

Eye–Hand Coordination during Reaching. I. Anatomical Relationships between Parietal and Frontal Cortex

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The anatomical and physiological substrata of eye–hand coordination during reaching were studied through combined anatomical and physiological techniques. The association connections of parietal areas V6A and PEc, and those of dorso-rostral (F7) and dorso-caudal (F2) premotor cortex were studied in monkeys, after physiological characterization of the parietal regions where retrograde tracers were injected. The results show that parieto-occipital area V6A is reciprocally connected with F7, and receives a smaller projection from F2. Local parietal projections to V6A arise from areas MIP and, to a lesser extent, 7m, PEa and PEc. On the contrary, parietal area PEc is strongly and reciprocally connected with the part of F2 located close to the pre-central dimple (pre-CD). Local parietal projections to PEc come from a distributed network, including PEa, MIP, PEci and, to a lesser extent, 7m, V6A, 7a and MST. Premotor area F7 receives parietal projections mainly from 7m and V6A, and local frontal projections mainly from F2. On the contrary, premotor area F2 in the pre-CD zone receives parietal inputs from PEc and, to a lesser extent, PEci, while in the peri-arcuate zone F2 receives parietal projections from PEa and MIP. Local frontal projections to F2 pre-CD mostly stem from F4, and, to a lesser extent, from F7 and F3, and CMA_d; those addressed to peri-arcuate zone of F2 arise mainly from F5 and, to a lesser extent, from F7, F4, dorsal (CMA_d) and ventral (CMA_v) cingulate motor areas, pre-supplementary (F6) and supplementary (F3) motor areas. The distribution of association cells in both frontal and parietal cortex was characterized through a spectral analysis that revealed an arrangement of these cells in the form of bands, composed of cell clusters, or 'columns'. The reciprocal connections linking parietal and frontal cortex might explain the presence of visually related and eye-position signals in premotor cortex, as well as the influence of information about arm position and movement direction in V6A and PEc. The association connections identified in this study might carry sensory as well as motor information that presumably provides a basis for a re-entrant signaling. This might be necessary to match retinal-, eye- and hand-related information underlying eye–hand coordination during reaching.

Introduction

Understanding the cortical mechanisms of the visual control of movement requires knowledge not only of the functional properties of neurons within different cortical areas, but also of the anatomical relationships among these areas.

In recent years, considerable attention has been devoted to the superior parietal areas, now regarded as the main sources of visual input to the frontal lobe (Cavada and Goldman-Rakic, 1989a,b; Johnson *et al.*, 1993, 1996; Tanné *et al.*, 1995; Matelli *et al.*, 1998; Shipp *et al.*, 1998). The work has been the subject of several reviews (Caminiti *et al.*, 1996, 1998; Wise *et al.*, 1997; Battaglia-Mayer *et al.*, 1998). Among the areas, the cortex of the rostral bank of the parieto-occipital sulcus [area PO (Colby *et al.*,

1988)] has recently been subdivided (Galletti *et al.*, 1996) into a dorsal area, V6A [visual area 6A, area 19 (part)], and a ventral one, V6. A visuomotor role has been attributed to V6A, based both on its pattern of association connections (Matelli *et al.*, 1998; Shipp *et al.*, 1998; Caminiti *et al.*, 1999), and on the observation that neurons in this area process not only visual and oculomotor signals, but also arm-related information (Galletti *et al.*, 1997; Johnson *et al.*, 1997; Battaglia-Mayer *et al.*, 1998, 2000; Caminiti *et al.*, 1998, 1999).

Very little is known about the anatomical and functional organization of another parietal area, PEc [parietal area PEc; area 5 (part)]. In fact, only the description of the efferent projections of PEc to frontal (Petrides and Pandya, 1984; Johnson *et al.*, 1993, 1996; Tanné *et al.*, 1995; Matelli *et al.*, 1998) and parietal (Pandya and Seltzer, 1982) cortex is available in the literature, together with preliminary reports concerning its functional properties (Ferraina *et al.*, 2001; Squatrito *et al.*, 2001).

This study was aimed at elucidating the pattern of association connections between areas V6A and PEc, and some premotor areas, such as F7 [rostral part of dorsal premotor area; PM_{dr}, area 6a β (part)] and F2 [caudal part of dorsal premotor area; PM_{dc}, area 6a α (part)], considered as the main sources of visuomotor signals to motor cortex. The operations occurring in these parietal and frontal regions may be regarded as potential early and late stages, respectively, of a unique information processing flow leading from vision to movement. Their interplay with frontal cortex and with the many other reach-related regions so far described in parietal cortex can only be based on signals carried by a network of reciprocal association connections, those that are the subject of this study.

To this goal, different anatomical tracers were injected, in different combinations, in area V6A, PEc, rostral (PM_{dr}, F7) and caudal (PM_{dc}, F2) parts of dorsal premotor cortex (Matelli *et al.*, 1985; Barbas and Pandya, 1987). In the parietal cortex, tracers injections were made in regions that were first characterized physiologically in behaving monkeys (Caminiti *et al.*, 1999; Battaglia-Mayer *et al.*, 2000, 2001), as related to visuo-spatial processing, coding of eye and arm movement direction and position in space.

Materials and Methods

Animals

Three rhesus monkeys (*Macaca mulatta*; body weights 3.7, 3.5 and 4.6 kg) were used in this study. In two cases (NI and ME), the parietal injection sites were characterized physiologically (Table 1), as described in a companion paper (Battaglia-Mayer *et al.*, 2001).

Anatomical Studies

The animals were anaesthetized with sodium pentobarbital (25 mg/kg;

Table 1
Retrograde tracer injections and physiological characterization

Animal	Hemisphere	Injections	Tracer	Number × amount	Survival (days)	Physiology (V6A, PEc)
Case NI	left	F7	DY	4 × 0.1 μl	20	– visual fixation tasks – reaching tasks – saccadic task
		F2 pa	FB	4 × 0.1 μl		
		V6A	FR	4 × 0.15 μl		
Case ME	right	F2 pre-CD	FB	4 × 0.2 μl	15	
		PEc	FR	6 × 0.2 μl		
Case BO	left	PEc rostral	FB	1 × 0.15 μl	15	
		PEc caudal	DY	1 × 0.15 μl		

F2 pa = peri-arcuate zone of F2; area 6ax (part).

i.v.) and the dura was opened. The fluorescent tracers were injected with a Hamilton micro syringe, according to the scheme of Table 1. In case NI, injections of Fluoro-Ruby (FR; Molecular Probe; 10% in saline) were made at 2 and 4 mm depth, in the dorsal part of the rostral bank of the parieto-occipital sulcus (POS; Fig. 2, insets a–c), in area V6A. Injections of Fast blue (FB; Illing; 2% in saline) in F2 (Fig. 2, insets d–g), and Dyamidino yellow (DY; Illing, 2% in saline) in F7 (Fig. 1C,D; Fig. 2, insets h–k) were made at ~1.5 mm depths. In case ME, FR was injected at 1.5 mm depth in the flat exposed part of the posterior pole of the SPL (superior parietal lobule; Fig. 1A; Fig. 3, insets a–c), in area PEc, while FB was injected in the cortex just lateral to the pre-central dimple (pre-CD, Fig. 1E,F; Fig. 3, insets d–g), in area F2. In case BO, FB and DY were respectively injected in the rostral and caudal parts of area PEc, at a depth of ~1.5 mm (Fig. 4, insets a–f). The dura was then sutured closed and the animals returned to their cages for the survival period (Table 1), at the end of which they were anaesthetized (sodium pentobarbital, 50 mg/kg; i.v.) and perfused with 0.9% saline followed by 4% Para formaldehyde in 0.1 M phosphate buffer (pH 7.2). After removal, the brains were post-fixed in the same fixative and then placed in a solution of 30% buffered sucrose until they sank. The brain blocks were cut in the coronal plane. One section (80 μm thick) was mounted on gelatin-coated slides, air-dried and cover-slipped for fluorescent labeling analysis. The adjacent section (40 μm thick) was stained with thionin (0.025%) for cytoarchitectonic analysis. Two additional series (40 μm thick) were used for immunohistochemical analyses, which are not described in this study. The borders of different frontal and parietal areas, as illustrated in the summary Figure 7, were drawn on the histological material, using the criteria defined in the literature (Pandya and Seltzer, 1982; Matelli *et al.*, 1985, 1991, 1998; Barbas and Pandya, 1987; Galletti *et al.*, 1996; Johnson *et al.*, 1996; Picard and Strick, 1996).

Data Analysis

For each animal, a series of coronal sections at 400 μm intervals was plotted. The X and Y coordinates of labeled neurons, injection sites of tracers, microelectrode penetrations, and other landmarks of interest were plotted through a computer-microscope (Glaser and Van der Loos, 1965). Cores and halos at the injection sites were classified as described in the literature (Bentivoglio *et al.*, 1980; Bharos *et al.*, 1981; Keizer *et al.*, 1983; Schmued *et al.*, 1990). Two-dimensional flattened maps of the tangential distribution of retrogradely labeled neurons in frontal and parietal cortices were generated as detailed elsewhere (Johnson *et al.*, 1989, 1996). Briefly, labeled cells from each section were 'projected' onto a reference line running parallel to the pial surface at a depth constantly proportional to the distance between this and the white matter. This projection occurred along radial segments mimicking the columnar arrangement of cell bodies in the cortex. The reference line was then flattened and divided into 160 μm wide bins. The sections were finally aligned on a common reference point, and the number of cells contained in each bin was expressed through a color-coded scale. The palette used saturated when cell count in any given bin exceeded by 50% the maximum number of cells observed throughout all the bins of the map.

