain adapted such mechanisms through evolution in a world that can essentially be experienced in a multisensory way. Since also the low-level primary areas can be affected as well by the presence of information coming from a different sensory channel, the question arises as to whether it is still valuable to distinguish unisensory processing and unimodal areas from multisensory areas (Ghazanfar and Schroeder 2006). However, despite this evidence, unisensory areas show stronger preference for one particular modality with respect to others. They thus are more “sensory-specific” rather than “unisensory” but they still retain their functional specialisation in the elaboration of sensory information. On the other side, the proper multisensory integration, arising at the single cell level should also present an adaptive function with respect to other form of multisensory modulation. In the next chapter I will present in detail the mechanisms underlying the multisensory convergence between visual and tactile information and the characteristics of this multisensory link between information external to the body and information present onto the body.

Chapter II

Multisensory and motor representations of peripersonal space

The binding of visual information available far outside the body with tactile information arising, by definition, on the body, allows for the construction of a representation of the space which lies in-between. This reachable part of the external space is often the theatre of our interactions with objects. This representation of intermediate space has become known as "peripersonal space" (Rizzolatti et al. 1981b, c). The definition of peripersonal space originates from neurophysiological studies in monkeys where single cell investigations have highlighted the existence of bimodal neurons responding to visual as well as tactile stimulations. In this chapter I will review some basic features of visuo-tactile interactions, as revealed by the single units recording studies in monkeys. A crucial point that will be stressed is that these neuronal populations are not only responsive to sensory solicitation from the environment, but they also present motor-related activity. The peculiar nature of their activation qualifies them as multisensory-motor interfaces, a bridge between the (multisensory) perception and the planning and execution of actions.

1. Multisensory features of peripersonal space: Visuo-tactile interaction around the body

A class of multisensory, predominantly visual-tactile, neurons has been proposed to provide the neural mechanism for the the peripersonal space representation. These class of neurons are present in several regions of the monkey brain (Figure 2.1). These include cortical areas in the parietal cortex (Broadmann's area 7b and the ventral intraparietal area, VIP) and in the frontal premotor cortex (Broadmann's area 6), but also subcortically such as the putamen (Fogassi et al. 1999; Graziano 2001; Rizzolatti et al. 1997). These neurons' most relevant characteristic for present purposes is that they respond both to visual and tactile stimulation; in particular, their visual receptive fields (RFs) are limited to a region of space surrounding the body in such a way that their visually evoked responses are modulated by the distance between the visual object and the tactile RF.

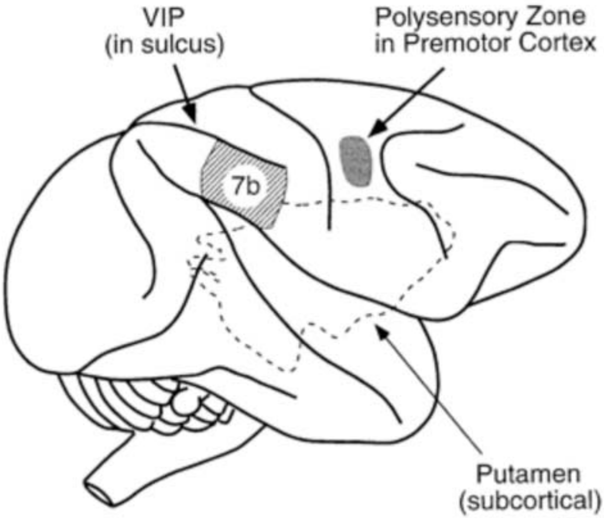

Fig. 2.1 Side view of a macaque monkey brain showing the location of four interconnected multimodal areas. Graziano 2001.

1.1. Parietal Visuo-tactile interactions

The posterior parietal lobe in non-human primates can be subdivided into two different regions, with respect to the intraparietal sulcus, as shown in Figure 2.2: A superior and an inferior part, corresponding to areas 5 and 7, respectively (Broadmann's classification). Area 7 contains two functionally distinguishable subdivisions (7a and 7b). While area 5 appears to be activated mostly by complex somatosensory stimulation (Duffy and Burchfiel 1971; Sakata et al. 1973), the lateral area 7b is composed of bimodal cells. Electrophysiological studies conducted on awake monkeys revealed that the visuo-tactile integration in these

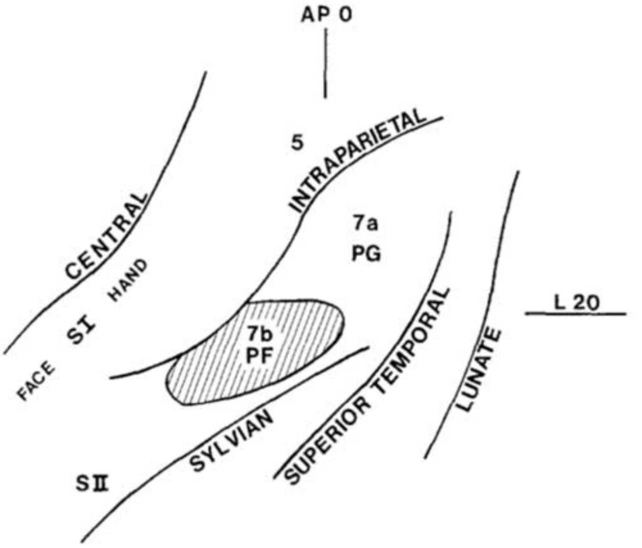

Fig. 2.2 Macaque monkey parietal lobe: intraparietal sulcus separates a superior and an inferior parietal region, area 5 and area 7 respectively. In turn area 7 can be differentiated in area 7a and 7b. From Leinonen et al. 1979.

posterior parietal areas is based on a convergence mechanism of different sensory afferents at the single unit level (Hyvärinen and Poranen 1974; Hyvärinen 1981; Leinonen et al. 1979; Leinonen and Nyman 1979; Mouncastle et al. 1975; Robinson et al. 1978; Robinson and Burton 1980a, b)[1]. Most neurons in this area have been shown to be responsive to tactile stimuli. They presented a somatotopic organization, with separate face, arm and hand representations encountered along the latero-medial axis (Hyvärinen and Shelepin 1979; Hyvärinen 1981; Robinson and Burton 1980a). It is overall within the face and arm regions of this map, that visuo-tactile cells have been reported (33% of the total sample, Hyvärinen and Poranen 1974; Hyvärinen and Shelepin 1979; Hyvärinen 1981; Leinonen et al. 1979; Leinonen and Nyman 1979; Leinonen 1980). Researchers initially interpreted these visual responses as an “anticipatory activation” that appeared before the stimulating object enters into the neurons’ tactile receptive field (RF) (Hyvärinen and Poranen 1974, page 675). The critical characteristic of these neurons is that their activation have shown to be dependent on the distance of the effective visual stimulus from the body-part. Most of the bimodal cells responded to cutaneous stimulations, and to visual stimuli moving towards the animal within about 10 cm from the tactile RF, even though in some cases, stimulation presented further away, but still within a reachable distance, was also effective. Some cells presented a direction-selectivity for both visual and somatosensory

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[1] A possibly earlier report of neurons responding to both tactile and visual stimulation is in Sakata and colleagues’ report (1973, page 100), a study about the functional organization of area 5, where the authors stated: “Even the relatively rare neurons which we could activate visually were more powerfully driven by somatosensory stimuli”. However, no further detail or discussion was offered concerning the limitation in depth of the visual RF.

stimulation (Leinonen et al. 1979). Furthermore, a close correspondence between the tactile and visual RFs has been documented, especially for tactile RFs on the arm (Leinonen et al. 1979). The location of the visual effective stimulus needed to be changed, for example, when the arm was placed in different locations. In other words, the authors described the spatial correspondence between visual and tactile receptive fields. This characteristic, described later in detail, is based on the continuous up-dating of the peripersonal space at each body movement. However, this first series of investigations were affected by some technological limitations. For instance, authors did not control for eye movements which are numerous and unpredictable in awake, behaving monkeys. Thus, their results have to be restricted to the still important finding of a neuronal system where visual information close to the body converges together with tactile information in single neurons within posterior parietal areas.

Multisensory neurons have also been found in monkey area VIP, in the fundus of the intraparietal sulcus (Avillac et al. 2005; Colby and Duhamel 1991; Colby et al. 1993; Duhamel et al. 1998). VIP neurons respond to tactile and visual stimulations presented within a few centimetres of the tactile RF (Figure 2.3). Unlike neurons pertaining to area 7b, tactile RFs in VIP are primarily localised to the face and head, and visual RFs are restricted to a very shallow region of space around the face (Colby et al. 1993). Compared to the few neurons of area 7b that showed a directional selectivity for visual and tactile moving stimuli, the

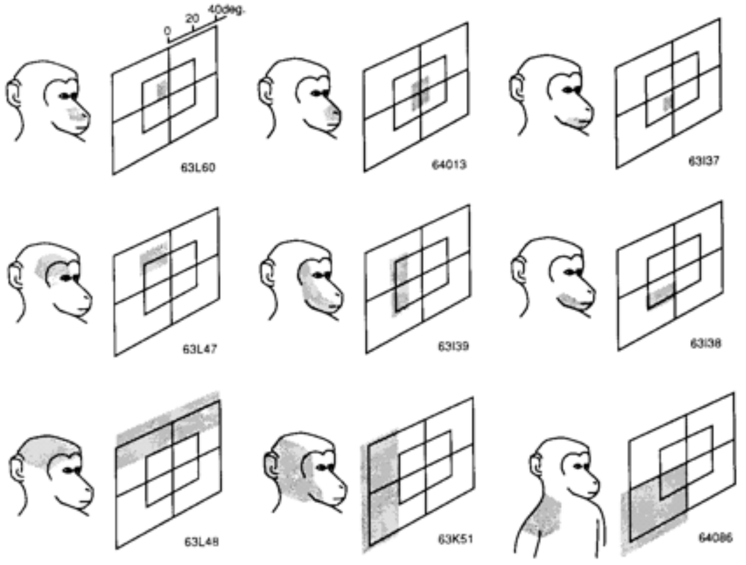

Fig. 2.3 Schematic representation of somatosensory and visual receptive fields of bimodal (VIP) neurons mapped in alert monkeys. Tactile responses were elicited with the monkey blindfolded, and visual responses were elicited with the monkey looking at a central fixation target on the tangent screen. Shaded areas represent tactile and visual RF surfaces. From Duhamel et al. 1998.

VIP cells are strongly characterised by a preferred direction that often matches between both sensory modalities. Their visual RFs have been clearly shown to be anchored to the face independently of the gaze direction (Colby et al. 1993). Noteworthy, VIP is a multisensory region of the cortex in which the majority of VIP neurons perform multisensory integration following the same general rules (e.g., spatial congruency and temporal synchrony) that have been previously documented in other cortical and subcortical regions (Avillac et al. 2007).

An interesting recent finding showed that visuo-tactile neurons within area 7b and VIP also respond when another individual's body-part is approached by a visual stimulus (Ishida et al. 2009). Similarly to the multisensory neurons described above, these "body-matching neurons" respond to visual stimuli presented near the tactile RF. Moreover, these "body-matching neurons" are responsive to a visual stimulus presented close to the corresponding body-part of another individual (a human experimenter). For instance, a neuron displaying a tactile RF on the arm responded to a visual stimulus presented close to the monkey's own arm, but also responded to visual stimuli presented close to another individual's arm (Figure 2.4). For some of these neurons, this matching property seems to be independent of the position of the observed individual with respect to the observing monkey (up to 35 degrees of rotation).

The studies presented in this section indicate that the initial cortical convergence of vision and somatosensation occurs in a pool of areas within the parietal lobe. These cortical regions present also several direct and indirect connections. The intraparietal sulcus receives projections from both somatosensory and visual areas respectively in its medial (Jones and Powell 1970), and lateral bank (Seltzer and Pandya 1980; Maunsell and Van Essen 1983; Ungerleider and Desimone 1986; Boussaoud et al. 1990; Baizer et al. 1991). Most importantly, both projections overlap in the fundus, where VIP is located (Maunsell and Van Essen 1983; Ungerleider and Desimone 1986; Colby and Duhamel 1991). These three regions of the intraparietal sulcus send projections to area 7b (Jones and Powell 1970; Mesulam et al. 1977), which also receives more direct somatosensory input from SII (Stanton et al. 1977) and from area 5 (Jones and Powell 1970), the superior part of the posterior parietal area.

In this way, multisensory perception arises as the result of a physiological convergence of visual and tactile input on the same neurons (Jones and Powell 1970) from the respective

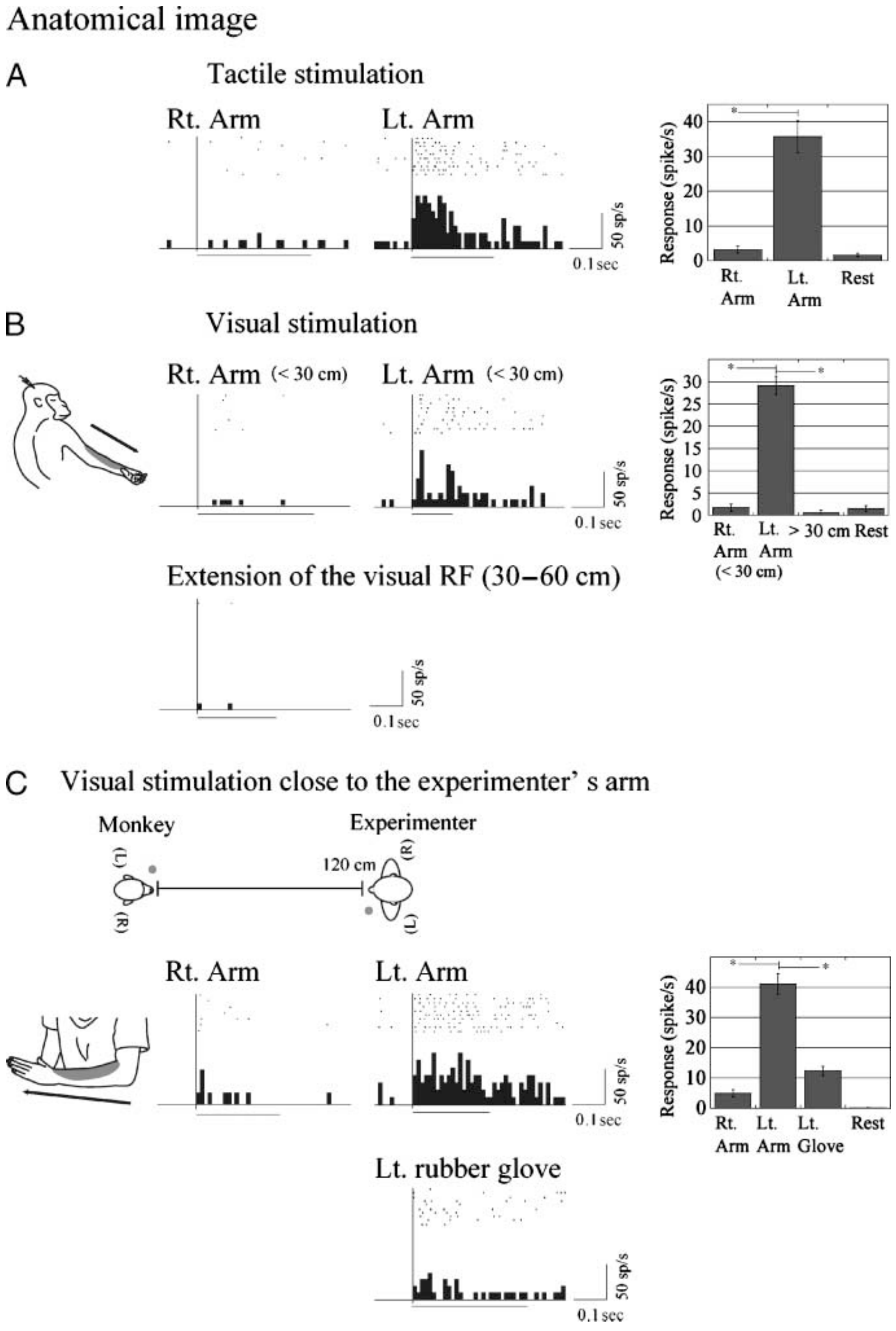

Fig. 2.4 An example of an anatomical image body-matching neuron. (A, B) Location of tactile RF on the monkey's left forearm, with visual RF anchored close to the same part of the tactile RF. (C) Visual responses to experimenter's forearms. This neuron was active when the monkey observed the experimenter stroking his own left forearm from proximal to distal. From Ishida et al. 2009.

areas of initial elaboration. Moreover, the multisensory parietal areas appear to be, to a certain extent, differentially involved in the representation of the space around different sectors of the body. Most part of the VIP neurons present RFs on the face and head while neurons within parietal area 7b are more representative of the arm and hand regions.

1.2. Premotor visuo-tactile interactions

A detailed series of studies on the properties of visuo-tactile neurons has been also made available by investigating monkeys' bimodal neurons contained in the premotor cortex. Numerous studies have focussed on the single cell recording on units within F4 and F5 regions of macaque monkey (Matelli et al. 1985), composing respectively the rostral and the caudal inferior part of area 6, in the proximity of the arcuate sulcus as illustrated in Figure 2.5 (Fogassi et al. 1992; Fogassi et al. 1996; Gentilucci et al. 1983; Gentilucci et al. 1988; Godschalk et al. 1985; Graziano et al. 1994; Graziano and Gandhi 2000; Rizzolatti et al. 1981a, b, c; Rizzolatti et al. 1987; Rizzolatti and Gentilucci 1988; Rizzolatti and Luppino 2001).

Neurons in the F4 sub-region are strongly responsive to tactile stimulation. They are characterised by relatively large tactile RFs located primarily on the animal's face or arm/hand regions. Some of these neurons also present RFs in separated body parts. They are responsive for tactile stimuli on the peribuccal region, for instance, as well as for touches delivered on the hand (Gentilucci et al. 1988; Rizzolatti et al. 1981a). A large proportion (85%) of the tactile cells in this area discharges also in response to visual stimuli. According to the depth of the visual RFs extending out from the body, multisensory neurons have been subdivided into pericutaneous (54%) and distant peripersonal neurons (46%) (Figure 2.6, upper and lower panel). The former proved to be better responding to stimuli presented a few centimetres from the skin (10 cm or less, Rizzolatti et al. 1981b); the latter are, instead, activated by stimuli delivered a bit farther from the body, but always within the animal's reaching distance. Therefore, an important property of these neurons, like the cells described in multisensory parietal areas, is that their visual RFs are limited in depth to a few centimetres (in most cases from ~5 to ~50 cm) from the tactile RFs. The visual RFs are generally

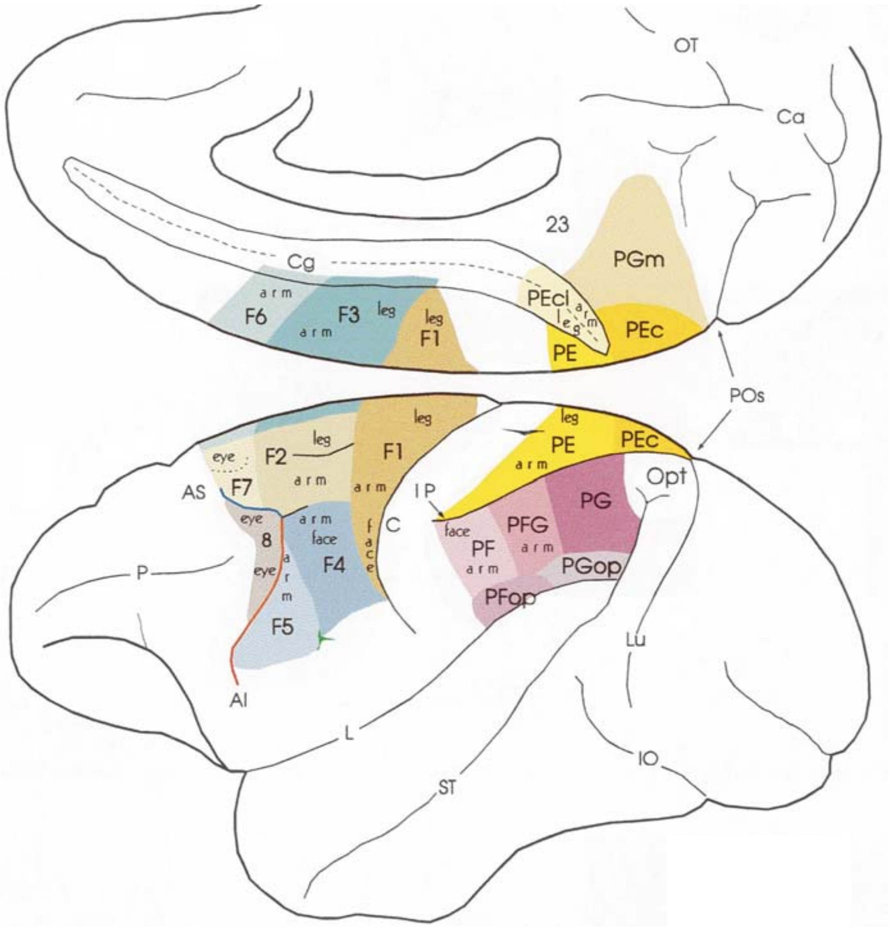

Fig. 2.5 Schematic representation of the functional parcelisation within prefrontal and parietal areas in the macaque monkey brain. In particular, within visuo-tactile premotor cortex, different sub-areas are distinguishable, such as F4 and F5 in the ventral premotor cortex. From Rizzolatti et al. 1998.

independent of gaze direction (Fogassi et al. 1992; Gentilucci et al. 1983), being spatially related instead to the body-parts on which the tactile RFs are located. Gentilucci and colleagues' study provided the first evidence of a peripersonal space codification independent of eye position. The authors moved the visual stimulus close to the face during monkey's spontaneous eye movements. The neuron always responded when the visual stimulation approached the same body part, where the tactile RF of the neuron was located. At similar conclusion brings Fogassi's investigation (Fogassi et al. 1992), which proved that neurons within sub-region F4 code the visual stimulus position in spatial and not in retinal coordinates. This is true also for neurons with tactile RFs on the arm and hand: when the arm is moved under the monkey's view, the visual RF follows the body-part, staying 'anchored' to the tactile RF (Graziano and Gross 1993; 1995) keeping a rough spatial match with its

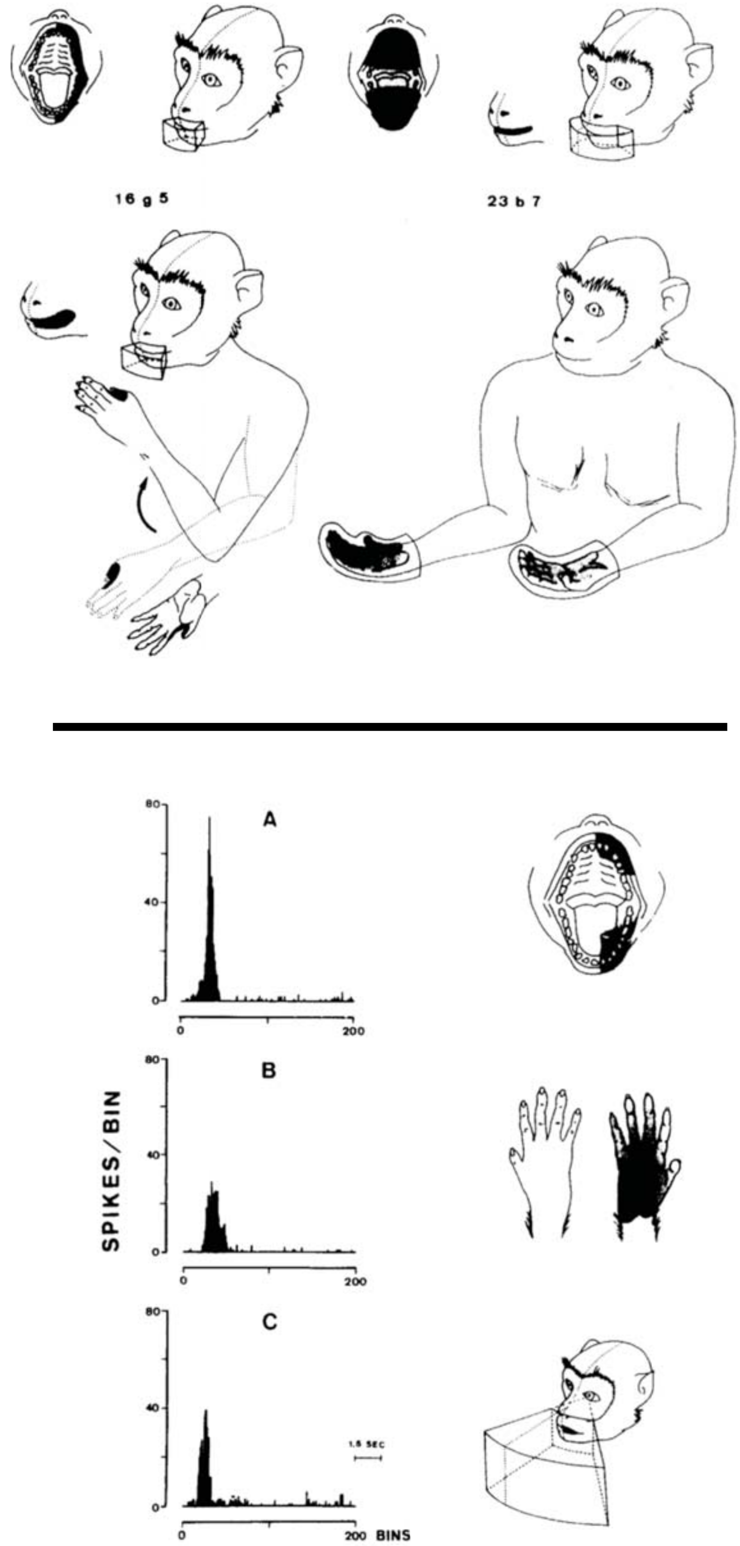

Fig. 2.6 Examples of visuo-tactile neurons in the ventral premotor area. **Upper Panel** Pericutaneous peripersonal neuron presenting tactile and visual RFs on the mouth or the hands (right part) or tactile RFs on both mouth and hand and visual RFs on the mouth (left part). **Bottom Panel** Distant peripersonal neuron. A and B represent neuron response for tactile stimuli to mouth and hand respectively. C represents the visual response of the same neuron for a visual stimulus presented in the region of space around the mouth, as represented in the figure. From Rizzolatti et al. 1981

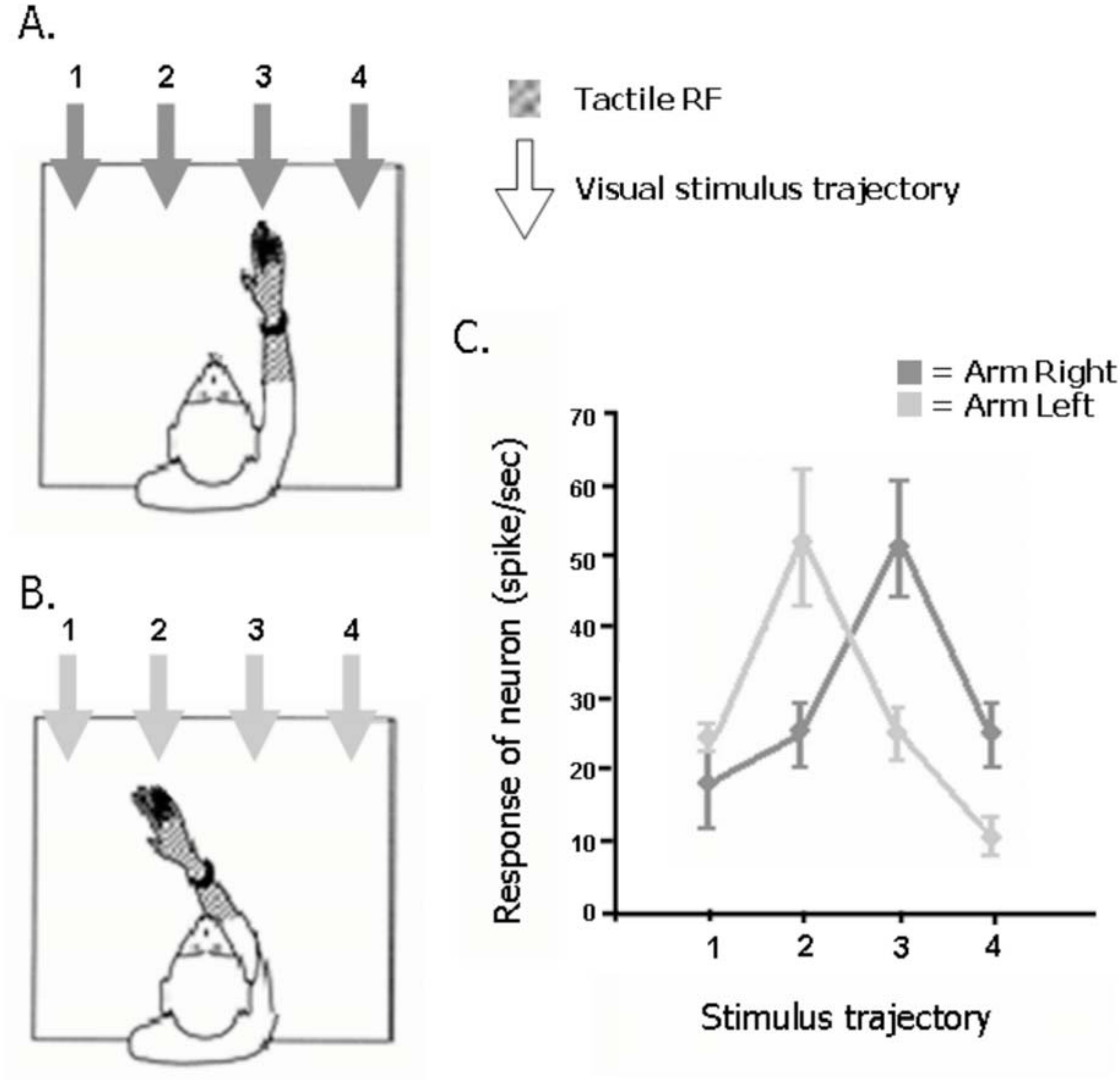

Fig. 2.7 Visual and tactile RFs of visuo-tactile neurons are in rough spatial register. When the arm is on the right side (A), for example, the visuo-tactile neuron presenting a tactile RF on the arm, also respond for a visual stimulus approaching the arm along the trajectory 3 (dark grey line in the graph C). When the arm moves on the left side (B), the same visuo-tactile neuron now responds better to a visual stimulus approaching the arm along the trajectory 2 (light grey line in the graph C). Modified from Graziano et al. 1997.

location at every displacement (see Figure 2.7; Graziano et al. 1994; Graziano et al. 1997).

Although less numerous, visuo-tactile neurons are present also in the rostral sub-region F5 of area 6, presenting smaller tactile RFs than F4 neurons, frequently located on the hand, the face or both. However, the visual properties of these neurons were shown to be quite different: While a stronger response was induced by stimuli presented within the reaching distance, visual RFs were usually difficult to define (Rizzolatti et al. 1988; Rizzolatti and Gentilucci 1988).

1.3. Subcortical visuo-tactile interactions

As described in the previous chapter, pools of multisensory neurons have also been found in subcortical structures of the brain such as the superior colliculus. The multisensory encoding of events in the superior colliculus (Stein and Meredith 1993; Wallace and Stein 2007), however, seems not to be primarily devoted to representing the space near the body (for a brief discussion of the properties and functional roles of multisensory neurons in the superior colliculus see the first chapter). More concerned into the codification of the space close to the body is another subcortical multisensory structure: the putamen (e.g., Graziano and Gross 1993; 1994; 1995) which presents a relevant visuo-tactile activity contributing to the peripersonal space representation (Graziano and Gross 1993; 1994; 1995). Visuo-tactile neurons in the putamen are somatotopically organized, just as in the cortical areas described above. Most of the somatosensory neurons with tactile RFs on the arm, hand and face are also responsive to visual stimulation. Also for neurons in this region the activity driven by visual stimulation is dependent on its distance with respect to the body. Neurons in the putamen respond as long as visual information is presented close to the tactile RF. A large portion (82%) of face-related neurons respond best to visual stimuli presented in a region of space within 10-20 cm from the tactile RF (Figure 2.8). Neurons with tactile RFs on the arm and hand also present very shallow visual RFs around the hand (up to 5 cm). As for the cortical visuo-tactile neurons, the visual and tactile RFs in the putamen roughly correspond spatially with the visual RFs anchored to the tactile ones.

1.4. Dynamic feature of peripersonal space representation

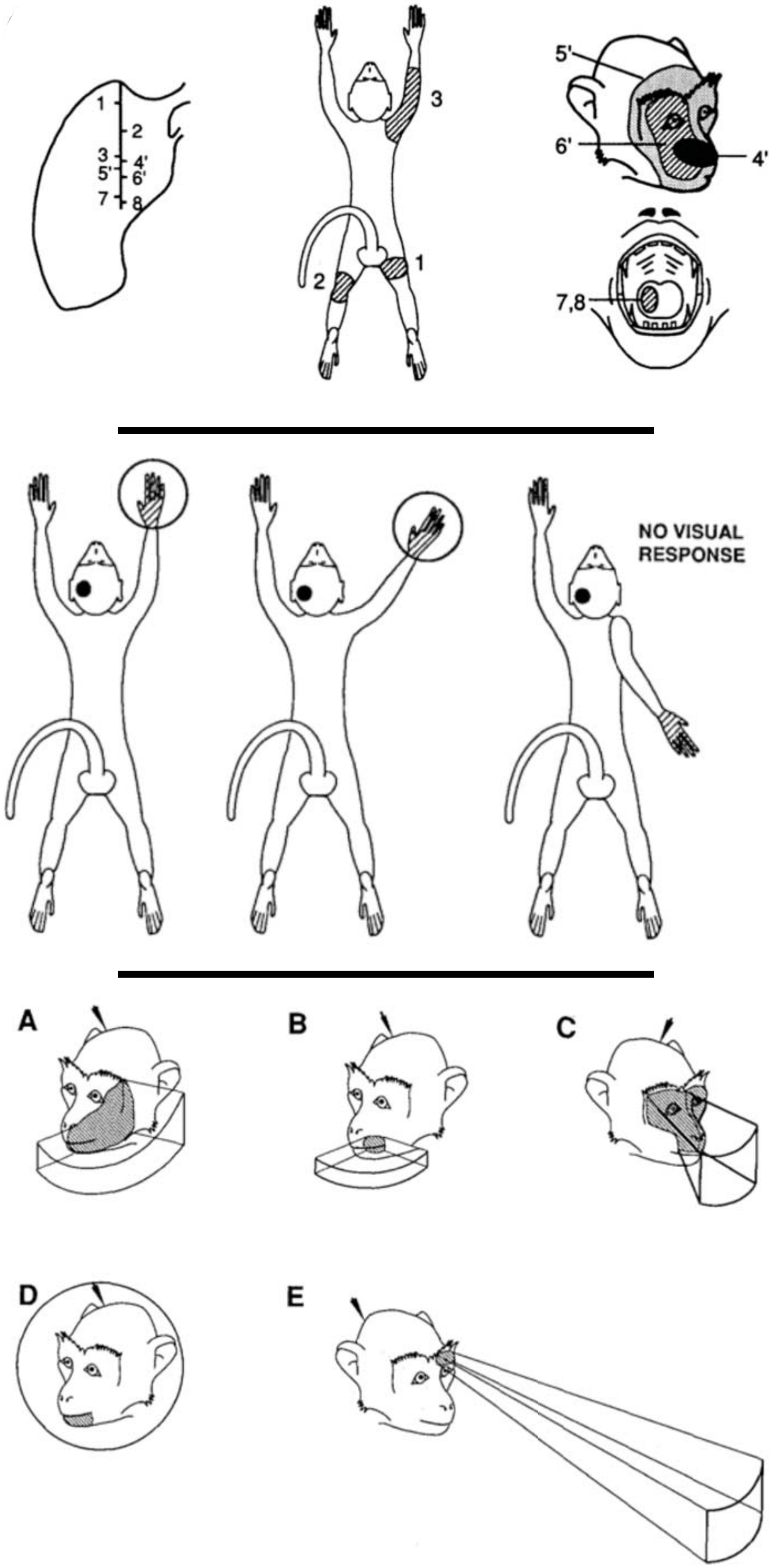

Fig. 2.8 Examples of visuo-tactile neurons recorded in the Putamen.
Upper Panel
Distribution of somatosensory RFs in the dorso-ventral dimension.
Central Panel
Peripersonal space neuron with tactile RFs on the hand and the visual RFs anchored to it.
Lower Panel
Peripersonal space neurons with tactile RFs on the face and visual RFs in the region around the face.
Modified from Graziano et al. 1993.

The visual receptive fields of some visuo-tactile neurons proved to present dynamic properties in such a way that they can be modified as a function of the interaction with the environment. Iriki and colleagues (Iriki et al. 1996), for instance, revealed that, the functional use of a tool can bring to a modification of the extent of bimodal neurons visual RFs. In their investigations, a group of monkeys has been trained to use a rake as a tool in order to reach food pellets placed in a region of space normally outside of the free-hand reaching space. In this paradigm, the functional use of the tool which elongates the monkeys' arm allows to interact with objects that are placed far from the body as if they were close to it. In such a way, the far space becomes functionally near. From a neurophysiological point of view, after the tool-use training, some neurons in the post-central gyrus (somewhat extending into the intraparietal sulcus) began to display visual responses for stimuli presented far from the body but close to the functional extremity of the tool (Figure 2.9). In addition, such visual responses appeared to be induced by the active, but not by passive, tool-use. When monkeys just held the tool without using it, the authors did not report any modifications of the visual RFs. In addition, a few minutes after active tool-use the expanded visual RFs shrank back to their original size when tool is not longer used. In other words, the dynamic aspects of the visual RF may depend on the execution of a

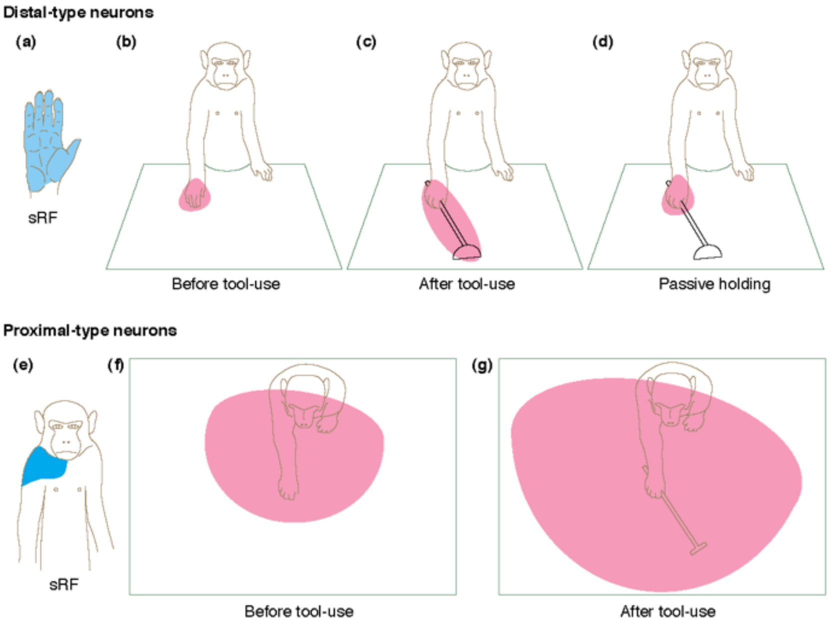

Fig. 2.9 Changes in bimodal receptive field properties following tool-use. The visual RF (vRF) was defined as the area in which cellular responses were evoked by visual probes. (a) tactile RF (blue area) of the 'distal type' bimodal neurons and their vRF (pink areas) (b) before tool-use, (c) immediately after tool-use, and (d) when just passively grabbing the rake. (e) tactile RF (blue area) of 'proximal type' bimodal neurons, and their vRF (pink areas) (f) before and (g) immediately after tool-use. From Maravita and Iriki 2004.

specific motor action (Rizzolatti et al. 1998). However, as Holmes and colleagues noticed (Holmes and Spence 2004), the intraparietal sulcus is a large and heterogeneous area in the monkey, and at least five functionally- and neuroanatomically distinct sub-regions are found there (Colby and Duhamel, 1991; Rizzolatti et al. 1998), with a variety of neuronal response properties ranging from purely somatosensory, to purely visual. It is therefore important to plot visual and somatosensory RFs while controlling for eye, head, and body movements. By contrast, in Iriki's study no control was exerted on eye and head movements. Even then, the influence of attention and response preparation may be serious confounding factors. Neurons in the area studied by Iriki and colleagues (1996) have been indeed studied elsewhere (Mountcastle et al. 1975). Two thirds of the cells in this area have been reported to be purely somatosensory, responding mainly to joint manipulation, and responding more vigorously for active than for passive movements (Mountcastle et al. 1975).

