The importance of being agranular: a comparative account of visual and motor cortex

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The agranular cortex is an important landmark—anatomically, as the architectural flag of mammalian motor cortex, and historically, as a spur to the development of theories of localization of function. But why, exactly, do agranularity and motor function go together? To address this question, it should be noted that not only does motor cortex lack granular layer four, it also has a relatively thinner layer three. Therefore, it is the two layers which principally constitute the ascending pathways through the sensory (granular) cortex that have regressed in motor cortex: simply stated, motor cortex does not engage in serial reprocessing of incoming sensory data. But why should a granular architecture not be demanded by the downstream relay of motor instructions through the motor cortex? The scant anatomical evidence available regarding laminar patterns suggests that the pathways from frontal and premotor areas to the primary motor cortex actually bear a greater resemblance to the descending, or feedback connections of sensory cortex that avoid the granular layer. The action of feedback connections is generally described as ‘modulatory’ at a cellular level, or ‘selective’ in terms of systems analysis. By contrast, ascending connections may be labelled ‘driving’ or ‘instructive’. Where the motor cortex uses driving inputs, they are most readily identified as sensory signals instructing the visual location of targets and the kinaesthetic state of the body. Visual signals may activate motor concepts, e.g. ‘mirror neurons’, and the motor plan must *select* the appropriate muscles and forces to put the plan into action, if the decision to move is taken. This, perhaps, is why ‘driving’ motor signals might be inappropriate—the optimal selection and its execution are conditional upon both kinaesthetic and motivational factors. The argument, summarized above, is constructed in honour of Korbinian Brodmann’s centenary, and follows two of the fundamental principles of his school of thought: that uniformities in cortical structure, and development imply global conservation of some aspects of function, whereas regional variations in architecture can be used to chart the ‘organs’ of the cortex, and perhaps to understand their functional differences.

Keywords: hierarchy; feedback; architecture; connectivity

To lose one layer, area 4, may be regarded as a misfortune; to lose two looks like carelessness.¹
(‘Lord Brodmann’)

1. INTRODUCTION

Brodmann’s enduring map of the human brain was the culmination of a decade’s study of cerebral structure and had broad foundations in his work on the brains of many other creatures, both primate and non primate. Many of Brodmann’s area borders were, by his own admission, indistinct and difficult to localize. However, his confidence in drawing them had been raised by finding similar, sometimes clearer cytoarchitectural features across the mammalian kingdom. If some of his area numbers are still in use today, it is because other anatomical or functional criteria have been found to concur with his system, establishing the ‘area’ as a distinct functional unit of some kind, within the larger cortical enterprise.

This, of course, was exactly Brodmann’s vision. He was one of the foremost exponents of the principle of functional localization in the cortex, and it must have been his faith in this principle that motivated the arduous and detailed study of so many species. He writes, ‘There is an undisputed axiom: physiologically dissimilar elements have dissimilar structures. Reversing this statement, one may equally justifiably conclude that parts of organs that are structurally different must serve different purposes’ (Brodmann 1909, 1994). Direct evidence to hand was the observed correlation of his areas 4 and 6 with electrically excitable motor cortex and good indications of correspondence between Henschen’s calcarine visual centre and area 17. For Brodmann, though, the aim was to chart *all* the constituent organs of the cerebral cortex, even without any notion of their functional quality, in the expectation of facilitating that eventual functional parcellation. Time has proved him right.

This was, and remains today, a purely *cartographical* examination of structure and function. The differing cytoarchitectonic fields may betray different cortical operations, but precisely how different functions

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dictate (or depend on) different structural patterns—what might be termed the *analytical* approach to structure and function—remains a puzzle. Typically enough, the nearest discussion of this question, concerning the function of the ‘giant’ cells that Betz had earlier described in motor cortex (area 4), was one that Brodmann approached critically. It had been proposed, among other ideas, that these cells were huge as a direct consequence of supporting a cortico-spinal axon, that the size of the nerve cell should be proportional to the length of the nerve fibre. Brodmann was unhappy with the idea, noting the lack of correlation of cell size and body size across species and, in man, that the giant pyramids serving the trunk were no larger than those activating the upper limb, although the former pathway was considerably longer (Brodmann 1994, pp. 66–74). His conclusion, that many factors might play a role in determining cell size, was later supported by the finding that Betz cells account for fewer than 5% of all cortico-spinal fibres (Lassek 1941).

Regarding the functional underpinning of the myriad other cytoarchitectural variations, there remains little to be said. Perhaps the most prominent is the sharp demarcation of the ‘agranular’ motor areas 4 and 6 from prefrontal and parietal cortical regions. Brodmann was able to identify a homologous agranular zone in the brain of every species he examined, although in the human brain its location was unusually posterior, a testament to the evolutionary expansion of the prefrontal cortex. Brodmann also noted that the presumptive cortex of areas 4 and 6 was of conventional, six-layered appearance during foetal development. The regression of the granular layer 4, and the development of the characteristic, almost unlayered, mature structure could be seen (in common with many other cytoarchitectural fields) as a developmental transformation from the prototypical laminar structure of neocortex. Yet the fundamental question ‘why does this happen?’ or ‘what is it that layer 4 does, for which motor cortex has no need?’, remains unanswered. Worst still, it generally remains unasked in any account of motor or cortical function.

2. OVERVIEW

Cortical layers must have different functions—literally a separate (radial) dimension of functional specialization compared with that expressed between separate areas of the cortical sheet. Physiological indications of layer differences are few in number and are becoming rarer (owing to the increasing use of alert recording techniques and the consequent lack of accurate electrode track reconstructions). Fortunately, the laminar systematics of cortical connectivity offer an alternative insight into layer function. All subcortical connections, for instance, derive from deep layers. Much of the return input to the cortex (e.g. from the thalamus) targets the middle layers. And the laminar pattern of cortico-cortical connections obeys a set of principles that allows the independent construction of a multi-tiered ‘hierarchy’ of cortical areas (Felleman & Van Essen 1991). In this scheme, layer 4 is a magnet for ascending (or forward) connections, and the same layer

is almost entirely avoided by descending (feedback) connections, a pattern that is repeated from tier to tier through the hierarchy. Hence, if Brodmann’s area 4 and area 6 lack granular layer 4, the inference that might be drawn is that they also lack an ascending pathway.

This elementary clue triggers a comparative survey of motor and visual function, with regard to laminar systematics and the functional characteristics of forward and backward connections (the visual system provides the most studied example of granular, sensory cortex). The exercise throws some light upon both systems. Assuming that some functional operations can be generalized throughout the cortex, there are cryptic aspects of motor control that can benefit from an analogy with visual operations and vice versa.

3. LAMINAR SYSTEMATICS OF CORTICAL HIERARCHY

The principle of complementary laminar terminations for forward and backward connections was initially established for area V1 (in respect of feedback from area V2, which was noted to avoid the principal geniculate input layers, 4C and 4A; Tigges *et al.* 1977) and the principle was rapidly generalized for connections among occipital visual areas, where the terms ‘forward’ and ‘backward’ were understood to mean leading away from or toward area V1 (Graham *et al.* 1979; Rockland & Pandya 1979; Wong-Riley 1979; Tigges *et al.* 1981). It was also noted that forward connections arose principally from supragranular cells, and backward connections from infragranular cells. The reification of these connection patterns into a formal ‘hierarchy’ of visual areas, with several discrete tiers (Maunsell & Van Essen 1983), amounted to a subtle redefinition of ‘forward’ and ‘backward’ as descriptors of the laminar characteristics, as opposed to the direction of the connection toward or away from V1 (which, for pairs of connected areas at increasing distances from V1, and perhaps sited in different lobes of the brain, becomes an increasingly arbitrary judgement). The principle of complementarity was also adapted to include a ‘lateral’ connection between areas located in the same tier of the hierarchy. This is a symmetrical arrangement in which both areas show a laminar pattern intermediate between the forward and backward types, involving a more even distribution of cells and terminals across all layers. The successful construction of the hierarchy thus depends on its internal consistency, and the absence of connections whose laminar characteristics break the rules (Felleman & Van Essen 1991).

