Published in final edited form as:

Eur J Neurosci. 2010 June ; 31(12): 2320–2340. doi:10.1111/j.1460-9568.2010.07291.x.

UNDERSTANDING THE PARIETAL LOBE SYNDROME FROM A NEUROPHYSIOLOGICAL AND EVOLUTIONARY PERSPECTIVE

Roberto Caminiti¹, Matthew V. Chafee², Alexandra Battaglia-Mayer¹, Bruno B. Averbeck³, David A. Crowe², and Apostolos P. Georgopoulos²

¹Department of Physiology and Pharmacology, SAPIENZA University of Rome, 00185 Rome, Italy

²Department of Neuroscience, University of Minnesota, and Brain Sciences Centre, VA Medical Centre, Minneapolis, MN 55417-2309USA

³Laboratory of Neuropsychology, NIMH, Bethesda, MD 20892-4415, USA.

Abstract

In human and non-human primates parietal cortex is formed by a multiplicity of areas. For those of the Superior Parietal Lobule (SPL) there exists a certain homology between man and macaques. As a consequence, *Optic Ataxia*, a disturbed visual control of hand reaching, has similar features in man and monkeys. Establishing such correspondence has proven difficult for the areas of the Inferior Parietal Lobule (IPL). This difficulty depends on many factors. First, no physiological information is available in man on the dynamic properties of cells in the IPL. Second, the number of IPL areas identified in the monkey is paradoxically higher than that so far described in man, although this issue will probably be reconsidered in future years, thanks to comparative imaging studies. Third, the consequences of parietal lesions in monkeys do not always match those observed in humans. This is another paradox if one considers that, in certain cases, the functional properties of neurons in the monkeys IPL would predict the presence of behavioral skills, such as construction capacity, that however do not seem to emerge in the wild. Therefore, *Constructional Apraxia*, which is well characterized in man, has never been described in monkeys and apes. Finally, only certain aspects, i.e. hand *Directional Hypokinesia* and *Gaze Apraxia* (Balint's *Psychic Paralysis of Gaze*), of the multifaceted syndrome *Hemispatial Neglect* have been described in monkeys. These similarities, differences and paradoxes, among many others, make the study of the evolution and function of parietal cortex a challenging “case”.

Keywords

parietal syndrome; behavioral neurophysiology; neuroanatomy; neuropsychology; evolution

Introduction

Lesions of posterior parietal cortex (PPC) in humans result in a constellation of symptoms often referred to as the “Parietal syndrome” (PS; Balint, 1909; for an historical perspective see Husain & Stein, 1988; Harvey & Milner, 1995). Since its original description the core of the PS consisted of optic ataxia (OA), psychic paralysis of gaze, and impaired spatial attention, now referred to as hemispatial neglect (HN). In subsequent years, a number of action disorders, such as constructional apraxia (CA; Kleist, 1934; Benton, 1967; De Renzi,

1982) have also been described after parietal damage, calling for an interpretation of the consequences of parietal lesions in terms of a general impairment of spatial cognition. A century of intensive neuropsychological study today offers a picture of the PS (see Husain & Stein, 1988; Harvey & Milner, 1995) which is more refined than that provided by earlier studies, in at least three main respects, i.e., the analysis of the behaviour of parietal patients, the anatomical localization of the lesions responsible for the different symptoms, as well as the conceptual frame/s adopted to understand them. Yet, the physiological mechanisms whose collapse results in the deficits typical of damage of the PPC remain elusive.

The scope of this review is to discuss the physiological studies that can help understand the consequences of parietal lesions from a neurophysiological perspective, thus providing a “positive image” of some of the disorders of parietal patients (Mountcastle *et al.*, 1975). Our attention will be confined to studies relevant to optic ataxia, hemispatial neglect and constructional apraxia. We believe that the study of the dynamic properties of parietal neurons and of their relationships with the premotor and motor areas of the frontal lobe *via* ipsilateral cortico-cortical connections, in other words the dynamics of the parieto-frontal system, can provide the necessary basis for a physiologically-founded interpretation of the PS.

We will start by describing the anatomical and functional organization of the parieto-frontal system, as it emerges from a detailed analysis in monkeys, and will compare it with the information available in man. Then we will briefly outline the main disorders of parietal patients together with the physiological results that can help their understanding. This will also offer the ground to speculate on the evolutionary elaboration of the PPC in comparing non-human primates to man.

The structural and functional architecture of the parieto-frontal system in monkeys and man

Studies of parietal cortex in monkeys

In monkeys, the parietal lobe includes both the superior and inferior parietal lobules, which are composed of many different architectonically defined cortical areas (Fig. 1A). The superior parietal lobule (SPL) is composed of the primary somatosensory cortex (area SI), area PE and PEc on the gyral surface, and areas PEa and MIP in the dorsal bank of the intraparietal sulcus (IPS). These areas, except SI, are all components of the classically defined Brodmann's area 5 (BA5). Areas V6A and V6 (Galletti *et al.*, 1996), respectively in the anterior bank and fundus of the parieto-occipital (POS) sulcus, are also part of the SPL. The SPL extends into the medial wall of the hemisphere, including area PEci in the caudal tip of the cingulate sulcus and area PGm (7m). The inferior parietal lobule (IPL, BA7) is composed of areas PF, PFG, PG and Opt on the gyral surface, as well as by areas AIP and LIP in the lateral bank of the IPS. Because of its cortico-cortical connectivity (see below), area VIP can also be included in this group, although it lies around the fundus of the IPS. Functionally it does seem to belong more to the IPL than to the SPL. All of the above areas, except SI, are globally referred to as the posterior parietal cortex (PPC).

In recent years the connectivity of the parietal lobe in monkeys has been mapped extensively with anterograde and retrograde tracing techniques. The anatomical afferents and efferents of PPC are primarily composed of reciprocal connections to the frontal motor and premotor cortex, temporal and occipital visual areas, as well as the prefrontal and cingulate cortex. There are very few if any connections with the amygdala, the hippocampus, and ventro-medial prefrontal cortex. Thus, there are few if any limbic inputs to these areas. However some inputs come from orbital cortical areas 12 and 13. Describing the complete set of connections between the parietal lobe and all other areas with which it is interconnected

would be highly complex and would not necessarily clarify the routes of information flow into and out of its constituent areas. Therefore in attempting this task we will mostly refer to a recent statistical study of the connectivity of these areas (Averbeck *et al.* 2009). This approach first clusters together sets of individual architectonically defined areas, based upon their inputs. Following this, one can look at the “anatomical fingerprint” of a cluster of areas, which is the proportion of inputs coming from different sets of areas.

This hierarchical cluster analysis shows that clusters in parietal cortex are composed of spatially adjacent areas. Specifically, there are 4 well defined clusters, each forming one branch of a bifurcation in a hierarchical tree (Fig. 2). A dorsal parietal cluster (*PAR-d*) includes areas MIP, PEc and PEa; a somatosensory cluster (*SS*) is composed of areas S1, SII and PE; a ventral parietal cluster (*PAR-v*) is formed by areas PF, PFG, PG and AIP, and a medio-lateral parietal cluster (*PAR-ml*) consists of areas PGm (7m), V6A, LIP, VIP, and Opt.

Given these clusters, we can analyze the inputs which characterize the areas belonging to each cluster, as well as the inputs to each cluster from other parietal and frontal areas, or from areas outside the parieto-frontal network. The strongest input to each parietal cluster from parietal cortex comes from other areas within the same cluster, which shows that connectivity tends to be stronger locally, i.e. cortical areas tend to receive strong connections from spatially nearby areas. The strongest input from frontal cortex to the *PAR-d* cluster stems from the dorsal premotor cluster, the major input to the *SS* cluster comes from MI, most of the input to the *PAR-v* cluster originates from ventral premotor areas, and the strongest input to the *PAR-ml* areas comes from the lateral prefrontal cluster (PFC). The connectivity between parietal and frontal motor areas is topographically organized. It is also reciprocal, as the strongest input to each corresponding frontal cluster tends to originate from the parietal cluster to which it provides the strongest input.

Thus, parietal areas tend to receive strong inputs from the other parietal areas within the same cluster as well as from topographically related frontal areas. However many parietal areas also receive inputs from outside the parietal-frontal network, and in fact these inputs can be more substantial than those from frontal cortex. Specifically, 31%, 10%, 7% and 23% of the inputs to the parietal clusters (*PAR-ml*, *SS*, *PAR-d*, and *PAR-v*) came from outside the parietal frontal network. Thus, both the *PAR-ml* and the *PAR-v* clusters receive more inputs from outside the parietal-frontal network than they do from the frontal areas. The external inputs into *PAR-ml* come from extrastriate visual areas, prefrontal area 9 and areas *MT*, *MST* and *STSD* in the caudal tip and dorsal bank of the superior temporal sulcus. The external inputs to *PAR-v* originate from *STSD*, *MT* and *MST*, as well as temporal visual areas *TE* and *TEO*, areas PFop and PGop in the dorsal insula, and orbital areas 12 and 13.

The reciprocity and overall pattern of the parieto-frontal connections clearly define the existence of privileged, although not private, routes of information flow between parietal and frontal cortex (Fig. 2). More specifically, the *medio-lateral parietal cluster* and its prefrontal counterpart are involved in the control of visually-guided eye movements and in the detection of saliency in the visual scene (Colby & Goldberg 1999). Most areas in this cluster, such as Opt, V6A and PGm (7m) are also involved in the early stages of the eye-hand coordination for reaching (Ferraina *et al.*, 1997a,b; Battaglia-Mayer *et al.*, 2000;2001;2003;2005;2007) and provide the oculomotor system with the visual information necessary for eye-movement control. The *dorsal parietal cluster*, together with the dorsal premotor one, is responsible for the combination of visual and somatic information necessary for visual reaching (Georgopoulos *et al.*, 1984; Kalaska *et al.*, 1990; Colby & Duhamel, 1991; Lacquaniti *et al.*, 1995; Johnson *et al.*, 1996; Battaglia-Mayer *et al.*, 2000;2001; Hamel-Paquet *et al.*, 2006). The *ventral parietal cluster* cooperates with the

ventral premotor one in the visual control of hand-object interaction underlying different forms of grasping (Taira *et al.*, 1990; Rizzolatti & Matelli, 2003). Furthermore, it has been suggested that areas PFG and AIP represent the parietal node of the mirror system (Fogassi *et al.*, 2005; Rizzolatti & Sinigaglia, 2010). Within this cluster, recent studies (Battaglia-Mayer *et al.*, 2005; 2007) have shown that neurons in areas PG and Opt are involved in directing reaches towards objects mainly located in contralateral space. In these areas, neural firing rates are higher when the hand moves toward the fixation point, as compared to any other possible form of coordinated eye-hand movement. It is worth stressing that this is the most common form of visuomotor behaviour in our daily life. The *ventral parietal cluster* is also involved in both the processing of visual information as well as in the preparation of movements in the context of more complex visuo-motor tasks, such as interception of moving targets (Merchant *et al.*, 2004). Closer to the motor output, neurons in the somatosensory cluster encode, among other variables, information related more directly to arm movement, such as limb position and velocity (Georgopoulos & Massey, 1985; Prud'homme & Kalaska, 1994; Averbach *et al.*, 2005; Archambault *et al.*, 2009), and conveys this information to frontal cortex via direct projections to MI.

All the above information is crucial to understanding the fine-grain architecture of the parietal-frontal system, which is characterized by the existence of trends in the functional properties of neurons along the rostro-caudal dimension of both frontal and parietal cortex. The gradient-like architecture mostly refers to the arrangement of visual, eye, and hand-related signals, as revealed by quantitative analysis in SPL, dorsal premotor, and motor cortex (Johnson *et al.* 1996; Burnod *et al.*, 1999; Battaglia-Mayer *et al.*, 2001; 2003 for a discussion; Ferraina *et al.*, 2009). In the caudal and rostral poles of the network, respectively in the parietal areas V6A (Galletti *et al.*, 1995; 1997; Battaglia-Mayer *et al.*, 2000; 2001), 7m (Ferraina *et al.*, 1997a,b) and dorso-rostral premotor (PMdr/F7) cortex (Johnson *et al.*, 1996; Fuji *et al.*, 2000), visual and eye-related signals predominate over coexisting hand information (Johnson *et al.*, 1996). On the contrary, hand information dominates over visual and eye signals in the rostralmost part of the SPL (area PE; Johnson *et al.*, 1996), and in the caudalmost part of the frontal cortex (PMdc/F2, MI; Johnson *et al.*, 1996). In intermediate parietal (areas MIP, PEc, PEa) and frontal (PMdc/F2) lobe regions, eye and hand signals coexist, with different relative strengths depending on the cortical zone considered (see Battaglia-Mayer *et al.*, 2003, for a review). Similar trends of eye and hand information, as well as of preparatory and movement-related signals, exist in the frontal node of the parieto-frontal network, across motor cortex, pre-SMA and SMA (Alexander & Crutcher, 1990; Rizzolatti *et al.*, 1990; Matsuzaka *et al.*, 1992; Hoshi & Tanji, 2004; see Nakev *et al.*, 2008 for a recent review). Throughout the network all these signals are directional in nature (Georgopoulos *et al.*, 1981; Kalaska *et al.*, 1983; Caminiti *et al.*, 1991; Johnson *et al.*, 1996; Battaglia-Mayer *et al.*, 2005).

Superimposed on this rostro-caudal dimension is a second gradient concerning the relative strength of different motor-related signals within the network. In fact a transition from preparatory (set- and memory-related) to genuine motor signals occurs moving from caudal to rostral in the SPL; the opposite holds true in the frontal cortex, as one moves from dorso-rostral to dorso-caudal premotor cortex toward MI. However, although in different proportions, cells encoding eye and/or hand position information are ubiquitous at all rostro-caudal levels in the network, so as to form a matrix of position representation in which preparatory and movement-related signal are embedded, and eventually selected for movement on the basis of task demands (Johnson *et al.*, 1996; Battaglia-Mayer *et al.*, 2001). This is not surprising if one considers that information about eye and hand position is essential under virtually all conditions for early planning of combined eye-hand movements, such as those typical of reaching to visual targets, or those necessary to manipulate objects of interest. In fact, if the modulation exerted by eye position on visual parietal neurons (for a

review see Andersen & Buneo, 2002) might favour the transformation of target location from retinal into body-centred coordinates, hand position signals are essential to compute the corresponding hand movement trajectory. As such, they exert a profound influence on encoding movement direction in the motor (Caminiti *et al.*, 1990), premotor (Caminiti *et al.*, 1991; Burnod *et al.*, 1992), and PPC (Lacquaniti *et al.*, 1995; Battaglia-Mayer *et al.*, 2000; 2005; Ferraina *et al.*, 2009). Similar trends of functional properties exist across the different architectonic areas (Pandya & Seltzer, 1982; Rozzi *et al.*, 2006) of the flat exposed part of IPL, since gradients have been reported for eye-related signals across areas 7a and LIP (lateral intraparietal area; Barash *et al.*, 1991), the first containing mostly post-saccadic neurons, the latter containing mainly pre-saccadic cells. A gradual transition of functional properties of neurons across the areas of the convexity of the IPL was first observed by Hyvärinen (1981) and recently confirmed and extended by Rozzi *et al.* (2008).

