Morphology, morphometry and probability mapping of the pars opercularis of the inferior frontal gyrus: an in vivo MRI analysis

F. Tomaiuolo,1* J. D. MacDonald,2 Z. Caramanos,2 G. Posner,2 M. Chiavaras,2 A. C. Evans2 and M. Petrides2

1IRCCS ‘S. Lucia’, Roma; Dipartimento di Scienze Neurologiche e della Visione, sez. Fisiologia Umana, Verona, Universita’ di Verona, Italy
2Montreal Neurological Institute, McGill University, Canada

Abstract

The pars opercularis occupies the posterior part of the inferior frontal gyrus. Electrical stimulation or damage of this region interferes with language production. The present study investigated the morphology and morphometry of the pars opercularis in 108 normal adult human cerebral hemispheres by means of magnetic resonance imaging. The brain images were transformed into a standardized proportional stereotaxic space (i.e. that of Talairach and Tournoux) in order to minimize interindividual brain size variability. There was considerable variability in the shape and location of the pars opercularis across brains and between cerebral hemispheres. There was no significant difference or correlation between left and right hemisphere grey matter volumes. There was also no significant difference between sex and side of asymmetry of the pars opercularis. A probability map of the pars opercularis was constructed by averaging its location and extent in each individual normalized brain into Talairach space to aid in localization of activity changes in functional neuroimaging studies.

Introduction

The posterior part of the inferior frontal gyrus in the left hemisphere is traditionally considered to constitute the classical Broca’s area, i.e. the anterior cortical area which is thought to play a critical role in speech production (Dejerine, 1914). The posterior half of the inferior frontal gyrus typically exhibits two general morphological subdivisions that are referred to as the pars triangularis, i.e. the triangular portion delimited by the vertical (ascending) ramus and the horizontal ramus of the Sylvian fissure, and the pars opercularis delimited by the vertical ramus and the inferior part of the precentral sulcus (see Fig. 1). Although it is not possible to specify more precisely the critical zone within this general region from clinical-anatomical correlation studies (e.g. Mohr et al., 1978), electrical stimulation work during brain surgery has indicated that speech arrest occurs most reliably from stimulation of that part of the inferior frontal gyrus that lies immediately anterior to the lower end of the precentral gyrus (Rasmussen & Milner, 1975; Ojemann, 1979).

Inspection of the caudal part of the inferior frontal gyrus in different human brains suggests that there is considerable morphological variability. In some cases, two small convolutions can be clearly seen on the lateral surface of the brain, lying between the vertical ramus and the inferior precentral sulcus, whereas in other cases only one is visible. One aim of the present study was to examine the morphological pattern of the region of the pars opercularis on a large-scale and to create a probability map of this region in a standardized proportional stereotaxic space, namely that of Talairach & Tournoux (1988) which has become the standard space within which activation foci are expressed in most modern functional neuroimaging studies with positron emission tomography (PET). The provision of a probability map in which the variability in location of a given brain region, in this case the pars opercularis, is quantified and is essential for accurate localization of the focus of activity changes in group studies with PET. Furthermore, the expression of the location of the average focus of activity changes in a standardized space provides a common frame of reference across studies.

In addition, the location of circumscribed brain lesions can be described in a standardized space in brains that have been appropriately transformed. Such an approach might provide a clearer definition of the critical area of damage in a group of patients exhibiting a common clinical feature (Koski et al., 1998). Thus, the creation of a probability map of the pars opercularis will provide key information for functional neuroanatomical studies of language.