Spectral and Coherency Analyses

The objective of the quantitative analysis was to quantify the periodic

nature of the fluctuation in cell densities evident in the histological sections. For this, a standard spectral analysis was performed (Johnson *et al.*, 1989). The binned cell counts along the medio-lateral dimension of each coronal section were used for this analysis. Histograms of cell numbers (bin size 200 μm) versus tangential location were computed for the different populations of association cells labeled in this study. This bin size was appropriate to investigate fluctuations in cell number with at least peak-to-peak distance of around 1 mm. The multiple-labeling strategy adopted in this study allowed not only the spectral analysis of the different populations of labeled cells, but also the analysis of their mutual relationships in the cortex. The coherency is a measure, in the frequency domain, of the similarity of two distributions in space. The phase is a measure of shift between two sinusoids of equal frequency. When in a given band of frequency the periodic components of two distributions have similar phases, the coherency value approach 1. This indicates a linear dependency between the two series, i.e. their shapes are very similar. On the contrary, if the phases are not coherent but vary widely, the coherency value in that range of frequency is close to zero. Therefore, for high values of coherency, the phase between two distributions expresses how they are arranged in space in relation to one another. For low values of coherency, the phase is meaningless.

The results of the coherency analysis were thus expressed in two ways: coherency and phase as a function of Fourier frequency. Since we were interested in the portions of the frequency domain that exhibit high values of coherency, we did use the squared coherency, which varied between 0 and 1, while the phase varied between $-\pi$ and π . Therefore, phase relationships between different distributions were studied only for coherency values greater than 0.2.

The program 1T of the BMDP statistical package (Statistical Software, Berkeley, CA, USA) was used to perform the spectral and coherency analyses (Bloomfield, 2000).

Results

Tangential Distribution of Parietal Cells Projecting to Parietal Cortex

Parietal Cells Projecting to V6A

The injections of FR (Table 1, Fig. 2) were all in the cortex of the rostral bank of the POS and around its crown. Rostro-caudally, the central cores and halos of diffusion involved ~5 mm of cortex, from 2 to 5 mm depth within the rostral bank of the POS. The results obtained showed that a major projection to V6A arose from area MIP (medial intraparietal; Fig. 2: 3), located in the cortex of the posterior part of the medial bank of the intraparietal sulcus (IPS). Other more discrete inputs to V6A originated from area 7m (mesial part of area 7; area PGm; Fig. 2: 2–7), in the cortex of the medial wall of the parietal lobe, from PEa [parietal area PEa; area 5 (part), Fig. 2: 7–9], in the rostral part of the medial bank of the IPS, and, to a lesser extent, from PEc (Fig. 2: 2–3), in the posterior pole of the SPL. Smaller inputs were observed from VIP (ventral intraparietal area; Fig. 2: 3–8), around the fundus of the IPS, PE, in the exposed part of the SPL (not shown in Fig. 2), PEci (parietal area PEci (cingulate); Fig. 2: 5), in both banks of the caudal tip of the cingulate sulcus (CiS) and LIP (lateral intraparietal area), in the lateral bank of the IPS (Fig. 2: 3–4).

Parietal Cells Projecting to PEc

Information on this projection comes from two different cases. In the first, one single tracer was injected throughout the entire extent of PEc (Table 1, case ME). The injections of FR (Fig. 3) were all in the exposed cortex of the caudal part of the SPL. The halos of tracer injections involved ~4 mm of cortex rostro-caudally, and ~6 mm medio-laterally, with some diffusion into the underlying white matter. Retrogradely labeled cells were

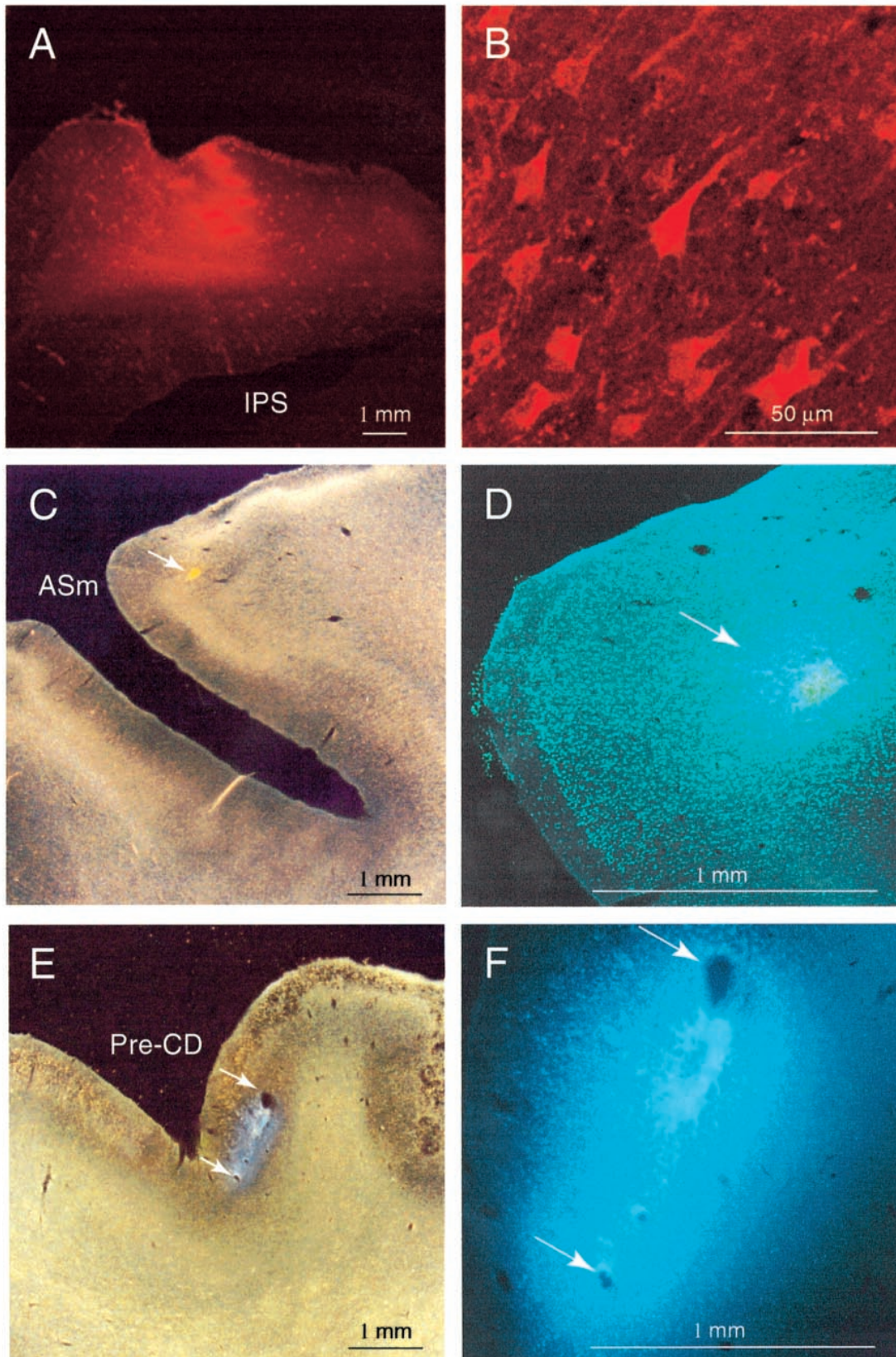


Figure 1. Photomicrographic evidence of injections sites of tracers in areas PFC (A, FR), F7 (C–D, DY), F2 (E–F, FB) and of retrogradely labeled cells (B, FR) in area MIP. (C)–(D) and (E)–(F) show the same injection site at two different magnifications.

