Structure of the Human Sensorimotor System. I: Morphology and Cytoarchitecture of the Central Sulcus

Leonard E. White, Timothy J. Andrews, Christine Hulette, Ann Richards, Marybeth Groelle, Joseph Paydarfar and Dale Purves

Department of Neurobiology, Duke University Medical Center, Durham, NC 27710, USA

We have studied the morphology of the central sulcus and the cytoarchitecture of the primary sensorimotor cortex in 20 human brains obtained at autopsy. Although the surface appearance of the central sulcus varies greatly from brain to brain (and between hemispheres of individual brains), its deep structure is remarkably consistent. The fundus of the central sulcus is divided into medial and lateral limbs by a complex junction midway between the sagittal and Sylvian fissures. Based on functional imaging studies, this junction appears to be a structural hallmark of the sensorimotor representation of the distal upper extremity. We also identified and measured area 4 (primary motor cortex) and area 3 (primary somatic sensory cortex) in Nissl-stained sections cut orthogonal to the course of the central sulcus. Although the positions of the cytoarchitectonic boundaries in the paracentral lobule showed considerable interindividual variation, the locations of the borders of areas 4 and 3 along the course of the sulcus were similar among the 40 hemispheres examined. In addition to describing more thoroughly this portion of the human cerebral cortex, these observations provide a basis for evaluating lateral symmetry of the human primary sensorimotor cortex.

Introduction

The human central sulcus, which divides the frontal and parietal lobes, harbors the primary motor cortex (Brodmann's area 4) in its anterior wall and a major portion of the primary somatic sensory cortex (Brodmann's area 3) in its posterior wall. We have investigated the morphology and cytoarchitecture of this region of the brain in some detail to allow an assessment of lateral symmetry in the human primary sensorimotor system, which we report in the accompanying article (White *et al.*, 1997). Despite several neuroanatomical studies of the central sulcus over the last century, we found it necessary to begin by characterizing the gross morphology of this part of the human brain. The classical studies of Cunningham (1892) and Campbell (1905) provide detailed descriptions of the pre- and post-central gyri, including both superficial and operculated structure; however, the paucity of illustration or quantification in these reports limits their usefulness. In particular, we wished to identify any homologous feature in the two hemispheres that might serve as a basis for quantitative comparison of corresponding segments of the left and right central sulci. The need for more complete knowledge of the structure of the pre- and post-central gyri, and a better appreciation of the range of their variation in the human brain, is also necessary to interpret a spate of functional imaging studies of the somatotopic organization of the sensorimotor representations along the central sulcus (e.g. Rumeau *et al.*, 1994; Sanes *et al.*, 1995). Thus, our first objective was to examine the central sulci of the left and right hemispheres for structural features that might be related to sensorimotor somatotopy.

A second objective was to define and measure area 4 and area 3 in the paracentral lobule and throughout the course of the central sulcus. These cortical areas are among the most distinct and well described cytoarchitectonic fields in the entire cerebral mantle (e.g. Brodmann 1903, 1909; Campbell, 1905; von Economo and Koskinas, 1925; Bailey and von Bonin, 1951; Braak, 1980). Nonetheless, the cytoarchitectonic boundaries that demarcate these areas from adjacent cortical regions, especially the anterior border of area 4 (i.e. between areas 6 and 4), have not been well characterized in the human brain (see, for example, Bailey and von Bonin, 1951; Wise, 1985; Zilles, 1990). Indeed, we found it difficult to glean from the cytoarchitectonic literature a set of criteria for the identification of these areal boundaries in Nissl-stained sections. Furthermore, the degree of interindividual variation in the positions of the cytoarchitectonic boundaries in and around the central sulcus has been uncertain. Accordingly, we have identified and measured area 4 and area 3 in 40 hemispheres from 20 brains, using mainly the descriptions of Brodmann (1903, 1909) to demarcate the boundaries of these cortical fields.

Thus, the present report characterizes the morphology of the central sulcus, including the region that contains the sensorimotor representation of the distal upper extremity, and describes the distribution of area 4 and area 3 in the paracentral lobule and along the full course of the central sulcus. In the accompanying paper (White *et al.*, 1997), we report morphometric data comparing the central sulcus and areas 4 and 3 in the left and right hemispheres, as well as bilateral measurements of subcortical sensorimotor centers; these data are then used to evaluate lateral symmetry in the human sensorimotor system. Our overall aim in these studies was to determine if preference for the use of the right hand in the majority of humans is reflected in an asymmetrical allocation of primary sensorimotor circuitry in the two sides of the nervous system.

Materials and Methods

Specimens

Twenty human brains were obtained at autopsy from the Duke University Medical Center in conformity with University guidelines and regulations. The specimens were taken from individuals of either sex who died of non-neurological causes (see Table 1, cases 1–20, in White *et al.*, 1997). All brains were removed within 24 h of death and placed in 10% formalin for at least a week prior to further processing. Each specimen was initially identified only by its autopsy case number; thus detailed information pertaining to gender, age and medical history was unknown to us until the analysis was complete. Subsequent review of the autopsy records confirmed that both upper and lower extremities were intact in every subject.

Tissue Processing

The specimens were dissected and sectioned after clearing the arachnoid and blood vessels from the cortical surface. The central sulcus was identified in each hemisphere according to standard anatomical criteria
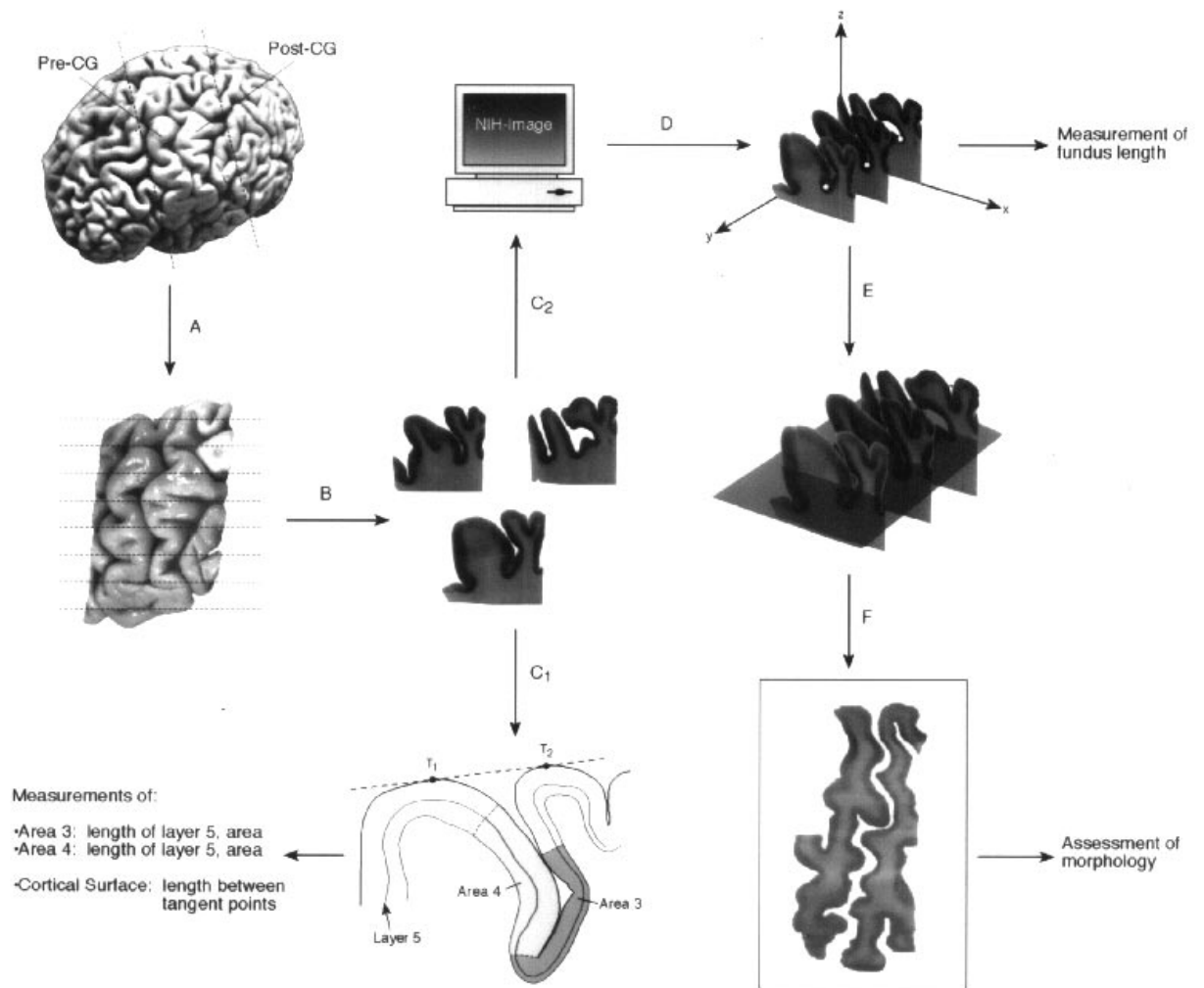
Figure 1. Methods used to isolate and measure the sensorimotor cortex within the human central sulcus. The mid-portions of the cerebrum containing the central sulci in the two hemispheres were isolated by making two cuts roughly parallel to the course of the sulcus, one anterior to the pre-central gyri (Pre-CG) and one posterior to the post-central gyri (Post-CG) (*A*). Each isolated piece of cerebrum containing the central sulcus was then sectioned into blocks of tissue each ~1.5 cm thick by a series of parallel cuts roughly orthogonal to the dorsolateral convexity of the cerebrum; each block was subsequently sectioned and the sections stained for the demonstration of Nissl substance (*B*). Each section was traced by camera lucida (*C_1*) and the extent of cortical surface in the banks of the central sulcus defined by drawing a line tangential to the pial contour at the crests of the pre- and post-central gyri (T_1 and T_2 respectively). The length of the contour line bounded by the tangent points was measured using a digitizing tablet and Bioquant IV morphometric software (Bioquant Inc., Nashville TN). In each camera lucida tracing, the length of cortical layer V in areas 4, 3a and 3b, and the area of these cytoarchitectonic fields, were traced and measured. These measurements were then used to estimate the overall area of the cortical surface in the central sulcus, and the overall area and volume of each cytoarchitectonic field (see White *et al.*, 1997). To measure the length of the central sulcus and to visualize its operculated structure, the pre- and post-central gyri were reconstructed using the stained sections, each of which was optically scanned and imported into the public domain NIH Image program (*C_2*). The position of the fundus of the central sulcus in three-dimensional space was determined for every section, and the overall length of the fundus of the central sulcus was calculated (*D*) (see White *et al.*, 1997). Finally, the set of aligned sections was 'resectioned' in a plane that was parallel to the course of the central sulcus (orthogonal to the plane of histological sectioning) (*E*), and the internal morphology of the central sulcus was examined (*F*).

