ORIGINAL ARTICLE

Methodologies for the analysis and classification of PET neuroimages

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Received: 18 September 2012/Revised: 20 May 2013/Accepted: 8 June 2013/Published online: 28 June 2013 © Springer-Verlag Wien 2013

Abstract Neuroimaging analysis aims to support clinicians in the diagnosis of neurological diseases by using radiological images. Positron emission tomography (PET) is a nuclear medicine imaging technique used to produce threedimensional images of the human brain for neurological studies. Due to the large number of generated images, there is a lot of effort in defining computer based tools to analyze and classify brain images. Such analyses are used to identify cerebral regions of interest (ROI) related to specific neurodegenerative diseases. Statistical tools, such as SPM (for Statistical Parametric Mapping) and its MarsBar plugin, are largely used by physicians for ROIs identification and for image analysis. Nevertheless, large datasets analysis (e.g. studying pathologies for many patients and for large sets of PET images) requires repetitive SPM procedures for each

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Experimental and Clinical Science Department, University Magna Graecia of Catanzaro, Catanzaro, Italy e-mail: cascini@unicz.it patient's image, mainly due to the lack of (i) automatic procedures for analysing set of patients, and (ii) validation of using SPM versus patient magnetic resonance as reference brain templates. Finally, SPM analysis requires human intervention, and there is no automatic system guiding physicians for pathologies identification. As a contribution for the latter issue, we defined an automatic classification tool using topological relations among ROIs to support physicians while studying a new patient. Starting from a set of known pathologies associated to medical annotated PET images (i.e. associated to neurological pathologies), we used SPM and MarsBaR tools to define a reference PET images dataset; ROIs extracted from input PET images have been compared with known dataset and classified, suggesting physicians with (a subset of) pathologies associated to those PET images. Experiments showed that the classifier performs well. Moreover, in order to improve the repeatability of experiments with large datasets, we use an SPM plugin called AutoSPET, which allows to perform SPM analysis on a large PET images dataset, using different SPM plugins within a unified user interface, and allowing to simply run statistical analyses. AutoSPET is available on our server and also as an SPM plugin on the SPM website. Finally we report experiments to validate the use of the standard T1 SPM template versus the magnetic resonance ones.

Keywords PET images analysis · Region of interest · Statistical analysis · Automatic procedure · Systems integration · Statistical parametric mapping

1 Introduction

Radiological and magnetic resonance (MR) images are generated by imaging devices able to detect functional or structural conformation of human brain regions. Neuroimaging tools are used by clinicians to analyse neurological images to identify known pathologies. Positron emission tomography (PET) is a powerful image-based analysis method of functional investigation which can be used to support brain neurological diseases discovery, allowing to measure specific biochemical brain processes and identifying changes that occur at cellular and molecular level. It is thus widely used for neurological studies where sense, motion and cognitive functions can be identified in brain regions through metabolic and/or blood flow tracers. E.g., in clinical neurology, PET is a suitable method to study brain changes associated with dementia because images variations can be associated to physiological parameters resulting in neurodegenerative changes (e.g., blood flow, neurotransmission etc.) (Herholz and Heiss 2004). The study of pathophysiology of neurodegenerative diseases using PET is carried out through a wider spread of radiopharmaceuticals already validated and used in diagnostic procedures (e.g., the 18F-fluorodeoxyglucose). Images are then studied by analysing their contents by using statistical tools that principally based on the analysis of voxels, i.e. the volumetric picture elements composing the images. Each voxel is a volume element that represents a value of signal intensity or color in a three-dimensional space, similarly to what pixels represent for two-dimensional images. Available tools allow to perform a voxel-by-voxel analysis, to identify image variations that can be associated to functional changes. Most of such tools report a (statistical) map which is studied to identify and select portions (i.e., voxels) responsible of functional diseases. In case of brain images, statistical maps are useful to clinicians for detecting the alterations of cerebral metabolism that can be associated to diseases. There exist many software tools and statistical modules for image analysis used to extract numeric values contained in neurological images. One of the most widely adopted tools is SPM (for Statistical Parametric Mapping) (Jeong et al. 2005; Schoenahl et al. 2003; Tzourio-Mazoyer et al. 2002). Many software tools or SPM plugins, such as MarsBar (Brett et al. 2002), are available to support clinicians in filtering the large volume of data obtained from diagnostic image-based instruments, but the image study and disease identification still requires human intervention. In this paper we report a framework for semi-automatic images analysis and disease classification based on regions of interest (ROIs) analysis.

The ROIs analysis is carried out by using SPM and MarsBaR plugin. MarsBaR extracts mean intensity values from regions thus being complementary to statistical map analysis which provides local maximum intensity values. Its output are spatial coordinates (x, y, z) and identifies maximum and minimum signal values for each ROI (Brett 2011). The here presented framework uses topological

relations among ROIs, treated as 3D minimal bounding boxes for set of voxels. PET images associated to known neurodegenerative diseases previously selected are used as reference sets. PET images of a patient that needs to be clinically analysed are given as input to the framework; then ROIs obtained with MarsBar are compared by using topological relations to the previously available reference set. Figure 1 shows an example of how the ROI based classification algorithm works for an input patient data.

ROIs of a patient, indicated as blind patient in the figure, are compared with ROIs of the previously evaluated reference diseases data set by using topological relations among bounding boxes. By applying a sequence of selected topological operations, i.e., intersection, containments, and disjoint, among ROIs, similarities of anomalies between the blind patient images with those of known diseases can be detected. In the example reported in Fig. 1, the proposed framework finds similarities among input PET images (left side in the figure) and a set of reference images associated to the disease number 3 of the reference dataset (bottom right part of the figure). Experimental results of framework applications proved the reliability of the classification algorithm¹.

To perform analysis on large data set images, and to automatize the preprocessing and preparation phases required to obtain statistical analysis and to extract ROIs, we defined a software tool, called AutoSPET (for Automatic SPM invocation for PET images analysis). AutoS-Pet allows to execute statistical procedures on PET images by using a unique and simple graphical user interface. AutoSPET uses SPM and its toolboxes as well as Matlab toolbox (MathWorks, Matlab, http://www.mathworks.it/). By using such a tool, it is possible to increase efficiency in terms of preparation and running of statistical tests. The tool allows to invoke preprocessing phases (such as Dicom data conversions, co-registration, normalization, smoothing) and test executions, such as Factorial Design Specification, Model Estimation, Contrast Manager, Result Report, by using a unique and simple graphical user interface. The AutoSPET tool has been included in the SPM official web page and it is freely available. In Fig. 2 we report the workflow diagram of the here proposed framework which uses the AutoSPET tool. Figure shows how input data (i.e., patients DICOM files) are first processed through SPM standard statistical routines, then elaborated with Marsbar to extract ROIs and finally classified. All of the described workflow is orchestrated through a user friendly user interface, as described in the Sect. 4.

