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NeuroImage

NeuroImage 19 (2003) 1233–1239

www.elsevier.com/locate/ynimg

Technical Note

An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets

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Received 6 November 2002; revised 27 February 2003; accepted 7 March 2003

Abstract

Analysis and interpretation of functional MRI (fMRI) data have traditionally been based on identifying areas of significance on a thresholded statistical map of the entire imaged brain volume. This form of analysis can be likened to a "fishing expedition." As we become more knowledgeable about the structure–function relationships of different brain regions, tools for a priori hypothesis testing are needed. These tools must be able to generate region of interest masks for a priori hypothesis testing consistently and with minimal effort. Current tools that generate region of interest masks required for a priori hypothesis testing can be time-consuming and are often laboratory specific. In this paper we demonstrate a method of hypothesis-driven data analysis using an automated atlas-based masking technique. We provide a powerful method of probing fMRI data using automatically generated masks based on lobar anatomy, cortical and subcortical anatomy, and Brodmann areas. Hemisphere, lobar, anatomic label, tissue type, and Brodmann area atlases were generated in MNI space based on the Talairach Daemon. Additionally, we interfaced these multivolume atlases to a widely used fMRI software package, SPM99, and demonstrate the use of the atlas tool with representative fMRI data. This tool represents a necessary evolution in fMRI data analysis for testing of more spatially complex hypotheses.

Introduction

As the number of functional MRI (fMRI) experiments increases, fMRI data analysis needs to become more sophisticated in order to extract meaningful information from the data. Analysis and interpretation of fMRI data are frequently based on identifying areas of significance on a thresholded statistical map of the entire brain volume. This form of analysis can be likened to a "fishing expedition." As we become more knowledgeable about the structure–function relationships of different brain regions, tools for a priori hypothesis testing are needed. Selecting a region of interest for a priori hypothesis testing reduces the number of multiple statistical comparisons, thereby increasing sensitivity to activation. Thus, tools that support hypothesis-driven statistical analysis are more sensitive than their fishing expedition counterparts. Performance of such an analysis requires the generation of an appropriate image volume mask for defining the region to be probed. This can be a time-consuming process, fraught with error. This is especially problematic when one considers that hypothesis-driven analysis may be based on increasingly finer anatomic scales ranging from lobar analysis and anatomic subregion analyses to selective Brodmann area, Talairach, or Montreal Neurological Institute (MNI) coordinate-based analyses. The use of region of interest (ROI) analysis with anatomically defined features is not new. This has been well-described for the PET literature, and more recently for MRI (Bohm et al., 1991; Collins et al., 1995; Evans et al., 1988, 1991, 1992; Greitz et al., 1991; Hammers et al., 2002; Yasuno et al., 2002). This type of analysis offers increased sensitivity to subtle activations. However, the inherent reality of ROI analyses is that activations outside the ROI will not be detected.

In this paper we describe an automated method of hy-

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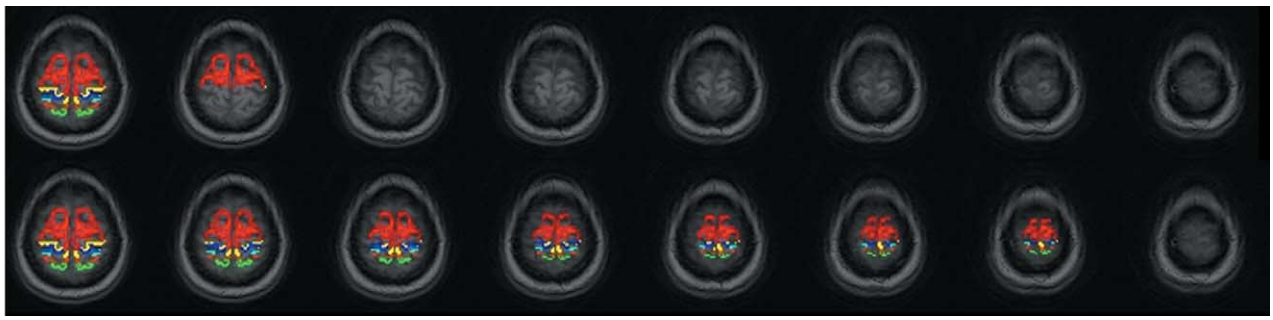
doi:10.1016/S1053-8119(03)00169-1