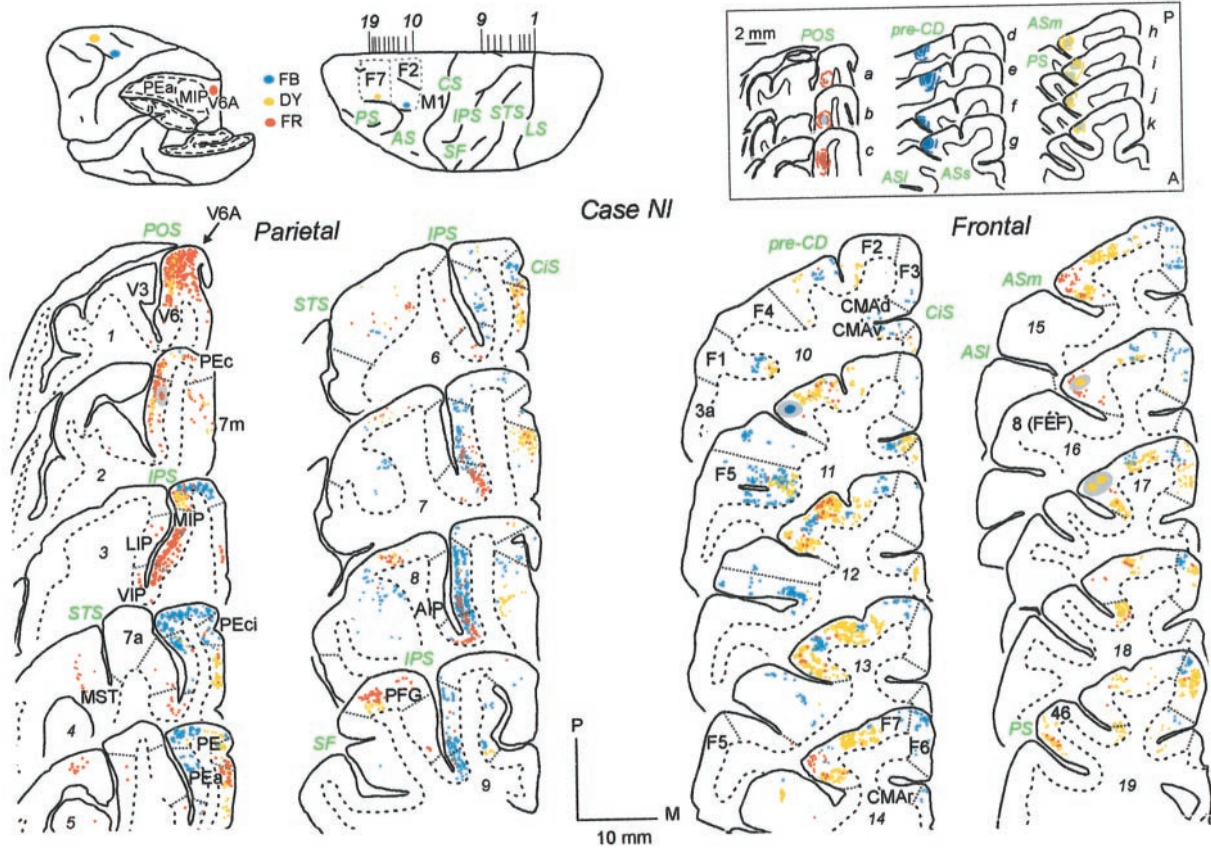


Figure 2. Distribution of retrogradely labeled parietal and frontal cells projecting to V6A (red dots), F7 (yellow dots) and peri-arcuate F2 (blue dots), after injections of FR (red oval in V6A), DY (yellow oval in F7) and FB (blue oval in F2), as indicated in the brain figurine (1–19). Details of the central core (filled area) and halos (gray area and white area delimited by a dashed line) of diffusion of FR (red area), FB (blue area) and DY (yellow area) are shown both on individual sections and in the inset (a–k) of the injection sites at different rostro-caudal levels of parieto-occipital and frontal cortex. In each section, continuous and interrupted lines indicate, respectively, the cortical surface and the border between layer VI and white matter. Architectonic borders, when possible, are indicated by dotted lines extending from the cortical surface to layer VI. The name of each cortical area is indicated only in the first section where it can be detected, while its boundaries are drawn throughout all sections in which it is present. P indicates posterior, M indicates medial.

mostly found in areas PEa (Fig. 3: 5–9), MIP (Fig. 3: 2–4) and PEci (Fig. 3: 5–9). Additional smaller projections arose from 7a (parietal area 7a; area PG; Fig. 3: 3–6), MST (medial superior temporal area; Fig. 3: 4–7), V6A (Fig. 3: 1), 7m (Fig. 3: 3–4) and V4 (visual area 4; Fig. 3: 1–3).

In the second case (Table 1, case BO), two different tracers were injected (Fig. 4), one (FB) in the rostral, the other (DY) in the caudal part of PEc. The FB injections rostro-caudally spread over ~1.2 mm of cortex; medio-laterally they extended for ~3.5 mm over the exposed flat part of PEc. Rostrally, the outer halo touched the dorsal part of the caudal tip of the CiS (area PEci). The halo of DY injections extended 1 mm rostro-caudally, and 3.3 mm medio-laterally, on the exposed part of the cortex. Parietal cells projecting to rostral PEc were most numerous in PEci (Fig. 4: 4–9), abundant in PE (Fig. 4: 7–8). Smaller proportions of labeled cells were observed in MIP (Fig. 4: 4–6), and 7m (Fig. 4: 5). Parietal cells projecting to caudal PEc were instead more numerous in PEa (Fig. 4: 7–10), with a smaller contribution offered by 7m and MIP (Fig. 4: 3–6). Discrete numbers of labeled cells were also observed in areas V6a, VIP and in the cortex of the exposed flat part of the IPL (inferior parietal lobule), areas PFG [parietal area PFG, area 7 (part)] and 7a. When compared with the distribution of the cells projecting to rostral PEc, their proportion decreased in PEci and PE, and increased in PEa.

Tangential Distribution of Parietal Cells Projecting to Dorsal Premotor Cortex

Parietal Cells Projecting to F7

In case NI, the lateral labeling of the injections of DY (Table 1) extended for ~6.4 mm rostro-caudally, around the crown of the medial limb of the arcuate sulcus (ASm; Fig. 2: 16–17), and in the upper part of its bank. Injections were within F7. In the parietal cortex, the highest number of cells labeled by DY was found in area 7m (Fig. 2: 4–8). Area V6A also contained a significant number of back-filled cells (Fig. 2: 1–2). Smaller projections originated from 7a (Fig. 2: 6–8), PEci (Fig. 2: 5–6), MIP (Fig. 2: 3–4) and PEc (Fig. 2: 2–3).

Parietal Cells Projecting to F2

Area F2 received FB injections in two different parts. In one animal (Table 1, case NI), the cores and halos of diffusion of FB were all contained within F2 (Fig. 2), mostly in its peri-arcuate part, in a region that extended rostro-caudally for ~6 mm, up to the spur of the AS. Retrogradely labeled cells were mostly found in area PEa (Fig. 2: 5–9), MIP (Fig. 2: 3–4); few were in areas PEc (Fig. 2: 3–4), PEci (Fig. 2: 4–6), PFG (not shown in Fig. 2) and VIP (Fig. 2: 6–9).

In a second animal (Table 1, case ME), the cores and the halos

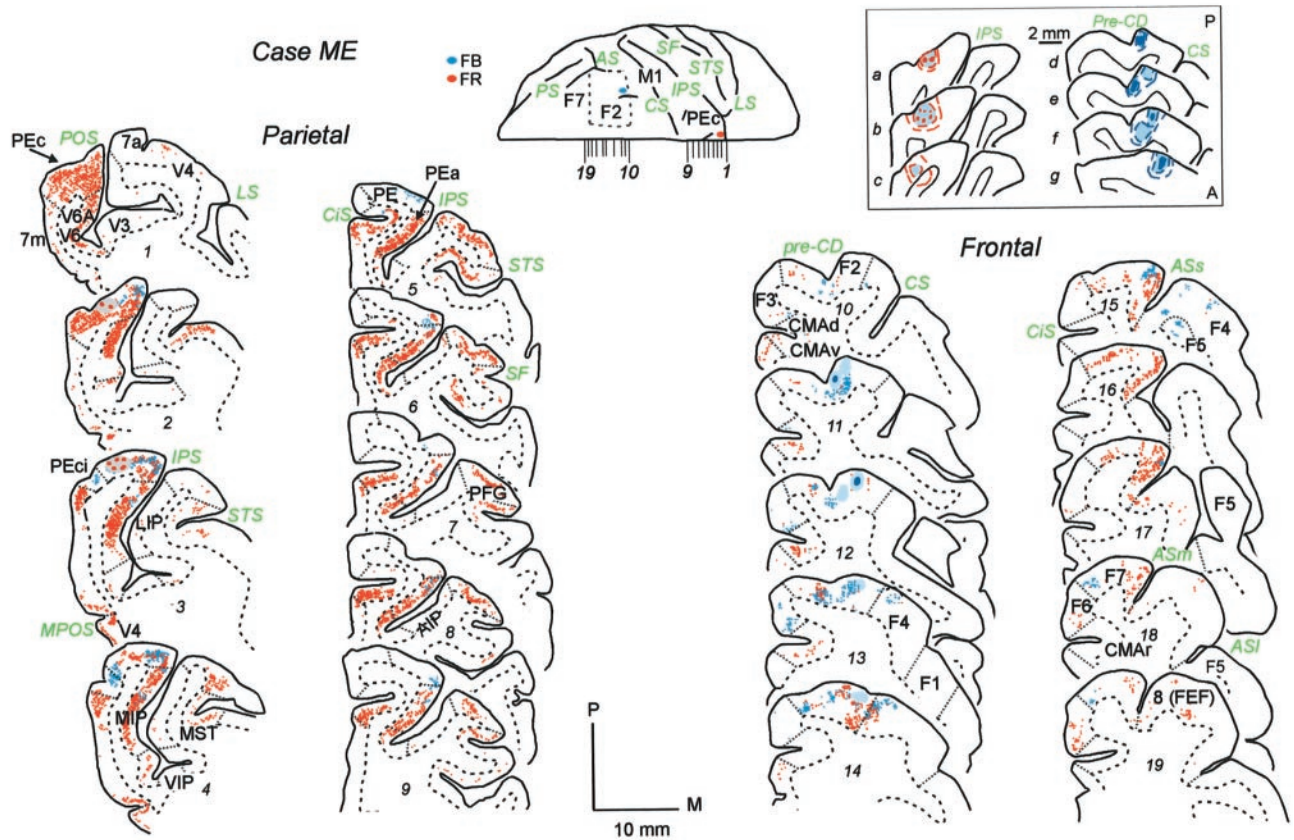


Figure 3. Distribution of retrogradely labeled parietal and frontal cells projecting to PEc (red dots), and F2 pre-CD (blue dots), after injections of FR (red oval in PEc), and FB (blue oval in F2), as indicated in the brain figurine (1–19). Details of the central core and halos of diffusion of FR and FB are shown both on individual sections and in the inset (a–g) of the injection sites at different antero-posterior (AP) levels of parietal and frontal cortex. Conventions and symbols as in Figure 2.

were all lateral and close to the pre-CD (Fig. 3). The halos extended rostro-caudally for ~5.5 mm of cortex, medio-laterally within a strip of ~2.7 mm. While three injections were all contained within the lateral bank of the pre-CD, the fourth one was just anterior and slightly ventral to it. Retrogradely labeled cells were mostly found in area PEc (Fig. 3: 2–4). Another substantial, although smaller, projection originated from PEci (Fig. 3: 3–4). Minor projections were seen from PEa (Fig. 3: 7–9), PE (Fig. 3: 5–7) and MIP (Fig. 3: 3–4).