¹ A preliminary version of the algorithm, with no experimental results has been presented as short papers in Vizza et al. (2011, 2012).



Fig. 1 Example of application of the ROI based classification algorithm. The ROIs comparison is performed between an input patient ROI (called blind patient) and a set of known diseases ROIs. The comparison is indicated as "vs" (standing for versus)



Fig. 2 AutoSPET integration of SPM tools: flow diagram

The paper also reports results of using SPM templates versus (available) magnetic resonance to find the best brain image model, to validate the use of SPM templates, as reference image to study PET. Alzheimer patients have been considered and specific regions of interest for this disease, have been extracted and examined according to Tzourio-Mazoyer et al. (2002). Tests are reported in Sect. 5.1.

In literature many statistical tools for managing and processing clinical images are described (Haidekker 2010; Neurostat/3d-ssp 2011; Loening and Gambhir 2003; Mricro 2011). Many research groups use SPM (Jeong et al. 2005; Schoenahl et al. 2003; Tzourio-Mazover et al. 2002) to perform statistical analysis on image datasets. SPM based analysis allows to identify regions of variation of the glucose in the brain (or in region of interests) that can be associated to known diseases (Jeong et al. 2005; Ishii et al. 2007; Kanda et al. 2008; Mosconi et al. 2008; Mosconi et al. 2005; Kim et al. 2011; Pavese et al. 2003; Gaura et al. 2004). For example, in Zhang et al. (2010) and in Vilardi et al. (2011), SPM analysis has been applied to PET images to investigate regional cerebral glucose metabolism in traumatic brain injuries or for early diagnose of Alzheimer's disease. For such diseases, SPM statistical analysis uses a comparison between the patient and a control group (Ishii et al. 2007). In Volkow et al. (2002) a study assessed the metabolic changes in the brains for subjects with Alzheimer's disease by estimating the coefficient of variation over the entire cortex as index of regional homogeneity measure. In Foster et al. (2007) authors prove that using statistical analysis for PET images increases diagnostic accuracy in distinguishing frontotemporal dementia from Alzheimer's disease. In Kim et al. (2006), SPM has been used to investigate the clinical significance of bilateral temporal hypometabolism in patients with mesial temporal lobe epilepsy. These studies suggest that, by using a specific statistical analysis technique, it is possible to localize neuronal brain areas involved in sensory, motion or cognitive processes.

The paper is organized as follows: Sect. 2 contains a description of Statistical Analysis performed on PET images. Section 3 reports the ROI based algorithm and Sect. 4 presents the use of AutoSPET. Section 5 reports experimental results and, finally, Sect. 6 concludes the paper.

2 PET images analysis

PET images are analysed by using SPM (Statistical Parametric Mapping, http://www.fil.ion.ucl.ac.uk/spm/), the Statistical Parametric Mapping tool that allows to map image voxels into a spatial map. It is based on the definition of assumptions (null hypothesis H0) and alternative hypothesis (called H1) and reliability levels (i.e., thresholds for the validation of input hypothesis) (Lyman Ott 2010). Since the studies rely on diseases, the null hypothesis H0 is an assumption about a population that is compared with an alternative hypothesis H1 to establish if the null hypothesis can be rejected. The null hypothesis is the assumption that will be maintained by the researcher unless the analysis of data provides significant evidence to disprove it. In this



Fig. 3 Null hypothesis verification

case, the null hypothesis represents the condition of normality for the subject (i.e. healthy subject). The probability to reject H0 when it is true is represented by the significance level α that sets the region of rejection for the null hypothesis (see Fig. 3). The *p* value (or probability level) expresses the probability to observe the statistical value under null hypothesis.

SPM reports results as statistical maps showing that values are distributed according to a known probability density function [usually the T-Student or the F-distribution (Friston et al. 2006)]. In case of PET images, results are reported as list of coordinates (x, y, z) in MNI (Montreal Neurological Institute) space. Each coordinate refers to a voxel in a spatial significant cluster above a predefined threshold. Main modules of SPM are reported in Fig. 4. Figure also reports the main steps required to perform the functional neuroimaging analysis (i.e., Spatial Pre-Processing, Model Specification and parameters estimation, Inferences) (Friston 2003).

PET images are pre-processed before being analysed. Mainly, preprocessing consists of mapping images to similar anatomical reference images to make them suitable for statistical analysis. In our methodology we used the following preprocessing phases.

Coregistration co-registered PET images to mix functional and anatomical information of PET and Magnetic Resonance (MR) respectively. PET images are represented in Dicom (M.C. Center, dcm2nii dicom to nifti conversion, http://www.mccauslandcenter.sc.edu/mricro/mricron/dcm2nii.html) format; such a format needs to be converted in a new format to be manipulated by SPM [i.e. the NIfTI format (NIH, NIfTI format, http://nifti.nimh.nih.gov/nifti-1/)]. The Dicom-to-NIfTI converter included in SPM is not platform independent, but depends on different devices. E.g., PET generated by using General Electric (http://www.gehealthcare.com/euen/fun_img/pet-ct-index.html) and Siemens (http://www.medical.siemens.com) devices, require co-registration with respect to a common reference system in



Fig. 4 General overview of SPM analysis



Fig. 5 PET and MR images for co-registration step

order to translate the converted images in the right orientation. PET images of each patient are co-registered with a magnetic resonance (MR) reference image (when available), as shown in Fig. 5.

Co-registration enables the visualization and localization of neuronal activation loci on PET images by using an MR image as anatomical reference (i.e., overlapped filter) (Kiebel et al. 1997). Nevertheless, to optimize this phase, the study should be performed by using the PET of the subjects as functional images and MR of the same patient as anatomical reference. Most studies uses a reference brain functional image, i.e. a template, available in SPM, to analyse PET images, e.g., the template T1-weighted MR reference. In Sect. 5.1, we report results on estimating using SPM template versus using patient MR. We show that the SPM template can be considered as a valid substitute of MR image. The results regard subjects affected by Alzheimer disease with both PET and RM studies available

• *Normalization* is used to convert the examined images into a common anatomical space, i.e. the Talairach's space, to remove the anatomical variability among different patients (Gispert et al. 2002; Liao et al. 2003). The target is to manipulate images thus to have correspondences among anatomic brain parts from different patients. Typically normalization involves the translation, rotation, reduction to a common scale and non-linear warping of brain surface, matching the template. It determines the optimum among the following 12-parameters: (i) 3 translations, (ii) 3 rotations, (iii) 3 shears and (iv) 3 zooms, as reported in Fig. 6.