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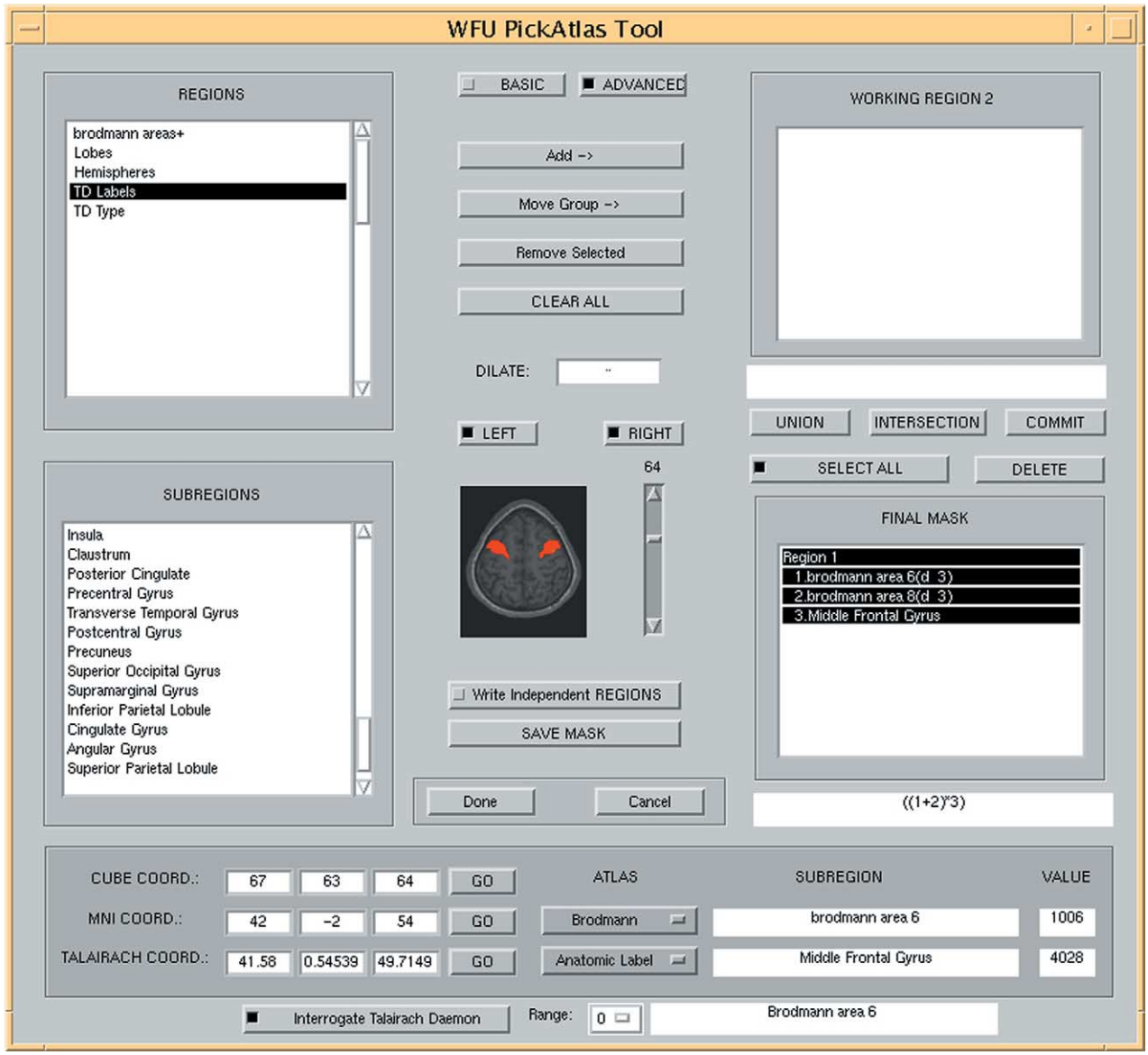

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Fig. 1. Superior-most slices of Brodmann atlas and the modified MNI Brodmann atlas overlaid on a single subject brain in MNI space. (Top row). Last slice returned from the Talairach Daemon results in partial slice in MNI space (*Z* coordinate 72) with 1 cm of brain at vertex remaining. (Bottom row) Modified MNI Brodmann atlas is constructed from the last complete slice (*Z* coordinate 71) for total brain coverage. Voxel dimensions are $2 \times 2 \times 2$ mm.

