THESES OF UNIVERSITY DOCTOR'S DISSERTATION (PH.D.)

Optimization of the protocol of brain activation PET studies

by

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DEBRECEN, 2003

I. INTRODUCTION

A significant amount of experimental data has documented – and therefore it has been generally accepted for quite a long time – that single mental functions or single brain activities are performed by a certain group of cerebral structures. To get to know the functioning of the central nervous system it is a must to localize these cortical regions according to function. Such knowledge can be obtained through brain activation experiments using the PET[1] technique as the active participation of neurons in the procession of information is accompanied by increased local energy uptake which, in principle, is easy to map via FDG[2], a sugar analog radiopharmacon. However, it presents a difficulty that equilibrium of FDG distribution in the tissues takes 30-90 minutes, thus this technique is only applicable in the functional study of conditions which can "clearly" (exclusively) be stabilized within this range. Otherwise, the measured FDG distribution only characterizes mean time to which the contribution of the functional state – the object of investigation – may be insignificant.

The use of tissue perfusion tracers[3] such as [^{15}O]-butanol or [^{15}O]-water may serve as a solution because there is a close link between increased glucose use and increased perfusion in the brain (this is how the locally increased energy requirement is fulfilled by an adequate amount of glucose). These tracer molecules are applicable in a short (second-minute) time-scale as the rather hydrophobic [^{15}O]-butanol diffuses in the tissues "almost freely" and the distribution of cerebral equlibrium ensues within 20-30 seconds. Most of the functional states of the central nervous system exists for only a short period of brain activity (functioning often means the "continuous change" in functional state), therefore these states are not detected clearly even in that short time scale. Consequently, the perfusion pattern characterizing these states is seen in a distorted way, i.e. *as the time average of distributions belonging to continuously changing functional state(s) in time*. The short period of data collection after the injection of the tracer (also resulting from the 2-minute halftime of the isotope) gives rise to further difficulties owing to a poor signal/noise ratio of the image reflecting the perfusion conditions in the tissue. That is why a selected function cannot be rendered to a given cerebral structure via the simple comparison (i.e. the mere establishment of differences) between test and reference (resting state) perfusion images. Changes in perfusion should be detected pixel by pixel in the image which is usually done through the analysis of results obtained from multiple measurements in test and reference states (several injections followed by data collection) using statistical hypothesis analysis (usually Student's t-test). Hypothesis analyses are performed in high numbers[4] applying the different versions of a special statistical evaluation program package (SPM96[5], SPM99, SPM2K).

Except for special cases, PET measurements are performed in several patients for statistical analysis, because lengthy investigation and non-negligible exposure to radiation pose a significant limit to the number of measurements to be carried out in the same patient in the same state. However, this limitation does not reduce the field of application in brain activation experiments since, in the majority of cases, the aim of the experiment is the investigation of a population homogeneous in one way or another. Statistical analysis at the population level has provided mathematically

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[1] PET: positron emission tomography
[2] [^{18}F]-2-fluoro-2-desoxyglucose
[3] tracer: radiopharmacon, a labeling substance
[4] The analyzed PET images include $0.5*10^6$ pixels, 15-20% of which belong to the gray matter.
[5] SPM : statistical parametric mapping

acceptable results, but, due to anatomical variability, a digital brain mapping technique is required for data procession. This technique enables researchers to transform individual cerebral PET images to a reference image (template, standard) defined in Talairach's space, i.e. standardization according to size and shape is made possible (*Talairach 1988*). Precise standardization is usually done through T1-weighted MRI images, which also show anatomical details, using the so-called brain mapping programs. Image transformation defined this way can be applied for a PET data file which makes it possible to transform a PET image into Talairach's stereotactic coordinate system.