(Ono *et al.*, 1990), photographed to record its surface features, and then excised from the rest of the brain. The specimens were cut into tissue blocks ~1.5 cm thick in a plane roughly orthogonal to the course of the central sulcus and the dorsolateral convexity of the cerebral hemisphere (Fig. 1). The blocks were cryoprotected by immersion in a graded series of buffered sucrose solutions (up to 30%), rapidly frozen on dry ice, and sectioned with a sliding microtome or cryostat in the same plane as the cut surface of the block. One 200 µm section or one 50 µm section was taken at 1 mm intervals and saved for histological processing. To minimize experimenter bias, all sections were mounted in the same orientation (i.e. sections from the left hemisphere were inverted so that all sections appeared to be from the right hemisphere) and coded to obscure the hemisphere of origin. The sections were routinely stained with cresyl violet acetate.

Assessment of Central Sulcus Morphology

To visualize the operculated structure of the central sulcus, the pre- and post-central gyri in each of the 40 hemispheres were reconstructed using the stained sections. Each section was optically scanned and imported into the public domain NIH Image program (Wayne Rasband, United States National Institutes of Health, Bethesda MD). The alignment and registration of the sections was facilitated by reference to fiducial marks (major radial blood vessels and the edges of the tissue block). The digitized set of aligned sections was then 'resectioned' in a plane parallel to the course of the central sulcus (i.e. orthogonal to the plane of histological sectioning), and the internal morphology of the central sulcus examined (see Fig. 1). To compare this view of the reconstructed central sulcus with a specimen dissected in the same plane, an additional brain was obtained and the pre- and post-central gyri sectioned parallel to the course of the central sulcus (illustrated in Fig. 3).
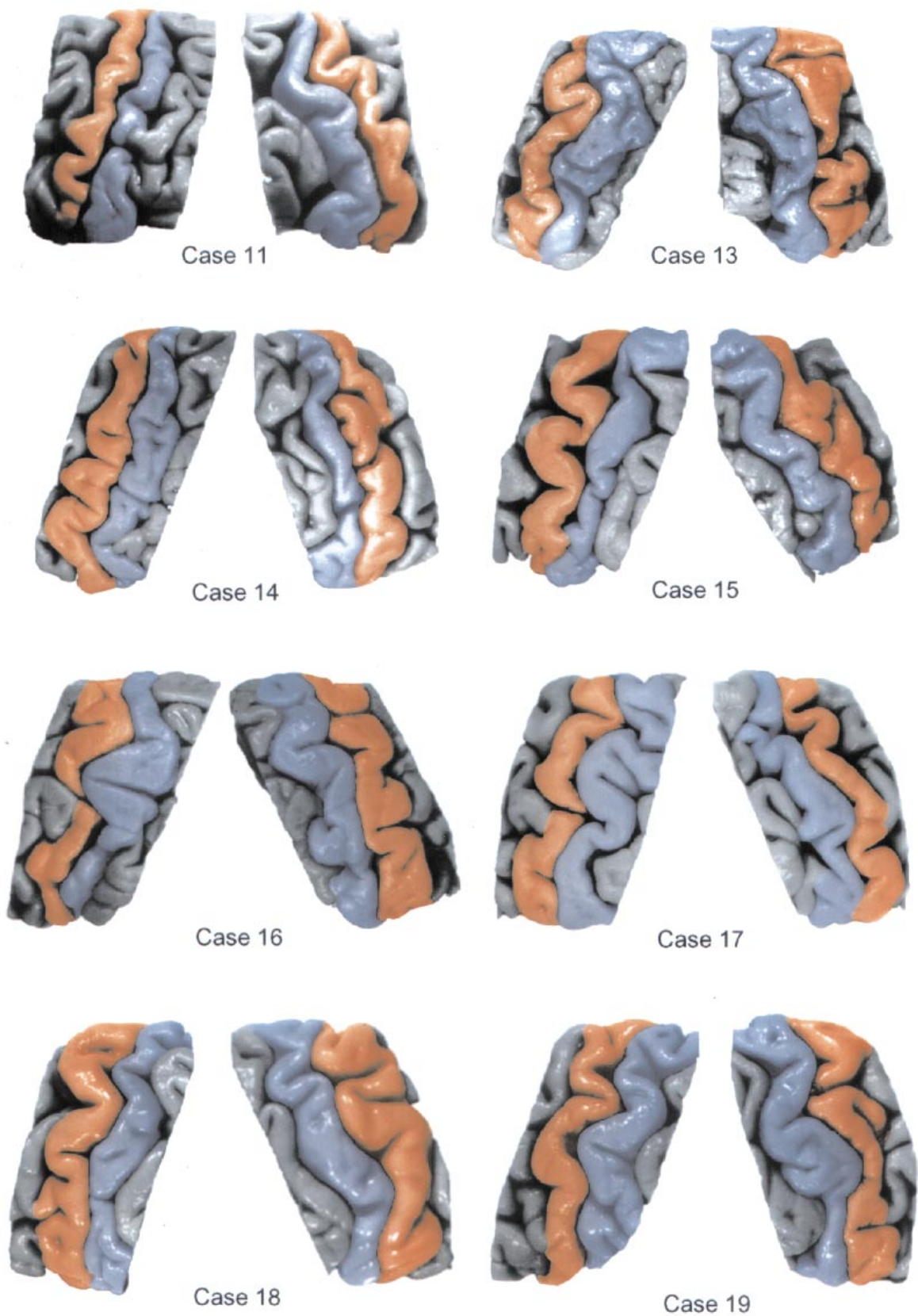
Figure 2. The superficial appearance of the left and right central sulci in eight specimens. Photographs were taken of the hemispheric blocks at an angle orthogonal to the dorsolateral convexity of the cerebral surface (red, pre-central gyrus; blue, post-central gyrus). Note the wide variation in the configuration of the central sulcus among specimens and between the two hemispheres of individual brains. The photographs were optically scanned, and image processing software was used to adjust the contrast and brightness and to color the pre- and post-central gyri.
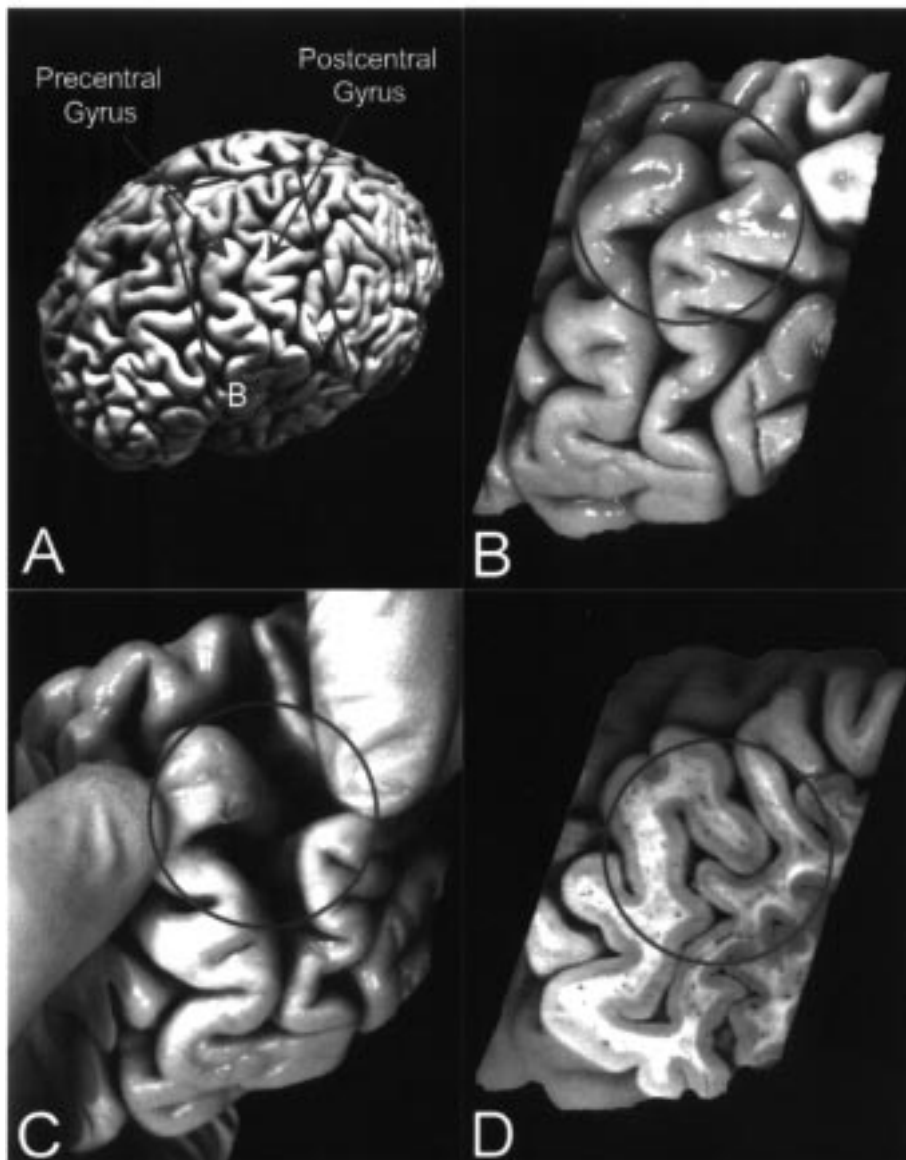
Figure 3. Demonstration of the operculated structure of the central sulcus. (*A*) Superficial appearance of the left hemisphere in an intact brain; the photograph was taken at an angle roughly orthogonal to the dorsolateral convexity of the cerebrum. (*B*) Photograph of the pre- and post-central gyri after isolation from the rest of the brain shown in *A* (see Fig. 1). (*C*) When the walls of the central sulcus were gently pried apart, a prominent interdigitation of the pre- and post-central gyri became evident (circle identifies the same region as in *B*). (*D*) This same structure (circle) was seen most clearly after 9 mm of tissue had been removed in a plane tangential to the cerebral surface. Each photograph was optically scanned; image processing software was used to adjust contrast and brightness.

