Parcellation of the human prefrontal cortex using MRI

Cynthia G. Wible\textsuperscript{a}, Martha E. Shenton\textsuperscript{a}, Iris A. Fischer\textsuperscript{a}, Jay E. Allard\textsuperscript{a}, Ron Kikinis\textsuperscript{b}, Ferenc A. Jolesz\textsuperscript{b}, Dan V. Iosifescu\textsuperscript{a}, Robert W. McCarley\textsuperscript{a,*}

\textsuperscript{a}Department of Psychiatry, Lab of Neuroscience 116A, Harvard Medical School and the Brockton Veterans Affairs Medical Center, 940 Belmont Street, Brockton, MA 02041, USA
\textsuperscript{b}Department of Radiology, Harvard Medical School and the MRI Division, Surgical Planning Laboratory, Brigham and Women's Hospital, Boston, MA 02115, USA

Received 20 December 1996; revised 6 October 1997; accepted 10 October 1997

Abstract

A methodology was developed for dividing prefrontal cortical gray matter into insular, orbital, inferior, middle, superior, cingulate, and frontal pole regions using anatomical criteria. This methodology was developed as a follow-up to one that measured whole prefrontal gray and white matter volumes in schizophrenic and control subjects. This study showed no overall volume differences in prefrontal cortex between schizophrenic and control subjects. The parcellation of prefrontal cortex was done to increase the probability of detecting abnormalities that were circumscribed to a particular portion of the region. A 1.5 Tesla magnet was used to acquire contiguous 1.5-mm coronal slices of the entire brain. Volumes were then measured in a group of right-handed male (n = 15) subjects. Gray matter was parcellated using criteria that were mainly based on gross anatomy, as visualized in 3-dimensional renderings of the brain. Reliability of the parcellation scheme was very high (r = 0.80 and above). This methodology should be useful in the study of cortical pathology in a number of neurological disorders, including schizophrenia.

Keywords: Frontal cortex; Dorsolateral prefrontal cortex; Cortical parcellation

* Corresponding author. Fax: +1 508 5860894; e-mail: mccarley@warren.harvard.med.edu; cindy@bwh.harvard.edu

025-4927/97/$17.00 © 1997 Elsevier Science Ireland Ltd. All rights reserved.

PII S025-4927(97)00060-7
1. Introduction

Pathology of the human prefrontal cortex is thought to underlie at least some symptoms of several major neurological syndromes (e.g. schizophrenia, Korsakoff's syndrome, Huntington's disease, and Alzheimer's disease). The frontal lobe in humans comprises ~30% of the total cortical area. Prefrontal cortex is often defined as areas of the frontal lobe anterior to Brodmann's area 6 (Brodmann, 1909); these regions are enervated by the parvicellular (dorsolateral region) and magnocellular (orbital and cingulate regions) portions of the dorsomedial nucleus of the thalamus (Pandya and Yeterian, 1990; Fuster, 1989).

The prefrontal cortex is composed of a number of regions that contribute to a wide range of functions including social behavior, planning, language production, working memory, language retrieval, search, and attention to name a few. In the present study, the prefrontal cortex was divided into left and right insular, orbital, inferior, middle, superior, cingulate, and frontal pole regions using a rule-based method that was closely based on conventional gross anatomy. The parcelation methods were developed to be as reproducible as possible (i.e. high intra-rater and inter-rater reliability) while still reflecting existing neuroanatomical distinctions. The method for parcelation was developed to examine the schizophrenic prefrontal cortex as the next stage of a previous study (Wible et al., 1995); however, the methodology could prove useful for other patient populations. Our laboratory has completed studies using MRI which showed volume reductions in temporal lobe regions in schizophrenic patients (Shenton et al., 1992), but not in whole prefrontal white or gray matter (Wible et al., 1995). It was reasoned that whole volume measurements of a large region such as the prefrontal cortex could obscure more circumscribed abnormalities.

The parcelation units used for the prefrontal cortex are very similar to those used by Caviness et al. (1996). However, in the current study, only the prefrontal cortex was examined, and the parcelation was based primarily on visualization of the 3-dimensional cortical surface, not the slice. Large sulci, ones conventionally used to distinguish gross anatomical regions, were used as the delimiters of the parcelation units for reasons of reliability and consistency with gross anatomical nomenclature and identification (see Sec. 4).