With the expansion of the visual hierarchy to the furthest reaches of the temporal and parietal lobes, it was found necessary to adopt more liberal criteria (Andersen *et al.* 1990; Boussaoud *et al.* 1990; Felleman & Van Essen 1991; Shipp *et al.* 1998). For instance, a bilaminar cell pattern (i.e. a set of cells of origin that are roughly equally distributed between the supragranular and infragranular layers) can be associated with either a forward or backward projection, as interpreted from the laminar

distributions of the axon terminals. This has led to somewhat greater empirical reliance on the terminal patterns in establishing the forward or backward character of a connection. The existence of a minority of connectional data that appears to violate even the more liberal rules might indicate local anomalies or might be attributable to experimental vagaries and/or defects in the current parcellation of areas (Felleman & Van Essen 1991). For instance, area FST is one trouble hot spot whose connection patterns cease to be illegal if the area is treated as two separate fields—a powerful hint that this is in fact the case² (Hilgetag *et al.* 2000). In all likelihood, laminar connection patterns exist as a continuum: there is evidence that the degree to which a particular connection fits the canonical forward or backward template depends on the number of hierarchical tiers that it traverses (Felleman & Van Essen 1991; Barone *et al.* 2000). Accordingly, the hierarchical 'rank' of an area may itself be a continuum, whose representation on a set of discrete levels is a convenient abstraction (Shipp *et al.* 1998). Certainly, the laminar systematics do not define a single, unique ordering: a computerized optimization algorithm reveals that these rules, operating on known connectivity data, actually specify huge numbers of equally valid, alternative hierarchies (Hilgetag *et al.* 2000).

Apart from its internal anatomical coherence, the reliability of the connectional hierarchy is also attested by the fact that it independently replicates orderings from physiological criteria, e.g. the growth in receptive field size and complexity along serial pathways. It is also immune to a common source of objection, that the sequence of activation of areas does not necessarily accord with hierarchical rank—i.e. that the shortest latencies may be near simultaneous in several successive tiers (Nowak & Bullier 1998; Schmolesky *et al.* 1998). The counter-argument here is simply that 'anatomical rank' in a connectional hierarchy, and 'temporal rank' in serial activation to a discrete event can, and do, reflect independent elements of cortical organization—as demonstrated by an anatomically faithful computer model of hierarchy that accurately replicates the observed timing relationships (Petroni *et al.* 2001).

What, then, do we stand to learn by deducing a regular anatomical hierarchy? Essentially, that certain local cortical operations, and certain transcortical interactions, must be conserved throughout the visual cortex. Or, in other words, if the 'Brodmann' school of thought is that structural differences imply functional differences, the complementary idea is that structural uniformity (in the sense of a six-layered cortex with a granular layer 4 and conserved laminar connection rules) implies aspects of functional uniformity. This does not just apply to the visual cortex, for similar anatomically defined hierarchies appear to exist in the auditory and somato-motor systems. The latter, however, involves the agranular frontal cortex: if we are looking for global principles of cortical function, how do the laminar systematics of connectivity adapt to the absence of a granular layer 4?

Figure 1. The somato-motor hierarchy of Felleman & Van Essen (1991), as revised with the addition of several new areas and pathways by Burton & Sinclair (1996). (Areas Ri, Id and Ig are within the insula; 35 and 36 are parahippocampal; 12M is orbitomedial.)

4. LAMINAR SYSTEMATICS IN SOMATO MOTOR CORTEX

Shortly after hierarchy was elucidated in the visual system, a similar arrangement was proposed for somatosensory processing (Friedman *et al.* 1986). Equivalent patterns of forward and backward connections were observed among the primary sensory areas 3a, 3b, 1 and 2 of Brodmann, and the secondary sensory area SII, to add to physiological evidence for hierarchy (Burton & Sinclair 1996; Iwamura 1998). The somatosensory hierarchy was subsequently extended, rather less securely, into the motor cortex by Felleman & Van Essen (1991). Figure 1 shows a modified version including a few extra areas and connections, but retaining exactly the same levels (Burton & Sinclair 1996). It should be noted that subsequent work has further fractionated a number of areas, and considerably multiplied the number of connections, so figure 1 does not represent a fully updated wiring diagram of the somato-motor system. It does however, express the main features to be examined here, namely that the agranular motor areas occupy the penultimate two strata, with area 6, and the SMA placed above area 4.

This arrangement (6 above 4) is paradoxical. In the simplest conception of there being a serial pathway from sensory input to motor output, area 4 (or M1, the primary motor cortex) rather than area 6 (the premotor cortex) is the obvious occupant of the final cortical station. M1 is the richest origin of the cortico-spinal tract, and has the densest termination upon spinal motor neuron pools (Maier *et al.* 2002); hence, as has been long known, it has the lowest threshold for electrically evoked motor movements. If so, the serial

Figure 2. (Caption opposite.)

sensorimotor pathway must have a ‘forward’ character in the sensory cortex, but reversing to ‘backward’ in the motor cortex in order to culminate in area 4, not 6. However, before any exploration of the functional implications of such an organization, it is prudent to check the anatomical validity of the relative levels assigned to motor areas.

To preface, it deserves comment that many accounts of motor cortex connectivity do not lend themselves to hierarchical analysis. Details of laminar patterns may be negligible, limited to blanket descriptions of several areas at once or discernible only from low-power diagrams designed to illustrate the tangential (inter areal) patterns of connectivity. In the original scheme (Felleman & Van Essen 1991), for instance, only three studies were found to provide reliable support for placing motor cortex superior to sensory areas 1, 2 and 5, and higher order association areas such as SII and 7B (Jones *et al.* 1978; Friedman *et al.* 1986; Andersen *et al.* 1990). The basis for this assignment was the designation of terminations concentrated upon layer 3 of the agranular cortex as a ‘forward’ pattern. Given the absence of a granular layer, this does not seem

unreasonable, since ascending pathways typically terminate heavily in layer 3, as well as granular layer 4, in sensory cortex. It gains in credence from the existence of a complementary feedback pattern in motor cortex, i.e. one that avoids lower layer 3 as observed in the projection of area 8 to area 6 (Arikuni *et al.* 1988). The latter evidence was available at the time, but escaped citation since the original somato-motor hierarchy did not extend to the prefrontal cortex (Felleman & Van Essen 1991). The key placement of area 6 above area 4 was based on a single abstract: this noted a forward pattern of terminations from 4 to 6, and a backward pattern in the reverse direction—findings that were never published at greater length (Primrose & Strick 1985). If the notion of a motor hierarchy has subsequently been received sceptically, it is quite justifiable. However, on re-examination, it is possible to base these strata assignments on a firmer body of evidence. Figure 2 documents this enhanced hierarchical scheme for the motor cortex, which is constructed as follows:

- (i) The focus is upon the vertical rather than horizontal structure, i.e. upon hierarchy as

