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A Proposed Interleaved Echo Planer Imaging Technique for High Resolution fMRI

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Abstract

An interleaved Echo Planar Imaging (EPI) fMRI technique has been proposed here for obtaining spatially high resolution activation map overlaid on EPI image to reduce image acquisition time. First of all, the 2D and 3D anatomical high resolution and 3D + Time series (4D) low resolution functional images have been reconstructed and normalized. Slice timing correction for avoiding disorder and motion correction for small head motion during the scan has been provided using the post-processing image registration algorithms. The extent of translational and rotational head movements in fMRI data that can be corrected has also been determined and observed that 1-2 mm of translational and 2-4^0 (deg) of rotational head movement correction can be achieved. The effect of hemodynamic response (HDR) on the neural activation has been observed and the relevant activation map has been found for correlation coefficient, $r > 0.20$. In order to obtain highly reliable and noise-free activation map, spatial smoothing has been done using a Gaussian filter with different kernel width and 4 mm filter was found to be best with acceptable SNR. Frequency selective temporal filtering of fMRI data has been done to avoid cardiac, respiration and Cerebral Spinal Fluid (CSF) pulsation, which shows 0.10Hz upper cut-off frequency filtering is the most effective one. Finally high resolution functional and anatomical reference image have been obtained at 3.0T using the interleaved EPI technique. This fMRI analysis offers possibilities for improved neurological research and clinical neurosurgical applications.

I. Introduction

The 'pictures of the mind' that have been produced over the past few years have started to make a big impact on the way neuroscience is approached. It has been known that changes in blood flow and blood oxygenation in the brain (collectively known as hemodynamics) are closely linked to neural activity. When nerve cells are active they consume oxygen carried by hemoglobin in red blood cells from local capillaries. The local response to this oxygen utilization is an increase in blood flow to regions of increased neural activity, occurring after a delay of approximately 1-5 seconds. This hemodynamic response rises to a peak over 4-5 seconds, before falling back to baseline (and typically undershooting slightly). This leads to local changes in the relative concentration of oxyhemoglobin and deoxyhemoglobin and changes in local cerebral blood volume in addition to a change in local cerebral blood flow. These differential signals can be detected using an appropriate MR pulse sequence as blood-oxygen-level dependent (BOLD) contrast. The ultimate goal of fMRI data analysis is to detect correlations between brain activation and the task the subject performs during the scan. The BOLD signature of activation is relatively weak; therefore, other sources of noise in the acquired data must be carefully controlled. This means that a series of processing steps must be performed on the acquired images before the actual statistical search for activation can begin [1].

In an fMRI experiment a subject is required to perform a task while his brain is being scanned by an MRI scanner. In order to achieve a high quality analysis, the fMRI slices should be aligned. Hence, the subject is requested to avoid head movements during the entire experiment. However, due to the long duration of such experiments, head motion is practically unavoidable. As a result, imaging time and image quality has traditionally been at odds for all manner of magnetic resonance imaging. Using Echo Planar Imaging (EPI) technique in fMRI, the temporal resolution can be increased 10,000 times in comparison to high resolution anatomical imaging techniques but causes the increment of noise and reduces spatial resolution of the image. The 2D Fourier imaging techniques (2DFT) suffer much less from susceptibility distortion than EPI does, and this is one reason why these techniques are used in routine clinical scans. It is not impossible to carry out fMRI using 2DFT methods, particularly the fast techniques such as FLASH, but EPI will always have the speed advantage over such techniques. This is because the entire image is acquired from single free induction decay (FID), whereas FLASH only acquires one line in k-space from each FID [2-4]. In this work, an attempt has been made to reduce image acquisition time while keeping almost similar high resolution in the anatomical imaging with high resolution activation mapping by proposing technique called interleaved EPI, a hybrid of EPI and 2DFT, for both functional and anatomical image acquisition. To increase spatial resolution in EPI, two or more separate k-space traversals (interleaves) have been used to acquire different sets of k-space lines that are combined to produce one large data set. Interleaved EPI offers real benefits in carrying out high resolution fMRI at high field.

