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THE ROLE OF MEDIAL PARIETO OCCIPITAL CORTEX IN VISUOSPATIAL
ATTENTION AND REACH PLANNING: ELECTROPHYSIOLOGICAL
STUDIES IN HUMAN AND NON-HUMAN PRIMATES

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1. INTRODUCTION

Directing the arm towards a seen object that we want to grasp or touch in the peripersonal space is a typical example of visuomotor coordination. To achieve such actions our visuomotor system must transform stimulus position into coordinates suitable for producing the proper muscle contractions and must constantly update visual information about the object's location with respect to the viewer and to other objects. In fact, in everyday life, we perform actions in a dynamic visual environment. For example, we are able to grab our phone while we read a book or even to quickly intercept it in flight if it's falling. Crucial for these processes to smoothly occur is the ability to shift attention covertly (i.e. in absence of overt eye movements). This ability allows to select interesting information in the field of view in a voluntary way, as well as to quickly redirect the attentional focus when changes in location of an object unexpectedly occurs requiring an update of the current motor plan.

Recent behavioral studies in the human have demonstrated that attention is shifted to the goal of a reaching movement even when the eyes remain fixed, suggesting that, as for saccade, there is an obligatory attention shift to the reach goal before the reaching movement begins. (Baldauf et al., 2006; Baldauf and Deubel, 2008). In addition, other recent research has shown that attention was allocated in parallel in two locations when participants made simultaneous eye and hand movements towards separate locations (Jonikaitis and Deubel, 2011).

Previous neuroimaging and neurophysiological studies have shown that the mechanisms involved in the attentional selection of perceptual events and the execution of overt eye movements are implemented by partially overlapping brain systems in the posterior parietal cortex (PPC) and that attentional modulation in these regions may assist the control of eye movements (see Corbetta & Shulman, 2002 for a review). On the other hand, clear evidence about a direct involvement of reach-related areas of the PPC in attentional processes related to the control of arm movements exists (e.g. Goodale, 2011).

It is widely accepted that the PPC is critical for the on-line control of action. This has been highlighted especially by neuropsychological studies in Optic Ataxia (OA), a visuomotor deficit resulting from lesion of parieto-occipital region (Karnath and Perenin, 2005). These patients are unable (1) to perform accurate reaching movements especially for object located in the periphery of visual field (Perenin and Vighetto, 1988; Karnath and Perenin, 2005) and (2) to correct their arm movements in-flight to changes in target position (Pisella et al., 2003). Furthermore, recent studies have also demonstrated that the deficit in OA patients is not confined to movement execution but also appears to affect the ability to detect and respond to targets located in the periphery of visual field (Striemer et al., 2007; Striemer et al., 2009; McIntosh et al., 2011). These studies suggested that visuomotor symptoms in OA patients may be affected by the difficulty in shifting attention away from the current gaze position, or reorienting attention (Striemer et al., 2007; Striemer et al., 2009; McIntosh et al., 2011).

Consistent with these themes, the present thesis will examine whether in the PPC, similarly to oculomotor areas that provide signals for overt and covert shifts of attention, also reach-related regions may directly contribute in the shifts of spatial attention necessary to the planning and control of arm movements towards the object in the peripersonal space. To this aim we conducted studies in both monkey and human brain investigating whether a specific reach-related area, located in the dorsal part of the anterior bank of the parieto-occipital sulcus, has been implicated in a variety of attentional processes related to the control of goal-directed arm movements.

2. BACKGROUND AND MOTIVATION

A brief overview of the theoretical background is presented in this chapter. This study is focused on the PPC, and a brief overview of its anatomic and functional properties is given in the following section. Instead, in the subsequent sections, we focus on some well known studies in monkey and human brain in which the functional and anatomical properties of regions in the caudalmost part of superior parietal lobule (SPL) were investigated, discussing the main conclusions obtained from these studies. Finally, the motivations for the works presented in this thesis are described at the end of the chapter.

2.1 General Organization of the Posterior Parietal Cortex in Human and Monkey Brain

An extensive overview of anatomic division of the PPC identified regions are out of the scope of this work. The aim of this section is to provide the general background of the anatomical architecture of the PPC and illustrate a map of the anatomical subdivision of the more posterior region of the SPL (i.e. the region around the medial parieto-occipital cortex).

The parietal cortex is anatomically defined by the positions of the three sulci; the lateral sulcus (LuS) separates it from the temporal lobe, the central sulcus (CeS) from the frontal lobe, and the parieto-occipital sulcus (POS) from the occipital lobe. Anatomically the PPC is formed by two lobules: the SPL and inferior parietal lobule (IPL), separated by the intraparietal sulcus (IPS) (Fig. 2-1). The IPL in humans extends to the angular (Ang) and supramarginal (Smg) gyrus, the regions classified as Brodmann area 39 and 40, respectively. The latter occupies the junction of the parietal, temporal and occipital lobes. These two areas play an important role in attention, visual awareness and spatial orientation (see Driver and Mattingley, 1998 for a review). They are described only in the context of studies in humans, since no evidence of the equivalent regions is described in monkeys PPC (Mountcastle et al., 1975; Roland, 1980; Rizzolatti et al., 1998;

Michel and Henaff, 2004). On the other hand the regions classified as Brodmann areas 5 and 7a and 7b, the surface inside the IPS, and the related regions on the medial wall of the hemisphere in the parieto-occipital sulcus, have been extensively described in both human and monkey brain. Specifically, the caudalmost region of SPL contains the most medial part of Brodmann area 19, a cortical visual association area, and it is partly coextensive with area PO, an extrastriate visual area first defined on the basis of myeloarchitectural organization (Colby et al., 1988). More importantly, recent physiological and neuroanatomical studies in the macaque monkey have demonstrated that area PO contains two distinct areas, the visual area V6 and the visuomotor area V6A (V stands for visual, as it was originally identified for its visual properties) (Galletti et al., 1996). Thanks to neuroimaging methods these areas have been recently mapped also in the human brain and named in humans based on homologies in their visuotopic organization with non-human primate areas (Fattori et al., 2009; Cavina-Pratesi et al., 2010; Filimon, 2010; Pitzalis et al., 2012a; Pitzalis et al., 2012b; Pitzalis et al., 2013). Their anatomy and functional roles will be described in more details in the following chapter.

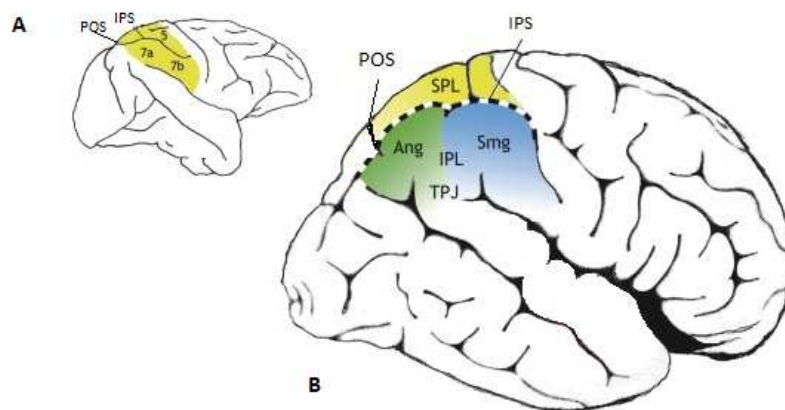


Figure 2 - 1 Representation of Posterior Parietal Cortex in the macaque monkey (A) and human (B) brain.

Each figure depicts the intraparietal sulcus dividing the posterior parietal cortex into superior and inferior regions. Modified from (Husain and Nachev, 2007).

2.2 Functional organization and cortico-cortical connection of regions of the medial parieto-occipital cortex

The results showed in this section are mainly obtained by recording electrical activity in the monkeys brain trained to follow visual or visuo-motor tasks. In a typical setup, a monkey is placed in front of a rear-projected screen or in front of a panel. Microelectrodes are advanced through the intact dura and inserted into the brain tissue, to record extracellular potentials. Finally, the spike trains are extracted from these signals and used to further analyze the typical cell behavior. For analyzing the visuomotor properties, the animal is trained to execute movements towards targets in the visual field. Introducing a delay between the visual input and the movement, separates the sensory and motor related signals.

Instead, the cortico-cortical connections of areas in the parieto-occipital cortex in monkey have been described in the past decade using neuronal tracers, which are substances that, once injected in a brain region, are captured by the neurons and/or by the terminals of nerve cells, and are transported along the neuronal axon up to other brain areas. In this way this technique allows tracing the information flow towards and from the injected region.

In human we cannot record from neurons, because of ethical reasons. Therefore, human studies that are summarized in this section were obtained through the use of non-invasive techniques such as functional magnetic resonance (fMRI).

In the following paragraphs we will discuss the main results about the functional and neuroanatomical characterization of the areas in the parieto-occipital sulcus (POS) in monkey and human brain. This research is focused on area V6A, a reach related region located in the dorsalmost part of the POS. To better understand the roles that area V6A played in processing visuospatial information for the planning and control of goal-directed arm movements, a brief overview of the functional organization of visual area V6, from which V6A area receives directly information, are reported.

2.2.1 Visual area V6

Area V6 is a retinotopically-organized visual area located in the ventral part of POS and was first described in the macaque monkey (Zeki, 1986; Galletti et al., 1999) and then, recently, in the human on the basis of functional criteria (Pitzalis et al., 2006). In both primates it is located medially in the parieto-occipital region of the brain, distinguished from contiguous extrastriate areas of the dorsal visual stream (V2, V3 and V6A). In particular area V6 borders with V6A anteriorly and V3 posteriorly (Galletti et al., 1999a; Pitzalis et al., 2006). Similar to the other extrastriate areas, V6 contains a retinotopic map of about 80° of the contralateral hemifield, although unlike other extrastriate areas it lacks an emphasis of the central visual field (Galletti et al., 1991).

Recent studies have demonstrated that area V6 in the macaque contains many cells sensitive to the direction of motion and real motion cells, which show a better response to stimulus movement in the visual field than to a similar retinal image movement self-induced by an eye-movement (Galletti and Fattori, 2003). Thus, these results indicate that V6 can act as real-motion detector to distinguish actual motion from self-induced motion of retinal images (see Fattori et al., 2009a for a recent review). More specifically, these evidences have suggested that area V6 could provide useful information to guide actions and to shift attention towards moving objects (Galletti and Fattori, 2003). According to these data, Pitzalis et al (2012a) recently suggested that V6, in both human and monkey brain, is involved in the “recognition” of movement in the visual field (Pitzalis et al., 2012a).

These conclusions are supported also by evidence from neuroanatomical studies using neuronal tracers in monkeys. These studies showed that area V6 receives visual information directly from V1 and from other extrastriate areas of the occipital lobe, and sends visual information to several parietal areas, all belonging to the dorsal visual stream, including V6A (Galletti et al., 1999a; Galletti et al., 2001; Luppino et al., 2005; Passarelli et al., 2011). In particular, following V6 injection, the neighbouring extrastriate areas V2, V3, V6A and the V1 cortex was marked strongly. Moreover, area V6 results connected also with

high-order visual areas MIP and LIPv of the intraparietal sulcus and with MT/V5, V4T and MST, classically considered the key motor region of the dorsal visual stream (Tanaka et al., 1986; Tootell et al., 1997) also involved in attentional processes (Bisley and Pasternak, 2000; Corbetta and Shulman, 2002; Martinez-Trujillo et al., 2007). In conclusion, in line with functional evidence, the pattern of connection among these areas involved in higher order function, such as attention regulations and motor function, confirm that the area V6 could perform the fast form and motion analyzes needed for the visual guiding of action (Pitzalis et al., 2012a).

2.2.2 Visuomotor area V6A

Area V6A is located in the dorsal part of the anterior bank of the POS and borders on areas V6 ventrally, PEc dorsally, PGm medially and MIP laterally (Galletti et al., 1999b). V6A is a non-retinotopically organized visuomotor area receiving visual input from V6 (Shipp et al., 1998; Galletti et al., 2001; Passarelli et al., 2011).

A large number of studies have demonstrated that visual, somatosensory or bimodal cells are present in V6A area (Breveglieri et al., 2002; Galletti et al., 2003). A characteristic of the cells in this region is that they have large visual receptive fields, related to coding of peripheral, rather than foveal signals. The activity of most of the cells is modulated by the eye position, although a minority of them are independent of the gaze angle (Galletti et al., 1999b). Furthermore, it has been shown that in a minority of V6A neurons the receptive field (RF) remained stable in space despite changes in eye position (Galletti et al., 1993). This observation has shown that area V6A contains also cells able to encode the position of objects in the environment (Galletti et al., 1993, 1995). Specifically, when the monkeys perform a task in which the direction of arm movements remain constant while the position of gaze changes, a large amount of neurons in V6A showed a reach related activity (Marzocchi et al., 2008). This was due to the location of reaching target respect to fixation point and not simply to the eye position per se (Marzocchi et al., 2008). Therefore, these studies have suggested

that many of cell of area V6A are influenced by the eye and target position signals, but the influence of the hand position, and hand movement signals was also observed (Fattori et al., 2005). In fact, more recent studies based on the delayed reaching and reach to grasp tasks in both human and monkey brain revealed the activity related to planning of the specific type of hand movements, indicating the role of the V6A in the control of hand orientation and grasping (Fattori et al., 2009; Cavina-Pratesi et al., 2010; Fattori et al., 2010).

More importantly, Galletti et al (1996) have shown that the cells of area V6A change in discharge rate after fixation also when the eyes remain fixed, but this change in discharge rate did not occurs during free visual searching in darkness. These observations have suggested (1) that the activity of these cells may reflect the monkey levels of attention (Galletti et al., 1996) and (2) that V6A may play an important role in the planning of motor commands for hand movements, and for visual monitoring of target and hand trajectories.

The role of V6A as a visuo-motor area was supported by neuro-anatomical studies performed in the macaque brain (Shipp et al., 1998; Galletti et al., 2001; Luppino et al., 2005; Gamberini et al., 2009). These studies demonstrate as V6A represents the source of most of the inputs to the motor and premotor regions of the frontal lobe, supplying the information necessary for initiation of the reaching movements. In particular Galletti et al. (2001) have demonstrated that V6A receives from V6 and projects the outputs directly to the dorsal premotor cortex in the frontal cortex. It is importantly to note that all these cortical connection are bidirectional suggesting that area V6A has both visual and motor properties, features which can be useful for the visual guidance of hand movements (Fig. 2-2). On the basis of these evidences Galletti et al (2004) have suggested that area V6A is a crucial node of the most direct pathways from V1 to the dorsal premotor cortex, that form a short route from vision to action which is thought to be useful for the on-line control of hand actions. In summary, this pattern of connections helped to highlight that the area V6A is crucial in spatial representation for control of arm movements, providing signals for visually guided reaching for the motor-related regions.

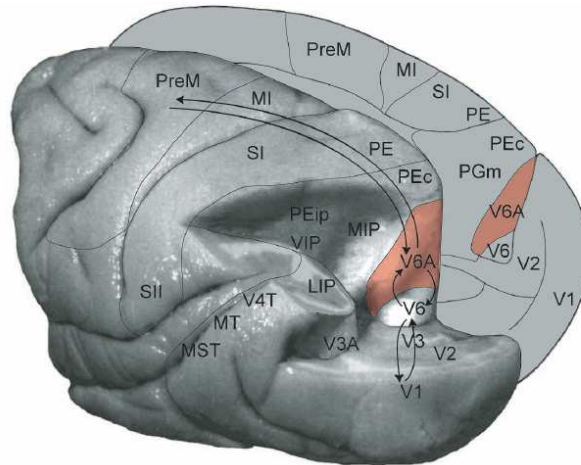


Figure 2 - 2 *Postero-lateral view of partially dissected left hemisphere and mesial surface of right hemisphere in macaque brain.*

Arrows trace anatomical bidirectional connections between different cortical areas of dorso-medial visual stream. It is a cortical loop that includes visual, visuomotor, and motor areas. This pathway connects the primary visual area with the premotor areas of the frontal cortex. As shown, area V6A receives and sends information from area V6. Likewise, area V6A exchanges information with the premotor cortex. From (Fattori et al., 2007).

2.3 Posterior parietal cortex in action: studies on patients with lesions in the parieto-occipital region

Valuable knowledge on the parieto-occipital region functions has been collected through clinical examination of patients with parietal lesions. Specific impairment of the visual control of limb movements has been observed in patients with lesions that involve the parieto-occipital region (Blangero et al., 2009).

2.3.1 Optic Ataxia: a specific disorder in visuomotor coordination

The term Optic Ataxia (OA), first introduced by Balint (1909) and followed by Holmes (1918), is a high-level visuomotor impairment characterized by incapacity to properly complete visually guided reaching and grasping tasks, which cannot be explained by any simple deficit in visual or motor processing. Although

discussions about which parietal regions are related to the emergence of OA still exist, the common believe is that this disorder appears as a consequence of lesions of the parieto-occipital region, which include the putative homologue of monkey area V6A (e.g. Khan et al., 2005).

Patients with OA exhibit large directional errors when reaching movements were performed towards objects located in the peripheral visual field, outside the field of view, whereas misreaching largely disappears if the patient performs reaching for object presented in central vision (Perenin and Vighetto, 1988; but see also Gréa et al., 2002; Milner et al., 1999). In particular, several studies have shown that the errors were towards the direction of gaze even when instructed to reach elsewhere, situation that gives rise to the “magnetic misreaching” and suggests that patients programmed they movements in oculocentric coordinates (Carey et al., 1997; Jackson et al., 2005) In addition, a number of studies have reported that specific property of this behavioral disorder is the hemispheric asymmetry that was observed when the lesion was unilateral (Perenin and Vighetto, 1988; Blangero et al., 2008). Right-handed patients with unilateral lesions on the right hemisphere, exhibited the so called “visual field effect”, a deficit that manifests in the inability to perform accurate reaching movements with both hands in the contralateral visual space. Instead, in the case of left-damaged patients, the “hand effect” was observed, the deficit in reaching appeared for the right hand only, for targets in both visual fields (Perenin and Vighetto, 1988; Blangero et al., 2008). On the basis of these results, recently Blangero et al., (2008) have developed a model to account for these effects. The authors have proposed that reaching movements are based on two independent spatial representations, i.e. the target and the hand location, probably controlled by two distinct modules. The target location would be coded first in gaze-centered coordinates and combined with the spatial representation of the hand to control the movements execution (Blangero et al., 2008).

Additional symptoms in patients with damage of parieto-occipital region are the problems in avoiding obstacles and correcting the hand trajectory during reaching (Schindler et al., 2004). In other words, in tasks where the target position

was changed during reaching execution (perturbed condition), patients were not able to correct the hand direction on time. In contrast, no major abnormal effects were observed in the foveal (unperturbed) condition (Pisella et al., 2000; Gréa et al., 2002; Blangero et al., 2008). Based on these evidences Rossetti et al., (2003) proposed that the impaired performance of OA patients in tasks requiring real-time automatic adjustments to moved objects could be explained by a deficit in the process of fast on-line visuomotor control, which is involved in rapid motor correction of the ongoing action. Moreover the authors suggested that this specific impairment in realtime motor control may explain the pattern of deficit observed in optic ataxia with respect to distinction between peripheral/central vision (Rossetti et al., 2003).

2.3.2 Is there a link between attention and visuomotor control deficits in patients with Optic Ataxia?

Studies on OA patients have argued and demonstrated that visuomotor deficits for visual targets, especially in the periphery of visual field, can occur independently from perceptual disorders. However, recent studies, which have investigated more thoroughly the perceptual and attentional deficit in OA patients, have revealed impaired discrimination of object location or the orientation in extrafoveal vision that may reflect an impairment in orienting attention towards objects located in the ataxic fields (Michel and Henaff, 2004; Rossetti et al., 2005; Pisella et al., 2009). In recent years, more stringent assessments have further supported this hypothesis (Striemer et al., 2007; Striemer et al., 2009), although their conclusions are mixed. For example, Striemer et al. (2007) have investigated the attentional deficit of two OA patients using a cued (exogenous and endogenous) paradigm. In this way, the authors have explored the ability to detect and respond to peripheral cued target in absence of overt goal-directed arm movement. The authors found that the deficit affects both the orienting and reorienting of attention in the ataxic field (i.e. the voluntary shift of attention towards peripheral target and the shift of attention generated by changes in the target location), suggesting that it was consistent with an overall decrease in the salience in this portion of visual fields.

Moreover, in a more recent study Striemer et al (2009) have investigated the possible relationship between attention and reaching comparing the response time to targets detection with the pattern of errors during the reaching execution to peripheral targets. The authors found a different pattern of errors between attention and reaching tasks in OA patients compared with control group, thus proposing that attentional and visuomotor deficits arise from independent mechanisms, accordingly with the most accepted theory about visual of visual processing (Goodale & Milner., 2006). Instead, in more recent studies McIntosh et al., (2011) using a task in which peripheral target jumps towards peripheral location have suggested that the two deficits could be linked, because peripheral target jumps slowed perceptual discrimination and mirrored the reaching deficit.

In conclusion, although the issue remains controversial, overall these studies suggested that the deficits seen in these OA patients could be caused by a deficit in initial decoupling of attention or in online monitoring of movements that imply covert attention shifts, of non-standard visually-guided reaches, rather than simply in the planning of reaching movements.