Once images have been normalized, voxels can be associated to the known anatomic brain regions. The normalization is performed in an automatic way. The affine transformation is performed by SPM and allows to fit PET images with templates.

• *Smoothing* is used to replace measures associated to each voxel, with a weighted average value obtained by considering voxels neighbours. Smoothing is performed

Fig. 6 Normalization step: 12-parameters affine transformations



using a Kernel Gaussian filter, which is a filter with the shape of a normal distribution curve. The aim of smoothing is to make data less influenced by sample variability artefacts (Reimold et al. 2005). The width of the curve is expressed as Full Width at Half Maximum (FWHM) and it determines how much the data is smoothed. Figure 7 shows the application of this filter with different FWHM values.

Normalized images are smoothed with FWHM equals to 12 mm Isotropic Gaussian Kernel to increase the signal to noise ratio.

The last step in SPM analysis is the Inference (see Fig. 4) (Poline et al. 2011), a procedure which compares voxels. It associate a t value to each voxel, where t value is obtained using the t student distribution applied to voxels. By comparing voxels and set of voxels, it is possible to identify significant changes between some hypotheses (e.g., diseases conditions). Changes are associated to threshold values, which can be defined by using probability functions. E.g., thresholds can be defined by using the probability that a cluster (containing voxels) presents a different activation value for conditions that would be expected under the null hypothesis. A pair of p statistics (uncorrected *p* value and corrected *p* value), for each voxel and cluster is used. Uncorrected mean values per-voxel are the probability that t value is greater than a fixed threshold, when the null hypothesis is verified (no activation); the corrected p value is the probability that all voxels are above the threshold when they are all unactivated. The voxellevel *p* value is the probability to find a voxel with *t* statistic (or with higher value) under null hypothesis. The cluster-level *p* value is the probability to find a cluster with a number of voxels equal or greater than k_e , where k_e is defined by the user (Laureys and Tononi 2008; Shallice and Cooper 2011) and represents the minimum number of voxels in a cluster, such that the cluster can be considered for statistical analysis. Clusters hosting more than k_e voxels are reported in the map results. In our experiments we set k_e to 125.

SPM statistical analysis results are reported in an image called MAP, where each voxel represents the result of a specific test. In a MAP, the areas highlighted voxels are those verifying the null hypothesis according to the specific statistical test. It is thus possible to investigate the significance of extracted clusters (i.e. set of voxels), by analysing the graphical representation. MAP reports in a unique image the list of clusters (set of voxels) and their statistical significance; moreover, for each cluster, the most significant voxels (also reported as local maxima), are indicated. An example of MAP is reported in Fig. 8.

Bottom part of the figure reports a table that contains the following information (from right to left):

- *x*, *y*, *z* (mm): Montreal Neurological Institute (MNI) space coordinates for each local maximum;
- voxel-level: corrected or non-corrected probability to find, under null hypothesis, an interesting voxel;
- cluster-level: probability to find a cluster with a number of voxels equal or greater than a specific size k_e for search volume;

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Fig. 8 SPM result: statistical MAP



1.000

0.483

set-cluster: probability to find a number of clusters equal or greater than a specific number.

3 ROI based classification Tool

A ROI based classification tool has been developed and it is here described. The main idea is to use topological relations (Clementini et al. 1994) among minimal bounding boxes (ROIs). PET images related to the so-called blind patient are evaluated by considering relations between discovered ROIs and ROIs referred to known diseases. ROIs are extracted using MarsBaR (Brett et al. 2002; Brett 2011) as boxes, and associates to each box a minimum and a maximum value. An example of extracted ROI is reported in Fig. 9.

The algorithm uses the following topological operations defined as follows for two ROIs, x_1 and x_2 :

3.66

0.000

12.33

- intersection $(x_1, x_2) = \text{true}$, when $x_1 \bigcap x_2$, false . otherwise;
- containment (x_1, x_2) = true, when $x_1 \subseteq x_2$, false otherwise;
- disjoint (x_1, x_2) = true, when $x_1 \notin x_2$. •

ROIs belonging to different patients are compared and, for each couple of analysed ROIs, topological relations are evaluated in the following order: intersection, containment and disjoint. In case of intersection and containment, a percentage of overlapping is evaluated. An example of the use of ROI based algorithm is reported in Fig. 1.



Fig. 9 ROI extracted from voxels defined in the statistical MAP

The classification algorithm spreads over two distinct phases: (i) a training phase for data preprocessing and analysis, and (ii) a test phase running the algorithm on blind patients. The training phase consists in defining a set of ROIs that can be considered representative of a specific disease. For each set of known diseases, available PET images (expert referred studies) have been analysed. Each disease is thus associated to a set of geometrically defined bounding boxes in a commonly adopted reference space. The training phase generates a set of values, mapped into matrices data structures. Mean values are also considered and stored in a vector data structure. A function of mutual relation is evaluated to consider the relations among ROIs of different diseases. This phase generates a reference data set and it is evaluated off line when reference set is defined. The second phase consists in analysing ROIs of a blind patients and evaluating topological relations with respect to ROIs in the reference data set. Topological relations are considered with respect to a priori defined thresholds (e.g. greater than 50 % of overlapping among ROIs). A function cost is defined as metric function to choose the set of ROIs (and thus the corresponding disease) closest to the input analysed ROIs. Finally the input PET images (blind patient) is associated to one or more ROIs with a given probability. In the following the two phases are detailed. The training phase consists of the following steps:

1. Selection of N patients, as control reference, among the N_c patients with no diseases. Selecting the set of pathological patients P among an available set P_a of pathological patients, clustered in known disease set.



label:

Centre of mass

Volume (mm)

Maximin Ximm)

Max/min Yimm)

Max/min Z(mm):

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32964.00

662

-62 20

30.50

ROI

- ROI minimal bounding box vertices: x_{min}/x_{max}, y_{min}/y_{max}, z_{min}/z_{max};
- coordinates of local maxima (points with maximum intensity value): *x*, *y*, *z*;
- mean intensity signal values.
- 3. Classify ROIs with respect to their known disease, and for each known pathology, analyse topological relations between ROIs and intensity values. A function REL(ROI₁,ROI₂) is evaluated applying topological relations for each couple of ROIs. For instance, some of the following topological relations are evaluated:

$$\operatorname{ROI}_1$$
 $\operatorname{ROI}_2 \geq 50 \% \lor \operatorname{ROI}_1 \subseteq \operatorname{ROI}_2 \lor \operatorname{ROI}_1 \supseteq \operatorname{ROI}_2;$

Topological relations are thus evaluated to define a ROIs reference set associated to each known disease.

