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# Early motor influences on visuomotor transformations for reaching: a positive image of optic ataxia

**Abstract** Coding of reaching in the cerebral cortex is based on the operation of distributed populations of parietal and frontal neurons, whose main functional characteristics reside in their combinatorial power, i.e., in the capacity for combining different information related to the spatial aspects of reaching. The tangential distribution of reach-related neurons endowed with different functional properties changes gradually in the cortex and defines, in the parieto-frontal network, trends of functional properties. These visual-to-somatic gradients imply the existence of cortical regions of functional overlaps, i.e., of combinatorial domains, where the integration of different reach-related signals occurs. Studies of early coding of reaching in the mesial parietal areas show how somatomotor information, such as that related to arm posture and movement, influences neuronal activity in the very early stages of the visuomotor transformation underlying the composition of the motor command and is not added "downstream" in the frontal cortex. This influence is probably due to re-entrant signals traveling through fronto-parietal-association connections. Together with the gradient architecture of the network and the reciprocity of cortico-cortical connections, this implies that coding of reaching cannot be regarded as a top-down, serial sequence of coordinate transformation, each performed by a given cortical area, but as a recursive process, where different signals are progressively matched and further elaborated locally, due to intrinsic cortical connections. This model of reaching is also supported by psychophysical studies stressing the parallel processing of the different relevant parameters and the "hybrid" nature of the reference frame where they are combined. The theoretical frame presented here can also offer a background for a new interpretation of a well-known visuomotor disorder, due to superior parietal lesions, i.e., optic ataxia. More than a disconnection syndrome, this can now be interpreted as the consequence of the breakdown of the operations occurring in the combinatorial domains of the superior parietal segment of the parieto-frontal network.

**Key words** Reaching · Fronto-parietal network · Combinatorial domain · Visuomotor transformations · Optic ataxia

## Coding of reaching occurs within a distributed parieto-frontal network

Cortical coding of reaching occurs within a distributed network, including different parietal and frontal areas (Fig. 1), heavily interconnected by reciprocal sets of association connections (Fig. 2). Areas of interest are V6 and V6A in the rostral bank of the parieto-occipital sulcus; area 7m, SMA (supplementary motor area, F3), pre-SMA (F6), and some cingulate motor areas in the medial wall of the hemisphere; areas MIP (medial intraparietal), PE, and PEa in the superior parietal lobule (SPL); areas 7a and LIP (lateral intraparietal) in the inferior parietal lobule; primary motor cortex (M1, F1), dorsolateral premotor cortex (PMd, F2 and F7), and dorsomedial premotor cortex in the frontal lobe.

In the last 15 years, the study of the dynamic properties of neurons in behaving monkeys performing a variety of arm-reaching tasks and the analysis of the cortico-cortical connectivity in these areas have provided new insights on the basic operations performed within this network. We will briefly illustrate only those anatomical and functional aspects of the network that we believe are relevant for in-

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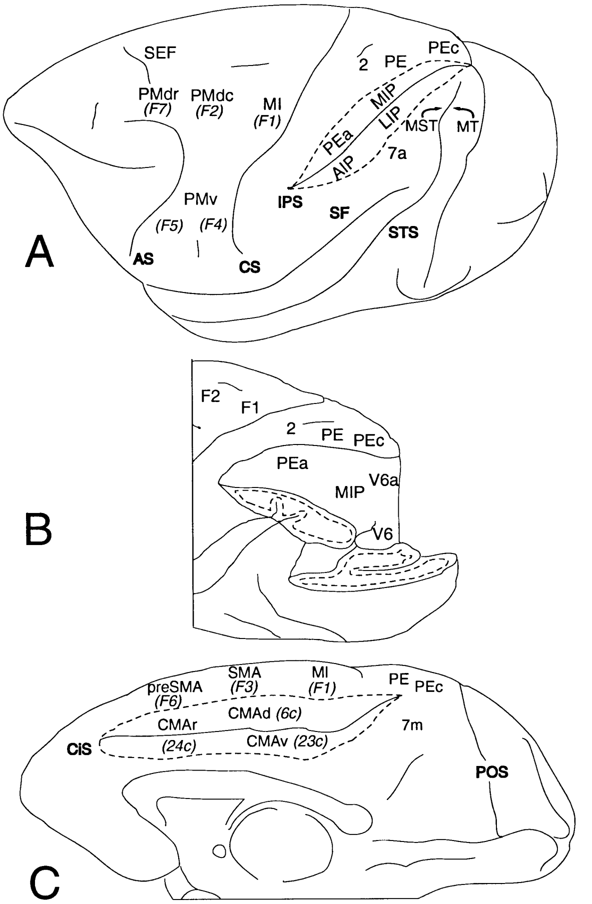

**Fig. 1A–C** Cortical areas involved in reaching. **A** Lateral view of the macaque hemisphere. **B** View of the parieto-occipital part of the hemisphere after removal of large parts of the parietal and occipital lobes to show the location of areas in the medial bank of the intraparietal sulcus and in the rostral bank of the parieto-occipital sulcus (redrawn with modifications from Galletti et al. 1996). **C** View of the medial aspect of the hemisphere. *AS, CS, IPS, STS, CiS, POS* indicate, respectively, arcuate, central, intraparietal, superior temporal, cingulate and parieto-occipital sulci; *SF* indicates sylvian fissure. *CMAd, CMAr, CMAv* caudodorsal, rostral, caudoventral cingulate motor areas; *AIP, MIP, LIP* anterior, medial, lateral intraparietal; *MI* primary motor cortex; *MST* medial superior temporal; *MT* middle temporal; *PEa, PEc, PE* cortical fields of the superior parietal lobule; *PMdc, PMdr, PMv* dorsocaudal, dorsorostral, ventral premotor cortex; *SEF* supplementary eye fields; *SMA, preSMA* caudal, rostral supplementary motor areas

terpreting a new set of results on cortical coding of reaching.

## The occipito-parietal cortex

This region forms most of the rostral bank of the parieto-occipital sulcus (Fig. 1B). Originally labeled as area PO (Gattas et al. 1985) and later redefined in its boundaries (Colby et al. 1988), it has recently been divided into a ventral visual area (V6), roughly coextensive to traditional area PO, and a dorsomedial visuomotor area (V6A) of more complex visual properties. Here a significant proportion of cells has no visual relationships (Galletti et al. 1996). Since this new parcellation has been proposed, only two preliminary notes have appeared in the literature (Matelli et al. 1995; Shipp and Zeki 1995) devoted to the analysis of the cortico-cortical connectivity in one of these regions, V6A. Complications arise from the fact that the dorsoventral extent of the PO, as defined by Colby et al. (1988), is larger that that of V6, as defined by Galletti et al. (1996). Therefore, in this manuscript, we will refer to the cortico-cortical connectivity of V6A as it emerges from the available preliminary results and as it can be deduced from Tanné's et al. (1995) and Johnson's et al. (1996) studies; concerning PO, we will refer the results from the original paper by Colby et al. (1988).

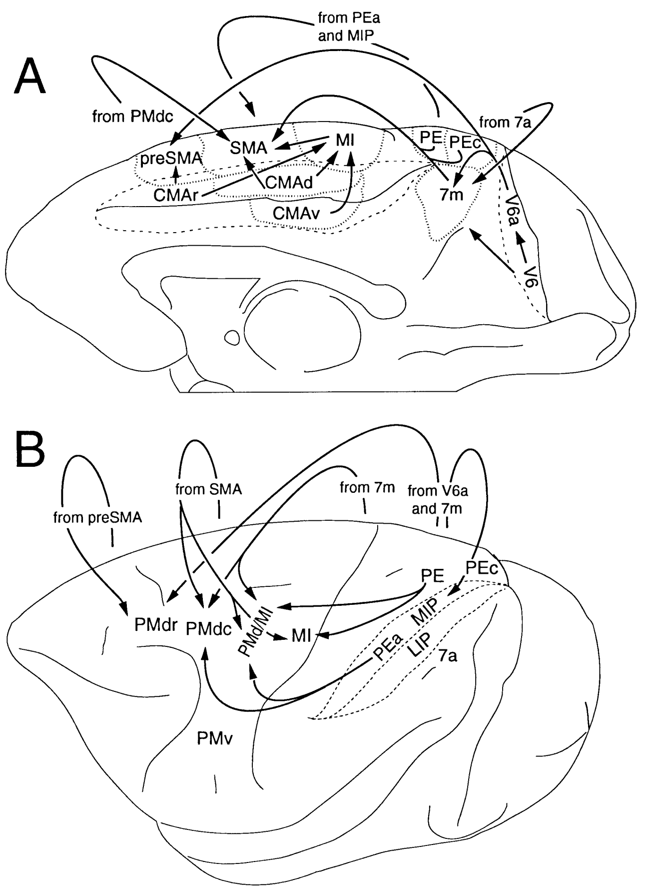

**Fig. 2A, B** Main cortico-cortical connections between areas involved in reaching. Medial (**A**) and lateral (**B**) views of the hemisphere with main cortico-cortical connections (*arrows*) between areas involved in reaching. These connections are reciprocal. However, only the parieto-frontal and not the fronto-parietal connections are shown. Conventions and symbols as in Fig. 1

Area V6 receives cortico-cortical inputs from V1, V2, V3, and MT. These inputs are organized retinotopically and originate from zones of representation in the periphery of the visual field. Parietal projections to V6 originate from areas LIP, VIP (ventral intraparietal; Maunsell and Van Essen 1983), MIP, and PIP (posterior intraparietal). The frontal eye fields (FEF) are additional sources of cortico-cortical input. Area V6 (Fig. 2A,B) projects to V6A (Matelli et al. 1995; Shipp and Zeki 1995), 7m (Cavada and Goldman-Rakic 1989a,b), MIP, and LIP (Blatt et al. 1990).