Figure 2. (*Opposite.*) Laminar systematics in the somato-motor hierarchy. The diagrams *a*, *b* and *c* show patterns of terminations (*a* and *b*), and cells of origin (*c*), in selected areas comprising the somato-motor hierarchy. Not all connections are shown, only those for which an adequate indication of laminar characteristics is obtainable (the blue numbers provide a key to the literature). In order to compile data across studies with variable terminology and placement of injected tracers, some areas are combined into single blocks. Hence the diagrams are intended to give an accurate indication of ascending or descending relationships, but not the precise number of pathways, or levels involved. S1, for instance, is known to comprise separate levels for areas 3a, 3b, 1 and 2. (*a* and *b*) Schematic illustrations of terminal patterns: forward (1 and 12); intermediate (2–5 and 13); and backward (6–11, 14 and 15). Forward patterns have a concentration upon layer 3. Intermediate patterns are described as columnar, with little or no laminar differentiation. Backward patterns are concentrated in layers 1 (and 6) and/or tend to avoid the lower part of layer 3. Feedback from M1 to S1 tends to avoid layer 4. (*c*) Laminar distribution of cells of origin, coded as the relative density of labelled cells in layers 3 and 5 ('3 > 5' or '3 >> 5'). In general, ascending connections are associated with a high 3 : 5 ratio, and descending connections with a lower 3 : 5 ratio (that may still exceed unity). Factors influencing cell density can vary considerably across studies and few provide quantitative cell count data. The diagram, therefore, uses colour boxes to emphasize three studies which provide comparative cell data for connections at separate levels. For example, the ascending input to M1 from S1 has a 3 : 5 ratio at least sevenfold greater than the descending input to M1 from F2, F3 or F7 (pink boxes: ratios derived from data of Ghosh *et al.* 1987). The ascending and descending inputs to the premotor cortex show a similar relationship (green boxes: Barbas & Pandya 1987). For the connections of F3 (area SMA) to M1 and premotor cortex (lilac box) Johnson & Ferraina (1996) cite statistical analysis that neurons projecting to M1 are more evenly distributed in depth ($p < 0.0001$). There are no quantitative data where the density of layer 5 cells exceeds layer 3 cells in motor connections, but qualitative descriptions to this effect for the projection from F5 to M1 may be found in references Godschalk *et al.* (1984), Leichnetz (1986) and Stepniewska *et al.* (1993) (not illustrated in diagram). Key to references: (1) Jones *et al.* (1978), Kunzle (1978*b*) and Pons & Kaas (1986); (2) Kunzle (1978*b*); Leichnetz (1986) and Stepniewska *et al.* (1993); (3) Barbas & Pandya (1987); (4) Barbas & Pandya (1987); (5) Kunzle (1978*a*); (6) Preuss & Goldman-Rakic (1989); (7) Kunzle (1978*a*) and Barbas & Pandya (1987); (8) Barbas & Pandya (1987); (9) Kunzle (1978*a*) and Barbas & Pandya (1987); (10) Barbas & Pandya (1987); (11) Kunzle (1978*b*), Leichnetz (1986) and Stepniewska *et al.* (1993); (12) Shipp *et al.* (1998); (13) Barbas & Pandya (1987); (14) Arikuni *et al.* (1988); (15) Kunzle (1978*a*); (16) Godschalk *et al.* (1984), Leichnetz (1986), Ghosh *et al.* (1987), Huerta & Pons (1990) and Stepniewska *et al.* (1993); (17) Matelli *et al.* (1986), Barbas & Pandya (1987) and Kurata (1991); (18) Arikuni *et al.* (1988); (19) Barbas & Pandya (1987); (20) Muakassa & Strick (1979), Godschalk *et al.* (1984), Leichnetz (1986), Ghosh *et al.* (1987) and Stepniewska *et al.* (1993); (21) Pons & Kaas (1986) and Burton & Fabri (1995); (22) Ghosh *et al.* (1987) and Johnson & Ferraina (1996); (23) Johnson & Ferraina (1996). (*d*) Motor areas F2–F7 on the medial (upper part) and lateral (lower part) surfaces of a left hemisphere. Area F1 is equivalent to area M1, as marked here. Somatosensory regions S1, area 5 and area 7b are also marked. ps, as, cs, ips and ls are principal, arcuate, central, intraparietal and lunate sulci, respectively.

opposed to details of parallel, cross linked component pathways.

- (ii) The motor cortex is represented on three levels, with the premotor cortex (area 6) subdivided into anterior and posterior components, above area 4 (M1). The sensory strata below area 4 are, for convenience, denoted as a single stage, and there is an additional top stratum, represented by prefrontal areas (e.g. 8, 46 and 9).
- (iii) The evidence represented by laminar terminations (figure 2*a,b*) and laminar origins of projection (figure 2*c*) are shown separately. Figure 2*b* represents direct connections to the premotor cortex from higher order bimodal areas that bypass area 4. The labelling patterns shown are diagrammatic conventions, not exact renditions of published material.
- (iv) Most connections are described by at least two studies with compatible results, although the exact descriptions may differ. The diagram adopts the 'F2–F7' terminology introduced by Matelli and colleagues³ (figure 2*d*; for review see Geyer *et al.* 2000; Rizzolatti & Luppino 2001); several boxes combine 'F' areas, where they are not readily distinguishable in the original studies.
- (v) The systematics adopted for cellular labelling (figure 2*c*) refine the existing guideline (that a bilaminar pattern of cells may be the origin of either a forward or backward connection) to focus on the *ratio* of cells in layers 3 and 5. Descriptions of relative densities of tracer-labelled cells differ quite widely across studies but, using a 'ratio of

ratios' approach, there is some consensus that the 3 : 5 ratio of an ascending connection is significantly greater than the 3 : 5 ratio of a descending connection. There is one existing report that uses this same device in quantifying motor cortex connectivity (in this case with prefrontal cortex) and which illustrates a clear increase in 3 : 5 ratio from rostral area 6 to caudal area 4, in line with present conclusions (fig. 1D in Barbas 1986).

In summary, the somato-motor hierarchy of figure 2 is more robust than previous accounts, but it is still over-reliant on a few key papers that are not ideally suited to this analysis. It might yet be overturned by better quality data, or it might be subsumed within a related system that uses cortical structure to predict the patterns of connectivity (see figure 3; Barbas 1986; Barbas & Rempel-Clower 1997). Provisionally, however, we can adopt either a low- or high-resolution working model of the somato-motor hierarchy. In the former, the agranular areas occupy essentially a single tier, above somatic association areas (e.g. area 5, SII) and below prefrontal areas, and exchanging lateral connections among themselves. At higher resolution, accepting indications that motor connections are asymmetric: (i) area 6 occupies a higher tier than area 4, and (ii) area 6 itself has a two-tier organization, such that its anterior components (F5, F7 and F6/pre-SMA) belong to a higher tier than its posterior components (F4, F2 and F3/SMA). On either basis, the organization of motor cortex should bear some comparison with functional correlates of laminar systematics in visual cortex.

Figure 3. A structural model for laminar connectivity. Developed by analysis of prefrontal cortex (Barbas 1986; Barbas & Rempel-Clover 1997), this scheme bears a substantial resemblance to the conventional hierarchical scheme established for sensory cortices (and as adapted for somato-motor areas in figure 2), differing in two respects. (i) The direction of connection is defined in relation to the degree of laminar definition of areas, as opposed to their functional status. The 'forward' direction is from richly laminar areas to poorly laminar areas; 'backward' is the reverse. (NB The labels 'forward' and 'backward' are not germane to the structural scheme, but can be defined by reference to sensory cortices). (ii) Laminar patterns: 'forward' projections are held to terminate preferentially within the deeper layers, (i.e. layers 4, 5 and 6 as opposed to layers 3 and 4 of standard sensory pathways); 'backward' projections are held to terminate in upper layers (i.e. layers 1, 2 and 3 as opposed to layers 1 and 6). The origin of 'forward' and 'backward' projections is the same in both schemes. These rules are expressed in a graded fashion, in proportion to the difference in laminar definition of the areas connected. The diagram shows a chain of connections across three stages, from granular, to dysgranular (having only an incipient, poorly developed layer 4) to agranular cortex. The first step (granular–dysgranular) links a pair of areas with a greater difference in laminar definition, so their 'forward' and 'backward' connection patterns are correspondingly more distinct. Agranular and dysgranular regions of prefrontal cortex (also known as periallocortex and proisocortex, respectively) are situated on the margins of the cortex (if considered as an unfolded, two-dimensional sheet of tissue). The gradient of increasing laminar definition leads centripetally toward prefrontal areas 8 and 46. The scheme can be extended to sensory cortex, e.g. to the ventral visual pathway, where the chain of projections from V1 to ventral IT cortex also describes a gentle gradient of decreasing laminar definition, culminating in dysgranular and agranular cortices of the rostral temporal pole, and medial parahippocampal, perirhinal and entorhinal cortices; interconnections between prefrontal and rostro-medial IT cortex follow the rules described above (Rempel-Clover & Barbas 2000). Although motor cortex as a whole is agranular, the architecture of area 4 is not equivalent to the agranular regions found on the margins of the cortical sheet. It may be possible to define a similar gradient of laminar definition from area 4, through area 6 and SMA to cingulate (pericallosal) regions of motor cortex; following this strategy, the laminar patterns of connections from motor cortex to

prefrontal cortex have also appeared to satisfy the proscriptions of the structural scheme (Barbas 1986). (Figure redrawn from Barbas & Rempel-Clover (1997), ©O.U.P. with authors' & publishers' permission.)