 Evaluation of a Mutual Relation function between diseases, to evaluate the relation between them. The function has the following form:

$$M_m M_n = (1 - \alpha) \times k_{mn} + \alpha g_m, \tag{1}$$

where m, n = 1, ..., K, and K is the number of considered diseases. k_{mn} represents the mutual relation among two diseases M_m and M_n . g_m represents the relation between the disease M_m with the other diseases of the dataset. The constant α has been set to 0.25, to



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give greater weight to the first term; the factor k_{mn} is obtained by evaluating relations between ROIs of M_m with each ROIs of M_n .

The factor g_m , has been calculated as the relation between each ROI_c of M_m with each ROI_c of all other diseases. Finally, all mutual relations are evaluated and stored in a matrix $A [M_K \times M_K]$.

The test phase works as follows for PET images associated to a blind patient.

- 1. Evaluate statistical analysis and ROIs by using SPM and MarsBaR for the PET images of patient P_b , and evaluate ROIs, maximum intensity values for voxels contained in ROIs and mean intensity values.
- 2. Evaluate the relation between ROI_{P_b} and ROIs in reference data set and store information relations on a matrix, and define a weight vector to relate the patient disease to known diseases.
- 3. Evaluate a matrix containing information about relations among maximum values in patient ROIs and known studies.

Finally, the tool compares weighted functions representing mutual relations among ROIs of the blind patient with those of the known diseases. The disease in correspondence of an index with the lowest value is proposed as possible disease for the input patient. An example output for the algorithm is reported in Fig. 1.

4 Automatize the SPM analysis phase

SPM users know that often it is required to run several statistical experiments, varying parameters, currently requiring manual procedures using SPM by means of its user interface. In our tests we used the AutoSPET tool, to automate SPM analysis steps. It is a useful graphical user interface to improve efficiency in running SPM experiments. It integrates SPM, Matlab (i.e. the engine of SPM), MarsBaR and any other SPM plug-in. It manages all phases of PET statistical analysis and allows to evaluate and run parametrized tests in parallel. It allows Dicom import and conversion in NIfTI format, preprocessing, statistical step and ROI-based algorithm. The main modules of AutoSPET as a PET images analysis tool are shown in Fig. 2. AutoSPET has been designed and implemented in the Bioinformatics Laboratory of University Magna Græcia of Catanzaro and it is freely available SPM on the official Web site at http://www.fil.ion.ucl.ac.uk/spm/ext/, linking the application running on the Bioinformatics lab servers. Figure 10 reports the graphical user interface of the tool, and the choice of parameters for preprocessing phases on loaded PET image data set, while Fig. 11 reports the coregistered images by using AutoSPET.

AutoSPET includes the ROI based classification tool module for disease identification. It has been integrated in

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Fig. 12 AutoSPET: results of an instance of ROI based classification tool

AutoSPET as a Java module but it can also be used as a stand alone application. The results of an automatic procedure for disease identification is shown in Fig. 12.

5 Experimental results

In this section we report the experimental results of the here presented study. The used data set is firstly described, with patients diseases. We then report about the contribution of validating the use of SPM template while co-registering brain images. The aim is to estimate the reliability of SPM templates, and in particular of T1 template, with respect to use patient magnetic resonance. Then use of ROI based algorithm is reported with experimental results.

PET images acquisition phase. We considered PET related to healthy and pathological subjects. The data set is composed of 28 control and 59 pathological ones. PET-TC GE Health-care Discovery ST Scanner has been used; 18-FDG PET scans have been acquired in the Nuclear Medicine laboratory of Magna Graecia University Hospital, where 18-FDG stands for nuclide [18F] used as contrast and FDG (370 Mega Becquerel, MBq) as tracer used during image acquisition phase. The delay between the injection and acquisition phase is of 60 min, whereas 47 slices PET acquisition is run in approximately 18 min.

For each analysed PET images, a voxel-by-voxel based analysis has been performed using the following criteria:

- intensity image values were corrected to a mean value of 50 ml/dl/min, using a proportional scaling;
- filters (i.e. masks) were used with 0.8 intensity value to select only voxels with activity >80 % of the total

value; this is done in order to exclude extra cranial activities;

- a *t* contrast value has been defined to consider hypometabolism;
- a probability *p* value <0.001 and an extent threshold equal to 125, have been used.

The used p value (i.e. 0.001) means that the probability to reject erroneously the null hypothesis is of 0.1 %; the extent threshold of 125 voxels has been chosen to select clusters with an high number of voxels.

Control dataset. Out of 28 subjects, we selected a control dataset of 25 ones, by using the following enrolment criteria:

- absence of brain diseases;
- older than 40 years;
- possible presence of cancer (diagnosys or suspect);
- absence of medication;
- not under chemiotherapia and/or radiotherapia cures;
- absence of anomalies and/or structural lesions in brain;

The 28 subjects are patients with some form of (non neurological) suspect diseases and that thus were studied by means of PET analysis. Statistical analysis has been performed on the 28 PET image dataset using the above reported criteria. Three out of 28 have been used as reference normality data set selected by clinicians. An FDR (False Discovery Rate) statistical method has been used for multiple comparison. FDR is applied in multiple hypothesis statistical tests to verify the expected proportion of false positives among supra-threshold voxels. The subjects selected as *control dataset* have been chosen in according to the following criteria:

- there is no cerebral difference compared to the reference normality dataset group;
- the (brain) voxels mean value verifies the following equation:

$$X_c = X_g \pm 2\sigma \tag{2}$$

where X_c represents the mean value of the patient, X_g is the mean value of the reference group and σ is the standard deviation.