2.4 Posterior parietal cortex in action: “virtual lesion” approach afforded by TMS to mimic neuro-psychological conditions

In this section, I would like to discuss the more recent advances in our understanding of the role of the PPC in visuo-motor planning and control provided by Transcranial Magnetic Stimulation (TMS) studies. In the last few years, TMS has been used to investigate in details the relationships between the PPC and visuo-motor control (see Vesia and Crawford, 2012 for a recent review). In fact, TMS, by directly interfering with ongoing neural activity to create transient “virtual lesions”, provides exactly the information on causal relations between brain and behavior that cannot be provided by correlative functional imaging or other neurophysiological techniques (Sandrini et al., 2011). This technique has an exquisite temporal resolution, allowing a detailed investigation of visuo-motor control while it unfolds over time. In addition, TMS has a good

spatial resolution, allowing a study of functional topography for visuo-motor function within human PPC. In other words this technique allows one to interfere with a specific stage of visuomotor transformation in a particular cortical area.

In a series of recent studies Busan and collaborators used TMS to stimulate medial parieto-occipital, parietal and premotor regions. In this way the authors have identified a discrete network of regions that were involved in the preparation of reaching movements (Busan et al., 2009b; Busan et al., 2009a). In particular, stimulating on-line (i.e. during the execution of task) with a single pulse of TMS the medial parieto-occipital region at the start of reaching preparation, independently of the use of foveal or peripheral vision and independently of the target position, they found a facilitation in reaction time. This result was explained by the state-dependent theory of TMS (Silvanto and Muggleton, 2008), which suggests that TMS may pre-activate this region that is involved in the planning of reaching movements.

In a more recent study, Vesia and collaborators (2010) used TMS to determine effector specificity in human PPC. In particular, Vesia and collaborators (2010) used online 10 Hz repetitive TMS (rTMS) to examine the specific functional role of one posterior-medial site, which likely includes area V6A, and two anterior-lateral parietal sites, angular gyrus and midposterior intraparietal sulcus (mIPS), which likely includes LIP and MIP areas, in the planning of saccades versus reaches. Vesia et al. (2010) conducted three separate experiments using a delayed saccade and reach paradigm with six visual targets (aligned horizontally in steps of 10° from 30° left to 30° right). In the first experiment, subjects were required to perform saccades or reaching movements (randomly interleaved) with the right hand in complete darkness; in the second experiment, reaching movements were performed with the left hand (again in complete darkness); and in the last one, reaching movements were performed with the right hand, but now with visual feedback (Fig. 2-3).

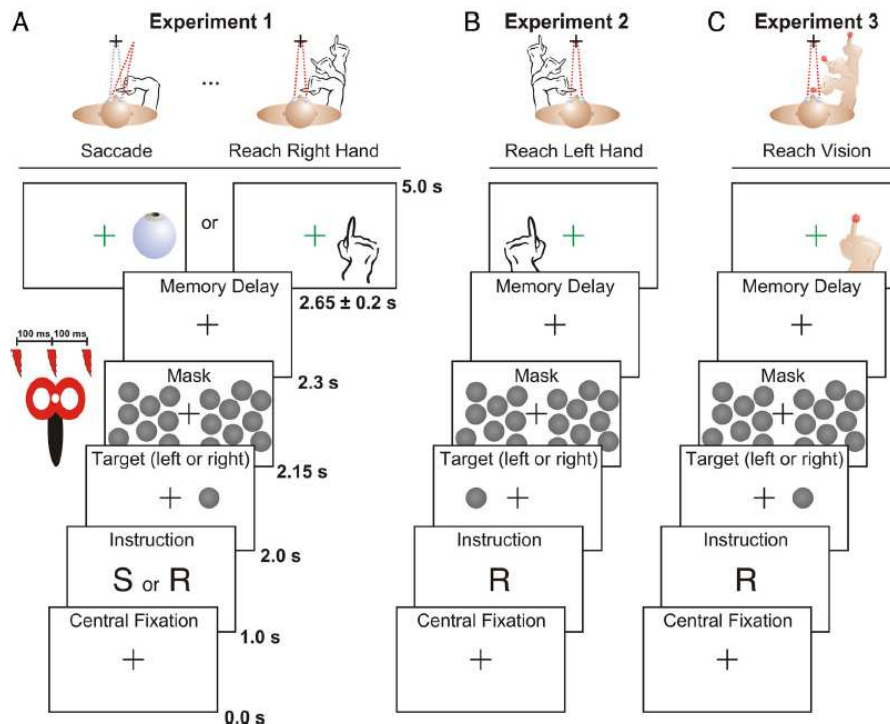


Figure 2 - 3 Experimental condition from Vesia et al., 2010.

A: delayed saccade and reaching movement with right hand. B: delayed reach task with the left hand. C: experiment 3, delayed reach task with visual feedback of the hand.

Task performance was evaluated in terms of movement accuracy and precision. Accuracy was measured as the signed difference between mean endpoint and target positions, whereas precision was measured as the area of 95% confidence ellipses fitted to endpoint distributions. One of the main findings of this study was the reduced accuracy of saccades and the reduced precision of reaches to contralateral targets after stimulation over right mIPS and AG. The TMS-induced effect in these anterior–lateral sites was further reduced by the visual feedback of the hand and, more importantly, it was limb specific, showing a contralateral limb related bias in precision measures. In contrast, stimulation of more posterior site around the parieto-occipital sulcus in either hemisphere did not affect saccade precision or accuracy and did produce a significant shift of mean horizontal reach endpoints toward central fixation (i.e., hypometria), which persisted even when

the hand was visible. Based on these data, Vesia et al. (2010; 2012) have proposed that the parieto-occipital region (likely includes area V6A) bilaterally is specialized for encoding reach targets in retinal coordinates, whereas the more anterior– lateral parietal regions are involved in computations for both reach and saccade motor vectors. In conclusion, Vesia and collaborators (2010) have used this innovative method (rTMS), complementary to functional neuroimaging and electrophysiological technique, to establish a causal link between the function of particular cortical regions and behavioural performance, although it is worth to note that some results and interpretation of this study were raised in a critical review by Ciavarro & Ambrosini (2011) and, therefore, further research is needed to clarify these complex issues.

2.5 The present research

Several studies have suggested that the reach-related area V6A is a crucial node of the dorsomedial visual stream, the most direct pathway from V1 to the dorsal premotor cortex, which is thought to be useful for planning and on-line control of hand action (Galletti et al., 2004). Electrophysiological studies have demonstrated that area V6A contains arm movement-related cells (active during spatially-directed reaching movements) (Fattori et al., 2005; Marzocchi et al., 2008) as well as visual cells (Galletti et al., 1996; Galletti et al., 1999b), and cells that change in discharge rate after fixation, also when the eyes remain fixed (Galletti et al., 1996). These latter observations have suggested that the activity of these cells may reflect the monkey levels of attention (Galletti et al., 1996). On the other hand, neuroanatomical studies using tracers have shown as area V6A receive directly information from area V6 (Galletti et al., 2001; Galletti et al., 2004), which is a visual area very sensitive to the direction of motion and therefore could provide useful information to guide actions and to shift attention towards moving objects (Galletti and Fattori, 2003). Thus, these results from monkeys seem to provide evidences to support the hypothesis that area V6A may participate in visuo-spatial processes related to the control of arm movements. Moreover, a

possible causal role of area V6A in attention processes seems to be supported also by recent neuropsychological evaluation in OA patients (Striemer et al., 2007; Striemer et al., 2009; McIntosh et al., 2011) (see paragraph 2.3.2). Finally recent TMS study has suggested that in human this cortical region is causally involved in the encoding of reach goals (Vesia et al., 2010). However, at present, despite these encouraging results, direct evidences of an involvement of area V6A in attentional processes associated with the planning and control of arm movements are still unknown. To this aim, we conducted studies in both monkey and human brain investigating whether area V6A is implicated in a variety of attentional processes related to the target detection as well as the planning of peripheral arm movements.

In a first study (Chapter 3) we performed single cells recordings in three macaque monkeys to investigate whether the activity of single cells in V6A is influenced by shifts of covert attention (i.e. in the absence of overt eye or arm movements). To this aim we designed a task that required covert attention shifts from a central fixation point outward to a peripheral location, and then inward shifts of attention back to the fixation point. Behaviorally we found faster response times for outwards shift of attention towards cued targets. More importantly, we found that the covert shift of attention influences the activity of V6A neurons. In particular, the spatially-directed modulation observed during outwards shifts of attention suggested that this modulation may be helpful in guiding the hand during the reach-to-grasp movements, particularly when the movements are directed towards non-foveated objects. In addition, the modulations observed during the inward shift of attention from the periphery have suggested that area V6A may be involved in the processes of disengagement of attention from current focus.

In human we have conducted two studies, one behavioral (Chapter 4) and one using Transcranial Magnetic Stimulation (Chapter 5) to investigate the performance of healthy subjects while performing naturalistic reaching movements towards memorized- and cued targets, respectively. To this aim, we have developed a specific apparatus to investigate the kind of errors (spatial

accuracy) while subjects performed fast-reaching movements, without visual feedback of the hand, towards peripheral targets located at different eccentricities. In this way we have investigated (1) the frames of reference involved in the visuomotor transformation during reaching movements towards memorized target (Chapter 4), and (2) the possible causal role of the putative homologue of area V6A (pV6A) in the planning of reaching movements in which the location of targets is validly or invalidly predicted by spatial cues (Chapter 5). In particular, in this TMS study, we have tested the involvement of pV6A in the reorienting of attention towards unattended target (i.e. the target changes in location with a probability 25%) by introducing a manipulation to increase the magnitude of the validity of the cues (the cue correctly predicted target location with 75%). To this aim, in addition to the kinematic parameter of reaching movements we have recorded also the response time to target detection. The results have shown as on-line TMS on the pV6A selectively interfere with the encoding of goal-directed movements directed towards unattended target, affecting both the response to targets detection and the end-point of reaching movements. On the basis of these results, we have demonstrated that area V6A plays a crucial role in the disengaging/reorienting of attention, an indispensable process to make a rapid and adaptive motor response such as reaching, grasping or pushing away when a behaviorally relevant object unexpectedly appears at an unattended location.

3. COVERT SHIFT OF ATTENTION MODULATES THE ONGOING NEURAL ACTIVITY IN A REACHING AREA OF THE MACAQUE DORSOMEDIAL VISUAL STREAM¹

3.1 Abstract

Attention is used to enhance neural processing of selected parts of a visual scene. It increases neural responses to stimuli near target locations and is usually coupled to eye movements. Covert attention shifts, however, decouple the attentional focus from gaze, allowing to direct the attention to a peripheral location without moving the eyes. We tested whether covert attention shifts modulate ongoing neuronal activity in cortical area V6A, an area that provides a bridge between visual signals and arm-motor control.

We performed single cell recordings from 3 *Macaca Fascicularis* trained to fixate straight-head, while shifting attention outward to a peripheral cue and inward again to the fixation point. We found that neurons in V6A are influenced by spatial attention. The attentional modulation occurs without gaze shifts and cannot be explained by visual stimulations. Visual, motor, and attentional responses can occur in combination in single neurons.

This modulation in an area primarily involved in visuo-motor transformation for reaching may form a neural basis for coupling attention to the preparation of reaching movements. Our results show that cortical processes of attention are related not only to eye-movements, as many studies have shown, but also to arm movements, a finding that has been suggested by some previous behavioral findings. Therefore, the widely-held view that spatial attention is tightly intertwined with - and perhaps directly derived from - motor preparatory processes should be extended to a broader spectrum of motor processes than just eye movements.

¹ A version of this chapter was originally published in PLoS ONE journal: *Galletti C, Breveglieri R, Lappe M, Bosco A, Ciavarro M, Fattori P (2010)*.

3.2 Introduction

When we want to recognize an object in the field of view, or want to grasp it, we typically direct our gaze towards the object. The shift of gaze is the consequence, and the overt evidence as well, of the shift of our attention towards the object of interest. Although under normal circumstances the direction of attention and the direction of gaze are aligned, we are able to disengage attention from the point of fixation. This ability, known as covert spatial attention, allows us to select and acquire peripheral visual information without shifting the gaze (Posner, 1980).

Attention enhances both behavioral and neuronal performances (Spitzer et al., 1988). Reaction to attended targets is faster than to unattended targets (Posner et al., 1980), and responses of neurons to covertly attended stimuli enhance above those of unattended stimuli (Fischer and Boch, 1985; Desimone and Duncan, 1995; Colby et al., 1996; Connor et al., 1997; Kodaka et al., 1997). Thus, attention modulates the processing of information in visual cortical maps, and selects parts of the scene to receive increased processing resources.

The selection of the part of the scene to receive attention, i.e. the control of the focus of attention, is driven by the saliency of the stimuli and by the requirements of the task that is currently performed. If motor actions are to be performed on the selected targets, the focus of attention is closely related to these actions. The initiation of a saccade, for instance, is preceded by a mandatory shift of attention towards the saccade goal (Hoffman and Subramaniam, 1995; Kowler et al., 1995; Deubel and Schneider, 1996; Awh et al., 2006). The deployment of attention are linked to the mechanisms of selecting a saccade target and preparing the saccade even for covert attention shifts (Moore et al., 2003; Cavanaugh and Wurtz, 2004; Ignashchenkova et al., 2004; Hamker, 2005; Thompson et al., 2005; Liu et al., 2010).

The link between attention and goal-directed motor action is not confined to eye movements. Also the preparation of reaching movements is paralleled by a shift of attention to the goal of the reach (Castiello, 1996; Deubel et al., 1998). Therefore, one might expect that, similar to oculomotor areas that provide signals

for overt and covert shifts of attention, also cortical areas that are involved in arm movements may contribute to shifts of attention, or may use spatial attentional signals to prepare arm movement or direct the hand towards the object to be grasped.

The medial posterior-parietal area V6A acts as a bridge between visual processing and arm motor coding (Galletti et al., 2003). Our aim in this work was to find out whether the activity of single cells in V6A is influenced by shifts of covert attention. Since, usually, the direction of gaze and the direction of attention are aligned, and since area V6A contains a high percentage of gaze-dependent neurons (Galletti et al., 1995), we had to disengage attention from the point of fixation (covert attention) in order to demonstrate that the direction of attention, and not the direction of gaze, modulates V6A neurons. In a task specifically designed for this, we found that the neural modulation was still present when the covert attention was shifted without any concurrent shift of the direction of gaze. We suggest that this attentional modulation is helpful in guiding the hand during reach-to-grasp movements, particularly when the movements are directed towards non-foveated objects.

3.3 Materials and Methods

3.3.1 Experimental procedures

Experiments were carried out in accordance with National laws on care and use of laboratory animals and with the European Communities Council Directive of 24th November 1986 (86/609/EEC), and were approved by the Bioethical Committee of the University of Bologna and authorized by Ministero della Salute (Permit N° DM 47/2008-B, 6/4/2008, signed by the Direttore of the Dipartimento Sanità Pubblica Veterinaria). In accordance with the European Legislation and Guidelines and with the recommendations of the Wheatherall report, “The Use of non-human primates in research”, many measures were taken to ameliorate animal welfare: monkey training adopted positive reinforcement techniques. No deprivation, punishment, or suffering was inflicted. All procedures used have

been approved and controlled by the Central Veterinary Service of the University of Bologna. Monkey food and water intake, as well as daily weight, were controlled by researchers and veterinarians, in order to monitor the wellbeing of the monkeys. Veterinarians were ready to detect, if present, clinical signs of pain or distress and to suggest the appropriate measures to increase animal welfare.

Three trained *Macaca fascicularis* of 6, 5 and 4 kg (Monkey L, Monkey C and Monkey X) sat in a primate chair and performed an attentional task with their head restrained. We performed single microelectrode penetrations using homemade glass-coated metal microelectrodes with a tip impedance of 0.8-2 MOhms at 1 KHz, and multiple electrode penetrations using a 5 channel multielectrode recording minimatrix (Thomas Recording, GmbH, Giessen, Germany). The electrode signals were amplified (at a gain of 10,000) and filtered (bandpass between 0.5 and 5 kHz). Action potentials in each channel were isolated with a dual time-amplitude window discriminator (DDIS-1, Bak electronics, Mount Airy, MD, USA) or with a waveform discriminator (Multi Spike Detector, Alpha Omega Engineering, Nazareth, Israel). Spikes were sampled at 100 KHz and eye position was simultaneously recorded at 500 Hz. Eye position was recorded using an infrared oculometer (Dr. Bouis, Karlsruhe, Germany) and was controlled by an electronic window (5 x 5 degrees) centered on the fixation target. Behavioral events were recorded with a resolution of 1 ms. We performed extracellular recordings on all the 3 animals; on two of them we also performed behavioral recordings.

Surgery to implant the recording apparatus was performed in asepsis and under general anesthesia (sodium thiopental, 8 mg/kg/h, i.v.). Adequate measures were taken to minimize the animal's pain or discomfort. Specifically, analgesics were used postoperatively (ketorolac trometazyn, 1mg/kg i.m. immediately after surgery, and 1.6 mg/kg i.m. on the following days). Extracellular recording techniques and procedures to reconstruct microelectrode penetrations were similar to those described in other reports (Galletti et al., 1995b).

3.3.2 The attentional task

Data were collected while monkeys were performing a task specifically designed to study the effect of covert spatial displacements of the spotlight of attention on neural responses. The monkeys sat in front of a fronto-parallel panel which was located 14 cm from the animal's eyes. The panel contained 3 green/red light emitting diode (LED; 4 mm in diameter; 1.6° of visual angle) that served as fixation point and target to be detected. The fixation point was the green/red LED located in the straight-ahead position. Two circular rings (12 mm in diameter; 4.8° of visual angle), illuminated by a yellow LED, served as a cue that indicated the spatial position of the subsequent target to be detected. The cue and target LEDs were located 15° peripherally on opposite sides from the fixation point.

The time sequence of the task is shown in Figure 3-1 a. A trial began when the monkey decided to press the home-button near its chest. After pressing the button, the animal waited for instructions in complete darkness. It was free to look around and was not required to perform any action. After 1000 ms, the fixation LED lit up green. The monkey was required to look at the fixation target and to maintain the button press while waiting for an instructional cue.

After 1700-2200 ms, another LED (the CUE) lit up for 30-150 ms in one out of the two peripheral positions located 15° apart from the fixation point. After 1000-1500 ms a red flash (TARGET) of 5 ms occurred in the cued position. The monkey had to release the home-button as soon as it detected the target. The maximum time allowed to release the button was 1000 ms. If the monkey did not release the button during this period the trial was marked as error trial. After 1000-1500 ms, the fixation point changed in color from green to red. The monkey had to press the home-button again (maximum time to press was 1000 ms) to drink the reward. Home-button pressing ended the trial, issued monkey reward, and started the next trial.

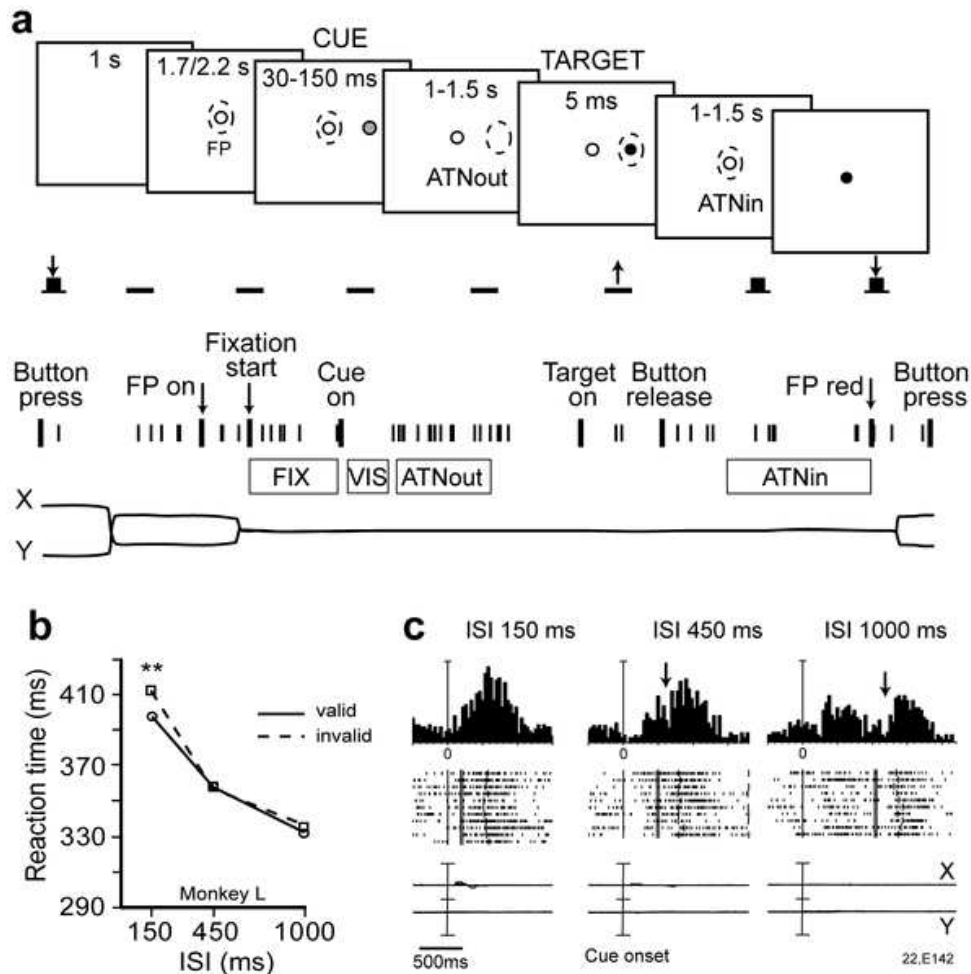


Figure 3 - 1 Attentional Task and effects in V6A

a) Schematic representation of the task. Top: Sequence of events in a single trial. After button pressing, the monkey maintained fixation on the central fixation point (white dot, FP) all throughout the trial while covertly shifting attention (dashed circle) towards the cued location (grey dot). After target (black dot) detection, the animal released the button, continuing to gaze the fixation point until it changed in color (from green to red). Color-change detection was reported by the animal by button pressing. Bottom: typical example of neural activity and eye traces during a single trial. Short vertical ticks are spikes. Long vertical ticks among spikes indicate the occurrence of behavioral events (markers). Below the neural trace, time epochs during a typical trial are indicated. ATNout: outward attention epoch, ATNin: inward attention epoch. *b)* Performance of 1 monkeys expressed as

reaction time to detect the target at different inter-stimulus-intervals (ISIs). Results from valid (continuous) and invalid (dashed) trials are shown. Significant difference in reaction times between valid and invalid trials at ISI 150 shows that attention is directed towards the peripheral cue location at this time. c) Peri-stimulus time histograms of an example neuron recorded with different ISIs. Trials are aligned to cue onset. The neuron shows two discharges (after cue onset and button release, respectively) that separate (arrow) clearly at longer ISIs.