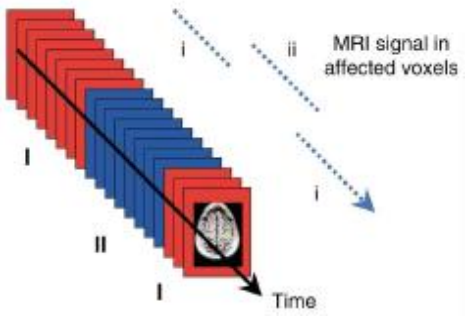


Fig. 1. In a block design experiment, sequences of images are acquired in contrasting conditions (I and II). After acquisition, those voxels whose signals change in synchrony (i to ii) with the stimulus or task can be identified [5].

fMRI Experiment Design

Among the many types of study that can be performed, three main experimental paradigms are in common use, which are block design experiments, event-related designs and hybrid block/event-related designs. Block design has been chosen for this work because of its simplicity. In so-called block designs, stimuli are presented in alternating short runs ("blocks") of several seconds' duration, and the MRI signals are then compared for the two types of blocks. For a visual-stimulation task to localize primary visual areas a subject might recording that lasts under 6 minutes. During that time, images may be recorded for many different parallel slices (typically 10–20), such that the slices are imaged about every 2 seconds. In this example, 80 images would be acquired for each slice for both conditions (stimulus ON and OFF). Those volume elements (voxels) within the brain that are affected by the stimulus (such as the primary visual cortex) view a bright flickering checkerboard for 20 seconds, followed by a dark screen for 20 seconds, with these blocks repeated several times; eight pairs of blocks, for example, would require a total provide a sequence of data points in which the signal alternates in intensity in synchrony with the stimulation because of the BOLD effect (Figure 1). Through detection of voxels showing this alternating pattern, the visual cortex can be identified [5].

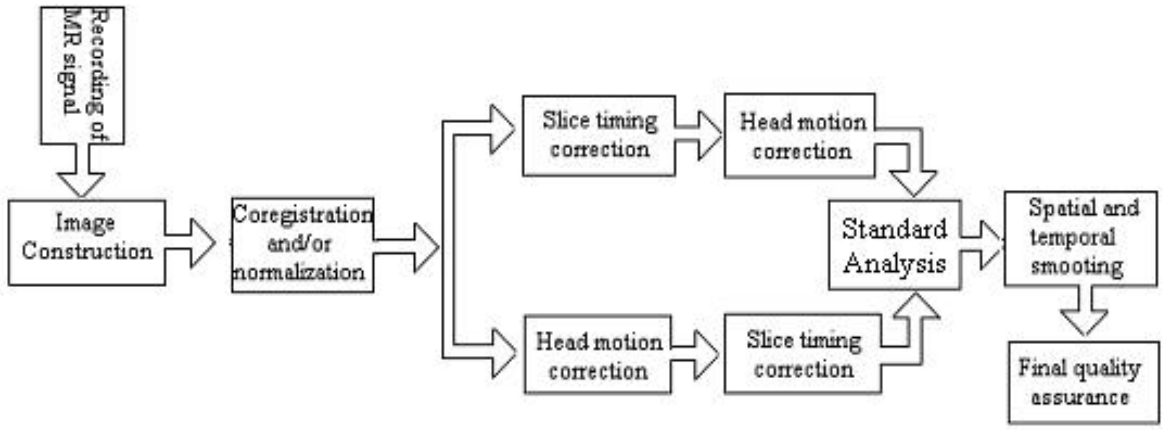


Fig. 2. Processing steps of fMRI data

II. Analysis of Functional Imaging Data

The aim of this analysis is to determine those regions in the image in which the signal changes upon stimulus presentation. There are many stages to the analysis of the data from any fMRI experiment (Figure 2). Firstly there are the pre-processing steps, which can be applied to the data to improve the detection of activation events. This includes raw data processing, image construction, centering and alignment. Then post- processing of fMRI data is performed which include registering the images to correct for subject movement during the experiment, and slice timing correction, which is performed to recover slice disorder. Next, the statistical analysis, which detects the pixels in the image that show a response to the stimulus, is carried out. Then temporal and spatial smoothing of the data is done to improve the signal to noise ratio. Finally the activation images are to be displayed, and probability values, which give the statistical confidence that can be placed in the result, are to be quoted.