Mean value and standard deviation calculated on the 3 reference subjects, are respectively 42.8576 and 2.6952; thus, for each analysed subject, its mean value must be between 37.4672 and 48.248. Obviously, such values vary when including additional subjects into reference set. Table 1 reports the 28 subjects; for each patient, the sex, the age, the diagnosis (i.e. that brings patient to undertake a PET analysis), the range of normality and mean are reported. The selected and considered normality dataset is composed by 25 out of 28 patients. The 3 ones excluded

Table 1 Subjects enrolled for the definition of the control data set

Patient

P1 (F)

P2(F)

P3(M)

P4 (F)

P5 (F)

P6 (F)

P7 (F)

P8 (F)

P9 (F)

P10 (F) P11 (F)

P12 (F)

P13 (F)

P14 (M)

P15 (M)

P16 (M)

P17 (F)

P18 (F)

P19 (F)

P20 (F)

P21 (M)

P22 (M)

(sex)

	Age	Diagnosis	Normality range	Mean value
	55	NDD Lymphadenopathy	Reference subject	43.10
	60	NDD Lymphadenopathy	Reference subject	40.04
	62	Intestinal polyps	Reference subject	45.41
	65	Breast nodule	37.46:48.24	42.15
	57	Breast nodule	38.22:47.13	44.14
	45	Non-Hodgkin's lymphoma	38.89:47.05	42.21
	61	Unknown	39.39:46.96	43.54
	57	Non-Hodgkin's lymphoma	39.76:46.69	41.22
	53	Unknown	39.47:46.49	43.99
	60	Intestinal polyps	39.74:46.44	43.80
	57	Suspect ovarian cancer	39.97:46.35	41.62
	43	HepatoCellular Carcinoma	39.86:46.19	43
	51	Thymoma	40:46.04	43.11
	51	Non-Hodgkin's lymphoma	40.14:45.92	42.33
	71	Pulmonary nodule	40.17:45.78	42.94
	65	Pulmonary nodule	40.27:45.68	43.41
	61	Breast nodule	40.38:45.62	44.50
	54	Rectal cancer	40.45:45.73	42.84
	49	Hodgkin's lymphoma	40.51:45.64	44.08
	42	Endometrial cancer	40.60:45.66	43.86
)	59	Unknown	40.68:45.65	50.32
)	47	LymphoHematopoietic Neoplasms	40.68:45.65	56.62

		Neopiasiiis		
P23 (M)	47	NDD Lymphadenopathy	40.68:45.65	43.56
P24 (M)	64	Unknown	40.76:45.61	49.31
P25 (M)	56	Unknown	40.76:45.61	42.84
P26 (M)	77	Unknown	40.79:45.54	44.55
P27 (M)	82	Unknown	40.84:45.62	42.51
P28 (M)	51	Unknown	40.84:45.56	43.08

Bold and italic values refer to healthy condition of analyzed patients

are reported in bold font (i.e. patients identified as P21, P22, P24). Moreover, the first three ones (in italic font) are subjects used as reference set. Finally, whereas the diagnosis is not well defined, the it is indicated as "unknown"; however the selected subjects verified the enrolment criteria reported above.

Pathological class dataset. The pathological class disease is composed of patients that present brain neurological diseases. We performed statistical analysis and studies on 59 pathological subjects. PET images have been compared with the normality class dataset reported above. As result, regions **Table 2** Hypometabolicregions extracted fromstatistical analysis

Disease	Ster coord (x, y, z)	Brain area	T Thr	T value	Z score
AD	-26 -54 38	Left cerebrum, parietal lobe, subgyral	3.50	12.44	6.71
	-44 -46 28	Left cerebrum, parietal lobe, supramarginal gyrus		8.71	5.67
	36 - 46 - 8	Right cerebrum, occipital lobe, fusiform gyrus		8.14	5.47
	-54 12 -6	Left cerebrum, temporal lobe, superior temporal gyrus		6.25	4.69
	-38 12 -24	Left cerebrum, temporal lobe, superior temporal gyrus		4.04	3.46
SCA	-38 - 48 - 42	Left cerebellum, posterior lobe, cerebellar tonsil	3.53	14.10	6.96
	-44 - 64 - 40	Left cerebellum, posterior lobe, cerebellar tonsil		12.72	6.68
	-30 - 54 - 8	Left cerebellum, posterior lobe, declive		6.74	4.86
	34 - 48 - 8	Right cerebrum, occipital lobe, fusiform gyrus		6.69	4.84
	32 24 -26	Right cerebrum, temporal lobe, superior temporal gyrus		5.90	4.48
CBD	-34 -34 16	Left cerebrum, temporal lobe, superior temporal gyrus	3.53	7.41	5.25
	40 - 34 16	Right cerebrum, temporal lobe, superior temporal gyrus		7.31	5.21
	38 20 - 26	Right cerebrum, temporal lobe, superior temporal gyrus		6.46	4.83
	-34 -46 40	Left cerebrum, parietal lobe, inferior parietal lobule		8.24	5.45
	-46 -40 36	Left cerebrum, parietal lobe, supramarginal gyrus		8.08	5.39
	-28 -56 36	Left cerebrum, parietal lobe, subgyral		7.55	5.23
	40 - 38 38	Right cerebrum, parietal lobe, inferior parietal lobule		6.85	4.91
	30 - 44 44	Right cerebrum, parietal lobe, subgyral		6.46	4.74
	-46 18 -12	Left cerebrum, temporal lobe, superior temporal gyrus		6.41	4.72
	-48 -4 -8	Left cerebrum, temporal lobe, superior temporal gyrus		4.49	3.72
	52 16 -16	Right cerebrum, temporal lobe, superior temporal gyrus		5.55	4.31
	-50 - 42 - 12	Left cerebrum, temporal lobe, fusiform gyrus		5.07	4.05
FTD	4 18 26	Right cerebrum, limbic lobe, cingulate gyrus	3.43	7.88	5.58
	6 32 16	Right cerebrum, limbic lobe, anterior cingulate		7.69	5.51
	16 8 10	Right cerebrum, sub-lobar, extra-nuclear		6.24	4.83
	50 48 14	Right cerebrum, frontal lobe, Md frontal gyrus		6.09	4.76
	48 52 6	Right cerebrum, frontal lobe, Md frontal gyrus		5.96	4.69
	-42 56 4	Left cerebrum, frontal lobe, Md frontal gyrus		5.49	4.43
	2 -4 32	Right cerebrum, limbic lobe, cingulate gyrus		5.23	4.28
	-10 10 6	Left cerebrum, sub-Lobar, caudate		4.93	4.10
	12 -22 16	Right cerebrum, sub-lobar, thalamus		4.70	3.96
	$-52\ 14\ -2$	Left cerebrum, frontal		4-70	3.97
		Temporal space			
	-32 62 4	Left cerebrum, frontal lobe, Md frontal gyrus		4.64	3.93
	54 44 -2	Right cerebrum, frontal lobe, inferior frontal gyrus		4.60	3.90
	56 18 -6	Right cerebrum, frontal lobe, inferior frontal gyrus		4.38	3.76
	16 -6 18	Right cerebrum, sub-lobar, caudate		4.33	3.72

