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Understanding the parietal lobe syndrome from a neurophysiological and evolutionary perspective

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Abstract

In human and nonhuman 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 monkey's 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.

Introduction

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

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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 ispilateral corticocortical connections, in other words the dynamics of the parietofrontal system, can provide the necessary basis for a physiologically-founded interpretation of the parietal syndrome.

We will start by describing the anatomical and functional organization of the parietofrontal 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 nonhuman primates to man.

The structural and functional architecture of the parietofrontal 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

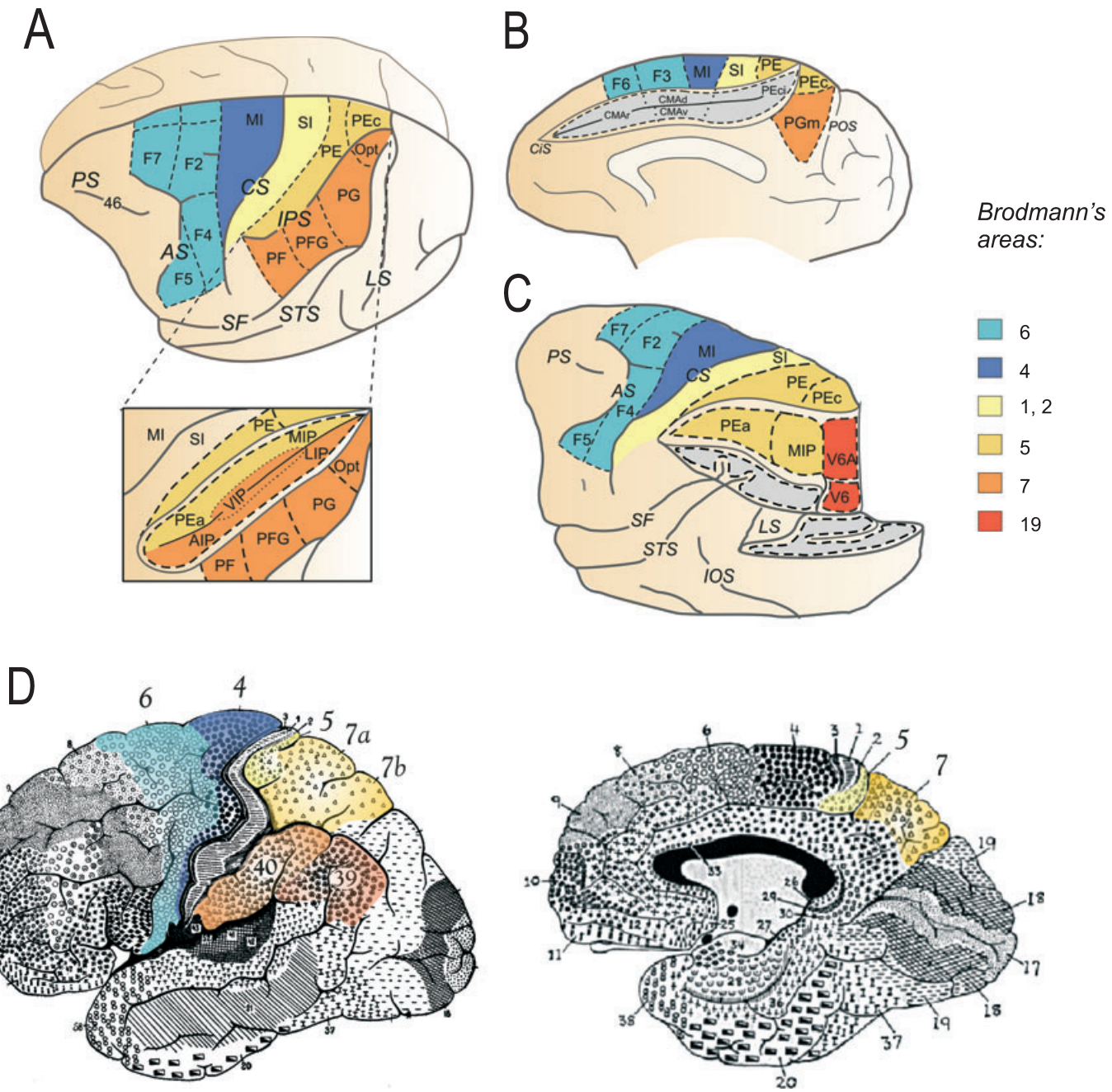

FIG. 1. The parietofrontal network. (A) Parcellation of the parietal and frontal cortex in the monkey. Lateral view of the areas (PE, PEc) of the exposed part of the SPL (top), of the surface of the inferior parietal lobule (IPL; Opt, PG, PFG, PF) and of the intraparietal sulcus (IPS; MIP, PEa, VIP, 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 (PEc, PGm) of the mesial aspect of the hemisphere, together with area PEci and the cingulated motor areas (CMAr, CMAd, CMAv). (C) The inferior parietal lobule (IPL) has been removed to show the areas lying in the rostral bank of the parietooccipital sulcus (V6A) and in the medial wall of the IPS (MIP, PEa). All SPL areas except PGm (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 and 7b; yellow) and of the IPL (Brodmann's areas 39 and 40; orange).