Data Sources

In this work, secondary data of Massachusetts General Hospital of UK and *AFNI* [6] and NIfTI server at the NIMH, a research organization of USA have been used for both anatomical and functional MRI in raw format as no fMRI research center is available locally.

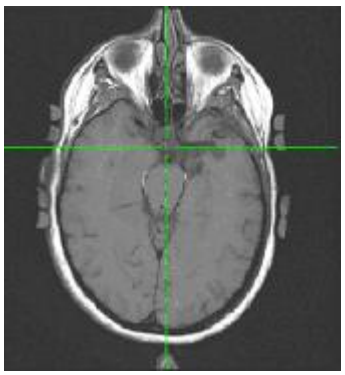


Fig. 3(a). Series 2 Images "2D Anatomical"

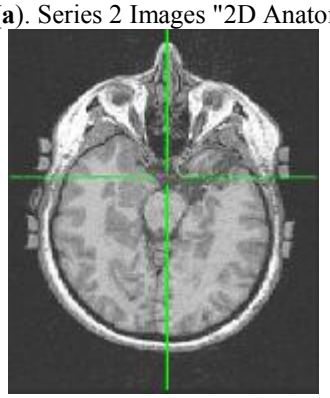


Fig. 3(b). Series 4 Spoiled Grass Recalled (SPGR) Images "3D Anatomical"

In order to reconstruct the *k*-space data into real space so that the image may be viewed and analyzed, a Fourier

transform is generally required. This may be run in 2D or 3D, depending on the MR sequence used. The "2D" series which is usually 17-19 images in axial orientation and the "3D" series which is usually ~124 images taken sagittally from left to right are the anatomical datasets of *AFNI*. The 2D/3D format stores one value per voxel.

Since the functional data overlays on the anatomical image, so to have a relevant activation mapping centering and aligning of the anatomical image have to be done. This has been done by placing the cross-hair in same place in both images and computing the differences between the location of the anatomical landmark in the 2D and 3D images.

Preprocessing Functional Images

The functional data is saved from the scanner in K-space form. That is, the data is actually the Fourier transform of the image data itself. G*recons5x* [7] program has been used to Fourier transform (FT) the data back to image space. Each image is a single slice through the brain. Because each slice has thickness, the images are made up of voxels rather than pixels. Image voxels are typically about 3.5mm×3.5mm×5mm. This relatively low resolution limits our ability to pinpoint the locations of activations. Each slice is 64×64 voxels and a set of approximately 17-19 slices will represent a brain volume. Depending on the length of the experiment, ~80 to ~250 brain volumes may be recorded.

Slice timing correction and motion correction of functional images

In analyzing the image intensity at each voxel over a time series of brain volumes, the assumptions are made that we are sampling an identical region of the brain at every point in an experiment. Head motion renders this assumption incorrect by moving samples of other, nearby, brain regions in and out of the voxel being studied [8]. If the head moves in time with the experimental stimulus, the resulting changes in image intensity may be indistinguishable from a 'true' experimental response.

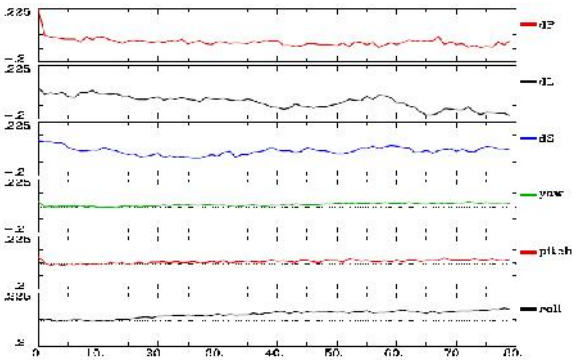


Fig. 4. Translational and rotational movement of the subject in different slices.