In a similar vein, Fogassi and colleagues (Fogassi et al. 1996) found that the depth of the visual RFs of F4 visuo-tactile neurons can increase with increases in the velocity (20-80 cm/s) of a visual stimulus approaching the cutaneous RF. The authors trained the monkey to fixate a LED while moving three-dimensional moving stimuli were presented in the visual scene through a robot arm. By changing the position of the visual fixation, it could be possible to dissociate the retinocentred from the somatocentred codification of the stimulus. Moreover, through the precise robotic presentation device, these authors could measure the extent in depth of the visual RFs, as well as their rapid modification as a function of the stimulus' approaching velocity. Results clearly showed that the extension in depth of F4 visual RFs revealed to be not fixed. It dynamically changed as a function of the stimulus velocity, in particular expanding in the direction of the approaching stimulus for higher velocities. This neurophysiological result could be linked to the behaviour described in humans performing reaching movements toward moving targets (Chieffi et al. 1992). Although the kinematic of the arm movement was not affected by the velocity of the target, the movement onset was modulated of target velocity. The dynamic property of visuo-tactile neurons could thus be crucial for preparing and/or executing actions towards nearby objects.

1.5. A visuo-tactile network

The neurophysiological findings described in the previous sections define a set of at least four distinctive areas with similar visuo-tactile responses: parietal area 7b and VIP, part of inferior premotor cortex (mainly F4) and the putamen. These regions are heavily interconnected, forming a tight network (Matelli and Luppino 2001; Rizzolatti et al. 1997; Rizzolatti et al. 1998). Posterior parietal areas send projections to the premotor cortex. In particular, superior parietal area 5 and the inferior parietal area 7b project respectively to superior and inferior part of premotor area 6 (Pandya and Vignolo 1971; Strick and Kim 1978; Godschalk et al. 1984; Matelli et al. 1984a and b; Luppino et al. 1999). Reciprocal connections are also sent back from premotor area 6 to the respective parietal areas (Rizzolatti et al. 1997). This reciprocal interconnected parieto-frontal network projects also to the putamen (Kunzle 1978; Weber and Yin 1984; Cavada and Goldman-Rakic 1991; Parthasarathy et al. 1992).

Neurons in this network share several common features:

1) The visual responses lie primarily within a head-face or arm-hand centred somatosensory representation of the body;

2) Visual stimuli near the monkey drive the cells better than farther stimuli;

3) The visual and tactile receptive fields are in spatial register, independent of gaze since they relation is up-dated with the movement of the concerned body-part.

This suggests that these neurons allow for body-part centred coding of visual stimuli within sectors of space adjacent to the tactile surface. This network possesses all of the necessary properties to bind together external visual information around the body and tactile information on a specific body part (Fogassi et al. 1992; Graziano and Gross 1993; Rizzolatti et al. 1997). Indeed, in the somatotopically organised maps encountered in these areas, each somatosensory body-part representation contains also the representation of the visual space that closely surrounds this same body-part. For instance, the arm region contains a representation of visual space around the arms as well as the face region contains a representation of visual space around the head (particularly in area VIP). This modular representation allows the brain to compute the spatial relation between an external object and a specific body-part. Furthermore, the spatial correspondence between visual and tactile RFs of these cells allows up-dating of the spatial relation between external objects and body-parts whenever the body moves. In conclusion, this bimodal visuo-tactile network provides the brain with the neurophysiological basis for the representation of the space between the body and the external world, where each body-part becomes the reference system: the peripersonal space.

2. Motor features of peripersonal space: Visuo-tactile interactions around the acting body

Why should the brain maintain a representation of the space around the body separate from a representation of far extrapersonal space? One possibility is that it could serve purely perceptual aims, giving a greater perceptual relevance to visual events occurring in the vicinity of the body. Following this idea, the parieto-frontal network together with the subcortical visuo-tactile maps would code for a visual space, with individual body-parts as the reference. This is suggested by the most obvious sensory properties of this set of neurons. However, this interpretation does not describe fully the potential functional aspects of this system, since it does not correspond with some of the evidence described above. First, a purely perceptual account does not fit with the presence of such multisensory neurons in a predominantly 'motor' area such as the premotor cortex. Second, it may be difficult to interpret the complex tactile RFs of some of these neurons (for instance, single cells representing both the hand and peribuccal territories, as reported by Rizzolatti et al. 1981a, b). Similarly, the dynamic changes of their visual RFs observed in case of objects approaching the body (Fogassi et al. 1996) or after active tool-use (Iriki et al. 1996) point to a more “active” role of this multisensory network. More critically, a purely perceptual hypothesis does not take into account the intriguing common point of the visuo-tactile areas described so far: their motor properties. Numerous visuo-tactile cells in the parietal areas 7b (Hyvärinen 1981; Hyvärinen and Poranen 1974; Hyvärinen and Shelepin 1979; Leinonen 1980; Leinonen et al. 1979; Leinonen and Nyman 1979; Robinson et al. 1978), inferior area 6 (Gentilucci et al. 1988; Rizzolatti et al. 1981c; Rizzolatti et al. 1987; Rizzolatti et al. 1988; Rizzolatti and

Gentilucci 1988; Rizzolatti et al. 1997) and putamen (Crutcher and DeLong 1984) respond not only passively to visual and tactile stimulation, but also during motor activity.

These findings raise the more compelling possibility that the multisensory representation of peripersonal space might serve motor functions. Objects in the vicinity of the body are indeed more relevant by virtue of all the possible interactions the body can establish with them (Graziano et al. 1993; Rizzolatti et al. 1997, 1998). The hand-centred representation of peripersonal space provides us with extremely valuable information regarding the spatial position of objects with respect to our hands.

2.1. Inferior premotor cortex

The motor properties of neurons in inferior premotor cortex appear to be very relevant concerning the perception-action link characterising the peripersonal space. In particular, the visual responses of such neurons may be enhanced when a reaching movement is performed towards an object (Godschalk et al. 1985). Moreover, inferior area 6 neurons are active during reaching and grasping movements of the arms (Godschalk et al. 1981; Godschalk et al. 1985; Kurata et al. 1985; Kurata and Tanji 1986; Rizzolatti and Gentilucci 1988), as well as the mouth (Rizzolatti et al. 1981c). They also show a rather precise degree of motor representation (Gentilucci et al. 1988; Kurata and Tanji 1986; Murata et al. 1997; Raos et al. 2006; Rizzolatti et al. 1987; Rizzolatti et al. 1988; Rizzolatti and Gentilucci 1988). Proximal and distal movements are represented separately, in area F4 (Figure 2.10) and medially in the rostral part of area F1 for the former, and in the periarcuate region F5 for the latter. Distal neurons discharge in relation to specific and complex motor acts such as “grasping with hand and mouth” or “grasping with the hand” or simply “holding”. In the case of “grasping” neurons, the activation occurred only if the approaching movement of the hand (or mouth) to an object was aiming to grasp the target. Movements with other purposes, even activating similar pattern of muscles, did not produce any response of the neuron. Even more noteworthy is the fact that grasping neurons show selectivity for the type of prehension, so that some neurons are selectively activated during a grasping action performed with a precision grip (only the thumb and index finger) rather than during a whole hand prehension.

Among the proximal neurons, most appear to be correlated to arm and face movements. Crucially, the passive RFs and the active movements are closely related functionally: neurons with tactile RFs on the face also have visual RFs in the upper space and discharged during arm reaching movements towards the upper space. Thus, not only visual and tactile RFs are in

	Arm reaching	Bringing to the mouth	Bringing to the body	Other arm movements	Hand movements	Facial movements	Neck movements	Total
Number of neurons	14 (29,2%)	9 (18,8%)	1 (2%)	8 (16,7%)	3 (6,3%)	12 (25%)	1 (2%)	48 (100%)

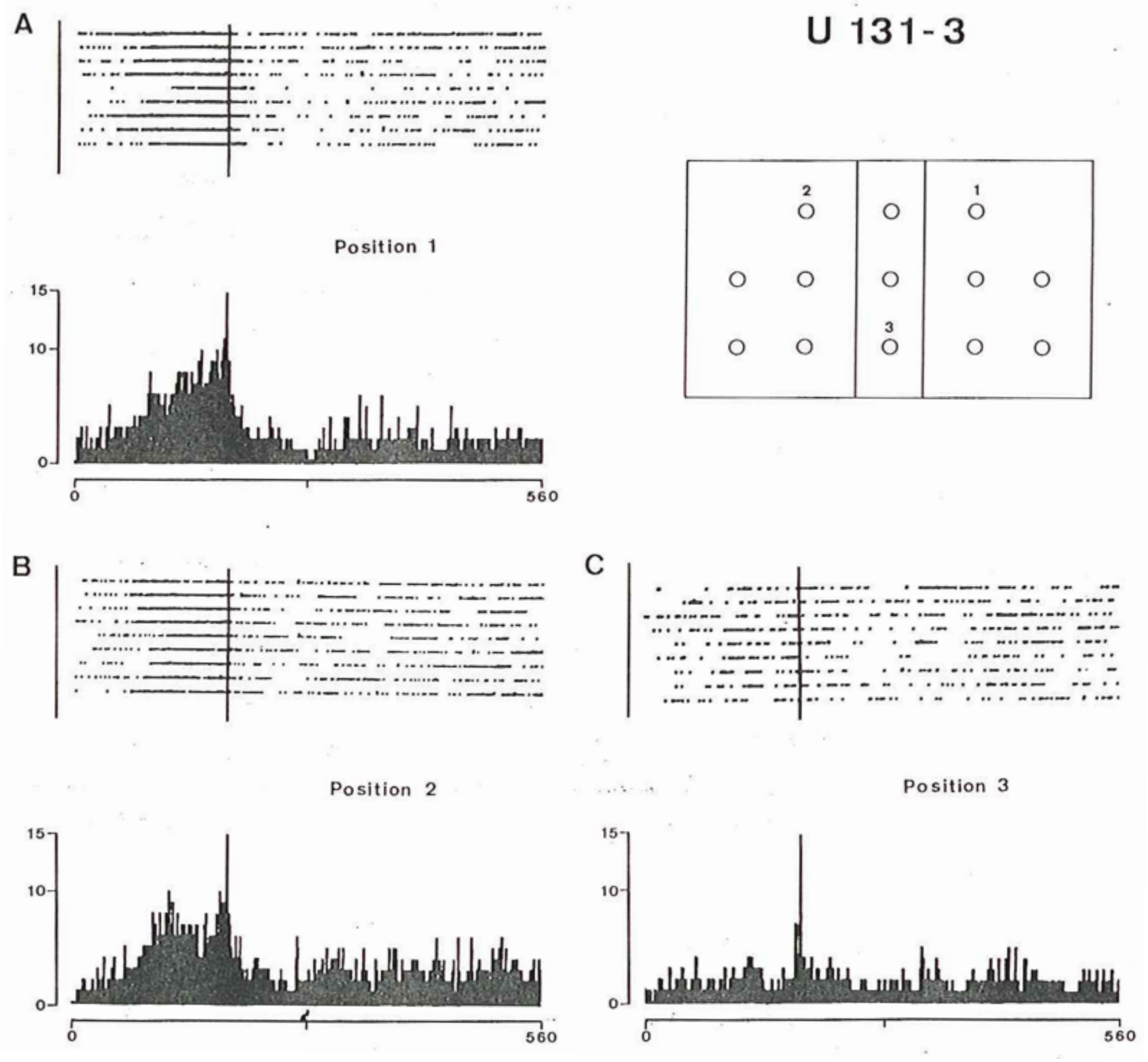

Fig. 2.10 Distribution and example of motor reponses in Gentilucci and colleagues' F4 neurons recording study (1988). A, B and C represent an F4 visuo-tactile neuron response during a reaching movment toward one of the three positions shown in the panel.

spatial register, but the motor activity of these neurons is maximal when the animal's movement is directed to reach into the region of space corresponding to its visual RF. This suggests that the sensory and motor responses are expressed in a common coordinate system for locating objects in the space close to the body and for guiding a movement toward them.

The premotor cortex, indeed, has both direct (Martino and Strick 1987) and indirect (Godschalk et al. 1984; Matsumura and Kubota 1979; Muakkassa and Strick 1979; Pandya and Vignolo 1971) access to the control of upper limbs movements, via projections to the spinal cord and the primary motor cortex, respectively. That is, visuo-tactile premotor neurons could potentially modulate motor activity and control down to the final stages of movement. Indeed, coupled electrical stimulation experiments in the two corresponding hand fields of the premotor (F5 region) and motor cortex, clearly showed the modulatory effects of premotor over motor cortex during a grasping action (Cerri et al. 2003; Prabhu et al. 2009; Shimazu et al. 2004). Depending on the temporal interval between the conditioning electrical stimulation over the premotor cortex and the target stimulation over the correspondent hand field in the motor cortex, premotor neurons can both excite or inhibit the primary motor area, producing effects on distal muscle control.

This complex link between sensory and motor properties shown by the premotor bimodal system of neurons already points out they can not subserve a mere perceptual function. Rather, they appear more as a functional system to guide the acting body in the sensory-motor transformation from perception to action.

2.1.1. Mirror neurons: a particular class of visuo-motor neuron

Inferior area 6, in the F5 sub-region is also characterized by the presence of 'mirror' neurons, a special class of motor neurons with visual properties (di Pellegrino et al. 1992; Gallese et al. 1996; Rizzolatti et al. 1996)[2]. Activity of these neurons appears to be correlated to the

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[2] A first report of neurons responding while the monkey was watching an action performed by another individual is already present in an early electrophysiological study over the parietal area 7b (Leinonen 1980, page 305) : « […] two cells discharged when the monkey grasped an object […] or when the monkey saw an investigator grasp an object »

execution of a specific motor act, such as a grasping. Moreover, they discharge also when the monkey observes someone else executing the same or a similar action. Relevant for this dissertation is a recent finding which showed how a sub-group of mirror neurons can be characterised by selectivity for actions performed within the observer's peripersonal space (Caggiano et al. 2009). Indeed, a sub-population of mirror neurons appeared to be activated preferentially by the sight of an action performed in the observer monkey's peripersonal space rather than in its extrapersonal space (peripersonal mirror neurons). A different sub-population of mirror neurons showed the opposite preference. Moreover, peripersonal and extrapersonal space appeared to be defined according to a functional criterion: Reducing the extent of the accessible peripersonal space by putting a screen in front of the monkey, reduced also the responses of several peripersonal mirror neurons during the observation of actions performed in the inaccessible portion of the peripersonal space. This suggests that the portion of no more accessible peripersonal space had been re-coded as farther extrapersonal space. This was supported by the finding that extrapersonal mirror neurons started to respond to the observation of actions performed in the inaccessible peripersonal space.

2.2. Parietal areas

The more posterior parietal areas also have motor properties and, similarly to the premotor cortex, parietal motor functions seem to be related to approaching movements of a body-part toward an object (Debowy et al. 2001; Fogassi and Luppino 2005; Gardner et al. 2002; Lacquaniti and Caminiti 1998; Rizzolatti et al. 1997; Stepniewska et al. 2005; Ferraina et al. 2009). The posterior parietal cortex, indeed, is part of the dorsal stream of action-oriented visual processing (Milner and Goodale 1995). Here, as described in the previous sections, the sensory information converge and start to be linked to the motor activity. Both inferior and superior parietal lobules are interconnected with premotor cortex.

Gardner's studies investigated the "anticipatory activation", as it was defined in the early studies in the 70‘s, during a monkey's voluntary grasping movement. Through an interesting approach, where the authors conjugated low-resolution kinematic and single cell recordings, they revealed the pattern of activation in posterior parietal areas as a function of

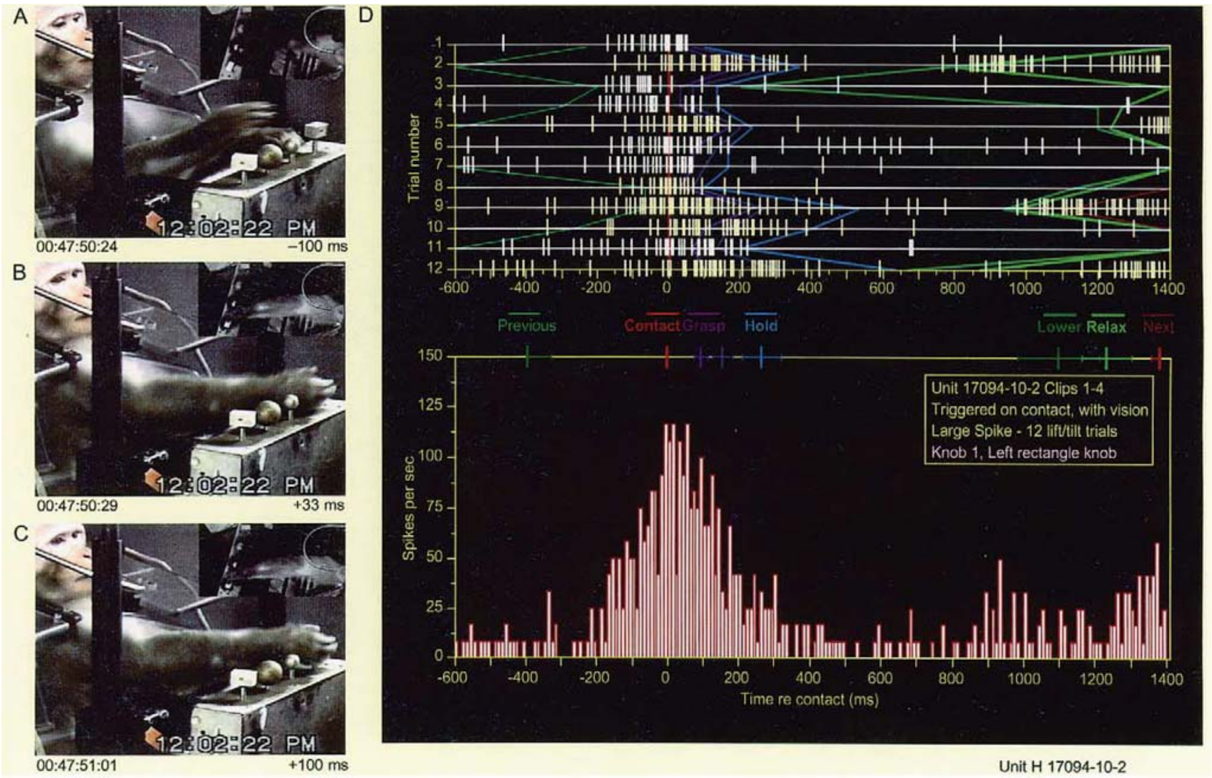

Fig. 2.11 Rasters aligned to contact of the left rectangle knob in an animal particpating to the Gardener and colleagues' study (2002). Neurons are recorded in area 7b/AIP. Firing began during reach, and peaked at contact; activity ceased when the knob was fully lifted. Bursts at the right margin show the start of another trial. Video images capture hand kinematics during approach (A), grasp (B), and lift (C) on trial 1; numbers below each image indicate time code (left) and trial times relative to contact (right). From Gardner et al. 2002.

the on-set and execution of the action until the hand enters in contact with the target of the grasping. The activation so described starts just before the beginning of the movement and bimodal neurons were active during all the duration of the action (Figure 2.11). Only when the hand enters in contact with the object, the predominant activation moves to SI (Gardner et al. 2002). The digitalised video recording system employed in these studies presents several limits for investigating the kinematics of the movement (low frequency of acquisition), which do not allow, for instance, relying the neural activity to the kinematic parameters of the movement or to precise phases of the hand motor evolution. Despite these evident limitations, these authors showed posterior parietal activation during the motor activity and, more interesting, well before the hand enters in contact with the object. This activation involves areas of the brain where bimodal neurons have been found, such as area 7b.

Similar evidence of parietal bimodal neurons motor properties comes from electrical micro-stimulation studies. Electrical micro-stimulation of portions of parietal cortex produces motor activity of the arm/hand or the head/face. In particular, the parietal lobe appears functionally fractionated in specialised sub-regions as a function of different complex movements such as a reaching or a retrieving movement of the arm (Cooke et al. 2003; Stepniewska et al. 2005).

3. Lesion studies

Another possible approach to identify the motor role of parietal and premotor bimodal areas is to investigate the motor behaviour that might be affected by a dysfunction of one or both of these areas. Permanent ablation and reversible inactivation studies in monkeys have tested for the behavioral consequences of a lesion within premotor and posterior parietal areas, where visuo-tactile neurons have been found.

Interestingly, lesions to the anterior or posterior part of this network seem to produce very similar patterns of impairments, most of which affect in particular the execution of visually guided reaching actions (Battaglini et al. 2002; Deuel and Regan 1985; Ettlinger and Kalsbeck 1962; Faugier-Grimaud et al. 1978; Gallese et al. 1994; Halsban and Passingham 1982; Moll and Kuypers 1977; Rizzolatti et al. 1983). After premotor region ablation, for instance, the animals were unable to reach around an obstacle with the contralesional arm. Arm movements were executed without correctly taking into account visual information within action space (Battaglini et al. 2002; Moll and Kuypers 1977). Similarly, removal of postarcuate regions where the mouth is represented caused a severe impairment in grasping with the mouth (Rizzolatti et al. 1983). Attentional deficits have also been reported after selective damage of visuo-tactile parietal and premotor regions (Rizzolatti et al. 1983) in the form of spatial hemineglect and extinction. The animals appeared to be unaware of visual (or tactile) stimuli presented in the contralesional space. Crucially, the deficit was selective for the space around the body.

4. Conclusion: A multisensory-motor network for peripersonal space

The above reviewed studies provide a large body of evidence in favour of the proposal that this parieto-frontal network binds together visual and tactile information, in order to generate an appropriate motor program, based on the available sensory information. When an object is visually available in the space around the body, it is also potentially available to the tactile system, by virtue of the possibility to physically interact with it. The brain can link the visual information about the object to the tactile input which comes or could come from it and can use the result of this sensory processing to establish the most correct motor plan as a function of the desired interaction. According to this model, it is impossible to draw a strict separation between perception and action, due to both multisensory and motor processing occurring within these areas. The network should thus be considered of as providing an interface between perception and action.

Here I would therefore suggest that the multisensory body-part centred representations are coded to generate the appropriate motor responses towards objects in the world.

Chapter III

Multisensory based peripersonal space in humans

Several studies investigated the characteristics of the multisensory perception in humans, as described in the first chapter. Here, in particular, examples of interactions between visual and tactile information in humans will be presented. More relevant for this dissertation is the strong dependence of the visuo-tactile interactions on the distance of visual information from the body. This peculiarity has been taken as evidence in humans of the existence of a representation of the space around the body similar to what I described in monkeys in the previous chapter. In this respect, the study of a neuropsychological condition called 'extinction' (Bender 1952) has provided considerable insight into the behavioural characteristics of multisensory spatial representation in the human brain (Làdavas 2002; Làdavas and Farnè 2004; Legrand et al. 2007). Evidence for visuo-tactile interactions is also available in healthy people, in the form of distance-modulated interference exerted by visual inputs over touch (Spence et al. 2004c, 2008). The crucial point of these studies is the presence, both in the healthy and brain-damaged populations, of stronger visual-tactile interactions when visual stimuli are displayed in near, as compared to far space, providing support for the idea that the human brain also represents peripersonal space through an integrated multisensory visuo-tactile system. In this section the pathological phenomenon of extinction will be introduced and more deeply discussed in condition of multisensory stimulation. Finally, I will review part of the literature supporting the idea of a homologous representation of peripersonal space in humans.

1. Modularity of space through cross-modal extinction

Neuropsychology allows having an insight over brain mechanisms through behavioural deficits affecting brain damaged patients in their life. The fundamental assumption is that a circumscribed lesion in the brain can selectively affect the behaviour the damaged area is responsible for. The patients' deficient behaviour can thus open the possibility of studying the modularity of the brain functions.

The deficit of extinction, generally consecutive to a lesion in the right inferior parietal areas is a window over the processing underlying the representation of the space around the body through cross-modal perception. Extinction patients are usually defective in reporting an event presented contralesionally, but only when it is accompanied by an event in the ipsilesional hemispace. The patients most often present no deficits in reporting a single stimulation delivered in the contralesional side. The deficit thus arises despite no gross sensory loss, suggesting that the problem might be more on the construction of spatial representations rather than on low-level perceptual processes. The deficit can be limited to a single sensory modality or arise in more than one sensory modality at the same time. Cases are known of motor extinction, where the concurrent motor activity of both side of the body results in a disruption of the contralesional side movements.

Extinction has been commonly associated to the more severe deficit of hemineglect, where after a parietal and/or frontal lesion, patients are no more aware of the contralesional side. Even though the two syndromes present some common characteristics, their neurophysiological bases have been shown to be different (Vallar et al. 1994). In particular the extinction phenomenon appears more related to a competition between spatial representations which are activated by the simultaneous presence of bilateral sensory inputs[1]. By virtue of its spatial nature, cross-modal visuo-tactile extinction has become an interesting phenomenon through which approaching the study of the modularity of the spatial representations.

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[1] Extinction could be considered of as the effect of a limit of the physiological perceptual system responding to the presence of several inputs in different sectors of space. Evidence in favour of this possibility is the recent finding of an extinction-like phenomenon in a normal population (Marcel et al. 2004; Farnè et al. 2007a). Following this model, patients would present a constant bias toward the ipsilesional side, mostly due to the unbalanced representation of the two hemispaces caused by the unilateral lesion.

EXTINCTION

Neglect and extinction: Within and between sensory modalities

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Neglect and extinction: Within and between sensory modalities

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Abstract. *Purpose:* The interest in human conscious awareness has increasingly propelled the study of neglect, the most striking occurrence of an acquired lack of conscious experience of space. Neglect syndromes commonly arise after unilateral brain damage that spares primary sensory areas nonetheless leading to a lack of conscious stimulus perception. Because of the central role of vision in our everyday life and motor behaviour, most research on neglect has been carried out in the visual domain. Here, we suggest that a comprehensive perspective on neglect should examine in parallel evidence from all sensory modalities.
Methods: We critically reviewed relevant literature on neglect within and between sensory modalities.
Results: A number of studies have investigated manifestations of neglect in the tactile and auditory modalities, as well as in the chemical senses, supporting the idea that neglect can arise in various sensory modalities, either separately or concurrently. Moreover, studies on extinction (i.e., failure to report the contralesional stimulus only when this is delivered together with a concurrent one in the ipsilesional side), a deficit to some extent related to neglect, showed strong interactions between sensory modality for the conscious perception of stimuli and representation of space.
Conclusions: Examining neglect and extinction by taking into account evidence from all sensory modalities in parallel can provide deeper comprehension of the neglect syndrome mechanisms and possibly more effective multi-sensory based rehabilitation approaches.

1. Introduction

Unilateral spatial neglect is a relatively common deficit that most frequently arises after right brain damage (RBD). Its main characteristic is a lack of awareness for sensory events located in the contralesional side of space (towards the left side space following a right lesion) and a loss of exploratory search and other actions normally directed toward that side. Most readers would be familiar with some of the classic presentation (and descriptions) of neglect patients: they typically behave as if the left half of their world no longer existed, so that in daily life they may only eat from one side of their plate, shave or make-up only one side of their face [50,89], draw or verbally describe only the right side of a remembered image or place [22,136]. This shortened version of a commonly used description of what neglect is, already conveys the equally common (though often implicit) assumption that neglect is mainly a visual disturbance. This probably relies on the well-funded argument that visually-guided behaviour entails most of our daily living activities. As such, visual neglect certainly gained most of the scholars' at-

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tention over the expression of this syndrome in other modalities and, accordingly, the main visually-centred aspects of neglect will be first briefly reviewed here.

However, there is now large consensus that neglect and extinction[1] can virtually affect all of the other sensory modalities (separately or jointly), as well as the motor domain. We will address such a diversity of the neglect symptomathology to provide an up-to-date multisensory-motor framework. In addition, we will argue that the multisensory nature of neglect is most likely to have profound implications for rehabilitation of this cognitive deficit. Accordingly, we will conclude by reviewing some recent multisensory-based approaches to neglect rehabilitation.

2. Visual neglect and extinction

The last "decade of the brain" studies have brought convergent and definite evidence that neglect is a protean disorder, whose definition escapes from the boundaries of any theoretical unifying attempt [75]. Despite its heterogeneity, several core aspects of visual spatial neglect have been identified and, although they might be present at different levels in different patients, they are quite widely acknowledged to represent main aspects of this multifaceted syndrome. It is beyond the scope of this work to provide a comprehensive review of visual neglect and its theoretical accounts (see [107]). What follows is instead a brief list of examples with two purposes. First, to show how deeply the study of visual neglect has contributed to the understanding of the anatomo-functional structure of human conscious experience. Second, to recall the core aspects of the syndrome that should be taken into account when examining the literature on non-visual manifestations of neglect and extinction.

The diagnosis of visual neglect typically requires a comparison of performance on the left-side of a display with that on the right-side in tasks such as line bisection, cancellation, drawing (from model or memory). These tasks commonly reveal the presence of a spatial bias towards the ipsilesional side, in terms of rightward deviation and/or omissions of left-sided items. The presence of abnormal biases across hemispaces, in absence of contralateral primary sensorimotor loss, highlights neglect as a higher-order deficit of spatial cognition. This defective behaviour has been alternatively taken as evidence of patients' defective spatial attention and/or representation, or altered computation of an egocentric reference frame (for review, see [149]).

Indeed, neglect patients suffer from reduced visual spatial attention [49], especially in its exogenous component ([95] for review, see [6]). Not only simple reaction time (RT), but also search times for contralesional target are lengthened, increasing with the number of ipsilesional distractors, thereby indicating a difficulty in disengaging attention from ipsilesional stimuli [11, 127]. Despite the presence of attentional deficits, preattentive processing has been shown to be relatively preserved in visual neglect and extinction, proceeding up to the level of the extraction of the meaning of contralesional "neglected" items [19,50,97], thus confirming that implicit visual processing can influence explicit visuo-motor performance.

Problems of attentional orienting towards the left side of space are compelling when observing neglect patients' behaviour. An interesting debate in the recent past has concerned what should be intended as "left" in left visual neglect and extinction. When asked to copy, for example, neglect patients typically draw the right side of a perceptual scene, omitting several details, or even leaving incomplete the left part of centrally located, single element of the scene. This behaviour is most likely responsible for the word "hemispatial" neglect, as implicitly referring to a corporeal midline that should represent the vertical cleavage line with respect to which conscious perception is preserved (to the right), or more or less absent (to the left). Although the trunk is one of the most important egocentric reference frames' origin [85], visual neglect and extinction can also be manifest according to other reference frames. For example, neglect patients have been reported to miss out the respective left part of two objects present in a scene (object-based neglect), instead of missing the leftmost one (space-based neglect), and vice-versa [48, 74]. Moreover, visual neglect can be selectively present for the vertical, not the horizontal dimension [123,128].

Dissociations of this kind have largely contributed to thinking of visual neglect as an increasingly fractionating entity [73,107]. Along the same line, patients may show left visual neglect for a limited sector of space around their body, the peripersonal/reaching space [20, 72]. On the contrary, neglect can affect selectively a farther sector of the extrapersonal space [5,157]. Neglect for near space can also be "transferred" into far

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[1] The issue of whether (and to what extent) neglect and extinction should be conceived of as separate deficits is outside the scope of this work (for review, see [106]; see also [64]). Nonetheless, throughout this review we will clearly specify whether the reported studies concerned extinction or neglect patients.

space when using tools as physical extensions of the body for bisecting lines of constant visual angle [20]. Visual neglect can even be confined to either internally generated representations of visual images or perceptually presented scenes [70].

The role potentially played by non lateralised deficits of sustained attention and arousal on the genesis of visual neglect has been recently stressed [83,135]. By studying sustained attention through the use of an auditory target detection test, Hjaltason and colleagues [80] found a strong relationship between the presence of sustained attention deficits and visual neglect severity. Similarly, neglect patients may show a significantly longer "dwell time" for a secondary visual target being detected after presentation of a first target (attentional blink [82]). However, the degree of impairment on tasks for sustained attention does not always differentiate between RBD patients populations with and without visual neglect, although neglect patients are certainly affected by non lateralised attentional deficits when compared with age-matched healthy subjects [55]. Indeed, neglect seems to be mainly characterised by spatial deficits, though non lateralised attentional deficits are also present, without being specifically responsible for the major manifestations of the syndrome.

Another non-lateralised aspect of visual neglect that has recently raised great interest is the possible involvement of a spatial working memory deficit in the genesis of the syndrome. When invited to ocularly explore a scene to report targets amidst distractors, neglect patients do not only avoid exploring left-sided elements, but also produce a high number of rightwards saccades bringing their eyes to re-fixate items on their ipsilesional side that had already been "visited" [100]. Most important, many of these re-fixations were associated with a failure to keep track of spatial locations across saccades, the patients being unaware of revisiting previously visited locations. The presence of spatial working memory deficits should not be conceived of as an alternative account for visual neglect, but could certainly contribute to exacerbating omission of left sided items, especially in patients with lateral parietal involvement [100].

A different approach has been undertaken by Pisella and Mattingley [122], whose arguments propose that the origin of some re-visiting behavioural deficits in neglect might not be due to the proposed spatial working memory disorder. They suggest that the manifestations of visual neglect that are hardly grasped by more traditional accounts solely based upon deficits of spatial attention, representation, or working memory can actually be accounted for by an additional underlying disorder of spatial remapping due to parietal dysfunction (for another alternative account, see [139]).

One important issue that is currently the object of a very lively debate is the fine-grained anatomy of visual neglect. There is controversy as to whether lesions of the inferior posterior parietal cortex are still to be considered as the crucial anatomo-pathological counterpart of visual neglect [150], or whether and to what extent the mid-temporal gyrus may also play a role in the genesis of neglect [86,137]. Most of the recent studies, although employing different techniques, seem to confirm the crucial involvement of the inferior parietal lobule and the temporo-parietal junction [27,55, 75,109], as well as the crucial contribution of parieto-frontal connections [44,46]. It is out of the scope of this review to fully address this topic, but the interested reader can also refer to neurointerference studies using TMS in healthy participants [58,111], although it is worth noting that the criteria used for defining neglect are becoming important for comparing anatomical lesions studies [107].

As noted by Halligan and colleagues [75, p. 125], "Deficits of attention, intention, global-local processing, spatial memory and mental representation can all contribute to the clinical picture of neglect, which accordingly cannot be traced back to the disruption of a single supramodal process." More recently, the neglect literature has actually seen some attempts to provide a re-unifying interpretation, not by referring to a unique feature of the syndrome, as was the tendency in the past three decades, but by advocating the need of the joint presence of (some) deficits of lateralised and non-lateralised attention, eye movement, and manual exploratory behaviour, spatial working memory and remapping to fully account for the puzzling lack of awareness for contralesional events that is the hallmark of neglect (see [35,83,122]).

From this brief review, it is apparent how much the study of visual neglect has contributed to the refinement of our understanding of human conscious awareness. Although this supremacy of vision studies over the other sensory modalities can be explained, at least in part, by the fact that the appropriate technology has been made available for vision well before than for touch, audition or the chemical senses, it is quite surprising that relatively few(er) studies have addressed neglect and extinction in the other senses, or even in the motor domain [77,102]. In the following sections, we will review the current knowledge for non-visual manifestations of neglect and extinctions.

3. Tactile neglect & extinction

Generally, neglect is less evident and usually less strong in the tactile domain than for the visual modality. Many authors [30,62,79] failed to demonstrate tactile neglect in right brain damaged patients with visual neglect, when using tasks such as rod tactile bisection or haptic exploration. Fuji and colleagues asked visual neglect patients to bisect a tactually presented stick. The examiner placed the blindfolded patients' index finger on the centre of the stick and asked him to move the finger and stop it at the estimated midpoint of the stimulus. Although the patients showed rightward errors on a visual bisection task, they performed normally on the tactile test. Similar findings were described by Hjaltason and colleagues in an analogous study, where RBD patients were asked to perform the visual and tactile bisection, as well as a visuo-tactile variant of the same task. In the latter task, patients had to indicate the midpoint of a rod in the same way as in the tactile version, but in a free vision condition. Rightward bias was present only in the visual task and no difference was found between the tactile and the visuo-tactile rod bisection.

Evidence for tactile neglect comes from studies that employed spatial exploration tasks like in the maze test [41], whereby RBD patients were asked to move their forefinger along the alleys of a maze hidden behind a curtain, in order to search marbles placed at the end of one of its four lateral arms. Failure to find the targets in the contralesional part of the maze was taken as evidence of tactile neglect. Following this criterion, RBD patients with visual neglect showed more "tactile neglect" than control groups. Although these results have been replicated [21], Villardita [154] reported that patients with left visual neglect engaged at the same test preferred to explore the left part of the maze, thus suggesting an inconsistency between the phenomena described for vision and touch. Other studies have concentrated on the weak relationships between visual and tactile neglect, which seem to be double dissociable [21, 30,33]. One of the possible reasons for the paucity of tactile neglect studies may derive from its definition, most often diverging from the classical "omission" of left-sided targets that is so clearly and astonishingly present in the visual modality. Strictly speaking, one may ask the question of whether pure tactile neglect exists at all. Indeed, the difficulties in describing tactile neglect might be overcome if one admits that some cases of apparent hemisensory loss are, at least partially, mimicked by tactile neglect ([25], see also [108]). Several studies have shown that vestibular stimulation (cold water in the left ear) may induce a transient remission of diverse neglect symptoms in RBD patients. However, a contralesional supposedly somatosensory deficit may also be ameliorated by vestibular stimulation [25,151], thus revealing a higher order problem and suggesting that tactile neglect may be mistaken for a mere sensory deficit. In this respect, it would be interesting to establish which proportion of RBD patients seemingly affected by hemisensory loss is, in fact, affected by unisensory tactile neglect.

While tactile neglect has been rarely documented, tactile extinction is much more frequently reported [113], even when assessed by simple confrontation methods. Extinction patients are able to detect a single stimulus presented alone either to the ipsi- or the contralesional side of space, but fail to report the same contralesional stimulus when this is delivered concurrently to a second one in the ipsilesional side of space (for review, see [103]). In the tactile domain, extinction has been reported to occur at the level of the hands, the face-neck, the arms-legs, both in case of symmetrical and asymmetrical stimulation [7,15,56], or between the two sides of a single body-part [110,147].

To some extent, both neglect and extinction show a similar lack of awareness for tactile inputs delivered in the side of the body opposite to the brain lesion, despite relatively intact primary sensory pathways, such that extinction has long been considered as a residual form of spatial neglect [50]. However, they also differ in some respects and double dissociations have been documented [31,64,134,153], suggesting that the underlying neural mechanism of extinction and neglect might differ [87].

Both "tactile neglect" and tactile extinction may manifest according to different reference frames. For example, they can be modulated by body posture and by the relative position of the stimulated body parts. Left tactile extinction is reduced when the left hand crosses the body midline and lies in the right hemispace, or even occupies a relative left location as compared to the right hand in the same hemispace [1,7,141]. Moreover, a single-case study of a RBD patient [148] illustrated that right hand touches may also be extinguished by a concurrent ipsilesional elbow stimulus (see [15,63]) when the right hand lies on the left and the elbow on the right of the patient's body midline. Similar effects of posture arise in neglect patients [109], whereby detection of single contralesional tactile stimuli increases when the stimulated hand lies in the ipsilesional hemispace, whereas touches delivered to the ipsilesional "good" hand are omitted to a variable degree when the right hand lies in the contralesional affected hemispace [1, 7]. Similar to what has been reported for visual neglect [124], improvements in tactile neglect and extinction have been observed following a reduction of gravitational inputs, obtained by placing the subjects in a supine position [120].

Moreover, in the visual domain it is typically assumed that extinction is maximal under conditions in which competing stimuli occur simultaneously [95]. One may ask whether, in addition to posture, time (e.g., asynchronous stimulation) could also modulate tactile extinction in a similar fashion. The more a stimulus is temporally tied apart from another, the more reliably contralesional events should be perceived [26]. In this respect, Mattingley et al. [103] examined tactile detection in a RBD patient with tactile extinction, introducing a variable stimulus onset asynchrony (SOA) between bilateral stimulations. The occurrence of a right-sided competitor interfered with detection of left targets across a range of asynchrony from -400 to 1200 ms (minus means that left leads), showing an asymmetry in the effect. The point of subjective simultaneity appears thus to be biased in favour of ipsilesional stimuli. These results suggest that sensory timing problems might be present in both visual and somatosensory neglect [10].

