Available online at www.sciencedirect.com
ScienceDirect
Psychiatry Research: Neuroimaging 148 (2006) 151–163
PSYCHIATRY RESEARCH NEUROIMAGING
www.elsevier.com/locate/psychresns

Inter-rater reliability of manual segmentation of the superior, inferior and middle frontal gyri

John P. John[a,b,*], Lei Wang[b], Amanda J. Moffitt[b], Harmeeta K. Singh[b], Mokhtar H. Gado[c], John G. Csernansky[b,d]

[a]*Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560 029, Karnataka, India*
[b]*Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, United States*
[c]*Radiology, Washington University School of Medicine, St. Louis, MO, United States*
[d]*Anatomy and Neurobiology, Washington University School of Medicine, St. Louis, MO, United States*

Received 13 February 2006; received in revised form 28 April 2006; accepted 13 May 2006

Abstract

Precise rules for locating the anatomical boundaries of the dorsolateral prefrontal cortex (DLPFC) or its subdivisions, i.e., superior, inferior and middle frontal gyri (SFG, IFG and MFG) on magnetic resonance images (MRI), have not been defined. The present study describes the inter-rater reliability of manual segmentation of the SFG, IFG and MFG using guidelines based on sulcal–gyral anatomical boundaries as well as the cytoarchitectonic features of the sub-regions of the prefrontal cortex (PFC). Variations in the application of these guidelines in different subjects to account for normal sulcal variability were developed using the atlas of Ono et al. (Ono, M., Kubik, S., Abernathey, C.D., 1990. Atlas of the Cerebral Sulci. Georg Thieme Verlag, New York). Based on previous cytoarchitectonic studies, the coronal plane of the anterior termination of olfactory sulcus (ATOS) was used as a landmark for delimiting the boundary between the frontal pole (FP) and the frontal gyri. The left hemisphere gray-matter volumes of the SFG, IFG and MFG were determined using a set of 10 MRIs (5 normal and 5 schizophrenia subjects) by two trained raters independently. The intra-class correlation coefficients (ICC) for the SFG, IFG and MFG volumes by the two raters were 0.97, 0.94 and 0.93, respectively. Thus, we describe a reliable method of parcellating the SFG, IFG and MFG, which constitute the DLPFC, a brain region involved in a variety of neuropsychiatric conditions.

Keywords: DLPFC; Superior; Inferior; Middle; Frontal gyri; Parcellation; MRI; Schizophrenia

Abbreviations: aHR, anterior horizontal ramus; ATOS, anterior termination of the olfactory sulcus; CC, corpus callosum; CiG, cingulate gyrus; CiS, cingulate sulcus; CSI, circular sulcus of insula; DLPFC, dorsolateral prefrontal cortex; FMS, fronto-marginal sulcus; FP, frontal pole; ICC, intra-class correlation coefficient; IFG, inferior frontal gyrus; IFS, inferior frontal sulcus; LOS, lateral orbital sulcus; MaPCS, marginal pre-central sulcus; MFG, middle frontal gyrus; MFS, middle (intermediate) frontal sulcus; MPFC, medial prefrontal cortex; OPFC, orbital prefrontal cortex; OS, olfactory sulcus; PaCiG, paracingulate gyrus; PaCiS, paracingulate sulcus; PaCS, paracentral sulcus; PCG, precentral gyrus; PCS, precentral sulcus; PFC, prefrontal cortex; SF, Sylvian Fissure; SFG, superior frontal gyrus; SMA, supplementary motor area; SRS, superior frontal sulcus.

* Corresponding author. Department of Psychiatry, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560 029, Karnataka, India. Tel.: +91 80 26995349/26995306; fax: +91 80 26564822.
E-mail addresses: jpj@nimhans.kar.nic.in, jpjinc@yahoo.com (J.P. John).

0925-4927/$ - see front matter © 2006 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.pscychresns.2006.05.006

1. Introduction

Structural and functional abnormalities of the frontal lobes, and more specifically the prefrontal cortex (PFC), have been suggested to play a central role in neuropsychiatric conditions such as schizophrenia (Andreasen, 1997) and depression (Drevets, 2000). The PFC, usually defined as the part of the frontal cortex anterior to the precentral sulcus (PCS), is the most phylogenetically advanced area of the cerebral cortex (Brodmann, 1909; Ariëns Kappers et al., 1960; Poliakov, 1966; Fuster, 1997). In structural imaging studies, the term 'pre-frontal' generally refers to that portion of the frontal cortex anterior to the pre-central gyrus (PCG) (Duffy and Campbell, 2001).

The PFC is a heterogeneous region comprising several areas that are distinct at the cytoarchitectural and functional levels (Brodmann, 1909; Economo and Koskinas, 1925; Sarkisov, 1955; Preuss and Goldman-Rakic, 1991; Petrides and Pandya, 1999). The lateral PFC, usually referred to as the dorsolateral prefrontal cortex (DLPFC) is considered the central executive for cognitive control. Through its sub-cortical connections, the DLPFC mediates attentional processes, memory, language functions, as well as executive functions that include planning, working memory, selective attention and set shifting. Volumetric and neuropathological abnormalities of the DLPFC have been reported in schizophrenia (Zipursky et al., 1992; Selemon et al., 2002). The term DLPFC is commonly used to refer to the lateral convexity of the frontal lobe and comprises of the inferior frontal gyrus (IFG), the middle frontal gyrus (MFG) and the lateral aspect of the superior frontal gyrus (SFG).

Shenton et al. (2001) highlighted the importance of studying different sub-regions of the PFC with as much precision as possible, in view of the fact that different sub-regions of the frontal lobe have quite different and specific brain functions. Additionally, previous neuropathological studies in schizophrenia have reported abnormalities in specific areas within the frontal lobe, providing support to the above notion (Benes et al., 1986).

Other experts have offered guidelines for the anatomical parcellation of the PFC and its major components (Crespo-Facorro et al., 1999; Wible et al., 1997; Rademacher et al., 1992). However, these studies have employed varying definitions for defining the sub-regions. For example, Crespo-Facorro et al. (1999) included the cortex up to the tip of the frontal pole (FP) as part of the superior, middle and inferior frontal gyri, whereas Wible et al. (1997) defined the FP as the anterior-most 10 "slices" of the brain. The variability of these guidelines highlights the importance of striving for uniformity in the parcellation of the sub-divisions of the PFC, especially their anterior boundaries.

Previous studies have utilized reference planes to delimit areas where there are no clear-cut sulcal separations. The use of reference planes has been justified because of the tremendous inter-individual and inter-hemispheric variation in sulcal–gyral patterns, which can make the application of anatomical landmarks to delimit the subdivisions of the PFC extremely difficult. Moreover, a clear-cut relationship between gross anatomical areas defined by the surface patterns of sulci and gyri, cortical areas delimited by microstructural borders, cytoarchitectonic areas, and functional domains has not been conclusively demonstrated (Roland and Zilles, 1998; Wible et al., 1997). However, the use of reference planes introduces unwanted arbitrariness into the definition of the sub-regions of the PFC and inconsistencies in measurements across studies that use different reference planes (Wible et al., 1997).

Since the anatomical boundaries of the DLPFC have not been precisely defined, we aimed at defining and developing a method of parcellating the gyri that constitute the DLPFC, viz., SFG, IFG and MFG. In the present study, the SFG was demarcated with reference to its sulcal boundaries, and therefore both the medial as well as the lateral parts of the gyrus were delineated. However it must be borne in mind that DLPFC includes only the part of SFG on the lateral convexity of the brain. Thus, in this article, we present a method of parcellating the SFG, IFG and MFG using sulcal–gyral patterns wherever possible, and taking into account known sulcal variations (Ono et al., 1990). Where sulcal–gyral patterns could not be employed for this purpose, we referred to existing knowledge of cytoarchitectonic differences within the various sub-regions to frame rules for parcellation. The primary objective of this study was to improve the reliability and uniformity of parcellation of the three prefrontal gyri – in the absence of a gold standard to prove validity – using a set of guidelines that has its foundations in functional neuroanatomy, thereby arriving at precise and reliable definitions for volumetric comparisons of these gyri in schizophrenia subjects and healthy controls.