Differences in perfusion between test and reference states result from several simultaneous effects. In addition to the specific effect of stimulation (condition effect), fluctuation of global perfusion (global effect) and perfusion component characteristic only of the individual (subject effect) also play a role in changes in the perfusion of a selected pixel. Change in perfusion associable with the specific effect of stimulation can only be defined from the measured primary data if it is assumed that the contribution of different components to the measured perfusion takes place in a definite manner (according to a presumed model) and calculations are based on those grounds. It often happens that the statistical evaluation of several models is required prior to the selection of the suitable one. The latest versions of the SPM program package, elaborated to perform statistical analysis at the pixel level and developed continuously, are more and more perfect, however, the comfortable and simple fitting of models is a service still missing from the palette offered by SPM.

II. AIM

To improve the efficiency of brain activation investigations using the PET technique we have aimed at further development of the key components of the SPM technique. We have decided to pay special attention to the *methodology of measurements and data-acquisition* using a PET camera, also the *optimization of programs and procedures influencing the accuracy of spatial normalization* as well as the *improvement of SPM applied in the production of the activation pattern*. The *creation of conditions for brain activation clinical research projects* has been the most important goal of methodological development. Simultaneously with software development, three topics have been devoted to such investigations, thus data procession has provided an excellent opportunity to carry out optimizations and validate the newly developed algorithms.

A. IMPROVEMENT OF MEASUREMENTS AND DATA FILING

1. For the registration of certain physiological features measured simultaneously with recording brain perfusion data using a PET camera we have wished to elaborate a method allowing for the investigation of correlation between perfusion and simultaneously determined other physiological parameters.

2. We have tried to find a solution for changing the data collection "time window" applied in perfusion distribution calculations to allow us to optimize the contribution of the functional state to the measured (or calculated on the basis of the time window) mean of the perfusion pattern.

B. DEVELOPMENT CONCERNING THE SUPPLEMENTATION AND OPTIMIZATION OF THE SPM-TECHNIQUE

1. It has also been our aim to minimize errors accompanying standardization when automatic and manual methods of spatial normalization are applied together.

2. The automation of the procedure of choosing an SPM model, i.e. the elaboration of a model-fitting technique, has also been our task.

3. A brand new development project has been designed for the study of the voxel-level correlation between perfusion changes and other physiological parameters accompanying changes in functional states. Also, the new project has been used in mapping the functional relationships between cerebral structures.

4. It is due to the nature of brain activation experiments that the results of voxel-by-voxel statistical analysis are influenced differently by the characteristics of the measuring device, physical features of the measurement procedure, as well as the preparatory interventions carried out before the SPM analysis. It has also been our aim to elaborate an SPM-simulating program package to study the aforementioned effects. With the aid of the simulator it is possible to generate (simulate) measurement data for a well-defined perfusion change (i.e. a change of known localization, size and intensity). Afterwards it is possible to study the accuracy of the activation pattern of the SPM-analysis, performed in a certain way, compared to the real perfusion changes.

III. MATERIAL AND METHODS

Brain activation experiments can only be performed if the arsenal of measuring devices, infrastructure of informatics and methodology are adequate as this is the only possible way to guarantee an exact answer to the questions brought up. Therefore, methodological development has affected the whole field of PET technology including data collection as well as the expansion of statistical analysis. As a result, perfusion measurements and data evaluation are done using standard investigation protocols and data processing methods today.

A. POPULATION

Homogeneitiy and sensitivity are the most critical aspects when candidates for brain activation measurements are selected. A population is regarded homogeneous if there is no significant difference among the individuals as far as the risen questions are concerned. Sensitivity, however, presumes a pre-screening, which can ensure that the individuals react to stimulation, performed under the PET camera, in a relevant manner.

B. PERFUSION MEASUREMENTS

Measurements have been carried out using a GE-4096 PET camera. The VAX/VMS-based informatics system of this device contains only the minimum of the

necessary data collection control software. A *control work station* (working in a synchronized manner with the data acquisition unit of the PET camera) can be used to synchronize the assistants' and doctors' work and, also, do the special job of data collection.

