

Anatomical variability of the lateral frontal lobe surface: implication for intersubject variability in language neuroimaging

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Received 12 May 2004; revised 13 August 2004; accepted 25 August 2004

The lateral surface of the frontal lobe shows functional activation in a large number of language related tasks. Group analyses, however, demonstrate remarkable intersubject variability of activation. There are different sources for functional variability, anatomical variability being considered as one of them. The aim of the present study therefore was to qualitatively and quantitatively investigate the anatomical variability of the lateral frontal lobe surface and to search for reliable and stable landmarks connected to language functions.

MRIs of 23 healthy right-handed subjects were investigated using the publicly available software “Anatomist/BrainVISA”. After standardization of the brains (SPM) and sulci identification, the most frequent pattern was determined and the variance of selected landmarks calculated. The variability of the lateral frontal lobe surface is remarkable, particularly in the prefrontal region. Relatively stable landmarks were selected as follows: (1) connection between the superior frontal sulcus (SFS) and the superior precentral sulcus (SPCS); (2) connection between the inferior frontal sulcus (IFS) and the inferior precentral sulcus (IPCS); (3) inferior end of the precentral sulcus (PCS); and (4) origin of the ascending ramus (AscR) of the Sylvian fissure (SYF). The variability (standard deviation) of the spatial coordinates along the 3 axis of these landmarks after normalization ranged from 2.5 to 5.7 mm.

The present study demonstrates that intersubject variability of selected landmarks of the frontal lobe surface remains notable even after spatial normalization of the brains. These results support the concept that anatomical variability is a relevant source of functional variability. We therefore suggest to express functional activation in relation to landmarks obtained from individual anatomy. This approach may contribute to a better analysis of the differences between individuals.

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Keywords: Anatomical variability; Cerebral sulci; Frontal lobe; Functional variability; Language; Broca’s area

Introduction

Language-related functions were among the first to be ascribed a specific location in the human brain (Broca, 1861). The “classical model” of language function, based on observations of aphasic patients, proposes an area in the left inferior frontal gyrus (IFG) for planning and executing speech and writing, named after Broca (1861). Functional magnetic resonance imaging (fMRI) has confirmed and enlarged the knowledge about the role of the frontal cortex in language processing. Broca’s area is reproducibly activated in fMRI (Binder et al., 1997; Bookheimer, 2002; Brannen et al., 2001; Herholz et al., 1996; Hund-Georgiadis et al., 2002; Nolde et al., 1998; Poldrack et al., 1999; Rutten et al., 1999; Stippich et al., 2003). However, fMRI demonstrated the involvement of numerous other cerebral areas, in particular in the premotor and prefrontal cortex. These areas are activated by well defined and validated tasks encompassing phonological, semantic, syntactic, orthographic, and lexical components (Billingsley et al., 2001; Friederici et al., 2000; Frost et al., 1999; Fujimaki et al., 1999; Hund-Georgiadis et al., 2002; Kuperberg et al., 2000; Poldrack et al., 1999; Seghier et al., 2004; Stippich et al., 2003).

As far as hemispheric dominance of language processing is concerned, the reliability of fMRI to determine lateralization was shown in several investigations (Carpentier et al., 2001; Frost et al., 1999; Hund-Georgiadis et al., 2002; Rutten et al., 2002a; Seghier et al., 2004). This fMRI assessing of language lateralization corroborates well with the invasive intracarotid amobarbital procedure (Wada test, Wada and Rasmussen, 1960; Binder et al., 1996; Fernandez et al., 2003; Lehericy et al., 2000; Rutten et al., 2002b; Woermann et al., 2003).

However, functional imaging studies have generated a large amount of sometimes inconsistent results (Cabeza and Nyberg, 2000). With the same task, results in terms of frequency of occurrence, localization, intensity, and extent of activation can largely differ from one study to another. Reasons for this inconsistency are presumed to be (1) the subject factor (handedness, gender, age, native language), (2) the paradigm itself (production or comprehension tasks, language component, presentation modality),

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(3) the methodology used (block or event-related approach, data acquisition, data processing), or (4) anatomical differences between individuals. In order to obtain statistically relevant results, individual functional mappings are routinely averaged across subjects. To this purpose, brains are generally normalized to the same shape and size into a stereotaxic coordinate system like the Talairach space (Talairach and Tournoux, 1988) or the Montreal Neurological Institute (MNI) brain template (Collins et al., 1998) using linear or nonlinear spatial normalization techniques (Ashburner and Friston, 1999; Collins et al., 1994; Schormann and Zilles, 1998).

However, due to a very large variability of cortical folding across subjects, a major concern regarding nonlinear methods in particular, is the lack of validity of matching different brains with respect to preservation of cortical architecture (Crum et al., 2003). An alternative approach to account for intersubject sulcal variability is to use a morphological image analysis aimed at identifying the individual sulcal and gyral pattern and interpreting the functional data in relation to this individual morphology (Mangin et al., 2004). Doing so, group analyses could be based on comparing subjects in terms of functional activation related to proper anatomical borders.

The objectives of the present study were to investigate the sulcal patterns of the lateral frontal lobes, to search for stable anatomical landmarks connected to language functions, and to quantify the variability of spatial coordinates of these landmarks after affine spatial normalization to the brain template. The definition of stable anatomical landmarks may improve functional areas localization based on individual data. For instance, we expect a better characterization of different areas connected to language functions in the frontal lobe.