2. Materials and methods

2.1. Subjects

Magnetic resonance (MR) scans acquired from five healthy control subjects and five subjects with schizophrenia, randomly selected from a pool of subjects recruited for a longitudinal study of schizophrenia conducted by one of the authors (J.G.C.), were used for

the study. We included both schizophrenia subjects and healthy control subjects in this study to lay the groundwork for further comparisons of these two groups. The healthy control subjects were ascertained to have no present or past neuropsychiatric disorders; in addition, there was no history of psychotic disorders in their first-degree relatives. The subjects with schizophrenia were diagnosed using criteria from the Diagnostic and Statistical Manual for Mental Disorders-Fourth edition (DSM-IV) (American Psychiatric Association, 1994) based on the consensus of a research psychiatrist who conducted a semi-structured interview and a trained research assistant who used the Structured Clinical Interview for DSM-IV (SCID-IV; First et al., 1995). The exclusion criteria for both groups of subjects included unstable medical conditions, head injury with loss of consciousness, and substance abuse or dependence meeting DSM-IV criteria during the 3 months preceding the study.

Three of the five control subjects were males while all the five schizophrenia subjects were males. All the control subjects were right-handed, whereas among the schizophrenia subjects, three were right-handed and two left-handed. The mean age of the control group was 20.6 (S.D. = 3.1) years while that of the schizophrenia group was 22.7 (S.D. = 4.7) years.

2.2. Image acquisition and processing

MR scans were acquired using an MPRAGE sequence (TR = 9.7 ms, TE = 4 ms, flip angle = 10°, section thickness = 1.25 mm, field of view = 256 × 256 mm, matrix = 256 × 256, number of acquisitions = 1, number of slices = 128, scanning time = 6 min, 36 s) that acquires 1.25 mm × 1 mm × 1 mm voxels across the entire cranium. The raw MR data were reformatted using Analyze™ 6.0 software (Robb et al., 1989) from signed 16-bit MR data sets to unsigned 8-bit MR data sets, using the voxel intensities in the corpus callosum (CC) and the lateral ventricle as limiting values. MR scans were then interpolated into 0.5 mm × 0.5 mm × 0.5 mm isotropic voxels using trilinear interpolation. The scans were then rotated into AC–PC coordinates.

The skull in the MR image was removed using an automated brain extraction program (Sandor and Leahy, 1997; Shattuck and Leahy, 2001) using Brainsuite (Version 0.20 alpha). The skull-stripped cerebral images were then binarized [typically, the threshold values ranged from 90–100 (minimum) to 255 (maximum)] to expose the cortical sulcal patterns at the approximate pial surface in 3-D view (see Fig. 3B). The sulcal patterns in these binarized 3-D cerebral renderings as identified by the atlas texts were then used as a visual guide in manual outlining of SFG, IFG and MFG.

2.3. Segmentation guidelines

The guidelines for parcellation of the SFG, IFG and MFG, were developed by two of the authors (J.P.J. and M.H.G.) using a non-overlapping set of five MR scans and the brain atlas by Duvernoy (1999). Variations in the application of these guidelines in different individuals were developed using the atlas of Ono et al. (1990), to account for normative sulcal variability. Two raters (H.K.S. and A.J.M.) were then trained in the application of these guidelines using the "learning set" of 5 MR scans. More specifically, the raters were trained to identify the limiting sulci and to apply conventions to be followed in instances where the limiting sulci were interrupted. The raters were also trained in the guidelines to be followed in relationship to the described sulcal variations in Ono et al. (1990).

The trained raters performed independent manual segmentations using the "test" set of 10 MR scans selected from a pool of available MR scans (see above). Manual outlining of the contours of the gray matter of SFG, IFG and MFG in the left hemisphere was performed using Analyze™ 6.0 software (Robb et al., 1989) on successive coronal sections, with frequent reference to the corresponding axial and sagittal sections, as well as views of the binarized 3-D cerebral renderings. The following convention was followed whenever the limiting sulci were discontinuous. When a particular sulcus could not be visualized in consecutive coronal sections, the tracing from the coronal section that last contained the sulcus was copied onto the neighboring sections until the sulcus could be visualized again. This allowed the joining of 'broken' sulci along straight lines that represented the shortest distance in the AC–PC plane. Training of the raters in this "bridging method" was straightforward and facilitated manual parcellation of neocortical sub-regions where substantial sulcal variability was encountered.

2.4. Neuroanatomical definitions

2.4.1. Superior frontal gyrus

The SFG is a functionally heterogeneous frontal subregion (Passingham, 1993; Roland, 1993), and can be visualized on the medial, superior and lateral aspects of the frontal lobe. On the medial aspect, it includes Brodmann's area (BA) 6, which is the supplementary motor cortex. Further rostral to BA 6 on the medial side are (BA 8 and 9. The paracingulate gyrus (PaCiG), which consists of a cingulo-frontal transitional cytoarchitecture (BA 32

and 32′) and is known to be cytoarchitectonically distinct from the cingulate gyrus (CiG) (Stark et al., 2004), was included as part of the SFG. The lateral convexity is constituted by BA 6, 8 and 9. However, BA 46 and 9/46 (Rajkowska and Goldman-Rakic, 1995a,b) are also present at the transition zone with the MFG. A landmark-based definition of the anterior extent of the SFG was used considering the fact that there are no consistent sulcal boundaries that delineate the SFG (BA 6, 8, 9, 32, 32′) from the cytoarchitectonically distinct frontal pole (FP) (BA 10) anteriorly. The plane of the anterior termination of the olfactory sulcus (ATOS) was used for this purpose as detailed later, based on the evidence accrued from previous cytoarchitectonic studies (Ongur et al., 2003, Semendeferi et al., 2001, Hof et al., 1995) (Fig. 1A–D).

2.4.1.1. Posterior boundaries. On the lateral convexity of the brain, the superior PCS is the posterior boundary of the SFG in the typical case of a two-segment type of PCS, or when the PCS has three segments. If the superior PCS has a forked termination, the most posterior of the two limbs is considered as the posterior boundary of the SFG. The posterior limit of the marginal pre-central sulcus (MaPCS) forms the posterior boundary of the SFG, when it constitutes the superior-most segment of the PCS. Medially, the PaCS is used to define the posterior boundary of the SFG. This sulcus occurs most commonly as a sulcus from the lateral surface (an extension of the superior PCS or the medial PCS of Eberstaller), as a branch of the cingulate sulcus (CiS), or both (Ono et al., 1990). The PaCS can also be used to define the posterior border of the supplementary motor area (SMA) on the medial wall (Crespo-Facorro et al., 1999). The SMA occupies the posterior part of SFG (Chainay et al., 2004; Zilles et al., 1996).

2.4.1.2. Infero-lateral boundaries. On the lateral aspect of the cerebral hemisphere, the inferior boundary is the superior frontal sulcus (SFS). Posteriorly, the SFS is almost always connected to the PCS (Ono et al., 1990). In cases where the two are not connected, the posterior end of the SFS can be connected to the PCS using the general procedure for bridging broken sulci described above. When the SFS is itself present as an interrupted sulcus, the individual segments are similarly connected to ensure anatomical continuity of the gyrus.