Fig. 2. Pickatlas Tool. Advanced Mode use of the pickatlas tool to generate ROIs for frontal eye fields (FEFs). The left-most column of the tool contains windows showing the major regions such as BAs (top), and displays the subregions within the selected major region (bottom). In this example the TD Labels region is selected and the subregions include the cortical gyri. The middle column contains the buttons for advanced and basic modes and for selecting and removing subregions from a working mask. The input area for performing dilation functions is located just below these buttons. A high-resolution image with the overlaid mask is also displayed for rapid visualization of the selected brain regions/mask. The right-most column includes a working region and a final mask region. Between these windows are the buttons for selecting unions and intersections. The final mask window in this example contains a region defined for the FEFs. This includes Brodmann areas 6 and 8 from the Brodmann area atlas. These areas were dilated by 3 (noted beside each area with (d 3)). These

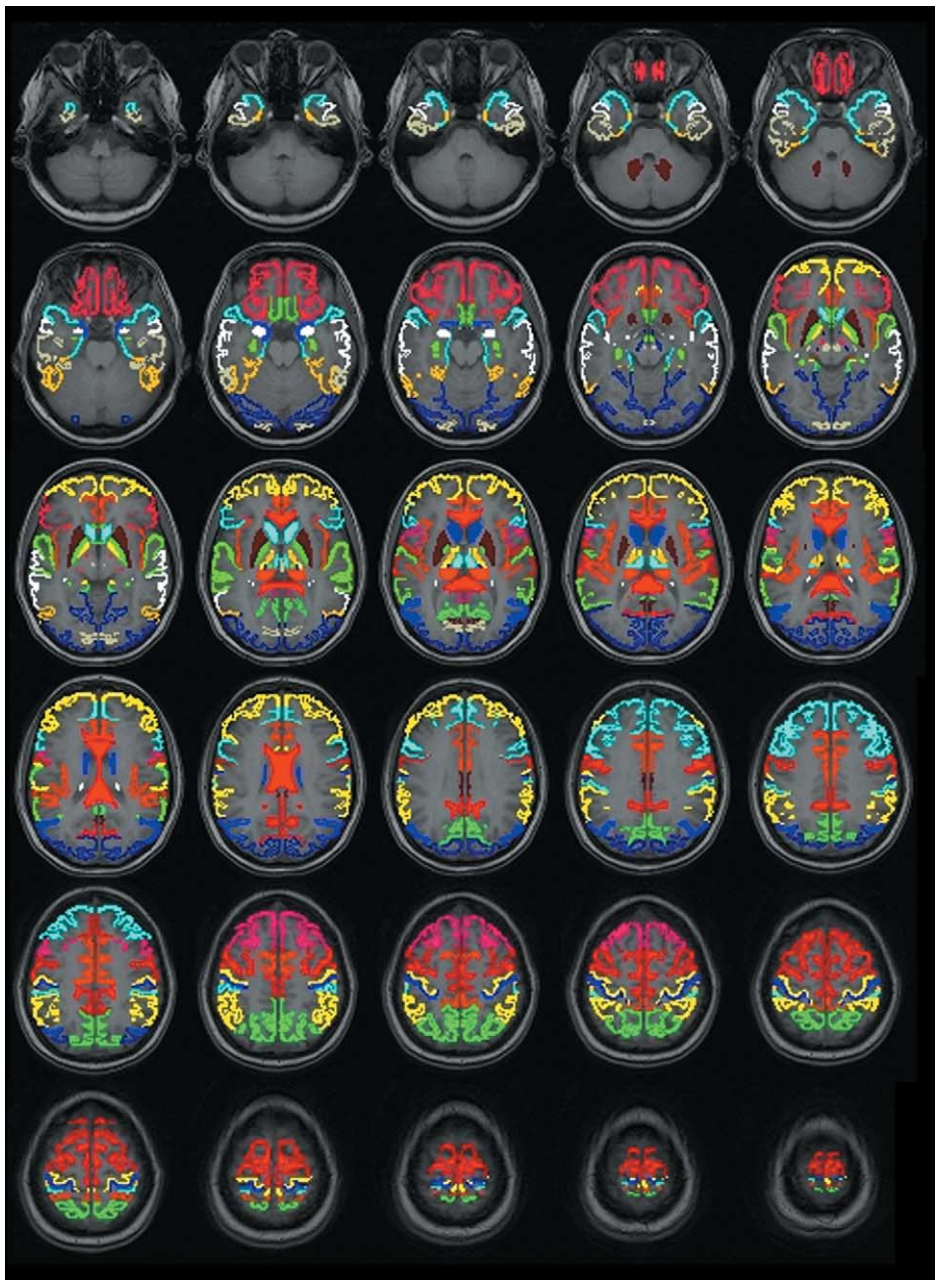

Fig. 3. MNI Brodmann atlas overlaid on single subject MRI. Images are representative slices at 4-mm intervals. Individual Brodmann areas are color coded. In addition to Brodmann areas, the atlas includes subcortical structures including the basal ganglia, the geniculate nuclei, limbic structures, the corpus callosum, and the thalamic nuclei (as returned from the Talairach Daemon).