In the case of tactile extinction considerable processing can still take place prior to the level at which loss of awareness arises. Although the extinguished tactile stimulus does not access consciousness, it may interfere with perception of the ipsilesional one [2]. More direct evidence comes from measures of patients' neural activity through functional imaging or event-related potentials. Some studies in the visual domain observed that the relatively early components of visual processing may be abnormal for contralesional stimuli in visual extinction [101]. Similarly, it is possible to examine the fate of extinguished tactile stimuli in those bilateral conditions where extinction arises, by comparing correct unilateral ERPs with incorrect ones in case of extinction [52]. In a single RBD patient study, bilateral trials with extinction still revealed residual early components (P60 & N110) over the right hemisphere in response to the extinguished left touches. These components were completely absent in the right hemisphere after a single right hand stimulation, although these kind of stimuli have the same conscious report of the other ones. However, the somatosensory neural activity in the right hemisphere was reduced in amplitude when compared to the one elicited by right hand stimulation on the left hemisphere. This suggests that, although tactile extinction is not a pure sensory deficit and is defined in conditions of bilateral stimulation, there may be an underlying pathology for the contralesional unilateral stimulation too, in agreement to what has been suggested for visual extinction [101]. Finally, these results demonstrate that somatosensory cortex activity is not sufficient for tactile inputs to reach awareness. In the same vein, a PET study [129] revealed that tactile extinction is associated with reduced activity in the secondary somatosensory cortex, but not in the primary one, suggesting that processing of bilateral tactile stimuli takes place at a "higher" stage and that extinction arises at a high level of tactile input processing.

4. Chemical neglect & extinction

To date, only a limited number of investigations concerning the suppression of (or competition among) spatial information processed through the so-called 'chemical senses' (i.e., olfaction and taste) have been reported [12,13,16,18,105]. A number of various different reasons may account for this lack of research. First, the distinction between pure chemical versus somatosensory information is often problematic (e.g. [18]). Second, it is widely assumed that olfaction and taste are senses that are not specialized for conveying spatial information (e.g. [92]). In olfaction, in particular, it is still unclear whether humans can localize at all the source of the olfactory stimulation by distinguishing between odours that are processed through the right versus the left nostril. This is particularly true when the stimulus is a pure odorant rather than trigeminal, that is when the odour does not cause any somatosensory stimulation that is known to be encoded by the trigeminal system (see [47]).

4.1. Olfaction

With respect to olfaction, Mesulam [105] first described a case of left-sided olfactory extinction revealed under double simultaneous stimulation of both nostrils in a patient with a brain lesion localized in the right parietal cortex. A few years later, Bellas and colleagues [12,13] assessed the ability of a group of fifteen RBD patients who were affected by left tactile extinction on the hand to identify and localize a series of bilaterally presented olfactory stimuli. On each trial, patients were presented with two stimuli (one in each nostril) using squeezing bottles and their task was to name each of the odours that were perceived. Participants could receive either the same pure odorant in both nostrils, or different odorants in each nostril, or else an odorant in one nostril and a trigeminal odour (vinegar) in the other. As the authors could not find another appropriate trigeminal odour, the vinegar odour was only presented singularly to one of the two nostrils while the other nostril was stimulated with a pure odorant. Bellas and colleagues [12] reported the presence of an extinction-like phenomenon in the patients' performance. Specifically, when two different stimuli (being either two pure odorants or an odorant and the trigeminal odour) were delivered to each nostril, RBD patients consistently failed to report the stimulus delivered to the left nostril. As the olfactory system would predominantly project its fibres ipsilaterally while the trigeminal system would be a contralaterally innervated system, the authors considered these results as evidence supporting the representational theory of neglect (see [22]). Indeed, if the sensory theory (see [37]) was responsible for the olfactory and trigeminal extinction, the pure odorants presented to the right nostril rather than those presented to the left nostril should have been extinguished. Bellas et al. [13] also reported that the patients affected by olfactory extinction showed a large number of displacements in that the correctly-identified stimuli presented to the left nostril were described as being in the right nostril.

The studies conducted by Bellas and colleagues represent a first step in the investigation of phenomena such as extinction and neglect in the olfactory modality. Nevertheless, it is not completely possible to determine the exact influence exerted by the nasal somatosensation in the olfactory extinction reported, since one of the odours considered as being pure odorants was later found to be processed probably also by the trigeminal system (i.e., a soap odour; see [13]). Finally, the possibility of highlighting deficits related to the localization of stimuli in the olfactory sensory modality should be interpreted within a much wider debate regarding whether the olfactory system could extract spatial information from pure odorants (i.e., without any interventions of the trigeminal system; e.g., see [47,92]; though see [126,155]).

Kobal and colleagues [92], for instance, claimed that the human olfactory system appears to be able to localize the source of the olfactory stimulation only when the odour elicits also a trigeminal response. This would appear to be in contradiction with the pioneering work of von Békésy [155] who showed that trained participants localized both trigeminal stimuli and pure odorants between the two nostrils. Moreover, Porter et al. [126] showed recently that naive participants were able to reliably localize pure odorants between the two nostrils in a setting in which olfactory stimuli were delivered by a computer-controlled air-dilution olfactometer that controlled for the exact timing in stimuli presentation. The stimuli were presented to the nose through a compartmentalized nasal mask that allowed for mono-rhinal odour presentation and the sniff flowrate was controlled in real-time. Clearly, if the ability of the olfactory system to extract spatial information from non-trigeminal stimuli turns out to be true, new light could be shed on the extinction phenomena described for odours. In fact, the relative contribution of pure odorant and somatonsensory information to olfactory localization could be disentangled using experimental methods similar to those described by Porter and colleagues.

4.2. Taste

The existence of neglect and/or extinction in taste has been even less explored than in olfaction, even though in humans the ability to localize taste stimuli presented on the tongue has been previously described (e.g. [140, 156]). Bender and Feldman [17] first reported a single case of a patient with a wide parietal-occipital tumor and tactile extinction on the upper limbs who also showed extinction of taste sensations on the left part of the tongue when two tastes were presented simultaneously on each hemi-tongue. Taste stimuli were applied on the tongue surface by means of cotton buds and they were all accurately identified and localized by the patient when presented singularly. The results of the assessment revealed that the patient was not only affected by unimodal taste extinction, but that he also displaced taste sensations under crossmodal taste-tactile stimulation. In particular, when a touch or a pinprick was delivered to the right hemi-tongue and a taste was applied on the left hemi-tongue, the patient repeatedly reported bilateral taste stimulation, thus surprisingly extinguishing the right touch and partially misplacing the left taste stimulus. Unfortunately, Bender and Feldman did not describe in detail the method that was used to generate the tactile sensations.

More recently, Berlucchi and colleagues [18] described a study carried on two groups of patients (i.e., having a right or left brain lesion) and a control group. The RBD patients were affected by tactile (on the hands), visual, and/or auditory extinction with different degrees. By using a highly controlled stimulus presentation (e.g., use of micro-pipettes and controlled water temperature), Berlucchi and colleagues could disentangle (contrary to [17]) between the presence of taste and/or tactile extinction on the tongue. A sub-group of the RBD patients showed tactile extinction under bilateral simultaneous stimulation of the tongue. However, the authors failed to find any significant presence of taste extinction even among these tactile extinguishing patients, thus highlighting for the first time the existence of dissociations between extinction phenomena occurring in somatonsensory or in purely chemical information processing. There also appeared not to be any consistent correlations between the presence of tactile extinction on the tongue and that of tactile (on the hands), visual, and auditory extinction. Berlucchi and colleagues suggested that a distributed taste representation could account for the existence of such dissociation. Namely, the processing of somatosensory information coming from the tongue would be predominantly contralateral, whereas the taste stimulation would activate the brain areas ipsilateral to the hemitongue being stimulated (e.g., see [3,114]). Moreover, according to Berlucchi and colleagues, the fact that a dissociation between gustatory and tactile extinction could be highlighted would suggest that gustatory extinction occurs consequently to a severe tactile extinction (see [17]). The patients involved in their study would have been affected by a mild tactile extinction, thus allowing the gustatory information to be processed by the preserved left hemisphere.

To date, thus, there is still no clear evidence of the existence of purely taste extinction and/or neglect, while few studies provided evidence about the presence of tactile extinction on the tongue or inside the mouth following a right brain lesion [4,18]. In the study of extinction and neglect, a wide number of questions related to the chemical senses are still waiting for answers. Today, it would appear to be possible to devise studies where information conveyed by the chemosensory modalities and by the collateral somatosensory modality could finally be investigated separately [18, 126,140]. Therefore, future research will be in charge of furthering our understanding about odours and tastes and their links with spatial representations.

5. Auditory neglect & extinction

Patients with focal brain lesions can also suffer a number of disturbances in the auditory modality that can be characterised as auditory manifestations of the neglect syndrome. Patients with right hemispheric lesions might either fail to respond when addressed verbally from the left, or more commonly behave as if they heard the voice originating from their right (e.g. [16, 38]). This suggested a deficit in detection and localisation of auditory stimuli, especially when they originate in contralesional space, which could emerge for hearing as well as for vision. Although this clinical observation has generally been confirmed, a number of recent evidence has now highlighted important differences between the manifestations of neglect in hearing and vision.

5.1. *Deficits of sound localisation*

The disturbance for sound localisation, originally described as ‘alloacusis’ [16], has been the topic of several experimental works in the last two decades (see [118] for review). A first aspect that emerged from these systematic investigations is that auditory spatial disturbances in neglect patients might reflect increased spatial uncertainty for sound position, especially for contralesional stimuli, instead of a strictly systematic shift in heard azimuth towards the ipsilesional side. For instance, when asked to discriminate verbally the relative position (same vs. different) of two sounds in close succession, neglect patients typically perform worse for pairs of sounds originating from the contralesional side (e.g. [117,146]; see also [40] for evidence of reduced mismatch negativity response in scalp recordings of event-related potentials for contralesional vs. ipsilesional free-field sounds). In addition, it has recently been shown that patients with neglect perform less efficiently than control right-hemisphere patients without neglect in a discrimination task that concerns the vertical position free-field sounds [116,119]. Thus, a disturbance in auditory space perception emerges even when localisation involved the vertical dimension, orthogonal to any potential horizontal shift.

Horizontal bias in sound localisation have instead been typically documented when neglect patients are asked to point to a sound presented in free-field (i.e., from an external source [115,121]; but see [138]), or over headphones (pointing to a location on their head; e.g. [23]). In addition, deficits have been observed when using ‘auditory midline’ tasks, in which patients adjust a continuous sound (or make judgments on a discrete sound) to locate it relatively to the centre of the head or body midline (e.g. [23,90,146,152]; but see [34]). For sounds presented over headphones (with either varied intensity at the two ears, or varied interaural timing cues to sound localization), neglect patients typically report a sound to be central when it is actually lateralized towards the left (i.e. more intense or arriving earlier at the left ear), as if there were a rightward shift in perceived location (e.g. [23,146]). By contrast, for sounds presented free-field, neglect patients often reported that an external sound seemed aligned with their head/body midline when it was actually presented to the right (thus implying a leftward shift in sound localization if one assumes that perceived head/body midline is veridical, which it might not be in neglect patients [90, 152]). As proposed recently [115], some of these discrepancies concerning the direction of lateral shifts in sound localization for neglect patients might actually relate to non-auditory aspects of the task. Specifically, motor or visuo-motor biases in pointing tasks [115], or pathological distortions of perceived head/body midline in auditory-midline tasks [57] could in principle affect performance.

5.2. *Detection and identification deficits*

Although auditory spatial deficits have often been reported in neglect patients for single auditory stimuli, especially when they originate in contralesional space, the patients usually detect these single sounds with apparent ease in most localization studies (e.g. [23,115–119,121,146]. This might appear to contrast with characteristic clinical deficits affecting the visual modality in neglect patients, where complete failures to detect or respond to contralesional visual events are commonly noted, rather than merely failures in localization. Two critical differences between hearing and vision may account for this discrepancy. First, the anatomical organization of the auditory system, which is less crossed than for other senses, with some ipsilateral as well as major contralateral cortical projections of the input reaching each ear. Second, the typical reduced complexity of the auditory environment in experimental setups. Unlike experiments in vision, in which targets are often embedded among many distracters, the typical experiment in the auditory domain presents a single strong sound against silence [115]. Indeed, when even a minimal version of concurrent competing stimulation is produced, usually by presenting one sound on each side of the head, a consistent failure to detect and/or identify contralesional sounds emerged, for both free-field sounds [39,142] and headphone stimuli [14,42]. Strictly speaking, however, such effects with two concurrent competing sounds might be considered the auditory equivalent of visual or tactile extinction, rather than manifestations of neglect.

A long standing debate in relation to detection and/or identification deficits under double simultaneous auditory stimulation has been whether poor detection of sounds at the contralesional ear could be related to neglect of contralesional auditory space [81], or instead should be ascribed solely to poor processing (or suppression) of the auditory information entering the contralesional ear [8,9]. Indeed, free-field sounds presented from a contralesional location will tend to be more intense at the contralesional ear, and if presented monaurally over headphones, will only reach that ear. However, there is now mounting evidence suggesting a role for higher-level spatial factors (e.g., perceived external position, spatial attention, relation to visual neglect) in the contralesional detection/identification deficits for auditory stimuli observed for neglect patients (e.g. [14,29,142]). For instance, it has been shown that identification of left free-field sounds can sometimes improve in the presence of a fictitious visible sound source (a ‘dummy’ loudspeaker) on the right, which reportedly made it seem that the sounds originated from the right side [142]. In addition, a direct investigation of the role of apparent sound location with respect to which ear the information enters was recently conducted by Bellman and colleagues [14], presenting each auditory stimulus (heard words) either to one ear only (‘dichotic’ stimulation), or binaurally but with interaural time difference serving as the only lateralization cue (‘diotic’ stimulation). Under double simultaneous presentation, two out of four neglect patients tested in the study showed poorer performance for left than right words only with dichotic presentation (consistent with a deficit for sounds entering the contralesional ear), whereas the other two patients were impaired in reporting left words for both methods of lateralized presentation (consistent with an identification deficit for sounds perceived as originating from contralesional space).

5.3. *Non spatial auditory deficits*

A final aspect that merits attention is the description of non-spatially-lateralized auditory deficits in patients with visual neglect [34,80,135]. Robertson and colleagues, for instance, documented a non-spatial difficulty in sustaining attention and maintaining arousal in the auditory modality, in a task where neglect patients were required to count the number of occurrences of a particular auditory target among a stream of sounds, of variable length, all presented centrally. Non-spatial auditory deficits have also emerged when patients with visual neglect were asked to listen to a short rapid sequence of auditory stimuli over headphones, to detect which of the stimuli had a higher pitch [34]. Despite auditory stimuli were always presented centrally, and patients were able to detect subtle pitch modulation for single auditory objects, they were severely impaired at any comparison between two sounds in a rapid sequence, possibly as a result of pathologically limited attentional capacity.

6. Multisensory neglect and extinction

The previous sections on non-visual manifestations of neglect and extinction clearly showed that in many circumstances neglect and extinction can emerge for a single sensory modality, or for multiple sensory modalities in a given patient [43,153]. Note however that all the works reviewed so far were concerned with stimulation delivered within a single sensory modality at a time. We now turn to examine how neglect and extinction affecting a unimodal sensory system can be influenced (enhanced or degraded further) by the concurrent activation of another modality.

A number of evidence has now systematically shown that extinction in particular can emerge even when concurrent stimuli are presented in different sensory modalities, i.e., different sensory inputs delivered to the ipsi- and contra-lateral side of the patient's body [17, 45]. Tactile extinction, for example, can be modulated by visual events simultaneously presented in the space region near the tactile stimulation, increasing or reducing tactile perception, depending upon the spatial arrangement of the stimuli. In particular, the visual stimulation in the ipsilesional side exacerbates contralesional tactile extinction, whereby the presentation of visual and tactile stimuli on the same contralesional side can reduce the deficit [96]. Moreover, the modulation described is most consistently manifest when visual-tactile interaction occurs in the space close to the body than when the space far from the body is visually stimulated.

In a similar way, visual and tactile information are integrated in other peripersonal space regions, such as around the face [56,99]. In this case, extinction patients were presented with unilateral and bilateral tactile stimulation on both cheeks and, in addition, visual stimuli were concurrently presented in the contralesional or ipsilesional side. As for the hand, exacerbation of the deficit was found in the ipsilesional visual condition, whereby the visual stimulus enhanced tactile detection when delivered in the contralesional side. The modulation, again, is more evident when the visual stimulus is presented in a near-body region of space rather than in a farther region, thus implying that sensory integration arising from the same near-the-body location allows for the tactile input to reach awareness.

Similar modulations of tactile extinction have been reported following another kind of multisensory interaction, between audition and touch [98]. When sounds are concurrently presented with single touches delivered at the level of the neck in tactile extinction patients, their contralesional tactile detection is most likely to be hampered by proximal, as compared to far loudspeakers. Interestingly, such a multisensory effect observed in the front space with respect to the patients' head was even stronger when cross-modal auditory-tactile extinction was assessed in the patients' back space, thus suggesting that different degrees of multisensory integration may occur depending upon the functional relevance of a given modality for that particular sector of space [54].

These results support the existence of a peripersonal multisensory space in humans, akin to that described in animals studies [94]. Evidence from animal studies [51,68,69,131,132] revealed a dissociation between a space far from the body that can not be reached by a simple arm movement, and a near peripersonal space, a region of space extending only a few centimetres out from the body surface. Indeed, a strong multisensory integration takes place at single neuron level in this region of space: the same neurons activated by tactile stimuli delivered on a given body-part are also activated by visual or auditory stimuli delivered in the space near that body-part. In this respect, the selectivity of visual-tactile extinction for the proximal sector of space is reminding of the spatial bias observed in unimodal visual neglect, which may selectively arise in the near peripersonal space [32,72].

An interesting characteristic of the space region surrounding the body is its plasticity. Through tool-use, for example, it is possible to remap the space so that "far becomes near" [20]. When asked to use a long stick to bisect distant horizontal lines the neglect patients' selective bias, formerly present only in the near space, was transferred to the far space. Similar results have been described in extinction patients who, after tool-use, showed increased contralesional tactile extinction when a visual stimulus was presented far from the body at the extremity of a hand-held tool. Therefore, using a tool to retrieve distant objects increases the strength of visual-tactile integrative effects in a region of space far from the patients' body. Such a phenomenon has been ascribed to a tool-use dependent size-change of the peri-hand multisensory space [53].

Altogether, these results show that the expression of cross-modal interaction seems to be a rather frequent occurrence, which can be selectively modulated by several parameters relative to the relationship between the stimulus and the body: like distance, spatial location, auditory complexity, spatial and temporal coincidence. Therefore, these findings are in good agreement with a modular organization of space in which several neuronal structures are devoted to the processing of different space sectors, in different co-ordinates, across different modalities, most probably for different behavioral purposes [143]. Among these structures, the representation of near and far peripersonal space in humans parallels the functioning of the circuit of multisensory areas that has been well documented in monkeys, which is similarly sensitive to the same parameters listed above.

7. Multisensory-based rehabilitation approaches

The reported frequency of hemispatial neglect varies widely from 13% to 81% of patients who have had right hemisphere stroke [145]. The presence of neglect has been associated with poor outcome measures on functional activities following a stroke [55,65,67]. Patients with neglect[2] have been found to have longer lengths of stay in rehabilitation facilities and lower scores on the Functional Independence Measure (FIM) [71] and thus require more assistance at discharge than patients without neglect [36,88]. Neglect severity also predicts the degree of family burden more accurately than the extent of brain damage [27].

These are the main reasons why it is important to know whether or not neglect spontaneous pattern of evolution tends towards recovery, in which proportion of patients and to which degree. In this respect, a recent study [55] has shown that only 43% of neglect patients improved spontaneously during a two-week long assessment in the acute phase (up to six weeks post-stroke) and only 9% of patients showed complete recovery. When a subset of this patient population was re-assessed during the chronic phase, the proportion of patients who recovered increased up to 63%, although recovery was complete only in 25% of them. Since spontaneous recovery in the acute and chronic phase of the disease is not axiomatic and, when present, does not allow for complete remission of neglect symptoms in most patients, it is very important to individuate efficient treatment strategies to improve recovery of patients with chronic and persistent unilateral neglect.

Neglect rehabilitation approaches have been classically divided into two classes: rehabilitation procedures based on a voluntary reorientation of attention toward the contralesional space and rehabilitation procedures based on the sensory stimulation of the affected (contralesional) field, or sensory deprivation of the good (ipsilesional) field. The second class of rehabilitation procedures are based on an interpretation of neglect as an attentional-representational deficit due to the competition between left and right space representations. After a right brain damage, the contralateral space representation is weak and, as a consequence, the competition with intact ipsilesional space representation induces neglect in that sector of space. The antagonism between left and right space representation may be reduced by sensory stimulating the contralesional hemispace (i.e. vestibular, optokinetic, left-sided transcutaneous mechanical vibration, left-sided electrical nervous stimulation and left-limb proprioceptive stimulation), or by suppressing sensory inputs from the ipsilesional hemispace (i.e., hemiblinding technique). Needless to say, most of the studies focussed on the visual components of neglect, although several nonvisual aspects of neglect and associated disorders may also benefit from some of these approaches [104,149].

More recently, many studies have outlined that space representation is based not only on input and output responses, that is on sensory and motor information, but on the integration of these information from multiple sensory modalities. As reviewed above, neuropsychological findings have shown the existence of multisensory systems devoted to the integrated coding of spatial information, e.g., a visuotactile system [96,99], an auditory – tactile system [54,98], and an auditory-visual system [59,61]. These integrated systems can offer a unique opportunity to improve the performance of patients with spatial representational deficit, such as patients with visual neglect. As a consequence, potential therapeutic implications could derive from the integration of visual and proprioceptive information, and visual and auditory information; for example, a multisensory based approach to neglect rehabilitation may

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[2] To date, rehabilitation studies have focussed on neglect rather than extinction, most likely because extinction is not known to have such a negative impact on patients' everyday life as neglect, although some approaches have nonetheless proved to ameliorate extinction, for example in the tactile modality [76,112].

enable patients to detect "bimodal" stimuli for which unimodal components are below behavioural threshold. Concerning the integration of proprioceptive and visual information it has been shown that passive movements of the contralesional arm in the contralesional space may improve visual neglect. As far as the integration of visual and auditory integration, bimodal audiovisual stimulation of the affected field can improve perception of the visual events in the neglected hemispace [59]. This amelioration of visual detection was observed only when the two simultaneous stimuli were spatially coincident, or when they were located near one another in space (at a distance of 16°). In contrast, when the spatial disparity between the two sensory stimuli was larger than 16°, patients' visual performance remained unvaried. Moreover, multisensory enhancement was greater when visual stimuli were presented in the most peripheral positions of the affected visual field where the impairment was more severe. This is in keeping with the functional properties of multisensory neurons described in animal studies [144]: a greater enhancement of bimodal neurons' response is observed when visual and auditory stimuli originate at the same time (temporal rule) and from the same position and, as a consequence, fall within the excitatory receptive fields of a visual-auditory multisensory neuron (spatial rule), and when two weaker, rather than two strong stimuli are combined (inverse effectiveness rule). These functional integrative properties are well suited to explain the amelioration of visual neglect patients following multisensory stimulation, thus providing a potential neuronal substrate for a multisensory based treatment of neglect.

Beyond the existence of beneficial effects of audiovisual stimulation, showing that a sound can ameliorate visual detection in neglect patients, the characteristics of patients who can benefit from audio-visual integration effects would be important to establish. It is well known that sensory deficits, such as visual field deficit (e.g. hemianopia), are frequently associated with neglect and may represent a negative predictive factor for cross-modal audiovisual integration in neglect patients [61]. Moreover, since it has been shown that, not only the superior colliculus [144], but also "heteromodal" [66] and "sensory-specific" [28,66] cortices are involved in cross-modal integration, it is possible that the site of cerebral lesions may affect audio-visual integration. The presence of cross-modal audio-visual integration effects has been recently investigated in patients with either neglect or hemianopia and in patients with both hemianopia and neglect [61]. Patients were asked to detect visual stimuli presented alone or in combination with auditory stimuli that could be spatially aligned or not with the visual ones. As in the previously reported study, an enhancement of visual detection was found when a sound was presented in the same position of the visual one, but only in patients affected either by neglect or hemianopia; by contrast, enhancement dependent upon the multisensory integration did not occur when patients presented with both deficits. Moreover, a different influence of the site of the cortical lesion on multisensory integration has been found. When patients' lesion was mainly confined to fronto-temporo-parietal areas (neglect patients), or to the occipital areas (hemianopic patients), the visual and auditory stimuli were effectively integrated, whereas when the lesion involved all the previous lobes, although to different degrees in different patients, the effects of multisensory integration were no longer present (neglect patients with hemianopia).

The results of these studies underline the relevance of cross-modal integration in enhancing visual processing in neglect patients and in patients with visual field deficits. The possibility of a sound improving the detection of visual stimuli is very promising with respect to the possibility to take advantage of the brain's multisensory capabilities for a rehabilitation approach of visual attention deficit and visual field defects [24,61]. In this respect, one question which needs to be addressed in the future is whether a systematic bimodal stimulation, by affecting orientation towards the neglected/blind hemifield and modulating the processing of visual events, can improve visual exploration, perhaps with long-lasting effects. A cross-modal training might reinforce the innate ability of our brain to perceive multisensory events, hidden in the normal condition in which unimodal processes are usually at work on unisensory events that are sufficiently salient to be perceived. This possibility is particularly relevant in terms of rehabilitation perspectives because it is non-invasive, as compared with other rehabilitative procedures, and does not require the voluntary displacement of the patients' attention to the affected side, which can be particularly difficult for neglect patients.

8. Summary and conclusions

As it results from the experimental evidences reviewed above, some core aspects of neglect and extinction are observed across different modalities. Whatever explanation is proposed for the lack of perceptual awareness, the deficits can not be solely attributed to early sensory problems. For example, patients' performance in visual and tactile detection may strongly vary according to different reference frames and postural changes. In addition, Pavani and colleagues [119] recently showed that discrimination performance for auditory stimuli presented in the contralesional auditory hemifield of visual neglect patients can actually improve when patients gaze towards the left. A pure sensory deficit would imply a complete loss of perception irrespective of spatial relationship between bodyparts or gaze direction. However, the presence of subtle sensory dysfunctions has been recently consistently reported in visual, tactile, and auditory studies of neglect and extinction. Although still unclear, the role possibly played by early sensory deficits can no longer be excluded, as degradation or slowing of sensory inputs processing may concur to the difficulty in perceiving contralesional events.

Other features of neglect and extinction studies recently gained considerable interest, such as the presence of non lateralised deficits and their contribution to the syndrome. However, the latter have been mainly reported in vision and audition, whereas their potential role in the chemical and tactile modalities has not been systematically explored. In the same vein, clear evidence of processing without awareness is mainly available for the visual and tactile modality.

Although we did not intend to provide an exhaustive critical review of what the multisensory approach tells us about the current neurocognitive models of neglect and extinction, we believe the study of unisensory and multisensory neglect and extinction is both theoretically and clinically relevant. The within- and between-modality approach would hopefully proceed in parallel, the other senses possibly filling the gap with vision, which is still dominant. We undertook this direction as it may provide a wider framework within which multisensory-based rehabilitation approaches may be devised. An increasing attention devoted to non-visual manifestations of neglect may be of great interest for deepening our knowledge of human spatial awareness.

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1.1. Peripersonal space in humans: neuropsychological evidence

As described, extinction is a pathological sign following a brain lesion, usually affecting the right inferior parietal lobe, as a consequence of what patients may fail to perceive contralesional stimuli only under conditions of double simultaneous stimulation. This characteristic reveals the competitive nature of the extinction deficit (di Pellegrino and De Renzi 1995; Driver 1998; Ward et al. 1994).

A number of studies have shown that extinction can emerge when concurrent stimuli are presented in different sensory modalities: a visual stimulus close to the ipsilesional hand can extinguish a touch delivered on the contralesional hand (di Pellegrino et al. 1997). Crucially, cross-modal visual-tactile extinction appears to be stronger when visual stimuli are displayed in the near as compared to the far space, providing neuropsychological support for the idea that the human brain represents the space around the body separately from

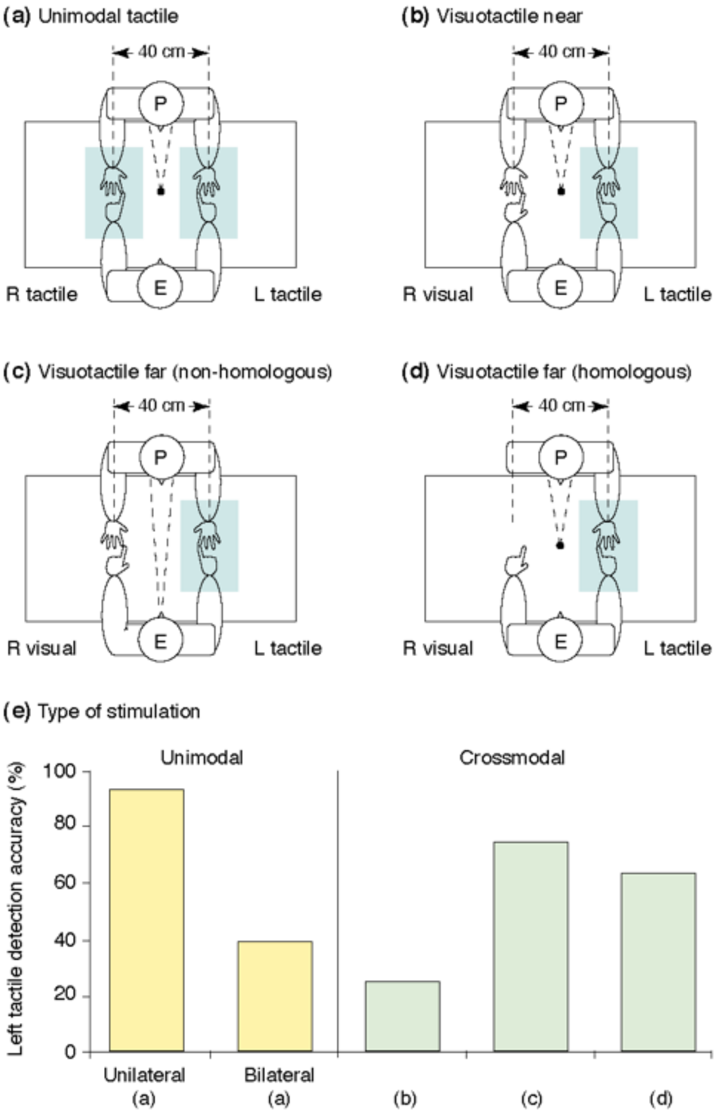

Fig. 3.1 Schematic drawing of the experimental set-up for the assessment of cross-modal visuo-tactile extinction. **(a)** Tactile extinction, related to results in left part of **(e)**. **(b)** Visuo-tactile extinction for visual stimuli presented near the hand. In the far visuotactile condition, the right visual stimulus could either be presented above the right hand, at the level of patient's eyes (non-homologous position) **(c)**, or in a homologous location to the tactile one **(d)**. From Làdavas 2002.

the space far from the body (Figure 3.1). In particular the spatial representation close to the body is characterised by a stronger interaction between visual and tactile information. Thus, the near space in humans presents similarities with the peripersonal space described before and represented in monkeys through an integrated multisensory visuo-tactile system. Another common point is the fact that, as described in monkey studies, also in humans the visual representation of stimuli in near-hand space remains anchored to the hand when this is moved in another hemi-space, suggesting that visual information in the space around the hand is coded in a hand-centred coordinate system (di Pellegrino et al. 1997; Farnè et al. 2003b). As for the hand, a multisensory mechanism is involved in representing the space close to the human head. By showing stronger visual-tactile extinction for homologous (left and right cheek) than non-homologous combinations of stimuli (e.g., left hand and right cheek), Farnè and colleagues' elegant study demonstrated the modular organisation of the representation of space around the body. That is, authors found that different spatial regions, adjacent to different body-parts, are represented separately (Farnè et al. 2005b).

In a series of further studies, Farnè and colleagues (unpublished data) formally tested four cross-modal extinction patients by presenting visual stimuli close and far from the patients' as well as the experimenters' hand. However, no effect was found in the direction of a possible body-matching property of the human visuo-tactile system similar to that described in monkeys (see chapter II, paragraph 1.1). One possibility is that in their research authors employed a more radical change in orientation between the observer's own and the observed hands (more than 35 degrees).

Finally, it has been shown that the representation of the region of space around the human body also features plastic properties, akin to those shown in the monkey. Authors employed a similar paradigm as that employed in monkeys. A group of cross-modal extinction patients has been tested before and after a training period during which they became familiar with a tool. A re-coding visual stimuli located in far space, as if they were closer to the participants' body, has been documented behaviourally in extinction patients following the use of a tool to retrieve (or act upon) distant objects (Farnè and Làdavas 2000; see also Berti and Frassinetti 2000; Bonifazi et al. 2007; Farnè et al. 2005a, 2007b; Maravita and Iriki 2004). In this interesting study, cross-modal visual-tactile extinction was assessed by presenting visual stimuli far from the patients' ipsilesional hand, at the distal edge of a 38 cm-long rake, passively held in their hand. The patients' performance was evaluated before tool-use, immediately after a 5 minute period of tool-use, and after a further 5 to 10 minute resting period. Far visual stimuli were found to induce more severe contralesional extinction immediately after tool-use, than before tool-use (Figure 3.2). These results demonstrate that while near and far spaces are separately represented, this spatial division is not defined a priori. Rather the definition of near and far is derived functionally, depending upon movements that allow the body to interact with objects in space. Other researches confirmed this finding, also showing how much dependent might be the re-mapping on the functional relationship between space and body. Berti and Frassinetti's elegant study on a neglect patient (Berti and Frassinetti 2000), for example, showed how the far space can be re-mapped as near only when a physical continuity between the body and the far target of the action is present. They asked a right brain damaged patient presenting neglect for left near space to perform a visual line bisection task, classically employed to assess the presence of neglect symptoms. Since this kind of patients "neglect" the contralesional side of space (generally the left side following a right brain lesion), when requested to mark the middle point on a line they manifest a rightward bias. In this study, the patient had to bisect lines placed far from the body by using either a stick or a laser-pointer. While the patient transferred the rightward bias when bisecting far lines with a stick, this re-mapping of far space as near did not arise when the laser-pointer was used.

The research here presented on extinction patients' pathological behaviour shows that also in humans it is possible to define the peripersonal space with similar properties as the monkeys' peripersonal space:

- Peripersonal space in humans is a region of space limited in depth with respect to the body, where visual and tactile information strongly interact.
- Human peripersonal space is a body-part centred representation of space, so that when hands cross the mid-line, the respective peripersonal space is up-dated consequently.
- Human peripersonal space appears as dynamical as that described in monkeys, as tool-use studies revealed.

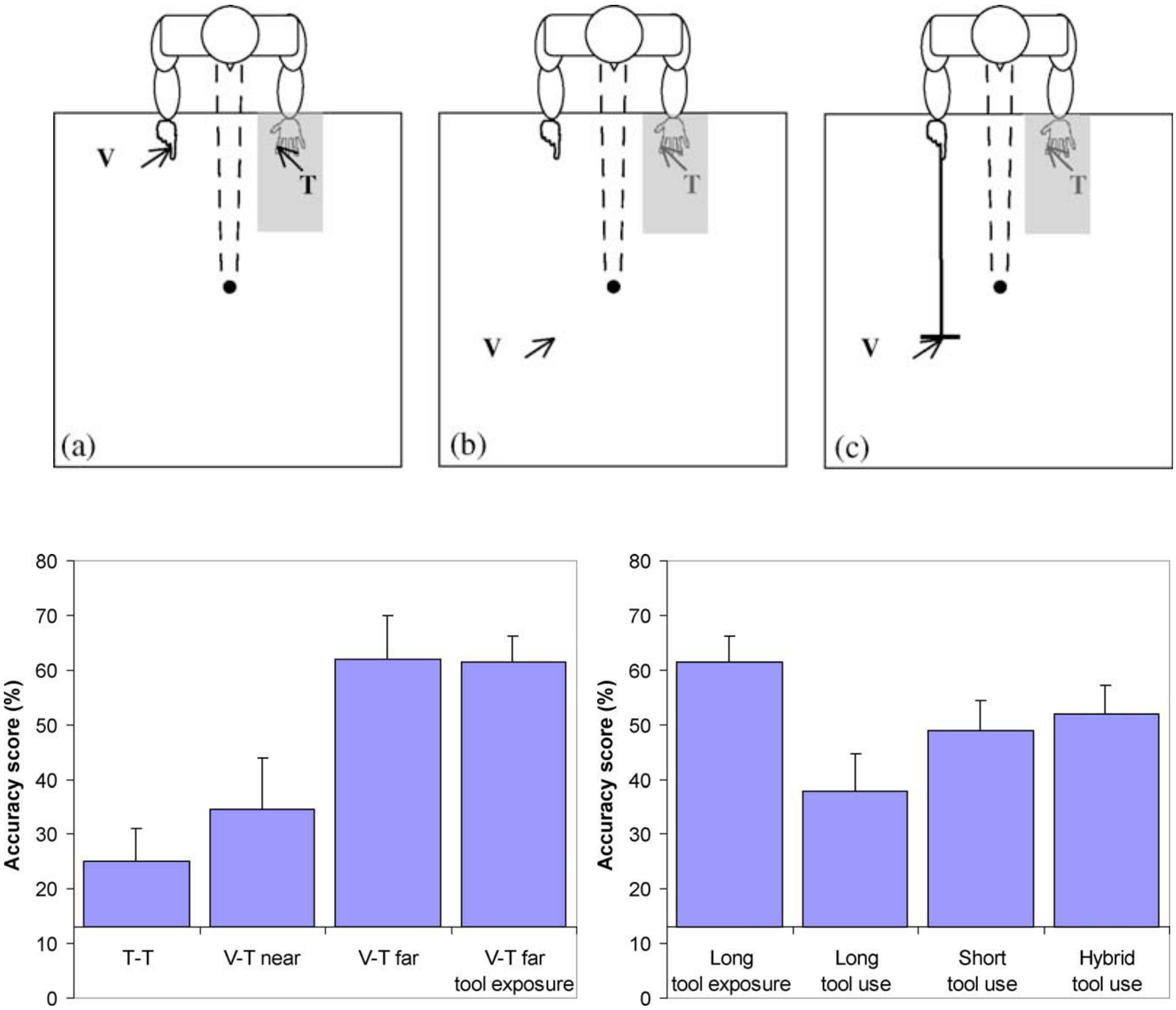

Fig. 3.2 Upper Panel Schematic representation of the assessment of visuo-tactile extinction modulations induced by tool-use. **Bottom Panel** Modulation of visuo-tactile extinction induced by the use of a tool. Extiction is present in case of unimodal tactile (T-T) and bimodal (V-T) condition of stimulation. Morover it is dependent on the distance between visual and tactile information, being reduced when visual stimulus is delivred far from the hand (V-T far). While a passive exposure to the tool do not affect visuo-tactile extinction (V-T far exposure), tool-use clearly modulated the deficit (Long tool use). From Farnè et al. 2005a).

1.2. Peripersonal space in humans: evidence from healthy behaviour

Evidence in favour of a representation for the space near to the body separated from a representation of the space far from the body is also present in healthy populations. The dissociation between peripersonal and extrapersonal space has been also investigated by means of the line bisection task, for instance, on healthy participants. When presented with lines located in the peripersonal space, healthy participants show a systematic displacement of the midpoint to the left, an opposite phenomenon with respect to patients' behaviour, known as "pseudoneglect" (see Jewell and McCourt 2000 for a review). Some studies reported a significant effect of the distance at which the to-be-bisected line is presented. In the transition from the peripersonal space to the extrapersonal space subjects present a left-to-right shift of the bisection point, so that they present a stronger "pseudoneglect" (mean shift to the left of the true midpoint) in the bisection of lines presented in the peripersonal rather than in the extrapersonal space (Bjoermont et al. 2002; Longo and Lourenco 2006; Varnava et al. 2002; Gamberini et al. 2008 however, see Cowey et al. 1999; Weiss et al. 2000). Longo and Lourenco (2006) reported more precisely a gradual left-to-right shift of the bisection point in the transition from the peripersonal to the extrapersonal space, presenting the lines at different distances from the body. They also confirmed in normal participants, the dynamic property of the human peripersonal space representation that might be extended by the use of a tool allowing for a physical continuity between the body and the far space (see Berti and Frassinetti 2000; Berti et al. 2001). A recent interesting study of the same group asked whether it is possible to induce contraction in the size of near space (Lourenco and Longo 2009). As in previous studies, they measured the leftward shift of the midpoint in a bisection task in normal participants, as a function of increasing distance. Participants bisected lines, while, in some cases, wearing weights. The increase of the effort involved on the line bisection task lead to a relative rightward shift in bias at closer distances (as if the lines were thus perceived as being in far space), with little to no rightward shift as distance increased, since near and far space may be considered less distinct.

Other perceptual tasks also provided evidence in favour of the dissociation between peripersonal and extrapersonal space in normal subjects. In the next section I will present a similar visual modulation of tactile perception as in patients that has been shown, with some differences, in healthy individuals.

