A visuo-somatomotor pathway through superior parietal cortex in the macaque monkey: cortical connections of areas V6 and V6A

S. Shipp, M. Blanton and S. Zeki
Wellcome Laboratory of Neurobiology, University College, Gower Street, London WC1E 6BT, UK

Keywords: area PO, callosal connections, hierarchy, laminar organization, premotor cortex, visually guided reaching

Abstract
This report addresses the connectivity of the cortex occupying middle to dorsal levels of the anterior bank of the parieto-occipital sulcus in the macaque monkey. We have previously referred to this territory, whose perimeter is roughly circumscribed by the distribution of interhemispheric callosal fibres, as area V6, or the ‘V6 complex’. Following injections of wheatgerm agglutinin conjugated to horseradish peroxidase (WGA-HRP) into this region, we examined the laminar organization of labelled cells and axonal terminals to attain indications of relative hierarchical status among the network of connected areas. A notable transition in the laminar patterns of the local, intrinsic connections prompted a sub-designation of the V6 complex itself into two separate areas, V6 and V6A, with area V6A lying dorsal, or dorsomedial to V6 proper. V6 receives ascending input from V2 and V3, ranks equal to V3A and V5, and provides an ascending input to V6A at the level above. V6A is not connected to area V2 and in general is less heavily linked to the earliest visual areas; in other respects, the two parts of the V6 complex share similar spheres of connectivity. These include regions of peripheral representation in prestriate areas V3, V3A and V5, parietal visual areas V5A/MST and 7a, other regions of visuo-somatosensory association cortex within the intraparietal sulcus and on the medial surface of the hemisphere, and the premotor cortex. Subcortical connections include the medial and lateral pulvinar, caudate nucleus, claustrum, middle and deep layers of the superior colliculus and pontine nuclei.

From this pattern of connections, it is clear that the V6 complex is heavily engaged in sensory-motor integration. The specific somatotopic locations within sensorimotor cortex that receive this input suggest a role in controlling the trunk and limbs, and outward reaching arm movements. There is a secondary contribution to the brain’s complex oculomotor circuitry. That the medial region of the cortex is devoted to tightly interconnected representations of the sensory periphery, both visual and somatotopic—which are routinely stimulated in concert—would appear to be an aspect of the global organization of the cortex which must facilitate multimodal integration.

Introduction
Areas V6 and V6A are located at the interface of the somatic and peripheral visual representations in the cerebral cortex; the basic hypothesis is that they are specialized to feed visuo-spatial information to the somatomotor system (Zeki, 1986; Galletti et al., 1996) – part of a wider visuomotor network involving superior parietal cortex (Johnson et al., 1993; Tanné et al., 1995; Johnson et al., 1996; Caminiti et al., 1996). This report concerns the cortical connectivity of V6 and V6A, and has twin aims: to detail the visual and somatomotor networks in which these areas participate, and to sharpen their definition by establishing better criteria for their borders with neighbouring areas.

V6 and V6A are the most medial components of Brodmann’s prestriate area 19 (Brodmann, 1909), a cytoarchitectonic territory that, with area 18, comprises many separate functional areas. Although the tasks of establishing the separate identity of these areas and studying their connections are formally independent, it has been found in practice that connectional criteria offer an extra dimension for the definition of areal borders. For example, it has been generally established that the pattern of distribution of interhemispheric, callosal axons can serve as a map to subdivide the cortex into topographically distinct zones. In the visual prestriate cortex, where there is substantial topographic order, maps of callosal connections were instrumental in the definition of areas, e.g. V3, V3A and V4 (Zeki, 1977; Van Essen & Zeki, 1978; Van Essen et al. 1982), by virtue of the fact that the edges of areas – representing the vertical meridian (VM) or nearby ipsilateral field – receive relatively strong callosal input. This principle was invoked in the initial demarcation of ‘callosal’ area V6 (Zeki, 1986). A problem arises, however, as the underlying topography evolves greater distortions or re-representations: the callosal pattern presumably reflects these contortions and, taken in isolation, can

Correspondence: S. Shipp, as above. E-mail: s.shipp@ucl.ac.uk
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Intrinsic diffuse 1, 2 & 3, 5 & 6
Lower 1, 5 & 6

Laminar distributions of terminal label classified according to relative rank in a cortical hierarchy. The patterns under ‘main sequence’ form a continuum, but they do not account for all the patterns that may be observed; variants that we also classified in hierarchical terms are listed to the right.

No attempt has been made to capture variations in relative density between layers 2 and 3, or between layers 5 and 6. Hence ‘2 and 3’ and ‘5 and 6’ represent the maximum density to be found in either layer of each pair.

It is recognized that the density of terminal label depends in part on the density of retrogradely filled cells, whose local axon collaterals may contribute to the observed patterns. This effect will be greatest where labelled cells are most profuse, typically layers 3 and 5. The above scheme relies principally on the relative weights of layers 1 and 4.

**Table 1. Classification of laminar patterns**

<table>
<thead>
<tr>
<th></th>
<th>‘Main sequence’</th>
<th>Variants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>4 only</td>
<td>4 = 2 &amp; 3 only</td>
</tr>
<tr>
<td></td>
<td>4 &gt; 2 &amp; 3 only</td>
<td>4 = 2 &amp; 3 &gt; 1, 5 &amp; 6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>all equivalent</td>
<td>4 &gt;= 5 &amp; 6 &gt; 2 &amp; 3, 1</td>
</tr>
<tr>
<td></td>
<td>1 = 4 only; 1 = 4 &gt;= others</td>
<td></td>
</tr>
<tr>
<td>Intrinsic</td>
<td>diffuse</td>
<td>1, 2 &amp; 3, 5 &amp; 6 &gt; 4</td>
</tr>
<tr>
<td>Lower</td>
<td>1, 5 &amp; 6 &gt; 2 &amp; 3</td>
<td>1 &gt; 2 &amp; 3, 5 &amp; 6 &gt; 4</td>
</tr>
<tr>
<td></td>
<td>1 = 5 &amp; 6 only</td>
<td>1 &gt; 5 &amp; 6 or 1 only</td>
</tr>
</tbody>
</table>

FIG. 1. Postero-lateral view of a macaque hemisphere dissected to reveal the anterior banks of the parieto-occipital and intraparietal sulci. This exposed sulcal surface corresponds to the structure that is illustrated in many of the 3D reconstructions of an isolated superior parietal gyrus (SPG), displayed from roughly this viewpoint. The dotted outlines superimposed onto the posterior face of the SPG represent the injection sites of WGA-HRP in five different animals, as coded in the diagram to the left. The zones depicted are where TMB reaction product is sufficiently dense to obscure local labelled cell somata, probably a modest overestimation of the region of effective uptake. Their relative positions are an approximation, due to the fact that the gross morphology of individual hemispheres shows appreciable variability. However, one consistent morphological feature, typified by this example, is the greater depth, ventrally, of the POS compared to the IPS. This lends the SPG reconstructions a ‘foot’ at their postero-ventral end, and a consequent discontinuity in the contour lines just beneath the junction of the IPS with the POS.

A region of area V6, but not V6A, extensively overlaps with that of parieto-occipital area (PO), whose definition relies principally on myeloarchitectural (Colby et al., 1988). The relationship between the criteria defining PO and V6 is treated at length by Galletti et al. (1996). The basic principle we have followed is that there is little merit in equating the terminology in advance of a demonstration that the respective boundaries precisely coincide: we are uncertain of the exact relationship because we have been unable to replicate the elementary myeloarchitectural features that demarcate PO – although we did find a number of alternative, more subtle features, that could equally have had some significance in border determination (Galletti et al., 1996). Furthermore, we doubt that areas V6 and V6A directly correspond to areas PO and Pod (dorsal parieto-occipital), as they have been described in the New World Cebus monkey (Neuenschwander et al., 1994); as far as we can judge, V6 is more likely to match the sum of areas PO and Pod in Cebus, and the homologue of V6A has yet to be described in Cebus (Galletti et al., 1996).