5. 'UP' AND 'DOWN' FUNCTIONAL RELATIONSHIPS IN THE VISUAL HIERARCHY

The forward direction in the hierarchy corresponds to a 'classical' assessment of visual processing as a sequential analysis of raw visual information, leading to activation of increasingly more abstract, or more complex representations of the external world. The simple observation that receptive fields increase in size in the 'up' direction is sufficient to infer that ascending connections must be relatively efficient, in that (for example) a layer 4 cell in any given tier can be driven by activity among a small fraction of the convergent, ascending afferents it receives (Zeki & Shipp 1988); indeed, ascending connections are also known as 'driving' connections (Crick & Koch 1998). However, the processing of the ascending signals favours certain patterns of input over others, leading to a progressive evolution of response selectivity. For instance, cells in area V5 (MT) selective for certain local directions of motion, hand on to cells in V5A (MST) with considerably larger RFs and selectivity for more global motion patterns (such as optic-flow, e.g. radial expansion from a focal point; Orban 1997). Contrasting with the deterministic flavour of the ascending pathway, the descending pathways are more subtle in operation; they are associated with modulatory effects at a physiological level and, at a cognitive level, with top-down aspects of perception (i.e. attention). In preparing to consider the nature of feedback from premotor to motor cortex (see the following section), it is first necessary to examine visual feedback in greater detail.

(a) 'Adaptive resonance' theories of feedback

From a theoretical perspective, feedback allows prior knowledge of visual objects to influence ongoing perception. As reviewed by Pollen (1999), such ideas can be traced back to the concept of 'unconscious inference' discussed by Helmholtz and collectivized under the generic title of 'adaptive resonance' theories (Grossberg 1980). The key idea is that feedback acts to select certain ascending signals in preference to others, culminating in a (temporary) steady-state resonance, in which the feedback and forward activity is mutually reinforcing, over several hierarchical levels (e.g. Harth *et al.* 1987; Finkel & Edelman 1989; Mumford 1992; Ullman 1995; Engel *et al.* 2001). For example, segregating an object (perhaps a predator) from a camouflaged background can be facilitated by knowing in advance what it is; yet identifying it may require just such segregation and edge detection (Grossberg 1994): both processes are thus likely to occur concurrently, within recursive loops. A similar (well-known) example is provided in figure 4. The more recent proposals, such as Ullman's 'sequence seeking/counter streams' scheme, take full advantage of the known anatomical organization of these pathways. The counter streams are successive feedback relays involving layer 6, and forward relays ascending through the superficial layers

(figure 5). A descending stream represents a particular hypothesis, such as the presence of a (particular) face, and the aim is to forge a link between incoming sensory data and one such stored template, of which several may be under active evaluation. The process is explained in greater detail in figure 5.

(b) *Fundamental physiology of feedback*

The physiological operation of adaptive resonance theory is far from firmly established, but many of the basics are in place. There is good evidence from a variety of sources that descending connections are fundamentally excitatory, i.e. operate as a positive feedback loop. Firstly, all long range connections originate from excitatory pyramidal cells. Secondly, at least in area V1 of the rat, they terminate predominantly on pyramidal cells: the proportion of contacts on inhibitory neurons and the frequency of inhibitory postsynaptic potentials (IPSPs), are both significantly lower in feedback than in forward pathways (Johnson & Burkhalter 1996; Shao & Burkhalter 1996). Thirdly, abolition of feedback (e.g. by cooling, or application of GABA to the source of a descending pathway) reduces single neuron responsiveness, providing the visual stimulus is restricted to the test receptive field. This has been demonstrated in V1-LGN (Przybylski *et al.* 2000), V2-V1 (Sandell & Schiller 1982; Payne *et al.* 1996; Hupe *et al.* 2001a) and V5-V3, -V2 and -V1 (Hupe *et al.* 1998; Hupe *et al.* 2001b). Fourthly, global reductions of responsiveness following abolition of feedback have been demonstrated, e.g. the motion-blind patient LM (with bilateral lesions of area V5) shows no significant activation of V1 to a coherent motion stimulus, unlike normal subjects (figure 6; Shipp *et al.* 1994); interestingly, awareness of motion can also be compromised by using transcranial magnetic stimulation to disrupt V5-V1 feedback (Pascual-Leone & Walsh 2001). A similar global effect has been shown in cat area 18, whose direction-specific map is near abolished by cooling of the suprasylvian motion area (Galuske *et al.* 2002).

Temporary abolition of feedback (by cooling V5) does not systematically reduce spontaneous activity in V1 (Hupe *et al.* 2001b). This signifies an important principle—that the positive feedback loop has only a modulatory influence, i.e. it is incapable of sustaining activity in the absence of a simultaneous ascending input (Crick & Koch 1998; Grossberg & Raizada 2000). This is an obvious expectation, long inherent in the observation that convergent, descending influences from neurons with larger receptive fields at higher levels do not succeed in enlarging the (classical) receptive fields of the target neurons (e.g. Zeki & Shipp 1988). Thus, for instance, a particular, V5-efferent cell in layer 4B of V1 does not respond to an isolated moving dot as it approaches or skirts past the receptive field, despite the concurrent activation of feedback from V5; the effect of the feedback is only noted when the stimulus enters the receptive field, potentiating its response (Hupe *et al.* 2001b). Finally, exposed to something other than such a simple display, it is obvious that the effects of feedback will be mediated indirectly through intrinsic

circuits, in addition to any direct action upon a recorded neuron—and possibly with opposing consequences. For instance, resumption of feedback from V5 (upon recovery from cooling) was observed to *suppress* the response of a V3 neuron to a centre-surround motion stimulus, when the antagonistic RF-surround was being stimulated by motion in the same direction as that preferred by the RF-centre (Hupe *et al.* 1998). According to a more general treatment (termed ‘folded feedback’), the descending input to layer 6 may be modelled as exerting a centre-surround influence upon layer 4, once relayed through the layer 4–6 intrinsic circuitry (Grossberg & Raizada 2000).

(c) *Feedback and attention*

The response enhancements predicted by adaptive resonance theories of feedback are concordant with many reported neural correlates of selective attention, and it is a reasonable inference that these modulations of activity are mediated by feedback connections. Among the most direct observations are those of Mehta *et al.* (2000a,b). This study measured the effect of intermodal attention (i.e. sight versus sound) upon the response to a central flashed stimulus, as measured by simultaneous, translaminar recordings of current source density and multi-unit activity. Evidence for a feedback chain was provided by the progressively greater latency of the attentional modulations recorded from V4, followed by V2, then V1, within a period of 100–300 ms after stimulation. This effect could be noted across all layers, or sometimes only within the superficial layers—as opposed to the earliest onset of forward-going activation, in layer 4, that was always unmodulated by attention. This laminar pattern, and the fact that activity was greater (or longer-lasting) in the attended condition, suggested an excitatory modulation mediated by descending afferents (Mehta *et al.* 2000b).