Methods

Standard T1-weighted GRE 3D-MRI (TR/TE/flip 15ms/4.7ms/25°, plane resolution 0.98 mm, slice thickness 1.1 mm) were obtained from 23 healthy right-handed volunteers (16 male, 7 female; age ranging from 21 to 42 years, average 25.6). Images were first spatially normalized to the MNI brain template (Collins et al., 1998) using affine transformation (SPM2, Ashburner and Friston, 1999; Friston et al., 1995) and then processed with the publicly available software “Anatomist/BrainVISA” (<http://anatomist.info/>) for MRI segmentation, sulci detection, 3D reconstruction and sulci identification (Mangin et al., 1995; Rivière et al., 2002). Affine transformation was used to normalize brains into standardized space while preserving individual sulcal topology. Detected sulci were reviewed by a neuroanatomist, and misclassified sulci segments were corrected. Possible landmarks were defined in the 3D reconstructions and their coordinates determined in the original MRI acquisitions (Fig. 1) thanks to the 3D visualization capabilities of “Anatomist.” For each selected landmark, the average and the standard deviation of the spatial coordinates after spatial normalization were calculated.

Results

The main results obtained concern the anatomical variability of sulci and of possible landmarks. Other findings will be mentioned in Discussion, in the context with observations reported in the literature.

Anatomical variability of sulci

The sulci of interest in the context of the present study were the central sulcus (CS) as the posterior border of the frontal lobe; the precentral sulcus (PCS) with its different parts including superior (sPCS), middle (mPCS), inferior (iPCS), medial (mePCS, lying rostrally to the CS and reaching the superior margin) and marginal precentral sulcus (maPCS, localized superiorly to the sPCS and coursing in a horizontal direction); the frontal sulci: superior (sFS), middle (mFS), inferior (iFS), fronto-marginal (FMS), and fronto-orbital (FOS); the rami of the Sylvian fissure (SYF): anterior horizontal ramus (AHR), ascending ramus (AscR), and diagonal sulcus (DiaS, located between AscR and iPCS). A synoptic view of these sulci is given in Fig. 2.

The above-mentioned sulci presented high anatomical variability in terms of length, orientation, and side branch patterns (Fig. 3). In Fig. 3a, the sulcal patterns of all subjects were superimposed on an underlying normalized brain. Because the brain reconstruction hides some of the sulcal parts, Fig. 3b shows the sulci alone, without adjacent cortex. We chose to perform topological analysis of the sulci for later determination of stable points. The results of this analysis are summarized in Table 2.

The configurations of the anterior horizontal (AHR) and ascending ramus (AscR) of the Sylvian fissure (SYF) were defined according to the classification proposed by Foundas et al. (2001, Figs. 4 and 5): V-shape: two rami with a common origin at the Sylvian fissure; Y-shape: two rami with a common stem; U-shape: origins of both rami separated; and J-shape: AscR much longer than AHR. In some cases the AHR may be absent (I-shape according to Eberstaller, 1890).

Selected landmarks

Landmarks selection was based on two criteria: high occurrence rate in Table 2, and proximity to the inferior frontal gyrus (Broca's area).

Broca's area

Three points were used forming a triangle limiting Broca's area (Fig. 6): (1) postero-superior limit of Brodmann area (BA) 44: Connection between posterior end of iFS and iPCS; (2) rostro-inferior limit of the triangular part BA 45: origin of AscR from SYF; and (3) posterior limit of BA 44: caudal end of iPCS.

The connection between the inferior end of the iFS and the iPCS was observed in 61% of right and 78% of left hemispheres. If there was no connection between these two sulci, the posterior end of the iFS itself was chosen. In those few cases where there was a descending end branch of the iFS between the AscR and the iPCS, the origin of a side branch of the iPCS, rostrally directed, was selected. As far as the triangular part of the inferior frontal gyrus was concerned, the common origin of the AscR and AHR was used in cases with V- and Y-shape, and the origin of the AscR was used in cases with U- and J-shapes.

Superior precentral region

The connection in the superior precentral region (BA 4/6) between the sFS and the sPCS was present in 74% of the right and 87% of the left hemispheres. If there was no connection, the posterior end of a segment of the sFS was detected closely to the sPCS.

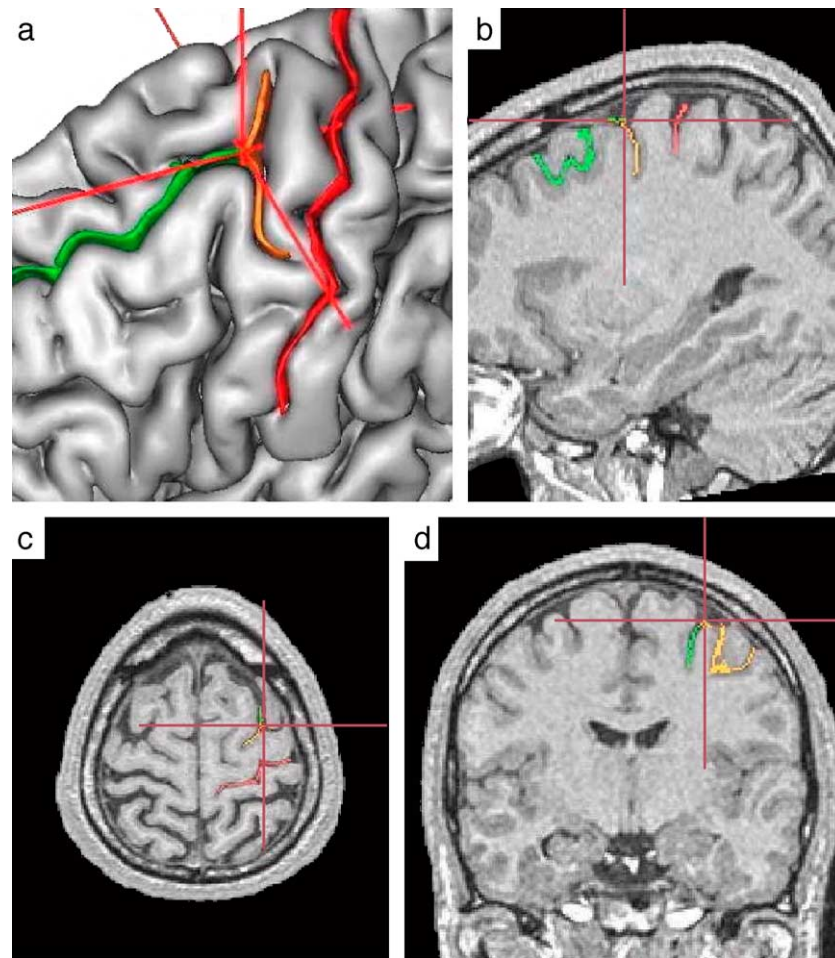


Fig. 1. Example of “Anatomist” windows allowing 3D navigation and precise landmark localization: (a) linked cursor position on the brain surface with selected sulci (CS—red, sFS—green, sPCS—orange) and (b–d) on the corresponding orthogonal views of MRI with the same sulci.