Area PO has previously been reported to connect with the peripheral (> 10°) representations of other visual cortical areas, a feature that implied a role in visuospatial function (Colby et al., 1988). Other connections, with surrounding areas of somatomotor association cortex, and with the frontal eye fields (FEF), also suggest involvement with the visuomotor system, Colby et al. (1988), specifically proposing a role in the visual guidance of eye movements. Broadly, the connections of V6 and V6A follow this earlier description, although there are one or two distinct differences (between PO and V6, and between V6 and V6A); a key one is that the frontal connections of the V6 complex concern the premotor cortex more than the FEF, the latter being a far more prominent target of visual output from other prestriate areas (Huerta et al., 1987; Stanton et al., 1993; Stanton et al., 1995). The fact that the SPG plays a very significant role in relaying visual information to the motor cortex, and in particular for guiding reaching movements, is one that has only recently been recognized (Caminiti et al., 1996). Finally, the specific regions of somatomotor cortex that communicate with V6/V6A seem to coordinate the lower parts of the body (trunk and hindlimbs) and the arm, but not the hands or face. Their connection with V6 and V6A presumably reflects the cortical integration of the

Support a number of rival border assignments. For this reason, we now refer to callosal V6 as the ‘V6 complex’. Resolution of the ambiguity requires consideration of multiple criteria, be they connectional, architectural or physiological.

The laminar patterns of connectivity that are revealed by joint retrograde/orthoradial tracers, e.g. wheatgerm agglutinin conjugated to horseradish peroxidase (WGA-HRP), offer one such additional resource, for it is now generally established that these patterns reflect the relative levels of distinct visual areas within an overall processing hierarchy (Felleman & Van Essen, 1991). In the present report, we adopt this principle to infer that an injection site and a nearby patch of labelled terminals, sited either side of a strip of callosal fibres, must belong to separate areas: the callosal strip is thereby suitably placed to denote their common border. Another inference derived from laminar patterning is the anatomical partition of the V6 complex; the internal border, dividing V6 from V6A, can be seen as a transition in the laminar characteristics of local connections surrounding injection sites within the complex. The distinction between V6 and V6A supported the earlier discovery of a functional difference between the dorso-medial and ventro-lateral parts of the posterior superior parietal gyrus (SPG), in recordings from alert animals (Galletti et al., 1991). To test the correspondence more directly, the present anatomical material and the physiological data were cross-referenced by reconstruction in an identical normalized format; the borders established by the two datasets were then found to coincide, at least within the margins of error imposed by comparing different brains (Galletti et al., 1996). This exercise showed that V6A has larger receptive fields than V6, and more complex combinations of retinal and extraretinal response properties.

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A visuo-somatomotor pathway in the macaque

**Fig. 2.** Three views of an isolated SPG from a right hemisphere (case SP05, not injected with WGA-HRP) showing the banded distribution of transcallosal fibres that has been interpreted to demarcate area V6. Top left: brain outline to show the plane of section; the shaded area corresponds to the portion of the medial wall displayed in the 3D reconstruction immediately below (lower left). Top right and lower right: lateral and posterior views of the same structure, after rotation, to show the anterior banks of the IPS and POS. Broken lines trace the course of the callosal bands interpreted to define the perimeter of area V6; the exact placement of the boundary cannot be specified so accurately. The reconstruction is an orthographic projection, viewed from a superior vantage. The viewpoint for each rotation is displayed by the discs showing antero-posterior and medio-lateral axes. The scale bar indicates the distance in the fronto-parallell plane.

**Table 2. Qualitative ranking of the connection strengths observed in each case**

<table>
<thead>
<tr>
<th>Prestriate</th>
<th>Lateral parietal</th>
<th>Medial parietal</th>
<th>Lateral premotor</th>
<th>Medial premotor</th>
<th>Prefrontal</th>
</tr>
</thead>
<tbody>
<tr>
<td>V2</td>
<td>V3</td>
<td>V3A</td>
<td>V6</td>
<td>V5</td>
<td>V5A</td>
</tr>
<tr>
<td>SP19</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>SP25</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>SP14</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>SP24</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>VG17</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

DP = dorsal prelunate area; LIP = lateral intra-parietal area; VIP = ventral intra-parietal area; MIP = medial intra-parietal area; AIP = anterior intra-parietal area; FEF = frontal eye field; * — not examined.

peripheral visual and somatic worlds. The anatomical essentials of the current results have been reported in abstract (Shipp & Zeki, 1995a); this expanded account allows additional comment on their functional significance with regard to the visuo-spatial and oculometric properties of neurons recorded from V6 and V6A, particularly in that some neurons in V6A have receptive fields anchored to head-centred (as opposed to retinally-centred) coordinates in visual space (Galletti et al., 1991, 1993, 1995).

**Materials and methods**

To trace the connections of V6, we placed injections of WGA-HRP into the posterior pole of the SPG in the left hemisphere of four macaques (*M. fascicularis*) and the right hemisphere of one other. In three of these cases (SP14, SP24, VG17), the splenium of the corpus callosum had been transected at least 5 days previously so that the distribution of interhemispheric fibres could be revealed by staining for degeneration. The corpus callosum of one animal (SP25) was left intact to allow interhemispheric transport of the WGA-HRP. The final animal (SP19) had the callosum transected immediately prior to bilateral injection of WGA-HRP, and staining for degeneration was not attempted (the hemisphere not injected in area V6 is not described here). Results from three other callosal transections are also presented.

All the brains were sectioned horizontally at 40 or 60 μm. Every third section was reacted for WGA-HRP using tetra-methyl-benzidine (TMB) according to the methods of Mesulam (1982). Some sections from each brain were also stained for cytochrome oxidase (Wong-Riley, 1979). In later animals, we began to use the technique of Gallyas (1979) to stain for myelin; although good quality results were only obtained for the last brain (VG17) of this particular series, subsequent material was available to support general myelo-architectural observations, at least four further hemispheres being examined in detail. Sections treated for callosal degeneration were stained initially by the method of Fink & Heimer (1967), as modified by Wiitanen (1969). Subsequently, we have employed the
methods of Gallyas et al. (1980). The latter described two procedures, one suitable for degenerate axons, the other more sensitive to degenerate terminals. Both have yielded excellent results, though we have concentrated on the latter for routine plotting and reconstruction, partly because it can give clearer images in dark field illumination.

Sections were drawn at between $\times 20$ and $\times 40$ magnification. Excluding case SP14, one set covered the entire cerebral cortex at a frequency of 1-in-6, including several subcortical structures (although only cortical connections are reported here). Other sets covered individual gyri at higher power and greater frequency (1-in-3). WGA-HRP and callosal silver stains of adjacent sections were compiled on superimposed diagrams, using blood vessels to guide registration. Label was assigned qualitatively to one of four density levels and projected to a layer 4 contour line. Contour lines and label densities were digitized and submitted to 3D reconstruction software (Romaya & Zeki, 1985).

Analysis of laminar patterns of labelling

The distribution of labelled cells and terminals across the cortical layers of a particular area is related, at least in part, to the relative ranks of the injected and labelled areas within a systematic hierarchy (reviewed by Felleman & Van Essen, 1991). We examined three cases fairly closely in order to establish whether each patch of labelled cells and terminals could be assigned to one of three classes: higher, lower or equal in rank to the area injected. The basic scheme is that an intermediate pattern (1 – denoting equal rank) has a roughly even distribution of label over all layers: terminals through 1–6 and cells from 2 to 6, including some in layer 4. The higher pattern (H) is characterized by a relatively greater density of terminals in layers 4, 3 and 2, the lower pattern (L) by a bias toward layers 1, 5 and 6.labelled cells may be more numerous in layers 2 and 3 in the L pattern, and in layers 5 and 6 in the H pattern. As explained later, we chose to modify these criteria in order to permit a more systematic classification; the modified criteria are listed in Table 1. Essentially, we classified the relative densities into four separate compartments: layers 1; 2 and 3; 4; and 5 and 6. These were qualitative assessments, performed by eye. However, to minimize observer variability, we adopted the following heuristics listed below:

1. The patterns displayed by successive sections may differ substantially, especially where the plane of section is oblique to the columnar axis of label and fails to sample all of its layers. Classifications should thus be based on the sum of the sections which sliced through any given patch.

2. The laminar pattern of terminals is more systematic, and meaningful, than that of cells.

3. There are no discrete classes, but a continuum of observable patterns. Classification is thus a selection of the set point on the continuum that any patch of labelling most closely resembles.

4. The default class is neutral; i.e. the classification is L, unless it is convincingly H or L.

Format of illustrations and terminology

The anatomical results are illustrated by 3D reconstructions of an isolated SPG, generally as a trio of lateral, posterior and medial viewpoints. To help orient the reader, Fig. 1 shows a real hemisphere from which parts of the operculum and inferior parietal lobe have been dissected to afford a comparable view of the SPG. The lateral and posterior aspects of the SPG respectively correspond to the medial bank of the intraparietal sulcus (IPS) and the anterior bank of the parieto-occipital sulcus (POS); the medial aspect of the gyrus is part of the medial wall of the hemisphere. Viewed in this way, the exact demarcation of the IPS from the POS is somewhat arbitrary, and of little significance. It is worth noting, however, that the anterior bank of the POS normally extends more ventrally than the medial bank of the IPS, a morphological feature which lends many of our 3D reconstructions a ‘foot’ at their posterior end.

