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Anatomical Definition in PET Using Superimposed MR Images

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Techniques such as PET and SPECT provide tomographic images of function. These images may also represent underlying structure, but to a variable extent, depending on the type of physiological activity that is being imaged. MRI can provide images with exquisite anatomical detail, and can potentially be used to define underlying structure in PET and SPECT images of the brain. In the presence of anatomical distortion of the brain or focal or global atrophy, existing methods for anatomical localization (e.g., stereotactical localization) in functional images are deficient. We have developed a method of superimposing MR images onto PET images in an objective fashion. Using the outermost contour of the two images to derive, mathematically, the center of mass and the major and minor axes, we obtain the translational and rotational parameters to accomplish the superimposition of images. The aspect to this method that requires the most attention to detail is the positioning of the patient in the two tomographic devices and immobilization of the patient during the scans. We have obtained an estimate of error of the superimposition process by performing phantom studies which revealed an overall error of alignment for any point in the skull to be 1.54 ± 0.8mm. We have found this method to be convenient and accurate by visual inspection in a variety of patients with dementia. The method also lends itself to such applications as correction of measured isotope concentration for the effects of atrophy and for attenuation correction of emitted photons.

Functional imaging of the human brain is now possible through the use of positron emission tomography (PET) and single photon emission tomography (SPECT). These tests can provide information of great physiological importance, but only if the images are analyzed in a quantitative fashion. How should regions of interest be defined in functional images? Even though anatomic boundaries may have little or no functional relevance, anatomic labelling is currently the only means by which the pattern of functional

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activity can be comprehended and communicated (Mazziotta, 1984). Could such brain images be analyzed entirely on the basis of functional patterns using, for example, isotherm-type contour maps? It is unlikely that such contour maps could be interpreted without reference to anatomic landmarks.

Recognition of brain anatomy in any image is inherently dependent on the contrast ratio between grey and white matter in that image (Duara, 1985). The regional patterns formed by the boundaries of grey and white matter impart a recognizable appearance to internal brain structure. The improved grey/white matter contrast ratio in magnetic resonance imaging (MRI), compared to X-Ray CT scans, results in better appreciation of structure in MRI.

Some types of functional brain images correspond fairly closely to structural images obtained by CT scans, for example. Images of glucose or oxygen metabolism or of cerebral blood flow are examples of functional images which bear a fair likeness to the underlying brain structure. In these metabolic or flow studies the true ratio of activity in grey matter to that in white matter is about 4:1 (Sokoloff, 1980), which results in good grey/white matter contrast. Images such as those of cerebral blood volume, oxygen extraction fraction or of dopaminergic receptor concentration bear only vague resemblance to brain structure because of poor grey/white matter contrast, necessitating some method of anatomic localization in these images. Even in images of glucose metabolism, the apparent structural boundary may alter as a function of the structural metabolic rate. For example, activation of the medial occipital cortex by visual stimulation may make that structure appear larger than in the unactivated state (Phelps, et al., 1981). Many other functional perturbations may affect the apparent anatomical boundaries within which that function is located, mainly because of partial volume artifacts (Hoffman and Phelps, 1986).

Definition of individual anatomy is important in PET and SPECT images not only for localization of function but also for correction of the measured values of isotope concentration for the effects of brain atrophy. Regional or global atrophy of the cortex or subcortical structures cannot be detected on functional images, yet underestimation of isotope concentration occurs in regions affected by the atrophic process (Herscovitch, Auchus, Gado, Chi, and Raichle, 1986). This underestimation can be substantial, because atrophic grey matter is replaced by metabolically inert cerebrospinal fluid. This results in underestimation of the metabolic rate of the remaining grey matter, because of partial volume effects (Hoffman and Phelps, 1986).