Tangential Distribution of Frontal Cells Projecting to Parietal Cortex

Frontal Cells Projecting to V6A

In the frontal lobe (case ND), the highest proportion of labeled cells was found in F7, where they occupied a region including the exposed part of dorso-lateral frontal cortex, up to the crown and bank of the medial limb of the AS (Fig. 2: 14–19); a substantial, although smaller, projection arose from F2 (Fig. 2: 11–13). Projections were scant from F6 [pre-supplementary motor area; pre-SMA, area 6a β (part); Fig. 2: 17–19].

Frontal Cells Projecting to PEc

Information on this projection comes from two different cases. In the first, one single tracer was injected throughout the entire extent of PEc (Table 1, case ME). In the second case (Table 1, case BO), two different tracers were injected, one (FB) in the

rostral, the other (DY) in the caudal part of PEc. For both cases, the description of the injection sites has been given above. When the entire PEc was injected, labeled cells were almost exclusively found in F2 (Fig. 3: 10–17), in a region including the flat exposed part of dorso-lateral frontal cortex and extending up to the cortex of the medial bank of the medial limb of the AS. The cingulate motor area ventral (CMAv; area 23c) (Dum and Strick, 1991; Picard and Strick 1996; Fig. 3: 10–13), area 46 (Walker, 1940; Preuss and Goldman-Rakic, 1991, not shown in Fig. 3), F7 (Fig. 3: 18–19) and F4 [caudal part of ventral premotor area; PMvc, area 4c (part); Fig. 3: 13–15] contained few labeled cells. Cells projecting to the rostral part of PEc were mostly found in F2 (Fig. 4: 11–17), they were scant in F7 (Fig. 4: 18–20), F6 (Fig. 4: 18–20), CMAAd (dorsal cingulate motor area; area 6c; Fig. 4: 13–16) and F3 (supplementary motor area; SMA, area 6a α ; Fig. 4: 15–16). The overall tangential distribution of labeled cells projecting to the caudal part of PEc (Fig. 4) was similar to that just described. In addition, frontal cells projecting to the caudal part of PEc were always located laterally to those projecting to its rostral part (Fig. 4).

Tangential Distribution of Frontal Cells Projecting to Frontal Cortex

Frontal Cells Projecting to F7

The major input to F7 originated from F2 (Fig. 2: 10–13), both in the exposed dorso-lateral frontal cortex and in the medial bank of

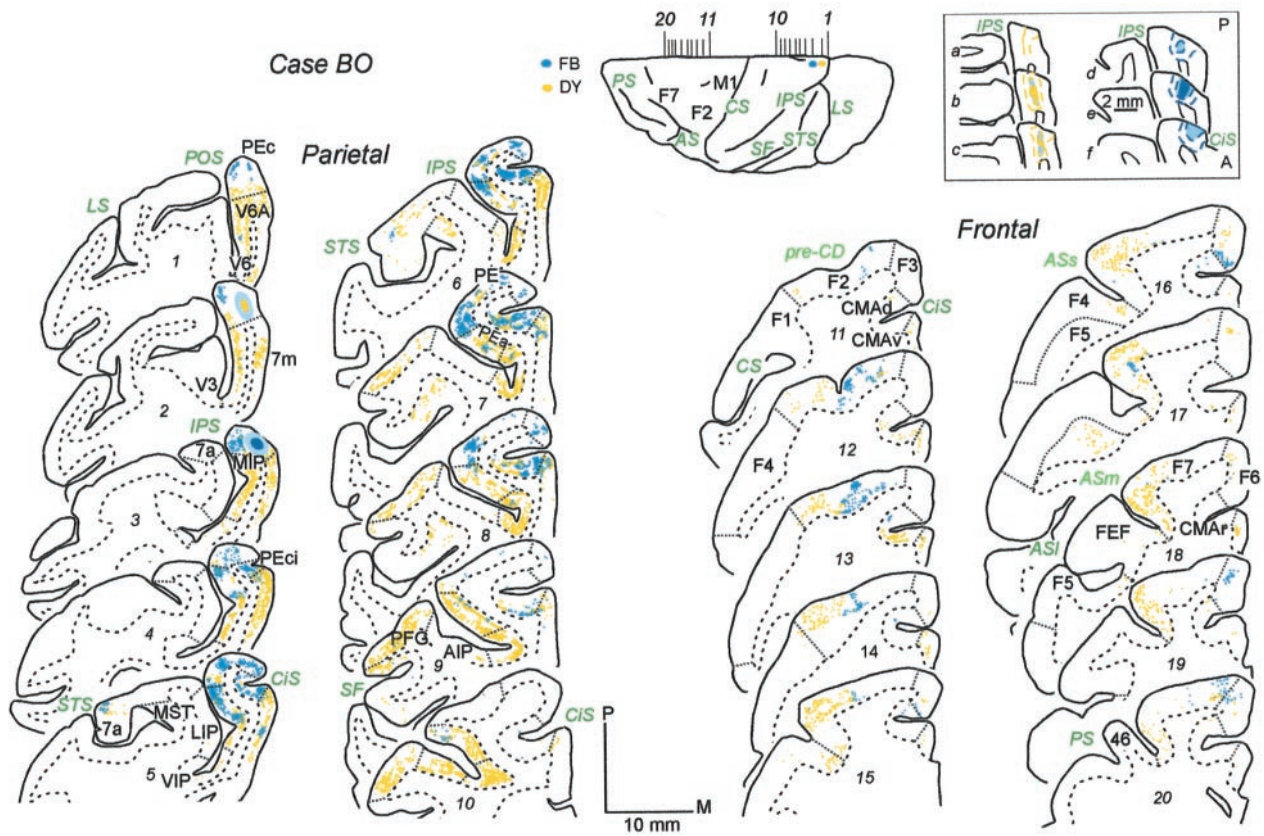


Figure 4. Distribution of retrogradely labeled parietal and frontal cells projecting to the rostral (blue dots) and caudal (yellow dots) parts of PEc (blue and yellow ovals in PEc), after injections of FB and DY in the rostral and caudal PEc, respectively, as indicated in the brain figurine (1–20). Details of the central core and halos of diffusion of DY and FB are shown both on individual sections and in the inset of the injection sites at six different rostro-caudal levels (a–f) of parietal cortex. Conventions and symbols as in Figure 2.

the medial limb of the AS. Labeled cells were also found in F6 (Fig. 2: 16–19) and, to a lesser extent, in area F5 [rostral part of ventral premotor area; PMvr, area 6α (part); Fig. 2: 11–12], in the cortex of the caudal bank of the lateral limb of the AS. Few labeled neurons were also found in CMAv (Fig. 2: 10–11), in the cortex of the ventral bank of the CiS.

Frontal Cells Projecting to F2

In one animal (Table 1, case NI), area F2 received FB injections mostly in its ventral part, while in a second animal (Table 1, case ME) injections were all lateral and close to the pre-CD, as detailed earlier on in this manuscript. The frontal cells projecting to peri-arcuate F2 were more numerous in the rostral part of ventral premotor cortex, in area F5 (Fig. 2: 11–12), and in F7 (Fig. 2: 14–19); additional projections originated from F4 (Fig. 2: 11–12), F6 (Fig. 2: 14–17) and F3 (Fig. 2: 10–12), and from dorsal