Another aim of the present investigation was to examine whether there are hemispheric differences in the grey matter volume of the pars opercularis. Several studies, using different kinds of measurements, examined the hemispheric and sex-related differences of the anterior speech areas, such as the pars triangularis and pars opercularis of the inferior frontal gyrus (e.g. Wada et al., 1975; Falzi et al., 1982; Foundas et al., 1996, 1998). An earlier study by Wada et al. (1975) measured the pars opercularis together with a large part of the pars triangularis and found the overall region to be slightly larger in the right hemisphere. However, as the authors pointed out, as a large part of the cortex hidden within the sulci was not measured, the possibility remained that there might still be an asymmetry in favour of the left hemisphere if this cortex were to be included (see p. 245 of Wada et al., 1975). Witelson & Kigar (1992) reviewed the work on the asymmetry of the frontal operculum and reported no left–right hemispheric differences on the lateral aspect of this area, but...
like Wada et al. (1975), they suggested that if the intrasulcal cortex of the frontal operculum were to be included, an asymmetry might be demonstrated. Falzi et al. (1982) examined the posterior portion of the inferior frontal gyrus in 12 right-handed adults and found no interhemispheric differences when they compared only the convexity of this area, but a significantly larger left hemisphere was found when the comparison was performed by considering both the convexity and the intrasulcal cortex of the posterior portion of the inferior frontal gyrus. However, these investigators, did not include in their measurement the pars opercularis in isolation, but together with the pars triangularis. Recently, Foundas et al. (1996) measured the volume of the pars triangularis on the magnetic resonance scans of subjects who, for clinical reasons, had also undergone an intracarotid sodium Amytal test (Wada &
Rasmussen, 1960) to establish the side of speech lateralization. They found that 10 out of 11 right-handed subjects had a larger pars triangularis and this was consistent with the side of speech lateralization. The present investigation aimed to evaluate whether there are hemispheric differences in the grey matter volume of the whole pars opercularis.
Materials and methods

The MRIs of the brains of 54 randomly selected subjects were studied: 19 females aged (mean ± SD) 25.6 ± 10.1 years and 35 males aged 25.4 ± 7.0 years. All the subjects were right-handed and none had a positive history for neurological or psychiatric disorder. The subjects gave informed consent. The MRI scans were made by means of a Philips Gyroscan 1.5-T superconducting magnet system using a 3-D fast-field echo-acquisition sequence T1-weighted (TR, 18 ms, TE, 10 ms and flip angle 30°), collecting 160 slices of 1 mm thickness, in the sagittal plane.

In order to standardize the images and correct for any interindividual differences in gross brain size, each MRI volume was separately transformed into the standardized proportional stereotaxic space of Talairach & Tournoux (1988) by means of an automatic registration program which uses a 3-D cross-correlation approach to match the
FIG. 3. (a and b) The pars opercularis (identified by the yellow colour), as visualized from the lateral view of the 3-D reconstructed left hemisphere of each one of the brains that were studied. The hemispheres are presented on a grid where the stereotaxic Z-values range from +50 mm (ventral) to +70 mm (dorsal) and the Y-values range from ±30 mm (caudal) to ±50 mm (rostral). The surface rendering of the left hemisphere is shown at ±30 mm lateral to the midline. The sulci that define the pars opercularis can be identified on these grids as follows. The sulcus just caudal to the region indicated in yellow is the inferior precentral sulcus, the one dorsal is the inferior frontal sulcus, the one ventral is the Sylvian fissure and the one just rostral is the vertical ramus of the Sylvian fissure. The sulcus diagonalis, when it is present, can be seen within the yellow region.
single MRI volume with the intensity average of 305 MRI brain volumes previously aligned into the standardized stereotaxic space (Collins et al., 1994). This resampling results in a volume of 160 axial slices with an in-plane matrix of 256 × 256 pixels. The thickness of the interpolated sagittal, axial and coronal slices were 0.67, 0.75 and 0.86 mm, respectively. It is important to note that transformation into the Talairach & Tournoux (1988) stereotaxic space is the usual procedure for averaging functional activity obtained in different brains with PET in order to describe the location of the activation peaks.

Region of interest: anatomical landmarks and boundaries

The pars opercularis can be delimited macroscopically as follows: rostrally, by the vertical (ascending) ramus of the Sylvian fissure (Vr); dorsally, by the inferior frontal sulcus (IFs); caudally, by the
inferior part of the precentral sulcus (Ps); ventrally, by the Sylvian fissure (Sf). Cytoarchitectonic analyses have indicated that the surface area of the pars opercularis is characterized by a distinct type of cortex that was labelled as area 44 by Brodmann (1908) and Sarkissov et al. (1955) and area FCBm by Economo & Koskinas (1925) (see Fig. 2).