Results

Location of the injection sites

We injected WGA-HRP into V6 in the right hemisphere of one animal (SP14) and in the left of four others: all are illustrated as right hemispheres. The relative locations are portrayed by the insets in Fig. 1. If their functional locations were equivalent, there should be broadly equivalent patterns of cortical connectivity (Table 2). Although the level of consistency was quite high, a number of discrepancies did emerge. In what follows, we assess how far these variations may be attributed to divergence amongst the injection sites with respect to three distinct topographic criteria.

Callosal topography

We have found that callosal fibres are distributed over the SPG as a series of dorso-ventrally oriented bands, as illustrated in Figs 2–5. Area ‘V6’ was provisionally identified as visually responsive cortex on the posterior face of the SPG that was enclosed by a ring of callosal fibres running from the POS onto the medial wall of the hemisphere (Zeki, 1986), see Fig. 2. Subsequently, we have found that the interhemispheric connections of V6 are not limited to its margins (Shipp & Zeki, 1987), and that the callosal pattern over the entire SPG has much variability. Figure 3 shows two further high-density callosal reconstructions of the SPG. The upper one (Fig. 3A) has an irregular series of callosal bands distributed over the medial, posterior and lateral surfaces of the SPG. The bands in the other (Fig. 3B) are more linked, rendering the overall dorso-ventral configuration less prominent. Both patterns may be interpreted according to the model of ‘callosal V6’ in Fig. 2. In the reconstruction of Fig. 3A, the medial boundary of callosal V6 is sharply demarcated and there is also a likely lateral boundary within the POS. There is single band crossing between these two borders, but the remainder of the enclosed territory is free of callosal fibres. In Fig. 3B, the callosal perimeter of V6 may be identified with a ring-shaped zone which traverses the lateral and medial surfaces of the SPG, roughly matching the model configuration. The border is sharpest within the lateral part of the POS, but becomes more diffuse elsewhere and much of the enclosed zone also receives callosal fibres. The examples illustrated in Figs 2 and 3 are supplemented by the trio of cases shown in Fig. 4, and we have examined at least three more full callosal reconstructions of the SPG (not illustrated). Each of these bears, in essence, the recognizable stamp of ‘callosal V6’, but also in each case, there remains an unresolved measure of ambiguity. The border might be drawn along the internal or external edge of the callosal perimeter or, in cases where the perimeter bifurcates, it is undetermined which branch the border should follow. In short, we regard the callosal topography of the SPG as consistent enough to designate a distinct area in a generic, schematic map of macaque cortex, while noting that it may lack the resolution to specify the borders in all individuals. Additional criteria are necessary for this purpose, one of which can be the pattern of local connections. The first step is to chart the location of the injection sites on the callosal maps.

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Fig. 3. Two further 3D reconstructions of the SPG to show the distribution of transcallosal fibres (neither hemisphere being treated with WGA-HRP). (A) (case M10) stained by the Fink-Heimer method and drawn under brightfield illumination. (B) (case VG08) stained by the Gallyas method and drawn under darkfield. Left: medial views, corresponding to the shaded portions of the hemisphere outlines. Right: lateral views, showing the interior of the POS and IPS. The dashed lines approximate the perimeter of callosal V6. There is no available evidence to specify whether it should lie on the inner or outer edge of the callosal band, or internally. CgS is cingulate sulcus. Other conventions follow Fig. 2.
Figure 4. Part I. Reconstructions of the SPG from three brains (all shown as right hemispheres) to show the distribution of intrahemispheric connections revealed by injection of WGA-HRP (blue) in relation to the pattern of transcallosal inputs (orange). The injection sites, on the posterior aspect of the SPG, are shown in dotted blue lines. Left: medial viewpoints, the reconstructed regions corresponding to the darker shading on the brain outlines. Right: lateral viewpoints, to show the anterior banks of the POS and IPS. Likely cortical areas are assigned to each patch of label on the basis of its position. The approximate border of V6/V6A is indicated, as derived from an analysis of the laminar pattern of labelling. Numerals in haloes in (A) and (C) refer to components of part II. The lateral view of (C) also has arrows to indicate the level of sections illustrated in Fig. 9. Other conventions follow Fig. 2.

Figure 4 shows three dual reconstructions of callosal and local connections on the SPG. Each injection was placed on or about the lateral convexity of the posterior face of the gyrus, no less than 5 mm deep from the dorsal surface of the brain. Immediately anterior in each case there is a prominent, vertically oriented callosal band, readily interpretable as the perimeter of callosal V6. Thus, all three of these injections were within V6 according to the callosal model. The two injections that were not accompanied by callosal reconstructions were also located on the posterior face of the SPG, but they extended more ventrally (see Fig. 1). The interhemispheric connections of one of these (SP25) are shown in Fig. 5. Bands of labelled cells and terminals were oriented dorso-ventrally on the posterior face of the SPG, a pattern resembling the results of callosal transection (Shipp & Zeki, 1987). Evidently, this injection was not made into a zone entirely free of interhemispheric connections. Yet it did not necessarily coincide with the callosal perimeter of V6, given that the ‘body’ of the area may also contain many callosal fibres (e.g. Fig. 3).

Retinotopy
The location of each injection site within the map of the visual field can be determined by charting the label in other well-mapped cortical areas (V2, V3) or subcortical structures, e.g. the superior colliculus. All five cases produced terminal labelling in the deeper layers of the colliculus. And, in all five, label was restricted to the lateral posterior quadrant of the tectum, implying a topographic location in the peripheral lower visual field (Cynader & Berman, 1972). In two cases (SP19 and SP25), the location of label in cortical area V2, within the most anterior part of the upper bank and lip of the calcarine sulcus, enabled us to refine this allocation. According to standard maps, e.g. Gattass et al. (1981), this would be 30°/40° eccentric inferior...
FIG. 4. Part II. Examples of H, I and L patterns of connectivity at various marked locations on the SPG in cases SP24 and VG17, following an injection of HRP-WGA into area V6A (cf. A and C). The brightfield view shows the laminar location of labelled cells with respect to the nissl-counterstained cytoarchitecture; the darkfield (cross-polarizing) view gives a more sensitive indication of the distribution of labelled terminals. SP24 Medial view: 1 = H, area V6A (on the margin of injection site); 2 = I, area V6A (a more remote patch of intrinsic connectivity); SP24 Lateral view: 3 = H, area MIPd; 4 = I, area MIPv. VG17 Medial view: 5 = H, area PEc; 6 = I, area V6A (a remote patch of intrinsic connectivity); VG17 Lateral view: 7 = H, area MIPd; 8 = I, area MIPv.
field. An alternative technique, to record receptive fields at the injection site, is not one that we used. It would not be satisfactory, for the receptive fields from single penetrations demonstrate substantial scatter (Galletti et al., 1991) and the spread of tracer exceeds the range that can be adequately sampled by a single recording device.

**Topography of laminar characteristics of labelled cells and terminals**

These laminar patterns co-vary with the hierarchical rank of interconnected areas (Felleman & Van Essen, 1991) – and therefore a local change in the pattern can indicate the presence of a border between two separate areas. In essence, we were able to use this approach to segment the SPG into a series of three zones, featuring a ‘higher’, ‘intermediate’ or ‘lower’ laminar pattern, along its dorso-ventral axis. The zone with the higher (H) pattern was always located most dorsally, generally extending on to the dorsal surface of the SPG. However, the transition between the middle ‘intermediate’ zone and the ventral ‘lower’ zone was found to transect the cortex of V6 enclosed by a callosal perimeter, implying that ‘callosal V6’ is not a unitary area. The two partitions were called V6A and V6 (V6A being the more dorsal) after collating the anatomical observations with physiological data obtained from the same region (Galletti et al., 1996).

For three cases (SP14, SP24, VG17), the intermediate/lower (I/L) transition was ventral to the injection site, so we consider these injections of tracer to have been within area V6A, not V6: we interpreted the I zone to represent intrinsic connections within area V6A (Fig. 4, part II #2) and the L zone to represent connections with area V6. The other two injections extended relatively more ventrally. Case SP25 showed the same three H, I and L zones, but here the level of the I/L transition intersected the injection site. We concluded that this injection must have straddled the V6/V6A border. There was some residual I patterning ventral to the level of the I/L transition, but only on the immediate fringe of the injection, owing to short range intrinsic connections in V6; other connections within V6 had the L pattern (Fig. 6, part II #3). Finally, the injection in case SP19 was sited still more ventrally and judged to be, effectively, within V6 alone; this injection had an extended dorsal ‘tail’, due to leakage along the syringe track, but sections through the tail revealed a pinpoint deposition of tracer with no sign of local transport. We do not believe that this ‘tail’ was part of the effective uptake zone or contributed significantly to the observed patterns of extrinsic labelling. Laminar patterns in case SP19 were less well resolved, but all indications of H/L character seemed consistent with the other cases.