An additional and crucial feature of the network emerges when considering that frontal and parietal areas displaying similar neuronal activity-types are linked by reciprocal association connections (Johnson *et al.*, 1996; Chafee & Goldman-Rakic, 2000; Marconi *et al.*, 2001), indicating that the parieto-frontal association system probably both reflects and imposes functional specialization on cortical regions within the network. As a consequence, in the parietal and frontal cortex different forms of visuomotor activities involving the coordination of eye-hand movements might emerge as a result of a progressive match of spatial information representing the positions of the two effectors and their relation to visual targets. This match of signals could be based on a recursive signalling operated through ipsilateral association connections, and refined locally by intrinsic connectivity, *i.e.* by short intracortical connections (see Burnod *et al.*, 1999 for a theoretical frame). This interpretation is consistent with a number of experimental observations and with the predictions of network modelling. Experimental results (Johnson *et al.*, 1996; Chafee & Goldman-Rakic, 2000) indicate that association connections are likely to confer common physiological properties to frontal and parietal neurons during behaviour. These connections are also likely to play a major role in shaping network dynamics that are a product of both input activation and previous learning, as a Bayesian collective decision process (Koechlin *et al.*, 1999). Furthermore, populations of units that combine retinal, hand, and eye signals, and are linked by recurrent excitatory and inhibitory connections, are necessary to shape the directional tuning properties of SPL neurons (Mascaro *et al.*, 2003). When lateral inhibition is removed from this recurrent network, such spatial tuning properties are disrupted.

Studies of parietal cortex in man

In humans (Fig 1B), as in monkeys, the PPC is composed of both SPL and IPL, which are divided by the Intraparietal Sulcus (IPS). According to Brodmann's parcellation, the SPL is coextensive with areas 5 and 7, while the IPL includes areas 39 and 40, *i.e.* the angular and supramarginal gyrus, respectively. In von Economo's view, the SPL is composed of area PE, the IPL by areas PF and PG, roughly corresponding to areas 40 and 39 of Brodmann. Thus, critical scrutiny of the various architectonic parcellations available in the literature, supports the conclusion of von Bonin and Bailey (1947) that, in spite of certain differences that will be highlighted later, there is a basic similarity in the organization of the parietal lobe in human and non-human primates.

Very little is known of the detailed cortico-cortical connectivity in man. Recent developments in MRI, such as Diffusion Tensor Imaging (DTI), offer preliminary information on parieto-frontal connectivity. This information will be of crucial importance in the near future, since ongoing parcellations of cortical areas are largely performed on the basis of cortico-cortical connectivity, and less on the basis of architectonic criteria. Gaining a better understanding of cortical connectivity of parietal areas in humans is likely to have a positive impact on our understanding of the evolution of the parietal lobe and of its

pathology across species. So far, these studies have shown that the pattern of parieto-frontal connectivity obtained from monkey studies is very similar to that of man (Croxson *et al.*, 2005). Furthermore, the lateral premotor cortex of humans has been divided into two distinct regions (Rushworth *et al.*, 2006; Tomassini *et al.*, 2007), a dorsal one corresponding to monkey dorsal premotor cortex (PMd), having the highest probability of connections with the SPL and the adjacent areas of the IPS, and a ventral one corresponding to the monkey's ventral premotor cortex, with the highest probability of connections with the IPL, in particular the anterior part of the angular gyrus and the supramarginal gyrus. Interestingly, when the locations of these anatomically-defined subregions of PMd were compared with dorsal and ventral premotor areas as defined functionally by fMRI studies (see Mayka *et al.*, 2006 for a meta-analysis), a clear overlap was found. By adopting a similar probabilistic tractography approach, the medial premotor cortex of humans has been subdivided into a supplementary (SMA) and pre-supplementary (pre-SMA) motor area based on the pattern of cortico-cortical connectivity (Joansen-Berg *et al.*, 2004). Furthermore a high degree of anatomical similarity has been found in the division into subcomponents of the superior longitudinal fascicle in monkeys (Petrides & Pandya, 1984, 2002; Shmahmann *et al.*, 2007) and humans (Croxson *et al.*, 2005; Makris *et al.*, 2005; Rushworth *et al.*, 2006).

From a functional point of view, the parieto-frontal network appears to perform different computations related to sensorimotor control, such as converting sensory representations from one set of sensory coordinates into another (inter-sensory predictions), spatial representations from sensory to motor coordinates (sensory-motor transformations or inverse models), and spatial representations from motor to sensory coordinates (forward models). Thus, coordinate transformation for visually guided eye and/or hand movement during reaching could emerge in the operations of the parieto-frontal segment of the network, while the fronto-parietal connections, by providing information about the sensory consequences of motor plans, might contribute to the composition of forward models of movement.

In conclusion, the functional architecture of the parieto-frontal network, as described in monkey studies, and its similarity with that of man, derived from fMRI and tractography analysis, provides a reasonable background to attempt an explanation of some of the disorders of parietal patients from a neurophysiological perspective.

The cognitive-motor disorders of parietal patients: Optic ataxia, Directional hypokinesia, and Constructional apraxia

Among the cognitive-motor disorders of parietal patients we will consider Optic Ataxia, Directional Hypokinesia, and Constructional Apraxia.

Optic ataxia

Optic ataxia (OA) is mostly observed after lesions of the SPL and adjacent areas of the IPS (Perenin & Vighetto, 1988), including the parieto-occipital junction (Karnath & Perenin, 2005). The hallmark of OA is misreaching, i.e. errors of hand movement end-point occurring mostly in the peripheral visual field, but also in central vision when reaches are made in the absence of visual feed-back (for reviews see Battaglia-Mayer & Caminiti, 2002; Rossetti *et al.*, 2003; Battaglia-Mayer *et al.*, 2006a). More recently, slowness of both arrest and directional corrections of hand movement (Pisella *et al.*, 2000), as well as the inability to smoothly update hand movement trajectory (Gréa *et al.*, 2002) have been reported in a case of an OA patient, when a sudden jump of target location in space occurs. Under these conditions, patients make two distinct movements, one to the first and the other to the second target's location, whereas normal subjects smoothly correct hand trajectory in-flight. In normal subjects reversible inactivation of PPC through TMS affects the accuracy of hand

movement trajectory (Desmurget *et al.* 1999; Johnson & Haggard 2005) and prevents adaptation to new dynamics when the movement is made in a velocity-dependent force field (Della-Maggiore *et al.* 2004). In essence, the main feature of OA seems to be a disordered composition and control of directional hand movements to visual targets, although an impaired use of proprioceptive information has also been reported (Blangero *et al.*, 2007) in these patients. Based on a case report (Pisella *et al.*, 2000; Gréa *et al.*, 2002) it has been claimed (Rossetti *et al.*, 2003) that the essence of OA consists of a problem in the fast on-line control of reaching rather than in its early composition. However, a more recent study performed on a large number of OA patients with parietal lesions (T. Shallice, personal communication) has found impaired reaching without impaired on-line control. Therefore the relative degree to which OA reflects a deficit in motor planning or on-line motor control remains to be precisely determined.

It has often been claimed that the mild motor deficits observed in monkeys after parietal lesions do not provide a picture of the involvement of parietal cortex in visually-guided reaching that is comparable to that offered by OA in humans (Classen *et al.*, 1995; Karnath & Perenin, 2005; Tziridis *et al.*, 2009), and that the conceptualization of the parieto-frontal system based on studies in monkeys over the last 20 years would be of little help to understanding the visual control of movement and its breakdown in parietal patients. We believe that this claim mostly reflects a difficulty in interpreting the behavioural consequence of the parietal lobe lesion in monkeys. Most literature on this topic lacks consistency, since experiments could not be guided by the detailed knowledge we now have of the architecture of the parieto-frontal system. From the late fifties to about the end of the seventies (see Hartje & Ettlinger, 1974; LaMotte & Acuña, 1978) lesion studies reported defects of visually-guided reaching after extensive PPC lesions encompassing SPL and IPL, but rather included both of them. This literature will not be discussed here. When neuropsychological studies on monkeys were guided by more advanced parcellation schemes of PPC, a different picture smoothly emerged. Misreaching in the light was observed after bilateral removal of IPL areas 7a, 7ab and LIP, while reaching inaccuracy in the dark was observed after bilateral lesions of SPL areas 5 and MIP, and of IPL area 7b (Rushworth *et al.*, 1997). In the last case, the most severe impairment in the visual control of arm movements was described in an animal where the lesion extended into the medial wall of the SPL affecting area PGm (7m) as well. This is not surprising if one considers that neural activity in area 7m is deeply influenced by visual feed-back signals about hand movement trajectory and hand position in space (Ferraina *et al.*, 1997a, b). Rushworth *et al.* (1997) stress that their SPL lesions “did not remove all of the visually responsive areas in the depth of posterior medial bank of the IPS”. In a more recent, although qualitative analysis, both grasping and reaching movements were impaired after lesions of area V6a (Battaglini *et al.*, 2002). Further, muscimol injections limited to a restricted sector of the SPL, specifically area PE/PEa, result in increased hand reaction- and movement-time, while also increasing the spatial dispersion of hand trajectories in 3-D space, as compared to controls (Battaglia-Mayer *et al.*, 2006b).

The distributed nature of the system discussed above predicts that only very large lesions interrupting the information flow from the *many* reaching-related regions of SPL to dorsal premotor cortex will severely affect the visual control of arm movement. This is very difficult to achieve in a well controlled experiment. Finally, most neurophysiological and anatomical studies of motor, premotor, and parietal cortices of monkey indicate that all the information necessary for the composition, execution and control of reaching are encoded and combined in the SPL, dorsal premotor and primary motor cortex (for recent reviews see Andersen & Buneo, 2002; Battaglia-Mayer *et al.*, 2003). Thus, as far as the cortical control of visual reaching is concerned, taking into account possible differences in parietal cortex

functions in monkeys and humans, the claim that the parieto-frontal system is not critically involved in the visual control of hand movements has no foundation.

Instead, we believe that the functional architecture of the parieto-frontal network provides a coherent framework in which to interpret OA from a physiological perspective. A key feature of neurons in the SPL is their ability to combine different neural signals relating to visual target location, eye and/or hand position and movement direction into a coherent frame of spatial reference. In fact, the preferred directions of neurons in areas V6A, PEc and PGm, when studied across a multiplicity of behavioural conditions (Battaglia-Mayer *et al.*, 2000; 2001; 2003) cluster within a limited part of space, the *Global Tuning Field (GTF)*. Each SPL neuron is endowed with a spatially-selective *GTF* (Fig. 3A-B), however at the population level the distribution of the mean vectors of the *GTFs* is uniform in space (Fig 3C). Thus, every time a command is made for a combined eye-hand movement, such as reaching, in a given direction, a selection process will recruit mostly those neurons with *GTFs* oriented in that particular direction. Therefore the *GTFs* of SPL neurons can be regarded as a spatial frame suitable to dynamically combine directionally congruent visual, eye and hand signals, and therefore as basis for representations of reaching. It is our hypothesis that OA is the result of the breakdown of the combinatorial operations occurring within the *GTFs* of SPL neurons (Battaglia-Mayer & Caminiti, 2002; Caminiti *et al.*, 2005; Battaglia-Mayer *et al.*, 2006a).

Anatomical studies (Marconi *et al.*, 2001; Averbeck *et al.*, 2009) suggest that the spatial information encoded in the *GTFs* of SPL neurons is derived from inputs from extrastriate, parietal, and frontal areas, and that it can be addressed not only to other parietal areas by virtue of local intraparietal fibers, but also to dorsal premotor and prefrontal cortex via output connections (see Fig. 2). The composition of motor plans for coordinated eye-hand actions can undergo further and final shaping thanks to re-entrant signaling operated by the fronto-parietal pathway. Thus, parietal cortex can act as a recurrent network where dynamic mechanisms might control the relative contributions made by directional eye and hand signals to neural activity, by weighting them in a flexible way and on the basis of task demands.

The lesions of the SPL knock-out this parieto-frontal interplay, and therefore OA might be interpreted as a cortico-cortical disconnection syndrome. However, alternative interpretations exist as to the pathway subserving visually-guided reaching (Stein, 1986; Khrebtkova *et al.*, 1998) whose collapse would be responsible for the reaching impairment observed in OA patients (Classen *et al.*, 1995). According to this view, a parieto-ponto-cerebellar system provides motor cortex, via the cerebello-thalamo-cortical pathway, with the spatial information necessary for the composition of motor commands for visually-guided arm reaching. Unfortunately, knowledge of the anatomo-functional architecture of this circuits and its relevance to reaching is still rather primitive. To fill this gap, a recent study (Tziridis *et al.*, 2009) has described, in the dorsal pontine nuclei, separate populations of directional eye and hand movement-related cells whose effector-specificity, however, stands in contrast with the features of the *GTF* of SPL neurons. This leaves open the problem of where in this pathway the integration of the eye and hand signals necessary for eye-hand coordination during reaching occurs. In addition, it is hard to reconcile the multi-synaptic nature of this potential pathway with the need to operate fast in time, as required for visual reaching and its on-line control. Further studies will be necessary to evaluate the functional role and relevance of this ponto-cerebellar pathway for hand movement control in general, and for coordinated eye-hand movement such as visual reaching in particular. It is worth stressing that the interpretation of OA as a consequence of the collapse of the combinatorial mechanism of the *GTFs* of SPL neurons maintains all its validity regardless of

the exact parietal efferent pathway (parieto-frontal vs parieto-ponto-cerebellar-thalamo-cortical) involved.

Another crucial point to be addressed concerns the difficulty of OA patients to make fast online adjustments of hand movement trajectories. An answer to this question might come from a recent neurophysiological study (Archambault *et al.*, 2009) of neurons in the SPL of monkeys trained to make direct reaches to visual targets as well as online corrections of movement trajectories after a sudden change of target location in 3-D space (Fig. 4). It was found that the activity of reaching-related cells encoded different movement parameters, such as hand position, speed and movement direction, with neural activity mostly leading the onset of hand movement (Fig. 4). When a change of target location occurred, the pattern of activity associated with the hand movement to the first target smoothly evolved into that typical of the movement to the second one, predicting the corresponding changes of hand kinematics (Fig. 4). Therefore, the on-line control of hand trajectory in the SPL resides in the relationship between neural activity and hand kinematics, and is characterized by the coexistence of signals reflecting ongoing hand movements with other predicting future changes of movement direction. The causality of this relation is shown by the elongation of both hand reaction- and movement-time and by spatial dispersion of hand trajectories after muscimol injections limited to the SPL area where these relationships between neural activity and hand kinematics have been found (Battaglia-Mayer *et al.* 2006b).

Consistent with this picture, the failure of OA patients to make fast, in-flight corrections of hand movement trajectory may be due to the loss of those populations of parietal cells whose activity carries predictive signals concerning corrections of hand movement direction.

These results are consistent also with those obtained about 25 years ago by a similar study of motor cortex (Georgopoulos *et al.* 1983). Motor cortex is linked to SPL both directly (Strick & Kim 1978; Johnson *et al.* 1996) and indirectly, through dorso-caudal premotor cortex (Johnson *et al.* 1996; Matelli *et al.* 1998). Transient inactivation of premotor cortex with TMS results in a reduction of visually-dependent on-line corrections of reaching during sensorimotor adaptation (Lee & van Donkelaar, 2006). Therefore, it is reasonable to assume that the visuomotor information used by motor cortical cells to update hand movement trajectory in response to a change in target location originates in large part from the SPL.