**FIG. 4.** (a and b) The pars opercularis (identified by the yellow colour), as visualized from the lateral view of the 3-D reconstructed right hemisphere of each one of the brains that were studied. The hemispheres are presented on a grid where the stereotaxic Z-values range from +50 mm (ventral) to +70 mm (dorsal) and the Y-values range from −30 mm (caudal) to +50 mm (rostral). The surface rendering of the right hemisphere is shown at +30 mm lateral to the midline. The sulci that define the pars opercularis can be identified on these grids as follows. The sulcus just caudal to the region indicated in yellow is the inferior precentral sulcus, the one dorsal is the inferior frontal sulcus, the one ventral is the Sylvian fissure and the one just rostral is the vertical ramus of the Sylvian fissure. The sulcus diagonalis, when it is present, can be seen within the yellow region.
This area can be distinguished from the posteriorly adjacent premotor cortex (Brodmann's ventral area 6 or Economo and Koskinas' area FB), which lies on the precentral gyrus, by the presence of an incipient layer IV and very large pyramidal neurons in the deeper portion of layer III. Rostrally, area 44 is replaced by Brodmann’s area 45 (Economo and Koskinas’ area FDI) which has a well-developed layer IV. The cytoarchitectonic studies of Petrides & Pandya (1994) have shown that the surface of the cortex occupying the pars opercularis is area 44 in all brains and that this area extends into the adjacent sulci (i.e. Vr, IFs and Ps) for a considerable distance, although the precise limit varies across brains. However, the cortex within the Sylvian fissure that joins the pars opercularis with the insula is a different architectonic area (see Fig. 2C; Economo and Koskinas, 1925) and was therefore not included in the region of interest. Thus, as can be seen in Fig. 1, the region of interest in this study included, apart from the cortex on the surface of the brain, the cortex of the posterior bank of the vertical ramus of the Sylvian fissure, the cortex on the lower bank of the inferior frontal sulcus and the cortex of the anterior bank of precentral sulcus up to the level of the inferior frontal sulcus. We defined the ventral limit of the region of interest as a straight line running from the ventromedial edge of the vertical ramus up to the ventralmost part of the precentral sulcus. When the diagonal sulcus was present at that position, the cortex lining it was also included as part of the region of interest. A straight line was drawn from the dorsalmost point of the vertical ramus up to the inferior frontal sulcus to delimit the dorsorostral limit of the region of interest, as the vertical ramus does not reach the inferior frontal sulcus. Similarly, whenever the inferior frontal sulcus did not merge with the precentral sulcus, a straight line was drawn from the dorsalmost point of the inferior frontal sulcus to the precentral sulcus to delimit the dorsocaudal limit of the region of interest.

Grey-matter labelling in the region of interest

The grey matter in the region of interest was mapped using DISPLAY, an interactive program developed at the Montreal Neurological Institute by J. D. MacDonald. This program permits labelling of voxel regions on each slice of the MRI volume and allows for the simultaneous visualization of the movement of the cursor on the screen within the sagittal, horizontal and coronal planes of the MRI. The movement of the cursor can also be viewed on a 3-D reconstruction of the brain surface (see Fig. 1). The reconstruction of the surface in 3-D of each brain was made by means of a 3-D model-based surface deformation algorithm (MacDonald, 1998).

The grey matter was estimated by selecting a range for the contrast intensity voxels following a DISPLAY procedure that produces a histogram of the full-brain MRI volume contrast intensity. The plotting of the contrast intensity for the full brain results, typically, in three peaks; the first indicates the ‘cerebrospinal’ fluid, the second the ‘grey matter’ and the third the ‘white matter’. The grey-matter range was determined by identifying the midpoint between the first and the second peaks and the midpoint between the second and the third peaks. The MRI intensities are imperfectly correlated with tissue type and always result in relative, not absolute, values (see Clarke et al., 1995; for review). These intensity values, however, should affect grey and white matter definition equally, and should therefore be consistent across the hemispheres of the same brain (for discussion see Paus et al., 1996 and Penhune et al., 1996). A selection of any area can be performed by using the DISPLAY ‘mouse brush’ that marks the voxels, by colouring. This colouring procedure accompanied by the simultaneous 3-D view of the MRI planes allows a better identification of the cortex contained in the depths of the sulci (see Fig. 1). The region of interest was first identified by the landmarks outlined above; then the area to be marked was brushed by the ‘mouse brush’ in DISPLAY. This act resulted in the selection by DISPLAY of those voxels previously defined as grey matter according to the established contrast ranges.

