# Group Average Activation Maps of Functional MRI: Methodology of Identifying Group Brain Areas Activated during Painful Thermal Stimuli, Motor and Vibrotactile Tasks in Humans

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**SUMMARY** – *Pain perception activates a complex network of cortical regions. The functional specializations of the various components comprising this network remain for the most part unknown. Moreover, the cortical networks described for pain perception include cortical regions involved in touch perception, and motor execution. We performed functional MRI (fMRI) studies to compare between cortical networks activated during a thermal painful stimulation with cortical networks activated during vibrotactile, and motor tasks. The fMRI scans for all three tasks were done in every subject, in single scanning sessions. This procedure enables the comparison between activation maps in individual subjects. A group average activation map was necessary to compare our fMRI results with earlier positron emission tomography (PET) studies of thermal pain, most of which have been based on group averages, and in order to examine the task dependent brain activations within a population of normal subjects. Here we describe the methodology developed for generating fMRI population activation maps.*

## Introduction

Functional MRI can generate brain activation maps at a higher spatial resolution than PET [2,3]. The technology of fMRI is well suited for determining brain activations in individual subjects [1]. Group activation maps are necessary for two reasons: to decrease variability or increase confidence in the activation maps obtained, and to obtain activation maps that reflect brain properties within a population of subjects.

Decreased variability in brain activation maps for specific tasks can be readily achieved by repeat fMRI studies performed in the same individual. However, across subject population fMRI activation maps are necessary when fMRI results are compared with population based PET studies.

We wanted to compare fMRI brain activation maps of thermal pain perception to vibrotactile stimulation, and motor execution brain maps. The subjects perform all three tasks in separate scans during a single session, enabling within subject across task comparisons. It was apparent, however, that the individual subject based analysis could not be compared to similar PET studies, unless the individual subject results are pooled to generate population activation maps. Below we describe a method for transforming fMRI data into a standard human brain atlas [4], and evaluate its performance with different anatomic images and transformation methods.

## Methods

Nine normal right-handed subjects took part in the study. Each subject underwent a single scanning session, during which a high-resolution anatomical scan was obtained in the sagittal plane, in the coronal plane, and three functional imaging series using Echo-Planar-Imaging pulse sequences. The painful task consisted of the subject alternating the right ventral fingers between two thermodes.

One thermode delivered a non-painful warm stimulus, and the second thermode delivered a painful hot stimulus. A pneumatically driven imbalanced wheel