Directional hypokinesia

Directional hypokinesia (DH) is found after both frontal and inferior parietal lesions, and is characterized by an impaired representation of action space, evident as a difficulty in planning and execution of hand movements toward the contralesional part of egocentric space. More specifically DH involves a prolongation of reaction- and movement-time, as well as an increased inaccuracy of reaching to visual targets in the contralesional part of space, regardless of the limb used. DH often coexists with directional bradykinesia and hypometria, so that arm movements have reduced velocity and amplitude as well. These features, together with the difficulty of initiating the movement, distinguish DH from OA. DH is generally considered the hallmark of the output-related components of neglect (Watson *et al.*, 1978; Heilman *et al.*, 2000; for reviews see Vallar *et al.*, 2003; Fink & Marshall, 2005). In an attempt to better characterize DH, neglect patients with inferior frontal and parietal lesions in the right hemisphere (Mattingley *et al.*, 1992, 1998) have been contrasted when making reaches performed to left visual targets from right and left starting positions relative to the movement end-point. Under this condition, both frontal and parietal patients displayed longer reaction times to initiate the reach toward the contralesional target. However, only parietal patients exhibited a specific directional motor impairment, since they were much slower in initiating leftward, as compared to rightward, hand movements towards visual targets in the left side of space.

In monkeys, only studies relevant to the issue of directional motor components of neglect will be discussed here. Both inactivation (Stein, 1976) and unilateral lesion (Faugier-Grimaud *et al.*, 1985) of area 7 lead to increased inaccuracy of reaching and to longer reaction-time for reaches to contralateral visual targets. In the first study, this effect was reported for both arms. In the latter, it was observed for monkeys using the contralesional arm, and was more severe for movements toward contralateral rather than ipsilateral space. In one animal, an increase in RT was observed also for the ipsilesional arm, especially for movements directed to targets in the contralateral space. In this latter study (Faugier-Grimaud *et al.*, 1985) the two limbs were tested each in only one direction of movement, i.e., the right arm for leftward movements and the left arm for rightward ones. Therefore, it is difficult to conclude whether the prolongation of reaction-time was related to the arm used, or to the direction of movement (toward or away from the side of the lesion). In any case, the impaired movements were mainly those directed to the target located in the contralesional space. An additional study (LaMotte & Acuña, 1978) reported a directional impairment of reaches to visual targets performed with the contralesional arm, either in the presence or absence of visual guidance of movement. In fact reaches towards targets in contralesional space were consistently hypometric, since they were systematically misdirected toward the midline, as if the contralateral space was somehow “compressed” or under-represented. In this experiment, the lesion included both SPL and IPL. Finally, monkeys with unilateral lesions confined to area 7a (Deuel & Farrar, 1993) were observed to be reluctant, slow and inaccurate when reaching to moving targets only in the contralesional space, although they were able to detect and glance at them.

Therefore, in both monkeys and humans IPL lesions severely impair the representation of directional motor information concerning action space. Understanding such representations was a necessary step toward understanding the directional movement disorders of neglect from a neurophysiological perspective. To this end, we will refer to recent studies of the dynamic properties of neurons in area 7a of the IPL of monkeys examined during the performance of several tasks aimed at assessing the relationships between neural activity and the direction of visually- and memory-guided eye/hand movements (Battaglia-Mayer *et al.*, 2005; 2007). The tasks adopted in these studies were designed to reproduce in the laboratory set-up the forms of behaviour that are compromised by IPL lesions in neglect patients. In this experiment, monkeys made eye and hand movement in isolation or in a coordinated fashion to memorized target locations within a directional array. It was found that the distribution of preferred directions of a very large population of cells in area 7a studied during eye and/or hand movement was highly anisotropic and favoured the representation of the contralateral space (Fig. 5). Interestingly, this anisotropy was not observed in the memory epoch, when the animal kept in working memory the location of the target toward which, after a go-signal, an eye and/or a hand movement had to be made. Therefore, this anisotropy in the representation of motor space in IPL is of a dynamic nature, since it emerges only at the moment when all necessary information is available to transform the motor plan into action. It is our hypothesis that the loss of this representation and the difficulty in continuously combining and updating all the spatial information necessary to select the direction of visually-guided movement lies at the core of Directional hypokinesia. In this respect, it is noteworthy that network models of neglect mostly rest on anisotropy of spatial representations (Pouget & Sejnowski, 1997; Pouget & Driver, 2000). The assumption is that a gradient of spatial representation is embedded in the activity of neurons in the left and right IPL, such that lesions in one hemisphere primarily disrupt information concerning the contralesional space. Therefore the data illustrated and discussed above offer a neurophysiological underpinning for understanding the motor impairments following parietal damage and provide new data to constrain future theoretical models of neglect.

Constructional apraxia

Apraxia in general has been defined as the “inability to perform certain subjectively purposive movements or movement complexes with conservation of motility, of sensation and of coordination” (Wilson, 1909). Apraxia is typically the result of parietal lobe damage, and several types have been identified, including ideational, ideomotor, and constructional apraxia. In *ideational* apraxia (Liepmann, 1920) there is a failure to perform a complex series of actions, such as an inability to perform the sequence movements needed to fold a piece of paper and place it inside an envelope. In *ideomotor* apraxia (Liepmann, 1920) the patient cannot execute a familiar action on verbal command or by imitation. In *constructional* apraxia (CA) there is a disturbance “in formative activities such as assembling, building and drawing, in which the spatial form of the product proves to be unsuccessful, without there being an apraxia for single movements” (Kleist, 1934).

There is a basic difference between ideational and ideomotor apraxia on one hand and CA on the other; namely, in the first two forms the patients have difficulty in reproducing previously well learned motor tasks, whereas in CA the difficulty is with reproducing visual figures or constructing a complex object made by different parts. Because apraxias reflect the loss of skilled movement, often under verbal command or visual guidance, they could reflect the disruption of a number of different fundamental information processing operations. For example, the mechanisms that underlie ideomotor apraxia have been proposed to involve disconnections between parietal language and frontal motor areas (Geschwind, 1975), thereby disrupting the capacity to execute a gesture on verbal command. Alternatively, ideomotor apraxia has been attributed to the loss of stored representations of learned movement gestures (Gonzalez Rothi *et al.* 1991; Poizner *et al.* 1995).

The inability to copy a visual model, either by drawing or by physical assembly, is central to the definition of CA. The core symptom of the disorder is made apparent when patients are presented with a model object and attempt to produce a faithful copy of it. The copies that patients produce are spatially disorganized, in the sense that components are often put into incorrect spatial relationships with respect to one another so that the spatial structure of the object is lost (Benson & Barton, 1970; Piercy *et al.*, 1960). The deficit is evident both when patients attempt to draw copies of simple geometric figures (e.g. a square or a triangle) (Benton 1967, Gainotti, 1985), and also when they attempt to copy a model object by assembling together its component parts (Benton & Fogel, 1962). The inability to produce accurate copies could be caused either by a failure to effectively analyze the spatial structure of the model or effectively orchestrate motor output to reproduce this structure through a sequence of actions (Arena & Gainotti, 1978; Mack & Levine, 1981). The deficit tends to be most severe following damage to the PPC, though it can follow frontal damage as well (Villa *et al.*, 1986), and although early studies pointed to a special role of the right hemisphere in constructional praxis (Piercy *et al.* 1960; Benton, 1967; Mack & Levine 1981), more systematic later work (reviewed in De Renzi, 1982; Gainotti, 1985) supports the notion that this function is most probably encoded by both hemispheres. It should be noted that the inability to draw a figure is not by itself a sign of CA. For example, it has been shown that the inability to draw objects from memory is a defect independent of constructional apraxia and especially common in aphasic patients with severe semantic-lexical disturbances (Gainotti *et al.*, 1983).

The above neuropsychological data indicate that constructional praxis is a distributed function, involving at a minimum parietal and prefrontal cortex. To characterize the involvement of parietal neurons in the analysis of object structure, a recent series of physiological experiments examined the neural representation of space in parietal area 7a of monkeys as they performed an object construction task (Chafee *et al.*, 2005; 2007; Crowe *et al.*, 2008). The construction task was designed to simulate clinical tests of constructional

ability in humans, and in particular to allow for the identification of neural signals associated with a spatial cognitive analysis of object structure taking place upstream of motor processing. During this task, monkeys were presented with a model object consisting of a varying configuration of square components (Fig. 6A; 'Model'), and were required to remember the model configuration during a subsequent delay period. At the end of the delay, they were presented with a copy of the preceding model object, identical except that a single component was missing (Fig. 6A; 'Copy'). The task was for monkeys to localize and replace the missing component, which they did by timing when they pressed a single response key in relation to a choice sequence (Fig. 6A; '1st choice', '2nd choice') at the end of the trial. The sequential choice method of behavioural report ensured that the locations of object components were not confounded with the direction of the upcoming movement. This facilitated identifying of neural signals related to a cognitive analysis of object structure, and made it possible to differentiate these signals from others present in parietal cortex that code the direction of forthcoming movements. However, it is important to note that as the construction task did not require monkeys to physically assemble objects, how signals in parietal cortex that reflect object structure ultimately shape motor commands to direct object construction has yet to be addressed.

During the copy period when monkeys were required to localize the component that was missing from the copy object relative to the preceding model, the activity of single neurons in area 7a reflected this spatial computation by signalling the location of the missing component (Fig. 6B; Chafee *et al.*, 2005). This neural signal did not reflect the spatial features of the visual input, since neural activity varied to reflect the location of the missing component even when the form and position of the copy object remained constant (Fig. 6B; top row). Neurons were comparably activated by diverse pairs of model and copy objects that jointly localized the missing component to each neurons preferred position (Fig. 6B; second column from left). Nor did activity reflect a spatial motor plan, as the spatial information coded by neural activity was uncorrelated with the direction of the forthcoming motor response (which did not vary across trials). Rather, the signal appeared to be a cellular correlate of a spatial cognitive process analyzing object structure in order to direct the construction operation, without being correlated with the spatial aspects of individual stimuli presented or movements made during the trial. Consistent with this interpretation is the observation that neurons carrying this signal during object construction were generally inactive during simpler sensorimotor tasks in which monkeys either planned saccades or directed attention toward peripheral stimuli falling at the same retinocentric coordinates where missing components were located during the object construction task (Chafee *et al.*, 2005).

By shifting the position of the reference objects relative to the gaze fixation target, it was possible to determine whether neurons represented the position of missing components in viewer-centered or object-centered spatial coordinates. If neurons coded the position of missing object components in viewer-centered coordinates, their activity would vary as a function of whether they were located to the left or right of the gaze fixation target (at the midline of viewer-centered frames of reference). If instead, neurons coded the position of missing object components in object-centered coordinates, their activity would vary as a function of whether components were missing from the left or right side of the copy object, relative to its intrinsic midline. A population of neurons in area 7a was found which represented the position of missing components in object-centered coordinates, relative to the midline of the object (Chafee *et al.*, 2007). These neurons were comparably activated during the copy period whenever the missing component was located on a preferred side of the copy object, regardless of where the copy object was presented in viewer-centered space (Fig. 7A). The above data provided evidence that the parietal neurons supported a spatial cognitive process during the object construction task that analyzed object structure and that

represented the results of the analysis in object-centered coordinates. However, parietal neurons were heterogeneous in terms of the spatial coordinate system they used to represent space, and neurons coding position in viewer- and object-centered position were both present in area 7a (Chafee *et al.*, 2007). A decoding analysis quantified the information carried by the activity of the two simultaneously active population in their respective coordinate systems, and found that variation in viewer-centered information preceded and could predict variation in object-centered information over time within a trial (Crowe *et al.*, 2008). This observation was consistent with the hypothesis that spatial information provided by the visual input coding position initially in viewer-centered (retinocentric) coordinates, was converted into spatial information coding position in object-centered coordinates over time, and that a correlate of this transform could be detected in parietal cortex.

The above neural data provide evidence that parietal neurons encode spatial information that is the product of a spatial cognitive analysis applied to the visual input to meet a specific behavioural objective. That functional conclusion was further substantiated by the results of neurophysiological recordings in parietal area 7a of monkeys performing a visual maze task (Fig. 8). In this task, monkeys maintained their gaze fixated on a central target as a large (30° in diameter) visual maze stimulus was presented, centered on the fixation target. Each maze contained a central start box, from which a single path (referred to as the main path) extended through the maze. On one-half of trials, the main path reached an exit in the maze perimeter (Fig. 8A; 'Exit'). On the remaining half of trials, the main path reached a blind ending (Fig. 8A; 'No exit'). The monkey was required to determine whether the main path reached an exit or blind ending, and press one of two response keys to indicate their judgment. The task was intended to recruit a covert analysis of the spatial structure of the maze, specifically of the main path. The radial direction of the main path varied randomly over trials, and was either straight (Fig. 8A; 'Straight main path'), or contained a single 90° turn (Fig. 8A "One-turn main path"). During the performance of this task, many parietal neurons were robustly activated at the onset of the maze as a function of the direction of the main path that was mentally tracked (Fig. 8B) (Crowe *et al.*, 2004). As in the construction task, neurons active in the maze task generally carried spatial information only during maze solution, and were not active during simpler sensorimotor tasks in which monkeys planned eye movements in directions that corresponded to the path directions during maze solution (Crowe *et al.*, 2004). When monkeys mentally tracked a path that turned, the neuronal population vector constructed from spatially tuned neurons in area 7a rotated in the direction of the turn as the mental analysis of the maze progressed (Fig. 8C) (Crowe *et al.*, 2005), when no movements were made and no changes in the visual input occurred. Neural data from the construction and maze tasks provide convergent evidence that spatial information processing in parietal cortex can be decoupled from the spatial attributes of stimuli and movements in order to support a cognitive process, as distinguished from a sensorimotor one. Both experiments demonstrate that parietal neurons contribute to a covert analysis of the visual input that extracts the embedded spatial information specifically needed to achieve a behavioural goal.

Hemispatial neglect

In addition to the impairments in visuomotor control and spatial cognition reviewed above, damage particularly to right parietal cortex disrupts the conscious awareness of visual space, producing a syndrome referred to as hemispatial neglect (Gainotti *et al.*, 1972; Colombo *et al.*, 1976; Bisiach *et al.*, 1979; Adair & Driver & Halligan, 1991; Driver *et al.*, 1992; Barrett, 2008). Neglect is not a symptom that is limited to damage of parietal cortex, however, and the locus of the lesion producing the strongest neglect is controversial, with some studies placing this locus in the temporal cortex (Karnath *et al.*, 2001). Patients with this disorder fail to consciously perceive stimuli or events that occur in the side of space opposite their

damaged cerebral hemisphere. Clinical tests of hemispatial neglect include the line bisection, object cancellation, and copying tasks. In the line bisection task, patients are instructed to place a mark on a line where they perceive the midpoint of that line to be. Patients with right cortical damage place a mark that is frequently deviated toward the right end of the line (Reuter-Lorenz & Posner, 1990; Koyama *et al.*, 1997; Ishiai *et al.*, 2000). This has been explained as a failure to entirely perceive or attend to the full leftward (contralateral) extent of the line, shifting its perceived midpoint to the right. In object cancellation tasks, patients are instructed to draw a line through each of a relatively large number of stimuli printed on a page. Patients with right parietal damage typically fail to draw lines through ('cancel') objects printed on the left side of the page (Ferber & Karnath, 2001; Sarri *et al.*, 2009). Neglect is also evident in copy tasks – for example neglect patients with right cortical damage typically fail to include features belonging to the left part of scenes or objects (Colombo *et al.*, 1976; Villa *et al.*, 1986; Ishiai *et al.*, 1996). In making their self-portraits, neglect patients omit to draw the half of their face contralateral to the damaged cerebral hemisphere (Fig. 9). In each case, there is a loss of visual awareness of stimuli presented in the side of space opposite the lesion.