Table 2 continued

Disease	Ster coord (x, y, z)	Brain area	T Thr	T value	Z score
PPF	-14 8 10	Left cerebrum, sub-lobar, caudate	3.40	12.91	7.31
	8 - 18 12	Right cerebrum, sub-lobar, thalamus		10.88	6.75
	16 4 12	Right cerebrum, sub-lobar, extra-nuclear		10.20	6.54
	-46 16 -14	Left cerebrum, temporal lobe, superior temporal gyrus		5.73	4.62
	6 -44 -36	Right brainstem, medulla		4.29	3.73
PSP	$-10\ 12\ 8$	Left cerebrum, sub-lobar, caudate	3.48	8.52	5.67
	-4 14 26	Left cerebrum, limbic lobe, cingulate gyrus		7.44	5.26
	-4 -14 12	Left cerebrum, sub-lobar, thalamus		6.63	4.91
PD	-26 - 80 2	Left cerebrum, occipital lobe, subgyral	3.40	11.59	6.96
	-26 - 56 36	Left cerebrum, parietal lobe, subgyral		10.85	6.75
	48 16 -18	Right cerebrum, temporal lobe, superior temporal gyrus		11.02	6.80
	36 - 58 - 6	Right cerebrum, occipital lobe, subgyral		9.34	6.24
	-50 42 8	Left cerebrum, frontal lobe, inferior frontal gyrus		5.37	4.41
	34 32 18	Right cerebrum, frontal lobe, subgyral		4.39	3.80
	34 20 28	Right cerebrum, frontal lobe, midfrontal gyrus		4.05	3.56
	38 10 22	Right cerebrum, frontal lobe, subgyral		3.54	3.19
DLB	-18 38 -26	Left cerebrum, frontal lobe, orbital gyrus	3.42	7.18	5.32
	-36 -36 12	Left cerebrum, temporal lobe, transverse temporal gyrus		6.41	4.95
	-26 - 76 0	Left cerebrum, occipital lobe, subgyral		6.00	4.74
	4 - 36 22	Right cerebrum, limbic lobe, posterior cingulate		5.74	4.60
	44 16 -20	Right cerebrum, temporal lobe, superior temporal gyrus		5.69	4.57
	38 - 32 14	Right cerebrum, temporal lobe, superior temporal gyrus		4.47	3.84
	46 - 38 26	Right cerebrum, parietal lobe, inferior parietal lobule		4.91	3.52
	-42 14 -26	Left cerebrum, temporal lobe, superior temporal gyrus		4.01	3.52
	-48 18 -12	Left cerebrum, temporal lobe, superior temporal gyrus		3.97	3.49
ED	14 8 6	Right cerebrum, sub-lobar, extra-nuclear	3.53	9.12	5.74
	32 32 20	Right cerebrum, frontal lobe, subgyral		8.33	5.48
	34 -64 22	Right cerebrum, temporal lobe, subgyral		8.05	5.39
	24 - 44 - 34	Right cerebellum, posterior, lobe, cerebellar tonsil		6.02	4.54
	-24 -44 -34	Left cerebellum, posterior lobe, cerebellar tonsil		5.84	4.45
	4 -56 2	Right cerebellum, anterior lobe, culmen		5.44	4.25
	-26 -62 26	Left cerebrum, temporal lobe, subgyral		5.13	4.08
	-22 - 60 32	Left cerebrum, parietal lobe, precuneus		4.94	3.98
	-14 -48 32	Left cerebrum, parietal lobe, precuneus		4.34	3.63

of interests (ROIs) with different glucose metabolism for each neurodegenerative disease have been identified and hypometabolic ROIs have been identified and measured on PET images. Such values are reported in Table 2. Moreover, on such subjects we also run the ROIs based algorithm.

The pathological PET images data set interests the following pathologies:

- *Alzheimer disease* (indicated as AD in the following); at an early stage of the disease, the metabolic reduction affects mesial temporal brain areas, and the posterior cingulate brain cortex presents an early hypometobolism.
- *Frontotemporal Dementia* (indicated as FTD in the following); it is a neurodegenerative syndrome,



Fig. 13 Areas of diseases versus control dataset. Ipo-metabolism condition of a specific disease is compared to the control dataset (e.g. Control vs Parkinson, where vs stands for versus)

associated to frontal and rear temporal lobes reduction of perfusion and metabolism.

- *Dementia with Lewy body* (indicated as DLB in the following), where cortical and subcortical brain stem structures present Lewy body.
- *Spino-Cerebellar Ataxia* (indicated as SCA in the following); it is a degenerative genetic disorder where brain glucose metabolism is variable and out of normality range, generating multiple SCA disease types (Wang et al. 2007).
- *Multiple System Atrophy* (indicated as MSA in the following); it is associated to cells degeneration in well defined brain areas, inducting a degenerative neurological disorder.
- *Parkinson Disease* (indicated as PD in the following); PD is a central nervous system degenerative disorder.
- *Cortico Basal Degeneration* (indicated as CBD); it is a rare neurodegenerative disease with deterioration of the cerebral cortex and the basal ganglia;
- *Progressive Primary Freezing* (indicated as PPF); it is a progressive freezing gait disorder;

- *Progressive Suprenuclear Palsy* (indicated as PSP); it is a rare disease with degeneration of brain stem structures;
- Epilepsy Disorder (indicated as ED); brain disorders.