Cytoarchitectonic structure bears a relationship to sulcal/gyral patterns in non-human primates (e.g. the principal sulcus and area 46), and there are also examples of the functional specificity of these cytoarchitectonic regions (see Goldman-Rakic and Friedman, 1991). However, the relationship between sulcal/gyral pattern and functionality in the human brain is unclear at this point. Firstly, the cortical gyral patterns of individual human subjects can vary considerably. Even major sulci vary in their appearance. For example, a treatise on sulcal/gyral variability showed that the central sulcus was not continuous in all individuals (92%), and other sulci in the frontal lobe were found to be much more variable in terms of several factors including continuity, side branchings and connections with other sulci (Ono et al., 1990).

It is generally not known how these sulcal/gyral variations relate to variations in cytoarchitectonic regions in human subjects, especially in higher order regions such as those in frontal cortex; only a few studies have examined this issue systematically. A cytoarchitectonic mapping study of the human cingulate cortex examined sulcal/gyral patterns and cytoarchitectonic fields using a cortical unfolding technique to visualize the fields (Vogt et al., 1995). This study describes a complex and limited relationship between some fields and some sulcal/gyral features.

Another recent study mapped frontal lobe regions 9 and 46 using cytoarchitectonic characteristics and reconstructed the regions so that they could be more systematically examined in relationship to the gross anatomy of the frontal cortex, and to Talairach coordinates (Rajkowska and Goldman-Rakic, 1994a,b). This study showed some consistency in the spatial relationship of regions 9 and 46 between subjects and in their relationship to sulcal/gyral patterns. For example, area 9 was located on the first frontal gyrus
(superior frontal gyrus), and area 46 was consistently found to occupy some portion of the middle frontal gyrus and extended into the middle frontal sulcus in all cases. However, although there was, for both regions, some commonality in spatial extent that was related to sulcal/gyral pattern, there was still considerable variability between subjects in the exact location and extent of the fields.

There is evidence that at least some human primary sensory and motor regions can be identified by gross anatomy. For example, the primary auditory region is consistently located in the superior temporal gyrus, often in the dorsal plane of this region (see Galaburda and Sanides, 1980). Primary visual cortex can also be identified by gross anatomical landmarks. Examination of 52 human brains revealed that an average of 67% of the striate cortex was located within the calcarine fissure of the occipital lobe (Stensaas et al., 1974). The relationship of several primary cytoarchitectonic fields to gyral topography was systematically examined in serial sections from 20 human subjects (Rademacher et al., 1993). These fields were found to have a relationship to sulcal/gyral landmarks. In addition, a review of cerebral blood-flow and lesion studies showed consistencies in the location of the human frontal eye fields. It was concluded that the human frontal eye field was located either in the precentral sulcus and/or in the caudal-most part of the superior frontal gyrus (Paus, 1996).

These studies, and other evidence from functional imaging, lesion, and stimulation studies, indicate that there is at least some correspondence between gross morphology and function in the human brain. The evidence for a relationship was felt to be strong enough to warrant developing a method to subdivide the prefrontal cortex. The utility of parcellation studies using MRI will not be known until several groups use subdivision or parcellation methods and apply them to analyzing regional volumes in neurological populations. Two issues are central to testing the utility of this method. Firstly, the parcellation method itself must be reliable and reproducible. Secondly, it must be kept in mind that the parcellation units themselves are limited in the extent to which they are homogeneous with respect to cytoarchitectonic features.

The parcellation scheme presented here used sulci as dividing points for the parcellation units simply because they were the most reliably identifiable features. The methodology reported here shows that it is possible to reliably identify gross anatomical regions of human prefrontal cortex and use these features to subdivide the cortex. It is hoped that the ability to reliably measure the volume of these portions of the prefrontal cortex will increase the precision with which we can identify abnormalities in neurological and psychiatric syndromes.

2. Methods

2.1. Subjects

MR scans were obtained for a previous study (Shenton et al., 1992) from 15 control subjects, all right-handed males. Detailed subject characteristics are reported elsewhere (Shenton et al., 1992; Wible et al., 1995).

2.2. MRI methodology

All MR scans were acquired at the Brigham and Women's Hospital with a 1.5 T General Electric SIGNA System (GE Medical Systems, Milwaukee, WI). The MR methodology is described in detail elsewhere (Shenton et al., 1992; Wible et al., 1995), and will be summarized briefly here. For the measurement of specific regions of interest (ROI), a 3D Fourier transform spoiled gradient-recalled acquisition in steady state (3DFT SPGR) was used to obtain scans throughout the entire brain which were reformatted into 124 contiguous 1.5-mm coronal slices. This protocol creates images with good gray/white matter contrast. The SPGR images were obtained with the following parameters: echo time (TE) = 5 ms, repetition time (TR) = 35 ms, one repetition, nutation angle = 45 degrees, field of view = 24 cm, acquisition matrix = 256 × 256 × 124, voxel dimensions = 0.9375 × 0.9375 × 1.5 mm³.