Extinction is a milder residual defect in visual attention that often persists after patients have recovered from frank neglect (Adair & Barrett, 2008). In extinction, patients demonstrate a defect in attention only when two stimuli are presented in left and right visual hemifields simultaneously, in which case they fail to consciously perceive the stimulus contralateral to their lesion (Di Pellegrino *et al.*, 1997; Mattingley *et al.*, 1997; Rorden *et al.*, 2009). Patients can typically detect the same contralateral stimulus if it is the only one presented. The phenomenon of extinction has been taken to reflect the loss of a neural process that biases competition between visual stimuli for conscious perception according to the behavioural salience of each stimulus (Desimone & Duncan, 1995). Under this model, stimuli presented simultaneously in the left and right visual hemifield compete for central representation and conscious visual awareness. Because one of these stimuli is represented by a compromised parietal cortex (the stimulus contralateral to the lesion), it receives a weaker bias, is represented by a weaker neural signal and, as a result, 'loses out' in the competition between stimulus representations, escaping conscious detection.

The detrimental effect of parietal lesions on attention implies that parietal neurons participate in controlling attention, which in turn predicts that neural signals coding visual stimuli in parietal cortex should modulate as a function of whether attention is directed toward the stimulus or not. Neural recording experiments in nonhuman primates have confirmed this prediction at the single neuron level – visual signals evoked in parietal neurons are modulated as a function of whether or not the visual stimulus is attended (Mountcastle, 1978b; Bushnell *et al.*, 1981; Mountcastle *et al.*, 1981; Steinmetz *et al.*, 1994; Constantinidis & Steinmetz, 2001b; Ipata *et al.*, 2006;). Further, the spatial location coded by the active population of parietal neurons corresponds with the locus of spatial attention as behaviourally defined, namely as a circumscribed region of space where visual processing is enhanced (Powell & Goldberg, 2000; Bisley & Goldberg, 2003). When monkeys are presented with multi-stimulus displays, parietal neurons preferentially encode the location of the most salient stimulus (Gottlieb *et al.*, 2008b; Gottlieb *et al.*, 1998; Kusunoki *et al.*, 2000; Constantinidis & Steinmetz, 2001a, 2005), and have been proposed to provide 'priority map' of visual space (Gottlieb *et al.*, 2008a). Consistent with this is the finding that visual responses of parietal neurons are suppressed to the degree that visual stimuli are effectively ignored (Ipata *et al.*, 2006). The above data indicate that the activity of parietal neurons is correlated with the deployment of attention toward (or away from) particular locations in space. However it is also possible to direct attention to a specific feature of a visual stimulus (Maunsell & Treue, 2006), irrespective of its spatial position. Interestingly, neurons in the visual motion area MT reflect feature-based attention. Visual signals that are evoked by a

motion stimulus presented in the receptive field of MT neurons are stronger if the motion stimulus is moving in the preferred direction of the neuron and the monkey is attending to that direction of motion, even when spatial attention is directed outside of the receptive field (Treue & Martinez Trujillo, 1999).

In parietal area 7a, under specific behavioural conditions, visual signals are suppressed if attention is already directed toward the location of a stimulus when the stimulus appears (Robinson *et al.*, 1995; Steinmetz *et al.*, 1994; Powell & Goldberg, 2000; Constantinidis & Steinmetz, 2001b). This effect has been interpreted to indicate that the activity of area 7a neurons is maximal when stimuli appear that cause spatial attention to move (as in the case that an attention-grabbing stimulus appears outside the current location of attention). The collapse of such a mechanism following parietal damage could explain the difficulty of parietal patients in shifting the locus of spatial attention, which is the essence of what Balint referred to as the “psychic paralysis of gaze”. The relative magnitudes of the enhancing and suppressing effects of attention on neural activity in parietal cortex may vary as a function of parietal subdivision and task paradigm; however both effects substantiate the involvement of PPC in the control of spatial attention at the cellular level.

Hemispacial neglect following parietal damage can manifest in either viewer-centered or object-centered spatial coordinates (Hillis *et al.*, 1998; Driver & Halligan, 1991; Driver *et al.*, 1994; Tipper & Behrmann, 1996; Driver & Pouget, 2000; Olson, 2003). In viewer-centered neglect, patients neglect visual stimuli appearing in the half of visual space that is contralateral to the damaged cerebral hemisphere (in the left visual hemifield after a right parietal stroke, for example). In object-centered neglect, patients neglect the contralateral side of objects (the left side of objects after right parietal stroke, for example), irrespective of where the objects are located in viewer-centered space. The fact that parietal damage can produce both forms of neglect implies that parietal cortex contains neurons that code space using different frames of spatial reference. This has been confirmed by neurophysiological experiments in nonhuman primates. Largely different groups of parietal neurons code position using spatial coordinates that are retina-centered (Motter & Mountcastle, 1981; Colby *et al.*, 1995; Batista *et al.*, 1999; Cohen & Andersen, 2000), head-centered (Andersen *et al.*, 1985; 1990; Brochier *et al.*, 1995), body-centered (Lacquaniti *et al.*, 1995; Snyder *et al.*, 1998b), object-centered (Chafee *et al.*, 2007; Crowe *et al.*, 2008), and world-centered (Snyder *et al.*, 1998b). Loss of object-centered spatial representations following damage to parietal cortex could contribute directly to the behavioural phenomenon of object-centered neglect, as several properties of object-centered representation in parietal cortex at the cellular level parallel properties of object-centered neglect at the behavioural level. For example, the object-centered location coded by parietal neurons during the object construction task corresponds to the object-centered location of spatial attention behaviourally defined as a region of enhanced sensorimotor processing (Fig. 7B) (Chafee *et al.*, 2007). In addition, most parietal neurons coding object-centered position in each cerebral hemisphere prefer the contralateral side of objects (Fig. 7C) (Chafee *et al.*, 2007). Loss of these neurons could explain why damage to parietal cortex in one cerebral hemisphere impairs conscious perception of the contralateral side of objects in humans.

Parietal cortex also contains neurons that code the directions of forthcoming eye and arm movements (Batista & Andersen, 2001; Bracewell *et al.*, 1996; Snyder *et al.*, 1997; Ferraina *et al.*, 1997a,b; Snyder *et al.*, 1998a; Batista *et al.*, 1999; Mazzoni *et al.*, 1996; Battaglia-Mayer *et al.*, 2000; 2001; Battaglia-Mayer *et al.* 2005; Quiroga *et al.*, 2006; Battaglia-Mayer *et al.* 2007; Ferraina *et al.*, 2009;), even in the case that no visual stimulus was presented at the endpoint of the planned movement (Mazzoni *et al.*, 1996). Importantly, this motor intention activity can also reflect which effector is going to be moved (eyes and/or hand, for example), indicating a clear role in motor planning that can be dissociated from

spatial vision or attention (Snyder *et al.*, 1997, 2000). Historically, parietal cortex has been considered to function in spatial attention or spatial motor control, but not both, as the functions were considered to be mutually exclusive. However, given the strength of data supporting a role for parietal cortex in both forms of spatial processing, it seems likely that ultimately our understanding of how parietal cortex supports spatial behaviour will integrate these functions. For example, parietal cortex may serve as a selective visuomotor controller, transforming neural signals that code the positions of salient or behaviourally relevant stimuli into body-centered frames of reference useful for motor control (Lacquaniti *et al.*, 1995; Buneo *et al.*, 2002; Buneo & Andersen, 2006). This is in keeping generally with the idea that spatial information must pass through a processing bottleneck at the point where sensory representations are converted into motor representations, because sensory systems typically represent many more stimuli than can be effectively or advantageously used to control motor output. From that perspective, sensorimotor control implies attention, or a selective sensorimotor transformation. Visual awareness (e.g. attention) may be a product, at least to some degree, of this bottleneck, in the sense that we are most aware of those stimuli that we intend to move or respond to. As reviewed above, damage to parietal cortex manifests as a diverse set of spatial problems, producing deficits that range from visuomotor control to spatial attention to spatial cognition, many of which now have identified physiological correlates at the level of single neurons in parietal cortex. This diversity of spatial impairments undoubtedly reflects the fact that the neural representations of space instantiated by the activity of parietal neurons are integral to an enormous range of thoughts and actions.

The evolution of posterior parietal cortex and its consequence for the emergence of spatial cognition and its pathology

From the data considered above an overall homology between the PPC of the monkey and that of man emerges when comparing the SPL across the two species, although an expansion of the IPL has certainly occurred. The conclusion nonetheless that considerable homology exists between monkey and human SPL does not stem only from comparative architectonic analyses, but rather from the analysis of the parcellation of parietal cortex based on cortico-cortical connectivity in both species. This has become possible thanks to studies using axoplasmic tracers in monkeys and, more recently, probabilistic tractography from DTI imaging in humans. However, homology does not imply identity. For instance, fMRI studies (for a review see Orban *et al.*, 2004) suggest that, together with areas that are similar in the two species, a number of higher-order intraparietal areas that are not present in monkeys have emerged during human evolution. These areas belong to the visuomotor processing stream involved in coding action space (see also Simon *et al.* 2002). This is in keeping with the suggestion, coming from paleoneurology, that a specific enlargement of parietal cortex has occurred even at late stages of human evolution. This recent expansion of human parietal cortex emerges when comparing the endocasts of archaic Western European Neanderthals to those of modern *Homo* who, although belonging to different evolutionary lines, share the same cranial capacity and overall brain dimensions. This occurrence favours the identification of specific departures from the *Homo* allometric trajectory during the evolution of *Homo sapiens*, made apparent by the method of subtraction (Gould, 1966). For example, multivariate morphometrics and geometrical modelling (Bruner *et al.* 2003; Brunner, 2008) indicate that modern human endocasts show a significant midsagittal enlargement of the parieto-frontal outline, which is more pronounced at the level of parietal cortex, and a dorso-vertical lengthening of the parieto-cerebellar volumes. We interpret this result as reflecting an enlargement of the entire distributed system of which parietal cortex is a crucial node, and that probably includes also the parieto-cerebellar pathway through the pontine nuclei.

Additional insight into the evolution of human parietal cortex can be gained by comparing the deficits of parietal lesions in monkeys and humans. Generally speaking, some basic features of the parietal lobe syndrome in humans can also be found in monkeys, especially when considering optic ataxia. However, experimental evidence showing that directional hypokinesia (DH) can be reproduced in monkeys after unilateral cortical lesions is controversial. In fact testing for DH in animal models has proven to be problematic, because the over-training required to get monkeys to perform the visuomotor tasks necessary to measure DH can lead to an important mitigation of the lesion effects, especially when measured by some forms of testing. Therefore, in monkey studies the definition that has been generally adopted for indicating the presence of “motor neglect” can be summarize as follows: “Diminished responses to sensory stimulation and disuse of limbs in half of personal and extrapersonal space under certain conditions or testing with preservation of primary sensory and motor response on that side” (Deuel, 1987). According to this view, lesions of different cortical areas, including IPL (Heilman et al, 1970; Deuel & Farrar, 1993), area PE and PFG in marmosets monkeys (Marshall et al, 2002), superior temporal cortex (Watson *et al.* 1994; Luh et al, 1986) and premotor cortex (Rizzolatti *et al.*, 1983) lead to behavioural deficits that overall have been interpreted as a form of DH. Furthermore the lack of quantitative analyses of most lesion studies in monkeys does not allow any conclusive statement on neglect. Visual neglect in monkeys has been described (Gaffan & Hornack, 1997) after unilateral visual disconnection of PPC from the visually related-areas of the occipital lobe, but not after damage of parietal cortex and/or frontal eye fields. This is in keeping with results suggesting that white matter lesion in humans are an important determinant of neglect (Thiebault de Schotten et al, 2005), a view which however is not shared by other authors (Karnath *et al.*, 2009).

To our knowledge, constructional disorders have never been studied after parietal or cortical lesions in monkeys, probably because this species does not display constructive ability in the wild or, at least, this ability has never been tested in natural conditions. However, when forced in a laboratory setting, monkeys do show limited constructional abilities as a result of training. Under such conditions, certain properties of parietal neurons that are of interest to pathology emerge, since their collapse could explain constructional disorders of the type observed in man, as documented in a previous section of this manuscript. Although these properties are likely to be shaped as a result of extensive behavioural training, they could also be considered as the substrate of an early form of spatial cognition encoded in parietal cortex. Some forms of spontaneous spatial construction have been described in chimpanzees (Potì & Langer 2001; Potì, 2005; Potì *et al.*, 2009), although their constructive space is very primitive when compared to that of humans, especially when manipulating simultaneous spatial relationships between multiple objects is required, a task on which chimpanzees systematically fail. Why did elaborate constructional abilities emerge so late during primate evolution? The same question applies to hemispatial neglect, for which a full-blown syndrome closely resembling that observed in man has never been described in monkeys after parietal lesions, this in spite of the fact that parietal neurons encoding visual space in different reference frames have been described, the loss of which could very well explain different forms of neglect.

An answer to this paradox can only be speculative. It is possible that, in spite of 30 million years of independent evolution, the basic parietal circuits that subserve attentional and cognitive motor behaviour were preserved in the brains of humans and monkeys, as suggested by the similarities in parieto-frontal connectivity of both species. However, during human evolution, an increase in the complexity of this elementary cortical circuit must have occurred. The specialization of this distributed system (Mountcastle, 1978) has probably involved changes in the organization of parietal cortex, and/or of its connections with other cortical areas. The former probably involved an expansion of the upper cortical layers

(Marin Padilla, 1992) during human evolution, perhaps by extending the period of neurogenesis (Kornack & Rakic, 1998) when the neurons that eventually inhabit the upper cortical layers are born. The cell types involved would be likely to include both locally projecting intrinsic interneurons, as well as neurons giving rise to cortico-cortical projections. These latter projection systems probably provide the anatomical substrate for top-down control systems, such as those linking parietal cortex to an expanding lateral prefrontal cortex (Semendeferi *et al.*, 2001; 2002), thus increasing the role of the latter in the selection (Genovesio *et al.*, 2005) and monitoring (Genovesio *et al.*, 2008) of behavioural strategies, as well as in decision making (Kim & Shadlen, 1999) processes related to cognitive analysis of the visual space and to the action performed within it. With respect to this, there is a remarkable symmetry between frontal and parietal systems and the connectivity between them (Averbeck *et al.*, J Neurophys, 2009). While both parietal and frontal systems receive inputs from and send outputs to a broad range of areas, they share a reciprocal connectivity pattern that also maps onto the gross morphology of the cortex, and is likely associated with the dominant white matter tracts that connect areas of the cortex, as discussed above. Frontal cortex is important for flexible behaviour not driven by immediate sensory inputs (Goldman-Rakic, 1987), for example rule based cognitive sensory motor transformations (Wallis *et al.*, 2001), categorization (Freedman *et al.*, 2001, 2002), or working memory processes (Funahashi *et al.*, 1989; Funahashi *et al.*, 1993; Constantinidis *et al.*, 2001). The connection of these flexible frontal systems to the spatial motor capacities of parietal cortex may give rise to abstract, cognitive spatial motor processes like construction behaviour, as opposed to sensory driven spatial motor processes, like orienting or reaching towards objects in space. It is of interest that this anatomical expansion during evolution does not only concern prefrontal and parietal cortex, but also certain thalamic nuclei, such as the *medialis dorsalis* and *pulvinar*, both disproportionately large in humans, especially in those parts, such as the dorsal pulvinar, that entertain connections with prefrontal, temporal and parietal areas (Romanski *et al.*, 1997; Gutierrez *et al.*, 2000). This expansion and increased complexity of an entire distributed system might have played a permissive role for the emergence in man of cognitive spatial skills not evident in monkeys, together with new pathologies affecting these skills after cortical damage. The emergence of these new pathologies is probably the price paid for the evolution of new and more elaborate forms of spatial cognition mediated by frontal-parietal networks.