When it is possible to define not only the individual brain anatomy in a PET image, but also the overlying skull, air sinuses and skin, yet another important correction of regional brain isotope concentrations becomes possible: correction for attenuation of emitted photons. Attenuation correction in PET is usually done either by a calculated correction or a measured correction (Hoffman and Phelps, 1986). In calculated attenuation correction a standard skin and skull thickness is assumed and fitted around the outline of the PET

image of the brain. Attenuation of photons in the cross-section of the image is then estimated. In measured attenuation correction, the use of a transmission scan, in addition to the PET scan, is required to obtain a measure of the attenuation properties of the brain. Both of these methods present difficulties since calculated correction is somewhat arbitrary and does not take into account individual anatomical factors—and measured correction adds considerable statistical noise to the final PET image, besides requiring an additional procedure and added radiation dose. The use of MR images that correspond to each PET image would allow individualized attenuation correction to be calculated for each PET image taking into account individual anatomical features, without adding noise to the data.

Our approach to anatomical definition in functional brain images is to develop a method of superimposing the subject's structural brain images on the functional brain images. We obtain MR images on each subject undergoing PET studies and match the plane of scanning in the two studies. The advantage of this approach is that individual anatomy, which can vary enormously, is utilized when the individual's structural image is superimposed on the functional image. Also, atrophy correction and, if desired, attenuation correction is allowed by this method. The major disadvantage is that structural images have to be obtained in the same plane and orientation as the functional brain images. This does require meticulous attention to positioning of the head in both studies. However, this disadvantage appears tolerable when it is realized that there is no alternative way of defining anatomy in functional images when the subject has a distortion of normal brain anatomy, such as with space occupying lesions or focal or global atrophy. Furthermore, there is no alternative way of performing atrophy correction, especially for regions of focal atrophy.

Methods

Positron Emission Tomography (PET)

We have conducted our preliminary work entirely on a PETT V positron camera designed by Ter-Pogossian and his associates (1978) at Washington University, St. Louis and constructed in-house at Mount Sinai Medical Center, Miami Beach. The PETT V obtains seven simultaneous slices of 15 mm thickness, with image resolution in the z-axis and in-plane being 15 mm (FWHM).

The positron camera is interfaced to a Perkin-Elmer 3220 computer (Oceanport, New Jersey) and raw and processed image files are stored on disc. All software in this application was written in-house using Fortran or Assembly language on the Perkin-Elmer computer.

All the human studies done for this application were with the tracer [F-18]

fluorodeoxyglucose (FDG), used to measure regional cerebral metabolic rate of glucose (Phelps, et. al., 1979). Phantom studies employed a variety of compounds labelled with [F-18].

Magnetic Resonance Imaging (MRI)

A Siemens Magnetom (Iselin, New Jersey) MR scanner was used in this study. A portion of the studies were done at a field strength of 0.35 Tesla and the remainder at 0.5 Tesla. The resolution of the machine is 1 mm, when using a head coil. A typical protocol included 11 slices of 10 mm thickness with 3 mm between axial slices. A relatively T_1 weighted spin-echo image series was obtained with TR = 1.5 sec. and TE = 35 msec. A relatively T_2 weighted spin-echo series was also obtained with TR 1.5 sec. and TE 105 msec. Human studies and phantom studies were done using the same protocol.

Co-Alignment of Subjects During MR and PET Scanning

Alignment of the head during MR and PET scanning is of utmost importance for the superimposition process to work. Therefore, we have taken care to ensure that the subject's head is positioned appropriately prior to the commencement of the scans. This, of course, does not ensure that movement of the head does not occur during the scans. To reduce the likelihood of head movement occurring, we perform the PET and the MR scans with the subject's head relatively immobilized by a customized headmold (Kearfott, Rottenberg, and Knowles, 1984).