2.4.1.3. Anterior boundaries. Anteriorly, the SFG is limited by the posterior extent of the FP. The definition of the FP is based on cytoarchitectonic features of subdivisions in the area, since there is no sulcal delimitation. The FP extends onto the lateral, orbital and medial surfaces of the cortex, and contains BA 10 in both monkeys and humans (Chiavaras et al., 2001). The

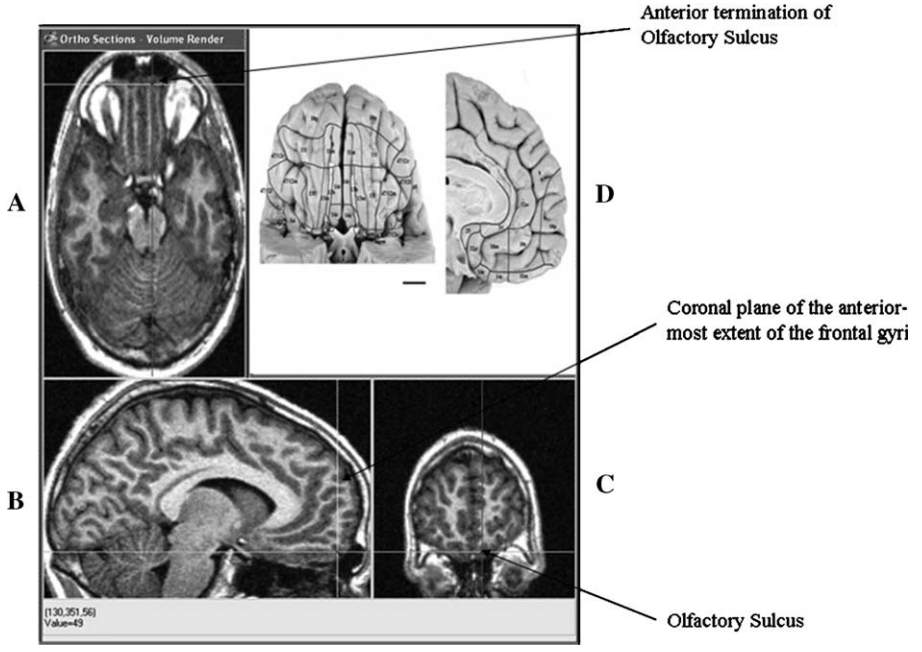

Fig. 1. (A) Axial, (B) sagittal and (C) coronal sections depicting the plane of the Anterior Termination of the Olfactory Sulcus (ATOS) that is used as a landmark to define the anterior limit of the frontal gyri. (D) Cytoarchitectonic subdivisions of the human orbital and medial surfaces (Ongur et al., 2003) (reproduced with permission from Wiley-Liss Inc.).

frontal cortex anterior to the termination of olfactory sulcus (OS) on the orbital and medial surfaces has been labeled as area 10p by Ongur et al. (2003; ref. Fig. 1D). BA 10 is bordered by areas 14 and 11 on the ventral surface, by areas 9, 46 and 47/12 on the lateral convexity, and by areas 9, 32 and 14 on the sagittal surface (Chiavaras et al., 2001). Ongur et al. (2003) also describe areas 10m, 10r and 10p that occupy most of the ventral half of the medial wall from area 32pl to the anterior tip of the hemisphere (Fig. 1D). However, from a phylogenetic evolutionary perspective, area 10p is the equivalent of area 10o in monkeys and occupies the rostral orbital region of the FP. This area was designated as 10p by Ongur et al. (2003), considering its high level of differentiation as compared to the area 10o of the monkey brain and because of its position, size and distinct structure. Semendeferi et al. (2001) have also extensively studied the cytoarchitectonics of the FP, and their findings agree with the cytoarchitectonic maps of Brodmann (1909), Sarkisov (1955) and Economo and Koskinas (1925) suggesting that in the human, the FP is constituted by BA 10. Thus, the area comprising the FP (described as BA10 or BA 10p as mentioned above) is distinct from neighbouring areas, is phylogenetically more evolved, and has distinct connections with higher-order association areas (Semendeferi et al., 2001). These studies form the rationale for dividing the FP from the three frontal gyri in volumetric studies of the brain.

Unfortunately, there is no sulcal boundary to delimit the FP (BA 10) from the frontal gyri. Therefore, landmarks were identified to demarcate these cytoarchitectonically and functionally heterogeneous areas. We evaluated the anterior termination of the OS (ATOS) for this purpose. Based on a careful study of the cytoarchitectonic maps of Brodmann (1909), Sarkisov (1955) and Economo and Koskinas (1925), as well as the results of the study of architectonic subdivisions of the human orbital and medial PFC by Ongur et al. (2003), Semendeferi et al. (2001) and Hof et al. (1995), we concluded that the posterior limit of the FP (BA 10) could be best defined as the coronal section passing through the ATOS (Fig. 1A–D).

OS is the least variable orbitofrontal sulcus (Chiavaras et al., 2001), with an overlapping surface in over 90% of subjects (Kringelbach and Rolls, 2004). It is the first orbitofrontal sulcus to appear during development, is visible at 16 weeks (Chi et al., 1977) and so is comparable to the inter-hemispheric and transverse cerebral fissures (at 8 weeks), the Sylvian fissure (SF) and callosal sulcus (at 14 weeks), the calcarine fissure (at 16 weeks) and the central sulcus (at 20 weeks) (Kringelbach and Rolls, 2004). The ATOS was chosen as a reference guide to separate the FP from the rest of the frontal lobe inferiorly and medially, based on the fact that it appears to separate BA 10 in front from BA 11 behind on the orbital surface and area 10r on the medial surface (Ongur et al., 2003; ref. Fig. 1D), in the absence of any naturally occurring sulcal separation between FP and posterior structures. The study of BA 10 by Semendeferi et al. (2001) indicates that this coronal plane may be a useful boundary on the lateral convexity as well. Therefore, regardless of any naturally occurring sulcal boundary, the anterior limit of the SFG was defined as the plane of the ATOS, to maintain conformity.

2.4.1.4. Infero-medial boundaries. Infero-medially, the CiS forms the boundary of the SFG (Crespo-Facorro et al., 1999). In case of an interrupted CiS, the segments are again connected using the general guidelines described above. Ono et al. (1990, p. 113) state that a double-parallel type of CiS, enclosing the PaCiG in between the two segments, is found in 24% of brains on the right and left sides. However, other researchers report that the paracingulate sulcus (PaCiS) is present in a variable percentage of individuals on either hemisphere (Fornito et al., 2004; Le Provost et al., 2003; Yucel et al., 2002). The PaCiG, which is enclosed by the CiS and PaCiS, is cytoarchitectonically distinct from the cingulate gyrus (CiG) and consists mainly of a cingulo-frontal transitional zone (Stark et al., 2004). Thus, in order to ensure consistency in the definition of the inferior boundary of the SFG on the medial wall, the CiS is taken as the inferior limit of the SFG; the PaCiG, if present, is considered as part of the SFG. More anteriorly on the medial aspect, the superior rostral sulcus (SRS) constitutes the inferior boundary (Crespo-Facorro et al., 1999). SRS may have a connection to the CiS or exists separate from it. If the SRS is unconnected to the CiS, the inferior boundary of the SFG is completed by extending the posterior aspect of SRS to intersect the CiS (Crespo-Facorro et al., 1999).

There may be more than one sulcus running in an antero-posterior direction on the medial surface of the anterior part of the frontal lobe. These are variously described as SRS, the inferior rostral sulcus (Ono et al., 1990), the susorbital sulcus (Duvernoy, first edition, 1991) and the supraorbital sulcus (Duvernoy, second edition, 1999). The SRS is the most superior of these antero-posterior sulci. Crespo-Facorro et al. (2000a,b) have suggested that when there is difficulty in identifying the SRS, it should be defined as the sulcus most nearly above the AC–PC axis on the anterior portion of the medial surface of the cerebrum. However, we defined the SRS as the superior-most of the supra-orbital sulci,

and which is closest to a line in the mid-sagittal plane that is parallel to the AC–PC line and passing through the highest point on the inferior border of the body of the CC (Fig. 2).