1. Protocol of investigations

In brain activation investigations, several PET measurements have to be used even for one patient depending on how many functional states and repetitions are required to record perfusion distributions. In the same project, the order of applied stimulations and perfusion measurements made at rest may change individual by individual. For example, in a double-state measurement series, where reference (A) and test (B) states alternate, it is recommended to alternately apply the ABABAB and BABABA order of measurement for each individual. PET measurements, however, are made according to the same measurement protocol, independently of the order of stimulation.

1. Preparation. The patient is informed about the details of the protocol and the *branül* required for administering the injection is inserted. If special measurements are taken, electrodes (ECG, EEG) or stimulation devices (headphone) have to be fixed.

2. Setting the camera's field of vision. The target area of the examination is fixed via the patient's accurate positioning which is aided by a triple laser system. Because of the relatively long (1-3 hours) examination period, the head is fixed using a *Cawo* pillow.

3. Transmission measurement. Each perfusion measurement series is started with a 10-20-minute transmission measurement prepared via a 10-20 mCi ^{68}Ge line-source. (The length of the measurement period is decided on the basis of the activity of the line-source.)

4. Perfusion measurements. Transmission measurements are followed by perfusion measurements at 10-12-minute intervals. The correctness of setting is controlled prior to each injection using the laser lines of the gantry and accidental shifts are corrected. Should a shift turn out to be a significant one (2-3 cm) it is recommended to make a new transmission measurement. Parallel to the control or correction of setting, the conditions for the next stimulation or rest should be ensured. Dynamic measurement is started simultaneously with injection.

Application of an optimally chosen window of data collection during perfusion investigations

In quantitative investigations, the blood curve, obtained from arterial blood, and dynamic PET investigation are enough to produce rCBF images. In this case, the camera is started simultaneously with the injection of the tracer, and the dynamic investigation lasts for 2.5-3 minutes (e.g. a series of 36x5s frames).

In practice, quantitative rCBF measurements are used in exceptional cases only, owing to the difficulty of drawing arterial blood and the comparative nature of using perfusion investigations. One of the critical points of non-dynamic brain perfusion investigations is the determination of the start and duration of data collection. The method elaborated by us allows for producing accumulative images from a dynamic series at discretional measurement times if data collection is started simultaneously with the administration of the pharmacon and the dynamic investigation consists of 5s exposures. Using special software, the time curve of the average activity of intracranial voxels is produced for the 5s exposures constituting the series, and based on this, the pharmacon's time of arrival at the brain is established. From that time on, 40, 60 and 90-second total sinograms are produced from the sinograms of the dynamic investigation for further procession.

2. Reconstruction

Data collection is followed by a double archiving process (the tape system of VAX and storing on CD) in order to save primary data in a secure way. Parallel to this procedure, the reconstruction of images is done (accumulative perfusion images are produced using the combined sinograms).

The standard reconstruction program of the GE-4096 Plus PET camera produces 15 axial sectional images form the 10.5 cm field of vision. Resolution in these planes corresponds to 6 mm. The filtered back-projection reconstruction algorithm corrects for tissue absorption, scattering and distortions resulting from accidental coincidence and dead time. In brain perfusion measurements, reconstruction parameters have always been chosen according to the manufacturer's recommendations (4.2 mm Hannaing filter; correction for tissue absorption is done by applying transmission measurement of adequate quality). After reconstruction and corrections, the 3D distribution of the perfusion tracer is obtained in 15x128x128 image matrices and 6.5x2x2 mm voxels.

Reconstruction programs run automatically, they are sent to the department's file server also in an automatic fashion, where the conversion of *Scanditronix*[6] into *MINC*[7] file-format is also automatic. Further procession involves the exclusive use of MINC data files stored in the file server.