In summary, the five injections seemed comparable with regard to their placement within the callosal and visual maps. It is thus the differential involvement of V6 and V6A that we take into account for some of their discordant features of connectivity, as detailed below.

**Connections with prestriate areas V1–V3A**

The label in V2 was found only at a representation of the far inferior periphery, at the rostral end of the calcarine sulcus (CS), and on the external surface, just above the dorsal lip of the CS, see Fig. 6. Only two cases (SP19 and SP25), whose injection sites extended more ventrally on the SPG than the others, showed this connection to V2. In neither case, however, did we find any label in V1: even where label in V2 directly abutted the anterior boundary of V1, the zone of labelling terminated abruptly at the border between the two areas. Area V3 showed some labelling in all five cases, again in a region associated with extreme, peripheral, inferior visual field (Figs 6 and 7); this is the most medial component of V3, at the foot of the SPG just caudal to the junction of the IPS with the anterior bank of the POS (Van Essen & Zeki, 1978; Van Essen et al., 1986; Gattass et al., 1988). As Fig. 6 demonstrates, the label in V3 was thus some way distant from the topographically equivalent part of V2, fortunately facilitating the task of distinguishing label in these two areas (cf. Van Essen et al., 1986). Once again, cases SP19 and SP25 were those with the heaviest labelling in V3, and these were also the only brains where label was present in area V3A. In the former, it extended from the posterior bank of the POS, across the annectant gyrus into the anterior bank of the LS. In the latter, it was found in the POS only. In no case did we find any label in area V4.

These observations accord with the subdivision of ‘callosal V6’ noted above, as they imply that the more ventral part of this region forms substantially stronger connections with V2, and V3/V3A, than does the more dorsal part. In other words, we can interpret the presence of a connection to V2 as a factor distinguishing V6 from the dorsally adjoining area, V6A.

**Area PGm (7m or MDP) and area PE**

The H zone on the dorsal surface of the SPG is part of area PE (von Bonin & Bailey, 1947), a caudal subdivision called PEC by Pandya & Seltzer (1982). Lying ventral to it, on the medial wall of the hemisphere, is a cortical territory variously named PGm (Pandya & Seltzer 1982), MDP (medial dorsal parietal, Colby et al., 1988), or 7m (Cavada & Goldman-Rakic, 1989a). Both areas are connected at least as strongly to V6 as V6A (compare Figs 4 and 8). Our material gave no indication of a border between PEC and 7m, although their posterior boundary is provisionally demarcated by the medial callosal perimeter of the V6 complex. All bands of label within either PEC or 7m were of H laminar character (Fig. 6, part II #1 and #2). This classification was evident from the concentration of terminal label in

![Fig. 5. Bilateral 3D reconstruction of the posterior aspect of the SPG to show interhemispheric connections to the right hemisphere following injection of WGA-HRP into the left (injection site shown by broken contour lines). Haloed numeral 4 refers to a component of Fig. 6 part II. Conventions as for Fig. 2.](image)
layer 4, but rather less so from the location of labelled cells; the latter were concentrated in three belts, one in the middle of layer 3, one at the layer 4/layer 5 interface, and one in layer 6. It is noteworthy that the presence of H patterns of labelling in areas 7m and PEC, separated from the injection site by a callosal band, is additional evidence that the callosal band does indeed demarcate the border between separate cortical areas. By contrast, patches of label inside the medial callosal perimeter of V6A were uniformly of I character, whether adjacent to the injection site (Fig. 4, part II #1), or several mm removed (Fig. 4, part II, #2 and #6).

Three cases showed a patch of label on the posterior lip of the cingulate sulcus that probably fell within a third area, PECi, designated as lying just inside the cingulate sulcus (Pandya & Seltzer, 1982). This patch was of H character in two cases (SP25 and VG17, Fig. 4, part II #5), but possibly of I character in the third (SP24).

**Intraparietal areas: MIP, VIP and LIP**

A region on the lateral wall of the SPG (i.e. the medial bank of the IPS) was termed area MIP (medial intraparietal) by Colby et al. (1988) on account of its retrograde labelling from area PO; it is otherwise a part of architectonic zone PEA which occupies the entire medial bank of the IPS (Pandya & Seltzer, 1982). In adopting this term, we note that the portion of PEA that is occupied by MIP is uncertain, for the location of label is quite variable (Figs 4 and 8). Figure 4 shows three cases with V6A injections: one, VG17 (Fig. 4C) has a solitary, long band of label that abuts, and partially overlaps the callosal perimeter of the V6 complex. In the other two cases, the labelled zones are further anterior, partially overlapping with the next callosal band along the sulcus (Fig. 4A,B). Importantly, in all three cases, there are one or more patches of connectivity lying adjacent, but clearly external, to the callosal boundary of V6/V6A that display H laminar character. Thus, as with the medial callosal boundary, the indication is that the lateral callosal band conceals the border between the V6 complex and a neighbouring area of higher rank, even if, the band being somewhat broad, the exact location of this border is rather indistinct.

Is the border between the V6 complex and MIP better localized in myelin material? Colby et al. (1988) report area MIP to be characterized by a thin dense inner band of Baillarger, well separate from the white matter—a moot distinction from the architecture of PO, where both the inner and outer bands of Baillarger are distinct (Colby et al., 1988; Galletti et al., 1996). Preuss & Goldman-Rakic (1991a) comment that they were unable to distinguish MIP architecturally from the surrounding cortex. In our own experience, the bistratified myelarchitectural typical of V6 is less prominent further inside the IPS, but the point of transition is neither sharp nor regularly located. Figure 9 shows a case where the callosal border seems to coincide with a local minimum of bistratia character. Perhaps the incoming callosal fibres are directly responsible for this local myelopetal architectural feature, but it is not a feature that we can recognize in all brains. As we are unable to delineate area MIP by its architecture, we use the term to refer to the projection zone directly adjoining V6 and V6A within the IPS.

In recording from MIP, Colby & Duhamel (1991) have noted a gradual transition from units with purely somatic sensory properties near the lip of the IPS, through a bimodal zone, to a zone at the foot of the sulcus with purely visual responses. We also found some evidence that MIP is not a unitary area. Specifically, in two cases with V6A injections, the bands of label in MIP had two components, the upper part of the band showing an H pattern and the lower part an I pattern. The point of transition occurred about one third of the way down the medial bank of the IPS in SP24 (Fig. 4, part II #3 and #4) and about midway in VG17 (Fig. 4, part II #7 and #8). The ventral component (MIPv) is thus of equivalent rank to V6A, and the dorsal component (MIPd) is of higher rank than V6A. The terminology for these subdivisions is clearly provisional, pending direct evidence for the correspondence of architectural, connectional and physiological boundaries.

Area MIP is adjoined in the fundus of the IPS by area VIP (ventral intraparietal), although their respective territories are ill defined. VIP was initially defined as the V5-projection zone within the fundus of the IPS (Maunsell & Van Essen, 1983). It has latterly been revised, on physiological criteria, to a smaller territory within the anterior half of the sulcus, ceding the most lateral zone of V5 connectivity to area LIP (lateral intraparietal, Colby et al., 1993). Even so, we think our results demonstrate connections to VIP. Both cases with V6 injections show label within the anterior portion of the medial bank, situated toward the fundus (Figs 5, 6 and 8). The V6A cases were equivocal, only SP14 having an intense band of label crossing the fundus of the IPS from bank to bank, and thus seeming to span the full width of VIP. Labelling in VIP was of H character, at least where it was sufficiently intense to characterize (Fig 6, part II #4). VIP is known to rank above V5; we would assign it a rank above V6 and, possibly, above V6A too.

Area LIP, adjoining VIP in the lateral bank of the IPS, mirrors the pattern of dorso-ventrally oriented bands seen on the medial bank. This pattern is also duplicated by inputs to LIP from areas V4 and V5, and by callosal connections (Shipp & Zeki, 1995b). The two cases with the most extensive sets of connections are shown in Fig. 10. Both probably invade LIP, but they occupy separate territories. One, SP19, shows connections from V6 that are concentrated toward the border with area VIP, and were of H character. This observation tallies with previous reports of a connection between LIP and area PO (Colby et al., 1988; Cavada & Goldman-Rakic, 1989a; Andersen et al., 1990; Blatt et al., 1990; Morel & Bullier, 1990; Baizer et al., 1991). The other case shown in Fig. 10, SP24, has connections from V6A that adopt a more rostromedial location. LIP occupies roughly the caudal half of the IPS, as specified by the zone of rich connectivity to the frontal eye field (Andersen et al., 1985; Blatt et al., 1990). Hence, the anterior band of labelling in SP24 probably exceeds LIP and represents a connection with the anterior parietal area (AIP, Preuss & Goldman-Rakic, 1991a). The bands had unusual laminar characteristics – supragranular cells were more prominent than infragranular cells, and terminal label was heaviest in layers 1 and 4. By our heuristics, this defaults to I category.