Cytoarchitectonic Assessment

The Nissl-stained sections were then used to define and measure the extent of the primary motor cortex, area 4, and a major portion of the primary somatosensory cortex, area 3. A number of investigators have published detailed descriptions of the cytoarchitectural structure of the pre- and post-central gyri in the human brain (e.g. Campbell, 1905; Brodmann, 1909; von Economo and Koskinas, 1925; Bailey and von Bonin, 1951; Braak, 1980). It was not our aim to evaluate the merits of the different schemes of dividing the Rolandic cortex by cytoarchitectonic criteria. Rather, our goal was to identify area 4 and area 3 in each of 40 hemispheres and assess the reliability and consistency with which a given set of cytoarchitectonic criteria could be employed. Consequently, we adopted, with minor modification, the criteria established by Brodmann (1903, 1909) for the recognition of areas 4 and 3, with the additional criteria described by Jones and Porter (1980) for the division of area 3 into subfields 3a and 3b.

To measure areas 4 and 3 — and the cortical surface within the central sulcus (see White *et al.*, 1997) — all sections from both hemispheres that included the pre- and post-central gyri and/or the paracentral lobule were traced at 7× using a stereomicroscope equipped with a drawing tube. Each tracing included the pial surface, cortical layer V, the border between cortical layer VI and white matter, and radial lines that indicated the boundaries between adjacent cytoarchitectonic fields. In each camera lucida tracing, the linear extent of the cortical surface within the central sulcus, and the linear extent and planimetric area of areas 4, 3a and 3b, were measured using a digitizing tablet and Bioquant IV morphometric software (see Fig. 1).

Data Analysis

Because of the inherent subjectivity of cortical cytoarchitectonic methods (see, for example, Lashley and Clark, 1946), two investigators independently traced each section, identified tangent points on the crests
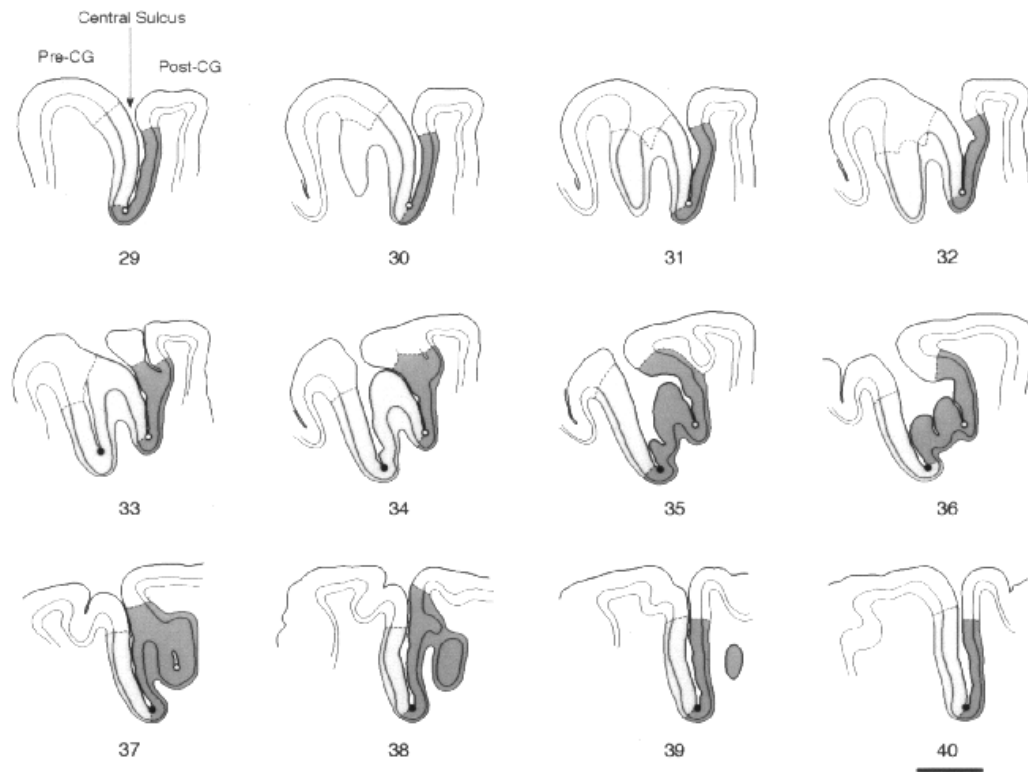
Figure 4. Appearance of the junctional region between the medial and lateral limbs of the central sulcus in histological sections. Each figure is a camera lucida tracing of one of a series of consecutive 50 μm sections taken every millimeter in the plane illustrated in Figure 1 from the right hemisphere of case 15. Light shading indicates area 4 and dark shading indicates area 3, with dashed lines demarcating the boundaries between adjacent cytoarchitectonic fields; an open circle marks the fundus in the medial limb of the central sulcus, and a filled circle marks the fundus of the lateral limb. Note the increased gyral complexity and the apparent discontinuity in the fundus of the central sulcus. Two fundus points were recognized in sections 33–37, reflecting the overlap of the medial and lateral limbs of the central sulcus in this region. Scale bar = 1 cm; abbreviations: Pre-CG, precentral gyrus; Post-CG, postcentral gyrus.

of the pre- and post-central gyri, marked cytoarchitectonic boundaries, and measured each cortical structure. Corresponding length and area values obtained for every section in each of the 40 hemispheres examined by the two investigators were compared by Pearson correlation tests to assess reliability. These measurements were then used to estimate the total cortical area and volume of each cytoarchitectonic division in the two hemispheres, as described in the accompanying report (White *et al.*, 1997). For the purposes of the present study, the linear measurements of the extent of cortical layer V in area 4 and area 3 were plotted by section number along the course of the central sulcus to assess the overall distribution of these cortical fields within the central sulcus in each of the 40 hemispheres studied.

Results

Gross Morphology of the Central Sulcus

We first examined the gross morphology of the pre- and post-central gyri for any structural feature of the central sulcus that might provide a basis for identifying homologous regions in the two hemispheres. The central sulcus is often described as showing two bends: a superior genu (concavity forwards) and an inferior genu (convexity forwards) (e.g. Ono *et al.*, 1990). Despite this convention, we found it difficult to recognize consistent structural features of the central sulcus viewed from the surface of the cerebrum. Indeed, we noted — as have others over the past 100 years (e.g. Symington and Crymble, 1913) — great variability in the configuration of the central sulcus, not only among different brains, but between the two hemispheres of individual brains (Fig. 2).

A remarkably consistent feature was observed, however, when the banks of the central sulcus were gently pulled apart. In the majority of brains, a prominent interdigitation of the walls of the pre- and post-central gyri was readily apparent in the depths of the sulcus about halfway between the midline and the Sylvian fissure (Fig. 3). This interdigitation effectively divides the central sulcus into two segments: a medial portion that extends from the midline to the protrusion of the posterior wall of the sulcus, and a lateral portion that extends from the protrusion of the anterior wall to the Sylvian fissure (see Fig. 3*D*). Examination of sections cut in a plane orthogonal to the course of the central sulcus confirmed that the junction of its medial and lateral components is a distinct region of increased gyral complexity in the depth of the sulcus (Fig. 4). Proceeding from the midline toward the Sylvian fissure, this region is usually evident as an outgrowth of the precentral gyrus (Fig. 4, section 31), which creates an apparent discontinuity in the floor of the central sulcus. The medial limb of the fundus (open circle in Fig. 4) becomes enveloped by the postcentral gyrus (section 37), whereas the lateral limb (filled circle in Fig. 4) emerges from the precentral gyrus (section 33) and continues on toward the Sylvian fissure. A similar characterization of the three-dimensional structure of the human central sulcus was recently reported by Sastre-Janer *et al.* (1995).