defined cortical areas (Fig. 1A). The superior parietal lobule (SPL) is composed of area PE and PEc on the gyral surface, and areas PEa and MIP (medial intraparietal) in the dorsal bank of the intraparietal sulcus (IPS). These areas 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 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 anterior intraparietal and lateral intraparietal areas (AIP and LIP) in the lateral bank of the IPS. Because of its corticocortical 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 are globally referred to as the 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 and 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 or the ventromedial 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 four 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 the first (SI; a ventral parietal cluster (PAR-V) is formed by areas PF, PFG, PG and AIP, and a mediolateral parietal cluster (PAR-ml) consists of areas PGm (7m), V6A, LIP, VIP and Opt.

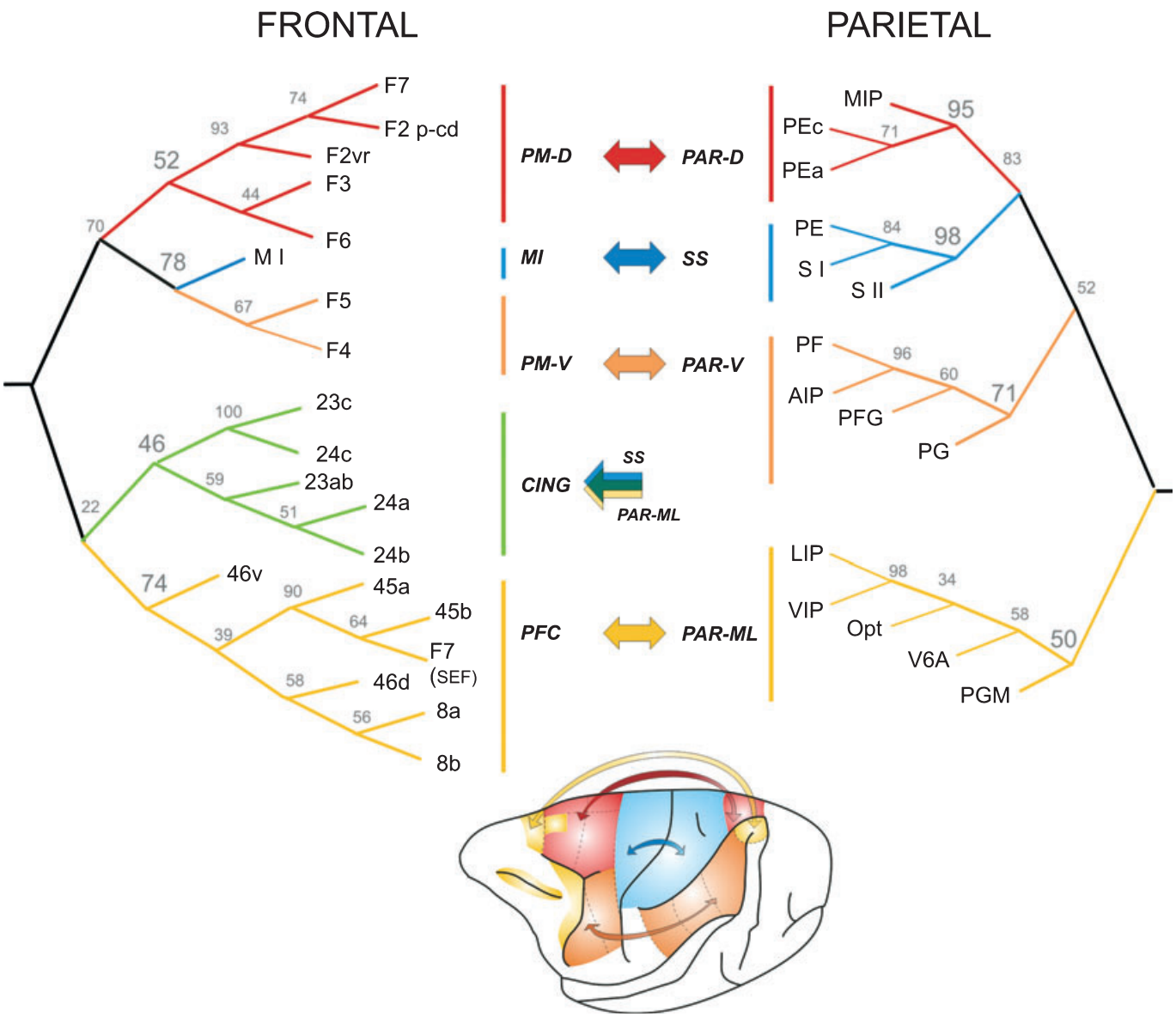

FIG. 2. Hierarchical cluster analysis of the parietofrontal system. Clusters of architectonically defined areas based upon their inputs. The identified clusters were represented in different colors on the basis of the dominant connections (arrows) that each cluster of the parietal (frontal) lobe has with groups of frontal (parietal) areas. Left, clusters of frontal areas. [PM-D (dorsal premotor cluster), red; MI, blue; PM-V (ventral premotor cluster), orange; CING (cingulate cluster), green; PFC (prefrontal cluster), yellow]. Right, clusters of parietal areas. (PAR-D, red; SS, blue; PAR-V, 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.*, 2009).