The variability of the prefrontal region was too high to detect any reliable landmark there. Particularly, the FOS and FMS did not show acceptable constancy regarding connection to the

neighboring frontal sulci segments (<30%). For instance, connection between FOS and iFS was observed in 22% of all subjects (Table 2). The variability of the sFS, intFS, and iFS is also illustrated in Fig. 3.

Calculation of variance of selected landmarks

The mean coordinates (\pm standard deviations) of the selected landmarks along the x , y , and z axis in the MNI space are given in Table 3. The standard deviations, ranged from 2.5 to 5.7 mm., assessing landmarks variability. In general, the smallest variation is observed along the x axis, while larger variance is present in y and z directions. Fig. 7 illustrates this variability on the left hemisphere, and shows also that landmark no. 2 is the most stable, whereas the three others present more scattering.

Discussion

The present study confirms the high sulcal variability of the lateral frontal lobe surface in terms of number, localization, and shape (continuity, number of interruptions, connections with neighboring sulci), as shown in Fig. 3. As for all studies

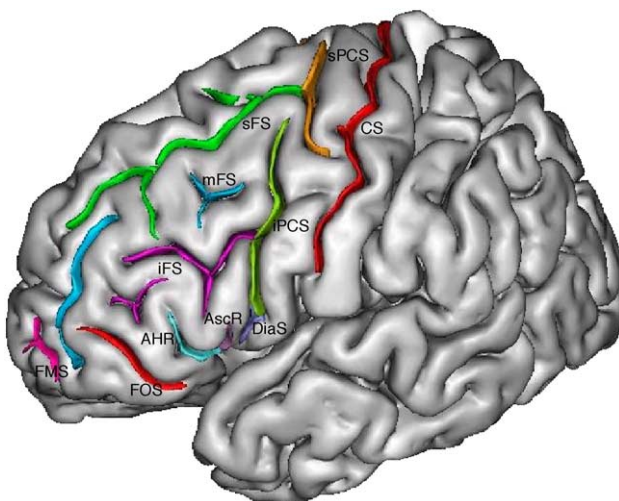


Fig. 2. Most frequent sulcal pattern of the lateral frontal lobe surface. For abbreviations, see Table 1.

Table 1
Abbreviations used throughout the article

Abbreviation	
SPM	statistical parametric mapping
MNI	Montreal neurological institute
CS	central sulcus
PCS	precentral sulcus
sPCS	superior precentral sulcus
mPCS	middle precentral sulcus
iPCS	inferior precentral sulcus
maPCS	marginal precentral sulcus
mePCS	medial precentral sulcus
SYF	Sylvian fissure (=Lateral sulcus)
AHR	anterior horizontal ramus of the Sylvian fissure
AscR	ascending ramus of the Sylvian fissure
DiaS	diagonal sulcus of the Sylvian fissure
sFS	superior frontal sulcus
mFS	intermediate frontal sulcus
iFS	inferior frontal sulcus
FOS	frontoorbital sulcus
FMS	frontomarginal sulcus
BA	Brodman area
AC–PC plane	plane through anterior and posterior commissure
IFG	inferior frontal gyrus

concerned with anatomical variability, systematic description of variations and comparison with results obtained by other investigators meet with several difficulties. One of them is due to the fact that there is by far no uniform terminology, in our case for the cerebral sulci. Since the present International Anatomical Terminology (FCAT, 1998) is not detailed enough for the purpose of our investigation, we decided to follow the parameters and nomenclature introduced by Ono et al. (1990) in a complete study of the cerebral sulci. Their results are compared with ours in the following sections.

Most frequent pattern

The following sulci were observed in all subjects: CS, sFS, iFS, sPCS, iPCS, and AscR (Fig. 2). In Broca's area, the most frequent pattern is characterized by the juxtaposition of AscR and iPCS as well as the presence of a junction between iFS and iPCS (61% on right and 78% on left hemispheres). Ebeling et al. (1989) detected this configuration in 90% of hemispheres from 20 healthy volunteers studied in MRI and 76% of hemispheres in a

sample of 62 anatomic specimens. Ono et al. (1990) found a connection between the iFS and iPCS in 88% on both hemispheres from 25 anatomic specimens.

As far as the triangular part of the inferior frontal gyrus is concerned, we could observe the different shapes described by Foundas et al. (2001). The prevalence of the V-, U-, Y-, and J-shape was equally distributed (ranging between 24% and 26%), but the following side differences were noted. On the left hemispheres the U-shape was predominant (39%), followed by the V- and Y-shapes (22% both), as illustrated in Fig. 4. The right hemispheres most often displayed Y- and J-shapes (30% both). Foundas et al. (2001) observed the V-shape in 58% and the Y-shape in 17% of hemispheres in a sample of 12 brains investigated by MRI. Ono et al. (1990) detected the AHR and AscR separated from each other (according to the V- and U-shape of Foundas et al. (2001) in 62%, which is in very good accordance with our results.

The sFS and the sPCS were connected with each other in the majority of cases (74% on right and 87% on left hemispheres). If there was no connection, the posterior end of the sFS was located closely to the sPCS. Ono et al. (1990) found this connection in 92% of right and in all left hemispheres.