Area V6A (Fig. 2A,B) receives association fibers from V6, V5, and V3/V3A (Shipp and Zeki 1995) and is interconnected with V5A/MST (medial superior temporal), 7a, 7m, MIP, and VIP (Matelli et al. 1995; Shipp and Zeki 1995). Frontal projection of V6A terminates in the caudal bank of the superior limb of the arcuate sulcus, in the lateral part of area F2 (Matelli et al. 1995; Shipp and Zeki 1995). A projection to a frontal zone corresponding to area F7 has also been described (Tanné et al. 1995; Johnson et al. 1996). This projection is addressed to a region located rostrally to the reaching-related zone of the dorsal premotor cortex (Johnson et al. 1996).

Salient features of visual neurons in both V6 and V6A include the large, mostly peripheral, receptive fields (Gattas et al. 1985; Colby et al. 1988), the dependence of visual activity on the angle of gaze, and the presence, for a minority of cells, of gaze-independent "spatial" fields (see Galletti et al. 1996 for an overview). It has been proposed that these properties allow the coding of target position in head-centered coordinates (Galletti et al. 1993). Neurons in V6A are also tuned to the direction of arm-reaching movement and to the position of the arm in space (Johnson et al. 1997; Lacquaniti and Caminiti 1998). Limb movement-related activity in V6A has also been observed during simple, stereotyped wrist movements (Galletti et al. 1997).

## Area 7m

Area 7m (Cavada and Goldman-Rakic 1989a,b) lies in the medial wall of the hemisphere and is largely coextensive with area PGm (Pandya and Seltzer 1982) and MDP (medial dorsal parietal; Colby et al. 1988). 7m (Fig. 2A,B) entertains reciprocal cortico-cortical relationships with portions of V2, V6, V6A, PEc, LIP, the visual motion sensitive areas of the upper bank of the superior temporal sulcus MT (middle temporal) and MST, 7a, 5, MIP (Cavada and Goldman-Rakic 1989a,b), area 23c in the lower bank of the posterior part of the cingulate sulcus, and area 24c more anteriorly (Petrides and Pandya 1984; Cavada and Goldman-Rakic 1989a,b). Whether these last projections are addressed to those parts of cingulate cortex including the caudoventral (CMAv) and rostral (CMAr) cingulate motor areas (Dum and Strick 1991a,b; He et al. 1995), respectively, remains to be determined. Of special interest are the 7m's outputs (Cavada and Goldman-Rakic 1989a,b), addressed to MIP and, within premotor cortex, to the reaching-related zone of PMdc (Johnson et al. 1993, 1996; Tanné et al. 1995), to PMdr (Johnson et al. 1993, 1996; Tanné et al. 1995; Matelli et al. 1995), pre-SMA, SMA, and the supplementary eye fields (SEF; Schlag and Schlag-Rey 1987). Reciprocal connections with prefrontal cortex interest mostly the caudal part of the dorsal bank of the principal sulcus (Cavada and Goldman-Rakic 1989a,b). Recent neurophysiological studies (Ferraina et al. 1997a,b) have shown that 7m's neural activity relates to a combination of hand and gaze signals, as it will be illustrated later in the manuscript.

## Area 5

The regions of the SPL traditionally labeled as area 5 have recently been parcellated into at least three cortical fields (Pandya and Seltzer 1982; Fig. 1), area PE covering the exposed part of the dorsal aspect of the SPL and the adjoining cortex of the mesial part of the hemisphere, area PEc on the posterior pole of the SPL on both its lateral and medial aspects, and area PEa, which is coextensive with the cortex and buried in the entire extent of the upper bank of the intraparietal sulcus. The posterior part of PEa is now referred to as area MIP (Colby et al. 1988). This recent distinction has been proposed on the basis of myeloarchitectonic criteria, which, however, have not been recognized by other authors (Preuss and Goldman-Rakic 1991). Therefore, it is controversial how to trace the borders of the MIP. Considering that the MIP receives, while PEa lacks, a cortico-cortical input from visually-related areas (for a review, see Caminiti et al. 1996), the "border" between these superior parietal regions can be tentatively located in the zone of the medial bank of the IPS, where visually-derived activity (such as signal-related activity; Johnson et al. 1996) and preparatory arm-movement activity (such as set-related activity; Johnson et al. 1996) are first encountered when recording during instructed-delay reaching tasks.

## Area MIP

Physiological studies (Colby and Duhamel 1991) have shown that individual neurons in this area combine visual and somatosensory signals. Studies on behaving monkeys performing an instructed-delay reaching task (Johnson et al. 1996) revealed that, in addition, cell activity in the MIP is tuned to the direction of arm movement and to the static posture of the arm. Furthermore, MIP neurons fire in relation to the presentation of visuo-spatial signals about target location and during the preparatory activity for arm movement. Although no evidence has been provided on the influence of gaze signals on the MIP, the cortico-cortical connectivity of this area (Johnson et al. 1993, 1996; Tanné et al. 1995) predicts such relationship. MIP (Fig. 2A,B) is reciprocally connected with 7m and V6A (Matelli et al. 1995; Shipp and Zeki 1995) and receives additional inputs (Lewis and Van Essen 1984) from area VIP. Frontal projections are mostly addressed to PMdc and to the border between this and M1 (Johnson et al. 1993, 1996; Tanné et al. 1995). Since the MIP is included and occupies part of the traditional area PEa (Pandya and Seltzer 1982), one can conclude from previous studies (Jones et al. 1978; Caminiti et al. 1985; Johnson et al. 1989) that MIP connections with frontal-lobe motor areas are reciprocal.

## Areas PE and PEa

Areas PE and PEa have the functional features proper of a somatomotor center. Neurons in these areas are endowed with a large representation of the arm, which is mapped in a rather coarse manner, as are the other body parts. The majority of neurons have large, multiarticular somatosensory receptive fields, which are generally larger than those found in area 2 (Duffy and Burchfiel 1971; Burbaud et al. 1991). These fields are often multimodal (cutaneous and proprioceptive; Duffy and Burchfiel 1971; Sakata et al. 1973; Mountcastle et al. 1975; Burbaud et al. 1991) and encompass chest, shoulder, elbow, and wrist. Neurons with receptive fields in single joints code steady joint positions (Mountcastle et al. 1975). Another population of neurons, unresponsive to passive stimuli, is arm-movement related (Mountcastle et al. 1975; Burbaud et al. 1991), perhaps due to corollary signals from motor cortex (Kalaska et al. 1983) or as part of a command mechanism for movement in extrapersonal space (Mountcastle et al. 1975; Bioulac and Lamarre 1979). The activity of these neurons is generally tuned to the direction of arm movement (Kalaska et al. 1983) and to the static posture of the arm (Georgopoulos et al. 1984). Cells activity in these areas often precedes the onset of arm movement, as seen in frontal motor areas (Mountcastle et al. 1975; Kalaska et al. 1983; Chapman et al. 1984; Burbaud et al. 1991), and predicts the direction of the next arm movement (Seal et al. 1983; Crammond and Kalaska 1989; Ferraina and Bianchi 1994). Interestingly, this neural activity is not linked in a obligatory fashion to the execution of movement, since it can also be observed during no/go trials of a go-no/go task, therefore reflecting potential movements (Kalaska and Crammond 1995).

Coding of arm posture and movement in these areas may therefore reside in a high order representation, probably based on the sensory information available. For instance, hand azimuth could be estimated by combining proprioceptive information about the horizontal rotation of both shoulder and elbow joints; hand elevation and distance could be similarly derived from combinations of horizontal and vertical rotations of these two joints. As for the source of the vertical reference that is necessary for computing arm coordinates in geotropic space, area 5 could receive this information from area 2, which is in turn recipient of vestibular inputs. Alternatively, the reference could correspond to the trunk midsagittal axis. In this context, one may note that several neurons in area 5 have receptive fields encompassing both chest and shoulder.

There is recent evidence that dorsal area 5 (area PE) might be a substrate for egocentric representations of reaching in the monkey (Lacquaniti et al. 1995; Lacquaniti 1997; Lacquaniti and Caminiti 1998). In this study, monkeys were trained to make arm movements directed to visual targets placed in different parts of the 3D workspace in a reaction-time task. It was found that the mean activity of most neurons during the movement is monotonically related to the position of either the target or the hand with respect to the head and body. This activity is irrespective of the starting position of the hand in the workspace and, therefore, of the direction of movement. The activity of some neurons may reflect the current position of the limb, as derived from peripheral feedback or efferent copy of motor commands. However, the activity of many other neurons relates to the final point, although this has not yet been reached, i.e., during reaction time or movement time, reflecting a preplanned desired position (Hocherman and Wise 1991) or “command function” (Mountcastle et al. 1975), rather than current kinematics.

An additional observation is that the tuning functions across the whole population of area-5 neurons are not uniformly distributed in 3D space. Instead, some neurons are tuned selectively along the coordinate axis of the azimuth, whereas others are tuned for elevation and still others the distance. Thus, each spatial coordinate tends to be encoded in a different subpopulation of neurons. However, the separation is incomplete, as there is significant crosstalk among the three channels. Non-uniform distribution of neural tuning has also been reported in primary somatosensory cortex (Helms Tillery et al. 1996).