AFNI's 3D image-registration algorithm has been used for the motion correction. Each 3D sub-brick have been registered from the input dataset to the base brick 'dataset' using the command *3dvolreg (Appendix)*. This command specifies the final time point of the third functional run as the reference, or base image. The motion parameters are:
n = sub-brick index
Roll, pitch & yaw = rotation about the I-S, R-L & A-P axis respectively} degrees CCW

dS, dL & dP = displacement in the Superior, Left & Posterior direction } mm

For a given brain volume, each slice image is acquired at a slightly different time. The exact timing of the slices depends on the acquisition setup. In case of interleaved EPI, the time offset between adjacent slices will lead to differences in signal that can be substantial. In *AFNI* this can be done using the command *3dTshift [6]*, but a simpler way is to use the *–tshift* option during motion correction. The correction is applied prior to motion correction, since motion correction involves interpolating between adjacent slices – such interpolation will be inaccurate if adjacent slices represent different time points.

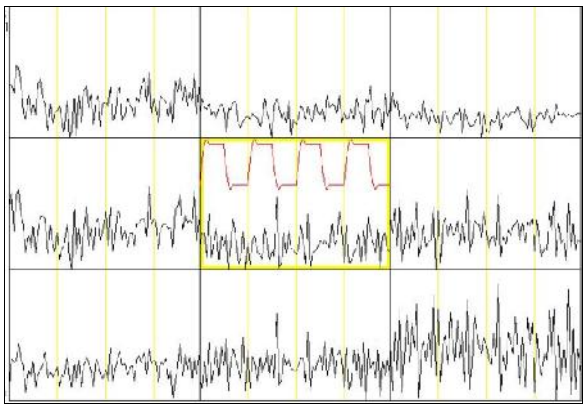


Fig. 5. Intensity pattern correlated the hemodynamic response (1-D file)

III. Statistical Analysis of the Data

Many techniques exist for statistically analyzing fMRI data and a variety of these are in general use [9]. The aim of such analysis is to produce an image identifying the regions which show significant signal change in response to the task. This has been done through correlations between the predicted pattern and the pattern in each voxel. This can identify locations in the brain that appear to be activated during the task. Program *3dfim* calculates a functional image from a 3d+time data file by cross correlation of each voxel time series with a user specified reference time series (figure 5). The functional image may then be used as input to program *Afni* to provide a visual display of the locations of those voxels showing a statistically significant correlation of intensity with the reference time series.

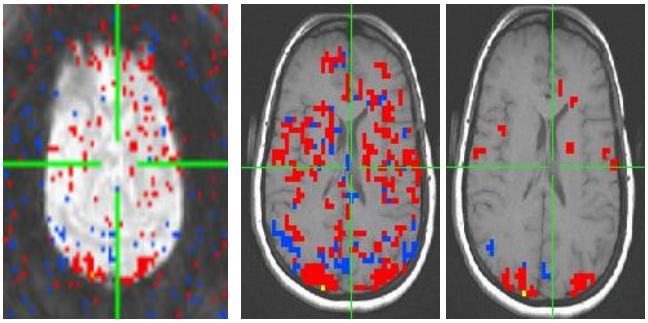
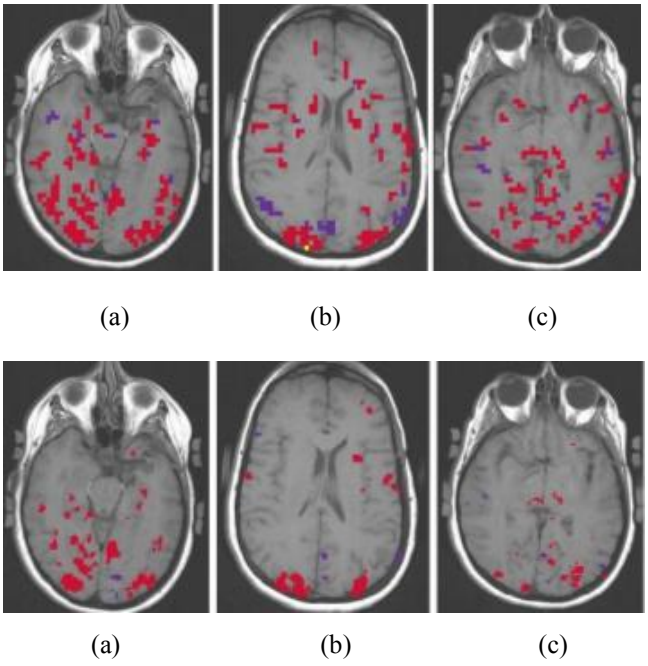