This headmold is created prior to the subject's first tomographic scan. Typically it takes 10 to 15 minutes to make, and is constructed by mixing polyurethane resin and catalyst in a plastic bag and evenly spreading the mixture into a uniform layer. An exothermic reaction takes place with a maximum temperature of 105°F. The mixture expands, trapping air within it, and then hardens. The plastic bag with the mixture in it is positioned between a plexiglass shell and the posterior and lateral aspects of the subject's head. The expanding mixture surrounds most of the subject's head except for the face, forming a mold. Immediately after the headmold has hardened it is trimmed appropriately to allow it to fit in both imaging machines and a slit is cut out on one side to expose the area between the outer canthus of the eye and the external ear and allow alignment of the subject by means of a laser beam. The headmold is reusable for multiple PET or MR studies. We have found this device very useful, as it is not as uncomfortable as many other types of restraints and yet it discourages any significant degree of movement during the scan. Patients with neurological diseases including strokes, Alzheimer's disease, Huntington's disease and progressive supranuclear palsy have usually found the device acceptable.

Prior to the commencement of each tomographic examination an adhesive tape is placed on one side of the subject's head extending linearly from the inferior margin of the orbit to the middle of the anterior wall of the external auditory meatus (inferior orbitomeatal line). The head is then aligned, by means of the laser light, so that scans are obtained in the inferior orbitomeatal plane.

Z-axis Alignment in PET and MR

If care is taken at the time of tomographic studies to ensure that the zero position of each tomograph corresponds with the baseline chosen for the patient, i.e., the inferior orbito-meatal line, in this case, then the z-axis position of each of the slices will be known in both sets of images. Typically, the number of slices obtained for MR is approximately twice the number for PET, given the usual constraints of available time on the MR machine and patient tolerance. Thus, we have found, that even without a conscious attempt at ensuring correspondence of PET and MR slices in the z-axis, correspondence does in fact occur within a range of 2–3 mm in most cases. This "hit rate" can be improved further by pre-programming the position of the slices of the MR. It is important, nevertheless, to check z-axis positioning by visual inspection of purportedly corresponding PET and MR images, as patient movement in the machine is not uncommon. We have determined that it is possible for trained observers to detect a change in PET slice position in the z-axis, when a patient's position is adjusted by 3–5 mm by the operator. Thus, misalignment of this magnitude, of supposedly aligned PET and MR slices, can be detected for FDG images using the PETT V tomograph.

Superimposition of PET on MRI

Image data from the MR system are recorded on tape, transported to the PET laboratory and copied onto disc for further analysis.

Discrete Contour Mapping (DCM) of Digital Image Matrices

Once the corresponding PET and MR images have been displayed alongside each other, a DCM program (Winter, 1984) is employed to obtain the boundary between the brain and the background. In effect this program uses the grey level at each pixel to create a series of contours. The outermost contour in the PET image corresponds roughly to the contour of the brain when the threshold for the image is appropriate (approximately 40%). For the MR image the contour used is the boundary between the brain and the CSF or the inner table of the skull. The two outermost contours (PET and MR) are used to calculate the parameters to align the images. These contours are generally elliptical.

Calculating Principal Axes

The co-alignment parameters are calculated using these contours, delineating the brain from the background. Pixels inside the contour are set to an intensity of one, and pixels outside the contour are set to an intensity of zero. The zero and first order moments of this binary image are calculated and used to compute the center of mass. The second order central moments are then computed and used to calculate the orientation of the principal axes. The scale factor between the two tomographs is measured by phantom study.

Co-alignment of PET and MR Images

The final step applies these parameters to the PET image, geometrically transforming the PET image so that it has the same translation, rotation, and scale as the MR image. A slight modification to our image reconstruction software allows the rotational and scaling corrections to be applied during the back projection phase of the reconstruction. The translational correction, after correction for rotation and scaling, is applied to the reconstructed image.

Regions of Interest (ROI) Analysis

The MR scan is used for placement of regions of interest. We use square 8mm × 8mm ROIs which are placed contiguously along the outer margin of the brain, over the cortex, by a program that uses the outermost contour of the brain for positioning of the ROIs. Fine tuning of ROI placements is possible along with placement of additional ROIs in deeper brain locations. An operator must label the ROIs or groups of ROIs using a menu of brain regions for each slice of brain. The ROI placement co-ordinates are then used to display these ROIs on the PET image. Activity data from each labelled ROI or group of ROIs are entered into a data file along with a separate file of ROI location co-ordinates. (This allows redisplay of ROI locations for checking purposes, or for other applications.)