For measurement of the total intracranial contents, 108 (54 for each echo) contiguous double
echo spin-echo 3-mm axial slices were obtained throughout the extent of the brain. Imaging parameters were: TE = 30 ms, TR = 3000 ms, field of view = 24 cm, acquisition matrix = 256 × 256, voxel dimensions = 0.9375 × 0.9375 × 3 mm³. No gross abnormalities were found in the scans when they were evaluated by a clinical neuroradiologist.

2.3. Image processing

The image-processing stages were different for the whole brain and the individual region of interest (ROI) measurements. The image processing for the initial segmentation of gray matter on the SPGR scans proceeded in several stages that were described previously in detail (Wible et al., 1995). Briefly, those stages included filtering the image to reduce noise (Gerig et al., 1990), extracting the intracranial cavity, and segmenting gray and white matter using semi-automated algorithms (Cline et al., 1987, 1988, 1991; Kikinis et al., 1992) in conjunction with manual editing.

The results of the segmentation were then superimposed on the original SPGR image and edited using an image editing program. This gray matter segmentation was further subdivided into the eight prefrontal regions. The slice editor contained algorithms to perform manual drawing of ROI, and a connectivity algorithm to change pixel values within a given region. The MR image and the segmented image could also be reformatted in any of three axes (sagittal, axial, and coronal), but the coronal plane was used for the majority of the editing. These tools were used to separate the gray matter into different regions. A line was drawn through the sulcus on the boundary of each region to delineate the region, and the connectivity algorithm was used to reassign the pixel values to those designated for that subdivision (see Fig. 1 for representative slices from one case).

A dividing cubes algorithm was used to create a three-dimensional (3D) view of each tissue class (see Fig. 2) (Cline et al., 1988, 1990, 1991). Most of the subdivisions were parcellated according to criteria from the 3D reconstruction. The gray matter would be subdivided on each coronal slice and then checked and revised based on the 3D information. In addition, 3D reconstructions of the gray matter for each case were done using tissue segmentations in which the sulci were enhanced by overinclusively categorizing pixels in the sulci as CSF. These sulci-enhanced 3D representations were examined during the parcellation process to help identify sulcal boundaries. Following parcellation of the original segmentations, the voxels for each tissue class were then summed to compute the volume for each slice and the cumulative volume.

The image-processing procedures for the measurement of intracranial content using the 3-mm double-echo axial scans (used to compute the relative volume measurements) have been described in detail in a previous study (Shenton et al., 1992). Since the prefrontal parcellations were not based on these scans, they will not be described here.

2.4. Prefrontal cortex landmarks

The boundaries for the prefrontal region have been described in detail elsewhere (Wible et al., 1995). Briefly, the gray matter measurements extended from the most anterior slice containing gray matter to three slices anterior to the temporal stem. The posterior landmark coincided with the most posterior area where the frontal and temporal lobes were not adjoined.

2.5. Parcellation of the prefrontal cortex into regions of interest (ROI)

The prefrontal cortex was divided into insular, orbital, inferior, middle, superior, cingulate, and frontal pole regions (see Fig. 1 and Fig. 2). The neuroanatomical terms used, and the identification of sulci were based largely on those from Duvernoy (1991). The landmarks and methods used to parcellate the prefrontal cortex will be described for each of the seven areas. The delineating sulci used to define the ROI will be discussed in terms of three anterior-posterior levels of the prefrontal cortex (designated anterior, intermediate, and posterior); for some regions the boundaries changed at these transition points. Fig. 1 shows representative slices from the pre-
Fig. 1. Representative slices from a control case showing the ROI. The correspondence between region and color is as follows: insula, pink; orbital cortex, green; inferior frontal gyrus, yellow; middle frontal gyrus, blue/green; superior frontal gyrus, red; cingulate gyrus, blue, and frontal pole, gray.
frontal cortex; slices A–C are representative of the posterior level, D and E of the intermediate level, and F–H of the anterior level, with the slice in panel H being from the frontal pole region. The dorsolateral and ventromedial boundaries will be described only for the orbital region, and the dorsolateral boundary will be described for each remaining region. The other regions will be described in turn from the most ventral to the most dorsal. Each region’s dorsal boundary was the same as the ventral boundary of the region immediately superior to it.

