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Technical Note

A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data

Simon B. Eickhoff,[a,b] Klaas E. Stephan,[c] Hartmut Mohlberg,[a] Christian Grefkes,[a,b,d] Gereon R. Fink,[a,d,e] Katrin Amunts,[a,e,f] and Karl Zilles[a,b,e,*]

[a]*Institut für Medizin, Forschungszentrum Jülich, Jülich, Germany*
[b]*C. and O. Vogt Institut für Hirnforschung, Düsseldorf, Germany*
[c]*Wellcome Department of Imaging Neuroscience, University College London, UK*
[d]*Neurologische Klinik, Universitätsklinikum Aachen, Germany*
[e]*Brain Imaging Center West (BICW), Jülich, Germany*
[f]*Klinik für Psychiatrie und Psychotherapie, Universitätsklinikum Aachen, Germany*

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Correlating the activation foci identified in functional imaging studies of the human brain with structural (e.g., cytoarchitectonic) information on the activated areas is a major methodological challenge for neuroscience research. We here present a new approach to make use of three-dimensional probabilistic cytoarchitectonic maps, as obtained from the analysis of human post-mortem brains, for correlating microscopical, anatomical and functional imaging data of the cerebral cortex. We introduce a new, MATLAB based toolbox for the SPM2 software package which enables the integration of probabilistic cytoarchitectonic maps and results of functional imaging studies. The toolbox includes the functionality for the construction of summary maps combining probability of several cortical areas by finding the most probable assignment of each voxel to one of these areas. Its main feature is to provide several measures defining the degree of correspondence between architectonic areas and functional foci. The software, together with the presently available probability maps, is available as open source software to the neuroimaging community. This new toolbox provides an easy-to-use tool for the integrated analysis of functional and anatomical data in a common reference space.

Keywords: Functional magnetic resonance imaging; Structure; Mapping; Atlas; PET

Introduction

Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) provide information about the functional organization of the human cerebral cortex with a spatial resolution in the range of a few millimeters. Several concepts can be applied for the anatomical interpretation of functional activations, e.g., stereotaxic coordinates or macroanatomical landmarks. These concepts, however, do not appropriately take into account the microscopical architectonic organization of the human brain (Amunts and Zilles, 2001; Zilles et al., 2002). In turn, there is plenty of evidence from studies of non-human primates that the microstructure and connectional architecture of the cortex are the main determinants of the regional segregation of its functions (e.g., Luppino et al., 1991; Matelli et al., 1991). Consequently, there is a general consensus that cortical areas, defined by their microstructure and/or connectivity, can be regarded as functional modules of the cortex (for reviews, see Felleman and Van Essen, 1991; Passingham et al., 2002). Therefore, the anatomical interpretation of functional imaging results with respect to microstructurally defined areas is the most appropriate topographical reference for regionally specific activations observed in functional imaging studies.

One of the most widely used anatomical references is the brain atlas of Talairach and Tournoux (1988). This atlas was seminal for the development of functional neuroimaging by introducing a spatial reference system for the human brain, which is independent of skull landmarks: the reference brain is an individual post-mortem brain, which is aligned according to a plane defined by the anterior and posterior commissures (AC–PC plane). Stereotaxic locations are then described in coordinates relative to the origin (coordinates 0,0,0) defined by the intersection of the AC with the interhemispheric plane.

The use of "Talairach labels" for the cytoarchitectonic allocation of functional activations is, however, problematic for several reasons. The atlas does not provide information with respect to the inter-individual variability of the cytoarchitectonic areas or the relative probabilities for different areas at a given position. This causes the impression that a stereotaxic location necessarily belongs to a specific cortical area, although recent and previous

* Corresponding author. Institut für Medizin, Forschungszentrum Jülich GmbH, D-52425 Jülich, Germany. Fax: +49 2461 61 2990.
E-mail address: K.Zilles@fz-juelich.de (K. Zilles).
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cytoarchitectonic studies demonstrate considerable inter-individual differences in size and location of cortical areas (Amunts et al., 2000; Geyer et al., 1999; von Economo and Koskinas, 1925).

More importantly, the cytoarchitectonic labels shown in the Talairach atlas are not based on a microstructural analysis. Rather, the authors inferred, based on sulcal landmarks and gross morphology, where the areas depicted on Brodmann's (1909) map could be located in this subject. Many studies have demonstrated, however, that the borders of microstructural areas do not always show a precise and reliable relationship to macroanatomical landmarks (Amunts et al., 1999; Geyer et al., 1999; Grefkes et al., 2001; Zilles et al., 2002). For example, BA 44 usually occupies the opercular part of the inferior frontal gyrus, whereas BA 45 is found on the triangular part. However, BA 44 can also encroach on the triangular part and BA 45 may also reach aspects of the opercular part, respectively. Similarly, BA 44 may border BA 6 in either the anterior or the posterior bank of the precentral sulcus (Amunts et al., 1999, 2004). Furthermore, the correspondence between macroanatomical features and microstructural areas is quite variable across the cortex. Particularly, it is frequently not possible to correlate the borders of cytoarchitectonic areas with macroscopical landmarks, whereas centers of a cytoarchitectonic area may be well identified by macroscopical features (e.g., the borders of the primary visual cortex V1, which is always found in the calcarine sulcus, vary considerably regarding sulcal features). Although there is a reliable relationship for some areas like the primary cortical area 3b, the correspondence is much worse in other regions of the brain, in particular in parietal or frontal association areas.

