Section 1: Anatomy of the sensorimotor system

A major aim of this thesis is to investigate reorganisation of cortical sensorimotor systems after stroke. This section provides an overview of the anatomy of the human motor and somatosensory systems and demonstrates that sensorimotor control depends on activity across networks of cortical and subcortical areas. Connections and functional overlap between specialised regions raise the possibility of intact areas of cortex taking over the function of damaged or disconnected areas. Most of this section relates to motor cortical anatomy and particular attention is paid to primary and premotor cortex, as these areas are a focus for many of the experiments in this thesis. Figures 1.1 and 1.2 illustrate the major divisions of the cortex and the principle sulci and gyri labelled as they will be referred to in the text.

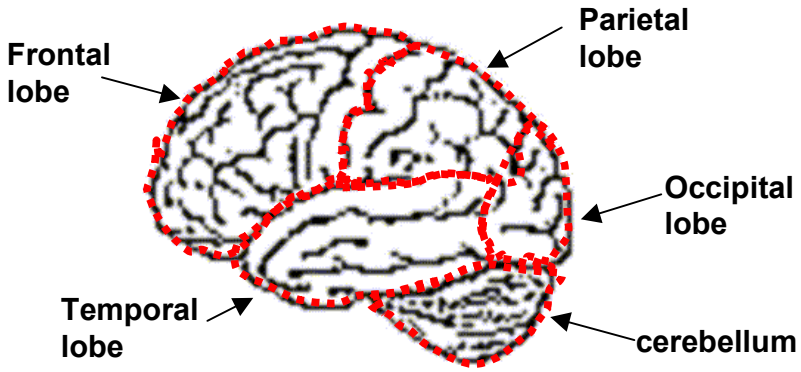

Figure 1.1: Schematic lateral view of the brain showing the position and extent of the four lobes of the neocortex and the cerebellum

1.1 The motor system

Knowledge of the structure and function of the motor system has advanced considerably over the last century. The emerging picture is an increasingly complex one, with ever-finer fractionation of functionally and microanatomically distinct subunits, operating as specialised components within multiple circuits. Advances have been made in our understanding of the histology, physiology and anatomy of the different motor areas, and the way in which they interact to carry out motor behaviour.

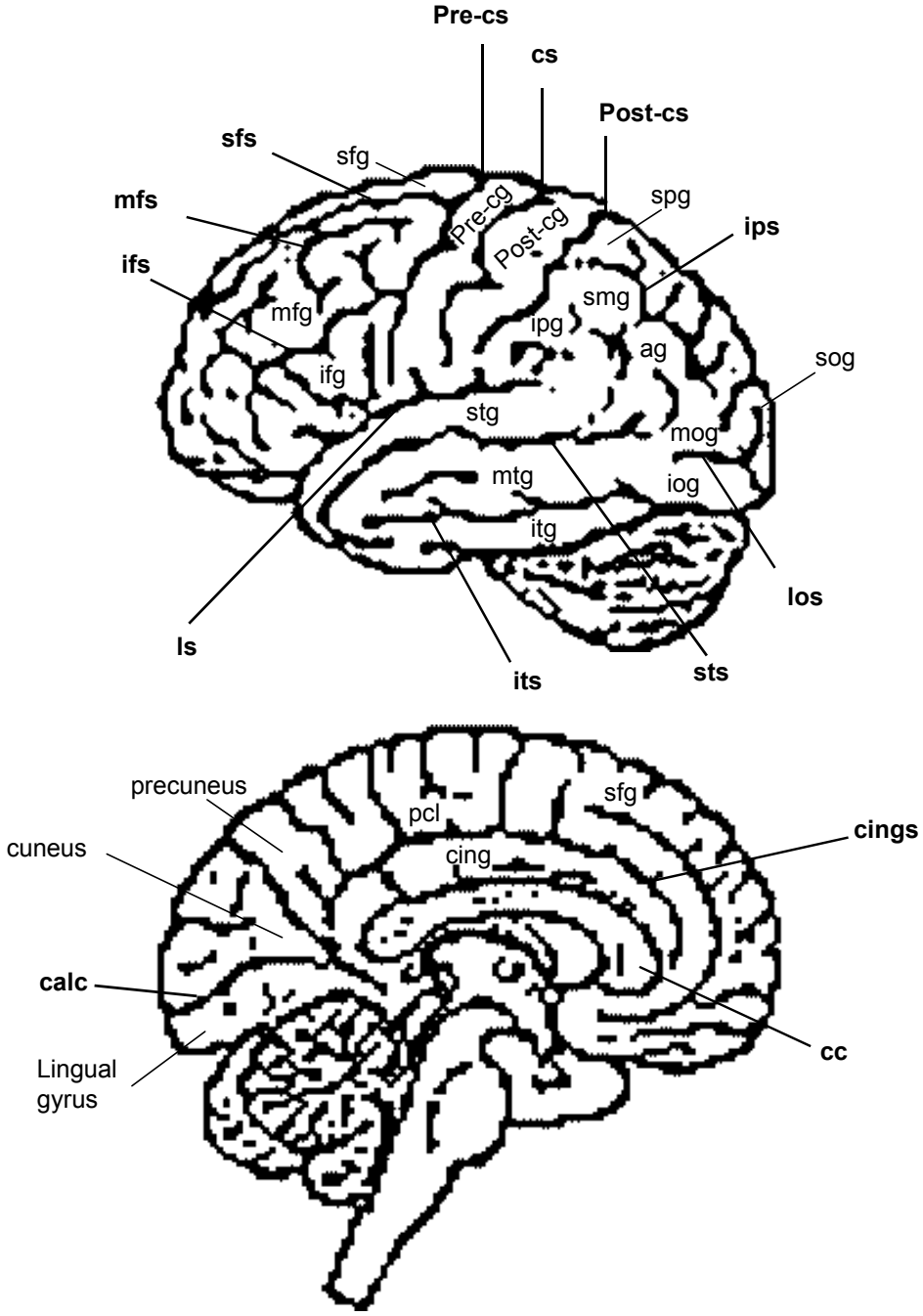

Figure 1.2: Schematic lateral and medial views of the human brain showing major sulci (in bold) and gyri. Abbreviations: cs=central sulcus, cg=central gyrus, spg=superior parietal gyrus, ag=angular gyrus, smg=supramarginal gyrus, ipg=inferior parietal gyrus, ips=intraparietal sulcus, sog=superior occipital gyrus, mog=middle occipital gyrus, iog=inferior occipital gyrus, los=lateral occipital sulcus, ls=lateral sulcus, stg=superior temporal gyrus, mtg=middle temporal gyrus, itg=inferior temporal gyrus, sts=superior temporal sulcus, its=inferior temporal sulcus, ifg=inferior frontal gyrus, mfg=middle frontal gyrus, sfg=superior frontal gyrus, sfs=superior frontal sulcus, ifs=inferior frontal sulcus, mfs=middle frontal sulcus, calc=calcarine sulcus, cc=corpus callosum, cing=cingulate gyrus, cings=cingulate sulcus, pcl=paracentral lobule

1.1.1 Localising and mapping the motor cortex

Attempts to localise specific brain regions responsible for motor function accelerated in the later part of the 19th century with the work of Sherrington, Ferrier and others (Porter and Lemon 1993). Evidence accumulated that removal of cortex in the precentral region produced movement abnormalities, and that stimulation of the same cortex could elicit muscle responses in dogs (Fritsch and Hitzitg 1870) and monkeys (Ferrier 1876). Working on chimpanzees, gorillas and orang-utans, Sherrington and colleagues mapped out motor responses elicited by stimulating points along the precentral gyrus (Leyton and Sherrington 1917; Grunbaum and Sherrington 1908).

Around the same time Brodmann was performing histological studies to map out cortical cytoarchitecture (Figure 1.3). Suggestions were made that anatomical divisions would correspond to functional divisions. The first clear link was made between histology and physiology when Campbell, who had been performing similar work to Brodmann, performed histological analysis of tissue from some of the animals that had been studied electrophysiologically by Sherrington and Leyton (Campbell 1905). Just as Sherrington and Leyton had localised the physiologically excitable cortex to the precentral gyrus, so Campbell found the distinct histology of this region meant that "it is just as possible to define the motor area on the histological bench, as on the operating table."

In their experiments on non-human primates, Sherrington and colleagues demonstrated that stimulation of different points along the precentral gyrus evoked movements of different body parts. A similar somatotopic organisation of excitable cortex was later found in human subjects by Penfield and colleagues who stimulated pre- and post-central sites during surgery for removal of tumours or epileptic foci (Figure 1.4). They found that the majority of effective sites were in the precentral cortex, and movements of

the hand were most commonly elicited (Penfield and Boldrey 1937; Penfield and Rasmussen 1952).

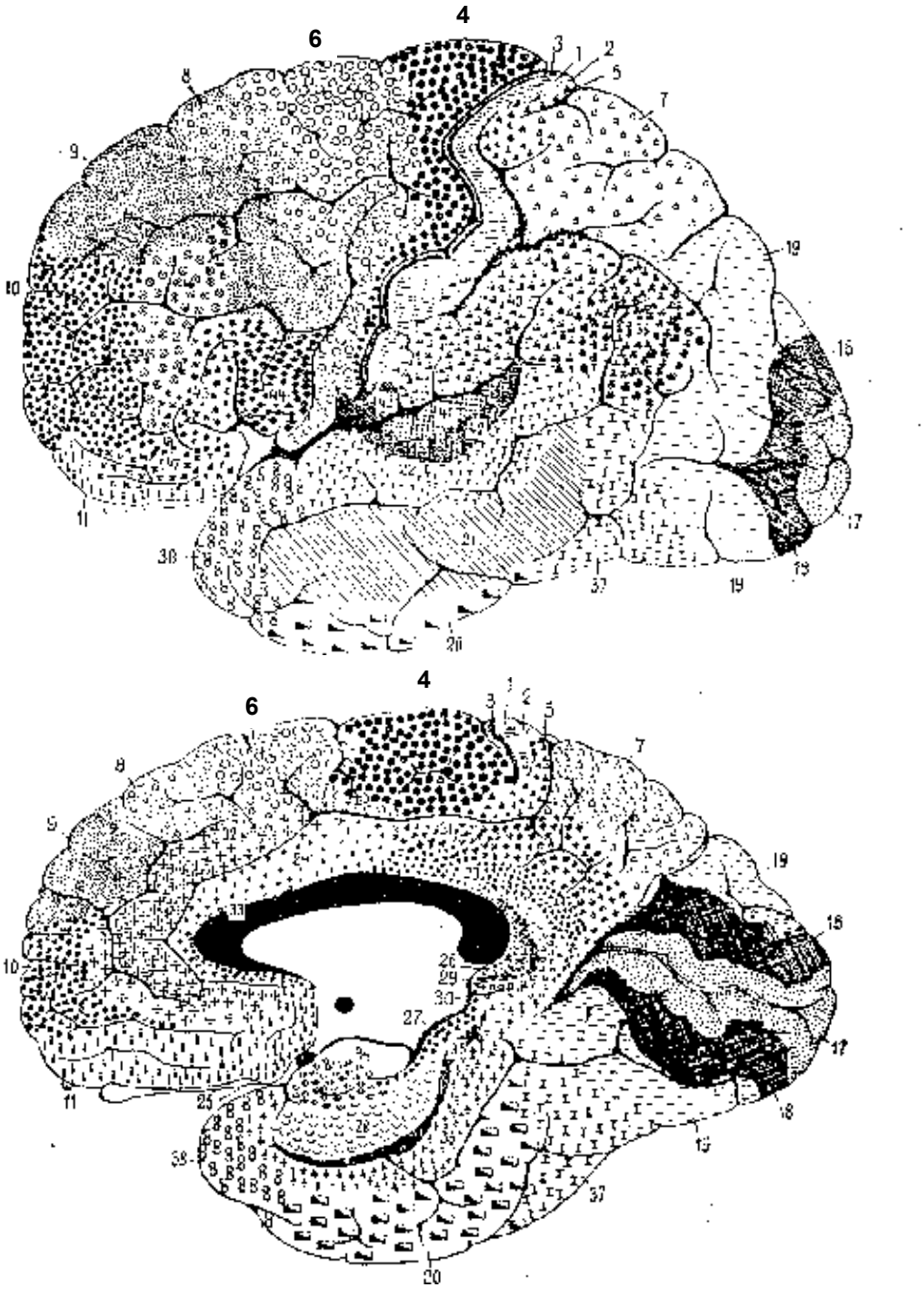

Figure 1.3: Brodmann's cytoarchitectonic map of human cortex. Different patterns represent cytoarchitectonically distinct regions. **Top:** lateral view, **bottom:** medial view. The primary motor cortex, or precentral region is labelled area 4 and patterned with black dots. Anterior to this is the premotor cortex, labelled area 6 and patterned with open dots.