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 parietofrontal 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 the primary motor cortex (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 parietofrontal connections clearly define the existence of privileged, although not private, routes of information flow between parietal and frontal cortex (Fig. 2). More specifically, the mediolateral 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. PAR-D, together with the dorsal premotor cluster, 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). PAR-V cooperates with the ventral premotor cluster 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. PAR-V is also involved in both the processing of visual information and the preparation of movements in the context of more complex visuomotor 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; Averbeck *et al.*, 2005; Archambault *et al.*, 2009), and convey 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 rostrocaudal 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 dorsorostral premotor cortex (Johnson *et al.*, 1996; Fuji *et al.,* 2000), visual and eye-related signals predominate over coexisting hand information (Johnson *et al.*, 1996). In contrast, 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 parietofrontal network, across motor cortex, supplementary motor area (SMA) and pre-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 rostrocaudal 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 dorsorostral to dorsocaudal premotor cortex toward MI. However, although in different proportions, cells encoding eye and/or hand position information are ubiquitous at all rostrocaudal 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) areas. 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, as gradients have been reported for eye-related signals across areas 7a and LIP (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 parietofrontal 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 on 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 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 supramargynal gyrus, respectively. In von Economo's view (1925), the SPL is composed of area PE and the IPL of 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 & 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 nonhuman primates.

Very little is known of the detailed corticocortical connectivity in man. Recent developments in MRI, such as diffusion tensor imaging, offer preliminary information on parietofrontal connectivity. This information will be of crucial importance in the near future, as ongoing parcellations of cortical areas are performed largely on the basis of corticocortical 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 parietofrontal 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 functional magnetic resonance imaging (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 SMA and pre-SMA based on the pattern of corticocortical connectivity (Johansen-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 parietofrontal network appears to perform different computations related to sensorimotor control, such as converting sensory representations from one set of sensory coordinates into another (intersensory 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 parietofrontal segment of the network, while the frontoparietal 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 parietofrontal 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 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 optic ataxia 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 feedback (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 optic ataxia 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 transcranial magnetic stimulation 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 optic ataxia 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 optic ataxia consists of a problem in the fast on-line control of reaching rather than in its early composition. However, the relative degree to which optic ataxia reflects a deficit in motor planning or on-line motor control remains to be precisely determined.

Is 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 optic ataxia in humans (Classen *et al.*, 1995; Karnath & Perenin, 2005; Tziridis *et al.*, 2009), and that the conceptualization of the parietofrontal system based on studies in monkeys over the last 20 years would be of little help in 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, as experiments could not be guided by the detailed knowledge we now have of the architecture of the parietofrontal system. From the late 1950s to about the end of the 1970s (see Hartje & Ettlinger, 1973; 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 in which 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 feedback 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 PMd 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 parietofrontal system is not critically involved in the visual control of hand movements has no foundation.

Instead, we believe that the functional architecture of the parietofrontal network provides a coherent framework in which to interpret optic ataxia 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 and 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 a basis for representations of reaching. It is our hypothesis that optic ataxia 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).

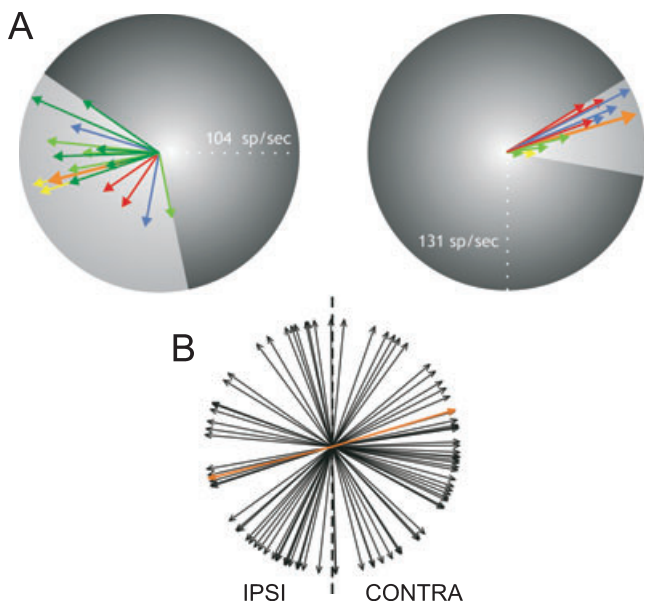

FIG. 3. (A) Global tuning field (GTF) of two SPL cells studied in a multiple tasks approach. In each GTF, arrows of different colours represent the cell's preferred directions related to different signals, such as planning and execution of eye and/or hand movement, as well of eye and hand position, in both the presence and absence of visual feedback 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).