pothesis-driven data analysis using an automated atlas-based masking technique. We provide a powerful method of probing data using automatically generated masks based on lobar anatomy, cortical and subcortical anatomy, and Brodmann areas. We have interfaced these multivolume atlases to a widely used fMRI software package, SPM99 (from the Wellcome Department of Cognitive Neurology, London, UK) (Friston et al., 1995a, 1995b; Holmes and Friston, 1998).

were then joined using the Union feature. The middle frontal gyrus was then selected from the TD label atlas and intersected with the union of BA 6 and 8 to generate the final ROI. Below the Final Mask window is an equation window that shows the operators applied to the subregions. A union is represented by a "+" and an intersection by a "*." Below the mask generation tool is a coordinate converter that will transform coordinates between cube, Talairach, and MNI space. The user can click on any point in the high-resolution brain and get the coordinates as well as the labels from any of the provided atlas for a coordinate. The lower-most functions allow the user to directly interrogate the Talairach Daemon.

Materials and methods

Atlas lookup tables

The Talairach Daemon (Lancaster et al., 1997, 2000) is a web-based application that returns anatomic and Brodmann area information based on Talairach (Talairach and Tournoux, 1988) coordinates. This is a widely used application for determining Brodmann areas based on surviving areas of activation. For example, the Talairach coordinates −40, −25, −54 will return the following responses:

Left Cerebrum, Parietal Lobe, Post Central Gyrus,

Gray matter, Brodmann area 3.

In order to generate our multivolume masks, we wrote an automated routine that probed the Talairach Daemon across the entire range of Talairach space and generated lookup tables based on coordinate position. The points were chosen to span the range of MNI coordinate space [−90, −126, −72] to [90, 90, 108] sampled at 2-mm intervals. This sampling interval was chosen to match the MNI normalization templates provided in SPM. For the remainder of this paper, we will use the term "MNI space" to represent a bounding box of −90:91, −126:91, −72:109 sampled at 2-mm intervals encompassing the SPM99 template brain. Coordinates were converted to Talairach space using a nonlinear transformation originally described by Matthew Brett (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) (Duncan et al., 2000). Although there is no published clear validation of this transform, it is widely used to convert from SPM99-MNI coordinates to Talairach space. Thus, at the end of the procedure, segmentation lookup tables were generated in both MNI and Talairach space for a total of 91 × 109 × 91 coordinates.

Generation of segmented atlas volumes

An automated routine was written to read in each coordinate from the lookup tables, create a segmented atlas, and generate segmentation lookup tables for each unique value encountered in the segmented atlas. MNI space atlas volumes were generated in this fashion for each category of response from the Talairach Daemon including a hemisphere atlas, lobar atlas, anatomic label atlas, tissue-type atlas, and Brodmann area atlas. For example, all coordinates corresponding to Brodmann area 3 were assigned a value of 3 in the Brodmann area atlas. The Brodmann segmentation lookup table was updated with each instance of a new Brodmann area. This procedure generated the multiple segmented atlas volumes in MNI space with corresponding lookup tables. The segmented atlases were saved as integer data ANALYZE format (Mayo Clinic, Rochester, MN) volumes.

Atlas modifications

The last uniquely labeled slice returned from the Talairach Daemon is at Talairach *Z* coordinate 65. The information returned from slice 66 is identical to that at slice 65, and nearly identical at slice 67. There is approximately 1 cm of additional brain tissue in the *Z* direction that is unlabeled. This region encompasses the superior-most extent of the sensorimotor cortex and includes portions of Brodmann areas 1, 2, 3, 4, 5, and 6. In MNI space, the Talairach Daemon atlas labels terminate in a partial slice at MNI *Z* coordinate 72. In order to complete the atlas to the vertex in MNI space, we replicated the last completely labeled slice (MNI *Z* coordinate 71) with a 0.9 demagnification factor for successive slices in the *Z* direction (MNI *Z* coordinate 72–78). Since Brodmann areas 1, 2, 3, 4, 5, and 6 continue to the vertex, this approach affords a good approximation for the intracranial contents (Fig. 1).