As a basis for speculation, let's imagine the level of neural control required to a child during constructive play. To put it in Forman's (1982) words: "In the act of placing, removing, releasing and rearranging blocks, children are constructing spatial relations. They are both expressing their knowledge of objects in space and inventing new relations as they turn their thoughts to what they have done". Before embarking upon the act of construction, an accurate analysis of the visual scene is required to explore the objects available and their geometry., a prerequisite for their appropriate selection. This spatial analysis is upstream of motor control. However, to achieve the goal of a constructed object, a strategy on how to proceed is required and a motor plan suitable to achieve the goal has to be chosen and implemented. At every step, the adopted strategy and its outcomes must be monitored, and a continuous online control of the hand/s in action is required. It is reasonable to assume that the neural representation of this complex form of spatial cognition requires an interaction between the lateral prefrontal cortex, at least as far as the selection of strategies and decision making is concerned, and the PPC with the parieto-frontal system, as far as the analysis of the visual scene, the selection, implementation and control of actions and of their serial order are concerned. Which of these specific functions might be the key to understanding the emergence of spatial cognition during human evolution can probably be inferred from an analysis of the maturation of constructive skills during infants' and chimps' post-natal development, on Heckel's assumption that ontogeny somehow recapitulates phylogeny. Infants start combining a limited number of objects at an age of 6 months (Langer, 1980;

1986), but this combination results in stable constructions only around the third year of life (Langer, 1980; 1986; Forman, 1982). This gives them the opportunity to observe the result of their actions as one which remains stable in time, outlasting the completion of the motor operations needed during building. After this point in development, constructions become more stable, numerous, complex, and made from a larger numbers of components parts (Sugarman, 1983; Langer, 1986; Stiles-Davis, 1988), and also begin to include inter-object spatial relations. Therefore the spatial cognitive and motor skills that enable object construction become mature only when their outcome is regarded as a stable one, in other words when the internal monitoring of the infant's own actions conveys the certainty that a success has been obtained and new and more complex constructions can be made. At the age of 4, young chimpanzees' constructions are simpler and remain unstable; throughout their postnatal life the ability to control inter-object spatial relationships is and will remain definitely poor. Furthermore, adult chimps never develop the ability to construct non-functional, symmetrical spatial relationships (Poti & Langer, 2001), in this resembling right-hemisphere damaged children (Stiles *et al.*, 1985).

The above hypothesis identifies an anatomo-functional substrate driving the emergence of greater spatial-cognitive and constructional abilities during human evolution – namely the expansion of parietal cortex along with the elaboration of an increasingly complex network of cortico-cortical connections linking it with the lateral prefrontal cortex. That prefrontal networks were successively elaborated during primate evolution is supported by the fact that the macaque's lateral prefrontal cortex has certain connections that are not present in prosimians (Preuss & Goldman-Rakic, 1991). Although in man detailed data relevant to the organization of parieto-prefrontal networks are not yet available, future studies and improvements in probabilistic tractography, if compared to data from monkeys, may offer an answer to this question, thus shedding light on the evolutionary trajectory of the brain structures responsible for the emergence of advanced spatial cognitive abilities in man.

Acknowledgments

This work was supported by the MIUR of Italy (Project 2008J7YFNR to Roberto Caminiti). Bruno B. Averbeck was supported by the Intramural Program of the NIH, National Institute of Mental Health, USA.

Abbreviations

AIP	anterior intraparietal area
Area Opt	parietal area Opt
Area PE	parietal area PE
Area PEc	parietal area PEc
Area PEa	parietal area PEa
Area PF	parietal area PF
Area PFG	parietal area PFG
Area PG	parietal area PG
Area PGm (7m)	parietal area 7m
Area V6	visual area 6
Area V6A	visual areas V6A
BA5	Brodmann's area 5

BA7	Brodmann's area 7
CA	constructional apraxia
DH	directional hypokinesia
DTI	diffusion tensor imaging
fMRI	functional magnetic resonance imaging
GTF	global tuning field
HN	hemispatial neglect
IPL	inferior parietal lobule
IPS	intraparietal sulcus
LIP	lateral intraparietal area
MIP	medial intraparietal area
MI	primary motor cortex
OA	optic ataxia
PMd	dorsal premotor cortex
PPG	psychic paralysis of gaze
PPC	posterior parietal cortex
PAR-d	dorsal parietal cluster
PAR-v	ventral parietal cluster
PAR-ml	medio-lateral parietal cluster
PMdc/F2	dorso-caudal premotor cortex
PMdr/F7	dorso-rostral premotor cortex
pre-SMA	pre-supplementary motor area
SI	primary somatosensory cortex
SMA	supplementary motor area
SPL	superior parietal lobule

References

- Andersen RA, Essick GK, Siegel RM. Encoding of spatial location by posterior parietal neurons. *Science*. 1985; 230:456–458. [PubMed: 4048942]
- Archambault P, Caminiti R, Battaglia Mayer A. Cortical mechanisms for on-line control of hand movement trajectory. The role of the posterior parietal cortex. *Cereb. Cortex*. 2009; 19:2848–2864. [PubMed: 19359349]
- Arena R, Gainotti G. Constructional apraxia and visuoperceptive disabilities in relation to laterality of cerebral lesions. *Cortex*. 1978; 14:463–473. [PubMed: 738057]
- Averbeck BB, Chafee MV, Crowe DA, Georgopoulos AP. Parietal representation of hand velocity in a copy task. *J. Neurophysiol*. 2005; 93:508–518. [PubMed: 15269226]
- Averbeck B, Battaglia-Mayer A, Guglielmo C, Caminiti R. Statistical analysis of the parieto-frontal cognitive-motor network. *J. Neurophysio*. 2009; 102:1911–1920.
- Balint R. Seelenlähmung des “Schauens”, optische Ataxia, räumliche Störung der Aufmerksamkeit. *Monatsschrift für Psychiatrie und Neurologie*. 1909; 25:51–81.

- Barash S, Bracewell RM, Fogassi L, Gnadt JW, Andersen RA. Saccade-related activity in the lateral intraparietal area. I. Temporal properties and comparison with area 7a. *J. Neurophysiol.* 1991; 66:1095–1108. [PubMed: 1753276]
- Batista AP, Buneo CA, Snyder LH, Andersen RA. Reach plans in eye-centered coordinates. *Science.* 1999; 285:257–260. [PubMed: 10398603]
- Batista AP, Andersen RA. The parietal reach region codes the next planned movement in a sequential reach task. *J. Neurophysiol.* 2001; 85:539–544. [PubMed: 11160491]
- Battaglia-Mayer A, Ferraina S, Mitsuda T, Marconi B, Genovesio A, Onorati P, Lacquaniti F, Caminiti R. Early coding of reaching in the parieto-occipital cortex. *J. Neurophysiol.* 2000; 83:2374–2391. [PubMed: 10758140]
- Battaglia-Mayer A, Ferraina S, Genovesio A, Marconi B, Squatrito S, Molinari M, Lacquaniti F, Caminiti R. Eye-hand coordination during reaching. II. An analysis of the relationships between visuomanual signals in parietal cortex and parieto-frontal association projections. *Cereb. Cortex.* 2001; 11:528–544. [PubMed: 11375914]
- Battaglia-Mayer A, Caminiti R. Optic ataxia as a result of the breakdown of the global tuning fields of parietal neurones. *Brain.* 2002; 125:225–37. [PubMed: 11844724]
- Battaglia-Mayer A, Caminiti R, Lacquaniti F, Zago M. Multiple levels of representation of reaching in the parieto-frontal network. *Cereb. Cortex.* 2003; 13:1009–1022. [PubMed: 12967918]
- Battaglia-Mayer A, Mascaro M, Brunamonti E, Caminiti R. The over-representation of contralateral space in parietal cortex: a positive image of directional motor components of neglect? *Cereb. Cortex.* 2005; 15:514–525. [PubMed: 15319306]
- Battaglia-Mayer A, Archambault PS, Caminiti R. The cortical network for eye-hand coordination and its relevance to understanding motor disorders of parietal patients. *Neuropsychologia.* 2006a; 44:2607–20. [PubMed: 16458334]
- Battaglia-Mayer A, Archambault PS, Cardone C, Iaconelli S. Program No. 307.7 2006 Neuroscience Meeting Planner. Society for Neuroscience; Atlanta, GA: 2006b. Effects of reversible inactivation of posterior parietal cortex during reaching movements with target jump.
- Battaglia-Mayer A, Mascaro M, Caminiti R. Temporal evolution and strength of neural activity in parietal cortex during eye and hand movements. *Cereb. Cortex.* 2007; 17:1350–63. [PubMed: 16920885]
- Battaglini PP, Muzur A, Galletti C, Skrap M, Brovelli A, Fattori P. Effects of lesions to area V6A in monkeys. *Exp. Brain. Res.* 2002; 144:419–22. [PubMed: 12021823]
- Benson DF, Barton MI. Disturbances in constructional ability. *Cortex.* 1970; 6:19–46. [PubMed: 5426574]
- Benton AL, Fogel ML. Three-dimensional constructional praxis. A clinical test. *Arch Neurol.* 1962; 7:347–54. [PubMed: 13967554]
- Benton AL. Constructional apraxia and the minor hemisphere. *Confin. Neurol.* 1967; 29(1):1–16. [PubMed: 6065746]
- Bisiach E, Luzzatti C, Perani D. Unilateral neglect, representational schema and consciousness. *Brain.* 1979; 102:609–618. [PubMed: 497807]
- Bisley JW, Goldberg ME. Neuronal activity in the lateral intraparietal area and spatial attention. *Science.* 2003; 299:81–86. [PubMed: 12511644]
- Blangero A, Ota H, Delporte L, Revol P, Vindras P, Rode G, Boisson D, Vighetto A, Rossetti Y, Pisella L. Optic ataxia is not only ‘optic’: impaired spatial integration of proprioceptive information. *Neuroimage.* 2007; 36:61–68.
- Bracewell RM, Mazzoni P, Barash S, Andersen RA. Motor intention activity in the macaque's lateral intraparietal area. II. Changes of motor plan. *J. Neurophysiol.* 1996; 76:1457–1464. [PubMed: 8890266]
- Brotchie PR, Andersen RA, Snyder LH, Goodman SJ. Head position signals used by parietal neurons to encode locations of visual stimuli. *Nature.* 1995; 375:232–235. [PubMed: 7746323]
- Bruner E. Comparing endocranial form and shape differences in modern humans and Neandertal: a geometric approach. *PaleoAnthropology.* 2008; 2008:93–106.

- Bruner E, Manzi G, Arsuaga JL. Encephalization and allometric trajectories in the genus *Homo*: Evidence from the Neandertal and modern lineages. *Proc. Natl. Acad. Sci., USA*. 2003; 100:15335–15340. [PubMed: 14673084]
- Buneo CA, Andersen RA. The posterior parietal cortex: sensorimotor interface for the planning and online control of visually guided movements. *Neuropsychologia*. 2006; 44:2594–2606. [PubMed: 16300804]
- Buneo CA, Jarvis MR, Batista AP, Andersen RA. Direct visuomotor transformations for reaching. *Nature*. 2002; 416:632–636. [PubMed: 11948351]
- Burnod Y, Grandguillaume P, Otto I, Ferraina S, Johnson PB, Caminiti R. Visuomotor transformations underlying arm movements toward visual targets: A neural network model of cerebral cortical operations. *J. Neurosci*. 1992; 12:1435–1453. [PubMed: 1556602]
- Burnod Y, Baraduc P, Battaglia-Mayer A, Guigon E, Koehlin E, Ferraina S, Lacquaniti F, Caminiti R. Parieto-frontal coding of reaching: an integrated framework. *Exp. Brain Res*. 1999; 129:325–346. [PubMed: 10591906]
- Bushnell MC, Goldberg ME, Robinson DL. Behavioral enhancement of visual responses in monkey cerebral cortex. I. Modulation in posterior parietal cortex related to selective visual attention. *J. Neurophysiol*. 1981; 46:755–772. [PubMed: 7288463]
- Caminiti R, Johnson PB, Galli C, Ferraina S, Burnod Y. Making arm movements within different parts of space: The premotor and motor cortical representation of a coordinate system for reaching to visual targets. *J. Neurosci*. 1991; 11:1182–1197. [PubMed: 2027042]
- Caminiti R, Sbriccoli A. The callosal system of the superior parietal lobule in the monkey. *J. Comp. Neurol*. 1985; 237:85–99. [PubMed: 3930578]
- Caminiti, R.; Ferraina, S.; Battaglia-Mayer, A.; Mascaro, M.; Burnod, Y. Parallel fronto-parietal circuits for sensori motor transformation. In: Jeannerod, M.; Hallet, M.; Freund, HJ.; Leiguarda, R., editors. *Higher Order Motor Disorders: From Neuroanatomy and Neurobiology to Clinical Neurology*. Oxford University Press; New York, Oxford: 2005. p. 23-42.
- Caminiti R, Johnson PB, Burnod Y, Galli C, Ferraina S. Shift of preferred directions of premotor cortical cells with arm movements performed across the workspace. *Exp. Brain Res*. 1990; 83:228–32. [PubMed: 2073945]
- Chafee MV, Goldman-Rakic PS. Inactivation of parietal and prefrontal cortex reveals interdependence of neural activity during memory-guided saccades. *J. Neurophysiol*. 2000; 83:1550–66. [PubMed: 10712479]
- Chafee MV, Averbach BB, Crowe DA. Representing spatial relationships in posterior parietal cortex: single neurons code object-referenced position. *Cereb. Cortex*. 2007; 17:2914–2932. [PubMed: 17389630]
- Chafee MV, Crowe DA, Averbach BB, Georgopoulos AP. Neural correlates of spatial judgement during object construction in parietal cortex. *Cereb. Cortex*. 2005; 15:1393–1413. [PubMed: 15635058]
- Classen J, Kunesch E, Binkofski F, Hilperath F, Schlaug G, Seitz RJ, Glickstein M, Freund HJ. Subcortical origin of visuomotor apraxia. *Brain*. 1995; 118:1365–74. [PubMed: 8595470]
- Cohen YE, Andersen RA. Reaches to sounds encoded in an eye-centered reference frame. *Neuron*. 2000; 27:647–652. [PubMed: 11055445]
- Colby CL, Duhamel JR. Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey. *Neuropsychologia*. 1991; 29:517–537. [PubMed: 1944859]
- Colby CL, Goldberg ME. Space and attention in parietal cortex. *Annu. Rev. Neurosci*. 1999; 22:319–349. [PubMed: 10202542]
- Colby CL, Duhamel JR, Goldberg ME. Oculocentric spatial representation in parietal cortex. *Cereb. Cortex*. 1995; 5:470–481. [PubMed: 8547793]
- Colombo A, De Renzi E, Faglioni P. The occurrence of visual neglect in patients with unilateral cerebral disease. *Cortex*. 1976; 12:221–231. [PubMed: 1000990]
- Constantinidis C, Steinmetz MA. Neuronal responses in area 7a to multiple-stimulus displays: I. neurons encode the location of the salient stimulus. *Cereb. Cortex*. 2001a; 11:581–591. [PubMed: 11415960]