**Areas V5, V5A (MT/MST) and 7a**

Label was found within both banks of the superior temporal sulcus (STS) in all five cases, but only within its most dorsal extent (Fig. 11). We took the label in the posterior bank to represent area V5, since we know that peripheral parts of area V5 are reciprocally connected to V6 (Colby et al., 1988; Galletti et al., 1996), and that the peripheral representation in V5 lies dorsally within the STS (Gattass & Gross, 1981; Van Essen et al., 1981; Maunsell & Van Essen, 1987). The pattern of label in V5 was judged to be of L character in cases where area V6A was injected (SP24 and VG17), suggesting that V5 is of lower rank than V6A. In SP25, the laminar patterns showed greater variability; V5 in this case seemed to contain both L and I patterns of connectivity at opposite ends of a single continuous band of labelling. Since the injection site in SP25 was one that involved both V6 and V6A, the additional labelling of I character in V5 might be attributed to the connection with V6.

The label in the anterior bank was continuous with a broader zone of labelling found on the surface of the IPG (inferior parietal gyrus) –
part of a region referred to as 7a (Andersen et al., 1985; Cavada & Goldman-Rakic, 1989a; Andersen et al., 1990), or as PP (posterior parietal, Desimone & Ungerleider, 1986; Colby et al., 1988). All cases showed labelling in 7a that was of H laminar character (Fig. 12). Area 7a can be distinguished architecturally by its prominent radial fibre bundles and strings of cells (Andersen et al., 1990); it is basically bistriate, although the outer fibre plexus is more marked. This architectural pattern extends into the anterior bank of the STS and at least halfway to the fundus, eventually giving way to a non-striate pattern which lacks prominent radial bundles. The latter is known as ‘the densely myelinated zone’ and it occupies the boundary of area MST (medial superior temporal area, Desimone & Ungerleider, 1986; Ungerleider & Desimone, 1986; Andersen et al., 1990). Connections between V6A and MST were sparse, if present at all. Case VG17 (Fig. 11A), for instance, had strong H patches of labelling within 7a (Fig. 12, #2 and #3), but across the myeloarchitectural 7a/MST border, closer to the fundus, labelling was fainter, and possibly of I character. By contrast, the zone of H labelling in cases SP25 and SP19 extended far nearer to the fundus than the cases with injections restricted to V6A alone (Fig. 11C,D). Although the available material did not directly reveal the MST/7a border in these two cases, we draw the overall inference that V6 has heavier connections to area MST than does area V6A.

Frontal cortex

The major frontal connections of the V6 complex were with the dorsal premotor cortex (area 6). In all cases (except SP14, in which the frontal cortex was not examined), these were centred on the dorsomedial bank of the arcuate sulcus and extended on to the cortex lying medial to the arcuate sulcus, in one case as far as the superior precentral sulcus (Fig. 13). There was a separate and less intense connection with the ventral limb of the arcuate sulcus. There was
also minor labelling of supplementary motor cortex, on the medial wall above the cingulate gyrus. This zone was always separate to that within the arcuate sulcus. Connections with the anterior bank of the arcuate sulcus — the site of the physiologically determined frontal eye field (FEF) — were present only in two cases, SP19 and SP25. Since these are the pair with V6 involvement, it implies that V6, not V6A, is reciprocally linked to the FEF. Finally, in three cases, there were small amounts of label sited posteriorly within the medial bank of the principal sulcus, area 46dr (Walker, 1940; Preuss & Goldman-Rakic, 1991b). The one case lacking a connection here, SP19, was the only one with no involvement of V6A.

We sought to localize the label in dorsal area 6 with respect to cytoarchitectural features that demarcate separate premotor areas. Barbas & Pandya (1987) have defined area 6DR as a dorso-rostral sector of area 6 lacking giant pyramidal cells in layer 5. Such cells can be found in area 6DC (the caudal part of dorsal area 6), and are still more numerous within the primary motor cortex — the traditional architectural distinction between areas 4 and 6 (Brodmann, 1909; Vogt & Vogt, 1919; Wehrich & Wise, 1982). Our label in the dorsal premotor cortex was situated several mm anterior to the main field of these giant cells, and anterior to the caudal border of 6DR, as illustrated by Barbas & Pandya (1987). However, we note (as do Matelli et al., 1991) that rostrally, the progressive scarcity of giant cells makes the task of locating their anterior frontier an unpleasantly arbitrary judgement. In fact, one or two sporadic, giant (or conspicuously large) cells were commonly found within the columns of labelling in each section, occasional giant cells themselves being filled with tracer. Matelli et al. (1991) rely on more subtle cytoarchitectural features to demarcate their rostral partition of dorsal area 6 (area F7), from the caudal area (area F2). While able to recognize some of these architectural trends, we were still unable to draw firm boundaries on our nissl-counterstained material. However, referring to the published illustrations, it is clear that our zone of labelling straddled the border between areas F7 and F2, perhaps being more concentrated in F7, and that medi ally our connections were located near the border of areas F6 and F3 (SMA, Matelli et al., 1991; Luppino et al., 1993).

The laminar patterns of labelling of premotor cortex were consistent between cases. Normally labelled cells were prevalent in the upper layers (2 and 3), and terminals were concentrated in the middle layers, which in the premotor cortex are commonly denoted 3 and 5; layer 4 is deemed absent (Fig. 14). In some patches of label, the terminals were more diffuse superficially, extending into layer 1. In general, the pattern appeared to be of H character. However, given the absence of a granular layer 4, it is prudent to note that the laminar systematics derived from the visual cortex (where layer 4 is always obvious) may not necessarily be applicable (see Discussion). Labelling in the principal sulcus and the FEF, where the cortex is once again granular, was too light or inconsistent to classify with confidence.

Discussion

We amplify a previous report (Galletti et al., 1996) to distinguish areas V6 and V6A (the V6 complex) which occupy the most medial sector of the prestriate visual cortex and its interface with the parietal cortex on the posterior aspect of the SPG. By analysing their extrinsic circuitry amongst the network of visual areas, it appears that V6 ranks alongside V4 and V5, whilst V6A may be level with areas, e.g. MST or LIP; and, surveying the network from a horizontal

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![Image](image-url)
FIG. 7. Coronal and sagittal re-sections of a 3D reconstruction (not illustrated) to show the distribution of label following an injection of WGA-HRP into area V6A (top row, case SP24 and bottom row, case VG17). The selected sagittal (left), coronal (centre) and horizontal (right) sections are those that intersect the labelled region of area V3. The distribution of transported label is indicated by red dots or lines. The injection site (‘inj’) is marked by regions of oblique hatching. Separate dials show the orientation of antero-posterior, medio-lateral and dorso-ventral axes in the three planes of section. The transects at the level of the depicted horizontal section in the coronal and sagittal re-sections are shown in dark grey, and the sagittal and coronal planes are shown by superimposed hair-lines; other conventions are the same as Fig. 6. The 5 mm scale applies to both sets of diagrams.

perspective, that the V6 complex lies at one extreme. This is evident from its position near the edge of the cortical sheet, its input from neighbouring peripheral V2 – setting up an emphasis on peripheral visual field – and its output, much of which is directed to nearby areas of the parietal lobe; the latter are traditionally regarded as areas of somatosensory association cortex, linking to the motor cortex. Together with physiological findings (Galletti et al., 1991, 1993, 1995, 1996), it appears that V6 and V6A play a specialized role in gross spatial analysis along the superior parietal pathway for visuomotor integration (Caminiti et al., 1996).

Areas V6 and V6A as defined by patterns of connectivity

The borders of the V6 complex, provisionally defined by the patterns of interhemispheric connectivity (Zeki, 1986), are supplemented by details of intrahemispheric connections. That there are two separate areas within the V6 complex, V6 and V6A, was suggested by the fact that injections of HRP-WGA into the dorsal SPG had to pass a certain depth (roughly halfway down the vertical extent of the POS) in order to yield label in V2; V6A does not appear to be connected to V2, and this is the major difference in the sources of input to the two areas. Colby et al. (1988) also reported that V2 was the strongest source of input to area PO (approximating to V6, see Galletti et al., 1996). The projection from V2 to PO has lately been studied by orthograde tracer injections into peripheral V2, but the anatomical reconstructions lack the resolution to indicate its dorso-ventral extent (Gattass et al., 1997). However, injections into V6A, or into peripheral V5 (see Fig. 4B; also figs 5 and 6 of Galletti et al., 1996) can produce broad swathes of labelling over the posterior face of the SPG, indicative of the territory of V6.

