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Identifying homologous anatomical landmarks on reconstructed magnetic resonance images of the human cerebral cortical surface

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ABSTRACT

Guided by a review of the anatomical literature, 36 sulci on the human cerebral cortical surface were designated as homologous. These sulci were assessed for visibility on 3-dimensional images reconstructed from magnetic resonance imaging scans of the brains of 20 normal volunteers by 2 independent observers. Those sulci that were found to be reproducibly identifiable were used to define 24 landmarks around the cortical surface. The interobserver and intraobserver variabilities of measurement of the 24 landmarks were calculated. These reliably reproducible landmarks can be used for detailed morphometric analysis, and may prove helpful in the analysis of suspected cerebral cortical structured abnormalities in patients with such conditions as epilepsy.

Key words: Brain; morphometry; dysgenesis; epilepsy.

INTRODUCTION

In clinical neurology, a wide spectrum of disorders, including epilepsy and learning disability, have gross structural neuropathological substrates, commonly malformations of cortical development, which may manifest macroscopically as abnormal dispositions of the sulci and gyri (Yakovlev & Wadsworth, 1946*a*, *b*; Evrard et al. 1978; Williams, 1989). Previously these have only been easily identifiable at postmortem, and have been difficult to identify in vivo due to the difficulty of appreciating the 3-dimensional (3-D) structure of the cortical surface from 2-D tomographic imaging. However, recent advances in postprocessing technology have enabled reconstruction of 2-D data into 3-D images, so that we can now view images of reconstructed cerebral cortical surfaces (RCCS), and move them around in virtual space to different orientations, thus enabling easier and more reliable identification of features such as sulci and gyri than is possible in 2-D images (Vannier et al. 1991). Using these advances, studies such as those by Sisodiya et al. (1996) have shown that visually abnormal cortical gyrification patterns can be demonstrated in some patients with chronic epilepsy whose MR imaging, when viewed 2-dimensionally, would be regarded as normal.

The next step is to perform morphometric analyses on the cortical surface. Previous studies (Zilles et al. 1988; Mayhew et al. 1996) have used measures of cortical folding such as gyrification index to demonstrate changes associated with phylogenetic and ontogenetic development and, more recently, neurodevelopmental changes in vivo in patients with schizophrenia (Kulynych et al. 1997), but these methods do not specifically localise shape changes, nor allow appreciation of shape variation within a specific object. To do this requires landmarks, or fixed points (Bookstein, 1991). Studies using landmarks have generated significant information about the growth and development of various body parts, including the skull and craniofacial shape (Shea, 1985; Leutenegger & Masterson, 1989; O'Higgins & Dryden, 1992), as well as allowing quantification of

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dysmorphogenesis, including the subtle morphological effects of teratogens such as phenytoin on the facial features of children (Bookstein, 1991).

As yet, landmarks on the cerebral cortical surface which are reproducibly identifiable in vivo have not been documented, not least because of the difficulty of identifying cortical features on 2-D imaging. The aim of this study, therefore, is to use our ability to examine the reconstructed human cortical surface 3 dimensionally in vivo, to identify reproducible landmarks, as follows. (1) To discuss current concepts of anatomical landmarks and the biological justification for designating certain features on the cerebral cortical surface as homologous (defined below). (2) In study 1, to determine which features are visually identifiable on RCCS derived from 2-D MR images. Based on those homologous features that we show are reproducibly identifiable, we propose 24 candidate landmarks. (3) In study 2, to determine the variability of measurement of these landmarks, both within and between observers. (4) Based on our findings in studies 1 and 2, to propose some homologous landmarks on the brain surface for use in more detailed morphometric analysis to identify normal and abnormal gyrification patterns.

Current concepts of anatomical landmarks and homology

Landmarks are used to indicate the location of biological features. Thus the validity of inferences drawn from the morphometric analysis depends upon the biological justification for designation of the landmarks, as noted by Bookstein (1991): 'Landmarks are the points at which one's explanations of biological processes are grounded'.

Hence it is important to examine how one selects landmarks, particularly on the cerebral cortical surface where the information gained will be used to guide patient treatment. Landmarks can be distinguished as 'true' or 'pseudo' depending on the method used for placement (Bookstein, 1991). True landmarks are placed according to a biological hypothesis of equivalence, or homology. Pseudolandmarks are placed on a surface according to a mathematical rule, such as a series of points distributed evenly along a given surface, and since they lack homology, analyses based on pseudolandmarks may be less useful in testing biological hypotheses.

There is considerable debate among biologists about what constitutes homology. Hall (1994) has commented that concepts are no clearer than when Szarski (1949) stated: 'After examining the present status of the concept of homology, one arrives at disquieting results. A basic term … of comparative anatomy cannot be exactly defined'.

Homologous features are defined as those which are structurally and functionally equivalent between different organisms, and are usually self-evident. However, these equivalences are difficult to define in the cerebral cortex, so the concept of homology needs to be clarified to use it meaningfully. The variety of opinions about what constitutes homology can be grouped under 3 major headings (Baker et al. 1981; Wagner, 1994).

1. *Historical or phylogenetic homology concept*. This tests homology by criteria indicating a common phylogenetic origin, and came about after Darwin's Origin of Species (1859), which used homology as support for evolution by natural selection. The main criterion indicating a common phylogenetic origin is that of synapomorphy (inheritance of shared derived characteristics). However it has been noted by commentators such as Rehkamper & Zilles (1991) that the existence of morphologically similar adaptations in closely related species does not guarantee homology, since they have noted evidence of parallel evolution producing striking similarities in highly complex structures.