To examine this region of the central sulcus in another plane, the series of stained sections from each hemisphere was optically scanned, digitized and registered using NIH Image software to render the pre- and post-central gyri in their entirety
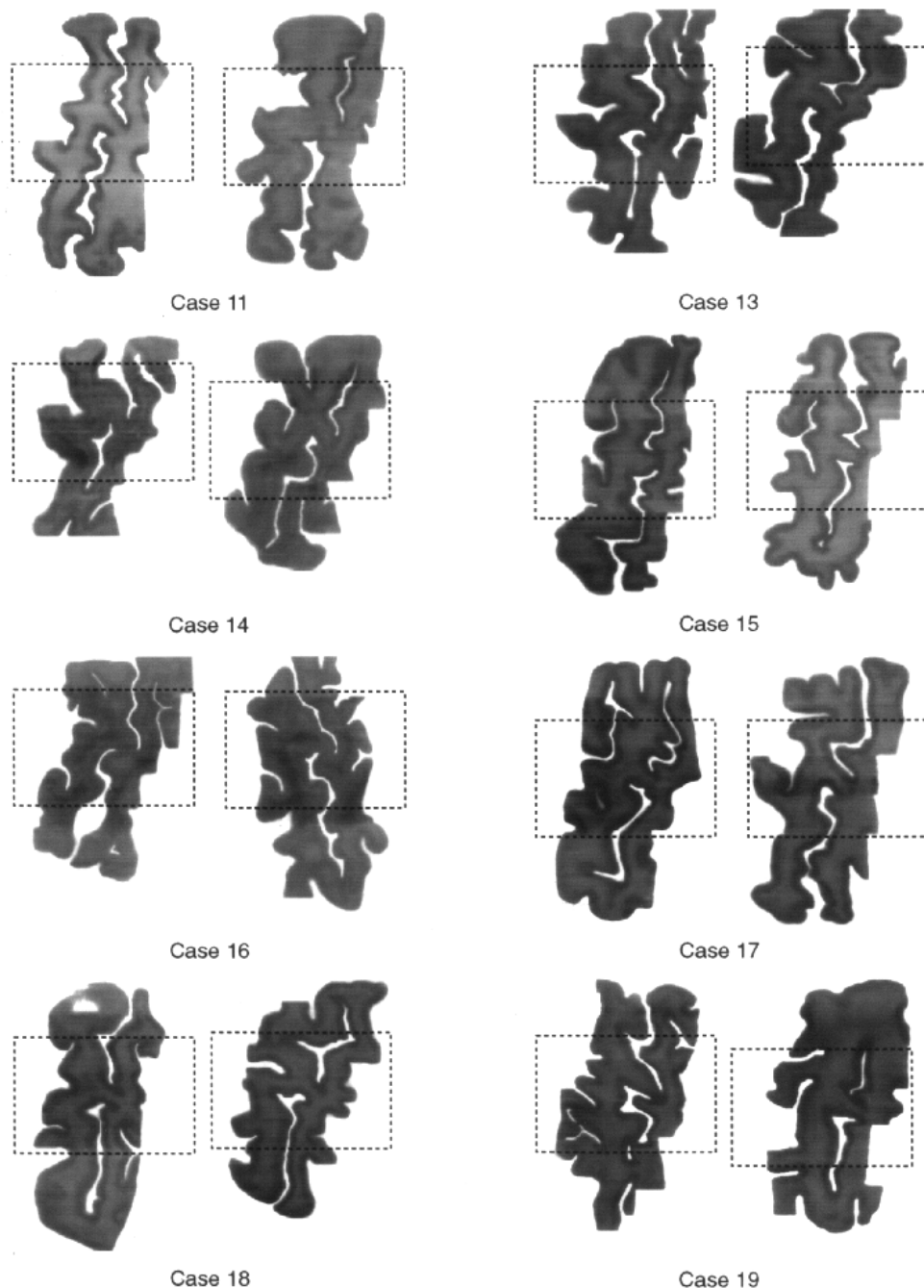
Figure 5. The 'bridging' between the pre- and post-central gyri in 16 reconstructed hemispheres from the same eight brains illustrated in Figure 2. Serial histological sections were reconstructed using NIH Image software; each rendered hemispheric block was then resectioned in a plane parallel to the course of the central sulcus (see Fig. 1). Note the consistent presence of a gyral bridge connecting the walls of the central sulcus, despite the considerable variability in the superficial appearance of the pre- and post-central gyri (cf. Fig. 2). This feature was recognized in 39 of 40 hemispheres; a gyral bridge was not evident in the right hemisphere of case 4 (not illustrated). The dashed box represents the 3 cm sample of the presumptive hand region centered on the gyral bridge (see Discussion and White *et al.*, 1997).

(see Fig. 1). The digitized data set was then 'resectioned' in a plane parallel to the course of the central sulcus (i.e. orthogonal to the plane of histological sectioning). Examination of the junctional region in this view demonstrates more clearly the reflexive interdigitation of the pre- and post-central gyri; it also reveals a distinct elevation of the fundus of the central sulcus in this region (Fig. 5). The base of the interlocking protrusions of the walls of the central sulcus thus creates an elevated bridge

between the pre- and post-central gyri in the depths of the sulcus (boxed regions in Fig. 5; see also Symington and Crymble, 1913). This distinct region of the central sulcus was observed in all 20 of the left hemispheres and 19 of the 20 right hemispheres. The other right hemisphere (case 4) had a much less pronounced interdigitation of the walls of the central sulcus with little evidence of an elevation of the fundus.

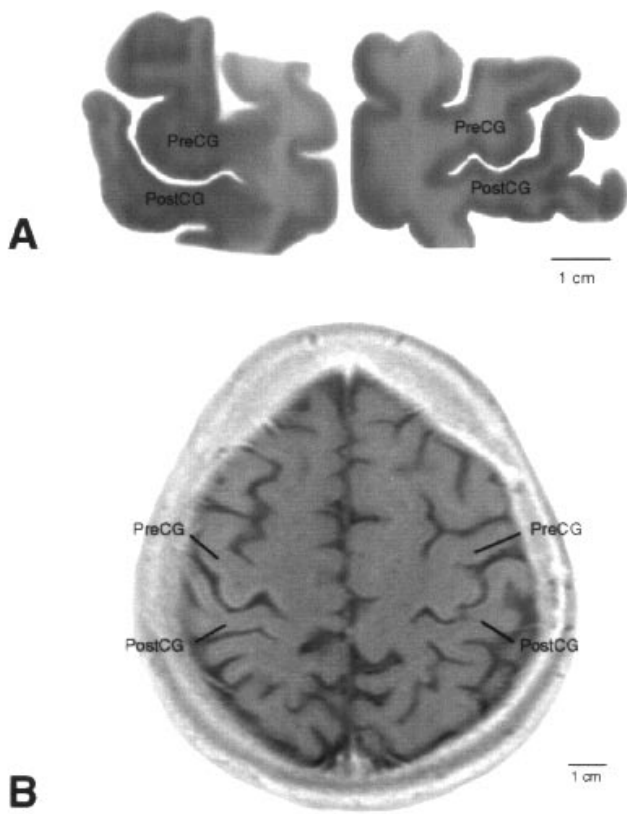To compare the appearance of this specialized region of the

Figure 6. Prominent interdigitation of the pre- and post-central gyri viewed in an axial plane in an autopsy specimen and a brain *in vivo*. (*A*) Serial histological sections from the left and right hemispheres of case 11 were reconstructed using NIH Image software, and the rendered hemispheric blocks were then resectioned in an axial plane. The prominent interdigitation of the walls of the central sulcus evident in the 'parallel' plane (cf. Fig. 3*D*) is seen predominantly in the axial plane as a posterior protrusion of the precentral gyrus recessed in a concavity of the postcentral gyrus. (*B*) This same configuration of the pre- and post-central gyri is easily recognized in this axial magnetic resonance image of a brain from a normal subject (kindly provided by Dr J.R. Macfall, Department of Radiology, Duke University Medical Center). Abbreviations: Pre-CG, precentral gyrus; Post-CG, postcentral gyrus.

Figure 7. Photomicrographs of 50 μm sections through the central sulcus stained for the demonstration of Nissl substance. (*A*) Area 4 (primary motor cortex) photographed in the anterior wall of the central sulcus. Note the giant pyramids (Betz cells) in cortical layer V. (*B*) Area 3a (a portion of primary somatic sensory cortex) photographed at the fundus of the central sulcus. (*C*) Area 3b (a portion of the primary somatic sensory cortex) photographed in the posterior wall of the central sulcus. This field is characterized mainly by the exceptional breadth and granularity of cortical layer IV (cf. area 3a, panel *B*). Scale bar = 500 μm.

central sulcus with images of brains *in vivo* viewed in a standard radiological plane, left and right digitized hemispheres from a representative specimen were rotated and 'resectioned' in an axial (horizontal) plane (Fig. 6). The interdigitation of the walls of the central sulcus evident in the plane parallel to the central sulcus (cf. Fig. 3*D*) is seen in the axial plane as a posterior protrusion of the precentral gyrus, recessed in a concavity of the postcentral gyrus (Fig. 6*A*). The same configuration of the pre- and post-central gyri evident in the autopsy specimen is easily recognized in axial magnetic resonance images of brains in normal subjects (Fig. 6*B*).
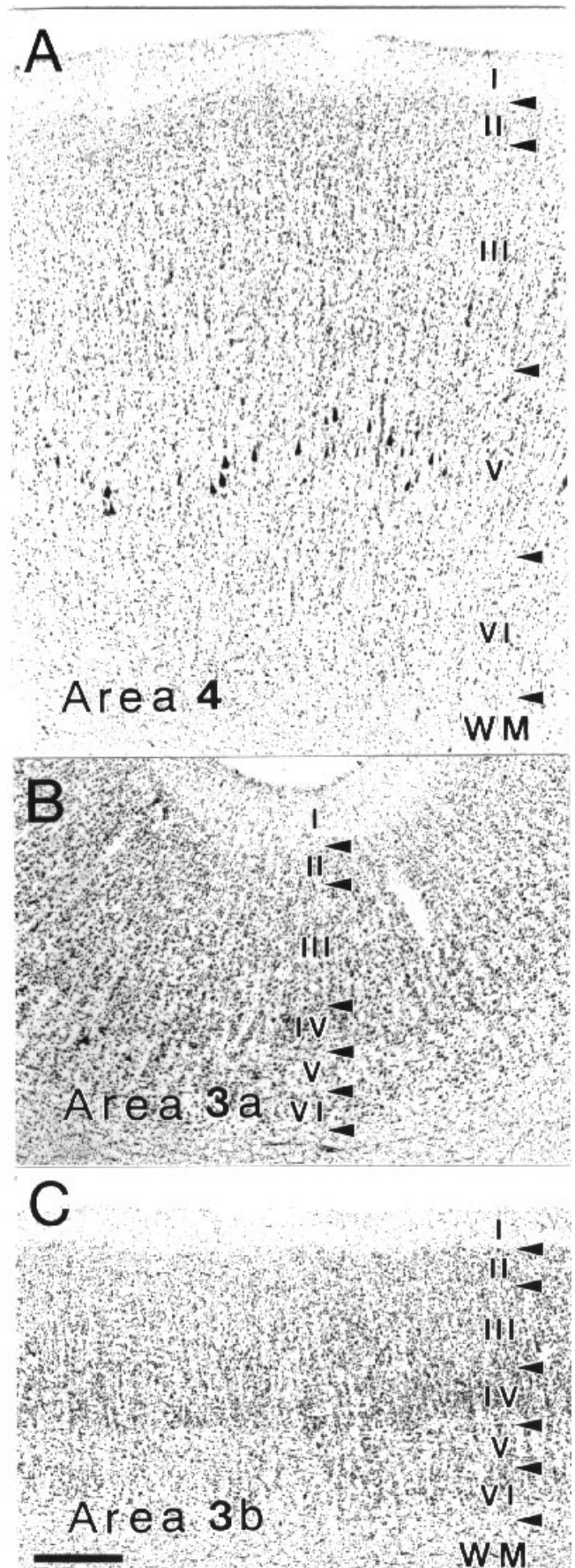
Cytoarchitectonic Structure of the Primary Sensorimotor Cortex