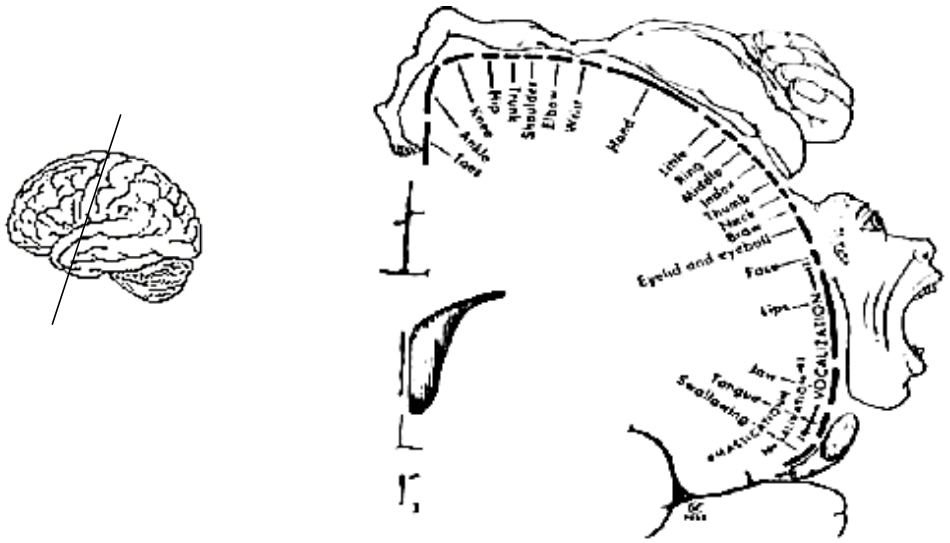

Figure 1.4: Penfield's motor homunculus (right). A schematic cross-section though the pre-central gyrus depicting the general principle of somatotopy. Direct electrical stimulation of different points along the pre-central gyrus evokes movements of different body parts. The section is taken at roughly the level indicated by the line through the brain on the left. The representation of the body is distorted, with a disproportionate volume of cortex devoted to the hand

1.1.2 Subdivisions within the cortical motor system

There is currently controversy over exactly how many cortical motor areas exist. This is further confounded by disagreement over what criteria should be used to define a motor area. Proposed criteria include requirements that a motor area has projections to spinal motor neurons and a full representation of the body, is always active during execution and planning of voluntary movements and rarely active in other circumstances (Roland and Zilles 1996). However, many of these criteria are difficult to test in the human brain, and many areas that are conventionally known as motor areas do not possess all these features. Therefore discussion here will include cortical areas that are conventionally described as motor areas, and that have been proven to be active during movement planning or execution. However, this does not rule out the possibility that they might be also involved in other, non-motor functions.

The original cytoarchitectonic maps of the human cortex differentiated between precentral and intermediate precentral cortex (Brodmann's areas 4 and 6 respectively, figure

1.3). Fulton proposed a functional distinction between "primary" motor cortex (area 4) and "premotor" cortex, lateral area 6, based on lesion studies (Fulton 1935). Area 6 on the medial wall was also designated a functionally distinct unit, the "supplementary" motor area (Woolsey *et al.* 1952).

Subsequently however, the model has become significantly more complex (Rizzolatti *et al.* 1998; Roland and Zilles 1996; Geyer *et al.* 2000). More fine-grained fractionation of the motor cortical system is based on cytoarchitecture, myeloarchitecture, metabolic architecture, connectivity and receptor mapping. In the monkey a number of these techniques can be performed on the same animal, allowing for detailed structure-function relationships to be defined. In the human brain less direct methods must be used, and assumptions must be made to relate post-mortem study to in vivo functional studies. Nevertheless, progress has been made in fractionating the human motor system and one candidate scheme is illustrated in figure 1.5.

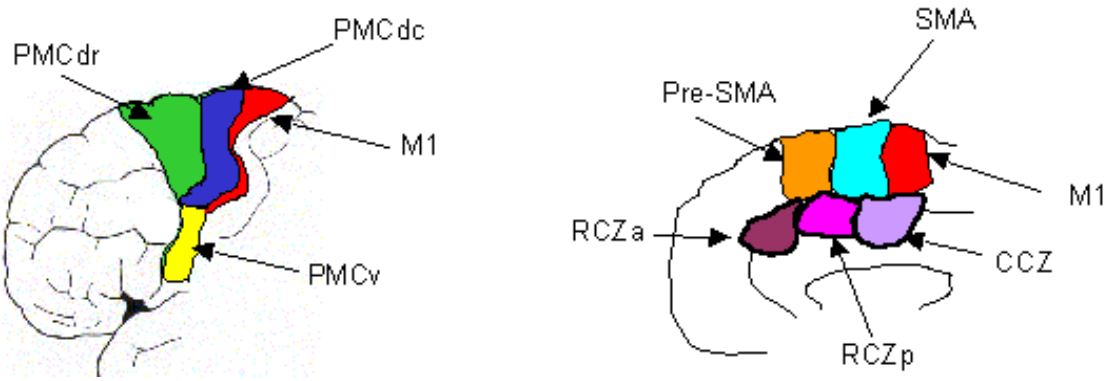

Figure 1.5: General scheme used for classifying subunits of the human motor system in this thesis. **Left:** lateral view; **right:** medial view. M1=primary motor cortex; PMC=premotor cortex; SMA=supplemetary motor area; RCZ=rostral cingulate zone; CCZ=caudal cingulate zone; d=dorsal; v=ventral; r=rostral; c=caudal; a=anterior; p=posterior

According to this scheme area 4 (primary motor cortex, M1) is divided into an anterior (4a) and a posterior (4p) segment (Geyer *et al.* 1996; Figure 1.6; Section 1.1.2.1). Medial area 6 (supplementary motor area, SMA) is divided into pre-SMA and SMA proper (Zilles *et al.* 1995; Section 1.1.2.3). Lateral area 6 (premotor cortex, PMC) is divided into a

dorsal (PMCd) and a ventral (PMCv) segment and PMCd is further divided into a rostral (PMCdr) and a caudal (PMCdc) portion (Barbas and Pandya 1987; Section 1.1.2.2). Finally, the cingulate motor areas are divided into a rostral (RCZ) and caudal (CCZ) zone, and RCZ is further divided into an anterior and posterior portion (Picard and Strick 1996; Section 1.1.2.4). Evidence for these subdivisions is presented in more detail below. This is the scheme that has generally been used to localise motor cortical activations in this thesis. Particular attention is paid to the primary motor and dorsal premotor cortices, though other motor areas are considered in specific experiments.

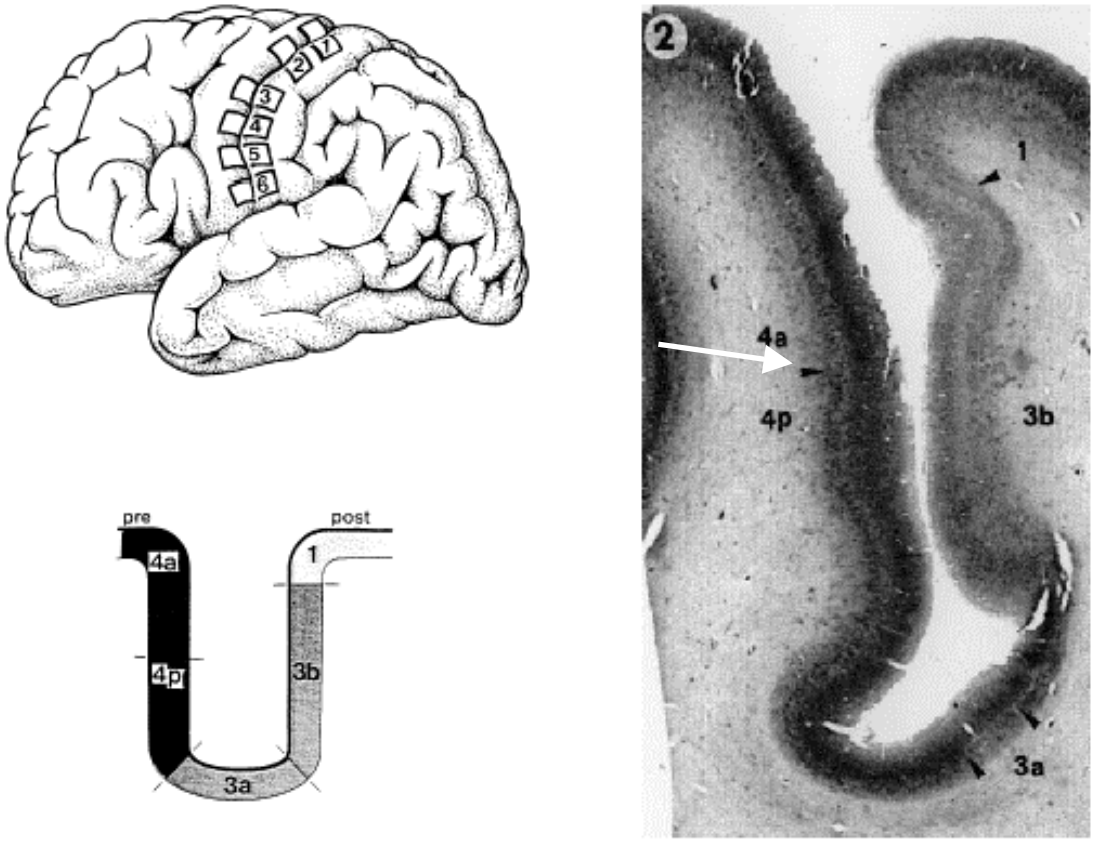

Figure 1.6: The primary motor cortex consists of two cytoarchitectonically distinct subregions, 4a and 4p. The boundary between 4a and 4p is indicated by the arrow in the right hand figure. The right hand figure shows a section through the central sulcus stained with *wisteria floribunda* agglutinin, a lectin that produces area-specific binding that correlates well with cytoarchitecture. The lateral brain view (top left) shows levels at which sections were taken. The section shown is taken at the point marked 2 on the lateral brain view. A schematic of the boundaries between cortical areas in the central sulcus is shown bottom left. In the posterior bank, areas 1, 3b and 3a form the primary somatosensory cortex. In the anterior bank, areas 4a (towards the surface of the sulcus) and 4p (in the depths of the sulcus) form the primary motor cortex. Figures from (Hilbig *et al.* 2001).