Fig. 6. (a) Non-correlated functional data on Interleaved EPI EPI image, No.correlated functional data after automasking overlaid on anatomical image of 2D (b) images. (c) Correleted data overlaid on anatomical image.

Spatial Smoothing

Any reduction in the random noise in the image will improve the ability of a statistical technique to detect true activations. Spatially smoothing each of the images improves the signal-to-noise ratio (SNR), but will reduce the resolution in each image, and so a balance must be found between improving the SNR and maintaining the resolution of the functional image [10]. An approach for spatial smoothing is to convolve the image with a three dimensional Gaussian function, of the form

$$f(x,y,z) = \exp\left\{-\left(\frac{x^2}{2S_x^2}+\frac{y^2}{2S_y^2}+\frac{z^2}{2S_z^2}\right)\right\}$$



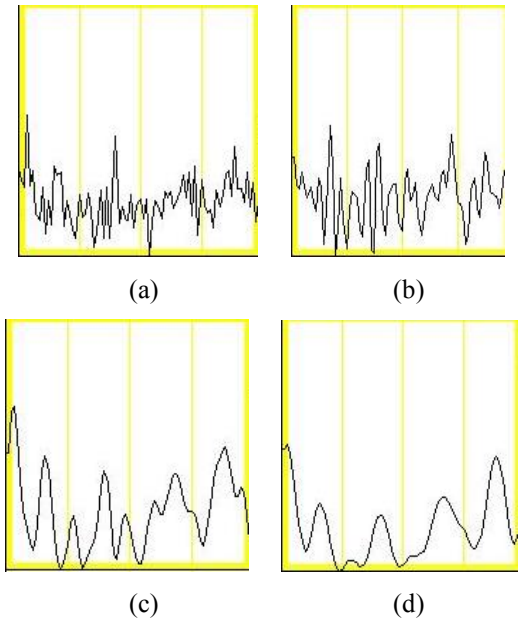
(a) (b) (c)

(a) (b) (c)

Fig. 7. (a-c) fMRI images without spatial filtering (d-f) images with filtering kernel 4 mm

So to smooth an image of resolution 3.5×3.5×5 mm^3 with a Gaussian kernel of FWHM 4 mm, therequired parameters are where S_x, S_y and S_z are the standard deviations of the Gaussian in each direction. A good estimate of the extent of such a smoothing is given by the full width at half maximum (FWHM) of the Gaussian kernel. The relationship between standard deviation and FWHM is given by, FWHM = 2.35×S, where S is the standard deviation.

$$Sx=\frac{4}{2.35\times3.5}=0.49, Sy=\frac{4}{2.35\times3.5}=0.49, Sz=\frac{4}{2.35\times5}=0.34$$



(a) (b)

(c) (d)

Fig. 8. Temporal filtering : Without filtering (a); Filtering with upper cut-off frequencies 0.15Hz (b), 0.10 Hz (c), 0.05 Hz (d)