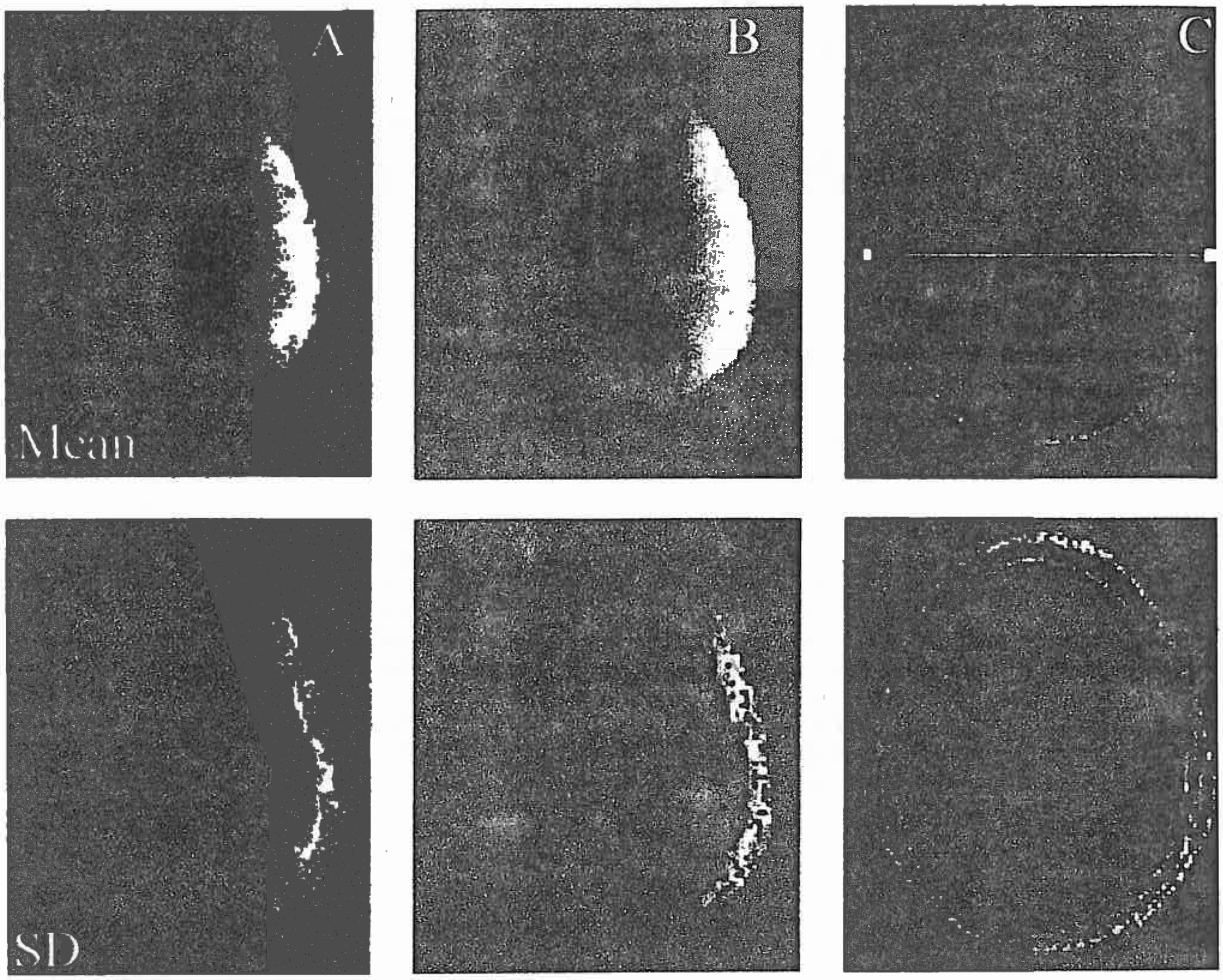


*Figure 1* Population averaged MR images (mean) and their variability (SD) are shown for three transformations (A, B, and C). See text for details.

generated a 50 Hz vibrotactile stimulus, applied to digits 2-5. The motor task consisted of sequential apposition of digit one with the remaining digits on the right hand.

*Scanning Sequence Procedure*

All fMRI studies were done on a 1.5 Tesla GE scanner equipped with the ANMR system, allowing echo-planar imaging, and a surface coil. Functional imaging used the following EPI GRE acquisition sequence: TR = 3500 ms; TE = 60 ms; flip angle = 90°; FOV = 40 cm x 20 cm. Six cycles of control and stimulus were performed during a functional imaging series, each cycle lasting 35 seconds. High-resolution anatomic data from 18 subjects, in two studies one utilizing a surface coil and the other a head-coil were used to evaluate the performance of atlas transformation method.

*Data Analysis*

Head movement was corrected. Unpaired t-values were calculated for each brain voxel, combined with a clustering criterion to determine single subject activation maps.

Across subjects statistical comparisons were then made based on multiple parameters defining statistically significant ROIs. For more details see Gelnar et Al[2,3].

*Group activation maps*

In order to determine the group activations, the unclustered t-maps had to be transformed into Talairach space[4] and averaged for each task. This was performed using commercial software, MEDx. The sagittal images were used to identify the anterior and posterior commissures (AC, PC).

The sagittal images provide an accurate identification of AC and PC because these structures are readily visible. The voxels defining the centers of AC and PC in the slice where they are best visualized were marked. The coronal anatomic images were then registered with the corresponding marked sagittal images, using the three-dimensional AIR [5]. This step defines the coordinates of AC and PC in the coronal images.

Then the boundaries of the brain and the midline are defined and adjusted on the coronal data set, thus identifying the transformation to map these images into Talairach space (images are re-sliced into 2 x 2 x 2 mm voxels). Since the t-maps are already in register with the coronal images, the latter step automatically defines the transformation for placing the t-maps into Talairach space.

The t-maps are then re-sliced to 2 x 2 x 2 mm voxels, spatially filtered with a Gaussian having a 5 x 5 x 5 mm FWHM and a 5 x 5 kernel. The latter step is necessary to diminish the variability in activation centers due to differences in brain anatomy between subjects, and should substantially increase the signal-to-noise ratio of the averaged activations [6].

The individual Talairach-transformed t-maps are then averaged over the number of subjects, and the distribution of the t-values in the brain area of interest is determined.

Since the latter distribution closely approximates a normal distribution, two standard deviations above its mean is used to delineate cortical regions significantly involved in each task.

A clustering criterion may then be superimposed to compensate for the expected false positive rate, given the large number of voxels that span the brain region of interest.