C. T1-WEIGHTED MRI INVESTIGATIONS

Accurate data procession requires a T1-weighted MRI image in digital format for each patient. At present, MRI data collected according to a jointly agreed protocol are obtained from the *Diagnostic Center of the University of Kaposvár* and *HUNIKO Ltd*. Investigations at the Kaposvár Diagnostic Center have been carried out using a 1.5 T Siemens MAGNETOM SP63 scanner and 3D gradient-echo collection (TR=13 ms, TE=5 ms, flip angle=10º, width of section=2.5 mm), or applying a 1.5 T Siemens Vision scanner and 3D gradient-echo collection sequence (TR=14 ms, TE=7 ms, flip

[6] The reconstructed images of GE 4096 PET camera are made in Scanditronix format which, in practice, is only recognized by software marketed by GE.

[7] MINC: Medical Image Network Change Data Format is a file format elaborated at Montreal Neurological Institute and used in Montreal brain map programs. This has been regarded as the best suitable format at our Department as several diagnostic and research software programs recognize it.

angle=8º, width of section=2 mm). The MPRAGE sagittal MRI measurements by *HUNIKO Ltd*. are done using a Siemens MAGNETOM Harmony 1.0T Whole Body MR apparatus, the layer thickness being 1.5 mm (TR=11.1 ms, TE=4.3 ms).

MRI measurements are forwarded on a CD or in a closed data transfer channel. Having run the relevant conversion programs, we also store these images in the department's file server in MINC format.

D. PREPARATION OF PERFUSION IMAGES FOR STATISTICAL ANALYSIS

The first step of preparation aimed at the spatial normalization of PET investigations involves the re-naming, sorting, noise filtering of PET data files and the *interpolation* of 2x2x6.5 mm voxel sizes into 2x2x2 mm ones.

Standardization, which is a complex task in image processing, should be carried out individual by individual. Choice from among the seven semi-automatic programs is made on the basis of the availability of the given person's MRI data file.

1. Spatial standardization in the absence of MRI investigation

The semi-automatic process includes four steps and interactive intervention is needed at one point only:

1. *Double phase shift correction.* In the first phase, all of the perfusion images obtained through perfusion investigation are transformed into the image system of co-ordinates of the very first reference investigation using PET-PET registration. The images belonging to different investigations are placed in the same system of co-ordinates, covering one another. The transformed images are used in preparing the patient's average perfusion pattern, of consequently good statistics, which later serves as a basis for spatial standardization. In the second phase, this averaged image is regarded to be the reference image during PET-PET registration, so at the end of the registration process, the images of each investigation are put in the same spatial position with the averaged perfusion pattern.

2. *Automatic spatial standardization.* Applying the averaged perfusion investigation and an automatic brain mapping program we determine the affine transformation, involving nine parameters, which helps transform the averaged perfusion image into the system of co-ordinates of the MNI template.

3. *Interactive spatial standardization.* Owing to the limited axial field of vision of the PET camera, the result of the previous step does not yield optimal results for fitting it with the template. Therefore 'correction transformation' is needed to more precisely fit the average transfusion image with the template. Correction transformation can be determined using an interactive registration program.

4. *Transformation of all of the perfusion investigations.* In this step, the transformation determined in steps 2 and 3 is applied for the image whose spatial position falls in with that of the averaged investigation in the case of each shift correction.

2. Spatial standardization utilizing MRI investigations

We have to interactively intervene into the six-step semi-automatic process at one point only:

1. *Segmentation of the MRI image.* Using the automatic segmentation program, we delete the non-intracranial elements of the image.

2. *Standardization of the MRI image.* Standardization is done via a modified automatic brain mapping program, which defines a 12-parameter affine transformation and a 3D deformation field. The two together ensure that the images of the individual MRI investigations fit in with the MNI template in the best possible way. In addition to the original – T1-weighted MRI – image, the technique also uses the segmented image.

3. *Double phase shift correction.* This step is the same as the relevant step of processing in the absence of MRI investigation. The averaged perfusion image of the patient, which is consequently of good statistics, is not used for standardization but for future MRI-PET registration.