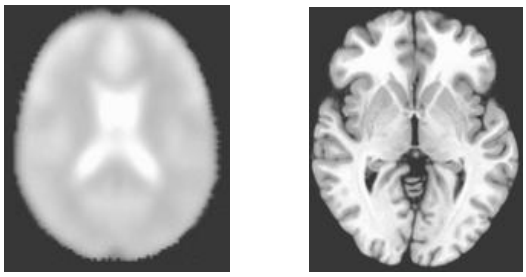
Temporal Smoothing

As well as smoothing in the spatial domain, improvements in the signal-to-noise ratio can be made by smoothing in the temporal domain. Since the BOLD contrast effect is moderated by blood flow, the rate at which the signal changes, in a genuinely activated region, is limited. Therefore smoothing each pixel's time series with a filter of similar shape will improve the SNR. As well as removing the high frequency fluctuations from the time series, it can be beneficial to remove any long term drift that may appear in the data. Such drifts can arise from instability in the scanner hardware, and will reduce the power of the statistical technique in detecting activations. Figure 8 shows the effect of temporal filtering on time-series data for different value of upper cut-off frequencies; i.e., f = 0.05, 0.1 & 0.15 Hz. Cutoff frequencies of the filter should be chosen carefully and visual inspection of the time series in *AFNI* after temporal filtering should be done.

Implementation of High Resolution fMRI at 3.0 Tesla

An interleaved EPI technique acquires the image in two or more free induction decays (FID), thereby trading some of

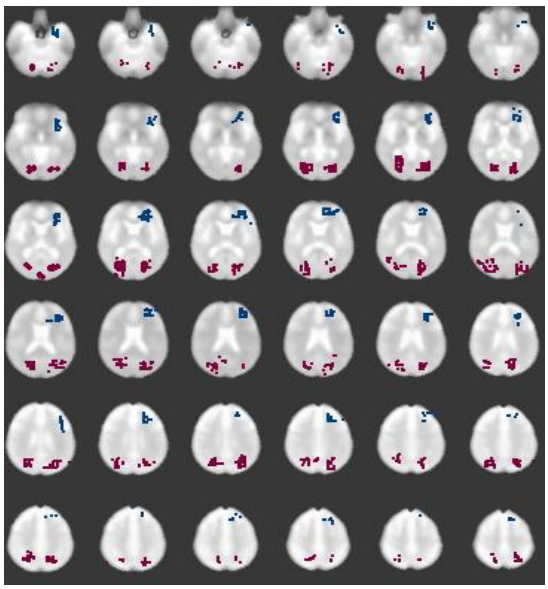
the speed of EPI to gain some of the image quality of 2DFT. A two shot multislice interleaved EPI technique has been used to acquire a 256×256 matrix size image. Eight slices of thickness 4.5 mm, covering the visual cortex were acquired in eight seconds, during periods of visual stimulation from the pattern reversal (4 Hz) of a checkerboard pattern. There were 32 seconds of stimulation followed by 32 seconds of rest, repeated 16 times. The in-plane resolution was 0.75 × 0.91 mm^2. The resulting image is shown in Figure 9 for the images drawn from 1.5T and 3.0T scanners.



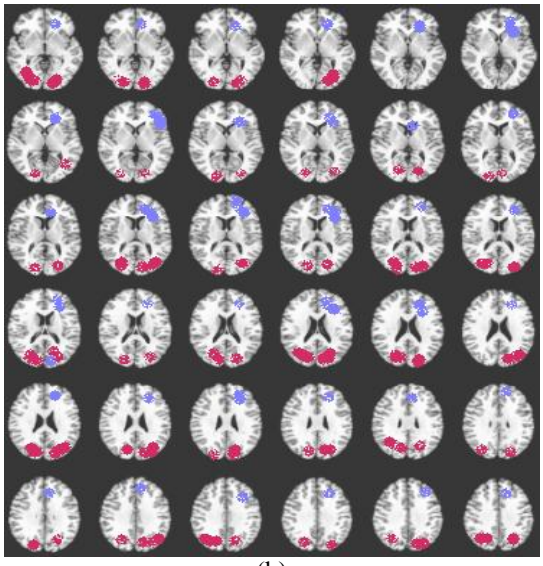
(a) (b)

Fig. 9. Anatomical interleaved EPI Image acquired in 1.5T (a) and 3.0T (b) scanners.