Cytoarchitectonic Criteria

We next examined the series of Nissl-stained sections from 40 hemispheres (20 brains) that contained the paracentral lobule and the pre- and post-central gyri using a set of cytoarchitectonic criteria for identification of the boundaries of area 4, the primary motor cortex, and area 3, a major portion of the somatic sensory cortex.

Area 4 was recognized primarily by the presence of Betz cells in cortical layer V (Fig. 7A). Betz cells are identified in Nissl preparations by their exceptionally large size, relatively small spherical nuclei, conspicuous nucleoli and deeply staining cytoplasm (Braak and Braak, 1976). Other characteristic features of area 4 include the absence of a granular layer IV, the absence of prominent pyramids in the deep part of layer III, a blurring of the border between cortical layer VI and white matter, and, consequently, the lack of much laminar definition (Braak, 1979, 1980). Geyer *et al.* (1995) recently proposed a subdivision of human area 4 into anterior and posterior parts based on cytoarchitectonic data, patterns of radioligand binding, and functional imaging studies of normal subjects performing sensorimotor tasks (see also Preuss *et al.*, 1995). Given the limitations of our methods, we did not attempt to subdivide area 4.

The anterior border of area 4 (i.e. between areas 4 and 6) has caused considerable trouble for investigators — ourselves included — who have attempted to identify it on cytoarchitectonic grounds (see Brodmann, 1909; Bailey and von Bonin, 1951; Wise, 1985). This is because the distribution of Betz cells in layer V, which constitute the most obvious cytoarchitectonic feature of the primary motor cortex, does not end abruptly or in strict concordance with other features of area 4. Although their numbers become markedly attenuated in the border region, some giant pyramids may be seen in layer V for >1 cm in the anterior direction, especially in the superior third of the central sulcus (typically, in the posterior bank of the precentral sulcus and the anterior margin of the paracentral lobule). However, we consistently observed another feature of this border region that aided our placement of the anterior boundary of area 4. Passing from area 4 anteriorly, pyramidal cells in the deep part of layer III become larger and the overall lamination of the cortex becomes more conspicuous; both are characteristic features of area 6 (see Bailey and von Bonin, 1951). Thus, we placed the area 4/area 6 border in the middle of this 'transitional' zone (usually <3 mm wide) in which the density of Betz cells becomes attenuated and the size of layer III pyramids increases (Fig. 8A). These criteria were satisfactory for most sections along the central sulcus. Because it is difficult to distinguish Betz cells from other layer V pyramids of comparable somal size in Nissl preparations near the Sylvian fissure (see Bailey and von Bonin, 1951; Braak, 1979), we relied on the changes in layer III and the overall appearance of lamination to identify the anterior border of area 4 in this region of the central sulcus. The posterior border of area 4 (i.e. between areas 4 and 3) was much more definite throughout the course of the central sulcus; we placed it where granular layer IV — a prominent feature of area 3 (see below) — became discernible (Fig. 8B).

Area 3 was recognized by the exceptional breadth and definition of granular layer IV, the high cell packing density of supragranular layers, the paucity of neurons in layer V, and the relatively sharp delineation of layer VI from white matter (see
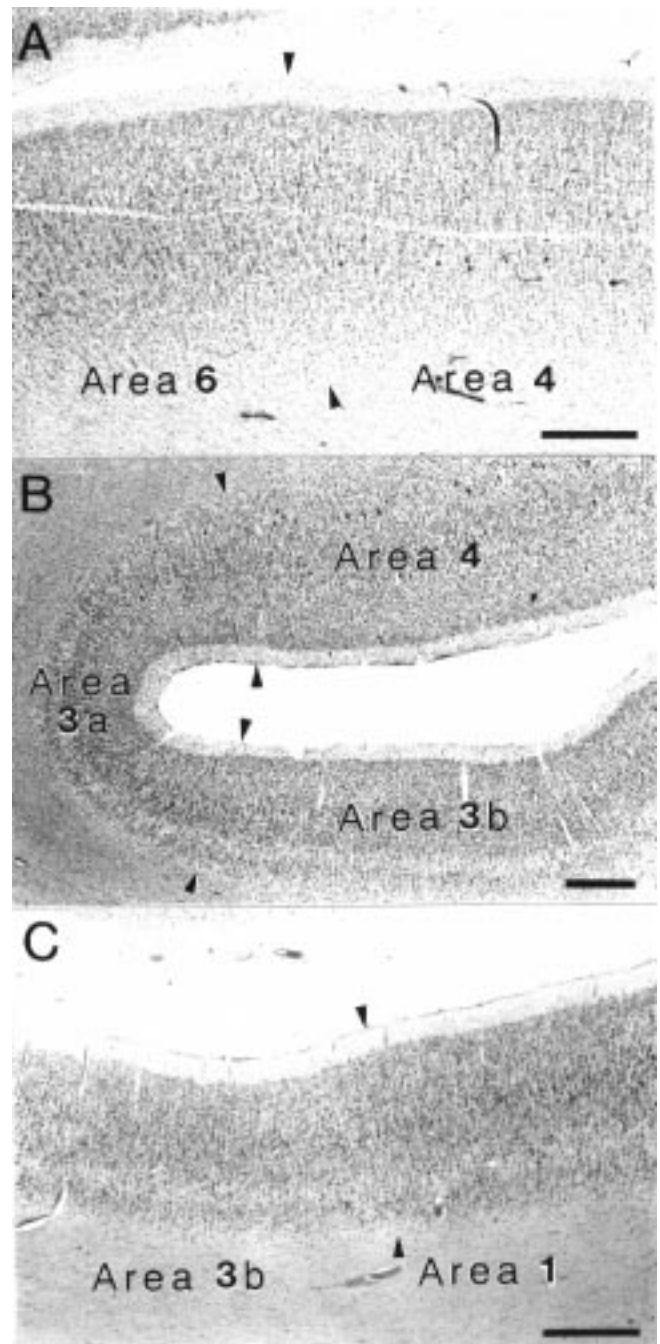

Figure 8. Cytoarchitectonic boundaries of primary sensorimotor cortical fields in the central sulcus. (*A*) Area 6/area 4 border. This border was recognized in the middle of a 'transitional' zone in which the density of Betz cells becomes attenuated and the size of layer III pyramids increases from area 4 toward area 6. (*B*) Area 4/area 3a border and area 3a/area 3b border. The border between areas 4 and 3a was placed where granular layer IV was no longer discernible. The border between areas 3a and 3b was placed where granular layer IV becomes thinned, with respect to its appearance in area 3b. (*C*) Area 3b/area 1 border. This border was characterized by a decrease in the packing density of cells in granular layer IV and layer VI, an increase in the size of pyramids in the deep portion of layer III, and an increase in the size and density of pyramids in layer V. Scale bars = 1 mm.