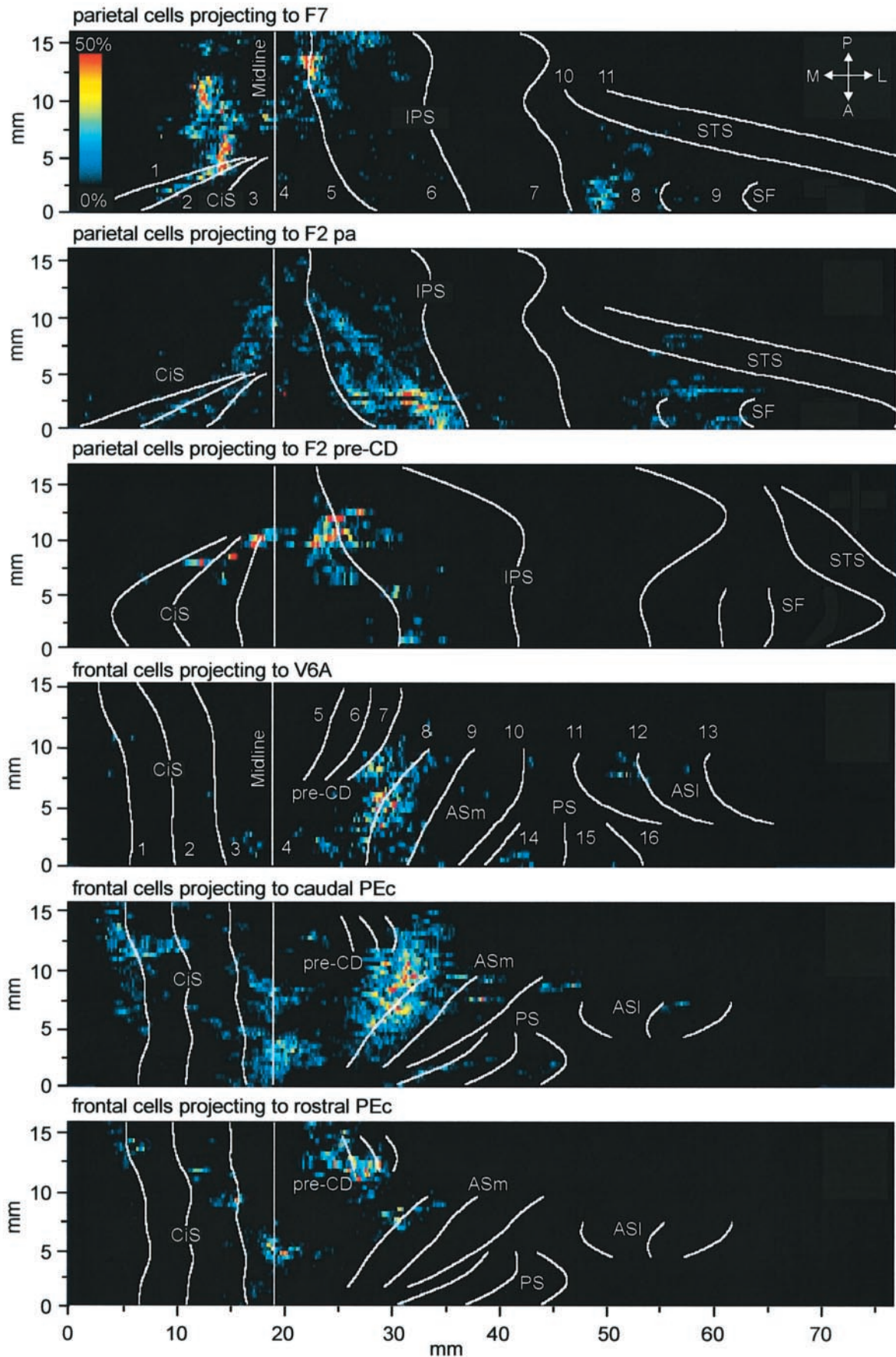
(CMAd) and ventral (CMAv) cingulate motor areas (Fig. 2: 10–12). The frontal cells projecting to the pre-CD region of F2 (Fig. 3) had an overall tangential distribution similar to that of cells projecting to the peri-arcuate part of F2, although in the latter case the major input was observed from F5, while in the previous the major projection arose from F4.

Two-dimensional Maps of the Tangential Distribution of Parieto-frontal and Fronto-parietal Association Cells

Figure 5 shows the overall tangential distribution of the cells of origin of the reciprocal association system linking parietal and frontal cortex, in the form of two-dimensional flattened views of the cortical tissue. These maps will be used to describe the main features of this pattern of connectivity.

The cells of origin of these association pathways are arranged in the form of bands that extend mostly along the rostro-caudal

Figure 5. Two-dimensional flattened views of the parietal and frontal lobe showing the tangential distribution of parieto-frontal and fronto-parietal association cells, according to their area of projection. For the generation of these maps, all retrogradely labeled neurons of each section were projected, along radial line mimicking cortical columns, onto a reference line running parallel to the pial surface at a depth constantly proportional to the distance between the cortical surface and the bottom of layer VI. This line was then flattened and divided into 160µm wide bins. The labeled cells contained in each bin were then expressed as colored pixels, using a scale from black (zero cells) to red. Sections were aligned on a common reference point, the midline of the hemisphere (straight line, 4). In each parietal map, numbers indicate the following anatomical landmarks: crown of the ventral bank of the CiS (1), fundus of the CiS (2), crown of the dorsal bank of the CiS (3), edge of the hemisphere (4), crown of the medial bank of the IPS (5), fundus of the IPS (6), crown of the lateral bank of the IPS (7), crown of the medial bank of the Sylvian fissure (SF; 8), fundus of the SF (9), crown of the medial bank of the STS (superior temporal sulcus; 10), fundus of the STS (11). In each frontal map, numbers indicate: crown of the ventral bank of the CiS (1), fundus of the CiS (2), crown of the dorsal bank of the CiS (3), edge of the hemisphere (4), medial crown of pre-CD (5), fundus of pre-CD (6), lateral crown of pre-CD (7), medial crown of the ASm (8), fundus of ASm (9), lateral crown of ASm (10), medial crown of ASI (lateral limb of arcuate sulcus; 11), fundus of ASI (12), lateral crown of the ASI (13), medial crown of the PS (principal sulcus; 14), fundus of PS (15), lateral crown of PS (16). A is anterior, P is posterior; M indicates medial, and L the lateral part of the cortex.



dimension of the cortex, in a gradient-like fashion. In fact, the parietal cells projecting to the rostral-most premotor field, area F7, form two main bands; one located in the medial wall of the hemisphere, in area 7m, the other in the most caudal sector of the SPL, over parts of V6A and PEc. A third smaller band of association cells occupies part of the IPL, mostly over area 7a. If one then considers the distribution of parietal cells to the anterior part of the more caudal premotor field, area F2, the bands of association cells move rostrally in the parietal cortex and their relative 'weight' changes, with a decrease in the proportion of cells projecting from the medial wall and an increase in that of cells projecting from the medial bank of the IPS, areas MIP and PEa. Furthermore, the smaller band previously seen in the IPL now moves laterally, within the cortex of the medial bank of the Sylvian fissure. The parietal cells projecting to the caudal-most part of F2 define a smaller band, confined to a region included between the dorsal crown of the IPS, laterally, and the caudal tip of the CiS, medially.

Two-dimensional Maps of the Tangential Distribution of Intrinsic Parietal and Frontal Association Cells

The tangential distribution of intrinsic association parietal and frontal cells (Fig. 6) is relatively more widespread than that of parieto-frontal and fronto-parietal cells, respectively. In the parietal cortex, intrinsic association cells form two main bands merging at the parieto-occipital junction. One band extends over the medial wall of the hemisphere and includes mostly areas 7m (cell projecting to V6A), and 7m and PEci (cells projecting to caudal and rostral PEc). The second band is mostly buried within the medial bank of the IPS, where it occupies parts of MIP and PEa (cells projecting to V6A), the entire rostro-caudal extent of MIP and PEa (cells projecting to caudal PEc), the more posterior part of the cortex around the crown of the medial bank of the IPS (cells projecting to rostral PEc). Association cells projecting to V6A and mostly those projecting to caudal PEc, sculpture a third band extending over areas 7a and PFG in the IPL.

The intrinsic frontal association cells projecting to F7 form a main organized band in area F2, while the frontal cells projecting to different sectors of F2 does not seem to define any visible organized pattern in the frontal lobe.

The Distributed Nature of Parieto-frontal Networks Underlying Visual Reaching and the Periodic Distribution of Association Cells in the Frontal and Parietal Cortex

The systems of reciprocal association connections between parietal and frontal cortices, as well as those of intrinsic frontal and parietal connections, have a common distributed nature. This is well illustrated by Figure 7, where the color scale of association connections expresses the strength of connectivity, as measured by the number of labeled cells giving rise to each of the association connections shown. No single parietal area entertains private relationships with a unique frontal area. On the contrary, any given parietal area projects, although with different strength, therefore in a gradient-like fashion, to different frontal areas, and vice versa. The intrinsic parietal and frontal connections obey the same principle, since any given frontal or parietal area receives from a variety of other frontal or parietal regions in a gradient-like fashion.

The number and density of association cells labeled in parietal and frontal cortex varied in a periodic fashion along the tangential cortical domain. Their distributions were characterized in a quantitative way through a spectral analysis (Johnson *et al.*, 1989). This periodicity consisted of low and high frequency components. The Fourier analysis revealed the relative importance of these components.

Median spectra were computed for all distributions (Fig. 8). The median estimated spectra of frontal cells projecting to different parts of parietal area PEc were similar (Fig. 8A). In both, most of the power spectrum was found in the domain of the low spatial frequencies (0.2 cycles/mm), which corresponded to periodicities in cell density with a peak-to-peak distance of ~5 mm. This finding suggests an arrangement of fronto-parietal association cells in the form of bands. Subsidiary peaks occurred at higher Fourier frequencies (0.4-0.5 cycles/mm). They probably corresponded to periodicities in cell density with a peak-to-peak distance of 2.5-2 mm. This suggests an arrangement of these cells in the form of columns (Jones *et al.*, 1975) of ~1-1.25 mm width.

This pattern was common also to the distributions of parietal cells projecting to F7, to F2 (Fig. 8B), and to those of intrinsic frontal (Fig. 8C) and parietal (Fig. 8D) association neurons. In general, the coherency of the cross-spectra and the phase of the distributions studied varied, depending both on the family of association cells and the cortical area considered. As an example, the coherency of the cross-spectrum of parietal cells projecting to the caudal and rostral parts of PEc (Fig. 8E) was low, as expected from the inspection of the two-dimensional maps (Fig. 6), which show local variations and different extents for these distributions.