Neural parcellation could be a correlate of the psychophysical observation that these spatial parameters are processed in parallel and largely independent from one another (Flanders et al. 1992). Projecting the spatial information onto separate axes of neural coding could be important for sensorimotor coordination, because information related to motor commands could be matched more easily with incoming sensory feedbacks. Spatial axes that result from a hybrid combination of sensory and motor axes would be best suited to accomplish this matching process (Carrozzo and Lacquaniti 1994). Although spatial information is parcellated at the level of single neurons, the complete information about limb position can be reconstructed by simple summation of the individual contributions over a population of neurons, because positive and negative spatial coefficients tend to be evenly distributed (Lacquaniti et al. 1995). This can be demonstrated by using a neural network model. A layered neural network, whose intermediate layer contains positionally tuned neurons, can be trained to generate the position of the hand in body-centered coordinates. It is not known whether global reconstruction of limb position takes place at a cortical level or at a subcortical level (Mountcastle 1995).

PE and PEa (Fig. 2A,B) do not receive direct cortico-cortical input from V6A, contrary to area MIP (see Caminiti et al. 1996 for a review). They have reciprocal cortico-cortical connections with M1 and the M1/PMd border (Jones et al. 1978; Strick and Kim 1978; Johnson et al. 1989, 1993), somatosensory cortex, SMA, and cingulate cortex (Jones et al. 1978; Pandya and Seltzer 1982; Luppino et al. 1993). These patterns of connectivity suggest that they play no role in the visual control of movement, but can exert a crucial role in composition of motor commands and in movement control based on somatosensory information. A detailed description of the cortico-cortical connectivity of this parietal regions is given in the study by Pandya and Seltzer (1982).

## Inferior parietal lobule

The inferior parietal lobule can contribute to coding of reaching due to different populations of neurons, whose functional properties can be relevant for different aspects of visuomotor behavior. A large population of neurons has been described as being related to arm reaching toward targets of interest in the extrapersonal space (Hyvarinen and Poranen 1974; Mountcastle et al. 1975; MacKay 1992; Sakata et al. 1995; Snyder et al. 1997). Furthermore, neural activity in areas 7a (Sakata et al. 1980) and LIP (Gnadt and Mays 1995) is modulated by the depth of visual targets and displays separate directional and depth tuning, possibly coding for direction and distance of the target. A recent study (Mattingley et al. 1998) of parietal patients with focal lesions of the IPL has shown, in addition to unilateral neglect, a specific impairment in the initiation of movement, which was not found in patients with focal frontal lesions. This further supports the command-function hypothesis of the parietal cortex (Mountcastle et al. 1975; Mountcastle 1995). However, since there are no significant cortico-cortical projections from the inferior parietal lobule areas to either PMd or M1, the IPL projection to 7m, which in turn projects to dorsolateral premotor cortex, may well represent a potential route whereby these inferior parietal areas can influence the command mechanism in the frontal lobe for reaching.

## SMA and pre-SMA

The cortex lying in the mesial wall of the frontal lobe has been divided into different areas on the basis of architectonic features, connectivity patterns, and neuronal functional properties. Traditional SMA has recently been divided into a rostral part, pre-SMA (F6, Matelli et al. 1991; Matsuzaka et al. 1992), and a caudal part, SMA proper (F3; Luppino et al. 1991; Matelli et al. 1991; Matsuzaka et al. 1992). Studies of cell activity in the two areas during instructed-delay tasks have shown a predominance of directional signal- and set-related activity in pre-SMA, and of movement-related activity in SMA (Alexander and Crutcher 1990; Matsuzaka et al. 1992). Overall, these properties are not different from those of cells studied in the frontal and parietal cortex under the same experimental conditions (Johnson et al. 1996; for reviews, see Caminiti et al. 1996; Wise et al. 1997). However, during sequential motor tasks (Mushiake et al. 1991; Tanji and Shima 1994) based on either vision or memory, while M1 neurons are active during all behavioral epochs of these tasks and premotor cortex neurons fire mainly during preparatory and movement epochs of the visually-guided trials, SMA cells fire during memorized delay times. Interestingly, cells in premotor cortex are more frequently tuned to learning of new movement sequences, while in the SMA they are more frequently active during retrieval of specific sequence of memorized movements. Thus, it seems that the SMA plays an important role in planning sequences of arm movements. Recent preliminary results, however, indicate that the pre-SMA, rather than SMA, represents a critical area for learning new movement sequences (Miyashita et al. 1996).

SMA and pre-SMA also differ in their cortico-cortical connections (Fig. 2A,B). While pre-SMA receives association fibers mainly from the anterior cingulate motor area, ventral premotor area F5, and prefrontal cortex (Bates and Goldman-Rakic 1993; Luppino et al. 1993; Lu et al. 1994), SMA receives from M1, somatosensory cortex, premotor area F4, cingulate area 24d, and from parietal areas PE, PEa, and PEc (Luppino et al. 1993). SMA projects directly to the spinal cord (Dum and Strick 1991a,b; He et al. 1995), while pre-SMA does not have substantial spinal projections (Dum and Strick 1991a,b; Luppino et al. 1993; Tokuno and Tanji 1993; Lu et al. 1994).

## The dorsomedial premotor cortex

Recent preliminary evidence (Chou and Schiller 1997) suggest that, in addition to oculomotor behavior, neuronal activity in that cortical regions, including the SEF, relates to arm movement as well. The activity of most neurons is influenced by coordinated arm and eye movements, while a consistent population of these seems to carry genuine arm motor signals.

## The cingulate motor areas

The medial wall of the hemisphere contains different areas, some of which have traditionally been considered as part of the limbic system and for which there is now evidence of motor functions (Fig. 2). Three cingulate motor areas have been described (for a review, see Picard and Strick 1996), a rostral one (CMAr) in area 24c on the cortex of both the dorsal and ventral banks of the cingulate sulcus (CiS) and two caudal ones. Of these, one (CMAd) is located on the dorsal bank of the CiS in area 6c, the other (CMAv) on its ventral bank, in area 23c. All three areas connect to motor and parietal cortex, although they project to different parts within their target zones (Dum and Strick 1993; Johnson and Ferraina 1996). CMAd and CMAv project to M1 and to the border region between M1 and PMdr. Less substantial projections are addressed to PMdr (Johnson and Ferraina 1996). CMAv is also connected with prefrontal cortex (Lu et al. 1994; Bates and Goldman-Rakic 1993). All three cingulate areas project to the spinal cord (Dum and Strick 1991a,b, 1996; He et al. 1995), although these projections are less abundant from CMAr; coherently, the microstimulation effects of this area are weaker than those of the other cingulate motor areas (Luppino et al. 1991).

The involvement of the CMAs in visually guided reaching, as it emerges from metabolic mapping studies using 2-DG, is controversial. Savaki et al. (1997) have reported a significant increase in activity in areas 23 and 24 during performance of a visually guided arm reaching task. On the contrary, according to Picard and Strick (1997), intense changes in metabolic activity occurs in area CMAd and only during performance of remembered sequences of reaching movements. Cell-recording studies in behaving monkeys (Shima et al. 1991) have shown the existence of two foci of arm-movement related activity in the cortex of the CiS, a rostral one roughly corresponding to CMAr and a caudal one, probably including both CMAd and CMAv. Neurons firing well in advance of movement onset during self-paced movement were found more numerous at the rostral site.

### Dorsal premotor cortex and primary motor (M1) cortex

The dorsolateral part of the frontal lobe includes (Matelli et al. 1985; Barbas and Pandya 1987; Preuss et al. 1996) a rostral (PMdr, F7) and a caudal (PMdc, F2) premotor field, and M1 (F1). Ipsilateral cortico-cortical projections (Fig. 2A,B) to these regions originate mainly from other frontal and parietal areas. Thus, PMdr receives parietal projections mainly from V6A and 7m (Johnson et al. 1993, 1996; Matelli et al. 1995; Tanné et al. 1995), PMdc is connected to 7m, MIP, PE, and PEa (Petrides and Pandya 1984; Johnson et al. 1993, 1996; Matelli et al. 1995; Tanné et al. 1995), while the main parietal input to M1 comes from PE and PEa (Jones et al. 1978; Strick and Kim 1978; Petrides and Pandya 1984; Johnson et al. 1993, 1996). PMdr, different from PMdc and M1, is connected with prefrontal cortex (PF), but receives less substantial projections from CMAs than PMdc and M1 (Johnson and Ferraina 1996). PMdr projects to PMdc, which provides an input to M1 (Johnson et al. 1993, 1996). PMdc and M1 have substantial projections to the spinal cord (Dum and Strick 1991a,b). These parietal and frontal inputs to frontal cortical areas are largely reciprocal.

The involvement of PMdc and M1 in reaching is well documented by a large number of studies, for which extensive reviews are now available (Georgopoulos 1995; Caminiti et al. 1996; Wise et al. 1997). Here, we will illustrate only the results of some of them, which are relevant to the problem of the information-processing stream underlying reaching in frontal and related parietal areas.

## Dynamic properties of reach-related cells

The different functional types of cells of the network underlying visually-guided reaching have been studied in a variety of behavioral tasks. These have assessed the relationships between neural activity and different reaching-related spatial variables, such as target position in space, static posture of the arm at the origin and endpoint of movement, eye position and movement, and preparation for and execution of arm movement in different directions.

It has been shown that, in all areas of the network, most of these signals influence neural activity, although with different strengths in the different areas. Thus, arm position and movement direction influences neuronal activity in PMdc (Caminiti et al. 1990, 1991; Fu et al. 1995; Crammond and Kalaka 1996; Johnson et al. 1996), M1 (Georgopoulos et al. 1982, 1984; Kalaska et al. 1989; Caminiti et al. 1990), parietal areas 5 (Kalaska et al. 1983; Ferraina and Bianchi 1994; Lacquaniti et al. 1995), MIP (Johnson et al. 1996), 7m (Ferraina et al. 1997a,b) and V6A (Johnson et al. 1997; Lacquaniti and Caminiti 1998). Modulation of arm-movement related activity by arm posture has been shown in PMdc (Caminiti et al. 1990, 1991), M1 (Caminiti et al. 1991), area 5, and MIP (Ferraina and Bianchi 1994). Arm orientation is reflected in the activity of neurons in M1 (Scott and Kalaska 1997), PMd and area 5 (Scott et al. 1997). The influence of eye position on reaching-related activity has been studied and found in PMdc (Boussaoud 1995) and 7m (Ferraina et al. 1997a). The functional properties of neurons in V6A (Galletti et al. 1996) and MIP (Johnson et al. 1996) and the input-output relations of these areas predict an influence of eye position signals on their reach-related activity. Activity related to the visuospatial signals about target location and to preparation for arm movement has been found in all areas of the network (Johnson et al. 1996; Ferraina et al. 1997a,b; see Wise et al. 1997).