The correctness of the animal's performance was evaluated by a software supervisor system (Fattori et al., 2005) which checked the status of microswitch (monopolar microswitches, RS components, UK) mounted under the home-button. Button presses/releases were checked with 1 ms resolution.

Displacements of the spotlight of attention towards the two peripheral positions were typically tested as a randomized sequence in order to collect trials in one position intermingled with the other. Up to ten trials for each position were collected (20 trials in total). The panel could be rotated in 4 different positions (horizontal, vertical, and 2 oblique positions in between the two), allowing to test up to 8 spatial displacements of the spotlight of attention.

The task was performed in darkness. Eye fixation was always maintained in the straight ahead position within an electronic window of 5° amplitude. Fixation had to remain within this window throughout each trial until the fixation point switched off, otherwise the trial was aborted and a new one began without any reward. Off line inspection of eye records allowed to check for actual performance of fixation.

3.3.3 Neuronal data analysis

We divided the trial into functional epochs, defined as follows (see bottom part of Figure 3-1a):

- **FIX:** steady fixation of the LED from its appearance to the cue onset; it contains the baseline activity of the neuron, used to compare the cell activity during the other epochs.

- VIS: from 40 to 150 ms after the cue onset; it could contain the passive visual response evoked by the cue appearance.
- outward attention epoch (ATNout): from 200 to 500 ms after the cue onset; it could contain the response due to the covert, peripheral displacement of the spotlight of attention.
- inward attention epoch (ATNin): from 400 ms after button release to the change in color of the fixation point; during this epoch the animal concentrates attention on the fixation point, as it has to detect the fixation point's change in color.

For behavioral analysis, the reaction time between target onset and button release was determined.

Only units which were tested in at least 7 trials for at least two target positions were included in the analysis. This is a conservative choice connected to the implicit high variability of biological responses (Kutz et al., 2003).

For each neuron, the mean firing rate was calculated for each trial in outward attention epoch and inward attention epoch, and statistically compared with the mean firing rate in epoch FIX (two-tailed Student's t-test; significance level, $p < 0.02$ with Bonferroni correction for multiple comparisons). Units with a significant discharge during at least one of the two attentional epochs were considered task related and were further analyzed. Excited cells during ATNout were defined as those cells whose discharge during ATNout was stronger than the one during FIX. Inhibited cells during ATNin were defined as those cells whose discharge during ATNin was stronger than the one during FIX. The same was done for the epoch ATNin.

The spatial tuning of activity in the task-related cells was analyzed statistically by comparing the mean firing rate in each target position (one-way ANOVA, F-test; significance level, $p < 0.05$) for each of the functional epochs described above. A neuron was defined as 'spatially tuned' when it showed a statistically significant difference in mean firing rate in the same epoch in different spatial locations. Direction selectivity of neurons modulated during outward attention

epoch and/or during inward attention epoch was quantified by a preference index (PI) for each functional epoch as follows:

$$PI = \text{abs}(D - OD)/(D + OD)$$

where D = maximal discharge for cells excited with respect to FIX or minimal discharge for cells inhibited with respect to FIX, and OD = discharge for the opposite position.

PI ranged from 0 to 1.

Population activity of tested neurons was calculated as averaged spike density functions (SDFs). A SDF with a Gaussian kernel of half-width 40 ms was calculated for each neuron included in the analysis, averaged across all the trials for each tested condition, and normalized to the peak discharge of the neuron in the behavioral epochs of interest. The normalized SDFs were then averaged to derive population responses. We statistically compared the population SDFs with a permutation test with 10,000 iterations comparing the sum of squared errors of the actual and randomly permuted data.

3.3.4 Behavioral data

We performed psychophysical measurements in separate sessions on 1 animal. In these sessions for monkey L we collected reaction times of the monkeys in valid trials, in which the target appeared in the cued position, and in invalid trials, in which the target appeared in the uncued position. These reaction times were recorded separately from the physiological data because the physiological recordings contained only valid trials. We recorded behavior during batteries of trials containing 20% of invalid trials randomly interleaved with valid trials. We tested two opposite target positions, to the right and to the left of the fixation point.

Various inter-stimulus-intervals (ISIs) were tested; we used ISIs = 150 ms, 450 ms, 1000 ms (similar to the ISIs tested in Bowman et al., (1993). ; A repeated measures ANOVA ($p < 0.05$) with factors: ISI (3 levels) and validity (2 levels) was used to assess the effect of validity, of ISI, and of the interaction

between the two, on reaction time to target detection. To assess the validity effect for each ISI, post hoc comparisons using the Newman Keuls correction were used.

3.4 Results

We performed extracellular recordings on 182 single cells of area V6A in 3 *Macaca fascicularis*. Cells were ascribed to V6A following the functional criteria described in Galletti et al. (1999a), and on cytoarchitectonic criteria according to Luppino et al. (Luppino et al., 2005).

Animals were trained to fixate a light-emitting diode (LED) in the straight-ahead position in darkness while pressing a button located outside their field of view. While fixating, the monkeys had to detect a target (5 ms red flash) in one out of several peripheral positions and respond to it by releasing the button without moving the eyes (Fig. 3-1a). The target position was cued by a yellow flash (30-150 ms) preceding the target onset by 1-1.5 s. The cue signal prompted the monkeys to covertly displace attention towards the periphery. After target detection, the monkeys shifted attention back towards the straight-ahead position to detect the change in color of the fixation LED. This change in color had to be reported by pressing the button again. The monkeys were trained to maintain gaze in the straight-ahead position all throughout the trial. Their fixation was checked using an electronic window and off line inspection of recorded eye traces.

We quantified each cell's discharge during three time epochs (see Fig. 3-1a): the starting fixation epoch before cue onset (baseline activity, FIX), the epoch from 200 to 500 ms after cue onset (covert attention shifted towards the cue location, 'outward attention'), and the epoch from 400 ms after button release to the change in color of the fixation LED, when attention is again directed towards the central fixation point ('inward attention'). We also analyzed passive visual response to the cue appearance in an epoch from 40 to 150 ms after the cue onset (VIS; see supporting information).

3.4.1 Behavioral bases of covert attention shift

To check whether our experimental conditions induced covert attention shifts, we measured reaction times (RTs) between target onset and button release in one

monkeys. These measurements were collected in separate behavioral testing sessions before the onset of single unit recording. These sessions contained valid trials as described above, and invalid trials in which the cue was misleading because the target appeared on the opposite side. It is well known that effects of covert attention shifts are reflected in differences in the reaction times between valid and invalid trials both in human (Posner, 1980) and monkey (Bowman et al., 1993). In valid trials, especially with brief inter-stimulus-interval (ISI), the reaction time are expected to be shorter than during invalid trials because the location where the target appears benefits from attentional enhancement evoked by cue appearance.

As reported in Figure 3-1b, reaction times for target detection in valid and invalid trials were recorded at ISIs of 150, 450 and 1000 ms (Monkey L). Mean reaction times were 400.01 ms (ISI 150), 360.01 ms (ISI 450) and 335.90 ms (ISI 1000) for valid trials, and 412.89 ms (ISI 150), 357.35 ms (ISI 450) and 336.16 ms (ISI 1000) for invalid trials. These data were entered in 3x2 repeated measures ANOVA with ISI (150, 450 and 1000) and validity (Valid vs invalid trials) as within factors. The ANOVA has revealed a significant interaction ISI x validity ($F(2,36)=5.47$, $p=0.008$) with a difference in reaction time between valid and invalid trials occurred for the ISI of 150 ms ($p=0.0009$, Newman-Keuls *post hoc* test). The shorter RT for valid trials is an index of attention allocated to the cue, and confirms that the experimental paradigm we used elicited covert attention shifts in our monkey subjects. For longer ISIs, the validity effect was no longer significant, although reaction time for both trial types decreased with increasing ISI (repeated measures ANOVA, main effect of factor ISI, $F(2,36)=72.87$, $p=0.000001$) suggesting an increase of alertness when the ISI is longer.

3.4.2 Single-unit recordings

Since significant RT difference between valid and invalid trials was observed for ISI of 150 ms but not for ISIs of 450 ms and higher, and because we wanted to exclude from the analysis the effect of putative visual responses to cue onset (see

supporting information), we restricted the analysis of the effect of outward attention shifts to a time epoch from 200 and 500 ms after cue appearance. However, we performed also the analysis with a time window from 150 ms to 450 ms and the results were the same. Below, we report the results of the former analysis as a more conservative approach.

Since key-press and key-release actions elicited neural responses in V6A (Galletti et al., 1997; Marzocchi et al., 2008), we wanted to separate in time the responses related to inward shifts of attention from the responses related to the button press. To this aim, in preliminary experiments we varied ISI during cell recordings. Figure 3-1c shows an example of a cell recorded with different ISIs (150, 450 and 1000 ms, tested in randomly interleaved trials) and a cue duration of 30 ms. When the ISI was 150 ms (Fig. 3-1c left), the cell had a strong and long discharge starting immediately after the cue onset. An increase of the ISI to 450 ms (Fig 3-1c, center) caused the tendency of the discharge to separate in 2 components (see arrow in Fig 3-1c, center). These two components became further separated and distinguishable at an ISI of 1000 ms (see arrow in Fig 3-1c, right), the first component related to the cue, the second to the button release. Since these components were clearly separable only at an ISI of 1000 ms, when recording from neurons we used ISIs of 1000 and 1500 ms, to be able to correlate each discharge component with the different events occurring during the trial.

Of 182 recorded cells, 83 (46%) showed neural discharges during the outward and/or inward attention epochs that were significantly different from the baseline (epoch FIX) as assessed by Student's t-test (with Bonferroni correction, $p < 0.02$). From now on, we will refer to these cells as 'task-related cells'.

3.4.3 Neural responses during outward attention

Fifty-one task-related cells were modulated during outward attention epoch (Student' t-test, $p < 0.05$). In particular, 24 cells (47%) were inhibited (i. e. the discharge during outward attention epoch was weaker than during FIX), and 27

cells (53%) were excited (i. e. the discharge during outward attention epoch was stronger than during FIX).

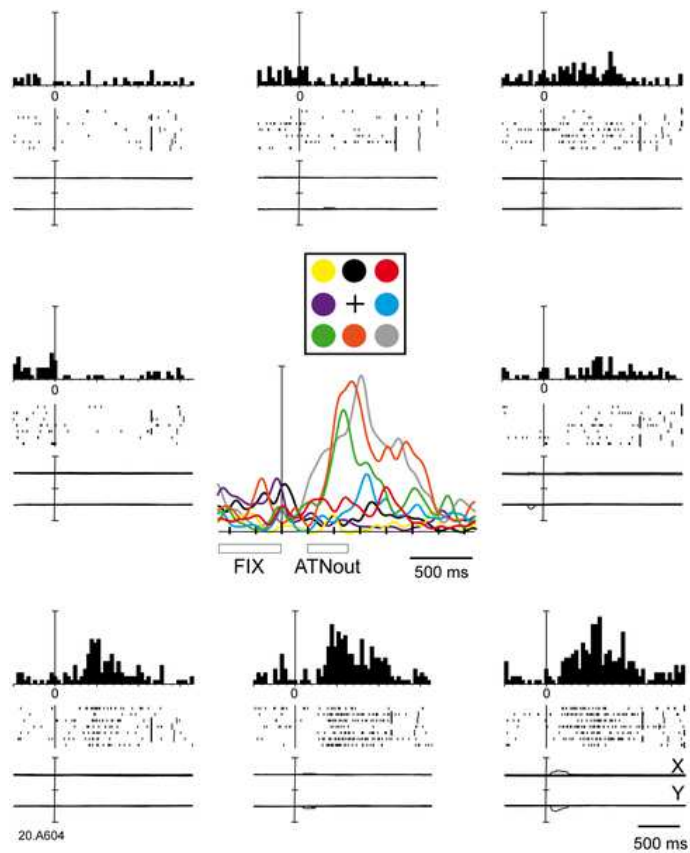


Figure 3 - 2 Example of spatially-tuned modulations of neural activity during outward attention epoch.

The neuron shows a strong discharge during outward attention epoch preferring covert shifts of attention towards the bottom part of the space. Each inset contains the peri-event time histogram, raster plots and eye position signals, and is positioned in the same relative position as the cue on the panel. In the central part of the figure, the spike density functions (SDFs) of the activity for each of the 8 cue positions are superimposed and aligned on the cue onset. The mean duration of epochs FIX and outward attention is indicated below the SDFs. Neural activity and eye traces are aligned on the cue onset. Scalebar in peri-event time histograms, 70 spikes/s. Binwidth, 40 ms. Eyetraces: scalebar, 60°. Other details as in Figure 3-1.

Figure 3-2 shows a cell with a typical outward attention response for cues presented in the lower space. The spatially-tuned outward attention activity had a very long latency (on average 283 ms). The cell discharged strongly after cue onset and continued to discharge well after cue offset. In some trials, the response lasted until target onset, that is 1 s or more later than cue onset. This discharge was very different from a typical V6A visual response (Galletti et al., 1999c). To compare the effect of what we call “outward attention” to a purely visual response in our neuronal sample we assessed the influence of the visual stimulation by the cue appearance (epoch VIS) on the firing rates. Consistent with earlier observations that a stationary light stimulus like the cue is not the most effective stimulus for V6A visual cells (Galletti et al., 1999c), only 40% of the cells (72/182) were modulated during VIS with respect to the baseline epoch FIX (Student’ t-test, p,0.05).

One example of a cell with a typical visual response to cue onset is shown in Figure 3-3. The response started about 80 ms after the cue onset. The cell showed a brisk response whose duration was similar to the duration of the stimulus (150 ms).

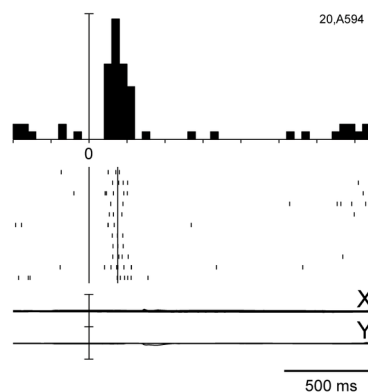


Figure 3 - 3 Typical visual response in V6A.

Neural activity and eye traces are aligned with cue onset. Peri-event time histograms: binwidth, 40 ms; scalebars, 38 spikes/s. Eyetraces: scalebar, 60u. Other details as in figures 3-1 and 3-2. The response started about 80 ms after the cue onset. The cell showed a brisk response whose duration was similar to the duration of the stimulus (150 ms).

Comparing the discharges after cue presentation in Fig. 3-2 and 3-3, it is evident that the duration of the outward attention response was much longer than the visual stimulus, contrary to what happens in typical visual responses where stimulus and response durations are nearly the same. Second, the latency of outward attention response was much longer and less strictly time locked than the latency of a typical visual response.

Spatial tuning of the outward attention activity was a common finding in our sample of V6A neurons: twenty-six out of 51 cells (51%) resulted significantly spatially tuned (one-way ANOVA, $p, 0.05$).

To investigate the direction sensitivity of cells with outward attention activity, we computed a preference index (PI, see Experimental Procedures). Figure 3-4 a shows, separately, the distributions of PIs for excited (red) and inhibited (blue) cells. About half of the excited cells were direction selective, with a PI higher than 0.2. Note that the cell shown in Figure 3-2, that was strongly direction-selective, had a PI of 0.44. The inhibited cells were even more sensitive to the direction of covert attention, showing higher number of cells with high preference index.

Figure 3-4 b shows the population activity of V6A cells that were excited (red lines) or inhibited (blue lines) during the epoch of outward attention. The continuous lines represent the average mean activity of cells in trials in which the cue appeared in the position evoking the maximum (excited) or the minimum (inhibited) discharge rate. The dashed lines represent the average mean activity of the cells in trials in which the cue appeared in the opposite position. The plots have been aligned on cue onset.

The discrimination between two opposite spatial positions at population level began around 100 ms after cue onset and peaked around 300 ms (Fig. 3-4b). This agrees with the time course of the shift of the spotlight of attention as assessed from the behavioral data: a behavioral effect of attention at the cued location was detectable 150 ms after the cue onset and ceased within 450 ms after the cue onset. Also the rapid change of population activity just after cue onset reported in Figure 3-4b well agrees with the fact that the displacement of the

spotlight of attention during outward attention epoch is exogenously driven by the cue.

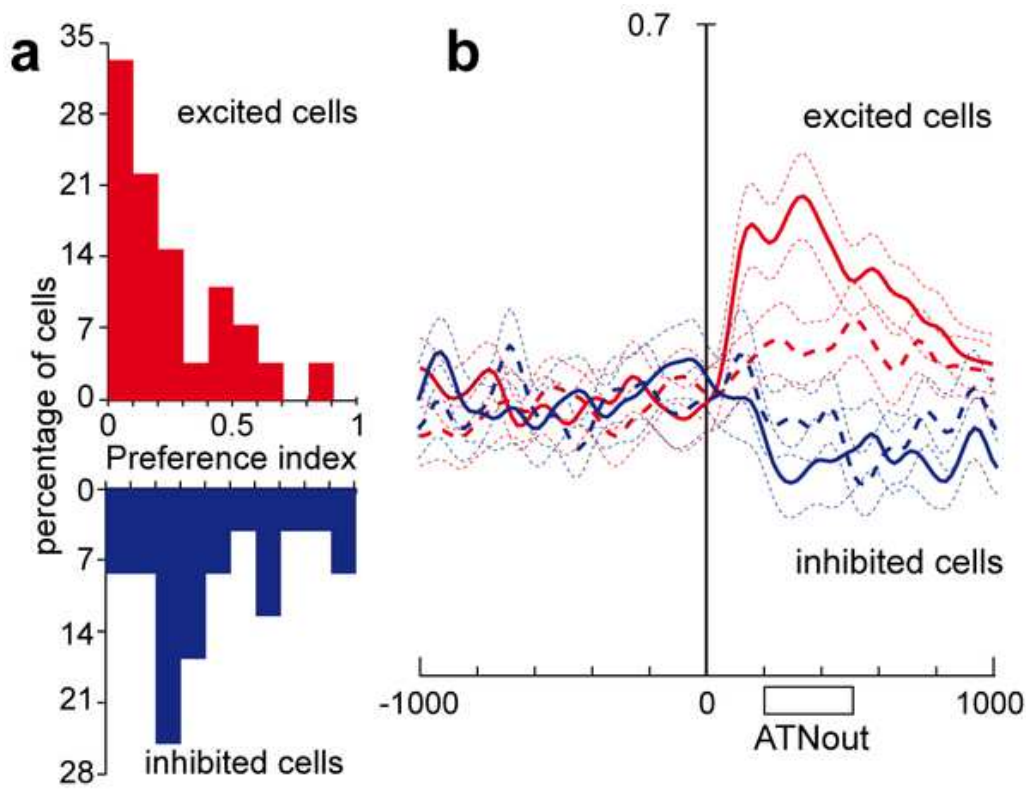


Figure 3 - 4 Activity modulation during outward attention epoch.

a) Distribution of preference index (see Experimental procedures) for cells excited (red histogram) and inhibited (blue histogram) during outward attention epoch. b) Effect of the covert dislocation of the spotlight of attention on the activity of V6A cells during outward attention epoch. The average SDF for the excited (red lines) and inhibited (blue lines) cells are shown. Continuous lines represent the average SDF for the cue location evoking the maximal (excited cells) or minimal (inhibited cells) activity, and the dashed line that for the opposite location. Two dotted lines for each SDF indicate the variability band (SEM). The activity of cells in each population is aligned on the cue onset. Scale in abscissa: 200 ms/division; vertical scale 0.7. Other details as in Figure 3-1.

Independently from the effect of outward shift of attention (excitation or inhibition), the number of cells preferring contralateral shifts of covert attention (i.e. cells whose maximal discharge was for shifts towards parts of the space contralateral with respect to the recording site) was the same as that of cells preferring ipsilateral shifts (i.e. cells whose maximal discharge was for shifts towards parts of the space ipsilateral with respect to the recording site). Interestingly, the spatial distribution of visual receptive fields in V6A, mostly contralateral, is significantly different from the spatial selectivity of attentional responses (Chi-squared test, $p,0.0001$), as shown in Figure 3-5. This fact is against the view that the attentional effect could be the result of a modulation of the visual response, suggesting a functional separation between the two phenomena.