2.5.1. Insular region
The insular region was determined by visualizing sagittal views of the brain. It was bounded dorsally and ventrally by the circular insular sulcus. In the most posterior extent, the insula was divided from the orbital cortex by designating cortex on the ventral surface orbital cortex, and on the lateral surface, insular cortex (Fig. 1). In the most anterior extent, it consists of a small gyrus between the orbital and inferior gyrus regions (Fig. 1).

2.5.2. Orbital region
The orbital region included the orbital gyri and the gyrus rectus on the ventral surface, and some of the inferior cingulate. This region was defined primarily by sulci visible on the slices rather than by viewing the 3D reconstruction, since the sulci were not prominent enough to be reliably discernible on the 3D reconstruction.

At the posterior level, the orbital region was bounded by the circular sulcus of the insula, a prominent sulcus that can be easily detected, and by the corpus callosum and cerebral longitudinal fissure (Fig. 1A–C). Moving anteriorly to an intermediate level (Fig. 1D and E), the circular sulcus was less prominent, but was still visible as a large ventrolateral sulcus. The intermediate level boundaries were the ventral border of the inferior frontal gyrus, pars orbitalis, and the corpus callosum.

The pars orbitalis was difficult to distinguish
from the insular cortex. In the coronal plane, the pars orbitalis consisted of a thin gyrus inferior to the horizontal ramus of the lateral fissure. At the most anterior levels (Fig. 1F–H) the circular sulcus (and insula) was no longer evident, and the boundary was designated as the most lateral and ventral orbital sulcus, usually the sulcus between the lateral orbital and posterior orbital gyri. The medial boundary was the most inferior sulcus on the medial edge, the susorbial sulcus, which lies superior to the gyrus rectus.

2.5.3. Inferior frontal gyrus

At all levels, the dorsal boundary of this gyrus was the inferior frontal sulcus, which was identified primarily from 3D reconstructions. At an intermediate level, the inferior frontal gyrus includes the pars orbitalis, which was visible on the slice as a small gyrus situated immediately inferior to the circular insular gyrus (Fig. 1D and E). The pars orbitalis was difficult to distinguish from the insular cortex on coronal slices, and therefore was identified primarily from 3D reconstruction and from sagittal views. Note also that the true border of the inferior frontal gyrus often lies on the lateral, not ventral surface. However, we found the lateral orbital sulcus to be difficult to consistently identify, and so at levels anterior to the pars orbitalis, we chose to use the most ventral and lateral orbital sulcus as the boundary. The middle and superior frontal gyri extend more anteriorly than the inferior frontal gyrus, so at the most anterior level (Fig. 1H), the gyrus usually occupied a relatively small part of the brain.

In the 3D reconstruction, the inferior frontal gyrus was identified by the appearance of the pars opercularis, triangularis, and orbitalis (Fig. 2). If the border of the inferior frontal gyrus in the most anterior end of the measured region was unclear, then the superior boundary of the gyrus was determined by extending the last clear boundary horizontally to the anterior-most end of the measured region.

2.5.4. Middle frontal gyrus

The middle frontal gyrus was the most difficult to identify, and was primarily segmented using information from 3D reconstructions. In the coronal plane, the gyrus was often split into an inferior and superior portion by the middle frontal sulcus, and so consisted of at least two separate gyri with a deep sulcus between them. The middle frontal gyrus was usually defined after first identifying the superior and inferior frontal gyri.

2.5.5. Superior frontal gyrus

This gyrus was also identified primarily from the 3D reconstructions. At posterior levels, the gyrus often consisted of a large single gyrus in the superior aspect that was bounded medially by the cingulate gyrus (Fig. 1A–C). At anterior levels, anterior to the corpus callosum (Fig. 1F and G), the superior frontal gyrus was arbitrarily defined as tissue occupying most of the medial aspect of the brain, with the ventral boundary being the susorbial sulcus. Near the frontal pole, a transverse component often invaded the space usually occupied by the middle frontal gyrus; these transverse gyri were included in the superior region (see Fig. 2).

The superior frontal gyrus was defined to consist of the first large gyrus on the superior aspect of the brain, although occasionally it bifurcated into two or more branches. Other gyri were included if they joined the most superior gyrus at points between the precentral sulcus and the frontal pole, and if the two gyri appeared to be parallel to each other. In the coronal plane, especially at anterior levels, the middle frontal sulcus was relatively deep and gave the appearance of grouping gyri above and below it into two groups. However, it is important to note that the gyrus above the middle frontal sulcus most often consists of the superior portion of the middle frontal gyrus, not the superior frontal gyrus (see Fig. 1).