A second crucial observation concerning frontal and parietal reaching-related populations is that the different signals illustrated above are not segregated within different classes of neurons, but influence the activity of individual cells, although in different combinations and with different strength (Johnson et al. 1996). This implies that these neurons combine signals of different origin. This combinatorial power could be a crucial property, since it is probably the substratum whereby coordinate transformation occurs throughout the network.

Finally, no cortical operation can be understood without knowledge of the spatial distribution of the cell types involved and, therefore, of the anatomical and functional relationships within the network. In this respect, a combined anatomical and neurophysiological study on behaving monkeys has revealed that the tangential distribution of the different information encoded in the activity of reach-related cells in the fronto-parietal network defines trends of functional properties, which are symmetrical relative to the central sulcus (Johnson et al. 1996). Thus, the number of cells displaying signal-, set-, movement-, and position-related activity progressively increases from the central sulcus rostralward toward PMdc and caudalward toward MIP. Within these visual-to-somatic trends, regions displaying similar activity types in both frontal and parietal cortices are linked by association connections (Johnson et al. 1996). This implies the existence in both parietal and frontal cortex of regions of functional overlap; in other words, of combinatorial domains, where different signals can be matched due to both the combinatorial power of individual neurons and to the smooth transition of functional properties along the tangential domain of the cortex. This gradient-like architecture can also be observed in the mesial parietal cortex, where a gradual transition has been described from signal- and set-related activity, which is more frequent in pre-SMA, to movement-related activity, which predominates in SMA (Alexander and Crutcher 1990; Matsuzaka et al. 1992). In this respect, it is interesting that the anatomical arrangement of the projections from these movement-related mesial areas to PMd and M1 is also arranged in a trend-like fashion (Johnson and Ferraina 1996). The incidence on neural activity and the spatial distribution of gaze-position signals seem to follow similar trends (Boussaoud 1995; Galletti et al. 1996; Ferraina et al. 1997a,b).

This gradient-architecture ensures that the dorsolateral and mesial frontal areas as well as the parietal areas involved in reaching all have access to a variety of information, which could then be further combined locally within each area due to intrinsic connections.

## Early motor influences on visuomotor transformation

The analysis of the early stages of the composition of motor commands for reaching is of interest since it can reveal how early different signals influencing reaching-related activity are combined and, therefore, may shed some light on the nature of the visuomotor transformation performed in the network. Classical schemes have so far stressed a top-down serial mode of coordinate transformation and have assigned unique roles to given cortical areas in this process. These schemes have been influenced by the assumption that individual neurons in different cortical areas were encoding just one given variable or parameter of movement and have ignored the potential implied by the reciprocity of cortico-cortical connections. When this reciprocity had indeed been taken into account, it was only considered to be a substratum for efferent copies of motor commands. This role is probably not exhaustive of the functions of cortico-cortical connections, since re-entrant signals can influence the initial cortical operations underlying reaching well beyond the operation as a substrate for corollary signals. How this can be exerted has been well illustrated in recent studies (Ferraina et al. 1997a,b; Johnson et al. 1997) on the dynamic properties of neurons in areas 7m and V6A of alert behaving monkeys. These areas occupy a crucial position in the information-processing flow leading from vision to movement since, as illustrated above, they receive visual input from extrastriate cortices and project to both parietal and frontal cortex. They are therefore an ideal node where the influence of somatomotor signals on the early stages of the visuomotor transformation for reaching can be evaluated.

Neurons in area 7m have been studied during different behavioral tasks (Figs. 3, 4), aimed both at assessing the relationships between neural activity and arm- and eye-position and movement signals and at dissociating their influence. The task used consisted of a canonical reaction-time arm reaching task (R task), a reaching task to peripheral targets while maintaining central fixation ($R_{fix}$ task), an instructed-delay reaching task (IDT task), and an eye-position task (EPO task), where the eyes were maintained immobile while fixating the peripheral targets that, in the R and IDT tasks, were at the same time the endpoints of the arm movement and the positions on which the arm was actively held immobile. The IDT task was performed both under normal light conditions and in total darkness to assess the influence of the hand position and movement in the visual field on cell activity. In all cases, arm and/or eye movements were from a central position to eight peripheral targets (subtending 0.5° visual angle), located on a circle of 13 cm radius (30° visual angle), at 45° angular intervals.

During the IDT task (Fig. 3A–C), neuronal activity in 7m relates in a directional fashion to saccadic eye movement and to preparation and execution of arm reaching. Furthermore, positional signals about static hand posture influence neural activity. This occurs not only when movement is performed in normal light conditions, but also in total darkness and, therefore, in absence of visual information about hand trajectory. This suggests that genuine hand motor and positional signals influence 7m neurons. However, neural activity is different when the movement of the hand is visible compared with the absence of such visual monitoring, which implies a role of this neuron in the visual control of reaching. The relationships of cell activity to eye position is shown by the EPO task (Fig. 3D). Finally, Fig. 4 illustrates, through the analysis of cell activity during the R, $R_{fix}$, and EPO tasks how eye and arm position and movement signals interact in this neuron's activity.

The involvement of V6a in reaching is suggested by its cortico-cortical input-output relationships, as detailed above. The relationships between neural activity in V6a and arm position and movement direction have been studied by using the R task and the IDT task, performed both under normal light conditions and in total darkness (Johnson et al. 1997). Figure 5 illustrates such relationships. This neurons' activity is directionally modulated during all epochs of the task. Quantitative analyses during the initial part of the delay-time (after the instruction-signal is presented and the eyes saccade to the target) and the remaining of the instructed-delay period (when the hand is immobile at the center of the workspace and prepares to move, and the eyes are fixating the peripheral target), show a significant difference between cell activity in these epochs. This implies that neural activity relates in a directional way to the presentation of the instruction-signal (signal-related activity) and/or to the saccadic eye movement as well as to the preparation for hand movement. The significant difference in cell activity observed when hand and eyes positions are dissociated during the last part of the delay-time and the target-holding time (THT), when eye and hand positions coincide, indicates that a positional signal concerning static arm posture influences cell activity. Finally, the presence of arm-movement related activity in both light and dark conditions shows that genuine motor signals influence this neuron's activity, which, however, differs under such conditions, suggesting a role in the visual monitoring of hand trajec-