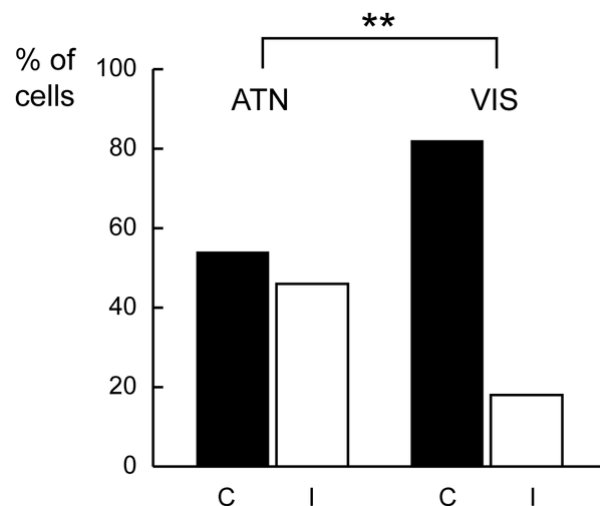


Figure 3 - 5 Preferred attentional and visual receptive-field locations in area V6A.

Columns indicate the percentages of neurons modulated during outward attentional epoch (ATN) preferring contralateral (C) or ipsilateral (I) targets, and the percentages of visual cells (VIS) with the receptive-field center in the contralateral (C) or ipsilateral (I) hemifield. ATN and VIS populations include 26 and 684 cells, respectively. The percentage of visual cell with receptive fields centered in the contralateral hemifield was significantly higher than those centered in the ipsilateral hemifield (Chi-squared test, $\text{chisquared} = 14.92$, $p,0.0001$).

3.4.4 Neural responses during inward attention

After target detection (i. e. after button release) the animal was requested to respond to a change in color of the fixation LED that occurred 1000 to 1500 ms after button release (see Fig. 3-1a). Thus, it is plausible that, during this period, the focus of attention was brought back to the fixation point (inward attention epoch). Because the fixation LED remained illuminated in the same color throughout the inward attention epoch, and because no further visual stimulation was given after the target presentation and the button release, modulations occurring in the inward attention epoch cannot be ascribed to a visual stimulation. They had to be related to endogenously driven shifts of attention towards the fixation point.

Out of the task-related cells, 63 (76%) were significantly modulated during inward attention epoch with respect to the baseline (Student t-test, $p < 0.05$): 33% of these cells were excited whereas the majority (67%) were inhibited. Figure 3-6a shows a cell with a strong discharge during inward attention epoch. This discharge occurred independently of the direction of covert attention during the preceding outward attention epoch (cue location). Most of the excited cells of our population showed this behavior (71%). Figure 3-6b shows a cell with direction selectivity: its response during inward attention epoch was different for the different cue positions. Neurons like these, showing a change in discharge in periods in which neither the processing of visual information, nor the execution of motor acts is taking place, strongly support the notion that attention modulates V6A neurons.

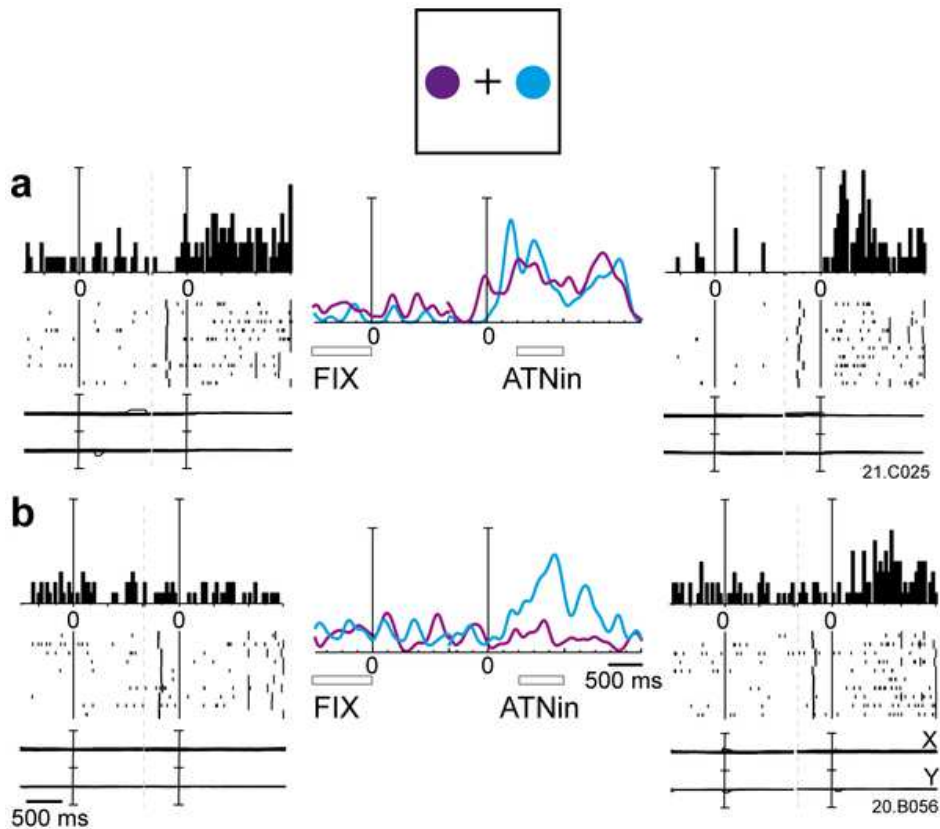


Figure 3 - 6 Examples of two neurons excited during inward attention epoch.

a) neuron excited during inward attention epoch, insensitive to the direction of the focus of attention. **b)** Neuron excited during inward attention epoch, sensitive to the direction of the focus of attention. Left and right: neural activity, raster dot displays and eye traces are aligned twice, with the cue onset (left) and with the button release (right). Center: SDFs of the two cue positions are superimposed (blue line: right position, purple line: left position). Peri-event time histograms: binwidth, 40 ms; scalebars, 18 spikes/s (a), 25 Spikes/s (b). Eyetraces: scalebar, 60u. Other details as in Figures 3-1 and 3-2.

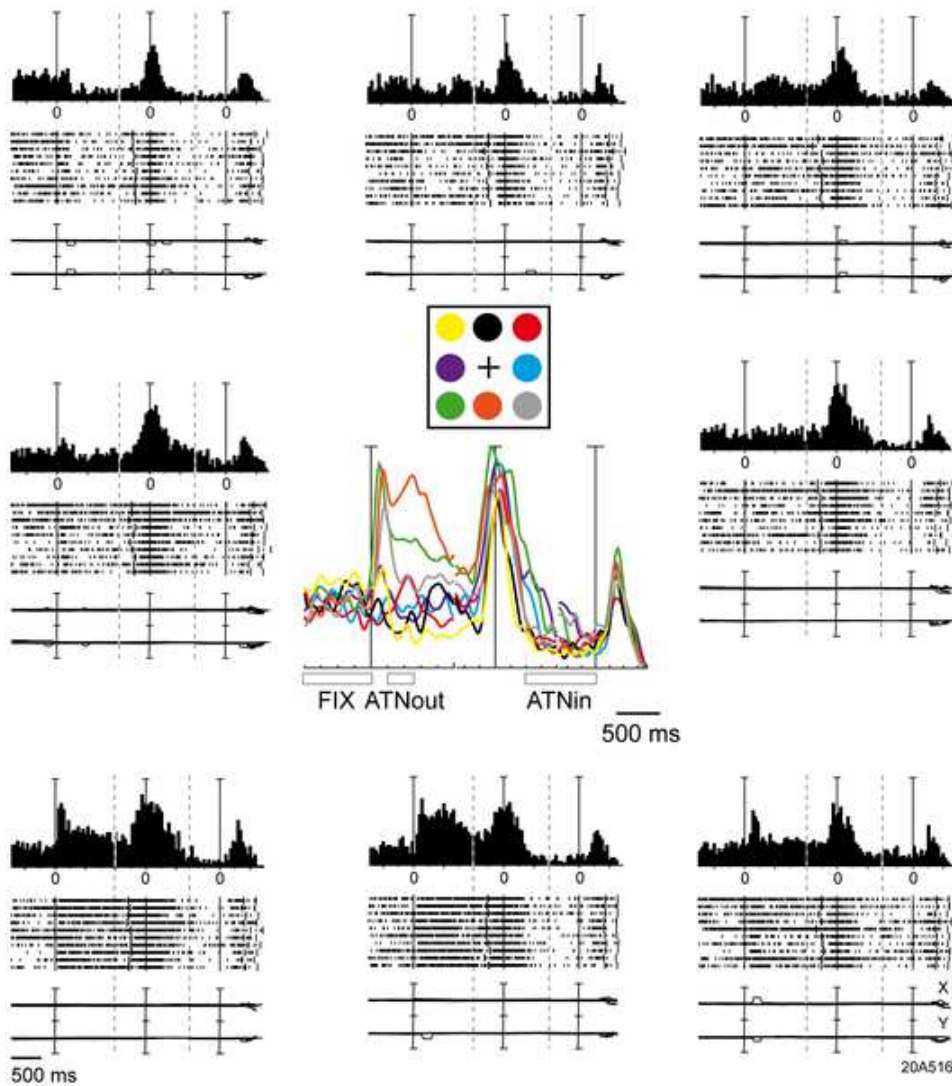


Figure 3 - 7 Example of a cell modulated during outward and inward attention epochs.

This cell was excited during outward attention epoch when attention was covertly directed towards bottom locations, and inhibited during inward attention epoch for all attended locations. In addition, this cell was excited during button release and in the visual epoch, especially in the 3 lower positions. Neural activity and eye traces are aligned three times: from left to right: with the cue onset, with the button release and with the change in color of the fixation point. Peri-event time histograms: binwidth, 40 ms; scalebars, 180 spikes/s. Eye traces: scalebar, 60u. Other details as in Figures 3-1 and 3-2.

Selective responses in the different task epochs could be found in combination in individual neurons: 31 cells were driven by both outward and inward shifts of attention, as the example reported in Figure 3-7. This is a cell whose activity was strongly modulated by the covert shift of attention towards the cue (outward attention epoch), but also by the action of button press, and by the bringing back of attention focus towards the fixation point (inward attention epoch). This last modulation was actually an inhibition. A one-way ANOVA on the activity of this cell around the button press (from 150 ms to 650 ms after target onset) gave a significant influence of target position ($p,0.05$). Therefore, the example of Figure 3-7 shows that the effect of attention can modulate not only the ongoing activity but also the motor-related activity of a single cell. The large majority of V6A cells are of this type.

Spatial tuning for inward attention epoch was less common than for outward attention epoch (17/63, 27%; 1-way ANOVA $p<0,05$). We calculated the distribution of preference indices separately for the population of excited and inhibited cells. The majority of excited cells (15/21, 71%) showed weak directional selectivity, with PI lower than 0.2 (Fig. 3-8a, red histogram). The directional selectivity of cells inhibited during inward attention epoch (Fig. 3-8a, blue histogram) was slightly higher than that of excited cells.

Figure 3-8b shows the population activity of the cells significantly excited (red lines) or inhibited (blue lines) during inward attention epoch ($N=21$ and 42, respectively). The plots have been aligned on the button release. On average, cell activity changes after the button release, i.e, at a time when attention is redirected to the fixation point in order to detect its upcoming change in color. Cell activity then remained high or low (according to the type of cell) up to the end of the trial. This behavior is in line with a shift of attention to the fixation point and can not be explained by visual stimulation, oculomotor, or any other motor-related activity. The delay of the change in cell discharge is longer than that observed in outward attention epoch (see Fig. 3-4b), in agreement with the view that the phenomenon is endogenously driven.

3.5 Discussion

We have recorded responses of cells in monkey area V6A in a task that required covert attention shifts from a central fixation point outward to a peripheral location, and then inward shifts of attention back to the fixation point. The outward shift was exogenously driven by a visual cue while the inward shift was endogenously driven by the learned requirements of the task.

We found that the activity of V6A cells was modulated by the outward shift of covert attention, often in a direction-selective way, with half of the cells excited and half inhibited by the attentional shift. The onset and duration of attentional response correspond well to the typical temporal profile of exogenous attention shifts in humans (Posner, 1980) and to the attentional benefits on reaction times in our monkeys. Because the outward attention shift is driven exogenously by the visual cue signal, the cell response may contain a visual component. However, the latency and duration of attentional responses are clearly different from the typical visual responses in V6A (see Fig. 3-3). Visual responses have short latency, small variability between trials, and a duration that matches the duration of the stimulus (Galletti et al., 1979). Attentional responses have longer latency and higher variability (see for instance rasters of spikes in the bottom part of Fig. 3-2). In cases where both visual and attentional responses were present in the same cell (e.g. in the bottom insets of Fig. 3-7), the brief visual response (same duration as the stimulus) was sometimes seen alone (e.g. in the bottom right panel), while in other cases (e.g. in the bottom central and left panels) it was followed by a tonic (attentional) discharge lasting hundreds of ms after the end of visual stimulation.

The activity of about 35% of V6A cells (63/182) was modulated by inward shifts of attention (inward attention epoch). The majority of the affected cells (about two-thirds) were inhibited, one-third were excited. These activity modulations were usually not spatially tuned, that is they did not vary significantly with the change in location of the cue. This was in agreement with the fact that during inward attention epoch the attention was focused on the same spatial location (the fixation point) regardless of cue location. It is worthwhile to

note that contrary to outward shifts, inward shifts were endogenously driven, so they were not prompted by any visual stimulation. Therefore, cell activity during inward attention epoch cannot be ascribed to a visual stimulation.

Activity modulations during outward and inward attention epochs may reflect a process representing the spatial location of the focus of attention. The spatial sensitivity of many cells is in line with this view. The excitation observed in the majority of neurons after outward attention shifts might reflect the better responsiveness at the new cued location commonly found in attentional studies. The inhibition observed in the majority of neurons when attention was directed back to the fixation point might reflect the decreasing responsiveness at the formerly cued location. Inhibition at previously cued locations is a common finding in attention research (Klein, 2000) and an important contribution to the shaping of the “attentional landscape”. Comparison of the population activities in the outward and inward attention cases (Figs. 3-3 and 3-7) shows that the magnitude of the modulation is higher in the inward cases. This could be because in inward cases gaze and attentional focus are aligned, or because the inward attention shift is an endogenous process whereas the outward shift is exogenously driven. It is also possible that the modulation in the outward attention cases is smaller because attention is not maintained at the outward locus long enough to reach the same level of modulation as in the inward case.

It may be argued that the responses observed during the outward and/or inward attention epochs could be related to other cognitive processes, such as the preparation of the monkey to get ready for the button release/press, or arousal, or also the expectation of a later reward. Nevertheless, we believe that, if this were the case, we would have no spatial tuning of the responses, because the arm actions are button presses occurring in a fixed spatial location. Since many cells here are spatially tuned in their attentional shifts, we believe we can rule out other interpretations of the results.

Many studies have focused on the influence of attention on neural activity in different brain areas, namely area LIP (Colby et al., 1996; Gottlieb et al., 1998; Goldberg et al., 2006; Buschman and Miller, 2007; Bisley and Goldberg, 2010;

Herrington and Assad, 2010; Liu et al., 2010), superior colliculus (Ignashchenkova et al., 2004), frontal eye fields (Wardak et al., 2006; Buschman and Miller, 2007), area 7a (Bushnell et al., 1981; Constantinidis and Steinmetz, 2001; Raffi and Siegel, 2005; Rawley and Constantinidis, 2010), area DP (Raffi and Siegel, 2005), area MT (Cook and Maunsell, 2002; Herrington and Assad, 2010), area VIP (Cook and Maunsell, 2002). While a large amount of those studies shows that spatial attention modulates the neuronal response to a stimulus (Desimone and Duncan, 1995; Constantinidis, 2006), our findings provide evidence that spatial attention modulates the ongoing activity of a neuron, and this happens in an area never studied before in the attentional context. Other previous studies have demonstrated that the ongoing activity of cells in a high number of cortical areas, including V6A, is modulated by the direction of gaze (Galletti et al., 1995; Bremmer et al., 1998). This was generally interpreted as an oculomotor effect. However, since the direction of gaze and the spotlight of attention are usually aligned, the gaze modulation could be the result of an attentional process which modulates the neuronal activity, rather than a direct oculomotor effect. By disengaging the attention from the point of fixation we have shown that this is the case for at least 30% of the neurons in area V6A (outward attentional effect). For these neurons, neural modulation was still present when covert attention was shifted without any concurrent shift of gaze direction, confirming that the modulating factor is the attentional process.

Recent brain imaging studies have shown that in the human medial superior parietal lobe there were transient activations by shifts of covert attention from one peripheral location to another (Chiu and Yantis, 2009; Esterman et al., 2009). The activation was located in the anterior bank of the dorsalmost part of the parieto-occipital sulcus, that is just in front of where area V6 is located in human (Pitzalis et al., 2006). Since in macaque, area V6A is located just in front of area V6, in the anterior bank of the parieto-occipital sulcus, we suggest that the medial superior parietal region described by Chiu and Yantis (2009) is the human counterpart of the macaque area V6A. If this were the case, we could conclude

that in both macaque and human, area V6A is modulated by covert shifts of attention.

3.5.1 Why an attentional modulation in a reaching area?

V6A is an area that contains visual, gaze, and arm movement-related neurons (Galletti et al., 2003). Present results show that V6A neurons are also modulated by covert spatial shifts of attention, and that visual, motor, and attentional responses can co-occur in single V6A cells. We had previously demonstrated that several single V6A cells were particularly sensitive to arm movements directed towards non-foveated objects (Marzocchi et al., 2008). The covert attentional modulations could allow these cells to select the goal of reaching during movement preparation, as well as to maintain encoded, and possibly update, the spatial coordinates of the object to be reached out during movement execution.

Our results have shown a homogeneous spatial tuning of attention. This behavior parallels the homogeneous distribution of preferred gaze and reach directions observed in area V6A (Galletti et al., 1995; Fattori et al., 2005), while it is in contrast with the preferred contralateral representation of the visual field, since the distribution of visual receptive fields in V6A mainly represents the contralateral visual field (Galletti et al., 1999b) (see also Fig. 3-4). In other words, the spatial tuning of attentional preference does not follow the sensory tuning, but rather the oculomotor and arm-reaching tuning found in V6A.

We believe that present results provide crucial support for the hypothesis that spatially-directed attention is linked to motor programming. Our study thus extends previous findings of a connection between attention and eye movement control (Moore et al., 2003; Cavanaugh and Wurtz, 2004; Ignashchenkova et al., 2004; Hamker, 2005; Thompson et al., 2005; Bisley and Goldberg, 2010) to the case of reaching control, and points towards a neural substrate for interactions between attention and reaching that are known from human behavioral data (Castiello, 1996; Deubel et al., 1998).

4. BEHAVIORAL INVESTIGATION ON THE FRAMES OF REFERENCE INVOLVED IN VISUOMOTOR TRANSFORMATIONS DURING PERIPHERAL ARM REACHING²

4.1 Abstract

Several psychophysical experiments found evidence for the involvement of gaze-centered and/or body-centered coordinates in arm-movement planning and execution. Here we aimed at investigating the frames of reference involved in the visuomotor transformations for reaching towards visual targets in space by taking target eccentricity and performing hand into account. We examined several performance measures while subjects reached, in complete darkness, memorized targets situated at different locations relative to the gaze and/or to the body, thus distinguishing between an eye-centered and a body-centered frame of reference involved in the computation of the movement vector. The errors seem to be mainly affected by the visual hemifield of the target, independently from its location relative to the body, with an overestimation error in the horizontal reaching dimension (retinal exaggeration effect). The use of several target locations within the perifoveal visual field allowed us to reveal a novel finding, that is, a positive linear correlation between horizontal overestimation errors and target retinal eccentricity. In addition, we found an independent influence of the performing hand on the visuomotor transformation process, with each hand misreaching towards the ipsilateral side.

While supporting the existence of an internal mechanism of target-effector integration in multiple frames of reference, the present data, especially the linear overshoot at small target eccentricities, clearly indicate the primary role of gaze-centered coding of target location in the visuomotor transformation for reaching.

² A version of this chapter was originally published in PLoS ONE journal: *Ambrosini E*, Ciavarro M*, Pelle G, Perrucci MG, Galati G, Fattori P, Galletti C, Committeri G (2012) *Equal contribution*

4.2 Introduction

Directing the arm towards a seen object that we want to grasp or touch is a typical example of visuo-motor coordination. Albeit apparently simple, this operation actually requires a series of complex processes. The stimulus position is initially coded by the visual system in retinal coordinates, whereas the motor output guiding the arm movement is coded in intrinsic muscular coordinates. Therefore, the representation of target location must be transformed into coordinates suitable for producing the proper muscle contractions (Soechting and Flanders, 1989b, a; Henriques et al., 1998). Moreover, retinotopic information about target location must be integrated with the position of the effector to compute higher-level movement parameters, such as the direction and distance that the hand must cover to reach the target (movement vector) (Buneo et al., 2002).

To investigate the reference frames involved in arm-movement planning, many psychophysical studies have focused on the spatial pattern of reach errors, basing on the assumption that the error pattern is directly determined by the specific reference frames involved. Several works have found evidence of an oculocentric spatial coding (Henriques et al., 1998; Henriques and Crawford, 2000; Poljac and van den Berg, 2003; Beurze et al., 2006; Sorrento and Henriques, 2008), showing that errors in goal-directed arm-movements vary as a function of the position of the target relative to the current gaze. It has been shown that the spatial position of a reach target is encoded and updated in an eye-centered frame of reference, regardless of whether the target is visual, auditory, tactile or even imaginary (Pouget et al., 2002). Interestingly, a gaze-centered coding of the location of visual and proprioceptive targets has also been proposed in position judgments (Fiehler et al., 2010) and even in tactile localization (Harrar and Harris, 2009).