Could there be more than one area within this territory? The question is prompted by recognition of a number of potential discrepancies with the earlier study of Colby et al. (1988), that reports the results of five injections of fluorescent dyes into area PO at the foot of the SPG, all sited rather more ventrally than our own. Differences include connections of PO: (i) with V1, V4, and V4T; (ii) with representations of superior visual field in areas V1, V2, V3 and V4; and (iii) with the FEF but not area 6 of the frontal cortex. Some rationalization, perhaps, can be advanced for all these discrepancies. (i) The labelling in V1 and V4/V4T was described as ‘moderate’ and ‘sparse’, respectively, so it might reflect superiority of dyes over WGA-HRP for revealing retrograde transport to these areas. (ii) Two PO injections were deliberately placed on the medial
surface of the hemisphere, within the superior field representation of PO as identified physiologically – none of our injections was placed so far medial. (iii) Although the FEF is the only frontal area directly identified by Colby et al. (1988), the report does mention that label in the frontal cortex extended from the posterior bank of the arcuate sulcus to the principal sulcus—a zone that actually incorporates part of area 6 in addition to area 8. The alternative, nonetheless, would be to regard the cumulative impact of these discrepancies as greater than the sum of their parts – the emergent idea being that area V6/PO is itself composed of two distinguishable zones, Colby et al. (1988) having studied the ventral one and ourselves the more dorsal one. A complementary idea is the view expressed by Galletti et al. (1996) that the pair of areas PO/POd described in the New World Cebus monkey by Neuenschwander et al. (1994) together correspond to PO, as defined by Colby et al. (1988) in macaques. As the conflicting evidence is far from conclusive, we shall continue to treat ‘V6’ as a unitary area.

Further evidence of separate areas (V6/V6A) derives from the laminar patterns of connectivity. Having divided the posterior face of the SPG into three zones, characterized by H, I or L laminar patterns, we traced a provisional border between areas V6A and V6 as the locus of the transition from the I zone, around the injection site, to the L zone found more ventrally (Galletti et al., 1996). We also used laminar analysis to support demarcation of the V6 complex by its callosal perimeter, since some patches of label separated from the injection site by a callosal band were found to be of a H hierarchical status, indicative of an area distinct from V6 or V6A.

Laminar criteria for assessing hierarchical status of remote areas

An association between the laminar origins and terminations of reciprocal forward and feedback pathways has been noted by many authors, in particular Rockland & Pandya (1979) and Maunsell & Van Essen (1983), the latter being the first to construct a systematic hierarchy based on the consistency of these associations across a number of separate visual areas. Subsequent examination of the interconnections of prestriate areas, and the extension of the scheme to parietal and temporal cortex, have revealed that laminar relationships are not always so orderly; yet they can be accommodated within a systematic hierarchy under more liberal criteria for identifying a connection as forward or backward (Andersen et al., 1990; Boussaoud et al., 1990; Feleman & Van Essen, 1991). Using the bidirectional tracer WGA-HRP, the expectation is to find a systematic relationship between the terminal elements of a projection and the origins of the reciprocal connection.

The standard pattern for a higher area is supragranular cells with terminals in 1 and 6, and infragranular cells with terminals in 4 for a lower area. An area at the same hierarchical level should show ‘intermediate’ laminar distributions – bilaminar cells and diffuse terminals.

What we found, in fact, was that a forward termination could also be accompanied by a bilaminar distribution of labelled cells: one example was area 7m, where supra- and infragranular cells were about equally numerous, though the concentration of terminals in layer 4 indicated a forward-going input; another was in either bank of the IPS, where again the termination was ‘forward’, yet supragranular cells were often predominant. We thus preferred to downgrade the significance of the cellular labelling in the assessment of hierarchical relationships, and effectively made dominant use of the terminal pattern in identifying the H, I or L categories. A further complication is that the range of terminal laminar patterns is more variable than allowed by a simple continuum between the canonical extremes. For instance, Andersen et al. (1990) note that the projection from parietal area LIP to temporal area TF terminates most densely in layers 4 and 6. We classified this pattern as intermediate (I), as with other patterns which showed equal concentrations of terminals.

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Fig. 8. Three views of a 3D reconstruction of the SPG of SP19, following an injection of WGA-HRP predominantly within area V6; the dorsal ‘tail’ of this injection represents minor leakage along the syringe track. Medial view, at left, shows the medial wall of the hemisphere including the cingulate sulcus (CgS) and a medial accessory sulcus to the POS (mPOS). Posterior and lateral views show the anterior banks of the POS and IPS. Likely cortical areas are assigned to each patch of label on the basis of its position. Conventions as in Fig. 2.
in layer 4 and another layer, e.g. layer 1. The set of conventions we finally adopted is summarized in Table 1. The emphasis that we place on axonal terminations is not unique to the connectivity of V6: the review of Felleman & Van Essen (1991), also sets out a consensus that the laminar pattern of projecting terminals is the more consistent index of hierarchical status.

Hierarchical rank of V6

Figure 15 is a mini-hierarchy to summarize the major connections between V6, V6A and other areas, as constructed from the data presented here. Basically, V6 appears to be at the same level as V5. This is level 5 in the scheme of Felleman & Van Essen (1991) (also Andersen et al., 1990), but level 4 in ours due to the inclusion of V3A at a rank equal to that of V5 and V6. The number of levels in any such scheme depends on the resolution at which one feels confident of drawing fine anatomical distinctions. Felleman and Van Essen themselves point out that the clarity with which the laminar pattern of a particular connection fits the forward or backward category depends on the number of levels it crosses. We tend toward the view that ‘hierarchical rank’ is best thought of as a continuum, and that its representation as discrete levels is a convenient abstraction.

But what is the broader functional significance of ‘rank’, as determined in a narrow sense by these purely anatomical criteria, and can it be extended to motor cortex? The least sophisticated viewpoint would be to consider the network linking visual to motor cortex as a single hierarchical system, with a basic input–output polarity: downstream from V1, sensory inputs diminish in density and motor outputs rise more frequently. The final downstream terminus should be M1 (1° motor cortex) itself, and it is the general thrust of our results, and others (Fig. 16) that the visuomotor pathway arrives at this end via certain rostral areas of premotor cortex. There is a likelihood, however, that following established laminar connectivity criteria, premotor area 6 ranks above area 4 (i.e. M1) (see the somatomotor hierarchy of Felleman & Van Essen, 1991). If so, the ranks inferred from laminar connectivity would here be in opposition to the overall polarity of the visuomotor pathway. Conceivably, the distinct architecture of the motor cortex – the fact that it lacks a granular layer 4 – may be a related phenomenon; the factors that govern the laminar specificity of connections, and their relation to laminar differentiation of function, are far from understood. These simple observations challenge the idea of ‘rank’ as an ordinal level of processing, and they preclude the construction of a grander visuomotor hierarchy.

**Fig. 9.** Illustration of transcallosal and intrahemispheric connections in relation to myeloarchitecture, following an injection into V6A (case VG17). The location of these horizontal sections, through the medial bank of the IPS, is indicated in Fig. 4C; anterior is to the right. (A) and (D) Darkfield view of a patch of transcallosal axonal degeneration. The large arrowhead indicates the point of maximal intensity, marking the border between V6A and MIPd. Dark dots divide cortical layer 6 from white matter. (B) and (E) Cross-polarizing view of WGA-HRP labelling, showing the injection site to the left of the transcallosal patch and an ascending projection to MIPd to its right. (C) and (F) Myeloarchitecture of this region, in which a bistriate pattern is weakly discernible on the margins of the transcallosal patch, but not at its focus. Small arrowheads point to blood vessels that help to align the sections. Scale bar (in F) is 1 mm (uncorrected for shrinkage), applicable to all panels; the scales of reproduction of (A), (B), (D) and (E) have been adjusted to compensate for the relatively greater shrinkage induced by the associated histological procedures.
Fig. 10. Three-dimensional reconstruction of the lateral bank of the IPS from two cases to contrast the patterns of connection from V6A (above, SP24) and V6 (below, SP19). The outline of a single horizontal section, at the ventral-most level of the IPS, is included for ease of reference. Patches of label are assigned to the ventral, lateral and anterior intraparietal areas (VIP, LIP and AIP). Other conventions follow Fig. 2.