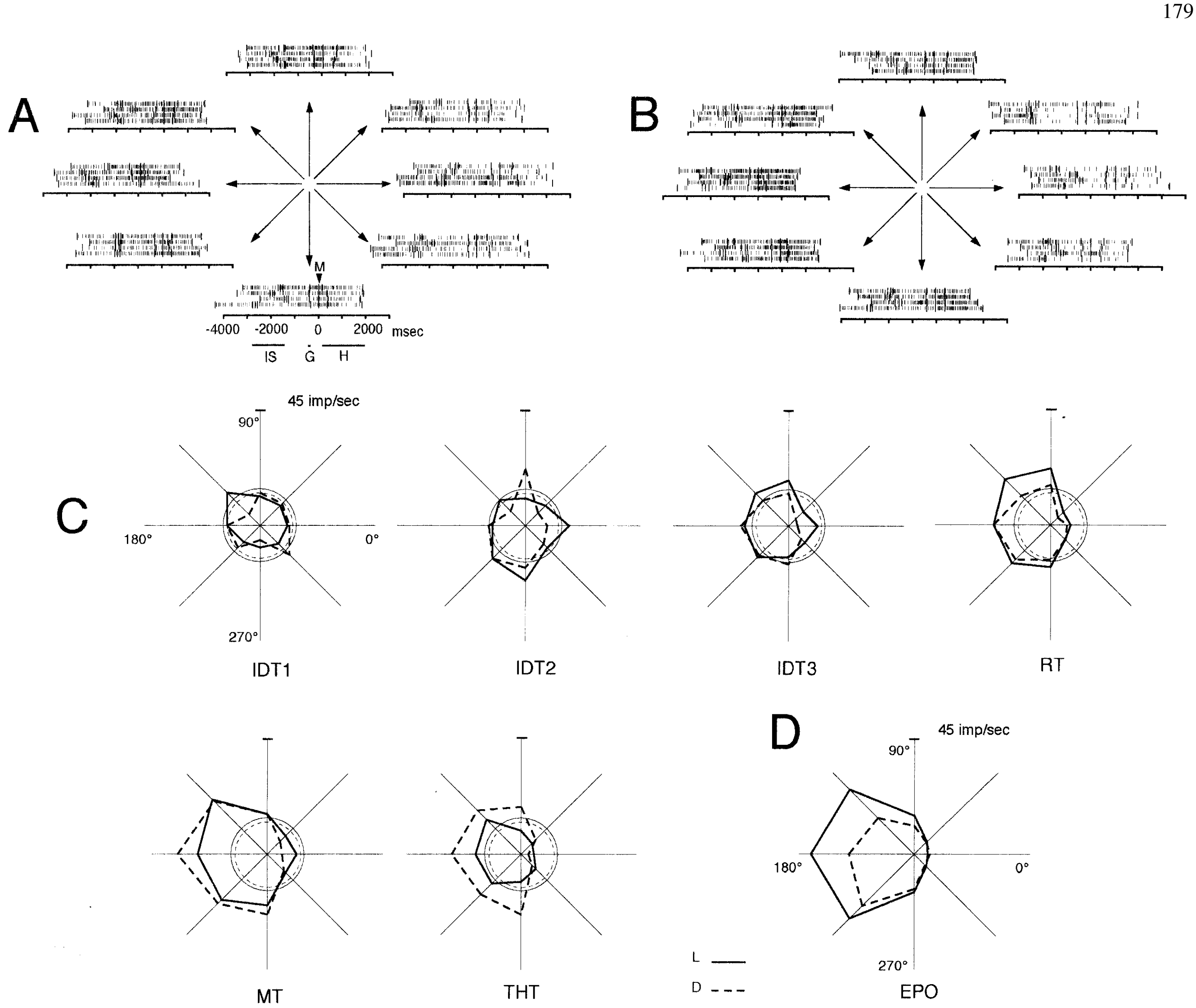

**Fig. 3** Impulse activity of a neuron studied in area 7m during the IDR (**A–C**) and EPO task (**D**). Rasters of four replications for each movement direction (*arrows*) are aligned to movement onset (*M*) under both light (**A**) and dark (**B**) conditions. *Longer vertical bars* indicate, from left to right, beginning of the trial, presentation of the instruction-signal (*IS*), presentation of the GO-signal (*G*), movement onset (*M*), beginning and end of target-holding (*H*) time (*THT*). **C** Polar plots of impulse activity for different epochs of both task conditions (*continuous line* light, *interrupted lines* dark). For both task conditions, *circles* indicate frequency of discharge during center holding time, taken as control time. In this epoch both hand and eyes were immobile on a central target; *IDT1* and *IDT2* indicate reaction and movement time of the saccade to the target; *IDT3* instructed-delay time, during which the animal kept the eyes immobile on the target, while the hand was immobile at the center of the workspace preparing for the next movement; *RT* and *MT* indicate reaction and movement time of the hand; *THT* indicates target-holding time, during which hand and eyes remained immobile on the target. **D** Polar plots of the activity of this same neuron in the EPO task, during which the animal was simply fixating the same targets that in the IDT task were the endpoints of both hand and eyes movement. (Reproduced with permission from Europ J Neurosci 9:1090–1095, 1997)

tory. Another interesting feature is that neural activity is significantly higher in light than in dark during all epochs of the task except THT; this is more so during RT, when, ready to move, the difference between actual and desired (final) hand position is maximal. It could be hypothesized that a motor error is encoded in the activity of this neurons. Finally, the similarity of cell-preferred direction (Fig. 5D; Georgopoulos et al. 1982) across behavioral epochs and task conditions implies that coding of the relevant parameters occurs in a spatially congruent fashion. These neurons were not active when visual stimuli were presented in a conventional visual fixation task.

Re-entrant signals using fronto-parietal connections, as well as thalamic inputs, can be the sources of these early motor influences on the initial processing of visual information for reaching in areas V6A and 7m. These influences not only assign a novel role in motor control to these posterior parietal areas, but, together with the combinatorial properties of parietal and frontal cells and the gradient-architecture of the network, impose a reconsideration of the nature of the computation underlying reaching. This, in fact, cannot be regarded as a stepwise serial pro-

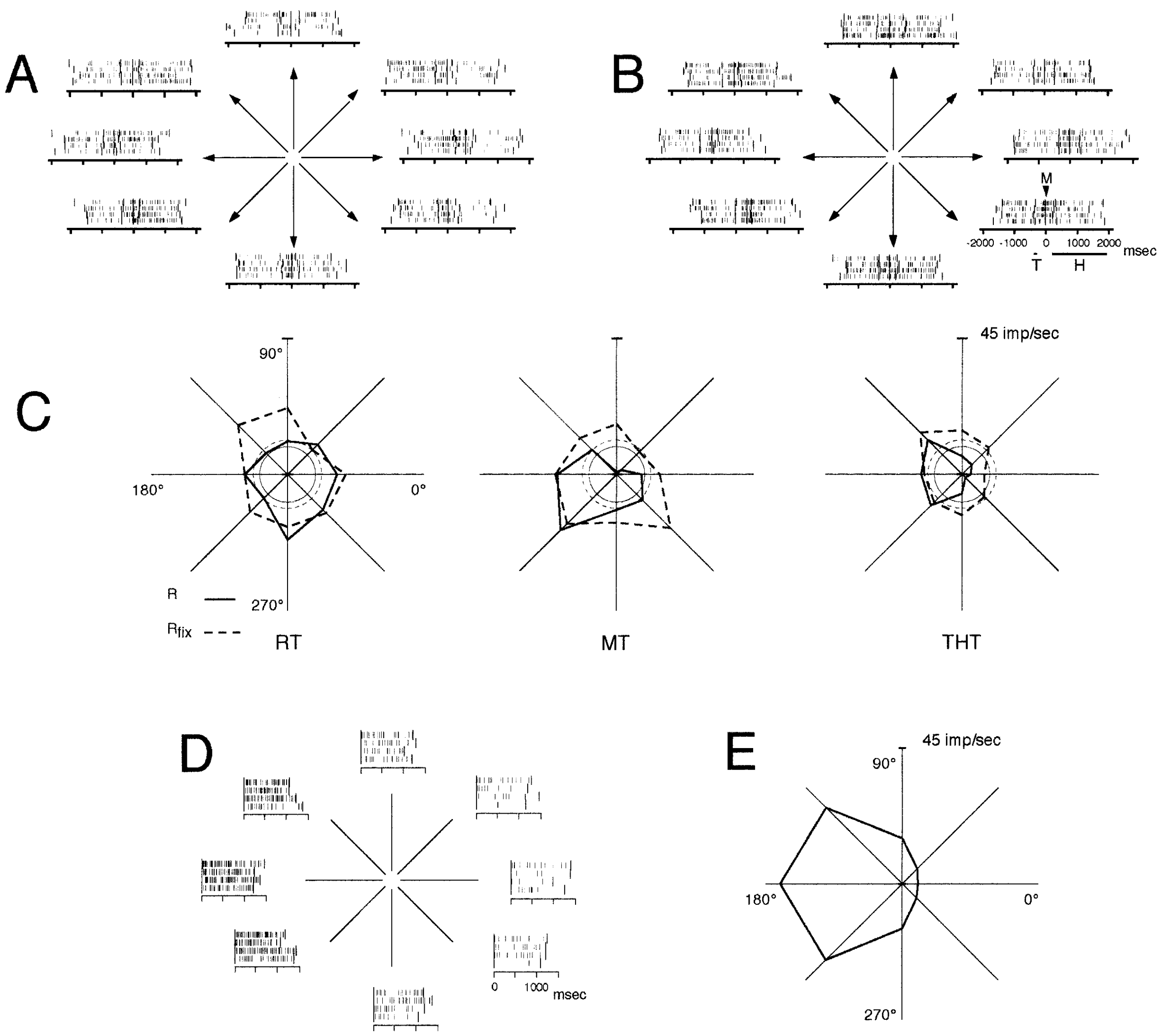

**Fig. 4** Impulse activity of a neuron studied in area 7m during the R (**A**) and $R_{fix}$ (**B**) tasks. Same neuron as in Fig. 3. Rasters of four replications for every movement directions (*arrows*) are aligned to movement onset (*M*). *Longer vertical bars* indicate, from left to right, beginning of the trial, target presentation (*T*), hand-movement onset (*M*), beginning and end of hand-target holding (*H*) time (*THT*). During this epoch, the hand remained immobile on the different peripheral targets, while the eyes where still fixating at the center of the workspace (**C**) in the $R_{fix}$ task, while both hand and eyes were on the target in the R task. Polar plots of impulse activity for different epochs of both task conditions (*continuous line* R, *interrupted lines* $R_{fix}$). For both task conditions, *circles* indicate frequency of discharge during center holding time, taken as control time; *RT* and *MT* indicate reaction and movement time of the hand, respectively. In **D** the rasters and, in **E**, the polar plots of the activity of this same neuron in the EPO task are shown. The positions of the rasters indicate the different locations in space where the animal was fixating during the eye-target holding time. These locations were the same that served as targets for both hand and eyes movements in the R task and for hand movement only in the $R_{fix}$ tasks. (Reproduced with permission from J Neurophysiol 77:1034–1038, 1997)

cess from retinal to body- and arm-centered coordinates, but as a parallel, iterative process, based on intra- and interareal interactions, which combines *all* available sensorimotor information to select the appropriate motor command. The "hybrid" nature of these operations is well supported by a large set of data coming from behavioral studies in humans (Soechting and Flanders 1989a,b; Flanders et al 1992; Carrozzo and Lacquaniti 1994; Gordon et al 1994; McIntyre et al 1997).