1.2.1. Cross-modal congruency effect: a perceptual paradigm for the investigation of the peripersonal space representation in healthy humans

Highly converging evidence in favour of a distinct visuo-tactile representation of the peripersonal space with respect to the extrapersonal space comes from studies about the interference that visual information can exert over touch percepton in healthy humans. In a series of studies, participants were asked to discriminate the location of a tactile stimulus while a visual distractor could be delivered in a congruent or incongruent spatial position. More in detail, in a typical crossmodal congruency study, participants are required to hold two foam cubes, one in each hand (see Figure 3.3 for a schematic illustration). A target tactile stimulation is presented together with a visual distractor, independently in an unpredictable trial-by-trial basis from one of the four possible stimulus locations. Participants are required to make a series of speeded elevation discrimination responses, reporting whether tactile target stimuli are presented at the index finger or thumb of either hand. Simultaneously, participants have to try ignoring the visual distractors presented at approximately the same time. The overall effect is that participants are normally significantly worse (both slower and less accurate) at discriminating the elevation of the touches when the visual distractors are presented at an incongruent rather than at a congruent elevation. The difference in performance between incongruent and congruent trials is thus a measure of the amount of the

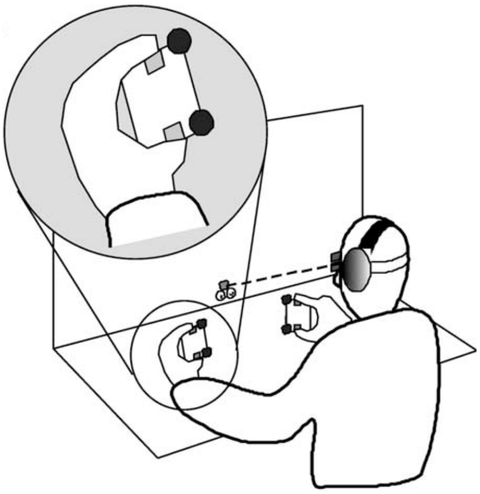

Fig. 3.3 Schematic view of the typical set-up for the study of visuo-tactile congruency effect. Participants held a foam cube in each of their left and right hands. Two vibrotactile stimulators (shaded rectangles) and two visual distractor lights (filled circles) were embedded in each cube, by the thumb and index finger. Participants made speeded elevation discrimination responses (by raising the toe or heel of their right foot), in response to vibrotactile targets presented either from the ‘top’ by the index finger of either hand, or from the ‘bottom’ by either thumb respectively. Maximal crossmodal congruency effects were always reported for visual distractors placed closest to the location of the vibrotactile target (i.e., on the same foam cube), no matter whether the hands were held in an uncrossed or crossed posture. From Spence et al. 2004c.

cross-modal visuo-tactile interaction. In particular, this value is known as Cross-modal Congruency Effect (CCE), as it has been termed after the original work presented by Spence and colleagues (Spence et al. 1998). The modulation exerted by visual distractors over touches in this paradigm seems to be resistant to practice. People cannot ignore what they see, even if they are instructed to respond only to what they feel.

Crossmodal congruency effects have also been observed when the role of the two stimulus modalities is reversed (Walton and Spence 2004), with participants instructed to respond to the elevation of the visual stimuli, while ignoring the elevation of the vibrotactile stimuli. However, the crossmodal congruency effects elicited by vibrotactile distractors on visual elevation discrimination responses tend to be somewhat smaller in magnitude.

There are at least two possible explanations for the crossmodal congruency effect. One possibility is that this modulation reflects a response competition, between the response tendencies elicited by the target and distractor in case of incongruent trials. However, whenever a delay is inserted between the stimulation and the response (750 ms), a procedure which is meant to reduce errors merely due to a response choice difficulty, the cross-modal congruency effect is still significantly present. This finding suggests that this visuo-tactile interaction should at least reflect another kind of mechanism.

The other possibility is indeed that the CCE is a phenomenon reflecting the integration of visual and tactile information, possibly sensitive to the kind of visual-tactile interaction occurring around the body and described in the previous sections. The presence of a visual distractor integrated with the tactile information would bias the localisation of the second input (tactile target) in a sort of visuo-tactile ventriloquism phenomenon (such as the audio-visual example described in chapter I). The interesting point of this account is that, if so, the cross-modal congruency effect could reveal itself as a perceptual measure of the extent of the region where visual and tactile information are tightly interconnected as that investigated in monkeys: the peripersonal space. I will discuss consequently whether the CCE reflects the three main characteristics of the visuo-tactile integration arising in the peripersonal space coding.

Spatial modulation of CCE

As described previously for monkeys and neuropsychological patients presenting cross-modal extinction, the visuo-tactile interaction in peripersonal space appears dependent upon the distance between visual information and the tactually stimulated body part. Spence and colleagues (Spence et al. 2004c) investigated the cross-modal congruency effect displacing one hand in a far position with respect to visual distractors. The distracting lights were now mounted on two boxes attached to the top of the table in front of participants. With this arrangement, the stimulated hand could either be held adjacent to the visual distractors in the same hemifield, or could be positioned far from them within the same hemifield. Critically, the spatial proximity between the two stimuli (tactile target and visual distractor) could now be systematically varied (Figure 3.4). The interference exerted by the visual distractors over the tactile modality was dependent upon the spatial distance between them. In analogy with the cross-modal extinction studies and the neurophysiological properties of bimodal visuo-tactile neurons, the visuo-tactile interference observed within this study was stronger when the stimulated body-part was closer to the visual information. In other terms, the cross-modal congruency effect reveals itself as a measure of the strength of the interaction between visual and tactile information in the space immediately surrounding the body, fulfilling one of the three criteria for the definition of the peripersonal space.

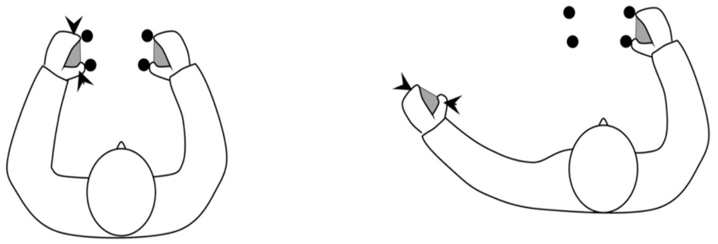

Fig. 3.4 Schematic view of the distance manipulation between visual distractors and tactile target in the cross-modal congruency paradigm. Ibidem.

Body-part-centred reference frame for the CCE

A critical characteristic of the peripersonal space representation is its body-part centred nature. Spence and colleagues (Spence et al. 2004c; Spence et al. 2001) also investigated whether there is any role at all for the initial hemispheric projection of the target and distractor stimuli in determining cross-modal congruency effect. They thus assessed whether the cross-modal congruency effect is based on a spatial representation that is updated in such a way to follow the body-part. When participant's hands cross the mid-line for example (Figure 3.5), the left hand is situated close to visual distractors on the participant's right side, while the right hand is situated close to distractors on the participant's left side. These authors tested the modulation of the CCE in these conditions, finding that there was a complete re-mapping: stronger CCE for visual distractors close to hands in the external space (for instance, touch on the right hand, placed on the left side and visual distractors close to the hand in the left side of space) rather than when the two information were projecting to the same hemisphere (for instance, touch on the right hand, placed on the left side, and visual distracters from the right side). In other terms, the CCE arises in a reference system that is anchored to the stimulated body-part, thus exhibiting the second property of the peripersonal space representation, as known since neurophysiological and neuropsychological investigations: its body-part centred nature.

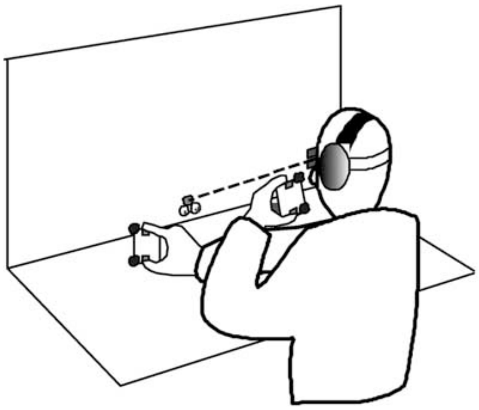

Fig. 3.5 Schematic view of the set-up for the spatial reference of the cross-modal conguency effect. Since visuo-tactile interaction arises in body-part centred coordinates, visual distractors on one side (left for instance) are more interferring with tactile target on the closest hand (right hand in this case). Ibidem.

Tool-use dependent modulations of CCE

The paradigm of CCE has been assessed also in conditions following a training of tool-use, in healthy individuals (Holmes et al. 2004, 2007a, b; Maravita et al. 2002). These studies have shown that active tool-use increases the salience or effectiveness of visual stimuli presented at the tip of the hand-held tool. These visual enhancements have been demonstrated from the effects of visual stimuli on the detection or discrimination of simultaneous tactile stimuli. Maravita and colleagues, for instance, asked a group of normal participants to judge the

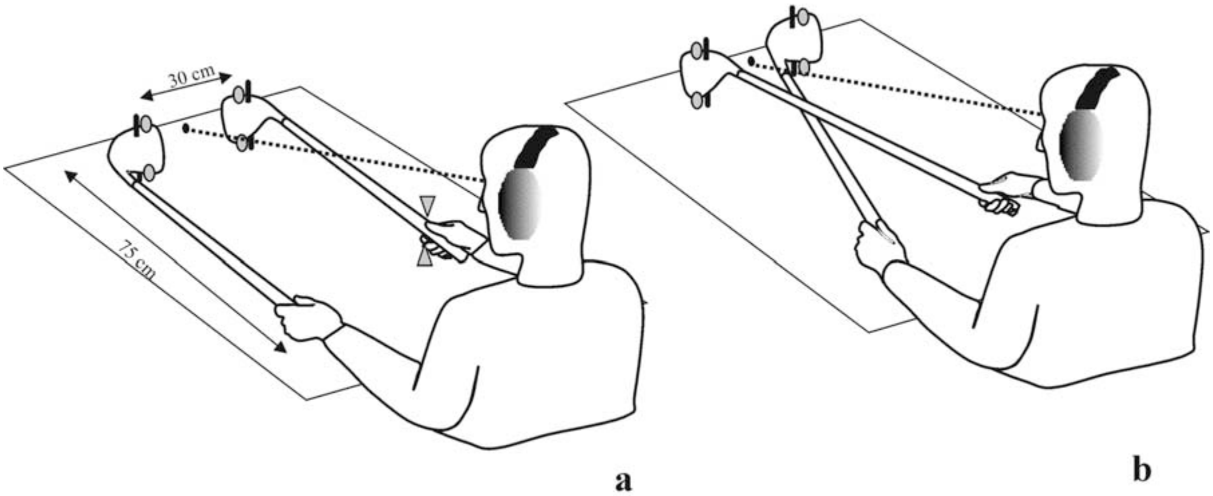

Fig. 3.6 Schematic view of the set-up used for studying the modulation of cross-modal congruency effect induced by the tool in (a) straight position and (b) crossed position. In either case, a peg at the far end of the tool (shown by thick black vertical lines) was inserted into a hole to locate it, while hand locations were kept constant. Unseen tactile stimulators were placed on each tool handle at the forefinger and thumb (indicated symbolically here, for the right hand only in the straight-tool situation (a) with grey triangles). Potential visual distractors are shown as grey circles. From Maravita et al. 2002.

elevation of tactile vibrations delivered to the thumb or index finger on either hand as in the typical version of the CCE paradigm. However, visual distractor lights were fixed in vertical pairs at the far end of each of two "tools" grasped with each hand (Figure 3.6). These authors showed that as a consequence of an active use of the tools, the interaction between visual information on the tip of the tools (far from the subject's hands) and the tactile stimuli on the hands was modulated by the position of the tools. This effect did not arise when tools were not actively used. This result provided evidence for a modification of the area of visuo-tactile interaction after the use of a tool (see however Holmes et al. 2004 and Holmes et al. 2007a) and about the fact that CCE could be a sensitive measure of such a change.

In conclusion, even if parallels between single cell recordings in monkeys' studies and behavioural studies in humans require caution to be made, CCE reveals to feature all the characteristics to be a sensitive measure of the peripersonal space in humans:

- it proved to be dependent on the distance between visual information and the tactually stimulated body-part
- it proved to arise in a reference system that is centred on the body-part
- it proved to be sensitive to the dynamic modulations induced by the use of a tool, even when attentional issues/confounds are controlled for (Holmes et al. 2004).

1.3. Peripersonal space in humans: neuroimaging studies

Evidence is now accumulating also from neuroimaging studies in healthy humans that can provide further support for the homologies between some of the neurophysiological evidence reviewed in the previous chapter and the neural bases of peripersonal space in the human brain. Specifically, brain areas that represent near-face and near-hand space in body-centred coordinates through visual and tactile maps have been reported in the anterior section of the intraparietal sulcus and in the ventral premotor cortex (Bremmer et al. 2001; Makin et al. 2007; Sereno and Huang 2006). These findings correspond nicely to the anatomical locations of the monkey visuo-tactile network. Moreover, recent studies have identified the superior parietal occipital junction as a potential site for representing near-face and near-hand visual space (Gallivan et al. 2009; Quinlan et al. 2007). This new evidence extends our current knowledge of the peripersonal space neural network, and may guide further electrophysiological studies to come.

2. Conclusions

The findings presented here for human beings, coming from neuropsychological, behavioural and imaging studies, converge supporting the existence in the human brain of mechanisms that are specialised for representing visual information selectively when it arises from the space near the hand (and face). In other terms, the human brain, similarly to monkey's, builds a peripersonal space representation separated from a representation of the space that is farther from the body. This distinction is based on a different multisensory integration arising in the region close to the body, where visual information appears more tightly connected to tactile information on the close body-part. As the previous section highlighted, indeed, a strong binding mechanism of visual and tactile inputs has repeatedly been shown also in humans. The homologous representation of the peripersonal space in humans is codified in a body-part centred reference system and is up-dated with body posture changes. Finally, the human homologous of peripersonal space also presents dynamic properties, induced for instance by the active use of a tool that can change the functional relationship between the body and the reachable space. Importantly, the CCE described in this section appears as a sensitive paradigm to study the modulations of peripersonal space.

These converging results have refined and extended our understanding of the neural processes underlying multisensory representation of peripersonal space in the human brain, namely, by identifying various cortical areas that are involved in different sensory-motor aspects of peripersonal space representation.

Chapter IV

Peripersonal space: a multisensory interface for body-object interactions?

The review in the previous sections showed that visual and somatosensory information are integrated in the brain, both cortically in parietal and frontal areas and sub-cortically in the putamen. The characteristics of the visuo-tactile integration through systems of bimodal neurons differentiate the representation of the space around the body from a farther space. The peripersonal space so defined, becomes the space between the body and the external space where visual information are not mere events occurring outside the body, but they also represent the possibility of an interaction between the body and the external world. When I leave my cup of coffee close to me while working, for instance, not only I can interact with it as it commonly -and preferably- happens when I grasp it in order to drink my coffee. In fact, I have also to be careful when I'm moving because, for the simple reason that my cup is close to my body, in the space where my movements take place, I could also accidentally -and dangerously- collide with it. Also true is the fact that often, when an unknown insect is flying around our arm, for instance, we could have the involuntary tendency to move the arm in order to avoid the contact between the body and the unknown -and potentially threatening- insect. It is therefore conceivable that an object in the peripersonal space is not visible in the same way as are objects or events occurring in the far space: only the former might be intrinsically available for active interactions with body-parts without needing the full body to move. The peripersonal space could be thus considered of as an interface between the body and the objects.

For these reasons, it appears striking that, until recently, all investigations of peripersonal space representation in humans have assessed its characteristics in completely static conditions. I will present a series of findings in monkeys that, together with the electrophysiological findings on bimodal neurons, clearly indicate the strong link existing between peripersonal space and action. As I will discuss in this chapter, also research about human peripersonal space representation is ready to fill the gap between the multisensory perceptual investigation of this representation and its involvement in the execution of actions. This point represents the novel contribution of this dissertation to our knowledge about the peripersonal space. In particular, two original methodological considerations will be presented, through which I have tried to experimentally assess the link between multisensory space representation and the execution of actions.

1. What kind of body-object interactions can the body-centered PpS representation subserve?

Since the multisensory space based on the visuo-tactile properties of bimodal neurons defines a boundary zone limited in depth between the body and the environment, some researchers have suggested that it might have evolved for the execution of defence or object-avoidance movements (Cooke and Graziano 2004; Cooke et al. 2003; Graziano et al. 2002; Stepniewska et al. 2005). Protect the body against physical threats is one of the vital function the system should guarantee. By acting as an anticipatory multisensory-motor interface, the peripersonal space representation may serve for the early detection of potential threats approaching the body (Fogassi et al. 1996) in order to drive involuntary defensive movements (Cooke and Graziano 2004; Graziano and Cooke 2006). As already described, the visual RFs of bimodal neurons are sensitive to objects approaching the body and more specifically also to the velocity of their approaching, as a function of which they can modify their area of response. The most direct evidence in favour of the hypothesis that peripersonal space serves defensive actions is the result of cortical stimulation studies, although some concerns have been raised in this respect (Strick 2002; Graziano et al. 2002). The electrocortical microstimulation allows to artificially induce electrical activity directly in a specific area in order to study, for instance, the cartography of the motor control in the motor areas. Graziano and colleagues applied this method for the study of the motor properties of visuo-tactile network (Graziano and Cooke 2006). They thus described that the electrocortical stimulation of visuo-tactile areas can elicit a pattern of complex movements that is compatible with defensive arm (and face) movements and withdrawing of the arm or the head (Cooke and Graziano 2003; Stepniewska et al. 2005). The most important concern other electrophysiologists underlined was the intensity and the duration/length of train stimulation employed in this research (Strick 2002). By employing a similar paradigm, however, other researchers have found that the stimulation of parietal visuo-tactile areas can induce not only movements that are compatible with defensive behaviour, but also movements compatible with "appetitive" behaviours, such as reaching and grasping (Stepniewska et al. 2005).

As a consequence, the same anticipatory feature might also have evolved to serve voluntary object-oriented actions (Gardner et al. 2007; Kaas 2004; Rizzolatti et al. 1981a, b;

Rizzolatti et al. 1997; Stepniewska et al. 2005). In support of this view are the results of the described single unit recording studies showing the motor properties of both parietal and periarcuate visuo-tactile neurons, whose discharge is mostly correlated with reaching and grasping movements (see Chapter II, section 2). Moreover, since peripersonal space represents a boundary-zone between one's own body and the external environment, it could also indirectly have a role in the self-attribution of sensory signals (Makin et al. 2008). This system may therefore be involved in the multisensory representation of limb position: the visuo-tactile neurons, constantly updated with the varying positions of the body parts, achieve a body-part-centered representation of visual space, even while the body moves.

The thesis of this dissertation, I would like to propose, is that the multisensory-motor neural machinery represented by the bimodal visuo-tactile network has been selected throughout evolution, not only to drive involuntary avoidance reactions, but also voluntary approaching movements towards objects, via the continuous monitoring of action space, the space within reach.

2. CCE in action

Until recently, however, the characteristics of visuo-tactile peripersonal space in humans had been assessed exclusively while the relevant body parts were held statically. Even the most 'dynamic' properties of peripersonal space, the post tool-use modulation of the visuo-tactile interaction, have been studied in the static phase preceding or following the active use of the tool. Some researches have assessed tool-use induced modulations of peripersonal space after very brief intervals (i.e., several seconds) following the use of the tool (Holmes et al. 2007b), or after several minutes of tool use (Maravita et al. 2002), and have showed rapid changes in visuo-tactile interactions on these time-scales. However, in these studies too, the perceptual visuo-tactile task was performed in a "transient" but still static post tool-use session, interleaved with the tool-use training sessions. An exception could be found in those studies showing dynamic changes of peripersonal space *during* tasks such as line bisection, where distant stimuli were acted on through the use of a long tool (e.g., Berti and Frassinetti 2000).

However, multisensory integration was not explicitly measured in these studies, meaning the link with peripersonal space remains speculative.

If the peripersonal space representation is indeed directly involved in body-object interactions, then modulations of visuo-tactile interaction should be found without the need of any tools. On the contrary, the visuo-tactile interaction, or the dynamic 're-mapping' of near space should be a basic, primary property that only secondarily can be generalised to tool-use. In this respect, the execution of a voluntary free-hand action, for instance grasping an object, should induce a rapid on-line re-mapping of visuo-tactile spatial interactions, as the action unfolds.

2.1. The multisensori-motor task

Even if the CCE paradigm revealed to be a useful frame of investigation for the assessing of the multisensory interaction in peripersonal space, an adaptation was needed in order to assess the visuo-tactile interaction on-line during action.

First of all, an action is required and in particular, in a first step, we choose a grasping action. Three main reasons supported this choice. First, the execution of grasping, as the execution of reaching actions, has been deeply investigated in the neurophysiological studies on visuo-tactile network, as described in other sections of this dissertation. These studies revealed the high degree of functional specialisation of the bimodal network for different kind of grasping (i.e., precision vs. whole-hand grip). Second, the kinematics of grasping in human and non human primates has been revealed to be highly comparable (Castiello 2005; Roy et al. 2002; 2006) so that the possible functional homologies, previously established on the basis of bimodal neurons properties, will hold true across species when the same action of grasping an object is performed. Finally, grasping objects is one of the most common actions we execute in our everyday life. Thus, grasping appeared the right choice to link our research to animal's studies and at the same time to maintain an ecological approach to our investigation in humans. Participants were thus requested to grasp a cylinder along its longitudinal axes, with a precision grip (thumb and index fingers) and extract it from the horizontal support in which it was inserted. The cylinder was placed far from the hand (47 cm), and presented in different orientations. In this way, participants had to perform a complex action composed by a hand transport phase, a finger grip and a wrist rotation component (Figure 4.1).

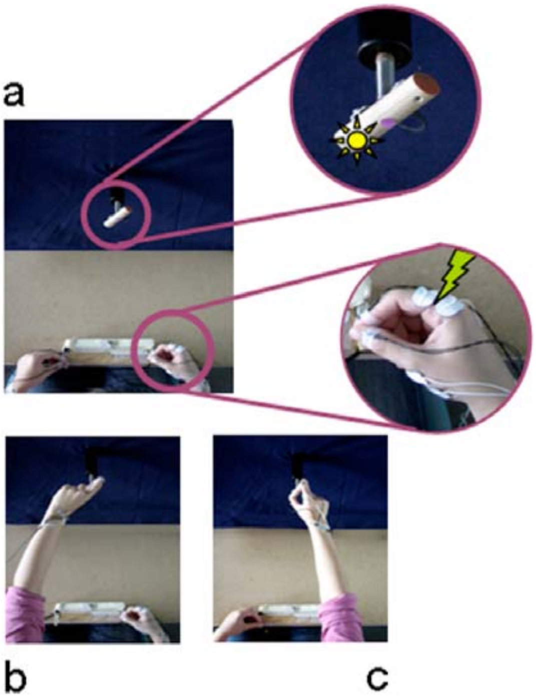

Fig 4.1 View of the cross-modal congruency paradigm modified in order to assess the multisensory interaction during the execution of an action. **(a)** tactile target on the hand as in the typical CCE condition while visual distractors are embedded into the to-be-grasped object. **(b)** and **(c)** are example of grasping actions.

Secondly, the CCE paradigm has been implemented in these active conditions. The same perceptual discrimination task of the elevation of tactile stimuli delivered on the thumb (“down” position) or on the index finger (“up” position) has been maintained. However, instead of presenting the visual distractors from a position close to the hand, as in the typical CCE paradigm, they have been embedded in the object, target of the action. The cylinder presented two LEDs above and below the fixation point marked at its centre. The spatially congruent and incongruent visuo-tactile stimuli could be thus reproduced. At each trial, participants were requested to respond where they perceived the tactile stimulation trying to ignore the visual distractor on the object.

This arrangement allowed us to couple the perceptual and motor task at each trial and at different timings of the unfolding action. The evolution of the visuo-tactile interaction could thus be assessed along the execution of the action and in particular three epochs have been chosen. The visuo-tactile interaction was assessed either before the on-set of the action, on the action on-set itself, or in the early execution phase. The first constitutes a baseline, where the hand does not move yet, to be compared with the two ‘dynamical’ phases. The hypothesis supporting the involvement of peripersonal space in action execution would predict a modulation of the visuo-tactile interaction in terms of CCE as a function of the moment when it is assessed along the execution of the action.

3. The kinematic recording of movements: a real-time method for linking multisensory perception and action

In order to study the relationship of the multisensory based peripersonal space and the execution of an action, it is necessary to measure the updating of the visuo-tactile interplay in real-time with the unfolding action. This aim revealed challenging since, as we described in previous sections, the peripersonal space has been assessed only in static conditions. The adaptation of the CCE paradigm allowed the real-time assessment of the multisensory perception induced by the execution of an action. However, in order to investigate the link possibly existing between the perceptual and the motor domain, also the latter needs to be measured.

In the early 80's, the development of kinematic methods allowed the on-line recording and a quantitative description of movements executed during actions. For instance, Jeannerod's studies that were mainly focussed on grasping actions, provided a model of the grasping as a two components movement: transport and grip components. The two components could be thus defined by their respective kinematic parameters, such as velocity and acceleration for the transport component and velocity of finger aperture and maximum grip aperture for the grip component.

With the aim of investigating the link between peripersonal space and execution of voluntary actions, we assessed the multisensory perception during action execution and simultaneously recorded the kinematic of each movement. This novel approach conjugates a multisensory perceptual task in real-time with the movement and provided the necessary method to link the perception to the kinematic characteristics of the action.

In this section, the main characteristics of the kinematics will be briefly reviewed in particular showing the normal structure of a grasping movement from a kinematic point of view. The neural bases of grasping will also be briefly presented.

3.1. The kinematics of grasping

When we move the hand in order to grasp an object, we need to shift the hand closer to the object and simultaneously to adapt the finger grip to the size and orientation of the object. Despite the enormous variability in aspects of movement such as force, posture, duration and speed, the underlying control principles appear elegant and show a constancy in the overall basic (or molar) structure. It is indeed possible to identify A) a transport component toward the object, which can be defined by the acceleration, velocity and deceleration of the hand (as derived from the wrist displacement); B) a grip component, which develops during the evolution of the transport (Jeannerod 1981).

Jeannerod (1981; 1984) coded grasping in terms of changes in grip aperture, the separation between the thumb and the index finger. During a reach-to-grasp movement, there is first a progressive opening of the grip, with straightening of the fingers, followed by a gradual closure of the grip until it matches the object’s size (Figure 4.2). The point in time at which the thumb–finger opening is the largest (maximum grip aperture) is a clearly identifiable landmark that occurs within 60-70% of the duration of the reach and is highly correlated with the size of the object (Smeets and Brenner 1999). Other properties, including fragility (Savelsberg et al. 1996), size of the contact surface (Bootsma et al. 1994), texture (Weir et al. 1991b) and weight (Weir et al. 1991a) of the object that is the target of the action are all factors that can influence the kinematics of grasping. Object’s weight constrains the positioning of the fingers, in such a way that heavier objects need to be grasped more accurately and with a larger grip than lighter objects. Grasping slippery objects requires a

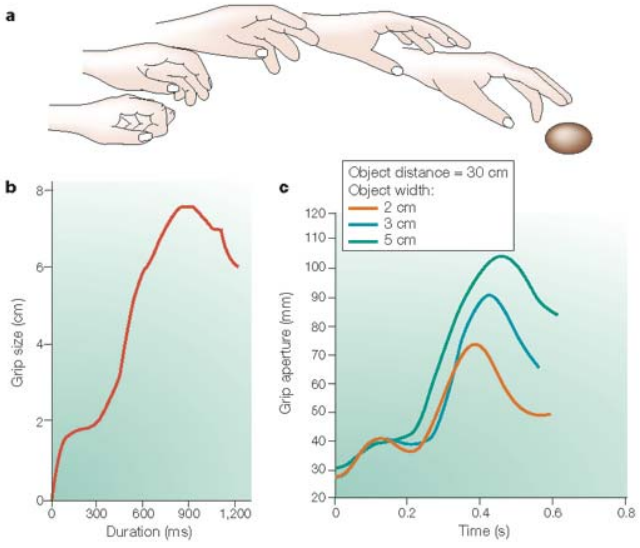

Fig. 4.2 (a) Representation of a grasping action. The hand approaches the object and simultaneously takes an optimal shape in order to grasp it. Fingers open reaching a maximum of aperture **(b)** and then close on the object. The maximum of the grip aperture is a function of the size of the to-be-grasped object **(c)**. From Castiello 2005.

larger approach parameter, leading to a larger grip earlier in the movement compared with grasping rough-surfaced objects. On these bases Jeannerod proposed a model based on two different visuo-motor channels (Jeannerod and Biguer, 1982). The transport component, that is the spatial shift of the hand toward the object, requires the knowledge of the spatial configuration of the to-be-grasped object with respect to the grasping body-part. To reach an object in the external space with our hand, we need indeed to know its spatial location (and its orientation) with respect to the hand. In other words, we need to know the extrinsic characteristic of the object, i.e., those characteristics that not dependent upon the object itself, but are determined by the spatial configuration and location of the object with respect to the body. By contrast, intrinsic information is required for the development of the grip component, such as the size, the texture and the shape of the object itself.

It is clear from these considerations that large part of information about how an object has to be optimally grasped derives from the visual modality (orientation, shape, size of the available landing surfaces) sometime associated with the experience of tactile information (texture or weight). The tactile system, nonetheless, seems to be important for the optimal evolution of the hand-shaping (Gentilucci et al. 1997; Witney et al. 2004): cutaneous receptors in the hand provide information about the action of the hand, including its kinematics and posture, as well as the grip forces and load forces that are used during grasping and manipulation of objects. Finally, the visual information about the object can also create expectancies about the tactile feedback the grasping hand will receive at the end of the action, when it will enter in contact with the object itself (Gentilucci et al. 1997).

The kinematics recording represents a powerful technique which allows quantitatively describing movement. More important for the experimental contribution of this thesis, the real-time kinematics of the movement allows for establishing direct link between the perceptual assessment of the visuo-tactile interaction and the evolution of the grasping action. For this reason, each grasping movement performed by participants has been kinematically recorded and analysed off-line. Three infrared emitters have been placed in the standard locations on the grasping hand: one on the wrist, for recording the parameters associated to the transport component; two on the last phalanx of the thumb and of the index finger for recording the development of the grip component.

3.2. Neural network for grasping

Three specific areas involved in hand grasping execution have been identified in the monkey cortex: the primary motor cortex (F1), part of ventral premotor cortex (F5) and the anterior intraparietal sulcus (AIP). The integrity of the primary motor cortex (F1) is necessary for performing a successful grasping action. A lesion of this area indeed produce a severe deficit in the control of individual fingers and consequently disrupt normal grasping (Lawrence and Kuypers 1968a). Lesioning the corticospinal tract, through which motor commands are conveyed from the primary motor cortex to cells in the spinal cord, also impairs the control of independent finger movements (Lawrence and Kuypers 1968b). However, after such kind of lesion, synergistic finger flexion typical of a power grip prehension might be not affected.

More interesting for this dissertation, is another fundamental process needed for a successful grasp to be executed. To grasp an object involves indeed a transformation of the intrinsic properties of the object, which are visually available, into the correct motor shaping of the hand. The visuo-motor transformations for grasping seem to involve two key cortical areas: the AIP and area F5, already described in the second chapter of this dissertation. AIP and F5 neurons activity shows striking similarities and important differences (Rizzolatti et al. 2002). For example, both AIP and F5 show a functional specialisation for type of grasping, which in turn depends on the visual characteristic of the object to be grasped (Murata et al. 1997; 2000). Different populations of neurons are activated during different kinds of grasping (i.e., precision grip or whole-hand prehension). However, AIP neurons seem to represent the entire action, whereas F5 neurons seem to be concerned with a particular segment of the action (Rizzolatti et al. 1998). Another important difference is that AIP, more than F5, presents a visual response to the presentation of three-dimensional objects (Murata et al. 2000). Based on these findings, Fagg and Arbib (1998) have thus proposed a model in which area AIP provides multiple descriptions of three-dimensional objects for the purpose of manipulation, whereas area F5 might be mainly involved in selecting the most appropriate motor prototype from a “motor vocabulary” (Rizzolatti et al. 1988a) for example, the type of grip that is effective in interacting with a specific target object.

Similarly to monkeys, lesions of the human primary motor cortex or corticospinal fibres dramatically disrupt the execution of a grasping movement. Such lesions typically lead to grasping movements that are initially characterised by the loss of independent control of the fingers, although synergistic movements of all fingers (a power grip) might remain intact (Lang and Shieber 2004).

Due to the difficulty of establishing a correct homology between human and monkey brains, it is difficult to integrate the known grasping deficits in humans after lesions of the superior parietal lobe (SPL) with the results of neurophysiological work in monkeys. For instance, in monkeys, the SPL (possibly area 5) seems to be mainly related to the somatosensory rather than visuomotor elaboration (Rizzolatti et al. 2002). Secondly, although in monkeys some parts of the SPL do receive visual information, activity in these areas seem to be more correlated with reaching rather than grasping (Galletti et al. 1997). Finally, there is reason to believe that, the relative expansion of the parietal lobes characterising humans' brain relative to monkeys', the human SPL might be the homologue of the monkey IPL (Milner 1997). However, with all the possible cautions, there is evidence that a possible homologue of AIP has a specific role in grasping in humans. Binkofski and colleagues (Binkofski et al. 1998) localised the area responsible for grasping in humans to the AIP, contralateral to the impaired hand. In line with the results obtained from monkeys in which AIP has been inactivated, human patients with AIP lesions present deficits in grasping, whereas reaching remained relatively intact.

The most compelling evidence for a deficit in visually guided grasping in humans comes from patients presenting a deficit known as optic ataxia (Perenin and Vighetto 1988; Rossetti et al. 2003) classically considered to be a specific disorder of the visuomotor transformations caused by posterior parietal lesions. Various optic ataxic patients have been described showing specific deficits in the on-line control of reaching (Pisella et al.2009; Blangero et al. 2008), but only a few cases have investigated the kinematics of grasping actions. Patient V.K. (Jakobson et al. 1991), for example, showed an apparently normal early phase of hand opening during attempts to grasp an object, but her on-line control of grip aperture quickly degenerated, resulting in numerous secondary peaks in the grip aperture profile, rather than a single peak, which is typical of a healthy subject. Patient I.G. (Milner et al. 2003) also showed considerable deficits in the scaling of her maximum grip aperture to the size of an object. Patient G.T.'s prehension movements were not normally tuned either by intrinsic or extrinsic visual properties of objects (Roy et al. 2004), his grasping component not being appropriately modulated by object's size. Overall, these patients present a deficit in translating the visually available information about an object into the correct motor configuration to interact with it.

4. Conclusion: kinematic-perceptual co-recording

The general hypothesis underlying the experimental contribution presented here is that peripersonal space constitutes a multisensory interface serving for the interactions between the body and the objects in the external space. This hypothesis is based on the neural mechanism on which peripersonal space representation is built through. The kinematic recording coupled with an on-line assessment of the multisensory interaction during action is the method through which I tried to investigate the link between the multisensory perception and the execution of action. This novelty meant to fill the gap till now existing between a static and dynamic view of multisensory perception.

RESULTS

As described, electro-cortical microstimulation studies in monkeys provided evidence in favour of an involvement of visuo-tactile parieto-frontal structures in the execution of movements that are compatible with a defensive or avoidance reaction. This is compatible with the hypothesis that the peripersonal space representation might be a multisensory interface with a protective function in response to possible threatening objects approaching the body. In the first study presented here, we tested this hypothesis in healthy humans, investigating the reference frame the brain employs for coding the location of real three-dimensional objects suddenly appearing near the body. We used a single pulse transcranial magnetic stimulation (TMS) approach in order to measure the excitability of the motor cortex in correspondence to the hand representation. TMS is a technique allowing to momentarily interfere with the normal electrical activity of a relatively small area of the brain. When applied to the motor cortex, TMS single pulse elicits a motor evoked potential (MEP) that can be measure in the peripheral muscle, which reflects the level of cortical excitability in the respective motor cortex representation. The cortical excitability reflects in turn, the readiness for a motor response. We hypothesised that an object suddenly approaching the hand, for instance, should modulate the cortical activity in correspondence of the motor cortex hand representation. We also hypothesised that, if peripersonal space is involved in the detection and localisation of stimuli approaching the body, the cortical activity modulation should arise in a reference frame centred to the body-part (the hand in the example).

We asked subjects to make a simple response to a visual ‘Go’ signal while they were simultaneously presented with a task-irrelevant distractor ball, which could rapidly approach the peripersonal space in a location either near to or far from participants’ responding hand.

As expected, we found that motor excitability was modulated as a function of the distance of approaching balls from the hand: MEPs amplitude was selectively reduced when the ball approached near the hand, both when the hand was on the left and on the right of the midline. Strikingly, this reduction occurred as early as 70 ms after ball appearance. The effect arose in hand-centred coordinates since it was not modified by the location of visual fixation relative to the hand. Furthermore, it was selective for approaching balls, since static visual distractors did not modulate MEP amplitude.

Together with additional behavioral measurements, this series of experiments provides direct and converging evidence for automatic hand-centered coding of visual space in the human motor system during motor preparation. These results provide direct evidence in favour of the interpretation of peripersonal space as a multisensory interface for translating potentially relevant visual information into rapid actions.

STUDY 1

Coding of visual space during motor preparation: approaching objects rapidly modulate corticospinal excitability in hand-centred coordinates

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Behavioral/Systems/Cognitive

Coding of Visual Space during Motor Preparation: Approaching Objects Rapidly Modulate Corticospinal Excitability in Hand-Centered Coordinates

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Defensive behaviors, such as withdrawing your hand to avoid potentially harmful approaching objects, rely on rapid sensorimotor transformations between visual and motor coordinates. We examined the reference frame for coding visual information about objects approaching the hand during motor preparation. Subjects performed a simple visuomanual task while a task-irrelevant distractor ball rapidly approached a location either near to or far from their hand. After the distractor ball appearance, single pulses of transcranial magnetic stimulation were delivered over the subject's primary motor cortex, eliciting motor evoked potentials (MEPs) in their responding hand. MEP amplitude was reduced when the ball approached near the responding hand, both when the hand was on the left and the right of the midline. Strikingly, this suppression occurred very early, at 70 – 80 ms after ball appearance, and was not modified by visual fixation location. Furthermore, it was selective for approaching balls, since static visual distractors did not modulate MEP amplitude. Together with additional behavioral measurements, we provide converging evidence for automatic hand-centered coding of visual space in the human brain.

Introduction

In daily life, sensorimotor integration is required for the execution of a wide range of movements, each of which poses different computational challenges (Rizzolatti et al., 1998; Graziano, 2006). Consider the ongoing processes of movement and response selection while you wash the dishes: although you might still attempt to catch a slippery glass as it is falling, at some point you must withdraw your hand to avoid injury.

The majority of human research on coordinate transformations for hand movements has studied goal-directed reaching and grasping (Crawford et al., 2004; Medendorp et al., 2005; Beurze et al., 2006; Fernandez-Ruiz et al., 2007; Brozzoli et al., 2009), whereas the reference frames in which avoidance movements are coded have been relatively neglected. However, electrophysiological experiments in macaques in which three-dimensional stimuli were moved rapidly toward the monkey's body have revealed body part-centered representations of visual space (Graziano et al., 2004). For example, certain neurons in the ventral and dorsal premotor cortex represent objects in hand-centered coordinates (Graziano et al., 1994, 1997; Fogassi et al., 1996, 1999; Graziano, 1999) and may be involved in the preparation and guidance of movements both toward and away from objects (as suggested by Rizzolatti, 1987; Maravita et al., 2003; Cooke and Graziano, 2004; Avillac et al., 2005). Neuroimaging and neuropsychological studies have suggested the involvement of possibly homologous structures in the hand-centered coding of space in the human brain (di Pellegrino et al., 1997; Bremmer et al., 2001; Farnè et al., 2003, 2005; Makin et al., 2007; Quinlan and Culham, 2007) (for review, see Makin et al., 2008).

In the current study, we used an active motor task to determine the reference frame for coding the location of real, three-dimensional objects approaching the hand. Subjects abducted their right index finger in response to a visual "go" signal and were simultaneously presented with a task-irrelevant distractor ball, rapidly approaching a location either near to or far from their responding hand.