As an alternative to the post-mortem reference brain of the Talairach and Tournoux atlas, fMRI or PET data are often normalized to the templates provided by the Montreal Neurological Institute (MNI). The most widely used MNI templates are a single-subject template and a group template created from 152 individual brains, both aligned to the Talairach-like MNI305 reference space (Collins et al., 1994; Evans et al., 1992; Holmes et al., 1998). Although these templates are roughly based on the Talairach space, they do not match the Talairach brain in size and shape (Brett et al., 2002).

In contrast to classical cytoarchitectonic maps (e.g., Brodmann, 1909), probabilistic cytoarchitectonic maps provide stereotaxic information on the location and variability of cortical areas in the MNI reference space (Amunts and Zilles, 2001; Mohlberg et al., 2003; Zilles et al., 2002). They are based on the observer-independent analysis of the cytoarchitecture in a sample of ten human post-mortem brains. Such maps have been published for various brain regions, including the motor, somatosensory, visual, auditory, and language related areas (Table 1).

Table 1
List of probabilistic cytoarchitectonic maps published in journal articles or monographs

Primary auditory cortex (Te 1.0, 1.1, 1.2)	Morosan et al., 2001; Rademacher et al., 2001
Broca's region (BA 44, 45)	Amunts et al., 1999, 2004
Primary motor cortex (areas 4a, 4p)	Geyer et al., 1996
Premotor cortex (BA 6)	Geyer, 2003
Primary somatosensory cortex (BA 3a, 3b, 1)	Geyer et al., 1999, 2000b
Somatosensory cortex (BA 2)	Grefkes et al., 2001
Visual cortex (BA 17, 18)	Amunts et al., 2000

Further cortical and subcortical regions are currently under investigation.

Several studies have used these maps for the anatomical interpretation of functional imaging experiments analyzing, e.g., motor somatosensory and language processing (e.g., Amunts et al., 2004; Binkofski et al., 2002; Bodegard et al., 2001; Naito et al., 1999). The results of these studies show that the combination of functional imaging with cytoarchitectonic data can greatly enhance the structural information behind functional imaging experiments. However, the methods for combining cytoarchitectonic maps and functional imaging data had to be set up individually for each study. One reason for this time-consuming task is that the probabilistic cytoarchitectonic maps have not yet been integrated into a standard neuroimaging software package.

One of the most popular packages for the analysis of functional imaging data is SPM2 (The Wellcome Dept. of Imaging Neuroscience, London; www.fil.ion.ucl.ac.uk/spm). We here introduce a new SPM toolbox enabling the comparison of cytoarchitecture and function in this software environment to provide a routine, standardized application of probabilistic cytoarchitectonic maps as an anatomical reference for functional activations. The features of this toolbox include:

i) The display and statistical description of the probabilistic maps for each cytoarchitectonic area in stereotaxic space.
ii) The combination of the individual maps into a summary map to define non-overlapping volumes of interest for each area.
iii) The description of the anatomical location of functional activation clusters and local maxima.
iv) The functional characterization of anatomical areas by evaluating their response to different experimental conditions.

Overview of the method

The "SPM Anatomy toolbox" was developed for the integration of cytoarchitectonic probabilistic maps of the human cerebral cortex into the SPM software package. It consists of a set of scripts coded in the platform-independent MATLAB programming language (The MathWorks Inc., Natick, MA). Only the core version of MATLAB (version 5.5 or above) is required, no additional extensions are necessary. In combination with the freely available probability maps, the SPM Anatomy toolbox handles all of the steps necessary for an integrated analysis of structural and functional data, e.g., the visualization and statistical description of probabilistic maps, the generation of summary maps combining the information of the different probabilistic maps and finally the anatomical interpretation of functional imaging results using different measures of correspondence as described below. Since the functional analysis can be performed entirely within SPM, no specific requirements on the experimental setup or statistical analysis of the functional data are enforced. Rather, functional imaging data can be analyzed using all options offered by SPM2 including available toolboxes and extensions. The SPM Anatomy toolbox is also compatible with data processed in SPM99. Statistical maps, which have been calculated using alternative functional image analysis programs, such as AFNI (http://afni.nimh.nih.gov/afni/), FSL (http://www.fmrib.ox.ac.uk/fsl) or FMRISTAT (http://www.math.mcgill.ca/keith/fmristat/) can also be analyzed using the SPM Anatomy toolbox. The statistical maps resulting from the analyses in these programs which were saved in analyze or MINC volumes can be loaded and thresholded by the