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 signalling operated by the frontoparietal 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 parietofrontal interplay, and therefore optic ataxia might be interpreted as a corticocortical disconnection syndrome. However, alternative interpretations exist as to the pathway subserving visually-guided reaching (Stein, 1986; Khrebtukova *et al.*, 1998), the collapse of which would be responsible for the reaching impairment observed in optic ataxia patients (Classen *et al.*, 1995). According to this view, a parietopontocerebellar system provides motor cortex, via the cerebellothalamocortical pathway, with the spatial information necessary for the composition of motor commands for visually-guided arm reaching. Unfortunately, knowledge of the anatomofunctional 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 multisynaptic 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 pontocerebellar 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 optic ataxia 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 (parietofrontal vs. parietopontocerebellar–thalamocortical) involved.

Another crucial point to be addressed concerns the difficulty for optic ataxia patients to make fast on-line 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 on-line 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 others predicting future changes of movement direction. The causality of this relation is shown both by the elongation of 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 optic ataxia 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 approximately 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 dorsocaudal premotor cortex (Johnson *et al.*, 1996; Matelli *et al.*, 1998). Transient inactivation of premotor cortex with transcranial magnetic stimulation results in a reduction in 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 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, directional hypokinesia 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. Directional hypokinesia 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 directional hypokinesia from optic ataxia. Directional hypokinesia 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 directional hypokinesia, 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, as they were much slower in initiating leftward rather than 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 times 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 also observed 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

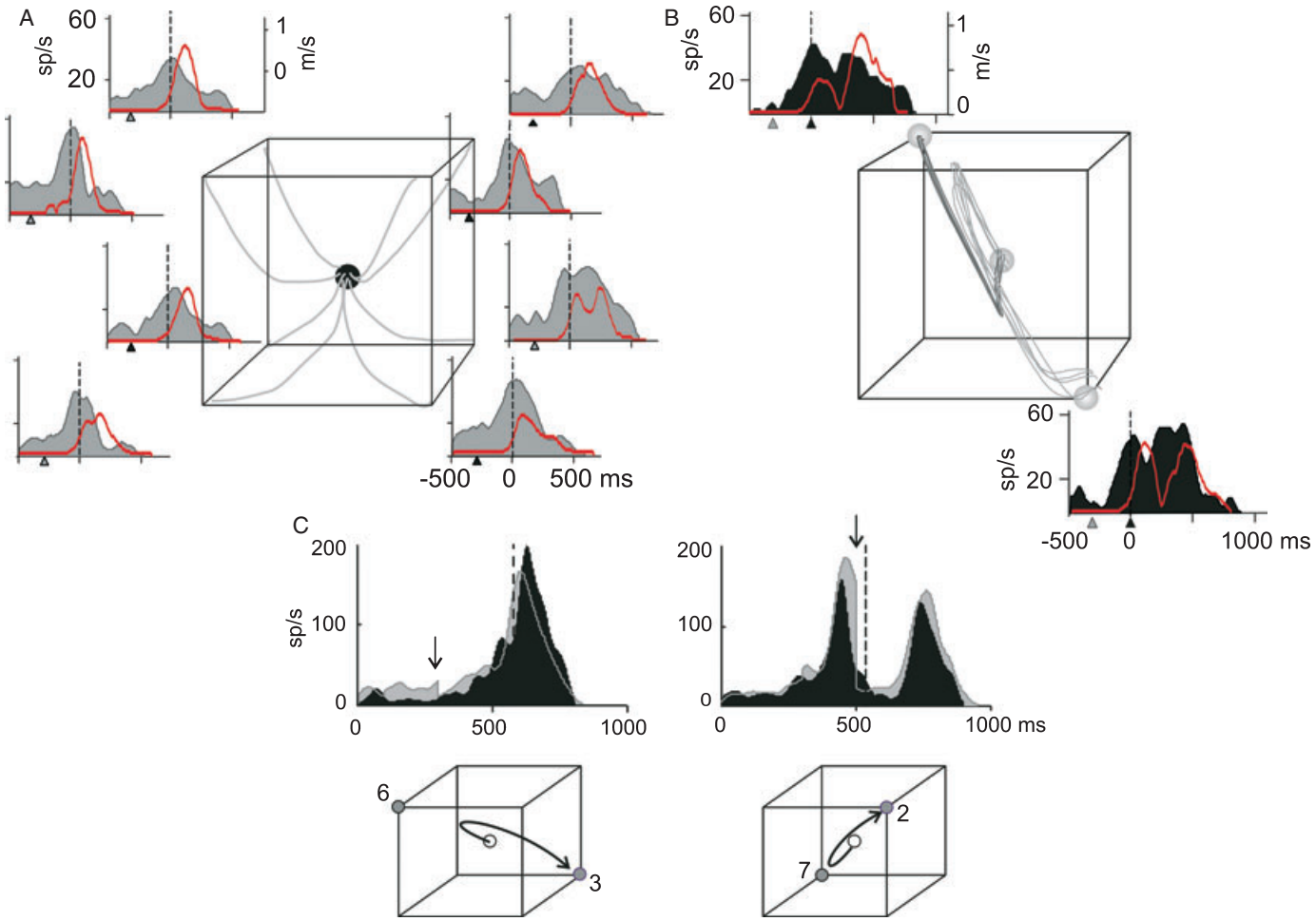

FIG. 4. Neural mechanisms for the on-line control of hand movement trajectory. (A) The activity of one parietal (area PE) cell is shown as spike density function (SDF; filled grey curves) when a monkey made direct reaches in eight different directions to visual targets located at the vertices of an imaginary 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.