A considerable range of attentional effects has been reported in the visual cortex, varying with the nature and difficulty of the behavioural task, and the area sampled. Two consistent factors are (i) that the magnitude of the modulation tends to be greater in higher areas, and (ii) that the effect is generally a change in the gain of the response, rather than its underlying feature selectivity (Maunsell & Cook 2002). The former is not taken to imply that feedback afferents are any less influential, or prevalent in lower areas, a notion soundly contradicted by anatomical evidence. More probable, perhaps, is that the hierarchical system imposes a form of cascade effect, amplifying the dynamic effects of attention from level to level (e.g. the dynamic routing circuit model of Olshausen *et al.* 1993). The latter (i.e. the gain-change effect, (ii) above) is the typical observation when a single item in the RF is made the target of attention and, once again, is generally consistent with a potentiating or modulatory action by feedback afferents. The change in gain is not always excitatory; suppressive effects may be observed, especially when there is more than one object within the RF, and the attended item is a non preferred category of stimulus for the neuron under study (Luck *et al.* 1997; Reynolds *et al.* 1999). The effect of attention here is viewed as biasing the outcome

Figure 4. An image which relies on top-down processing for interpretation. Imagine a naive observer who sees only black blobs. On instruction to ‘think Dalmatian’, descending influences from ‘dog’ cells⁴ can be envisaged to select sufficient anomalous (or Kanizsa-like) orientation selective units around the animal’s outline to induce resonance between higher and lower centres, and engender a ‘dog’ percept. Once the hidden image is recognized, it is hard not to see it. Those familiar with the image may not have noticed that the left-hind limb is largely invisible.

of competition between stimuli (Desimone & Duncan 1995; Deco *et al.* 2002) and mediated partly through intrinsic networks, as mooted above. It has even proved possible to isolate separate contextual effects, by switching behavioural tasks without shifting focal attention. Thus, while inspecting identical stimulus arrays, two distinct tasks (vernier alignment and line bisection) yielded different profiles of activity in neurons recorded from V1, as if alternating between different, feedback-induced states of intrinsic processing (Li *et al.* 2004).

The one attentional effect that is not readily consistent with a modulatory action of feedback is an increase in baseline (i.e. spontaneous) activity, when focal attention falls within an RF prior to the appearance of a target stimulus (e.g. Luck *et al.* 1997). Although a minor effect, it might indicate a physiological variant of feedback. Alternatively, it might indicate a different mechanism of attention, since a subcortical pathway operating via the colliculus and pulvinar is a viable alternative route (Shipp 2004). This pathway, or any other modulation of thalamic activity, could feed into the middle layers of the cortex, where thalamic afferents are known to have a more direct, driving action (Sherman & Guillery 1998; Gil *et al.* 1999). The existence of subcortical attentional circuits implies that attentional effects cannot be equated with direct cortical feedback automatically.

(d) *There and back again? Network dynamics*

Following a visual event, the first wave of activation can be traced to the highest levels of visual cortex—and the frontal lobes—within little more than 100 ms (Schmolesky *et al.* 1998; Lamme & Roelfsema 2000; Foxe & Simpson 2002). The first spikes recordable from IT cells may be evoked no less selectively than the subsequent train of activity, and indeed the degree of

Figure 5. Diagram illustrating how ascending and descending streams may operate semi-autonomously within a serial pathway. The ascending pathway relays through layers 4 and 3, while the descending pathway relays through layer 6, with additional feedback to layer 1. In the counter stream model of Ullman (1995), multiple ascending and descending streams are launched in parallel, using multiple, separate nodes at each level, in order to seek the optimal linkage between sensory input and stored information. As one stream passes through a node, that node is primed to facilitate its recruitment by a complementary counter stream. The bottom-up and top-down streams thus reinforce each other at many different levels. The counter stream model fits several aspects of the architecture of ascending and descending cortical pathways, and also accounts for intermediate (or lateral) connection patterns as the sum of top-down and bottom-up links acting bidirectionally between nodes at the same level.

processing power that, theoretically, may be harnessed from the variations of first spike latency is impressive (Lamme & Roelfsema 2000; VanRullen & Thorpe 2002). However human reaction times and perception are not quite this fast. Typically, there will be 100–400 ms of sensory processing before motor output, leaving a considerable period over which a network of activity can evolve through recurrent processing in cortical and subcortical feedback circuits (Foxe & Simpson 2002). One good demonstration involves a curve-tracing task, where the cued (i.e. target) curve alternates unpredictably across trials (Roelfsema *et al.* 1998). The response of orientation selective cells in V1 is enhanced when they code for the target curve, in comparison to a distractor curve. The enhancement is not immediate, but develops over a period of 200–500 ms latency. The delay is therefore presumed to reflect the time taken for an attentive process to initiate the activation of a descending, multistage loop from a higher centre back to V1 (Lamme & Roelfsema 2000).

It is not necessarily the case that the hierarchy uniformly enters a period of reverse operation, following a pre-attentive feed-forward sweep, as sometimes implied (Lamme & Roelfsema 2000; Hochstein & Ahissar 2002). A more accurate portrayal is likely to be one of continual, simultaneous, multi level interactions between ascending and descending influences: a hum, rather than an echo. Attention-related effects can often be seen from the onset of stimulus-driven activity, if the attended target is expected (as with a ‘block’ design of stimulus presentation; e.g. Luck *et al.* 1997; Li *et al.* 2004). Even in response to an unanticipated target, it is known that feedback can begin very early, e.g. within 20–30 ms for feedback from V5 to V1 (Hupe *et al.* 2001b). Also, the faster onset of activity in dorsal pathways fed largely by the magnocellular stream

Figure 6. The motion blind patient LM (left), with bilateral lesions of area V5, shows an abnormal pattern of activation to a coherent motion stimulus in regions of intact cortex. In a normal subject under the same conditions (right) there is significant activity in areas V1 and V2, as well as V5. The result in LM was one of the first indications that a normal profile of activity in V1/V2 may depend partly on 'reactivation' by feedback. PET data from Watson *et al.* (1993) and Shipp *et al.* (1994).

allows lateral or possibly feedback input to precede direct ascending signals within ventral areas such as V4, as indexed by the timing of simultaneous, multilayer recordings (Schroeder *et al.* 1998).

Another related view is that network activity, both forward and backward, evolves by continual recruitment of neurons and processing nodes to a distributed coalition unified by temporal correlation in firing (Engel *et al.* 2001). The coalition need not be limited to the visual cortex since, for instance, frontal and parietal elements are known to be involved in the perceptual shifts seen in rivalry or bistable images (Kleinschmidt *et al.* 1998; Lumer *et al.* 1998). Such perceptual fluctuations, with relatively long time constants, find their most likely neural correlate in the state of a global network, rather than in the faster dynamics of its local components (Pollen 1999).

In summary, the operation of the hierarchy is characterized by the continual asymmetry between simultaneously acting forward and backward pathways—figuratively, between raw data seeking an explanation (bottom-up) and hypotheses seeking confirmation (top-down). The consensus percept depends on a global state of activity, which may be influenced by centres beyond the visual system. However, within the visual system, the different areas still play their specialized roles. Take the hypothetical example of figure 4: the 'dog' cell dictates a canine percept but, if it resembles documented face cells, it will have spatial and size invariance. Activity of the dog cell by itself, therefore, will not define a dalmatian at a given location and distance; perceptual embodiment of a dog requires activity in other centres, too. To see the dalmatian's spots and outline will arguably require V2 and, perhaps, V1—considered the ultimate repository of finely detailed achromatic form information (Pollen 1999).

6. STRUCTURE AND FUNCTION IN MOTOR CORTEX

As noted above, motor cortex is relatively alaminar. Also, despite the absence of granular layer 4, layer 3 is

of relatively reduced thickness in areas 4 and 6, for example, in comparison to areas 1, 2, 3a and 3b (Zilles *et al.* 1995). Since the ascending pathway involves primarily layers 4 and 3 (figure 5), it is the very layers mediating this pathway that are the most atrophied. In consequence, both the architecture and internal connectivity (see above) of motor areas seem to imply that all relationships are of the feedback and lateral variety. The overall aim of this section is thus to examine the functional analogy between recurrent processing in the motor and visual systems.