Atlas validation

After the atlas volumes were generated, they were validated against the Talairach Daemon at every voxel. A single volume was generated with areas of mismatch assigned a value of 1. Any discrepancy between any of the segmented MNI atlas volumes and the response from the Talairach Daemon for that voxel was recorded in the mismatch volume. Percentage fidelity was computed as the (total number of probed voxels − total number of mismatched voxels)/(the total number of probed voxels). Since we modified our atlas volumes for the superior-most extent of the brain, the fidelity was not expected to be 100%.

Automated atlas-based mask generation

A widget application (pickatlas) was created in Matlab for accessing the atlas volumes, selecting regions, and generating masks (Fig. 2). The graphical user interface provides the user with a list of major headings (Brodmann areas, Lobes, Hemispheres, Anatomic labels, and Tissue type) and all the corresponding subregions within each major heading. A visual display of a high-resolution T1-weighted brain MRI normalized to the SPM MNI template is also provided. As regions are selected, they appear as colored overlays on the template brain MRI. This allows for rapid atlas-based mask generation, using the full complement of segmented atlas volumes. The pickatlas routine was designed to allow extreme flexibility in defining masks including multiple combinations of segmented regions. The pickatlas tool can operate in basic or advanced modes. In basic mode, any atlas region selected is added to the final mask. This essentially performs a union function for all selected regions. In advanced mode, the user is allowed to create unique regions based on user-defined unions and intersections of the individual atlas regions. This provides a powerful means of generating unique ROIs. Thus, if the user is interested in the

Brodmann area 37 portion of the inferior temporal gyrus, an intersection of these two regions can be selected.

Atlas-based masking enhancements

One of the most exciting aspects of the atlas-masking analysis is the ability to define hypotheses on the basis of Brodmann areas. The Brodmann atlas areas, however, define a relatively thin cortical strip. In order to increase the volume of a masked area while maintaining its anatomic localization, we have incorporated the optional use of a morphologic dilatation operator using a unary 3×3 kernel. The user selects which regions to perform the dilation upon and the number of iterations before generating the final mask. This has the net effect of "growing" the region 1 voxel in each direction in-plane for every iteration of the dilatation function. The statistical inference for multiple comparisons is then based on the area of the dilated mask. In Basic Mode, all regions are dilated the same amount. However, in advanced mode, there is the capability to dilate each region independently. This added functionality may be useful for generating an intersection of anatomic and cytoarchitectural subregions. For example, the superior parietal lobule could be intersected with a dilated Brodmann area 7. Although the dilation function may extend the ROI beyond the strict anatomic borders defined by the atlas, the search region remains focused about the area of interest. It is important, however, that the investigator notes any area of activation that extends beyond the anatomic area of interest, especially with a large number of iterations of the dilation function (i.e., greater than 3). It is also important to treat the BA labels as candidate labels (within our atlas and the Talairach Daemon database atlas). These labels represent a generalization from Brodmann's descriptions as published in the 1988 atlas and rule-based boundaries assigned by the Talairach Daemon developers. Although these labels provide a standardized approach to searches in spatially normalized images, they should not be overinterpreted as searching absolute anatomy.

Integration with SPM

The pickatlas routine was integrated into the SPM software environment by modifying the spm_getSPM.m file. When viewing SPM data sets the user is given the option of performing an ROI analysis. If an ROI analysis is chosen, the user is prompted to either select a previously constructed ROI or use the pickatlas tool to select atlas-based regions for a priori atlas-based hypothesis testing. The selected mask is applied to the desired SPM contrast image prior to viewing. In addition, when an atlas_mask is selected, the SPM small volume correction is automatically implemented on the basis of the mask limiting the number of multiple statistical comparisons for more robust inference.