Fig. 7B,C; Braak, 1980; Kaas, 1990). The posterior border of area 3 (i.e. between areas 3 and 1) was characterized by a decrease in the packing density of cells in granular layer IV and layer VI, an increase in the size of pyramids in the deep portion of layer III,
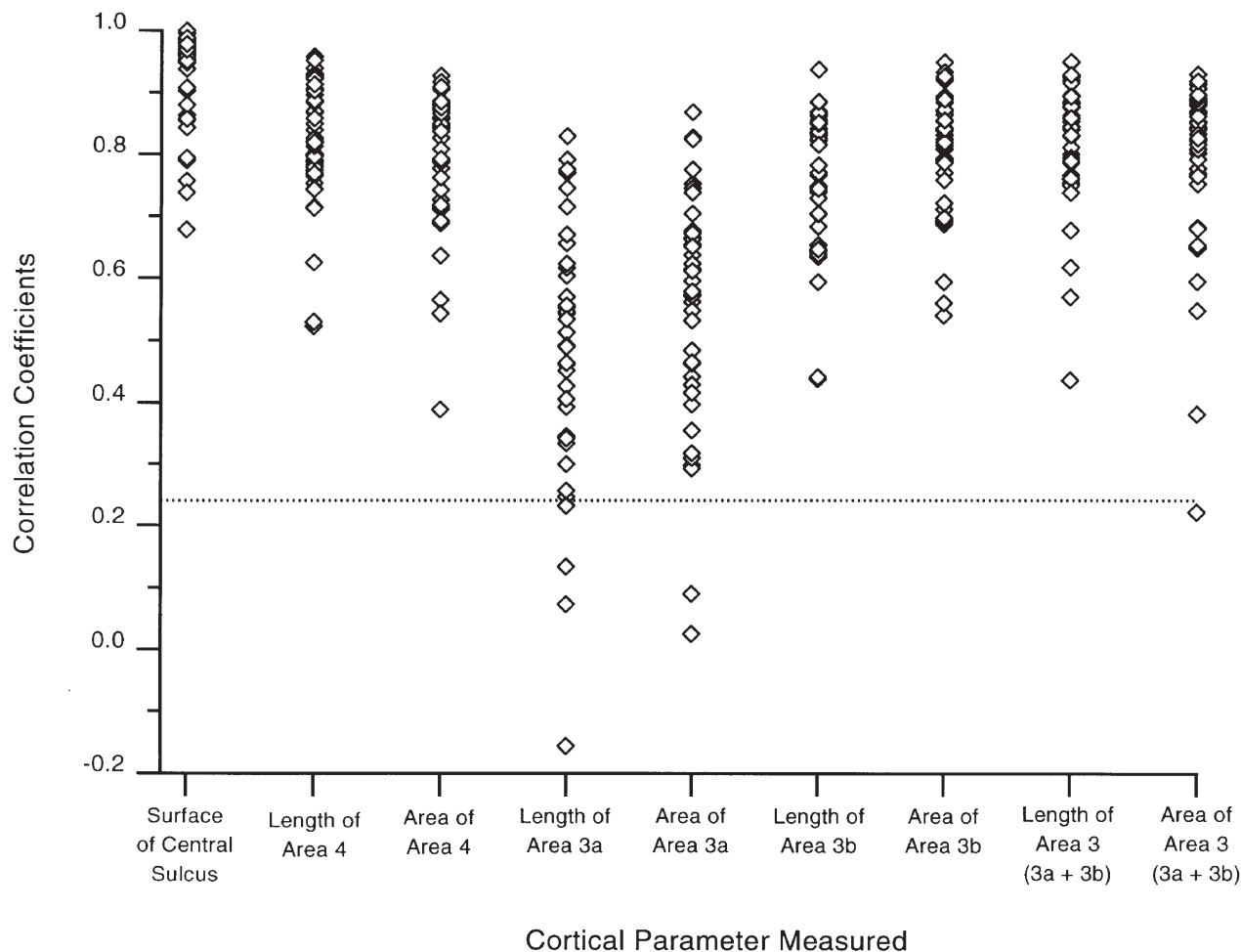
Figure 9. Correlation of independent sets of cortical measurements. Each of the seven cortical regions was identified, drawn and measured by two investigators. For each of 40 hemispheres, the measurements obtained by the two investigators for every serial section were compared using Pearson correlation tests (each symbol represents a correlation coefficient from a single hemisphere); all values above the dotted line are statistically significant ($P < 0.05$). Among the 40 hemispheres, the correlation between the two data sets was greatest and most consistent for measurements of the surface of the central sulcus (see White *et al.*, 1997), whereas measurements of area 3a exhibited the least consistent correlation. Measurements of areas 4 and 3b were intermediate, but displayed strong positive correlations for the majority of hemispheres.

and an increase in the size and density of pyramids in layer V (see Fig. 8C). We also defined and measured area 3a, a small zone in the fundus of the central sulcus that displays features of both area 4 and area 3b. This field is recognized primarily by the reduced thickness of granular layer IV, with respect to adjacent area 3b, and by the overlap of granular layer IV and giant pyramids (i.e. presumptive Betz cells) of layer V (see Fig. 7B; Jones and Porter, 1980; Kaas, 1990; Zilles, 1990). The border between areas 3a and 3b was placed where granular layer IV becomes thinned, with respect to its appearance in area 3b (see Fig. 8B).

Measurements of Areas 4 and 3

In order to assess the reliability with which these cyto-architectonic boundaries could be recognized, two investigators independently traced each section, marked cytoarchitectonic boundaries, and measured the length and areas of each cortical structure. Corresponding length and area values obtained from each of the 40 hemispheres examined were then compared using Pearson correlation tests (Fig. 9). The distribution of correlation coefficients for each hemisphere examined indicates

good correspondence between the two data sets for measurements of the length and area of area 4 and area 3b (the best correlation was obtained for measurements of the cortical surface in the central sulcus — see White *et al.*, 1997). The correspondence was less good for measurements of area 3a. The lack of consistency between the two sets of measurements of area 3a and the overall concordance of measurements of areas 4 and 3b indicate that we could not identify the area 3a/area 3b border with a level of accuracy necessary for quantitative assessment. Accordingly, we combined the measurements of area 3a and area 3b at the level of individual histological sections; this produced length and area measurements of area 3, which yielded an acceptable level of correspondence between investigators (see Fig. 9). For the purposes of quantitative assessment, we assumed that an average of the two sets of independent measurements would best represent the actual dimensions of each cortical structure. Thus, the two sets of data were averaged on a section-by-section basis, thereby creating an 'average' data set for each hemisphere that was used for all subsequent analyses in this and the accompanying report (White *et al.*, 1997).
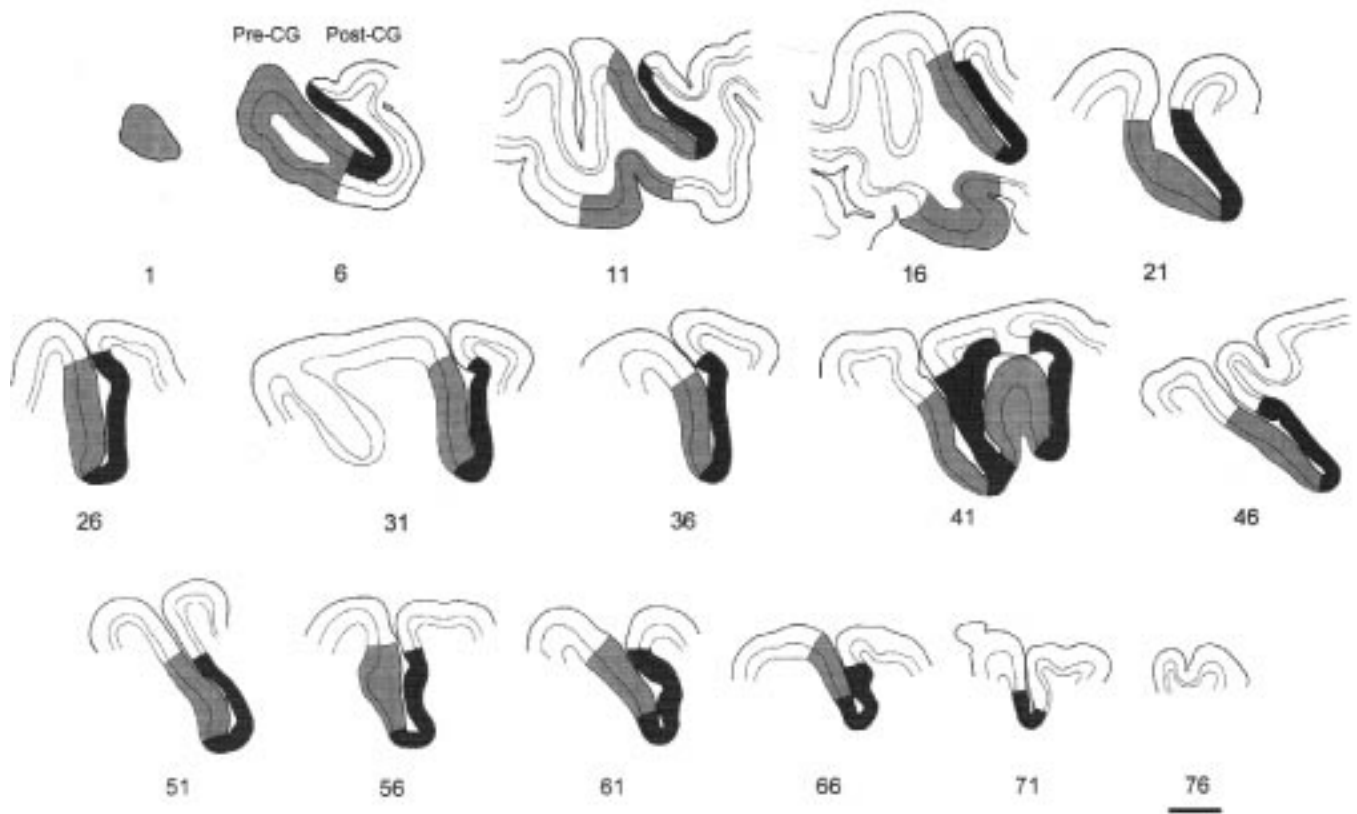
Figure 10. Illustration of the human central sulcus in sections cut orthogonal to the course of the sulcus. Each section is a camera lucida tracing of a 50 μm section taken every 5 mm, as illustrated in Figure 1, from case 20. Note the posterior regression of the anterior border of area 4 (light gray) in the first two centimeters (sections 1–21), and the more constant location of the posterior border of area 3 (dark gray) with respect to the mouth of the central sulcus. In most hemispheres, a significant portion of area 4 — but very little of area 3 — extended into the paracentral lobule on the medial face of the hemisphere. This general pattern of cytoarchitectonic progression from midline (section 1) to the Sylvian fissure (section 76) was evident in each of the 40 hemispheres examined. Abbreviations: Pre-CG, precentral gyrus; Post-CG, postcentral gyrus.

Distribution of Areas 4 and 3

Among the 40 hemispheres examined, the portion of sensori-motor cortex that showed the most interindividual variability was the extension of areas 4 and 3 onto the mesial face of the hemisphere in the paracentral lobule – an observation also made by Brodmann (1909) and more recently by Rademacher *et al.* (1993). In contrast to this variability, the locations of the cytoarchitectonic borders of areas 4 and 3 along the central sulcus were remarkably consistent among individual specimens; a representative hemisphere is illustrated in Figure 10.