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, in either the presence or absence of visual guidance of movement. In fact, reaches towards targets in contralesional space were consistently hypometric as 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, as it emerges only at the moment when all necessary information is available to transform the motor plan into action. It is our hypothesis

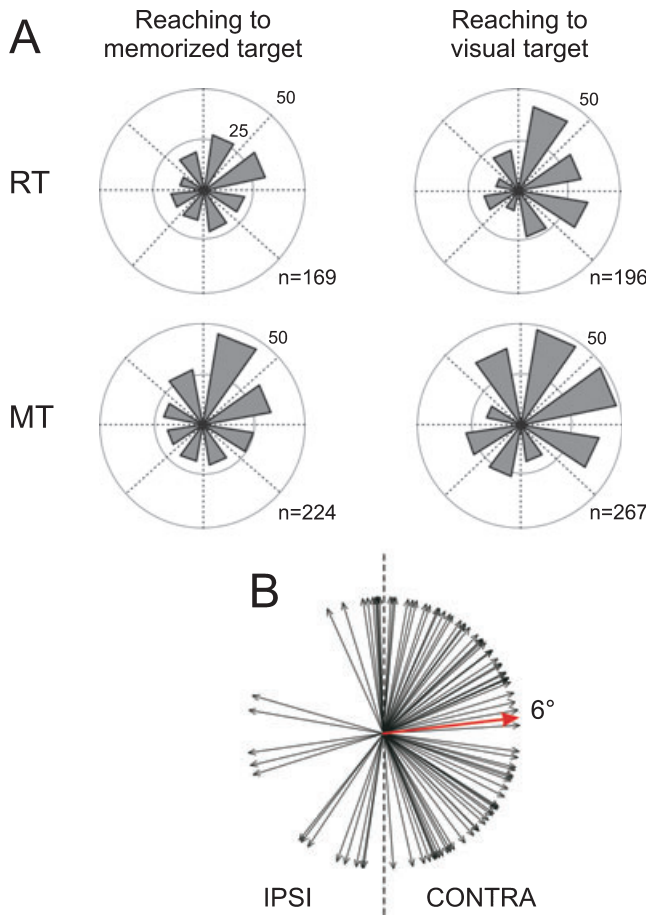

FIG. 5. (A) Distribution of the preferred direction (PD) of neurons studies in area 7a of the right hemisphere of monkeys making hand reaches to memorized (left) or visual (right) targets. RT indicates hand reaction time and MT indicates hand movement time. Numbers in the rose diagrams are impulses/s; 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 GTFs of a neuronal population in area 7a studied under the same conditions as in A.

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 hypokynesia. 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 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 constructional apraxia on the other; namely, in the first two forms the patients have difficulty in reproducing previously well learned motor tasks, whereas in constructional apraxia 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, it has been proposed that the mechanisms that underlie ideomotor apraxia 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 constructional apraxia. 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 (Piercy *et al.*, 1960; Benson & Barton, 1970). 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; Gainotti *et al.*, 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 by a failure to either 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 *et al.*, 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 constructional apraxia. 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 identification 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, as 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 similarly 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 similarly 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 populations 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. 8; '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.