4. *Automatic MRI-PET registration.* During registration we define the 6-parameter affine transformation which derives the averaged perfusion image into the image system of co-ordinates of the MRI investigation of the same patient. The segmented MRI image is used as a reference image.

5. *Correction of the MRI-PET registration.* The correction transformation, which renders the anatomical fitting of the averaged PET image and MRI image more accurate, is produced applying an interactive program.

6. *Transformation of all of the perfusion investigations.* In this step, transformations determined in steps 4, 5 and 2 are applied in a sequence for each investigation brought into the same spatial position due to shift correction.

E. SPM ANALYSIS

Statistical analysis of brain activation investigations at the population level is done using the SPM99 program package. To be able to comfortably use this program it is recommended to store all of the spatially standardized and filtered investigations in one subdirectory. The program is an interactive one, i.e. several of the parameters having a significant influence on the results have to be determined prior to calculations. Some of these parameters are applied in a standard manner (*global normalization*: based on the ANCOVA model, *gray matter threshold*: 80% of the average voxel value). The selection of the applied linear model or the choice of correlation parameters, however, may be different from project to project.

The analysis can also be carried out using automatic model fitting. In this case, a whole series of calculations can be made if the pilot program prepared in Matlab language is rewritten. After running the program, a subdirectory is created for each calculation, in which all of the parameters, initial and final results of the calculation

are found. Having chosen a subdirectory like this, one can document SPM results or interactively carry out further calculations based on the model.
Documentation of the results is performed by applying an image fusion program specially elaborated for this purpose. Image fusion can be obtained from the averaged standardized MRI investigation of the population and SPM.

F. CORRELATION ANALYSIS AND MAPPING FUNCTIONAL CONNECTIVITY

During correlation analysis, a single 3D correlation-coefficient distribution is generated in Talairach's system of co-ordinates, for each of the chosen pairs of parameters. Using Fischer's transformation, this distribution can be converted into Student's t-distribution, from which the high correlation areas can be identified by setting a threshold. Applying a 3D cluster analysis the parameters of a high correlation area (location of the maximum and its Student's t-value, size) can be presented in a table.

Mapping functional connectivity is done in three steps. In the first step, a 6D correlation distribution is prepared using distributions containing perfusion components and setting a correlation threshold at the same time too. Next, the cluster analysis, which helps with identifying area-pairs of high correlation, can be run. Simultaneously, each of these correlation area-pairs marks two points, in which each measured perfusion value can be used in a further correlation analysis. As a result of calculations, pairs of regions with presumed close positive or negative correlations can be collected.

IV. RESULTS AND DISCUSSION

Several technological problems had to be solved before launching research projects applying the brain activation technique. Simultaneously, software development tasks of different levels and complexity had to be taken on, too. Methodological development has involved the whole field of PET technology from data collection to statistical analysis. Their listing follows the logic of steps applied during the procession and evaluation of data and PET analyses. The procession and evaluation of brain activation investigations (series of investigations) at the population level is a complex process requiring significant computer capacities and computing time. Among others, the complexity of the job is due to the fact that the changes in perfusion under the influence of the selected stimulation are superpolated to a high noise background, and, owing to the restriction of doses of irradiation, series of investigations can only be performed if several patients are available. These patients' neuroanatomy and their reactions to stimulation may be very different. The listed circumstances – alone and together alike – result in the fact that only sophisticated statistical methods can be used in the evaluation of the mass of data of perfusion parameters detected in the initial state and in stimulated functional states.

In accordance with the aims of the dissertation, methodological development has been done in each important field of the complicated evaluation system. New scientific results achieved by this work are as follows:

1. Applying the dynamic perfusion time window, a method has been developed for the preparation of images of brain activation investigations prior to reconstruction.

This method ensures that a measurement interval, optimal for registration and statistical analysis alike, is established for each independent perfusion investigation.