- Constantinidis C, Steinmetz MA. Neuronal responses in area 7a to multiple stimulus displays: II. responses are suppressed at the cued location. *Cereb. Cortex.* 2001b; 11:592–597. [PubMed: 11415961]
- Constantinidis C, Franowicz MN, Goldman-Rakic PS. The sensory nature of mnemonic representation in the primate prefrontal cortex. *Nat. Neurosci.* 2001; 4:311–316. [PubMed: 11224549]
- Constantinidis C, Steinmetz MA. Posterior parietal cortex automatically encodes the location of salient stimuli. *J. Neurosci.* 2005; 25:233–238. [PubMed: 15634786]
- Crowe DA, Chafee MV, Averbach BB, Georgopoulos AP. Neural activity in primate parietal area 7a related to spatial analysis of visual mazes. *Cereb. Cortex.* 2004; 14:23–34. [PubMed: 14654454]
- Crowe DA, Averbach BB, Chafee MV, Georgopoulos AP. Dynamics of parietal neural activity during spatial cognitive processing. *Neuron.* 2005; 47:885–891. [PubMed: 16157282]
- Crowe DA, Averbach BB, Chafee MV. Neural ensemble decoding reveals a correlate of viewer- to object-centered spatial transformation in monkey parietal cortex. *J. Neurosci.* 2008; 28:5218–5228. [PubMed: 18480278]
- Crosson PL, Johansen-Berg H, Behrens TE, Robson MD, Pinski MA, Gross CG, Richter W, Richter MC, Kastner S, Rushworth MF. Quantitative investigation of connections of the prefrontal cortex in the human and macaque using probabilistic diffusion tractography. *J. Neurosci.* 2005; 25:8854–66. [PubMed: 16192375]
- De Renzi E, Faglioni P, Sorgato P. Modality-specific and supramodal mechanisms of apraxia. *Brain.* 1982; 105:301–12. [PubMed: 6177376]
- Della-Maggiore V, Malfait N, Ostry DJ, Paus T. Stimulation of the posterior parietal cortex interferes with arm trajectory adjustments during the learning of new dynamics. *J. Neurosci.* 2004; 24:9971–9976. [PubMed: 15525782]
- Desimone R, Duncan J. Neural mechanisms of selective visual attention. *Ann. Rev. Neurosci.* 1995; 18:193–222. [PubMed: 7605061]
- Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST. Role of the posterior parietal cortex in updating reaching movements to a visual target. *Nat. Neurosci.* 1999; 2:563–7. [PubMed: 10448222]
- Deuel, R. Neural dysfunction during hemineglect after cortical damage in two monkey models. In: Jeannerod, M., editor. *Neurophysiological and neuropsychological aspects of spatial neglect.* Elsevier Science Publishers B.V.; North-Holland: 1987. p. 315–334.
- Deuel RK, Farrar CA. Stimulus cancellation by macaques with unilateral frontal and parietal lesions. *Neuropsychologia.* 1993; 31:29–38. [PubMed: 8437680]
- Di Pellegrino G, Basso G, Frassinetti F. Spatial extinction on double asynchronous stimulation. *Neuropsychologia.* 1997; 35:1215–1223. [PubMed: 9364492]
- Driver J, Halligan PW. Can visual neglect operate in object-centred co-ordinates? An affirmative single case study. *Cogn. Neuropsychol.* 1991; 8:475–496.
- Driver J, Baylis GC, Rafal RD. Preserved figure-ground segregation and symmetry perception in visual neglect. *Nature.* 1992; 360:73–75. [PubMed: 1436078]
- Driver J, Baylis GC, Goodrich SJ, Rafal RD. Axis-based neglect of visual shapes. *Neuropsychologia.* 1994; 32:1353–1365. [PubMed: 7877744]
- Driver J, Pouget A. Object-centered visual neglect, or relative egocentric neglect? *J. Cogn. Neurosci.* 2000; 12:542–5. [PubMed: 10931777]
- Faugier-Grimaud S, Frenois C, Peronnet F. Effects of posterior parietal lesions on visually-guided movements in monkeys. *Exp. Brain. Res.* 1985; 59:125–38. [PubMed: 4018192]
- Ferber S, Karnath HO. How to assess spatial neglect: line bisection or cancellation tasks? *J. Clin. Exp. Neuropsychol.* 2001; 23:599–607. [PubMed: 11778637]
- Ferraina S, Garasto MR, Battaglia-Mayer A, Ferraresi P, Johnson PB, Lacquaniti F, Caminiti R. Visual control of hand-reaching movement: activity in parietal area 7m. *Eur. J. Neurosci.* 1997a; 9:1090–1095. [PubMed: 9182962]
- Ferraina S, Johnson PB, Garasto MR, Battaglia-Mayer A, Ercolani L, Bianchi L, Lacquaniti F, Caminiti R. Combination of hand and gaze signals during reaching: activity in parietal area 7m of the monkey. *J. Neurophysiol.* 1997b; 77:1034–1038. [PubMed: 9065868]

- Ferraina S, Brunamonti E, Giusti MA, Costa S, Genovesio A, Caminiti R. Reaching in depth: hand position dominates over binocular eye position in the rostral Superior Parietal Lobule. *J. Neurosci.* 2009; 29(37):11461–11470. [PubMed: 19759295]
- Fink, GR.; Marshall, JC. Motor aspects of unilateral neglect and related disorders. In: Jeannerod, M.; Hallett, M.; Freund, HJ.; Leiguarda, R., editors. Higher-order motor disorders. Oxford University Press; New York, Oxford: 2005. p. 273–289.
- Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Parietal lobe: from action organization to intention understanding. *Science.* 2005; 308:662–667. [PubMed: 15860620]
- Forman, GE. A Search for the Origins of Equivalence Concepts through a Microanalysis of Block Play. In: Forman, GE., editor. Action and Thought. Academic Press; New York: 1982. p. 97–135.
- Freedman DJ, Riesenhuber M, Poggio T, Miller EK. Categorical representation of visual stimuli in the primate prefrontal cortex. *Science.* 2001; 291:312–316. [PubMed: 11209083]
- Freedman DJ, Riesenhuber M, Poggio T, Miller EK. Visual categorization and the primate prefrontal cortex: neurophysiology and behavior. *J. Neurophysiol.* 2002; 88:929–941. [PubMed: 12163542]
- Funahashi S, Bruce CJ, Goldman-Rakic PS. Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. *J. Neurophysiol.* 1989; 61:331–349. [PubMed: 2918358]
- Funahashi S, Chafee MV, Goldman-Rakic PS. Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature.* 1993; 365:753–756. [PubMed: 8413653]
- Gaffan D, Hornak J. Visual neglect in the monkey. Representation and disconnection. *Brain.* 1997; 120:1647–1657. [PubMed: 9313646]
- Gainotti G, Messerli P, Tissot R. Qualitative analysis of unilateral spatial neglect in relation to laterality of cerebral lesions. *J. Neurol. Neurosurg. Psychiatry.* 1972; 35:545–550. [PubMed: 5049813]
- Gainotti G, Silveri MC, Villa G, Caltagirone C. Drawing objects from memory in aphasia. *Brain.* 1983; 106:613–622. [PubMed: 6640272]
- Gainotti, G. Constructional Apraxia. In: Frederiks, JAM., editor. Handbook of Clinical Neurology. Vol. 1. Elsevier; Amsterdam: 1985. p. 491–506.
- Gainotti G, D'Erme P, Diodato S. Are drawing errors different in right-sided and left-sided constructional apraxics? *Ital. J. Neurol. Sci.* 1985; 6:495–501. [PubMed: 4086270]
- Galletti C, Battaglini PP, Fattori R. Eye position influence on the parieto-occipital area PO (V6) of the macaque monkey. *Eur. J. Neurosci.* 1995; 7:2486–2501. [PubMed: 8845954]
- Galletti C, Fattori P, Battaglini PP, Shipp S, Zeki S. Functional demarcation of a border between areas V6 and V6A in the superior parietal gyrus of the macaque monkey. *Eur J Neurosci.* 1996; 8:30–52. [PubMed: 8713448]
- Galletti C, Fattori R, Kutz DF, Battaglini PP. Arm movement-related neurons in the visual area V6A of the macaque superior parietal lobule. *Eur. J. Neurosci.* 1997; 9:410–3. [PubMed: 9058060]
- Genovesio A, Brasted PJ, Mitz AR, Wise SP. Prefrontal cortex activity related to abstract response strategies. *Neuron.* 2005; 47:307–20. [PubMed: 16039571]
- Genovesio A, Tsujimoto S, Wise SP. Encoding problem-solving strategies in prefrontal cortex: activity during strategic errors. *Eur. J. Neurosci.* 2008; 27:984–90. [PubMed: 18279367]
- Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT. On the relations between the direction of two dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.* 1981; 1:1527–1537.
- Georgopoulos AP, Kalaska JF, Caminiti R, Massey JT. Interruption of motor cortical discharge subserving aimed arm movements. *Exp. Brain Res.* 1983; 49:327–340. [PubMed: 6641831]
- Georgopoulos AP, Caminiti R, Kalaska JF. Static spatial effects in motor cortex and area 5: quantitative relations in a two-dimensional space. *Exp. Brain. Res.* 1984; 54:446–454. [PubMed: 6723864]
- Georgopoulos AP, Massey JT. Static versus dynamic effects in motor cortex and area 5: comparison during movement time. *Behav. Brain Res.* 1985; 18:159–166. [PubMed: 4096830]
- Geschwind N. The apraxias: neural mechanisms of disorders of learned movement. *Am. Sci.* 1975; 63:188–95. [PubMed: 1115438]

- Goldman-Rakic, PS. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Mountcastle, VB.; Plum, F.; Geiger, SR., editors. *Handbook of Physiology. The Nervous System. Higher Functions of the Brain*. Bethesda, MD: 1987. p. 373-417. *Am. Physiol. Soc.*
- Gonzalez Rothi LJ, Ochipka C, Heilman KM. A cognitive neuropsychological model of limb praxis. *Cogn. Neuropsychol.* 1991; 8:443-458.
- Gottlieb J, Balan P, Oristaglio J, Suzuki M. Parietal control of attentional guidance: the significance of sensory, motivational and motor factors. *Neurobiol. Learn. Mem.* 2008a; 91:121-8. [PubMed: 18929673]
- Gottlieb J, Balan PF, Oristaglio J, Schneider D. Task specific computations in attentional maps. *Vision Res.* 2008b; 49(10):1216-26. [PubMed: 18502468]
- Gottlieb JP, Kusunoki M, Goldberg ME. The representation of visual salience in monkey parietal cortex. *Nature.* 1998; 391:481-484. [PubMed: 9461214]
- Gould SJ. Allometry and size in ontogeny and phylogeny. *Biological Review.* 1966; 41:587-640.
- Gréa H, Pisella L, Rossetti Y, Desmurget M, Tilikete C, Grafton S, Prablanc C, Vighetto A. A lesion of the posterior parietal cortex disrupts on-line adjustments during aiming movements. *Neuropsychologia.* 2002; 40:2471-2480. [PubMed: 12417474]
- Gutierrez C, Cola M, Seltzer B, Cusick C. Neurochemical and connectional organization of the dorsal pulvinar complex in monkeys. *J. Comp. Neurol.* 2000; 419(1):61-86. [PubMed: 10717640]
- Hamel-Paquet C, Sergio LE, Kalaska JF. Parietal area 5 activity does not reflect the differential time-course of motor output kinetics during arm-reaching and isometric-force tasks. *J. Neurophysiol.* 2006; 95:3353-3370. [PubMed: 16481461]
- Hartje W, Ettlinger G. Reaching in light and dark after unilateral posterior parietal ablations in the monkey. *Cortex.* 1973; 9:346-54. [PubMed: 4206285]
- Harvey M, Milner DA. Balint's patient. *Cogn. Neuropsychol.* 1995; 12:261-281.
- Heilman KM, Pandya DN, Geschwind N. Trimodal inattention following parietal lobe ablations. *Trans. Amer. Neurol. Ass.* 1970; 95:259-261. [PubMed: 4998763]
- Heilman KM, Valenstein E, Watson RT. Neglect and related disorders. *Semin. Neurol.* 2000; 20:463-70. [PubMed: 11149702]
- Hillis AE, Rapp B, Benzing L, Caramazza A. Dissociable coordinate frames of unilateral spatial neglect: "viewer-centered" neglect. *Brain. Cogn.* 1998; 37:491-526. [PubMed: 9733562]
- Hoshi E, Tanji J. Area-selective neuronal activity in the dorsolateral prefrontal cortex for information retrieval and action planning. *J. Neurophysiol.* 2004; 91:2707-22. [PubMed: 14749313]
- Husain M, Stein J. Rezső Bálint and his most celebrated case. *Arch. Neurol.* 1988; 45:89-93. [PubMed: 3276300]
- Hyvärinen J. Regional distribution of functions in parietal association area 7 of the monkey. *Brain Res.* 1981; 206:287-303. [PubMed: 7214136]
- Ipata AE, Gee AL, Gottlieb J, Bisley JW, Goldberg ME. LIP responses to a popout stimulus are reduced if it is overtly ignored. *Nat. Neurosci.* 2006; 9:1071-1076. [PubMed: 16819520]
- Ishiai S, Seki K, Koyama Y, Yokota T. Mechanisms of unilateral spatial neglect in copying a single object. *Neuropsychologia.* 1996; 34:965-971. [PubMed: 8843062]
- Ishiai S, Koyama Y, Seki K, Izawa M. Line versus representational bisections in unilateral spatial neglect. *J. Neurol. Neurosurg. Psychiatry.* 2000; 69:745-750. [PubMed: 11080226]
- Johansen-Berg H, Behrens TE, Robson MD, Drobniak I, Rushworth MF, Brady JM, Smith SM, Higham DJ, Matthews PM. Changes in connectivity profiles define functionally distinct regions in human medial frontal cortex. *Proc. Natl. Acad. Sci. U S A.* 2004; 101(36):13335-40. [PubMed: 15340158]
- Johnson H, Haggard P. Motor awareness without perceptual awareness. *Neuropsychologia.* 2005; 43:227-37. [PubMed: 15707907]
- Johnson PB, Ferraina S, Bianchi L, Caminiti R. Cortical networks for visual reaching: physiological and anatomical organization of frontal and parietal lobe arm regions. *Cereb. Cortex.* 1996; 6:102-119. [PubMed: 8670643]