Validation of Method

Three principal sources of error, namely the calculation of (1) the location of the centroids of each ellipse (translational parameter) (2) the extent of head rotation (rotational parameter) and (3) the scale factor between MR and PET, were examined. The first two errors were examined using images of synthetically created ellipses on the computer. Ellipses were categorized according to their aspect ratio (ratio of major axis to minor axis length) and degree of rotation from the vertical position. The scale error was measured using a scaling phantom (two point sources placed 15 cm apart and embedded

in styrofoam) which was imaged in the PET and MR machines. Finally, the total error of the alignment process was measured using an alignment phantom (a flask with three liter capacity and elliptical cross section) within which were three point sources (1 mm diameter cylinders in the z-axis) in a triangular arrangement. This phantom was imaged in the MR machine and the PET machine. During the MR imaging, cylinders were filled with vegetable oil and during PET imaging, the phantom was filled with low concentration and cylinders were filled with high concentration [F-18] labelled compounds. In all cases, i.e., for ellipses, scaling phantom or alignment phantom, the DCM program was used to draw outer contours of the structures. In the case of the ellipses, the major and minor axes and the centroids were computed from these contours. In the case of the phantoms, the contours around the outermost margins and point sources were used for estimating translational and rotational errors and scaling factors.

Results

Center of Mass of Synthetic Ellipses (Centroid Location)

The average error over 49 trials was 0.04 ± 0.33 mm for the X coordinate and 0.015 ± 0.11 mm for the Y coordinate of the centroid.

Rotation of Synthetic Ellipses

In 49 trials the average error of angle of rotation was 0.19 ± 0.22 degrees. The aspect ratio of the ellipse was found to play a part in the production of the rotational error, with largest errors encountered as the aspect ratio approached unity (i.e. when the ellipse becomes closer to a circle in shape, errors increase).

Scaling

For 26 trials with the scaling phantom, the average error of measurement was $0.7 \pm 1.3\%$.

Overall Alignment Error

The alignment phantom was scanned in the MR and PET scanners on eight separate occasions, and five slices from each set of scans, with three points in each slice, were used to calculate the average error of point alignment. The mean error was 1.54 ± 0.8 mm for 120 trials.

Partial results are illustrated in Figures 1–3. Figure 1 shows the MR and PET outline of the alignment phantom without the DCM outline and without co-alignment of the PET and MR images. Figure 2 shows the MR and PET images