Generation of the probability map

The probability map of the region of interest was generated by averaging the labelled voxels of the individual grey matter volumes across the different normalized brains in the Talairach space.

Statistical analyses

We carried out separate statistical analyses of the volumes obtained in both the transformed standardized space (i.e. Talairach & Tournoux, 1988) and the nontransformed native space. The latter represents the original brain image obtained from each subject. In this manner, it was possible to obtain a better between-subject evaluation. By using the standardized space, size and site variability between subjects is reduced. On the other hand, the use of the native space permits a better comparison with previous investigations of the morphology of the inferior frontal gyri (e.g. Wada et al., 1975; Falzi et al., 1982).

To produce the voxel volumes in native space for each hemisphere, the procedure used to transform the brains in standardized space was inverted.

A correlation between the region-of-interest subject volumes obtained in standardized and in native spaces was carried out. In addition, the correlations between the left and right hemisphere on the region of interest volumes obtained in standardized and in native space were carried out. Interhemispheric grey-matter asymmetries were calculated on the grey matter volumes obtained in standardized and in native space separately with the asymmetry index used by Rademacher et al. (1993). The index was computed for each subject as follows: asymmetry = (left volume − right volume)/(left volume + right volume)/2. Then, a 2 × 2 χ² test (sex and side of the asymmetry index) was carried out for each space.

Moreover, two-factor ANOVA with the between-subject factor being sex (female vs. male) and the within subject factor being side (left vs. right hemisphere) in region of interest volumes, both in standardized and in native space, were carried out.

Results

The vertical ramus could not be identified in two of the cerebral hemispheres studied; this was also the case with the precentral sulcus in two different hemispheres. These four brains were excluded from the final analysis and, therefore, the results reported below are based on 100 cerebral hemispheres studied in 50 subjects. The region of interest was labelled bilaterally in the brains of 17 females aged 24.97 ± 10.19 years and 33 males aged 25.63 ± 7.18 years. There was no significant difference in age between males and females (t₁₄₈ = 0.266).

Morphological findings

The morphology of the pars opercularis, as visualized from the lateral view of each one of the 100 hemispheres examined, is presented in Fig. 3 (a and b) for the left hemisphere and in Fig. 4 (a and b) for the right hemisphere. The bright yellow represents the part which can be observed on the surface of the brain, whereas the pale yellow represents the part which is hidden within the sulci and can therefore not be visualized from the surface of the brain. As can be seen in Figs 3 and 4, there was
considerable variability in the shape of the pars opercularis. In some of the brains, almost the entire pars opercularis, appearing as a single or a double gyrus, was visible from the surface of the brain (Figs 1 and Fig. 5a); in other brains, a variable part of the pars opercularis was submerged in the inferior precentral sulcus (see Fig. 5b) and, in four left hemispheres and one right hemisphere, there was only one gyrus interspersed between the vertical ramus and the precentral sulcus, and this gyrus was completely submerged (see Fig. 3b, right half, subjects 34, 39, 41 and 42, and Fig. 4b, right half, subject 49, and also Fig. 6a and b). In such cases, the vertical ramus and the precentral sulcus could not be distinguished on the lateral surface of the brain (see red arrow in Fig. 6a and b), but they could be distinguished on axial sections of the brain (see white arrows in Fig. 6a and b).

Fig. 5. (a) An example of a brain in which the entire pars opercularis consisted of a double gyrus. (b) An example of a brain with a variable part of the pars opercularis submerged in the precentral sulcus. The solid blue line indicates the level of the horizontal section in b.
FIG. 6. (a and b) Two examples of brains in which there is only one gyrus interspersed between the vertical ramus (Vr) and the inferior precentral sulcus (Ps), and this gyrus was completely submerged. Note that in such cases, the vertical ramus and the inferior precentral sulcus cannot be distinguished on the lateral surface of the brain (see red arrow), but they can easily be identified on the horizontal sections of the brain (see white arrows).
Morphometric findings

Correlations

Across the different brains, there was an almost perfect linear relationship between the grey-matter volumes of the region of interest in standardized stereotaxic space and those in native space. This was true both for the region-of-interest volumes labelled in the left hemisphere ($r^2 = 0.89$, $P < 0.001$) and for those labelled in the right hemisphere ($r^2 = 0.91$, $P < 0.001$). This merely reflects the fact that values in standardized and in native space are simply transformations of one another.