Connections between different motor cortical areas and the spinal cord are illustrated in figure 1.7. The corticospinal tract is discussed in more detail in Section 1.1.4. The characteristics of each of the subdivisions of the cortical motor system are discussed briefly below:

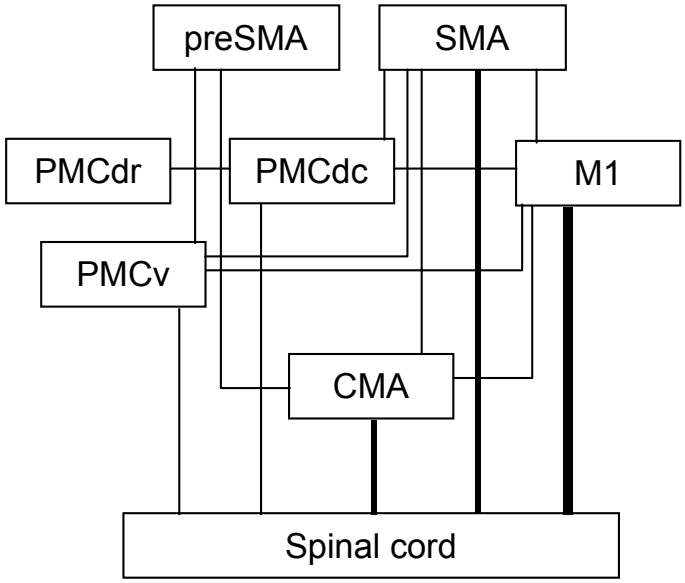

Figure 1.7: Simplified diagram of connections between motor cortical areas and projections to the spinal cord. For corticospinal projections line thickness roughly represents projection strength (see Section 1.1.3). For simplicity CMA subdivisions are not included.

1.1.2.1 Primary motor cortex (M1, Area 4)

Primary motor cortex (M1) is classically characterised by a lack of granule cells in layer IV and a high density of giant Betz cells, which can have diameters up to 120μm, in layer V (Meyer 1987). The concentration of Betz cells is greatest in the leg area of motor cortex suggesting that their size is related to the length of their axons. Betz cells contribute only 3% of the fibres of the pyramidal tract. The remainder of the corticospinal tract is made up of fibres from other layer V pyramidal cells. There is a greater diversity of pyramidal cell sizes in M1 than any other area of the cortex. For example, there is a tenfold range of pyramidal cell body area in M1 compared to a fourfold range in the precentral gyrus (Jones and Wise 1977).

The basic somatotopic arrangement of human motor cortex proposed by Sherrington, Penfield and others has been confirmed by modern neuroimaging techniques (Grafton *et al.* 1991; Rao *et al.* 1995). However, the concept of discrete regions of M1 representing movements of individual body parts may need updating (Schieber and Hibbard 1993). The picture has been complicated somewhat by the fact that intracortical stimulation of sites in motor cortex typically evokes movements of more than one muscle, and that individual muscles can be activated by multiple, distributed sites in motor cortex (Donoghue *et al.* 1992). This suggests that rather than representing individual muscles, regions of motor cortex represent functional muscle groups.

The cytoarchitectonic maps of Brodmann and Campbell both describe M1 as a single homogeneous region (e.g., area 4 in figure 1.3). The first suggestion that there could be subdivisions within motor cortex 4 came from Vogt and Vogt's studies of myeloarchitecture in the 1920s (Roland and Zilles 1996). More recently, Zilles and colleagues have proposed that area 4 should be subdivided into an anterior (4a) and posterior (4p) portion based on cyto- and myeloarchitecture and receptor density (Geyer *et al.* 1996; Figure 1.6). Brain imaging evidence suggests that there are separate representations of some digits in the two regions and there are tentative suggestions of functional differences between them, though at present these are poorly defined (Geyer *et al.* 1996; Nakada *et al.* 2000).

The caudal border of M1 lies close to the fundus of the central sulcus. The rostral border of M1 is difficult to define, as the cytoarchitectural transition between areas 4 and 6 is gradual. However, there has been some success in defining the border based on receptor mapping (Zilles *et al.* 1995).

Information on connectivity between motor areas comes mainly from studies of non-human primates and there is little direct evidence to confirm whether the same patterns

of connectivity hold in the human. In the macaque, M1 receives inputs from parietal cortex, premotor cortex and thalamus (summarised in (Passingham 1993)). The majority of inputs come from parietal cortex (37%), including direct projections from primary somatosensory cortex (in the postcentral gyrus) and from the secondary somatosensory cortex (in the superior bank of the lateral sulcus). There are also direct projects from regions of posterior parietal cortex that provide M1 with information on changes in joint position. M1 also receives inputs from non-primary motor cortical areas (27%), including somatotopic projections from lateral PMC, SMA and cingulate motor areas. Thirdly, M1 receives thalamic inputs (36%), mainly from the ventrolateral (VL) and ventral anterior (VA) groups of nuclei. These connections indirectly provide M1 with information from the basal ganglia via VA and the cerebellum via VL (Figure 1.11, Section 1.3).

1.1.2.2 Premotor cortex (PMC, lateral area 6)

When Campbell (1905) identified the 'intermediate precentral region' based on cytoarchitecture, he hypothesised that it was involved in the higher aspects of motor control:

> "I am of the opinion that this particular stretch of cortex is specially designed for the execution of complex movements of an associated kind, of skilled movements, of movements in which consciousness or volition takes an active part, as opposed to automatic movements."

The lateral premotor cortex (PMC) was first described functionally by Fulton (1935). Recent studies in macaque have distinguished between a dorsal and ventral premotor cortex, each containing a caudal and a rostral subdivision (Barbas and Pandya 1987; Matelli *et al.* 1985) Figure 1.8b, areas F2, F4, F5, F7).

However, the homology between human and macaque premotor cortex is not clear (Figure 1.8). In fact, of all the motor regions it is the premotor cortex that shows the greatest enlargement in humans relative to non-human primates (Von Bonin 1944). In

monkeys, the border between agranular premotor cortex, and the granular prefrontal cortex is the arcuate sulcus. There is no obvious homologue of this in the human.

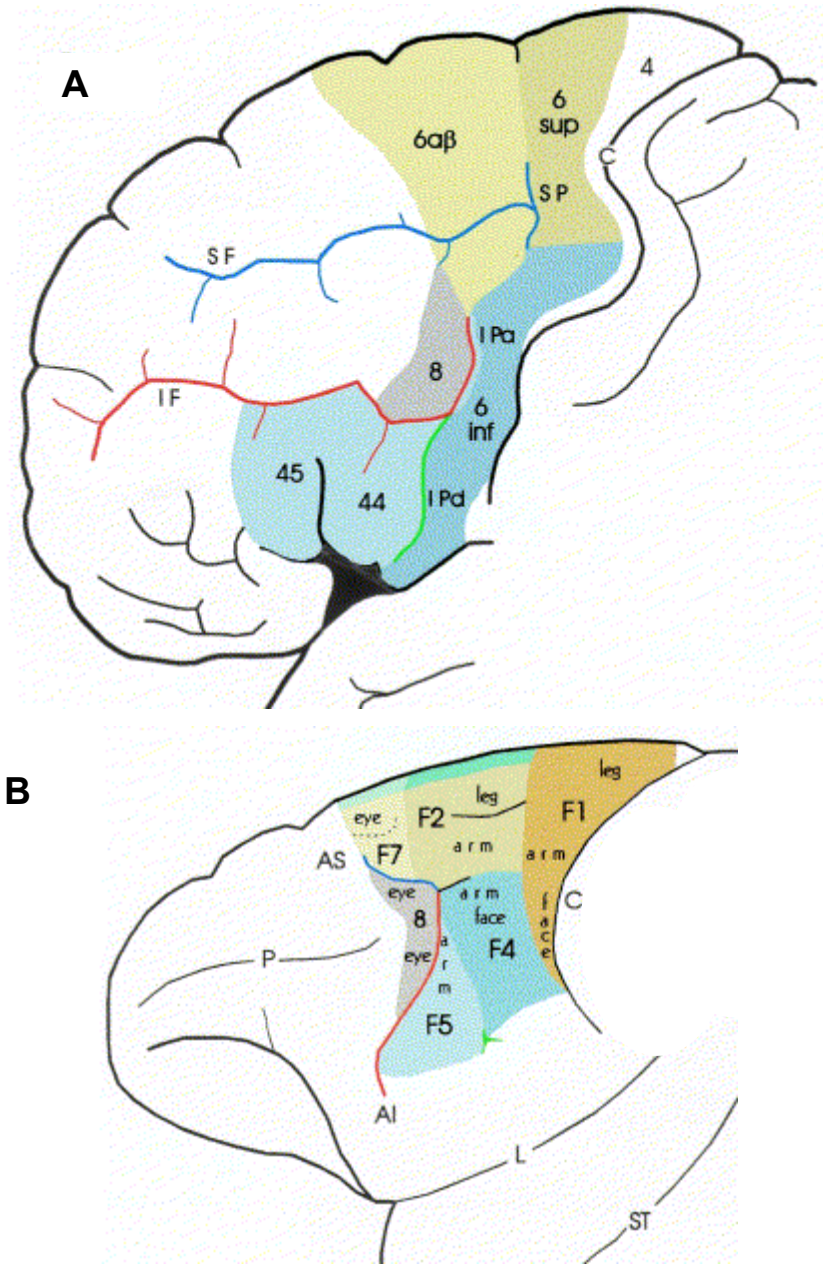

Figure 1.8: Divisions of the human motor cortical system (**A**) according to homology with macaque (**B**). Shading of gyri and sulci indicate proposed homology between the two species. Macaque cortical areas F2-F7 are labelled according to Matelli et al (1985). Human cortical areas defined according to Brodmann with additional subdivision of area 6 according to Vogt and Vogt. Sulci labelled as follows: Human: C=central, SF=superior frontal, IF=inferior frontal, SP=superior precentral. Macaque: C=central, AS=superior arcuate, AI=inferior arcuate, L=lateral, ST=superior temporal. Figure adapted from Rizzolatti et al (1998)

However, it has been argued on the basis of neurodevelopmental branching of the precentral sulcus that the inferior portion of the arcuate sulcus in the monkey corresponds

to the ascending branch of human inferior precentral sulcus plus inferior frontal sulcus (coloured blue in figure 1.8) and that superior portion of the arcuate sulcus in the monkey corresponds to human superior precentral sulcus plus superior frontal sulcus (coloured red in figure 1.8, (Rizzolatti *et al.* 1998)). By this scheme the dorsal part of the premotor cortex (above the join between the superior and inferior precentral sulci) is divided into two parts: a caudal part that corresponds to monkey F2 (i.e., the rostral part of the precentral gyrus, dark beige in figure 1.8), and a rostral part that corresponds to monkey F7 (i.e., the caudal part of the superior frontal gyrus, light beige in figure 1.8). Similarly the ventral part of human precentral gyrus is divided into a rostral part (BA 44, light blue in figure 1.8) and a caudal part (ventral area 6, dark blue in figure 1.8) corresponding to monkey F5 and F4 respectively. Human premotor cortex includes two further regions that are difficult to relate to monkey anatomy. BA45, and the dorsal agranular region caudal to the middle frontal gyrus (Rizzolatti *et al.* 1998).

1.1.2.3 Supplementary Motor Area (SMA, medial area 6)

Penfield and Rasmussen (1952) reported that they could elicit motor responses not only from stimulation of the classical sensorimotor area but also from:

> "an area from which bilaterally *synergic movements* may be produced. For lack of a more descriptive term we have called it the supplementary motor area to distinguish it from the classical sensorimotor area and the second sensory and motor representation. This supplementary motor area is comparatively small and is situated within the superior intermediate frontal regions within the longitudinal fissure."