2.5.6. Cingulate gyrus

The cingulate gyrus in the posterior extent, defined as the one or two gyri superior to the corpus callosum, was identified primarily from 3D reconstructions and sagittal reformattting of the scans. The most ventral portion of the cingulate gyrus, posterior to the genu of the corpus callosum, was classified as orbital cortex. In the ante-
rior extent, the gyrus was identified mainly by 3D reconstruction.

2.5.7. Frontal pole
The frontal pole measurement was arbitrarily defined as the anterior-most 10 slices of brain (see Fig. 2). This grouping was done because the fusing of gyri makes reliable differentiation in this region problematic.

2.6. Notes on parcellation — rules for classifying difficult or unusual sulcal / gyral patterns

2.6.1. Long transverse gyri
Transverse gyri (with the exception of the superior frontopolar gyrus) were classified using 3D surface criteria according to the region they occupied. For example, if a transverse gyrus from the middle frontal region invaded the inferior frontal region, that part of the gyrus would be classified as inferior frontal gyrus. This gyral pattern occurred only in a few cases.

2.6.2. Discontinuous or unclear sulcal boundaries
If a sulcal boundary was not present on a slice, the tissue was segmented so that the boundary between regions was a straight line between two regions where there were clear boundaries.

2.7. Assessment of reliability of tissue segmentation and prefrontal parcellation

2.7.1. Frontal gray matter
The methods for the assessment of inter-rater reliability and intra-rater reliability for the segmentation of whole frontal gray matter and identification of the landmarks used to delineate gray matter boundaries were assessed and are published in a previous study (Wible et al., 1995).

One rater (CGW) did the parcellation of prefrontal gray matter for all of the cases. The intrarater reliability was assessed by having this rater blindly parcellate the gray matter for a randomly chosen case on three separate occasions that were months apart. The segmentations for all reliability cases were done several months after the initial segmentation was completed. The percent error was calculated by taking the absolute value of the difference scores between the volumes for each segmentation and the average value of the three segmentations. The volumes for each individual prefrontal region, left and right hemisphere separately, were used in the calculation.

Inter-rater reliability was assessed by having two raters (DI and IAF) parcellate a randomly chosen case without examining the original parcellation for that case. These raters were instructed with the rules for parcellation in one short (~ 20 min) session, and received no specific instruction on the parcellation of the case chosen to compute the reliability. Neither rater had prior experience in parcellating prefrontal cortex, but both were experienced in using the image-processing tools in conjunction with MR scans. The percent error was calculated by taking the absolute value of the difference scores between the volumes for each rater’s segmentation and the average value of the three segmentations. An additional measure of reliability was performed by having one rater (IAF) blindly identify and segment only the middle frontal gyrus on the left on 10 randomly chosen cases. The intraclass correlation was computed between volumes from this region using the original classifications (rater CGW) and the ones from rater IAF. This measurement was included because the correlations using all measures could be artificially inflated because the parcellation units of different regions are of different sizes.

2.8. Statistical analyses

Analyses for the mean volumes were computed separately for absolute volumes, and for relative volumes — the latter corrected for head size by dividing the absolute volume by the volume of the intracranial contents and multiplying by 100.

3. Results

3.1. Reliability of tissue segmentation and prefrontal parcellation

3.1.1. Segmentation of prefrontal gray matter
Inter-rater reliability and intra-rater reliability
for the segmentation of whole frontal gray matter resulted in average intraclass correlations of $r_i = 0.98$ (see Wible et al., 1995). Intra- and inter-rater reliability for the identification of the landmarks used to delineate gray resulted in an intraclass correlation of $r_i = 0.99$.

3.1.2. Parcellation of prefrontal gray matter

Intra-rater reliability was for the rater (CGW) who did the parcellation of prefrontal gray matter for all of the cases. The average percent error for parcellation on three separate occasions, months apart, was 3%. The intraclass correlation for the intrarater reliability was $r_i = 0.99$. Reliability (both intra- and inter-rater) for a schizophrenic case was also measured, and was very high. This will be reported in a subsequent article.