2.4.2. Inferior frontal gyrus

The IFG is identified as the inferior-most of the three frontal gyri running an antero-posterior course on the lateral convexity of the frontal lobe. The IFG is subdivided by the anterior ascending ramus and the anterior horizontal ramus (aHR), stemming from the anterior segment of the lateral part of the SF, into pars opercularis, pars triangularis and pars orbitalis (Ebeling et al., 1989). The pars opercularis of the IFG is constituted by BA 44, the pars triangularis by BA 45 and 46 and the pars orbitalis by BA 45 and 47.

2.4.2.1. Posterior boundaries. The posterior boundary of the IFG is the inferior PCS. In cases where the inferior PCS does not connect to the lateral part of the SF, the inferior end of the PCS is extended to the SF to complete the posterior border. In the event of a double parallel type of PCS, the most posterior of the two limbs is taken as the posterior limit of the IFG (reference: http://ucla/loni).

2.4.2.2. Superior boundaries. The inferior frontal sulcus (IFS) represents the superior boundary of IFG throughout its length. When the IFS is interrupted, the segments are connected to complete the superior border. In cases where the IFS does not connect to the inferior PCS, the posterior end of the IFS is extended to connect to the inferior PCS.

2.4.2.3. Anterior boundaries. The anterior limit of the IFG is defined as the coronal plane at which the IFS joins the lateral orbital sulcus (LOS) (this is the case in 16% of left brains and 20% of right brains) or the fronto-marginal sulcus (FMS) (right: 4%; left: 4%) (Ono et al., 1990, p. 56). This coronal plane is usually posterior to the plane of the ATOS. In rare cases, these sulci intersect at a coronal plane anterior to ATOS. In such instances, the plane of the ATOS is taken to be the anterior limit of the IFG. In cases where the IFS does not connect with the LOS or FMS, the anterior limit of the IFG is defined by connecting the IFS with the LOS or FMS using the 'bridging method'.

2.4.2.4. Inferior boundaries. The inferior extent of the IFG consists of the FMS and LOS anteriorly and the junction of the anterior, middle and posterior segments of the lateral part of SF (Duvernoy, 1999) as well as the circular sulcus of insula (CSI) posteriorly. This boundary is highly variable anteriorly, and depends somewhat on the positions of the LOS and the aHR of the SF. The guidelines presented below consider each of several possibilities to ensure that the pars orbitalis and the pars triangularis are preserved within the IFG, as these are structures of the IFG.

The LOS is present as an uninterrupted sulcus without connections in 32% of right brains and 48% of left brains (Ono et al., 1990, p. 92). In 20% of brains on either side, it is connected to the IFS, and the IFG is enclosed by these sulci. The LOS terminates inferior to the aHR in 44% of right and left brains (Ono et al., 1990, p. 93). In these cases, the LOS is extended to connect with the lateral part of the SF to form the inferior boundary. In cases where the LOS terminates blindly at the same horizontal (AC–PC) plane as the aHR (right: 16%; left: 12%), these two are connected to form the inferior boundary. In cases where the LOS terminates between the aHR and the ascending ramus (right: 32%;

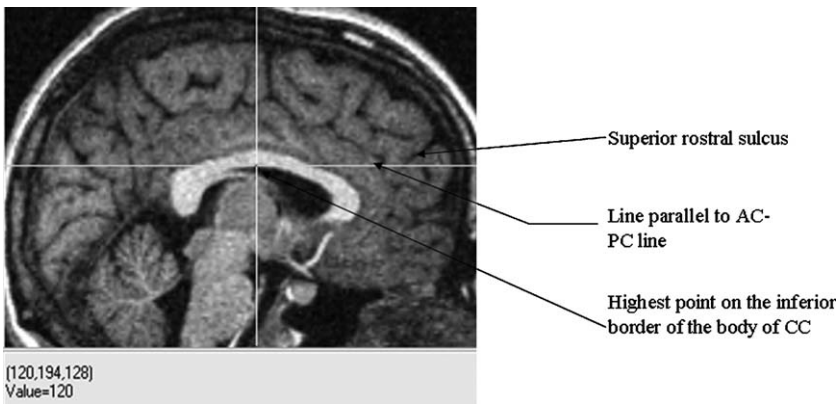

Fig. 2. Application of the guideline to identify the superior rostral sulcus (SRS).

left: 36%) (i.e., when the LOS runs into the pars triangularis), the LOS in the coronal plane that contains the anterior-most extent of the IFG and the anterior end of the aHR are connected. In the case of an absent LOS [8% on left and right each, (Ono et al., 1990, p. 92)], the aHR forms the inferior boundary of the IFG. In these cases, the anterior end of the aHR is extended anteriorly to the coronal plane at which IFS connects with the FMS. If the aHR is absent [right: 8%; left: 16%, (Ono et al., 1990, p. 142)], the posterior end of LOS is connected to the lateral part of the SF.

2.4.3. Middle frontal gyrus

The MFG lies between the SFG and IFG and constitutes the major component of the DLPFC (Rajkowska and Goldman-Rakic, 1995a). It is involved in performance of executive functions; however, the frontal eye field is also located within the posterior aspect of the MFG. The