There are close homologies between human and macaque medial area 6 (Geyer *et al.* 2000). Medial areas F3 and F6 in macaque correspond to human SMA-proper and pre-SMA respectively. SMA-proper and pre-SMA can be differentiated on the basis of cytoarchitecture and neurochemistry (Zilles *et al.* 1995).

In the case of the medial motor areas there is a rough correspondence between cytoarchitectonic borders and gross anatomy. The border between SMA and pre-SMA corresponds to the VCA line (the line passing through the anterior commisure and perpendicular to the line between the anterior and posterior commisures (AC-PC)). The border between M1 and the SMA-proper corresponds approximately the to VCP line (the vertical line passing the posterior commisure and perpendicular to the AC-PC line) (Vorobiev *et al.* 1998).

1.1.2.4 Cingulate motor areas (CMA, areas 23, 24, parts of medial area 6)

In the monkey the cingulate motor areas are located in the depths of the cingulate sulcus and can be divided into rostral (CMAr, area 24c), ventral (CMAv, area 23c) and dorsal (CMAd, area 6c) subregions (Picard and Strick 1996). Different subregions receive inputs from different thalamic nuclei and have reciprocal connections with distinct regions within primary motor cortex and parietal cortex. Cingulate motor areas also give rise to corticospinal projections that terminate in the intermediate zone of the spinal cord (see Section 1.1.3).

There are motor regions in the cingulate sulcus and along the cingulate gyrus in the human. However, precise homologies between monkey and human CMAs have yet to be established. Human CMAs are divided into a rostral (RCZ) and a caudal zone (CCZ). RCZ can be further divided into an anterior (RCZa) and a posterior portion (RCZp). One proposal suggests that RCZa corresponds to monkey area CMAr; RCAp to CMAv, and CCZ to CMAd (Picard and Strick 1996).

A review of PET studies reporting motor-related activations on the medial wall found functional distinctions between human cingulate motor areas and multiple representations of body parts along the cingulate sulcus and gyrus (Picard and Strick 1996). CCZ was activated by simple arm movements whereas different types of complex arm

movements activated distinct foci within RCZ. For example, arm movements requiring conditional associations between cues and movements activated RCZp (Paus *et al.* 1993). Whereas when subjects are asked to make arm movements in a direction of their choice, compared to a fixed direction (so called "willed action"), activation is seen in RCZa (Playford *et al.* 1992). The most anterior portions of RCZa and RCZp were activated by complex tasks involving eye or face movements (Picard and Strick 1996).

1.1.3 Subcortical motor systems

1.1.3.1 Cerebellum

The cerebellum consists of an outer cortical layer and an inner core of white matter. The cerebellar cortex has a distinctive architecture consisting of an outer molecular layer, an intermediate Purkinje cell layer and an inner granular layer (Carpenter 1978; Figure 1.9). Within the white matter of the cerebellum are four pairs of nuclei (fastigial, globose, emboliform and dentate).

The cerebellar cortex can be divided on the basis of phylogeny: the oldest region (archicerebellum) consists of the flocculonodular lobe; the next oldest region (paleocerebellum) consists of the anterior and posterior parts of the vermis; the newest region (neocerebellum) consists of the midportion of the vermis and the cerebellar hemispheres. Functional-anatomical subdivisions of the cerebellar cortex overlap with phylogenetic subdivisions and are described in more detail in the following subsections (Brodal 1998).

The vestibulocerebellum (Figure 1.10) consists of the flocculonodular lobe. It is involved in the control of balance and eye movements. It receives direct and indirect (via the vestibular nuclei) vestibular inputs and contributes outputs to the vestibulospinal tract.

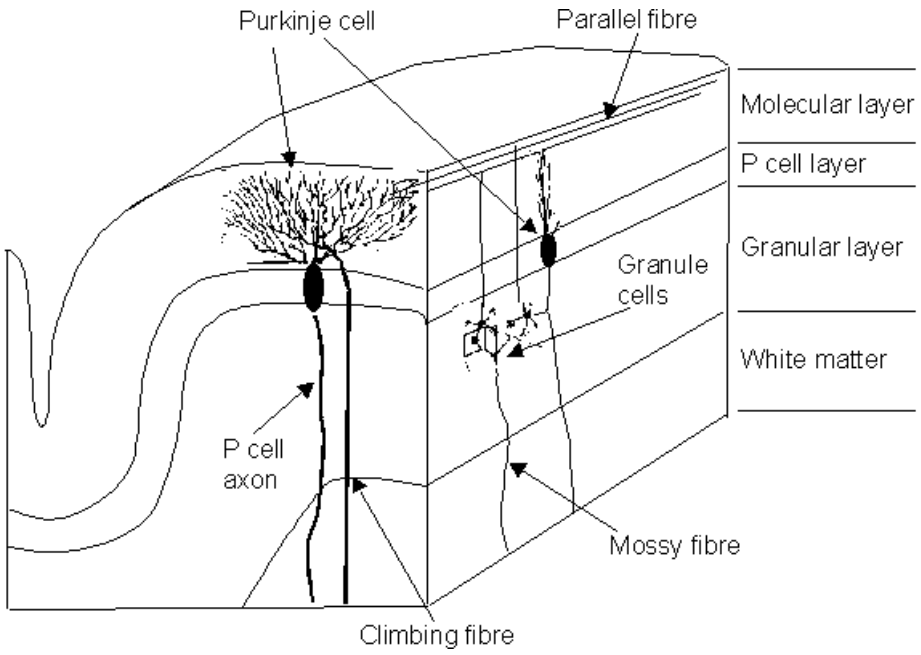

Figure 1.9: The cerebellar cortex has a unique cellular architecture (Eccles *et al.* 1967). It receives inputs from the spinal cord, inferior olive, vestibular nucleus and pons. The inferior olive gives rise to climbing fibres which synapse with Purkinje (P) cells. P cell bodies are found in the P cell layer, and their dense dendritic arborisations are found in the molecular layer. Each climbing fibre makes many synapses with a single P cell. Other projection areas give rise to mossy fibres which synapse with granule cells. Axons of granule cells project to the molecular layer where they bifurcate to produce two parallel fibres. Each parallel fibre synapses with numerous P cells as they traverse the molecular cell layer. Axons of P cells project mainly to the deep cerebellar nuclei.

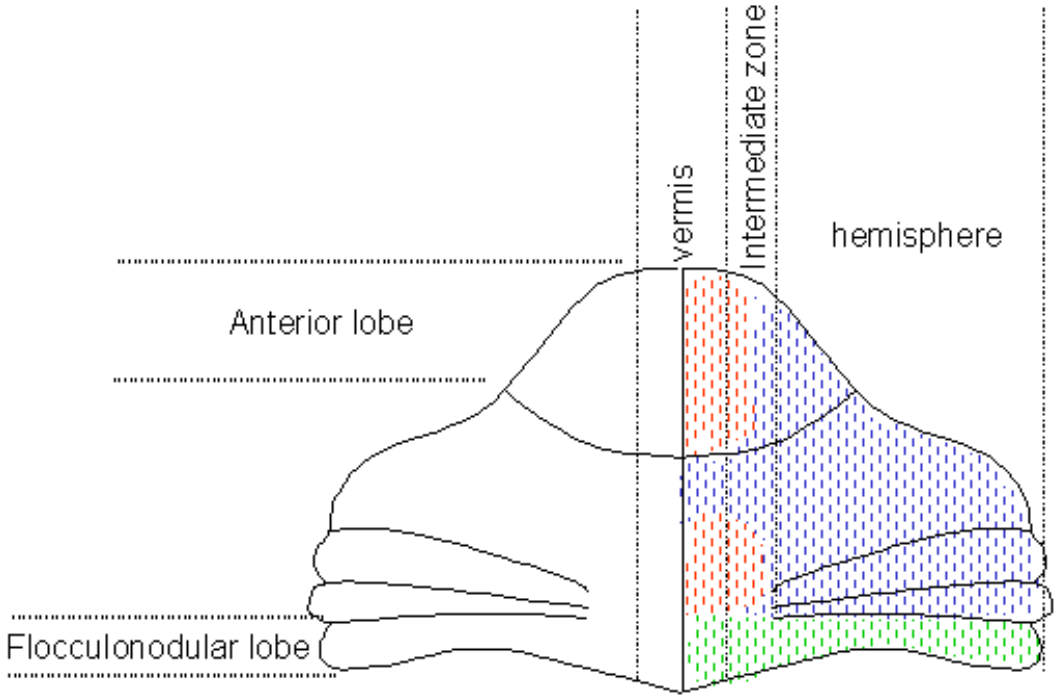

Figure 1.10: The functional and anatomical subdivisions of the cerebellum. **Blue:** Cerebrocerebellum. **Red:** Spinal cerebellum. **Green:** Vestibulocerebellum.

The spinocerebellum (Figure 1.10) consists of the anterior and posterior vermis plus adjoining areas of the intermediate zone (medial part of cerebellar hemispheres). The spinocerebellum receives inputs from a number of direct and indirect spinocerebellar tracts that convey information about motor commands and the sensory consequences of movements. The two main direct tracts are the dorsal and ventral spinocerebellar tracts. The dorsal spinocerebellar tract originates from neurons in the dorsal part of the spinal cord white matter (in the column of Clarke), ascends on the same side and enters the cerebellum through the inferior cerebellar peduncle. Neurons in the column of Clarke receive inputs from muscle spindles, tendon organs, joint and cutaneous receptors. The dorsal spinocerebellar tract transmits information from various receptor types activated by complex joint movements. The ventral spinocerebellar tract originates from neurons in the ventro-lateral part of the spinal white matter, crosses the midline once in the cord, but most fibres then cross again in the cerebellum. The ventral spinocerebellar tract conveys information about levels of activity in spinal interneurons.

The cerebrocerebellum (Figure 1.10) consists of the cerebellar hemispheres and the middle part of the vermis. It receives inputs from the cerebral cortex via the pontine nuclei. Projections from the cerebral cortex to the pontine nuclei are uncrossed whereas ponto-cerebellar fibres cross, therefore the cerebrocerebellum receives input from the opposite cerebral cortex. Cerebro-cerebellar inputs are organised topographically, with inputs from different cortical areas remaining somewhat segregated in the pontine nuclei and cerebellum. Cortico-pontine fibres arise mainly in sensorimotor areas including primary motor and somatosensory cortex, SMA, premotor cortex and areas of the posterior parietal cortex. Fibres are also received from visual cortex, hypothalamus and limbic system. Outputs from the cerebrocerebellum to the cortex ascend via the dentate nucleus and the thalamus. The

cerebrocerebellum is therefore in a position to monitor and influence visually-guided movement.

The cerebellar nuclei relay information to and from different parts of the cerebellum and thalamus. There is segregation of inputs from Purkinje cells in different parts of the cerebellum: the vermis projects to the fastigial nucleus, the intermediate zone projects to the globose and emboliform nuclei and the hemispheres project to the dentate nucleus. The dentate nucleus is particularly involved in motor control. It projects to the contralateral ventrolateral (VL) nucleus of the thalamus (Asanuma *et al.* 1983) which then projects to the primary motor and premotor cortex (Matelli *et al.* 1989) and supplementary motor area (Matelli and Luppino 1996; Figure 1.11).