To obtain an index of corticospinal excitability with which to assess the effects of rapidly approaching distractor stimuli, we used single pulse transcranial magnetic stimulation (TMS), applied to the left primary motor cortex, eliciting motor-evoked potentials (MEPs) in the subject's right hand. We hypothesized that the hand-centered coding of approaching visual stimuli should have, as one consequence, some modulatory effect on

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Table 1. Experimental conditions

				Trial proportion (%)				
Experiment	*N*	Blocks	Trials per block	Hand position (L/R)	Distractor position (L/R/none)	Task (go/stop/stay)	TMS time point(s)	Comments
(1) Time course	10	4	50	50/50	50/50/0	100/0/0	40, 60, 80, 100, 120	—
(2) Eye position	10	2	60	50/50	40/40/20	100/0/0	70, 80 (75)[a]	Two fixation positions (L/R); eye monitoring
(3) Go/stop balls	11 (10[b])	4	72	50/50	33/33/33	75/25/0	70, 80, 90, 100, 110, 120; (80, 110)[c]	Eye monitoring
(4) Go/stop LEDs	10 (9[b])	4	72	50/50	33/33/33	75/25/0	70, 80, 90, 100, 110, 120; (80, 110)[c]	Eye monitoring
(5) Go/stay balls/LEDs	10	4	48	50/50	25/25/0[d]	50/0/50	70	Behavioral data analyzed
(6) Selectivity	6	4	60	50/50	50/50/0	100/0/0	65, 70, 75, 80, 85	MEPs from FDI and ADM; eye monitoring
(S1) Exog. attention	10	2	60	50/50	50/50/0	75/0/25	70, 80, 75[e]	Run with experiment 2; eye monitoring

N, Sample size; L, left; R, right.

[a] No-distractor trials.

[b] One dataset from experiment 3 discarded because of insufficient valid trials; one dataset from experiment 4 lost because of hardware failure.

[c] Stop trials.

[d] Per distractor type (balls, LEDs).

[e] Stay trials.

corticospinal excitability as a function of the distance of the approaching object from the hand (near vs far). We report that corticospinal excitability is indeed modulated in a hand-centered manner, while subjects are preparing to respond to the targets.

In a set of complementary experiments, we examined the relative contributions of visual fixation position and distractor type [approaching ball vs static light-emitting diode (LED)] to this hand-centered coding of space. We further examined the process of "proactive inhibition," the ability to inhibit in advance one movement to execute another (Koch et al., 2006; Mars et al., 2007; van den Hurk et al., 2007; van Elswijk et al., 2007), in relation to the suppression of possible avoidance responses elicited by the approaching ball.

Materials and Methods

Subjects

A total of 23 healthy right-handed subjects participated in seven experiments (supplemental Table S1, available at www.jneurosci.org as supplemental material). The subjects gave written, informed consent and were screened for contraindications to TMS. The experiments were conducted in accordance with the Declaration of Helsinki and were approved by the local ethical review board.

Data acquisition and apparatus

Physiological measurements. MEPs were recorded from the right first dorsal interosseus (FDI) muscle using three self-adhesive electrodes (Neuroline; Ambu) in a belly-to-tendon manner. EMG data were acquired using a BioPac system (BioPac Systems). EMG signals were sampled for 2 s at 2 kHz, amplified 1000 times, and bandpass filtered (25–250 Hz). At the end of each trial, trigger pulses were sent to allow automated identification of trials. Data were stored for off-line analysis (see below).

Transcranial magnetic stimulation. A Magstim Super Rapid stimulator and figure-of-eight, 70-mm-diameter TMS coil were used. The position and orientation of the TMS coil and the intensity of the single pulses was optimized for each subject to elicit reliable MEPs in the FDI, following standard procedures (Hallett, 2007). Resting motor threshold (RMT) was defined as the minimum TMS intensity (in percentage of maximum stimulator output) required to elicit only 5 of 10 MEPs with peak-to-peak amplitudes equal to or above 0.5 mV, while the subject's right hand was relaxed and placed on the right side of the workspace. We set this (relatively) high amplitude criterion for the RMT and stimulated at 110% of this RMT to elicit MEPs on virtually every trial and to allow detection of MEP suppression (Cantello et al., 2000) (supplemental Table S1, available at www.jneurosci.org as supplemental material).

Visual stimuli. Two types of visual stimuli were used as distractors: balls and LEDs. The balls were 5-cm-diameter red foam spheres, mounted on the end of 55-cm-long aluminum rods (stimulus arms). The LEDs were 5 mm in diameter, green for the central go signal, and red for peripheral distractors/fixations and the central "stop" LED.

A custom apparatus controlled stimulus delivery (see Fig. 1*A*). Two stimulus arms were mounted on rotating wheels positioned opposite the subject and occluded from the subject's sight. After a cue, the experimenter released one of the stimulus arms from its vertical position, and the ball fell under gravity toward the workspace, entering the subject's field of view (see supplemental Videos 1, 2, available at www.jneurosci.org as supplemental material). The ball traversed $\sim$37 cm in $\sim$100 ms after becoming visible to the subject, having a mean velocity when visible of $\sim$370 cm/s, and stopped with minimal bouncing $\sim$3 cm above the workspace. The landing position of the ball was either directly above the middle finger of the subject's hand (near trials) or 30 cm laterally to the hand (far trials).

During their trajectories, the stimulus arms interrupted the beams of two lasers, triggering pulses from two detectors mounted on the apparatus. The second laser was positioned to intersect the stimulus arm at the point at which the distractor balls first became visible to the subject, thus providing a precise timing signal for distractor ball appearance. The first laser was positioned close to the start of the movement of the stimulus arms and was used in experiments in which a stop signal or peripheral visual cue was provided in advance of distractor ball appearance. The time taken for the stimulus arms to pass between the two laser beams was approximately constant, with a trial-to-trial timing range of <5 ms.

Additional apparatus. Two response buttons were firmly attached, with the button facing rightward, 20 cm to the left and 15 cm to the right of the visual midline, so that the middle finger of the subject's hand in both positions was $\sim$17.5 cm from the midline. For experiments 2, 3, 4, 6, and S1, a small infrared camera was mounted 5 cm behind the central fixation LED, allowing the experimenter to monitor the subject's eye position. A large ventilator was placed under the workspace near the subject, providing constant background noise and airflow, minimizing any acoustic and airflow artifacts induced by stimulus delivery. In pilot experiments, blindfolded subjects were unable to determine the position of balls with respect to their hand.

Design and procedure

Because the seven experiments differed in several respects from each other, the general design and procedures are described here. For additional details, see Table 1, supplemental material (available at www.jneurosci.org), and the individual section for each experiment in Results.

The two principal variables in every experiment were the position of the right hand (on the left or right of the workspace, in separate, counterbalanced blocks), and the position of the distractor stimulus (left or right of the workspace, pseudorandomized trial-by-trial). Additional variables for each experiment are detailed in Table 1. Subjects performed a short (10–20 trials) practice session before each experiment.

Trials began with the illumination of the central fixation LED, on which subjects fixated for the duration of the trial. To maintain subjects' attention during stimulation and to ensure that hand movement was task-relevant, subjects performed a speeded abduction of their right index finger, pushing a button in response to the target, which was a brief

(130 ms) offset of the fixation LED. In trials with a distractor ball, the offset of the fixation was simultaneous with the appearance of the ball, triggered by the interruption of the second laser beam (see supplemental Videos 1, 2, available at www.jneurosci.org as supplemental material). Targets and distractors were presented 3–5 s after trial onset (see Fig. 1*B*). A single pulse of TMS was applied, at different time points (between 40 and 120 ms) after distractor appearance, over the hand area of the subject's left primary motor cortex. In trials with distractor LEDs, one of two LEDs, positioned underneath the endpoint of the trajectory of each ball was illuminated for 130 ms simultaneously with the go signal. On these trials, and on other trials without distractor balls, the timing of the go signal was determined by using the distribution of target delays with respect to trial onset from experiment 1. These had an approximately uniform rectangular distribution between 750 and 1500 ms.

Analysis

Data analysis was performed with custom software written in Matlab (available at http://www.neurobiography.info).

MEPs. The peak-to-peak MEP amplitude was determined automatically by finding the minimum and maximum values within a search window, starting ~20 ms and ending ~70 ms after TMS. In all cases, individual MEPs were visually inspected and rejected if they were contaminated with a voluntary contraction or large fluctuations in the baseline before the TMS pulse. MEP amplitudes <0.25 mV were discarded as being indistinguishable from baseline. A mean ± SE of 10.5 ± 2.1% of trials across experiments was discarded because of outlying reaction times (RTs) (<150 or >1500 ms), noisy EMG background, or the absence of MEPs.

To rule out the possibility that differences in MEP amplitude were attributable to differences in RT for near and far trials, we regressed out the effect of RT on MEP amplitude and report here only the corrected MEP amplitudes (additional data are provided in supplemental Tables S2 and S3, and supplemental material, available at www.jneurosci.org).

To correct for between-subject differences in baseline MEP amplitude (e.g., because of electrode placement or muscle size), peak-to-peak MEP amplitudes were standardized with respect to the mean MEP amplitude on no-ball trials (collapsing across hand positions), separately for each subject and TMS time point. In experiments in which a no-ball condition was not performed (experiments 1, 5, 6, and S1), the mean MEP amplitude across both near and far conditions was used for standardization purposes (supplemental Tables S2, S3, available at www.jneurosci.org as supplemental material). The effects of these standardization procedures on the statistical significance of the reported results were minimal (supplemental Table S3, available at www.jneurosci.org as supplemental material).

EMG. EMG data were rectified and the mean EMG baseline activity was compared statistically between experimental conditions, to verify that changes in the baseline EMG activity did not confound our results (supplemental Table S4, available at www.jneurosci.org as supplemental material). We also extracted the onset of voluntary EMG activity, defined as the first point after MEP offset at which the mean EMG over the next 10 ms was ≥3.09 SD above baseline (Hodges and Bui, 1996). These onsets were used to determine EMG "twitches" in experiment 5b.

Statistical analysis. We used separate two-tailed *t* tests, rather than omnibus ANOVAs, to test novel hypotheses (e.g., experiments 1, 4, 5, and S1) for two reasons: (1) Since MEPs were standardized for each TMS time point separately, pooling across near and far distractor conditions, there could not be a main effect of TMS time point; (2) in experiments without a separate baseline, data from near and far conditions were not independent. In these cases, the near data were compared against the null hypothesis of 1.0. In other cases, near and far conditions were compared directly. For experiments 2, 3, and 6, we tested one-tailed hypothesis-driven predictions concerning differences between the effects of near and far distractors, using *t* tests and planned comparisons. To protect against false positives, we used a Bonferroni correction for multiple comparisons. Throughout this manuscript, corrected *p* values are reported. In addition, we performed numerous bootstrapping and resampling procedures to construct null distributions for each of the critical reported comparisons. In every case, this bootstrapping procedure supported the inferences derived from the *t* tests, so we report only the standard parametric tests in this manuscript. The bootstrap statistics are presented in supplemental Table S6 (available at www.jneurosci.org as supplemental material). Additional details of the methods are available in supplemental material (available at www.jneurosci.org).

Results

Experiment 1: early hand-centered modulation of corticospinal excitability

We first determined whether and when corticospinal excitability was modulated as a function of the distance of a rapidly approaching three-dimensional visual distractor ball with respect to the subject's hand (experiment 1). Subjects made a speeded right index finger abduction movement in response to a central go signal (the offset of the central fixation LED) while a distractor ball appeared, approaching the workspace on the left or right side (Fig. 1; supplemental Videos 1, 2, available at www.jneurosci.org as supplemental material). On one-half of the trials within each block, and unpredictably, the distractor ball fell near to the subject's hand, and in the other one-half it fell far from their hand. The go signal was simultaneous with, and triggered by, the appearance of the distractor ball. The subjects were instructed to ignore the distractor stimuli and respond only to the target. We found no significant differences between near and far trials with respect to behavioral performance [supplemental Table S2 (available at www.jneurosci.org as supplemental material) shows RT, error, and d' data across all seven experiments].

For 10 subjects, TMS was applied at five time points (40–120 ms, in 20 ms intervals) after the appearance of the distractor ball (Table 1, experiment 1). This enabled us to measure corticospinal excitability over most of the interval between the appearance of the ball and the very earliest voluntary EMG responses.

Across all TMS time points, the mean MEP amplitude for trials with near distractor balls (standardized mean ± SE amplitude, 0.973 ± 0.011) was significantly lower than for trials with far distractor balls (1.027 ± 0.011; $t_{(9)} = 2.41$; $p = 0.039$). Considering each time point separately, the effect of distractor ball distance was significant only at 80 ms after distractor appearance [$t_{(9)} = 4.08$; $p = 0.014$, comparing the mean of near distractor ball trials (mean ± SE, 0.91 ± 0.022) against 1.0, and after correcting for five comparisons] (Fig. 2*A*). For the other four time points, no significant effects were found, suggesting a return to baseline (i.e., no differences between near and far distractor balls) within 20 ms. Within the 80 ms TMS time point, when the hand was on the left of fixation, distractor balls appearing on the left resulted in smaller MEPs than distractor balls appearing on the right, and vice versa for the right hand position (interaction between distractor ball position and hand position; $F_{(1,9)} = 16.63$; $p = 0.003$) (Fig. 2*B*). That is, balls approaching near the hand reduced corticospinal excitability compared with balls falling far away. These results demonstrate a significant modulation of corticospinal excitability at 80 ms after visual stimulation, which is consistent with a hand-centered coding of the approaching objects.

Experiment 2: hand-centered coding of approaching objects is independent of eye position

We next examined whether corticospinal excitability during response preparation is also modulated by the distance of the distractor ball from the location of subjects' visual fixation, or rather is fixed predominantly in hand-centered coordinates, similarly to certain neuronal populations in macaque premotor and parietal cortices (Graziano et al., 1994, 1997; Fogassi et al., 1996, 1999; Graziano, 1999).

With another group of 10 subjects, we repeated the experimental design described above, with some modifications (Table 1, experiment 2). Rather than maintaining fixation centrally throughout the experiment, at the beginning of each trial, one of two fixation LEDs was illuminated, pseudorandomly either on the left or on the right side of the workspace, underneath the end of the left and right distractor ball trajectories, respectively. Thus, in one-half of the trials with a distractor ball, the ball appeared peripherally, on the opposite side to the visual fixation position, whereas in the remaining trials, the ball appeared parafoveally, on the same side as visual fixation. Based on the results of experiment 1 (i.e., a significant effect at 80 ms and a nonsignificant trend at earlier time points), two TMS time points were tested, at 70 and 80 ms after distractor ball appearance.

We predicted a significant reduction of corticospinal excitability when the distractor ball fell near to compared with far from the hand (i.e., in a hand-centered manner) and that this hand-centered representation would be found regardless of the distance of the distractor ball from the fixation position. We used one-tailed planned comparisons for these hypothesis-driven predictions.

A significant effect was found for the 70 ms TMS time point, in which, as predicted, and in accordance with the results of experiment 1, the mean MEP amplitude for near-hand distractor ball trials (mean ± SE amplitude, 0.936 ± 0.045) was significantly lower than for far-hand distractor ball trials (1.013 ± 0.034; $F_{(1,9)} = 3.79$; $p = 0.020$) (Fig. 3). There was also a weak (power, 0.259) and nonsignificant trend toward an effect of fixation position, with smaller MEPs for trials with distractor balls presented on the same side as visual fixation, compared with on the opposite side (0.954 ± 0.042 vs 0.995 ± 0.035, respectively; $F_{(1,9)} = 2.35$; $p = 0.080$). Note that fixation position was manipulated orthogonally to hand position. There was no effect of distractor ball distance at the 80 ms time point, possibly indicating that the hand-centered effect is maximal at 70 ms after visual presentation or that there is some variability between subjects (see experiment 6). These results suggest that, 70 ms after the presentation of a visual distractor, corticospinal excitability reflects the coding of visual objects primarily with re-

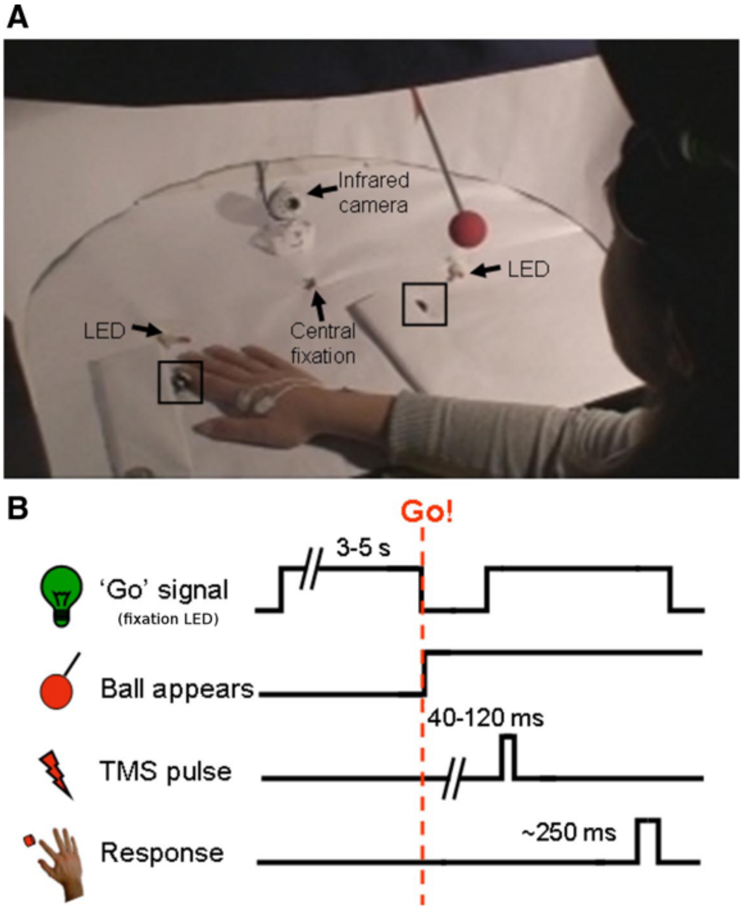

Figure 1. General experimental setup and design. ***A***, Experimental setup. ***B***, Time course. Subjects positioned their right hand 17.5 cm to the left (shown in ***A***) or right of the central fixation LED. They were instructed to respond to a transient (130 ms) offset of the fixation LED by abducting their right index finger to push a button (black square) while ignoring the distractor ball (red sphere). The distractor ball appeared simultaneously with the go signal, approaching a position pseudorandomly either on the left or right (shown in ***A***) of fixation. Between 40 and 120 ms after the appearance of the distractor ball, a single pulse of TMS was delivered to the hand area of the left hemisphere primary motor cortex, eliciting a MEP in the right FDI muscle.

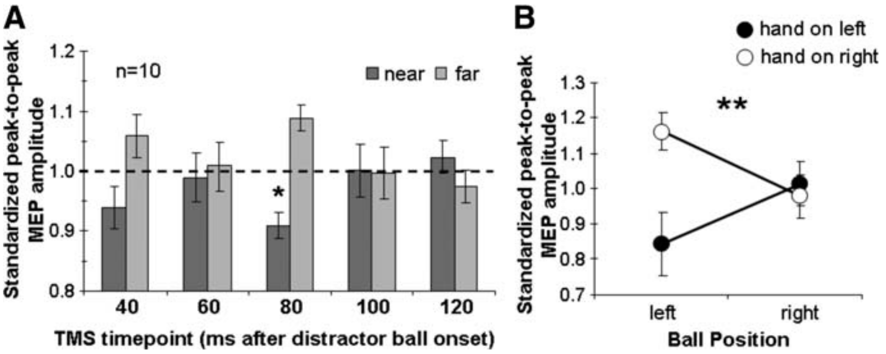

Figure 2. Rapid modulation of corticospinal excitability by visual stimuli in hand-centered coordinates. ***A***, Mean ± SE peak-to-peak MEP amplitude for near (dark gray) and far (light gray) distractor balls across five TMS time points (40–120 ms). Early after distractor onset (40–80 ms), mean peak-to-peak MEP amplitude in trials with near distractor balls was lower compared with trials with far distractors, but this difference was significant only at the 80 ms time point (*$p < 0.05$). The near condition was tested against 1.0, and *p* values were corrected for five comparisons. ***B***, Mean ± SE peak-to-peak MEP amplitude for distractor balls presented to the left and right of fixation for the two hand positions separately, at the 80 ms time point. The difference between peak-to-peak MEP amplitudes for left and right distractor balls reversed when the position of the right hand shifted from left (filled circles) to right (open circles). This pattern was reflected in a significant interaction between hand position and distractor ball position. The asterisks denote statistical significance of the interaction between hand and ball positions, as evaluated with ANOVA (**$p < 0.01$).

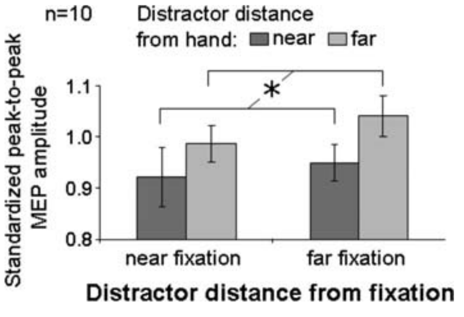

Figure 3. Hand-centered modulation of corticospinal excitability by visual distractors is independent of eye position. Mean ± SE peak-to-peak MEP amplitude with TMS delivered 70 ms after distractor ball appearance shows a significant effect of distractor ball distance relative to the hand (dark grays, near; light grays, far). MEP amplitudes were modulated primarily by the distance of the distractor balls from the hand and less, and independently, by the distance from visual fixation. The asterisk denotes statistical significance of planned comparisons using hand-centered predictions (*$p < 0.05$).

spect to the distance from the hand and does so independently from any potential contribution of visual fixation position.

Experiment 3: near distractor balls suppress corticospinal excitability during response preparation

The first two experiments provided evidence for decreased corticospinal excitability after presentation of approaching visual distractor balls near to compared with far from subjects' hands. We hypothesized that this early reduction reflects the proactive inhibition of an undesirable response (Koch et al., 2006; Mars et al., 2007; van den Hurk et al., 2007; van Elswijk et al., 2007), such as an avoidance movement elicited by the approaching ball. We therefore measured the effect of voluntary inhibition of the motor response at the time of distractor presentation (Coxon et al., 2006, 2007) to examine whether this would suppress MEP amplitudes to a similar level as found with near distractor balls. Additionally, we included a no-distractor "baseline" condition to assess whether near balls decrease, or else far balls increase, corticospinal excitability. For this purpose, we repeated the basic design of experiment 1 with a different group of 10 subjects (Table 1, experiment 3). This time, 25% of the trials contained a central red stop signal, presented randomly 200–300 ms before the go signal, instructing subjects to inhibit their response to the upcoming go signal. We also included trials (33%) in which no visual distractor was presented ("no-ball" control trials).

We predicted that a process of proactive inhibition by near distractor balls should result in the following: (1) lower MEP amplitudes for near trials at early TMS time points (70–90 ms), compared with both far and with no-ball trials; (2) no differences for late TMS time points (100–120 ms) between either near and far, or near and no-ball trials; and (3) no significant difference in MEP amplitudes on near distractor trials between go and stop conditions, for the early (70–90 ms) TMS time points.

In the go trials when a distractor ball was presented, we again found a hand-centered reduction of MEP amplitudes, with a significant effect of distractor distance (near vs far), when averaged across the early TMS time points (70–90 ms; near, 0.954 ± 0.025; far, 1.011 ± 0.016; $t_{(9)} = 2.87$; $p = 0.037$, corrected for two comparisons) (Fig. 4), but not across the late TMS time points (100–120 ms; $t_{(9)} = 1.75$; $p = 0.226$). Looking separately at the 70, 80, and 90 ms TMS time points, only at 70 ms were there significantly lower MEP amplitudes for near than far distractor trials (0.946 ± 0.028 vs 1.036 ± 0.038, respectively; $t_{(9)} = 3.07$; $p = 0.040$, corrected for three comparisons). This confirms that the reduction of corticospinal excitability peaks at the 70 ms time point, and then diminishes, replicating the findings of experiment 2.

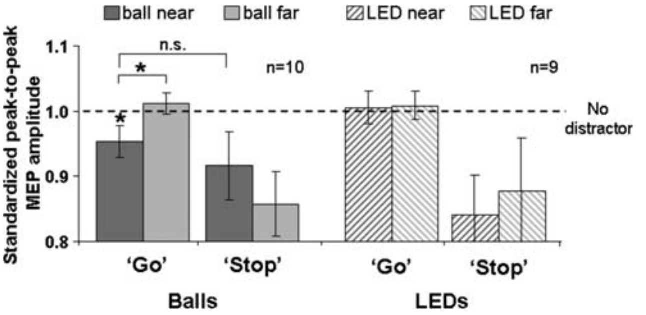

Figure 4. Suppression of corticospinal excitability is found for distractor balls approaching the hand, but not for static LED flashes. Mean ± SE peak-to-peak MEP amplitude for near (dark gray) and far (light gray) distractor balls (filled columns) and distractor LEDs (striped columns), pooled over the 70–90 ms TMS time points. When subjects responded to the go signal, peak-to-peak MEP amplitudes were significantly suppressed by distractor balls approaching near to compared with far from the hand, and also for near compared with control trials with no ball. No such suppression was found when distractor LEDs (positioned at the end of the trajectories of the balls) were illuminated instead of the approaching balls. When subjects voluntarily inhibited their motor responses after a stop signal, no significant difference was found between MEP amplitudes on near and far distractor trials, regardless of the distractor type. The asterisks denote statistical significance of *t* tests between near and no-ball (*$p < 0.05$), and near and far distractor ball trials (*$p < 0.05$, one-tailed corrected for two comparisons). n.s., Not significant.

Furthermore, mean MEP amplitude for early TMS time points on trials with near distractor balls was significantly reduced compared with no-distractor control trials ($t_{(9)} = 1.89$; $p = 0.046$, compared against 1.0), whereas MEPs for trials with far distractor balls were not significantly different from no-ball trials (Fig. 4). These results show that MEP amplitudes were reduced for the near condition, and not enhanced for the far condition, extending the results of experiments 1 and 2.

Additional support for the early suppression of corticospinal excitability after near distractor balls is provided by comparison of MEP amplitudes between stop trials in which subjects were instructed to inhibit their motor responses before ball appearance, and go trials with either near or far distractor balls. For early TMS time points, mean MEP amplitudes on stop versus go trials with near distractor balls did not differ significantly ($t_{(9)} = 0.54$; corrected $p = 1$, with a statistical power of 0.82, based on the effect size of the near vs far go conditions for the early TMS time points) (Fig. 4). This was not the case when comparing MEP amplitudes between go and stop trials for far distractor balls ($t_{(9)} = 2.85$; $p = 0.038$, corrected for two comparisons).

Finally, MEP amplitudes on stop trials were not significantly different between near and far distractor ball trials, either for the early or the late TMS time points (Fig. 4). That is, after voluntary inhibition of motor responses, we did not detect any hand-centered modulation of MEP amplitudes. We cannot, however, definitively rule out the possibility that hand-centered modulation may still exist in the stop trials but was not observed because of possible floor effects on MEP amplitudes.

Although these results do not allow conclusions regarding the precise mechanisms involved in these forms of inhibition, they do at least support the hypothesis that an inhibitory process is responsible for the decrease in corticospinal excitability after the appearance of the near ball.

The data presented thus far provide clear evidence for the suppression of corticospinal excitability after the presentation of rapidly approaching three-dimensional visual stimuli near to relative to far from the hand. Together, these results might best be explained in terms of a form of response competition between the ongoing go task and a newly emerging motor plan, elicited by the approaching ball, possibly for an avoidance response. To examine this possibility further, we needed to establish that such effects were not evident when the distractor was not a rapidly approaching object.

Experiment 4: hand-centered coding of visual space is observed with approaching balls, but not static LED flashes

We next determined whether the hand-centered suppression that we identified after distractor ball presentation can be attributed merely to the sudden occurrence of visual events near the hand. We therefore repeated experiment 3 (with the additional stop trials) on a different group of 10 subjects (Table 1, experiment 4). This time, the moving distractor balls were replaced with static distractor LEDs, positioned beneath the endpoints of the trajectories of the balls. One of the distractor LEDs flashed for 130 ms, simultaneously with the central go signal, either near to or far from the responding hand. We predicted that corticospinal excitability would not be modulated by the static visual distractor LEDs. Specifically, we expected to find no reduction of MEP amplitudes after presentation of distractor LEDs near to relative to far from the hand.

Overall, the subjects' percentage correct performance in this experiment was similar to that of experiment 3 (98.2 ± 0.6 vs 98.1 ± 0.3% correct; $d' = 3.71 \pm 0.03$ vs 3.79 ± 0.06, respectively). No significant differences in performance were found with respect to the distance of the distractor LED from the hand, the trial type (go vs stop), or between the two experiments. Regarding the MEP amplitudes, as predicted, we found no difference between near and far distractor LED trials, both for early and late TMS time points (Fig. 4). Furthermore, and contrary to the results of experiment 3, significantly smaller MEPs were found on stop compared with go trials with near distractor LEDs, specifically for early TMS time points ($t_{(8)} = 3.47$; $p = 0.017$, one-tailed, corrected for two comparisons).

These results are similar to certain results from neurophysiological studies of bimodal neurons in premotor cortex, which showed visual selectivity for three-dimensional objects approaching toward and receding from the hand, and lower responses to static or two-dimensional visual stimuli (Graziano et al., 1997).

Experiment 5a: behavioral indices show hand-centered response inhibition for approaching balls, but not for static LEDs

Additional support for the inhibition of motor responses in a hand-centered reference frame derives from behavioral error rates in a "go/stay" task. This experiment was conducted with a different group of 16 subjects (Table 1, experiment 5). In this experiment, on 50% of the trials the go signal did not appear. Subjects were instructed to respond as quickly as possible, only on go trials, and to withhold responses when the go signal was not presented ("stay"). A visual distractor, which was pseudorandomly either moving (a ball) or static (an LED), was presented on every trial, either near to or far from the responding hand. TMS pulses were applied to the motor cortex contralateral to the responding hand. The MEP data are reported in the following section (experiment 5b).

On go trials, performance with near distractor balls was significantly worse than on trials with far distractor balls (92.9 ± 1.3 vs 97.3 ± 1.0% correct, respectively; $t_{(15)} = 3.02$; $p = 0.017$, two-tailed, corrected; $d' = 3.16 \pm 0.09$ vs 3.51 ± 0.07, respectively; $t_{(15)} = 3.16$; $p = 0.013$, two-tailed, corrected for two comparisons). As presented in Figure 5*A*, when a ball approached the responding hand, subjects were more likely not to respond (i.e., there were more missed responses) than when the ball appeared far from the hand. The effects were similar for both left ($p = 0.003$) and right hand positions separately ($p = 0.07$). In contrast, performance with near and far distractors on stay trials did not differ significantly (96.0 ± 1.1 vs 97.1 ± 0.9%; $d' = 3.30 \pm 0.06$ vs 3.35 ± 0.12, respectively).

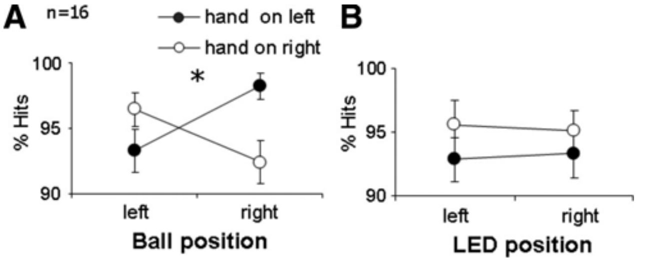

Figure 5. Behavior demonstrates selective response inhibition by distractor balls approaching the hand. Mean ± SE percentage of "hits" for distractor balls (***A***) and LEDs (***B***) presented to the left or right of fixation, separately for the two hand positions (filled circles, left; open circles, right). When the probability of responses on each trial was 0.5 (i.e., a go signal appeared in only one-half of the trials), subjects were prone to inhibit their response to the targets (i.e., to miss) with a concurrent near distractor ball. No such hand-centered modulation of performance was evident with static LED distractors. The asterisk denotes significance of the interaction between hand position and ball position ($*p < 0.05$, two-tailed corrected for two comparisons).

This hand-centered modulation of behavioral performance was also selective for approaching balls, compared with static flashing distractors. Overall, performance was nearly identical between trials with distractor balls (95.8 ± 0.5% correct; $d' = 3.33 \pm 0.06$) and LEDs (95.9 ± 0.6% correct; $d' = 3.33 \pm 0.08$). Contrary to what was found for balls, however, no differences were found between near and far distractor LEDs on go trials (Fig. 5*B*).

These results converge with the MEP data obtained from experiment 4, which showed that the decrease in corticospinal excitability during response preparation is selective for a ball approaching the hand and is not merely attributable to sudden visual changes near the hand in the peripheral visual field. Since the ball and LED distractors differed in several respects (e.g., size, luminance), it is impossible at present to establish definitively which aspects are critical for driving the hand-centered suppression that we report here. However, we found no behavioral evidence (i.e., in RT, percentage correct, or d' measures) to suggest that the two distractor types varied in salience (which might be expected to affect behavioral performance) (see also supplemental Table S2, available at www.jneurosci.org as supplemental material).

Experiment 5b: hand-centered enhancement of corticospinal excitability with response uncertainty

We suggest that our results thus far may best be explained in terms of proactive inhibition during an action selection process: to perform the go task as rapidly and successfully as possible, any avoidance response evoked by the approaching ball needs to be inhibited. According to this account, if subjects were not able sufficiently to prepare a motor response before the appearance of the go signal, the effects of proactive inhibition would not be observed. To test this directly, we used the go/stay task in which, while a distractor appeared on every trial (either a ball or an LED), the go signal appeared on only 50% of the trials (as described above) (Table 1, experiment 5). In this way, we introduced a substantial degree of response uncertainty, forcing subjects to adopt a more conservative response preparation strategy. Subjects were encouraged to perform the task quickly and to refrain from making errors, both misses and false alarms.

Two hypotheses were entertained: first, it is possible that, when no motor response is prepared, there should be no difference between MEP amplitudes on near and far trials, regardless of the visual distractor type (moving ball vs static LED) or response type (go vs stay). Second, in the absence of any preparation to push the response button, the avoidance movement elicited by the approaching ball would remain unchallenged by any competing responses. This might result in greater MEP amplitudes on near relative to far ball go trials. For this experiment, TMS was delivered 70 ms after the appearance of the distractor. Since this experiment was designed to test both a negative (i.e., no difference between near and far ball trials with response uncertainty) and a positive prediction (MEP enhancement with near vs far balls), we used a larger group of subjects ($n = 16$; power $= 0.998$, based on the near vs far effect size for the 80 ms TMS time point of experiment 1).

Contrary to the first hypothesis, and consistent with the second, the TMS results continued to support the notion of hand-centered modulation of MEP amplitude for the go ball trials only. This was demonstrated by a significant effect of distance from the hand for the distractor balls ($t_{(15)} = 2.58$; $p = 0.042$, two-tailed, corrected for two comparisons), but not for the LEDs. Furthermore, the MEPs were now larger for the near ball trials (1.044 ± 0.019), compared with the far ball trials (0.992 ± 0.022). No such trend was found for the stay trials. That is, with no advanced response preparation, MEP amplitude may now reflect the additional excitatory effects of the distractor ball approaching the hand (i.e., a potentially avoidance-related response), early in the process of response selection.

This interpretation is further supported when we focus, *post hoc*, on the trials in which subjects produced a voluntary EMG response (here called a muscle "twitch") (see supplemental material, available at www.jneurosci.org) after the MEP, compared with trials in which no twitch was produced. This analysis was performed regardless of MEP size, whether a response was required, or whether a button press was registered. Within these twitch trials, we found a significant increase of MEP amplitudes for near compared with far trials, and specifically for the distractor balls ($t_{(15)} = 3.13$; $p = 0.014$, two-tailed, corrected for two comparisons) (Fig. 6*A*), but not for the LEDs. Importantly, this result did not depend on differences in EMG baseline activity before the MEP (supplemental Table S4, available at www.jneurosci.org as supplemental material). By sharp contrast, on trials in which no voluntary EMG response occurred, there were no significant effects of distractor distance, either for balls or LEDs. This finding provides direct support for our interpretation of proactive inhibition during response selection: when competition between the avoidance and the go responses was eliminated or, at least, desynchronized, the hand-centered suppression of MEP amplitudes was reversed and became hand-centered enhancement, specifically on those trials in which the hand was most ready to respond.

Additional evidence for the enhancement of MEP amplitudes for "near" trials during response uncertainty is provided in experiment S1, reported in supplemental material (available at www.jneurosci.org). This experiment additionally demonstrates that any contribution of exogenous attentional orienting cannot be solely responsible for the hand-centered coding of approaching objects reported here.

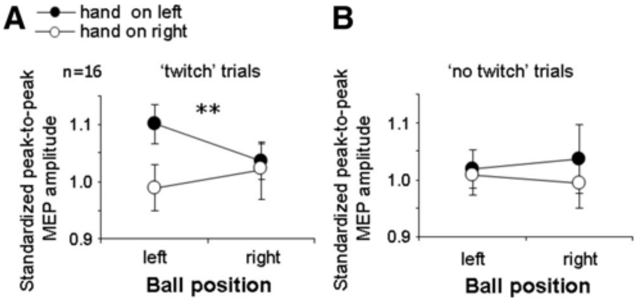

Figure 6. With response uncertainty, late muscle activation predicts hand-centered enhancement of MEP amplitude by approaching balls. Mean ± SE peak-to-peak MEP amplitude for distractor ball trials in which a voluntary EMG activity onset (twitch) was recorded after the MEP (***A***) and for trials in which no late muscle activation was recorded (***B***). On the EMG twitch trials, near distractor balls elicited greater MEP amplitudes, compared with far distractor balls, both in the left and the right hand positions. Importantly, this was not the case for the left and right no twitch trials. The asterisks denote statistical significance of the interaction between hand position and ball position, as evaluated with ANOVA (**$p < 0.01$, corrected for two comparisons).

Experiment 6: precise time course and muscle specificity of hand-centered coding of approaching objects

An additional experiment was run to answer questions concerning the precise time course of the hand-centered modulation of corticospinal excitability. Specifically, across the replications of our basic finding, slight differences arose in latency between the 80 ms (experiments 1 and S1) and the 70 ms time points (experiments 2, 3, and 5b). We hypothesized that the hand-centered effect starts or peaks at ~70 ms and has a duration of ~10–20 ms, perhaps with some intersubject variability in its time course. For this reason, the effect may also be seen at 80 ms after ball appearance.

To test this hypothesis, we repeated experiment 1 with a new group of six subjects, with several minor adjustments (see supplemental material, available at www.jneurosci.org). First, we used five TMS time points between 65 and 85 ms after ball appearance, in 5 ms intervals. Second, we recorded MEPs from both the FDI and the abductor digiti minimi (ADM) muscles. We hypothesized that the excitability of the ADM, which is not directly involved in the task-related index finger abduction response, should not be in competition with any responses elicited by the approaching ball, and therefore should not show hand-centered suppression of MEP amplitudes, contrary to the FDI.

The mean MEP amplitudes across the high-resolution time course are presented in Figure 7. As predicted, we observed the greatest effect of distractor ball position on MEP amplitudes at the 70 ms time point, in which MEP amplitudes were again significantly smaller for near (mean ± SE, 0.862 ± 0.053) compared with far trials ($t_{(5)} = 2.64$; $p = 0.023$, comparing the mean of near distractor ball trials against 1, one-tailed). The mean MEP amplitude pooled across the 70, 75, and 80 ms time points was also significantly lower than one, suggesting that the effect endured for as long as 10 ms. The time course of the effect in individual subjects confirmed this suggestion, with each subject showing at least a 7% suppression of MEP amplitudes for near compared with far trials of at least two adjacent time points (i.e., of ~10 ms), typically at 70–80 ms after ball appearance.

In the ADM, no significant differences were found between the near and far conditions at any of the five time points (all values of $p \geq 0.49$) nor did we observe any clear trends across the time course (supplemental Fig. S2, available at www.jneurosci.org as supplemental material). This result should be interpreted

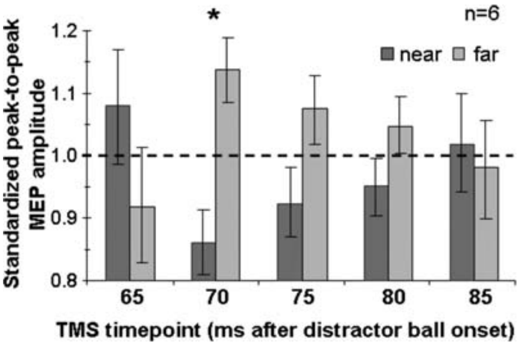

Figure 7. Hand-centered modulation of corticospinal excitability by approaching balls: high-resolution time course. Mean ± SE peak-to-peak MEP amplitude for near and far distractor balls across five TMS time points, at 5 ms temporal resolution (65–85 ms). The captions are as in Figure 2. The asterisk denotes statistical significance of one-tailed *t* tests between the near condition and the null hypothesis of 1.0 (*$p < 0.05$).

with some caution, however, given the relatively small number of subjects and the fact that MEPs were not elicited from one subject's ADM muscle. However, given that we found a significant effect in the FDI in the same group of subjects, even after excluding all the data of the subject without MEPs in the ADM ($p = 0.039$), this result further strengthens our interpretation of proactive inhibition during response selection at 70–80 ms after distractor ball appearance.