As can be seen in Fig. 7, there was no significant linear relationship in the grey-matter volumes in the region of interest between the left and the right hemispheres. This was true in both standardized space (Fig. 7: $r^2 = 0.07$, $P = 0.059$) and in native space ($r^2 = 0.02$, $P = 0.318$).

An asymmetry score was calculated for each brain. A negative asymmetry score indicates that the volume of the left hemisphere is smaller than that of the right hemisphere, whereas a positive score indicates a smaller right-side volume. The distribution of interhemispheric asymmetry scores, grouped by sex, as well as the group means and standard deviations are shown in Fig. 8. There was no effect of sex on the distribution of which hemisphere had a greater overall grey-matter volume ($\chi^2 = 0.677$, $P = 0.41$).

Two separate ANOVAs for the volumes in standardized and in native space, respectively, did not reveal significant differences between the male and the female brains ($F_{1,48} = 1.22$, for standardized space; $F_{1,48} = 0.066$, for native space) in region-of-interest volumes or in the crucial comparison between left and right hemispheres ($F_{1,48} = 1.222$, for standardized space; $F_{1,48} = 0.868$, for native space). No significant interactions were obtained in either analyses ($F_{1,48} = 0.114$, for standardized space; $F_{1,48} = 0.065$, for native space; see Fig. 9a and b).

Probability map

The probability map of the pars opercularis constructed from the present analysis is shown in Fig. 10. This figure presents contour outlines for 18 coronal sections overlaid on grids corresponding to the Talairach & Tournoux (1988) stereotaxic space. These grids are taken 2 mm apart in the rostrocaudal direction ($Y$). $Y$ represents the distance of the coronal section rostral from the anterior commissure which, in the Talairach & Tournoux (1988) space, is defined as $Y = 0$. The dorsoventral direction ($Z$) is shown on the ordinate of the grid. The positive numbers represent distance in mm dorsal to the anterior commissure-posterior commissure horizontal line, which is defined as $Z = 0$, and the negative numbers refer to distance ventral to this line. The medial-to-lateral ($X$) distance relative to the midline ($X = 0$) is shown on the abscissa (positive numbers indicate right hemisphere and negative numbers left hemisphere). The white, grey, and black areas in the contour outline represent different ranges of frequency of occurrence of a given voxel in the region of interest (white = 5%-25%, grey = 25%-50%, black = 50%-75%). None of the voxels had a frequency of occurrence higher than 74%.

Discussion

Variability of the region of the pars opercularis

The present investigation examined the morphology of the pars opercularis of the inferior frontal gyrus in a large sample of normal human adult brains. This region, which is defined as the part of the inferior frontal gyrus that lies between the inferior precentral sulcus and the vertical ramus of the Sylvian fissure, exhibits considerable morphological variability. As can be seen in Figs 3 and 4, in some of the brains, the pars opercularis consists of two small convolutions, whereas in other brains only one can be identified. Furthermore, in some of the cases where there are two convolutions, one of these may lie on the surface of the brain while the other may lie hidden within the depth of the inferior precentral sulcus (see Fig. 5). This convolution may be completely or partially submerged. In four left hemispheres and one right hemisphere, there was only one convolution interspersed between the vertical ramus and the inferior precentral sulcus, and this was completely submerged. In such cases, the vertical ramus and the inferior precentral sulcus could not be distinguished on the lateral surface of the brain (see red arrow in

© 1999 European Neuroscience Association, European Journal of Neuroscience, 11, 3033–3046
Fig. 6), but they could easily be identified on horizontal sections of the brain (see white arrows in Fig. 6).

These findings have relevance to the identification of the anterior speech area by means of electrical stimulation in patients undergoing brain surgery. Rasmussen & Milner (1975) pointed out that speech arrest or interference with speech can occur as a result of electrical stimulation ‘from one or the other, or both of the two frontal opercular convolutions immediately anterior to the lower end of the precentral gyrus’ (see p. 241 of their paper). Ojemann (1979) also emphasized that this region of the inferior frontal gyrus is the part from which speech arrest with brain stimulation can most reliably be elicited, but he went on to stress the variability of the precise location within this region from which speech arrest can occur. Although some of this variability may be due to variability in the stimulation parameters and the nature of the behavioural response required, the possibility that this variability also reflects morphological differences must seriously be entertained. For instance, in brains where all or a part of the pars opercularis is submerged in the inferior precentral sulcus, electrical stimulation may evoke motor responses as a result of stimulating the precentral gyrus, just posterior, but no or only minor speech interference may be evoked from stimulation immediately in front of it because the critical area may be lying largely within the precentral sulcus.