2. Segmentation algorithm has been elaborated for the high-accuracy and fully automated transformation of individual T1-weighted MRI images into Talairach's system of co-ordinates. The procedure has been validated through using the MRI images of a population of 23 individuals, and parallel to this, we have created the first national, stereotaxially standardized population average images of T1-weighted brain MRI and [15O]-butanol PET investigations.

3. A manifold program package has been developed for the automated spatial standardization of perfusion PET images. The software allows for the control of the individual steps of registration via the image fusion technique, and, if necessary, the correction of the results of automated registration algorithms based on the so-called landmark method. Statistical analysis of standardized data distorted by minor registration errors may yield results even in cases in which small-scale activations cannot be detected owing to the inaccurate registration of the MRI template and MRI-PET.

4. The applicability of the SPM99 program package has been widened via the introduction of special software modules. The automation of choosing a model for statistical analysis has also been solved and it may significantly help with data procession, especially if neurophysiological parameters are used in a statistical model.

5. A method has been elaborated for correlation analysis at image level. The new technique is applied in correlation investigations between neurophysiological parameters and perfusion components responsible for stimulation. The methods has successfully been applied in mapping functional connectivity in the 6D correlation field and based on cluster analysis.

6. An SPM simulator has been developed for simulating the derivation of perfusion changes in the brain using the PET technique. This complex software package has been used in the analysis of the features of the bolus and statistical images obtained via the protocol of continuous injection. It has been established that if injecting is carried out in a bolus, a perfusion change of the same degree is reflected as an activation area of higher level of significance in the statistical images. It has been demonstrated that, with the aforementioned method, the optimal data collection time-window is 40-50 sec, presuming the perfusion change is permanent in time. Applying a simulator we have proved that the size of the activation areas highlighted via the $p<0.05$ corrected threshold probability is very close to the size of the area of the true perfusion change.

7. Using perfusion distributions based on auditory stimulation and recorded during the solution of cognitive tasks we have identified all of the ipsy and contralateral cerebral cortical regions being in functional relationship with one another.

8. We have used the PET technique to investigate what perfusion differences, associated with the information derived from arterial baroreceptors, can be

detected between the cerebral hemispheres. Stimulation of the carotid sinus baroreceptor resulted in an increase in perfusion on both sides in Brodmann areas No. 6 and 8 and, also, in the infero-latero-frontal region of the prefrontal area of the right hemisphere (BA 10, 44 and 47). Results point at certain stages of the procession of information taking place mainly in the right hemisphere.

9. The central projection of the vestibular system has been investigated at the population level using a comparative technique. Caloric stimulation has been conducted in 6 healthy patients and 6 patients suffering from anacusis and sinistrolateral vestibular lesion owing to tumor surgery affecting the cerebello-pontine junction. Statistically significant difference was found only in one region of the activation patterns representing the perfusion changes of the two populations. The region located in the Ri/SII area can definitely be regarded as the cerebral representation of then sensory entrance of the vestibular nerve. The results support the assumption that this region is the human analog of the PIVC area identified in primates.

V. PRACTICAL IMPORTANCE OF RESULTS

The results outlined in the dissertation are of importance in the field of statistical parametric image processing applied in basic research and diagnostics. The SPM99 software package, generally used in the procession and evaluation of brain activation investigation series, has been supplemented with new elements significantly improving the applicability of this technique. Thus, compared to the SPM99 program, the spatial normalization of brain activation PET investigations can be performed faster, more precisely and in a more controllable manner. The automation of choosing a model for statistical analysis has also been solved which – especially if neurophysiological parameters are applied in a statistical model – can be of great help during data procession.

To be able to successfully accomplish the above listed methodological development, we had to create a complex software-developing environment consisting of several libraries. The high quality components of this software package can be published, giving an opportunity for us to enter the software competition in which the aim is to elaborate up-to-date and freely accessible scientific programs.

VI. PUBLICATIONS

A. PUBLICATIONS CLOSELY RELATED TO THE DISSERTATION

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