Discussion

In the current study, we provide direct evidence for hand-centered coding of approaching visual stimuli during motor preparation. Such a coding was manifested in modulations of corticospinal excitability evoked by presenting three-dimensional visual distractors rapidly approaching subjects' hands. These hand-centered effects were repeatedly observed across independent experiments, occurred when the responding hand was positioned both on the left and on the right of the body midline (Figs. 2, 6, 7), regardless of visual fixation position (Fig. 3), and were dependent on motor response preparation. Furthermore, they did not occur for static distractors (Fig. 4), suggesting that this hand-centered modulation may be specific for potentially aversive approaching distractors, although the latter point awaits confirmation by future studies.

The latency at which visual spatial information began selectively to influence corticospinal excitability was 70 ms after ball appearance, with an effective duration of as short as 10 ms. In this narrow time window, hand-centered processing of visual information had already occurred, even while the visual distractor ball was still falling toward the hand, highlighting the rapidity of the hand-centered coding of visual space identified here.

Proactive inhibition of avoidance movements during response selection

In our study, when a go response was required on every trial and the subjects were able to prepare the appropriate response (i.e., pushing the response button) in advance, a distractor ball approaching near the hand reduced corticospinal excitability at 70–80 ms after ball appearance (experiments 1, 2, 3, and 6) (Figs. 2–4, 7). This reduction may reflect the inhibition of an avoidance-related motor plan, which automatically emerges only when the ball approaches the responding hand (experiment 3) (Fig. 4). Indeed, flexible motor behavior requires the ability to inhibit one movement while concurrently executing another (i.e., selective inhibition) (Coxon et al., 2007). Such inhibition can be effective to suppress undesirable movements not only after they have been initiated but also proactively before any EMG response is released (Boulinguez et al., 2008).

Numerous TMS studies have shown suppression of MEP amplitude during instructed delay periods (foreperiods), which serves to hold back the premature execution of responses (Hasbroucq et al., 1997, 1999a,b; Touge et al., 1998; Davranche et al., 2007). Similarly, during response selection, MEP amplitudes are suppressed for the nonprepared effector and increased for the prepared response (Koch et al., 2006; van Elswijk et al., 2007), but only when sufficient foreperiod information about the response was available to the subjects (Mars et al., 2007; van den Hurk et al., 2007). Likewise, in our study, the reduction of corticospinal excitability by the distractor was evoked only when both advance preparation was possible, and when an approaching, potentially aversive distractor was used. When response uncertainty was introduced, such that the go response could not confidently have been prepared in advance, and a temporal offset was therefore created between the task-related and the avoidance responses, corticospinal excitability was enhanced for active trials in which the ball approached near the responding hand (experiments 4 and S1) (Fig. 6; supplemental Fig. S1, available at www.jneurosci.org as supplemental material). Conversely, for a muscle that did not participate in the preparation for the go response (i.e., the ADM), no hand-centered modulation of corticospinal excitability was observed. In other words, when competition between the avoidance and go responses is eliminated (or temporally desynchronized), no suppression of the avoidance response is required, and an active component of the avoidance movement may be revealed in the MEP amplitude. Our results therefore indicate an interaction between the motor consequences of the rapid visual processing of objects approaching the hand and the voluntary task-related motor plans for that hand.

Mechanisms underlying rapid visual modulation of corticospinal excitability

Threat-induced freezing

The early onset of corticospinal modulations in the present study (70–80 ms after the appearance of the ball) reflects the very rapid transformation of visuomotor information. One possible framework within which to interpret our results could be threat-induced startle or freezing responses. A recent functional magnetic resonance imaging study (Butler et al., 2007) reported decreased activity in bilateral primary motor cortex during periods in which subjects expected to receive painful stimuli (compared with a condition without pain expectation). Using TMS, Cantello et al. (2000) found a significant reduction of corticospinal excitability at 55–75 ms after the onset of unexpected, sudden, and very bright task-irrelevant light flashes. Similar results were reported after the presentation of electrical shocks (Maertens de Noordhout et al., 1992) or loud auditory stimuli (Furubayashi et al., 2000). Pain-inducing stimulation to the hand also causes immediate (Urban et al., 2004) and long-lasting (Farina et al., 2001; Svensson et al., 2003) decreases of corticospinal excitability for distal arm muscles. Furthermore, MEPs were inhibited at later stages of processing (>1 s after stimulus presentation) when subjects passively viewed movies of painful simulation applied to specific muscles on a model (Avenanti et al., 2005). It has been suggested that such inhibition may act as a sort of motor "decerebration," allowing the spinal motor system freely to develop protective responses after noxious stimulation (Farina et al., 2003).

We believe that the results described in the studies mentioned above do not directly correspond with our findings, and that pain- or startle-related inhibition cannot explain the results we report here, for two reasons. First, it cannot explain the reversal of the direction of hand-centered modulation when subjects could not confidently prepare a response in advance. Second, the time course of startle-related inhibition based on TMS studies (Cantello et al., 2000) just precedes the corticospinal modulations reported here, which are restricted to 70–80 ms after distractor ball appearance. Furthermore, Cantello et al. (2000) did not provide (or search for) evidence for any hand-centered mechanisms, so any direct links with our results remain speculative. We therefore propose that, although fear-induced startle might play some role in the mechanism under investigation, our hand-centered modulation represents a later stage of selection between an appropriate avoidance/defensive response and the task-related response.

Cortical mechanisms

Numerous cortical areas have been shown to modulate corticospinal excitability and may therefore contribute to the results reported here. These include the primary somatosensory area (Avenanti et al., 2007), posterior parietal areas, and the premotor cortex (for review, see O'Shea et al., 2008).

Cooke and Graziano (2003) studied macaque muscle activity during defensive movements evoked by aversive cutaneous stimulation. They distinguished between startle-related EMG activity occurring as early as ~20–30 ms after stimulus onset and later muscle activity starting ~70 ms after stimulus onset [Cooke and Graziano (2003), their Fig. 2*C*]. Only the latter activity was spatially specific to the muscles involved in the defensive response. Very similar motor responses were evoked by electrical macrostimulation of bimodal regions of the premotor cortex (Graziano et al., 2002). Indeed, M1 and the premotor cortex are densely interconnected, both in humans and in monkeys (Shimazu et al., 2004; Dum and Strick, 2005; Koch et al., 2006; O'Shea et al., 2007; Davare et al., 2008). The modulation of MEP amplitude with respect to approaching balls that we report here may therefore reflect ongoing activity in the premotor cortex.

Some premotor neurons are active after visual stimulation at time periods similar to the ones we have described and are thought to encode the significance of visual cues for response selection (Cisek and Kalaska, 2005). In humans, the premotor cortex has been shown to participate in the visuomotor transformations required to configure hand posture with respect to objects (Davare et al., 2006). Furthermore, recent studies have shown a direct influence of premotor over primary motor cortex as early as 75 ms after a go signal (Koch et al., 2006; O'Shea et al., 2007). Although any comparisons between data drawn from monkeys and humans, and using such different methods, should be made with caution, given the timing and the spatial specificity of the above responses with respect to visual events, these mechanisms fit very well with our results and suggest the involvement of human premotor areas with the hand-centered coding of visual space. Following Band and van Boxtel (1999), we tentatively suggest that one source of the hand-centered modulation that we report may be the premotor cortex, the site of modulation may be the primary motor cortex, and the modulation is manifested by changes in MEP amplitudes (Band and van Boxtel, 1999).

Pruszynski et al. (2008) demonstrated rapid arm muscle responses that were sensitive to the direction and distance of visual targets at 95 ms after a go signal. This timing fits very well with our findings, assuming a 20–25 ms conduction time between the primary motor cortex and the intrinsic hand muscles. Pruszynski and colleagues suggested that such rapid motor responses are capable of all the sophistication attributed to voluntary control, within the constraints of their limited processing time. Additional research is required to determine the precise neurophysiological mechanisms that might enable such rapid and sophisticated visuomotor spatial processing in the human brain.

Subcortical mechanisms

In monkeys, spinal interneurons have been shown to participate in the control of movement during preparation periods, displaying both excitatory changes in the same direction as the subsequent movement-related activity, and inhibitory changes that may reflect superimposed mechanisms suppressing muscular output (Prut and Fetz, 1999). It is possible that the hand-centered modulation that we observed reflects such subcortical movement preparation, although it is important to note that, in our results, the critical movement selection processes occurred based on the position of the visual distractor ball relative to the responding hand, so any candidate subcortical source of the reported modulations of corticospinal excitability would have to have access to such information.

Hand-centered visual space and attention

In our experiments, both near and far balls were distractors; however, it is possible that near distractors were more salient than far distractors and that this somehow resulted in reduced levels of corticospinal excitability. Such differences in salience could have been the result of subjects covertly attending toward their responding hand, despite the instructions and the central visual task. We addressed these concerns in several experiments.

First, when the balls were substituted with LEDs positioned near and far from the hand, we found no significant hand-centered modulations of corticospinal excitability (experiment 4) (Fig. 3) or of percentage correct performance (experiment 5) (Fig. 5). Second, we manipulated subject's overt attention, by shifting their fixation between positions on the same or opposite side as the impending distractor ball (experiment 2). When shifting the fixation position with respect to the ball and hand positions, we found a small, but nonsignificant difference between balls approaching the same side, and balls approaching the opposite side of fixation (Fig. 3). At the same time, however, the distance of the ball from the hand (manipulated orthogonally and independently from the distance from fixation) significantly modulated corticospinal excitability. Finally, we used a cueing paradigm to attract subjects' exogenous covert visuospatial attention toward versus away from the distractor ball, just before its appearance (experiment S1; supplemental Fig. S1*A*; supplemental material, available at www.jneurosci.org). Again, this manipulation did not significantly modulate corticospinal excitability, while the distance of the distractor from the hand remained most effective (albeit marginally significantly), regardless of whether subjects' attention was cued toward or away from the hand (supplemental Fig. S1*B*, available at www.jneurosci.org as supplemental material).

We therefore conclude that the role of overt and covert visuospatial attention in the results that we report here is marginal, or, at most, complementary, to the role of hand position. A rapid and automatic hand-centered response to potentially aversive approaching visual stimuli is a better description of our results as a whole.

Conclusions

We demonstrate here that the human motor system is rapidly informed about potential collisions between nearby objects and specific body parts that are about to move. This specialized system for transforming nearby sensory inputs into rapid and appropriate motor outputs is ideally suited to serve as a sensorimotor interface for driving defensive movements away from potentially harmful approaching objects.

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SUPPLEMENTAL MATERIALS

General methods

Subjects

Healthy right-handed subjects (n = 23; 12 female; mean±s.e. age=29.9±1.3 years, range=22-47 years; mean±s.e. handedness laterality quotient=88.1±1.7, range=38-100, Oldfield, 1971) were recruited from the local population of research staff and students, and gave their written, informed consent to participate. Over the course of twenty-five months, individual subjects participated in a mean±s.e. of 3.0±1.3 experiments (range=1-7), with a mean±s.e. duration between experimental sessions of 108±26 days (range=3-598) (Supplemental Table S1). There were seven independent experiments, involving transcranial magnetic stimulation (TMS), and electromyographic (EMG) and motor-evoked potential (MEP) measurements. Behavioral data were extracted from one of the TMS experiments (Experiment 5a) and are presented separately from the MEP data (Experiment 5b) in the main text. Of the seven TMS experiments, five longer experiments were conducted on different days, and two shorter experiments were conducted in different blocks on the same day in the same subjects.

Additional apparatus, materials, & data acquisition

PCs

All stimulus presentation and response collection was controlled via the parallel port of one PC running in MS DOS and programmed using TurboPascal. This PC sent trigger signals to a second PC running the EMG data acquisition software ('EMG PC'). The EMG PC received 2 or 3 channels of input from a BioPac (http://www.biopac.com) data acquisition unit via the USB port.

Apparatus

A custom apparatus was built to control stimulus delivery. Two stimulus arms were mounted in a wooden frame (50 x 76 x 80cm depth x height x width) on a rotating wheel, attached to the far side of the frame from the subjects' perspective. The side of the frame closest to the subjects was open, enabling the subjects to position their hand in the workspace. The upper half of the workspace was occluded from the subjects' sight by a dark fabric curtain, determining the point of initial visibility of the arm-mounted balls when falling downwards (Figure 1, Supplemental Movie 1 and 2).

An LED panel, mounted on the rear of the frame and invisible to the subject, was used to instruct the experimenter regarding the timing and position of 3D stimulus delivery.

Procedures

After giving informed written consent, subjects completed a handedness questionnaire (Oldfield, 1971), and the experimenter explained the task. The skin over the belly of the subjects' first dorsal interosseus (FDI) muscle, the distal insertion of the muscle (the base of the forefinger), and at the styloid process of the ulna (the lateral bony protrusion at the wrist) of the right wrist was prepared, and an electrode was positioned at each site. A tight-fitting cap was placed on subjects' heads. The distances along the axes between the inion and nasion, and between the tragi of the two ears were measured, and the intersection of the two axes was defined as the vertex. The approximate expected location of the left primary motor cortex hand area was marked on the cap. One experimenter then began searching for the hand area of the motor cortex, using single pulses of TMS to elicit visible muscle contractions selectively in the FDI of the right hand. The second experimenter inspected the EMG trace and the MEPs. The position and orientation of the TMS coil and the intensity of the single pulses was varied to elicit reliable MEPs in the FDI (Supplemental Table S1).

Throughout each experiment, the TMS coil was held in place by a mechanical arm and tripod, and one experimenter stood directly behind the subject, continuously monitoring the coil position, and correcting the position of the head and/or coil following any small (~2mm) head movements. The second experimenter controlled the hardware and stimulus presentation. If MEPs were not observed in two or three consecutive trials, the TMS coil was repositioned. Trials with absent MEPs (defined as a peak-to-peak amplitude of <0.25mV) were excluded during data analysis.

Analysis

MEP/EMG

Offline, the data were segmented into 2s epochs, linear trends were removed with a high-pass filter, and MEP data were extracted. Following the end of the MEP, EMG data were rectified, and a number of parameters describing the EMG data were extracted: 1) The mean and standard deviation of rectified EMG between 30-60ms after trial onset (in Experiment 1, between 1-30ms), and; 2) The onset of voluntary EMG activity, defined as the first time-point after the offset of the MEP for which the following 10ms had a mean EMG activity greater than 3.09 standard deviations above the baseline mean (i.e., where $p<0.001$) EMG activity (see Hodges and Bui, 1996). These parameters were chosen primarily for their robustness in ignoring any small spikes of EMG activity, which were not followed by full EMG responses. These same onset criteria were used to determine EMG 'twitches' in Experiment 5b.

MEP pre-processing: Regressing-out the effect of RT on MEP amplitude

The measurement of MEP amplitude reflects excitability of the corticospinal tract, and may therefore be affected by the motor responses that the subjects were performing in the task. Indeed, throughout the experiments, shorter RTs (faster responses) were associated with greater peak-to-peak MEP amplitudes (Supplemental Table S2). Importantly, this negative correlation between RT and MEP amplitude cannot explain our principal finding of smaller MEP amplitude for *near*, *as* compared to *far* ball trials: Since RTs were overall slightly *shorter* for *near* than *far* trials (Supplemental Table S2), they should therefore elicit *larger* MEP amplitudes than *far* trials, if RT was the only variable influencing MEP amplitude. Nevertheless, in order to reduce the influence of RT on MEP amplitudes, we regressed out the effect of RT on MEP amplitude, pooling the data across all conditions. This was done for each subject in each experiment, by adjusting the MEP amplitudes based on the slope of the regression of MEP amplitude on RT, as follows:

$$rMEP_i = MEP_i + m((\Sigma RT/n) - RT_i)$$

where $rMEP_i$ = regressed MEP amplitude for trial i; MEP_i = original MEP amplitude for trial i; m = slope of the regression of MEP on RT across all trials for this subject; $\Sigma RT/n$ = mean RT of this subject across all trials; RT_i =

individual RT for trial i. As can be seen in Supplemental Table S3, this procedure increased the t-statistics and decreased the p-values for several of the *near* vs. *far* comparisons, but in no cases did this result in a ‘non-significant’ effect becoming ‘significant’ or vice versa.

‘Bootstrap’ analysis of main reported findings

For each comparison reported in Supplemental Table S6, the data from the significant or principle condition of interest (e.g., the *near* distractor ball trials with TMS delivered at 70ms after distractor appearance) were compared against a null distribution. The null distribution was constructed by randomly sampling with replacement one data point per subject from all the data pooled across several conditions (e.g., pooled across the *near* and *far* distractor ball trials and across all TMS time-points). The mean across these (e.g., ten) data points was recorded, and the resampling process was repeated 10,000 times for each comparison of interest. The obtained means were given a 'p' value by counting the number of resampled means that were lower (or higher, depending on the prediction) than the actual mean from the null distribution, and dividing by 10,000. p-values lower than 0.05 were considered significant. All the raw data and the Octave/Matlab scripts used to run these resampling procedures are available from http://www.neurobiography.info.

Experiment 6

The experimental design of Experiment 1 was repeated, with the following changes: A MagStim (Magstim Company Ltd.) Rapid2 stimulator was used and two pairs of Delsys bar electrodes, one attached to the FDI and another attached to the ADM, both on the right (responding) hand. The reference electrode was placed over the bone near the elbow (the olecranon process). The position and orientation of the TMS coil, and the intensity of the single pulses, was optimised for each subject in order to elicit reliable MEPs both in the FDI and the abductor digiti minimi (ADM). The MEP peak-to-peak amplitude criterion for establishing the resting motor threshold (RMT) was reduced to 0.05mV, and during the experiment we stimulated at 117% of this RMT. Since the signal to noise ratio was higher, and the bar electrodes closer together using the new apparatus, the exclusion criterion for excluding MEPs as being indiscernible from the baseline was decreased to a peak-to-peak amplitude of 0.05mV for the FDI and 0.025mV for the ADM. One subject's ADM data were excluded from the analysis, after discarding, or else failing to observe, MEPs from 67% of the trials.

Supplemental Results

Experiment S1: Hand-centred coding of visual space is independent of visuospatial attention shifts

It is possible that distractor balls approaching *near* the subjects' hand were more salient visual stimuli, as compared with balls approaching the *far* position, because subjects may have been selectively attending towards their responding hand or to the space nearby. One way to test this hypothesis would be to manipulate the location of subjects' exogenous attention (e.g., Klein & Shore, 2000; van der Lubbe and Postma, 2005), either towards or away from the upcoming distractor ball, with the prediction that directing attention towards the distractor position should increase its salience, and therefore modify the hand-centred effect. For this final experiment, we used the same group of subjects as in Experiment 2, with a slightly modified experimental design (see Experiment S1, Table 1, and Supplemental Figure S1A): A peripheral cue (red LED) was illuminated 75ms before distractor ball appearance, either to the left or to the right of central fixation, with equal probability for each position. The 'Go' signal appeared in only 75% of trials, thus creating response uncertainty, as in Experiment 5.

At the 70ms TMS time-point, we found no significant effect of the distance of the distractor ball from either the hand or from the peripheral cue. However, at the 80ms time-point we found a marginally significant effect of distractor ball distance from the hand, regardless of its position relative to the peripheral cue (t(9)=1.74, p=0.058, 1-tailed, compared against 1.0): As in the 'Go/Stay' task (Experiment 5), mean MEP amplitude was greater when distractor balls were presented *near* to (1.050±0.029), as compared to *far* from the hand (0.950±0.029). No such effect was found for the distance of the distractor ball from the peripheral cue (1.006±0.013 vs. 0.994±0.013 for near and far trials, respectively, t(9)=0.48, p=0.323, Supplemental Figure S1B). This result supports our claim that corticospinal excitability is modulated in a hand-centred manner, and is unaffected by the presentation of exogenous spatial cues prior to the appearance of the distractor stimulus.

Supplemental References

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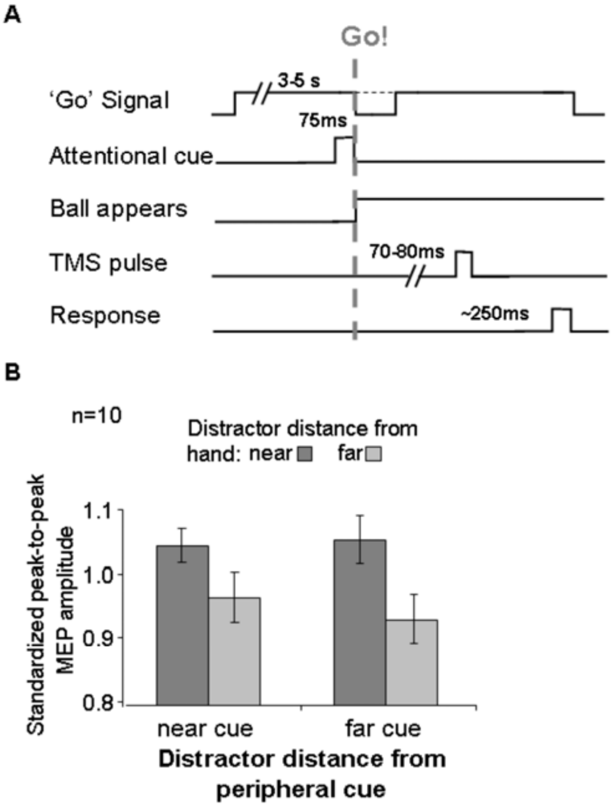

Figure S1. Cueing participants' exogenous attention towards or away from the location of the distractor ball does not abolish hand-centered modulation of corticospinal excitability

(A) Time course. A 'Go' signal appeared in 75% of the trials, while distractor balls appeared on every trial. An irrelevant peripheral cue (LED) appeared pseudorandomly on the left or right side of the workspace, 75ms before the appearance of the ball. 70 or 80ms after the appearance of the distractor ball, a single pulse of TMS was delivered to the left primary motor cortex, contralateral to the participant's responding (right) hand. (B) Mean±s.e. peak-to-peak MEP amplitude for the 80ms TMS time-point showed a marginally significant effect ($p=0.058$) of distractor ball distance relative to the hand (dark gray=near to the hand, light gray=far from the hand).

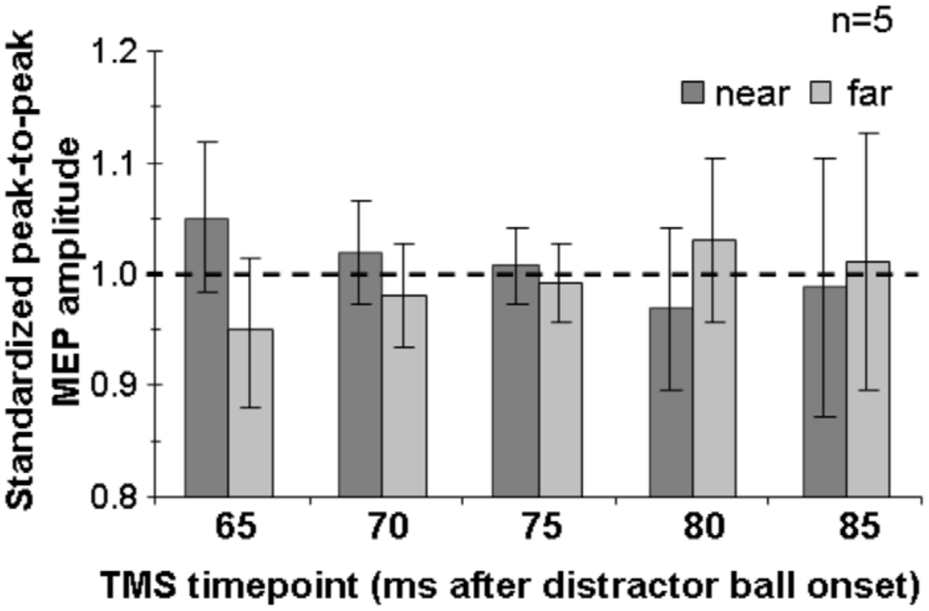

Figure S2: No hand-centred modulation of MEP amplitude for the abductor digiti minimi (ADM) muscle

Mean±s.e. peak-to-peak MEP amplitude for near (dark gray) and far (light gray) distractor balls across all TMS time-points (65-85ms). We found no significant differences in MEP amplitude between *near* and *far* trials at any of the measured time-points. Since the ADM did not participate in the task-relevant ‘Go’ response, this result strengthens our interpretation of the proactive inhibition of ball-related avoidance movements during the preparation of a competing voluntary movement.

Table S1: Subjects and TMS parameters

Experiment		Subjects		TMS					
	N [male]	Age, years	Hand., LQ	Distance from vertex, cm		Threshold intensity, %		Test intensity, %, relative to:	
				Lateral†	Anterior	0.05mV§	0.5mV	max output	0.05mV threshold
1: Time-course	10 [6]	31.2±2.0	87.5±4.0	6.1±0.2	0.9±0.2	57.5±4.5	60.8±4.0	66.0±3.8	114±2.4
		(23-43)	(65-100)	(5.0-7.0)	(0.0-2.0)	(46-68)	(46-76)	(48-83)	(107-118)
2: Eye position	10 [5]	31.8±2.2	84.3±4.1	5.9±0.2	1.0±0.1	64.1±5.3	67.2±4.2	72.3±4.4	114±2.3
		(25-43)	(65-100)	(5.0-6.5)	(0.5-1.5)	(46-87)	(52-87)	(54-90)	(103-124)
3: ‘Go/Stop’ Balls	10 [5]	31.2±2.0	87.0±4.5	6.3±0.2	1.0±0.2	57.0±3.6	65.4±2.7	71.9±2.9	122±1.3
		(26-43)	(65-100)	(5.5-7.0)	(0.0-1.6)	(46-68)	(53-78)	(58-85)	(118-126)
4: ‘Go/Stop’ LEDs	9‡ [6]	31.5±2.3	85.9±3.9	5.7±0.1	0.8±0.1	60.5±4.3	63.5±3.7	69.4±4.0	116±2.5
		(22-43)	(65-100)	(5.0-6.5)	(0.0-1.0)	(46-87)	(48-87)	(50-90)	(101-130)
5: ‘Go/Stay’	16 [6]	30.1±1.9	84.3±4.4	6.0±0.2	1.1±0.1	57.6±3.5	65.6±2.5	68.9±2.5	118±2.4
		(22-47)	(38-100)	(4.0-7.0)	(0.0-2.0)	(46-68)	(50-86)	(52-88)	(112-125)
S1: Exog. Attention	10 [5]	31.8±2.2	84.3±4.1	5.9±0.2	1.0±0.1	64.1±5.3	67.2±4.2	72.4±4.4	114±2.3
		(25-43)	(65-100)	(5.0-6.5)	(0.5-1.5)	(46-87)	(52-87)	(55-90)	(103-124)
6: Selectivity (FDI)	6[3]	30.8±0.9	85.1±4.6	5.0±0.3	0.8±0.1	60.7±3.5	(not tested)	71.7±4.0	118±0.7
		(27-33)	(70-100)	(4.0-6.0)	(0.3-1.0)	(52-75)		(61-88)	(117-121)

Values show mean±s.e. Values in parentheses show ranges. N: Sample size; Hand.: Handedness; LQ: Laterality Quotient (Oldfield, 1971); TMS: Transcranial Magnetic Stimulation; †Left of the mid-sagittal plane; §Based on a minimum of 4 subjects per experiment; ‡1 subject’s data were lost due to hardware failure; Exog.: Exogenous.

Table S2: Behavioral performance, RT-MEP correlations, and standardization procedures

Experiment	**Performance**				**RT-MEP correlation**	**Standardization by**	
	% valid	**RT (ms)**		**d’**			
		Near	**Far**		**Pearson’s r**	**Trial types**	**TMS time-point**
1: Time-course	95.1±1.9	254±15	257±15	n/a	-0.096±0.064	All	Yes
2: Eye position	98.1±0.5	246±7	262±15	n/a	-0.057±0.039	No ball	Yes
3: ‘Go/Stop’ Balls	98.1±0.3	295±11	302±15	3.71±0.03	-0.148±0.043**	No ball	Yes
4: ‘Go/Stop’ LEDs	98.2±0.6	307±12	309±11	3.79±0.06	-0.125±0.046*	No ball	Yes
5: ‘Go/Stay’	95.8±0.5	370±13[‡]	379±12[‡]	3.33±0.05	-0.138±0.038**	All	n/a
S1: Exog. Attention	92.2±1.5	299±9	293±7	2.79±0.21	-0.038±0.053	Go	Yes
6: Selectivity (FDI)	97.8±0.9	270±20	273±20	n/a	-0.211±0.032**	All	Yes

Values are mean±s.e. RT: Reaction time; MEP: Motor evoked potential peak-to-peak amplitude; ‡Ball trials only; *p<0.05, 2-tailed; **p<0.01, 2-tailed; n/a: Not applicable; Exog.: Exogenous.

Table S3: Effects of data preprocessing on the main reported findings: Comparison of t-statistics

Experiment	Near vs. far effect		Raw data			First stage[†]			Second stage[‡]		
	TMS time-point (ms)	**Condition**	**d.f.**	**t**	**p**	**d.f.**	**t**	**p**	**d.f.**	**t**	**p**
1: Time-course	80	Balls	**9**	**2.66**	**0.026**	**9**	**3.05**	**0.014**	**[*]9**	**4.08**	**0.003**
2: Eye position[#]	70	Balls	**9**	**2.49**	**0.017**	**9**	**2.24**	**0.026**	**9**	**2.41**	**0.020**
3: ‘Go/Stop’ Balls[#]	70-90	‘Go’, Balls	**9**	**2.40**	**0.020**	**9**	**2.12**	**0.032**	**9**	**2.45**	**0.018**
4: ‘Go/Stop’ LEDs[#]	70-90	‘Go’, LEDs	8	0.56	0.295	8	0.15	0.442	8	0.15	0.442
5: ‘Go/Stay’[§]	70	‘Go’, Balls	**15**	**2.81**	**0.013**	**15**	**2.68**	**0.017**	**15**	**2.57**	**0.021**
5: ‘Go/Stay’[§]	70	‘Go’, LEDs	15	1.07	0.302	15	0.70	0.495	15	1.04	0.315
5: ‘Go/Stay’[§]	70	‘Twitch’, Balls	**15**	**3.14**	**0.007**	**15**	**2.88**	**0.011**	**15**	**3.13**	**0.007**
5: ‘Go/Stay’[§]	70	‘Twitch’, LED	15	0.41	0.688	15	0.37	0.717	15	0.72	0.483
S1: Exog. Attention[#]	80	Balls	9	1.13	0.144	9	1.25	0.121	9	1.74	0.058
6: Selectivity (FDI)[#]	70	Balls	**5**	**2.33**	**0.034**	**5**	**2.60**	**0.024**	**[*]5**	**2.64**	**0.023**

Significant effects are highlighted in bold font. *Data compared against 1.00; †Experiments 1, 5, & S1: Regression; †Experiments 2, 3, & 4: Standardization; ‡Experiments 1, 5, & S1: Standardization; ‡Experiments 2, 3, & 4: Regression; #Hypothesis-driven 1-tailed t-tests, based on the results of Experiment 1; §Regressed by ‘Go’ trials only; d.f.: Degrees of freedom; t: t-test statistic; p: p-value; Exog. = Exogenous.

Table S4: Effects of mean baseline EMG activity on the main reported findings: Comparison of t-statistics

Experiment	MEP-EMG baseline correlation (Pearson's r)	Near vs. far comparison on mean EMG baseline				
		TMS time-point (ms)	Condition	d.f.	t	p
1: Time-course	**0.185±0.052**	80	Balls	9	0.16	0.875
2: Eye position	0.051±0.055	70	Balls	9	0.56	0.590
3: 'Go/Stop' Balls	-0.039±0.027	70-90	'Go', Balls	9	1.16	0.276
4:'Go/Stop' LEDs	0.054±0.054	70-90	'Go', LEDs	8	0.89	0.401
5: 'Go/Stay'	**0.155±0.031**	70	'Go', Balls	15	1.89	0.078
		70	'Go', LEDs	15	0.87	0.398
		70	TwitchBalls	15	1.24	0.233
		70	TwitchLED	15	0.74	0.469
S1: Exog. Attention	0.039±0.044	80	Balls	9	0.89	0.198
6: Selectivity (FDI)	0.053±0.042	70	Balls	5	1.94	0.111

Significant effects are highlighted in bold font; Exog.: Exogenous.

Table S5: Effect of hand position on MEP peak-to-peak amplitude: Comparison of t-statistics

Experiment	TMS time-point (ms)	Trials	MEP amplitude (mean±s.e.) per hand position		d.f.	t	p
			Left	Right			
1: Time-course	80	All	0.880±0.038	1.120±0.038	**9**	**-3.15**	**0.012**
2: Eye position	70	All	0.980±0.030	0.996±0.053	9	-0.33	0.749
3: ‘Go/Stop’ Balls	70-90	‘Go’	0.958±0.024	1.022±0.22	9	-1.76	0.112
4: ‘Go/Stop’ LED	70-90	‘Go’	1.014±0.025	1.046±0.025	8	-0.92	0.384
5: ‘Go/Stay’	70	‘Go’ ball	1.040±0.028	0.986±0.033	15	1.04	0.315
5 ‘Go/Stay’	70	‘Go’ LED	1.016±0.025	0.951±0.022	15	1.58	0.135
S1: Exog. Attention	80	All	1.002±0.038	0.988±0.036	9	0.18	0.861
6: Selectivity (FDI)	70	All	0.830±0.063	1.170±0.063	**5**	**-2.95**	**0.032**

Significant effects are highlighted in bold font. MEP: Motor evoked potential; d.f.: Degrees of freedom; t: t-statistic (negative value indicates greater MEP amplitude for the right hand position); p: p-value; Exog.: Exogenous.

Table S6: Comparison of ‘t’ and ‘bootstrap’ statistics

Experiment	**Near vs. far effect**		**T-test‡**			**Bootstrap**	
	TMS time-point (ms)	**Condition**	**d.f.**	**t**	**p**	**TMS time-points**	**p**
1: Time-course	80	Balls	**‡9**	**4.08**	**0.003**	40-120	**0.006**
2: Eye position	70	Balls	**9**	**2.41**	**0.020**	70, 80	**0.018**
3: ‘Go/Stop’ Balls	70-90	‘Go’, Balls	**9**	**2.45**	**0.018**	E, L	**0.021**
4: ‘Go/Stop’ LEDs	70-90	‘Go’, LEDs	8	0.15	0.442	E, L	0.051
5: ‘Go/Stay’	70	‘Go’, Balls	**15**	**2.57**	**0.021**	70	**0.012**
5: ‘Go/Stay’	70	‘Go’, LEDs	15	1.04	0.315	70	0.170
5: ‘Go/Stay’	70	‘Twitch’, Balls	**15**	**3.13**	**0.007**	70	**0.005**
5: ‘Go/Stay’	70	‘Twitch’, LED	15	0.72	0.483	70	0.245
S1: Exog. Attention#	80	Balls	9	1.74	0.058	70, 80	**0.045**
6: Selectivity (FDI)#	70	Balls	**‡5**	**2.64**	**0.023**	65-85	**0.021**

Significant effects are highlighted in bold font. ‡Data compared against 1.00; #Hypothesis-driven 1-tailed t-tests, based on the results of Experiment 1; §Regressed by ‘Go’ trials only; d.f.: Degrees of freedom; t: t-test statistic; p: p-value; Exog. = Exogenous; E = Early; L = Late.

The results of study 1 show that the location of a visually available three-dimensional object near to the body is coded in a reference frame that is centred on the body-part (the hand in the experiment present here) and that this information is rapidly available to the motor system. The results of the study 1 in this respect, support the idea that peripersonal space can play a role not only in the mere detection of visual information close to the body but also in subserving the possible consequent motor reaction. In particular, an effect of inhibition of irrelevant motor plans seems to be elicited by the suddenly appearance of an object near the hand. Possibly, this inhibition of irrelevant plans would be meant to readily prepare to an avoidance movement.

However, as previously pointed out, the same multisensory interface might be involved in other kinds of body-object interactions, where the body-part is voluntary projected toward the object location in order to manipulate it, such as in the everyday life when we grasp an object. The next study will thus investigate this possibility, employing the paradigm of the cross-modal congruency effect, adaptively modified for assessing the multisensory interaction during the execution of action. Participants were requested at each trial to grasp the object with the right stimulated hand index finger and thumb in a precision grip. At the same time, participants were requested to respond to the tactile target discriminating their elevation ("up" or "down") on the grasping hand, trying to ignore the visual distractors embedded into the to-be-grasped object. The visuo-tactile stimulation was presented at one of three different timings with respect to the execution of the action: Either in a static phase, when the grasping hand had not yet moved; At the onset of the movement (0 ms); Or, in the early execution phase (200 ms after movement onset).

When participants performed the action with the tactually stimulated hand, the multisensory interaction was enhanced (i.e., there was more interference from the visual distractor on the tactile task) as compared to the static phase. This effect was even more pronounced when the multisensory interaction was assessed during the early execution phase of the grasping.

The experiment was also repeated asking participants to grasp the object with the non-stimulated hand. Crucially, when the same action was performed with the non-stimulated hand, no multisensory modulation was observed.

The co-recording of the kinematics of the movement for each grasping action performed by participants, provided a quantitative description of the motor performance. On one hand this could rule out any possible confounds of differences in the left/right hand movements; on the other hand, it provided the necessary information in order to investigate the links possibly existing between the multisensory peripersonal space modulation during action and the action itself.

STUDY 2

Grasping actions remap peripersonal space

NeuroReport (2009)

Grasping actions remap peripersonal space

Claudio Brozzoli[a,b], Francesco Pavani[c,d], Christian Urquizar[a], Lucilla Cardinali[a,b] and Alessandro Farnè[a,b]

The portion of space that closely surrounds our body parts is termed peripersonal space, and it has been shown to be represented in the brain through multisensory processing systems. Here, we tested whether voluntary actions, such as grasping an object, may remap such multisensory spatial representation. Participants discriminated touches on the hand they used to grasp an object containing task-irrelevant visual distractors. Compared with a static condition, reach-to-grasp movements increased the interference exerted by visual distractors over tactile targets. This remapping of multisensory space was triggered by action onset and further enhanced in real time during the early action execution phase. Additional experiments showed that this phenomenon is hand-centred. These results provide the first evidence of a functional link between voluntary object-oriented actions and multisensory coding of the space around us. ***NeuroReport*** **00:000–000 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

The representation of the space near the body, termed 'peripersonal' space (PpS) [1,2], relies on multisensory processing, both in human and non-human primates. In monkeys, bimodal neurons in parieto-frontal and subcortical structures code for tactile events on a body part (e.g. the hand) and visual events near that body part, thus giving rise to body-centred representations of PpS [3–6]. In humans, a functionally homologous coding of PpS is largely supported by behavioural studies showing stronger visuotactile interaction in near rather than far space in brain-damaged [7–9] and healthy individuals [10–13]. For example, visual events occurring in the immediate proximity to the body induce more severe tactile extinction than farther ones [7–9]. Recent functional neuroimaging studies further support the existence of similar multisensory integrative structures in the human brain [11–13].

Despite the large body of knowledge accumulated across species on the multisensory properties of PpS, little is known about its function, and this issue has never been directly assessed in humans. By acting as an anticipatory sensorimotor interface, PpS may serve early detection of potential threats approaching the body to drive involuntary defensive movements [3]. The same anticipatory feature, however, may also have evolved to serve voluntary object-oriented actions [1,2,14]. Here, we tested the latter hypothesis by assessing the effects of grasping objects on the multisensory coding of PpS.

In Experiment 1, we modified a cross-modal paradigm [10], whereby participants indicate the elevation (up or down) of a tactile target delivered to a finger (index or thumb), while a visual distractor is presented at either congruent or incongruent elevation (Fig. 1). We then conducted three experiments in which participants were additionally required to grasp the object in which the visual distractors were embedded. Although the perceptual task was always performed on the right hand, the motor task was performed by either the right (Experiments 2 and 4) or left (Experiment 3) hand. This simple manipulation is crucial in two respects: it equalizes attentional demands for the target object in the stimulated and the nonstimulated hand actions, and it allows assessing whether any modulation of multisensory processing is hand-centred.

Experimental procedures

Participants

Fifteen healthy participants (nine men, mean age 27 ± 5 years) took part in Experiments 1, 19 (10 men, mean age 26 ± 6 years) in Experiments 2 and 3, and 16 (8 male, mean age 25 ± 3) in Experiment 4. All gave their verbal informed consent to take part in this study, approved by the local INSERM Ethics Board.