Diagonal sulcus

The diagonal sulcus is a small sulcus that is present in the pars opercularis (Eberstaller, 1890; Bailey & Bonin, 1951). It may lie within the pars opercularis without joining any of the sulci that surround the pars opercularis, or it may join, dorsally, the inferior frontal sulcus or the inferior precentral sulcus, caudally. The lower end of the diagonal sulcus may flow into the Sylvian fissure or it may stay clearly separate from it, separated by a bridge of cortex (Eberstaller, 1890; in Bailey & Bonin, 1951). Whereas Turner (1948) mentioned that the diagonal sulcus is a regular feature of the human brain, Bailey & Bonin (1951) reported that it is by no means a constant feature of the human brain. Recently Ono et al. (1990) reported the presence of the diagonal sulcus in 64% of the right and 72% of the left cerebral hemispheres that they examined. Galaburda (1980), however, on the basis of inspection of the photographs of 102 brains studied by Geschwind & Levitsky (1968) found the diagonal sulcus in 26.5% in the left hemisphere and 12.75% in the right one. In the present study, the diagonal sulcus, as shown in the maps of Brodmann (1908, 1909) and Economo & Koskinas (1925) could clearly be identified in 34% of the left and 32% of the right hemispheres. In addition, we observed a small dimple between the inferior precentral sulcus and the vertical ramus in almost all the hemispheres studied. The discrepancies in the reported incidence of the diagonal sulcus are probably due to the different criteria in defining it.

Morphometry

Although Wada et al. (1975) demonstrated a rightward asymmetry in the region of the inferior frontal gyrus that included the pars opercularis and a part of the pars triangularis, they suggested that a leftward asymmetry in this region might have been observed if the cortex lying in the sulci were to be included in the measurements. Indeed, Falzi et al. (1982) reported a leftward
asymmetry in this region, as did Foundas et al. (1996, 1998) in separate measurements of the pars triangularis and pars opercularis. The present investigation, in which measurements were made both of cortex lying on the lateral surface of the pars opercularis and cortex hidden in the sulci, did not reveal differences in cortical volume between the left and right hemispheres. The above discrepancies may have been due to the different extent to which specific cytoarchitectonic areas may have been included in the measurements. For instance, Galaburda (1980) reported that six out of 10 brains had a leftward asymmetry in area 44.

**Probability map**

The present study has provided a probability map of the pars opercularis within the Talairach and Tournoux proportional stereotaxic space (see Fig. 10). This map can be used to localize activation foci obtained in functional neuroimaging studies, within the pars opercularis region of the inferior frontal gyrus. The classical model of language organization in the human brain, which is based on clinical–anatomical correlations, posits the existence of an anterior speech area, located on the posterior part of the inferior frontal gyrus in the dominant hemisphere, that is involved in speech production (see Fig. 10).
Geschwind, (1970). Electrical stimulation studies during brain surgery indicate that the critical region for evoking speech interference is in the one or two convolutions immediately anterior to the precentral sulcus (Rasmussen & Milner, 1975; Ojemann, 1979). However, functional activation studies with PET have demonstrated that activation related to speech varies considerably between different studies, suggesting that the activation focus or foci within the inferior frontal lobe of the dominant hemisphere may vary depending on the specific requirement of the language task used (e.g. Petersen et al., 1988, 1990; Paulesa et al., 1993, 1997; Petrides et al., 1993). The availability of a probability map therefore becomes critical for establishing, with a known probability, whether the activation focus lies within the pars opercularis or whether it lies just anterior, in the pars triangularis, or just posterior, in the premotor cortex of the lower precentral gyrus.

Abbreviations

Hr, horizontal ramus of the Sylvian fissure; IFs, inferior frontal sulcus; PET, positron emission tomography; Ps, precentral sulcus; Sf, Sylvian fissure; Vr, vertical ramus of the Sylvian fissure.

References