Examples of variations

Concerning the prevalence of diverse anatomical patterns, some differences exist between our data and the observations reported particularly by Ono et al. (1990). These differences are summarized in Table 4.

They confirm a general observation in the field of variational anatomy, namely the fact that determination of pattern frequencies poses obvious problems: classification of variations unavoidably implies, indeed, subjective elements. If, for example, an anterior branch of the sPCS is observed, it can be classified as a sPCS-variational pattern; but if the basic concept considers the sFS to be connected to the sPCS, the same pattern can be interpreted as a segmentation of the sFS (Fig. 8). This difficulty is even amplified if the structure under consideration is extremely variable, not allowing for the definition of a basic pattern. In our context, the mFS is such a very variable sulcus (Fig. 3). It is highly observer-dependent to define a mFS and to decide about its segments and connections to neighboring sulci. Examples of morphologic variability of the iFS and iPCS are shown in Fig. 9. In other words, controversies on the frequency of variations in the

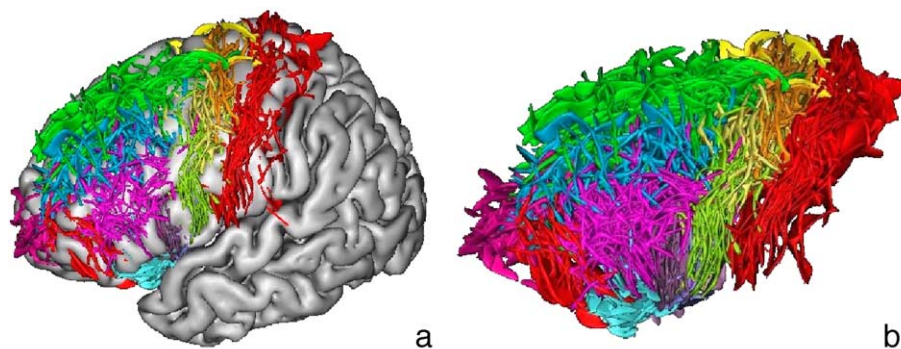


Fig. 3. Synoptic view of variability of sulcal pattern variability in the left frontal lobe, presented on an example brain surface (a) and without underlying gray matter (b). For color code of sulci, see Fig. 2.

Table 2
Selected parameters and frequency of occurrence

Sulcus	Parameter	Incidence rate
CS	interruption	right—0%; left—9%
	connection to Sylvian fissure	right—13%; left—4%
	not reaching the cranial margin of hemisphere	right—13%; left—13%
Anterior rami of Sylvian fissure	AHR not present	right—13%; left—0%
	V-shape	right—26%; left—22%
	Y-shape	right—30%; left—22%
	U-shape	right—13%; left—39%
DiaR	J-shape	right—30%; left—17%
	present	right—26%; left—43%
	SFS	right—52%; left—61%
mFS	1 segment	right—30%; left—22%
	2 segments	right—9%; left—17%
	3 segments	right—0%; left—4%
	connection to:	
	mFS	right—0%; left—4%
	iFS	right—0%; left—4%
	PCS	right—74%; left—87%
	FMS	right—9%; left—26%
	Is not present	right—4%; left—0%
	1 segment	right—69%; left—52%
	2 segments	right—17%; left—26%
	3 segments	right—0%; left—26%
	connection to:	
FMS	right—26%; left—30%	
FOS	right—0%; left—4%	
PCS	right—9%; left—4%	
sPCS	right—0%; left—0%	
mPCS	right—9%; left—0%	
sFS	right—4%; left—0%	
iFS	right—0%; left—4%	
iFS	1 segment	right—26%; left—56%
	2 segments	right—48%; left—35%
	3 segments	right—17,4%; left—17,4%
	connection to:	
	FOS	right—22%; left—22%
	FMS	right—13%; left—4%
	PCS	right—61%; left—78%
	mFS	right—0%; left—13%
	sFS	right—9%; left—4%
	PCS	1 segment
2 segments		right—4%; left—9%
3 segments		right—48%; left—69%
4 segments		right—43%; left—26%
mePCS is present		right—69%; left—52%
maPCS is present		right—48%; left—56%
connection to:		
SYF		right—57%; left—43%
sFS		right—74%; left—87%
mFS		right—9%; left—9%
iFS	right—61%; left—78%	

literature may not correspond to discrepancies in reality. This fact in mind, the following variational patterns can be reported from our study:

CS

Generally, the CS is not interrupted because the two sulcal roots forming it during fetal life do merge (Le Goualher et al., 2000; Manceaux-Demiau et al., 1998). If this merging process does not occur, the separating gyrus remains visible on the

brain surface or deeper on the sulcal wall (Cachia et al., 2003). In the 46 hemispheres investigated, we found two left hemispheres with an interrupted CS (Fig. 10). There are several single cases of this nature reported in the anatomical literature (Cunningham, 1892; Eberstaller, 1890; Retzius, 1896). Ono et al. (1990) found four hemispheres (2 right, 2 left) among 25 brains with an interrupted CS, localized in the inferior CS portion. In our subjects, the interruptions were localized in the inferior (Fig. 10a) and superior portion of the CS. In the subject with a superior interruption, the CS was cranially connected with the sFS, which extended posteriorly across the precentral gyrus (Fig. 10b).

PCS

Ebeling et al. (1989) investigated the localization of the iPCS both in MRI of living human brains and anatomic specimens. They distinguished four types of iPCS patterns. Our data are consistent with their observations with the most frequent pattern corresponding to type 1 in their classification. However, the values of the distance to the midsagittal plane are not comparable with our x values of coordinates, because Ebeling et al. (1989) did not spatially normalize the images.