These psychophysical results are in accordance with single-unit recordings in monkeys and human functional brain imaging studies, suggesting that a gaze-centered frame of reference is used to represent and update target locations in specific reach-related areas of the posterior parietal cortex (PPC) (Batista et al.,

1999; Cohen and Andersen, 2000; Medendorp et al., 2003; Medendorp et al., 2005). For example, Batista et al. (1999) showed that in the parietal reach region (PRR) of the monkey neuronal activity varied when gaze was changed relative to the reach target. More recently, Marzocchi et al. (Marzocchi et al., 2008) demonstrated that the reach-related activity of area V6A, a reaching area of the medial PPC, was modulated by the retinotopic coordinates of reaching target. Neuropsychological studies on unilateral and bilateral optic ataxia patients (with damage in PPC regions corresponding to monkey PRR and V6A) showed deficits in reaching that are consistent with a dynamic gaze-centered internal representation of reach space. For instance, previous studies (Khan et al., 2005a; Khan et al., 2005; Dijkerman et al., 2006; Blangero et al., 2009) have shown that patients with unilateral optic ataxia make large reaching errors when, after foveal target presentation, a saccade prior to movement onset forces them to ‘remap’ the location of the target into their ataxic visual field.

However, other psychophysical experiments have revealed that in the visuomotor transformation process the hand and target positions could be compared also in body-centered coordinates (Soechting and Flanders, 1989b, a; Flanders et al., 1992; Gordon et al., 1994; McIntyre et al., 1998; Vindras et al., 1998; Carrozzo et al., 1999) or in both gaze- and body-centered coordinates (Battaglia-Mayer et al., 2001; Battaglia-Mayer et al., 2003; Beurze et al., 2006; Khan et al., 2007; Marzocchi et al., 2008). For instance, in the study of Khan et al. (2007), reaching errors of both control subjects and patients revealed an influence of target position in gaze-centered coordinates, but also showed a large quasi-independent shoulder-centered influence of target position. Their results thus suggest that, during visuomotor transformations, the target and hand positions are compared in multiple reference frames at more than one level, and these comparisons are then integrated.

The purpose of the present study was to investigate the frames of reference involved in the visuomotor transformation process during reaching movements towards memorized visual targets in space. To this aim, we employed an experimental paradigm that allowed disambiguating the role of eye-centered and

body-centered reference frames, by measuring their relative weight in determining subjects' errors in a reach-to-point task towards the remembered position of visual targets in darkness. This was achieved by experimentally varying the position of the fixation point, as in previous works (e.g., Bock, 1986; Enright, 1995; Henriques et al., 1998). When only gaze fixation is varied, indeed, the reaching movement remains fixed with respect to the body (both initial hand position and reach target) and errors possibly arising from an intrinsic body-centered representation should remain constant; in contrast, errors arising from a gaze-centered frame of reference should vary depending on gaze direction. Notably, several works have shown that reaching errors vary as a function of the target position relative to current gaze, but it is still unclear if a linear influence does exist (e.g., Bock, 1986; Enright, 1995; Henriques et al., 1998). Therefore, to clarify this point, we used several perifoveal target positions. Finally, we also explored the impact of the performing hand on reach errors, that is, an issue which has not been systematically addressed so far.

4.3 Materials and Methods

4.3.1 Ethics Statement

Participants provided written informed consent before the beginning of the experiment, which was approved by the Ethics Committee of the “G. d’Annunzio” University, Chieti, and was conducted in accordance with the ethical standards of the 1964 Declaration of Helsinki.

4.3.2 Participants

Twelve human subjects (four males and eight females; mean age \pm SD = 24.1 \pm 1.1) participated in the experiment. All participants were right-handed, as defined by the Edinburgh Handedness Inventory (Oldfield, 1971) , without any known neurological or muscular deficits, and had normal or corrected-to-normal vision.

4.3.3 Apparatus

Subjects were seated on a height-adjustable chair in complete darkness, with the head mechanically stabilized with a chin rest and a head holder, which were mounted onto a wooden table directly in front of them. A Plexiglas screen (120 x 50 cm) covered with a matte black sheet was placed on the table in a frontal plane within the subject's reaching distance (at 42 cm). The height of the chair and the chin rest were adjusted so that the subject's cyclopean eye (located midway between the two eyes) was vertically and horizontally aligned with the central fixation light-emitting diode (LED) (see following section).

The stimuli array consisted of nine LEDs aligned on the horizontal plane. Three red LEDs, located at -17.2° , 0° , and 17.2° , served as fixation points. Six yellow LEDs, located at three different eccentricities (11.5° , 8.6° , and 5.7°) on both left and right sides of the central fixation LED, were used as reaching targets (Figure 3-1). All LEDs were installed behind the Plexiglas screen. They were visible only when illuminated and gave no tactile feedback when touched. The starting position of the hand reaching movement was a button placed under the chin rest and immediately in front of the subject's torso.

Movements of the left or the right index finger were monitored using an electromagnetic tracking device (3 Space Fastrak[®], Polhemus Navigation; Colchester, VT, USA), which detected the position of small sensors attached to the tip of the left and right index fingers (sampling rate: 120 Hz, static accuracy = 0.8 mm, resolution = 0.05 mm). Data were digitized and recorded on a PC for off-line analysis. During the experiment, eye movements were monitored with an infrared tracking system (ISCAN ETL-400, Burlington, MA, USA), which was placed behind the Plexiglas screen.

Stimulus presentation and recording of the participants' responses were controlled by a custom software (developed by Gaspare Galati at the Department of Psychology, Sapienza Università di Roma, Italy; see Galati et al., 2008), written in MATLAB (The MathWorks Inc., Natick, MA, USA) that implemented Cogent 2000 (developed at FIL and ICN, UCL, London, UK) and Cogent

Graphics (developed by John Romaya at the LON, Wellcome Department of Imaging Neuroscience, UCL, London, UK) platforms.

4.3.4 Experimental procedures

Participants were requested to reach to the remembered position of a target location in complete darkness, while maintaining fixation at the fixation LED. In order to dissociate the visual from the body spatial coordinates of the reach targets, four experimental conditions were tested by manipulating the position of the fixation LED as illustrated in Figure 3-1: A) fixation on the central LED and reach targets presented on the left visual field (VF) and left body field (BF) (lVF/lBF: Figure 3-1A); B) fixation on the central LED and reach targets presented on the right visual and right body fields (rVF/rBF: Figure 3-1B); C) fixation on the left LED and reach targets presented on the right visual and left body fields (lVF/lBF: Figure 3-1C); D) fixation on the right LED and reach targets presented on the left visual and right body fields (rVF/rBF: Figure 3-1D). The four conditions were studied separately in four experimental sessions and, to examine the influence of the performing hand on pointing errors, the four sessions were repeated for both hands. The resulting eight sessions were presented in pseudorandom order for each participant, with the constraint of alternate sessions performed with left and right hand.

At the beginning of each trial, subjects fixated the red fixation LED. Next, one of the yellow reach LEDs (target) was illuminated for 300 ms, while the subject was required to maintain fixation. After a variable delay (200, 300, or 400 ms) from the target offset, the fixation LED flickered, signaling the subjects to reach to and touch the remembered location of the target, while maintaining their gaze fixed at the fixation LED. Reaching movements were performed in darkness and the subjects reported being unable to see their moving arm. Participants were required to complete the reaching movement within 3000 ms, after which the next trial began. For every experimental condition, each of the three reaching targets was presented 16 times in random order, for a total of 48 trials in each session. To prevent darkness adaptation, at the end of every experimental session the room

light was switched on for two minutes. Subjects were instructed to perform a fast reaching movement as accurately and fluidly as possible. Before the experiment, subjects completed a brief training session to familiarize with the experimental procedure. The training section lasted until subjects learned to maintain fixation and to move their arm only after the go signal. At the end of the experiment, a calibration procedure was conducted. Participants reached all the LED targets (with visual feedback of the hand) while fixating them. Reaching errors that we report later are computed as the reaching position relative to the corresponding reached position during this calibration procedure.

4.3.5 Data analysis

Performance was evaluated by mapping the reaching movement endpoints on the horizontal (x) and vertical (y) axes of the screen. For every trial, endpoint position in the x and y axes was estimated at the point of minimum z position (i.e. the point at which the finger touched the screen). Errors were calculated as the difference between finger endpoint and target position as computed in the calibration procedure.

To quantify movement accuracy we computed three different types of constant errors. The first one, termed “distance” (in cm), was computed as the Euclidean distance between the mean endpoint and target position, and represents the absolute error. The other two measures, named “algebraic x and y errors” (in cm), are equal to the horizontal and vertical component, respectively, of the absolute error and were calculated as the signed difference between the horizontal and vertical components of endpoints and the corresponding values of each target position. “Movement precision” (variable error), instead, was measured by fitting the 95% confidence ellipse on the reaching endpoints distribution separately for each subject for every target and condition. Variable error was then calculated using the area (in cm²) of these ellipses.

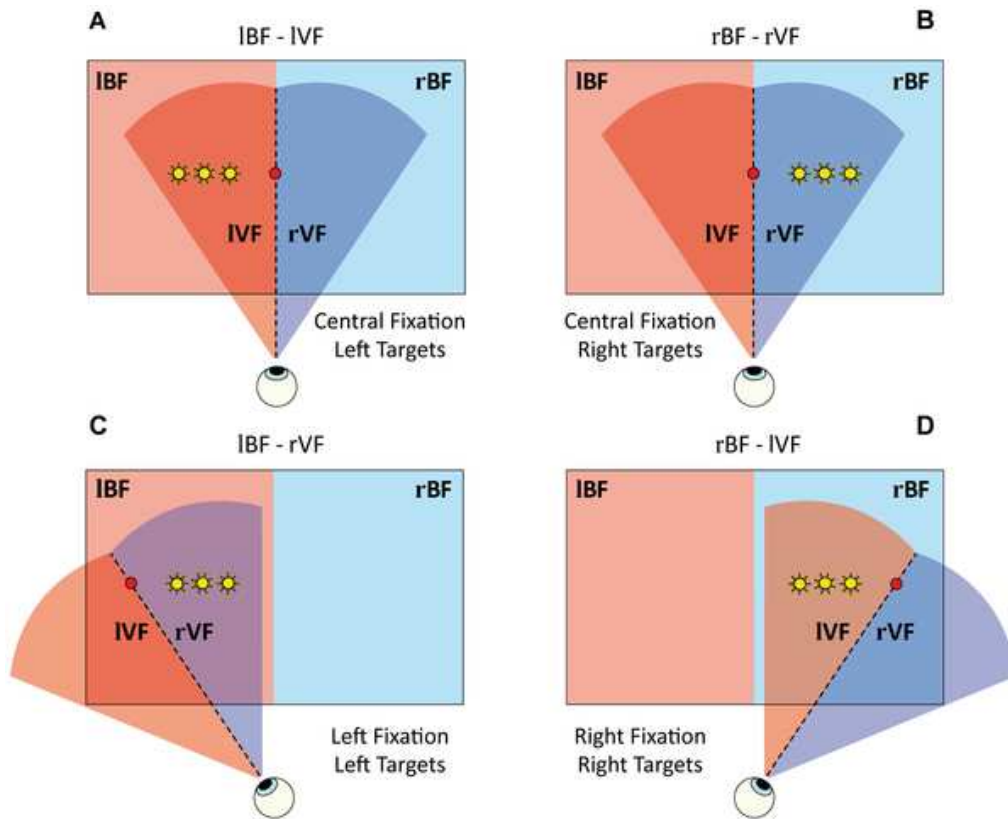


Figure 4 - 1 Schematic representation of the experimental paradigm.

Red circles represent the three possible red fixation LEDs (left, central, right) while the yellow stars indicate the six target positions used in the entire experiment. Note that three target locations were presented in each of the four conditions. Light red and light blue rectangular areas represent the left and right body fields (BF), respectively, whereas light red and light blue circular sector areas are determined by the fixation point and represent the left and right visual field (VF), respectively. The upper part of the figure illustrates the two experimental conditions with the central fixation, in which the three targets are presented in visual and body compatible fields (panel A: left compatibility; panel B: right compatibility). The lower part of the figure illustrates the two experimental conditions in which the visual and body hemifields are dissociated by varying the location of the fixation LED. In these cases, the fixation is lateral and the three targets are presented in visual and body incompatible fields (panel C: left fixation, left body field but right visual field; panel D: right fixation, right body field but left visual field). *l* = left; *r* = right.

For each dependent measure (mean constant errors and elliptical areas), the statistical significance of the difference between the experimental conditions was tested using repeated-measures analysis of variance (ANOVA) and Newman-Keuls post hoc tests. When the sphericity assumption was violated, we applied Greenhouse-Geisser correction of degrees of freedom (indicated as P_{GG}).

4.4 Result

The aim of the present study was to investigate the frames of reference used in planning and guiding visuomotor reach-to-touch arm movements. For this purpose, we have examined several measures of accuracy and precision. Each measure was entered as dependent variable in a $2 \times 2 \times 3 \times 2$ ANOVA with Visual Field (VF) (IVF vs. rVF), Body Field (BF) (IBF vs. rBF), Target Eccentricity (TE) (5.7° , 8.6° , 11.5°) and performing Hand (lHand vs. rHand) as repeated factors. Data were collected for a total of 4608 trials (384 for each subject). A small percentage of trials (323, i.e. 7% of the total) was discarded off-line because subjects did not maintain fixation or began the arm movement too early (i.e., when movement onset time was less than 100 ms).

4.4.1 Accuracy (constant errors)

The analysis conducted on the absolute constant errors (Distance) showed a clear influence of the oculocentric frame of reference. ANOVA, indeed, revealed significant main effects of both VF ($F_{1,11} = 7.95$; $P = 0.017$), with larger errors in the IVF ($M = 2.42$ cm, $SD = 0.94$ cm) than in the rVF ($M = 1.90$ cm, $SD = 0.71$ cm), and TE ($F_{2,22} = 15.71$; $P_{GG} = 0.002$), with larger errors as target eccentricity increases [$M = 1.82$, 2.09 and 2.5 cm ($SD = 0.58$, 0.77 and 1.02 cm) for 5.7° , 8.6° and 11.5° of TE, respectively]. The interaction of these two factors, instead, only approached statistical significance (VF \times TE: $F_{2,22} = 3.3$; $P_{GG} = 0.056$). Post-hoc analysis revealed a stronger influence of target eccentricity in the left visual field ($P < 0.001$ for all comparisons), whereas in the right visual field a difference

emerged only between targets presented at 11.5° and those presented at 5.7° and 8.6° ($P_s < 0.001$) (Fig. 4-2).

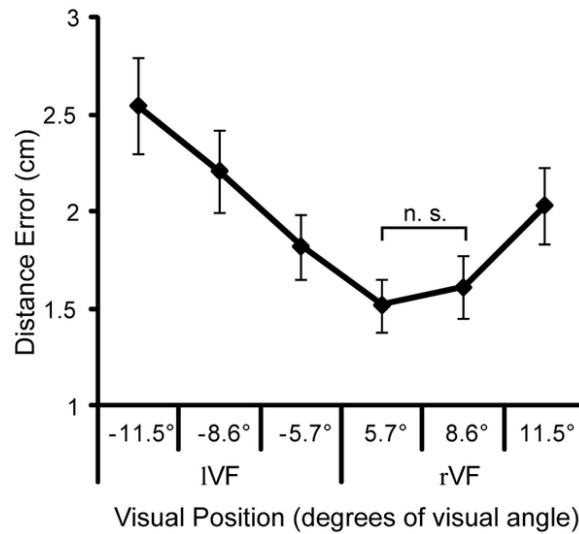


Figure 4 - 2 Absolute errors (Distance).

2-way Visual Field \times Target Eccentricity interaction. Absolute constant errors are represented as a function of visual position of the targets (i.e., with the eccentricity of the targets located in the left visual field indicated by negative values). Error bars represent standard error of the mean.

The analysis conducted on the horizontal algebraic errors (Fig. 4-3) revealed a high global accuracy across subjects (x error grand mean = -0.06 cm). The ANOVA revealed the significant main effects of VF ($F_{1,11} = 6.04$; $P = 0.032$), TE ($F_{2,22} = 7.79$; $P_{GG} = 0.005$) and their interaction (VF \times TE: $F_{2,22} = 7.05$; $P_{GG} = 0.021$). The main effect of VF showed that the participants systematically overshoot the targets (the so-called retinal exaggeration effect; see Discussion section). In other words, subjects made rightward errors when reaching towards the targets located in the right visual field ($M = 0.79$ cm, $SD = 1.02$ cm), and leftward errors when reaching towards the left visual field ($M = -0.92$ cm, $SD = 1.75$ cm). Post-hoc analysis of the 2-way interaction showed slighter overshooting errors for targets located at lowest eccentricity in the IVF (-5.7° vs. -8.6°: $P = 0.044$; -5.7° vs. -11.5°: $P = 0.005$) (Fig. 4-3A). Note that errors for targets located in the same VF and TE position are not affected by the fact of being in a different

BF. On the contrary, within the same BF, the fact of being in a different eye-centered position radically changes the pattern of errors.

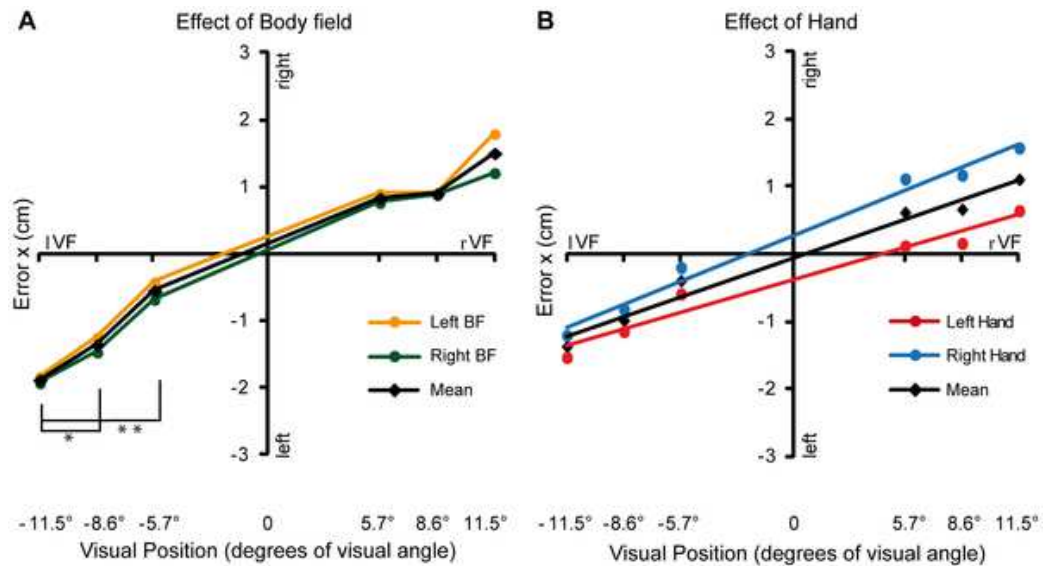


Figure 4 - 3 Horizontal errors.

(A) 2-way Visual Field \times Target Eccentricity interaction. The black diamonds represent mean horizontal errors as a function of the visual position of the targets (i.e., with the eccentricity of the targets located in the left visual field indicated by negative values) * indicates $P < 0.05$; ** indicates $P < 0.01$. For illustrative purpose, the data were also split by body field, with the data for the left BF shown in orange, and those for the right body field shown in green. (B) Linear regression analyses were computed, for each subject, on the same data of A (black diamonds), and on data splitted for performing hand (red and blue circles for left and right hand, respectively). For each of the three regression models, we calculated the mean regression parameters (averaged between subjects); the corresponding three mean regression lines, of the same color of the data points, are superimposed.

Moreover, the ANOVA revealed also a significant main effect of performing Hand ($F_{1,11} = 6.69$; $P = 0.025$), with the left hand misreaching towards the left ($M = -0.40$ cm, $SD = 0.92$) and the right hand towards the right ($M = 0.27$ cm, $SD =$

0.85). This effect seems to be purely additive, since it did not interact with other factors (Fig. 4-3B).

In order to better clarify the influence of the oculocentric frame of reference on horizontal errors, we applied a linear regression analysis approach evaluating, for each subject, the relationship between the visual position of the targets (in which the three positions with negative values indicate the IVF) and the horizontal error (pooled across hands and BFs). The regression model was significant in most (9 out of 12) of the subjects, predicting that horizontal error is proportional to target position (mean beta coefficient = 0.59; one sample one-tailed t test against 0: $t_{11} = 2.99$; $P = 0.012$). It is also important to note that the intercept (i.e., the error expected for targets presented at the fovea) is not significantly different from zero ($t_{11} = -0.29$; $P > 0.77$). Moreover, a linear regression was conducted for each hand to verify the additivity of the Hand main effect. Both regression models were significant and explain a large amount of variance in most of the subjects (mean $R^2 = 0.75$ and 0.73 for left and right hand, respectively; $P_s < 0.05$ in 8 out of 12 subjects for both hands). In addition, by comparing the beta coefficients of the two regression models, the regression lines for the two hands were not significantly different (mean beta coefficient = 0.66 and 0.39; two sample two-tailed t test: $t_{11} = -1.86$; $P = 0.09$).