The images were re-registered, but no spatial or temporal smoothing applied. The fMRI data was correlated to an ideal HDR wave of the same period and phase as the stimulus and r-values calculated on the basis on peak height and spatial extent of the correlation maps.



(a)



(b)

Fig. 10. Activation map implemented on interleaved EPI image from 1.5T (a) & 3.0T (b) scanners.

IV. Result

Interleaved EPI is proposed, as a way of implementing EPI on a standard clinical scanner, which did not have the necessary fast ramping gradients. It has been also realized that the lower image acquisition time with high resolution technique could be used for fMRI resulting in a lower image acquisition time with high resolution activation mapping. A spoiled grass (spgr) anatomical image and EPI functional image consumes 1-1.5 hours for image acquisition with low resolution activation mapping but in case of 3.0T interleaved EPI anatomical & functional imaging technique, almost 0.5 hour of imaging time has been saved and functional image resolution has also been improved. *3dvolreg* can handle small motions fairly well, but larger motion (>1mm) might not be properly corrected. Checking the motion-corrected dataset using *AFNI*, this is revealed. For most practical purposes a FWHM of 4 mm is suitable, but larger filters may be useful if the signal to noise ratio is particularly bad, and the activation expected to cover a large area, whilst a narrower filter can be used if the SNR is good enough. It has been observed that much accurate temporal smoothing of time-series data can be performed with upper cut-off frequency f = 0.10Hz as this is adequately lower than the frequency of noise sources. The spotted regions represent the regions that correlate well to the stimulus (r>0.20). The background images are the average of the actual fMRI data set, so that the resolution seen in these images is the same as that of the activation maps. Regions of activation can be seen in the primary visual cortex and visual association areas. The change in the primary visual cortex upon activation was approximately 20%.

V. Conclusion

The newly proposed fMRI imaging technique uses an interleaved acquisition of anatomical and functional image to produce high resolution activation mapping with minimized acquisition time. This has several advantages over existing methods. Interleaved EPI has benefits of reduced distortion, improved line width and increased SNR for the scanners which can carry out conventional EPI. All collected data is used for slice timing correction and motion correction and image reconstruction resulting in a more efficient fMRI technique. fMRI is playing an increasingly important role in presurgical planning where the real-time processing of fMRI data has become essential. Real-time processing is useful in that it allows the map of functional activation to be displayed immediately following the fMRI experiment, while the patient is still in the scanner. If the data are deemed to be inadequate, new data may be acquired immediately. Finally, robust and simple techniques for data analysis need to be developed, allowing those who do not specialize in fMRI, to carry out experiments and interpret results.

Appendix

Program 3dvolreg
Purpose
Registers each 3D sub-brik from the input dataset to the base brik.
Usage
3dvolreg [options] dataset
'dataset' may contain a sub-brik selector list..

Options
-verbose Print progress reports. Use twice for LOTS of output.
Interpolation options:
-Fourier Perform the alignments using Fourier interpolation
-heptic Use heptic polynomial interpolation
-quintic Use quintic polynomical interpolation
-cubic Use cubic polynomial interpolation
Default = Fourier [slowest and most accurate interpolator]
-clipit Clips the values in each output sub-brik to be in the same range as the corresponding input volume. The interpolation schemes can produce values outside the input range, which is sometimes annoying.
-prefix fname Use 'fname' for the output dataset prefix. The program tries not to overwrite an existing dataset.
Default = 'volreg'
-base n Sets the base brik to be the 'n'th sub-brik from the input dataset (indexing starts at 0)
Default = 0 (first sub-brik)
-base 'bset[n]' Sets the base brik to be the 'n'th sub-brik from the dataset specified by 'bset', as in
-base 'elvis + orig[4]
The quotes are needed because the '[]' characters are special to the shell.
-dfile dname Save the motion parameters in file 'dname'. The output is in 9 ASCII formatted columns:
n roll pitch yaw dS dL dP rmsold rmsnew

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