In contrast, the differences of segmentations of the PCS between our observations and the results obtained by Ono et al. (1990) are notable. In all our subjects, superior and inferior parts of the PCS were detectable (sPCS/iPCS). Additionally, at least one of the other precentral sulci (middle, marginal, and/or medial) was observed in the majority of cases. We detected the presence of sPCS and iPCS alone, that is, without any additional other part of the PCS, in 4% of right and 9% of left hemispheres only. On the contrary, Ono et al. (1990) found this configuration in 48% of right and 64% of left hemispheres.

IFG, triangular, and opercular part

Foundas et al. (2001) focused their interest on the morphology of the triangular part of the inferior frontal gyrus, that is, the portion lying between the AHR and the AscR (Fig. 2). This portion is considered to correspond to BA 45. Their study confirmed a leftward asymmetry in a group of 12 right-handed male humans by volumetric MRI. The most common shape of the limiting sulci was the V-configuration (58% of all hemispheres), observed more often on the left (75%) than on the right brain side (55%). We found a lower frequency (24% on all hemispheres) and we did not find a leftward asymmetry in the prevalence of the V-shape. Whereas Foundas et al. (2001) did not detect any J-configuration in their group, we did it in 24% of the hemispheres, predominantly on the right side (right: 30%; left: 11%). Some of the right hemispheres lacked an AHR (13%). The Y-configuration occurred in 17% in the study of Foundas et al. (2001) and in 26% in our investigation, more often on the right brain side (right: 30%, left: 22%). Ide et al. (1999) found the Y-shape in 26 hemispheres (32%), equally distributed on both hemispheres. They observed a predominance of either the AHR or the AscR, corresponding to the J-shape of Foundas et al. (2001), more often in the right hemispheres (right: 22%, left: 7%). Our results are in agreement with this latter observation. Foundas et al. (2001) also considered the V-configuration as being the most common form, but their classification did not include U-configurations. A possible explanation may be due to a V-shape connection located deeper in the brain, hidden in the

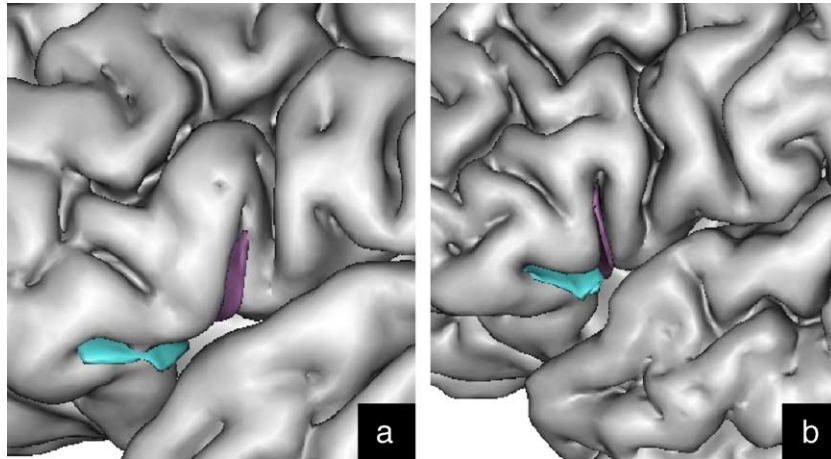


Fig. 4. Examples of the triangular part variability on left hemispheres: U-shape (a) and V-shape (b).

depth of the insular region. In this context, the direct anatomical examination of postmortem brains is the most reliable method since it allows a deeper look onto the insular region than it is possible by visualization of a 3D reconstruction obtained from MRI.

In our group of right-handed subjects left hemispheres more often displayed a V- or U-shape of the triangular part (61%, Fig. 4), whereas the J- and Y-configuration (60%) were predominantly found on right hemispheres (Fig. 5). We did not perform linear or volumetric measurements, but we found higher variability of the triangular and opercular parts on right hemispheres. The AscR was often longer than on the left hemispheres and lay closer to the iPCS. In those cases, the extent of BA 44, supposed to be located between the AscR and iPCS (according to Brodmann, 1909), can be expected to have been smaller. An Y-shape of the triangular part accounts for a smaller extend in inferior direction towards the SYF. Amunts et al. (1999) investigated the cytoarchitecture and intersubject variability of Broca's region and found a greater intersubject than intra-individual cytoarchitectonical variability of BA 44 and 45. The volumes of area 44 differed across subjects by up to a factor 10. Only BA 44, and not BA45 was left-over-right asymmetrical in

all brains. Foundas et al. (1998) investigated volumetry of the triangular and opercular parts. They detected leftward asymmetry of the triangular part both for left- and right-handers; however, more pronounced for the latter group. But for the opercular part it was the contrary, there was only leftward asymmetry for right-handers but rightward asymmetry for left-handers. In another study, Foundas et al. (1996) found leftward asymmetry of the triangular part by MRI volumetry in 9 of 10 subjects tested for left side lateralization of language using the Wada test. Herholz et al. (1996) investigated the PET activation in a silent verb task in a small group of healthy human men. They made an interesting observation: the most intense activation was detected in the triangular part of the left inferior frontal gyrus in all subjects. There was a considerable anatomical variation mainly due to the variability of the Y-position of the AscR. In the study of Herholz et al. (1996), five of the seven subjects had the most common configuration of the triangular part (V-shape) and these were the subjects with a particular clear increase in cerebral blood flow (CBF) in this investigation. One subject with a predominant AscR and a rudimentary AHR showed the smallest CBF increase. Another subject with the opposite pattern (i.e., a predominant AHR and a rudimentary AscR) showed the most