Results

Representative images of our MNI Brodmann atlas overlaid on a T1-weighted MRI of an individual subject normalized to the SPM MNI template are demonstrated in Fig. 3. In addition to the BAs, the atlas includes subcortical structures that are commonly of interest in brain imaging studies. Further examples of anatomic regions contained in the atlas volumes are depicted in Fig. 4. This figure includes various Brodmann areas and cortical gyri displayed on a surface-rendered brain from another subject. Interrogation of the atlas volumes using the Talairach Daemon demonstrated 99.76% fidelity for anatomic and cytoarchitechtural areas. As expected, areas of mismatch were limited to the portions of the atlas which we deliberately modified. The total number of mismatched voxels was 2923 (out of 902,629 probed). This included 548 voxels on slice 72, which was a partial slice returned from the Talairach Daemon database. The remainder of the mismatched voxels corresponded to Z slices 73–78, in which no data was returned from the Talairach Daemon. In addition, there were 28,989 voxels which exhibited minor name discrepancies between our lookup tables and the information returned from the Talairach Daemon. These discrepancies were located in the cerebellum and a small portion of the thalamus. The labels returned for these areas from our MNI atlas volumes and the Talairach Daemon database, respectively, were:

"Cerebellum Anterior Lobe" vs "Anterior Lobe",

"Cerebellum Posterior Lobe" vs "Posterior Lobe"

and "Ventral Anterior Nucleus"

vs "Anterior Nucleus."

These minor name changes were not classified as mismatches, and were related to modifications made to the Talairach Daemon database after we generated our atlases.

Use of atlas tools

As a representative example of the power and facility of our pickatlas tool, we present data from a previously published study of 12 subjects performing a visual object identification task. Details of the stimulation paradigm and image analyses have been previously published (Laurienti et al., 2003). This task required subjects to scan a visual display that is expected to produce activity in visual cortex and bilateral frontal eye fields (FEFs). If one had an a priori hypothesis concerning activity in the FEFs, the automated atlas tool could be used to focus the analysis and allow for small volume corrections. To illustrate the utility of this tool we performed both whole brain and ROI analyses on this data.

For the ROI analysis the advanced mode was used to make a union of Brodmann areas 6 and 8 with a 3-voxel