(a) Hierarchical basis of motor control

The 'primary' motor cortex acquired its name by analogy to the primary sensory cortices—being the motor area most densely connected to the spinal cord, and having the lowest threshold of electrical excitability (Fulton 1935). The 'premotor' cortex was thus regarded as a preceding stage in a serial output pathway, with a higher level control function. Support for this concept has steadily amassed, but not without some associated difficulties. On the debit side, the giant Betz cells, on which Fulton based his distinction, account for only a small proportion of the cortico-spinal output, which actually originates from a far wider distribution of cells across primary, premotor and supplementary motor cortex. Clearly, therefore, areas 6 and SMA must operate at least partly in parallel with area 4 (Dum & Strick 1991; He *et al.* 1993). The case in favour of a serial motor hierarchy relies on functional evidence that the premotor and supplementary motor areas are relatively more involved with the selection, preparation and initiation of movements and the primary area with the moment-to-moment control of motor output and maintenance of posture (Wise 1985; Georgopoulos 1991; Crammond & Kalaska 1996; Geyer *et al.* 2000). And, in the case of visually guided movements, that the pathways from V1 to M1 lead almost exclusively through premotor cortex (where many cells are known to possess visual, as well

as motor properties; Shipp & Zeki 1995; Burnod *et al.* 1999; Rizzolatti & Luppino 2001).

The analysis of visually guided movements helps to illustrate the nature of serial processing in the motor system. Basically, it can be considered to involve a transformation of target location from an extrinsic to an intrinsic frame of reference—i.e. from visual, spatial coordinates to the joint angles and muscle tensions required to reach out to the target location (Soechting & Flanders 1992). Hence, individual neurons can be tested for responses belonging to extrinsic or intrinsic coordinate systems. One, very instructive, application of this design involves visually guided wrist movements made from different initial postures (i.e. the animal is trained to move the wrist up (or down) starting from a palm-down (or palm-up) posture (Kakei *et al.* 1999, 2001, 2003). In PMv, most (80%) neurons with movement-direction tuned activity were found to be extrinsic—i.e. the response in the preferred direction of movement was invariant with regard to the initial posture. By contrast, in M1 a broader range of cell types included one quarter that was extrinsic and over one third that was clearly intrinsic, coding movement in muscle-related coordinates (Kakei *et al.* 2003). It is the latter ‘muscular’ class that is more likely to provide the cortico-spinal output from M1.

A limited repertoire of wrist movements (e.g. as above) is unlikely to reveal the optimal extrinsic properties of every neuron studied. In less constrained designs, the animal is trained to produce a greater variety of movements in search of the optimal response (at any given recording location). In PMv, this is frequently an arm movement in peripersonal space, or an object-grasping and manipulation action (Geyer *et al.* 2000). A recently uncovered alternative means of probing function is to electrically stimulate the test site for a prolonged period of 500 ms, far longer than the traditional technique (*ca.* 20 ms). The unexpected result was to produce a coordinated complex movement, often involving separate body parts—e.g. a hand, arm and mouth movement, as if in feeding (Graziano *et al.* 2002a,b). Prolonged stimulation was always found to result in a final characteristic posture, independent of starting posture, as if the stimulation were acting to reveal the postural goal of a select team of extrinsic units. Also, a unitary map of evoked postures was discovered, encompassing both premotor and primary motor cortex (Graziano *et al.* 2002a,b). At first sight, the inclusion of M1 by this system (described as a map of the position of the hand in space) favours a parallel rather than a serial relationship between the motor and premotor cortex. However, it is probable that the prolonged stimulation regime recruits a distributed network across the cortex (albeit one in which the stimulated location is a crucial node). Furthermore, the map of postures is consistent with known differences between M1 and PMv. For instance, after stimulation of M1, fine movements of the wrist and fingers were noted, while hand position was more coarsely controlled and generally driven to a large area of space in front of the chest. By contrast, area F5 (the sector of PMv located within the inferior arcuate convexity) included the hand-to-mouth part of the postural map, entirely

congruent with earlier descriptions of its functional organization (Rizzolatti *et al.* 1988). It seems reasonable to conclude, therefore, that the unitary map of postures across PMv and M1 is consistent with the presence of extrinsically coded units in both areas, but leaves open the question concerning their functional inter-relationship.

A further important property of about 10% of units in premotor area F5 is the capacity to respond to the sight of an action (‘mirror neurons’; Gallese *et al.* 1996; Ferrari *et al.* 2003). Normally, there is a high degree of congruence between the observed action, and the neurons’ own specificity in producing movements. However, the visual activation of a mirror neuron does not result in the monkey immediately replicating that movement; rather, the mirror response can be thought of as the monkey understanding the action it witnesses (Rizzolatti *et al.* 2001). Or, in other words, the mirror neuron represents the concept of a particular action, much as a face cell represents the visual concept of a face (or a ‘dog cell’, a dog, as discussed in figure 4). To pursue this analogy with the visual system, the logical inference is that the translation of motor concepts into actions relies on feedback processes ‘selecting’ the necessary components of the action from the intrinsically coded units in M1.

(b) *Feedback in motor cortex?*

Evidently, the fact that prolonged stimulation in premotor cortex produces a fully formed, complex movement (Graziano *et al.* 2002a,b) demonstrates that all necessary neural interactions can, ultimately, be driven from premotor cortex. However, these may very well include subcortical relays through the cerebellum and basal ganglia in addition to cortico-cortical effects, and the interaction of these alternative pathways is not well understood. Cortico-cortical influences may, however, be isolated in the short latency responses to very brief (<1 ms) stimulation, e.g. the excitatory, monosynaptic responses of M1 pyramidal neurons recorded within 1–4 ms of surface stimulation of premotor cortex (Ghosh & Porter 1988). Typically, the excitation was followed by a longer inhibitory response. The study compared the relative effect of stimulation delivered to somatosensory and premotor cortices, noting that responses elicited from the former were larger and more frequent (90% versus 30% of all activated M1 neurons), despite the fact that neurons retrogradely labelled from area 4 were found in much greater numbers in premotor than somatosensory cortical areas (Ghosh *et al.* 1987; Ghosh & Porter 1988). Taking the somatosensory projection to be forward, and the premotor projection to be backward (see above), the former fulfils the prediction that it should be the more effective in driving activity.

There is also evidence to support the prediction that premotor feedback should have a potentiating influence on M1 activity, as monitored by recording the cortico-spinal output from M1 (Cerri *et al.* 2003; Shimazu *et al.* 2004). It has been known for half a century that single-pulse stimulation of the motor cortex produces a series of volleys in the cortico-spinal

Figure 7. Visual input to rostral, dorsal premotor cortex (area F7) from area V6A of posterior parietal cortex is concentrated in the middle layers, 3 and 5, indicated by arrowheads. The same section in darkfield view (right) shows more clearly the full distribution of labelled axon terminals (Shipp *et al.* 1998).

tract (Amassian *et al.* 1987; Ziemann & Rothwell 2000): the first of these (attributed to direct electrical activation of the axon initial segment of cortico-spinal neurons) is known as the D (direct) wave, and subsequent waves, occurring at a periodicity of about 1.5 ms, are known as I-waves since they are thought to reflect indirect, synaptic activation of cortico-spinal projections. The intrinsic circuitry that mediates the production and the evident synchronization underlying I-waves remains uncertain, although there is some evidence that progressive I-waves are produced by different circuits (Ziemann & Rothwell 2000). It has recently been found that stimulation of premotor area F5 that was, by itself, ineffective at generating a measurable cortico-spinal output, had a strong facilitatory effect upon the generation of I-waves when coupled to later stimulation of M1. There was also a correlated facilitation of excitatory postsynaptic potentials (EPSPs) recorded from spinal motor neurons (Shimazu *et al.* 2004). Notably, it was only the later (I_2 and I_3) components of the cortico-spinal volley that were facilitated. Regarding timing, the earliest facilitatory effect (i.e. on the I_2 wave) was apparent at a latency of about 6 to 7 ms from F5 stimulation (Shimazu *et al.* 2004). Since, as mentioned above, the direct action of premotor cortex on M1 (recorded intracellularly) can be registered with a minimum latency of 1–4 ms (Ghosh & Porter 1988), the facilitatory effect of F5 on M1 cortico-spinal output would seem to be contingent on further rounds of interneuronal activity.