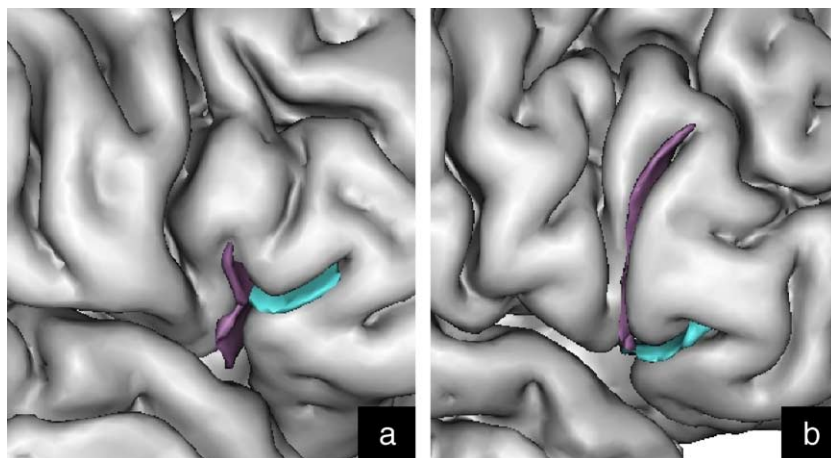


Fig. 5. Examples of the triangular part variability on right hemispheres: Y-shape (a) and J-shape (b).

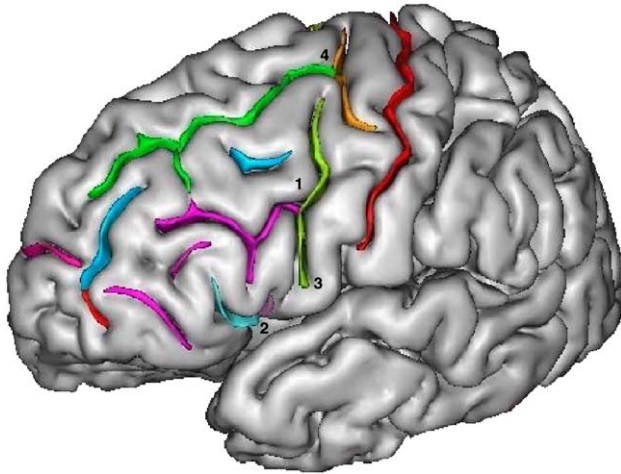


Fig. 6. Landmarks selected: (1) connection between iFS and iPCS, (2) origin of AscR, (3) inferior end of iPCS, (4) connection between sFS and sPCS.

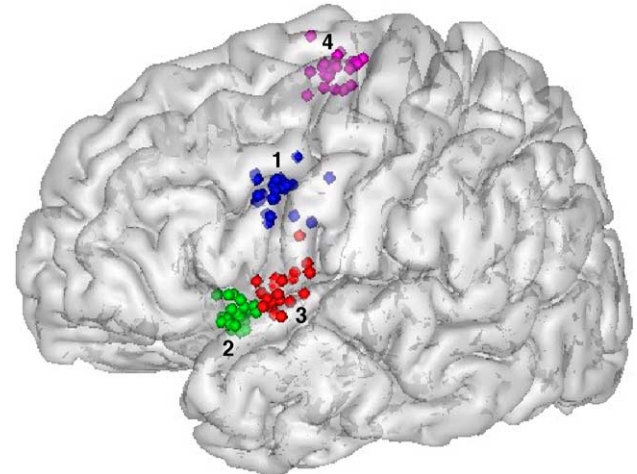


Fig. 7. Variability of the landmarks: (green) origin of AscR, (red) inferior end of iPCS, (blue) connection iFS-iPCS, (pink) connection sFS-sPCS.

intense increase in CBF in the orbital part. Although these observations are single subject findings, they support the hypothesis morphology of the posterior IFG to be of influence for the localization of functional activation related to language: the V-shape as the most common pattern of the triangular part was strongly related to the classical model of language function location, anatomical variations to not-classical localization, respectively.

Quantification of anatomical variability

Steinmetz et al. (1990) investigated perisylvian landmarks in a sample of 20 subjects undergoing MRI under stereotaxic conditions. The range of sulcal variational zones in these Talairach normalized brains measured 15–20 mm. Thompson et al. (1996) performed statistical surface analyses of the parieto-occipital sulcus, anterior and posterior rami of the calcarine sulcus, cingulate and marginal sulci, and supracallosal sulcus in a sample of 6 postmortem brains. The brains underwent 3D reconstruction and standardization into the Talairach stereotaxic grid using digital photography. The authors found variational zones of sulcal surfaces on 3D reconstructions ranging from 8 to 10 mm on the sulcal grounds up to 19 mm for the superficial parts of the sulci.

In order to find reliable landmarks, we did not focus on sulci as a whole. As known, they are highly variable in length, shape, and side branch patterns. We therefore investigated points with high frequency of occurrence, as is the case for connections

between two sulci or end points of sulci. The variability of the landmarks selected in our study, expressed as the standard deviation of coordinates along each axis (x , y , z), ranged from 2.5 to 5.7 mm (Table 3). The maximum range of coordinate differences was 24 mm and observed along the y direction for the sFS-sPCS landmark, which is consistent with Steinmetz et al. (1990). The difference between our results and those of Thompson et al. (1996) could be explained by the differences of subject populations (23 vs. 6) and different brain areas studied (frontal vs. occipital). Our results are also in excellent accordance with those obtained by Zilles et al. (1997). Investigating spatially normalized MRIs, this group found the central sulcus to show a maximal variability near the interhemispheric fissure ranging between 4 and 6 mm. They also found that both the CS and the AscR were more variable on the right, non-dominant hemisphere. With regard to the language dominant left hemisphere, the variability in our study ranged from 2.5 mm for the x coordinate of the origin of the AscR on the SYF to 5.7 mm for the z coordinate of the connection between the sFS and sPCS (Table 3).