Table 2 reports ROIs of the analysed pathological class data set, where table columns contain: (i) the disease, indicated using the above reported abbreviation (AD, for Alzheimer Disease, FTD for Frontotemporal Dementia, and so on); (ii) stereotaxic coordinates (indicated as Ster *Coord* in the table) of the voxel with a local maximum; (iii) the anatomical brain area corresponding to the stereotaxic coordinates; (iv) the T value threshold (indicated as T-Thr); (v) the T value; (vi) the Z score of each voxel identified by the stereotaxic coordinates. T value is evaluated by SPM using user-defined statistical parameters. In PET-image analysis, for each defined disease all PET images show a decreasing metabolism in similar areas. This is also shown in Fig. 13, which reports comparison among control data set and analysed brain neurological disease. For each analysed disease, ipo-metabolism brain area is identified and shown as darker area, while the "<" symbol (used as arrow in SPM results), indicates the center of axes. Note that in figure, vs stands for "versus".

5.1 Using SPM template versus MR

We performed tests to compare results obtained using SPM templates versus results obtained using brain magnetic resonance (MR) of the analysed patients (for patients where MR images are available). The aim is to estimate the reliability of SPM templates, and in particular of T1 template, in order to increase classification performances for those analysis where MR is not available. The comparisons between the reference images of SPM and MR of the patients are made in co-registration phase. Using the available dataset, we showed that there is no relevant difference in using SPM T1 template versus using MR of the patient as template, except for only two patients when considering particularly small ROIs areas (i.e. amygdala left and right zones), due to the small dimensions (less the 2,000 pixels) which leads to an higher probability of misalignment.

The following ROIs area have been used for comparisons among T1 based results and MR based results:

- Amygdala Left (also indicated as *AmL* in the following);
- Amygdala Right (also indicated as *AmR* in the following);
- Anterior Cingulum Left (also indicated as AnCinL);
- Anterior Cingulum Right (also indicated as AnCinR);
- Inferior Parietal Left (also indicated as InParL);
- Inferior Parietal Right (also indicated as *InParR*);
- Hippocampus Left (also indicated as *HippL*);
- Hippocampus Right (also indicated as *HippR*);
- Olfactory Left (also indicated as *OlfL*);
- Olfactory Right (also indicated as *OlfR*);
- Inferior Temporal Left (also indicated as *InTemL*);
- Inferior Temporal Right (also indicated as InTemR);
- Middle Temporal Left (also indicated as *MiTemL*);
- Middle Temporal Right (also indicated as MiTemR).

PET brain images where MRs of patients were available, have been studied, executing the coregistration phases

Table 3 Results in terms ofmean intensity value of cerebralmetabolic glucose rate in ml/dl/min by the comparison betweencoregistration with MR patientand SPM template

ROI	Ref	P1	P2	P3	P4	P5	P6	P7	P8
AmL	MR	73.56	73.86	62.83	77.31	74.17	66.86	76.01	73.85
	T1	68.05	70.6	50.98	71.94	67.55	71.61	67.77	69.67
AmR	MR	74.87	74.88	70.82	75.11	75.83	67.72	74.99	74.55
	T1	67.04	70.2	68.48	62.37	67.92	71.03	67.36	69.82
AnCinL	MR	74.04	73.3	74.49	74.67	72.46	70.79	73.25	73.81
	T1	74.09	73.34	74.52	74.76	72.53	70.75	73.18	73.84
AnCinR	MR	74.58	73.82	80.46	73.76	72.81	71.29	73.58	74.04
	T1	74.64	73.86	80.45	73.81	72.87	71.29	73.51	74.08
InParL	MR	68.98	70.29	46.5	72.36	67.95	71.06	68.81	68.59
	T1	68.91	70.28	46.45	72.44	67.96	70.98	68.97	68.56
InParR	MR	66.17	70.81	53.27	61.79	66.39	71.24	68.65	68.71
	T1	66.15	70.77	52.78	61.99	66.4	71.18	68.8	68.7
HippL	MR	73.72	72.34	46.96	77.42	71.35	68.22	75.07	74.04
	T1	73.78	72.35	47.08	77.53	71.45	68.26	75.07	74.09
HippR	MR	74.61	73.92	59.28	69.76	74.53	70.85	75.05	74.83
	T1	74.67	73.97	59.44	69.67	74.61	70.9	75.03	74.88
OlfL	MR	73.97	72.64	70.85	74.52	72.01	64.39	74.26	72.97
	T1	74.01	72.64	70.81	74.6	72.09	64.43	72.2	72.97
OlfR	MR	74.26	72.47	71.01	72.8	71.88	64.18	74.14	72.34
	T1	74.3	72.48	70.92	72.8	71.97	64.16	74.03	72.33
InTemL	MR	66.69	68.6	50.67	72.59	68.75	68.19	69.56	67.11
	T1	66.64	68.55	50.67	72.68	68.7	68.19	69.07	67.03
InTemR	MR	68.65	69.37	69.9	66.06	69.23	68.48	70.28	69.85
	T1	68.6	69.28	69.82	65.76	69.14	68.49	69.91	69.77
MiTemL	MR	68.12	68.47	52.29	72.01	68.54	68.92	68.81	69.31
	T1	68.08	68.43	52.29	71.87	68.49	68.91	68.46	69.29
MiTemR	MR	70.06	70.73	68.62	64.34	70.32	71.15	70.37	71.55
	T1	70.05	70.71	68.65	64.28	70.31	71.13	70.21	71.56

by using magnetic Resonance (MR) and by using SPM T1 template (T1). Cerebral metabolic glucose values have been evaluated and analysed for PET images of 8 patients, focusing on the above reported brain areas. For each brain area, mean intensity metabolic glucose values have been evaluated when coregistered with respect to MR and with respect to T1 template. Numerical results are reported in Table 3, where columns refer to considered ROI area (i.e., AmR for Amygdala Right ROI area, AmL for Amygdala Left ROI area, AnCinL for Anterior Cingulum Left ROI area and so on). Reading the table by row, for a given ROI area (first column), mean intensity values obtained by coregistering w.r.t. MR and w.r.t. T1 template are reported



Fig. 14 Mean intensity values for each ROI by using MR image or T1 image. Values on y axis are measured in cerebral metabolism glucose rate (ml/100 g/min)

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for each patient (P1, ..., P8). It is possible to verify that, except Amygdala Lef and Right (first two lines in the table, i.e. AmL and AmR), for each ROI area and for each patient, mean values of MR and T1 are almost the same (e.g., values 74.04 and 74.09 ml/dl for Patient P1 and for AnCinL area). The differences among values have been plot on Fig. 14, where mean intensity values plots for 8 patients are reported. One plot refers to coregistration with respect to MR, while the other one is coregistered with respect to T1 SPM template (i.e., the values of Table 3). Note that, as readable by values of first lines in Table 3, only for the Amygdala left and right there is a difference in the use of T1 or MR as reference image; for the other ROIs, the use of MR image of the patient or the use of T1 template of SPM as reference image does not produce significant differences. For example, for patient P1, the mean intensity value of cerebral metabolic rate of glucose in Amygdala left region with the MR is 73.56 in ml/dl/min (i.e., millilitres cerebral blood that flows in 1 dl of brain per minute); in the same region, instead, if template T1 of SPM is used, the value is 68.05 ml/dl/min. Moreover, for just two patients, due to the alignment of adjacent structures having low metabolic activities, we observed a lower information content for SPM template with respect to using MR. In these cases (i.e. smaller and low activity ROIs) we claim that using MR template usually leads to better results. Nevertheless, SPM template still maintains acceptable levels of reliability when considering group analysis.