2. *Morphological homology concept*. These criteria test homology on the basis of structural similarity, such as shape features and spatial arrangement. This group includes historical concepts of homology based on Aristotle's proposal that divine modifications were made to an original archetype for teleological purposes, and the work of Richard Owen (1868), who was the first anatomist to define the primary and secondary sulci of the cerebral cortex, in so doing expounding his definition of homology: 'In regard to the convolutions of the cerebrum … distinguishing the folds (gyri) … and the fissures (sulci) … finding that their homologues could be traced from species to species … I further defined the "primary" and "secondary" fissures and folds, showing that the "secondary" fissures were in general less observable than in the "primary" ones'. Campbell & Hodos (1970) proposed judging homology in the nervous system by assessing the multiplicity and accuracy of similarities of gross and fine morphology, topology, and the position of reliably occurring sulci.

3. *Developmental homology concept*. This uses criteria of similarity according to mode of development, including developmental origin, cell lineage and developmental constraints.

Thus homology is a concept of biological similarity

which can be tested using various criteria. We will attempt to establish the homology of the major features of the cerebral cortical pattern by adducing the available evidence according to these 3 different criteria. For the purposes of this study, the sulci were considered more likely to provide reproducible landmarks than gyri, since it is more difficult technically to draw a single clear line running along a particular gyrus than a sulcus (because the cross section of the gyrus tends to be flat on segmented images, as opposed to the sharper concavity of the sulci); therefore from here on, we consider only the sulci. The use of sulci rather than gyri has a precedent in the work of Rademacher et al. (1992) who noted: 'These (limiting fissures, a set of brain sulci) are the only intrinsic landmarks that support a reproducible parcellation of the surface anatomy of the cerebral hemispheres'.

Phylogenetic criteria

Synapomorphy is established by finding similar structure-function correlations in related species. Many of the major sulci have been demonstrated to have a characteristic relationship to important cytoarchitectonic fields serving specific functions (Rademacher et al. 1992; Watson et al. 1993; Roland & Zilles, 1994), so that it is recognised that some of the sulci separate functionally distinct regions of the brain and provide a natural topographic partition of its anatomy (Thompson et al. 1996). Furthermore, species closely related to man such as the chimpanzee have similar sulci delimiting similar functional areas (Bailey et al. 1950; Thompson et al. 1996). This lends support to the notion of some sulci as homologous structures, although the work by Rehkamper & Zilles (1991) should be noted.

Morphological criteria

Recognition of the stability of the gyral pattern between individuals, and subsequent naming of sulci and gyri did not occur until the late 17th century, after the advent of tissue fixation, the limiting factor to repeatable observation (Maudgil, 1997). Thereafter, naming proceeded rapidly, so that by 1866 the anatomist William Turner could write: 'we can now localise the different gyri, and give to each its approximate name'.

The naming of sulci and gyri is usually on the basis of their appearance or position on the cerebral cortex, showing that the shapes and positions of the multiple major sulci and gyri are constant enough to recognise visually (Welker, 1990). Moreover, 'pooling' of MR brain scans shows that the major sulci and gyri appear distinctly in averaged brain anatomy, implying that the major sulcal structure matches well between brains in vivo as well as postmortem (Evans et al. 1994). Cytoarchitectonic studies indicate that topology of cortical areas is highly conserved between brains (Rademacher et al. 1992). Bailey & von Bonin's comprehensive survey (1951) noted that many sulci were consistently identifiable visually in a large number of human brains at postmortem. Thus the morphological criteria for homology of Campbell & Hodos (1970) appear to be satisfied for the cerebral sulci. Based on Bailey & von Bonin's (1951) work, a number of sulci have been proposed (Table 1) which will be further tested for homology according to the developmental criteria below.

Developmental criteria

There are a large number of factors affecting convolutional development whose individual variability cannot be determined, and so direct evidence about developmental homology is unavailable. However, we can note the following: convolutional development follows a regular timetable which can be reproducibly altered by experimental manipulation and by genetic or vascular factors (Evrard et al. 1978; Williams, 1989). Development occurs in 2 stages: migration and gyrification.

Migration. Current models of cerebral cortical cell lineage such as those of Reid et al. (1995) propose that multipotential progenitor cells migrate tangentially whilst dividing asymmetrically to produce (1) regenerated multipotential cells which continue to migrate tangentially and divide asymmetrically, and (2) cells which do not migrate tangentially but undergo clonal growth along a radial axis, guided by radial glial fibres (Rakic, 1988; O'Rourke et al. 1992) to produce precisely specified cytoarchitectonic areas on the neocortex.

Gyrification. This is influenced by a large number of processes (Hofman, 1989; Welker, 1990), although there is considerable debate about their relative importance. A recent hypothesis (Van Essen, 1997) suggests that gyrification is prespecified by regional axon distribution, which is under close developmental control, with axons serving to anchor together certain regions, while other regions drift apart with cortical expansion.

Table 1. *Cerebral sulci noted by Bailey and von Bonin to be consistently visible, scored according to correspondence with cytoarchitectural, myeloarchitectural or thalamocortical borders*

Sulci	Brodmann (cytoarchitectural)	Flechsig (myeloarchitectural)	Williams (thalamocortical)
Lateral surface			
Precentral s.	+	+	+
Central s.	+	+	+
Postcentral s.	+	+	+
Superior frontal s.	−	+	−
Middle frontal s.	−	+	−
Inferior frontal s.	+	+	−
Superior temporal s.	+	+	−
Inferior temporal s.	−	+	−
Sylvian fissure	+	+	+
Intraparietal s.	+	−	+
Lunate s.	+	+	−
Medial and basal surface			
Cingulate s.	+	+	+
Parieto-occipital s.	+	+	+
Calcarine s.	+	+	+
Superior rostral s.	+	+	−
Callosal s.	+	+	+
Occipitotemporal s.	+	−	−
Collateral s.	+	+	−

+, corresponds to a border; −, does not correspond.