(c) Feed-forward sensory inputs to motor cortex

If, in keeping with the visual system analogy, motor movements are selected by internal feedback within the fronto-motor cortex, it is necessary to identify the forward pathways on which the potentiating action of feedback is exerted. Evidently, this should be the external inputs from visual and sensory cortices that are classified as ascending (see above) as they terminate in

layer 3 (figure 7). However, input to motor cortex from the thalamus is also concentrated upon layer 3 and should also be considered in this context. Unlike the sensory cortex, where this would mainly entail the cortico-thalamo-cortical loop, motor cortex participates in two additional loops, in which the thalamo-cortical projection completes circuits through the cerebellum and basal ganglia. Between them, these pathways carry several different types of instruction regarding the parameters of movement, e.g. (i) a description of biological motion (as with ‘mirror neurons’); (ii) the location, size and shape of a reachable target; (iii) proprioceptive information specifying limb position, ergo which muscles and joints need be exercised to acquire the target; and (iv) an executive ‘go’ decision to initiate the movement.

As noted above, sensory input to M1 is primarily somesthetic, from areas 1, 2 and 5, whereas the premotor cortex receives a combination of visual and somesthetic input from extensive, bimodal regions of parietal cortex (Burnod *et al.* 1999; Rizzolatti & Luppino 2001). For a class of ‘visuomotor’ neurons in ventral premotor cortex (F5) mere visual presentation of a graspable object is sufficient to elicit a response (Murata *et al.* 1997). This can be considered as the motor representation of a 3D visual object description sourced from area AIP, coding a potential act of grasping that is not necessarily executed (Rizzolatti & Luppino 2001). Visual responses in dorsal premotor cortex are more concerned with target location, but can equally be considered as the initial stage of a sensorimotor coordinate transformation for reaching (Shen & Alexander 1997a,b; Burnod *et al.* 1999). Similarly, sensory or sensorimotor activity can be recorded from M1 in the course of categorization tasks, in which a visual or tactile stimulus instructs an arbitrary choice of response (Zhang *et al.* 1997; Salinas & Romo 1998).

In addition to informing the goal of a movement, a major role of sensory input is to describe body state,

since the starting position and dynamics (i.e. speed and external load) of the limbs is self-evidently critical in determining the required sequence of muscular activity (Winters & Woo 1990). Accordingly, arm posture is known to be an important factor influencing M1 activity during reaching arm movements (Caminiti *et al.* 1990; Scott & Kalaska 1997) and in isometric force generation (Sergio & Kalaska 2003); also, application of an external torque load affects the patterns of activity associated with a fixed reaching movement (Crutcher & Alexander 1990). The kinaesthetic sensitivities that must underlie these properties have not been greatly investigated, although direct responses to passive joint flexion are known to exist in all areas of motor cortex (Hummelsheim *et al.* 1988; Butler *et al.* 1992). Signals from deep receptors in joints and muscles may be relayed to M1 from areas 3a and 2, where they are particularly in evidence (Huerta & Pons 1990; Krubitzer *et al.* 2004). However, such somatosensory signals are also known to reach the motor cortex directly from the dorsal spinal columns via the motor thalamus (VPLo nucleus; Lemon & van der Burg 1979; Asanuma *et al.* 1980; Stepniewska *et al.* 2003). Removal of both sources (by combined lesion of sensory cortex and dorsal column) produced a severe motor deficit, with loss of individual finger movements (Asanuma & Arissian 1984). Single spinal or somatosensory-cortical lesions have less obvious effects (Asanuma & Arissian 1984; Pavlides *et al.* 1993), although the spinal lesion was later noted to impair manual dexterity in a tricky task of retrieving food pellets from a rotating board (Favorov *et al.* 1988). Pre- and post-lesion recordings of M1 and muscle EMGs during this task found that the spinal lesion had abolished the pre-movement neural activity and raised muscle tone that was specific for one or the other direction of board rotation. The authors interpreted the findings to imply that the production of skilled finger movements was critically dependent on the pre-movement activity in M1, which in turn depended on the circulation of signals between motor cortex and muscles (Favorov *et al.* 1988).

Additional support for this idea derives from computational modelling of motor control. In the physiologically based model system of Bullock *et al.* (1998), describing the relationship between areas 4, 5 and the motor periphery in controlling a typical reaching movement, the main component of the output from 5 to 4 is depicted as an error signal, coding the difference between the current locations of the target and the arm. The area 5 output is continuously computed and triggers cortico-spinal output from area 4, its magnitude determining the speed of movement. Thus the excitatory drive and the resultant arm speed decrease as the hand nears its target. Notably therefore, in this model, the drive to area 4 is sourced from area 5 (rather than premotor cortex), in keeping with the predictions of the laminar scheme of connectivity. Area 5 is known to possess neurons with sensitivity to hand/arm position (Lacquaniti *et al.* 1995; Kalaska *et al.* 1997). The model develops this property from a combination of proprioceptive input to area 5 (i.e. muscle feedback) and cortical feedback

from area 4 that is interpreted to act as an efference copy signal (Bullock *et al.* 1998). However, because the arm and target positions must be subtracted (in order to generate the feed-forward difference signal) Grossberg (2000) later noted that, overall, this modelled feedback process is one of inhibitory matching—as opposed to the selective or excitatory matching that has so far dominated our discussion. The latter process is by no means excluded, however, since other components of feedback to area 5 from motor (or premotor) cortex could also be operational, e.g. in selecting which hand to use or which target to grasp.

Another indication of the significance of somatosensory input to motor cortex may be found in syndromes of focal dystonia (e.g. ‘writer’s cramp’). In humans, there is growing clinical evidence for the role played by aberrant cortical somatic representations (Tinazzi *et al.* 2003). In monkeys, heavily repetitive stimulation of specific fingers can lead to de-differentiated finger representations and clinical symptoms of focal dystonia (inaccurate, exaggerated or poorly timed movements; Blake *et al.* 2002). Theoretical explanation again invokes a loop through sensorimotor cortex and the peripheral effectors, in which the disordered sensory representation in S1 leads to excess drive of motor cortex and uncontrolled movements (Sanger & Merzenich 2000).

(d) Subcortical loops, through the cerebellum and basal ganglia...

The fundamentally different neural architectures of the basal ganglia and cerebellum imply an equally fundamental difference in function, although it is worth noting that the basal ganglia circuitry is understood in better detail than the cerebellar circuitry, where some important elements remain unknown (Mink 1996; Smith *et al.* 1998; Voogd 2003). One worthwhile distinction—that the cerebellum is relatively more important in externally guided movements, and the basal ganglia in internally generated movement—provides a useful hint, though it does not get to the heart of the matter since both circuitries do participate in both classes of movement (van Donkelaar *et al.* 1999, 2000; Debaere *et al.* 2003). Certainly, however, the cerebellum monitors all classes of sensory input (Glickstein 1997; Vassbo *et al.* 1999). An influential idea is that its role is to compare the actual sensory input to predicted input (e.g. as a consequence of motor actions), with strict regard to relative timing (Ivry *et al.* 2002; Miall & Reckess 2002; Ivry & Spencer 2004). Extending this notion, the prediction (of external events and/or body state) may also be fed to motor cortex, ahead of validation, as a means of enhancing temporal precision in skilled movements. Acting in this way as a ‘forward model’ or ‘feed-forward control’ system, the loop through motor cortex and cerebellum can function with high gain, such that the cerebellum is essentially driving the motor output (Miall *et al.* 1993; Miall & Reckess 2002; Ohyama *et al.* 2003). It is noteworthy therefore, that temporary inactivation of the cerebellar thalamic relay nucleus VLp (or VPLo of Olszewski) can result in hemiplegia⁵ (van Donkelaar *et al.* 2000). Inactivation at the earlier stage of the cerebellar output nuclei has the more

specific effect of deleting a particular component of a reach/grasp movement from the animal's repertoire, and the compensatory adoption of a less skilled movement to circumvent the specific loss of ability (Mason *et al.* 1998; Goodkin & Thach 2003; Monzee *et al.* 2004).