In particular, the analysis of the three-dimensional endpoint errors made by subjects who point to previously visible, memorized targets has provided the following results (McIntyre et al. 1997). Under conditions of dim light, which allow the vision of the hand during the movement, the axes of maximum variability of endpoint positions converge toward the head, indicating a viewer-centered reference frame. In darkness, on the other hand, the axes of maximum variability do not converge toward a unique origin, but their direction is affected by the starting position of the hand. Variability related to the starting position does not arise from errors in a serial transformation into a hand-to-target displacement vector. Instead, it probably depends on the addition of noise from parallel pro-

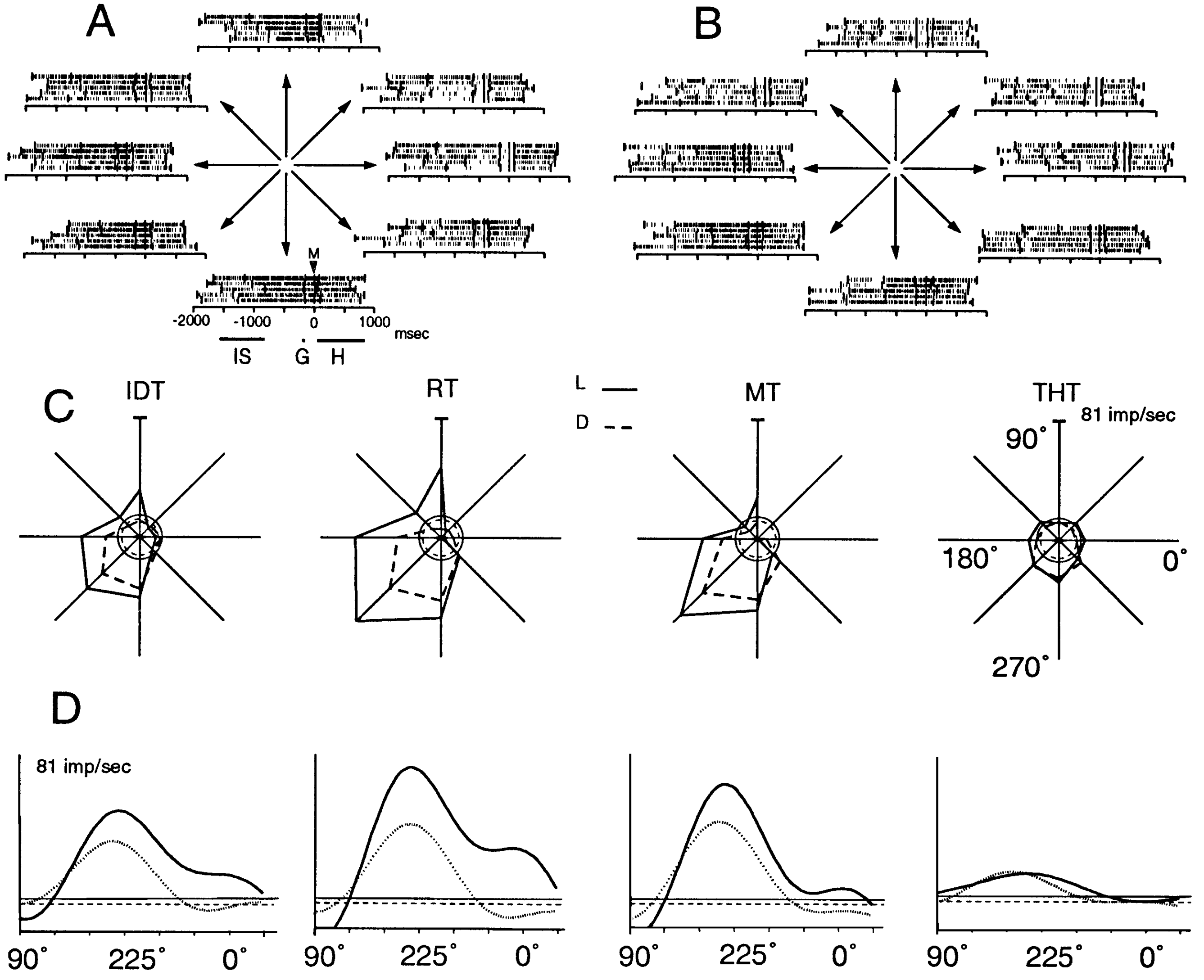

**Fig. 5** Impulse activity of a neuron studied in area V6A during the IDR task. Rasters of four replications for each movement direction (*arrows*) are aligned to movement onset (*M*) under both light (**A**) and dark (**B**) conditions. **C** Polar plots of impulse activity and **D** directional tuning curves across different epochs and task conditions (*continuous line* light, *interrupted lines* dark). In each plot, *horizontal lines* indicate average firing frequency during CHT. Directional tuning curves (Georgopoulos et al. 1982) and preferred directions of cells were determined by fitting the discrete firing rates measured at the eight target directions during the different epochs with a two-term harmonic Fourier series. Conventions and symbols as in Fig. 3

cesses converging on the final output stage. Dynamic components related to movement velocity (or higher time derivatives) might be added to the static component in the specification of the limb position. Encoding of hand displacement direction is thus more likely to be associated with movement planning or execution, rather than with the memory storage of target location. A dynamic motor command is computed from the memorized target position and proprioceptive information about current limb position, with a convergence of static and dynamic components to form the final motor command. It is reasonable to suggest that the CNS pre-computes and updates the dynamic command, as evidenced by priming experiments (Rosenbaum 1980), and that the update processing would be visible in the population of cells during the memory-delay period (Smyrnis et al. 1992).

## Cortical computation for reaching: a unified framework

Here we propose a framework that allows, in a coherent way, a combination of the anatomical and functional properties of the parietal and frontal areas with the computational demands of different forms of visuomanual coordination.

As seen, the computation for visually-guided reaching is distributed over a large reciprocal parieto-frontal network. Local computation in every part of this network is performed by discrete neuronal circuits (such as “cortical columns”: Mountcastle 1978, 1997), which relate different sets of inputs and outputs. The computational properties of these local circuits are determined by the architecture of the fronto-parietal network, based on three sets of axes. The functional properties of neurons are defined by their location on these axes.

## Cortico-cortical connections and axes of the network

The connections in the anatomical axes of the cortex define the *visual-to-somatic axis* (Fig. 6A,B). The computation is distributed on a visual-to-somatic gradient. Overlap of different functional properties along this gradient defines combinatorial domains where neurons integrate different retinal, gaze, arm, and muscle signals.

Neurons belonging to a same population can be differentiated along the *position-direction axis* (Fig. 6B). Neurons within each combinatorial domain are tuned for different position and direction (of arm, gaze, etc.). A combination of position and direction of arm or gaze can be viewed as representing 3D pathways for gaze or hand. Different populations of neurons coding 3D pathways for hand and gaze, which are related in external 3D space, have reinforced connections that identify processing routes along the visual-to-somatic axis.

The connections between parietal and frontal areas identify the *parieto-frontal axis* (Fig. 6B), where neurons with similar tuning have different temporal relationships with the signals relevant to reaching.

The underlying computation is performed by two sets of local networks, *matching units* and *condition units*. Matching units predict the sensory effects of motor commands and select the motor-command signals appropriate for matching sensory information available in the parieto-frontal flow. Successive learning steps generate different processing routes of matching units, which perform different visuo-motor transformations, such as visual tracking of the hand, reaching to foveated, or to non-foveated targets. Condition units selectively amplify matching operations compatible with the task demands on the fronto-parietal flow. Collective computation is due to a recruitment along the processing routes in both directions on each of the three axes of the network, resulting in a progressive match of retinal, gaze, arm, and muscle signals. The goal of this computation is to establish a spatial correspondence between the hand and the target position.

## Combinatorial domains: visual-to-somatic axis

The functional properties of reaching-related neurons within this network change along the tangential rostrocaudal domain of the cortex. In both parietal and frontal cortices, functional neuronal properties change gradually, thus defining a visual-to-somatic gradient whose spatial arrangement matches that of fronto-parietal association connections and is symmetrical with respect to the central sulcus (Johnson et al. 1996; Caminiti et al. 1996), as illustrated in Fig. 6. Extrinsic connections with sensory and motor systems, together with feed-forward or re-entrant connections, form a visual-to-somatic and a reciprocal so-

**Fig. 6A–C** Architecture of the cortical parieto-frontal network involved in reaching and combinatorial properties of neurons. **A** The cortical control of reaching is distributed in both frontal and parietal cortices. It requires the combination of retinal, gaze, hand, and muscle signals to move the hand toward the target. These four sets of sensorimotor signals are represented and distributed in large populations of cortical neurons on a visual-to-somatic gradient, symmetrical with respect to the central sulcus (*CS*) in both parietal and frontal cortex. These signals are schematized by different colors along the gradient. Retinal (*dark blue*): retinal information concerning object location and hand position in the visual field. Gaze (*light blue*): position and direction of gaze. Arm/hand (*green*): arm and hand position and movement direction. Muscles (*yellow*): spindle activity and muscle commands. The cortical computation for reaching is made by locally processing neuronal circuits across cortical layers, schematized as "cortical columns" and colored according to the type of information processed. Cortico-cortical connections in both parietal and frontal lobes relate columns tuned for similar sensory and motor signals and define combinatorial domains. Parieto-frontal connections can define similar combinatorial sensorimotor domains in related frontal and parietal columns, but with different timing and anticipatory properties (**B**). As shown in **A**, on the mesial and dorsolateral cortical surface, the different cortical areas involved in reaching and their set of connections define three combinatorial domains in the parietal cortex (*aP* anterior, *iP* intermediate, *pP* posterior) and three in the frontal motor and premotor areas (*aM* anterior, *iM* intermediate, *pM* posterior). Within these combinatorial domains, areas are also differentiated along a (medio-lateral) internal-external axis. Acronyms of cortical areas and sulci are as in Fig. 1 and 2. **B** The functional properties of each unit (shown by *circles*) depend upon its location with respect to the three axes of the network: (1) the *visual-to-somatic axis* displays four sets of sensorimotor information (muscles, arm/hand, gaze, retina); (2) *the parieto-frontal axis* contains four types of processing units (sensory, match, condition, motor); (3) *the position-direction axis* shows four *virtual 3D pathways* for hand (*left*) and gaze (*right*) with two initial position (*A, B*) and two directions for each position (*AC, AB, BA, BC*); equivalent 3D pathways are aligned horizontally. These pathways subserve the behavioral situations represented in **C**. *Black lines* indicate connections among units, curved *double lines* identify processing routes reinforced by learning. Information flows among matching and condition units through processing routes leading to the motor output, depending on available sensory information. **C** The three panels from top to bottom illustrate different processing routes that perform different visuo-motor transformations, such as visual tracking of hand trajectory (*top panel*), reaching to foveated targets (*middle panel*), or reaching to non-foveated targets (*bottom panel*). Bidirectional associations reinforced between units during each learning phase are represented with *lines*. Visual tracking of hand trajectory: pairs of columns tuned for similar positions and directions (*BA*) of hand and gaze are coactivated when gaze is attracted by the image of the hand; they generate anticipatory activities that predict the visual effect of somatomotor information and facilitate visual tracking or monitoring of the hand movement. Reaching to foveated targets: pairs of columns tuned for antiparallel directions of gaze and arm (*AB* and *BA*) are coactivated when the hand moves toward the fovea; they can generate directional information for hand movement toward the fixation point (reaching to foveated targets) and a directional information to move the gaze toward the hand (gazing at the hand). Reaching to peripheral targets: the network can accurately shift the attention to a virtual gaze position (at *C*). Pairs of columns tuned for convergent directions between virtual gaze and arm (*AC* and *BC*) are coactivated when the hand moves toward the attentional focus; they can generate directional information for hand movement toward a target that is not foveated. Conventions and symbols as in **B**. Only position-directions and visual-somatic axes are represented. Bidirectional association between units reinforced during each learning phase are represented with *lines*