Damage to the regions of the cerebellum impairs performance of co-ordinated movements (Flourens 1824). Early studies of patients with cerebellar damage from tumours or gunshot wounds found that symptoms included vertigo, nystagmus, loss of power and tone in ipsilateral limbs, abnormal posture and staggering gait (Holmes and Stewart 1904; Holmes 1917). The combination of symptoms observed depends on the location of the lesions: flocculonodular lobe damage results in disturbances in balance; vestibulocerebellar lesions causes nystagmus (jerking involuntary movements); damage to anterior lobe vermis and intermediate zone can cause unsteady walking, or gait ataxia; cerebellar hemisphere damage causes ataxia of voluntary non-automatic movements (Crossman and Neary 1995).

Flourens also noted the capacity of intact regions of the cerebellum to compensate for damage to other regions (Flourens 1842). This functional plasticity is thought to reflect the normal role of the cerebellum in motor learning. The unique cellular architecture of the cerebellum provides a suitable substrate for a learning mechanism (Eccles *et al.* 1967; Ito 1984). Learning could take place via cellular changes that instigate error-based Hebbian-like learning rules (Marr 1969; Albus 1971). For example, long term potentiation (LTP) and long

term depression (LTD) have been demonstrated at parallel fibre – Purkinje cell synapses in vitro (Ito 1984; Crepel and Jaillard 1991).

1.1.3.2 Basal ganglia

The organisation, structure and function of the basal ganglia is similar to parts of the cerebellum, in that the basal ganglia consist of subcortical structures reciprocally linked to cortical motor systems. This section will consider the basal ganglia to include the caudate, putamen, globus pallidus, substantia nigra and subthalamic nucleus. The caudate and putamen are separated by the internal capsule and have distinct connections. However, they are also functionally related and are known collectively as the neostriatum.

The neostriatum receives most of the inputs to the basal ganglia (Brodal 1998). Inputs originate mainly from the cerebral cortex but also from the intralaminar nuclei of the thalamus and the substantia nigra pars compacta. The putamen receives projections from primary sensory and motor cortices. The caudate receives inputs from frontal and parietal association areas. The neostriatum sends outputs to the globus pallidus and the substantia nigra pars reticulata.

The globus pallidus and the substantia nigra pars reticulata constitute the main output areas of the basal ganglia. The globus pallidus is divided into an internal and an external segment. The internal segment projects to the thalamus, mainly the ventral anterior nucleus (VA) but also the ventral lateral (VL) and centromedian (CM) (Jones 1987; Figure 1.11). The external segment projects to the subthalamic nucleus.

Damage to the basal ganglia does not usually result in paralysis or ataxia but does produce abnormal movement patterns and altered muscle tone (Crossman and Neary 1995). Abnormal movement patterns include involuntary movement (e.g. tremor, chorea) and poverty of movement (bradykinesia and akinesia).

Different components of the basal ganglia have been implicated at various stages in a range of motor functions. These include sequence learning (Miyachi *et al.* 1997) and reward learning (Schultz 1998).

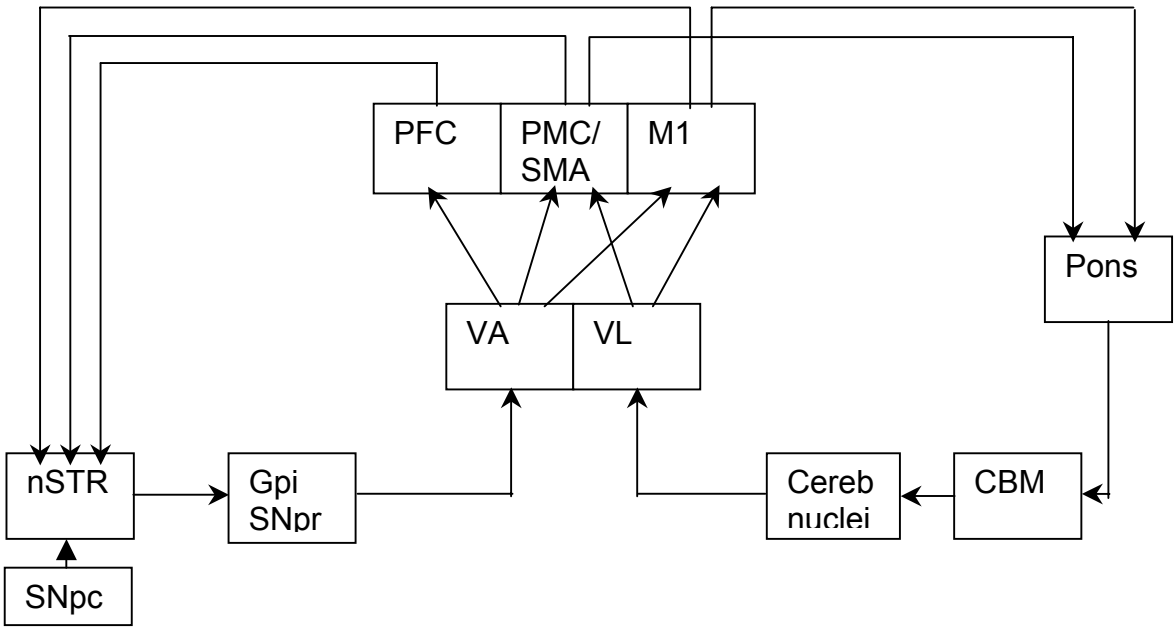

Figure 1.11: Schematic of some of the major connections between subcortical and cortical motor areas. The basal ganglia and cerebellum form reciprocal loops with cortical motor areas. The thalamus relays information from subcortical areas to the motor areas of the cortex. Information from the basal ganglia is relayed via VA, and information from the cerebellum is relayed via VL. CBM = cerebellum, nSTR= neostriatum, Gpi=globus pallidus, pars interna, SNpr=substantia nigra pars reticulata, SNpc=substantia nigra pars compacta, PFC=prefrontal cortex, PMC=premotor cortex, M1=primary motor cortex, VA=ventral anterior nucleus of the thalamus, VL=ventral lateral nucleus of the thalamus

1.1.3.3 Thalamus

The thalamus consists of a number of nuclei which relay information to and from the cerebral cortex. The thalamus is divided into three main groups of nuclei: anterior, medial and lateral and further subdivisions exist within these groups. The two most important nuclei for the motor system are both in the lateral nuclear group and have highly organised connections with cortical and subcortical motor areas (Jones 1987). Subcortical input is segregated between the two nuclei but they have overlapping motor cortical output (Passingham 1993; Figure 1.11). The ventral lateral nucleus (VL) receives direct inputs from the contralateral dentate nucleus of the cerebellum and projects to motor cortical areas (Matelli and Luppino 1996; Matelli *et al.* 1989). The ventral anterior nucleus (VA) receives

direct connections from parts of the ipsilateral basal ganglia including globus pallidus and substantia nigra and projects to motor cortical areas (Jones 1987).

1.1.4 Descending motor tracts

The cerebral cortex excites muscles directly via the corticospinal tract (Figure 1.12) and indirectly via tracts descending from brainstem structures (Table 1.1). Fibres from motor cortical areas project to pontine nuclei (corticopontine) and regions of the lower brain stem (corticobulbar). Corticospinal, corticobulbar and corticopontine fibres descend together through the internal capsule and crus cerebri.

Tract	Origin	Crossed?	Muscle groups
Lateral corticospinal	Motor and sensory cortical areas	Yes	Mainly distal
Ventral corticospinal	Motor and sensory cortical areas	No	Mainly proximal
Tectospinal	Superior colliculus	Yes	Head and eyes
Rubrospinal	Red nucleus	Yes	Distal
Vestibulospinal	Vestibular nucleus	No	Axial and proximal
Reticulospinal	Pontine and medullary reticular formations	No	Axial and proximal

Table 1.1: Summary of the major descending motor tracts.

1.1.4.1 The corticospinal tract

Axons of corticospinal neurons project from layer V of the cortex through the posterior limb of the internal capsule, the cerebral peduncle in the midbrain, the base of the pons and the medullary pyramids (Schieber 1999). Below the medulla 70-90% of pyramidal fibres decussate to form the lateral corticospinal tract and 10-30% remain uncrossed and form the ventral corticospinal tract (Nathan and Smith 1973). Corticospinal axons terminate at all layers of the grey matter of the spinal cord. The majority of corticospinal fibres synapse onto interneurons but some fibres synapse directly onto motorneurons. Monosynaptic projections to motorneurons are most common in axons from the anterior bank of the central sulcus, particularly from the hand area of motor cortex, that excite distal muscles

(Brodal 1998). The proportion of monosynatpic connections is greater in humans and great apes than in other primates and there are no monosynaptic connections in the cat (Porter and Lemon 1993). This is consistent with the proposed role of these monosynaptic connections in the fine control of fractionated distal movements.

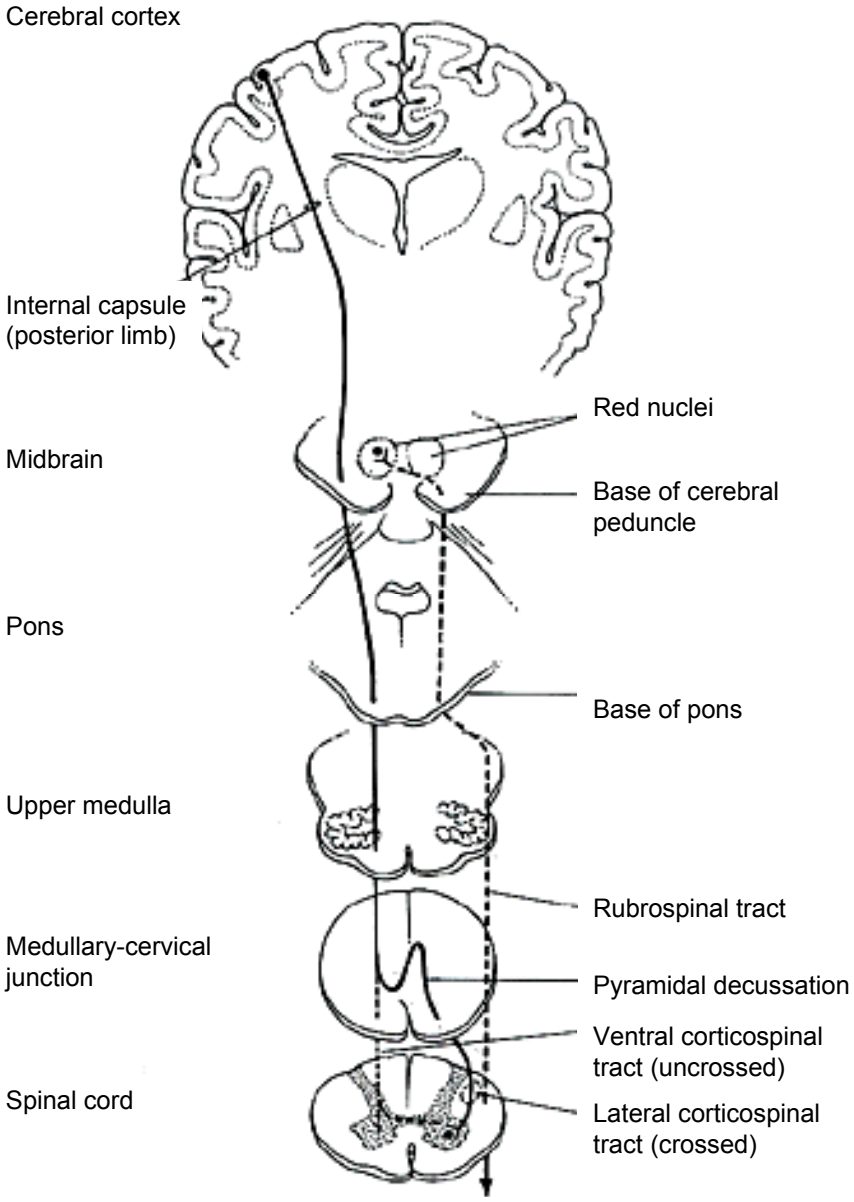

Figure 1.12: The corticospinal projection. Axons from corticospinal neurons leave the cortex via the internal capsule and project through the midbrain, pons and medulla before decussating to form the lateral corticospinal tract, or continuing uncrossed to form the ventral corticospinal tract.