Supplementary data are available at The NeuroReport Online (*http://links.lww.com/A1251*; *http://links.lww.com/A1250*; *http://links.lww.com/A1249*; *http://links.lww.com/A1248*; *http://links.lww.com/A1247*; *http://links.lww.com/A1246*)

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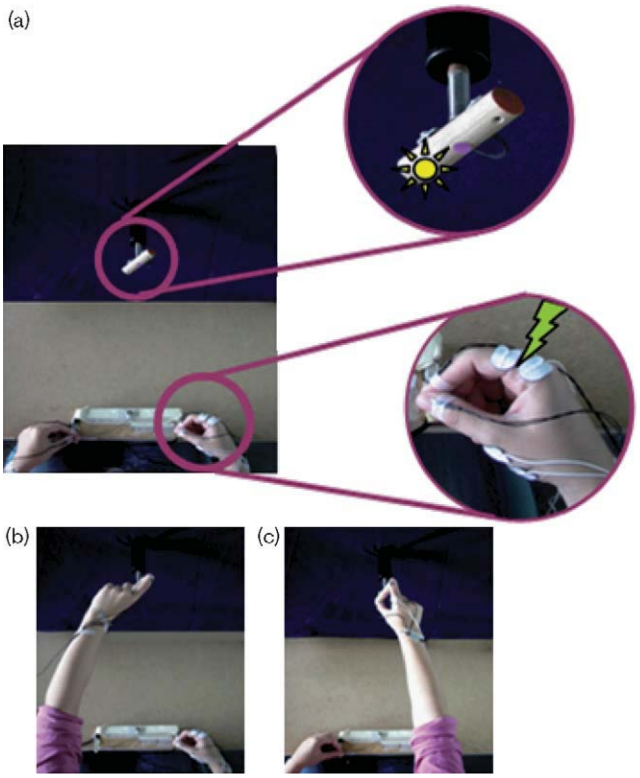
Fig. 1



Experimental setup. (a) Bird's eye view of the participant facing the cylinder (upper inset) with both hands in a pinch-grip position (lower inset). Electro-cutaneous targets (green zap) were delivered to the index finger (up) or thumb (down), while a visual distractor (yellow flash) could be presented from either the same (congruent, not shown) or different (incongruent) elevation. Grasping the clockwise tilted object required an inward wrist rotation of the left hand (b) but an outward wrist rotation of the right hand (c), the opposite pattern being required for the anticlockwise orientations.

Apparatus

A cylinder (7-cm height, 1.7-cm diameter) was presented in one of four orientations (18 and 36° clockwise or anticlockwise) 47 cm from the participant's hand. Visual distractors consisted of an LED flash (200 ms) delivered concurrently with the electro-cutaneous stimulation (see below), from either the top or the bottom extremities of the cylinder (Fig. 1). Neurology electrodes were used to present suprathreshold (100% detection accuracy) electro-cutaneous stimuli consisting of squared-wave pulse (100 μs, 400 V) delivered by constant-current stimulators (DS7A, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK) either on the index finger (up) or thumb (down) of the right hand. Participants discriminated tactile targets by releasing one of two foot pedals. The participants' eye movements (EyeLink-II, SR Research, Mississauga, Ontario, Canada; SMI) and spatial position of their grasping hand (Optotrak 3020, Northern Digital Inc., Waterloo, Ontario, Canada) were recorded online.

Design and procedure

In Experiment 1, participants performed only the perceptual task consisting of a speeded discrimination (up or down) of tactile stimulation regardless of the task-irrelevant distractor (the upper or lower LED in the cylinder). In Experiments 2, 3 and 4, participants additionally performed a motor task that consisted grasping the cylinder along its longitudinal axis with the index and thumb (precision grip, for details see movies 1–6 in supplementary data). An auditory signal warned the participant about the start of the trial, followed after a variable delay (1500–2200 ms) by a second auditory signal constituting the 'go' for the motor task. The motor task was performed using the stimulated (right) hand in Experiments 2 and 4, and the nonstimulated (left) hand in Experiment 3. The visuotactile stimulation could be delivered: (i) before movement start (Static condition) or (ii) at movement onset (action Start condition) or (iii) during the early phase of movement execution (action Execution condition). These temporal conditions were run across blocks in Experiments 2 and 3, and were fully randomized in Experiment 4. At the beginning of each trial, the tip of the thumb and index finger of each hand were kept in a closed pinch-grip posture on a start switch, whose release triggered the visuotactile stimulation in the Start and Execution conditions (0 and 200 ms delay, respectively).

Results

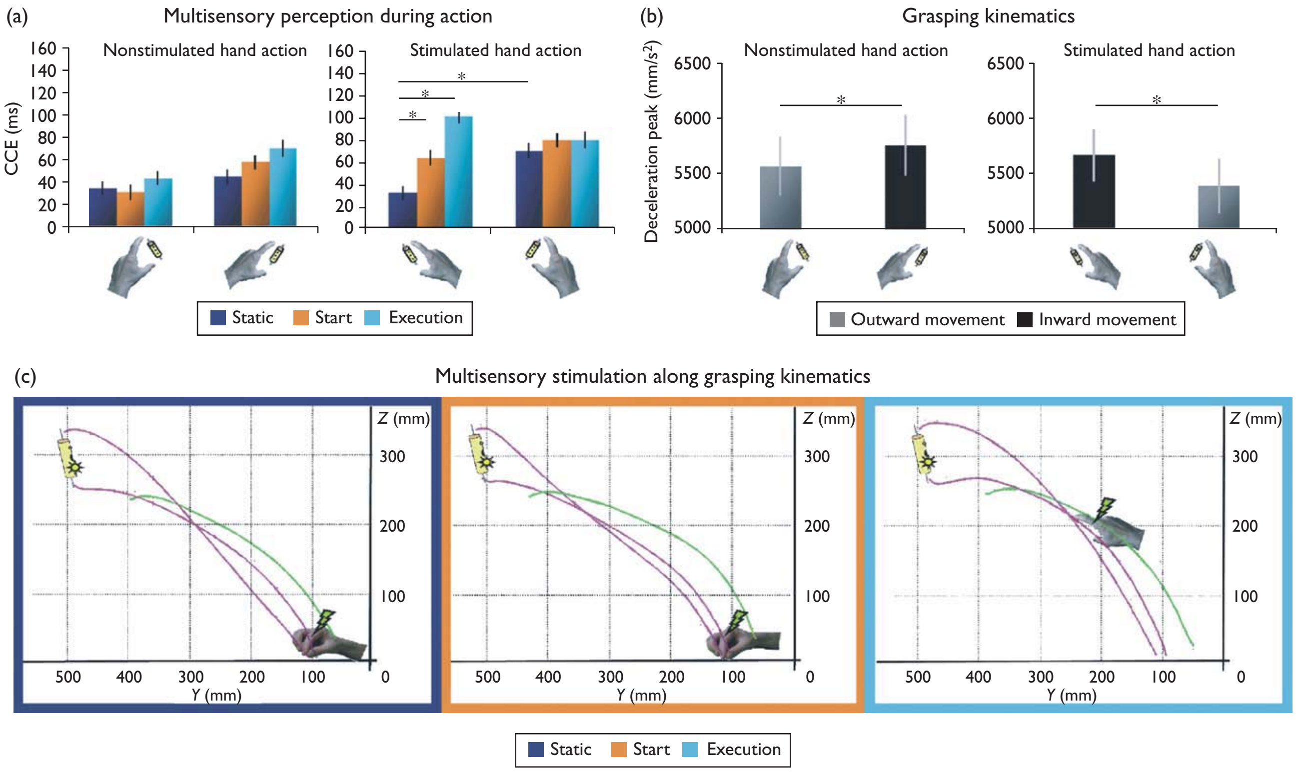
Multisensory interplay without action

When action was not required (Experiment 1), participants proved faster in responding to congruent (360 ms) than incongruent [394 ms; $t(14) = 4.99$, $P < 0.001$] trials, thus extending the typical cross-modal congruency effect (CCE) finding to a situation in which visual distractors were far from the stimulated hand [10]. Hereafter, the dependent variable will be the CCE, calculated as the (reaction times, RTs) difference between incongruent and congruent trials, in that it quantifies the strength of the interaction between visual and tactile inputs (similar trends were found on accuracy). In the absence of action, the CCE varied as a function of object orientation with stronger visuotactile interaction for clockwise (43 ms) rather than anticlockwise tilted object [24 ms; $t(14) = 2.15$, $P = 0.049$].

Action-dependent multisensory interplay

In the Static condition of Experiment 2, before the stimulated hand started to move, the CCE was again stronger when the object was tilted clockwise (66 ms) than anticlockwise [51 ms; $F(1,18) = 6.43$, $P = 0.021$]. Crucially, a modulation of the CCE was observed as soon as the stimulated hand started the action: Fig. 2a shows that the CCE changed on-line with action specifically for the objects oriented anticlockwise [$F(2,36) = 4.37$, $P = 0.020$]. For these orientations, the CCE was stronger when visuotactile stimuli were delivered at action Start

Fig. 2



Real-time modulation of visuotactile processing. (a) Bar plots (with SEM) show the modulation of cross-modal congruency effect (CCE) as a function of grasping hand and object orientation. (b) Movement deceleration peak, similarly modulated by object orientation across hands. (c) Mean movement trajectory of the wrist (green line) and the thumb and index fingers (purple lines). Hand position is schematically illustrated along the trajectory at the time when the tactile stimulus (green zap) was presented. *Refers to significant differences between conditions.

(63 ms) than in the Static condition (31 ms; $P = 0.037$). The CCE further increased during the Execution phase of the action (100 ms; $P < 0.001$ with respect to the Static condition; $P = 0.09$ with respect to the Start condition). Importantly, when the very same grasping action was performed by the nonstimulated hand (Experiment 3), no modulation of the CCE was observed (Fig. 2a), either in the Start or Execution condition compared with the Static condition.

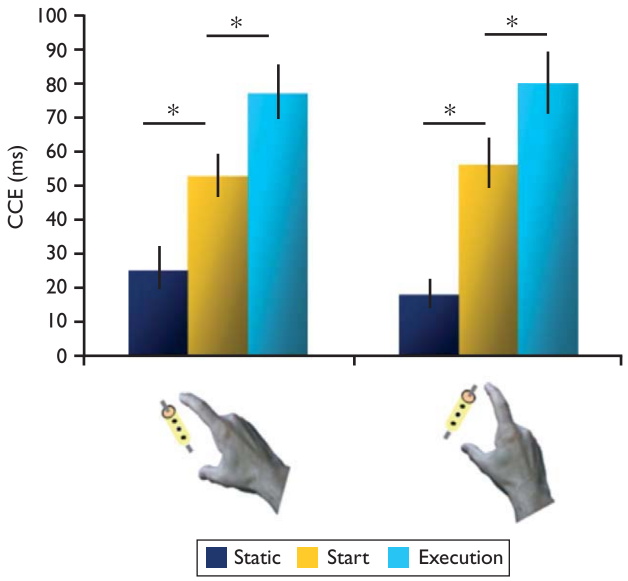
Experiment 4 further corroborated the finding that the action modulates the visuotactile interaction [$F(2,30) = 16.51$, $P < 0.001$]. Furthermore, in this fully interleaved design, the CCE was stronger at the action Start (55 ms) than in the Static condition (22 ms; $P = 0.026$), and in addition, this modulation emerged irrespective of object orientation. As shown in Fig. 3, the action-dependent modulation of the CCE was further increased during the Execution phase (79 ms), with respect to both the Start ($P = 0.022$) and the Static conditions ($P < 0.001$).

Grasping kinematics

To further establish multisensory motor relationships, we analysed the kinematic pattern of all reach-to-grasp movements. Comparison between Experiments 2 and 3 served the important purpose of controlling that hand-related difference between the on-line modulations of action over the CCE were not because of differences between hands kinematic patterns. In addition, through kinematic analyses, we tested for possible parallels between the motor and perceptual performance [15]. Depending on which hand performed the grasping (left or right), the object orientation imposed specific patterns of wrist orientation: clockwise and anticlockwise object orientations required, respectively, outward and inward movements of the right hand (for details see movies 1–2 in supplementary data). The reverse was applied to the left hand (for details see movies 4–5 in supplementary data).

Results of Experiments 2 and 3 showed an effect of object orientation on grasping kinematics. Crucially, however, the overall kinematic pattern proved remarkably similar for the two hands, both for the reaching and grasping components. Object orientations modulated motor RTs to the 'go' signal: it took more time for participants to start the action when the object had to be grasped with an inward (425 ms) than an outward wrist rotation [418 ms; $F(1,17) = 6.80$, $P = 0.018$]. In addition, as shown in Fig. 2b, deceleration peaks for both hands

Fig. 3



Grasping actions remap peripersonal space. Results from Experiment 4. Bar plots (with SEM) report the cross-modal congruency effect (CCE) increase at action Start (55 ms) and Execution (79 ms) compared with the Static condition (22 ms). * Refers to significant differences between conditions.

were more pronounced for inward (–5709 mm/s^2) than outward movements [–5474 mm/s^2; $F(1,17) = 23.19$, $P = 0.0002$]. Irrespective of which hand performed the task, acceleration peaks were higher when participants grasped the object with an inward (6337 mm/s^2) rather than an outward [6233 mm/s^2; $F(1,17) = 6.46$, $P = 0.021$] movement. The same tendency was present for the velocity peak [1267 mm/s and 1274 mm/s for inward and outward movements, respectively; $F(1,17) = 3.75$, $P = 0.069$]. Peak latencies were not modulated by object orientation with the exception of the acceleration peak, which was anticipated for inward (156 ms) than outward movements [160 ms; $F(1,17) = 5.81$, $P = 0.028$]. Kinematics of the grasping component of the movement showed little influence of the perceptual task.

In Experiment 4, kinematics of the reaching movement was less affected by object orientation. First, motor RTs did not differ between inward and outward movements (377 and 371 ms, respectively). Second, the remaining kinematic parameters were not modulated by object orientation [except the acceleration peak, differing between inward (8928 mm/s^2) and outward movement, 8690 mm/s^2; $F(1,14) = 5.15$, $P = 0.04$].

Discussion

These findings provide the first evidence that purposefully acting on objects links initially separated visual and somatosensory information, updating their interaction as a function of the required sensory motor transformations. When performing an action, our brain updates the relationship between visual and tactile information well before the hand touches the object. This perceptual reweighting is already effective at the very early stage of the action and seems to be continuously updated as action unfolds. This is clearly illustrated by the fact that from the very start of the action, the task-irrelevant visual information located on the to-be-grasped object interacts more strongly with the tactile information delivered on the hand that will eventually grasp the object. The specificity of such visuotactile reweighting for a given hand while naturally grasping an object confirms the hand-centred nature of the PpS [16–19], and reveals that tool use is not necessary for the human brain to remap space [19]. In addition, it critically extends this property to ecological and adaptive dynamic situations of voluntary manipulative actions, thus pointing to a fundamental aspect of multisensory motor control. By showing comparable pattern of movements across the grasping hands, the kinematics results rule out the possibility that the effector-specific increase of the CCE could merely reflect a difference between the motor performances of the two hands.

The modulation of the visuotactile interaction induced by action, limited to the objects oriented anticlockwise in Experiment 2, was clearly present for all object orientations in Experiment 4, thus fully supporting our hypothesis that voluntary grasping actions affect multisensory perception on-line. In addition, kinematic results were remarkably associated with the perceptual modifications in both the experiments. In Experiment 2, in which the perceptual reweighting was selective for inward object orientation, the kinematic differed between inward and outward reaching movements, in a direction that seemed reflecting more important wrist rotation required for hand pronation [20]. In Experiment 4, the perceptual reweighting was present for all object orientations and the associated kinematics was comparable across inward and outward rotations, thus paralleling, again, the perceptual modulation of action-dependent multisensory remapping. This parallel between movement kinematics and the CCE performance strengthens the functional link between multisensory coding of the hand-centred space and voluntary actions.

Peripersonal multisensory space may serve involuntary defensive reactions in response to objects approaching the body [3,6]. However, here we considerably add to this view by showing that such multisensory motor interface may be functionally involved in voluntary control of actions that bring the body towards objects. This fits well with the functional properties of visuotactile neurons documented in parieto-frontal circuits that present spatially aligned visual and tactile receptive fields for a given body part [1–6,21]. This feature allows bimodal neural systems to represent an object in a body-centred reference frame and to be continuously updated during bodily movements. This multisensory spatial representation has been suggested to serve involuntary defensive movements, because electrical microstimulation of some bimodal areas in the monkey brain [3] elicits stereotyped arm or face movements that are compatible with defensive behaviour. Remarkably, however, some bimodal neurons also respond when the arm is voluntarily moved within reaching space [14,15,22,23], and have been previously proposed to code goal-directed actions [1,2,22]. Neurophysiological studies on monkeys have shown activation in the posterior parietal cortex during grasping, in the early phase of the action when the hand has not yet reached the object. The activation gradually shifts towards the somatosensory cortex when the hand enters in contact with the object [14]. Finally, the on-line enlargement of the visual receptive fields of bimodal neurons in response to approaching objects [6] or tool use [17–19,24,25] also emphasizes the dynamic nature of their multisensory space coding, providing converging evidence for the involvement of the bimodal system in dynamic updating of the PpS. The multisensory motor neural machinery acting as an anticipatory interface between the body and nearby events may thus have been selected throughout evolution to drive both involuntary avoidance reactions and voluntary approaching movements, with common adaptive advantages for defensive and manipulative actions.

Conclusion

Voluntarily acting on objects triggers a hand-centred remapping of multisensory spatial processing that parallels action requirements and is regulated in real time as action unfolds.

Acknowledgements

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Results of the second study here presented clearly show that when grasping an object, a remapping of spatial representation arises in such a way that visual information on the to-be-grasped object, far from the hand, become more interacting with tactile information onto the grasping hand, with respect to a static condition. This remapping arises already at the on-set of the action and continues along the execution of the grasping. Furthermore, the remapping of the peripersonal space representation induced by action, arises in a coordinates system that is centred on the body-part (the hand in this experiment), since when participants employ the unstimulated left hand, no modulation is present. The kinematics of the movement rule out any possible confound due to a difference in the execution of the action between right and left hand. Moreover, it allowed investigating the link between the remapping of peripersonal space and the kinematic difficulty of the movements. These results constitute the first evidence in humans of a role played by the multisensory representation of peripersonal space in the execution of voluntary actions.

The intriguing relationship between kinematics of the movement and perceptual remapping of the peripersonal space is the further aspect investigated in the third study presented here. If, as the previous experiment results suggest, the remapping of peripersonal space is linked to the kinematic difficulty of the actions to be executed, then a difference should be found in the modulation of peripersonal space induced by actions that differ with respect to their kinematic complexity. In order to investigate more deeply the relationship between peripersonal remapping and the motor characteristics of the action, we tested whether different multisensory interactions may arise as a function of the required sensory-motor transformations. For example, we would expect that action-dependent multisensory remapping should be more important whenever performing actions requires relatively more complex sensory-motor transformations. Pointing towards an object without touching it, for instance, is a kind of action that only requires the computation of extrinsic properties of the object, such as the position of the target relative to the pointing hand. In contrast, in order to grasp the same object, the brain also needs to take into account the intrinsic properties of the object, such as its shape, size, and spatial orientation (Jeannerod 1988). Moreover, grasping, by definition, requires hand-object contact, and the intrinsic properties of the object will determine the available landing surface for the fingers and the wrist orientation that is needed for adopting a functional grip on the object. The pre-shaping of the hand (grip component) is smoothly implemented in the reaching phase (transport component), when the hand approaches the object (see Castiello 2005 for a review). Therefore, while both pointing and grasping have a reaching phase during which the hand is brought into the object's vicinity, grasping differs by requiring additional sensory-motor transformations mainly concerning the final part of the movement.

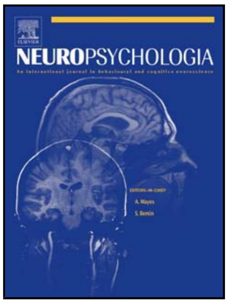
Participants were thus submitted to participate to the same motor-perceptual task as for the previous experiment. However, they had to perform either a grasping or a pointing toward the object.

For both actions, the interaction between task-irrelevant visual information on the object and the tactile information delivered on the acting hand increased already in the early component of the action, thus replicating our previous findings. However, a differential updating of the CCE took place during the execution phase of the two action types. While in the grasping condition the magnitude of the multisensory interaction was further increased during the execution phase, with respect to movement onset, in the pointing condition it did not present any further increase. In other words, during the phase in which the hand approached the object, the grasping movement triggered stronger CCE than pointing. Thus, not only a continuous updating of peripersonal space occurs during action execution, but this remapping varies with the characteristics of the required motor act.

STUDY 3

Action dependent modulations of peripersonal space

Neuropsychologia (In Press)



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ACTION-SPECIFIC REMAPPING OF PERIPERSONAL SPACE

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RUNNING HEAD: Action-specific modulations of peripersonal space

Abstract

Peripersonal space processing in monkeys' brain relies on visuo-tactile neurons activated by objects near, not touching, the animal's skin. Multisensory interplay in peripersonal space is now well documented also in humans, in brain damaged patients presenting cross-modal extinction as well as in healthy subjects and typically takes the form of stronger visuo-tactile interactions in peripersonal than far space. We recently showed in healthy humans the existence of a functional link between voluntary object-oriented actions (grasping) and the multisensory coding of the space around us (as indexed by visual-tactile interaction). Here, we investigated whether performing different actions towards the same object implies differential modulations of peripersonal space. Healthy subjects were asked to either grasp or point towards a target object. In addition, they discriminated whether tactile stimuli were delivered on their right index finger (up), or thumb (down), while ignoring visual distractors. Visuo-tactile interaction was probed in baseline static conditions (before the movement) and in dynamic conditions (action onset and execution). Results showed that, compared to the static baseline both actions similarly strengthened visuo-tactile interaction at the action onset, when grasping and pointing were kinematically indistinguishable. Crucially, grasping induced further enhancement than pointing in the execution phase, i.e. when the two actions kinematically diverged. These findings reveal that performing actions induce a continuous re-mapping of the multisensory peripersonal space as a function of on-line sensory-motor requirements, thus supporting the hypothesis of a role for peripersonal space in the motor control of voluntary actions.

Introduction

The representation of the space near the body, termed 'peripersonal' space (Rizzolatti, Scandolara, Matelli & Gentilucci 1981, Rizzolatti, Fadiga, Fogassi & Gallese 1997), relies on multisensory processing both in human and non-human primates. In monkeys, bimodal neurons have been described in inferior parietal areas (Hyvärinen & Poranen 1974) and premotor cortex (Duhamel, Colby & Goldberg 1998, Fogassi, Gallese, Fadiga, Luppino, Matelli & Rizzolatti 1996, Graziano & Cooke 2006, Graziano & Gross 1995). These neurons have the characteristics to be activated by visual as well as somatosensory stimulations with a higher activity for closer than farther visual stimuli. The activity of these cell assemblies across parieto-frontal and subcortical structures codes for tactile events on a body-part (e.g., the hand) and visual events near that body-part, thus giving rise to body-centred representations of peripersonal space (Rizzolatti et al 1981, Rizzolatti et al 1997, Gentilucci, Scandolara, Pigarev & Rizzolatti 1983, see for review Rizzolatti, Fogassi & Gallese 2002). In humans, a functionally homologous coding of peripersonal space is largely supported by behavioural studies, showing stronger visual-tactile interaction in near than far space in brain-damaged (di Pellegrino, Làdavas & Farné 1997, Farnè, Demattè & Làdavas 2005, Farnè, Pavani, Meneghello & Làdavas 2000, Brozzoli, Demattè, Pavani, Frassinetti & Farnè 2006) and healthy individuals (Spence, Pavani & Driver 2004, Spence, Pavani, Maravita & Holmes 2004, Pavani & Castiello 2004, Bremmer, Schlack, Shah, Zafiris, Kubishik et al 2001). The investigation in neurological patients, for example, revealed that visual events occurring in the immediate proximity to the body induce more severe visual-tactile extinction than farther events (Farnè et al 2000; Brozzoli et al 2006). Similarly, in healthy individuals, visual-tactile interaction has been shown to be stronger when visual information is presented close to the body than far from it (Spence et al 2004a; Spence et al 2004b). In addition to behavioural evidence, recent functional neuroimaging and electrophysiological studies support the existence of similar multisensory integrative structures in the human brain (Bremmer et al 2001a, 2001b; Sereno & Huang 2006; Makin, Holmes & Zohary 2007; Sarri, Blankenburg & Driver 2006).

Despite the large body of knowledge accumulated across species on the multisensory properties of peripersonal space, little is known about its function as this issue has been assessed in humans only recently (Brozzoli, Pavani, Urquizar, Cardinali & Farnè, 2009; Cardinali, Brozzoli & Farnè, 2009). Two not mutually exclusive hypotheses have been proposed on the basis of the neurophysiological findings in the monkey. By acting as an anticipatory sensorimotor interface, peripersonal space may serve early detection of potential threats approaching the body to drive involuntary defensive movements (Graziano & Cooke 2006). The most direct evidence in favour of this hypothesis is the result of cortical stimulation studies. When multisensory areas where visuo-tactile neurons have been found (Graziano & Cooke 2006) are electrically stimulated, a pattern of movements is elicited that is compatible with defensive arm movements and withdrawing of the arm or the head. Analogously, in humans, corticospinal excitability during motor preparation has been shown to be modulated by visually approaching objects in a hand-centred fashion (Makin, Holmes, Brozzoli, Rossetti & Farnè, in press).

The same anticipatory feature, however, may have also evolved to serve voluntary object-oriented actions (Rizzolatti et al 1981, Rizzolatti et al 1997; Gardner, Babu, Reitzen, Ghosh, Brown et al. 2007; Galletti, Kutz, Gamberini, Breveglieri & Fattori 2003). In support to this view are the results of single units recording studies showing the motor properties of both parietal (Hyvärinen & Poranen 1974; Mountcastle, Lynch, Georgopoulos, Sakata, & Acuna 1975; Leinonen 1980; Gardener et al 2007) and periarcuate (Rizzolatti et al 1981a, b, Gentilucci et al 1983; Rizzolatti, Gentilucci, Fogassi, Luppino, Matelli et al 1987, Rizzolatti

& Gentilucci 1988) visuo-tactile neurons. In particular, the visual sensory activation of bimodal neurons seems to be enhanced whenever a reaching movement is performed towards an object (Godschalk, Lemon, Kuypers & van der Steen 1985). Such a parieto-frontal network would thus compute the sensory-motor transformations that allow a body-centred coding of space. This, in turn, could be useful for the execution of voluntary actions toward objects (e.g., Fogassi, Gallese, di Pellegrino, Fadiga, Gentilucci, et al 1992). Recently, we provided evidence in humans of an involvement of the peripersonal space representation in the execution of a grasping (Brozzoli et al 2009). When compared to a static (no action) condition, the initiation of a grasping movement increased the interaction between visual inputs originating from the to-be-grasped object and tactile inputs delivered to the grasping hand. This action-dependent multisensory remapping was further enhanced during movement execution when the hand was brought towards the object, but still well before any hand-object contact. Notably, when the stimulated right hand remained still while the left (unstimulated) hand performed the same action these modulations of the multisensory interactions no longer emerged, suggesting that the observed effect was strictly hand-centred. These hand-centred effects of action on multisensory perception support the role of peripersonal space in voluntary object-oriented actions in humans.

In the present study, we took a step forward in the understanding of the functional link between peripersonal space coding and voluntary control of action by testing whether different object-oriented actions would induce different on-line modulations of multisensory coding of peripersonal space. We hypothesized that, if peripersonal space serves the control of voluntary object-oriented actions, action-dependent multisensory remapping should be more important whenever the action to be performed requires relatively more complex sensory-motor transformations. Two hand actions that differ clearly in this respect are reach-to-point and reach-to-grasp. When pointing the hand (closed in a fist configuration) towards an object without touching it, the brain needs to take into account only object's spatial position relative to the acting body-part (a so-called extrinsic object property; Jeannerod 1988). In contrast, when grasping the same object with the hand, the brain needs to take into account the spatial position of the target object with respect to the grasping hand (extrinsic object properties), as well as the shape, size of the target object (intrinsic object properties; Jeannerod 1988). In addition, because grasping requires hand-object contact by definition, the intrinsic object properties determine the available landing surface for the fingers and the appropriate wrist orientation for achieving an optimal functional grip on the object. The pre-shaping of the hand (grip component) is smoothly implemented in the reaching phase (transport component), while the hand approaches the object (see Castiello 2005 for a review). Therefore, while both pointing and grasping are composed by a reaching phase during which the hand is brought in the object's vicinity, the two actions are substantially different in the final part of the movement, with additional sensorimotor transformations implemented selectively for grasping movements.

To test our prediction that action-dependent multisensory remapping is modulated as a function of the sensorimotor transformations complexity, we contrasted the visual-tactile effects produced by performing a relatively simple action (pointing) with those produced by performing a more complex action (grasping). In the former condition, participants were asked to reach a target object with their right hand without touching it, keeping a fist hand-configuration (with a closed index-thumb pinch grip) along the entire movement. In the latter condition, participants reached and grasped the object using a precision grip with the same right hand. Kinematic recording was used to compare the reaching phase of both actions. Visual-tactile interaction was measured online in both conditions, by asking participants to discriminate the elevation of tactile stimuli delivered on either the index finger (up) or thumb (down) of the acting hand while ignoring visual distractors embedded into the target object.

< Insert Figure 1 about here >

Materials and methods

Participants

Sixteen neurologically healthy participants (8 male, mean age 25 year old, ± 4) took part in the experiment. Participants had normal or corrected-to-normal visual acuity and reported normal tactile sensitivity. All participants gave their verbal informed consent to take part in this study, which was approved by the local INSERM U864 ethics board.

Apparatus

The target object was a wooden cylinder (7 cm height, 1.7 cm diameter) located at a distance of 47 cm from the starting position of the participant's hands, at eye-level (Figure 1a). Two red LEDs were used to present visual distractor stimuli. These were embedded into the cylinder, each at 1 cm from the cylinder's extremities. Visual distractors consisted of a single flash (200 ms) from either the top or bottom LED embedded into the cylinder, delivered concurrently with the electro-cutaneous stimulation (see below). A dot (1 cm diameter) was marked in the center of the cylinder (between the two LEDs) to serve as visual fixation (Figure 1a, upper circle). To ensure that subjects planned a new action on each trial, the cylinder was unpredictably rotated manually from behind the wooden panel into one of four different orientations: 18° or 36° from the vertical position, in clockwise or anti-clockwise directions, around the virtual axis perpendicular to the longitudinal axis of the cylinder and passing through the fixation point. Disposable neurology electrodes (700 15-K, Neuroline, Ambu) were used to present supra-threshold electro-cutaneous stimuli. Tactile target stimulation consisted of squared-wave single pulse (100 µs, 400 V) delivered through constant-current electrical stimulators (DS7A Digitimer Ltd., UK) either on the index finger (upper stimulation) or on the thumb (lower stimulation) of the right hand (Figure 1a, lower circle). With respect to the classical static studies adopting the cross-modal congruency task, here electrods were fixated on the acting hand and stayed attached to it during the duration of the action movement. Electro-cutaneous target intensities were set out individually for each subject and stimulated location, so that participants could detect 100% of the stimuli in a serie of ten trials for index finger and thumb [Thumb mean current (s.e.m.) = 11,0 mA (0.6); Index finger mean current 11,0 mA (0.5)]. Participants were instructed to respond to the tactile target as fast as possible by releasing one of two foot-pedals (Herga electric Ltd, England). The real-time spatial position of the participant's grasping hand was recorded by means of an Optotrak 3020 system (Northern Digital Inc., sampling at 100 Hz, 0.01 mm 3D resolution at 2.25 m distance). The infra-red emissions were sampled at 100 Hz. Two infra-red emitting diodes (IRED) were stuck on the lateral part of the nail of the thumb and index fingers and one was placed on the interior part of the wrist at the styloid process level. These markers were used to reconstruct the transport component of both actions (the change over time of the wrist marker position) and the grip component of the grasping action (the change over time of the distance between the index and the thumb).

Design and Procedure

Participants sat at a table in a quiet and dimly illuminated room, in front of the apparatus, with two response pedals under their right foot. They were instructed to maintain fixation on the the black dot painted in the middle of the target cylinder. Participants performed two concurrent tasks during each trial: The perceptual task (speeded tactile discrimination) and the motor task. Across blocks, the motor task consisted in grasping the cylinder along its longitudinal axis with the index and thumb (precision grip, Fig 1b, upper circle) or pointing the closed hand towards the centre of the cylinder longitudinal axis without opening the fingers (Fig 1b, lower circle). In this latter condition, participants were instructed to stop the movement in close vicinity of the object but avoid contact with it. Each trial started with an auditory warning signal. After a variable delay (1500 – 2200 ms) a second auditory signal constituted the GO for the motor task. The motor task was performed using the stimulated right hand in both the pointing and grasping blocks. Regardless of which action had to be performed, visuo-tactile stimulation was unpredictably delivered between trials: 1) before movement start (Static condition) or, 2) at the beginning of the movement (action Start condition) or, 3) during the execution of the movement (action Execution condition). At the beginning of each trial the tip of the thumb and the index finger of each hand were kept in a closed pinch-grip posture on the start-switches. Start-switch release was used to trigger the visuo-tactile stimulation in the Start (0 ms) and Execution condition (with a 200 ms delay). Each trial was started manually by the experimenter concealed behind the apparatus, after the dowel had been rotated into one of the four possible orientations.

Results

Multisensory remapping of space

In a first ANOVA analysis, we contrasted all four factors: Action (Grasping vs. Pointing), Phase (Static vs. Start vs. Execution), Object Orientation (Anti-Clockwise vs. Clockwise) and Stimulation (Congruent vs. Incongruent). Briefly, we found a highly significant main effect of Stimulation [F(1,15)=15.57, p<.001], confirming the presence of the typical Cross-modal Congruency Effect (CCE, see Spence et al 2004a; Spence et al 2004b; Brozzoli et al, 2009): participants proved faster in responding to congruent (420 ms) than incongruent (469 ms) trials, with a similar pattern of results also for the accuracy score [95% for congruent vs. 85% for incongruent trials, F(1,15)=17.61, p<.001]. Hereafter, the dependent variable will thus be the CCE, calculated as the performance difference between incongruent and congruent trials, in that it quantifies the strength of the interaction between visual and tactile inputs. Unless otherwise specified, CCE will refer to the performance difference in terms of response times, which typically proved more sensitive in this type of experimental paradigms. However, we also examined the accuracy CCE (i.e., accuracy difference between congruent and incongruent trials) to exclude any speed-accuracy trade-offs. As a consequence, the following analyses only included Action (Grasping vs. Pointing), Phase (Static vs. Start vs. Execution) and Object Orientation (Anti-Clockwise vs. Clockwise) as variables.

A significant main effect of Phase [*F*(2,30)=16.18, p<.0001] showed the dependence of CCE on the phase of the action in which subjects received the visuo-tactile stimulation. As Figure 2 (upper panel) shows, an increase of the CCE was observed as soon as the stimulated hand started the action: the CCE was stronger when visuo-tactile stimuli were delivered at action Start (55 ms) than in the Static condition (26 ms; p<.001, Newman-Keuls post-hoc test). The increase of CCE was also observed during the Execution phase of the action (66 ms; p<0.001 with respect to the Static condition). The same effect was present in the accuracy CCE [*F*(2,30)=4.43, p<0.05); 6% for the Static condition, 7% for the Start (p=.05 with respect to Static) and 9% for the Execution (p<.05 with respect to Static)]. Critically, the effect of the Phase was differently modulated as a function of the action that participants were performing, as witnessed by the significant Phase X Action interaction [*F*(2,30)=6.19, p<.01] in the CCE (Figure 2, upper panel). In the Grasping condition, the CCE increased significantly in the Start (55 ms) with respect to the Static condition (22 ms, p<.001); and increased even further in the Execution phase (79 ms, p<.001 with respect to Static and p<.01 with respect to Start condition). In the Pointing condition, the CCE was similarly increased in the Start (56 ms) with respect to the Static condition (29 ms, p<.01), but no further increase was observed during the Execution phase (53 ms, p<.01 only with respect to Static condition, see Figure 2, upper panel). Finally, a direct comparison between the two types of action showed a significant difference in the level of CCE in the Execution phase, with stronger visuo-tactile interactions for the Grasping (79 ms) than the Pointing action (53 ms, $p<.01$). The post-hoc comparisons did not present any other significant difference between Grasping and Pointing, in the amount of the CCE in Static (22 and 29 ms respectively for Grasping and Pointing, $p=.32$) and Start (55 and 56 ms respectively, $p=.89$). A separate ANOVA performed only on Static and Start conditions confirmed this finding, revealing a significant effect of the Phase [$F(1,15)=15.65$, $p<.01$] but no interaction with the type of action [$F(1,15)=0.56$, $p=.46$]. When analysed in terms of accuracy CCE the interaction between Phase X Action was not significant, however a similar numerical trend was nonetheless evident excluding any speed-accuracy trade-off in the interpretation of the RT CCE results.

< Insert Figure 2 about here >

Differences in kinematics between Grasping and Pointing

Separate analyses were conducted on the kinematic parameters of reach-to-grasp and pointing movements recorded in 3D space throughout the study. This served the important purpose of assessing any possible parallel between the motor and the perceptual performance (see Figure 3 for a representative example from the Execution condition of one participant), in addition to documenting the difference between the two types of action. The following kinematic parameters of the movement were analysed: Acceleration, Velocity, Deceleration Peaks and relative Latencies since movement onset, Movement reaction time and Duration (up to the closing of the fingers on the object to be then extracted from its support to complete the required action). Each parameter was entered in an ANOVA with the following independent variables: Action (Grasping vs. Pointing), Phase (Static vs. Start vs. Execution), Object Orientation (Anti-Clockwise vs. Clockwise) and Stimulation (Congruent vs. Incongruent).

<Insert Figure 3 about here>

As expected, the two actions differed in the ending part of the reaching phase. As shown in Figure 2 (lower panel), the deceleration peak was influenced by the kind of action as a main effect [F(1,15)=14.72, p<.01]: when participants pointed to the object, their deceleration was more important (9668 mm/s2) than when they had to grasp it (8104 mm/s2). No modulation was observed for the Velocity and Acceleration Peaks of both Grasping and Pointing movements. The latencies of these kinematic peaks were only partially modulated by the different kinds of actions to be performed. Indeed, the kind of action impacted only on the Latency of Deceleration Peak, which occurred later in case of Pointing (434 ms) than in case of Grasping (424 ms) in all experimental conditions (p<.05 in all comparisons) with only two exceptions, where the same non-significant trend was present (movements towards anti-clockwise tilted object in the Start condition and movements toward clockwise tilted object in the Execution condition).

<Insert Table 1 about here>

Influence of the perceptual task on kinematics

Movement kinematics was partially affected by the different temporal coupling between the motor task and visuo-tactile stimulation. The incongruent trials presented delayed latencies of acceleration, velocity and deceleration peaks when stimulation occurred in Static (145 ms, 310 ms and 434 ms, respectively for the three parameters) rather than Start (136 ms, 305 ms and 423 ms, p<.05) or Execution (136 ms, 304 ms and 428 ms, p<.05) conditions. This is witnessed by the significant Phase X Stimulation interactions for Acceleration [F(2,30)=4.04, p<.05], Velocity [F(2,30)=7.00, p<.01] and Deceleration [F(2,30)=7.14, p<.01]. These modulations were present regardless of which action was performed, grasping or pointing. Among the peaks, only the Acceleration Peak showed to be marginally modulated by the stimulation [Phase X Stimulation interaction, *F*(2,30)=4.45, p<.05]: in case of congruent trials, Acceleration Peak resulted more important when stimulation occurred before (Static condition, 9411 mm/s2) than on (Start condition, 9059 mm/s2, p<.05) or after (Execution condition, 9101 mm/s2, p=.055) the movement onset. Again, this effect was present both in case of Grasping and Pointing movements. No modulation was present for Velocity and Deceleration Peak as a function of the Stimulation. Finally, neither movement time nor motor reaction times resulted affected by the perceptual task (Table 1).

Discussion

In a recent study we showed that, when performing an action, our brain updates the relationship between distal visual input and tactile information at the acting hand well before the hand contacts with the object (Brozzoli et al. 2009). This perceptual re-weighting occurs already at the very early stages of the action, when the hand has barely moved from its starting position. Furthermore, it is updated continuously as the action unfolds. This finding showed for the first time that the brain can update the interaction between initially separated visual and somatosensory inputs, as a function of the sensori-motor transformations required by the action itself and suggested a functional link between visuo-tactile peripersonal space and voluntary actions.

Action-specific remapping of peripersonal space

In the present study, we took one step forward and contrasted the effects of two different actions, grasping and pointing, on visual-tactile interaction to assess any specificity in the modulation of peripersonal space as a function of the required action. For both actions, the interaction between task-irrelevant visual information on the target object and the tactile information delivered on the acting hand increased already at action start, thus providing further support to our original observation (Brozzoli et al., 2009). However, a different updating of the visuo-tactile interplay took place during the execution phase of the two different actions. While in the grasping action the magnitude of the CCE was further increased during the execution phase, in the pointing action the visuo-tactile interaction did not present any further increase during execution with respect to movement onset. In other words, during the actual approaching phase of the movement, grasping triggered stronger visual-tactile interaction than pointing.