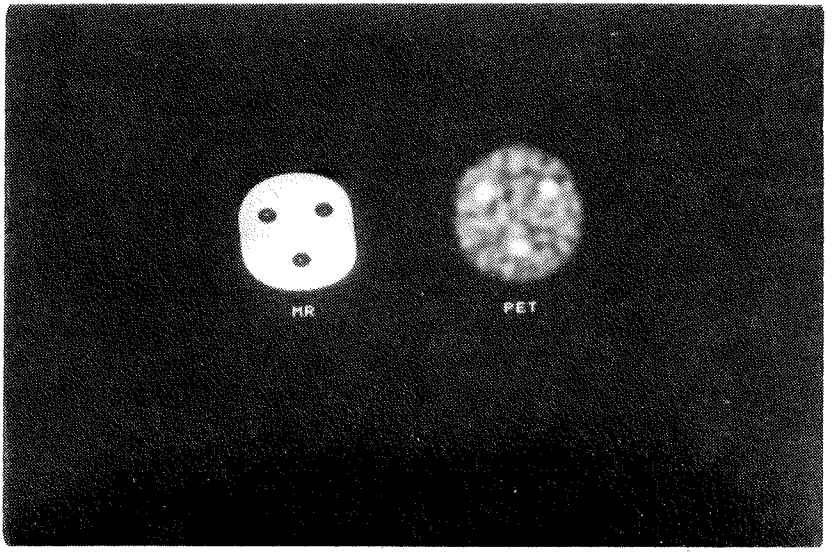

Figure 1: Magnetic resonance and PET images of an alignment phantom filled with water, containing three glass cylinders, arranged in triangular fashion, within each of which is a 1 mm inside-diameter bore. During MR scanning the bores are filled with vegetable oil to provide a strong signal. During PET scanning the water in the phantom contains [F-18] labelled compound at a concentration of 1 microcurie per ml and the inside bore contains water and [F-18] at a concentration of 10 microcurie per ml.

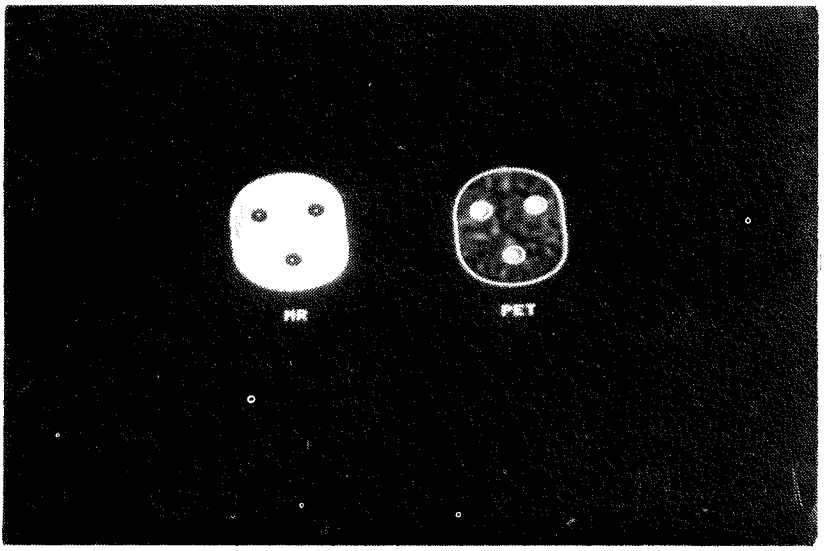

Figure 2: Magnetic resonance and PET images of alignment phantom. The Discrete Contour Map has been used to outline the outer boundary of the phantom, the inner cylinders and the point sources. The PET image has been co-aligned to the MR image.

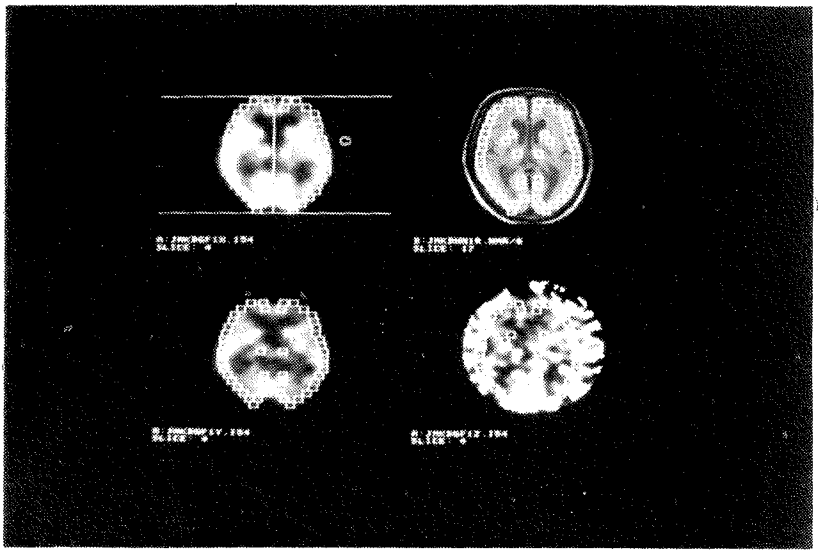

Figure 3: Counter clockwise from top left: PET image 1 from a behaviorally activated normal volunteer; PET image 2 from the same subject in the resting state. PET image 3 is a subtraction of PET image 2 from PET image 1; MR image at the same axial level as the PET images. All the PET images have been co-aligned to the MR image. Square 8 × 8 mm regions of interest in cortical and subcortical grey matter appear on the PET images at corresponding locations to those in the MR image.