Motorneurons of the spinal cord have a columnar organisation with cell bodies innervating a given muscle arranged in a longitudinal column spanning several levels of

spinal cord grey matter. While the columns are roughly 200μm in diameter, the dendritic trees of spinal motor neurons can branch up to 2mm from the soma and so extend far outside the column of cell bodies. Motorneurons innervating distal muscles tend to be located laterally whereas the motorneurons for proximal muscles are situated more medially.

Region	Labelled cells (%)
Primary motor cortex	48.5
Superior precentral sulcus	7.0
Arcuate premotor area	4.0
SMA	18.5
Cingulate motor areas:	
Dorsal	10.5
Ventral	6.8
rostral	4.0

Table 1.2: Retrograde labelling of corticospinal neurons in motor areas of the frontal and cingulate cortices after injection of WGA-HRP into the spinal cord of monkeys. From (Dum and Strick 1991)

Although the majority of corticospinal projections originate in the primary motor cortex a substantial proportion come from other motor areas of the frontal lobe (Table 1.2).

Region	**Labelled cells (%)**
Motor areas:	
Primary motor cortex	35
Dorsolateral 6a alpha	6
Arcuate premotor area	2.6
SMA	15
Cingulate area 24	6
Cingulate area 23	4
Sensory areas:	
Area 3a	2.2
Areas 3b/1	9
Areas 2/5	13
S2 and insula	3.4

Table 1.3: Retrograde labelling of corticospinal neurons in motor and sensory areas of the frontal, cingulate, parietal and insular cortices after injection of fluorescent markers into the spinal cord of monkeys. From (Galea and Darian-Smith 1994). S2=secondary somatosensory cortex

Other primate studies provide estimates ranging from 30-60% for the contribution of the primary motor cortex (Murray and Coulter 1981; Russell and DeMeyer 1961); for

humans, the figure is 60% (Jane et al. 1967). Corticospinal projections are not limited to frontal and cingulate cortices. A study using retrograde labelling with fluorescent tracers found projection areas in somatosensory areas of the parietal and insular cortices (Table 1.3).

1.1.4.2 Other descending motor tracts

There are also routes from subcortical areas to the spinal cord. These include the tectospinal, rubrospinal, vestibulospinal and reticulospinal tracts (Carpenter 1978).

The *tectospinal tract* originates in the superior colliculus, crosses the midline at the dorsal tegmental decussation and descends to the spinal cord (Harting 1977). The superior colliculus receives visual input and the tectospinal tract is thought to mediate visually triggered reflex responses.

The *rubrospinal tract* originates in the red nucleus in the midbrain, crosses the midline at the ventral tegmental decussation and descends to the spinal cord (Murray and Haines 1975). The red nucleus receives input from the motor cortex and cerebellum and so provides an indirect route for these areas to influence the spinal cord. In cats and monkeys the rubrospinal tract is thought to control tone in distal flexor muscle groups. However, the magnocellular part of the red nucleus, where the tract originates, is smaller in humans than in monkeys, and smaller in monkeys than in cats. The functional importance of the reticulospinal tract in humans is therefore debated (Brodal 1998).

The *vestibulospinal tracts* arise from the vestibular nuclei in the pons and medulla and descend to the spinal cord without crossing the midline (Carpenter 1978). They mainly innervate axial and proximal muscles and are thought to influence extensor muscle control and maintenance of posture.

The *reticulospinal tracts* originate in the pons and the medulla. The pontine and medullary reticulospinal tracts are largely ipsilateral (Carpenter 1978). Corticoreticular fibres from motor areas terminate in regions of the pontine and medullary reticular formations that

give rise to the reticulospinal tracts and provide another non-pyramidal route for motor cortical areas to influence the spinal cord. The reticulospinal tracts mainly innervate axial and proximal muscles and influence postural reflexes and crude voluntary movements of the extremities, such as extending an arm towards an object (Brodal 1998)

1.1.4.3 Corticobulbar and corticopontine fibres

Corticobulbar fibres originate mainly from the ventral portion of the motor cortex and project to parts of the lower brain stem including certain motor cranial nerve nuclei, parts of the reticular formation and sensory relay nuclei. Some of these motor cortical projection neurons, and also cells in the SMA and cingulate motor areas, give rise to branching fibres which project both to the spinal cord and to the lower parts of the brainstem (Keizer and Kuypers 1989). Corticobulbar fibres to motor cranial nerve nuclei arise directly from the precentral gyrus and indirectly via the reticular formation. Direct corticobulbar projections terminate bilaterally on trigeminal, facial, hypoglossal and supraspinal motor nuclei. These nuclei largely innervate muscle groups that are contracted bilaterally such as laryngeal, palatal and upper facial muscles. The bilateral innervation of these muscle groups means that they are rarely affected by unilateral lesions.

Corticopontine fibres arise from many regions of the cortex, descend without crossing and terminate on pontine nuclei of the ventral pons. The pontine nuclei then project to the contralateral cerebellum via the middle cerebellar peduncle.

1.2 The somatosensory system

Like the motor system, the cortical somatosensory system consists of a distributed network of specialised, interconnected brain regions. This section will briefly outline the cortical areas involved in somatosensory processing and will discuss conflicting evidence on the nature of the connections between somatosensory areas. Discussion here will focus on neural processing of the sense of touch, just one component of somatosensation. Included in somatosensation are senses such as temperature, pain, pressure and proprioception.

1.2.1 Functional Organisation of the somatosensory system

The sense of touch is initiated by mechanical stimulation of the body. Mechanoreceptors are situated at different depths in the skin and have different response properties. Studies on the glabrous (hairless) skin of the hand support the view that there are, in general, four different types of mechanoreceptive afferents: slowly adapting with small receptive fields; slowly adapting with large receptive fields; rapidly adapting with small receptive fields and rapidly adapting with large receptive fields (Bolanowski, Jr. *et al.* 1988).

Peripheral nerves project from mechanoreceptors to the dorsal root ganglia in the spinal cord. Fibres from the dorsal root ganglia project along the dorsal columns of the spinal cord to the dorsal column nuclei in the medulla. Fibres from these nuclei project to the ventroposterior thalamus (VP) which projects to somatosensory areas in the parietal cortex (Figure 1.13).

There are thought to be nine cortical areas with primarily somatosensory function: the primary somatosensory cortex (S1 – comprising areas 3a, 3b, 1 and 2, the second somatosensory area (S2) located along the superior bank of the lateral sulcus (Woolsey 1946; Maeda *et al.* 1999), the granular insula and retroinsular cortex (Schneider *et al.* 1993), and in the posterior parietal cortex areas 5 and 7b (Figure 1.14).

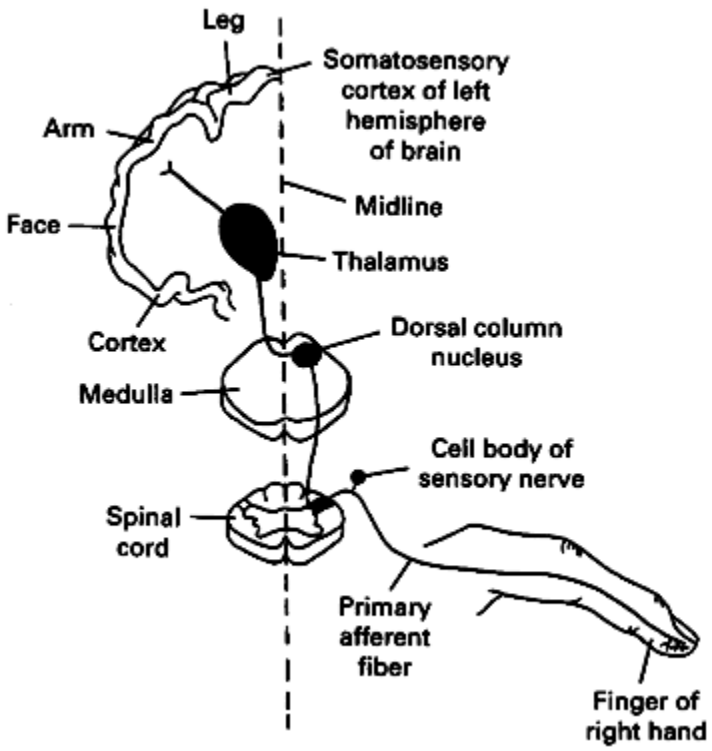

Figure 1.13: Somatosensory pathways from peripheral receptors to cortex, via spinal cord, midbrain and thalamus

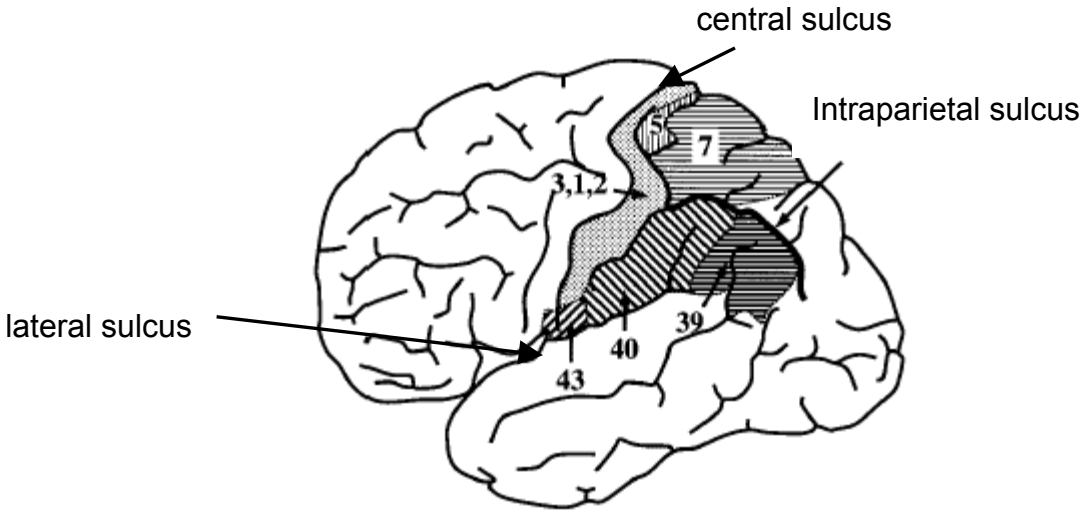

Figure 1.14: Anatomical subdivisions of human parietal cortex. Primary somatosensory cortex is located in the posterior bank of the central sulcus and the postcentral gyrus and comprises areas 1,2,3. Somatosensory regions in posterior parietal cortex include areas 5 and 7b. The secondary somatosensory cortex is located in the upper bank of the lateral sulcus.

Like the primary motor cortex, S1 is organised somatotopically (Penfield and Rasmussen 1952; Maldjian *et al.* 1999; Figure 1.15). There is also some evidence for rough

somatotopy along the secondary somatosensory cortex (Maeda *et al.* 1999). While S1 is typically only activated contralaterally by unilateral touch (Maldjian *et al.* 1999), it is common to see bilateral activation of S2 and the insula (Robinson 1973; Schneider *et al.* 1993).