Further indirect evidence about the results of the processes of gyrification comes from studies parcellating the cortex according to the following influences. (1) *Cytoarchitectonic criteria*, using Brodmann's (1909) map, depicting the predominant cell type by morphology and pigment content. It should be noted that Brodmann's actual maps did not depict whether a border occurred in the depths of a sulcus, or merely close to it. More recently Rademacher et al. (1993) have shown that some important cytoarchitectonic fields have characteristic relationships to sulci and gyri; many of these correlations have been shown to be extremely consistent (Sanides, 1962), and been applied in vivo on MR scans (Rademacher et al. 1992). Following Rademacher's work, Penhune et al. (1996) have used landmarks based on cytoarchitectural criteria to compare interhemispheric cortical anatomical differences in primary auditory cortex. (2) *Myeloarchitectonic criteria*, using the map by Flechsig (1920) numbering regions in order of myelination. (3) *Thalamocortical connexions*, from Williams et al. (1989), classifying areas according to their thalamocortical afferents.

The sulci identified by Bailey & von Bonin (1951) which correspond to borders according to these different criteria are noted in Table 1. Many sulci appear to form developmental borders consistently whichever method of parcellation is used. This supports the hypothesis that the sulci are not random in position, but reflect consistent developmental processes which are conserved within a species. The sulci identified are those consistently present in adults, since the studies have been based on adult brains. Size has been noted to affect the degree of cortical folding among different species of primates, although not within the same species (Armstrong et al. 1991), and so the distribution of cortical sulci would not be expected to vary with size across the range of adult humans at which this study is directed.

In conclusion, there is evidence for certain sulci having intraspecies homology by several criteria. Phylogenetic criteria indicate, in man and closely related species, that the pattern of the major sulci corresponds to similar functional divisions, and that the functional arrangement on the cortex is highly conserved: this is evidence of functional homology. From the morphological point of view, it has been noted that sulcal patterns are repeatedly observable, both in postmortem brains and in vivo using MRI, and that certain sulci are consistent in position. Consideration of developmental criteria indicates that the ontogeny of the cortical pattern, consisting of migration and gyrification, follows a predictable timetable leading to a sulcal arrangement which is reproduced according to the same blueprint (or 'Bauplan' as termed by Creutzfeld (1995)) with

consistency in different individuals. Cortical maps depicting parcellation according to different criteria show that the visible sulci represent boundaries according to developmental criteria, and that the same sulci tend to represent divisions between different areas. The sulci in Table 1 represent those sulci that appear homologous using these criteria: they are all assessed for visibility in vivo in Study 1. Despite the problems with visualising and identifying sulci, it is reassuring to note that the sulci that we have concluded are useful for designating landmarks are all 'primary' (as opposed to secondary or tertiary), according to order of appearance in the embryonic brain (Chi et al. 1977), giving our choices a degree of structural validation.

METHODS

Study 1. Identifying sulci visible on the reconstructed cerebral cortical surface

This study investigated how often and reliably the sulci that we had designated as homologous (all the sulci in Table 1) could be found on reconstructed cerebral cortical surface (RCCS) images. The subjects were 20 neurologically normal volunteers. All subjects gave informed consent for the scanning procedure. The study was approved by the Ethics committee of the National Hospital for Neurology and Neurosurgery.

Imaging and postprocessing. MRI was performed on a 1.5 T GE Signa unit (GE, Milwaukee, USA). A coronal spoiled gradient recalled (SPGR) sequence was used for image analysis (TE 5 ms, TR 35 ms, flip angle 35°, acquisition matrix 256×128, 1 NEX, field of view 24 cm, producing 124 contiguous slices each 1.5 mm thick). The studies were transferred to an imaging workstation (Allegro, ISG Technologies, Toronto, Canada). Each slice was viewed individually, and an operator assigned 'seeds' on each slice within the 'region of interest', which was the grey matter. The program expanded the seeds, pixel by pixel, within preset threshold limits, to assemble a whole 'object of interest'. The operator viewed the object obtained, and manually edited out unwanted areas, such as parts of the meninges. Thus all grey matter was selected semiautomatically. This process was referred to as *segmentation*. The segmented slices were reassembled or '*reconstructed*' to produce a 3-D object, which could be manipulated in a virtual space. For further details, see Sisodiya et al. (1996).

Sulcal assessment. The RCCS were assessed by 2 independent observers (DDM, SMS) for presence of the sulci listed in Table 2. Sulcal anatomy was defined from Duvernoy (1991) and Ono et al. (1990) using procedures detailed in the Appendix.

Table 2. *Percentage of hemispheres in which each sulcus was visible* (*average of both observers*) *and agreement rate between observers about visibility*

Surface	Sulcus	Visibility rate (%)	Agreement rate (%)
Lateral surface	Precentral s.	100	100
	Central s.	100	100
	Postcentral s.	100	100
	Sup. temporal s.	100	100
	Inf. temporal s.	90	100
	Sylvian fissure	100	100
	Intraparietal s.	95	90
	Sup. frontal s.	100	100
	Inf. frontal s.	100	100
	Middle frontal s.	95	65
	Lunate s.	50	70
Medial surface	Parieto-occipital s.	95	50
	Cingulate s.	100	100
	Callosal s.	95	100
	Calcarine s.	83	95
	Superior rostral s.	88	85
Basal surface	Collateral s.	13	90
	Occipitotemporal s.	40	85

Study 2. Reproducibility of landmarks

In the first part of this study, landmarks were derived from the homologous sulci found visible in Study 1. In the second part, the reproducibility of landmark measurement was assessed.