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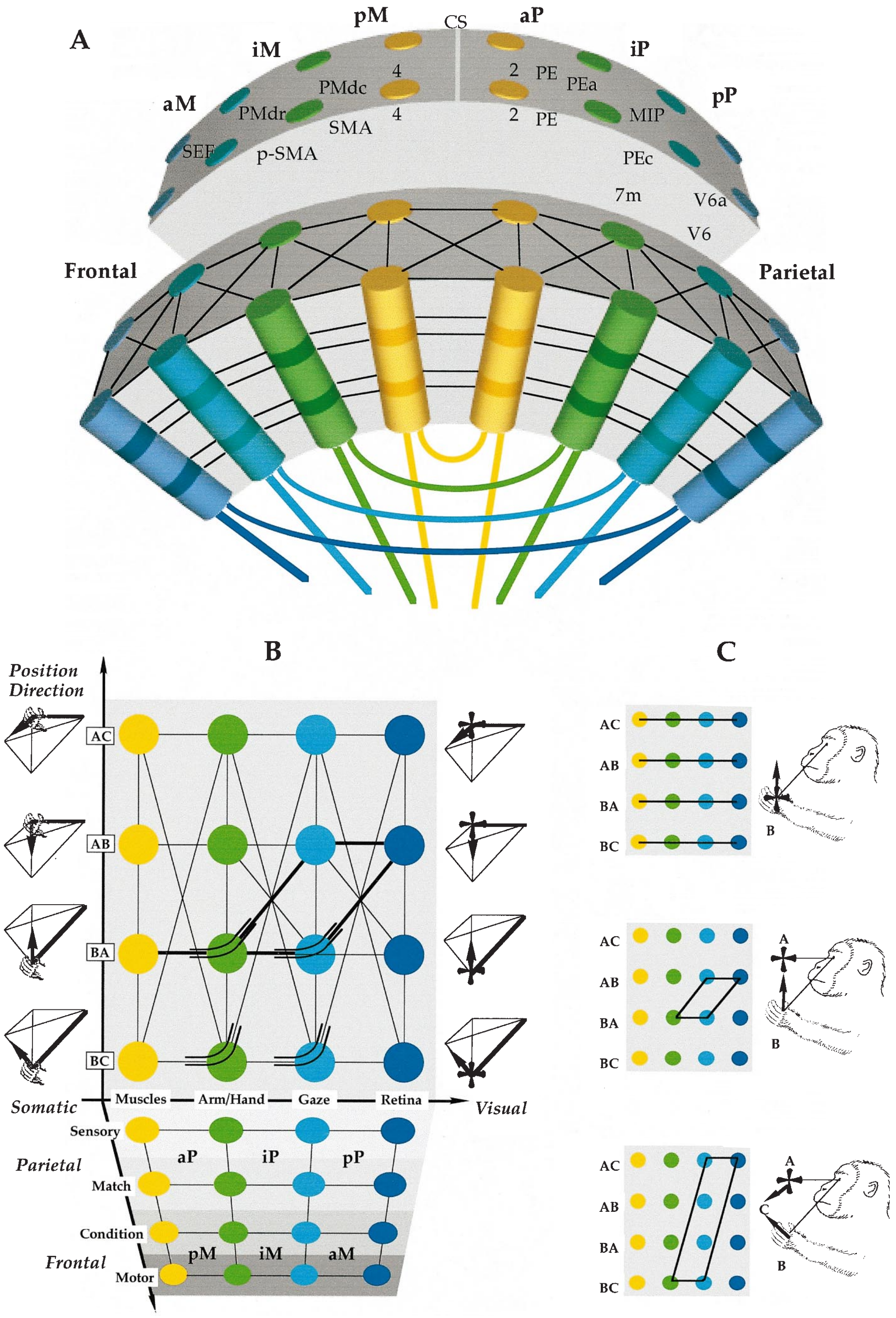

matic-to-visual processing pathway in both cortical regions. Different signals related to reaching are not confined within intra-area borders, but are distributed along this visual-to-somatic axis, both in the parietal and in the frontal lobe (Fig. 6): (1) neurons with dominant arm-movement related activity, and probably more linked to muscle output mechanisms, predominate in cortical regions flanking the central sulcus (Johnson et al. 1996), mainly in its rostral bank; these neurons also receive somatosensory signals about limb position; (2) neurons tuned to arm position in space are also abundant more rostrally in the frontal lobe and, symmetrically, more caudally in the superior parietal lobule (SPL; Johnson et al. 1996; Ferraina et al. 1997a,b); (3) neurons signaling the position or direction of gaze and for eye-movement related activity are distributed more caudally in the SPL (Galletti et al. 1996; Ferraina et al. 1997a) and rostrally in the frontal lobe (Boussaoud et al. 1993; Boussaoud 1995; Preuss et al. 1996); (4) neurons signaling for target location in retinal and/or extraretinal coordinates predominate in the SPL at the more caudal (V6A, V6; Galletti et al. 1991, 1996) and intermediate (MIP; Johnson et al. 1996) levels and in the more rostral part of the frontal lobe (Weinrich and Wise 1982; Weinrich et al. 1984; Tanné et al. 1995; Johnson et al. 1996).

This gradual change of properties results in regions of functional overlap, which define at least three combinatorial domains where the four main reach-related signals (retinal, gaze, arm position, muscle output) can be matched. These combinatorial domains are distributed, along the visual-to-somatic axis, in three reciprocally connected parietal and frontal regions (Fig. 6A): (1) in the posterior parietal region (pP, including areas V6 and V6a) and in the anterior frontal region (aM including PMdr and SEF), local networks relate positional and directional information on gaze and visual inputs on the retina; (2) in the intermediate parietal region (iP including areas 7m and MIP) and in the intermediate frontal zone (iM including PMdc), local networks relate arm and gaze positional and movement directional information; (3) in the anterior parietal region (aP), including areas PE, PEa, and 2, and in the posterior frontal lobe region (pM), including area 4, local networks relate two sets of information, positional and directional signals on the arm and information on muscle dynamics.

Gaze and arm-position signals play a unifying role within the entire parieto-frontal network. Neurons in most cortical areas of the network are, in fact, modulated by at least one of these two inputs. These properties reflect the underlying computation for different forms of visuomanual coordination: a subset of local circuits within the gradient is pre-selected, depending on gaze and arm position. This pre-selection process allows the learning and computation of stable relationships between visually-derived and somatomotor signals.

A similar somatic-to-visual gradient is observed in the mesial part of the frontal cortex with similar combinatorial domain: neurons in the SMA have similar sensory-motor combinatorial properties as in M1 (pM region), neurons in the pre-SMA are more similar to neurons in the PMdc (iM region), while neurons in the SEF combine arm and eye signals (aM region). Areas sharing similar combinatorial domains in mesial and dorsolateral frontal and parietal cortex are reciprocally connected.

## Population of neurons in the combinatorial domains: position/direction axis

Information within the same combinatorial domain is distributed over large populations of neurons tuned for different positions and directions (of arm, gaze, etc.). Reach-related neurons have both positional and directional properties. This has been observed in areas M1, PMd, PE, PEa, MIP, 7m, and V6A.

A combination of position and direction of gaze or arm can be viewed as representing 3D pathways for gaze or hand: (1) when a given position of gaze pre-selects a subset of local circuits, retinal signals on target position can be used to compute a possible next position for gaze, and the combination of both signals can be interpreted as a *virtual 3D pathway for gaze*; (2) when the position of the arm pre-selects a subset of local circuits, muscle signals are directly related to the next direction of hand movement, and the combination of both muscle and position signals defines a *virtual 3D pathway for the hand*.

The advantage of this simplified view is that virtual 3D-pathways for hand and gaze can be directly compared and related in 3D space, regardless of the combinatorial domain, as shown in Fig. 5B. When a gaze or arm movement is performed, the combinatorial domains in the parieto-frontal network favor local neural interactions. For example, a combinatorial domain in iP relates two columns that code, respectively, for hand and gaze virtual pathways, which are related in 3D space. The two columns are co-activated when the direction of the hand movement from its starting position points to the fixation point. An increased activity in the pair of columns trigger a local learning process, which increases the functional links between these two columns. These reinforced local networks are called *matching units*, since they are tuned to different sensory and motor signals congruent in 3D space, such as signals about hand movement toward the fixation point. After learning, these matching units can generate anticipatory activities: one column provides a directional somatomotor information to command hand movement in the direction of the actual fixation point; the other provides directional information to move the gaze towards the hand.