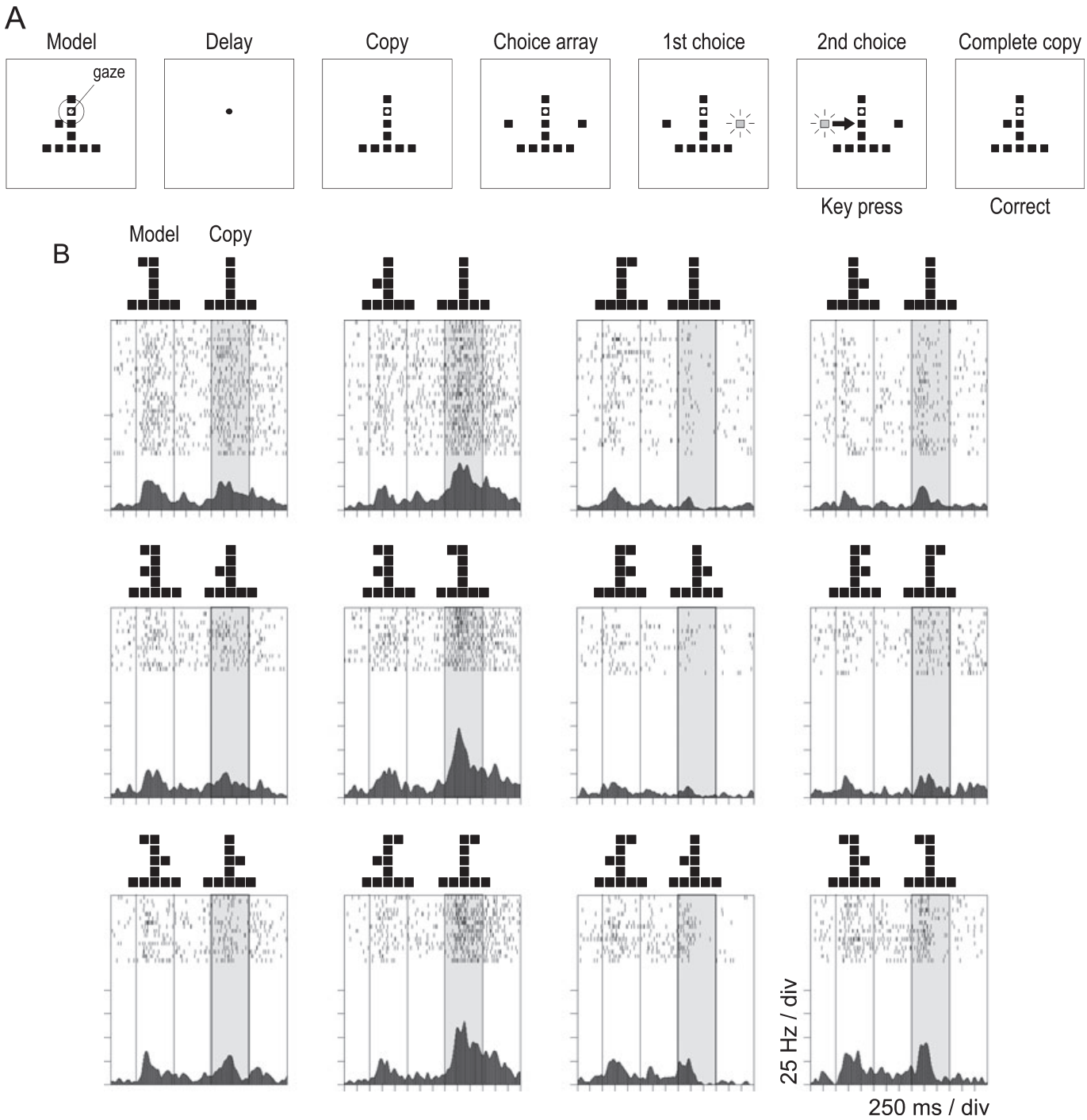

FIG. 6. Neural activity in area 7a coding the location of elements missing from objects being constructed relative to model objects stored in working memory. (A) Event sequence in the object construction task (left to right). Monkeys maintained gaze fixated on a central target throughout the trial ('gaze'). 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).