Deriving landmarks from the homologous sulci

To describe the disposition of the sulci, landmarks were required which were unequivocally placeable in 3 dimensions. Arbitrary points, such as the midpoint of a sulcus were not useable, nor were geometrical descriptors such as the frontal pole, which varied with brain orientation, and so were not true landmarks (Bookstein, 1991). A practical solution was to choose intersections of 2 homologous sulci, or intersections of homologous sulci with the midline, since these did not vary in position on the cerebral cortical surface with brain orientation. The intersections used were only those of sulci that were found to be visible in study 1. One further landmark was introduced for assessment in Study 2, that of the preoccipital notch. This was introduced since the observers looking at brains in Study 1 had noted it to be a constant feature, and it appears to have a homological basis, since it is

Table 3. *Reasons why some homologous sulci were not used for landmarks*

Poor visibility	No usable intersections
Collateral s.	Superior temporal s.
Occipitotemporal s.	Inferior temporal s.
Lunate s.	Intraparietal s.
	Callosal sulcus
	Middle frontal s.

close to a cytoarchitectural (between Brodmann's areas 19 and 37) and myeloarchitectural boundary. The landmarks selected are shown in Table 3.

Measuring the landmarks in 3-dimensional space

The images obtained in Study 1 were exported onto a Sun workstation for further analysis. The computer program AVS (Advanced Visual Systems, Inc.) enabled the user to visualise and manipulate the RCCS in a 3-D space, and to place a cursor at any point on the surface, whose coordinates were displayed by the program. It was assumed that the landmark formed by each sulcal intersection was actually at the level of adjacent cortical surface, rather than deep within the sulcus, since visualising the true base of a sulcus and measuring the landmark at the bottom of the sulcus was not possible with the technique. Since the program did not allow one to designate a point in empty space, the pointer was placed on the nearest adjacent cortex to the theoretical landmark.

In order to test whether the 24 landmarks (12 in each hemisphere) were reproducibly identifiable by the same and different observers, the 3-D coordinates of the landmarks were repeatedly measured in 6 brains by a single observer (DDM) 3 times and once by an independent observer (SLF). Written protocols were used to identify sulci (see Appendix). If no actual intersection was seen, the landmark was placed where the sulci would have met had they each continued in a straight line.

The intrarater and interrater variability of measurement of the proposed landmarks was measured, these quantities being expressed as the average of the distances in the x, y and z axes between different measurements of the landmarks and the mean configuration of the landmarks, these quantities being Δx, Δy and Δz respectively (Table 4). The euclidean (or 3-dimensional distance), d, was calculated as

$$d = \sqrt{(\Delta x^2 + \Delta y^2 + \Delta z^2)}.$$

RESULTS

Study 1

Results are presented in Table 2. The percentage of hemispheres in which a given sulcus could be identified visually (averaged between both observers) ranged from 100 % to 13 % (mean 86 %). Visual identification of sulci on the basal surface appeared particularly poor, in contrast to sulci on the lateral or medial surfaces. Agreement rate between the 2 observers as to whether a sulcus could be identified visually was calculated by noting the proportion of hemispheres in which both observers agreed on the visibility *or* invisibility of a sulcus: thus for example if both observers were to agree that the central sulcus was visible in 10 of the 20 hemispheres, disagreed about 5 of the hemispheres, and agreed that the central sulcus was not visible in 5 of the hemispheres, then the 'agreement rate' would be 15/20, or 75 %.

The agreement rate varied according to sulcus between 100 % and 50 %, with mean 90 %, and did not vary significantly according to surface.

Study 2

Based on the sulci found to be reproducibly identifiable in the Study 1 (Table 2), and according to the

Table 4. *Landmarks used in reproducibility study*

Lateral landmarks	Medial landmarks
Superior precentral s. with superior frontal s. (SPreCS/SFS)	Calcarine s. with parietooccipital s. (Calc/PO)
Central s. with midline (CS/ML)	Superior rostral s. with cingulate s.
Precentral s. with midline (PreCS/ML)	(SRS/Cing)
SF with precentral s. (SF/PreCS)	Parietooccipital s. with midline (PO/ML)
SF with central s. (SF/CS)	Terminal cingulate s. with midline (TC/ML)
SF with postcentral s. (SF/PostCS)	
Preoccipital notch (Preocc)	
Inferior precentral s. with inferior frontal s. (IPreCS/IFS)	

Table 5. *Mean and* S.D. *of euclidean distance between landmark estimation and mean landmark position**

	Intrarater				Interrater			
Landmark	Euclidean distance	x coord.	y coord.	z coord.	Euclidean distance	x coord.	y coord.	z coord.
SPreCS/SFS	5.0 (2.8)	3.2 (1.3)	2.7 (1.4)	2.8 (0.7)	19.9 (6.7)	10.6 (2.8)	6.5 (2.8)	15.6 (1.9)
CS/ML	3.7 (1.0)	2.5 (0.9)	1.2 (0.6)	2.4 (0.5)	6.6 (6.1)	3.4 (0.4)	2.7 (1.2)	12.2 (3.1)
PreCS/ML	3.5 (0.8)	2.2 (0.7)	1.4 (0.7)	2.4 (0.4)	8.7 (3.8)	3.6 (0.9)	1.4 (0.7)	16.5 (1.9)
SF/PreCS	3.3 (1.2)	1.9 (0.7)	1.5 (0.3)	2.2 (1.0)	3.0 (1.7)	3.1 (0.6)	3.5 (0.8)	3.4 (0.6)
SF/CS	3.3 (1.2)	2.1 (0.8)	1.6 (0.6)	2.0 (0.9)	3.2 (3.4)	3.5 (1.0)	1.7 (0.6)	4.8 (1.7)
SF/PostCS	3.1 (0.6)	2.0 (0.6)	1.8 (0.6)	1.6 (0.4)	4.0 (3.3)	2.8 (0.7)	3.4 (0.8)	6.5 (1.6)
Preocc	4.0 (3.7)	2.0 (0.7)	1.6 (0.8)	3.1 (1.8)	6.9 (4.8)	6.3 (1.6)	2.3 (0.6)	11.8 (2.3)
Calc/PO	3.1 (1.8)	1.1 (0.5)	2.0 (1.2)	2.2 (0.9)	2.8 (3.2)	2.1 (0.3)	3.3 (0.7)	3.7 (1.6)
SRS/Cing	2.9 (0.6)	0.8 (0.3)	2.4 (0.7)	1.4 (0.6)	7.4 (4.4)	1.1 (0.4)	12.6 (2.2)	6.9 (0.8)
PO/ML	3.9 (3.2)	2.6 (1.1)	2.4 (1.6)	1.8 (0.7)	3.4 (3.6)	3.5 (0.8)	4.3 (1.7)	3.8 (1.3)
TC/ML	4.2 (1.0)	2.6 (0.6)	2.5 (0.4)	2.1 (0.9)	4.0 (4.5)	3.2 (0.6)	3.9 (0.8)	6.0 (2.3)
IPreCS/IFS	2.8 (0.7)	1.7 (0.4)	1.5 (0.7)	1.6 (0.7)	3.5 (3.7)	5.1 (1.5)	3.7 (1.6)	2.9 (0.8)
Average for all landmarks	3.7				6.0			