The analysis conducted on the vertical algebraic errors revealed an overall downward bias (y error grand mean = -0.67 cm) and a significant main effect of target eccentricity ($F_{2,22} = 22.03$; $P_{GG} = 0.0002$). Moreover, also the VF×BF 2-way interaction ($F_{1,11} = 5.06$; $P_{GG} = 0.046$) and the VF×TE×Hand 3-way interaction ($F_{2,22} = 8.07$; $P_{GG} = 0.005$) were significant. Post-hoc analysis of the VF×BF interaction showed that VF affected performance only when targets were presented in the left BF, with subjects making larger errors for targets in the incompatible right VF [rVF = -0.81 cm (SD = 0.77 cm) vs. IVF = -0.53 cm (SD = 0.74 cm); $P = 0.05$] (Fig. 4-4A). Post-hoc analysis of the 3-way interaction showed larger errors for targets presented at highest eccentricities, but only when these were located in the visual field opposite to the performing hand [-11.5°: lHand = -0.59 cm (SD = 1.17 cm) Vs. rHand = -0.91 cm (SD = 0.60 cm); 11.5°:

lHand = -0.92 cm (SD = 0.70 cm) Vs. rHand = -0.74 cm (SD = 0.98 cm); $P_s \leq 0.031$) (Fig. 4-4B). Finally, we investigated the correlation between horizontal and vertical errors, finding that these two types of constant errors were independent ($n = 24$; $r = -0.14$; $P = 0.5$), in line with the pattern of obtained statistical results and with previous findings (Henriques et al., 1998; Henriques and Crawford, 2000).

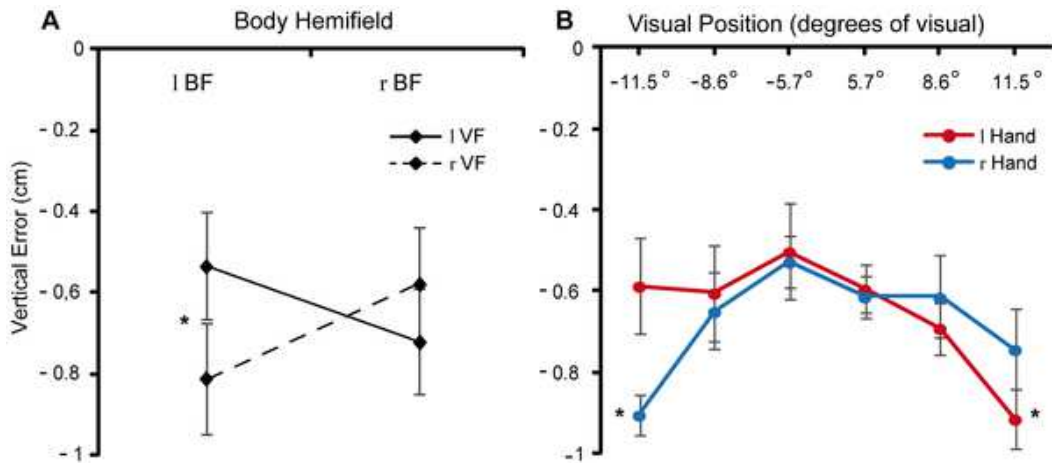


Figure 4 - 4 Vertical errors.

(A) 2-way Visual Field \times Body Field interaction (solid line = left visual field; dashed line = right visual field); (B) 3-way Hand \times Visual Field \times Target Eccentricity interaction (red circles = left hand; blue circles = right hand). Error bars represent standard error of the mean.

4.4.2 Precision (variable errors)

The ANOVA conducted on the finger endpoints distribution area showed the significant main effect of TE ($F_{2,22} = 5.71$; $P_{GG} = 0.01$) and the significant VF \times BF \times TE 3-way interaction ($F_{2,22} = 6.20$; $P_{GG} = 0.007$). Post-hoc analysis revealed that ellipse areas for targets located at 11.5° were larger than the other two degrees of Target Eccentricity, except for targets presented in the right compatible condition (rVF / rBF) (Fig. 4-5).

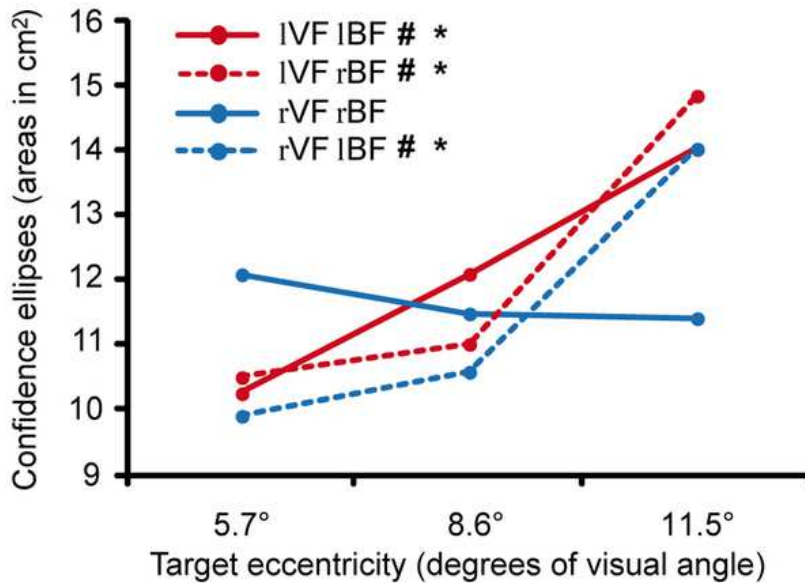


Figure 4 - 5 Confidence ellipses areas.

3-way Visual Field \times Body Field \times Target Eccentricity interaction. The areas of confidence ellipses in the four experimental conditions are represented versus target eccentricity relative to the fixation point (significant post-hoc comparisons are: * = 11.5° vs. 8.6°; # = 11.5° vs. 5.7°). Continuous lines represent compatible visual and body fields, whereas dotted lines represent incompatible visual and body fields (red circles = left hand; blue circles = right hand).

4.5 Discussion

The main purpose of the present investigation was to shed light on the frames of reference involved in planning and executing a real long-range reaching movement (Galati et al., 2011) towards visual targets in space. To this aim, we examined the kind of errors performed while subjects reached, in complete darkness and with both hands, memorized targets located at different locations relative to the gaze and/or to the body. This manipulation allowed us to distinguish between an eye-centered and a body-centered frame of reference involved in the computation of the movement vector. At the same time, it allowed us to gain insights into the influence of target eccentricity and performing hand.

4.5.1 Influence of visual and body fields

The main result indicated that errors were largely influenced by factors associated with the use of an oculocentric frame of reference. We indeed found that two reaching movements show similar errors if target locations are the same in eye-centered coordinates but not if they are identical only in body coordinates.

First, we found that subjects' accuracy was strongly influenced by the visual hemifield in which targets were presented. More precisely, subjects made horizontal errors that did not depend on target position relative to the screen or their bodies; instead, errors were influenced by target position relative to the fixation point. In other words, when subjects performed a movement towards a target located in the left or right visual hemifield, they made leftward or rightward errors, respectively, regardless of the position of the targets relative to the screen or their bodies. This pattern of errors is well known and mentioned as retinal exaggeration effect (Henriques et al., 1998; Henriques and Crawford, 2000; Medendorp and Crawford, 2002; Pouget et al., 2002; Khan et al., 2005) or retinal magnification effect (Bock, 1986), and was demonstrated also in more complex tasks in which subjects performed a saccade between the foveal target presentation and the pointing movement towards the stored position of the same targets (Henriques et al., 1998; Sorrento and Henriques, 2008). These latter works, in particular, suggest that the position of the remembered visual target is not converted into a coordinate system centered on the body or the effector, but is stored and updated in a gaze-centered frame of reference, at least during the preparation of arm movement. It is not clear what exactly produces this systematic mislocalization of targets relative to the gaze. Bock (Bock, 1986) originally described this constant overestimation of reaches relative to the gaze as a magnification of the retinal distance of the target relative to the fovea. Henriques and Crawford (Henriques and Crawford, 2000) suggested that this retinal magnification effect is the result of miscalibration in eye-head coupling when pointing to distant targets with deviated gaze.

Besides confirming the retinal exaggeration effect, the present results indicate a linear correlation between the overestimation errors on the horizontal

axis and the target retinal eccentricity (i.e. the distance between target and fixation). Figure 4-3B shows the good approximation of the linear model to the data, and since the intercept is very close to the origin and not significantly different from zero, no systematic errors were made in reaching the target at the center of the visual field. This suggests that the retinal eccentricity of targets has a linear influence on the representation of targets location in the perifoveal visual field (within 10° from the fovea), an influence that would remain constant upon entering the peripheral visual field (“saturation” effect for targets located beyond 10-15 degrees of eccentricity (Bock, 1986; Henriques et al., 1998; Henriques et al., 2002; Crawford et al., 2003). The present new observation of a linear influence within the perifoveal visual field was made possible by the use of several target eccentricities smaller than 10 degrees. Previous studies, which found the saturation effect, employed only one value smaller than 10 degrees, thus preventing such an important observation.

While the effects of the eccentricity discussed so far seem attributable to a systematic bias during the visuomotor transformation process (i.e. impairing subject’s accuracy), the results of the analysis on the dispersion measures suggest that target eccentricity affects also the precision of reaching movements (i.e., increased the variability of subject’s performance). Inspection of Figure 4-5 shows that increasing the distance between the target and the fixation point results in an increase of endpoint dispersion, regardless of the target distance from the body. In other words, in contrast with previous findings (Gordon et al., 1994), the increase of endpoint dispersion observed for more eccentric targets is not influenced by the distance that the arm has to cover to reach the target.

4.5.2 Influence of performing hand

Besides visual field and target eccentricity effects on accuracy and precision, our work provided further results about an issue which has not been systematically addressed so far: the influence of the performing hand on reaching errors. This influence has been highlighted by the analyses conducted on horizontal errors. These revealed that participants make rightward errors when performing the

reaching movement with the right hand, and, conversely, leftward errors with the left hand. In addition, the regression lines calculated for each hand were parallel. These results therefore suggest that the performing hand exerts an influence on the visuomotor transformation processes that is independent from that of the oculocentric frame of reference. The influence of the performing hand on reach errors observed in the present study could be explained by assuming an overestimation bias in proprioceptive localization of the hand starting position (Jones et al., 2010) that would occur independently of the visuomotor transformation cascade. However, it remains unclear at which stage this influence of the hand can occur. According to the multiple reference model (Battaglia-Mayer et al., 2003; Sober and Sabes, 2003, 2005; Blohm and Crawford, 2007; Marzocchi et al., 2008), hand–target information could be compared in multiple reference frames depending on task requirements or available information (Neely et al., 2008). Current evidence from neurophysiology, neuroanatomy, and psychophysics strongly supports the existence of multiple, independent, and coexisting levels of representation for combined eye–hand movements in the PPC and connected premotor areas. The parieto-frontal network combines information about target and effector locations during the visuomotor transformation process and neural activity in several parietal and premotor areas appears to be modulated by both hand and target position in different frames of reference (Batista et al., 1999; Burnod et al., 1999; Battaglia-Mayer et al., 2001; Battaglia-Mayer et al., 2003; Batista, 2005; Pesaran et al., 2006; Beurze et al., 2007; Marzocchi et al., 2008; Bernier and Grafton, 2010; Chang and Snyder, 2010; McGuire and Sabes, 2011). These results are also consistent with recent findings showing that an artificial neural network of the visuomotor transformation for reaching performs this comparison gradually across different frames of reference (Blohm and Crawford, 2007).

Our data also showed an interesting result that has not been observed in previous works, i.e. a downward bias of reaching errors that was modulated by both target eccentricity and performing hand. Other studies on goal-directed arm-movements showed an overall vertical undershoot of the target position (Enright, 1995;

Henriques et al., 1998; Henriques and Crawford, 2000; Poljac and van den Berg, 2005). Whereas the former hypothesis cannot account for our pattern of errors, since we did not find any bias toward initial hand position in the horizontal component of reaching errors (i.e., an undershoot, instead of an overshoot, in reaching peripheral targets), the latter hypothesis fits better with our results. In fact, a further interference due to a maintained muscle tonus may interact with the imperfect calibration of the retinal read-out, which is the cause of the retinal exaggeration effect, so leading to the target eccentricity modulation of the vertical error that we found.

To conclude, we showed that humans make different errors when reaching to remembered target locations with gaze at different directions. The present results suggest that the location of visual targets is primarily coded in an eye-centered reference frame. Furthermore, our data show that the performance is also influenced by the sensorimotor transformations converting the spatial coordinates of an action target in an independent hand-centered frame of reference. The present results thus support the existence of an internal mechanism of integration between target and effector information in multiple frames of reference. They are in line with the view of a visuomotor transformation in the dorsal visual stream that changes the frame of reference from retinocentric, typically used by the visual system, to arm/hand-centered, typically used by the motor system. It remains a challenge to understand the temporal dynamics of the sensorimotor transformation for reaching implemented by the dorsal visual stream of the human brain.

5. rTMS OF MEDIAL PARIETO-OCCIPITAL CORTEX INTERFERES WITH ATTENTIONAL REORIENTING DURING ATTENTION AND REACHING TASKS³

5.1 Abstract

Unexpected changes in the location of a target for an upcoming action require both attentional reorienting and motor planning update. In both macaque and human brain the medial posterior parietal cortex is involved in both phenomena but its causal role is still unclear. Here we used on-line repetitive transcranial magnetic stimulation (rTMS) over the putative human V6A (pV6A), a reach-related region in the dorsal part of the anterior bank of the parieto-occipital sulcus, during an attention and a reaching task requiring covert shifts of attention and planning of reaching movements towards cued targets in space.

We found that rTMS increased response times to invalidly cued but not to validly cued targets during both the attention and reaching task. Furthermore, we found that rTMS induced a deviation of reaching endpoints towards visual fixation, and that this deviation was larger for invalidly cued targets. The results suggest that reorienting signals are used by human pV6A area to rapidly update the current motor plan or the ongoing action when a behaviorally relevant object unexpectedly occurs in an unattended location.

The current findings suggest a direct involvement of the action-related dorso-medial visual stream in attentional reorienting and a more specific role of pV6A area in the dynamic, online control of reaching actions.

³ A version of this chapter is currently in press in *Journal of Cognitive Neuroscience*: Ciavarro M, Ambrosini E, Tosoni A, Committeri G, Fattori P, Galletti C.

5.2 Introduction

Effective goal-directed behavior depends on the ability to flexibly adapt a motor plan in response to unexpected changes of target location. Such motor reorganization requires that attention is rapidly shifted to the new spatial location even without an overt eye movement, a process typically defined as reorienting response (Corbetta et al., 2008). This adaptive response is typically associated with a right-lateralized ventral fronto-parietal network (Corbetta and Shulman, 2002; Corbetta et al., 2008). Recent human neuroimaging studies, however, have shown that attentional reorienting also induces a transient increase of neural activity in regions of the medial superior parietal lobule extending from the precuneus to more posterior regions around the dorsal aspect of the parieto-occipital sulcus (POS) (Yantis et al., 2002; Molenberghs et al., 2007; Kelley et al., 2008; Shulman et al., 2009; Vossel et al., 2009; Tosoni et al., 2012). This portion of cortex is also specialized for visuo-motor coordination during arm-reaching movements (Astafiev et al., 2003; Prado et al., 2005; Busan et al., 2009a; Cavina-Pratesi et al., 2010; Vesia et al., 2010; Galati et al., 2011; Striemer et al., 2011). In particular, the anterior region in the so-called superior parietal occipital cortex (SPOC) is robustly involved in both proximal (arm direction) and distal (hand orientation) aspects of reach-to-grasp movements (Cavina-Pratesi et al., 2010; Monaco et al., 2011).

The pattern of deficits exhibited by neuropsychological patients suffering from optic ataxia (OA) (Perenin and Vighetto, 1988; Karnath and Perenin, 2005) offers further insights on the particular combination of attentional and motor functions of the dorso-medial parietal cortex. OA patients typically fail to make fast corrections of reaching movements when the target is unexpectedly displaced, suggesting a role of the medial parietal cortex in dynamic aspects of visual control of action (Pisella et al., 2000; Gréa et al., 2002; Glover, 2003). More importantly, the deficit in these patients is not confined to movements execution, but also appears to affect the ability to detect and respond to targets located in the portion of the visual field (typically contralesional) in which the visuomotor deficit is most evident (Striemer et al., 2007; Striemer et al., 2009; McIntosh et al., 2011).

Striemer et al. (2007; 2009) suggested that the deficits in attention and visuomotor control are independent (i.e. the two deficits result from damage to distinct mechanisms), while McIntosh et al. (2011) have recently suggested a single mechanism, showing that the visuomotor deficits observed in these patients, and in particular their failure to use extrafoveal visual information to drive immediate actions, could depend from an impairment in the ability to shift attention between visual locations.

Evidence from monkey neurophysiology has shown that V6A neurons in the dorsal POS, which are particularly sensitive to arm movements directed to non-foveated objects (Marzocchi et al., 2008) and are modulated by gaze position (Galletti et al., 1995), also respond to covert shifts of attention (Galletti et al., 2010). In particular, Galletti and colleagues (2010) have shown that covert attentional modulations in V6A are consistent with the distribution of preferred reach direction in this area, suggesting that spatially-directed attentional signals could be linked to arm motor programming.

To summarize, neuroimaging, neuropsychological and neurophysiological evidence all converge to suggest a role of the cortex in the anterior dorsal part of the POS both in visuomotor transformations for goal-directed reaching movements and in attentional functions necessary to select salient or relevant information in the environment. It is unclear, however, whether action- and attention-related signals act independently (Striemer et al., 2007; Striemer et al., 2009) or interact with each other in this cortical region (Galletti et al., 2010; McIntosh et al., 2011) and whether they are causally associated with its functioning.

To investigate these issues we used a goal-standard technique of neural interference, such as transcranial magnetic stimulation (TMS), which allows to draw causal inferences about the role of a brain region in a particular cognitive or sensorimotor function by inducing a “virtual lesion” in a restricted portion of the cerebral cortex (Pascual-Leone et al., 2000; Paus, 2005; Bolognini and Ro, 2010); but also see (Casali et al., 2010), for a discussion of TMS effects on regions that are anatomically/functionally connected to the stimulated cortical sites).

Individual MRI-guided TMS was carried out over a region in the dorsalmost part of the anterior bank of the POS (i.e. anterior SPOC), that likely corresponded to the human homologue of monkey area V6A (Cavina-Pratesi et al., 2010; Pitzalis et al., 2012b) and that from now on we will refer to as the human putative area V6A (pV6A). We used a cueing paradigm in which participants performed both an attention and a reaching task. During the tasks, subjects were asked to detect the appearance of a brief visual target presented in the peripheral visual field and to respond as quickly as possible with a right-hand button release only (attention task) or with a right-hand reaching movement to the target location (reaching task) while maintaining central fixation.

By manipulating the validity of the cues in both tasks (the cue correctly predicted target location with 75% probability), we tested the involvement of the pV6A in attentional reorienting during both the attention and the reaching task. To provide a comprehensive account of the TMS effects on the reorienting of attention towards unattended targets both when they have simply to be detected (attention task) and when they have to be processed as a goal of a reaching movement, we measured response times (RTs) to target detection in both tasks and the end-points of reaching movements in the reaching task. We hypothesized that pV6A is causally involved in attentional reorienting, thus predicting a marked rTMS-induced increase of RTs for invalid trials in both tasks. Given that invalid targets, compared to valid ones, also require an update of the current motor plan, we additionally predicted a selective effect of validity on the pattern of rTMS-induced reaching errors.

5.3 Methods

5.3.1 Participants

Eight right-handed subjects (4 males, mean age 26.1 years) participated in the experiment. All participants had normal or corrected visual acuity and reported no history of neuropsychiatric illness or epilepsy, as well as any contraindication to TMS (Wassermann, 1998; Rossi et al., 2009). All gave written informed consent

in accordance with the guidelines of the local Ethics Committee and the ethical standards of the Declaration of Helsinki.

5.3.2 Stimuli and Apparatus

Subjects were seated on a height-adjustable chair in complete darkness, with the head mechanically stabilized by a chin rest and a head holder mounted onto a wooden table positioned directly in front of them. A Plexiglas screen (120 x 50 cm) covered with a matte black sheet was located on the table within a reaching distance (35 cm). The height of the chair and the chin rest were adjusted so that the subject's cyclopean eye (located midway between the two eyes) was vertically and horizontally aligned with the central fixation light-emitting diode (LED). The stimuli array consisted of nine LEDs aligned to the horizontal plane: one green LED, located at 0°, served as fixation point, whereas the remaining eight yellow LEDs were located at four different eccentricities (5°, 10°, 20° and 30°) on the left and the right of the central fixation LED and were used as cue and target stimuli. On each trial, a target was preceded by an informative peripheral cue of 10 ms duration, which correctly predicted the target location with a probability of 75% (valid trials). LEDs were installed behind the Plexiglas screen, were visible only when illuminated, and gave no tactile feedback when touched.

Eye position was monitored during both the attention and reaching task with an ISCAN ETL-400 remote infrared eye tracker (sampling rate: 120 Hz). Moreover, during the reaching task the accuracy of reaching movements were recorded in all trials with an electromagnetic tracking device (Fastrak Polhemus). This electromagnetic tracking system provides measures of the position of small sensors attached to the tip of the right index fingers, with a sampling rate of 120 Hz and a spatial accuracy of 0.8 mm. Data were digitized and recorded on a PC for off-line analysis.