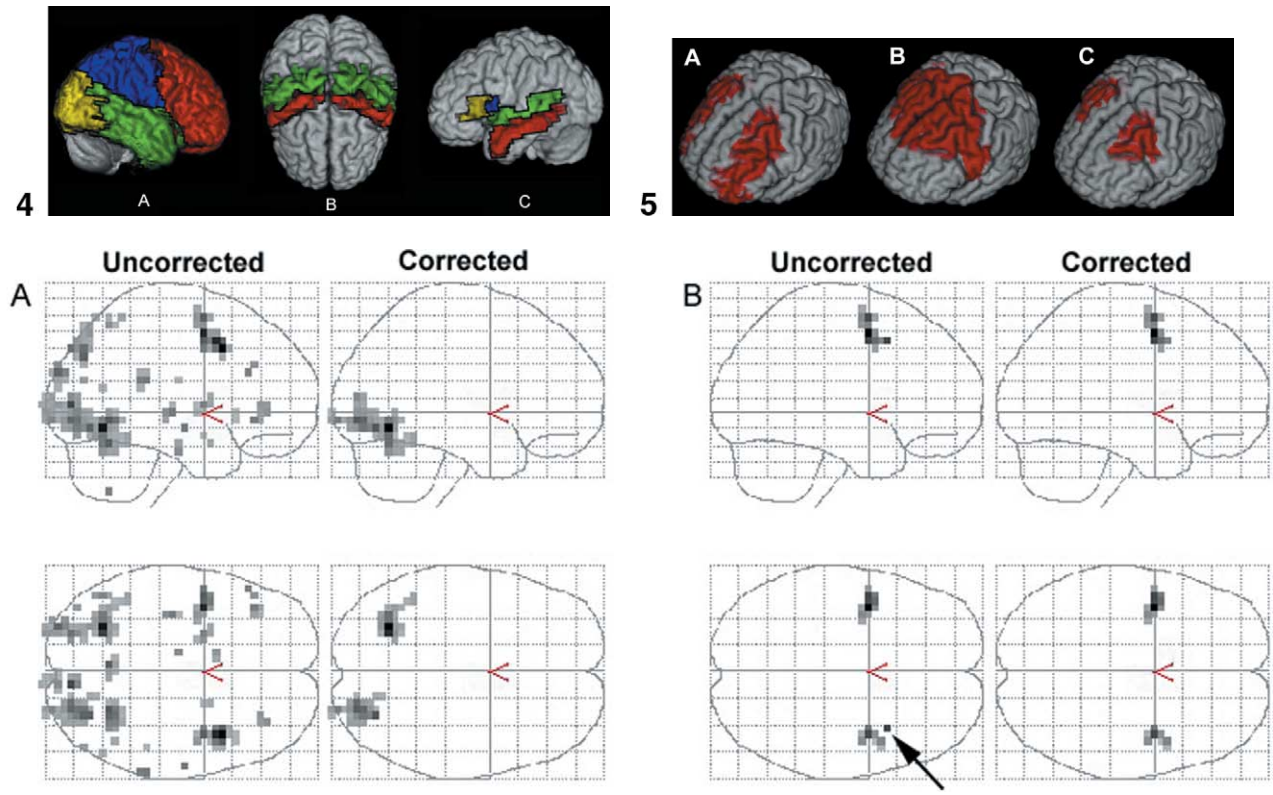

Fig. 4. Selected atlas regions overlaid on surface-rendered single subject brain normalized to MNI template. (A) Lobar atlas demonstrates frontal, parietal, temporal, and occipital lobes. (B) Precentral (red) and postcentral (green) gyri generated from anatomic label atlas. (C) Brodmann language areas 21 (red), 22 (green), 44 (blue), and 45 (yellow) generated from Brodmann area atlas.

Fig. 5. Generation of Frontal Eye Field mask. (A) Surface-rendered middle frontal gyrus mask generated from the pickatlas tool. (B) Surface-rendered Brodmann areas 6 and 8 mask generated using the union function in the pickatlas tool with a dilation of 3. (C) Frontal Eye Field mask generated using intersection of masks in A and B.

Fig. 6. Statistical parametric maps demonstrating the use of the pick atlas tool. (A) Whole-brain search. Uncorrected SPM glass brain views demonstrate activity in bilateral visual cortex and bilateral FEFs. Following correction for multiple comparisons using SPM extent threshold at $P < 0.05$, the visual cortex activation survives; however, the areas of activation in the FEFs do not reach significance. (B) Same data as in A analyzed using FEFs ROI mask. Uncorrected glass brain views demonstrate bilateral activity in the FEFs. Following correction for multiple comparisons using SPM extent threshold at $P < 0.05$, activity in the bilateral FEFs survive correction. Note a single voxel in the right FEF (arrow) that did not survive correction.

dilation. This area was then intersected with the middle frontal gyrus to encompass the FEFs (Figs. 2 and 5). The resulting SPMs for both the whole brain search and FEFs are demonstrated in Fig. 6. Note that the activated areas in the cluster level corrected SPMs ($P < 0.05$) are not significant for the FEFs using the whole-brain analysis, but are significant using the ROI analysis. The atlas-based tools provide the ability to perform hypothesis-based research based on previously established structure–function relationships.

Discussion

Functional MRI has revolutionized the field of neuroscience with the number of studies growing exponentially over the last decade. As sophistication in the forms of analyses grows, there is an increasing trend toward trying to define results using standard frames of reference. For many investigators this means using Talairach space and attempting a post hoc correlation of surviving clusters with Brodmann areas. In this paper, we demonstrate a powerful tool for performing hypothesis-driven research in a reproducible, accurate, and automated fashion.

Many fMRI studies report results in the form of tables of Talairach coordinates. As sophistication of research methodologies increases, additional information on specific anatomic regions and Brodmann areas can be provided. For many researchers, this involves converting MNI coordinates to Talairach coordinates, and inputting these values into the Talairach Daemon. This basic level of functionality can be easily achieved through manual data entry methods or by implementing some minor modifications to the SPM Matlab code distribution. These data analyses, however, do not achieve the statistical power possible by limiting the statistical search to a region of interest prior to data inference. Although a priori regions can be defined using manually drawn masks and ROIs, this can be a labor-intensive procedure, often based on arbitrary landmarks, and potentially fraught with error. These procedures also engender labora-

tory-specific data masks that limit reproducibility of results across laboratories. In contrast, our tool provides an automated and reproducible method for generating regions of interest that are based on standardized templates for a priori hypothesis testing.

While generating our atlases we noted that the Talairach Daemon database terminates prematurely relative to MNI space. This has implications for sensorimotor studies that rely on the Talairach Daemon database for labeling regions. There is approximately a 1-cm-thick section at the vertex of the brain for which the Talairach Daemon database provides no information. This region includes Brodmann areas 1, 2, 3, 4, 5, and 6. Our MNI atlases were extended superiorly to include this critical information.