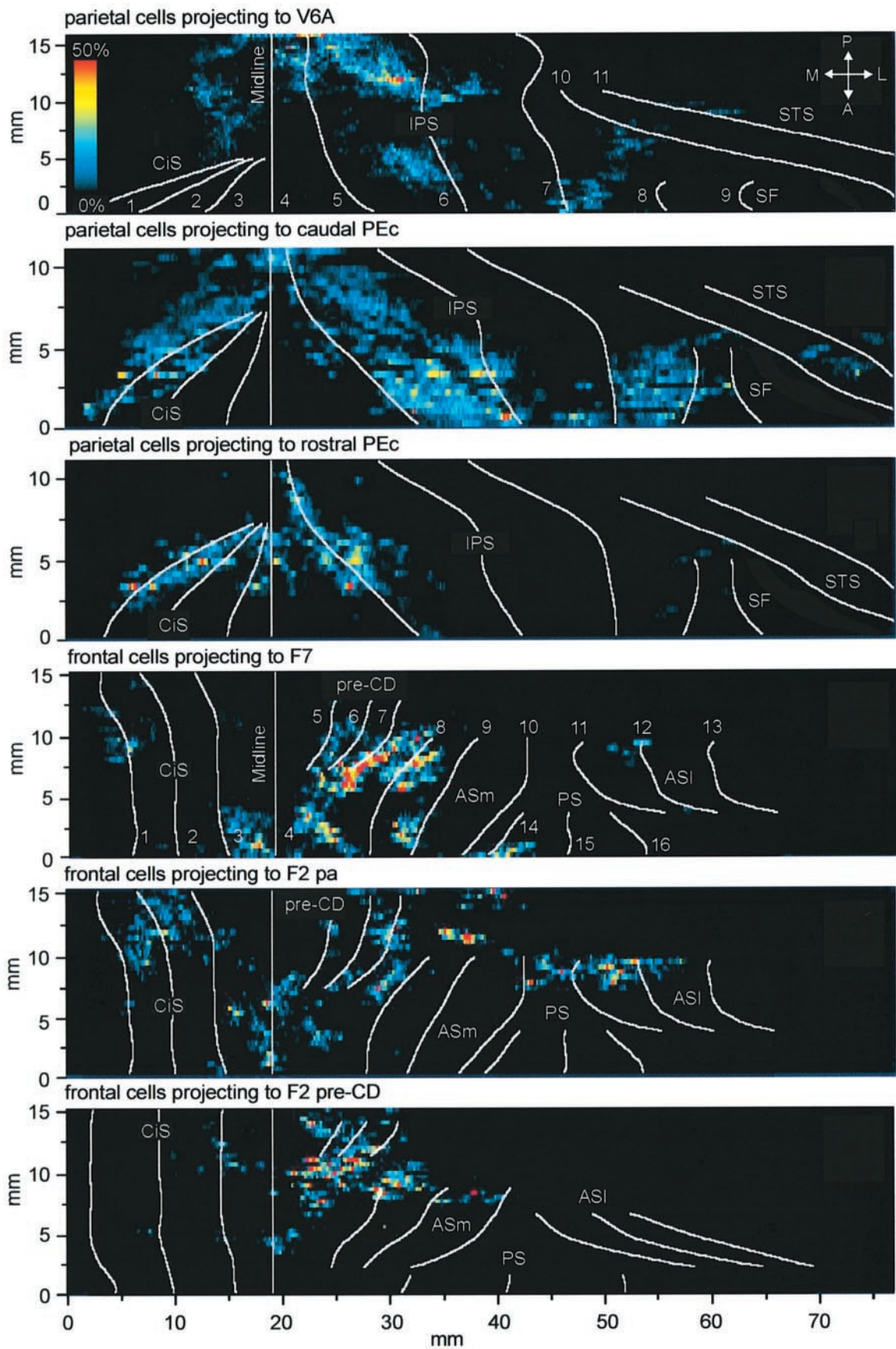
Discussion

The Superior Parietal Lobule as Main Source of Visual Input to Dorsal Premotor Cortex

Several reciprocal association systems connect parietal and frontal cortex. V6A receives its visual input from extrastriate cortex; see also Shipp *et al.*'s study (Shipp *et al.*, 1998), and projects mainly to F7. This is, in turn, the main source of frontal inputs to V6A. We found few projections from V6A to F2. These were more substantial in the study of Matelli *et al.*, probably due to differences in the injections sites (Matelli *et al.* 1998). The reciprocal projection linking F2 to V6A was instead well documented in our material. Thus, there exists a double reciprocal association system linking V6A to premotor cortex, one through F7, and the other through F2. Local parietal inputs to V6A come from a broad range of cortical areas, all located in the SPL, such as MIP, 7m, PEa and PEc. Interestingly, all these areas also project to premotor cortex. These results are in agreement with those of Colby *et al.* (1988) on cortico-cortical connections of the parieto-occipital cortex (PO). They also confirm the link between PO and 7m (Cavada and Goldman-Rakic, 1989a). The projection from MIP to V6A is reciprocal to that shown by Blatt *et al.* (1990).

Area PEc receives a modest input from V4, and is weakly connected to F7. PEc is the main source of parietal input to the pre-CD region of F2 that, in turn, projects back to PEc. This link

Figure 6. Two-dimensional flattened views of the parietal and frontal lobe showing the tangential distribution of intrinsic parietal and frontal association cells, according to their area of projection. Conventions and symbols as in Figure 5.



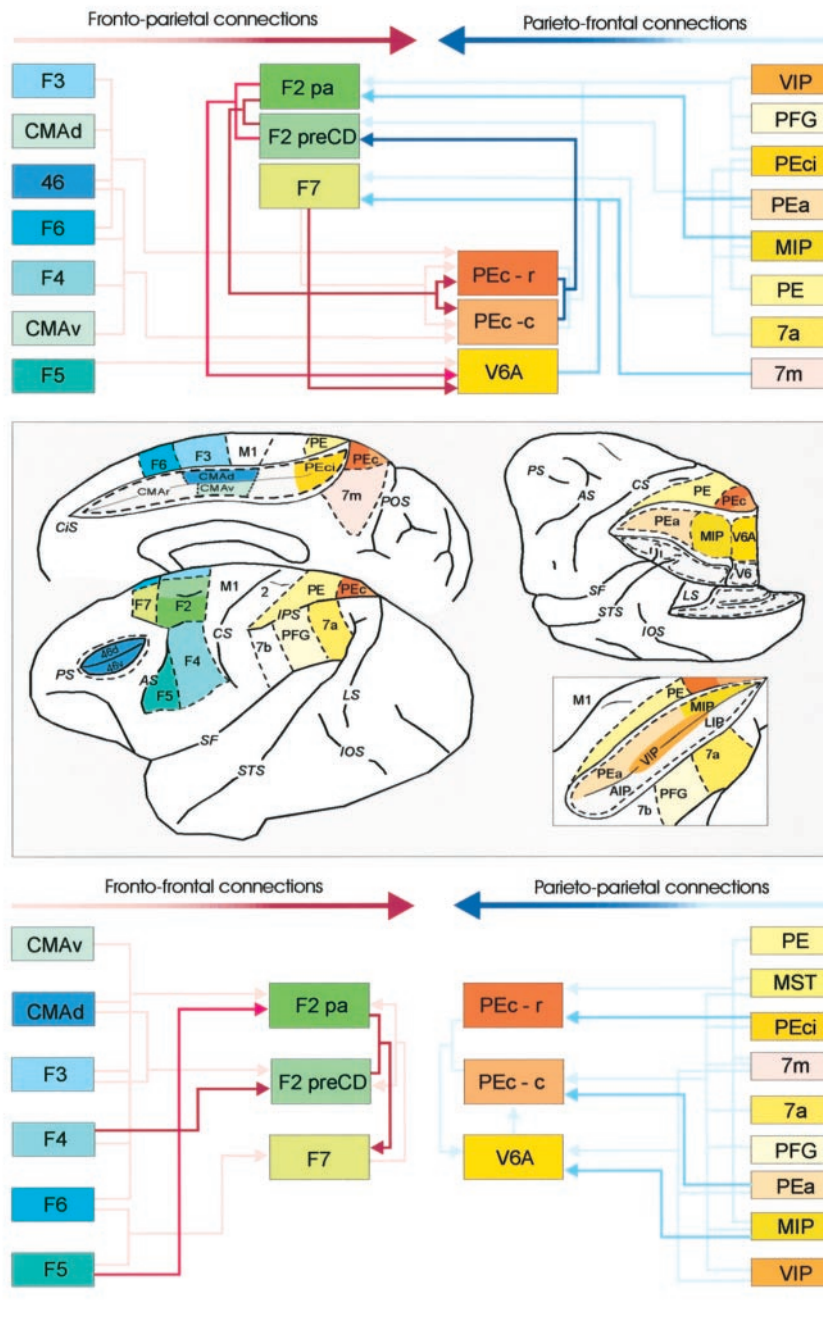


Figure 7. Schematic representation of the association connections evidenced in this study. The upper diagram refers to fronto-parietal and parieto-frontal connections. The lower diagrams refer to local frontal (left) and parietal (right) connections. The strength of connections was first determined by counting all cells labeled by a given injection throughout the cortex. The percentage of cells projecting from a given area was indicated by a three-level color scale (5–25%, 26–50% and 51–75%). Cortical areas contributing less than 5% to a given projection do not enter in these schemes. The insets of the brain figurines show the anatomical locations and borders of cortical areas [modified after (Caminiti *et al.*, 1996; Picard and Strick, 1996; Galletti *et al.*, 1998; Matelli *et al.*, 1998)]. The upper left figurine shows the medial aspect of the hemisphere with the location of mesial parietal areas (Caminiti *et al.*, 1996), and the cingulate sulcus opened (gray shading) to indicate the cingulate motor areas (Picard and Strick, 1996). The lower left figurine is a lateral view of the hemisphere with part of the principal sulcus opened to show the location of area 46. In the brain image of the upper right, large parts of the parietal and occipital lobe have been removed to show the location of the areas buried in the medial bank of the intraparietal sulcus and in the rostral bank of the parieto-occipital sulcus (Galletti *et al.*, 1996), where the physiological characterization of the injection site was performed (Battaglia-Mayer *et al.*, 2000). Finally (lower right), an enlargement of the parietal region flanking the intraparietal sulcus (IPS) is shown as opened to show the location of the areas buried in its medial and lateral banks (Caminiti *et al.*, 1996). PS, AS, CS, IPS, SF, STS, LS, IOS, POS indicate principal, arcuate, central, intraparietal, Sylvian, superior temporal, lunate, inferior occipital and parieto-occipital sulci. M1 is motor cortex (primary motor cortex; F1; area 4). CMAr, CMAAd, CMAv indicate cingulate motor areas rostral, dorsal and ventral; MIP, LIP, VIP and AIP indicate medial, lateral, ventral and anterior intraparietal areas.