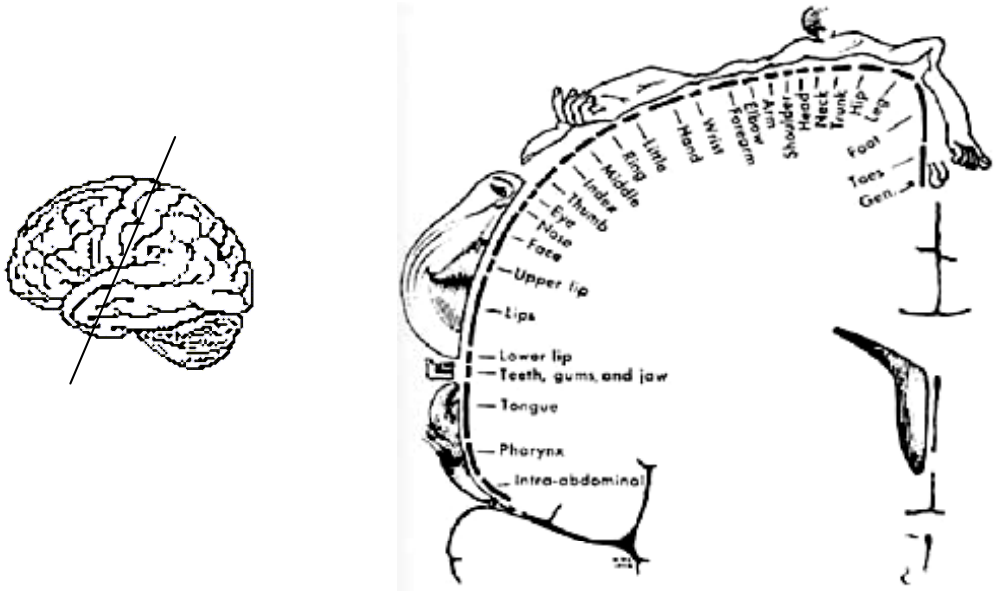

Figure 1.15: Penfield's somatosensory homunculus. Like the motor cortex, the somatosensory cortex is organised somatotopically. This cross section (right) through the postcentral gyrus (roughly the location indicated by the line on the lateral brain view, left) indicates the area of cortex where electrical stimulation evokes sensations in different body parts. Note the relative over-representation of the lips and under-representation of the trunk. The arrangement of body representations may provide an explanation for some phantom limb phenomena (see section 2.4.3.1). After amputation of the hand patients sometimes report phantom limb sensations evoked by touch to the face, which is adjacent to the deafferented hand regions of somatosensory cortex.

1.2.2 Flow of somatosensory information: serial or parallel pathways?

There has been controversy concerning the extent to which touch information is processed serially from S1 to S2 (Figure 1.16). Although initially it was thought that only S1 received thalamic input, it has now been demonstrated that the ventroposterior nucleus of the thalamus (VP) sends direct reciprocal projections to both S1 and S2 (Jones 1986; Jones and Powell 1969; Burton and Jones 1976). This therefore led to the belief that somatosensory information was processed in parallel (Figure 1.16b).

Whether processing occurs in series can also be tested by inactivating proposed early processing regions and seeing whether this silences other areas. Inactivation of S1 does not

affect responses in S2 in the cat (Manzoni *et al.* 1979), rabbit (Woolsey and Whang 1945), tree shrew or prosimian galago (Garraghty *et al.* 1991). These studies lend further support to the idea of parallel processing of somatosensory information.

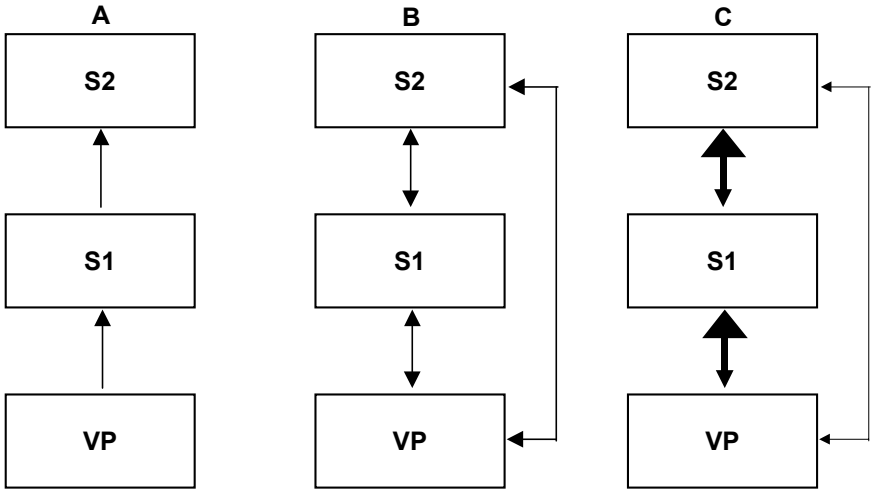

Figure 1.16: Schematic showing candidate schemes for flow of somatosensory information from the ventroposterior nucleus of the thalamus (VP) to the primary (S1) and secondary (S2) somatosensory cortices. **A:** Strict serial scheme **B:** Parallel scheme with strong reciprocal connections between VP and both S1 and S2. **C:** Less strict serial scheme with sparse projections from VP and S2 and dense projections from VP to S1.

However, in other primate species a different model is emerging. In macaques it appears that VP sends only sparse projections to S2 (Manzoni *et al.* 1984; Friedman and Murray 1986). By contrast there are dense projections from all four subregions of S1 to S2 (Friedman *et al.* 1980; Pons and Kaas 1986). This is consistent with a serial processing scheme with information passed mainly from VP via S1 to S2 (Figure 1.16c). In a study by Pons et al (Pons *et al.* 1987) selective lesions were made of the hand representation in the different subunits of S1 and S2 responses to touch stimuli were recorded. S1 lesions caused highly specific reductions of S2 responses. Responses were reduced only in the hand region of S2 and only to stimulus types corresponding to the processing selectivities of the lesioned S1 region (ie lesions to areas 3b and 1, which process mainly cutaneous information, led to reduced response only to cutaneous stimulation in the hand area of S2). This suggests a highly specific, somatotopically-organised serial processing stream.

Evidence from humans also supports the serial processing model. Using MEG, Mima et al (Mima *et al.* 1998) found that the earliest responses to electrical stimulation of the median nerve occurred at 20ms and were maximal over the hand area of contralateral S1. Later responses, at 100-200ms, were found over bilateral temporal-parietal areas, thought to correspond to S2.

The evolutionary stage at which the switch from parallel to serial processing occurs is debatable. Lesions of S1 in prosimian primates and tree shrews have been reported to render S2 unresponsive to peripheral stimulation (Garraghty *et al.* 1991). However, Zhang et al performed rapidly reversible cooling of S1 in marmosets and recorded from the same S2 cells before, during and after cooling. They found that S1 inactivation had very little effect on S2 responsiveness (Zhang *et al.* 1996).

In conclusion, in higher primates, and arguably in humans, processing of touch information occurs largely in series, with information passing from the thalamus to S1 and from S1 to S2. The fact that the anatomical evidence points towards a serial processing model has implications for studies of attention and plasticity in the somatosensory system. In a serial, hierarchical processing model there is typically controversy over the degree to which early areas can be modulated by factors such as attention. This issue is addressed in Section 6.

1.3 Conclusions

The cortical motor and sensory systems consist of networks of specialised regions that interact in the control of action. There are a number of different schemes for subdividing sensorimotor regions and these are becoming increasingly complex as evidence on microscopic architecture accumulates. This section has presented simple schemes for subdividing each system and in general it is these schemes that have been used to localise activations throughout this thesis. Clear models of sensorimotor anatomy are important for

subsequent sections on motor recovery after stroke, and on attentional modulation of sensorimotor processing.

One issue addressed by this thesis is the degree to which activity across the sensorimotor network can be modulated by attention (Sections 6 and 7). In the psychology literature there is debate over how 'early' the attentional filter operates. In physiological terms this can be addressed by determining stages in the neural processing pathways at which activity can be modulated by attentional factors. This section has provided an overview of the 'hierarchies' of sensorimotor processing that will be relevant to interpreting this evidence.

A major aim of this thesis is to investigate ways in which sensorimotor networks adapt after damage such as stroke (Sections 4, 8, 9). The network organisation of the normal sensorimotor system raises the possibility of adaptation: although there is specialisation across the network there is also functional and anatomical overlap. The following section discusses motor recovery and rehabilitation after ischemic stroke and gives examples of ways in which brain plasticity may contribute to recovery.

References

Albus, J. S. (1971) A theory of cerebellar function. *Math Biosci* **10,** 25-61.

Asanuma, C., Thach, W. T., and Jones, E. G. (1983) Distribution of cerebellar terminations and their relation to other afferent terminations in the ventral lateral thalamic region of the monkey. *Brain Res* **286,** 237-265.

Barbas, H. and Pandya, D. N. (1987) Architecture and frontal cortical connections of the premotor cortex (area 6) in the rhesus monkey. *J Comp Neurol* **256,** 211-228.

Bolanowski, S. J., Jr., Gescheider, G. A., Verrillo, R. T., and Checkosky, C. M. (1988) Four channels mediate the mechanical aspects of touch. *J Acoust Soc Am* **84,** 1680-1694.

Brodal, P. (1998) *The central nervous system: Structure and function*. Oxford University Press: Oxford.

Burton, H. and Jones, E. G. (1976) The posterior thalamic region and its cortical projection in New World and Old World monkeys. *J Comp Neurol* **168,** 249-301.

Campbell, A. W. (1905) *Histological studies on the localisation of cerebral function*. Cambridge University Press: Cambridge.

Carpenter, M. (1978) *Neuroanatomy*. Williams and Wilkins: London.

Crepel, F. and Jaillard, D. (1991) Pairing of pre- and postsynaptic activities in cerebellar Purkinje cells induces long-term changes in synaptic efficacy in vitro. *J Physiol* **432,** 123-141.

Crossman, A. and Neary, D. (1995) *Neuroanatomy*. Churchill Livingstone: Edinburgh.

Donoghue, J. P., Leibovic, S., and Sanes, J. N. (1992) Organization of the forelimb area in squirrel monkey motor cortex: representation of digit, wrist, and elbow muscles. *Exp Brain Res* **89,** 1-19.

Dum, R. P. and Strick, P. L. (1991) The origin of corticospinal projections from the premotor areas in the frontal lobe. *J Neurosci* **11,** 667-689.

Eccles, J. C., Ito, M., and Szentagothai, J. (1967) *The Cerebellum as a Neuronal Machine*. Springer-Verlag: Germany.

Ferrier, D. (1876) *The functions of the Brain*. Smith, Elder and Company: London.

Flourens, M. J. P. (1824) *Recherches Expérimentales sur les Propriétés et les Fonctions du Système Nerveux dans les Animaux Vertébrés*. J.B. Ballière: Paris.

Flourens, M. J. P. (1842) *Recherches Expérimentales sur les Propriétés et les Fonctions du Système Nerveux dans les Animaux Vertébrés (2nd Edition)*. J.B. Ballière: Paris.

Friedman, D. P., Jones, E. G., and Burton, H. (1980) Representation pattern in the second somatic sensory area of the monkey cerebral cortex. *J Comp Neurol* **192,** 21-41.

Friedman, D. P. and Murray, E. A. (1986) Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque. *J Comp Neurol* **252,** 348-373.

Fritsch, G. and Hitzitg, E. (1870) Uber die elektrische Erregbarkeit des Gross-hirns. *Archs Anat Physiol Wiss Med* **37,** 300-332 (Translation by Bonin, G. Von. In *The Cerebral Cortex*, pp. 73-96. Thomas, Springfield, Illinois.