In this paper we demonstrate a robust method for performing hypothesis-driven inference using atlas-based masking. We have integrated lobar, anatomic, and Brodmann atlases based on the Talairach Daemon into the SPM software environment. The atlases are stored as ANALYZE data volumes for easy accessibility. We have created a software tool that allows robust and flexible generation of atlas-based masks using any combination of unions and intersections of the individual atlas regions. This tool has been interfaced to the SPM software environment allowing on-the-fly definition of mask regions for hypothesis-based analyses. This tool represents a necessary evolution in fMRI data analysis for rapid testing of spatially complex hypotheses. The software described in this paper can be obtained at www.rad.wfubmc.edu/fmri.

References

Bohm, C., Greitz, T., Seitz, R., Eriksson, L., 1991. Specification and selection of regions of interest (ROIs) in a computerized brain atlas. J. Cereb. Blood Flow Metab. 11, A64–A68.

Collins, D.L., Holmes, C.J., Peters, T.M., Evans, A.C., 1995. Automatic 3-D model-based neuroanatomical segmentation. Hum. Brain Mapp. 3, 190–208.

Duncan, J., Seitz, R.J., Kolodny, J., Bor, D., Herzog, H., Ahmed, A., Newell, F.N., Emslie, H., 2000. A neural basis for general intelligence. Science 289, 457–460.

Evans, A.C., Beil, C., Marrett, S., Thompson, C.J., Hakim, A., 1988. Anatomical-functional correlation using an adjustable MRI-based region of interest atlas with positron emission tomography. J. Cereb. Blood Flow Metab. 8, 513–530.

Evans, A.C., Marrett, S., Torrescorzo, J., Ku, S., Collins, L., 1991. MRI-PET correlation in three dimensions using a volume-of-interest (VOI) atlas. J. Cereb. Blood Flow Metab. 11, A69–A78.

Evans, A.C., Marrett, S., Neelin, P., Collins, L., Worsley, K., Dai, W., Milot, S., Meyer, E., Bub, D., 1992. Anatomical mapping of functional activation in stereotactic coordinate space. NeuroImage 1, 43–53.

Friston, K., Holmes, A., Worsley, K., Poline, J., Frith, C., Frackowiak, R.S.J., 1995a. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2, 189–210.

Friston, K.J., Ashburner, J., Poline, J., Frith, C., Heather, J., Frackowiak, R.S.J., 1995b. Spatial registration and normalization of images. Hum. Brain Mapp. 2, 165–189.

Greitz, T., Bohm, C., Holte, S., Eriksson, L., 1991. A computerized brain atlas: construction, anatomical content, and some applications. J. Comput. Assist. Tomogr. 15, 26–38.

Hammers, A., Koepp, M.J., Free, S.L., Brett, M., Richardson, M.P., Labbe, C., Cunningham, V.J., Brooks, D.J., Duncan, J., 2002. Implementation and application of a brain template for multiple volumes of interest. Hum. Brain Mapp. 15, 165–174.

Holmes, A., Friston, K., 1998. Generalizability, random effects and population inference. NeuroImage 7, s754.

Lancaster, J.L., Summerln, J.L., Rainey, L., Freitas, C.S., Fox, P.T., 1997. The Talairach Daemon, a database server for Talairach Atlas Labels. NeuroImage 5, S633.

Lancaster, J.L., Woldorff, M.G., Parsons, L.M., Liotti, M., Freitas, C.S., Rainey, L., Kochunov, P.V., Nickerson, D., Mikiten, S.A., Fox, P.T., 2000. Automated Talairach atlas labels for functional brain mapping. Hum. Brain Mapp. 10, 120–131.

Laurienti, P.J., Wallace, M.T., Maldjian, J.M., Susi, C.A., Stein, B.E., Burdette, J.B., 2003. Cross-modal sensory processing in the anterior cingulate and medial prefrontal cortices. Hum. Brain Mapp. 19, 213–223, (published online before print).

Talairach, J., Tournoux, P., 1988. Co-planar Stereotaxic Atlas of the Human Brain: 3-Dimensional Proportional System: An Approach to Cerebral Imaging. Thieme Medical Publishers, Stuttgart.

Yasuno, F., Hasnine, A.H., Suhara, T., Ichimiya, T., Sudo, Y., Inoue, M., Takano, A., Ou, T., Ando, T., Toyama, H., 2002. Template-based method for multiple volumes of interest of human brain PET images. NeuroImage 16, 577–586.