between frontal and parietal cortex through PEC and F2 is strong and more substantial than that operated through V6A and F7-F2. The parietal input to PEC originates from a broad range of SPL

areas. These are, at least in part, those projecting to V6A as well, with some differences due to different contributions to the rostral and caudal parts of PEC. Main projections are those from

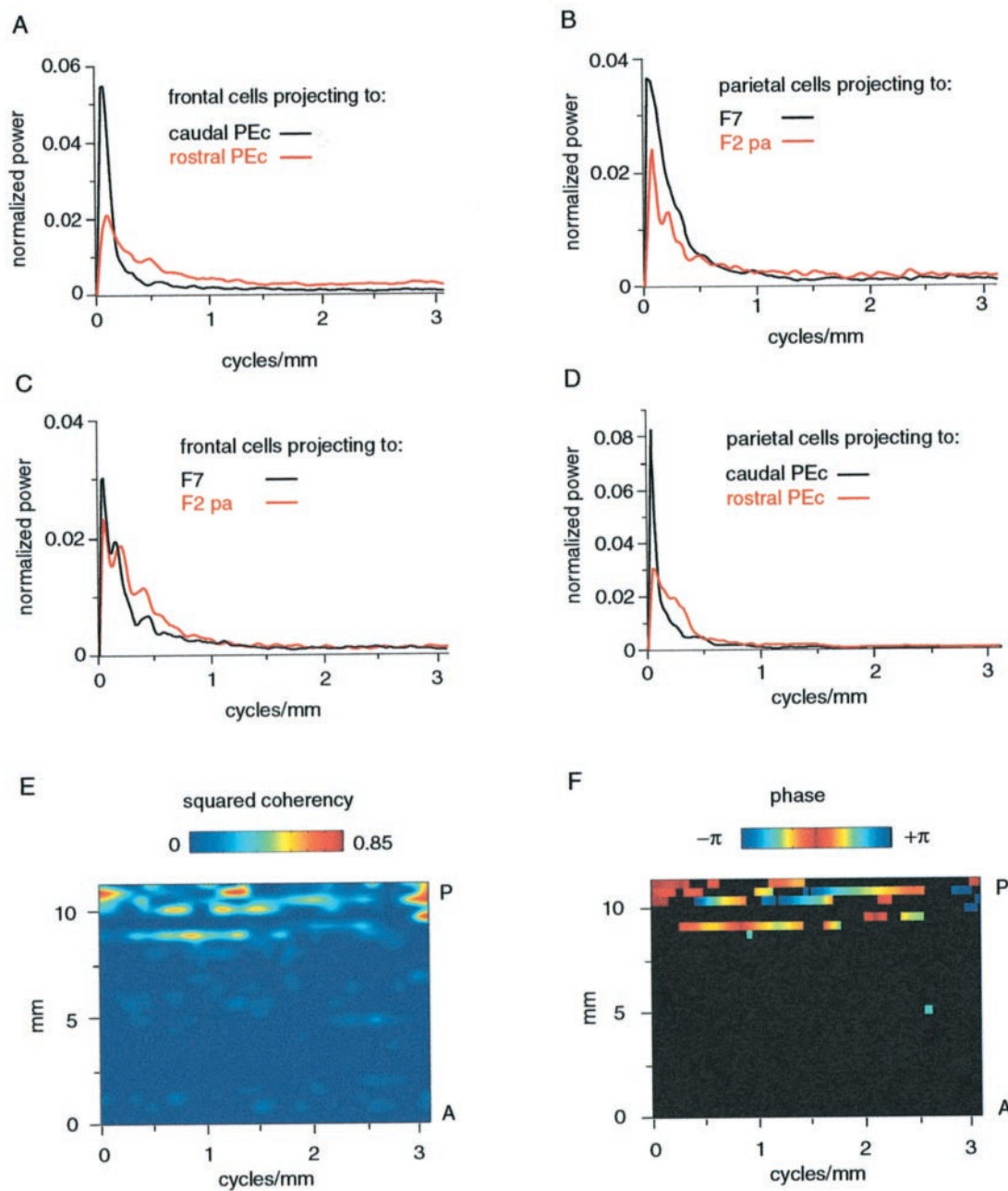


Figure 8. Spectral analysis of the distribution of association cells in frontal and parietal cortex. (A)–(D) Power spectra of different populations of association cells in the frontal and parietal cortex. Squared coherency (E) and phase relationships (F) of the distributions shown in (D). Coherency and phase values in the antero-posterior (A–P) dimension (mm) of the cortex are expressed as a function of the Fourier frequency (cycles/mm). Squared coherency values and phase relationships are color-coded. The black background in the phase insets indicates the regions where the coherency values were lower than 0.2 and, therefore, the phase relationships were meaningless.

MIP and PEa. The inputs from V6A, VIP, PFG, 7a and MST together represent ~25% of the total parietal input, and might be a source of visual input to PEc; see the companion paper (Battaglia-Mayer *et al.*, 2001).

Major sources of parietal projections to frontal cortex are PEa and MIP (Petrides and Pandya, 1984, Johnson *et al.*, 1993, 1996, Tanné *et al.*, 1995; Matelli *et al.*, 1998). Together they form almost the totality of the cortex of the medial bank of the IPS.

Contrary to PEc, which projects mainly to the pre-CD region of F2, PEa and MIP have a common target in the post-arcuate zone of F2.

Another substantial projection to premotor cortex stems from 7m, which projects mainly to F7 (Cavada and Goldman-Rakic, 1989a,b, Johnson *et al.*, 1993, 1996). This is quantitatively the main parietal input to F7. So far, MIP, PEa, and 7m have never received separate injections of different retrograde tracers.

Therefore, the topographic details of the reciprocal frontal-to-parietal projection (Johnson *et al.*, 1996) remain to be determined.

These data suggest that there exists a multiplicity of parallel systems of reciprocal association connections linking parietal and frontal cortex. However, each parietal area that is source of a 'private' projection to the frontal cortex also receives profuse local input from a broad range of other parietal areas. These, in addition, project to a different, sometime to the same, frontal region.

A similar pattern of intrinsic projections can be described when considering the origin of the frontal input to premotor areas F7 and F2. F7 receives almost exclusively from F2, to a much smaller extent from F5, and from CMAv. F2 pre-CD [area F2 around the pre-central dimple; area 6 α (part)] is recipient of frontal input mainly from ventral premotor area F4, and, to a lesser extent, from F7. The peri-arcuate zone of F2 receives large convergent inputs from a broader range of frontal areas, such as F5, F4, F7, F6, F3 and from CMAd. It is worth stressing that some of the frontal areas projecting to dorsal premotor cortex also receive one or more parietal inputs.

Tangential Organization of Association Cells in Parietal and Frontal Cortex

In both frontal and parietal cortex, the cell of origin of both long and local association connections are distributed unevenly in the tangential cortical domain. The spectral analysis revealed that they are ordered in bands of various shape and size, and that these bands contain periodicities that are reminiscent of the cortico-cortical columns (Jones *et al.*, 1975), first described in the somatosensory and motor cortex.

No simple phase relationships were observed between the distributions of the cell of origin of different association efferent systems studied, since, in some cases, they overlapped in space, in others they were largely segregated, or superimposed only over limited parts of their tangential extent. This periodic nature of the arrangement of the association cells in parietal and frontal cortex is of interest since it is paralleled by a similar periodic distribution of retinal-, eye- and hand-related signals in the cortex; see the companion paper (Battaglia-Mayer *et al.*, 2001).

The Association System of the Parietal and Frontal Cortex: a Source of Eye-Hand Signals for Different Visuomanual Actions

The study of the early stages of the composition of motor command in the cerebral cortex is central to any theory of internal representations of movement. The distributed, non-serial, nature of the cortico-cortical system linking parietal and frontal cortex is relevant to the functional operations underlying eye-hand coupling during different forms of reaching; see the companion paper (Battaglia-Mayer *et al.*, 2001).

The parietal regions that are the focus of this study, areas V6A and PEc, are parts of extrastriate area 19, and of area 5, respectively. No fine-grain topography of the visual field exists in V6A (Colby *et al.*, 1988; Galletti *et al.*, 1999), which contains a representation of both central and peripheral vision. The same holds true for area PEc (Battaglia-Mayer *et al.*, 2001, Squatrito *et al.*, 2001). In both V6A and PEc, visual neurons have rather large peripheral receptive fields, are very sensitive to the direction of motion of the visual stimulus, and, in PEc, to the optic flow as well. These latter properties could be dependent,

at least in part, on the input from MST; see the companion paper (Battaglia-Mayer *et al.*, 2001).