Fulton, J. (1935) A note on the definition of the "motor" and "premotor" areas. *Brain* **58,** 311-316.

Galea, M. P. and Darian-Smith, I. (1994) Multiple corticospinal neuron populations in the macaque monkey are specified by their unique cortical origins, spinal terminations, and connections. *Cereb Cortex* **4,** 166-194.

Garraghty, P. E., Florence, S. L., Tenhula, W. N., and Kaas, J. H. (1991) Parallel thalamic activation of the first and second somatosensory areas in prosimian primates and tree shrews. *J Comp Neurol* **311,** 289-299.

Geyer, S., Ledberg, A., Schleicher, A., Kinomura, S., Schormann, T., Burgel, U., Klingberg, T., Larsson, J., Zilles, K., and Roland, P. E. (1996) Two different areas within the primary motor cortex of man. *Nature* **382,** 805-807.

Geyer, S., Matelli, M., Luppino, G., and Zilles, K. (2000) Functional neuroanatomy of the primate isocortical motor system. *Anat Embryol (Berl)* **202,** 443-474.

Grafton, S. T., Woods, R. P., Mazziotta, J. C., and Phelps, M. E. (1991) Somatotopic mapping of the primary motor cortex in humans: activation studies with cerebral blood flow and positron emission tomography. *J Neurophysiol* **66,** 735-743.

Grunbaum, A. and Sherrington, C. S. (1908) Observations on the physiology of the cerebral cortex of some higher apes. *Proc R Soc* **69,** 72.

Harting, J. K. (1977) Descending pathways from the superior collicullus: an autoradiographic analysis in the rhesus monkey (Macaca mulatta). *J Comp Neurol* **173,** 583-612.

Hilbig, H., Bidmon, H. J., Blohm, U., and Zilles, K. (2001) Wisteria floribunda agglutinin labeling patterns in the human cortex: a tool for revealing areal borders and subdivisions in parallel with immunocytochemistry. *Anat Embryol (Berl)* **203,** 45-52.

Holmes, G. (1917) The symptoms of acute cerebellar injuries due to gunshot inuries. *Brain* **40,** 461-535.

Holmes, G. and Stewart, T. G. (1904) Symptamatology of cerebellar tumours: A study of forty cases. *Brain* **27,** 522-591.

Ito, M. (1984) *The Cerebellum and Neural Control.* Raven Press: New York.

Jane, J. A., Yashon, D., DeMyer, W., and Bucy, P. C. (1967) The contribution of the precentral gyrus to the pyramidal tract of man. *J Neurosurg* **26,** 244-248.

Jones, E. G. (1986) Connectivity of the primary sensory-motor cortex in cerebral cortex. In: *Sensory-motor areas and aspects of cortical connectivity*, pp. 113-183. Eds E. G. Jones, A. Peters. Plenum: New York.

Jones, E. G. (1987) Ascending inputs to, and internal organization of, cortical motor areas. *Ciba Found Symp* **132,** 21-39.

Jones, E. G. and Powell, T. P. (1969) The cortical projection of the ventroposterior nucleus of the thalamus in the cat. *Brain Res* **13,** 298-318.

Jones, E. G. and Wise, S. P. (1977) Size, laminar and columnar distribution of efferent cells in the sensory-motor cortex of monkeys. *J Comp Neurol* **175,** 391-438.

Keizer, K. and Kuypers, H. G. (1989) Distribution of corticospinal neurons with collaterals to the lower brain stem reticular formation in monkey (Macaca fascicularis). *Exp Brain Res* **74,** 311-318.

Leyton, S. S. F. and Sherrington, C. S. (1917) Observations on the excitable cortex of the chimpanzee, orangutan and gorilla. *Q J Exp Physiol* **11**.

Maeda, K., Kakigi, R., Hoshiyama, M., and Koyama, S. (1999) Topography of the secondary somatosensory cortex in humans: a magnetoencephalo-graphic study. *Neuroreport* **10,** 301-306.

Maldjian, J. A., Gottschalk, A., Patel, R. S., Detre, J. A., and Alsop, D. C. (1999) The sensory somatotopic map of the human hand demonstrated at 4 Tesla. *NeuroImage* **10,** 55-62.

Manzoni, T., Barbaresi, P., and Conti, F. (1984) Callosal mechanism for the interhemispheric transfer of hand somatosensory information in the monkey. *Behav Brain Res* **11,** 155-170.

Manzoni, T., Caminiti, R., Spidalieri, G., and Morelli, E. (1979) Anatomical and functional aspects of the associative projections from somatic area SI to SII. *Exp Brain Res* **34,** 453-470.

Marr, D. (1969) A theory of cerebellar cortex. *J Physiol* **202,** 437-470.

Matelli, M. and Luppino, G. (1996) Thalamic input to mesial and superior area 6 in the macaque monkey. *J Comp Neurol* **372,** 59-87.

Matelli, M., Luppino, G., Fogassi, L., and Rizzolatti, G. (1989) Thalamic input to inferior area 6 and area 4 in the macaque monkey. *J Comp Neurol* **280,** 468-488.

Matelli, M., Luppino, G., and Rizzolatti, G. (1985) Patterns of cytochrome oxidase activity in the frontal agranular cortex of the macaque monkey. *Behav Brain Res* **18,** 125-136.

Meyer, G. (1987) Forms and spatial arrangement of neurons in the primary motor cortex of man. *J Comp Neurol* **262,** 402-428.

Mima, T., Nagamine, T., Nakamura, K., and Shibasaki, H. (1998) Attention modulates both primary and second somatosensory cortical activities in humans: a magnetoencephalographic study. *J Neurophysiol* **80,** 2215-2221.

Miyachi, S., Hikosaka, O., Miyashita, K., Karadi, Z., and Rand, M. K. (1997) Differential roles of monkey striatum in learning of sequential hand movement. *Exp Brain Res* **115,** 1-5.

Murray, E. A. and Coulter, J. D. (1981) Organization of corticospinal neurons in the monkey. *J Comp Neurol* **195,** 339-365.

Murray, H. M. and Haines, D. E. (1975) The rubrospinal tract in a prosimian primate, Galago senegalensis. *Brain Behav Evol* **12,** 311-333.

Nakada, T., Suzuki, K., Fujii, Y., Matsuzawa, H., and Kwee, I. L. (2000) Independent component-cross correlation-sequential epoch (ICS) analysis of high field fMRI time series: direct visualization of dual representation of the primary motor cortex in human. *Neurosci Res* **37,** 237-244.

Nathan, P. W. and Smith, M. C. (1973) Effects of two unilateral cordotomies on the motility of the lower limbs. *Brain* **96,** 471-494.

Passingham, R. E. (1993) *The frontal lobes and voluntary action*. Oxford University Press: Oxford.

Paus, T., Petrides, M., Evans, A. C., and Meyer, E. (1993) Role of the human anterior cingulate cortex in the control of oculomotor, manual, and speech responses: a positron emission tomography study. *J Neurophysiol* **70,** 453-469.

Penfield, W. and Boldrey, E. (1937) Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* **60,** 389-443.

Penfield, W. and Rasmussen, T. (1952) *The cerebral cortex of man*. Macmillan: New York.

Picard, N. and Strick, P. L. (1996) Motor areas of the medial wall: a review of their location and functional activation. *Cereb Cortex* **6,** 342-353.

Playford, E. D., Jenkins, I. H., Passingham, R. E., Nutt, J., Frackowiak, R. S., and Brooks, D. J. (1992) Impaired mesial frontal and putamen activation in Parkinson's disease: a positron emission tomography study. *Ann Neurol* **32,** 151-161.

Pons, T. P., Garraghty, P. E., Friedman, D. P., and Mishkin, M. (1987) Physiological evidence for serial processing in somatosensory cortex. *Science* **237,** 417-420.

Pons, T. P. and Kaas, J. H. (1986) Corticocortical connections of area 2 of somatosensory cortex in macaque monkeys: a correlative anatomical and electrophysiological study. *J Comp Neurol* **248,** 313-335.

Porter, R. and Lemon, R. N. (1993) *Corticospinal function and voluntary movement*. Oxford University Press: Oxford.

Rao, S. M., Binder, J. R., Hammeke, T. A., Bandettini, P. A., Bobholz, J. A., Frost, J. A., Myklebust, B. M., Jacobson, R. D., and Hyde, J. S. (1995) Somatotopic mapping of the human primary motor cortex with functional magnetic resonance imaging. *Neurology* **45,** 919-924.

Rizzolatti, G., Luppino, G., and Matelli, M. (1998) The organization of the cortical motor system: new concepts. *Electroencephalogr Clin Neurophysiol* **106,** 283-296.

Robinson, D. L. (1973) Electrophysiological analysis of interhemispheric relations in the second somatosensory cortex of the cat. *Exp Brain Res* **18,** 131-144.

Roland, P. E. and Zilles, K. (1996) Functions and structures of the motor cortices in humans. *Curr Opin Neurobiol* **6,** 773-781.

Russell, J. and DeMeyer, W. (1961) The quatitative cortical orgin of pyramidal axons of Macaca rheus. With some remarks on the slow rate of axolysis. *Neurology* **11,** 69-108.

Sakai, K., Hikosaka, O., Takino, R., Miyauchi, S., Nielsen, M., and Tamada, T. (2000) What and when: parallel and convergent processing in motor control. *J Neurosci* **20,** 2691-2700.

Schieber, M. H. (1999) Voluntary Descending Control. In: *Fundamental Neuroscience*, pp. 931-949. Ed M. Zigmond. Academic Press: San Diego.

Schieber, M. H. and Hibbard, L. S. (1993) How somatotopic is the motor cortex hand area? *Science* **261,** 489-492.

Schneider, R. J., Friedman, D. P., and Mishkin, M. (1993) A modality-specific somatosensory area within the insula of the rhesus monkey. *Brain Res* **621,** 116-120.

Schultz, W. (1998) Predictive reward signal of dopamine neurons. *J Neurophysiol* **80,** 1-27.

Von Bonin, G. (1944) Architecture of the precentral motor cortex and some adjacent regions. In: *The precentral motor cortex*, pp. 7-82. Ed P. Bucy. University of Illinois Press: Urbana, IL.

Vorobiev, V., Govoni, P., Rizzolatti, G., Matelli, M., and Luppino, G. (1998) Parcellation of human mesial area 6: cytoarchitectonic evidence for three separate areas. *Eur J Neurosci* **10,** 2199-2203.

Woolsey, C. (1946) 'Second' somatic receiving areas in the cerebral cortex of cat, dog and monkey. *Fed Proc* **2,** 55-56.

Woolsey, C., Settlage, P., Meyer, D., Sencer, W., Pinto Hamuy, T., and Travis, A. (1952) Patterns of localization in precentral and "supplementary" motor areas and their relation to the concept of a premotor area. *Res Pub Assoc Nerv Ment Dis* **30,** 228-264.

Woolsey, C. and Whang, G. (1945) Somatic areas 1 and 2 of the cerebral cortex of the cat. *Abs Fed Proc* **4,** 79.

Zhang, H. Q., Murray, G. M., Turman, A. B., Mackie, P. D., Coleman, G. T., and Rowe, M. J. (1996) Parallel processing in cerebral cortex of the marmoset monkey: effect of reversible SI inactivation on tactile responses in SII. *J Neurophysiol* **76,** 3633-3655.

Zilles, K., Schlaug, G., Matelli, M., Luppino, G., Schleicher, A., Qu, M., Dabringhaus, A., Seitz, R., and Roland, P. E. (1995) Mapping of human and macaque sensorimotor areas by integrating architectonic, transmitter receptor, MRI and PET data. *J Anat* **187,** 515-537.