* Results averaged for whole group of 12 hemispheres and given as mean in mm (S.D. in mm). Sulcal abbreviations from Table 4.

considerations described above, the landmarks in Table 3 were designated for further study. The reasons why some sulci were not used are given in Table 5. The intra- and interrater variabilities, expressed as the average variation in each of the orthogonal planes, and the derived euclidean distances, are shown in Table 4. To assess the likely significance of the intra- and interrater variations in landmark coordinates (calculated as described above) from the anatomical point of view, the figures from Table 4 have been plotted on one subject's brain in Figures 1 and 2. In general the variations appeared small with respect to the differences between different landmarks.

DISCUSSION

Establishing homology

Homology is a complex concept, using various criteria to establish similarity at different levels of biological structure. We have found criteria with which to measure the brain at some of these levels, and have used those that we felt most relevant and practical, given that ultimately we will apply the method to detect anatomical differences related to abnormal patterns of development. Although data exists on the development of the gyri and sulci, no overall scheme for the ontogeny of gyrification has been established. Therefore we had to rely on less complete systems which parcellated the brain according to more readily measurable criteria gathered from architectonic, developmental and connectional studies. These different schemes show a remarkable degree of consensus about parcellation of the cortex, and their incompleteness is not a bar to establishing homology. Sneath & Sokal (1973) noted that it was acceptable to use incomplete or 'working definitions' of homology to initiate biological comparisons.

Previous studies, such as those by Ge (1991) or Thompson et al. (1996) have not attempted to establish homology before designation of significant features of the cortical surface. There are relatively few landmarks designated in this study because we have only selected landmarks fulfilling the criteria of homology as we have defined them.

Limitations to sulcal visualisation

Study 1 showed that certain sulci were poorly identified despite being well recognised on cadaveric brains. The reasons for this are biological and imaging-based.

The main biological limitation to identification of sulci is gyral abuttal, whereby a sulcus is obscured by overlying gyri. This is a particular problem with brains of young subjects (the average age of subjects in Study 1 was 28.9 y) since there is a fullness in general of the cerebral tissue, compared to cadaveric brains which are usually from older subjects (Courchesne & Plant, 1996). Furthermore, brain fixation causes a general tissue shrinkage which tends to part the gyri (Toga et al. 1994; Graham & Lantos, 1997), and removal of the meninges and skull allows the brain to distort under its own weight and the sulci to separate somewhat, so that 'traditional fixation only partly approximates the in situ conformation' (Toga et al. 1994). Thus some sulci which may be easily visualised

on cadaveric brains (especially minor ones) may not be so easily seen on in vivo radiological studies. This factor may account for the decreased visibility of sulci on the basal surface compared to sulci on the lateral and medial surfaces in this study.

Imaging factors can be divided into those affecting the original scan data, and those arising during postprocessing. A major problem on the original scan data was magnetic susceptibility artefact which occurred particularly in the temporal pole and the basal skull surface where the brain tissue is surrounded by the petrous temporal bone and the skull floor respectively. The difference in magnetic susceptibilities caused local magnetic field fluctuation and thus blurring of the grey matter/CSF border in the image acquisition process, with consequent problems with identification of landmarks on the sulci on the anterior temporal surface (furthermore, a high degree of anatomical variability hinders the identification of landmarks more posteriorly on the temporal lobe, as also noted by Bailey & von Bonin (1950)).

During postprocessing, limitations to accuracy arise from blurring of the grey matter/CSF border. This arises from limitations in spatial resolution (itself due to machine factors), patient movement and partial volume effects: less blurring would have allowed more accurate segmentations of the gyral surfaces and perhaps decreased the problem of gyral abuttal. Also, inconsistency of segmentation of the grey matter surface from the overlying CSF and meninges leads to an uneven reconstructed surface in 2 areas: the mesial border of the reconstructed hemisphere, and the lateral temporal surface. The first problem arises since when the images are segmented, they are viewed in a coronal orientation. The midline is judged by eye and drawn by hand, and is therefore subject to variation in the medial-lateral direction of up to 1–2 mm. As a result, the mesial surface of the segmented hemisphere has a less even surface, obscuring the smaller minor sulci and the callosal sulcus which are relatively narrow compared with the other sulci, and leading to a decreased visibility of the minor sulci compared with the major sulci. The second problem arises because blurring of the grey matter/CSF interface by susceptibility artefact causes inconsistent drawing of the border when segmenting, and hence an uneven surface on which it is difficult to recognise sulci. These problems may be reduced by using automated segmentation methods e.g. (Ashburner & Friston, 1997; Freeborough et al. 1997; Saeed et al. 1997).

It should be noted that some borders between cytoarchitectonic or functional areas may lie buried inaccessible to our technique in the depths of the sulcus, although most of these borders are not so sharp as to make a significant difference to the position of the landmarks given the precision (demonstrated above) with which we can measure them.