Patient	Amyg	AnCin	InPar	Hipp	Olfac	InTemp	MiTemp
P1	-0.0075	0.0036	-0.02	0.006	0.0019	0.0145	0.0142
P2	-0.0028	0.0036	0.0034	0.011	-0.0011	0.0053	0.0116
P3	0.1464	0.0383	0.0638	0.116	0.0007	0.1589	0.1468
P4	-0.0712	-0.0063	-0.0777	-0.0534	-0.0122	-0.05	-0.0134
P5	0.0027	0.0023	-0.0116	0.0216	-0.0008	0.0032	0.0112
P6	-0.0041	0.0038	0.0014	0.0189	-0.0021	0.0022	0.0081
P7	-0.003	0.0023	-0.0012	-0.0003	-0.0011	0.0061	0.0114
P8	0.0011	0.0016	0.001	0.0053	-0.0044	0.02	0.0054

Table 5	Results	s of asyn	nmetric
indexes	with MI	R patient	image

Table 4 Results of asymmetricindexes with SPM template

Patient	Amyg	AnCin	InPar	Hipp	Olfac	InTem	MiTemp
P1	0.0088	0.0036	-0.021	0.006	0.0019	0.0145	0.0141
P2	0.0068	0.0036	0.0037	0.011	-0.0011	0.0056	0.0163
P3	0.06	0.0386	0.0679	0.116	0.0012	0.1595	0.1351
P4	-0.0144	-0.0061	-0.0788	-0.0521	-0.0117	-0.0471	-0.0562
P5	0.0111	0.0024	-0.0116	0.0218	-0.0009	0.0035	0.0128
P6	0.0064	0.0035	0.0013	0.0189	-0.0016	0.002	0.0159
P7	-0.0068	0.0022	-0.0012	-0.0002	-0.0008	0.0051	0.0113
P8	0.0048	0.0016	0.0009	0.0053	-0.0044	0.02	0.016
P7 P8	-0.0068 0.0048	0.0022 0.0016	-0.0012 0.0009	-0.0002 0.0053	-0.0008 -0.0044	0.0051 0.02	0.0 0.0

5.2 Asymmetric indexes

We performed numerical evaluations to measure the brain asymmetries for patients, starting from the available set PET images data set. In this analysis we used both T1 template and MR on 8 patients (the ones used above to validate T1 template). The asymmetric indexes have been evaluated considering the ROIs of the SPM template validation (i.e., the one reported in Table 3). Indeed, even if the cerebral hemispheres are approximately equal in terms of (i) volume, (ii) weight and density, (iii) global and local structural, some functional asymmetries have been highlighted and reported in literature (Hugdahl 2005). We calculate the asymmetric indexes to estimate this asymmetry between right and left cerebral hemispheres. Different methods to evaluate these indexes have been proposed in literature (Kajimoto et al. 2007; Bruno et al. 2011; Kang et al. 2001); in this work the asymmetric indexes have been calculated according to the following equation:

$$AI = (R - L)/(L + R)$$
(3)

where AI means asymmetric index, L (left) and R (right) stand for the intensity mean values of signal referring to left (L) and right (R) hemispheres. If the AI value is >0, the left side signal is lower than the right one, representing a major hypo-metabolism. On the contrary (AI ratio <0), the hypo-metabolism is predominant in the right side. The Asymmetric Indexes evaluated coregistering (i) by using T1 template and (ii) by using MR patient images are respectively reported in Tables 4 and 5.

Evaluated coregistration values confirm the validity of using T1 template versus using MR, except for amygdala region. Again, the non standard in Amygdala region is also present for asymmetric indexes and depends on the different use of SPM templates and MR patient images.

Table 6	Results	of ROI-based	algorithm
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Subject	Input diagnosis	Output procedure
S1	Parkinson	Confirmed
S2	Parkinson	Confirmed
S3	Parkinson	Confirmed
S4	Parkinson	Confirmed
S5	Parkinson	Confirmed
S6	Parkinson	Confirmed
S7	Parkinson	Confirmed
S8	Parkinson	Confirmed
S9	Parkinson	Confirmed
S10	Frontotemporal	Not Confirmed
S11	Frontotemporal	Confirmed
S12	Lewy's Body	Not Confirmed

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5.3 Results on using ROI Based classification algorithm

The ROI based classification algorithm has been tested on four different pathologies (out of 9 available set of pathologies). These pathologies are Parkinson, Lewy's Body, Frontotemporal and Freezing for a total of 30 subjects: 18 subjects have been used to extract ROIs of diseases and for the definition of the reference dataset; 12 subjects have been used as input for the algorithm, hiding the referred diseases (indicating the patient data set as "blind patients"). Results of the algorithm are reported in Table 6, where patients are indicated as S1... S12 (note that it is a different set of patients with respect to P1... P28 reported in Table 1).

The results accuracy is of 100 % on the available cases for Parkinson diseases, 1 out of 2 Frontotemporal disease subjects, for an overall 83 % of accuracy on the available dataset. The classification module can be used in the AutoSPET tool, performing tests by using a single interface.

6 Conclusions

We developed an algorithm for disease classification based on region of interests extracted from PET images. The experiments show interesting results for a semi automatic process to support physicians in images analysis and diseases identification. Moreover, we performed statistical analysis on PET images relative to different diseases, and we tested the reliability of T1 SPM template, as reference space for PET image analysis, with respect to magnetic resonances (MR). Finally, by using AutoSPET it is possible to perform and repeat experiments several times avoiding manual invocation of SPM and Matlab interfaces.

Acknowledgments Authors thank Walter Morelli for his coding contributions during AutoSPET implementation.

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