## Results

The accuracy of the Talairach transformation method was determined by examining the preservation of the anatomic details of the brain in the average images. The mean and standard deviation images of one slice in the group average is shown in figure 1.

Figure 1A is generated using an affine transformation to Talairach space when 8 subjects' high-resolution anatomic images were collected using a surface coil. Figure 1B is the same as 1A although a linear transformation was used for registration into Talairach. Figure 1C is generated using linear transformation into Talairach space when 10 subjects' high-resolution anatomic images were collected using a whole-head coil.

Image intensity and standard deviation across the indicated horizontal line (figure 1C top panel) is plotted in figure 2.

Figure 2 shows that the standard deviation of these averaged anatomic images co-vary with the anatomy and is highest at the edges of the brain. For the whole-head coil image the average standard deviation was 2911 (figure 2C), while for surface coil affine transformation this value was 3787 (figure 2A), and for the surface coil linear transformation it was 3921 (figure 2B).

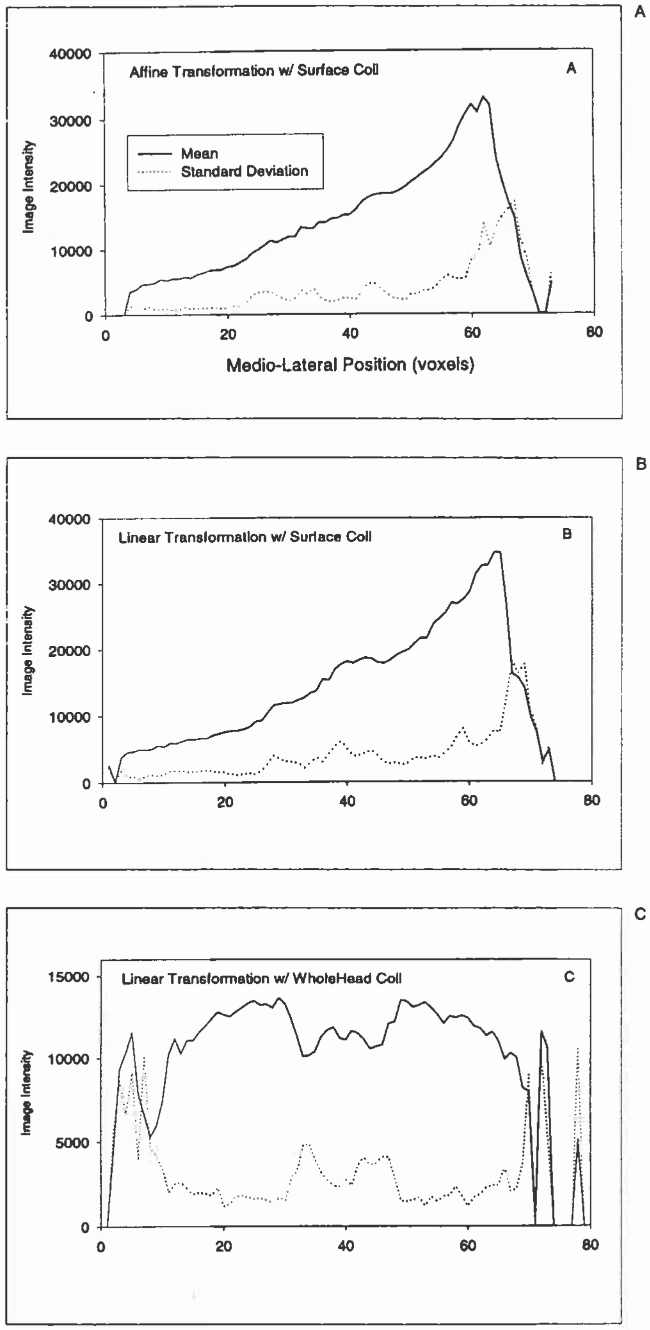


*Figure 2* Plots of intensity (mean) and variability (Standard Deviation) across the line indicated in figure 1C. A) Is for the image shown in figure 1A; B) is for the image shown in figure 1B; C) is for the image shown in figure 1C.

## Discussion

The analysis in figures 1 and 2 show that the whole-head Talairach registration of fMRI images results in the smallest standard deviations, while the surface coil affine transformation achieves the next best registration. However, the difference between affine and linear registration is minimal.

Moreover, in all three cases the largest variability occurs at the edge between the brain and outer structures.

This implies that implementing a procedure that automatically strips the tissue overlying the brain would render registration between functional data and anatomic data more precise [1].

With the method described here we have been able to register activation maps for different tasks into Talairach space, generate a population activation maps, and compare these maps across tasks [3].

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