of the alignment phantom with the DCM outlines and the PET image reconstructed after co-alignment. Figure 3 shows and MR image, two PET images under different physiological conditions and a subtraction of PET image 1 from PET image 2, all from the same slice in the same patient (the subtraction image has no anatomical detail within it, illustrating the use of this method in these circumstances). Boxes, i.e., square regions of interest, have been placed in all images, and show the applicability of this method in routine PET analysis (we currently have developed a program that will automatically place these boxes over the cortex; the operator is required only to make minor adjustments to these placements and indicate the positions for subcortical placement). All box placements are then designated an anatomical label using a cursor to assign each region. The MR structural image serves as the guide for anatomical designation. A standard atlas, cut in the same plane, may be used as well, to aid in naming the structures.

Discussion

This method of anatomical analysis of functional images is objective, and is the only method that truly respects individual anatomy. The error is as small or

smaller than any other method currently available. The method can be employed for making atrophy correction as well, and potentially for making attenuation correction. The major advantage of this approach of anatomical localization in PET and SPECT images, as opposed to the stereotactical approach (Fox, Perlmutter, and Raichle, 1985) which also gives relatively small error, is its applicability to abnormal brain morphology.

Drawbacks to this method include problems associated with the variation in slice thickness and resolution between the PET and MR machines. In this study, MR images were 10 mm thick, and the resolution of the MR scanner was 1 mm FWHM, whereas it was 15 mm for the PET scanner. The differences in resolution do not present a problem per se, as long as the MR image (structural definition) is at higher resolution than the PET image. The slice thickness differences, similarly, do not present a major problem as long as the center of the PET slices in the z-axis is relatively close (within 5 mm) to the center of the MR slice. However, patient positioning is of utmost importance. Previous MR examinations the patient may have had may be invalid for the purpose of alignment with PET, because of inappropriate positioning.

Another potential source of error in this method may come into play when the magnitude of distortion of either brain fuction or anatomy is so great that the outlines of the PET and MR scans no longer approach an ellipse. In this case the calculation of centroids and rotational angles of the ellipses is no longer valid. However, in reviewing over 50 PET scans from patients with moderate to severe Alzheimer's disease and multi-infarct dementia, only one patient with a massive hemispheric stroke had sufficiently reduced counts in the affected brain region so as to provide no identifiable definition of the original brain outline. In all other circumstances, in spite of distinctly abnormal appearance to the PET scans, the original outline of the brain could be detected. Moreover, by visual inspection, the correspondence of such features as indentations in the outlines, the mid-line location and of basal ganglia structures in the PET and MR images appeared very good in all cases. (Note: for this method to work it is necessary to have only one pair of PET and MR slices co-aligned so as to calculate the translational and rotational parameters for all other matching pairs of slices. It is highly unlikely that of the five or more available PET slices from any patient, every single slice will be so badly distorted in outline as to invalidate the estimation of translational and rotational parameters.)

As neuroimaging procedures increase in sophistication and as PET achieves status as a clinically useful tool, it is likely that the need for a structural image (e.g., MR scan) to accompany the PET scan will be recognized and be approved as part of a package. In such a situation the alignment of the patient and use of software to superimpose these images will become standard and can be offered as part of that package. As spatial resolution in PET improves, three dimensional reconstructions of PET images, representing the whole brain, can

be superimposed on the corresponding MR reconstructions, thus obviating the need for exact positioning during the scans. We believe that the superimposition of PET on a structural image is the only current method that is valid when anatomical distortion of the brain exists. All other methods make unverifiable assumptions about the ability to standardize human neuroanatomy. We have shown here that this superimposition can be done relatively simply and accurately.

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