From this study, the role of superior parietal areas as the main source of visual input to dorsal premotor cortex (Caminiti *et al.*, 1996; Johnson *et al.*, 1996) is confirmed and strengthened. Furthermore, a variety of SPL areas, including V6A, PEc and MIP, emerges as potential sources of eye-related, particularly eye-position, signals to premotor cortex.

The visual input to premotor cortex is reflected in the activity of those populations of premotor neurons which fire when a visual cue instructs the animal about the next hand movement (Weinrich and Wise, 1982) and about its direction in space (Johnson *et al.*, 1996; Wise *et al.*, 1997). This signal-related activity in premotor cortex is contingent upon the execution of the hand movement. Only a preliminary study (Fujii *et al.*, 2000) is available in the literature on signal processing in the rostral part of dorsal premotor cortex (PMdr, F7). When studied during saccadic and reaching tasks, 33% of the cells were related to saccadic eye movement and hand-reaching movements, 31% only to saccadic movements and 37% to hand reaching. On the contrary, this same study has shown that in the caudal part of dorsal premotor cortex (PMdc, F2), the proportion of reach-related cells represented the overwhelming majority (87%).

Influence of eye-related signals has been reported in dorso-caudal premotor cortex (Boussaoud *et al.*, 1998; Jouffrais and Boussaoud, 1999). However, the hypothesis that coding of reaching in this area occurs in eye-centered coordinates (Boussaoud *et al.*, 1998), although attractive, remains to be substantiated at the population level. The profound and systematic influence exerted on dorsocaudal premotor cortical activity by arm-related signals (Caminiti *et al.*, 1991) has been confirmed (Fujii *et al.*, 2000). In this area, eye-position signals seem to exert only a modulatory effect. A significant influence on the directional tuning properties of the population of premotor cortical neurons by eye-position remains to be shown. Neurons in dorsal premotor cortex seem to encode the direction of arm movement and its position in space in a shoulder-centered reference frame (Caminiti *et al.*, 1991; Johnson *et al.*, 1996), and probably use the eye-position information to build an intermediate representation of the visual stimulus in body-centered coordinates.

Therefore, the activity types observed in F7 are very similar to those of V6A and 7m (Ferraina *et al.*, 1997a,b), while the neural activities of F2 are very similar to those of PEc, MIP and PEa, as dictated by the pattern of association connections.

The reciprocal frontal projection to V6A originates primarily from the rostral part of dorsal premotor cortex (F7), while that to PEc from its caudal part (F2). It is reasonable to suggest that dorsal premotor cortex is the source of signals concerning hand-movement direction and position to areas PEc and V6A, where individual neurons combine these hand-related signals with eye-related information in their global tuning fields (Battaglia-Mayer *et al.*, 2000, 2001).

Our hypothesis that the association connections confer to parietal and frontal cortices their dynamic tuning properties does not exclude a potentially important contribution from the thalamus. However, the sources and nature of these thalamic inputs remain to be determined.

This anatomical layout of the parietal network is consistent with the hypothesis that reaching in parietal cortex can be coded either in arm-centered (Lacquaniti *et al.*, 1995) or in eye-centered (Lacquaniti *et al.*, 1995; McIntyre *et al.*, 1997, 1998; Batista *et al.*, 1999) coordinates.

The Architecture of the Network Underlying Eye-Hand Coordination During Reaching

This study confirms and extends the notion that cortical control of reaching is a process distributed over many different parietal and frontal areas, reciprocally linked through cortico-cortical connections (Johnson *et al.*, 1996; Caminiti *et al.*, 1996, 1998).

Cortical areas located more posterior in parietal cortex, such as V6A and 7m, are reciprocally linked to more anterior frontal areas, such as dorso-rostral premotor cortex (F7). Parietal areas located at more anterior levels in the SPL, such as PEc, MIP, PEa, connect mainly to dorso-caudal premotor cortex (F2); finally, the most anterior parietal field, area PE, is reciprocally linked to the most posterior frontal area, motor cortex (Johnson *et al.*, 1996). Additional sets of reciprocal cortico-cortical connections contribute to this gradient architecture of the network, which is reflected in the gradients of eye- and hand-related signals described in both frontal and parietal cortex (Johnson *et al.*, 1996, Battaglia-Mayer *et al.*, 2001).

Within this network, areas that are connected by reciprocal cortico-cortical fibers share some crucial functional properties. This holds true for parietal areas PEc, MIP, PEa and frontal area F2 (Johnson *et al.*, 1996; Joffrais and Boussaoud, 1999; Fujii *et al.*, 2000; Battaglia-Mayer *et al.*, 2001; Ferraina *et al.*, 2001), and for parietal area PE and motor cortex (Georgopoulos *et al.*, 1982, 1984; Kalaska *et al.*, 1983; Johnson *et al.*, 1996). Neurons in PMdr (F7) have eye- and hand-related properties (Fujii *et al.*, 2000) very similar to those of V6A (Battaglia-Mayer *et al.*, 2000) and 7m (Ferraina *et al.*, 1997a,b), as predicted by the pattern of association connections shown in this study.

Therefore, the gradients of cortico-cortical connections are associated with, and probably impose on the network, similar gradients of functional properties.

It is worth stressing that the same interpretation has been made for the role of cortico-cortical connections linking the inferior parietal and dorso-lateral prefrontal cortex, two areas that share not only strong reciprocal association connections (Barbas, 1988; Cavada and Goldman-Rakic, 1989b, Andersen *et al.*, 1990), but also similar neuronal activity types, as revealed by a memory-guided saccade task (Chafee and Goldman-Rakic, 1998). Reversible inactivation experiments (Chafee and Goldman-Rakic, 2000) have shown that the association connections between these two areas play a crucial role in sustaining the parallel activation of task-related neurons with similar activity types in both parietal and pre-frontal cortex, suggesting that cortico-cortical connections can be a crucial substrate of a re-entrant signaling.

This architecture of the parieto-frontal network underlying eye-hand coordination strongly implies that the coordinate transformation for visual reaching cannot be regarded as a top-down, serial process, where the outcome of 'private' computations performed by individual parietal areas become available to the next processing node, be another parietal area located 'downstream', or premotor cortex. On the contrary, the gradient architecture of the network would be ideally suited for a coordinate transformation based on re-entrant signaling (Edelman, 1993), where the activity types relevant to eye-hand coordination are combined in a recursive way, and further refined locally. A 'progressive match' of retinal, gaze, and hand-related signals could achieve this goal (Burnod *et al.*, 1999). The temporal relationships of cell activity to these signals (Johnson *et al.*, 1996; Kalaska, 1996) are consistent with the hypothesis of a simultaneous recruitment of neurons encoding eye- and hand-related information in different frontal and parietal areas.

In this conceptual framework there is no segregation of different reference frames within different frontal and parietal areas but a gradual shift between combinatorial domains, which is favored by the global tuning properties of parietal neurons, able to combine, in a conditional and task-dependent way (Battaglia-Mayer *et al.*, 2000, 2001), the eye- and hand-related signals necessary for reaching.

Notes

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Abbreviations

7a	parietal area 7a; area PG
7m	mesial part of area 7; area PGm
AIP	anterior intraparietal area; area 7 (part)
ASl	lateral limb of arcuate sulcus
ASm	medial limb of arcuate sulcus
CiS	cingulate sulcus
CMAd	dorsal cingulate motor area; area 6c
CMAr	rostral cingulate motor area; area 24c
CMAv	ventral cingulate motor area; area 23c
CS	central sulcus
DY	dyamidino yellow
F2	caudal part of dorsal premotor area; PMdc, area 6α (part)
F2 pa	peri-arcuate zone of F2; area 6α (part)
F2 pre-CD	area F2 around the pre-central dimple; area 6α (part)
F3	supplementary motor area; SMA, area 6α
F4	caudal part of ventral premotor area; PMvc, area 4c (part)
F5	rostral part of ventral premotor area; PMvr, area 6α (part)
F6	pre-supplementary motor area; pre-SMA, area 6αβ (part)
F7	rostral part of dorsal premotor area; PMdr, area 6αβ (part)
FB	fast blue
FEF	frontal eye fields; area 8
FR	fluoro-ruby
IOS	inferior occipital sulcus
IPL	inferior parietal lobule
IPS	intraparietal sulcus
LIP	lateral intraparietal area, area 7 (part)
LS	lunate sulcus
M1	primary motor cortex; F1; area 4
MIP	medial intraparietal area; area 5 (part)
MPOS	medial parieto-occipital sulcus
MST	medial superior temporal area
PE	parietal area PE; area 5 (part)
PEa	parietal area PEa; area 5 (part)
PEc	parietal area PEc; area 5 (part)
PEc- c	caudal part of parietal area PEc, area 5 (part)
PEc- r	rostral part of parietal area PEc, area 5 (part)
PEci	parietal area PEci (cingulate)
PFG	parietal area PFG, area 7 (part)
PO	parieto-occipital cortex, area 19 (part)
POS	parieto-occipital sulcus
pre-CD	pre-central dimple
PS	principal sulcus
SF	Sylvian fissure
SPL	superior parietal lobule
STS	superior temporal sulcus
V4	visual area 4
V6A	visual area 6A, area 19 (part)
VIP	ventral intraparietal area, areas 5 and 7 (part)

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