On the position-direction axis, lateral connections, both excitatory and inhibitory, shape the collective representation of position and direction in neuronal assemblies. Bi-directional excitatory and inhibitory connections reflect the similitude and differences of the 3D pathways for gaze and hand that are coded. Iterative interactions through these intrinsic connections can be viewed as a collective decision-making process; for example, the intrinsic connections in aM can store correlations in the output commands and thus force the population activity toward a common and coherent output, regardless of the initial set of inputs, which can convey contradictory and ambiguous information.

On the visual-to-somatic axis, matching units form bi-directional processing routes: matching units transform visual information in a prediction of a somatic event (for example, the future position of the hand) and transform somatic information in a prediction of a visual event (such as the future position of the hand on the retina). These processing units can compute the initial direction of hand movement toward the target (in the visual-to-somatic flow), monitor the direction of movement of the image of the hand on the retina (in the somatic-to-visual flow), and then correct hand trajectory during movement time, again in the visual-to-somatic direction.

## Anticipatory properties and the parieto-frontal axis

Neurons sharing the same combinatorial domain (visual-to-somatic axis) and having similar positional and directional tuning properties may have different temporal relationships with signals relevant to reaching. The reciprocal connections between parietal and frontal cortex are critical in shaping different anticipatory properties, which are intermediate between those of sensory inputs and of motor commands: functional properties are also differentiated along a parieto-frontal axis. Parietal and frontal columns, which are reciprocally connected, do not necessarily have the same cytoarchitectonic features (for example, they are granular in area 5 and agranular in area 4). In the parieto-frontal axis, this can be reflected in differential sensitivity to sensory inputs and relations to motor outputs, even if the related parietal and frontal columns share similar combinatorial domains. At least four sets of different temporal properties can be observed and interpreted as reflecting four sets of processing units on the parieto-frontal axis: (1) *sensory units*, time-locked to sensory signals: in the visual poles of the network, they process information about target location and hand trajectory in the visual field; in the somatic pole, they process somatic information about arm position and direction; (2) *motor units*, time-locked to motor events: in the somatic pole of the frontal lobe, they are more concerned with shaping the output motor command for the arm; in the visual poles of both parietal and frontal lobes, they can command eye movements; (3) *matching units* are influenced by both somatic and visual signals; they store sensorimotor congruences and have anticipatory properties; they are the main class of units in the iP; (4) *condition units*, closely related to matching units, have similar combinatorial domains and tuning properties along the visual-to-somatic axis, but differ in their sensitivity to reinforcement-related signals and, thus, to the task demands; they are represented in both parietal and frontal regions and are the main class of units in the iM.

As described above, matching units can store correlations between different sensory and motor signals, induced by arm or gaze movements, and can thus generate anticipatory activities about the sensory consequences of motor commands for hand or gaze. Matching units can store different sets of congruences, which identify, after learning, different processing routes subserving different visuomotor transformations.

Matching units that store the congruence between equivalent hand and gaze 3D virtual pathways (same initial position and direction) can compute the *visual tracking of the hand trajectory* (Fig. 6B,C top panel). Matching units that store congruences between hand and gaze 3D pathways with antiparallel directions can compute the direction of *reaching movements to foveated targets* (Fig. 6B,C middle panel). Matching units that store the congruence between convergent hand and gaze 3D pathways, can compute the direction of *reaching movement to non-foveated targets*. (Fig. 6B,C bottom panel). Different hand-movement directions use the same set of visually-derived information, i.e., movements toward the fixation point or toward a non-foveated target. At any given time, the selection of a target depends upon the task (in behaving monkey experiments, upon the training protocol), and thus upon the reinforcement contingencies. The task-dependent selection of a visual target and of a related motor command (for example, choose a non-foveated target rather than a foveated one) is produced by the interplay between matching units computing the visuomotor predictions (in the parietal-to-frontal information-processing flow) and another set of processing units, the condition units, which control sensorimotor flows compatible with the task demands (along the reciprocal fronto-to-parietal information flow). Thus, the activity of condition units should reflect not only positional and directional information, but also the arbitrary relationships imposed by the task-demand necessary to obtain a reinforcement. In contrast to matching units, which have stored congruences in the 3D space, condition units store reinforcement contingencies (for a neural net model, see Guigon et al. 1995).

Properties of condition units in this framework correspond to combinatorial and anticipatory properties of set-related reaching neurons (see Johnson et al. 1996; Wise et al. 1997). They are present not in a single area, but along functional gradients in both frontal and related parietal areas (Johnson et al. 1996). Set-related neuronal activity can both be selectively tuned to an arbitrary visual stimulus (signal-related activity) and, when a delay occurs or is imposed, selectively anticipate the upcoming movement direction in relation to the task-demand. Neural circuits anticipate the motor command on the basis of expected reinforcement signals, with a sustained activity during delays also when the visual positional and directional signals are no longer available (Smyrnis et al. 1992).

Collective computation in the network can be viewed as a progressive recruitment of the different groups of sensory, matching, condition, and motor units in both directions along the processing routes on the three axes of the network. This will result in a progressive match of retinal, gaze, arm, and muscle signals suitable for moving the hand toward the target. A timing of activation that strongly overlaps in different group of units is consistent with experimental results showing parallel recruitment of reach-related neurons in premotor, motor, and related parietal areas immediately after presentation of a visual stimulus serving as a target for arm movements (Johnson et al. 1996).

In this manuscript, we have tried to offer a unified framework for interpreting, in a coherent manner, different sets of anatomical, physiological, and behavioral data concerning various forms of visuomanual coordination, such as reaching to forveated or non-foveated targets and visual tracking of hand movement. In all such cases, arm movement is guided, although in a different way, by visual stimuli. Many arm movements are generated, however, in absence of sensory signals, as a result of an internal drive or decision to move. The present framework can be easily extended to these internally generated movements by assuming that several cortical areas, which share the same combinatorial domain along the (rostro-caudal) visual-to-somatic axis, can further be differentiated along a (medio-lateral) "internal-external" axis, depending on whether the computation for arm movement refers to externally or internally driven events. The anatomical and functional properties of the cortical areas lying in the mesial wall of the hemisphere are compatible with this interpretation. For instance, supplementary and cingulate motor areas, which are connected to motor cortex, are sensitive to internal signals that can be important for self-initiated movements and retrieval of specific temporal sequences of memorized movements. This network could be preferentially involved when arm/hand movements are internally-driven: circuits in this network would perform an internal match between motor commands and information related to previous sensory or motor events in the sequence. They could thus relate successive motor events in a precise manner, based on positional and directional information, without intervention of new external sensory signals. Thus, within each combinatorial domain, we can superimpose, to the anatomical rostro-caudal axis, a functional internal-external axis. Along the tangential domain of the cortex, neurons have a differential sensitivity to these sets of signals. Accordingly, along these two axes of the network, local circuits can either match external sensory information available in real time and motor commands, or internally match motor commands and information generated in the network, based on storage of sequences of previous motor events.

## A positive image of optic ataxia

The anatomical substrata and functional mechanisms underlying visually-guided arm movements, as outlined in this article, offer a positive image of optic ataxia. It has been long known that humans (Balint 1909; Holmes 1918; Riddoch 1935; Brain 1941; Hécaen and de Ajuriaguerra 1954; Corin and Bender 1972; Ratcliff and Davies-Jones 1972; Rondot et al. 1977; Levine et al. 1978; Damasio and Benton 1979; Perenin and Vighetto 1988; see De Renzi 1982; Caminiti et al. 1996 for reviews) with parietal lesions display a severe and persistent inaccuracy in directing the movements of the limb toward a visual target. "Optic ataxia" was first described by Balint (1909) in a patient with parietal lesion and free from visual, somatosensory, or motor deficits. It was interpreted as the result of a defective control of movement by vision, due to the lack of visual input to the motor areas.

Optic ataxia is today recognized as a specific entity (see Garcin et al. 1967; Perenin and Vighetto 1988 for a discussion). Since it occurs in absence of sensory impairments, it has been suggested to remane it "visuomotor ataxia" (Rondot et al. 1977). In their cases of "pure optic ataxia", from lesions centered around the intraparietal sulcus and in the superior parietal lobule, Perenin and Vighetto (1988) have observed that the defective control of reaching includes not only the transport component of the movement, but also the shaping of the proper configuration of the hand necessary for a variety of manual tasks. Unilateral involvement of the SPL has been described in cases of optic ataxia by other authors (Ratcliff and Davies-Jones 1972; Levine et al. 1978; Auerbach and Alexander 1981). It must be stressed that the "ataxie optique" of Garcin et al. (1967) and the "defective visual localization" described by Ratcliff and Davies-Jones (1972) are disturbances of reaching in the contralateral peripheral visual field.

Optic ataxia has traditionally been interpreted as a disconnection syndrome. The functional architecture of the parieto-frontal network suggest that optic or visuomotor ataxia is better interpreted as a failure of the progressive matching operation among directional and positional retinal-, gaze-, arm-, and muscle-related signals; in other words, as the result of the breakdown of the combinatorial mechanisms occurring in the parietal segment of the parieto-frontal network. This makes impossible, at very early stage, the multisensory and motor fusion necessary for visually-guided reaching, while leaving unaffected the cortical motor system controlling the arm when movement is not dependent on visual information. This combinatorial breakdown would result in a permanent failure to compute the spatial correspondence between hand and target position, which is the problem to be solved for any successful reaching movement.

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