- Kalaska JF, Caminiti R, Georgopoulos AP. Cortical mechanisms related to direction of two dimensional arm movements: relations in parietal area 5 and comparison with motor cortex. *Exp. Brain Res.* 1983; 51:247–260. [PubMed: 6617794]
- Kalaska JF, Cohen DA, Prud'homme M, Hyde ML. Parietal area 5 neuronal activity encodes movement kinematics, not movement dynamics. *Exp. Brain. Res.* 1990; 80:351–364. [PubMed: 2113482]
- Karnath HO, Ferber S, Himmelbach M. Spatial awareness is a function of the temporal not the posterior parietal lobe. *Nature.* 2001; 411:950–953. [PubMed: 11418859]
- Karnath HO, Perenin MT. Cortical control of visually guided reaching: evidence from patients with optic ataxia. *Cereb. Cortex.* 2005; 15:1561–9. [PubMed: 15716470]
- Karnath H-O, Rorden C, Ticini LF. Damage to white matter fiber tracts in acute spatial neglect. *Cereb. Cortex.* 2009; 19:2331–2337. [PubMed: 19168667]
- Khrebukova I, Michaud EJ, Foster CM, Stark KL, Garfinkel DJ, Woychik RP, Glickstein M, Buchbinder S, Iii JLM. Visual control of the arm, the wrist and the fingers: pathways through the brain. *Neuropsychologia.* 1998; 36:981–1001. [PubMed: 9845046]
- Kim J-N, Shadlen MN. Neural correlates of a decision in the dorsolateral prefrontal cortex of the macaque. *Nature Neuroscience.* 1999; 2:176–185.
- Kleist, K. Konstruktive (optische) Apraxie. Barth; Leipzig: 1934.
- Koechlin E, Anton JL, Burnod Y. Bayesian inference in populations of cortical neurons: a model of motion integration and segmentation in area MT. *Biol Cybern.* 1999; 80:25–44. [PubMed: 9951396]
- Kornack DR, Rakic P. Changes in cell-cycles kinetics during the development and evolution of primate neocortex. *Proc. Natl. Acad. Sci. USA.* 1998; 95:1242–1246. [PubMed: 9448316]
- Koyama Y, Ishiai S, Seki K, Nakayama T. Distinct processes in line bisection according to severity of left unilateral spatial neglect. *Brain Cogn.* 1997; 35:271–281. [PubMed: 9356166]
- Kusunoki M, Gottlieb J, Goldberg ME. The lateral intraparietal area as a salience map: the representation of abrupt onset, stimulus motion, and task relevance. *Vision Res.* 2000; 40:1459–1468. [PubMed: 10788652]
- Lacquaniti F, Guigon E, Bianchi L, Ferraina S, Caminiti R. Representing spatial information for limb movement: role of area 5 in the monkey. *Cereb. Cortex.* 1995; 5:391–409. [PubMed: 8547787]
- LaMotte RH, Acuña C. Defects in accuracy of reaching after removal of posterior parietal cortex in monkeys. *Brain. Res.* 1978; 13:309–326. [PubMed: 414819]
- Langer, J. The origins of logic: six to twelve months. Academic Press; New York: 1980.
- Langer, J. The origins of logic: one to two years. Academic Press; New York: 1986.
- Lee J-H, van Donkelaar P. The human dorsal premotor cortex generates on-line error corrections during sensorimotor adaptation. *J. Neurosci.* 2006; 26:3330–3334. [PubMed: 16554483]
- Liepmann H. Apraxia. *Ergbn. Der ges. Med.* 1920; 1:516–543.
- Luh KE, Butter CM, Buchtel HA. Impairments in orienting to visual stimuli in monkeys following unilateral lesions of the superior sulcal polysensory cortex. *Neuropsychologia.* 1986; 24:461–470. [PubMed: 3774132]
- Mack JL, Levine RN. The basis of visual constructional disability in patients with unilateral cerebral lesions. *Cortex.* 1981; 17:515–531. [PubMed: 7344818]
- Makris N, Kennedy, McInerney S, Sorensen AG, Caviness VS, Pandya DN. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb. Cortex.* 2005; 15:854–869. [PubMed: 15590909]
- Marconi B, Genovesio A, Battaglia-Mayer A, Ferraina S, Squatrito S, Molinari M, Lacquaniti F, Caminiti R. Eye-hand coordination during reaching. I. Anatomical relationships between parietal and frontal cortex. *Cereb. Cortex.* 2001; 11:513–27. [PubMed: 11375913]
- Marin Padilla M. Ontogenesis of the pyramidal cells of the mammalian neocortex and developmental cytoarchitectonics: a unified theory. *J. Comp. Neurol.* 1992; 321:223–240. [PubMed: 1500541]
- Marshall JWB, Baker HF, Ridley RM. Contralesional neglect in monkeys with small unilateral parietal cortical ablations. *Behav. Brain. Res.* 2002; 136:257–265. [PubMed: 12385812]

- Mascaro M, Battaglia-Mayer A, Nasi L, Amit DJ, Caminiti R. The eye and the hand: neural mechanisms and network models for oculomanual coordination in parietal cortex. *Cereb. Cortex.* 2003; 13:1276–1286. [PubMed: 14615294]
- Matelli M, Govoni P, Galletti C, Kutz DF, Luppino G. Superior area 6 afferents from the superior parietal lobule in the macaque monkey. *J. Comp. Neurol.* 1998; 402:327–352. [PubMed: 9853903]
- Matsuzaka Y, Aizawa H, Tanji J. A motor area rostral to the supplementary motor area (presupplementary motor area) in the monkey: neuronal activity during a learned motor task. *J. Neurophysiol.* 1992; 68:653–62. [PubMed: 1432040]
- Mattingley J.B, Bradshaw J.L, Phillips J.G. Impairments of movement initiation and execution in unilateral neglect. Directional hypokinesia and bradykinesia. *Brain.* 1992; 115:1849–1874. [PubMed: 1486464]
- Mattingley JB, Davis G, Driver J. Preattentive filling-in of visual surfaces in parietal extinction. *Science.* 1997; 275:671–674. [PubMed: 9005854]
- Mattingley J.B, Husain M, Rorden C, Kennard C, Driver J. Motor role of human inferior parietal lobe revealed in unilateral neglect patients. *Nature.* 1998; 392:179–82. [PubMed: 9515962]
- Maunsell JH, Treue S. Feature-based attention in visual cortex. *Trends Neurosci.* 2006; 29:317–322. [PubMed: 16697058]
- Mayka MA, Corcos DM, Leurgans SE, Vaillancourt DE. Three-dimensional locations and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage.* 2006; 31:1453–74. [PubMed: 16571375]
- Mazzoni P, Bracewell RM, Barash S, Andersen RA. Motor intention activity in the macaque's lateral intraparietal area. I. Dissociation of motor plan from sensory memory. *J. Neurophysiol.* 1996; 76:1439–1456. [PubMed: 8890265]
- Merchant H, Battaglia-Mayer A, Georgopoulos AP. Neural responses during interception of real and apparent circularly moving targets in Motor Cortex and Area 7a". *Cereb. Cortex.* 2004; 14:314–331. [PubMed: 14754870]
- Motter BC, Mountcastle VB. The functional properties of the light-sensitive neurons of the posterior parietal cortex studied in waking monkeys: foveal sparing and opponent vector organization. *Neurophysiol.* 1981; 46:755–772.
- Mountcastle VB, Lynch JC, Georgopoulos A, Sakata H, Acuna C. Posterior parietal association cortex of the monkey: command functions for operations within extrapersonal space. *J. Neurophysiol.* 1975; 38:871–908. [PubMed: 808592]
- Mountcastle, VB. An organizing principle for cerebral function: the unit module and the distributed system. In: Edelman, GM.; Mountcastle, VB., editors. *The mindful brain.* MIT Press; Cambridge and London: 1978a. p. 7-50.
- Mountcastle VB. Brain mechanisms for directed attention. *J. R. Soc. Med.* 1978b; 71(1):14–28. [PubMed: 416210]
- Mountcastle VB, Andersen RA, Motter BC. The influence of attentive fixation upon the excitability of the light-sensitive neurons of the posterior parietal cortex. *J. Neurosci.* 1981; 1:1218–1225. [PubMed: 6796657]
- Nakev P, Kennard C, Husain M. Functional role of the supplementary and pre-supplementary motor areas. *Nature Rev. Neurosci.* 2008; 9:856–869. [PubMed: 18843271]
- Olson CR. Brain representation of object-centered space in monkeys and humans. *Annu. Rev. Neurosci.* 2003; 26:331–354. [PubMed: 12626696]
- Orban GA, Van Essen D, Vanduffel W. Comparative mapping of higher visual areas in monkeys and humans. *Trends. Cogn. Sci.* 2004; 8:315–324. [PubMed: 15242691]
- Pandya DN, Seltzer B. Intrinsic connections and architectonics of posterior parietal cortex in the rhesus monkey. *J. Comp Neurol.* 1982; 204(2):196–210. [PubMed: 6276450]
- Perenin MT, Vighetto A. Optic ataxia: a specific disruption in visuomotor mechanisms. I. Different aspects of the deficit in reaching for objects. *Brain.* 1988; 111:643–74. [PubMed: 3382915]
- Petrides M, Pandya DN. Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. *J. Comp. Neurol.* 1984; 228(1):105–16. [PubMed: 6480903]

- Petrides, M.; Pandya, DN. Association pathways of the prefrontal cortex and functional observations. In: Strauss, DT.; Knight, RT., editors. *Principles of Frontal Lobe Function*. Oxford University Press; New York: 2002. p. 31-50.
- Piercy M, Hecaen H, De Ajuriaguerra J. Constructional apraxia associated with unilateral cerebral lesions: left and right sided cases compared. *Brain*. 1960; 83:225–242. [PubMed: 14432834]
- Pisella L, Gréa H, Tilikete C, Vighetto A, Desmurget M, Rode G, Boisson D, Rossetti Y. An 'automatic pilot' for the hand in human posterior parietal cortex: toward reinterpreting optic ataxia. *Nat. Neurosci*. 2000; 3:729–36. [PubMed: 10862707]
- Pisella L, Mattingley JB. The contribution of spatial remapping impairments to unilateral visual neglect. *Neurosci. Biobehav*. 2004; 28:181–200.
- Poizner H, Clark MA, Merians AS, Macauley B, Gonzalez Rothi LJ, Heilman KM. *Brain*. 1995; 118:227–42. [PubMed: 7895006]
- Potì P, Langer J. Spontaneous spatial construction by chimpanzees (*Pan troglodytes*, *Pan paniscus*). *Development science*. 2001; 4(4):474–484.
- Potì P. Chimpanzees' constructional praxis (*Pan paniscus*, *P. troglodytes*). *Primates*. 2005; 46:103–113. [PubMed: 15378424]
- Potì P, Hayashi M, Matsuzawa T. Spatial construction skills of chimpanzees (*Pan troglodytes*) and young human children (*Homo sapiens sapiens*). *Developmental Science*. 2009; 12:536–548. [PubMed: 19635081]
- Pouget A, Sejnowski TJ. A new view of hemineglect based on the response properties of parietal neurones. *Philos. Trans. R. Soc. Lond. B. Biol. Sci*. 1997; 352:1449–59. [PubMed: 9368933]
- Pouget A, Driver J. Relating unilateral neglect to the neural coding of space. *Curr. Opin. Neurobiol.* 2000; 10:242–249.
- Powell KD, Goldberg ME. Response of neurons in the lateral intraparietal area to a distractor flashed during the delay period of a memory-guided saccade. *J. Neurophysiol*. 2000; 84:301–310. [PubMed: 10899205]
- Preuss PS, Goldman-Rakic TM. Ipsilateral cortical connections of granular frontal cortex in the strepsirrhine primate Galago, with comparative comments on anthropoid primates. *J. Comp. Neurol*. 1991; 310:507–549. [PubMed: 1719039]
- Prud'homme MJ, Kalaska JF. Proprioceptive activity in primate primary somatosensory cortex during active arm reaching movements. *J. Neurophysiol*. 1994; 72:2280–2301. [PubMed: 7884459]
- Quiari Quiroga R, Snyder LH, Batista AP, Cui H, Andersen RA. Movement intention is better predicted than attention in the posterior parietal cortex. *J. Neurosci*. 2006; 26:3615–3620. [PubMed: 16571770]
- Reuter-Lorenz PA, Posner MI. Components of neglect from right-hemisphere damage: an analysis of line bisection. *Neuropsychologia*. 1990; 28:327–333. [PubMed: 2342639]
- Rizzolatti G, Matelli M, Pavesi G. Deficit in attention and movement following the removal of postarcuate (area 6) and prearcuate (area 8) cortex in macaque monkeys. *Brain*. 1983; 106:655–673. [PubMed: 6640275]
- Rizzolatti G, Gentilucci M, Camarda RM, Gallese V, Luppino G, Matelli M, Fogassi L. Neurons related to reaching-grasping arm movements in the rostral part of area 6 (area 6a beta). *Exp. Brain Res*. 1990; 82:337–50. [PubMed: 2286236]
- Rizzolatti G, Matelli M. Two different streams form the dorsal visual system: anatomy and functions. *Exp. Brain. Res*. 2003; 153:146–157. [PubMed: 14610633]
- Rizzolatti G, Sinigaglia C. The functional role of the parieto-frontal mirror circuit: interpretations and misinterpretations. *Nat. Rev. Neurosci*. 2010; 11:264–274. [PubMed: 20216547]
- Robinson DL, Bowman EM, Kertzman C. Covert orienting of attention in macaques. II. Contributions of parietal cortex. *J. Neurophysiol*. 1995; 74:698–712. [PubMed: 7472375]
- Romanski LM, Giguere M, Bates JF, Goldman-Rakic PS. Topographic organization of medial pulvinar connections with the prefrontal cortex in the rhesus monkey. *J. Comp. Neurol*. 1997; 379:313–32. [PubMed: 9067827]
- Rorden C, Jelsone L, Simon-Dack S, Baylis LL, Baylis GC. Visual extinction: the effect of temporal and spatial bias. *Neuropsychologia*. 2009; 47:321–329. [PubMed: 18817793]