Sulcal identification using 3-D visualisation

The observers found that they could identify sulci more easily on the 3-D reconstructed image than on the 2-D images since the former could be directly compared with whole brain atlases, and viewed from different perspectives (as also noted by Vannier et al. 1991). Thus, for example, to identify the central sulcus on the lateral surface, which proved difficult in some cases (see below), the observers could turn the image round to look at the medial surface and identify the terminal segment of the cingulate sulcus (which usually lies immediately posterior to the central sulcus) as an aid. In addition, the system of sulcal nomenclature has been based on the whole brain, and so the features used to identify sulci are more readily visible on 3-D images.

The procedures used for sulcal identification are based on classical neuroanatomical descriptions as well as more recent procedures for identifying features on MRI and CT scans. Nevertheless, in Study 2, the interrater, and (to a lesser extent) the intrarater studies showed up limitations in our ability to identify sulci consistently. In particular, there were occasional problems in identifying the precentral and central sulci: in 2 out of 12 hemispheres the RCCS was viewed jointly by both observers to decide the location of the precentral and central sulci. A similar problem was noted by Sobel et al. (1993), who found agreement of identification of central sulcus on axial scans of 76%. Our better agreement (10/12 i.e. 83%) is probably attributable to our ability to visualise the cortical surface 3-dimensionally and move it around in space.

It should be noted that 'direct' rather than 'indirect' procedures were used. Direct procedures rely on features pertaining to the sulci such as 'the most anterior major vertically oriented sulcus' for identification. In contrast, indirect procedures rescale each brain to a normalised configuration, using reference points (typically the anterior and posterior commissures), and then identify each sulcus by finding the sulcus on the normalised brain that matches closest. We used direct rather than indirect ones for 2 reasons: firstly the reference points are not easy to identify accurately, and even a small error in positioning of the centrally placed landmarks can lead to a large error on the cortex, as commented by

Steinmetz et al. (1990) who assessed the usability of the Talairach coordinate system to identify the central sulcus, and concluded: 'The variability of identification of the central sulcus … is no less than using external cranial landmarks such as nasion, inion and preauricular points'. The second reason is that even if the brain is accurately oriented with reference points, the features may still vary considerably in position, since the brain is not of a uniform shape in different people, nor symmetric (Galaburda et al. 1978), so for example Burzaco (1985) demonstrated a significant degree of error in locating subcortical areas using different stereotaxic systems, and this problem is magnified further away from the origin of the reference axes at the cortex. Thus Evans et al. (1994) showed an average deviation of around 5–7 mm in position of the frontal gyri (despite landmark-based warping of a brain atlas).

Choice of landmarks

Landmarks were chosen according to the protocols described in the Methods section. In addition the intraparietal sulcus, although well seen, had only a highly variable intersection with the postcentral sulcus and so was unsuitable as a landmark. The remaining sulci yielded 11 landmarks. One more landmark was introduced for assessment in Study 2, that of the preoccipital notch. This was introduced since the observers looking at brains in Study 1 had noted it as a constant feature, and as discussed it appears to have a homological basis.

The number of landmarks (24) finally obtained seems small, since there are many sulci on the brain. However, as this study has shown, there are relatively few sulci that we can both designate as homologous and identify reproducibly on RCCS, at least on the postprocessing derived from our MRI acquisition. Also the coverage of the brain is incomplete: in particular there are few landmarks on the parietal and occipital surfaces, and none on the temporal surfaces. We are currently working to improve this by (1) improving the image segmentation method, (2) by searching for homologous subcortical landmarks, and (3) identifying landmarks using automatic feature extraction.

The paucity and incomplete coverage bias the morphometric analysis more towards the frontal and mesial regions, although it should be noted that in studies of patients with partial epilepsy of extratemporal origin, frontal lobe seizures are the commonest type (Williamson & Spencer, 1986). Also because of the high degree of variability of the occipital and temporal lobe sulci (Bailey & von Bonin, 1951; Duvernoy, 1991), recognition of cerebral dysgenesis in that region may not be possible even with improved visualisation.

Measurement of landmarks

The landmarks and the mean error associated with their measurement are plotted on 1 subject's brain in Figures 1 and 2: the intra- and interrater errors are listed in Table 5. The average interlandmark euclidean distance for the control group was calculated as 63.3 mm. Therefore, the average intrarater error (in terms of euclidean distance, from Table 5) as a proportion of the average interlandmark distance is: (3.72 mm/63.3 mm) = 0.059, and the average interrater error is (6.0 mm/63.3 mm) = 0.095.

Therefore, in general the errors appear small in proportion to the brain itself, and most landmarks are well separated. The calculated intrarater variabilities would be unlikely in general to obscure the differences between different subjects, although the interrater variabilities in the 'z' axis of the first 3 landmarks might on occasions prove problematic. These landmarks are based on the positions of the precentral and central sulci as they run superiorly to the dorsomedial border of the hemisphere, and a 'z' error implies placing a landmark too far forwards or backwards, which may represent mistaking a precentral for a central sulcus or vice versa. Furthermore, once there is disagreement over which sulcus is the precentral, then the central sulcus will also be misplaced, since it is recognised as the next major sulcus posterior to the precentral. Also, for the first landmark, if the central sulcus is used rather than the precentral, there is a correspondingly larger 'x' and 'y' error since this landmark is placed on a highly curved surface (as opposed to the 2nd and 3rd landmarks). These findings underline the observations of Steinmetz et al. (1990) and Yousry et al. (1997) among others, that even with high resolution imaging it is difficult to define unequivocally the central and precentral sulci. From our study the most practical procedure for identifying the central sulcus appeared to be that of Kido et al. (1980) (see Appendix). The other well-known procedure, of identifying the precentral sulcus at first as being the most anterior vertically oriented sulcus, was less useful. Relatively large disparities also occurred in the 'y' coordinate of the junction of the superior rostral with the cingulate sulcus and the 'z' coordinate of the preoccipital notch, due to ambiguities in the protocol. The old protocols and