Xiong et al. (2000) investigated the variability of cortical activations in PET during a verb generation task. The variability in that study ranged from 5.2 to 9.9 mm along each axis and was uniformly distributed across the brain, uninfluenced by regional differences in the complexity of gyral anatomy. In a fMRI study with phonologic and semantic tasks, Seghier et al. (2004) reported an interindividual variability in the frontal lobe, ranged from 3 to 11 mm. The anatomical variability observed in our study could explain a part of that interindividual variability. In our inves-

Table 3
Coordinates of landmarks in MNI space (average \pm standard deviation in mm)

Landmark	Right			Left		
	x	y	z	x	y	z
iFS-iPCS	54.4 \pm 2.6	13.9 \pm 3.7	34.6 \pm 4.5	-54.8 \pm 2.6	12.5 \pm 4.2	35.2 \pm 4.7
AscR	50.8 \pm 3.1	15.7 \pm 2.8	0.7 \pm 3.3	-50.5 \pm 2.5	16.3 \pm 2.8	0.2 \pm 3.1
Caudal iPCS	57.9 \pm 3.4	7.1 \pm 4.8	8.4 \pm 5.2	-57.3 \pm 3.7	7.54 \pm 2.9	8.7 \pm 5.3
sFS-sPCS	31.0 \pm 2.9	5.8 \pm 5.7	68.7 \pm 3.1	-30.1 \pm 5.1	4.2 \pm 4.9	67.9 \pm 5.5

Table 4
Comparison of our results and the study of Ono et al. (1990)

Parameter	Incidence rate in our group	Incidence rate in the specimens of Ono et al. (1990)
Connection sFS-mFS	right—0%	right—20%
Connection sFS-sPCS	right—74%; left—87%	right—92%; left—100%
No mFS to detect	right—4%; left—0%	right—12%; left—16%
mFS: no interruption	right—69%; left—52%	right—20%; left—16%
mFS: 2 segments	right—17%; left—26%	right—52%; left—16%
Connection mFS-iPCS	right—9%; left—4%	right—20%; left—28%
Connection mFS-iFS	right—0%	right—16%
iFS: no interruption	right—26%; left—56%	right—56%; left—40%
Connection iFS-PCS	right—61%; left—78%	right—88%; left—88%
Connection iFS-mFS	right—0%	right—24%
PCS: 2 segments	right—4%; left—9%	right—48%; left—64%
PCS: 3 segments	left—69%	left—32%
PCS: 4 segments	right—43%; left—26%	right—0%; left—4%
maPCS is present	left—56%	left—16%
mePCS is present	right—69%; left—52%	right—92%; left—80%

tigation as well as in that of Xiong et al. (2000) and Seghier et al. (2004), there was a higher variance in the superior precentral region (BA 4/6). In our study, the coordinates for the left-sided junction between the sFS and sPCS ranged from 4.9 to 5.5 mm. The variability for the left BA 4/6 ranged from approximately 5 to 10 mm (Seghier et al., 2004; Xiong et al., 2000).

Furthermore, it was observed that the inferior frontal gyrus activation has large variability particularly in the *z* axis direction (Seghier et al., 2004). Here, we found larger variance along the *z* axis (distance in cranial direction above the AC–PC plane) for the left-sided junction between the iFS and iPCS ($SD \pm 4.7$ mm). A higher distance between this point and the SYF indicates a larger extent of Broca's area in superior direction. This fact is in good harmony with the leftward asymmetry in the volumes of Broca's area in right-handed humans reported by Foundas et al. (1996, 2001) and Amunts et al. (1999).

We conclude the base of the AscR (the common origin of the AHR and AscR, respectively) to be the most stable landmark for both hemispheres. The average *z* values (0.7 ± 3.3 mm on the right side; 0.2 ± 3.1 mm on the left one) indicate its vertical position just around the AC–PC plane. The distance to the vertical plane through the anterior commissure (AC) in rostral direction (positive *y* values) ranged between 15.7 mm (± 2.8) on the right and 16.3 mm (± 2.8) on the left hemispheres. The close relation of these coordinates to the AC–PC plane allows reliable identification of the base of the AscR on axial planes through the AC.

Fesl et al. (2003) investigated the functional activation of the primary motor tongue area (MTA) in relation to the inferolateral segment of the CS. Although the variability of the inferior portion of the CS precluded the assignment of the MTA to a specific anatomic configuration, the position of the MTA could be

approximated by the intersection between the CS and three axial planes through, just above, and just below the central part of the lateral ventricles.

A further problem of studies investigating anatomical and functional variability is the instable consistency of the macroscopic anatomical pattern and the limits of cytoarchitectonic areas. It has been demonstrated that the macroscopic anatomical variability is highly related to the microstructural one in the primary motor area (Geyer et al., 1996; Rademacher et al., 2001; Zilles et al., 1997), in the somatosensory area 3a (Zilles et al., 1997), but not in the inferior frontal gyrus and in the primary and secondary visual cortices (Amunts et al., 1999, 2000; Zilles et al., 1997). In their study of primary cytoarchitectonic fields, Rademacher et al. (1993) distinguished two classes of variability: class 1 variability being not predictable from visible landmarks, class 2 variability being closely predictable from those landmarks. The class 2 variability was prominent in all investigated fields (BA 17, 41, 3b, and 4). The authors concluded that direct reference to the landmarks that frame these fields may be expected to be a more reliable basis for functional mapping than reference to a template or stereotaxic coordinate-based system of reference. Rajkowska and Goldman-Rakic (1995) investigated the cytoarchitectonic variability in the superior prefrontal cortex. They also found high variability and concluded that this may underlie the individual differences in the visuospatial and cognitive capacities subserved by these areas. The problem of instable consistency between macroanatomy and cytoarchitecture in neuroimaging will only be solved in our view, by analyzing very large neuroimaging databases such as the European Computerized Human Brain Database (ECHBD) (Roland and Zilles, 1996) or the International Consortium for Brain Mapping (Mazziotta et al., 2001), both including cytoarchitectonic data, in order to create probabilistic maps of cytoarchitectonic fields and functional activation areas.