Functional properties of V6

In both anaesthetized and alert states, V6 shows levels of orientation and velocity tuning that are comparable to the properties of its antecedent and reciprocally connected visual areas (V3 and V3A) studied by identical methods (Zeki, 1978 and unpublished results; Galletti & Battaglini, 1989; Galletti et al., 1990, 1991, 1996). There is also a variety of extraretinal properties. Galletti et al. (1991) found 20% of neurons recorded in the V6 complex to display perisaccadic activity; about half were presaccadic, implying that V6 is part of the extensive oculomotor circuitry of the visual system, in accordance with its projection to the middle layers of the superior colliculus (Zeki, 1986). The other half, being postsaccadic, imply a function that is oculometric, one of adapting to the consequences of a shift in the direction of gaze. A better expression of this role is provided by gaze sensitivity, a property that Galletti et al. (1995) report for over half the visual cells tested. They occur in both V6 and V6A (Galletti et al., 1996) with properties not dissimilar to those found in strongly connected areas, e.g. V3A and 7a (Galletti & Battaglini, 1989; Squarrito & Maioli, 1996). V6A shows a further evolution of eye position dependency, in its synthesis of a small population of cells with receptive fields expressed in head-centred, as opposed to retinotopic, co-ordinates (Galletti et al., 1996): such fields retain an invariant location on the stimulation screen as the eyes adopt different angles of gaze, or in other words qualify as ‘real position’ cells (Galletti et al., 1993, 1995). Although the response of these cells to an object at a fixed location in space is now independent of eye position, their activity remains ‘oculometric’ in the sense that it cannot be attained without integration of retinotopic and eye-position signals. It is this inferred role in the construction of a map of body-centred space that informs the following analysis of the ascending outputs of V6.

Visuomotor connections of V6/V6A: a comparative analysis

As a rule, a cortical area is relatively heavily connected to neighbouring regions of the cortex (Young, 1992). V6 and V6A are no exception, but because many of the nearby areas in the superior parietal cortex also receive ascending somatosensory input, this sensory convergence establishes units with dual visual and tactile sensitivities. Such bimodal neurons have been found in at least two areas receiving input from V6, MIP and VIP (Colby & Duhamel, 1991; Duhamel et al., 1998), and may be inferred in others, e.g. PEc and 7m/MDP. These areas in turn have links with the frontal cortex, so setting up a visuomotor pathway from the SPG (reviewed by Caminiti et al., 1996). In this context, it comes as little surprise that V6 and V6A themselves make direct connections with the frontal lobe, mainly to a rostral zone of agranular cortex (area 6) that is generally referred to as the premotor cortex (Wise, 1985). Yet it does contrast with the majority of other visual areas, whose frontal connections are dominated by links to the frontal eye fields (granular area 8), lying in the anterior bank of the arcuate sulcus, to which V6/V6A make only very meagre connections (Huerta et al., 1987; Schall et al., 1995; Stanton et al., 1995). The contrast is particularly marked in comparison to area LIP, for instance, known to be robustly connected to the prearcuate cortex including the FEF, but hardly, if at all, to the postarcuate cortex (Andersen et al., 1985; Cavada & Goldman-Rakic, 1989b; Andersen et al., 1990; Blatt et al., 1990). LIP, of course, is a known oculomotor centre, with as many as 70% of neurons displaying presaccadic activity (Barash et al., 1991). The corresponding figure
for V6 is about 10% (Galletti et al., 1991). This pattern of anatomical and physiological evidence leads us to conclude that the involvement of V6 and V6A in guiding bodily movement is essentially skeletonmotor rather than oculomotor.

Connections between parietal and premotor cortex have formerly been considered in relation to the relay of information from the somatosensory association areas. Specifically, area 5/PE on the SPG has been well documented to be connected to the dorsal premotor cortex, and area 7b/ PF on the IPG to the ventral premotor cortex (Jones & Powell, 1970; Petrides & Pandya, 1984; Matelli et al., 1986; Cavada & Goldman-Rakic, 1989b; Andersen et al., 1990). The higher somatic-sensorimotor areas in the SPG and IGP receive parallel somatotopic input from opposite poles of the primary map of the body surface on the postcentral gyrus (Jones et al., 1978; Pandya & Selitzer, 1982). The output from the SPG is thus primarily concerned with the limbs and trunk, and that from the IGP with the hand, head and face; to reiterate, the V6 complex is far more heavily connected to the former than the latter. A corresponding polarity exists in the primary motor cortex and in the more fragmented representations to be found within the multiple areas that constitute the premotor cortex. In the ventral premotor cortex (PMv), e.g. the hand/arm field is known to reside in the vicinity of the spur of the arcuate sulcus, and the mouth field to lie more laterally (Muakassa & Strick, 1979; Godschalk et al., 1984; Matelli et al., 1986; Gentilucci et al., 1988). Leg-related fields are absent from PMv, but are found in the dorsal premotor cortex (PMD), sited medial to additional arm fields (Kurata et al., 1985; Kurata, 1989; Dum & Strick, 1991; He et al., 1993; Godschalk et al., 1995).

It is mainly to PMd that we observed a projection from V6/V6A – specifically to its rostral half, in the posterior bank of the superior limb of the arcuate sulcus and its dorsal lip. Smaller projections were found to PMv and motor areas on the medial wall. These connections had not been suspected until recently; most foregoing studies of premotor cortex connectivity had either targeted different regions of the premotor cortex or failed to examine sections sufficiently far caudal (Godschalk et al., 1984; Matelli et al., 1986; Barbas & Pandya, 1987; Kurata, 1991). However, the regions immediately around the V6 complex are known to connect with the dorsal premotor cortex. A back projection from the dorsal postarcuate cortex to area 7m/PGm on the medial wall of the hemisphere was illustrated by Kunzle (1978) (case ‘74-626’), and the text hints that the labelled region may have included V6/V6A. The reciprocal connection of 7m to PMd has also been demonstrated (Petrides & Pandya, 1984; Cavada & Goldman-Rakic, 1989b). Most recently reported are injections into PMd that reveal heavy inputs from area MIP and from other areas neighbouring V6A on the SPG, e.g. PEc and PGm/MIP/7m; it is reported that the region of labelled cells may also infringe on area PO (identified as a myeloarchitectural field), but it is equally clear that PO is not the primary focus of this connection (Johnson et al., 1993, 1996; Tanné et al., 1995). As MIP and 7m are known targets of PO/V6 itself, these pathways are capable of relaying visual signals to the dorsal premotor cortex. And this fact raises one possible concern: what if our injections had spread outside the V6 complex, and it is one of these neighbouring areas that is primarily responsible for the observed output to the premotor cortex? We suspect not, for if substantial quantities of WGA-HRP had been taken up by some part of area 5/PE (i.e. 7m, PEc or MIP), there should have been signs of transport to other somatosensory structures, e.g. the oral pulvinar and lateral posterior nuclei of the thalamus. Equally, we should have found L patches of labelling in a cortical area at an earlier stage in the somatosensory pathway. We observed neither. The most likely interpretation of our material is that areas V6A and V6 have a direct output to the frontal cortex – specifically to a region which is just rostral to that investigated by Johnson et al. (1993, 1996) and Tanné et al. (1995).

This zone of dorsal premotor cortex in receipt of input from V6/ V6A is within area F7 (Matelli & Luppino, 1992), or area 6DR (Barbas & Pandya, 1987). The connection of V6/V6A with the medial wall was much lighter and probably situated in area F6, perhaps bordering on area F3/SMA. The gap between the lateral and medial premotor sites that communicate with V6/V6A is at least partially occupied by the supplementary eye field, which (in comparison to the FEF) receives minor visual input and none directly from the region of V6 on the SPG (Huerta & Kaas, 1990). The superior arcuate zone (F7/6DR) receiving input from V6/V6A is not directly connected to the primary motor cortex (area 4), although it has been noted that the two areas can communicate via the intervening premotor area 6DC/F2 (Barbas & Pandya, 1987). Also, unlike the primary motor cortex and area 6DC/F2, area 6DR/F7 has little or no output to the spinal cord (Dum & Strick, 1991; He et al., 1993), and the latter authors question whether it should, in fact, be regarded as premotor cortex; accordingly, the same region proves unexcitable in microstimulation studies (Godschalk et al., 1995). This region lies just rostral to a motor arm field, as charted by maps of limb movement-related activity (Kurata, 1989), maps of the distribution of corticospinal neurons projecting to the cervical segments (He et al., 1993), and microstimulation motor maps (Godschalk et al., 1995). Yet the superior arcuate zone receiving input from V6/V6A is a ‘grey’ area on all of these maps and, to date, its functional properties are unknown. We infer that it must play some role in visually guided arm movements, for it is heavily connected to the arm field (see fig. 4 of Barbas & Pandya, 1987), where numerous studies have recorded activity during visually guided reaching. Individual neurons here can be specific for reaching in particular directions within a shoulder-centred coordinate system (Caminiti et al., 1991); by comparison, neurons in medial area F6 are active in a broader range of arm movements, the location (or presence) of a visual target not being such an important factor (Rizzolatti et al., 1990).