This finding adds to our previous results by revealing not only that a continuous up-dating of peripersonal space occurs during action execution, but also that this remapping varies with the characteristics of a given motor act. If (part of) the remapping of peripersonal space is already effective at the onset of the motor program, the perceptual modulation can be either further enhanced in case of a relatively complex object-oriented actions like grasping, or kept unchanged in case of simpler pointing actions. This on-line, motor-evoked “monitoring” of the action space opens the possibility of very fast modulations of the peripersonal space representation as a function of more ecological needs during actions execution. One could speculate that such rapid on-line updating, for instance, could parallel the fast, on-line motor corrections documented in motor control studies (Paulignan, MacKenzie, Marteniuk & Jeannerod 1991; Desmurget, Epstein, Turner, Prablanc, Alexander et al 1999; Pisella, Gréa, Tilikete, Vighetto, Desmurget 2000; Farnè, Roy, Paulignan, Rode, Rossetti, Boisson & Jeannerod 2003). Since deficits of the so-called “automatic pilot” (Pisella et al. 2000) have been documented after lesions o the posterior perietal cortex in humans, as well as in healthy subjects after parietal TMS (Desmurget et al 1999), one could suggest that the mechanism underlying the rapid remapping of peripersonal space could be damaged in these patients, thus depriving them from the “monitoring” of the action space. Ongoing research in our laboratory will help clarifying this hypothesis.

Peripersonal space remapping is selectively modified by specific kinematic patterns

The second main finding of the present study is that the kinematic results appeared remarkably associated with the perceptual modifications. We directly compared the transport component of the pointing and grasping actions. The overall kinematic structure of either pointing or grasping was not disrupted by the concurrent perceptual task. Whenever the tactile task affected some movement parameters both types of movement were affected similarly, thus showing that the visuo-tactile task did not differentially affected the kinematic pattern of pointing and grasping actions. Crucially, however, the opposite was not true, in that different kinematic patterns between pointing and grasping had a clear impact on the visuo-tactile task, which we used as a proxy of peripersonal space remapping. The only substantial difference appeared towards the end of the reaching component of the movement, during the deceleration phase. Namely, when subjects pointed towards the object, they needed to decelerate more than when they grasped it. This difference reflects the need for the subject to stop the movement before the collision with the object, with respect to the grasping, where deceleration is weaker due to the need of achieving a stable grip when the fingers contact the target. It is to worth noting the parallel between the kinematic evolution of the two actions and the perceptual modulation of the visuo-tactile interaction. When the visuo-tactile interplay was assessed in the phase of the movement that did not present kinematic differences between pointing and grasping (i.e., start phase), a similar remapping of peripersonal space was found across the two different actions. By contrast, when the visuo-tactile interaction was assessed in the execution phase, i.e. when pointing and grasping differ from a kinematic point of view, the peripersonal space was also differently remapped. This parallel between the perceptual and the motor behaviour strengthens our proposal of a link between multisensory peripersonal space representation and the execution of voluntary actions. Moreover, the kinematic results allow us ruling out the possibility that peripersonal space remapping might be induced by the relative approaching velocity of hand and object. Indeed, the visual receptive fields of monkeys' bimodal neurons have been shown to present dynamic modifications depending on the velocity of an object approaching the corresponding tactile receptive field on the body (Fogassi et al. 1996). Thus, it would in principle be possible that the different increase of visuo-tactile interaction observed as a function of the required action might reflect differences in hand velocity between types of movement. However, no significant difference was observed between grasping and pointing velocities, with instead a tendency for the peak to be higher in the pointing with respect to the grasping action. If the perceptual remapping reported here were due to on the object's approaching velocity, we should expect higher visuo-tactile interactions in case of pointing rather than in the grasping. Instead, the opposite was observed, clearly supporting the notion that the remapping of peripersonal space we reported in this study is induced by the execution of a voluntary action towards the object and can be modified on-line as a function of the action requirements.

This functional role is not (see Brozzoli et al, 2009) in contrast with the view that peripersonal multisensory space serves involuntary defensive re-actions in response to objects approaching the body (Graziano & Cooke 2006; Graziano & Gross 1995; Makin et al, in press). However, here we considerably add to this view by showing that in humans such multisensori-motor interfaces may be functionally involved in voluntary control of actions that bring the body towards objects. In particular, the present findings show a specific sensitivity of the peripersonal space to the kind of sensory-motor transformation that is required to execute an action. This fits well with the functional properties of visuo-tactile neurons documented in parieto-frontal circuits in the monkey, which code for peripersonal space. These neurons present spatially organised visual and tactile receptive fields (Rizzolatti et al 1981; Rizzolatti et al 1997, Fogassi et al 1996; Duhamel et al 1998; Graziano & Gross 1995; Graziano 1999; Avillac, Denève, Olivier, Pouget & Duhamel 2005) allowing this bimodal circuitry to represent an object in a coordinate system centred on the body and to be continuously up-dated during bodily movements. Indeed, some bimodal neurons also respond when the arm is voluntarily moved within the reaching space (Gardner et al 2007; Galletti et al 2003; Gentilucci, Fogassi, Luppino, Matelli, Camarda et al. 1988; Fattori, Kutz, Breveglieri, Marzocchi & Galletti 2005; Marzocchi, Breveglieri, Galletti & Fattori 2008) and have been previously proposed to code goal-directed actions (Rizzolatti et al 1981; Rizzolatti 1997; Gentilucci 1988). Neurophysiological studies in monkeys have additionally shown activation in the posterior parietal cortex during a grasping movement, in the early phase of the action, when the hand has not yet reached the object. This activation gradually shifts towards the somatosensory cortex when the hand enters in contact with the object (Gardner et al 2007). The on-line enlargement of the visual receptive fields of bimodal neurons in response to approaching objects (Graziano & Gross 1995) or tool-use (Holmes & Spence 2004; Maravita, Spence & Driver,2003; Iriki, Tanaka & Iwamura 1996; Berti & Frassinetti 2000; Farnè, Bonifazi & Làdavas 2005; Bonifazi, Farnè, Rinaldesi & Ladavas 2007; Farnè, Iriki & Làdavas 2005; Farnè, Serino & Làdavas 2005) converge in supporting the involvement of the bimodal system in the up-dating of the peripersonal space representation in dynamic conditions.

In conclusion, this study provides evidence that voluntarily acting on objects triggers specific remapping of multisensory perception as a function of action requirements, as specified possibly by the motor complexity alone, or its coupling with spatial information about the target object. Future studies will ascertain whether such a remapping mainly depends upon intrinsic (vs. extrinsic) properties, or reach-to-grasp (vs. reach only) components of movement. Most important at this stage is the fact that by showing that such a remapping is similar when action starts, but differs according to the differential kinematics of grasping and pointing during execution, we additionally demonstrate that action-dependent remapping of space is regulated in real-time and linked to the kinematic characteristics of the action. The multisensory-motor neural machinery acting as an anticipatory interface between the body and nearby events may thus have been selected throughout evolution to drive voluntary approaching movements via a continuous monitoring of action space.

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Figure captions

Figure 1. Experimental setup and tasks.

(a) Bird’s eye view of the participant, sitting in front of the target cylinder (upper inset) with both hands in a pinch-grip starting position (lower inset) on a desk. The cylinder was positioned along the participant’s mid-saggital plane, 47 cm away from hand’s starting position. In the perceptual task, participants were asked to discriminate the elevation (i.e. up or down) of an electro-cutaneous target (yellow zap) delivered to the index finger (up) or thumb (down). A concurrent task-irrelevant visual distractor (yellow flash) could be presented from either the same (congruent) or different (incongruent) elevation (an incongruent instance is depicted in the insets), from one of two LEDs embedded into the cylinder extremities. (b) Participants were instructed to grasp the object with a precision grip (thumb-index, as shown in the upper inset), or to point to it (lower inset)

Figure 2. Action specific remapping of visuo-tactile interaction

Upper panel. Means and standard errors are shown for the amplitude of the CCE as function of action phase. Lower panel. Means and standard errors of the parameters of the reaching component for both actions: peaks of acceleration (left part), velocity (central part) and deceleration (right part).

Figure 3. Temporal coupling of perceptual and motor task

The graph illustrates the time-line of a representative Execution condition of one participant. Mean Velocity (green) and Acceleration (grey) profiles are plotted in the graph as bold lines, with 2 standard deviations intervals indicated by dashed lines. Interleaved with the kinematic profile, the blue zap indicates when during the kinematics the visuo-tactile stimulation occurred. Means and standard errors of Reaction Times for Congruent (full blue vertical line) and Incongruent (dashed blue vertical line) stimulations are also plotted.

Table 1. Means and standard errors for motor reaction time (ms) from the go signal, duration (ms) of movements and absolute reaction time (ms) to the perceptual visuo-tactile task in all experimental conditions.

Motor Onset (mean ms, *s.e.m.*)

		Inward		Outward	
		C	I	C	I
Grasping	Before	346 *21*	375 *21*	340 *17*	347 *18*
	Start	395 *24*	387 *18*	384 *20*	402 *19*
	Execution	389 *20*	398 *27*	394 *18*	389 *20*
Pointing	Before	381 *24*	396 *17*	377 *20*	402 *22*
	Start	398 *22*	383 *18*	397 *21*	377 *20*
	Execution	392 *22*	380 *19*	395 *21*	399 *26*

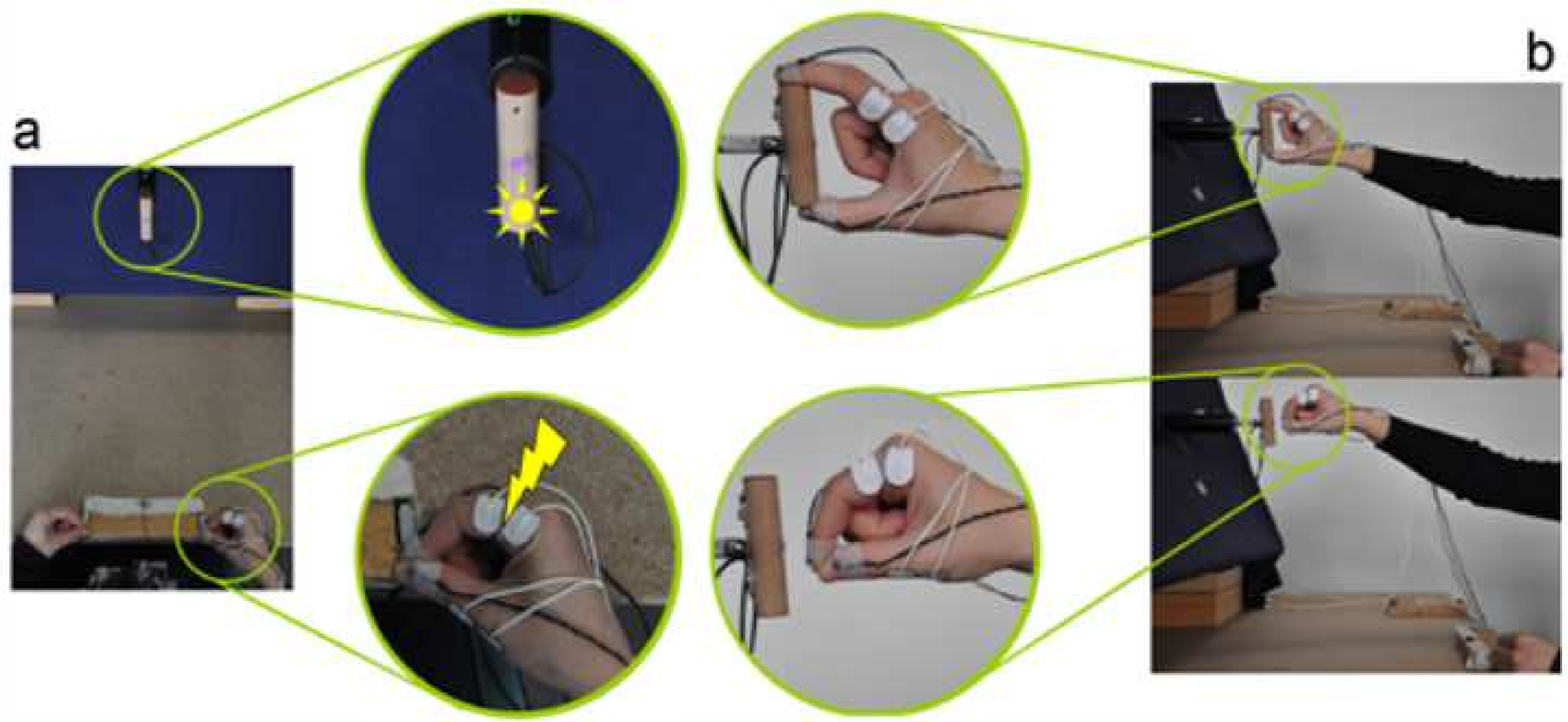
Duration (mean ms, *s.e.m.*)

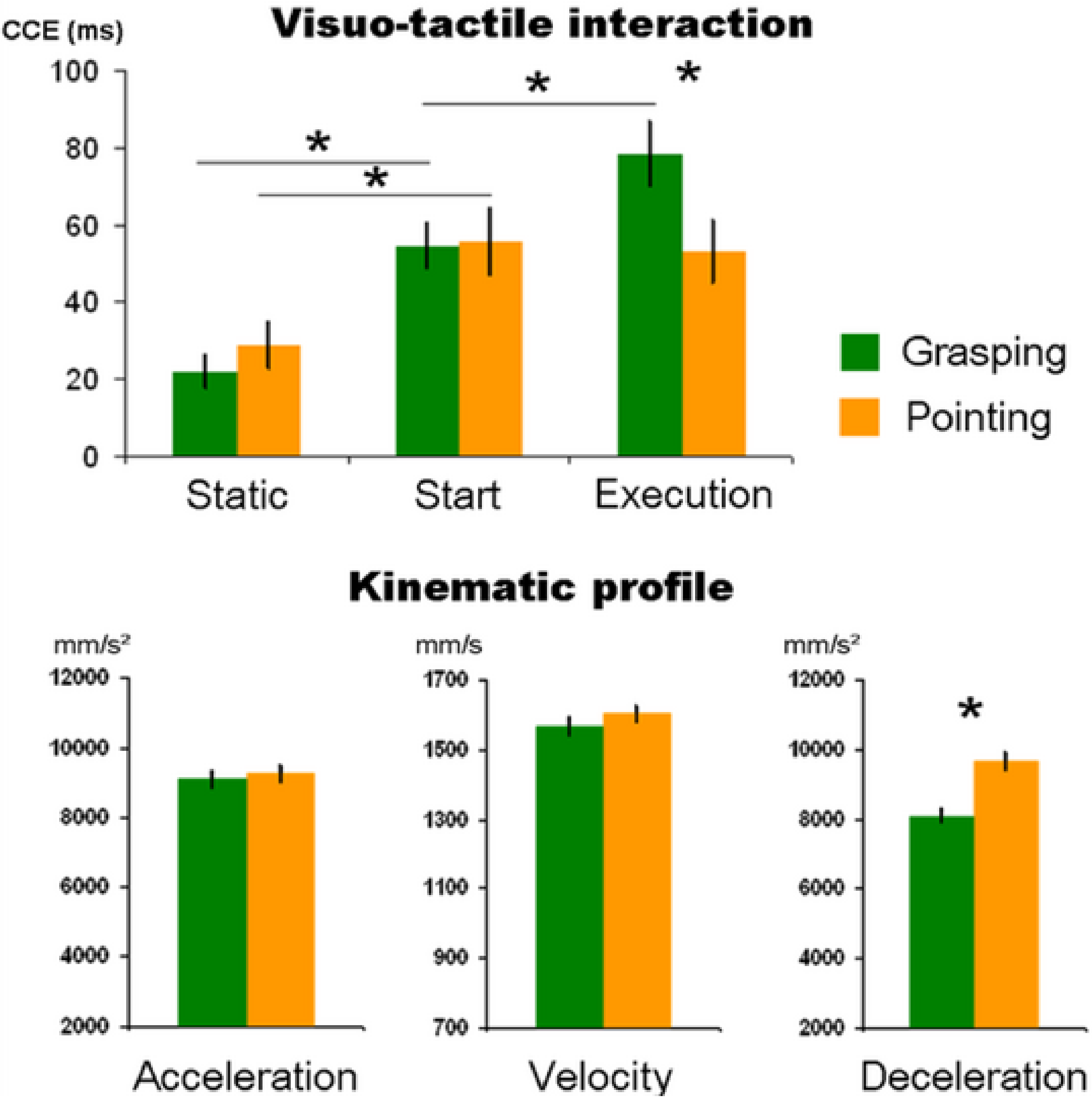
		Inward		Outward	
		C	I	C	I
Grasping	Before	686 *24*	703 *20*	718 *18*	722 *19*
	Start	724 *25*	707 *27*	723 *18*	725 *19*
	Execution	731 *24*	728 *24*	733 *21*	743 *18*
Pointing	Before	702 *18*	701 *20*	702 *21*	711 *20*
	Start	717 *23*	725 *25*	723 *28*	726 *25*
	Execution	733 *24*	726 *22*	722 *31*	728 *25*

Visuo-Tactile RTs (mean ms, *s.e.m.*)

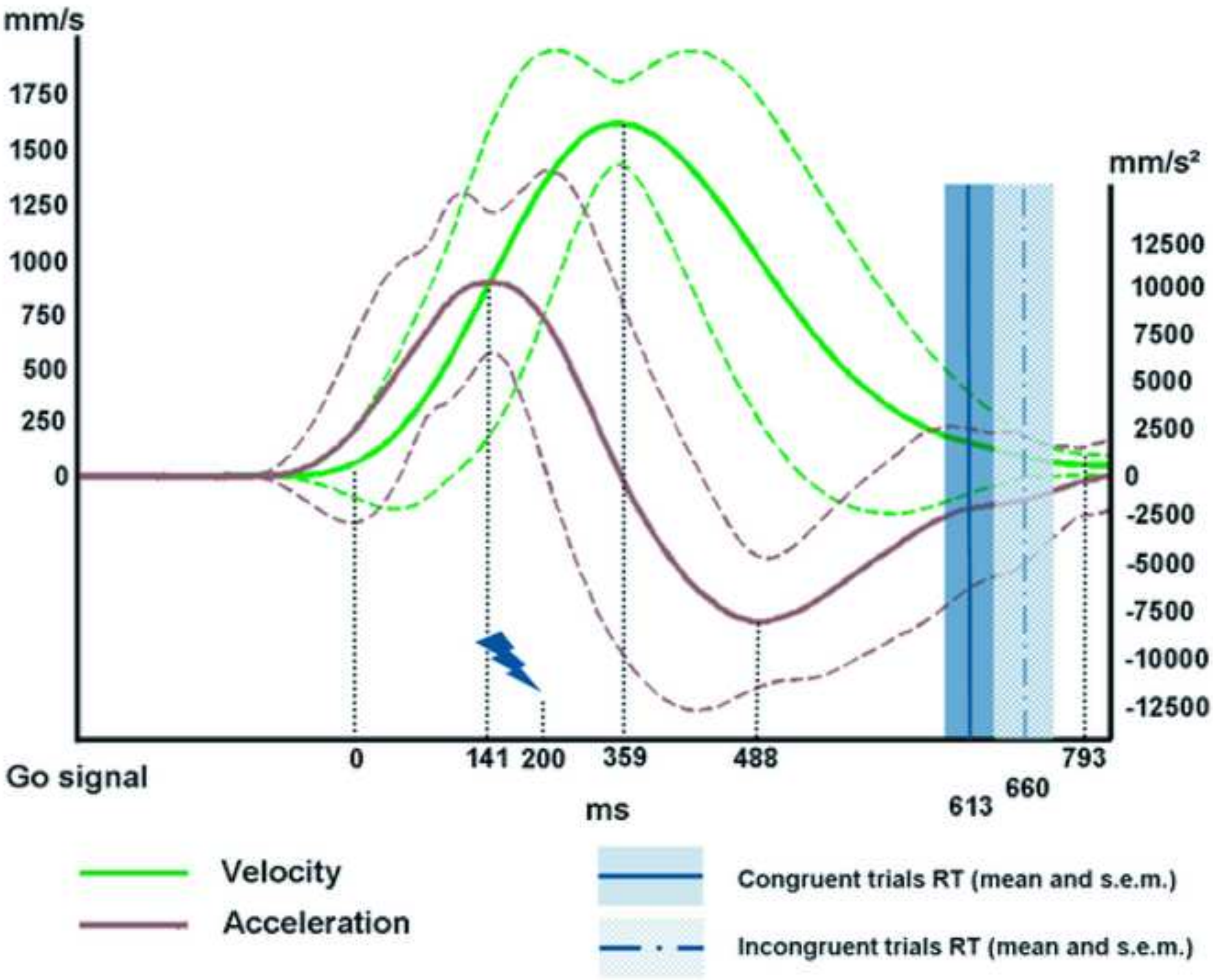
		Inward		Outward	
		C	I	C	I
Grasping	Before	419 *19*	444 *27*	413 *20*	431 *23*
	Start	463 *24*	516 *32*	453 *23*	509 *32*
	Execution	401 *18*	478 *31*	403 *18*	483 *30*
Pointing	Before	428 *19*	456 *27*	425 *20*	455 *27*
	Start	438 *21*	500 *31*	435 *24*	484 *30*
	Execution	384 *15*	427 *28*	377 *19*	440 *27*

Figure




Visuo-tactile interaction
CCE (ms)
100
80
60
40
20
0
*
*
*
*
Static
Start
Execution
Grasping
Pointing
Kinematic profile
mm/s²
12000
10000
8000
6000
4000
2000
Acceleration
mm/s
1700
1500
1300
1100
900
700
Velocity
mm/s²
12000
10000
8000
6000
4000
2000
*
Deceleration

Figure


mm/s
1750
1500
1250
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750
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-5000
-7500
-10000
-12500
0
141
200
359
488
793
660
613
Go signal
ms
Velocity
Acceleration
Congruent trials RT (mean and s.e.m.)
Incongruent trials RT (mean and s.e.m.)

DISCUSSION

Main results

Aim of the first study was to test the hypothesis of an involvement of the peripersonal space representation in the rapid detection of objects approaching the body for the preparation of involuntary defensive movements. In particular we measured how the excitability of the motor cortex in correspondence of the hand representation varied when an object become visible in the space around the hand. The series of experiments presented in this study showed that the motor cortex is very rapidly provided with information concerning the representation of the visual space around a particular body-part. When an object is approaching the hand, the visual information is thus available to the motor cortex in order to react in the most adaptive way to the environment. This spatial representation is centred on the body, following more the hand rather than the eye position. The inhibition of cortical excitability induced by an object approaching the hand is interpreted as a proactive inhibition in case of voluntary motor plans that are contradictory with the avoidance involuntary reaction. We have also suggested that the source of such information is most likely to be individuated in the premotor cortex, although other multisensory regions may also contribute.

The second study tested, the involvement of the peripersonal space representation in the execution of voluntary actions toward an object, such as an everyday grasping action. The well-known phenomenon of visuo-tactile interference has been used as a measure of the integration of visual and somatosensory information and so as a measure of peripersonal space. The novel approach of co-registration of perceptual multisensory effect and kinematics of the movement allowed to establish possible parallels between the perceptual and the motor domain. Results of this study showed that the multisensory link between visual information on a target object and tactile information on the acting body-part is modulated by the action. A remapping of peripersonal space is indeed induced since the onset of the movement. Moreover, the effect appeared to be present for those conditions which revealed to be the most demanding from a kinematic point of view.

Aim of the third study was to more deeply investigate the link between motor demands and perceptual effects. Employing the same paradigm, we contrasted the peripersonal space remapping induced by a grasping an object with that induced by a less complex action such as a pointing towards (without contacting) the same object. The two kinds of action are known to share a transport component of the hand toward the target; they diverge, by contrast, for the additional presence in the grasping of a grip component where the hand needs to be adjusted to fit the intrinsic characteristics of the target and its spatial orientation. Results of this study showed that the remapping of peripersonal space induced by a voluntary action is continuous and dependent on the sensori-motor transformations required by the particular action in progress. Indeed, the two actions present a similar remapping at the on-set of the movement; however during the execution phase, when the actions kinematically differ, they induce a different remapping of peripersonal space.

The following discussion will try to integrate the results of these studies in a general model of peripersonal space as an interface between the body and the external world.

Peripersonal space: an interface for avoidance reactions

The neurophysiological studies on monkeys have shown the body-centred nature of the peripersonal space representation (Graziano and Gross 1995); the visual receptive fields are in spatial register with the tactile ones; the visuo-tactile neurons areas in the brain receive proprioceptive input in order to update the peripersonal space representation at each body movement. Indeed, as Graziano's studies clearly showed, the visual receptive fields of bimodal visuo-tactile neurones follow the tactile receptive field, for example when the hand changes its position. Importantly, the visual receptive fields are also dynamic, as Fogassi and colleagues showed: an object approaching a body-part induces a modification of the visual receptive fields connected to the tactile ones on the same body-part, as a function of the approaching velocity.

On the basis of these characteristics, Graziano proposed the peripersonal space representation as a "defensive space", a sort of radar that, by anticipatorily detecting approaching objects can prevent the body be hurt by the possible dangerous collisions by rapidly feeding this information to the motor system. Following this hypothesis, Graziano's group collected data about defensive reactions in animals. They thus provided the only available link between peripersonal space representation and involuntary defensive reactions in animals, through the direct electrical microstimulation of bimodal visuo-tactile areas. However, they only showed that such a stimulation induces patterns of movements compatible with defensive reaction.

Our results of the first study reported here are the first direct demonstration in humans that the peripersonal space coding may indeed make available such information to the motor system very rapidly, providing compelling evidence in favour of the role that peripersonal space can play in detecting approaching objects and thus in defensive reactions.

Motor evoked potentials are a measure of the excitability of the motor cortex and thus considered a measure of the "readiness" of the motor cortex to send the motor command for the required movement to be executed. Our results show that motor cortex excitability of the hand representation is reduced when a three-dimensional object is approaching the hand rather than falling far from it. This means that motor cortex receives the information about the presence of a visible object near the body. Furthermore, it is worth noting that the location of the object is coded in a reference frame centred on the body-part. Indeed, our results clearly showed that the effect is more dependent on the position of the hand in the action space than on the direction of visual fixation, or the orienting of attention.

We hypothesized that this early reduction of motor cortex excitability might reflect the proactive inhibition of an undesirable response (Koch et al. 2006; Mars et al. 2007; van den Hurk et al. 2007; van Elswijk et al. 2007), consequence of the conflict between a voluntary motor response (to press the button) and an avoidance movement elicited by the approaching ball. Two arguments are directly available from our results to support this view. The first is the fact that after a voluntary inhibition of motor responses, we did not detect any hand-centered modulation of MEP amplitudes with a general suppression of motor excitability. In other words this result is compatible with the interpretation of the reduction in motor cortex excitability as an inhibition. Second, and more important, MEPs recorded from another muscle that is not involved in the task-related motor response, did not show any modulation depending on the distance of the object with respect to the hand. Therefore, when competition between the avoidance and go responses is eliminated (or temporally desynchronised), no suppression of the avoidance response is required anymore. Our results therefore indicate an interaction between the motor consequences of the rapid visual processing of objects approaching the hand and the voluntary task-related motor plans for that hand. These results represent the first evidence in humans in favour of the involvement of peripersonal space in serving defensive reactions.

A comparison with non-human primates studies

The results of this first study are compatible with an involvement of premotor cortex and posterior parietal areas in this phenomenon. M1 and premotor cortex are indeed densely interconnected, as described in the introduction, both in humans and in monkeys (Davare et al. 2008; Dum and Strick, 2005; Koch et al. 2006; O'Shea et al. 2007; Shimazu et al. 2004).

A point worth of consideration is the on-set of corticospinal modulations at 70-80 ms following the appearance of the object, a very rapid transformation of visual information into motor consequences. The modulation of motor cortex excitability with respect to approaching object may therefore reflect ongoing activity in the premotor cortex. In monkeys, neurons of premotor cortex have been found to be driven by visual stimulation at time periods similar to the ones we have described, and are thought to encode the significance of visual cues for response selection (Cisek and Kalaska, 2005). In humans, the premotor cortex has been shown to participate in visuomotor transformations required to configure hand posture with respect to objects (Davare et al. 2006). Furthermore, recent studies have shown a direct influence of premotor over primary motor cortex as early as 75 ms following a ‘Go’ signal (Koch et al. 2006; O’Shea et al. 2007).

The other point in favour of an involvement of posterior parietal areas is the selectivity of the motor cortex excitability modulation with respect to the three-dimensional characteristics of the object. Indeed, when the real three-dimensional balls were replaced by virtually bi-dimensional static LEDs, no effect was found of the body-centred modulation of the cortical excitability. As reviewed in the introduction, area AIP in the intraparietal sulcus of macaque monkeys shows a strong sensibility to three-dimensional objects with respect to bi-dimensional ones. Since AIP and premotor cortex are densely interconnected, it is plausible to think of an involvement of posterior parietal areas in modulating motor cortex excitability when a three-dimensional object becomes suddenly visible near the hand.

While any comparisons between data drawn from monkeys and humans using such different methods should be made with caution, given the timing and the spatial specificity of the above responses with respect to visual events, these mechanisms fit very well with our results, and suggest the involvement of human posterior parietal and premotor areas with the hand-centred coding of visual space.

These data and considerations support the idea of a parieto-frontal network as the neurophysiological basis of the peripersonal space representations. This specialised system for transforming nearby sensory inputs into rapid and appropriate motor outputs is ideally suited to serve as a sensori-motor interface for driving defensive movements away from potentially harmful approaching objects.

Peripersonal space: an interface for voluntary actions

When grasping an object, the brain updates the link between the visual information available on the target object and the tactile information on the grasping body-part. The results we provided in the second and third studies clearly show that this up-dating arises and that peripersonal space is re-mapped since the on-set of the execution of a grasping. When the hand starts to move - but well before it comes into contact with the object - visual inputs coming from the object are more strongly interacting with tactile information on the body, with respect to a static situation. Furthermore, the finding that such visuo-tactile re-weighting was observed selectively when both perceptual and grasping tasks concerned the same hand not only confirms the hand-centred nature of the peripersonal space representation, but critically extends this property to ecological and adaptive dynamic situations of voluntary manipulative actions. Any interpretation solely based on an attentional account can be ruled out by our results. Indeed, performing the grasping with the left hand as in the second study (experiment 3), required the participants to allocate the same amount of attention on the object as in the right hand grasping condition. Another point worth to be underline is the fact that visual and tactile information in our paradigm were delivered simultaneously. While in most part of the CCE studies, the visual distractor preceded the tactile target, working more as an attentional cue, in our paradigm we tried to avoid it in order to reduce the attentional effects on the visuo-tactile interaction. These results thus constitute the first evidence in humans of an involvement of peripersonal space in the execution of voluntary actions.

A crucial insight in these studies was gleaned from the kinematic analysis of the grasping movements. During the visuo-tactile and object-grasping task, movements of both hands were recorded kinematically. These findings ruled out the possibility that the effector-specific increase in CCE reflected a difference between motor performances for the two hands, since they displayed comparable kinematic profiles. Furthermore, the kinematics analysis revealed possible parallels between the motor and perceptual performances, showing that a difference in the kinematic pattern was reflected by a difference in the perceptual domain. In particular, orientations of the target object that elicited kinematically more demanding reaching movements (i.e., in terms of inward wrist rotation) also elicited stronger CCE. In a different experiment, when the kinematic difficulty of the movement was equalised across different object orientations, the action also triggered comparable perceptual remapping across object orientations, thus showing a comparable amount of CCE when grasping actions were comparably difficult in kinematic terms. This parallel between the motor and perceptual performance strengthens the functional link between multisensory coding of hand-centred space and voluntary action.

The increase in CCE triggered by the action, even if already present at the very on-set of the movement, kept increasing during the early execution phase. That is, an even stronger interference of visual on tactile information was revealed, as the action unfolded in time and space. This suggests that performing a voluntary action triggers a continuous monitoring of action space, which keeps ‘assisting’ the motor execution of the action during its whole dynamic phase. This consideration is indeed supported by the results of the third experiment were two kinematically different actions were proved to elicit different remapping of peripersonal space. If part of the remapping of peripersonal space is already effective at the onset of the motor program, the perceptual modulation can be either further enhanced in the case of relatively complex object-oriented actions like grasping, or kept unchanged in the case of simpler pointing actions. This on-line, motor-evoked “monitoring” of action space opens the possibility of very fast modulations of peripersonal space representation as a function of more ecological needs during action execution. One could speculate that such rapid on-line updating, for instance, could parallel the fast, on-line motor corrections documented in motor control studies (Desmurget et al. 1999; Farnè et al. 2003a; Paulignan et al. 1991; Pisella et al. 2000). Since deficits of the so-called “automatic pilot” (Pisella et al. 2001) have been documented after lesions of the posterior parietal cortex in humans, as well as in healthy subjects after parietal TMS (Desmurget et al. 1999), we suggest that the mechanism underlying the rapid remapping of peripersonal space could be damaged in these patients, thus depriving them from the “monitoring” of action space.

A comparison with non-human primates studies

What kind of mechanism could be responsible for the rapid on-line re-mapping of peripersonal space induced by the execution of a voluntary action?

It is plausible to suggest that a parieto-frontal network would be implied in the visuo-tactile re-weighting described in these experiments. From neuroimaging investigations in humans, as reviewed earlier in this dissertation, both parietal and frontal areas are involved in the execution of reaching and grasping movements. Also investigations on multisensory visuo-tactile perception pointed out the role of parietal and premotor areas. This series of neuroimaging data has provided some evidence about the network of neural structures which appears to be involved in the multisensory representation of near space in humans, namely the IPS and ventral premotor cortex. Activation in the posterior aspect of the medial IPS in humans has been shown to play a role in tasks requiring visuomotor coordination of hand movements with respect to targets (Chaminade and Decety, 2002; Simon et al. 2002; Grefkes et al. 2004). The same area has been reported to show a topographic mapping of space both for saccades and for pointing to targets, which is updated with eye movements (Medendorp et al. 2003, 2005). According to Ehrsson et al. (2004), activity in the medial wall of the IPS reflects the seen position of the hand. Futhermore, IPS has been shown to be activated for objects near the hand rather than far from it (Makin et al. 2006). These findings support the potential role of posterior IPS as an area that integrates visual and spatial information in hand-centered coordinates. The most anterior part of the IPS showed, instead, a significant preference for objects near to the hand also when the hand is not visible. Consistent with properties featured by the macaque anterior intraparietal (AIP) area, the human possible analogue hAIP (Culham et al. 2006) is highly activated by visuomotor tasks such as visually guided grasping (Binkofski et al. 1998; Shikata et al. 2003) and also responds to hand manipulation without visual feedback (Stoeckel et al. 2003). Furthermore, Macaluso and colleagues (2003) found visuo–tactile integration in this area, in addition to activations correlated with motor responses. Also the ventral premotor area in humans appears to be related to visuo-tactile peri-hand space representation. It is worth noting that it could represent the homologue of the premotor cortical area recognised as a region containing perihand neurons in monkeys.

Even if all monkey-human parallels require caution it is plausible to hypothesise a parieto-frontal circuit in humans corresponding to the posterior parietal-premotor cortex circuit in monkeys (Rizzolatti et al. 1997; 2002) that could provide the representation of peripersonal space and a rapid remapping of it during action execution.

CONCLUSIONS AND PERSPECTIVES

The spatial region where we can directly interact with objects has a limited extension. This simple consideration highlights the relevance of the region of space around the body. Indeed, a visually available object close to the body not only represents visual information per se, but from this information the brain has to select among all the possible motor interactions that can occur between the object and the body. When we see our mug of coffee next to us, for instance, not only can we appreciate its color and shape (which may be useful to recognise it as our own mug), but our brain is also translating the object into the movements required to grasp it and bring it to the mouth. Up to date, research partly revealed the multisensory mechanisms that allow this translation process, in monkeys as well as in humans. In particular, the studies of this dissertation revealed that the brain directly links the visual information available outside of the body with the tactile information on the body. Through a system of visuo-tactile neurons, the brain can relate visual information in the proximity of a body-part to the body-part itself, building a peripersonal space representation. Proprioceptive information also reaches this system, updating the link between visual and tactile information as each body-part moves. The brain has thus a multisensory interface between the body and the objects in the external world available for possible body-object interactions. In particular, we showed in humans that the action related properties of the peripersonal space representation feature the basic aspect necessary for allowing rapid avoidance reactions, i.e. a hand centred processing of proximal visual objects. We additionally provide converging evidence that peripersonal space representations are intimately tighted, and possibly deserve, voluntary action execution on nearby objects. Remapping of the peripersonal space representation is time-locked with the onset of an action and continuously operates during its execution, as a function of the sensory-motor transformations required by the action kinematics.

The two hypotheses (involuntary and voluntary object-oriented actions) are not mutually exclusive and one could speculate that, from a more primordial defensive function of this machinery, a more fine-grained and sophisticated function could have developed using the same, relatively basic visuo-tactile spatial computational capabilities. This development could lead to its involvement in the control of the execution of voluntary actions towards objects. Some comparative data showed, for instance, that prosimian sensory areas corresponding to the monkeys' parietal areas already present some approximate motor activity; however, the most represented movements are just very stereotyped limb retractions and defensive movements (Fogassi et al. 1994; see also Kaas 2004 for an interesting comparative approach about parietal functions).

The novel findings presented in this dissertation raise several important issues. First of all, a better knowledge about the homology of the involved areas in the human brain with respect to non-humans primates is necessary. Some interesting clues may come from parietal optic ataxic patients, who show a deficit in manual reaching of visual, but also somatosensory targets (Blangero et al. 2007). In particular, these patients are impaired in reaching with the contralesional hand toward both hemispaces (hand effect) and in reaching with both hands toward the contralesional hemispace (field effect). One possibility could be that the parietal damage impairs the multisensory interface normally available in healthy people to help guiding voluntary actions toward objects. The hypothesis could be made that the motor difficulties presented by optic ataxic patients parallel a lack of the action-triggered remapping of peripersonal space. In this respect, the novel perceptual and kinematic co-recording approach introduced in the experiments 2 and 3 presented here, appears as the best way to investigate the link between an impaired motor performance and a possible deficit in the remapping of peripersonal space. Preliminary results recently collected show indeed a different pattern of visuo-tactile interaction during the execution of an action with respect to healthy participants.

Other point worth discussing is how parietal and premotor areas interact in the modulation of peripersonal space. This is true for the functional involvement of peripersonal space both in defensive and voluntary actions, discussed in this thesis. A double pulse paradigm, with a first conditioning TMS pulse on parietal and/or premotor areas preceding the conditioned TMS pulse on the motor cortex, might be an interesting approach to study the timing of parietal and frontal areas interaction in the modulation of the MEPs.

Another interesting point still un-investigated is how the different sectors of the peripersonal space may interact. Everyday motor acts are rarely limited to a grasping without any other consequences; more often, in fact, we are confronted with complex series of motor acts which involve different parts of the body each with its respective peripersonal space representation. When we answer the phone or when we grasp a pistachio, for instance, we nest bring the object to the ear or into the mouth (respectively!). These simple actions put in a dynamic relation the hand-centred and the head-centred peripersonal space representations. Among the possibilities that could be investigated, the brain may use each representation in a serial way, as a function of the sequential mounting of the two motor components of the entire action: the hand-centred for the grasping and head-centred for the bringing-to-the-head movement. Alternatively, the brain might anticipate the consequences of the entire action, triggering a remapping of the head-centred representation already at the start of the hand movement toward the object.

Nonetheless, when an object is grasped it can also follow a different destiny. I can grasp a telephone or a pistachio, following the previous example, in order to offer it to someone else. In this case, another order of interaction is required, that is a “social” interaction with someone else’s acting body. Recent research on monkeys showed that parietal visuo-tactile neurons can also have a representation of another individual’s body, matching the observer’s own body representation. This correspondence, first of all opens the possibility of a remapping of the peripersonal space of an observer during the simple observation of an action performed by someone else. Preliminary results from our laboratory support this view. A fourth studyexperiment has been indeed performed, where an observer was present beside the active participants. The observer was requested to perform the same perceptual task as in studies 2 and 3, however without executing any actions. At the same time, the observer could see the active participant to reach and grasp the object. Results show that the simple observation of an action can elicit a remapping of peripersonal space also in the observer of the action. Secondly, this matching representation of peripersonal and other individuals’ peripersonal space could be useful both in case of competition in interacting with external object and in case of co-execution of actions. The peripersonal space appears thus to be the multisensory interface the brain developed to follow the dynamic relationship between the body and the world.

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