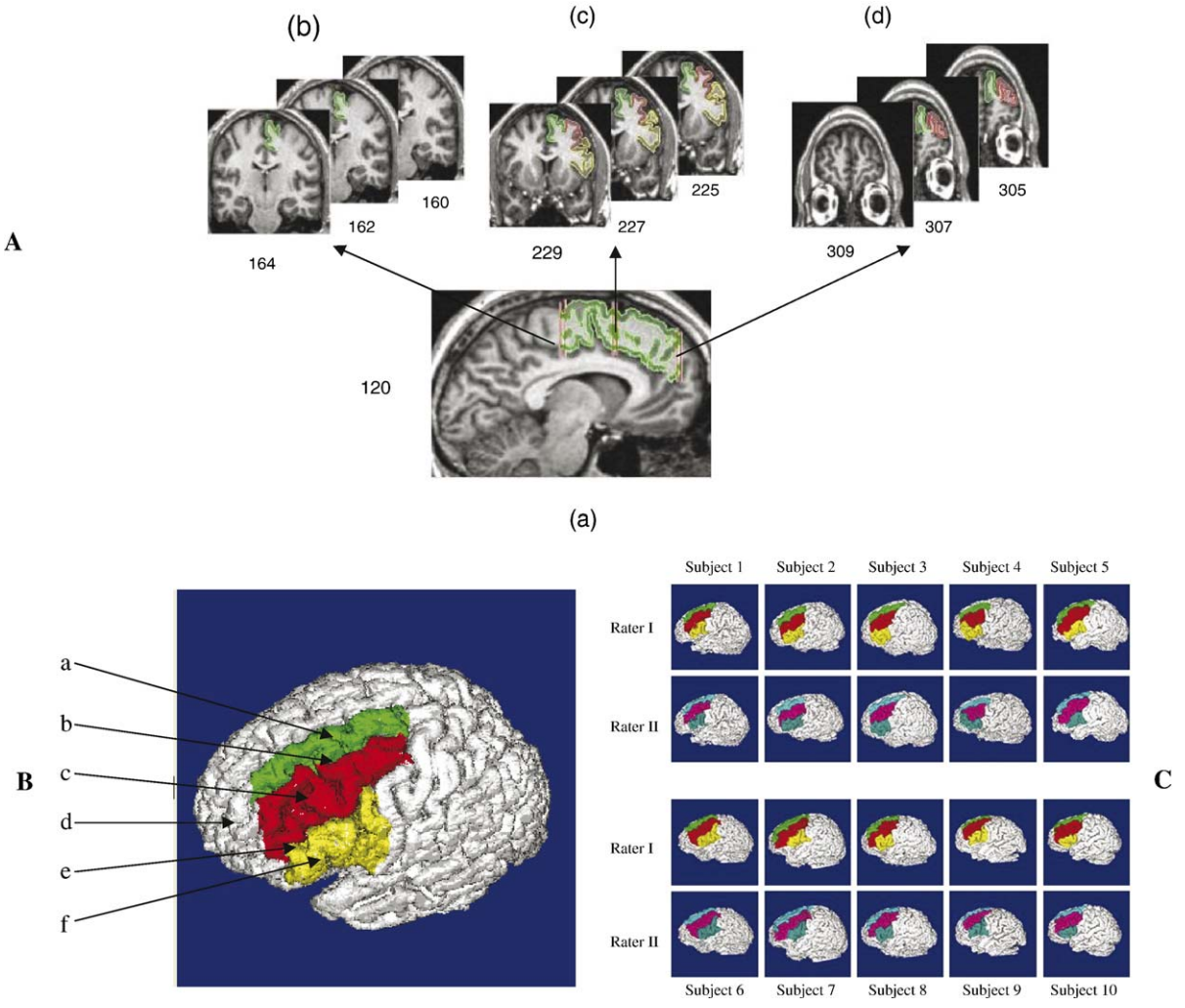

Fig. 3. A: Contiguous but alternate coronal sections showing the tracings of the left superior, middle and inferior frontal gyri (SFG, MFG and IFG). The SFG is depicted in green, the MFG in red and the IFG in yellow. (a) Mid-line sagittal section (slice no. 120) showing the tracing of the SFG. (b) Three contiguous but alternate coronal sections around the posterior boundary; slice no. 162 is the last coronal section containing the SFG. (c) Three contiguous but alternate coronal sections depicting the SFG, MFG and IFG. (d) Three contiguous but alternate coronal sections around the anterior boundary at the junction with the posterior boundary of the frontal pole (FP); slice no. 307 is the first coronal section containing the frontal gyri. In this case, the plane of the anterior termination of the olfactory sulcus (ATOS) was identified as slice no. 308. B: A typical binarized 3-D cerebral rendering on which the object maps of the left superior, middle and inferior frontal gyri are superimposed. a — SFG; b — superior frontal sulcus; c — MFG; d — FP; e — inferior frontal sulcus; f — IFG. C: 3-D cerebral renderings with superimposed object maps of the SFG, MFG and IFG for all the ten subjects generated by the two independent raters.

MFG is comprised of BA 46, 9, 9/46 as well as 6 and 8 (Rajkowska and Goldman-Rakic, 1995b; Petrides and Pandya, 1999).

2.4.3.1. Superior boundaries. The SFS forms the superior boundary of the MFG. The guidelines to be followed when the SFS exists as an interrupted sulcus and when it is not connected to the PCS are described under tracing guidelines of the SFG.

2.4.3.2. Inferior boundaries. The IFS forms the inferior boundary of the MFG. The rules to be followed to account for the variability in the patterns of IFS are mentioned under tracing guidelines for IFG. Anteriorly, the LOS or the FMS constitute the inferior boundary of the MFG in certain cases, separating it from the OPFC.

2.4.3.3. Posterior boundaries. This boundary is formed by the PCS (superior, inferior, and or intermediate segments) (Ono et al., 1990).

2.4.3.4. Anterior boundaries. The anterior limit of the MFG is determined by the plane of the ATOS as described under SFG, regardless of any naturally occurring sulci. This rule was necessitated due to the fact that no sulcus has been described so far that consistently delimits the MFG anteriorly and separates it from the FP in front. In cases where there is the unlikely event of a naturally occurring sulcus that completely delimits the MFG anteriorly, the point where the FMS or LOS meet the IFS is selected and extended anteriorly to the coronal plane of the ATOS. The SFS is also extended anteriorly to this same plane to complete the superior boundary of the MFG in such instances.

The MFG is usually divided into a superior and inferior portion by the middle (intermediate) frontal sulcus (MFS).

Fig. 3A depicts contiguous coronal sections showing the tracings of the three frontal gyri around the posterior boundary (b), the mid-section (c) and around the anterior boundary (d).

2.4.4. Cortical volume measurements and inter-rater reliability

After manual segmentation, gray matter volumes were calculated using Analyze™ 6.0 software (Robb et al., 1989) by multiplying the number of voxels assigned to each gyrus by 0.125 mm^3, which is the volume of one voxel (0.5 mm × 0.5 mm × 0.5 mm). The inter-rater reliability of manual segmentation for each of the three gyri was estimated by calculating the intra-class *R* coefficient (ICC) of gray matter volumes generated by the two raters. The extent of overlap between the two segmentations was also calculated by superimposing the manual tracing of the second rater over the first, and determining the proportion of shared voxels using the following equation:

$$\text{Voxel \% overlap} = \frac{\text{Vox}_1 \cap \text{Vox}_2}{\text{Vox}_1} \times 100.$$

Additionally, the ratio of the intersection and union (I/U) was determined separately for the SFG, IFG and MFG by $\frac{\text{Vox}_1 \cap \text{Vox}_2}{\text{Vox}_1 \cup \text{Vox}_2} \times 100$.

3. Results

A typical object map of the SFG, IFG and MFG superimposed on the binarized 3-D cerebral rendering is shown in Fig. 3B. Fig. 3C shows the 3-D cerebral renderings as an array with the superimposed object maps

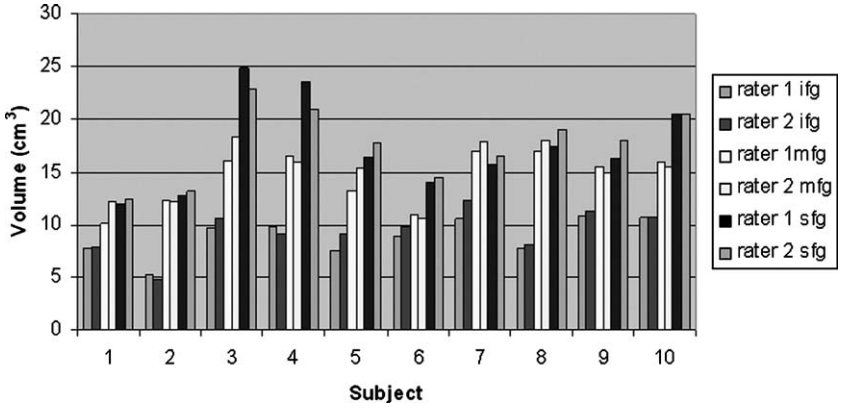

Fig. 4. Graphical plot of the volumes of the left inferior, middle and superior frontal gyri generated by the two raters for each of the ten subjects.

of the three frontal gyri generated by the two raters for all the ten subjects.

3.1. Inter-rater reliability of gray matter volumes

The mean cortical gray matter volumes (cm^3) of the SFG, IFG and MFG (averaged across both raters in all ten subjects) were 17.45 (S.D.=3.82), 9.11 (S.D.=1.91) and 14.76 (S.D.=2.60) respectively. The ICC for the volume measures were 0.97, 0.94 and 0.93 respectively for the SFG, IFG and MFG, and the voxel overlap percentages were 81.2 (S.D.=6.9), 78.9 (S.D.=8.7) and 82.5 (S.D.=6.9) respectively. The I/U ratio for the SFG, IFG and MFG for the two raters were 67.8 (S.D.=11.9), 63.8 (S.D.=14.1) and 68.0 (S.D.=12.0) respectively. The mean percentage differences in volume (cm^3) between the raters were 6.14 (S.D.=3.77), 7.41 (S.D.=5.62) and 7.09 (S.D.=5.69) respectively for SFG, IFG and MFG. Fig. 4 gives a graphical plot the SFG, IFG and MFG volumes for each of the 10 subjects generated from the segmentations of the two raters. The mean cortical gray matter volumes (cm^3) of the SFG, IFG and MFG averaged across both raters separately for schizophrenia subjects and healthy controls is given in Table 1.