Supporting a radical difference in function, the basal ganglia and cerebellar loops relay through largely separate sectors of the motor thalamus, although their cortical distributions are near to fully overlapping (Rouiller *et al.* 1994; Hoover & Strick 1999; Sakai *et al.* 2002). The function of the basal ganglia loop is normally discussed in terms of selection among competing motor programmes (Mink 1996; Nambu 2004). The three distinct circuits through the basal ganglia nuclei—known as the hyperdirect, direct and indirect pathways—respectively involve one, two or three inhibitory steps and thus, respectively, mediate negative, positive and negative feedback effects (Alexander & Crutcher 1990; Smith *et al.* 1998; Nambu 2004). The indirect pathway, for instance, exerts tonic suppression over thalamic cells. Because topography is preserved at each stage, the circuit operates as a 'closed loop', restraining any zone of relatively high cortical activity and its associated motor plan (Alexander & Crutcher 1990; Middleton & Strick 2000). The direct pathway, by contrast, is pictured to release the desired motor programme, through disinhibition of thalamic cells (Mink 1996). These ideas have recently been extended in a computational model, in which motor programmes compete locally within the cortex, and somewhat less locally within the striatum, to open their associated basal ganglia 'gate' through the direct pathway (Brown *et al.* 2004). The indirect pathway operates more globally to withhold immediate or reflex responses, allowing time for prefrontal cognitive and motivational factors to influence the selection of a winning programme. The hyperdirect pathway (which is less topographically organized) might act to suppress interfering actions, while the selected plan is executed (Brown *et al.* 2004). In all such theories, the relative activity of the thalamus is the key factor in initiating or suppressing a motor action.

(e) ...or, just through the thalamus

The final circuit requiring consideration is the simple cortico-thalamo-cortical (CTC) loop. Evidently, this calls into question the role of the cortico-thalamic projection, of which cerebellar and basal ganglia theories are largely oblivious. Possibly, it helps to mediate information flow between the (otherwise) closed cortico-basal ganglia loops, since the CTC circuitry is habitually found to possess some non reciprocity in its organization (Rouiller *et al.* 1998; McFarland & Haber 2002; Kultas-Ilinsky *et al.* 2003). A recent scheme (figure 8) depicts a unidirectional flow from prefrontal (working memory) through rostral (cognitive) to caudal (executive) motor cortex (McFarland & Haber 2002). Even in regions of visual cortex free from the complications of cerebellar and basal ganglia circuits, the general functions of CTC circuitry are little understood. However, the fact that

Figure 8. Schema for information flow between thalamic relay nuclei (MD, VA and VLo) left, and frontal cortical areas, right. Coloured gradients in boxes indicate the functional transitions from limbic to motor cortical areas. Each thalamic nucleus has strong reciprocal connections with a restricted region of cortex, but also receives nonreciprocal projections from a higher cortical station. The cortico-thalamo-cortical loops thus augment the cortical pathways that transmit information from prefrontal and rostral motor areas to more caudal motor areas, affecting motor output or behaviour (from McFarland & Haber 2002, ©2002 The Society for Neuroscience).

thalamo-cortical synapses are generally more effective than intracortical synapses, and the fact that cortico-thalamic projections include large, driving afferents, in addition to smaller modulatory afferents, implies that CTC circuitry is far from insignificant (Sherman & Guillery 1998; Gil *et al.* 1999; Guillery & Sherman 2002). One line of thought is that the CTC circuitry acts to initiate, propagate and regulate synchronized transcortical networks, that in turn are proposed to mediate various forms of binding phenomena (Llinas *et al.* 1998; Engel *et al.* 2001; Jones 2001). Further, the absence of a strict, locally reciprocal organization in CTC circuits means that separate cortical networks may compete to recruit (or be recruited by) the same elements of thalamic circuitry (Shipp 2003): CTC circuitry may therefore be a vehicle for organizing and sculpting patterns of cortical activity over a more global scale than achieved by cortico-cortical interactions alone. These ideas should be equally applicable to the motor cortex, since the equivalent neural elements of thalamic circuitry (Rouiller *et al.* 1998; Kultas-Ilinsky *et al.* 2003), the broadly topographic, yet overlapping and imperfectly reciprocal organization (Rouiller *et al.* 1999; Geyer *et al.* 2000; McFarland & Haber 2002) and the relevance of spike-synchronization to neural function (Liang *et al.* 2002; Grammont & Riehle 2003; Hatsopoulos *et al.* 2003; Jackson *et al.* 2003; Lee 2003) have all been well documented.

7. SO, WHAT IS THE IMPORTANCE OF BEING AGRANULAR?

A century after Brodmann, it is worth attempting an earnest answer to the question. M1, like V1, is the area most heavily linked to the periphery. However, the direction of signalling is reversed, and the absence of granular layer 4 (and the relative reduction of layer 3) reflects the absence of a major pathway ascending through area 4 to higher motor areas. The reciprocal connection—area 6 to area 4, or premotor to motor—is the one that might be thought to carry driving instructions for motor output. However, laminar analysis of the pattern of connection suggests a greater affinity to feedback (as in the visual system), whose action is modulatory or selective in function, rather than driving or instructive. If there are driving inputs within motor cortex, they are the sensory inputs from visual and somatic association cortices (or predictions arising from the cerebellum). Visual input to premotor cortex, for instance, may instruct the location and affordance (size, shape, angle) of a graspable object. No further sensory processing is required, so the activation is a motor concept, the beginning of planning activity to perform the grasping action. The motor plan involves selecting the appropriate muscular effectors. However, this, in turn, requires kinaesthetic information (or predictions) fed from somatosensory cortex (or cerebellum). The extrinsic planning code cannot be linked to the intrinsic (muscle) codes units by instructive (driving) inputs, because the requisite muscular activity—and hence the requisite neural linkage—is conditional upon the starting body posture and limb dynamics. It is therefore plausible to envisage motor planning activity selecting motor effectors within kinaesthetically preconditioned M1, much as visual feedback may select visual signals within retinally preconditioned V1. In the presence of multiple targets, rival motor plans must compete. One motor plan may achieve dominance through cortico-cortical or cortico-thalamo-cortical loops. The former may be implemented by lateral (i.e. ‘intermediate’ laminar-style) connectivity patterns between motor areas. Ultimately, the winning plan succeeds in opening its ‘gate’ through the basal ganglia circuitry, and it is the consequent volley of thalamic activity that finally drives the selected output of motor signals through the cortico-spinal output.

The many technical elements in this picture, exploiting the century of advances in tract tracing, electrophysiology, computer modelling and functional imaging, are likely to have surpassed Brodmann’s wildest dreams. It is at the conceptual core—the vital importance of structure–function analysis in brain biology—that his legacy deserves recognition.

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ENDNOTES

¹With apologies to Lady Bracknell and Oscar Wilde—whose most popular work, *The Importance of Being Earnest*, was first produced in 1895.

²Echoing subdivisions described in area FST of the owl monkey (Kaas & Morel 1993).

³There are several alternative terminologies for the motor cortex, with varying degrees of precision. This article adheres to the terms used by the original authors where possible, e.g. M1 is used for area 4 in physiological contexts. Area 6 is composed of ventral and dorsal premotor cortex (PMv and PMd) on the lateral surface, and supplementary motor cortex (SMA) on the medial surface. F5 and F4 are the anterior and posterior subdivisions of PMv; similarly F7 and F2 for PMd. F3 is SMA proper and F6 is a region otherwise known as ‘pre-SMA’.

⁴a conjectural example since ‘dog’ cells, *per se*, have not been identified and studied in monkey IT cortex; however, a few animal selective units have been recorded in human entorhinal cortex (Crick *et al.* 2004), suggesting that the concept of a ‘dog’ cell is not too implausible.

⁵The authors argue that this was not due to inadvertent interference with cortico-spinal fibres, because similar treatment of the adjacent, basal ganglia relay nucleus V1a (V1o of Olszewski), with equal proximity to the internal capsule, was not so severe in effect.

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GLOSSARY

- AIP: anterior intraparietal
 CTC: cortico-thalamo-cortical
 FST: fundus superior temporal sulcus
 IT: inferotemporal (cortex)
 LGN: lateral geniculate nucleus
 MT: middle temporal (area)
 MST: medial superior temporal (area)
 PMv: ventral premotor cortex
 RF: receptive field
 SMA: supplementary motor area