Near the superior margin of the central sulcus, the anterior border of area 4 (i.e. the area 4/area 6 border) was located in the posterior bank of the precentral sulcus (e.g. Fig. 10, section 6) or the junction between the superior frontal and precentral gyri. Thus, area 4 has its greatest anterior-to-posterior extent along the most medial portion of the central sulcus. Proceeding inferiorly toward the Sylvian fissure, the anterior border of area 4 withdraws posteriorly; near the junction of the superior frontal and precentral sulci it is typically located at the lip of the anterior bank of the central sulcus (e.g. Fig. 10, section 16). From this position, the anterior border of area 4 recedes from the crest of the precentral gyrus into the depths of the central sulcus. Throughout the middle third of the precentral gyrus, the area 4/area 6 border remains in this operculated position, with area 4 residing in the lower two-thirds of the anterior wall of the central sulcus. In the region of increased gyral complexity near the middle of the central sulcus, the protrusion of the anterior wall

of the central sulcus usually occurs in area 4, with little relative change in the location of the area 4/area 6 border (e.g. Fig. 10, section 41). The border then recedes gradually toward the fundus until area 4 gives way to area 6, usually ~1 cm superior to the inferior terminus of the central sulcus (e.g. Fig. 10, section 71).

The posterior border of area 4 (i.e. the area 4/area 3 border) was found at the base of the precentral gyrus, typically within 1 cm of the fundus of the central sulcus. Similar in its consistency was the posterior border of area 3 (i.e. area 3/area 1 border). Throughout the entire length of the postcentral gyrus, this border was found near the posterior lip of the central sulcus. Thus, the anterior-to-posterior extent of area 3 remains nearer the hemispheric surface than area 4 along the length of the central sulcus. Typically, area 3 extends ~1 cm beyond the lateral limit of area 4 and ends near the inferior terminus of the central sulcus (e.g. Fig. 10, section 71). This basic cytoarchitectonic pattern was found in each of the 40 hemispheres examined in histological sections.

Finally, the majority of hemispheres showed an expansion of area 4 and area 3 in the region of increased gyral complexity near the middle of the central sulcus (Fig. 11; see, for example, cases 1, 10 or 20). The relative expansion in the extent of areas 4 and 3 corresponded to the reflexive interdigitation of the pre- and post-central gyri in this same region (cf. Fig. 10, section 41). This expansion of areas 4 and 3 presumably represents additional cortical territory in this segment of the central sulcus (see also
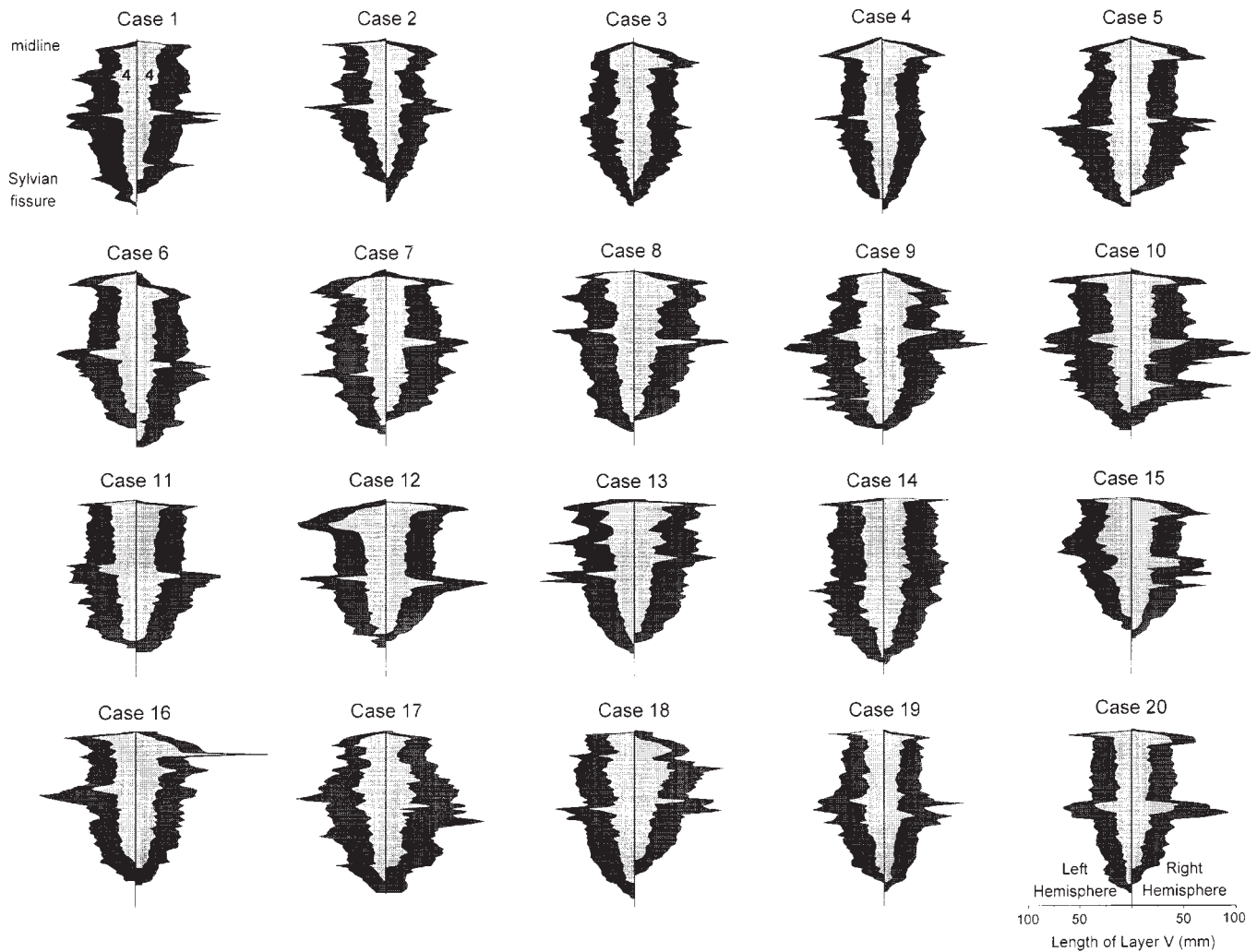
Figure 11. Extent of cytoarchitectonic fields area 4 and area 3 along the course of the central sulcus in the left and right hemispheres of 20 human brains. Each figure contains two histograms, one for measurements of the length of the layer V contours taken every millimeter from the left hemisphere (left side of vertical line) and one for the corresponding measurements from the right hemisphere (right side of vertical line). Values at the upper end of the vertical line represent data from the first section from the midline to contain the central sulcus; the lower end represents the inferior terminus of the central sulcus at or near the Sylvian fissure; the scale for case 20 applies to all. Note the relative expansion of area 4 (light gray) and 3 (dark gray) near the middle of the hemisphere evident in the majority of hemispheres; this region corresponds to the interdigitation of the pre- and post-central central gyri viewed in a plane parallel to the course of the central sulcus (cf. Fig. 5).

Rumeau *et al.*, 1994). Nonetheless, several hemispheres (see, for example, the right hemisphere of case 4 or the left hemisphere of case 15) showed little or no evidence of such an expansion, despite the typical interdigitation of the walls of the central sulcus in this region.

Discussion

We investigated the morphology of the central sulcus and the cytoarchitecture of the primary sensorimotor cortex in 40 hemispheres taken from 20 human brains. Our purpose in the present component of this work was twofold. We sought to examine the gross structure of the pre- and post-central gyri for any homologous feature in the two hemispheres that might be related to the somatotopic sensory and motor representations of the contralateral body. In addition, we wished to characterize the cytoarchitectonic boundaries of area 4, the primary motor cortex, and area 3, a major portion of the primary somatic sensory cortex. We subsequently use measurements of areas 4 and 3, together with measurements of subcortical sensorimotor

centers, to evaluate the nature and degree of lateral symmetry in the human sensorimotor system (White *et al.*, 1997).

Morphology of the Human Central Sulcus and Somatotopy

Despite obvious variation in the surface appearance of the central sulcus both among brains and between the hemispheres of individual specimens, there is a consistent morphological feature in the depth of the central sulcus. About halfway between the midline and the Sylvian fissure, the inner walls of the central sulcus interdigitate to form a complex junction between relatively straight medial and lateral segments. This same feature of the central sulcus was recognized and eloquently described, but not illustrated, nearly a century ago by both Cunningham (1892) and Campbell (1905). Indeed, our observations on the gross structure of the mid-portion of the central sulcus in the human brain are aptly summarized in the words of Cunningham (1892, p 167):

[in this region of the central sulcus] ... there is generally a shallowing of the fissure and a deep interlocking of its adjacent walls. Two of the interdigitating gyri – one projecting backwards from the anterior central convolution, and the other forwards from the posterior central convolution – are always larger and more pronounced than the others, and in a considerable number of cases they unite at the bottom of the sulcus in the form of a distinct deep gyrus, which constitutes a marked interruption in its floor. All gradations between a mere shallowing with an interlocking of the adjacent walls of the fissure and the presence of a distinct deep annectant gyrus are met with.