4. Discussion

The results of this study extend and refine previous approaches for sub-dividing the structures that constitute the DLPFC, namely the SFG, IFG and MFG on MR images (Crespo-Facorro et al., 1999; Wible et al., 1997). In addition, our approach is a reasonable extension of the methods suggested for delineation of the prefrontal gyri in previous parcellation studies of the frontal lobe and the entire neocortex (Rademacher et al., 1992; Caviness et al., 1996). However, the scope of the present study was restricted, in that we attempted to develop guidelines for parcellation of three specific sub-regions of the PFC, namely SFG, IFG and MFG; this may be considered a limitation of the present study in comparison to more comprehensive whole frontal lobe parcellation efforts. These regions were chosen as the focus of our study because abnormalities of their structure and function have been implicated in neuropsychiatric conditions, such as schizophrenia (Zipursky et al., 1992; Selemon et al., 2002). We chose to parcellate the SFG in its entirety thus including the medial and lateral parts of the gyrus, in order to stick to our resolve to define the frontal gyri on the basis of the sulcal patterns with additional reference to cytoarchitectonic divisions. However, as mentioned in the introduction, the DLPFC comprises only that part of the SFG on the lateral convexity of the cerebral hemisphere. Our data suggest that, despite the complexity of these frontal structures, rules could be developed and applied in a highly reliable manner. Although 10 individuals may not have been sufficient to encounter all possible neuroanatomical variations, a number of such variations were encountered.

While the present study extended the methods described in previous works, our results suggest that greater accuracy in the neuroanatomical definitions can be achieved. We constructed our guidelines for parcellation taking into account naturally existing sulcal–gyral boundaries wherever possible. However, since such boundaries are not always present or reliable enough to define the limits of prefrontal sub-regions, we also used landmarks derived from knowledge about the cytoarchitectonic subdivisions. Finally, we developed a ‘bridging method’ to complete the boundaries wherever we encountered broken or incomplete sulci. A mean of 2.1 bridges per brain were made for delimiting the three prefrontal gyri; the frequency of use of this bridging technique was not found to be different between control and schizophrenia brains as well as between the two raters. The above strategies allowed us to overcome problems associated with inter-individual variability in the sulcal–gyral patterns of the selected regions (Ono et al., 1990). More specifically, we developed guidelines to be followed in cases where such sulcal–gyral variations were encountered. This approach also enhanced the accuracy of neuroanatomical measurements by reducing ambiguity in the definition of cortical sub-regions.

Table 1
Left SFG, IFG and MFG volume comparisons between the present study and earlier parcellation studies

	Present study	Wible et al. (1997)	Crespo-Facorro et al. (2000a,b)	Buchanan et al. (2004)	Suzuki et al. (2005)
SFG (cm^3)	C: 19.49	C: 16.00	C: 17.80	C: 22.80	C: 29.64
	S: 15.40	S: 15.70	S: 18.10	S: 22.90	S: 27.49
IFG (cm^3)	C: 9.99	C: 11.40	C: 9.30	C: 10.45	C: 13.87
	S: 8.24	S: 10.20	S: 9.30	S: 9.70	S: 12.58
MFG (cm^3)	C: 16.71	C: 12.50	C: 20.90	C: 16.10	C: 27.31
	S: 12.82	S: 12.10	S: 20.70	S: 16.00	S: 25.87

C — Controls; S — Schizophrenia; SFG — Superior Frontal Gyrus; IFG — Inferior Frontal Gyrus; MFG — Middle Frontal Gyrus.

An important difference between the present study and previous parcellation studies of the PFC is in the definition of the anterior extent of the three gyri, which also defines the FP. The present study defined the anterior extent of these gyri as the coronal plane containing the ATOS. Crespo-Facorro et al. (1999, 2000a,b), Buchanan et al. (2004) and Suzuki et al. (2005) did not separate the FP from the rest of the frontal sub-divisions and therefore included BA 10 as part of the SFG and MFG. However, Wible et al. (1997) parcelled out the FP by defining the anterior-most 10 slices (1.5 mm) of the brain. While easy to implement, this approach has limited neuroanatomical meaning. Finally, Rademacher et al. (1992) defined the posterior extent of the FP as the anterior termination of the aHR of the SF. Thus, the definition of the FP in MRI volumetric studies has been a matter of debate. While trying to incorporate these previous approaches to defining the FP, we also took into account all available information about the cytoarchitectonic characteristics of the region and landmarks that had predictable relationships with such cytoarchitectonic divisions, as detailed in the Methods section. The ATOS was chosen as the landmark for these same reasons as described previously. It must be noted, however, that this boundary is more reliable for delimiting BA 10 from the other cytoarchitectonic areas on the orbital and medial surfaces (Ongur et al., 2003). The findings of Semendeferi et al. (2001) suggest that this may be a reliable boundary on the lateral convexity as well.

Considering the differences in the definitions of these three gyri between our study and previous studies, we compared the volumes generated by our study with the results of these earlier studies (Table 1). It should be kept in mind that in the present study, the volumetric assessments were performed on MR scans collected from five healthy control subjects and five individuals with schizophrenia. It is interesting to note that those studies that have not parcellated the FP separately and included the gray matter up to the anterior tip of the frontal lobe (Crespo-Facorro et al., 2000a,b; Buchanan et al., 2004; Suzuki et al., 2005) generally had larger SFG and MFG volumes as compared to the present study, the exceptions being SFG volume in control subjects in Crespo-Facorro et al. (2000a,b) and MFG volume in control subjects in Buchanan et al. (2004) (Table 1). The study by Wible et al. (1997), which defined the 10 anterior-most slices of the brain (employing 2.5 mm coronal cuts) as the FP, expectedly showed smaller SFG volumes (in controls) and MFG volumes (in controls) as compared to our study. Our IFG volumes were not substantially different from that of Crespo-Facorro et al. (2000a,b) and Buchanan et al. (2004) who used a boundary for the anterior extent of the IFG that roughly corresponded to our definition. The IFG volumes of Wible et al. (1997) were slightly higher. Notably, Wible et al. reported substantial difficulties in visualizing the natural sulcal boundaries in the inferior aspect of the dorsolateral convexity and so extended the anterior limit of the IFG to the FP boundary. Suzuki et al. (2005), who defined the anterior boundary of the IFG as the fronto-marginal sulcus expectedly reported higher IFG volumes when compared to our results as well as those of Crespo-Facorro et al. (2000a,b) and Buchanan et al. (2004). In fact, the reported volumes of all the three gyri were substantially higher in Suzuki et al. (2005) when compared to all the other studies mentioned, including ours, as shown in Table 1.

Since a major emphasis of the present study was to develop guidelines for parcellation of the three frontal gyri taking into account the sulcal variability in the region, it is appropriate to summarize the sulcal patterns in the region that we encountered. The patterns, as identified using the atlas of Ono et al. (1990) as reference, of the important sulci in the prefrontal region are summarized in Table 2. The MaPCS, which is a horizontally-oriented sulcus over the lateral convexity lying between the superior margin of the hemisphere and the upper end of the superior PCS, was observed in four out of the five schizophrenia subjects and in none of the control subjects. A two-segment type of PCS was observed only in normals (4/5) whereas a four-segment type of PCS was observed only in schizophrenia subjects (3/5). The PaCiS was clearly present on the left side in 6 out of the 10 brains studied (schizophrenia: 3; normals: 3) and this corresponds to previous reports of a 30–60% incidence of the sulcus, with a left preponderance (Paus et al., 1996; Yucel et al., 2001). There was no relationship between handedness, gender or diagnosis and presence or absence of PaCiS. The IFS joined with the LOS in all the 10 brains studied thus enclosing the IFG, in contrast to the much lower possibility of such an occurrence as described by Ono et al. (1990). In 9 out of the 10 brains, these sulci joined posterior to the coronal plane of the ATOS. Another interesting observation was that the SFS turned medially at its termination to join the SRS on the sagittal surface in 5 out of the 10 brains studied. Finally, the SRS was identified reliably using the proposed guidelines in 9 out of the 10 brains studied.