Conclusion

In conclusion, the present study confirms the high variability of anatomical patterns on the lateral frontal lobe surface. Spatial normalization of the brains and determination of selected land-

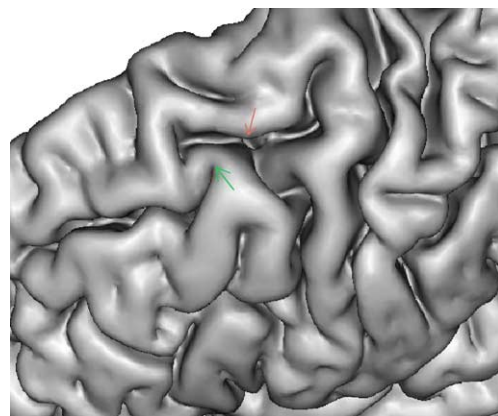


Fig. 8. Example of a left side connection between sFS and sPCS. Green arrow: posterior end of a segment of the sFS. Orange arrow: connection between a segment of sFS and sPCS (alternative interpretation: sPCS with branch in rostral direction).

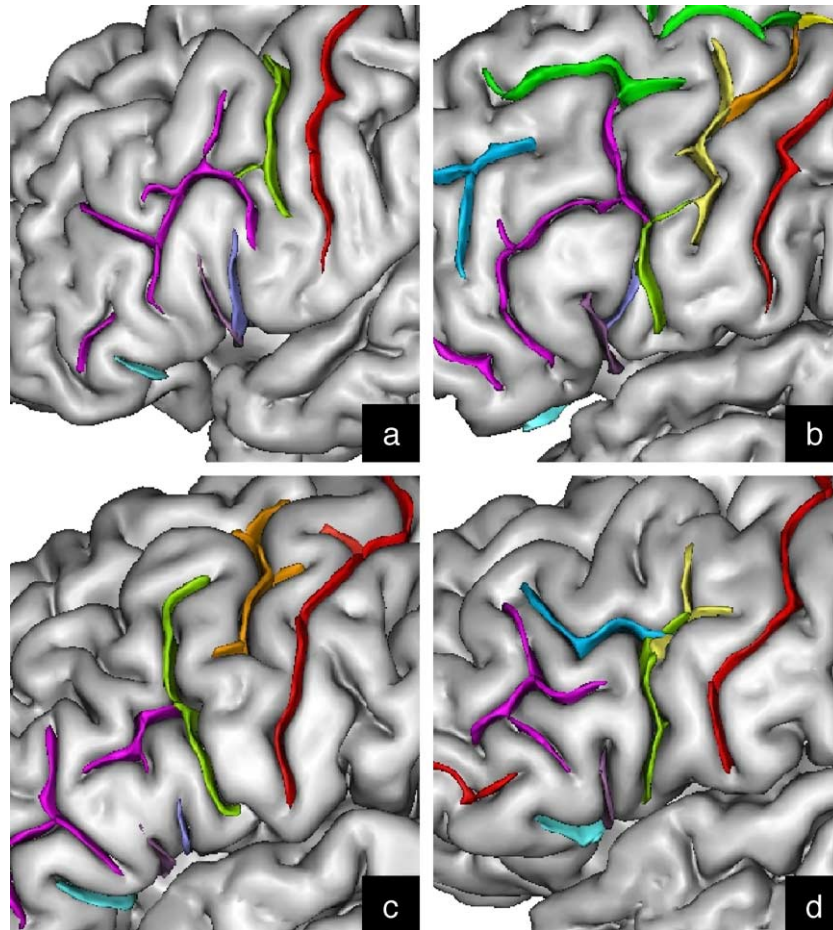


Fig. 9. Examples of iFS and iPCS variability: (a) inferior end of iPCS located more superiorly, (b) connection between iFS and sFS, (c) parallel overlapping position of sPCS and iPCS, and (d) descending end branch of iFS (type 3 according to Ebeling et al., 1989).

marks allowing for quantification of sulcal variability shows the intersubject variability of these landmarks to range between 2.5 and 5.7 mm. These results support the concept that anatomical variability is a relevant source of functional variability. We therefore suggest to express activation in relation to landmarks

obtained from individual anatomy to allow better analysis of intersubject differences. In order to confirm the reliability of this approach, we intend to investigate the fMRI data of a combined phonological/semantic task of the same group of subjects in relation to their individual anatomical pattern.

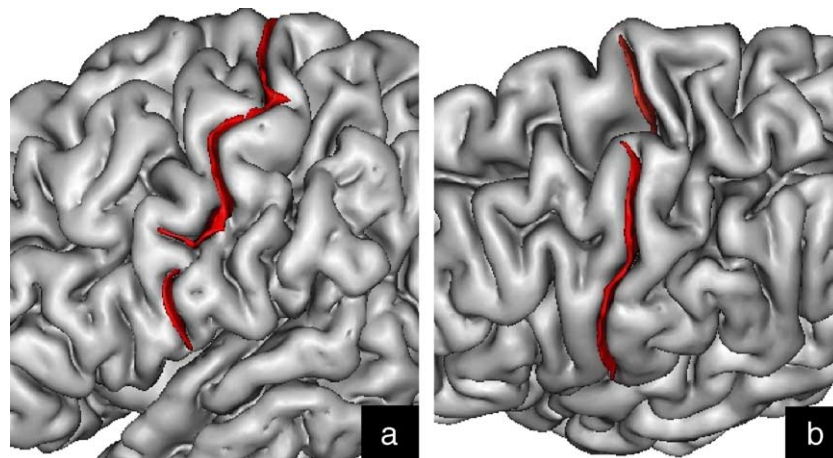


Fig. 10. Interrupted central sulcus on two left hemispheres, (a) in its inferior and (b) in its superior portion.

Acknowledgments

We would like to thank J.-F. Mangin and his colleagues for making “Anatomist/BrainVISA” available and providing support with the software and P. Hüppi for useful discussions. This work was supported by grants from the Swiss National Science Foundation, 3200B0-100717/1.

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