5.3.3 Individuation of Anatomical rTMS Sites

Cortical sites of rTMS stimulation were localized individually. To identify left and right pV6A stimulation sites within anterior SPOC, and to monitor the TMS

coil position at the end of each experimental block, we used a frameless stereotaxic neuronavigation system (Softaxic, EMS; Bologna, Italy). Prior to the experiment, a T1-weighted MR scan was obtained from each participant using a Siemens 3T scanner (1×1×1 mm, sagittal acquisition). Stimulation sites were then identified on the scalp by co-registering reference scalp locations to individual MR images using a neuronavigation system (Fastrak Polhemus digitizer, Polhemus; Colchester, VT) running a SofTaxic software. The pV6A sites on each hemisphere was localized according to individually determined anatomical landmarks, i.e. the region that is medial to the posterior end of the intraparietal sulcus and anterior to the dorsal end of the parieto-occipital sulcus (POS) (Fig. 1A). This is the region where the human area V6A should be located. In fact, in the monkey, area V6A is located just anterior to V6 (Galletti et al., 1999b; Galletti et al., 1999d). Since in humans area V6 is located in the dorsalmost part of POS (Pitzalis et al., 2006), the human homologue of monkey V6A should be located just anterior to the dorsalmost part of POS, as also suggested by recent works (Cavina-Pratesi et al., 2010; Pitzalis et al., 2012b). The target sites were marked on a tightly fitting Lycra cap worn by subjects, and the coil was maintained in that position by an articulated metallic arm for the whole duration of the experimental block. The localization procedure was performed at the beginning of the experimental session and was controlled at the end of each experimental block.

5.3.4 Procedure for rTMS Stimulation

TMS was delivered via a 70-mm figure-of-eight induction coil, connected to a MagStim Rapid system (MagStim Company; Whitland, U.K.) and applied tangentially to the target scalp site, with the handle pointing posteriorly. The intensity of TMS was set at 60% of the stimulator output in accordance with previous studies on reaching- and attention-related activity in parietal cortex (Dambeck et al., 2006; Vesia et al., 2010). The TMS train consisted of 3 pulses (10-Hz) delivered at 0, 100 and 200 ms following the offset of the cue stimulus. The on-line rTMS train frequency, intensity and duration were well within safe limits (Rossi et al., 2009; Wassermann, 1998).

The specificity of the behavioral effects of rTMS stimulation over left and right pV6A were controlled by including two control stimulation conditions in which rTMS was delivered, in equal number, over the same two sites but with the coil held perpendicular to the scalp (Sham) or over the Vertex (Cz according to the 10-20 EEG coordinate system).

5.3.5 Procedure

Each experimental block started with central fixation (green LED; cross in Fig. 5-1B). In each trial, a cue (yellow LED; filled grey circle in Fig. 5-1B) was flashed for 10 ms in one of the eight possible locations along an horizontal line at eye level (i.e., four locations in each hemifield), at 5°, 10°, 20°, 30° of eccentricity, respectively. After an inter-stimulus interval (ISI) of 240 ms, a target (yellow LED; filled black circle in Fig. 5-1B) was presented either at the very same location (valid trials, 75%), or at a corresponding location in the opposite hemifield (invalid trials, 25%). Behavioral indices were measured during an attentional and a reaching task in which participants were instructed to indicate target detection by releasing a response button with the right index finger. In both tasks, we measured the response time (RTs) as the time between the onset of the target stimulus and the release of the response button. In the reaching task, participants were also required to perform a ballistic reaching movement to touch the location of the target on the screen.

Participants were informed about the task to perform (i.e. attentional or reaching task) at the beginning of each block. The blocks included 64 experimental trials (48 valid and 16 invalid) and six catch trials, in which the ISI was extended to 1000 ms to prevent early responses to the cue stimulus. Catch trials were not included in the subsequent analyses. To minimize TMS exposure and fatigue and to exclude learning effects, each subject completed the entire experiment in four sessions (performed in different days). Each session comprised six blocks, with task order and order of stimulation sites (both blocked) counterbalanced across sessions and individuals. Each participant completed 24 blocks (six blocks for each session) for a total of 1536 trials.

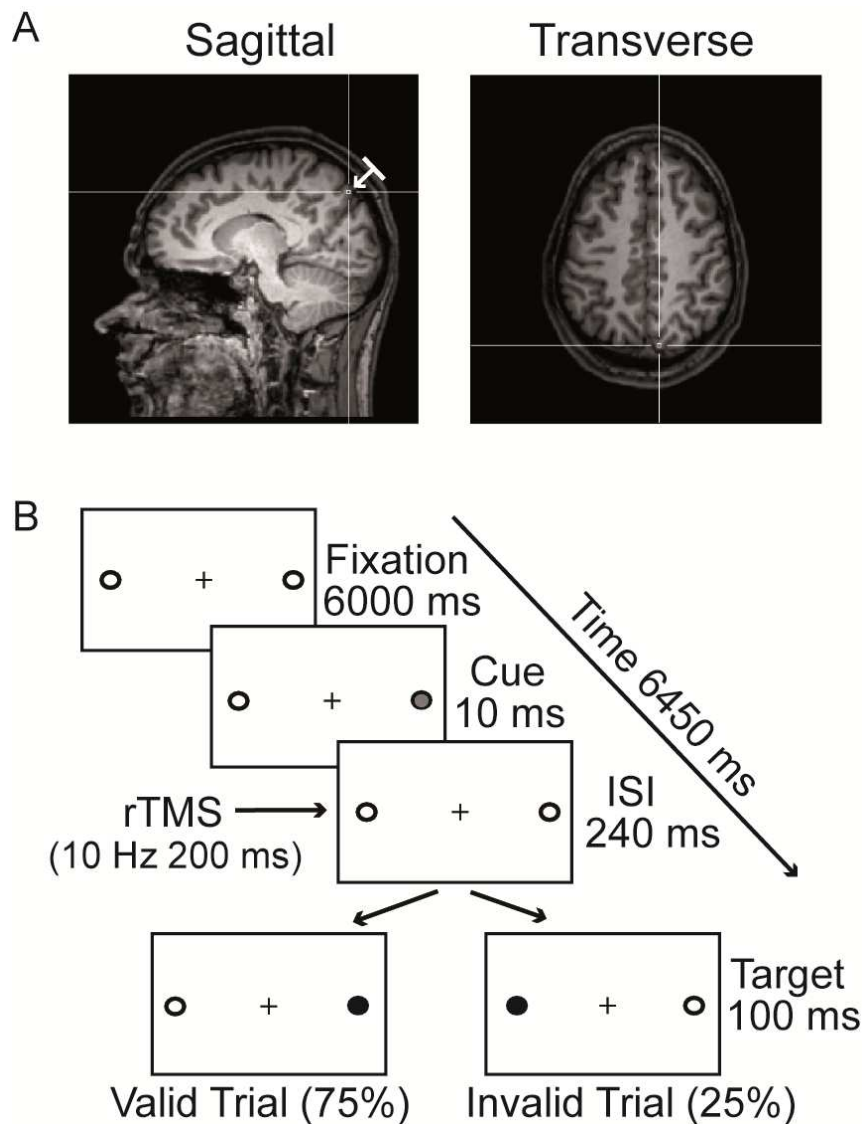


Figure 5 - 1 Stimulation Site and trial structure.

(A) The neuroanatomical region that was stimulated with rTMS (white arrow) in a representative subject, as determined by means of frameless stereotaxic neuronavigation, is indicated by the intersection line in the sagittal (upper) and transverse (bottom) sections of the T1-weighted MRI. Average (\pm SD) Talairach (Talairach J, 1988) coordinates of pV6A are the following: left hemisphere, $x = -10.4 \pm 3.5$, $y = -78.2 \pm 3.5$, $z = 40.2 \pm 2.7$; right hemisphere, $x = -10.7 \pm 1.7$, $y = -77.6 \pm 5.0$, $z = 40.4 \pm 3.2$. (B) Typical display sequence for a valid and an invalid trial. For illustrative purpose, only two of the eight possible locations are shown.

5.3.6 Data Analysis

Gaze position (right eye) on the Plexiglas screen was recorded in each participant using an eye-tracking system, which was recalibrated before each block by means of a standard calibration procedure. Trials with eye blinks or with gaze deviation greater than 3° from central fixation (364 trials, corresponding to ≈3% of total trials) were discarded from the analyses of rTMS effects on behavioral performance. The dependent measures for both tasks were RTs, i.e. the button release times. Trials with RTs shorter than 100 ms or longer than 1200 ms (626 trials, corresponding to 5% of total trials) were discarded from the analyses, because they were considered anticipatory or abnormally slow responses, respectively.

RTs were analyzed using a repeated measure ANOVA with Task (attention, reaching), Stimulation Site (right-pV6A, left-pV6A, Sham/Vertex), Target Validity (valid, invalid), Visual Hemifield (left HF, right HF), and Target Eccentricity ($\pm 5^\circ$, 10° , 20° , 30°) as factors. Note that because no differences were found between the two control stimulation conditions (see “Procedure for rTMS Stimulation” section), they were collapsed in a single control condition (Sham/Vertex). When the sphericity assumption was violated, Greenhouse-Geisser corrected p values (indicated as p_{GG}) were applied. The Newman-Keuls test was used for post-hoc analyses. The threshold for statistical significance was set at $p < .05$ for all comparisons.

The accuracy of the reaching movements was evaluated by mapping the reaching endpoints on the horizontal (x) and vertical (y) axes of the screen. Endpoints were defined as the points at which the z position of the finger crossed the value that demarcates the location of the Plexiglas screen. We then estimated horizontal endpoint errors, measured in degrees of visual angle, as the signed difference between finger endpoint and target position as computed in the calibration procedure. In this calibration procedure, which was conducted at the end of the experiment, participants were requested to fixate and reach each LED targets with the full vision of their hand, and without temporal constraints. We assessed the position of each target as the mean endpoint position averaged across

five of these calibration reaching movements. This was done to take into account the possible small differences in the location of the electromagnetic sensor between participants. Reaching endpoints were analyzed by a repeated measure ANOVA with the same factorial design described above, but without the Task factor.

5.4 Results

We first describe the main effects and interactions emerged from the RT analysis that did not involve the Stimulation Site factor (Fig. 5-2). As shown in Figure 5-2A, there was a significant effect of Validity ($F(1,7) = 20.54$; $p = 0.003$), with longer RTs for invalid than valid trials (424 vs. 371 ms, respectively) and a significant effect of Target Eccentricity ($F(3,21) = 25.3$; $p_{GG} < 0.0001$), with progressively longer RTs as a function of target eccentricity (364, 386, 409 and 430 ms for targets located at 5°, 10°, 20° and 30°, respectively; all post-hoc comparisons were significant). Validity was also modulated by Target Eccentricity ($F(3,21) = 4.02$; $p_{GG} = 0.036$) with post-hoc tests indicating a greater validity effect for targets located at 30° (66 ms) compared to other eccentricities (46, 52 and 50 ms for 5°, 10° and 20°, respectively; all $ps < .001$). These results, obtained during control baseline stimulation, confirm that our paradigm was effective in generating a bias of spatial attention to the cued location that progressively increased as a function of eccentricity. Moreover, as shown in Figure 5-2B, the results indicated a significant effect of Task, with slower RTs during the reaching compared to the attention task (428 ms vs. 367 ms; $F(1,7) = 11.73$; $p = 0.011$).

Finally, there was a significant Task by Visual Hemifield interaction ($F(1,7) = 10.5$; $p = 0.014$) with post-hoc tests showing longer RTs in the reaching task for target located in the left (431 ms) relative to the right (424 ms) visual hemifield, whereas no hemifield differences were observed in the attention task (364 and 370 ms for left and right hemifields, respectively). This finding suggests that RTs can be inflated by the additional processes required by movement

planning, especially during reaching to the left hemifield, i.e. the field contralateral to the responding hand.

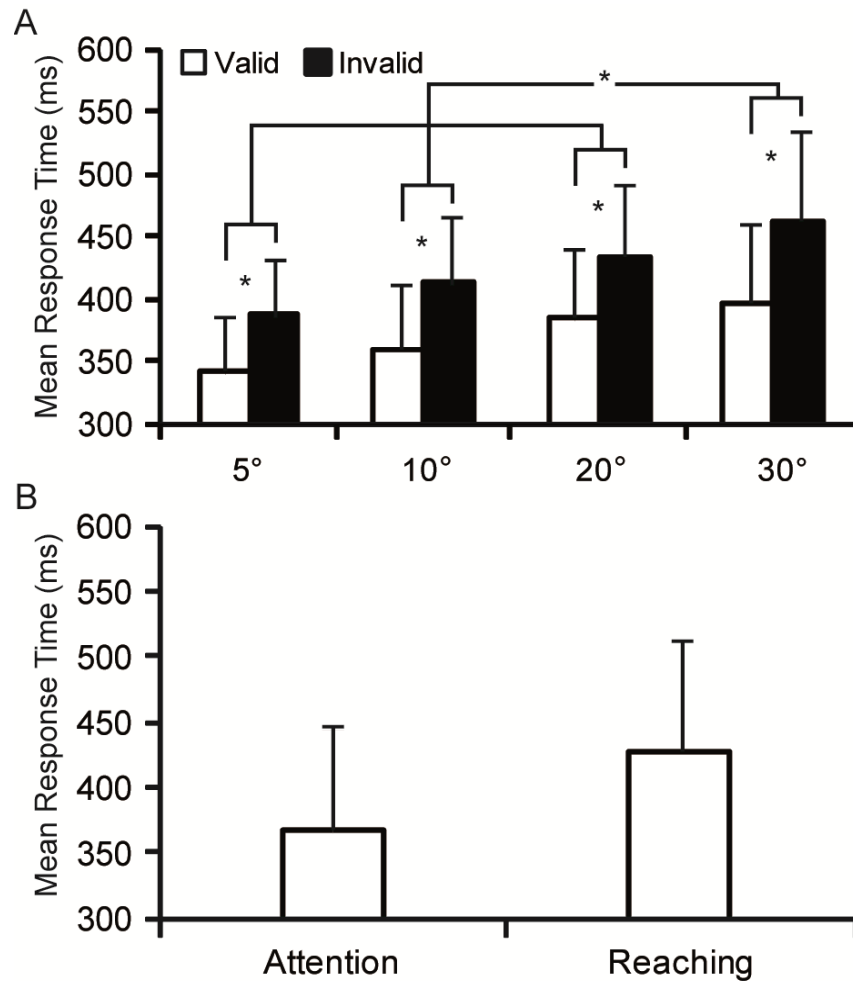


Figure 5 - 2 Mean response times during Sham/Vertex control stimulation.

(A) Validity by Target Eccentricity interaction. Post-hoc analysis revealed that the Validity effect i.e., significantly faster response times for valid than invalid trials, was higher for targets located at 30°. * $p < 0.001$. (B) Main effect of Task: response times in the reaching task were significantly higher than response times in the attention task.

5.4.1 TMS Effects

TMS Effects on Attentional Reorienting

The main finding of our study was that rTMS over pV6A selectively affected attentional reorienting in both the reaching and the attention task (Fig. 5-3). Specifically, we observed a significant, selective increase of RTs to invalidly cued targets during rTMS over both left and right pV6A compared to Sham/Vertex stimulation (Validity by Stimulation Site interaction: $F(2,14) = 8.58$; $p = 0.004$). Specifically, while TMS did not affect RTs on valid trials (left-pV6A: 372 ms and right-pV6A: 372 ms vs. Sham/Vertex: 368 ms; $ps > 0.6$), we observed a virtually identical increase of response times to invalid targets in the two tasks during TMS stimulation of mPOC compared to Sham/Vertex (left-pV6A: 433 ms and right-pV6A: 444 ms vs. Sham/Vertex: 394 ms; $ps < 0.001$). This result indicates that rTMS over pV6A specifically impairs attentional reorienting during invalid trials but not attentional orienting during valid trials.

TMS Effects on the Accuracy of Reaching Movements

Consistent with previous findings, the ANOVA on reaching endpoint errors (reaching task) indicated a significant decrease of horizontal hypermetria following rTMS stimulation of pV6A compared to Sham/Vertex (Vesia et al., 2010). In other words, the stimulation caused a deviation of reach endpoints towards visual fixation, thus reducing the classic tendency to reach too far peripherally relative to the central fixation point, a pattern of overshoot errors that we found in the Sham/Vertex condition and that is typically observed in reaching experiments. As shown in Figure 5-4, however, we also observed that this typical rTMS-induced decrease of hypermetria was modulated by the location of the visual target (Visual Hemifield by Stimulation Site interaction: $F(2,14) = 10.01$; $p = 0.002$). Specifically, we found that while rTMS over left pV6A vs. Sham/Vertex induced a significant decrease of hypermetria errors during reaching movements directed towards both hemifields (left HF: -0.01° endpoint errors, $p = 0.017$; right HF: 0.41° endpoint errors, $p = 0.038$), rTMS over right pV6A vs. Sham/Vertex only induced a significant decrease of endpoint errors for reaching movements

directed towards left contralateral targets (left contralateral targets: endpoint errors = -0.20° , $p = 0.013$; right ipsilateral targets: endpoint errors = 0.83° , $p = 0.065$).

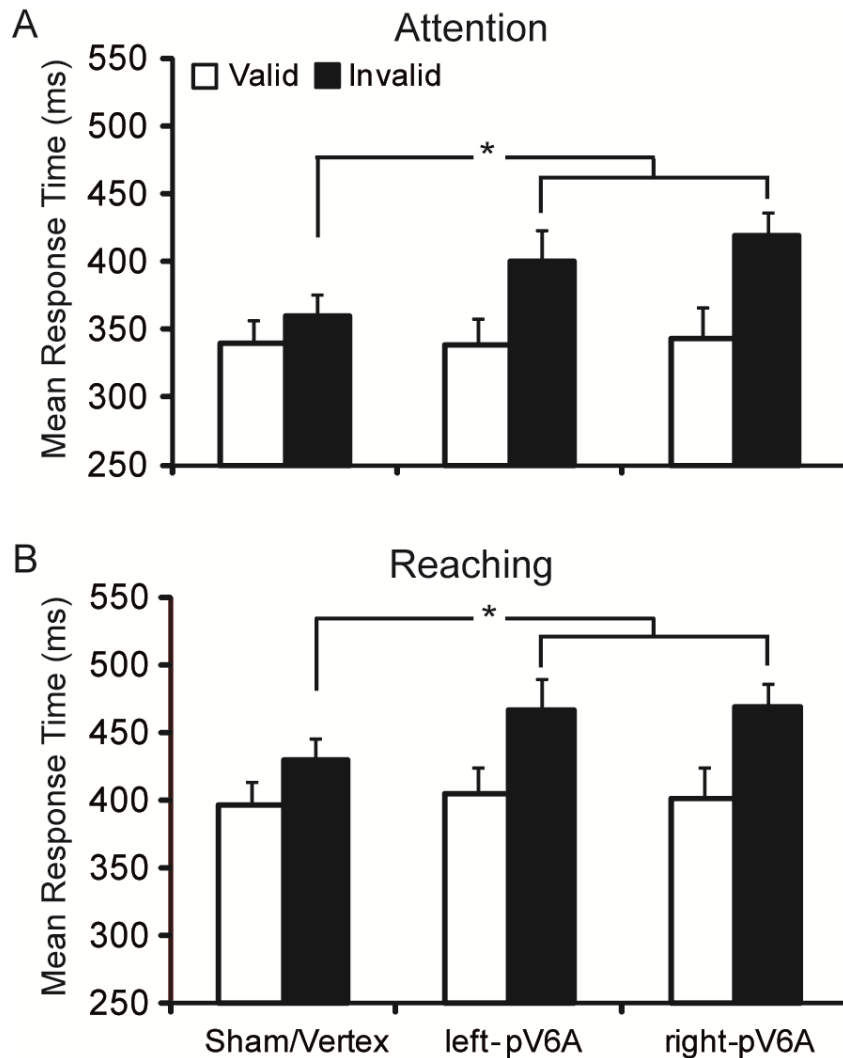


Figure 5 - 3 *rTMS effects on attentional orienting and reorienting during the attention and the reaching task.*

Mean response times (\pm s.e.m) to valid and invalid trials as a function of stimulation condition are plotted for both the reaching and the attention task to highlight that a similar effect of validity was observed in both tasks.

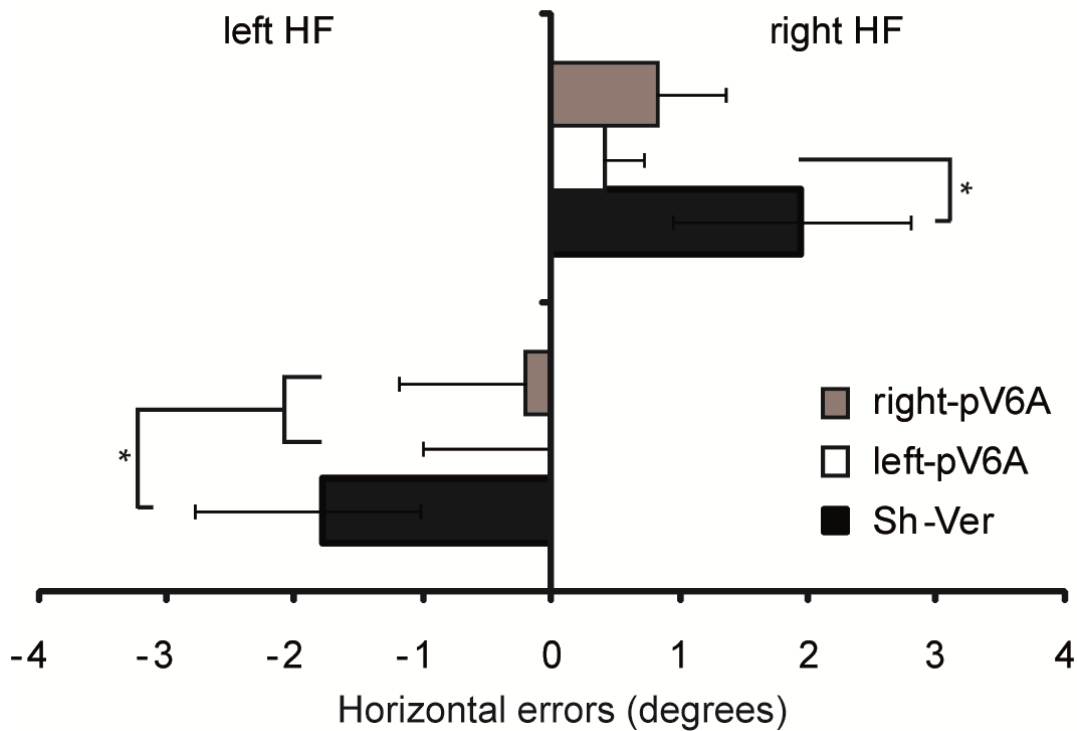


Figure 5 - 4 *rTMS effect on reaching endpoints.*

*Mean horizontal errors (\pm s.e.m) in degrees as a function of stimulation site and visual hemifield (HF). * indicates significant post-hoc comparisons ($p < 0.05$).*

The ANOVA on reaching endpoints also revealed a significant Stimulation Site by Target Validity by Visual Hemifield interaction ($F(2,14) = 8.29$; $p = 0.004$) (Fig. 5-5). Post-hoc analysis indicated that rTMS over pV6A led to a greater decrease of baseline hypermetria during Invalid than Valid trials, deviating reach endpoints even more towards visual fixation. In other words, the rTMS-induced reduction of reaching errors was stronger in invalid than valid trials, with this validity-dependent effect depending on the visual hemifield of target presentation (i.e., a greater rightward deviation for left targets, and a greater leftward deviation for right targets). This validity-dependent, rTMS-induced effect was significant in all conditions with the exception of those in which stimulation was applied to left pV6A and targets were presented in the left hemifield (endpoint errors: 0.12° and -0.14° in Invalid and Valid trials, respectively, $p = 0.12$).