As mentioned above, a limitation of the present study was the small number of subjects assessed. Certainly, additional variations in sulcal–gyral patterns will be encountered as measurements are made in additional subjects, and these variations may alter the reliability data and the average volume measurements reported in this paper. However, the guidelines for parcellation of the three gyri were defined *a priori* taking into account all the described

Table 2
Summary of the observed sulcal patterns in the prefrontal cortex of the left hemisphere

Sulci (left hemisphere)	Sulcal patterns: no. of subjects with the described pattern
Precentral sulcus (PCS)	2- segment type: 4 (schizophrenia: 0; controls: 4)
	3- segment type: 3 (schizophrenia: 2; controls: 1)
	4- segment type: 3 (schizophrenia: 3; controls: 0)
	Marginal PCS (MaPCS): 4 (schizophrenia: 4; Controls: 0)
	Medial PCS of Eberstaller: 7 (schizophrenia: 4; controls: 3)
	Double parallel type of PCS: 1 (schizophrenia)
Paracentral sulcus (PaCS)	Absent: 1 (control)
	Continuation of superior PCS: 1 (control)
	Continuation of medial PCS of Eberstaller: 7 (schizophrenia: 4; controls: 3)
	Contribution only from CiS: 1 (schizophrenia)
Paracingulate sulcus (PaCiS)	Absent: 2 (schizophrenia: 1; controls: 1)
	Rudimentary: 2 (schizophrenia: 1; controls: 1)
	Interrupted — 2–4 segments: 6 (schizophrenia: 3; controls: 3)
	Present predominantly on the anterior aspect of the SFG: 2 (schizophrenia: 1; controls: 1)
	Present almost for the entire length of the SFG: 4 (schizophrenia: 2; controls: 2)
Superior frontal sulcus (SFS)	Uninterrupted: 8 (schizophrenia: 4; controls: 4); one interruption: 2 (schizophrenia: 1; controls: 1)
	Turns medially, around the SFG to join the SRS: 4 (schizophrenia: 2; controls: 2)
	Turns medially, around the SFG to join the infraorbital sulcus: 1 (schizophrenia: 0; controls: 1)
Inferior frontal sulcus (IFS)	Uninterrupted: 9 (schizophrenia: 4; controls: 5)
	Interrupted: 1 (schizophrenia)
Middle frontal sulcus (MFS)	2 segments: 1 (schizophrenia)
	Multiply interrupted: 9 (schizophrenia: 4; controls: 5)
Lateral orbital sulcus (LOS) and IFS	Join posterior to the ATOS plane: 9 (schizophrenia: 4; controls: 5)
	Join anterior to the ATOS plane: 1 (schizophrenia)
LOS and anterior horizontal ramus (aHR)	LOS and aHR present in all 10 subjects; LOS inferior to aHR in all 10 subjects
Superior rostral sulcus (SRS)	Correctly identified as per the guideline used in the study: 9 (schizophrenia: 4; control: 5)
	Could not be identified exclusively using the guideline 1 (schizophrenia)

sulcal variations in the prefrontal regions according to Ono et al. (1990), a substantial majority of which were encountered in the ten brains that we studied (Table 2). Also, high inter-rater reliability was achieved despite the small sample size, which supports the robustness of the guidelines. Considering these arguments, we suggest that our sample, although small, was sufficiently representative with respect to the sulcal variations in the prefrontal region. Of course, application of the proposed guidelines in larger samples where greater sulcal variability are encountered will be needed to confirm our claim.

In view of the fact that the segmentations were restricted to the frontal gyri of the left hemisphere, we cannot comment on inter-hemispheric variability of the sulcal patterns in the prefrontal region. Also, while our measurements of volume in the three gyri of the PFC were reliable, we did not assess the validity of these measures. An assessment of their validity would require a comparison of the measures obtained from MR scans with analogous measures taken from post-mortem material. Finally, the applicability of the ATOS as the posterior limit of the FP on the lateral convexity awaits empirical validation. Nonetheless, high reliability of the measures offered in this study should facilitate the conduct of non-biased comparisons of groups of subjects with and without neuropsychiatric disorders.

In summary, our results demonstrate that the superior, inferior and middle gyri of the PFC can be reliably defined and measured in MR scans using guidelines with limited use of landmarks and relying instead, on naturally occurring sulcal boundaries and information about cytoarchitectonic divisions. Our results offer specific guidelines for parcellation of these regions, taking into account the substantial variability in sulcal patterns in this region. It is expected that this approach will provide greater accuracy and reproducibility for neuromorphological studies, by reducing ambiguity in the definition of the multiple substructures of this crucial brain region.

Acknowledgements

This work was supported by the Fogarty International Research Training in Clinical Sciences fellowship award 5D43TW05811 (J.P.J.). The authors also acknowledge PHS support: R01 MH56584 and the Conte Center for the Neuroscience of Mental Disorders (P50 MH071616) at Washington University School of Medicine.

References

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Press, Washington, DC.

Andreasen, N.C., 1997. Linking mind and brain in the study of mental illnesses: a project for a scientific psychopathology. Science 275 (5306), 1586–1593.

Ariëns Kappers, C.U., Huber, G.C., Crosby, E.C., 1960. The Comparative Anatomy of the Nervous System of Vertebrates, Including Man. Hafner, New York.

Benes, F.M., Davidson, J., Bird, E.D., 1986. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. Archives of General Psychiatry 43, 31–35.

Brodmann, K., 1909. Vergleichende lokalisationslehre der grosshirnrinde in ihren prinzipien dargestellt auf grund des zellenbaues. Barth, Leipzig.

Buchanan, R.W., Francis, A., Arango, C., Miller, K., Lefkowitz, D.M., McMahon, R.P., Barta, P.E., Pearlson, G.D., 2004. Morphometric assessment of the heteromodal association cortex in schizophrenia. American Journal of Psychiatry 161, 322–331.

Caviness, V.S., Kennedy Jr., D.N., Richelme, C., Rademacher, J., Filipek, P.A., 1996. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. Cerebral Cortex 6, 726–736.

Chainay, H., Krainik, A., Tanguy, M.L., Gerardin, E., Le Bihan, D., Lehericy, S., 2004. Foot, face and hand representation in the human supplementary motor area. Neuroreport 15, 765–769.

Chi, J.G., Dooling, E.C., Gilles, F.H., 1977. Gyral development of the human brain. Annals of Neurology 11, 86–93.

Chiavaras, M.M., LeGoualher, G., Evans, A., Petrides, M., 2001. Three-dimensional probabilistic atlas of the human orbitofrontal sulci in standardized stereotaxic space. NeuroImage 13, 479–496.

Crespo-Facorro, B., Kim, J., Andreasen, N.C., O'Leary, D.S., Wiser, A.K., Bailey, J.M., Harris, G., Magnotta, V.A., 1999. Human frontal cortex: an MRI-based parcellation method. NeuroImage 10, 500–519.

Crespo-Facorro, B., Kim, J., Andreasen, N.C., Spinks, R., O'Leary, D.S., Bockholt, H.J., Magnotta, V., 2000a. Cerebral cortex: a topographic segmentation method using magnetic resonance imaging. Psychiatry Research: Neuroimaging 100, 97–126.

Crespo-Facorro, B., Kim, J., Andreasen, N.C., O'Leary, D.S., Magnotta, V., 2000b. Regional frontal abnormalities in schizophrenia: a quantitative gray matter volume and cortical surface study. Biological Psychiatry 48, 110–119.

Drevets, W.C., 2000. Functional anatomical abnormalities in limbic and prefrontal cortical structures in major depression. Progress in Brain Research 126, 413–431.

Duffy, J.D., Campbell III, J.J., 2001. Regional prefrontal syndromes: a theoretical and clinical overview, In: Salloway, S.P., Malloy, P.F., Duffy, J.D. (Eds.), The Frontal Lobes and Neuropsychiatric Illness, 1st ed. American Psychiatric Publishing, Inc., Washington, DC.

Duvernoy, H.M., 1991. The Human Brain: Surface and Three-Dimensional Sectional Anatomy, 1st ed. Springer-Verlag, New York.