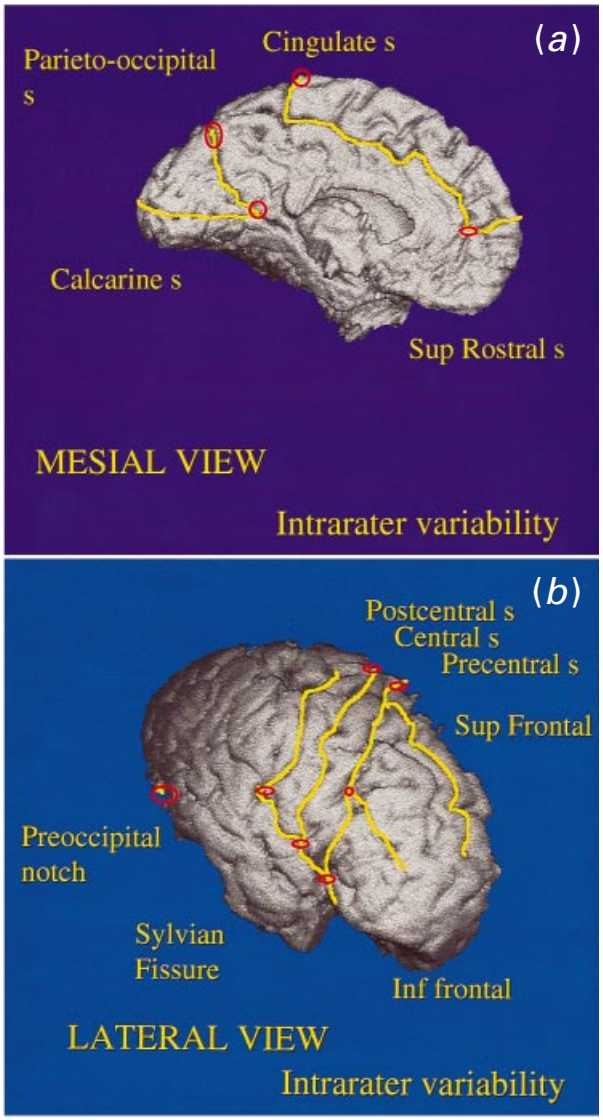

Fig. 1. Intrarater variation plotted on a sample brain: the radii of the ellipses along the anteroposterior and superoinferior axes represent the mean differences between observations for the intrarater study. (*a*) Mesial view. (*b*) Lateral view.

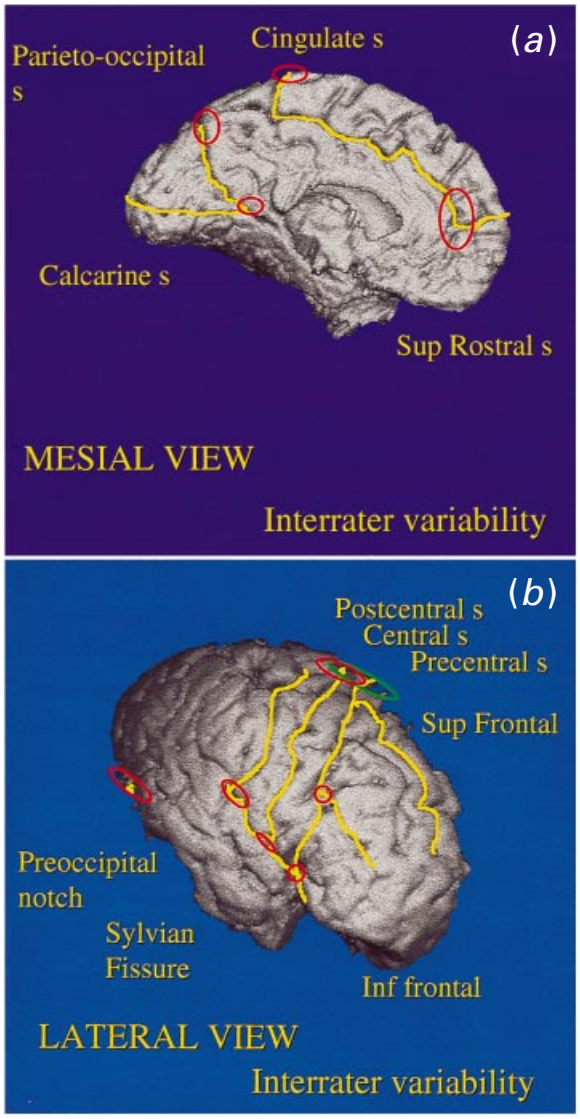

Fig. 2. Interrater variation plotted on a sample brain: the radii of the ellipses along the anteroposterior and superoinferior axes represent the mean differences between observations for the interrater study. (*a*) Mesial view. (*b*) Lateral view.

suggestions for a new protocol formulated to overcome these difficulties are presented in the Appendix.

The inability of the computer program to place a cursor exactly on the theoretical position of the landmark (since this is effectively in 'mid-air' above the sulcal intersection, and the program cannot measure the coordinates of a point in empty space, only a point occupied by MR data) may have introduced a discrepancy, especially since each observer may not have had the brain in exactly the same orientation when measuring a landmark. Moreover, although the observer endeavoured to place the landmark at the level of the cortical surface, this could not be exactly defined since the gyral tops were not flat. These errors may, in addition to errors introduced by misidentification of a sulcus, account for the larger errors noted in points such as the intersection of the precentral and central sulci with the midline, and preoccipital notch.

Comparison with previous studies

As far as we are aware, no previous studies have measured the location of homologous landmarks in vivo in an unrescaled 3-D space. Nor can we find previous studies measuring the variability of cortical landmarks in an undistorted space. In so doing we have taken advantage of the availability of MRI which has provided an accurate noninvasive method for anatomical examination in vivo without using ionising radiation.