Fig. 11. Three-dimensional reconstructions to contrast the patterns of connection with areas 7a, MST and V5 in the superior temporal sulcus, following injections into V6A and V6. (A) Three-dimensional reconstruction of a single hemisphere (presented as a right hemisphere) showing an injection site (I.S.) in V6A on the superior parietal gyrus (partly occluded broken lines). Visible labelled areas include DP and 7a on the prelunate and inferior parietal gyrus, and areas MIP, 7a and PMd within the intraparietal (IPS), superior temporal (STS) and arcuate sulci (AS), respectively; SS is the sylvian sulcus. The highlighted horizontal section is duplicated below, together with a portion of the anterior bank of the STS rising above it, containing label in area 7a. This assembly is rotated, to the right, to present a rear view, and the posterior bank of the STS is also presented from the identical rear viewpoint, to show labelling in area V5. Numbered locations (2) and (3) are the sites of photomicrographs shown in Fig. 12. (B)-(D) Separate 3D reconstructions of the anterior and posterior banks of the dorsal STS, from three additional brains. The outline of the base section gives a further indication of the viewpoint. These are all antero-medial views, the exact rotation being chosen to optimize visibility of the labelling patterns in areas 7a, MST and V5, dependent on the unique conformation of the STS in each case. (B) Connections of V6A; (C) connections of V6; (D) connections of V6/V6A. Conventions as in fig. 2.

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In the postarcuate arm field, it has recently been found that, while performing a reaching task involving a visual cue and a period of enforced delay, it is the more rostral components that show the most prominent 'visual-signal'- and 'set'-related activities (Johnson et al., 1996; Tanné et al., 1995). Both groups model their results as a functional gradient across this arm field (extending through F2 into the primary motor cortex), wherein activity related to target localization is expressed rostrally and activity related to movement generation more caudally. There is an accompanying anatomical gradient, with the rostral pole of the arm field receiving input from area MIP, and the caudal pole receiving input from parts of area 5/PE that are situated upon the SPG rostral and dorsal to MIP (Johnson et al., 1996; Tanné et al., 1995). If so, the connection of premotor area F7/6DR with V6 and V6A seems to extrapolate this gradient anatomically, as a projection from a yet more caudal part of the SPG to a yet more rostral part of agranular area 6; and physiologically as a signal from the visual precursor of MIP to the visually activated rostral frontier of the premotor cortex. Figure 16, examining routes from V1 to M1, summarizes these occipito-parieto-frontal connections.

Functional hypotheses

The connections between V6/V6A and premotor cortex appear to respect two gradients, not only the rostro-caudal one related to a hierarchy of motor preparation, but also a dorso-ventral one related to somatotopy. Although the connection to PMd was the most extensive, we did find a minor connection of V6A/V6 with PMv, specifically area F5 (Matelli & Luppio, 1992), or 6Va (Barbas & Pandya, 1987) in the posterior bank of the ventral limb of the AS. This area has a hand field and is reported to be active in specific forms of grasping, including feeding (Rizzolatti et al., 1988; Jeannerod et al., 1995). Thus, if PMv acts as a premotor cortex for the hand and face, PMd, with its partly intercalated leg and arm fields (Kurata, 1989; He et al., 1993), must be involved with directing lower body movements, as well as arm-reaching within body-space remote from the head. It is probably no coincidence to note that visual RFs recorded from V6 and V6A (in regions equivalent to those injected with WGA-HRP) are heavily concentrated around the peripheral lower vertical meridian (Galletti et al., 1991, 1995; Zeki & Shipp, unpublished results), doubtless the most common location within the field of view of the trunk and limbs. We suppose, therefore, that the nature of the field representation in V6/V6A predisposes these areas for participation in visual guidance of movements within more remote peripersonal space.

The rostro-caudal gradient can be discussed in terms of the control of reaching. As it has been proposed that the brain codes reaching movements as a vector of hand motion in external space (Georgopoulos, 1990), it is natural to suppose that V6/V6A provides the target coordinates, i.e. the end point of the vector, to the premotor cortex. Equally, V6/V6A could also help to signal the start point of the vector, especially as a recent study finds that initial hand position is coded by a ‘weighted fusion’ of visual as well as proprioceptive signals (Rossetti et al., 1995). Theoretical discussion of the control of reaching invokes a series of coordinate transformations of visual signals, from eye, to head, to body and shoulder-centred frames of reference (e.g. Flanders et al., 1992). The natural pathway for such a transformation lies through area 5, where visual signals can be integrated with proprioceptive and kinaesthetic feedback from the arm and neck. Some such fusion of visual and proprioceptive signals relating to the hand has been found in area 7m (Ferraina et al., 1997a, 1997b). Ultimately, the visual location of hand and target might be rendered in the intrinsic coordinates of the elbow and shoulder joint angles. Subtraction would yield the arm movement vector that appears to be coded in the premotor cortex, where the population of directional movement cells specifies the change of elbow and shoulder joint angles.
Fig. 13. Three-dimensional reconstructions to show the pattern of frontal connections made by V6/V6A. Top left: 3D reconstruction of a single hemisphere (SP25, presented as a right hemisphere) showing an injection site (I.S.) on the dorsal superior parietal gyrus (partly occluded dotted lines). Labelling is visible in area 7a on the inferior parietal gyrus, area MST within the superior temporal sulcus, area PMd within the superior precentral sulcus (SPcS) and arcuate sulcus (AS), and area 46 in the principal sulcus (PS). Top right: the prearcuate and postarcuate gyri have been 'dissected' and displayed as if viewed from inside the hemisphere. Naturally, this inverts the antero-posterior axis, such that the central sulcus (CS) forms the right hand margin of these extracts, and the infoldings of the arcuate and principal sulci appear on the left. The long arrowheads point from the superior lip of the arcuate sulcus in the whole brain to the corresponding point on the extract. Lower left and lower right: similar extracts from cases SP19 and SP24 following injections in V6 and V6A, respectively. Arrowheads indicate the level of the superior lip of the arcuate sulcus. Other conventions as in Fig. 2, except that the viewpoint for the three extracts is from an inferior vantage.
angles to reach in a given direction in 3D arm-centred space (Caminiti et al., 1991; Burnod et al., 1992). In general terms, the idea would be that the further the transformation by area 5, the less ‘work’ that is necessary in area 6; hence, the rostro-caudal gradients, or mirror symmetry of connected sites across the central sulcus. Thus, output from V6/V6A, at the caudal pole of the SPG, arrives most rostrally in the premotor cortex, suggestive of lengthier processing along the pathway leading caudally to 1° motor cortex. Although the presence of a direct anatomical link from V6 to area 6 implies that elaborate coordinate transformation is not obligatory, the circumstances in which alternative circuits are operational are speculative: perhaps in adjustment of trajectory toward the terminal phase of a reaching movement, where the hand is guided precisely to its target by visual feedback; or the relatively rapid compensation for displacement of the target once a reaching movement has been initiated (Goodale et al., 1986; Paulignan et al., 1991). Once the target is fixated, the optic axis is approximately in line with the axis of the arm. The two coordinate frames are then in spatial registration, perhaps promoting conversion of an oculocentric visual ‘error’ signal to a motor error

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signal for adjusting reach, and averting a reference to extraretinal eyeball, head, or hand position signals.

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Abbreviations

AIP anterior intraparietal area
CS calcareous sulcus
FEF frontal eye field
HI higher (characteristics of laminar labelling pattern)
I intermediate (characteristics of laminar labelling pattern)
L lower (characteristics of laminar labelling pattern)
IPG inferior parietal gyrus
IPS intraparietal sulcus
LIP lateral intraparietal area
MDP medial dorsal parietal area
MIP medial intraparietal area
MST medial superior temporal area
MT middle temporal area
PMd dorsal premotor area
PMv posterior parietal
TMb tetra-methyl-benzidine
SPG superior parietal gyrus
STS superior temporal sulcus
VIP ventral intraparietal area
WGA-HRP wheatgerm agglutinin conjugated to horseradish peroxidase

References


A visuo-somatomotor pathway in the macaque 3191