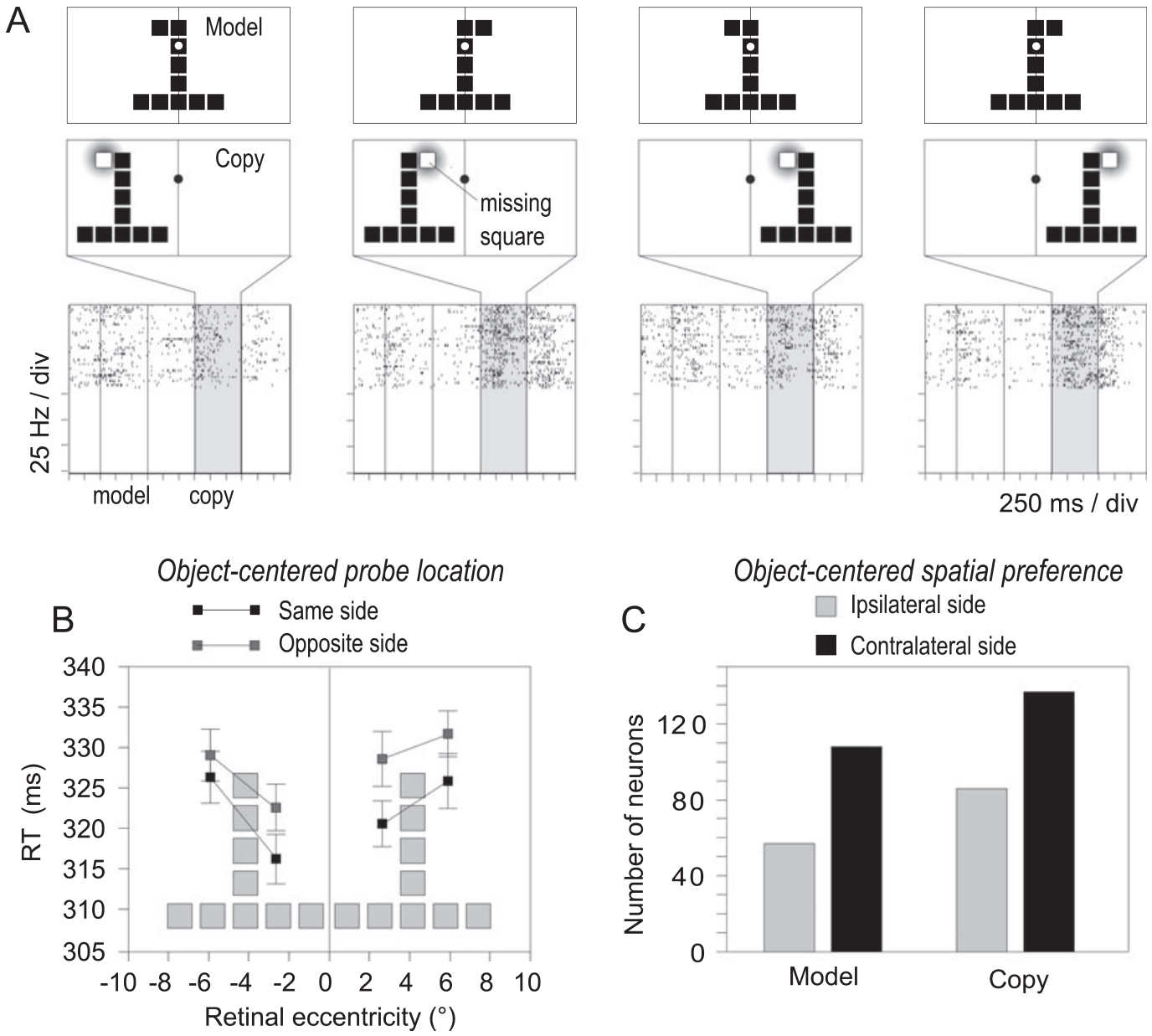

FIG. 7. Neural activity in area 7a represents object-centered position during the construction task. (A) Activity of a single neuron in area 7a that was activated during the copy period of the trial (shaded) when the critical square was missing from the preferred right side of the copy object (second and fourth columns from left), and not when the critical square was missing from the nonpreferred left side of the copy object (first and third columns). The neural signal was similarly 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).

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). 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