Several studies have used cortical sulci to demonstrate structural features of the cortex. Rademacher et al. (1992) identified 'limiting sulci' for their study in which they parcellated the cerebral cortex. Although homology was not established, the use of the limiting sulci was based on the observation of Sanides (1962) that they correlated well with cytoarchitectonic boundaries. The areas thus parcellated were then identified as functional areas based on comparison with Brodmann's (1909) classification. All the sulci that we propose to be homologous were noted to be limiting sulci in the study of Rademacher et al. Similarly Penhune et al. (1996) have compared cortical areas and demonstrated interhemispheric anatomical differences (in primary auditory cortex) using landmarks whose validity has been confirmed by cytoarchitectural criteria, although they did not justify the homology of their landmarks. In addition, previous studies have identified cortical and subcortical landmarks, based on sulci, to use for registration purposes, i.e. to form a basis for standardising brain anatomy rather than picking out differences. Ge et al. (1991) used similar sulci to those that we found were well identified, with the exception of the superior and inferior temporal sulci. It should be noted that some of their landmarks are either approximate (e.g. 'close to the anterior pole of the temporal lobe', for the startpoint of the superior temporal sulcus), or orientation dependent (e.g. 'before the fissure starts ascending' for the endpoint of the sylvian fissure). They found that using these cortical landmarks in addition to some subcortical landmarks dramatically improved their registration quality, implying that these landmarks were reproducible enough to be useful in characterising the cortex. Arndt et al. (1996), having noted that analysing landmark location would prove particularly useful in addressing issues of shape, and uncovering structure-function relationships, located 27 landmarks along a single slice along the midsagittal plane, although these landmarks were mainly extremal points of large structures such as anteriormost or posteriormost point of the corpus callosum, which were orientation dependent and whose homology was not established.

The variability of measurement of our landmarks is comparable to previous studies. Vannier et al. (1991) measured the lengths of 18 sulci in reconstructed MR images of the brains of 8 volunteers and 1 cadaver. Only the lengths of the central sulcus and the sylvian fissure are given, and the intraobserver variations are between 6 and 12 mm on average with a S.D. ranging from 5 to 11 mm. Our intraobserver results show a slightly smaller range of variation. Thompson et al. (1996) measured sulcal variability in a number of medial sulci, using brains standardised to Talairach space, and found a measurement error in the vertical plane of up to 0.1 to 0.3 mm. The reduced error may be because they used cryosectioned heads which could be imaged with a spatial resolution of 1024×1024 pixels as opposed to 256×256 pixels which we used. Talairach et al. (1967) in their atlas, in which they proposed the basis for their stereotaxic space, illustrated their repeatability data; by rescaling these to an average size brain, one arrives at the average variabilities tabulated in Table 6, which appear of comparable magnitude to our figures.

Table 6. *Mean variability of landmarks estimated from Talairach et al.* (1967)

Landmark	'*y*' error*	'*z*' error*
SPreCS/SFS	n/a	n/a
CS/ML	4	30
PreCS/ML	n/a	n/a
SF/PreCS	7.5	7.5
SF/CS	7.5	7.5
SF/PostCS	7.5	7.5
Preocc	n/a	n/a
Calc/PO	7.5	0
SRS/Cing	3.75	7.5
PO/ML	7.5	10
TC/ML	5	5
IPreCS/IFS	7.5	7.5

* Measurements in mm.

Future directions

Work is in progress to improve the process of landmark identification based on automatic feature extraction to outline the gyri and sulci, as well as better 3-D visualisation based on the surface curvature, and also to consider the use of subcortical landmarks. Neuroanatomical work is being undertaken to look at larger numbers of brains, and to increase the number of features recognised on the cortical surface and the reliability of identification. With these improvements we hope to be able to reproducibly identify more landmarks with a greater coverage of the brain. We plan to use these landmarks in morphometric analyses of patients with suspected cerebral cortical structural pathologies.

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APPENDIX

Algorithms for sulcal identification

Precentral, *central*, *superior frontal and inferior frontal sulci*. Kido et al. (1980) noted that the superior frontal sulcus usually ended at the precentral sulcus, and that the marginal (or terminal) segment of the cingulate sulcus was always posterior to the central sulcus in postmortem brains and in vivo. These observations were used for sulcal identification, and are particularly useful to this present study, since the reconstructed cortical surface can be rotated to allow views of the lateral and the medial surfaces. Once the central sulcus had been identified, the precentral sulcus was designated as the next major sulcus anterior to it, and then the superior frontal sulcus designated as the most superior major sulcus ending posteriorly at the precentral sulcus. The inferior frontal sulcus was designated as the next sulcus inferior to the superior frontal sulcus which could be seen extending from anterior to the precentral sulcus (or within 1 cm) posteriorly.

Superior rostral sulcus (*susorbital sulcus in Duvernoy, 1991*). This was defined from Ono et al. (1991). If there was only 1 rostral sulcus (rather than 2), this was defined as the superior one. The anatomical texts are equivocal about where the cingulate sulcus ends and the cingulate starts, so for this study the protocol states that the lines of each sulcus should be extrapolated and the junction of these lines forms the landmark.

Calcarine, *parieto-occipital*, *cingulate*, *sylvian fissure*, *preoccipital notch* (*temporo-occipital incisure in Duvernoy, 1991*). These were identified using the descriptions of Duvernoy (1991) and Ono et al. (1991). These anatomical texts state that the preoccipital notch is at the junction of the anterior occipical sulcus with the inferolateral border of the hemisphere. However this sulcus is not always easily visualised, leading to potential ambiguity. Our protocol is that the landmark is formed by the junction of a line running along the inferolateral border of the temporal lobe and one following the anterior border of the preoccipital notch. Note that before measurement of the landmark the brain was aligned as below.

The *midline* was defined by eye once the image had been aligned coronally by lining up the brain so that the inferior parts of both temporal lobes were at the same horizontal level.