Inter-rater reliability was measured between the original rater (CGW) and two raters (DI and IAF) who parcellated the prefrontal cortex according to the methods developed here. An average percent error of 7% was obtained for the case. The intraclass correlation for the three raters (CGW, DI, and IAF) was $r_i = 0.95$. The intraclass correlation for the reliability of the parcellation of left middle frontal gyrus on 10 cases was $r_i = 0.80$; a scatterplot of these data is shown in Fig. 3.

3.2. Volume measurements

3.2.1. Prefrontal volume

The volumes of left and right gray matter for the parcellated regions are shown in Table 1.

4. Discussion

4.1. The method for the parcellation of the prefrontal cortex

A reliable method was developed to parcellate the prefrontal region into an insular, orbital region, inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, cingulate gyrus, and frontal pole, an essential first step in the identification of specific or differential abnormalities in this large, heterogeneous region of cortex. The methods developed for parcellation yielded a high average reliability of $r_i = 0.97$ computed over all of the regions and a reliability of $r_i = 0.80$ for one region measured in 10 randomly chosen cases.

Although the parcellation units for the frontal lobe used here are similar to those used by Caviness et al. (1996) and Rademacher et al. (1992), the segmentation and parcellation methods differ in several respects. Firstly, their approach is larger in scope than the methods presented here. They parcellate the entire brain; the methods here specifically focus only on the parcellation of the prefrontal cortex. This region has been of intense interest to researchers studying schizophrenic brain pathology, and it is for this reason that we have developed these methods. With regard to more specific methodological differences, the segmentation method used by Caviness et al. (1996) is a modification of a slice-based thresholding, whereas the one used here is based on a parzen map algorithm with additional hand editing. The largest methodological difference is that their laboratory routinely uses 3-mm thick slices, and hence does not rely on 3D surface reconstruction to identify gyri (sulcal/gyral patterns are not very evident on reconstruction with 3-mm thick slices). The methods used here rely heavily on identified gyral patterns from 3D reconstruction of the cortical surface. Our laboratory routinely uses 1.5-mm thick slices, and we have several 3D reconstruction programs that allow for editing in 3

![Fig. 3. A scattergram plotting the volumes obtained by the original rater (CGW) graphed along the X axis, and a second rater (IAF), graphed along the Y axis, for the left middle frontal gyrus for 10 randomly chosen cases.](image-url)
dimensions and for identification of slice locations within a 3D reconstruction.

The methods developed here for parcellating the prefrontal cortex, based on established anatomical criteria, should aid in establishing structure-function relationships in patient populations with damage to this area. For example, the prefrontal cortex of the schizophrenic group from a previous study (Wible et al., 1995) was parcellated in addition to the control subjects used in this methodological article. These schizophrenic subjects had shown, in a previous study, volume reductions in several temporal lobe areas, primarily on the left (Shenton et al., 1992). When whole prefrontal cortex measures were used, a correlation was found between left prefrontal gray matter volume and anterior amygdala/hippocampal volume \( (r = 0.72) \) (Wible et al., 1995). The parcellation pinpointed specific regions that contributed to this correlation. For example, the left orbital region showed the highest correlation with left anterior amygdala/hippocampal volume \( (r_i = 0.81) \) in the schizophrenic subjects.

This study demonstrates that the volume of individual regions of the human prefrontal cortex can be reliably measured. Quantitative methods for the classification of human cortex could also aid in understanding the relationship between
damage to a circumscribed area and symptomatology in other disorders involving the prefrontal cortex such as aphasia and Huntington’s disease.

Acknowledgements

This research was supported by the National Institute of Mental Health (40,799), the Department of Veterans Affairs Schizophrenia Center the National Alliance for Research in Schizophrenia and Depression, the Commonwealth of Massachusetts Research Center (Dr. McCarley); a Health and Education Fund Award from the Massachusetts Mental Health Center (Dr. Wible); K02-MH-01110 and 1R29MH-50740, (Dr. Shenton); the Stanley Foundation (Drs. Shenton and Kikinis); a National Institute of Health Career Development Award (Dr. Jolesz); and the Swiss National Foundation (Dr. Kikinis). Maureen Ainslie and Mark Anderson provided excellent technical support. We are also indebted to Dr. Michael Murphy, who assisted with portions of the image processing.

References

Rajkowska, G., Goldman-Rakic, P.S., 1994a. Cytoarchitectonic definition of prefrontal areas in the normal human cortex: I. Remapping of areas 9 and 46 using quantitative criteria. Cerebral Cortex 5, 307–322.
Rajkowska, G., Goldman-Rakic, P.S., 1994b. 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 5, 323–337.