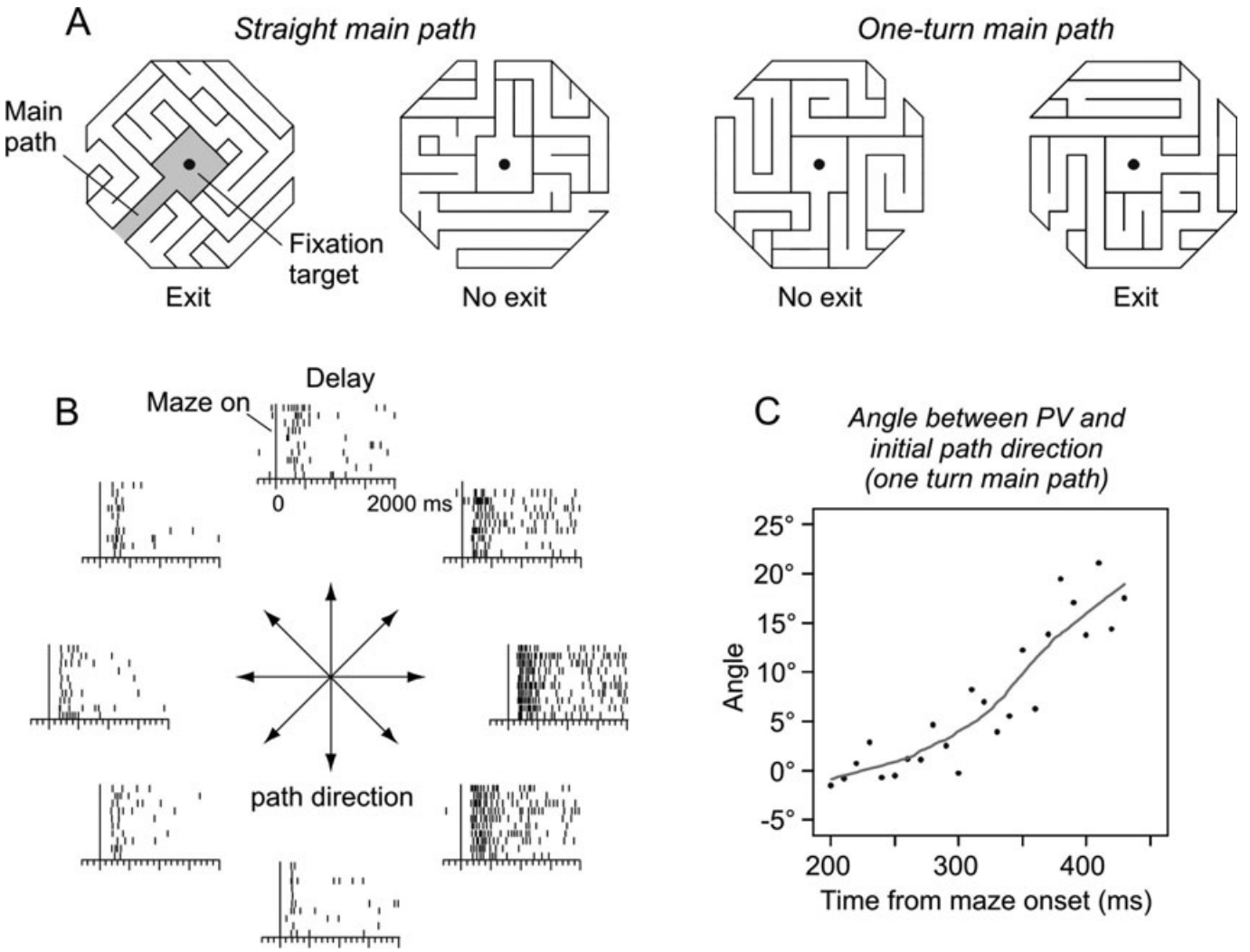

FIG. 8. Neural activity in area 7a during the solution of visual mazes. (A) Maze stimuli. Monkeys fixated a central gaze target as a randomly generated visual maze stimulus subtending the central 30° of vision was presented. Their task was to report, by pressing one of two response keys, whether the 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).

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.

FIG. 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 frontoparietotemporal 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.

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.*, 1998, 2008b; Kusunoki *et al.*, 2000; Constantinidis & Steinmetz, 2001a, 2005) and have been proposed to provide a '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 (Steinmetz *et al.*, 1994; Robinson *et al.*, 1995; 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.

Hemispatial neglect following parietal damage can manifest in either viewer-centered or object-centered spatial coordinates (Driver & Halligan, 1991; Driver *et al.*, 1994; Tipper & Behrmann, 1996; Hillis *et al.*, 1998; 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; Andersen *et al.*, 1990; Brotchie *et al.*, 1995), body-centered (Lacquaniti *et al.*, 1995; Snyder *et al.*, 1998b) and 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, 2005; Quian 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 PPC 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 stems not only from comparative architectonic analyses but also from the analysis of the parcellation of parietal cortex based on corticocortical connectivity in both species. This has become possible thanks to studies using axoplasmic tracers in monkeys and, more recently, probabilistic tractography from diffusion tensor 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; Bruner, 2008) indicate that modern human endocasts show a significant midsagittal enlargement of the parietofrontal outline, which is more pronounced at the level of parietal cortex, and a dorsovertical lengthening of the parietocerebellar volumes. We interpret this result as reflecting an enlargement of the entire distributed system of which parietal cortex is a crucial node, and which probably also includes the parietocerebellar 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 can be reproduced in monkeys after unilateral cortical lesions is controversial. In fact, testing for directional hypokinesia in animal models has proven to be problematic because the over-training required to get monkeys to perform the visuomotor tasks necessary to measure directional hypokinesia 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 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 marmoset monkeys (Marshall *et al.*, 2002), superior temporal cortex (Luh *et al.*, 1986; Watson *et al.*, 1994) and premotor cortex (Rizzolatti *et al.*, 1983) lead to behavioural deficits that overall have been interpreted as a form of neglect. 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 & Hornak, 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 (Thiebaut 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, and 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 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; Potı *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 by 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 parietofrontal connectivity of the two 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, 1978a) 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 and neurons giving rise to corticocortical 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 preformed within it. With respect to this, there is a remarkable symmetry between frontal and parietal systems and the connectivity between them (Averbeck *et al.*, 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 probably 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) and working memory processes (Funahashi *et al.*, 1989, 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 such as construction behaviour, as opposed to sensory-driven spatial motor processes such as orienting or reaching towards objects in space. It is of interest that this anatomical expansion during evolution concerns not only 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 by a child during constructive play. To put it in the words of Forman (1982), '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 on-line 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 parietofrontal 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' postnatal 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 and complex, and made from a larger numbers of component parts (Sugarman, 1983; Langer, 1986; Stiles-Davis, 1988), and also begin to include interobject 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 interobject spatial relationships is and will remain definitely poor. Furthermore, adult chimps never develop the ability to construct nonfunctional symmetrical spatial relationships (Potì & Langer, 2001), in this resembling right-hemisphere-damaged children (Stiles *et al.*, 1985).

The above hypothesis identifies an anatomofunctional 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 corticocortical 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 parietoprefrontal 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.

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Abbreviations

AIP, anterior intraparietal area; Opt, parietal area Opt; PE, parietal area PE; PEc, parietal area PEc; PEa, parietal area PEa; PF, parietal area PF; PFG, parietal area PFG; PG, parietal area PG; PGm (7m), parietal area 7m; V6, visual area 6; V6A, visual area V6A; BA5, Brodmann's area 5; BA7, Brodmann's area 7; fMRI, functional magnetic resonance imaging; GTF, global tuning field; IPL, inferior parietal lobule; IPS, intraparietal sulcus; LIP, lateral intraparietal area; MIP, medial intraparietal area; MI, primary motor cortex; PMd, dorsal premotor cortex; PM-D, dorsal premotor cluster; PM-V, ventral premotor cluster; PPC, posterior parietal cortex; PAR-D, dorsal parietal cluster; PAR-V, ventral parietal cluster; PAR-ML, mediolateral parietal cluster; PSI, primary somatosensory cortex; SMA, supplementary motor area; SPL, superior parietal lobule; SS, somatosensory cluster.

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