Our morphological observations add to these early descriptions (see also Symington and Crymble, 1913; Connolly, 1950) by documenting and illustrating this feature of the central sulcus in multiple planes of section. In particular, the ability to view this region of the sulcus in the axial plane has facilitated comparison of our morphological data with neurosurgical and radiological studies of the somatotopic organization of the human sensorimotor cortex. Examination of published figures in which brain activity has been mapped to axial structural images using non-invasive functional imaging techniques shows digit- and hand-related activity in this region near the middle of the hemisphere (Rumeau *et al.*, 1994; Sastre-Janer *et al.*, 1995; see also Figs 2 and 4 of Suk *et al.*, 1991; Fig. 3 of Kamada *et al.*, 1993; Fig. 2 of Kim *et al.*, 1993; Fig. 1 of Boecker *et al.*, 1994; Fig. 3 of van Gelderen *et al.*, 1995; Fig. 1 of Sanes *et al.* 1995; and Figs 3 and 4 of Yousry *et al.*, 1995). In fact, every such figure we are aware of depicts cortical activity associated with movement of the digits, hand or wrist localized in the depths of the central sulcus at or near the interdigitation of the pre- and post-central gyri that we describe. In light of these functional studies, we interpret this structurally distinct region of the central sulcus as the anatomical hallmark of the hand (and wrist) representation in the human sensorimotor cortex. This interpretation is generally consistent with the classical electrophysiological work on somatotopy along the human central sulcus, which has usually placed – albeit with some inconsistency – the sensorimotor representation of the distal upper extremity about midway between the sagittal and Sylvian fissures (Penfield and Boldrey, 1937; Scarff, 1940; Penfield and Rasmussen, 1951; Woolsey *et al.*, 1979).

We emphasize, however, that we found no morphological or cytoarchitectonic evidence to indicate the medial and lateral limits of the sensorimotor representation of the hand and wrist. Thus, the complex junction in the middle of the central sulcus that we have characterized should not be taken to be precisely co-extensive with the sensorimotor representation of the distal upper extremity (see also Scarff, 1940; Sanes *et al.*, 1995; Sastre-Janer *et al.*, 1995). Nonetheless, the consistent correspondence between the localization of digit- and hand-related activity and the set of morphological characteristics that we describe suggests that this feature is a reliable landmark for the position of the primary sensorimotor representation of distal upper extremity in the human brain. Accordingly, and for reasons of convenience, we subsequently refer to this distinct segment of the central sulcus as the 'presumptive hand region'.

Cytoarchitectonic Considerations
Our studies of Nissl-stained sections from 40 hemispheres generally confirm the classical descriptions of the cytoarchitecture of area 4 and area 3, especially those of Brodmann

(1903, 1909) and Bailey and von Bonin (1951) (although the latter used the terms 'isocortex agranularis gigantopyramidalis praecentralis' for Brodmann's area 4 and 'isocortex koniosus postcentralis' for Brodmann's area 3). In addition, our observations and other cytoarchitectonic studies (e.g. Campbell, 1905; von Economo and Koskinas, 1925; Braak, 1980) have established a set of criteria for the identification of the boundaries of these cortical fields in the human brain. Our ability to apply these criteria was corroborated by comparing two sets of morphometric measurements of areas 4 and 3 obtained independently by different investigators. The correlation between these sets of measurements indicates that our cytoarchitectonic criteria were consistently applied within the sample, which was presumably sufficient to represent the range of interindividual variation in the cytoarchitecture of the human primary sensorimotor cortex.

Finally, our analysis of a large series of specimens allowed us to evaluate both the individual differences and similarities that characterize the extent of area 4 and area 3 in the human brain (see Lashley and Clark, 1946, for discussion of the need for large sample sizes in cytoarchitectonic studies). Our most important observations concern the variation in the distributions of areas 4 and 3 in the paracentral lobule, and the consistency in the distributions of these fields along the central sulcus with respect to the crests of the pre- and post-central gyri and the fundus of the sulcus. This relationship between the borders of the primary sensorimotor cortex and the gross features of the central sulcus is maintained despite considerable interindividual (and interhemispheric) variation in the superficial appearance of the central sulcus. Thus, we confirm and extend the findings of Rademacher *et al.* (1993) who also found variation in the paracentral lobule and similarly concluded that the visible topographic landmarks of the central sulcus provide a reliable indication of the cytoarchitectonic borders of the dorsolateral portion of the primary sensorimotor cortex.

Conclusion
These morphological and cytoarchitectonic observations extend the classical anatomical studies on the human central sulcus and provide a basis for evaluating lateral symmetry of the human primary sensorimotor cortex. In the following paper (White *et al.*, 1997), we report morphometric data comparing the central sulcus and areas 4 and 3 in the left and right hemispheres, as well as bilateral measurements of the medullary pyramids and the cervical and lumbar enlargements of the spinal cord. Our aim in this further study was to determine if preference for the use of the right hand in the majority of humans is reflected in an asymmetrical allocation of cortical and subcortical space in the two sides of the primary sensorimotor system.

Notes

Address correspondence to Leonard E. White, Department of Neurobiology, Box 3209, Duke University Medical Center, Durham, NC 27710, USA

References
Bailey P, von Bonin G (1951) The isocortex of man. Urbana, IL: University of Illinois Press.

Boecker H, Kleinschmidt A, Requardt M, Hänicke W, Merboldt KD, Frahm J (1994) Functional cooperativity of human cortical motor areas during self-paced simple finger movements. A high-resolution MRI study. Brain 117:1231–1239.

Braak H (1979) The pigment architecture of the human frontal lobe. I. Precentral, subcentral and frontal region. Anat Embryol 157:35–68.

Braak H (1980) Architectonics of the human telencephalic cortex. New York: Springer-Verlag.

Braak H, Braak E (1976) The pyramidal cells of Betz within the cingulate and precentral gigantopyramidal field in the human brain. Cell Tiss Res 172:103–119.

Brodmann K (1903) Beiträge zur histologischen Lokalisation der Grosshirnrinde. Este Mitteilung: Die Regio Rolandica. J Psychol Neurol 2:79–107.

Brodmann K (1909) Vergleichende Lokalisationslehre der Grosshirnrinde. Leipzig: Barth.

Campbell AW (1905) Histological studies on the localisation of cerebral function. New York: Cambridge University Press.

Connolly CJ (1950) External morphology of the primate brain. Springfield IL: Charles C Thomas.

Cunningham DJ (1892) Surface anatomy of the cerebral hemispheres. Dublin: Academy House.

Geyer S, Zilles K, Dabringhaus A, Schormann T, Roland PE (1995) Morphological and functional evidence for two different subregions within the human primary motor cortex. Soc Neurosci 21:1419 (Abstract).

Jones EG, Porter R (1980) What is area 3a? Brain Res Rev 2:1–43.

Kaas JH (1990) Somatosensory system. In: The human nervous system (Paxinos G, ed), pp 813–844. San Diego: Academic Press.

Kamada K, Oshiro O, Takeuchi F, Kuriki S, Houkin K, Iwasaki Y, Abe Y (1993) Identification of central sulcus by using somatosensory evoked magnetic fields and brain surface MR images: three dimensional projection analysis. J Neurol Sci 116:29–33.

Kim SG, Ashe J, Hendrich K, Ellermann JM, Merkle H, Ugurbil K, Georgopoulos AP (1993) Functional magnetic resonance imaging of motor cortex: hemispheric asymmetry and handedness. Science 261:615–617.

Lashley KS, Clark G (1946) The cytoarchitecture of the cerebral cortex of Ateles: a critical examination of architectonic studies. J Comp Neurol 85:223–303.

Ono M, Kubik S, Abernathy CD (1990) Atlas of the cerebral sulci. New York: Georg Thieme Verlag.

Penfield W, 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, Rasmussen T (1950) Sensorimotor representation of the body. In: The cerebral cortex of man, pp 12–65. New York: Macmillan.

Preuss TM, Stepniewska I, Kaas JH (1995) Movement representation in precentral and premotor cortex of old world monkeys. Soc Neurosci 21:1901 (Abstract).

Rademacher J, Caviness VS, Steinmetz H, Galaburda AM (1993) Topographical variation of the human primary cortices: implications for neuroimaging, brain mapping, and neurobiology. Cereb Cortex 3:313–329.

Rumeau C, Tzourio N, Murayama N, Peretti-Viton P, Levrier O, Joliot M, Mazoyer B, Salamon G (1994) Location of hand function in the sensorimotor cortex: MR and functional correlation. Am J Neuroradiol 15:567–572.

Sanes JN, Donoghue JP, Thangaraj V, Edelman RR, Warach S (1995) Shared neural substrates controlling hand movements in human motor cortex. Science 268:1775–1777.

Sastre-Janer FA, Belin P, Mangin JF, Frouin V, Dormont D, Masure MC, Marsault C, Samson Y, Regis J (1995) Three dimensional structure of the human central sulcus and topography of the hand sensory-motor maps. Soc Neurosci 21:1419.

Scarff JE (1940) Primary cortical centers for movements of upper and lower limbs in man. Arch Neurol Psychol 44:243–290.

Suk J, Ribary U, Cappell J, Yamamoto T, Llinás R (1991) Anatomical localization revealed by MEG recordings of the human somatosensory system. Electroenceph Clin Neurophysiol 78:185–196.

Symington J, Crymble PT (1913) The central fissure of the cerebrum. J Anat Physiol 48:321–339.

van Gelderen P, Ramsey NF, Liu G, Duyn JH, Frank JA, Weinberger DR, Moonen CTW (1995) Three-dimensional functional magnetic resonance imaging of human brain on a clinical 1.5-T scanner. Proc Natl Acad Sci USA 92:6906–6910.

von Economo C, Koskinas GN (1925) Die Cytoarchitektonik der Hirnrinde des erwachsenen Menschen. Berlin: Springer-Verlag.

White LE, Andrews TJ, Hulette C, Richards A, Groelle M, Paydarfar J, Purves D (1997) Structure of the human sensorimotor system II. Lateral symmetry. Cereb Cortex 7:31–47.

Wise SP (1985) The primate premotor cortex: past, present, and preparatory. Annu Rev Neurosci 8:1–19.

Woolsey CN, Erickson TC, Gilson WE (1979) Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. J Neurosurg 51: 476–506.

Yousry TA, Schmid UD, Jassoy AG, Schmidt D, Eisner WE, Reulen H-J, Reiser MF, Lissner J (1995) Topography of the cortical motor hand area: prospective study with functional MR imaging and direct motor mapping at surgery. Radiology 195:23–29.

Zilles K (1990) Cortex. In: The human nervous system (Paxinos G, ed), pp 757–802. San Diego: Academic Press.