Duvernoy, H.M., 1999. The Human Brain Surface:, Blood Supply and Three-Dimensional Sectional Anatomy, 2nd ed. Springer-Verlag, New York.

Ebeling, U., Steinmetz, H., Huang, Y., Kahn, T., 1989. Topography and identification of the inferior precentral sulcus in MR imaging. AJNR American Journal of Neuroradiology 105, 937–942.

Economo, C., Koskinas, G.N., 1925. Die cytoarchitektonik der hirnrinde des erwachsenen menschen. Wien und. J. Springer, Berlin.

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1995. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition SCID-P, version 2.0. New York State Psychiatric Institute, Biometrics Research, New York.

Fornito, A., Yucel, M., Wood, S., Stuart, G.W., Buchanan, J.A., Proffitt, T., Anderson, V., Velakouis, D., Pantelis, C., 2004. Individual differences in anterior cingulate/paracingulate morphology are related to executive functions in healthy males. Cerebral Cortex 14, 424–431.

Fuster, J.M., 1997. The Prefrontal Cortex: Anatomy, Physiology, and Neuropsychology of the Frontal Lobe, 3rd ed. Lippincott-Raven, Philadelphia, PA.

Hof, P.R., Mufson, E.J., Morrison, J.H., 1995. Human orbitofrontal cortex: cytoarchitecture and quantitative immunohistochemical parcellation. Journal of Comparative Neurology 359, 48–68.

Kringelbach, M.L., Rolls, E.T., 2004. The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Progress in Neurobiology 72, 341–372.

Le Provost, J.B., Bartres-Faz, D., Paillere-Martinot, M.L., Artiges, E., Pappata, S., Recasens, C., Pérez-Gómez, M., Bernardo, M., Baeza, I., Bayle, F., Martinot, J.-L., 2003. Paracingulate sulcus morphology in men with early-onset schizophrenia. British Journal of Psychiatry 182, 228–232.

Ongur, D., Ferry, A.T., Price, J.L., 2003. Architectonic subdivision of the human orbital and medial prefrontal cortex. Journal of Comparative Neurology 460, 425–449.

Ono, M., Kubik, S., Abernathey, C.D., 1990. Atlas of the Cerebral Sulci. Georg Thieme Verlag, New York.

Passingham, R.E., 1993. The Frontal Lobes and Voluntary Action. Oxford University Press, New York.

Paus, T., Tomaiuolo, F., Otaky, N., Macdonald, D., Petrides, M., Atlas, J., et al., 1996. Human cingulate and paracingulate sulci: pattern, variability, asymmetry, and probabilistic map. Cerebral Cortex 6, 207–214.

Petrides, M., Pandya, D.N., 1999. Dorsolateral prefrontal cortex: comparative cytoarchitectonic analysis in the human and the macaque brain and corticocortical connection patterns. European Journal of Neuroscience 11, 1011–1036.

Poliakov, V.A., 1966. TSentral'nyæi institut usovershenstvovaniia vracheæi. Osobennosti techeniia i printsipy lecheniia kombinirovannykh radiatsionnykh povrezhdeniæi. Moskva.

Preuss, T.M., Goldman-Rakic, P.S., 1991. Myelo- and cytoarchitecture of the granular frontal cortex and surrounding regions in the strepsirhine primate galago and the anthropoid primate macaca. Journal of Comparative Neurology 310, 429–474.

Rademacher, J., Galaburda, A.M., Kennedy, D.N., Filipek, P.A., Caviness, V.S., 1992. Human cerebral cortex: localization, parcellation and morphometry with magnetic resonance imaging. Journal of Cognitive Neuroscience 4, 352–374.

Rajkowska, G., Goldman-Rakic, P.S., 1995a. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cerebral Cortex 54, 307–322.

Rajkowska, G., Goldman-Rakic, P.S., 1995b. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: II. Variability in locations of areas 9 and 46 and relationship to the Talairach coordinate system. Cerebral Cortex 54, 323–337.

Robb, R.A., Hanson, D.P., Karwoski, R.A., Larson, A.G., Workman, E.L., Stacy, M.C., 1989. Analyze: a comprehensive, operator-interactive software package for multidimensional medical image display and analysis. Computerized Medical Imaging and Graphics 136, 433–454.

Roland, P.E., 1993. Brain Activation. Wiley-Liss, New York.

Roland, P.E., Zilles, K., 1998. Structural divisions and functional divisions in the human cerebral cortex. Brain Research Reviews 26, 87–105.

Sandor, S., Leahy, R., 1997. Surface-based labeling of cortical anatomy using a deformable atlas. IEEE Transactions on Medical Imaging 161, 41–54.

Sarkisov, S.A., 1955. Atlas tsitoarkhitektoniki kory bol'shogo mozga cheloveka. Institut mozga. Akademiia meditsinskikh nauk, SSSR.

Selemon, L.D., Kleinman, J.E., Herman, M.M., Goldman-Rakic, P.S., 2002. Smaller frontal gray matter volume in postmortem schizophrenic brains. American Journal of Psychiatry 159, 1983–1991.

Semendeferi, K., Armstrong, E., Schleicher, A., Zilles, K., Van Hoesen, G.W., 2001. Prefrontal cortex in humans and apes: a comparative study of area 10. American Journal of Physical Anthropology 114, 224–241.

Shattuck, D.W., Leahy, R.M., 2001. Automated graph-based analysis and correction of cortical volume topology. IEEE Transactions on Medical Imaging 20, 1167–1177.

Shenton, M.E., Dickey, C.C., Frumin, M., McCarley, R.W., 2001. A review of MRI findings in schizophrenia. Schizophrenia Research 49, 1–52.

Stark, A.K., Uylings, H.B., Sanz-Arigita, E., Pakkenberg, B., 2004. Glial cell loss in the anterior cingulate cortex, a sub region of the prefrontal cortex, in subjects with schizophrenia. American Journal of Psychiatry 161, 882–888.

Suzuki, M., Zhou, S., Takahashi, T., Hagino, H., Kawasaki, Y., Niu, L., Matsui, M., Seto, H., Kurachi, M., 2005. Differential contributions of prefrontal and temporolimbic pathology to mechanisms of psychosis. Brain 128, 2109–2122.

Wible, C.G., Shenton, M.E., Fischer, I.A., Allard, J.E., Kikinis, R., Jolesz, F.A., Iofescu, D.V., McCarley, R.W., 1997. Parcellation of the human prefrontal cortex using MRI. Psychiatry Research: Neuroimaging 76, 29–40.

Yucel, M., Stuart, G.W., Maruff, P., Velakoulis, D., Crowe, S.F., Savage, G., Pantelis, C., 2001. Hemispheric and gender-related differences in the gross morphology of the anterior cingulate/paracingulate cortex in normal volunteers: an MRI morphometric study. Cerebral Cortex 11, 17–25.

Yucel, M., Stuart, G.W., Maruff, P., Wood, S.J., Savage, G.R., Smith, D.J., Crowe, S.F., Copolov, D.L., Velakoulis, D., Pantelis, C., 2002. Paracingulate morphologic differences in males with established schizophrenia: a magnetic resonance imaging morphometric study. Biological Psychiatry 52, 15–23.

Zilles, K., Sclaug, G., Geyer, S., Luppino, G., Matelli, M., Qu, M., Schleicher, A., Schormann, T., 1996. Anatomy and transmitter receptors of the supplementary motor area in the human and nonhuman primate brain. In: Lauders, H.O. (Ed.), Advances in Neurology: Supplementary Sensorimotor Area, vol. 70. Lippincott-Raven, Philadelphia, PA, pp. 29–43.

Zipursky, R.B., Lim, K.O., Sullivan, E.V., Brown, B.W., Pfefferbaum, A., 1992. Widespread cerebral gray matter volume deficits in schizophrenia. Archives of General 49, 195–205.