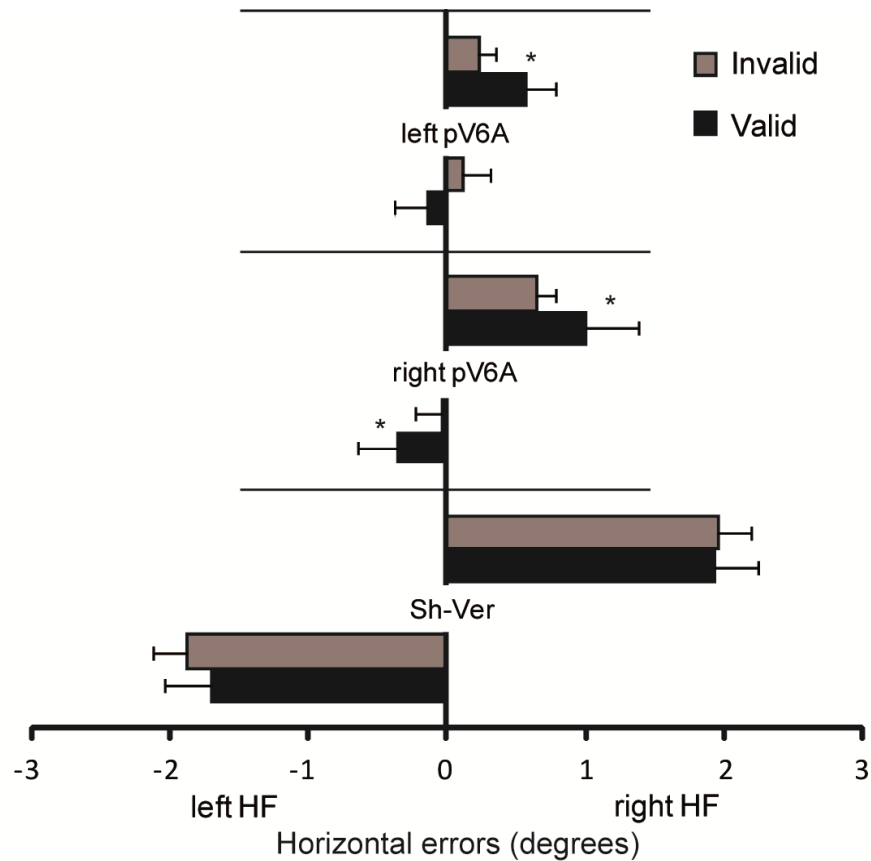


Figure 5 - 5 *Validity-dependent rTMS effect on reaching endpoints.*

*Mean horizontal errors (\pm s.e.m) in degrees as a function of stimulation site, visual hemifield (HF), and target validity. * indicates significant post-hoc comparisons ($p < 0.05$).*

5.5 Discussion

In the present study we used on-line rTMS to test the relationship between attentional modulations and reaching movement execution in a region of the anterior SPOC that likely corresponds to the human homologue of monkey area V6A (Cavina-Pratesi et al., 2010; Pitzalis et al., 2012b), an area known in the macaque to have both reaching and attentional responses (Fattori et al., 2005; Galletti et al., 2010). We designed two tasks requiring subjects to detect peripheral visual targets, which were either validly or invalidly cued, and to respond with a simple button release (attention task) or with a button release

followed by a ballistic reaching movement toward the target location (reaching task). In both tasks we evaluated the effect of rTMS stimulation (pV6A vs. control Sham/Vertex) on attentional components of orienting vs. reorienting to target location. In the reaching task, we further evaluated the effect of TMS on reaching kinematic (endpoint errors).

The results of the RTs analysis on simple behavioral effects first indicated that our cueing paradigm was effective in generating a bias of spatial attention to the cued location in both tasks (i.e., the validity effect) (Posner et al., 1980). Importantly, the validity effect increased as a function of target eccentricity, i.e. progressively longer RTs for invalid targets presented at greater eccentricities. This is in line with a widely accepted assumption of dominant models of attention, which poses that the longer the path of attentional shifting, the greater the response delay for target detection (Henderson and Macquistan, 1993; Hamilton et al., 2010).

The main result of the study is the finding of a selective rTMS-induced increase of RTs for invalid trials during both tasks. Consistent with recent neurophysiological findings (Galletti et al., 2010), these results demonstrate that pV6A does not simply participate in the sensory-motor transformations needed to encode reach goals during goal-directed actions, but also encodes critical signals for shifts of spatial attention. In particular, our findings suggest that pV6A plays a causal role in attentional reorienting, i.e. when attention must be disengaged from one peripheral location and redirected to another peripheral location, but not in attentional orienting. These findings are in agreement with recent neuroimaging results showing that signals for shifting attention between peripheral locations, i.e. reorienting, are specifically encoded in the medial aspect of the superior parietal cortex (Wojciulik and Kanwisher, 1999; Yantis et al., 2002; Serences and Yantis, 2006; Molenberghs et al., 2007; Kelley et al., 2008; Vossel et al., 2009; Tosoni et al., 2012), whereas spatially-selective signals for maintaining attention at a location, i.e. orienting, are encoded in more lateral parietal regions (Corbetta and Shulman, 2002; Serences and Yantis, 2007).

Importantly, our results also indicate that stimulation of pV6A during invalid condition is not associated with a modulation of RTs performance that depends on target eccentricity (Stimulation Site x Target Validity x Target Eccentricity: $p > 0.5$). Although this is a null result, it is an intriguing observation. One possible interpretation is that pV6A is specifically implicated in the disengagement phase of reorienting rather than in the subsequent shift to the new location (Posner et al., 1984). In fact, a region that specifically supports signals for shifting attention between peripheral locations would be expected to show a linear increase of invalid response times as target eccentricity increases, and this was not the case.

In the reaching task, the analysis of movement accuracy revealed that stimulation of pV6A significantly reduced the reaching “overshoot” errors by deviating reach endpoints toward visual fixation. This resembles the “magnetic misreaching” found in OA patients (Carey et al., 1997). In particular, we observed that reaching hypermetria, the classic tendency to reach too far peripherally relative to the central fixation point, which is typically observed in behavioral experiments involving spatially-guided reaching movements (Bock, 1986; Medendorp and Crawford, 2002; Ambrosini et al., 2012), was reduced following pV6A compared to Sham/Vertex stimulation. Such rTMS-induced effect on reaching kinematics is consistent with previous findings (Vesia et al., 2010), indicating that our stimulation sites effectively involved a reach-related cortical region.

The present rTMS results on reaching performance are also consistent with the visuomotor deficits observed in OA patients with unilateral posterior parietal lesions (Perenin and Vighetto, 1988). We indeed found that inactivation of right pV6A (ipsilateral to the responding hand) affected reaching accuracy only in the contralateral visual hemifield, resembling the so called “field effect” observed in OA patients (Perenin and Vighetto, 1988) and suggesting that reach accuracy is influenced by visual hemifield (Ciavarro and Ambrosini, 2011). Differently from right pV6A inactivation, the left pV6A inactivation (contralateral to the responding hand) impaired reaching movements directed to targets in both

hemifields, an effect which is also reminiscent of the so called “hand effect” typically observed in OA patients (Blangero et al., 2010). However, as we required participants to perform reach movements with the right hand only, further investigations are needed to confirm these conclusions.

Importantly, consistent with the selective effect of pV6A stimulation on RTs during invalid trials we found that rTMS over pV6A, compared to baseline, induced a greater reduction of baseline hypermetria when reaching movements were directed towards invalidly cued targets. Therefore, pV6A stimulation during invalid trials was associated with both an overall increase of RTs at target detection (in both attention and reaching tasks) and with an increment of reaching endpoint errors. This suggests a tight functional link between reaching and attentional processes when attention is reoriented from one location to another, as if shifts of attention are necessary for the corresponding update of reaching target. This result is consistent with recent neurophysiological data (Galletti et al., 2010) showing modulations for covert spatial attention in monkey area V6A, although a direct comparison between the studies is complicated by the absence in neurophysiological recordings of conditions in which monkeys are trained to reorient attention and execute reaching movements towards unattended targets. Galletti and colleagues (2010) showed that covert attention modulations in area V6A are consistent with the distribution of preferred gaze and reach direction observed in that area, rather than with the distribution of visual receptive fields (that in V6A are mainly located in the contralateral visual field), suggesting that attentional and reach activity are closely related in that cortical area.

Moreover, our findings can help disentangling different hypotheses about the link between attentional and visuomotor deficits in OA patients (Striemer et al., 2009; McIntosh et al., 2011). For example, McIntosh et al. (2011) have suggested that the two deficits could be linked because peripheral target jumps slowed perceptual discrimination and mirrored the reaching deficit. Although the experimental tasks in this neuropsychological study were mainly designed to test specific deficits associated with reaching on-line correction in OA patients, the findings are in line with our results. On the contrary, our results are in contrast

with those of Striemer and colleagues (2009), who did not find a common pattern of errors between attention and reaching tasks in OA patients compared with the control group, thus proposing that attentional and visuomotor deficits arise from independent mechanisms. However, it is worth noting that in this study the authors have not used a cued paradigm and compared very different behavioral measures (RTs and reaching accuracy), which does not represent an optimal basis to contrast the performance between attention processes and planning of arm-reaching movements.

It should be noted here that the issue of attentional and reaching functions in parietal cortex has been already addressed in two recent TMS studies. In particular, in the study by Vesia and colleagues (2010) rTMS was used to determine effector specificity (spatially-directed reaching and saccadic eye movements) in the posterior parietal cortex. One of the main findings was that stimulation of SPOC did not affect saccadic eye movements but deviated reach end-points toward visual fixation. This result is entirely consistent with our findings of a significant decrease of horizontal hypermetria following stimulation of pV6A, a region that is included in the SPOC. Compared to our work, however, the study by Vesia and colleagues (2010) did not address the question of attentional modulations in the reach-related SPOC region. Attentional effects associated with target spatial validity were instead investigated in the series of studies by Capotosto and colleagues (Capotosto et al., 2009, 2012a; Capotosto et al., 2012b), who employed a Posner-like task to examine TMS interference on EEG rhythms and behavioral performance during spatial orienting and reorienting. As in our work, Capotosto and colleagues (Capotosto et al., 2009, 2012a; Capotosto et al., 2012b) observed that TMS more strongly impaired performance during invalid than valid trials (note however that also a significant TMS effect on valid trials was observed in Capotosto et al 2012). One important difference, however, concerns the location of stimulation sites. Specifically, while Capotosto and colleagues applied TMS to parietal regions in the posterior IPS, we targeted the putative human V6A region, which is located in the anterior bank of the dorsalmost POS (i.e. anterior SPOC) and thus more medial and posterior than the

IPS by Capotosto (note that the estimated distance between the two cortical sites is ≈ 4 cm, that is beyond the spatial resolution of the TMS, (Wagner et al., 2007). Other notable differences include the use in our study, but not in that of Capotosto et al (Capotosto et al., 2009, 2012a; Capotosto et al., 2012b), of peripheral stimuli at different visual eccentricity, which allowed to test specific TMS effects on visual representations, and the combined evaluation of TMS effects on attentional and action-related (i.e. reaching) functions in pV6A.

To sum up, our findings represent both a confirmation and an extension of available data about attentional and reaching functions in the medial PPC. They are in line with current proposals of a functional segregation between medial and lateral PPC regions for attention (Capotosto et al., 2013) and reaching (Vesia & Crawford, 2012) processes. In particular, while lateral areas including the posterior IPS would encode spatially-selective signals for attending a location (Corbetta & Shulman, 2002) and encode also motor details for the reach vector (Vesia et al., 2010), our findings suggest that medial areas including pV6A would be specialized for encoding signals for shifting attention between peripheral locations (e.g., Yantis et al., 2002) as well as to peripheral reach goals (e.g., Vesia et al., 2010).

5.6 Conclusions

On the basis of the findings reported in this paper we propose that reorienting signals are used by the human pV6A to rapidly update the current motor plan or the ongoing action when a behaviorally relevant object unexpectedly appears at an unattended location, requiring a rapid and adaptive motor response such as reaching, grasping or pushing it away. On this basis, we suggest a direct involvement of the action-related dorso-medial visual stream in attentional reorienting and a more specific role of pV6A area in the dynamic, online control of reaching actions.

6. GENERAL CONCLUSIONS

In 1982, Mishkin and Ungerleider argued that visual information is segregated along two functionally specialized but complementary pathways originating in striate (V1) cortex: a ventral (occipito-temporal) stream that processes information for objects recognition (*what*), and a dorsal (occipito-parietal) stream that mediates the localization (*where*) of those same objects (Mishkin and Ungerleider, 1982). This model was proposed mainly on the basis of monkey studies and was interpreted as a distinction between subdomains of perception. This framework, though still important, has been superseded by a partially alternative formulation proposed ten years later by Goodale and Milner (1992) and revised in the two most recent updates by the same authors (Milner et al., 2006; Milner & Goodale 1995). In particular, Goodale and Milner introduced an important distinction between perception on the one hand and the guidance of action on the other hand, suggesting an important update to the original dual pathways model in which the dorsal pathway was not simply about spatial vision (*where*) but, instead carried out the necessary computations to control visually guided actions (*how*). Within this model the function of the dorsal stream has been inferred from a broad range of studies in monkey and from neuropsychological studies of the reaching movements in patients with optic ataxia (OA), which is considered to be a specific visuo-manual guidance deficit independent from perceptual and attentional deficits. At this regards Milner and Goodale have suggested that this does not preclude that OA patients can experience deficits of spatial attention but suggests that the two deficits, where they co-exist, likely result from “different neural systems” (Milner & Goodale, 1995).

Although discussions about which parietal regions are related to the emergence of visuomotor symptoms in OA still exist, recent studies suggested that this disorder appears as a consequence of lesions of the medial parieto-occipital region, which include the putative homologue of monkey area V6A (e.g. Khan et al., 2005). V6A area is considered to be a central node of the so called dorsomedial visual stream, a system that has been well described as an “express”

pathway that provides visual input from region of PPC to the dorsal premotor cortex (Rizzolatti and Matelli, 2003; Galletti et al., 2004). Monkey electrophysiological studies conducted in the last twenty years have provided detailed information on the functional properties of V6A area. Neurons in this region have large visual receptive fields (related to the coding of peripheral rather than foveal signals) and are influenced by combined eye-hand position signals as well as by hand movement signals. In addition, another noteworthy feature of this region is that its cells change in discharge rate after fixation also when the eyes remain fixed (e.g. Galletti et al., 1996). On the basis of these evidences it has been proposed that this activity may reflect the monkey levels of attention required for monitoring visually targets and/or hand trajectories (Galletti et al., 1996). However, these aspects were unclear before this study, because direct experimental evidence had not been provided.

In the present study we have investigated whether area V6A play a causal role in spatial function. To test this hypothesis (Chapter 3) we have conducted a study investigating in a systematic way whether the activity of single cells in V6A is influenced by shifts of covert attention (i.e. in the absence of overt eye or arm movements). To this aim we designed, and behaviorally tested, a task that required covert attention shifts from a central fixation point outward to a peripheral location, and then inward shifts of attention back to the fixation point. We have demonstrated that the firing rate of V6A neurons was modulated by covert shifts of spatial attention. In particular, we found that the activity of V6A cells was modulated by outward shift of attention, often in a direction-selective way. This finding suggests that V6A may play a causal role in attention function because spatially-directed modulation may reflects the levels of attention that is necessary both to select the goal of reaching during movement preparation, and to maintain encoded, and possibly update, the spatial coordinates of the object to be reached out during movement execution. Finally, we found that most of V6A neurons are modulated during the inward shift of attention from the periphery, suggesting that the activity of V6A neurons may reflects also the processes of reorienting of attention.

On the basis of this result we have conducted a further study in healthy human subjects using the on-line TMS to explore whether the putative homologue of area V6A (pV6A) is causally involved in attentional processes and whether these processes may modulate the execution of goal directed arm movements. To this aim we have used a MRI-guided TMS, to better localize and stimulate accurately the pV6A area, and a cuing paradigm in which, by manipulating the validity of the cues (i.e. the probability that the cue correctly predict the location of the target), we have tested specifically the involvement of the pV6A in attentional reorienting processes towards unattended targets. To test whether these attentional processes to target detection could influence the execution of reaching movements, in addition to the response time, we have recoded also the kinematic parameter of the long-range reaching movements performed towards the same cued targets, considering in particular the distribution of end-point errors. In this way we demonstrate not only that the pV6A is causally involved in the reorienting of attention to target detection (i.e. longer response time only for invalidly cued targets), but also that this process interferes with the execution of reaching movements (i.e. greater end-point error in invalid trials). In summary, these data demonstrate that pV6A stimulation during invalid trials was associated with both an overall increase of response time at target detection (in both attention and reaching tasks) and an increment of reaching endpoint errors. Moreover, our results indicate that stimulation of pV6A during invalid condition is not associated with a modulation of response time performance that depends on target eccentricity. This evidence suggest that pV6A is specifically implicated in the disengagement phase of attention reorienting rather than in the subsequent attention shift to the new location, because if this region would support directly signals for shifting attention between peripheral locations, it would be expected to show a linear increase of invalid response times as target eccentricity increases.

Beyond doubt, despite these encouraging results, many aspects remain to be investigated. For example, in our study we have demonstrated that TMS on pV6A area can alter reach endpoint errors and that these errors were greater when reaching movements were directed towards invalidly cued targets. These results

suggest that these processes may be helpful in the on-line control of action. It is important to note, however, that in our experiment the target changes its location before the movement initiation (i.e. during the planning phase). For this reason, further studies should be performed in order to investigate how the kinematic parameters, as well as the patterns of endpoint error, may change if we interfere with the normal activity of area V6A, when the target location changes during the movement execution. In addition, it is currently unclear whether the attentional processes that we reported impacts exclusively with the update of coordinates of the target location or whether it may influence also more complex events such as the integration between the hand and target positions required to compute higher-level movement parameters (i.e. movement vector, see Chapter 4). Therefore, further research is needed to clarify these issues.

In conclusion, our findings clearly demonstrated that area V6A, known as a reach-related region of the dorso-medial visual stream, is also causally involved in attentional process, encoding critical signals for disengaging/reorienting of attention to target detection (i.e, the shifting of attention focus upon an object or event potentially relevant or unexpected). This has been demonstrated both in the human and in the non-human primate.

These evidences have a great impact on clinical practice because can help disentangling different hypotheses about the link between attentional and visuomotor deficits, emerging from recent studies in OA patients (Striemer et al., 2007, Striemer et al., 2009; McIntosh et al., 2011). These studies have suggested that OA patients may have also an inability to detect and respond to targets located in the periphery of visual field, but they have used different methods to investigate these aspects, thus reaching different conclusions about the meaning of their data. Our results suggest that a more detailed assessment may be recommended for a better understanding of deficits in patients with lesions involving the medial region of the PPC, since attentional functions may influence directly visuomotor function. Therefore, it is important to include in the neuropsychological evaluation also techniques based on cuing paradigms which can allow to better understand if the visuomotor deficit in these patients may

depend also on an inability to shift the attention for target detection and/or for the update of object position.

More importantly, although these aspects need further investigations (see above), our findings are in line with recent data (e.g. Pisella et al., 2009; Schenk and McIntosh, 2010) that suggest a revision of the classic perception-action model of visual processing proposed by Milner and Goodale. In particular, our findings demonstrate that action related regions of the dorso-medial visual stream can process directly information related to spatial attention, bringing into question the radical dualism and then the independence between visuomotor and attentional/perceptual processes. Finally, our results are in line with other recent evidences showing that not only the ventral but also the dorsal fronto-parietal attention network, and specifically the more medial portion of PPC, would be specialized for encoding signals for shifting attention between peripheral locations (e.g. Yantis et al., 2002; Capotosto et al., 2013; Gillebert et al., 2013).

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I dedicate this PhD thesis to my wife Luana and my daughter Chiara, the joy of my life.

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