- Rossetti Y, Pisella L, Vighetto A. Optic ataxia revisited: visually guided action versus immediate visuomotor control. *Exp. Brain Res.* 2003; 153:171–9. [PubMed: 13680044]
- Rozzi S, Calzavara R, Belmalih A, Borra E, Gregoriou GG, Matelli M, Luppino G. Cortical connections of the inferior parietal cortical convexity of the macaque monkey. *Cereb. Cortex.* 2006; 16(10):1389–417. [PubMed: 16306322]
- Rozzi S, Ferrari PF, Bonini L, Rizzolatti G, Fogassi L. Functional organization of inferior parietal lobule convexity in the macaque monkey: electrophysiological characterization of motor, sensory and mirror responses and their correlation with cytoarchitectonic areas. *Eur. J. Neurosci.* 2008; 28:1569–88. [PubMed: 18691325]
- Rushworth MF, Nixon PD, Passingham RE. Parietal cortex and movement. I. Movement selection and reaching. *Exp. Brain Res.* 1997; 117:292–310. [PubMed: 9419075]
- Rushworth MF, Behrens TE, Johansen-Berg H. Connection patterns distinguish 3 regions of human parietal cortex. *Cereb. Cortex.* 2006; 16:1418–30. [PubMed: 16306320]
- Sarri M, Greenwood R, Kalra L, Driver J. Task-related modulation of visual neglect in cancellation tasks. *Neuropsychologia.* 2009; 47:91–103. [PubMed: 18790703]
- Semendeferi K, Lu A, Schenker N, Damasio H. Humans and great apes share a large frontal cortex. *Nat. Neurosci.* 2002; 5:190–2. [PubMed: 11865306]
- Semendeferi K, Armstrong E, Schleicher A, Zilles K, Van Hoesen GW. Prefrontal cortex in humans and apes: a comparative study of area 10. *Am. J. Phys. Anthropol.* 2001; 114:224–41. [PubMed: 11241188]
- Shmahmann JD, Pandya DN, Wang R, Dai G, D'Arceuil HE, de Crespigny AJ, Wedeen VJ. Association fibre pathways of the brain: parallel observations from diffusion spectrum imaging and autoradiography. *Brain.* 2007; 130:630–653. [PubMed: 17293361]
- Simon O, Mangin JF, Cohen L, Le Bihan D, Dehaene S. Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. *Neuron.* 2002; 33:475–487. [PubMed: 11832233]
- Snyder LH, Batista AP, Andersen RA. Coding of intention in the posterior parietal cortex. *Nature.* 1997; 386:167–170. [PubMed: 9062187]
- Snyder LH, Batista AP, Andersen RA. Change in motor plan, without a change in the spatial locus of attention, modulates activity in posterior parietal cortex. *J. Neurophysiol.* 1998a; 79:2814–2819. [PubMed: 9582248]
- Snyder LH, Grieve KL, Brochier P, Andersen RA. Separate body- and world-referenced representations of visual space in parietal cortex. *Nature.* 1998b; 394:887–891. [PubMed: 9732870]
- Snyder LH, Batista AP, Andersen RA. Intention-related activity in the posterior parietal cortex: a review. *Vision Res.* 2000; 40:1433–1441. [PubMed: 10788650]
- Stein JF. The effect of cooling parietal areas and 7 upon voluntary movement in awake rhesus monkey. *J. Physiol. (Lond).* 1976; 258:62–3.
- Stein JF. Role of the cerebellum in the visual guidance of movement. *Nature.* 1986; 323:217–221. [PubMed: 3762673]
- Steinmetz MA, Connor CE, Constantinidis C, McLaughlin JR. Covert attention suppresses neuronal responses in area 7a of the posterior parietal cortex. *J. Neurophysiol.* 1994; 72:1020–1023. [PubMed: 7983507]
- Stiles J, Sugarman S, Nass R. The development of spatial and class relations in four young children with right-cerebral-hemisphere damage: evidence for an early spatial constructive deficit. *Brain and Cognition.* 1985; 4:338–412. [PubMed: 4027066]
- Stiles-Davis J. Developmental change in young children's spatial grouping activity. *Dev. Psychol.* 1988; 24:522–531.
- Strick PL, Kim CC. Input to primate motor cortex from posterior parietal cortex (area 5) I. Demonstration by retrograde transport. *Brain Res.* 1978; 157:325–30. [PubMed: 102409]
- Sugarman, S. Children's early thought: developments in classification. Cambridge University Press; Cambridge: 1983.

- Taira M, Mine S, Georgopoulos AP, Murata A, Sakata H. Parietal cortex neurons of the monkey related to the visual guidance of hand movement. *Exp. Brain Res.* 1990; 83:29–36. [PubMed: 2073947]
- Thiebaut de Schotten M, Urbanski M, Duffau H, Volle E, Lévy R, Dubois B, Bartolomeo P. Direct evidence for a parieto-frontal pathway subserving spatial awareness in humans. *Science.* 2005; 309:2226–2228. [PubMed: 16195465]
- Tipper SP, Behrmann M. Object-centered not scene-based visual neglect. *J. Exp. Psychol. Hum. Percept. Perform.* 1996; 22:1261–1278. [PubMed: 8865621]
- Tomassini V, Jbabdi S, Klein JC, Behrens TE, Pozzilli C, Matthews PM, Rushworth MF, Johansen-Berg H. Diffusion-weighted imaging tractography-based parcellation of the human lateral premotor cortex identifies dorsal and ventral subregions with anatomical and functional specializations. *J. Neurosci.* 2007; 27:10259–69. [PubMed: 17881532]
- Treue S, Martinez Trujillo JC. Feature-based attention influences motion processing gain in macaque visual cortex. *Nature.* 1999; 399:575–579. [PubMed: 10376597]
- Tziridis K, Dicke PW, Thier P. The role of the monkey dorsal pontine nuclei in goal-directed eye and hand movements. *J. Neurosci.* 2009; 29:6154–66. [PubMed: 19439593]
- Vallar G, Bottini G, Paulesu E. Neglect syndromes: the role of the parietal cortex. *Adv. Neurol.* 2003; 93:293–319. [PubMed: 12894416]
- Villa G, Gainotti G, De Bonis C. Constructive disabilities in focal brain-damaged patients. Influence of hemispheric side, locus of lesion and coexistent mental deterioration. *Neuropsychologia.* 1986; 24:497–510. [PubMed: 3774135]
- Von Bonin, G.; Bailey, P. *The neocortex of Macaca mulatta.* University of Illinois Press; Urbana, IL: 1947.
- Wallis JD, Anderson KC, Miller EK. Single neurons in prefrontal cortex encode abstract rules. *Nature.* 2001; 411:953–956. [PubMed: 11418860]
- Watson RT, Miller BD, Heilman KM. Nonsensory neglect. *Ann. Neurol.* 1978; 3:505–508. [PubMed: 98100]
- Watson RT, Valenstein E, Day A, Heilman KM. Posterior neocortical systems subserving awareness and neglect. Neglect associated with superior temporal sulcus but not area 7 lesions. *Arch. Neurol.* 1994; 51:1014–1021. [PubMed: 7944999]
- Wilson SAK. A contribution to the study of apraxia with a review of the literature. *Brain.* 1909; 31:164–216.

Figure 1. The parieto-frontal network

A. Parcellation of the parietal and frontal cortex in the monkey. Lateral view of the areas (PE, PEG) of the exposed part of the superior parietal lobule (SPL) (top), of the surface of the inferior parietal lobule (IPL, Opt, PG, PFG, PF) and of the intraparietal sulcus (IPS, MIP, PEGa, VIP, AIP, LIP), which is shown as flattened in the inset of the brain figurine (bottom). Motor cortex (MI), dorsal (F2, F7) and ventral (F4, F5) premotor areas are shown in the frontal lobe. **B.** Parietal areas (PEG, PEGm) of the mesial aspect of the hemisphere, together with area PEGi and the cingulate motor areas (CMAr, CMAv, CMAAd). In **C**, the inferior parietal lobule (IPL) has been “removed” to show the areas lying in the rostral bank of the parieto-occipital sulcus (V6A) and in the medial wall of the IPS (MIP, PEGa). All SPL areas, but PEGm (7m) are part of Brodmann's area 5, while all IPL areas are part of Brodmann's area 7. **D.** Lateral (left) and mesial (right) aspects of the human brain showing the areas of the SPL (Brodmann's areas 5, 7a, 7b, yellow), and of the IPL (Brodmann's 39, 40, orange).

Figure 2. Hierarchical cluster analysis of the parieto-frontal system

Clusters of architectonically defined areas based upon their inputs. The identified clusters were represented in different colors on the basis of the dominant connections (arrows) that each cluster of the parietal (frontal) lobe has with groups of frontal (parietal) areas. **Left.** Clusters of frontal areas. (PMd: red, MI: blue, PMv: orange, CING: green, PFC: yellow). **Right.** Clusters of parietal areas. (PARd: red, SS: blue, PARv: orange, PARml: yellow). Arrows indicate connectivity, and numbers indicate the fraction (percentage) of the total input to each area that corresponds to each input. The main information streams revealed by the cluster analysis are indicated by arrows in the brain figurine at the bottom of the figure. (Modified from Averbeck *et al.*, 2010).

Figure 3.

A. Global tuning field (GTF) of two SPL cells studied in a multiple tasks approach. In each GTF, arrows of different colours represent the cell's preferred directions related to different signals, such as planning and execution of eye and/or hand movement, as well of eye and hand position, both in presence and absence of visual feed-back about the hand's position in space. The thick orange arrow is the mean vector of the GTF. Its value varies from 0 to 1, with 1 indicating sharpest tuning. Each PD's length is proportional to the cell's firing rate in that particular direction. **B.** Distribution of the mean vectors of the GTFs of a population of neurons in the SPL. The two red arrows are the mean vectors of the GTF of the two cells shown in A. (Modified from Battaglia-Mayer *et al.*, 2000).

Figure 4.

Neural mechanisms for the on-line control of hand movement trajectory. **A.** The activity of one parietal (area PE) cell is shown as spike-density function (SDF; filled grey curves) when a monkey made direct reaches in 8 different directions to visual targets located at the vertices of an imaginary cube. Red thin curves are corresponding hand speed profiles, temporally aligned to the cell's SDFs. Triangles indicate mean time of target presentation, vertical dashed lines onset of hand movement. **B.** The activity of the same cell is shown during on-line corrections of hand movements originally directed to the upper left target and then to the lower right one (grey trajectories), or in the opposite directions (black trajectories). **C.** The SDFs of parietal cells during changes (black curves) of hand movement trajectory (6-3) and (7-2) can be predicted by aligning tip-to-tail the individual SDFs (grey curves) associated to direct reaches toward target 6 and 3, and 7 and 2. The arrows indicate the moment in which the pattern of neural activity associated to one movement direction evolves into that typical of the second movement direction. Vertical dashed lines indicate onset of hand movement.

Figure 5.

A. Distribution of the preferred direction (PD) of neurons studies in area 7a of the right hemisphere of monkeys making hand reaches to memorized (left) or visual (right) targets. RT indicates hand reaction-time, MT indicates hand movement-time. Numbers in the rose diagrams are impulses/sec, n below the rose diagrams indicates the number of PDs studied in that particular condition. (Modified from Battaglia-Mayer *et al.*, 2007). **B.** Mean vectors of the global tuning fields of a neuronal population in area 7a studied under the same conditions as in A.

Figure 6.

Neural activity in area 7a coding the location of elements missing from objects being constructed relative to model objects stored in working memory. **A.** Event sequence in the object construction task (left to right). Monkeys maintained gaze fixated on a central target throughout the trial ('gaze'). A model object was presented ('Model') consisting of a varying configuration of square elements, followed, after a delay, by a copy object, which was identical to the preceding model except for the absence of a single critical square. Monkeys replaced the missing square to reproduce the model configuration by forced choice at the end of the trial. Two choice squares were presented flanking the copy object ('Choice array'), and then brightened one at a time in random order. The monkey selected one of the choice squares to add to the object by timing when it depressed a single response key. The bright square at the time of the key press was added automatically to the object by the task control program. If the monkey pressed the key at the correct time, it added the correct choice square, reproducing the model configuration. **B.** Activity of a single parietal area 7a neuron during the object construction task. Rasters show neural activity on trials in which a particular combination of model and copy objects was shown (above). Vertical lines in each raster delineate periods when model and copy objects were visible. The neuron is primarily activated during the copy period (shaded) of the trial, on trials in which the model and copy objects shown jointly localized the missing critical square to the lower left position in the object, which was the preferred position for this cell (second column from left). The neural signal illustrated does not reflect the form or position of the copy object (for example, identical copy objects were displayed at the same position in the display in all the rasters across the top row, but activity during the copy period clearly varied to reflect the location of the missing square). The neural signal does not code the direction of the required motor response (which did not vary over trials). Rather, neural activity appears to reflect a spatial cognitive process computing the value of a spatial parameter (the position of the missing square) critical to the solution of the problem posed by the object construction task. (Modified from Chafee *et al.*, 2005).

Figure 7.

Neural activity in area 7a represents object-centered position during the construction task. **A.** Activity of a single neuron in area 7a that was activated during the copy period of the trial (shaded) when the critical square was missing from the preferred *right* side of the copy object (second and fourth columns from left), and not when the critical square was missing from the non-preferred *left* side of the copy object (first and third columns). The neural signal was comparably strong irrespective of whether the missing critical square and copy object were located in the left visual hemifield (second column) or the right visual hemifield (fourth column), suggesting that neural activity represented the horizontal position of the missing square, right or left, with respect to the object midline, in object-centered coordinates, and not with respect to the gaze fixation target (and viewer-centered frames of reference). **B.** Location of covert attention during the object-construction task. On a minority of trials, a visual probe stimulus was flashed on the right or left side of the copy object at a random time during the copy period, and reaction time to detect the probe was measured. Monkeys were faster to detect the probe if it was presented on the same side of the copy object as the missing square (black symbols), than if it was presented on the opposite side of the copy object (gray symbols), regardless of the retinocentric position of the reference object. **C.** Hemispheric bias in the neural representation of object-centered space in parietal cortex. More neurons in each cerebral hemisphere exhibited a spatial preference for the contralateral (black bars) than the ipsilateral (gray bars) side of the reference object during both the model and copy periods, irrespective of the retinocentric position of the reference object. (Modified from Chafee *et al.*, 2007; Crowe *et al.*, 2008).

Figure 8.

Neural activity in area 7a during the solution of visual mazes. **A.** Maze stimuli. Monkeys fixated a central gaze target as a randomly generated visual maze subtending the central 30° of vision was presented. Their task was to report, by pressing one of two response keys, whether the single path leaving the central start box ('main path', shaded) reached an exit at the maze perimeter ('Exit') or a blind ending within the maze ('No exit'). The main path was either straight (left two mazes) or contained a single 90° turn (right two mazes). **B.** Activity of a single area 7a neuron during the solution of mazes containing a straight main path. The neuron was activated shortly after maze onset as a function of the direction of the main path extending from the central start box to the maze perimeter. **C.** Population representation of direction during the solution of mazes containing a one-turn main path. The population vector ('PV') was constructed from activity measured every 10 ms in a population of area 7a neurons that were spatially tuned for the direction of the main path. Symbols plot the angular difference between the direction of the population vector in each time bin and the direction of the initial section of the main path (closest to the start box), as a function of time after maze onset. The population vector rotates away from the direction of the initial section of the path in the direction of the turn (positive angles) as time progresses. The dynamic change in the representation of direction takes place in the absence of any concurrent change in visual input or motor output. This is consistent with the neural representation of direction in area 7a reflecting the progression of a covert spatial analysis that traces the main path from the center of the maze outward. (Under this hypothesis, neural activity codes the direction of a vector anchored at the fovea that points to a position that moves along the main path as the covert process unfolds). Modified from Crowe *et al.*, 2004, 2005)

Figure 9.

Self portrait of patient F.M (born 1943), made in April 2001 (left) and repeated in January 2004 (right). In October 1999 F.M. had a large fronto-parieto-temporal ischemic lesion in the right hemisphere. The hemispatial neglect and its recovery over the years can be fully appreciated from these two images. Courtesy of Dr. Daniela Rosi, Centro di riabilitazione neurologica Franca Martini A.T.S.M. Onlus, Trento, Italy.